Antitumor activity of NKTR-214 in combination with pmel-1 ACT in an aggressive murine melanoma model
Giulia Parisi, Justin Saco, Siwen Hu-Lieskovan, Ruixue Zhang, Paige Krystofinski, Cristina Puig Saus, Deborah H. Charych1, Antoni Ribas
Department of Medicine, Division of Hematology-Oncology, University of California Los Angeles (UCLA) Los Angeles, CA 90095
1Nektar Therapeutics, 455 Mission Bay Blvd South, San Francisco CA 94158

Introduction

- Interleukin-2 (IL-2) is a cytokine that activates and expands tumor killing lymphocytes, but also potently activates suppressive T regulatory cells (Tregs) by binding to the heterodimeric IL-2Rγγ.
- NKTR-214 is a CD223-based cytokine agonist conjugated with multiple releasable chains of polystyrene glycol (PEG), designed to provide sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rγγ) to preferentially activate and expand effector CD8+ T and NK cells over Tregs (1).
- NKTR-214 is being evaluated in an outpatient setting in a Phase I dose escalation trial. NKTR-214 has a favorable safety and tolerability profile (2).
- NKTR-214 as a single agent demonstrated a substantial increase in CD8+ T cells in the tumor microenvironment even in subjects pretreated with multiple prior immunotherapeutic agents (3).

References
2. ClinicalTrials.gov NCT: NCT02869295
3. Humm et al, ASCO-GI, February 2016, Orlando, FL

Results

NKTR-214 provides significant anti-tumor activity in combination with adoptive cell transfer (ACT) therapy

CT26/Bl6 mice were implanted subcutaneously with B16F10 (1x10⁶ per animal) syngeneic murine melanoma cell line on day 0 and lymphodepleted with 500 cGy on day 3. On day 0, mice were treated with the combination of ACT [pmel-1-2 pg100 TCR transgenic T lymphocytes activated in vitro with 1 μg/ml pg120] and NKTR-214 (0.8 mg/kg, i.v. x 3) or with IL-2 (0.4 mg/kg, q3d x 5) every 9 days for 3 cycles, i.p., or vehicle. The second and third treatment cycle did not include ACT.

Increased T cell expansion in the spleen and homing to the tumor is associated with NKTR-214 treatment

In vivo bioluminescence imaging (BLI) of adoptively transferred lymphocytes. Pmel-1 transgenic T cells were transduced with a retinovirus-firefly luciferase and used for ACT Representative figures on days 5 and 14, five replicate mice per group. T cell expansion in spleen (upper panels); mobilization to and persistence in tumor (lower panels).

Quantification of serial images in the region of interest (ROI) of spleen and tumor (counts per pixel) through day 19 after ACT of pmel-1 T cells expressing luciferase. A single NKTR-214+ACT treatment showed a statistically significant increase in T cell expansion in the spleen from day 5 to day 9 compared to 3 daily doses of IL-2+ACT or vehicle. The luciferase signal over time showed a stronger peak of tumor-infiltrating effector T cells in the NKTR-214 group compared to IL-2 or vehicle from day 5 to day 7. The second dose of NKTR-214 given at day 9 triggered a second expansion of effector T cells in the spleen and tumor from day 12 to day 17. In contrast, there was no expansion in spleen or tumor after the second IL-2 treatment. (** p<0.0001 compared to IL-2+ACT, # p<0.0001 compared to ACT+vehicle, paired-wise comparison using Tukey’s test, n = 5, mean ± SE).

Conclusions

- NKTR-214 + ACT is well tolerated and provides a robust anti-tumor response in the aggressive B16F10 model.
- NKTR-214 significantly increases the total number of pmel-1 CD8+ T cells but not regulatory T cells in tumor.
- Treatment with NKTR-214 + ACT robustly mobilizes T cells into the tumor where they durably persist.
- The robust and long-lasting effect of NKTR214 supports its potential use in combination with cell-based therapies.

Nektar Therapeutics, California Los Angeles (UCLA) Los Angeles, CA 90095
1Nektar Therapeutics, 455 Mission Bay Blvd South, San Francisco CA 94158

Here we evaluated the tumor immunology, biodistribution and anti-tumor activity of NKTR-214 combined with adoptive cell transfer (ACT) in a pre-clinical melanoma model

The adoptive cell transfer (ACT) of genetically engineered T cells expressing cancer-specific TCR (TDCR) is able to induce effective anti-tumor response. However, tumors frequently relapse after an initial response. Our hypothesis was that NKTR-214, could enhance the efficacy of ACT, compared to IL-2 by recruiting tumor killing T-cells, increasing their persistence, and reducing immunosuppressive T cells in the tumor microenvironment.