Practical Recommendations for Therapeutic Drug Monitoring of Kinase Inhibitors in Oncology

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Introduction

Despite the fact that pharmacokinetic exposure of kinase inhibitors (KIs) is highly variable and clear relationships exist between exposure and treatment outcomes, fixed dosing is still standard practice. This review aims to summarize the available clinical pharmacokinetic and pharmacodynamic data into practical guidelines for individualized dosing of KIs through therapeutic drug monitoring (TDM). Additionally, we provide an overview of prospective TDM trials and discuss the future steps needed for further implementation of TDM of KIs.

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1 Introduction

Numerous kinase inhibitors (KIs) have become available for the treatment of solid tumors and have improved outcomes for a wide range of malignant diseases. In contrast to most classical cytotoxic drugs, these agents target specific molecular aberrations of cancer cells and are administered orally.

Many KIs show exposure-response and exposure-toxicity relationships. As pharmacokinetic (PK) exposure (e.g. area under the plasma concentration time curve (AUC) or plasma trough level (C_{min})) varies highly between patients, some patients may be at risk of treatment related toxicity due to high exposure, while others may experience suboptimal efficacy caused by low exposure.

Therefore, PK is a relevant and obvious biomarker which could be used to optimize treatment through therapeutic drug monitoring (TDM) (figure 1). For some anti-cancer drugs, TDM targets have already been recommended previously [1]. Nonetheless, expansion and an update of these previous works is warranted given the rapid developments in oncology demonstrated by the large volume of new PK and pharmacodynamic (PD) data that has become available and the abundance of new agents in this class that have been approved in recent years.

The purpose of this review is to integrate the available clinical PK and PD data into practical recommendations which can be used to personalize the treatment with KIs approved for the treatment of solid tumors, using TDM. An overview of the selected KIs used in the treatment of solid tumors and their pharmacokinetic properties (most relevant to TDM) are provided in supplemental table 1. A discussion of the available data for each KI is provided below. First, an overview of the available exposure-toxicity studies is given and exposure-response data is discussed. Concentrations for metabolites are taken into account if these have been shown to be pharmacologically active and contribute substantially to the anti-cancer effect. Then, based on these data, TDM recommendations are provided, focusing on the PK target. These TDM recommendations for each drug are summarized in table 1 and 2. Where evidence based target exposure is lacking, the average exposure of the approved efficacious dose will be provided as a proxy (also see figure 2). Additionally, we provide a comprehensive general discussion on a broadly applicable PK-guided dosing algorithm, a weighting of the evidence for TDM of each drug, the use of the mean exposure as proxy for a PK target and an overview of previously conducted prospective TDM trials in oncology.

2 Practical Recommendations for TDM of KIs in Oncology

2.1 Anaplastic Lymphoma Kinase (ALK) inhibitors

2.1.1 Alectinib

In previous studies, no relationships between alectinib exposure and grade 3 toxicity have been found.[2] No relationship between best overall response and the combined average concentration of alectinib and its metabolite M4 was found (n=49). However, in an population pharmacokinetic analysis, a higher than median steady-state alectinib C_{min} ≥435 ng/mL has been associated with greater reduction in tumor size (n=46).[2]

Based on the available data, the best estimate for a cut-off for efficacy at this time is C_{min} ≥435 ng/mL. Yet, this preliminary finding should be confirmed in future studies.

2.1.2 Ceritinib

Higher ceritinib C_{min} has been associated with an increase of grade ≥3 adverse events (AEs) (p=0.002), specifically with grade ≥3 alanine transaminase (ALT) elevation, aspartate transaminase (AST) elevation, grade ≥2 hyperglycemia and probability of dose reduction (all $p < 0.01$), but not with grade ≥2 diarrhea (p=0.11), grade ≥3 gastro-intestinal tract AEs (p=0.86) or fatigue (p=0.92).[3] No significant exposure-response relationships were identified for the primary efficacy endpoint objective response rate (ORR) and secondary efficacy endpoint progression free survival (PFS) in the pivotal trial in non-small cell lung cancer (NSCLC),[3] but a trend towards higher ORR with higher C_{min} was reported.[4]

Based on the limited data no specific threshold can be proposed yet. For now, ceritinib concentrations measured for TDM could be interpreted in relation to the mean C_{min} of 871 ng/mL at the approved dose.[3]

2.1.3 Crizotinib

No relationships between exposure and toxicity have been reported for crizotinib, except for a suggested relationship with QTc prolongation.[5] In two trials (n=120 and 114), the ORR was 60% in the patients with a C_{min} in the upper three quartiles (≥235 ng/mL) compared to 47% in the lowest quartile (<235 ng/mL).[6] An increase in PFS with increasing C_{min} was also found. A stepwise Cox proportional analysis pointed toward a higher hazard of disease progression in the lowest quartile compared to the higher quartiles with a hazard ratio of 3.2 (90% CI: 1.62–6.36).[6] This threshold of >235 ng/mL is in accordance with the EC_{50} of 233 ng/mL found in preclinical models.[7]

Based on these data, it seems reasonable to use the threshold of C_{min} ≥235 ng/mL for TDM of crizotinib.

2.2 Break Point Cluster Region - Abelson (Bcr-Abl) oncoprotein inhibitors

2.2.1 Bosutinib

Few exposure-response and exposure-toxicity data have been reported for bosutinib in chronic myelogenous leukemia (CML).[8] PK-PD analyses indicated weak relationships between the incidence (but not severity) of diarrhea and rash and PK described by an E_{max} model.[9] The same study identified limited associations between AUC and C_{min} for both complete cytogenetic response and complete hematological response and between AUC, C_{max} and C_{min} with major molecular response. Moreover, C_{min} was reported to be higher in responders than in non-responders in the pivotal CML trial.[10] Although the limited data point towards both exposure-response and exposure-toxicity relationships, no cut-off values have yet been proposed. Therefore, the most pragmatic PK target for TDM would be the median C_{min} on the approved 500 mg QD dose of 147 ng/mL.[9,11]

2.2.2 Dasatinib

In a population PK-PD analysis of the several clinical trials including the phase III study in CML (n=981), the dasatinib trough concentration was significantly related to pleural effusion ($p < 0.01$).[12] Moreover, the dasatinib weighted average steady-state concentration was significantly associated with major cytogenetic response, with the odds of response increasing 2.11-fold for every doubling of the average steady-state concentration ($p < 0.001$).[12]

Another study in Japanse patients (n=51) found that the time above the IC_{50} of phosphorylated CT10 regulator of kinase like (p-CrkL) in CD43+ cells was related to early molecular response to dasatinib in CML.[13]

Given the solid relation of exposure (weighted average steady-state concentration) with treatment response, TDM could be of value for dasatinib. However, using an average concentration for TDM is not feasible. Therefore using the geometric mean C_{min} of 2.61 ng/mL may serve as a more practical proxy.

