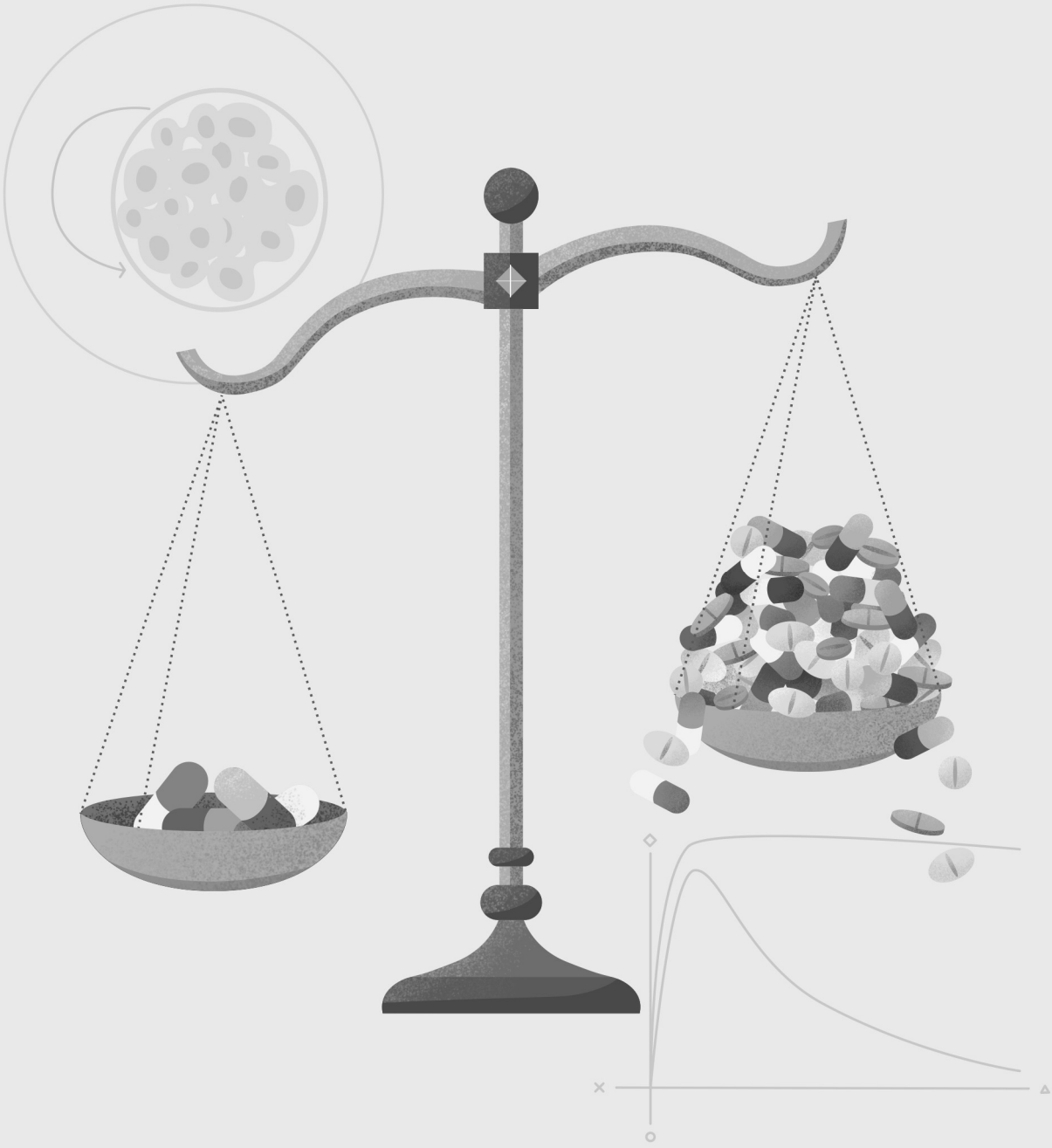
From labelled to the optimal clinical dose: model-informed dose optimization in medical oncology practice

Tan, Z.

Section V

General discussion



Chapter 7

General discussion and future perspectives

7.1. SUMMARY

Historically, oncology drug therapies were often dosed near the maximum tolerated dose (MTD) to maximize therapeutic effect, despite the increased risk of toxicity associated with these doses.[1] Inadequate dose optimization can lead to several negative outcomes for patients, primarily due to toxicity. These include a reduced quality of life, frequent dose adjustments when starting with the approved dose, decreased therapy effectiveness due to patients either discontinuing or switching treatments, and difficulties in developing effective combination therapies.[2,3] Regulatory initiatives such as the FDA's Project Optimus[4] emphasizes that dose optimization must be central to ongoing oncology drug development, encouraging the use of model-informed drug development for novel drugs, while little attention is given to the already approved therapies.

This thesis addresses the gap between the labelled and optimal clinical doses by combining systematic evaluation with population pharmacokinetic (POPPK) / pharmacodynamic (PD) modelling and simulation, a core tool for model-informed precision dosing (MIPD). POPPK/PD models allow the prediction of drug exposure and drug effect and variability across patients and can be used to inform the selection of the initial dose (a priori dose optimization) and to refine subsequent doses based on individual patient data (Bayesian dose optimization). In the end, the work presented in this thesis may help to lead to more personalized cancer treatments that maximize efficacy, minimize toxicity, and reduce drug-related expenses.

First, a systematic evaluation of the labelled dose and subsequent refinements of the dose of five approved targeted therapies (pazopanib, axitinib, cabozantinib, sunitinib, everolimus) and one immune checkpoint inhibitors (ICIs), nivolumab, in metastatic renal cell carcinoma (mRCC) was performed (**Chapter 2**). By reviewing labelled doses, dose-finding strategies, and real-world practice studies, we demonstrated that current tolerated doses in clinical practice for these targeted therapies were on average 46.1% to 86% lower than the approved dosages, with up to 75% of patients requiring adjustments due to toxicity. Among these, cabozantinib and pazopanib (discussed in more detail in **Chapter 3** and **Chapter 4**), showed the largest discrepancy between labelled and optimal clinical doses. Model-informed simulations suggested that for most targeted therapies, a 14–50% initial dose reduction would result in maintaining comparable efficacy while improving tolerability. For nivolumab, simulations confirmed adequate drug exposure with the approved flat-dose regimens, without an increase in adverse effects. These results highlight that for most of the targeted therapies studied, optimized

dosing regimens could improve patient outcomes and thus, should be considered in clinical practice and future labeling.

Having identified this gap, **Chapters 3–6** focused on applying POPPK/PD modelling and simulation for dose optimization and individualization. These chapters illustrate how MIPD can be used first for a priori dose optimization, identifying the optimal clinical dose at the population level, and subsequently for *Bayesian* dose optimization using individual patient data.

