Inhibition of TGFβ1 Activation with SRK-181 Overcomes Primary Resistance to Checkpoint Inhibition Therapy

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Disclaimer

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

• Why do nearly 80% of patients not respond to CPI therapies?¹

• Clinically-derived rationale points to significant opportunity to increase checkpoint therapy responses.

Challenges with TGFβ Inhibition

Inhibition of TGFβ signaling has been associated with dose-limiting toxicities, particularly cardiac toxicity


Implicating TGFβ1 Isoform as Resistance Culprit in Human Tumors

TGFβ1 is most prevalent isoform in most human cancers¹.

Cancer Genome Atlas RNAseq analysis of >10,000 samples spanning 33 tumor types²

Heat map showing percentage of positive patient tumor samples.

TGFβ1 expression correlates with TGFβ pathway activity in tumors¹.

Structure of proTGFβ1

This explains latency and provides basis for novel approach to pharmacological TGFβ1 inhibition.¹

Prodomain Targeting: Isoform Specificity

Targeting Latent TGFβs Creates Multiple “Handles” For Selectivity

- Proprotein is cleaved before secretion
- Prodomain & growth factor remain noncovalently bound
- Receptor binding requires growth factor release

### Percent Identity

<table>
<thead>
<tr>
<th></th>
<th>TGFβ1</th>
<th>TGFβ2</th>
<th>TGFβ3</th>
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<tr>
<td>TGFβ1</td>
<td>71.4</td>
<td>76.8</td>
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<tr>
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<tr>
<td>TGFβ3</td>
<td></td>
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<td>TGFβ3</td>
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SRK-181

- Fully human monoclonal antibody\textsuperscript{1}
- SRK-181 binds latent TGF\(\beta\)1 with picomolar affinity
  - Binds all TGF\(\beta\)1 large latent complexes
  - Crossreacts with mouse, rat, cyno
  - Minimal or no binding to latent TGF\(\beta\)2 and TGF\(\beta\)3 isoforms or to active TGF\(\beta\) growth factors
- Potent and selective inhibitor of latent TGF\(\beta\)1 activation
  - Inhibits latent TGF\(\beta\)1 activation triggered by integrins or proteolytic cleavage

Selecting Preclinical Models with Clinically Relevant Features

Reverse-translating clinical observation by matching syngeneic mouse tumor model to human tumor biology

Phenotype of Resistant Human Tumors in αPD-(L)1 Therapies

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

Selection Criteria for Mouse Tumor Models

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

TGFβ1 Blockade with SRK-181-mIgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD-1 Therapy

Cloudman S91 melanoma model: Combination treatment led to tumor regression and survival benefit

Similar results demonstrated in MBT-2 urothelial cancer model

SRK-181-mIgG1 Combination Therapy Enabled Infiltration and Expansion of CD8 T cells

In MBT-2 bladder cancer model, combination treatment with SRK-181-mIgG1/anti-PD1 led to:
- Significant increase in effector T cells (p<0.05)
- Significant decrease in intratumoral immunosuppressive myeloid cells (p<0.05)

Similar Anti-Tumor Effects in TGFβ1/3 Co-expressing EMT-6 Breast Cancer Model

Inhibition of TGFβ1 isoform is sufficient to elicit a profound combination therapy effect in the TGFβ1/3 co-expressing EMT-6 breast cancer model.

TGFβ1 Isoform Specificity of SRK-181 Improved Preclinical Toxicity Profile

Repeat dose pilot toxicology study in adult female Sprague Dawley rats:
- Cardiac findings were exhibited in animals dosed with a pan-TGFβ antibody or LY2109761 (inhibitor of ALK5, common TGFβ receptor kinase) as expected based on published data†
- No cardiotoxicities (valvulopathy) were noted with SRK-181
  - NOAEL for SRK-181 was the highest dose evaluated of 100 mg/kg QW

4-week GLP toxicology studies:
- Rats: NOAEL for SRK-181 was up to highest evaluated dose of 200 mg/kg QW
- Non-human primates: NOAEL for SRK-181 was up to highest evaluated dose of 300 mg/kg QW

Selectivity of SRK-181 offers potential to overcome toxicity and dose-limiting challenges of non-selective TGFβ pathway approaches

DRAGON Phase 1 POC Trial to Evaluate SRK-181’s Ability to Overcome Primary Resistance to Checkpoint Inhibitors

**Part A**

- **Part A1:**
  - SRK-181 as a single agent
  - Modified 3+3 dose escalation
  - Assess SRK-181 dose range of 80-2400 mg (avg weight 80 kg)

- **Part A2:**
  - SRK-181 with approved anti-PD-(L)1
  - 3+3 dose escalation

**Part B**

- SRK-181 in combo with approved anti-PD-(L)1 therapy
- 4 parallel cohorts – each will enroll up to 40 patients
- Target indications expected to include:
  - NSCLC
  - Urothelial carcinoma
  - Melanoma
  - Other solid tumor types

- Open-label, dose escalation, and dose expansion clinical trial
- Evaluate the efficacy, safety/tolerability, and PK/PD of SRK-181 in combination with approved anti-PD-(L)1 therapy
- Patients with locally advanced or metastatic solid tumors that exhibit primary resistance to anti-PD-(L)1 therapy
- Lack of response characterized as stable or progressive disease following ≥3 cycles of anti-PD-(L)1 therapy either alone or in combination with chemotherapy

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