Peter L. Bonate · Danny R. Howard
*Editors*

# Pharmacokinetics in Drug Development

## Problems and Challenges in Oncology, Volume 4

Springer

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**Peter L. Bonate** has acquired over 22 years of industrial experience: 19 years as a clinical pharmacologist/pharmacokineticist and 3 years in drug metabolism and bioanalysis. He is currently Executive Director of Pharmacokinetics, Modeling, and Simulation at Astellas. He received his Ph.D. from Indiana University in Medical Neurobiology with an emphasis on the pharmacokinetics of drugs of abuse. He also received an M.S. in Statistics from the University of Idaho and an M.S. in Pharmacology from Washington State University. He is a Fellow of the American College of Clinical Pharmacology and American Association of Pharmaceutical Scientists (AAPS). Within AAPS, he was a founder of the Pharmacometrics focus group, was chair of the Clinical Pharmacology and Translational Research Section, and was AAPS Fellows Committee Chair. Dr. Bonate is a recipient of the AAPS Research Achievement Award in Clinical Pharmacology and Translational Research. He is currently an Associate Editor of the *Journal of Pharmacokinetics and Pharmacodynamics*. He has served or currently serves on the editorial boards for the *Journal of Clinical Pharmacology*, *Pharmaceutical Research*, and the *AAPS Journal*. He has written more than 60 peer-reviewed publications and is author of the books *Pharmacokinetic-Pharmacodynamic Modeling and Simulation, 2nd edition* and *Be a Model Communicator (and sell your models to anyone)*.

**Danny R. Howard** received his Bachelor of Science degree in Pharmacy, and Ph.D. from the University of Missouri in Kansas City. He joined Novartis as the Head of Global Pharmacokinetics and Pharmacodynamics and is currently the Vice President of Oncology Clinical Pharmacology for the Novartis Oncology Business Unit. He began working in the pharmaceutical industry first as a biopharmaceutics consultant and then as a pharmaceutical scientist for Marion Merrell Dow, Hoechst Marion Roussel, Aventis, and Quintiles. His career has included responsibilities in both clinical and nonclinical pharmacokinetics and pharmacodynamics, bioanalytics, pharmaceutical business operations, and drug metabolism and pharmacokinetics. He has worked with numerous worldwide new drug submissions supporting both large and small molecules, within and outside the area of oncology. He was a charter member of the Missouri Biotech Association and served as its first Board Chairman.

Dr. Howards is also a member of American Association of Pharmaceutical Scientists (AAPS), American Society for Clinical Pharmacology and Therapeutics (ASCPT), and American Society of Clinical Oncology (ASCO). He is an accomplished author or coauthor of over 50 scientific publications and presentations in the area of clinical pharmacology and pharmaceutical sciences.

# Chapter 1
# Overview of Oncology Drug Development

**Laeeq Malik and Steven Weitman**

**Abstract** In recent years, the pharmaceutical industry has focused its efforts towards the development of novel combination targeted therapies for the treatment of cancer. In the battle against the most complex and heterogeneous disease, researchers have been increasing their understanding on cell signaling pathways and tumor biology. This knowledge supports the increasing interest in combinatorial approaches to overcome challenges such as drug resistance, or sub-optimal efficacy. The development of combination therapy faces several challenges: characterization of the synergy between the two chemical entities, definition of the appropriate doses and schedule to maximize efficacy without increasing the level of adverse events, which increased significantly its level of complexity. To address these obstacles several tools are made available. In vitro, the number of cell lines validated for pre-clinical testing and the availability of high throughput screening methods has increased significantly. The characterization of cells at a genomic and protein level have improved the predictability of effects in vivo and enabled the identification of synergistic, additive, or antagonistic effects of combination therapies. In vivo, xenograft models are frequently used to optimize combination therapies and understand mechanisms of drug resistance. Moreover, in silico approaches such as multi-scale mathematical models are gaining interest to integrate knowledge on cellular pathways, cellular environment, and tumor growth in order to optimize dosing strategies. The clinical development of combination therapies has prompted the need to reassess how clinical studies are designed in order to identify the right dose and the right schedule of administration for drugs in combination. Several strategies can be used for dose escalation in phase I combination studies but the use of pharmacokinetic properties of individual drugs and the collection of pharmacodynamics endpoints early in development has proven to be essential in

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optimizing combination therapies across the various phases of clinical development. Finally, an increased collaboration across the pharmaceutical industry is needed for the development of combination therapies for the successful treatment of cancer.

**Keywords** Clinical trials • Phase I • Phase II • Endpoints • Biomarkers

# 1 Historical Perspective of Cancer Drug Discovery

## *1.1 Evolution of Chemotherapy at a Glance*

The era of chemotherapy began with the discovery of nitrogen mustard (or cyclophosphamide) and methotrexate. Prior to this, only small and localized tumors were curable by surgery with radiation therapy sometimes being used to treat tumors that were not surgically resectable. Following World War II, nitrogen mustard related toxic changes in the bone marrow were observed (DeVita and Chu 2008). Methotrexate was successful in curing choriocarcinoma (Li et al. 1960). But it was the combination of nitrogen mustard (or cyclophosphamide), vincristine sulfate, procarbazine hydrochloride, and prednisone in the successful treatment of Hodgkin lymphoma that paved the way to further explore new agents and their combinations for other advanced cancers (Devita et al. 1970). Indeed, since these early combination studies, multiagent chemotherapy has resulted in a significant improvement in the survival rate for many tumor types compared to single-agent therapy alone. By the 1960s, alkylating agents, antimetabolites (methotrexate), antibiotics (actinomycin D), and vinca alkaloids were all being actively studied in clinical trials (Davis and Larionov 1964). Actinomycin D was found to be of a particular interest in the treatment of Wilms' tumor (Farber et al. 1956). Some other landmark events during this decade included the discovery of cisplatin, a cure for testicular cancer and acute lymphoblastic leukemia (Rosenberg et al. 1965). Since the introduction of cisplatin, many platinum-based regimens have become the standard of care in various advanced malignancies.

During the 1970s, doxorubicin had shown promising activity against breast cancer (Middleman et al. 1971). The cisplatin (P), vinblastine (V), and bleomycin (B) combination (PVB) chemotherapy regimen had also come into practice after demonstrating a significant response rate in testicular cancer (Einhorn and Donohue 1977). Early progress was also made in small cell and non-small cell lung cancers with a combination of cisplatin and etoposide (Kalemkerian et al. 2013). The discovery of fluorouracil (5-FU) was a landmark event in gastrointestinal cancer, and studies using a combination of 5-FU and radiation therapy were initiated in the management of locally advanced rectal cancer.

Treatment of patients with breast cancer changed substantially during the 1990s. The combination of anthracycline with cyclophosphamide became the standard of care in breast cancer as taxanes had shown activity similar to that of the anthracyclines in breast cancer (Smalley et al. 1977; Ghersi et al. 2005). Other cytotoxic agents including vinorelbine (vinca alkaloids), gemcitabine, capecitabine, ixabepi-

lone, and eribulin were also developed. Also around this time, active research was in progress for advanced lung cancer that subsequently led to the development of more effective regimens. The PVB regimen was successfully modified with an addition of etoposide, and a combination of cisplatin, etoposide, and bleomycin became the standard of care for advanced testicular cancer (Einhorn 2002). By the 1990s, several new cytotoxic agents such as irinotecan, oxaliplatin, and combinations (FOLFIRI and FOLFOX regimens) were developed against metastatic colorectal cancer (Douillard et al. 2000; de Gramont et al. 2000).

## *1.2 Era of Biologic Therapies*

The last two decades have witnessed a significant shift from cytotoxic to molecularly targeted agents due to an improved understanding of newly recognized metabolic and transduction pathways that could be therapeutically targeted. This biology-driven therapeutic approach has transformed the management of hematological, breast, lung, renal, and several other cancers. The development of all-trans-retinoic acid for acute promyelocytic leukemia (15;17 translocation) and rituximab for B-cell non-Hodgkin lymphoma represent a model for biomarker/targeted translational research and herald a new era of targeted therapy (Degos and Wang 2001). The success of imatinib in the treatment of chronic myelogenous leukemia is another landmark event in the history of targeted therapy (Baccarani et al. 2009). The development of these and other newer therapeutics in hematological malignancies has established a new paradigm for the development of targeted therapies in oncology.

The era of targeted therapy in solid tumors began when efforts were being pursued to target hormone-dependent breast cancer. Since the 1990s, tamoxifen has been the standard of care in both the metastatic and adjuvant hormone-receptor positive breast cancer (Fisher et al. 1998). After the introduction of tamoxifen, newer agents were developed for breast cancer such as the aromatase inhibitors and fulvestrant. Later, the discovery of the HER-2/neu oncogene has led to the development of trastuzumab, pertuzumab, and lapatinib (Giordano et al. 2014). These recent advancements have significantly improved the outcomes of breast cancer patients. The last two decades have also witnessed a significant survival improvement in patients with metastatic colorectal cancer with the use of bevacizumab and anti-epidermal growth factor receptor (EGFR) antibodies (cetuximab and panitumumab) (Price et al. 2014). During this period, several clinical trials of erlotinib, gefitinib, crizotinib, and afatinib have shown significant improvements in response rate and survival in selected patients with metastatic lung cancer (Johnson et al. 2014). This is associated with the recognition of specific driver EGFR mutations (deletions in exon 19 or point mutations in exon 21) as well as other oncogenes such as ALK, MET, KRAS, BRAF, and others (Takeuchi et al. 2012; Davies et al. 2012).

Until recently, the prognosis for melanoma, renal, thyroid, and hepatocellular cancers had been dismal. In the last decade, however, advancements recognizing the interplay between basic science research and clinical trials have led to the development of tyrosine kinase protein inhibitors, including sorafenib, sunitinib, and

vandetanib which have significantly reduced progression of disease in these patients (Motzer et al. 2007; Wells et al. 2010; Robert et al. 2015).

The targeted development strategy employed for these compounds has become the new standard of practice for the discovery and development of therapies for other malignancies.

## 2 Investigational New Drug Application (IND)

Prior to initiating a first-in-human study, an Investigational New Drug Application or IND is required by the Food and Drug Administration (FDA) in the United States, while a clinical trial application (CTA) is required in Europe by the European Medicines Agency (EMEA). The process and components of submitting and obtaining an IND or CTA have been outlined in a variety of guidances for the industry (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071597.pdf accessed January, 2015). There is also an opportunity to meet with regulatory authorities (e.g., pre-IND meeting) to discuss the proposed IND-enabling studies before these studies are conducted. The main focus of the IND is to understand the chemistry, manufacturing and controls (CMC), the safety toxicology around a new chemical entity, and the proposed clinical trial design and clinical development plan.

Obtaining an IND for the development of a new chemical entity to be used in patients with cancer may be different than what is required to conduct a first-in-human study for other therapeutic areas. A key outcome of IND-enabling studies is to identify the starting dose for the first-in-human study. This dose is typically a fraction of the dose found in nonclinical studies to produce significant toxicities in test animals. In most cases, both the FDA and EMEA require IND-enabling studies to be conducted in both rodent and non-rodent species before undergoing human studies. Once an IND application has been submitted to the FDA, there is a 30-day review cycle before clinical studies may be initiated.

There are a few situations where a marketed drug may be exempt from obtaining an IND for a clinical study (http://www.fda.gov/downloads/Drugs/Guidances/UCM229175.pdf accessed January, 2015). These include the following:

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication, and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for the review by an IRB and with the requirements for informed consent.

- The investigation is not intended to promote or commercialize the drug product.

Nevertheless, it is prudent that for every study with an approved marketed drug product, the sponsor or investigator seeks advice from regulatory authorities regarding the need for an IND or CTA before initiating any investigational clinical study. Prospective sponsors should thoroughly review the guidance for clinical investigators, sponsors, and IRBs related to whether the proposed human research can be conducted without an IND or CTD.

## 3 Phase 0 Clinical Trials in Oncology

Phase 0 trials were initially developed as a mechanism to accelerate the development of new anticancer drugs; however these trials are not a routine part of oncology drug development. Phase 0 trials are conducted under the FDA exploratory IND guidance on oncology drug development and differ from other trials in several aspects (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078933.pdf accessed December, 2014). Foremost, these studies are not designed to offer therapeutic benefit, define the toxicity profile of an agent, or identify the maximum tolerable dose. These studies are generally designed to evaluate pharmacokinetics (microdose studies), pharmacodynamics, and biomarkers which could help to define a pharmacologically relevant dose, the mechanism of action related to efficacy, or the metabolism of an investigational drug (Kummar et al. 2008). Hence, this approach may help to identify specific drug targets before proceeding to phase I testing. One major argument against using phase 0 studies is that a small dose (to avoid adverse effects) of an investigational agent is unlikely to provide meaningful information whether the agent is metabolically/biologically effective (Twombly 2006).

## 4 Novel Designs for First-In-Human Clinical Trials

The first-in-human trial is an important step for the clinical development of an investigational drug. The major scientific objectives of the first-in-human trial are (a) to investigate the safety and tolerability and understand the pharmacology of an investigational drug, (b) to establish a safe recommended dose and regimen for subsequent evaluation, and (c) to observe any antitumor activity (http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf accessed October, 2014). These are traditionally single-arm, open-label, sequential group design studies that typically include patients with incurable advanced cancer(s) who have exhausted the standard treatments. The adverse events of an investigational drug are assessed in a dose-dependent fashion. The recommended dose for subsequent evaluation, often referred to as the “RP2D” or “recommended phase II dose” for the

**Table 1.1** Characteristics of phase I clinical trials for anticancer agents approved by the US FDA between 2012 and 2013

| Drug | Phase I trial dose escalation method | Reason for stopping dose escalation |
|---|---|---|
| Afatinib (Yap et al. 2010) | Conventional 3 + 3 design | Toxicity |
| Trametinib (Infante et al. 2012) | Accelerated titration design | Toxicity |
| Dabrafenib (Falchook et al. 2012) | Accelerated titration design | Toxicity |
| Trastuzumab emtansine (Krop et al. 2010) | Accelerated titration design | Toxicity |
| Lenalidomide (Richardson et al. 2002) | Conventional 3 + 3 design | Toxicity |
| Pomalidomide (Richardson et al. 2013) | Conventional 3 + 3 design | Toxicity |
| Cabozantinib (Kurzrock et al. 2011) | Conventional 3 + 3 design | Toxicity |
| Regorafenib (Mross et al. 2012) | Conventional 3 + 3 design | Toxicity |
| Pazopanib (Hurwitz et al. 2009) | Conventional 3 + 3 design | Toxicity |
| Axitinib (Rugo et al. 2005) | Conventional 3 + 3 design | Toxicity |
| Pertuzumab (Agus et al. 2005) | Conventional 3 + 3 design | Pharmacokinetics |
| Enzalutamide (Scher et al. 2010) | Conventional 3 + 3 design | Toxicity |
| Carfilzomib (O'Connor et al. 2009) | Conventional 3 + 3 design | Toxicity |
| Bosutinib (Cortes et al. 2011) | Conventional 3 + 3 design | Toxicity |
| Aflibercept (Lockhart et al. 2010) | Conventional 3 + 3 design | Pharmacokinetics/ toxicity |

investigational drug, is determined by using a variety of dose escalation strategies until the toxicity rate within a dose cohort reaches 33 % (i.e., two of six patients) (Ivy et al. 2010). Table 1.1 presents characteristics of the phase I clinical trials for anticancer agents which were approved by the US Food and Drug Administration (FDA) between 2012 and 2013. Problems with first-in-human cancer trial designs are that some patients are treated at doses that are nontherapeutic and that these studies are slow to enroll. Because patients are typically recruited for participation in first-in-human studies of oncology therapeutics, it may take many months to reach the MTD (maximum tolerated dose) in this cancer study compared to a study conducted in healthy volunteers. As such, various alternative designs have been proposed to minimize the number of patients treated subtherapeutically and to identify the RP2D quicker.

## *4.1 Conventional 3 + 3 "Up & Stop" design*

As shown in Fig. 1.1a, a conventional "3 + 3" design typically evaluates a cohort of three patients per dose with the dose escalation rules and stopping criteria (i.e., dose-limiting toxicity (DLT)) predefined. The dose is escalated serially to the next higher level until one of the stopping criteria is met. As dose escalation increases, dose accretion becomes smaller. Traditionally, the modified Fibonacci sequence

has been applied for dose escalation purposes and is characterized by a 100 % initial dose increment and thereafter by 67, 50, 40, and 30–35 % of the preceding doses (Omura 2003). If one of the three patients at a dose level develops a drug-related dose-limiting toxicity (DLT), the cohort is expanded to a total of six patients. If two of the six patients in a cohort experience drug-related DLTs, the next lower dose level is expanded and declared maximum tolerated dose (MTD) if the predefined criteria are met. In order to further evaluate the safety and tolerability of the investigational drug, a few additional patients are normally enrolled at MTD.

Over the past decade, several variations of "3 + 3" design have been developed such as "2 + 4," "3 + 3 + 3," and "3 + 1 + 1" (Storer 2001). The major limitations of conventional "3 + 3" design include an uncertainty about the MTD and the potential for underestimation. As a result of the slow dose escalation process, many patients receive subtherapeutic doses (Le Tourneau et al. 2009). In contrast to the newer dose escalation methods discussed later in this chapter, only data from patients at the current dose level are employed for determining the dose for the next cohort.

## *4.2 "Up-and-Down" designs*

As shown in Fig. 1.1b, "up-and-down" designs evaluate a single patient or group of three patients and explore a large number of dose levels. The dose escalation/de-escalation process continues until a predetermined sample size is reached (Storer 1989). The dose escalation and de-escalation decisions are based on the observed adverse effect profile in the previously treated patients. These designs are not commonly used in drug development as they tend to treat a lot of patients at low doses, although variations have been developed to accelerate the process (Rogatko et al. 2007).

*Design A (traditional)*: In the traditional Storer's design, groups of three patients are treated and dose escalation occurs if no DLT is observed in all three; otherwise an additional three patients are treated at the same dose. If only one out of six patients has experienced a DLT, the dose escalation process continues. If more than one out of these six patients has experienced a DLT, the dose escalation stops. One of the major disadvantages of this design is that it allows the clinical trial to stop prematurely due to the emergence of multiple terminating opportunities.

*Design B:* This design treats a single patient per dose level. The next patient is treated at the next lower dose level if a DLT is observed, otherwise at the next higher dose level until the predefined sample size is reached.

*Design C:* A group of three patients are treated at each dose level, and dose escalation occurs if no DLT is observed and de-escalation occurs if more than one patient has developed a DLT. If only one patient has experienced a DLT, the next group of three is treated at the same dose level. This process continues until the sample size is reached. This is similar to the traditional design except that it allows de-escalation.

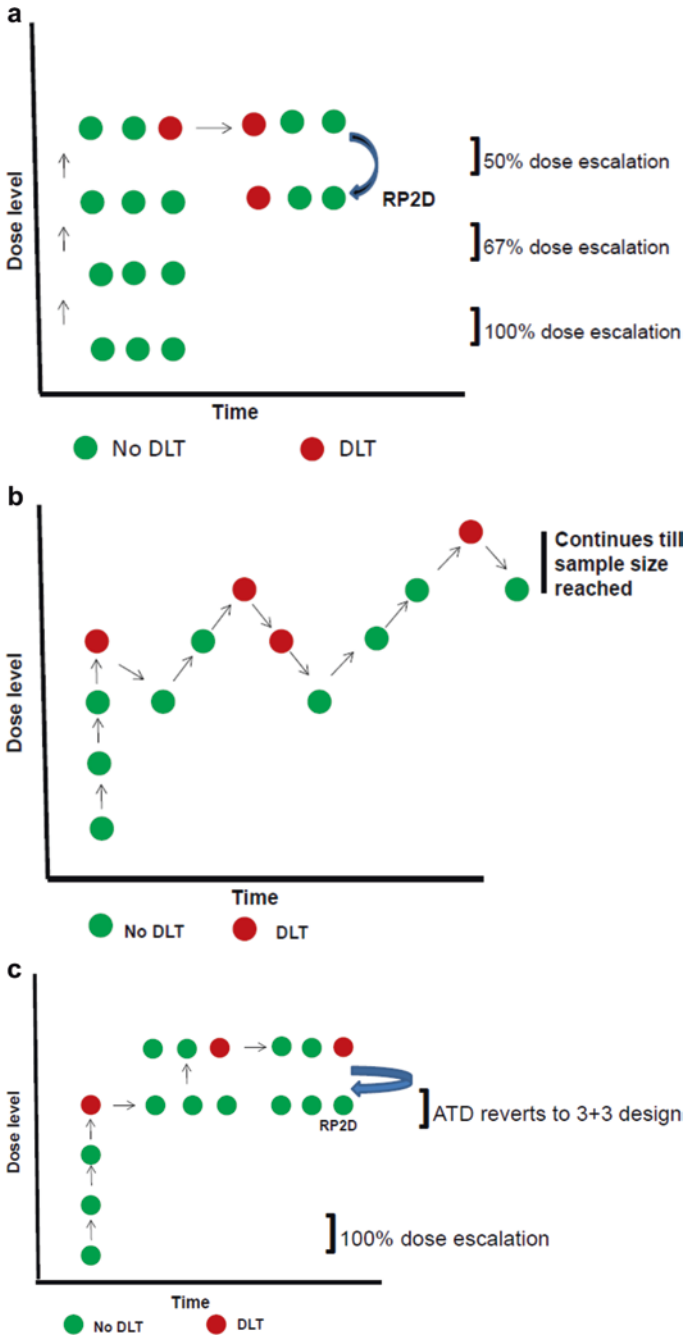


**Fig. 1.1** (**a**) Conventional 3+3 "Up & Stop" design with modified Fibonacci sequence. (**b**) "Up-and-down" design. (**c**) Accelerated titration design (ATD). (**d**) Pharmacologically guided dose escalation method

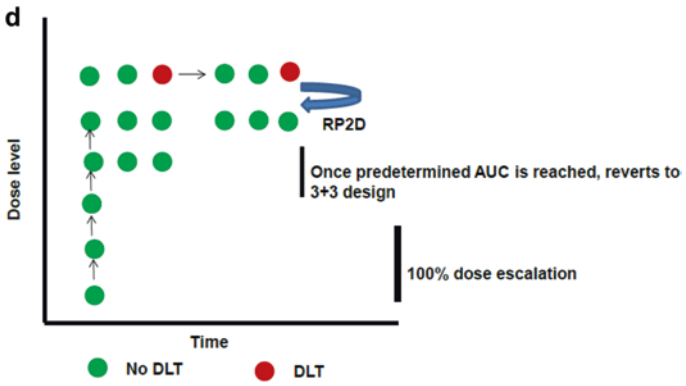


**Fig. 1.1** (continued)

## *4.3 Accelerated Titration Designs*

The contradictions between safety and efficacy in the first-in-man clinical trials are considered in the "accelerated titration" designs. From the ethical point of view, an ideal design should allow dose escalation to the MTD quickly, yet safely, to minimize the likelihood of treating patients at doses that are too low or high. Accelerated titration designs evaluate a single patient per dose level during the initial phase (accelerated phase) (Simon et al. 1997). If the first patient does not experience a significant toxicity (predefined in the protocol) or a DLT, a second patient is treated at the next higher level. Once the accelerated phase is complete, a standard "3 + 3" design model is used to determine the probability of the MTD occurring by incorporating all toxicity data from the trial (Fig. 1.1c). Once the MTD has been determined, a final "confirmatory" cohort is treated at that dose.

There are three variations of an accelerated titration design with minor differences among them (Simon et al. 1997). Two of these designs evaluate a single patient per cohort with 40 % and 100 % dose escalation, respectively. The dose escalation returns to a standard "3 + 3" design when a single DLT or two moderate toxicities are encountered during the first treatment cycle of subchronic treatment. The third design is similar except that it returns to "3 + 3" design when one DLT or two moderate toxicities are observed during any cycle.

In order to reduce the number of patients treated at subtherapeutic doses, intrapatient dose escalation is often employed. But there remains a concern that cumulative or delayed toxicities may be caused by intrapatient dose escalation. Hence, safety interpretation becomes more difficult to assign to a specific dose. Because escalation of dose occurs within an individual patient, these designs can allow for treatment of a greater proportion of patients at higher doses and make the dose escalation process more rapid. Another potential advantage is that cumulative toxicity and interpatient variability information from all patients can also be used in establishing the MTD/RP2D. Penel et al. (2009) compared the performance of

accelerated titration designs against conventional "3 + 3" designs in 270 published first-in-human trials. The accelerated titration design permitted exploration of more dose levels and reduced the rate of patients treated at doses below MTD/RP2D. However, it did not shorten the accrual time nor increase the efficacy of trials.

## *4.4 The Rolling Six Design*

One of the primary reasons for the development of the rolling six design was to shorten the overall development timeline of new agents in pediatric oncology. This design was introduced in 2008 to allow accrual of two to six patients concurrently at a dose level without waiting for the toxicity results of the first three patients. The dose escalation or de-escalation depends on several factors including the number of patients currently enrolled, the number of DLTs, and the number of patients still at risk of developing a DLT. Hence, a new patient is allowed to enter in the trial when other patients in the cohort are still at the risk of developing DLT. The results of a simulation study reported by Skolnik et al. (2008) showed that the rolling six design reduced trial duration when compared to the standard design without an increase in toxicity events.

## *4.5 Pharmacologically Guided Dose Escalation Design*

The rationale behind the pharmacologically guided dose escalation design shifts the focus from predicting DLTs from dose level to drug exposure (Graham and Workman 1992). This design involves extrapolating preclinical data to predict the drug exposure (AUC) associated with toxicity, under the assumption that similar exposures in animals and humans will have similar effects and toxicities. Subsequently, real-time pharmacokinetic data are obtained from individual patients and used during the dose escalation process (Fig. 1.1d). If the observed human exposure is far from the predicted toxic exposure, large dose escalation steps may occur. Once the predetermined toxic exposure level is reached, further evaluation can proceed in patient cohorts using any variation of the escalation approaches previously described. For example, single-patient cohorts with a 100 % dose escalation design which revert to the traditional "3 + 3" design (with smaller dose increments afterwards) may be employed. This method has the advantage of providing a rapid and safe completion of the study with fewer patients receiving subtherapeutic doses, but suffers from limitations associated with determining MTD in drugs with large interpatient variability in metabolism and the need for real-time bioanalysis and pharmacokinetic analysis for decision-making purposes. Neither of these conditions is attractive in oncology development, and the pharmacologically guided dose escalation design has not been widely used in oncology drug development.

A modification of this design is based on predicting an optimal dose based on an exposure or dose necessary to achieve a maximum target inhibition (MTI) (Meany et al. 2010). The rationale behind a trial design using MTI is based on the concept that the MTD for a new class of molecularly targeted drugs may be well above the dose required to achieve target modulation and efficacy. This approach requires identification of an appropriate drug target, developing a validated real-time assay for quantifying target modulation, and availability of suitable tissue (tumor or surrogate) for analysis. Further evaluation of this trial design in the development of molecularly targeted agents is warranted.

## *4.6 Bayesian Designs (Continual Reassessment Method and Related Designs)*

Using mathematical models based on Bayes probability to define DLTs and stopping rules, the continual reassessment method (CRM) incorporates all the available toxicity information from previously treated patients to determine the dose for the next patient cohort (O'Quigley et al. 1990). These designs offer some flexibility in choosing the number of patients per cohort. Once a "prior" guess is made as to the shape of the dose–response (or dose–toxicity) profile, the first patient is assigned to the "prior" MTD. The outcome of this patient is then used to update the "prior" guess once the required follow-up is complete. The next patient is assigned to a new "posterior" MTD. The trial is stopped when either (1) the prespecified stopping rules have been met or (2) the estimated DLT probability at the next dose level is higher than acceptable. Although, the original design allowed multiple dose escalations and de-escalations, several modifications have been made to improve patient safety. The escalation with overdose control (EWOC) is a modified CRM which avoids exposure of patients to high toxic doses (Babb et al. 1998). The time-to-event continual reassessment method (TITE-CRM) has an additional advantage of incorporating time-to-toxicity information for each patient and allows acknowledgment of late-onset or cumulative toxicities (Cheung and Chappell 2000). Other variants that also use efficacy endpoints have been developed (Yin et al. 2006).

Altogether, Bayesian designs are highly flexible, allowing enrollment of groups of any size, and they can be modified to allow incomplete information (e.g., it can incorporate prior information). However, despite these advantages, most of the CRM and related designs have not been widely implemented in clinical practice. Some of the logistical difficulties presented by these designs include a need to have the "prior" estimate of the MTD and real-time biostatistical support for computations after each patient or cohort of patients has completed their first cycle of treatment. In addition, the model may fail to reach the RP2D/MTD if the prior guess for dose–response (toxicity) curve was incorrect or insufficient (Paoletti et al. 2006).

### *4.7 Phase Ib Combination Trial Designs*

Phase Ib combination trial designs determine the safety, dose, and schedule of two or more investigational drugs that are administered together. In this design, one drug is often administered at or near its recommended full dose, and the dose of combination drug is adjusted in sequential cohorts. Hence, considerations for the existing preclinical and clinical data include important decisions for which drug will be given at (or near) the full recommended dose and determining the initial and subsequent dose levels of the second drug. The objective is to increase the dose of each drug as close to the single-agent MTD as possible while carefully monitoring for tolerability. This is achieved by escalating one agent to the RP2D or MTD, while keeping the other agent at a fixed dose. Phase Ib combination trial designs are usually able to explore only a limited number of dose levels and are conducted using both traditional and Bayesian designs (Thall et al. 2003). Bayesian designs guide the dose escalation process of the agents based on the observed toxicities in previous cohorts of patients.

*The complete phase Ib clinical trial design:* One of the primary reasons for the proposition of the complete phase Ib clinical trial design was to shorten the overall timeline for the development of new drugs in oncology and was introduced to allow the conduct of several combination phase I trials simultaneously within a single protocol (Von Hoff et al. 2007). This design involves administration of the first drug at full dose, whereas three patients are treated at one-third dose of investigational drug, three patients at two-thirds of the dose of investigational drug, and three to six patients at full dose of the investigational drug simultaneously. The initial results reported by Von Hoff et al. (2007) suggested that this approach may be safe with rapid accrual (of less pretreated patients) and efficient with several potential advantages over multiple sequential combination phase Ib studies that are conducted traditionally. Further evaluation of this trial design in the development of molecularly targeted agents is warranted.

## 5 Novel Designs for Phase II Clinical Trials

The main scientific objectives of a phase II trial of an investigational drug are to provide an initial assessment of its clinical activity at the RP2D and further verify safety. Phase II trials are performed to identify promising new drugs for further evaluation and screen out ineffective drugs from further development. Although phase II trials, which are often single arm, provide further evaluation of the RP2D, they can incorporate a few dose levels and may provide additional pharmacokinetic information. The primary endpoint of these studies is binary in nature, e.g., response vs. nonresponse. These trials typically enroll as few patients as necessary

to demonstrate a treatment benefit or failure, which not only minimizes the cost but also avoids an unnecessary exposure of patients to possibly an ineffective treatment. This can also reduce exposing patients to potentially effective drugs where the RP2D has been misestimated (too high or low). For instance, the approved dose of cabazitaxel in prostate cancer is 25 mg/m$^2$ every 3 weeks, but the commonly used dose in clinical practice is 20 mg/m$^2$ (Dieras et al. 2013). The original recommended phase II dose of 25 mg/m$^2$ was found to be associated with significant myelosuppression; hence a lower dose of 20 mg/m$^2$ is undergoing phases II–III evaluation (de Bono et al. 2010). Some important differences in the patient population; baseline characteristics such as disease status, severity, and age; primary endpoint; and other aspects could account for discrepancy between results of phases I and II/III trials. Some of the newer designs are presented in the following sections.

## *5.1 Two-Stage Designs*

Two-stage designs provide an opportunity to stop the study early if clinical activity observed is less than expected (predefined). The overall clinical activity (target response rate) is reviewed after the completion of stage I, and further patients are only enrolled if all the protocol predefined criteria for study continuation are met. The following are the commonly used two-stage designs for phase II clinical trials:

- Simon two-stage design.
- "Optimal" and "MinMax" design.
- Balanced design.
- Gehan two-stage design: This design has a first stage of 14 patients only. If no responses are observed, the phase II trial is terminated.
- Fleming two-stage design.

## *5.2 Bayesian Designs*

Bayesian trial designs rely on prior information ("prior distribution") which is updated with observed data to create the "posterior" distribution, from which inferences are made as the trial continues and more data accumulates. The initial reliance on the "prior distribution" can be a disadvantage for these approaches when the historic information upon which it is based is unreliable. For Bayesian inference, the posterior probability prediction interval and credible interval are used for interval estimation (instead of confidence interval).

## 5.3 Randomized Phase II Design

A randomized phase II trial is designed to explore the potential efficacy of an investigational drug before a higher investment is made in phase III trials. The use of randomized phase II trials in cancer research has increased in recent years because of smaller sample size requirements, although the accrual of patients in a randomized trial can still be as difficult compared to a non-randomized single-arm study for uncommon and rare tumors (Lee and Feng 2005).

There are three different types of randomized phase II trial designs as below:

- Pick-the-winner design: This phase II selection design involves two parallel, one arm studies, without direct comparison to each other (Simon et al. 1985). Simon et al. (1985) proposed the original pick-the-winner selection design in which one of two agents with a higher response rate would undergo further evaluation. This design has undergone modification so that each arm follows a two-stage design allowing comparison against a historically defined response rate (Liu et al. 2006). This allows conducting a trial in a time-efficient manner with a relatively small sample size and can be used when the goal is prioritizing which agent or schedule should proceed to larger safety and efficacy trials (Scher and Heller 2002).
- Phase II design with reference arm (a control arm): This may be viewed as an initial stage of a randomized phase II/III design where the sample size is kept sufficiently large to have enough power. It would allow early termination of phase III trial if the experimental arm demonstrated inferior response rate to that of the control arm in the phase II stage (Thall 2008). The major drawback of this approach is that the phase III trial may still continue if the experimental arm does not demonstrate an increase in the response rate.
- Randomized discontinuation design: This design allows treatment of all study patients initially with the experimental drug for a prespecified period of time (Rosner et al. 2002). After all patients are assessed, only those with evidence of at least stable disease are randomized to receive either the experiment drug or placebo. The outcomes of patients on experimental drug are then compared to those on placebo from the time of randomization. This design is less efficient as it requires a large number of patients.

## 5.4 Adaptive Randomization Design

Adaptive randomization is a study design in which the probability of treatment assignment could change (and adjusted) after incorporating all the available information from previously treated patients to determine the treatment assignment for the next patient. These trials in the beginning offer an equal chance of being randomized to any treatment arm (Berry and Eick 1995). Subsequently, randomization is adjusted based on accumulated information about the best treatment (assign with a higher probability to better therapy) which is achieved by assessing the efficacy

results from the previously treated patients and dropping of treatment arms that are found inferior during planned interim analysis. The stopping rules are clearly defined to terminate an arm when there is evidence that it has lower efficacy than the competing treatments.

An example of an adaptive randomization design is the BATTLE-1 trial in patients with non-small cell lung cancer (Kim et al. 2011). This phase II trial demonstrated that it is feasible to use multiple biomarkers to guide the treatment of lung cancer patients. Patients were adaptively randomized and treated with erlotinib, vandetanib, erlotinib plus bexarotene, or sorafenib using efficacy information from the previously treated patients with a given molecular signature. Pretreatment tumor biopsies obtained from all 255 patients were tested for 11 potential molecular signatures. Overall the disease control at 8 weeks was 46 % (primary endpoint), and a significant benefit from sorafenib was observed in the KRAS mutant patients. These biomarkers are being further explored in the prospective, biomarker-driven BATTLE-2 study.

Adaptive randomization is currently being used in I-SPY 2 trial in women with early-stage breast cancer (Barker et al. 2009). I-SPY 2 is an ongoing collaborative phase II trial comparing the efficacy of standard neoadjuvant chemotherapy against a combination of standard chemotherapy and several new novel agents, so as to identify more effective treatment regimens based on molecular signatures. Treatments are initially assigned using Bayesian methods of adaptive randomization based on standard biomarkers (ER/PR/HER-2). Tissue and blood samples are collected prospectively to develop qualifying and exploratory biomarkers. Agents that perform well within a specific molecular signature will progress through the trial more rapidly and graduate when the predictive probability of being successful in a subsequent phase III confirmatory trial reaches a specified level for that signature. It is anticipated that trials using innovative designs such as I-SPY 2 will not only reduce the cost of the lengthy drug development process but also improve the success rates with smaller study population. Although the adaptive designs are more efficient for selecting effective drugs, they require continuous statistical input. Another possible concern with the adaptation process is a possibility of type 1 error or false conclusion that the treatment is effective (potential bias).

## 6 Clinical Trial Endpoints

A clinical trial endpoint is defined as a measurement that can objectively assess the effect of treatment and determine if the null hypothesis of no treatment effect should be rejected. In oncology drug development, the choice of endpoints for clinical trials has become significantly complex and ranges from the evaluation of safety to improvement in survival. The primary endpoints of a phase I first-in-human clinical trial of an investigational drug are focused on safety, tolerability, pharmacokinetics, and an identification of predictive biomarkers. Traditionally, phases II and III trial endpoints assess a new treatment's therapeutic benefit, such as an improvement in

symptoms or overall survival (OS). OS defined as the time from randomization to death from any cause requires a large sample size and long follow-up and could be confounded by subsequent therapies. An objective response rate (ORR), defined as the percentage of patients with a prespecified extent of tumor volume reduction, is the commonly used endpoint in single-arm phase II trials. ORR is expressed as the percentage of patients observed to have partial and complete response and is assessed according to the Response Criteria in Solid Tumors guidelines (Therasse et al. 2000). When the era of chemotherapy began, some drugs were approved based on an ORR (Miller et al. 1981). In a review of 57 new cancer drug applications approved by the FDA between 1990 and 2002, approval for 26 drugs was based on ORR, 18 drugs for an improvement in survival, and 4 drugs for an improvement in symptoms (Johnson et al. 2003). More recently, ORR has been used as a surrogate endpoint for accelerated drug approval. In September 2013, pertuzumab was approved for neoadjuvant treatment of HER-2 positive breast cancer based on an improved pathologic complete response. Some of the concerns with ORR as an endpoint are that it does not evaluate the duration of response and not all clinically effective treatments lead to a significant tumor volume reduction as measured by computed tomography (Choi et al. 2007). In addition, clinically significant improvements in OS have been observed with minimal tumor size reductions (Llovet et al. 2008).

The FDA recommends that cancer drug approval should be based on direct measures of clinical benefit such as improvement in disease-related symptoms, quality of life, functional status, or survival (Pazdur 2008). An improvement in OS remains the gold standard for measuring clinical benefit. While the FDA is supportive of OS, this outcome measurement requires a very long follow-up and may be influenced by crossover designs, as well as subsequent therapies after patients discontinue treatment. These limitations have resulted in a search for intermediate or surrogate endpoints that correlate with an overall survival. In general, an intermediate endpoint can be accepted as valid if it demonstrates a strong association with an overall survival benefit.

Progression-free survival (PFS) is defined as the time from randomization to disease progression by either radiologic or clinical measures and, recently, has been used in clinical trials as a measure of clinical benefit. The major advantage of PFS as a primary endpoint is that it is neither affected by subsequent therapy nor by crossover design. However, this assessment is prone to investigator bias and may not translate into overall survival benefit in all tumor types. PFS is currently undergoing validation as a surrogate endpoint in various disease settings. In an analysis of 13 trials of chemotherapy in advance colorectal cancer, Buyse et al. (2007) reported that that PFS can be used to reliably predict OS in advanced colorectal cancer trials. It has also been used as a basis of regulatory drug approval for metastatic renal cell cancer (Motzer et al. 2007; Sternberg et al. 2010; Escudier et al. 2007; Negrier et al. 2014). However, PFS is not a reliable surrogate endpoint for overall survival in some malignancies such as metastatic breast cancer (Burzykowski et al. 2008). Thus, PFS as an endpoint must be validated in each disease setting before being considered as an established surrogate endpoint of clinical benefit.

**Table 1.2** Basis of new anticancer agent approval by the US FDA between 2012 and 2013

| Drug | Approval basis | Approved indication | Predictive biomarker (if any) |
|---|---|---|---|
| Afatinib | PFS | Non-small cell lung cancer | EGFR exon 19 deletion or exon 21 mutation |
| Trametinib | PFS | Metastatic melanoma | BRAF V600E or V600K mutation |
| Dabrafenib | PFS | Metastatic melanoma | BRAF V600E or V600K mutation |
| Trastuzumab emtansine | PFS | Metastatic breast cancer | HER-2/neu amplification or overexpression |
| | OS | | |
| Pomalidomide | ORR | Multiple myeloma | None |
| Cabozantinib | PFS | Metastatic medullary thyroid cancer | None |
| Crizotinib | PFS | Non-small cell lung cancer | ALK rearrangement |
| | ORR | | |
| Regorafenib | OS | Metastatic colorectal cancer | None |
| | PFS | Advanced GIST | |
| Pazopanib | PFS | Advanced soft tissue sarcoma | None |
| | PFS | Advanced renal cell carcinoma | |
| Axitinib | PFS | Advanced renal cell carcinoma | None |
| Pertuzumab | PFS | Metastatic breast cancer | HER-2/neu amplification or overexpression |
| | pCR | Early-stage breast cancer | |
| Enzalutamide | OS | Metastatic castration-resistant prostate cancer | None |
| Carfilzomib | ORR | Multiple myeloma | None |
| Bosutinib | MCyR | Chronic myelogenous leukemia | Philadelphia chromosome translocation between chromosomes 9 and 22 |
| Aflibercept | OS | Metastatic colorectal cancer | None |

*PFS* progression-free survival, *OS* overall survival, *GIST* gastrointestinal stromal tumor, *pCR* pathologic complete response, *ORR* overall response rate, *McyR* major cytogenetic response, *ALK* anaplastic lymphoma kinase, *EGFR* epidermal growth factor receptor, *HER-2/neu* human epidermal growth factor receptor 2

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/

Table 1.2 lists the approval basis and indications of new anticancer agents by the US FDA between 2012 and 2013.

Patient-reported outcomes (PROs) are used to measure the impact a new treatment has on the patient's perception of their general health status, quality of life, and symptoms. PROs are collected directly from the patient via interviews or questionnaires and are not subjected to interpretation by physicians. Although PROs have mostly served as secondary endpoints in oncology clinical trials, they are

being used as primary endpoints in clinical trials in other specialties such as gastroenterology (Williet et al. 2014). Health-related quality of life is increasingly being incorporated in cancer clinical trials. Between 1990 and 2002, symptomatic improvement alone has been the basis for regulatory approval in four of 57 new drug applications and also provided support for regulatory approval in nine other applications (Johnson et al. 2003). PRO is best used in randomized, controlled, blinded studies to avoid treatment bias and to control for the many influencing factors which could impact the self-reported results (i.e., study design, homogeneity of patient population, perceived efficacy of treatments, and control arms).

Time-to-treatment failure (TTF), rarely used as primary endpoint, is defined as the time from randomization to discontinuation of a treatment for objective tumor progression, treatment toxicity, or death. The major limitations of TTF are that it is unable to distinguish between treatment discontinuation due to disease progression from discontinuation due to patient withdrawal (toxicity/intolerance/other reasons). The FDA requires separate analyses of TTP, OS, and toxicity (not a composite endpoint) for cancer drug marketing application approval (Johnson et al. 2003).

In an adjuvant setting, disease-free survival (DFS), which is defined here as the time from randomization until cancer recurrence, second cancer, or death from any cause in the intent-to-treat population, is commonly used as a primary endpoint. This is in contrast to PFS which is usually used in advanced disease. Multiple meta-analyses have validated DFS as a surrogate endpoint for OS in gastric, colorectal, and lung cancers (Oba et al. 2013; Buyse et al. 2008; Mauguen et al. 2013). The main advantages of DFS in comparison to overall survival are that it does not require a very long follow-up period, and its measurement is not diluted by subsequent treatments for recurrent disease. This measure is best used in randomized, blinded studies to avoid any potential bias.

## 7 Biomarkers in Drug Development

Personalized medicine represents a treatment strategy that allows application of an individualized therapy in accordance with the existing knowledge of a biomarker, which refers to a tumor characteristic (molecular, genetic, or phenotypic) that could aid in predicting cancer development, behavior, prognosis, or response to a therapy (Hinestrosa et al. 2007). It is now possible to identify these characteristics due to an improved understanding of the tumor biology, new discovery of molecular targets, and an increasing appreciation for predictive biomarkers. The concept of biomarker-based personalized medicine is aimed at maximizing the likelihood of treatment benefit, improving the treatment efficacy, and reducing an unnecessary treatment-related toxicity by identifying a pharmacologically or biologically relevant signal which reliably anticipates the effect of the treatment. A well-known example of biomarker-based drug development is the approval of crizotinib for patients with anaplastic lymphoma kinase (ALK)-positive lung cancer. Patients with ALK-positive non-small cell lung cancer were enrolled in phase

I/first-in-human and phase II trials after an early recognition of the tumorigenic role of EML4/ALK rearrangements in a subgroup of patients with non-small cell lung cancer (Camidge et al. 2012). The FDA granted crizotinib accelerated approval as it demonstrated an ORR of 60·8 % in ALK-positive lung cancer patients (http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm376058.htm accessed October 2014).

A biomarker may have predictive and/or prognostic significance. A predictive biomarker is a disease, patient, or pharmacodynamic characteristic that is predictive of a biological response to the specific therapy. A reliable predictive biomarker should be able to accurately predict who will benefit from a therapeutic intervention and allow subgroup selection. In the absence of a therapeutic intervention, a predictive biomarker may not always relate to prognosis, but may predict other outcomes related to the effect of an intervention such as an improvement in quality of life or toxicity. One of the first biomarkers recognized to have a predictive value was estrogen receptor expression in breast cancer and response to tamoxifen therapy. A prognostic biomarker is a measurable characteristic (clinical or biologic) that provides information on the likely outcome in an untreated patient. This may help to identify and treat cancer individuals postoperatively who are at high risk of disease recurrence. A biomarker may have both a predictive and prognostic value. The presence of KRAS mutation in metastatic colorectal cancer predicts lack of benefit from monoclonal antibodies directed against the epidermal growth factor receptor as well as poor overall prognosis. Table 1.2 lists the predictive biomarkers for the new anticancer agents approved between 2012 and 2013.

Clinical trials with gefitinib started several years before a predictive molecular biomarker was first identified. It took an additional 4 years of retrospective research to demonstrate a significant clinical benefit in patients who were identified to have a predictive molecular aberration. Ultimately, a reliable diagnostic test was developed and validated for identification of patients who will most likely benefit from this treatment. Pharmaceutical companies are understandably hesitant to follow a similar development path for new agents. New innovative development strategies and biomarker-driven clinical trials are needed to make the drug development more efficient. Co-development of a drug and associated diagnostic test will improve the efficiency of the drug development process.

While it is important to incorporate genomic biomarkers in early drug development, it can present numerous challenges such as additional biopsies for analysis and even treatment delays. Also the positivity rate for some genomic biomarkers is so low that it can impede timely drug development. The task force on Methodology for Development of Innovative Cancer Therapies (MDICT) recommends that the genomic aberration presence should not routinely be an inclusion criterion for dose escalation part of first-in-human trials but appropriate for dose–expansion cohorts and advanced phases of drug development (Liu et al. 2014).

The development of a tumor biomarker for clinical use requires significant collaborative research work and is a complicated, resource intensive and challenging process. Biomarker development for early cancer detection occurs in several consecutive phases (Pepe et al. 2001). The initial phase employs immunohistochemistry,

Western blots, and gene-expression profiles in preclinical models to determine tumor characteristics that might lead to identification of potential biomarkers. A clinical assay is also developed in order to distinguish patients with cancer from those without cancer. Subsequently retrospective longitudinal repository studies are undertaken to provide evidence regarding the capacity of the biomarker to detect a disease during screening. In a prospective screening study, the number and nature of cases detected with the screening tool are determined (and the numbers of false-positive cases). The final phase evaluates whether screening has an effect on an overall disease burden in the population.

Similarly for the successful development and validation of a laboratory assay, several steps are considered. The initial step is selection of an appropriate assay for the intended purpose and a target sample. Once a reference standard has been selected, the process of optimizing an assay is undertaken by using the best scientific practice to achieve a reliable performance. The analytical sensitivity and specificity of an assay is evaluated during validation. Analytic validation provides an assurance of accuracy and reliably in measuring the molecular event of interest ensuring that the same result will be produced for the same sample within predefined technical variation. It is also necessary to determine the performance characteristics of the test being validated. The ability of an assay to provide consistent results is assessed. Validation methods are completed in line with regulatory requirements to ensure that the assay is accurate and reproducible before it is used to test patient specimens. Evidence-based guidelines are available regarding validation of different assays (Fitzgibbons et al. 2014). An ultimate evidence of usefulness of an assay is its successful application(s) in other laboratories or surveillance programs regionally and/or internationally. Once the assay has been validated, its daily performance is carefully monitored in a quality assurance program to assure that it consistently maintains the requirements as defined during validation of the assay. Clinical validation determines the level of agreement between assay results and the clinical event of interest ensuring that the clinical state is positive if the test is positive and vice versa. Clinical utility provides an assurance that the assay has an ability to improve the clinical decision-making and patient outcomes depending upon the clinical situation, availability of effective therapies, and magnitude of benefit. For example, the prostate cancer Gleason score has a proven analytic and clinical validity but provides no additional clinical utility.

## 8 The Way Forward

The slow rate of oncology drug development has recently accelerated due to the recognition of several molecular aberrations and pathways that could be therapeutically targeted. It is imperative to develop more effective, less toxic agents by incorporating the developments in molecular cancer research and improve the outcomes

**Table 1.3** FDA breakthrough therapy approvals in oncology for 2013–2014

| Drug | Year of approval | Indication |
|---|---|---|
| Obinutuzumab | 2013 | Chronic lymphocytic leukemia |
| Ibrutinib | 2013 and 2014 | Mantle cell lymphoma and chronic lymphocytic leukemia |
| Ofatumumab | 2014 (supplement) | Chronic lymphocytic leukemia |
| Ceritinib | 2014 | NSCLC (ALK positive) |
| Idelalisib | 2014 | Chronic lymphocytic leukemia |
| Pembrolizumab | 2014 | Metastatic melanoma |
| Blinatumomab | 2014 | Acute lymphocytic leukemia |
| Nivolumab | 2014 | Metastatic melanoma |

of cancer patients. The ongoing efforts in immuno-oncology to prevent tumors from evading adaptive immunity will likely lead to the development of effective immunotherapy agents for patients with advanced cancer. These discoveries have led to initiation of clinical trials to reinvigorate tumor-specific T-cell immunity using promising agents against the programmed cell death protein-1 (PD-1) immune checkpoint pathway (Malik 2014).

Although significant progress has been made recently, many important challenges remain open. Enhancing the access to clinical trials for minorities and disadvantaged patients requires new initiatives. Given the high unmet need in oncology, new drugs with a favorable benefit-to-harm balance should become available to patients more rapidly. Robust, as well as clinically meaningful, surrogate endpoints that are acceptable to regulatory agencies are needed to expedite the future drug approval process. Clinical trials using adaptive design may improve the overall efficiency of the drug development and may even improve development success rates by allowing adaptation to those elements that were not fully known when the study was initially planned and powered (Barker et al. 2009). The incorporation of novel genomic information may hold promise to improve the drug development process by increasing the overall response rate (ORR) of a drug, but may also slow the process if patients with novel molecular signatures are only allowed to enroll in clinical trials. The development of new biomarkers from tumors to select the most effective treatment by patient type will further expand the era of personalized medicine. While these strategies may further increase the cost, solutions to undertake this endeavor by a resource-efficient manner needs to be found. Amid concerns regarding a high cost of new oncology drugs, serious consideration needs to be given to the cost-effectiveness and value-based pricing. New innovative development strategies, new regulatory approaches, restructured cooperative groups, and biomarker-driven clinical trial designs will be needed to translate discoveries into a meaningful clinical benefit. Nevertheless, these specified challenges during the process of drug development can be overcome by a continued collaborative effort between academic scientists, pharmaceutical companies, and authorities controlling regulatory affairs (Table 1.3).

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# Chapter 2
# Overview of Oncology Biomarkers

**Mitsukuni Suenaga, Heinz-Josef Lenz, and Stefan J. Scherer**

**Abstract** Biomarkers, whether predictive or prognostic of disease, are an essential element of every modern targeted oncology drug development program. Because they can provide information about the mechanism of drug action, carcinogenesis, and patient characteristics specific to both disease and treatment, they offer the opportunity to individualize therapies and to realize potential of personalized medicine. This chapter provides an introduction to biomarkers, their definition and collection, with emphasis on the utility in colon, breast and lung cancers.

**Keywords** Biomarker • Predictive marker • Prognostic marker • Pharmacogenomics • Patient stratification • Patient selection • Precision medicine

## 1 Overview

In oncology, reliable biomarkers are crucial to realize individualized treatment for cancer patients. Biomarkers represent biological characteristics of patients or tumors in various cancer types that identify carcinogenesis mechanisms, individual genetic variations, or pharmacogenomics such as pharmacokinetics and pharmacodynamics. Finally, detected molecular biology-based biomarkers can serve as specified markers for tailor-made treatment especially with molecular-targeting agents.

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Biomarkers are generally divided into “predictive” and “prognostic” factors (Nalejska et al. 2014). Predictive markers provide optimal treatment indication with the likelihood of response to an applied chemotherapeutic therapy as well as of treatment-related side effects. By contrast, prognostic markers confer identification of patients with different clinical outcomes derived from somatic mutation, germline polymorphisms, change in DNA methylation, serum cytokine levels, expression of micro-RNA (miRNA) as well as circulating tumor cells (CTCs) (Mehta et al. 2010).

Thus, identification of biomarkers that highly correspond to clinical outcomes or antitumor effect of chemotherapy is a crucial concern in clinical practice when treating cancer patients.

## 2 Prognostic Marker

Prognostic biomarkers are objectively measurable and act as an intrinsic manner in both patients and tumors and also independent of treatment that provide useful information to the physicians about the likely clinical outcome. In advanced or metastatic cancers, overall survival is the most common prognostic marker (Nalejska et al. 2014). Furthermore, prognostic factors are attributed to assess the tumor staging such as likelihood of the lymph node or distant metastasis at the point of diagnosis of cancer, preoperative screening process, and decision of application of adjuvant chemotherapy to patients who underwent curative tumor resection with respect to risk of cancer relapse (James et al. 2007; Cohen et al. 2009; Coate et al. 2009). Thus, prognostic markers can be used for patient selection who receive benefit from cancer treatment in any tumor stages, but should not be employed to predict treatment efficacy.

Prognostic biomarkers in specific tumor type are identified by molecular analysis for gene expression, gene polymorphism, mutation, DNA methylation variation, CTC, or miRNA in the peripheral blood. Serum or plasma cytokine levels derived from the host or tumor can also become prognostic factors (Hegde et al. 2013).

## 3 Predictive Marker

Predictive markers are characterized as more practical during cancer treatment that provides information on the likelihood of benefit achieving objective response to treatment. Thereby, in general, predictive markers are used for identification of specific patient groups who are most likely to benefit from treatment, as well as therapeutic decisions. Somatic mutations are the most common predictive markers as shown in epidermal growth factor receptor (EGFR) signaling-related genes such as *KRAS*, *BRAF*, or *EGFR1* (Amado et al. 2008; Van Cutsem et al. 2011). Analysis of the expression of RNA and miRNA or determination of methylation status is recently more focused on detecting good responders to treatment (Ouchi et al. 2015; Perez-Carbonell et al. 2015).

## 4 Biomarkers in Various Cancers

In several common cancer types, predictive and prognostic markers have been successfully used to predict a response to treatment given to patients by genetic analysis mentioned above. Some examples in major solid tumors are shown below.

### *4.1 Colon Cancer*

#### 4.1.1 Predictive Marker

Epidermal growth factor receptor (EGFR) is a target of anti-EGFR monoclonal antibodies (cetuximab and panitumumab) in the treatment with metastatic colorectal cancer (mCRC). Although mechanism of the drugs is inhibiting downstream EGFR signaling and approximately 70 % of EGFR expression in CRC reported, EGFR expression has not been shown to correlate with efficacy of the anti-EGFR monoclonal antibodies (Cunningham et al. 2004).

Further analyses on genes in the EGFR signaling pathway demonstrated that such anti-EGFR antibodies could be effective only in mCRC harboring *KRAS* and *NRAS* [exon 2 (codons 12 and 13), exon 3 (codons 59, 61)], *BRAF*(V600E), and *PIK3CA* (exon 20) as wild type (De Roock et al. 2010). In addition, *PTEN* is known as a tumor suppressor gene inhibiting PI3K-Akt signaling that indirectly diminishes response to anti-EGFR antibodies with its mutation (Perrone et al. 2009; Sartore-Bianchi et al. 2009; De Roock et al. 2011). The latest guidelines indicate that clinical use of the anti-EGFR antibodies should be considered only in extended RAS (*KRAS* and *NRAS*) wild-type mCRC patients (Allegra et al. 2016; Sorich et al. 2015).

#### 4.1.2 Prognostic Marker

Familial adenomatous polyposis (FAP) is a familial syndrome, in which mutation of *APC* tumor suppressor gene predisposes the patients to adenoma or adenocarcinoma from the normal epithelium in the gastrointestinal tract. Annual screening or investigation of the family history is strongly recommended in patients with *APC* gene mutation or family history of FAP (Plawski and Slomski 2008).

Mismatch repair deficiency (dMMR) has been shown to involve many somatic mutations acting in a prognostic manner and also as predictive showing less response to 5-fluorouracil in adjuvant therapy (Sargent et al. 2010). Recently, a study demonstrated that dMMR was dramatically associated with enhanced response to programmed death 1 (PD-1) immune checkpoint inhibitor. In this mean, dMMR acts as a predictive marker and will be surely focused on its correlation with the immune microenvironment widely in many types of cancer (Le et al. 2015).

## 4.2 Breast Cancer

### 4.2.1 Predictive Marker

Breast cancer is the one that has been most investigated for biomarkers because of its characterization showing precise response to both biologic agents and hormone therapy. Hormone receptors such as estrogen receptor (ER) and progesterone receptor (PR) are targets of hormone therapy and expression of these genes serve as predictive markers in breast cancer (Chung and Christianson 2014; Dowsett et al. 2006), and current guidelines indicate clinical use of the hormone therapy as both adjuvant and in metastatic setting in specific patients with hormone receptor positive tumor (https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf). On the other hand, HER2 is the target of HER2 inhibitor including RTKs (trastuzumab, lapatinib, pertuzumab, and T-DM1). As a predictive factor, HER2-negative tumor does not respond to trastuzumab, as observed in different types of cancers with metastatic breast cancer and advanced gastric or gastroesophageal junction cancer (Bang et al. 2010; Blackwell 2010).

### 4.2.2 Prognostic Marker

The hormone receptors and HER2 status also serve as prognostic markers in breast cancer. HER2-positive tumors are significantly associated with poor survival compared to those without HER2 overexpression in breast cancer and possibly in gastric cancer (Rüschoff et al. 2010; Hofmann et al. 2008). Although the frequency of HER2 expression is around 20 % in both cancer types, HER2 testing is routinely underwent to provide benefit and to avoid unnecessary harmfulness to patients under the current clinical guideline (https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf).

## 4.3 Lung Cancer

### 4.3.1 Predictive Marker

In patients with non-small-cell lung carcinoma (NSCLC), *EGFR* kinase mutations in exons 19 or 21 are routinely tested to decide the indication of tyrosine kinase inhibitors (gefitinib and erlotinib) because of high sensitivity to these agents compared with normal gene status (Heuckmann et al. 2012). Although the frequency of mutation is small (around 5 %) in NSCLC, anaplastic lymphoma kinase (*ALK*) gene rearrangement leading to the constitutive expression and activation of ALK fusion protein has become a promising target of ALK inhibitor (crizotinib) (Camidge et al. 2012). However, recent studies demonstrated secondary ALK kinase mutations in relation to drug resistance by ALK fusion gene amplification, EGFR, or KIT

activation (Gainor et al. 2013). Ceritinib is approved as next-generation ALK inhibitor in patients confirmed with crizotinib-resistant tumor. Recently, p-glycoprotein overexpression was revealed as crizotinib resistance mechanism in ALK-rearranged NSCLC patients (Katayama 2015). Thus, testing for EGFR mutations and ALK gene rearrangement is standardized in the treatment decision for NSCLC. However, further drug-resistant tumors will still remain as an unavoidable issue along with novel drug development.

### 4.3.2 Prognostic Marker

Excision repair cross-complementation group (ERCC1) protein was reported as a predictive and prognostic factor that participates in the DNA repair in the nucleotide excision repair pathway caused by cisplatin. Highly expressed ERCC1 tumor was revealed to provide longer survival in patients who did not receive adjuvant therapy; by contrast, only low-expressed ERCC1 tumor was associated with good outcome in patients receiving adjuvant chemotherapy (Huang et al. 2016). As focused on CRC, *KRAS* mutation has been investigated in NSCLC as relevant biomarker to date and found to be poor prognostic marker of NSCLC (Zhu et al. 2008). Although abnormalities of these genes are conceivable to be prognostic markers with respect to their critical role in each signal transduction pathway, most of the results have not been validated for their true clinical values.

## 5 Timing of Biomarker Measurement

Although the impact of biomarkers is marvelous, testing them with inappropriate timing may provide a risk of false-positive or false-negative results that misleads the physician to incorrect choice of patients or treatment. We also recognize that biomarker characterization including pharmacodynamics of agents or gene status can be changeable by previous treatment or other extrinsic stimulation. In that regards, preoperative study is considered as one of the most reasonable tools to evaluate the true functions of biomarkers (Marous et al. 2015).

Candidate biomarkers discovered in small population study such as phase II trials are finally verified in randomized clinical trials that are stratified by the biomarkers. There are two types of biomarker study in clinical trial. An integral biomarker directly reflects its impact on clinical endpoints because treatment arms are stratified by the biomarker with enrolling patients randomly to each arm. By contrast, integrated biomarkers are obtained after the prospective randomized trial met the primary endpoint, at least meaning that biomarkers are not crucial factor directing treatment (Mankoff et al. 2014). However, most common biomarker approved for use in clinical practice is an integrated biomarker derived from additional research of clinical trials, because the large amount of time and cost will be carried on researchers.

Therefore annual review of the availability of biomarkers and amendment of guideline are necessary to avoid unfavorable outcome in patients who undergo biomarker-dependent treatment.

## 6 Future Perspective

Biomarker research has remarkably progressed in oncology and accelerates novel drug development. Analysis of DNA methylation and miRNA are recent topics in several types of cancer (Nalejska et al. 2014). On the other hand, technology of DNA and RNA sequencing, quantification of RNA, and SNP genotyping have been developed and provide us the opportunity to analyze numerous number of genes at one testing in short period such as genome-wide association study (GWAS) (Mehta et al. 2010; Easton et al. 2007). However, GWAS covers only common SNPs revealed as predictive or prognostic factors in treatment efficacy and carcinogenesis even though it examines more than 500,000 SNPs at once, and we thereby should recognize the disadvantage of GWAS as reward for amount of examination cost. Therefore, we should think more deeply about the candidate gene-related pathway before executing whole genome sequencing. If a hypothesis is well considered and biologically reasonable, conventional SNP analysis may be enough and defeat whole genome sequencing in terms of likelihood to find out specific biomarker as well as cost benefit.

In conclusion, recent biomarker research has been remarkably progressed and assisted early drug development especially molecular-targeting agents in oncology. To evaluate the true value of candidate or approved biomarker, the timing of testing and change of characterization by the environment such as previous treatment should be always considered when choosing patients and deciding treatment strategy.

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# Chapter 3
# A Global Perspective on First-in-Man Dose Selection: Oncology and Beyond

**Peng Zou, Sau Lee, Min Li, Lawrence Yu, and Duxin Sun**

**Abstract** First-in-human (FIH) studies of anticancer products differ from that of other drug products in that they are usually evaluated in cancer patients rather than healthy volunteers. The FIH dose for anticancer drugs is expected to have pharmacological effects in cancer patients and is reasonably safe to use. Therefore, it is challenging to estimate the starting dose for an anticancer drug. Furthermore, the emergence of targeted agents such as small molecule molecularly targeted agents (MTAs), monoclonal antibodies, and antibody–drug conjugates (ADCs) in oncology has posed additional challenges in FIH dose selection. Traditional FIH dose selection methods were developed in the era of cytotoxic drugs and these doses were determined by methods using preclinical toxicity data. For targeted agents, the interspecies variability in safety and efficacy, dose–efficacy curve, and dose–toxicity curve may differ from those for cytotoxic agents, and efficacy may occur at doses that do not reach the maximum tolerated dose (MTD). Therefore, traditional preclinical toxicological studies may be inadequate to support the selection of a safe and active FIH dose of targeted agents. The strategy for FIH dose determination has shifted from a primary focus on toxicity to identifying a dose that optimally inhibits the molecular target. This chapter reviews various approaches for determining FIH dose of anticancer drug products as well as preclinical studies to support the FIH dose selection.

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**Keywords** First-in-human dose • Anticancer drug • Monoclonal antibody • Molecularly targeted agent • Antibody–drug conjugate

## 1 Introduction

In oncology, one objective of the first-in-human (FIH) study is to determine the recommended phase II dose (RP2D). Because this is the first time the agent has been administered to humans, it is imperative that the first administered dose be well tolerated in patients. Selection of FIH dose is a complex process and is both an initial step and essential element in the clinical development of a potential drug molecule. The starting dose must be low enough to be safe in humans, but not too low to cause excessive costly and time-consuming dose escalations in the FIH study. In all the therapeutic areas except oncology, five different approaches are usually used to estimate FIH dose: (1) no observable adverse effect level (NOAEL) approach, (2) minimal anticipated biological effect level (MABEL) approach, (3) similar drug comparison approach, (4) pharmacokinetically guided approach, and (5) pharmacokinetic/pharmacodynamic (PK/PD)-guided approach. These five approaches, which are generally applicable to most small molecule and large molecule compounds, have been discussed previously (Zou et al. 2012).

The selection of the FIH starting dose for an anticancer drug is different from the general approaches for drugs in other therapeutic areas. Phase I studies are often the last hope for patients with advanced cancer who have exhausted other treatment options. Due to the unique balance of risks and benefits of anticancer drugs, some reversible adverse effects caused by the selected FIH dose might be considered acceptable in the face of meaningful clinical benefit, such as longer overall survival. An ideal FIH starting dose would be pharmacologically active but not result in unacceptable toxicity. Clinicians must carefully balance the safety of study subjects, the desired therapeutic effects in patients, and an efficient and rapid dose escalation process. It is desired to achieve pharmacologically active doses as quickly as possible and minimize the number of cancer patients treated at subtherapeutic doses while trying to ensure patient safety.

The traditional approaches for selecting the FIH dose of anticancer drugs such as cytotoxics were based on preclinical toxicity studies. The FIH dose was set as 1/10 of the severely toxic dose in 10 % of the animals (STD10) in rodents or 1/6 of the highest non-severely toxic dose (HNSTD) in non-rodents (ICH 2010). Although the STD10 and HNSTD approaches are recommended in the ICH *S9* Guidance and are widely used in anticancer drug development, there has been a concern that the two toxicity-based methods provide doses that are too conservative, resulting in a number of cancer patients treated with ineffective doses in the FIH study (Reigner and Blesch 2002). As such, it was advocated that preclinical PK and PD data should also be considered for estimating FIH dose of cytotoxic anticancer drugs.

The emergence of small molecule molecularly targeted agents (MTAs), monoclonal antibodies, and antibody–drug conjugates has resulted in a paradigm shift in

anticancer drug development. For these targeted agents, toxicological data alone may be insufficient to support FIH dose selection. PK and PD data should be employed to assist in the determination of the FIH dose of targeted agents. For example, it is important to develop and validate PD endpoints and in vitro assays to evaluate the impact of a target agent on its molecular target. The interspecies variability in drug–target interaction should be considered when estimating FIH doses based on preclinical toxicological and pharmacological data. Overall, the coordination with preclinical pharmacology and toxicology studies can save both time and resources in early clinical trials and reduce the number of patients treated at subtherapeutic doses.

## 2 Regulatory Guidances

FIH dose selection is a complex task. Preclinical toxicological and pharmacological studies and in vitro and ex vivo assays may be required to support FIH dose selection. There is no "gold standard" for estimating FIH dose of drugs in oncology and other therapeutic areas. The US FDA, EMA, and ICH have issued a number of guidances to industry for FIH dose selection (Table 3.1). These guidances provide recommendations for estimating FIH dose of general drugs and/or anticancer drugs as well as designing preclinical studies to support FIH dose selection. NOAEL method and MABEL method are recommended by the US FDA and EMA, respectively, for determining FIH dose of drugs in all the therapeutic areas except oncology. For small molecule oncology drugs, STD10 approach and HNSTD approach are adopted by the International Conference on Harmonisation (ICH) for FIH dose selection.

### *2.1 NOAEL Approach*

In July 2005, the US Food and Drug Administration (FDA) issued *Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (FDA 2005). In this guidance, the recommended process for selecting the maximum recommended starting dose (MRSD) includes five steps:

Step 1. Determine NOAEL in each animal species. The NOAEL refers to the highest dose level that does not produce significant adverse effects compared with the control group. The NOAEL for each toxicology study is usually reported in mg/kg.

Step 2. Convert the NOAEL to a human equivalent dose (HED) using allometric scaling factors. For most systemically administered low molecular weight therapeutics, the conversion is based on the normalization of doses to body surface area (BSA). For the small molecule agents administered by alternative routes

**Table 3.1** Current regulatory guidance on FIH dose selection and preclinical evaluation of anticancer agents

| Guidance title | Organizations or regulatory agencies/ publication year | Recommendations | References |
|---|---|---|---|
| Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers | US FDA/2005 | No observed adverse effect level (NOAEL) approach was recommended for estimating human maximum recommended starting dose (MRSD) of general drug products | FDA (2005) |
| Guidance for industry, investigators, and reviewers—exploratory and studies | US FDA/2006 | The study design and microdose studies for exploratory IND studies are recommended | FDA (2006) |
| Guideline on the strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (finalized) | EMA/2007 | Minimal anticipated biological effect (dose) level (MABEL) approach is recommended for general drug products | EMA (2007) |
| ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals | ICH/2010 | The guidance recommends 10 % STD10 in rodents or 1/6 of HNSTD in non-rodents for cytotoxic anticancer agents and MABEL approach for anticancer biologics with immune agonistic properties | ICH (2010) |
| ICH guideline S6 preclinical safety evaluation of biotechnology-derived pharmaceuticals | ICH/1997 | Provided recommendations for preclinical safety study on biologics | ICH (1997) |
| ICH guideline S6 addendum to preclinical safety evaluation of biotechnology-derived pharmaceuticals | ICH/2012 | Update recommendations for species selection and study design in preclinical safety study of biologics | ICH (2012) |
| Guideline on the evaluation of anticancer medicinal products in man | EMA/2012 | Different recommendations are provided for anticancer cytotoxic agents, non-cytotoxic agents, immunomodulating agents, and biologics | EMA (2012) |

*STD10* The severely toxic dose in 10 % of the animals, *HNSTD* the highest non-severely toxic dose

(e.g., topical, intranasal, subcutaneous, intramuscular) and therapeutic proteins with a molecular weight >100,000 daltons administered intravascularly, the conversion to HED should be based on body weight.

Step 3. Select HED from the most appropriate species. The species that generates the lowest HED is deemed the most sensitive species. Usually, the HED determined in the most sensitive species is used to calculate human MRSD. However, when information indicates that a particular species is more relevant for assessing human risk, the HED for that species may be used in subsequent calculations, regardless of whether this species is the most sensitive.

Step 4. Apply a safety factor. A safety factor, generally at least tenfold, is applied to the HED derived in step 3 to give a human MRSD. The safety factor, usually tenfold, can be adjusted based on preclinical study results. For example, if a steep dose–response curve, severe toxicities, irreversible toxicities, or nonlinear PK is observed in a preclinical model, the safety factor will be increased. On the other hand, a smaller safety factor can be applied if toxicities produced by the therapeutic are easily monitored, reversible, and predictable.

Step 5. Compare MRSD with pharmacologically active dose (PAD). Adjustment of the MRSD based on the pharmacologically active dose (PAD) needs to be considered. If the predicted human PAD is lower than the MRSD, it may be suitable to select the human PAD as the FIH dose.

The NOAEL approach is based solely on preclinical toxicological data. Therefore, it is often criticized for ignoring preclinical PK and PD data. The choice of the safety factor is also often criticized because it is empirically chosen without scientific justifications. For small molecule chemical entities, the MSRD approach usually generates a very conservative FIH dose resulting in numerous dose escalation steps to find the therapeutical range and RP2D (Lowe et al. 2010). Furthermore, the toxicology-based NOAEL approach may not be applied to agonistic monoclonal antibodies (mAbs), which is highlighted in TGN1412 case. TGN1412 is an immunomodulatory IgG mAb originally intended for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) and rheumatoid arthritis. TGN1412 is a superagonist of CD28 expressed on T cells and upon binding to CD28 stimulates T cells to release cytokines. TGN1412 caused multi-organ failure in six healthy volunteers in an FIH clinical trial in March 2006 (Suntharalingam et al. 2006). For TGN1412, the NOAEL determined in the most appropriate species, cynomolgus monkey, was 50 mg/kg. Scaling based on body weight gave an HED 16 mg/kg. Although a very conservative safety factor of 160 was applied to generate an MRSD of 0.1 mg/kg, the first six healthy subjects administered a single dose of TGN1412 still suffered from a cytokine storm and severe adverse events resulting in hospitalization. What went wrong? Subsequent research has shown that the cytokine storm was caused by overstimulation due to the interspecies differences in TGN1412-CD28 binding affinity, which could not be predicted from preclinical toxicological data. In this particular case, the FIH dose selection process ignored step 5 of the NOAEL approach and the PAD of TGN1412 in human was not predicted. The TGN1412 incident clearly revealed the importance of in vitro and in vivo PK and PD data in

FIH dose selection. Interestingly, clinical development of TGN1412 has restarted in Russia using a dose of 0.1 % of the dose used in the original study (0.0002 % of the maximal dose used in cynomolgus monkeys). Under these conditions, no adverse events were seen (Kenter and Cohen 2015).

## 2.2 MABEL Approach

Soon after the TGN1412 incident, the European Medicines Agency issued a guideline on strategies to identify and mitigate risks in FIH trials with investigational medicinal products, in which the MABEL approach was introduced to estimate the FIH dose of therapeutic proteins and small molecules (EMA 2007). MABEL is the dose leading to a minimal anticipated biological effect level in humans. In the MABEL approach, the interspecies differences in PK and PD of a therapeutic agent are considered when estimating the FIH dose. The MABEL is calculated by using the following PK/PD data: (1) in vitro target binding and receptor occupancy in target human and animal cells, (2) in vitro concentration–response curves in target human and animal cells, (3) dose–response/exposure–response in vivo in the relevant animal species, and (4) exposures at pharmacological active doses in the relevant animal species. To minimize the potential risks of adverse effects in humans, a safety factor is applied in the selection of the MABEL FIH dose. The value of the safety factor depends on the novelty of the active substance, the biological potency, the mode of action, the degree of species specificity, the shape of the dose–response curve, and the degree of uncertainty in the calculation of the MABEL. Once the FIH doses are calculated from the NOAEL and MABEL, the lowest value is recommended for FIH trial (EMA 2007). Although the MABEL approach was developed based on an incident with a biologic, it is also applicable to FIH dose selection of small molecule chemical agents.

## 2.3 STD10 Approach and HNSTD Approach

In the International Conference on Harmonisation (ICH) *S9* Guidance (*Nonclinical Evaluation for Anticancer Pharmaceuticals*), it is recommended that the toxicity of small molecule cytotoxic anticancer agents be evaluated in both rodent and non-rodent species before undergoing human phase I trial evaluation. FIH doses for small molecule cytotoxic anticancer agents are determined based on 1/10 of the severely toxic dose to 10 % of animals (STD10) in rodents or 1/6 of the highest non-severely toxic dose (HNSTD) in non-rodents, using BSA-based allometry for interspecies dose scaling. Figure 3.1 shows the US FDA's recommendations using the STD10 or HNSTD approaches to calculate the FIH dose of small molecule cytotoxic anticancer agents (Senderowicz 2010). The first step is to determine STD10 in mice or rats. The STD10 is the dose that causes severe toxicity (or death) in 10 % of

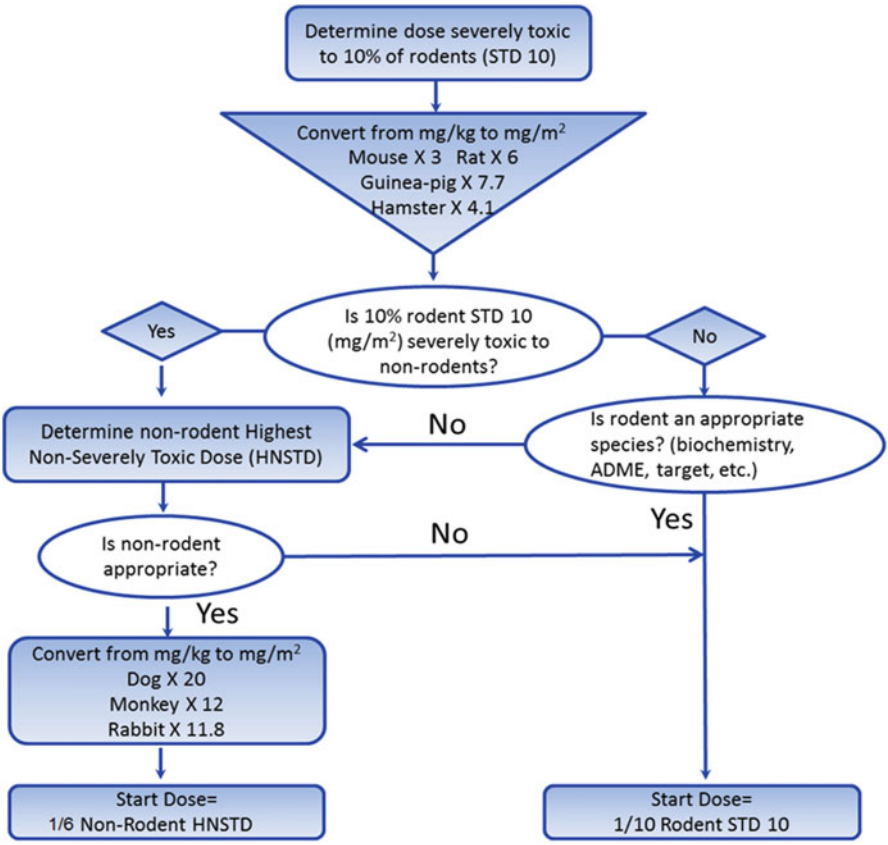


**Fig. 3.1** US FDA general guide for FIH dose selection for a cytotoxic agent and small molecule MTAs (Senderowicz 2010)

rodents. The unit of STD10 dose is converted from mg/kg to mg/m$^2$ using scaling factors and then a safety factor of 10 is applied to obtain FIH dose. Meanwhile, toxicity studies in non-rodents (most typically dogs) generate the HNSTD, defined as the highest dose level tested in non-rodents that does not cause lethality, life-threatening toxicity, or irreversible toxicity. The HNSTD in non-rodent is then converted from mg/kg to mg/m$^2$ using scaling factors. The FIH dose calculated by HNSTD approach is one sixth of the HNSTD in mg/m$^2$. Usually, the lowest one of the FIH doses determined by STD10 and HNSTD approaches is chosen as the actual FIH dose in humans. However, there are situations in which the starting dose may differ from the lowest FIH dose. For example, if 1/10 of the STD10 determined in rats is the lowest dose but the rat is not relevant to the human in terms of pharmacokinetics, target expression, toxicity profile, and others, the dose determined in non-rodents by HNSTD approach should be used instead. Unlike FIH dose selection for non-oncology drugs, the safety factors (10 for STD10 or 6 for HNSTD) used for

FIH dose selection in oncology drug trials are usually not altered to reflect special cases, such as a steep dose–toxic response curve, because of the desire to achieve therapeutic effects in FIH study.

## 3 Emergence of Targeted Agents

A significant therapeutic shift in the field of oncology drug development has been the emergence of targeted agents such as MTAs, monoclonal antibodies (mAbs), and antibody–drug conjugates (ADCs). From 2011 to 2015, 42 oncological new molecular entities (NMEs) or new biologics were approved by the US FDA to be marketed in the US market. As shown in Fig. 3.2, among these approvals, MTAs were the most common with 59 % ($n=25$), followed by mAbs with 28 % ($n=8$), miscellaneous agents with 7 % ($n=3$), cytotoxic agents with 5 % ($n=2$), and ADCs with 5 % ($n=2$). When the 42 drugs approved between 2011 and 2015 are compared with the 41 oncological NMEs or new biologics approved between 1999 and 2010, there were more approvals of MTAs ($n=25$ vs. $n=19$ or 59 % vs. 46 %), more approvals of mAbs ($n=8$ vs. $n=5$ or 19 % vs. 12 %), and less approvals of cytotoxic agents ($n=2$ vs. $n=13$ or 5 % vs. 32 %). The most impressive changes are the shrinkage of conventional cytotoxics and the expansion of small molecule MTAs and mAbs.

The tragic incident of TGN1412 revealed the risks in FIH dose selection for targeted oncologic agents. Traditional FIH dose selection methods such as STD10, HNSTD, and NOAEL approaches were developed in the era of cytotoxic drugs, and the FIH doses determined by these methods were based on preclinical toxicity data. For targeted agents, the interspecies variability in safety and efficacy, dose–efficacy curve, and dose–toxicity curve may largely differ from cytotoxic agents, and efficacy may occur at doses that do not reach the maximum tolerated dose (MTD). Therefore, traditional preclinical toxicological studies may be inadequate to support the selection of a safe and active FIH dose of targeted agents.