The primary objective of **Chapter 3** was to evaluate the POPPK model of cabozantinib, developed for its registration, using real-world therapeutic drug monitoring (TDM) data from patients. Model evaluation results showed that the cabozantinib TDM concentrations were adequately predicted by the published FDA cabozantinib POPPK model, except for a slightly higher clearance (CL) of 3.11 L/h compared to the reported value (2.23 L/h). A possible explanation could be that the clinical performance status of real-world patients was worse compared with the patients in registration studies. Consistent with post-marketing data analyzed in **Chapter 2**, we observed that a reduced dose of 40 mg once daily (QD) results in similar efficacy with improved tolerability. Additionally, model-based simulations showed that an alternative dosing regimen – taking 60 mg of cabozantinib fasted for 2 days followed by 1 day off – results in average exposure comparable to a 40 mg fasted daily dose, while reducing total drug expenses by 33.3% per month.

As presented in **Chapter 2**, pazopanib also has a relatively high dose reduction rate ranging from 36–60%, from the approved 800 mg QD dose. While a target trough concentration ($C_{min,ss}$) of ≥ 20.5 mg/L has been established for mRCC,[5] no specific threshold existed for liver toxicity. Therefore, in **Chapter 4**, we first investigated the POPPK and then explored the exposure-liver toxicity and exposure-tumor size relationship in 135 patients with mRCC and soft tissue sarcoma (STS). The liver toxicity model, based on 27 cases of Grade ≥ 2 liver toxicity out of 135 patients (20%), identified a Cmin,ss threshold of > 34 mg/L, which was associated with a 3.35-fold increased risk of toxicity ($p < 0.01$). Tumor size modeling confirmed a flat exposure-efficacy benefit relationship above the current 20.5 mg/L target. Overall, these findings suggest that decreasing the initial pazopanib dose from 800 mg QD to 600 mg QD, followed by TDM to maintain $C_{min,ss}$ within the optimal 20.5–34 mg/L range, can improve the efficacy-toxicity balance and mitigate treatment interruptions.

Although traditional chemotherapy was not investigated in **Chapter 2**, dose optimization of this group of very toxic drugs may still be warranted to improve patient outcomes

and quality of life. In **Chapter 5**, we evaluated 5-Fluorouracil (5-FU), a classical chemotherapy agent with narrow therapeutic window defined by an area under the curve ($AUC_{0\text{-}inf}$) target of 20–30 mg·h/L.[6] An a priori dose exploration was performed based on the developed 5-FU POPPK model, which was a two-compartment Michaelis-Menten model with body surface area as covariate on clearance, that was evaluated using data from 4 different clinical PK studies. For bolus and continuous infusion, the median AUC0-inf for the standard starting dose 400 mg/m^2 + 2400 mg/m^2 was 29 mg*h/L while 45% of the population exceed the 30 mg*h/L threshold due to temporary saturation of 5-FU metabolizing enzyme by bolus. Decreasing the dose to 200 mg/m^2 + 2400 mg/m^2 was predicted to improve the target achievement percentage. For continuous infusion, the 5-FU starting dose was advised to be increased from 2400 mg/m^2 to 2800 mg/m^2 for a higher target achievement rate. Limited sampling strategies and a dose adjustment MIPD application were developed enabling subsequent dose adjustment based on measured concentrations from previous cycles.

Finally, in addition to nivolumab in **Chapter 2**, we investigated the dose individualization of pembrolizumab in **Chapter 6**, another frequently used ICI. A time-dependent reduction in clearance was observed which correlated with the individual treatment response. This dynamic PK behavior implied that fixed dosing may result in overexposure later in therapy. To address this, we first evaluated and refined the published pembrolizumab POPPK model. Subsequently, we developed and evaluated model-informed dose and interval individualization algorithms. For patients with ≥ 30% reduction in clearance before the 5th cycle, dosing intervals could be extended from the labelled 200 mg every three weeks to 200 mg every six weeks, while maintaining adequate exposure. In addition, a < 10% reduction in clearance before the 5th cycle indicated inferior response to pembrolizumab. The "dose-stretching" approach not only preserves therapeutic benefits but also reduces cumulative drug burden and treatment costs, supporting more sustainable use of immunotherapy in practice.

7.2. GENERAL DISCUSSION AND PERSPECTIVES

Part I. Why dose reduction and modeling matter

7.2.1. Gaps between labelled and the optimal clinical dose

In oncology, the maximum tolerated dose (MTD) is still frequently used as the selected dose for phase III trials. This approach, that is common for cytotoxic chemotherapies, may not be appropriate for targeted therapies[7] and immune-modulating agents,[8] where higher doses do not necessarily lead to better efficacy.[9] Project Optimus aims to enhance the identification of the minimum effective dose for new submissions. However, for drugs approved before the Project Optimus era, there is a need to assess whether the labelled dose truly represents the optimal clinical dose[7-10] because in daily clinical practice these approved therapies frequently require dose reductions or premature discontinuation, which could hamper treatment adherence and interfere with optimal treatment outcomes.[11]

In this context, a post-marketing study analyzing recently approved oncology target therapies, showed that most drugs (65% of 31 reviewed anticancer agents) are considered candidates for dose optimization either by reducing the dose (32%) or modifying dosage regimens (32%).[12] Our study (**Chapter 2**) also identified high rates of required dose reductions or discontinuations for pazopanib, axitinib, cabozantinib, sunitinib and everolimus due to adverse effects, reflecting the fact that registered doses are frequently too high for real-world mRCC patients. These real-world findings highlight the importance of considering not only initial dose selection but also long-term tolerability in routine clinical practice in which patient characteristics may be different compared to those in clinical trials. When discrepancies between labelled dose and optimal dose are found, alternative dosing regimens should be considered supported by real-world and clinical trial data, to reduce toxicity while at the same time maintaining efficacy, and thus improving tolerability, patient quality of life.[13]

In addition to reviewing dose-limiting toxicities in clinical trials, it is also important to consider adverse events reported like late-onset toxicities, lower-grade toxicities, and necessary dose interruptions or reductions at any time. In particular, persistent low-grade toxicities can significantly diminish patients' quality of life. Therefore, Project Optimus[9] recommended that, in addition to reviewing dose-limiting toxicities, it is important to consider adverse events reported beyond the dose-limiting toxicities period (i.e. late-onset toxicities). It was also recommended that patient-reported

outcomes data should be collected where possible.[14] By implementing these considerations, the exposure–toxicity gap between clinical trials and routine practice could be closed.

To further understand the relationship between dose, exposure and efficacy, we leveraged a tumor size dynamics model to further provide evidence of pazopanib efficacy in real-world populations. Contrary to previously published tumor size models,[15] neither dose nor exposure had impact on tumor shrinkage in our analysis of both mRCC and STS patients, where the median $C_{min,ss}$ was 26.6 mg/L with IQR 20.6–31.1 mg/L. Pazopanib is not the only drug in oncology that shows an exposure target for efficacy with no additional benefits beyond this target. In **Chapter 2**, we provide evidence that the approved fixed dose of cabozantinib, sunitinib, and everolimus might be unnecessarily high due to the flat exposure-efficacy relationships in the evaluated doses. Therefore, starting at a lower dose with model-informed dose individualization to ensure that the patient stays within the therapeutic window could improve treatment tolerability, leading to less drug discontinuation, and potentially decreasing the risk of disease recurrence and treatment failure for most approved targeted therapies.

