A Long-acting and CD122-enhanced IL-2 analog, HM16390, synergizes with immune checkpoint inhibitor by remodeling an immune cell profile in tumor microenvironment

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Introduction

Immune checkpoint inhibitors (ICPIs) are widely used in cancer immunotherapy. However, the response to ICPIs depends on the phenotype of the tumor microenvironment (TME)\(^1\). Cold tumors, also known as immune-excluded or desert tumors, have shown a poor response to ICPIs due to the absence of effector T cells in the TME\(^2\). IL-2, which is an immune stimulator able to expand cancer-fighting cells in the TME, may be a promising therapeutic partner to overcome a limitation of ICPIs\(^2\).

Here, we investigated the immune cells composition in TME following HM16390 treatment and synergistic anti-tumor activity after combination with anti-PD1 in poorly immunogenic tumor syngeneic mice model.

Method & Result

TME modulation in a poorly immunogenic tumor model

Figure 1. Experimental design for evaluating immune cell phenotyping in tumor.

- **HM16390** expands tumor-infiltrating cytotoxic lymphocytes, switching **cold tumor** to **hot tumor** that are more responsive to CPI.

- **Cold tumor**
  - (Poor immunogenic)
  - Tumor cell with CTLs

- **Hot tumor**
  - (Highly Immunogenic)
  - Tumor cell with CTLs

Figure 2. HM16390 induced favorable tumor immune microenvironment in B16F10 melanoma mice.

(a) CD8+ T cell population in TILs
(b) Treg population in TILs

- A single subcutaneous administration of HM16390 increased the frequency of tumor infiltrating CD8+ T cells in dose-dependent manner (A). Furthermore, regulatory T cells were downregulated in TILs (B).

- A significant increase in the CD8+ T cell / Treg ratio in TME (C) represents favorable tumor immune microenvironment modulation, leading to significantly decreased tumor growth in a poorly immunogenic B16F10 melanoma mouse model (D).

- CD8+ T cells stimulated by HM16390 significantly expressed intracellular effector molecules, including GrzB and granzyme B compared to the aldesleukin treated group (E). TIL: tumor-infiltrating lymphocytes, i.p: intraperitoneal, QD: once daily, s.c: subcutaneous

Figure 3. Experimental design for evaluating the synergistic effect with anti-PD1.

- With anti-PD1 in poorly immunogenic tumor syngeneic mice model.

- Tumor volume was assessed three times per week by a digital caliper and survival was monitored up to study day 49.

Figure 4. Tumor growth during the respective therapies in B16F10 mice.

- HM16390, a long-acting IL-2 analog, showed a tremendous synergy in tumor growth inhibition after combination with an anti-PD1 antibody within the tolerable dose range.

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Synergy with CPI in a poorly immunogenic tumor model

Table 1. Comparison of anti-tumor activity at the end of study (Day 49)

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Vehicle</th>
<th>Anti-mPD1</th>
<th>Aldesleukin</th>
<th>HM16390</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR rate (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>TGI (%)</td>
<td>47.8</td>
<td>69.3</td>
<td>78.2</td>
<td>104.1</td>
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<tr>
<td>mOS (day)</td>
<td>10</td>
<td>22.5</td>
<td>34.5</td>
<td>40</td>
</tr>
</tbody>
</table>

- Since 49 days after drug treatment, complete response was observed in 97% (n=7/8) of animals treated with a combination of HM16390 and anti-PD1. On the other hand, none of the animals survived in the group of aldesleukin and anti-PD1 combination.

- HM16390 effectively inhibited tumor growth and prolonged survival by synergistic action with anti-PD1 therapy. TGI (tumor growth inhibition) was calculated on day 10 after treatment, when the vehicle group had all survived. mOS: mean overall survival

Concluding Remarks

- **HM16390**, a long-acting IL-2 analog, markedly inhibited tumor growth and significantly prolonged overall survival by effectively infiltrating and activating the cytotoxic immune cells into the tumor microenvironment. Moreover, this immune profile remodeling and effects on T cell expansion/activation provides the immune-checkpoint inhibitor to be in sufficiently responsive environments.

References