Chapter 6
Role of HSP90 Inhibitors in the Treatment of Cancer

Geraldine O'Sullivan Coyne, Cecilia Monge, and Alice P. Chen

Abstract The 90-kDa heat shock protein HSP90 is a member of a highly evolutionarily conserved class of molecular chaperone proteins indispensable for the development of cancer; when activated by cellular stress, HSP90 stabilizes oncogenic substrate "client" proteins involved in cellular processes that promote tumorigenesis. HSP90 inhibition attenuates this stabilization of aberrant client proteins in tumor cells, allowing for simultaneous targeting of multiple pathways involved in cancer cell survival. HSP90 inhibitors have been assessed as potential oncologic therapies in several preclinical and clinical studies. Although preclinically promising results have been measured, these results have not translated yet into major clinical efficacy. Combinations of HSP90 inhibitors with approved and investigational oncology drugs may represent further opportunities for the use of these agents in patients with cancer. This chapter reviews some of the important early clinical milestones observed in studies of first- and second-generation HSP90 inhibitors used as single agents and in combination. In the conclusion, possible reasons for the lack of therapeutic benefit in clinical studies are considered.

Keywords Angiogenesis · Heat shock protein 90 · HSP90 inhibitor · Metastasis · Molecular chaperone · Oncogenic driver

Authors Geraldine O'Sullivan Coyne and Cecilia Monge have equally contributed to this chapter.

G. O'Sullivan Coyne · C. Monge · A. P. Chen (✉)
Division of Cancer Treatment and Diagnosis and Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
e-mail: chenali@mail.nih.gov

A. A. A. Asea, P. Kaur (eds.), *Heat Shock Protein 90 in Human Diseases and Disorders*, Heat Shock Proteins 19,
https://doi.org/10.1007/978-3-030-23158-3_6

Abbreviations

AE	Adverse event
ALK	Anaplastic lymphoma kinase
BRAF	Serine/threonine-protein kinases B-Raf
CDK	Cyclin-dependent kinase
CRAF	Serine/threonine-protein kinases C-Raf
CRC	Colorectal carcinoma
DLT	Dose-limiting toxicity
EGFR	Epidermal growth factor receptor
EMT	Epithelial-to-mesenchymal transition
GDNF	Glial cell line-derived neurotrophic factor
HER2	Human epidermal growth factor receptor 2
HGF	Hepatocyte growth factor
HSP	Heat shock protein
HSP90	Heat shock protein 90
MBC	Metastatic breast cancer
MTD	Maximum tolerated dose
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
TNBC	Triple-negative breast cancer

6.1 Introduction

The development of malignancy in humans is a stepwise process involving both genetic and epigenetic events that drive the transformation of normal cells. Apart from late detection, other factors such as immune evasion and drug resistance also contribute to the lack of effective treatment for many patients with advanced disease, making cancer a leading cause of mortality, with an estimated 9.6 million deaths projected worldwide for 2018 (Bray et al. 2018). Despite significant efforts and advances from the research community to discover and develop new anti-cancer drugs, there continues to be a need for novel, effective oncologic treatments.

6.2 HSP Deregulation and Cancer Development

Heat shock proteins (HSP) are highly conserved, ATP-dependent chaperone molecules that stabilize key proteins (or "client proteins") involved in cellular signal transduction and homeostasis, enabling cells to survive diverse stressors and death stimuli (Soga et al. 2013, Chatterjee and Burns 2017). Mammalian heat shock

proteins are classified into six families based on their molecular sizes; well-studied HSP family members include HSP90, HSP70, and HSP27 (Wang et al. 2014). HSP90 modulates hundreds of protein substrates, making it a key regulator of diverse cellular processes such as protein folding, immune regulation, stress response, and DNA repair (Graner 2016; Wu et al. 2017). Approximately 60% of the human kinome is reported to be associated with HSP90, and 30% of E3 ubiquitin ligases and a small fraction of human transcription factors also depend on HSP90 for activity (Taipale et al. 2012). It has been a challenge to precisely define HSP90 client proteins, however, as the binary classification of intracellular proteins as clients or nonclients has been questioned in light of the outcomes of sophisticated high-throughput HSP90 interactome studies demonstrating a continuous distribution for HSP90 binding affinity (Taipale et al. 2012).

