**Supplementary Information**

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# Supplementary methods

## Inclusion criteria

To be eligible for this trial, patients were to meet all the following criteria:

1. Patients had read and fully understood the requirements of the trial, were willing to comply with all trial visits and assessments, and were willing and able to give informed consent.
2. Histologically or cytologically confirmed solid tumor, either refractory to standard therapy or for which no effective standard therapy was available.
3. Measurable or evaluable disease, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.
4. Estimated life expectancy >3 months.
5. Men or women aged ≥18 years.
6. Women of childbearing potential had to have a negative blood pregnancy test at the screening visit (baseline in Germany). For this trial, women of childbearing potential were defined as all women after puberty, unless they were postmenopausal (described as 2 years without menses) for at least 12 months, were surgically sterile (defined as oophorectomy, hysterectomy, and/or tubal ligation) or were sexually inactive.
7. Patients and their partners had to be willing to avoid pregnancy during the trial and until 3 months after the last trial treatment. Male patients with female partners of childbearing potential and female patients of childbearing potential had to, therefore, be willing to use adequate contraception as approved by the Investigator, such as a two-barrier method or one barrier method with spermicide or intrauterine device. In Germany, it was specified that highly effective methods of contraception must be used (defined as one that results in a failure rate of less than 1% per year when used consistently and correctly). Examples were combined oral contraceptives, intrauterine devices, implantable or injectable hormonal contraceptives together with a barrier method. In addition, male patients were to use adequate contraception throughout the trial (eg, condom and spermicidal jelly). This requirement was to begin 2 weeks before receiving the first trial treatment and end 3 months after receiving the last treatment.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
9. Adequate hematological function:

* Hemoglobin ≥9.0 g/dL
* Neutrophils >1.5 x 109/L
* Platelets ≥75 x 109/L.

1. Adequate liver function:

* Total bilirubin ≤1.5 x upper limit of normal (ULN)
* Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 x ULN.

For patients with liver metastases:

* Total bilirubin ≤1.5 x ULN
* AST/ALT ≤5 x ULN.

1. Adequate renal function:

* Serum creatinine <1.5 x ULN, or
* Calculated creatinine clearance >60 mL/min.

1. Resolution of all acute chemotherapy, radiotherapy, or surgery-related adverse events (AEs) to grade ≤2, except for alopecia.
2. Recovered from any surgical intervention.
3. After the maximum tolerated dose/recommended phase II dose had been determined, patients enrolling in the MET alteration expansion cohorts were to have *MET* amplification or overexpression in their tumor. These alterations had to be determined in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory.

## Exclusion criteria

Patients who met any of the following criteria were ineligible for this trial:

1. Received chemotherapy, immunotherapy, hormonal therapy (except patients with prostate cancer), biologic therapy, or any other anticancer therapy or unapproved investigational agent within 28 days (or five half-lives for noncytotoxics, whichever is shorter) of Day 1 of trial treatment (6 weeks for nitrosureas or mitomycin C).
2. Received extensive prior radiotherapy on more than 30% of bone marrow.
3. Symptomatic primary tumors or metastasis of brain and/or central nervous system, uncontrolled with anti-epileptics and required high doses of steroids.
4. Known human immunodeficiency viruses (HIV) positivity, active hepatitis C, or active hepatitis B.
5. Medical history of liver fibrosis/cirrhosis.
6. Signs and symptoms suggestive of transmissible spongiform encephalopathy, or family members who suffered from such.
7. Medical history of difficulty swallowing, malabsorption or other chronic gastrointestinal disease, or conditions that could have hampered compliance and/or absorption of the tested product.
8. Medical history of surgery within 6 weeks prior to enrollment.
9. Impaired cardiac function (left ventricular ejection fraction <45% defined by echocardiograph, serious arrhythmia, unstable angina pectoris, congestive heart failure).
10. New York Heart Association III and IV, myocardial infarction within the last 12 months prior to trial entry; signs of pericardial effusion.
11. Hypertension uncontrolled by standard therapies (not stabilized at 150/90 mm Hg).
12. Peripheral neuropathy grade ≥2.
13. Medical history of any other significant medical disease, major surgery, or psychiatric condition that could have impaired the patient’s well-being or precluded full participation in the trial.
14. Women who were pregnant or nursing.
15. Known drug abuse or alcohol abuse.
16. Required concurrent treatment with a nonpermitted drug.
17. Known hypersensitivity to any of the trial treatment ingredients.
18. Legal incapacity or limited legal capacity.
19. Any other reason that, in the opinion of the Principal Investigator, precluded the patient from participating in the trial.