Currently, there is a lack of consensus regarding the level of evidence required to implement model-based alternative dosing regimens in clinical practice.[16] It is emphasized that Phase III randomized controlled trials are the most rigorous way of determining whether a favorable benefit-risk relation between treatment regimen and outcome exists.[17] In **Chapter 2**, we proposed an approach which consists of exposure simulations to leverage and interpolate between dose regimens investigated in dose-finding and/or registration trials, and efficacy and toxicity data from routine clinical practice. This approach could serve as prior information for designing dosing regimens for new trials or even serve as pivotal evidence to support the approval of untested doses, which has proven it value for the pediatric population.[18] In line with this, the FDA recently published a guideline to support the development of alternative dosing regimens for PD-1/ PD-L1 antibodies derived from a PK-based model-informed approach.[19] This shows that modelling and simulation is an important tool to develop alternative dose regimens suitable for application in clinical practice. This approach has, thus far, been employed to switch from weight-based dosing to flat dosing regimen of nivolumab/ pembrolizumab, for the purposes of patient and prescriber convenience without compromising therapy efficacy.[20]

7.2.2. Decrease of financial burden by modeling and simulation

Unlike most of the current chemotherapies, new modalities like mAbs are typically expensive and can be a financial burden for the patients or the healthcare system. Previous published case studies[21] have demonstrated how PK modeling complemented traditional pharmacoeconomic analyses by identifying the impact of specific patient subgroups, dose, dosing schedules, and adherence on cost-effectiveness during clinical development. In **Chapter 3** and **Chapter 6**, the possibility of saving drug expenses from leveraging PK data has been shown and discussed. The simulation study for cabozantinib indicated that an alternative dose regimen that consists of 60 mg of cabozantinib for two days and then skipping one day results in comparable average exposure when compared with 40 mg daily dose, while it could save 33.3% of the total drug expenses per month. In **Chapter 6**, we show that the dose interval of pembrolizumab can be extended from Q3W to Q6W if the clearance percentage decreases > 30% before 5th treatment cycle, which would save 50% of the drug expenses.

It can therefore be concluded that PK/PD modeling offers considerable potential in reducing the financial burden, particularly in oncology, where treatment costs can be prohibitively high. By accurately establishing the minimum effective dose that ensures adequate drug exposure, PK/PD modeling can additionally prevent overuse of expensive medications, thereby minimizing wastage. This is particularly important in mAbs therapies,[22-24] where the drug is often administered based on a linear body weight-based algorithm, while the actual relationships between clearance and body weight are often reported to be allometric with exponents of 0.75 or even lower[25] leading to significant drug wastage, specifically in certain body weight subgroups combined with partial vial usage per patient. More evidence has been published in studies[23, 24] showing that alternative dosing strategies, such as weight-band dosing, can result in significant cost savings for mAbs and new modalities like the antibody-drug conjugate sacituzumab govitecan.[23] A study on the dosing of mAbs for lung cancer demonstrated that modeling could potentially reduce drug expenses by as much as 28%, without compromising therapeutic efficacy.[24]

7.2.3. Role of modeling real-word data in dose optimization

When there is little or low-quality evidence available in publicly available sources, real-world data (RWD) from clinical practice is essential for dose optimization as it can provide information about the diverse and heterogeneous clinical population. RWD

can be incorporated into the PK/PD modeling framework[26] and hospital information systems can provide longitudinal PK/PD data to support model-based analysis.

However, as data complexity grows in RWD, multiple data-quality challenges, which could limit its application and usefulness, also arise.[27] RWD is often retrospective and observational, which will lead to i) biases and missing data, ii) inconsistent measurement or noise and iii) unrealistic parameter variability. In addition, the relatively smaller sample size of RWD may not provide sufficient statistical power to detect covariate effects or introduce false parameter-covariate relationships.

Modeling real-world clinical data using PK/PD approaches necessitates the integration of prior knowledge to address inherent data limitations and variability. Prior knowledge derived from controlled clinical trials, mechanistic models, and physiology may provide a foundational framework to guide data interpretation and ensure model robustness.[28, 29] The incorporation of prior knowledge allows models to anchor predictions in biological plausibility and historical data, reducing overfitting and improving the reliability of conclusions drawn from limited or noisy RWD. Bayesian frameworks are particularly effective in this context, as they enable the use of prior distributions to inform parameter estimation, allowing for continuous updating as new data becomes available.[30, 31] For instance, in oncology, prior knowledge about tumor growth dynamics or drug exposure-response relationships can significantly enhance the predictive capacity of models used for dose individualization.[28] However, to maximize its utility, prior knowledge must be critically assessed to avoid inadequate model extrapolation and be continuously updated using real-world evidence to reflect the evolving clinical landscape.[31]

Herein, we proposed a general workflow on how to incorporate multi-source data combined with real-world oncology routine practice evidence to inform dose optimization (Figure 7.1).

