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First-in-Man Phase I Trial of the Selective MET Inhibitor Tepotinib in Patients with Advanced Solid Tumors

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Running title: Phase I Trial of Tepotinib in Solid Tumors

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Translational Relevance

Tepotinib is a potent, highly selective MET inhibitor. In this first-in-man trial, tepotinib was shown to be well-tolerated and active against solid tumors, particularly those expressing high levels of MET. Tepotinib proved well-tolerated up to the highest dose administered (1400 mg once daily), while a recommended phase II dose of 500 mg once daily was defined based on a translational modeling approach integrating preclinical pharmacokinetic, target modulation, and efficacy data, along with clinical pharmacokinetic and tumor target modulation data. Taken together, the results support exploring tepotinib for the treatment of patients with non-small cell lung cancer whose tumors are either driven by *MET* alterations, including *MET* exon 14-skipping, or in which MET is implicated in secondary resistance to epidermal growth factor receptor inhibitors.

Abstract

Purpose: Tepotinib is an oral, potent, highly selective MET inhibitor. This first-in-man phase I trial investigated the maximum tolerated dose (MTD) of tepotinib to determine the recommended phase II dose (RP2D).

Patients and Methods: Patients received tepotinib orally according to one of three dose-escalation regimens (R) on a 21-day cycle: R1, 30–400 mg once daily for 14 days; R2, 30–315 mg once daily 3 x /week; or R3, 300–1400 mg once daily. After two cycles, treatment could continue in patients with stable disease until disease progression or unacceptable toxicity. The primary endpoint was incidence of dose-limiting toxicity (DLT) and treatment-emergent adverse events (TEAEs). Secondary endpoints included safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor effects.

Results: 149 patients received tepotinib (R1: *n* = 42; R2: *n* = 45; R3: *n* = 62). Although six patients reported DLTs (one patient in R1 [115 mg], three patients in R2 [60, 100, 130 mg], two patients in R3 [1000, 1400 mg]), the MTD was not reached at the highest tested dose of 1400 mg daily. The RP2D of tepotinib was established as 500 mg once daily, supported by translational modeling data as sufficient to achieve ≥95% MET inhibition in ≥90% of patients. Treatment-related TEAEs were mostly grade 1 or 2 fatigue, peripheral edema, decreased appetite, nausea, vomiting, and lipase increase. The best overall response in R3 was partial response in two patients, both with MET overexpression.

Conclusions: Tepotinib was well-tolerated with clinical activity in MET-dysregulated tumors. The RP2D of tepotinib was established as 500 mg once daily.

Statement of Significance

MET abnormalities can drive tumorigenesis. This first-in-man trial demonstrated that the potent, highly-selective MET inhibitor tepotinib can reduce or stabilize tumor burden and is well-tolerated at doses up to 1400 mg once daily. A recommended phase II dose of 500 mg once daily, as determined from translational modeling and simulation integrating human population pharmacokinetic and pharmacodynamic data in tumor biopsies, is being used in ongoing clinical trials.

Introduction

MET receptor tyrosine kinase activation increases cellular proliferation, survival, mobilization, and invasive capacity (1,2). Chronic MET activation in advanced solid tumors occurs via mechanisms including activating *MET* mutations (3), *MET* amplification (4), and overexpression of MET or its ligand hepatocyte growth factor (HGF) (5,6). Activated MET can drive tumorigenesis (7) and make tumors resistant to epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor inhibitors, and anti-human EGFR-2 therapies (1). Tumor MET activity is also associated with aggressive cancer phenotypes (8) and poor prognosis (9,10). MET inhibitors may, therefore, have a role in cancer therapy (11,12).

Tepotinib is an oral, highly selective and potent MET inhibitor that inhibits MET phosphorylation and downstream signaling. The 50% inhibitory concentration (IC_{50}) of MET was determined as 1.7 nM, and screening against >400 kinases showed high selectivity of tepotinib for MET. Tepotinib inhibits both HGF-dependent and -independent MET kinase activity, providing greater suppression of MET signaling than inhibitors of only ligand-dependent activity (13). In preclinical studies, tepotinib inhibited the growth of MET-dependent human xenograft tumors and cancer explants (14-17). This phase I first-in-man study was conducted to establish the recommended phase II dose (RP2D) of tepotinib in patients with advanced solid tumors.

Patients and Methods

Study design and treatment

This open-label, non-randomized, dose-escalation phase I trial in patients with advanced solid tumors (ClinicalTrials.gov ID: NCT01014936) was conducted in compliance with the Declaration of Helsinki, the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice, and all applicable regulatory requirements. The institutional review board for each site approved the study and all patients provided written informed consent to participate.

Dose-escalation used a classic 3+3 design. Patients received one of three tepotinib regimens (R) on a 21-day cycle (Fig. 1A). Patients were alternately assigned to R1 or R2 until R3 was introduced based on emerging clinical data from the trial, when R1 was discontinued and patients were alternately assigned to R2 or R3. Dose escalation was guided by the occurrence of dose-limiting toxicity (DLT) and grade 2 clinically relevant treatment-emergent adverse events (TEAEs). If no grade ≥2 TEAEs were observed, 100% dose increments were applied; otherwise, lesser increments were applied. Patients received tepotinib until disease progression, unacceptable toxicity, or withdrawal of consent. After dose-escalation, an additional cohort of 12 patients with *MET* amplification and a cohort of 12 patients with MET overexpression were enrolled at the RP2D.

Tepotinib was supplied in three formulations: non-micronized in capsules (initial formulation [IF]); micronized in capsules (optimized formulation [OF]); and micronized in tablet form. Patients received one type of formulation (micronized or non-micronized), with their daily dose comprising multiple capsules or tablets of 15

mg to 100 mg to reach the required dose. The tablet formulation was given exclusively to patients in R3.

The primary objective was to determine the maximum tolerated dose (MTD) of tepotinib for each regimen in patients with solid tumors. Secondary objectives included safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of tepotinib. If it was determined impossible or unnecessary to establish an MTD in a given regimen, an RP2D would be established.

Patients

Patients had measurable or evaluable solid tumors, either refractory to standard therapy or for which no effective standard therapy was available, Eastern Cooperative Oncology Group performance status 0–2, and adequate hematological, liver and renal function. MET status was not used for initial recruitment, while patients in the RP2D expansion cohort (R3) required either *MET* amplification or MET overexpression. Patients who had received systemic anticancer therapy within 28 days of trial treatment or prior radiotherapy to >30% of bone marrow were ineligible. See Supplementary Information for full inclusion and exclusion criteria.

