PET/CT-IMAGING KINETIC OF TKI OSIMERTINIB: POWER PREDICTIONS

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ABSTRACT

Inleiding: De epidermale groeifactorreceptor (EGFR) tyrosinekinaseremmer (TKI) osimertinib wordt goed verdragen en is effectief bij T790M-positieve NSCLC-patiënten. De weefselopname van osimertinib kan worden voorspeld met een fysiologisch gebaseerd farmacokinetisch model (PBPK). Het model is echter nog niet gevalideerd. In dit onderzoek berekenen we het aantal patiënten, met een power van 80%, dat nodig is voor een correcte voorspelling van gesimuleerde PK parameters en dat nodig is voor een geheel lichaam PK studie om verschil in opname in de hersenen tussen hersenmetastase (BM) en glioblastoma (GBM) patiënten te detecteren en voor modelvalidatie.

Methode: Met behulp van 200 Monte Carlo simulaties werd het PK-profiel van osimertinib in bloed en weefsels voorspeld na dosering van 80 mg iedere 24 uur gedurende 7 dagen. Voor elke patiënt werden de patiëntkarakteristieken genomen uit een normale verdeling, waarbij de variabiliteit in klaring (CL) en distributievolume (V) respectievelijk 20,8% en 26,8% was. De hersenpenetratie (RPT) was 25% groter in de GBM groep dan in de BM groep als gevolg van verstoring van de bloed-hersenbarrière (BBB). De powerberekening voor de PK-parameters is gebaseerd op de methode van Ogungbenro et. al, werd uitgevoerd in NONMEN en gevisualiseerd in R (pakket ggplot).

Resultaten: Het NONMEM model gaf individuele PK parameters die werden gebruikt voor de powerberekeningen. Wanneer 29 patiënten worden geïncludeerd, kunnen PK-parameterschattingen (CL en V) worden geschat met een nauwkeurigheidsniveau van 20% en een power >80%. Indien in de PK studie 19 patiënten worden geïncludeerd, is de power 80% om een minimaal effect van een 1,25-voudig verschil in biomarkerprestatie tussen primaire en metastatische patiënten te detecteren.

Conclusie: De powerberekeningen gaven het aantal patiënten dat nodig is voor een correcte voorspelling van PK parameters en voor een nieuwe PK studie. De powerberekening voor PK-parameters zorgt ervoor dat de gesimuleerde PK-parameters beter overeenkomen met de werkelijkheid. In de toekomst kunnen de berekeningen worden gebruikt voor andere onderzoeken.

Introduction: The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) osimertinib has shown to be well-tolerated and effective in T790M-positive NSCLC patients. The tissue uptake of osimertinib can be predicted with a physiologically-based pharmacokinetic model (PBPK). However, validation of the model is necessary. In this research, we aim to calculate the number of patients, with a power of 80%, required for correct prediction of simulated PK parameters and required for a whole body PK study to detect difference in brain uptake between brain metastasis (BM) and glioblastoma (GBM) patients and for model validation.

Methods: Using 200 Monte Carlo simulations, the PK profile of osimertinib in blood and tissues was predicted after dosing 80 mg every 24 hours for 7 days. For each patient, patient characteristics were taken from a normal distribution, where variability in clearance (CL) and distribution volume (V) were 20.8% and 26.8%, respectively. Brain penetration (RPT) was 25% greater in the GBM group than in the BM group due to disruption of the blood brain barrier (BBB). The power calculation for the PK parameters is based on the method of Ogungbenro et. al, was performed in NONMEN and visualized in R (package ggplot).

Results: The NONMEM model gave individual PK parameters that were used for power calculations. When 29 patients are included, PK parameter estimates (CL and V) can be estimated with an accuracy level of 20% and power >80%. If 19 patients are included in the PK study, the power is 80% to detect a minimal effect of a 1.25-fold difference in biomarker performance between primary and metastatic patients.

Conclusion: The power calculations gave the number of patients needed for correct prediction of PK parameters and for a new PK study. The power calculation for PK parameters ensures that the simulated PK parameters better match reality. In the future, the calculations could be used for other studies.

