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ARTICLE

Translational pharmacokinetic-pharmacodynamic modeling of preclinical and clinical data of the oral MET inhibitor tepotinib to determine the recommended phase II dose

Wenyuan Xiong[1] | **Manja Friese-Hamim**[2] | **Andreas Johne**[2] | **Christopher Stroh**[2] | **Manfred Klevesath**[2] | **Gerald S. Falchook**[3] | **David S. Hong**[4] | **Pascal Girard**[1] | **Samer El Bawab**[2]

[1]Merck Institute of Pharmacokinetics (an affiliate of Merck KGaA, Darmstadt, Germany), Lausanne, Switzerland

[2]Merck KGaA, Darmstadt, Germany

[3]Sarah Cannon Research Institute at HealthONE, Denver, Colorado, USA

[4]MD Anderson Cancer Center, Houston, Texas, USA

Correspondence
Samer El Bawab, Translational Medicine, Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany.
Email: Samer.Elbawab@merckgroup.com

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Abstract

Tepotinib is a highly selective and potent MET inhibitor in development for the treatment of patients with solid tumors. Given the favorable tolerability and safety profiles up to the maximum tested dose in the first-in-human (FIH) trial, an efficacy-driven translational modeling approach was proposed to establish the recommended phase II dose (RP2D). To study the in vivo pharmacokinetics (PKs)/target inhibition/tumor growth inhibition relationship, a subcutaneous KP-4 pancreatic cell-line xenograft model in mice with sensitivity to MET pathway inhibition was selected as a surrogate tumor model. Further clinical PK and target inhibition data (derived from predose and postdose paired tumor biopsies) from a FIH study were integrated with the longitudinal PKs and target inhibition profiles from the mouse xenograft study to establish a translational PK/pharmacodynamic (PD) model. Preclinical data showed that tumor regression with tepotinib treatment in KP-4 xenograft tumors corresponded to 95% target inhibition. We therefore concluded that a PD criterion of sustained, near-to-complete (>95%) phospho-MET inhibition in tumors should be targeted for tepotinib to be effective. Simulations of dose-dependent target inhibition profiles in human tumors that exceeded the PD threshold in more than 90% of patients established an RP2D of tepotinib 500 mg once daily. This translational mathematical modeling approach supports an efficacy-driven rationale for tepotinib phase II dose selection of 500 mg once daily. Tepotinib at this dose has obtained regulatory approval for the treatment of patients with non-small cell lung cancer harboring *MET* exon 14 skipping.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Phase II dose selection in solid tumor indication is mostly driven by preclinical pharmacodynamic (PD) and efficacy data and phase I toxicity/tolerability data.

WHAT QUESTION DID THIS STUDY ADDRESS?

A translational modeling approach integrating preclinical pharmacokinetic (PK) and PD data, along with clinical population PK and PD data in tumor biopsies, was adopted to establish a recommended phase II dose for tepotinib.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Tepotinib is one of the very few kinase inhibitors (or even of any drug class) in solid tumor indications that has a dose selected based on solid quantitative pharmacologic rationale to target nearly maximum target inhibition, with iterative translational modeling.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This study provides a case study showing the value of iterative translational modeling approach, which integrates preclinical and FIH PK and target modulation data to guide phase II dose selection of a kinase inhibitor in a solid tumor indication. The recommended tepotinib 500 mg once-daily dose has been approved for treating *MET*ex14-altered non-small cell lung cancer in Japan based on its promising efficacy and safety profiles.

INTRODUCTION

MET is a receptor tyrosine kinase encoded by the MET proto-oncogene. Binding of hepatocyte growth factor (HGF), the only ligand of MET, to the receptor results in dimerization and transphosphorylation of MET, leading to the activation of intracellular signaling cascades including the Ras/ERK and P13K/Akt pathways.[1–3] Dysregulated MET activity due to MET gene mutation or amplification, or overexpression of MET/HGF, can drive tumorigenesis, including lung cancer, hepatocellular carcinoma, and renal carcinoma.[4–8] Increased MET activity in tumors promotes mitogenesis, cell survival, adhesion, angiogenesis, motility, and invasion, and is associated with poor prognosis, an aggressive phenotype, and increased metastasis.[1–3,9–13] MET is therefore considered an attractive molecular target for anticancer therapies.

Several tyrosine kinase inhibitors (TKIs) with activity against MET are being evaluated in clinical trials. The multikinase inhibitors cabozantinib and crizotinib inhibit other tyrosine kinase receptors in addition to MET and are associated with a variety of side effects.[14–16] The HGF antagonists onartuzumab and rilotumumab inhibit only HGF-dependent MET activation, so they may have limited efficacy in tumors with HGF-independent MET activity.[17,18] In contrast, selective MET TKIs can inhibit both HGF-dependent and HGF-independent MET activation and are more likely than other types of agent to achieve full MET inhibition at clinical doses.[19,20]

Tepotinib (MSC2156119J) is an orally available, reversible, ATP-competitive, highly selective, and potent MET TKI that has demonstrated antitumor activity in preclinical xenograft tumor models and cancer explants[21–24] and has been approved in Japan for patients with *MET* exon 14-altered non-small cell lung cancer (NSCLC; 500 mg once daily).[25]

In a first-in-human (FIH) trial of safety, tolerability, pharmacokinetics (PKs), and pharmacodynamics (PDs) in patients with solid tumors (NCT01014936), tepotinib was well-tolerated up to the maximum tested dose of 1400 mg once daily, but the maximum tolerated dose (MTD) could not be defined.[26] The primary objective of this investigation was to use translational PK/PD models[27,28] to integrate preclinical and clinical data[29,30] of tepotinib and its major circulating metabolite MSC2571109A to select the recommended phase II dose (RP2D) of tepotinib that would achieve target modulation corresponding to preclinical efficacy in the patient population. The RP2D was determined by establishing mathematical models to describe the relationship between PK/MET inhibition (reduction in phospho-MET levels), and PK/tumor growth inhibition (TGI) in xenograft tumors from mice. A second step involved fitting the clinical PK and sampled phospho-MET inhibition data from a tepotinib FIH trial with the structural mathematical model identified by preclinical longitudinal PK/PD data. The corresponding plasma concentration for the RP2D was also compared with the protein binding-corrected tumor regression concentration. Herein, we describe the development of these preclinical and clinical mathematical models and subsequent simulations, which led to the selection of tepotinib 500 mg once daily as the RP2D.

