CLINICAL AND TRANSLATIONAL RESPONSES TO PLINABULIN, RADIATION AND ANTI-PD-1 IN RELAPSED REFRACTORY CLASSICAL HODGKIN LYMPHOMA (RRHL)

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Introduction

Plinabulin is a "real-time" radio/chemo- and immune-enhancing anti-cancer tubulin-blinding agent. Its immunomodulatory mechanism of action (MoA) is fundamentally linked to GEF-H1-dependent immune modulation of the tumor microenvironment on dendritic cells (DC) and other antigen-presenting cells which promotes better anti-tumor immune responses.

A phase 1 study (NCT04902040) of plinabulin plus anti-PD-1 (ICB) with radiotherapy (RT) was conducted at MD Anderson Cancer Center for patients with ICB-relapsed/refractory cancers. This triple regimen was well-tolerated with a durable disease control rate (PR/SD) of 54% (irRECIST). Responding tumors included non-small-cell-lung-cancer (2/2 PR+SD), head-and-neck-squamous-cell-carcinoma (2/3 PR+SD) and Hodgkin's lymphoma (2/2 PRs).

Overall, significantly higher baseline GEF-H1 immune signature scores associated with plinabulin immune activation were detected in responding (PR+SD) patients.

Objectives

There are limited treatment options for patients with RRHL after ICB, brentuximab vedotin, and stem cell transplant. Both RRHL patients were heavily pretreated with prior 12 and 16 lines of therapy and prior ICB. In this study, both patients had durable PRs with duration of responses of 19 and 23 months. Only 1 G3 adverse event of post-infusion hypertension was associated with study treatment. Here we report on clinical and translational responses of 2 RRHL patients treated with plinabulin, RT, and ICB.

Methods

RRHL-specific treatment:

Patients received plinabulin (30 mg/m2) C1D1 and 4 and C2D1 q4 week cycle, nivolumab (240mg D1, 15) and focal radiation to 20Gy in 5 fractions starting C1D1. Blood for peripheral blood mononuclear cells (PBMC), was collected prior to treatment on C1D1, C1D4, and C3D1.

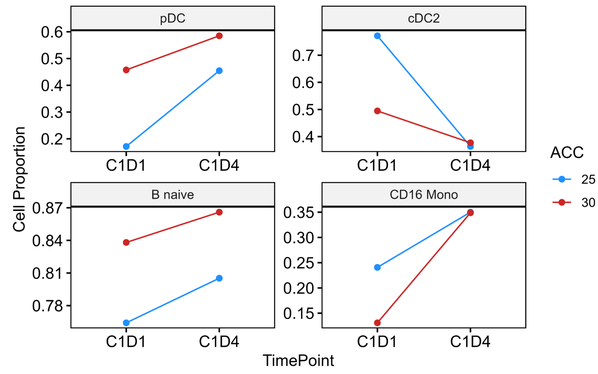
Biomarker analysis:

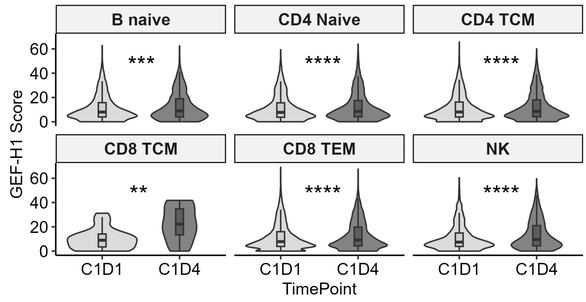
Single-cell RNA and TCR sequencing analysis were performed on PBMC using Evercode kits (Parse Biosciences) based on the SPLiT-seq method. Whole transcriptome sequencing was performed on a DNBSEQ T7 genetic sequencer using Complete Genomics' 100 bp paired end (PE100) High-Throughput Sequencing Kit. We examined a 47-gene GEF-H1 immune signature in PBMC cell subsets and GEF-H1 signaling dynamics in effector memory T cells, stratified by CD4 and CD8 lineages, as well as by clonal size, across timepoints.

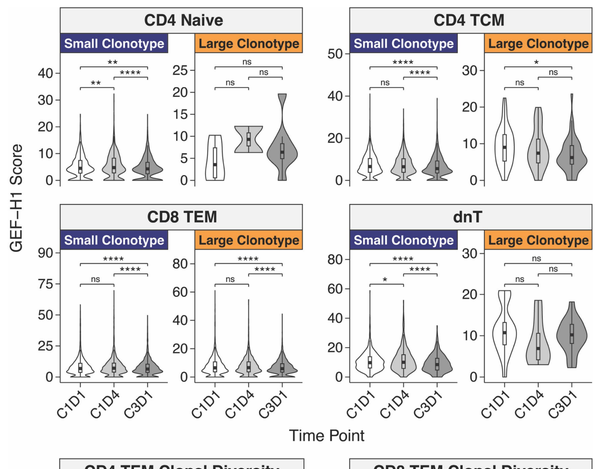
Summary

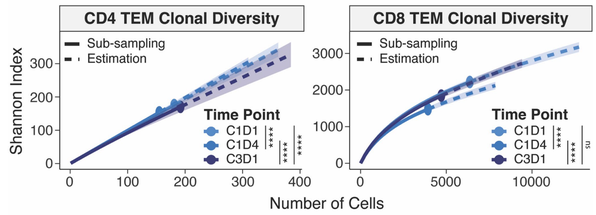
- Increased proportion of pDCs and a concurrent decrease in cDC2 from C1D1 to C1D4.
- Increased proportions of B naive cells and CD16 monocytes at C1D4, a trend accompanied by elevated GEF-H1 immune score in B naïve, NK and T cells, particularly in CD4 and CD8 TEM and TCM, suggesting enhanced GEF-H1 immune activation.
- TCRseq analysis showed significant differences between clonal expansion in CD4 and CD8 TEM and GEF-H1 signaling among CD4 and CD8 TEM small clones over time.

Results









Discussion

Heavily pretreated RRHL patients responded well to plinabulin, ICB and radiation. Translational analysis in these patients support treatment-specific enhanced immune activation with treatment. An expanded Phase 2 confirmatory trial is warranted.

References

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