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ORIGINAL ARTICLE

Therapeutic drug monitoring-based precision dosing of oral targeted therapies in oncology: a prospective multicenter study☆

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Background: Oral targeted therapies show a high pharmacokinetic (PK) interpatient variability. Even though exposure has been positively correlated with efficacy for many of these drugs, these are still dosed using a one-size-fits-all approach. Consequently, individuals have a high probability to be either underexposed or overexposed, potentially leading to suboptimal outcomes. Therapeutic drug monitoring, which is personalized dosing based on measured systemic drug concentrations, could address these problems.

Patients and methods: Patients were enrolled in this prospective multicenter study (www.trialregister.nl; NL6695) if they started treatment with one of the 24 participating oral targeted therapies. Primary outcome was to halve the proportion of underexposed patients, compared with historical data. PK sampling was carried out after 4, 8 and 12 weeks, and every 12 weeks thereafter. In case of C_{min} below the predefined target and manageable toxicity, a pharmacokinetically guided intervention was proposed (i.e. checking compliance and drug—drug interactions, concomitant intake with food, splitting intake moments or dose increments).

Results: In total, 600 patients were included of whom 426 patients are assessable for the primary outcome and 552 patients had $\geq$1 PK sample(s) available and were therefore assessable for the overall analyses. Pharmacokinetically guided dosing reduced the proportion of underexposed patients at the third PK measurement by 39.0% (95% confidence interval 28.0% to 49.0%) compared with historical data. At the third PK measurement, 110 out of 426 patients (25.8%) had a low exposure. In total, 294 patients (53.3%) had $\geq$1 PK sample(s) below the preset target at a certain time point during treatment. In 166 of these patients (56.5%), pharmacokinetically guided interventions were carried out, which were successful in 113 out of 152 assessable patients (74.3%).

Conclusions: Pharmacokinetically guided dose optimization of oral targeted therapies was feasible in clinical practice and reduced the proportion of underexposed patients considerably.

Key words: therapeutic drug monitoring, kinase inhibitors, targeted therapies, oncology, personalized medicine, dose optimization

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INTRODUCTION

Over the last two decades, oral targeted therapies have emerged as promising treatment options for almost all tumor types. Although oral treatment comes with many advantages, including the possibility of outpatient treatment and being more convenient for patients, a major drawback of oral targeted therapies is their high inter-individual variability in exposure, with coefficients of variation typically around 40%-70%.[1] Many factors contribute to this high variability, including poor pharmaceutical formulations (as low bioavailability results in high inter- and intra-individual variability in exposure[2,3]), drug—drug and drug—food interactions, patient non-adherence, genetic polymorphisms in metabolizing enzymes and (patho-)physiological differences between patients resulting in altered pharmacokinetics.[2,4-7]

Systemic exposure (i.e. blood levels) to many of these drugs is related to both efficacy and toxicity.[1,8,9] As a result, administration of oral targeted therapies at the currently approved fixed doses has the undesirable effect that a substantial part of patients is being treated outside the therapeutic window. Supratherapeutic exposure can cause unnecessary toxicities in some patients (i.e. ±15%), whereas underexposure, resulting in suboptimal efficacy, is an even more frequently encountered problem (i.e. ±30%) and remains often unnoticed.[8-10]

Therefore, rational precision medicine would not only include selecting the right drug based on molecular characteristics of the tumor, but also selecting the right dose for each patient.[11] By use of therapeutic drug monitoring (TDM), which is adjusting the dose based on measured drug levels, the right dose could be selected for each individual patient, thereby optimizing tumor exposure to the drug.

To apply TDM in clinical practice, practical guidelines on pharmacokinetic targets need to be available, which we have previously published for kinase inhibitors and anti-hormonal drugs.[8,9] Furthermore, an adequate infrastructure for sample collection, shipment, bioanalysis, interpretation and reporting of results should be in place, with a short turnaround time.

Previous feasibility studies have already demonstrated that pharmacokinetically guided dosing of pazopanib and sunitinib is a promising tool to achieve therapeutic exposure in a larger proportion of patients.[12,13] To further evaluate the feasibility of TDM, we have set up the Dutch Pharmacology Oncology Group—Therapeutic Drug Monitoring (DPOG-TDM) study, which is an ongoing, prospective protocol providing a framework to investigate the feasibility, tolerability and efficacy of individualized dosing for multiple oral targeted therapies simultaneously.[14]

The aim of this analysis was to investigate whether pharmacokinetically guided dose optimization is feasible in clinical practice and if it reduces the proportion of underexposed patients.

METHODS

Study design and participants

The DPOG-TDM study [Clinical trials number NL6695 Netherlands Trial Register (www.trialregister.nl)] is a prospective, multicenter study in 10 hospitals in the Netherlands. The protocol has previously been reported in detail elsewhere.[14] Figure 1A provides a schematic overview of the study design. In short, cancer patients could be enrolled if they initiated regular treatment with one of the oral targeted therapies included in the protocol at the approved dose. Exceptions were cabozantinib, for which patients needed to start at 40 mg once daily, and sorafenib, for which a step-up dosing schedule was allowed (mostly starting at 200 mg twice daily), because of the toxicity of these compounds at the approved dose. Pharmacokinetic samples were collected 4, 8 and 12 weeks after start of treatment for most compounds, and every 12 weeks thereafter. Drug concentrations were quantified using validated liquid chromatography-tandem mass spectrometry assays.[15-19] For compounds that were analyzed in multiple centers, proficiency testing schemes and inter-laboratory comparisons were carried out to guarantee interchangeability of results. Pharmacokinetic samples were either drawn predose or randomly during the dosing interval (but after the time to maximum plasma concentration). In the latter case, the minimum plasma concentration (C_{min}) was estimated using log-linear extrapolation (i.e. based on the average elimination half-life of the drug and the time between sampling and dosing).[20] C_{min} was taken as a measure of exposure, because previously published efficacy thresholds are based upon this pharmacokinetic parameter, and because only one sample is needed to estimate it. In case of C_{min} below the predefined TDM target and manageable toxicity (as assessed by the treating physician), a pharmacokinetically guided intervention was recommended. This could include emphasizing compliance, adjusting concomitant medication due to drug—drug interactions, concomitant intake with food (abiraterone, cabozantinib and pazopanib), splitting intake moments (pazopanib) or dose increases. Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.06.010, provides an overview of the approved dose and TDM target per compound.