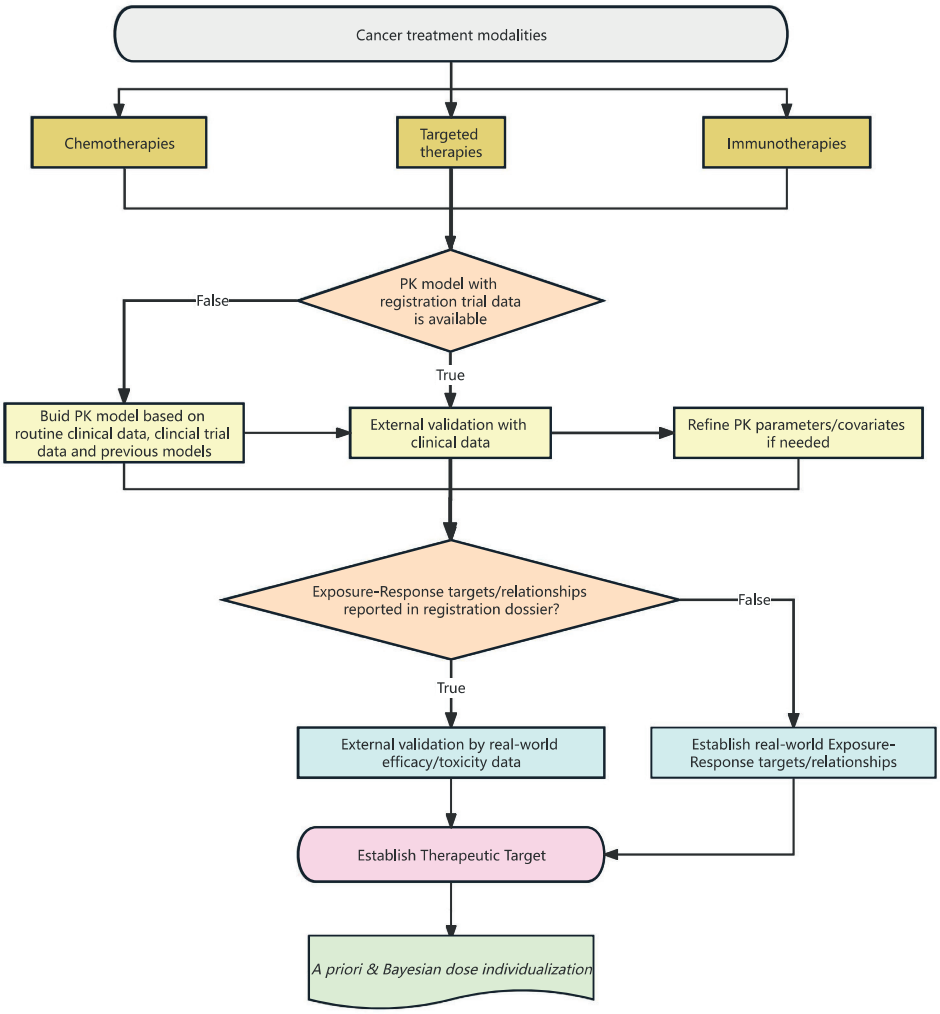


Figure 7.1. Workflow of PK/PD modeling with real-world oncology data.

Part II. How MIPD bridges evidence to implementation in oncology clinical practice

In oncology practice, MIPD seeks to account for not only inter-individual, but also time-dependent changes in drug exposure and response to optimize dosing for each individual patient over the entire cancer treatment duration. To allow for MIPD to be carried out, an evidence-based, clear, pre-defined therapeutic target needs to be available. For many clinicians and clinical pharmacists, PK/PD modeling using tools like NONMEM may be too labor-intensive and/or complex to use. To allow for easy use of MIPD, dedicated tools are therefore likely to come in the form of a mobile or web-based application that contain algorithms for drawing inferences from available individual clinical data

and evaluating future personalized treatment courses.[32] Therefore, the key elements of successful MIPD in medical oncology practice are: i) a well-established POPPK model for a priori dose optimization; ii) an appropriate sampling design to obtain individual Empirical *Bayesian* Estimates for subsequent dose adjustment; iii) a clear, robust PK/PD target to guide dose-optimization algorithms; and iv) user-friendly MIPD applications to broaden the use of pharmacometrics models in daily clinical practice.

7.2.4. Sampling designs

The limited sampling strategies (LSS) selection with the objective to reduce the number of samples while keeping appropriate estimation precision.[33] In a *Bayesian* MIPD setting, LSS determine which time points throughout the dosage interval are most relevant for predicting secondary PK parameters that serve as PKPD targets like $C_{min,ss}$ (**Chapter 4**), $AUC_{0\text{-}inf}$ (**Chapter 5**) and clearance percentage change (**Chapter 6**). Empirically, the LSS selection was based on manually selected time points where a few sampling regimens were tested.[34-38] Without model-based methods, trial-and-error selection may miss the best sampling scenarios. In **Chapter 5**, a workflow to evaluate an optimal LSS based on the Fisher Information Matrix or simulation was proposed Parameter precision and the ability to estimate model parameters are obtained by assessing the Bayesian Fisher Information Matrix.[39] **Chapter 5** focused on optimizing LSS for precise 5-FU individual $AUC_{0\text{-}inf}$ estimation, using both empirical and model-based approaches. Our results refine LSS designs by establishing a simulation-based workflow and achieving high agreements with the "true" AUC values while maintaining low prediction errors. This approach balances patient adherence and clinical utility, a key challenge identified in previous research.[35, 36]

7.2.5. Therapeutic PK/PD targets

For successful MIPD implementation in routine clinical practice, a solid and reliable PK/PD target is an important key prerequisite. Due to the high variability of both the PK and individual tumor heterogeneity,[40] oncology drugs often lack a "singular target" exposure that guarantees efficacy with minimized toxicity from a population level. Early pharmacodynamic markers (like short-term tumor shrinkage or biomarker changes) do not always predict long-term outcomes or survival because adaptive resistant clones can emerge.[41] The absence of a clear exposure–response relationship for efficacy because of the limited number of applied dosages is another challenge in target selection; therefore, it is critical to leverage the totality of evidence and model-based analyses rather than relying on any single target.

In **Chapter 5**, the previous established 5-FU $AUC_{0\text{-}inf}$ target of 20–30 mg*h/L[6] was directly used for dose optimization since it was based on several clinical trials and applied to modern 46-hour continuous infusion schedules, such as FOLFOX, FOLFIRI, FOLFIRINOX regimens[42] and also FLOT regimen which were all included in our analysis.

The target selection for ICIs like pembrolizumab was based on biomarkers like receptor occupancy rate or interleukin-2 (IL-2) stimulation. Due to the flat dose-response and exposure-response relationship of ICIs for the evaluated dosages, different studies utilize different targets for dose optimization strategies. The first target was a minimum effective concentration of 1.5 mg/L, defined as the steady-state trough maintained by ≥ 95% of the population given 1 mg/kg every 3 weeks for melanoma patients. In **Chapter 6**, we investigated the evidence from an early phase clinical trial and derived a target of 10 mg/L according to a published pembrolizumab PK/PD relationship with data from KEYNOTE-001 trial.[43] Saturation of ex vivo target IL-2 engagement in blood began at > 1 mg/kg every 3 weeks. More specifically, according to the PK/PD Emax equation in KEYNOTE-001, pembrolizumab trough concentration of 5 mg/L would lead to 90% of the IL-2 stimulation while 10 mg/L could result in 95% of the IL-2 stimulation. Therefore, in this study, the 10 mg/L target was used for generating clinical MIPD recommendations and the 5 mg/L target was used for exploration purpose for melanoma patients.

7.2.6. MIPD tools for broader application of PK/PD models in routine clinical practice

In both **Chapter 4** and **Chapter 5**, MIPD tools were developed since the dose optimization algorithm was complex and a shiny-based application would be more convenient for routine clinical practice. MIPD applications, such as InsightRX Nova,[44] ModVizPop,[45] and gPKPDviz,[46] represent promising solutions since they combine user-friendly interfaces with the computational power of advanced PK/PD models. Most applications leverage the flexibility of the R Shiny framework to create interactive, web-based platforms that allow clinicians to visualize real-time simulations, explore alternative dosing regimens, and tailor treatments to individual patients without requiring extensive expertise in pharmacometrics. By integrating population models with *Bayesian* frameworks,[47] Shiny-based applications simplify the process of dose optimization, offering intuitive workflows that align with clinical decision-making processes.

