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)

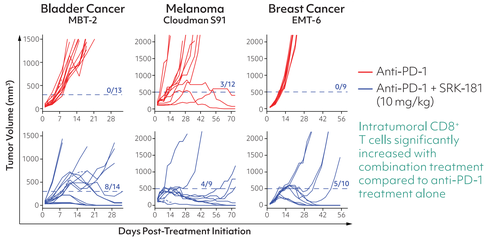
Timothy A. Yap[1], Minal Barve[2], Justin F. Gainor[3], Bruno Bockorny[4], Yawen Ju[5], Shaun Cote[5], Sharon Lu[5], Sanela Bilic[5], Lan Liu[5], Yung Chyung[5], Michelle Legler[5], Lu Gan[5], Meredith McKean[6]

[1] The University of Texas MD Anderson Cancer Center, Houston, TX; [2] Mary Crowley Cancer Research, Dallas, TX; [3] Massachusetts General Hospital Harvard Medical School, Boston, MA; [4] Beth Israel Deaconess Medical Center, Boston, MA; [5] Scholar Rock, Inc., Cambridge, MA; [6] Sarah Cannon Research Institute, Nashville, TN

Background

- Despite clinical advances made with CPI therapy, resistance to CPI treatment remains an unmet medical need[1]
- TGFβ plays an important role in driving immune exclusion and primary resistance to CPIs[2,3]
- Human data implicate that TGFβ signaling is mainly driven by TGFβ1 in most tumor types[4]
- SRK-181 is a fully human, selective IgG4 monoclonal antibody that inhibits latent TGFβ1 activation[4]

TGFβ1 Blockade with SRK-181 Renders Mouse Tumor Models Susceptible to Anti-PD-1 Therapy[4]

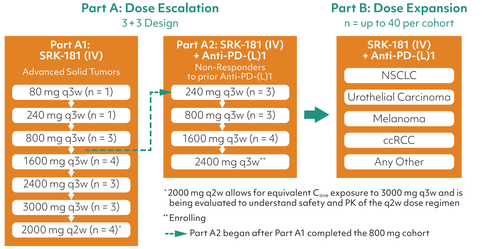


Intratumoral CD8⁺ T cells significantly increased with combination treatment compared to anti-PD-1 treatment alone

- Unlike other broad TGFβ inhibitors, SRK-181 showed an improved toxicity profile (including no cardiotoxicities) in 4-week GLP nonclinical toxicology studies[4,5]
- SRK-181 may potentially decrease PD-(L)1 inhibitor resistance and toxicity of nonselective TGFβ pathway approaches in human cancer patients

Phase 1 Clinical Trial Overview

- The DRAGON trial (NCT04291079) is a multicenter, open-label, Phase 1, FIH, dose-escalation, and dose-expansion trial to evaluate the safety, tolerability, PK, pharmacodynamics, and efficacy of SRK-181 alone and in combination with anti-PD-(L)1 therapy in patients with advanced solid tumors



Study Objectives (Part A)

Primary Objectives

- Evaluate the safety and tolerability of SRK-181 alone (Part A1) and in combination with anti-PD-(L)1 (Part A2)
- Determine the MTD or MAD, and recommended dose for Part B

Secondary Objectives

- Evaluate the PK and ADA profile

Exploratory Objectives

- Evaluate anti-tumor activity
- Evaluate biomarkers

Eligibility Criteria (Part A)

Key Inclusion Criteria

- Age ≥ 18 years, with a predicted life expectancy of ≥ 3 months
- Measurable disease per RECIST v1.1 at screening
- Part A1: Patients have advanced solid tumors and have failed available standard of care treatment
- Part A2: Patients did not respond to prior anti-PD-(L)1 therapy, presenting either as progressive disease or stable disease after 3 cycles of treatment (non-responsive)

Exclusion Criteria

- ECOG performance status ≥ 2
- Concurrent anti-cancer treatment
- Hypersensitive or presence of ADA to anti-PD-(L)1 therapy

Assessment

- Safety endpoints include AEs, clinical observations (e.g., vital signs, physical examination), laboratory tests, electrocardiograms, and echocardiograms
  - » DLT evaluation period is 21 days for q3w regimen and 14 days for q2w regimen
- Response is assessed using RECIST v1.1 by PI; the scan is performed during screening, 6 weeks after first dose, every 9 weeks for the next 6 months of treatment, and every 12 weeks thereafter; central reads are also being conducted, with a comprehensive review of the central reads to be performed once completed across the cohorts
- A biomarker strategy to assess both the immune status and TGFβ pathway activity as well as orthogonal approaches are being developed[6]

Demographics and Baseline Characteristics

- As of September 7, 2021, 29 patients have been dosed
  - » In Part A1, 19 patients were dosed
  - » In Part A2, 10 patients were dosed