Assessments

Patients were monitored for toxicity throughout the trial. TEAEs were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0. A DLT was defined as one of the following TEAEs observed during cycle 1, regardless of tepotinib relationship: grade 4 neutropenia >7 days; grade ≥3 febrile neutropenia for >1 day; grade 4 thrombocytopenia or grade 3 with bleeding; grade ≥3 nausea and vomiting despite optimal treatment; grade ≥3

non-hematological TEAE (except nausea and vomiting with no adequate treatment, and alopecia); grade ≥3 liver event requiring >7 days recovery to baseline or to grade ≤1 for patients without liver metastases or to grade ≤2 for those with metastases; grade ≥3 lipase and/or amylase rise with pancreatitis confirmation; or any other event that caused a delay of >21 days in planned tepotinib administration due to prolonged recovery to grade ≤1 or baseline status. TEAEs assessed by the investigator to be exclusively related to the patient's underlying disease or medical condition were not considered DLTs. The MTD was defined as the dose level below that at which two of three patients or two of six patients (depending on the size of the cohort) experienced a DLT.

Tumors were assessed at baseline and the end of every second cycle by radiography, computed tomography, or magnetic resonance imaging. Tumor response assessments were based on Response Evaluation Criteria in Solid Tumors version 1.0; best overall response (BOR) was assessed between baseline and disease progression. Partial (PR) and complete responses were confirmed 6 weeks after first evaluation.

Pharmacokinetics

Blood samples were taken for PK analysis during cycle 1 (R1 and R3: up to 24 hours post-dose days 1 and 14, and pre-dose days 3, 8, and 17; R2: up to 48 hours post-dose days 1 and 19 and pre-dose days 3 and 8). Additional blood samples were taken pre-dose on day 1 of each subsequent cycle for all regimens. Standard non-compartmental methods were used to calculate PK parameters using WinNonlin (version 6.3, Certara INC, Princeton, USA). Effects of food on the PK characteristics

of tepotinib were explored in R1 and R2 patient subsets. The bioavailability of capsule and tablet formulations was compared for tepotinib 500 mg dosing. Differences in area under the plasma concentration curve (AUC) and observed maximum plasma concentration (C_{max}) between groups (fed vs. fasted, tablet vs. capsule) were assessed using analysis of variance (ANOVA) and differences in time to reach the maximum plasma concentration (t_{max}) by computing the Hodges–Lehmann shift estimate. Dose proportionality was assessed using ANOVA.

Human PK profiles, including 2914 data points from 419 patients who received tepotinib 30–1400 mg orally once daily, were analyzed with compartmental models using a population approach. The population PK model characterized both the dose–plasma concentration relationship of tepotinib after oral administration in humans, and the associated PK variability between individuals and the intrinsic/extrinsic factors predictive of such variability. Further details on population PK modeling are included in the Supplementary Information.

Biomarkers

Paired tumor biopsies for MET status and PD biomarker assessment were performed when possible and were required from all patients recruited after October 15, 2010 unless archived tumor samples were available. The first biopsy was taken during screening, and the second between days 9 and 14 of cycle 1 (R1), or days 17 and 21 of cycle 1, or, if continuing treatment, on day 1 of cycle 2 (R2 and R3). A Luminex^{TM} assay was used to assess total MET and phosphorylated MET (phospho-MET) as described in the Supplementary Information. Blood samples for PD

assessment were taken on days 1, 3, 8, 14, and 17 (R1 and R3), and days 1, 3, 8, and 19 (R2) of cycle 1.

Tumor MET status was assessed for MET overexpression using immunohistochemistry (IHC) and for *MET* amplification using *in situ* hybridization (ISH) or next-generation sequencing. For IHC, MET antibodies D1C2 (Cell Signaling Technology) and SP44 (Roche/Ventana) were used. Tumors were classified as overexpressing MET if >50% of cells showed strong MET staining (3+ on a scale of 0–3+; MET IHC3+); otherwise, they were classified as MET IHC≤2. For ISH, *MET* and *CEP7* probes were used, with *MET* amplification defined as a mean *MET*:*CEP7* ratio ≥2, or clusters of >5 *MET* copies in >10% of tumor nuclei (>50 nuclei counted). *MET* amplification was also determined by a next-generation sequencing-based method (Foundation Medicine, Cambridge, USA) on either archived or fresh pre-treatment tumor biopsies.

Statistical plan

Statistical determination of sample size was unnecessary as the protocol followed a classic 3+3 design. The primary endpoint was the incidence of DLTs occurring during the first treatment cycle and treatment-related TEAEs. Summary statistics (means, medians, ranges, and appropriate measures of variability) were calculated for each dose level. Secondary endpoints included safety, tolerability, PK, PD, and antitumor activity. All statistical analyses are regarded as exploratory.

Model-informed selection of the recommended Phase II dose

Preclinical PK/PD model simulations were performed to evaluate the correlation between target inhibition and tumor growth inhibition (TGI) as measured by the

tumor volume (T) of treated groups in relation to control (C; % T/C). Consequently, a PD criterion for the level of tumor MET phosphorylation inhibition associated with tumor regression was introduced to guide the clinical dose selection. PK and PD bioanalytical assays, together with full details of modeling of preclinical and human data, are presented in Fig. 1B, as well as in the Supplementary Information and Fig. S1.

The KP-4 human pancreatic ductal cell carcinoma cell line (RCB1005; Riken Cell Bank, Japan) was used to generate xenografts in BALB/c-nu/nu mice because it is considered representative of human tumors with MET pathway activation and sensitivity to MET inhibitors. Xenograft tumors were generated as previously reported (15). All animal studies were conducted at Merck KGaA, Darmstadt, Germany, in compliance with the institutional ethical guidelines. Tepotinib was produced at Merck KGaA, Darmstadt, Germany, and prepared for oral administration, as previously described (18). The effect of tepotinib on KP-4 xenograft-bearing mice was determined in a short-term (1–4 day) 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 TGI 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 (pre- and on-treatment) from patients in the first-in-man study (NCT01014936) were then integrated into mathematical models. This translational modeling approach enabled the prediction of an effective dose in humans, targeting a phospho-MET level that was relevant for preclinical efficacy.

To investigate plasma PK and tumor target inhibition, (phospho-MET), KP-4 xenograft-bearing mice (five per group) were randomly assigned to receive a single dose of tepotinib (5, 15, 50, or 200 mg/kg) or vehicle by oral gavage when xenograft tumors reached 250–600 mm^3. Blood and tumor samples were collected 0.5, 2, 6, 12, 24, 48, and 72 hours post-dose. 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.

Two experiments assessed the effects of tepotinib on TGI. In the first experiment, 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. Tumor volume was calculated as $l*w^2/2$, where l = length of the longest axis of the tumor, and w = perpendicular width.

Results

Patient characteristics and disposition

Overall, 203 patients were screened at four sites: MD Anderson Cancer Center, Houston, Texas; University of Chicago Medical Center, Chicago, Illinois; Roswell Park Medical Center, Buffalo, New York, USA; and Universitätsklinikum Köln, Cologne, Germany. One-hundred-and-forty-nine patients were enrolled between November 2009 (first patient screened) and October 2015 (last patient last visit). The database was locked for final analysis on February 15, 2016.

