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Time-Dependent Pharmacokinetics of Immune Checkpoint Inhibitors and their Implications and Considerations for Exposure–Response Analysis

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Abstract

Purpose The purpose of this review is to provide a comprehensive summary of recent studies characterizing the pharmacokinetics of newly approved immune checkpoint inhibitors (ICIs) monoclonal antibodies and highlight the latest finding and advancements in understanding time-dependent PK, wherein their clearance changes with time. Additionally, the article will discuss key considerations and implications when conducting exposure–response analysis.

Recent Findings The majority of papers documenting time-varying PK are fairly recent as ICIs as a class of drugs have emerged as successful anti-cancer agents in the last 10 years or so. The review paper is split in two, somewhat connected, parts. The first one is focused on the association of time-varying PK and disease state. In order to provide a comprehensive context, the review paper starts with the cases of nivolumab and pembrolizumab, and then look at publications documenting that phenomenon for other therapies, such as cemiplimab, retifanlimab, atezolizumab, avelumab, durvalumab, ipilimumab, tremelimumab, and relatlimab.

The second part discusses the implication of varying PK for the exposure response of efficacy. Building upon the strong correlation between drug clearance over time and the overall survival highlighted above, this part of the paper studies how the potential for this interaction between treatment response and PK leads to biased E-R (exposure–response) relationships, especially for efficacy. Special emphasis is placed on a recent white paper with authors from industry, academia, and government (Ruiz-Garcia et al. JPKPD 50:147-172, 2023) that highlights the various challenges and some possible solutions for conducting and interpreting ER-efficacy analyses in oncology.

Summary Recognizing and accounting for the dynamic PK characteristics are crucial for optimizing dosing strategies, predicting drug exposure, and understanding the association between drug exposure and clinical outcomes in patients undergoing checkpoint inhibitor therapy. This paper provides a succinct summary of relevant publications and some practical considerations.

Keywords Immune checkpoint inhibitors · Time-dependent pharmacokinetics · Exposure response · Confounding factors

Introduction

Immune checkpoint inhibitors are a class of drugs that have revolutionized cancer treatment by enhancing the body's immune response against cancer cells. These inhibitors target key proteins, such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and lymphocyte-activation gene 3 (LAG-3), which regulate immune responses [1, 2]. Although both CTLA-4 and PD-1 are negative regulators of T cells, each plays a nonredundant role in the coinhibitory mechanism of immune responses. While the interaction between CTLA4 and B7 ligands limits priming of naive T cells, the interaction between PD-1 and PD-L1 renders effector T cells to be exhausted in the tumor microenvironment, raising hopes for therapeutic synergy in the combination strategy [3]. LAG-3 is also a co-inhibitory receptor to suppress T cells activation and cytokine

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secretion, and showed a remarkable synergy with PD-1 to inhibit immune responses [4]. By blocking the interactions between these proteins, ICIs unleash the immune system's ability to recognize and attack cancer cells, leading to durable and often remarkable responses in a variety of cancer types. The mechanism of action of ICIs makes it applicable across various types of tumors (melanoma, non-small cell lung cancer, renal cell carcinoma, bladder cancer, head and neck squamous cell carcinoma) [5–7]. That broad spectrum, coupled with milder side effects, has turned this class into the standard of care. Currently, there are ten approved ICIs by the US Food and Drug Administration (FDA) (https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications) [8].

Of the 10 ICI mAbs approved by the FDA thus far, five have dosing recommendations in the USPI that are different or additional to the dosing regimen evaluated in the pivotal studies. In general, the changes/additions to the recommended dosing were enabled by model-based bridging to the efficacy/safety observed in the pivotal studies. Some of these changes (such as increasing the dosing interval) were particularly valuable in decreasing clinic visits during the COVID-19 pandemic.

