First-in-Human Phase 1 Trial (DRAGON) of SRK-181: A Potential First-in-Class Selective Latent TGFβ1 Inhibitor, Alone or in Combination with Anti-PD-(L)1 Treatment in Patients with Advanced Solid Tumors

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Introduction

- Nearly 80% of patients do not respond to CPI therapies[1]
- Human data implicate TGFβ1 as a key driver of immune exclusion and primary resistance to CPIs[2,3]
- SRK-181 is a fully human monoclonal antibody that selectively inhibits latent TGFβ1 activation with picomolar affinity in pre-clinical studies[4]
  - ➢SRK-181 has minimal or no binding to latent TGFβ2 nor TGFβ3 isoforms[4]
  - ➢SRK-181 does not inhibit active TGFβ growth factors[4]
  - ➢In mouse tumor models (bladder, melanoma, and breast cancer), SRK-181 in combination with anti-PD-1 therapy overcame primary anti-PD-1 resistance and led to anti-tumor activity (Fig. 1)[4]
  - ➢Intratumoral CD8+ T cells significantly increased in tumors treated with anti-PD-1 and SRK-181 (Fig. 2)[4]
  - ➢SRK-181 treatment increased the circulatory latent TGFβ1 in a mouse tumor model (Fig. 3)[5]
  - ➢Unlike non-selective TGFβ inhibitors[6,7,8], SRK-181 has not been associated with any cardiotoxicities (valvulopathy) in nonclinical toxicology studies (Fig. 4)[4,9]
- Thus, the potency and selectivity of SRK-181 may overcome PD-1 inhibitor resistance and toxicity of nonselective TGFβ pathway approaches in human cancer patients.

Figure 1.

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

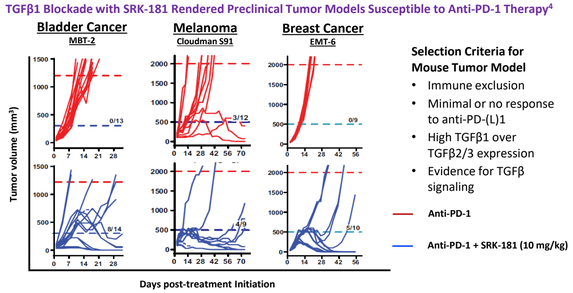
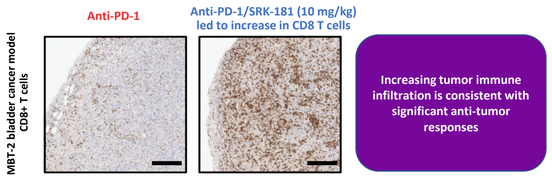


Figure 2.

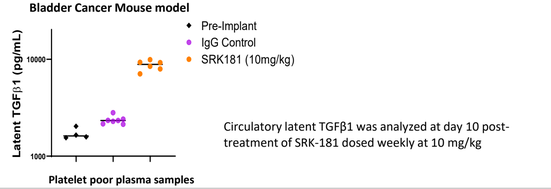
Combination Therapy of SRK-181 + Anti-PD-1 Enabled Infiltration and Expansion of CD8 T cells[4]



- In a bladder cancer model, SRK-181 and anti-PD-1 combination leads to:[4]
  - Significant increase in effector T cells ($p < 0.05$)
  - Significant decrease in intra-tumoral immunosuppressive myeloid cells ($p < 0.05$)

Figure 3.

SRK-181 Induced a Marked Increase in Level of Circulatory Latent TGFβ1 in a Mouse Tumor Model



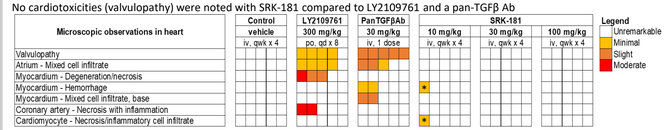
Circulatory latent TGFβ1 was analyzed at day 10 post-treatment of SRK-181 dosed weekly at 10 mg/kg

Figure 4.

Inhibition of TGFβ1 Isoform by SRK-181 Shows Improved Toxicology Profile in Comparison to Pan-TGFβ Inhibition[4]

4-week Rat Toxicology Study, Heart Pathology

No cardiotoxicities (valvulopathy) were noted with SRK-181 compared to LY2109761 and a pan-TGFβ Ab

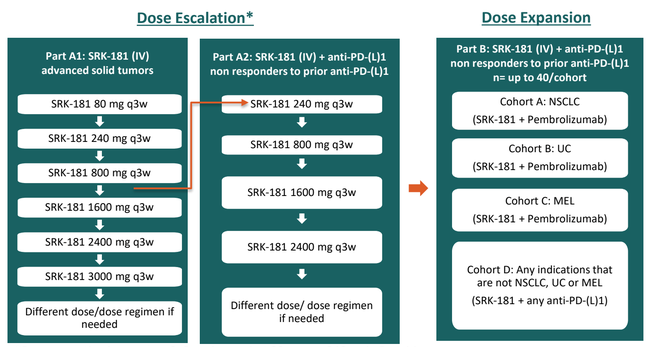


* Not test article related

In 4-week rat and cynomolgus monkey toxicology studies, no SRK-181-related adverse findings were noted at doses of up to 200 mg/kg/wk and 300 mg/kg/wk, respectively. The NOAEL for these studies was the maximum dose tested.

