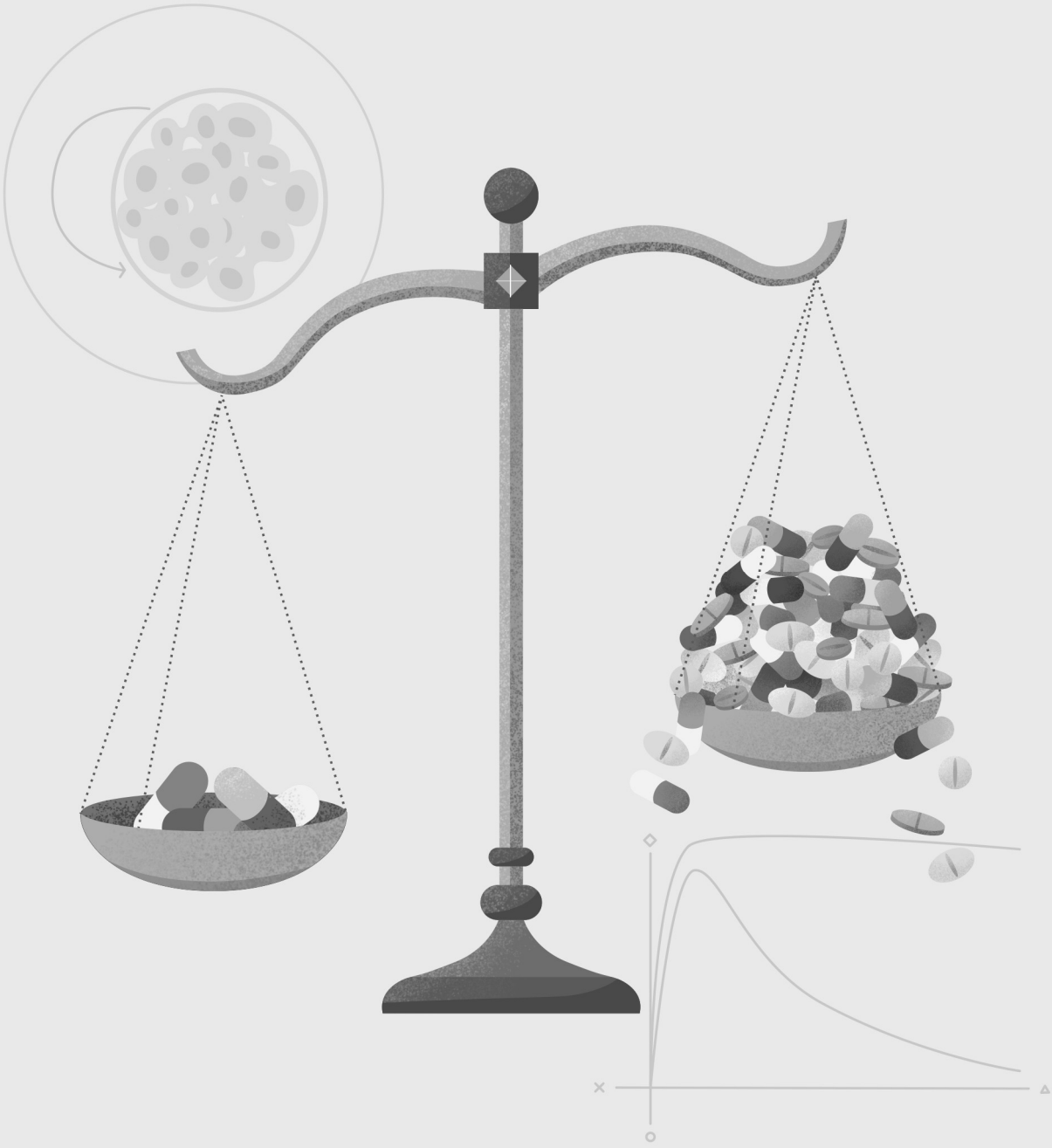
From labelled to the optimal clinical dose: model-informed dose optimization in medical oncology practice

Tan, Z.

Section II

Closing the gap between the labelled and optimal clinical dose with publicly available data



Chapter 2

A systematic evaluation of the dosing regimens for approved targeted therapies and immune checkpoint inhibitors in metastatic renal cell carcinoma from a Project OPTIMUS perspective

Zhiyuan Tan, Swantje Völler, Aymara Sancho-Araiz,
Catherijne A. J. Knibbe, Dirk Jan A. R. Moes

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ABSTRACT

Targeted therapies and immune checkpoint inhibitors have significantly improved survival outcomes in metastatic renal cell carcinoma (mRCC) but are often associated with high rates of adverse events, leading to dose reductions or treatment discontinuation. The FDA's recent initiative, Project OPTIMUS, emphasizes the importance of optimizing dosing regimens in oncology clinical development, and moves beyond the conventional maximum tolerated dose approach.

In this study, we aimed to review and redefine the approved dosing strategies for targeted therapies and immune checkpoint inhibitors in mRCC from the Project OPTIMUS perspective, including pazopanib, axitinib, cabozantinib, sunitnib, everolimus and nivolumab. A comprehensive summary of FDA clinical pharmacology reviews and clinical studies performed in routine clinical practice was conducted, alongside model-informed simulations of pharmacokinetic profiles with approved and alternative regimens.

Results demonstrated that actual tolerated doses in clinical practice were 46.1% to 86% lower than the approved dosages, with up to 75% of patients requiring dose adjustments. Model-informed simulations suggested that for most targeted therapies, a 14–50% dose reduction maintained comparable efficacy while improving tolerability. For nivolumab, simulations confirmed adequate drug exposure with the approved flat-dose regimens, without an increase of adverse effects.

In conclusion, we identified optimized dosing regimens that could improve drug tolerability while maintaining efficacy for approved targeted therapies and immune checkpoint inhibitors in mRCC. We suggest that these optimized dosing regimens should be considered for use in clinical practice and that the optimal exposure range be included in drug labels to support pharmacokinetically guided dose individualization in clinical practice.

Key words: Pazopanib, axitinib, cabozantinib, sunitinib, everolimus, nivolumab, dose reduction, dose optimization, dose selection

1. INTRODUCTION

1.1. Targeted therapies and immune checkpoint inhibitors for metastatic renal cell carcinoma

Metastatic renal cell carcinoma (mRCC) is the most common tumor of the urological system with poor prognosis.[1] Over the last decades, the treatment of mRCC has improved considerably with targeted therapies that block vascular endothelial growth factor (VEGF) or mechanistic target of rapamycin (mTOR) pathways. These therapies significantly improved objective response rates (ORR) and/or median progression free survival (PFS).[2] Since 2005, FDA and EMA approved several tyrosine kinase inhibitors (TKIs) such as sunitinib, pazopanib, axitinib, cabozantinib and the mTOR inhibitors everolimus and temsirolimus.[3] Despite superior outcomes, tumors treated with small molecules are prone to develop drug resistance.[4] Therefore, the treatment landscape is advancing towards novel immune checkpoint inhibitors (ICIs)-based strategies, either monotherapies or in combination.[5] These therapies, which target the interaction between immune cells and tumor cells, have shown success in improving mRCC outcomes,[6] with more durable efficacy compared to small molecules.[7]

1.2. Current problem in clinical development

The maximum tolerated dose (MTD), which is defined as the highest dose that does not cause dose-limiting toxicity (DLT, the same grade 3 or 4 adverse event (AE) in three or more patients[8]), has been the gold standard for dose selection in oncology dose-finding trials and is often adopted as the recommended Phase II dose (RP2D).[9] However, targeted therapies demonstrate a different dose-response relationship compared to classic cytotoxic chemotherapy. More specifically, doses below the MTD may have similar efficacy to the MTD but may be associated with less toxicity.[10] This idea is supported by high rates of dose reduction in routine clinical practice for many well-established targeted agents like cabozantinib and everolimus in mRCC at similar efficacy[11,12] reflecting potentially inadequate dose selection prior to the registration trial.[13] In addition, the traditional MTD paradigm often does not adequately evaluate other data, such as low-grade symptomatic toxicities (i.e., grade 1–2), dosage modifications, dose- and exposure-response relationships.[10] An even larger inconsistency of exposure-response and exposure-toxicity relationship is observed in immune checkpoint inhibitors. For nivolumab, a flat exposure-response relationship was well established and has led to label change from weight-based dosing to alternative flat dosing strategy.[14] It has even been shown that nivolumab 20 mg versus placebo every 3 weeks

(q3w) leads to improved 1-year overall survival (OS) in head and neck cancer,[15] with 20 mg being considerably lower than the standard dose (3 mg/kg q2w or 240 mg q2w).

1.3. FDA Project OPTIMUS

The emerging evidence that targeted therapies are poorly-tolerated at the approved recommended MTD-based dosage was also noted by FDA.[10] FDA reviewed the dose-related post-marketing requirements[16] between 2010–2015 and found 33.3% new molecular entities (NMEs) had dose-related post-marketing requirements. As a result, in 2021 FDA project OPTIMUS[10] was initiated, aiming to reform and improve dose optimization and selection in oncology drug development.[17] The main recommendations are to collect and interpret all available clinical pharmacokinetic, pharmacodynamic, and pharmacogenomic data to identify the optimal dose rather than taking the MTD, as well as identifying a target dosage range early and then further evaluating several dosages.[10] Another focus is to improve tolerability, which enables patients to remain on the effective targeted therapies or ICI treatment for longer period and results in reduced medical expenses.

In this report on six approved targeted therapies and ICI in mRCC (i.e. pazopanib, axitinib, cabozantinib, sunitinib, everolimus and nivolumab), we reviewed the approved dosages together with the dose-finding strategy, followed by an evaluation of routine clinical practice studies on the actual tolerated and effective doses and exposures observed in clinical practice. Finally, published pharmacokinetic (PK) models were assessed and selected for model-informed simulations to evaluate dosing from the perspective of optimal target achievement in the post-marketing context.

2. METHODS

2.1. Overall methods

For five targeted therapies (i.e. pazopanib, axitinib, cabozantinib, sunitinib and everolimus) and one ICI product (i.e. nivolumab) approved for mRCC, we first retrieved the approved dose and dose-finding strategy reported in the FDA clinical pharmacology review dossier. Secondly, routine clinical practice studies on dose reduction and alternative dose regimen information are presented and qualitatively summarized. Finally, published PK models of these targeted and immune checkpoint inhibitors are summarized and one of the models of each drug is selected for generating model-based optimal dose regimen that achieves the desired target exposure.

2.2. Literature search and PK model selection

The literature search is divided into three parts. First, FDA clinical pharmacology reviews of each drug were retrieved from FDA drug approval database (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).

