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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Abstract #1814

Introduction

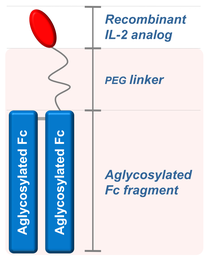
Although recombinant IL-2 was approved for the treatment of metastatic renal cell carcinoma and melanoma, suboptimal ligand interaction required high-dose administrations, resulting in dose-limiting toxicity such as vascular leak syndrome[1].

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 consequences[2,3].

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



[General profile]

- **Drug moiety rationally designed for intensive anti-tumor effect with immune balance**
  : Intensified IL-2Rβ binding elicits outstanding lymphocyte expansion
  : Optimal IL-2Rα binding minimizes a toxicity such as vascular leak syndrome (VLS) and cytokine release syndrome (CRS).
- **Extended half-life allows once per chemo-cycle**
- **Convenient subcutaneous treatment option for patient adherence**

Method & Result

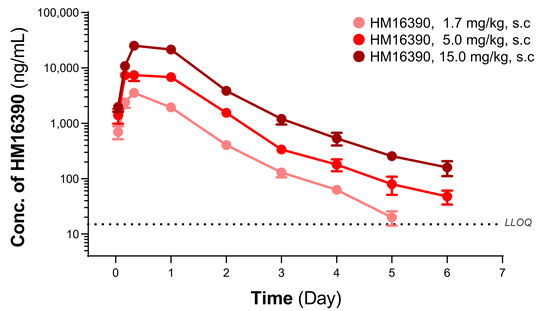
Pharmacokinetics of HM16390 in mice

- **Experimental design for pharmacokinetics of HM16390 in mice**
  - *ICR mice (n=3/group) were given HM16390 in various dosages via single and subcutaneous administration.*
  - *Serum concentrations of HM16390 were quantified by a modified ELISA.*
  - *PK parameters were calculated by a non-compartmental method using WinNonlin® 8.1*

Table 1. PK parameters of HM16390 in mice

Test material	HM16390		
	1.7 mg/kg	5.0 mg/kg	15.0 mg/kg
AUC_{INF} (ng*hr/mL)	92,046.4	272,423.4	804,878.1
C_0 or C_{max} (ng/mL)	3,540.0	7,375.7	25,223.6
T_{max} (hr)	8.0	8.0	8.0
$t_{1/2}$ (hr)	14.5	24.9	24.5
BA (%)	35.4	43.0	37.9

Figure 1. Pharmacokinetic profiles of HM16390 in mice.



➢ Based on the results, systemic exposure of HM16390 was increased in dose-dependent manner and clearly showed linear PK profile in mice. s.c: subcutaneous; LLOQ: lower limit of quantification.

Anti-tumor efficacy in highly immunogenic tumor model

Figure 1. Experimental design for anti-tumor efficacy in CT26 colorectal carcinoma syngeneic mice

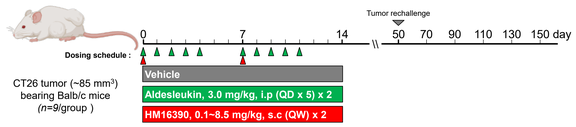
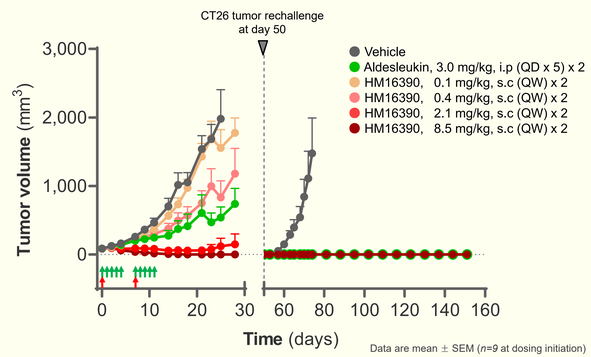
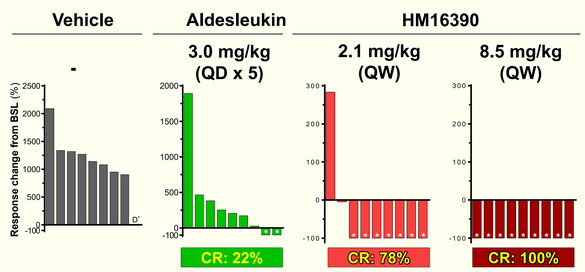


Figure 2. Tumor growth in CT26 colorectal carcinoma syngeneic mice



Data are mean ± SEM (*n*=9 at dosing initiation)

Figure 3. Change in tumor growth (% *vs.* baseline at day 18)

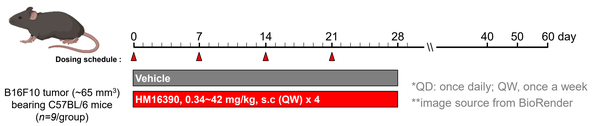


➢ HM16390 led to dose-dependent delays in tumor growth in CT26 syngeneic mice. In particular, all mice in the 8.5 mg/kg treated group showed a complete response (CR), whereas only 22% of the mice showed CR after treatment with aldesleukin.

➢ HM16390 was tremendously effective in terms of not only growth inhibition of primary tumor but also memory response to protect against tumor relapse. QD: once daily, QW, once weekly

Anti-tumor efficacy in poorly immunogenic tumor model

Figure 4. Experimental design for anti-tumor efficacy in B16F10 melanoma syngeneic mice



*QD: once daily; QW, once a week
**image source from BioRender

Figure 5. Tumor growth in B16F10 melanoma syngeneic mice

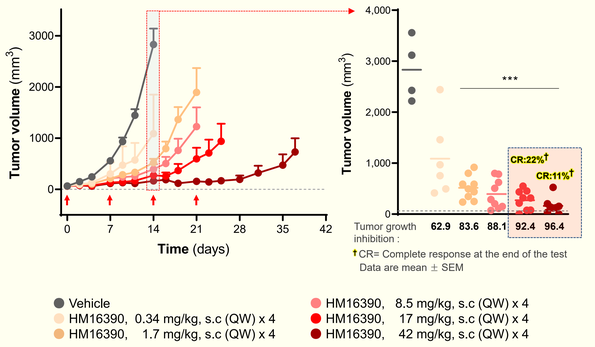
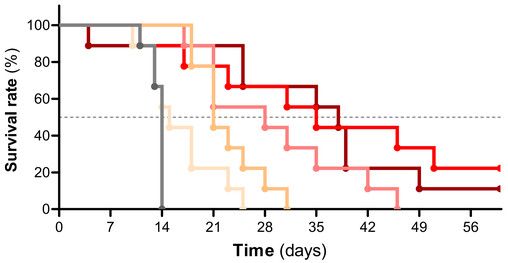


Figure 6. Survival benefits of HM16390 in B16F10 melanoma mice



	Dose (mg/kg)	Median overall survival (day)
Vehicle	-	14
HM16390	0.34	15
	1.7	21
	8.5	28
	17	35
	42	38

➢ HM16390 inhibited tumor growth and improved median overall survival (mOS) in a dose-dependent manner without significant adverse events within tolerable doses.

➢ Notably, complete response was observed in up to 22% of animals in high dose groups.

Concluding Remarks

- **HM16390, a long-acting and CD122-intensified 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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2. Lopes, Jared E *et al*. J Immunother Cancer. **2020** Apr;8(1):e000673
3. Hashimoto, Masao *et al*. Nature. **2022** Oct;617(7930):173-181

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