Table 1 shows baseline patient and tumor characteristics. Patients were initially treated orally with nonmicronized tepotinib in R1 (30–230 mg once daily for 14 days) and R2 (30–115 mg once daily 3 x/week for 3 weeks). Following a protocol amendment, dosing was switched from nonmicronized tepotinib to micronized tepotinib capsules. Subsequently, patients received micronized tepotinib capsules in R1 (30–400 mg once daily for 14 days) and R2 (60–315 mg once daily 3 x/week for 3 weeks). In R3, patients received micronized tepotinib capsules (300–1400 mg once daily for 3 weeks). After the introduction of R3, R1 ceased enrollment. An additional cohort of 12 patients with *MET* amplification and a cohort of 12 patients with MET overexpression were included in R3 and received micronized tepotinib 500 mg orally, once daily. The tablet formulation of micronized tepotinib was introduced for testing at the 500 mg dose level in R3; in total, 42 patients received tepotinib 500 mg. Dosing above 1400 mg daily was limited by pill burden.

Overall, 149 patients received treatment with a median time on treatment of 6.0 weeks for each regimen: 42 patients on R1 (range 2.1–153.3 weeks), 45 patients on

R2 (range 1.0–27.6 weeks), and 62 patients on R3 (range 0.7–94.9 weeks). In the 500 mg cohort, the median time on treatment was 6.0 weeks (range 0.7–42.4 weeks). Full details of time on treatment for all dose cohorts are shown in Supplementary Table S1.

Safety

Six patients reported DLTs: in R1, one patient (115 mg IF) had asymptomatic grade 4 lipase and grade 3 amylase increase; in R2, two patients (60 and 100 mg OF) had asymptomatic grade 3 lipase increase (one with a prior history of elevated lipase and transaminases), and one (130 mg OF) had grade 3 nausea and vomiting; and in R3, one patient (1000 mg OF) had grade 3 alanine aminotransferase (ALT) increase and one (1400 mg OF) grade 3 fatigue. The MTD was not reached at the maximum tested dose of 1400 mg once daily (R3).

Most (97.3%) patients experienced at least one TEAE. TEAEs led to permanent tepotinib treatment discontinuation for 20 (13.4%) patients. Seventy-six (51.0%) patients experienced treatment-related TEAEs (Table 2), most frequently grade 1/2 fatigue, peripheral edema, decreased appetite, nausea, vomiting, and lipase increase. Treatment-related grade ≥3 TEAEs occurred in 13 (8.7%) patients and led to discontinuation in three (2.0%) patients (one in R1 and two in R3). Most treatment-related TEAEs resolved without intervention. There were no treatment-related TEAEs leading to death. Overall, there was a higher frequency of treatment-related TEAEs reported in R3, where higher doses of tepotinib were administered. For the 500 mg cohort (*n* = 42), incidence of any grade treatment-related TEAEs were similar to the overall study population, with the most common being peripheral

edema (11, 26.2%), fatigue (9, 21.4%) and decreased appetite (7, 16.7%) (Supplementary Table S2). Of the patients receiving tepotinib 500 mg, six (14.3%) and nine (21.4%) temporarily or permanently discontinued treatment due to TEAEs, respectively. Two (4.8%) patients in the 500 mg cohort had their dose reduced.

Overall, 53 (35.6%) patients reported serious adverse events (SAEs). In one patient these were considered related to study treatment (grade 3 nausea and grade 3 vomiting, R2). The most frequent SAEs in R3 were grade 2 or 3 gastrointestinal disorders. One patient (R3, tepotinib 500 mg once daily) died due to an SAE of hepatic failure recorded as disease progression unrelated to the study drug.

Pharmacokinetics

In fasting patients, the initial capsule formulation produced highly variable AUC and C_{max}, so the formulation was optimized and administered with food. The following PK results were obtained in fed patients using the optimized formulation, including the 500 mg tablet formulation (see Supplementary Data, Tables S3, S4, S5, and S6). Tepotinib was absorbed slowly after the first dose, with a median t_{max} of 8–10 hours. Increases in C_{max} and $AUC_{0–24h}$ with increasing dose were observed after single and multiple dosing for both once daily and 3 x/week tepotinib administration. A dose-proportional increase in C_{max} and $AUC_{0–24h}$ occurred for once-daily doses ≤300 mg, with less than dose-proportional increases at higher doses. Apparent clearance at steady state ($Cl_{ss/f}$) was stable for tepotinib doses ≤315 mg ($Cl_{ss/f}$ 11.35–24.50 L/h) but increased at doses ≥700 mg ($Cl_{ss/f}$ 35.24–40.92 L/h). $Cl_{ss/f}$ for the tablet formulation at 500 mg was estimated to be 26.43 L/h. Multiple dosing resulted in accumulation of tepotinib in all regimens.

Based on the median $AUC_{0–24h}$ accumulation ratio of 3.3 after multiple once-daily dosing (500 mg tablet formulation), the average effective $t_{1/2}$ was estimated to be approximately 46 hours. Correspondingly small peak-to-trough fluctuations were observed at steady state, eg, patients receiving tepotinib 500 mg in tablet form exhibited fluctuations of 32.1% around the geometric mean C_{av} of 1097.9 ng/mL (Supplementary Table S4 and Supplementary Fig. S2).

Steady-state exposure to tepotinib was increased for patients receiving 500 mg tepotinib as tablets vs. capsules, with geometric mean $AUC_{0–24h}$ and C_{max} higher by 37% and 38%, respectively. t_{max} was unaffected by formulation as assessed after the first dose.

Clinical antitumor activity of tepotinib

The BOR in R3 was PR in two patients (Table 3): a 77-year-old male with MET IHC3+ (*MET* not amplified) esophageal cancer who received tepotinib 500 mg once daily (tablet formulation); and a 56-year-old female with MET IHC3+ (*MET* not amplified) lung cancer who received tepotinib 1400 mg once daily and completed 32 cycles of tepotinib treatment with a progression-free survival (PFS) time of 21.8 months. Two further patients had unconfirmed PRs; one (R2; MET status unknown) had nasopharyngeal carcinoma and one (R3; *MET* amplified and MET IHC3+) had colorectal cancer. Thirty-four patients had a BOR of standard deviation (SD), including 12 in R3. The BOR according to MET status is shown in Table 4. The change in the sum of longest diameters of target lesions from baseline is shown in Supplementary Fig. S3.

Targeted pharmacokinetics and pharmacodynamic threshold

In the preclinical efficacy studies, tumor control was observed in treatment groups receiving a daily dose of tepotinib ≥25 mg/kg (Fig. 2A). The Simeoni tumor growth model was found to adequately fit the treatment effects of tepotinib. Concentrations of tepotinib required to achieve 90% (EC_{90}) to 95% (EC_{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).

