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

Thomas Schurpf, Ph.D.

January 28, 2021

ScholarRock™

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]
  - Mariathasan S, Turley SJ, Nickles D, et al. TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature*. 2018;554:544-548.
  - Hugo W, Zaretsky JM, Sun L, et al. Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. *Cell*. 2017;168:542.
- Clinically-derived rationale points to significant opportunity to increase checkpoint therapy responses.

1. Carretero-González A, Lora D, Ghanem I, et al. Analysis of response rate with anti-PD-1/PD-L1 monoclonal antibodies in advanced solid tumors: a meta-analysis of randomized clinical trials. *Oncotarget*. 2018;9:8706-8715.

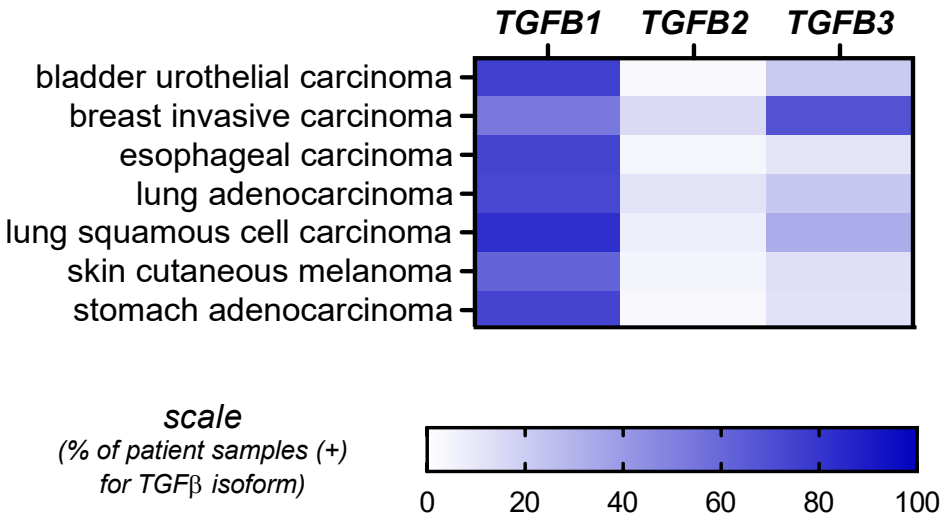
Challenges with TGFβ Inhibition

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

- Anderton MJ, Mellor HR, Bell A, et al. Induction of Heart Valve Lesions by Small-Molecule ALK5 Inhibitors. *Tox Pathol*. 2011;39:916.
- Stauber AJ, Credille KM, Truex LL, et al. Nonclinical Safety Evaluation of a Transforming Growth Factor β Receptor I Kinase Inhibitor in Fischer 344 Rats and Beagle Dogs. *J Clin Pract*. 2014;4:3
- Mitra MS, Lancaster K, Adedeji AO, et al. A Potent Pan-TGFβ Neutralizing Monoclonal Antibody Elicits Cardiovascular Toxicity in Mice and Cynomolgus Monkeys. *Toxicol Sci*. 2020;175(1):24.

