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

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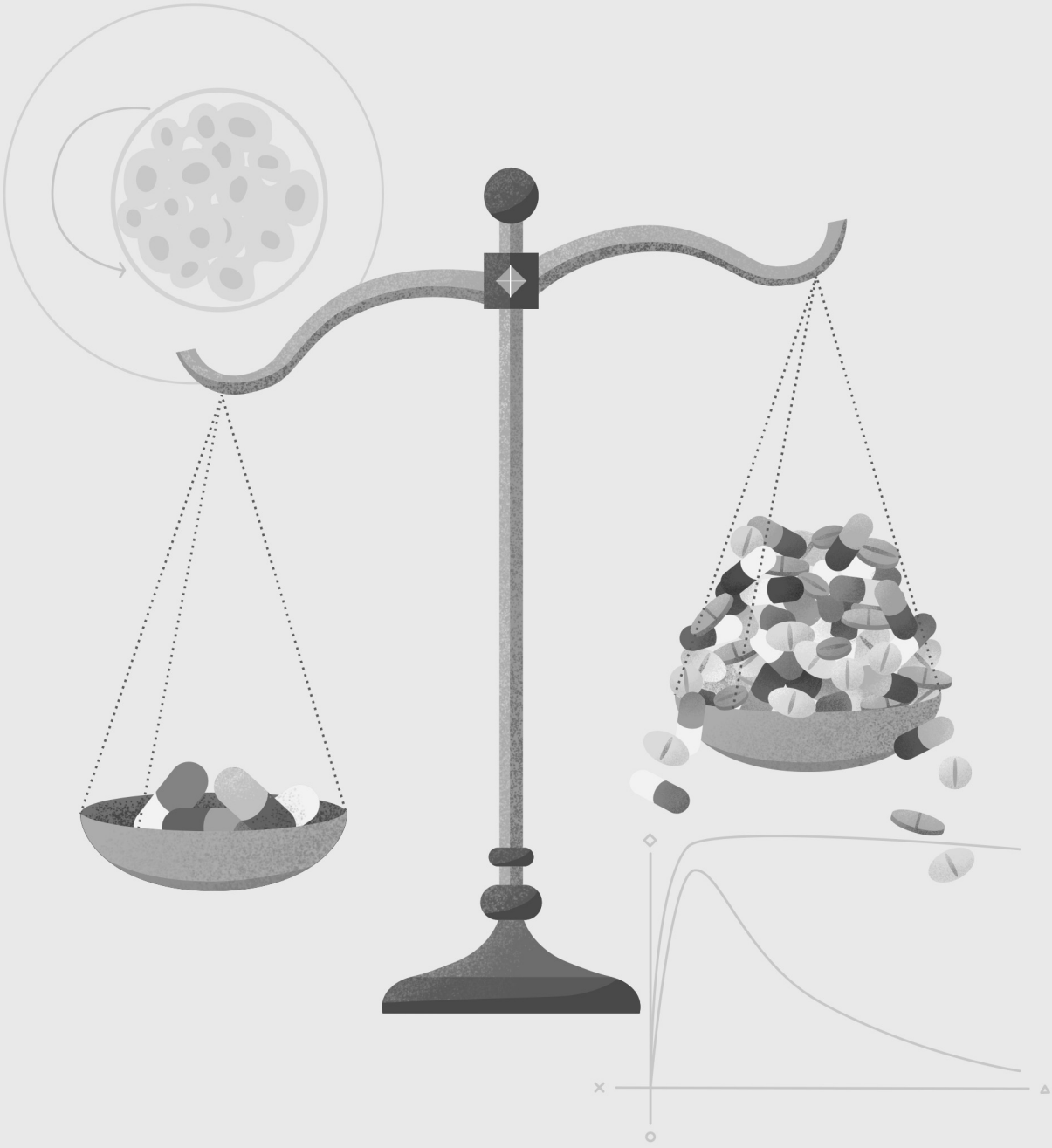
Section I

