



Deep Insights, Impactful Medicines

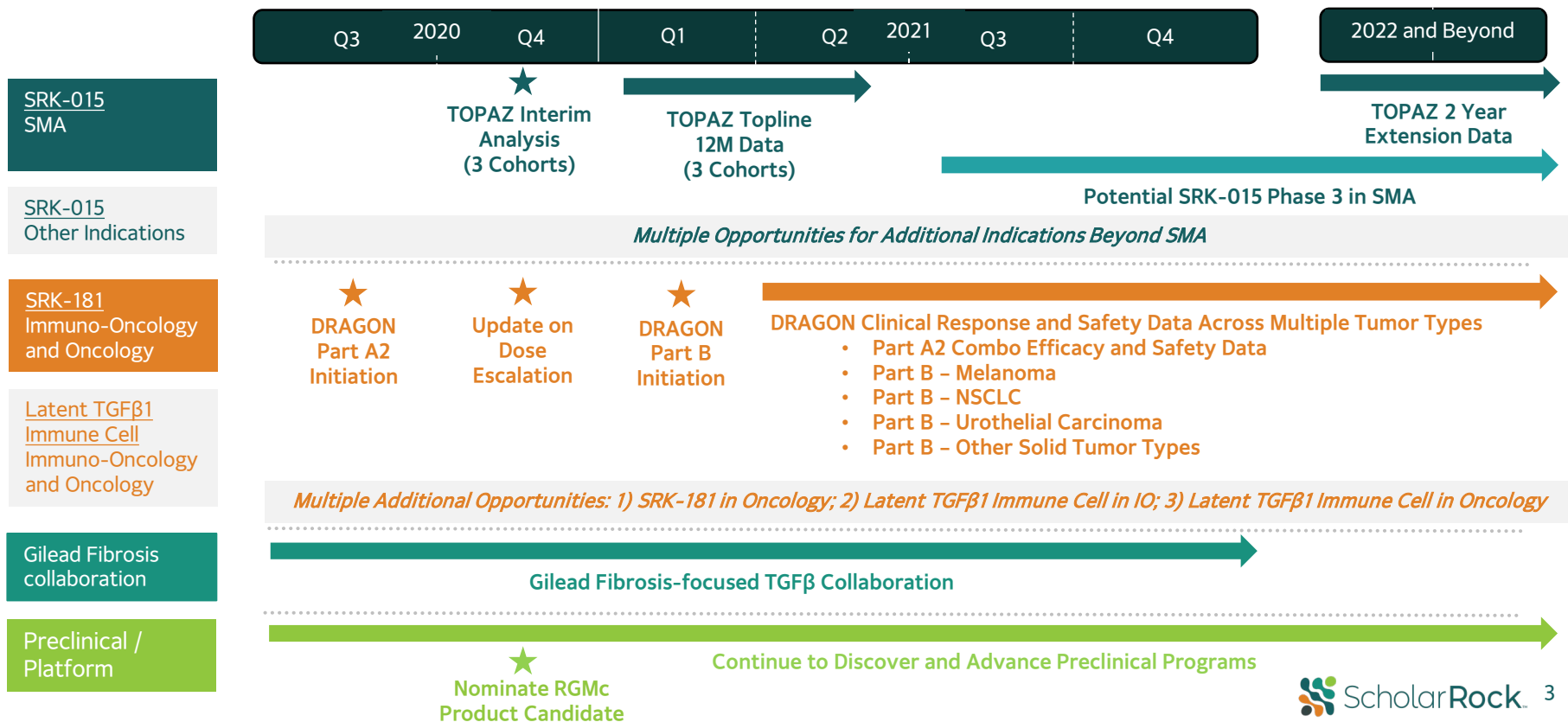
September 2020



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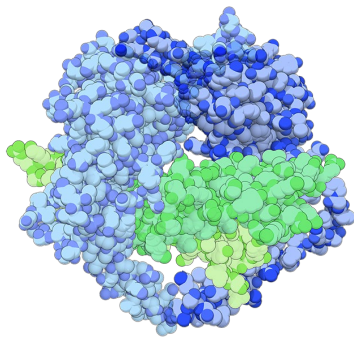
Differentiated Pipeline with a Series of Anticipated Milestones



Bringing a Revolutionary Approach to Highly Sought-After Growth Factors Implicated in Devastating Diseases

Scholar Rock's Target

Growth Factor Precursor (Latent Form)