2.2.3 Nilotinib

Large population PK-PD analyses identified several exposure-response and exposure-safety relationships for nilotinib. Higher C_{min} was associated with the occurrence of all-grade elevations in total bilirubin and lipase levels and increases in QTcF changes.[14,15]

Also, patients in the lowest C_{min} quartile had significantly longer time to complete cytogenetic response or major molecular response and shorter time to progression compared with patients in the higher quartiles.[14] For each of these analyses this Q1-Q2 threshold varied from 469 to 553 ng/mL. Based on the above, nilotinib TDM could be employed with a target of $C_{min} \geq 469$ ng/mL.

2.2.4 Imatinib

Several relationships between imatinib concentrations and toxicity, including C_{min} with thrombocytopenia[16] and AUC (unbound) with absolute neutrophil count decrease have been established.[17] A trend towards higher incidences of hematological grade 3 / 4 adverse events for patients with patients with very high C_{min} (>3180 ng/mL) was reported.[18]

Multiple studies in CML patients point towards increased efficacy of imatinib in CML with higher exposure.

In a subanalysis of the IRIS trial (n=351), significantly reduced incidences of major molecular and complete cytogenetic response and a trend towards reduced event free survival were observed in the lowest C_{min} quartile.[19] Another study in Japanese patients found (n=254) found a significant

correlation between C_{min} ≥1,002 ng/ml and higher probability of achieving a major molecular response.[20]

An Israeli study (n=191) also found a significantly higher C_{min} in CML patients who achieved a complete cytogenetic response compared to those without those without (1078 versus 827 ng/mL, p = 0.045).[21]

A study in 353 CML patients found higher incidences of major molecular response and complete cytogenetic response rates for patients with an exposure >1165 ng/mL.[18] A subanalysis of an imatinib adherence study (n=84) also found a statistically significant increased incidence of major molecular response (83.2 versus 60.1%) for patients with C_{min} >1000 ng/mL.[22]

Several other studies have also that patients with better treatment outcomes also had higher C_{min} values.[23,24]

Given the large number of studies reporting the importance of imatinib C_{min}, a prospective TDM study was conducted in 56 CML patients.[25] It set a PK target of 750 – 1500 ng/mL. Due to low adherence to the dosing recommendations this study did not meet its formal endpoint. Yet, in patients who were dosed in accordance with the recommendation experienced significantly fewer unfavorable events (28 versus 77%, p=0.03).[25]

The studies above all seem to support the use of a threshold of ≥1000 ng/mL for efficacy for imatinib in CML. Moreover the feasibility of imatinib dosing based on C_{min} has been established in a prospective study.[25] Future studies are needed to conclusively demonstrate the added benefit of personalized imatinib dosing in CML patients.

2.2.5 Ponatinib

For ponatinib, analyses of the dose intensity-safety relationship (defined as the average ponatinib dose of each subject while on study, which ranged from 0.34 to 45.2 mg) indicated a significant increase in grade ≥ 3 safety events such as AST, ALT and lipase increases, myelosuppression, hypertension, pancreatitis, rash, neutropenia and thrombocytopenia, with increasing dose intensity.[26] A statistically significant relationship between dose intensity and probability of major cytogenetic responses in CML patients has been described.[26]

Given the relation between dose intensity and major cytogenetic response, targeting the geometric mean (CV%) C_{min} of the approved 45 mg QD dose 34.2 (45.4) ng/mL (corresponding to 64.3 nM) seems a reasonable target.[27]

2.3 Epidermal Growth Factor Receptor (EGFR) inhibitors

2.3.1 Afatinib

Diarrhea and rash are the most common AEs of afatinib. These toxicities have been correlated to AUC and maximum plasma concentration (C_{max}) ($p < 0.0005$).[28] C_{min} in patients experiencing grade 3 diarrhea was higher (35.8 ng/mL) than those experiencing grade 1-2 diarrhea (25.2 – 31.6 ng/mL). In patients experiencing grade 3 rash, C_{min} was 31.4 ng/mL versus 26.8 – 27.6 ng/mL in those with only grade 1-2 rash.[29] A consistent relationship between exposure and response has not been found yet for afatinib.[30]

Awaiting future exposure-response analyses, TDM of afatinib could focus on targeting a steady state C_{min} of the 40 mg once daily (QD) dose of 14.4 – 27.4 ng/mL.[30]

2.3.2 Erlotinib

Erlotinib exposure has been significantly correlated to rash in several studies.[31] However, there was significant overlap in the range of PK values with patients who had no rash. No correlation was found with diarrhea.[31] Two clinical exposure-response studies have been reported. The first was conducted in head and neck squamous cell carcinoma (HNSCC) patients and found a trend toward increased overall survival (OS) for a C_{min} >950 ng/mL ($p=0.09$). The second found a relationship between the ratio of erlotinib and its O-desmethyl metabolite and PFS and OS (both $p<0.01$).[32] This metabolite ratio was also associated with grade 2 rash ($p=0.02$). This study found no relationships between PFS or OS and erlotinib concentrations. It should be noted however, that these results are based on a pooled analysis of NSCLC and pancreatic cancer patients (n=63 and 33, respectively).

More studies are needed to elaborate the role of erlotinib and O-desmethyl erlotinib concentrations, as no threshold for monitoring of the metabolic ratio is currently available.[32] At the moment, the

previously established preclinical threshold of >500 ng/mL still seems the most rational target for TDM.[1,33]

2.3.3 Gefitinib

Gefitinib AUC_{0-24} and C_{min} were higher in patients experiencing diarrhea and hepatotoxicity.[34,35] Rash-based dosing of gefitinib has been explored in head and neck squamous cell carcinoma, but even though this was found to be feasible, it did not result in increased anti-tumor activity, measured as response rate or PFS.[36] This study did find higher gefitinib C_{min} levels in patient with disease control compared to patient with progressive disease as best response, 1,117 ng/ml versus 520 ng/ml (p=0.01). In another study, OS was linked to gefitinib C_{min} in NSCLC patients (n=30). Patients with C_{min} <200 ng/mL had an OS of 4.7 months compared to 14.6 months for patients ≥200 ng/mL (p=0.007).[35] The available data support TDM of gefitinib in NSCLC using a threshold C_{min} of ≥200 ng/mL.

