Deep Insights, Impactful Medicines

January 2021

ScholarRock™

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Various statements in this presentation concerning the future expectations, plans and prospects of Scholar Rock, Inc. ("Scholar Rock"), including without limitation, Scholar Rock's expectations regarding its strategy, its product candidate selection and development timing, including timing for the initiation of and reporting results from its clinical trials for its product candidates, its disease indication selection and timing for such selection, the ability of apitegromab (SRK-015) to affect the treatment of patients suffering from Spinal Muscular Atrophy (SMA) either as a monotherapy or in conjunction with the current standard of care, and the ability of SRK-181 to affect the treatment of cancer patients in a manner consistent with preclinical data constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. The use of words such as "may," "might," "will," "should," "expect," "plan," "anticipate," "believe," "estimate," "target," "project," "intend," "future," "potential," or "continue," and other similar expressions are intended to identify such forward-looking statements. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including, without limitation, Scholar Rock's ability to identify and develop multiple product candidates on the expected timeline, competition from others developing products for similar uses, the preliminary nature of interim clinical data, the impacts of the COVID-19 pandemic, Scholar Rock's ability to obtain, maintain and protect its intellectual property, Scholar Rock's dependence on third parties for development and manufacture of product candidates including to supply any clinical trials, and Scholar Rock's ability to manage expenses and to obtain additional funding when needed to support its business activities and establish and maintain strategic business alliances and new business initiatives as well as those risks more fully discussed in the section entitled "Risk Factors" in the Quarterly Report on Form 10-Q for the quarter ended September 30, 2020, which is on file with the Securities and Exchange Commission, as well as discussions of potential risks, uncertainties, and other important factors in Scholar Rock's subsequent filings with the Securities and Exchange Commission. Any forward-looking statements represent Scholar Rock's views only as of today and should not be relied upon as representing its views as of any subsequent date. Scholar Rock explicitly disclaims any obligation to update any forward-looking statements unless required by law.

2020 Achievements

- [x] Announced positive 6-month interim data from apitegromab's TOPAZ Phase 2 trial in spinal muscular atrophy

- [x] Initiated and progressed patient enrollment in the SRK-181 DRAGON Phase 1 trial in cancer immunotherapy
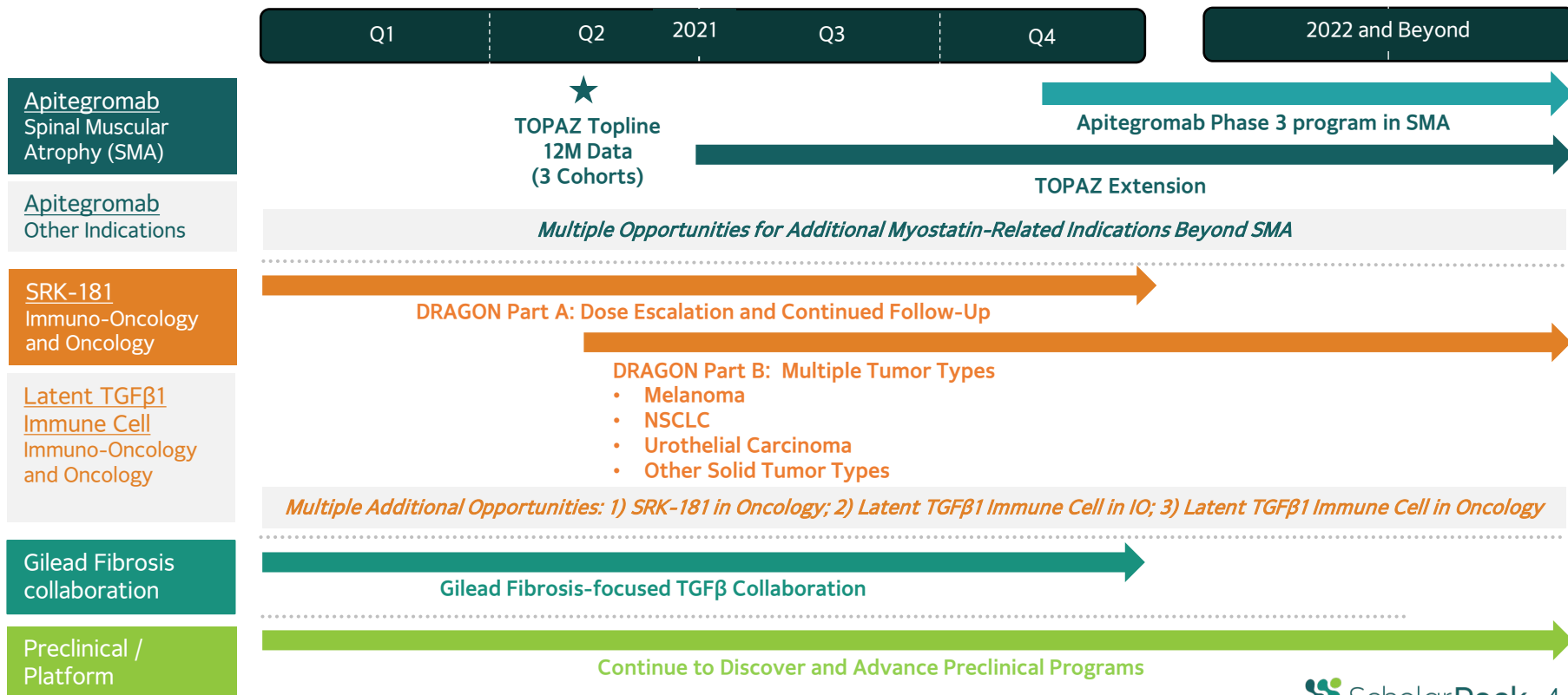
- [x] Completed follow-on offering that raised $230 million in gross proceeds and secured $50 million debt facility; ended year with ~$340M in cash and cash equivalents