MATERIALS AND METHODS

Work frame overview

A translational modeling approach was used to predict an effective tepotinib dose in humans, targeting a phospho-MET

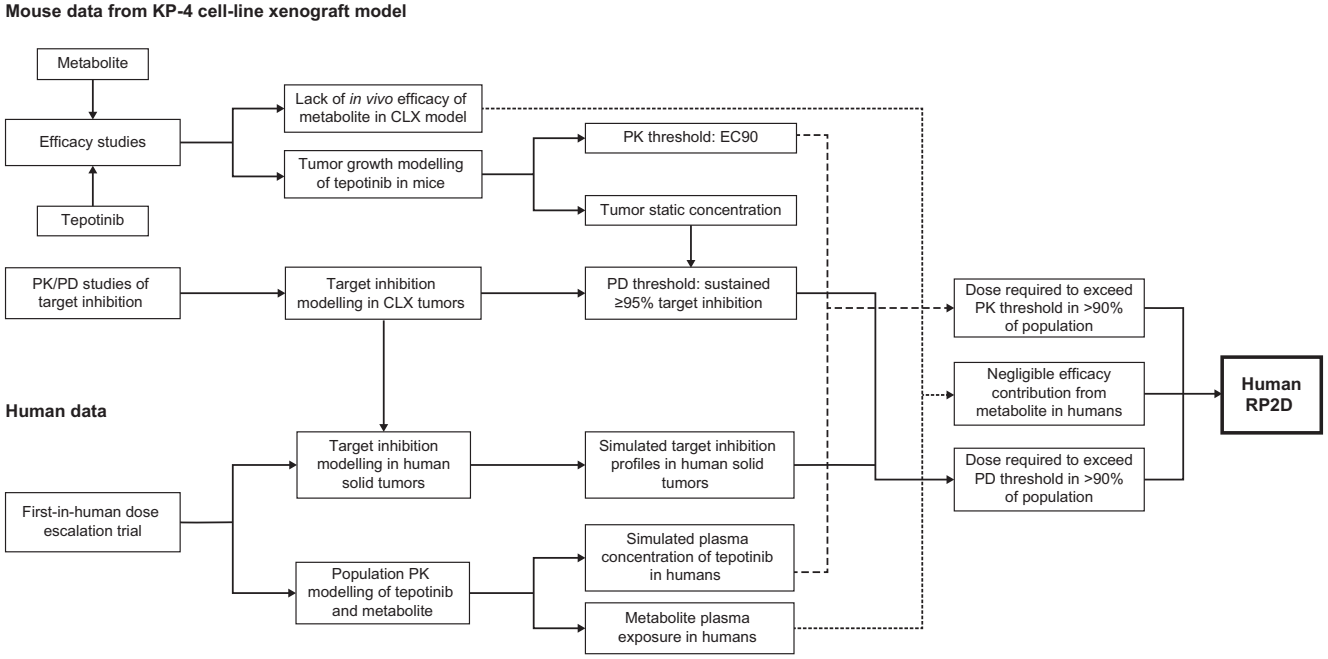

FIGURE 1 Workflow of model development. The effects of tepotinib and MSC2571109A, the major human circulating metabolite of tepotinib, on KP-4 tumors in BALB/c mice were determined in a short-term (1–4 day) pharmacokinetic/pharmacodynamic (PK/PD) study and longer-term (10–16 day) efficacy studies. In the preclinical PK/PD study, target inhibition was assessed according to phospho-MET modulation in xenograft tumors; in tumor growth inhibition studies, tumor size was measured. Longitudinal PK and PD measurements from KP-4 tumor-bearing mice in these studies, and clinical PD assessments based on paired biopsies (pretreatment and on-treatment) from patients in a first-in-human study were then integrated into mathematical models. CLX, cell line xenograft; EC_{90}, effective concentration 90%; RP2D, recommended phase II dose

level that was relevant for preclinical efficacy. An overview of the workflow development is shown in Figure 1.

Study oversight

Animal studies were conducted at Merck KGaA, Darmstadt, Germany, in compliance with the institutional ethical guidelines. The FIH study (NCT01014936)[26] was sponsored by Merck KGaA and conducted in accordance with the ethical principles of the Declaration of Helsinki, and in compliance with International Conference on Harmonization–Good Clinical Practice guidelines. The institutional review board for each site approved the study and all patients provided written informed consent to participate.

Tepotinib and MSC2571109A

Tepotinib and the metabolite MSC2571109A were produced at Merck KGaA, Darmstadt, Germany. For oral administration in animal studies, the compounds were prepared as described in the Supplementary Methods. MSC2571109A is the R-enantiomer of the oxidative metabolite of tepotinib, which was first identified in a human mass balance trial.[31] MSC2571109A represents 65% of parent exposure; however, it is not formed in mice.

Preclinical and clinical studies

Xenograft models in mice

The KP-4 human pancreatic ductal cell carcinoma cell line (RCB1005; Riken Cell Bank, Japan) was used to generate xenografts. KP-4 is considered representative of human tumors with MET pathway activation and sensitivity to MET inhibitors. Xenograft tumors were generated from frozen stocks of KP-4 cells that were rapidly thawed at 37°C, washed with phosphate buffered saline (PBS), and suspended in PBS at 1×10^8 viable cells/ml. Aliquots (100 µl) of cell suspension were injected subcutaneously into the right flanks of 6–12-week-old BALB/c-nu/nu mice (Charles River Laboratories, Sulzfeld, Germany). Similarly, the Hs746T gastric cancer cell line (ATCC, Nat. No JCRB0820), and a NIH3T3/TPR cell line (NIH3T3 cells, ATCC Cat. No CRL 1658, transfected with the truncated c-Met receptor linked to TPR) with differing levels of MET expression were used to generate xenografts by injecting 5×10^6 cells into mice.

Preclinical target modulation study in KP-4 xenograft tumor model

Plasma PK and tumor target inhibition were investigated in KP-4 xenograft-bearing mice (5 per group) treated

with tepotinib at a dose range of 5–200 mg/kg in a single-administration PK/PD study, as described elsewhere.[26] At necropsy, tumor samples weighing ~ 100 mg were placed in Precellys beaded tubes (PeqLab Biotechnologie GmbH, Erlangen, Germany), shock-frozen in liquid nitrogen, and stored at –80°C. A Luminex assay was used to semiquantitatively determine total MET and phospho-MET in tumor tissue samples, as described in the Supplementary Methods. Plasma was prepared from blood by centrifugation at 9000 rpm at 4°C for 5 min and stored at −20°C for subsequent tepotinib analysis.