Phase 1 Clinical Study Overview

- The DRAGON trial (NCT04291079) is a multi-center, open-label, Phase 1, FIH, dose-escalation, and dose expansion study to evaluate the safety, tolerability, PK, PD and efficacy of SRK-181 and/or in combination with anti-PD-(L)1
- The DRAGON trial comprises 3 parts:



*Dose escalation is based on 3+3 design; n=1 at 80mg and 240mg in Part A1

Eligibility

Key Inclusion Criteria

1. Age ≥ 18 years, predicted life expectancy of ≥ 3 months
2. Measurable disease per RECIST v1.1 at Screening
3. Part A1: patients have advanced solid tumors and have failed available standard of care treatment
4. Part A2 and B only: Patient did not respond to prior anti-PD-(L)1 therapy, presenting either as progressive disease or stable disease after 3 cycles of treatment
5. Part B only: Patient must have received their most recent dose of anti-PD-(L)1 antibody therapy within 6 months of enrollment (9 months for UC cohort)

Key Exclusion Criteria

1. ECOG performance status ≥ 2
2. Concurrent anti-cancer treatment
3. History of active metastatic CNS disease
4. An active or prior history of autoimmune disease
5. Hypersensitive or presence of anti-drug ADA to anti-PD-(L)1 antibody therapy
6. Concurrent second malignancy

Study Objectives

PART A

- **Primary Objectives**
  - Evaluate the safety and tolerability of SRK-181 (Part A1) or in combination with anti-PD-(L)1 (Part A2)
  - Determine the MTD or MAD, and the RP2D and evaluate DLTs
- **Secondary Objectives**
  - Evaluate the PK and ADA
- **Exploratory Objectives**
  - Evaluate anti-tumor activity
  - Evaluate biomarkers

PART B

- **Primary Objectives**
  - Evaluate the safety and tolerability of SRK-181 + anti-PD-(L)1
- **Secondary Objectives**
  - Evaluate the anti-tumor activity
  - Evaluate the PK and ADA
- **Exploratory Objectives**
  - Evaluate biomarkers

Assessment

- Safety endpoints include adverse events, clinical observations (e.g., vital signs, physical examination), laboratory tests, ECGs, and echo
  - DLT evaluation period is 21 days for q3w regimen
- Response will be assessed using RECIST v1.1 by Principal Investigator (PI) and by independent central review
- A biomarker strategy to assess both the immune status and TGFβ pathway activity as well as orthogonal approaches are being developed including: (Fig. 5)
  - CD8 positive T cells to evaluate the ability of SRK-181 to increase immune infiltration in the tumor
  - TGFβ pathway such as circulatory TGFβ1 or tumor phospho-Smad2 (P-Smad2), a key signaling mediator of TGFβ downstream signaling[11], to evaluate pathway modulation by SRK-181
  - Multiple biologically related pathways to determine the systemic effects of SRK-181 through multiplex IHC, NGS and additional blood-based biomarkers
- To implement the biomarker strategy, select biomarker assays were developed and refined including:
  - Establishment of CD8 IHC digital pathology analysis plan to enable classification of tumor phenotypes (Fig. 6)
  - Development of IHC assay for P-Smad2, (Fig. 7)

Summary

- SRK-181 is a potential first-in-class, selective latent TGFβ1 inhibitor that is being investigated across multiple cancer types in patients who have failed available standard of care treatment and who are non-responsive to prior anti-PD-(L)1 treatment.
- Preclinical studies showed that SRK-181 in combination with anti-PD-1 therapy overcame primary anti-PD-1 resistance and led to anti-tumor activity[2,3]
- The DRAGON Study is an ongoing first-in-human phase 1 clinical trial

Trial Status

- As of April 01, 2021, 20 patients have been dosed (14 in A1 and 6 in A2). Dose escalation is ongoing
- **Part A1**
  - Dose of SRK-181 has been escalated from 80 mg to 2400 mg with no DLT observed
  - Dose of 3000 mg is under evaluation
- **Part A2**
  - Dose of SRK-181 + an anti-PD-(L)1 has been escalated from 240 mg to 800 mg with no DLT observed
  - Dose of 1600 mg SRK-181 + an anti-PD-(L)1 is under evaluation
- Initiation of Part B of DRAGON is planned for mid-year 2021

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Acknowledgements

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Figure 5.