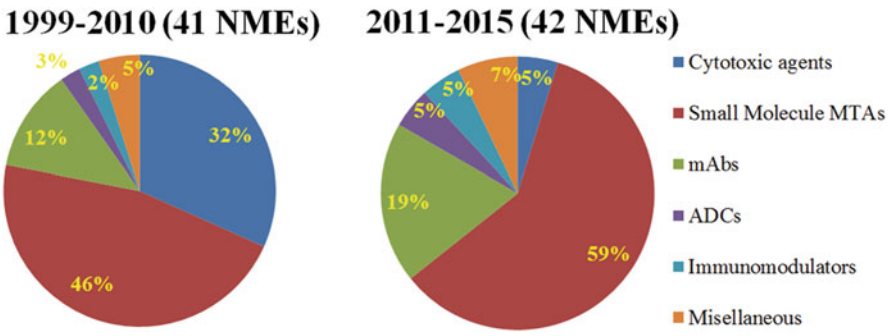


**Fig. 3.2** Trends in the oncological NMEs and new biologics approved by the US FDA between 1999 and 2015

## 4 Characteristics of Cytotoxics, MTAs, and mAbs in Preclinical Toxicity and FIH Studies

The EMA guideline published in 2012 has classified current anticancer drugs as cytotoxic agents, non-cytotoxic agents, immunomodulators, and mAbs (EMA 2012). Non-cytotoxic agents refer to small molecule MTAs including hormonal agents. In addition, ADCs are a new class of targeted biologics composed of an antibody/antibody fragment, a chemical linker, and a cytotoxic small molecule. Different classes of anticancer agents have distinct mechanisms of action, PK/PD profiles, toxicity profiles, and study designs for preclinical toxicity study and FIH study (as shown in Table 3.2). Due to the differences among conventional cytotoxic agents, MTAs, mAbs, and ADCs, it is not feasible to estimate FIH dose of all classes of anticancer agents using a universal standard approach. In the following sections, the preclinical toxicity study design and FIH dose selection for each class of anticancer agents will be discussed.

## 5 Cytotoxic Agents

Cytotoxic compounds induce irreversible lethal cellular damage following short-term exposure through interference with DNA replication, mitosis, etc. (EMA 2012). Classic cytotoxic chemotherapeutic agents include the nitrogen mustard derivatives (e.g., cyclophosphamide, melphalan), antimetabolites (e.g., fluorouracil, methotrexate), platins (e.g., cisplatin, oxaliplatin), antimicrotubule agents (e.g., taxol, vinblastine), and antitumor antibiotics (e.g., doxorubicin, mitomycin C) (Tam 2013). Cytotoxic agents act on all rapidly dividing normal and cancerous cells, and therefore their adverse events are related to hematological toxicity, resulting in a narrow therapeutic window. Usually, for these conventional cytotoxic agents, there are standard measurements of toxicological endpoints, such as weight gain, food consumption, hematology, clinical chemistry, and histopathology (Rosenfeldt et al. 2010). For efficacy studies, tumor size changes or tumor cell apoptosis is generally considered suitable PD endpoints. Only patients with advanced cancer are allowed to be enrolled in the clinical trials of these conventional cytotoxic agents. The STD10 approach and HNSTD approach recommended in the ICH *S9* Guidance are the most widely used approaches for estimating FIH dose of small molecule cytotoxic agents.

As recommended in the ICH *S9* Guidance, the preclinical toxicological assessment of small molecule cytotoxic agents should be conducted in at least two species, one rodent and one non-rodent. When the STD10 approach and HNSTD approach are used to select the FIH dose of cytotoxic agents, the selection of animal species and dose schedule in preclinical toxicity studies is critical. For example, the FIH dose of deoxyspergualin determined in dogs administered with continuous infusion was 25 times higher than the FIH dose determined in mice treated with

**Table 3.2** Key differences among conventional cytotoxic agents, MTAs, mAbs, and ADCs, in FIH studies and preclinical toxicity studies supporting FIH dose selection

| Key differences | Cytotoxics | MTAs | mAbs | ADCs |
|---|---|---|---|---|
| Mechanism of action | Nonselective | Modulate a molecular target | Modulate a molecular target | Modulate a molecular target |
| Animal species for toxicity study | One rodent and one non-rodent which are metabolically comparable to human | One rodent and one non-rodent which reflect off-target toxicity and dose-limited toxicity (DLT) in human | Nonhuman primates or genetically modified animals | Nonhuman primates or genetically modified animals |
| Duration of toxicity study | Less than 28 days | Less than 28 days | Less than 6 months | Less than 6 months |
| Cellular effects | Cytotoxic | Cytotoxic or cytostatic | Cytotoxic, cytostatic, or immunomodulating | Cytotoxic |
| Therapeutic window | Narrow | Wide | Wide | Wide |
| Maximum tolerated dose | Should be determined in phase I study | May not be able to determine for some MTAs | May not be able to determine for some mAbs | Should be determined in phase I study |
| PK profile | High tissue penetration and short half-life | High tissue penetration and short half-life | Low tissue penetration and long half-life | Low tissue penetration and long half-life |
| PD endpoint | Toxic effects (i.e., tumor size, cell apoptosis) | Effects of MTAs on molecular target | Level of antigen or receptor occupancy | Toxic effects (i.e., tumor size, cell apoptosis) |
| Toxicity profile | Hematological toxicity | Non-hematological toxicity such as cardiovascular, gastrointestinal, cutaneous, or renal toxicity | On-target toxicity (exaggerated pharmacological effects) and immunogenicity | Usually depends on the toxicity of conjugated cytotoxic |
| FIH study subjects | Cancer patients | Healthy subjects or cancer patients | Healthy subjects or cancer patients | Cancer patients |

i.v. bolus. The i.v. infusion in dogs matched the proposed clinical use of deoxyspergualin and minimized the risks of toxicity caused by peak drug concentrations. By selecting the higher dose determined in dogs as the final FIH dose, the investigators at the National Cancer Institute (NCI) estimated that 24 months were saved in the phase I FIH trial of deoxyspergualin (Collins et al. 1990). This study illustrates that it is necessary to match clinical dosing approach in planning preclinical toxicity studies.

There has been an evolutionary process in the selection of animal species for toxicological study of cytotoxics. Historically, FIH doses of cytotoxic anticancer agents were first estimated based on toxicological data measured in large animal species (e.g., dog and monkey) (Reigner and Blesch 2002). In 1979, a retrospective analysis of 12 antitumor agents demonstrated that mouse data could be effectively used in determining FIH doses (Penta et al. 1979). Later in 1981, another study showed toxicological data obtained in mice could predict safe FIH doses of 21 anticancer agents (Rozencweig et al. 1981). However, the NCI moved away from the use of mouse for toxicity studies of cytotoxics in the 1980s because the small size of a mouse precludes serial blood sampling for hematological tests, clinical chemistry tests, and biomarker measurements. Furthermore, mice generally cannot predict the potential human toxicity profile (18). For example, a retrospective analysis of 51 drug candidates which had completed phase I trials showed that toxicology studies in mice can predict only 50% of dose-limiting toxicity (DLT) events in human (19). Today, toxicity studies at the NCI are usually conducted in rats (rodent) and dogs (non-rodent) for most small molecule oncology drug candidates (Tomaszewski 2004), which is espoused by the US FDA (Senderowicz 2010). Other species such as mice, rabbits, miniature swine, hamsters, guinea pigs, or nonhuman primates (cynomolgus, rhesus, marmosets) are only used when rats and dogs are deemed inappropriate. Beagle dogs are typically used as the non-rodent in toxicity studies due to the fact that the dog is suitable for intensive serial blood sampling, continuous intravenous infusion, multiple daily oral doses, and cardiovascular telemetry. Nonhuman primates are generally used for toxicity studies only when the beagle is not appropriate, such as with toxicity studies using platinum-containing cytotoxics (Tomaszewski 2004). In addition, in vitro drug metabolism assays conducted with animal and human liver microsomes, hepatocytes, or liver slices may be used to guide the selection of species (Tomaszewski 2004). The species which best approximates the human metabolically and pharmacologically should be selected for toxicity studies.

For designing preclinical toxicity studies to support FIH dose selection, one needs to consider the duration of study. Since pathological examinations are usually conducted to detect serious organ toxicities such as liver, kidney, heart, and eye toxicity, repeat dosing for at least several days is often required for the expression of pathological change in tissues (Senderowicz 2010). The duration of toxicity study should be designed according to the proposed dosing regimen in clinical studies. The preclinical study should follow the proposed clinical route, schedule, and duration. According to Greaves et al. (Greaves et al. 2004), most repeat-dose toxicity studies last at least 2 weeks. Based on the NCI's experience, preclinical toxicity studies longer than 28 days are rarely needed for chronic administration and are generally not recommended by the US FDA for cytotoxics (Tomaszewski 2004).

If irreversible toxicities are produced at the 1/10 STD10 in rodents or if the non-rodent is known to be the more appropriate animal model, then the FIH dose is calculated as 1/6 of the HNSTD in non-rodents. Therefore, the identification of irreversible toxicities is important for determining the most sensitive species and FIH dose. ICH S9 recommends that assessment of the potential to recover from

toxicity should be included in the toxicity studies to understand whether serious adverse effects are reversible or irreversible (ICH 2010). A study that includes a terminal non-dosing period is called for if there is severe toxicity at approximate clinical exposure and recovery cannot be predicted by scientific assessment. This scientific assessment can include the extent and severity of the pathologic lesion and the regenerative capacity of the organ system showing the effect. If a study of recovery is called for, it should be available to support clinical development although the demonstration of complete recovery is not considered essential (ICH 2010). Moreover, pathological examination should be performed off therapy to show the reversibility of toxicities (Senderowicz 2010). All these data will help determine the most sensitive species.

In general, the STD10 approach and HNSTD approach have been demonstrated to be able to provide a safe FIH dose for most small molecule anticancer agents. However, these two approaches have been considered too conservative (Reigner and Blesch 2002). When the human MTD is much higher than the FIH dose, a large number of escalation steps are required, and most of the cancer patients in phase I studies receive doses with no therapeutic effects (Collins et al. 1990). One possible way out of this dilemma for small molecule anticancer agents is to conduct PK, PD, and range-finding toxicity studies in both species (the rodent and non-rodent approximate human metabolically and toxicologically) (Tomaszewski 2004). PK- or PK/PD-guided approaches may provide a reasonable dose FIH dose in case that all the information coming from toxicological, pharmacological, and pharmacokinetic preclinical studies are considered (Tomaszewski 2004).

## 6 Small Molecule MTAs

MTAs are agents that block the growth and spread of cancer by interfering with specific molecules (“molecular targets”) involved in the growth, progression, and spread of cancer (National Cancer Institute 2014). MTAs can be classified as small molecule MTAs and large molecule MTAs. Small molecule MTAs include hormonal agents, signal transduction inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, and small molecule immunomodulators. Large molecule MTAs include monoclonal antibodies, antibody fragments, and antibody–drug conjugates (ADCs).

The key differences between small molecule MTAs and cytotoxics are summarized in Table 3.2. Despite their more selective mechanisms of action, small molecule MTAs have a wide spectrum of adverse effects and have a toxicity profile different from that of cytotoxics. Non-hematological toxicities, such as cardiovascular, gastrointestinal, cutaneous, or renal toxicity, are in general prominent with small molecule MTAs. While cytotoxic oncology agents have traditionally been evaluated in cancer patients in FIH studies, there is the possibility that some of the MTAs will be evaluated in healthy volunteers (Millar et al. 1998).

As shown in Fig. 3.2, 59 % of FDA-approved oncological NMEs between 2011 and 2015 are small molecule MTAs. Most small molecule oncological NMEs currently under phase I development are MTAs. However, there is not an available US FDA or EMA guidance for FIH dose selection for small molecule MTAs (Tam 2013). In the absence of a specific FIH dose selection approach for MTAs, approaches developed in the era of cytotoxic agents are applied to small molecule MTAs (Le Tourneau et al. 2010). Currently, the FIH doses for most small molecule MTAs were determined based on preclinical toxicological parameters. There is a concern whether the approach-based toxicological parameters such as STD10 and HNSTD approaches can provide a safe and pharmacologically active FIH dose for small molecule MTAs. A retrospective analysis of 81 FIH studies of small molecule MTAs showed that the FIH doses for MTAs derived from rodent or non-rodent toxicological parameters, such as MTD, lethal dose for 10 % of animals (LD10), toxic dose low (TDL), NOAEL, and STD10, are generally safe (Le Tourneau et al. 2010). Among the 81 studies, the predicted FIH dose exceeded the human MTD dose in only three trials. The failure of the FIH dose selection for these three agents was due to the lack of sensitive animal species and/or pharmacokinetic discordance between animals and humans. Although a safe FIH dose for MTAs is likely produced by traditional toxicological approaches, for the 81 studies, the median number of dose levels to reach an MTD or maximum administered dose (MAD) was 5 (range of 1–14 dose levels), indicating conservative estimates of FIH dose.

An alternative method is to use a pharmacologically guided approach to select the FIH dose for MTAs although this approach has not been widely validated. If a range of biologically active doses could be predicted from preclinical models, using PK or PD endpoints, this information could be applied alongside preclinical toxicology data to inform FIH dose selection. This PK/PD approach may be particularly valuable for MTAs that do not have MTD defined in animals and are unlikely to reach MTD in human and could represent an alternative to STD10 or HNSTD approach. For this approach, the development of appropriate animal models and the identification of appropriate biomarkers to assess target modulation are critical. A reliable and sensitive assay is needed to measure the impact of drug treatment on target(s) in the tumors and selected normal tissues in preclinical models. A relationship among dose, drug exposure, and PD response should be established if possible.

An agent-directed approach based on preclinical pharmacology and toxicology has been developed by the NCI for FIH dose selection for both traditional cytotoxic and molecular target-based small molecules (Tomaszewski 2004). In this approach, PK, PD, and range-finding toxicity studies are conducted in the most suitable rodent and non-rodent species, and the more sensitive species is used for the IND-enabling study using the clinical route and schedule. If a radiolabeled compound is available, biodistribution studies should be conducted to determine possible target organs of toxicity. If possible, PD, genomics, and proteomics should be evaluated in conjugation with PK studies in animals. Besides the biomarkers to assess target modulation in tumor, if possible, appropriate surrogates for tumor targets such as peripheral blood mononuclear cells (PBMCs), skin biopsy, saliva, buccal mucosa cells, etc. are

developed to facilitate clinical efficacy studies. On the other hand, MTDs, DLTs, and reversibility of toxicity are determined in both rodent and non-rodent species in single-dose studies. The combined PK/PD and toxicity studies in non-rodents will identify efficacious drug concentrations (peak plasma concentration, AUC, or time above a threshold) and determine the impact of these concentrations on selected biomarkers, genomics, proteomics, safety, and toxicity. Ideally, this binomial approach based on preclinical PK/PD and toxicity has the potential to avoid starting at a subtherapeutic dose and reduce the number of dose escalations.

## 7 Monoclonal Antibodies

Monoclonal antibodies (mAbs) and ADCs are important strategies for treating patients with hematological malignancies and solid tumors. As shown in Fig. 3.2, 19 % and 5 % of new oncological drug products approved by the US FDA between 2011 and 2015 are mAbs and ADCs, respectively. mAbs and ADCs can kill tumor cells and/or inhibit tumor cell growth through multiple mechanisms. As shown in Fig. 3.3a (Scott et al. 2012), direct tumor cell killing can be achieved by receptor blockade or through agonist activity of the mAb. An antibody binding to an enzyme

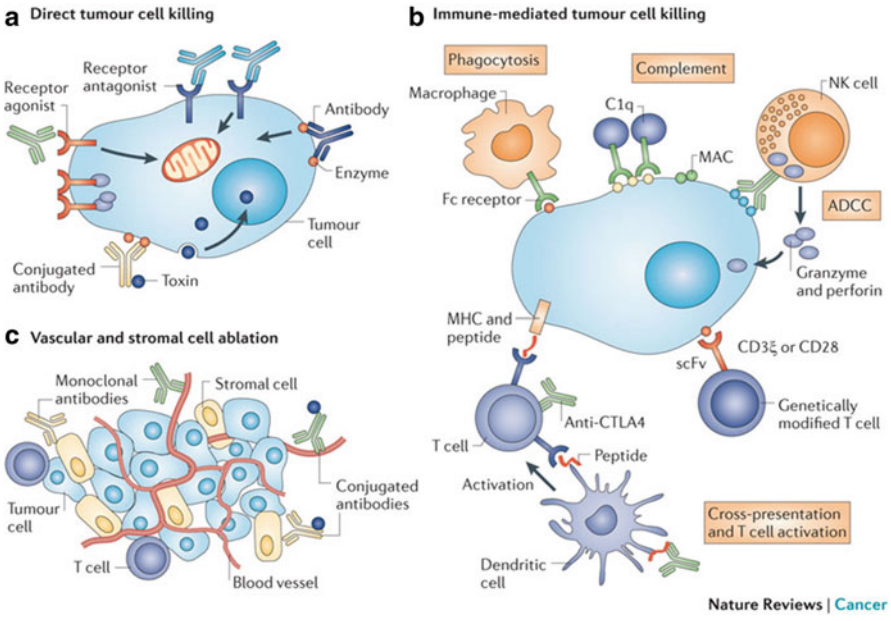


**Fig. 3.3** Mechanisms of tumor cell killing by antibodies (Scott et al. 2012). (**a**) direct tumor cell killing (**b**) immune-mediated tumor cell killing (**c**) vascular and stromal cell ablation

on tumor cell surface can lead to neutralization, signaling abrogation, and cell death. ADCs can deliver a payload (such as a drug, toxin, small interfering RNA, or radioisotope) to a tumor cell and kill the tumor cells through the toxicity of the payload. Figure 3.3b shows that immune-mediated tumor cell killing can be realized by complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and regulation of T-cell function. Angiogenesis inhibition is another mechanism of mAbs and ADCs for cancer therapy. As shown in Fig. 3.3c, mAbs and ADCs can inhibit tumor cell growth by ablating tumor vascular and stromal cells. The mechanisms of action of individual mAbs and ADCs should be considered when designing preclinical pharmacological and toxicological studies and FIH studies and selecting FIH dose. For example, for anticancer mAbs with an agonistic mode of action, the potential species-specific differences in mAbs–antigen binding should be carefully investigated and the selection of the FIH dose should be considered using the MABEL approach (Muller and Brennan 2009).

The choice and availability of a pharmacologically relevant preclinical species for assessment of toxicity is a critical factor in determining an FIH dose. A pharmacologically relevant animal model should meet the following criteria (ICH 1997; Tibbitts et al. 2010):

(a) The therapeutic target or antigen is expressed in that species with a tissue distribution similar to humans.
(b) Similarity in the interaction of the therapeutic agent and its target in the preclinical species and humans, which includes target homology, epitope for monoclonal antibodies, binding affinity and kinetics, similar dose, and concentration–response curve.
(c) The downstream pharmacologic effects in the preclinical species reasonably mimic those expected in humans.

To justify the selected animal model, the data related to target sequence homology between animal and human, in vitro binding affinity data in humans and each preclinical species, receptor/ligand occupancy, binding kinetic data, comparative in vitro or ex vivo studies of the concentration–response relationship, and in vivo PD evaluations/functional activity in animal species (e.g., target modulation and cytotoxicity) should be collected (ICH 1997; Tibbitts et al. 2010). When an appropriate preclinical species is not available, alternative systems such as homologous proteins or transgenic animals expressing the human target may be considered for preclinical studies (ICH 1997). Given its genetic and pharmacological similarity to humans, the nonhuman primate (NHP) is the most commonly selected animal model for safety assessment of mAbs. For practicability reasons, cynomolgus monkey is the preferred NHP species. Marmosets and rhesus macaques are also used occasionally (Muller and Brennan 2009).

Different from small molecule MTAs where off-target toxicity is often observed, the clinical adverse effects of mAbs are mainly related with on-target toxicity (exaggerated pharmacological effects) and immunogenicity (Brennan et al. 2010; Vugmeyster et al. 2012). For example, the life-threatening "cytokine storm" caused by TGN1412 is an exaggerated pharmacological effect due to the high receptor

occupancy by the TGN1412 superagonist mAb. The TGN1412 incident indicates that receptor occupancy is a critical factor for mAbs FIH dose selection. When the PK/PD data are very limited and do not allow PK/PD modeling, the FIH dose can be calculated based on an in vitro human receptor occupancy curve (Agoram 2009). Combining this range of concentrations with the interspecies scaling based on human PK prediction can provide an estimated FIH dose. One of the limitations of this approach is that it is often unknown what degree of receptor occupancy corresponds to a clinical response. The intended receptor occupancy in FIH study depends on the nature of the target and potential on-target toxicities. The duration of receptor occupancy is dependent on the actual dose administered, clearance of mAb, and rate of turnover of the target receptor (Muller and Brennan 2009). For agonist mAbs, a low receptor occupancy (<10 %) is desired to generate a maximal PD response, but for antagonist mAbs, a high receptor occupancy (>90 %) is required to generate a maximal PD response (Muller and Brennan 2009). However, it is worthy to note that low receptor occupancy may not be appropriate or sufficient to ensure safety of mAbs when receptor occupancy is not the most sensitive biological effect and/or the relationship between receptor occupancy and downstream biological effects is not known (Agoram 2009). For example, mAbs that produce their pharmacological effects through CDC, ADCC, or regulation of T-cell function may not have a receptor occupancy–efficacy/toxicity relationship, while the absolute number of cell membrane-bound mAb molecules is more important. Therefore, understanding the dose–biomarker response is necessary to ensure a safe and pharmacologically active FIH dose.

In vitro and in vivo PK/PD data can assist the selection of FIH dose. When sufficient PK/PD data in pharmacologically relevant preclinical species are available, a PK/PD modeling approach is recommended by EMA for selecting the FIH dose of mAbs (EMA 2007). All the available in vitro and in vivo animal and human PK/PD data should be integrated into the PK/PD model. The typical data for PK/PD modeling are summarized in Box 3.1 (Tibbitts et al. 2010). A general four-step PK/PD modeling approach was proposed for anticipating the FIH doses of both mAbs and small molecule drugs (Lowe et al. 2007) which is summarized in Box 3.2.

**Box 3.1: Typical Data Required for Selecting the FIH Dose of a mAb Using PK/PD Modeling Approach (Tibbitts et al. 2010)**

- Mechanism of action
- Receptor occupancy, binding affinity, and potency
- Duration of action
- Downstream biologic effects
- Concentration– or dose–response
- Animal and human PK
- Species differences—both qualitative and quantitative

**Box 3.2: Anticipating the FIH Dose from Multiple Source Information Using a Four-Step Approach (Lowe et al. 2007)**

Step 1: Characterization of nonhuman exposure–response relationships
Step 2: Correction for interspecies differences
Step 3: Diagnosing compound absorption, distribution, metabolism, and excretion (ADME) properties and prediction of human pharmacokinetics
Step 4: Prediction of human dose–responses and dose selection for phase I protocols

When extrapolating the PK model from animal to human, the unique PK characteristics of mAbs should be carefully considered. Unlike small molecule drugs, the PK of mAbs may be influenced by target-mediated drug disposition (TMDD) which shows large interspecies variability, complicating the interspecies extrapolations of PK parameters and starting doses. At clinical doses, target-mediated clearance (internalization of the mAb–target complex) is the major elimination mechanism of some mAbs such as anti-EGFR antibodies which leads to problems in the interspecies scaling of PK parameters of mAbs (Deng et al. 2011). This unique PK characteristic of mAbs highlights the importance of using the appropriate species for conducting preclinical studies of mAbs, understanding the ADME process of individual class of mAbs, and referring to clinical PK data of prior mAbs in the same class.

Most human-derived proteins are immunogenic in animals (Tibbitts et al. 2010). The administration of humanized mAbs to animals may result in the formation of antidrug antibodies (ADAs), which may increase or decrease drug clearance, decrease pharmacologic effect by blocking or interfering with drug–target binding, or cause toxicities as a result of antibody–drug complexes (Tibbitts et al. 2010). When estimating the FIH dose of mAbs from preclinical PK, PD, and toxicity data, the influence of ADAs on preclinical data should be considered.

Overall, FIH dose selection for mAbs should integrate all relevant information and follow a weight-of-evidence approach. The key factors to be taken into account include the mechanisms of action of mAbs, the selection of pharmacologically relevant animal species, the binding affinity to targets in animals and humans, and the interspecies differences in location, expression, and turnover of the target. All the available in vitro and in vivo toxicological and pharmacological data and prior experience with similar mAbs should be considered when selecting an FIH dose for a mAb.

## 8 Antibody–Drug Conjugates

Antibody–drug conjugates (ADCs) are a unique class of targeted agents consisting of a mAb conjugated to cytotoxic small molecule(s) that exhibit their pharmacological effects through the conjugated small molecule cytotoxics. The small

molecule cytotoxics in ADCs are typically potent and poorly tolerated when used as free agents. Although the conjugation with mAbs reduces systemic exposure to cytotoxics, the release of the small molecule cytotoxics after the internalization of ADCs into cells causes substantial toxicity. Therefore, FIH studies with ADCs are usually conducted in cancer patients (Deslandes 2014).

Currently, there is no published guidance regarding methodology for FIH dose selection specifically for ADCs. It is necessary to evaluate which animal models are suitable to support FIH dose selection for ADCs and which approaches can be employed for FIH selection. A recent analysis of 20 ADC applications submitted to US FDA showed that the FIH doses for the 20 ADCs are selected based on STD10, HNSTD, and/or NOAEL determined in mouse or rat (rodent) and cynomolgus monkey (non-rodent) (Saber and Leighton 2015). When the animal dose is extrapolated to human dose, either body weight or BSA was used for conversion. The retrospective analysis showed that 1/6 of the HNSTD in cynomolgus monkeys or 1/10 of the STD10 in rodents scaled according to BSA generally resulted in acceptable FIH doses for ADCs. One-tenth of the NOAEL in monkeys or rodents using body weight for scaling also produced acceptable FIH doses. The results indicated that FIH dose for ADCs may be determined based on toxicological parameters measured in one rodent species and cynomolgus monkeys.

The retrospective analysis of 20 ADCs also revealed that dose-limiting toxicities of ADCs are related to the small molecules but independent of antibody target or target binding. The human MTD was independent of the antibody isotype used (IgG1 or IgG2), indicating a limited role for antibody-mediated effector functions (e.g., ADCC) in causing toxicities. The conjugation with cytotoxic small molecules usually significantly lowers human MTD of the ADC compared with free mAb. This emphasizes that the conjugated small molecule drives the human toxicity making the free antibody less informative for FIH dose decisions. Therefore, it is recommended that the FIH dose of the ADC not be based on the human doses of the free antibody (Saber and Leighton 2015).

Besides chemistry of the linker and the toxicity of small molecules, the ratio of small molecules to antibody could affect human MTD. The higher the ratio of small molecules to antibody, the lower the human MTD is anticipated to be (Saber and Leighton 2015). For ADCs sharing the same small molecule drug, the same linker, and the same small molecule to antibody ratio, available prior clinical data can guide the selection of FIH dose of a following ADC.

## 9 Conclusions

With the paradigm shift in anticancer drug development from cytotoxics to targeted therapeutics, the latter are currently the majority of approved anticancer drugs. Although conventional 1/10 of STD10 approach or 1/6 of HNSTD approach for FIH dose selection relying solely on toxicity data is still widely used in anticancer drug development, these conventional methods are inefficient for the development

of targeted anticancer agents. It is recognized that there is no simple algorithm for estimating the FIH dose. Each compound is different, and the exact method to be used to calculate the FIH dose will depend on the unique characteristics of the anticancer agents and the results from preclinical studies. It is highly recommended that, especially for targeted anticancer agents, drug developers should rely on all the relevant in vitro and in vivo toxicological and pharmacological data along with clinical and preclinical information from similar compounds to estimate FIH dose. The improved FIH dose selection and incorporation of PK and PD parameters may safely reduce the number of escalations in phase I studies.

**Disclaimer** This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

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# Chapter 4
# Controversies in Oncology: Size Based vs. Fixed Dosing

**Peter L. Bonate**

**Abstract** To find the right dose and regimen is crucial for the therapeutic effectiveness of oncolytics. Prior to the 1960s, early oncologists dosed their patients at the maximum tolerated dose (MTD) using either fixed doses (sometimes called flat doses) or doses standardized to total body weight (TBW). In the 1960s, this changed as oncology dosing switched to the MTD expressed per patient body surface area ($mg/m^2$), because it was shown that, expressed in this manner, the MTD was approximately the same in humans as in animal species. This remained for decades until in the 1990s when molecularly targeted therapeutics and monoclonal antibodies began to be introduced into clinical practice, and it was no longer necessary to dose patients at the MTD. Further, pharmacokineticists started to realize that using size-based dosing did not reduce interpatient variability for many drugs. Today, the dose regimen developed for new anticancer drugs can be fixed dose, BSA dosed, or TBW dosed. The choice is rigorously evaluated based on sound scientific practice in confirmed in clinical trials. The purpose of this chapter is to discuss the history regarding size-based dosing and current practices for getting "the right dose" in oncology.

**Keywords** Dosing • Fixed dose • Weight-based dosing • Body surface area dosing • Monoclonal antibodies • Calvert formula • Obesity • Pediatrics

## 1 Introduction

It is the current mantra of drug development to find *the right drug*, *for the right patient*, *at the right dose*, *at the right time*. Modern drug discovery and preclinical oncology development are aimed at finding *the right drug* for a particular tumor

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through the use of animal models like mouse tumor xenografts and through understanding molecular pathways. By using different treatment schedules, like changing the order of different combination therapies, *the right time* can be identified. Personalized medicine aims to identify *the right patient* through genetic molecular analysis, but clinical pharmacology is aimed at getting *the right dose*, which can be a challenge because of individual differences in pharmacokinetics and pharmacodynamics. Even after a drug is approved for marketing by regulatory agencies, there still may be questions as to whether the right dose was chosen. It is well known that many drugs require dose reductions after the drug is first marketed because the marketed dose was originally too high.

Early oncologists dosed their patients using either fixed doses (sometimes called flat doses) or doses standardized to total body weight (TBW). That changed in the 1950s and 1960s when it was recognized that the clinical doses used for chemotherapy were similar to the maximum tolerated dose (MTD) in animals when standardized to body surface area (BSA). Thereafter, physicians began to dose their patients using doses standardized to BSA. This remained for decades until in the 1990s when molecularly targeted therapeutics began to be introduced into clinical practice, and it was no longer necessary to dose patients at the MTD. Further, pharmacokineticists started to realize that using size-based dosing standardization did not reduce interpatient variability for many drugs. Today, the dose regimen developed for new anticancer drugs can be fixed dose, BSA dosed, or TBW dosed. The choice is rigorously evaluated based on sound scientific practice in confirmed in clinical trials. The purpose of this chapter is to discuss the history regarding size-based dosing and current practices for getting "the right dose" in oncology.

## 2 On the History of Body Surface Area Dosing

The relationship between body size metrics, like TBW and BSA, and physiological parameters has been known since before the twentieth century. Rubern (1883) noted that smaller animals utilized more oxygen and generated more heat than larger animals because of the relatively larger surface area of smaller animals. Further reports followed over the decades. Dreyer and Ray (1910, 1912) reported that human blood volume correlated with surface area. Grollman (1929) reported that human cardiac output correlated with BSA. Kleiber (1932) plotted log metabolic rate against log body size for mammals and birds and found that the exponent was approximately 0.75. Smith (1951) reported that human renal function correlated with BSA. These studies, and many more, led Crawford et al. (1958) to divide pediatric patients having a wide weight range into four groups based on their BSA and gave each group the same BSA-equivalent dose of sulfadiazine or acetylsalicylic acid. Blood concentrations of both drugs were similar across groups leading to the conclusion that BSA-based dosing might be useful in clinical practice.

These results led Pinkel (1958) to compare the appropriate therapeutic dose of the chemotherapeutic agents mechlorethamine, methotrexate, 6-mercaptopurine,

actinomycin D, and triethylenethiophosphoramide. Mouse, rat, dog, infants, older children, and adults were compared. When standardized by BSA, the daily clinical dose across groups was similar. This did not hold when doses were standardized to TBW. For example, the doses for methotrexate were:

| Subject | Total body weight (kg) | BSA ($m^2$) | Dose per day (mg) | Dose/kg weight/ day (mg) | Dose/$m^2$/day (mg) |
|---|---|---|---|---|---|
| Mouse | 0.018 | 0.0075 | 0.027 | 1.5 | 3.6 |
| Rat | 0.25 | 0.045 | 0.125 | 0.5 | 2.8 |
| Infant | 8.0 | 0.4 | 1.25 | 0.15 | 3.1 |
| Older child | 20.0 | 0.8 | 2.5 | 0.12 | 3.1 |
| Adult | 70.0 | 1.85 | 5.0 | 0.07 | 2.7 |

Freireich et al. (1966) expanded the work of Pinkel and compared the MTD for four antimetabolites and eight alkylating agents in mouse, rat, hamster, dog, monkey, and humans. When standardized to BSA, the MTD was approximately the same in humans as in animal species. The similarity did not hold when standardized to TBW. For example, the MTD in man was about 1/12 the MTD in mice but about 1/2 the MTD in dogs.

Prior to the work of Pinkel and Freireich, chemotherapy doses were given in fixed amounts or in doses standardized to TBW. Further, experimental chemotherapy agents were tested in animals at doses standardized to BSA. Based on the work of Pinkel and Freireich, pediatricians started dosing based on BSA, and medical oncologists followed, albeit for different reasons. Pediatricians wanted to standardize blood concentrations, whereas oncologists wanted to be able to extrapolate chemotherapy doses from animals to humans. Since these reports more than 50 years ago, the rationale for how they began has been lost to most practicing medical oncologists. For decades, even up into the early twenty-first century, dosing per BSA was accepted as common practice.

Starting in the 1990s, oncologists began to question this belief. Grochow et al. (1990) studied how the pharmacokinetic parameters clearance and volume of distribution were related to height, TBW, and BSA of nine different chemotherapeutic agents in 287 patients. Of the 96 relationships examined, only five had a correlation coefficient greater than 0.7, which is the point that explains 50 % of the variability in the data. Clearance was correlated with only one measure of body size, height, for one drug, paclitaxel ($r=0.697$, $p=0.003$). The authors concluded that standardization of doses to BSA does not substantially reduce the between-subject variability for these drugs and that BSA-based dosing is of "minimal clinical value." Many individual publications have confirmed this finding. BSA normalization did not reduce the between-subject variability in clearance for irinotecan (Mathijssen et al. 2002), cisplatin (de Jonge et al. 2001), topotecan (Loos et al. 2000), cyclophosphamide (Felici et al. 2002), etoposide (Felici et al. 2002), and methotrexate (Felici et al. 2002). Felici et al. (2002), in a review article, compiled the published relationship between BSA and pharmacokinetic parameters for 18 different drugs. Of these,

11 had no relationship between BSA and any pharmacokinetic parameter. In that same year, Baker et al. (2002) obtained data from 1650 adult patients treated with 33 anticancer drugs (predominantly cytotoxic agents) developed over a 10-year period from 1991 to 2001. A total of 12 drugs were administered orally, 19 were administered intravenously, and 2 were administered by both routes. In only five drugs was the between-subject variability in clearance reduced when clearance was expressed per BSA. The authors conclude that BSA "should not be used to determine starting doses of investigational agents and future phase 1 studies."

## 3 On the Pharmacokinetic Rationale for BSA Dosing

Population pharmacokinetic analysis methods were developed in the 1980s using nonlinear mixed effect models (Sheiner and Beal 1980, 1981, 1983). Whereas previous methods to identify patient characteristics explaining the between-subject variability of a drug relied on data-rich pharmacokinetic sampling schemes and noncompartmental analyses; population methods use relatively sparse pharmacokinetic data collected from patients during the course of scheduled visits in clinical trials. With earlier methods the best one could do was to show via correlation analysis whether covariates, like weight or age, were correlated with pharmacokinetic parameters, like apparent oral clearance or apparent volume of distribution. But with population methods, the relationship between covariate and pharmacokinetic parameter could be mathematically characterized. For example, Bruno et al. (1996) reported that docetaxel total systemic clearance was dependent on BSA, α1-acid glycoprotein (AAG) concentration, age, albumin (ALB) concentration, and hepatic (HEP) function and could be expressed mathematically as

$$\mathrm{CL} = \mathrm{BSA}\left(22.1 - 3.55 \times \mathrm{AAG} - 0.095 \times \mathrm{AGE} + 0.225 \times \mathrm{ALB}\right)\left(1 - 0.334 \times \mathrm{HEP}\right). \tag{4.1}$$

In this manner CL was directly related to BSA. In this analysis, TBW was not tested in the model because docetaxel was administered on a mg/m$^2$ basis, and chemotherapy drugs were more commonly given on a BSA basis. That BSA included in the model had nothing to do with the historical basis of chemotherapy dosing on a per-BSA basis. BSA was included in the model because it reduced the unexplained variability in the model and increased the ability to predict CL, as evidenced by increased goodness of fit when CL was included in the model compared to when it was not in the model. The report by Bruno was one of the first reports showing the utility of population pharmacokinetics. Since then, size-based covariates have been shown to be predictive of the pharmacokinetics of many cytotoxic drugs, including clofarabine (Bonate et al. 2004), cisplatin (de Jonge et al. 2004), etoposide (Nguyen et al. 1998), and temozolomide (Jen et al. 2000). In fact, body size has been shown to be one of the most important predictors of pharmacokinetics for all drugs, not just chemotherapeutics.

The functional form of the relationship between body size metrics and pharmacokinetics comes in many forms. A common form is the power model. For example, Bonate et al. reported that clofarabine CL was related to TBW in pediatric patients with acute lymphocytic leukemia using a model of the form

$$\mathrm{CL}\left(\mathrm{L/h}\right) = 32.8\left(\frac{\mathrm{TBW}}{40\,\mathrm{kg}}\right)^{0.75}. \tag{4.2}$$

The power model has its basis in the seminal work of Harold Boxenbaum, who showed that the pharmacokinetics of many drugs, including benzodiazepines (Boxenbaum 1982), antipyrine, and phenytoin (Boxenbaum 1980), could be described using a power model with TBW as the predictor. The exponent in these models was near the value of 0.75, which was consistent with reports in the physiological literature that many biologic process scales to a multiple of 0.25. For example, metabolic rate scales to a value of 0.75, life span scales to a value of 0.25, and heartbeat scales to a value of −0.25 (Peters 1983). Why this happens has yet to be adequately explained, but theories range from changes in body composition with size (White and Seymour 2005) to fractal explanations (West et al. 1997).

There are two schools of thought regarding determination of the value of the exponent in the power model: empirically estimate it based on the data on hand (Mahmood 2010) or fix it to a value of 0.75 a priori (Anderson and Holford 2008). The proponents of both are quite vehement on their position. Regardless of whether the exponent is fixed or estimated, the power model has an important implication, and that the pharmacokinetic parameter does not increase in proportion to the size of the animal, i.e., it is not isometric. An alternative model is an isometric model where the parameter does increase in proportion to the size of the animal. Volume terms in pharmacokinetics often follow isometric models. For example, in the clofarabine analysis reported by Bonate et al., peripheral volume was modeled as

$$\mathrm{Vp}\left(\mathrm{L}\right) = 94.5\left(\frac{\mathrm{TBW}}{40\,\mathrm{kg}}\right). \tag{4.3}$$

Notice that the isometric model is a power model with an exponent fixed to 1. The same arguments for estimating or fixing the exponent in a power model for CL apply to volume terms.

The point of all this is that TBW has become ingrained as a covariate in the minds of most pharmacometricians, particularly newer ones, and the history of its use and its relation to early dosing in oncology has become lost. Pharmacometricians look at size-based dosing as a way to individualize doses and reduce the variability in concentrations among patients receiving the same dose. It is well known that many intrinsic factors, like age and TBW, as well as extrinsic factors, like food and smoking habits, affect the pharmacokinetics of drugs and contribute to the total variability in their pharmacokinetics. Individualized dosing that reduces the intersubject variability should be desired as it allows for tighter control over exposure.

This was illustrated by a study from Smorenberg et al. (2003) who showed in a prospective randomized crossover study using a paclitaxel BSA-based dose of 175 mg/m$^2$ for cycle 1 (treatment A) and a flat dose of 300 mg for cycle 2 (treatment B) that BSA-based dosing reduced the between-subject variability in total unbound paclitaxel AUC by 53 % with no change in mean exposure (A vs. B: 1.34 ± 0.16 μg h/mL vs. 1.30 ± 0.329 μg h/mL). A similar reduction in the variability of Cmax was also reported. This report is taken as evidence that BSA-based dosing improves outcomes, but this conclusion may be questionable. Smorenberg concluded that this study "provides a pharmacokinetic rationale for BSA-dosing of drugs." While this observation may apply to paclitaxel, the broad application of this conclusion is clearly an overstatement.

Furthermore, the more important question is: *does the reduction in variability reduce the incidence of adverse events or improve the response rate*? Unfortunately the design of the Smorenberg study precludes the ability to analyze adverse effects or efficacy because of carryover effects. Further, there are no randomized clinical trials doing such a head-to-head comparison. All limit themselves to comparing pharmacokinetic variability. Pharmacometric analyses could provide such an answer but again, these have been limited to comparing pharmacokinetic variability. For example, Ng et al. (2006) reported on the population pharmacokinetics of pertuzumab, a monoclonal antibody, in patients with solid tumors. Using computer simulation they compared the pharmacokinetic variability in different measures of exposure, like steady-state trough concentrations (Css, trough), under a fixed-dose, TBW-based, and BSA-based dosing scheme and found that variability was similar among dosing regimens and that only the variability in Css, trough was moderately reduced through the use of size-based dosing. Insufficient data were available to perform an exposure-response analysis. Today, pertuzumab (Perjeta®) is dosed in combination with Herceptin® and docetaxel using 840 mg as a 1-h intravenous infusion followed every 3 weeks by 420 mg as a 0.5–1-h infusion.

## 4 On the Convergence of Pharmacokinetics and Oncology

In the 1990s, however, oncology started to change. With the introduction of gefitinib and imatinib, the face of oncology started to change from the use of cytotoxic agents to molecularly targeted therapies that specifically targeted molecular pathways necessary for cell growth. With the introduction of monoclonal antibodies like trastuzumab, alemtuzumab, and rituximab, oncology became further refined through the application of biologics with extremely high affinity for their targets. Over the next two decades, as the problems associated with BSA-based dosing became more widely known and with the introduction of targeted therapies that were orally administered, the use of BSA-based dosing has become less reflexive. In 2008, Leveque (2008) reviewed all non-pediatric phase 1 trials presented at the American Society of Clinical Oncology and the American Society of Hematology in 2005. Of the 42 targeted therapies presented at these conferences, 62 trials used a fixed dose,

13 used BSA-based dosing, 2 used TBW-based dosing, and 2 were not reported. Of the 45 conventional cytotoxic drugs reported, 70 trials used BSA-based dosing compared to 1 using a fixed dose. Of the 40 orally administered drugs, 62 trials used a fixed dose, 13 used BSA-based dosing, and 2 used TBW-based dosing. Interestingly, of the 82 intravenously administered drugs, 86 used BSA-based dosing, nine used a fixed dose, and 23 used TBW-based dosing.

A similar transition appears to be occurring with monoclonal antibodies. Whereas cytotoxic and targeted therapies are frequently either flat-based dosed or BSA dosed, monoclonal antibodies are more frequently dosed either using a fixed dose or per TBW, not BSA. There are exceptions to the TBW rule, foremost being rituximab and cetuximab. Both rituximab and cetuximab were developed in the early 1990s, prior to some of the publications that were discussed earlier. A review of the Summary Basis of Approval issued by the Food and Drug Administration indicates that neither of these compounds were ever tested using TBW-based dose standardization. But there were other drugs approved around that time that are dosed per TBW, including bevacizumab and abciximab. For these drugs, it appears that BSA dose standardization was not studied. There are also monoclonal antibodies approved at that time that are dosed on a fixed-dose basis; these include muromonab-CD3 (the first approved monoclonal antibody) and basiliximab. Why some drugs were dosed per TBW, some were dosed per BSA, and some used a fixed dose appear to be an arbitrary decision chosen by the company and not based on scientific evidence.

If any drug makes sense to be administered per size-based standardization, it would be the monoclonal antibodies because size-based metrics, like BSA and TBW, are often reported as a significant covariate in human population pharmacokinetic analyses (Dirks and Meibohm 2010). However, sometimes the population pharmacokinetic analyses confirm the use of size-based dosing and are consistent with labeled dosing recommendations, sometimes not. For instance, bevacizumab is dosed mg/kg, and the population analysis confirmed TBW as a covariate for clearance and central volume (Lu et al. 2008). But sometimes the results of the population analysis and dosing recommendations are not aligned. For instance, cetuximab is dosed mg/m$^2$, but its clearance (which is nonlinear) and central volume are dependent on ideal body weight (Dirks et al. 2008). Another example is ofatumumab, which uses fixed-based dosing, although the population analysis found a significant relationship between TBW and clearance and central volume (Arzerra® package insert, 2011).

Wang et al. (2009) tried to make sense of these different dosing regimens and systematically evaluated the dosing regimens for many monoclonal antibodies. Using the reported population pharmacokinetic models for many different monoclonal antibodies, they compared the typical exposures using fixed- and TBW-based dosing regimens. The results for 12 different drugs are shown in Fig. 4.1. The results show that both approaches perform similarly with fixed dosing being better for some antibodies and size-based dosing being better for others. They recommended that first time in human studies be conducted using fixed dosing, and then as knowledge accumulates switch to size-based dosing if warranted.

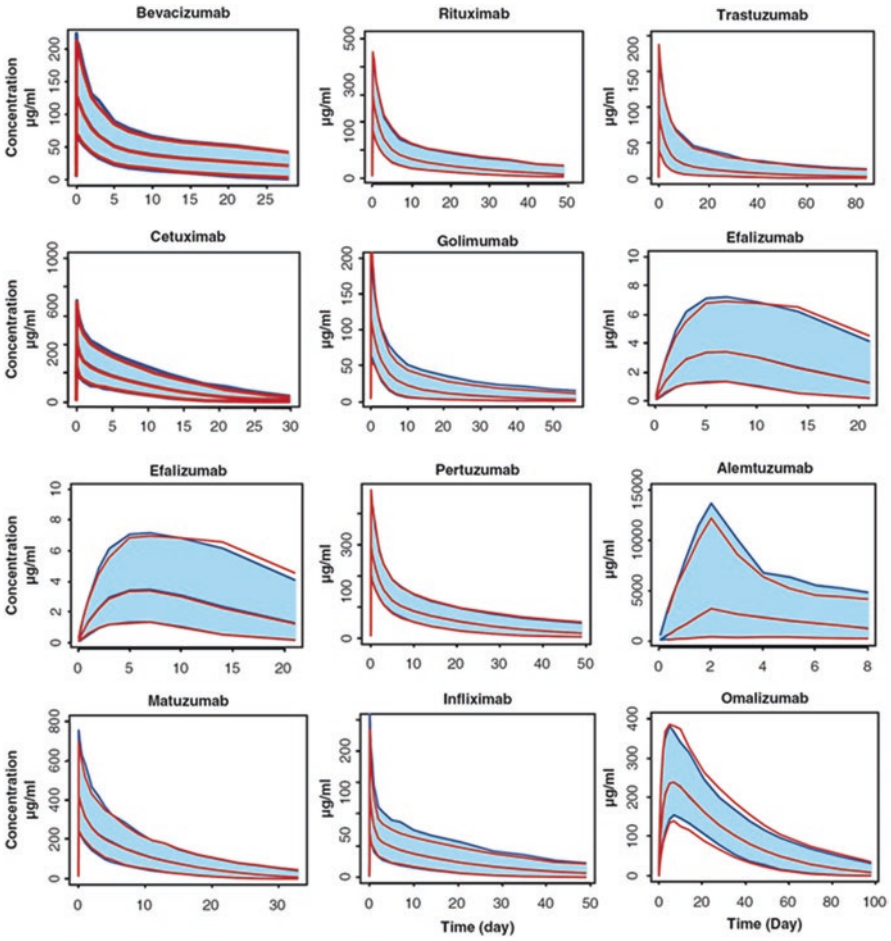


**Fig. 4.1** The median, 97.5th, and 2.5th percentiles of the simulated concentration-time profiles of 1000 subjects following a single-fixed (*red* lines) and body weight/BSA (BW/BSA)-based (*blue* lines) dose. The shaded area represents the 95th percentile interval of the simulated concentrations after a BW/BSA-based dose. Figure reprinted from Wang et al. (2009) reprinted with permission from Wiley

Bai et al. (2012) expanded on the work of Wang et al. wanting to better understand under what conditions which dosing scenario was better than the other. They developed a generic two-compartment linear population pharmacokinetic model where TBW was a covariate on clearance and central volume. Using their model they used simulation to evaluate exposure differences over a broad range of scenarios, from no effect to a strong effect of TBW on the key pharmacokinetic parameters, using fixed dose and TBW-based dose regimens. The model they used was

$$\begin{aligned} \mathrm{CL} &= \theta_1 \left( \frac{\mathrm{TBW}}{78\,\mathrm{kg}} \right)^{\theta_{\mathrm{BW-CL}}} \exp\left(\eta_{\mathrm{CL}}\right) \\ \mathrm{V1} &= \theta_2 \left( \frac{\mathrm{TBW}}{78\,\mathrm{kg}} \right)^{\theta_{\mathrm{BW-V1}}} \exp\left(\eta_{\mathrm{V1}}\right) \\ Q &= \theta_3 \\ \mathrm{V2} &= \theta_4 \end{aligned} \tag{4.4}$$

In looking at the extremes of the population, under certain conditions fixed dosing could lead to overexposure in underweight subjects and underexposure in overweight subjects, whereas the opposite was true with size-based dosing. Still, the difference in exposure variability between fixed- and TBW-based dosing was less than 20 % and less than 40 % for under- and overweight subpopulations. In general, they concluded that, in contrast to expectations, controlling for body weight does not always reduce variability in drug exposures. When both $\theta_{\mathrm{BW-CL}}$ and $\theta_{\mathrm{BW-V1}}$ were less than 0.5, fixed dosing resulted in less variability than body weight-based dosing. When both $\theta_{\mathrm{BW-CL}}$ and $\theta_{\mathrm{BW-V1}}$ were greater than 0.5, the opposite was true; fixed dosing resulted in greater variability than weight-based dosing. In most instances however, weight had little to modest effect on exposure. This conclusion was consistent with Keizer et al. (2010) who concluded that although TBW was a significant covariate in many population pharmacokinetic analyses, in practice TBW has little clinical significance with respect to reducing between-subject variability in drug exposure. Bai also states that with regard to the different regimens, little change in variability is observed when monoclonal antibodies are dosed using a fixed- or TBW-based dosing regimen and that a good strategy during clinical development would be to start initial clinical trials using fixed dosing, but then as knowledge accumulation develops, evaluate whether size-based dosing reduces between-subject exposures using the decision tree presented in Fig. 4.2. The conclusions of Bai et al. are similar to the ones reported by Wang et al.

## 5 A Pharmacometric Approach to Dose Selection

When should a drug use a fixed-dose regimen or a dose regimen standardized to some body size metric? As mentioned previously, the real answer to this question depends on whether a particular regimen reduces the variability in a clinically meaningful way. Since pharmacokinetic exposures are used as a surrogate for the clinical outcomes, the best regimen is the one that *significantly* reduces the variability in the exposure metric that best correlates with response. Small reductions in variability at the expense of a more complex administration and dosing algorithms are not practical or desirable for patients or clinicians. For example, a reduction in variability of just a few percent using a BSA-based dosing regimen may actually

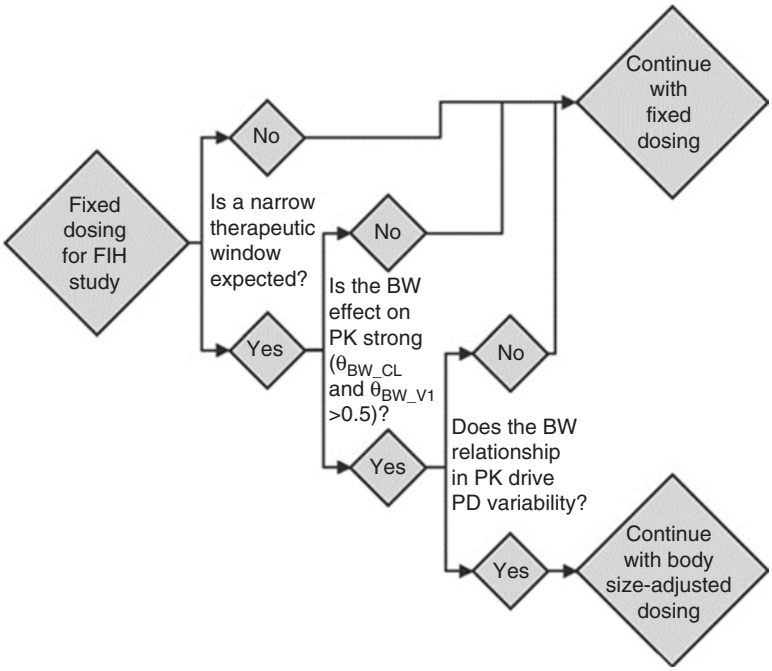


**Fig. 4.2** Proposed decision tree from Bai et al. (2012) for dosing monoclonal antibodies in adult patients during clinical development. Figure reprinted with permission from Springer. *Legend*: $\theta_{BW-CL}$ exponent of the relationship between body weight and clearance based on a power model, $\theta_{BW-V}$ exponent of the relationship between body weight and central volume based on a power model. *BW* body weight, *FIH* first in human, *PD* pharmacodynamics, *PK* pharmacokinetics

result in more frequent dosing errors because of miscalculation in estimating a patient's BSA.

Assessing the variability and exposure using experimental clinical data can be problematic for a number of reasons. First, it requires a clinical study prospectively comparing the different dosing regimens. Second, having the appropriate sample size to make such a comparison would require large numbers of patients, which translate to large-scale expensive clinical trials. An easier and more statistically robust method would be to make this assessment using Monte Carlo simulation based on a validated population pharmacokinetic model. Under this scenario, a population pharmacokinetic model is developed characterizing the relationship between the pharmacokinetic parameters and a size-based metric. Using Monte Carlo simulation, thousands of subjects are simulated using each of the different dosing regimens, and concentration-time profiles are generated from each subject. Non-compartmental analysis is then used to calculate the summary exposure measures. Statistical analysis is then performed to compare the different dosing groups. For certain exposure measures, it is not necessary to simulate the entire concentration-time profile. For example, if total AUC was correlated with response, then AUC could be simulated directly if clearance was known using the formula AUC = Dose/CL.

Ng et al. (2006) used this approach to compare pertuzumab exposure after fixed, BSA-based, and TBW-based dosing. In their pharmacokinetic model, which was a linear two-compartment model, clearance was defined as

$$\mathrm{CL}\left(\mathrm{L}/\mathrm{day}\right) = 0.214\left(\frac{\mathrm{TBW}}{69}\right)^{0.587}\left(\frac{\mathrm{ALB}}{39.2}\right)^{-1.01}\left(\frac{\mathrm{ALKP}}{107}\right)^{0.169} \tag{4.5}$$

where ALB is serum albumin concentration (g/L) and ALKP is serum alkaline phosphatase activity (IU/L). A total of 1000 subjects were simulated by resampling from the original analysis data set of 153 patients. Simulated subjects received a dose of 840 mg, 12.2 mg/kg, or 485 mg/m$^2$ as an intravenous infusion over 90 min on day 0 and then 420 mg, 6.1 mg/kg, or 242.5 mg/m$^2$ as an intravenous infusion over 30 min on days 21, 42, and 63. Concentration-time profiles were simulated at steady state on day 84. Steady-state trough concentrations were assessed on day 84 for each of the dosing regimens, and AUC was calculated using the formula AUC = dose/CL. The results of the simulation are shown in Fig. 4.3. Little difference was observed between the different dosing regimens suggesting that a fixed-dosing regimen would be superior because of ease of use. Similar results were obtained for AUC (data not shown). Ng et al. also used the model to compare exposures in subjects at the extreme of the weight range. Subjects were resampled conditional on their weight being in the upper and lower decile of observed values. These results are also shown in Fig. 4.3. Using weight-based dosing, subjects with lower weights appeared to be underdosed, while subjects with heavy weights appeared to be overdosed. Similar results were obtained using BSA-based dosing, though not to the same extent as weight-based dosing. The authors concluded that even though pertuzumab pharmacokinetics was related to TBW and BSA, these covariates explain only a small percent of the between-subject variability in that size-based dosing does not improve the predictability of steady-state exposures. They therefore recommended that pertuzumab be administered using a fixed-dosing regimen.

In the case of pertuzumab, the authors had a data set of 153 patients from a phase 1 and two phase 2 studies. In cases where the analyst does not have access to a sample size such as this, it may be necessary to simulate the proposed target population using external databases. A useful database that might be sampled is the National Health and Nutrition Examination Survey (NHANES) coordinated by the Center for Disease Control and Prevention (US Department of Health and Human Services and Health Statistics 2007). The current database contains thousands of randomly sampled individuals from the United States and includes information on their demographics, laboratory variables, electrocardiogram results, and many other variables. Instead of sampling from the observed database in a clinical study, it may be possible to resample from the NHANES database, although care should be taken to ensure that the distribution of weights in the NHANES database is similar to the distribution of weights in the patient population. This assumption may or may not be a strong one depending on the type of cancer and stage of treatment under consideration. Alternatively, parametric models may be developed by estimating TBW from age and sex. Bonate (2011) presents a discussion of simulating covariate distributions in clinical trial simulations.

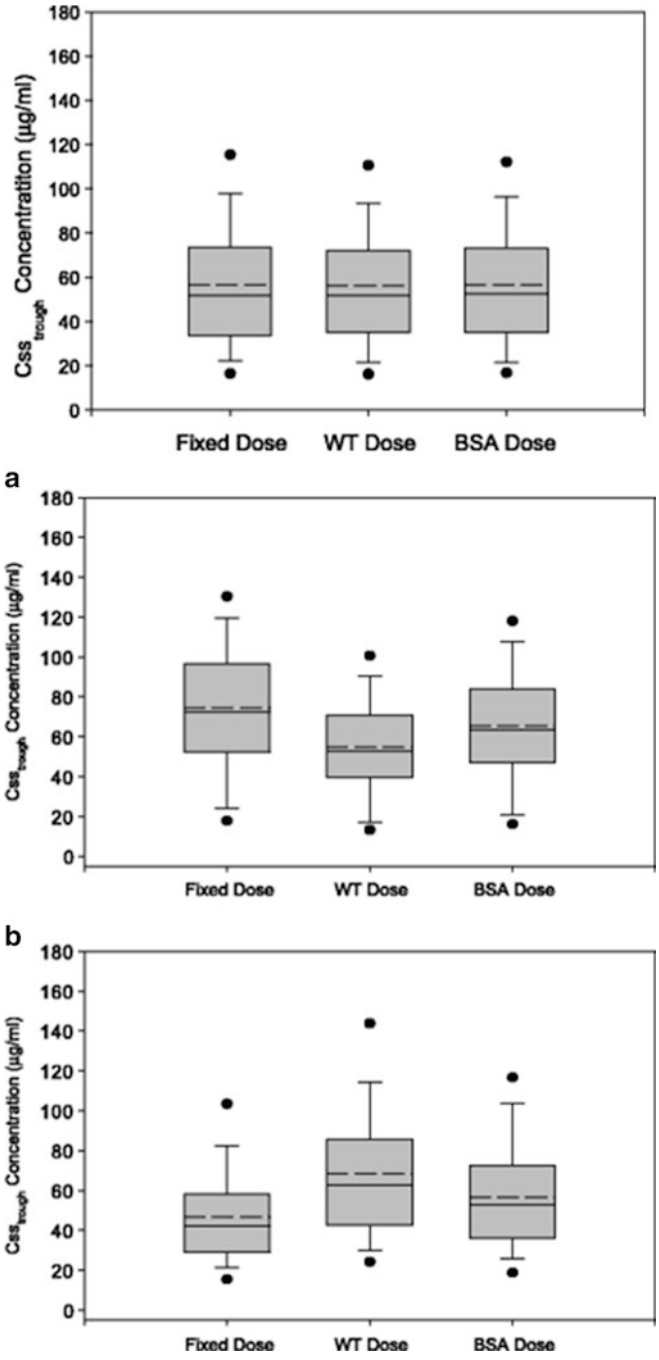


**Fig. 4.3** Predicted pertuzumab steady-state trough concentration after a fixed, weight-based, or BSA-based dose for 1000 simulated subjects bootstrapped from the original analysis data set (*top* figure). Predicted pertuzumab steady-state trough concentration after a fixed, weight-based, or BSA-based dose for patient populations with *lower* weight (<10th percentile, middle figure labeled as (**a**)) and *upper* weight (≤≥90th percentile, *bottom* figure labeled as (**b**)) values. Figure reprinted from Ng et al. (2006) with permission from Springer

## 6 Carboplatin and the Calvert Formula

The dosing of carboplatin has a special place in the pantheon of oncology drugs because the clinical dose is based on a patient's glomerular filtration rate (GFR), which can also be considered a type of body-sized metric since body weight is one component in its calculation. Carboplatin, a platinum-based chemotherapeutic agent, is used to treat certain types of cancer, particularly lung and breast, and whose mechanism of action is release of free platinum leading to formation of irreversible DNA adducts and cell death. The concentration-time profiles for both carboplatin and free platinum are almost identical. With 70 % of the carboplatin dose being excreted unchanged in the urine, carboplatin renal clearance closely approximates the GFR. Calvert et al. (1989), using simple linear regression models, developed an equation relating dose to target AUC and GFR. The recommended formula is

$$\text{Dose}(\text{mg}) = \text{AUC}(\text{GFR} + 25) \tag{4.6}$$

where AUC has units of mg/mL min and GFR has units mL/min. Using 18 patients having different solid tumor types, Calvert et al. showed that a target AUC between 5 and 7 mg/mL min resulted in manageable hematologic toxicity.

Since the original publication of this equation, a number of caveats and criticisms have been reported. First, the target AUC of 5–7 mg/mL min is for patients with previous chemotherapy experience. For patients without previous chemotherapy experience, the target AUC is 6–9 mg/mL min. Second, the range of GFR values used in the study was 33–136 mL/min. Hence, the Calvert formula is not recommended in patients with end-stage renal disease. Further, the GFR used in the Calvert equation should not exceed 125 mL/min. Third, in the original Calvert et al. study, GFR was estimated using chromium-labeled EDTA clearance. Today's use of the Calvert formula requires GFR estimation based on different formula, like the Cockcroft-Gault equation or Modification of Diet in Renal Disease (MDRD) equation, all of which use serum creatinine as one component in their equations. In 2006 clinical laboratories across the United States switched assays for the measurement of serum creatinine. The new assay results in creatinine values slightly lower than the old assay resulting in overestimation of GFR values and possible overestimation of dose requirements in patients (Ivy et al. 2010). Based on this change, patients with an estimated GFR higher than 150 mL/min are capped at 150 mL/min. Also, a maximum carboplatin dose should not exceed an AUC × 150 mL/min, e.g., 900 mg for a target AUC of 6 mg/mL min. Despite its utility, the Calvert formula has been criticized for lacking statistical rigor. Mazundar et al. (Mazundar et al. 2000) reported the results of an analysis of 45 studies conducted between 1989 and 1999 using the Calvert formula. In those studies where target AUC was compared to the observed measured AUC, the Calvert formula led to 10–20 % underestimation of the target AUC. Despite the problems with the Calvert equation, it is still used today in its original form.

## 7 Size-Based Dosing in Obesity

Obesity is defined as having a body mass index greater than 30 kg/m$^2$, and it has been estimated today in the United States that roughly 1/3 of the population is obese. Obesity as a disease is not just an abnormal increase in body fat but also has a low-level inflammatory component resulting in an increased release of cytokines, changes in cardiac output, and metabolic disturbances resulting in changes in protein binding and relative tissue distribution. Despite a paucity of studies in obese patients, many pharmacokinetic processes are affected by obesity such as changes in protein binding, metabolism, and excretion leading to altered pharmacokinetics of some drugs in obese patients (Brill et al. 2012). Despite there being no evidence of increased toxicity among obese patients receiving full TBW-based doses, with drugs that are dosed using size-based metrics, such as TBW or BSA, there is concern among practicing physicians about possible overdosing. Because of this concern, many oncologists use either ideal body weight, adjusted ideal body weight, cap the dose at some upper limit, or cap the BSA to some arbitrary value like 2.0 m$^2$. Recently the American Society of Clinical Oncology (ASCO) published guidelines for chemotherapy dosing in obese adult cancer patients (Griggs et al. 2012) followed by a review article from some members on the panel further clarifying their position (Lyman and Sparreboom 2013). They recommend full weight-based chemotherapy dosing for obese patients with cancer, subject to consideration of other comorbidities that may affect toxicity. Failure to use the full weight-based dosing may result in underdosing that could potentially lead to poorer disease-free survival and overall survival rates. Interestingly, one of the recommendations by the ASCO panel is that fixed dosing of cytotoxic chemotherapy be recommended only for certain agents. They then list carboplatin and bleomycin as examples. Beyond these examples, they don't provide any additional guidance for future chemotherapy agents and how they might be dosed. It must be pointed out that these guidelines were developed for cytotoxic agents and may not necessarily apply to targeted agents or biologic agents. There are no guidelines for these latter agents.

## 8 Size-Based Dosing in Pediatrics

That BSA has not been shown to be an important determinant in the pharmacokinetics of many drugs in adults and is not surprising given the range of BSA in adults is fairly narrow. The coefficient of variability for BSA and weight in normal weight adults is typically less than 15 % (Verbraecken et al. 2006). To be able to detect an effect of BSA on a pharmacokinetic parameter-like clearance would require either a very large sample size or a very strong relationship between the two. Using flat dosing in adults for most drugs makes sense because it would follow that the range of

doses in adult patients would also be fairly narrow. However, the BSA for a 2400 g neonate is approximately 0.22 $m^2$, one-ninth that of an adult. As a child grows into an adult, its BSA increases ninefold. Its weight increases even more, from 3.4 to 70 kg, more than 20-fold change. For pediatric patients it makes more sense to dose using size-based standardization. And this is often the case. Most pediatric doses are administered per TBW or BSA. As an example, consider imatinib, which is used for the treatment of Philadelphia positive chronic myelocytic leukemia and acute lymphocytic leukemia. The usual adult dose is 400 or 600 mg QD, but, based on equivalent AUC matching in children, the dose is 260 mg/$m^2$ QD (not to exceed 400 mg QD) or 340 mg/$m^2$ (not to exceed 600 mg QD). Unfortunately, imatinib is a rarity with regard to having a labeled pediatric dose. Most newly approved drugs do not have pediatric doses reported in the label despite regulatory attempts to encourage sponsors to do so.

It is important to understand that children are not "little adults." When a child is born, many physiologic processes, like cytochrome P450 activity and renal function, are not mature compared to adults. Further, their body composition is different from adults and changes as they mature (Yaffe and Aranda 2010). Hence, size-based standardization only works once the major processes that control a drug's pharmacokinetics have matured to that of an adult. Earlier than that, the degree of maturation needs to be controlled for as well. The reader is referred to Bartelink et al. (2006) for an excellent review on pediatric dosing guidelines, and whether BSA or TBW is more appropriate.

## 9 Conclusions

Early in the history of oncology, drugs were dosed using either fixed- or TBW-based dosing. When it became apparent that the MTD of cytotoxic agents correlated across species and in man when standardized to BSA, drugs began to be dosed per BSA standardization. Separately, pharmacokineticists approach dosing from a different point of view under the assumption that the appropriate dosing regimen was one that reduced the overall exposure variability. As the use of cytotoxic agents began to decline with the rise of biologics and targeted therapies, oncologists began to question the use of BSA dosing for these agents. At the same time, pharmacokineticists noted that size-based dosing reduced pharmacokinetic variability in a few instances. Today, the reflexive assumption for dosing a drug per size-based standardization does not occur. A more rational approach to dosing is used, and a combination of pharmacometric and experimental approaches is applied for its evaluation. Dosing per size-based metric should be selected based on a drug's therapeutic window, whether the metric reduces overall-subject exposure variability and how the exposure metric affects the clinical safety and efficacy endpoints.

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# Chapter 5
# Clinical QTc Assessment in Oncology

**Margaret R. Britto and Nenad Sarapa**

**Abstract** Cardiac proarrhythmia due to drug-induced QTc interval prolongation is an important concern in oncology since novel therapies can result in prolonged survival of cancer patients already predisposed to cardiotoxicity, and a number of anticancer agents, such as some of the tyrosine kinase inhibitors, are known to cause this risk. While not specifically requested by the ICH E14 guidance, a certain degree of QTc assessment in preapproval trials has emerged as the regulatory expectation with novel anticancer agents, particularly those that are small molecule chemical entities. This chapter reviews the challenges of evaluating QTc effect in oncology and proposes three integrated approaches to QTc risk assessment of anticancer agents (i.e., a "classic ICH E14-type" scenario, a "front-loaded" scenario, and a "full-development" scenario), which can be customized to different development plans and be evaluated using quantitative outcome criteria.

**Keywords** ECG • Electrocardiogram • Thorough QT • Concentration-QT • TQT • Clinical trials • Cardiac repolarization

## 1 Introduction

It has been more than a decade since the publication of the original International Conference on Harmonisation (ICH) E14 guidance for the assessment of QTc interval (hereafter simply referred to as "QTc") prolongation by non-antiarrhythmic

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drugs during clinical development, which was issued in response to several well-known drugs that had to be taken off the market due to proarrhythmic effects culminating in torsade de pointes (TdP) (Viskin 1999; Shah 2002; Stockbridge and Throckmorton 2004; Morganroth 2007). Following the release of that guidance, evaluation of QTc effects during preclinical and clinical development and the conduct of a thorough QTc (TQT) study became standard practice for almost all systemically available non-antiarrhythmic drugs. Additionally, a number of refinements and efficiencies in preclinical techniques, clinical study design, methods of ECG interval measurement, and data analysis techniques were incorporated into clinical QTc and TQT methodology.

At the same time, however, there was a fair amount of soul searching at the industry and regulatory level about whether the QTc evaluation process, starting with its battery of preclinical testing and culminating with a TQT study in its classic design, provided optimal value in the drug development process. There was an industry-wide recognition that, though the initiative had significantly improved drug safety, the entire process was laborious, labor-intensive, and expensive (Sager and Kowey 2014). Additionally, it often resulted in the termination of otherwise promising drug candidates due to "positive" preclinical or clinical signals for QTc prolongation, many of which may never have resulted in TdP if properly managed by adequate labeling and risk management after marketing approval.

The actual occurrence of TdP in the population is very low, and it is well recognized that QTc is at best a nonspecific predictor of its occurrence since QTc prolongation alone is not the sole prognostic factor, but various other factors including advanced age, general cardiac health, electrolyte status, comorbidities, and genetic/environmental interactions all play a part in the development of TdP. For example, arsenic trioxide, a drug which has life-extending effects in patients with acute promyelocytic leukemia, has been associated with TdP (Arsenic trioxide Prescribing Information). It has been suggested that though this drug does cause QTc prolongation, this effect is usually asymptomatic and may not necessarily lead to serious arrhythmias in patients who are on standard doses and who do not have underlying heart disease or metabolic problems, or are not taking other QTc-prolonging medications (Kwong 2004). Additionally, all drug-related QTc prolongation is not created equal; some drugs have a higher propensity to cause TdP, while others do not in spite of a significant preclinical signal or lengthening of the interval, particularly in cases where multichannel blockade is involved (Johannesen et al. 2014). All of this however, is not meant to minimize the importance of proper characterization of QTc effect. The fact is that regulatory authorities have little choice but to require ECG monitoring during preapproval clinical trials, since the abovementioned variability in the impact of drug-related QTc prolongation makes it difficult or impossible to prospectively define TdP risk without actually doing some level of structured ECG monitoring, even in cases of advanced cancer. Rather, the ultimate goal has always been to develop good or better alternatives to the classic TQT study and not to negate the importance of structured ECG monitoring.

Given this backdrop, there have been multiple efforts over the past few years to better understand the complex biological mechanisms leading to TdP, develop more

precise and predictive surrogate markers, improve on measurement techniques, develop new or improved methods to streamline the development process (Darpo and Garnett 2013; Johannesen et al. 2014), and revise the implementation of the ICH E14 guidance (through the Step 5 Questions and Answers [Q&A] process) to reflect the evolution of thought in these areas (ICH E14 Q&A R3).

To this effect, exposure-QTc response (i.e., drug concentration-QTc response [C-QTc]) analysis has been evaluated both in the context of the standard TQT and as part of the search for alternative approaches to TQT. The results have shown that when applied to the ECG data in a variety of settings (e.g., single TQT study, single Phase 2/3 study, or pooled data from early or late phase studies), the C-QTc analysis can be used to complement or improve the QTc assessment and interpretation of results, and as more recently shown, even potentially eliminate the need for a standard TQT study. A recent study was conducted in a collaborative effort between industry and the Food and Drug Administration (FDA) to determine whether testing for QTc effect can be performed within routine early clinical studies, to avoid the necessity of doing a separate dedicated TQT study later in clinical development (Darpo et al. 2014a; 2015). The question that needed to be answered was whether ECG testing in Phase 1 could exclude a QTc effect (i.e., detect every positive signal) at the low threshold of regulatory scrutiny (5-10 ms) with the same or very similar sensitivity as the TQT. The results of this study were very promising and, together with the compelling body of data that had been compiled in support of C-QTc analysis, led to a revised implementation of the E14 guidance on this topic, as described in the ICH E14 Q&A R3 document issued in December 2015. Both the results of this study and the E14 revised implementation are discussed later in this chapter.

## 2 Rationale for QTc Assessment in Oncology

Superimposed on the background of changing industry and regulatory landscape is the special case of ECG assessment in oncology. Even at the time of publication of the original ICH E14 guidance, it was acknowledged that the standard paradigm for clinical assessment of QTc prolongation that is laid out in the guidance is generally not feasible for therapeutic areas like oncology, where the clinical database is small, the use of healthy volunteers as well as administration of doses well above the therapeutic dose is usually precluded, and the speed to market is often of life-saving importance to patients. As a result, clinical ECG assessment in preapproval trials in oncology before the ICH E14 and in the initial phase of its implementation were generally much less rigorous than in other therapeutic areas, and study designs as well as the data obtained from them were often less than ideal.

In spite of the challenges encountered in oncology, however, this does not obviate the need for adequate testing of new drugs. While drug-related proarrhythmia may be a relatively minor risk in cases of rapid and aggressive forms of cancer, there has been a gradual shift in focus from short-term, intensive use of cytotoxics and other drugs in patients with more advanced disease, to less toxic and more targeted

treatments including small molecules, biologics, and hormones at optimal biological dose levels (Dancey and Sausville 2003), which are aimed at long-term or even lifelong treatment and maintenance of quality of life in patients with minimal to no residual disease. For such drugs, cardiac arrhythmias can be an increasingly important safety risk, particularly if they are coupled with preexisting cardiac dysfunction due to prior chemotherapy, a high potential for pharmacokinetic (PK) drug interactions, and/or metabolic inhibition. It is well known that many anticancer agents are cardiotoxic, either through myocardial toxicity or via proarrhythmic effects. There are several reviews that summarize the cardiotoxicity of older and newer agents, including QTc prolongation by many members of the drug class of tyrosine kinase inhibitors (Locatelli et al. 2015; Bhave et al. 2014; Suter and Ewer 2013; Yeh 2006).

With the current emphasis on speed to market in those cancer types accepted by the regulatory authorities for expedited regulatory review and the relatively small numbers of patients studied in oncologic clinical development programs prior to approval, there is an increased risk that important adverse effects such as QTc prolongation and TdP may not being fully recognized during clinical development. Given the evidence of QTc prolongation with many chemotherapeutic agents and the likelihood of many targeted therapies being administered chronically, inadequate or delayed QTc assessment can have safety implications for patients during clinical trials as well as in the post-approval phase. Careful and timely preclinical and clinical assessment of proarrhythmic risk is therefore warranted for all new oncologic drug candidates. The clinical assessments should be of customized intensity and designed to ensure (1) an acceptable safety profile during clinical development, (2) timely regulatory review and approval of the drug, and (3) adequate labeling and guidance for management of any proarrhythmic risk after approval (Fingert and Varterasian 2006).

It is beyond the scope of this chapter to review the preclinical battery of tests to be considered when evaluating an anticancer agent for proarrhythmic effect, since considerations are generally similar to drugs in other therapeutic areas. The reader is referred to the original ICH S7A and ICH S7B guidances published in 2000 and 2005 and developed for safety pharmacology and QTc prolongation, respectively, as well as reviews on the methodologies and performance of various preclinical tests currently in use or under evaluation (Townsend and Brown 2013; Holzgrefe et al. 2014). As with the clinical arena, scientific and regulatory opinions on the best methods for testing of proarrhythmic effect have evolved significantly since the issue of ICH S7A and ICH S7B, most recently culminating in the well-publicized Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative (Sager et al. 2014; Sager 2014; ICH E14 Q&A R3 Concept Paper). It should be noted that the ICH S9 guidance, which is specific to anticancer agents, does allow more limited cardiovascular safety testing compared to other therapeutic areas. While it is not our objective to impose a larger burden on developers of new anticancer agents during translation from nonclinical to clinical, it is important to recognize that thorough preclinical testing of proarrhythmic effect using carefully selected and appropriate nonclinical assays can provide invaluable data to help estimate the proarrhythmic risk in patients and thereby inform the design of the subsequent clinical development plan. It is in

therapeutic areas like oncology, where options for clinical QTc testing are more limited, that a more thorough approach may be warranted at the preclinical stage, in order to better leverage the information obtained for clinical development.

## 3 Differences and Challenges of Clinical QTc Assessment in Oncology

Several issues in oncology make it challenging to conclusively characterize QTc prolongation in the clinical setting. Besides the toxicity of most oncologic agents, which generally precludes evaluation in healthy volunteers, population characteristics and clinical development practices in oncology differ markedly from other therapeutic areas. The life-threatening nature of the underlying disease and the possibility of quick progression to a lethal outcome leads to an increased risk tolerance in oncology, resulting in more aggressive therapy, greater use of investigational or incompletely evaluated drugs (particularly in refractory patients), and a higher tolerance for treatment-emergent adverse effects by both the clinician and patient (Sarapa and Britto 2008; Rock et al. 2009).

While the original ICH E14 guidance provides a good framework for evaluation of QTc effects in a vast majority of drugs, the classic TQT study model described in the guidance is usually not feasible for drugs which must be tested in oncology patients. Since the objectives of all clinical trials in cancer patients must include adequate treatment of the neoplastic disease, dosing regimens that are known to be non-beneficial or subtherapeutic, or the use of placebo and non-oncologic positive controls (such as moxifloxacin) in QTc evaluation may be problematic, or sometimes even unethical based on the study design. Even when positive control and placebo treatments are feasible, a proper randomized sequence of treatments with an anticancer agent is not likely to be accepted by investigators and patients because it would impose the need for interruption of antineoplastic therapy. Additionally, in most oncology trials, "supratherapeutic" doses would be associated with unacceptable toxicity or would not be viable if the therapeutic dose is at or close to the maximum tolerated dose (MTD). Patient inability to tolerate long confinement at the study site or to attend frequent outpatient visits, particularly in the case of advanced disease, can make the enrollment and conduct of a measurement-intensive QTc study in cancer patients difficult. Lack of training of the oncology site staff in implementing intensive schedules of replicate ECGs and rigorously standardized experimental conditions may also be an issue, though most clinical sites have accepted more robust ECG monitoring paradigms with serial ECG time points in repeat cycles and replicate ECGs at each time point (although training of the site staff by the central ECG laboratories is still required).

Even in cases where QTc effects of oncologic drugs can be studied in healthy volunteers, the magnitude of effect from a TQT study may not be directly applicable as cancer patients may have multiple risk factors predisposing them to cardiac

**Table 5.1** Factors predisposing to QTc prolongation and torsades de pointes

| | |
|---|---|
| Demographic factors | Advanced age |
| | Female sex |
| Cardiac disorders | Long QT syndrome and other genetic ion channelopathies |
| | Cardiac hypertrophy |
| | Cardiomyopathy (especially ischemic and associated with CHF) |
| | Myocardial ischemia, infarction |
| | Myocarditis |
| | Bradycardia, complete AV block |
| Metabolic and endocrine disorders | Obesity |
| | Diabetes, hypoglycemia |
| | Thyroid disorders |
| Electrolyte disturbances | Hypokalemia |
| | Hypocalcemia |
| | Hypomagnesemia |
| CNS disorders | Ischemic or hemorrhagic cerebrovascular accidents |
| | Parkinson's disease |
| | Head trauma, subarachnoidal hemorrhage |
| Organ impairment | Hepatic disease, especially cirrhosis |
| | Renal disease |
| Concomitant drugs | Increased drug exposure in plasma through PK interaction |
| | Direct QTc prolonging effect |
| | Electrolyte modifiers (e.g., diuretics) |

*AV* atrioventricular, *CNS* central nervous system, *CHF* congestive cardiac failure, *PK* pharmacokinetic

*Notes*: This list is not exhaustive. Additionally, the combination of several of these factors may further increase the proarrhythmic risk

Viskin (1999), Bednar et al. (2001) and Sarapa and Britto (2008)

arrhythmia (Table 5.1) (Viskin 1999; Bednar et al. 2001; Sarapa and Britto 2008). In many cases, observed effects may be erroneously attributed to the study drug rather than to these existing comorbid conditions or concomitant medications. Cancer patients have also been shown to have a higher baseline QTc than healthy volunteers (Varterasian et al. 2003; 2004; Sarapa et al. 2005). However, in spite of the potential for patient characteristics to confound the assessment of QTc effects, restricting patient eligibility based on these factors may not be acceptable to patients, investigators, or institutional review boards (IRBs) because it would limit patient access to potentially life-saving treatments (Fingert and Varterasian 2006). Additionally, in the oncologic population, a much higher risk for proarrhythmic potential may be acceptable for a drug that has potential for significant clinical benefit (survival rate or time to progression), particularly with the institution of appropriate risk management strategies (Fingert and Varterasian 2006). Vandetanib and arsenic trioxide provided good examples of this, where in spite of having significant QTc prolongation liability (mean QTc change from baseline of 35 and 47 ms,

respectively; i.e., double the perceived FDA acceptance limit) (Vandetanib Prescribing Information; Barbey et al. 2003), both drugs were nevertheless approved by the FDA because of their highly favorable benefit/risk ratio. A Risk Evaluation and Mitigation Strategy (REMS) was instituted for vandetanib which includes careful patient selection based on medical history of cardiovascular and renal dysfunction, regular ECG monitoring during treatment, electrolyte monitoring and prompt correction of imbalances, a dose reduction strategy in case of QTc elevations (above 500 ms), and avoidance of concomitant medications that increase the QTc interval (Vandetanib Prescribing Information). Similarly, the REMS for arsenic trioxide includes correction of any predisposing conditions such as electrolyte imbalances prior to start of therapy, discontinuation of any nonessential concomitant medications with known QTc effect, as well as close monitoring and management of risk factors during therapy, such as monitoring/correction of electrolyte imbalances, regular ECG measurements, monitoring of concomitant medications, and potential discontinuation of treatment for QTc values >500 ms that cannot be controlled by adjustment of other factors (Arsenic trioxide Prescribing Information).