However, broader deployment of these tools in patient care faces substantial regulatory hurdles. Currently, most MIPD applications are classified as medical devices,[48] which means they must comply with rigorous requirements that come with high costs.

Extensive legal documentation, validation, and testing are mandatory for every version of change, even when a tool is used solely within ISO 15189 laboratory settings. This regulatory ambiguity complicates widespread clinical implementation. In the absence of clear regulatory pathways, particularly in the EU under MDR 2017/745 or FDA requirements, many users may resort to using these tools outside their intended use ("off-label use"). Off-label dosing decisions carry uncertainties: without proper oversight and validation, they may potentially expose patients to safety risks.[48, 49] Additionally, the integration of MIPD into clinical workflows requires overcoming operational barriers, such as the need for precise data input/check, model validation, and proper healthcare professional education.[49, 50] Given these challenges, collaborative efforts involving regulators, pharmacometricians, and clinical stakeholders are urgently needed. Clear regulatory pathways, standardized validation processes, and effective implementation with professional education are warranted.[48-50]

To date, no high-quality (randomized) trials have been conducted to evaluate the performance of MIPD or dose-optimization tools, even though such evidence would be of value for convincing stakeholders of the value of these model-based approaches. The efficacy and safety of MIPD-based dosing and BSA-based dosing of 5-FU will be further evaluated in the ongoing PERFUPANC study (EUCT number:2024-510576-21-00). Studies on other anti-cancer drugs or even other disease are warranted.

7.2.7. MIPD in clinical practice: from dose adjustment to treatment decision

For several oncology mAbs, POPPK/PD analysis has revealed that CL decreases over time, often described using a sigmodal Imax function (e.g. pembrolizumab in **Chapter 6**), reflecting improved disease status or tumor shrinkage during therapy. The first example is nivolumab, for which the steady state CL is estimated to decrease by approximately 20% from the first dose, although individual changes vary widely (from 75% decrease to a 25% increase), depending on patient prognosis.[51] Subsequent studies also revealed a time-dependent reduction of CL of pembrolizumab for which the extent of the decrease correlated with tumor size dynamics and best overall response.[52] Further model-based analyses incorporating longitudinal covariates (e.g. tumor shrinkage over time, improving albumin) were able to better capture this decrease in CL over time.[53] Therefore, accounting for time-dependent changes in CL is critical for accurate, early exposure predictions and exposure–response assessments in immuno-oncology settings in addition to standard radiology and imaging examinations.

Based on the information above, the value of PK/PD modeling should not only be limited to initial dose optimization but should also play a role in supporting clinical decision making on treatment continuation or discontinuation. This can be achieved by evaluating the PK profile during early treatment using TDM samples. Early pembrolizumab CL is proven to be a feasible prognostic biomarker for survival[52-54] while the uncertainty of this early prediction is inherent due to the individual variability in both PK and response. In a recent study, pembrolizumab clearance showed high sensitivity, but moderate positive predictive value to predict the overall survival.[54] Emerging PD biomarkers, such as circulating tumor DNA (ctDNA), can be a powerful tool to complement the PK information. It has been applied for cancer early diagnosis, prognosis prediction, and treatment monitoring over a wide range of cancer types.[55] With non-linear mixed effect modeling, the percentage change from baseline of ctDNA features can be used as early biomarker to distinguish responders and non-responders to immune therapies.[56] providing an additional quantitative tool for personalized treatment decision. Together, these modeling approaches can expand MIPD from dose optimization towards real-time treatment guidance.

7.3. CONCLUSIONS

This thesis comprehensively evaluates the opportunities of model-based dose optimization of approved targeted therapies, immunotherapies and chemotherapy in medical oncology. The thesis started with a comprehensive review and systematic evaluation to evaluate the currently approved dosing regimens of pazopanib, cabozantinib, axitinib, sunitinib, everolimus and nivolumab in mRCC, in the context of project Optimus. Through a combination of literature review, real world evidence on toxicity and efficacy, and model-informed simulations, we identified optimized dosing regimens that could improve drug tolerability while maintaining efficacy. We recommend that these optimized dosing regimens should be considered for being used in routine clinical practice, and that the optimal exposure range should be included in drug labels and/or guidelines to support pharmacokinetically guided dose individualization. After this review, we specifically studied two specific targeted therapies in mRCC, i.e. cabozanitnib and pazopanib, to quantitatively characterize and bridge the gaps between the labelled and optimal clinical dose with routine clinical practice data. For cabozantinib, the publicly available FDA POPPK model with re-estimated CL resulted in adequate prediction of real-world cabozantinib pharmacokinetic data. Alternative dosing regimens with and without the presence of known food interactions were

proposed which resulted in potential strategies to significantly reduce cabozantinib drug expenses. For pazopanib, an initial pazopanib dose of 600 mg fasted, followed by model-informed precision dosing to maintain $C_{min,ss}$ between 20–34 mg/L, was identified to likely improve the efficacy-toxicity balance and mitigate treatment interruptions. In the following section, the thesis focused on providing a basis for the implementation of MIPD of 5-FU and pembrolizumab in routine clinical pharmacy care. For the chemotherapeutic agent 5-FU, based on the POPPK model using data from four clinical studies, we proposed to decrease the initial dose to 200+2400 mg/m^2 for bolus and continuous infusion, while for continuous infusion only, we propose to increase the initial dose to 2800 mg/m^2 to better achieve the $AUC_{0\text{-}inf}$ target of 20–30 mg·h/L on the population level. The utilization of optimal sampling together with the developed MIPD shiny application subsequently allows for precise estimation of 5-FU $AUC_{0\text{-}inf}$ in routine clinical practice and may provide dose individualization recommendations that lead to a reduction in severe toxicities without compromising efficacy. For pembrolizumab, following external evaluation and refinement of a published pembrolizumab POPPK model, model-based simulations evaluating the extension of the dosing interval based on individual CL reduction showed that for individuals with ≥ 30% reduction in CL, the dosing interval could be stretched from 200 mg Q3W to 200 mg Q6W. A CL reduction < 10% at the fourth cycle indicated inferior best overall response to pembrolizumab in this population.

Throughout the analyses, we learned new lessons in bridging the dose between the labelled and optimal clinical dose from exposure, efficacy, safety and financial perspectives. We shared our insights to serve as a reference for achieving successful MIPD implementation in medical oncology, varying from a priori dose optimization, optimal sampling design, Bayesian dose optimization to a user-friendly MIPD application.