Amendments to the study protocol after the previous publication of the study design[14] include the addition of cabozantinib to the list of study drugs, and the use of a different extrapolation method for abiraterone (i.e. by taking the ratio of the observed concentration and the typical population concentration and multiplying this ratio with the typical population value of C_{min}).[20]

Our DPOG-TDM study was built up according to a three-stage-design (Figure 1B). First-stage cohorts enrolled at least 30 patients, after which the feasibility of TDM was evaluated. The aim of the second-stage cohort was to confirm the feasibility of TDM in a larger cohort of 100 patients and to evaluate preliminary efficacy data. Third-stage cohorts enable further nationwide implementation of TDM using the existing infrastructure of the DPOG-TDM study and ensure continuous collection of real-life data. Also, the collected data will allow meaningful efficacy analyses and further optimization of the TDM algorithms where needed. Data from third-stage cohorts will be analyzed separately to prevent an unbalanced distribution among cohorts in the combined analysis. The members of the

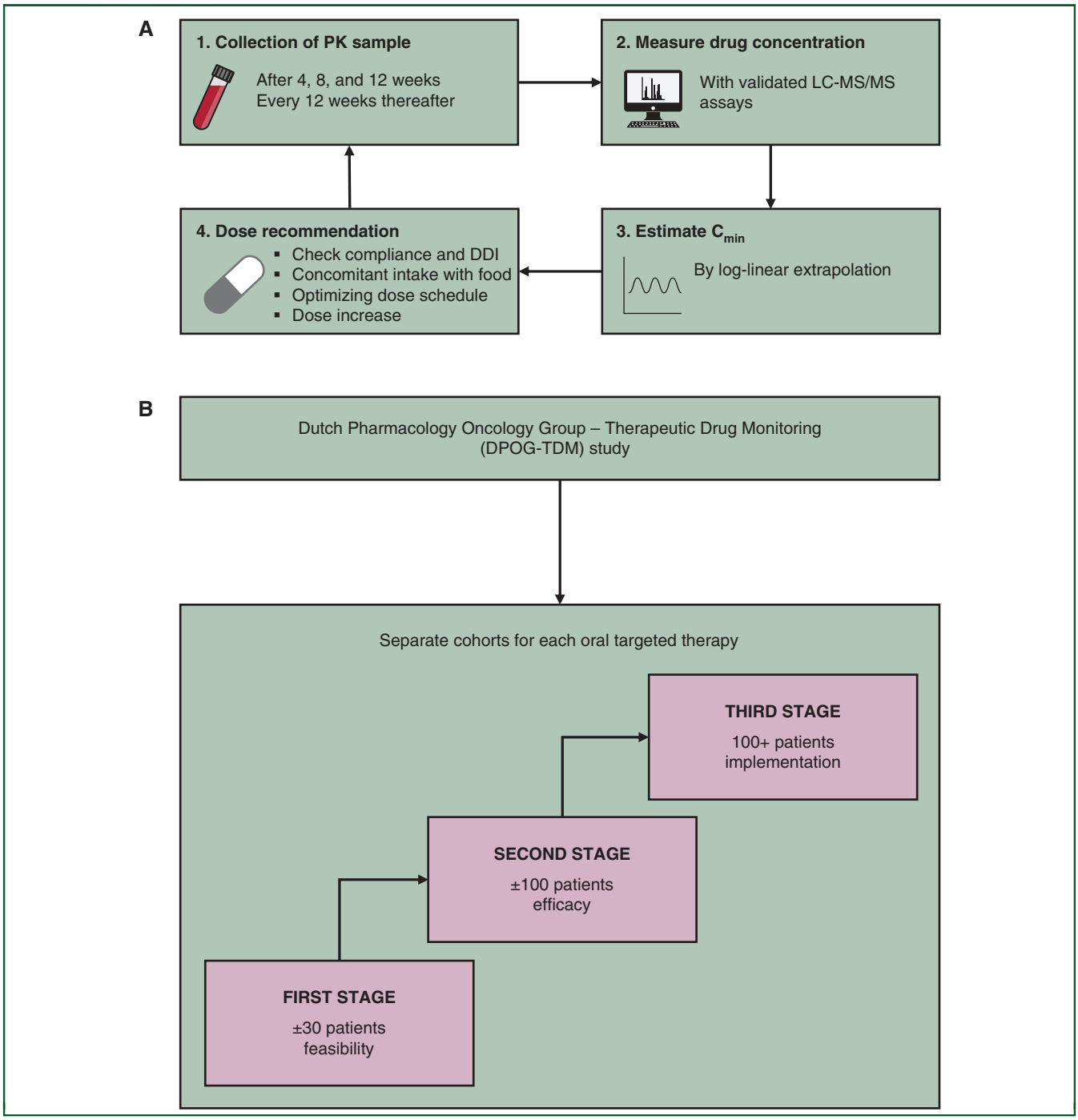

Figure 1. Study design.

(A) Schematic overview of workflow that was followed for each individual patient: 1. Pharmacokinetic samples were collected 4, 8 and 12 weeks after start of treatment and every 12 weeks thereafter (for most compounds); 2. Drug concentrations were quantified using validated LC-MS/MS assays; 3. C_{min} was estimated using log-linear extrapolation (i.e. based on the average elimination half-life of the drug and the time between sampling and dosing),[20] except for abiraterone, for which the extrapolation method was switched halfway to taking the ratio of the observed C_{min} and the typical population concentration and multiplying this ratio with the typical population value of C_{min}; 4. Dose recommendations were provided to the treating physician—these could include checking compliance and drug—drug interactions, concomitant intake with food (for abiraterone and pazopanib), splitting intake moments (for pazopanib) or dose increases. (B) Schematic overview of the three-stage design. Separate cohorts were opened for each compound included in the study protocol. In the first stage, the feasibility of pharmacokinetically guided dosing was evaluated in ±30 patients. If pharmacokinetically guided dosing was considered promising, second-stage cohorts aimed to confirm the feasibility in a larger cohort of patients and to evaluate preliminary efficacy in ±100 patients. Then it was decided whether or not to proceed with third-stage cohorts, which enable further nationwide implementation of TDM using the existing infrastructure of the DPOG-TDM study and ensure continuous collection of real-life data. Also, the collected data will allow meaningful efficacy analyses and further optimization of the TDM algorithms where needed. Data from third-stage cohorts will be analyzed separately to prevent an unbalanced distribution among cohorts in the combined analysis.

C_{min}, minimum plasma concentration; DDI, drug—drug interactions; DPOG, Dutch Pharmacology Oncology Group; LC-MS/MS, liquid chromatography-tandem mass spectrometry; PK, pharmacokinetic; TDM, therapeutic drug monitoring.

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DPOG evaluated and decided after completion of a stage whether or not to proceed to the following stage.

The study was approved by the institutional review board of The Netherlands Cancer Institute (Amsterdam, Netherlands) and approval from the board of directors of each individual hospital was obtained for all participating centers. All patients provided written informed consent. Participating centers are listed in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.06.010. This study is registered within the Netherlands Trial Register (www.trialregister.nl; number NL6695).

Outcomes

The primary objective of this study was to reduce the proportion of patients with an exposure below the TDM target at the third pharmacokinetic measurement (i.e. after two potential pharmacokinetically guided interventions) by 50%, compared with historical data. The historical data on percentages of patients with an exposure below the target were reported in our previous publication on the study design[14] and in Table 2. Secondary outcomes were to assess the feasibility, tolerability and efficacy of TDM, and a physician adherence to our dosing recommendations $\geq$ 90%. Pharmacokinetically guided interventions were considered successful if the median C_{min} after the intervention was above the predefined TDM target and if no dose reduction due to toxicity was needed within 1 month. Physician adherence was defined as the percentage of patients who actually received a pharmacokinetically guided intervention, calculated from the total of patients with a low exposure and manageable toxicity in whom a pharmacokinetically guided intervention had been recommended.