## Pharmacokinetic (PK) bioanalytical assay

An enantioselective high-performance liquid chromatography–mass spectrometry (HPLC–MS/MS) method was used to quantify tepotinib. Plasma tepotinib concentration 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. In brief, the isotopically labeled internal standard [2H]MSC2156119A was added to K2EDTA plasma. Tepotinib was extracted by liquid–liquid extraction with methyl t-butyl ether. Samples were centrifuged, dried, reconstituted in 0.2% NH4OH in 5 mM ammonium bicarbonate, pH unadjusted: MeOH (50:50 v/v), and 10 µL aliquots of the supernatant were injected onto an Xbridge C18 column (2.1 x 50 mm; 5 µM; Waters, Milford, MA, USA). Separation was performed using a mobile phase gradient (eluent A: 0.2% NH4OH in 5 mM ammonium bicarbonate, pH unadjusted, eluent B: methanol) with a flow rate of 0.5 mL/min. Detection was performed in positive ionization mode on an AB Sciex API-4000 triple quadrupole mass spectrometer (AB Sciex, Framingham, MA, USA) with selected reaction monitoring (m/z 493.3–112.2 for tepotinib and 496.3–115.2 for its deuterated internal standard).

## Pharmacodynamic (PD) bioanalytical assay and calculation of target inhibition in tumors

A Luminex™ assay was used to semi-quantitatively determine total MET and phospho-MET in tumor tissue from patient biopsy samples. The extracellular domain of MET was detected using monoclonal antibody 95106 (R&D Systems) and phospho-MET was detected using monoclonal antibody D26 (Cell Signaling Technology) in a multiplex assay format. Total MET values were normalized by the respective total protein values to adjust for differences in biopsy material. Cut-off values were defined for total and phospho-MET depending on the sensitivity of the different measurements. Ratios (%) of phospho-MET to normalized total MET at baseline vs. on-treatment were calculated to assess inhibition of MET activity by tepotinib in paired biopsies.

MET phosphorylation in tumor, defined as phospho-MET fractional change from baseline (pMET), was calculated as the florescent intensity of tyrosine   
1234–1235 (Y1234-1235) double-normalized by the total MET concentration and by the baseline value, as expressed by the equation below:

Target inhibition, defined as phospho-MET inhibition, was calculated as shown below:

## 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, plasma concentration data were combined across individuals 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.

### 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.

### Mathematical modeling of PK–target modulation in human tumors

In the first-in-man trial, inhibition of MET kinase activity was assessed using paired tumor biopsies from patients: one obtained pre-treatment and one obtained on-treatment during Cycle 1. Data from 13 patients with evaluable phospho-MET inhibition were included in the PK/PD analysis (Supplementary Fig. S1).

Constrained by the limited human PD data, 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 first-in-man trial data, Monte-Carlo simulations were performed to predict the dose-dependent time profiles of target modulation at the population level. The PK inter-individual 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 and PD data. The data were fitted to the model using the least-squares procedure and Gauss-Newton with the Levenberg modification algorithm.

NONMEM® (version 7.3.0) was used to analyze clinical PK/PD data and for human simulations, first-order conditional estimation with interaction (FOCEI) implemented in NONMEM was used for model estimation.

# Supplementary Figure S1. Data exclusion tree for clinical PD analysis set.

LLD, lower limit of detection; PD, pharmacodynamics.

Patients with paired biopsies &

LLD

*n* = 28

LLD

*n* = 11

>>

*n* = 2

The rest

*n* = 9

≤ LLD

*n* = 17

2\*LLD &

2\*LLD

*n* = 4

The rest

*n =*  13

Analysis Set

Outliers

Unquantifiable pMET inhibition

Tumor PD data were collected from 28 patients for whom reliable data could be derived from paired biopsies and quantifiable phospho-MET levels in pretreatment samples, defined as mean florescence intensity (MFI) at phosphorylation site Y1234-1235 greater than the lower limit of detection (LLD). Eleven patients had quantifiable phospho-MET levels in on-treatment samples, with two having significantly higher levels (>50%) on treatment than at baseline. Data for those two patients were excluded from the analysis due to implausibility. Seventeen patients had phospho-MET levels below the LLD. Thirteen of these had moderate-to-low phospho-MET levels at baseline (pretreatment MFI Y <2x LLD); treatment-related phospho-MET inhibition was considered unevaluable and they were excluded from the analysis. Therefore, data from 13 patients were included in the PK/PD analysis.