2.3.4 Lapatinib

No thorough exposure-response or exposure-toxicity studies have been reported for lapatinib. Although one trial found that the majority of responders had a C_{min} in the 300 to 600 ng/ml range.[37] Future studies should focus on establishing exposure-response and exposure-toxicity relationships. Meanwhile, lapatinib C_{min} could be interpreted in reference to the mean C_{min} of 780 ng/mL.[1]

2.3.5 Osimertinib

For osimertinib, a relationship was found between steady state AUC and the probability of rash (p=0.0023) and diarrhea (p=0.0041) in a population of NSCLC patients.[38] However, no evidence of a relationship between exposure and tumor response, duration of response or change in tumor size has been established.[38,39]

In the absence of conclusive exposure-response analyses, C_{min} could be compared to the geometric mean (coefficient of variation (CV)) of the approved 80 mg daily dose of 166 (48.7) ng/mL (corresponding to 332 nM).[39]

2.4 Vascular Endothelial Growth Factor Receptor (VEGFR) inhibitors

2.4.1 Axitinib

Exposure-safety analysis has demonstrated that axitinib AUC was significantly related to increased hypertension, proteinuria, fatigue, and diarrhea.[40] Diastolic blood pressure (dBP) ≥90 mm Hg has been associated with increased probability of response, PFS and OS in RCC patients.[41,42] Based on these results, a randomized phase II trial to individualize axitinib dose based on dBP has been performed.[43] In total, 122 RCC patients were randomized to either axitinib or placebo dose titration. The axitinib dose titration group showed an increased ORR compared to the placebo group (p=0.019)[43], but this did not result in improved OS (p=0.162).[44] One small study (n=24) also found a relationship between axitinib C_{min} >5 ng/mL and tumor response and the occurrence of hypertension, hyperthyroidism and proteinuria.[45] In renal cell carcinoma (RCC) patients, an AUC ≥300 ng*h/mL was significantly associated with increased PFS (13.8 versus 7.4 months, p=0.03) and OS (37.4 versus 15.8 months, p<0.01).[42]

The available data support using an AUC ≥300 ng*h/mL as a target for TDM.[42] However, given that prospective studies using dBP are already available, an integrated approach using both PK and dBP to guided dosing may be the most appropriate strategy to optimize treatment, as has been advocated previously.[46] Although more evidence is available to support the AUC target, the more practical C_{min} target of >5 ng/mL could also be considered (as it requires only a single plasma sample). [45]

2.4.2 Cabozantinib

Steady state AUC derived from a population PK model of combined phase I, II, and III studies has been correlated to dose reductions and lower achieved dose intensity. These dose modifications, however, did not appear to impact PFS.[47] Population pharmacodynamic modelling suggested that a concentration of only 59-78 ng/mL would already result in 50% of maximum effect in medullary thyroid cancer patients.[48]

As no PK thresholds for cabozantinib have been reported, future studies should first establish these before TDM of cabozantinib can move forward. Meanwhile, cabozantinib concentrations could be

referenced relative to the mean C_{min} in the medullary thyroid cancer phase III trial of 1380 ng/mL (on 140 mg) or 1125 ng/mL in renal cell carcinoma.[49,50]

2.4.3 Lenvatinib

An increase in the incidence of grade 3 or higher hypertension, grade 3 or higher proteinuria, nausea and vomiting with higher lenvatinib dose intensity has been observed.[51] Analyses of the pivotal study in thyroid cancer indicated similar PFS across the full range of exposures (AUC_{0-24} between 1,410 and 10,700 ng*h/mL).[52] However, a model based PKPD analysis indicated that lenvatinib AUC_{0-24} was correlated to reduction in tumor size.[52]

As no exposure-response and exposure-toxicity thresholds are established yet for lenvatinib, TDM could target the mean C_{min} of 51.5 ng/mL.[51]

2.4.4 Nintedanib

Nintedanib has only shown modest relationships between exposure and safety and efficacy.[53] In exploratory analyses, higher nintedanib concentrations have been associated with hepatotoxicity, but not with gastrointestinal AEs. Exposure-response analyses are currently not available for clinical endpoints, except for a statistically significant association between nintedanib exposure and dynamic contrast enhanced MRI response[54] and a decrease in soluble vascular endothelial growth factor (VEGFR) levels with increasing C_{min} in a phase I study (r=-0.46, n=15).[55]

As no specific threshold for nintedanib has been proposed, TDM should focus on targeting the mean C_{min} value of the approved dose (calculated for a 200 mg dose, based on the dose-normalized C_{min} value of 0.0654 ng/mL/mg) of 13.1 ng/mL.[56]

2.4.5 Pazopanib

Pazopanib exposure has been correlated to hypertension.[57] This correlation was stronger for C_{min} than for AUC_{0-t} (R^2 of 0.91,p =0.0075 and 0.25 respectively, p =0.23). Relations were also found between C_{min} and diarrhea, ALT-elevations, hand-foot syndrome and stomatitis.[58] The probability of grade ≥3 ALT increased with higher pazopanib concentration.[59] However, a recent study suggested that

pazopanib hepatotoxicity maybe related to genetic mutations in human leukocyte antigen (HLA) and, therefore, unrelated to PK.[60] Analysis of data from 177 RCC patients showed an increased PFS in patients with C_{min} ≥20.5 mg/L compared to patients with a C_{min} below this threshold (52.0 versus 19.6 weeks, p=0.0038).[57] This threshold seems to be in accordance with preclinical data showing optimal VEGFR2 inhibition by pazopanib *in vivo* at a concentration ≥17.5 mg/L.[61] Plasma concentrations have also been correlated with radiographic response in a phase II study of patients with progressive, radioiodine-refractory, metastatic differentiated thyroid cancer.[62] Two trials have investigated individualized dosing of pazopanib in cancer patients. The first used pazopanib AUC_{0-24h} as a target (715-920 mg*h/L) and set a reduction in variability as the primary endpoint.[63] AUC-guided dosing did not significantly reduce inter-patient variability, probably due to intra-patient variability or sampling time issues. Based on this trial the authors concluded it may be more beneficial to target the C_{min} threshold rather than an AUC window. The second study was a prospective study in 30 patients with advanced solid tumors, using a C_{min} ≥20 mg/L as target.[64] The dosing algorithm, based on dose adjustments after 2, 4 and 6 weeks, led to patients being treated at dosages ranging from 400 to 1800 mg daily. C_{min} in patients whose dose was successfully escalated above 800 mg (n=10) increased significantly from 13.2 (38.0%) mg/L (mean (CV%)) to 22.9 mg/L (44.9%).

