801

PRIME™ IL-15 (RPTR-147): Preliminary clinical results and biomarker analysis from a first-in-human Phase 1 study of IL-15 loaded peripherally-derived autologous T cell therapy in solid tumor patients

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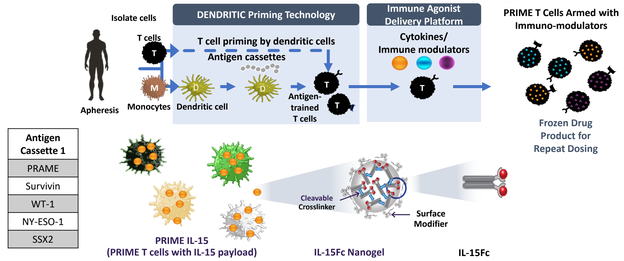
BACKGROUND & METHODS

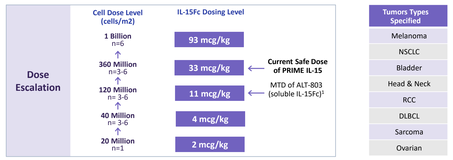
Figure 1

PRIME IL-15 Antigen Primed Multi-Clonal T Cells Loaded with an IL-15Fc Nanogel



Product Description: The cell product was derived from rare peripheral anti-tumor T cell clones that were primed against a multi-antigen cassette containing tumor associated antigens (TAA). Autologous anti-TAA T cells were generated with a proprietary dendritic cell priming process and then loaded with an IL-15Fc nanogel to generate PRIME IL-15 product.

Study Design: A phase 1/2, first-in-human, multi-center study to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of RPTR-147 administered i.v. as a monotherapy in patients with relapsed/refractory metastatic or locally-advanced solid tumors



Tumors Types Specified
Melanoma
NSCLC
Bladder
Head & Neck
RCC
DLBCL
Sarcoma
Ovarian

RESULTS

Figure 2

Patient Population and Safety Profile

Tumor Type	Number of Patients
Melanoma	6
Non-Small Cell Lung Carcinoma	4
Renal Cell Carcinoma	2
Head & Neck	2
Appendiceal Carcinoma	1
Ovarian Carcinoma	1
Synovial Carcinoma	1

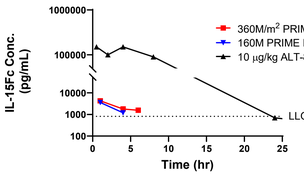
Table 1: Tumor types of the 17 patients with advanced metastatic disease refractory to SOC who took part in the PRIME IL-15 study.

Safety Summary

- No Dose Limiting Toxicities
- 10 SAEs
  - Majority of SAEs were due to disease
  - A single patient had three grade 2 infusion reactions
    - Events all were resolved
    - Patient had history of similar reactions to previous biologic therapies
- No cytokine release syndrome, neurotoxicity or other concerning immune-related toxicity
  - At highest cell dose, 2 patients had transient elevated IFNγ and IL-18 levels
- 5 related non-serious AEs all grade 1-2, resolved (other than Grade 2 fatigue)
- Dose escalation meeting for 360M/m² dose: Investigators & Sponsor agreed to escalate to the next dose level

