



Therapeutic drug monitoring of oral targeted antineoplastic drugs

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Abstract

Purpose This review provides an overview of the current challenges in oral targeted antineoplastic drug (OAD) dosing and outlines the unexploited value of therapeutic drug monitoring (TDM). Factors influencing the pharmacokinetic exposure in OAD therapy are depicted together with an overview of different TDM approaches. Finally, current evidence for TDM for all approved OADs is reviewed.

Methods A comprehensive literature search (covering literature published until April 2020), including primary and secondary scientific literature on pharmacokinetics and dose individualisation strategies for OADs, together with US FDA Clinical Pharmacology and Biopharmaceutics Reviews and the Committee for Medicinal Products for Human Use European Public Assessment Reports was conducted.

Results OADs are highly potent drugs, which have substantially changed treatment options for cancer patients. Nevertheless, high pharmacokinetic variability and low treatment adherence are risk factors for treatment failure. TDM is a powerful tool to individualise drug dosing, ensure drug concentrations within the therapeutic window and increase treatment success rates. After reviewing the literature for 71 approved OADs, we show that exposure-response and/or exposure-toxicity relationships have been established for the majority. Moreover, TDM has been proven to be feasible for individualised dosing of abiraterone, everolimus, imatinib, pazopanib, sunitinib and tamoxifen in prospective studies. There is a lack of experience in how to best implement TDM as part of clinical routine in OAD cancer therapy.

Conclusion Sub-therapeutic concentrations and severe adverse events are current challenges in OAD treatment, which can both be addressed by the application of TDM-guided dosing, ensuring concentrations within the therapeutic window.

Keywords Targeted antineoplastic drugs · Tyrosine kinase inhibitors · Therapeutic drug monitoring · Oral anticancer drugs · Personalised medicine

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Introduction

With the approval of imatinib in 2001 [1], kinase inhibitors (KIs) have significantly improved the prognosis of many cancers. As of April 2020, 71 oral antineoplastic drugs (OADs) targeting a large assortment of molecular targets (Supplementary Fig. 1) are approved by the European Medicines Agency (EMA) and/or the US Food and Drug Administration (FDA).

With more OADs available, both the route of administration and the treatment setting are changing. While i.v. chemotherapy is mainly administered in an in-patient setting, OADs allow outpatient care with both its advantages and disadvantages. Strong advantages are the level of independence, and, due to outpatient treatment, a reduction of health care costs. At the same time, the responsibility for adhering to treatment schedules is moved to the patient. Given the often-complex treatment regimens, patients must be well trained and motivated to take their medication correctly. Moreover, patients should have knowledge on the frequency and severity of possible adverse events (AEs) and on preventive and responsive measures to limit them. Yet, adherence to targeted OADs is variable.

Other aspects to consider are the complex pharmacokinetics (PK) of OADs [2]. Although the right drug (‘what’) is increasingly selected based on the tumour characteristics, a fixed dose (‘how much’) is mostly given in OADs, leading to large differences between individual plasma concentrations. High interindividual variability (IIV) in exposure at standard dosing, mostly ranging from 19 to 100% [3] and up to 16-fold for gefitinib [4], has been described for OADs. While modern phase I studies increasingly assess exposure-response relationships and maximum tolerated doses (MTD) become harder to identify, the fixed dose for a new antineoplastic drug is historically established in a phase I study using a 3 + 3 design, which focuses on toxicity [5]. The MTD, defined as the dose level below the toxic dose level, is usually adopted as the recommended phase II dose [5]. Few patients participate in phase I trials (median $n = 26$ [6]) which limits the generalisability of the selected dose. Based on the lack of focus on efficacy, a proportion of patients will show sub-therapeutic plasma concentrations [7] and be at risk for treatment failure at the early determined MTD. At the same time, some patients will show toxic plasma concentrations and thus an increased risk for non-adherence [8] as consequence of AEs [9].

One strategy to prevent sub-optimal drug concentrations is the use of therapeutic drug monitoring (TDM), i.e. dosing based on measured drug exposure [10], guiding OAD dosing [7, 11–14]. By tailoring drug doses to individual patients, the proportion of patients with sub-optimal drug concentrations can be reduced. TDM has already been well-adopted in other therapeutic areas such as antimicrobial and antiepileptic

therapy [15–17]. Despite its value in oncology becoming more recognised [18–21], it is still not commonly used in antineoplastic treatment.

In the following sections, we elaborate on the unexploited value of TDM in OAD therapy. After introducing various forms of TDM and TDM for OADs specifically, an overview of current evidence for drug target concentrations is provided. Moreover, we describe available PK models, observed PK exposure, TDM targets and data on exposure-response and exposure-safety relationships for OADs that are approved by at least one regulatory agency. Finally, TDM recommendations are given for OADs, for which targets were established and TDM has proven feasible.

Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) refers to measuring drug concentrations to assess if drug concentrations are within the therapeutic target range and, if necessary, individualise dosing regimens. An unpredictable dose-exposure relationship, a small therapeutic window with a defined target concentration, a high PK and/or pharmacodynamic (PD) IIV and nonlinear PK are best indicators for a benefit from TDM [7, 22]. The absence of an exposure-response relationship and high intraindividual and interoccasion (IOV) PK/PD variability relative to the IIV are characteristics of drugs unsuitable for TDM [23, 24] (Supplementary Fig. 2). Several forms of dose individualisation exist. These are classified as a priori and a posteriori approaches, depending on the level of individualisation before treatment initiation [15]. In an a priori framework, information on both drug and patient characteristics are used to guide initial dosing [25]. Based on established relationships between patient characteristics and PK parameters, initial dosing can be individualised to patient sub-populations [26]. However, no individual PK information is included in an a priori framework, resulting in moderate average bias and precision [26].

Individual drug concentrations obtained after treatment start are used in a posteriori TDM [15]. Following the detection of non-optimal drug concentrations, different procedures for dose adjustments are possible: in the simplest case, oncologists will use the drug label, dosing algorithms or nomograms to determine a new dose [27]. Although simple, this approach requires to abide with the scheduled blood sampling times and is unsuitable if the patient is not represented by the population on which drug label or dosing algorithm have been developed on [28].