For cancer cells within a rapidly proliferating cellular environment, metabolic need and proteolytic stress create a unique dependence on heat shock proteins such as HSP90, as many client proteins are involved in cellular processes (such as cell survival and proliferation) that can promote tumorigenesis if dysregulated (Rappa et al. 2012). HSP90 is overexpressed in many types of cancers (Yufu et al. 1992; McCarthy et al. 2008; Patel et al. 2014) and has been shown to be a negative prognostic factor in some malignancies (Burrows et al. 2004; Pick et al. 2007; Shi et al. 2014). Furthermore, several HSP90 client proteins are known oncoproteins, including BCR-ABL, human epidermal growth factor receptors 1 and 2 (EGFR and HER2, respectively), cyclin-dependent kinase 4 (CDK4), the serine/threonine-protein kinases B-Raf and C-Raf (BRAF and CRAF, respectively), the hepatocyte growth factor (HGF) receptor MET, the glial cell line–derived neurotrophic factor (GDNF) receptor RET, and protein kinase B/AKT (Jhaveri et al. 2014b).

Dysregulation of other heat shock proteins has also been implicated in the development of cancer and other diseases. For example, HSP70 is strongly associated with carcinogenesis, cancer progression, and poor cancer outcomes for various tumor types (Rerole et al. 2011; Wu et al. 2017). Considered a co-chaperone, HSP70 delivers client proteins such as HER2, CRAF, AKT, and CDK4 to HSP90, thereby promoting survival through the inhibition of both cell senescence and apoptotic pathways (Wu et al. 2017). Indeed, the interaction between HSP70 and HSP90 forms the core of the "epichaperome" complex, consisting of numerous chaperone and co-chaperone proteins, that promotes tumor survival and is found in over half of cancer cell lines (Rodina et al. 2016). This interplay between HSP70 and HSP90 also renders HSP70-expressing cancer cells more sensitive to HSP90 inhibition (Ghosh et al. 2008; Rodina et al. 2016). However, though strategies targeting various heat shock proteins have been explored, HSP90 inhibition has demonstrably resulted in ubiquitination and proteasomal degradation of client proteins (Whitesell and Lindquist 2005; Zuehlke and Johnson 2010), supporting the premise that oncogenic transformation and progression is deeply linked to HSP90. Thus, targeted inhibition of HSP90 has emerged as a novel anti-cancer therapeutic strategy.

6.2.1 Development of HSP90 Inhibitors as Anti-cancer Agents

HPS90 and its inhibition have been studied extensively over the past two decades. This has led to the development of several clinically viable inhibitors that disrupt the interaction between HSP90 and its client proteins, which occurs via the N-terminal ATPase domain (Soga et al. 2013). These N-terminal domain–binding molecules are denoted as 'classical inhibitors,' though none of these have received regulatory approval to date. HSP90 inhibitors have several advantageous characteristics as potential oncology therapeutic agents. First, the distribution of HSP90 client proteins across several different cell signaling pathways potentially enables simultaneous modulation of multiple pathways by HSP90 inhibitors. Additionally, tumor cells are reportedly more sensitive to HSP90 inhibition than normal cells (Kamal et al. 2003; Chiosis and Neckers 2006). Finally, the unusual pharmacokinetic profile of these agents—i.e., rapid clearance from plasma and normal tissues, together with prolonged, selective retention in tumor cells (Eiseman et al. 2005, Daozhen et al. 2007)—may contribute to an exploitable therapeutic index (Straume et al. 2012).

Upregulation of other heat shock response proteins, in particular HSP70 and HSP27, occurs in response to HSP90 inhibition (Biamonte et al. 2010) and has been postulated as a mechanism of resistance to these inhibitors. While small-molecule inhibitors of HSP70 have also been investigated preclinically (Radons 2016), as of yet, none have progressed to a clinical trial. However, given that the interplay between HSP70 and HSP90 contributes substantially to the role of these proteins in malignancy, the combination of HSP70 and HSP90 inhibitors has been proposed as a strategy for achieving enhanced antitumor effects.

