Received: 22 June 2023 | Revised: 20 September 2023 | Accepted: 22 September 2023

DOI: 10.1111/bcp.15918

ORIGINAL ARTICLE

Results of the first international quality control programme for oral targeted oncolytics

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Funding information
TUNE Project, Grant/Award Number: 11575; Dutch Cancer Society (KWF Kankerbestrijding); Dutch Foundation for Quality Assessment in Medical Laboratories (SKML), Utrecht, the Netherlands

Aims: With the rising number of oral targeted oncolytics and growing awareness of the benefits of therapeutic drug monitoring (TDM) within the field of oncology, it is expected that the requests for quantifying concentrations of these drugs will increase. It is important to (cross-)validate available assays and ensure its quality, as results may lead to altered dosing recommendations. Therefore, we aimed to evaluate the performance of laboratories measuring concentrations of targeted oral oncolytics in a one-time international quality control (QC) programme.

Methods: Participating laboratories received a set of plasma samples containing low, medium and high concentrations of imatinib, sunitinib, desethylsunitinib, pazopanib, cabozantinib, olaparib, enzalutamide, desmethylenzalutamide and abiraterone, with the request to report their results back within five weeks after shipment. Accuracy was defined acceptable if measurements where within 85%–115% from the weighed-in reference concentrations. Besides descriptive statistics, an exploratory ANOVA was performed.

Results: Seventeen laboratories from six countries reported 243 results. Overall, 80.7% of all measurements were within the predefined range of acceptable accuracy. Laboratories performed best in quantifying imatinib and poorest in quantifying desethylsunitinib (median absolute inaccuracy respectively 4.0% (interquartile range (IQR) 1.8%–6.5%) and 15.5% (IQR 8.8%–34.9%)). The poorest performance of desethylsunitinib might be caused by using the stable-isotope-labelled sunitinib instead of desethylsunitinib as an internal standard, or due to the light-induced cis (Z)/trans(E) isomerization of (desethyl)sunitinib. Overall, drug substance and performing laboratory seemed to influence the absolute inaccuracy ($F = 16.4$; $p < 0.001$ and $F = 35.5$; $p < 0.001$, respectively).

Conclusion: Considering this is the first evaluation of an international QC programme for oral targeted oncolytics, an impressive high percentage of measurements were

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within the predefined range of accuracy. Cross-validation of assays that are used for dose optimization of oncolytics will secure the performance and will protect patients from incorrect advices.

KEYWORDS

drug analysis, oncology, pharmacokinetics, therapeutic drug monitoring

1 | INTRODUCTION

Over the past few decades, the treatment landscape for patients with cancer has changed drastically with the introduction of novel targeted therapies. These novel targeted therapies can be subdivided into oral targeted oncolytics and monoclonal antibodies. While monoclonal antibodies and cytotoxic chemotherapeutic agents are given intermittently, oral targeted oncolytics are often used on a daily basis until there is no further treatment benefit. The daily use of these agents comes with new challenges like drug–drug and drug–herb interactions, but also tolerability issues due to continuous exposure to multiple low grade toxicities. Oral targeted oncolytics normally show large interpatient variability in exposure, which could lead to toxicity but also treatment failure.[1,2] One strategy to objectivate under- and overtreatment with oral targeted oncolytics is the use of therapeutic drug monitoring (TDM), by which individual dose adjustments can be made based on drug concentrations. In previous studies, both the exposure–response and toxicity–response relationships have been established for many oral targeted oncolytics.[1,3] Moreover, a recent study has proven the feasibility of pharmacokinetically guided dose optimization for oral targeted therapies.[4]

With the rising number of oral targeted oncolytics and increased awareness of the use of TDM within the field of oncology, it is expected that the number of laboratories performing TDM will increase in the coming years. Likewise, the number of requests for performing these measurements is expected to rise. This expectation is endorsed by the initiators of the Dutch national TDM project, who are investigating the feasibility of pharmacokinetically guided dosing. Ultimately, the authors are striving for a nationwide network for TDM for oral targeted therapies in which many laboratories are expected to participate.[4] Similar initiatives are the European ON-TARGET project and PREDICT programme in Australia, reflecting the worldwide interest in implementing pharmacokinetically guided dosing as a strategy for dose optimization of oral targeted therapies in clinical practice.[5,6]