Traditional target:
“Mature” growth factor

Scholar Rock's R&D Platform

Transform Medical Practice

- Pursue important targets with well-validated biology but difficult to drug
- Apply revolutionary approach to tough targets
 - Engineer antibodies for exquisite selectivity
 - Leverage deep insights into structure and function
- Aim for efficient path to proof of concept



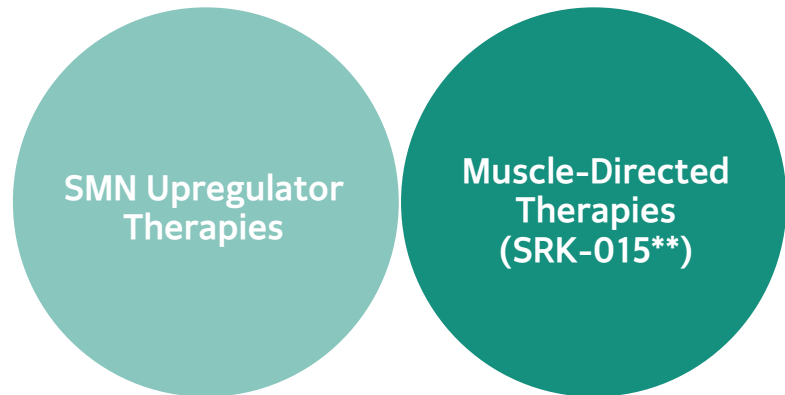
Clinical Programs: SRK-015 and SRK-181

Yung Chyung, MD
Chief Medical Officer

SMA Treatment Landscape: The Shifting Focus to Muscle-Directed Therapies

Muscle-directed therapies needed to complement disease-stabilizing benefits of SMN upregulators*

*Overall prevalence of patients with SMA
30,000-35,000 in U.S. and Europe*



Address SMN deficiency to prevent further motor neuron deterioration

Act directly on muscle with aim to improve motor function

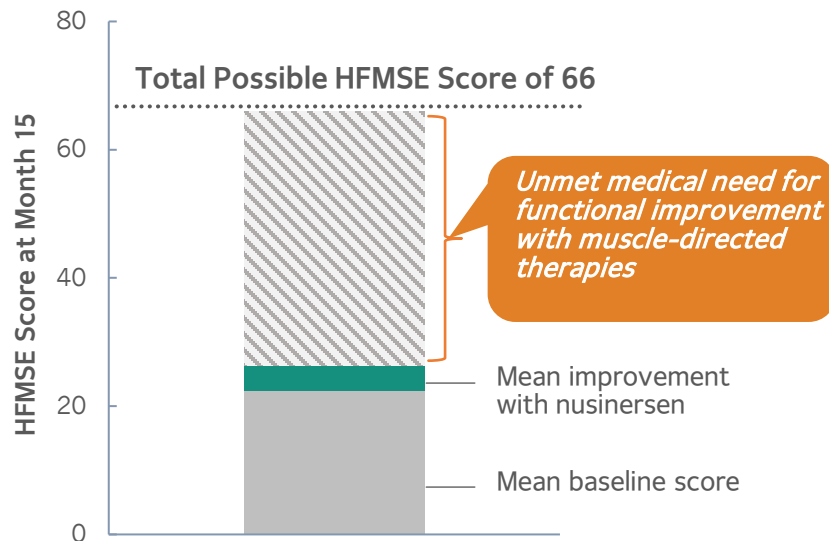
SMN = survival motor neuron.

**Also referred to as SMN correctors.*

*** SRK-015 is an investigational therapy under development.*

† Source: Mercuri E, et.al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med. 2018;378:625-635.

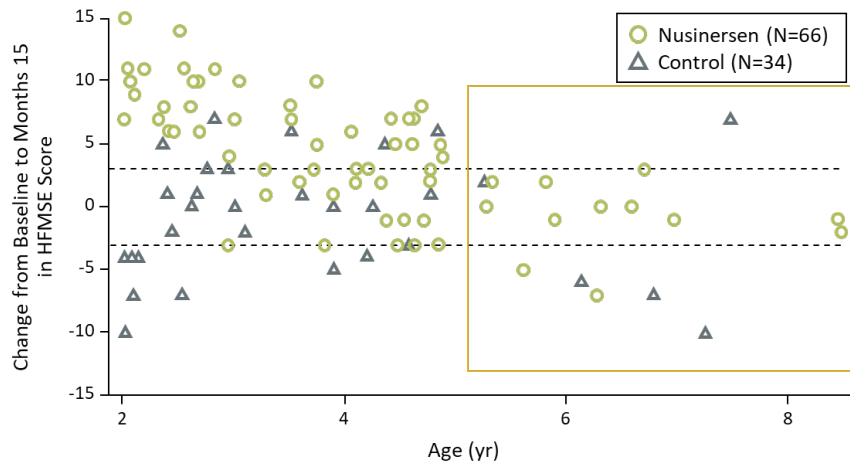
Muscle function in SMA (human)
Hammersmith Functional Motor Scale Expanded (HFMSE)



