

SHORT COMMUNICATION

Pharmacokinetically-guided dosing to improve the efficacy of brigatinib in non-small cell lung cancer patients

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Brigatinib was recently approved for the treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer and is dosed according to a one-dose-fits-all paradigm. We aimed to identify a pharmacokinetically-guided precision dosing strategy to improve treatment response with brigatinib through simulations using a previously published pharmacokinetic-pharmacodynamic model. Dosing strategies explored were the approved 180 mg QD; the highest tolerable dose tested in clinical trials: 240 mg QD; and two precision dosing strategies targeting the median trough concentrations following 180 mg QD, and 240 mg QD. We investigated the impact of alternative dosing regimens on progression-free survival (PFS), overall survival (OS) and the probability of developing a grade ≥ 2 rash or grade ≥ 2 amylase increase. Median PFS and OS increased by 1.6 and 7.8 months, respectively between the currently approved dosing strategy and precision dosing to the median trough concentration of the 240 mg dosing strategy, with only a minor increase in the probability of developing toxicity.

KEYWORDS

brigatinib, non-small cell lung cancer, pharmacokinetic-pharmacodynamic, pharmacometrics, precision dosing, simulation, therapeutic drug monitoring

1 | INTRODUCTION

Brigatinib is a recently approved drug for the treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer (ALK+NSCLC). It exerts its effect by inhibiting **ALK receptor tyrosine kinase**, **c-ros oncogene 1** and **insulin-like growth factor 1 receptor**, inhibiting downstream phosphorylation of **STAT3** and thereby inhibiting tumour growth.^{1,2} Brigatinib was approved through fast track of the Federal Drug Administration based on the results of the phase II trial in which brigatinib showed higher progression-free survival (PFS) and objective response rate in ALK+NSCLC patients with increasing exposure.³ Brigatinib was shown to significantly increase PFS in ALK+ NSCLC

patients compared to the first-generation ALK inhibitor **crizotinib**.⁴ Brigatinib is administered orally in a one-dose-fits-all paradigm, with a seven-day lead-in period of 90 mg QD, followed by 180 mg QD.¹ The highest acceptably tolerated tested maintenance dose in adults is 240 mg.⁵

From the data of the dose-finding studies, a pharmacokinetic-pharmacodynamic model has been developed, which describes the relationship between pharmacokinetics, survival and toxicity. This model showed that for the approved dosing regimen, variation in systemic exposure explains variation in survival as well as toxicity, thus indicating that brigatinib is not yet dosed in the plateau phase of efficacy.⁶ Using the pharmacokinetic/pharmacodynamic model, we aimed

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to explore dosing opportunities to improve the efficacy of brigatinib with minimal impact on safety.

2 | METHODS

We performed an *in silico* study of four different dosing strategies in a virtual population of ALK+ NSCLC patients using a previously published and validated pharmacokinetic-pharmacodynamic model.⁶ In summary, the drug's pharmacokinetics were described by a three-compartment model combined with multiple transit absorption compartments. Albumin was identified as a covariate on the clearance in the initial PK model. Interindividual variability and residual variability were also included. All relevant pharmacokinetic parameters were scaled to the apparent oral bioavailability. A parametric time-to-event model was used to describe the hazard functions for the prediction of PFS, and overall survival (OS), with brigatinib exposure and baseline target lesions as covariates for the PD model. Toxicity was described with a logistic regression function based on drug exposure. Common terminology criteria for adverse events (CTCAE) (v4.0) grade >2 rash and grade >2 amylase increase were used as toxicity parameters. Using this model, we explored the predicted efficacy and toxicity of the following dosing scenarios:

- Fixed-dose scenario 1: 90 mg QD for 7 days followed by 180 mg QD (the approved dosing regimen).
- Fixed-dose scenario 2: 90 mg QD for 7 days followed by 240 mg QD (maintenance dose at the highest clinically proven tolerable dose).
- Therapeutic drug monitoring scenario 1: 90 mg QD for 7 days, followed by a dose adaptation to 180 mg QD for 7 days, whereafter a pharmacokinetically-guided dose adaptation was made to reach the median trough plasma concentration associated with 180 mg QD at steady state.
- Therapeutic drug monitoring scenario 2: 90 mg QD for 7 days, followed by a dose adaptation to 240 mg QD for 7 days, whereafter a pharmacokinetically-guided dose adaptation was made to reach the median trough plasma concentration associated with 240 mg QD at steady state.

Trough concentrations in steady state have a strong linear relationship with the effect driving AUC during steady-state dosing. Therefore, we chose to make dose adaptations based on trough concentrations in the therapeutic drug monitoring (TDM) scenarios, as this is a commonly used and feasible pharmacokinetic endpoint in clinical practice in the target population.⁷ Dose adaptations were made after Day 14 of the treatment and the dose was rounded to the nearest dose possible with the smallest tablet size (30 mg). For doses >300 mg, the maintenance dose was rounded to 360 mg, 450 mg, 600 mg, 900 mg or 1800 mg.

