Identifying predictive biomarkers for HM16390, a novel long-acting IL-2 analog, By analyzing single-cell and bulk transcriptomic data of immune checkpoint inhibitors treated patients

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Abstract #137

Introduction

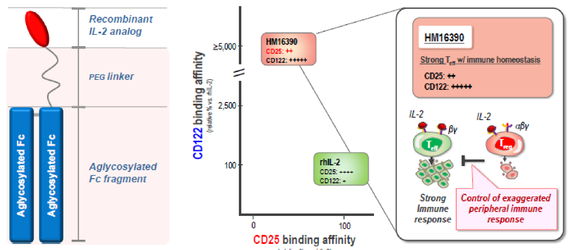
Background

Interleukin-2 (IL-2), which stimulates T-cell activation, has regained attention as a target for cancer immunotherapy. However, its clinical efficacy remains limited without appropriate patient stratification. **HM16390** is an IL-2 analog engineered with enhanced IL-2Rβ binding and optimized IL-2Rα affinity. This study aimed to **identify transcriptomic biomarkers** predictive of therapeutic response to HM16390 in cancer patients, using comprehensive datasets from patients previously treated with immune checkpoint inhibitors (ICIs).

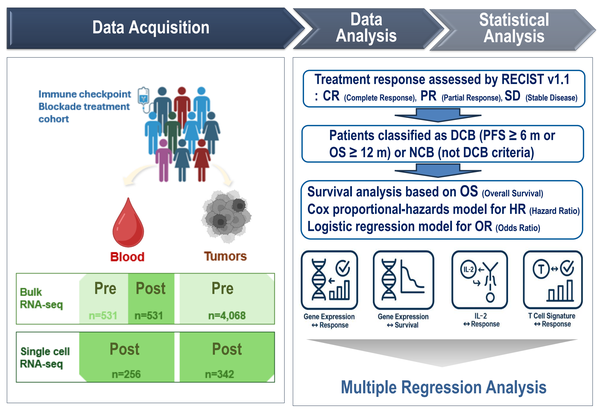
HM16390, a Novel Long-Acting IL-2 Analog

HM16390: The Right Balance of Potency and Safety

- **Potent Efficacy**: Intensified IL-2Rβ binding drives a strong anti-tumor response.
- **Enhanced Safety**: Optimal IL-2Rα binding minimizes toxicity.
- **Simplified Treatment**: A convenient subcutaneous option for greater patient adherence.
- **Phase 1 Clinical Trial in Progress (NCT06724016).**

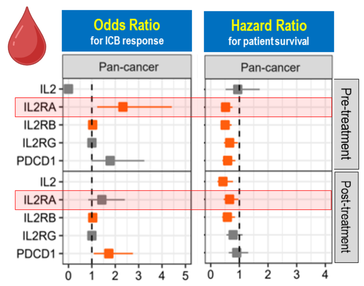


Methods

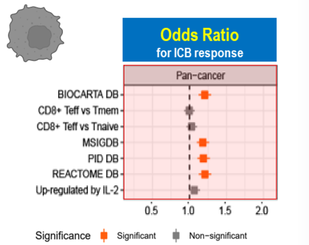


Gene expression Pre-existing IL-2 Pathway Activity as a Predictive Biomarker

Blood IL-2Rα Expression and Tumor IL-2 Pathway Activation with Favorable Outcome

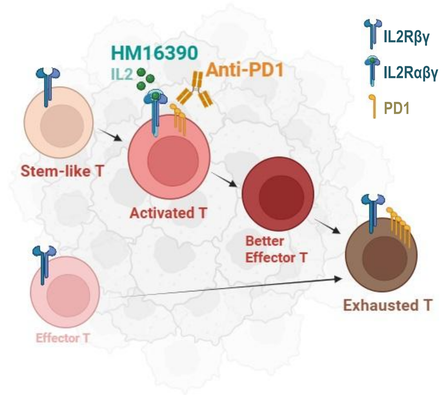


Baseline IL-2Rα (CD25) expression in bulk RNA-seq of blood and tumor is a significant indicator of Immune Checkpoint inhibitor therapy outcomes (significantly higher Odds Ratio and lower Hazard Ratio).



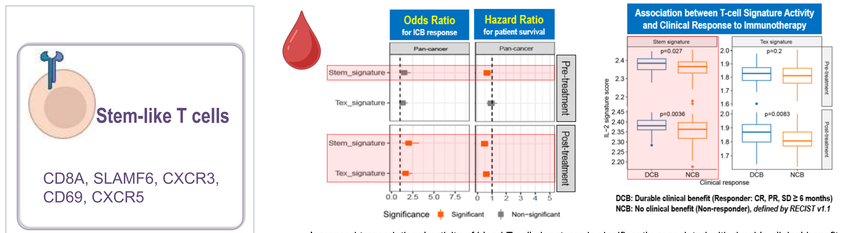
In bulk RNA-seq analysis, a pre-existing IL-2 pathway activity in tumors correlates with a positive therapeutic outcome from ICIs. Several gene sets related to the IL-2 pathway and T-cell activation show a significantly higher Odds Ratio for ICB response in various cancer types, including Melanoma and Lung.