† Mean improvement in HFMSE score experienced by patients with later-onset SMA in the Phase 3 CHERISH clinical trial of nusinersen

Later-Onset SMA: High Unmet Need for Muscle-Directed Therapy to Complement SMN Upregulator Therapy

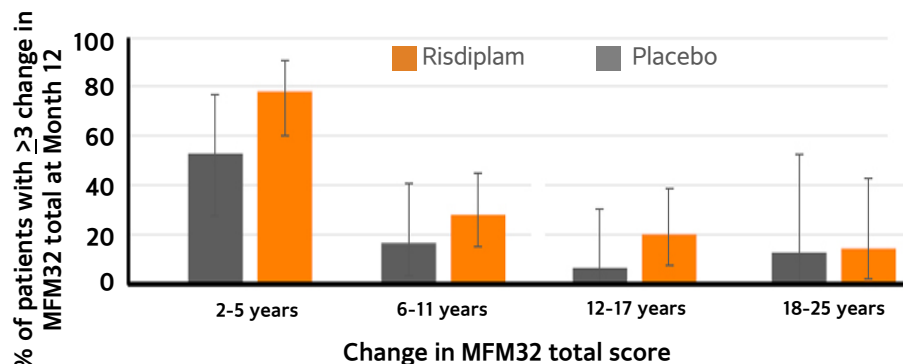
Nusinersen CHERISH Trial in Later-Onset SMA[†]



In patients with later-onset SMA who were age ≥ 5 at screening...

- Primary benefit of nusinersen - stabilization of motor function
- Attainment of ≥ 3 -point increase - rare (<15% of patients) even with nusinersen treatment

Risdiplam SUNFISH Trial in Later-Onset SMA^{††}



- Low percentage of patients over the age of 5 achieved ≥ 3 -point increase on MFM32 scale, even with risdiplam treatment
- HFMSE secondary endpoint showed a mean 0.58-point improvement over placebo (not statistically significant)

[†]Source: Mercuri E, et.al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018;378:625-635.

^{††}Efficacy and safety of risdiplam (RG7916) in patients with Type 2 or non-ambulant Type 3 spinal muscular atrophy (SMA) Roche/PTC Therapeutics

Progress on Path Towards Investigating SRK-015's Therapeutic Potential in SMA

Strong translational rationale for investigating myostatin blockade in SMA



Therapeutic effects in SMA preclinical mouse model



Phase 1 trial in adult healthy volunteers demonstrated:

- Initial safety
 - PK profile supporting every 4-week dosing regimen
 - PD data confirming robust target engagement
-



Phase 2 TOPAZ trial showed:

- Preliminary PD analysis demonstrates target engagement in patients with SMA
-



Phase 2 TOPAZ interim analysis to evaluate efficacy and safety in SMA

*Results anticipated
4Q20*

Interim Efficacy and Safety Results Expected 4Q20; Top-line 12-Month Data 1H21

	Cohort 1	Cohort 2	Cohort 3
Design	- N= 23*; ages 5-21 - Open-label, single-arm 20 mg/kg SRK-015 IV Q4W 12-month treatment period	- N= 15; ages 5-21 - Open-label, single-arm 20 mg/kg SRK-015 IV Q4W 12-month treatment period	- N= 20; ages ≥2 - Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg SRK-015 IV Q4W 12-month treatment period
Patients	- Ambulatory Type 3 SMA - Receiving treatment with approved SMN upregulator or as monotherapy	- Type 2 or non-ambulatory Type 3 SMA - Receiving treatment with approved SMN upregulator	- Type 2 SMA - Initiated treatment with approved SMN upregulator before age 5
Primary Objectives	- Safety - Mean change from baseline in RHS	- Safety - Mean change from baseline in HFMSE	- Safety - Mean change from baseline in HFMSE

We believe SRK-015 has the potential to be backbone therapy to all SMN upregulators

