Model-Guided Development of Immune Checkpoint Inhibitors

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Abstract

Immune checkpoint inhibitors, as a novel anti-tumor therapeutic modality, have gained widespread recognition for their remarkable efficacy and favorable safety profile across multiple tumor types. Model-informed Drug Development (MIDD), which emerged from the advancement of quantitative pharmacology, can accelerate the clinical trial process for new drugs and improve the accuracy of decision-making throughout the drug development process, particularly achieving success in the development of immune checkpoint inhibitors that are challenging to develop yet in substantial demand. This article primarily uses pembrolizumab as an example to elaborate on the specific applications of the MIDD methodology throughout the development process of immune checkpoint inhibitors, including the formulation of effective dosing regimens in early-stage development, the evaluation of clinical efficacy and validation of dosing regimen feasibility in late-stage development, and the post-approval re-evaluation and modification of dosing regimens, thereby providing a reference for MIDD-guided development of novel anti-tumor drugs.

Full Text

Model-Informed Drug Development for Immune Checkpoint Inhibitors

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Abstract: Immune checkpoint inhibitors (ICIs) have gained widespread recognition as a novel anticancer therapeutic modality due to their remarkable efficacy and favorable safety profile across multiple tumor types. Model-informed

drug development (MIDD), which has emerged from the advancing field of pharmacometrics, can accelerate clinical trials for new drugs and improve decision-making accuracy throughout the research process, particularly for ICIs that face high development challenges yet address substantial unmet medical needs. This review uses pembrolizumab as a primary example to illustrate the specific applications of MIDD in ICI development, including dose regimen selection in early development, clinical efficacy assessment and regimen validation in late-stage development, and post-market dose regimen re-evaluation and modification, thereby providing a reference for MIDD-guided development of novel anticancer agents.

Keywords: model-informed drug development; modeling and simulation; pharmacometrics; immune checkpoint inhibitors; pembrolizumab

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Immune checkpoint inhibitors (ICIs) represent a highly promising approach to cancer immunotherapy. By inhibiting immune checkpoint activity and blocking immunosuppressive pathways, ICIs can overcome immune tolerance and enhance the body's ability to recognize and eliminate tumor cells, thereby exerting potent antitumor effects and significantly improving treatment outcomes and quality of life for cancer patients [1]. Given their broad clinical application prospects, ICI drug development has rapidly become a major focus in anticancer therapy research [2]. Model-informed drug development (MIDD), an advanced approach grounded in pharmacokinetic-pharmacodynamic-disease progression modeling and simulation (M&S), provides guidance throughout all stages of new drug development [3]. Applying MIDD to ICI development can effectively reduce costs, enhance efficiency, and ultimately improve clinical care for cancer patients. This review synthesizes literature reports on MIDD-guided ICI development to provide insights for future anticancer drug research.

1. Immune Checkpoint Inhibitors

Since the first CTLA-4 inhibitor ipilimumab was approved in the United States in 2011, seven ICIs—primarily PD-1 (programmed cell death protein 1) and PD-L1 (programmed cell death-ligand 1) inhibitors—have subsequently received FDA approval and entered widespread clinical use [4]. In recent years, ICIs have demonstrated powerful antitumor activity in melanoma, non-small cell lung cancer, urothelial carcinoma, and other malignancies, earning FDA approvals for these indications [5-7]. As a novel drug class with unique mechanisms of action, significant efficacy against malignant tumors, and promising development

prospects, ICIs offer new hope for patients who have failed chemotherapy or targeted therapy.

Despite rapid advances in ICI-based cancer immunotherapy and substantial unmet patient needs, ICI development faces considerable challenges. First, compared with small-molecule chemotherapeutic agents, ICIs exhibit distinct pharmacokinetic/pharmacodynamic (PK/PD) characteristics. Traditional drug development methods and toxicity assessment protocols are not fully applicable to ICIs, necessitating new development paradigms to guide ICI research and clinical trial design [8]. Second, multiple ICI candidates have received FDA accelerated approval status [9], significantly shortening development timelines and placing greater emphasis on early-phase clinical trials [10]. Consequently, MIDD based on PK/PD-disease progression modeling and simulation has gained increasing attention and favor among researchers compared to conventional empirically-driven development processes [3, 11, 12].