Preclinical efficacy studies in xenograft tumor models

The preclinical efficacy of tepotinib and MSC2571109A in xenograft tumors was evaluated in five TGI studies of three cell-lines. In the first efficacy study, KP-4 xenograft-bearing mice (10 per group) were randomly assigned to receive tepotinib at 25, 50, or 200 mg/kg/day, or vehicle for 15 days (starting on day 0) by oral gavage when the xenograft tumors reached 80–300 mm^3. Tumor volume was assessed on days 0, 3, 6, 10, 13, and 16. In the second study, KP-4 xenograft-bearing mice received tepotinib at 5, 15, 25, and 200 mg/kg/day, or vehicle for 10 days. Tumor volume was assessed on days 0, 3, 7, and 10. In the third study, KP-4 xenograft-bearing mice received MSC2571109A at 2, 10, or 50 mg/kg/day, tepotinib at 200 mg/kg/day, or vehicle for 10 days. Tumor volume was assessed on days 0, 3, 6, 8, and 9. Tumor volume was calculated as $l*w^2/2$, where l = length of the longest axis of the tumor, and w = perpendicular width.

Similarly, efficacy studies were performed to evaluate TGI in Hs746 T and NIH3T3/TPR xenograft tumors. NIH3T3/TPR tumor bearing mice (10 per group) were randomly assigned to receive tepotinib at 3, 6, 12.5, or 25 mg/kg/day, or vehicle for 9 days (starting on day 0) by oral gavage when the xenograft tumors reached 60–130 mm^3. Tumor volume was assessed biweekly. Hs746T tumor-bearing mice (10 per group) were randomly assigned to receive tepotinib at 3 and 6 mg/kg/day or 10, 20, and 30 mg/kg every second and every third day, or vehicle for 14, 11, or 17 days, respectively, (starting on day 0) by oral gavage when the xenograft tumors reached 40–200 mm^3. Tumor volume was assessed biweekly.

FIH trial

In the FIH trial in patients with solid tumors, patients received tepotinib according to one of three dose-escalation regimens (R1–3) on a 21-day cycle.[26] Clinical and PK and PD assessment methods and results of the FIH trial are reported elsewhere.[26]

Pharmacokinetic bioanalytical assay

An enantioselective high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) method allowed the simultaneous quantification of tepotinib and its circulating metabolite MSC2571109A, as described in the Supplementary Information. Briefly, tepotinib concentration in plasma was determined using two validated LC-MS/MS methods with respective quantitation ranges of 0.186–93.0 ng/ml and 20.0–10,000 ng/ml. MSC2571109A was determined quantitatively using a validated enantioselective LC-MS/MS method with a quantitation range of 0.500–500 ng/ml.

Pharmacodynamic bioanalytical assay and calculation of target inhibition in tumors

A Luminex assay was used to semiquantitatively determine total MET and phospho-MET in tumor tissue from paired patient biopsy samples, as described in the Supplementary Methods. Target inhibition, defined as phospho-MET inhibition, was calculated as:

$$\text{pMET inhibition } \% = 100\% - \text{pMET} * 100\%$$

Modeling of preclinical data

Mathematical modeling of PK–target-modulation relationship in xenograft tumors

The preclinical PK–target-modulation relationship was analyzed in a sequential manner. For the PK part, all plasma and tumor concentration data were pooled across animals and fitted simultaneously using a compartmental modeling approach. For the PD part, estimates of PK parameters were used to predict the tepotinib plasma concentration, which was later correlated to the phospho-MET level measured in KP-4 xenografts in mice. Based on the results of graphical exploratory analysis, either direct response models (maximum effect [E_{max}] model and sigmoid model with or without effect compartment) or indirect response models were tested.

Mathematical modeling of TGI in xenograft tumors

Using a similar approach, KP-4 xenograft tumor volume data from two efficacy studies of tepotinib were combined across animals and linked to model-predicted tepotinib plasma concentrations. The Simeoni TGI model[29] was applied to fit the longitudinal tumor volume profiles that described the dynamics of tumor proliferation and apoptosis. The drug effect was incorporated via a Hill function:

$$I = Kmax \times C/(\mathrm{KC50} + C).$$

The same TGI model was used to describe the data from the Hs746 T and NIH3 T3/TPR xenograft tumors.

Definition of PD threshold and heuristic PK scaling from mice to men

Preclinical PK/PD model simulations were performed to evaluate the correlation between target inhibition and TGI as measured by percentage tumor volume of treated groups in relation to the control (% T/C) on the last day of the experiment in KP-4 xenograft tumors, matching by dose regimen. The % T/C was calculated according to:

$$\%\Delta T/\Delta C = \left(\mathrm{TV}_f - \mathrm{TV}_i/\mathrm{TV}_{f-\mathrm{Ctrl}} - \mathrm{TV}_{i-\mathrm{Ctrl}}\right) \times 100\%$$

where TV = tumor volume, f = final, i = initial, and Ctrl = control.

Consequently, a PD criterion for the level of tumor MET phosphorylation inhibition associated with tumor regression was introduced to guide the clinical dose selection.

In addition to the PD threshold, the plasma concentration required for tumor inhibition estimated in mice was scaled to humans allowing for in vitro protein binding differences. The protein binding-adjusted preclinical effective concentration range was also used to inform the clinical dose selection.

Modeling of human data

Population PK modeling of human data from a FIH trial

Human PK profiles including 2914 data points from 149 patients who received tepotinib 30–1400 mg once daily in the FIH trial were analyzed with compartmental models using a population approach. The population PK model characterized both the dose–plasma concentration relationship of tepotinib and the metabolite MSC2561109A after oral administration in humans, and the associated PK variability between individuals and the intrinsic/extrinsic factors predictive of such variability.

The parent and metabolite PK models were developed sequentially; first the tepotinib model was developed, then the final tepotinib model was extended to characterize the MSC2571109A data while keeping the individual parameters of the tepotinib model fixed. Different absorption and disposition models were tested, including first-order absorption, sequential zero-order and first-order absorption, and one and two-compartmental disposition with first-order elimination from the central compartments. The impacts of formulation and dose amount on the oral absorption property of tepotinib were evaluated as a covariate over the absorption parameters. Discrimination between models was mainly based on inspection of graphical diagnostics and statistical criteria of changes in the objective functions provided by the model estimation software.

Mathematical modeling of PK–target modulation in human tumors

In the FIH trial, inhibition of MET kinase activity was assessed using paired tumor biopsies from patients.[26] Data from 13 patients with evaluable phospho-MET inhibition were included in the PK/PD analysis (see Supplementary Methods for description of analysis set). All 13 patients achieved on-treatment phospho-MET inhibition greater than 70%, with 8 achieving inhibition of greater than 95%. The relationship between tepotinib exposure (calculated as area under the concentration curve at 24 h [$AUC_{24\,h}$] on the day of on-treatment biopsy) and target inhibition was explored using log-linear, E_{max}, and sigmoid E_{max} regression models.