Each Cohort Represents Important POC Opportunity With Significant Potential

	N	Age (mean)	Baseline* (mean)	Efficacy – Therapeutic Goals			Safety Goals	Efficacy signal enables investigation of SRK-015's broader potential	
Cohort 1	23	12.6	RHS = 49.0	RHS: Absolute increase in mean change from baseline	RHS: Substantial % of patients attain ≥ 3 -point increase	Additional outcomes: timed motor tests	No significant safety signals	➔	• Broader age range • Any SMN upregulator • Monotherapy in some settings • Additional neuromuscular indications
Cohort 2	15	11.7	HFMSE = 22.3	HFMSE: Absolute increase in mean change from baseline	HFMSE: Substantial % of patients attain ≥ 3 -point increase	Additional outcomes: RULM, WHO motor developmental milestones	No significant safety signals	➔	• Broader age range • Any SMN upregulator • Additional neuromuscular indications
Cohort 3	20	4.0	HFMSE = 25.0	HFMSE: Substantial improvement in mean change from baseline	Explore potential differentiation (e.g. timing to onset of therapeutic effect) between high dose and low dose arms	Additional outcomes: RULM, WHO motor developmental milestones	No significant safety signals	➔	• Any SMN upregulator • Additional early intervention settings (Type 1 and pre-symptomatic) • Additional neuromuscular indications

*maximum RHS score = 69, maximum HFMSE score = 66

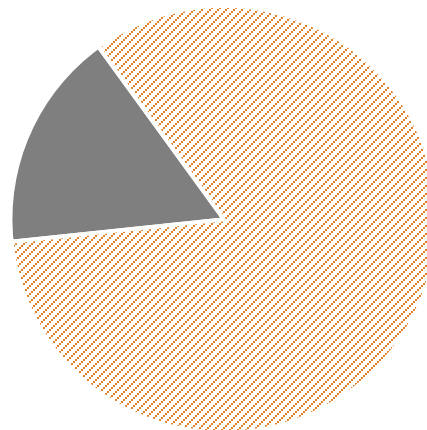
SRK-181 Has Potential to Increase Response and Be Backbone Therapy to All Checkpoint Inhibitors



Current Checkpoint
Inhibitor Market: \$25B+*



~20% of patients respond
to checkpoint inhibitors†



Significant Unmet
Potential to Increase
Response to
Checkpoint Inhibitors
(CPIs)

■ Current CPIs

▨ Potential with increased response rates

*Source: Company information, Wall Street research, Evaluate Pharma.

†Source: Carretero-Gonzalez A, et al. *Oncotarget*. 2018;9:8706-8715. Meta-analysis of 12 randomized trials with control arm or adequate safety profile (includes nivolumab, pembrolizumab, and atezolizumab),

Significant Interest in Potential Role of TGFβ Inhibition in Immuno-Oncology

Nature (online), Feb. 14, 2018.

TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells

Sanjeev Mariathasan^{1*}, Shannon J. Turley^{1*}, Dorothee Nickles^{1*}, Alessandra Castiglioni¹, Kobe Yuen¹, Yulei Wang¹, Edward E. Kadel III¹, Hartmut Koeppen¹, Jillian L. Astarita¹, Rafael Cubas¹, Suchit Jhunjhunwala¹, Romain Banchereau¹, Yagai Yang¹, Yinghui Guan¹, Cecile Chalouni¹, James Ziai¹, Yasin Şenbabaoğlu¹, Stephen Santoro¹, Daniel Sheinson¹, Jeffrey Hung¹, Jennifer M. Giltman¹, Andrew A. Pierce¹, Kathryn Mesh¹, Steve Lianoglou¹, Johannes Riegler¹, Richard A. D. Carano¹, Pontus Eriksson², Mattias Höglund², Loan Somarriba³, Daniel L. Halligan³, Michiel S. van der Heijden⁴, Yohann Loriot⁵, Jonathan E. Rosenberg⁶, Lawrence Fong⁷, Ira Mellman¹, Daniel S. Chen¹, Marjorie Green¹, Christina Derleth¹, Gregg D. Fine¹, Priti S. Hegde¹, Richard Bourgon¹ & Thomas Powles⁸

February 2019: *“GSK and Merck KGaA, Darmstadt, Germany announce global alliance to jointly develop and commercialise M7824, a novel immunotherapy with potential in multiple difficult-to-treat cancers”*

- €300 million upfront and up to €3.7 billion total

June 2019: *“Merck to Acquire Tilos Therapeutics: Merck Gains Portfolio of Investigational Antibodies Modulating TGFβ”*

- \$773 million total potential deal value

Cell

Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma

Authors

Willy Hugo, Jesse M. Zaretsky, Lu Sun, Douglas B. Johnson, Antoni Ribas, Roger S. Lo