Another a posteriori approach involves the collection of 4–8 blood samples within a dosing interval and the subsequent calculation of the area under the concentration-time curve (AUC) [11]. Based on the calculated AUC, individual PK parameters can be obtained and used for PK calculations to

determine a more suitable dose. However, dense blood sampling is rarely feasible in clinical practice [29].

Population PK (nonlinear mixed-effects) modelling and simulation [30] can aid in optimising TDM in multiple ways: first, PK information from the population can be incorporated into model parameters during model development. Use of this information allows to refrain from dense blood sampling in model-informed precision dosing (MIPD) and often few samples are enough to obtain sufficiently precise individual PK estimates [26]. Second, sampling at fixed time points is no longer necessary and can also be performed prior to steady-state attainment [26]. As long as actual sampling times are documented, samples from virtually every time point can be used for PK analyses in MIPD [26]. Still, there are more and less informative sampling time points. Optimal design, another part of the model-informed dose individualisation process, can aid in systematically determining the most informative sampling time point(s) within a given time frame [31]. Finally, Bayesian TDM in MIPD combines model-informed TDM with the ability to learn and subsequently forecast drug concentrations at various possible dosing regimens. Similarly to traditional population PK, the Bayesian approach uses information from the population to estimate the most likely PK parameter values for a given drug and population [32]. If specific patient characteristics influence one or more of the PK processes, this information can already be used in an a priori dose selection process. At the beginning of treatment, when no concentration measurements are available, predicted PK parameter values for a specific patient will be identical with the population estimates [29]. As measured drug concentrations become available, they are used to refine the patient's predicted PK parameter values. The more patient-individual information (i.e. drug concentrations) is available, the more weight is set on this information in the parameter estimation process and the more individual parameter estimates will be allowed to deviate from the population estimates [29]. Moreover, Bayesian TDM can account for IOV that is lower than the safe and effective variability [33] and still predict future doses based on at least two sampling occasions [34, 35]. A disadvantage of Bayesian TDM is the high shrinkage of predicted individual PK parameters if only a single PK sample is available: when the population outweighs the individual information, individual information on the patient will get lost as the empirical Bayes estimates shrink to the typical population parameters [29]. Moreover, applying Bayesian TDM requires special knowledge, can be time intensive and thus difficult to implement in clinical practice.

Sampling minimum plasma concentrations at steady-state ($C_{\min,SS}$) is often performed in clinical practice and, if done correctly, the currently most precise approach as it avoids shrinkage of individual information to the population mean. However, it requires precise information about the patient's dosing schedule and good coordination between patient and

treatment team. An easy and time-efficient way to circumvent the need to sample at $C_{\min,SS}$ is to account for the difference between the time of minimum concentrations and time of measurement and extrapolate based on the time after last dose and the terminal half-life of the drug. In this method, based on an algorithm described and validated for imatinib [10], samples can be taken at random time points in the elimination phase of the drug and the corresponding $C_{\min,SS}$ can be calculated using Eq. (1).

$$C_{\min,SS} = C_{\text{measured}} * 0.5^{\frac{\text{Dosing Interval [h]} - \text{Time after last dose [h]}}{\text{Half-life [h]}}} \quad (1)$$

Of note, this method assumes that C_{measured} is sampled in the terminal phase of a monoexponential decline. For drugs with a nonlinear clearance or a short half-life (i.e. dasatinib, axitinib), an alternative method has to be used. For example, the $C_{\min,SS}$ can also be estimated based on a randomly taken concentration measurement (C_{measured}) and a simulated typical concentration-time curve, using an existing population PK model. Based on the ratio of the measured concentration at t_{measured} with the concentration in the simulated PK profile, the corresponding $C_{\min,SS}$ in this patient can be estimated [36].

Therapeutic drug monitoring for oral targeted antineoplastic drugs

Several OAD characteristics suggest individualised dosing:

- 1 OADs show highly variable drug exposure, caused by IIV in absorption, distribution, metabolism and excretion (ADME). Oral bioavailability (BA) differs between and within agents (i.e. 14–34% in dasatinib and 98% in imatinib) and depends on drug formulation [37], absorption, first-pass hepatic metabolism and food intake. Moreover, almost all OADs are metabolised by monooxygenases of the Cytochrome P450 (CYP) family [3]. Up to 20-fold variability in expression and activity of CYP3A4 has been reported, and polymorphisms in the isoenzymes CYP2D6, CYP2C9 and CYP2C19 additionally contribute to the variable metabolic activity [3]. The activity of CYP enzymes may be additionally influenced by concomitant administration of CYP inducers/inhibitors, environmental factors, smoking and food intake [3, 38]. Polymorphic transporters are also involved in the excretion of many agents (i.e. axitinib, dasatinib and sorafenib) [3].
- 2 Efficacy is challenging to assess during OAD treatment, as benefits in clinical outcome parameters such as overall survival (OS) and progression-free survival (PFS) take long until evaluable. Objective response rates using CT scans can be assessed earlier and for a few malignancies, reliable biomarkers are available (i.e. prostate specific antigen for prostate cancer or complete cytogenetic response

(CCyR) for chronic myeloid leukaemia (CML)). Furthermore, advances in PKPD modelling allow to use tumour dynamics in exposure-response analyses [39]. If an exposure-response relationship has been established, achieving target concentrations can serve as a proxy for achieving beneficial outcomes.

As disease progression can be fatal in oncology, treatment at an exposure above the efficacy threshold should be assured from the start of treatment or at least achieved as soon as possible, while individual patient toxicity should be monitored carefully. Furthermore, dose increases should only be implemented in case of acceptable toxicity and patients with low exposure and considerable toxicity should be switched to another treatment option.

Of note, while TDM might be crucial for agents with a narrow therapeutic window (i.e. pazopanib, sunitinib), it might be less relevant for agents with a wider therapeutic window (i.e. erlotinib, osimertinib).

Considering the high costs of OADs, cost-neutral PK-guided dose interventions to increase exposure, i.e. concomitant intake with food [40–42], split intake moments [43] or boosting (i.e. with a CYP3A4 inhibitor), should be considered before conventional dose increments, particularly in countries with poor healthcare systems.