6.2.1.1 Preclinical Assessments of HSP90 Inhibitors

Molecular studies of HSP90 inhibitors in cancer cell lines have shed light on key mechanisms of action, while subsequent testing in human tumor xenograft models has provided some confirmation of this mechanism of action and has also established the antitumor activity of these agents across several tumor types. The enormous number of HSP90 client proteins implies that the key client proteins driving malignancy may differ across different tumor types, rendering it difficult to determine the precise molecular underpinnings of HSP inhibitor activity in various cancers; indeed, it has been suggested that nearly every oncogenesis-associated protein is an HSP90 client (Chiosis and Neckers 2006; Vartholomaiou et al. 2016).

Despite this complexity, preclinical studies have identified several key oncogenic client proteins for which expression is modulated by HSP90 inhibition, and which therefore may serve as potential selection markers for HSP90 inhibitor therapy. These key client proteins include a number of receptor tyrosine kinases, such as HER2 (Mimnaugh et al. 1996), EGFR (Ahsan et al. 2012), FLT3 (Yao et al. 2003), IGF-1R (Breinig et al. 2011), RET (Alfano et al. 2010), and MET (Miyajima et al.

2013). Several receptor tyrosine kinase fusion proteins that are drivers of oncogenesis are also stabilized by HSP90 and therefore sensitive to HSP90 inhibition, including ALK (anaplastic lymphoma kinase) (Bonvini et al. 2002; Sang et al. 2013) and fibroblast growth factor receptor 2 (FGFR2) fusion proteins (Lamberti et al. 2018). In addition, other signaling kinases, such as RAF-1, BRAF, and AKT, and transcriptional regulators such as NF-κB, HIF-1α, and p53, are also key oncogenic HSP90 client proteins, as is the cell cycle regulator CDK4 (Wu et al. 2017). Just as HSP90 enhances stability of fusion proteins, it can also prolong the half-life of proteins with other types of destabilizing mutations, as is the case for p53 variants with oncogenic point mutations (Whitesell et al. 1998).

In response to HSP90 inhibition, compensatory upregulation of HSP70, and its consequent anti-apoptotic signaling, has been implicated as a mechanism of therapeutic resistance (Garrido et al. 2003; Garrido et al. 2006). HSP70 has been shown to block recruitment of procaspase-9 to the Apaf-1 apoptosome (Beere et al. 2000; Saleh et al. 2000) and to directly antagonize apoptosis-inducing factor (AIF) (Ravagnan et al. 2001). Several in vitro studies have shown that attenuation of HSP70 activity enhances HSP90 inhibitor-mediated cell death (Guo et al. 2005; Powers et al. 2008). Such studies indicate that HSP70 may serve as an important biomarker of HSP90 inhibition, and highlight the potential therapeutic value of HSP70/HSP90 inhibitor combinations. HSP90 inhibitors have demonstrated antitumor activity in several human tumor xenograft models, including those carrying aberrations in the oncogenic client proteins described above. For example, ganetespib and other second-generation HSP90 inhibitors have yielded antitumor activity (ranging from tumor growth inhibition to tumor regression) in multiple breast cancer models, including both HER2-positive and triple-negative breast cancer (TNBC) models (Jensen et al. 2008; Caldas-Lopes et al. 2009; Friedland et al. 2014). HSP90 inhibitors have likewise shown promising single-agent in vivo activity in models of non-small cell lung cancer (NSCLC) driven by ALK fusion proteins or EGFR mutations (Chen et al. 2010; Normant et al. 2011; Graham et al. 2012; Sang et al. 2013) and in melanoma models driven by BRAF mutations (Acquaviva et al. 2014). Such studies have also established in vivo proof-of-concept for HSP90 inhibition, demonstrating decreased levels of various oncogenic HSP90 client proteins (e.g., HER2, BRAF, AKT, EGFR) coincident with antitumor activity in these models. Unfortunately, the impressive preclinical activity of HSP90 inhibitors has not been observed in clinical testing, which has more recently focused on HSP90 inhibitor combination therapies, as described below.