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INTRODUCTION

With an estimate of 2.2 million new cases and 1.8 million deaths each year, lung cancer is the main cause of cancer-related mortality worldwide.(1) Besides lung cancer, the prognosis of primary and secondary brain tumors such as glioblastoma (GBM) and brain metastases (BM) of breast cancer (BC-BM) or Non-Small Cell Lung Carcinoma (NSCLC-BM) is grim, with median overall survival of only 16 and 13 months respectively.(2, 3) The treatment of these types of cancer changed over the past decades. Where in the past, cancer was mostly treated with chemotherapy, currently cancer is treated with more effective and better tolerated target therapies against specific oncogenic driver pathways.(4) In NSCLC, the most common oncogenic driver pathway is the epidermal growth factor receptor (EGFR) pathway.(4) The EGFR pathway regulates growth, survival, proliferation and differentiation in mammalian cells.(5) An activating mutation in the kinase domain of the receptor can lead to ligand-independent activation.(6, 7) EGFR activation leads to the excitation of subsequent intracellular signaling pathways, such as the PI3K/Akt and MAPK. Tyrosine kinase inhibitors (TKIs) inhibit the intracellular ATP-binding pocket in the kinase domain and effectively inhibit the EGFR pathway by inhibiting the downstream signaling.(4, 8) Three generations of EGFR-TKIs are approved. The first generation binds reversibly to wild-type EGFR. The second generation binds irreversible to the wild type EGFR receptor. Despite superior survival in NSCLC patients using the first or second generation EGFR-TKIs over conventional chemotherapy, drug resistance generally develops in less than a year.(4, 9) Requiring mutations like EGFR T790M mutation is the mechanism behind the resistance in half of the cases.(10, 11) The third generation binds irreversible to the mutated T790M EGFR receptor and to a lesser extent to the wild type. Osimertinib, the drug of interest in this research, is a third generation EGFR TKI and has shown to be well-tolerated and effective in T790M-positive NSCLC patients.(4, 12, 13)

The bio distribution of small molecules such as EGFR TKIs, can be described using physiologically-based pharmacokinetic models (PBPK). PBPK modeling combines drug specific parameters (pKa, logP, target affinity) with system specific parameters of different organs and tissues (blood flow, pH, target abundance) and disease (e.g. acidity of the tumor microenvironment). At the Amsterdam UMC, a PBPK model has recently been developed, with the aim to predict positron emission tomography (PET) image quality and the population whole-body distribution of three generations of radiolabeled EGFR-TKI tracers in advanced stage NSCLC patients (14). The model needs evaluation and validation which can be done by comparing the PBPK model predicted tissue uptake with actual PET image derive patient tracer tissue uptake. The validation is needed for both microdose and therapeutic dose, because tumor uptake (penetration) of a low dose of radiolabeled TKIs may differ from that at the therapeutic dose. Enzymes involved in metabolism and TKI binding, EGFR-binding and drug-specific transporter may become saturated at therapeutic doses, while this is less likely to present at micro doses saturation.(15) Therefore, if a PET/CT is executed with radiolabeled micro doses, the involvement of non-linear processes can result in PK characteristics that differ from those observed at therapeutic doses, especially for small molecules with a high affinity for their target. In addition, Osimertinib shows high inter-patient variability on PK.(16, 17). Therefore, a better knowledge of the variability in PK may provide more insight into the exposure-response relationships and the inter-individual variability (IIV). Prior knowledge on PK can be used as priors in a simulation study to determine how many patients are needed to correctly predict correct PK parameters with a power of 80% in a new clinical PK-study.(18) This knowledge may lead to greater understanding of drug efficacy and contribute to the potential development of individualized dosing regimens. If the model is validated, it could be used to predict the whole body distribution of osimertinib and other TKIs and it could characterize variability between drug uptake.

EGFR is overexpressed in > 50% of glioblastoma (GBM) patients. (4, 19, 20) Therefore, EGFR TKIs are good candidates for more targeted therapies provided that the drugs sufficiently cross the BBB. The third generation EGFR TKI osimertinib showed high BBB penetration, improving the overall survival from 22.2 to 37.7 (osimertinib vs placebo) in NSCLC-BM patients.(21-25) The brain vasculature differs between healthy brain tissue and tumorous brain tissue. In particular, GBM is a highly angiogenic and infiltrative tumor. Previous

studies shows that prior to treatment, GBM patients have a more disrupted BBB compared to healthy volunteers or metastatic patients.(26-28) In addition, the heterogeneity of EGFR drug exposure in the tumor has not yet been characterized for osimertinib. To characterize this and to validate the PBPK model, a PK-trial of osimertinib in GMB is going to be set up at the Amsterdam UMC. This study contains 3 aims: 1) Investigate the predictive value of microdosed TKI-tracer PET imaging kinetics and MRI imaging data for therapeutic PK, 2) quantify and predict sources of variability in brain tumor penetration and 3) develop a precision dosing algorithm to improve patient outcomes.