Multiple laboratories around the world have developed bioanalytical assays for quantifying concentrations of oral targeted oncolytics. A variety of these methods have been published over the past years.[7–19] Ideally, all available methods are internally validated according to the guidelines for bioanalytical method validation and study sample analysis,[20–22] the goal of which is to demonstrate the performance of the bioanalytical method in terms of selectivity, accuracy, precision, dilution integrity, matrix effect and stability. To subsequently demonstrate the quality of the bioanalytical method to external parties, participation in an independent quality control (QC) programme is essential. An example of such a QC programme is the oral oncolytic QC programme of the Dutch Foundation for Quality Assessment in Medical Laboratories (SKML), which has been active since 2019.[23] Nevertheless, the included drug substances are limited to imatinib, sunitinib, desethylsunitinib and pazopanib, and the number of participating laboratories is relatively small.

As it is expected that the need for dose recommendations based on drug concentrations will be increasingly recognized, there should be sufficient laboratories worldwide able to measure these drug concentrations. Likewise, it is of great importance to (cross-)validate all available assays and ensure their quality, since dose adjustments are based on the concentrations measured. Therefore, we aimed to investigate the feasibility of extending the existing international QC programme to seven oral targeted oncolytics, and two important metabolites, for which TDM is commonly used for both clinical care and research purposes.

What is already known about this subject

- With the rising number of oral targeted oncolytics and increased awareness of the use of therapeutic drug monitoring (TDM) within the field of oncology, the number of laboratories performing TDM will increase in the coming years.
- According to the European Medicines Agency (EMA) and Food and Drug Administration (FDA) guidelines for analytical method validation and study sample analysis, cross-validation is required to demonstrate the quality of the bioanalytical method to external parties.

What this study adds

- Of all measurements 80.7% were within the predefined range of acceptable accuracy, which is impressive as this is the first report on an international QC programme for oral targeted oncolytics.
- Results of this international QC programme will give laboratories the opportunity to improve their methods when performing poorly.

2 | METHODS

2.1 | Design

The drugs that were included in this international oral targeted oncolytic QC programme were imatinib, sunitinib, pazopanib, cabozantinib, olaparib, enzalutamide and abiraterone. The metabolites desethylsunitinib and desmethylenzalutamide were additionally added. All drug substances had a high specified purity (>99%) and were obtained from certified manufacturers (Medchem Express and LC laboratories). Samples were prepared in the Radboud University Medical Centre in Nijmegen, The Netherlands. Drug-free ethylenediaminetetraacetic acid (EDTA)-plasma from healthy volunteers was obtained from the Dutch Blood Bank Sanquin® and spiked with low, medium and high concentrations of the analytes. Samples A to C contained imatinib, sunitinib, desethylsunitinib and pazopanib in concentrations covering the therapeutic range. Similarly, samples D to F contained olaparib and cabozantinib, samples G to I contained desmethylenzalutamide and enzalutamide, and samples J to L contained abiraterone. Samples were analysed using our in-house validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method as a confirmatory check before they were released into the QC programme. A deviation of <5.0% from the weighed-in (reference) concentration was considered acceptable. Hereafter, 0.5 mL samples were dispensed in vials and stored at <−20°C, a temperature at which all drugs were assessed to be stable. Samples A to I were shipped at room temperature, and samples J to L were shipped on dry ice due to the known instability of abiraterone at room temperature.[7] All laboratories receiving samples J to L received an announcement of their shipment in advance and were instructed to store the samples in the freezer directly after receipt. The stability of samples A to I at room temperature was demonstrated for at least 14 days, including three freeze–thaw cycles.[8,13,17]

The participating laboratories were asked to measure the concentrations of the included QC samples and to report their results back within 5 weeks after shipment. All participants received feedback on their performances within 6 weeks after the closing date of the programme. The performances of other participating laboratories were reported anonymised.