Secondly, routine clinical practice studies including dose reduction or interruption information and studies that compared the approved dose with alternative regimens were retrieved. The approved dose, Dose Reduction Rate and dose intensity are summarized in Table 2.1.

Thirdly, published population pharmacokinetic (PK) modeling studies and reviews on exposure targets are used to perform model-informed simulations, summarized in Table 2.2. The dose regimens selected for the simulations are listed in Supplemental Table S2.1. Simulation regimens were chosen based on factors such as Dose Reduction Rate in routine clinical practice, the available dose strengths on the market and other possible doses that can result in achieving the exposure target. Detailed search terms and retrieved PK models are provided in Supplemental Materials. For drugs with more than one PK model, the following priorities are applied to select the preferred model for simulations: (1) The model derived from registration files, with external validation using routine clinical data (if available), is the preferred option; (2) If the preferred model is not available, the registration file model should be used; (3) If neither of the above models is available, a model based solely on routine clinical data should be considered; (4) Ideally, a model based on a larger population and without inter-occasion variability should be selected. Models that do not clearly define the occasions will be excluded; (5) Information on individuals included in the model who had concomitant therapy (potential drug-drug interaction, combination therapy) is excluded. Parameter estimates and covariates information of the selected models are provided in the Supplemental Materials.

2.3. Model-informed simulations to guide optimal dosing regimens

The approved and alternative dose regimens retrieved as described in 2.2 are used for model-informed simulations. To this end, 1000 virtual adult patients per regimen are generated by the copula covariate simulator (CoCoSim) web application (https://cocosim.lacdr.leidenuniv.nl/) based on the covariates in National Health and Nutrition Examination Survey dataset.[18] If the model includes a covariate that cannot be generated by COCOsim, for example the prognosis score, random generation and assignment using the mean and standard deviation statistics from the original PK model publication will be used. Previously published reviews on exposure targets of these therapies are utilized

Table 2.1. Results on dose reduction and dose intensity in routine clinical practice studies

Study	Labelled dose	Number of patients	Starting dose in the studies	Dose Reduction Rate [% of patients]*	Dose intensity [mean dose$] OR Relative Dose intensity& (%)
Pazopanib	800 mg QD				
Shah et al.[28]		19	-	40%	-
Johnston et al.[29]		-	800 mg QD	60%	78%
Gaillard et al.[30]		18	800 mg QD (60% of patients^)	-	672 mg QD
Masini et al.[156]		279	800 mg QD	36–66%	-
Axitinib	5 mg BID				
Johnston et al.[29]		-	5 mg BID	22%	95%
Gaillard et al.[30]		12	5 mg BID (60% of patients^)	-	8.6 mg per day (4.3 mg BID)
Cabozantinib	60 mg QD				
Albiges et al.[58]		410	60 mg QD (71% of patients^)	57%	-
Krens et al.[59]		59	60 mg QD (46% of patients^)	58%	-
Campbell et al.[61]		30	-	60%	-
Gan et al.[62]		413	-	50%	-
Martini et al.[56]		87	60 mg QD	68%	-
Prisciandaro[64]		17	60 mg QD	47%	-
McElwee et al.[63]		35	-	-	33 mg QD
Sunitnib	50 mg 4/2				
Gaillard et al.[30]		12	50 mg QD 4/2 (60% of patients^)	-	34 mg QD
Porta et al.[113]		85	50 mg QD 4/2	30%	-
Park et al.[112]		270	50 mg QD 4/2	54%	-
Miyake et al.[84]		110	50 mg QD 4/2	93%	63%
Abd Ghafar et al.[75]		51	50 mg QD 4/2	61%	-
Noize et al.[85]		302	50 mg QD 4/2 (83.4% of patients^)	65%	-
Everolimus	10 mg QD				
Nozawa et al.[122]		180	10 mg QD	40%	-

QD, once daily; BID, twice daily; 4/2, 4 weeks on and 2 weeks off treatment.
* The percentage of patients that experienced dose reduction during follow-up.
$ The mean dose was calculated by dividing the sum of overall daily doses by number of days on therapy for all patients as reported by the studies.
& Relative dose intensity was calculated by dividing the actual daily dose (the mean of the sum of all daily doses divided by the number of days on therapy) by the starting dose as reported by the studies.
^ with the remaining patients starting at lower dosages.
- No information reported by the study.

Table 2.2. Recommended starting dose based on labelled dose, routine clinical practice studies and model-informed results

Drug	Labelled dose	Dose in routine clinical practice*	Efficacy target concentration [REF]	Toxicity target concentration [REF]	Model-informed dose[$]	Conclusions and recommended starting dose[&]
Pazopanib	800 mg QD	600 mg QD	$C_{min,ss} \geq 20.5$ mg/L[19,20]	$C_{min,ss} < 46$ or 50 mg/L[19,20]	600 mg QD	600 mg QD
Axitinib	5 mg BID	4 mg BID	$C_{min,ss} > 1.76$ ng/mL[19,21]	$C_{max,ss} > 40.2$ ng/ mL[19,21]	5 mg BID	5 mg BID
Cabozantinib	60 mg QD	40 mg QD	$C_{min,ss} > 336$ ng/mL[67]	$C_{min,ss} < 750$ ng/ mL[67]	60 mg QD * 2 days + 1 day skip; 40 mg QD	60 mg QD * 2 days + 1 day skip; 40 mg QD
Sunitinib[#]	50 mg QD 4/2	37.5 mg QD	$C_{min,ss} \geq 50$ ng/mL[19]	$C_{min,ss} < 100$ ng/ mL[19]	50 mg QD 2/1	50 mg QD 2/1; 37.5 mg QD
Everolimus	10 mg QD	-	$C_{min,ss} > 10$ ng/mL[19]	$C_{min,ss} \leq 26.3$ ng/ mL[19]	5 mg QD	5 mg QD
Nivolumab	3 mg/kg; 240 mg Q2W; 480 mg Q4W	-	$C_{min,ss} > 2.5$ mg/L[136]	/	3 mg/kg; 240 mg Q2W; 480 mg Q4W; 360 mg Q3W	3 mg/kg; 240 mg Q2W; 480 mg Q4W; 360 mg Q3W

QD, once daily; BID, twice daily; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks; 4/2, 4 weeks on and 2 weeks off treatment; 2/1, 2 weeks on and 1 week off treatment; Cmin,ss, trough concentration at steady state; Cmax,ss, maximum concentration at steady state.

* The information of this column was taken from Table 2.1 and rounded to the nearest tablet/pill/vial strength.

[REF] The references for the efficacy and toxicity exposure targets.

[$] Derived from the model-informed simulations as described under paragraphs 3.3, 4.3, 5.3, 6.3, 7.3, using the selected PK models and exposure targets.

[&] The conclusions and recommended starting dose regimens are based on the previous columns and expert opinion if there is discrepancy between dose in routine clinical practice and model-informed dose.

- No solid evidence from routine clinical practice studies.

[#] Sunitinib exposure metric is the composite Cmin,ss of both parent drug and main metabolite (sunitinib and SU12662).

/ No solid relationship available of nivolumab exposure with toxicities.

directly as simulation exposure targets.[19-21] If multiple targets have been reported for one drug, the evidence evaluation hierarchy was applied: (1) the evidence from systematic review/meta-analysis; (2) the evidence from prospective studies; (3) the evidence from retrospective studies used in model-based exposure-response analysis; (4) if none of the above evidence could be retrieved, then no solid target could be used for simulation. In addition, percentage of target attainment (PTA) at steady state is summarized (the percentage of patients achieving the therapeutic target at steady state in the 1000 virtual patients). All simulations were performed in NONMEM 7.4.4. Further statistical comparison and visualization of exposure over time was performed in R.

3. PAZOPANIB

3.1. Approved dose and dose-finding strategy

Pazopanib was approved for mRCC in 2009 by the FDA22. Its primary mechanism of action can be described through its antiangiogenic properties via inhibition of the intracellular tyrosine kinase of VEGF receptor (VEGFR).[23] The recommended dose is 800 mg orally once daily (QD) without food. Pazopanib has a bioavailability range of 14% to 39% and is highly bound to protein (> 98.8%).[24] It is primarily metabolized by CYP3A4, therefore 200 mg QD is recommended for moderate hepatic impairment and its use in severe hepatic impairment should be avoided.[22]

As for the dose-finding strategy of pazopanib, a Phase I dose escalation study involving 63 patients was performed where doses ranging from 50 to 2000 mg were evaluated in the dose-escalation phase and 300 mg BID, 400 mg BID, 800 mg QD were evaluated in the dose-expansion phase. Exposure seemed to increase proportionally with doses between 50 and 400 mg even though variability was high,[25] and dose-proportionality beyond 400 mg was marginal. Mean trough concentrations at steady state ($C_{min,ss}$) on day 22 were similar for four dosing regimens (800 mg QD, 1000 mg QD, 300 mg BID, and 400 mg BID). Despite these findings, no MTD was reached during this study. Figure 2.1 (a) summarizes the number of responders for the different dose levels, showing that pazopanib doses ≥ 400 mg result in clinical response. Regarding safety, DLTs were identified in four out of 63 patients, occurring at 50 mg (2/9), 800 mg (1/3), and 2000 mg QD (1/3). These data led to the selection of 800 mg QD as the dose for registration trials.[26]

Subsequently, exposure-response analysis conducted by FDA combined available data across trials[27] and stratified the patients into quartiles based on the $C_{min,ss}$ for survival analysis. The survival curves of patients with different trough concentration-quartile

groups overlapped at several points, indicating an absence of an exposure-response relation for efficacy at the registered dose. In contrast, logistic regression analysis using data from the registration trial[26] demonstrated that the probability of Grade 3+ ALT elevations increased with increased pazopanib exposure (Figure 2.1 (b)), revealing a significant exposure-toxicity relationship.