6.2.1.2 Clinical Development of HSP90 Inhibitors

Two natural products prompted the identification and testing of the first generation of N-terminal HSP90 inhibitors: geldanamycin, a benzoquinone ansamycin antibiotic derived from *Streptomyces hygroscopicus*, and radicicol, a macrocyclic lactone antibiotic derived from *Monosporidum bonorden* (Soga et al. 2013; Chatterjee and Burns 2017). However, novel drug development strategies have continued to

identify new HSP90-targeting agents, including C-terminal–binding inhibitors. As these agents have progressed through clinical testing, newer agents have been developed to improve upon target binding, efficacy, and toxicity, as discussed below.

6.2.2 First-Generation HSP90 Inhibitors

Despite several encouraging preclinical studies, use of geldanamycin was hampered by unacceptable clinical toxicity and structural volatility, particularly from a quinone ring moiety that contributes to its hepatotoxicity (Supko et al. 1995). The C-17 methoxy group of geldanamycin was eventually replaced by an amine group, resulting in various synthetic analogues created to mitigate these early drug design issues (Table 6.1).

17-N-allylamino-17-demethoxygeldanamycin (**17-AAG, tanespimycin**; Kosan Biosciences), was the first of the geldanamycin analogs to undergo clinical evaluation in the 1990s. Though it demonstrated a better adverse event (AE) profile than geldanamycin (Yuno et al. 2018), it had poor solubility and bioavailability (Banerji et al. 2005) and did not demonstrate substantial activity as a single agent in multiple phase I and II trials (Goetz et al. 2005; Ronnen et al. 2006; Solit et al. 2008). Tanespimycin did demonstrate modest activity when combined with other antineoplastic agents. A combination with the HER2-targeted antibody trastuzumab in patients with metastatic HER2-positive breast cancer showed an overall response rate (ORR) of 22% and an overall survival (OS) of 17 months (Modi et al. 2011). In a phase I/II study of tanespimycin and bortezomib, an ORR of 27% was reported in

Table 6.1 Classification of HSP90 inhibitors

Inhibitor	Class	Administration Route
First generation		
Geldanamycin	–	Intravenous
Radicicol	–	–
17-AAG (tanespimycin)	GM	Intravenous
17-DMAG (alvespimycin)	GM	Intravenous, oral
IPI-504 (retaspimycin)	GM	Intravenous
Second generation		
AUY922 (luminespib)	RD	Intravenous
STA-9090 (ganetespib)	RD	Intravenous
AT13387 (onalespib)	RD	Intravenous, oral
BIIB021	Purine scaffold	Intravenous
PU-H71	Purine scaffold	Oral
XL888	Aminoterphthalamide	Oral
TAS-116	Pyrazolopyridine	Intravenous
NVP-HSP990	Aminopyrimidine	Oral

GM geldanamycin-based, *RD* radicicol-based

bortezomib-naïve patients with refractory multiple myeloma (Richardson et al. 2011). Though a phase III trial of this combination versus bortezomib alone was initiated in patients with multiple myeloma, this trial was subsequently closed; formulation issues may have been a consideration. Interestingly, Triolimus®—a triplet agent containing tanespimycin together with the microtubule-disrupting chemotherapeutic paclitaxel and the mTOR inhibitor rapamycin—has been formulated using a polymeric micelle drug delivery platform to improve solubility, and is reported to have preclinical activity without the toxicity associated with the previous tanespimycin formulation (Hasenstein et al. 2012).