Statistical analysis

Patients were considered assessable for the primary outcome if three or more pharmacokinetic samples were collected and measured. Secondary outcomes were evaluated using data of all patients with one or more pharmacokinetic samples available.

To compare the percentage of patients with an exposure below the TDM target to historical data, exact binomial tests were carried out. The historical percentage for all drugs combined was compiled of the weighted average of the historical percentages of the individual drugs. If enough patients were included in a cohort to attain a power above 80% to demonstrate a 50% reduction compared to the historical percentage, an exact binomial test was carried out for that cohort separately as well.

An additional meta-analytic approach was applied to test the 'proof-of-principle' of TDM-guided dosing, for which the standardized changes in the percentage of patients with a low exposure compared to historical data were calculated per compound and graphically displayed in a forest plot, using the following formula:

$$Standardized\ change = \frac{Percentage\ \ below\ target\ exposure\ \ at\ \ third\ pharmacokinetic\ \ measurement}{Percentage\ \ below\ \ target\ \ exposure\ in\ \ historical\ \ data}.$$

Secondary outcomes were described using descriptive statistics.

Statistical analyses were carried out using R version 3.6.1 (R Project, Vienna, Austria).

RESULTS

Between June 2017 and June 2020, 600 patients were enrolled in the study, of which 552 patients had one or more pharmacokinetic samples available and were thus assessable for the overall analyses (Figure 2). Of these patients, 426 patients completed three or more pharmacokinetic measurements and were therefore assessable for the primary outcome, while 114 patients discontinued treatment before the third pharmacokinetic measurement and 12 patients did not complete these pharmacokinetic measurements yet. Patients were treated with 20 different oral targeted therapies. Thirteen patients were enrolled twice in separate treatment lines, and two patients three times. The study population thus consisted of 583 unique patients. In this manuscript, however, the results are described separately for each treatment line, and thus 600 patients are described. Baseline characteristics of all patients are provided in Table 1, and were similar between patients with one or more low and all adequate pharmacokinetic samples. Data cut-off for follow-up was 1 October 2020. In total, 2740 evaluable pharmacokinetic samples were collected, with a median of 4 samples per patient (range: 1-18). Supplemental Table S1, available at https://doi.org/10.1016/j.annonc.2022.06.010, provides the intra-individual variability in C_{min} at the approved dose for each compound.

The results of the primary outcome are summarized in Table 2. Overall, 110 patients (25.8%) had a low exposure (i.e. below the preset target) at the third pharmacokinetic measurement, compared with 42.2% in historical data ($P < 0.001$). Thus, TDM-guided dosing reduced the proportion of patients with a low exposure by 39.0% [95% confidence interval (CI) 28.0% to 49.0%], not reaching the primary endpoint of 50%. For abiraterone, imatinib and sunitinib, the calculated power was above 80% and exact binomial tests were carried out for these drugs separately. Figure 3 provides a forest plot of the standardized changes in the percentage of patients with a low exposure of TDM-guided dosing compared with historical data per compound and in total.

The results of the first three pharmacokinetic measurements and the carried-out pharmacokinetically guided interventions are graphically displayed in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.06.010. Pharmacokinetically guided interventions have been carried out in 99 patients after the first and/or second pharmacokinetic measurement. This resulted in adequate exposure at the third pharmacokinetic measurement in 66 out of these 99 patients. In 16 additional patients, adequate exposure was eventually reached at a later

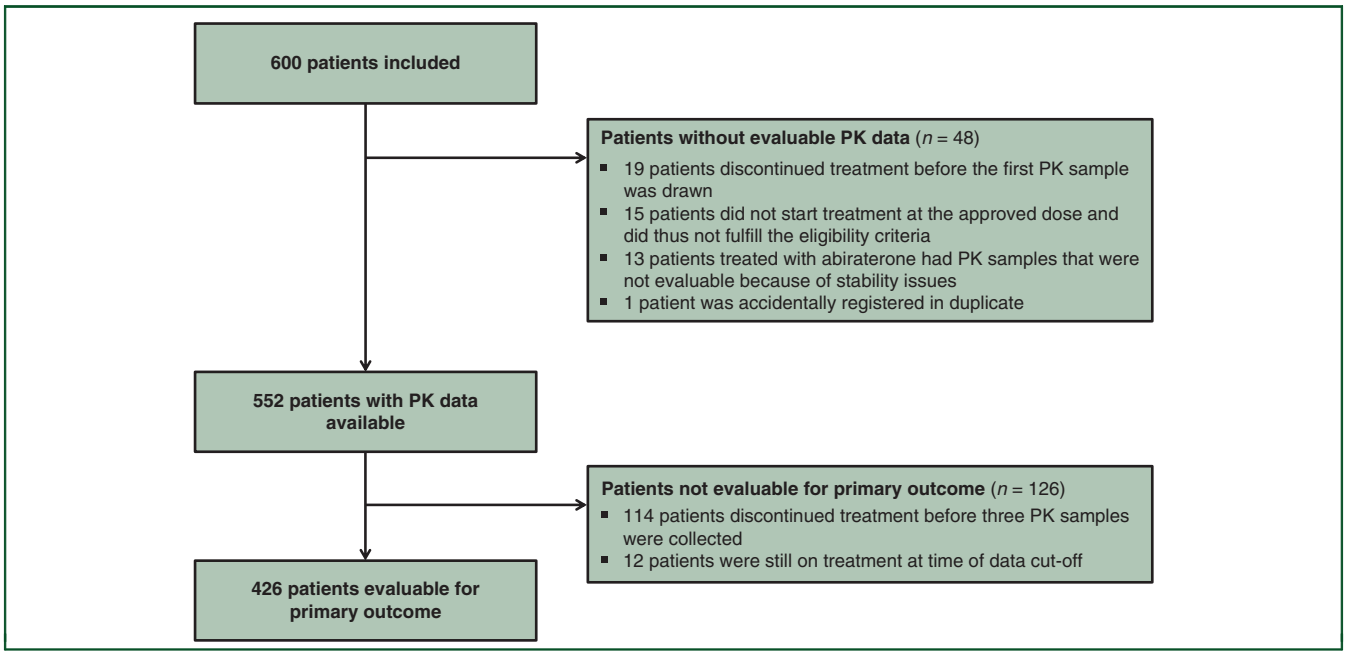

Figure 2. Flow diagram of patient enrolment.
PK, pharmacokinetic.

time point than the third pharmacokinetic measurement. Of the 110 patients with a low exposure at the third pharmacokinetic measurement, 37 patients (33.6%) had a low exposure for the first time, and no pharmacokinetically guided interventions could have been carried out yet in these patients, whereas 73 patients had a low exposure before, but a pharmacokinetically guided intervention was either not feasible ($n = 40$) or not (yet) successful ($n = 33$) in these patients. Dose reductions below the standard dose were carried out in 8.2%, 13.1% and 19.6% of patients