The scarcity of clinical target inhibition data precluded accurate characterization of the longitudinal PK–target modulation relationship based on human data alone. Instead, the preclinical PK/PD model developed based on KP-4 xenograft tumor data was used to inform the clinical PK/PD development. Data on clinical phospho-MET inhibition and the time-paired predicted concentration from the population PK model were fitted using the structural model determined from preclinical phospho-MET data.

Simulation of target modulation in humans and clinical dose selection

Combining the population PK model and the PK–target modulation model established based on FIH trial data, Monte-Carlo simulations were performed to predict dose-dependent time profiles of target modulation at the population level. The PK interindividual variability and the PD residual variability contributed to the predicted variability of target modulation.

Modeling software

Phoenix WinNonlin (version 6.2.1) was used to analyze preclinical PK/PD data. Data were fitted to the model using the least-squares procedure and Gauss-Newton with the Levenberg modification algorithm. The best models were chosen based on residuals (plot of residual vs. time and plot of residual vs. predicted), parameter precision, correlation between parameters, and Akaike information criterion.

NONMEM (version 7.3.0) with pre-processor Perl-speaks-NONMEM (PsN, version 4.4.8) was used to analyze

clinical PK/PD data and for human simulations. R and Xpose 4.5.3 were used for the exploratory analysis and model diagnosis. First-order conditional estimation with interaction implemented in NONMEM was used for model estimation. Criteria for the assessment of mode stability included goodness of fit plots, number of significant digits for estimated parameters, the magnitude of correlations, and condition number.

RESULTS

Modeling of preclinical data

A two-compartment model with linear absorption and elimination best described the tepotinib plasma PK data in mice. Limited by solubility, the exposure of tepotinib was found to be disproportional to dose, and the relative bioavailability was negatively correlated to the oral dose level. The tumor PK data were best described by a first-order distribution between the central compartment and the tumor compartment.

For MSC2561109A, the plasma PK data was best described by a one-compartment model with linear absorption and elimination. The relative bioavailability was found to be linearly decreasing when dose increased and the distribution between plasma and tumor followed a first-order kinetic process.

Target modulation of tepotinib in KP-4 xenograft tumors

Graphical analysis of phospho-MET against plasma concentration showed hysteresis (clockwise), which did not completely collapse when plotted against tumor concentrations in KP-4 tumor-bearing mice (Figure S1), suggesting that the hysteresis is only partially explained by the equilibration time with the target tissue. An indirect response model was selected to describe the turnover of phospho-MET in KP-4 tumors,

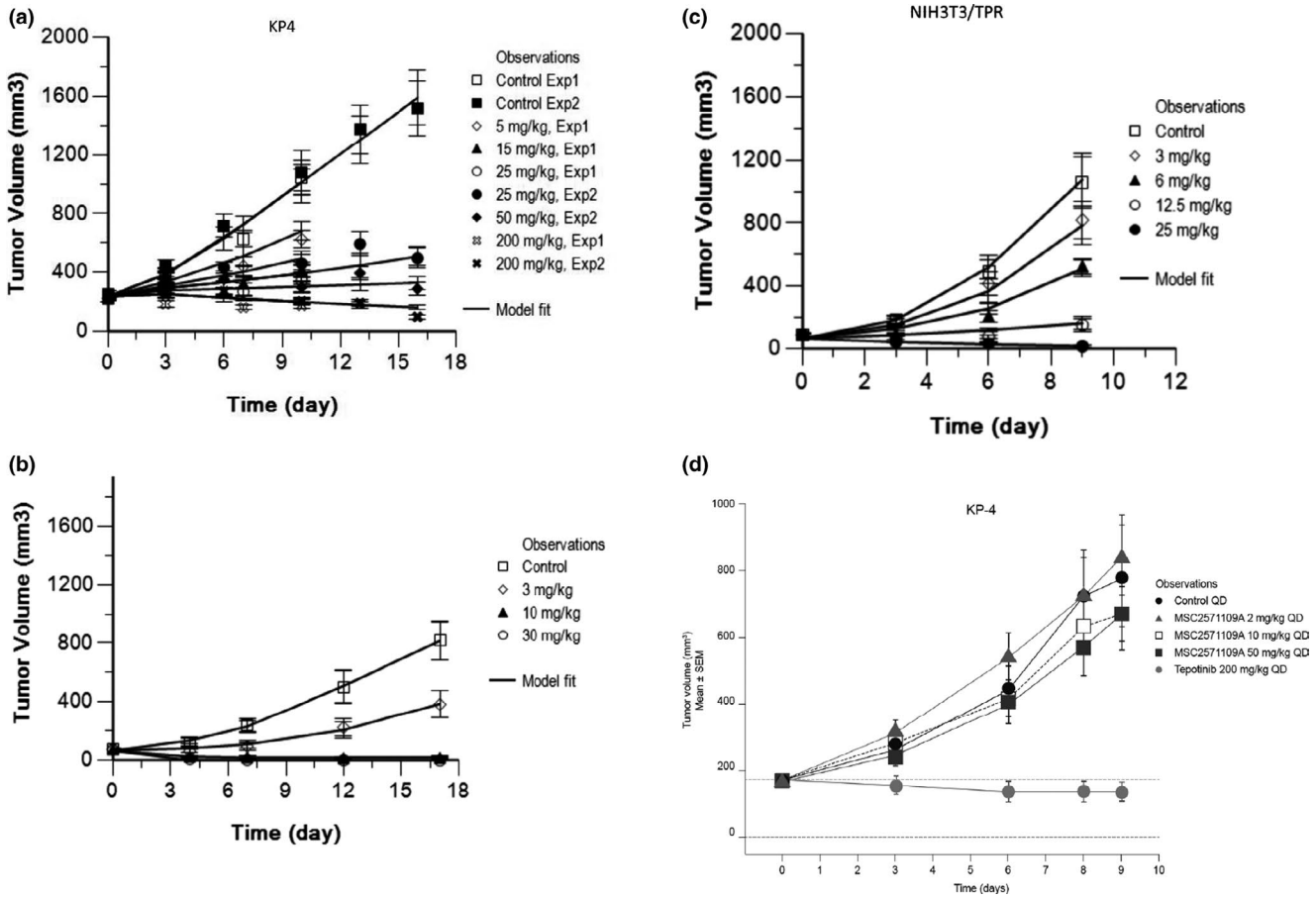

FIGURE 2 Tumor growth inhibition in cell-line xenograft tumors. Observed versus predicted tumor volumes after fitting the pharmacokinetic/efficacy model to tumor volume data (means from two independent experiments) from the KP-4 (a), Hs746T (b), and NIH3T3/TPR (c) xenograft efficacy studies. (d) Efficacy study of metabolite MSC2571109A in KP-4 cell-line xenograft tumors. Panel a, adapted from Falchook G, Kurzrock R, Amin HM, Xiong W, Fu S, Phia-Paul SA, et al. First-in-Man Phase I Trial of the Selective MET Inhibitor Tepotinib in Patients with Advanced Solid Tumors. Clin Cancer Res 2020;26(6):1237–46. Copyright 2020 American Association for Cancer Research. Reproduced with permission of the authors