17-demethoxy-17-N,N-dimethylaminoethylamino-geldanamycin (**17-DMAG**, **alvespimycin**; Bristol-Myers Squibb) is another semi-synthetic derivative of geldanamycin, with significant antitumor activity, improved water solubility, and oral bioavailability (Hollingshead et al. 2005; Georgakis et al. 2006). This agent was advanced to clinical trials with both intravenous (IV) and oral (PO) formulations in both solid tumor and hematological malignancies (Hollingshead et al. 2005; Kummar et al. 2010; Lancet et al. 2010). However, significant dose-limiting AEs were reported, including fatigue, nausea, and diarrhea, as well as cardiac, liver, lung, and ocular toxicities (Pacey et al. 2011).

IPI-504 (**retaspimycin**, Infinity Pharmaceuticals) is a reduced formulation of tanespimycin that showed promise given its improved water solubility (Chatterjee et al. 2016). Retaspimycin hydrochloride has shown single-agent antitumor activity in early-phase trials of patients with soft tissue sarcomas/gastrointestinal stromal tumors, as well as in ALK-rearranged NSCLC; however, significant hepatic toxicity was noted in these studies (Sequist et al. 2010; Wagner et al. 2013). Retaspimycin has also been evaluated together trastuzumab in patients with HER2-positive metastatic breast cancer (MBC) refractory to HER2 targeted therapy; although the combination showed modest activity, it did not meet predefined criteria to expand the trial (Modi et al. 2013).

6.2.3 Second-Generation HSP90 Inhibitors

Second-generation HSP90 inhibitors are improved small molecule classes; the first of these are derivatives of radicicol, as they contain an ATP-binding resorcinol moiety (Neckers and Workman 2012), while molecules in the second class utilize a purine scaffold (Jhaveri et al. 2012). Radicicol itself was deemed unsuitable for clinical development because of little or no activity in animals secondary to chemical instability (Soga et al. 2003).

NVP-AUY922 (**luminespib**, Novartis) was identified via a high-throughput screen and demonstrated activity in multiple human cancer cell lines and tumor xenograft models (Eccles et al. 2008). Phase II trials have noted activity in both *EGFR*-mutated and *ALK*-rearranged NSCLC as well as in refractory HER2-positive breast cancer, with response rates between 10% and 25% (Schroder et al. 2011; Garon et al. 2012). Recently, promising antitumor activity has also been observed in

NSCLC patients with a rare subtype of *EGFR* exon 20 insertions that are typically refractory to EGFR-specific tyrosine kinase inhibitors (NCT01854034), though results for this study are pending. Dose-limiting toxicities (DLTs) reported in various trials include darkening of vision, atrial flutter, diarrhea, and fatigue. Results for various other ongoing trials are awaited, including combination studies with both chemotherapy and targeted agents (Table 6.2).

AT-13387 (**onalespib**, Astex Therapeutics), is another second-generation inhibitor that has gone through early-phase clinical testing, with a notable difference (relative to other HSP90 inhibitors) of exhibiting prolonged duration of activity in the preclinical setting (Graham et al. 2012). Single-agent trials (Do et al. 2015; Shapiro et al. 2015) as well as combination trials with imatinib (Wagner et al. 2016) or docetaxel (Ramalingam et al. 2015) have been reported. Other combination studies, including with abiraterone (NCT01685268) or crizotinib (NCT01712217), are awaiting results. The agent is currently being studied in a phase I trial in combination with AT7519M, a small molecule inhibitor of CDKs 1, 2, 4, 5, and 9 (NCT02503709; Table 6.2).

STA-9090 (**ganetespib**, Madrigal Pharmaceuticals), a radicicol-derived compound, has been considered one of the most promising HSP90 inhibitors (Chatterjee and Burns 2017), yielding objective responses in phase II studies of MBC (in both patients with HER2-positive tumors and those with TNBC) and NSCLC (in patients with *EML4-ALK* rearrangements) (Socinski et al. 2013; Jhaveri et al. 2014). No objective responses were observed in early-phase studies of ganetespib in patients with hematological malignancies (Lancet et al. 2010b; Padmanabhan et al. 2010). With regard to combination therapies, a phase I study of ganetespib together with paclitaxel and trastuzumab in HER2-positive MBC patients refractory to trastuzumab yielded an ORR of 22% (Jhaveri et al. 2017), and a phase II study of ganetespib in MBC patients was expanded to also examine the combination with paclitaxel following progression on single-agent ganetespib (Cameron et al. 2014). In NSCLC, a significant survival benefit was observed in a phase II study of ganetespib combined with docetaxel in a small subset of patients who had progressed on chemotherapy (Ramalingam et al. 2015); the corresponding phase III study of this combination is ongoing (Ramalingam et al. 2014). However, toxicities have also been problematic for ganetespib combination therapies; in a phase I study of ganetespib combined with the anti-angiogenic agent ziv-aflibercept, the combination resulted in serious adverse events, including small intestinal perforation and one sudden death (a potential gastrointestinal hemorrhage), prompting discontinuation of the trial (Meehan et al. 2018).