## 4 Clinical QTc Assessment in Oncology

It is the expectation of the regulatory authorities that Sponsors in the oncology area include at least some degree of ECG monitoring in their development program. The level of testing is not explicitly specified in the guidances, but it is evident in the labeling of many anticancer agents with QTc liability that this information is closely scrutinized by regulators. The Sponsor needs to justify the chosen level of intensity in the context of the perceived risk (e.g., based on preclinical data available, or vulnerability of patients in target indications) and the benefit/risk ratio. For example, a high unmet medical need coupled with strong potential for benefit may lead to approval for an expedited development plan and regulatory review, in which case the regulatory authorities might accept less robust ECG monitoring during the development program. However, regardless of the circumstance, the absence of a formal analysis of QTc in clinical trials would not be accepted. It is highly recommended that interaction with the regulatory authorities occur early; well before the pivotal study/studies.

Thus, the real question for pharmaceutical Sponsors of oncology trials is when, to what extent, and how to best incorporate ECG testing into the overall clinical development plan. In oncology, the answer to these questions can vary based on a number of scientific considerations, including the size (e.g., small molecule chemical, therapeutic peptide, or monoclonal antibody) and class of molecule, whether the drug can be administered to healthy volunteers or it can only be evaluated in patients, the benefit/risk ratio of the drug as determined by the proposed patient population and disease stage (e.g., for non-adjuvant therapy in patients with advanced cancer and short-term prognosis, versus adjuvant therapy for long-term management of residual disease), the size of the development program (small pro-

grams with only a limited number of studies and patients provide more limited opportunities for incorporation of an ECG assessment plan, compared to larger), and study sample size, as well as practical considerations such as the complexity of the protocol (based on assessments needed for primary objectives) and the number of study sites/geographical spread, as well as cost/benefit ratios, and the Sponsor's risk tolerance. The implications of some of these factors on the QTc assessment plan are discussed further below.

The first consideration is the size and class of molecule. Small molecules will all have to undergo some level of clinical ECG testing, regardless of whether or not they show a positive signal on preclinical testing (Darpo and Garnett 2013), though the level of testing intensity would necessarily be greater for a previously identified positive signal or a drug from a therapeutic class known to be associated with proarrhythmic effects (such as the small-molecule tyrosine kinase inhibitors). In the case of large-molecule biologics like monoclonal antibodies, the general opinion is that since these have high target specificity and are too large to access the inner pore of human ether-a-go-go-related gene (hERG) potassium channels (Rodriguez et al. 2010; Joshi 2010), they are unlikely to have QTc prolonging effects, and therefore more intensive ECG testing may not be needed. However, in the absence of any clear regulatory guidelines exempting these molecules, a fair level of clinical QTc testing is being done for these molecules (e.g., trastuzumab, pertuzumab, cetuximab, siltuximab) (Xu et al. 2014; Garg et al. 2013; Deeken et al. 2013; Thomas et al. 2014). There may be room for negotiation with the regulatory authorities, though it should be noted that ECG testing may be required for reasons other than assessment of QTc prolongation, since some monoclonal antibodies (e.g., trastuzumab) are associated with left ventricular dysfunction (Trastuzumab Prescribing Information). Finally, there are the therapeutic peptides, which fall into the intermediate size range between small molecules and large-molecule biologics; these molecules would likely be subjected to similar requirements as small molecules.

The benefit/risk ratio for an anticancer agent can significantly affect the type and level of testing done. As already stated, drugs having a high benefit/risk ratio may be approved for an expedited development plan and regulatory review, with less robust ECG monitoring. When the planned use of the drug is for advanced cancer with a short-term prognosis, health authorities are likely to be more accommodating with respect to the amount of monitoring they will require in preapproval trials, compared to a drug being developed for a longer-term adjuvant setting or for an indication with good existing treatment options.

The overall size of the development program and the study sample size are factors that impact almost all ECG assessment plans in oncology. Oncology development programs are small in general, and the relatively smaller development programs, with only a limited number of studies and patients (such as for drugs selected for expedited approval), will provide more limited opportunities for incorporation of ECG assessment compared to larger ones. Sample sizes for QTc assessment studies are another important consideration since it is rarely possible to power oncology studies to the extent required for a TQT study. In such situations, C-QTc modeling provides a powerful tool for maximizing the information obtained from

such studies, particularly if ECG and blood concentration data can be obtained in the upper part of the therapeutic range or, when possible, at supratherapeutic exposures. The applications and advantages of C-QTc modeling are discussed in more detail later in this chapter.

Financial considerations also play an important part in determining the path for ECG clinical assessment. For example, robust, "TQT-type" serial ECG monitoring during the first-in-human study or other early Phase 1 studies can yield very useful information about a drug's potential QTc liability, particularly since these studies can evaluate QTc over a range of doses and exposures, with some being conducted at high doses/exposures which may not be tested again in subsequent studies. In fact, some large-company Sponsors have routinely done such monitoring as part of their standard drug development process (Sager and Kowey 2014; ICH E14 Q&A R3 Concept Paper). However, this type of testing is expensive, particularly since the majority of drugs evaluated at this stage will fail prior to registration. Thus, the cost/benefit ratio is a big consideration for some Sponsors, particularly for small and medium size companies with more limited funds for development. In such cases, some might choose to collect and store robust ECG data in the early Phase 1 trials, but not incur the cost of data analysis (i.e., central laboratory ECG reads and statistical analysis) until later in the development program when the drug's outcome is more certain. Others might opt to take a strategy more focused on efficacy and general safety trial objectives initially, where they perform only limited ECG testing early in the development program and instead focus their resources towards conducting some type of QTc assessment later in the development program (either as a dedicated standalone study or as an add-on to an ongoing Phase 2 or Phase 3 study), once the probability of a successful drug is more assured.

## 5 Options for ECG Assessment Plans During Drug Development

Expectations for ECG assessment during clinical drug development have progressed significantly over the past decade in the oncology area. "Historic" practice, where very little ECG assessment was done at any point during preapproval oncology trials, changed gradually after the approval of arsenic trioxide, which was closely scrutinized for QTc liability by the FDA despite its sizeable benefit for a life-threatening disease, and with growing awareness of the proarrhythmic effects of molecular-targeted agents such as the histone deacetylase (HDAC) and receptor tyrosine kinase (RTK) inhibitors (Sarapa and Britto 2008). However, as alluded to earlier, there is no "one size fits all" approach to ECG assessment in oncology. Rather, based on the factors described earlier, a "fit for purpose" approach should be developed for implementation of ECG assessment into the drug development plan, and agreed upon with the health authorities (Sarapa and Britto 2008; Curigliano et al. 2008). While there can be many variations, there are probably three broad

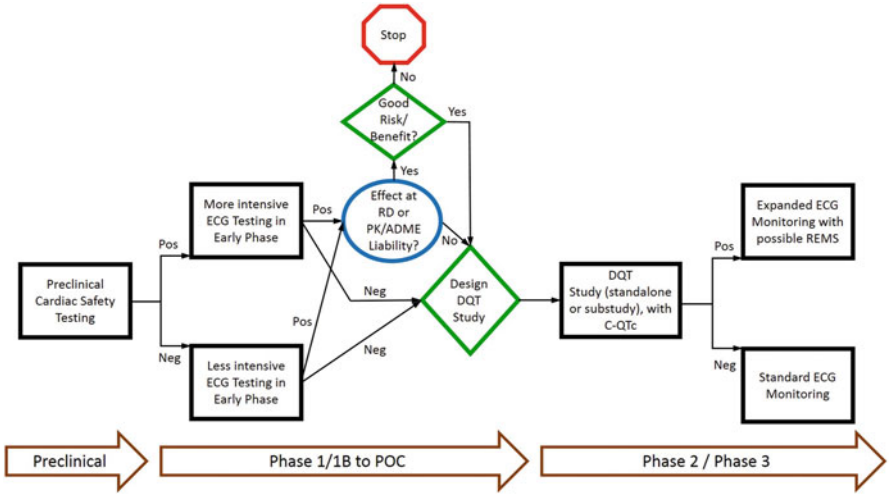


**Fig. 5.1** Decision tree for QTc evaluation in anticancer drug development ("classic ICH E14-type" scenario). *Note*: *Black boxes* represent drug development steps, *blue oval* represents a Sponsor assessment point, *green diamonds* represent interaction or decision points between the Sponsor and regulatory authorities, and *red octagon* represents decision to stop further development. *C-QTc* exposure-response modeling (i.e., concentration-QTc), *DQT* definitive QTc study in oncology (i.e., a "thorough" ECG study which has been suitably modified for oncology application), *Neg* negative (or non-clinically significant) QTc effect; *PK/ADME Liability* susceptibility to a positive QTc effect due to a perturbation in absorption, distribution, metabolism, or elimination (ADME), or some other pharmacokinetic (PK) interaction, *POC* proof of concept, *Pos* positive (or clinically significant) QTc effect, *REMS* risk evaluation and mitigation strategy, *RD* recommended dose for Phase 2/3 trials

approaches that one could follow, which for ease of identification, we will refer to as the "classic ICH E14-type" development program, a "front-loaded" development program, and finally a "full-development" program.

In the first "classic ICH E14-type" model, a more prototypical development plan is followed, whereby more basic ECG information to obtain an approximate idea of effect size is collected in the early phase studies, and a "definitive" QTc (DQT) study (a "thorough" ECG study which has been suitably modified for oncology application) is run either as a standalone study or as a sub-study (i.e., add-on to a pivotal trial) at the time of Phase 2 or pivotal trials, when more information about the therapeutic dose, the potential for increased plasma exposure through drug interactions or organ impairment, and the clinically manifest QTc effect is known.

Figure 5.1 illustrates our recommendations for a decision tree that can be used for clinical evaluation of QTc effects in oncology under this model. After completion of nonclinical cardiovascular safety testing, some degree of limited but intensive ECG monitoring should be incorporated into Phase 1/2a studies, irrespective of a negative or positive nonclinical QTc signal. As stated earlier, inclusion of robust ECG monitoring in early dose-escalating single- or multiple-dose trials has an important advantage of allowing assessment across the range of therapeutic and

supratherapeutic doses, including the MTD level and the level inducing dose-limiting toxicities that are normally evaluated only in such early phase studies. This monitoring should be customized to take into account the results of the nonclinical tests as well as other available QTc information on the drug or its therapeutic class. For example, a drug expected to have a wide safety margin for QTc effect based on nonclinical cardiovascular safety testing, with no arrhythmogenic effects, bradycardia, or morphological ECG changes in animals in vivo, no potential for therapeutic class effects, and showing no potential for metabolic inhibition or major drug interactions in the nonclinical ADME (absorption, distribution, metabolism, and excretion) studies, might be classified as having "no to low risk" for TdP development in humans, thereby requiring less intensive ECG assessment during Phase 1/2a. On the other hand, a drug failing one or more of these criteria might be classified as having an "increased risk" for TdP, which would thereby necessitate more intensive ECG assessment during Phase 1/2a development. In particular, the proarrhythmic risk of all "first-in-class" *small molecules* should be diligently considered, as very little is known about their expected clinical behavior in inherently vulnerable cancer patients. For a drug classified as "no to low risk," ECG assessments scheduled around the time of Cmax may be sufficient, whereas for a drug classified as "increased risk" or having major late-occurring or accumulating metabolites or tissue redistribution, more numerous ECG assessments scheduled over a more extended period during the dosing interval may be necessary. Regardless of the frequency and timing chosen for such ECG measurements, the monitoring scheme should include quality ECGs and corresponding PK measurements. The practicalities associated with obtaining these are discussed later in this chapter.

Following completion of Phase 1/2a, the design of a "thorough" DQT study should be considered and discussed with regulators (Fig. 5.1). A DQT design is a hybrid "fit for purpose" design that substitutes for the TQT and takes into consideration various factors regarding the drug characteristics, doses to be studied (therapeutic and/or supratherapeutic), dosing scheme, and possible study population. There are a number of good examples of such "thorough" DQT studies performed for both small and large molecules in the literature, and illustrate many of the design concepts that can be considered based on the drug being studied.

The simplest case is when a drug can be administered to healthy subjects, usually as a single dose or rarely multiple dosing to steady state, at a dose level high enough to evaluate QTc effect at relevant drug exposures. Vismodegib, a non-adjuvant, small molecule drug provides such an example (Graham et al. 2013). Vismodegib was found to have low risk for QTc prolongation during both preclinical and Phase 1 testing in patients, and the Sponsor followed this up with a multiple-dose active- (moxifloxacin) and placebo-controlled TQT study in healthy subjects. While it may not be possible to incorporate all features of the standard TQT study designs into such a study due to oncology-related issues (such as the inability to test supratherapeutic doses, or to dose for more extended periods due to time-dependent toxicity), the ability to dose in healthy subjects can nevertheless allow for simpler, more intensive (in terms of number of ECG time points), and less variable testing of QTc effects than would be feasible in patients. One important point to ensure in a

healthy-volunteer "thorough" DQT study is that the PK exposures achieved in the study adequately cover therapeutic exposures, as well as potential "worst case" exposures due to PK interactions, organ impairment, or other factors. This point is illustrated by the clinical development of vandetanib (discussed further below), which included such a single-dose "thorough" DQT study in healthy subjects. However, the study was deemed to be of limited use in assessing QTc effect because PK exposures achieved in the study were >40 % lower than the steady state exposures after repeat dosing at the therapeutic dose in patients; thus, the "thorough" DQT study in healthy subjects needed to be followed up by a more definitive assessment of QTc in the pivotal trial in cancer patients.

When assessment must be done in patients, the task becomes more challenging, but nevertheless, there are a number of examples of "fit for purpose" study designs that have been used to assess QTc prolongation. Study designs vary due to considerations specific to the drug, dosing-regimens, and PK profile, but there are some commonalities that these studies share, such as relatively small sample sizes (typically around 20–25 patients) compared to classic TQT studies, collection of replicate ECGs at several predose time points (e.g., 90, 60, and 30 min before first dosing) or serial time-matched ECGs prior to start of treatment (to allow for proper baseline correction), and the use of C-QTc modeling to maximize the precision of information obtained.

When a "thorough" DQT study must necessarily be conducted in patients, it may deviate from the standard TQT study design on several characteristics, including a lack of placebo and/or positive control. However, it should be emphasized that though not always possible to include, placebo and positive controls are very important components of conclusive QTc assessment, so their inclusion should at least be seriously considered when developing the "thorough" DQT study design. An example for incorporation of these elements would be a short randomized run-in phase at the start of the study (e.g., single doses of placebo and a positive control, given as single doses in a crossover fashion, followed by a therapeutic course of anticancer drug), thereby eliminating the need for anticancer treatment to be interrupted (e.g., pazopanib; Heath et al. 2013). Another option for inclusion of a positive control during actual treatment would be to use a positive control relevant to oncology such as granisetron or ondansetron (e.g., sunitinib and vandetanib; Bello et al. 2009; Vandetanib FDA QT-IRT Review). If inclusion of placebo is not possible, it is important to obtain robust baseline measurements via multiple predose measurements and/or serial time-matched measurements prior to start of treatment, to allow for proper baseline correction. Extended exposure to supratherapeutic doses of oncologic drugs may not be possible in a "thorough" DQT study due to unacceptable toxicity, but in some cases, administration of a single high dose or a loading dose (e.g., sunitinib and trastuzumab; Bello et al. 2009; Xu et al. 2014) or an enzyme inhibitor if clinically relevant (e.g., dasatinib; Johnson et al. 2010) may be a feasible means of transiently raising concentrations high enough to evaluate QTc effects at supratherapeutic exposures in plasma. Though sample sizes of "thorough" DQT studies will most likely be lower than those used in standard TQT studies, the study does need to be powered sufficiently to detect a clinically relevant

effect (e.g., vismodegib; Graham et al. 2013). Due to the smaller size of the "thorough" DQT study, the value of the categorical analysis of QTc outliers will likely be minimal so the primary statistical outcomes will be derived from the statistical "by time point" analyses of QTc prolongation (i.e., intersection–union test; IUT) and/or the modeling of the C-QTc relationship. In particular, C-QTc modeling can significantly improve the predictive capability of a smaller trial, compared to the standard ICH E14 statistical "by time point" analysis, and is discussed later in this chapter.

Sometimes "thorough" DQT study designs can be combined with other objectives (e.g., in PK studies, or in Phase 3 efficacy/safety studies as a substudy) (e.g., linifanib and pertuzumab; Chiu et al. 2014; Garg et al. 2013), while others may be dedicated QTc studies. Dedicated QTc studies may have study designs specifically purposed for measurement of QTc (e.g., single dose, randomized or nonrandomized crossover in patients) (e.g., vorinostat, trabectedin, and ridaforolimus; Munster et al. 2009; Thertulien et al. 2012; Lush et al. 2012), or the PK and ECG assessment plan in the study may be optimally aligned with efficacy and safety objectives (e.g., incorporation into the cyclic dosing scheme of the anticancer agent), for maximal efficiency. Additionally, if the dosing regimen includes drug-free periods between cycles, these may be used to assess the reversibility of QTc effect.

If the outcome of a "thorough" DQT study conducted during Phase 2 is negative, ECG monitoring in Late Phase (Phase 3) development can be conducted according to the principle advocated in the ICH E14 guidance, whereby a negative TQT study allows for ECG schedules in accordance with the current investigational practices in the given therapeutic field. Since the routine practice in oncology includes only a minimal number of single ECGs at baseline and on therapy, a negative "thorough" DQT result can translate into significant potential for reduced cost and effort, and a reduced likelihood of a false positive QTc finding in less-controlled multicenter pivotal trials. On the other hand, if a positive effect is found in a "thorough" DQT study but the drug/dose level is still considered to provide a favorable benefit/risk advantage, then expanded ECG monitoring with a customized, more intensive schedule will be required in Late Phase development in all patients or in subgroups at risk. In addition, the implementation of an appropriate risk management plan will be necessary, as was done for arsenic trioxide and vandetanib.

The next ECG drug development option to be discussed is the "front-loaded" program (Fig. 5.2) whereby the QTc effect is studied and defined early in the development program (i.e., preclinical and early clinical), via collection of extensive "DQT-type" ECGs (i.e., triplicate, centrally read ECGs under well-controlled conditions, as described later in this chapter) and PK data in early-phase studies (Phase 1/1b to Proof of Concept [POC]). Proper characterization of the relevance of the QTc effect at this early stage would allow Sponsors to determine what level of intensity is necessary for adequate ECG assessment during the Phase 2 and pivotal trials. If the QTc results are considered to be adequately robust and definitive, based both on the quality of the ECG data obtained (i.e., the collection and analysis, including the C-QTc) and determination of the effect size at exposures that are adequate to cover the upper part of the exposure range likely to be encountered in therapeutic practice, it may be possible to obtain a "TQT study waiver" from

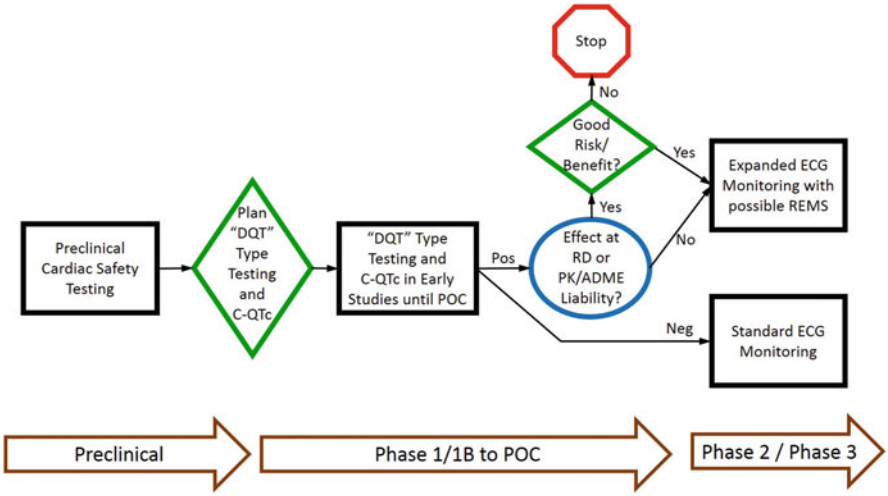


**Fig. 5.2** Decision tree for QTc evaluation in anticancer drug development ("Front-loaded" scenario). *Note*: *Black boxes* represent drug development steps, *blue oval* represents a Sponsor assessment point, *green diamonds* represent interaction or decision points between the Sponsor and regulatory authorities, and *red octagon* represents decision to stop further development. *C-QTc* exposure-response modeling (i.e., concentration-QTc), *DQT* definitive QTc study in oncology (i.e., a "thorough" ECG study which has been suitably modified for oncology application), *Neg* negative (or non-clinically significant) QTc effect, *PK/ADME Liability* susceptibility to a positive QTc effect due to a perturbation in absorption, distribution, metabolism, or elimination (ADME), or some other pharmacokinetic (PK) interaction, *POC* proof of concept, *Pos* positive (or clinically significant) QTc effect, *REMS* risk evaluation and mitigation strategy, *RD* recommended dose for Phase 2/3 trials

regulatory authorities (ICH E14 Q&A R3 Concept Paper; ICH E14 Q&A R3). Support for the viability of this approach was provided by a recent, elegant "proof-of-concept" study conducted by Darpo et al. (2014a, 2015) on behalf of the Innovation Quality (IQ) Consortium and the Cardiac safety Research Consortium (CSRC). Though this study was conducted in healthy subjects with placebo control and a partial crossover design, it nevertheless has a number of features which are applicable to the oncology setting. For example, the study utilized a small sample size (approximately 6–9 subjects per treatment). Despite the parallel design and smaller sample size available at some dose levels in the dose escalation, the Phase 1 studies in oncology (3 + 3) may offer a good opportunity to acquire robust PK and ECG data from multiple dose levels invariably inclusive of the MTD in patients; moreover, more patients (e.g., 20–30) are generally evaluated at the MTD in the expansion cohort, which often represents the recommended dose (RD) for the late phase trials. While crossover designs may be precluded, longitudinal intra-patient assessment, sometimes at multiple dose levels, may be available if PK and ECG data are collected in patients over multiple cycles and dose changes. The use of placebo and positive controls may not be possible in these studies, but recording of predose ECGs at multiple time points (e.g., 90, 60, and 30 min before first dosing)

or serial time-matched baseline ECGs can provide fairly robust baseline-adjusted data in the oncology setting. The IQ-CSRC study also shows the power of C-QTc analysis for studies of smaller sample size, as well as the value and importance of getting input and agreement from regulatory authorities on the study design and proposed assessment plan (ICH E14 Q&A R3 Concept Paper).

Ponatinib and ceritinib provide examples where first-in-human MAD studies with small patient cohorts per dose (2–12 patients per cohort for ponatinib and 2–14 patients per cohort for ceritinib) were used for this purpose (Sonnichsen et al. 2013; Ceritinib FDA QT-IRT Review). For both drugs, the studies consisted of a standard open-label, parallel group, dose escalation phase, followed by a smaller expansion for ponatinib at the two highest dose levels (approximately 20–30 patients in total per dose group at 45 and 60 mg) and a larger expansion phase for ceritinib at the MTD (245 patients in total). For ceritinib, patients were dosed once daily and PK and ECG data were collected at single dose and steady state in both the escalation and expansion phases. The statistical "by time point" analysis and C-QTc modeling from this study were accepted by the FDA for describing the magnitude of QTc effect in the ceritinib label (an upper bound on the 90 % CI for QTc change from baseline of 16 ms with "by time point" analysis, and a concentration-dependent QTc prolongation) (Ceritinib Prescribing Information). In the case of ponatinib, "by time point" results of the MAD study at the higher dose levels (30–60 mg) were used in the label to rule out mean QTc changes greater than 20 ms (Ponatinib Prescribing Information).

Results from such an early phase QTc study in this "front-loaded" model could subsequently be used to develop appropriately safe and cost-effective ECG assessment strategies in future studies including non-pivotal and pivotal late phase trials. The intensity of ECG assessment in late-phase trials could vary from the standard for the oncology therapeutic area (i.e., sparse) to more robust (5–6 ECGs in replicate). The latter would result from a drug with a strongly positive QTc effect in Phase 1 but with a good benefit/risk ratio (i.e., still a good candidate for development), with the data collected from this monitoring being utilized for C-QTc modeling, similar to what is described for the "full-development" model below. Based on the conclusiveness of the results obtained from such an early phase QTc study with regard to QTc effect, the data might also be used to obtain a "TQT waiver" from regulatory authorities (Liu 2014; ICH E14 Q&A R3 Concept Paper), or for design of subsequent early phase QT evaluation studies or a "thorough" DQT study (to be run preapproval, peri-approval, or post-approval).

There are of course risks associated with trying to definitively quantify the QTc liability at this early stage. Besides the small sample sizes that may make conclusions difficult, the data collected may be inadequate or incomplete since information on the drug's clinical QTc effect, PK characteristics, and the target dose and exposure for optimal therapeutic effect is unknown or incompletely defined. Additionally, there may be differences in QTc effect since these early studies generally enroll patients with multiple types of cancer in the advanced and/or refractory stages of disease that do not fully represent the patients for whom the drug will be indicated. Moreover, many patients in early phase studies do not complete more

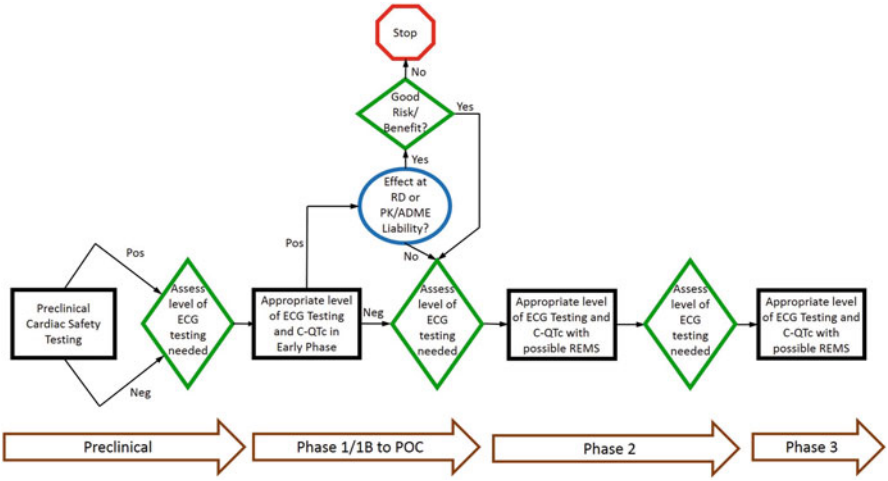


**Fig. 5.3** Decision tree for QTc evaluation in anticancer drug development ("Full-development" scenario). *Note*: *Black boxes* represent drug development steps, *blue oval* represents a Sponsor assessment point, *green diamonds* represent interaction or decision points between the Sponsor and regulatory authorities, and *red octagon* represents decision to stop further development. In this scenario, it should be noted that while multiple interactions with regulatory authorities are shown for completeness, all may not be needed, but could add value (i.e., to obtain feedback) if regulatory interaction will be occurring for another purpose. *C-QTc* exposure-response modeling (i.e., concentration-QTc), *DQT* definitive QTc study in oncology (i.e., a "thorough" ECG study which has been suitably modified for oncology application), *Neg* negative (or non-clinically significant) QTc effect, *PK/ADME Liability* susceptibility to a positive QTc effect due to a perturbation in absorption, distribution, metabolism, or elimination (ADME), or some other pharmacokinetic (PK) interaction, *POC* proof of concept, *Pos* positive (or clinically significant) QTc effect, *REMS* risk evaluation and mitigation strategy, *RD* recommended dose for Phase 2/3 trials

than 1–3 treatment courses and have incomplete or missing observations, mainly due to disease progression, comorbidities, and drug intolerance (primarily of non-cardiac nature). Considering these limitations, further ECG evaluation may be occasionally warranted in subsequent studies to better define or confirm the observed effect.

Finally, the third option for ECG assessment in oncology drug development is a "full-development" program (Fig. 5.3), whereby one would perform a customized level of ECG assessment throughout the development program from early phase all the way through the pivotal studies. The extent of ECG assessment included at different stages of the program would depend on the scientific information available at each step as well as other practical considerations such as Sponsor financial resources. More intensive assessment would be needed for a drug with a positive QTc signal at preclinical or early clinical phase, or with PK characteristics or potential for drug–drug interactions that could lead to increased QTc risk, or for a target patient population with cardiovascular vulnerability. One could use C-QTc modeling to evaluate the QTc effect across data from single or multiple studies (Rohatagi et al. 2009; ICH E14 Q&A R3) in the development program. Pooling of data across

studies could improve the power for QTc detection even if each individual study has included a less intensive ECG measurement schedule, as long as the quality of the ECGs collected are comparably high in all studies. As before, based on the conclusiveness of the results obtained at each stage, this could provide support for request of a "TQT waiver" from regulatory authorities (Liu 2014; ICH E14 Q&A R3 Concept Paper), or inform the design of a "thorough" DQT study, if deemed necessary.

Vandetanib, a small molecule, multi-tyrosine kinase inhibitor approved for the treatment of metastatic medullary thyroid cancer (MTC), provides a good example of such a "full-development" program. Vandetanib was identified in preclinical studies to have significant QTc liability, with activity in the hERG assay (half maximal inhibitory concentration [IC50] of 0.4, 1.3, and 4.0 nM for vandetanib and its N-desmethyl and N-oxide metabolites, respectively), concentration-dependent increase in action potential duration in a canine Purkinje fiber study, and increases in heart-rate corrected QTc and a dose-related increase in T-wave amplitude in anesthetized dogs (Vandetanib FDA QT-IRT Review). Consequently, the Sponsor instituted intensive ECG monitoring in several clinical studies including a QTc study in healthy volunteers (a single-dose, crossover study with an active comparator, ondansetron, which provided limited information since maximum vandetanib exposures were less than 60 % of multiple-dose therapeutic exposures in the pivotal trial), a Phase 2 trial in MTC patients, and the pivotal Phase 3 trial in MTC. The Sponsor's description of the development program is particularly illuminating: "QTc prolongation with vandetanib was initially seen in Phase 1 and preclinical studies, and over the course of the clinical development the vandetanib protocols have included a management plan including ECG schedules, criteria to define QTc prolongation, and guidance for dose reduction. This management plan has been amended, in consultation with cardiology experts and FDA, as data became available over the course of the clinical studies. The Phase 3 QTc management plan was agreed at the end of Phase 2 with FDA" (Vandetanib Tablets Oncologic Drugs Advisory Committee (ODAC) Meeting Briefing Document and AstraZeneca 2010).

In the Phase 3 trial of vandetanib (a double-blind comparison of vandetanib to placebo in a 2:1 ratio, conducted in 331 patients), 12-lead ECGs were collected in all patients at baseline (predose), and PK and 12-lead ECGs were collected at approximately 4–8 h postdose (Tmax of vandetanib and metabolites observed from early phase trials) during weeks 1, 2, 4, 8, and 12, and then every 12 weeks until discontinuation of treatment; ECGs were also collected in the post-prolongation period if QTc was prolonged (Vandetanib FDA QT-IRT Review). All ECGs were centrally read and QTc prolongation (defined as a single QTcB value of ≥550 ms, ≥100 ms increase over baseline, a confirmed prolongation of the QTc interval to a value of ≥500 ms, or an increase from baseline of ≥60 ms to a level ≥480 ms) mandated that the dose be interrupted until resolution, with a restart at a reduced dose. While population size and the effect size in this trial were large enough to discern a significant effect using the statistical "by time point" analysis (upper bounds of the 90 % CIs >33 ms), the C-QTc modeling results are of particular interest. In addition to the analysis the Sponsor conducted, the FDA did a full reanalysis of the data

using log linear and Emax models to fit the available data and evaluate the influence of intrinsic and extrinsic factors such as gender, body weight, renal impairment, and cytochrome P450 3A4 (CYP3A4) induction (vandetanib is a CYP3A4 substrate), and these results were used as a basis for QTc-related information and precautions in the label (Vandetanib Prescribing Information). Dose reduction is also indicated for this drug in patients with moderate and severe renal impairment, which is at least in part due to the proarrhythmic risk in those segments due to large QTc prolongation (Vandetanib FDA QT-IRT Review).

Regardless of which development scenario one chooses for ECG assessment in preapproval clinical trials in oncology, three important overall points need to be made. The first is that flexibility and frequent assessment points should be built into any chosen plan to allow for adjustments based on drug- or patient population-specific factors, emerging clinical QTc results, changes in competitive landscape, as well as regulatory feedback obtained on an ongoing basis. The second is that these scenarios are based on a more "classic" oncology drug development program. However, some development programs in oncology progress very quickly from Phase 1 to filing for marketing approval when the results in Phase 1 are very good, and/or when the unmet medical need is high because the efficacy of the standard-of-care is very weak. In such cases, the next step after Phase 1 could become a registration trial instead of the POC study. These registration trials might even be allowed to be single-arm (i.e., not controlled by placebo or standard-of-care) because it is considered that such comparisons would be unethical in light of the very strong preliminary evidence of tumor response in Phase 1. Such situations would warrant skipping over certain steps in the scenarios, and the ECG assessment would have to be incorporated in the abbreviated/expedited development program. For example, these fast-track programs could perhaps combine the first part of the "front-loaded" approach and the last part of the "full-development" approach. The third point is to stress the importance of proactively engaging in data-driven discussions with the regulatory authorities at various key time points throughout the clinical development program (Liu 2014), in order to ensure that Sponsor and regulatory opinions are in alignment. Besides avoiding any unexpected surprises at the time of NDA review, this can provide benefits to the Sponsor, such as more informed planning of the timing, size, logistics, and cost of subsequent standalone QTc studies and/or QTc assessment programs within other trials, as well as the possibility (as discussed earlier) of obtaining a "TQT waiver" from conducting a "thorough" DQT study if the QTc effect (positive or negative) has been clearly defined based on data from previous studies (Liu 2014; ICH E14 Q&A R3 Concept Paper).

## 6 Practical Considerations for Clinical QTc Assessment

Whether one follows the classic "ICH E14-type" development model or the "front-loaded" or "full-development" models, there are a number of practical details that need to be considered in any clinical study in which ECG data will be collected for the purpose of QTc proarrhythmic risk assessment, including QTc prolongation.

Inclusion and exclusion criteria are an important consideration for such studies. While cancer patients' access to potentially life-extending therapy cannot be hampered by overly strict entry criteria, it may be possible to correct some confounding baseline issues such as electrolyte imbalance, or to switch or temporarily discontinue nonessential concomitant medications affecting QTc. Alternatively, study designs and/or analyses can be modified to handle subgroups with these or other issues that may be relevant to the drug's QTc profile, such as renal or hepatic impairment.

With regard to QTc-related inclusion/exclusion criteria, a higher upper limit for the acceptable value should be used than the >450 ms cutoff commonly utilized in healthy volunteers and recommended by the ICH E14 guidance. An appropriate alternative is to use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria for QTc abnormalities, which can provide a link between standard therapeutic practices and drug development in oncology based on risk–benefit considerations. While there is no clear consensus or guideline that has been established or published regarding this, an example might be to use a cutoff of QTc <480 ms (i.e., not greater than CTC Grade 1) for patients in all studies (including the first-in-human study) (Rock et al. 2009), except in situations where the patient population is vulnerable (thereby warranting a decrease), or in situations where the mean QTc prolongation is (or is expected to be) ≥20 ms. For QTc prolongation ≥20 ms, a cutoff of <450 ms could be used if the patient population is not vulnerable. Measurement of the QTc interval for establishing this eligibility could be based on a single replicate ECG at screening (at least triplicate) as well as the robust baseline measurements at predose (i.e., replicate ECGs at several time points, such as 90, 60, and 30 min before first dosing, or the serial time-matched baseline measurement). Other QTc-related exclusion criteria that can be added, which have been historically acceptable to investigators, patients, IRBs, and regulators, particularly for drugs with increased risk, are electrolyte levels (potassium, calcium, or magnesium) that are found to be low on repeat testing, the presence of or family history of congenital long QT syndrome (particularly for drugs with strong preclinical liability and/or prior documented mean QTc prolongation >10 ms), a history of clinically significant ventricular dysrhythmias, or concomitant use of medications that are known to significantly prolong the QTc interval. In some cases, patients may be declared eligible after addressing some of these issues (such as correction of electrolyte abnormalities and stoppage of nonessential medications, prior to start of treatment with the anticancer drug under study) (Fingert and Varterasian 2006).

During conduct of the QTc assessment in clinical trials including a "thorough" DQT study, appropriate dose stopping or modification strategies (at the patient level, and based on the study design, at the dose/cohort level) should be implemented for risk management of treatment-emergent QTc effects that are deemed unacceptable according to predefined criteria for dose-limiting toxicity (DLT), i.e., the QTc stopping rules. For example, the stopping rules may be defined as treatment emergent absolute QTc >500 ms or QTc change from baseline >60 ms (both would need to be confirmed on two separate replicate ECGs taken 1 h apart in order to be considered a DLT). These stopping rules could be adjusted (lowered) if

warranted by the available data. The outcome of such a DLT could be treatment interruption with monitoring, dose reduction, or treatment discontinuation at the investigator's discretion, after making an assessment of the overall benefit/risk ratio in the individual patient. If digital ECG data collected specifically for the purpose of QTc analysis are not available for immediate assessment, a reasonable schedule of robust, replicate, 12-lead safety ECGs should be conducted for making this evaluation. The ECG data should undergo a real-time safety review, and any results potentially triggering a safety signal should be repeated, preferably at hourly intervals or more frequently at the investigator's discretion (if continuous ECG data are not available for safety assessment) and undergo thorough analysis by the site investigator or cardiologist to ensure that the result is real (no measurement error by the ECG recorder's algorithm) and drug-related, since transient QTc changes of large magnitude (e.g., change >60 ms or absolute values >500 ms) have been observed during drug-free observation even in healthy volunteers (Morganroth et al. 1991).

The "thorough" DQT studies and other QTc assessment studies in oncology (including early phase/Phase 1 studies or pivotal trials, if they will be used for that purpose) have objectives in common with standard TQT studies. Therefore, TQT-type conditions should be applied wherever applicable. The ICH E14 Q&A R3 document states that C-QTc "data acquired in studies with other purposes requires as much quality control as is needed for a dedicated study." ECGs and PK samples should be obtained at several time points around the Cmax of the drug (and major active metabolites, if known) after single dose and at steady state, in the first cycle of therapy, and in subsequent cycles. In order to capture possible delayed-onset QTc prolongation, ECG and PK measurements could be done at the 24-h time point after the first dose (i.e., on Day 2), or alternatively, predose at steady-state, or predose on Day 1 of the next treatment cycle (Zhang and Stockbridge 2011). Multiple ECGs should be obtained for baseline assessment before start of dosing and/or on a predose day at clock times which are time-matched to on-treatment measurement times. ECGs should be obtained in triplicate to decrease the biological variability and measurement error, and the average of the three QTc values from each triplicate should be used as a single observation in the statistical "by time point" analysis and in C-QTc modeling (Sun et al. 2004; Agin et al. 2003). Rigorous control and standardization of experimental conditions should be implemented during the periods of ECG assessment, such as restriction of patient activity, and the absence of noise and other ambient stimuli, in order to avoid artifactual ECG results (Morganroth 2007). Meals should not be served shortly before the ECGs. To minimize the influence of autonomic tone on QTc interval duration, replicate ECGs should be obtained after at least 5-10 min of quiet rest in a fully supine position and before any type of blood draw scheduled at the same time point. As with a TQT study, collection of digital ECGs using uniform, recently calibrated ECG equipment, and the evaluation of ECG interval duration and waveform morphology by a central laboratory are essential for any study assessing QTc effect. The FDA also requests that annotated digital ECG data be provided as sup-

porting evidence of cardiac safety in NDAs, in order to verify the quality of the ECG data from the key QTc studies (Stockbridge and Brown 2004), and to conduct their own analyses of these data, as warranted. Thus, when a central laboratory is used for analyzing the ECG data from oncology studies, storage of the data in a proper format for submission should be considered.

Another practical point for consideration is the method to be used to correct the QT interval for heart rate in oncology QT studies. There is no perfect correction method; the correction formulas are variably inaccurate in certain parts of the observed range of QT and heart rate values in healthy subjects (Kowey and Malik 2007) and cancer patients (Strevel et al. 2007) and individual correction methods are not feasible in the oncology area because they require a large number (possibly >450) of ECGs per subject (Couderc et al. 2005). In fact, the ICH E14 Q&A R3 document states that "corrections that are individualized to a subject's unique heart rate QT dynamic are not likely to work well when the data are sparse." Based on a wide range of experience with TQT studies since the release of ICH E14, the Fridericia's correction (QTcF) offers reliable and cost-effective performance in the QTc assessment of drugs without a prominent effect of heart rate. This is again supported by the ICH E14 Q&A R3 document which states that "presentation of data with a Fridericia's correction is likely to be appropriate in most situations." An additional QT correction method, such as the study population-specific correction method (i.e., QTcS, also known as QTcP), could also be considered based on the prespecified comparison of the slopes of relationship between the QTc values corrected by each method and the corresponding RR interval using the drug-free data pooled from all patients (Hodges 1997).

Study conduct and compliance problems associated with ECG acquisition in oncology clinical trials (e.g., inability of patients to tolerate long inpatient confinement or frequent outpatient visits) can be partially addressed using ECG acquisition by continuous digital 12-lead Holter monitoring. Besides its convenience (no need to repeatedly connect and disconnect the lead electrode cables), an additional advantage of continuous digital 12-lead Holter over the acquisition of discrete 12-lead standard ECGs is the ability to retrospectively extract more ECGs at the time points of interest according to the timing of treatment-emergent adverse events or deviations from the expected PK profile of the drug (Sarapa 2005). A recent development that could further improve tolerability for the oncology patient is the possibility of using novel Bluetooth-enabled ECG recording devices connected wirelessly to laptops and printers, thereby allowing the ECG result to be visualized on computer screen, printed off at the bedside and/or emailed to the investigator/cardiologist for review. This eliminates the need to take the patient from the drug administration unit to the ECG laboratory at the site, a process that is usually cumbersome, time consuming, and can interfere with the PK and ECG sampling time schedule. Additionally, the real-time availability of the ECG data to the investigator allows safety assessments to be done on the same ECG data being analyzed by the central laboratory.

## 7 Concentration: QTc Effect Modeling

Modeling of the concentration-QTc (effect) relationship, primarily using linear mixed effects (LME) models, from data pooled across dose groups or treatments in a single study, or across clinical studies across the entire clinical development program, is a very valuable approach for assessing QTc prolongation (Darpo et al. 2014b; Darpo and Garnett 2013). In fact the recognition of its importance as a technique for assessing the magnitude and relevance of QTc effect has increased markedly from the regulatory opinion in the original ICH E14 document (which stated that C-QTc modeling "may provide additional information to assist the planning and interpretation of studies assessing cardiac repolarization") to the current consensus (which states that C-QTc modeling "has matured sufficiently to warrant consideration of this approach as a reasonable [or in some situations a better] approach to the assessment of QT prolongation, that could serve as an alternative to a TQT study and therefore satisfy the regulatory requirement for QT assessment") (ICH E14 Q&A R3 Concept Paper). Concentration-QTc analysis has played a key role in the regulatory reviews of TQT studies (Darpo et al. 2014b). In fact, the FDA's QT-IRT group routinely performs C-QTc analysis on all TQT studies using ECG data submitted to them as part of the NDA submission, including those submitted for anticancer drugs (Krudys 2014). ICH regulators have also commented that C-QTc modeling is consistent with the use of concentration-response modeling in other aspects of drug development, such as drug–drug interactions, influence of intrinsic and extrinsic factors on exposure, and formulation effects (ICH E14 Q&A R3 Concept Paper).

Concentration-QTc modeling has a number of advantages over the statistical "by time point" analysis (i.e., the intersection union test; IUT). It may perform robustly even with smaller sample sizes compared to the IUT (since it utilizes data from all time points, rather than a by-time point analysis), it is less sensitive to outliers, and is useful in interpreting the significance of mean QTc effects at therapeutic and supratherapeutic doses obtained from standard IUT results in the form of more clinically useable information (Darpo et al. 2014b; Liu 2014). C-QTc modeling is useful in evaluating potential differences in patient subpopulations and determining appropriate dose adjustment, if needed. C-QTc modeling is also useful in identifying false positive results from IUT analyses (Russell et al. 2008), which might be particularly useful in oncology. Even with no drug effect, a positive outcome for the mean QTc prolongation in TQT studies can occur with the IUT analysis, with rates ranging from negligible to nearly 60 %, depending on the design, sample size, and patient status (Hutmacher et al. 2008). The risk of such a false positive outcome would be greater in oncology where QTc studies may often be underpowered. Thus, C-QTc can be very useful in this regard. Additionally, if permitted by study designs, the QTc data from multiple studies (early to late phase) can be combined to increase the power of detecting QTc prolongation in small numbers of patients and significantly improve the predictive capability of the QTc results from these studies (ICH E14 Q&A R3; Rohatagi et al. 2009; Garnett et al. 2008). A combined analysis of

such studies can allow for an estimation of the C-QTc relationship over a wider concentration range and also takes advantage of all of the data collected rather than restricting the evaluation to specific time points or doses/exposures (ICH E14 Q&A R3; ICH E14 Q&A R3 Concept Paper), though it is important to test for heterogeneity to make sure that such pooling is valid. Another advantage of C-QTc modeling is the possibility of using the results obtained to simulate or predict effects under conditions of interest. For example, simulating the risk of exceeding a threshold of safety concern using the QTc results that may be collected in early phase studies can be useful in decision-making and planning for doses and exposures to be used in later phase (Piotrovsky 2005). Similarly (though caution should be exercised in the interpretation of such extrapolations), C-QTc modeling can be used to "estimate" the approximate effect size of QTc prolongation expected at higher concentrations or in vulnerable populations not evaluated in an actual study, which can be helpful in oncology since supratherapeutic doses cannot be tested in a "thorough" DQT or any other study for the majority of anticancer agents, but there is still a possibility that patients could be exposed to drug concentrations above those tested, due to PK interactions and/or organ impairment (Garnett et al. 2008). The insight that can be provided by simulations under varying conditions (such as change in dose, dosing regimen, route of administration, formulation, or varying intrinsic and extrinsic factors affecting PK) has also been acknowledged by the regulatory authorities (ICH E14 Q&A R3).

In the oncology area, where sample sizes are generally smaller or optimal designs for applying the IUT methodology cannot be used, C-QTc modeling is a particularly powerful tool for quantifying the magnitude of QTc effect. There are a number of examples, in both the oncology and non-oncology areas, where the results of C-QTc analysis have played a key role in regulatory decisions and consequently the drug label (e.g., dolasetron, ondansetron, citalopram, vandetanib, ceritinib, and ranolazine) (Darpo et al. 2014b; Krudys 2014). In the case of vandetanib and ceritinib, the FDA used the C-QTc modeling results to address several topics including the definition of the magnitude of effect over the exposure range, assessment of benefit/risk, and support for postmarketing requirements (PMRs) for investigation of lower doses.

Though there are many benefits of linear C-QTc modeling, one area of concern is the potential for underprediction of the QTc change if the assumption of model linearity is invalid (Darpo et al. 2014b). It is therefore important to test model and other analysis assumptions using prespecified criteria and goodness-of-fit tests including tests for hysteresis, to assess the reliability of C-QTc results before applying this technique (ICH E14 Q&A R3; Ferber 2014). Though not very common, one reason for violation of this assumption would be a delayed effect, such as that caused by a later-forming active metabolite or inhibition of hERG channel trafficking, or due to a QTc effect of more than one drug moiety (e.g., multiple drugs, or parent and/or metabolites). In cases of more complex or nonlinear effects, more sophisticated C-QTc models such as nonlinear PK/PD models may need to be used (Piotrovsky 2005; Rohatagi et al. 2009). Additionally, regardless of the model used, it is very important in all cases to specify the modeling approach and methodology,

as well as the objective decision criteria to be used a priori, in order to avoid compromising the outcome of the analysis due to operator bias (ICH E14 Q&A R3).

Another important consideration for C-QTc analysis is that sufficient concentration-QTc data should be collected over a wide enough concentration range to allow the model to properly assess effect at relevant supratherapeutic concentrations, if feasible. The ICH E14 Q&A R3 document states that if sufficient data characterizing response are available at these high exposures, a separate positive control would not be necessary, which is a marked advantage over the classical TQT-type study.

## 8 Outcome Criteria for QTc Assessment

Statistical "by time point" analysis (i.e., UIT), as done in the TQT study, is still considered by regulators to be a primary analysis for assessment, because it is based on fewer model assumptions and is easy to implement (Liu 2014). However, as previously discussed, C-QTc modeling is now recognized by regulators as a viable alternative to the "by time point" analysis if it is well conducted (ICH E14 Q&A R3), and has been used to support labels for multiple drugs (Darpo et al. 2014b) including a number of anticancer agents. The primary endpoint for such an analysis has been defined in ICH E14 Q&A R3 as the upper bound of the two-sided 90 % confidence interval (UCI) for the predicted QTc effect at a clinically relevant exposure. While a standard criterion of <10 ms is specified for this endpoint in the guidance, different limits for acceptable QTc prolongation may be more suitable for oncology (e.g., upper bound of <10 or <20 ms for the predicted QTc change from baseline at the observed geometric mean Cmax, as discussed below). In some cases, it may also be prudent to apply a second criterion for the slope, similar to what was done in the IQ-CSRC study (i.e., lower bound of the 2-sided 90 % confidence interval for the C-QTc slope estimate from the LME model is above zero; Darpo et al. 2015), in order to ensure that the study has provided data with sufficiently low variability to allow a precise slope estimate, since the CIs could be wider due to greater intrinsic QTc variability in cancer patients and the small sample size in individual dose cohorts. It is important to again reiterate that the C-QTc analysis would add value to all three of the development approaches previously discussed (i.e., the "ICH E14-type," the "front-loaded," and the "full-development" program) and is particularly beneficial in the "front-loaded" scenario where data are being collected from studies with small sample sizes per dose cohort as well as a wide range of drug concentrations.

With respect to the statistical "by time point" (UIT) analysis, the endpoint in a "thorough" DQT study in oncology would be similar to a TQT study, i.e., the UCI of the largest mean baseline-adjusted QTc increase at any time point after dosing [ΔQTc(max)], computed for the study population at each dose level (ICH E14, Patterson et al. 2005a, b). If placebo is used in the "thorough" DQT study (e.g., when drug could be adequately tested in healthy subjects), the mean QTc value

would be adjusted for both placebo and baseline according to the ICH E14 principles.

The threshold of regulatory concern for QTc prolongation, defined in the ICH E14 guidance as 5–10 ms, is appropriate for the risk assessment of drugs used in more benign diseases where the tolerance for drug-induced proarrythmia is low. The outcome of a properly powered TQT study in healthy subjects below this threshold is believed to translate to a very low likelihood of a false negative outcome, and conveys negligible proarrhythmic risk in patients (Darpo et al. 2006; Kowey and Malik 2007). However, the 10 ms threshold would not appropriately reflect the risk–benefit ratio for most anticancer agents in the non-adjuvant setting, where a certain risk of TdP at a dose proven to have potential for life-saving benefit may be acceptable (de Jonge and Verweij 2008; Fingert and Varterasian 2006; Curigliano et al. 2008). The ICH E14 guidance asserts that any drug causing mean QTc prolongation >20 ms has a substantially increased likelihood of causing clinical arrhythmic events even in clinical trials and increasingly so in postmarketing use.

To achieve some consistency of QTc risk assessment across anticancer agents while ensuring adequate recognition of their potential therapeutic benefit, one could further characterize the QTc effect of these agents as either "mild to moderate" or "large." A UCI of ΔQTc(max) ≥20 ms at any time point after dosing would be the arbitrary threshold for a large, clinically significant QTc prolongation, while a ΔQTc(max) with a UCI ≥10 ms but <20 ms would constitute a "mild" or "moderate" QTc effect size, depending on the actual numeric value (Sarapa and Britto 2008).

As mentioned earlier, the results of the categorical analysis of QTc outliers (the number and percent of maximum individual absolute QTc and QTc changes from baseline above a threshold value) would generally be of negligible value in oncologic studies due to the small sample size (Sarapa and Britto 2008).

## 9 Conclusion

Many anticancer drugs are associated with significant QTc prolongation, which makes it essential that their proarrhythmic potential be properly evaluated in preapproval development. This reflects the current regulatory expectations for approval of novel anticancer agents, particularly the small molecule chemical entities. While the original ICH E14 guidance for clinical assessment of drug-induced QTc prolongation and its clarifications/revised implementations (ICH E14 Q&A R3) apply well to the vast majority of drugs, its principles are not easy to fully implement in oncology, where population characteristics, tolerance for risk, clinical development practices, and acceptable standards of therapy differ markedly from the norm.

We have proposed that adequate characterization of QTc prolongation and proarrhythmic risk induced by cancer drugs can be made through integrated approaches and outline three possible broad and flexible scenarios for this assessment in drug

development, a "classic ICH E14-type" scenario, a "front-loaded" scenario, and a "full-development" scenario. All of these include an informed use of preclinical cardiac safety pharmacology results, inclusion of some degree of robust ECG monitoring in early phase as well as late phase clinical studies, the possible conduct of a "definitive" QTc (DQT) study (i.e., a "thorough" ECG study which has been suitably modified for oncology application) or a DQT-like study if needed at the appropriate phase of development depending on the model, and very importantly, the benefits of utilizing concentration-QTc (C-QTc) modeling in these studies or from data pooled from different stages of development to better leverage the information obtained at any stage. Additionally we have discussed the various factors that should be considered when selecting one of these scenarios or when determining whether a change needs to be made. We have also summarized the various practicalities to be considered when running ECG assessment trials in cancer patients as well as potential modifications in inclusion/exclusion criteria as well as analysis acceptance criteria in such analyses in oncology patients.

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# Chapter 6
# Expediting Drug Development: Breakthrough Therapy Designation

**Carmen Ladner**

**Abstract** In 2012, Congress approved the Food and Drug Administration Safety Innovation Act (FDASIA), and as part of that act, a new designation was recognized—breakthrough therapy designation. Breakthrough drugs are drugs that are intended alone, or in combination with one or more other drugs, to treat a *serious or life-threatening disease* and for which preliminary clinical evidence suggests that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Drugs assigned breakthrough status are granted fast-track status, more extensive FDA guidance on development of the drug, and eligibility for priority and rolling review by the FDA. As of 2015, a total of 384 requests for breakthrough therapy designation status were received by the FDA, of which 118 (31 %) were granted. This chapter summarizes breakthrough therapy designations and reviews specific examples related to oncology drug development.

**Keywords** Oncology • Food and Drug Administration • Food and Drug Administration Safety Innovation Act • FDASIA • Fast track • Regulatory

The Food and Drug Administration (FDA) has established expedited development and approval pathways to support faster development and approval of drugs intended for serious and life-threatening diseases (Table 6.1). Under the Prescription Drug User Fee Act (PDUFA) of 1992, the FDA established goals to reduce the review time of drug applications by creating a two-tiered system: standard and priority review. Priority review reduces the review timeline to 6 months for drugs demonstrating major improvement over existing therapies or for drugs where there is no existing treatment. To support the increased resources necessary to reduce review timelines, a PDUFA fee to sponsors was introduced. Accelerated approval, codified in 1992, speeds approval of drugs by establishing effectiveness with a

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**Table 6.1** Comparison of FDA's expedited programs for serious conditions

| | Fast track | Breakthrough therapy | Accelerated approval | Priority review |
|---|---|---|---|---|
| Qualifying Criteria | A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR<br>A drug that has been designated as a qualified infectious disease product | A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies | A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates and effect on a surrogate endpoint that is reasonable likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonable likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint) | An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR<br>Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A OR<br>An application for a drug that has been designated as a qualified infectious disease product OR<br>Any application for a drug submitted with a priority review voucher |
| Features | Actions to expedite development and review and rolling review | Intensive guidance on efficient drug development, Organizational commitment, rolling review, and other actions to expedite review | Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit | Shorter clock for review of marketing application (6 months compared with the 10-month standard review) |
| Additional Consider-ations | Designation may be rescinded if it no longer meets the qualifying criteria for fast track | Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy | Promotional materials, confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit and subject to expedited withdrawal | Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing |

*Reference*: FDA Guidance for Industry: Expedited Programs for Serious Conditions, May 2014

surrogate endpoint that is clinically meaningful. In 1997, the Food and Drug Administration Modernization Act (FDAMA) further established methods to speed the availability of drugs to patients with the fast-track program. Drugs with fast-track designation promise treatment in a serious life-threatening disease and have the potential to fill unmet need. Accelerated approval, fast-track designation, and priority review are each unique but commonly intended to accelerate drug development and approval contributing to speed of FDA review of new drugs.

Each of these expedited development and approval paths still requires substantial evidence of proven benefit-risk, which typically means that three phases of clinical investigation and a controlled phase 3 study are needed to support full approval. The exception is accelerated approval which relies on a qualified surrogate endpoint to demonstrate clinical benefit, thereby potentially providing drugs more quickly to patients through conditional approval with a follow-on confirmatory trial post-accelerated approval to establish full approval. This has resulted in feasibility and reproducibility issues as ethical concerns of randomizing patients to placebo or less active or tolerated products post-approval cause clinical trial sponsors to conduct confirmatory studies in nonidentical patient populations to that supporting approval and has at times not resulted in confirmation to support full approval. Fast-track designation and priority review promised more communication between the FDA and sponsors and a reduction in the FDA review by 4 months, respectively, but neither shorten clinical development. While extending some benefits in an effort to provide patients new drugs quickly, limitations exist in these approaches to drug development.

In spite of the benefits of these existing expedited pathways to approval, limitations persist making these approaches less impactful than hoped. In 2011 the FDA was perceived to be too slow to approval and out of sync with growing biomedical innovation (California Healthcare Institute, 2011). Lobbying of US Congress by patient advocacy groups and trade associations resulted in growing pressure on FDA to complement innovation in drug development with subsequent approval of promising new therapies.

Growing experience with targeted therapies and therapeutic breakthroughs provided the possibility to explore a pathway complimentary to existing expedited pathways. Molecular targeted therapies, and its goal to provide personalized health care, advanced the speed for which drugs could be developed. Development and approval in 2011 of vemurafenib (Zelboraf®), a targeted therapy that selectively inhibits the kinase activity of $BRAF^{V600}$ in melanomas, included interactive communication between the FDA and the sponsor (Genentech) and resulted in a clinical development plan conserving patients, resources, and time. Similarly, crizotinib (Xalkori®), an inhibitor of anaplastic lymphoma kinase (ALK) in non-small cell lung cancer (NSCLC), was approved in 2011 based on exceptional response in a rare patient population with a commitment to post-marketing requirements of ongoing randomized confirmatory trials. Vismodegib (Erivedge®), an inhibitor of the hedgehog pathway in metastatic and locally advanced basal cell carcinoma, received full approval in 2012 after a 3-month review due to absence of therapeutic options in an uncommon condition and based on impressive efficacy seen in phase 2. Although vismodegib is a targeted agent, no companion diagnostic was necessary

for development because the vast majority of basal cell carcinomas express the target. Ivacaftor (Kalydeco®) targets a defective form of the transmembrane regulatory (CFTR) protein (G551D mutation in CFTR gene) in cystic fibrosis. Full approval was achieved in 2012 after a 3-month review with consultation of the Center for Devices and Radiological Health (CDRH) to confirm adequacy of available tests to identify the gene mutation and ensure FDA-cleared diagnostic tests were available.

Breakthrough therapy designation emerged from conversations within the oncology community including FDA, patient organizations, academia, and industry, and the concept was initiated by Friends of Cancer Research (FOCR) in partnership with the Brookings Institution at the Conference on Clinical Cancer Research (CCCR) in November 2011 (Fleming et al. 2011). Through the FDA Safety and Innovation Act (FDASIA) and PDUFA V, legislation was enacted into law in July 2012 to "expedite the development and review of such drug if the drug is intended … if the drug is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development …" (FDA 2014). In contrast to other expedited pathways, breakthrough therapy designation can occur early in drug development complimenting existing expedited pathways to accelerate drug development and approval. The designation of breakthrough therapy addresses expedition of drug development by shortening the time needed to conduct the major clinical trial to support substantial evidence and minimizes the number of study participants placed on comparatively ineffective treatment control regimens. The breakthrough therapy designation encouraged both the FDA and sponsors to reevaluate drug development in its traditional phase 1-2-3 process using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate which may result in fewer, smaller, or shorter clinical trials for the intended patient population or targeted subpopulations.

In November 2012 FOCR issued a brief on "Developing Standards for Breakthrough Therapy Designation" focusing on a proposal for criteria for breakthrough therapy designation, applying these criteria to different categories of potential breakthrough therapies, and discussing the process by which FDA could make a breakthrough therapy designation. In addition to more effective and efficient drug development, breakthrough therapy designation offers increased interaction with the FDA to facilitate approvals of drugs. A framework for intense engagement between the FDA and sponsors includes meetings held throughout drug development, timely advice, and communication to ensure collection of nonclinical and clinical data necessary to make approval as efficient as possible. Additionally, involvement of senior managers and experienced review staff from the FDA is assigned to work in a collaborative, cross-disciplinary review, and steps are taken to ensure the clinical trial design is efficient, is practicable, and is scientifically appropriate, allowing for the minimization of patients exposed to potentially less efficacious treatment.

Prior to the FDA Guidance for Industry on "Breakthrough Therapy Designation" defining criteria and processes, industry was already engaging the FDA with proposals to receive the designation for a number of new molecular entities. By September 2013, the FDA received 94 requests for breakthrough therapy designation, of which 28 were granted and 42 denied (10 granted for oncology; 12 for non-oncology). Two broad categories of drugs submitted for designation comprised those that are "game changers" with impressive clinical data and those whose sponsors had high hopes but unimpressive data. Initially, drugs granted designation were not representative of the types of drugs that may be granted designation in the future. Although considered game changing based on impressive clinical data, these designations included drugs in late stages of development and previously approved drugs seeking approval of additional indications or line extensions.

As of 31 December 2015, 319 designation requests had been submitted to the Center for Drug Evaluation and Research (CDER), and 65 breakthrough therapy designations were granted (Table 6.2). Fewer requests were received by the Center for Biologics Evaluation and Research (CBER): 65 received and 18 granted. As seen by the statistics, the approval rate is low and about similar by the different centers.

The first drug with breakthrough therapy designation to receive approval was Gazyva® (obinutuzumab) for the use in combination with chlorambucil to treat patients with previously untreated chronic lymphocytic leukemia (CLL). As communicated in FDA's press release in 1 November 2013,

> "The designation was requested by the Sponsor (Genentech) after the biologic license application (BLA) to support marketing approval was submitted to the FDA. The FDA can designate a drug a breakthrough therapy at the request of the sponsor if preliminary clinical evidence indicates the drug may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases."

Genentech discussed the possibility of an application for breakthrough therapy designation based on the phase 3 data (stage 1) at the pre-BLA meeting and submit-

**Table 6.2** Breakthrough therapy designation requests

| Breakthrough therapy designation requests as of 31 December 2015 | | | | |
|---|---|---|---|---|
| | Requests received | Requests granted | Requests denied | Withdrawn |
| CDER | 319 | 100 | 160 | 46 |
| CBER | 65 | 18 | 42 | 5 |
| FDA Total | 384 | 118 | 202 | 51 |

*Reference*: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/UCM481539.pdf
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/UCM481540.pdf
http://www.fda.gov/downloads/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/UCM485142.pdf
http://www.fda.gov/downloads/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/UCM485141.pdf

ted the application following the Type B meeting. Gazyva® met the criteria of treatment of a serious condition, early clinical evidence, and substantial improvement over an existing therapy. CLL is a life-threatening hematological cancer without a cure, and Gazyva® demonstrated evidence of substantial benefit over existing therapy chlorambucil. A phase 3 randomized study against the approved standard of care for patients who cannot tolerate more aggressive therapies was conducted with the outcome of the head-to-head comparison against Rituxan® (stage 2) expected during the review of the BLA (Fig. 6.1). Gazyva® in combination with chlorambucil demonstrated a substantial improvement vs. chlorambucil at stage 1 (15.6 month improvement in median progression-free survival), and in general the toxicity profile of Gazyva® was similar to Rituxan®.

Breakthrough therapy designation provided enhanced interaction and collaboration with FDA as there was visible and consistently available senior FDA management support, more frequent interactions, and timely resolution of questions or issues, joint discussions between FDA reviewers and Genentech/Roche across clinical and chemistry, and manufacturing and controls (CMC) disciplines, all leading to a common understanding of the data and development strategy. Gazyva® was approved 6 weeks earlier than the PDUFA action date (Fig. 6.2). Other benefits to the breakthrough therapy designation for Gazyva® included launching with clinical supply in advance of commercial supply availability. This was possible because the clinical supply met the specifications of the commercial supply. This required close collaboration with FDA and alignment between manufacturing capabilities with clinical development of a promising molecule, planning for launch readiness 3–4 months after BLA/NDA submission, and preparedness to seek/consider fast-track rolling submission.

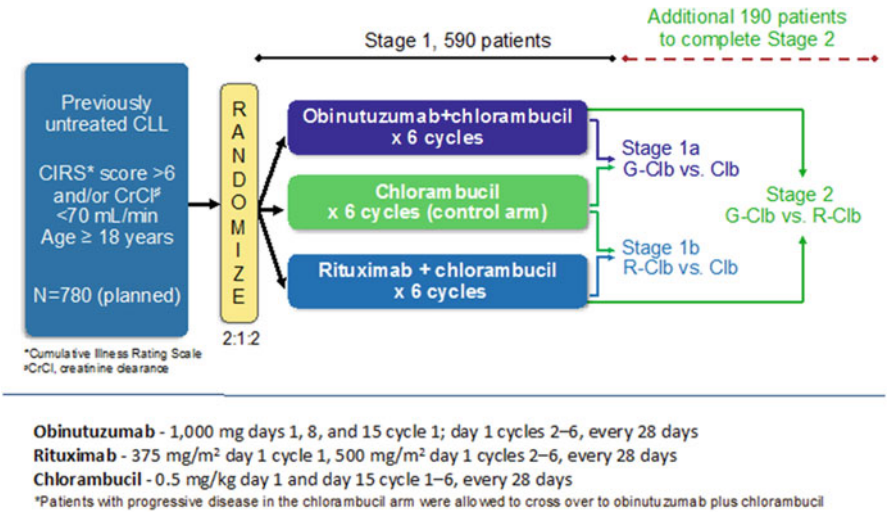


**Fig. 6.1** The phase 3 study design for study CLL11 (Jones 2014)

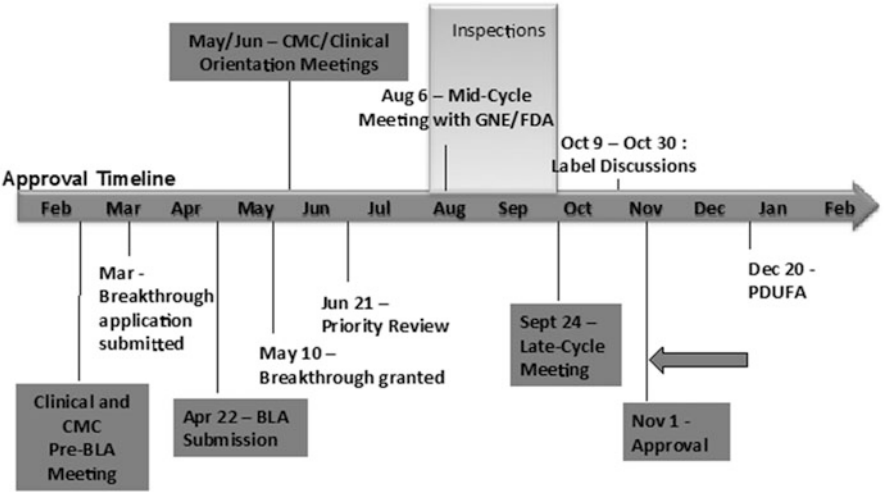


**Fig. 6.2** Insights from FDA review interactions from BLAs in 2013 (Jones 2014)

Breakthrough therapy designation has been widely accepted by industry as a means to collaborate more closely with FDA and provide promising therapeutics to patients with serious, life-threatening diseases and unmet need. However, challenges remain for both industry and FDA. To date, the FDA has rejected approximately two-thirds of designation requests, mostly related to failure to demonstrate substantial drug effect. This may be attributable to a lack of clear understanding by sponsors of criteria or qualification to meet the requirements for designation. Alternatively, it may be a perception, or hope, by sponsors that their drugs demonstrate better efficacy than the data supports. Although the FDA has attempted to provide such criteria as a part of FDASIA, within a draft guidance issued June 2013 and in a final guidance issued May 2014, the current guidance does not clearly define parameters for the level of improved efficacy or safety that would qualify a drug for breakthrough status. Sponsors currently rely on incremental experience and attempt to either receive or be denied designation of their own drugs or disclosure by other sponsors which has been typically limited. At a FOCR briefing in May 2014, CDER Director Janet Woodcock noted that guidance is forthcoming to assist sponsors in determining whether their drug meets the hurdle of breakthrough therapy designation (Sutter 2014). At the conference, which focused on oncology, Woodcock stated that designees typically showed 50 % risk reduction, such as disease progression, over a comparator. However, while the magnitude of effect has the greatest impact on obtaining breakthrough status, the requirements are still difficult to describe as multiple elements influence the data, e.g., sample size, size of unmet need patient population, and whether there are any other available approved therapies (Table 6.3).

An evaluation of the breakthrough therapy designation program after 2 years of its introduction (Table 6.2) was presented at the November 2014 FOCR Brookings

**Table 6.3** Characteristics of drug products designated and rejected as breakthrough therapies in 2014

| Category | Breakthrough designees | Breakthrough denials |
|---|---|---|
| Average enrollment of trials submitted in request | 184.3 (median: 88) | 114.4 (median: 51) |
| Average number of trials submitted in request | 1.52 | 1.23 |
| Maximum trial phase | 1.94 | 1.73 |
| Request included randomized or blinded trials | 56 % randomized/32 % blinded | 56 % randomized/46 % blinded |
| Available therapy for the disease | 64 % | 49 % |
| Rare and/or orphan | 60 % | 55 % |
| Genetic/targeted therapy | 38 % | 20 % |
| *Note*: *Based on total of 50 breakthrough therapy designations and 86 denials analyzed* | | |
| *Genetic component to therapy* | | |
| *Type of therapy* | *Designees* | *Denials* |
| With a genetic component in the indication | 19 | 17 |
| No genetic component in the indication | 31 | 69 |
| *Orphan vs. non-orphan* | | |
| *Status* | *Designees* | *Denials* |
| Median enrollment in highest trial phase submitted with orphan status | 69 | 47 |
| Median enrollment in highest trial phase submitted without orphan status | 161 | 56 |
| *Alternative therapies available* | | |
| *Availability of alternative* | *Designees* | *Denials* |
| Approved and unapproved therapy available | 9 | 10 |
| Only approved therapy available | 23 | 32 |
| Only unapproved therapy available | 14 | 28 |
| No alternative therapy available | 4 | 16 |
| *Maximum trial phase of evidence in the designation request* | | |
| *Phase* | *Designees* | *Denials* |
| 0 | 2 | 1 |
| 1 | 9 | 27 |
| 2 | 29 | 47 |
| 3 | 10 | 7 |
| No data submitted | 0 | 4 |
| *Median trial enrollment* | | |
| *Phase* | *Designees* | *Denials* |
| 1 | 19 | 28 |
| 2 | 73 | 62 |
| 3 | 161 | 147 |
| Other (requests that included expanded access data) | 16 | 31 |

*Reference*: Dougherty et al. (2014)

Conference on Clinical Cancer Research which provides some insight into FDA's thinking on criteria that meet the breakthrough hurdle. Starting in 2012, more than 240 designation requests have been received and 69 have been granted. Orphan drug status did not affect success of obtaining designation, but targeted therapies or those with a genetic component were more successful. However, it is interesting that the lack of available therapy for a disease, while likely an advantage, did not impact designation success as more designees had alternative therapies available than the denials. There is consistency between the FDA review divisions and the Medical Policy Council (MPC), the body responsible for the oversight of the designation process, in their recommendations. In greater than 90 % of cases, the MPC agreed with the division recommendation to grant or deny a designation. In 47 of 50 instances, the division recommendation and the MPC agreed, while in 79 of 87 instances, the division recommended denial and the MPC agreed. In two cases, the division recommended denial and the MPC recommended designation of which both were granted. There were six cases in which the division recommended designation, and the MPC denied all six.

While there is commitment for more interactive communication between FDA and sponsors through development, review, and approval of products, there has been impact to the FDA review staff's workloads by the large number of designation requests. It is not clear how many reviewer positions are needed to manage breakthrough therapy designation requests along with other projects. FDA will complete further evaluation of resources in the next 6 months.

With expedited drug development within the clinic for products holding breakthrough therapy designation come the challenges of coordinating other important aspects of drug development that are necessary to bring promising therapeutics to patients. Alignment of the clinical development pathway to manufacturing processes necessary to support launch with commercial material and companion diagnostic development to support molecular targeted therapies can be challenging under standard drug development conditions, with each potentially becoming the rate-limiting step to moving products to market at different time points over the course of product development. It is important to note that the breakthrough therapy designation program focuses on clinical drug development although FDA recognizes the pressure expedited clinical plans put on CMC and companion diagnostic development.

With breakthrough therapy, pressure is placed on industry to incorporate CMC development into expedited clinical development timelines. There is a lack of clarity on what CMC processes may be supportive of marketing approval and whether some processes could be provided post-marketing to match the pace of clinical drug development under breakthrough therapy designation. In the general considerations of the May 2014 FDA Guidance for Industry "Expedited Programs for Serious Conditions—Drugs and Biologics," sponsors are encouraged to start communicating with the FDA early to ensure that a plan for manufacturing development and timing of submissions will meet FDA expectations to support marketing approval. Upon designation of breakthrough therapy, FDA will review the sponsor's proposal for manufacturing under expedited development to ensure product of acceptable

quality is available when approved. This proposal must include the estimated market demand, the manufacturing facilities providing commercial product, and a life cycle approach to process validation. As with clinical drug development, under breakthrough therapy designation, frequent communication between the FDA and the sponsor is expected. Sponsors should be aware that breakthrough products are subject to quicker application reviews, so earlier submission of the CMC section including the product quality section may be required to match clinical review and to support inspection activities. Often products with breakthrough therapy designation are reviewed under fast-track status allowing a rolling submission of the market application and thereby facilitating an earlier CMC review. Flexibility on the FDA's part may be extended on which CMC components are critical for review to support the marketing approval vs. components subject to review after approval as post-marketing commitments. This is a case-by-case determination which considers product characteristics, seriousness of the condition and medical need, manufacturing processes, the robustness of the sponsor's quality system, and the strength of the sponsor's risk-based quality assessment. Due to the earlier need than standard drug development, CMC issues identified for breakthrough products include product scale-up, optimization, characterization, and validation, the stage of analytical development, stability data and expiration dating, and potential elevation in the role of comparability data. Because there is simply less time to generate as much knowledge and experience as obtained with standard drug development, processes, lots, and methods must be bridged to fill this gap. Breakthrough therapy designation will not warrant sponsors' exclusion of required data to ensure quality of product, e.g., shelf life cannot be justified without stability data, and to adhere to quality principles, sponsors may have to negotiate submitting stability updates during the review of the marketing application to support shelf life upon approval (Schacter 2014).

Codevelopment of a drug and its companion diagnostic to undergo review and approval for use in the market at the same time is an issue further exacerbated by an expedited clinical development pathway. Many of the drugs obtaining breakthrough therapy designation are molecular targeted agents that personalize treatment to specific patient populations as identified through companion diagnostics. Changes to the regulatory requirements for diagnostics are necessary to align timelines with accelerated clinical development. During the FOCR and Alexandria Real Estate Equities forum on the codevelopment of drugs and companion diagnostics, held 6 September 2013, two panels discussed possible approaches to expedited development of a companion diagnostic device intended for use with a breakthrough therapy. The first panel "Development Strategies for Breakthrough Therapy Diagnostics" focused on optimal processes and proposed novel risk-based approaches to drug/diagnostic codevelopment allowing diagnostic development to stay aligned with the pace of expedited clinical development of breakthrough therapy drugs. Akin to the original FOCR—Brookings Institute CCCR in November 2011, the panel introduced five proposals in a multi-stakeholder document, "A Risk-based Approach for In Vitro Companion Diagnostics Device FDA Approval Process Associated with Therapies that have Breakthrough Designation":

1. Automatic designation of in vitro companion diagnostic (IVD) devices for use as part of a breakthrough drug approval as eligible for priority review
2. The use of highly coordinated administrative processes and management commitments for review of IVD companion diagnostics associated with breakthrough therapies that are commensurate with those processes offered for breakthrough therapies
3. The use of risk-based processes to determine required companion diagnostic analytical studies for each assay type at time of premarket approval (PMA) or 510(k) filing
4. The use of risk-based approaches to determine requirements for data and testing related to quality systems, manufacturing processes, and software testing and documentation
5. The use of a "continued access" supplement IDE to enable a broader set of labs to be ready for testing immediately upon contemporaneous approval of the companion diagnostic and therapeutic product

During the second panel, "Policy and Practices to Facilitate Personalized Medicine," Jeff Shuren, Director of the Center for Devices and Radiological Health (CDRH), stated that the CDRH is working on formalizing a policy shifting certain premarket requirements to post-market, much like the accelerated approval process for drug development (FOCR 2013). Although CDRH's Liz Mansfield acknowledged the absence of specific breakthrough therapy designation program recommendations for diagnostics, there are processes existing related to codevelopment and consideration being made for an investigational device exception supplement (McNeil 2013).

In April 2014, the FDA CDRH issued the Guidance for Industry: Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions. The draft guidance proposes a voluntary expedited access PMA (EAP) program containing features from CDRH's Innovation Pathway, piloted in 2011 to facilitate the development and expedite the review for breakthrough technologies. The pilot intends more interactive communication between FDA and the sponsor during device development and more interactive review of Investigational Device Exemption (IDE) applications and PMA applications. FDA and the sponsor work closely to create a data development plan specific to the device that outlines all data the sponsor will collect, premarket, and post-market, to support device approval. FDA's approval of an EAP device demonstrates acceptance of a higher degree of uncertainty about the benefit-risk profile but with enough data to provide assurance that safety and efficacy are maintained under statutory standards for premarket approval. Certain data continues to be collected as post-market requirements to build the safety and efficacy profile and reliability of the device for its intended use. The EAP program intends to bring the development timelines of device and breakthrough therapy together to enable both drug and companion diagnostic getting to patients at the same time.

With the coveted designation of breakthrough therapy designation comes the possibility of having the designation taken away. FDA's Guidance for Industry "Expedited Programs for Serious Conditions—Drugs and Biologics" May 2014 designates the breakthrough status based on preliminary clinical evidence, and as data is generated, it must continue to support this evidence to maintain the designation. "If the designation is no longer supported by subsequent data, FDA may rescind the designation." This supports the original principle of the designation to provide opportunity for faster drug development and approval to provide beneficial therapies to patients in need but also focuses FDA resources on products that potentially have the greatest impact to patients. Per the guidance, significant resources are provided to work closely with sponsors on the development, review, and approval of products with the designation; therefore, continuance to meet the designations' qualifying criteria is mandatory to support FDA prioritization of their own resources.

To date, the FDA has rescinded two breakthrough therapy designations in the competitive hepatitis C landscape. Gilead advanced its breakthrough product Sovaldi® as a component of a combination antiviral treatment for the treatment of hepatitis C infection in patients with virus genotypes 1, 2, 3, or 4 to approval on 6 December 2013. Abbvie's Viekira Pak®, a 4-drug combination of new drugs ombitasvir, paritaprevir, dasabuvir, and previously approved ritonavir, was approved 19 December 2014, also a product with breakthrough therapy designation status at the time of approval, for treatment of patients with chronic hepatitis C virus genotype 1 infection and cirrhosis. Approval of these new treatments reduced the unmet need, and for the first time, the FDA rescinded the designation from Merck's investigational oral combination closely followed by rescission of Bristol-Myers Squibb's combination of daclatasvir with two other direct-acting antivirals. While multiple products under development may hold the designation, the status can be quickly removed once another product(s) reaches the market and fills the unmet need. This may result in longer review and approval timelines for products losing designation status. Maintaining the status in the presence of another approved product would require continuing to meet the qualifying criteria such that there is differentiation between products.

