The Immune-modulation of HM16390, Firing Up The Poor Tumor Microenvironment to Induce A Potent Anti-tumor Efficacy

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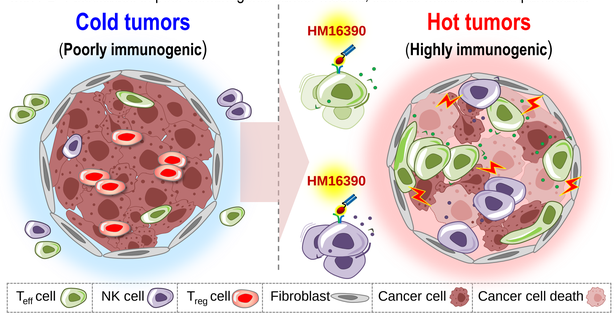
Abstract #LB119/7

Background

Immunotherapy, encompassing immune checkpoint blockades (ICBs) and immune stimulators, has become a widespread approach in cancer treatment. However, the effectiveness of these strategies relies significantly on the characteristics of the current tumor microenvironment (TME)[1]. This reliance underscores the urgent need for a potent immune modulator capable of inducing a favorable TME, particularly in non-immunogenic cold tumors[2,3].

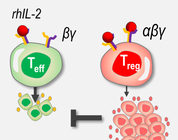
Here, we demonstrate that HM16390, a novel long acting IL-2 analog, has the potential to modify the immunogenicity of the TME by expanding, recruiting, and activating cytotoxic effector cells in cold tumors. These modulations culminate in a potent anti-tumor effect and synergies with PD-1 blockades in poor immunogenic cancer models, such as melanoma and pancreatic.



HM16390: Well-balanced IL-2R binding profiles

[Recombinant human IL-2] Aldesleukin

Marginal IL-2Rβ Binding
High IL-2Rα Binding

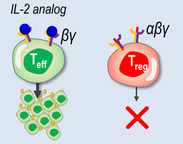


Not enough Immune response — *Immune suppression*

Dose limiting toxicity (VLS)
Short half-life

[Engineered IL-2 analog] IL-2 Superkine

Intensified IL-2Rβ Binding
No IL-2Rα Binding

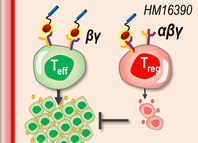


Excessive Immune response — *Absent modulation*

Possible dose-limiting factor related with CRS

[Fine-tuned IL-2 analog] HM163690

Intensified IL-2Rβ Binding
Optimal IL-2Rα Binding

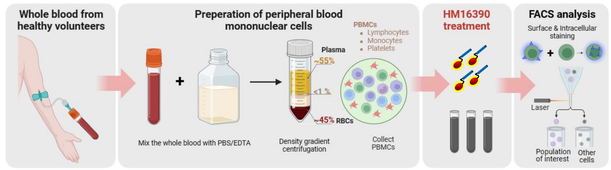


Strong Immune response — *Immune modulation*

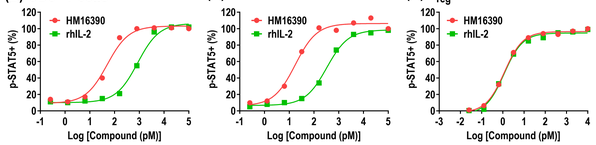
Potent anti-tumor activity w/ remarkable safety

p-STAT5 analysis of HM16390 in human PBMCs

(A) Experimental scheme



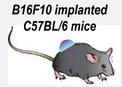
(B) CD8⁺ T cells **(C) NK cells** **(D) T_{reg} cells**



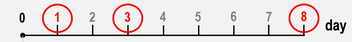
Data obtained from 3 independent experiments (each sample was analyzed in singlet)
Data are presented as mean ± S.D

Tumor infiltrating lymphocyte phenotyping of HM16390 in B16F10 syngeneic mouse model

(A) Study design

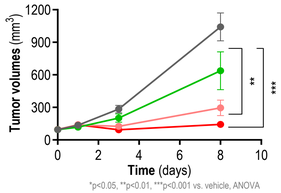


B16F10 tumor (~95 mm³) bearing C57B/L6 mice were treated with aldesleukin or HM16390 by IP or SC, respectively.



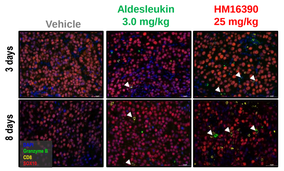
Vehicle	
Aldesleukin, 3.0 mgkg, i.p, (QD x 5)	
HM16390, 8.5 mg/kg , s.c, single	Measurement (@D1, D3, and D8)
HM16390, 25 mg/kg, s.c, single	1. Immune cell phenotyping in tumor tissue
	2. Cytokines level in serum

(B) Tumor volume



*p<0.05, **p<0.01, ***p<0.001 vs. vehicle, ANOVA

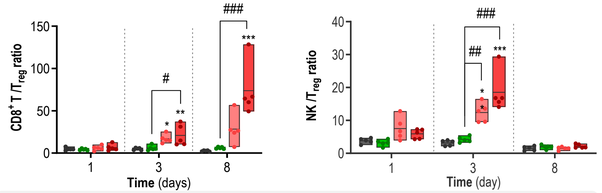
(B) Multiplex IHC in TME



Arrows indicate the co-localization of Granzyme B and CD8 nearby SOX10

Tumor infiltrating lymphocyte phenotyping of HM16390 in B16F10 syngeneic mouse model