PU-H71 (Samus Therapeutics) was developed following implementation of structural biology techniques to identify new HSP90 inhibitors. High-resolution x-ray crystal structures of the HSP90 N-terminal domain, with and without ATP or ATP analogs (Obermann et al. 1998; Li et al. 2012), have enabled the rational design of new HSP90 inhibitors using purine or pyrimidine scaffolds. PU-H71 was the first synthesized second-generation HSP90 inhibitor of this class. A first-in-human study in solid tumors demonstrated that PU-H71 was well tolerated, though no objective responses were reported (Speranza et al. 2018); however, determination of the max-

Table 6.2 Selected ongoing HSP90 inhibitor trials

Tumor type	Phase	Agent tested	Mechanism of action (single agent/combination)	Molecular eligibility criteria	Trial objective	NCT number
Solid tumor; NOS	I	HS-196	ATP binding domain inhibitor linked to near-infrared dye	–	Tumor imaging (contrast agent for tumor detection)	NCT03333031
Solid tumor; NOS	Ia/Ib	TAS-116	Non-resorcinol, non-purine selective inhibitor of cytosolic HSP90α/β isoforms	NSCLC *EGFR*+ or *ALK*+ (only at selected doses)	Safety of different dosing regimes	NCT02965885
Solid tumor; NOS (selected histologies in expansion)	I/IIa	PEN-866	HSP90-targeting ligand linked to SN-38, a topoisomerase 1 inhibitor	–	Safety and MTD	NCT03221400
NSCLC (adenocarcinoma, stage IIIB-IV)	I/II	Luminespib + erlotinib	Radicicol-derived HSP90α/β inhibitor/tyrosine kinase inhibitor targeting *EGFR*	*EGFR*+	Safety, MTD, and RP2D of the combination	NCT01259089
NSCLC (non-squamous, stage IV)	Ib	Luminespib + pemetrexed	Radicicol-derived HSP90α/β inhibitor/antimetabolite chemotherapy	*EGFR*+, *ALK*+, or *KRAS*/*EGFR*/*ALK* WT	Safety and tolerability of the combination	NCT01784640
TNBC	I	Onalespib + paclitaxel	Non-ansamycin HSP90 inhibitor/microtubule inhibitor chemotherapy	–	Safety and RP2D of the combination	NCT02474173
Solid tumor; NOS (expansion: ovarian, fallopian tube, primary peritoneal, and TNBC)	I	Onalespib + olaparib	Non-ansamycin HSP90 inhibitor/PARP inhibitor targeted therapy	–	Safety and MTD	NCT02898207
Solid tumor; NOS	I	Onalespib + AT7519	Non-ansamycin HSP90 inhibitor/CDK 1,2,4,5 and 9 small molecule inhibitor	–	Safety and MTD of the combination	NCT02503709

(continued)

Table 6.2 (continued)

Tumor type	Phase	Agent tested	Mechanism of action (single agent/combination)	Molecular eligibility criteria	Trial objective	NCT number
Solid tumor (gastrointestinal tumors)	Ib	XL888 + pembrolizumab	Selective ATP-competitive inhibitor of HSP90/ anti-PD-1 immune checkpoint inhibitor	–	Safety and RP2D of the combination	NCT03095781
Solid tumor (malignant melanoma, stage III/IV)	I	XL888 + vemurafenib + cobimetinib	Selective ATP-competitive inhibitor of HSP90/BRAF enzyme inhibitor/MEK kinase inhibitor	$BRAF^{V600E}$ mutation–positive	Safety, MTD, and RP2D of the combination	NCT02721459