2. Model-Informed Drug Development

Modeling and simulation techniques trace back to the 1990s and have become commonplace in drug development [13-15]. However, the concept of "model-informed drug development" gradually crystallized over the past decade, representing a landmark advancement in the field. MIDD fundamentally employs mathematical modeling, simulation, and statistical analysis to quantitatively describe and analyze extensive preclinical and clinical data, predict drug PK/PD behavior in vivo, and quantify uncertainties to provide rational decision-making support for drug development and therapy [16]. Since Sheiner and Jelliffe first proposed applying mathematical models to individualized drug therapy in the late 1960s [17, 18], the concept of MIDD [11] has emerged alongside the development and widespread application of pharmacometrics.

The core elements of MIDD involve integrating preclinical and clinical data through modeling and simulation to analyze the drug-disease-human relationship, thereby accelerating drug development, improving the accuracy of critical decisions, and guiding the entire development process [3]. Commonly used MIDD models include but are not limited to: population pharmacokinetic (PopPK) models, PK/PD models, exposure-response models, physiologically-based pharmacokinetic models, disease progression models, and model-based meta-analyses [3].

As an advanced drug development approach, MIDD follows a "Learn and Confirm Cycle" paradigm [19]: models are built from existing information to make predictions, which are then validated against data from actual studies. This iterative process allows continuous optimization and refinement of models throughout each stage of drug development. Compared with traditional approaches, MIDD plays a crucial role in guiding drug development, market authorization, and lifecycle management.

Given that MIDD application in China remains in its infancy, the Center for

Drug Evaluation of the National Medical Products Administration issued the country' s first MIDD technical guidance document, "Principles for Model-Informed Drug Development (Draft for Comment)," in August 2020 [20]. Drawing on domestic and international literature, this guidance elaborates general considerations and principles, emphasizing MIDD' s role in guiding drug development processes and decision-making. By leveraging modeling and simulation for precise quantitative trial design, MIDD can accelerate clinical trials, improve development paradigms, reduce costs, save time, and ultimately benefit more patients [21, 22].

3.1 Overview

The primary applications of MIDD across ICI development stages are summarized in Figure 1 [Figure 1: see original paper] and can be categorized into three aspects: (1) Early-stage development: MIDD helps determine effective doses and optimize clinical trial protocols to guide subsequent studies (examples in Table 1); (2) Late-stage development: MIDD evaluates benefit-risk profiles and explores intrinsic/extrinsic factors affecting PK/PD, integrating with clinical studies to validate dosing regimens and support labeling (examples in Table 2); and (3) Post-market stage: MIDD serves as a reliable decision-support tool to evaluate pre- and post-market data for dose re-evaluation and adjustment, promoting rational drug use [3, 23] (examples in Table 3).

To better illustrate MIDD' s value in ICI development, the following sections use pembrolizumab as a paradigm to detail MIDD' s specific applications following the "Learn and Confirm Cycle."

Table 1. Early-Stage Development Applications: Determining Effective Doses for Human Trials

MIDD Application Examples	Details
Ipilimumab	Phase II trial results showed 95% of patients receiving 10 mg/kg Q3W achieved target trough concentration of 20 g/mL [24], establishing this as the recommended regimen.

MIDD Application Examples	Details
Nivolumab	Phase I results demonstrated 3 mg/kg Q2W significantly reduced tumor progression and achieved higher objective response rates with saturated peripheral target occupancy [25], selecting this as the recommended regimen.
Pembrolizumab	(1) Murine translational PK/PD modeling showed receptor binding saturation and maximal probability of >30% tumor volume reduction at 2 mg/kg Q3W [26]; (2) Phase I data confirmed >90% target binding at 2 mg/kg Q3W with significantly higher probability of achieving 95% occupancy compared to lower doses [27].

