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Therapeutic Drug Monitoring of Oral Anticancer Drugs: The Dutch Pharmacology Oncology Group–Therapeutic Drug Monitoring Protocol for a Prospective Study

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Background: Oral anticancer drugs show a high interpatient variability in pharmacokinetics (PK), leading to large differences in drug exposure. For many of these drugs, exposure has been linked to efficacy and toxicity. Despite this knowledge, these drugs are still administered in a one-size-fits-all approach. Consequently, individual patients have a high probability to be either underdosed, which can lead to decreased antitumor efficacy, or overdosed, which could potentially result in increased toxicity. Therapeutic drug monitoring (TDM), personalized dosing based on measured drug levels, could be used to circumvent underdosing and overdosing and thereby optimize treatment outcomes.

Methods: In this prospective clinical study (www.trialregister.nl; NL6695), the feasibility, tolerability, and efficacy of TDM of oral anticancer drugs will be evaluated. In total, at least 600 patients will be included for (at least) 23 different compounds. Patients starting regular treatment with one of these compounds at the approved standard dose can be included. PK sampling will be performed at 4, 8, and 12 weeks after the start of treatment and every 12 weeks thereafter. Drug concentrations will be measured, and trough concentrations (C_{min}) will be calculated. In cases where C_{min} falls below the predefined target and acceptable toxicity, a PK-guided intervention will be recommended. This could include emphasizing compliance, adapting concomitant medication (due to drug–drug interactions), instructing to take the drug concomitant with food, splitting intake moments, or recommending a dose increase.

Discussion: Despite a strong rationale for the use of TDM for oral anticancer drugs, this is currently not yet widely adopted in routine patient care. This prospective study will be a valuable contribution to demonstrate the additional value of dose optimization on treatment outcome for these drugs.

Key Words: TDM, oral anticancer drugs, PK, individualized dosing, personalized dosing

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BACKGROUND

Although in the past century intravenously administered chemotherapy has always formed the backbone of cancer therapy, this paradigm has shifted in the past 2 decades toward personalized treatment in which oral anticancer drugs are indispensable. Despite the high interpatient variability in pharmacokinetic (PK) exposure and the fact that for most of these oral anticancer drugs, an exposure–response relationship has been identified, these drugs are still administered at fixed doses. As a consequence, individual patients have a high probability to be either underdosed (>30% of patients) or overdosed (>15% of patients), leading to decreased antitumor efficacy and increased toxicity, respectively.[1–6] Therapeutic drug monitoring (TDM), personalized dosing based on measured drug levels, can be used to address these problems and thereby optimize treatment.

Practical guidelines for TDM of kinase inhibitors and oral antihormonal drugs have been developed and published previously.[4,5] Also, feasibility studies have been performed

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TABLE 1. Summary of TDM Targets, PK Parameters, and Defined Dose Levels per Oral Anticancer Drug

Drug	Indication	TDM Target* (ng/mL)	$t_{1/2}$ (h)	t_{max} (h)	Starting Dose	Stepwise Increases in Daily Dose per Dose Level (mg)	Maximum Dose	Remarks
Abiraterone	PC	8.4	12	2	1000 mg QD	250	1500 mg QD	First step is intake concomitant with light meal or snack
Alectinib	NSCLC	435	32	4	600 mg BID	300	900 mg BID	
Axitinib	RCC	5	4	3	5 mg BID	4–6	10 mg BID	
Bosutinib	CML	147	34	6	500 mg QD	100	600 mg QD	
Cobimetinib†	Mel	127	44	2	60 mg QD	20	100 mg QD	
Crizotinib	NSCLC	235	42	5	250 mg BID	100	200 mg–400 mg	
Dasatinib	CML	2.61	6	1	100 mg QD	40	180 mg QD	
Enzalutamide‡	PC	5000	139	1	160 mg QD	40	240 mg QD	
Erlotinib	NSCLC	500	36	4	150 mg QD	50	300 mg QD	
Everolimus	RCC, NET, and BC	10	38	1	10 mg QD	2.5	15 mg QD	
Gefitinib	NSCLC	200	41	5	250 mg QD	250	750 mg QD	
Imatinib	GIST and CML	1100§	19	3	400 mg QD	200	400 mg BID	In case of very low PK (C_{min} < 550 ng/mL), an increase of 2 dose levels will be recommended
Nilotinib	CML	469	17	3	300 mg BID	200	600 mg BID	
Olaparib	OC	1290	12	2	400 mg BID	200	600 mg BID	
Palbociclib†	BC	61	27	4	125 mg QD	25	200 mg BID	
Pazopanib	RCC and STS	20,500	31	4	800 mg QD	200	1000 mg BID	First step is to split intake moments into 400 mg BID, second step is intake concomitant with food
Regorafenib†	CRC and GIST	1400	28	4	160 mg QD	40	200 mg QD	
Sorafenib	HCC and TC	3750	26	8	400 mg BID	200	800 mg BID	
Sunitinib¶	GIST, NET, and RCC	50‖	50/95#	5	50 mg QD	12.5	75 mg QD	
Tamoxifen**	BC	5.97	336	2	20 mg QD	10	60 mg QD	In case of very low PK ($C_{steady\text{-}state}$ < 3 ng/mL), an increase of 2 dose levels will be recommended
Trametinib††	Mel	10.6	96	2	2 mg QD	0.5	3 mg QD	
Vemurafenib	Mel	42,000	34	5	960 mg BID	480	1440 mg BID	
Vismodegib**	BCC	11.4	96	4	150 mg QD	150	450 mg QD	