Volume 165, Issue 1, 24 March 2016, Pages 35-44

Article

NATURE REVIEWS | CLINICAL ONCOLOGY

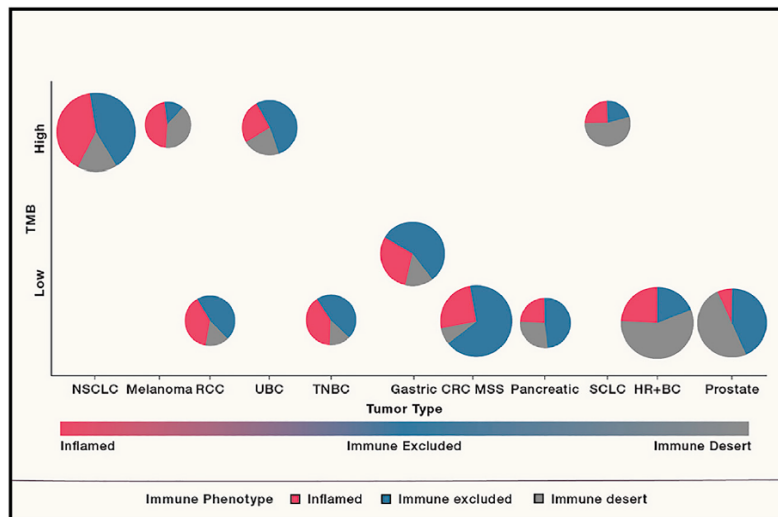
TGFβ biology in cancer progression and immunotherapy

Rik Derynck^{1,2,3}✉, Shannon J. Turley⁴✉ and Rosemary J. Akhurst^{1,2,3}✉

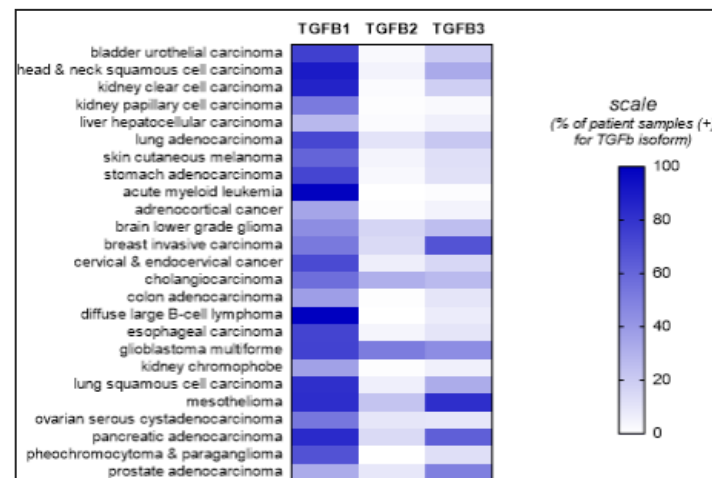
July 24, 2020: <https://doi.org/10.1038/s41571-020-0403-1>

Broad Potential for TGF β Blockade Across Many Solid Tumors

Substantial proportion of solid tumors exhibit immune exclusion[†]



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



Human Tumor Analyses Reveal TGF β 1 as Most Likely Driver of TGF β Pathway Signaling in Cancers

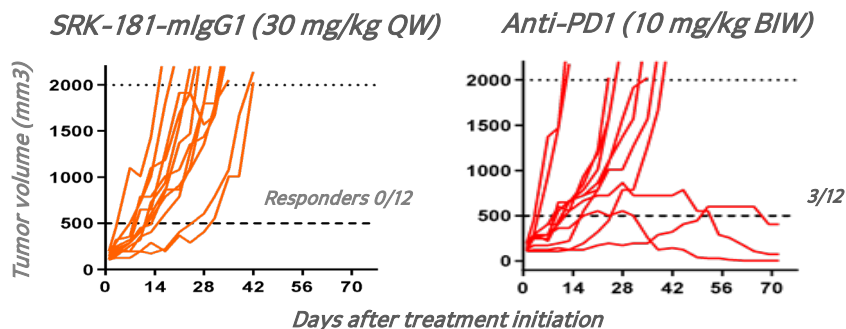
*Source: National Cancer Institute - Cancer Genome Atlas Program.

[†]Priti H, et al. Top 10 challenges in cancer immunotherapy. *Immunity*. 2020 Jan 14;52(1):17-35. <https://doi.org/10.1016/j.immuni.2019.12.011>.