Table 1. Baseline characteristics

Characteristic	All patients ($n = 600$)	Patients assessable for overall analyses ($n = 552$)	Patients with ≥ 1 low C_{min} ($n = 294$)	Patients with all adequate C_{min} ($n = 258$)	Patients assessable for primary outcome ($n = 426$)
Age, years	63.9 ± 11.5	63.8 ± 11.4	64.0 ± 11.3	63.6 ± 11.6	64.2 ± 11.4
Sex					
Female	222 (37.0%)	204 (37.0%)	107 (36.4%)	97 (37.6%)	160 (37.6%)
Male	378 (63.0%)	348 (63.0%)	187 (63.6%)	161 (62.4%)	266 (62.4%)
Tumor type					
Basal cell carcinoma	5 (0.8%)	4 (0.7%)	4 (1.4%)	0	1 (0.2%)
Breast cancer	48 (8.0%)	44 (8.0%)	21 (7.1%)	23 (8.9%)	30 (7.0%)
Dermatofibrosarcoma protuberans	1 (0.2%)	1 (0.2%)	1 (0.3%)	0	0
Desmoid-type fibromatosis	1 (0.2%)	1 (0.2%)	1 (0.3%)	0	0
Differentiated thyroid carcinoma	7 (1.2%)	6 (1.1%)	5 (1.7%)	1 (0.4%)	4 (0.9%)
Gastrointestinal stromal tumor	125 (20.8%)	120 (21.7%)	92 (31.3%)	28 (10.9%)	103 (24.2%)
Hepatocellular carcinoma	40 (6.7%)	30 (5.4%)	25 (8.5%)	5 (2.0%)	14 (3.3%)
Melanoma	80 (13.3%)	76 (13.8%)	28 (9.5%)	48 (18.6%)	50 (11.7%)
Neuroendocrine tumor	5 (0.8%)	3 (0.5%)	2 (0.7%)	1 (0.4%)	2 (0.5%)
Non-small-cell lung cancer	23 (3.8%)	22 (4.0%)	9 (3.1%)	13 (5.0%)	17 (4.0%)
Ovarian cancer	21 (3.5%)	21 (3.8%)	17 (5.8%)	4 (1.6%)	20 (4.7%)
Perivascular epithelioid cell tumor	1 (0.2%)	1 (0.2%)	1 (0.3%)	0	1 (0.2%)
Prostate cancer	148 (24.7%)	134 (24.3%)	56 (19.0%)	78 (30.2%)	116 (27.2%)
Renal cell carcinoma	62 (10.3%)	58 (10.5%)	22 (7.5%)	36 (14.0%)	48 (11.3%)
Soft-tissue sarcoma	32 (5.3%)	30 (5.4%)	10 (3.4%)	20 (7.8%)	20 (4.7%)
Urothelial cell cancer	1 (0.2%)	1 (0.2%)	0	1 (0.4%)	0
Previous lines of systemic treatment					
0	364 (60.7%)	344 (62.3%)	194 (66.0%)	150 (58.1%)	273 (64.1%)
1	135 (22.5%)	121 (21.9%)	57 (19.4%)	64 (24.8%)	95 (22.3%)
2	62 (10.3%)	54 (9.8%)	28 (9.5%)	26 (10.1%)	36 (8.5%)
≥ 3	39 (6.5%)	33 (6.0%)	15 (5.1%)	18 (7.0%)	22 (5.2%)
Total number of PK samples	2818	2740	1647	1093	2536
Number of PK samples per patient	4 (2-6)	4 (3-6)	5 (3-7)	4 (2-6)	5 (4-7)

Data are expressed as mean ± SD, median (IQR) or *n* (%), as appropriate.
C_{min}, minimum plasma concentration; IQR, interquartile range; PK, pharmacokinetic; SD, standard deviation.

https://doi.org/10.1016/j.annonc.2022.06.010

Table 2. Percentage of patients below the TDM target and C_{min} levels at the first three pharmacokinetic measurements

Oral targeted therapy	Number of enrolled patients	Number of assessable patients	C_{min} PK #1 (ng/ml)	PK #1 below target	C_{min} PK #2 (ng/ml)	PK #2 below target	C_{min} PK #3 (ng/ml)	PK #3 below target	Historical comparison[a]	*P* value[b]
Abiraterone	105	79	21.9 (95.9%)	15 (19.0%)	26.1 (88.9%)	11 (13.9%)	24.5 (91.4%)	12 (15.2%)	38.5%[33,34]	< 0.001
Alectinib	18	14	647.4 (24.3%)	2 (14.3%)	579.6 (33.6%)	3 (21.4%)	524.9 (33.5%)	4 (28.6%)	35.1%[35,36]	—
Axitinib	2	2	5.2 (100%)	1 (50.0%)	5.4 (61.1%)	1 (50.0%)	6.0 (95%)	1 (50.0%)	38%[37]	—
Cabozantinib	7	6	1,050 (39.3%)	1 (16.7%)	947.5 (43.2%)	2 (33.3%)	631.3 (38.7%)	4 (66.7%)	50%[38]	—
Crizotinib	2	1	458 (NA)	0	554 (NA)	0	516 (NA)	0	32.4%[36,39]	—
Dabrafenib/ trametinib[c]	68	44	16.4 (34.1%)	6 (13.6%)	16.0 (35.6%)	8 (18.2%)	17.2 (40.1%)	4 (9.1%)	27%[40]	—
Enzalutamide	43	37	11 100 (24.3%)	1 (2.7%)	11 100 (23.4%)	1 (2.7%)	10,800 (28.7%)	2 (5.4%)	1.6%[24,41]	—
Erlotinib	3	2	1863 (26.1%)	0	1975 (7.6%)	0	2024 (32.0%)	0	11%[42]	—
Everolimus	9	4	10.2 (37.3%)	2 (50.0%)	10.1 (81.2%)	2 (50.0%)	10.3 (84.5%)	3 (75.0%)	37%[43]	
Imatinib	104	91	1290 (52.2%)	38 (41.8%)	1309 (53.8%)	45 (49.5%)	1256 (37.1%)	36 (39.6%)	70.4%[10,30,42]	< 0.001
Lapatinib[d]	1	0	—	—	—	—	—	—	50%[44]	—
Olaparib	21	20	2173 (96.1%)	11 (55.0%)	1869 (78.6%)	7 (35.0%)	1777 (62.8%)	8 (40.0%)	50%[45]	—
Palbociclib	22	15	58.7 (29.6%)	7 (46.7%)	50.2 (36.3%)	10 (66.7%)	65.6 (46.3%)	5 (33.3%)	50%[46]	—
Pazopanib	49	36	31 700 (57.4%)	9 (25.0%)	2800 (44.6%)	9 (25.0%)	29 700 (38.7%)	6 (16.7%)	26.7%[12,47-49]	—
Regorafenib	16	2	701.5 (43.0%)	2 (100%)	989.0 (87.4)	1 (50.0%)	1355 (62.6)	1 (50.0%)	50%[50]	—
Sorafenib[e]	39	17	3911 (55.7%)	11 (64.7%)	4284 (70.4%)	8 (47.1%)	3610 (78.9%)	12 (70.6%)	50%[51]	—
Sunitinib[f]	50	35	74.0 (37.8%)	5 (14.3%)	75.4 (40.8%)	4 (11.4%)	66.0 (44.4%)	5 (14.3%)	44.3%[10,42,52]	< 0.001
Tamoxifen[g]	24	14	10.1 (52.5%)	4 (28.6%)	11.4 (38.6%)	1 (7.1%)	10.6 (38.7%)	1 (7.1%)	21.9%[53-55]	—
Vemurafenib/ cobimetinib	12	6/5	47 700 (41.3%)/ 188.1 (24.6%)	2 (33.0%)/1 (20.0%)	41 900 (48.0%)/ 167.5 (84.1%)	3 (50.0%)/ 3 (60.0%)	48 900 (36.5%)/ 106.8 (63.5%)	4 (67.0%)/ 4 (80.0%)	52%[56]/50%[57]	—
Vismodegib	5	1	12 900 (NA)	0	10 500 (NA)	1 (100%)	12 000 (NA)	0	50%[58]	
All patients	600	426	—	118 (27.7%)	—	119 (27.9%)	—	110 (25.8%)	42.2%	< 0.001