REFERENCES

1. Fourie Zirkelbach, J.; Shah, M.; Vallejo, J.; Cheng, J.; Ayyoub, A.; Liu, J.; Hudson, R.; Sridhara, R.; Ison, G.; Amiri-Kordestani, L.; et al. Improving Dose-Optimization Processes Used in Oncology Drug Development to Minimize Toxicity and Maximize Benefit to Patients. Journal of Clinical Oncology 2022, 40 (30), 3489-3500. DOI: 10.1200/JCO.22.00371 (acccessed 2025/05/25).
2. Cannistra, S. A. Challenges and Pitfalls of Combining Targeted Agents in Phase I Studies. Journal of Clinical Oncology 26 (22), 3665-3667. DOI: 10.1200/JCO.2008.17.2676 (acccessed 2025/05/25).
3. Levit, L. A.; Arora, S.; Kluetz, P. G.; Magnuson, A.; Rahman, A.; Harvey, R. D. Call to Action for Improving Oral Anticancer Agent Adherence. Journal of Clinical Oncology 2022, 40 (10), 1036-1040. DOI: 10.1200/JCO.21.02529 (acccessed 2025/05/25).
4. Murphy, R.; Halford, S.; Symeonides, S. N. Project Optimus, an FDA initiative: Considerations for cancer drug development internationally, from an academic perspective. Front Oncol 2023, 13, 1144056. DOI: 10.3389/fonc.2023.1144056

5. Suttle, A. B.; Ball, H. A.; Molimard, M.; Hutson, T. E.; Carpenter, C.; Rajagopalan, D.; Lin, Y.; Swann, S.; Amado, R.; Pandite, L. Relationships between pazopanib exposure and clinical safety and efficacy in patients with advanced renal cell carcinoma. British Journal of Cancer 2014, 111 (10), 1909-1916. DOI: 10.1038/bjc.2014.503.
6. Beumer, J. H.; Chu, E.; Allegra, C.; Tanigawara, Y.; Milano, G.; Diasio, R.; Kim, T. W.; Mathijssen, R. H.; Zhang, L.; Arnold, D.; et al. Therapeutic Drug Monitoring in Oncology: International Association of Therapeutic Drug Monitoring and Clinical Toxicology Recommendations for 5-Fluorouracil Therapy. Clin Pharmacol Ther 2019, 105 (3), 598-613. DOI: 10.1002/cpt.1124
7. Gurram, S.; Al Harthy, M.; Ball, M. W. The changing landscape of systemic therapy in metastatic renal cell carcinoma: an update. Discovery medicine 2020, 29 (158), 191-199. From NLM.
8. Hizal, M.; Sendur, M. A. N.; Bilgin, B.; Akinci, M. B.; Sener Dede, D.; Yalcin, B. A historical turning point for the treatment of advanced renal cell carcinoma: inhibition of immune checkpoint. Current medical research and opinion 2020, 36 (4), 625-635. DOI: 10.1080/03007995.2020.1716705
9. U.S. Food and Drug Administration. Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases, Guidance for Industry. 2024.
10. Kurzrock, R.; Lin, C.-C.; Wu, T.-C.; Hobbs, B. P.; Pestana, R. C.; Hong, D. S. Moving Beyond 3+3: The Future of Clinical Trial Design. American Society of Clinical Oncology Educational Book 2021, (41), e133-e144. DOI: 10.1200/EDBK_319783 (acccessed 2025/01/02).
11. Hoog, C.; Mehra, N.; Maliepaard, M.; Bol, K.; Gelderblom, H.; Sonke, G. S.; de Langen, A. J.; van de Donk, N.; Janssen, J.; Minnema, M. C.; et al. Dose selection of novel anticancer drugs: exposing the gap between selected and required doses. Lancet Oncol 2024, 25 (8), e340-e351. DOI: 10.1016/s1470-2045(24)00134-7
12. Hoog, C. J. P. O. t.; Mehra, N.; Maliepaard, M.; Bol, K.; Gelderblom, H.; Sonke, G. S.; de Langen, A. J.; van de Donk, N. W. C. J.; Janssen, J. J. W. M.; Minnema, M. C.; et al. Dose selection of novel anticancer drugs: exposing the gap between selected and required doses. The Lancet Oncology 2024, 25 (8), e340-e351. DOI: 10.1016/S1470-2045(24)00134-7 (acccessed 2024/12/25).
13. Wessel, K. M.; Drezner, N.; Shord, S. S.; Shah, M.; Theoret, M. R.; Donoghue, M. Dosage Optimization of Pediatric Oncology Products: Our Patients Deserve Better. Clin Cancer Res 2025, 31 (13), 2552-2555. DOI: 10.1158/1078-0432.Ccr-24-4325
14. Alger, E.; Van Zyl, M.; Aiyegbusi, O. L.; Chuter, D.; Dean, L.; Minchom, A.; Yap, C. Patient and public involvement and engagement in the development of innovative patient-centric early phase dose-finding trial designs. Res Involv Engagem 2024, 10 (1), 63. DOI: 10.1186/s40900-024-00599-7
15. Bonate, P. L.; Suttle, A. B. Modeling tumor growth kinetics after treatment with pazopanib or placebo in patients with renal cell carcinoma. Cancer Chemother Pharmacol 2013, 72 (1), 231-240. DOI: 10.1007/s00280-013-2191-0
16. Overbeek, J. K.; Ter Heine, R.; Verheul, H. M. W.; Chatelut, E.; Rudek, M. A.; Gurney, H.; Plummer, R.; Gilbert, D. C.; Buclin, T.; Burger, D. M.; et al. Off-label, but on target: the evidence needed to implement alternative dosing regimens of anticancer drugs. ESMO Open 2023, 8 (1), 100749. DOI: 10.1016/j.esmoop.2022.100749
17. Sibbald, B.; Roland, M. Understanding controlled trials: Why are randomised controlled trials important? BMJ 1998, 316 (7126), 201. DOI: 10.1136/bmj.316.7126.201.
18. Bi, Y.; Liu, J.; Li, F.; Yu, J.; Bhattaram, A.; Bewernitz, M.; Li, R.-j.; Ahn, J.; Earp, J.; Ma, L.; et al. Model-Informed Drug Development in Pediatric Dose Selection. The Journal of Clinical Pharmacology 2021, 61 (S1), S60-S69. DOI: https://doi.org/10.1002/jcph.1848.
19. U.S. Food and Drug Administration. Pharmacokinetic-based criteria for supporting alternative dosing regimens of programmed cell death receptor-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) blocking antibodies for treatment of patients with cancer: guidance for industry. 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetic-based-criteria-supporting-alternative-dosing-regimens-programmed-cell-death-receptor (accessed 2023 05-01-2023).
20. ter Heine, R.; van den Heuvel, M. M.; Piet, B.; Deenen, M. J.; van der Wekken, A. J.; Hendriks, L. E. L.; Croes, S.; van Geel, R. M. J. M.; Jansman, F. G. A.; Boshuizen, R. C.; et al. A Systematic Evaluation of Cost-Saving Dosing Regimens for Therapeutic Antibodies and Antibody-Drug Conjugates for the Treatment of Lung Cancer. Targeted Oncology 2023, 18 (3), 441-450. DOI: 10.1007/s11523-023-00958-6.