- [x] FDA granted Rare Pediatric Disease Designation for apitegromab for the treatment of SMA

- [x] Strengthened patent portfolio; composition of matter patent for apitegromab and a patent broadly covering antibodies that modulate TGFβ activation
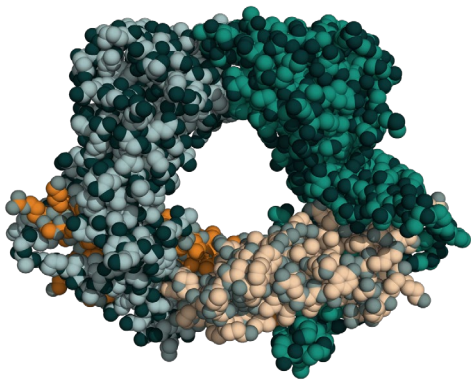
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2021: Potential for Another Transformative Year

	Q1	Q2	2021 Q3	Q4	2022 and Beyond

Apitegromab
Spinal Muscular Atrophy (SMA)

★ TOPAZ Topline 12M Data (3 Cohorts)

Apitegromab Phase 3 program in SMA

TOPAZ Extension

Apitegromab
Other Indications

Multiple Opportunities for Additional Myostatin-Related Indications Beyond SMA

SRK-181
Immuno-Oncology and Oncology

DRAGON Part A: Dose Escalation and Continued Follow-Up

DRAGON Part B: Multiple Tumor Types
- Melanoma
- NSCLC
- Urothelial Carcinoma
- Other Solid Tumor Types

Latent TGFβ1 Immune Cell
Immuno-Oncology and Oncology

Multiple Additional Opportunities: 1) SRK-181 in Oncology; 2) Latent TGFβ1 Immune Cell in IO; 3) Latent TGFβ1 Immune Cell in Oncology

Gilead Fibrosis collaboration

Gilead Fibrosis-focused TGFβ Collaboration

Preclinical / Platform

Continue to Discover and Advance Preclinical Programs

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

Scholar Rock's Target
Growth Factor Precursor (Latent Form)

Scholar Rock's R&D Platform
Transform Medical Practice

- Pursue important targets with well-validated biology but are difficult to drug

- Apply revolutionary approach to tough targets

  - Leverage deep insights into structure and function

  - Engineer antibodies for exquisite selectivity

Apitegromab interim analysis data provides first clinical demonstration of the therapeutic potential of inhibiting the latent forms of growth factors

Apitegromab = non-proprietary name for SRK-015

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Apitegromab Has Potential to Pioneer a New Treatment Era to Improve Motor Function in Patients with SMA

SMN Upregulator Therapies + Muscle-Directed Therapy
Could Potentially Enhance Outcomes for Patients*

Overall Prevalence of 30,000-35,000 in U.S. and Europe

SPINRAZA®
(nusinersen) injection 12 mg/5 mL

($2B+ LTM sales)

Biogen

zolgensma®
(onasemnogene abeparvovec-xioi)
suspension for intravenous infusion

($850M+ LTM sales)

NOVARTIS avexis

Evrysdi™
risdiplam 60 mg powder for oral solution

(FDA approved August 2020)

Genentech
A Member of the Roche Group

Apitegromab (SRK-015)**

SMN Upregulator Therapies

Address SMN deficiency to prevent further motor neuron deterioration

Muscle-Directed Therapy

Act directly on muscle with aim to improve motor function

SMN = survival motor neuron.
*Also referred to as SMN correctors.
**apitegromab is an investigational therapy under development.