Data are expressed as mean (CV%) or *n* (%), as appropriate. PK #1, #2 and #3 represent the first, second and third pharmacokinetic measurement (i.e. for most compounds 4, 8 and 12 weeks after start of treatment). Exact binomial tests were carried out to compare the percentage of patients with a low exposure at the third pharmacokinetic measurement with historical data.

BID, twice daily; C_{min}, minimum plasma concentration; CV, coefficient of variation; NA, not applicable; PK, pharmacokinetic(ally); TDM, therapeutic drug monitoring.

[a]Historical percentages were previously described in the publication of the study protocol,[14] and have been complemented with more recent literature. In case of multiple cohorts a weighted average was calculated. The historical percentage for all drugs combined was compiled of the weighted average of the historical percentages of the individual drugs.

[b]*P* values are only reported for cohorts that attained a power above 80%.

[c]Pharmacokinetically guided interventions were only carried out for trametinib, not for dabrafenib; data are thus only reported for trametinib.

[d]Lapatinib has been removed from the list of study drugs before the previous publication of the study protocol,[14] as it was rarely being prescribed. However, one patient had already been enrolled.

[e]Sorafenib patients were allowed to start treatment according to a step-up dosing schedule (mostly starting at 200 mg BID).

[f]C_{min} is the sum concentration of sunitinib and its active metabolite *N*-desethylsunitinib.

[g]Steady-state concentrations of the active metabolite endoxifen are reported.

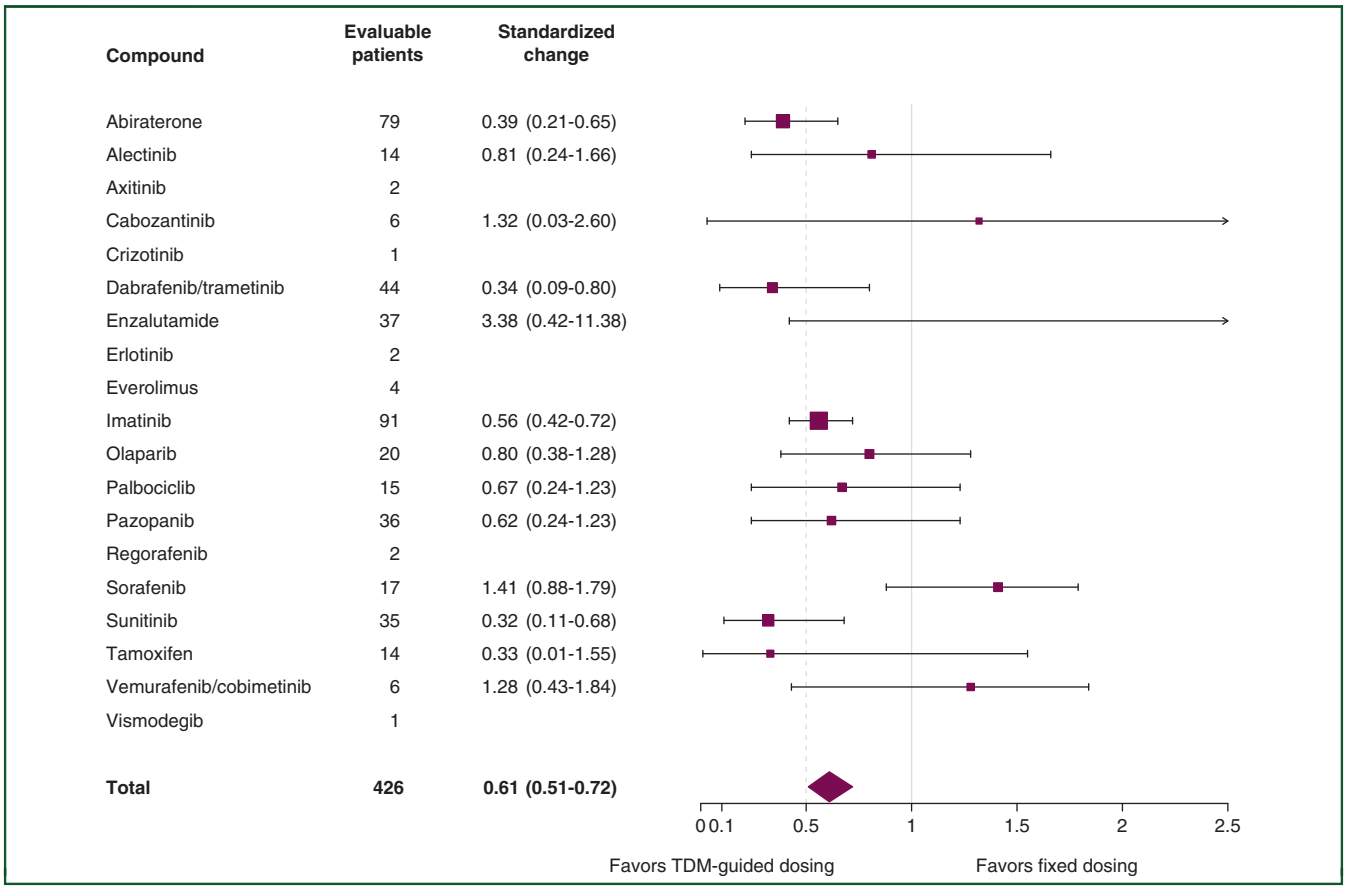

Figure 3. Forest plot of standardized change in underexposed patients with precision dosing compared to fixed dosing.
Standardized change is expressed as proportion of the historical comparison (see Table 2) with 95% CI, and is only displayed for compounds with more than five patients. The dashed line represents the point where the proportion of underexposed patients is halved. Standardized change was calculated by dividing the percentage of patients with a low exposure at the third pharmacokinetic measurement in the current study by the historical percentage from literature.
CI, confidence interval; TDM, therapeutic drug monitoring.

before the first, second and third pharmacokinetic measurements, respectively.