The correlation plot of efficacy reflected by TGI vs. target modulation model-predicted average phospho-MET inhibition suggested that regression in KP-4 xenograft tumors corresponded to approximately 95% phospho-MET inhibition (Fig. 2B). Therefore, a PD criterion of sustained nearly complete inhibition of phospho-MET (greater than 95%) was introduced as the targeted PD threshold in phase II development.

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. Targeting the PD criterion of sustained close-to-complete (≥95%) phospho-MET inhibition in tumors, simulations suggested that a regimen of tepotinib 500 mg once daily could achieve the PD threshold in 90% of the population (Fig. 2C). The clinical PK data on day 14 show that at a tepotinib dose of 500 mg once daily in humans, the individual trough tepotinib concentrations were within or above the target range and the mean steady-state concentration is

above the range (390–823 ng/mL) as determined from KP-4 efficacy experiments (Supplementary Fig. S2).

Both PK and PD evidence supported the selection of tepotinib 500 mg once daily as the RP2D, which was well tolerated in the first-in-man trial and expected to deliver clinical efficacy in the target population. Further results from the modeling of preclinical and human data are presented in Supplementary Fig. S4 and Supplementary Table S7.

Discussion

This first-in-man study was conducted to establish the MTD of tepotinib in patients with advanced solid tumors, using a classic 3+3 dose-escalation design. We analyzed data from 149 patients treated according to three dose-escalation regimens (R1–3). Tepotinib treatment was well-tolerated up to 1400 mg but no MTD could be defined. We have used a translational modeling approach to establish the tepotinib RP2D for patients with solid tumors. Phospho-MET inhibition in human tumors was fitted to a turnover model structurally developed based on KP-4 xenograft tumor data. Based on tumor shrinkage and MET inhibition results from mice with KP-4 xenografts, an active concentration range of tepotinib was predicted and scaled up to humans. 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. In addition, continuous daily dosing with 500 mg of tepotinib was predicted to achieve the target exposure range (390–823 ng/mL). This dose is predicted to achieve continuous ≥95% MET inhibition in 90% of the population. Steady-state concentration time profiles at the 500 mg dose level, both for the capsule and the tablet formulation, showed exposure beyond the threshold as shown in Supplementary Fig. S2, and dosing of 42 patients confirmed the safety and tolerability of tepotinib at the RP2D of 500 mg once daily. The translational approach applied here highlight the utility of integrating preclinical and emerging first-in-man clinical data to support RP2D selection. Further, the characterization of PK and PD

relationships in patients will allow doses and dose schedules to be modified for specific patient populations as appropriate.

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 do not reflect the heterogeneity of tumors in patients, which may develop MET-independent clones. For a conservative estimate of the tepotinib dose-efficacy relationship, the pancreatic cancer model KP-4 was chosen. HGF/MET autocrine KP-4 tumors are sensitive to tepotinib treatment but require substantially high doses to provoke partial tumor regression (15). Moreover, 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 (19).

Among the several types of MET inhibitors in development, potent, selective MET inhibitors are most likely to deliver optimal inhibition of MET with an optimal benefit–risk ratio. The potency of tepotinib reduces its effective dose, and its selectivity minimizes the risk of toxicity due to off-target kinase inhibition, increasing its therapeutic margin. The main TEAEs associated with tepotinib were grade 1 or 2 peripheral edema, fatigue, decreased appetite, and nausea and vomiting. Some patients experienced increases in serum lipase, amylase, ALT, and aspartate aminotransferase, which are asymptomatic, and generally resolve without treatment modification. Clinical studies of selective MET inhibitors capmatinib and savolitinib also reported peripheral edema, decreased appetite, and nausea among the most

common treatment-related TEAEs (20,21). While the incidence of grade ≥3 treatment-related TEAEs was highest in the cohort that received continuous daily tepotinib (R3), tepotinib was well-tolerated at the RP2D of 500 mg once daily with no DLTs and only two treatment-related TEAEs leading to discontinuation. The PK characteristics of tepotinib allow oral once-daily dosing, which assists compliance, and its long half-life ensures a small peak–trough variation over 24 hours, reducing the risk of toxicity at peak and suboptimal inhibition at trough. These PK characteristics also support steady target inhibition, and in conjunction with available safety and tolerability results, constitute a promising drug profile for tepotinib.

Although preclinical studies suggested that MET alterations, either overexpression or more especially genetic alterations such as *MET* amplification, may trigger a tumor to become more sensitive to MET inhibitors (1), the majority of patients in this study were not selected according to MET status. This non-selected recruitment to the trial was primarily designed to investigate safety, tolerability, PK, and PD; nevertheless, antitumor activity was observed. The BOR was a PR in two patients with MET IHC3+ tumors and SD in 12 patients in R3. Although data are limited with only 16 patients with MET IHC3+ and nine patients with *MET* amplified tumors, the antitumor activity of tepotinib appeared greatest in patients with MET IHC3+ tumors.

These data suggest that tepotinib warrants further investigation in cancer patients with MET dysregulation. Phase Ib/II trials of tepotinib 500 mg once daily in patients with MET-overexpressing hepatocellular carcinoma (NCT01988493 and NCT02115373) and non-small cell lung carcinoma (NSCLC) with *MET* alterations

(NCT01982955 and NCT02864992) have confirmed both the tolerability of tepotinib and demonstrated clinical activity (22-25). A pooled safety analysis of 260 patients who received tepotinib 500 mg in five phase Ib/II studies also showed the 500 mg dose to be generally well tolerated (26). In patients with *MET*-amplified *EGFR*-mutant NSCLC with resistance to EGFR tyrosine kinase inhibitors, treatment with tepotinib plus gefitinib greatly improved outcomes vs. the chemotherapy control arm (PFS 16.6 vs. 4.2 months, hazard ratio [HR] 0.13 [90% confidence interval (CI), 0.04–0.43]; overall survival 37.3 vs. 13.1 months, HR 0.09 [90% CI, 0.01, 0.54) (23). Interim data from an ongoing study of patients with NSCLC harboring *MET* exon 14-skipping alterations reported an overall response rate of 45% to 55% (27).

In summary, the RP2D of 500 mg tepotinib orally once daily is well-tolerated by patients with advanced solid tumors. This first-in-man trial also demonstrated that tepotinib can be administered safely up to 1400 mg/day. Patients with high-level MET-expressing tumors appear to benefit most from treatment, and additional clinical studies in patients with MET dysregulated tumors are ongoing.