Despite the different targets and different mechanism of action, ICIs primarily belong to the class of monoclonal antibodies (mAbs), and they exhibit similar PK properties as other therapeutic monoclonal antibodies which are long half-life and target mediated disposition with a combined linear and nonlinear phase [9]. In general, mAbs may exhibit target-mediated drug disposition (TMDD) at low doses, which is driven by their binding with high affinity to their pharmacological target in a way that affects its pharmacokinetic characteristics, and the linear phase is associated with a saturation of the target and the downstream effects of the drugs. However, time-dependent pharmacokinetics has been reported for several mAb ICIs, in many (but not all) indications. This phenomenon was first identified during FDA reviews of the first two approved PD-1 inhibitors, nivolumab and pembrolizumab [10]. Literature reviews have been published to better understand the clinical PK/PD relationships of ICIs [11] as well as an overview of the PK modelling strategies used to describe the variations in the PK of mAbs with time [12].

This time-dependent pharmacokinetic phenomenon of ICIs is hypothesized to be associated with patient disease status and clinical outcome and can have significant implications to the understanding of the exposure–response relationships for efficacy [10, 13]. Therefore, in this review, we would like to take an in-depth look at the time-dependent pharmacokinetics of the currently approved ICIs by FDA and provide a systematic analysis of the potential mechanisms underlying the time-dependent CL and the key implications during exposure–response evaluations. To achieve this goal, this review will focus on the most recent advancements in the evaluation of pharmacokinetics, exposure–response of ICIs, and regulatory perspectives. Consideration of these dynamics is essential for optimizing dosing strategies, predicting drug exposure, and understanding the relationship between drug exposure and clinical outcomes in patients receiving checkpoint inhibitor therapy.

Time-dependent pharmacokinetic and its association with disease status

Time-dependent pharmacokinetics (PK) in checkpoint inhibitors refers to changes in PK attributes (most commonly clearance (CL)) over time during the course of treatment.

The phenomenon of time-dependent CL was first reported in 2016 for anti-PD-1 agents. A population PK (popPK) model of nivolumab with time-varying CL was developed based on such findings [14]. The analysis confirmed that the model with time-varying CL provided a better description of the clinical data and that, on the population level, the nivolumab CL decreases over time with ~ 25% maximal reduction from baseline values.

Around the same time, two additional papers were published on immune checkpoint inhibitors evaluating the time-varying clearance for various drugs (nivolumab and pembrolizumab) in advanced settings [13, 15]. The key message in these two publications is that overall clearance decreases over the period of treatment in a typical patient and that the magnitude of this decrease is associated with the best overall response for both drugs. In addition, in the work conducted by Li et al. [16]. The authors also addressed the longitudinal effect of pembrolizumab clearance via four time-varying covariates related to the mechanism of action of the drug, namely tumor size, lymphocyte count, serum albumin, and serum LDH. This work was an advancement as compared to the previous two papers as it demonstrated that CL could decrease and then increase, reflecting the change in health status of the patient. While all these papers were conducted in a retrospective manner, they strongly suggested that time-varying CL can be viewed as a surrogate for disease progression. Coupled with the earlier work on the significance of baseline CL, this suggests a strong coupling between a parameter, typically associated with PK and clinical outcome.

Time-dependent reduction in CL is not specific for nivolumab [17] and pembrolizumab [18], and has now been reported for the other approved ICIs against various targets across the advanced settings including cemiplimab [19], retifanlimab [20], atezolizumab [21], avelumab [22], durvalumab [23], ipilimumab [24], tremelimumab [25], and relatlimab [26] as shown in Table 1.