2.2 | Statistical analysis

Descriptive statistics were performed after standardization of all laboratory measurements to percentages relative to the weighed-in concentrations. The weighed-in concentrations were considered reference concentrations. The absolute inaccuracy was calculated using the following formula: (100 * [measured concentration/reference concentration]) – 100%. Moreover, the consensus concentrations were calculated, defined as the median measured concentrations per concentration level per oral targeted oncolytic. Accuracy of the measured concentrations was defined acceptable if measurements where within 85%–115% from the reference concentrations, as indicated in the guideline for bioanalytical method validation and study sample analysis, and maximum allowable error specifications for drug measurements defined by the United States Clinical Laboratory Improvement Amendments.[20–22] In addition, an exploratory analysis of variance (ANOVA) was performed to gain insight into the influence of several covariates on the median absolute inaccuracy. First, a univariate ANOVA was performed for the covariates drug substance, performing laboratory and drug concentration level (e.g. low, medium, high). Despite the limited number of measurements and therefore lack of sufficient power, variables with a *P*-value of <.05 were subsequently included in the exploratory multifactorial ANOVA. To control for the possibility of a type I error, we performed a Bonferroni correction after conducting the multifactorial ANOVA. We therefore divided our chosen *P*-value of .05 by the number of covariates included to obtain the corrected significance level. Statistical analyses were performed using IBM SPSS statistics 27.4.

3 | RESULTS

3.1 | Participating laboratories and descriptives

A total of 17 laboratories from six different countries, in the United States, the Pacific region and Europe, participated in this international QC programme 'oral targeted oncolytics'. Laboratories measured a median of three (range 1–7) oral targeted oncolytics in all three concentration levels. Imatinib was the most frequently measured drug ($n = 14$) and abiraterone was the least frequently measured drug ($n = 5$), as described in Table 1. All laboratories used high-performance liquid chromatographic (HPLC) or ultra-performance liquid chromatographic (UPLC) with mass spectrometry (MS) detection. Altogether, 243 measurements of drug substances were obtained, of which 80.7% ($n = 196$) were within the predefined range of accuracy. Of the 47 results outside this range, 24 were below 85% and 23 were above 115%. Overall, median absolute inaccuracy was 6.6% (interquartile range [IQR] 3.4%–12.5%). The maximum deviation between the reference concentration and the consensus concentration was 16.7%.

3.2 | Results per drug substance

The number of measurements within acceptable accuracy was the lowest for desethylsunitinib, whereas all measurements of olaparib were within the predefined range of acceptable accuracy. With respect to the median absolute inaccuracies with corresponding IQRs, laboratories performed best in measuring imatinib (4.0%; 1.8%–6.5%), followed by olaparib (4.1%; 1.1%–7.5%), desmethylenzalutamide (5.3%; 3.4%–11.8%), pazopanib (6.0%; 3.7%–11.8%), sunitinib (6.6%; 3.8%–13.3%), enzalutamide (7.6%; 4.0%–12.4%), cabozantinib (8.3%; IQR 2.8%–13.3%), abiraterone (12.0%; 10.0%–17.0%) and desethylsunitinib (15.5%; 8.8%–34.9%).

TABLE 1 Results from international QC programme oral oncolytics.