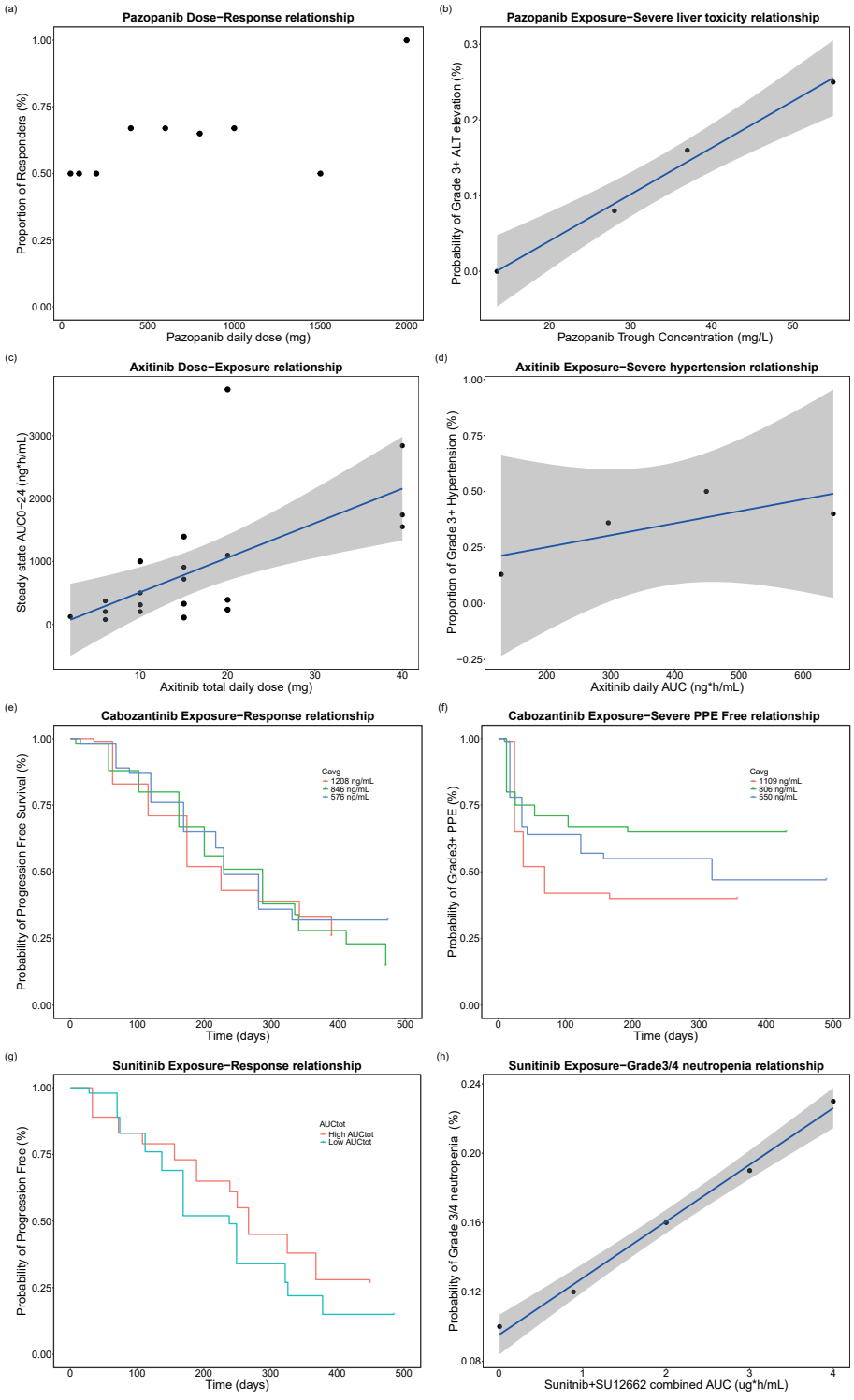
3.2. Clinical routine practice studies of dose reduction and alternative regimens

In clinical practice, Dose Reduction Rate and related outcomes have been reported in several published studies (Table 2.1), ranged from 40%[28] to 60%[29, 30] in different studies, starting with 800 mg QD. Given the 200 mg per tablet formulation, alternative dosing strategies such as 600 mg QD and 400 mg QD have emerged as potential starting doses.

Evidence from retrospective studies highlights the potential benefits of dose adjustments. A study[31] involving 179 patients with mRCC, almost exclusively receiving pazopanib as first-line treatment, found a statistically significant improvement in PFS and OS for patients who underwent dose reductions ($p < 0.0001$ for both PFS and OS), temporary interruption ($p < 0.0001$ for both PFS and OS) and schedule modifications ($p = 0.007$ for PFS and $p = 0.012$ for OS) compared to those who maintained the original dosing schedule.

Further support for dose reduction comes from a larger study by Lacovelli et al.,[32] including 591 mRCC patients receiving pazopanib. Of these, 45.7% (270 out of 591 patients) required a dose reduction due to toxicity. Interestingly, patients who reduced their dose, achieved a median OS of 49.4 months, significantly longer than the 24.0 months observed in those who continued the standard dose (hazard ratio = 1.80, $p = 0.001$).

However, not all studies have demonstrated consistent outcomes. Grassi et al.[33] retrospectively compared the outcome of 69 mRCC patients treated with pazopanib, dividing them into three groups: group 1 included 34 patients who started with 800 mg QD and did not have a dose reduction, group 2 included 19 patients that started with 800 mg QD but reduced their dose to 400 or 600 mg QD due to toxicity, and group 3 included 16 patients that started with 400 or 600 mg QD due to poor prognosis. ORRs were 44%, 11% and 19% in the three groups, respectively. Discontinuation rates due to progressive disease (PD) were higher in groups 2 and 3 (42%, and 44%, respectively) than group 1 (28%). However, the authors noted that these differences might reflect the worse prognosis of groups 2 and 3, and therefore the results should be interpreted with caution.


(a)
Pazopanib Dose−Response relationship
Proportion of Responders (%)
Pazopanib daily dose (mg)
(b)
Pazopanib Exposure−Severe liver toxicity relationship
Probability of Grade 3+ ALT elevation (%)
Pazopanib Trough Concentration (mg/L)
(c)
Axitinib Dose−Exposure relationship
Steady state AUC0−24 (ng*h/mL)
Axitinib total daily dose (mg)
(d)
Axitinib Exposure−Severe hypertension relationship
Proportion of Grade 3+ Hypertension (%)
Axitinib daily AUC (ng*h/mL)
(e)
Cabozantinib Exposure−Response relationship
Probability of Progression Free Survival (%)
Cavg
1208 ng/mL
846 ng/mL
576 ng/mL
Time (days)
(f)
Cabozantinib Exposure−Severe PPE Free relationship
Probability of Grade3+ PPE (%)
Cavg
1109 ng/mL
806 ng/mL
550 ng/mL
Time (days)
(g)
Sunitinib Exposure−Response relationship
Probability of Progression Free (%)
AUCtot
High AUCtot
Low AUCtot
Time (days)
(h)
Sunitinib Exposure−Grade3/4 neutropenia relationship
Probability of Grade 3/4 neutropenia (%)
Sunitinib+SU12662 combined AUC (ug*h/mL)

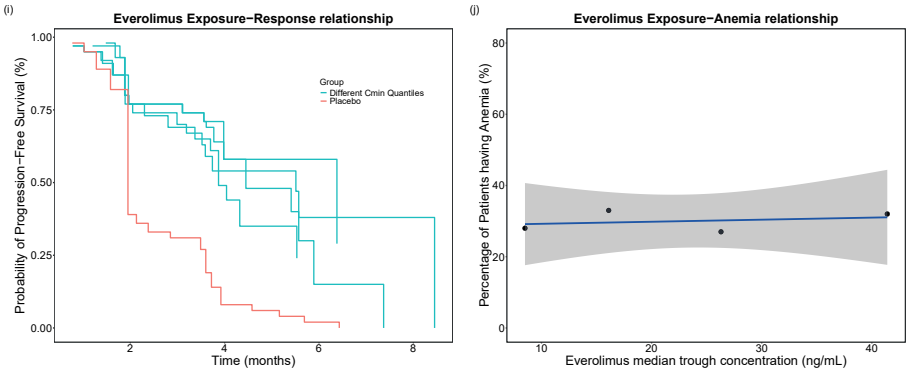


Figure 2.1. Dose-exposure, dose/exposure-response or exposure-toxicity relationship of the investigated targeted therapies and ICI in clinical trials. **(a)** Pazopanib dose-response relationship based on Phase I trial data.[27] The plot represents the proportion of responders (best response – partial response or stable disease of any duration) vs. pazopanib dose. For this plot, a subset of patients who received once daily pazopanib dose were selected; **(b)** Pazopanib exposure-severe liver toxicity relationship based on registration study; **(c)** Axitinib dose-exposure relationship based on Phase I trial;[41] **(d)** Axitinib exposure-severe hypertension relationship based on registration trial;[41] **(e)** Cabozantinib exposure-response relationship in registration study;[55] **(f)** Cabozantinib exposure-severe hand-foot syndrome relationship in registration study;[55] **(g)** Sunitinib exposure-response relationship split by AUC in registration study.[72] Red curve indicates the group of high sunitinib AUCtot (AUC_{tot} > 1900 ng*h/mL) and blue curve indicates the group of low sunitnib AUCtot (AUC_{tot} < 1900 ng*h/mL); **(h)** Sunitinib exposure-Grade3/4 neutropenia relationship in registration study;[72] **(i)** Everolimus exposure-efficacy relationship divided by placebo and different $C_{min,ss}$ groups.[119] The red curve indicates the placebo group and the blue curves indicate different $C_{min,ss}$ quantile group; **(j)** Everolimus exposure-anemia relationship.[119] All sub-figures were replotted from the FDA CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW of pazopanib,[27] axitinib,[41] cabozantinib,[55] sunitnib,[72] everolimus.[119]

3.3. Model-informed dose based on published exposure target and PK model

The current exposure target of pazopanib, specifically the $C_{min,ss}$ target, ranges between 20.5 mg/L and 46–50 mg/L (Table 2.2). The upper threshold aimed at minimizing overall CTCAE ≥ 3 toxicity.[21]

In total, 4 pazopanib PK models[34-37] were identified, and based on the model selection workflow as described in Methods section 2.2, we selected the model developed by our own group[37] for simulations. This model is based on routine clinical practice data while utilizing the model structure based on the large clinical trial datasets for marketing authorisation, and contained no covariates. Considering the current tablets available on the market (200 mg/table), simulations were performed at three starting dose levels: 800 mg QD, 600 mg QD and 400 mg QD. For the three simulated dosing regimens (Figure 2.2), although dose-related exposure differences are still discernible, there is an overlapping of the 90% prediction intervals (PI) due to high variability. While a starting dose of 400 mg QD may not result in the desired target for some patients, both 600 mg and 800 mg QD meet the $C_{min,ss}$ target of 20.5 mg/L. In addition, 600 mg

QD could also meet the safety threshold of 46 mg/L. The therapeutic target achievement calculation results (Supplemental Table S2.1) show that 600 mg QD results in a similar efficacy target attainment (75.6%) compared to 800 mg (85.9%), but with a lower incidence of toxicity (5.8% vs. 16.1%).