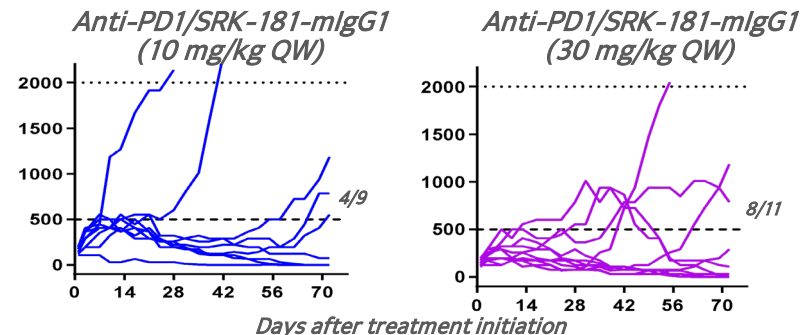
TGF β 1 Blockade with SRK-181-mIgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

Melanoma (Cloudman S91) model: Combination treatment led to tumor regression and survival benefit

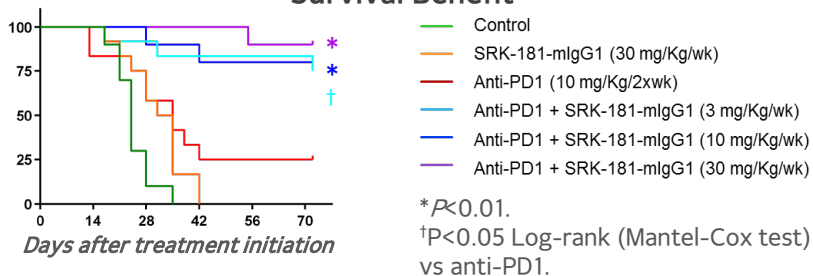
Tumor Regression: Monotherapy



Tumor Regression: Combination Therapy

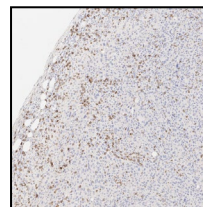


Survival Benefit

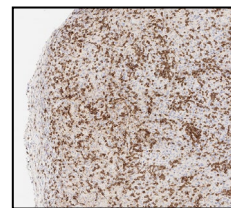


Overcoming immune exclusion

Anti-PD1

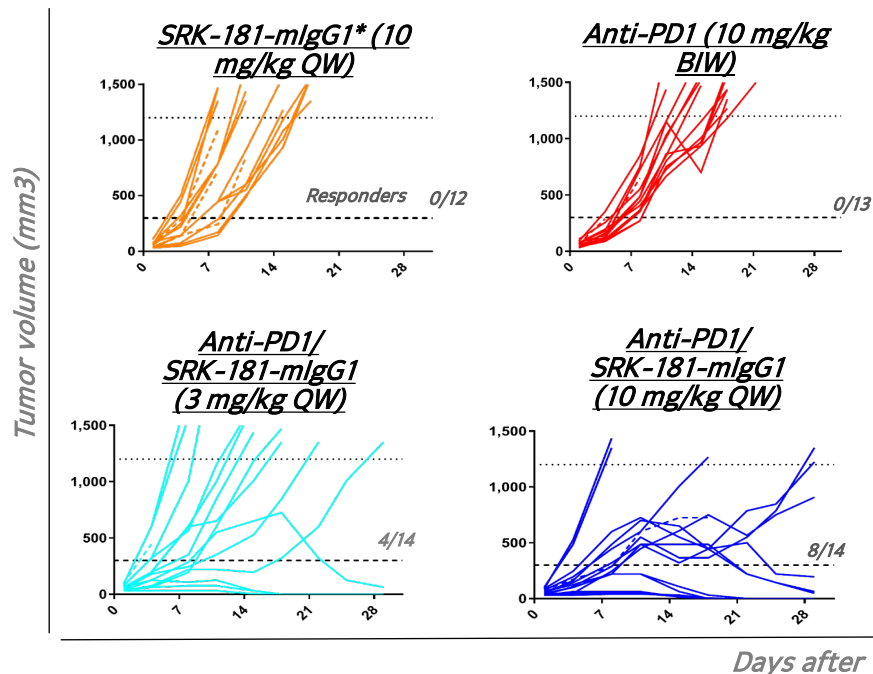


Anti-PD1/ SRK-181-mIgG1 led to influx of CD8+ cells in preclinical bladder tumor model