Implicating TGFβ1 Isoform as Resistance Culprit in Human Tumors

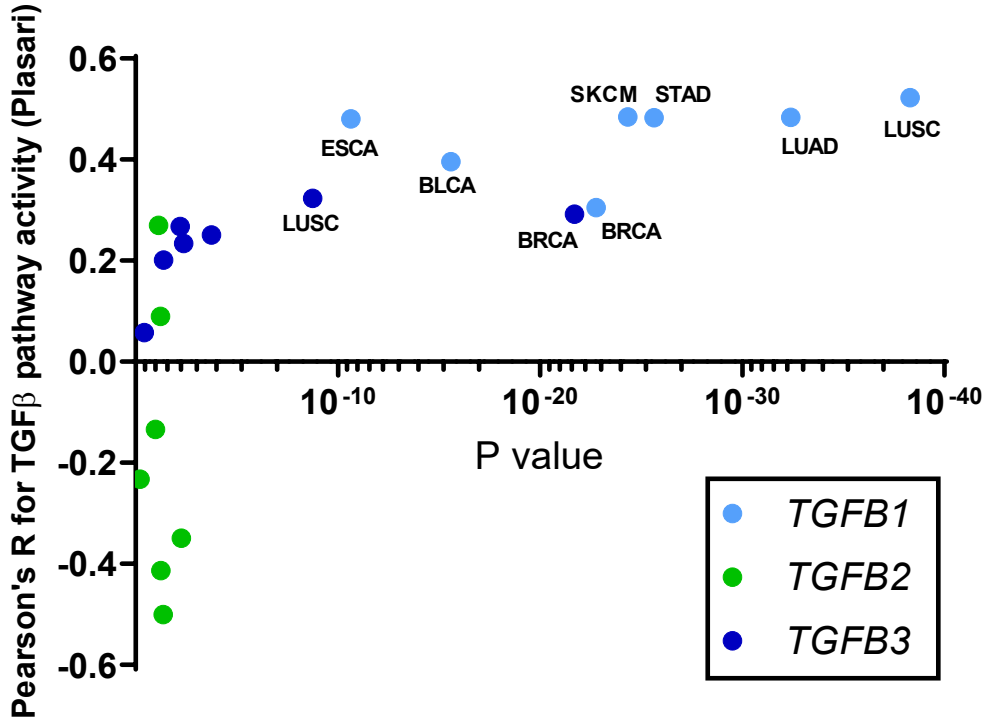
TGFβ1 is most prevalent isoform in most human cancers[1].



Cancer Genome Atlas RNAseq analysis of >10,000 samples spanning 33 tumor types[2]

Heat map showing percentage of positive patient tumor samples.

TGFβ1 expression correlates with TGFβ pathway activity in tumors[1].



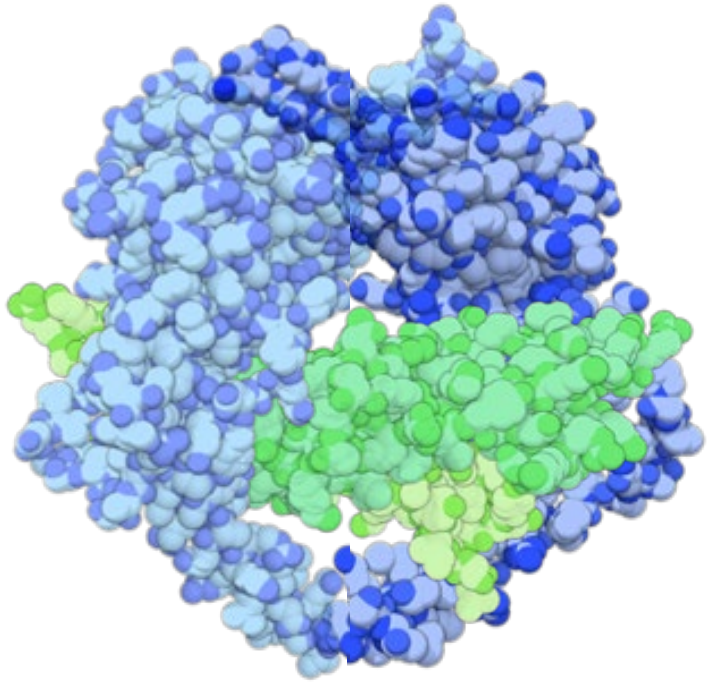
1. Martin CJ, Datta A, Littlefield C, et al. Selective inhibition of TGFβ1 activation overcomes primary resistance to checkpoint blockade therapy by altering tumor immune landscape. *Sci Transl Med*. 2020;12:eaay8456.
2. 2. National Cancer Institute. The Cancer Genome Atlas. Available:https://www.cancer.gov.