Table 1 Summary of the estimated geometric mean reduction of CL at steady state compared to baseline for ICIs

	Target	Maximum reduction from baseline
Cemiplimab	PD-1	11%
Nivolumab	PD-1	24.5%
Pembrolizumab	PD-1	23%
Retifanlimab-dlwr	PD-1	23%
Atezolizumab	PD-L1	17%
Avelumab	PD-L1	32.1%
Durvalumab	PD-L1	23%
Ipilimumab	CTLA-4	18%
Tremelimumab	CTLA-4	17%
Relatlimab	LAG3	10%

The time-dependent changes in clearance (CL) of checkpoint inhibitors can be explained by two hypothesized mechanisms: (1) indirect effect via reversal of cancer-induced cachexia and improvement of patient disease status. Cachexia, a metabolic syndrome associated with underlying diseases, leads to the loss of muscle mass due to a hypermetabolic state [27, 28]. Cancer-induced cachexia increases protein catabolism, including the breakdown of endogenous proteins and monoclonal antibodies used in treatment. In advanced cancer patients, this hypermetabolic state can result in increased elimination of both endogenous proteins and therapeutic antibodies [29]. As the patient's metabolic state improves during treatment, the catabolic state is reduced, leading to an increase in protein levels. Albumin, as an abundant protein, has been associated with cachexia and the hypermetabolic state [30]. This suggests that patients with cachexia and a hypermetabolic state have higher protein turnover rates, leading to increased elimination. Consequently, patients who demonstrate a pronounced response to treatment may also exhibit significant decreases in CL over time. (2) Reduction in tumor-driven drug elimination: Tumors can contribute to drug elimination through various mechanisms, such as metabolism within the tumor or sequestration of drugs within tumor tissues. However, the example of pembrolizumab showed that TMDD was observed at a dose up to 0.1 mg/kg, which is 20 times lower than the dose studied in the pivotal trial [15]. The impact of TMDD is generally considered negligible at the clinically relevant doses for the checkpoint inhibitors such as nivolumab, pembrolizumab, and durvalumab [31], suggesting that tumor-driven drug elimination is unlikely to be the primary driver for time-dependent CL.

The association of covariates to patient disease status is also an important consideration. Several covariates have been recognized as the covariates commonly influencing the CL of ICIs [32]. These covariates include baseline body weight, baseline albumin, and sex. For atezolizumab, the impact of baseline and time-varying covariates on the pharmacokinetics (PK) of atezolizumab was investigated [33]. The analysis employed a population PK model incorporating time-varying covariates such as body weight, albumin, ADA, gender, neutrophil count, alkaline phosphatase, bilirubin levels, and sum of longest diameter of target lesions (SLD). This comprehensive approach provided a broader understanding of the relationship between disease status (tumor burden and cancer inflammation) and the PK of atezolizumab. The inclusion of time-varying covariates allowed for the representation of patients' disease status over time. Notably, variations in albumin levels emerged to have potential association with changes in CL over time. Specifically, an increase in albumin levels (indicating an improvement in patient status) corresponded to a decrease in CL. Additionally, the change in SLD over time also influenced CL, although to a lesser extent. These findings support the hypothesis that the changes in CL over time are associated with patients' prognostic factors and disease status.

Interestingly, although time-dependent PK has been observed across ICIs, some differences in tumor types were also noted. For example, a population pharmacokinetic (PK) analysis was performed to evaluate avelumab across 14 distinct cancer types [34]. Among these tumor types, a noticeable decrease in clearance (CL) was observed in only two specific cancer types out of the 14 included in the analysis. These two types were Merkel cell carcinoma (mMCC), exhibiting a maximum CL decrease of 32.1% compared to the baseline, and squamous cell carcinoma of the head and neck (SCCHN), which displayed a maximum CL decrease of 24.7%. The analysis further revealed that the time-dependent changes in CL were associated with post-treatment effects, and the reduction in CL was more prominent in responders compared to non-responders. In patients with Merkel cell carcinoma, the observed time-dependent effect on CL may be attributed to a longer follow-up period compared to patients with other tumor types.

Furthermore, in the adjuvant melanoma setting, it was observed that the baseline clearance (CL) of nivolumab was lower compared to other advanced tumor types [35]. Contrary to previous observations, it was also noted that clearance did not decrease over time in this setting. Furthermore, it was also shown that patients with adjuvant melanoma, who have no measurable tumor burden and an improved disease state, exhibited a lower baseline CL similar to the steady-state CL observed in patients with advanced melanoma who achieved a complete response. These findings provided additional support for the association between nivolumab CL and the disease state in advanced malignancies.

