DRAGON: Phase 1 trial of SRK-181, a latent TGFβ1 inhibitor, in combination with anti-PD-(L)1 inhibitors for patients with solid tumors unresponsive to anti-PD-(L)1 therapy alone

Johanna Bendell[1], Minal Barve[2], Timothy Yap[3], Si Tuen Lee-Hoeflich[4], Ryan Faucette[4], Ashish Kalra[4], Guochen Song[4], Yung Chyung[4], Michelle Legler[4], Lu Gan[4], Justin F. Gainor[5]
[1] Sarah Cannon Research Institute, Nashville, TN; [2] Mary Crowley Cancer Research, Dallas TX ; [3] The University of Texas MD Anderson Cancer Center, Houston, TX; [4] Scholar Rock, 620 Memorial Drive, Cambridge, MA;
[5] Massachusetts General Hospital Harvard Medical School, Cambridge, MA

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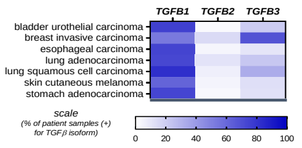
Introduction

- Nearly 80% of patients do not respond to Checkpoint Inhibitor (CPI) therapies[1]
- The transforming growth factor beta (TGFβ) family includes three isoforms (TGFβ1, TGFβ2, and TGFβ3)[2]
- Human data implicate TGFβ1 as a key driver of immune exclusion and primary resistance to CPIs[3,4]
- Nonselective inhibition of TGFβ signaling has been associated with dose-limiting toxicities, particularly cardiac toxicity[5,6,7]

Figure 1: Implicating TGFβ1 Isoform as Resistance Culprit in Human Tumors

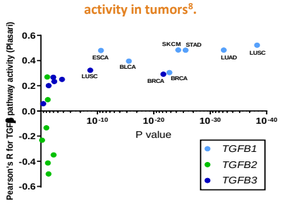
TGFβ1 is most prevalent isoform in most human cancers[8].



Cancer Genome Atlas RNAseq analysis of >10,000 samples spanning 33 tumor types[9]

Heat map showing percentage of positive patient tumor samples.

TGFβ1 expression correlates with TGFβ pathway activity in tumors[8].



SRK-181[8]

- Fully human monoclonal antibody
- Potent and selective inhibitor of latent TGFβ1 activation offers potential to overcome toxicity and dose-limiting challenges of non-selective TGFβ pathway approaches.
  - Binds latent TGFβ1 with picomolar affinity
  - Binds all TGFβ1 large latent complexes
  - Minimal or no binding to latent TGFβ2 and TGFβ3 isoforms or to active TGFβ growth factors
  - No cardiotoxicities (valvulopathy) were noted with SRK-181 in 4-week GLP nonclinical toxicology studies

Study Objectives (Part A)

Primary Objectives

- Evaluate the safety and tolerability
- Determine the maximum tolerated dose (MTD) or maximum administered dose (MAD), and the recommended Phase 2 dose (RP2D) and evaluate DLTs

Secondary Objectives

- Evaluate the PK and anti drug antibody (ADA)

Exploratory Objectives

- Evaluate anti-tumor activity
- Evaluate biomarkers

Study Objectives (Part B)

Primary Objectives

- Evaluate the safety and tolerability.

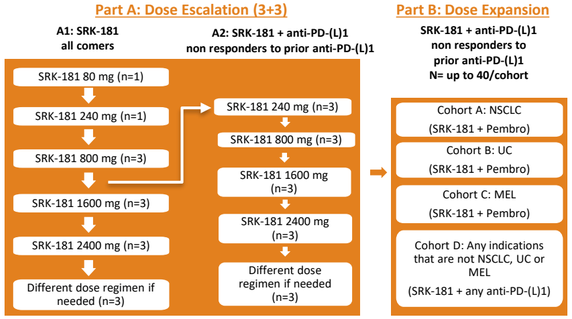
Secondary Objectives

- Evaluate the anti-tumor activity.
- Evaluate the PK and ADA.

Exploratory Objectives

- Evaluate biomarkers

Figure 4: Phase 1 (DRAGON) Study Design



NSCLC: non-small cell lung cancer UC: urothelial carcinoma MEL: melanoma

Inclusion

1. Be age ≥ 18 years, with a predicted life expectancy of ≥ 3 months
2. Measurable disease per RECIST v1.1 as assessed at Screening
3. ECOG performance status 0-1
4. Part B only: Patient must have received their most recent dose of anti-PD-(L)1 antibody therapy within 6 months of enrollment

Exclusion

1. Concurrent anticancer treatment
2. History of active metastatic CNS disease
3. An active or prior history of autoimmune disease

Assessment

- Safety endpoints include AEs, clinical observations (e.g., vital signs, physical examination), laboratory tests, ECGs, and echo.
  - Dose-limiting toxicities (DLTs) evaluation period is 21 days
- Response will be assessed using RECIST v1.1 by PI and by independent central review