Drug	Concentration level	Reference concentration, µg/L	Relative deviation of the consensus concentration to the reference value[a] %	Number of measurements, *n*	Measured concentration relative to reference value, median % (IQR)	Absolute inaccuracy[b], median % (IQR)	Number of measurements with acceptable accuracy[c]		
							n	%	Overall %
Imatinib	low	150	0.0	14	99.3 (93.5–104.8)	5.8 (1.6–7.7)	12	85.7%	88.1%
	medium	1000	0.1	14	100.1 (95.8–104.4)	4.0 (0.7–5.6)	13	92.9%	
	high	4000	2.9	14	97.1 (94.9–101.9)	3.5 (2.1–5.0)	12	85.7%	
Sunitinib	low	8	3.3	12	96.9 (94.0–107.2)	5.6 (2.8–10.6)	10	83.3%	80.6%
	medium	50	5.6	12	105.6 (101.7–113.2)	5.6 (1.9–13.2)	9	75.0%	
	high	120	8.0	12	108.0 (101.8–114.1)	9.5 (5.9–14.1)	10	83.3%	
Desethylsunitinib	low	8	1.3	10	95.0 (80.0–146.3)	20.0 (10.6–46.3)	4	40.0%	50.0%
	medium	50	3.6	10	96.4 (86.6–137.8)	14.3 (2.7–37.8)	5	50.0%	
	high	120	9.9	10	90.1 (84.3–120.0)	14.6 (8.8–28.9)	6	60.0%	
Pazopanib	low	3000	4.0	11	104.0 (99.1–110.0)	6.0 (2.8–10.0)	9	81.8%	81.8%
	medium	20 000	2.7	11	102.7 (95.5–112.4)	5.9 (2.7–12.4)	9	81.8%	
	high	60 000	5.7	11	105.7 (94.0–109.4)	7.2 (5.7–12.8)	9	81.8%	
Cabozantinib	low	292	5.1	10	105.1 (94.5–109.2)	8.3 (3.9–10.3)	9	90.0%	90.0%
	medium	800	1.8	10	101.9 (93.2–106.6)	5.2 (3.0–12.8)	9	90.0%	
	high	2000	0.5	10	99.5 (88.5–111.3)	10.7 (1.6–14.3)	9	90.0%	
Olaparib	low	583	7.3	9	92.7 (90.3–97.2)	7.3 (2.8–9.7)	9	100.0%	100.0%
	medium	2000	5.5	9	94.5 (92.7–98.1)	5.5 (3.4–7.3)	9	100.0%	
	high	5000	0.2	9	99.8 (98.5–102.0)	0.9 (0.7–5.4)	9	100.0%	
Enzalutamide	low	1000	4.5	6	95.5 (90.9–107.9)	7.6 (5.3–10.2)	6	100.0%	83.3%
	medium	7500	0.4	6	99.6 (90.0–108.8)	7.0 (3.9–15.8)	4	66.7%	
	high	20 000	3.8	6	96.3 (85.6–105.6)	10.0 (2.9–14.4)	5	83.3%	
Desmethylenzalutamide	low	1000	1.3	4	98.8 (89.6–104.5)	5.3 (3.5–10.4)	4	100.0%	83.3%
	medium	7500	0.0	4	100.0 (85.2–109.1)	7.2 (3.4–16.7)	3	75.0%	
	high	20 000	3.1	4	96.9 (80.4–103.2)	5.8 (2.1–19.6)	3	75.0%	
Abiraterone	low	3	16.7	5	83.3 (80.0–123.3)	20.0 (13.3–28.3)	1	20.0%	60.0%
	medium	10	12.0	5	88.0 (83.0–89.0)	12.0 (8.0–17.0)	3	60.0%	
	high	60	4.0	5	96.0 (87.7–104.5)	10.5 (2.8–12.3)	5	100.0%	
Overall	-	-	-	243	99.5 (93.3–106.6)	6.6 (3.4–12.5)	196	80.7%	80.7%

Note: All numbers are medians, unless stated differently.

Abbreviation: IQR Interquartile range.

[a]100-([consensus concentration/reference concentration]*100%).

[b]100-([measured concentration/reference concentration]*100%).

[c]Acceptable measurements are within the 85%–115% limits of the reference concentrations.

3.3 | Results per concentration level

The percentages of measurements within acceptable accuracy were respectively 79.0% ($n = 64$), 79.0% ($n = 64$) and 84.0% ($n = 68$) for the low, medium and high concentration and were thus not notably different. In line, the median absolute inaccuracy with IQR was the lowest for measurements at medium concentration QCs (100.0%; 94.3%–105.8%), followed by the high QCs (99.9%; 92.2%–107.1%) and low QCs (98.2%; 92.7%–107.5%). In the median concentration level, laboratories performed best in measuring imatinib (absolute inaccuracy 4.0%) and worst in measuring desethylsunitinib (absolute inaccuracy 14.3%).

