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Combining Transcriptomic- and Tissue-Based Immune Biomarkers to Evaluate GB1275, a CD11b Modulator, as a Single Agent or With Pembrolizumab in Patients With Advanced Solid Tumors

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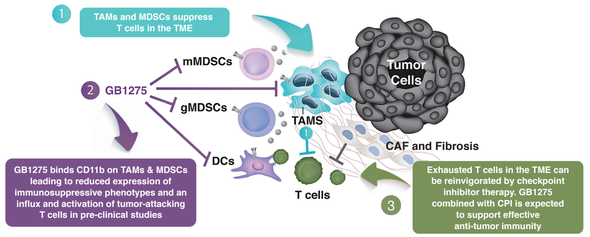
INTRODUCTION

- GB1275 is a first-in-class CD11b modulator in clinical development as monotherapy and in combination with pembrolizumab or chemotherapy for the treatment of advanced solid tumors
- Nonclinical data show that GB1275 reduced influx of tumor-associated myeloid-derived suppressor cells (MDSCs) and macrophages (TAMs), and repolarized M2 immunosuppressive TAMs toward an M1 phenotype[1] (**Figure 1)**
- We hypothesize that GB1275 administration can alleviate myeloid cell-mediated immunosuppressive effects and improve cancer treatment outcomes
- A phase 1 trial evaluating GB1275 as monotherapy and in combination with pembrolizumab in specified advanced tumors is ongoing (NCT04060342) (**see poster P388**)

Figure 1. GB1275 mechanism of action: CD11b modulation is a novel MDSC / TAM-targeting approach



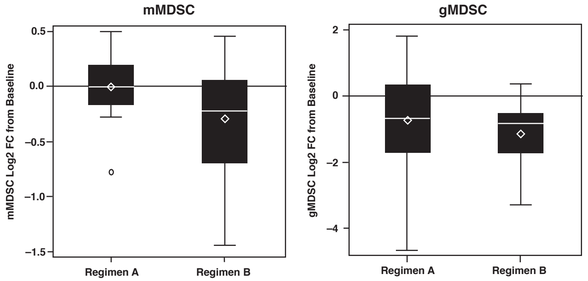
METHODS

- Following informed consent, peripheral blood was collected for exploratory biomarker assessment pre- and post- 2-week treatment from 31 patients; core tissue biopsies were obtained pre-dose and at pre-specified (C3) cycles from 13 patients
- The frequency of MDSCs in whole blood was measured using the Serametrix MDSC FACS Assay
- Olink proteomics platform was used to assess changes in circulating protein pre- and post- treatment
- Whole blood gene expression transcriptome profiles were generated using NovaSeq platform
- H&E and CD8 IHC was performed at Neogenomics, tumor infiltrating lymphocyte (TIL) and CD8 quantification was performed by an independent pathologist
- LMMA (Linear Models for Microarray Data) was used to perform differential expression analysis, Benjamini-Hochberg correction was used as the adjustment method for calculating p-values with significance cut-off at < 0.05 level
- Unbiased analysis of relative changes in expression (post/ pre- treatment) and correlations between gene changes and clinical variables such as tumor type, regimen and dose received was performed

RESULTS

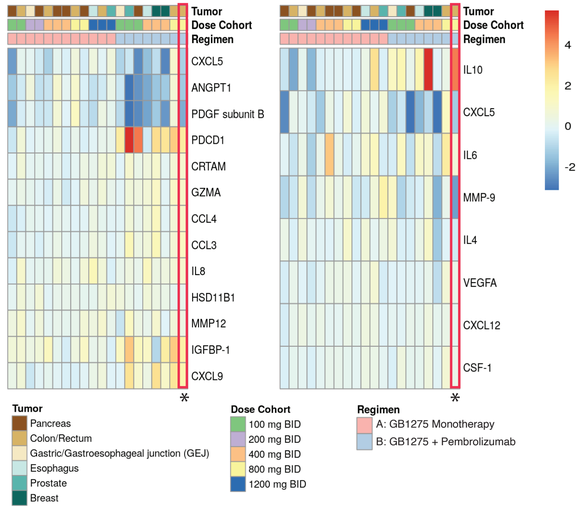
MDSCs

Figure 2. Down modulation of peripheral MDSCs was observed after GB1275 alone (Regimen A, n = 18) or in combination with pembrolizumab (Regimen B, n = 13)