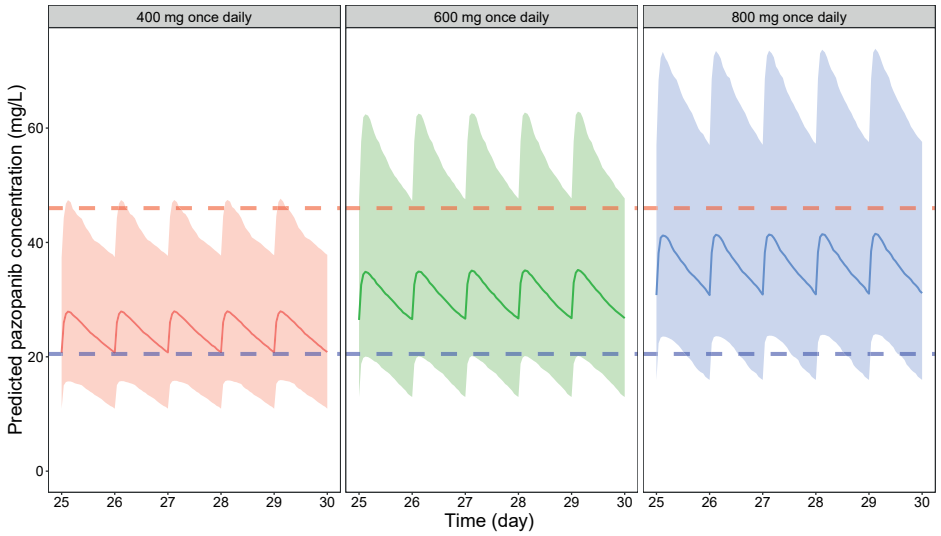


Figure 2.2. Model-informed pazopanib dose exploration using the model of Tan et al.[37] Blue dashed line indicates the efficacy target $C_{min,ss}$ > 20.5 mg/L. Red dashed line indicates the toxicity target $C_{min,ss}$ < 46 mg/L. The solid lines indicate median exposure. The shaded areas indicate 90% prediction interval.

4. AXITINIB

4.1. Approved dose and dose-finding strategy

Axitinib was approved by the FDA in 2012 for mRCC in patients who had failed one prior systemic therapy38. Its mechanism of action is to inhibit VEGFR-1, 2 and 3 selectively.[39] The approved labelled oral dose is 5 mg twice daily (BID), with dose titration up to 7 mg BID and further to 10 mg BID, based on tolerability. The PK is dose-proportional within the clinical dose range.[40] Following oral administration, axitinib is absorbed rapidly, with maximum observed plasma concentrations (C_{max}) reached within 4 hours. Its effective plasma half-life ranges between 2.5 to 6.1 h after a single oral dose.[41] Axitinib has a mean absolute bioavailability of 58% and has > 99% protein-binding.[40]

Dose selection was based on MTD criteria in a phase I PK and tolerability study that assessed various doses, including 10 mg QD,15 mg QD, 5 mg BID, 10 mg BID, 20 mg BID, 30 mg BID. Substantial inter-individual variability was observed, with a coefficient of variation of 60% in area under the curve (AUC) following an axitinib dose of 5 mg BID.[41]

The dose-exposure relationship was generally linear (Figure 2.1 (c)) within the studied range based on the Phase I trial.[41] Exposure-response studies pooled data from three phase II trials (178 patients) and the pivotal phase III trial (55 patients). Patients tolerating the initial 5 mg BID dose with upward titrations showed lower axinitib exposures at the starting dose, suggesting potential benefits from higher initial doses.[41] However, insufficient data from the Phase III trial and other public databases prevented establishing a conclusive exposure-response relationship for PFS.[41] In the exposure-toxicity evaluation, the logistic regression model demonstrated an exposure-dependent increase in hypertension (Figure 2.1 (d)), proteinuria, fatigue, and diarrhea.[41]

4.2. Clinical routine practice studies of dose reduction and alternative regimens

Several studies have evaluated axitinib tolerance in routine clinical practice setting (Table 2.1). Yasuoka et al.[42] retrospectively collected data from 17 mRCC patients treated with axitinib at 5 mg of BID (10 mg/day) following first-line nivolumab therapy. All patients experienced AEs, with nine patients (52.9%) requiring dose reduction or treatment interruption. Similarly, another retrospective study,[30] which included 12 axitinib-treated patients, reported a median relative daily dose of 8.6 ± 2.6 mg/day with 50% of patients requiring dose reductions due to toxicity.

In contrast, a larger cohort study[29] reported a lower Dose Reduction Rate of 22%, despite a similar median starting dose of 5 mg BID. Notably, most patients in this cohort (63%) received axitinib as part of combination therapy, potentially influencing the lower rate of dose adjustment.

4.3. Model-informed dose based on published exposure target and PK model

Axitinib has a reported efficacy target of $C_{min,ss}$ > 1.76 ng/mL at 1–3 months after start of treatment from an exposure-response analysis based on clinical practice data[43] (Table 2.2). The cumulative incidence of DLT was significantly higher in patients with $C_{max,ss}$ > 40.2 ng/mL[44] which was selected as toxicity target (Table 2.2).

Three axitinib PK models were retrieved,[45-47] all with the same model structure. The model published by Rini et al.[47] (Rini model[47]) based on 17 clinical trials was selected for simulation due to the solid design, large sample size and robust parameter estimates. The simulated doses included 3, 5, 7 and 10 mg BID that were used as dose-titration/de-escalation in drug approval. Figure 2.3 depicts simulated PK profiles for the explored regimens. Numerical results for these simulations can be found in Supplemental Table S2.1. The approved starting dose of 5 mg BID results in achievement of $C_{min,ss}$ target in

86.8% of the patients which is in line with the routine clinical practice summary that 5% of the 5 mg BID group would beyond the target that may need dose de-escalation to 3 mg BID (Supplemental Table S2.1).

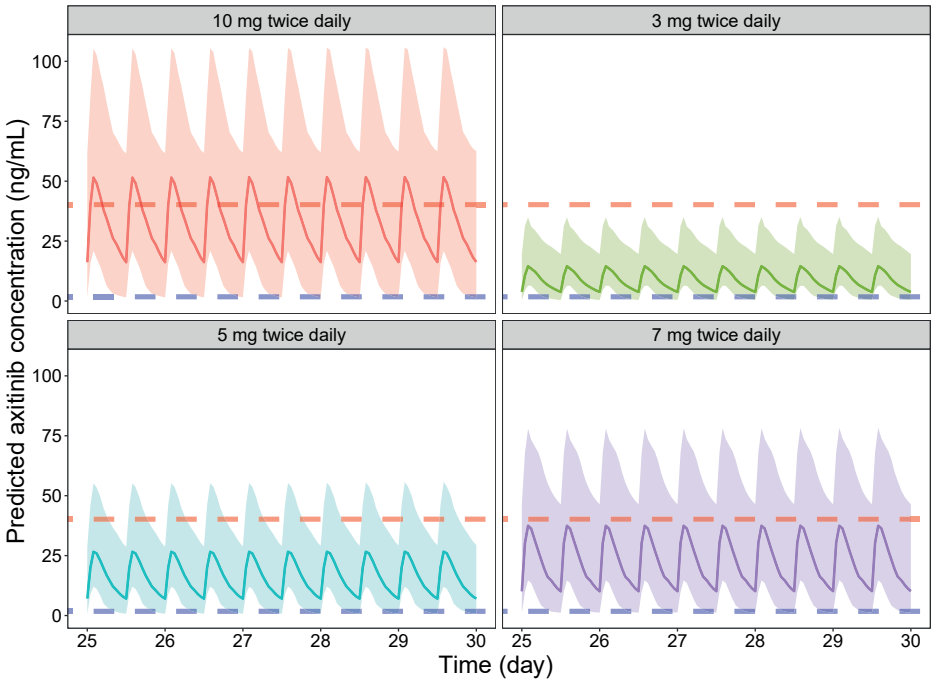


Figure 2.3. Model-informed axitinib dose exploration using Rini model.[47] Blue dashed line indicates the efficacy target $C_{min,ss}$ > 1.76 ng/mL. Red dashed line indicates the toxicity target $C_{max,ss}$ < 40.2 ng/mL. The solid lines indicate median exposure. The shaded areas indicate 90% prediction interval.

5. CABOZANTINIB

5.1. Approved dose and dose-finding strategy

Cabozantinib was approved by the FDA in 2012 for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy. This multi-kinase TKI exerts its effects by inhibiting several key pathways involved in cancer progression.[48] Specifically, cabozantinib targets the MET proto-oncogene (MET) and VEGFR2, reducing angiogenesis and diminishing drug resistance and metastasis.[49] The labelled dose is 60 mg QD fasted[50] since high-fat diet increases its bioavailability on average by 57%.[51] Available tablet strengths include 60 mg, 40 mg and 20 mg. Following oral administration, cabozantinib showed dose-proportional increases in mean plasma concentrations. It has an exceptionally long terminal half-life ($t_{1/2}$) of approximately 99 hours, which supports once-daily dosing.

The dose selection was based on a phase I study that investigated 20, 40, 60 mg and 140 mg QD, with 60 mg QD chosen as starting dose. An exposure-response study[52] was performed using data from a Phase III METEOR study,[53] where all patients received an initial dose of 60 mg QD. The analysis used a previously developed PK model[54] (PK model developed using healthy volunteers and patients with different tumor types) to predict average steady-state concentrations ($C_{avg,ss}$) for 60 mg QD (1125 ng/mL), 40 mg QD (750 ng/mL) and 20 mg QD (375 ng/mL) doses. Simulations showed hazard ratios (HR) for disease progression or death of 1.10 (40 mg) and 1.39 (20 mg) compared with 1125 ng/mL group. Based on these results, while 60 mg QD was considered superior for efficacy, the Kaplan-Meier plot (Figure 2.1 (e)) showed no significant survival differences between the exposure quartiles, suggesting inconclusive exposure-response relationship for PFS.[52] Regarding safety, an exposure-response analysis revealed a dose-dependent increase in the risk of severe hand-foot syndrome (Figure 2.1 (f)). The predicted HR 2.21 (60 mg vs. 20 mg) and 1.49 (60 mg vs. 40 mg). Overall, while 60 mg QD dose showed better efficacy than lower doses it may not be optimal due to safety concerns and AE risks.[55]

5.2. Clinical routine practice studies of dose reduction and alternative regimens

Martini et al.[56] included 87 mRCC patients, 33% of whom received cabozantinib as first-line therapy. Among the cohort, 68% required a dose reduction from 60 mg or started the treatment at a reduced dose without escalation. Patients receiving reduced doses were more likely to have ≥ 3 distant metastatic sites and ≥ 2 prior lines of systemic therapy compared to full dose patients. Regression analysis revealed a trend towards shorter OS (HR: 1.78, p = 0.095), shorter PFS (HR: 1.50, p = 0.107), and lower chance of objective response (HR: 0.42, p = 0.149) in reduced dose patients. However, these trends did not remain significant in multivariable analysis (OS HR: 1.20, p = 0.636; PFS HR: 1.23, p = 0.4662).