Combination of HM16390 with ICIs



T-cell Transcriptional Signatures as Predictive Biomarkers for Immunotherapy Response

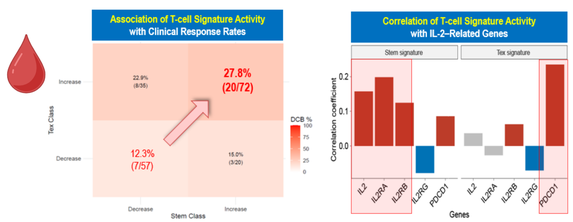
Association of Blood T-cell Signatures with Favorable Immunotherapy Outcomes



DCB: Durable clinical benefit (Responder: CR, PR, SD ≥ 6 months)
NCB: No clinical benefit (Non-responder), *defined by RECIST v1.1*

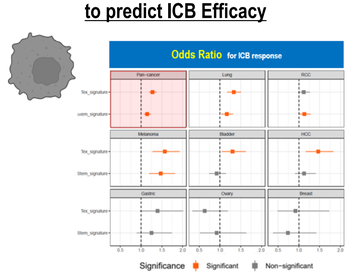
Increased transcriptional activity of blood T-cell signatures is significantly associated with durable clinical benefit and prolonged survival in patients receiving ICB therapy (Wilcoxon rank-sum test)

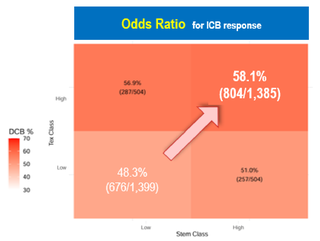
Synergistic Mechanism of IL-2 and Anti-PD-1/PD-L1 Combination



IL-2 pathway activation promotes the expansion of stem-like T cells that sustain anti-tumor immunity. In parallel, the exhausted T-cell signature strongly correlates with PDCD1 expression, supporting a mechanistic link between IL-2 signaling and responsiveness to PD-1/PD-L1 blockade.

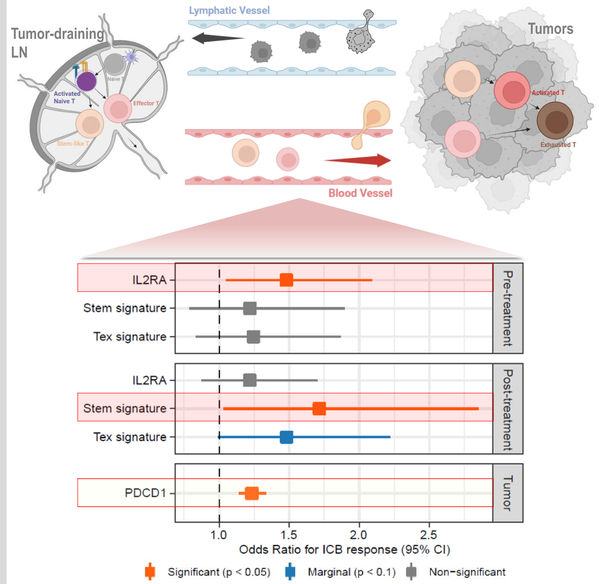
Pre-treatment Tumor T-cell Signatures to predict ICB Efficacy





Each cell represents the percentage of patients achieving DCB, expressed as the number of DCB cases divided by the total number of patients in that Stem × Tex signature category.

Multivariate Validation of IL-2RA and T-cell Signatures



Multivariate analysis confirms IL2RA and stem-like T-cell transcriptional signatures as robust predictive biomarkers of ICI response. Their predictive value is maintained across both pre- and post-treatment blood samples, while PDCD1 is significant only within tumor tissue.

Concluding Remarks

- **IL-2Rα (CD25) expression** and **stem-like T cell signatures** were identified as transcriptomic biomarkers predictive of response to Immune checkpoint inhibitors.
- Both markers highlight the critical role of IL-2 binding to the CD25 receptor on T cells, underscoring the importance of CD25 engagement in immunotherapy.
- We propose that patient stratification by two specific biomarkers may enable HM16390 to enhance the clinical response to immune checkpoint blockade, thereby providing a rationale for biomarker-driven combination strategies.
- Their accessibility in blood samples enables non-invasive patient stratification and the clinical utility of these biomarkers is being validated in the ongoing clinical trial (NCT06724016, companion poster no. ###) of HM16390, characterized by optimal affinity for IL-2Rα and enhanced IL-2Rβ binding (companion poster no. ### & ###) .

References

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