It is important to note that investigations into time-varying pharmacokinetics (PK) for immune checkpoint inhibitors (ICIs) have predominantly focused on single-agent treatments. However, considering that time-varying clearance (CL) is linked to treatment effects, we thought it would be interesting to conduct similar investigations with combination treatments to assess differences in CL changes during various treatments.

A recent study conducted on ipilimumab, a first-in-class ICI monoclonal antibody approved as a monotherapy for melanoma and adjuvant melanoma, as well as in combination with nivolumab for melanoma and other solid tumors, serves as a good example [24]. The initial characterization of ipilimumab's PK [36] did not include time-varying CL, as the analysis only incorporated data from patients with melanoma receiving ipilimumab monotherapy for up to four doses every 3 weeks. No clear trend of change in CL over time was observed during the 12-week administration duration. In an updated analysis, a more refined ipilimumab population PK model was developed to assess time-varying CL and the impact of combination therapy with nivolumab. This study benefited from the longer dosing of ipilimumab when administered in combination with nivolumab in patients with non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC) (not limited to four cycles as previously studied in the monotherapy setting). This enabled a more robust evaluation of time-varying CL. The results showed that the magnitude of CL decline was approximately 6% with ipilimumab monotherapy and around 18% when combined with nivolumab. The extent of CL decrease with combination therapy was similar to that observed for nivolumab alone. These findings align with clinical efficacy outcomes [37], as patients with melanoma who received ipilimumab and nivolumab combination therapy exhibited significantly longer progression-free survival compared to those receiving ipilimumab alone. Further characterization of nivolumab PK was also conducted to evaluate the effect of combination therapy and time-varying covariate on nivolumab PK [38]. When administered in combination with ipilimumab, nivolumab baseline CL was slightly higher, possibly due to the combination's effect on inflammatory status. The decrease of nivolumab CL was also greater with the combination compared to nivolumab monotherapy. The time-varying CL was partially explained by time-varying covariates. At baseline, higher body weight and a performance score greater than 0 were associated with greater CL within a given population. However, the effect of time-varying body weight showed an opposite effect to baseline. An increase in body weight over time was associated with a decrease in CL. Furthermore, increase in albumin was associated with a decrease in CL, and increases in LDH and PS were associated with increased CL.

A similar observation was reported for tremelimumab [39], which also exhibited time-varying clearance associated primarily with therapy regimen and changes in disease status. Tremelimumab clearance increased by ~ 16% as monotherapy, but decreased by ~ 17% as a combination therapy over 1 year of treatment, respectively. This observation is aligned with the better clinical efficacy achieved with the tremelimumab and durvalumab combination therapy [40], and further supports the hypothesis that a decrease in CL over time may serve as a marker of treatment response.

Implications of time-varying pharmacokinetics for exposure response of efficacy

Understanding the relationship between drug exposure and response is crucial in the development of drugs as it informs dose selection, aids in patient population considerations, and is pivotal in the regulatory approval process. In the classical paradigm for conducting exposure–response (E-R) analyses, the drug exposure is considered the cause while the response is the outcome. However, as discussed previously, for ICIs this process is not uni-directional due to their time-dependent pharmacokinetics with change in clearance in time due to disease progression or emission; and therefore, there is a strong correlation between drug clearance over time and the overall survival. The potential for this interaction between treatment response and PK to lead to biased E-R relationships, especially for efficacy, must be considered.

This situation has two important implications. First, due to the improved disease status of patients, there is a possibility of decreased clearance, which could affect drug exposure in the later phase of the trial and be influenced by the efficacy outcome, even with the same dosing regimen. Therefore, when evaluating the efficacy of a drug, it is crucial to consider the increased exposure that occurs in the later stages of treatment, such as at steady state. Relying solely on this higher exposure to conclude better efficacy could be misleading without accounting for the underlying changes in drug clearance over time.