TABLE 1 Preclinical efficacy and modeling of tepotinib in preclinical models with different levels of MET expression and selection of KP-4 for human dose projection

Cell line	MET pathway activation	Tumor static concentration (ng/ml) (CV%)	Lowest tepotinib dose necessary for tumor control	Best response
Hs746T (human gastric cancer cells)	High level *MET* amplification + *MET* exon 14 skipping	8 (2.7)	10 mg/kg every 3 days	Complete regression
NIH3T3/TPR (mouse fibroblasts with oncogenic transformation)	TPR-MET fusion	65 (5.1)	12.5 mg/kg daily	Complete regression
KP-4 (human pancreatic tumor cells)	HGF/MET autocrine	80 (27.4)	50 mg/kg daily	Tumor shrinkage

Abbreviations: CV%, percent coefficient of variation; HGF, hepatocyte growth factor.

assuming zero-order production and first-order degradation of phospho-MET (Figure S2). The treatment effect of tepotinib was assumed to inhibit the rate of phospho-MET formation according to saturable function with maximum inhibition fixed to 100%, because complete inhibition was observed even at the lowest dose of 15 mg/kg. The estimated parameters are reported in Table S1.

Antitumor activity of tepotinib and MSC2571109A in xenograft tumors

In the tepotinib efficacy studies, tumor control or inhibition was observed in treatment groups receiving a daily dose of tepotinib greater than or equal to 25 mg/kg in KP-4 cell-line xenografts (Figure 2a). Lower tepotinib doses were observed for tumor control or inhibition in the Hs746T and NIH3T3/TPR cell-line xenografts (Figure 2b,c). The sensitivity of KP-4 tumors to tepotinib-dependent tumor inhibition was lower than that of the other cell-line xenografts, as exemplified by the higher tumor static concentrations in KP-4 model (Table 1). Given its dose-dependent but lower sensitivity to tepotinib, the KP-4 model was chosen to provide a conservative prediction of the human dose of tepotinib.

Treatment groups of mice with KP-4 cell-line xenografts receiving MSC2571109A up to 50 mg/kg showed negligible tumor control, which was not statistically different from the vehicle group (Figure 2d). In contrast, the group that received tepotinib at 200 mg/kg achieved significant tumor inhibition. Limited by the solubility of MSC2571109A, the highest oral dose tested in the preclinical efficacy study was 50 mg/kg, with a steady-state area under the curve (AUC_{SS}) plasma concentration in KP-4 cell-line xenograft mice calculated as 10,408 ng/ml/h. The model-predicted MSC2571109A plasma/tumor AUC_{SS} ratio in mice on day 9 is 24-fold greater than the corresponding value for tepotinib (Table 2), indicating limited tumor tissue penetration by MSC2571109A.

The Simeoni model[29] was found to be adequate for describing TGI with a saturable treatment effect of tepotinib.

TABLE 2 Predicted values of AUCτ for tepotinib and MSC2571109A on day 1 and day 9 in mice

		AUCτ on day 1	AUCτ on day 9
MSC2571109A	Plasma, ng*h/ml	6699.40	8832.50
	Tumor, ng*h/g	2737.00	3608.90
	P/T ratio	2.45	2.45
Tepotinib	Plasma, ng*h/ml	5338.20	5903.30
	Tumor, ng*h/g	50,461.00	58,335.00
	P/T ratio	0.11	0.10

AUCτ, area under the concentration curve during a dosing interval; P/T, plasma/tumor.

Estimated parameters for KP-4 cell-line xenograft mice are described in Table S2. Based on this model, a daily dose of 77 mg/kg was predicted to achieve tumor stasis in KP-4 cell line xenograft mice (Figure 3a). Additionally, the concentrations of tepotinib required to achieve 90–95% maximum tumor inhibition were estimated to be within the range 390–823 ng/ml in humans after correcting for protein binding differences (2.9% in mice and 1.6% in humans).

Pharmacodynamic threshold

At the predicted tumor static daily dose of 77 mg/kg, the PK–target modulation model predicted trough phospho-MET inhibition of 90% at steady-state (Figure 3a), indicating that a high level of sustained target inhibition needs to be maintained to provide meaningful efficacy. The correlation plot of efficacy reflected by TGI versus target modulation model-predicted average phospho-MET inhibition suggested that regression in KP-4 cell line xenograft tumors corresponded to ~ 95% phospho-MET inhibition (Figure 3b). Therefore, a PD criterion of sustained nearly complete inhibition of phospho-MET (≥95%) was introduced as the targeted PD threshold in phase II development.