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Apitegromab Phase 2 Trial Design

Ambulatory Patients (Revised Hammersmith Scale)	Non-Ambulatory Patients (Hammersmith Functional Motor Scale Expanded)	
Cohort 1	**Cohort 2**	**Cohort 3**

	Cohort 1	Cohort 2	Cohort 3
Design	• N= 23; ages 5-21 • Open-label, single-arm • 20 mg/kg apitegromab IV Q4W • 12-month treatment period	• N= 15; ages 5-21 • Open-label, single-arm • 20 mg/kg apitegromab IV Q4W • 12-month treatment period	• N= 20; ages ≥2 • Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg apitegromab IV Q4W • 12-month treatment period

Patients	• Ambulatory Type 3 SMA
	• Two subgroups:
	  1) Receiving background nusinersen
	  2) Apitegromab monotherapy
		• Type 2 or non-ambulatory Type 3 SMA
		• Receiving background nusinersen
			• Type 2 SMA
			• Receiving background nusinersen (initiated 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

56 patients have completed the 12-month study and all 56 have opted into the extension period*

*As of January 8, 2021
Apitegromab = non-proprietary name for SRK-015
HFMSE=Hammersmith Functional Motor Scale Expanded; RHS=Revised Hammersmith Scale
Data on file. Scholar Rock, Inc. Cambridge, MA

TOPAZ Interim Analysis Results Demonstrate Proof-of-Concept
*Multiple lines of evidence supporting the potential clinical effect of apitegromab*

	Ambulatory Patients (Revised Hammersmith Scale)			Non-Ambulatory Patients (Hammersmith Functional Motor Scale Expanded)		
	Cohort 1			Cohort 2*	Cohort 3*	
	20 mg/kg pooled (n=23)	20 mg/kg monotherapy (n=11)	20 mg/kg +nusinersen (n=12)	20 mg/kg +nusinersen (n=14)	2 mg/kg +nusinersen (n=9)	20 mg/kg +nusinersen (n=9)
Mean change from baseline (95% CI)	0.5 (-1.1, 2.2)	0.7 (-2.5, 4.0)	0.3 (-1.4, 2.0)	1.4 (0.1, 2.7)	2.4 (-0.9, 5.8)	5.6 (2.5, 8.7)
# (%) patients achieving ≥1-pt increase	12/23 (52%)	7/11 (64%)	5/12 (42%)	10/14 (71%)	6/9 (67%)	9/9 (100%)
# (%) patients achieving ≥3-pt increase	6/23 (26%)	4/11 (36%)	2/12 (17%)	3/14 (21%)	4/9 (44%)	6/9 (67%)

✓ **Mean improvements from baseline in HFMSE/RHS observed in each of the 3 cohorts**

- 67% of total patients achieved ≥1-point improvement in Hammersmith scores

✓ **Substantial proportion of patients in each cohort attained ≥3-point improvement in HFMSE/RHS**

- High bar and uncommon to observe in any given patient
- 35% of total patients achieved ≥3-point improvement in Hammersmith scores

✓ **Dose response demonstrated in Cohort 3** *(randomized, double-blind, parallel arm design)*

- Greater improvements in HFMSE scores for high-dose arm across evaluated timepoints
- Supportive PK/PD results; high dose led to higher drug exposure and target engagement

*3 patients (1 in Cohort 2 and 2 in Cohort 3) each missed 3 doses of apitegromab and the 6-month interim analysis timepoint due to COVID-19-related site access restrictions; the six-month timepoint from these patients was not included in the interim analysis.
Data on file. Scholar Rock, Inc. Cambridge, MA