For some agents, TDM has already proven feasible [44]. Strong evidence exists for imatinib in CML [18, 45] and gastrointestinal stromal tumours (GIST) [46]. Additional compounds for which TDM was feasible in prospective studies are sunitinib [47], pazopanib [48], tamoxifen [20] and abiraterone [40]. For other agents, i.e. alectinib [49], axitinib, crizotinib [49], trametinib [50] and vemurafenib [51–54], a PK target associated with either efficacy or toxicity has been established, but not yet evaluated in prospective clinical studies [13]. Lastly, no information about the value of TDM is available for some compounds. Most of these are new, and exposure-response relationships have not been established yet. For those drugs, we suggest to target the mean/median exposure as proxy for a PK target, as previously established PK targets amounted to 85% ($\pm 19\%$) [14] and 82% ($\pm 17\%$) [13] of the mean population exposures in AHDs and KIs, respectively. This is already applied in the DPOG-TDM study [55] and similar approaches are suggested by the FDA for special populations [56–58]. In the DPOG-TDM study [55], the feasibility, tolerability and efficacy of TDM for 23 different OADs is currently being evaluated (www.trialregister.nl; NL6695) and preliminary results are promising [59].

The rapid improvement in OAD treatment together with the continuous development of new compounds poses a challenge for the timely establishment of viable TDM targets. While exposure-safety relationships are determined early during drug development, observing exposure-response relationships requires extensive time. Accordingly, there is often a

discrepancy between the level of viability of proposed PK/PD targets and the clinical relevance of a compound. For example, while imatinib was approved in 2001 [1], the exposure-response relationships in CML and GIST became publicly available in 2008 [45] and 2009 [46], respectively. Sunitinib was first approved in 2006, but the exposure-response relationship was published in 2010 [60]. Likewise, pazopanib was approved by the EMA in 2010 and the exposure-response relationship was first described in 2014 [61].

In the following section, we explore the potential of TDM-guided dosing to optimise OAD treatment. For each drug, we searched PubMed and Google Scholar using the terms ‘pharmacokinetics’, ‘exposure response’, ‘exposure efficacy’, ‘exposure safety’, ‘exposure toxicity’, ‘therapeutic drug monitoring’ and ‘TDM’ together with the respective drug name. Additionally, we reviewed the respective EMA European Public Assessment Reports and the FDA Clinical Pharmacology and Biopharmaceutics Reviews. In Supplementary Tables 1a-c, KIs, AHDs and other OADs are summarised together with their molecular target(s), therapeutic indication and date of first approval. Table 1 presents current evidence for TDM-guided dosing of OADs. In this table, each drug is classified according to the level of evidence currently available for TDM. If there is an established exposure-response relationship and a PK target, TDM is considered potentially useful. If additionally, a feasibility study has been performed, TDM is recommended. If on top of that, randomised, prospective studies demonstrated a positive effect of TDM, it is strongly recommended. If there is no evidence for an exposure-response relationship, TDM is considered exploratory. If there are minimal data on the PK of a drug, there are more useful targets than plasma concentration or there is evidence that TDM is not useful, it is not recommended. Compounds with the highest clinical relevance as monotherapy and for which TDM is classified as recommended are discussed below.

Abiraterone

In an observational study in 61 metastatic castration-resistant prostate cancer patients, $C_{\min} \geq 8.4$ ng/mL were associated with a significantly longer PFS compared to $C_{\min} < 8.4$ ng/mL (PFS 7.4 vs 12.2 months, $p = 0.044$) [62]. This threshold was later confirmed in a real-world patient cohort ($n = 62$, PFS 6.1 vs. 16.9 months, $p = 0.033$) [63]. Yet, at the standard dose of 1000 mg once daily (QD), 35% and 42% of patients, respectively, did not reach this target [62, 63]. A prospective study ($n = 32$) demonstrated that 20 patients (63%) had at least one $C_{\min} < 8.4$ ng/mL with standard care [40]; however, when a light meal or snack was concomitantly taken with abiraterone, adequate exposure in 28 patients (87.5%) without

additional toxicities was achieved [40]. Thus, TDM of abiraterone and concomitant food intake as a cost-neutral PK-guided intervention to reach $C_{\min} > 8.4$ ng/mL has proven feasible. Given the absence of an exposure-toxicity relationship, a pragmatic option could be to include concomitant food intake in the drug label.

Everolimus

In a meta-analysis, it has been reported that a two-fold increase in C_{\min} was linked to an increased reduction in tumour size and $C_{SS,\min} \geq 10$ ng/mL could be used as a cut-off value [64]. At the same time, $C_{SS,\min} > 26.3$ ng/mL have been associated with a 4-fold increased risk of toxicity compared to $C_{SS,\min} < 26.3$ ng/mL [21]. As the occurrence of AEs seemed to be associated with high maximum concentrations (C_{\max}) [65], Verheijen et al. investigated the potential of alternative dosing to reduce C_{\max} -related AEs while maintaining therapeutic $C_{SS,\min}$. In a crossover study in 11 patients, administering 5 mg twice daily (BID) instead of 10 mg QD significantly reduced everolimus C_{\max} while $C_{SS,\min}$ increased from 9.6 to 13.7 ng/mL [65]. Given the established exposure-response and exposure-toxicity relationships, we propose to combine 5 mg BID dosing with TDM to target a therapeutic window of $C_{SS,\min} \geq 10$ ng/mL and < 26.3 ng/mL. The developed population PK model by Combes et al. [66] could serve as a starting point in a MIPD framework.

Imatinib

Higher frequencies of CCyR and major molecular response (MMR) have been reported in CML patients with high imatinib $C_{\min,SS}$ [45, 67]. Current evidence supports the use of a

$C_{\min,SS} \geq 1000$ ng/mL as PK target to achieve improved CCyR and MMR in CML [68]. Imatinib $C_{\min,SS} > 3000$ ng/mL have been associated with higher rates of AEs [67]. Therefore, a therapeutic window of $1000 \leq C_{\min,SS} < 3000$ ng/mL seems reasonable [68]. In gastrointestinal stromal tumours (GIST), one study determined a longer time to disease progression in patients ($n = 73$) with $C_{SS,\min} \geq 1100$ ng/mL [46]. In another study, a significantly longer PFS was found in patients with $C_{\min,SS} \geq 760$ ng/mL compared to patients with $C_{\min,SS} < 760$ ng/mL (PFS not reached vs. 56 months, respectively), although this patient population was not representative of routine clinical practice [69]. The feasibility of TDM-guided dosing to achieve imatinib $C_{\min,SS}$ of 750–1500 ng/mL has been proven in a prospective randomised controlled trial [18], and several population PK models [70–72] are available for use in MIPD of imatinib. As the fraction of patients reaching durable $C_{\min,SS} \geq 1000$ ng/mL has been reported to be as low as 33.3% [73], individualised imatinib dosing is highly relevant. As imatinib C_{\min} have been reported to decrease during the first 3 months of treatment [74], it is important to keep measuring imatinib $C_{\min,SS}$ during treatment and after dose adjustments.