Understanding that efficacy could affect PK and utilizing steady-state exposure in the exposure efficacy analysis may introduce bias to the exposure–response (ER) relationship. A simulation study [13] was conducted to evaluate the selection of an appropriate exposure metrics in the E-R efficacy analysis and assess the quantitative impact of time-varying pharmacokinetics (PK) on the ER relationship. In this analysis, the use of exposure metrics derived from a later phase of the treatment (e.g., Cavgss) was strongly confounded by the post-treatment outcome. Conversely, employing early-exposure metrics (e.g., Cavg1) yielded less biased results,

allowing for a more accurate representation of the causal effect of exposure on clinical response.

The second implication pertains to the potential imbalance in prognostic risk factors across different groups, which can impact the analysis of exposure efficacy. It is essential to ensure that prognostic risk factors are balanced among the groups being compared. Failure to achieve this balance may introduce bias and confound the relationship between exposure and efficacy analysis. Therefore, careful consideration and adjustment for these imbalances are crucial when conducting exposure efficacy analyses to obtain accurate and reliable results.

In 2017 and 2018, Bajaj et al. and Turner et al. independently published papers on the significance of baseline clearance beyond the PK of nivolumab and pembrolizumab. More specifically, it was shown [41] that while nivolumab exposure was not a significant predictor of the hazard of death in the full ER model, ECOG status, baseline BW, nivolumab CL, age, and baseline LDH had a significant effect on overall survival, with the greatest magnitude of effect being associated with CL for patients with previously treated and untreated melanomas [42]. The sensitivity analysis conducted, excluding the impact of baseline CL, further confirmed a flat exposure–response relationship between the exposures achieved at the evaluated doses and clinical efficacy. In addition, a comprehensive ER analysis of nivolumab in patients with non-small cell lung cancer (NSCLC) also showed similar findings [43]. The analysis results indicated that nivolumab exposure (Cavg1) was not a significant predictor of overall survival (OS) in patients with squamous and non-squamous NSCLC when utilizing a multivariable Cox proportional hazards analysis model. In this analysis, baseline clearance (CL) was also included as a covariate to capture the initial disease status of patients, and it was found to have a significant association with OS. Considering that the analysis incorporated Cavg1 values derived from a wide range of doses (1–10 mg/kg), the inclusion of both Cavg1 and baseline CL did not introduce any confounding effects. These findings revealed a relatively flat exposure–response relationship across the range of nivolumab exposures (as measured by Cavg1) and indicated a broad therapeutic margin for nivolumab monotherapy.

Shortly after, Turner, Kondic, and colleagues demonstrated a strong association between baseline clearance and OS in two different tumor types (melanoma and NSCLC) using data from two randomized clinical trials in these indications. Very importantly, these were studies where two, very different doses of pembrolizumab (2 mg/kg and 10 mg/kg) were being evaluated and compared to standard of care (SoC). An unusual pattern of improved OS in subjects with higher exposure within each dose is incongruent with the similarity in OS across the fivefold dose/exposure range, suggesting a confounding of PK and OS independent of direct pharmacologic effects on patient outcome. This work clearly demonstrated that the worst clinical outcome (overall survival) was observed in the highest CL quartile independent of dose. Inversely, patients with similar exposure, calculated as dose/CL, had very different outcomes, driven by the value of CL in the denominator, rather than the dose in the numerator. This phenomenon would have masked itself as a positive ER relationship should there have been a single dose. The dose–response analyses further supported the lack of exposure-dependency in outcome, with trends in CL0-OS underscoring a correlation between OS and pembrolizumab elimination. The authors hypothesized that decreased OS in subjects with higher pembrolizumab CL_0 paralleled disease severity markers associated with end-stage cancer anorexia-cachexia syndrome. The cachexia-related factor associated with change in body weight accounted for a portion of survival variability in both populations in melanoma and NSCLC, suggesting a disease-level involvement of weight loss and OS.