*TDM target concentrations are all C_{min}, except for tamoxifen, for which the TDM target refers to the steady-state concentration of its active metabolite endoxifen.

†Because these drugs have an intermittent dosing schedule, PK samples will be drawn 3, 7, and 11 weeks after the start of treatment.

‡Because enzalutamide has a long half-life (±6 days), PK samples will be drawn 4, 10, and 16 weeks after the start of treatment.

§For CML patients, the TDM target is $C_{min} \geq 1000$ ng/mL.

¶For patients receiving sunitinib in an intermittent dosing schedule, PK samples will be drawn 4, 10, and 16 weeks after the start of treatment.

‖TDM target for intermittent dosing schedule is $C_{min} \geq 50$ ng/mL (sum of concentrations of both sunitinib and its active metabolite N-desethylsunitinib), whereas for continuous dosing schedule, TDM target is $C_{min} \geq 37.5$ ng/mL.

#$t_{1/2}$ is different for sunitinib (50 hours) and its active metabolite N-desethylsunitinib (95 hours).

**Because (active metabolites of) these drugs have a very long half-life, PK samples will be drawn each 12 weeks.

††For dabrafenib, drug concentrations will only be measured; no dose adaptations will be recommended because this might not be the ideal drug for TDM.

BC, breast cancer; BCC, basal cell carcinoma; BID, twice daily; C_{min}, minimum plasma concentration/trough concentration; $C_{steady\text{-}state}$, steady-state concentration; CML, chronic myelogenous leukemia; CRC, colorectal cancer; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; Mel, melanoma; NET, neuroendocrine tumors; NSCLC, non–small-cell lung cancer; OC, ovarian cancer; PK, pharmacokinetics; QD, once daily; PC, prostate cancer; RCC, renal cell carcinoma; STS, soft tissue sarcoma; TC, thyroid cancer; t_{max}, time to maximum concentration; $t_{1/2}$, elimination half-life.

for several anticancer drugs, and they showed TDM to be feasible and safe.[1,2,6–8]

Despite the strong rationale for TDM, it has not yet been implemented as the standard of care in clinical practice. Reasons for this include reimbursement and regulatory issues for higher than approved doses of these expensive drugs and reimbursement of drug level measurement. In addition, clinicians might be reluctant to increase the dose in fear of toxicity, although several studies have shown TDM to be feasible and safe.[1,2,6–8] Furthermore, indisputable evidence on the efficacy of TDM, demonstrated in prospective studies, is lacking. Although randomized controlled trials (RCTs) are considered the golden standard in evidence-based medicine, it would be challenging to perform a RCT on TDM of oral anticancer drugs. This is mainly because a high number of patients with mostly rare cancers would be needed and it would be challenging to secure funding for this. These difficulties are illustrated by the premature termination of a randomized trial of TDM in imatinib patients.[9] Also, it could be argued that not performing dose increments in part of the patients is unethical when clear exposure–response relationships exist.[10]

Therefore, it is necessary to obtain prospective clinical data on the feasibility, tolerability, and efficacy of TDM of oral anticancer drugs. In this study, we aim to implement TDM for these drugs in multiple large medical centers across the Netherlands assembled in the Dutch Pharmacology Oncology Group (DPOG, www.dpog.nl) and to build a prospective registry to structurally collect data on patients' clinical outcome and the effectiveness of the interventions.