Figure 3

PRIME IL-15 Results in Low Systemic Exposure of IL-15Fc

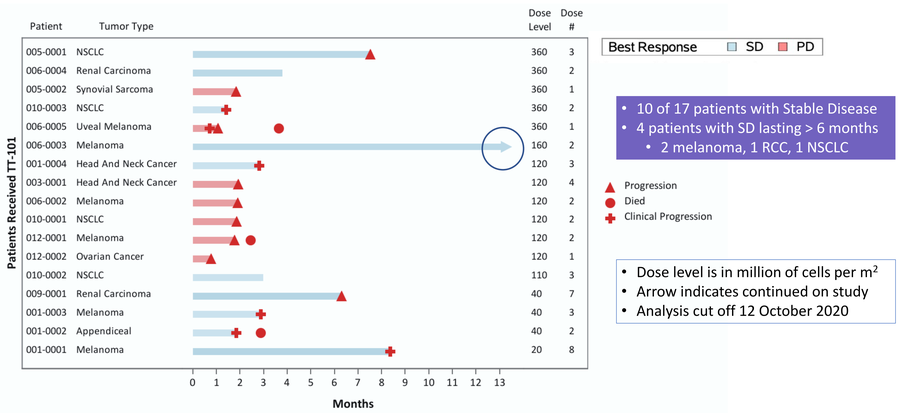


- The 360M/m² dose of PRIME IL-15 contained 3X more IL-15Fc than the MTD of ALT-803[1], but produced less than a tenth of the systemic exposure to free IL-15Fc
  - PRIME IL-15 is designed to function in an autologous manner, so low exposure is expected
  - In cohorts treated with 20, 40 and 120 M cells/m² IL-15Fc was not detected
  - IL-15Fc PK curve of PRIME IL-15 is >10X less than ALT-803 at 10µg/kg (C_{MAX} ~150ng/mL i.v.)[1]
  - There was no ADA observed

1. Romee R, Cooley S, Berrien-Elliott MM, et al. First-in-human phase clinical study of the IL-15 superagonist complex ALT-803 to treat relapse after transplantation. Blood. 2018;131(23):2515-2527.

Figure 4

Swimmer Plot : Best Overall Response

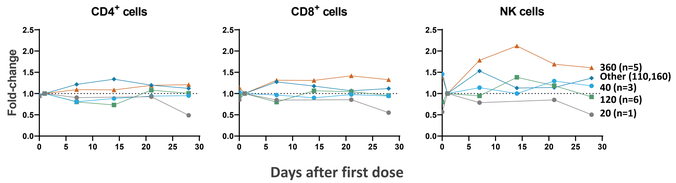


- 10 of 17 patients with Stable Disease
- 4 patients with SD lasting > 6 months
  - 2 melanoma, 1 RCC, 1 NSCLC

- Dose level is in million of cells per m²
- Arrow indicates continued on study
- Analysis cut off 12 October 2020

Figure 5

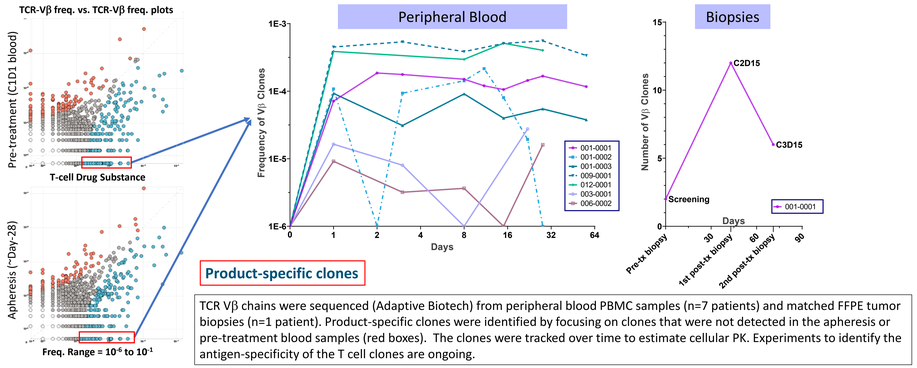
Flow Cytometry: Non-significant Increase of NK & CD8+ T Cells in Circulation at 360M cells/m2



A non-significant increase in the average cell number of NK & CD8⁺ T cells but not CD4⁺ T cells was observed at the highest cell dose. This is consistent with the expected mechanism of action and pharmacokinetics of IL-15.