Recently, a retrospective analysis[57] of 71 mRCC patients revealed that 39.1% of patients were offered an alternative dose regimen due to intolerance. These alternative schedules included intermittent dosing patterns such as 14 days on treatment followed by 7 days off treatment, or 7 days on treatment followed by 4 days off treatment. Starting doses were 60 mg and 40 mg in 50.7% and 32.4% of patients, respectively. Compared to continuous dosing, alternative treatment schedules were associated with longer PFS (12.2 months vs. 6.1 months, p = 0.014). Toxicities were similar between the groups, with all-grade AE reported in 96.9% of patients on continuous dosing and 96% on alterna-

tive schedules. However, grade 3 or higher AEs occurred more often in the continuous dosing group (84.4% vs. 75%).

Additional studies have provided additional information regarding routine clinical practice tolerance of cabozantinib[58-66] (Table 2.1). High rates of dose reduction were consistently observed across multiple retrospective analyses. For instance, a study with 410 mRCC patients[58] revealed that 57.0% of patients had a dose reduction, and 15.6% had an alternative dose schedule, with a median average daily dose of 40 mg. Similarly, another study involving 413 patients[62] reported that approximately 50% of patients required dose reductions with an average relative dose of 33 mg (55.4% of the standard 60 mg dose). Dose reductions were associated with significantly longer time to treatment failure (TTF) and overall survival (OS) compared to those who did not require dose reductions (adjusted hazard ratios of 0.37, $p < 0.01$ for TTF and 0.46, $p = 0.04$ for OS).

Consistent findings were reported by Krens et al.,[59] who observed a Dose Reduction Rate of 58% and improved progression-free survival (PFS) for patients with dose reductions (65 vs. 31 weeks, $p = 0.001$). Smaller studies also reported Dose Reduction Rate ranging from 47% to 57%, showing that dose reductions are common and potentially beneficial in routine clinical practice settings.[61, 64, 65]

5.3. Model-informed dose based on published exposure target and PK model

Cabozantinib is suggested to have a therapeutic window[67] of $C_{min,ss} > 336$ ng/mL and $C_{min,ss} < 750$ ng/mL (Table 2.2), though these values have not yet been widely accepted. Several PK models developed with clinical trial data were retrieved.[52, 54, 68, 69] The model adapted from the FDA registration file68 for mRCC with routine clinical data (Tan model[51]) was selected which did not include other tumor types and could better reflect the routine clinical setting. Results of simulated regimens with this model[51] are shown in Figure 2.4. The approved 60 mg QD starting dose exhibited substantially higher exposure than desired $C_{min,ss}$ target for both efficacy and safety while an alternative dose of 40 mg QD seems to maintain the balance between efficacy and safety in a better way. Taking into consideration the flat-pricing strategy of cabozantinib for all available strengths (the 20-mg tablet, 40-mg tablet, and 60-mg tablet share exactly the same price), another starting dose of 60 mg QD given 2 days and skip 1 day could not only offer the same target achievement compared to the 60 mg QD continuous dose (35.6% versus 20.8%, Supplemental Table S2.1) but also save drug expenses.[51]

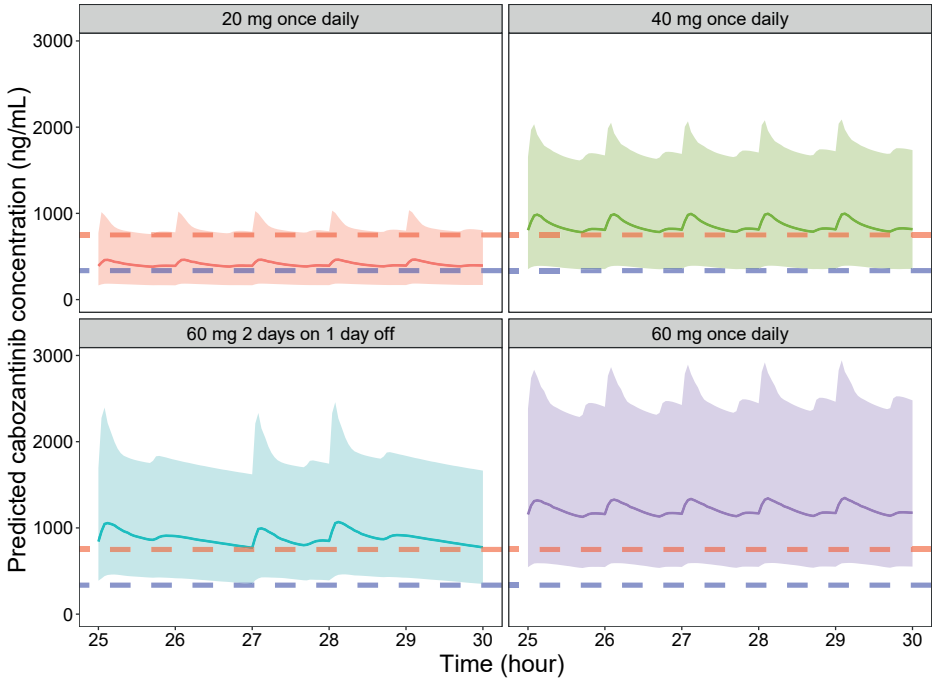


Figure 2.4. Model-informed cabozantinib dose exploration using model of Tan et al.[51] Blue dashed line indicates the efficacy target $C_{min,ss}$ > 336 ng/mL. Red dashed line indicates the safety target $C_{min,ss}$ ≤ 750 ng/mL. The solid lines indicate median exposure. The shaded areas indicate 90% prediction interval.

6. SUNITINIB

6.1. Approved dose and dose-finding strategy

Sunitinib was among the first approved TKIs by the FDA in 2006 indicated for all mRCC patients. Sunitinib was identified as a potent inhibitor of VEGFR-1, -2 FLT3, KIT, PDGFR with antitumor and antiangiogenic activities.[70] The approved oral dose is 50 mg QD with 4 weeks on and 2 weeks off (4/2).[71] It is slowly absorbed, reaching peak concentrations (T_{max}) between 6 and 12 hours, regardless of food intake. After absorption, sunitinib undergoes CYP3A4 mediated de-ethylation metabolism, producing SU012662, an active and equipotent metabolite. This metabolite contributes approximately 23–37% of the total AUC of the parent drug. The elimination of half-life ($t_{1/2}$) of the parent compound and the metabolite are prolonged, with values of 40–60 hours and 80–100 hours, respectively.[72] The PK models have shown significant inter-individual variability, with estimated coefficient of variation (%) of 21–71% for CL and 25–60% for AUC.[72]

Dose finding studies for sunitinib began with a phase I study in solid tumors, testing doses from 50 mg once every other day (QOD) to 150 mg QD.[73] Based on dose-linearity and DLT observed at the next dose level of 75 mg QD 4/2, 50 mg QD was chosen for further development.[72]

Following phase I, two single-arm studies were conducted to evaluate the PK and PD relationship in mRCC patients. Exposure, measured as the combined steady state AUC of sunitinib and SU012662 (AUC_{tot}) was evaluated in relation to both the efficacy and safety endpoint. For efficacy, time to tumor progression was used as the primary endpoint. Non-parametric Kaplan-Meier curves and parametric time-to-event modeling showed no clear exposure-response relationship for either AUC_{tot} or parent AUC alone. However, when Kaplan-Meier plots were stratified by exposure (low AUC [AUC_{tot} < 1900 ng*h/mL] and high AUC [AUC_{tot} > 1900 ng*h/mL]), the high AUC group appeared to show slightly longer time to progression and improved OS according to Figure 2.1 (g).[72] For safety, logistic regression revealed significant exposure-toxicity relationships across multiple endpoints, including grade 3/4 neutropenia (Figure 2.1 (h)).[72] In further Phase III registration trial, only 50 mg QD 4/2 was used. Dose reduction was seen in 32% of the patients,[74] and despite the relative high response rates across the exposure levels, there was no apparent exposure-partial response observed at 50 mg QD 4/2.[72]

6.2. Clinical routine practice studies of dose reduction and alternative regimens

In clinical practice, a substantial number of studies have evaluated alternative regimens for sunitinib[32, 75-110] (detailed information is summarized in Supplemental Material 2.2). Among these, 23 studies[32, 88-110] compared outcomes between the standard regimen and various alternative regimens. The most commonly studied alternative dose was 50 mg 2 weeks on and 1 week off (2/1) as alternative regimen (50 mg 2/1), which provides the same overall dose as 50 mg 4/2. A meta-analysis has summarized these studies and compared the efficacy and safety of the 50 mg 2/1 with standard 50 mg 4/2 dosing.[111] It demonstrated that initiating treatment with 50 mg 2/1 significantly prolonged PFS compared to 50 mg 4/2 (HR: 0.75 [95% CI: 0.60–0.94]), while no difference was seen for OS. Additionally, switching from 50 mg 4/2 to 50 mg 2/1 resulted in a trend towards improved PFS (HR: 0.4 [95% CI: 0.14–1.12]). In terms of safety, the standard dose 50 mg 4/2 was associated with significantly higher odds of Grade 3–4 hand-foot syndrome compared with the alternative 50 mg 2/1 (OR:0.33 [95% CI 0.12–0.79]).

Other reduced or alternative regimens have also been reported. Boegemann et al.[89] conducted a retrospective analysis including 297 mRCC patients receiving sunitinib as

first-line therapy, comparing those who remain on 50 mg 4/2 standard dose with those who underwent subsequent treatment modification to 37.5 mg 4/2, 25 mg 4/2 or 50 mg 2/1. Patients with treatment modifications achieved significantly better outcomes compared to the standard regimen, including median time to progression (15.1 versus 3.9 months; $p < 0.0001$), PFS (15.1 versus 6.0; $p < 0.0001$), and OS (38.1 versus 13.7; $p < 0.0001$). However, the modification group experiences a higher frequency of AE, including diarrhea (34%/17%), fatigue (30%/11%), hand foot syndrome (28%/10%), and stomatitis (20%/6%).

Another study, Ohba et al.,[101] compared a reduced regimen of 50 mg QOD dose with 50 mg 4/2. Median PFS and OS were significantly longer in the 50 mg QOD group compared with the 50 mg 4/2 group (27.6 vs. 6.2 and 87.1 vs. 24.6 months, respectively). The incidence of dose interruption caused by AE was significantly lower in the QOD group than in the standard group (28.1% vs. 56.3%, $p = 0.042$).[101]

An alternative regimen of 37.5 mg 4/2 as starting dose was also explored in two studies in Asian people.[107, 108] These studies found no significant differences in overall survival from treatment initiation ($OS_{initiation}$), overall survival from the first documented metastasis (OS_{total}), or PFS between the standard and attenuated dose regimens ($OS_{initiation}$: 18.3 vs. 16.5 months, respectively; $p = 0.54$; OS_{total}: 27.4 vs. 21.8 months, respectively; $p = 0.45$; PFS: 6.7 vs. 7.9 months, respectively; $p = 0.64$). These findings were consistent with routine clinical outcomes observed in studies involving Caucasian populations. Importantly, the attenuated regimen was associated with a significant lower incidence of severe toxicities, dose delays, and dose reductions compared to standard regimen. As depicted in Table 2.1, the Dose Reduction Rate for sunitinib with the initial 50 mg QD 4/2 has been reported to range from 30% to 92.7% according to the evidence from routine clinical practice.[30, 75, 84, 85, 112, 113] The mean dose intensity has been reported to be approximately 34 mg QD,[30] aligning with the alternative 37.5 mg QD regimen.

