Durable anti-tumor effect induced by a long-acting and ‘Beta-intensified’ IL-2 mutein, HM16390, in various immunological conditions

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INTRODUCTION

• While recombinant human IL-2 (rhIL-2) was approved for metastatic renal cell carcinoma and melanoma, its suboptimal binding affinities to IL-2 receptor subunits require high-dose treatment, leading to dose-limiting toxicities, such as vascular leak syndrome (VLS) and cytokine release syndrome (CRS).
• To overcome these unwanted toxicities, next-generation IL-2 analogs were developed through blocking the IL-2 receptor alpha (CD25). In some cases, however, a binding affinity to IL-2 receptor beta (CD122) involved in immune activation was also decreased.
• Since IL-2 analog with increased CD122 binding affinity and absence of CD25 binding exhibited not only potent anti-tumor effect, but also dose-limiting toxicities, we focused more on optimal effectiveness by tuning the affinity balance between CD122 and CD25.
• Here, we developed HM16390, a long-acting IL-2 analog with enhanced CD122 binding affinity to elicit a potent anti-tumor efficacy. Additionally, instead of eliminating CD25 binding, optimal binding affinity to CD25 was explored and incorporated to prevent unwanted toxicities.
• The aim of this study was to demonstrate the novel development strategy of HM16390 and to evaluate its potent anti-tumor activity in various tumor syngeneic mouse models.

Figure 1. Structural features LAPILIL-2 analogs

Figure 2. Development strategy of LAPILIL-2 analogs

Figure 3. Safety and efficacy LAPILIL-2 analogs in normal mice

RESULTS

Study #1, Safety and efficacy of LAPILIL-2 analogs, HM16390 and HM16325 (without CD25 binding) in normal mice

• Drug moiety rationally designed for intensive anti-tumor effect with immune balance
  - Increased CD122 binding elicits outstanding lymphocyte expansion
  - Optimal CD25 binding minimizes a risk of VLS and buffers an intensified CD122 binding-derived CRS
  - Extended half-life allows once per-chemo-cycle
  - Convenient s.c. treatment option for patient adherence

CONCLUSION

• HM16390 was designed with “Beta-intensified” and “Alpha-optimized” molecular features, and given a long-acting property to cover once-per-cycle s.c. injection.
• Due to the optimal CD25 binding, HM16390 was more tolerable to systemic toxicity caused by uncontrolled excessive immune response in normal mice. In the B16F10 mice, which is a poorly immunogenic tumor model, HM16390 exhibited a superior survival rate compared to HM16325 (absence of CD25 binding) at tolerable dose.
• In the CT26 mice, which is highly immunogenic, HM16390 not only completely inhibited tumor growth but also effectively prevented the growth of re-challenged tumor cells through a memory response, demonstrating its potential to prevent tumor relapse.

Data regarding the immune response induced by HM16390 within the TME and its synergistic effect with anti-PD-1 are available in the poster presentation (abstract number #1046, Jaehyuk Choi et al.).

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