ScholarRock

Structure of proTGFβ1

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

The “Cage”:
TGFβ1 Propeptide



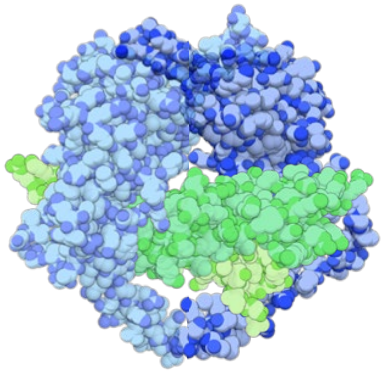
Active Growth Factor: TGFβ1

1. Shi M, Zhu J, Wang R, et al. Latent TGF-β structure and activation. *Nature*. 2011;474:343-9.

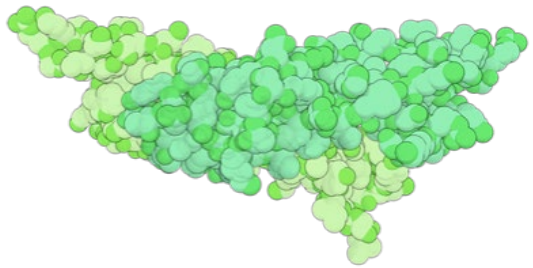
Prodomain Targeting: Isoform Specificity

Targeting Latent TGFβs Creates Multiple "Handles" For Selectivity[1]

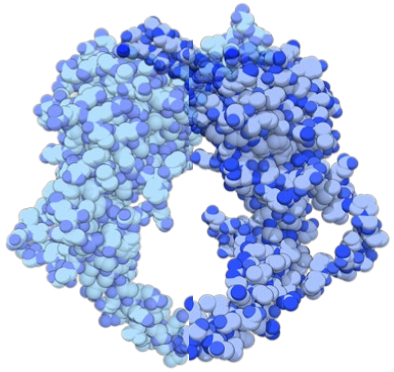
Latent TGFβ



Mature Growth Factor



Prodomain



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

Percent Identity

TGFβ1	TGFβ2	TGFβ3	
	71.4	76.8	TGFβ1
		79.5	TGFβ2
			TGFβ3

Percent Identity

TGFβ1	TGFβ2	TGFβ3	
	37.4	37.1	TGFβ1
		48.7	TGFβ2
			TGFβ3

1. Martin CJ, Datta A, Littlefield C, et al. Selective inhibition of TGFβ1 activation overcomes primary resistance to checkpoint blockade therapy by altering tumor immune landscape. *Sci Transl Med*. 2020;12:eaay8456.

SRK-181

- Fully human monoclonal antibody[1]
- SRK-181 binds latent TGFβ1 with picomolar affinity
  - Binds all TGFβ1 large latent complexes
  - Crossreacts with mouse, rat, cyno
  - Minimal or no binding to latent TGFβ2 and TGFβ3 isoforms or to active TGFβ growth factors
- Potent and selective inhibitor of latent TGFβ1 activation
  - Inhibits latent TGFβ1 activation triggered by integrins or proteolytic cleavage

1. Martin CJ, Datta A, Littlefield C, et al. Selective inhibition of TGFβ1 activation overcomes primary resistance to checkpoint blockade therapy by altering tumor immune landscape. *Sci Transl Med*. 2020;12:eaay8456.

Selecting Preclinical Models with Clinically Relevant Features

Reverse-translating clinical observation by matching syngeneic mouse tumor model to human tumor biology[1]