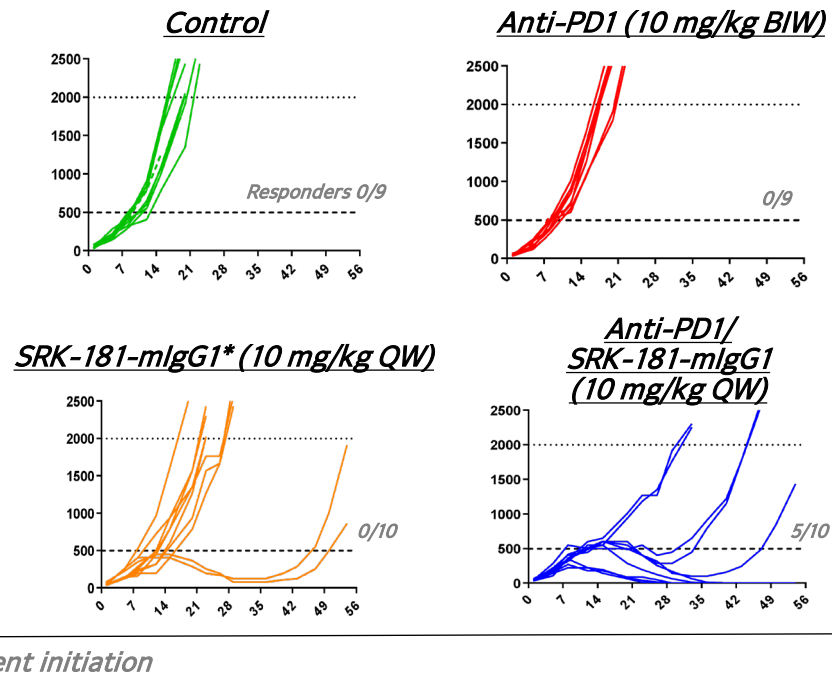


TGF β 1 Blockade with SRK-181-mIgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

Bladder Cancer



Breast Cancer (TGF β 1/3 co-expressing)

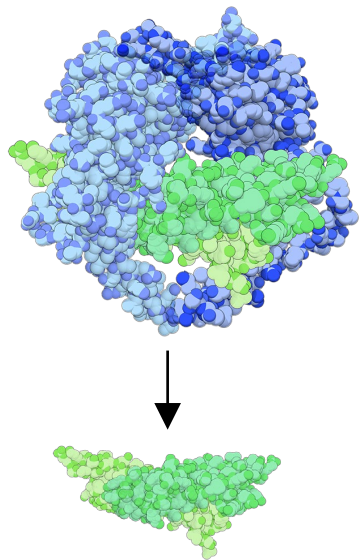


Preclinical data published in *Science Translational Medicine*. Martin CJ, et al. *Sci Transl Med*. 2020 Mar 25;12(536):eaay8456.
<https://scholarrock.com/platform/publications/>.

*SRK-181-mIgG1 is the murine version of SRK-181; responder defined as tumor size <25% endpoint volume at study end.

SRK-181: Unique TGF β 1-Selective Approach to Overcoming Checkpoint Inhibitor Resistance

Scholar Rock's Target SRK-181: Latent TGF β 1 Inhibitor



Traditional target:
“Mature” growth factor

- ✓ Inhibits TGF β 1 pathway - implicated in CPI resistance
- ✓ Highly selective targeting - avoids binding to latent TGF β 2 and TGF β 3 isoforms
- ✓ Aimed at increasing therapeutic window - potentially avoids toxicities associated with non-selective TGF β inhibition
- ✓ Therapeutic flexibility - pair with any CPI and optimize dosing of each component of combination therapy

TGFβ1 Isoform Specificity of SRK-181 Improved Preclinical Toxicity Profile

Microscopic observations in heart	Control	LY2109761	PanTGFβAb	SRK-181			LEGEND
	Vehicle	300 mg/kg	30 mg/kg	10 mg/kg	30 mg/kg	100 mg/kg	
	iv, qwk x 4	po, qd x 8	po, qd x 8	iv, qwk x 4	iv, qwk x 4	iv, qwk x 4	□ Unremarkable
Valvulopathy							■ Minimal
Atrium—Mixed cell infiltrate							■ Slight
Myocardium—Degeneration/necrosis							■ Moderate
Myocardium—Hemorrhage							
Myocardium—Mixed cell infiltrate, base							
Coronary artery—Necrosis with inflammation							
Cardiomyocyte—Necrosis/inflammatory cell infiltrate							

