Introduction

• Nearly 80% of patients do not respond to Checkpoint Inhibitor (CIPI) therapies.
• The transforming growth factor beta (TGFβ) family includes three isoforms (TGFβ1, TGFβ2, and TGFβ3).
• Human data implicate TGFβ1 as a key driver of immune exclusion and primary resistance to CPIs.
• Nonspecific inhibition of TGFβ signaling has been associated with dose-limiting toxicities, particularly cardiac toxicity.

Figure 1: Implicating TGFβ1 as Resistance Culprit in Human Tumors

TGFβ1 is most prevalent (isoform in most human cancers).

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 pharmacokinetic and anti-angiogenic activity.
• 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.
• Evaluate biomarkers.

Inclusion
1. Be ≥18 years, with a predicted life expectancy of ≥2 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 most recent dose of anti-PD-1/PD-L1 antibody therapy within 6 months of enrollment.

Exclusion
1. Concurrent antinecancer therapy.
2. History of active metastatic CNS disease.
3. An active or prior history of autoimmune disease.

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

Figure 2: SRK-181+PD-1 Combined with Anti-PD1 Therapy Led to Significant Survival Benefit in Preclinical Tumor Models

Preclinical Tumor Models Represent Clinically Relevant Features

Figure 3: SRK-181+PD-1 Combination Therapy Enabled Infiltration and Expansion of CD8 T Cells

Anti-PD-1
Anti-PD-1/181 (at 10 mg/kg) for 40 days in CD8 T-cells

Funding barriers "T-cell" infiltration and expansion in immune-competent cells are consistent with significant anti-tumor response.

Figure 4: Phase 1 (DRAGON) Study Design

Part A: Dose Escalation (1–3x)

Part B: Dose Expansion

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:
  2. Part A2: combination dose expansion of SRK-181 + an anti-PD-L1 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).
  3. Part B: dose expansion of SRK-181 + an anti-PD-L1 in patients who did not respond to prior CPI treatment. Indications include N0LC, UC, NEL or other advanced solid tumors.
• Administration by IV infusion: SRK-181 every 3 weeks (q3w) alone or with an anti-PD-L1.
• Additional dose regimens may be explored pending emerging data.

Figure 5: Overview of Biomarker Evaluation to Complement Clinical Investigation

Orthogonal biomarkers

1. Immunophenotyping
Assessment of the tumor immune landscape

2. TGFβ signaling pathway
Assessment of TGFβ signaling pathway

3. Multiple pathways
Assessment of biologically related pathways

Tumor-based biomarkers

• PD-1 measurement of SRK-181 to convert tumors "hot" to "cold" or immune excluded at baseline to predict response.
• PD-L1 measurement of SRK-181 to modulate TGFβ pathway activation.
• Predictive identification of tumor pathobiology to predict response.

Ex. CD8 (cytotoxic T cells). PD-L1
Ex. P-dm2a (TGFβ signaling)
Ex. blood biomarkers, tumor-based multiplexes (HCA).

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

References

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=1).

Part A2
• Dose of 240 mg SRK-181 + an anti-PD-L1 is under evaluation (N=2).

Initiation of Part B of DRAGON planned for 1Q21.

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