Pazopanib

An association of $C_{SS,\min} \geq 20.5$ mg/L with improved PFS (19.6 vs. 52.0 weeks, $p = 0.004$) and tumour shrinkage was found in a retrospective analysis in 177 patients with advanced renal cell carcinoma (RCC) [61]. This efficacy threshold was later validated in the adjuvant setting [75] and in a real-life patient cohort [76]. However, 16–20% [61, 76] of patients do not reach this threshold and are thus at risk of decreased efficacy. In a prospective feasibility study of individualised

Table 1 Evidence for TDM for targeted oral antineoplastic drugs

Evidence level	Recommendation	Description
1	Strongly recommended	Randomised, prospective studies demonstrated positive effect of routine TDM with regards to efficacy and/or safety.
2	Recommended	There is an established exposure-response relationship using standard dosage from retrospective studies, a target is established and a feasibility study has been performed.
3	Potentially useful	An exposure-response or exposure-safety relationship using standard dosage has been identified and a potential target has been reported.
4	Exploratory	An exposure-response or exposure-safety relationship using standard dosage has been identified but no target has been reported.
5	Not recommended	No exposure-response or exposure-safety relationship using standard dosage has been identified and/or - there is very few data on pharmacokinetics of the drug; - there are more useful targets than plasma concentration (PD); - there is evidence that TDM is not useful

Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median $C_{SS,min}$ at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Abiraterone	Recommended	$C_{SS,min} \geq 8.4$ [62,63]	35[62]-42[63]	9.3 (70%)[63]	Yes (PFS)[62,63]	No[63]	Yes[99]	<ul style="list-style-type: none"> TDM with food intervention has been proven feasible and cost-efficient[40,100]
Axitinib	Recommended	$AUC \geq 300^b$ [101] $C_{SS,min} \geq 5$ [102]	38[101]	$AUC: 367^b$ (77%)[103]	Yes (PFS, PR, OS)[101,102]	Yes (hypertension, proteinuria, fatigue, diarrhoea)[104]	Yes[101]	<ul style="list-style-type: none"> Diastolic blood pressure (dBp) has additionally been related to efficacy[105] A placebo-controlled randomised dose titration trial was successfully performed[106] An integrated approach using both PK and dBp might be the most promising option Exposure-response relationship only evaluated for axitinib monotherapy but not for combination therapy with an immune checkpoint inhibitor
Everolimus	Recommended	$C_{SS,min} \geq 10$ [64]	37[64]	15.65 (90% CI: 14.79-16.55)[64]	Yes (PFS)[64,107]	Yes (pulmonary events, stomatitis)[64,108]	Yes[109]	<ul style="list-style-type: none"> 5 mg BID instead of 10 mg QD decreases C_{max} (potentially decreased risk for toxicity)[65] PK-guided dosing has been proven feasible[110] TDM-guided everolimus dosing already SoC in transplantation medicine[111]
Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median $C_{SS,min}$ at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Gefitinib	Recommended	$C_{SS,min} \geq 200$ [4]	30[4]	266 (41%)[4]	Yes (OS)[4]	Yes (skin toxicity, diarrhoea, hepatotoxicity)[4,112]	No	<ul style="list-style-type: none"> Treatment at increased doses has been proven feasible[113] Gefitinib has lost most of its relevance in the treatment of EGFR mutated lung cancer
Imatinib	Recommended	CML: $C_{SS,min} \geq 1000$ [45,67,114] GIST: $C_{SS,min} \geq 1100$ [46]	73[115]	979 (54%)[45] 926 (52%) [115]	Yes (MMR, CcyR) [45,67,114] Yes (TTP)[46,69]	Yes (neutropenia, rash, diarrhoea, arthralgia, oedema) [67,116,117]	Yes[70]	<ul style="list-style-type: none"> Feasibility of TDM has been proven in a cohort study[44] and a RCT[18] An alternative threshold of 760 ng/mL has been proposed for GIST [69]
Pazopanib	Recommended	$C_{SS,min} \geq 20500$ [61,75,76]	16[76]-20[61]	28100 (40%)[76]	Yes (PFS) [61,75,76]	Yes (fatigue, anorexia, hypertension) [77]	Yes[78]	<ul style="list-style-type: none"> PK-guided dosing has been proven feasible[48] 400 mg BID instead of 800 mg QD as cost-neutral strategy to increase exposure[43] Concomitant intake with food as cost-neutral strategy to increase exposure[42,118]
Sunitinib	Recommended	Intermittent dosing: $C_{SS,min} \geq 50^c$ [60] Continuous dosing:	49[115]-52[119]	51.6 (39%)[115]	Yes (TTP, OS)[60]	Yes (hypertension, fatigue, anorexia, myelosuppression, HFSR, altered taste, mucositis) [79,80,120,121]	Yes[81]	<ul style="list-style-type: none"> PK-guided dosing has been proven feasible[119]

Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median C _{SS,min} at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
		C _{SS,min} ≥ 37.5 ^c [12]						
Tamoxifen	Recommended	C _{SS} ≥ 5.97 ^d [83]	20[83]	9.72 ^d <1.73-30.8> ^d [122]	Yes (RR)[83]	No[89]	Yes[92]	<ul style="list-style-type: none"> • TDM-guided dosing has been proven feasible[20] • Genotype-guided dose escalations have been proven safe[87–89]
Trametinib	Recommended	C _{SS,min} ≥ 10.6 [50]	27[123]	12.1 <6-34>[124]	Yes (PFS)[50]	No[124]	Yes[50]	<ul style="list-style-type: none"> • Exposure-response relationship only evaluated for trametinib monotherapy but not for combination therapy with dabrafenib
Alectinib	Potentially useful	C _{SS,min} ≥ 435 [49,125]	33[125]	572 (48%)[126]	Yes (tumour size, PFS)[49,125]	No[127]	Yes[126]	
Crizotinib	Potentially useful	C _{SS,min} ≥ 235 [49,128]	48[49]	244 (45%) [49]	Yes (PFS, ORR) [49,128]	Yes (neutropenia, AST elevation)[129]	Yes[130]	
Erlotinib	Potentially useful	C _{SS,min} > 500 [131]	11[115]	1011 (69%)[115]	Yes (preclinical efficacy, PFS, OS)[131,132]	Yes (skin toxicity) [133,134]	Yes[135]	
Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median C _{SS,min} at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Gilteritinib	Potentially useful	C _{SS,min} >100 [136]	0.6[136]	456 (NA) [136]	Yes (CR)[136]	Yes (CK, AST, ALT, ALB)[136]	Yes[136]	
Letrozole	Potentially useful	C _{SS,min} > 85.6 [137]	NA	88.4 <0-349.2>[138]	Yes (TTP)[137]	Not reported	Yes[139]	
Nilotinib	Potentially useful	C _{SS,min} ≥469 [140]	25[140]	1123 (64%) (300 mg BID)[141] 1239 (52%) (400 mg BID)[141]	Yes (TTP, trend for MMR) [140,141]	Yes (bilirubin and liver enzyme elevations) [140–142]	Yes[140]	<ul style="list-style-type: none"> • Feasibility of TDM has been reported in a case study [143] • Dose selection with respect to UGT1A1 genotype could prevent elevation of bilirubin levels[142]
Vemurafenib	Potentially useful	C _{SS,min} ≥4200 [51–53]	39[144]-52[145]	61000(41%)[144]	Yes (PFS, OS) [51–54]	Yes (QTc prolongation, rash)[53,146]	Yes[147]	<ul style="list-style-type: none"> • An alternative threshold of C_{SS,min} >50 mg/L has been proposed [54]
Abemaciclib	Exploratory	NA	NA	181 (47%)[148]	Yes (tumour shrinkage, BOR, PFS)[148]	Yes (neutropenia) [148]	Yes[149]	
Afatinib	Exploratory	NA	NA	NA <14.4-27.4>[150]	No[150]	Yes (diarrhoea, anorexia)[150–152]	Yes[153]	<ul style="list-style-type: none"> • Daily doses <20 mg have been associated with a significant shorter PFS[152]
Alpelisib	Exploratory	NA	NA	AUC: 33224 (21%) ^b [154]	Inconclusive (trend for PFS)[154]	Yes (hyperglycemia) [154]	Yes[155]	
Anastrozole	Exploratory	NA	NA	33.2 <0.0-98.8> [156]	Yes (oestradiol suppression) [156]	Not reported	NA	<ul style="list-style-type: none"> • Relationship of anastrozole C_{SS,min} with both oestrogen levels and efficacy endpoints should be further investigated[14]

Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median $C_{SS,min}$ at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Apalutamide	Exploratory	NA	NA	3700 (32%)[157]	No[157]	Yes (fatigue, fall, rash, weight loss, arthralgia) [157]	Yes[158]	• A target of $C_{SS,min} \geq 34.2$ ng/mL has been proposed [156]
Avapritinib	Exploratory	NA	NA	593 (NA)[159]	No (ORR)[159]	Yes (G 3/4 AEs, cognitive effects)[159]	Yes[159]	• Because of the high response rate and small sample size, the results of the exposure-response analysis should be interpreted with caution[159]
Binimetinib	Exploratory	NA	NA	53.3 (49%) [160]	Yes (PFS)[161]	Yes (CK increases, retinal events)[161]	Yes[161]	
Bosutinib	Exploratory	NA	NA	400 mg QD: 112 (73%) 500 mg QD: 147 (70%) [162]	Yes (CcyR, MMR, CHR)[163,164]	Yes (diarrhoea, rash)[164]	Yes[162]	
Brigatinib	Exploratory	NA	NA	520 (61%) [165]	Yes (PFS, OS) [165]	Yes (diarrhoea, increased CK, skin events, pneumonitis, pneumonia)[165]	Yes[165]	
Cabozantinib	Exploratory	NA	NA	Pred. $C_{avg,SS}$: 1125 (NA) [166]	Yes (PFS) [166,167]	Yes (HFS, fatigue, diarrhoea, hypertension)[166]	Yes[168]	• Concomitant intake with food as cost-neutral PK-guided intervention [41]
Ceritinib	Exploratory	NA	NA	871 (47%) [169]	Inconclusive (trend for ORR) [170]	Yes (ALT and AST elevation, hyperglycaemia)[169]	Yes[171]	
Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median $C_{SS,min}$ at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Dabrafenib	Exploratory	NA	NA	46.6 (84%)[172]	No[173]	Yes (AEs requiring dose reduction)[174]	Yes[172]	• As AUC seems to differ between dose levels but $C_{SS,min}$ not, AUC might be a more useful measure of exposure[172]
Dacomitinib	Exploratory	NA	NA	73.1 (45%)[175]	Inconclusive (trend for PFS, tumour shrinkage) [175]	Yes (rash/dermatitis, diarrhoea, treatment alteration) [175]	Yes[175]	
Dasatinib	Exploratory	NA	NA	2.61 (26%)[176]	Yes (McyR, MR)[176,177]	Yes (pleural effusions, treatment alteration) [176,178]	Yes[179]	
Enasidenib	Exploratory	NA	NA	AUC_{0-24} : 21515 ^b (60%)[180]	Yes (ORR, only for patients with R140 mutation) [180]	Yes (bilirubin elevation, hepatic safety)[180]	Yes[180]	• A trend for an exposure-response relationship (ORR) has been reported for patients with R172 mutation[180]
Encorafenib	Exploratory	NA	NA	23 (320%)[181]	No[181]	Yes (G 3/4 AEs, G1+ retinopathy) [181]	Yes[181]	
Erdafitinib	Exploratory	NA	NA	AUC: 36608 ^b (NA) [182]	Inconclusive (trend for PFS) [182]	Yes (nail disorders)[182]	Yes[183]	• Statistically significant relationships between average daily serum phosphate concentrations and both response and safety have been reported[182]
Fedratinib	Exploratory	NA	NA	AUC: 33500 ^b (41%)[184]	Inconclusive (trend for change in spleen	Yes (anaemia, thrombocytopenia,	Yes[186]	

Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median C _{ss,min} at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Glasdegib	Exploratory	NA	NA	365 (81%)[187]	No[187]	diarrhoea, nausea, vomiting, G3 AEs)[184]	Yes[188]	
Ibrutinib	Exploratory	NA	NA	AUC: 680 ^b [189]	Yes (BTK occupancy, clinical response) [189]	No[189]	Yes[190]	
Ivosidenib	Exploratory	NA	NA	AUC ₀₋₂₄ : 117000 ^b (50%)[191]	No[191]	Yes (QTc prolongation)[191]	Yes[191]	
Ixazomib	Exploratory	NA	NA	NA	Yes (clinical benefit)[192]	Yes (anaemia, neutropenia, thrombocytopenia, diarrhoea, fatigue, nausea, PN, rash)[192,193]	Yes[194]	
Lenvatinib	Exploratory	NA	NA	43.4 (42%) (8 mg QD) 95.6 (48%) (24 mg QD)	Yes (reduction in tumour size) [195,196]	Yes (treatment alteration, hypertension, proteinuria, nausea, vomiting, AST, ALT and bilirubin elevation) [195,197,198]	Yes[199]	<ul style="list-style-type: none"> • A reduction in tumour size has been associated with longer PFS[195] • 14 mg QD with up-titration or 18 mg QD without up-titration potentially provides comparable efficacy and improved safety[196]
Lorlatinib	Exploratory	NA	NA	NA <70-125>[200]	No[200,201]	Yes (hypercholesterol-	Yes[201]	<ul style="list-style-type: none"> • Different minimum effective concentrations have been
Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median C _{ss,min} at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Midostaurin	Exploratory	NA	NA	467 (30%)[203] (50 mg BID) 919-1060[204] (54%)[205] (100 mg BID)	Yes (blood blast response)[206]	No[204]	Yes[207]	<ul style="list-style-type: none"> • A trend for higher probability of response with higher C_{ss,min} has been reported[204] • A significantly increased risk of death with lower exposure to the metabolite CGP2221 has been reported[204]
Neratinib	Exploratory	NA	NA	AUC: 1,402 ^b (56%)[208]	Yes (OR (only monotherapy)) [209]	No[209]	Yes[209]	
Nintedanib	Exploratory	NA	NA	13.1 ^c (70%)[210]	Yes (sVEGFR decrease)[211]	Yes (gastrointestinal disorders)[210]	Yes[212]	<ul style="list-style-type: none"> • Weak exposure-response and exposure-safety relationships observed[213]
Niraparib	Exploratory	NA	NA	649 ±135[214]	Yes (PFS)[215]	Yes (thrombocytopenia)[216]	Yes[216]	
Olaparib	Exploratory	NA	NA	Tablets: 1570 (86%) [217] Capsules: 1860 (84%) [217]	Yes (PFS)[218]	Yes (diarrhoea, anaemia, decreased appetite, dysgeusia, fatigue, nausea, vomiting) [218,219]	Yes[217]	
Osimertinib	Exploratory	NA	NA	166 ^e (49%) [220]	No[220,221]	Yes (rash, diarrhoea)[221]	Yes[222]	

Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median C _{SS,min} at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Palbociclib	Exploratory	NA	NA	61 (42%) [223]	Inconclusive (trend for PFS) [223]	Yes (neutropenia) [223, 224]	Yes [225]	
Panobinostat	Exploratory	NA	NA	AUC ₀₋₂₄ : 174 ^b (92%) [226]	Yes (trend for ORR) [227]	Yes (thrombocytopenia, diarrhoea) [227]	Yes [228]	
Pexidartinib	Exploratory	NA	NA	AUC ₀₋₁₂ : 77465 ^b (32%) [229]	Inconclusive (trend for ORR) [229]	Yes (AST and ALT elevation) [229]	Yes [229]	
Ponatinib	Exploratory	NA	NA	34 (45%) [230]	Inconclusive (trend for McyR, MaHR) [231]	Yes (hypertension, ischemia) [231]	No	• A dose intensity-safety relationship was identified [231]
Regorafenib	Exploratory	NA	NA	1400 (57%) [232]	Yes (sVEGFR2 level decrease) [232]	Yes (rash, bilirubin) [233, 234]	Yes [235]	
Ribociclib	Exploratory	NA	NA	732 (91%) [236]	Inconclusive [236]	Yes (QTcF prolongation, neutropenia) [236]	Yes [236]	• Due to lack of data, an exposure-response analysis could not be performed [236]
Rucaparib	Exploratory	NA	NA	1754 ± 805 [237]	Inconclusive (RECIST response rate) [238]	Yes (creatinine, ALT and AST elevation, fatigue, thrombocytopenia) [237]	Yes [237]	
Ruxolitinib	Exploratory	NA	NA	5.52 ± 5.82 ^h (10 mg BID) 11.4 ± 6.01 ^h (15 mg BID) [239]	Yes (spleen volume reduction, total symptom score) [239]	Yes (reduced platelet count, reduced haemoglobin) [239]	Yes [240]	
Sorafenib	Exploratory	NA	NA	3750 (104%) [241]	Yes (PFS, OS) [242, 243]	Yes (G3/4 AEs, HFS, hypertension) [242–246]	Yes [247]	• Exposure has been reported to decrease over time [244]
Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median C _{SS,min} at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Talazoparib	Exploratory	NA	NA	3.54 (63%) [248]	Yes (PFS) [248, 249]	Yes (G3 AEs, anaemia, thrombocytopenia) [248, 249]	Yes [250]	
Tivozanib	Exploratory	NA	NA	NA < 16.0–30.9 > [251]	Yes (tumour shrinkage, PFS) [251]	Yes (hypertension, HFS) [251]	Yes [251]	• The exposure-response relationship described in [251] is convincing: PFS was 26.4 weeks vs 72.1 weeks in patients with C _{avg} in the lowest vs highest quartile, respectively
Vandetanib	Exploratory	NA	NA	795 (NA) [252]	Yes (best calcitonin response) [252]	Yes (diarrhoea, fatigue, QTc prolongation) [252]	Yes [252]	• IC ₅₀ values (190 ng/mL) have been used to support dose selection in early clinical trials [253]
Bicalutamide	Not recommended	NA	NA	8850 < 1380–21700 > (50 mg QD) [254]	No [256]	No [256]	No	
Cobimetinib	Not recommended	NA	NA	16400 < 2400–44600 > (150 mg QD) [255]	No [257]	No [257]	Yes [258]	
Darolutamide	Not recommended	NA	NA	3780 (NA) [259]	NA	NA	Yes [259]	

Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median $C_{SS,min}$ at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Duvelisib	Not recommended	NA	NA	AUC ₀₋₁₂ : 7888 ^b (77%)[260]	No[261]	No[261]	No	
Entrectinib	Not recommended	NA	NA	NA <812-872> ⁱ [262]	No	Inconclusive (trend for probability of AE Grade≥3) [262]	Yes[262]	
Enzalutamide	Not recommended	NA	NA	11400 (26%) [263]	No[263,264]	No[263]	Yes[263]	
Exemestane	Not recommended	NA	NA	4.1 [1.3-38.1] ^j [14]	NA	NA	Yes[265]	
Idelalisib	Not recommended	NA	NA	426 (NA) [266]	No[266–268]	No[266–268]	Yes[269]	
Lapatinib	Exploratory	NA	NA	490 {50-5230} (1000 mg QD)[270] 635 ^k (NA) (1250 mg) 780 {520-1180} (1500 mg QD)[271]	NA	NA	Yes[272]	• No exposure-response or exposure-safety relationships established but majority of responders reported to have $C_{SS,min}$ 300-600 ng/mL[270]
Larotrectinib	Not recommended	NA	NA	5.14 ^l (NA)[273]	No[274]	No[274]	Yes[274]	
Venetoclax	Not recommended	NA	NA	520 (NA)[275]	Inconclusive (trend for CR)[276]	No[276]	Yes[277]	
Substance	Evidence level for TDM	Proposed TDM target [ng/mL]	Patients below TDM target at standard dose (%)	Reported mean/median $C_{SS,min}$ at standard dose [ng/mL] (IIV ^a)	Exposure-response relationship [yes/no] (associated parameter(s))	Exposure-safety relationship [yes/no] (associated parameter(s))	NLME model available	Comments
Vismodegib	Not recommended	NA	NA	11367 ±4084 ^m [278]	No[278]	No[278]	Yes[278]	
Vorinostat	Not recommended	NA	NA	AUC _{0-∞} : 1430 ^{b,n} (NA)[279]	Inconclusive (trend for ORR) [280]	Inconclusive (trend for QTc prolongation)[280]	No	

^aInterindividual variability in mean/median exposure is reported as (CV%), [interquartile range], ±standard deviation, {95% CI} or <range>, according to the available data.

^bAUC units are ng*h/mL.

^cTarget concentrations are the sum of concentrations of both sunitinib and its active metabolite N-desethylsunitinib.

^dTarget concentration and mean/median exposure for tamoxifen are reported for tamoxifen's most active metabolite endoxifen.

^eCalculated based on the dose-normalised steady-state trough concentration of 0.065 ng/ml/mg and a dose of 200 mg BID[210].

^fCalculated based on the the weighted average of two groups (A: n=10, B: n=26) at the standard dose [nmol/L] and the molecular weight of 320.4 g/mol.

^gCalculated based on the reported concentrations in nM and the molecular weight of 499.6 g/mol.

^hCalculated based on the reported concentrations in nM and the molecular weight of 306.4 g/mol.

ⁱCalculated from the predicted PK exposures [nM] in two simulation scenarios (1: weight effect on clearance, 2: allometric scaling) using a molecular weight of 560.6 g/mol.

^jCalculated based on median C_{max} (7.7 ng/mL, range 2.5-72.0)[281] and $t_{1/2}$, calculated with the formula proposed by Wang et al. [10].

^kCalculated based on the reported C_{min} at 1500 mg and 1000 mg and dose-linear pharmacokinetics[282].

^lCalculated based on the reported unbound concentration in nM and the molecular weight of 428.4 g/mol.

^mCalculated based on the reported concentrations in nM and the molecular weight of 421.3 g/mol.

ⁿCalculated based on the reported concentrations in nM and the molecular weight of 264.3 g/mol.

Abbreviations: AE: adverse event; ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUC: area under the concentration-time curve; BID: twice daily; BOR: best objective response; BTK: Bruton's tyrosine kinase; CCyR: complete cytogenetic response; CI: confidence interval; CK: creatinine kinase; $C_{avg,ss}$: average concentration at steady-state; $C_{SS,min}$: minimum concentration at steady-state; C_{SS} : concentration in steady state, no further specification of sampling time; CHR: complete hematologic response; CML: chronic myeloid leukemia; CR: complete response; *dbp*: diastolic blood pressure; *Gx*: grade x; *GIST*: gastrointestinal stromal tumours; *HFS*: hand-foot syndrome; *IIV*: interindividual variability; *IC₅₀*: half maximal inhibitory concentration; *IRR*: independent radiology review; *MaHR*: major hematologic response; *MCyR*: major cytogenetic response; *MMR*: major molecular response; *MR*: molecular remission; *NA*: not available; *OR*: objective response; *ORR*: objective response rate; *OS*: overall survival; *PFS*: progression-free survival; *PK*: pharmacokinetics; *PN*: peripheral neuropathy; *PR*: partial response; *QD*: once daily; *RCC*: renal cell carcinoma; *RECIST*: Response evaluation criteria in solid tumors; *RR*: recurrence rate; *SoC*: standard of care; *STAT3*: Signal transducer and activator of transcription 3; *sVEGFR*: soluble vascular endothelial growth factor receptor; *TDM*: therapeutic drug monitoring; *TTP*: time to progression

pazopanib dosing, 57% of all patients ($n = 30$) showed pazopanib $C_{SS,min} < 20$ mg/L under standard treatment and 41% of these successfully achieved therapeutic $C_{SS,min}$ upon dose increases to 1000–1800 mg QD [48]. Furthermore, all patients who achieved a partial response showed $C_{SS,min} \geq$

20 mg/mL. In a recent retrospective observational clinical study in 27 RCC patients, a significant correlation between pazopanib $C_{SS,min} \geq 20.5$ mg/mL and objective response was established [77]. Based on the evidence for an exposure-response relationship and the proven feasibility of

individualised dosing, we recommend TDM-guided pazopanib dosing, targeting plasma $C_{SS,min} \geq 20$ mg/mL. A published population PK model [78] can be used in a MIPD framework for pazopanib. However, due to a dose-dependent decrease in the relative BA of pazopanib, conventional dose increases are an inefficient strategy to increase exposure. Alternative cost-neutral strategies have been described in literature. Splitting intake moments (i.e. 400 mg BID instead of 800 mg QD) resulted in a 79% increase in C_{min} [43]. Moreover, concomitant intake with food successfully increased exposure as well [42].