Through FDASIA and PDUFA V legislation, breakthrough therapy designation was initiated to address unmet medical need in patients with serious conditions and committed to faster drug development and approvals for products that promise to yield impressive game-changing evidence and data over existing available therapies. As part of the 21st Century Cures, a collaborative and multi-faceted initiative launched on 20 April 2014, by Representatives Fred Upton (R-MI), chair of the House and Energy commerce Committee, and Diana DeGette (D-CO); updates to the breakthrough therapy program will continue to streamline the drug development process. Sponsors have been receptive to the breakthrough therapy program, and industry has expressed positively to the Title I, Subtitle C, Section 1041 (A Focus on Patients: Approval of Breakthrough Therapies), proposal of the 21st Century Cures Act by which US Congress will facilitate transformation to the pathways for new treatment approved and marketed in the USA. "Pharmaceutical Researchers and Manufacturers of America (PhRMA) has long supported the FDA's appropriate

use of innovative approaches and regulatory flexibility to establish the safety and efficacy of innovative medicines to address unmet medical needs. We strongly supported the passage of FDASIA, which enhanced the authority of FDA to consider appropriate scientific data, methods, and tools, and to expedite development and access to novel treatments for patients with a broad range of serious or life-threatening disease or conditions" (Gray 2015).

The Cures Act builds upon FDASIA to allow FDA to approve drugs based on "early-stage clinical safety and effectiveness data that provide sufficient evidence for approval of the drug as safe and effective." With an early approval, FDA is granted authority to require sponsors to continue assessment of the safety and effectiveness of the drug in the post-marketing setting. Post-marketing commitments, introduced in the 2007 FDA Amendment Act, have not always been adhered to by sponsors, prompting some commitments to be established as post-marketing requirements (PMRs), per FDASIA, with monetary penalties employed for failure to comply. Additionally, the Cures Act will enable FDA to withdraw drugs from the market for failure to complete PMRs. The bill further states that the breakthrough therapy guidance for industry will be updated within a year (Gaffney 2015).

The breakthrough therapy designation program is meeting the mission envisioned in those early conversations within the oncology community that was comprised of FDA, patient organizations, academia, and industry. In a new CDER Manual of Policies and Procedures released 9 March 2015, titled "Good Review Practice: Review of Marketing Applications for Breakthrough Therapy-Designated Drugs and Biologics that Are Receiving and Expedited Review," an expedited review of a breakthrough therapy will reduce the review timeline by at least 1 month before the PDUFA goal date should applicable criteria be met. Not all breakthrough products will receive an expedited review and criteria consisting of the following: a preliminary review of results from clinical trials must indicate that the drug has demonstrated substantial improvement over existing therapies, marketing application must be designated as a priority review, and review team must have determined that a first cycle approval is likely. If criteria are met, there are other factors that may influence whether an expedited review is granted or not, such as resources to expedite the review are not available because of competing public health priorities (e.g., anthrax, Ebola, influenza), and an advisory committee meeting is needed for reasons such as clinical trials results or safety issues. During the review it is possible for the expedited review to be deemed no longer appropriate resulting in a reversion to the original priority review timeline.

The greatest impact, as hoped, has been to the patients. Based on game-changing, compelling data Pfizer's palbociclib, a drug developed to treat women with HER2-negative-advanced breast cancer, was granted breakthrough therapy designation. A doubling of progression-free survival (PFS), from 10.2 months with letrozole to 20.2 months with palbociclib in combination with letrozole, was reviewed and approved by FDA in less than 6 months and more than 2 months in advance of its PDUFA action date. The close working relationship between FDA and Bristol-Myers Squibb brought Opdivo® (nivolumab) to patients in record time as FDA approved the product for squamous NSCLC 3 months earlier than the PDUFA

action date. This speed was facilitated by establishing a plan through the breakthrough therapy designation that provided FDA insight into the overall survival data prior to the sponsor from a randomized trial to giving FDA confidence in the early clinical evidence generated in a single-arm trial. This innovation, data, and commitment by many stakeholders including regulators and industry to bring life-altering drugs to patients based on early clinical evidence have come to realization through the FDASIA 2012 breakthrough therapy designation program. The 21st Century Cures Initiative will continue to build on this success further abbreviating the drug development process and the regulatory framework.

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# Chapter 7
# Pharmacokinetics and Pharmacodynamics of Tyrosine Kinase Inhibitors

**Ana Ruiz-Garcia and Shinji Yamazaki**

**Abstract** The importance of modeling and simulation approach is well recognized and established in the pharmaceutical industry. Establishing exposure-response relationships for new molecular entities's efficacy and toxicity using a modeling and simulation approach has been shown to be critical in many aspects of regulatory decision making, including labeling. Among modeling and simulation approaches, pharmacokinetic-pharmacodynamic (PKPD) modeling is a powerful approach linking drug exposures to biological and pharmacological responses, providing a quantitative assessment of in vivo drug potency with mechanistic insight on drug action.

Protein tyrosine kinases (PTKs) play a key role in the regulation of a variety of transduction pathways. This protein family has proved to have a key role in cancer cells which has resulted in the design of highly selective tyrosine kinase inhibitors (TKIs) in oncology. This chapter presents a comprehensive overview of the PKPD work done for TKIs with preclinical data as well as the analyses performed in the clinical setting.

For the pre-clinical PKPD models, an appropriate PKPD model is generally selected based upon the underlying pharmacological mechanisms. This chapter will present examples of preclinical models for relationships between drug exposure and biomarker responses and relationships between drug exposure and antitumor effect. The PKPD modeling of clinical efficacy endpoints presented in this chapter included event free survival, cytogenetic and molecular responses, time to tumor progression, overall survival, objective response rate, tumor size changes and biomarker changes over time. The PKPD modeling of safety endpoints summarizes analyses preformed for fatigue, neutropenia, blood pressure changes, diarrhea, rash, and QT prolongation.

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## 1 Introduction

Protein tyrosine kinases (PTKs) play a key role in the regulation of a variety of transduction pathways. These proteins are frequently deregulated in cancer, by constitutive activation, mutation, or overexpression. Shaw et al. (2013) indicated that chromosomal rearrangements that lead to oncogenic kinase activation are observed in several cancers. These tumors express activated fusion kinases that drive the initiation and progression of malignancy and often have a considerable response to small-molecule kinase inhibitors, which validates these fusion kinases as "druggable" targets. The key role of PTKs' function in cancer cells has resulted in the design of highly selective tyrosine kinase inhibitors (TKIs). There are more than 90 known protein kinase genes: 58 encode transmembrane receptor tyrosine kinases (rTKs) distributed into 20 subfamilies and 32 encode cytoplasmic, non-receptor tyrosine kinases in 10 subfamilies (Baselga and Arteaga 2005). rTKs include an extracellular domain, a transmembrane domain, and a catalytic intracellular domain. Upon activation, rTKs dimerize and autophosphorylate their intracellular domain, initiating downstream signaling that commonly includes non-receptor tyrosine kinases. Non-receptor TKs include a catalytic domain and a regulatory domain, which vary for each family. A list of TKIs approved to date is summarized in Table 7.1.

## 2 Translational Pharmacology in Oncology

Human tumor xenografts implanted subcutaneously into immunocompromised mice have played a significant role in drug discovery and development of anticancer agents over the past several decades. The advantages and disadvantages of the use of xenograft models have been extensively discussed (Kerbel 2003; Kelland 2004; Peterson and Houghton 2004; Burchill 2006; Hollingshead 2008; Richmond and Su 2008). Although human tumor xenograft models had been historically developed to evaluate in vivo antitumor potency of cytotoxic anticancer agents, they have also recently been used to evaluate an in vivo antitumor efficacy of molecularly targeted agents such as TKIs (Kelland 2004; Burchill 2006; Hollingshead 2008), often in conjunction with a mathematical modeling approach to facilitate translation (Bueno et al. 2008; Yamazaki et al. 2008; Choo et al. 2010; Salphati et al. 2010; Yamazaki et al. 2011a, b; Wong et al. 2012; Yamazaki et al. 2014).

TKIs are prescribed for a wide variety of solid tumors, whereas both hematopoietic and lymphoid malignances can also be successfully treated with TKIs. Hematological malignancies may derive from either of the two major blood cell lineages: myeloid and lymphoid cell lines. Roeder et al. proposed a new theoretical framework of tissue stem organization with a dynamic quantitative model of stem cell organization, which

**Table 7.1** TKIs classification

| Type | Family | Kinase | Drug name |
|---|---|---|---|
| Membrane rTKs | *ALK* | ALK, LTK | Crizotinib |
| | *AXL* | AXL, MERTK, TYRO3 | |
| | *DDR* | DDR1, DDR2 | |
| | *EGFR* | EGFR, ERBB2 (HER2), ERBB3, ERBB4 | Erlotinib, afatinib, cetuximab, gefitinib, lapatinib, panitumumab, trastuzumab, vandetanib |
| | *EPH* | EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA7, EPHA8, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6 | Ponatinib |
| | *FGFR* | FGFR1, FGFR2, FGFR3, FGFR4 | Ponatinib |
| | *INSR* | IGF1R, IGF2R, INSR, INSRR | |
| | *MET* | MET, MST1R (RON) | Crizotinib, cabozantinib |
| | *PDGFR* | CSF1R, FLT3, KIT (CD117), PDGFRA, PDGFRB | Sunitinib, axitinib, pazopanib, regorafenib, ponatinib, dasatinib |
| | *ROR* | ROR1, ROR2 | |
| | *TIE* | TIE1, TEK (TIE2) | Ponatinib |
| | *TRK* | NTRK1, NTRK2, NTRK3 | |
| | *VEGF* | FLT1 (VEGFR1), FLT4 (VEGFR2), KDR (VEGFR3) | Axitinib, sunitinib, sorafenib, bevacizumab, pazopanib, pegaptanib (wet macular degeneration), ranibizumab, vandetanib, regorafenib, ponatinib, cabozantinib, aflibercept |
| | *Other genes:* | MUSK, PTK7, RET, ROS1, RYK | Ponatinib, vandetanib, regorafenib, cabozantinib |

(continued)

**Table 7.1** (continued)

| Type | Family | Kinase | Drug name |
|---|---|---|---|
| Cytoplasmic TKs | *ABL* | ABL1, ABL2 (ARG) | Imatinib, nilotinib, dasatinib, bosutinib, ponatinib |
| | *ACK* | TNK1, TNK2 (ACK1) | |
| | *CSK* | CSK, MATK | |
| | *FAK* | PTK2 (FAK), PTK2B (PYK2) | |
| | *FES* | FER, FES | |
| | *FRK* | FRK, PTK6 (BRK), SRMS | |
| | *JAK* | JAK1, JAK2, JAK3, TYK2 | Ruxolitinib (myelofibrosis), tofacitinib (rheumatoid arthritis) |
| | *SRC-A* | FGR, FYN, SRC, YES1 | |
| | *SRC-B* | BLK, HCK, LCK, LYN | Ponatinib, dasatinib |
| | *TEC* | BTK, ITK, TEC, TXK | Ibrutinib |
| | *SYK* | SYK, ZAP70 | Fostamatinib (rheumatoid arthritis, autoimmune thrombocytopenia and lymphoma) |

allows the quantitative characterization of anticancer efficacy nonclinically in the stem cell organization (Roeder and Loeffler 2002; Roeder et al. 2005). However, since tumors of the hematopoietic and lymphoid tissues affect the blood, bone marrow, lymph, and lymphatic system, subcutaneous nonclinical xenograft models may not be an appropriate model to evaluate this type of cancerous diseases.

From the translational standpoint, since TKIs are designed to interfere with specific molecular pathways, different pathway-related pharmacodynamic endpoints could directly or indirectly be correlated with a measure of drug exposure, i.e., unbound drug concentration at the target site, and ultimately with antitumor response. Collectively, a rapidly growing emphasis is being placed upon the collection and incorporation of biomarker endpoints to translate observed pharmacology response from nonclinical models to cancer patients.

To achieve a reliable nonclinical-to-clinical extrapolation of in vivo antitumor efficacy of molecularly targeted agents, it is critical to select the appropriate in vivo nonclinical model. Thus, the use of a given human tumor cell line will require consideration of the molecular pathway and the relevant genetic events occurring in the intended patient population (i.e., mutations, amplification, overexpression or translocation of oncogenic proteins). In addition, it is important to choose the most appropriate nonclinical experimental conditions, such as dosing regimen, formulation, treatment period, number of animals, frequency of data collection, etc. (Hollingshead 2008). Last, there are important assumptions required for a reliable nonclinical-to-clinical extrapolation of antitumor efficacy. One of the main assumptions is that the tumor microenvironments are physiologically and functionally comparable between subcutaneous tumor xenograft models and human tumors, growing in either an organ or a group of tissues spread across the body. This assumption also presumes similar overall unbound drug distribution into tumors or target sites between nonclinical models and the clinical setting. Differences in baseline (untreated) tumor growth rate between nonclinical models and cancer patients may have a significant impact on the quality of the nonclinical-to-clinical extrapolation. The most important question in translational pharmacology is whether the relationships between drug exposure, biomarker endpoints, and pharmacological effects can be quantitatively extrapolated from nonclinical models to cancer patients. Figure 7.1 summarizes two key translational pharmacokinetic-pharmacodynamic

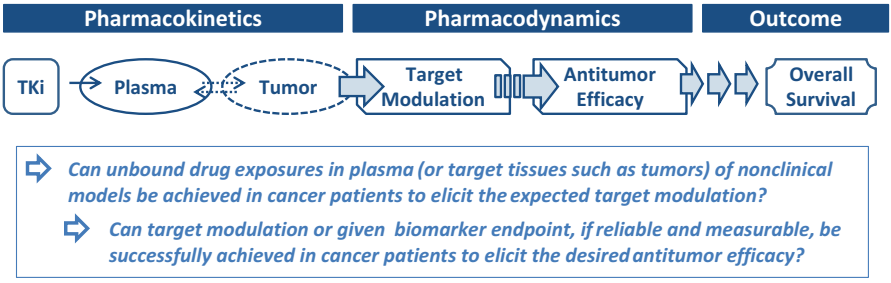



**Fig. 7.1** Two key aspects for translational PKPD understanding from nonclinical models to the clinic

(PKPD) aspects that need to be carefully examined in cancer patients when considering the translational value from nonclinical models to the clinical setting.

When new molecular entities (NMEs) are able to meet these two criteria in the clinic, clinical development success or attrition could be reasonably well predicted through translational pharmacology. This should minimize attrition due to efficacy, which is often high in early drug development. Accordingly, the pharmaceutical industry is moving toward gaining a deeper understanding of translational pharmacology by proactively utilizing more quantitative and mechanistic modeling and simulation approaches early in the drug development process (Morgan et al. 2012).

## 3 Nonclinical PKPD Knowledge

A variety of different PKPD models have been proposed and used to characterize the PKPD relationship of TKIs in nonclinical models (Sheiner et al. 1979; Dayneka et al. 1993; Levy 1994; Mager et al. 2003; Bernard et al. 2012; Felmlee et al. 2012). An appropriate PKPD model is generally selected based upon the underlying pharmacological mechanisms, although a "fit-for-purpose" model is often utilized to estimate in vivo drug potency. To understand quantitative PKPD relationships of TKIs, the application of PKPD modeling can be typically divided into two main tiers: (1) PKPD relationships between drug exposure and biomarker responses, such as target modulation in nonclinical models, and (2) PKPD relationships between drug exposure and antitumor effect, such as xenograft tumor growth inhibition.

### *3.1 Evaluation of Drug Exposure-Biomarker Endpoint Relationships*

The sigmoidal $E_{max}$ model may be the most popular and simple model to characterize PKPD relationships for biomarker endpoints (Hill 1910; Wagner et al. 1968; Levy 1994; Gabrielsson and Weiner 2000; Felmlee et al. 2012). Since the sigmoidal effect model does not take into account any time delays (i.e., the so-called hysteresis) between the emergence of drug concentrations and biomarker endpoints, the model can be of value when biomarker endpoints change closely parallel drug concentrations, without any discernible time delay. However, target modulation often lags behind the time course of drug concentrations. In these circumstances, the estimate of drug potency from PKPD data can be biased. In order to account for the time delay of the biomarker endpoint, several PKPD models accounting for lag times have been proposed to estimate in vivo drug effect (Sheiner et al. 1979; Dayneka et al. 1993; Gabrielsson and Weiner 2000; Mager et al. 2003; Felmlee et al. 2012). Among these, two PKPD models, the link model and the indirect response model, have mainly been applied to characterize the PKPD relationships of TKIs in nonclinical models. The *link model* assumes that the rates of onset and offset of biomarker endpoints are governed by the rate of drug distribution to and

from a hypothetical effect site (the *biophase*) remote from plasma. This implies that the drug distribution to the biophase can be a rate-limiting step in the biomarker endpoint. Subsequently, PKPD parameters, such as $E_{max}$ and $EC_{50}$, are determined by a sigmoidal $E_{max}$ model built on the estimated drug concentration in the hypothetical biophase and the observed biomarker endpoint in the target organ (e.g., tumor). The *indirect response model*, which is based upon the turnover concept, assumes that the delay in biomarker response is caused by the time needed for changes in rates of formation ($k_{in}$) or degradation ($k_{out}$) to be fully reflected in the physiological and pharmacological responses (Dayneka et al. 1993; Jusko and Ko 1994). The indirect response model can thus account for known physiology. As summarized below, TKIs are generally assumed to inhibit phosphorylation rates of their targets or surrogate biomarkers (i.e., $k_{in}$) in many cases because of their inhibition mechanism (e.g., ATP-competitive inhibition). This makes their pharmacological response a good candidate for representation by an indirect response model.

## 3.2 Evaluation of Drug Exposure-Antitumor Effect Relationships

For tumor growth and tumor growth inhibition, one of the main objectives of mathematical modeling is to accurately describe temporal tumor growth curves in each animal and/or each group of nonclinical models. Historically, in vivo tumor growth curves in nonclinical (xenograft) models have been described by exponential growth equations in the early phase, followed by a linear growth that eventually reaches a plateau (Gompertz 1825; Bissery et al. 1996). The inhibition in the late phase of growth is considered to be caused mainly by insufficient supplies of oxygen and nutrients, due to the large tumor mass. Thus, a full-temporal profile of in vivo tumor growth curves can be described by either the Gompertz model (Gompertz 1825) or an exponential model with logistic growth, which constrains the tumor trajectory to an attainable maximal tumor volume (Hart et al. 1998). In PKPD data analysis, three different tumor growth models have mainly been applied to characterize tumor growth curves in untreated (vehicle control) groups : (1) the first-order exponential growth model without a logistic function (exponential growth), (2) the first-order exponential growth model with a logistic function (logistic growth), and (3) the exponential-to-linear growth switch model (characterized by an exponential growth followed by a linear growth) (Skipper et al. 1970; Hart et al. 1998; Simeoni et al. 2004; Bernard et al. 2012). Subsequently, in drug-treated groups, the sigmoidal $E_{max}$ model is often incorporated into the tumor growth parameters to estimate in vivo antitumor effect. This type of drug-treated tumor growth model can be viewed as a modified indirect response model and has been applied to characterize the PKPD relationship for antitumor effect of TKIs in nonclinical models (Yamazaki et al. 2008, 2011a, b, 2014; Choo et al. 2010; Salphati et al. 2010; Wong et al. 2012).

In addition to the models described above, transduction models have also been proposed to evaluate antitumor effect in presence of pharmacodynamic delays

(Lobo and Balthasar 2002; Simeoni et al. 2004; Yang et al. 2010). There are basically two types of transduction models, the signal transduction model and the cell distribution model. Transduction models consist of homogenous multiple transit compartments, where it is assumed that the pharmacokinetics of the anticancer agent does not affect the time of signal propagation. The multiple transit compartments have a mean transit time (MTR) that accounts for a time delay in the pharmacological response relative to systemic drug exposure. These transduction models are often called *semi-mechanistic*, because they bring increased realism compared to the indirect response models. Transduction models have been mainly applied to date to characterize the PKPD relationships of cytotoxic agents (Simeoni et al. 2004; Fetterly et al. 2013; Tate et al. 2014).

### *3.3 PKPD Understanding of TKIs as Case Studies*

A few published examples of translational pharmacology of TKIs facilitated by modeling and simulation approaches will now be reviewed highlighting how PKPD modeling increased the translational value of available data and enabled data-driven mechanistic interpretations.

Nonclinical PKPD relationships of crizotinib (PF02341066), an orally available small-molecule TKI of multiple rTKs including anaplastic lymphoma kinase (ALK) and mesenchymal-epithelial transition factor (MET), were characterized in athymic nu/nu mice implanted with either H3122 non-small cell lung cancer (NSCLC) cells or GTL16 gastric carcinoma cells (Yamazaki et al. 2008, 2012). Crizotinib maximal plasma concentration in both xenograft models was observed earlier than the maximal inhibition of ALK and MET phosphorylation in tumors. The ALK and MET inhibition was also sustained relative to the decline of crizotinib plasma concentrations. The observed time delay of ALK or MET inhibition in tumor relative to crizotinib plasma concentration was possibly due to rate-limiting distribution of crizotinib from peripheral blood to the target tumors. Thus, the pharmacodynamic responses for both ALK and MET were adequately modeled using a link model, which provided unbound $EC_{50}$ values of 19 and 1.5 nM for ALK and MET inhibition, respectively. Tumor growth curves in the vehicle control groups were characterized by an exponential tumor growth model either with or without a logistic function. Crizotinib antitumor effect in both xenograft models was fitted reasonably well by a modified indirect response model. The estimated unbound $EC_{50}$ values were 20 and 17 nM for ALK- and MET-driven xenograft models, respectively. Interestingly, the $EC_{50}$ value for antitumor effect for an ALK-driven xenograft model was comparable with the ALK inhibition $EC_{50}$, whereas the $EC_{50}$ against MET-driven tumors was approximately tenfold higher than the $EC_{50}$ value for MET inhibition. This implies that the $EC_{50}$ value for antitumor effect is roughly comparable to the $EC_{90}$ value for MET inhibition (13 nM unbound). Collectively, the PKPD modeling results suggest that >50 % ALK inhibition would be required for a significant antitumor effect (>50 % tumor growth inhibition), while near-complete MET inhibition (>90 %) would be

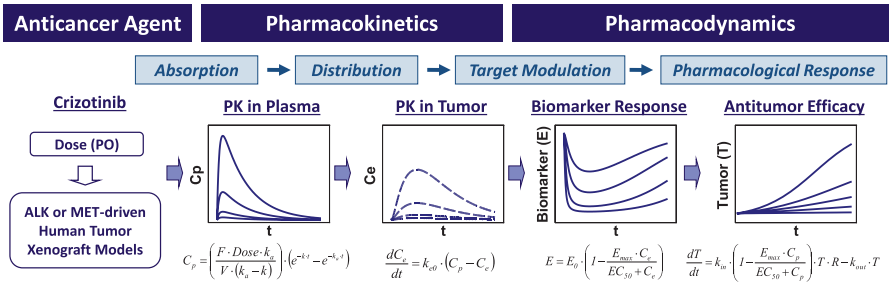



**Fig. 7.2** PKPD modeling summary of crizotinib-mediated target modulation and antitumor efficacy in human tumor xenograft models. $C_p$ plasma concentration, $F$ oral bioavailability, $k_a$ absorption rate constant, $V$ volume of distribution, $k$ elimination rate constant, $t$ time after dosing, $C_e$ effect-site concentration, $k_{e0}$ rate constant for equilibration with the effect site, $E$ biomarker response ratio to baseline ($E_0$), $EC_{50}$ concentration causing 50 % of maximum effect ($E_{max}$), $T$ tumor volume, $R$ logistic function ($1 - T/T_{ss}$), where $T_{ss}$ is a maximum sustainable tumor volume ($R = 1$ for exponential growth model) (Reproduced with permission from Yamazaki S. et al., AAPS J 2013; 15:354–366)

required for the same degree of antitumor effect. Thus, the crizotinib PKPD relationships of target modulation relative to tumor growth inhibition in nonclinical models appear to be different between the two targets, suggesting that, to achieve similar levels of antitumor effect in cancer patients, targeting ALK may be more effective than targeting MET. Overall, the PKPD relationships among crizotinib systemic exposures, target modulation, and antitumor efficacy in tumor xenograft models were well characterized in a quantitative manner using mathematical PKPD modeling, as summarized in Fig. 7.2.

Pictilisib (GDC0941) is a novel small-molecule inhibitor of phosphatidylinositol 3-kinase (PI3K). The PKPD relationships between the pictilisib plasma concentrations and pharmacodynamic biomarker responses of phosphorylated AKT and phosphorylated proline-rich Akt substrate of 40 kDa (PRAS40) were characterized in athymic nu/nu mice implanted with MCF7-1 breast carcinomas (Salphati et al. 2010). The indirect response model reasonably fit both the biomarker responses for AKT and PRAS40 with total drug $EC_{50}$ estimates of 0.36 and 0.29 μM, respectively. The estimated $EC_{50}$ value for AKT in the nonclinical model was consistent with that (0.3 μM) in platelet-rich plasma from cancer patients (Sarker et al. 2009), suggesting pictilisib-mediated AKT responses were consistent between nonclinical models and patients. The antitumor efficacy of pictilisib was also adequately characterized by a modified indirect response model, based upon an exponential growth model in a vehicle control group. The model-estimated concentrations required for tumor stasis (i.e., 100 % tumor growth inhibition) was 0.3 μM, which was roughly comparable to the $EC_{50}$ estimates for AKT and PRAS40 inhibition (0.36 and 0.29 μM, respectively). Thus, the PKPD modeling results suggested that approximately 50 % inhibition of AKT and PRAS40 phosphorylation would be associated with tumor stasis in the nonclinical model.

An orally available selective inhibitor of ALK and ROS oncogene 1 (ROS1), PF06463922, is a second-generation ALK inhibitor for crizotinib-resistant NSCLC patients. The PKPD relationship of PF06463922 between the systemic exposure, ALK inhibition in tumors, and antitumor efficacy was characterized in athymic mice implanted with H3122 NSCLC cells expressing echinoderm microtubule-associated protein-like 4 (EML4)-ALK mutation (EML4-ALK$^{L1196M}$) (Yamazaki et al. 2014, 2015). Interestingly, a dose-dependent rebound of ALK phosphorylation was observed at 24–36 h post-dose (i.e., the ALK phosphorylation ratio was greater than 1 in the treatment groups relative to the vehicle control group). In order to take into account the observed rebound, a modulator was incorporated into the basic indirect response model as a precursor. This allowed to estimate the in vivo potency, unbound $EC_{50}$ for ALK inhibition (36 nM), which was >twofold lower than the estimated $EC_{50}$ value by a simple indirect response model without a modulator (84 nM). Based upon the difference in objective function values between these models, the indirect response model with a modulator fitted the time course of ALK inhibition statistically better than the indirect response model without a modulator, indicating the importance of selecting the appropriate PKPD model to accurately characterize the PKPD relationship. Tumor growth curves in the xenograft control groups with EML4-ALK$^{L1196M}$ and ROS1 were well characterized by an exponential tumor growth model, without and with a logistic function, respectively. Tumor growth inhibition by PF06463922 was then fitted adequately by a modified indirect response model. The model-estimated unbound concentrations required for tumor stasis were of 51 and 6.2 nM in the xenograft models with EML4-ALK$^{L1196M}$ and ROS1, respectively. Thus, the unbound $EC_{50}$ to $EC_{60}$ estimates for ALK inhibition (36–52 nM) roughly corresponded to the unbound tumor stasis concentration (51 nM) in the xenograft models, suggesting that near 60 % ALK inhibition would be required for tumor stasis.

The previous examples illustrated how translational research groups have applied a two-step approach to characterize the PKPD relationships of TKIs in nonclinical models. The PKPD relationships of TKIs for biomarker responses and antitumor efficacy were separately characterized in parallel as a function of plasma concentrations; subsequently, the efficacious concentrations of TKIs were estimated by comparing the exposure-response relationships established between plasma concentrations and biomarker responses and between plasma concentrations and antitumor efficacy. To facilitate translation, the plasma concentrations associated with biomarker responses (e.g., >50 % inhibition), which lead to a desired degree of antitumor efficacy (e.g., 50–100 % tumor growth inhibition) in nonclinical models, could be considered and used as minimum target efficacious concentrations in clinical trials such as phase I studies. Thus, PKPD modeling is a key approach to quantitatively establish exposure-response relationships of TKIs in nonclinical models and can greatly facilitate a deeper understanding of translational pharmacology. This understanding can be used to make advancement decisions in the early development stage and also to guide trial designs and dose adjustments in the clinic.

### *3.4 Extrapolation of Antitumor Efficacy from Nonclinical Models to the Clinical Setting*

In drug discovery and development, the efficacious concentrations at the target site of clinical drug candidates are routinely projected by characterizing a quantitative PKPD relationship in nonclinical models, as described above. Projected efficacious concentrations of TKIs can be then used as a surrogate marker in guiding the phase I dose-escalation study, as well as establishing a recommended phase II dose and dose schedule. Establishment of a quantitative exposure-response relationship should be one of the main objectives of nonclinical in vivo TKI PKPD studies. For instance, the PKPD relationship of crizotinib exposure, ALK and/or MET inhibition, and tumor growth inhibition was quantitatively characterized in human tumor xenograft models using mathematical modeling as described above (Yamazaki et al. 2008, 2012; Yamazaki 2013). The PKPD modeling results in nonclinical models suggest that 50 % ALK inhibition would be required for a significant antitumor efficacy (i.e., >50 % tumor growth inhibition), whereas >90 % MET inhibition would be required for the same degree of tumor growth inhibition. Accordingly, the minimal target efficacious concentrations of crizotinib in patients with ALK- and MET-positive tumors were projected as the steady-state trough concentrations required for >50 % ALK inhibition (i.e., ALK $EC_{50}$ = 19 nM free) and >90 % MET inhibition (i.e., MET $EC_{90}$ = 13 nM free), respectively. Following this analysis, the clinical PKPD relationship of crizotinib in a phase I dose-escalation study (e.g., a starting dose of 50 mg once daily to the highest dose of 300 mg twice daily) was simulated based upon the clinically observed/predicted human PK parameters and the PD parameters obtained from nonclinical models. Crizotinib-mediated ALK and MET inhibition in patient tumors at the recommended phase II dose, twice daily doses of crizotinib 250 mg (500 mg/day), was projected to be >75 % and >95 %, respectively, which was higher than the projected minimal target modulations of 50 % and 90 %, respectively. The projection of the expected PKPD relationship at a recommended phase II dose could be critical for a go/no-go decision. Thus, despite the lack of crizotinib-mediated ALK- or MET-related biomarker data in cancer patients, the modeling and simulation approach was applied to phase I dose-escalation study to support the selection of recommended phase II dose associated with systemic exposures; this dosing regimen later demonstrated promising clinical responses in cancer patients (Kwak et al. 2010; Ou et al. 2011; Ou 2012).

An interesting PKPD modeling analysis has been reported for molecularly targeted and cytotoxic agents (Wong et al. 2012). This analysis established a relationship between clinically observed plasma drug concentrations and antitumor efficacy in nonclinical xenograft/allograft models. The authors first performed PKPD modeling to characterize the relationship between plasma concentrations of anticancer agents and antitumor efficacy in nonclinical models. Subsequently, a PKPD simulation with the PD parameter estimates in nonclinical models was carried out at clinically relevant dosing regimen, yielding plasma concentrations comparable to clinically observed exposures. In other words, antitumor efficacy of each agent in

nonclinical models was simulated at clinically relevant plasma concentrations with the PD parameters obtained from nonclinical models. The results suggest that anticancer agents showing >60 % tumor growth inhibition at clinically relevant exposures in nonclinical models likely lead to promising responses in the clinic. Despite these encouraging observations, it should be noted that the degree of target tumor growth inhibition could depend upon several factors, such as the nonclinical xenograft model used, the maximum attainable tumor growth inhibition, the target modulation vs. tumor growth inhibition relationship, and the specifics of the clinical indication. These factors should be carefully considered to project a minimal target efficacious concentration based on a target tumor growth inhibition. In some cases, tumor stasis or even tumor regression could be appropriate for a minimal target antitumor efficacy. As an example, tumor stasis concentration has been reported as a minimal target efficacious concentration of the second-generation ALK inhibitor, PF064639322, in NSCLC patients with EML4-ALK rearrangements with and without ALK mutations (Yamazaki et al. 2014). The PKPD modeling results showed that the unbound $EC_{50}$ to $EC_{60}$ estimates for ALK inhibition (36–52 nM) roughly corresponded to the unbound tumor stasis concentration (51 nM) in nonclinical xenograft models, suggesting that near 60 % ALK inhibition would be required for tumor stasis as described above. Accordingly, the unbound $EC_{60}$ for ALK inhibition (~50 nM) has been proposed to be a minimum target efficacious concentration of PF06463922 in NSCLC patients with EML4-ALK rearrangements. In addition, the unbound $EC_{75}$ estimate (100 nM) for PF06463922-mediated ALK inhibition has been proposed to be a target plasma concentration for crizotinib-resistant NSCLC patients. This was dimensioned against the drug levels required to achieve equivalent antitumor efficacy as was observed in crizotinib-sensitive NSCLC patients with wild-type ALK rearrangements. It reflects the (previously described) projected >75 % crizotinib-mediated ALK inhibition in patients at the clinically recommended dose of 250 mg twice daily. It remains to be seen whether the projection of efficacious concentrations of PF06463922 in patients will be consistent with clinical responses, since PF06463922 has just recently entered a phase I dose-escalation study.

The projected minimal efficacious concentrations of molecularly targeted agents, such as TKIs, generally target steady-state systemic exposures required to achieve promising efficacy in cancer patients. Therefore, the projected minimal efficacious concentrations of TKIs are often used as surrogate markers of antitumor efficacy in clinical studies. In particular, phase I studies are generally conducted in a manner of dose escalation, to determine safety profiles including maximal tolerated dose (MTD), dose-limiting toxicities, PK profiles, and the recommended phase II dose (RP2D). Operationally, whether plasma concentrations of TKIs would reach projected minimal efficacious concentrations in phase I studies could be the basis of a go/no-go decision. Clinical PKPD relationships of systemic exposure of molecularly targeted agents to target modulation and/or its surrogate biomarker response (e.g., proof of mechanism) could in principle be established in phase I studies in an expanded cohort setting of selected patient populations. However, pharmacodynamic biomarker measurements in cancer patients are not common, since tumor biopsy samples, especially serial samples, are difficult to obtain from patients.

In fact, only 20 % of ~2500 phase I trials submitted to the American Society of Clinical Oncology incorporated biomarker assessments (Goulart et al. 2007). In addition, human tumors are generally highly heterogeneous, with large inter- and intraindividual variation, typically resulting in large variability in target modulation/biomarker responses in the clinic (Godschalk et al. 2003; Butterfield et al. 2011). Despite these limitations, the phase I dose-escalation study of the poly(ADP-ribose) polymerase inhibitor (PARP), AG014699, was conducted to establish the PARP inhibitory dose by measuring target modulation as the primary endpoint (Plummer et al. 2008). This approach based upon a pharmacologically active dose can maximize potential benefits and minimize possible risks of anticancer agents in patients (Plummer et al. 2008; Le Tourneau et al. 2009; Stroh et al. 2014). Unfortunately, this practice remains rare in the oncology field. In addition, if a pharmacologically active dose associated with systemic unbound exposures was established for a first-in-class candidate drug based upon its target modulation and/or reliable surrogate biomarker response, this knowledge could be valuable for subsequent drug candidates, such as second-generation inhibitors, to conduct phase I dose-escalation studies safely and effectively. The quantitative understanding of translational pharmacology by mathematical PKPD modeling and simulation is needed to make this approach successful.

## 4 Clinical PKPD Knowledge

When clinical data are available, the purpose of PKPD modelling changes relative to pre-clinical data analysis and modeling changes. In the clinical context, the value added of PKPD modeling lies in (1) finding correlates (covariates) of drug exposure in humans and (2) determining relationships of exposure with response (or adverse events) in the clinic, when biomarkers or endpoints of efficacy (or safety) are available. We will now describe a few case studies where PKPD modeling was able to elucidate mechanistic relationships or shed light on the determinants of drug disposition in vivo in humans. These examples make use of different kinds of data and reflect a variety of clinical study designs for targeted agents.

### *4.1 Imatinib*

CML or chronic granulocytic leukemia (CGL) is a hematopoietic disorder (bone marrow stem cell disorder) associated with the oncogenic BCR-ALB1 fusion gene expression due to an abnormal chromosome known as the Philadelphia chromosome (Ph). The presence of the BCR-ABL1 protein in the cells is responsible for the expansion of the malignant clone resulting in the displacement of normal bone marrow stem cells. Imatinib (STI-571) is a selective inhibitor of BCR-ABL kinase activity used as standard therapy in the treatment of Philadelphia

chromosome-positive (Ph+) chronic myelogenous/myeloid leukemia (CML) and GIST.

Roeder et al. implemented a nonclinical mathematical model to describe the biphasic decline and fast relapse of BCR-ABL1 levels in mouse (Roeder et al. 2005) that later the authors adapted to CML patients (Roeder and Loeffler 2002; Roeder et al. 2006). This model assumes a heterogeneous population of hematopoietic stem cells (HSCs) as well as differentiated cells. In the model, the malignant cell clone (BCR-ABL1-positive cells) expands and, in the long run, out-competes the normal cell population. This is due to the chromosome translocation impairing proliferation control, together with altered cell microenvironment. Using this stem cell organization model, the authors were able to model and simulate the effect of imatinib treatment as a modulation of the competitive properties of BCR-ABL1-positive cells, assuming that imatinib selectively induces the inhibition of proliferative activity and degradation of these particularly mutated stem cells. The time course of percentage of BCR-ALB1 transcript was modeled as a biphasic decline curve. The first phase of the decline is the result of the initial reduction of proliferating BCR-ABL1-positive cells due to the assumed degradation effect. The latter and prolonged decline is largely based on changes in the regulatory response of the system due to reduced stem cells.

Larson et al. carried out an analysis of imatinib PK, measured as trough plasma concentrations at steady state ($C_{\text{trough}}$ at day 29), and assessed how variability in imatinib exposure correlates with cytogenetic (CCyR) and molecular responses (MMR), as well as event-free survival (EFS), adverse events, and patient disposition during the follow-up (5 years) (Larson et al. 2008). The data generated from the IRIS trial was used for this analysis. The IRIS trial enrolled 553 Ph+CML patients; however, plasma concentration data was available only for part of the patients enrolled ($N=351$).

Using linear regression analysis, the analysis showed that imatinib $C_{\text{trough}}$ was correlated with age, body weight, and body surface area (BSA) at baseline. Correlations of $C_{\text{trough}}$ with clinical endpoints were done by grouping $C_{\text{trough}}$ into quartiles. Therefore, the lower quartile (Q1) included data on 25 % of patients with the lowest imatinib $C_{\text{trough}}$ values, Q2 and Q3 when 25 % below and above the median $C_{\text{trough}}$ value, and the upper quartile (Q4) the highest imatinib $C_{\text{trough}}$ values. Q2 and Q3 were combined for all analyses and referred as Q2-Q3, thus providing three distinct $C_{\text{trough}}$ categories, used for stratification as appropriate. Cumulative cytogenetic and molecular response rates were estimated using the Kaplan-Meier method, and strata were compared using the log-rank test. EFS was plotted by the three grouped $C_{\text{trough}}$ levels using the Kaplan-Meier method. Adverse events other than neutropenia, thrombocytopenia, and anemia were included in this analysis if the occurrence rate was more than 10 %. An exploratory multivariate analysis was performed by stepwise logistic regression to examine CCyR rates relative to imatinib $C_{\text{trough}}$ but also baseline patient demographics (age, sex, body weight, and BSA) and disease characteristics (Sokal score, hemoglobin, white blood cells, basophils, absolute neutrophil counts, platelet counts, and blasts in bone marrow and peripheral blood).

The analysis showed that better clinical responses (CCyR, MMR or EFS) were observed in patients with higher imatinib trough concentrations. Fluid retention, rash, myalgia, and anemia showed higher incidence among patients with higher imatinib $C_{trough}$. However, the lower frequency of fatigue, abdominal pain, joint pain, and neutropenia happened among patients with the highest imatinib plasma levels. According to the authors, certain adverse effects may be more dependent on disease or disease stage, or indicative of slower response to therapy and less a consequence of drug plasma concentrations. Patients in the lowest PK quartile had the highest discontinuation rate, as well as the highest percentage of patients who discontinued therapy for "unsatisfactory therapeutic effect." Multivariate analysis showed that both imatinib trough concentrations and Sokal risk group were predictive for achievement of CCyR. In summary, assuming that patients maintained adherence to imatinib therapy for the duration of treatment, imatinib $C_{trough}$ measured following the first month of treatment correlated with long-term complete cytogenetic and molecular responses as well as long-term EFS. The authors concluded that maintaining plasma trough levels at or above 1 μg/mL may be important for achieving improved CCYR and MMR rates.

## *4.2 Dasatinib*

Dasatinib is an oral BCR-ABL1 TKI and SRC family TKI approved for first-line use in patients with Ph + CML and Ph + acute lymphoblastic leukemia (ALL).

Glauche et al. carried out a comparison between BCR-ABL1 transcript levels (expressed by the ratio of BCR-ABL1 to ABL1) in peripheral blood of imatinib- and dasatinib-treated CML first-line patients as a surrogate of overall tumor load (Glauche et al. 2014). As described above for imatinib, the authors applied a bi-exponential regression model to describe individual patient dynamics. Dasatinib showed a significant steeper early treatment response compared to imatinib, as well as a deeper response level at the end of the early response phase (around 7 months). The authors concluded that dasatinib presented a more efficient cytotoxic effect on proliferating leukemic cells compared to imatinib. Based on these results, the model-based prediction strategy used could be applied to prediction of long-term responses, including estimates of leukemic stem cells using parameter estimates of activation, deactivation, toxicity, and TKI effect incidence.

## *4.3 Sunitinib*

Sunitinib is an oral multitargeted TKI that inhibits tumor cell proliferation and angiogenesis (Rini 2007). Sunitinib presents inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), vascular endothelial growth factor

receptors (VEGFR-1, VEGFR-2 and VEGFR-3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT-3), colony-stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line-derived neurotrophic factor receptor (RET). Sunitinib is indicated for the treatment of advanced renal cell carcinoma (RCC), gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate, and progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease (http://labeling.pfizer.com/ShowLabeling.aspx?id=607#section-11).

Houk et al. carried out a PKPD meta-analysis using data collected from six patient studies. Patients presented either any solid tumor, advanced GIST, or metastatic RCC (Houk et al. 2010). Sunitinib doses ranged from 25 to 150 mg once daily (QD) or once every other day (QOD), with either 6-week cycles of 4/2 schedule (4 weeks on treatment, 2 weeks off treatment), 4-week cycles of 2/2 schedule (2 weeks on treatment, 2 weeks off treatment), or 3-week cycles of 2/1 schedule (2 weeks on treatment, 1 week off treatment). Pharmacokinetic parameters were correlated with efficacy (time to tumor progression, TTP, overall survival, OS, investigator assessed the response evaluation criteria, RECIST, and tumor size changes) and safety endpoints (incidence of fatigue, neutrophil counts, and diastolic blood pressure (DBP)). The result of this meta-analysis indicated that increased exposure to sunitinib is associated with improved clinical outcomes as well as some increased risk of adverse events.

$AUC_{ss}$ was evaluated against each efficacy endpoint. Patients were subdivided into two groups according to their exposure value (less than the median $AUC_{ss}$ and greater or equal to the median $AUC_{ss}$) for the Kaplan-Meier analysis. Weibull probability distribution model was used to the time to event analysis for TTP and OS (Sheiner 1994; Gieschke et al. 2003). Categorical endpoints (RECIST-defined response) were investigated using a mixed-effect modeling approach with repeated-measure logistic regression (Mould et al. 2002; Kowalski et al. 2003; Wählby et al. 2004). Tumor growth kinetics was assessed using the sum of longest diameter (SLD), and tumor changes were described using a tumor growth dynamic model (Frances et al. 2011). The highest sunitinib and total drug (sunitinib plus its active metabolite) exposure correlated with longer TTP and OS across tumor types, more so in GIST and mRCC (see Fig. 7.3). Further, there was a significant relationship between sunitinib exposure and the probability of partial response (PR) or complete response (CR) in mRCC patients ($p=0.00001$; see Fig. 7.4). This trend was consistent but did not reach statistical significance for patients with GIST ($p=0.06$). Model-based tumor size predictions were consistent with the observed data for both GIST and mRCC patients. Simulations suggested that 38 % more mRCC and 23 % more GIST patients would be expected to achieve a 30 % reduction in tumor size when administered sunitinib 50 mg versus 25 mg QD.

Fatigue data were analyzed using repeated-measure logistic regression with a two-part mixture model to account for the high proportion of observations of no event (Kowalski et al. 2003). Sunitinib exposure-absolute neutrophil count (ANC) relationships were established using repeated-measure mixed-effect modeling methods. For the relationship between sunitinib exposure ($C_{trough}$) and DBP, a linear,

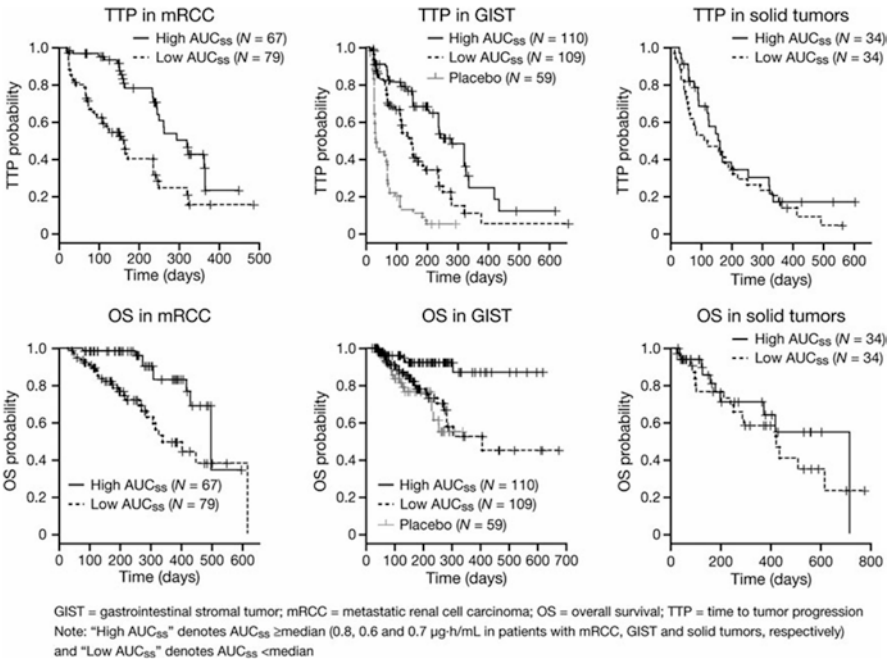
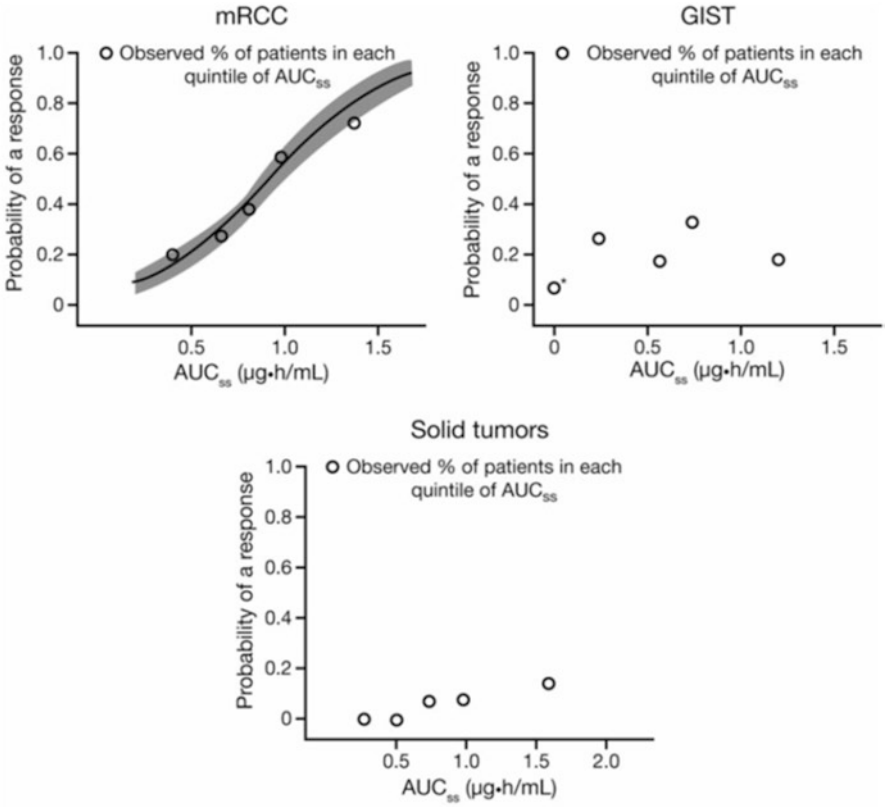



**Fig. 7.3** Relationship between average daily exposure (mean daily AUC at steady state, AUCss) to sunitinib and TTP/OS across tumor types

a $E_{max}$, and a power model were considered, with the $E_{max}$ model being the one better describing the observations. A positive relationship between exposure (total drug AUCss) and incidence, but not severity, of fatigue was identified. The model showed a relationship between sunitinib exposure and the probability of grade ≥1 fatigue in the different tumor types for the 25 and 50 mg QD doses as follows: GIST, 46 and 65 %; mRCC, 57 and 74 %; and solid tumors, 85 and 92 %. The analysis of ANC over the course of treatment revealed a negative relationship between ANC and total drug exposure. ANC changes occurred predominantly after one cycle of sunitinib treatment and did not progress with later cycles. A positive relationship was identified between DBP changes and total drug exposure. The estimated maximum drug-mediated change in DBP for the population was 17 mmHg, with an interindividual variability of approximately 36 %. The median $C_{trough}$ for the population on sunitinib 50 mg QD was 0.068 μg/mL, below the estimated $EC_{50}$ of the effect of DBP of 0.084 μg/mL.

Lindauer et al. conducted a tumor-independent pharmacological response to sunitinib by PKPD analysis in 12 healthy volunteers receiving 50 mg of sunitinib for 3–5 consecutive days (Lindauer et al. 2010). The PD endpoints included blood pressure (BP) and circulating proteins as biomarkers (vascular endothelial growth factor A (VEGF-A) and soluble VEGF receptor-2 (sVEGFR-2)). Numerous reports have shown that the levels of several circulating proteins, as well as BP, consistently




GIST = gastrointestinal stromal tumor; mRCC = metastatic renal cell carcinoma;
RECIST = Response Evaluation Criteria in Solid Tumors [21].
*An $AUC_{ss}$ value of zero reflects the quintile of patients with GIST who received placebo rather than sunitinib.

**Fig. 7.4** Probability of partial or complete response (by RECIST Criteria) versus average daily exposure to sunitinib

change in response to anti-angiogenic therapy (Motzer et al. 2006; Deprimo et al. 2007; Ebos et al. 2007; Norden-Zfoni et al. 2007; Kontovinis et al. 2009), which suggest that dose optimization and monitoring of response could be achieved through an in-depth understanding of the dose-concentration-biomarker relationship. The final PK model consisted of one- and two-compartment dispositions for the sunitinib active metabolite, SU12662, and sunitinib, respectively, and multiple transit compartments for the absorption phase. The BP changes over time at baseline (systolic and diastolic) were best described by a function with two cosine terms previously used by Hempel et al. This was modified in presence of sunitinib by a term that affects BP based on sunitinib's intrinsic activity to produce an effect in diastolic or systolic BP, an immediate signal parameter set equal to the fractional TK inhibition, and a slower, transduced signal with an estimated transduction time

delay (Hempel et al. 1998). The dual mechanism of action incorporated in the BP model is compatible with the theory of how hypertension is induced by anti-angiogenic therapy (Horowitz et al. 1997; Mourad et al. 2008). A semi-mechanistic model to relate biomarker data to drug concentrations using drug-specific (TK inhibition) and biological system-specific (biomarker signal) components was developed. The drug-specific part was a simple hyperbolic function relating the sum of unbound sunitinib and its active metabolite concentrations to fractional tyrosine kinase inhibition. For VEGF-A, a factor accounting for its intrinsic activity, signal amplification during the transduction process, and a time delay in response relative to drug concentration were included in the model (Mager and Jusko 2001). Changes in sVEGFR-2 concentrations were described in terms of an indirect response model, with the drug-specific term affecting the zero-order release rate of this soluble protein (Dayneka et al. 1993). Simulations of BP time courses successfully compared with published data in patients; however, observed changes in circulating VEGF-A and sVEGFR-2 in patients were greater than the simulation indicated. The authors hypothesized that VEGF-A release from tumor cells adds substantially to the VEGF-A derived from other body cells. Likewise, sunitinib's effect of inhibiting the release of sVEGFR-2 into the circulation may be more pronounced in tumor tissue than in healthy tissue.

Subsequently, Hansson et al. published a PKPD model linking drug exposure, biomarkers, tumor dynamics, and OS in a unified structure (Hansson et al. 2013). The database consisted of four clinical studies, which comprised a total of 303 patients with imatinib-resistant GIST receiving sunitinib and/or placebo treatment. The patients received sunitinib doses ranging from 25 to 75 mg orally and/or placebo in a 4/2, 2/2, 2/1 schedule (weeks on/weeks off treatment), or continuous treatment schedule. The exposure-effect analysis was characterized using nonlinear mixed-effect PKPD models to evaluate VEGF, sVEGFR-2, sVEGFR-3, and KIT as potential predictors of tumor response and subsequent overall survival following sunitinib treatment.

For the biomarker models, plasma concentrations of VEGF, sVEGFR-2, sVEGFR-3, and KIT over time were described by indirect response models with sigmoid $I_{max}$ (VEGF, sVEGFR-2) or $I_{max}$ (KIT, sVEGFR-3) drug effect relationships. Sunitinib AUC was the selected drug exposure parameter. The final model was simplified to include a common drug potency parameter (the daily sunitinib AUC resulting in half of the maximum drug effect, IC50) for all the four biomarkers, where VEGF, sVEGFR-2, and sVEGFR-3 were found to be highly correlated. The tumor growth inhibition model used the longitudinal tumor size (SLD) over time and accounted for the tumor growth dynamics, sunitinib exposure-driven tumor shrinkage, and resistance development leading to tumor regrowth. A variable was introduced to consider tumor size reduction rate constant related to biomarker response, which was significant for KIT and sVEGFR-3 soluble proteins. A dropout model was also developed to enable prospective simulations of tumor growth over time, because dropout was not completely at random (since those patients with larger tumor size or poorer tumor response were more likely to drop out after data collection). Overall survival predictions accounted for a dynamic change in tumor size in contrast to the models proposed by Wang et al. and Claret et al., where

constant value predictors were adopted (Claret et al. 2009; Wang et al. 2009). However, when model-predicted sVEGFR-3 over time was related to survival, there was no additional improvement by incorporating tumor size. Evaluating the capability to predict survival based on early changes in sVEGFR-3 based on longitudinal data from only the first 6 or 12 weeks of treatment resulted in similar fit of the survival model as when using the full time course of sVEGFR-3. The developed model enables prediction of OS for different doses and schedules, since it allows the integration of the whole biomarker time course (instead of discrete values, which are schedule dependent). In summary, sVEGFR-3 was found to be the most promising variable for predicting clinical outcome following sunitinib treatment in GIST.

According to the PKPD published data, sunitinib is a good example of a well-understood targeted therapy with an appropriate set of biomarkers that allow the prediction of efficacy endpoints early on during treatment.

### *4.4 Axitinib*

Axitinib is a potent and selective second-generation inhibitor of vascular endothelial growth factor receptors VEGFR-1, VEGFR-2, and VEGFR-3 (Choueiri 2008; Hu-Lowe et al. 2008; Kelly and Rixe 2009). Axitinib is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy. The safety profile of axitinib is consistent with that expected for this class of agents, with hypertension, fatigue, and diarrhea being common adverse events. The mechanism(s) involved in the elevation of blood pressure (BP) following inhibition of VEGF or VEGFR is not well understood: endothelial dysfunction and microvascular rarefaction via decrease availability of nitric oxide have been postulated (Veronese et al. 2006; Kamba and McDonald 2007; Mourad et al. 2008).

Rini et al. carried out several PKPD analyses between axitinib exposure, elevated BP, and efficacy endpoints (PFS and OS) (Rini et al. 2013). Patients from three metastatic RCC studies were included in the analyses ($N = 168$). As a measure of axitinib exposure, AUC at the end of 4 weeks of study treatment, as well as AUC for the entire study treatment, was tested. AUC was calculated from the average of total daily dose for a given duration, the mean estimate of bioavailability, and the individual post-hoc estimates of CL. For BP, diastolic BP (dBP) was used rather than systolic BP (sBP), since the latter tends to be more labile. Maximum observed dBP during the first 4 weeks of treatment, the first 8 weeks, and any time during the study was assessed. Relationships between axitinib exposure, dBP, and categorical efficacy endpoints (objective response rate, ORR) were evaluated using logistic regression. Relationships between AUC, dBP, and time-to-event efficacy (PFS and OS), as well as prognostic factors, were initially analyzed using univariate Cox regression, for inclusion in a final multivariate Cox regression. In a first step, a multivariate model with significant prognostic factors was developed; then AUC and dBP were tested as predictors of response as continuous and categorical variables (300 ng h/mL and 90 mmHg were the cutoffs for AUC and dBP, respectively).

Previous analyses identified serum hemoglobin, corrected calcium level, and Karnofsky performance status (KPS) as prognostic factors predictive of survival in second-line mRCC patients (Motzer et al. 2004). These variables, except KPS (not recorded), were evaluated as prognostic factors in this analyses, as well as baseline Eastern Cooperative Oncology Group (ECOG) scores, prior therapy (cytokine vs. sorafenib refractory), age, and gender.

The correlation between prognostic factors and efficacy endpoints by univariate analysis found significant gender, prior therapy, ECOG scores, and hemoglobin for PFS and prior therapy, ECOG scores, hemoglobin, and corrected calcium for OS. Following multivariate analysis with backward elimination, all prognostic factors were retained in the model, with the exception of corrected calcium. After accounted for significant prognostic factors potentially predictive of PFS and OS, axitinib exposure and dBP were tested as additional independent predictors. The results indicated that high AUC and an increase in dBP were both associated with longer PFS and OS and were independent predictors of survival. Furthermore, logistic regression indicated that patients with high AUC and an increase in dBP had a higher probability of achieving a partial response.

## *4.5 Erlotinib*

Erlotinib is an inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase. Erlotinib is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen and, in combination with gemcitabine chemotherapy, for treatment of locally advanced, inoperable, or metastatic pancreatic cancer (Shepherd et al. 2005; Moore et al. 2007).

Lu et al. evaluated the relationship of erlotinib exposure to diarrhea and rash in patients with advanced metastatic NSCLC from the pivotal single-agent phase 3 study ($N=339$) (Shepherd et al. 2005; Lu et al. 2006). The erlotinib exposure data explored included steady-state area under the plasma concentration-time curve (AUC) from 0 to 24 h and maximum concentration ($C_{max}$) generated on the basis of a population PK model developed for the single-agent data. Spearman rank correlation analyses were performed to test for any consistent correlation between maximum rash and diarrhea grades. Rash and diarrhea were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. The Spearman rank correlation was calculated with the same method as the Pearson correlation, but used the ranks of the data rather than the data themselves. Statistical significant correlations between population PK estimates of $AUC_{tau}$ and $C_{max}$ at steady state were observed for severity of rash but not for diarrhea. It is important to note that even when descriptive summary statistics for PK parameters categorized by grades for rash and diarrhea suggested a general trend for higher exposure to correlate with higher grade, the range of values for each of the exposure PK parameters within the toxicity grade group showed significant overlap between the patients

who had no toxicity, that is, grade = 0, and the patients who had toxicity (grades 1–4). Rash and diarrhea have been the primary adverse effects of treatment with small-molecule EGFR inhibitors and are presumed to be caused by the biological activity of these agents in normal EGFR-expressing tissue (Baselga 2002). Further, analyses performed with clinical data with erlotinib and other EGFR inhibitors for a variety of indications in several clinical settings have reported a correlation between rash and survival rate (Kris et al. 2003; Perez-Soler et al. 2004; Pao and Miller 2005; Perez-Soler and Saltz 2005).

## 5 Cardiovascular Safety of Tyrosine Kinase Inhibitors

Cardiovascular safety is a major public health issue that needs to be carefully evaluated during drug development. In 2012, Shah et al. carried out an intensive review of 16 approved TKIs in oncology as their association with cardiac toxicity was not well understood (Shah et al. 2013). The authors evaluated for QT liability preclinical as well as the reported clinical data from regulatory reviews along with prescribing information for all 16 TKIs. The authors also questioned if potential QT liabilities could be due to a pharmacological effect (on- or off-target) linked to inhibition of one or more TKIs, which may regulate hERG function, or an effect related to a particular chemical class (off-target effect). The relatively mild QTc prolongation effect found for the group of TKIs reviewed (except for sunitinib, lapatinib, nilotinib, and vandetanib) couldn't be associated to either the therapeutic class or the chemical structure. However, the reviewed data suggested that the effect of TKIs on left ventricular dysfunction may be associated with morbidity in a greater extent than associated with their QT liability.

The International Conference on Harmonization (E14 2005) recommends that all systemically available drugs should be tested during clinical development for their proclivity to cause QT prolongation. The guidance indicates that the tested doses of the investigational drug need to generate plasma concentrations well in excess of those expected in patients. QT studies in healthy volunteers for TKIs are often challenging since the majority of this group of molecules are oncology drugs and hence, to some extent genotoxic, which usually limits its QT evaluation to cancer patients. Lenvatinib (Shumaker et al. 2014) and axitinib (Ruiz-Garcia et al. 2015) are two examples of TKIs where QT evaluation was carried out in healthy volunteers at supratherapeutic concentrations.

Lenvatinib QT evaluation followed the requirements to be considered a thorough QT study (TQT). TQTs are well controlled, with mechanisms to deal with potential bias, including use of randomization, appropriate blinding, and concurrent placebo control group. Since it is important to have a high degree of confidence in the ability of the study to detect differences of clinical significance, the presence of a positive control group increases the confidence in the ability of the study to detect QT/QTc prolongation. The TQT for lenvatinib was a randomized-, placebo-, and positive-controlled single-dose, 3-period, crossover study. Moxifloxacin was the positive

control (Florian et al. 2011); the relationship between changes in QT prolongation from baseline placebo-corrected and lenvatinib concentrations was established using a linear mixed-effect modeling approach with three tested models, a linear model with intercept, a linear model with mean intercept fixed to zero, and a linear model with no intercept. The mixed-effect model used for ΔΔQTcF was also repeated for other ECG parameters (i.e., HR, PR, QRS, and QTcB). No changes in HR were observed due to lenvatinib other than the expected ones due to diurnal changes. A small shortening was observed after dosing lenvatinib at supratherapeutic concentrations (32 mg QD) excluding a ΔΔQTc prolongation exceeding 10 ms.

The effect of axitinib on corrected QT was evaluated using data from a randomized crossover phase I study in healthy volunteers administered with axitinib alone or in presence of steady-state ketoconazole (400 mg QD), a strong CYP3A4 inhibitor, which increased axitinib plasma concentrations above the therapeutic range as axitinib is a CYP3A4 substrate. The analyzed data revealed three important findings: (1) axitinib and ketoconazole, respectively, had statistically significant effect decreasing and increasing HR; (2) standard fixed correction factors did not remove the correlation factor between QT and RR; and (3) axitinib at supratherapeutic concentrations did not have a clinically meaningful effect on QT interval. Due to the significant impact of axitinib on HR, authors used mixed-effect modeling to establish the relationship between QT and axitinib concentration using one-stage analysis (Garnett et al. 2012) as opposed to the two-stage approach done for lenvatinib. QTc-concentration response analysis was initially conducted using fixed correction factors based on baseline data (i.e., using

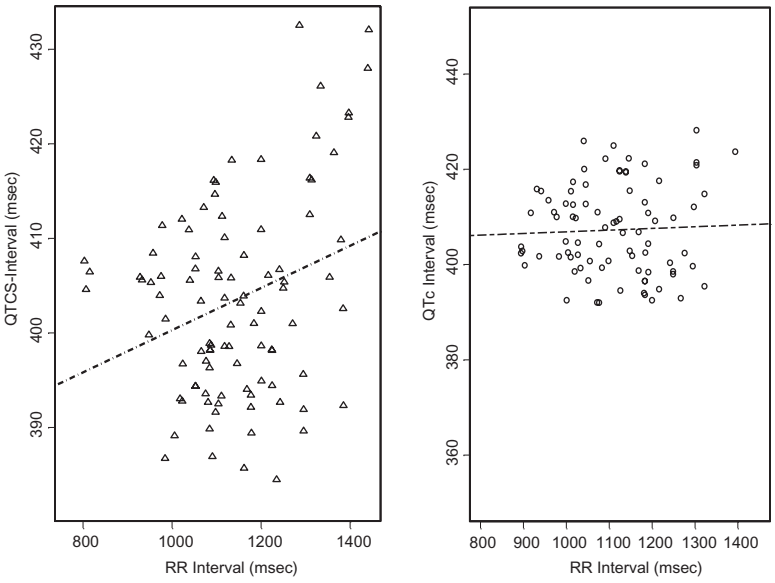



**Fig. 7.5** Axitinib QT-corrected vs. RR interval using study-specific fixed correction (*left panel*) and QT corrected obtained from the model based on one-stage method (*right panel*)

Friedericia's, Bazett's, and study-specific correction factors). However, QTc values obtained using these corrections retained a dependency on HR due to study drug, and therefore, the relationship was characterized using one-stage approach (see Fig. 7.5), where QT corrected as well as its relationship with axitinib concentrations was estimated simultaneously.

## 6 Closing Remarks

A dynamic modeling and simulation approach is increasingly being employed in all phases of drug discovery and development to establish robust exposure-response relationships for NMEs. The FDA encourages pharmaceutical companies to use modeling and simulation to determine the best dosing strategies, e.g., to explore dose adjustments for drug-drug interaction and drug-disease interaction (Lalonde et al. 2007; Huang and Lesko 2009; Huang and Rowland 2012; Milligan et al. 2013). Drug discovery and development can thus be viewed as a model building process, where growing knowledge and expertise about NMEs should be continuously applied to decision-making, following the predict/learn/confirm paradigm. Establishing exposure-response relationships for NMEs' efficacy and toxicity using a modeling and simulation approach would be critical in many aspects of regulatory decision-making, including labeling. Among modeling and simulation approaches, PKPD modeling is a powerful approach linking drug exposures to biological and pharmacological responses, providing a quantitative assessment of in vivo drug potency with mechanistic insight on drug action, as summarized in the many examples above. Thus, a growing emphasis is being placed upon more mechanistic and quantitative mathematical modeling approaches to understand in vivo PKPD relationships, both in nonclinical and clinical settings.

Initiatives such as the FDA's critical path (Woodcock and Woosley 2008) and the NIH Roadmap led academia and industry to reconsider how nonclinical and clinical research should interact to better drive the course of drug development. It is imperative to transform the way biomedical research is conducted by overcoming specific hurdles or filling existing knowledge gaps. An exceptional example of the importance to bridge nonclinical and clinical should be oncology drug development, which has an extraordinarily high attrition rate. The traditional concept of maximum tolerated dose is no longer the preferred pathway for drug development of molecularly targeted agents such as TKIs. Clinically effective doses could be achieved in advance to any adverse effects. Thus, identification of biomarkers should be used to enable dose optimization and monitoring of response. Nonclinical models could increase the understanding of the mechanism of action; their translation into the clinical setting could drive study design, including patient selection, and help demonstrate proof of concept in early clinical phases. Mechanistic and quantitative PKPD modeling is among the key assets for successful translational pharmacology of TKIs and could ultimately increase the success rate of target cancer therapies in the clinic.

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# Chapter 8
# Combination Development

**Annie St-Pierre, Maribel Reyes, and Vincent Duval**

**Abstract** In recent years, the pharmaceutical industry has focused its efforts towards the development of novel combination targeted therapies for the treatment of cancer. In the battle against the most complex and heterogeneous disease, researchers have been increasing their understanding on cell signaling pathways and tumor biology. This knowledge supports the increasing interest in combinatorial approaches to overcome challenges such as drug resistance, or sub-optimal efficacy. The development of combination therapy faces several challenges: characterization of the synergy between the two chemical entities, definition of the appropriate doses and schedule to maximize efficacy without increasing the level of adverse events, which increased significantly its level of complexity. To address these obstacles several tools are made available. In vitro, the number of cell lines validated for pre-clinical testing and the availability of high throughput screening methods has increased significantly. The characterization of cells at a genomic and protein level have improved the predictability of effects in vivo and enabled the identification of synergistic, additive, or antagonistic effects of combination therapies. In vivo, xenograft models are frequently used to optimize combination therapies and understand mechanisms of drug resistance. Moreover, in silico approaches such as multi-scale mathematical models are gaining interest to integrate knowledge on cellular pathways, cellular environment, and tumor growth in order to optimize dosing strategies. The clinical development of combination therapies has prompted the need to reassess how clinical studies are designed in order to identify the right dose and the right schedule of administration for drugs in combination. Several strategies can be used for dose escalation in phase I combination studies but the use of pharmacokinetic properties of individual drugs and the collection of pharmacodynamics endpoints early in development has proven to be essential in optimizing combination therapies across the various phases of clinical development. Finally, an increased collaboration across the pharmaceutical industry is needed for the development of combination therapies for the successful treatment of cancer.

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Combination therapies have become the standard of care in many disease areas such as infectious disease (e.g., HIV), hypertension, and cancer. In oncology, the concept of combination chemotherapy was introduced in the 1960s and early 1970s after the discovery of effective regimens to cure acute childhood leukemia and advanced Hodgkin's disease (Frei et al. 1965; DeVita and Chu 2008). These results led to increased efforts in cancer biology research. Today, over one hundred chemotherapy regimens are used to treat both hematological malignancies and solid tumors (Cancer Treatment Advisor 2015).

In the mid-1980s, the focus in cancer research shifted toward targeted therapies (Drebin et al. 1985). As opposed to traditional chemotherapy, which interferes with cell division in both normal and cancer cells, targeted therapies interfere with specific targets needed for the growth, progression, and spread of cancer (NCI 2014). The advantage of targeted therapies is that they are generally better tolerated than traditional chemotherapy and can often be tailored to a specific patient population, making their outcome more predictive. Development of targeted therapies has in some instances resulted in great clinical success, such as the case of trastuzumab and imatinib. Although targeted therapies offer reduced toxicity and enhanced efficacy, often their effects are not durable, and over time cancer cells have a tendency to become resistant to the drug (Kamb et al. 2007). Resistance of targeted therapies can occur in two ways: the target itself changes through mutations so that the targeted therapy no longer interacts well with it and/or the tumor finds a new pathway to achieve tumor growth that does not depend on the target (NCI 2014). This has led researchers and oncologists in recent years to focus their efforts on the development of combined targeted therapies in an attempt to overcome drug resistance and prolong duration of response. The current approach is to target horizontally by interfering with two or more parallel pathways in a network or to target vertically by interfering at multiple points in a linear pathway (Yap et al. 2010, 2013). Various combination therapies are currently being developed for cancer patients, but only a few success stories have been approved until now. In January of 2014, the US Food and Drug Administration (FDA) approved the targeted drug combination of trametinib and dabrafenib for treatment of patients with metastatic or unresectable melanoma with *BRAF* V600K or V600E mutations (FDA 2014). The field of combination cancer therapies continues to evolve as methods and knowledge expand in drug discovery, preclinical research, and translational and clinical research.

This chapter will outline the current approaches for oncology and combination therapies as well as identify challenges and opportunities to optimize the combinatorial approach from preclinical research to market. The discussion will mainly focus on the combination of targeted therapies such as tyrosine kinase inhibitors. Current expectations from health authorities and considerations needed throughout the clinical development of combinations will also be discussed. Drug development faces many unique challenges, and the application of systems biology, pharmacoki-

netics (PK), and pharmacodynamics (PD) is essential in prioritizing and improving development of these combinations in order to ensure a higher success rate.

## 1 Preclinical Development

Identification and validation of a drug target is the beginning of a lengthy drug development process. In the past, anticancer agents were selected for further testing based on evidence of antiproliferative properties, with little knowledge of the biological pathways involved. Currently, the selection of a drug is based on its capacity to target the biological process involved in cancer (DeVita and Chu 2008; Hidalgo 2008; Yan et al. 2014). The drug target may be a protein involved in the pathway that plays a role in cell proliferation, survival, metastasis, or other pro-cancerous process (Lord and Ashworth 2010; Schenone et al. 2013). Currently, the common approaches for target identification may include proteomics, genetics, bioinformatics, and comparative profiling-based approaches. The targets identified in this process need to undergo validation, using available experimental models (genetic assays, cell-based assays, and animal models) in order to evaluate the effects of modulating the activity of the target (e.g., protein) on the biological pathway of the disease (Benson et al. 2006). Subsequently, assay development (in vitro cancer cell-based assays), high-throughput screening, hit identification, lead optimization, and selection of a candidate molecule for clinical development need to be carried out in order for the compound to move forward in the development process. The details of the processes mentioned above are beyond the scope of this chapter. Here we aim to discuss the in vitro and in vivo approaches used to assess efficacy once a lead molecule has been selected for further development and how these approaches are used to guide first in human (FIH) studies. The in vitro and in vivo approaches used in drug development continue to be optimized in order to improve their predictive value of combinatorial therapeutic effects in the clinic (Al-Lazikani et al. 2012; Tortora et al. 2008; Clark et al. 2010).

## 2 Combination Therapy Assessment In Vitro

Human cancer cell lines are an essential tool in drug discovery and efficacy assessment of targeted therapies. Testing potential anticancer compounds against a variety of patient-derived tumor cancer cell lines is routinely performed in preclinical development. In the past, the predictability of efficacy using these cell lines was adequate for cytotoxic agents; however, the predictability for targeted agents has been poor in part due to cancer heterogeneity and the limited number of cell lines such as the National Cancer Institute 60 (NCI60) cell line platform previously used in drug screening (Sharma et al. 2010). The importance of a wide variety of cell lines used to test the compound of interest is illustrated by targeting tyrosine kinases

(TK) involved in tumor pathways. The targeting of TK has resulted in high response rate in chronic myeloid leukemia (CML), while in other cancers it has shown response in only a subset of patients (Le et al. 2008).

With the analysis of more and more cancer cell lines, it was recognized that tumors represent a wide range of genetic heterogeneity between and within cancer types. The application of genetic analysis of these cell lines, together with the ability to analyze larger panels of a variety of cell lines, has led to an improvement in the predictability of efficacy. In the Cancer Cell Line Encyclopedia (CCLE) project, researchers used genomic data to investigate 24 anticancer drugs in 479 cancer cell lines which led to the identification of genetic, cell lineage, and gene-expression predictors of drug sensitivity (Barretina et al. 2012). Current cell line platforms include >500 cell lines, and the Center for Molecular Therapeutics has established a platform that includes 1200 cell lines with genomic profiles (Barretina et al. 2012; Yang et al. 2013).

These cell-based methods are now routinely used in the development of targeted anticancer drugs by screening the different cell's sensitivity toward a compound. However, targeted agents are subject to eventual drug resistance; therefore, current research efforts are aimed at addressing drug resistance and/or improving efficacy by developing combination therapies. In this respect, using cell-based assays for combination development becomes more complex due to the multitude of possible combinations and the limitations this implies. Combination therapies aim to target parallel signaling pathways or different nodes in the same pathways that are involved in cancer, or compensatory loops linked to the pathway (Yap et al. 2010, 2013). Several preclinical strategies can be employed in determining which combinations have the most potential for further development: hypothesis-free drug-combination screening, rational drug-combination screening, proteomics, and evolutionary computational techniques (Al-Lazikani et al. 2012; Carragher et al. 2012).

Unbiased approaches to drug combinations refer to a systematic high-throughput/high-content screening without a hypothesis or knowledge of the underlying biology. This approach is complimentary to hypothesis-driven approaches and may result in unexpected combinations that would not have been conceived of otherwise. In high-content screening, cell-based assays using fluorescent microscopy can be used to assess different modes of action of a compound in cell viability: mitosis, DNA damage, cell cycle arrest, and caspase-mediated apoptosis. This methodology can be employed in deciding which future drug-combination studies to pursue based on the two (or more) drug's distinct mechanism of action (Carragher et al. 2012).

Another unbiased approach is the systematic genome-wide screen for loss or gain of function in tumor cells. In this approach, the aim is to identify genes that when silenced (using RNA interference [RNAi]) results in a loss of function or when activated (using cDNA overexpression) results in a gain of function (Ashworth and Bernards 2010). The simplest screening in this approach measures cancer cell viability using a colorimetric assay in a high-throughput manner. In an RNAi screen targeting thousands of genes, the tumor suppressor NF1, which inhibits RAS activity, was identified as a mediator for resistance of RAF inhibitors in $BRAF^{V600E}$-mutant cancers (Whittaker et al. 2013). The functional genomic approach is being applied more readily to identify optimal and rational combination therapies with synergistic properties (Ashworth and Bernards 2010; Bernards 2014).

Functional proteomics is an emerging approach to optimize combination drug therapy. Although genetic alterations are the basis for cancer, tumor cell characterization and drug response are regulated by protein function. Functional proteomics examines protein function via protein activation, protein-protein interactions, and pathway activation and mapping (Petricoin et al. 2005). Ultimately, proteomics may provide information regarding the relationship between different pathways involved in cancer and aid in optimizing drug combinations.

In contrast to the hypothesis-free approach, the rational combinatorial approach relies on prior knowledge of the pathways involved in cancer and thereby targets oncogenic signaling pathways (parallel or linear pathways). One approach is to target proteins involved at nodes in parallel pathways such as the phosphatidylinositol 3-kinase (PI3K)–AKT–mammalian target of rapamycin (mTOR) involved in angiogenesis and cell survival and the RAS/RAF/MEK/mitogen-activated protein kinase (MAPK) pathway involved in cell progression, proliferation, and migration (Chappell et al. 2011). Clinical trials investigating combination therapies of MEK inhibitor and PI3K or mTOR inhibitors are currently being conducted in various cancers [clinicaltrials.gov]. In testing combination therapies in vitro using any of the aforementioned methods, it is important to quantify the combinatorial effects and determine if these effects are synergistic, additive, or antagonistic. A combination of therapeutic drugs should ideally have synergistic effects with less toxicity and reduced or delayed time to resistance (Chou 2010). The Chou–Talalay method or a modification of such is typically employed to quantify the synergy in combination cell assays. The dose–effect relationship is characterized for each agent independently, since the potency and dose–effect curve may be different for each agent. Subsequently, the assay is carried out using the agents in combination, and the combinatorial index is determined using the equations put forth by Chou–Talalay.

Integrating all the data outputs from the different experimental approaches mentioned above using a systems biology approach is essential in harnessing all the information to make better decisions on which are the combinations with the highest chance of success. Currently, most combinations in late-stage development are tested for their combinatorial effects by assessing one drug that is either approved or in late-stage development in combination with one that is in the early-stage development pipeline. This has the advantage that one anticancer agent is relatively well characterized, and this can reduce the number of combinations to be tested preclinically by eliminating those compounds with overlapping toxicities, overlapping metabolic pathways, etc. The codevelopment of two or more new molecular entities in vitro can be achieved following the principles mentioned above; however, the translation of this in a clinical setting as the first in man study remains a challenge.

Using in vitro cell-based assays in the past had the limitation of poor predictability of effects in vivo or in the clinic. This limitation has been reduced as more cell lines are characterized and validated for preclinical screening, as well as the availability of high-throughput screening to characterize the cells at a genomic and protein level (Wilding and Bodmer 2014). In vitro tools are important in combination drug development given that testing the vast number of combinations in vivo is not feasible. Still, preclinical studies in animal models play a central role in drug development.

## 3 Combination Therapy Assessment In Vivo

Animal models of human cancer contribute to the understanding of the pathophysiology of cancer, help identify therapeutic agents in combination or as single agents, and contribute to understanding mechanism of drug resistance. Furthermore, important translational information such as in vivo pharmacology, pharmacokinetics, and pharmacodymamics can be acquired via animal models. Oncology animal models include ectopic (subcutaneous, intramuscular, etc.) xenografts, orthotopic xenografts applied to the organ or tissue type where cancer was detected, germ-line transgenic or conditional transgenic models, carcinogen-induced models, and patient-derived tumor xenografts (PDTX) (Ruggeri et al. 2014). Each of these models has its strengths and weaknesses and different levels of clinical predictability. The most common models used in oncology drug development are the ectopic and orthotopic xenograft; however, the PDTX continues to gain notoriety for its potential in improving efficacy predictions in humans. The PDTX allows for the propagation of freshly excised human tumors in immunocompromised mice. The advantage of this model is that it preserves the genetic, histological, and phenotypic features of the tumor, maintains stem cell components, maintains the potential to metastasize, allows for biomarker assessment, and provides relatively high clinical predictability. The limitations of this model is the need to use freshly excised human tumors, a laborious process, the dependency on engraftment success (which can vary between cancer types), and longer time required for the tumor development compared to other in vivo models (Ruggeri et al. 2014; Williams et al. 2013).