A power analysis helps to select the number of patients needed to adequately predict the (variability in) the whole body PK of osimertinib in a new clinical PK-trial. The statistical power calculation indicates how presumably it is that the study will produce a statistically significant result and is performed to determine the number of individuals to detect the effect of a covariate.(29, 30) When testing a hypothesis, data is used to decide if there is enough evidence to reject the null hypotheses. The null hypotheses states that there is a 25% difference in drug brain penetration between two research groups, GBM and BM, and when it is rejected, there is no significant difference between the two research groups. To perform a statistical power calculation, first acceptable levels for p-value (α) and the power must be set.(31) P-value, often called significance, is the probability that the null hypotheses is unjustifiably rejected and is typically 0.05.(30, 31) The power is the ability to correctly reject the null hypothesis and is typically 0.80.(29-31) Another important value is the effect size. Unlike the significance and power, the effect size is determined by the outcome of a variable of interest rather than being set by researcher. Effect size is the difference in osimertinib uptake in the brain and is an intrinsic characteristic of the study population; it measures the strength of an observation.(31) When the power of a study is too low, it is possible that the outcome of the study is not statistically significant, even though there is an clinically relevant effect. When an overly large sample size is used, the power is likely to be very high, but the study may be over expensive and unethical. (30) Therefore, it is really important that osimertinib study has a good power and a correct sample size.

The aim of this research project is to define how many patients are needed to achieve a power of 80% in a new PK study to adequately predict the variability and population whole body PK and to detect a difference in tumor drug uptake in the brain between GBM and BM patients. This research will be used to expand and understand the PBPK of TKIs in tumor and healthy tissues and for power calculations in the future.

METHODS

DATASET AND PRIORS

A simulation consisted of 80mg oral dose of osimertinib given every 24 hours for 7 days. For each patient, patient characteristics were sampled from a normal distribution with a mean of 1.8 m^2 and sd of 0.1 for body surface area (BSA), 35 g/L and sd of 0.3 for albumin (ALB) and 70kg and sd of 10.0 for body weight (BW).

A PK model characterized the variability in osimertinib concentrations in the brain between GBM and BM patients within a patient population. Penetration into the brain, plasma to tissue constant (KPT), was predicted using brain-to-blood ratios derived from PET images.(32) Inter individual variability is concluded for clearance, distribution volume, KPT and RPT. Proportional error for both tumor and plasma and additive errors were added for the (unexplained) residual variability (table 1).

To calculate the predicted PK/PD parameters of osimertinib, the patients were divided into two groups (1:2); group 1 = GBM patients, group 2 = NSCLC-BM and BC-BM patients based on difference in blood-tumor barrier permeability and tumor blood volume.(28, 33) The brain vasculature differs between healthy brain tissue and tumorous brain tissue. In particular, GBM is a highly angiogenic and infiltrative tumor. Cells invade along blood vessels to support tumor growth (co-option), resulting in disruption of the blood-brain-barrier (BBB).(27, 34) The disruption may lead to enhance drug penetration into the brain in diagnosed GBM patients. A study in rats showed a 25 to 6 times higher uptake in GBM in the tumor than in the surrounding tissue.(26) It is not known yet how severely the BBB is disrupted in humans. For the new study therefore, a conservative scenario is selected for the degree of BBB disruption in humans. The disruption of the BBB is expected to result in a 25% higher plasma tissue ratio (RPT) in GBM compared with the NSCLC-BM and BC-BM group.(28)