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

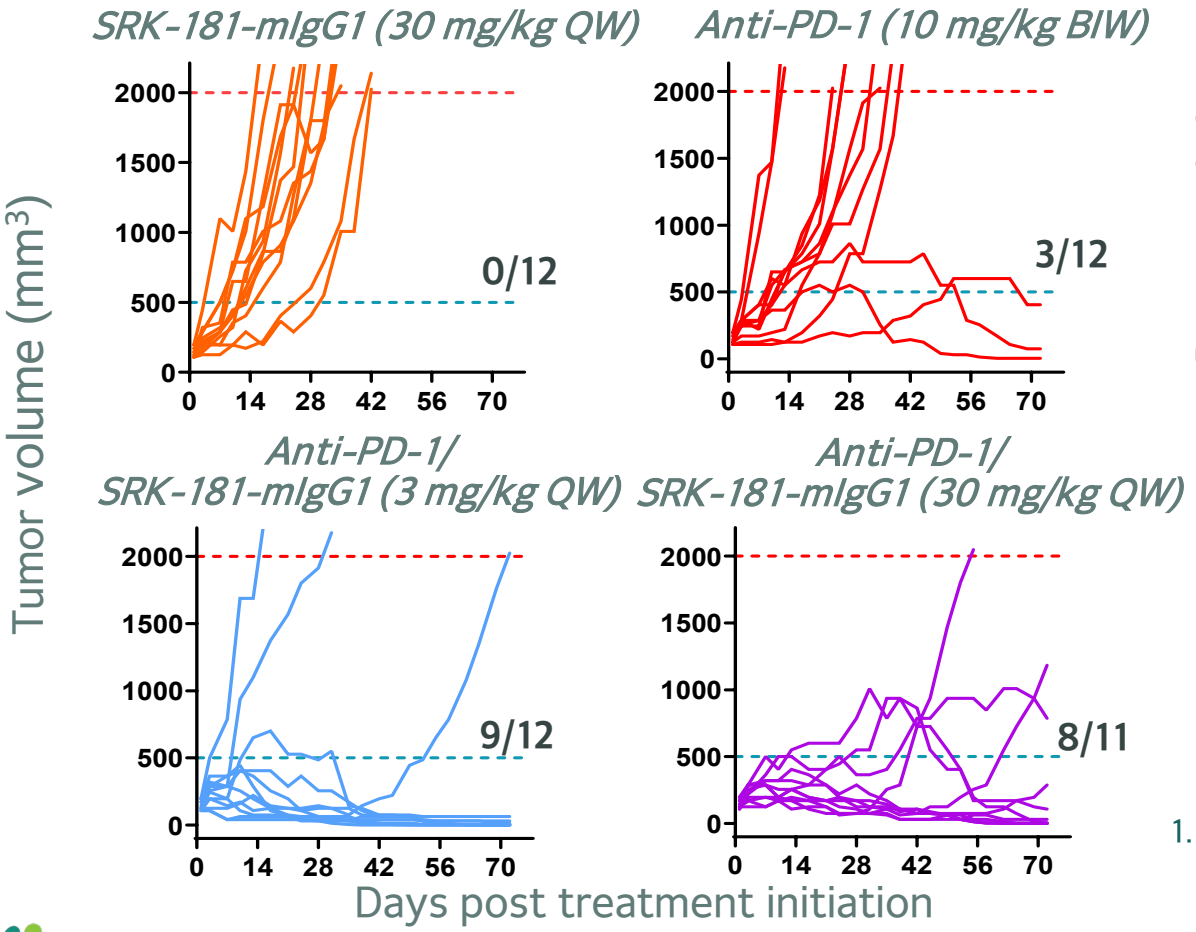
Selection Criteria for Mouse Tumor Models

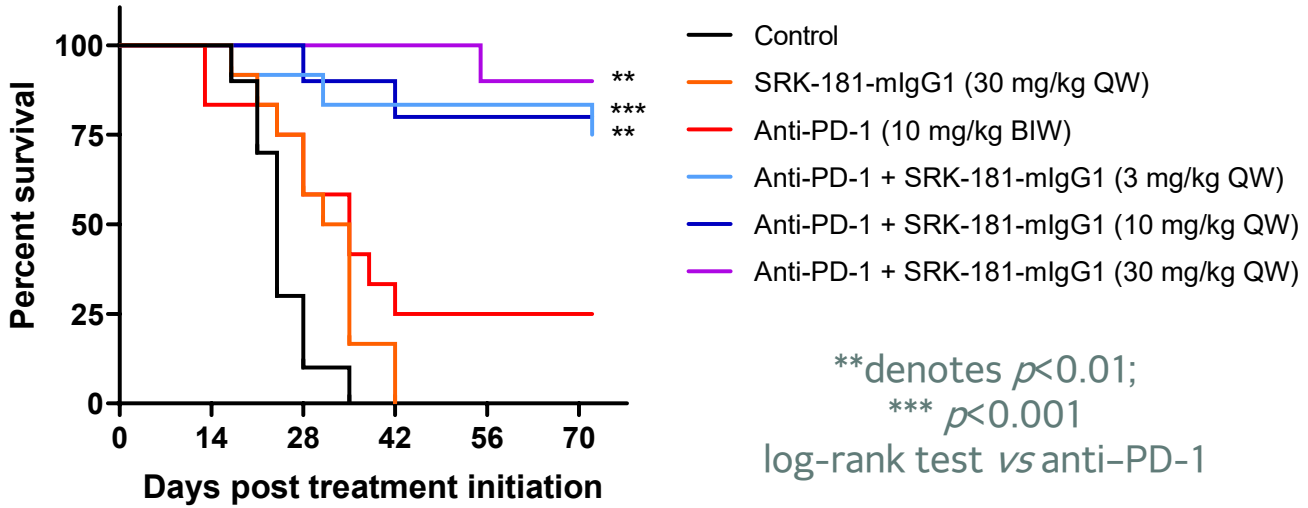
- Minimal or no response to anti-PD-(L)1
- Immune exclusion
- High TGFβ1 over TGFβ2/3 expression
- Evidence for TGFβ signaling

