A Long-acting and CD122-enhanced IL-2 analog, HM16390, shows a potent and durable anti-tumor effect in both syngeneic B16F10 or CT26 mouse models

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Introduction

Although recombinant IL-2 was approved for the treatment of metastatic renal cell carcinoma and melanoma, suboptimal ligand interaction required high-dose administrations, resulting in dose-limiting toxicity such as vascular leak syndrome. To overcome the limitation, a number of pharmaceutical companies have developed CD25 binding attenuated IL-2 muteins via various platform technology. These physical changes, however, accompanied a decrease in CD122-mediated signaling which was associated with cytotoxic lymphocyte expansion, leading to unsatisfied clinical consequence. In this context, we developed HM16390, a long-acting IL-2 analog with enhanced CD122 binding affinity to elicit potent anti-tumor efficacy. Furthermore, optimal binding affinity to CD25 was incorporated to prevent unwanted toxicity.

The aim of this study was to evaluate the long-lasting PK profile of HM16390 and to investigate the anti-tumor activity of HM16390 in tumor syngeneic mouse models representing different tumor immune microenvironments.

Structural features of HM16390

- Recombinant IL-2 analog
- No linker
- Aglycosylated Fc fragment

Antitumor efficacy in poorly immunogenic tumor model

- Experimental design for pharmacokinetics of HM16390 in mice
- Pharmacokinetics of HM16390 in mice
- Table 1. PK parameters of HM16390 in mice

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<table>
<thead>
<tr>
<th>Test sample</th>
<th>AUC(0-24h) (ng*h/mL)</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (hr)</th>
<th>T1/2 (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>95,046</td>
<td>3,940</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>HM16390</td>
<td>273,424</td>
<td>7,270</td>
<td>120</td>
<td>22.52</td>
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<tr>
<td>Aldesleukin</td>
<td>804,878</td>
<td>20,293</td>
<td>288</td>
<td>8.0</td>
</tr>
</tbody>
</table>

- Pharmacokinetic profiles of HM16390 in mice.
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- Figure 1. Pharmacokinetic profiles of HM16390 in mice.

Concluding Remarks

- HM16390, a long-acting and CD122-enhanced IL-2 analog, demonstrated potent and durable anti-tumor activity in murine models with a wide range of immunogenic states through CD122-enhanced IL-2 agonism.

It is noteworthy that HM16390 exhibited potent antitumor activity, significant inhibition of tumor growth and extension of overall survival despite the poor immunogenicity of the B16F10 melanoma model.

Data on the immune response of HM16390 in the tumor microenvironment and the synergistic effect with anti-PD1 are available for poster presentation at the 2023 AACR (abstract presentation number #1831/3, section 24, Jaehyuk Choi, et al).

References


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