The examples of nivolumab and pembrolizumab showed that baseline clearance was reflective of the overall baseline disease state of patients and was strongly associated with clinical outcome. The inclusion of baseline clearance in the multivariable analysis could further alleviate any potential imbalance in the prognostic factors and account for other unknown markers that were not included in the analysis. In another study [44, 45], Wang et al. utilized a machine learning approach to predict baseline clearance (CL) of nivolumab based on a composite of cytokine signatures. They found that patients with a predicted high nivolumab CL had poor survival outcomes, irrespective of the treatment received (nivolumab or chemotherapy). This finding provides support for the hypothesis that nivolumab clearance can serve as a prognostic marker for the disease status of patients with advanced melanoma and renal cell carcinoma (RCC). These results highlight the potential utility of nivolumab clearance as a predictive factor in assessing patient prognosis.

A more recent multi-institutional white paper with authors from industry, academia, and government [46] further highlighted the various pitfalls and some possible solutions for conducting and interpreting ER-efficacy analyses in oncology. Although the white paper provided a broader insight regarding preferred analysis methods, safety and efficacy endpoints selection, and special consideration when modelling for hematologic malignancies and in cell therapies, the challenges associated with the time-dependent pharmacokinetic (PK) was highlighted as remaining a significant one. The selection of the exposure metrics to be used in the analysis is one of the key considerations, and inclusion of more than one dose level in E-R analyses would further reduce the confounding effect between exposure and CL.

Although the focus of this paper is on mAb ICIs, the phenomenon of time-varying pharmacokinetics has been reported and summarized for other therapeutic mAbs [47]. Additional paper has been published that summarizes the collective experience and methods that can be used to address the confounding of interpreting ER analyses for mAbs in oncology as a consequence of time-varying clearance. In Kawakatsu et al. [48], the authors focus on three different approaches, namely (i) Cox-proportional hazards (CPH) modelling and case-matching; (ii) tumor growth inhibition–overall survival modelling; and (iii) multiple dose-level study design. CPH modeling enables the estimation of the relationship between exposure and response while adjusting for baseline covariate factors that may act as prognostic confounders. Case-matching analysis further balances the distribution of confounding factors by ensuring the baseline risk factors are distributed evenly across different treatment arms. However, the application of these methodologies requires careful consideration of data availability, sample size, selection of covariates, and evaluation of exposure metrics. TGI-OS modeling is another methodology that incorporates tumor growth dynamics and a multivariable survival model to evaluate treatment effects and overall survival. By directly separating treatment effects from disease effects, this approach reduces the risk of confounding by prognostic factors. While limitations should be considered, successful examples utilizing this approach have been reported, gaining recognition from regulatory agencies. The final approach highlighted in the review is the selection of a multiple dose-level study design for registrational trials. By incorporating randomization and multiple dose levels, this design ensures baseline characteristics are balanced across groups and allows for the identification of the true exposure–response relationship, as was the case in the example of pembrolizumab [42].

The Food and Drug Administration (FDA) has recently issued a draft guidance [49] that offers additional recommendations for dose optimization in registrational trials within the field of oncology. The guidance emphasizes the importance of studying a range of doses during the clinical development process. By incorporating multiple dose levels, this approach would further facilitate the analysis of the relationship between exposure and response and mitigate potential confounding factors that may arise during the analysis.

Conclusions

Immune checkpoint inhibitors (ICIs) represent critical and novel therapies in the field of cancer treatment. Their distinctive pharmacokinetic (PK) profile and the association with clinical outcomes necessitate a comprehensive understanding of the challenges and limitations that arise during study design and data analysis. By acknowledging and addressing these factors, researchers can better interpret the data, optimize dose levels, and ultimately enhance clinical outcomes in immunotherapy.