MIDD Application Examples	Details
Avelumab	Phase I data showed >95% target occupancy at 10 mg/kg Q2W, with PopPK analysis revealing no significant relationship between clearance and body weight [28].
Durvalumab	Phase I/II results demonstrated good safety and efficacy at 10 mg/kg Q2W, achieving target trough concentration of 50 g/mL with saturated receptor binding [29].

Table 2. Late-Stage Development Applications: Validating Recommended Dosing Regimens

MIDD Application Examples	Details
Ipilimumab	PopPK analysis of Phase II data showed linear PK across 0.3-10 mg/kg and clearance increased with body weight, supporting weight-based dosing [30].

MIDD Application Examples	Details
Nivolumab	PopPK analysis indicated apparent volume of distribution and clearance increased with body weight, with no other significant factors requiring dose adjustment [31].
Pembrolizumab	(1) PopPK analysis found no clinically meaningful PK 影响因素 beyond body weight [32]; (2) Tumor growth kinetic modeling showed increased exposure did not improve response rates, with maximal effect across 2-10 mg/kg Q3W [33].
Atezolizumab	(1) PopPK showed linear PK across 1-20 mg/kg including labeled 1200 mg dose, with no significant covariates [34]; (2) Pediatric and adult studies supported 15 mg/kg Q3W in children despite 20% lower exposure, with similar safety profiles [35].

MIDD Application Examples	Details
Avelumab	PopPK modeling found no clinically meaningful covariates affecting PK, requiring no dose adjustment [36].
Durvalumab	PopPK simulations showed similar exposure between solid tumor and hematologic malignancy patients, with IgG levels being an important factor in multiple myeloma [37].

Table 3. Post-Market Applications: Dose Re-evaluation and Adjustment

MIDD Application Examples	Details
Nivolumab	PopPK model-based benefit-risk analysis supported transitions from 3 mg/kg Q2W → 240 mg Q2W → 480 mg Q4W, all FDA-approved [38].

MIDD Application Examples	Details
Pembrolizumab	PopPK modeling of exposure and clearance supported transition from 2 mg/kg Q3W to fixed 200 mg Q3W [39, 40], then to 400 mg Q6W, both FDA-approved [41].
Atezolizumab	PopPK modeling and simulation demonstrated similar exposure, efficacy, and safety for 840 mg Q2W and 1680 mg Q4W compared to labeled 1200 mg Q3W, supporting approval of these alternative regimens [42].
Avelumab	PopPK analysis showed comparable exposure and benefit-risk between weight-based 10 mg/kg Q2W and fixed 800 mg Q2W, supporting the regimen change [43].

MIDD Application Examples	Details
Durvalumab	PopPK analysis of fixed 1500 mg Q4W, 750 mg Q2W versus 10 mg/kg Q2W showed similar exposure without need for physiological/disease-based adjustments, supporting fixed-dose regimens [44, 45].

3.2 Pembrolizumab

Pembrolizumab is a highly potent and selective IgG4- humanized monoclonal antibody that binds to the PD-1 receptor, blocking its interaction with ligands and thereby reversing PD-1 pathway-mediated immune suppression to inhibit tumor immune evasion and restore antitumor immunity [46]. On September 4, 2014, the FDA granted accelerated approval for pembrolizumab in advanced melanoma patients previously treated with ipilimumab or BRAF inhibitors. Subsequently, pembrolizumab received additional approvals for unresectable/metastatic melanoma, metastatic non-small cell lung cancer, head and neck squamous cell carcinoma, and other cancers [47].

3.2.1 Early-Stage Development

In the initial phase of pembrolizumab development, determining the effective dose for subsequent clinical trials was the primary objective.