This study demonstrated the safety and feasibility of C_{min} (≥20 mg/L) guided dosing for pazopanib and merits further investigation of pazopanib TDM for instance in a randomized clinical trial (RCT) to demonstrate the relevance of individualized over fixed dosing on a clinical endpoint such as PFS or OS.

2.4.6 Regorafenib

Regorafenib is metabolized by CYP3A4 into the active metabolites M2 (N-oxide) and M5 (N-oxide, N-desmethyl), which at steady state form a major component of the total exposure.[65] An exposure-dependent increase was seen for rash, total bilirubin and median indirect bilirubin in gastro-intestinal stromal tumor (GIST) patients, for parent and total (including M2 and M5) regorafenib exposure.[66] No exposure-response relationships for efficacy have been reported for regorafenib hitherto. [65]

More studies are needed to investigate exposure-response and -toxicity relationships of regorafenib. These should take into account M2 and M5, as these have been shown to be pharmacologically active and present at similar or higher concentrations than the parent compound. Currently, the most appropriate TDM target for regorafenib (parent compound only) is the mean C_{min} of 1.4 mg/L.[65]

2.4.7 Sorafenib

In a study of patients with advanced solid tumors (n=54), a cut-off at a cumulative AUC (calculated over day 0 to 30) of 3,161 mg*h/L was associated with the highest risk to develop any grade ≥3 toxicity (p=0.018).[67] A patient series found that sorafenib C_{min} was higher in patients who experienced grade 3 AEs (n=8) than those who did not (n=14), 7.7 ± 3.6 mg/L versus 4.4 ± 2.4 mg/L, (p=0.0083).[68] Sorafenib steady state concentrations were found to be higher in patients with grade ≥2 hand-foot syndrome and hypertension than in those not experiencing these AEs (p=0.0045 and 0.0453, respectively). Optimal cut-offs were 5.78 mg/L for hand-foot syndrome and 4.78 mg/L for hypertension.[69] In a small cohort of 25 hepatocellular carcinoma patients, the AUC-ratio of sorafenib and its metabolites resulted in even better prediction of toxicity (p=0.002).[70] The same cohort found that not sorafenib AUC but that of its metabolite seemed significantly associated with dose reduction or discontinuation (p=0.031) and increased PFS (p=0.048).[70] A study in Japanese patients (n=91) found a trend toward increased OS in hepatocellular carcinoma patients at a sorafenib C_{max} of ≥4.78 mg/L (12.0 versus 6.5 months, p=0.08).[69]

Future studies need to confirm the proposed exposure-response and -toxicity relations described in these small patients cohorts, taking into account the N-oxide metabolite. Currently, the most appropriate target for sorafenib TDM is >3.75-4.30 mg/L (parent compound only), based on preclinical experiments and the mean exposure in humans, as was advocated previously.[1]

2.4.8 Sunitinib

Sunitinib is metabolized by CYP3A4 into its active metabolite N-desethylsunitinib also known as SU12662. TDM for sunitinib is generally performed using the sum of concentrations (total C_{min}) of both sunitinib and SU12662.[71] Dose limiting and grade ≥3 toxicities of sunitinib have been associated

with total C_{min} ≥100 ng/mL.[17,72] Grade ≥2 mucositis and altered taste have also been related to higher total C_{min} .[73] A relationship was also found between sunitinib AUC and grade ≥3 toxicity (p=0.0005).[74] Based on the above, an upper C_{min} cut-off of <100 ng/mL could be considered.

In RCC, increasing AUC has been related to higher response rates, longer PFS and OS.[74–77] A meta-analysis found AUC of sunitinib combined with its active metabolite N-desethylsunitinib to be significantly associated with PFS and OS in both GIST (n=401) and RCC (n=169), all p<0.01.[76] An increased OS was found for an AUC ≥1973 ng*h/mL in another study in RCC patients (n=55).[74] C_{min} correlated with AUC (r^2=0.8-0.9), suggesting C_{min} could be used for TDM as substitute.[76] A PK target of 50-100 ng/mL[17] has been suggested for intermittent dosing in RCC (50 mg daily for 4 weeks in a 6 week cycle) and based on PK linearity a target of ≥37.5 ng/mL was extrapolated for continuous dosing in GIST (37.5 mg daily continuously) .[1]

A TDM-feasibility trial has been conducted in cancer patients using C_{min} ≥50 ng/mL as PK target allowing for dose adjustments after 3 and 5 weeks of treatment.[78] A third of the patients <50 ng/mL at the standard dose, could be treated successfully at an increased dose and additional patients reached the target exposure. This study demonstrates the feasibility using C_{min}≥50 ng/mL (sunitinib + metabolite) as TDM target. Future studies are now needed to confirm the efficacy of TDM over fixed dosing for sunitinib.

2.4.9 Vandetanib

Grade ≥2 diarrhea and fatigue have significantly been associated with steady state vandetanib C_{min} (p=0.03 and 0.02, respectively), but no relationship was found for hypertension or rash.[79] Importantly, a substantial dose and exposure related QTc prolongation has been observed.[79] No clear relationship between PFS and exposure has been found in the pivotal trial in patients with thyroid cancer [79], although multiple studies have used IC_{50} values established *in vitro* (190 ng/mL) to support dose selection in early clinical trials.[80]

In absence of studies that establish specific PK thresholds, current exploratory TDM efforts could focus on targeting the population mean exposure of 795 ng/mL.