Sunitinib

Significant increases in toxicities in patients with sunitinib + active metabolite SU012662 $C_{SS,min} \geq 100$ ng/mL have been reported [79, 80]. For RCC patients, an efficacy PK target of 50–100 ng/mL has been proposed in intermittent dosing at 50 mg QD [80]. Exploiting dose linearity, this target was extrapolated to $C_{SS,min} \geq 37.5$ ng/mL for continuous dosing at 37.5 mg QD in GIST patients [12]. Based on a summary of exposure-response analyses [60], TDM-guided sunitinib dosing targeting a sunitinib + SU012662 $C_{SS,min}$ of 50–100 ng/mL was prospectively tested in a clinical study in 43 patients with advanced solid malignancies [47]. Of the patients eligible for PK-evaluation ($n = 29$), 52% ($n = 14$) showed sunitinib + SU012662 $C_{SS,min} < 50$ ng/mL at treatment initiation, and among those, 5 patients reached therapeutic total trough levels after dose escalation without experiencing additional toxicities. These findings underline both the need and feasibility of TDM-guided sunitinib dosing, for which a published population PK/PD model can be used [81]. Biomarkers such as the soluble vascular endothelial growth factor receptor may provide additional information on individual response and have been integrated into PK/PD models [82]. Because of the different half-lives of sunitinib and SU012662, $C_{SS,min}$ should be calculated separately when using the log-linear extrapolation method. Due to the long half-lives and time to reach steady-state, it is important to collect PK samples in the last treatment week before the off-treatment period.

Tamoxifen

Compared to higher values, C_{SS} of < 5.97 ng/mL [83] and < 5.2 ng/mL [84] of tamoxifen's active metabolite endoxifen have been associated with more additional breast cancer events and shorter distant relapse-free survival, respectively. While body weight and age have a significant impact as well [85], CYP2D6 phenotype accounts for 18–43% of the observed IIV of 40–49% in endoxifen C_{SS} [14]. Considering this, TDM of endoxifen might be promising to identify patients with sub-optimal target concentrations [86]. Because no

toxic tamoxifen dose has been identified, dose increases up until 120 mg QD for patients with endoxifen $C_{SS} < 5.97$ ng/mL have been investigated and TDM has proven feasible [20, 87–92]. As it takes about 3 months to attain endoxifen steady state, we propose to use MIPD for early endoxifen target attainment [92].

Discussion

While exposure-response and exposure-safety relationships have been observed for many OADs, viable PK targets are only available for a few. Future clinical and 'real-world' studies are needed to identify clear target ranges associated with favourable outcome. More PK/PD analyses conducted in (pre-)clinical development could help to characterise exposure-response relationships earlier. More focus must also be dedicated on the establishment of TDM as part of routine patient care. This might be challenging, as bio-analytical assays should be available and a solid logistic system with a short turnaround time in place. At the Netherlands Cancer Institute, TDM has been implemented in routine care, and PK samples are collected at routine visits to the outpatient clinic. Concentrations of 35 different OADs are measured weekly using liquid chromatography-tandem mass spectrometry [93–96], treatment recommendations are reported within 24 h to the treating physician and results can be discussed with patients 1–2 weeks after their visit. This approach is also emerging in Australia with several OADs being measured on request with current efficacy-implementation studies underway. Additional data should be prospectively collected (i.e. in registries) to further investigate the effect of TDM on treatment outcomes. Novel microsampling techniques, i.e. volumetric absorptive microsampling (VAMS) [97], could help to provide the TDM results even before patients visit the outpatient clinic. VAMS allows to precisely sample a small volume of capillary blood from the fingertip with a dedicated sampling device. After blood collection, the device is dried in the open air and shipped to a laboratory via regular mail without pre-processing or cooling during transport. Given its easy and minimally invasive character, this technique shows high potential: in the future, VAMS samples could be obtained at home and shipped to a laboratory by patients themselves. Upon sample analysis, results would be communicated to the treating oncologist and discussed with the patient at the next visit. Of note, the disadvantages of VAMS are not fully elucidated yet. Current limitations are variable analyte recoveries dependent on haematocrit [98] and the time-consuming determination of capillary-to-venous blood conversion factors, needed to compare measured capillary whole blood with venous plasma target concentrations [97]. Furthermore, to make this approach feasible, a well-connected infrastructure of oncologists, laboratories and PK-specialists must be available.

Conclusion

In this review, we summarised the opportunities and challenges associated with TDM of OADs and outlined different TDM approaches, their respective advantages and disadvantages. We provided strong arguments why routine TDM should be established as a part of OAD treatment and reviewed the available evidence for all oral targeted antineoplastic drugs currently approved by the EMA and/or FDA. Finally, we provided an outlook into the future and proposed a strategy to increase feasibility and acceptance of TDM as part of routine clinical care.

Code availability Not applicable.

Authors' contributions AM, OS, UJ and CK developed the research question. AM, OS and SLG conducted the searches and extracted the data. AM, OS and SLG analysed the data and did the quality assessment. AM wrote the first draft of the manuscript. All authors discussed the analysis results, contributed to the revision of the manuscript and reviewed and approved the final version.

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Data availability Not applicable.

Compliance with ethical standards

Conflict of interest CK and WH report grants from an industry consortium (AbbVie Deutschland GmbH & Co. KG, Astra Zeneca, Boehringer Ingelheim Pharma GmbH & Co. KG, Grünenthal GmbH, F. Hoffmann-La Roche Ltd., Merck KGaA and Sanofi) for the PharMetrX PhD program. CK reports grant for the Innovative Medicines Initiative-Joint Undertaking ('DDMoRe'). CK and RM report grants from the Federal Ministry of Education and Research within the Joint Programming Initiative on Antimicrobial Resistance Initiative (JPIAMR), all outside the submitted work. OS reports endowed professorship grant (Horphag research Ltd) and funding for the project 'Individualized cancer therapy with kinase inhibitors using drug monitoring – optimization by minimally invasive at-home sampling' (Hector Stiftung II gGmbH). The remaining authors declare that the research was conducted in absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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