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

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Background Transforming growth factor-beta 1 (TGFβ1) plays an important role in mediating the primary resistance to PD-1/PD-L1 [PD-(L)1] blockade. SRK-181 is a fully human, selective anti-latent TGFβ1 IgG4 monoclonal antibody under investigation as a monotherapy or in combination with anti-PD(L)1 therapy in patients with solid tumors. Compared to broad TGFβ inhibitors, SRK-181 was observed to have improved safety profile (no cardiotoxicities) in four-week GLP nonclinical toxicology studies.

Methods The DRAGON trial (NCT04291079) is an ongoing open-label, phase 1 study. Part A followed a 3+3 dose escalation design to evaluate SRK-181 in patients with advanced solid tumors at 80-3000mg every three weeks (q3w) and 2000mg q2w in Part A1, and SRK-181+anti-PD-(L)1 in patients who did not respond to prior anti-PD-(L)1 therapy at 240-2400mg q3w in Part A2. In Part B (expansion phase), SRK-181 (1500mg q3w or 1000mg q2w)+anti-PD-(L)1 are administered in anti-PD-(L)1-resistant patients with non-small cell lung cancer (NSCLC), urothelial carcinoma, melanoma, clear cell renal cell carcinoma (ccRCC) or other advanced solid tumors. The level of circulatory TGFβ1 was assessed as a target engagement biomarker.

Results As of 2 June 2022, Part A1 and Part A2 enrolled 19 and 15 patients, respectively, with median prior lines of therapies of 4 (range 1-10). No dose limiting toxicity (DLT) were observed in Part A. In Part A1, the most common treatment-related AEs (TRAEs, >10%) of any grade were fatigue (16%, n=3), decreased appetite and nausea (each: 11%, n=2). Eight patients had stable disease (SD) as best response (3/colorectal, 3/ovarian, 1/pancreatic, and 1/testicular). The three patients with ovarian cancer were stable for 25 to 42 weeks. In Part A2, the TRAEs (>10%) of any grade were pruritus, rash and rash maculo-papular (each: 20%, n=3), diarrhea (13%, n=2). One confirmed RECIST1.1 partial response (PR) was observed at 800mg in a patient with anti-PD-1 resistant RCC who stayed on study for 30 weeks. Nine patients had best response of SD and five of them were stable for more than 16 weeks (2/head and neck, 1/melanoma, 1/skin squamous cell carcinoma, 1/RCC). SRK-181 treatment resulted in increased levels of circulatory TGFβ1, which suggested target engagement. Part B enrollment is ongoing.

Conclusions As of 2 June 2022, SRK-181 has been tolerated as monotherapy and in combination with anti-PD-(L)1. No DLT was observed up to 3000mg q3w/2000mg q2w as monotherapy and up to 2400mg q3w as combination treatment. Early evidence of efficacy was observed with prolonged stable disease and a confirmed PR.