Background and introduction



Chapter 1

General introduction and scope of the investigations

1. CURRENT STATUS OF CANCER THERAPIES

Cancer is among the leading causes of death across the world[1] and has a major impact on society as a whole. In 2022, there were almost 20 million new cases and 9.7 million cancer-related deaths worldwide. By 2040, the number of new cancer cases per year is expected to rise to 29.9 million and the number of cancer-related deaths to 15.3 million.[2] Globally, kidney cancer, melanoma and gastro-intestinal cancers are among common cancers.[1] A wide spectrum of systemic therapies has become available throughout the years which have led to declining cancer-related mortality.[3] The Cancer Statistics 2023 estimate that overall cancer mortality has declined by 33% since 1991.[4]

Traditional therapeutic approaches such as chemotherapy and radiation therapy were the cornerstone for cancer treatment. The landscape of tumor treatment has undergone a comprehensive and remarkable transformation. New modalities now fervently pursued include small-molecule targeted agents, monoclonal antibodies (mAbs), antibody–drug conjugates (ADCs), cell-based therapies, and gene therapy.[5]

Systemic cancer therapies possess distinct pharmacological profiles. Chemotherapeutic agents, such as 5-fluorouracil (5-FU), disrupt the cell cycle through various mechanisms, including the inhibition of microtubule function and interference with DNA synthesis.[6] However, chemotherapies can also adversely affect healthy cells, leading to detrimental effects on proliferative cell populations such as myelosuppression and those lining the gastrointestinal tract.[7]

Targeted therapies used in kidney cancer include tyrosine kinase inhibitors (TKIs) such as pazopanib, sunitinib and cabozantinib, which inhibit the vascular endothelial growth factor (VEGF) pathway to reduce angiogenesis crucial for tumor growth and metastasis.[5] By focusing on these molecular targets, targeted therapies aim to minimize harm to normal, healthy cells. These VEGF inhibiting therapies can be administered as small molecule inhibitors or as mAbs. Immunotherapies are designed to stimulate or guide the immune system to identify and eliminate cancer cells. The field of immuno-oncology is rapidly advancing, with the development of novel treatments. Among these, immune checkpoint inhibitors (ICIs) have emerged as a significant and effective class of immunotherapeutic agents like nivolumab and pembrolizumab, which block the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis to activate T-cells against tumor cells.[8, 9] The combination of nivolumab or pembrolizumab with the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody ipilimumab, has shown significant efficacy by synergistically activating immune

responses.[10, 11] The number of indications for immunotherapies has rapidly expanded in recent years.[12]

2. THE GAP BETWEEN THE LABELLED AND OPTIMAL CLINICAL DOSE IN ONCOLOGY CLINICAL PRACTICE

Historically, dose selection in oncology has been centered on identifying the maximum tolerated dose (MTD) through traditional trial designs such as the "3+3" method, which often prioritizes safety over optimal (long-term) efficacy and tolerability considerations.[13] Modern oncology drugs, such as targeted therapies, frequently exhibit efficacy at doses below the MTD, where the risk of chronic low-grade toxicity and its impact on patient adherence becomes critical.[14, 15] Despite these advances, registration trials for these therapies often continue to favor the MTD or the maximum clinically administered dose, leading to higher-than-optimal recommended dosages that compromise quality of life and sometimes overall treatment success and more side effects.[14, 16] In pivotal studies of most newly approved anticancer agents, high percentages of toxicity are noted with the investigated doses. These poorly tolerated doses often end up on the label and the high percentages of dose modifications, reductions, or interruptions during pivotal studies keep occurring in routine clinical practice.[17]

The United States Food and Drug Administration (FDA) initiated Project Optimus in 2023, which was aimed to address these disparities by promoting dose optimization strategies that incorporate long-term safety, efficacy, and patient-focused outcomes.[15] The main recommendations of Project OPTIMUS are to collect and interpret all available clinical pharmacokinetic (PK), pharmacodynamic (PD), and pharmacogenomic data to identify the optimal dose rather than taking the MTD, as well as identifying a target dosage range in early phase. Subsequently several dosages are then to be evaluated in more detail in registration trials.[15] Using this approach, tolerability is improved, enabling patients to remain on the effective dosage of targeted therapies or ICI treatment for longer periods ultimately resulting in reduced medical expenses due to additional visits required to extend the dosing interval or decrease the dose.