Concentrations above the in vitro derived unbound half-maximal inhibitory concentration (IC50) indicate sufficient cellular inhibition. Therefore, we examined whether the osimertinib concentration predicted by the model exceeded the IC50 values of osimertinib for different EGFR mutations. These results indicate whether and how many GBM and BM patients may respond to osimertinib. The most common EGFR mutation in GBM is the in-frame deletion of exon 2-7, called EGFRVIII. This type of mutation occurs in 50% of GBM cases with EGFR amplification.(35) Another common EGFR mutation is exon19del, which occurs in 50% of patients with NSCLC.(36) The IC50 values given in Table 1 are after accounting for the unbound fraction.(37) Published population plasma PK model of osimertinib is derived from literature as described in Table 1.(32, 37-40)

Table 1: Population PK parameters

Parameter	Osimertinib 80mg QD for 7 days in 20 patients Median value (95%CI)	Inter-individual variability
Clearance (L/h)	14.2 (13.9-14.5)[1]	0,207936[1]
Volume of distribution (L)	986 (±28)[1]	0,268324[1]
CMAX (nM/L) plasma & brain	501[1]	-
Ctrough (nM/L) plasma & brain	417/199[1]	-
AUC (nM*h/L) plasma / brain	12802 (5524-26140) [1]	-
Ka (1/h)	0,24[1]	-
KPT	0,79[2]	0,25[1]
RPT	Group 1: 3,03 Group 2: 3,7875[2]	0,1[1]
Proportional error plasma	0,244[1]	-
Proportional error tumor	0,244[1]	-
Additive error	0,105[1]	-
IC_{50} EGFRVIII (nM)	943,396[3,4]	-
IC_{50} exon19del (nM)	149,0567[3,5]	-

PK= pharmacokinetics, CMAX = maximum concentration, AUC = average area under the concentration time curve per day at steady state, Ctrough = concentration before the next dose (24 hours after the last dose at steady state), Ka= absorption rate constant. KPT = plasma to tissue constant. RPT = plasma to tissue ratio. 1 = Brown et. al, 2 = Bartelink et. al, 3 = chagoya et. al, 4 = SMPC osimertinib, 5 = Masuzawa et. al.

Model development, analysis and simulation were performed in R (version 4.0.3, https://www.r-project.org/) using the Rstudio development environment (version 1.3.1093) and NONMEM (version 7.4.2 and Perl-Speaks-NONMEM (PsN) version 5.3.0, Piraña version 3.0.0 was used as interface platform for NONMEM and PsN). The R-scripts are stated in the appendix. A linear structural model with two compartments was investigated. Clearance was calculated as:

1. $$\theta CL = 14{,}2 * (BSA/1.8)^{0.56} * (BW/70)^{0.99}$$

Where θCL is population osimertinib clearance, BSA is body surface area (m^2) and BW is bodyweight (Kg).

Distribution volume is linearly influenced by ALB and BW as:

2. $$\theta V = 986 * (ALB/35)^{1.33} * (BW/70)^{0.65}$$

Where θV is the population distribution volume of osimertinib. ALB is albumin (g/L) and BW is body weight (kg).

Inter-individual variance was modelled as a lognormal distribution on the parameters:

3. $$P_i = \theta_p * \exp(\eta_i)$$

Where P_i is the individual parameter estimate, θ_p is the typical parameter value and η_i is the individual's deviation from the typical value. η is derived from a normal distribution with mean 0 and variance ω^2. RUV was modelled via a combinational error structure as:

4. $$Obs_{i.j} = Pred_{i,j} * (1 + \varepsilon_{ij}) + \varepsilon_{ij}$$

Where $Obs_{i,j}$ is the observed osimertinib concentration at time *j* for individual *i,* $Pred_{i,j}$ the model predicted osimertinib concentration at time *j* for individual *i*, and ε derived from a normal distribution with mean 0 and variance σ^2.

The unit of IC50 is nM, therefore the simulated concentration should also be in nM. This is calculated with the following equation:

5. $(V1/1000000) * (mW) = nM$

Where V1 is the volume in L and mW the molecular weight in g/moll. The molecular weight of osimertinib = 499,6 g/moll.(41)

POWER CALCULATIONS

We performed a power calculation to calculate the number of patients needed in the simulations to correctly predict population PK parameters with a power of 80%. This calculation was based on the method described by Ogungbenro et. al. and conducted for the PK parameters clearance and volume of distribution.(18) Calculations to obtain the precision limits were made on the log-transformed parameters estimate as:

6. $\mathrm{LW\_LIM_p} = \ln(0.8) + \theta'$
7. $\mathrm{UP\_LIM_p} = \ln(1/0.8) + \theta'$
8. $\Delta_p = \mathrm{UP\_LIM_p} - \mathrm{LW\_LIM_p}$

Where $\mathrm{LW\_LIM_p}$ is the lower limit of the precision interval, θ' is the ln-value of the true estimate of the parameter, $\mathrm{UP\_LIM_p}$ is the upper limit of the precision interval and Δ_p is the precision interval.