1. Mariathasan S, Turley SJ, Nickles D, et al. TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature*. 2018;554:544-548.

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[1]





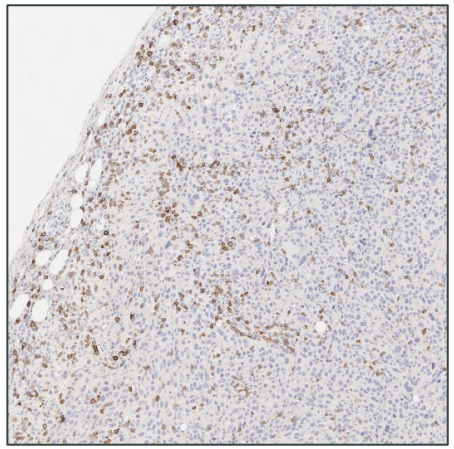
**denotes $p<0.01$;
*** $p<0.001$
log-rank test *vs* anti–PD-1

Similar results demonstrated in MBT-2 urothelial cancer model[1]

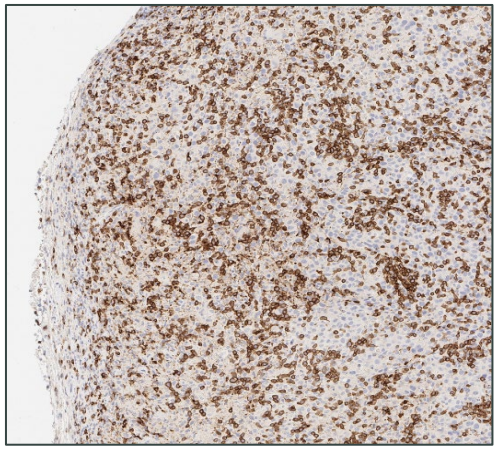
1. Martin CJ, Datta A, Littlefield C, et al. Selective inhibition of TGFβ1 activation overcomes primary resistance to checkpoint blockade therapy by altering tumor immune landscape. *Sci Transl Med*. 2020;12:eaay8456.