An overview of all carried-out pharmacokinetically guided interventions, and also those carried out after 12 weeks, is provided in Figure 4 and Table 3, including all patients with ≥ 1 pharmacokinetic samples available. In total, 294 out of 552 patients (53.2%) had one or more C_{min} below the predefined TDM target and were thus potentially underexposed. Pharmacokinetically guided interventions could be carried out in 166 out of these 294 patients (56.5%) and were successful in 113 out of 152 assessable patients (74.3%). In 14 patients, it could not be assessed (yet) whether the pharmacokinetically guided intervention was successful, because they were still on treatment and no new pharmacokinetic sample has been collected yet ($n = 7$) or they discontinued treatment before a new pharmacokinetic sample had been drawn ($n = 7$). In total, 224 pharmacokinetically guided interventions were carried out (i.e. in 44 patients more than one intervention), including emphasizing compliance ($n = 4$), adjusting concomitant medication ($n = 7$), splitting intake moments ($n = 12$), concomitant intake with food ($n = 45$) and dose increases ($n = 156$). Reasons why pharmacokinetically guided interventions could not be carried out in the other 128 patients were toxicity ($n = 80$, 62.5%), lack of physician adherence ($n = 23$, 18.0%, of which five patients had a borderline low pharmacokinetic exposure, i.e. within 10% below TDM target), treatment discontinuation ($n = 18$, 14.1%) or other ($n = 7$, 5.5%). Physician adherence to our dosing recommendations was 87.8% (i.e. 166 out of 189 patients with low pharmacokinetic exposure and manageable toxicity in whom a pharmacokinetically guided intervention was recommended), ranging from 56% to 100% between participating centers.

Figure 5 compares the median time on treatment in patients with one or more low pharmacokinetic samples who did (group 1A) and did not (group 1B) receive a pharmacokinetically guided intervention, and in patients with all adequate pharmacokinetic exposure (group 2).

DISCUSSION

We carried out a prospective nationwide study on pharmacokinetically guided dosing in 600 patients with 24 different oral targeted therapies. Our results show that pharmacokinetically guided dose individualization is feasible in clinical practice. The proportion of underexposed patients at the third pharmacokinetic measurement was reduced by 39.0% (95% CI 28.0% to 49.0%) compared with historical data, not reaching our primary endpoint of 50%. Overall, more than half of the patients had a low exposure at a certain time

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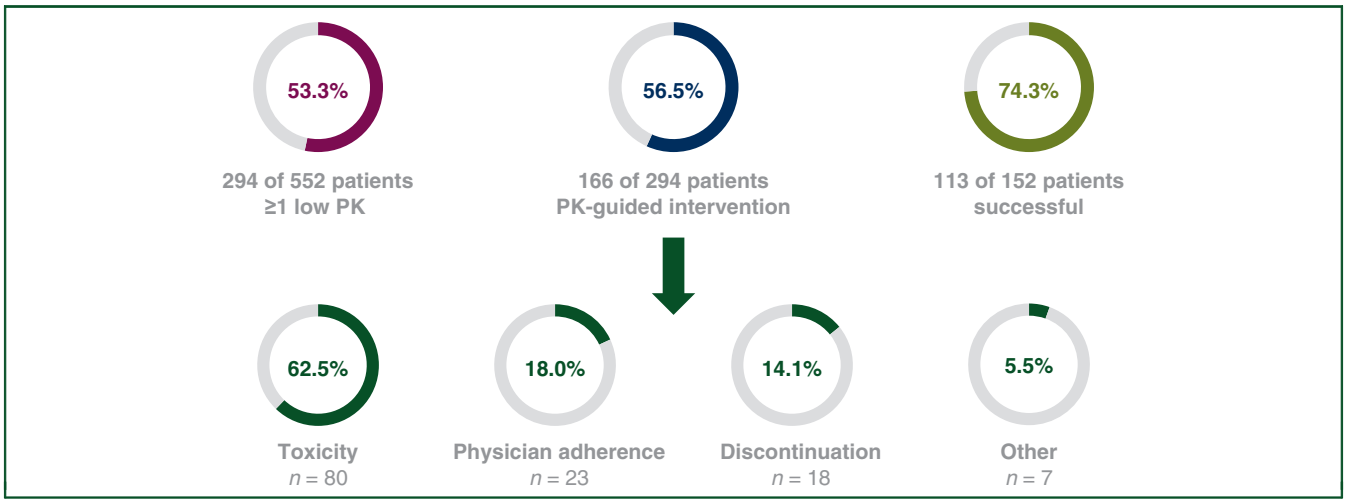

Figure 4. Overview of carried-out pharmacokinetically guided interventions.
Pharmacokinetically guided interventions were considered successful if the median C_{min} after the intervention was above the predefined TDM target and if no dose reduction due to toxicity was needed within 1 month. The percentage of successful interventions was calculated from the total number of evaluable pharmacokinetically guided interventions. In seven patients the effect was not evaluated yet, and seven patients discontinued treatment before the pharmacokinetically guided intervention could be evaluated. Other reasons why no pharmacokinetically guided intervention was carried out included withdrawal of informed consent ($n = 2$), participation in a compassionate use programme where dose increases were not allowed ($n = 1$), patient preference ($n = 1$), treatment beyond progression ($n = 1$), sample drawn before t_{max} was reached ($n = 1$) and delay in reporting of results ($n = 1$).
C_{min}, minimum plasma concentration; PK, pharmacokinetically; TDM, therapeutic drug monitoring; t_{max}, time until maximum plasma concentration is reached.

point during treatment. In more than half of these patients it was feasible to implement a pharmacokinetically guided intervention, which was successful (i.e. adequate exposure and manageable tolerability) in the majority of patients. Overall, successful pharmacokinetically guided interventions were carried out in 20.5% of patients, while an additional 46.7% of patients had an adequate exposure at all time and thus did not need any intervention.

Table 3. Overview of carried-out pharmacokinetically guided interventions

Oral targeted therapy	Number of enrolled patients	Number of assessable patients	Low exposure[a]	PK-guided intervention[b]	Successful[c]
Abiraterone	105	92	54 (58.7%)	46 (83.3%)	35/36 (97.2%)
Alectinib	18	17	8 (47.1%)	3 (37.5%)	2/2 (100%)
Axitinib	2	2	1 (50.0%)	1 (100%)	0/1 (0%)
Cabozantinib	7	7	6 (85.7%)	1 (16.7%)	1/1 (100%)
Crizotinib	2	2	1 (50%)	—	—
Dabrafenib/trametinib[d]	68	66	18 (27.3%)	7 (38.9%)	4/6 (66.7%)
Enzalutamide	43	42	2 (4.8%)	1 (50.0%)	1/1 (100%)
Erlotinib	3	3	0	—	—
Everolimus	9	6	4 (66.7%)	1 (25.0%)	1/1 (100%)
Imatinib	104	103	84 (81.6%)	51 (60.7%)	35/50 (70.0%)
Lapatinib	1	1	0	—	—
Olaparib	21	21	17 (81.0%)	10 (58.8%)	6/10 (60.0%)
Palbociclib	22	21	13 (61.9%)	5 (35.7%)	4/5 (80.0%)
Pazopanib	49	47	18 (38.3%)	15 (83.3%)	12/15 (80.0%)
Regorafenib	16	7	5 (71.4%)	1 (20.0%)	0/1 (0%)
Sorafenib[e]	39	34	29 (85.3%)	10 (34.5%)	3/9 (33.3%)
Sunitinib	50	46	13 (28.3%)	5 (42.9%)	4/5(80.0%)
Tamoxifen	24	21	7 (33.3%)	5 (71.4%)	4/5 (80.0%)
Vemurafenib/cobimetinib[f]	12	10/9	8 (80.0%)/7 (77.7%)	0 (0%)/3 (42.9%)	0/3 (0%)
Vismodegib	5	4	4 (100%)	1 (25.0%)	1/1 (100%)
All patients	600	552	294 (53.3%)	166 (56.5%)	113/152 (74.3%)