METHODS

The DPOG-TDM study is a multicenter investigator-initiated prospective clinical study. Patients with a regular indication for selected oral anticancer agents start treatment at the standard approved dose according to the label, which includes regular monitoring on drug–drug interactions, contraindications, and other treatment-specific parameters. Then, drug levels will be measured at 4, 8, and 12 weeks after the start of treatment and every 12 weeks thereafter, except for compounds with intermittent dosing schedules or a long elimination half-life ($t_{1/2}$). An overview of the PK sampling schedule per compound can be found in Table 1. For each of these agents, detailed drug-specific TDM and dosing guidelines have been formulated based on currently available evidence and best practice (see **Supplemental Data File**, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A341). According to the (calculated) trough levels (C_{min}) of the drug and the reported toxicities, treatment recommendations will be provided to the treating physician. This could include PK-guided interventions such as emphasizing compliance, adapting concomitant medication (due to drug–drug interactions), instructing the patients to take the drug concomitant with food, splitting intake moments, or recommending a dose increase.

In total, at least 600 patients will be included for 23 different oral anticancer drugs, with a possibility to extend with additional agents (and patients) when additional funding is secured.

Figure 1 presents a schematic overview of the study design. Table 1 summarizes the PK sampling schedules, TDM targets, and dose levels per drug.

Objectives

The primary objective of this study is to halve the proportion of patients with a drug exposure below the TDM target after 2 potential PK-guided interventions, which for most compounds will be after 12 weeks. Table 2 provides the historically presented fraction of patients with an exposure below the TDM target, which will be used as comparison.

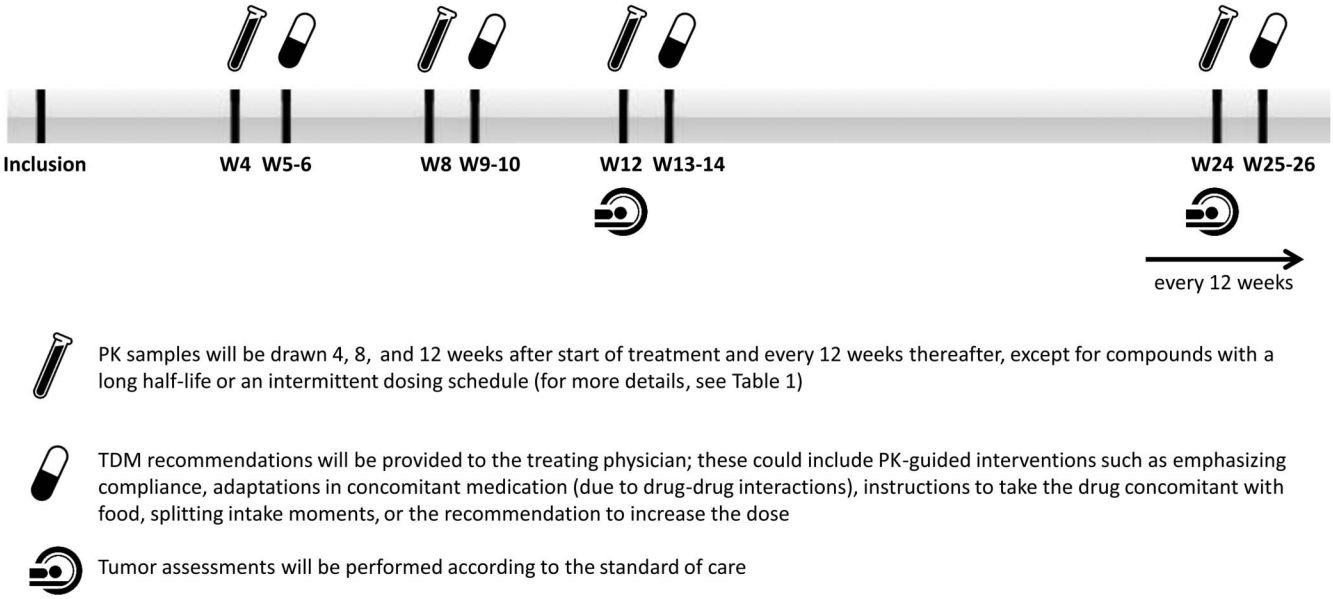

FIGURE 1. Study schedule. PK, pharmacokinetic; W, week.