21. Srinivasan, M.; White, A.; Chaturvedula, A.; Vozmediano, V.; Schmidt, S.; Plouffe, L.; Wingate, L. T. Incorporating Pharmacometrics into Pharmacoeconomic Models: Applications from Drug Development. Pharmacoeconomics 2020, 38 (10), 1031-1042. DOI: 10.1007/s40273-020-00944-0
22. Kicken, M. P.; Deenen, M. J.; Moes, D.; Hendrikx, J.; van den Borne, B.; Dumoulin, D. W.; van der Wekken, A. J.; van den Heuvel, M. M.; Ter Heine, R. An Evidence-Based Rationale for Dose De-escalation of Subcutaneous Atezolizumab. Target Oncol 2024, 19 (5), 779-787. DOI: 10.1007/s11523-024-01087-4
23. Moes, D.; Hendrikx, J.; Guchelaar, H. J.; Mathijssen, R. H. J.; Bakker, J. L.; Dezentjé, V. O.; de Rouw, N.; van Erp, N. P.; Smit, E. F.; van den Heuvel, M. M.; et al. Model-Informed Development of a Cost-Saving Dosing Regimen for Sacituzumab Govitecan. Target Oncol 2024, 19 (5), 789-796. DOI: 10.1007/s11523-024-01075-8
24. Ter Heine, R.; van den Heuvel, M. M.; Piet, B.; Deenen, M. J.; van der Wekken, A. J.; Hendriks, L. E. L.; Croes, S.; van Geel, R.; Jansman, F. G. A.; Boshuizen, R. C.; et al. A Systematic Evaluation of Cost-Saving Dosing Regimens for Therapeutic Antibodies and Antibody-Drug Conjugates for the Treatment of Lung Cancer. Target Oncol 2023, 18 (3), 441-450. DOI: 10.1007/s11523-023-00958-6
25. Germovsek, E.; Cheng, M.; Giragossian, C. Allometric scaling of therapeutic monoclonal antibodies in preclinical and clinical settings. MAbs 2021, 13 (1), 1964935. DOI: 10.1080/19420862.2021.1964935
26. Tyrer, F.; Bhaskaran, K.; Rutherford, M. J. Immortal time bias for life-long conditions in retrospective observational studies using electronic health records. BMC Med Res Methodol 2022, 22 (1), 86. DOI: 10.1186/s12874-022-01581-1
27. Ho, Y. F.; Hu, F. C.; Lee, P. I. The Advantages and Challenges of Using Real-World Data for Patient Care. Clin Transl Sci 2020, 13 (1), 4-7. DOI: 10.1111/cts.12683
28. Maier, C.; de Wiljes, J.; Hartung, N.; Kloft, C.; Huisinga, W. A continued learning approach for model-informed precision dosing: Updating models in clinical practice. CPT: pharmacometrics & systems pharmacology 2022, 11 (2), 185-198. DOI: 10.1002/psp4.12745
29. Maier, C.; Hartung, N.; de Wiljes, J.; Kloft, C.; Huisinga, W. Bayesian Data Assimilation to Support Informed Decision Making in Individualized Chemotherapy. CPT: pharmacometrics & systems pharmacology 2020, 9 (3), 153-164. DOI: 10.1002/psp4.12492
30. Hughes, J. H.; Keizer, R. J. A hybrid machine learning/pharmacokinetic approach outperforms maximum a posteriori Bayesian estimation by selectively flattening model priors. CPT: pharmacometrics & systems pharmacology 2021, 10 (10), 1150-1160. DOI: 10.1002/psp4.12684
31. Leil, T. A. A bayesian perspective on estimation of variability and uncertainty in mechanism-based models. CPT: pharmacometrics & systems pharmacology 2014, 3 (6), e121. DOI: 10.1038/psp.2014.19
32. Keizer, R. J.; Ter Heine, R.; Frymoyer, A.; Lesko, L. J.; Mangat, R.; Goswami, S. Model-Informed Precision Dosing at the Bedside: Scientific Challenges and Opportunities. CPT Pharmacometrics Syst Pharmacol 2018, 7 (12), 785-787. DOI: 10.1002/psp4.12353
33. Xavier, R. M.; Sharumathi, S. M.; Kanniyappan Parthasarathy, A.; Mani, D.; Mohanasundaram, T. Limited sampling strategies for therapeutic drug monitoring of anti-tuberculosis medications: A systematic review of their feasibility and clinical utility. Tuberculosis 2023, 141, 102367. DOI: https://doi.org/10.1016/j.tube.2023.102367.
34. Goirand, F.; Lemaitre, F.; Launay, M.; Tron, C.; Chatelut, E.; Boyer, J.-C.; Bardou, M.; Schmitt, A. How can we best monitor 5-FU administration to maximize benefit to risk ratio? Expert Opinion on Drug Metabolism & Toxicology 2018, 14 (12), 1303-1313. DOI: 10.1080/17425255.2018.1550484.
35. Jacob, J.; Mathew, S. K.; Chacko, R. T.; Aruldhas, B. W.; Singh, A.; Prabha, R.; Mathew, B. S. Systemic exposure to 5-fluorouracil and its metabolite, 5,6-dihydrofluorouracil, and development of a limited sampling strategy for therapeutic drug management of 5-fluorouracil in patients with gastrointestinal malignancy. British journal of clinical pharmacology 2021, 87 (3), 937-945. DOI: https://doi.org/10.1111/bcp.14444.
36. Mueller, F.; Büchel, B.; Köberle, D.; Schürch, S.; Pfister, B.; Krähenbühl, S.; Froehlich, T. K.; Largiader, C. R.; Joerger, M. Gender-specific elimination of continuous-infusional 5-fluorouracil in patients with gastrointestinal malignancies: results from a prospective population pharmacokinetic study. Cancer chemotherapy and pharmacology 2013, 71 (2), 361-370. DOI: 10.1007/s00280-012-2018-4.
37. Gusella, M.; Ferrazzi, E.; Ferrari, M.; Padrini, R. New limited sampling strategy for determining 5-fluorouracil area under the concentration-time curve after rapid intravenous bolus. Therapeutic drug monitoring 2002, 24 (3), 425-431. DOI: 10.1097/00007691-200206000-00016