Study Design

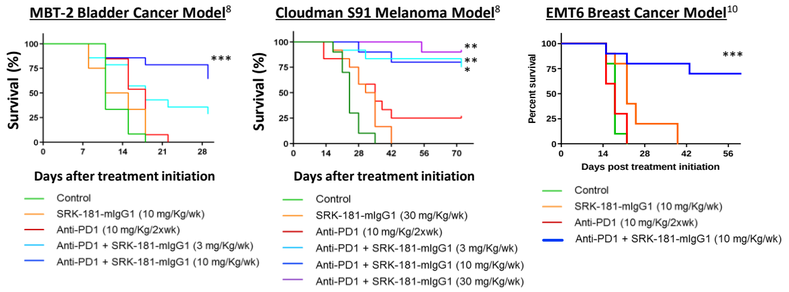
- The Dragon trial is a multi-center, open-label, Phase 1, first-in-human (FIH), dose-escalation, and dose expansion study
- The study is divided into 3 parts:
  - Part A1: single agent dose escalation in patients with advanced solid tumors and have failed available standard of care (SOC) treatment
  - Part A2: combination dose escalation of SRK-181 + an anti-PD-(L)1 in patients who did not respond to prior CPI treatment (defined as best response on prior CPI treatment is progressive disease or stable disease after at least 3 cycles of treatment)
  - Part B: dose expansion of SRK-181 + an anti-PD-(L)1 in patients who did not respond to prior CPI treatment. Indications include NSCLC, UC, MEL or other advanced solid tumors
- Administration by IV infusion: SRK-181 every 3 weeks (q3w) alone or with an anti-PD-(L)1
  - Additional dose regimen may be explored pending emerging data

Figure 5: Overview of Biomarker Evaluation to Complement Clinical Investigation

	Tumor-based biomarkers		Orthogonal biomarkers
	1. Immunophenotyping Assessment of the tumor immune landscape	**2. TGFβ signaling pathway** Assessment of TGFβ1 signaling pathway	**3. Multiple pathways** Assessment of biologically related pathways
	• PD → measurement of SRK-181 to convert tumors 'hot' • Predictive → identify hot, cold or immune excluded at baseline to predict response	• PD → measurement of SRK-181 to modulate TGFβ pathway activation • Predictive → identify target/pathway prevalence to predict response	• PD → measurement of SRK-181 to modulate multiple biomarkers simultaneously • Predictive → identify combination of biomarkers to predict response
	Ex. CD8 (cytotoxic T cells), PD-L1	Ex. P-Smad2 (TGFβ signaling)	Ex. blood-based biomarkers, tumor-based multiplex IHC, NGS

Biomarker evaluation to characterize mechanistic effects upon treatments and to retrospectively assess for potential predictive markers to inform future development

Figure 2: SRK-181-mIgG1 Combined with Anti-PD1 Therapy Led to Significant Survival Benefit in Preclinical Tumor Models



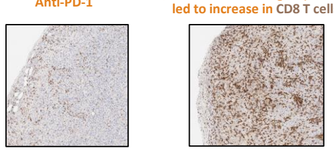
* P<0.05 Log-rank (Mantel-Cox test) vs. anti-PD1
**P<0.01
*** P<0.001

Preclinical Tumor Models Represent Clinically Relevant Features

Selection Criteria for Mouse Tumor Models

- Immune exclusion
- Minimal or no response to anti-PD-(L)1
- High TGFβ1 over TGFβ2/3 expression
- Evidence for TGFβ signaling

Figure 3: SRK-181-mIgG1 Combination Therapy Enabled Infiltration and Expansion of CD8 T Cells



Turning tumors "hot", and reduction in suppressive myeloid cells are consistent with significant anti-tumor responses

In MBT-2 bladder cancer model, combination treatment with SRK-181-mIgG1/anti-PD1 led to[8]:

- Significant increase in effector T cells
- Significant decrease in intratumoral immunosuppressive myeloid cells

References

1. Carretero-González A, Lora D, Ghanem I, et al. *Oncotarget*. 2018;9:8706-8715.
2. Derynck R, Budi EH (2019). Sci Signaling 12(570): eaav5183.
3. Mariathasan S, Turley SJ, Nickles D, et al. Nature. 2018;554:544-548.
4. Hugo W, Zaretsky JM, Sun L, et al. Cell. 2017;168:542.
5. Anderton MJ, Mellor HR, Bell A, et al. Tox Pathol. 2011;39:916.
6. Stauber AJ, Credille KM, Truex LL, et al. J Clin Pract. 2014;4:3
7. Mitra MS, Lancaster K, Adedeji AO, et al. Toxicol Sci. 2020;175(1):24.
8. Martin CJ, Datta A, Littlefield C, et al. *Sci Transl Med*. 2020;12:eaay8456.
9. National Cancer Institute. The Cancer Genome Atlas. Available: https://www.cancer.gov.
10. Data on file. Scholar Rock.

Dose Escalation Progress

As of October 1, 2020, 10 patients have been dosed (8 in A1 and 2 in A2). Dose escalation is ongoing.

Part A1

- Dose of SRK-181 has been escalated from 80 mg to 800 mg with no DLTs observed (80 mg: N=1; 240 mg: N-1; 800 mg: N=3)
- Dose of 1600 mg is under evaluation (N=3)

Part A2

- Dose of 240 mg SRK-181 + an anti-PD-(L)1 is under evaluation (N=2)

Initiation of Part B of DRAGON planned for 1Q21.