The secondary objectives of this study are to determine the tolerability and feasibility of PK-guided dosing, to determine the objective response rate [according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1], to determine the time to tumor progression and progression free survival, to determine the proportion of patients with drug exposure below the TDM target after 1 potential PK-guided intervention, and to have a physician adherence of >90% in following the provided treatment recommendations. Objective response rate will be defined as the proportion of patients with confirmed complete response or confirmed partial response according to RECIST version 1.1. Time to tumor progression will be defined as the time from the start of treatment to the first documentation of objective tumor progression. Progression-free survival will be defined as the time from the start of treatment to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first.

Inclusion Criteria

Patients are eligible for this study if they are aged 18 years or older, have a diagnosis of cancer, an indication to start treatment with one of the oral anticancer drugs included in the study protocol, have a World Health Organization (WHO) performance status of 0, 1, or 2, have a life expectancy of at least 3 months, allowing adequate follow-up of toxicity and antitumor efficacy, and are willing to provide written informed consent.

Exclusion Criteria

Patients are excluded if they start treatment at a reduced dose, are known with alcoholism, drug addiction, and/or a psychiatric or physiological condition, which, in the opinion of the investigator, would impair treatment compliance, have any other disease, neurological or metabolic dysfunction, a physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of the drug or puts the patient at high risk of treatment-related complications, or are legally incapable.

TDM Targets

The TDM targets used in this study are based on previously published practical guidelines on TDM of kinase inhibitors and oral antihormonal drugs and are shown in Table 1.[4,5] For most drugs (16 of 23), this TDM target is based on exposure–efficacy analyses. If these analyses were not available (yet), the mean or median exposure of the drug was taken as a reference. For the compounds with TDM targets based on exposure–efficacy analyses, the PK targets amounted to 81%–85% of the average population exposure.[4,5] Therefore, targeting the mean or median concentration will generally lead to an efficacious exposure. In the meantime, thorough exposure–efficacy analyses will be awaited, which can provide a definitive target for TDM.

Dose Levels

Levels for dose adjustments have been defined for each drug, indicating the maximum dose of the drug and the steps with which the dose should be increased in case of low exposure or decreased in case of toxicity. The highest dose level is based on the maximum tolerated dose found in the phase I study. If the maximum tolerated dose was not reached, the highest dose tested in the phase I study was taken as the maximum dose. In case of saturated absorption, concomitant intake with food (abiraterone and pazopanib) or splitting intake moments (pazopanib) will be recommended, based on findings from previous studies.[11,12] In Table 1, the maximum dose levels and stepwise increases are reported for each drug. All dose levels per drug are described in the **Supplemental Digital Content 1** (see **Supplemental Data File**, http://links.lww.com/TDM/A341).

TABLE 2. Historical Data of the Percentage of Patients Below TDM Target per Oral Anticancer Drug

Drug	Patients Below TDM Target at Standard Dose (%)	Reference
Abiraterone	35	25
Alectinib	33	26
Axitinib	38	27
Bosutinib	50	28
Cobimetinib	50	29
Crizotinib	25	30
Dasatinib	50	31
Enzalutamide	2	32
Erlotinib	11	3
Everolimus	37	33
Gefitinib	26	34
Imatinib	73	3
Nilotinib	25	35
Olaparib	50	36
Palbociclib	50	37
Pazopanib	16–20	38,39
Regorafenib	50	40
Sorafenib	50	41
Sunitinib	49	3
Tamoxifen	20	42
Trametinib*	27	43
Vemurafenib	52	44
Vismodegib	50	45

*Data reported only for trametinib, as for dabrafenib, no dose adjustments will be recommended because little evidence for an exposure–response relationship for dabrafenib is available.

Pharmacokinetic Measurements

Concentrations of the drug will be measured using validated liquid chromatography–tandem mass spectrometry assays.[13–18] Quality of measurements will be secured by interlaboratory comparison. Patients will be instructed to let the blood sample be drawn after the time to maximum concentration (t_{max}) of the drug has been reached. Each time a PK sample is drawn, the patient will be asked the date and time of the last drug intake, and this will be recorded, as well as the time of blood sampling, to calculate the time after dose. Trough concentrations will then be calculated based on the time after dose and the $t_{1/2}$ of the drug using the following formula:

$$C_{min} = C_{measured} \times 0.5^{\frac{\text{dosing interval} - TAD}{t_{1/2}}},$$

where C_{min} is the minimum drug concentration, $C_{measured}$ is the measured drug concentration, TAD is the time after dose, and $t_{1/2}$ is the average elimination half-life of the drug.[19]

Table 1 shows the PK sampling schedule per drug and the corresponding t_{max} and $t_{1/2}$ values, which will be used to calculate the trough levels.