Different group sizes were simulated 200 times to acquire different values for the PK parameters. Calculations to obtain the 95% confidence interval were made on the log-transformed parameters estimate as:

9. $\mathrm{LW\_LIM_{CI}} = \theta\text{^} - (1.96*\mathrm{SE}(\theta\text{^}))$
10. $\mathrm{UP\_LIM_{CI}} = \theta\text{^} + (1.96*\mathrm{SE}(\theta\text{^}))$
11. $\Delta_{CI} = \mathrm{UP\_LIM_{CI}} - \mathrm{LW\text{-}LIM_{CI}}$

Where $\mathrm{LW\_LIM_{CI}}$ is the lower limit of the confidence interval, θ^ is the ln-value of the simulation estimate of the parameter, SE is the standard error of θ^, $\mathrm{UP\_LIM_{CI}}$ is the upper limit of the confidence interval and Δ_{CI} is the 95% confidence interval.

The equation to calculate the power is described as:

12. $\mathrm{Power} = \text{fraction of simulations where } \Delta_{CI} \leq \Delta_p$

The power is the fraction of the simulations where the 95% confidence interval is equal or greater than the prediction interval. The power calculation was performed using Monte Carlo simulations of 200 studies with 10 - 56 patients.

To detect a differences between GBM/BM, a two-tailed unpaired t-test was used to compare the mean concentration at steady state in the brain between two normally distributed groups: GBM versus BM.(42).

RESULTS

Overall PK results of osimertinib in plasma and brain tissue over a dose interval of 7 days are shown in Figure 1. The plot shows much greater uptake in brain compared to blood and it shows an increase in variability in penetrance in the brain.

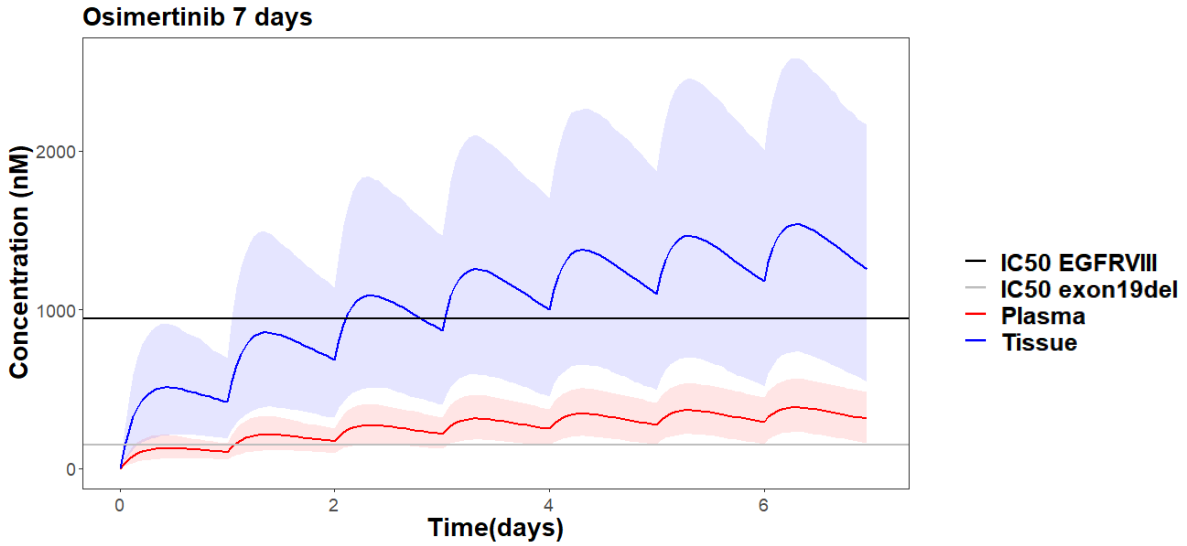

Figure 1: Predicted median and variability (CI95%) in therapeutic concentration-time upon one week dosing of osimertinib compared to relevant in vitro derived IC50 values

Power calculation described by Ogungbenro et. al. to calculate the number of patients needed in a new study to correctly predict population PK parameters with a power of 80%.