For each scenario, we simulated 10 000 virtual patients with a mean serum albumin concentration of 35 g/L (coefficient of variation: 15%) and a baseline target lesion of 3.7 mm (coefficient of variation:

What is already known about this subject

- Brigatinib is a recently approved drug for the treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer and was shown to significantly increase progression-free survival compared to the first-generation drug crizotinib.
- A pharmacokinetic-pharmacodynamic model has been developed by the manufacturer that characterizes both efficacy and toxicity.
- Brigatinib is currently dosed in a one dose-fits-all paradigm.

What this study adds

- We show that the dose-response relationship of brigatinib can be optimized through pharmacokinetically guided precision dosing.

21%), based on data in the lung cancer population.⁶ We assessed the mean maintenance dose and the predicted trough concentration during the maintenance phase. Full pharmacokinetic-time profiles for all virtual patients were generated. These were used as input for the prediction of OS, PFS and for predicting the probabilities of developing a grade ≥ 2 rash or grade ≥ 2 amylase increase. Kaplan-Meier survival curves were generated for PFS and OS.

Data preparation, virtual patient population generation and, pharmacokinetic-pharmacodynamic simulations were performed in R v3.4.3 using mrgSolve v0.10.4, and RStudio v1.3 as an interface.⁸⁻¹⁰ The simulations were based on R-scripts developed by the authors of the pharmacokinetic-pharmacodynamic model of brigatinib.⁶

2.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.^{11,12}

3 | RESULTS

The predicted serum trough concentrations at steady state are presented in Figure 1. The predicted median trough concentrations of the 180 mg QD and 240 mg QD scenarios were 459.6 and 612.6 $\mu\text{g/L}$, respectively. Large variations in steady-state trough plasma concentrations were predicted in the fixed-dose scenarios with the 25th and

75th quartiles of 308.4–682.6 $\mu\text{g/L}$ and 411.2–909.3 $\mu\text{g/L}$ for the 180 mg QD and 240 mg QD dose, respectively. It can be observed that through the use of pharmacokinetically guided precision dosing, this variability can be decreased significantly with the 25th and 75th quartiles of the 180 mg QD and 240 mg QD scenarios at 434.0–517.1 $\mu\text{g/L}$ and 578.7–683.0 $\mu\text{g/L}$, respectively.

Predicted mean doses, median trough concentrations, efficacy and safety outcomes for the explored scenarios are presented in Table 1. A marginal increase in the probability to develop a grade ≥ 2

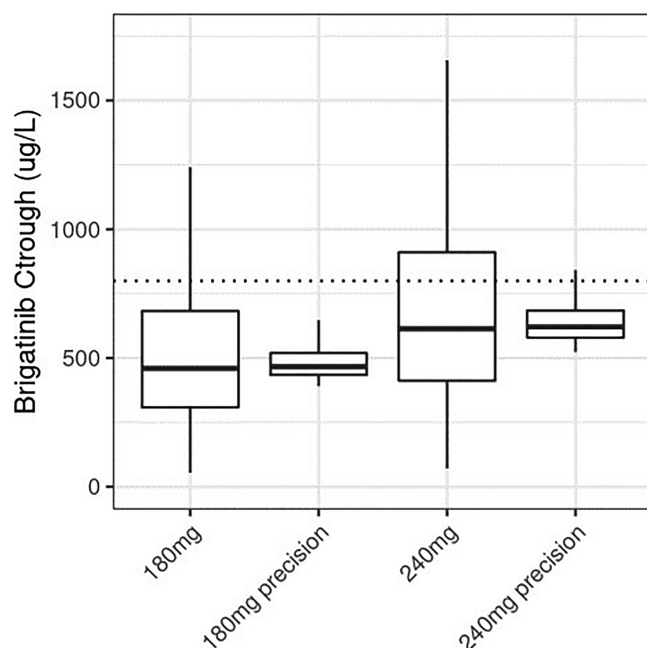


FIGURE 1 Box-and-whisker-plot of the predicted C_{trough} concentrations during steady state of the maintenance dosing phase. From left to right: 180 mg brigatinib QD, precision dosing of brigatinib to the population mean of the 180 mg QD strategy, 240 mg brigatinib QD, and precision dosing of brigatinib to the population mean of the 240 mg QD strategy. The dotted line represents the *in vitro* IC₉₀ of brigatinib (adjusted for *in vivo* protein binding) of 800 $\mu\text{g/L}$, as described in Gupta et al.¹³

rash and grade ≥ 2 amylase increase was predicted for the precision dosing strategies. The mean maintenance dose is predicted to increase using the precision dosing strategies compared to the one-dose-fits-all strategies.

Kaplan–Meier survival curves for PFS and OS are presented in Figure 2. Median PFS and OS were predicted to increase when using the precision dosing strategies compared to the fixed dosing strategies.