PK-Guided Interventions

If the estimated trough concentration is below the predefined TDM target and the patient does not show any treatment-related ≥grade 3 toxicity, a PK-guided intervention will be recommended to the treating physician within 1–2 weeks. This could include emphasizing compliance, adapting concomitant medication (due to drug–drug interactions), instructing to take the drug concomitant with food, splitting intake moments, or recommending a dose increase. If patients show any ≥grade 3 toxicity, dose will be interrupted until the toxicity is ≤grade 1. If the toxicity was treatment-related, the dose will be reduced with 1 dose level.

In case of concentrations below the TDM target, compliance will be checked directly with the patient. If compliance seems to be the cause of low PK exposure, no dose increments will be performed. Instead, compliance will be emphasized, and a new PK sample will be drawn after steady-state concentrations have been reached again. In this way, compliance will be assessed before making dose increases.

Tolerability and Efficacy Assessments

Toxicity will be evaluated during routine visits to the outpatient clinics. Tumor assessments according to RECIST version 1.1 will be performed at least every 12 weeks as part of standard care.

Statistics: Sample Size

The primary objective of this study is to halve the proportion of patients with a PK exposure below the predefined TDM target after 2 PK-guided interventions. If we consider the percentages reported in the literature as historical controls (Table 2), then using an exact binomial test with a nominal 0.05 two-sided significance level will provide the power, as indicated in Table 3, assuming different levels of the null and alternative hypothesis and various sample sizes. Obviously, if a higher proportion of patients have a low PK exposure, fewer patients are needed to provide a reasonable power. Sample size calculations were performed using the power.binom.test function of the pwr package in R.[20]

Regarding the secondary outcome of evaluating the tolerability and feasibility of TDM, generally ±25–30% of the total patient group will be eligible for dose escalation. To assess the feasibility of PK-guided interventions in at least 8 patients, about 3–4 times as many patients need to be included. Therefore, the aim is to include at least 30 patients per compound. For abiraterone, imatinib, pazopanib, sunitinib, and trametinib, patient inclusion will be expanded to be able to evaluate the influence of TDM on efficacy as well.

TABLE 3. Sample Size Calculation Showing Power at Different Levels of Null and Alternative Hypothesis and Three Examples of Sample Size

Proportion of Patients With a Drug Exposure Below TDM Target		No. of Patients		
		30	60	90
Null	Alternative	Power (%, 1 − β)		
0.10	0.05	1	19	33
0.20	0.10	18	43	71
0.30	0.15	32	71	92
0.40	0.20	60	92	98
0.50	0.25	80	97	
0.60	0.30	91		

Statistics: Analysis

The full analysis set will include all patients who received at least 1 dose of the oral anticancer drug. Patients will only be considered evaluable for the primary endpoint if they have completed the first 3 PK measurements. An exact binomial test will be performed for each drug. In some situations of drug and target combinations, it may prove difficult to obtain a sufficient number of patients for an acceptable level of power. Therefore, an additional meta-analytic approach will be applied to test the "proof-of-principle" of TDM. For each drug, the standardized change in percentage of patients with a concentration below the predefined target at the third PK measurement after the start of treatment will be calculated. Secondary endpoints will be described using descriptive statistics.

Logistic and Administrative Arrangements

The DPOG-TDM study was assessed by the accredited Medical Ethics Committee of The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital (NKI-AVL) on May 3, 2017, and it was decided that the study did not fall under the Dutch Medical Research Involving Human Subjects Act because no additional procedures are required for the participants. The institutional review board authorized the study on August 7, 2017. Patients do need to give written informed consent because data will be collected and shared. The study protocol follows the principles of the Declaration of Helsinki and the code of conduct of the Dutch FEDERA guidelines.

The NKI-AVL is the coordinating center. Other participating centers are the Erasmus Medical Center (EMC), Radboud University Medical Center (RadboudUMC), Leiden University Medical Center (LUMC), and University Medical Center Groningen (UMCG). Additional participating centers of the study are currently being recruited.

Data on baseline characteristics, measured blood concentrations, TDM recommendations, dose adjustments, toxicity, efficacy, and survival will be collected in the electronical case report form. Members of the study team will have access to the final data set.

