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 RNA-seq.

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.