666 SAFETY, EFFICACY, AND BIOMARKER RESULTS OF SRK-181, A LATENT TGFβ1 INHIBITOR, IN ANTI-PD-1 RESISTANT METASTATIC CCRCC PATIENTS

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Background Transforming growth factor-beta (TGFβ), specifically the TGFβ1 isoform, drives tumor immune escape by promoting an immunosuppressive pro-tumor microenvironment, including reducing antigen presentation, as well as impairing T-cell infiltration and tumor-killing activity. SRK-181 is a fully human, selective, IgG4 monoclonal antibody targeting latent TGFβ1 under investigation as monotherapy or in combination with anti-PD-(L)1 therapy to overcome resistance to immune checkpoint inhibition.

Methods DRAGON (NCT04291079) is an ongoing open-label, phase 1 study. Part A (3+3 dose escalation) evaluated SRK-181 in Part A1 and SRK-181+anti-PD-(L)1 in Part A2.[1] In Part B (expansion phase), SRK-181 (1500mg q3w)+pembrolizumab are administered in anti-PD-1 resistant patients with clear cell renal cell carcinoma (ccRCC), non-small cell lung cancer, melanoma, urothelial carcinoma, and head and neck cancer. Initial results in ccRCC cohort along with biomarkers assessing the tumor immune landscape are reported here.

Results As of 26 May 2023, 20 anti-PD-1-refractory metastatic ccRCC patients were enrolled (2 in Part A2 and 18 in Part B), with median prior lines of therapies of 3 (range 1–6). All patients received at least one tyrosine kinase inhibitor and one anti-PD-1 therapy. The best responses on prior anti-PD-1 therapy were stable disease (SD) or disease progression (PD) and all patients progressed on prior anti-PD-1 therapy. Patients (4 females and 16 males) had a median age of 59 (range 43–80) years. The most common treatment-related AEs (TRAE,>10%) of any grade were pruritus (15%, n=3), rash maculo-papular (15%, n=3), and rash (10%, n=2). No grade 4 or 5 TRAEs were observed. Treatment-related SAEs include immune-mediated hepatitis, pemphigoid, and rash (n=1 each). Sixteen of the 20 patients are response evaluable since 4 ongoing patients are pending post-treatment radiographic evaluation. Four patients had confirmed partial response (PR) based on RECIST1.1 criteria by PI assessment (ORR=25%). The 4 PR patients, who had been previously treated with 2 to 5 prior lines of therapies, achieved tumor reduction of –50% to -84%, and remained on study for 5+ to 14+ months. Seven patients had SD (4 remain on study for 2+ to 8+ months). Biomarker data will be shared; initial results suggest that treatment decreased circulatory myeloid derived suppressor cell levels below baseline by Day 30 post-treatment.

Conclusions As of 26 May 2023, combination treatment of SRK-181 and anti-PD-1 (pembrolizumab) was generally well tolerated with an ORR of 25% and clinical benefit rate of 69% in heavily pre-treated, anti-PD-1-refractory ccRCC patients. Enrollment is ongoing for all cohorts.

REFERENCE

1. Yap T, Gainor J, McKean M, *et al.* 780 SRK-181, a latent TGFβ1 inhibitor: safety, efficacy, and biomarker results from the dose escalation portion of a phase I trial (DRAGON trial) in patients with advanced solid tumors. *Journal for ImmunoTherapy of Cancer* 2022;**10:**doi: 10.1136/jitc-2022-SITC2022.0780

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