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

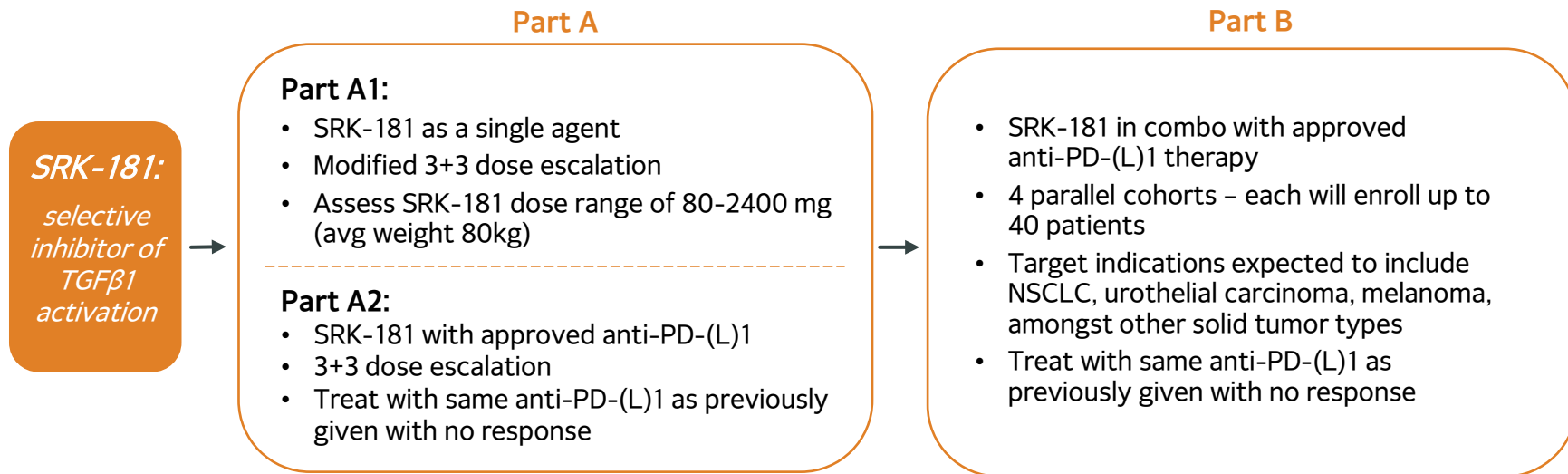
Selectivity of SRK-181 offers potential to overcome toxicity and dose-limiting challenges of non-selective TGFβ pathway approaches

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

Update on dose escalation expected in 4Q20; clinical response and safety data expected in 2021



- 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

DRAGON Part A: Commenced Evaluation of SRK-181 with Anti-PD-(L)1 Therapy

DRAGON Part A1

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

Safety and PK Data as Single-Agent

- Enables progression to evaluation of combination treatment

DRAGON Part A2

- SRK-181 with approved anti-PD-(L)1
- 3+3 dose escalation
- Focus on patients with primary resistance to single-agent anti-PD-1 or anti-PD-L1
- Treat with same anti-PD-(L)1 as previously given with no response

Potential for Early Efficacy Signals

- Anti-tumor response from combination treatment in individual patients would be unexpected given prior resistance to anti-PD-(L)1 therapy

Advanced to Part A2 in September 2020; update on dose escalation expected in 4Q20

DRAGON Part B: Multiple Opportunities for Efficacy Signals

DRAGON Part B



- Study population focused on patients already shown to have primary resistance to single-agent CPI
- 4 parallel cohorts; each to enroll up to 40 patients
 - **NSCLC:** SRK-181 + pembrolizumab
 - **Urothelial carcinoma:** SRK-181 + pembrolizumab
 - **Melanoma:** SRK-181 + pembrolizumab*
 - **Additional tumor types:** SRK-181 + anti-PD-(L)1 therapy for which patient experienced primary resistance

Potential for Rapid Path to Proof-of-Concept

- Anti-tumor response and safety with combination treatment
 - Response in individual patients would be unexpected given prior resistance to anti-PD-(L)1 therapy
 - Evaluation of patients with stable or progressive disease
- Ability to evaluate response across multiple tumor types
- Patient population with high unmet medical need
 - Strong proof-of-concept signal could support efficient registrational path

DRAGON Part B initiation planned 1Q21; anti-tumor and safety data expected starting in 2021

* Planning to open eligibility to patients with history of primary resistance to either pembrolizumab or nivolumab NCT04291079 on www.clinicaltrials.gov.

Differentiated Pipeline with a Series of Anticipated Milestones