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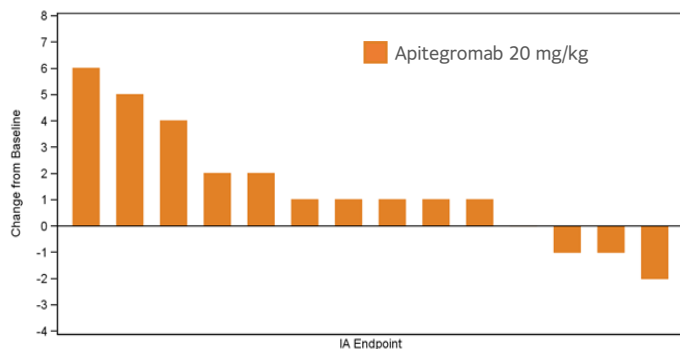# Improvements in Hammersmith Scores Observed Across All 3 Cohorts

Cohort 1 (ambulatory Type 3) individual RHS responses
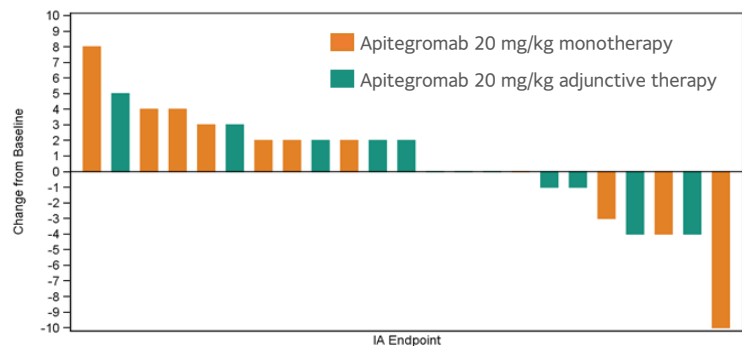
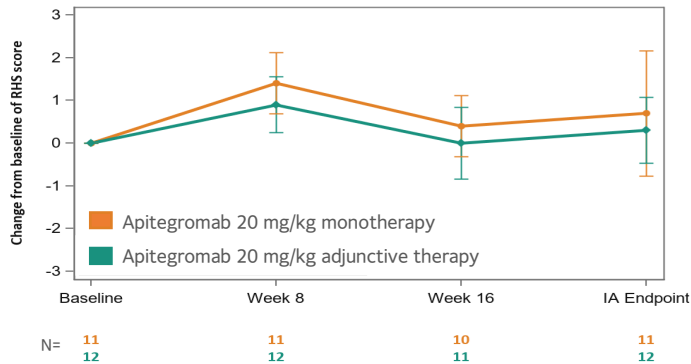### Cohort 3 (Type 2) individual HFMSE responses
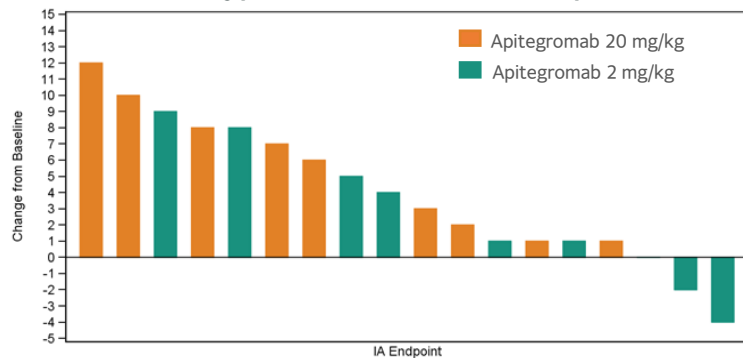
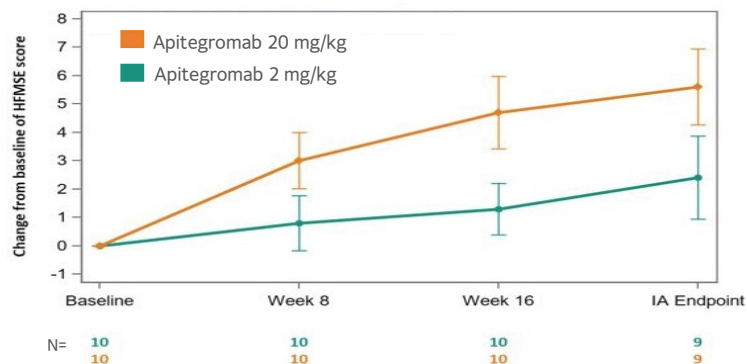### Cohort 2 (Type 2 & non-amb. Type 3) individual HFMSE responses