In vivo models of PDTX are also being used in combination drug development in assessing efficacy of combinations. The use of PDTX in combination drug development has demonstrated its predictability of efficacy in the clinical setting. An example of this predictability was demonstrated using pancreatic PDTX where the combination of gemcitabine and nab-paclitaxel demonstrated synergistic tumor regression compared to use of either single agent (Tentler et al. 2012). Further, when the combination was tested in phases 1–2 clinical trials, the combination demonstrated a survival benefit in patients with pancreatic cancer (Von Hoff et al. 2013). Although PDTXs have greater clinical predictability over other in vivo models, there are examples where this predictability has not been shown in the clinical setting. This may be due to various reasons: the low number of PDTX tested preclinically, the use of PDTX from early stages of the disease which would not be predictive of efficacy in advance disease, and finally the lack of clinically relevant doses used in the animal models (Rosfjord et al. 2014). In the evaluation of targeted therapies, a recent study investigated the therapeutic potential of PI3K pathway inhibition in the treatment of basal-like breast cancer via the antitumor effect of the mTOR inhibitor MK-8669 and AKT inhibitor MK-2206 in two patient-derived xenograft models (Xu et al. 2013). The authors of this study observed a synergistic effect on cell proliferation and tumor growth with these two inhibitors, thus providing a preclinical rationale for clinical investigation of this combination in basal-like breast cancer. Clinical studies of this combination will

determine if the predictability of efficacy of the xenograft models were accurate. These examples highlight the importance of utilizing more than one xenograft model well as the importance of drug exposure in improving the predictability in a clinical setting. Using PDTX in optimizing combination therapy to improve treatment of cancer may also allow for the study of mechanisms of drug resistance. Current efforts are being taken to establish tumor tissue banks that include samples from treatment-naïve patients who have relapsed in order to investigate the molecular and genetic components that may contribute to drug response and resistance (Das Thakur et al. 2014).

These in vivo models are also essential in translational aspects of drug development by assessing pharmacokinetic/pharmacodynamic (PK/PD) relationships in the disease model. The PK/PD data from these animal models can then be integrated with quantitative approaches to aid in appropriate dose selection for clinical trials which is essential in obtaining an appropriate benefit/risk ratio for patients (Venkatakrishnan et al. 2014). Similar translational approaches can be used to assess drug interactions of combinations and dose scheduling. Assessing the PK/PD in preclinical tumor models is important for translating the results to a clinical setting, especially in trying to predict the clinically relevant doses to be tested in cancer patients.

In complement to in vitro and in vivo approaches, in silico approaches have been developed to formalize the knowledge on cellular signaling pathways and assess the perturbation of systems by targeted agents. This systems biology approach allows the characterization of different pathways and their potential interactions. Even though the methodology has been known for several years, its application has only started to be utilized recently due to the availability of more selective substrates and/or inhibitors. The accurate perturbation of the system by identified target allows a better characterization of the pathways and their interplay. A model of the EGFR pathways was proposed by Klinger et al. detailing the interplay between the RAF and PI3K pathways (Klinger et al. 2013). Based on in silico models, the authors identified major cross talk between both ERK and AKT. This initial experiment supported the need for a combination inhibiting both pathways. Their hypothesis was secondly tested in a DLD-1 colorectal xenograft model treated with either erlotinib or GDC-0973 as single agents or as combination therapy. The results confirmed the superiority of the combination. Melas et al. and Kirouac et al. propose a review of the application of a simplified approach of these complex systems biology models in oncology (Melas et al. 2013; Kirouac and Onsum 2013). As it is currently difficult to provide an extended description of the different cellular signaling pathways in the tumor, a pragmatic approach is to define the pathways through functional modules and nodes. This modular approach allows mitigating the complexity of a complete description of the system by focusing on its main element of interest. Kirouac et al. applied this proposed methodology to a specific example (Kirouac et al. 2013). They linked the molecular target of interest, ErbB receptors, with two specific pathways, PI3K/AKT and Ras/MEK/ERK, to tumor growth. Cross talk and feedback loops were implemented based on calibration experiments. The in silico results showed a synergistic activity of an ErbB3 inhibitor, MM-111, with lapatinib

and herceptin. These initial outcomes were used as basis for further in vitro and in vivo experiments. This specific example supports the benefit of a systematic approach in the context of the development of combinations to aid in better understanding of the interplay between the different pathways and to better design preclinical experiment. In the context of combination therapy, it is crucial to identify the concentrations necessary to achieve proper pharmacological activity. A simpler example of a similar strategy with a single agent was described by Salphati et al. (2010) and Wong et al. (2012). In their work, the authors initially established a PKPD model to relate the concentration of GDC-0973, a MEK-1 inhibitor, with the percentage of change of pERK. Once established, the percentage of change of pERK influenced tumor growth. Finally, the results obtained preclinically were in line with the proposed dose in the clinic.

A more general description of the quantitative interplay between two drugs in combination was proposed by Rochetti et al. which extended the tumor growth model to the combination of two anticancer drugs initially developed by Simenoni et al. (Rocchetti et al. 2007; Simeoni et al. 2004). These compartmental models described the kinetic of the tumor through pools of cells connected to each other through first-order constant. Terranova et al. applied this model to different drug combinations, demonstrating the ability of such a model to capture and quantify the impact of a combination therapy in a preclinical xenograft models (Terranova et al. 2013). One of the main limitations of this type of model in the context of combination of targeted agents is its empiricism and absence of integration of the underlying pharmacological mechanism.

Overall, there is a large interest in the use of in silico models to allow a better integration and interpretation of the available knowledge in preclinical research. In the context of combination therapies, few axes of research are currently explored to provide a better support to the definition of the human pharmacological dose. Despite the progresses made so far, many challenges remain ahead with the multiplicity of the mechanism of action including immunotherapies. The evaluation of such combinations will necessitate a better understanding of the tumor and its environment to allow an improved predictability of the efficacy and safety of tested therapies. Such a perspective supports the need for multi-scale mathematical models integrating cellular pathways, cellular environment, and tumor growth.

## 4 Preclinical Safety

Once promising combination therapies have been identified in vitro in cell assays and confirmed via in vivo pharmacology studies, the safety profile of the combination needs to be characterized. Nonclinical toxicological evaluations, including toxicokinetic data, should be conducted for each drug individually, and data supporting the rationale for the combination should be provided prior to starting a clinical study. This can be achieved by doing an integrative nonclinical toxicity assessment for each drug where toxicological findings are identified by target organ in an attempt to predict overlapping toxicities expected from the combination. For

organs at risk of additive toxicity, histopathological evaluations may be added to pharmacology studies evaluating the combination.

In general, toxicology studies investigating the safety of combined drugs intended to treat patients with advanced cancer are not warranted. In addition, nonclinical studies evaluating the combination are not warranted if the human toxicity profile of the individual drugs has already been characterized. The ICH S9 guidance specifies that in cases where human toxicity data is available for one drug but not the other, a pharmacology study to support the rationale for the combination should be provided. This study should provide evidence of increased activity in the absence of a substantial increase in toxicity on the basis of limited safety endpoints, such as mortality, clinical signs, and body weight (FDA 2010b).

## 5 Current Regulatory Guidance for Codevelopment

In December 2013, the FDA issued guidance on the codevelopment of two or more unmarketed investigational drugs for use in combination (FDA 2013). This guidance provides a roadmap for characterizing the preclinical and clinical safety and effectiveness of novel–novel drug combinations.

Before this, the only guidance on combinations is related to fixed-dose combinations where multiple drugs were combined into one pill. Fixed-dose combinations offer the advantage of reducing the pill burden for patients, and their approval relies on the characterization of the clinical safety and effectiveness of each drug included in the combination. Fixed-dose combinations are usually not an attractive development strategy in oncology as most cancer drugs exhibit high toxicities which often require dose reductions and/or dose interruptions. In an era of targeted agents, on-target toxicities can sometimes be attributable to a specific drug, and therefore, oncologists testing potential combinations have the flexibility to titrate one drug while maintaining the other one at its therapeutic dose. The recent guidance on codevelopment of two or more unmarketed drugs clarifies the amounts and types of data needed to demonstrate the contribution of each drug to the overall effect and offers more flexibility to facilitate the development of novel targeted therapies for use in combination regimens in diseases such as cancer for which a large factorial study (requiring monotherapy treatment groups) is not always possible (Woodcock et al. 2011).

Although the European Medicines Agency (EMA) has not provided a specific guidance on the development of combination therapies using novel agents, they have recently published a guidance on the "Evaluation of Anticancer Medicinal Products in Man" where combination therapies are discussed (EMA 2012a). In general, their recommendations are aligned with the FDA when it comes to the level of evidence needed for development of combination therapies. The EMA also emphasizes on the need of PK and PD (biomarkers and clinical markers) sampling for PK/PD analysis related to safety and efficacy for a rational selection of treatment strategies in patients who are at risk for excessive toxicity or ineffective therapy.

## 6 Clinical Development

The clinical development of combination therapies has prompted the need to reassess how clinical studies are designed in order to characterize (1) the most appropriate combination dose, (2) the right schedule of administration, and (3) the enhanced efficacy of the combination as opposed to monotherapy. Current approaches used in clinical development along with considerations needed throughout development from early safety studies to supporting clinical pharmacology study are discussed in the next few paragraphs. Special attention is given on the use of pharmacokinetic properties of individual drugs in optimizing combination therapies.

## 7 Phase 1: Assessing Safety: The Maximum Tolerated Dose and the Optimal Biological Dose

Phase 1 studies in oncology are dose-escalation studies aiming to establish the maximum tolerated dose (MTD) of a drug and obtain reliable information on safety and PK. For cytotoxic agents, the fundamental assumption is that the concentration–effect relationship is very steep, and thus a higher drug concentration would likely lead to more DNA damage, resulting in more cell death (Moore 1991; Mathijssen et al. 2014). Cancer patients are then treated at the MTD or recommended phase 2 dose (RP2D) in subsequent trials designed to characterize the efficacy profile of the drug. Dose-level combinations are typically explored based on the single-agent MTD which is also aligned with regulatory guidance.

In the guidance on codevelopment of novel drugs, the FDA states that when possible, the safety profile of each individual drug should be characterized in phase 1 studies in the same manner as would be done for development of a single drug, including determination of the maximum tolerated dose (MTD), the nature of the dose-limiting toxicity (DLT), and pharmacokinetic parameters (FDA 2013). In absence of this information, the FDA recommends to conduct nonclinical studies of the combination to support initial dosing of the combination in humans.

Dose-escalation methods for phase 1 cancer clinical trials fall into two broad classes: the rule-based designs, which include the traditional 3 + 3 design and its variations, and the model-based designs.

The rule-based designs assign patients to dose levels according to prespecified rules based on actual observations of target events (i.e., the dose-limiting toxicity or DLT) from the clinical data (Le Tourneau et al. 2009). A recent publication reviewing the designs of drug-combination phase 1 trials in oncology revealed that 88 % of clinical studies still use traditional or modified 3 + 3 dose-escalation designs (Riviere et al. 2014). Under this relatively simple design, patients are treated in cohorts of 3, and based on the number of DLT seen in that cohort, decisions on which dose to give the next cohort are made. However, the escalation phase of a combination trial in the context of codevelopment implies a higher level of complexity. Rather than navigating in one dimension, the trial is evolving in a two-dimensional space, the

dose of drug A and the dose of drug B. The determination of MTD highly depends on the escalation-step strategy which could virtually lead to a large number of MTDs. It is therefore critical to properly define the hypothesis underlying the tested combination, i.e., potential pharmacokinetic and/or pharmacodynamic interactions in order to restrict the space of potential clinical doses to be researched in dose combination (Hamberg et al. 2010). In the context of potential interactions, another level of complexity needs to be considered with the dosing schedule of the two drugs. The relative time of administration of the two drugs might have a significant impact on the exposure of the tested drugs in the case of PK interactions. The importance of drug scheduling will be elaborated later in this chapter.

Several strategies can be used for dose escalation in phase 1 trials of two drugs: (1) simultaneous escalation of both agents, (2) alternate escalation of the agents in the series of dose levels, or (3) escalation of one agent to RP2D dose while holding the other agent at a fixed dose (Le Tourneau et al. 2009). The last two strategies may allow the treatment of cohorts in parallel in order to save time in establishing the MTD. Phase 1 combination trials can usually explore only a limited number of dose levels since the MTD for single agents is often known at that time. After declaration of the MTD for a combination regimen, uncertainty may remain about the optimal combination dose that yields the best therapeutic index.

The model-based designs assign patients to dose levels and define the RP2D based on the estimation of the target toxicity level by a model depicting the dose–toxicity relationships. Model-based designs have demonstrated superior operating characteristics compared to rule-based designs in simulation settings: a higher proportion of patients are treated at levels closer to the MTD, and fewer numbers of patients are required to complete the trial (Mandrekar 2014). Several Bayesian model-based designs specific for combination trials have been developed in an attempt to minimize the uncertainty around the optimal combination dose (Thall et al. 2003; Huang et al. 2007; Yuan and Yin 2008; Yin and Yuan 2009). These designs do not require any prior assumptions about the best dose combination, and they aim to guide the dose escalation of the agents based on all toxicities observed. In the approach proposed by Yin and Yuan (2009), the Bayesian model is continuously updated with additional "posterior" data as more patients enter the trial and more outcomes are observed. These newer designs offer a better coverage on the range of treatment dose by allowing exploring unanticipated dosing regimen. In these methods, the dose–toxicity probability curves are updated after each cohort of patients for all agents by using all available toxicity data so that the subsequent cohort of patients may be assigned to the most appropriate dose combination. The ultimate goal is to determine the most active drug combination among those deemed to be safe (Le Tourneau et al. 2009). A disadvantage of using these methods is that they require real-time biostatistical support throughout the escalation part of the trial. Another drawback is that most of them exclusively incorporate toxicity endpoints to establish the MTD although newer designs are also considering efficacy endpoints (Yin et al. 2006; Yin and Yuan 2009).

Interestingly, Cai et al. (2014) published an ascending dose study of two biological agents where the escalation part was based on both safety and efficacy. The two

investigated agents targeted the same pathway (PI3K/AKT/mTOR). Both agents demonstrated partial inhibition of the pathway. The combination of the two agents aimed to a more complete inhibition. Their aim was therefore to define the biological optimal dose combination. Two models were used, one investigating the safety of the combination and the other investigating its efficacy. The design of the trial consisted of two stages: the first stage investigating the safety and the second stage investigating the efficacy. During the first stage, doses were escalated along the diagonal starting from a low-dose combination. The second stage included efficacy information in addition to safety and allowed exploring a new range of doses. However, to restrict potential big escalation or de-escalation that may affect toxicity or efficacy, step rules were put in place to limit the scope to the neighboring previous dose (Cai et al. 2014). The benefit of the proposed approach is to rapidly achieve the area of interest and then allow a more systemic exploration of the zone of interest. However, this approach implies that elements of efficacy need to be readily available. Sweeting and Mander found, as well, this two-step approach was more efficient than decisions based solely on safety data (Sweeting and Mander 2012).

An additional consideration for phase 1 combination trials is the possible interactions between the different drugs used in the combination. This is particularly true for small molecules. The starting dose in dose-escalation studies for drugs used as monotherapy is typically derived from the no observed adverse effect levels (NOAEL) in the most sensitive preclinical species, the conversion from NOAEL to human equivalent dose (HED), and the application of safety factors (FDA 2005). In the case of combination therapies, a drug–drug interaction assessment should be performed using all available in vitro and preclinical information from each drug in order to characterize the interaction risk and establish the most appropriate starting dose in the phase 1 combination study.

The inclusion of pharmacokinetic sampling/analysis is essential in combination trials in order to assess potential interactions between the anticancer drugs being tested. This can be done by comparing the PK data of the drug when used in combination to historical data of the drugs when used as monotherapy. The limitation of this approach relies on the heterogeneity that may exist between different patient populations and variations in assay sensitivities (Le Tourneau et al. 2009). The other alternative is to include a run-in period by administering only one drug, followed by concurrent dosing of other drugs. This strategy would allow one to compare within the same patient the pharmacokinetic profile of the first drug given alone with that obtained in the presence of other drugs (Le Tourneau et al. 2009).

Although toxicity has traditionally been the primary endpoint for phase 1 trials involving cytotoxic agents, this standard MTD approach does not take into considerations important aspects of clinical pharmacology. Most exploratory trials using molecular targeted agents in combinations are failing in the clinic due to enhanced toxicity and little efficacy. The decision to escalate to the next level for combination regimens such as molecular targeted anticancer agents should not only be based on toxicity but also supported by available and relevant PK, PD, and efficacy data. For example, real-time pharmacokinetic assessments during a dose-escalation phase help to understand if exposure to a given drug increases with dose or reaches a pla-

teau at a certain level. It also informs on the interaction between drugs administered concomitantly. The biochemical and biological effects of the combination may be quite complex, and the concentration–effect relationship may depend largely on unknown pharmacokinetic and/or pharmacodynamic interactions between the agents (Le Tourneau et al. 2009). Efforts are being made to integrate information on drug–drug interactions in phase 1 model-based designs. Cotterill et al. recently presented a Bayesian model including the prior information relative to the pharmacokinetic interaction based on physiologically based pharmacokinetic modeling (Cotterill et al. 2015). Moreover, classical oncology drug development programs usually focus on the toxicities observed in the first cycle of treatment (usually 21 or 28 days) and do not adequately evaluate changes in tolerability or cumulative toxicities than can occur over time. This limitation is especially important as targeted therapies are usually intended to be administered chronically, and the tolerability of these agents may be reduced over time.

The emergence of molecular targeted anticancer agents has prompted a shift from the MTD paradigm toward the determination of optimal biological dose (OBD). The identification of an optimal biological dose requires defining the target plasma concentration needed to inhibit a target. The magnitude of inhibition necessary for clinical benefit also needs to be known (Adjei 2006). This can be based on the free fraction of drug which is the concentration that inhibits, for example, 90 % ($IC_{90}$) of the activity of the target (Adjei 2006). To incorporate the OBD strategy in phase 1 trials, a few critical pieces of knowledge are required: (1) the drug hits the target, (2) the target is altered by the drug, (3) the tumor is altered by hitting the target, and (4) giving a higher dose fails to improve outcomes further (Marshall 2012). In order to achieve this, a good understanding of the drug target is needed along with practical methods to measure the target in a clinical trial setting. Since targeted agents are designed to block a specific molecule or intracellular pathway, measuring the activity of downstream markers and alternate pathways may facilitate the determination of pharmacodynamic (PD) effects. The incorporation of pharmacokinetic and predictive biomarker samples in early clinical trial is essential in the determination of the OBD. Predictive biomarkers, including both tumor-specific and surrogate biomarkers, indicate the likelihood of response to a specific antitumor therapy (Smith et al. 2014). Inhibition of BCR-ABL in chronic myeloid leukemia, inhibition of ALK or EGFR in lung cancer; inhibition of BRAF, MEK, or CTL-4 in melanoma cancer; inhibition of HER2 in breast cancer; and inhibition of KIT in GIST are all examples of predictive biomarkers that have been identified over the past decade which led to the approval of several targeted therapies (Smith et al. 2014). Predictive biomarker samples are collected from the tumor ideally or in surrogate tissues when feasible. Collecting biopsies from fresh tumors can be quite invasive for patients with certain types of cancer, especially when needed at repeated occasions, and using normal tissues such as blood or plasma (i.e., circulating tumor cells, platelet-rich plasma, peripheral blood mononuclear cells), skin, or hair follicles may be more practical in some instances (Perkins et al. 2012; Smith et al. 2014). In the absence of validated and clinically qualified predictive biomarkers, information from in vitro cell assays or in vivo pharmacological studies conducted

in xenograft mice models may also provide information on the concentration needed to inhibit the target. The main challenges in identifying the OBD in cancer patients are the significant interpatient PK variability observed with many oral targeted agents and the interpatient tumor heterogeneity.

## 8 Phase 2 and 3: Assessing Efficacy of Combination Therapies

The evaluation of the optimal dose and appropriate schedule is often limited in early clinical trials, and phase 2 trials are an opportunity to collect this information in an attempt to minimize toxicity and maintain efficacy of a combination. Therefore, several combination doses should be tested in parallel in phase 2 trials. Measurements of PK and PD endpoints should be obtained in these trials to characterize the relationships between exposure and clinical outcomes.

The optimization of the appropriate dosing regimen can also be refined during phase 2 studies. Should a drug with a short half-life be administered more frequently in order to maintain levels above the efficacious "target" concentration? Does the safety profile differ between daily dosing and twice daily dosing? What about alternate dosing in comparison to continuous dosing? These are some of the questions that need to be considered during the development of combination therapies. For chemotherapy combinations, several clinical studies were conducted in an attempt to determine the most effective sequence to deliver these drugs. For example, it has been shown that the administration of paclitaxel before cisplatin led to additive and super-additive effects (Panetta et al. 2000). In fact, the sequence of cisplatin before taxol, which has less antitumor activity in vitro, induced more profound neutropenia than the alternate sequence in a clinical study (Rowinsky et al. 1991). Van Moorsel et al. also tested four different schedules of a combination of two cytotoxic agents in patients with solid tumors and determined that the optimal schedule was the administration of cisplatin 24 h before gemcitabine (van Moorsel et al. 1999). More recently, in an effort to understand the resistance to BRAF inhibitor vemurafenib, it was shown that a discontinuous dosing strategy, which exploits the fitness disadvantage displayed by drug-resistant cells in the absence of the drug, forestalls the onset of lethal drug-resistant disease (Das Thakur et al. 2013). The risk of escape or developing compensatory mechanisms may also potentially be reduced by avoiding sustained target blockade and decreasing continuous selection pressures by pursuing alternative dosing/scheduling regimens such as pulsatile dosing (Yap et al. 2013). The incorporation of strategic treatment breaks might help to "reset" tumor resistance and avoid the onset of acquired resistance (Vasudev and Reynolds 2014). This theory has been confirmed in the clinic until now. Although the likelihood of response to BRAF inhibitors is higher in naïve melanoma patients with BRAF mutations, it has been shown that certain melanoma patients will have a secondary antitumor response to BRAF inhibition after cessation of BRAF inhibitor treatment owing to acquired drug resistance (Seghers et al. 2012). Moreover, in

a melanoma patient previously resistant to vemurafenib that had subsequently developed leukemia, the intermittent treatment of vemurafenib and MEK inhibitor cobimetinib caused remission of the melanoma and suppressed progression, proliferation, and ERK activation of leukemia (Abdel-Wahab et al. 2014). The use of pulsatile schedules should be considered for targeted cancer therapies to determine a possible advantage in delivering maximal safe target blockade (Yap et al. 2013).

The measurement of PK and PD endpoints is considered essential in phases 2 and 3 efficacy studies to try to characterize the relationships between drug exposure and the drug effect on the target pathway and downstream cellular processes (Yap et al. 2010). Pharmacodynamic endpoints can refer to both safety and efficacy. In large phase 3 studies testing combination therapies, PK sampling should be included, at a minimum, in a subset of the patients to allow exposure–safety and exposure–efficacy analysis in the target population. Both FDA and EMA encourage PK/PD analysis to support the selection of the combination dose in pivotal phase 3 studies and the clinical benefits of the combination tested (FDA 2013; EMA 2012a).

The safety of combination therapies remains a challenge to overcome. Many targeted agents such as inhibitors of VEGF, EFGR, mTOR, and HER2 pathways have demonstrated enhanced or unexpected toxicity when used in combinations in comparison to monotherapy (Park et al. 2013). However, there have been a few successful cases where the combination was better tolerated than when the drug was used as a single agent. For example, the phase 2 trial that led to the approval of the combination of dabrafenib and trametinib demonstrated higher response rates, longer median progression-free survival (PFS), and less cutaneous toxicity for the combination arm than the dabrafenib monotherapy arm (Menzies and Long 2014). By inhibiting along the MAPK pathway, the addition of trametinib prevented the paradoxical activation of hyperproliferative skin lesions associated with BRAF inhibitors such as dabrafenib. The understanding of opposing functions of some targeted agents as inhibitors or activators of signaling pathways provides new insight into strategies for combining targeted agents that enable both enhanced antitumor efficacy and reduced normal tissue toxicity (Hatzivassiliou et al. 2010; Park et al. 2013).

Overall survival (OS), progression-free survival (PFS), time to progression (TTP), overall response rate (ORR), and duration of response (DoR) are examples of commonly used clinical endpoints in oncology that may be used in the evaluation of exposure–response relationships for combination therapies. In solid tumors, assessing the relationship between drug concentration and tumor shrinkage over time may provide information on the occurrence of resistance, or lack thereof, for combined targeted therapies.

The appropriate design to use in pivotal studies assessing combination therapies should be based on what has been previously demonstrated about the effects of the combination and the individual drugs. In cases where both drugs contribute to the combination and the development of each individual as monotherapy is not possible, the comparison of the combination to the current standard of care (SOC) may be sufficient. However, when monotherapy has proven clinical benefit, the use of one or more of the individual drugs as monotherapy in a study arm, the contribution of the individual drugs may need to be demonstrated using a factorial design, for example (FDA 2013).

## 9 Clinical Pharmacology

In terms of supporting clinical pharmacology programs for the codevelopment of two or more unmarketed drugs, the FDA recommends to conduct the same clinical pharmacology studies for each of the individual drugs in the combination as would be done if the drugs were being developed separately (FDA 2013). However, studies to address intrinsic and extrinsic factors could be conducted with the combination instead of the individual drugs. Supporting clinical pharmacology studies should be conducted with the combination in situation where *the individual drugs in the combination cannot be administered separately*. The role of pharmacogenomics should also be investigated and incorporated into the combination drug development plan to identify potential sources of pharmacokinetic or pharmacodynamic variability.

Food and drug interactions are examples of extrinsic factors that can influence the exposure of drugs by interfering with how they are absorbed or metabolized.

The absorption of drugs may increase, decrease, or remain unchanged when taken simultaneously with food depending on the physical properties of the drug. In the recent approval of GSK's combination trametinib and dabrafenib, a decrease in exposure was observed for each drug when administered as monotherapy with food, and thus a food restriction has been added to the label: patients are instructed to take the combination at least 1 h before or at least 2 h after a meal. In a scenario where one drug has no food effect but the other has a food restriction, one could assume that the restriction would apply to both drugs when taken in combination. In some cases, a food effect study with the combination may allow a less restrictive label. Information on food effect should ideally be obtained as early as possible in the development (i.e., phases 1–2 studies) as it may help in defining the optimal combination dose as well as reduce interindividual PK variability.

Another factor that may affect the extent of drug absorption is the gastric pH (EMA 2012b; Mathijssen et al. 2014). A review of anticancer drugs recently approved has shown that drug–drug interaction studies with agents that can suppress gastric acid, such as proton pump inhibitors, antacids, or histamine receptor antagonists, are becoming a standard in the clinical pharmacology assessment of drugs. Most targeted anticancer agents are small molecules administered orally. These usually fall into either the BCS class 2 category (low solubility, high permeability) or the BCS class 4 category (low solubility, low permeability) with often pH-dependent solubility making them potential victims when combined with drugs that can alter the gastric pH. As with food, it may be of relevance to assess this potential interaction with combination therapies.

Human ADME studies are essential in the drug development process and should be conducted for each of the individual drugs in a combination. The identification of the major biotransformation pathways of a drug helps in understanding how coadministration of another drug may impact the PK in humans. The most common drug–drug interactions are caused by changes in metabolic routes that are related to an expression or functionality of cytochrome P450 iso-enzymes (Mathijssen et al. 2014). 50 % of all currently prescribed drugs are metabolized by the CYP3A4

enzyme (Eichelbaum and Burk 2001). Once again, it may be of relevance to conduct drug-interaction studies with the combination, especially in cases where both drugs are known to affect the same enzyme. Two combined week inducers of CYP3A4 may potentially lead to a significant decrease in plasma concentration which in turn may result in a loss of efficacy of drugs that are substrates of CYP3A4 such as many oral contraceptives, for example. The combination of a moderate inhibitor of CYP3A4 with a weak inhibitor of the same enzyme could lead to a significant increase in plasma concentration and thus a potential increase in toxicity of co-medications metabolized by CYP3A4. In these two examples, a contraindication on the use of CYP3A4 substrates could be needed for the combination but not when each drug is used individually.

Hepatic and renal impairments are examples of intrinsic factors that can influence the exposure of drugs by interfering with how they are excreted. When there is sufficient information to indicate that the PK of the individual drugs is affected by impaired hepatic or renal function, it may be reasonable to recommend dosing adjustments for a combination according to the degree of hepatic or renal impairment (FDA 2003). As anticancer drug combinations are normally not developed as fixed-dose combination, dose titration remains a possibility for physicians. In cases where the information on hepatic or renal impairment is unknown for individual drugs, it may be relevant to conduct such studies with the combination. If two drugs in a combination are both eliminated via hepatic metabolism, the assessment of renal impairment is still warranted as it can inhibit some pathways of hepatic metabolism, leading to increases in drug concentrations. The FDA and the EMA recommend that drugs intended for long-term administration be subjected to pharmacokinetic assessment in patients with both hepatic and renal impairment (FDA 2003, 2010a; EMA 2005, 2014).

The caveat of conducting clinical pharmacology studies with combinations is that it may be difficult to determine which drug is responsible for the overall observed effect. One concern of the regulatory authorities is that concurrent development of two or more novel drugs for use in combination generally will provide less information about the safety of the individual drugs than would be obtained if the individual drugs were developed alone (FDA 2013). For supporting clinical pharmacology studies, one could consider having multiple arms in the patient studies in order to assess the properties of the drugs when administered alone and in combination. This may particularly be of interest for studies that are known to have long enrollment periods such as hepatic and renal impairment studies in non-cancer populations as it may allow saving time during the development of the combination.

## 10 Additional Considerations

In addition to the considerations needed throughout preclinical research and clinical development, additional challenges may be encountered during the development of combinations.

The number of tablets or capsules that a patient takes on a regular basis should be considered when developing combination therapies with orally administered drugs. Formulations should be optimized as early as possible in the development process of combination therapies in order to limit the pill burden for patients and ensure better compliance.

Collaboration between drug companies and between academia and industry has become essential in prioritizing promising combination therapies based on compelling biologic rationale and strong preclinical data. There are several examples of collaboration in the clinical testing of combination cancer therapies such as I-SPY 2 TRIAL and BATTLE 1 and 2. Many drug companies are joining their efforts in the development of combination cancer therapies: Merck and AstraZeneca, Bristol-Myers Squibb and Novartis, and Lilly and Merck, to name a few. The Biomarkers Consortium is another example of public–private biomedical research partnership that endeavors to accelerate the development of biomarker-based technologies, medicines, and therapies for the prevention, early detection, diagnosis, and treatment of disease such as cancer (The Biomarker Consortium 2015).

Several financial challenges are linked to combination drug development including the expense of developing knockout and other animal models and RNA sequence libraries and creating enough study drug to test (National Cancer Policy Forum 2011). In addition to development costs, the introduction of costly new cancer drug combinations on the market will further increase pricing pressure on pharma companies. In 2012, the FDA approved using the targeted therapy medicine pertuzumab in combination with trastuzumab and docetaxel to treat HER2-positive, metastatic breast cancer which hasn't been treated with either trastuzumab or chemotherapy yet. The addition of pertuzumab to trastuzumab more than doubled the monthly cost of the treatment for breast cancer patients (Staton 2012). Current pricing models will lead to very high costs for cancer combinations and may be prohibitive in some countries. The cost of combination therapies should not solely be driven by adding individual drug cost, but also longer duration of treatment due to improvement in clinical benefits should be considered. Reimbursement solution will likely require use of an innovative pricing model or managed entry agreement tailored to specific payer's need and feasibility of implementation in local markets. For example, one could envision pricing a novel–novel combination as a regimen and not as individual drugs, thus introducing substantial discounts relative to individual pricing (Life Science Leader 2014). The focus will increasingly be on whether incremental value of combination regimen versus standard of care (and the component of combo) is worth the price. Some patients could face financial challenge when they have to pay significant out-of-pocket copayment for cancer drugs. Once again, the industry would benefit from working together to introduce new pricing models.

## 11 Conclusion

Several nonclinical approaches such as in vitro cell lines, in vivo xenografts model, and in silico models are currently used for the selection of potential combination therapies for cancer patients and to guide first in human studies. Today, access to

larger cancer cell banks, high-throughput screening methods to characterize the cells at a genomic and protein level, and a variety of xenograft models have improved the predictability of combinatorial therapeutic effects in the clinic. The use of combined targeted agents in xenograft models and improvement of biomarker measurements in tissues may eventually allow a better understanding of mechanisms of drug resistance.

Dose-escalation methods in phase 1 studies are now being revised in an attempt to move from sole safety assessment toward the characterization of optimal biological combination dose which is both safe and ensure inhibition of drug target(s). Efforts also need to be continued in the refinement of dosing regimen and dosing schedules. The use of systems biology and the incorporation of pharmacokinetic and pharmacodynamic strategies throughout clinical development are essential in improving our understanding on the relationships between exposure, target engagement, safety, and efficacy. Knowledge on the pharmacokinetic properties of individual drugs plays a key role in optimizing supporting clinical pharmacology studies needed for the development of combination therapies. Finally, the pill burden, the cost of developing and commercializing combination therapies, and the increased need for collaborations between industries also need to be considered.

The combination of tyrosine kinase inhibitors has revolutionized the way cancer therapies are being developed in the industry, but unfortunately, the number of success stories has been lacking, often due to enhanced toxicity. The field of combination therapies is now shifting to include immunotherapies with the recent success of targeted agents such as the CTL-4 inhibitor ipilimumab for melanoma cancer and PD-1 and PDL-1. Immunotherapies have increased the level of complexity of combination development. This emphasizes the need for a better understanding of tumor physiology and advocates the development of more complex mathematical model to integrate all available information. However, in addition to tumor heterogeneity, interpatient variability and drug resistance remain the biggest challenges to overcome in oncology.

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## Generic

EMA (2012a) Guideline on the evaluation of anticancer medicinal products in man

EMA (2012b) Guideline on the investigation of drug interactions

EMA (2014) Draft guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function

FDA (2003) Pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling

FDA (2005) Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers

FDA (2010a) Draft guidance: pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling
FDA (2010b) S9 Nonclinical evaluation for anticancer pharmaceuticals
FDA (2013) Co development of two or more new investigational drugs for use in combination
FDA (2014) Trametinib and Dabrafenib

## Serial (Book, Monograph)

NCI (2014) Targeted cancer therapies. National Cancer Institute

# Chapter 9
# Role of Pharmacokinetics: Pharmacodynamics in Biosimilar Assessment

**Antonio da Silva and Didier Renard**

**Abstract** The rapid advancement of recombinant DNA technology throughout the 1980s and the 1990s combined with progress in our scientific and pharmacological understanding of the functions of growth factors, cytokines, and cell receptor proteins in the mediation of human physiology and their eventual role in driving disease led to the development of biologically derived therapies that were either copies of those proteins (e.g., growth factors) or targeted them (e.g., monoclonal antibodies, mAbs). However, the complexity in the development and manufacturing of these biological therapies, aka "biologics," associated with lack of competition, led to them being priced at very high levels resulting in restrictions to patient accessibility and financial straining of healthcare systems (Kaul..). More recently, the patents associated with those biologics have started to expire, paving the way for the development and commercialization of follow-on biologics, aka biosimilars, that may be marketed at a lower cost than the brand name biologic product improving patient access. The development of biosimilars in highly regulated markets follows a very strict step-by-step pathway that is distinct to that used for the development of small molecule generics. It includes the conduct of pharmacokinetic/pharmacodynamic (PK)/(PD), efficacy, and safety studies in one or more indications to confirm the established high degree of structural and physicochemical similarity to the reference biological and rule out any differences in safety, efficacy, and immunogenicity resulting from any differences in the manufacturing process. This chapter aims to describe the increasingly important role pharmacokinetics and pharmacodynamics assessments play in biosimilar development and how they provide a setting for creative and innovative methods to support the regulatory approval of high quality biologics.

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## 1 Introduction

Significant advancements in the last decades of the twentieth century in molecular biology, such as gene identification and cloning, recombinant DNA technology, and large-scale manufacturing of recombinant proteins for clinical use, led to a revolution in healthcare with the introduction of therapeutic biologics. These first biologics were either copies of naturally occurring proteins, such as growth factors, cytokines, insulin and peptide hormones, or immunoglobulin (IgG)-based therapeutics composed of full length mAbs and receptor fusion proteins made to target specific plasma circulating proteins or cell surface receptors. Today, a large number of biologics have been authorized as therapeutic agents in a broad spectrum of diseases and have had a significant impact in clinical outcomes. However, costs associated with these biologics have been a significant factor in restricting accessibility and thus optimal value in healthcare systems (American Cancer Society 2010).

These recombinant therapeutic proteins are typically produced by large-scale fermentation using either bacterial (e.g., *E. coli*) or eukaryotic (e.g., CHO—Chinese Hamster Ovary) cell systems and are typically large molecules ranging from approximately 16–20 kDa for growth factors to 150 kDa for full length therapeutic mAbs. Their molecular composition (primary structures) is complex and express secondary, tertiary, and quaternary structures as a result of local structural confirmations, three-dimensional shape, folding, and subunit interactions which form the overall protein complex. Structural modifications also include degradation, aggregation, and oxidation, and, in the case of eukaryotic expression, post-translational modifications inside the cell during production and manufacturing. Amongst these post-translational modifications are acetylation, phosphorylation, and methylation. These modifications can have an impact on the pharmacological properties of the biologics by affecting their pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity and, therefore, safety and efficacy profiles.

A biosimilar is a manufactured biologic that is highly similar to an approved reference biologic. The proposed biosimilar for development is developed via a reverse engineering approach resulting in a new biologic with the same selectivity and specificity to the target, mechanism of action, primary structure, and comparable physicochemical and purity profiles as the reference biologic. In highly regulated markets, biosimilars are only authorized for marketing approval after demonstrating sufficient similarity to the original biologic from both an analytical and clinical perspective. Any analytical differences between the reference product and biosimilar must be justified and shown to have no clinically meaningful effect on the efficacy, immunogenicity, and safety of the biosimilar.

Development starts with comprehensive and sensitive analytical testing to ensure comparable quality, followed by biological characterization and in vivo pharmacokinetic (PK)/pharmacodynamic (PD), safety, and efficacy studies. The clinical development strategy is not to demonstrate clinical benefit per se, as this has already been shown for the reference

biologic, but to confirm that the two products are highly similar in regard to efficacy, safety, and immunogenicity meaning that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product, notwithstanding any minor differences in clinically inactive components. Hence, traditional clinical endpoints commonly used for a new-in-class biologic, such as overall survival (OS) or progression-free survival (PFS) in oncology, may not be sensitive enough to address those minor differences to establish biosimilarity. Instead, the clinical development of biosimilars is tailored based on scientific reasoning to most sensitively detect and assess potential small structural and physicochemical differences between the biosimilar and the reference product (Weise et al. 2012).

The development of a biosimilar relies on creation of a design space based on analysis of the reference product and then iterative development of the biosimilar to fit the defined specifications. Early process development is essential, and later development cannot compensate for this initial generation of a "highly similar" candidate product. As the complexity of the reference product increases, the initial technical development phase, spanning from molecular design and definition of analytical methods through the establishment of the final clinical manufacturing process for commercial use, becomes more challenging, and the likelihood that multiple iterations will be needed increases (Fig. 9.1, McCamish and Woollett 2011, 2012).

The aim of this chapter is to review the biosimilar guidances in highly regulated markets, such as the United States (US), European Union (EU), and Japan, and the critical role PK and PD plays. The clinical studies and data generated for already approved biosimilars and how these guidances evolved to address the greater complexity of therapeutic IgG1/antibody based biologics versus the growth factors class of biosimilars that characterized the first wave of regulatory approvals will be reviewed. As such, the increasingly central role that PK/PD will play in the future provides simultaneously a challenge but also an opportunity to open new innovative pathways to support the approval of biosimilars.

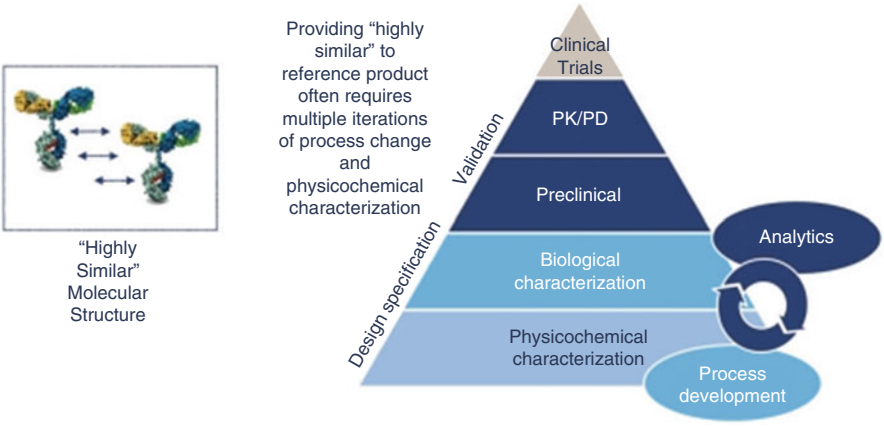


**Fig. 9.1** The biosimilar development paradigm

## 2 Biosimilar Guidance Overview

The definition of a biosimilar is different depending on the region. Table 9.1 depicts the definition of a biosimilar according to the EMA, FDA, and WHO. In 2005, the European Medicines Agency (EMA) was the first region to implement a guidance for biosimilars, thereby defining an overarching and step-by-step approach to establish similarity to an approved reference biologic (CHMP/437/04 30 October 2005). Subsequently, a draft guidance was published to guide the development of antibody-based biosimilars (EMA 2012) In the USA, the Biologics Price Competition and Innovation (BPCI) Act of 2009 was signed into law in 2010 as a component of the Affordable Care Act and aimed at reducing costs and increasing patient access.

In February 2012, the US Food and Drug Administration (FDA) issued three draft guidance documents for industry on biosimilars: quality considerations, scientific considerations, and questions and answers regarding implementation of the BPCI Act of 2009. These were subsequently finalized in 2015 (FDA 2015a, b). In these guidances, the FDA defined that the assessment of biosimilars would be determined case-by-case and based on a "risk-based totality of evidence" approach. The overarching scope of the assessment plan is nevertheless quite similar in its general principles to the EMA guidance and is based on a comprehensive, in-depth structural and functional characterization, nonclinical evaluation, and clinical data from two studies in humans: one addressing pharmacokinetic/pharmacodynamic (PK/PD) comparability and a second one in a sensitive therapeutic indication to confirm comparable efficacy, safety, and immunogenicity to the reference biologic. Based on this "totality of evidence," approval could then be granted to include all of the indications in the label of the reference biologic. Table 9.2 describes the key differences in the scope of clinical studies between an innovative biologic and a biosimilar.

The first biosimilar (Omnitrope®, human growth hormone) was approved in the European Union (EU) in 2006 and followed soon thereafter by the approval of other recombinant proteins of the growth factor type, such as erythropoietin and G-CSF (filgrastim). About 15 biosimilar medicinal products have been market authorized from 2006 to 2014 in the EU as shown in Table 9.3. The first biosimilar market authorizations for a therapeutic monoclonal antibody were granted in 2013 by the EMA for Remsima®/Inflectra®, which are biosimilar versions of Remicade® (infliximab), and Zarxio® (filgrastim-sndz) became the first biosimilar to be approved by the FDA in 2015.

**Table 9.1** Definition of biosimilar products

| |
|---|
| EMA: A biosimilar is a biologic medicine that is developed to be similar to an existing biologic medicine (the "reference medicine") |
| FDA: A product highly similar to an FDA-approved reference product without clinically meaningful differences in safety, purity, and potency |
| WHO: A biotherapeutics product similar to an already licensed reference biotherapeutics product in terms of quality, safety, and efficacy |

**Table 9.2** Unique features of biosimilar studies compared to noninferiority studies for a new biological medicine

| Design features | Noninferiority/superiority study for a new biologic | Biosimilar study |
|---|---|---|
| Objective | Establish positive risk/benefit | Confirm comparability (not patient benefit per se) |
| Comparator/reference product | Specific indication | Often approved for multiple indications |
| Disease model | Disease specific | Usually focusing on the most sensitive indication (if same mechanism of action for all indications) |
| Endpoint | Clinical endpoint (e.g., PFS/OS) | PD marker or semi-surrogate (PFS/OS not feasible) |
| Statistical inference | Formal hypothesis testing | Formal hypothesis testing/ robust estimation (good precision) |
| Analysis approach | 95 % CI | 90 or 95 % CI |
| Design type | Noninferiority (one margin) or superiority | Noninferiority or equivalence (symmetric or asymmetric margins) |
| Role | For specific indication | Totality of evidence and for extrapolation |

*CI* Confidence interval, *NI* Noninferiority

More recently, the FDA has published draft guidance on the use of clinical pharmacology studies for biosimilar development (FDA 2014). These studies are regarded as a critical part of the overall demonstration that there are no clinically meaningful differences between the proposed biosimilar and the reference product. The guidance provides instructions on appropriate study design (population, dose selection and route, choice of PK and PD endpoints) to make the study most sensitive to detect and evaluate differences in the PK and PD. It further provides guidance on the appropriate confidence interval for the ratio of geometric means in biosimilarity assessment. Overall, the guidance emphasizes the importance and sensitivity of PD data and PK/PD assessments in the overall biosimilarity exercises and includes the possibility that PK/PD studies may be sufficient to completely assess clinically meaningful differences between products and to support definition of biosimilarity.

## 3 Analytical Considerations

The successful development of a biosimilar relies fundamentally on the ability of its manufacturer to ensure that it is identical in amino acid sequence and comparable (EU) or highly similar (United States) to a previously approved biologic by

**Table 9.3** Currently approved biosimilars in EU and USA (adapted from Tsiftsoglou et al. (2013))

| Biosimilar | Sponsor | Market and date |
|---|---|---|
| Omnitrope® (somatropin, rHGH) | Sandoz GmbH | EU-2006 |
| Valtropin® (somatropin, rHGH) | Biopartners GmbH | EU-2006 |
| Binocrit® (epoetin alfa) | Sandoz GmbH | EU-2007 |
| Epo Hexal® (epoetin alfa) | Hexal AG | EU-2007 |
| Abseamed® (epoetin alfa) | Medice Arzneimittel Putter GmbH & Co. KG | EU-2007 |
| Silapo® (epoetin alfa) | Stada Arzneimittel AG | EU-2007 |
| Retacrit® (epoetin alfa) | Hospira UK Limited | EU-2007 |
| Ratiograstim® (G-CSF) | Ratiopharm GmbH | EU-2007 |
| Biograstim® (G-CSF) | AbZ-Pharma GmbH | EU-2008 |
| Tevagrastim® (G-CSF) | Teva GmbH | EU-2008 |
| Filgrastim Hexal® (G-CSF) | Hexal AG | EU-2009 |
| Zarzio® (G-CSF) | Sandoz GmbH | EU-2009 |
| Nivestim® (G-CSF) | Hospira UK Ltd | EU-2010 |
| Remsima® (infliximab, anti-TNFα) | Celltrion Healthcare Hungary Kft. | EU-2013 |
| Inflectra® (infliximab, anti-TNFα) | Hospira UK Limited | EU-2013 |
| Zarxio® (filgrastim-sndz) | Sandoz Inc. | US-2015 |

*rHGH* recombinant Human Growth Hormone, *G-CSF* granulocyte colony-stimulating factor
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correlating the structural and physicochemical attributes (i.e., the so-called Quality Attributes) of the product to the quality, safety, and efficacy (Europe) or safety, purity, and potency (United States) of the previously approved product. This is accomplished by an extensive and in-depth characterization of the reference biologic using state-of-the art analytics and technologies. Post-translational modifications such as glycosylation are not directly controlled by the recombinant DNA sequence encoding for the biological but rather by the host cell used and environment in which the host cell expresses it, i.e., media, cell density, etc. In addition, the extent to which these modifications are imbedded in the molecule will vary between different manufacturing batches. This variability defines a range, or "goal posts," within which each of these multiple quality attributes are defined for the reference biological. This is a key step because any one of these given quality attributes can have an impact on the pharmacological profile of the biological that will be reflected in its PK, immunogenicity, efficacy, and/or safety. Guided by this predefined quality profile of the reference biological, the sponsor will then optimize a technical development process, following a reiterative process (Fig. 9.1), that is expected to

ultimately generate a biosimilar with a comparable or highly similar profile. This characterization is complemented by sensitive in vitro functional characterization analytics to ensure correspondingly comparable pharmacological properties, such as affinity by Surface Plasma Resonance (e.g., BiaCore®) to the target (e.g., growth factors in the case of filgrastim or TNFα in the case of anti-TNFα mAbs) as well as to a comprehensive panel of Fcγ-Receptors (e.g., CD64, CD32, and CD16) that are known to play a key role in the interaction of therapeutic antibodies to effector cells and to the neonatal Fc-receptor (FcRn) that plays a key role in the clearance mechanisms of therapeutic antibodies. These data are then further complemented by in vitro and in vivo testing to confirm comparable potency to the reference biological. Ultimately, the sponsor should be able to demonstrate that its biosimilar displays a high degree of similarity at this stage before embarking onto the clinical studies. The extent of clinical work to be carried out should then be defined based on any residual differences in some quality attributes and a good degree of confidence that they are of no clinical relevance in terms of efficacy and safety based on a sound scientific rationale.

## 4 Role of PK/PD in the Development of Biosimilars

Bioequivalence studies are normally required and performed to evaluate the PK and PD comparison of the proposed biosimilar to the reference marketed biologic. The objective is to demonstrate the biosimilar is not meaningfully different from the reference originator biologic in terms of PK/PD outcomes. Therapeutic equivalence is concluded when the 90 % or 95 % confidence interval for PK and PD, respectively, is completely contained within the prespecified equivalence limits. Two biologicals are expected to be bioequivalent, i.e., no significant differences, and result in the same clinical outcomes if they have been shown to be highly similar at the molecular characterization level and when administered with the same route of administration. In certain circumstances, PK/PD data that demonstrate similar exposure and response between a proposed biosimilar product and the reference product may be sufficient to support approval of a biosimilar in the absence of a confirmatory efficacy clinical study. The rationale to support this development pathway would depend heavily on a comprehensive and in-depth characterization of the biosimilar using sensitive analytics that would demonstrate high degree of similarity at the structural and physicochemical level. This is envisaged in current regulatory guidance (FDA 2014).

For PK studies, bioequivalence is assessed using the same methods as with a small molecule, i.e., comparing the rate and extent of absorption as assessed using $C_{max}$, (AUC0 → last), and AUC0 → ∞ $C_{max}$ as primary endpoints. Parameters such as time to reach maximum concentration ($t_{max}$), elimination rate constant, and half-life ($t_{1/2}$) may be included as secondary endpoints together with a general assessment of immunogenicity and overall safety and tolerance. However, any relevant pharmaco-

kinetic evaluation will include all parameters which are meaningful for the intended evaluation.

For PD assessments, a similar approach has been followed as with growth factors such as G-CSF measuring Absolute Neutrophil Counts (ANC) and more recently with anti-CD20 rituximab biosimilars measuring B-cell depletion either as primary or secondary endpoints, respectively (Table 9.4).

The application of PK and PD modeling in drug development has emerged during the last few decades and it has been suggested that the investigation of PK-PD relationships through the application of modeling and simulation during drug development may facilitate and optimize the design of subsequent clinical development.

While guidance documents for biosimilarity have opened the door to modeling and simulation, it should be noted that emphasis has been put on the use of noncompartmental approaches to formally assess equivalence of PK and PD outcomes between the biosimilar and reference products. However, nonlinear mixed-effects modeling approaches can be valuable for establishing biosimilarity (Dubois et al. 2012) and might be required to correctly interpret bioequivalence results in situations where noncompartmental approaches are biased, e.g., with nonlinear pharmacokinetics (Dubois et al. 2010).

There are specific opportunities for the stronger impact of modeling and simulation techniques in the clinical development of biosimilars that can be achieved by leveraging knowledge generated from the reference product. Thus, previously published PK-PD models for the reference product can be utilized to support efficient study design through clinical trial simulations and provide insight into the choice of informative doses for evaluating biosimilarity. The latter aspect has been emphasized in the FDA guidance and is motivated by the fact that many approved biological products have registered doses lying on top of the dose–response curve, i.e., at pharmacologically saturated levels, which may render them insensitive to differ-

**Table 9.4** Examples of PK/PD studies used to support biosimilar development

| | PK/PD studies | Efficacy studies |
|---|---|---|
| Epoetin alfa | Comparative assessment of AUC over dosing interval (AUC$\tau$) of epoetin following a 4-week exposure (100 µg/kg t.i.w.) in HVs | Therapeutic equivalence; mean absolute change in hemoglobin levels between the screening/baseline period as primary endpoint and the evaluation period in CRF patients on hemodialysis |
| G-CSF/filgrastim | Comparative 1–10 µg/kg/day in healthy volunteers measuring PK (G-CSF levels) and PD: pharmacodynamic effect of absolute neutrophil count (ANC) | Breast, lung, and non-Hodgkin lymphoma cancer patients with chemotherapy (CTX). Measurement of absolute neutrophil count (ANC) as primary endpoints |
| Rituximab (anti-CD20) | Comparative PK/PD, efficacy, and safety studies in rheumatoid arthritis patients (1000 mg 2X). PD marker: $CD19^+$ B-cells as secondary endpoint | Comparative efficacy study in follicular lymphoma patients. Pharmacodynamic assessment of $CD19^+$ B-cells as supportive endpoint |

ences in analytical properties that could impact efficacy and/or safety. The FDA's recommendation is that such a study may involve evaluating PK/PD at multiple dose levels (e.g., low, intermediate, and the highest approved dose) to obtain dose–response and/or exposure-response data. Characterization of the complete concentration-effect time profile, including a washout phase, could be an efficient alternative to address this question, possibly by studying a single dose level. This raises the question of how to best demonstrate statistical equivalence of two concentration-response curves or a set of parameters (e.g., $EC_{50}$ and $E_{max}$). Some statistical methods have been developed for this purpose (Steiger et al. 2011) but may be conservative and lack power; this should be an area of further research. Note a limitation with such studies is that they should be conducted in healthy volunteers as it would be unethical to dose patients at subtherapeutic dose levels.

Finally, population analyses can shed additional insight into the assessment of PK and/or PD similarity, or lack thereof. Indeed, noncompartmental analyses can reveal apparent differences between the two products. Relying on more mechanistic models might be helpful to understand the origin of any differences.

## 5 Selection of PD Markers in the Development of Biosimilars

Since clinical benefit has already been established for the reference biological, the focus of the clinical study to support a biosimilar development should be on more sensitive and meaningful clinical endpoints. For example, although survival is generally a preferred endpoint in many oncology clinical trials, it may not provide the degree of sensitivity for the purpose of demonstrating biosimilarity if there are any remaining residual uncertainties related to minor differences between products in regard to analytical characterization. Thus, selected and justified PD markers may be more relevant for biosimilar development than the usually requested endpoint for a new-in-class mAb such as PFS or OS. The rationale behind this is that a biosimilar with the same amino acid sequence, same affinity for the target, very close structure, etc. would be expected to have the same response with conventional endpoints, as described previously. The best example of different biologics sharing the same pharmacological target and having similar clinical outcomes comes from autoimmunity: there are 5 anti-TNFs on the market, all having different scaffolds, sequences, etc. yet they all have roughly similar efficacy in rheumatoid arthritis (RA) patients when looking at ACR responses at week 24 (in RA) (Weinblatt et al. 1999; Weinblatt 2004; Maini et al. 1999; Keystone et al. 2008, 2009). A biosimilar would not respond any differently. PD markers that measure the immediate downstream pharmacological effects would be more sensitive to address the clinical relevance of specific differences in physicochemical characterization.

A guideline on comparability from the European Medicines Agency (EMA) (EMA 2014) specifies the following requirements for PD endpoints: (a) sensitive enough to detect small differences; (b) measurable with sufficient precision; and (c) clinically relevant for the target population. The FDA Clinical Pharmacology guidance

for biosimilars goes further to indicate that "PD assays" should be sensitive for a product or product class and designed to quantitatively evaluate the pharmacologic activity of the biologic product. Ideally, the activity measured by the PD assay should be relevant to a clinical outcome; however the PD assay should at least be relevant to a pharmacological effect of the biologic product. If the selected PD endpoint(s) are not closely related to clinical outcome, use of multiple complimentary PD assays may be most useful. Because the PD assay is highly dependent on the pharmacological activity of the product, the approach for assay validation and the characteristics of the assay performance may differ depending on the specific PD assay. However, the general guiding principles for choosing PK assays (i.e., demonstration of specificity, reliability, and robustness) also applies to PD assays. Sponsors should provide supporting data for the choice of assay and the justification of PD markers in submissions to FDA (FDA 2014)

The recent approval of Zarxio® (filgrastim-sndz) by the FDA was based on a series of single dose studies that evaluated subcutaneous (SC) doses of 1–10 μg/kg in healthy subjects with regard to PK and PD, as well as a repeat dose study in patients with breast cancer treated with myelosuppressive chemotherapy. As PD markers, these studies evaluated absolute neutrophil counts (ANC) and CD34+ cell counts. Furthermore, the demonstration of clinical PD bioequivalence was deemed adequate to justify minor differences in PK that were the result of a different formulation used in the final product when compared to the reference product. Importantly, the bioequivalence shown for the two PD markers also supported extrapolation to all indications including mobilization of peripheral blood stem cells. A similar approach was used for the approval of Binocrit® (epoetin alfa), which was compared with the reference product in one main study involving 479 patients with anemia due to renal impairment. The main measure of effectiveness was the change in the levels of hemoglobin between the start of the study and the evaluation period, between weeks 25 and 29.

In contrast to growth factors, which have clearly understood and validated downstream pharmacodynamic effects, the identification of PD markers for therapeutic mAbs is much more challenging. One exception is rituximab, where B-cell depletion is routinely evaluated. Partly to address the general lack of truly validated PD markers associated with clinical outcomes for therapeutic monoclonal antibodies, the FDA Clinical Pharmacology draft guidance (FDA 2014) also envisages the possibility of alternative and innovative pathways. The use of more than one PD marker (including "–omics" platforms) that collectively provide information on the mechanism of action and downstream pathway may be considered. The selection of PD markers would then be made to scientifically and more sensitively address the particular analytical properties to be evaluated. Thus, the search for PD markers in comparability assessments has increased, driven partly by a greater effort to identify valuable markers and by regulatory guidance for biosimilars.

In summary, PD evaluations can be very useful to supplement PK assessment in a biosimilar equivalence package and data assessed in the context of the entire comparability package on a case-by-case basis. The challenge of identifying validated

PD markers for therapeutic antibodies can be addressed with novel and innovative approaches provided that they can be scientifically justified.

## 6 Case Study

Zarzio®/Zarxio® (filgrastim/filgrastim-sndz) was recently also approved as a biosimilar to Neupogen® (filgrastim) by the FDA (Zarxio Prescribing Information 2015). Filgrastim is a granulocyte colony-stimulating factor (G-CSF) used to stimulate the proliferation and differentiation of granulocytes. The EP2006 program followed the step-by-step approach of biosimilar development based on a strong similarity at the structural, physicochemical, and in vitro pharmacology level. The preclinical and clinical programs that ensued were thus tailored to provide a final confirmation of similarity of the product to the reference product.

The clinical package consisted of five comparative Phase 1 PK/PD studies in healthy volunteers testing different doses and routes of administration and complemented by two comparative Phase 3 studies in breast cancer patients. Its development for EMA approval in 2009 (Table 9.3) took place at an earlier timepoint and was subsequently complemented with studies targeting a submission to the FDA in 2014. Given the current alignment between the two regions in respect to biosimilar guidance, a biosimilar program currently still in development may require fewer studies. As PD markers, both absolute neutrophil counts (ANC) and CD34+ cells were used in the Phase 1 studies as surrogates of efficacy. The ANC directly reflects the change in the number of peripheral neutrophils and the CD34+ cell count is an indicator of peripheral progenitor cells (PBPCs) mobilization. Both are well-established clinically relevant markers for the effectiveness of filgrastim. ANC drives diagnosis (e.g., grade of neutropenia), predicts prognosis (duration of severe neutropenia), and is utilized to monitor G-CSF treatment effects. CD34+ represents a useful marker for the characterization of cells necessary for engraftment of PBPC in recipients after myeloablative therapy. The bone marrow in healthy volunteers, in contrast to myelosuppressed patients, is fully responsive to G-CSF treatment. Therefore, a healthy volunteer study is a very sensitive model for the assessment of biosimilarity. For the Phase 3 studies, the primary clinical efficacy endpoint was the mean duration of severe neutropenia during Cycle 1 chemotherapy, which in itself is also based on neutrophil counts, i.e., a PD read-out. The clinical development of Zarxio® is summarized below in Table 9.5 (in the Sörgel et al. (2015) and Blackwell et al. (2015)).

The studies consistently showed PK bioequivalence albeit with a tendency for lower exposure by Zarzio®/Zarxio® when compared to Neupogen® (both EU and US sourced). The fundamental reason for this difference was a change in the formulation of the finished biosimilar product that had to be introduced during the development due to patent restrictions. This line of argumentation is supported by preclinical PK/PD studies in rats which showed a much closer point estimate when Zarzio®/Zarxio® was formulated in Neupogen® formulation (Zarxio Briefing Document

**Table 9.5** Overview of clinical studies conducted to support approval of Zarxio®, a filgrastim biosimilar

| Study number | Study population | *N* | Dose | PK | PD | Efficacy | Safety | Immunogenicity |
|---|---|---|---|---|---|---|---|---|
| EP06-101 (EU) | Healthy volunteers | 32 | 10 μg/kg s.c. | X | X | | X | X |
| EP06-102 (EU) | Healthy volunteers | 24 | 5 μg/kg i.v. | X | X | | X | X |
| EP06-103 (EU) | Healthy volunteers | 28 | 2.5 μg/kg | X | X | | X | X |
| | | 27 | 5.0 μg/kg | | | | | |
| | | | i.v. | | | | | |
| EP06-105 (EU) | Healthy volunteers | 23 | 1.0 μg/kg | X | X | | X | X |
| EP06-109 (USA) | Healthy volunteers | 28 | 10 μg/kg s.c. | X | X | | X | X |
| EP06-301 (EU) | Breast cancer patients | 170 | 30 MIU <60 kg | X | | X | X | X |
| | | | 48 MIU ≥ 60 kg | | | | | |
| EP06-302 (USA) | Breast cancer patients | 218 | 5.0 μg/kg | X | | X | X | X |
| | | | s.c. | | | | | |

EU—European approved Neupogen as comparator; USA—US reference Neupogen as comparator

2015). Despite this lower exposure, the PD endpoints consistently showed bioequivalence eliciting superimposable profiles in both neutrophil and CD34+ cell response across all doses and routes of administration. Based on the physicochemical characterization and PK/PD data, the FDA granted market authorization in 2015 to all indications on Neupogen® label.

## 7 Conclusions

The development of regulatory guidance in highly regulated regions has led to the first introduction of biosimilars. Biosimilar development and regulatory review is still an evolving paradigm, but as sponsors and regulators become more experienced with the exercise and the learnings combined with new technologies and scientific knowledge, new concepts in clinical study design, data analysis, and modeling are coming to the forth.

In this chapter, the role of PK/PD clinical endpoints as more sensitive tools to address any remaining residual uncertainties related to minor differences in analytical characterization between the proposed biosimilar and the reference biological is described. Furthermore, the challenges associated with the identification of clinically meaningful PD markers, in particular for therapeutic mAbs, are pushing the industry with the support regulatory guidance, into new ways of thinking. The manner in which these PD markers would be incorporated into the clinical trial

designs would result in strategies not normally used in standard drug development. As new tools are being introduced, novel approaches in data collection and analysis are being developed. As such, biosimilars are exploring and establishing innovative principles guiding regulatory approval that may also become applicable to new drug development in the near future.

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# Chapter 10
# Pharmacokinetics and Pharmacogenetics of Metronomics

**Nicolas André, Joseph Ciccolini, Marie Amélie Heng, and Eddy Pasquier**

**Abstract** Over the last 15 years, metronomic chemotherapy (MC) has been undergoing major evolution since its initial description as an antiangiogenic therapy. The discovery of both its proimmune and direct anticancer effects has led to the acceptance of its intrinsic multi-targeted properties. MC is frequently combined in the clinic with drug repositioning (DR), which consists of using non-anticancer drugs for which their anticancer properties have been described. Metronomics has been defined as the combination of MC and DR and paves the way for both broadening and/or fine-tuning the potential of MC. Despite the many clinical studies conducted on metronomic chemotherapy in the past 15 years, there is a lack of pharmacokinetic and pharmacogenetics data. Indeed, only the pharmacokinetics of anticancer agents given in a metronomic manner, such as vinorelbine, irinotecan, and UFT, has been reported, but surprisingly no data are available on the most commonly used agents like capecitabine or cyclophosphamide. Moreover, few data are available on

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the pharmacogenetics of metronomic chemotherapy, to what extent genetics can impact on pharmacokinetics and, in turn, affect pharmacodynamics. Trials integrating pharmacokinetic and pharmacogenetics research are necessary to better evaluate the clinical benefit of MC and represent a mandatory step to treatment personalization.

**Keywords** Oncology • Dosing • Chemotherapy • Angiogenesis inhibitors • Clinical trials

## 1 Introduction

In the early 1970s, Folkman (1971) introduced the concept of targeting tumor angiogenesis as an anticancer treatment. Over the next decades, further exploration of this concept led to the development of bevacizumab and other antiangiogenic drugs that followed. Many conventional anticancer drugs can also display strong antiangiogenic properties (Miller et al. 2001), especially when given following a frequent schedule at low dose and without prolonged drug-free breaks (Kerbel and Kamen 2004). These modalities of administration defined the concept of metronomic chemotherapy (MC) that was first reported in 2000 in two seminal contributions (Browder et al. 2000; Kontopodis et al. 2013). The term "metronomic" was originally coined by Hanahan et al. (2000) to the concept of antiangiogenic chemotherapy. MC is opposed to conventional chemotherapy, which is administered at or close to the maximal tolerated dose (MTD), usually every 2–3 weeks. On the one hand, this extended period of drug-free rest allows the patient to recover from chemotherapy-induced secondary effects but on the other hand each prolonged drug-free break also provides an opportunity for the tumor to regrow (Kim and Tannock 2005) at least in part through tumor neovascularization (Schwartz 2009). By relying on more frequent administration and lower doses, MC can reduce toxic side effects and prevent vascular rebound (Browder et al. 2000; Bertolini et al. 2003; Shaked et al. 2005). Thus, the introduction of MC opened the door for the development of oral, less expensive, well-tolerated treatment, which does not necessarily aim to eradicate cancer at all cost, but instead at controlling its progression for an extended period of time (Pasquier et al. 2010).

In clinical practice, MC is very often combined with drug repositioning, a term to describe the use of already approved drugs for new medical applications (Ashburn and Thor 2004). Repositioned drugs commonly used in metronomic protocols include thalidomide, retinoic acid, metformin, statins, valproic acid, and rapamycin. In fact, drug repositioning and MC share many similarities which has led us to propose the more generic term "metronomics" to encompass all anticancer treatment regimens combining MC and drug repositioning (André et al. 2013b and André et al. 2014).

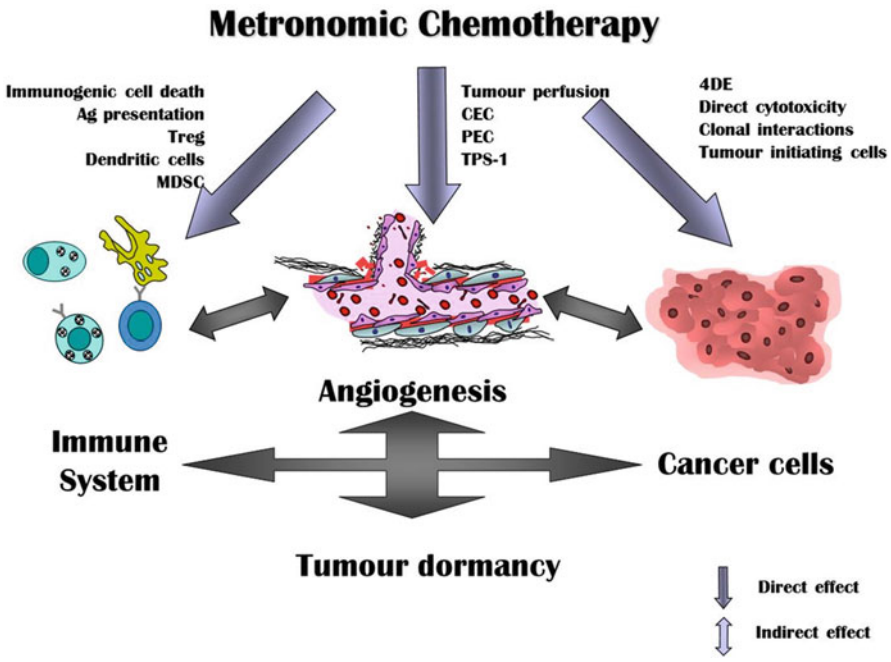


**Fig. 10.1** Mechanisms of action of metronomic chemotherapy. Metronomic chemotherapy can directly target several components of the tumor; the tumor vasculature, the immune system, and cancer cells. These three compartments can in turn affect one another, leading to the global anticancer effects of metronomic chemotherapy

## 2 Mechanisms of Action

Over the years, following the description of new anticancer properties, MC has moved from an antiangiogenic therapy to a multi-targeted therapy (Fig. 10.1) (Pasquier et al. 2010).

### *2.1 Antiangiogenic Properties*

The historical antiangiogenic paradigm of MC is entrenched in the original studies performed in the Folkman and Kerbel laboratories (Browder et al. 2000; Klement et al. 2000). By targeting tumor endothelial cells, MC can indirectly attack both sensitive and drug-resistant cancer cells, by destroying existing vessels and preventing neoangiogenesis, in turn leading to hypoxia and nutrient deprivation. Many preclinical studies have since then confirmed this hypothesis (Kerbel and Kamen 2004).

In addition to targeting rapidly dividing endothelial cells, the antiangiogenic effects of MC can be mediated depending on the drug, or combination of drugs used, by: (1) an increase in endogenous angiogenesis inhibitor thrombospondin-1 (Bocci et al. 2003), (2) the impairment of the angiogenic potential of vascular endothelial cells (Pasquier et al. 2011), (3) the inhibition or apoptosis of circulating endothelial cells, and/or (4) the blockage of endothelial progenitor cell (EPC) mobilization (Shaked et al. 2005, 2006).

## *2.2 Proimmune Properties*

The immunological effects of chemotherapeutic drugs are extremely diverse and complex (Galluzzi et al. 2013; Zitvogel et al. 2011) and, at least in part, related to the dose and schedule of the anticancer agents used. Understanding the complex drug-, dose-, and schedule-dependent effects of chemotherapy on the immune system has only just begun (Landreneau et al. 2015; Nars and Kaneno 2013). Still, growing evidence indicates that anticancer immune responses may be crucial for the long-term control of cancer treated with chemotherapy (Pasquier et al. 2013a, b). Therefore, one of the objectives of MC is to switch immunological effects of chemotherapy from immunosuppression to immunostimulation. MC protocols could be fined-tuned to minimize immunosuppressive effects while maximizing treatment efficacy. Additionally, the immunostimulatory effects of MC depend on the type of agent and could be adapted to each tumor as several effects can be observed:

- The induction of immunogenic cell death (Tesniere et al. 2008)
- The enhancement of antigen presentation through modulation of dendritic cells (DCs) (Ghiringhelli et al. 2007) and increased immunogenicity of cancer cells (Kaneno et al. 2011)
- The preferential depletion of regulatory T cells (Ghiringhelli et al. 2007; Katsetos and Dráber 2012; Zhao et al. 2010)
- The modulation of myeloid-derived suppressor cells (Michels et al. 2012)
- The enhancement of the cytotoxic activity of immune effector cells, such as tumor-specific T cells (Geary et al. 2013; Sierro et al. 2011) and γδT cells (Todaro et al. 2013)

Furthermore, these findings provide a strong rationale for the combination of MC and immunotherapy strategies, such as tumor vaccines and γδT cell-based therapy and recent immune checkpoint inhibitor.

## *2.3 Effects on Tumor Initiating Cells*

A growing body of evidence suggests that MC may also exert direct effects on cancer cells beyond its effects on tumor angiogenesis and antitumor immune response. Indeed, Folkins et al. (2007) demonstrated that metronomic cyclophosphamide

could significantly decrease the number of primary and secondary tumor spheres formed by glioma cells isolated from drug-treated tumors. In line with these findings, Vives et al. (2013)) reported a reduction in the number of CD133+ precursor cells and triple-positive CD133+/CD44+/CD24+ cancer stem cells in human pancreatic tumor xenografts treated with metronomic cyclophosphamide. Elsewhere, metronomic exposure of prostate and colon cancer cells to paclitaxel and etoposide in vitro led to the generation of the so-called drug-tolerant cells (Yan et al. 2011), which exhibited both impaired tumorigenicity in vivo and reduced proportion of CD44+ cells. Altogether, these findings show that MC can target CD44+ tumor initiating cells and/or cancer stem cells.

### *2.4 Additional Mechanisms of Action*

Like pure antiangiogenic drugs, MC can induce vessel normalization and increase tumor perfusion resulting in increased tumor oxygenation and/or blood flow (Cham et al. 2010; Doloff et al. 2009; Francia et al. 2012; Mupparaju et al. 2011). Another recently unveiled mechanism of action is the targeted inhibition of HIF-1α. Indeed, Topoisomerase I inhibitors (topotecan, camptothecin) was identified as inhibitors of HIF-1α transcriptional activation through high-throughput screening (Rapisarda et al. 2002). Elsewhere, Lee et al. (2009) screened 3120 clinically tested drugs and identified doxorubicin and daunorubicin as potent inhibitors of HIF-1α (Folkins et al. 2007) and confirmed this potential new mechanism of action in vivo. Lastly, by inhibiting HIF-1α binding to DNA, metronomic doxorubicin was able to overcome evasive resistance to VEGF inhibition in sarcoma xenografts (Kim et al. 2013), thus providing further rationale for the combination of MC and antiangiogenic drugs.

## 3 How Metronomic Doses Are Chosen?

The very concept of "low," repeated doses with little or no drug-free interval is very intuitive but is associated with a major concern: the dosing levels (André et al. 2013a, b; Maraveyas et al. 2005). Indeed, the metronomic concept covers quite a lot of possible dosing, so that determining the optimal protocol using a traditional underpowered empirical design looks like an unreachable task. The task is even more complex when considering metronomic combinations and the many potential mechanisms of action. Therefore, choosing a metronomic dose in the clinic remains largely empirical and has doubtlessly contributed to significantly delaying progress in the field. All the studies published so far were based upon empirical determination of the metronomic schedule, not only in terms of doses but also with regard to drug-free intervals and repartition of the administrations throughout time (André et al. 2013a, b; Maraveyas et al. 2005; Pasquier et al. 2010). The starting dose for MC is empirical with initiating clinical or preclinical trials at doses ranging from

10 to 33 % of conventional doses. Of note, very little effort is then made to define an optimal dose. Some authors have suggested using the Optimal Biologic Dose (André et al. 2013a, b). Nevertheless, no reliable biomarkers are currently available to define OBD. Elsewhere, Maraveyas et al. (2005) proposed to use doses that would not lead to bone marrow perturbation, which cannot be applied to non-hematotoxic drugs. Fortunately, for many anticancer agents, enough data are already available to allow for a principled approach to metronomic dosing. Computational pharmacology could be a way forward (Barbolosi et al. 2014, 2015). In this context, mathematical modeling offers invaluable in silico tools to help determining the optimal metronomic schedule among a variety of possibilities. For instance, a phenomenological model describing the impact of metronomic regimen, based mostly on a simplified PK/PD basis, incorporating some critical features such as resistance to treatment has been developed for temozolomide (Faivre et al. 2013). This model has been then adapted to identify an optimal metronomic protocol for lung cancer patients, based upon clinical data already published in patients with solid tumors. In silico simulations suggested that an alternative 60–30–60 mg dosing given on a D1–D2–D4 basis should lead to higher efficacy with a good tolerance as compared with all other metronomic regimens tested thus far. Of note, such contra-intuitive schedule could not have been identified simply by analyzing the results of the dozen of phase I or phase II trials conducted with metronomic vinorelbine (Barbolosi et al. 2014).

## 4 Towards Personalized Metronomic Chemotherapy?

The current development of targeted therapies is making the concept of personalized therapy a reality in oncology (Martini et al. 2011). Personalized therapy is implicitly used as molecular driven personalized therapy although oncologists have been individualizing for decades their treatment, based on various parameters such as weight, comorbidities, metastatic vs. localized disease, and upfront vs. relapse setting. In the field of metronomics, similar approaches must be developed. Empirical experience has taught us that the “one metronomic fits all” regimen was an unrealistic goal. According to the current paradigm of molecular medicine, metronomics could therefore also be molecularly guided. Another way to individualize treatment relies on biological biomarkers such as angiogenic (i.e., circulating endothelial cells, VEGF) (Jain et al. 2009) or tumor biomarkers such as EGF-R and ALK mutations. Nevertheless, as for antiangiogenic therapies, no reliable biomarker has been identified to select a metronomic regimen for a given patient and result. For instance, Kieran et al. had identified thrombospondin-1 as a marker predictive of response in children receiving a 4-drug metronomic protocol (Kieran et al. 2005). Since MC acts at least in part via an increase in thrombospondin-1 (Bocci et al. 2003), patients with tumors harboring low TSP-1 levels could benefit from MC. Stempak et al. (2006) did not reproduce the results using different metronomic protocols in children with refractory

tumors. In adult patients receiving metronomic regimens, several studies confirmed that although thrombospondin 1 mediates, in part, the action of MC, its levels cannot be used as a reliable universal marker (Lansiaux et al. 2012; Pectasides et al. 2012). Elsewhere, Cominelli et al. (2015) identified that EGFR amplified and overexpressing glioblastoma had a better response to metronomic temozolomide. Additionally, the longer overall survival was not associated with MGMT status. Further, Dellapasqua et al. (2012) reported about the potential role of macrocytosis (mean corpuscular volume >100 fL) as a marker of longer response in patients with metastatic breast cancer receiving a metronomic capecitabine and cyclophosphamide in combination with bevacizumab. Levels of HIF alpha may be used to determine if low dose doxorubicin or low dose topoisomerase inhibitor is a priori well suited for a given tumor (Hashimoto et al. 2010; Lee et al. 2009).

The decreases of beta-III tubulin isotypes may also indicate a greater sensitivity to antitubulin agents (Katsetos and Dráber 2012). Furthermore, long-term exposure of endothelial cells to vinblastine leads to a decrease in BIII isotypes which in turn contribute to their greater sensitivity to chemotherapy and their capacity to form new vessels (Pasquier et al. 2013a, b).

Lastly, immune components of the tumor may also be used to identify compounds of interest. Thus, the presence of regulatory T-lymphocytes ($T_{regs}$) within tumors could also indicate that a metronomic regimen containing low dose cyclophosphamide or low dose temozolomide can be used (André et al. 2014). Their combination with new immunosuppressive therapies such as anti-PD1 deserves further investigations in a close future.

The association of DR to MC also paves the way for introducing already available targeted therapy agents like arsenic or itraconazole for sonic hedgehog medulloblastoma (Kim et al. 2013) or also beta-adrenergic positive tumors with the use of beta-blockers for breast cancer, ovarian cancer, or neuroblastoma (Pasquier et al. 2011, 2013a, b), tricyclic antidepressants as inhibitors of small cell lung cancer (Jahchan et al. 2013) or recently digoxin for retinoblastoma (Winter et al. 2015). Nevertheless, these emerging data, although requires to be confirmed, have opened the doors to a better selection of the patients when using biomarkers. In the absence of reliable biologic biomarkers, a better understanding of interindividual variability of drug metabolism, and reducing it, is a promising but neglected way of metronomic personalization through dose individualization (Weng et al. 2013).

## 5 Pharmacokinetics of Metronomic Regimens

Today, anticancer agents cover a wide variety of chemical structures and mechanisms of action. Consequently, determining common PK/PD relationships of metronomic combinations is an unreachable goal because of the diversity of anticancer drugs combination that can be potentially proposed. Usually PK/PD relationships

are extensively studied in nonclinical models, then in phase I/II studies. Yet, it is widely acknowledged that the recommended Phase 2 doses (RP2D) are frequently poorly estimated—the increase in fast-track approvals and the absence of DLT in the several blockbusters recently developed targeted therapies make the determination of an optimal schedule far from being granted upon approval. Consequently, the clinicians have to learn how to use properly a given drug, beyond the standard recommended dosing and schedules. Paclitaxel in breast cancer or sunitinib in renal carcinoma is paradigmatic of the gap between the approved dosage and the implementation of alternative schedule deconstructing official recommendations. Optimizing dosing, scheduling, and the route of administration can improve clinical outcome and better manage the efficacy/toxicity balance of most anticancer drugs (Paci et al. 2014). This optimization step, including the switch towards metronomics, requires a sound understanding of the PK/PD relationships of the drugs of interest, in addition to a reasonable picture of the basic endpoints one can achieve with a metronomic regimen. In addition, integrating the sources for PK variability, such as demographic data, genetic status, or exogenous factors (DDI, comorbidities, smoking habits) (Gillis et al. 2014), not to mention pharmacodynamic issues such as changes in tumor burden or tumor population (Allegrini et al. 2008), is critical.

Integrating these factors should help achieve more personalized treatments for cancer patients. Several biomarkers are indeed currently used in the clinic for the determination the best regimen, mostly based upon pharmacogenomics (Paci et al. 2014). However, decision-making in metronomics remains largely empirical because no predictive markers of efficacy have been validated, and little application for routine drug monitoring has been made available. As mentioned above, such markers have been investigated as part of early clinical phases, with no validation in larger patient studies.

Little is known about the dose-exposure relationships of most metronomic regimens (Hashimoto et al. 2010; Yan et al. 2011) and only the pharmacokinetic profiles of temozolomide, paclitaxel, vinorelbine, irinotecan, and topotecan have been investigated in patients (Baruchel et al. 2006; Briasoulis et al. 2013; Di Paolo et al. 2006; Moes et al. 2013; Panetta et al. 2008). This lack of data on metronomic schedules may affect the efficacy of the regimen, because little is known about the possible cause for variability in the resulting exposures.

