Model–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 survival, proliferation, and migration.\textsuperscript{1} c-Met overexpression is correlated with aggressive tumor growth, leading to poor clinical prognosis.\textsuperscript{2} Therefore, inhibition of this signaling pathway is expected to improve clinical outcomes.\textsuperscript{3,4} 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.\textsuperscript{5}

Tepotinib has shown to improve growth and induce regression of c-Met-dependent and c-Met-independent tumors in preclinical models.\textsuperscript{2,3,5–7} The maximum tolerated dose of tepotinib was not reached at 1,400 mg/day in a first-in-man study in patients with solid tumors.\textsuperscript{5}

The preclinical phase I dose escalation study selected based on the translational modeling approach that integrated the quantitative relationship between dose, pharmacokinetics, target inhibition, and tumor growth inhibition in humans and in mice to define a biologically active dose.\textsuperscript{2}

This dose has been used to design the three ongoing phase III trials (NCT02458038, NCT02115373, and NCT02116265).

Objectives

\textbullet{} To estimate the level of target inhibition required to achieve tumor regression
\textbullet{} To evaluate the dose–response-target inhibition relationship for c-Met in patients with solid tumors
\textbullet{} To determine the RP2D of tepotinib based on the simulated human pharmacodynamic (PD) and therapeutic effect in the KP4 xenograft model

Methods

\textbf{Preclinical}

The 4P3 cell line xenograft was selected as a conservative model for human c-Met-dependent tumors because of its high expression of c-Met and good xenograft properties.\textsuperscript{5}

\textbf{Clinical}

The inhibition of c-Met in humans was determined using a phospho-c-Met Western blot assay. The test uses a monoclonal antibody specific for the c-Met tyrosine kinase phosphorylated at Tyr1234-1235.\textsuperscript{5}

\textbullet{} Target specificity and sensitivity and assay reproducibility have all been validated using standard cell lines (A549 and PC-3). Linearity and interassay variations were determined using frozen normal and tumor lysates.

\textbullet{} Tumor volume was calculated as \(l \times w^2 / 2\), where \(l\) represents the longest diameter and \(w\) the perpendicular to the longest diameter.

\textbf{Results}

\textbf{KP4 PK model}

A two-compartment linear model with first-order absorption and transit compartments best described the PK of tepotinib from four phases (0–1410 mg up to 1410 mg) (Figure 2).

\textbf{KP4 human PD study}

\textbullet{} Phospho-c-Met inhibition in the KP4 xenograft model with first-order absorption and transit compartments best described the PK of tepotinib from four phases (0–1410 mg up to 1410 mg) (Figure 2).

\textbf{Simulation of human target inhibition}

Simulations demonstrated that nearly complete phospho-c-Met (95%) inhibition is required for tumor regression. An assumed additional 30% inter-individual variability of the IC\textsubscript{50} parameter led to the simulation of 500 mg daily dose regimen could achieve continuous phospho-c-Met inhibition of >50% in 95% of the population.

\textbf{Conclusions}

The population PK of tepotinib was fitted to a non-compartmental model with a sigmoidal doseresponse relationship. c-Met inhibition in human tumor lesions was described by a tumor model structurally developed and validated using gold-standard mice, showing a 1.3-times higher potency in humans than in mice.\textsuperscript{8}

Efficacy profiles in KP4 xenograft suggested that nearly complete phospho-c-Met (\(>95\%\)) inhibition is required for tumor regression.

With the translational modeling approach, a biologically active dose of 520 mg was proposed as the RP2D for single-agent tepotinib. This dose is considered to achieve a level of c-Met inhibition of \(>50\%\) in 95% of the population. The 500 mg dose of tepotinib has been set as the target RP2D in three ongoing phase I trials (NCT01964949, NCT01215732, and NCT02116265).

Table 1. Parameter estimates of population PK model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (CV)</th>
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<tbody>
<tr>
<td>(k_{a})</td>
<td>1/54 (18.4)</td>
</tr>
<tr>
<td>(k_{e})</td>
<td>1/54 (18.4)</td>
</tr>
<tr>
<td>(k_{t})</td>
<td>1/54 (18.4)</td>
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\textbf{Table 2. Parameter estimates for the Simeoni tumor growth model}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (CV)</th>
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<tbody>
<tr>
<td>(K_{m})</td>
<td>0.211 (0.9%)</td>
</tr>
<tr>
<td>(K_{1})</td>
<td>0.33 (4.6%)</td>
</tr>
<tr>
<td>(k_{m})</td>
<td>46.0 (21.7)</td>
</tr>
<tr>
<td>(k_{r})</td>
<td>0.9 (46.0)</td>
</tr>
</tbody>
</table>

\textbf{References}

4. Serono, Lausanne, Switzerland.
5. AJ, FB, MK, SEB: Employee of Merck KGaA, Darmstadt, Germany.
8. Serono, Lausanne, Switzerland.

\textbf{Acknowledgments}

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\textbf{Disclosures}

Merck KGaA, Darmstadt, Germany, sponsored the study. The study sponsors had influence on the study design and were involved in the interpretation of the data. The corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication.

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