2.5 Serine/Threonine-Protein kinase B-Raf (BRAF) inhibitors

2.5.1 Dabrafenib

Dabrafenib is metabolized into its carboxy, hydroxyl and desmethyl metabolites.[81] The hydroxyl metabolite showed similar IC_{50} values to dabrafenib *in vitro*. No relationships between AEs and exposure, except for pyrexia, have been reported.[82] Pyrexia seemed to be related to $C_{average}$ dabrafenib and hydroxy-dabrafenib C_{min}, but not to desmethyldabrafenib C_{min}.[83] At the moment, no evident exposure-response relationships have been reported for dabrafenib and/or for any of its metabolites.[84]

In absence of a validated target, current TDM efforts could target the median C_{min} (sum of parent dabrafenib and its hydroxyl metabolite) of 99.6 ng/mL.[84]

2.5.2 Vemurafenib

In melanoma patients, vemurafenib concentrations were significantly higher in those patients who developed grade ≥2 rash compared to those who did not (mean ± standard deviation (SD) of 61.7±25.0 vs. 36.3±17.9 mg/L, $p<0.0001$).[85] Another study found an exposure-dependent QTc prolongation for vemurafenib.[86] Vemurafenib concentrations have also been related to treatment response. Responders had a mean concentration of 56.4 mg/L, whilst non-responders had a mean of 38.8 mg/L ($p=0.013$).[87,88] Moreover, melanoma patients in the lowest exposure quartile (<40.4 mg/L) had a PFS of 1.5 months compared to that of 4.5 months of patients in the higher three quartiles ($p=0.029$).[85] This effect was confirmed in an independent cohort after 12 months of follow up with a threshold of 42 mg/L ($p=0.005$).[89]

The available data support the use of a threshold C_{min} of >42 mg/L. A real-world study however, found that in routine care only half of patients had a C_{min} <42 mg/L,[90] demonstrating the opportunities for dose optimization.[90]

2.6 Mitogen Activated Protein Kinase (MEK) inhibitors

2.6.1 Cobimetinib

Exploratory exposure-toxicity analyses for safety identified a trend towards increased diarrhea with increasing cobimetinib and vemurafenib exposure.[91] No significant exposure-response relationship has been established for cobimetinib on the primary endpoint of PFS in the pivotal registration trial.[91]

On the basis of the available data no clear PK target can yet be identified for cobimetinib. Therefore, the currently most appropriate target would be the mean C_{min} of the approved dose of 127 ng/mL.[91]

2.6.2 Trametinib

No exposure- toxicity relationships have been identified for trametinib. A population analysis was performed to explore the effect of trametinib C_{min} and average concentration on ORR and PFS.[92] The proportion of responders seemed to increase with increasing exposure and reached a plateau at a C_{min} of 10 ng/mL. No relationship between exposure above or below the mean C_{min} of 13.6 ng/mL and PFS has been identified in phase 3 trials. However, in an analysis of the phase 2 study, patients with C_{min} above 10.6 ng/mL, had longer PFS than those below this C_{min} value.[92] Furthermore, the C_{min} threshold of 10.6 ng/mL is supported by preclinical data pointing towards a target of 10.4 ng/mL based on efficacy in BRAF mutant melanoma cell lines.[93]

Given the above, the threshold of a C_{min} ≥10.6 ng/mL seems the most appropriate target to be used for trametinib TDM.

2.7 Other Kinase Inhibitors used in Oncology

2.7.1 Everolimus

In transplantation medicine, TDM is routinely applied for everolimus, using a window of 6-10 ng/mL or 3-8 ng/mL in combination therapy.[94] No target for TDM has been validated in oncology. Higher C_{min} has been associated with increased risk of high-grade pulmonary and metabolic (such as hyperglycemia) AEs and stomatitis. However, this meta-analysis of everolimus phase II trials (n=945), found that a 2-fold increase in everolimus C_{min} was associated with improved tumor size reduction, regardless of cancer type.[95] No specific target window has been proposed, but in RCC and pNET cut-offs at ≥10 and 30 ng/mL resulted in numerically higher PFS values than C_{min}<10 ng/mL.[95] A

retrospective analysis of 45 RCC patients showed a trend toward increased PFS for patients with a C_{min} ≥14.1 ng/mL of 13.3 versus 3.9 months, p=0.06.[96]

Based on experience in transplant and pediatric patients, everolimus TDM seems feasible.[94,97] Although exposure-response relations are seen for everolimus in oncology, no formal PK-target has been established yet. Based on the available data, a cut-off for efficacy of C_{min} ≥10 ng/mL seems a reasonable target for TDM of everolimus in oncology.

2.7.2 Ibrutinib

For ibrutinib no exposure-safety relationships were found.[98] A phase 1 study indicated maximum Bruton's tyrosine kinase occupancy at doses of ≥ 2.5 mg/kg (corresponding to a 175 mg dose for average weight of 70 kg). This complete target inhibition was already seen at an AUC of 160 ng*h/mL.[99]

In absence of a clearly defined pharmacokinetic thresholds for clinical patient outcomes, ibrutinib TDM could target the mean +SD AUC at the approved 560 mg QD dose of 953 ± 705 ng*h/mL for mantle cell lymphoma patients or 680 ± 517 ng*h/mL at 420 mg QD for patients with chronic lymphocytic leukemia (no C_{min} data was reported).[98]

2.7.3 Imatinib

In addition to its use in CML, imatinib is also used as an inhibitor of the stem cell receptor KIT and platelet derived growth factor receptor (PDGFR) in GIST. In an analysis of 73 GIST patients randomized to either 400 or 600 mg QD, an increase in time to disease progression was found for patients with a C_{min} >1100 ng/mL.[100] Another study did not find a relationship between imatinib C_{min} and treatment response, but did find a relationship between free (unbound to plasma proteins) imatinib concentration >20 ng/mL and complete response.[101] Two real-world studies suggest a relationship of imatinib C_{min} and efficacy. The first, found that responders had a median C_{min} of 1271 ng/mL, whilst C_{min} in non-responders was 920 ng/mL (p=0.23).[102] The second, did not find a significant relationship between a C_{min} >1100 ng/mL threshold of imatinib and PFS (p=0.1107). However, a threshold of >760 ng/mL was associated with a significantly longer PFS (p=0.0256).[103]