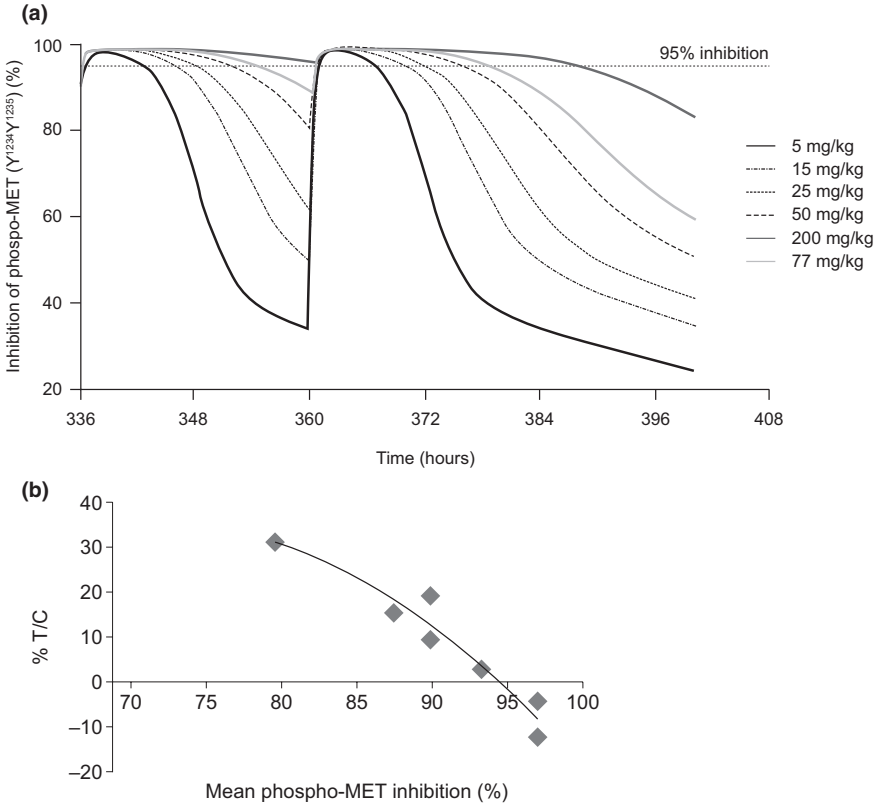

FIGURE 3 Inhibition of phosphorylated MET. (a) Sustained high level of phospho-MET inhibition is required for efficacy. Simulation of phospho-MET inhibition using the established pharmacokinetic/pharmacodynamic (PK/PD) model after repeated treatment with tepotinib at doses that caused tumor regression indicates that high and sustained levels of phospho-MET inhibition must be maintained. A daily dose of tepotinib 77 mg/kg was predicted to achieve tumor stasis in mice with KP-4 cell line xenografts, corresponding to continuous greater than 90% phospho-MET inhibition based on simulation from the PK/PD model. (b) Correlation of efficacy (% T/C) to PD modulation phospho-MET inhibition ($Y^{1234-1235}$) in the KP-4 xenograft tumor model. Near-complete inhibition (≥95%) of phospho-MET is required for tumor stasis or regression. Using the PK/PD model, phospho-MET modulation was simulated under daily treatment conditions and at the doses tested in the efficacy experiments (5–200 mg/kg). The average phospho-MET over time was then calculated and plotted against % TGI. The black line represents the fit to the data and shows that tumor regression (% T/C > 0) is achieved when mean phospho-MET is greater than 95% over the treatment period. The % T/C represents the tumor volume of treated groups in relation to control and is calculated according to: $\%\Delta T/\Delta C = (TVf - TVi/TVfCtrl - TViCtrl) \times 100\%$; where, TV = tumor volume, f = final, i = initial, and Ctrl = control. TGI, tumor growth inhibition. Panel (b), Falchook G, Kurzrock R, Amin HM, Xiong W, Fu S, Phia-Paul SA, et al. First-in-Man Phase I Trial of the Selective MET Inhibitor Tepotinib in Patients with Advanced Solid Tumors. Clin Cancer Res 2020;26(6):1237–46. Copyright 2020 American Association for Cancer Research. Reproduced with permission

Modeling of human data

Population pharmacokinetics in humans

A two-compartment model with sequential zero-order and first-order absorption and first-order elimination from the central compartment best described the PK of tepotinib in humans. Exposure to tepotinib was dose-dependent and increased for patients who received tepotinib (500 mg) in tablet formulation versus capsules. Interindividual variability was high for absorption parameters and moderate for clearance.

The major human circulating metabolite MSC2571109A was also characterized by a two-compartment model with input from the central compartment of the parent compound, scaled by a fraction of tepotinib metabolized to MSC2571109A, and a first-order elimination from the central compartment. Model parameter estimation is reported in Table S3.

Target modulation of tepotinib in human tumors

All biopsy-evaluable patients achieved greater than 70% phospho-MET inhibition, and those who received tepotinib at a dose greater than or equal to 300 mg/day achieved greater than or equal to 90% phospho-MET inhibition (Figure 4). The full inhibitory turnover model developed based on KP-4 xenograft tumor data was applied to fit the human data, with a treatment

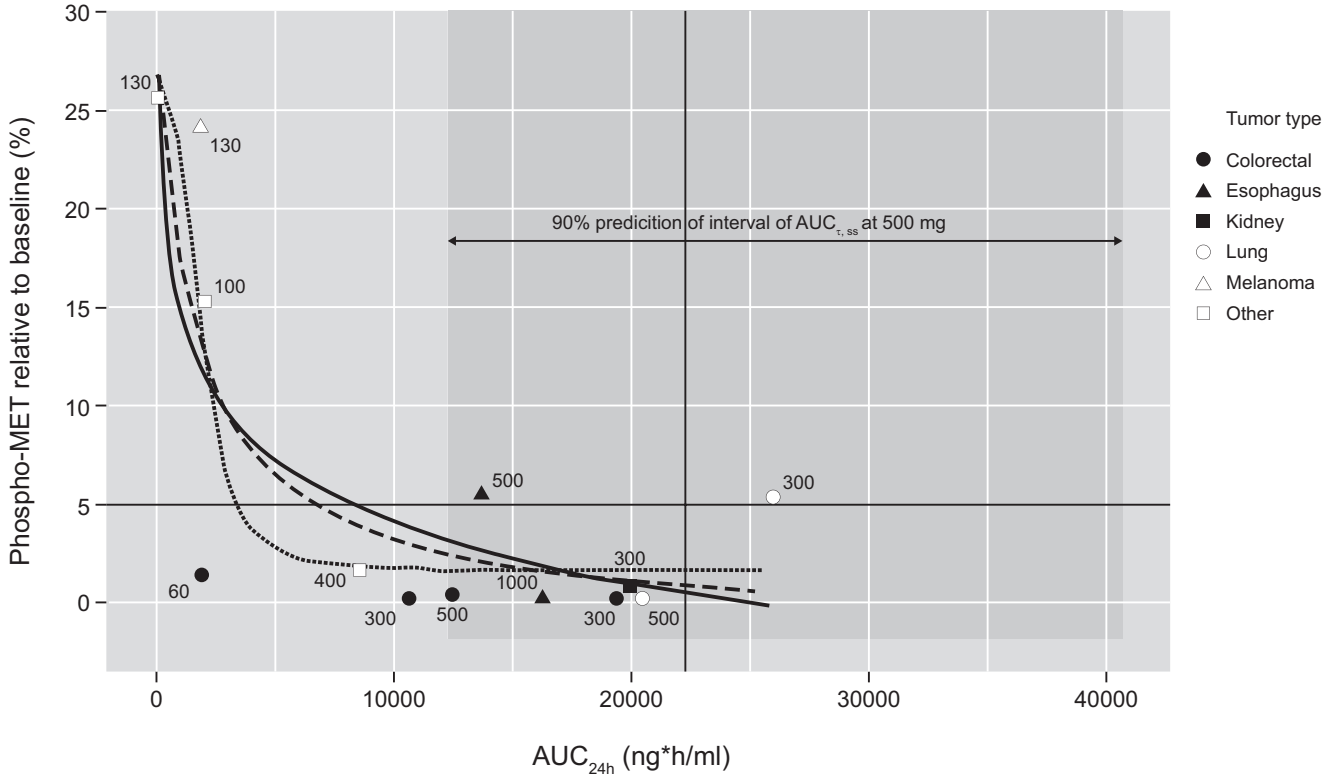

FIGURE 4 Statistical regression of phopho-MET to tepotinib exposure. The shape icons represent the observed percentage phospho-MET inhibition relative to baseline marked with tepotinib dose level (mg/day). The solid, dashed, and dotted curves represent the regression lines with linear, maximum effect (E_{max}) and sigmoid E_{max} models, respectively. The horizontal line represents the PD threshold of 95% phospho-MET inhibition. The vertical line and the shade area represent the population median and 90% prediction interval of steady state AUC ($AUC_{\tau,SS}$) at 500 mg once daily dose, respectively. AUC, area under the concentration curve; PD, pharmacodynamic