Figure 6

Product Specific Clones Show Persistence in Blood and Tumor

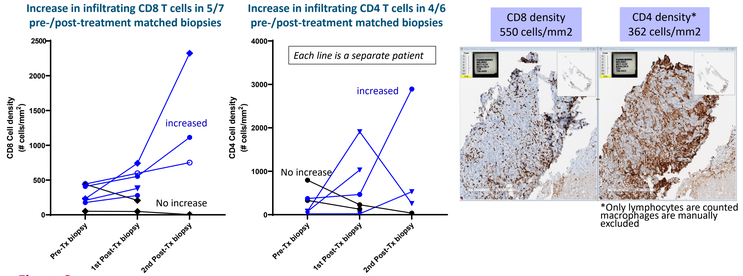


Product-specific clones

TCR Vβ chains were sequenced (Adaptive Biotech) from peripheral blood PBMC samples (n=7 patients) and matched FFPE tumor biopsies (n=1 patient). Product-specific clones were identified by focusing on clones that were not detected in the apheresis or pre-treatment blood samples (red boxes). The clones were tracked over time to estimate cellular PK. Experiments to identify the antigen-specificity of the T cell clones are ongoing.

Figure 7

Majority of Evaluable Matched Biopsies Demonstrate an Increase in CD8 & CD4 T cell Tumor Infiltrates

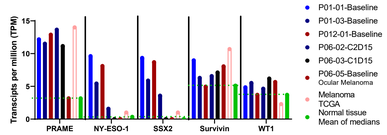


*Only lymphocytes are counted macrophages are manually excluded

Figure 8

Expression of Targeted TAAs in Tumor Biopsies was confirmed by RNASeq and IHC

- Tumor associated antigen(TAA) expression by RNASeq of patient biopsies compares well with TCGA database across multiple tumor types (RCC, NSCLC, & HNSCC- data not shown)
- Example of RNASeq expression of the 5 TAAs and PRAME expression by IHC are shown below.
  - As expected, PRAME expression is high in the majority of melanoma patients (4/5)



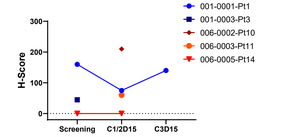
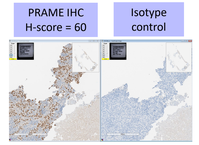


Figure legend: FFPE tissue curls from patient biopsies were used for whole transcriptome RNASeq and the data was normalized to public databases (TCGA & GTEx) by using the Recount2 algorithm (doi.org/10.1038/nbt.3838). The peach open bars represent the mean TPM values for TAA antigen expression within specific tumor types. The green bars represent an average normal expression across a variety of healthy tissues. IHC=immunohistochemistry
H-score = [1 × (% cells 1+) + 2 × (% cells 2+) + 3 × (% cells 3+)]; range 0-300



CONCLUSIONS

RPTR-147 has been well-tolerated to date with preliminary evidence of biological activity

- PRIME IL-15 T cell therapy (RPTR-147) has a favorable safety profile
  - No DLTs observed up to and including 360M cells/m² dose
  - Nanogel formulation attached to cells results in low systemic exposure to IL-15Fc
  - Dose-Escalation is proceeding
- Preliminary evidence of clinical activity
  - 10 of 17 late-stage tumor patients experienced stable disease
  - In 4 patients, stable disease lasted longer than 6 months
- Pharmacodynamic changes in immune system and tumor microenvironment were consistent with MOA
  - Increase in tumor infiltrating CD8 and CD4 T cells observed post infusion
  - Evidence of persisting product-specific T cell clones in blood and tumor (analysis of antigen specificity ongoing)
- Ongoing biomarker analysis will inform future clinical strategies to optimize PRIME IL-15 immunotherapy
  - Determine product reactivity towards individual antigens and assess for epitope spreading
  - Proprietary antigen decoding technologies will be applied to track epitope-specific CD8 and CD4 clonotypes in products, periphery and tumors
  - Deeper understanding of the effects of PRIME IL-15 therapy on the tumor microenvironment

Trial registered with clinicaltrials.gov NCT03815682
The study was approved by local institutional IRBs after acceptance of the IND by the FDA. Written informed consent was obtained from patients for publication of this poster and any accompanying images.

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