6.3. Model-informed dose based on published exposure target and PK model

Table 2.2 summarized the established therapeutic target range of combined sunitinib parent drug and metabolite SU12662 from $C_{min,ss}$ 50 to 100 ng/mL, based on exposure-response and exposure toxicity analysis from clinical practice patients.[114, 115] Several PK models were identified for both sunitinib and SU12662. The Diekstra model,[116] consisting of a two-compartment model for sunitinib and a biphasic distribution for SU12662, was selected due to a rigorous prospective design and good model performance. 50 mg QD 2/1 could result in a better target attainment than the approved 50 mg QD 4/2 regimen

(Figure 2.5). These findings are in line with what was observed in different clinical studies reported in 6.2. The therapeutic target achievement calculation results (Supplemental Table S2.1) show that 50 mg QD 2/1 achieves a similar target attainment (74%) compared to 50 mg QD 4/2 (75%), but with a lower incidence of toxicity (2% vs. 14%).

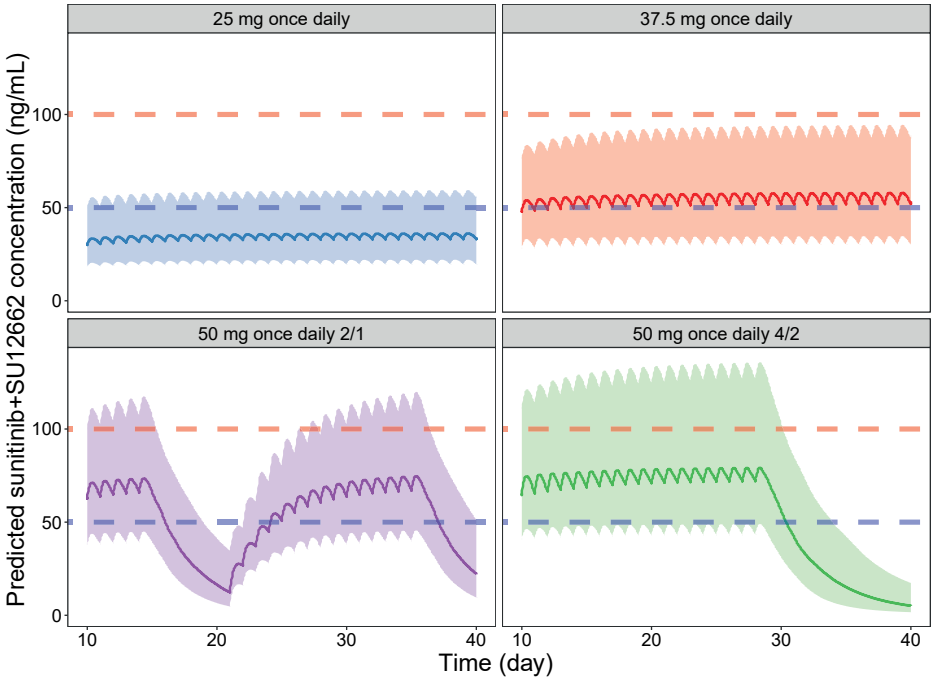


Figure 2.5. Model-informed sunitinib dose exploration with Diekstra model.[116]. Blue dashed lines indicate the efficacy target $C_{min,ss}$ > 50 ng/mL. Red dashed lines indicate the safety target $C_{min,ss}$ ≤ 100 ng/mL. The solid lines indicate median exposure. The shaded areas indicate 90% prediction interval.

7. EVEROLIMUS

7.1. Approved dose and dose-finding strategy

Everolimus was approved by FDA in 2009 for patients with advanced RCC after failure of treatment with sunitinib or sorafenib. Everolimus is an oral protein kinase inhibitor of the mTOR signal transduction pathway.[117] The labelled dose for advanced RCC is 10 mg QD.[118] After oral administration, everolimus is absorbed with T_{max} of approximately 1–2 hours.[119] The drug exhibits a dose-proportional AUC across the dose range of 5–70 mg. Nearly complete inhibition of S6 phosphorylation, which is the major mediator of anti-tumoral effects exerted by everolimus,[120] at a dose of 10 mg/day and 50 mg/week, led to the recommendation that these doses should be explored further.[119]

Dose-finding studies began with a phase I trial that evaluated both weekly regimens (5, 10, 20, 30, 50, 70 mg) and daily regimens (5 and 10 mg). These studies identified 10 mg QD as an appropriate dose based on pharmacokinetic properties and clinical safety. In the pivotal trial,[121] all patients were treated with 10 mg QD. FDA reviewers[119] conducted an exposure-response analysis using $C_{min,ss}$ and PFS data. The analysis revealed similar median PFS across all $C_{min,ss}$ subgroups (Figure 2.1 (i)), indicating no apparent exposure-response relationship for efficacy. Similarly, no trend was observed when AE were plotted against $C_{min,ss}$,[119] as shown in Figure 2.1 (j) for anemia. These findings raised concerns about the appropriateness of 10 mg QD dose as starting point for routine clinical practice, given the unclear dose-response or dose-toxicity relationship. Available everolimus tablet strengths are 2.5, 5 and 10 mg for cancer patients.

7.2. Clinical routine practice studies of dose reduction and alternative regimens

Evidence from clinical routine practice regarding everolimus in the mRCC patients is limited (Table 2.1). A retrospective study[122] included 180 mRCC patients mostly treated with everolimus as second-line therapy.[122] The study found that patients who required dose reductions due to AE experienced a longer time to failure (4.2 months; 95% CI 3.4–5.0) than patients without dose reduction (1.7 months; 95% CI 1.0–2.3). These findings align with the observations made by FDA, as discussed in section 7.1. Another study reported the Dose Reduction Rate to be 6.2%[123] but due to a very short follow-up time of 28 days, it was excluded from the final summary.

7.3. Model-informed dose based on published exposure target and PK model

As shown in Table 2.2, everolimus has a published $C_{min,ss}$ target between 10 ng/mL and 26.3 ng/mL based on a model-based analysis with pooled Phase II/III clinical trials data.[124] Only one everolimus PK model could be retrieved[125] (Tanaka model[125]), based on a prospective cohort routine clinical study in mRCC patients. Another model that was based on thyroid cancer exhibited same model structure with comparable simulation results.[126] Results of simulated regimens (displayed in Supplemental Table S2.1) are shown in Figure 2.6. The approved 10 mg QD starting dose exhibited higher exposure than the desired safety target while a half dose of 5 mg QD could have better therapeutic target achievement (55% vs. 42%, Supplemental Table S2.1). Overall, the approved 10 mg QD may not be suitable in routine clinical practice from both clinical evidence and simulation study. Optimizing the starting dose to 5 mg QD could be a more suitable alternative.

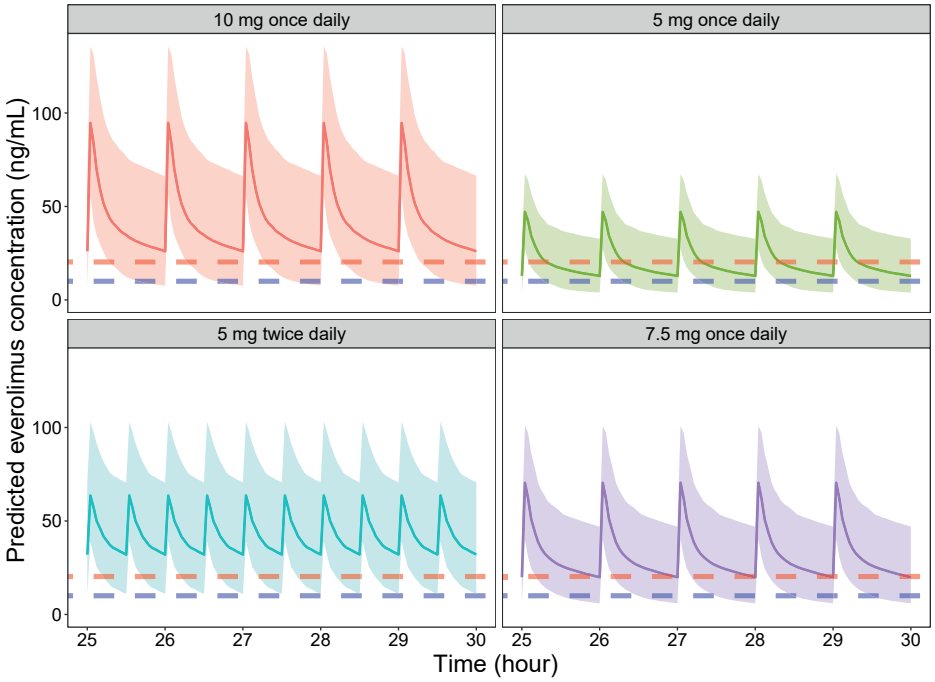


Figure 2.6. Model-informed everolimus dose exploration with Tanaka model.[125] Blue dashed lines indicate the efficacy target $C_{min,ss}$ > 10 ng/mL. Red dashed lines indicate the safety target $C_{min,ss}$ ≤ 26.3 ng/mL. The solid lines indicate median exposure. The shaded areas indicate 90% prediction interval.

8. NIVOLUMAB

8.1. Approved dose and dose-finding strategy

Nivolumab, an immune checkpoint inhibitor, was approved for use as monotherapy in mRCC patients who have received prior anti-angiogenic therapy.[127] Its mechanism of action involves blocking the PD-1 receptor, thereby enhancing T-cell mediated immune responses against tumors.[128] The current recommended dose is either 240 mg every 2 weeks (Q2W) or 480 mg every 4 weeks (Q4W).[129] Nivolumab clearance is linear over the dose range of 0.3–10 mg/kg,[130] and time-dependent, with decreasing clearance over prolonged treatment.[130] Evidence supporting these dosing regimens was summarized in the EMA's Clinical Pharmacology Summary,[131] as no specific FDA review for this indication was available.