All trials listed are open only to patients with metastatic disease. Trials are open and/or recruiting patients as of October 2018
NOS not otherwise specified, *MTD* maximum tolerated dose, *NSCLC* non-small cell lung cancer, *EGFR+* epithelial growth factor receptor mutation–positive, *RP2D* recommended phase II dose, *ALK+* anaplastic lymphoma receptor tyrosine kinase rearrangement–positive, *KRAS* Kirsten rat sarcoma viral oncogene, *WT* wild type (non-mutated), *TNBC* triple-negative breast cancer, *PARP* poly ADP-ribose polymerase, *CDK* cyclin-dependent inhibitor, *PD-1* programmed cell death-1 lymphocyte receptor, *MEK* mitogen-activated protein kinase enzyme, *BRAF* serine/threonine kinase B-Raf

imum tolerated dose (MTD) was not achieved, and the trial was stopped because of drug supply issues.

CNF2024/BIIB021 (Biogen) has been tested in phase I clinical studies in patients with solid tumors as well as hematologic malignancies; DLTs included hypoglycemia, hyponatremia, liver abnormalities, fatigue, dizziness, and syncope (Saif et al. 2014). Evaluation in phase II trials included patients with gastrointestinal stromal tumors, in which the agent was well tolerated but did not result in significant responses (Shapiro et al. 2015). The combination of BIIB021 with trastuzumab in a phase I study of HER2-positive MBC patients resulted in DLTs including partial seizures, headache, dizziness, fatigue, and rash (Jhaveri et al. 2012).

A number of new HSP90 inhibitors have entered clinical trials in the past few years. **XL888** (Exelixis) is an orally administered small molecule with selective inhibition for both HSP90α and β isoforms (Table 6.1). Both in vitro and in vivo, this agent inhibited growth and induced cell death and tumor regression of melanoma cell lines harboring the oncogenic BRAF V600E mutation and resistant to the BRAF inhibitor vemurafenib, through a variety of mechanisms (Paraiso et al. 2012). In a phase I study of XL888 in patients with refractory solid tumors, the MTD of XL888 was reported to be 135 mg twice weekly, and diarrhea was noted as a DLT (Eroglu et al. 2018). Given these findings, a trial of this agent has been initiated in patients with advanced melanoma harboring the BRAF V600E mutation, and the results are awaited (Table 6.2). TAS-116, another oral agent, has shown good bioavailability and antitumor activity in several xenograft models, as well as reportedly reduced ocular toxicity in various animal species (Ohkubo et al. 2015; Chatterjee and Burns 2017); a phase I study of this agent in pre-defined solid tumor molecular cohorts is ongoing (NCT02965885, Table 6.2). Finally, several radioactive isotopes and clinical imaging agents targeting HSP90 have also been developed (Barrott et al. 2013). One of these, **HS-196**, is an imaging agent containing an HSP90 inhibitor covalently linked to a near-infrared fluorescent dye (Table 6.2). HS-196 selectively and competitively binds to HSP90 in cells following intravenous administration; given that HSP90 is upregulated in a variety of tumor cells, accumulation of this fluorescent dye–tethered agent allows for in vivo detection of these cells due to enhanced uptake of HS-196.

6.2.3.1 Common Toxicities Associated with HSP90 Inhibitors

Clinical development of several HSP90 inhibitors has been halted due to ocular and liver toxicities. Ocular symptoms have been reported as a characteristic toxicity across all classes of HSP90 inhibitors, though, as noted above, not all second-generation inhibitors have resulted in severe ocular toxicity (Jhaveri et al. 2014). Rodent modeling would suggest that prolonged retinal inhibition of HSP90 induces photoreceptor cell death, and that this is dependent on the retina/plasma exposure ratio and retinal elimination rate for each individual inhibitor, rather than their chemical class (Zhou et al. 2013). In the case of elevated liver transaminase toxicities, results from studies of second-generation HSP90 inhibitors suggest that the

severe hepatotoxicity that halted development of several first-generation compounds was class-specific (i.e., associated with the quinone ring moiety) rather than target-driven (Jhaveri et al. 2014). Thus, there is evidence that existing and forthcoming second-generation HSP90 inhibitors may avoid both the hepatic and ocular toxicities that have plagued development of previous agents targeting HSP90.