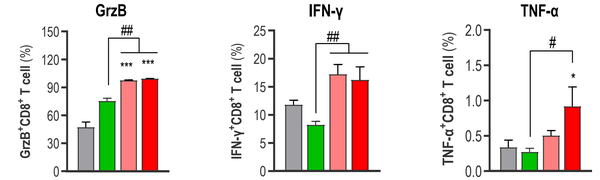
(A) $CD8^+$ T cell/T_{reg} ratio in TILs **(B) NK cell/T_{reg} ratio in TILs**



Vehicle
Aldesleukin, 3.0 mg/kg, QD x 5, i.p
HM16390, 8.5 mg/kg, single, s.c
HM16390, 25 mg/kg, single, s.c

*p<0.05, **p<0.01, ***p<0.001 vs. vehicle, ANOVA
#p<0.05, ##p<0.01, ###p<0.001 vs. aldesleukin, ANOVA

(C) Effector molecules on $CD8^+$ T cells

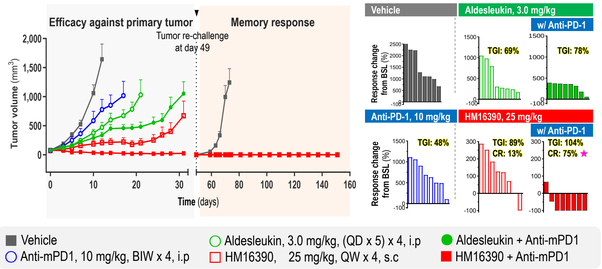


Vehicle
Aldesleukin, 3.0 mg/kg, QD x 5, i.p
HM16390, 8.5 mg/kg, single, s.c
HM16390, 25 mg/kg, single, s.c

*p<0.05, **p<0.01, ***p<0.001 vs. vehicle, ANOVA
#p<0.05, ##p<0.01, ###p<0.001 vs. aldesleukin, ANOVA

Anti-tumor efficacy of HM16390 with Anti-mPD-1 in B16F10 syngeneic mouse model

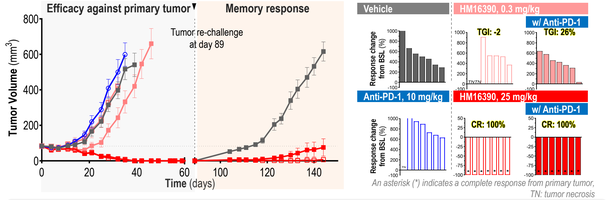
(A) B16F10 melanoma model **(B) Individual tumor volumes (Day10)**



Vehicle
Anti-mPD1, 10 mg/kg, BIW x 4, i.p
Aldesleukin, 3.0 mg/kg, (QD x 5) x 4, i.p
HM16390, 25 mg/kg, QW x 4, s.c
Aldesleukin + Anti-mPD1
HM16390 + Anti-mPD1

Anti-tumor efficacy of HM16390 with Anti-mPD-1 in Panc02 syngeneic mouse model

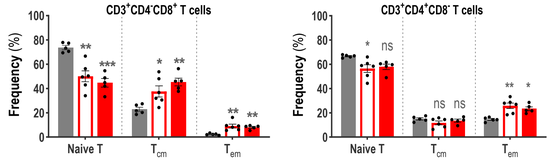
(A) Panc02 pancreatic cancer model **(B) Individual tumor volumes (Day39)**



An asterisk (*) indicates a complete response from primary tumor.
TN: tumor necrosis

Vehicle
Anti-mPD1, 10 mg/kg, BIW x 4, i.p
HM16390, 0.3 mg/kg, QW x 4, s.c
HM16390, 25 mg/kg, QW x 4, s.c
HM16390, 0.3 mg/kg + Anti-mPD1
HM16390, 25 mg/kg + Anti-mPD1

(B) $CD8^+$ memory T cells **(C) $CD4^+$ memory T cells**



Vehicle
HM16390, 25 mg/kg, QW x 4, s.c
HM16390, 25 mg/kg + Anti-mPD1

The frequencies of central memory T (T_{cm}; $CD4^+CD62L^+$) and effector memory T (T_{em}; $CD4^+CD62L^-$) cells were calculated on indicated parent cell populations (*p<0.05, **p<0.01, ***p<0.001 vs. vehicle, ANOVA).

Conclusion

- HM16390 induced improved expansion and functions of effector tumor-infiltrating lymphocytes, correlating with exposure, and exhibits a safe T_{reg} modulation pattern in B16F10 melanoma model.
- The tumor-immune microenvironment modulation occurred by HM16390 showed a potent anti-tumor effect and synergies with PD-1 blockade therapy in the PDAC model, which recognized as poor immunogenic murine models with low TIL frequency[4].
- Taken together, HM16390 shows promise approach in modifying the TME to much immunogenic condition, thereby activating a proper immune responses.

References

1) Shiravand Y, Khodadadi F, Kashani SMA, *et al.* Curr. Oncol. **2022**, 29(5), 3044-3060.
2) Andersen R, Borch TH, Draghi A, *et al.* Ann Oncol. **2018** Jul 1;29(7):1575-1581.
3) Hutmacher C, Liuzzi AR, Becher B, Neri D, *et al.* Cancer Immunol Res. **2019** Apr;7(4):572-583.
4) Kanaya N, Kuroda S, Kakiuchi Y, *et al.* Molecular Therapy. **2020** Jan 9;28(3):794-804.

Acknowledgements

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