BID, twice daily; C_{min}, minimum plasma concentration; PK, pharmacokinetically; TDM, therapeutic drug monitoring.
[a]Number of patients with C_{min} below the predefined TDM target at a certain time point during treatment.
[b]Pharmacokinetically guided interventions could include emphasizing compliance, adjusting concomitant medication due to drug—drug interactions, concomitant intake with food (abiraterone, cabozantinib and pazopanib), splitting intake moments (pazopanib) or dose increases.
[c]Pharmacokinetically guided interventions were considered successful if the median C_{min} after the intervention was above the predefined TDM target and if no dose reductions due to toxicity were needed within 1 month. Percentages were calculated from the total number of evaluable pharmacokinetically guided interventions. The effect of the pharmacokinetically guided intervention has not been evaluated yet in seven patients [abiraterone ($n = 6$), imatinib ($n = 1$)]. Also, seven patients discontinued treatment before the effect of the pharmacokinetically guided intervention could be evaluated [abiraterone ($n = 4$), alectinib ($n = 1$), sorafenib ($n = 1$) and dabrafenib/trametinib ($n = 1$)].
[d]Pharmacokinetically guided interventions were only carried out for trametinib, not for dabrafenib.
[e]Sorafenib patients were allowed to start at a lower dose, mostly 200 mg BID.
[f]Reported figures are for vemurafenib and cobimetinib combined.

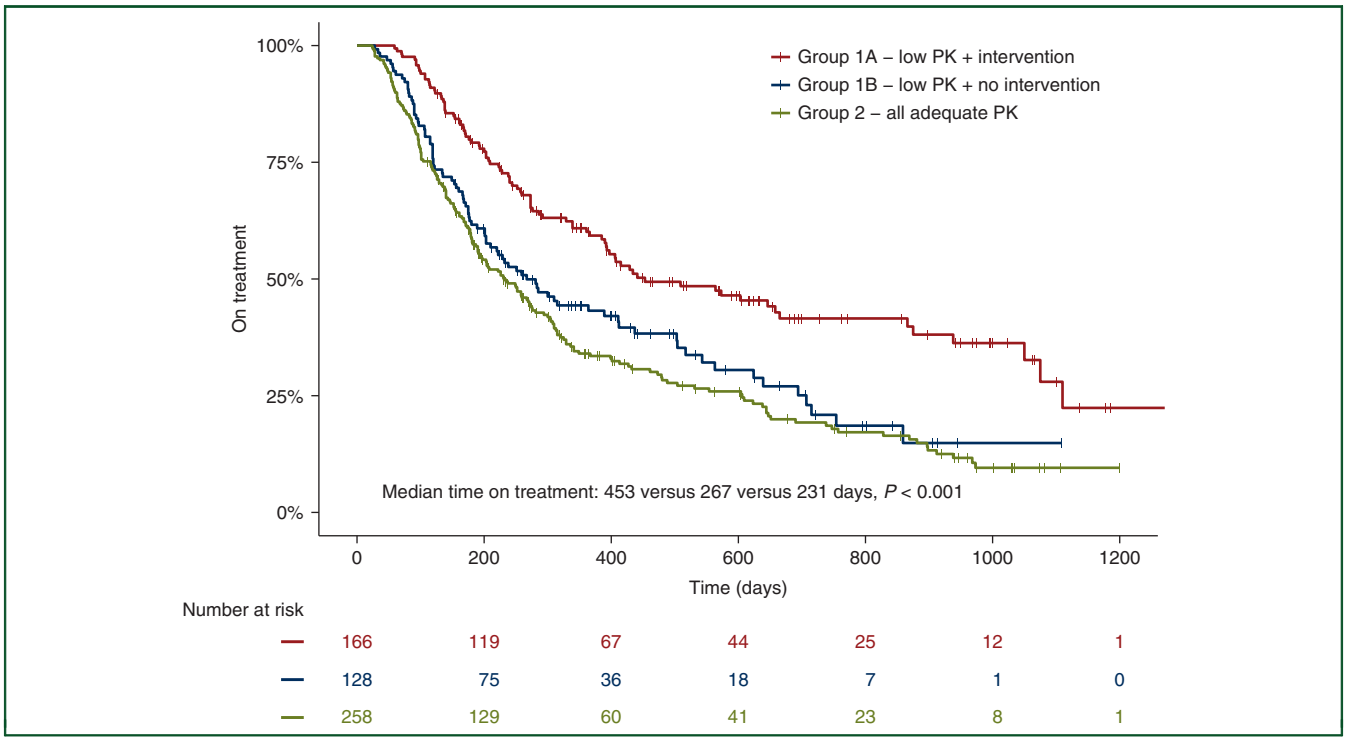

Figure 5. Kaplan–Meier curve of time on treatment.
Group 1A are patients with one or more PK samples below the target who received a pharmacokinetically guided intervention. Group 1B are patients with one or more PK samples below the target who did not receive a pharmacokinetically guided intervention due to various reasons (i.e. toxicity, physician adherence, treatment discontinuation). Group 2 are patients with all PK samples above the target.
PK, pharmacokinetic.

An important complicating factor in TDM of oral targeted therapies is the relatively high intra-individual variability. As a result, not all patients with a low exposure are identified at the first pharmacokinetic measurement. Instead, low exposure may occur at any time point during treatment, as can also be appreciated from Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.06.010. For over one-third of the patients with a low exposure at the third pharmacokinetic measurement, this was the first time that a low exposure was detected in these patients, and therefore, no pharmacokinetically guided interventions could have been implemented yet in these patients. Most importantly, the substantial intra-individual variability underscores the importance of continuing pharmacokinetic measurements at frequent time points throughout the entire treatment period. Besides, for some kinase inhibitors it has been reported that exposure can decrease over time due to auto-induction of metabolism (i.e. for imatinib and dabrafenib[21,22]). Furthermore, the number of patients treated at a reduced dose due to toxicity increases over time (i.e. from 8.2% at the first pharmacokinetic measurement to 19.6% at the third pharmacokinetic measurement, possibly due to cumulative toxicity), also affecting the percentage of patients reaching the target exposure.