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

Anti-PD-1



Anti-PD-1/SRK-181-mIgG1 (10 mg/kg) led to increase in CD8 T cells



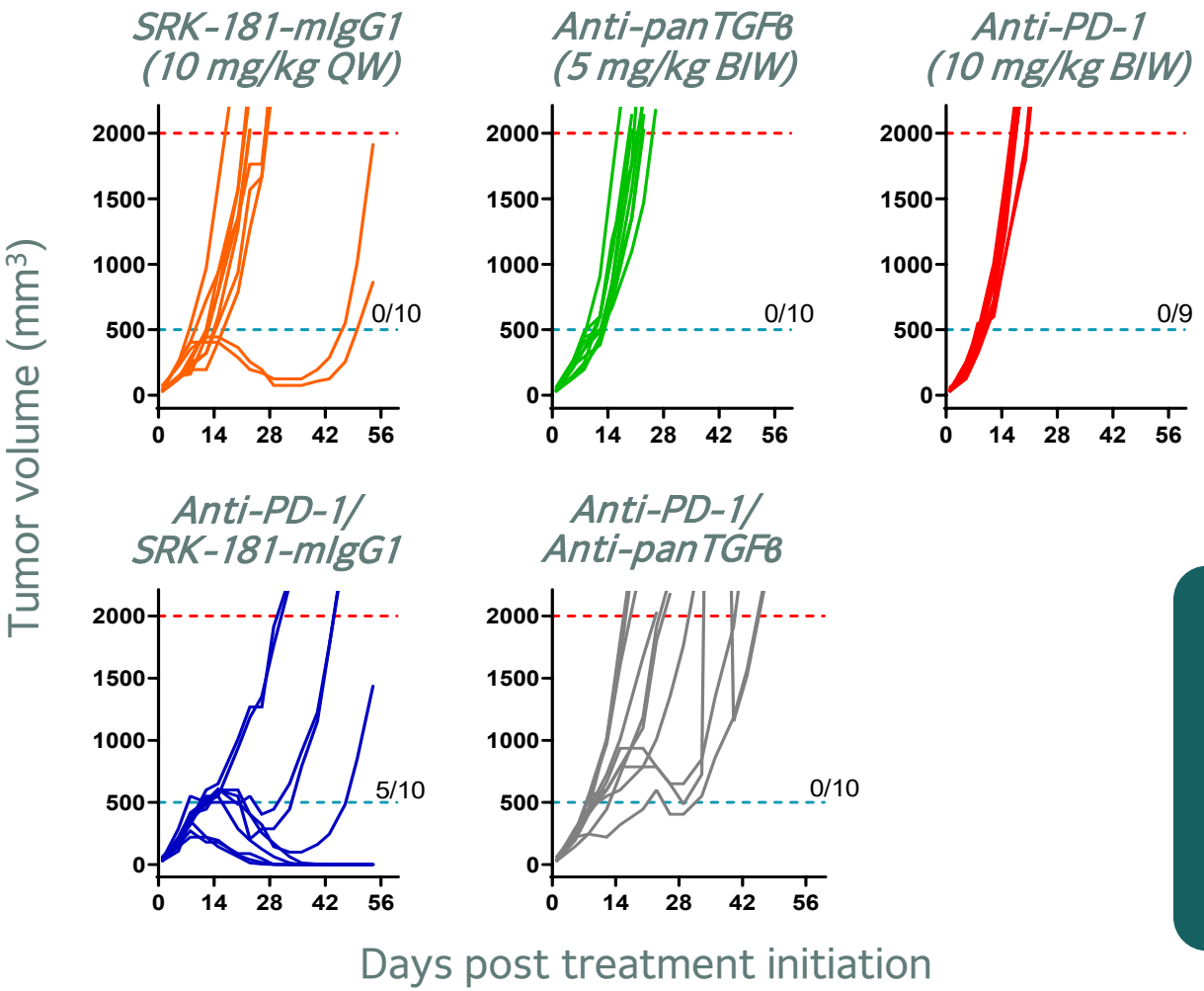
Turning tumors “hot”, and reduction in suppressive myeloid cells are consistent with significant anti-tumor responses