The available studies point towards different targets for imatinib TDM in GIST patients (≥760 and ≥1100 ng/mL). The more pragmatic approach may be to use the C_{min} >1100 ng/mL threshold, as it is based on PFS data from a RCT [100] and seems to be confirmed by data from an independent observational cohort.[102] Moreover, a retrospective cohort study of 68 GIST patients, indicated the feasibility of dosing imatinib based on the 1100 ng/mL threshold, with more patients reaching the prespecified target exposure.[104]

2.7.4 Idelalisib

No exposure-response or exposure-safety relationships have been identified for idelalisib in chronic lymphocytic leukemia or non-Hodgkin lymphoma, using either AUC or C_{min} as pharmacokinetic parameters.[105] However, dose selection was supported by that fact that the exposure achieved on the approved dose achieved the EC_{90} of 125 ng/mL for inhibition of PI3Kδ in vitro.[105] In absence of more conclusive data, TDM of idelalisib should for now target the median C_{min} at the approved 150 mg QD dose of 318 ng/mL.[105,106]

2.7.5 Palbociclib

A greater reduction in absolute neutrophil count (ANC) appears to be associated with increased palbociclib exposure.[107] No conclusive exposure-response relationship has been found in 81 patients treated at the 125 mg fixed dose.

Based on the limited exposure response and toxicity analyses no specific PK target for palbociclib can be formulated. More thorough PKPD analyses are needed. Until these come available palbociclib concentrations can be compared to the population mean (CV) C_{min} of 61 (42) ng/mL.[107]

3 Discussion

Currently, KIs are administered at a fixed starting dose which is only adjusted in case of intolerable toxicity (figure 1, left). As many KIs show an exposure-response and exposure-toxicity relationship

and exposure varies highly between patients, we propose that an individualized PK-guided dosing or TDM algorithm should be explored for KIs (figure 1, right).

Based on the PK targets discussed above, dose increments could be considered for patients with low exposure in absence of significant toxicity. These dose increments could for instance follow the dose-escalation schedule explored in the phase I dose-escalation study of the respective drug. Yet if available, a prospectively validated and safe TDM-dose algorithm would be preferred (see table 3).

For patients with a high plasma concentration not experiencing toxicity, dose reductions could be considered. However, in contrast to for example TDM of aminoglycosides in infectious diseases, in oncology the main focus of TDM will probably be directed towards improving efficacy by increasing the dose in low exposure patients. Concerns for lasting side-effects may in most cases be less relevant.

Nonetheless, monitoring of plasma concentrations may be useful in patients requiring dose reductions for toxicity. Here, it could be used to differentiate between patients who had toxicity due to high exposure (who might be successfully treated at the lower dose) and those who do not tolerate treatment despite an exposure below the efficacious concentration (red box, figure 1). Taking together the considerations above, a proposal for a generic decision tree for PK-guided dosing is provided in figure 1.

Ideally, individualized dosing should be based on thorough exposure-response and exposure-toxicity analyses. A weighting of the robustness of the evidence has been provided for each of the proposed TDM recommendations in table 1 and 2 as either *negative, exploratory, promising, viable or standard of care*.

None of the included drugs has been qualified as *negative*. Based on the mechanism of action of KIs and the clinical pharmacological properties, exposure-response relationships are to be expected for most of these drugs. A fully negative recommendation can only be provided if evidence from a adequately sized and powered study demonstrates that at the recommended dose no relationship between drug exposure and response exist.

For the drugs in the *exploratory* category (table 1 and 2), no PK-targets have been specified yet. Therefore it is too early to recommend implementation of TDM for these drugs. Further PK sampling

in clinical trials and routine patient care could help to identify exposure-response and exposure-toxicity relationships. TDM, however, could already be of value in specific patient populations, such as patients with hepatic impairment, patients not able to swallow medication or patients having possible drug interactions and compliance issues. The mean population exposure could be used as reference for interpretation of the exposure of these individual patients.[1] An updated analysis of the relationship between available TDM targets and the average population exposure support this (figure 2). Overall the targets (n=11) amounted to 81.7% of the population exposure, with a relatively small SD of 17.4%. Although this is no substitute for thorough exposure-response analyses, the data support the view that targeting the mean or median exposure will generally result in efficacious concentrations for KIs in oncology.

If an exposure-outcome relationship and a PK target have been established, TDM could be considered a promising strategy for treatment optimization. The agents for which a TDM target is available are therefore classified as *promising* in table 1 and 2. For these drugs, the feasibility of individualized dosing based on this target should preferably be demonstrated in a prospective clinical trial.

For KIs where feasibility studies have already been conducted (table 3), TDM is classified as *viable* (table 1 and 2). All but one of these studies have used PK endpoints, aiming to establish the safety and feasibility of reaching the target exposure.[25,63,64,78,108] One study used a PD endpoint, a one-armed trial with the purpose to show efficacy in a rare pediatric tumor (subependymal giant cell astrocytoma).[97]

Currently, for none of the discussed agents TDM is performed as the standard of care. Before TDM can become standard for drugs in the *viable* category, the relevance of this dosing strategy over fixed dosing should, if feasible, be clinically validated in a prospective randomized trial. Such studies are scarce, but have been conducted previously for TDM of cytotoxic drugs such as paclitaxel,[109] indicating the feasibility of conducting randomized individualized dosing trials in cancer patients. This type of trials should now be initiated to demonstrate an effect of TDM for targeted anti-cancer agents on relevant clinical endpoints in oncology.

4 Conclusion

For KIs with an exposure-response and/or exposure-toxicity relationship and high inter-patient variability in exposure, a PK parameter such as C_{min} is an obvious and relevant biomarker for dose individualization through TDM.

Several clinical trials demonstrate the safety and feasibility of TDM of KIs, such as imatinib, pazopanib, tamoxifen, everolimus and sunitinib. Randomized clinical trials are now needed to confirm an effect of TDM over fixed dosing on relevant clinical efficacy endpoints such as PFS and OS, before TDM can become universally implemented as standard care of cancer patients treated with KIs.

5 Disclosures

The authors declare they have no conflicts to disclose.