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Declarations

Conflict of Interest All authors are current or previous employee and stock shareholders of Bristol Myers Squibb.

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References

1. Brahmer JR, Tykodi SS, Chow LQM, Hwu W-J, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455–65.
2. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12:252–64.
3. Lee H et al. Molecules. 2019;24:1190. https://doi.org/10.3390/molecules24061190.
4. Andrews LP, Marciscano AE, Drake CG, Vignali DA. LAG3 (CD223) as a cancer immunotherapy target. Immunol Rev. 2017;276:80–96.
5. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443–54.
6. Marin-Acevedo JA, Dholaria B, Soyano AE, Knutson KL, Chumsri S, Lou Y. Next generation of immune checkpoint therapy in cancer: new developments and challenges. J Hematol Oncol. 2018;11:39.
7. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348:56–61.
8. Marin-Acevedo JA, et al. Next generation of immune checkpoint inhibitors and beyond. J Hematol Oncol. 2021;14:45.
9. Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther. 2008;84:548–58.
10. Wang Y. Special considerations for modeling exposure-response relationships for biologics. Presented at the 117th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, San Diego, CA, March 8, 2016.
11. Centanni M, et al. Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. Clin Pharmacokinet. 2019;58:835–57.
12. Petitcollin A, et al. Modelling of the time-varying pharmacokinetics of therapeutic monoclonal antibodies: a literature review. Clin Pharmacokinet. 2020;59(1):37–49.
13. Liu C, Yu J, Li H, Liu J, Xu Y, Song P, et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. Clin Pharmacol Ther. 2017;101:657–66.
14. Bajaj G, et al. Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors. CPT Pharmacometrics Syst Pharmacol. 2017;6:58–66.