In this study, pharmacokinetically guided dosing has been applied for 20 different oral targeted therapies. Although combining cohorts enables interpretation of the results of pharmacokinetically guided dosing for oral targeted therapies as a class, the feasibility differs between compounds. The three-stage design of our study ensures evaluation of separate cohorts once sufficient number of patients have been enrolled for that specific compound. Currently, two cohorts have proceeded to the second stage (pazopanib and sunitinib) and two cohorts to the third stage (abiraterone and imatinib). Also, four cohorts have been closed for further enrolment after the first stage: dabrafenib/trametinib, enzalutamide, sorafenib and tamoxifen. For dabrafenib/trametinib, new exposure–response analyses in real-life patients treated with the combination of dabrafenib plus trametinib indicated that a higher trametinib threshold (i.e. 15.6 ng/ml) might be more appropriate.[23] For enzalutamide, TDM was not needed as almost all patients had an exposure above the TDM target at the standard dose. Also, no exposure–response relationship was demonstrated in a real-life patient cohort.[24] For sorafenib, pharmacokinetically guided interventions were rarely feasible due to toxicity. For tamoxifen, the willingness of the treating physicians to proceed with pharmacokinetically guided dosing was insufficient because of discussion regarding the exposure–response relationship for tamoxifen.

Although not the aim of the current paper, we did perform a preliminary efficacy analysis with time on treatment as a surrogate for efficacy (Figure 5). This preliminary analysis shows that the time on treatment of the group of patients with low pharmacokinetic exposure who underwent pharmacokinetically guided dose adjustments is not inferior to the time on treatment of patients with adequate exposure. This could mean that the outcome of patients with a low exposure is improved to a level where it is equal

to patients with an adequate exposure. It has to be noted, however, that these data are difficult to interpret, because the distribution of patients among groups and the time on treatment differ per drug and because the chance of detecting a single low C_{min} due to intra-individual variability increases with a longer time on treatment.

The fact that patients know that their drug levels are being monitored could improve patients' compliance and thereby already optimize exposure without any pharmacokinetically guided interventions having been carried out. This is also known as the Hawthorne effect (i.e. people can behave differently if they are aware of being observed).[25] As a result, the percentage of underexposed patients may be lower compared with historical data, where patients might not have been aware that their drug concentrations were being monitored. This may have played a role in the current study as well, as 27.7% of patients had a low exposure before any intervention was carried out, which is considerably lower than the 42.2% of underexposed patients in the historical data.

Physician adherence to our dosing recommendations was high. One of the reasons why treating physicians did not carry out pharmacokinetically guided interventions in some patients was a borderline low C_{min}. Ideally, however, there should be some margin between patients' exposure and the C_{min} threshold, especially because of the relatively high intra-individual variability. Therefore, pharmacokinetically guided interventions should be carried out in patients with a borderline low pharmacokinetic exposure as well, to prevent that exposure in these patients falls below the pharmacokinetic target again. Another reported reason for physicians' noncompliance to our recommendations was patients not showing response to treatment.

Strengths of the current study include the fact that it was carried out in a daily clinical care setting. For most compounds, sampling was carried out 4, 8 and 12 weeks after start of treatment, and every 12 weeks thereafter. This could easily be combined with regular visits to the outpatient clinic, to support patient compliance. Additionally, our protocol provides a framework for the nationwide implementation of pharmacokinetically guided dosing, and could be used for this purpose internationally in the future. Thirdly, we applied cost-neutral strategies to optimize exposure where possible (i.e. for abiraterone, cabozantinib and pazopanib, by splitting intake moments or concomitant intake with food). On the other hand, some limitations of the DPOG-TDM study should be kept in mind. Firstly, due to the non-randomized design, no direct control group is available. Therefore, data were compared with historical cohorts, which may differ on several aspects from the study cohorts. Most importantly, historical data often only provide the mean or median exposure over time, but do not report the percentage of patients with a low exposure at a specific time point (i.e. 12 weeks). Furthermore, data were often collected in selected patients in a clinical trial instead of a real-life setting, and treatment lines or tumor types could differ. Secondly, the applied extrapolation methods have their inherent limitations.[20] In particular, these assume an equal clearance between patients, while it is well known that the inter-individual variability in clearance is substantial, which is in fact one of the main reasons that we apply pharmacokinetically guided dosing. However, the collection of actual trough levels is not always feasible in clinical practice. As the ratio between the maximum plasma concentration (C_{max}) and C_{min} is rather low for most oral targeted therapies, the introduced imprecisions are considered acceptable. Thirdly, the distribution of included patients among the different compounds reflects the patient populations as treated in the participating centers, some of which are specialized in certain tumor types (e.g. GIST, which explains the relatively high number of patients treated with imatinib). Therefore, this distribution is not representative for the incidences of tumor types in the general population. Fourthly, lower-than-approved starting doses were used in this study for cabozantinib and sorafenib, as this is common practice in many patients. However, this limits the external validity of the results for these two drugs. Finally, the cut-off values used as pharmacokinetic targets are based upon previous literature reviews, but are not for all drugs consensual.[8,9,26-28] Figures at baseline and after pharmacokinetically guided dosing are inherently affected by the chosen targets.

In the near future, the dynamic protocol of the DPOG-TDM study will be further developed by adding new compounds, new participating centers and exploring the opportunities for international collaborations. Also, the TDM algorithms will be kept up-to-date with the available scientific evidence. More detailed data on specific cohorts will be provided as separate reports, as we previously have published for abiraterone and imatinib (complemented with other imatinib patients not participating in this study).[29,30] In the current paper, we only report on the feasibility of pharmacokinetically guided dosing. As this study demonstrated that pharmacokinetically guided dosing resulted in additional patients reaching the target exposure, it is expected that this would also result in improved clinical outcome.[31] In follow-up papers, efficacy data will be reported (i.e. with sufficient patient numbers and follow-up time, correcting/matching for heterogeneity in treatments and underlying diseases). Although randomized studies are considered the gold standard, it is questionable whether these are needed to confirm the clinical value of precision dosing in oncology.[31] For alectinib, a randomized study on TDM-guided dosing is currently planned, the results of which can then be used as a showcase for other kinase inhibitors.[32] Furthermore, when self-sampling methods would become available, these would allow patients to draw pharmacokinetic samples as soon as steady-state concentrations have been attained, in order to predict potential issues with drug exposure as soon as possible.

In conclusion, we showed that pharmacokinetically guided dose optimization of oral targeted therapies is feasible in clinical practice and it markedly reduced the proportion of underexposed patients. Over half of the patients are underexposed at a certain time point during treatment; pharmacokinetically guided interventions could

be carried out in 56.5% of them, which resulted in target attainment without additional toxicities in 74.3% of these patients. Therefore, efforts should be made to provide access to TDM for each individual patient treated with oral targeted therapies.

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DISCLOSURE

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All authors confirm that they had full access to all data in the study and accept responsibility to submit for publication.

DATA SHARING

Data from this study can be made available to other researchers in the field upon request and approval by the Dutch Pharmacology Oncology Group and subject to appropriate data transfer agreements. Requests should be directed to SLG and NS.

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