4 | DISCUSSION

We show that there is an opportunity to improve the treatment response of brigatinib. We show that pharmacokinetic variability can be greatly reduced and extremely high exposure can be prevented using TDM. By titrating the individual exposure to the median trough concentration of 240 mg QD, PFS, and OS can be increased by 1.6 and 7.8 months, respectively, with only a minor increase in the probability of developing additional toxicity. Because of the rapidly progressive nature of this disease, increases in survival of even weeks to months are of added value to the patients.

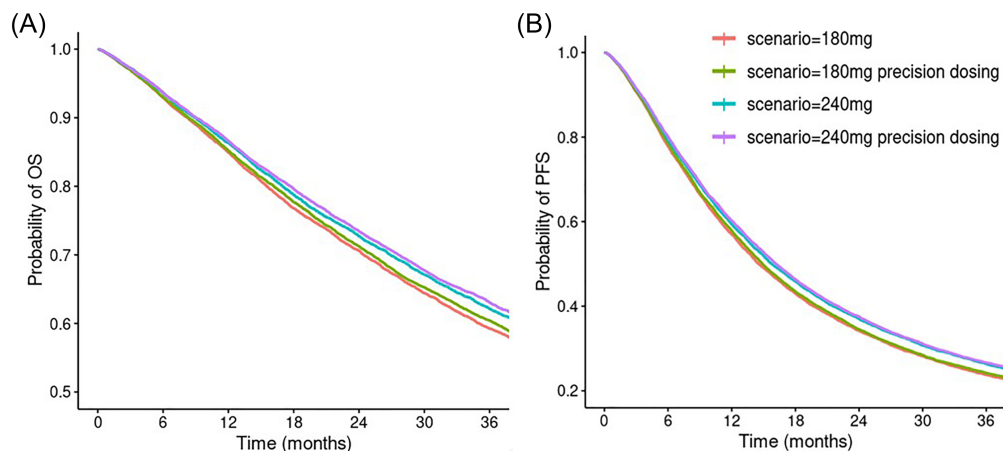
Oral anticancer drugs may show intra-individual variability in bio-availability.¹⁴ The pharmacokinetic model used in the simulations did not include intra-individual variability and, therefore, we may predict a lower variability in pharmacokinetics and pharmacodynamics than may be expected in a real-world population. Furthermore, as the scenarios evaluated in this paper were based on the summary level data and the model published by the manufacturer of brigatinib,⁶ covariate data (e.g., serum albumin or baseline target lesions) may differ in other populations, and outcomes in the real world may therefore also be different. Lastly, although we predict that the benefit-to-risk ratio may be improved by dose individualization, it should be noted that this strategy has not been tested in clinical practice. The safety and efficacy of TDM-guided dose individualization with a trough concentration of 620 $\mu\text{g/L}$ as the pharmacokinetic target should be assessed thoroughly before implementing it in routine clinical practice. Nonetheless, our findings are in line with previous suggestions by the

TABLE 1 Predicted outcome measures of the four dosing scenarios

Scenario	Mean maintenance dose (mg)	Median PFS (months)	Median OS (months)	Probability of grade ≥ 2 rash (%)	Probability of grade ≥ 2 amylase increase (%)	Median (25th–75th) trough concentration at steady state ($\mu\text{g/L}$)
Fixed dose scenario 1	180	14.6	49.4	8.7	7.5	459.6 (308.4–682.6)
Fixed dose scenario 2	240	15.8	55.3	10.3	8.8	612.6 (411.2–909.3)
Therapeutic drug monitoring scenario 1	224	14.9	51.2	8.8	7.6	464.9 (434.0–517.1)
Therapeutic drug monitoring scenario 2	305	16.2	57.2	10.5	8.9	619.8 (578.7–683.0)

PFS, progression-free survival; OS, overall survival

FIGURE 2 (A) Probability of OS under the four brigatinib dosing strategies. (B) Probability of PFS under the four brigatinib dosing strategies



manufacturer that intra-patient dose escalation to 240 mg QD may be useful to improve treatment response.³ As the exposure associated with 240 mg is the highest clinically tested safe dose, we did not investigate and propose dosing regimens that lead to higher exposures.

Lastly, we predict that on a population level, the dose has to be increased by approximately 70% compared to the approved dosing regimen to reach the target trough concentration of 620 $\mu\text{g/L}$. Considering the relatively high costs of innovative cancer drugs like brigatinib, it may be questioned whether the proposed dosing strategy is cost-effective.¹⁵ Other strategies, like pharmacokinetic boosting by deliberate inhibition of drug metabolism, may be used to enhance brigatinib exposure, without increasing the dose.¹⁶

In summary, we provide a proof of concept that the benefit–risk profile of brigatinib can be optimized through dose individualization.

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COMPETING INTERESTS

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CONTRIBUTORS

S.E.K., S.W.B. and R.T.H. conceived and designed the study. S.E.K. and S.W.B. performed the formal analysis. S.E.K. prepared the manuscript. SEK, SWB, AJW, BP, MMH, RTH were responsible for data interpretation, reviewed the manuscript and study design. R.T.H. provided supervision.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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