Researchers first constructed a murine PK/PD tumor growth inhibition model based on preclinical mouse data to predict the relationship between pembrolizumab plasma concentration and target receptor binding in tumors, then extrapolated the model to humans to predict tumor growth inhibition [26]. Results showed that at plasma concentrations >10 g/mL, maximal receptor binding in mouse tumors was approximately 60% and did not increase with higher concentrations. Additionally, doses $ $2 mg/kg Q3W reduced tumor diameter by >40% across various growth patterns, with the probability of >30% tumor volume reduction plateauing at 2 mg/kg Q3W. Further dose increases or shortened intervals (Q2W) did not significantly reduce tumor volume, supporting 2 mg/kg Q3W as the therapeutic regimen.

To validate this dose in humans, the first-in-human Phase I study (KEYNOTE-001) was initiated in 2011 to evaluate pembrolizumab' s safety, PK, and PD in

advanced solid tumors [46, 48]. This multicenter, multi-cohort, randomized trial included Cohort A to determine the effective dose. Part 1 (A & A-1) enrolled 17 subjects using a classic 3+3 dose-escalation design: nine subjects (Part A) received 1, 3, or 10 mg/kg with a second dose at day 28 then Q2W; seven subjects (Part A-1) started at 10 mg/kg Q2W. Ex vivo plasma IL-2 stimulation rate served as a surrogate for PD-1 receptor occupancy.

Results showed no dose-limiting toxicities across the three dose levels, precluding determination of a maximum tolerated dose (MTD). However, the pembrolizumab concentration producing 90% inhibition of IL-2 stimulation (IC90) was identified as approximately 10 g/mL, corresponding to 90% PD-1 receptor occupancy. Dose escalation (1-10 mg/kg) within 21 days did not significantly alter IL-2 stimulation rates or target binding. The 10 mg/kg Q2W regimen was safe, with saturated target binding at 10 g/mL and sustained inhibition for three weeks.

To further characterize PK/PD and confirm the effective dose, Part 2 (A-2) employed the "Learn and Confirm" framework. Thirteen subjects underwent dose escalation from low (0.005-0.06 mg/kg) to high doses (2 or 10 mg/kg) over three weeks, followed by 2 mg/kg Q3W or 10 mg/kg Q3W. PK/PD data from A-2 were combined with Parts A & A-1 to build a final PK/PD model for predicting behavior under different regimens.

PK data from A-2 demonstrated that steady-state trough concentrations exceeded 10 g/mL at both 1 mg/kg Q3W and 2 mg/kg Q3W, with >90% target binding for both doses. Model-based inference revealed that at steady state, 1 mg/kg Q3W yielded 50-60% probability of achieving 95% target binding, whereas 2 mg/kg Q3W increased this probability to 90% [27]. Notably, human target binding reached 90-95%, substantially higher than the 60% maximum observed in mouse tumors—possibly due to IL-2 stimulation rate being an imperfect surrogate for intratumoral binding and inherent interspecies differences. Based on these findings, 2 mg/kg Q3W was selected for subsequent clinical studies. Figure 2 [Figure 2: see original paper] summarizes this early-stage dose determination process.

3.2.2 Late-Stage Development

In late-stage development, MIDD focuses on identifying factors influencing PK/PD and re-evaluating clinical efficacy to validate dosing regimens. By systematically evaluating intrinsic and extrinsic factors affecting pembrolizumab exposure, researchers can verify regimen suitability and inform dosing for special populations such as those with hepatic or renal impairment.

Ahamadi et al. conducted a comprehensive PopPK analysis of pembrolizumab using data from KEYNOTE-001, -002, and -006 trials in advanced melanoma, NSCLC, and other solid tumors [32]. The analysis evaluated covariate effects using geometric mean ratio (GMR) of AUC, with clinically meaningful impact defined as GMR $ $0.5 or $ $5. Results showed that except for body weight,

factors including sex, age, hepatic/renal function, tumor type, and tumor burden had no clinically significant impact on PK (Figure 3 [Figure 3: see original paper]), supporting no dose adjustments and confirming the 2 mg/kg Q3W regimen.