3.4 | Results per performing laboratory

Of 17 participating laboratories, four laboratories reported all measurements within the predefined range of acceptable accuracy. The results per laboratory are visualized in Figure 1. When laboratories reported multiple inaccurate measurements, this was usually the case for different concentration levels of the same drug.

3.5 | Statistical analysis

First, three univariate ANOVAs were performed to assess the effect of respectively the drug substance, concentration level and performing laboratory on the absolute inaccuracy. All models passed the Levene's test, not violating the assumption of homogeneity. Both the drug substance and performing laboratory seemed to be of influence on the absolute inaccuracy ($F = 2.9$; $P = .004$ and $F = 6.4$; $P < .001$, respectively). The concentration level did not influence the absolute inaccuracy, which was to be expected due to the little variation as described above. Subsequently, an exploratory two-way ANOVA was performed to assess the effect of the drug substance and performing laboratory on the absolute inaccuracy, as well as the interaction between both covariates. A P-value of .025 was considered to be statistically significant, due to Bonferroni correction. Similarly, this model passed the Levene's test. Both the drug substance and performing laboratory remained of influence on the absolute inaccuracy ($F = 16.4$; $P < .001$ and $F = 35.5$; $P < .001$, respectively). An interaction between these factors was observed ($F = 19.1$; $P < .001$), suggesting that the effect of these factors on the absolute inaccuracy depended on one another.

4 | DISCUSSION

In this first published evaluation of an international QC programme for the oral targeted oncolytics imatinib, sunitinib, its metabolite desethylsunitinib, pazopanib, cabozantinib, olaparib, enzalutamide, its metabolite desmethylenzalutamide and abiraterone, we show that 80.7% of all measurements passed the predefined accuracy criteria. Only the performing laboratory and drug to be analysed seemed to be of influence on the absolute inaccuracy.

These results are in line with the performance of other QC programmes for other type of drugs (e.g. antimicrobial and antifungal drugs), with 80.8% and 81.0% of measurements with acceptable accuracy, respectively, showing that the assays used for patient care and research perform generally well.[24,25] Presumably this is due to the guidelines that are available for bioanalytical method development[20–22] or due to participation bias in these QC programmes.

Over the past few years, multiple studies have shown the feasibility of pharmacokinetically guided dose optimization for the oral