Category	Part A1	Part A2
N	19	10
Age, median (range)	66.0 (41, 79)	62.5 (32, 75)
Gender (F/M)	8 / 11	1 / 9
Ethnicity		
Hispanic or Latino	0	2
Not Hispanic or Latino	18	8
Not Reported	1	0
Race		
White	19	10
Prior Lines of Therapy, median (range)	4 (1, 9)	4 (2, 6)

Patient Disposition

Category	Part A1	Part A2
Enrolled	19	10
On Study	3	1
Stopped Treatment	16	9
Reason for Completion/Discontinuation		
Adverse Event*	1	2
Clinical Progression	3	3
Disease Progression based on RECIST v1.1	11	3
Investigator Decision	1	0
Withdrawal of Consent	0	1

Clinical cutoff date: September 7, 2021
*3 patients discontinued from the study due to AEs deemed unrelated to SRK-181 treatment

Determination of MTD and Recommended Dose for Part B

- As of October 12, 2021, no DLTs were observed up to 3000 mg q3w and 2000 mg q2w in Part A1; and up to 1600 mg q3w in Part A2
- The recommended Part B dose is 1500 mg q3w and/or 1000 mg q2w
  - » In the mouse preclinical efficacy model (Background), the observed C_{ave} for SRK-181 was ~80 μg/mL at 10 mg/kg
  - » The recommended Part B dose of 1500 mg q3w has been chosen based on the ability to attain C_{trough} ≥ ~80 μg/mL at the lower bound of the 90% CI
  - » The dose of 1000 mg q2w was chosen since it allows for equivalent C_{ave} exposure to 1500 mg q3w, which would provide flexible dose frequency when combining with different anti-PD-(L)1 in Part B

Safety

Treatment-Emergent AEs, All Grades ≥ 20% (Part A1)

Dose (mg)	80 (n = 1)	240 (n = 1)	800 (n = 3)	1600 (n = 4)	2400 (n = 3)	3000 (n = 3)	2000 (n = 4)	All (n = 19)
Decreased appetite	1	0	1	1	1	0	1	5 (26.3%)
Fatigue	1	1	0	0	2	0	1	5 (26.3%)
Abdominal pain	0	0	0	1	1	1	1	4 (21.1%)
ALT increased	0	0	1	0	1	1	1	4 (21.1%)
AST increased	0	0	1	0	1	1	1	4 (21.1%)
Back Pain	0	0	1	0	0	2	1	4 (21.1%)
Nausea	1	0	0	1	0	0	2	4 (21.1%)
Vomiting	0	0	0	0	1	1	2	4 (21.1%)

All dose levels were administered q3w except 2000 mg, which was administered q2w. Clinical cutoff date: September 7, 2021

Treatment-Emergent AEs Related to SRK-181, All Grades > 10% (Part A1)

Dose (mg)	80 (n = 1)	240 (n = 1)	800 (n = 3)	1600 (n = 4)	2400 (n = 3)	3000 (n = 3)	2000 (n = 4)	All (n = 19)
Fatigue	0	1	0	0	1	0	1	3 (15.8%)
Decreased appetite	1	0	1	0	0	0	0	2 (10.5%)
Nausea	1	0	0	0	0	0	1	2 (10.5%)

All dose levels were administered q3w except 2000 mg, which was administered q2w. Clinical cutoff date: September 7, 2021

Treatment-Emergent AEs, All Grades ≥ 20% (Part A2)

Dose (mg)	240 (n = 3)	800 (n = 3)	1600 (n = 4)	All (n = 10)
Dyspnoea	0	1	2	3 (30%)
Blood creatinine increased	0	1	1	2 (20%)
Hypokalaemia	0	2	0	2 (20%)
Hypomagnesaemia	1	1	0	2 (20%)
Rash maculo-papular	1	1	0	2 (20%)

All dose levels were administered q3w. Clinical cutoff date: September 7, 2021

Treatment-Emergent AEs Related to SRK-181/Anti-PD(L)1, All Grades > 10% (Part A2)

Dose (mg)	240 (n = 3)	800 (n = 3)	1600 (n = 4)	All (n = 10)
Rash maculo-papular	1	1	0	2 (20.0%)

*All dose levels were administered q3w. Clinical cutoff date: September 7, 2021

- Treatment-related Grade 3 AEs were alanine aminotransferase increased (1 patient in Part A1); lipase increased, hypoxia and rash maculo-papular (1 patient each in Part A2); no Grade 4 or 5 treatment-related AEs occurred
- Treatment-related SAE of elevated troponin I (1 patient) was observed in Part A1 (at 2000 mg q2w); no SRK-181 treatment-related SAEs were observed in Part A2