Proteomics

Figure 3. Differentially expressed proteins in peripheral blood pre- and post-treatment

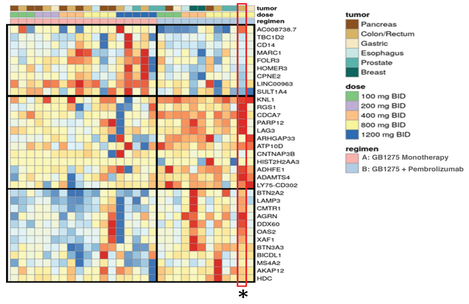


Heatmap for proteins that were significantly differentially modulated in circulation: PD1 (PDCD1) levels are increasing in circulation with Reg B (potential pembrolizumab effect); CXCL9, CXCL5, CXCL12, GMZA, MMP9, and IL10 level changes in blood reflect impact on myeloid biology (GB1275 effect)

*PR patient - **see poster P388**

Transcriptomics

Figure 4. Clustering of regimen-dependent gene expression changes in whole blood post treatment

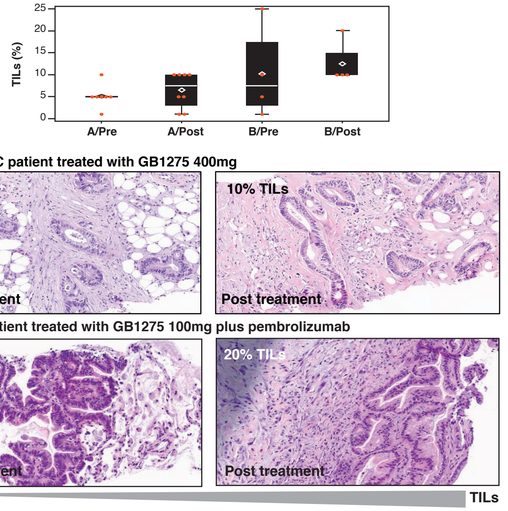


Downmodulation of myeloid genes (CD14, MARC1, TBC1D2) observed in subsets of patients in both regimens, potentially reflecting changes in peripheral MDSCs. Increased expression of IFN response associated genes observed in Reg B and subsets of Reg A patients (OAS2, DDX60, XAF1, LAG3).

*PR patient - **see poster P388**

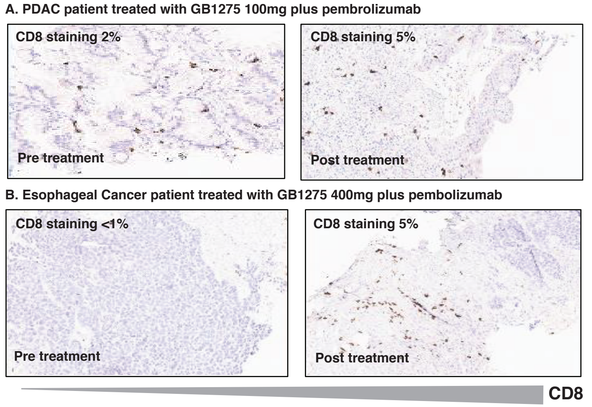
TILs scoring

Figure 5. Tumor infiltrating lymphocyte (TIL) counts in tumor tissue increased with GB1275 monotherapy (Regimen A, n = 9, 7 evaluable) and in combination with pembrolizumab (Regimen B, n = 4, 4 evaluable)



CD8 scoring

Figure 6. Evolution of the tumor microenvironment in patients treated with GB1275 plus pembrolizumab: CD8 count



CONCLUSIONS

GB1275 alone or in combination with pembrolizumab demonstrates biological activity in patients with advanced solid tumors:

- MDSCs levels in blood are modulated by GB1275 alone or in combination with pembrolizumab
- Blood proteomics and transcriptomics data support the hypothesis that GB1275 modulates peripheral myeloid biomarkers
- Observed post-treatment increases in TILs and CD8s in subsets of tumor biopsies (in both regimens) support the mechanism of action of GB1275, reflecting reduced myeloid cell mediated T cell suppression

This emerging biomarker dataset suggests that GB1275 may modulate myeloid cell biology in the tumor microenvironment and thus may be effective in combination with pembrolizumab.

REFERENCE

1. Panni RZ, et al. *Transl Med.* 2019;11:eaau9240.

DISCLOSURES

This study was funded by GB006, Inc, a wholly owned subsidiary of Gossamer Bio, Inc

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