To date, there are many targeted therapies and immune checkpoint inhibitors (ICIs) on the market of which the labelled doses were obtained in the pre- Project OPTIMUS era. Therefore, efforts should be made to reveal and bridge the gap between the labeled doses and the doses patients can tolerate in routine practice for these approved agents. In addition to toxicity concerns, new modalities such as mAbs like the ICIs pose practical

challenges: they require regular injections and hospital visits, and their high costs make them unaffordable in many regions worldwide. For ICIs, relatively flat exposure-response relationships have been identified[18] and recent reports have accordingly proposed alternative dosing regimens for certain mAbs (e.g. either reduced doses or extended dosing intervals).[19] These proposals are based on an FDA guideline for in silico dose adjustments of PD-1/PD-L1 inhibitors, which was originally developed to support the registration of alternative dosing regimens (e.g. switching from weight-based to flat dosing) without a new Phase III trial.[20] This guideline provides criteria and support for developing alternative, more cost-effective dosing regimens through pharmacokinetic and pharmacodynamic modelling.[20] Similar like other therapeutic mAbs, it was shown that the change in clearance of ICIs was linked to the clinical response. Thus, patients with a greater and faster decrease in the clearance of the mAb over time were more likely to obtain partial or complete response, putatively because the reduction in tumor mass and cachexia resulted in a decrease in target-specific clearance and non-specific clearance, respectively.[21]

3. POPULATION MODELING METHODS IN PHARMACOKINETICS AND PHARMACODYNAMICS

The core content of Project OPTIMUS is the use of the totality of all data for which pharmacometrics modeling serves as a crucial tool. Pharmacometrics is a field that integrates mathematical-statistical models (nonlinear mixed effect modeling, NLME) with biological, pathophysiological, and pharmacological principles to characterize the interactions between xenobiotics and patients, including both beneficial and adverse effects.[22] Within the concept of pharmacometrics, population pharmacokinetics (POPPK) and PD modeling is the cornerstone for optimizing drug regimens in oncology, where different kinds of drugs generally exhibit narrow therapeutic windows and substantial variability in patient response.[23] These models leverage a population-based approach to sequentially and/or simultaneously analyze PK and/or PD data, quantifying variability between patients and identifying covariates such as age, organ function, and genetic polymorphisms that influence drug exposure and response.[24]

A critical application of population PK/PD models in oncology is their ability to inform dose optimization and treatment individualization for both single agents and combination regimens. Semi-mechanistic models, such as those developed for chemotherapy-induced myelosuppression, describe the dynamics of proliferating and maturing blood cells, enabling precise predictions of hematological toxicity across various dosing

regimens.[23, 25] Apart from toxicity analysis, such models have been instrumental in establishing relationships between drug exposure metrics and different oncological efficacy outcomes, including tumor growth inhibition and progression free survival (PFS)/overall survival (OS).[23, 26]

In a real-world patient setting, PK/PD models have proven invaluable in addressing the challenges of heterogeneous oncology populations, particularly in patients with altered organ function or comorbidities. For example, PK/PD modeling has guided dose adjustments in cancer patients with renal or hepatic impairment, where standard dosing may lead to excessive toxicity.[23, 25]. The integration of population PK/PD modeling into oncology clinical practice offers a robust framework for achieving the dual objectives of maximizing therapeutic efficacy while minimizing adverse effects, thereby contributing to the broader goal of optimal therapy.[24, 26]

4. MODEL-INFORMED PRECISION DOSING IN ONCOLOGY

The term of model-informed precision dosing (MIPD) was formally introduced in the mid-2010s[27] with the goal of attaining even more accurate exposure or response in every patient. It encompasses both initial (*a priori*) dose individualization and subsequent (*Bayesian*) dose adjustments, incorporating feedback through therapeutic drug monitoring (TDM) of drug concentrations or pharmacodynamic measures to ensure efficacy while minimizing toxicity.[28] In contrast to a one-size-fits-all approach to dosing, MIPD uses PK/PD models and patient-specific data to optimize therapy.[29] Implementing PK/PD-guided individualized therapy often requires access to TDM and specialized analytical tools; the required sampling frequency depends on the drug and clinical indication. Practical barriers include the limited availability of sensitive bioanalytical methods, the complexity of NLME modelling and limited familiarity with these approaches among healthcare providers.[30] In contrast to traditional and well-established TDM or biomarker monitoring, MIPD may provide quantitative decision support to healthcare professionals for real-world patient populations integrating multi-level data[31] and limited sampling strategies are possible to release the burden on individual patients.