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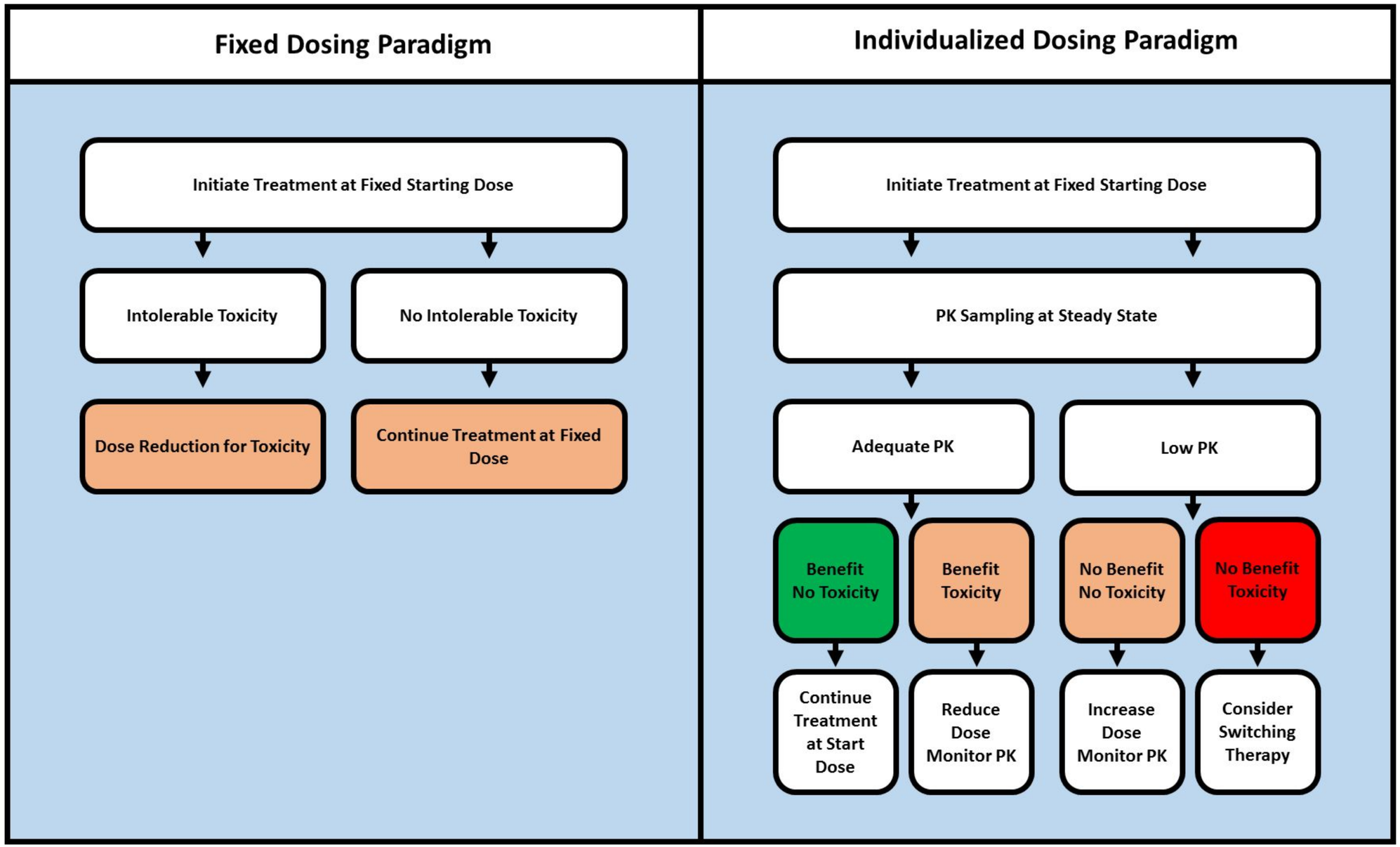
Figure 1: Current fixed dosing paradigm (left) versus the proposed individualized or TDM dosing algorithm (right).

Figure 2: The TDM-thresholds of selected KIs as percent of the mean/median exposure of the approved dose (blue bars). Overall, the thresholds were 81.7 % of the mean exposure across all agents (orange bar), with a standard deviation of 17.4%. Dotted horizontal lines indicate 100% of mean exposure and 81% (the mean of the thresholds). This analysis suggests that across all kinase inhibitors, the target exposure matches with 81.7% of the population exposure and supports the view that targeting the population average could serve as a proxy, in absence of a definitive TDM target.