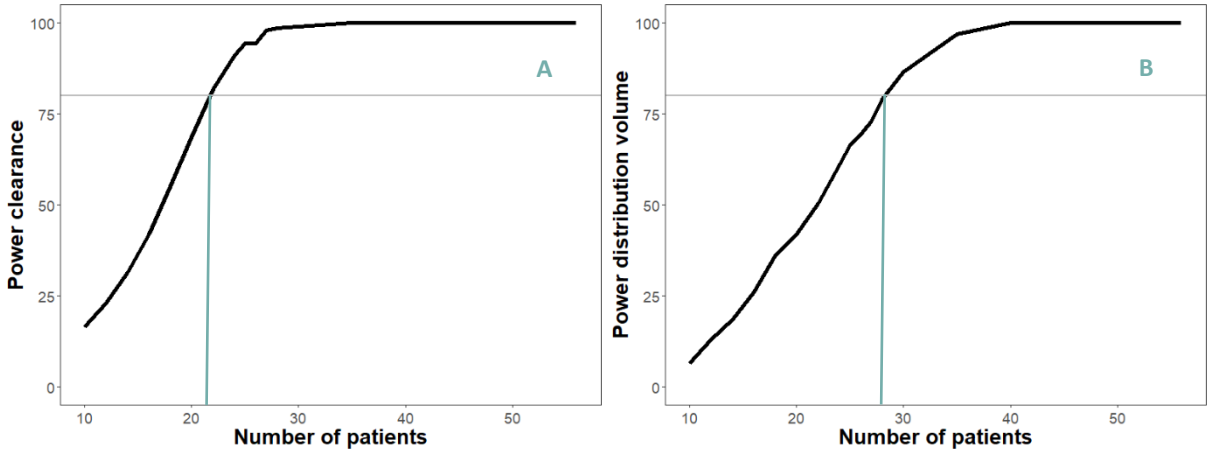

Figure 2 Power plot PK for (A) clearance and (B) distribution volume

As shown in figure 2A, it is necessary to simulate 21 patients for a correct prediction of the PK parameter clearance. As shown in figure 2B, it is necessary to simulate 29 patients for a correct prediction of the PK parameter distribution volume. Therefore, 29 patients were used for follow-up calculations and determinations.

For the calculation of the predicted PK/PD parameters of osimertinib, the mean and confidence interval were calculated (Table 2a). The Monte Carlo simulations showed that the using the current PK-model, osimertinib Ctrough during a 80 mg QD dosing would be above the target concentration in 33.3% of NSCLC-BM patients and 72.8% GBM patients with an disrupted BBB (Table 2b).

Table 2: Predicted plasma and brain tumor PK in clinical study of 29 patients (38, 43)

	Osimertinib 80mg QD for 7 days in 29 BM & GBM patients
a) PK parameter	Median value (95%CI)
Clearance (L/h)	BM: 15.72 (10.23-35.25) GBM: 15.69 (10.31-35.30)
Volume of distribution (L)	BM: 1137 (695-2778) GBM: 1124 (680-2752)
RPT	BM: 3.52 (2.66-6.40) GBM: 3.98 (3.07-6.97)
Ctrough (nM) plasma; brain	BM: 378 (258-793); 1326 (793-3278) GBM: 376 (255-756); 1489 (914-3530)
AUC (µM*h/L) brain	BM: 184886 (115289 – 437250) GBM: 209020 (133473-466610)
b) PD prediction	Median number BM & GBM patients (95%CI)
Ctrough > IC50	BM: 33.3% GBM: 72.8%

PK= pharmacokinetics, RPT = the brain to plasma ratio, Ctrough = concentration before the next dose (24 hours after the last dose at steady state), AUC = average area under the concentration time curve per day at steady state, PD= pharmacodynamics and IC50 = half-maximal inhibitory concentration.