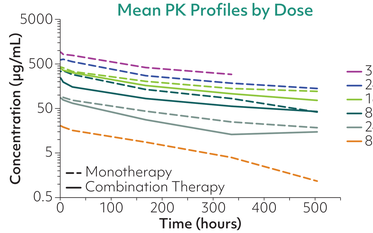
Abbreviations: ADA, antidrug antibody; Anti-PD-(L)1, programmed death ligand-1 antibody/programmed cell death protein-1 antibody; C_{ave}, average plasma concentration; ccRCC; clear cell renal cell carcinoma; CPI, checkpoint inhibitor; CL_{ss}, clearance at steady state; C_{trough}, trough concentration; DLT, dose-limiting toxicity; FIH, first in human; MAD/MTD, maximum administered/tolerated dose; NSCLC, non-small cell lung cancer; PD, disease progression; PI, principal investigator; PR, partial response; q2w, every 2 weeks; q3w, every 3 weeks; SCC, squamous cell carcinoma; SD, stable disease; TGFβ1, transforming growth factor beta-1; V_{ss}, volume distribution at steady state.

References: 1) Carretero-González, et al. *Oncotarget*. 2018;9:8706-8715. 2) Mariathasan, et al. *Nature*. 2018;554:544-548. 3) Hugo, et al. *Cell*. 2017;168:542. 4) Martin, et al. *Sci Transl Med*. 2020;12:eaay8456. 5) Welsh, et al. *Int J Toxicol*. 2021 Mar 19; https://doi.org/10.1177/10915818211998945. 6) Bruckner, et al. AACR 2021; Abstract 1801.

Disclosures: SRK-181 is an investigational drug candidate that is currently being evaluated in a Phase 1 clinical trial. The safety and efficacy of SRK-181 have not been established. SRK-181 has not been approved by the U.S. Food and Drug Administration or any other health authority for any indication.

Preliminary PK Summary of SRK-181

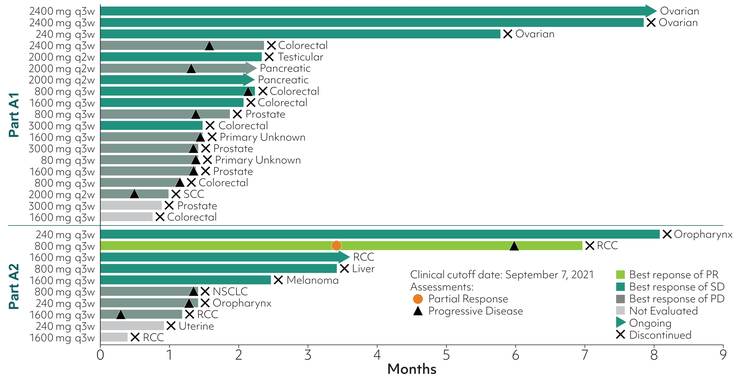
Mean PK Profiles by Dose



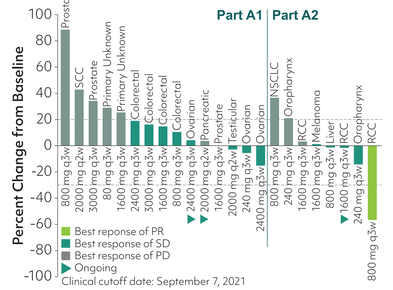
- SRK-181 displayed typical monoclonal antibody PK characteristics, with observed CL_{ss} that ranged from 0.0164 to 0.0225 L/h and V_{ss} that ranged from 4.21 to 6.85 L
- Based on a power model, dose-proportional PK was observed for SRK-181
- The $T_{½}$ of SRK-181 was 5.4 to 10.7 days

Preliminary Efficacy

Duration of Treatment



Best Response in Target Lesions



- Among 19 patients in Part A1
  - » 8 patients had a best response of SD (3/ovarian, 3/colorectal, 1/pancreatic, 1/testicular)
  - » 3 ovarian cancer patients were stable for ≥ 153 days with tumor regressions
- Among 10 patients in Part A2
  - » At 800 mg q3w, 1 confirmed RECIST1.1 PR was observed in a patient with anti-PD-1-resistant RCC
  - » 4 patients had best response of SD (1/oropharynx, 1/liver, 1/melanoma, 1/RCC)
  - » 1 oropharynx cancer patient was stable for 245 days with tumor regressions

Summary and Next Steps

- As of September 7, 2021, SRK-181 has been well-tolerated both as monotherapy and in combination with anti-PD-(L)1
- The recommended Part B dose was determined to be 1500 mg q3w and/or 1000 mg q2w
  - » No DLT was observed up to 3000 mg q3w and 2000 mg q2w with SRK-181 monotherapy
  - » No DLT was observed up to 1600 mg q3w with SRK-181 + pembrolizumab combination treatment
- Next planned dose in Part A2 will be 2400 mg q3w
- SRK-181 efficacy will be evaluated in Part B, which was initiated on October 12, 2021

ScholarRock
medicalinquiry@ScholarRock.com