

FIRST-IN-HUMAN PHASE 1 TRIAL OF SRK-181: A LATENT TGFβ1 INHIBITOR, ALONE OR IN COMBINATION WITH ANTI-PD-(L)1 TREATMENT IN PATIENTS WITH ADVANCED SOLID TUMORS (DRAGON TRIAL)

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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 monoclonal antibody that selectively inhibits latent TGFβ1 activation. Mouse tumor models (bladder, melanoma, and breast cancer) demonstrated that treatment with SRK-181+anti-PD-1 overcame primary anti-PD-1 resistance. Four-week GLP non-clinical toxicology studies showed that SRK-181 has improved safety profile (no cardiotoxicities) compared to broad TGFβ pathway inhibition.

Methods The DRAGON trial (NCT04291079) is an ongoing open-label, phase 1 study. Part A of the study follows a standard 3+3 dose escalation design to determine the dose for Part B. Part B (expansion phase) evaluates combination treatment in patients with non-small cell lung cancer (NSCLC), urothelial carcinoma, melanoma, or other advanced solid tumors. SRK-181 is administered IV every 3 or 2 weeks (Q3W/Q2W) alone in patients with advanced solid tumors (Part A1), or in combination with anti-PD-(L)1 in patients who did not respond to prior anti-PD-(L)1 therapy (Part A2/B).

Results As of 7 June 2021, 25 patients have enrolled to Part A; median 4 prior lines of therapies (range 1–9). Cancer types: colorectal, ovarian, prostate, and unknown primary (Part A1); liver, melanoma, NSCLC, oropharynx, renal cell carcinoma (RCC) and uterine (Part A2). In Part A1, 15 patients were treated with SRK-181 monotherapy at doses of 80, 240, 800, 1600, 2400, 3000mg Q3W, with no dose limiting toxicity (DLT) observed. The last cohort (2000mg Q2W) remains under evaluation. The most common treatment-related AEs (TRAE, >10%) of any grade were decreased appetite and fatigue (each: 13.3%, n=2). Six patients had stable disease (SD) as best response (2/colorectal cancer, 1/prostate cancer, and 3/ovarian cancer). Three ovarian cancer patients were stable ≥153 days with tumor regressions. In Part A2, 10 patients were treated with SRK-181 at doses of 240, 800 and 1600mg Q3W+pembrolizumab. No DLT was observed up to 800mg. 1600mg Q3W is under evaluation. No TRAE (>10%) of any grade were observed. One confirmed RECIST1.1 partial response (PR) was observed (800mg) in a patient with anti-PD-1 resistant RCC and 2 patients had best response of SD (1/oropharynx cancer, 1/liver cancer). The half-life of SRK-181 ranged from 3.9 to 19.3 days across the doses tested.

Conclusions As of 7 June 2021, SRK-181 has been well tolerated as monotherapy and in combination with anti-PD-(L)1. One RECIST1.1 PR (800mg) was observed in a patient with anti-PD-1 resistant RCC. Next planned dose in Part A2 will be 2400mg Q3W.

Trial Registration DRAGON trial (NCT04291079)

Ethics Approval The human study was approved by the Massachusetts General Hospital and Beth Israel Deaconess Medical Center (20–286), Sarah Cannon Research Institute (1276118), Mary Crowley Cancer Research (20–06), MD Anderson

Cancer Center (2020–0110) Institutional Review Boards with written informed consent obtained from each participant and/or their legal representative, as appropriate.

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