In addition to the calculated values, a density plot was made to show the difference between the two osimertinib groups; BM and GBM(38). This is shown in figure 3. As expected, there is a clear difference between the two groups. The BM group has a higher and narrower peak than the GBM group.

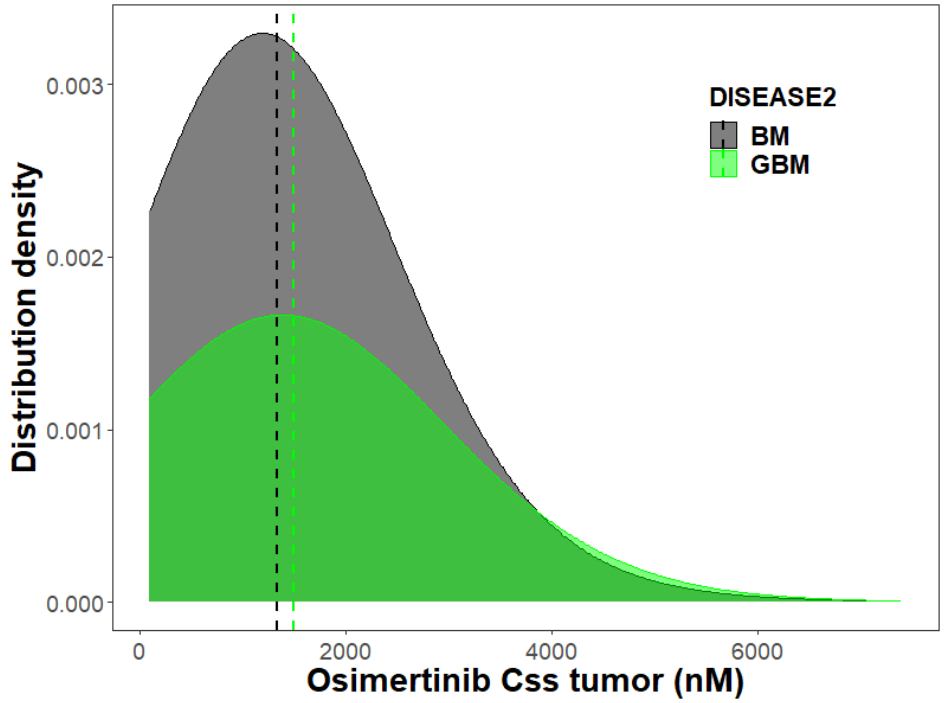

Figure 3: Distribution density Css tumor between BGM and BM.

After the calculation of the predicted PK/PD values and the visualization of the density plot, the power calculation for the new whole body PK trail could be performed. The result is shown in figure 4.

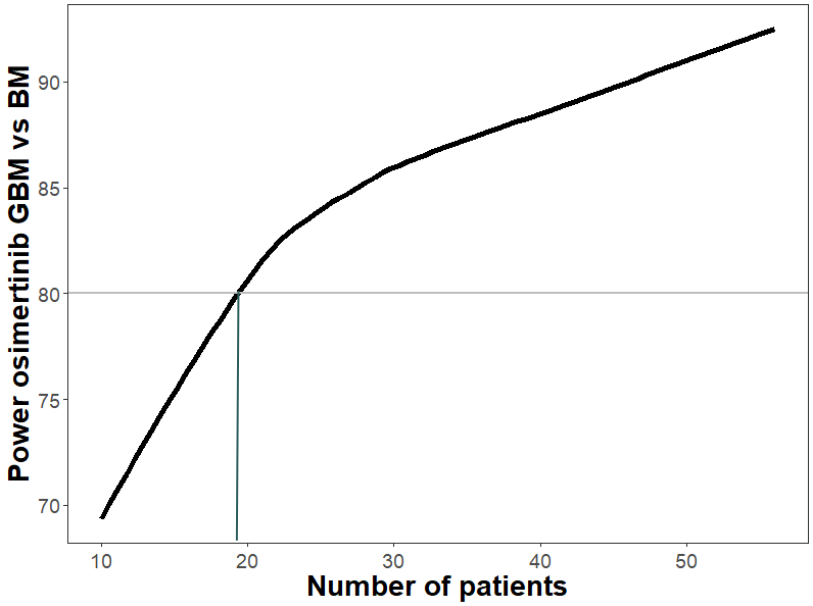

Figure 4: The study power to detect a significant difference between GBM and BM

If 19 patients are included there will be 80% power to detect a minimum effect size of a 1.25-fold difference in biomarker performance among primary and metastatic patients (i.e. OR ratio associated with linear 25% increase in drug brain penetration).