## *5.1 Camptothecins*

### 5.1.1 Irinotecan

Irinotecan and its active metabolite SN-38 have been extensively studied, including for PK/PD relationships and UGT1A1-related pharmacogenetics in standard dosing regimens (Falcone et al. 2001). The pharmacokinetic profile of metronomic irinotecan has been first investigated in the late 2000s in patients with metastatic colorectal cancer (CRC) (Falcone et al. 2001). Metronomic irinotecan was extrapolated using

previous data from standard schedules (Herben et al. 1999). Up to three different metronomic dosing regimens of continuous irinotecan were tested with a starting dose of 16 % MTD when given every 3–4 weeks (Bocci et al. 2013). Interestingly, changes in dosing showed a marked difference in exposure profiles. Further pharmacokinetic analysis demonstrated that steady-state concentration (*C*ss) of active SN-38 was in line with concentrations required to exert antiangiogenic activity in preclinical studies (Herben et al. 1999).

### 5.1.2 Topotecan

Metronomic topotecan tested in several preclinical models exhibited antiangiogenic properties (Hashimoto et al. 2010; Kumar et al. 2011; Merritt et al. 2009; Tillmanns et al. 2008). This led investigators to translate a variety of metronomic schedules in early clinical trials, 1 mg a day over 30 consecutive days finally being the recommended dosing (Kerklaan et al. 2013). As for irinotecan, a strong dose/exposure relationship has been observed with low doses topotecan (Kerklaan et al. 2013). After experimental studies demonstrated the absence of PK interactions between the drugs (Merritt et al. 2009), metronomic topotecan (i.e., 0.25 mg daily) has been further combined with up to 800 mg daily oral pazopanib in patients with gynecological tumors (Merritt et al. 2009). Because drug interactions have been described elsewhere with these drugs used following standard schedules, the feasibility of combining counter-indicated drugs by switching to a metronomic schedule is of particular interest (Kerklaan et al. 2013).

## *5.2 Antimicrotubules Agents*

Developing alternative metronomic regimen is of particular interest with antimicrotubule agents since these chemotherapeutic drugs are amongst the most antiangiogenic (Bocci et al. 2002; Kontopodis et al. 2013; Schwartz 2009).

### 5.2.1 Vinorelbine

Vinorelbine is a semisynthetic *Vinca* alkaloid that has been recently relaunched in oral form. Metronomic oral vinorelbine has been tested in several phase I or phase I/II studies in patients with solid tumors, mostly of the breast and lung (Addeo et al. 2010; Briasoulis et al. 2009; Gebbia and Puozzo 2005). The PK profile of oral vinorelbine is relatively linear with little interpatient variability in the absorption phase, and elimination mainly driven by CYP-metabolism in the liver and biliary excretion (Pappas et al. 2008). The PK of metronomic oral vinorelbine has been extensively studied by Briasoulis et al. (2009), showing a linear dose/exposure relationship over the tested doses. Interestingly, PK of metronomic dosing was found to

be stationary over months, a requirement when administering drugs in a near continuous fashion as with metronomic schedules. Of note, steady-state concentrations were in line with drug concentrations required to exert antiangiogenic effects, thus suggesting that the efficacy reported in patients could be, at least in part, related to direct effects on the tumor vasculature (Briasoulis et al. 2013; Pappas et al. 2008). Confirmatory studies have been performed (Briasoulis et al. 2009), showing similar PK profiles to those previously reported (Briasoulis et al. 2013) and consistent with the hypothesis that antiangiogenesis-related efficacy could be achieved with metronomic oral vinorelbine. Based on PK/PD modeling of published data, Barbolosi et al. (2015) have proposed a theoretically more active metronomic dosing.

### 5.2.2 Paclitaxel

The antiangiogenic properties of paclitaxel have been discussed almost since the very beginning of using this drug (Schwartz 2009). The PK profile of paclitaxel is challenging because of its poor water solubility and the need for toxic solvents such as cremophor to dissolve it prior to its administration. Nonlinear PK, hypersensitivity reactions, and risks of micelle formation in the blood have been frequently reported. Therefore recent studies have focused on the development of nanoparticle-based formulations of paclitaxel (either liposomal or Nab-conjugated) to improve its PK profile and its selectivity towards malignant tissues (Luo et al. 2013).

Of note, the antiangiogenic properties of metronomic liposomal paclitaxel have been recently evidenced in HT1080 fibrosarcoma-bearing rats (Wang et al. 2003). Additional PK investigations showed that liposomal paclitaxel exhibited a long-circulating profile as compared with the standard formulation, in part due to reduced plasma clearance (Wang et al. 2003). Liposomal paclitaxel is thus compatible with the concept of sustained exposure to continuous drug levels required to achieve efficacy of metronomic scheduling.

Recently, an oral formulation of paclitaxel has been developed for metronomic dosing and tested in a first-in-man study with a booster effect based upon the co-administration of cytochrome P450 inhibitor ritonavir (Katsetos and Dráber 2012). Resulting plasma exposure consistent with the concentrations required to exert antiangiogenic effects as described by several groups (Addeo et al. 2010; Bocci et al. 2002; Katsetos and Dráber 2012) while being lower than the threshold associated with hematological toxicities (Gianni et al. 1995), thus ensuring a maximal benefit-risk balance.

## *5.3 Alkylating Agents*

Alkylating agents (e.g., cyclophosphamide, temozolomide) are probably the oldest anticancer drugs to have been tested following metronomic schedules, both in children and in adults (André et al. 2013a, b, 2014; Chen et al. 2013; Kerbel and Kamen

2004; Penel et al. 2012). Still, few studies have investigated the PK profiles of these drugs when given in a metronomic manner.

### 5.3.1 Cyclophosphamide

PK studies of metronomic cyclophosphamide have been mostly undertaken in mice (Emmenegger et al. 2011; Man et al. 2002), despite cyclophosphamide being the backbone of the majority of metronomic regimens evaluated in the clinic to date (André et al. 2014; Kerbel and Kamen 2004; Pasquier et al. 2010; Penel et al. 2012). Stationary PK was evidenced, thus suggesting absence of accumulation, an important requirement for safety when switching to a metronomic schedule. Currently, no clinical data is available on the PK/PD relationships of metronomic cyclophosphamide. The only PK studies have focused on co-administered drugs such as imatinib, rather than on cyclophosphamide itself (Adenis et al. 2013).

### 5.3.2 Temozolomide

As with cyclophosphamide, the PK characteristics of metronomic temozolomide have been mostly studied in animal models of human cancer. A comparative study of standard vs. metronomic schedules has been performed in rats (Zhou et al. 2007). The PK profile of metronomic temozolomide proved to be linear and stationary. Of note, drug delivery to the tumor was found to be identical between standard and metronomic schedules, despite the significant decrease in dosing (Zhou et al. 2007). A PK study in children with brain tumors was also performed (Baruchel et al. 2006). Temozolomide PK proved to be linear, however with an important interpatient variability. Consequently, PK/PD relationships were unclear because little association could be made between drug exposure levels and clinical endpoints (Baruchel et al. 2006).

## 6 Pharmacogenetics and Pharmacogenomics of Metronomic Chemotherapy

Identifying genetic factors likely to interfere with drug response (pharmacogenomics) and drug PK (pharmacogenetics) represents a critical step towards achieving personalized treatments in oncology (Gillis et al. 2014). Defining predictive markers of response, of nonresponse, or of atypical exposure related to germinal changes in drug-metabolizing enzymes or efflux transporters should help to custom anticancer therapy, based upon the preliminary determination of the molecular and genetic status of the patient and the tumor (Burt and Dhillon 2013). Surprisingly, only two pilot studies have focused on the pharmacogenetics of metronomic regimens (André et al. 2014; Orlandi et al. 2013).

Because the tumor microenvironment and neovessels are now recognized as key players (Blansfield et al. 2008) and constitute the primary targets of metronomic schedules, genetic variations affecting the expression and/or the secretion of pro-angiogenic factors (e.g., IL-8 or VEGF) or endogenous angiogenesis inhibitors (e.g., THBS-1) could significantly impact clinical outcomes. For instance, a pharmacogenetic study was performed in patients treated with the association of metronomic cyclophosphamide and bevacizumab (Schultheis et al. 2008). In this study, patients harboring the IL-8 + 251AA or AT genotypes displayed lower response rates, whereas patients with the VEGF-A +936CT genotype showed a trend towards longer median progression-free survival, as compared with patients harboring the TT genotype (Schultheis et al. 2008). Consequently, these results suggest that the IL-8 251A/T polymorphism could be a molecular predictor of response for the combination therapy of metronomic cyclophosphamide and bevacizumab. Of note, the fact that antiangiogenic bevacizumab was also administered is an important confounding factor, rendering conclusions difficult to draw. Interestingly, a recent study focusing on VEGF-A polymorphism showed that it could impact the clinical outcome of metastatic prostate cancer patients treated with metronomic cyclophosphamide (Orlandi et al. 2013). Here, the -634CC and -2578CC VEGF-A SNPs were both associated with poor response and reduced progression-free survival (Orlandi et al. 2013). This pivotal study strongly suggests that genetic polymorphisms affecting the tumor microenvironment could play a crucial role in the efficacy of metronomic regimens. In addition to tumor genetic or molecular abnormalities, several germinal polymorphisms related to ADME processes could impact on the toxicity/efficacy balance of drugs administered following metronomic schedules. For instance, polymorphisms affecting UGT1A1 or CYPs could alter the liver metabolism of irinotecan metabolite SN38 and taxoid drugs, respectively (André et al. 2013a, b; Ciccolini et al. 2015). Of note, such prospective pharmacogenetic studies often require large patient cohorts to be relevant unless large differences in PK are observed. Such large cohorts of patients are not the usual setting of phase I/II trials investigating the safety and efficacy of metronomics (André et al. 2014; Kerbel and Kamen 2004; Pasquier et al. 2010) and are usually not the priority in large randomized trials as with the recent CAIRO 3 trial (Simkens et al. 2015).

## 7 Conclusions and Perspectives

Despite being a promising alternative strategy to MTD-based regimens, metronomic chemotherapy has been poorly investigated from a PK or PK/PD standpoint. Consequently, the strategies undertaken at the bedside are mostly based upon empirical approaches with little room for optimization, apart from intuitive search for the best combination between dose, frequency, and duration of administrations. In addition, the lack of clear PK/PD relationships prevents clinicians from performing therapeutic drug monitoring to adjust dosing to a target exposure

level. Consequently, the optimization of metronomic chemotherapy remains hard to perform, especially since each drug is administered following a wide range of regimens in different studies. Moving towards personalized and precision metronomic regimens is nevertheless not out of reach and will very likely require innovative strategies based on adaptive clinical trials relying on sophisticated mathematical models combining PK/PD relationship (taking into account the multi-targeted nature of metronomic chemotherapy), pharmacogenetics, and pharmacogenomics.

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# Chapter 11
# Modeling Tumor Growth in Animals and Humans: An Evolutionary Approach

**Dean C. Bottino and Arijit Chakravarty**

**Abstract** Disease progression modeling allows more precise quantitation of therapeutic interventions, which in turn enables better decision-making in drug research and development. Cancer biology has a rich history of disease progression modeling both in the animal and patient setting, from exponential growth to carrying capacity models, not to mention enhancements that represent biochemical pathways, cell cycle state, and tumor microenvironment. Recent observations of tumor heterogeneity and treatment emergent resistance to every pharmacologic modality to date support an evolutionary approach to characterizing tumor kinetics. This approach represents an individual's tumor burden as a collection of independently exponentially growing subpopulations with varying degrees of innate sensitivity or resistance to the therapeutic intervention being studied. A two-population simplified evolutionary model can recapitulate a wide variety of tumor kinetic trajectories observed in the clinic, including primary resistance, initial shrinkage followed by relapse, and durable response, depending on the estimated pre-existing fraction $\phi_R$ of initial tumor burden resistant to therapy. Under the assumption that tumor burden exceeding a critical threshold results in death of the patient, it can be shown that this initial resistant fraction $\phi_R$ and the growth rate $g_R$ of cells resistant to treatment are the key drivers of survival benefit, whereas the kill rate of the treatment on sensitive cells has a negligible effect on survival. By utilizing the totality of continuous tumor burden measurements over the entire course of treatment, evolutionary tumor kinetics modeling enables more accurate treatment benefit assessment and therefore better drug development decision-making than categorical, nontemporal criteria like RECIST.

**Keywords** Oncology • Mathematical modeling • Mathematical oncology • Xenograft • Clinical trials • Evolutionary dynamics

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# 1 Introduction

In the broader field of pharmacometrics, there exists a rich history of modeling disease progress and response to treatment, starting from early longitudinal assessments of the natural history of chronic disease (Rösch et al. 1976; Fuller et al. 1975), and extending to early applications of mathematical modeling (Holford and Sheiner 1981; Griggs et al. 1981). Such quantitative models of disease progression have played a fundamental role in developing our understanding of disease biology and patient response (see Holford 2015, for a review), in a diverse range of therapeutic areas such as infection (Yano et al. 1998; Admiraal et al. 2014; for a review see Nielsen and Friberg 2013), central nervous system disorders (Holford and Peace 1992), and cardiovascular/metabolic disease (Landersdorfer and Jusko 2008).

A notable example where mathematical modeling played a decisive role in understanding the disease itself was HIV modeling, where the prevailing thought at the time was that HIV infection led to an indolent disease which became virulent upon encountering a trigger or stimulus of some sort. In the 1980s, the identification of triggers of progression to full blown AIDS was a lively field of academic research. The question was fundamentally reframed by a seminal 1995 paper by Ho et al., which used mathematical modeling of HIV disease progression. Using the experimentally determined rate of replication for HIV, the authors showed that, rather than being indolent, the disease is actually highly active with virions replicating repeatedly in a mutation-prone manner. Most of the progeny are poorly viable until one comes along with strong replicative potential. This successful subclone of HIV then takes over the population leading to the manifestation of clinical AIDS. The simple mathematical understanding of the HIV infection to AIDS continuum revolutionized the field and the correct reframing of AIDS as a disease of evolution eventually led to the design of effective therapies for its control. (Parenthetically, this paper—among others—led to the first author, David Ho, being named Time magazine's person of the year for 1996, in a notable first for the disease progress modeling community).

## *1.1 What Good Is a Model of Tumor Growth?*

Cancer biology, too, has a rich history of mathematical modeling of tumor progression (Ribba et al. 2014; Swanson et al. 2003; Neal et al. 2013). There are two primary reasons for building a model of cancer—gaining a better understanding of disease etiology and progression, or providing translational predictions for therapeutic outcome.

A common perception is that, to be effective, a model must be able to incorporate a wealth of mechanistic information. For cancer, this has led to the development of very complex multiscale models based on a Systems Biology philosophy. Naturally, it is not possible to parameterize such models with experimental data derived

in-house, so modelers will typically spend much of their time mining the literature for quantitative estimates that can then be incorporated into the parameters of their model. This data-mining approach to modeling can lead to problems of the garbage-in-garbage-out (GIGO) variety, as one is forced to rely on external datasets of unknown quality.

That said, if the goal of building a model is to provide mechanistic insights, such an approach has merit, provided that the underlying conception of the mechanism is accurate, and the system is complex enough that modeling is the only way in which the behavior of the system can be decomposed into the behavior of its constituent parts. In the field of antibody-drug conjugates (ADCs), there are examples of models that demonstrate these properties (Lobo et al. 2003; Aston et al. 2011), where modeling is beginning to play a driving role in the design of new antitumor therapies. Another area of cancer biology where such rich mechanistic models have played a very fundamental role is that of mitosis, where fundamental cell biology models derived from Newtonian mechanics have shaped our understanding of the forces involved in spindle assembly and cell division (see, for example Van Heesbeen et al. 2014; Stephens et al. 2013). It is worth noting that the better models in this context tend to minimize their reliance on Other People's Data (OPD).

In the drug discovery and development setting, much of the emphasis has been on building translational models that can be used for preclinical-to-clinical translation. In this setting, there is an inherent tension between model complexity and utility, and several factors tip the balance in favor of rigorously parsimonious models. First, parsimonious models are easier to communicate, and in a cross-disciplinary setting, model complexity can lead to the message being lost. Models in the drug development setting are easier to leverage when they can be clearly understood by the entire project team. Second, a parsimonious model minimizes the problems of data quality (OPD, GIGO) and error propagation that are so often observed in higher complexity models. Third, parsimonious models are easier to use for translation as they minimize the burden of data collection which can be significant obstacles to rapid progress in both the preclinical and clinical settings. Finally, (the case will be made in the subsequent sections that) parsimonious models are actually a better representation of the underlying biology of tumor growth and response to treatment.

## *1.2 Cancer as an Evolutionary Process*

An increasing body of literature frames cancer as a process of somatic Darwinian evolution. The evidence for this is based on three major findings: clonal diversity, stochastic progression, and differential survival of clones upon treatment.

With advances in deep sequencing technology over the last decade, cancer scientists are finally getting a close look at the clonal architecture of tumors, and the results are building a very different view of cancer. A fundamental point of dogma in the field, dating back almost four decades (Nowell 1976), has been that tumors

are derived from a single cell, with the stepwise accumulation of somatic cell mutations. This sequential process would lead to the development of a maximally malignant clone that contained all of the mutations necessary for full blown cancer. In contrast, the data that has been pouring in over the past decade paints a view of a polyclonal disease with dramatic levels of heterogeneity, and a dynamically changing genome. A number of recent reports have shown that the mutational spectrum of tumor subclones within a single patient tends to vary widely with different sections of the same tumor being genetically distinct from each other and from metastases (Gerlinger et al. 2012; Le Pennec et al. 2015; Gawad et al. 2014; Zhang et al. 2014). Mutational spectra also differ from one patient to the next within the same cancer subtype (Gawad et al. 2014; Zhang et al. 2014; Nik-Zainal et al. 2012), suggesting that inter- and intra-tumor heterogeneity are both driven by a process of parallel evolution occurring within each patient (Martinez et al. 2013). The process has been represented in recent publications as a natural history (Nik-Zainal et al. 2012), with various subclones arising and fading away during the progression of the disease (Gerlinger et al. 2012). Similar diversity has been reported in the literature for xenograft tumors (for example, see Monsma et al. 2015) and cell lines (see, for example Tegze et al. 2012).

Perhaps not surprisingly, such a tremendous diversity of tumor genomes—derived from errors in the division process—leads to stochastic disease progression (Heng et al. 2006a, b), with subclones competing against each other. Recent publications have pointed to a branching nature of cancer progression within a single patient with changes in mutational spectra within a single tumor, as well as between the original lesion and the metastases (Gerlinger et al. 2012; Mehine et al. 2015; Le Pennec et al. 2015; Gawad et al. 2014; Zhang et al. 2014). Here again, recent findings directly contradict the textbook view of cancer initiation and progression—the mental model most are familiar with (Vogelstein and Kinzler 1993)—which postulates a defined, linear sequence of mutations leading to malignant progression.

Response to therapy is similarly complex. Basic cell biology studies, conducted using real-time video microscopy, have shown a staggering degree of diversity in the response of cells to various treatments, ranging from antimitotics (Gascoigne and Taylor 2008; Orth et al. 2008), to apoptosis inducers (Spencer et al. 2009) to targeted therapies (Thurber et al. 2013). In these studies, there is a high degree of variation in drug response from cell line to cell line and from cell to cell. Drug response can typically take one of three forms: slowed growth, growth arrest, and death. For a given treatment, the proportion to which these three responses can be seen in vitro varies by cell line, dose, and time point (Abend 2003; Roninson et al. 2001). A similar diversity of cellular fate has been demonstrated in response to targeted therapies in the in vivo xenograft setting (Driscoll et al. 2014). Consistent with this stochastic complexity in response to treatment, clinical observations point to differential tumor cell survival during the process of drug treatment and response (Shah et al. 2007), and leading to different proliferation patterns at diagnosis and relapse (Stiehl et al 2014; Sachs et al. 2007; Fakir et al. 2009).

So, in a nutshell, the three elements of Darwinian evolution (diversity, competition for resources, differential survival) are demonstrably present in the cancer setting (for reviews see Gerlinger et al. 2014; Merlo et al. 2006; Bahlis 2012). The evolving nature of the disease has strong implications for what can and cannot be modeled mathematically, as will be discussed in the next section.

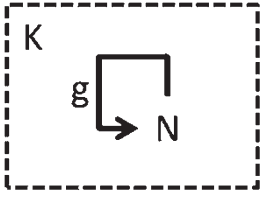
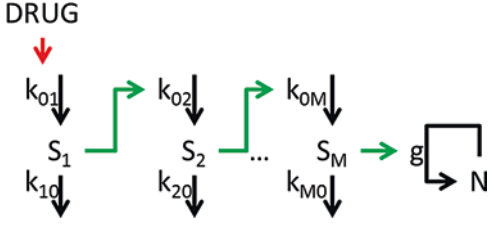
## *1.3 Modeling Cancer: Options and Limitations*

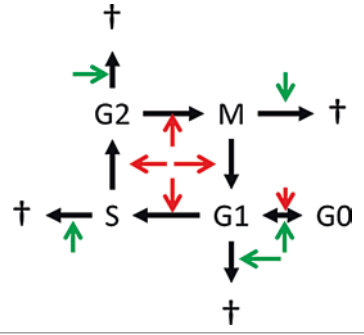
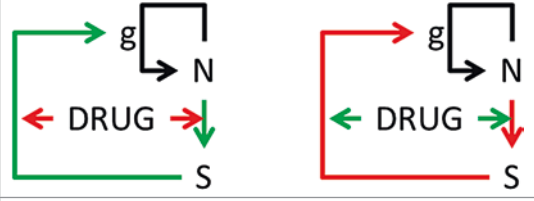
All modeling begins essentially as an act of abstraction, with the modeler choosing which parts of the system to represent and which parts to ignore. Including more detail typically permits a finer-grained set of predictions about system behavior, but it comes at a cost, as discussed previously. Somewhat obviously, if the goal is to study a particular aspect of tumor behavior, then that aspect needs to be included in the model. In this section, models that are designed for the study of tumor growth and regression under treatment will be developed, with particular emphasis on the in vivo xenograft setting.

The problem of modeling xenograft tumor growth in vivo is an old one, and much ink has been shed in the academic literature about the search for fundamental laws of tumor growth (Steel and Lamerton 1966; Gerlee 2013). The debate in the field has been intense at times (Heitjan 2011) and has focused on two aspects of the problem in particular.

First, what is the correct functional form for tumor growth in the absence of treatment? The earliest studies in this space, dating back to the first half of the twentieth century, proposed a simple exponential model (Table 11.1, Eq. (1)). For a review, see Steel and Lamerton 1966. This model describes the log-linear phase of tumor growth precisely, but will fail if the tumor growth rate slows as it gets larger due to nutrient limitation or internal tumor necrosis, for example. To tackle this problem, alternative models have been proposed (see for example, Wu 2011; Zhao et al. 2011; Bernard et al. 2012; Wu and Houghton 2009), and range in complexity from the simple logistic model that is a standard population biology approach for describing carrying capacity limitations (Eq. (2)), to more empirical models such as the Gompertz model (Laird 1964) and the Simeoni model (Simeoni et al. 2004). It is worth pointing out that the more complex models in this space can often take on a curve-fitting philosophy, as they will contain parameters that are difficult to assign a biological meaning (see, for example, Kong and Yan 2011, and the $\psi$ parameter in the growth equation in Simeoni et al. 2004). Interestingly, over the past decades, Institutional Animal Use and Care Committee (IACUC) guidelines mandate the tumor volume at which mice must be sacrificed humanely (Office of Laboratory Animal Welfare 2002). As IACUC humane guidelines have been enforced more consistently, the ability to observe carrying-capacity-limited growth in the in vivo experimental setting has also decreased. To put it one way, if you are an in vivo researcher today, and your xenograft data is able to shed more light on the fundamental model of carrying-capacity-limited growth, your IACUC would probably like to speak with you!

**Table 11.1** A few commonly used tumor kinetic model schematics and example equations

| # | Name | Schematic | Equation |
|---|---|---|---|
| (1) | Exponential |  | $\frac{dN}{dt} = gN$ |
| (2) | *Carrying capacity*<br>$N$ = # of tumor cells<br>$K$ = carrying capacity<br>$g$ = NET growth rate (growth-death) |  | $\frac{dN}{dt} = gN\left(\frac{K-N}{K}\right)$ |
| (3) | *Biochemical*<br>$N$ = # of tumor cells<br>$S_1,\ldots,S_M$ = signaling compartments<br>$K_{0j}$ = signal inputs as function of drug or upstream signals<br>$g$ = function of final signal |  | $\frac{dS_1}{dt} = k_{01}(D) - k_{10}S_1$<br>$\frac{dS_M}{dt} = k_{0M}(S_{M-1}) - k_{M0}S_M$<br>$\frac{dN}{dt} = g(S_M)N$ |

| # | Name | Schematic | Equation |
|---|---|---|---|
| (4) | *Cell Biological*<br>$G_0$ = # resting cells<br>$G_1$ = # cycling cells<br>$S$ = # cells synthesizing DNA<br>$G_2$ = # cells waiting to enter mitosis<br>$M$ = # cells in mitosis<br>+ = dead cells |  | $N(t) = G_0 + G_1 + S + G_2 + M$<br>$\frac{dG_1}{dt} = 2k_{mg}M - k_{10}G_1 - k_{1S}G_1 - k_{1+}G_1 + k_{01}G_0$<br>$\frac{dM}{dt} = k_{2M}G_2 - k_{mg}M - k_{M+}M$<br>… and so on<br>All rate constants potentially functions of drug depending on mechanism of action |
| (5) | *Microenvironmental*<br>$N$ = # of tumor cells<br>$g$ = function of stromal cells S<br>$f$ = function of tumor cells $N$ |  | $\frac{dN}{dt} = g(S;D)N$<br>$\frac{dS}{dt} = f(N;D)$ |
| (6) | *Evolutionary*<br>$N$ = # of tumor cells<br>$N_S$ = # sensitive cells<br>$N_R$ = # resistant cells<br>$g^*$ = net fitness |  | $\frac{dN_S}{dt} = g_S^{net}(D)N_S$<br>$\frac{dN_R}{dt} = g_R N_R$<br>$N(t) = N_S(t) + N_R(t)$ |

*Black arrows* represent fluxes, while *green arrows* represent positive relationships and *red arrows* negative relationships

A second fundamental question in the tumor modeling field has been, how much mechanistic data can be included? As discussed previously, a greater level of mechanistic detail may be appropriate if the system justifies it, and can lead to deeper insights. Three potential types of mechanism that can be explored will be discussed: biochemical (Eq. (3)), cell biological (Eq. (4)), or microenvironmental (Eq. (5)). The biochemical model (Eq. (3)) would contain details of the upstream molecular mechanism of tumor growth and death. Such models rely heavily on a linear, homogeneous and deterministic view of cancer progression and treatment and are contradicted in many cases by the available data, as described in the earlier sections. Cell biological models (Eq. (4)) are typically based on a cell cycle arrest vs. apoptosis dichotomy. Such models are confounded by the diversity of responses observed upon treatment (discussed above), as well as a second, more subtle problem. For many drugs, the primary mode of response in vivo is a slowly developing growth arrest (cellular senescence) that often will not manifest until several days after treatment (see, for example, Huck et al. 2010). In an in vitro setting, where such parameters are most easily derived, these outcomes may not be visible within the time window of treatment. Finally, microenvironmental models (Eq. (5)) attempt to incorporate aspects of tumor microenvironment, such as tumor-stromal interactions or vascularity (Port et al. 2010). These models, operating on a more macroscopic scale, are often less vulnerable to the problems described above, but are challenging to parameterize in vivo. Even for studies that have been able to estimate parameters for tumor-level interactions in the xenograft setting, the question of how to translate those parameters to the clinical setting remains open.

## 2 An Evolutionary Dynamics Model of Tumor Growth and Response to Treatment

So, where does that leave us? The goal is to use a model that reflects the underlying biology of tumor growth and response to treatment, which uses parameters that can be estimated directly from the data, and that ideally provides predictive capacity as well as insights. If the underlying biology of tumor growth is heterogeneous and time-varying and if the easiest parameters to estimate are tumor volume (in both the preclinical and clinical settings), then one could perhaps build an empirical model of tumor growth based on an exponential (or logistic, if the data warrants) curve, but what good would such a model be?

In this and subsequent sections, a population biology model of tumor growth and treatment that is based on fitting exponential models to the number of observed log-linear trajectories within the tumor growth curve will be derived. For small-molecule drugs specifically, such an approach works well. The practical utility of the model in the drug discovery and development setting will then be discussed.

## 2.1 Applying a Tumor Growth Model to Xenograft Studies

Consistent with an evolutionary biology view of the problem, tumor kinetic modeling can be viewed in its most general form by expressing the total number of tumor cells $N(t)$ as a sum of independently exponentially growing and shrinking clones:

$$N(t) \equiv \sum_{i=1}^{n} N_i^0 e^{g_i t} \tag{11.7}$$

where $n$ is the number of clones having distinct intrinsic growth rates and/or sensitivities to the treatment, $N_i^0$ is the number of cells of the i$^{th}$ clone at $t=0$ (the moment treatment starts), and $g_i$ is the growth/shrinkage rate of the i$^{th}$ clone. In population biology terms, this is equivalent to a number of independent subpopulations growing with density-independent fitness.

In typical short-term xenograft experiments, the dose level is kept constant, only one exponential is observed, and the time resolution is not sufficient to permit observation of concentration-time effects, so this model simplifies even further to the exponential case:

$$N = N_0 e^{gt} \tag{11.8}$$

But what good is a simple exponential model, in practical terms? In an analysis performed by the authors several years ago, looking at 216 in vivo experiments from 36 tumor models, the authors found that a simple exponential growth curve was sufficient to describe control tumor growth—the $R^2$ values for the fits among all the control group animals yielded an interquartile range of 0.93–0.98 (Hather et al. 2014), and diagnostic plots for the tumor growth curves showed close agreement of the exponential model with the data.

Some of the advantages of using a model-fitted estimate of tumor growth and response are, of course, independent of model choice—a model-fitted estimate of T/C (treated/control growth) uses all available data, so it has better signal-to-noise properties and is not sensitive to study length or informative right censoring (the bias that occurs when the largest control animals are sacrificed due to IACUC guidelines) (Hather et al. 2014). A growth rate-based estimate of T/C is also independent of baseline growth rate, allowing comparisons to be made between different xenograft models. Bootstrap analyses performed in the same analysis showed that the improved signal-to-noise ratio derived from using an exponential model yielded the same power and statistical significance using substantially shorter treatment periods and fewer mice (Hather et al. 2014). For our datasets, it was observed that the study quality (power, statistical significance) with 6 mice treated for 14 days using the model was equivalent to the study quality for 10 mice treated for 21 days without using the model.

It must be pointed out that not all datasets will warrant a simple exponential model. If the observed dataset contains evidence of carrying capacity limitation,

then the model would need to account for that. (This was not the case for our data—our IACUC guidelines mandate sacrifice of the animals before nutrient-limited growth is observed in control tumors. Nutrient-limited growth is expected to occur only in control and not in treated tumors, as those molecules for whom nutrient-limited growth is observed in the treated tumors are typically not of therapeutic interest.)

Similarly, for large molecules, if there is a clear time lag between the initiation of treatment and tumor response, then the underlying tumor growth model will need to be supplemented with a pharmacokinetic (PK) model that accounts for target-mediated disposition. In other words, all rules of common sense modeling still apply! That being said, the simple exponential model is a practical and useful way of representing modern xenograft data, and can be extended readily to a translational setting, in the modeling of clinical tumors under treatment. This idea will be expanded upon in the next section.

## 2.2 Clinical Tumor Kinetic Modeling

Over the past few years, modelers in academia, regulatory agencies, and industry have moved in the general direction of exploiting the kinetics of tumor burden measurements to more accurately assess antitumor effect, the factors driving them, and their relationship to survival benefit (Foo et al. 2013; Stein et al. 2008, 2012, 2013; Claret et al. 2013a, b; Wang et al. 2009; Claret et al. 2009; Claret and Bruno 2014). These models take on many forms depending on the modeler, indication, treatment, and sampling frequency (Ribba et al. 2014), but many have found, including the authors, that exponential growth is both biologically plausible and pragmatic over the often relatively short time scales over where clinical response is measured in a single trial (as patients leave the trial immediately upon Response Evaluation Criteria In Solid Tumors (RECIST) disease progression).

Folding in the general view of cancer as an evolutionary disease, kinetic modeling of tumor growth and response in the clinic can be expressed as a general formulation of PK-tumor kinetic modeling through an evolutionary lens. Therefore the tumor burden time course $N(t)$ can be expressed as the sum of clones that grow or shrink independently of each other depending on drug concentration $c(t)$:

$$N(t) \equiv \sum_{i=1}^{n} N_i(t) \tag{11.9}$$

$$\frac{\mathrm{d}N_i}{\mathrm{d}t} = g_i\left(c(t)\right) N_i \tag{11.10}$$

$$\Rightarrow N_i(t) = N_i^0 \mathrm{e}^{\int_0^t g_i(c(\tau))\mathrm{d}\tau} \tag{11.11}$$

where $n$ is the number of clones having distinct intrinsic growth rates and/or sensitivities to the treatment, $N_i^0$ is the number of cells of the $i$th clone at $t=0$ (the moment treatment starts), and $g_i(c)$ is the signed growth/shrinkage rate of the $i$th clone as a decreasing function of drug concentration $c(t)$. (Note that this is just the concentration-dependent form of Eq. (11.7) from the previous section on xenograft modeling).

The number of clonal compartments that can be adequately identified and characterized in practice depends not only on the tumor composition and drug PK and mechanism of action, which dictate the tumor trajectory, but also on the frequency and precision of tumor burden assessments. Before discussing potential algorithms for detecting the appropriate number and nature of clones within a given dataset, an illustrative simplification of the general model in which there are two subclones—a drug-sensitive clone S and a drug-resistant clone R—will be discussed:

$$N(t) = N_S^0 e^{\int_0^t g_S(c(\tau))d\tau} + N_R^0 e^{g_R t} \tag{11.12}$$

In this case, $N_S^0$ and $N_R^0$ are the initial numbers of sensitive and resistant cells, $g_s(c)$ is a decreasing function in concentration $c$, and $g_R$ is the growth rate of the resistant cells, which by definition is unchanged by drug concentration.

For the purpose of understanding how the parameters affect the growth curve, further assume $c(t)$ can be neglected in favor of an average concentration, $c_{ave}$ due to the separation of time scales between the dosing frequency and the sampling frequency for tumor size assessments (see Appendix). Indeed, let $g_S^{max} = g_s(0)$ denote the growth rate of the sensitive clone prior to treatment and $g_S^{min} = g_s(c_{ave})$ denote the growth rate of the sensitive clone under treatment. Normalizing the model to initial tumor size and re-expressing the growth kinetics in terms of initial resistant fraction $\phi_R$, Eq. (11.13) is obtained:

$$\frac{N(t)}{N_0} = (1-\phi_R)e^{g_S^* t} + \phi_R e^{g_R t}, \tag{11.13}$$

where $g_S^* \equiv g_S^{max}$ when $t<0$ and $g_S^{min}$ when $t \geq 0$.

Figure 11.1 illustrates the dynamics of the subpopulations, as well as the emergent tumor kinetics for a parameter set corresponding to a typical response/relapse tumor burden trajectory.

The range of tumor trajectories that can be described by this simple model is illustrated in Fig. 11.2. Of course, if the sampling design is rich enough to support it, more subpopulations can provide even more complex trajectories, for example multiple distinct downward slopes during the response phase.

### 2.2.1 Parameter Identifiability

The attentive reader may have noticed that more than one parameter setting can result in the same trajectory, for example the $\phi_R = 1$ "primary resistance" curve can also be obtained by setting $g_S^{min} = g_S^{max} = g_R$ and $\phi_R = 0$. To illustrate, Fig. 11.3

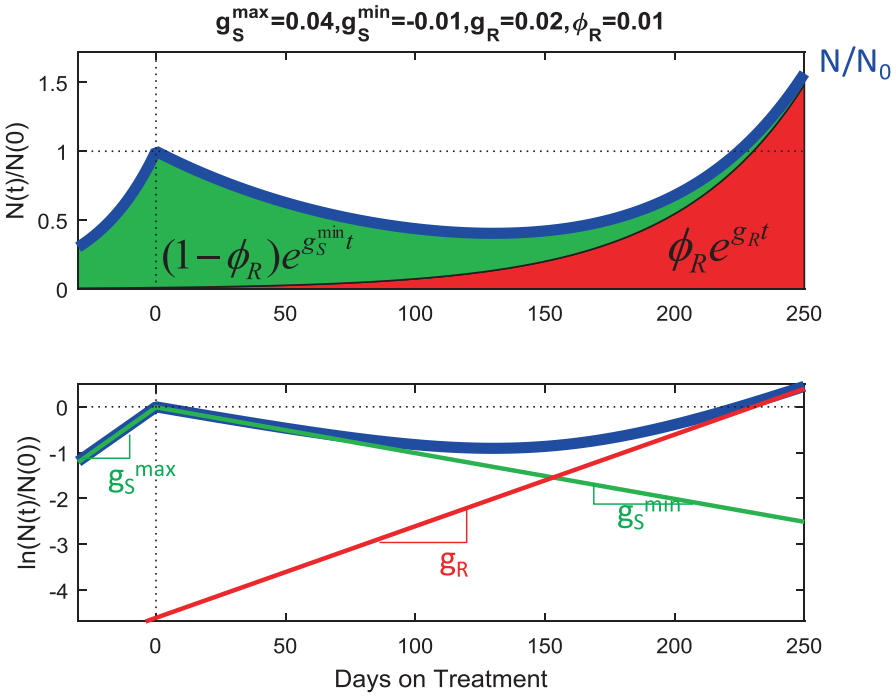



**Fig. 11.1** Illustration of sensitive and resistant cell contributions to tumor kinetics. The *blue* curve indicates the normalized total tumor burden time course. The *green* area (*top*) and *green* curve (*bottom*) represent the contribution of the drug-sensitive subpopulation to the total tumor burden, while the *red* area (*top*) and *red* curve (*bottom*) represent the contribution of the resistant subpopulation. The parameter values were chosen to illustrate the initial response followed by relapse trajectory often seen in cancer patients

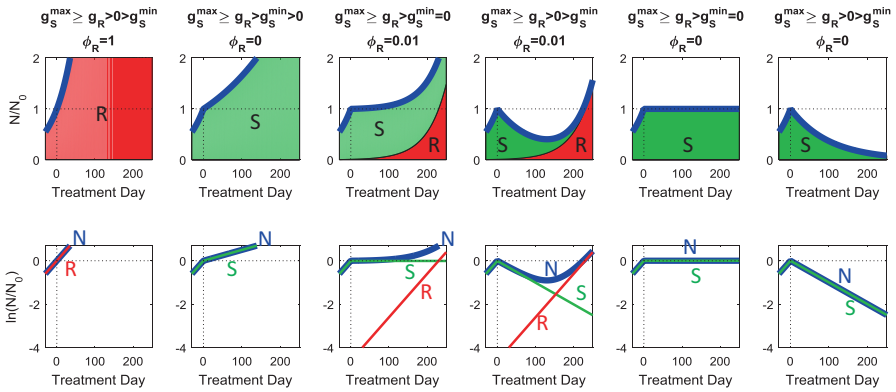



**Fig. 11.2** Dynamics of sensitive and resistant cell populations leading to wide range of typical clinically observed emergent tumor kinetic trajectories. Each column represents the normalized total tumor burden (*blue* curve) in linear (*top* row) or log (*bottom* row) scale. The *green* areas (*top*) and curves (*bottom*) represent the contributions of drug-sensitive cells to the total tumor burden, while the red areas (*top*) and curves (*bottom*) represent the contributions of drug-resistant cells

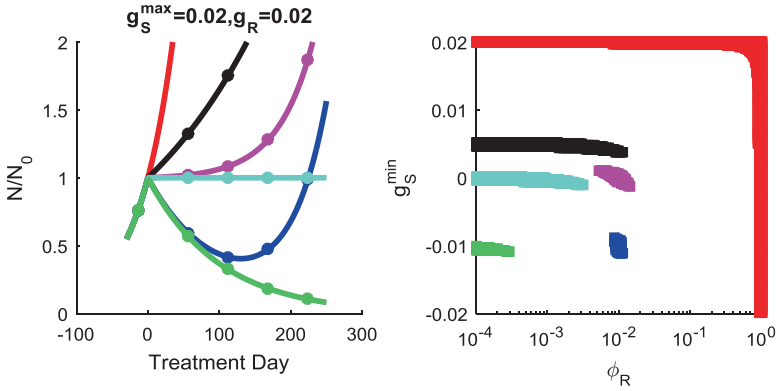



**Fig. 11.3** Mapping from tumor trajectories to parameter space illustrating parameter ambiguity for certain trajectories. The curves on the *left* are normalized tumor time courses generated by varying $\phi_R$ and $g_S^{min}$ to generate a variety of typically observed clinical trajectories. Each colored area on the right shows the set of $(\phi_R, g_S^{min})$ parameter pairs that lead to trajectories within measurement error of the correspondingly colored reference curve on the *left*

shows a mapping between parameter space and six different types of tumor trajectories. The color-coded regions on the right of Fig. 11.3 represent $(\phi_R, g_S^{min})$ parameter ranges resulting in tumor trajectories that are within measurement error (8.5 %) of the corresponding reference trajectories shown on the left. In this $(\phi_R, g_S^{min})$ parameter plane (assuming fixed/known $g_S^{max}$ and $g_R$), the "primary resistance" patient phenotype (red trajectory on the left) poses the most significant ambiguity in parameter values; this trajectory can be equally described by a not-so-sensitive population ($g_S^{min}$–$g_S^{max}$) or a totally resistant cell population ($\phi_R = 1$).

One way around this problem is to select for each patient the most parsimonious model from among various submodels representing various limiting cases of the full model. For any exposure-growth function $g_s(c(t);p)$ with $n_p$ parameters contained in the vector $p$, the solution of the full two-population model can be written as follows:

$$N(t) = N_0\left[\left(1-\phi_R\right)e^{\int_0^t g_s(c(\tau);p)d\tau} + \phi_R e^{g_R t}\right] \tag{11.14}$$

The nested "primary resistance" model is equivalent to setting $\phi_R = 1$ in the full model:

$$N(t) = N_0 e^{g_R t} \tag{11.15}$$

The nested "durable response" model is given by setting $\phi_R = 0$ in the full model:

**Table 11.2** Parameter settings for nested tumor kinetic models

| Parameter | Dimensions | Description | Full two-population model | Primary resistance model | Durable response model |
|---|---|---|---|---|---|
| $N_0$ | Length, volume, or # of cells | Tumor burden at start of treatment[a] (SLD) | $(0,+\infty)$ | $(0,+\infty)$ | $(0,+\infty)$ |
| $p$ | Varies | $n_p$ parameters of $g_S(c(t))$ | variable | NA | variable |
| $g_R$ | 1/time | Growth rate of resistant population | $(0,+\infty)$ | $(0,+\infty)$ | NA |
| $\phi_R$ | 1 | Resistant fraction at treatment start | $(0,1)$ | 1 | 0 |
| | | *Number of free parameters*: | $3+n_p$ | 2 | $1+n_p$ |

[a]Tumor burden at start of treatment $N_0$ should not be confused with the baseline observation, which is not typically measured at the moment of treatment start and is no less noisy than any subsequent tumor size measurements

$$N(t) = N_0 e^{\int_0^t g_s(c(\tau);p)d\tau} \tag{11.16}$$

Table 11.2 summarizes the parameter settings and parameter counts for these three models. If patient trajectories are to be fit individually, calculating the corrected Akaike Information Criterion (AICc) score for each of the three models and then selecting the model providing the best AICc for each patient is recommended. In a nonlinear mixed effects (NLME) framework, one can either use the previous technique to first classify patients then perform a supervised "mixture of models" estimation in NLME or attempt an unsupervised "mixture of models" estimation in NLME directly.

For example, assume that the growth rate of sensitive cells falls off linearly in concentration from their pretreatment growth rate $g_S^{\max}$, that is: $g_s(c) = g_S^{\max}(1-mc)$. In the above notation, $p = \left[g_S^{\max}, m\right]$ and $n_p = 2$. Since $g_s(c)$ is linear in $c$, (11.14) can be integrated to arrive at a solution of the full two-population model in terms of $\mathrm{AUC}(t) \equiv \int_0^t c(\tau)d\tau$:

$$N(t) = N_0\left[\left(1-\phi_R\right)e^{g_S^{\max}\left(t-\mathrm{mAUC}(t)\right)} + \phi_R e^{g_R t}\right] \tag{11.17}$$

The primary resistance model is unchanged and the durable response model is obtained by setting $\phi_R = 0$ above. The parameter sensitivity analysis in Fig. 11.4 illustrates the range of trajectories each of the three models is capable of representing.

In practice, distinguishing between $g_S^{\max}$ and $g_R$ requires estimating the pretreatment growth rate, which can be done only if pre-baseline scans are obtained, or if there is

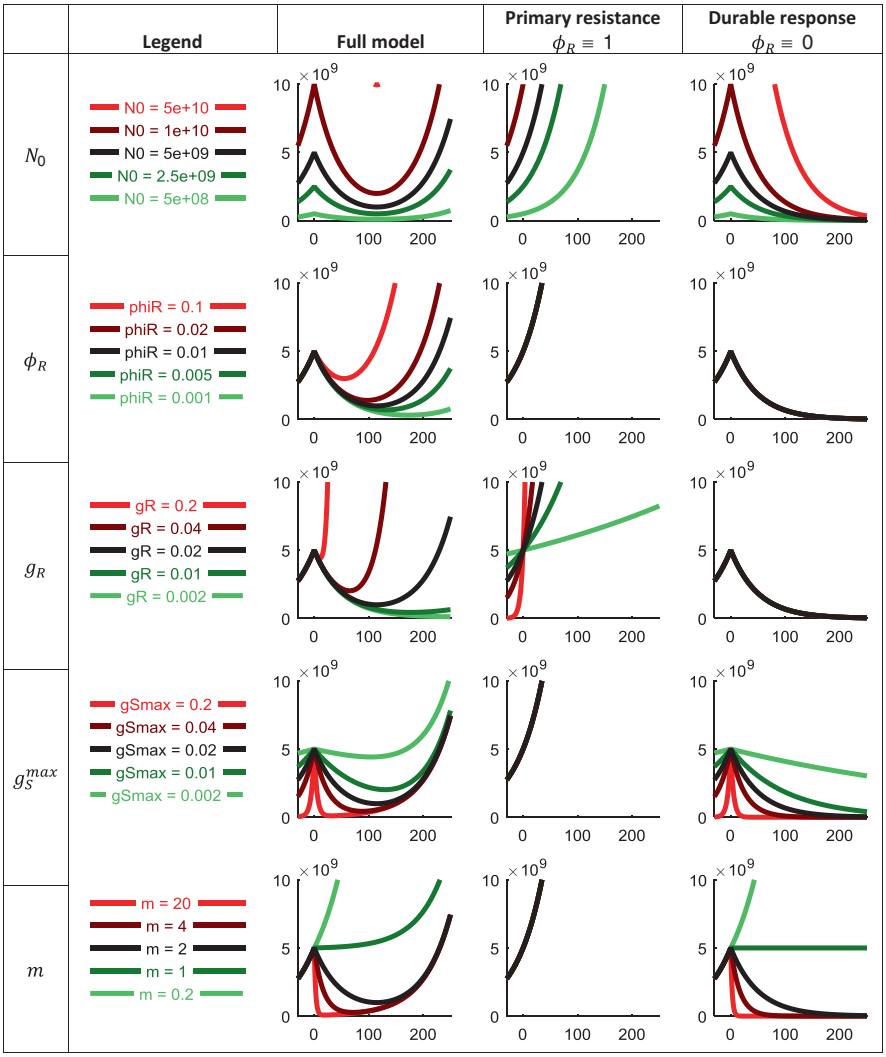



**Fig. 11.4** Sensitivity to parameters of "full two-population" model, "primary resistance" model, and "durable response" model. For these simulations assume concentration = 1, so AUC($t$) = $t$. The reference parameter values are in *black*, while *red* curves represent increased parameter values and *green* curves represent below-reference parameter values. The reference values were chosen to illustrate a typical initial response + relapse trajectory for the two-population model

a sufficiently wide range of exposures across the population allowing $g_S^{max}$ to be estimated. In terms of which parameters should be fitted as fixed effects (one parameter shared by entire population) or random effects (a unique value for each patient), starting with random effects on $N_0$, $\phi_R$ and possibly $g_R$, then proceeding to random effects on the concentration-growth rate parameters as required by the data is

recommended. Note that $N_0$, the estimated tumor size at treatment start, is not to be confused with the baseline observation which usually occurs days to weeks before start of treatment. Furthermore normalizing by the baseline observation is not recommended, as this measurement is no less noisy than the subsequent observations, and in some cases may be noisier if it is acquired outside of the study protocol.

Note in Fig. 11.4 the tumor trajectories obtained for increasing values of $m$ represent the potency of the investigational drug against the sensitive subpopulation; after a certain point, more potency results in a faster initial dip in tumor burden, but has no effect whatsoever on the relapse kinetics, which are dominated by the resistant clone. In the following section, the implications of this observation on the key measure of success of a cancer drug, the extent to which it prolongs a patient's life, will be explored.

### 2.2.2 What Drives Survival Benefit?

A "holy grail" of tumor kinetic modeling is to establish a relationship between tumor kinetics (and other patient factors) and overall survival (OS). Indeed, there is a growing body of literature suggesting that features of tumor kinetics are predictive of OS in a drug-independent, indication-dependent manner (Wang et al. 2009; Claret et al. 2013a; Claret et al. 2013b; Claret and Bruno 2014; Claret et al. 2009). Early work related model-predicted tumor deflection from baseline at a given time point (often 6–8 weeks after treatment initiation) to OS with surprising success (Wang et al. 2009). Subsequent work showed that "Time to Growth (TTG)," that is, the predicted time of tumor burden nadir, was a better predictor than tumor deflection in some indications (Claret et al. 2013a, b).

What is the relationship between the evolutionary model parameters $(\phi_R, g_S^{max}, g_S^{min}, g_R, N_0)$, which summarize a patient's tumor biology and the investigational drug's pharmacology, and ultimate survival benefit to the patient? Which of these parameters are predicted to be the key drivers of survival, and what does that imply in terms of what should be measured to get an idea of whether a drug is likely to help patients live longer? This section aims to address these questions.

If it is assumed for simplicity that the tumor size reaching a pre-set threshold $N_D$ results immediately in death (which has been employed in other modeling efforts—see (Swanson et al. 2003) for example), the time of death as $t_{death}$ can be calculated satisfying:

$$N\left(t_{death}\right) = N_0\left[\left(1-\phi_R\right)e^{g_S^{min}t_{death}} + \phi_R e^{g_R t_{death}}\right] = N_D \tag{11.18}$$

In general this doesn't allow a closed-form expression for $t_{death}$. If $g_S^{min} < 0$ and $1 \gg \phi_R > 0$, however, then after initial response, the resistant clone will eventually kill the patient:

$$t_{death} \approx \tau_T \equiv \frac{1}{g_R}\ln\left(\frac{1}{\phi_R}\bullet\frac{N_D}{N_0}\right) \tag{11.19}$$

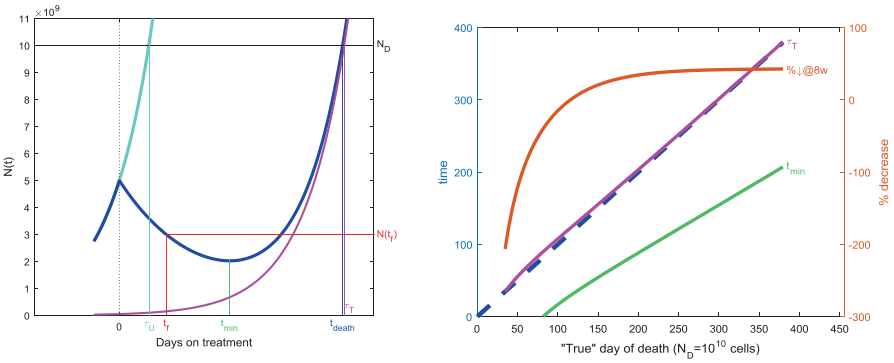



**Fig. 11.5** (**a**) Illustration of tumor size-based time of death treated ($t_{\text{death}}$), untreated (tau_U) and related approximations. (**b**) Comparison of % change from baseline (%↓@8w), time to regrowth ($t_{\min}$, *green*), and time when resistant clone alone would kill the patient ($\boldsymbol{\tau}^{\boldsymbol{T}}$, pink) as a function of true day of death (*X* axis). The *dashed blue* represents a hypothetically perfect predictor

It has been noted that the nadir of the tumor kinetic curve (referred to as "Time to Growth" or "TTG" in the literature) is more predictive of survival than the "Change in Tumor Size" (CTS), $\text{CTS} \equiv 100\left(1 - N\left(t_f\right)/N_0\right)$, at a fixed time point $t_f$ (Claret et al. 2013a, b; Claret and Bruno 2014). In the evolutionary model, the time of nadir can be determined by setting $N'(t) = 0$ and solving for *t*:

$$t_{\min} = \frac{1}{g_{\text{S}}^{\min} - g_{\text{R}}} \ln\left(\frac{g_{\text{R}}}{-g_{\text{s}}^{\min}} \cdot \frac{\phi_{\text{R}}}{1-\phi_{\text{R}}}\right) \tag{11.20}$$

To understand the relationship between these three metrics and the true day of death, in Fig. 11.5, the metrics — $\text{CTS} \sim N\left(t = 8 \text{ weeks}\right)/N_0$, $\text{TTG} \sim t_{\min}$, and $\tau_T$ — as a function of "true" day of death $t_{\text{death}}$ are plotted to assess the potential accuracy of each metric to predict overall survival as the initial resistant fraction $\phi_{\text{R}}$ is varied between 0 and 1. For reference, the identity line is shown in dashing blue. While the percent decrease from baseline measured at a fixed time point (in this case 8 weeks) does rise monotonically as a function of $t_{\text{death}}$, for the parameter values tested ( $g_{\text{R}} = 0.02, g_{\text{S}}^{\min} = -0.01, N_0 = 5\times10^9, N_D = 10^{10}$ ), the relationship is far from linear. In contrast, $t_{\min}$ is linear in $t_{\text{death}}$, but with a downward shift, which is to be expected because reaching nadir does not kill the patient. By far the best approximation to $t_{\text{death}}$ is $\tau_T$, which lies nearly on the identity line for all values of $\phi_{\text{R}}$.

This surrogacy of $\tau_T$ for $t_{\text{death}}$ implies that death is caused by tumor burden reaching a given threshold $N_D$, survival time depends strongly on the initial fraction $\phi_{\text{R}}$ of the resistant clone, the growth rate $g_{\text{R}}$ of that clone, and how close the initial tumor burden $N_0$ is to killing the patient ($N_D$), but *negligibly on the net fitness* $g_{\text{s}}^{\min}$ *of the sensitive clone during treatment, which dominates the initial dip in tumor size upon treatment initiation.*

To reiterate: this result suggests that the initial decline in tumor size following treatment, that is, the backbone of both RECIST response criteria and many tumor kinetic modeling efforts to date, has little to do with survival benefit! This may explain why time to nadir is a better OS predictor than initial decline in colorectal carcinoma (Claret et al. 2013a, b), and also why appearance of new lesions, and not initial change in SLD from baseline, is predictive of OS in metastatic renal cell carcinoma (Stein et al. 2013).

While it may be counterintuitive that initial tumor kill rate doesn't matter for overall survival, this is not to say that the patient does not benefit from this initial dip in tumor burden; rather, the duration of life gained due to the treatment is given by the difference between the time when the resistant clone eventually kills the patient ($\tau_T$) and when the more prevalent "sensitive" clone would have killed the untreated patient ($\tau_U$):

$$\tau_U \approx \frac{1}{g_S^{\max}} \ln\left(\frac{N_D / N_0 - \phi_R}{1 - \phi_R}\right) \to \frac{1}{g_S^{\max}} \ln\left(\frac{N_D}{N_0}\right) \quad \text{as} \quad \phi_R \to 0 \tag{11.21}$$

So for a small $\phi_R$, the "days of life gained" (modifying a term coined by Neal et al. 2013) would be approximately:

$$\tau_T - \tau_U \approx \left(\frac{1}{g_R} - \frac{1}{g_S^{\max}}\right) \ln\left(\frac{N_D}{N_0}\right) - \frac{\ln(\phi_E)}{g_R} \tag{11.22}$$

Alternately, the gain in life can be expressed as a ratio, which under certain conditions equals the reciprocal of the hazard ratio (Carroll 2003):

$$\mathrm{HR}^{-1} \approx \frac{\tau_T}{\tau_U} \approx \frac{g_S^{\max}}{g_R}\left(1 - \frac{\ln(\phi_R)}{\ln(N_D / N_0)}\right) \tag{11.23}$$

In other words, for a small $\phi_R$, the hazard ratio between treated and untreated depends on the ratio $g_S^{\max}/g_R$ of the growth rates of the sensitive and resistant clones, the prevalence $\phi_R$ of the resistant clone at start of treatment, and how close to death the patient is at start of treatment ($N_D/N_0$).

In practice, calculation of either days of life gained or the above ratio would require estimation of $g_S^{\max}$, which as stated previously requires either more than one scan before start of treatment or a wide range of drug concentrations.

While most patients do not go untreated, the HR calculation above can be thought of also as standard of care alone (untreated) versus standard of care + investigational agent (treated). For the case of head-to-head comparison of drug A vs. drug B, let us denote by $\phi_A$ the fraction of tumor cells resistant to drug A at baseline, and likewise $\phi_B$ for drug B. Similar to the previous derivation, if $g_S^{\min} < 0$ for both A and B and $1 \gg \phi_A, \phi_B > 0$, the HR of A versus B can be approximated as the inverse ratio of the times when the respective resistant clones kill the patient:

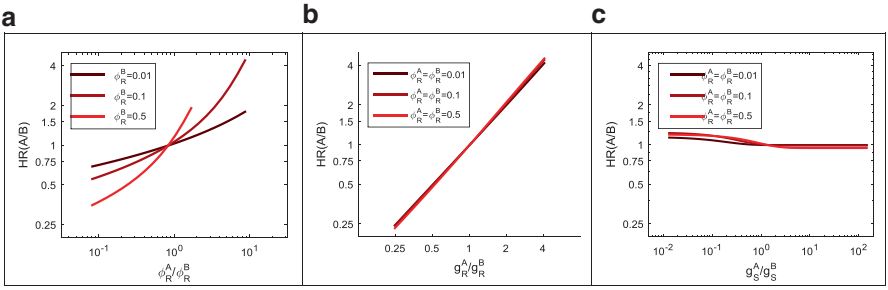



**Fig. 11.6** Sensitivity of predicted head-to-head hazard ratio to evolutionary model parameters. In addition to varying each parameter ratio as shown on the *X* axis, three scenarios, represented by three differently shaded curves, corresponding to different resistant fractions to the comparator drug B are shown in each plot. (**a**) varying ratio of fractions of cells resistant to drug A vs. B. (**b**) varying ratio of growth rates of cells resistant to drug A vs. B. (**c**) varying ratio of "kill" rates of drugs A and B on sensitive cells

$$\mathrm{HR}_{\mathrm{A/B}} \approx \frac{\tau_T^{\mathrm{B}}}{\tau_T^{\mathrm{A}}} \approx \frac{g_{\mathrm{R}}^{\mathrm{B}}\left[\ln\left(\frac{N_D}{N_0}\right) - \ln\left(\phi_{\mathrm{B}}\right)\right]}{g_{\mathrm{R}}^{\mathrm{A}}\left[\ln\left(\frac{N_D}{N_0}\right) - \ln\left(\phi_{\mathrm{A}}\right)\right]} \tag{11.24}$$

Once again, in this limit, the kill rates of the two drugs on their sensitive cells don't appear in the expression. Figure 11.6 shows the results of a sensitivity analysis on the estimated HR between A and B using the numerical solution of the full model (not the above approximation). In Fig. 11.6a, the ratio $\phi_{\mathrm{A}}/\phi_{\mathrm{B}}$ between the resistant fractions to drugs A and B has a significant effect on HR, which becomes even more pronounced for larger values of $\phi_{\mathrm{B}}$. In Fig. 11.6b, the ratio of the growth rate of cells resistant to drug A (under drug A treatment) to the growth rate of cells resistant to drug B (under drug B treatment) also has a profound effect on the hazard ratio; indeed if $\phi_{\mathrm{A}} \sim \phi_{\mathrm{B}}$ (as in the figure) this degree of sensitivity is independent of the absolute values of $\phi_{\mathrm{A}}, \phi_{\mathrm{B}} < 1$. Finally, in Fig. 11.6c, the ratio between the kill rates of drug A and B on their sensitive cells, even when varied over several orders of magnitude, has a much weaker effect on the predicted hazard ratio.

It should be pointed out that as pioneering work goes, using the initial change in tumor size (CTS) as a predictor for OS does have a pretty good track record empirically, although there is no way to measure how many failed attempts went unpublished. Systematic empirical analyses comparing relapse growth rate to TTG and CTS in clinical datasets are needed to shed light on which predictors are most predictive of survival benefit as a function of therapeutic modality and indication.

### 2.2.3 Evolutionary Dynamics Approaches Applied to Clinical Datasets

Approaches similar to the one described here have been used successfully to predict time to failure (TTF) in prostate cancer from PSA kinetics. Individual PSA time courses were fit using a hybrid of two-stage and nonlinear mixed effects techniques and then TTF was predicted from the first few measurements after PSA nadir. The predicted TTF had an R-squared of 0.73 relative to the observed TTF and it was noted that the estimated growth rate of the resistant clone dominated the TTF prediction (Patel et al. 2015).

The kinetics of BCR-ABL transcript levels in chronic myeloid leukemia (CML) under imatinib treatment have also been modeled extensively, initially from an evolutionary perspective (Michor et al. 2005). While this first model predicted every patient would relapse even in the absence of imatinib resistance mutations, subsequent improvements properly described durable responses (Bottino 2009; Stein et al. 2009, 2011). NLME mixture modeling has been applied to these newer structural models to estimate the existence and prevalence of imatinib-resistant clones in a subpopulation of patients (Bottino 2009; Stein et al. 2011).

## *2.3 Summary: Applying Tumor Growth Models to Clinical Development*

There are three key questions around the efficacy of investigational antitumor agents in early clinical development:

1. How potent is the antitumor effect of the investigational agent across the target population?
2. How strongly do anticipated drivers of antitumor effect (like dose, PK, and covariates such as baseline sensitivity biomarkers) influence this antitumor effect?
3. What is the anticipated survival benefit of the investigational agent (vs. a current or emerging standard of care) as a consequence of the antitumor effect observed thus far?

Standard practice for addressing these three questions relies heavily on the RECIST, which assigns each patient to one of four response classifications at a given follow-up time based on the percent change from baseline of the sum of the longest diameters (SLD) of up to 5 target lesions identified by the radiologist at baseline (Eisenhauer 2009): Complete Response (CR), corresponding to disappearance of target lesions and no new lesions; Partial Response (PR), corresponding to SLD decreasing more than 30 % from baseline (and no new lesions); Progressive Disease (PD), triggered by increase of SLD greater than 20 % from baseline or nadir or the appearance of new lesions; everything else is considered to be Stable Disease (SD). These cutoffs have their basis not in prediction of long-term benefit but rather on the reproducibility of the measurements themselves (Moertel and Hanlet 1976).

While RECIST continues to be the mainstay in many clinical development programs, tumor kinetic modeling as a means of quantifying clinical response has

started to gain momentum. In this chapter, an alternative formulation of tumor kinetic modeling has been put forth where the tumor growth and response is framed as an evolutionary process subject to selection pressure due to the treatment of interest. (In practice, mixtures of models may be required to uniquely determine individual parameters). Notably—and with direct implications for how cancer biologists think about translating results from Phase II to Phase III-evolutionary modeling suggests that the survival benefit due to a treatment depends strongly on initial growth rate, resistant fraction, and resistant growth rate but negligibly on initial response.

## 3 Conclusions

It has been shown in this chapter that evolutionary models are relatively simple but powerful and flexible, and have the advantage of providing mechanistically relevant insights as well as providing the ability to predict downstream response. Framing the early clinical development paradigm in terms of evolutionary models provides a way of thinking about the process that is more consistent with the emerging picture of tumor biology, and allows, in many cases, for cleaner and more statistically sound answers to the three questions outlined at the beginning of this section. While much still remains to be learned about the fundamental mechanisms and processes of cancer, using more empirical and simple models that capture our limited understanding of the biology may lead to a more robust development process.

## Appendix

### *When Can Tumor PK Be Replaced with Cave/AUC?*

It is common pharmacometrics practice to use full time course of PK to drive the PD model, in this case the tumor kinetics. However, in the case where PK oscillates on a rapid time scale of say hours for daily dosing, and the tumor kinetics are measured over the course of months, this level of temporal resolution is about as necessary (and potentially computationally costly) as modeling the peristaltic contractions of pill swallowing to predict PK over the next 24 h. If, however, the concentration-effect relationship is approximately linear over the range of relevant concentrations, say, $g(c) = g^{\max}\left(1 - mc(t)\right)$, then for a given clone (suppressing clone subscript i):

$$N(t) = N^0 \mathrm{e}^{\int_0^t g(c(\tau))\mathrm{d}\tau} = N^0 \mathrm{e}^{\int_0^t g^{\max}(1-mc(\tau))\mathrm{d}\tau} = N^0 \mathrm{e}^{g^{\max}\left[t - m\int_0^t c(\tau)\mathrm{d}\tau\right]} = N^0 \mathrm{e}^{g^{\max}(t - m\ AUC(t))} \quad (11.25)$$

where $\mathrm{AUC}(t) \equiv \int_0^t c(\tau)\mathrm{d}\tau$ is the cumulative area under the concentration curve from time 0 to t.

### *Tumor Growth Is Dominated Initially by the More Frequent Clone and Eventually by the Resistant Clone*

Note that if the normalized growth rate for the two-population model is examined

$$\tilde{N} \equiv \frac{N(t)}{N_0} = \left(1-\phi_{\mathrm{R}}\right)\mathrm{e}^{g_{\mathrm{s}}^{\min} t} + \phi_{\mathrm{R}}\mathrm{e}^{g_{\mathrm{R}} t} \tag{11.26}$$

The rate of change of $\tilde{N}$ at any time $t$ is of course given by its first derivative:

$$\tilde{N}'(t) = \left(1-\phi_{\mathrm{R}}\right) g_{\mathrm{s}}^{\min}\mathrm{e}^{g_{s}^{\min} t} + \phi_{\mathrm{R}} g_{\mathrm{R}}\mathrm{e}^{g_{\mathrm{R}} t} \tag{11.27}$$

This implies that initially,

$$\tilde{N}'(t \sim 0) \approx \left(1-\phi_{\mathrm{R}}\right) g_{\mathrm{s}}^{\min} + \phi_{\mathrm{R}} g_{\mathrm{R}} \tag{11.28}$$

In other words, the kinetics are dominated by which clone is more prevalent at time zero (assuming $g_{\mathrm{s}}^{\min}$ and $g_{\mathrm{R}}$ are of similar magnitude).

At longer times, however, since $g_{s}^{\min} < 0$, the sensitive clone term goes to zero while the resistant clone dominates, ie,

$$\tilde{N}'(t \gg 1) \approx \phi_{\mathrm{R}} g_{\mathrm{R}}\mathrm{e}^{g_{\mathrm{R}} t} \tag{11.29}$$

That is, the derivative of the tumor burden is dominated by the derivative of the resistant term.

### *Other Commonly Used Tumor Kinetic Model Formulations*

Long lists of tumor kinetics models that have been used in a clinical nonlinear mixed effects context are available in the literature (Ribba et al. 2014). Two of the more prevalent models in the context of our evolutionary modeling framework will be discussed.

The Claret/Bruno TGI model looks like this:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \left(g - k(c)\mathrm{e}^{-\lambda t}\right) N \tag{11.30}$$

where $g$ is the untreated growth rate, $k(c)$ is the kill rate as a function of drug concentration, and $\lambda$ is the decay rate of the drug effect (Claret et al. 2013a, b).

Expressed in our notation under similar concentration averaging assumptions the equation becomes:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \left(g_{\mathrm{S}}^{\max} - \left(g_{\mathrm{S}}^{\max} - g_{\mathrm{S}}^{\min}\right)\mathrm{e}^{-\lambda t}\right)N \tag{11.31}$$

This approximation has an analytic solution:

$$N(t) = N_0 \exp\left[g_{\mathrm{S}}^{\max} t + \frac{1}{\lambda}\left(g_{\mathrm{S}}^{\max} - g_{\mathrm{S}}^{\min}\right)\left(\mathrm{e}^{-\lambda t} - 1\right)\right] \tag{11.32}$$

This model has one less parameter than the evolutionary model because it assumes that the pretreatment growth rate is equal to the tumor growth rate at relapse. While one might assert that $g_{\mathrm{R}} < g_{\mathrm{S}}^{\max}$ at least in patients with an initial response, the authors are aware of no evidence to support the assumption that the initial growth rate equals the relapse rate, i.e., $g_{\mathrm{R}} = g_{\mathrm{S}}^{\max}$. Again, acquisition of pre-baseline tumor scans may shed light on this question.

That said, in a world where NONMEM convergence or failure is considered to be an acceptable acceptance or rejection criterion for a given structural model, the Claret/Bruno model likely has more readily estimable parameters, which may suffice when interpretability of model parameters is not a concern. Additionally many papers are already written relating parameters from this model to OS, so this model might be useful for predicting survival in an indication for which there is already a published tumor kinetics-to-OS relationship.

Another popular tumor kinetic model is of the form:

$$\frac{N}{N_0} = \mathrm{e}^{g_{\mathrm{S}}^{\min} t} + \mathrm{e}^{g_{\mathrm{R}} t} - 1. \tag{11.33}$$

This expression is nearly equivalent to the special case of the evolutionary model where $\phi_{\mathrm{R}} = 0.5$. While this model has also been used successfully to relate tumor growth rates to survival (Stein et al. 2008), the authors are not aware of any data supporting the assumption that resistant cells make up half the tumor burden at start of treatment.

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# Chapter 12
# Practical Considerations for Clinical Pharmacology in Drug Development: A Survey of 44 FDA Oncology Approvals

**Danny R. Howard**

**Abstract** This chapter presents the practical challenges facing the oncology clinical pharmacologist by surveying the cancer chemotherapies approved by the FDA in the period between January 2009 and June 2015. For each new medicine, the contents of the review summaries published by the FDA in the Drugs@FDA database at the time of first approval are examined. The comments of reviewers in the areas of subject and patient selection, dose and regimen justification, characterization of food and pH-altering drug interactions, evaluation of dose adjustment for organ impaired populations, and QTc assessment of new oncology therapeutics are presented. The information gleaned from the 44 approvals for new oncology drugs during this period provides the reader with an insight into the expectations and requirements for initial approval and provide practical information for how regulatory guidance is applied in clinical pharmacology.

**Keywords** Regulatory • Food and Drug Administration • Package insert • Product label • Clinical development

## 1 Introduction

The commonly understood approach for the development of new drugs is frequently presented as follows: a new molecule is vetted for gross pharmacology and safety in preclinical studies, enters Phase I to determine the clinical safety, tolerability, and maximum tolerated dose (MTD), proceeds to Phase II where, if the mechanism of action and a measurable stabilization or regression of disease are verified, it may

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enter Phase III studies and can be compared to the established standard of care. Phase I defines the pharmacokinetics and safety, Phase II optimizes dose, regimen, and indication selection, and Phase III confirms these findings and defines the overall benefit–risk ratios. This simple paradigm is appealing because it is general enough to be applied to any therapeutic area and because the "Phase I-Phase II-Phase III" jargon is a shared lexicon among drug development scientists and regulators worldwide.

Today, however, the limitations of the Phase-based mentality in drug development are more apparent than ever before. This is especially true in the therapeutic area of oncology where the life-threatening nature of the disease and often limited treatment options create an urgent unmet medical need. New review strategies, like the United States' Food and Drug Administration's Breakthrough Therapy Designation (Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics 2014) combined with the accelerated and priority approval designations have allowed for safety, efficacy, dose, pharmacokinetics, indication, treatment population, and marketable formulation to be defined as early as the first-in-human study. Overall, fewer studies are being required for initial approvals—83 % of new oncology drugs approvals between 2006 and 2011 were based on a single study (Martell et al. 2013). These pressures require development scientists to reexamine the old development schemes. There are now several examples for expedited review and drug approval obtained for drugs given the Breakthrough Therapy Designation. Given the extraordinary benefit the Breakthrough Therapy designation brings to patients, and the appeal it has for pharmaceutical companies whose mission it is to bring new medicines to them, we can safety assume we are on the cusp of realizing a new drug development paradigm.

The very nature of our drug treatments for oncology has changed significantly over the last 20 years. Cytotoxic agents, which dominated the chemotherapeutic treatment landscape for decades, are being replaced by small-molecules and monoclonal antibodies targeted to specifically inhibit oncogene function or promote suppression directly at the tumor. Prior to 2000, only three targeted agents were available to oncologists: one small-molecule (imatinib), one antibody (trastuzumab), and the antibody-drug conjugate, gemtuzumab ozogamicin, which was withdrawn from the US market in 2010 when a confirmatory trial failed to demonstrate clinical benefit (Petersdorf et al. 2013). Today targeted agents make up greater than 80 % of all new oncology drug approvals since 2009. Unlike cytotoxic agents which inhibit all actively dividing cells, targeted agents interfere with tumor cell signaling pathways to block cell proliferation, growth, and metastases. Immunotherapies meant to exploit the body's own defenses by upregulating the immune system, blocking interactions of cellular surface proteins which interfere with T-cell response, or genetically modifying host immune system components to target tumor cells are fast becoming the next major therapeutic advancement. Nearly 30 % of all approvals since 2009 have been monoclonal antibodies.

We have also seen a significant change in the effectiveness of our cancer therapies. Patients are living longer. Chemotherapy for some cancers, including forms of leukemia, lymphoma, small-cell lung cancer, and ovarian cancers, are curative.

In just under 40 years, the 10-year relative survival rate for patients diagnosed with leukemia has doubled from under 24 % to nearly 50 % and the life expectancy of a patient diagnosed with leukemia has extended by 40 years (Howlader et al. 2015). Significant progression-free survival has also been observed in renal, breast, liver, and gastrointestinal cancers. Clinical studies with anti-PD1, CTLA-4, and CDK4/6 inhibitors have already shown great promise for extending the lives of patients with melanoma, lung, and breast cancers. We now recognize cancer as a multi-organ disease where genetic coding errors may be targeted, suppressed, or overwritten.

The primary focus of the industrial clinical pharmacologist has always been to characterize the sources of variability to drug exposure and response, optimize dose and regimen within an indication, and provide appropriate labeling instructions to control or accommodate the variability. However, for indiscriminately cytotoxic drug therapies, or when the disease is acute and terminal, dose-optimization and characterization of variability due to drug interactions, demographics, or comorbidities may have little meaning for both doctor and patient. Many cytotoxic agents are intravenous injections; the formulations are rarely complex, and could be optimized in the laboratory, not in the clinic. The issues of clinical pharmacology are lesser importance for cytotoxic agents. However, the recent emphasis on targeted and oral agents, which may be taken by patients over long periods of time, has increased the importance of clinical pharmacology in oncology drug development. The expectations of regulatory bodies can be expected to evolve accordingly (Minasian et al. 2014).

This chapter will present the practical challenges facing the oncology clinical pharmacologist by surveying the cancer chemotherapies approved by the FDA in the period between January 2009 and June 2015. For each new medicine, the contents of the Drugs@FDA database are examined for practical insights to the expectations of reviewers in the areas of subject selection, dose and regimen justification, characterization of food and pH-altering drug interactions, evaluation of dose adjustment for organ impaired populations, and QTc assessment of new oncology therapeutics.

## 2 The Approval Database

The drugs reviewed for this exercise include all new medicines with a primary indication to treat cancer, approved by the Center of Drug Evaluation and Research (CDER) between January 2009 and June 2015. It excludes approvals for new indications or new formulations of previously approved therapeutics. Furthermore, since the focus is on drugs intended to treat disease, approvals for supportive care and diagnostic agents were also excluded. The information contained in this chapter is based on the published contents of the FDA Approval Letter, Label, Clinical Pharmacology and Biopharmaceutics Review, Medical Review and Interdisciplinary Review Team for QT Studies Consultation for each drug published on the FDA website at the time of drug approval (Drugs@FDA). The purpose of this survey was

to understand the decisions made at the time of review which led to the approval, and the focus of this survey is on the information presented for review by the agency at that time. Any additional or follow-up information from sources published after the approval are noted and referenced.

As shown in Table 12.1, this review covers the 44 new oncology approvals granted by the Food and Drug Administration during this time period. This group was dominated by small molecules and targeted therapeutics, with few new cytotoxic drug approvals. Thirty-two of the new approvals were for targeted therapeutic agents, two were hormone therapies, and ten were cytotoxics. Of the targeted therapeutics, 19 were small molecules, nine were antibodies, two were antibody-drug conjugates, and two were protein/peptides.

Most of the oncology drugs approved during this period (77 %) were given priority, accelerated or breakthrough therapy status. The high rate has been a consistent feature of oncology drug development for over two decades (DiMasi and Grabowski 2007). Priority review is granted for drugs expected to provide significant improvement in safety or efficacy in the treatment of serious conditions. The goal is to provide for the review of priority drugs in a 6 month timeframe, or about 4 months faster than standard review times of approximately 10 months. Under the agency's accelerated approval program, the approval may be based on a surrogate endpoint reasonably likely to predict the clinical benefit in a serious or life-threatening disease, and this designation is intended to provide earlier access to promising new drugs while confirmatory clinical trials are being performed. The Breakthrough Therapy Designation was established in 2012 to provide for the fast approval of treatments intended for serious or life-threatening illnesses. It provides all of the benefits associated with the other designations, plus the addition of more intensive FDA guidance, communication, collaboration, and interaction.

The first breakthrough therapy designate, Gazyva (obinutuzumab), was approved in November 2013. Since then, there have been 15 new oncology drugs approved and eight of these have been breakthrough therapy designates.

## *2.1 Use of Patients and/or Healthy Volunteers*

For reasons of safety, clinical evaluation of cytotoxic oncology agents necessarily excluded the participation of healthy volunteers and restricted testing only to those patients for whom the risks associated with the treatment might be off-set by the potential benefits. As indicated previously, targeted agents—small molecules, monoclonal antibodies, and antibody-drug conjugates—currently dominate the new drug approvals.

