activation (4-1BB) and proliferation (Ki67) of peripheral CD8 + T cells measured by flow cytometry. Exploratory objectives were characterization of PD effects in plasma/serum and measurement of intra-tumoral immune activation. The endpoints were change in peripheral cytokines (TNF-alfa, IFN-gamma, IL-6) and soluble(s) factors (sCD25, s4-1BB) concentration measured by ELISA, and intra-tumoral changes in gene expression measured by RNAseq.

**Results**

In the periphery, we observed transient expression of 4-1BB on CD4+ and CD8+ T cells, along with secretion of s4-1BB and inflammatory cytokines, suggesting 4-1BB targeting and potent T cell activation. The concomitant induction of proliferating T cells indicated the potential association to priming and formation of tumor-reactive T cells. In the tumor, we detected increased CD8+ T cells infiltration and proliferation, in both Parts. Proliferating CD8+ T cells increased in both tumor nests and surrounding stroma, with a preferential accumulation in the latter. RNAseq analysis revealed induction of 4-1BB, PD-1 and IFN-gamma, indicating intra-tumoral T cell activation in Part B.

**Conclusions**

PD activity was consistent with the postulated MoA, confirming RO to be a potent tumor-targeted 4-1BB agonist in the clinical setting. Our observations suggest that RO can synergize with endogenous T cell receptor stimulation, both as SA and in combination with ATZ.

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**THE ASSOCIATION OF THE GUT MICROBIOTA AND CLINICAL RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH ADVANCED CANCER**

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**Background**

The gut microbiome is associated with the immune function of the host. No consensus has been reached regarding to the association between microbiota and the treatment response to immune checkpoint inhibitor (ICI). This study is designed to explore the relationship between gut microbiome composition and clinical outcomes in patients with advanced cancer treated with ICI.

**Methods**

Fifty patients were enrolled in this study. Fecal samples were collected at the baseline, 3 months after treatment and when disease progression was noted. To explore the gut microbiota as a potential predictive biomarker for immunotherapy, 16S ribosome RNA gene sequencing was used to analyze the gut microbiota profiles. Peripheral immunity parameters were determined by multicolor flow cytometry and cytokine array. Alpha-diversity of healthy individuals was used as a cut-off.

**Results**

When subgrouping patients into benefiter and non-benefiter according to the clinical response assessed, non-benefiter patients harbored lower alpha-diversity of gut microbiome at the baseline. Patients with low microbiome diversity had poor clinical benefiter according to the clinical response assessed, non-benefiter patients harbored lower alpha-diversity of gut microbiome at the baseline. Patients with low microbiome diversity had poor baseline. Patients with low microbiome diversity had poor progression-free survival (HR=0.569, p=0.219) when compared to those with high diversity. Composition difference was observed between the two groups as well with the enrichment of g_Fusicatenibacter in benefiter whereas f_Veillonellaaceae enriched in non-benefiter. Analysis of immune responses using multicolor flow cytometry revealed that patients with a high diversity of gut microbiota had decreased CD4+/CD25+/FoxP3+ regulatory T cells in response to ICI. After ICI treatment the CD4/CD8 ratio of PBMCs was decreased in clinical benefiter. The serum MIF and CXCL12 levels were decreased in clinical benefiter.

**Conclusions**

Low alpha diversity of the gut microbiota is associated with poor response to immune checkpoint inhibitors in patients with advanced cancer. Further confirmation in the clinical trials is warranted.

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