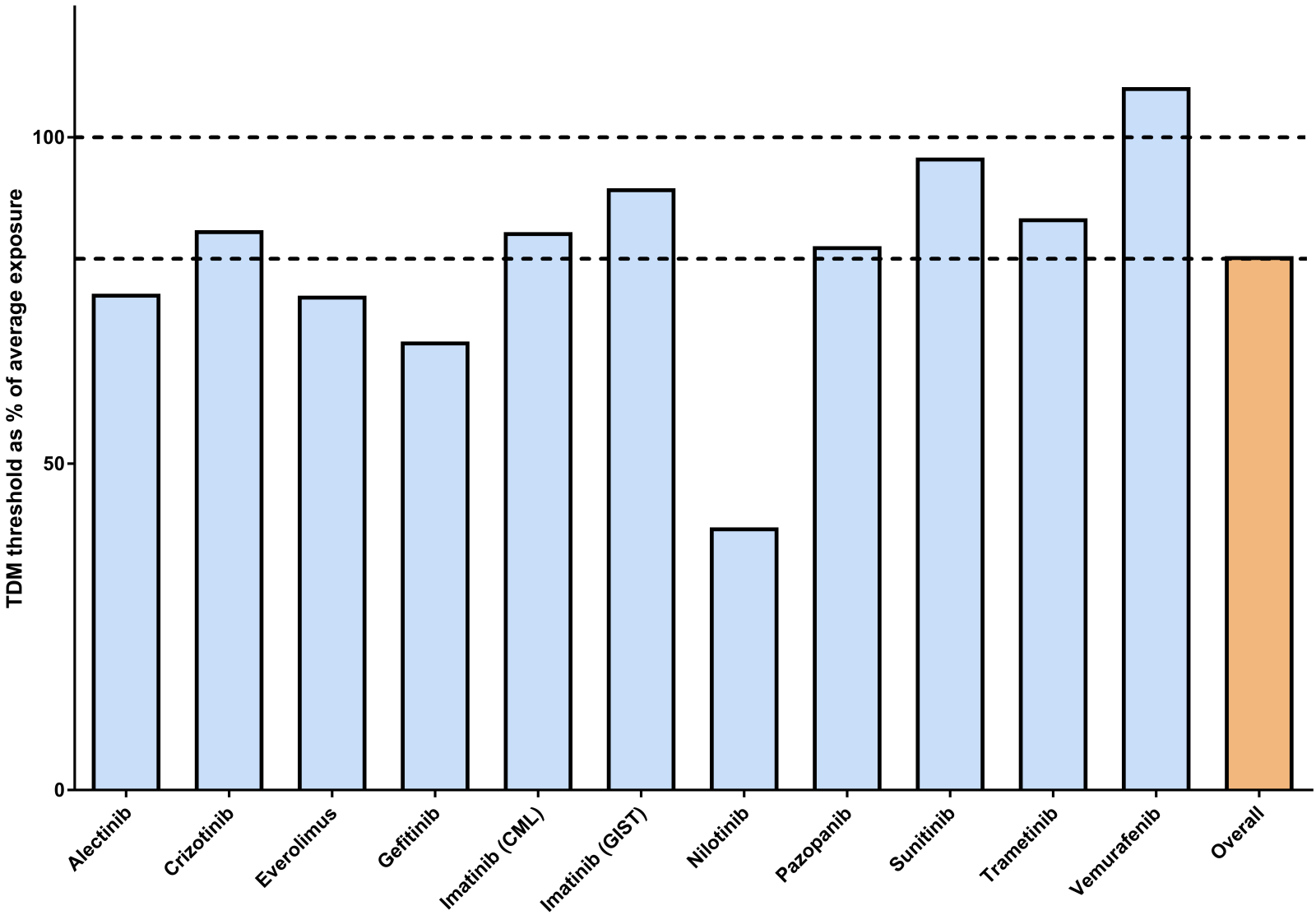


Table 1: Overview of practical TDM recommendations for KIs approved by the FDA for the treatment of solid tumors.*

Drug	TDM Recommendation	Proposed Target (ng/mL)	Mean / Median Exposure (C_{min} in ng/mL)	Outcome Parameter Associated with TDM Target	References
Afatinib	Exploratory		14.4		
Alectinib	Promising	C_{min} ≥435	572	Increased ORR	[2]
Axitinib	Promising	AUC ≥300†	375†	Increased OS	[42]
Ceritinib	Exploratory		871		
Cabozantinib	Exploratory		1380		
Cobimetinib	Exploratory		127		
Crizotinib	Promising	C_{min} ≥235	274	Increased PFS	[6]
Dabrafenib	Exploratory		96.1		
Erlotinib	Exploratory		1010		
Everolimus	Promising	C_{min} ≥10.0	13.2	Increased PFS	[95]
Gefitinib	Promising	C_{min} ≥200	291	Increased OS	[35]
Imatinib	Viable	C_{min} ≥1100	1193	Increased PFS	[100]
Lapatinib	Exploratory		780		
Lenvatinib	Exploratory		51.5		
Nintedanib	Exploratory		13.1		
Osimertinib	Exploratory		166		
Palbociclib	Exploratory		61		
Pazopanib	Viable	C_{min} ≥20,000	24,000	Increased PFS	[57,64]
Regorafenib	Exploratory		1400		
Sorafenib	Exploratory		3750		
Sunitinib	Viable	C_{min} ≥50 (inter), ≥37.5 (cont)	51.6 (sum of parent & SU12662)	Increased OS	[76]
Trametinib	Promising	C_{min} ≥10.6	12.1	Increased PFS	[110]
Vandetanib	Exploratory		795		
Vemurafenib	Promising	C_{min} ≥42,000	39,000	Increased PFS	[85,89]

**The provided recommendation is considered promising if a pharmacokinetic TDM target is available or viable if a prospective TDM study has been conducted. Otherwise the recommendations should be considered exploratory.*

*† For axitinib the AUC is provided in units of ng*h/mL.*

‡ Average steady state concentration.

AUC: Area under the curve; C_{min}: Minimum plasma concentration / trough concentration; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival;

Table 2: Overview of practical TDM recommendations for KIs approved by the FDA for the treatment of hematological malignancies.*

Drug	TDM Recommendation	Proposed Target (ng/mL)	Mean / Median Exposure (C_{min} in ng/mL)	Outcome Parameter Associated with TDM Target	References
Bosutinib	Exploratory		147		
Dasatinib	Exploratory		2.61		
Nilotinib	Promising	C_{min} ≥469	1165	Prolonged TTP	[14]
Idelalisib	Exploratory		318		
Ibrutinib	Exploratory		680†		
Imatinib	Viable	C_{min} ≥1000	1170	Improved MMR, CCYR	[19]
Ponatinib	Exploratory		34.2		

**The provided recommendation is considered promising if a pharmacokinetic TDM target is available or viable if a prospective TDM study has been conducted. Otherwise the recommendations should be considered exploratory.*

CCYR: Complete cytogenetic response; MMR: Major molecular response; TTP; Time to progression.

Table 3: Overview of prospective dose individualization trials of KIs.

Drug	n	Patient Population	PK Parameter	Target	Dose Change	PK-guided dose escalations (↑) or reductions (↓)†	Endpoint	Reference
Everolimus	28	Pediatric SEGA patients	C_{min}	5-15 ng/mL	-	↑ and ↓	PD	[97]
Sunitinib	37	Advanced solid tumors	C_{min}	≥50 ng/mL	After 3 and 5 weeks	↑ only	PK	[78]
Imatinib	56	Chronic myelogenous leukemia patients	C_{min}	750 – 1500 ng/mL	-	↑ and ↓	PK	[25]
Pazopanib	13	Renal cell carcinoma patients	AUC	715-920 mg*h/L	After 2 weeks	↑ and ↓	PK	[63]
Pazopanib	30	Advanced solid tumors	C_{min}	≥20 mg/L	After 2, 4 and 6 weeks	↑ only	PK	[64]

AUC: Area under the curve; C_{min}: Minimum plasma concentration / trough concentration; PD: Pharmacodynamic; PK: Pharmacokinetic; SEGA: Subendymal giant cell astrocytoma

†Per protocol, some trials had dosing algorithms which allowed for dose reductions (in absence of toxicity) based on PK, while others only allowed for dose escalation based on PK. All allowed for dose reductions based on toxicity.