Dose selection was informed by early clinical studies. A large phase Ib open-label, dose-escalation, cohort-expansion study evaluated nivolumab's anti-tumor activity and safety across multiple tumor types including mRCC. Patients received doses of 1 mg/kg or 10 mg/kg,[132] and no MTD was observed, even at the highest dose. The safety profile was consistent across dose levels, with similar nature, frequency and severity

of AE.[133] Exposure-response analysis[131] included data from a phase II (CA209010) and a phase III trial (CA209025) comprising 569 mRCC patients. The analysis revealed a flat relationship between Cavg,ss and OS, indicating no significant exposure-response relationship for efficacy within the investigated dose range. Subsequent efficacy-bridging evaluations[134] were conducted to compare weight-based dosing and fixed dosing using pooled exposure-response modeling. These analyses, which included data from multiple tumor types including mRCC, support similarities in the benefit-risk profiles for 240 mg Q2W, 480 mg Q4W and 3 mg/kg Q2W. Based on these findings, all the three dose regimens were approved as labelled dose of nivolumab.

8.2. Clinical routine practice studies of dose reduction and alternative regimens

Evidence from routine clinical practice regarding nivolumab use in mRCC is relatively limited (Table 2.1). However, a prospective cohort study[135] involving 195 mRCC patients reported that those who completed all four cycles of nivolumab, with or without ipilimumab as first-line therapy, had significantly longer PFS and OS compared to those who received fewer than four cycles ($p < 0.0001$). Recently, model-informed simulations[136, 137] have been conducted to explore the feasibility of extending the dosing intervals of nivolumab. These studies suggest that alternative regimens, such as 240 mg every 6 weeks (Q6W), could potentially reduce the financial burden while maintaining equivalent efficacy. For instance, in France, this alternative dosing schedule could potentially lower the annual treatment cost from €78,744 to €26,248.[136] These findings highlight the possibility of implementing extended dosing intervals as a cost-effective strategy without compromising clinical outcomes while clinical trials are warranted to confirm the non-inferiority of extended interval compared to standard regimen.

8.3. Model-informed dose based on published exposure target and PK model

As shown in Table 2.2, a previously used[136] putative minimal effective plasma concentration of 2.5 mg/L based on observed $C_{min,ss}$ in patients treated with nivolumab 0.1 mg/kg Q2W in a Phase I trial[138] is utilized. This concentration is about 60-fold higher than that required to occupy in-vitro more than 70% of PD-1 receptors on T cells (0.04 mg/L).[136] One PK model of nivolumab, Zhang model,[139] integrating 25 clinical trials including mRCC subpopulation was retrieved and used for simulation.[139] As shown in Figure 2.7, all approved flat-dose regimens, as well as weight-based dosing, achieved targets well. An alternative regimen of 360 mg every 3 weeks (Q3W) had 100% PTA, which could provide more flexibility for routine clinical practice. Numerical results of the simulations can be found in Supplemental Table S2.1.

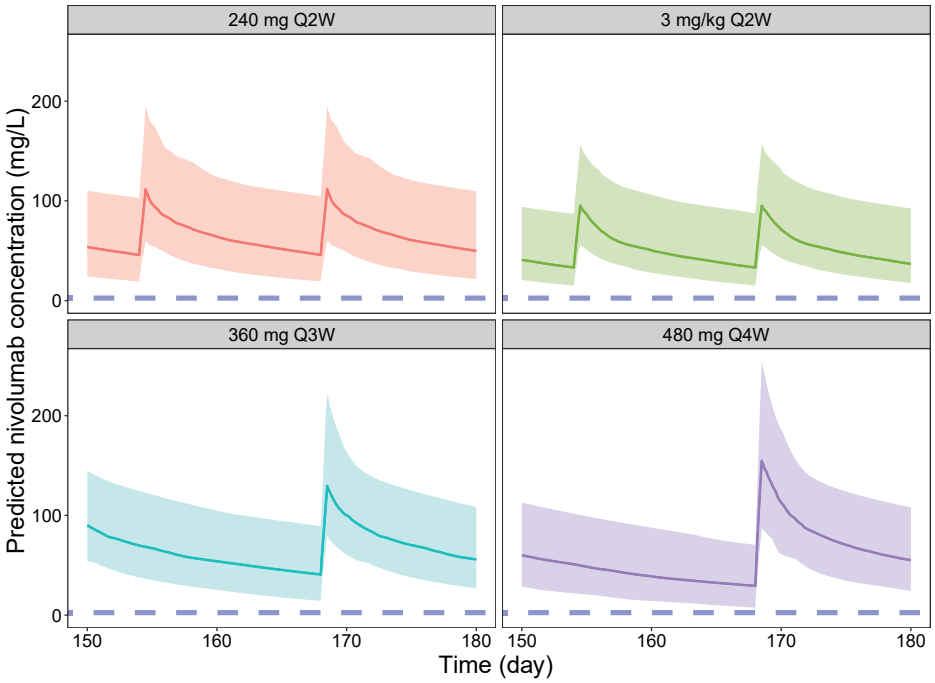


Figure 2.7. Model-informed nivolumab dose exploration with Zhang model.[139] Blue dashed lines indicate the efficacy target $C_{min,ss}$ > 2.5 mg/L. The solid lines indicate median exposure. The shaded areas indicate 90% prediction interval.

9. LESSONS LEARNED

Recently, the FDA project OPTIMUS was initiated which is intended to assist sponsors in identifying an optimal dosage for new investigational drugs for the treatment of oncologic diseases during clinical development.[10] Up to now, a well-controlled randomized registration trial was required using the MTD as selected dose for the phase III trial which was often unnecessarily high but still could achieve a favorable benefit-risk profile. However, project OPTIMUS further aims to increase the possibility of finding the optimal dosage beyond MTD before market approval since it is more challenging to conduct dosage optimization trials post-approval.[140] Nevertheless, according to the landmark learn-confirm concept proposed by Lewis Sheiner in 1997, a continuous learning process remains important after drug approval.[141]

In the current study, several mRCC target therapies were investigated including TKIs (pazopanib, axitinib, cabozantinib and sunitinib), an mTOR inhibitor (everolimus) and an immune checkpoint inhibitor (nivolumab). In line with project OPTIMUS, we combined data from both approval and post-approval to a) re-examine the approved dose and

dose-finding strategy, b) summarize routine clinical practice studies on best tolerated dose and c) explore model-informed optimal doses based on established therapeutic target (if available) or published evidence. Table 2.2 presents a final summary of the recommended starting dose regimens based of all the information retrieved in this systematic evaluation.

Our findings highlighted the limitation of the "one size fit all" dosing strategy applied to the four TKIs currently used in mRCC, except for axitinib. The starting dose of axitinib is 5 mg BID, with the option to titrate to 7–10 mg BID based on tolerability. However, its label does not recommend dose reductions below 5 mg BID even if the patient is already experiencing intolerability. The model-informed simulations of our study (Figure 2.3) highlight significant inter-individual variability in axitinib exposure, suggesting that not only dose titration but also dose de-escalation could have been considered at drug approval. In the case of pazopanib and cabozantinib, the approved doses appear higher than what many patients can tolerate in routine clinical practice. As shown in the simulations in Figures 2.2 (pazopanib) and 2.4 (cabozantinib), the exposure of approved dosages is higher than the toxicity threshold. Consequently, after the comprehensive evaluation presented here, the recommendation would be to reduce the starting dose to 600 mg QD for pazopanib and to 40 mg QD (or 60 mg 2 days on, 1 day off regimen) for cabozantinib (Table 2.2). By considering these dose reductions, a better balance between therapeutic exposure and safety could be achieved. For sunitinib, the approved 50 mg 4/2 regimen could potentially be replaced by a 50 mg 2/1 regimen, maintaining the same dose intensity but with lower toxicity and improved PFS in routine clinical practice. Overall, a common characteristic of TKIs is their complex oral absorption process[142] and huge inter-individual variability of exposure,[143] which means that different doses may highly lead to considerably overlapping proportions of the 95% percentiles of the model-informed simulations from a population perspective. Therefore, starting at a lower dose with model-informed individualization to ensure that the patient stays within the therapeutic window could improve the treatment tolerability, lead to less drug discontinuation, and potentially decrease the risk of disease recurrence and treatment failure.

For the mTOR inhibitor everolimus, the dose finding process was similar to that of TKIs, with a flat dose-response relationship and clear exposure-toxicity relationship. However, everolimus was registered at a high dose of 10 mg QD, which could be an unnecessarily higher dose based on both exposure-response analysis from clinical trials data and routine clinical practice studies. A pre-published TDM target for everolimus (Cmin

range of 10–26.3 ng/mL) generated from a model-based analysis of pooled clinical trials data,[124] and our simulation results depicted in Figure 2.10, indicated that 7.5 mg QD or 5 mg QD could would result in a higher target attainment rate and therefore be more suitable starting regimens, rather than 10 mg QD.

When it comes to immune checkpoint inhibitors, nivolumab is currently used as monotherapy or in combination with ipilimumab or cabozantinib as one of the standard treatments in previously untreated mRCC patients. Although nivolumab has demonstrated significantly improved survival, due to its high cost, accessibility remains a challenge worldwide.[144] Despite the fact that limited routine clinical practice evidence was retrieved for mRCC patients, our simulations suggested that approved flat dose regimens could achieve sufficient drug exposure. Nevertheless, there are currently other dose optimization strategies being explored including reduced unit dose, less frequent schedule and/or shorter duration of treatment.[145] For example, a phase III randomized controlled trial is enrolling mRCC patients who have responded to nivolumab for one year, to either discontinue or continue treatment [jRCT1031200071]. For other tumor types, there are also many attempts to decrease the treatment intervals and treatment dose. One retrospective, non-randomized, study compared the efficacy of nivolumab 20 and 100 mg Q2W among patients with hepatocellular carcinoma.[146] The study indicated that 20 mg Q2W had a longer PFS than those who received 100 mg Q2W (4.5 months vs 2.3 months, $p = 0.007$).[146]

To sum up, based on the results of all investigated targeted therapies and ICIs, except for axitinib, the approved fixed-dose regimens are either higher than the doses actually tolerated in routine clinical practice for small molecules[27, 55, 72, 119] or are unnecessarily high due to the flat exposure-response/exposure-toxicity relationships, as in the case of nivolumab.[131] Therefore, it is crucial that the focus should not only be identifying the optimal dose for the patient population as a whole, since considerable inter-patient variability in exposure will remain present with fixed dosing. Ideally the optimal exposure range should also be reported which can subsequently be used for pharmacokinetically guided dose individualization in the clinic.

