520 PRELIMINARY BIOMARKER AND PHARMACODYNAMIC (PD) ACTIVITY OF THE TGFβ INHIBITOR SAR439459, ALONE OR IN COMBINATION WITH CEMIPLIMAB, IN A PHASE 1 CLINICAL STUDY IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background Transforming growth factor beta (TGFβ) is a bifunctional regulator of tumor growth playing a role in tumor immune evasion and resistance to checkpoint blockade. Increased activation of TGFβ pathway correlated with reduced overall survival in patients with PD-1 resistance/refractory tumors. Therefore, the combination of a TGFβ inhibitor with an anti-PD-1 agent may benefit patients who are resistant to checkpoint blockade. SAR439459 is a "second generation" human anti-TGFβ IgG4 monoclonal antibody. Here we report the preliminary PD results and patient selection strategy (mesenchymal CRC) of SAR439459 ± anti-PD-1 cemiplimab in patients with advanced tumors from an on-going phase 1 study (NCT03192345).

Methods Peripheral blood, serum and tumor biopsies from patients were collected for the assessment of both predictive and PD biomarkers. A consensus molecular subtyping 4 (CMS4) gene classifier was developed and used to identify mesenchymal CRC tumors based on an in-silico experiment followed by a validation using ~200 procured CRC tumor biopsy samples with customized NanoString assay. TGFβ level in plasma and tumor was measured by ELISA to assess target engagement of SAR439459. Well-known immune modulation events as the PD readout were measured: 1) immunophenotyping of circulating immune cells ; 2) cytokine/chemokine production by MSD assay; 3) PD-L1, CD8+ T cells and FoxP3+ Tregs in tumor micro-environment (TME) by immunohistochemistry; 4) TGFβ pathway activation gene signature in TME by RNAseq.

Results SAR439459 ± cemiplimab, induced inhibition of plasma TGFβ level ≥ 90% at doses ≥ 0.25mg/kg Q2W, together with a clear trend of decrease in intra-tumoral TGFβ. RNAseq data from paired biopsies revealed concomitant down-regulation of TGFβ pathway. In periphery, SAR439459 ± cemiplimab increased proliferating T and NK cells. Concomitantly, enhanced production of pro-inflammatory cytokines/chemokines confirmed peripheral immune activation. In TME, a trend of increased CD8+ T cell infiltration and conversion from "immune-excluded" to "immune-inflamed" phenotype was observed following the combination treatment in several cases. No significant modulation of PD-L1 or FoxP3 was observed from the available paired biopsies. Out of 137 pre-screened CRC patients, 58 (42%) were identified as carrying the CMS4 phenotype based on the gene classifier.

Conclusions Clinical modulation of TGFβ level and the related pathway demonstrated SAR439459's target engagement. Further analysis confirmed the peripheral immune activation in patients treated with SAR439459 ± cemiplimab. Coupled with CD8+ T cell modulation in TME, these findings suggest the identification of early PD biomarkers impacted by SAR439459 which is consistent with the mechanism of action and biological activity of TGFβ blockade therapy.

Trial Registration NCT03192345

Ethics Approval The study protocols were approved by the institutional review board or independent ethics committee of each participating institution. All patients provided written informed consent priorto enrollment.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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