38. Saif, M. W.; Choma, A.; Salamone, S. J.; Chu, E. Pharmacokinetically Guided Dose Adjustment of 5-Fluorouracil: A Rational Approach to Improving Therapeutic Outcomes. JNCI: Journal of the National Cancer Institute 2009, 101 (22), 1543-1552. DOI: 10.1093/jnci/djp328 (acccessed 12/1/2024).
39. Combes, F. P.; Retout, S.; Frey, N.; Mentré, F. Prediction of shrinkage of individual parameters using the bayesian information matrix in non-linear mixed effect models with evaluation in pharmacokinetics. Pharmaceutical research 2013, 30 (9), 2355-2367. DOI: 10.1007/s11095-013-1079-3
40. McQuerry, J. A.; Chang, J. T.; Bowtell, D. D. L.; Cohen, A.; Bild, A. H. Mechanisms and clinical implications of tumor heterogeneity and convergence on recurrent phenotypes. J Mol Med (Berl) 2017, 95 (11), 1167-1178. DOI: 10.1007/s00109-017-1587-4
41. Gao, W.; Liu, J.; Shtylla, B.; Venkatakrishnan, K.; Yin, D.; Shah, M.; Nicholas, T.; Cao, Y. Realizing the promise of Project Optimus: Challenges and emerging opportunities for dose optimization in oncology drug development. CPT Pharmacometrics Syst Pharmacol 2024, 13 (5), 691-709. DOI: 10.1002/psp4.13079
42. Kaldate, R. R.; Haregewoin, A.; Grier, C. E.; Hamilton, S. A.; McLeod, H. L. Modeling the 5-fluorouracil area under the curve versus dose relationship to develop a pharmacokinetic dosing algorithm for colorectal cancer patients receiving FOLFOX6. Oncologist 2012, 17 (3), 296-302. DOI: 10.1634/theoncologist.2011-0357
43. Elassaiss-Schaap, J.; Rossenu, S.; Lindauer, A.; Kang, S. P.; de Greef, R.; Sachs, J. R.; de Alwis, D. P. Using Model-Based "Learn and Confirm" to Reveal the Pharmacokinetics-Pharmacodynamics Relationship of Pembrolizumab in the KEYNOTE-001 Trial. CPT: Pharmacometrics & Systems Pharmacology 2017, 6 (1), 21-28. DOI: https://doi.org/10.1002/psp4.12132 (acccessed 2025/06/17).
44. Del Valle-Moreno, P.; Suarez-Casillas, P.; Mejías-Trueba, M.; Ciudad-Gutiérrez, P.; Guisado-Gil, A. B.; Gil-Navarro, M. V.; Herrera-Hidalgo, L. Model-Informed Precision Dosing Software Tools for Dosage Regimen Individualization: A Scoping Review. Pharmaceutics 2023, 15 (7). DOI: 10.3390/pharmaceutics15071859
45. Vaddady, P.; Kandala, B. ModVizPop: A shiny interface for empowering teams to perform interactive pharmacokinetic/pharmacodynamic simulations. CPT: pharmacometrics & systems pharmacology 2021, 10 (11), 1323-1331. DOI: 10.1002/psp4.12697
46. Lu, T.; Poon, V.; Brooks, L.; Velasquez, E.; Anderson, E.; Baron, K.; Jin, J. Y.; Kågedal, M. gPKPDviz: A flexible R shiny tool for pharmacokinetic/pharmacodynamic simulations using mrgsolve. CPT: pharmacometrics & systems pharmacology 2024, 13 (3), 341-358. DOI: 10.1002/psp4.13096
47. Le Louedec, F.; Puisset, F.; Thomas, F.; Chatelut, É.; White-Koning, M. Easy and reliable maximum a posteriori Bayesian estimation of pharmacokinetic parameters with the open-source R package mapbayr. CPT: pharmacometrics & systems pharmacology 2021, 10 (10), 1208-1220. DOI: 10.1002/psp4.12689
48. Keizer, R. J.; Dvergsten, E.; Kolacevski, A.; Black, A.; Karovic, S.; Goswami, S.; Maitland, M. L. Get Real: Integration of Real-World Data to Improve Patient Care. Clinical Pharmacology & Therapeutics 2020, 107 (4), 722-725. DOI: https://doi.org/10.1002/cpt.1784.
49. Dibbets, A. C.; Koldeweij, C.; Osinga, E. P.; Scheepers, H. C. J.; de Wildt, S. N. Barriers and Facilitators for Bringing Model-Informed Precision Dosing to the Patient's Bedside: A Systematic Review. Clinical Pharmacology & Therapeutics 2025, 117 (3), 633-645. DOI: https://doi.org/10.1002/cpt.3510.
50. Darwich, A. S.; Ogungbenro, K.; Vinks, A. A.; Powell, J. R.; Reny, J.-L.; Marsousi, N.; Daali, Y.; Fairman, D.; Cook, J.; Lesko, L. J.; et al. Why Has Model-Informed Precision Dosing Not Yet Become Common Clinical Reality? Lessons From the Past and a Roadmap for the Future. Clinical Pharmacology & Therapeutics 2017, 101 (5), 646-656. DOI: https://doi.org/10.1002/cpt.659.
51. Liu, C.; Yu, J.; Li, H.; Liu, J.; Xu, Y.; Song, P.; Liu, Q.; Zhao, H.; Xu, J.; Maher, V. E.; et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. Clin Pharmacol Ther 2017, 101 (5), 657-666. DOI: 10.1002/cpt.656
52. Li, H.; Yu, J.; Liu, C.; Liu, J.; Subramaniam, S.; Zhao, H.; Blumenthal, G. M.; Turner, D. C.; Li, C.; Ahamadi, M.; et al. Time dependent pharmacokinetics of pembrolizumab in patients with solid tumor and its correlation with best overall response. J Pharmacokinet Pharmacodyn 2017, 44 (5), 403-414. DOI: 10.1007/s10928-017-9528-y
53. Li, H.; Sun, Y.; Yu, J.; Liu, C.; Liu, J.; Wang, Y. Semimechanistically Based Modeling of Pembrolizumab Time-Varying Clearance Using 4 Longitudinal Covariates in Patients With Non–Small Cell Lung Cancer. Journal of Pharmaceutical Sciences 2019, 108 (1), 692-700. DOI: 10.1016/j.xphs.2018.10.064 (acccessed 2025/04/28).

54. de Vries, F.; Otten, L.-S.; Piet, B.; Franssen, E. J. F.; Smit, A. A. J.; van den Heuvel, M. M.; ter Heine, R.; The, D.-S. G. Early pembrolizumab clearance as prognostic biomarker for non-response in patients with advanced non-small cell lung cancer. International Journal of Cancer 2025. DOI: https://doi.org/10.1002/ijc.70052 (acccessed 2025/08/04).
55. Yin, A.; van Hasselt, J. G. C.; Guchelaar, H. J.; Friberg, L. E.; Moes, D. Anti-cancer treatment schedule optimization based on tumor dynamics modelling incorporating evolving resistance. Sci Rep 2022, 12 (1), 4206. DOI: 10.1038/s41598-022-08012-7
56. Nguyen Phuong, L.; Salas, S.; Benzekry, S. Computational Modeling for Circulating Cell-Free DNA in Clinical Oncology. JCO Clinical Cancer Informatics 2025, (9), e2400224. DOI: 10.1200/CCI-24-00224 (acccessed 2025/07/02).