# Supplementary Results

# Supplementary Figure S2. Mean pharmacokinetic profiles of tepotinib on day 14 in patients assigned to R1 and R3



500 mg\* = tablet micronized formulation. All other doses were given in the capsule micronized formulation.

# Supplementary Figure S3. Tumor response to tepotinib in evaluable patients according to dosing regimen, MET expression, and *MET* amplification status

Data for 10 patients are missing because post-baseline measurements were unavailable or disease could not be measured. MET expression score: 0–3.   
*MET* amplification status: + = amplified, – = not amplified. No recorded value indicates data missing.

SOLD, sum of longest diameters.

# Supplementary Figure S4. Phospho-MET inhibition in tumor biopsies compared with baseline after repeated dosing for at least 9 days.



On-treatment biopsies were taken between days 9–14 or 17–21 of cycle 1, or on day 1 of cycle 2. Horizontal line shows 95% phospho-MET inhibition. \*Complete phospho-MET inhibition.

# Supplementary Table S1. Median time on treatment (weeks) at each dose level by regimen

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Dose, mg** | **30a** | **30** | **60a** | **60** | **100** | **115b** | **115c** | **130** | **145** | **175** | **215** | **230a** | **300** | **315** | **400** | **500** | **700** | **1000** | **1400** | **Total** |
| **R1** | *n =* 3 | *n =* 3 | *n =* 3 | *n =* 3 | *n =* 3 | *n =* 6 | *n =* 6 | – | *n =* 3 | – | *n =* 3 | *n =* 3 | *n =* 3 | – | *n =* 3 | – | – | – | – | *n =* 42 |
| Median (range) | 6.0 (3.0–153.3) | 5.9 (2.9–6.4) | 6.1 (6.0–22.0) | 5.9 (3.0–25.0) | 6.0 (6.0–12.6) | 6.0 (4.9–12.0) | 5.5 (2.1–6.0) | – | 18.1 (3.0–24.3) | – | 6.0 (6.0–6.0) | 18.3 (6.0–45.7) | 9.0 (6.0–18.0) | – | 30.1 (6.1–57.0) | – | – | – | – | 6.0 (2.1–153.3) |
| **R2** | *n =* 3 | – | *n =* 4 | *n =* 6 | *n =* 6 | *n =* 6 | *n =* 7 | *n =* 6 | – | *n =* 3 | – | – | – | *n =* 4 | – | – | – | – | – | *n =* 45 |
| Median (range) | 6.0 (6.0–17.7) | – | 5.5 (2.0–6.1) | 6.0 (1.0–6.1) | 3.4 (2.7–16.9) | 9.1 (3.0–27.6) | 5.1 (1.0–7.7) | 5.9 (3.0–24.0) | – | 6.0 (6.0–15.0) | – | – | – | 10.5 (2.0–23.9) | – | – | – | – | – | 6.0 (1.0–27.6) |
| **R3** | – | – | – | – | – | – | – | – | – | – | – | – | *n =* 3 | – | – | *n =* 42 | *n =* 3 | *n =* 7 | *n =* 7 | *n =* 62 |
| Median (range) | – | – | – | – | – | – | – | – | – | – | – | – | 6.0 (3.9–13.0) | – | – | 6.0 (0.7–42.4) | 4.9 (4.7–12.0) | 6.0 (2.1–9.0) | 6.0 (5.9–94.9) | 6.0 (0.7–94.9) |

aNon-micronized tepotinib; bFasted; cFed. R, regimen.

# Supplementary Table S2. Treatment-related TEAEs for patients receiving the RP2D of tepotinib (500 mg, *n =* 42) occurring in 2 or more patients at any grade

|  |  |  |
| --- | --- | --- |
| **Patients, *n* (%)** | **Any grade** | **Grade ≥3a** |
| Treatment-related TEAEs | 27 (64.3) | 5 (11.9) |
| Peripheral edema | 11 (26.2) | 1 (2.4) |
| Fatigue | 9 (21.4) | 1 (2.4) |
| Decreased appetite | 7 (16.7) | 0 |
| Nausea | 5 (11.9) | 0 |
| Vomiting | 4 (9.5) | 1 (2.4) |
| Blood creatinine increased | 3 (7.1) | 0 |
| Constipation | 3 (7.1) | 0 |
| Transaminases increased | 3 (7.1) | 0 |
| Anemia | 2 (4.8) | 0 |
| Diarrhea | 2 (4.8) | 0 |
| Hypomagnesemia | 2 (4.8) | 0 |
| Rash | 2 (4.8) | 0 |

aGrade ≥3 hypoalbuminemia, hyponatremia, ALT increased, and thrombocytopenia were also reported (each *n =* 1).

ALT, alanine aminotransferase; RP2D, recommended phase II dose; TEAE, treatment-emergent adverse events.

# Supplementary Table S3. PK data at day 1 in fed patients (R1+R3, once-daily dosing) after first dose

| **Dose (mg)** | ***n*** | **Cmax (ng/mL)** | **tmax (h)** | **tlag (h)** | **AUC0–24h, h\*ng/mL** |
| --- | --- | --- | --- | --- | --- |
| 30 (C, R1) | 3 | 57 (20.4) [46–69] | 8.0 [2.0–24.1] | 0.52 [0.25–2.00] | 849 (24.3) [657–1058] |
| 60 (C, R1) | 3 | 71 (19.3) [61–88] | 10.0 [8.0–24.0] | 0.60 [0.25–1.00] | 1283 (23.9) [1037–1652] |
| 100 (C, R1) | 3 | 107 (29.6) [83–147] | 10.0 [4.0–24.0] | 1.00 [0.30–1.00] | 1731 (14.9)a [1559–1922] |
| 145 (C, R1) | 3 | 147 (24.0) [112–173] | 8.0 [8.0–10.0] | 0.50 [0.25–1.00] | 2455 (15.4) [2067–2771] |
| 215 (C, R1) | 3 | 194 (55.3) [111–308] | 8.0 [4.0–24.0] | 0.25 [0.25–0.50] | 3090 (61.2) [1794–5531] |
| 300 (C, R1) | 3 | 306 (42.2) [221–482] | 10.0 [4.1–24.0] | 0.50 [0.25–0.58] | 5463 (49.9) [3628–9154] |
| 300 (C, R3) | 3 | 247 (32.7) [181–342] | 8.0 [8.0–24.0] | 0.25 [0.25–0.50] | 4207 (33.5) [3291–6087] |
| 400 (C, R1) | 3 | 348 (18.6) [283–403] | 8.0 [8.0–10.1] | 0.53 [0.25–1.00] | 6176 (17.8) [5078–7148] |
| 500 (C, R3) | 19 | 330 (72.4) [61–1110] | 10.0 [4.0–24.0] | 1.00 [0.00–4.00] | 5918 (74.8)b [1026–20,200] |
| 500 (T, R3) | 22 | 461 (58.7) [165–1430] | 8.0 [4.0–24.1] | 0.75 [0.25–4.03] | 7637 (66.7) [1423–28,024] |
| 700 (C, R3) | 3 | 434 (27.6) [326–559] | 10.0 [4.0–24.0] | 0.50 [0.33–0.50] | 7576 (24.6) [6381–8995] |
| 1000 (C, R3) | 7 | 666 (46.0) [402–1100] | 10.0 [4.0–10.2] | 1.00 [0.25–1.00] | 11,796 (48.1)c [6575–19,036] |
| 1400 (C, R3) | 6 | 863 (37.4) [529–1240] | 24.0 [8.0–24.0] | 1.00 [0.50–1.00] | 15,542 (41.9) [9421–24,407] |

a*n* = 2; b*n* = 18; c*n* = 6.

Cmax and AUC0–24h values are geometric mean (% CV) [range], Tmax and Tlag values are median [range].

AUC0–24h, area under the plasma concentration vs. time curve from time zero (dose given) to the last sampling time (24 hours) within one dosing interval; C, capsule; Cmax, maximum plasma concentration; PK, pharmacokinetic; R1, regimen 1; R3, regimen 3; T, tablet; Tmax, time taken to reach maximum plasma concentration; Tlag, time prior to the first measurable (non-zero) concentration.

# Supplementary Table S4. Steady-state PK data at day 14 in fed patients after once-daily dosing (R1+R3)

| **Dose (mg)** | ***n*** | **Cmax (ng/mL)** | **tmax (h)** | **CLss/f (L/h)** | **Cav (ng/mL)** | **AUC0–24h, h\*ng/mL** |
| --- | --- | --- | --- | --- | --- | --- |
| 30 (C, R1) | 2 | 113 (26.1)  [94–135] | 2.1  [0.0–4.3] | 13.24 (29.5)  [10.79–16.24] | 94.44 (29.5)  [77.0–115.9] | 2267 (29.5)  [1847–2781] |
| 60 (C, R1) | 3 | 205 (24.2)  [156–245] | 8.0  [4.0–8.0] | 13.50 (28.1)  [11.08–18.51] | 185.13 (28.1)  [135.1–225.7] | 4443 (28.1)  [3241–5416] |
| 100 (C, R1) | 3 | 263 (10.2)  [234–283] | 8.0  [4.0–24.0] | 18.18 (7.0)  [16.77–18.97] | 229.15 (7.0)  [219.6–248.4] | 5500 (7.0)  [5271–5961] |
| 145 (C, R1) | 3 | 379 (19.8)  [333–475] | 4.0  [0.0–24.0] | 17.90 (18.0)  [14.57–19.96] | 337.5 (18.0)  [302.7–414.7] | 8100 (18.0)  [7264–9953] |
| 215 (C, R1) | 3 | 697 (49.8)  [524–1200] | 8.0  [4.0–8.0] | 15.43 (50.9)  [9.02–22.78] | 580.77 (50.9)  [393.2–993.1] | 13,938 (50.9)  [9438–23,835] |
| 300 (C, R1) | 3 | 811 (12.3)  [724–923] | 8.0  [0.0–10.2] | 16.41 (12.4)  [1468–18.73] | 761.52 (12.4)  [667.3–851.6] | 18,277 (12.4)  [16,016–20,438] |
| 300 (C, R3) | 3 | 742 (45.7)  [449–984] | 10.0  [0.5–10.0] | 19.12 (50.8)  [13.37–32.95] | 649.8 (50.0)  [379.3–916.9] | 15,598 (50.0)  [9104–22,019] |
| 400 (C, R1) | 3 | 563 (45.0)  [358–841] | 0.3  [0.0–10.0] | 32.64 (49.1)  [21.07–53.13] | 510.7 (49.1)  [313.7–791.0] | 12,257 (49.1)  [7529–18,985] |
| 500 (C, R3) | 17 | 943 (34.6)  [497–1570] | 8.0  [0.0–24.0] | 24.74 (33.5)  [14.92–45.30] | 840.4 (33.5)  [459.9–1396.1] | 20,169 (33.5)  [11,038–33,507] |
| 500 (T, R3) | 18 | 1291 (48.1)  [599–2960] | 8.0  [2.0–24.0] | 26.43 (87.5)  [7.31–92.60] | 1097.9 (47.1)  [540.0–2848.5] | 27,438 (51.7)a  [13,741–68,365] |
| 700 (C, R3) | 3 | 1006 (39.4)  [815–1560] | 3.2  [0.3–8.0] | 40.92 (3.2)  [39.76–42.35] | 916.9 (43.2)  [717.1–1477.9] | 21,972 (42.9)  [17,210–35,309] |
| 1000 (C, R3) | 6 | 1219 (59.2)  [653–2940] | 8.8  [0.0–24] | 36.08 (58.6)  [14.68–68.20] | 1133.4 (59.4)  [610.9–2793.4] | 27,214 (59.4)  [14,662–67,062] |
| 1400 (C, R3) | 4 | 1805 (31.2)  [1150–2220] | 9.1  [2.8–24.0] | 35.2 (29.5)  [26.74–52.44] | 1639 (28.1)  [1112.3–2095.6] | 39,284 (28.0)  [26,696–50,040] |

a*n* = 13.

Cmax, CLss/f, Cav and AUC0–24h values are geometric mean (% CV) [range], Tmax values are median [range].

AUC0–24h, area under the plasma concentration vs. time curve from time zero (dose given) to the last sampling time (24 hours) within one dosing interval; C, capsule; Cav, average concentration at steady state; CLSS/f, apparent total body clearance of drug at steady state; Cmax, maximum plasma concentration; PK, pharmacokinetic; R1, regimen 1; R3, regimen 3; T, tablet; Tmax, time taken to reach maximum plasma concentration.

# Supplementary Table S5. PK data at day 1 in fed patients (R2, 3 times a week dosing) after first dose

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Dose (mg)** | ***n*** | **Cmax (ng/mL)** | **tmax (h)** | **tlag (h)** | **AUC0–48h (h\*ng/mL)** |
| 60 (C, R2) | 6 | 56 (53.6)  [26–100] | 9.0  [4.0–24.2] | 0.50  [0.00–1.00] | 1772 (43.1)  [850–2677] |
| 100 (C, R2) | 6 | 116 (59.3)  [43–226] | 8.0  [4.0–23.8] | 0.50  [0.08–0.50] | 3657 (42.0)  [1758–5224] |
| 130 (C, R2) | 6 | 135 (22.3)  [94–171] | 9.0  [4.0–24.3] | 0.50  [0.27–1.00] | 3794 (32.1)  [2475–5246] |
| 175 (C, R2) | 3 | 142 (58.9)  [101–267] | 8.0  [4.0–24.0] | 0.50  [0.00–1.00] | 4660 (44.9)  [3614–7644] |
| 315 (C, R2) | 4 | 334 (78.5)  [158–846] | 24.0  [8.0–24.0] | 2.00  [1.00–2.05] | 10,786 (49.4)  [5893–18,191] |

Cmax and AUC0–24h values are geometric mean (% CV) [range], tmax and tlag values are median [range].

AUC0–48h, area under the plasma concentration vs. time curve from time zero (dose given) to the last sampling time (48 hours) within one dosing interval; C, capsule; Cmax, maximum plasma concentration; PK, pharmacokinetic; R2, regimen 2; T, tablet; Tmax, time taken to reach maximum plasma concentration; Tlag, time prior to the first measurable (non-zero) concentration.

# Supplementary Table S6. PK data at day 19 in fed patients after dosing three times weekly (R2)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Dose (mg)** | ***n*** | **Cmax (ng/mL)** | **tmax (h)** | **CLss/f (L/h)** | **Cav (ng/mL)** | **AUC0–48h (h\*ng/mL)** |
| 60 (C, R2) | 5 | 89 (53.0)  [47–161] | 10.0  [4.1–10.1] | 19.79 (55.8)  [10.33–33.14] | 63.16 (55.8)  [37.7–121.0] | 3032 (55.8)  [1811–5808] |
| 100 (C, R2) | 5 | 181 (34.4)  [129–263] | 10.0  [2.0–24.1] | 13.22 (35.0)a  [9.83–18.05] | 157.62 (35.0)a  [115.4–211.9] | 7566 (35.0)a  [5540–10,169] |
| 130 (C, R2) | 6 | 178 (67.6)  [61–300] | 8.0  [4.0–10.0] | 24.50 (62.6)**b**  [15.55–53.83] | 110.53 (62.6)b  [50.3–174.2] | 5306 (62.6)b  [2415–8362] |
| 175 (C, R2) | 3 | 301 (8.9)  [272–323] | 10.0  [8.0–10.0] | 19.34c | 188.6c | 9051.1c |
| 315 (C, R2) | 3 | 722 (32.2)  [508–930] | 8.0  [8.0–25.9] | 11.35 (25.1)  [9.56–15.07] | 578.34 (25.1)  [435.5–686.7] | 27,760 (25.1)  [20,905–32,962] |

a*n* = 4; b*n* = 5; c*n* = 1.

Cmax, CLss/f, Cav and AUC0–48h values are geometric mean (% CV) [range], tmax values are median [range].

AUC0–48h, area under the plasma concentration vs. time curve from time zero (dose given) to the last sampling time (48 hours) within one dosing interval; C, capsule; Cav, average concentration at steady state; CLSS/f, apparent total body clearance of drug at steady state; Cmax, maximum plasma concentration; R2, regimen 2; PK, pharmacokinetic; Tmax, time taken to reach maximum plasma concentration.

# Supplementary Table S7. PK/PD parameters in human (phospho-MET inhibition in tumor)

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 full inhibitory turnover model developed based on KP-4 xenograft tumor data was applied to fit the human data, with a treatment effect inhibiting the rate of phospho-MET production by tepotinib concentration following a sigmoidal Imax function. The system turnover parameters (kin, kout) were fixed to preclinical estimates, assuming similarities of phospho-MET build-up and degradation between KP-4 xenograft tumors and human solid tumors, while the potency parameter of tepotinib-dependent inhibition (IC50) was estimated based on clinical data.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phosphorylation site | Kout (1/h) | λ | IC50 (ng/mL) | R0 (%) |
| Estimate  CV% | 2.43  n.a. | 0.984  n.a. | 9.43  37 | 100 Fixed  n.a. |

λ, Hill coefficient; CV, coefficient variation; IC50, drug concentration inducing half of the maximum effect; Kout: rate constant for loss of the response; n.a., not applicable; PD, pharmacodynamic; PK, pharmacokinetic; R0: percentage phospho-MET level at baseline.