Many of these targeted agents are neither genotoxic nor mutagenic, and restrictions for the participation of health volunteers in clinical pharmacology studies do not exist. But, while it may be possible to initiate first-in-human dose-escalation and tolerance studies in healthy volunteers, this approach was rarely employed. In fact, of the last 44 new oncology drugs approved by the FDA since 2009, only idelalisib

**Table 12.1** New oncology therapeutics approved by the FDA between 2009 and June 2015

| Drug | Approval year | Company | Indication | Chemical type | Chemo type | Chem subtype | Route | Approval type |
|---|---|---|---|---|---|---|---|---|
| Unituxin (dinutuximab) | 2015 | United Therapeutics | Pediatric neuroblastoma | Antibody | Targeted | Anti-GD2 | IV infusion | Priority |
| Farydak (panobinostat) | 2015 | Novartis | Multiple myeloma | Small molecule | Cytotoxic | HDAC Inhibitor | Oral | Priority, accelerated |
| Ibrance (palbociclib) | 2015 | Pfizer | ER-positive, HER2-negative breast cancer | Small molecule | Targeted | CDK/4/6 inhibitor | Oral | Breakthrough therapy, priority, accelerated |
| Lenvima (lenvatinib) | 2015 | Eisai | Thyroid cancer | Small molecule | Targeted | VEGFR2/R3 inhibitor | Oral | Priority |
| Beleodaq (belinostat) | 2014 | Spectrum pharmaceuticals | Peripheral T-cell lymphoma | Small molecule | Cytotoxic | HDAC Inhibitor | IV infusion | Priority, accelerated |
| Blincyto (blinatumomab) | 2014 | Amgen | Philadelphia chromosome-negative acute lymphoblastic leukemia | Antibody | Targeted | Anit-CD19 | IV infusion | Breakthrough therapy, accelerated |
| Cyramza (ramucirumab) | 2014 | Eli Lilly | Gastric cancer | Antibody | Targeted | VEGFR2 antagonist | IV infusion | Standard |
| Keytruda (pembrolizumab) | 2014 | Merck | Unresectable or metastatic melanoma | Antibody | Targeted | PD1 inhibitor | IV infusion | Breakthrough therapy, accelerated |
| Lynparza (olaparib) | 2014 | AstraZeneca | BRCA-mutated ovarian cancer | Small molecule | Targeted | PARP inhibitor | Oral | Priority, accelerated |
| Opdivo (nivolumab) | 2014 | Bristol-Myers Squibb | unresectable or metastatic melanoma | Antibody | Targeted | PD1 inhibitor | IV infusion | Breakthrough therapy, accelerated |

(continued)

**Table 12.1** (continued)

| Drug | Approval year | Company | Indication | Chemical type | Chemo type | Chem subtype | Route | Approval type |
|---|---|---|---|---|---|---|---|---|
| Zydelig (idelalisib) | 2014 | Gilead | Chronic lymphocytic leukemia, follicular B-cell NHL and small lymphocytic lymphoma | Small molecule | Targeted | Pi3K inhibitor | Oral | Breakthrough therapy, priority, accelerated |
| Zykadia (ceritinib) | 2014 | Novartis | ALK+ metastatic non-small cell lung cancer | Small molecule | Targeted | ALK inhibitor | Oral | Breakthrough therapy, priority, accelerated |
| Gazyva (obinutuzumab) | 2013 | Genentech | chronic lymphocytic leukemia | Antibody | Targeted | Anti-CD20 | IV infusion | Breakthrough therapy, priority |
| Gilotrif (afatinib) | 2013 | Boehringer Ingelheim | Metastatic non-small cell lung cancer with EGFR mutations | Small molecule | Targeted | EGFR inhibitor | Oral | Priority |
| Imbruvica (ibrutinib) | 2013 | Pharmacyclics | Mantle cell lymphoma | Small molecule | Targeted | BTK inhibitor | Oral | Breakthrough therapy, priority, accelerated |
| Kadcyla (ado-trastuzumab emtansine) | 2013 | Genentech | HER2-positive metastatic breast cancer | Antibody-drug conjugate | Cytotoxic | Microtubule toxin | IV infusion | Standard |
| Mekinist (trametinib) | 2013 | GlaxoSmithKline | Unresectable or metastatic melanoma with BRAF V600E or V600K mutations | Small molecule | Targeted | MEK inhibitor | Oral | Standard |
| Pomalyst (pomalidomide) | 2013 | Celgene | Multiple myeloma | Small molecule | Targeted | Immunomodulator | Oral | Accelerated |

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|---|---|---|---|---|---|---|---|---|
| Tafinlar (dabrafenib) | 2013 | GlaxoSmithKline | unresectable or metastatic melanoma with BRAF V600E mutation | Small molecule | Targeted | BRAF Inhibitor | Oral | Standard |
| Xofigo (radium Ra 223 dichloride) | 2013 | Bayer Healthcare pharmaceuticals | Prostate cancer with bone metastases | Radioisotope | Cytotoxic | Alpha emitting agent | IV infusion | Priority |
| Bosulif (bosutinib) | 2012 | Pfizer | Ph+chronic myelogenous leukemia | Small molecule | Targeted | BCL-ABL Inhibitor | Oral | Standard |
| Cometriq (cabozantinib) | 2012 | Exelixis | Metastatic medullary thyroid cancer | Small molecule | Targeted | Multi Kinase Inhibitor | Oral | Priority, accelerated |
| Erivedge (vismodegib) | 2012 | Genentech | Basal cell carcinoma | Small molecule | Targeted | Hedgehog inhibitor | Oral | Priority |
| Iclusig (ponatinib) | 2012 | Ariad Pharmaceuticals | Chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia | Small molecule | Targeted | ABL Inhibitor | Oral | priority, accelerated |
| Inlyta (axitinib) | 2012 | Pfizer | Advanced renal cell carcinoma | Small molecule | Targeted | VEGF inhibitor | Oral | Standard |
| Kyprolis (carfilzomib) | 2012 | Onyx Pharmaceuticals | Multiple myeloma | Tetrapeptide | Targeted | Proteasome inhibitor | IV infusion | Accelerated |
| Perjeta (pertuzumab) | 2012 | Genentech | HER2+ metastatic breast cancer | Antibody | Targeted | Anti-HER2 antibody | IV infusion | Priority |
| Stivarga (regorafenib) | 2012 | Bayer HealthCare pharmaceuticals | Metastatic colorectal cancer | Small molecule | Targeted | Multi Kinase Inhibitor | Oral | Priority |

(continued)

**Table 12.1** (continued)

| Drug | Approval year | Company | Indication | Chemical type | Chemo type | Chem subtype | Route | Approval type |
|---|---|---|---|---|---|---|---|---|
| Synribo (omacetaxine mepesuccinate) | 2012 | Teva Pharmaceutical | Chronic or accelerated phase chronic myeloid leukemia | small molecule | Cytotoxic | alkaloid | SC injection | accelerated |
| Xtandi (enzalutamide) | 2012 | Medivation | Metastatic castration-resistant prostate cancer | Small molecule | Hormone therapy | Anti-androgen | Oral | Priority |
| Zaltrap (ziv-aflibercept) | 2012 | Sanofi-Aventis | Metastatic colorectal cancer | Protein | Targeted | Rec fusion protein | IV infusion | Standard |
| Adcetris (brentuximab vedotin) | 2011 | Seattle genetics | Hodgkin's lymphoma and anaplastic large cell lymphoma | Antibody-drug conjugate | Cytotoxic | Microtubule toxin | IV infusion | Accelerated |
| Caprelsa (vandetanib) | 2011 | AstraZeneca | Thyroid cancer | Small molecule | Targeted | Multi Kinase inhibitor | Oral | Priority |
| Xalkori (crizotinib) | 2011 | Pfizer | ALK+non-small cell lung cancer | Small molecule | Targeted | ALK inhibitor | Oral | Priority, accelerated |
| Yervoy (ipilimumab) | 2011 | Bristol-Myers Squibb | Metastatic melanoma | Antibody | Targeted | CTLA-4 antibody | IV infusion | Standard |
| Zelboraf (vemurafenib) | 2011 | Roche | BRAF+ melanoma | Small molecule | Targeted | BRAF Inhibitor | Oral | Priority |
| Zytiga (abiraterone acetate) | 2011 | Centocor Ortho Biotech | Prostate cancer | Small molecule | Hormone therapy | Anti-androgen | Oral | Priority |
| Halaven (eribulin mesylate) | 2010 | Eisai | Metastatic breast cancer | Small molecule | Cytotoxic | Non-taxane microtubule agent | IV infusion | Priority |
| Jevtana (cabazitaxel) | 2010 | Sanofi aventis | Prostate cancer | Small molecule | Cytotoxic | Anti-microtubule agent | IV infusion | Priority |

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|---|---|---|---|---|---|---|---|---|
| Afinitor (everolimus) | 2009 | Novartis | Renal cell carcinoma | Small molecule | Targeted | mTOR inhibitor | Oral | Priority |
| Arzerra (ofatumumab) | 2009 | GlaxoSmithKline | Chronic lymphocytic leukemia | Antibody | Targeted | Anti-CD20 | IV infusion | Priority, accelerated |
| Folotyn (pralatrexate injection) | 2009 | Allos therapeutics | Peripheral T-cell lymphoma | Small molecule | Cytotoxic | Antimetabolite | IV push | Priority, accelerated |
| Istodax (romidepsin) | 2009 | Gloucester pharmaceuticals | Cutaneous T-cell lymphoma | Small molecule | Cytotoxic | HDAC Inhibitor | IV infusion | Standard |
| Votrient (pazopanib) | 2009 | GlaxoSmithKline | Renal cell carcinoma | Small molecule | Targeted | VEGF inhibitor | Oral | Standard |

was studied in healthy volunteers prior to patients, as it was initially thought to be a treatment for allergic rhinitis.

It is possible for many of these agents, however, to collect and characterize more fully the pharmacology and pharmacokinetics in studies utilizing healthy volunteers, as is common for non-oncology indications. Of the drugs in this review, about half utilized healthy volunteers in their clinical pharmacology development plans. If biologics and cytotoxics are excluded, almost 90 % included healthy volunteer clinical pharmacology studies in the initial submission.

## *2.2 Formulation and Route of Administration*

Among the approvals, orally administered drugs have become the dominant route of administration. Just over half (24 of the 44) of the new oncology therapeutics approved since 2009 were for small molecules intended for oral administration. Prior to 2012, just over 30 % of the approved drug oncology drug products were orally administered; since then, nearly 60 % of the approvals were for oral drug products. Year by year, with the exception of 2014, new oral small molecule treatments dominated the approval landscape by two-to-one. Over 75 % the non-biologic oncology drug products given by the oral route of administration.

The remainder of the approvals was intravenously or subcutaneously administered, with the majority administered by intravenous infusion. All of the biologics were injectable products.

All of the oral drug products' first approvals were for tablets and capsules. For the 24 oral drug products represented in this review, half were first approved as tablets and half were as capsules.

Unlike non-oncology indications, where the number of tablets and capsules are generally limited to 1 or 2 per dose, it is not uncommon for 4 or more dosing units to be given with each dose. Over a third of the approved products require more than two capsules or tablets per dose. Olaparib had the largest number of dosing units administered per dose and per day. It was originally approved for a 400 mg dose given twice daily as eight capsules, for a total of 16 per day. Ceritinib was first approved as a 750 mg dose, given as five 150 mg capsules. Six other products require four capsules or tablets to reach the labeled starting dose: ibrutinib, cabozantinib, regorafenib, enzalutamide, vismodegib, and abiraterone.

Formulation considerations are especially notable for both olaparib and ibrutinib. The approval of olaparib in December 2014 was based on the maximally tolerated dose (MTD), 400 mg given twice daily as eight 50 mg capsules. A tablet was developed, which was intended to replace the need for patients to take 16 capsules each day. However, 300 mg (2 × 150 mg) of the tablet formulation was shown to have 1.5-fold higher exposure at steady-state compared to the 400 mg capsules. While no definitive exposure–response was shown for the primary efficacy variable, progression-free survival (PFS), a clear exposure–response was shown in the rate of occurrence of grade 2 or higher anemia. The greater steady-state exposure of the

tablet would be expected to result in a potentially less desirable benefit–risk ratio. Confirmatory studies are underway with the new tablet formulation and it remains yet to be seen how patients will tolerate the higher exposures.

The to-be-marketed formulation of ibrutinib was used in >70 % of the cycles in the two pivotal trials submitted on behalf of the drug. Another earlier test formulation was used for other trials and for the remainder of the pivotal trials. Though some patients received both formulations, no relative bioavailability studies were conducted to demonstrate comparability of these two formulations. The clinical pharmacology reviewer recommended for a post-marketing study to be conducted to provide this information, however, it was not required as part of the final approval letter.

## 3 Identification of Dose and Regimen

One of the most difficult tasks in the development of new oncology agents is the identification of the optimal dose and regimen. Traditionally first-in-human studies have focused on characterizing the pharmacokinetics, biological effects, and determining of the limits of tolerability for a new agent. A small number of patients, usually 3–6, are administered increasing doses in successive cohorts until a predefined fraction (e.g., 33 %) of patients are either observed or predicted to have toxicities limiting further dose escalation. The dose below that which is deemed intolerable is identified as the MTD. Many cytotoxics, hormonal agents, and kinase inhibitors have identified MTDs in first-in-human studies. When the tolerability of an agent is high enough, or when biological effects related to the efficacy of the drug can be measured at doses lower than the MTD, an optimum biological dose (OBD) may be defined. MTDs are not commonly defined for first-in-human studies of biologics because of their comparatively high safety profiles and therapeutic indices.

Oncology first-in-human trials frequently recruit a diverse population of patients with a variety of tumor types who have typically failed one or more previous therapies. With so little data, the pharmacokinetic and pharmacodynamic data are usually insufficient for evaluating anything except the simplest dose–response relationships. Despite the small cohorts and heterogeneous populations, first-in-man studies for 61 approved oncology drugs between 1990 and 2012 were found to identify 70 % of the clinically relevant toxicities observed in later trials (Jardim et al. 2014).

Of the 44 approvals, 13 (30 %) were issued post-marketing commitments for studies or analyses to further investigate the dose for their approved indication. With the exception of pazopanib and ipilimumab, all were submitted by their sponsors for approval at their MTD. For omacetaxine the reviewers questioned the sponsor's choice for weight-based dosing, and questioned the choice of fasted drug administration for ceritinib. For ipilimumab and radium-223, testing of higher doses was requested. For all others, optimization of the dose and regimen was requested in order to provide evidence that lower doses could not provide the same or better benefit–risk profiles.

It is of note that of the ten cytotoxic drugs approved during this timeframe, six received requests for post-marketing commitments regarding dose and regimen selection; only one monoclonal antibody received a request to better optimize the dose.

## *3.1 Characterizing Exposure–Response*

In every new submission, FDA reviewers have attempted to use the sponsor's data to construct an exposure–response relationship for the primary efficacy outcomes, and the principle safety and adverse event findings. The exposure data were also used to support QTc-prolongation assessments and population pharmacokinetic evaluation of special patient populations, organ impairment groups, and covariate analyses. Where these data were collected, and were made available, they were used to support the dose and regimen in the target population and in subpopulations prone to changes in drug exposure. In the absence of this data, dose-intensity analyses were performed in an effort to link the efficacy and safety events to a surrogate for the missing pharmacokinetics and exposure data. Generally, if a sponsor failed to collect adequate pharmacokinetics and exposure data in their confirmatory trials, and there was a significant question about dose selection, a post-marketing study to verify dose or collect appropriate exposure data to perform the analyses was recommended by the clinical pharmacology reviewer, and examples are discussed in subsequent sections of this chapter.

Based on the approved portfolio, however, it was uncommon for oncology drugs to show a definitive exposure–response relationship for efficacy. This is illustrated for the non-cytotoxic targeted agents in Table 12.2. Often, this inability can be ascribed to insufficient data provided for a conclusive analysis. Panobinostat, ponatinib, olaparib, and pomalidomide did not collect sufficient pharmacokinetic data in the pivotal trials to permit exposure–response analysis. No pharmacokinetic samples were collected in dinutuximab confirmatory trials. Axitinib only collected pharmacokinetic data from 15 % of patients in pivotal trial. An up-titration scheme was applied to the patient studies to increase tolerability and individualize the dose. Only 20 of 407 patients in the pivotal pertuzumab study had pharmacokinetic samples taken. Lenvatinib analyses were limited to the exposures from only the 24 mg dose where 90 % of the patients had dose interruptions and/or reductions. For cabozantinib, dose modifications (86 % of patients) in the pivotal trial limited definitive interpretation of the exposure–response analyses and a modified dose-intensity adjusted exposure calculation was employed for the exposure–response analyses conducted by the FDA. These analyses, in addition to the high number of dose modifications, were the basis for justifying post-marketing requests for additional studies to evaluate lower starting doses of cabozantinib, panobinostat, and lenvatinib.

**Table 12.2** Exposure–response evaluations for approved non-cytotoxic targeted agents

| Drug | Year of approval | First approved starting dose and regimen | MTD | Exposure–efficacy response | Exposure–safety response[a] | PMR for dose |
|---|---|---|---|---|---|---|
| Palbociclib | 2015 | 125 mg BID | Yes | Inconclusive (PFS) | Yes (neutropenia) | No |
| Lenvatinib[b] | 2015 | 24 mg QD | Yes | No (PFS) | Yes (hypertension, proteinuria, nausea) | Yes |
| Olaparib | 2014 | 400 mg BID | Yes | No (PFS) | Yes (anemia) | No |
| Idelalisib | 2014 | 150 mg BID | No | No (ORR, PFS) | Yes (diarrhea[c]) | No |
| Ceritinib[d] | 2013 | 750 mg QD | Yes | No (ORR, PFS) | Yes (LFT, hyperglycemia) | Yes |
| Afatinib | 2013 | 40 mg QD | No | Yes (PFS) | Yes (G3AE) | No |
| Ibrutinib | 2013 | 560 mg QD | No | No (ORR) | No | No |
| Trametinib | 2013 | 2 mg QD | No | No (PFS) | Yes (diarrhea) | No |
| Pomalidomide | 2013 | 4 mg QD | Yes | No (No Analysis) | No (No Analysis) | No |
| Dabrafenib | 2013 | 150 mg BID | No | No (PFS) | No | No |
| Bosutinib | 2012 | 500 mg QD | Yes | No (mCYR) | No | No |
| Cabozantinib | 2012 | 140 mg QD | Yes | No (PFS) | No | Yes |
| Vismodegib | 2012 | 150 mg QD | No | No (ORR) | No | No |
| Ponatinib | 2012 | 45 mg QD | Yes | Yes (mCYR) | Yes (G3AE) | Yes |
| Axitinib | 2012 | 5 mg BID | Yes | Inconclusive (PFS) | Yes (hypertension, proteinuria, diarrhea, fatigue) | No |
| Regorafenib | 2012 | 160 mg QD | Yes | No (Unk)[e] | No (Unk)[e] | No |
| Enzalutamide | 2011 | 160 mg QD | No | No (OS) | No | No |
| Vandetanib | 2011 | 300 mg QD | Yes | No (PFS) | Yes (diarrhea, fatigue) | Yes |
| Crizotinib | 2011 | 250 mg BID | Yes | Yes (PFS) | No | No |
| Vemurafenib | 2011 | 960 mg BID | Yes | Yes (PFS) | Yes (squamous cell carcinoma) | No |
| Abiraterone | 2011 | 1000 mg QD | No | No (OS) | No | No |
| Everolimus | 2009 | 10 mg QD | No | No (PFS) | No | No |
| Pazopanib | 2009 | 800 mg QD | No | No (PFS) | Yes (LFT) | Yes |

*PMR* post-marketing requirement, *PFS* progression-free survival, *ORR* overall response rate, *OS* overall survival, *LFT* AST and/or ALT, *G3AE* Grade 3 Adverse Events, *mCYR* major cytogenetic response

[a]Where more than one variable was tested, key variables are given

[b]MTD was determined to be 25 mg QD, final dose approved was 24 mg QD

[c]For non-Hodgkin's Lymphoma patients only

[d]MTD was determined to be 750 mg QD, however, this dose was tolerated and no larger doses were tested in the clinic

[e]Exposure-response analyses were requested as post-marketing commitment

### 3.2 Dose Selection Strategies for Biologics

Of the biologic drugs approved since 2009, only one is administered at its MTD. In general, these drugs have a wide therapeutic index—and often an MTD is not even defined before an effective dose, or doses, is selected for further testing in confirmatory studies. Only dinutuximab is recommended for administration at its MTD. The dose of dinutuximab was declared acceptable, given the very high medical need for new treatments and the substantial benefit patients achieved on treatment.

Thirteen biologic drugs were approved between 2009 and June 2015. The approved monoclonal antibodies included dinutuximab, blinatumomab, ramucirumab, pembrolizumab, nivolumab, obinutuzumab, pertuzumab, ipilimumab, and ofatumumab. Two protein drugs were approved: ziv-aflibercept and carfilzomib. Two antibody-drug conjugates were approved, and are discussed with the cytotoxic agents. Dose and regimen justification are generally provided using one or more of the following arguments: (1) selected dose and regimen maintain target drug concentrations for tumor regression in preclinical studies, (2) the PK/PD modeling of clinical and/or nonclinical data for drug effect shows no difference between tested doses and regimens, and (3) the selected dose and regimen has been confirmed in patient trials. Typical of this approach are the justifications provided for nivolumab, pembrolizumab, pertuzumab, and ipilimumab. Of the monoclonal antibodies, proteins and peptides, only ipilimumab received a post-marketing request to further optimize the dose and regimen.

A flat dose– and exposure–response for overall response rate was observed for nivolumab and pembrolizumab doses of 0.1–10 mg/kg (Topalian et al. 2012) or 2–10 mg/kg (Patnaik et al. 2015), respectively. No exposure–response was apparent in either drug for the incidence of adverse events. For nivolumab, the response rate determined by the exposure–response modeling was approximately 30 % across all doses. A 3 mg/kg dose of nivolumab administered every 2 weeks was chosen based on ex vivo receptor binding data which demonstrated target saturation, nonclinical models suggesting a human-equivalent exposure and regimen would effective, and on the safety and efficacy demonstrated in the clinical trials using this dose and regimen. For pembrolizumab, the argument supporting 2 mg/kg Q3W was based on PK/PD analyses conducted for a biomarker (IL-2) and for projected efficacy estimated from in vivo and in vitro preclinical activity which predicted full target saturation and response for Q3 week regimens of 2 mg/kg and higher, but limited or no activity at doses 1 mg/kg and lower. The initial clinical study found similar time to response, duration of response, and rate of absence of progression in patients. In addition, the confirmatory clinical data to support the approval of pembrolizumab assessed both 2 mg/kg and 10 mg/kg Q3W, and no difference was observed in response rate for melanoma patients (Robert et al. 2014). While confirmed responses were observed for doses 2 mg/kg Q3 weeks and greater, very few patients received doses of pembrolizumab below 2 mg/kg (Patnaik et al. 2015). Maximum tolerated doses were not determined for either drug. In both cases, the wide therapeutic index and the significant duration of response at the defined doses made dose further optimization

unnecessary. However, in neither case can we absolutely conclude patients were given the smallest effective dose.

The final approved dose and regimen of pertuzumab is a loading dose of 860 mg over 60 min by intravenous infusion, followed every 3 weeks by a dose of 420 mg given over a 30–60 min infusion. The initial dose escalation study was conducted using a weight-based dosing regimens ranging from 0.5 mg/kg to 15 mg/kg every 3 weeks (Agus et al. 2005). According to the authors, the every 3-week regimen and dose range was selected based on pharmacokinetic simulations indicating achievement of target steady-state serum trough concentration of 25 mcg/mL in most subjects. This target concentration was determined from preclinical studies where tumor regression was observed in the range of 5–25 mcg/mL. The clinical pharmacology reviewer acknowledged this range, and that population pharmacokinetic modeling predicted a target concentration of 20 mcg/mL would be achieved in >90 % of the patients given the selected dose and regimen.

For the initial approval of ipilimumab for the treatment of advanced melanoma, a dose of 3 mg/kg IV every 3 weeks was tested in a single three-arm confirmatory trial, alone, with and without vaccine (gp100: melanocyte protein vaccine). Doses up to 10 mg/kg had been tested in previously, and it was concluded that the 3 mg/kg dose was appropriate for confirmatory studies since efficacy was similar, but the potential for adverse effects was greater at the larger dose. In the FDA review, a clear improvement in PFS was predicted from exposure–response modeling of the early data, with the highest exposures demonstrating a statistically significant improvement in PFS. As it was unclear whether 3 mg/kg was in fact the optimal dose, a dose comparison study was requested to more fully examine and compare the benefit–risk ratio for the 3 and 10 mg/kg doses. Unlike other post-marketing requests for dose-optimization, this request for ipilimumab was to test higher, not lower, doses than the initially approved regimen.

## *3.3 Dose Selection Strategies for Cytotoxics*

Conversely, all of the cytotoxic chemotherapeutic agents approved during this timeframe, except one: romidepsin, had therapeutic doses approved at their MTD. For cytotoxic drugs whose efficacy depends on nonspecific reactions to disrupt cell proliferation and maturation, it follows that the dose necessary for clinical effect would be the highest tolerable dose a patient can withstand. The indiscriminate nature of their action makes them effective over a wide range of cancer types—but increases the risk associated with destruction of fast growing tissues of bone marrow, the gastrointestinal tract, skin, and hair. In general, a therapeutic dose at or near the MTD for the cytotoxic would be expected. For cytotoxics whose mechanism is more selective, like the histone deacetylase (HDAC) inhibitors, the choice of MTD could be questioned, and as shown in this review, many were. There were ten new cytotoxic drugs approved since 2009, three were histone deacetylase (HDAC) inhibitors, two were antibody-drug conjugates, and the

remaining five were anti-metabolites, inhibitors of microtubules or protein synthesis and the radiopharmaceutical radium-223. Romidepsin, an HDAC inhibitor approved in 2009, was the only cytotoxic during this period noted during review to demonstrate an exposure–response relationship with PFS. At the final selected dose, the AUC represented a cutoff point above which there was a twofold greater proportion of responders and below which progression of disease was faster.

Two antibody-drug conjugates, ado-trastuzumab emtansine and brentuximab vedotin, were also approved during this timeframe. Both are designed to deliver cytotoxic payloads, and both were administered at their MTDs (brentuximab MTD: Younes et al. 2012).

Six cytotoxic drugs were issued post-marketing requests to justify the selection of dose. Several failed to collect adequate pharmacokinetic information from the confirmatory trials to justify selection their benefit–risk ratio using exposure–response measures. By failing to collect exposure data in the confirmatory trials for omacetaxine, the reviewers and the sponsor were unable to show if the observed reduced efficacy in female patients was related to the lower exposures resulting from the weight-based dosing of the drug. The FDA requested a post-approval study to evaluate fixed (non-weight based) doses. The FDA's exposure–response analysis for ado-trastuzumab suggested that lower exposures to drug resulted in poorer patient outcomes (OS and PFS). In this case, the sponsors were requested to collect additional exposure data from ongoing trials and perform exposure–response analyses to verify dose selection. For belinostat, the FDA and sponsor agreed the post-approval confirmatory studies should include as comparator the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone). As belinostat and the CHOP regimen had not previously been given together, a post-marketing study was issued for the sponsor to determine the correct dose for coadministration.

Panobinostat was approved for the treatment of patients with multiple myeloma who previously received at least two prior regimens, including bortezomib and an immunomodulator. The approved dose of 20 mg three-times-weekly administered with intravenous bortezomib 1.3 mg/m$^2$ for 2 weeks on, 1 week off, was also the MTD. The accelerated approval was based on PFS. Because no pharmacokinetic data were collected in the confirmatory trial, it was not possible to evaluate the relationships for exposure–response for either efficacy or safety in the target patient population. Also, since the regimen and dose had not been optimized with the recognized standard of care, subcutaneous bortezomib, and because overlapping toxicity profiles of the two drugs obscured interpretation of the benefit–risk ratio for the combination, additional dose optimization and confirmatory trials were required as part of the post-approval commitments.

A post-marketing study to evaluate the optimum dose of cabazitaxel was requested when no exposure–response relationship could be established for overall survival or time to tumor progression. Because limited PK data was provided from a patient subset in the confirmatory trial at the dose of 25 mg/m$^2$ ($n = 67$), and the slope of the exposure–neutropenia relationship was shallow, it was suggested that a

dose reduction from 25 to 20 mg/m$^2$ might reduce the risk of neutropenia in the absence of prophylactic G-CSF.

A post-marketing request was issued for the optimization of the dose regimen of radium-223 dichloride. No MTD of radium-223 dichloride was identified in clinical studies up to a cumulative dose of 250 kBq/kg. Because higher body weight was associated with better overall survival, and patients with body weight lower than 73 kg did not have improved overall survival compared to placebo, it was surmised that a higher dose could benefit the lower weight subpopulation, and possibly the overall population.

## *3.4 Non-cytotoxic Targeted Agents*

After excluding drugs approved earlier for other indications, and those which were new formulations of previously approved compounds, there were 23 approvals for new small-molecule chemotherapeutic oncology treatments. All but three are targeted protein kinase inhibitors. Thirteen (57 %), including ten targeted protein kinase inhibitors, had their therapeutic doses approved at the MTD. As a targeted agent would be expected to have a better tolerability profile compared to nonspecific cytotoxic, and therefore a wider therapeutic index, one might question the appropriateness of selecting the MTD as the therapeutic dose for these agents.

Overall, only few compounds were able to show an exposure–response relationship for the primary efficacy variables. Most often, this can be attributed to the limited exposure range provided by the clinical studies supporting the registration. These confirmatory studies are either conducted with a single dose and regimen (e.g., lenvatinib, palbociclib, ibrutinib, dabrafenib, bosutinib, vismodegib, and pazopanib) or have several doses but the dataset is dominated by one (e.g., ceritinib). For some drugs, the sponsor did not collect adequate pharmacokinetic samples in the confirmatory trials to permit a proper exposure–response analysis. Only 20 % of the patients in the confirmatory trial for abiraterone had pharmacokinetic data collected. For pomalidomide and axitinib, only 14 and 55 patients, respectively, had pharmacokinetic data collected in the confirmatory trials. The sponsor for ponatinib collected no exposure data in its confirmatory trial, so a dose-intensity analysis was performed with average daily dose defined for each patient as the cumulative daily dose divided by the number of days on the study. The sponsor for regorafenib submitted no population pharmacokinetic or exposure–response analyses, and received a post-marketing commitment to perform and submit both.

However, presenting data on more than one dose or for a titration scheme to widen the range of exposures is no guarantee an exposure–response relationship can be described for efficacy. Both olaparib and idelalisib provided data from more than one dose, yet neither was able to define a relationship with PFS, while the afatinib titration scheme provided enough data to show a negative relationship between the highest exposures and PFS. Vemurafenib exposure–response was shown with the data from a single dose strength.

### 3.4.1 Non-cytotoxic, Small Molecule Targeted Agents Approved at the Maximum Tolerated Dose

Of the 13 non-cytotoxic small molecules approved at their MTDs, five were required to reexamine the dose in post-marketing requests following approval. These requests for dose-optimization originated in the clinical pharmacology review, where exposure–response analyses are performed to evaluate the impact on efficacy and safety measures. Typically, a high rate of dose reduction, interruption, or discontinuation due to adverse effects signals the dose may be intolerable. When the analyses show higher exposures are associated with greater adverse events, but efficacy remains unchanged, the conclusion is that the benefit–risk ratio may be improved for lower doses, and further exploration is necessary. In these examples, the magnitude of medical need provided for a positive overall benefit–risk ratio despite the less than optimal dose and regimen.

The following five targeted agents were approved at their MTD, but required post-marketing evaluation to justify the dose selection:

Lenvatinib was approved at a dose of 24 mg daily. In the registration trial (Schlumberger et al. 2015), adverse events led to dose reductions in 68 % of the patients given this dose, and 82 % underwent either dose interruption. Furthermore, the reviewer concluded that, while there was no apparent exposure–response relationship with respect to PFS, the probability of significant hypertension, proteinuria, nausea, and vomiting were increased with increasing exposure to the drug. Taken together, these results suggested patients were generally intolerant to the selected dose, and lower doses could be anticipated to maintain the desired effect with fewer side effects.

Like lenvatinib, a majority (79 %) of patients who received the 140 mg daily dose of cabozantinib required dose reduction (Elisei et al. 2013), and 86.4 % required reduction, interruption, or discontinuation (OCP Review). The reviewer's exposure–response modeling for efficacy showed that a lower exposure could provide similar benefit, and that patients with the highest predicted exposures were also those with the earliest dose modifications. While no clear evidence of an exposure–response was found for the major adverse events, it was found to have a concentration-dependent QTc prolongation in the 10–15 ms range. These findings led the agency to request a randomized dose-comparison study "comparing the safety and activity of oral cabozantinib 140 mg daily to a biologically active and potentially safer lower daily cabozantinib dose."

Eighty percent of patients initiated on a dose of 300 mg of vandetanib required dose reduction or interruption. The reviewer examined the relationship between PFS and dose by comparing the Kaplan Meier curves for patients with and without a dose reduction. No difference between doses was observed and it was concluded that reduced doses of 100 and 200 mg could be providing similar efficacy to the higher 300 mg dose.

Ceritinib was approved as a breakthrough therapy at a dose of 750 mg given once daily. During the initial dose escalation trial, the 750 mg dose was selected as the MTD, though no higher dose was tested. Dose reductions occurred in approximately

60 % of patients starting on this dose, with gastrointestinal side effects reported in 98 % of patients. Administration of ceritinib with either a low-fat or high-fat meal was observed to increase exposure 58–73 %. It was recommended a study be conducted to evaluate the gastrointestinal tolerability and efficacy of a lower dose given with food to determine if this regimen could improve the gastrointestinal tolerability and compliance.

Ponatinib was approved at 45 mg once daily in December 2012. The clinical pharmacology reviewer determined that the dose was not supported by the dose-intensity analyses which showed that the probability of a major cytogenetic response appeared to reach a plateau at 30 mg for chronic phase CML patients. In accelerated phase and blast crisis patients, no relationship was evident. In addition, increasing exposure was associated with a greater probability of grade 3 or greater adverse events; the reduction in the probability of observing pancreatitis, for instance, was ninefold for a dose reduction from 45 to 30 mg. A proper exposure–response analysis was not possible because there were no pharmacokinetic samples taken in the confirmatory trial. The post-marketing request, therefore, specified these samples were to be taken from an ongoing trial, with exposure–response analyses conducted on the results to determine if an additional trial to evaluate dose would be necessary. Ponatinib was voluntarily removed from the market in October 2013 when the frequency of serious vascular occlusive raised questions about the overall benefit–risk of the drug. It was returned to the market in early 2014 when the company agreed to provide enhanced safety evaluation, additional analyses, and studies to evaluate the dose and exposure–response.

### 3.4.2 Non-cytotoxic, Small Molecule Targeted Agents Approved Below the Maximum Tolerated Dose

For those targeted small molecules where the MTD was not selected, the arguments supporting justification for the selection of the dose vary. For some, the justifications for selecting a dose lower than the identified MTD include saturation of exposure at higher doses or reduced tolerability to higher doses. For others, a more rational approach based on a critical examination of multiple regimens, PK/PD modeling, and impact on biomarkers has been applied. The compounds approved below their MTDs include the PI3Kδ inhibitor idelalisib, the EGFR inhibitor afatinib, the BTK inhibitor ibrutinib, MEK inhibitor dabrafenib, BRAF inhibitor trametinib, hedgehog inhibitor vismodegib, anti-androgenics enzalutamide and abiraterone, mTOR inhibitor everolimus, and VEGF inhibitor pazopanib. To understand the rationale used for dose selection, each is examined below.

Though technically not administered at the defined MTD of 50 mg QD, the therapeutic dose of 40 mg afatinib is the highest dose most patients can tolerate on a continuous schedule. In the initial clinical studies for afatinib, intermittent administration schedules were tested for doses of up to 100 mg daily, 14 days on and 14 days off, and for continuous daily administration for doses up to 60 mg QD (Agus et al. 2005, Lewis et al. 2006, Eskens et al. 2008, Yap et al. 2010). The continuous

dose MTD for afatinib was found to be between 40 mg QD (Agus et al. 2005) 50 mg QD (Yap et al. 2010). In the initial phase 2 trial, 66/99 patients (67 %) starting treatment with the 50 mg dose required a reduction to 40 mg, and 36 of these required reduction to 30 mg due to intolerability and adverse events (Yang et al. 2012). A starting dose of 40 or 50 mg was selected as for subsequent patient studies, and when the 40 mg was found to be better tolerated, confirmatory patient studies were initiated with 40 mg starting doses with the option for dose escalation to 50 mg, or reduction in 10 mg increments to reach 20 mg QD, if necessary. An exposure–response analysis of the pivotal trial results showed that the highest exposure quartiles were associated with a shorter PFS, and that higher exposures resulted in an increased probability for adverse events of grade 3 or higher (using the Common Terminology Criteria Adverse Events, or CTCAE, grading). Since pivotal trials had been conducted with the 40 mg starting dose, and the benefit–risk profile was not improved for higher exposures, the clinical pharmacology reviewer recommended that doses should be capped at 40 mg QD. Unlike the pivotal trial, the approved label, therefore, does not include an option to escalate the dose above 40 mg.

For both vismodegib and pazopanib, doses above the chosen therapeutic dose did not result in increased drug exposure. As the highest attainable biological exposure was tolerated by patients, no MTD was defined. Drugs of this type, which also includes those with highly variable pharmacokinetics, illustrate how arbitrary the MTD concept really is. Vismodegib was submitted for approval as the first in class smoothened inhibitor for the treatment of advanced basal cell carcinoma and both dose and regimen were studied in separate clinical trials. Daily doses of up to 540 mg were tested in patients in the phase I trial, however because steady-state exposure to drug was similar for all doses above 150 mg, higher doses were not tested and an MTD was not established (LoRusso et al. 2011a). The therapeutic dose of 150 mg QD was selected after further testing of three-times weekly and once-weekly regimens found decreases in unbound concentrations of 50 and 80 % below the threshold concentration estimated most effective in preclinical models (Lorusso et al. 2011b).

The initial dose-escalation study of pazopanib evaluated daily doses of 50–2000 mg, in 12 escalation cohorts, and four expansion cohorts testing once, twice and three-times daily regimens (Hurwitz et al. 2009). The numbers of subjects at each dose and regimen tested were small, ranging from two patients at the 50 mg QD regimen to 17 patients tested at the 800 mg daily dose (for which three patients were tested at 400 mg BID, and the remaining were given the QD regimen). The study did not identify an MTD, as the total exposure to drug appeared to plateau at doses 800 mg and above. Patient responses were observed for doses of 300 mg QD and greater, with the most frequent occurrence of response at 800 mg. In renal cell carcinoma patients, 5 (83 %) were observed to have their best response with steady-state trough plasma concentrations at or above 15 mcg/mL; in patients receiving 800 mg QD, 93 % had steady-state values above this threshold. Furthermore, this value was supported by preclinical models which predicted optimal pharmacodynamic effects in mice maintained at similar plasma concentrations (Kumar et al. 2007). The FDA Clinical Pharmacology reviewer verified the exposure–response relationships for

both safety (hypertension, liver toxicity) and response rate by logistic regression. Given the supporting preclinical evidence for the threshold concentration, acceptable tolerability and response profile, and saturation of exposure at greater doses, a dose of 800 mg QD was selected for further study in pivotal patient trials.

The remaining drugs approved at doses below MTD are, to varying degrees, illustrations of how preclinical and clinical PK/PD, comparison of different regimens, testing of more than one expansion cohort, and exposure–response data can be combined to provide for the justification of dose and regimen.

For idelalisib, dose selection and justification were drawn from both preclinical data and a clinical dose-finding study. Beginning as a drug originally thought to be a useful in the treatment of allergic rhinitis, idelalisib began first-in-human testing in healthy volunteers. Safety and pharmacokinetic data collected for single doses up to 400 mg and after 7 days of 200 mg BID, verified tolerability and a half-life of 8 h (Webb 2010). MTD was not reached, but a 150 mg BID dosing regimen was found to maintain minimum concentrations >10-fold above the EC50 for the in vitro inhibition of PI3Kδ. In cancer patients, a dose-finding study was conducted examining both once and twice-daily administration, and doses ranging from 50 to 350 mg BID, and 150 and 300 mg QD (Flinn has several pubs Blood 2014). In patients, no relationship was identified for idelalisib dose up to 350 mg BID and adverse events. Higher response rates were observed for doses >150 mg, for doses greater than 100 mg BID, a modest flattening of the dose–exposure curve was observed. A dose of 150 mg BID was chosen for further patient studies. According the Clinical Pharmacology review by the FDA, Gilead scientists further supported the selection of the dose by showing the median best reduction in tumor size reached a plateau for trough concentrations around 280 ng/mL or greater, and that this concentration was above the in vitro EC90 (~125 ng/mL) for PI3Kδ inhibition in almost 90 % of the patients given a dose of 150 mg BID. The argument was strengthened by the fact that the quartiles for the concentration range used to explore the relationship were from 14 to 1051 ng/mL.

To support the registration of ibrutinib in mantle cell lymphoma (MCL), two pivotal clinical trials were submitted, however, only one was in the intended target population. This study was an open-label non-randomized trial in relapsed and refractory MCL and employed a dose of 560 mg QD. Like idelalisib, no MTD was established for ibrutinib. Justification to support the dose was based on the observation of sustained and complete (>90 % at 24 h) occupancy of the BTK active site for daily doses at or above ~175 mg (approximately threefold lower than the proposed 560 mg dose). There was no difference in the overall response rate for doses ranging from 2.5 to 12.5 mg/kg QD. Preliminary evidence for efficacy was observed in 5 of 9 patients given 560 mg QD in the first-in-human study. There was no evidence in patient studies of an exposure–response relationship between ibrutinib and adverse events grade 3 or greater over a range of doses from 420 to 840 mg QD. In their review, the clinical pharmacologist recommended exploration of lower doses in future development. The approval was given for 560 mg QD, and no official request was made for further testing of doses.

The dose-escalation study for trametinib evaluated doses ranging from 0.125 to 10 mg in once daily and loading-dose regimens (Infante et al. 2012). Loading doses

were selected based on real-time pharmacokinetic evaluations. In addition, once a dose and regimen was selected, two expansion dose cohorts (2 and 2.5 mg QD) were conducted to better define the final dose. This study found an MTD of 3 mg QD, but this dose was poorly tolerated beyond the first treatment cycle. Since a 2 mg QD dose had a response rate similar to the 2.5 mg QD, and was associated with the with a better safety profile than higher doses, it was selected for further testing in pivotal studies.

Dabrafenib pharmacokinetics and pharmacodynamics were explored for both BID and TID regimens in the first-in-human dose-escalation study (Falchok 2014). A single patient was evaluated for 35 mg QD, but the regimen was not pursued further as dabrafenib was observed to have a half-life of 4.0–6.8 h. The relationship between pERK inhibition and systemic exposure was described by an $E_{max}$ model and the inhibition reached a plateau at total daily doses of >100 mg BID; doses of 150 mg BID were predicted to approach the $E_{max}$ of approximately 80 % inhibition. No benefit was observed for TID over BID administration. The relationship between change in tumor size and daily dose was described by an $E_{max}$ model, but as the $E_{max}$ value (801 mg daily) was greater than the largest tested dose (600 mg daily), the model was essentially linear between 35 and 300 mg BID. Two expansion cohorts were tested to further define the dose–efficacy relationship: 50 and 150 mg BID. In the expansion cohorts, the response rates were 22 % and 60 % for the 50 mg and 150 mg doses, respectively.

The first-in-human study for enzalutamide was the basis for the determination of the MTD, pharmacokinetics, pharmacodynamics, and clinically effective dose (Scher et al. 2010). This study was a dose escalation trial in seven cohorts, each with more than 20 patients except the lowest and highest, covering a range of daily doses from 30 to 600 mg. All doses were QD, except doses greater than 360 mg, which were BID to avoid administration of an excessive number of 30–40 mg capsules. An MTD of 240 mg QD was determined for enzalutamide. A dose-dependent reduction in PSA was observed between 30 and 150 mg, with saturation of the inhibition occurring between 150 and 240 mg per day. A dose-dependent increase in adverse events also occurred, with fatigue rising from approximately 3 % for 240 mg to 20 % at 480 mg daily. With the observation of a plateau of effect above 150 mg, an MTD of 240 mg, and a formulation that included a 40 mg capsule, a dose of 160 mg was chosen for further study.

Three phase I studies were conducted to determine the oral dose of abiraterone (an antiandrogen) needed to significantly suppress testosterone in stable castrate and non-castrate male patients. Single doses ranged from 200 to 800 mg. Daily administration for 12 days at a starting dose of 500 mg (escalating to 800 mg) were also tested. These studies determined that a daily dose of at least 800 mg was necessary to suppress testosterone to target levels (O'Donnell et al. 2004). A subsequent phase I/II dose-escalation study was conducted in 21 chemotherapy-naıve men with castration and antiandrogen-resistant prostate cancer. Abiraterone was administered in daily doses ranging from 250 to 2000 mg in 28-day cycles (Attard et al. 2008). The pharmacodynamic effect of abiraterone was observed to plateau at 750 mg and no MTD was determined. Given that all doses were well tolerated, and the high variability of

the pharmacokinetics, a dose of 1000 mg was selected for subsequent patient studies. Because only 15 % of the patients participating in the confirmatory trials had pharmacokinetic samples collected, a definitive exposure–response could not be performed during the review. A treatment effect was apparent for an improvement in overall survival 3.9 months, however for those patients in whom samples were taken, there were no clear differences between high and low exposures. Similarly, there were no clear trends between high and low exposures and the adverse events of elevated ALT, hypokalemia, peripheral edema, and hypertension.

Like enzalutamide, early clinical studies conducted for everolimus evaluated the safety, pharmacokinetics, and pharmacodynamics to determine the appropriate dose and regimen for administration in patients with advance solid tumors. A wide range of doses and both QW and QD regimens were explored. Using peripheral blood mononucleocyte-derived p70 S6 kinase 1 (S6K1) activity as a marker for mTOR inhibition, weekly administration was associated with a reduction of S6K1 activity linked with dose-dependent suppression of tumor growth (Boulay et al. 2004). On the basis of this observation, the initial clinical dose-escalation study evaluated both daily and weekly regimens (O'Donnell et al. 2008). Doses greater than or equal to 20 mg QW verified the week-long duration of S6K1 inhibition in these patients. MTD was not reached. A physiologically based pharmacokinetic (PBPK) model was employed to evaluate the data, and dosing regimens of 20–30 mg weekly or 5 mg daily were predicted to achieve sufficient antitumor effects (Tanaka et al. 2008). A phase 1 dose-finding and pharmacodynamic study was conducted with doses ranging from 50 to 70 mg weekly, and 5 and 10 mg daily (Tabernero et al. 2008). In this study, additional biomarkers in tumor and skin were tested to verify mTOR blockade, and profound inhibition of the biomarkers was observed at all doses, especially in the daily regimen. Based on the clinical results, and the PBPK modeling, a 10 mg daily regimen was selected for pivotal studies.

## 4 Absorption: Food and pH

### *4.1 Assessment of High-Fat Food Interaction*

The assessment of the interaction of an orally administered drug with food is an essential requirement for every new medicine and formulation. There is no exception for oncology. An early assessment of the impact food has on the rate and extent of absorption permits the researcher to decide on the most appropriate administration scheme for the patient. Because coadministration with food can alter exposure, variability, improve tolerability, it can change the overall benefit–risk ratio for the treatment. Selecting a regimen which is easy for the patient to follow can also improve compliance. Because the interaction with food can be formulation dependent, every new formulation should be tested.

The assessment of the impact of food is a more than a matter of drug labeling. It is part of a product development strategy. The use of a high-fat meal, as described

in the Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies Food (2002), is generally regarded as a worst-case scenario and is not meant to represent the typical meal taken by patients during the course of their regular diet. By using the high-fat meal as a specification-limit for the assumed maximum impact, the information can guide the selection of formulations, guide the design of subsequent patient studies, and provide critical labeling information regarding concomitant administration of food and drug product. Ordinarily, all new and to-be-marketed oral formulations require an assessment of food-effect.

Selecting a regimen to include or exclude coadministration with food requires an understanding of the impact food has on both drug absorption and pharmacokinetic variability, and this information is coupled with the knowledge of the therapeutic index and the slope of the exposure–response curve. In general, regimens are selected to maximize bioavailability and minimize variability—all within the context of the relationship to exposure–response. Where the coadministration of food has no significant clinical impact on rate or extent of absorption and does not increase variability, a regimen permitting patients to take the medication without regard to food can be selected. Where variability and exposure are increased, the selection of a regimen with or without food will depend on the magnitude of the increase and the therapeutic index. Where exposure is significantly decreased on coadministration with food but there is no change in the variability, selection of the regimen depends largely on the slope of the exposure–response curve.

As shown in Table 12.3, 24 new oral oncology agents were approved by the FDA between January 2009 and June 2015. Fifteen conducted their food interaction bioavailability assessment in healthy volunteers (vemurafenib was ongoing at time of submission), and nine in patients. All results are shown following a single dose assessment with a high-fat meal as described in the guidance.

Ordinarily, the regimen employed in confirmatory patient trials serves as the basis for the labeling of the new drug. Of the new oral oncology drugs approved, 17 were labeled with a regimen that matched the instructions given in their confirmatory trials. Of these, seven were agreed to have no clinically significant food interaction when coadministered with a high-fat meal and were labeled to be taken without regard to food. These include panobinostat, lenvatinib, idelalisib, vismodegib, enzalutamide, vandetanib, and everolimus. For these drugs, the impact on exposure, measured with AUC, ranged from −16 % for everolimus to +36 % for idelalisib. The range for $C_{max}$ was significantly larger (−60 % to +39 %), however was deemed unimportant since drug benefit was not expected to depend on $C_{max}$ and the benefit–risk had already been established with this variability present. The largest increase in exposure among this group was idelalisib where coadministration with food resulted in a 36 % increase in exposure. However, because the maximum administered dose of 350 mg BID was sufficiently greater than the approved dose of 150 mg BID, and no dose-limiting toxicities were observed at the 350 mg BID dose, the increased exposure was not clinically meaningful. Furthermore, dose reductions at the 150 mg BID dose occurred at a rate of only 34 % or less in the pivotal patient trials where drug was administered without regard to food.

**Table 12.3** Characterization and impact of food effect

| Drug | Subjects | Meal | $C_{max}$ impact | AUC impact | Food-effect labeling | Pivotal studies instruction[a] |
|---|---|---|---|---|---|---|
| Panobinostat | Pts | HF | −44 % | −15 % | Should be taken orally once on each scheduled day at about the same time, either with or without food | Same |
| | | Normal | −36 % | −12 % | | |
| Palbociclib | HV | HF | 21 % | 38 % | Should be taken with food | Fast 1 h before and 2 h after dosing |
| | | MF | 12 % | 24 % | | |
| | | LF | 13 % | 27 % | | |
| Lenvatinib | HV | HF | 5 % | 6 % | Taken once daily with or without food | Same |
| Olaparib | Pts | HF | 0 % | 20 % | Label is not specific in 2.2 Rec Dosing. CP section indicates 20 % change with HF | 1 h before or 2 h After meal |
| | Pts | Std | 10 % | 20 % | | |
| Idelalisib | HV | HF | −3 % | 36 % | Can be taken with or without food | Same |
| Ceritinib | HV | HF | 41 % | 73 % | Administer on an empty stomach (i.e., do not administer within 2 h of a meal) | Same |
| | | LF | 43 % | 58 % | | |
| Afatinib | Pts | HF | −50 % | −39 % | Take at least 1 h before or 2 h after a meal | Not stated in review or publications |
| Ibrutinib | Pts | HF | 120 % | 70 % | Once daily at approximately the same time each day | At least 30 min before or at least 2 h after a meal |
| Trametinib | Pts | HF | −70 % | −24 % | Take at least 1 h before or 2 h after a meal | Same |
| Pomalidomide | HV | None | PMR | PMR | Should be taken without food (at least 2 h before or 2 h after a meal) | Same |
| Dabrafenib | Pts | HF | 51 % | 31 % | Take either at least 1 h before or at least 2 h after a meal | Same |
| Bosutinib | HV | HF | 80 % | 70 % | Once daily with food | Same |
| Cabozantinib | HV | HF | 41 % | 57 % | Instruct patients not to eat for at least 2 h before and at least 1 h after taking | Same |
| Vismodegib | Pts | HF | 39 % | 32 % | May be taken without regard to meals | Same |

(continued)

**Table 12.3** (continued)

| Drug | Subjects | Meal | $C_{max}$ impact | AUC impact | Food-effect labeling | Pivotal studies instruction[a] |
|---|---|---|---|---|---|---|
| | | LF | 13 % | 11 % | | |
| Ponatinib | HV | HF | −6 % | 10 % | May be taken with or without food | Take 2 h after a light meal, do not eat or drink anything other than water for 2 h after taking tablets |
| | | LF | −5 % | −2 % | | |
| Axitinib | HV | HF | 11 % | 19 % | Administer doses approximately 12 h apart with or without food | Take with food |
| | | MF | −16 % | −10 % | | |
| Regorafenib | HV | HF | 73 % | 48 % | Take with low-fat breakfast, with example given[b] | Same |
| | | LF | 54 % | 36 % | | |
| Enzalutamide | HV | HF | −30 % | −1 % | Can be taken with or without food | Same |
| Vandetanib | HV | HF | −17 % | −10 % | Can be taken with or without food | Same |
| Crizotinib | Pts | HF | −14 % | −15 % | Can be taken with or without food | Study 1001: refrain from food or beverages (except water) for 2 h before to 2 h after dosing, study 1005 amended for drug to be taken without regard to food |
| Vemurafenib[b] | Pts | HF | PMR | PMR | Can be taken with or without a meal | Same |
| Abiraterone | HV | HF | 1583 % | 869 % | Must be taken on an empty stomach. No food should be consumed for at least 2 h before the dose is taken and for at least 1 h after the dose is taken | Same |
| | | LF | 626 % | 362 % | | |
| Everolimus | HV | HF | −60 % | −16 % | Once daily at the same time every day, either with or without food | Same |
| Pazopanib | Pts | HF | 110 % | 130 % | Once daily without food (at least 1 h before or 2 h after a meal) | Same |
| | | LF | 90 % | 110 % | | |

[a]Instructions listed are for the key registrational study in first submission, and may not reflect other ongoing confirmatory studies or amendments following review
[b]Ongoing at time of submission

Five of the 17 drugs measured increases in exposure when coadministered with a high-fat meal: ceritinib, dabrafenib, cabozantinib, abiraterone, and pazopanib. One, trametinib, measured a 24 % decrease in exposure when given with a high-fat meal. Because all were tested under fasting conditions in their confirmatory trials, all were labeled to be given in a fasted state. Arguably, one could make a case based on therapeutic index and magnitude of effect that dabrafenib and trametinib might be taken without regard to meals.

A post-marketing clinical study was requested for ceritinib to evaluate the impact of a meal on the systemic exposure and safety of the drug in patients. While the MTD/therapeutic dose was stated to be 750 mg QD, no larger dose was tested and no intolerable dose was observed. A high-fat meal was found to increase the exposure of a 500 mg dose by 73 %. Because gastrointestinal side effects were observed in >80 % of patients treated at 750 mg QD, and because it was postulated that taking ceritinib with food could improve the tolerability, this study could permit the identification of a more tolerable dose and regimen combination. This postulate was supported by the experience with bosutinib, where coadministration of food was previously shown to increase tolerability. When administered with a high-fat meal, food increased bosutinib exposures twofold. In the fasting cohorts of the dose escalation trial, escalation was stopped at 400 mg due to gastrointestinal adverse events, while for the cohorts given food with bosutinib, doses up to 800 mg were reached before gastrointestinal adverse events halted further escalation. Average exposures obtained for 400 mg fasted were 1150 ng*h/mL, while those for 800 mg fed were 4003 ng*h/mL (Abbas et al. 2012). This early evaluation and understanding of the impact of food on bosutinib exposure and tolerability allowed the sponsor to perform confirmatory studies with instructions that the drug be taken with food. An early evaluation of food-effect in the first crizotinib trial, where coadministration of a high-fat meal showed no clinically significant impact on exposure, allowed the sponsor to amend the ongoing confirmatory patient study to permit the drug to be taken without regard to meals.

Like bosutinib, regorafenib had positive food effects (48 %) and is labeled to be taken with food—as were the instructions patients were given in confirmatory trials. It is significant to note, however, that for regorafenib there are three active circulating species with similar anticancer activity (parent, M2 and M5). When assessed for change in total circulating active species, the change in overall exposure was 8 % lower following a high-fat meal and 33 % higher after a low-fat meal—indicating that the impact of a meal on circulating active drug is much less than estimated from measuring the parent alone.

Two drugs, vemurafenib and pomalidomide, required food-effect studies as part of a post-approval commitment. The clinical trial for the evaluation of the food effect for vemurafenib was underway at the time of the submission. The compound has both low solubility and low-to-medium permeability, a BCS IV compound, where the impact of food cannot be easily anticipated (Wu and Benet 2005). According to the clinical pharmacology review, the sponsor proposed drug administration should be under fasting conditions. However, since the impact of coadministration was unknown at the time of submission (drug approved August 2011), vemurafenib was

labeled to be taken without regard to food to match the instructions patients followed in confirmatory trials. The results of the food-interaction trial conducted in patients were published in 2014. Exposure increased by approximately 4.7-fold and variability reduced by almost half when vemurafenib was given with a high-fat meal. The label was updated to include this new information, but the dosing instructions remain unchanged with respect to meals. For pomalidomide, the food interaction study was conducted with a formulation which was not bioequivalent to the final to-be marketed formulation.

Where the drug labels do not match the instructions given in the confirmatory trials, modifications to the instructions are chosen based on maintaining or improving the benefit–risk ratio. This was true for palbociclib, ibrutinib, vismodegib, ponatinib, and axitinib.

For a small subset of patients (about 13 %), palbociclib given under fasting conditions was observed to have lower bioavailability. Coadministration with food was found to increase exposures for these patients, without significantly increasing the exposures in the rest. It was recognized that the drug should be given with food to reduce the overall inter-subject variability.

Ibrutinib was given in a "modified fasting" regimen in confirmatory trials, i.e., taken at least 30 min before or at least 2 h after a meal. A 1.7-fold increase in exposure to ibrutinib was observed in patients given the drug concomitantly with a high-fat meal compared to a fasted control. In pivotal studies, exposures to the drug were expected to be greater than those of a fasted control group. As no MTD was established for ibrutinib, and there was no relationship between exposure and efficacy or safety over the range of doses from 420 to 840 mg QD, the measured pharmacokinetic impact was relatively small, and the drug was labeled to be taken without regard to food. The measured food effect for vismodegib, ponatinib, and axitinib was determined to be clinically unimportant (all within about 30 %), and these drugs were labeled to be taken without regard to food.

Though instructions for administering drugs with or without food vary from study to study, the most commonly employed labeling language is in one of the following forms:

- Fed: *Take with food*
- Fed or Fasted: *Take without regard to meals*
- Fasted: *Take 1 h before or 2 h after a meal*

Variations from these forms generally add specificity or unnecessary complexity. For instance, labels for ceritinib and pomalidomide specify a different time-window and indicate drug should not be taken within 2 h of a meal. Labels for everolimus and panobinostat indicate the drugs should be taken at the same time every day (which, incidentally, matches the instructions given in the confirmatory studies). The label for regorafenib specifies the type of low-fat breakfast for coadministration:

> *Examples of a low-fat breakfast include 2 slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly, and 8 ounces of skim milk (319 calories and 8.2 g fat); or 1 cup of cereal, 8 ounces of skim milk, 1 slice of toast with jam, apple juice, and 1 cup of coffee or tea (520 calories and 2 g fat).*

Other labels are not so clear. The labels for cabozantinib and abiraterone are written with respect to when a meal should be taken before or after a dose, which can be confusing even for the informed (see Table 12.3). Unlike the other oral medications in this review, the labels for olaparib and ibrutinib provide no instruction with regard to food in the Dosage and Administration section, though the impact is described in the clinical pharmacology section. In both cases, however, the clinical pharmacology reviewer acknowledged that these drugs could be taken without regard to food, so the impact of any assumed oversight may not be meaningful.

It is worth noting that, with the exception of ibrutinib, all drugs labeled to be taken without regard to food have a 36 % or less change in exposure on coadministration. With the exception of trametinib (−24 %) and dabrafenib (31 %), all drug labeled to be taken with food (excluding palbociclib described above) or labeled to be taken fasted have changes of 39 % or more.

## *4.2 Assessments Using Non-high-fat Meals*

All high-fat meals used in food-effect assessments were conducted using the test meal similar to that described in the FDA's food-effect guidance (Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies Food 2002). This meal is between 800 and 1000 cal, with approximately 150, 250, and 500–600 cal from protein, carbohydrate, and fat, respectively.

Sponsors have also used a variety of other meal types in addition to the high-fat test meal to evaluate food interactions, presumably to understand the impact of fat content on the absorption of the drug. Examples are presented in Table 12.4. These meals have been described as standard (aka regular and normal), moderate-fat and low-fat. Unfortunately, the exact contents of the meals are not always disclosed in review documents and publications. As there are no guidelines to standardize these other meal types, sponsors are free to define them as they wish. This variation and the lack of detail on meal content, means comparison for results between drug products is nearly impossible.

In addition to the high-fat meal, moderate-fat, low-fat, and standard meals were tested in the evaluation of palbociclib, olaparib, ceritinib, abiraterone, regorafenib, vismodegib, ponatinib, axitinib, and pazopanib. Publications and reviews do not specify the meal compositions for either abiraterone or pazopanib. Comparison of the total calories, protein, carbohydrate, and fat content for those available indicates there is little or no difference between the meal types and for the most part the categorization is meaningless. Total calorie content for the meals, regardless of description, ranged from 319 to 700 cal, with the most frequent content in the range of 500 cal. Fat content for the low-fat meals range from 7 % to <30 %, while for moderate/normal meals the range is from 25 to 35 %.

It might be argued that all of the non-high-fat meals using 20 % or more fat content are representative of a normal healthy diet. The acceptable macronutrient distribution ranges for a healthy diet recommend a range for adults of 20–35 % of

**Table 12.4** Compositions for various meal types used in food effect trials

| Drug | Meal description | Meal composition | Results |
|---|---|---|---|
| Palbociclib | Moderate-fat | Total 500–700 cal | Exposure similar for all meal types. Food decreases variability by increasing bioavailability in low exposure patient subset |
| | Low-fat | Protein 15 % | |
| | | Carb 50 % | |
| | | Fat 35 % | |
| | | Total 400–500 cal | |
| | | Protein 120 cal 24 % | |
| | | Carb 250 cal 50 % | |
| | | Fat 28–35 cal (~7 %) | |
| Panobinostat | Normal | Total 500 cal | Exposure comparable to high-fat meal type |
| | | Fat 35 % | |
| Olaparib | Standard | Total 400–500 cal | Exposure comparable to high-fat meal type |
| | | Fat <25% NA | |
| Ceritinib | Low-fat | Total 330 cal | Exposure 15 % higher for high-fat meal |
| | | Protein 15 % 50 cal | |
| | | Carb 60 % 206 cal | |
| | | Fat 25 % 78 cal | |
| Regorafenib | Low-fat | Total 319–520 cal | Exposure 12 % higher for high-fat meal |
| | | Protein 17 g | |
| | | Carb 93 g | |
| | | Fat 2–8.2 g | |
| | | <30 % fat | |
| Vismodegib | Low-fat | Total 520 cal | Single dose exposure 21 % higher for high-fat meal. Steady-state exposure of patients fed low-fat meal similar to fasted group |
| | | 1 cup cereal | |
| | | 8 oz skim milk | |
| | | Toast with jam | |
| | | Apple juice | |
| | | Coffee or tea | |
| | | (Estimated fat: <10 %)[a] | |
| Ponatinib | Low-fat | Total 547 cal | Exposure 12 % higher for high-fat meal |
| | | Protein 56 cal | |
| | | Carb 428 cal | |
| | | Fat ≤20 %, 63 cal | |
| Axitinib | Moderate-fat | Total 500–700 | Exposure 29 % higher for high-fat meal (19 % vs. −10 %) |
| | | Protein 15 % | |
| | | Carb 55 % | |
| | | Fat 30 % | |

[a]Assuming fat content for toast (1–2 g) and cereal (2 g) only

caloric intake from fat (Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids / Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of

Dietary Reference Intakes, Food and Nutrition Board 2005). This suggests that a "regular," "normal," "standard," or even moderate-fat meal would be expected to conform to this range. For a diet consisting of 1800–2000 cal per day, one could reasonably expect any single meal could be in the range of 600–700 cal. A moderate fat meal is described by the European Medicines Agency (Guideline on the Investigation of Drug Interactions 2012) as having a fat content of 150 cal of a 400–500 cal meal (approximately 30–38 % fat).

Many of the clinical pharmacology studies for idelalisib were conducted with the coadministration with a "standard" meal. This meal was used in the QTc study, and described as having a total calorie content of 475 cal, with 10 % protein, 66 % carbohydrates, and 22 % fat. Though no study was conducted comparing this meal to the high-fat standard, the lack of a food effect in the latter suggested no effect would be expected for this meal, and no further evaluation was necessary.

In addition to the examples in Table 12.4, the sponsor for everolimus also conducted low-fat meal study after approval, and updated label May 2010. The "light fat" meal reduced AUC by 32 % and $C_{max}$ by 42 % (Afinitor® everolimus Prescribing Information Label 2010). This "light-meal" was identified in the label as containing approximately 500 cal and 20 g of fat. When food effect was evaluated, it is almost always evaluated for single doses. However, for vismodegib, the sponsor also elected to measure the impact of a low-fat meal on the steady-state pharmacokinetics of the drug (Sharma et al. 2013). Patients received vismodegib once daily 30 min after a healthy breakfast and their pharmacokinetic results were compared to a parallel group of patients who took the medication following a standard 10-h fast. The results of this evaluation found a 7 and 5 % increase in $C_{max}$ and AUC on coadministration with a low-fat meal at steady-state, supporting the reviewer's conclusion that "Although food slightly impacted single-dose vismodegib plasma exposure as indicated by an increase in $C_{max}$ and AUC0-168 (1.38-fold maximum, HF group), there was no apparent impact of food on vismodegib plasma exposure at steady-state."

Finally, it is worth noting that when comparing the results of the high-fat and low-fat meal, the differences among this group are relatively small, and ranged from no difference to 21 % for vismodegib and 29 % for axitinib. Both are labeled to be given without regard to meals, and the overall inter-subject variability in exposure of 49 % and ~70 %, respectively, further supports the notion that the difference is not clinically important.

### *4.3 Assessment of Acid-Reducing Agent Interaction*

As shown in Table 12.5, 15 of the 24 approved oral agents were identified during the submission review as having pH-dependent solubility. Only three conducted drug interaction studies with acid-reducing agents prior to submission: palbociclib, axitinib, and bosutinib. In the three studies where acid-reducing agents were tested, all were with proton pump inhibitors (PPIs): two with rabeprazole and one with lansoprazole. Six had requests for post-marketing studies to evaluate the interaction. Of the remaining six oral agents with pH-dependent solubility, five successfully

**Table 12.5** Evaluation of acid-reducing agent interactions

| Drug | Characterized solubility | Method to evaluate PPI interaction | Evaluation result | Review outcome |
|---|---|---|---|---|
| Panobinostat | pH dependent: high solubility at pH 1.2–6, low solubility above pH 7.6 | PBPK model | Altered absorption not observed in simulations | Model was accepted. Label mentions PBPK modeling |
| Palbociclib | pH dependent: at or below pH 4, high-solubility. Above pH 4, the solubility reduces significantly | Clinical Study: rabeprazole administered with and without food in healthy volunteers | Fasted: $C_{max}$ −80 % and AUC −62 % | Label: under fed conditions, no clinically relevant effect |
| | | | Fed: $C_{max}$ −41 % and AUC −13 % | |
| Lenvatinib | pH dependent: becomes practically insoluble from very slightly soluble as pH increases | PopPK Assessment | Inconclusive, however review states "data suggest gastric pH modifying agents may be concomitantly used" | Label does not mention acid-reducing agents (ARAs) |
| Olaparib | Not pH dependent: practically insoluble at physiological pHs between 1 and 6.8 | None | None | No action needed |
| Idelalisib | pH dependent: <0.1 mg/mL at pH 5–7 to over 1 mg/mL at pH 2 | PopPK method and comparative analysis for safety and efficacy | Similar exposure and efficacy anticipated. Overlapping toxicity for rash and diarrhea | CP Reviewer suggests no dose adjustment needed. Label does not mention ARAs |
| Ceritinib | pH dependent: 11 mg/mL at pH 1, 0.0002 at pH 6.8 | PopPK analysis | Inconclusive | Post-marketing study requested |
| | | | | Label: ARAs may reduce bioavailability |
| Afatinib | Not pH dependent: highly sol up to pH 6 | None | None | No action needed |
| Ibrutinib | pH dependent: However, slightly or practically insoluble in aqueous media | PopPK analysis | Analysis found ARA delayed absorption 1.6 h | No action needed |
| Trametinib | Not pH dependent: practically insoluble pH 2–8 | None | None | No action needed |
| Pomalidomide | Not pH dependent: | None | None | No action needed |
| Dabrafenib | pH dependent: Solubility sixfold higher at gastric pH than simulated gastric fluid pH 1.2 | None | PMR | Post-marketing study requested |
| | | | | Label: drugs that alter pH may reduce bioavailability |

| | | | | |
|---|---|---|---|---|
| Bosutinib | pH dependent: highly soluble below pH 5, reduced above pH 5 | Clinical Study: lansoprazole administered to fasting healthy volunteers | $C_{max}$ −46 %<br>AUC −26 % | Label includes study results in DDI section; recommends use of short acting ARA instead |
| Cabozantinib | pH dependent: practically insoluble pH >4 | PopPK analysis | Assessment inconclusive | Post-marketing study requested |
| Vismodegib | pH dependent: 0.99 mg/mL pH 1, at pH 7, 0.1 mcg/mL | PopPK analysis | Potential effect was noted on absorption and trend for effect on efficacy | Post-marketing study requested<br>Potential interaction noted in original label |
| Ponatinib | pH dependent: solubility decreases with increasing pH | Proposed clinical trial for DDI with lansoprazole submitted during review | Reviewer agreed with study | Post-marketing study requested<br>Label: drugs that elevate pH may reduce bioavailability/ should be avoided |
| Axitinib | pH dependent: lower pH, higher solubility | Sub-study conducted in patients also given Rabeprazole | Interaction not clinically significant: $C_{max}$ −42 %, AUC −15 % | Label indicates no dose adjustment needed with coadministration |
| Regorafenib | Not pH dependent: Poor solubility independent of pH | None | None | No action needed |
| Enzalutamide | Not pH dependent: practically insoluble in aqueous media | None | None | No action needed |
| Vandetanib[a] | pH dependent: practically insoluble in water with increased solubility at low pH and reduced solubility above pH 6 | None | None | Original label did not address potential for interaction with ARAs |
| Crizotinib | pH dependent: decreases from 10 mg/mL at pH 1.6–0.1 mg/mL at pH 8.2 | PopPK analysis | Impact on absorption rate was noted | Post-marketing study requested |
| Vemurafenib | Not pH dependent: insoluble across physiological pH range 1–7.5 | None | None | No action needed |
| Abiraterone | Not pH dependent: practically insoluble pH 2–12 | None | None | No action needed |
| Everolimus | Not pH dependent: solubility 1 mg/10 mL in aqueous media | None | None | No action needed |
| Pazopanib | pH dependent: slightly soluble at pH 1 and insoluble at pH 4 | PopPK analysis | Predicted increased exposure of 39 % on coadministration[b] | No action taken. Inter-individual variability (52 %) greater than anticipated effect |

[a]The March 2014 label update includes results demonstrating a lack of interaction between vandetanib and H2-antagonist (ranitidine) and a proton-pump inhibitor (omeprazole)
[b]However, subsequent publication of full drug interaction study indicates exposure was decreased by 40 % (Tan et al. 2013)

supported a lack of interaction by testing for absorption interactions via PBPK (panobinostat) or PopPK (lenvatinib, idelalisib, ibrutinib, and pazopanib). The discussion for vandetanib is largely missing from the reviews, and though apparently no post-marketing request was issued for the studies, the sponsor updated their label in March 2014 with drug interaction information showing no clinically important interaction with either ranitidine or omeprazole (Caprelsa® vandetanib Prescribing Information Label 2014).

Of the new compounds whose labeling for acid-reducing agents was supported with pharmacometric analyses, several are worthy of further discussion. To evaluate the potential impact of coadministration of acid-reducing agents on the bioavailability of panobinostat, a PBPK model was developed using GastroPlus® advanced compartmental and transit model connected with a three-compartment pharmacokinetic model. The model was validated with clinical data from the food effect trial, and used to simulate increasing pH in the gastrointestinal tract and determine how these changes might impact absorption. The model utilized physicochemical properties, in vitro, in vivo, and population pharmacokinetic models to simulate drug exposures from both fed and fasted states over a variety of conditions, including changes in pH, increasing gastric transit times, and different bile salt concentrations. The FDA reviewer used the sponsor's model to simulate results for the effect of coadministration of food with panobinostat and concluded that the model adequately predicted the results obtained in the clinic. The sponsor used the model to test the impact on panobinostat bioavailability over the pH range of 0.5–8.0. There was no change in the predicted bioavailable fraction over the entire range. In addition, the reviewer used an alternative model built in Simcyp® using first order absorption and the advanced dissolution, absorption, and metabolism mechanistic absorption model to perform a similar sensitivity analysis over the same pH range. The simulations from this model supported the original conclusions. Using this orthogonal approach, it was concluded that no impact was likely, and the label states "altered panobinostat absorption was not observed in simulations using physiologically based pharmacokinetic (PBPK) models."

Equally interesting among this group, is the approach employed for idelalisib. During the review, it was noted that idelalisib solubility was pH dependent, and at increased pH values associated with coadministration of acid-reducing agents (pH 6 or higher), the gastric concentration of drug would exceed its solubility. The sponsor conducted an exploratory analysis to assess the effects of acid-reducing agents on the PK, safety, and efficacy. For the model, a patient was defined as having taken the drugs concomitantly if the patient was receiving the acid-reducing agent during any pre-dose sampling time or ≥50 % of the time that coincided with PK sampling. A total of 121 non-Hodgkin's lymphoma and 102 chronic lymphocytic leukemia patients were included, and 35 and 62 patients in each group, respectively, were classified has having concomitantly received acid-reducing agents. The population analysis of the combined data from the clinical studies indicated that the exposures and pharmacokinetic results were similar for patients taking idelalisib with or without an acid-reducing agent. The safety analysis revealed that a higher incidence of diarrhea and rash for patients receiving the combination, which was ascribed to

overlapping toxicity profiles and/or a potential metabolic drug interaction which could have increased the exposure of the acid-reducing agent. The response rates and PFS values within each disease group were similar for patients with and without coadministration of the acid-reducing agents. This combined safety, efficacy, and population pharmacokinetic analysis was considered enough to satisfy the reviewer that while coadministration would impact the tolerability, it would not affect the pharmacokinetics or the efficacy of idelalisib.

For those drugs issued written requests for the conduct of acid-reducing agent interaction studies, examination of the requests reveals the expectations the FDA with regard to these evaluations. The written requests for the post-marketing studies for ceritinib (2014) and dabrafenib (2013) are similar:

> *Conduct a clinical trial to evaluate if proton pump inhibitors, H2-receptor antagonists, and antacids alter the bioavailability of Zykadia (ceritinib) and to determine how to dose Zykadia (ceritinib) with regard to concomitant gastric acid reducing agents.*

Prior to 2013, except where the sponsor had already agreed to conduct a DDI with a specific PPI (lansoprazole for ponatinib), the requests generically require conduct of a study including a "PPI, H2-antagonist, and antacid" (e.g., crizotinib). For vismodegib and cabozantinib, however, the request was prescriptive:

> *Conduct a drug-drug interaction clinical trial in healthy volunteers to evaluate if gastric pH elevating agents alter the bioavailability and impact the steady-state exposure of vismodegib. The trial may be conducted in a gated manner, first evaluating the effect of proton pump inhibitors (PPIs) on the steady state exposure of vismodegib. In the event that concomitant administration of PPIs has a large impact on vismodegib steady state exposure, H2 antagonists and antacids will be subsequently evaluated. The number of subjects enrolled in the trial should be sufficient to detect PK differences. The trial results should allow for a determination on how to dose vismodegib with regard to gastric pH elevating agents.*

This "gated" approach (Zhang et al. 2014) is analogous to the methods used to evaluate inhibition DDIs—where strong inhibitors are evaluated to determine the impact, and moderate inhibitors are only requested if the impact of the worst-case strong inhibitor is large. The question of why a PPI might be considered a worst-case scenario for gastric pH-elevating agent is worth considering. The key differences (other than mechanism) between PPIs and H2-blockers are onset of action, depth, and duration of effect—and since both onset of action and depth of effect are greater with H2-blockers, one could make the case that H2-blockers are a worst case scenario for the immediate effect on gastric pH. Furthermore, a BID regimen of an H2-blocker would overcome the difference in duration of effect. In fact, in a study comparing the effect of concomitant administration of omeprazole or ranitidine with anticancer drug erlotinib, erlotinib pharmacokinetic exposure was found to be significantly and similarly reduced (AUCinf 54 % vs. 33 %; $C_{max}$ 58 % vs. 54 %) (Kletzl et al. 2015).

So why would the FDA reviewers request PPIs as the first assessment in a gated approach to DDI assessment? According to Zhang et al. 2014, "*Because PPIs generally have a longer duration of suppression effect on gastric acid secretion than do H2 blockers and antacids, and are expected to interfere with the intestinal absorption*

*of WBDs to a greater extent, use of a PPI may be considered a worst-case scenario in the* in vivo *evaluation of the pH effect."* Under this assumption, we can conclude that, right or wrong, PPIs will be viewed as the standard for the initial assessment of the DDI for acid-reducing agents.

A few compounds have already updated their labels to reflect the results of the requested drug interaction study. The March 2015 label for crizotinib indicates that coadministration with esomeprazole did not result in a clinically important change in exposure (Xalkori® crizotinib Prescribing Information Label 2015). The July 2014 update for the ponatinib label indicates that coadministration with lansoprazole resulted in only a 6 % change in exposure for ponatinib (Iclusig® idelalisib Prescribing Information Label 2014). Both studies were designed to evaluate the concomitant administration of multiple doses of the acid-reducing agent on a single-dose of drug. Vismodegib, as it had done for food-effect, evaluated the impact of the interaction on steady-state vismodegib. Its label was updated in May 2015 to indicate that coadministration of a proton pump inhibitor, rabeprazole, had no effect on the steady-state systemic exposure of vismodegib (Erivedge® vismodegib Prescribing Information Label 2015).

## 5 Organ Impaired Populations

Table 12.6 presents a summary of the methods employed and results of the evaluation of renal and hepatic impairment on the pharmacokinetics of approved oncology agents. These results compile the information presented from the original submission calculated to reflect change in exposure from the reported values for either clearance or AUC in the review. For results of dedicated clinical studies, data are expressed as change in exposure relative to subjects with normal organ function. For population pharmacokinetic (PopPK) assessments, clinically nonsignificant changes or lack of covariate identification for organ impairment is indicated by "Not sig." The labeling information was taken from the first issued label at time of approval. The evaluation method shown is the one reported in the Clinical Pharmacology and Biopharmaceutics Review, and represents as best as could be determined either the sponsor or reviewer interpretation used for labeling.