Biomarker Strategy Focuses on Evaluation of Immune Landscape and TGFβ pathway status

1. Immunophenotyping
Assessment of the tumor immune landscape

- PD → assess SRK-181 to convert tumors to be 'Inflamed'
- Predictive → identify inflamed, immune excluded or immune desert tumors at baseline to predict response

Include CD8 (tumoral cytotoxic T cells)

2. TGFβ signaling pathway
Assessment of TGFβ1 signaling pathway

- PD → assess SRK-181 to modulate TGFβ pathway activation
- Predictive → identify target/pathway prevalence to predict response

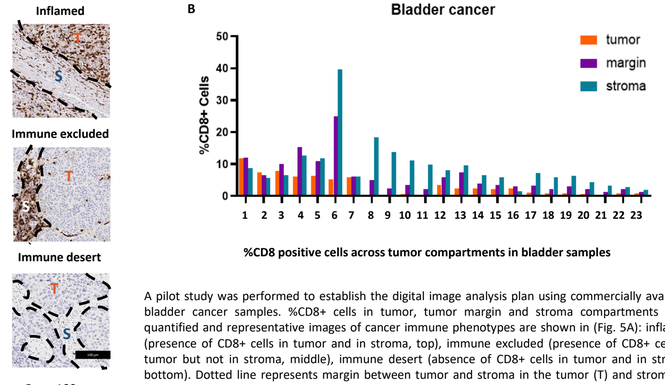
Include Circulatory TGFβ1, Tumor P-Smad2

3. Orthogonal biomarker strategy
Future direction to simultaneously assess multiple biologically related pathways include tumor-based multiplex IHC, NGS and additional blood-based biomarkers

Figure 6.

Establishment of CD8 IHC Digital Pathology Analysis Plan for Tumor Immunophenotyping[5]

Evaluating the distribution of CD8⁺ T cells across the tumor compartments enables classification of tumor phenotypes[10]

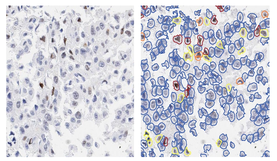


A pilot study was performed to establish the digital image analysis plan using commercially available bladder cancer samples. %CD8+ cells in tumor, tumor margin and stroma compartments were quantified and representative images of cancer immune phenotypes are shown in (Fig. 5A): inflamed (presence of CD8+ cells in tumor and in stroma, top), immune excluded (presence of CD8+ cells in tumor but not in stroma, middle), immune desert (absence of CD8+ cells in tumor and in stroma, bottom). Dotted line represents margin between tumor and stroma in the tumor (T) and stroma (S) compartments.

Figure 7.

Establishment of P-Smad2 IHC assay to detect modulation of TGFβ signaling[5]

Decreased expression in P-Smad2 indicates inhibition of TGFβ pathway[12]



- High p-Smad2 Nucleus
- Medium p-Smad2 Nucleus
- Low p-Smad2 Nucleus
- Negative p-Smad2 Nucleus

P-Smad2 IHC assay is developed using commercially available cancer samples and digital image analysis was established that enables identification of a range of P-Smad2 nucleus staining intensity ranging from high (red), medium (orange), low (yellow) to negative (blue).

Nucleus mask is a digital image analysis parameter to enable visualization and measurement of IHC signal intensity of individual marked cell or nucleus.

ADA, antidrug antibody; Anti-PD-(L)1, programmed death ligand-1 antibody/programmed cell death protein-1 antibody; CD8, cluster of differentiation 8; CNS, central nervous system; CPI, immune checkpoint inhibitors; DLT, dose limiting toxicities; ECG, electrocardiogram; echo, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EMT-6, epithelial-mesenchymal-transition-6 breast cancer cell line; FIH, first in human; IgG, immunoglobulin; IHC, immunohistochemistry; IV; Intravenously; LY2109761, TGFβ receptor 1,2 inhibitor; MAD, maximum administered dose; MBT-2, mouse bladder tumor line-2; MEL, melanoma; mg/kg, milligram/kilogram; µm, micrometer; mm^3,cubic millimeter; MTD, maximum tolerated dose; NGS, Next-Gen Sequencing; NOAEL, no observed adverse effect level; NSCLC, non-small cell lung cancer; pan-TGFβ Ab, TGFβ-1,2,3 antibody; PD, pharmacodynamics; PD-1, programmed cell death protein-1; Pembrolizumab, a selective, humanized IgG4 kappa monoclonal antibody that inhibits the PD-1 receptor; PK, pharmacokinetics; P-SMAD-2, Phospho-Smad2; qd, every day; qwk, every week; q3w, every 3 weeks; RP2D, Recommended Phase 2 dose; SMAD2, small worm phenotype, mothers against decapentaplegic homolog 2; SRK, Scholar Rock Inc; TGFβ1, transforming growth factor beta-1; UC, urothelial carcinoma

Disclaimer: 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.