effect inhibiting the rate of phospho-MET production by tepotinib concentration following a sigmoidal maximum unbound systemic concentration (I_{max}) function. The system turnover parameters (k_{in} and k_{out}) were fixed to preclinical estimates, assuming similarities of phospho-MET build-up and degradation between KP-4 xenograft tumors and human solid tumors, whereas the potency parameter of tepotinib-dependent inhibition was estimated based on clinical data (Table S1).

Simulation of population target inhibition–time profiles and clinical dose selection

Population PD simulation was performed using the full inhibitory turnover I_{max} PD model driven by the concentrations simulated from the population PK model, including estimated PK and PD variability. The population PK model predicted a steady-state concentration in the targeted range (390–823 ng/ml at trough level) with tepotinib 500 mg once daily in humans (Figure 5). Targeting the PD criterion of sustained close-to-complete (≥95%) phospho-MET inhibition in tumors, simulations suggested that tepotinib 500 mg once daily could achieve the PD threshold in greater than 90% of the population (Figure 5). The collective PK and PD evidence supported the selection of tepotinib 500 mg once daily as the RP2D, which was well-tolerated in the FIH trial and expected to deliver clinical efficacy in the targeted population.

Efficacy contribution of MSC2571109A, the major human circulating metabolite of tepotinib

Based on a population PK model, maximum human exposure of the metabolite MSC2571109A in the FIH trial was similar to the maximum mouse exposure in the preclinical efficacy study, even after correcting for protein binding (unbound fraction 1.2% in both human and mouse plasma): AUC_{SS} of 10,212 ng/ml/h in patients receiving a daily dose of 1400 mg tepotinib versus AUC_{SS} of 10,408 ng/ml/h in mice receiving a daily dose of 50 mg/kg MSC2571109A. The latter dose regimen failed to demonstrate antitumor activity in KP-4 cell-line xenograft mice. Consequently, we concluded that the metabolite MSC2571109A has a negligible contribution to the efficacy of tepotinib at clinical doses and could be reasonably discarded from this analysis.

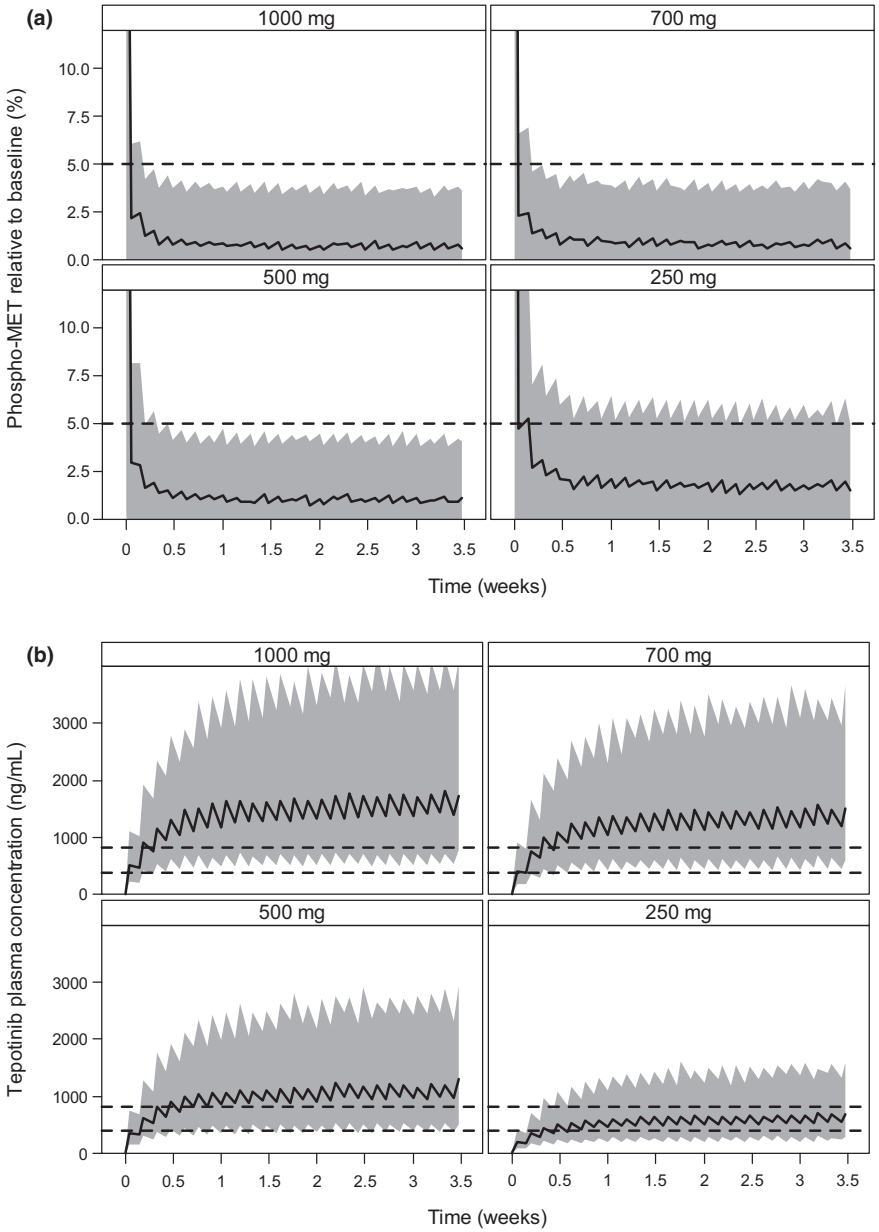

FIGURE 5 Simulation of dose-dependent phospho-MET inhibition (relative to baseline) in humans and of tepotinib plasma concentration. Left to right and top to bottom: tepotinib 1000 mg, 700 mg, 500 mg, and 250 mg once daily, respectively. (a) The solid black line represents the median prediction of percentage phospho-MET inhibition relative to baseline, and the shaded area represents a simulation-based 10%–90% prediction interval for phospho-MET inhibition relative to baseline. The dashed lines indicate the PD threshold of 5% phospho-MET corresponding to 95% phospho-MET inhibition. (b) The solid black line represents the median tepotinib plasma concentration, and the shaded area represents a simulation-based 10%–90% prediction interval for tepotinib plasma concentration. The dashed lines indicate the free fraction-corrected effective concentration 90% (EC_{90}) or EC 95% (EC_{95}) of 390 or 823 ng/ml in the preclinical tumor growth inhibition model. PD, pharmacodynamic

