DURABLE ANTI-TUMOR EFFECT INDUCED BY A LONG-ACTING AND 'BETA-INTENSIFIED' IL-2 MUTEIN, HM16390, IN VARIOUS IMMUNOLOGICAL CONDITIONS

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Background IL-2 was approved for the treatment of metastatic renal cell carcinoma and melanoma as an immune-oncology agent. However, its biased binding to IL-2 receptor (IL-2R) alpha requires a high-dose administration, resulting in dose-limiting toxicity such as vascular leak syndrome. Here, we developed a novel long-acting IL-2 mutein, HM16390, that preferentially binds to IL-2R beta and an optimal binding property to alpha subunit to elicit a potent anti-tumor activity with improved safety.

Methods Pharmacokinetics of HM16390 were evaluated in mice after single subcutaneous (SC) administration. In addition, syngeneic tumor mouse models, CT26 and B16F10 representing highly and poorly immunogenic tumor microenvironments respectively, were chosen to investigate anti-tumor effect under different immunological conditions. The animals were given once a week of HM16390 via SC or 5 consequence days per week of aldesleukin via intraperitoneal, and monitored tumor growth and survival rate. Cured animals were re-challenged with the same primary tumor on the opposite side flank and the memory response was evaluated.

Results The pharmacokinetic in mice supported an extended duration of action ($t_{1/2} = 24.9$ hr) and potential of SC administration (bioavailability$ = 43.0\%$) of HM16390. After two weeks treatment in CT26 mice, complete responses (CRs) were observed in 89% and 100% of the mice given HM16390 at the dose of 2.1 and 8.5 mg/kg/QW respectively, while only 22% of the mice given aldesleukin showed CRs at the dose of 3.0 mg/kg/QD (5 consecutive days per week). The median overall survival (mOS) was significantly increased by aldesleukin (39 days) and HM16390 2.1 mg/kg (35 days) compared to vehicle. On day 46, HM16390 at 2.1 and 8.5 mg/kg achieved an overall survival (OS) of 89% and 100% respectively, while aldesleukin showed an OS of 22%. Cured mice had no evidence of relapse after tumor re-challenges on days 50 and 152. This immunological memory response against the CT26 tumor was demonstrated by an increase in tumor-specific memory T cells in spleen and blood. Next, after four weeks treatment in B16F10 mice, HM16390 was well tolerated up to 42 mg/kg/QW, and led to significant delay in tumor growth from 62.9% to 96.4% compared to vehicle. The mOS was prolonged up to 38 days compared to vehicle (14 days) and CR was observed in up to 22% of the mice at doses ≥17 mg/kg.

Conclusions HM16390 demonstrated potent and durable anti-tumor activity in murine models with a wide range of immunogenic states through its IL-2R beta intensified IL-2 agonism.

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