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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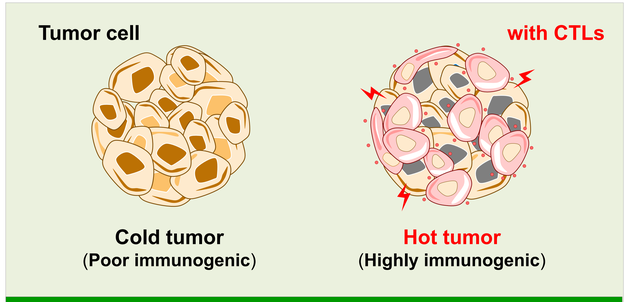
Abstract #1831

Introduction

Immune checkpoint inhibitors (CPIs) are widely used in cancer immunotherapy. However, the response to CPIs 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 CPIs 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 CPIs[3].

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.



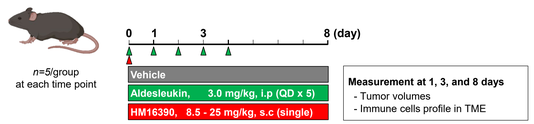
HM16390 expands tumor-infiltrating cytotoxic lymphocytes, switching "cold tumor" to "hot tumor" that are more responsive to CPI.

Method & Result

TME modulation in a poorly immunogenic tumor model

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

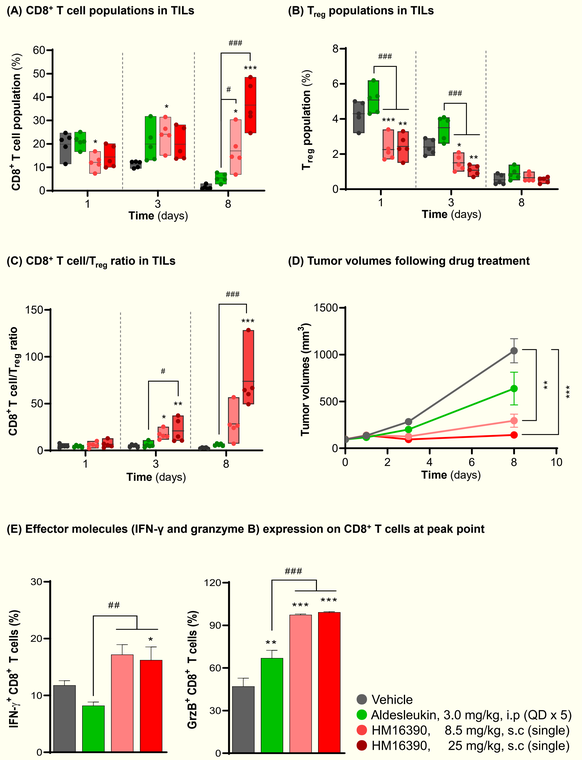
*B16F10 tumor (~85 mm³) bearing C57BL/6 mice were treated with HM16390 or aldesleukin.



- *The expansion of cytotoxic T cells, and regulatory T cell (T_{reg}) in TME were evaluated by flow cytometry ($CD8^+$ T cell marker: $CD3^+CD8^+$), T_{reg} ($CD3^+CD4^+Foxp3^+$).*
- *Tumor volumes were assessed at the designated date by a digital caliper.*

* The structural feature of HM16390 is available for poster presentation at the 2023 AACR (abstract presentation number #1814/14, section 23, Jinyoung Kim, *et al*).

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



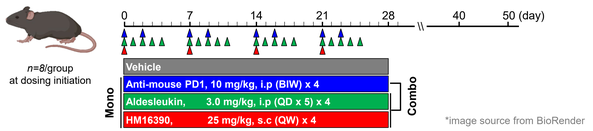
*p<0.05, **p<0.01, ***p<0.001 vs. vehicle group by One-way ANOVA test
#p<0.05, ##p<0.01, ###p<0.001 vs. aldesleukin group by One-way ANOVA test

- 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 down-regulated in TILs (B).
- A significant increase in the $CD8^+$ T cell / T_{reg} 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 IFN-γ and granzyme B compared to the aldesleukin treated group (E). TIL: tumor-infiltrating lymphocytes, i.p: intraperitoneal, QD: once daily, s.c: subcutaneous

Synergy with CPI in a poorly immunogenic tumor model

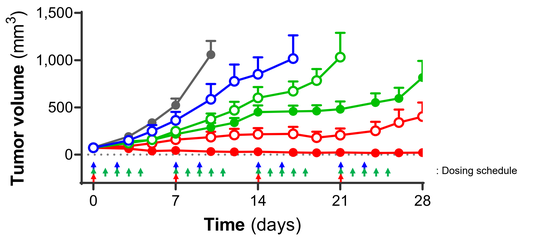
Figure 3. Experimental design for evaluating synergistic effect with anti-PD1.

*B16F10 tumor (~75 mm³) bearing C57BL/6 mice were treated with IL-2 mono or in combination with anti-mouse PD1.



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

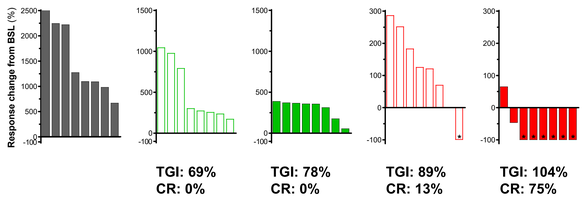
Figure 4. Tumor growth during the respective therapies in B16F10 mice.



Data are mean ± SEM (*n=8* at dosing initiation)

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

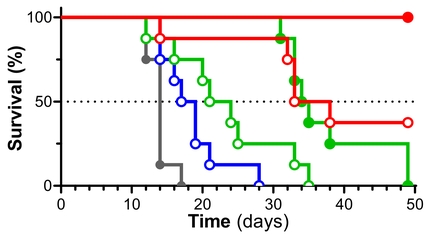
Figure 5. Change in tumor volume of B16F10 melanoma mice.
(% *vs* baseline at day 10)



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

- 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. TGI: tumor growth inhibition ratio, CR: complete response (asterisk mark).

Figure 6. Survival rate in B16F10 melanoma mice.



Data are mean ± SEM (*n=8* at dosing initiation)

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

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

Treatment strategy	Vehicle	Anti-PD1 (10 mg/kg, BIW)	Aldesleukin (3 mg/kg, QD x 5)		HM16390 (25 mg/kg, QW)	
	-	Mono	Mono	Combo	Mono	Combo
TGI (%, at day 10*)	-	47.8	69.3	78.2	88.6	104.1
CR rate (%)	0	0	0	0	25	87.5
mOS (day)	14	18	22.5	34.5	37.5	>49

- Since 49 days after drug treatment, complete response was observed in 87.5% (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

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3. Hutmacher, Cornelia *et al*. Cancer Immunol Res. **2019** Apr ;7(4):572-583

Acknowledgements

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