Therapeutic alternatives for treating mRCC are increasing, with combination therapies including antiangiogenic agents and tyrosine kinase/mTOR/immune checkpoint inhibitors now considered as the gold standard, as supported by recent clinical studies.[147] These combination therapies have been evaluated using various trial designs, including sequential escalation, parallel escalation, monotherapy lead-in (intra-patient crossover)

and combination escalation.[148] However, despite these advancements, the dose-finding strategies and exposure-response relations for approved combination regimens in mRCC patients remain poorly defined. Recent recommendations advocate for the integration of a quantitative clinical pharmacology framework in dose-finding studies for combination therapy. This approach combines data from in vitro, preclinical in vivo and clinical trials, along with insight from competitive therapeutic landscape.[149] While promising, evidence from routine clinical practice for these combination therapies in mRCC remains scarce and was therefore not discussed in this study. Given the increasing reliance on combination therapies for mRCC treatment, it is critical to prioritize efforts in optimizing dose regimens. Such optimization will ensure that these therapies deliver their full potential in terms of efficacy and safety within routine clinical practice.[150]

It is emphasized that the Phase III randomized controlled trials (RCTs) are the most rigorous way of determining whether a favorable benefit-risk relation exists between treatment regimen and outcome.[151] In the current study, we leveraged and interpolated the dose regimens that had been investigated in early phase dose-finding trials with exposure simulations and include efficacy and toxicity data from routine clinical practice. This approach could be useful for future study designs or even serve as pivotal evidence to support the approval of untested doses which is as often applied in the pediatric population.[152] In addition, the FDA recently published a guideline to support the development of alternative dosing regimens for anti-PD-1/PD-L1 antibodies that are derived using PK-based model-informed approach, if both the AUC and the Cmin at the steady state for the test regimen are no more than 20% lower compared with the parameters of the reference dosing regimen used in registration study.[153] 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 develop fixed dosing regimens and prolonged dosing intervals for the purposes of patient and prescriber convenience.[154] To sum up, the final recommendations of the present study, which are based on interpolation of regulatory registration data, routine clinical evidence and PK simulations, should be further evaluated in clinical practice and/or clinical trials.

Lastly, while our study provides valuable insights into dosing strategies for targeted therapies in mRCC, it also has certain limitations. Our analysis was limited to therapies with available data on three key points: 1) the approved dose and dose-finding strategy, 2) drug tolerance and alternative regimens in clinical practice, and 3) well-defined exposure targets for model-informed simulations. Consequently, combination therapies

and newer treatments such as tivozanib were not included. In the present study, routine clinical practice evidence was summarized and most of these observational studies have non-randomized, retrospective design which may be susceptible to confounding and selection bias.[155] Furthermore, although we selected a representative pharmacokinetic model for each drug based on a predefined approach, alternative models might yield different outcomes. Future research could expand on comparing different published models to refine our understanding. Despite these limitations, our study offers valuable guidance on optimizing dosing strategies to improve the efficacy and tolerability of targeted therapies and check point inhibitors in clinical practice.

10. CONCLUSION

This study comprehensively evaluates the opportunities of dose optimization of approved mRCC target therapies and immune checkpoint inhibitors 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 further evaluation for existing therapies and that the optimal exposure range should be included in drug labels to support pharmacokinetically guided dose individualization in clinical practice.

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SUPPLEMENTAL MATERIAL 2.1

Literature search strategy

Part A: Dose reduction/alternative regimens

((alternative[tiab] OR adapt*[tiab] OR reduct*[tiab] OR reduce*[tiab] OR reducing*[tiab] OR adjust*[tiab] OR optimisa*[ti] OR optimisi*[ti] OR optimise*[ti] OR optimiz*[tiab] OR minimiz*[tiab] OR minimis*[tiab] OR modif*[tiab] OR personalis*[tiab] OR personaliz*[tiab] OR "Precision Medicine"[Mesh] OR precision*[tiab] OR individualiz*[tiab] OR individualis*[tiab] OR "higher dose"[tiab:~1] OR "lower dose"[tiab:~1] OR "highered dose"[tiab:~1] OR "lowered dose"[tiab:~1] OR "high dose"[tiab:~1] OR "low dose"[tiab:~1] OR "higher dosis"[tiab:~1] OR "lower dosis"[tiab:~1] OR "highered dosis"[tiab:~1] OR "lowered dosis"[tiab:~1] OR "high dosis"[tiab:~1] OR "low dosis"[tiab:~1]) AND ("cabozantinib"[Supplementary Concept] OR "cabozantinib*"[Title/Abstract] OR "pazopanib"[Supplementary Concept] OR "pazopanib*"[Title/Abstract] OR "sunitinib"[MeSH Terms] OR "sunitinib*"[Title/Abstract] OR "axitinib*"[MeSH Terms] OR "axitinib"[Title/Abstract] OR "AG 013736"[Title/Abstract] OR "AG013736"[Title/Abstract] OR "lenvatinib"[Supplementary Concept] OR "lenvatinib*"[Title/Abstract] OR "pembrolizumab"[Supplementary Concept] OR "pembrolizumab*"[Title/Abstract] OR "nivolumab"[MeSH Terms] OR "nivolumab*"[Title/Abstract] OR "ipilimumab"[MeSH Terms] OR "ipilimumab"[Title/Abstract] OR "avelumab"[Supplementary Concept] OR "avelumab*"[Title/Abstract] OR "everolimus"[MeSH Terms] OR "everolimus*"[Title/Abstract] OR "temsirolimus"[Supplementary Concept] OR "temsirolimus*"[Title/Abstract]) AND (mRCC[tiab] OR (("Kidney neoplasms"[majr] OR RCC[tiab] OR ccRCC[tiab] OR (("Kidney"[majr] OR kidney[tiab] OR kidneys[tiab] OR kidneycell*[tiab] OR renal[tiab]) AND (neoplasm*[ti] OR cancer[ti] OR cancers[ti] OR tumor[ti] OR tumors[ti] OR tumour[ti] OR tumours[ti] OR malignan*[ti])))) AND ("Neoplasm Metastasis"[majr] OR metastasis[ti] OR metastase*[ti] OR metastatic[ti] OR Metastasiz*[ti] OR "stage IV Cancer" [ti] OR "secondary"[Subheading] OR "Clear-cell metastatic renal cell carcinoma" [Supplementary Concept]))))) NOT ("Review"[Publication Type] OR "Systematic Review" [Publication Type] OR "review"[ti] OR "Letter"[Publication Type] OR "Editorial"[Publication Type] OR "Comment"[Publication Type] OR "Case Reports" [Publication Type] OR "case report"[ti] OR "case study"[ti] OR "Clinical Trial, Phase I" [Publication Type] OR "Clinical Trial, Phase II" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type] OR "phase 1 trial"[ti] OR "phase 1"[ti] OR "phase I"[ti] OR "phase 2"[ti] OR "phase II"[ti] OR "phase 3"[ti] OR "phase III"[ti] OR preclinical[ti] OR animal*[ti] OR mouse[ti] OR mice[ti] OR mus[ti] OR rodent*[ti] OR rat[ti] OR rats[ti] OR "In Vitro Techniques"[Mesh] OR "in vivo"[ti] OR (("Animals"[Mesh]) NOT "Humans"[Mesh]))

Part B: PK models

((“Pkmodel*”[tiab] OR ((“Pharmacokinetics”[Mesh] OR pharmacokinetic*[tiab] OR “pharmaco-kinetic*”[tiab] OR “PK”[tiab]) AND model*[tiab])) AND (“cabozantinib”[Supplementary Concept] OR “cabozantinib*”[Title/Abstract] OR “pazopanib”[Supplementary Concept] OR “pazopanib*”[Title/Abstract] OR “sunitinib”[MeSH Terms] OR “sunitinib*”[Title/Abstract] OR “axitinib*”[MeSH Terms] OR “lenvatinib”[Supplementary Concept] OR “lenvatinib*”[Title/Abstract] OR “pembrolizumab”[Supplementary Concept] OR “pembrolizumab*”[Title/Abstract] OR “nivolumab”[MeSH Terms] OR “nivolumab*”[Title/Abstract] OR “ipilimumab”[MeSH Terms] OR “ipilimumab”[Title/Abstract] OR “avelumab”[Supplementary Concept] OR “avelumab*”[Title/Abstract] OR “everolimus”[MeSH Terms] OR “everolimus*”[Title/Abstract] OR “temsirolimus”[Supplementary Concept] OR “temsirolimus*”[Title/Abstract])) NOT (“Review”[Publication Type] OR “Systematic Review” [Publication Type] OR “review”[ti] OR “Letter”[Publication Type] OR “Editorial”[Publication Type] OR “Comment”[Publication Type] OR “Case Reports” [Publication Type] OR “case report”[ti] OR “case study”[ti] OR preclinical[ti] OR animal*[ti] OR mouse[ti] OR mice[ti] OR mus[ti] OR rodent*[ti] OR rat[ti] OR rats[ti] OR “In Vitro Techniques”[Mesh] OR “in vivo”[ti] OR ((“Animals”[Mesh]) NOT “Humans”[Mesh]))

Table S2.1. Labelled dose, alternative dose regimens that used in model-based simulations and simulated percentage therapeutic window achievements results

Drug	Labelled dose	Other dose evaluated in model-informed simulation[$]	Therapeutic window achievement (%)*	Efficacy target achievement (%)	Beyond toxicity target (%)
Pazopanib	800 mg QD	-	70	86	16
		600 mg QD	70	76	6
		400 mg QD	51	52	1.0
Axitinib	5 mg BID		82	87	5
		10 mg BID	57	94	37
		7 mg BID	75	91	16
		3 mg BID	78	78	0
Cabozantinib	60 mg QD	-	21	100	79
		40 mg QD	38	97	58
		20 mg QD	55	62	7.6
		60 mg QD 2 days on 1 day off	36	99	63
Sunitinib	50 mg 4/2	-	75	89	14
		50 mg 2/1	74	76	2
		37.5 mg QD	56	57	1
		25 mg QD	9	9	0
Everolimus	10 mg QD	-	42	91	49
		5 mg QD	55	66	11
		7.5 mg QD	49	83	34
		5 mg BID	33	96	62
Nivolumab	240 mg Q2W	-	/	100	/
		3 mg/kg Q2W	/	100	/
		360 mg Q3W	/	100	/
		480 mg Q4W	/	99	/

QD, once daily; BID, twice daily; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks; 4/2, 4 weeks on and 2 weeks off treatment; 2/1, 2 weeks on and 1 week off treatment.

[$] The dose regimens that explored in model-informed simulations are generated from the routine clinical practice studies with the nearest tablet/pill/vial strength and one dose level lower. For axitinib and nivlumab, a higher dose level is also considered due to the well tolerability of the labelled dose.

* The percentage of individuals that exposure within the therapeutic window when simulating 1000 individuals per drug per regimen.

SUPPLEMENTAL MATERIAL 2.2

The file could be accessed from https://github.com/tanzy1995/JCP-supplements/tree/main.