The definitions for organ impairment used in these assessments included those criteria presented in FDA Guidance for Industry (Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function 2010, Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function 2003) or by the National Cancer Institute (NCI) organ dysfunction working group (National Cancer Institute (NCI) Common Toxicity Criteria (CTC) 1999). When divided into groups for analysis, renal impairment groups were most often described using calculated creatinine clearance values as follows: normal >90 mL/min, mild impairment 60–89 mL/min, moderate impairment 30–59 mL/min, and severe impairment <30 mL/min. Any differences existing between products were not materially important. For hepatic impairment, either the Child-Pugh definitions recommended

**Table 12.6** Evaluation of organ impaired populations

| | | | *Hepatically impaired populations* | | | *Renally impaired populations* | | |
|---|---|---|---|---|---|---|---|---|
| Drug | Year of approval | Chem Type | Evaluation method | Results[a]& | Review outcome | Evaluation method | Results & | Review outcome |
| Dinutuximab | 2015 | Antibody | None | NA | Label indicates drug has not been studied in patients with hepatic impairment | None | NA | Label indicates drug has not been studied in patients with renal impairment |
| Panobinostat | 2015 | Small Molecule | Full ($n=25$)<br>Mild ($n=8$)<br>Mod ($n=6$)<br>Sev ($n=1$) | 43 %<br>105 %<br>ND | Reduce dose to 15 mg (75 % of standard dose) for mildly and 10 mg (50 % of standard dose) moderately impaired, Avoid use in severely impaired patients. | Full ($n=37$)<br>Mild ($n=10$)<br>Mod ($n=10$)<br>Sev ($n=6$) | –36 %<br>–1 %<br>–41 % | Mild [creatinine clearance (CrCl) ≥50 to <80 mL/min] to severe renal impairment (CrCl <30 mL/min) did not impact the plasma exposure of panobinostat |
| Palbociclib<br>PMR: Hepatic | 2015 | Small Molecule | PopPK ($n=183$)<br>Mild ($n=40$)<br>Mod ($n=1$) | Not Sig | No adjustment needed in mildly impaired. Post-marketing request for final report of hepatic study. | PopPK<br>$N=183$<br>Mild ($n=74$)<br>Mod ($n=29$) | Not sig | Mild and moderate renal impairment had no effect on the exposure of palbociclib |
| Lenvatinib | 2015 | Small molecule | Full ($n=26$)<br>Mild ($n=6$)<br>Mod ($n=6$)<br>Sev ($n=6$) | U –35 %<br>T 19 %<br>U 22 %<br>T 7 %<br>U 173 %<br>T 80 % | No dose adjustment is recommended in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, the recommended dose is 14 mg taken once daily (58 % of standard dose) | Full ($n=26$)<br>Mild ($n=6$)<br>Mod ($n=6$)<br>Sev ($n=6$) | U –46 %<br>U 29 %<br>U 84 %<br>T 20 % | No dose adjustment is recommended in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended dose is 14 mg taken once daily (58 % of standard dose). |

(continued)

**Table 12.6** (continued)

| Drug | Year of approval | Chem Type | *Hepatically impaired populations* | | | *Renally impaired populations* | | |
|---|---|---|---|---|---|---|---|---|
| | | | Evaluation method | Results[a]& | Review outcome | Evaluation method | Results & | Review outcome |
| Belinostat<br>PMR: Hepatic<br>PMR: Renal | 2014 | Small molecule | PopPK ($n=249$)<br>Mild ($n=59$) | Not sig | Label indicates there are insufficient data to recommend a dose in patients with moderate and severe hepatic impairment. Post-marketing request for final report of hepatic study. | PopPK ($n=249$)<br>Mild ($n=31$) | Not sig | Label indicates exposure is not altered in patients with CrCL >39 mL/min and that there is insufficient data to recommend a dose in patients with CrCL <39 mL/min. PMR for study to evaluate the impact of various degrees of impairment on clearance |
| Blinatumomab | 2014 | Antibody | None | NA | Label notes no formal pharmacokinetic studies were conducted in patients with hepatic impairment | NCA PK ($n=298$)<br>Mild ($n=62$)<br>Mod ($n=21$) | 47 %<br>106 % | Label indicates no dose adjustment is needed for patients creatinine clearance equal to or greater than 30 mL/min and that there is no information available in patients with creatinine clearance less than 30 mL/min or patients on hemodialysis |
| Ramucirumab | 2014 | Antibody | None | NA | Label notes no clinical studies have been conducted to evaluate the effect of hepatic impairment | None | NA | Label notes there were no dedicated clinical studies conducted to evaluate the effect of renal impairment |
| Pembrolizumab | 2014 | Antibody | PopPK ($n=476$)<br>Mild ($n=59$)<br>Mod ($n=2$)<br>Sev ($n=1$) | Not sig | Label notes population pharmacokinetic analysis found no dose adjustment was needed with mild hepatic impairment. Also notes drug has not been studied in moderate or severe impairment | PopPK ($n=476$)<br>Mild ($n=210$)<br>Mod ($n=43$)<br>Sev ($n=2$) | Not sig | Label acknowledges population pharmacokinetic analysis and notes no dose adjustment is needed for patients with renal impairment |

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|---|---|---|---|---|---|---|---|---|
| Olaparib<br>PMR: Hepatic<br>PMR: Renal | 2014 | Small Molecule | None<br>Dedicated study was ongoing at time of submission. | NA | Label notes the effect of hepatic impairment on exposure has not been studied and that patients with more than mild impairment were excluded from clinical trials. A PMR was issued for submission of the final report for the ongoing study. | Reduced study ongoing at time of submission.<br>Mild ($n=14$) | 50 % | Label indicates that no dose adjustment to the starting dose is required for patients with mild renal impairment, but patients should be monitored closely for toxicity. PMR was issued for submission of the final report for the ongoing study. |
| Nivolumab | 2014 | Antibody | PopPK<br>($n=909$)<br>Mild ($n=92$) | Not sig | No dose adjustment is recommended for patients with mild hepatic impairment and drug has not been studied in patients with moderate or severe hepatic impairment | PopPK<br>($n=909$)<br>Mild ($n=313$)<br>Mod ($n=140$)<br>Sev ($n=3$) | Not sig | Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with renal impairment |
| Idelalisib | 2014 | Small Molecule | Reduced<br>($n=32$)<br>Mod ($n=10$)<br>Sev ($n=10$) | 66 %<br>62 % | Label does not recommend a dose for hepatic impairment, however, provides dose modification instruction for varying degrees of acute AST or ALT increases. Patients with more than moderate impairment were excluded from clinical trials. | Reduced<br>Sev ($n=6$) | 27 % | Label notes that no dose adjustment is needed for patients with CrCL ≥15 mL/min |
| Ceritinib<br>PMR: Hepatic | 2013 | Small Molecule | PopPK<br>($n=302$)<br>Mild ($n=48$) | Not sig | No dose adjustment recommended for patients with mild hepatic impairment and no recommended dose determined for patients with moderate to severe hepatic impairment. PMR was issued for submission of the ongoing hepatic study. | PopPK<br>($n=302$)<br>Mild ($n=97$)<br>Mod ($n=22$) | 9 %<br>19 % | Label indicates exposures were similar in patients with mild and moderate renal impairment and normal renal function. |

(continued)

**Table 12.6** (continued)

| Drug | Year of approval | Chem Type | *Hepatically impaired populations* | | | *Renally impaired populations* | | |
|---|---|---|---|---|---|---|---|---|
| | | | Evaluation method | Results[a]& | Review outcome | Evaluation method | Results & | Review outcome |
| Obinutuzumab | 2013 | Antibody | PopPK ($n=208$) Mild ($n=2$) Mod ($n=6$) | NC | Label indicates that drug has not been studied in patients with hepatic impairment. | PopPK ($n=201$) Mild ($n=82$) Mod ($n=85$) Sev ($n=5$) | Not sig | Label notes population pharmacokinetic analysis shows exposure to drug is not changed in patients with up to moderately impaired renal function (CrCL >30 mL/min) and has not been studied severely impaired patients (CrCL <30 mL/min) |
| Afatinib PMR: Renal | 2013 | Small Molecule | Reduced ($n=38$) Mild ($n=8$) Mod ($n=14$) | –7 % –5 % | No dose adjustment needed for mildly or moderately impaired; drug has not been studied in patients with severe impairment. Closely monitor patients with severe hepatic impairment and adjust if not tolerated | PopPK ($n=1010$) Mild ($n=470$) Mod ($n=187$) Sev ($n=2$) | 14 % 37 % NC | Label indicates drug has not been studied in severely impaired renal function and that no adjustments to starting dose are necessary in mildly impaired patients. Moderately and severely impaired subjects are to be monitored for tolerability and dose adjusted accordingly. A post-marketing study was requested to evaluate moderate and severe renal impairment. |

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|---|---|---|---|---|---|---|---|---|
| Ibrutinib<br>PMR: Hepatic | 2013 | Small Molecule | Trial was ongoing, with preliminary data provided for review | NA | Label notes lack of clinical trials in patients with impaired hepatic function. Indicates preliminary data show sixfold higher exposure in 3 moderately impaired subjects. PMR was issued for full hepatic study. | PopPK ($n=179$)<br>Mild ($n=72$)<br>Mod ($n=21$)<br>Sev ($n=1$) | Not sig | Label indicates less than 1 % drug is renally excreted and exposure is not altered with creatinine clearance above 25 mL/min. There are no data in patients with severe renal impairment (CLcr <25 mL/min) or patients on dialysis. |
| Ado-trastuzumab emtansine<br>PMR: Hepatic | 2013 | ADC | Reduced trial was ongoing at time of submission | NA | Label indicates influence of hepatic impairment on drug not been determined. PMR issued for hepatic study | PopPK ($n=668$)<br>Mild ($n=254$)<br>Mod ($n=53$)<br>Sev ($n=1$) | Not sig | Dose adjustments were not needed with mild or moderate renal impairment; no recommendation could be made for severely impaired patients because of limited data. |
| Trametinib<br>PMR: Hepatic | 2013 | Small Molecule | PopPK ($n=493$)<br>Mild ($n=64$) | Not sig | Label notes lack of formal clinical trial to evaluate hepatic impairment, and indicates no dose adjustment is recommended in patients with mild hepatic impairment based on a population pharmaco-kinetic analysis. Sponsor requested to conduct hepatic impairment trial and PMR was issued. | PopPK ($n=489$)<br>Mild ($n=223$)<br>Mod ($n=35$) | Not sig | Label notes no formal clinical trial conducted to evaluate the effect of renal impairment. Further indicates no dose adjustment is necessary in mild or moderate renal impairment based on a population pharmacokinetic analysis. |
| Pomalidomide<br>PMR: Hepatic<br>PMR: Renal | 2013 | Small Molecule | None | NA | Label states to avoid use in patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0× ULN to match exclusion criteria of confirmatory study. PMR issued for hepatic impairment study. | Study ongoing at time of submission | NA | Label state to avoid use in patients with a serum creatinine greater than 3.0 mg/dL to match exclusion criteria of confirmatory study. PMR issued for renal impairment study. |

(continued)

**Table 12.6** (continued)

| Drug | Year of approval | Chem Type | *Hepatically impaired populations* | | | *Renally impaired populations* | | |
|---|---|---|---|---|---|---|---|---|
| | | | Evaluation method | Results[a]& | Review outcome | Evaluation method | Results & | Review outcome |
| Dabrafenib<br>PMR: Hepatic<br>PMR: Renal | 2013 | Small Molecule | PopPK ($n=595$)<br>Mild ($n=65$)<br>Mod ($n=3$) | Not sig | No dose adjustment is needed in mild hepatic impairment based on the results of the population pharmacokinetic analysis. PMR issued for study in moderately and severely impaired subjects. | PopPK ($n=595$)<br>Mild ($n=233$)<br>Mod ($n=30$) | Not sig | No dose adjustment recommended for patients with mild or moderate renal impairment based on the results of the population pharmacokinetic analysis. PMR issued for study in severe renal impairment. |
| Radium-223 dichloride | 2013 | Radio-isotope | Subgroup analysis ($n=614$)<br>Mild ($n=134$)<br>Mod ($n=1$) | Analysis showed similar OS and AE rates for mild and normal controls | Label indicates lack of dedicated hepatic impairment trial and that hepatic impairment is unlikely to affect pharmacokinetics since drug is neither metabolized nor eliminated in bile. A subgroup analysis indicates dose adjustment is not needed in patients with mild hepatic impairment and no doses are recommended for patients with moderate or severe hepatic impairment due to lack of clinical data. | Subgroup analysis ($n=612$)<br>Mild ($n=162$)<br>Mod ($n=69$)<br>Sev ($n=2$) | Analysis showed similar AE rates for mild, moderate and normal controls | Label indicates lack of dedicated renal impairment study, and adds that based subgroup analysis, dose adjustment is not needed in mild or moderate renal impairment. No dose adjustment can be recommended for severe renal impairment due to limited data. |
| Bosutinib | 2012 | Small Molecule | Full ($n=27$)<br>Mild ($n=6$)<br>Mod ($n=6$)<br>Sev ($n=6$) | 117 %<br>105 %<br>95 % | Dose reduction to 200 mg daily (40 % of standard dose) in patients with any hepatic impairment | PopPK ($n=903$)<br>Mild ($n=102$)<br>Mod ($n=14$) | Not sig | Based on population pharmacokinetics, creatinine clearance had no meaningful influence on exposure (25–120 mL/min) |

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|---|---|---|---|---|---|---|---|---|
| Cabozantinib<br>PMR: Hepatic | 2012 | Small Molecule | Trial was ongoing at time of submission.<br>PopPK ($n=289$)<br>Review indicates PopPK found minimal impact on exposure for mildly impaired populations | NA<br>Not sig | Label notes that drug was not been studied in patients with hepatic impairment and drug is not recommended for use in patients with moderate or severe hepatic impairment. PMR was issued for hepatic impairment study. | PopPK ($n=289$)<br>Review indicates PopPK found similar exposure for mild, moderate and normal patient populations. | Not sig | Label notes no formal study was conducted in renal impairment, and that results of a population pharmacokinetic analysis suggested mild to moderate renal impairment has no clinically relevant impact. No dose adjustment is recommended for patients with mild or moderate renal impairment; there is no experience in patients with severe renal impairment. |
| Vismodegib<br>PMR: Hepatic<br>PMR: Renal | 2012 | Small Molecule | Full trial ongoing at time of submission | NA | Label notes drug exposure was not evaluated in patients with hepatic impairment. PMR issued for conduct of hepatic impairment study. | Trial ongoing at time of submission<br>Review indicates PopPK found no meaningful influence of creatinine clearance over the range of 30–80 mL/min | Not sig | Label acknowledges drug has not been studied in renal impairment, and notes that population pharmacokinetic analysis did not find creatinine clearance (30–80 mL/min) to significantly impact exposure. PMR issued for reduced renal impairment study to evaluate severely impaired subjects. |

(continued)

**Table 12.6** (continued)

| Drug | Year of approval | Chem Type | *Hepatically impaired populations* | | | *Renally impaired populations* | | |
|---|---|---|---|---|---|---|---|---|
| | | | Evaluation method | Results[a]& | Review outcome | Evaluation method | Results & | Review outcome |
| Ponatinib<br>PMR: Hepatic | 2012 | Small Molecule | Trial ongoing at time of submission. | NA | Label notes lack of study in hepatic impairment. Indicates to avoid use in patients with moderate to severe hepatic impairment due to possible risk of ponatinib overexposure. PMR was issued for conduct of hepatic impairment study. | None | NA | Label notes lack of study in patients with renal impairment. It also indicates the potential for moderate or severe renal impairment to affect hepatic elimination has not been determined. |
| Axitinib | 2012 | Small Molecule | Reduced ($n=24$)<br>Mild ($n=8$)<br>Mod ($n=8$) | U 12 %<br>T −22 %<br>U 100 %<br>T 99 % | Label indicates no starting dose adjustment is required for mild hepatic impairment. Starting dose is to be reduced by half in patients with moderate hepatic impairment and that the drug was not studied in patients with severe hepatic impairment. | PopPK ($n=590$)<br>Mild ($n=139$)<br>Mod ($n=64$)<br>Sev ($n=5$)<br>ESRD ($n=1$) | Not sig | Label notes lack of dedicated renal impairment trial. Indicates that based on the population pharmacokinetic analyses, no significant difference in clearance was observed in patients with mild to severe renal impairment and no dose adjustment is needed. Caution should be used in patients with end-stage renal disease. |
| Carfilzomib<br>PMR: Renal | 2012 | Peptide | None | NA | Label notes lack of hepatic impairment study. PMR was issued for conduct of hepatic impairment study | Phase II trial ($n=43$)<br>Mild ($n=12$)<br>Mod ($n=8$)<br>Sev ($n=7$)<br>CD ($n=8$) | Exposures overlapping for all groups | Label indicates the pharmacokinetics and safety were not influenced by the degree of renal impairment, including the patients on dialysis. PMR was issued for conduct of renal impairment study |

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|---|---|---|---|---|---|---|---|---|
| Pertuzumab | 2012 | Antibody | None<br>However, PopPK analysis examined for transaminase as covariate | Not sig | Label states no clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of pertuzumab | PopPK<br>($n=440$)<br>Mild ($n=158$)<br>Mod ($n=38$)<br>Sev ($n=3$) | Not sig | Label specifies that no dose adjustments are needed in mild or moderate renal impairment. Label further states no dose adjustment can be recommended for severe renal impairment due to limited pharmacokinetic data, but also indicates there was no relationship between creatinine clearance and exposure over the range from 27–244 mL/min |
| Regorafenib<br>PMR: Renal | 2012 | Small Molecule | Post-hoc subgroup in HCC patients ($n=28$)<br>Parent:<br>Mild ($n=14$)<br>Mod ($n=4$)<br>M-2<br>Mild ($n=14$)<br>Mod ($n=4$)<br>M-5<br>Mild ($n=14$)<br>Mod ($n=4$) | Single-dose data<br>−18 %<br>1 %<br>−22 %<br>18 %<br>4 %<br>−16 % | Label notes there are no clinically important differences in the exposures in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function, and no dose adjustment is recommended. | Post-hoc subgroup ($n=29$)<br>Mild ($n=10$)<br>Mod ($n=1$) | Steady-state data<br>−34 %<br>ND | No clinically relevant differences in drug or active metabolite exposure were observed in renal impairment compared to patients with normal renal function, and no dose adjustment is recommended. Label notes limited data are available from patients with moderate impairment and drug was not studied in patients with severe renal impairment or end-stage renal disease. Sponsor requested PMR for conduct of repeat-dose study in severely impaired patients. |

(continued)

**Table 12.6** (continued)

| Drug | Year of approval | Chem Type | *Hepatically impaired populations* | | | *Renally impaired populations* | | |
|---|---|---|---|---|---|---|---|---|
| | | | Evaluation method | Results[a]& | Review outcome | Evaluation method | Results & | Review outcome |
| Omacetaxine PMR: ADME | 2012 | Small Molecule | None | NA | Label indicates no formal studies assessing hepatic impairment have been conducted. PMR was issued for mass balance trial, with potential for hepatic impairment studies based on results. | None | NA | Label indicates no formal studies assessing renal impairment have been conducted. PMR was issued for mass balance trial, with potential for hepatic impairment studies based on results. |
| Enzalutamide PMR: Hepatic | 2011 | Small Molecule | Reduced ($n=33$)<br>Parent:<br>Mild ($n=8$)<br>Mod ($n=8$)<br>M2<br>Mild ($n=8$)<br>Mod ($n=8$)<br>Submitted during the review | T 5 %<br>U 0 %<br>T 29 %<br>U 17 %<br>T 18 %<br>U 20 %<br>T 7 %<br>U 11 % | Label indicates no initial dosage adjustment is necessary for mild or moderate hepatic impairment and that severe hepatic impairment has not been assessed. PRM issued for study of severe hepatic impairment. | PopPK ($n=933$)<br>Mild ($n=332$)<br>Mod ($n=88$)<br>Sev ($n=1$) | Not sig | Label indicates no dedicated renal impairment trial has been conducted. Notes that population pharmacokinetic analysis found no significant difference in patients with mild to moderate renal impairment compared to patients and volunteers with normal renal function. No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Label acknowledges that severe renal impairment and end-stage renal disease have not been assessed. |

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|---|---|---|---|---|---|---|---|---|
| Ziv-aflibercept | 2011 | Protein | PopPK ($n=1507$)<br>Mild ($n=63$)<br>Mod ($n=5$) | Not sig | Label indicates there are no dedicated clinical studies conducted to evaluate the effect of hepatic impairment on drug, and that the population pharmacokinetic analysis indicated similar exposures were expected in mild and moderate impairment compared to patients with normal function. Also noted there are no data available in severe hepatic impairment. | PopPK ($n=1507$)<br>Mild ($n=549$)<br>Mod ($n=96$)<br>Sev ($n=5$) | Not sig | Label indicates no dedicated clinical studies were conducted to evaluate the effect of renal impairment. Notes population pharmacokinetic analysis in patients with mild, moderate, and severe renal impairment were similar to those in patients with normal renal function. |
| Brentuximab vedotin | 2011 | ADC | Study ongoing at time of submission PopPK ($n=173$) was performed | Not sig | Label notes frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function, and to avoid the use in patients with moderate or severe impairment. | Study ongoing at time of submission PopPK ($n=173$) was performed | Not sig | Label notes frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Recommends avoiding the use in patients with severe renal impairment. |
| Vandetanib | 2011 | Small Molecule | Full ($n=26$)<br>Mild ($n=8$)<br>Mod ($n=7$)<br>Sev ($n=6$) | 4 %<br>−6 %<br>−7 % | Label indicates exposures were comparable to normal hepatic function for mild, moderate and severely impaired subjects. However, it also indicates drug is not recommended for use in patients with moderate and severe hepatic impairment, as safety and efficacy have not been established. | Full ($n=30$)<br>Mild ($n=6$)<br>Mod ($n=8$)<br>Sev ($n=6$) | 14 %<br>39 %<br>41 % | Label notes exposure is increased in patients with impaired renal function and the starting dose should be reduced to 200 mg (66 % of normal dose) in patients with moderate to severe renal impairment. Label notes there is no information available for patients with end-stage renal disease requiring dialysis. |

(continued)

**Table 12.6** (continued)

| Drug | Year of approval | Chem Type | *Hepatically impaired populations* | | | *Renally impaired populations* | | |
|---|---|---|---|---|---|---|---|---|
| | | | Evaluation method | Results[a]& | Review outcome | Evaluation method | Results & | Review outcome |
| Crizotinib<br>PMR: Hepatic<br>PMR: Renal | 2011 | Small Molecule | PopPK Review indicates analysis did not select transaminase as significant covariate. | NA | Label notes drug has not been studied in hepatic impairment, and that population pharmacokinetic analysis did not select transaminases as significant covariates influencing crizotinib. A PMR was issued for the conduct of a multiple dose study to evaluate the appropriate dose in various degrees of hepatic impairment. | PopPK<br>($n=108$)<br>Mild ($n=47$)<br>Mod ($n=27$)<br>Sev ($n=1$) | Not sig | Label indicates that no starting dose adjustment is needed for mild or moderate renal impairment based on a population pharmacokinetic analysis. The label also states that limited data are available in patients with severe renal impairment and no data are available in end-stage renal disease. A PMR was issued for the conduct of a study to evaluate the appropriate dose in severe renal impairment. |
| Ipilimumab | 2011 | Antibody | PopPK Review indicates no clinically meaningful effect of hepatic impairment on PK | Not sig | Label notes lack of formal studies in hepatic impairment. AST, total bilirubin, and ALT levels did not have a clinically important effect on pharmacokinetics in patients with various degrees of hepatic impairment. | PopPK<br>($n=420$)<br>Mild ($n=127$)<br>Mod ($n=48$)<br>Sev ($n=3$) | Not sig | Label notes lack of formal studies in renal impairment. Creatinine clearance at baseline did not have a clinically important effect on pharmacokinetics in patients with calculated creatinine clearance values of 29 mL/min or greater. |

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|---|---|---|---|---|---|---|---|---|
| Vemurafenib<br>PMR: Hepatic | 2011 | Small Molecule | PopPK<br>(*n* = 246)<br>Mild (*n* = 58)<br>Mod (*n* = 27)<br>Sev (*n* = 3) | Not sig | Label indicates no adjustment to the starting dose is needed in mild and moderate hepatic impairment. Notes population pharmacokinetic analysis found mild and moderate hepatic impairment did not influence clearance. Due to insufficient data in severe hepatic impairment, the starting dose adjustment cannot be determined. PRM issued for study of severe hepatic impairment. | PopPK<br>(*n* = 459)<br>Mild (*n* = 94)<br>Mod (*n* = 11)<br>Sev (*n* = 1) | Not sig | Label indicates no adjustment to the starting dose is needed in mild and moderate renal impairment.<br>Notes the population pharmacokinetic analysis found mild and moderate renal impairment did not influence clearance. Due to insufficient data in severe renal impairment, starting dose adjustment cannot be determined. |
| Abiraterone<br>PMR: Hepatic | 2011 | Small Molecule | Reduced<br>(*n* = 24)<br>Mild (*n* = 8)<br>Mod (*n* = 8) | 10 %<br>260 % | Label indicates 1.1 and 3.6-fold increase in mild and moderate impairment. No dosage adjustment necessary for patients with mild hepatic impairment. Dose reduction to 250 mg once daily (1/4th dose once daily) in moderate impairment. Notes severely impaired patients should not receive drug. PRM issued for study of patients with severe hepatic impairment | Reduced<br>(*n* = 16)<br>ESRD (*n* = 8) | Exposures similar between groups | Label indicates no dose adjustment is necessary for patients with renal impairment |

(continued)

**Table 12.6** (continued)

| Drug | Year of approval | Chem Type | *Hepatically impaired populations* | | | *Renally impaired populations* | | |
|---|---|---|---|---|---|---|---|---|
| | | | Evaluation method | Results[a]& | Review outcome | Evaluation method | Results & | Review outcome |
| Eribulin<br>PMR: Renal | 2010 | Small Molecule | Reduced ($n=18$)<br>Mild ($n=7$)<br>Mod ($n=5$) | 75 %<br>148 % | A dose of 1.1 mg/m$^2$ (79 % of standard dose) is recommended in mild and 0.7 mg/m$^2$ (50 % of standard dose) in moderate hepatic impairment. Label notes severe hepatic impairment was not studied. | PopPK ($n=269$)<br>Mild ($n=96$)<br>Mod ($n=20$)<br>PK subset ($n=77$)<br>Mild ($n=27$)<br>Mod ($n=6$) | 70 %<br>130 %<br>NR<br>106 % | No dose adjustment necessary in mild renal impairment. A dose of 1.4 mg/m$^2$ (79 % of standard dose) is recommended in moderate renal impairment. Label notes severe renal impairment was not studied. PMR issued for study of patients with severe renal impairment |
| Cabazitaxel<br>PMR: Hepatic | 2010 | Small Molecule | None<br>A PopPK analysis was conducted, but was inconclusive | ND | Label indicates no formal study was conducted in hepatically impaired subjects, and because the drug class was known to increase risk to hepatically impaired patients, label indicates drug should not be given to hepatically impaired patients. PMR issued for study of patients with hepatic impairment | PopPK ($n=170$)<br>Mild ($n=96$)<br>Mod ($n=14$)<br>Sev ($n=1$) | Not sig | Label indicates that no difference in clearance observed in mild and moderate renal impairment based on a population pharmacokinetic analysis. The label also states that no data are available in patients with severe renal impairment and end-stage renal disease. |

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|---|---|---|---|---|---|---|---|---|
| Everolimus<br>PMR: Hepatic | 2009 | Small Molecule | Reduced ($n=8$)<br>Mod ($n=8$) | 115 % | Label notes drug should not be used in severely impaired patients, and dose should be reduced to 5 mg in moderate renal impairment (50 % of standard dose). PMR issued for study of patients with severe hepatic impairment. | PopPK ($n=170$)<br>Evaluated CrCL range of 25–178 mL/min | Not sig | Label notes that no clinical studies were conducted in renal impairment, and that in a population pharmacokinetic analysis, no significant influence of creatinine clearance was detected. No dosage adjustment is recommended. |
| Ofatumumab | 2009 | Antibody | None | NA | Label notes only that no formal studies were conducted. Review indicates that patients are unlikely to require dose adjustment because drug is eliminated by proteolytic catabolism | PopPK<br>Evaluated CrCL range of 33–287 mL/min | Not sig | Label notes that creatinine clearance did not have a clinically important effect on pharmacokinetics in patients with creatinine clearance ranging from 33–287 mL/min. |
| Pralatrexate<br>PMR: ADME<br>PMR: Renal | 2009 | Small Molecule | None<br>PopPK inconclusive | NA | Label notes lack of formal studies for hepatic impairment and that patients with moderate and severe impairment were excluded from clinical trials. PMR was issued for mass balance trial, with potential for hepatic impairment study based on results. | PopPK<br>Evaluated CrCL range from 29.5 mL/min and greater | At lowest values, parent and metabolite were reduced 19 % and 23 % | Label notes population pharmacokinetic analysis result for decreased drug clearance with decreasing creatinine clearance. Notes that age-related decreases in renal function may result in increased drug exposure. PMR was issued for full renal study. |
| Romidepsin<br>PMR: Hepatic | 2009 | Small Molecule | PopPK ($n=137$)<br>Mild ($n=15$)<br>Mod ($n=2$) | Not sig | Label notes lack of dedicated hepatic study. Indicates population pharmacokinetic analysis found mild impairment did not alter exposures. PMR was issued for conduct of study of moderate and severe hepatic impairment. | PopPK<br>Evaluated CrCL range 0.23–198 mL/min | Not sig | Label notes lack of dedicated renal study. Indicates population pharmacokinetic analysis found renal impairment not an influence on drug exposure. Notes that end-stage renal disease has not been studied. |

(continued)

**Table 12.6** (continued)

| Drug | Year of approval | Chem Type | *Hepatically impaired populations* | | | *Renally impaired populations* | | |
|---|---|---|---|---|---|---|---|---|
| | | | Evaluation method | Results[a]& | Review outcome | Evaluation method | Results & | Review outcome |
| Pazopanib PMR: Hepatic | 2009 | Small Molecule | Full study ongoing at submission Interim results ($n=24$) provided Mild ($n=5$) Mod ($n=7$) | MTD was 200 mg QD in mod impaired patients 0 % 80 % | Label indicates dose for moderate hepatic impairment should be reduced to 200 mg per day (25 % of standard dose) and notes since there are no data, use is not recommended in severely impaired patients. PMR was issued for the submission of hepatic report from ongoing study. | PopPK ($n=408$) Evaluated CrCL range 30–150 mL/min | No sig | Label indicates population pharmacokinetic analysis found creatinine clearance did not influence clearance and no dose adjustment is necessary. |

[a]*U* unbound concentrations, *T* total, *ND* not determined, *NC* inconclusive, *Not sig* result not clinically significant, *NR* not reported, *Mild/Mod/Sev/ESRD/CD* mildly/moderately/severely impaired/end-stage renal disease/chronic dialysis, *CrCL* creatinine clearance & Reported as relative change in exposure (AUC) from unimpaired groups

in the guidance were applied, or a variation of the NCI criteria using total bilirubin (TB) and liver transaminases (AST and ALT) were employed. For reference, mild hepatic impairment is defined as TB ≤ ULN and AST > ULN or TB > 1.0 to 1.5× ULN and any AST or AST > ULN. Moderate hepatic impairment is TB >1.5 to 3× ULN and any AST; severe hepatic impairment is TB >3 × upper-limit of normal (ULN) and any AST. Most of the small molecules represented in this review included criteria for participation in the pivotal study that limited TB to ≤1.5× ULN, and AST/ALT ≤ 2 to 3× ULN, except where a subject had liver metastases, and the transaminase levels were permitted to be ≤5× ULN. Since inclusion and exclusion criteria for participation in any clinical study varied by product, and in order to provide for the simplest presentation of the data across projects, this review attempts to categorize to the closest impairment group where these criteria were not strictly followed.

Overall, when sponsors presented information regarding the impact of organ impairment on the exposure to drug, they applied one of three approaches: population pharmacokinetics, dedicated renal or hepatic clinical study, or a post hoc analysis of clinical pharmacokinetic data taken from the patient studies. Most frequently, sponsors focused on presenting population pharmacokinetic assessment of the clinical data in renally and hepatically impaired patients. This was especially true for antibodies; and of the nine products represented, only blinatumomab used clinical data in a non-compartmental pharmacokinetic assessment of exposures in renally impaired patients to measure the impact on exposure to the drug. All other antibodies presented population pharmacokinetic assessments for labeling (hepatic $n=4$; renal $n=6$) or presented no information at all (hepatic $n=5$; renal $n=2$).

For small molecules, the preferred approach was different for each impairment group: hepatic impairment was most often assessed by dedicated study and renal impairment was assessed by population pharmacokinetics. Of the 31 small molecules 14 and 9 conducted dedicated studies for hepatic and renal, respectively, while 8 and 20 were assessed for labeling by population pharmacokinetic assessment, respectively. The remainder presented no analyses or dedicated studies (hepatic $n=8$; renal $n=3$).

As indicated above, monoclonal antibodies approved since 2009 did not present data from formal renal or hepatic clinical trials in their initial submission. For therapeutic proteins, the dominant method for excretion is by systemic proteolytic degradation and very little measurable unchanged drug is excreted in the urine. There is no anticipation for decreased renal function to decrease the clearance or alter the exposure of large proteins with molecular weights greater than the filtration cutoff of approximately 60 kDa. Those below the cutoff are subject to both filtration and catabolism via cellular uptake and degradation in renal tubular cells. Similarly, hepatic impairment would not be expected to influence peptide and protein exposure unless the biologics were excreted significantly in the bile (e.g., octreotide). For large monoclonal antibodies, these studies are viewed as unnecessary; and the reviewers often make note of this (e.g., ramucirumab, dinutuximab, ofatumumab). Hence, either no study was conducted or a population pharmacokinetic assessment was performed on the clinical data to examine for relationships of transaminase or

creatinine clearance with drug clearance. In all population pharmacokinetic assessments measuring the impact of organ impairment on the pharmacokinetics of antibodies, none were significant, and in no case were post-marketing requests issued for new studies or additional data.

The only antibody where clinical pharmacokinetic data was examined was blinatumomab (MW 55 kDa), where a standard non-compartmental analysis was used to evaluate changes in drug clearance by degree of renal impairment. The analysis for blinatumomab was conducted on data taken from 298 patients from four clinical trials. Impairment groups were defined by creatinine clearance as follows: normal renal function was ≥90 mL/min ($n=215$), mild renal impairment was 60–89 mL/min ($n=62$), and moderate renal impairment was 30–59 mL/min ($n=21$). The results showed decreased blinatumomab clearance with decreasing renal function, with clearance values of 3.3 (CV = 96 %), 2.2 (CV = 79 %), and 1.6 (CV = 62 %) L/h for the normal renal function, mild and moderate renal impairment groups, respectively. This finding was also confirmed in the population pharmacokinetic analysis where a 50 % drop in the creatinine clearance was associated with a 30 % increase in drug exposure. The reviewer, however, concluded that with the high inter-subject variability observed for the all groups, "the clearance ranges estimated in subjects with mild and moderate renal impairment were essentially within the range estimated in subjects with normal renal function." However, and possibly more important, an analysis of the safety and efficacy data performed for the same impairment groups found comparable efficacy results. Though there was an increase in some adverse events, dose interruption, and discontinuation due to adverse events, these data were confounded by the significantly increased ages of the impaired groups (62 and 69 years vs. 32 years for the unimpaired). Ultimately the drug was labeled to indicate that no dose adjustment was needed for patients with baseline creatinine clearance equal to or greater than 30 mL/min.

Population pharmacokinetic assessment of organ impairment continues to be the preferred method for antibodies, even for updates to the labels following first approval. The most updated labels (as of June 2015) for ramucirumab and ipilimumab have focused their recommendations based on the population pharmacokinetic analyses for both antibodies. The initial submission for ramucirumab contained no assessments for either renal or hepatic impaired populations. The review indicated that neither was necessary, since, as a large monoclonal antibody, it was not expected to be eliminated by the kidney or metabolized by the liver. The new ramucirumab label has been updated for the population pharmacokinetics analyses conducted on both hepatic and renal impairment; and the results indicate no dose adjustments are necessary for mild or moderate hepatic impairment, or for any degree of renal impairment. The label for ipilimumab was updated to provide detail for updated population pharmacokinetic analyses of the clinical data, and the new labeling language maintains the conclusions for renal impairment, but provides statements of comparability for mild hepatic impairment and normal patients only. The new label indicates patients with moderate or severe hepatic impairment have not been studied.

For small molecules, both dedicated studies and population assessments play significantly in the final labeling for hepatic impairment. Fourteen compounds presented full or reduced dedicated clinical hepatic study results to provide for the labeling of the drug at the time of first submission review. Post-marketing requests were issued where data was preliminary or the study was ongoing (ibrutinib and pazopanib) or where the reduced study design did not provide for information in patient groups felt to be an important part of the indication; requests for studies collecting information for severely hepatically impaired subgroups were issued for enzalutamide, abiraterone, and everolimus. For those small molecules whose labels were supported by population pharmacokinetic analyses, post-marketing studies were issued where ongoing studies were being conducted (palbociclib, belinostat, ceritinib, and cabozantinib), where the data was felt to be insufficient for conclusive interpretation (moderate and severe impairment for dabrafenib and romidepsin, severe impairment for vemurafenib, and multiple-dose assessment of crizotinib), or where the sponsor requested (trametinib). For all compounds where no data were presented, a post-marketing request was issued for a study, report (if ongoing), or mass balance study to assess the need for an additional hepatic study. Of the 31 small molecules presented, all who either submitted no data or only population assessments received post-marketing requests. Of the 14 who presented dedicated hepatic studies, only five received post-marketing requests, and two of those were for submission of ongoing studies.

The assessment of the impact of renal impairment on the exposure of small molecules was primarily by population pharmacokinetic methods. In most cases (14/20), these assessments were sufficient for labeling and did not require additional post-marketing requests. Where dedicated studies were conducted, the results were employed for the determination of dose adjustments, if needed (panobinostat, lenvatinib, idelalisib, vandetanib, and abiraterone) and where data was inconclusive or insufficient, post-marketing requests were issued (olaparib, carfilzomib, and regorafenib). Where no studies or analyses were presented, post-marketing requests were issued for the renal impairment studies or mass balance study to determine the need (pomalidomide and omacetaxine, respectively). No renal study was presented in the original submission for ponatinib, and though the FDA reviewer (and label) ultimately recognized the potential for renal impairment to impact the exposure of drug via impairment of metabolic clearance—the review contains the following unusual comment with regard to timelines:

> *While this issue could have been further explored by the reviewer using a mechanistic approach (see Sect. 4.2), the truncated review timeline did not permit this to occur*

If assessed by the requirement of other compounds providing the same limited information, one would have certainly expected a post-marketing request for a renal study evaluating the impact of impairment on ponatinib exposure. None, however, was issued.

In cases where safety data clearly indicate an impaired subgroup may be at risk, the results of a dedicated pharmacokinetic study will be secondary to any recommendations for treatment. For instance, the exposure to idelalisib increased up to

1.7-fold in subjects with moderate or severe hepatic impairment. Because patients with baseline TB greater than 1.5× ULN and AST or ALT values greater than 2.5× ULN were excluded from confirmatory trials, and because fatal hepatotoxicity had occurred in patient trials, safety and efficacy data were not considered sufficient for the recommendation of a dose in hepatic impairment. Instead, the label provides instruction for dose modifications based on ALT/AST measures.

The inclusion and exclusion criteria employed in the confirmatory clinical studies effectively excluded participation of most patients with moderate and severe hepatic impairment, as can be seen in the labeling recommendations provided in Table 12.6. However, where sponsors provided dedicated studies to measure the impact of hepatic impairment on the exposure to drug, labels can reflect these findings. Lenvatinib and bosutinib, for instance, conducted dedicated hepatic impairment studies that included severely impaired subjects. Both products excluded participation of patients with severe hepatic impairment from confirmatory studies. The 2.7-fold increase in unbound concentrations of lenvatinib, and the overall roughly twofold increase observed in any hepatic impairment with bosutinib led to labeling instructions for reduced doses in these groups for both drugs.

Curiously, vandetanib also provided data from a full hepatic impairment study which, based on the results, would indicate that no dose adjustment would be necessary in this population. Vandetanib pivotal patient studies used the same exclusion criteria for hepatic function as bosutinib (TB ≤1.5× ULN and ALT/AST ≤ 2.5× ULN or ≤5× ULN if subject has liver metastases). Population pharmacokinetic assessment of the clinical data also supported the lack of an impact of mild hepatic impairment on the exposure to the drug. However, during the review the sponsor proposed a label indicating *the drug would not be recommended for use in patients with hepatic impairment* because of the limited clinical data in these patients. This highly conservative approach by the sponsor at the time of submission review had the overall impact of disregarding the results of the dedicated study. The drug is not recommended for use in moderately or severely hepatically impaired patients. This same approach was not used, however, for labeling of vandetanib with regard to the results of its dedicated renal impairment study. Though the pivotal trial excluded patients with creatinine clearances calculated to be below 30 mL/min (severe renal impairment), the label reflects the dose reduction in severely (and moderately) impaired patients based on the 1.4-fold increase in exposure measured in the renal impairment study.

Full or reduced renal impairment studies were conducted and the data was provided as a part of the original submission for panobinostat, lenvatinib, idelalisib, vandetanib (mentioned above), and abiraterone. For lenvatinib and vandetanib, patients with creatinine clearance values below 30 mL/min (severe impairment) were excluded from participation in the pivotal clinical trials. For abiraterone, patients with creatinine clearance values less than 60 mL/min were excluded. Panobinostat's inclusion criteria of serum creatinine 1.5× ULN *or* creatinine clearance greater than 60 mL/min ultimately provided for the participation of mild, moderate, and some severely impaired patients in the confirmatory trial. Nevertheless, the dedicated renal studies for these compounds provided the necessary information

for the selection of doses in the impairment groups, including those excluded from participating in the pivotal trials (severely impaired for all, and additionally for moderately impaired patients to receive abiraterone).

## 6 Assessment of QTc Prolongation Potential

There are a number of ways in which sponsors have provided for the evaluation of the drug concentration related effects on QTc prolongation. For the oncology drugs in this review, data were collected from dedicated thorough QTc (TQT) studies, from dedicated but uncontrolled clinical pharmacology studies in patients, from metabolic or food-interaction studies, and most commonly, as secondary or exploratory objectives in ongoing patient studies. A few studies, particularly those focused on clinical pharmacology objectives, employed the use of healthy volunteers. Most, however, were collected from patients in one or more clinical studies. Guidelines (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use 2005) indicate that systemically available new agents should undergo electrocardiographic evaluation in clinical studies, and advocate the conduct of a dedicated and positively controlled, TQT study to evaluate the concentration-effect relationship between QTc and exposure. However, for numerous reasons explored elsewhere in this book (see Chap. 5), this approach cannot be easily employed for oncology studies.

The methods for analysis and collection of data to support the QTc assessment for oncology agents are expected, however, to follow the principles outlined in the E14 guidance. In a practical sense, this means that studies will include serial, replicate ECGs (usually triplicate) and time-matched pharmacokinetic samples collected at time of maximum expected drug concentration ($C_{max}$) and for a suitable duration of time to permit the evaluation of delayed cardiographic effects. While a positive control for QTc-prolongation is desirable to demonstrate the validity of the results, it is not frequently employed for oncology agents.

Where clinical safety data do not indicate a concern for arrhythmic effects, the results of the QTc assessment generally lead to labels based on the strength of the results defining the relationships. The largest upper bounds of the two-sided 90 % confidence interval (which is equivalent to the one-sided 95 % confidence interval) for the mean difference between drug and placebo at any time-point is used to define the magnitude of the effect. If this value is below 10 ms in a positively controlled study, the drug is labeled as having no clinically important effect (e.g., idelalisib, bosutinib, vismodegib, everolimus). If the study was did not have a positive control, and the value was below 20 ms, the label will indicate "no large change" was observed, but small increases (<10 ms) cannot be ruled out (e.g., axitinib, pertuzumab, ziv-aflibercept, brentuximab). Any impact larger than 20 ms results in warnings, precautions, and other restrictions, including "black box" labeling (e.g., vandetanib).

Based on the submissions evaluated in this review, an analysis of the relationship between drug concentrations and ECG parameters for all new drug approvals has become a standard practice for the industry—including large proteins, where direct ion channel interactions are generally considered unlikely. Nevertheless, all but one of the oncology drugs approved since 2009 have either included an analysis or provided evidence that a study was planned or ongoing at the time of submission.

Failure to provide an appropriate analysis of clinical patient data at the time of submission has resulted in a request for a post-marketing commitment. Eleven of the 44 approved oncology drugs in this review were issued post-marketing requests for QTc studies or analyses. Of these 11, only ofatumumab provided no analysis for QTc prolongation potential at the time of submission. Where a study was ongoing or planned, a request was written for submission of the final results. The seven sponsors conducting studies at the time of their submission: trametinib, pomalidomide, dabrafenib, regorafenib, crizotinib, cabazitaxel, and pazopanib, received this type of request. Three applicants submitted analyses considered insufficient for evaluation of the prolongation potential (ibrutinib, romidepsin, and ponatinib) and they were issued post-marketing commitments to collect new data from additional or ongoing studies.

When analyses did not follow the principles of the ICH-E14 guideline, post-marketing requests for the conduct of appropriate studies or analyses usually followed. Ibrutinib was issued a request to conduct a post-marketing TQT study, when the results of their analyses were rejected as inconclusive because they did not collect appropriate baseline ECGs and triplicate ECGs in the patient studies used in their analysis. Likewise, a request for a new analysis of patient data for romidepsin was made when the submitted analyses were considered inappropriate due to failure to collect adequate time-matched pharmacokinetic samples in enough patients to provide for definitive conclusions.

During the review of their submission, the sponsor for ponatinib submitted an analysis of the QTc prolongation potential of the drug based on data taken from the dose escalation trial. This trial included doses as high as 60 mg QD which were 50 % higher than the sponsor's recommended therapeutic dose. While these data supported the reviewer's conclusion that no large QT prolongation effect was present, the safety results in a single arm phase 2 trial included reports of cardiac conduction defects and QT prolongation in a few patients. It was, therefore, felt that additional analyses from the phase 3 study would be warranted, and it was requested as a post-marketing commitment.

A post-marketing study was considered for radium-223, but ultimately it was not requested. The study performed to assess the impact of drug on QT-prolongation was considered insufficient to measure the effect, because it did not collect matched pharmacokinetic samples and the ECGs were only collected for 4–6 h after injection. A formal request to conduct a new study was not made at approval, however, because (1) there were no cardiac adverse events to indicate concern in the clinical studies, (2) radium-223 was rapidly cleared from the circulation with only 4 % of the radioactivity at 4 h, and (3) the in vivo distribution of radioactivity indicated a low affinity for the heart. It was labeled to indicate that no large changes in mean

QT interval were observed in a subgroup analysis, but also stated that the potential for delayed effects on the QT interval were not evaluated.

A variety of successful study approaches have been employed to evaluate the proarrhythmic potential of a new oncologic agent. Five sponsors provided dedicated TQT studies with their initial submissions. Lenvatinib, vismodegib, bosutinib, idelalisib, and everolimus provided details for QT trials in healthy volunteers receiving doses of the drug, placebo or moxifloxacin 400 mg as a positive control. Doses for lenvatinib were 32 mg (about 30 % higher than therapeutic dose), for everolimus were 20 and 50 mg (two and fivefold higher than therapeutic doses), for idelalisib the highest dose was 400 mg (2.7-fold higher than therapeutic dose) and were 150 mg vismodegib (equal to the therapeutic dose). For bosutinib, the sponsor administered the therapeutic dose of 500 mg, however, took advantage of a metabolic drug interaction by administering the dose with 400 mg ketoconazole, and was thereby able to achieve a 6.5-fold increase AUC and 2.9-fold increase in $C_{max}$. All the studies concluded there was no significant clinical impact of the drug on QT-prolongation, as all found the upper bounds of the 90 % confidence interval for the change in QTc from baseline to be below 10 ms (Note: the upper bound was found to be 10.3 ms for bosutinib, however, this was not felt to be meaningful). However, because clinical safety data taken from the lenvatinib confirmatory studies indicated that QTc prolongation was observed at a rate of 8.8 %, a warning in the labeling recommends monitoring electrocardiograms in all patients.

For idelalisib, 46 healthy volunteers received single doses of 150 and 400 mg (2.7-fold greater than therapeutic dose). The drug was administered with a "standard meal," however, since the impact of food was relatively small, one can assume this was to match the clinical instructions that were provided to patients taking the drug in the ongoing confirmatory trials. No important QTc prolongation was detected for either dose; the upper bounds of the two-sided 90 % confidence interval for the mean difference between drug and placebo was below the regulatory threshold of 10 ms.

Two sponsors included evaluation of QTc-prolongation as an objective in drug interaction or food effect studies. These included olaparib and axitinib. For olaparib, ECGs and pharmacokinetics were taken in both the food-effect and the itraconazole drug interaction trials and the data were pooled for analysis. These assessments did not include a moxifloxacin positive control. Because itraconazole inhibits the metabolism of olaparib, an increase in exposure was expected, and a lower dose of 100 mg olaparib (25 % of therapeutic dose) was given. However, since the interaction with itraconazole increased $C_{max}$ and AUC by 1.4-fold and 2.7-fold, the resulting exposures would not be anticipated to greater than those following the therapeutic dose at steady-state. Nevertheless, no clinically relevant (e.g., >10 ms) QT-prolongation was observed. Axitinib evaluated the potential for QTc-prolongation in a randomized, two-way crossover drug interaction study with ketoconazole in 35 healthy subjects. A 5 mg dose of axitinib was administered with 400 mg ketoconazole. However, though a twofold increase in exposure to axitinib was observed due to the metabolic interaction, this exposure was not expected to cover the range of steady-state exposures for therapeutic doses of the drug. The

largest upper bounds of the 90 % confidence interval, however, was only 8.4 ms. Given the study limitations, and the lack of a positive control, the drug labeling states "No large changes in mean QTc interval (i.e., >20 ms) from placebo were detected up to 3 h post-dose."

Most applicants, however, collected the necessary data as part of an ongoing clinical patient study or pooled data from several studies in their development program for presentation in their submission. This was the approach employed for vandetanib, belinostat, and palbociclib. For belinostat, the sponsor provided an exposure-QTc analysis from the combined data of eight clinical studies comprising 380 patients. In addition, ECG information across 13 clinical studies ($N=529$) was also summarized. Based on these analyses, it was concluded that while the potential for QT prolongation with belinostat could not be excluded, a large QT prolongation (e.g., > 20 ms) with belinostat was nevertheless unlikely. The label was written to indicate there was no significant clinical effect on QTc.

For palbociclib, data were pooled from three clinical studies, including the first-in-human study where doses up to 225 mg QD (1.8-fold greater than therapeutic dose) were administered to patients. Pooled data from 184 patients in three clinical studies were analyzed by a linear mixed effects model for QTc and drug concentration. All slopes relating drug concentrations to QTc intervals were found to be significantly different from zero ($p<0.05$), and the sponsor concluded there was a slight positive linear relationship between drug concentration and QTc interval. But they concluded that since the upper bound for the confidence interval did not exceed 10 ms, QT prolongation was not an issue at the therapeutic dose. The FDA reviewer's independent analysis, however, showed that for the 12 patients in the clinical study with the highest steady-state drug exposures for the therapeutic dose, the largest upper bounds of the confidence interval for the mean changes from baseline was 14.2 ms. In addition, without the benefit of a positive control, it is not possible to rule out changes in the range of 10 ms. The drug was labeled has having detected no large change in QTc (>20 ms) for maximal steady-state concentrations of the therapeutic dose.

A significant and sustained concentration-dependent prolongation of QT interval was observed for vandetanib. The sponsor performed and extensive analysis of the clinical data, and concluded from their population pharmacokinetic model that at the maximum steady-state concentration (~800 ng/mL) from daily administration of the 300 mg therapeutic dose, the mean predicted change in QTc would be 33.5 ms. The FDA reviewer's independent central tendency analysis predicted the largest upper bounds of the 90 % confidence interval for the mean change in QTc over time to be approximately 40 ms. The exposure–response analysis for the relationship between change in QTc and concentration, using data from the confirmatory patient study, predicted the mean change for the highest observed vandetanib concentrations to be approximately 35 ms. Because these predictions were based on therapeutic doses, the impact on QTc was also evaluated in patient subpopulations prone to higher drug exposures (e.g., renal impairment, female patients, and patients with low body weight). The reviewer concluded that female patients, those with renal impairment, or patients concomitantly taking metabolic inducers of CYP3A4,

may be prone to a slightly longer QTc prolongation. Vandetanib was labeled with a black-box warning for QT prolongation, a contraindication for patients with congenital long QT syndrome, and a restricted distribution program was implemented as part of a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of the drug.

## 7 Conclusions

We are looking ahead to a time when many common malignancies will become chronic diseases where patients may be treated for many years, and even decades, with targeted chemotherapy. As the effectiveness of our oncology treatments increase, the need for establishing optimum doses and regimens, pharmacokinetics in special patient populations, and understanding the exposure–response relationship with safety measures like QTc can be expected to become a more important part of ensuring patient compliance and maintaining the safety and efficacy for chronic drug treatment. As a result, clinical pharmacology will assume an increasingly more important role in oncology drug development.

In recent years, there has also been a trend toward the development and approval of more oral oncology treatments. With this shift, it becomes necessary to characterize the influences on drug absorption—including those due to food and pH-altering drugs, in order to identify the best conditions that will maintain the benefit–risk ratios established in confirmatory patient studies.

This survey of the FDA Clinical Pharmacology and Biopharmaceutics reviews from the new oncology drug approvals since 2009 indicates that the regulatory expectations in this therapeutic are aligned with these trends. Applicants for new drug approval can expect a comprehensive regulatory review of the exposure–response data for both efficacy and safety for every dossier in order to support dose and regimen selection. For most of the drugs in this review, no relationship could be drawn between exposure and efficacy. But when the results of the reviewer's analyses showed higher exposures were related to an increased incidence of adverse events, the selected dose was questioned. This was especially true when a high rate of dose reduction, interruption, or discontinuation was also observed. Selection of the MTD for any new oncology product will not stand without appropriate justification, exceptional medical need, and/or spectacular efficacy results. Integration of the preclinical pharmacology, clinical pharmacokinetics, and clinical exposure–response data are expected in support of dose and regimen justification.

Characterization of the changes in drug exposure, variability, and tolerability are a necessary component of food-interaction assessment. The potential for concomitant administration of food to reduce variability or to improve tolerability and bioavailability are now recognized as key to selecting an appropriate drug regimen. Where drug solubility is pH dependent, it is expected that sponsors will have evaluated the interaction, first with a proton-pump inhibitor.

Understanding how organ impairment influences pharmacokinetics and drug exposure permits the selection of appropriate doses in these patient subgroups to maintain the expected efficacy and safety profile. For the oncology drug products approved since 2009, the conduct of dedicated organ impairment studies is one method sponsors have employed to collect this information. However, for the characterization of most renal impairment groups, and many hepatic impairment groups, pharmacometric analyses of the exposure data collected in patient trials have replaced the need for some of these dedicated studies. Where sponsors have permitted in their clinical studies the inclusion of patients with broad enough criteria to address the impairment demographic of their target populations, the "classic" dedicated full organ impairment studies would be redundant.

Likewise, collection of appropriate cardiographic and pharmacokinetic data in clinical patient trials has permitted a majority of sponsors to submit pharmacometric analyses for QTc-interval prolongation, without the need for the conduct of a dedicated thorough QTc interval study. As can be seen from this review, submission of an analysis for the relationship between exposure and QTc-prolongation has become a de facto standard of practice among applicants—for both small and large molecules.

The FDA has increased its application of processes for expedited, priority review and breakthrough therapy designation. This can only be expected to continue. To provide the necessary information for the safe and effective, chronic use of these new oncology treatments, sponsors must understand and give appropriate consideration for the expectations of the reviewing authorities as they assemble their drug development plans.

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# Chapter 13
# New Advancements in Exposure-Response Analysis to Inform Regulatory Decision Making

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**Abstract** To date, Exposure-Response (E-R) analyses have been recognized and routinely utilized in regulatory reviews, mainly to address key questions such as whether the proposed dosing regimen for a new drug is optimal or is warranted for further adjustment in specific populations in the context of the overall risk/benefit profile. This chapter will start from a summary of E-R methods commonly used in current applications followed with new methodology development and applications of E-R analyses on other aspects of reviews. Reporting on new methodology development is focused on case–control analyses when drug exposure is confounded with baseline disease status for several antibody oncology drugs. Reporting on applications of E-R analysis in new areas of review falls into using E-R analysis to derive the effect size for the noninferiority trial and subgroup analyses to identify favorable risk/benefit profile in specific population(s). The chapter also mentioned the potential role of E-R analysis in precision medicine by leveraging individual drug exposure to achieve balanced risk/benefit at the individual level.

**Keywords** Oncology • Pharmacokinetics • Pharmacodynamics • Modeling • Simulation • Case control

## 1 Introduction

Drug exposure-response (E-R) analyses for efficacy and/or safety endpoints have been considered as one of the major innovative approaches in modern drug development. One of the pivotal benefits of E-R analysis is to inform drug developers and regulatory reviewers whether E-R supports the dosing recommendation or whether there is room for further dose optimization. E-R analyses can be used to address

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whether a reduced dose is needed in the event of a flat E-R relationship for efficacy and a relatively steep E-R relationship for safety endpoints or whether additional therapeutic benefit can be achieved by increasing the dose in the event of a steep E-R relationship for efficacy and relatively shallow E-R relationship for safety. Additionally, E-R analysis allows for the assessment of alternative dosing schemes for special populations or in presence of metabolic drug-drug interactions. A prominent example where E-R analysis served as one on the key reasons for the Food and Drug Administration (FDA) to recommend testing of lower doses in a postmarketing trial was during the approval of vandetanib for medullary thyroid cancer (MTC) in which a steep E-R relationship for safety (QTc prolongation) was observed while the E-R relationship for efficacy (progression-free survival) was flat (Thornton et al. 2012). A recent publication highlights several such cases where E-R analysis was used for regulatory decision making (Minasian et al. 2014).

In confirmatory Phase 3 trials the primary endpoint for approval is often based on traditional statistical analysis using pairwise comparisons between the drug of interest and comparator arm. E-R analysis offers benefits over pairwise comparison in terms of power to detect a statistically significant difference between the drug of interest and the comparator, or between two doses levels of the same drug, and the ability to make inferences about treatment effect at untested doses. Because pairwise comparisons often only focus on data at a specific time point, such as at the end of a clinical trial, pairwise comparisons often require large sample sizes to have sufficient power to detect statistically significant treatment differences. However, given the inherent variability in pharmacokinetics among individuals, a broad range of exposures are achieved for the same sample size and dose levels, as well as the fact that E-R analyses often use more "data" per subject than pairwise comparison, thereby providing more power to detect a relationship through E-R analysis. However, E-R analysis does not provide the same level of evidence as a prespecified statistical analysis does due to the fact that it is often conducted in a retrospective and sometimes exploratory manner. E-R analyses also suffer from the issue of non-randomization of exposures and the validity of the underlying assumptions of the model. Therefore, attention should be paid to these issues when conducting the E-R analysis and interpreting the results.

Simultaneous modeling of exposure-PD response and PD response-clinical response has been considered an ideal approach for dosing regimen justification (Mager et al. 2003). In the case of fingolimod, a drug approved for relapsing remitting multiple sclerosis, an exposure-lymphocyte count (PD response) and lymphocyte count-annualized relapse rate (clinical endpoint) relationship was established. It suggested a lower dose might be as effective as the studied dose in the phase 3 trial and thus a postmarketing commitment was recommended to the sponsor to study lower dose (U.S. FDA 2010). It should be noted that predictive empirical models, as well as all other types of models, rely on the availability of sufficient high-quality data, which calls for well-designed studies with prospectively defined PK, PD, and clinical response endpoints. However, in certain therapeutic areas, application of PK-PD-clinical response models is limited by data requirements and the difficulty in identifying measurable biomarkers that have a clear relationship with the clinical endpoint.

The major goal of this chapter is to provide an overview of currently applied E-R methodologies and advancement in their development, with an emphasis on oncology.

## 2 Traditional Exposure-Response Analysis in the Regulatory Setting

Traditional E-R analysis in the regulatory setting is a task-oriented process designed to address submission-specific regulatory questions of public health interest. These questions often relate to dose optimization or dose selection in subpopulations, as well as in the general patient population. In addition to dose optimization, E-R analysis has been used as supportive evidence of efficacy (U.S. FDA 2003). The E-R analysis of oncology products in Phase 3 confirmatory trials is preferably conducted on the primary clinical endpoint, which is often of time-to-event variable (TTE, e.g., overall survival (OS) and progression-free survival (PFS)), or binary or categorical variable (e.g., objective response rate (ORR)). In most cases, OS and PFS are the preferred endpoints. However, under certain circumstances such as for breakthrough, fast track, accelerated approval applications, ORR has been accepted as a primary clinical endpoint (see the chapter by Ladner in this volume for further details). However, the sponsor is still expected to complete the corresponding phase III study based on the preferred endpoint for full approval. As it is outlined in Sect. 4, there are limited applications of PD biomarkers as surrogate endpoints in oncology. Therefore, E-R analysis is often conducted to examine the relationship between drug exposures to a clinical outcome.

Analysis of the primary endpoint is usually graphically explored and subsequently analyzed with Cox regression in the case of TTE variables, or logistic regression in the case of categorical variables, in either a univariate and/or multivariate manner. The initial graphical exploration of the data is based on the visual assessment of Kaplan–Meier survival curve or observed ORR stratified by predicted or observed PK exposure parameters. Subsequently, a multivariate model-based analysis is often undertaken to assess the E-R relationship after adjusting for other risk factors. Limitations in empirical exposure-response analysis of dichotomous outcomes are discussed in the sections below and proposed corresponding methods to address the limitations are showcased by recent regulatory examples.

## 3 New Advances in Exposure-Response Analysis in the Regulatory Setting: Case Control

Efficacy identified based on an E-R analysis should be carefully examined before its results can be fully trusted. Conventional E-R analyses, such as multivariate Cox and logistic regression models, have limitations that have driven the need for innovative methodologies in the field. For example, it has been found in a few cases

that monoclonal antibody (mAb) exposure was confounded with disease severity, which can be potentially explained by varying target capacity and target-mediated drug disposition (TMDD). Therefore, patients who have low drug exposure may at the same time have high disease severity and consequently less efficacy response. Because of these limitations and under these circumstances, case–control analysis can be used for a more objective assessment of exposure-response.

## *3.1 Case Control*

One caveat associated with E-R analysis noted at the Division of Pharmacometrics at FDA is that it may lead to overestimation of efficacy effect size, especially when drug exposure is confounded with other predictors of efficacy response (Wang et al. 2014a, b; Yang et al. 2013). Various approaches have been employed to address the efficacy-over-estimation problem, as described previously, when the randomization code for treatment assignment is broken. Traditionally, effects of drug exposure and other predictors have been modeled simultaneously with a multivariate Cox model. However, the Cox model, when not fully validated, may not completely eliminate bias in efficacy estimation. Consequently, case–control analysis was introduced to the field of E-R analysis by Yang et al. (2013).

Case–control studies are usually retrospectively performed using observational studies involving two groups of patients, one who have the condition/disease (termed "cases") and one who do not have the condition/disease but are otherwise similar (termed "controls"), with the goal of identifying the casual/confounding factor(s) that may contribute to a medical outcome difference between groups. The use of case–control studies to adjust for measured confounding factors has become increasingly popular in observational studies because they require fewer resources than a randomized controlled trial.

### 3.1.1 Case I: Trastuzumab

Case control reduces bias introduced by an imbalanced distribution of predictors for efficacy across exposure base subgroups. Yang et al. (2013) reported the first E-R analysis incorporating a case–control comparison to evaluate whether the current dosing regimen for Trastuzumab (Herceptin®) in patients with metastatic gastric cancer (mGC) is optimal. As shown by Fig. 13.1, the authors found that after case matching patients with mGC in the lowest quartile for trough concentrations of Trastuzumab in cycle 1 had shorter OS than those in other quartiles based on the Kaplan–Meier survival analysis, suggesting that the patients with the low exposure did not benefit from the addition of Trastuzumab treatment to chemotherapy.

Regulatory Impact: The identified subgroup without survival benefit and the E-R relationship substantiated a postmarketing requirement (PMR) on conducting clinical

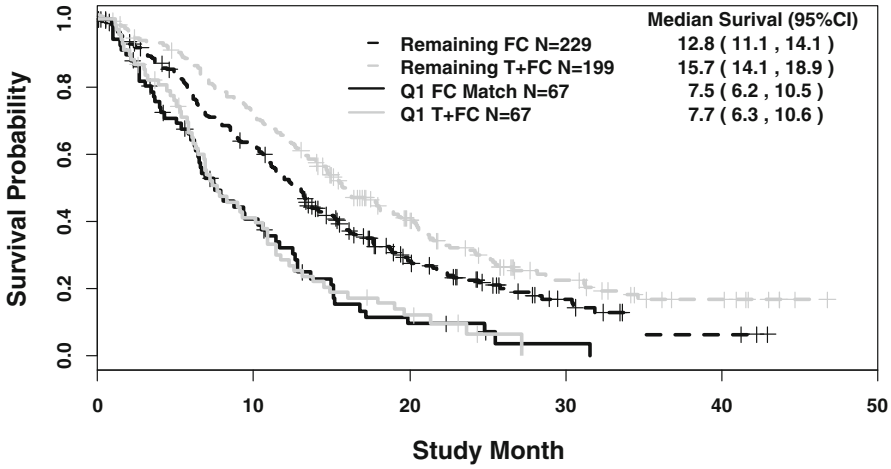


**Fig. 13.1** Kaplan–Meier curves for the matched subgroups. *CI* confidence interval, *FC* fluoropyrimidine and cisplatin, *Q1* quartile 1 for trastuzumab PK exposure, *T + FC* trastuzumab in combination with fluoropyrimidine and cisplatin. Figure adapted from Yang et al. (2013)

trials to identify a treatment regimen with greater exposure and acceptable safety profile, as well as prospectively evaluating whether this treatment regimen will result in survival benefit for the identified subgroup.

### 3.1.2 Case II: Ado-Trastuzumab Emtansine

Wang et al. (2014a) from FDA reported an analysis for ado-trastuzumab emtansine (T-DM1, trade name: Kadcyla). Kadcyla is approved as a single agent for the treatment of HER2-positive, metastatic breast cancer patients who have previously received trastuzumab and taxane, separately or in combination. Kaplan–Meier survival analyses stratified by T-DM1 trough concentration on day 21 of cycle 1 were performed for overall survival (OS) and progression-free survival (PFS). Furthermore, multivariate Cox proportional hazard analysis was conducted adjusting for known baseline risk factors. Case–control analysis was employed internally to further assess the E-R relationship. The results indicated that after adjusting for baseline risk factors, higher T-DM1 exposure is associated with improved efficacy. These findings suggested that there may be an opportunity to optimize T-DM1 dose in the patient subgroup with low T-DM1 exposure for improved efficacy with acceptable tolerability.

Regulatory Impact: A postmarketing commitment was issued that recommended sponsor to conduct an additional E-R analysis based on the ongoing phase 3 trial in metastatic breast cancer (Hoffmann-La Roche 2011; U.S. FDA 2014). The results of the E-R conducted, as described above, along with the analysis to be conducted

using data from the ongoing phase 3 trial, will be assessed to determine how the dose can be optimized in patients with metastatic breast cancer who have lower exposure to T-DM1 at the approved dose.

### 3.1.3 Case III: Ramucirumab

Ramucirumab (trade name: Cyramza) was approved by the FDA for the treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma in combination with paclitaxel after prior fluoropyrimidine- and platinum-containing chemotherapy. Pharmacometric reviewers at the FDA conducted the combination of E-R analysis and case–control comparison to assess the proposed Ramucirumab dosing regimen (Casak et al. 2015; Jin et al. 2015).

Regulatory impact: The exploratory E-R analyses showed a decreased OS effect in patients with lower ramucirumab exposures. An incremental OS benefit was observed with increasing exposure of ramucirumab after case control, suggesting that patients with higher ramucirumab exposure may derive more benefit from the addition of ramucirumab to paclitaxel. Exploring alternative dosing regimens of ramucirumab with greater exposure and acceptable safety profiles is needed. A post-marketing clinical trial is recommended to explore the benefits and safety of a higher dosing regimen of ramucirumab.

### 3.1.4 Summary for Case–Control Analysis

Although having many advantages, Case–Control analysis has its limitations. A case–control study cannot replace a randomized study and thus still bears certain bias due to imbalanced distribution of undiscovered predictors. Further, its use is still relatively new and there are not many publications regarding the degree of objectivity of Case–Control analysis under various scenarios. In the same time, although Case Control can only be employed to derive a more valid assessment of the efficacy size, it cannot be used to predict the increase or decrease of drug efficacy for a different dosing regimen without the support of clinical data. Therefore, there is still a need to develop valid models that can be used to assess the effects of different risk factors.

## *3.2 Utility of E-R Analysis to Derive the Effect Size for the Noninferiority Trial*

As previously mentioned, the objectives of E-R analyses are largely focused on dose selection and justification in the overall population and subgroups at each phase of clinical development and at the time of submission of the New Drug Application. To the best of our knowledge, we are not aware of any examples where

E-R analysis was utilized to derive the effect size in the case of oncology drug approvals. However, in a recent example in the area of transplant medicine, an innovative E-R approach was utilized to derive the effect size (M1) of a noninferiority (NI) margin (Wang et al. 2014b). This example in transplant medicine can shed light on novel benefits of E-R analysis in deriving effect size in other therapeutic areas.

Everolimus (EVR) is a macrolide immunosuppressant and an inhibitor of the mammalian target of rapamycin (mTOR). In 2011 an indication was proposed for use in combination with reduced dose tacrolimus (TAC) and corticosteroids to prevent organ rejection in adult liver transplant recipients. The benefit of EVR introduction may address the medical need of renal function maintenance by allowing the reduction or the elimination of TAC early after the transplant. The pivotal study testing this combination was a 24-month, multicenter, open-label, randomized, and controlled study that evaluated two EVR containing dosing arms (EVR + reduced TAC, and EVR + TAC elimination) in comparison to the standard TAC control group. The TAC elimination arm was discontinued due to the high rate of acute rejection. The study was designed as a NI study to support either of the EVR containing arms being noninferior to the standard TAC control group. Due to the safety profile of EVR, the randomization happened 1 month after the transplant. As a result, the randomized patients are a subset of all the patients who received liver transplant and those patients who experienced early graft loss and death (GL/D) were excluded by design. Therefore, it is challenging to estimate the NI margin as the effect size (M1) between the standard TAC treatment and a putative placebo treatment (reduced TAC without adding EVR) in such a subset of patients is unknown. The FDA disagreed with the sponsor's estimate for the NI margin to be 12 % from a statistical perspective. As shown in Fig. 13.2, the wide range of TAC trough exposures in the standard TAC control arm provided a

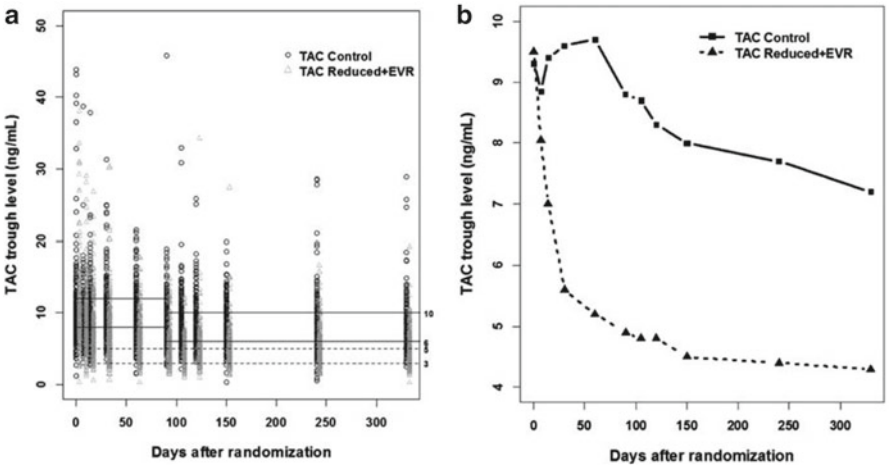


**Fig. 13.2** Time course of TAC trough level (**a**): individual observed values with the *horizontal lines* representing the target ranges, *solid lines* for TAC control arm, and *dashed lines* for TAC reduced + EVR arm; (**b**): median values)

unique opportunity to use E-R analysis to derive M1, which can be used for deriving the NI margin (M2) in the pivotal trial.

E-R analysis was conducted with data from patients in the TAC control arm having the same characteristics as patients in the investigated new regimens (i.e., EVR + reduced TAC) due to the randomization. Therefore this E-R based approach does not bear the burden of proving constancy (i.e., constancy assumption), which is a common concern for using historical data to derive M1.[1]

The major concern for E-R analysis is whether TAC exposure is confounded with certain risk factors as the TAC exposures were not randomized within the TAC control arm. There are two potential ways of confounding. One possible confounding is that the patients with low risk had high exposure while the patients with high risk had low exposure. This type of confounding is of real concern because the E-R slope would be overestimated if the confounded risk factors cannot be appropriately adjusted in the model. As a result, M1 will be overestimated and if a NI margin is derived based on this M1, a treatment that may be inferior to the control arm could be approved as a NI treatment. The other possible confounding is the opposite: patients with a low risk for the composite event received low exposure while the patients with high risk for the composite event received high exposure. In this case, the E-R slope would be underestimated if the confounded risk factors cannot be appropriately adjusted in the model and M1 will be underestimated and a conservative NI margin will be derived under such conditions. Data exploration in this pivotal trial suggested that those patients with higher risk for the composite event tended to have higher TAC exposure. Therefore, the confounding relationship in this particular E-R analysis favors a more conservative M1 estimate, which is desirable from a regulatory perspective.

A Cox model with TAC concentration as a time-dependent covariate was utilized in this E-R analysis. Given the planned decreasing TAC concentration over time and the observed decreasing median TAC concentration over time, it is not appropriate to use the time-normalized exposure concentration (average concentration between randomization and the time when an event or censoring happened) as a covariate for each patient in an E-R analysis. By design, those patients who will not experience the composite event will tend to have a lower average TAC concentration while those who will have early events will tend to have a higher average TAC concentration. Therefore, such an E-R analysis is not appropriate. In order to assess the impact of changing TAC concentrations on the risk of experiencing the composite event, TAC concentration was treated as a time-dependent covariate in the Cox model. A regular Cox proportional hazard model would assume a linear functional form for TAC exposure. However, a nonlinearity test implemented in the smoothing spline fit for the Cox model revealed that the relationship between the log-hazard and the time-dependent TAC exposure is nonlinear (Fig. 13.3). Therefore, a Cox model with TAC concentration as a time-dependent covariate of nonlinear form was developed and was used to predict the difference between the two survival probabilities under two different TAC exposure

[1] Under constancy assumption, the active control drug would have shown same efficacy as it did in historical trial(s).

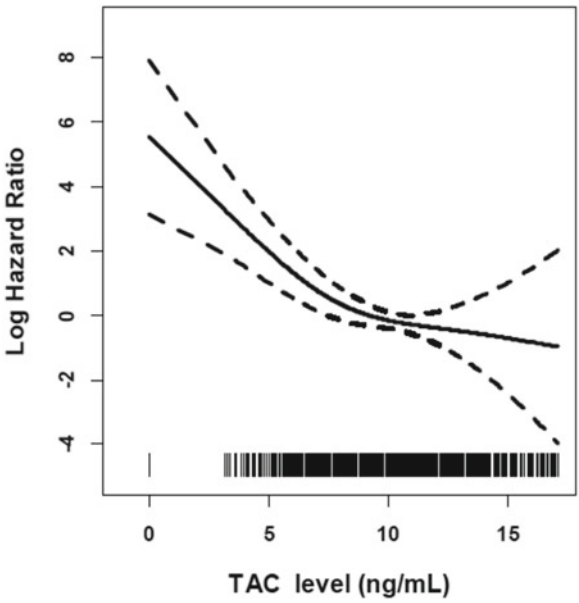


**Fig. 13.3** Nonlinear relationship between log-hazard and time-dependent TAC concentration by Cox model

distributions (standard exposure and reduced exposure). The median difference from 1000 simulations was determined as a reasonably conservative point estimate of M1, which can be used to derive M2 (the NI margin).

This particular case highlights advancements in E-R analysis in both technical and regulatory aspects. A novel pharmacometric approach was applied to derive a new margin so that the observed efficacy results became interpretable. This novel analysis was an important contributor to the "totality of evidence" approach that led to the approval of everolimus for the proposed indication.

## *3.3 Subgroup Analysis*

Subgroup analysis, in the context of study design and data analysis, refers to investigating treatment effects in well-defined subsets of the trial population, the results of which are usually presented as a forest plot. Subgroup analysis is an integral part of clinical trial planning, analysis, and inference that follows the inspection of the primary outcome of the trial (Committee for Medicinal Products for Human Use (CHMP) 2014). In general, the objective of a subgroup analysis is to either evaluate the consistency of the benefit-risk profile in multiple subgroups in a successful clinical trial or to identify a potential beneficial subpopulation in a failed clinical trial. Of note, PK exposure is less considered in current subgroup analysis and should be further integrated in future endeavors.

Due to the problems closely related to the multiple tests, however, subgroup analysis results should be interpreted with caution. The more subgroup analyses conducted, the higher the probability of one or more chance findings that may be misinterpreted as clinically directive (Lagakos 2006). A subgroup analysis can be either predefined in the study protocol or conducted in a post hoc manner when a trend is identified for a completed trial. Post hoc subgroup analyses or selective reporting of certain subgroup analyses can be especially misleading (Yusuf et al. 1991). Subgroup analyses will not usually rescue failed trials (Committee for Medicinal Products for Human Use (CHMP) 2014). In very rare circumstances, if a drug gets accelerated approval based on a subgroup analysis of a failed trial, Phase III confirmatory trial(s) using an enrichment design are usually required to secure the regulatory decision.

### 3.3.1 Case I: Gefitinib

In 2003 Iressa (gefitinib) received accelerated approval in the United States (US) as monotherapy for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel therapies. The two Phase 3 studies failed to show a statistically significant improvement in OS versus control (Giaccone et al. 2004; Herbst et al. 2004). A subgroup analyses identified pronounced heterogeneity in survival outcomes between groups of patients, with some evidence of benefit among never-smokers and Asian ethnicity. At the time when this difference was identified, the underlying mechanism was not known. Since the discovery of the common EGFR mutations in 2004 (Lynch et al. 2004), further studies and subgroup analyses have shown that certain EGFR mutations may be a predictive factor for efficacy in the first-line setting (Gridelli et al. 2011). In 2013 efficacy of Iressa as first-line therapy for Caucasians with EGFR mutation-positive advanced non-small-cell lung cancer was confirmed with a response rate of 70 % (95 % CI 61–78) (Douillard et al. 2014).

### 3.3.2 Case II: Nab-Paclitaxel Plus Gemcitabine

Positive findings from a phase III trial led to the regulatory approval of nab-paclitaxel plus gemcitabine as a treatment option for patients with metastatic pancreatic cancer. A total of 861 patients with metastatic pancreatic cancer and a Karnofsky performance status of 70 or greater were randomly assigned (1:1) to receive nab-paclitaxel + gemcitabine (PG) or gemcitabine alone (G). Exploratory analyses of carbohydrate antigen 19-9 (CA19-9) and neutrophil-to-lymphocyte ratio (NLR) were conducted in a post hoc efficacy analysis. The primary efficacy endpoint was OS analyzed by the Kaplan–Meier method. The median OS was longer for PG vs. G alone (8.7 vs. 6.6 months, hazard ratio [HR] = 0.72, 95 % confidence interval [CI] = 0.62 to 0.83, $P < 0.001$). Long-term (>3 years) survivors were identified in the PG arm only (4 %). In pooled treatment arm analyses, higher CA19-9 level and

NLR at baseline were statistically significantly associated with worse OS (Goldstein and El-Maraghi 2015). Due to limitations, the E-R correlation was not available in any of the cases listed in this section. As a typical exposure-response case in oncology, one may refer to a paper about ado-trastuzumab emtansine (Wang et al. 2014a).

### 3.3.3 Case III: Iniparib Plus Gemcitabine/Carboplatin

The effect of iniparib plus gemcitabine and carboplatin (GCI) versus gemcitabine and carboplatin (GC) in patients with metastatic triple-negative breast cancer was compared in a Phase III Study, where 519 patients were randomly assigned (261 GCI; 258 GC). In the primary analysis, no statistically significant difference was observed for neither OS (hazard ratio [HR] = 0.88; 95 % CI, 0.69 to 1.12; $P = 0.28$) nor PFS (HR = 0.79; 95 % CI, 0.65 to 0.98; $P = 0.027$). An exploratory analysis showed that patients in the second-/third-line had improved OS (HR = 0.65; 95 % CI, 0.46 to 0.91) and PFS (HR = 0.68; 95 % CI, 0.50 to 0.92) with GCI. The safety profile for GCI was similar to GC (O'Shaughnessy and Schwartzberg 2014).

## 4 Utility of Pharmacodynamic Markers in Oncology Drug Approval

Approval of oncology drugs has relied on endpoints that show survival benefit for patients. While overall survival is considered the gold standard for evaluating the efficacy of new drugs, it often poses several challenges such as clinical trials that require long-term follow-up and difficulty in interpreting the results due to a large number of cross-overs. Therefore, the recent majority of oncology trials have utilized progression-free survival or time to progression as surrogate endpoints. In general, there has been limited utility of pharmacodynamics markers measured in the blood as surrogate endpoints in the approval of oncology drugs as it is unclear if improvements in these biomarkers predict clinical benefit. However, in hematological indications such as treatment of neutropenia in cancer patients, pharmacodynamic marker based endpoints were utilized as secondary endpoints in the registration trial. In the Phase 3 trial for Tbo-filgrastim (Granix), depth of absolute neutrophil count (ANC) nadir and time to ANC recovery were assessed as secondary endpoints. The primary endpoint was the duration of severe neutropenia (DSN) which is defined as the number of days with grade 4 neutropenia with an ANC $<0.5 \times 109/^{9}$L. In 2012, eltrombopag, a thrombopoietin receptor agonist, obtained approval for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy (Promacta label 2014). PK/PD modeling based on platelet counts was utilized to justify the starting dose recommendations of eltrombopag in specific populations (east Asians, hepatic impairment). Another example is argatroban, a synthetic thrombin inhibitor, which is approved as an anticoagulant for prophylaxis or treatment of thrombosis in adult

patients with heparin-induced thrombocytopenia (HIT), as well as in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (Argatroban label 2011). The starting dose approved in adults for HIT is 2 μg/kg/min as a continuous infusion. PK/PD modeling based on a coagulation biomarker (activated plasma thromboplastin time, aPTT) was utilized to derive dosing recommendations in pediatrics with HIT or Heparin-Induced Thrombocytopenia and Thrombosis Syndrome. The effect on aPTT was found to be concentration-dependent. Dosing recommendations were based on a goal of aPTT prolongation of 1.5–3 times the baseline value and avoidance of aPTT > 100 s. Simulations were conducted using the established PK/PD model to show that a dose of 0.75 μg/kg/min in pediatric patients was comparable in performance to 2.0 μg/kg/min approved in adults for attaining target aPTT and risk for bleeding (Madabushi et al. 2011).

While the utility of biomarkers as surrogate has been limited, biomarkers are being utilized significantly for defining the inclusion criteria in clinical trials and ultimately defining the patient population intended for a particular drug. For example, Herceptin is approved for the treatment HER2 overexpressing breast cancer and gastric cancer patients. In this case, positive Her-2 expression is needed for treatment. Similarly, Crizotinib, a kinase inhibitor was approved for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive. As of March 2015, publically available information at the FDA website (http://www.fda.gov/drugs/sciencereresearch/researchareas/pharmacogenetics/ucm083378.htm) states that 41 oncology drugs have relevant biomarker information incorporated in the label.

Given the limited utility of pharmacodynamics markers in drug approval, E-R analysis from a regulatory perspective during the review of NDA and BLA has primarily focused on clinical endpoints as described in Sect. 3. However, biomarker response analysis, e.g., tumor size as a biomarker, can play a critical role in early drug development in terms of screening candidates, optimizing trial design and dose selection. To this end, data from four non-small-cell lung cancer (NSCLC) registration trials was used to develop a relationship between tumor size and survival (Wang et al. 2009). Similar models were also developed for thyroid cancer, multiple myeloma and colorectal cancer (Bruno et al. 2011; Claret et al. 2009, 2010a, b). Additionally, biomarkers such as tumor volume are likely to play a key role in approval for rare diseases where a large trial assessing PFS or survival is not feasible. An example is the accelerated approval of everolimus in patients with subependymal giant-cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) not amenable to curative surgical resection which was based on reduction in the volume of the largest SEGA lesion (primary SEGA tumor) as determined by magnetic resonance imaging. The full approval that was later granted was based on durable objective response, as evidenced by reduction in SEGA tumor volume. Eventually, with the advancement in understanding of signaling pathways involved in cancer and better target identification coupled with improvement in imaging techniques and in cell- and tissue-based assays it may be possible that PD markers will have a critical role in oncology drug approval in the future. Consequently PK-PD analysis will influence not only trial design but approval decisions.

## 5 Summary

E-R analyses have been routinely applied in regulatory reviews to address key questions such as whether the dosing regimen for a new drug is optimal in terms of risk/benefit for every patient. Different from the traditional dose–response analysis, E-R analyses are applied to identify the safe and effective exposure for each patient even though data from most clinical trials are limited to provide sufficient information to derive individual E-R relationships. Such an effort is consistent with the Precision Medicine Initiative advocated by President Barack Obama (Obama 2015). Once a drug product is selected to treat a certain disease, drug exposure becomes the most important factor to be optimized in order to achieve balanced risk/benefit at the individual level. Despite the challenges to derive the safe and effective exposure for each patient based on the data from the typical clinical trials, advances in E-R analyses, combined with novel clinical trial designs, will take us closer to the era of Precision Medicine when a truly individualized regimen can be applied to treat every patient.

**Acknowledgments** Disclaimer: Opinions expressed in this chapter are those of the authors and do not necessarily reflect the views or policies of the FDA.

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# ERRATUM TO

# Pharmacokinetics and Pharmacodynamics of Tyrosine Kinase Inhibitors

**Ana Ruiz-Garcia and Shinji Yamazaki**


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In the chapter, 'Pharmacokinetics and Pharmacodynamics of Tyrosine Kinase Inhibitors', the authors as stated in the uncorrected versions are Ana Ruiz-Garcia and Kenji Yamazaki. Please have it be noted that the correct spelling of the second author's name is Shinji Yamazaki.

The name Shinji Yamazaki also replaces the name of Kenji Yamazaki on the list of contributors.

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