15. Li H, et al. Time dependent pharmacokinetics of pembrolizumab in patients with solid tumor and its correlation with best overall response. J Pharmacokinet Pharmacodyn. 2017;44:403–14.
16. Li H, et al. Semimechanistically based modeling of pembrolizumab time-varying clearance using 4 longitudinal covariates in patients with non–small cell lung cancer. J Pharm Sci. 2019;108:692–700.
17. Opdivo (nivolumab) [package insert] (Bristol-Myers Squibb Company Princeton, NJ Feb23).
18. Keytruda (pembrolizumab) [package insert] (Merck & Co., Inc., Whitehouse Station, NJ, April 2023).
19. Libtayo (cemiplimab)[package insert] (Regeneron Pharmaceuticals, Inc., Tarrytown, NY, April 2023).
20. zynyz (retifanlimab-dlwr) [package insert] (Incyte Corporation, Wilmington, DE, March2023).
21. Tecentriq (atezolizumab) [package insert] (Genentech, Inc., South San Francisco, CA, May 2023).
22. Bavencio (avelumab) [package insert] (EMD Serono, Inc.,Rockland, MA, Jul 2022).
23. Imfinzi (durvalumab) [package insert] (AstraZeneca Pharmaceuticals LP, Wilmington, DE,June 2023).
24. Population pharmacokinetics of ipilimumab in combination with nivolumab in patients with advanced solid tumors. CPT Pharmacometrics Syst Pharmacol. 2020; 9: 29–39.
25. Population pharmacokinetic modelling of tremelimumab in patients with advanced solid tumours and the impact of disease status on time-varying clearance. Br J Clin Pharmacol. 2023;89(5):1601–1616.
26. Opdualag [package insert] (Bristol-Myers Squibb Company Princeton, NJ March22).
27. Evans WJ, et al. Cachexia: a new definition. Clin Nutr. 2008;27:793–9.
28. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev. 2013;39:534–40.
29. Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. CPT Pharmacometrics Syst Pharmacol. 2017;6:576–88.
30. Liu X, et al. One-year mortality in patients with cancer cachexia: association with albumin and total protein. Cancer Manag Res. 2021;29(13):6775–83. https://doi.org/10.2147/CMAR.S318728.
31. Baverel PG, et al. Population pharmacokinetics of durvalumab in cancer patients and association with longitudinal biomarkers of disease status. Clin Pharmacol Ther. 2018;103:631–42.
32. Bajaj G, et al. Evaluation of covariate effects on pharmacokinetics of monoclonal antibodies in oncology. Br J Clin Pharmacol. 2019;85:2045–58.
33. Marchand M, et al. Time-dependent population PK models of single-agent atezolizumab in patients with cancer. Cancer Chemother Pharmacol. 2021;88:211–21.
34. Wilkins JJ, et al. Time-varying clearance and impact of disease state on the pharmacokinetics of avelumab in Merkel cell carcinoma and urothelial carcinoma. CPT Pharmacometrics Syst Pharmacol. 2019;8:415–27.
35. Hamuro L, et al. Nivolumab clearance is stationary in patients with resected melanoma on adjuvant therapy: implications of disease status on time-varying clearance. CPT. 2019;106(5):1018–2027.
36. Feng Y, et al. Model-based clinical pharmacology profiling of ipilimumab in patients with advanced melanoma. Br J Clin Pharmacol. 2014;78:106–17.
37. Wolchok JD, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017;377:1345–56.
38. Zhang J, et al. Population pharmacokinetics of nivolumab in combination with ipilimumab in patients with advanced malignancies. CPT Pharmacometrics Syst Pharmacol. 2019;8:962–70.
39. Hwang M, et al. Population pharmacokinetic modelling of tremelimumab in patients with advanced solid tumours and the impact of disease status on time-varying clearance. Br J Clin Pharmacol. 2023;89(5):1601–16.
40. Kelley RK et al. J Clin Oncol. 2021;39(27):2991–3001. https://doi.org/10.1200/JCO.20.03555.
41. Bajaj G, et al. Exposure–response analysis of nivolumab in patients with previously treated or untreated advanced melanoma. J Clin Pharmacol. 2017;57(12):1527–33.
42. Turner DC, Kondic AG, Anderson KM, Robinson AG, Garon EB, Riess JW, Jain L, Mayawala K, Kang J, Ebbinghaus SW, Sinha V, de Alwis DP, Stone JA. Pembrolizumab exposure-response assessments challenged by association of cancer cachexia and catabolic clearance. Clin Cancer Res. 2018;24(23):5841–9. https://doi.org/10.1158/1078-0432.CCR-18-0415.
43. Feng Y, et al. Nivolumab exposure–response analyses of efficacy and safety in previously treated squamous or nonsquamous non–small cell lung cancer. Clin Cancer Res. 2017;23(18):5394–405.
44. Wang R, Shao X, Zheng J, Saci A, Qian X, Pak I, et al. A machine-learning approach to identify a prognostic cytokine signature that is associated with nivolumab clearance in patients with advanced melanoma. Clin Pharmacol Ther. 2020;107:978–87.
45. Wang R, Zheng J, Shao X, Ishii Y, Roy A, Bello A, et al. Development of a prognostic composite cytokine signature based on the correlation with nivolumab clearance: translational PK/PD analysis in patients with renal cell carcinoma. J Immunother Cancer. 2019;7:348.
46. Ruiz-Garcia A, et al. A comprehensive regulatory and industry review of modeling and simulation practices in oncology clinical drug development. JPKPD. 2023;50:147–72.
47. Petitcollin A, et al. Modelling of the time-varying pharmacokinetics of therapeutic monoclonal antibodies: a literature review. Clin Pharmacokinetics. 2020;59:37–49.
48. Kawakatsu S, et al. Confounding factors in exposure–response analyses and mitigation strategies for monoclonal antibodies in oncology. Br J Clin Pharmacol. 2021;87:2493–501.
49. Optimizing the dosage of human prescription drugs and biological products for the treatment of oncologic diseases. Draft Guidance for Industry, Food and Drug Administration Rockville, MD 20852. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases.