Model-based phase II dose selection of the c-Met inhibitor tepotinib (MSC2156119J)

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Introduction

- The mesenchymal-epithelial transition factor (c-Met) receptor tyrosine kinase is a cell surface receptor mediating cell migration, survival, and proliferation.[1–3]
- c-Met overexpression is correlated with aggressive tumor growth, leading to poor clinical prognosis.[1,2] Therefore, inhibition of this signaling pathway is expected to be a promising therapeutic strategy.
- Tepotinib is an orally administered, reversible, ATP-competitive, highly potent and selective c-Met receptor tyrosine kinase inhibitor that has promise as an anticancer agent.
  - Tepotinib has been shown to impede growth and induce regression of HGF-dependent and HGF-independent tumors in preclinical models.[4]
- The maximum tolerated dose of tepotinib was not reached at up to 1,400 mg/day in a first-in-man study in patients with solid tumors.[5]
- The recommended phase II dose (RP2D) was selected based on a translational modeling approach that integrated the quantitative relationship between dose, exposure, target inhibition, and tumor growth inhibition in humans and in xenograft mice to define a biologically active dose.
- This dose has been used to guide the design of three ongoing phase Ib/II trials in hepatocellular carcinoma and non-small cell lung cancer (NCT01988493, NCT02115373, and NCT01982955).

Objectives

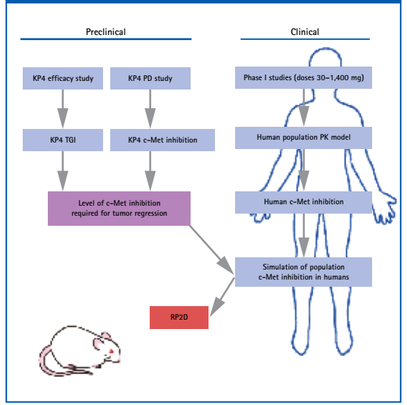
- To estimate the level of target inhibition required to achieve tumor regression in KP4 xenograft mice.
- To evaluate the dose–exposure–tumor target inhibition relationship of tepotinib in patients with solid tumors.
- To determine the RP2D of tepotinib based on the simulated human phosphorylated c-Met (phospho-c-Met) inhibition profiles.

Methods

Preclinical

- The KP4 cell line xenograft was selected as a conservative model for estimating the preclinical pharmacodynamic (PD) effect and efficacy (Figure 1).
- Target inhibition was determined by comparing the phospho-c-Met levels (Y^{1234}/Y^{1235}) in on-treatment biopsies and pre-treatment biopsies. Measured phospho-c-Met levels were normalized using total protein and total c-Met protein levels
- Model evaluation of both target inhibition (one single-dose study + one multiple-dose study) and tumor growth inhibition (two multiple-dose studies) was performed using Phoenix WinNonlin® version 6.2.1.

Figure 1. Study model



PD, pharmacodynamic; PK, pharmacokinetic; RP2D, recommended phase II dose; TGI, tumor growth inhibition.

Clinical

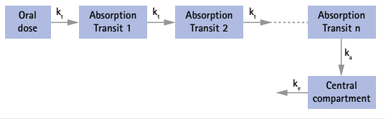
- The inhibition of c-Met in humans was determined using a Luminex-based assay:[6]
  - The test uses a monoclonal antibody specific for the c-Met autophosphorylation (Y^{1234}/Y^{1235}) site.
  - Target specificity and sensitivity and assay reproducibility have all been validated using lung carcinoma A549 cell line lysates and tumor homogenates.
  - Paired biopsies (pre- and on-treatment) from patients in the FIM study dose-escalation cohorts (60–500 mg) were tested for c-Met autophosphorylation.
  - Total protein-corrected c-Met concentrations were used for normalization of phospho-c-Met levels (Figure 1).
- Human plasma pharmacokinetic (PK; dose level 30–1,400 mg) and target inhibition data were analyzed using the population approach, utilizing a structural model of target inhibition previously developed using data from KP4 xenograft mice.
- To determine the RP2D, human PK profiles and c-Met inhibition were simulated, aiming for a level of c-Met inhibition that achieves tumor regression in mice.
- Model evaluation and simulation were performed using NONMEM® version 7.2.

Results

Population PK model

- A two-compartment linear model with first-order absorption and transit compartments best described the PK of tepotinib from four phase I/Ib trials dosed from 30–1,400 mg (Figure 2).

Figure 2. Human PK model



k_a, absorption rate constant; k_e, elimination rate constant; k_t, transit rate constant.

- Inter-individual variability of the absorption rate constant (174.8%), apparent clearance (40.7%), and apparent volume of distribution (47.1%) were identified (Table 1).

Table 1. Parameter estimates of population PK model

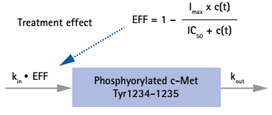
Structural parameters	Estimate	RSE
K_A: Absorption rate constant [/h]	0.522	17.5%
CL: Apparent clearance [L/h]	19.1	4%
V_1: Apparent central volume of distribution [L]	1060	5.1%
Q: Apparent inter-compartment clearance [L/h]	3.35	4.6%
V_2: Apparent peripheral volume of distribution [L]	1110	14.6%
K_t: Absorption transit rate constant [/h]	2.28	3.8%
Proportional residual error	0.211	0.9%
Additive residual error	14	0.1%

Inter-individual variability (RSE)	K_A	CL	V_1	Shrinkage
K_A	174.8% (11.2%)			15.7
CL	-0.5% (0.0531)	40.7% (7.2%)		8.8
V_1	50.8 (0.067)	31% (0.018)	47.4% (5.9%)	12.6

Target inhibition model

- In preclinical KP4 xenograft mice, phospho-c-Met inhibition in tumors was described by a turnover full maximum of treatment inhibition effect (I_{max}) model (Figure 3).

Figure 3. Turnover model for phospho-c-Met inhibition



c, concentration; IC_{50}, drug concentration inducing half of the maximum inhibition effect; I_{max}, maximum of treatment inhibition effect; k_{in}, zero-order rate constant of system build-up; k_{out}, first-order output rate constant; t, time.

- The turnover model developed from mouse data was utilized to evaluate the level of c-Met inhibition in human tumors. System turnover parameters (zero-order rate constant of system build-up [k_{in}], first-order output rate constant [k_{out}]) were set equal to the estimates in mice, while the potency parameter (half-maximal inhibitory concentration [IC_{50}]) in humans was estimated to be 27.5 ng/mL using the available human data from tumor biopsies (Table 2).

Table 2. Parameter estimates for the pMET inhibition model

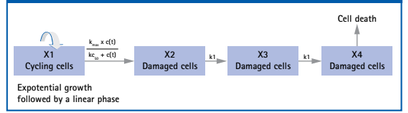
		Estimate	CV%
KP4 mice	K_{in}: zero-order rate constant of system build-up (h^{-1})	2.34	41.3
	I_{max} – maximum of treatment inhibition effect	1 FIX	–
	IC_{50}: drug concentration inducing half of the maximum inhibition effect (ng/mL)	46.0	21.7
Human	K_{in}: zero-order rate constant of system build-up (h^{-1})	2.34 FIX	–
	I_{max} – maximum of treatment inhibition effect	1 FIX	0.9
	IC_{50}: drug concentration inducing half of the maximum inhibition effect (ng/mL)	27.5	2.04

CV, coefficient of variance.

Preclinical tumor inhibition model

- Tumor volume was calculated as $l*w^2/2$, where l represents the longest diameter of the tumor mass and w represents the diameter perpendicular to the longest diameter.
- KP4 xenograft tumor growth inhibition was best described by the Simeoni model with a maximum achievable response (Emax) treatment effect (Figure 4, Table 3).[7]
- Simulations demonstrated that nearly complete phospho-c-Met inhibition (≥95%) is required for tumor stasis or regression in this model (KP4).

Figure 4. Simeoni tumor growth model with E_{max} treatment effect



c, concentration; kc_{50}, drug concentration inducing half of the maximum effect; k_{max}, the maximum effect attributed to the drug; t, time.

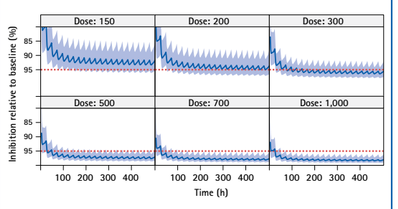
Table 3. Parameter estimates for the Simeoni tumor growth inhibition model in KP4 xenograft mice

	Estimate	CV%
Λ_0: first-order rate constant of exponential growth (h^{-1})	0.00678	11.5
Λ_1: zero-order rate constant of linear growth (h^{-1})	3.99	6.9
k_{max}: maximum effect attributed to drug (h^{-1})	0.00880	12.5
kc_{50}: drug concentration inducing half of the maximum effect (ng/mL)	23.9	44.4
k_1: first-order rate constant of cell death (h^{-1})	0.136	85.9
ω_0: tumor volume at baseline (mm^3)	239	7.4
Ψ: constant describing system passing from exponential to linear growth	20 FIX	

Simulation of human target inhibition

- Assuming additional 30% inter-individual variability of the IC_{50}, human c-Met inhibition profiles were simulated based on the population PK/target inhibition model (Figure 5).
- Simulations suggested that a 500 mg daily dose regimen could achieve continuous phospho-c-Met inhibition of ≥95% in 90% of the population.

Figure 5. Simulation of human phospho-c-Met inhibition (80% CI)



Conclusions

- The population PK of tepotinib was fitted to a two-compartment PK model with delayed absorption. c-Met inhibition in human tumor lesions was described by a turnover model structurally developed in KP4 xenograft mice, showing a 1.7-times higher potency in humans than in mice.
- Efficacy profiles in KP4 xenograft mice suggested that nearly complete phospho-c-Met (95%) inhibition is required for tumor regression.
- With this translational modeling approach, a biologically active dose of 500 mg was proposed as the RP2D for single-agent tepotinib. This dose is considered to achieve a continuous inhibition level of ≥95% in 90% of the population.
- The 500 mg/day dose of tepotinib has been set as the target RP2D in three ongoing phase I/II trials (NCT01988493, NCT02115373, and NCT01982955). Interim evaluation of the pharmacokinetic characteristics of the specific trial populations will allow dose justification, if necessary.

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Acknowledgments

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Disclosures

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*An affiliate of Merck KGaA, Darmstadt, Germany.

Tepotinib is currently under clinical investigation and has not been approved by any regulatory authority. Status: April 2015.