DISCUSSION

The power calculations in this study were performed to calculate the number of patients, with a power of 80%, required for correct prediction of simulated PK parameters and required for a population whole body PK study to detect a difference in tumor drug uptake in the brain between GBM and BM patients. With the calculation of the PK parameters, an estimate has been made of what the observed PK parameters will be if a study is conducted.(29, 34) With the calculation for the population whole body PK study, a new study can be set up whose results to detect a difference in tumor drug uptake in the brain GBM and BM patients. The study can also be used for validation of the PBPK model.(18-20) If validated, the model could eventually be used to predict the whole-body distribution of osimertinib and other TKIs.

Prior knowledge of PK was used to predict whole body PK. The population PK model is this study is currently simplified with uptake in blood and brain, due to the main interest in the difference in brain uptake between GBM and BM patients. The power calculation described by Ogungbenro et. al. was used to calculate the number of patients needed in a new study to correctly predict population PK parameters with a power of 80%. These calculations showed that the new study should include 21 patients for correct prediction of PK parameter clearance and 29 patients for distribution volume. It was expected that more patients were needed for correct prediction of distribution volume because there is more variability in this parameter between patients. 29 patients were used for follow-up calculations and determinations. In this study, we made an assumption about the RPT. Studies have shown that the BBB is disrupted in GBM patients. This leads to higher RPT in GMB patients compared to BM patients, which is also reflected in the results of predicted RPT.(25) It is not known how severe the BBB is disrupted, so further research will need to show this. It may be possible to demonstrate this in the whole body PK trial. For this study, it is assumed that the disruption leads to 25% RPT increase in the GBM group.(28, 33) However, if this is actually higher or lower, this will also affect the power calculations. Fewer patients are required when the RPT increases more than 25%, while more patients are required when the RPT increases less than 25%. An unexpected outcome is the Ctrough>IC50. Osimertinib is registered for NSCLC-BM, therefore we would expect the Ctrough>IC50 to be higher for the BM than for the GBM group. Osimertinib is not registered for GBM so it is possible that the predicted values for the GBM group do not match values from the literature, which will also effect Ctrough>IC50.(37) Therefore, the results from the whole body PK clinical trial will show whether the predictions are correct. The power calculation for the new whole-body PK trail showed that with inclusion of 19 patients, there will be 80% power to detect a minimum effect size of a 1.25-fold difference in biomarker performance between primary and metastatic patients (i.e. OR ratio associated with linear 25% increase in drug penetration into the brain). To conclude, a minimum of 29 patients must be included in the new whole body pk trial for proper estimation of both PK parameters and difference in osimertinib uptake between GBM and BM patients in the brain.

For clinical practice, this study demonstrates the importance of performing calculations and simulations prior to a study so that prior knowledge can be used to predict the PK for a new study. This knowledge and the number of patients deemed necessary for outcomes can be incorporated into the study design.

The population PK model is currently simplified and primarily focused on blood and brain. In the future, we want to extend this to off-target binding to receptors and toxicity, allowing us to make predictions for the individual patient. A power calculation to determine the number of patients to be simulated before determining PK parameters from simulations is an important step that can be extended to future clinical PK studies. This will allow the simulated PK parameters to better match the parameters that will be determined using new clinical trials and the optimal number of patients to be included. Furthermore, better knowledge of the PK can provide more insight into exposure-response relationships and the IIV. This knowledge may lead to greater understanding of drug efficacy and contribute also to the possible development of individualized dosing regimens.

CONCLUSION

To conclude, the aim of this research project is to determine the number of patients needed to achieve a power of 80% in a new PK study to adequately predict the variability and population whole body PK and detect a difference in tumor drug uptake in the brain between GBM and BM patients. When 29 patients are included, PK parameter estimates (CL and V) can be estimated with an accuracy level of 20% and power >80%. When 19 patients are included, there will be 80% power to detect an effect of a 1.25-fold difference between GBM and BM patients. Therefore, in the new PK study, 29 patients should be included.

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APENDIX

Available on request