DISCUSSION

We used a translational modeling approach to establish the tepotinib RP2D for patients with solid tumors. The clinical population PK of tepotinib was described by a two-compartment PK model with sequential zero-order and first-order absorption. Phospho-MET inhibition in human tumors was fitted to a turnover model structurally developed based on KP-4 xenograft tumor data. Efficacy and PD profiling in KP-4 xenograft tumors suggested that near-complete inhibition of MET kinase activity (≥95% reduction in phospho-MET) is required to achieve tumor regression. Targeting this PD threshold, a biologically active dose of 500 mg once daily was proposed as the RP2D for tepotinib in patients with solid tumors. This dose is predicted to achieve continuous greater than or equal to 95% MET inhibition in 90% of the population. Furthermore, sustained target modulation leading to small peak-trough fluctuations in tumor tissue, makes tepotinib suitable for once-daily

dosing, as compared with other MET inhibitors available in the clinic that require more frequent dosing.

A limitation of translational modeling is that some equivalence between the preclinical and clinical settings must be assumed, particularly with respect to conservation of PK/PD/efficacy relationships, and the similarity of preclinical xenograft tumor models to human malignancies. In addition, cell-line xenograft tumors, such as the KP-4 cell-line xenografts we adopted as the reference tumor model, do not reflect the heterogeneity of tumors in patients, which may develop MET-independent clones.

The pancreatic cancer cell line KP-4 co-expresses HGF and MET resulting in autocrine activation of MET. KP-4 xenografts demonstrated dose-dependent sensitivity to tepotinib treatment indicating a critical role of MET for growth and survival in these tumors. However, compared with tumor xenografts derived from the lung cancer cell line EBC-1, in which doses of tepotinib as low as 15 mg/kg daily are sufficient to induce complete tumor regression, KP-4 tumors require a substantially higher dose of tepotinib for even partial tumor shrinkage.[21] EBC-1 cells have high level *MET* gene amplification, which appears to render EBC-1 tumors highly sensitive to MET inhibition. In addition, in the present work, different models with various levels of MET pathway activation have been considered in a head-to-head translational modeling comparison. Results showed that lower tumor static concentrations are required for Hs746T and NIH3T3/TPR tumor models. Therefore, the KP-4 model was chosen as it provides a conservative prediction of the human dose, which might differ depending on the *MET* alteration to be targeted in different tumor indications. Additionally, KP-4 xenografts have allowed reasonable dose predictions to be made for MET inhibitors in the past, increasing confidence in their relevance as a model of MET-positive tumors.[32]

In the current study, we incorporated clinical tumor PD data, despite being limited, to better predict the potency of tepotinib-dependent target modulation in humans. The preclinical PK/PD model, together with human tumor PD data obtained from clinical biopsies, can be further refined as more PK data become available from phase II trials, allowing doses and dose schedules to be modified for specific patient populations as appropriate.

The major human circulating metabolite MSC2571109A failed to demonstrate antitumor activity in KP-4 cell-line xenograft models at a dose level matching the highest clinical exposure of MSC2571109A in patients from the FIH trial. Therefore, we could reasonably conclude that MSC2571109A contributes marginally to the clinical efficacy of tepotinib. Although MSC2571109A has relevant clinical exposure and in vitro affinity to the target, the absence of preclinical efficacy may be explained by poor distribution in the tumor tissue: the plasma-tumor partition coefficient of the metabolite was found to be 24-fold higher than that of the parent compound in KP-4 cell-line xenograft mice.

Translational PK/PD modeling is increasingly being used to guide dose selection of targeted agents for which MTD may not be the optimal approach. Examples include dose selection for the anti-MET monoclonal antibody onartuzumab, the MEK inhibitor GDC-0973, and the epidermal growth factor receptor (EGFR) inhibitor osimertinib.[32–34] The onartuzumab example predicted human PK from animal data, targeting a tumor static concentration in a xenograft model. The GDC-0973 example applied a human PK driving animal PD approach, targeting an effective PD threshold estimated from an integrated PK/PD/efficacy model in xenograft tumors.[35] For osimertinib, mathematical modeling was used to predict human dose scheduling by bridging preclinical and clinical data and elucidating the relative contributions of parent and metabolite.[36] Like these examples, most translational modeling reported to date established only the quantitative relationship of drug exposure and target inhibition in xenograft tumors. In such models, human plasma PK data are considered to scale from animal to human, assuming the same relationship between plasma-free drug concentration and target modulation/efficacy in xenograft tumors and human solid tumors. Therefore, such scaling approaches are susceptible to bias, due to differences in the plasma-tumor distribution of anticancer agents and/or sensitivity to treatment-dependent target modulation between xenograft tumors and human tumors.

Several phase I/II trials of tepotinib are ongoing (NCT01988493, NCT02115373, NCT01982955, and NCT02864992), and initial phase Ib data have shown that tepotinib 500 mg once daily is well-tolerated.[37–39] This dose has been used in the phase II parts of these trials both as a single agent and combined with other anticancer agents.[40–42] There is now evidence that the 500 mg once daily dose of tepotinib is associated with tumor responses in patients with *MET*-positive, EGFR-mutation positive NSCLC after EGFR TKI relapse.[39] In addition, tepotinib also showed efficacy in *MET* exon 14-altered NSCLC[42] and 500 mg once daily tepotinib has been approved in this setting in Japan. Together, these data indicate that the human dose prediction from the translational modeling process was successful.

In summary, based on preclinical PK/PD and tumor growth modeling, analysis of MET inhibition in on-treatment patient biopsies, and population PK modeling, a biologically effective tepotinib dose of 500 mg once daily was selected as the RP2D. This dose achieves greater than or equal to 95% phospho-MET inhibition and results in sufficiently high steady-state (trough) exposure levels in greater than or equal to 90% of patients to have activity in tumors with moderate to high sensitivity to MET inhibition.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

W.X. and S.E.B. wrote the manuscript. W.X., A.J., M.K., and S.E.B. designed the research. M.F.-H., C.S., G.S.F., and D.S.H. performed the research. W.X. and S.E.B. analyzed the data. P.G. contributed analytical tools.

DATA AVAILABILITY STATEMENT

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck KGaA's Data Sharing Policy. All requests should be submitted in writing to Merck KGaA's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck KGaA has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck KGaA will endeavor to gain agreement to share data in response to requests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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