6.2.4 Novel Perspectives and Targets

An entirely new structural class of HSP90 inhibitors has been identified in the past few years. Though they are less well characterized than inhibitors that target the N-terminal ATP binding domain, their interruption of HSP90 chaperone activity is reported to occur in a similar manner to that of the classic inhibitors (Marcu et al. 2000). Compounds that target the C-terminal domain of HSP90 include novobiocin, coumermycin, and 'novologues' such as KU-32 and KU596 (Lancet et al. 2010). These agents were found to have neuroprotective properties when a biarylamide side chain modification was introduced, causing HSP90 client degradation without induction of the heat shock response, prompting clinical evaluation of these agents in neurodegenerative diseases such as diabetic neuropathy (Zhao et al. 2014). Further chemical modifications—specifically, the inclusion of a benzamide side chain—have resulted in compounds with marked anti-proliferative activity against a variety of cancer cell lines (Zhao et al. 2014; Forsberg et al. 2017). These agents have not yet reached the clinic.

Recognition of the importance of T-cells in anti-tumor immunity has led to very promising results in a subset of cancer patients. Multiple clinical trials evaluating several immune checkpoint inhibitor antibodies, cytokines, and engineered T-cell approaches are ongoing, with a view to informing rational combination strategies. HSP90 inhibitors have been identified as compounds that can synergistically potentiate anti-tumor responses when combined with checkpoint immunotherapy (Mbofung et al. 2016), and can sensitize tumors to client protein–specific T-cells (Raveendran et al. 2014). A number of novel clinical combination trials are underway, including XL888 together with the immune checkpoint inhibitor pembrolizumab (NCT03095781, Table 6.2), which will evaluate the hypothesis (informed by preclinical data) that HSP90 has a central role in modulating the tumor microenvironment as well as inflammatory signaling pathways associated with tumor immunosuppression (Akce et al. 2018). Immunotherapy combinations are not only limited to HSP90 inhibitors. Preclinically, HSP70-positive tumors were recognized by natural killer (NK) cells when the NK cells were activated by preincubation with HSP70 peptides and low-dose interleukin-2 (Multhoff et al. 2001); this strategy is currently undergoing testing in a randomized phase II study in patients with stage III/IV NSCLC after chemoradiotherapy (NCT02118415), though no results have been reported to date (Specht et al. 2015).

6.3 Conclusions

HSP90 plays an important role in the biology of human cancer, making it a potential target for therapy that may result in the inhibition of tumor development. Although the combination of HSP90 inhibitors and other oncologic clinical agents may herald exciting future outcomes, the clinical activity of pharmacological inhibition of HSP90 with small molecules (as single agents or in combination with other oncologic agents) has been limited up to now. Even though HSP90 modulates various oncogenic substrate proteins involved in crucial pathways that allow malignant tumors to thrive, the effectiveness of HSP90 inhibitors in the treatment of cancer has not been overwhelmingly successful to date. In current times, when oncology treatment is often decided based on multiomic molecular profiling, the ability to discover a biomarker predictive of response to HSP90 inhibitors is an area worth investigating. Developing the ability to better recognize which tumors are more likely to respond to this type of inhibition may be the door to a more promising future for research and development of novel HSP90 inhibitors in the oncology treatment arena—bringing a more prominent role to HSP90 inhibitors. Over the past 20 years, promising preclinical and clinical results have come from early-phase studies of HSP90 inhibitor agents, but this has not resulted in these agents being incorporated as standard-of-care for any malignancy.

Acknowledgements Special thanks to Sarah Miller, PhD.

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