Key challenges that may hinder the successful implementation of MIPD in routine clinical practice were summarized previously in a recent published perspective.[31] First, MIPD may only be beneficial when a clear dose–exposure-response relationship is present. Several articles underlined a low trust in MIPD approaches among end-users including medical doctors and pharmacists, which was attributed to a lack of knowledge as well

as limited transparency of MIPD tools.[32] Most health care practitioners viewed precision medicine merely as fine tuning for a small number of patients, rather than a game-changer for all and still believed in a "one-size-fits-all" approach to dosing. Second, the selection of the evidence or synthesis of the evidence should be carefully considered. Finally, translation of research findings into easy-to-use software tools is a crucial and challenging part of MIPD implementation.

5. AIMS AND OUTLINE OF THIS THESIS

In this PhD thesis, available data on the PK and/or PD of different targeted therapies, chemotherapy and immunotherapies obtained during both routine clinical practice and prospective clinical studies were analyzed. The primary aim of this project was to optimize oncology drug treatment by analyzing available pharmacokinetic and pharmacodynamic data from patients treated with these therapies using different modeling and simulation approaches. Ultimately these efforts may lead to optimized and individualized cancer treatment with optimal efficacy, reduced toxicity and less drug expenses.

Section I, which includes **Chapter 1**, is the general introduction of this thesis describing the current cancer therapies landscape, the knowledge gaps, the concept of the population modeling approach and the challenges of performing MIPD.

In **Section II**, we aimed to quantitatively characterize and bridge the gaps of the labelled and optimal clinical dose of targeted therapies in mRCC with publicly available data.

In **Chapter 2**, we reviewed the labelled dosages of a total of five targeted therapies and immunotherapies in mRCC resulting from the dose-finding strategy, followed by an evaluation of routine clinical practice studies concerning the actual tolerated and effective doses observed in clinical practice. Finally, published POPPK models were assessed and selected for model-informed simulations to evaluate dosing from the perspective of optimal target achievement in the post-marketing context.

Section III aims to quantitatively characterize and bridge the gaps of the labelled and optimal clinical dose of two specific targeted therapies in mRCC, i.e. cabozantinib and pazopanib with routine clinical practice data.

In **Chapter 3**, we evaluated the POPPK model of cabozantinib developed for its registration using real-world patients' TDM data. Alternative dose regimens were subsequently

developed with the aim to reduce drug expenses using the known drug-high fat meal interaction.

In **Chapter 4**, a pazopanib POPPK model was developed based on drug concentrations versus time data obtained during TDM in routine clinical practice. Furthermore, the exposure-liver toxicity relationship and exposure-response relationship in mRCC and STS patients were studied using a model-based approach.

In **Section IV**, we aimed to characterize the PK/PD relationships and MIPD strategies of chemotherapy and immunotherapy.

In **Chapter 5**, a multi-center data analysis was performed which aimed evaluate existing POPPK models and develop a final PK model including covariates for accurate prediction of individual 5-FU exposure. In addition, identify optimal limited sampling strategies to accurately estimate individual AUC0-inf, facilitating MIPD using a fit-for-use application.

In **Chapter 6**, the first objective was to evaluate and refine the published pembrolizumab POPPK models. The second objective was to determine the limited sampling strategy (LSS) to estimate the individual percentage change in CL (ΔCL_perc). Lastly, the POPPK model with the LSS were used to evaluate whether ΔCL_perc can be used as a descriptive biomarker for (non-)responders and design model-informed dose interval individualization to reduce drug expenses.

General discussion, future perspective and summary of this thesis are presented in **Section V**. In **Chapter 7** we conclude this thesis with a general summary and a view on future perspectives regarding data availability, bridging the gap between clinical trials and routine clinical practice, and implementation of the developed models and model-informed optimal dosing regimens into clinical practice.

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