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Table 1. Baseline patient and tumor characteristics

	Regimen 1 (*n* = 42)	Regimen 2 (*n* = 45)	Regimen 3 (*n* = 62)	Total (*N* = 149)
Median age, years (range)	62.8 (21.1–83.1)	61.3 (19.2–81.6)	57.8 (23.2–80.5)	61.0 (19.2–83.1)
Male/female, *n* (%)	24 (57.1)/ 18 (42.9)	22 (48.9)/ 23 (51.1)	37 (59.7)/ 25 (40.3)	83 (55.7)/ 66 (44.3)
Race, *n* (%)				
White	39 (92.9)	37 (82.2)	57 (91.9)	133 (89.3)
Black	2 (4.8)	4 (8.9)	2 (3.2)	8 (5.4)
Asian	1 (2.4)	2 (4.4)	3 (4.8)	6 (4.0)
Other	0	2 (4.4)	0	0
ECOG PS, *n* (%)				
0	8 (19.0)	6 (13.3)	9 (14.5)	23 (15.4)
1	33 (78.6)	36 (80.0)	48 (77.4)	117 (78.5)
2	1 (2.4)	3 (6.7)	4 (6.5)	8 (5.4)
3	0 (0)	0 (0)	1 (1.6)	1 (0.7)
Location of primary tumor, *n*				
Colorectal	13	10	5	28
Lung[a]	4	2	11	17
Esophagus	3	1	11	15
Breast	0	2	7	9
Ovary[b]	0	5	2	7
Prostate	3	1	2	6
Liver[c]	2	1	3	6
Stomach	0	2	4	6

	Regimen 1 (*n* = 42)	Regimen 2 (*n* = 45)	Regimen 3 (*n* = 62)	Total (*N* = 149)
Skin	2	1	0	3
Bone	0	1	2	3
Pancreas	1	1	1	3
Melanoma	0	2	0	2
Kidney	0	1	1	2
Bladder	1	0	1	2
Head and neck	1	0	0	1
Soft tissue	0	0	1	1
Other[d]	12	15	11	38
Tumor type, *n*				
Adenocarcinoma	21	15	30	66
Melanoma	4	10	0	14
Sarcoma	2	4	5	11
Squamous cell carcinoma	2	2	1	5
Undifferentiated carcinoma	0	1	0	1
Other	13	13	26	52
Measurable disease at baseline, *n* (%)	39 (92.9)	42 (93.3)	59 (95.2)	140 (94.0)
Median number of prior therapies (range)	7 (2–22)	7 (1–25)	6 (1–15)	6 (1–25)
MET expression by IHC, *n* (%)				
MET IHC3+	2 (4.8)	5 (11.1)	9 (14.5)	16 (10.7)
MET IHC≤2	19 (45.2)	22 (48.9)	32 (51.6)	73 (49.0)

	Regimen 1 (*n* = 42)	Regimen 2 (*n* = 45)	Regimen 3 (*n* = 62)	Total (*N* = 149)
Not available	21 (50.0)	18 (40.0)	21 (33.9)	60 (40.3)
MET amplification, *n* (%)				
Amplified	0	0	9 (14.5)	9 (6.0)
Not amplified	17 (40.5)	20 (44.4)	34 (54.8)	71 (47.7)
Missing	25 (59.5)	25 (55.6)	19 (30.6)	69 (46.3)

[a]1 small-cell carcinoma (R2), 2 non-small cell carcinoma (R3), 2 neuroendocrine carcinoma (R1), 1 oat cell (R1). The remainder were defined as adenocarcinoma or carcinoma.

[b]Includes 1 sarcoma extending into the fallopian tube.

[c]1 adenocarcinoma, (R1), the remainder hepatocellular carcinoma, including 1 fibrolamellar (R3).

[d]Other locations (R1, R2, R3): adrenocortical (1, 0, 0), alveolar (0, 1, 0), brain (0, 0, 2), chest (0, 1, 0), duodenum (1, 0, 0), eye (1, 5, 0), gastro-esophageal junction (0, 0, 2), jejunum (1, 0, 0), mediastinum (0, 0, 1), mouth (0, 1, 0), nasopharyngeal/nose (1, 1, 0), ocular (1, 0, 0), parotid (1, 0, 0), pelvis (0, 0, 1), peritoneum (0, 1, 1), ribs (0, 1, 0), scalp (0, 1, 0), shoulder (1, 0, 0), peri-seminal vesicle (0, 0, 1), small bowel (1, 0, 1), thyroid (2, 0, 0), toe (0, 1, 0), tongue (0, 0, 1), urethra (0, 0, 1), uveal (1, 1, 0), and undefined (0, 1, 0).

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Treatment-related TEAEs

	Regimen 1 (*n* = 42)		Regimen 2 (*n* = 45)		Regimen 3 (*n* = 62)		Total (*N* = 149)	
Patients, *n* (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Treatment-related TEAEs[a]	14 (33.3)	1 (2.4)	23 (51.1)	3 (6.7)	39 (62.9)	9 (14.5)	76 (51.0)	13 (8.7)
Peripheral edema	1 (2.4)	0	2 (4.4)	0	16 (25.8)	3 (4.8)	19 (12.8)	3 (2.0)
Fatigue	3 (7.1)	0	5 (11.1)	0	11 (17.7)	2 (3.2)	19 (12.8)	2 (1.3)
Decreased appetite	2 (4.8)	0	0	0	10 (16.1)	0	12 (8.1)	0
Nausea	1 (2.4)	0	2 (4.4)	1 (2.2)	6 (9.7)	0	9 (6.0)	1 (0.7)
Vomiting	2 (4.8)	0	2 (4.4)	1 (2.2)	5 (8.1)	1 (1.6)	9 (6.0)	2 (1.3)
Lipase increased	1 (2.4)	1 (2.4)	4 (8.9)	2 (4.4)	1 (1.6)	0	6 (4.0)	3 (2.0)
Rash	0	0	2 (4.4)	0	2 (3.2)	0	4 (2.7)	0
AST increased	1 (2.4)	0	0	0	3 (4.8)	1 (1.6)	4 (2.7)	1 (0.7)
Diarrhea	0	0	1 (2.2)	0	3 (4.8)	0	4 (2.7)	0
ALT increased	0	0	0	0	3 (4.8)	2 (3.2)	3 (2.0)	2 (1.3)
Anemia	0	0	0	0	3 (4.8)	0	3 (2.0)	0

Blood creatinine increased	0	0	0	0	3 (4.8)	0	3 (2.0)	0
Constipation	0	0	0	0	3 (4.8)	0	3 (2.0)	0
Transaminases increased	0	0	0	0	3 (4.8)	0	3 (2.0)	0
Peripheral neuropathy	1 (2.4)	0	1 (2.2)	0	1 (1.6)	0	3 (2.0)	0
Renal failure	2 (4.8)	0	0	0	1 (1.6)	0	3 (2.0)	0
Edema	0	0	0	0	1 (1.6)	1 (1.6)	1 (0.7)	1 (0.7)
Amylase increased	1 (2.4)	1 (2.4)	0	0	0	0	1 (0.7)	1 (0.7)
Hypoalbuminemia	0	0	0	0	2 (3.2)	1 (1.6)	2 (1.3)	1 (0.7)
Hyponatremia	0	0	0	0	2 (3.2)	1 (1.6)	2 (1.3)	1 (0.7)

[a]For any-grade treatment-related TEAEs, events occurring in >2 patients with any regimen are reported; for treatment-related TEAEs grade 3 or higher, all events are shown.

ALT, alanine aminotransferase; AST, aspartate transaminase; TEAE, treatment-emergent adverse event.

Table 3. Best overall response, objective response rate, and clinical benefit rate by regimen

Response	Regimen 1 (*n* = 42)	Regimen 2 (*n* = 45)	Regimen 3 (*n* = 62)	Total (*N* = 149)
Partial response, *n* (%)	0	0	2 (3.2)	2 (1.3)[a]
Stable disease, *n* (%)	12 (28.6)	10 (22.2)	12 (19.4)	34 (22.8)
Progressive disease, *n* (%)	25 (59.5)	27 (60.0)	38 (61.3)	90 (60.4)
Not evaluable, *n* (%)	5 (11.9)	8 (17.8)	10 (16.1)	23 (15.4)
Objective response rate, *n* (%) [90% CI]	0 [0–6.9]	0 [0–6.4]	2 (3.2) [0.6–9.8]	2 (1.3) [0.2–4.2]
Clinical benefit rate, *n* (%) [90% CI]	12 (28.6) [17.4–42.1]	10 (22.2) [12.6–34.8]	14 (22.6) [14.2–33.0]	36 (24.2) [18.5–30.6]

[a]Two further patients with a best overall response of stable disease (one each in regimen 2 and regimen 3) had an unconfirmed partial response.

CI, confidence interval.

Table 4. Best overall response, objective response rate, and clinical benefit rate by tumor MET status

Response	MET IHC≤2 (*n* = 73)	MET IHC3+ (*n* = 16)	Not amplified (*n* = 71)	Amplified (*n* = 9)
Partial response, *n* (%)	0	2 (12.5)	2 (2.8)	0
Stable disease, *n* (%)	17 (23.3)	4 (25.0)	17 (23.9)	2 (22.2)
Progressive disease, *n* (%)	47 (64.4)	7 (43.8)	42 (59.2)	5 (55.6)
Not evaluable, *n* (%)	9 (12.3)	3 (18.8)	10 (14.1)	2 (22.2)
Objective response rate, *n* (%) [90% CI]	0 [0, 4.0]	2 (12.5) [2.3 34.4]	2 (2.8) [0.5, 8.6]	0 [0, 28.3]
Clinical benefit rate, *n* (%) [90% CI]	17 (23.3) [15.4, 32.9]	6 (37.5) [17.8, 60.9]	19 (26.8) [18.3, 36.7]	2 (22.2) [4.1, 55.0]

CI, confidence interval; IHC, immunohistochemistry.

Figures Legend

Figure 1. Clinical study patient allocation and pharmacokinetic modeling

A, Patient allocations and regimens.

B, Workflow of pharmacokinetic model development.

FIM, first-in-man; PD, pharmacodynamic; PK, pharmacokinetic; RP2D, recommended phase II dose.

Figure 2. Tumor growth inhibition and dose-dependent phospho-MET inhibition.

A, Tumor growth inhibition in KP-4 cell-line xenograft tumors. Observed versus predicted tumor volumes after fitting the PK/efficacy model to tumor volume data (means from two independent experiments) from the KP-4 xenograft efficacy studies.

B, Correlation of efficacy (% T/C) to PD modulation phospho-MET inhibition ($Y^{1234\text{-}1235}$) in the KP-4 xenograft tumor model on the last day of the experiment, matching by dose regimen. 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 >95% over the treatment period. % 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, Ctrl = control.

C, Simulation of dose-dependent phospho-MET inhibition (relative to baseline) in humans. Left to right panel: tepotinib 300 mg, 500 mg, and 1000 mg once daily every other week, respectively. The solid black curve represents the time profile of population 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 dotted lines indicate the PD threshold of 95% phospho-MET inhibition.