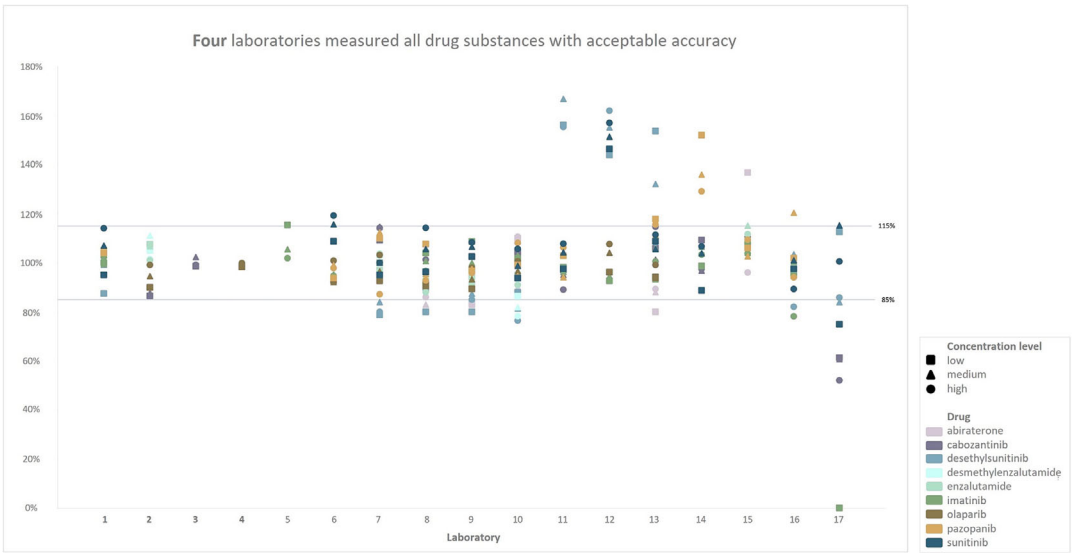

FIGURE 1 Results per laboratory per drug substance. The y-axis represents the measured concentration relative to the reference concentration in percentages. The x-axis represents the 17 different laboratories. Accuracy of the measured concentrations was defined acceptable if measurements where within 85%–115% from the reference concentrations.

oncolytics imatinib, sunitinib and pazopanib.[26,27] A recent publication by Groenland et al. demonstrated similar results in 600 patients treated with 20 different oral targeted therapies. They showed that it was feasible to reduce the proportion of patients underneath a drug-specific target by 39.0% with the use of pharmacokinetically guided dosing.[4] Due to the increased evidence for a therapeutic threshold that should be reached together with the feasibility to research this threshold, it is expected that TDM will play an increasingly important role in the individualization of cancer therapy. However, in order to reliably give dose recommendations based on plasma concentrations, laboratories should be able to accurately measure these drug concentrations. The results of this study highlight the importance of cross-validating analytical assays, especially when results are used for the purpose of dose optimization for individual patients. An example to illustrate the importance of an accurate assay is given for quantification of pazopanib and cabozantinib. Pazopanib is one of the possible treatment options in patients with metastatic renal cell carcinoma, for which a trough level of >20.5 mg/L was shown to be associated with improved efficacy.[28,29] In the current QC programme, the medium concentration level was set to a similar reference concentration of 20.0 mg/L. Although the median reported concentration was 20.5 mg/L, results ranged from 18.8 to 27.2 mg/L, which might lead to different dosing advice when used for dose optimization. The same was true for cabozantinib, for which dose advise is formulated for patients with exposure levels of <750 μg/L. The reference concentration was spiked at 800 μg/L, while the results ranged from 486 to 916 μg/L. This might have led to contrary dose recommendations, as was also described in the treatment algorithm based on measured exposure and clinical response proposed by Krens et al.[30] In contrast to pazopanib, however, no clear exposure–response relationship has been established for cabozantinib thus far and TDM is not yet routinely used for this drug.[31,32]

The overall performances seem to largely depend on the drug being analysed. This was to be expected for some of the oral targeted oncolytics of the QC programme due to their drug-specific properties. One of the drugs foreseen to perform worse was abiraterone because it is unstable in plasma at room temperature, though shipped on ice, and it adsorbs to glass materials.[7] Especially at low concentrations the loss of abiraterone was expected to result in a large deviation from the reference concentration, which was also visible in the results of this QC programme (median absolute inaccuracy 20.0%). It would thus be recommended to process the plasma sample on ice at all times and use polypropylene material in all steps of the analysis as described earlier.[7] In contrast, for pazopanib and enzalutamide, the samples in the high concentration level appeared to be measured with larger median absolute inaccuracy (7.2% and 10.0%, respectively). This might be caused by the relatively high plasma levels that are reached under pazopanib and enzalutamide treatment in comparison with other oncolytics. As a result, dimer adduct formation might occur in the MS source or saturation of the MS signal could take place, leading to less accurate results.[14,33] This is also reflected in the small number of published assays for simultaneous determination of various oral targeted oncolytics including pazopanib.[12,16,17] Most appear to have excluded pazopanib in their multidrug assays, potentially due to large concentration differences.[9,11,14,34,35] The large concentration differences can be overcome by diluting pazopanib and enzalutamide plasma samples or reducing the volume injected onto the chromatographic column. Laboratories that measured pazopanib or enzalutamide, or both, outside the predefined range of accuracy could possibly benefit from the previously described suggestions. A similar problem might explain why some laboratories had difficulties in measuring desmethylenzalutamide. For the measurement of metabolites it is preferred to use stable-isotope-labelled internal standards, even though this might be more challenging due to availability issues or high costs. In most of the assays published, the internal standards used for the quantification of desmethylenzalutamide and desethylsunitinib are deuterated enzalutamide and sunitinib, respectively.[8,10,12,18] Despite similar structural formulas between the parental compounds and metabolites, small differences could already lead to distinct MS signals and therefore less accurate and precise results. Lastly, as previously mentioned, laboratories performed worse in measuring desethylsunitinib (absolute inaccuracy 14.3%) compared to sunitinib (6.6%). Besides the above-mentioned challenge for desethylsunitinib, it has been described in literature that both sunitinib and desethylsunitinib undergo light-induced *cis(Z)/trans(E)* isomerization, resulting in two chromatographic peaks on the MS signal with potentially a different MS signal.[10,15,19] The sum of areas is used to calculate the sunitinib and desethylsunitinib concentrations but this approach might introduce more variability.