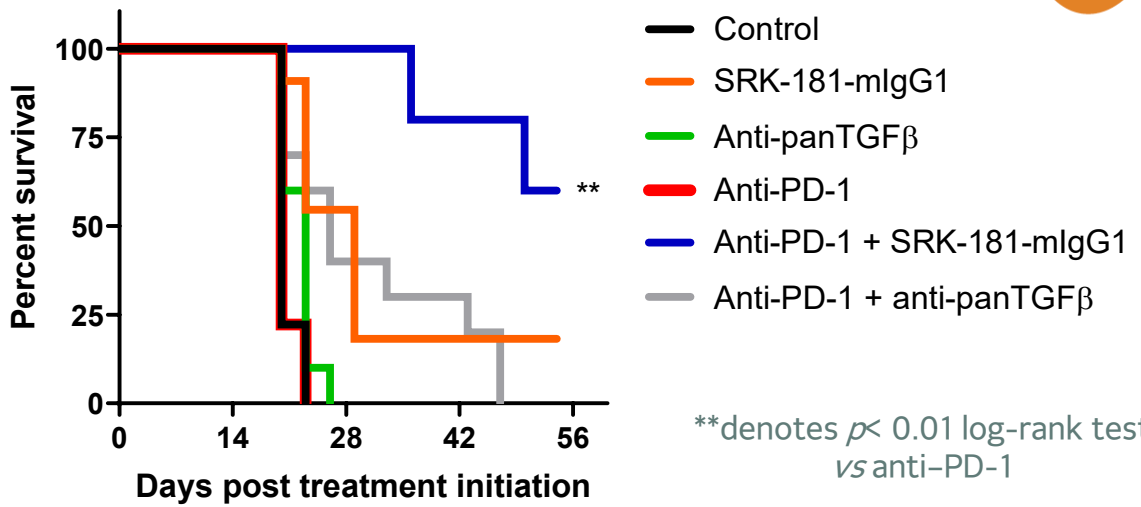
In MBT-2 bladder cancer model, combination treatment with SRK-181-mIgG1/anti-PD1 led to[1]:

- Significant increase in effector T cells ($p<0.05$)
- Significant decrease in intratumoral immunosuppressive myeloid cells ($p<0.05$)

1. Martin CJ, Datta A, Littlefield C, et al. *Sci Transl Med.* 2020;12:eaay8456.

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



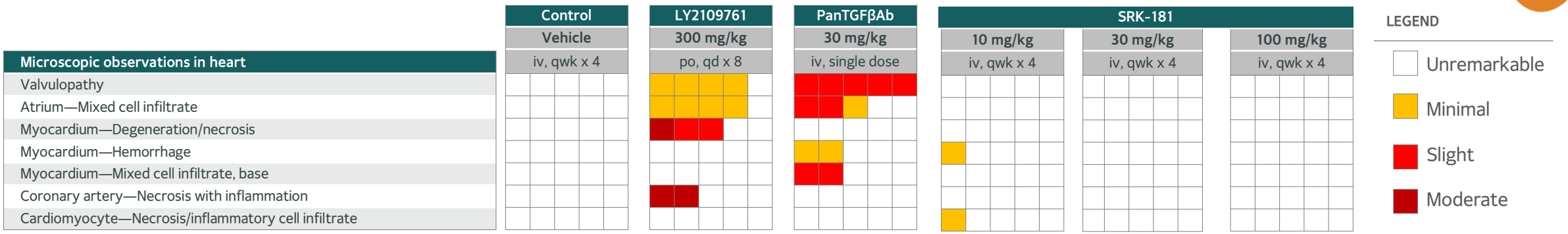


**denotes $p < 0.01$ log-rank test *vs* anti-PD-1

Inhibition of TGFβ1 isoform is sufficient to elicit a profound combination therapy effect in the TGFβ1/3 co-expressing EMT-6 breast cancer model[1]

1. Martin CJ, Datta A, Littlefield C, et al. *Sci Transl Med.* 2020;12:eaay8456.

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

Preclinical data published in *Science Translational Medicine*. Martin CJ, et al. *Sci Transl Med* 2020 Mar 25;12(536): eaay8456.
†Source: Anderton MJ, et al. Induction of heart valve lesions by small-molecule ALK5 inhibitors. *Toxicol Pathol*. 2011;39: 916-924.; and Stauber AJ, et al. Nonclinical safety evaluation of a transforming growth factor β Receptor I kinase inhibitor in Fischer 344 rats and beagle dogs. *J Clin Pract*. 2014: 4:3.

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

DRAGON

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

NCT04291079 on www.clinicaltrials.gov.

Acknowledgements

Connie Martin
Abhishek Datta
Alan Buckler
Greg Carven
Ashish Kalra
Stefan Wawersik
Chris Brueckner

…and the entire SRK-181 team