DISCUSSION

Currently, all patients treated with oral anticancer drugs receive a standard fixed dose (ie, all patients receive exactly the same dose, independent of their weight or body surface area), although it is well known that these drugs show a large interpatient variability, and for many of them, exposure has been linked to efficacy and adverse events, providing a strong rationale for TDM. Also, other strategies such as body surface area-based dosing do not lead to an improvement in PK exposure.[21] This study aims to demonstrate the added value of TDM in collaborating hospitals.

In the development of the study design, several choices had to be made. Ideally, one would choose to perform a RCT. However, this would require an even larger sample size. Also, it could be considered unethical to fail to increase the dose in case of measured low exposure when a clear relationship between exposure and efficacy exists. Therefore, we decided to perform this prospective intervention trial.

Furthermore, we decided to only recommend dose increments in case of low PK exposure; however, it could be argued that dose reductions in case of high PK exposure might be beneficial as well, as this could be associated with less toxicity and lower costs. However, in oncology, cautions are warranted regarding dose reductions based on PK exposure because disease progression is an irreversible event. Of course, dose reductions would be made in case of toxicity, as this is regular routine patient care, which is also included in the labels.

In addition, we chose to calculate C_{min} using the abovementioned formula based on time after dose and the average elimination half-life of the drug, assuming a one-compartment model or that distribution has largely been completed by the time the sample is drawn. Alternative methods could be to draw actual trough levels or to estimate C_{min} using existing population PK models. However, these methods are not feasible in clinical practice because the timing of actual trough samples would be inconvenient for patients and the use of population PK models would be time consuming and would seriously delay the report of PK results and treatment advice to the treating physician and patient. Furthermore, Bayesian estimates of trough concentration based on a single sample suffer from shrinkage (regression to the mean), which will result in the misclassification of patients with low trough levels. Therefore, we chose to use this method, as it is easy to use, relatively precise, and thereby suitable to implement in routine care.

Many factors could contribute to low PK exposure, including drug–drug interactions, absorption problems (eg, caused by poor bioavailability, food effects, or altered stomach pH), pharmacogenetics, and compliance.[22] Compliance can be defined as the extent to which the patient follows the dosing schedule as intended by the prescriber. Especially in case of long-term treatment, compliance is known to decrease over time, potentially leading to low PK exposure and thereby decreased efficacy.[23] For example, poor adherence to imatinib has been related to suboptimal treatment outcomes.[24] TDM could play a role in detecting poor compliance to oral anticancer drugs.

Previous attempts to evaluate the efficacy of TDM have failed to do so because of the unwillingness of treating physicians to follow treatment recommendations.[8] We realize it is important that treatment recommendations should be followed to adequately evaluate the feasibility, tolerability, and efficacy of TDM. This is one of the reasons why physician adherence was chosen as one of the secondary objectives. We hope to achieve a high physician adherence by providing treating physicians with the available scientific evidence on exposure–efficacy relationships. Also, we summarize for them the number of patients previously treated at the proposed dose level (eg, in the phase I study) and the tolerability in these patients.

We believe that the current fixed dosing paradigm should be changed. Subtherapeutic treatment with these expensive drugs due to low PK exposure at the standard dose is senseless. It is our opinion that personalized dosing based on individual drug levels is far more rational. If this large prospective study underscores the results of previous retrospective studies and prospective feasibility studies,[1,2,6–8] this will support the implementation of PK-guided dose optimization as the new standard, although we realize that classical endpoints such as improvement of survival and/or quality of life will not be explored in this study. Because reimbursement of drug level measurements and administration of higher than approved doses of these expensive drugs could remain a challenge in the implementation of TDM as the standard of care in oncology, next steps would be to perform cost-effectiveness analyses and to address this with the concerning health care authorities.

The DPOG-TDM study protocol has been developed to be a dynamic protocol, meaning that future oral anticancer drugs could be added to the protocol. Also, when new literature on exposure–efficacy relationships becomes available, the TDM targets could be updated. The guidance provided in this protocol could also be used outside this study for the implementation of TDM of oral anticancer drugs in the rest of the world.

In conclusion, this prospective clinical trial evaluating the feasibility, tolerability, and efficacy of TDM of oral anticancer drugs will be a valuable contribution to the fields of clinical pharmacology and oncology and holds promise to optimize treatment outcomes for patients treated with these agents.

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