Due to the limited sample size, we performed an exploratory ANOVA, not claiming any definitive conclusions. However, both the drug substance and performing laboratory seemed to be of influence on the absolute inaccuracy. Especially the influence of the drug substance was to be expected due to the described challenges and difficulties in the quantification of some oral targeted oncolytics. Contrarily, multiple factors could cause laboratories to perform less accurately. One might think of differences in reference materials, sample (pre)treatment, quality and maintenance of equipment used in laboratories, and adequate validation of the assays.

One limitation of this QC evaluation is that not all participating laboratories were able to measure all oral targeted oncolytics. As a result, a limited number of measurements were reported for (desmethyl)enzalutamide and abiraterone. In contrast, a surprisingly high number of participants were able to quantify olaparib and cabozantinib. As there seems to be an unmet need for external validation programmes, both drugs will be included in the upcoming rounds of the SKML oral oncolytics programme (starting 2024). Besides expanding the panel with other drugs, it could be of added value to add pooled patient samples instead of spiked plasma samples only, as this could give a more accurate view on the performances of the assays in the actual matrix of the target population (e.g. patients with cancer). Another recommendation for future improvement of this QC programme could be to request more information on the used assay, for example the range of detection, own validation results and use of a uniplex or multiplex assay. Ideally, laboratories should participate in a QC programme at least once a year to confirm the performance of their assays used in daily clinical care.

5 | CONCLUSIONS

Considering this is the first report on an international QC programme for oral targeted oncolytics, an impressively high percentage of measurements were within the predefined range of accuracy. With 17 laboratories from the United States, the Pacific region and Europe, a worldwide coverage was achieved. Results from this programme will give laboratories insight and assurance on the performance of their assays which is crucial when these assays are used for dose recommendations in patients with cancer. In addition, results highlight the unmet need for adding olaparib and cabozantinib to the already existing oral targeted oncolytics QC programme, currently consisting of imatinib, sunitinib, desethylsunitinib and pazopanib.

AUTHOR CONTRIBUTIONS

Eline L. Giraud: Conception and design; data collection and interpretation; drafting of the manuscript; final approval. **Lindsey M. H. Brake** and **Ingrid M. E. Desar**: Revising the manuscript; final approval. **Erik C. A. Hombergh**: Sample preparation; revising the manuscript; final approval. **Dina M. Kweekel** and **Nielka P. van Erp**: Conception and design; data interpretation; drafting and revising the manuscript; final approval.

ACKNOWLEDGEMENTS

We kindly thank all laboratories who participated in this quality control programme. This project was part of the TUNE Project (grant no. 11575), funded by the Dutch Cancer Society (KWF Kankerbestrijding).

This study was funded by a development grant from the Dutch Foundation for Quality Assessment in Medical Laboratories (SKML), Utrecht, the Netherlands.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data generated during and/or analysed during the current study is available from the corresponding author on reasonable request.

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How to cite this article: Giraud EL, te Brake LMH, van den Hombergh ECA, Desar IME, Kweekel DM, van Erp NP. Results of the first international quality control programme for oral targeted oncolytics. *Br J Clin Pharmacol*. 2024;90(1):336-343. doi:10.1111/bcp.15918