Early translational PK/PD modeling had predicted tumor growth inhibition in humans. With accumulating clinical data, Chatterjee et al. built a tumor growth kinetic model using PopPK/PD analysis of KEYNOTE-001, -002, and -006 data to explore the exposure-response relationship [33]. The study demonstrated that increased pembrolizumab exposure did not improve response rates, with maximal clinical effect achieved across 2-10 mg/kg Q3W, further supporting 2 mg/kg Q3W. In September 2014, pembrolizumab received FDA approval for unresectable/metastatic melanoma after first-line therapy failure, with a recommended dose of 2 mg/kg Q3W [48, 49].

3.2.3 Post-Market Stage

Given interpatient PK variability, most anticancer drugs use weight-based dosing. However, for monoclonal antibodies like ICIs, distribution and clearance are minimally affected by body weight [50-52], and ICIs typically have wide therapeutic windows [53]. Transitioning to fixed dosing maintains efficacy while reducing drug waste and improving convenience [54], making it an attractive option.

Freshwater et al. re-evaluated pembrolizumab dosing based on PopPK analysis of 1,622 subjects from KEYNOTE-001, -002, and -006 [32, 39]. Allometric models described relationships between body weight and clearance/volume of distribution, showing minimal advantage for weight-based dosing. Additional data from KEYNOTE-010, -055, -024, -164, -045, and -052 were incorporated for model re-evaluation. Using steady-state AUC from 0-6 weeks (AUCss, 0-6weeks) as the evaluation metric, the PopPK model predicted exposure across regimens. While weight-based 2 mg/kg Q3W resulted in lower exposure in smaller patients, fixed 200 mg Q3W showed the opposite pattern, yet individual exposure ranges overlapped substantially between low- and high-weight patients, with similar PK variability. At the median weight of 77 kg, 154 mg Q3W would provide equivalent exposure to 2 mg/kg Q3W, but 200 mg Q3W was selected to ensure similar exposure across all patients, particularly heavier individuals, and to provide a convenient round number.

Further analysis showed similar concentration-time profiles and PK parameter distributions between the two regimens, with no significant differences in AUC or clearance across tumor types. For melanoma patients receiving 2 mg/kg Q3W over an average 6.2-month treatment course, eight doses would be administered. With pembrolizumab available only in 50 mg and 100 mg vials, each administration would waste at least 27 mg, totaling 216 mg over the course, whereas fixed dosing eliminates waste. Based on this comprehensive analysis, the benefit-risk profiles were similar, and in February 2018, the FDA approved the change to a

fixed 200 mg Q3W dose [40].

Lala et al. further evaluated the benefit-risk of 400 mg Q6W, 200 mg Q3W, and 2 mg/kg Q3W using PopPK analysis of 2,993 subjects from five trials across different tumor types [41]. Simulations compared average steady-state concentrations, peak concentrations, and trough concentrations (Figure 4 [Figure 4: see original paper]). While average steady-state concentrations were similar across all three regimens, 400 mg Q6W yielded slightly lower trough concentrations that overlapped with the 95% confidence intervals of the other regimens. Although 400 mg Q6W produced higher peak concentrations, these remained far below those of 10 mg/kg Q2W without significant safety concerns. These findings demonstrated similar benefit-risk profiles, with the extended interval reducing healthcare visits, saving patient time, and lowering medical costs. Based on these modeling results without additional clinical studies, the FDA approved the 400 mg Q6W fixed-dose regimen in April 2020 [55].

4. Conclusion and Outlook

Given the complex development processes and high costs of new drug research, MIDD can accelerate development, optimize clinical trial design, significantly shorten timelines, and improve success rates, benefiting both developers and patients. Using pembrolizumab as an example, this review has traced ICI development from early-stage dose determination through late-stage efficacy assessment and regimen validation to post-market dose re-evaluation and modification, demonstrating MIDD' s role as a reliable decision-making tool across all stages of anticancer drug development. As quantitative pharmacology techniques continue to evolve, MIDD will undoubtedly play an increasingly important role in anticancer drug development.

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Note: Figure translations are in progress. See original paper for figures.