Figure 1A

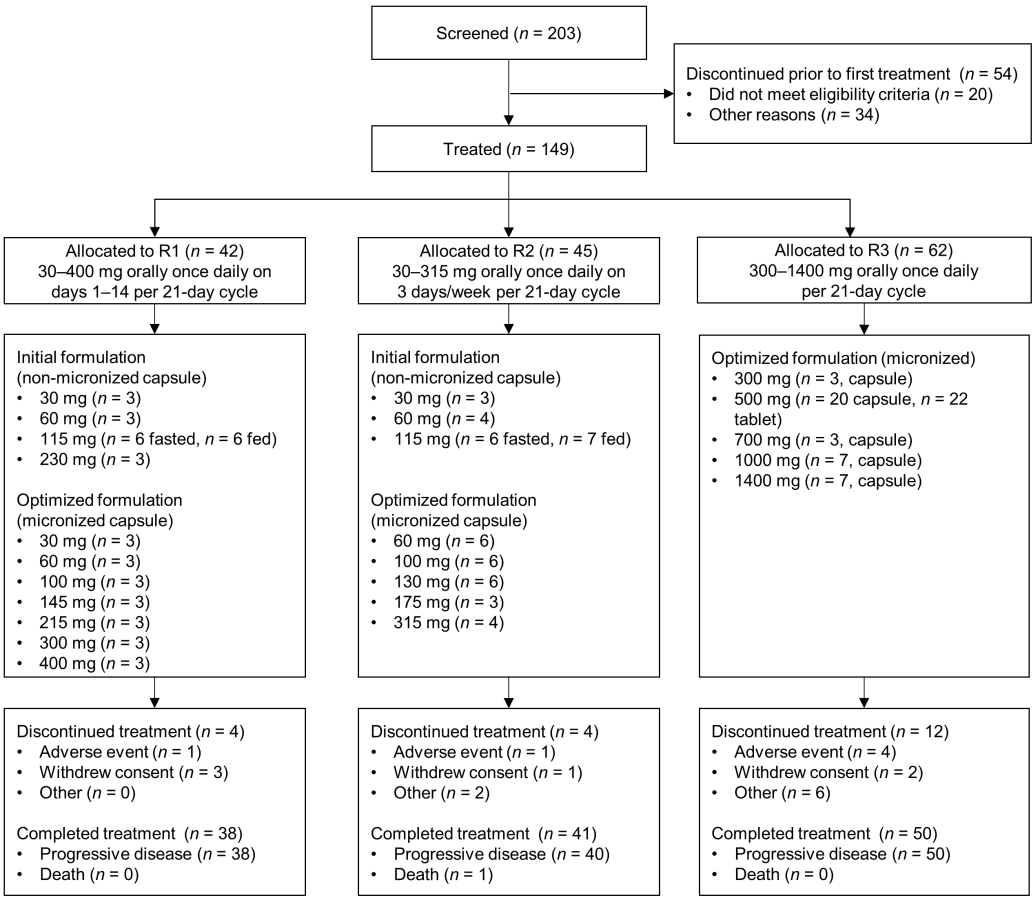


Figure 1B

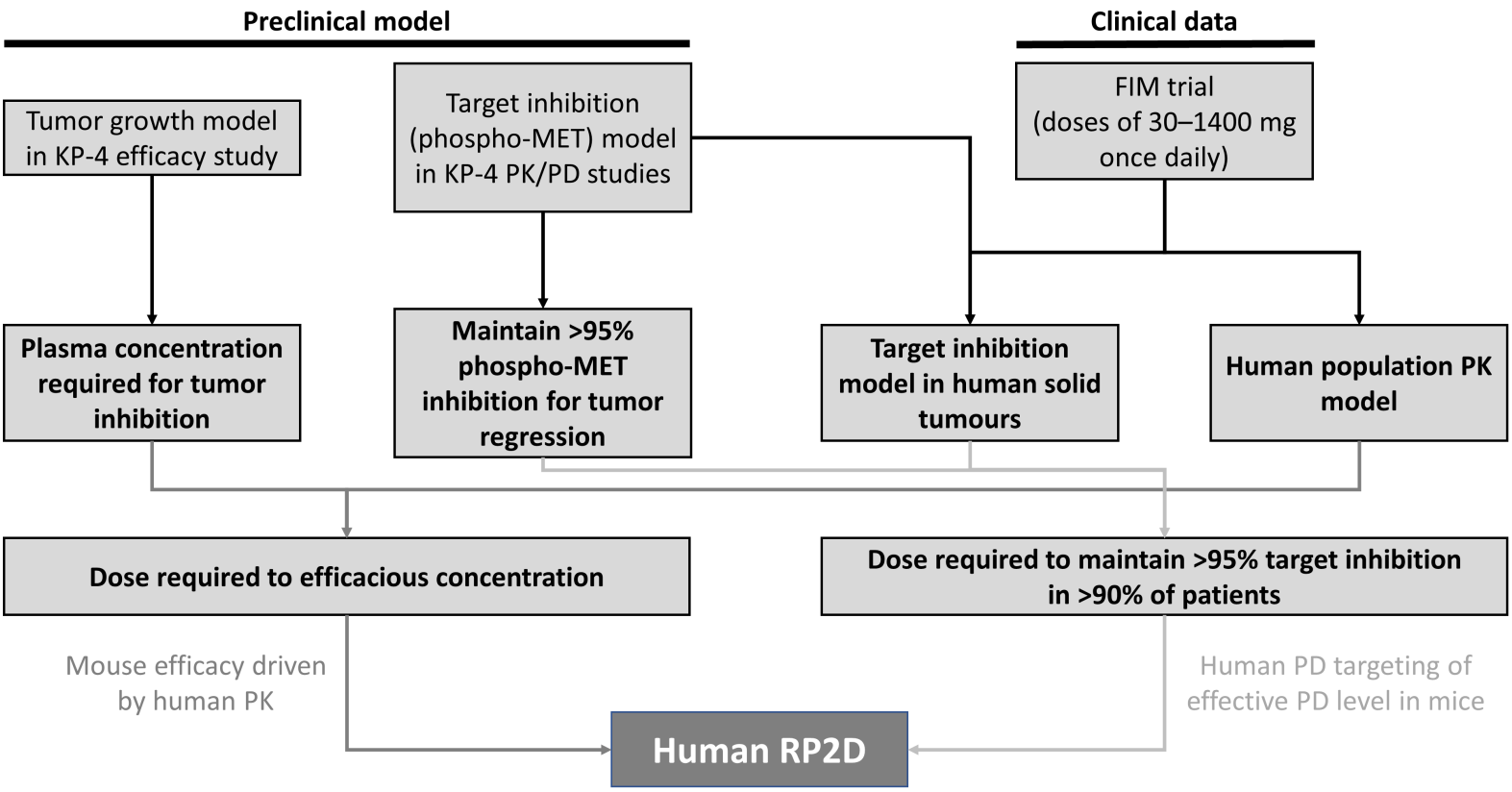


Figure 2A

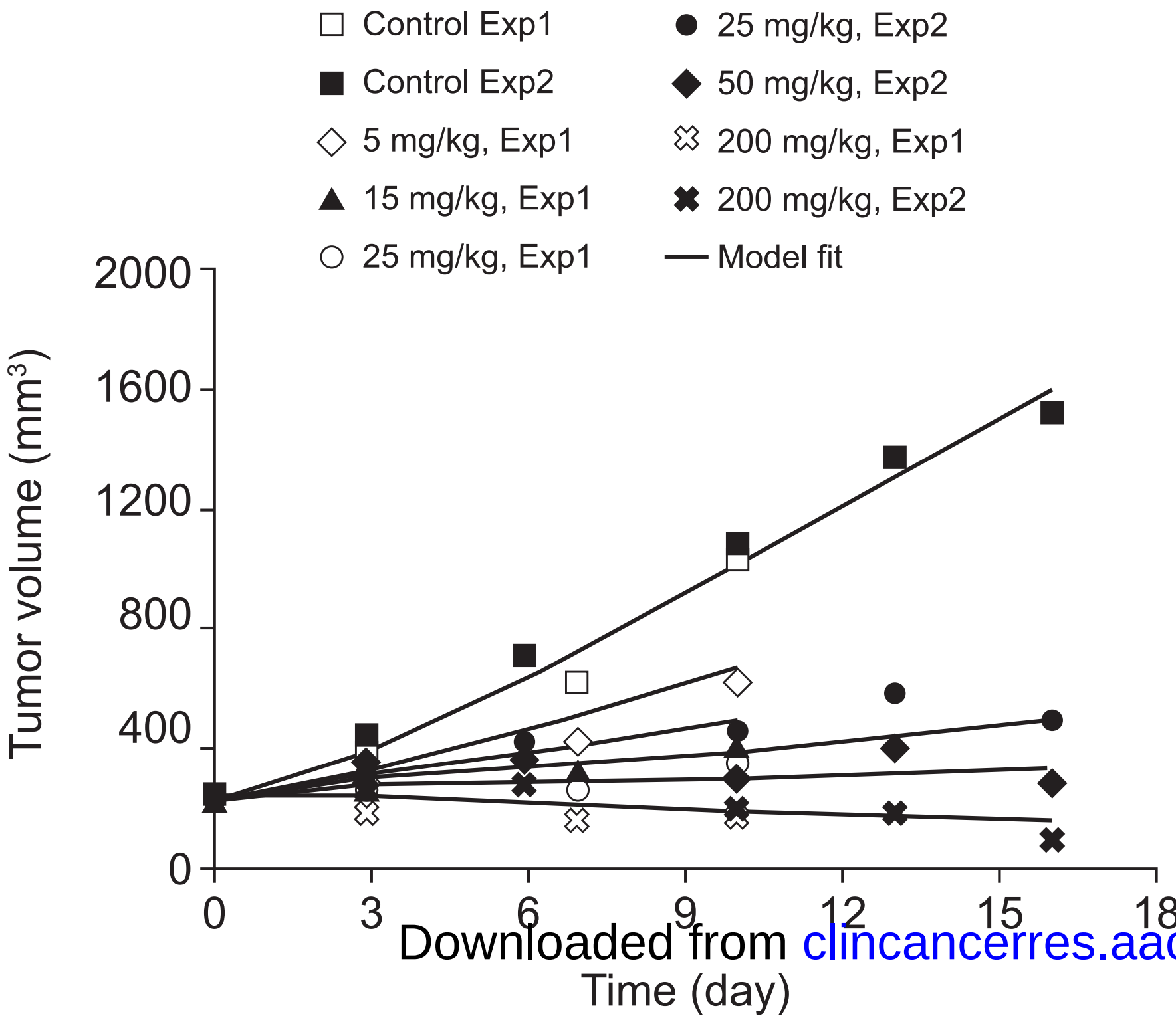


Figure 2B

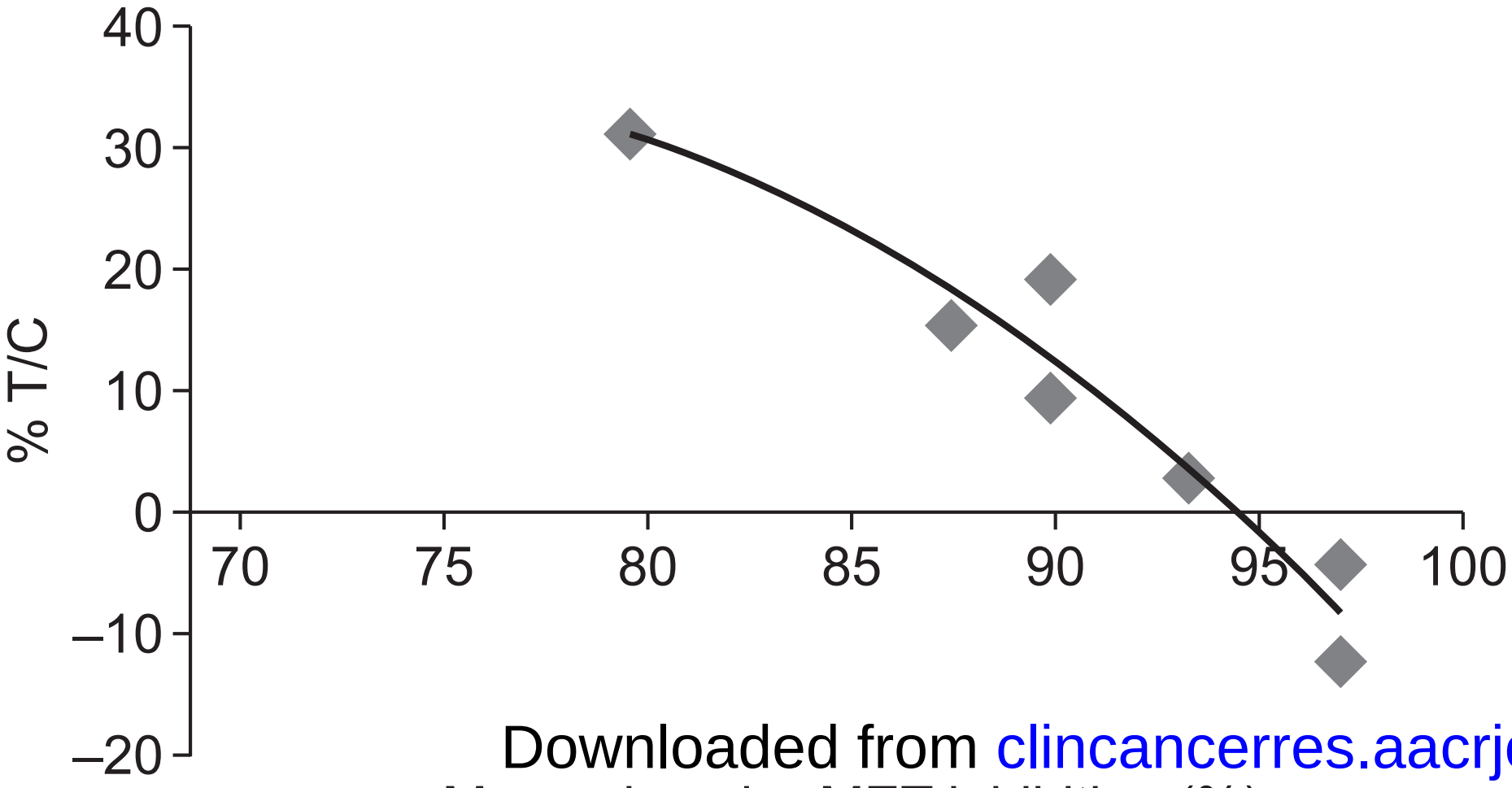
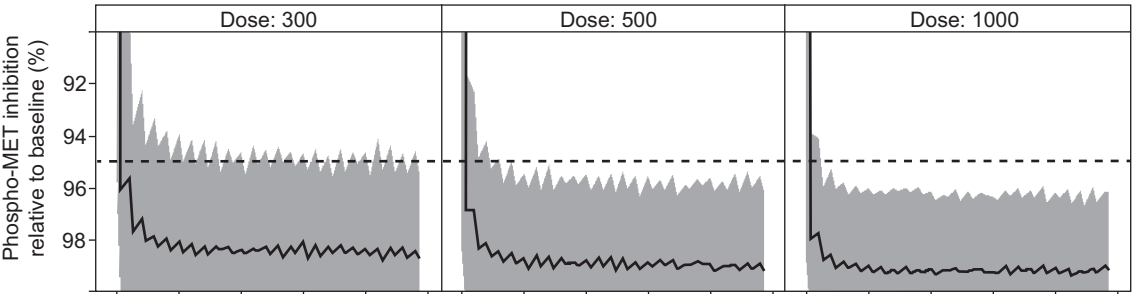


Figure 2C



AACR American Association for Cancer Research

Clinical Cancer Research

First-in-Man Phase I Trial of the Selective MET Inhibitor Tepotinib in Patients with Advanced Solid Tumors

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