- Most patients experienced an improvement
  - 67% of total patients achieved ≥1-pt increase in Hammersmith scores
- Dose response demonstrated in Cohort 3 (randomized, double-blind, parallel arm design)
  - High-dose arm showed greater improvements; supported by PK/PD results

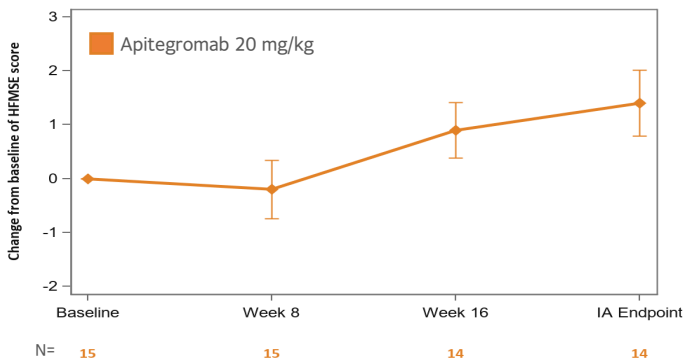# Effects on Hammersmith Scores Observed Through 6 Months of Treatment

Cohort 1: Mean (±SEM) change from baseline in RHS scores

Apitegromab 20 mg/kg monotherapy
Apitegromab 20 mg/kg adjunctive therapy

N=
11 11 10 11
12 12 11 12

Cohort 3: Mean (±SEM) change from baseline in HFMSE scores

Apitegromab 20 mg/kg
Apitegromab 2 mg/kg

N=
10 10 10 9
10 10 10 9

Cohort 2: Mean (±SEM) change from baseline in HFMSE scores

Apitegromab 20 mg/kg

N=
15 15 14 14

- Plateau in improvement appears to not yet have been reached at the 6-month interim timepoint

- 12-month and extension data enable evaluation for potential durability of effect and further improvements

No Safety Signals Identified from Interim Analysis

| Treatment-emergent adverse events (TEAEs)	Apitegromab 2 mg/kg dose (n=10)	Apitegromab 20 mg/kg dose (n=48)	Total (n=58)
Any TEAE	9 (90%)	40 (83.3%)	49 (84.5%)
Any Serious TEAE	0 (0.0%)	1 (2.1%)	1 (1.7%)
Any TEAE leading to study drug discontinuation	0 (0.0%)	1 (2.1%)	1 (1.7%)
Any Grade 3 (severe) or higher TEAE	0 (0.0%)	0 (0.0%)	0 (0.0%)

- **Five most frequently reported TEAEs:** Headache, upper respiratory tract infection, pyrexia, nasopharyngitis, and cough.

- **1 serious TEAE (Cohort 1):** Assessed by trial investigator as unrelated to apitegromab. Grade 2 viral upper respiratory infection (prior history) and was hospitalized. Event resolved without sequelae.

- **1 study drug discontinuation (Cohort 1):** Assessed by trial investigator as unrelated to apitegromab. Grade 2 leg muscle fatigue (developed prior to enrollment). Withdrew consent after ~2 months on trial.

Incidence and severity of AEs are consistent with underlying patient population and background therapy

Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug or start prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug.
Data on file. Scholar Rock, Inc. Cambridge, MA

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Unlocking the Potential of the Scholar Rock R&D Engine

TGFβ Superfamily: More than 30 Related Growth Factors that Mediate Diverse Biological Processes

Targeting the latent forms of growth factors
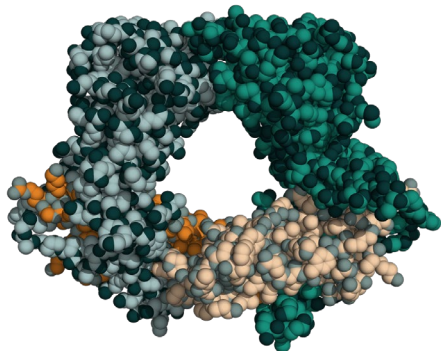
Scholar Rock seeks to unlock the therapeutic potential of modulating growth factor biology

Emerging Insights

Demonstration of initial proof-of-concept for apitegromab in SMA

Validation of therapeutic potential for blocking the activation of latent myostatin with apitegromab

Validation of therapeutic potential in targeting latent forms of growth factors

Opportunities Beyond TOPAZ

- Broader exploration of SMA types, age range, and background SMN therapies

- Exploration of additional myostatin-related indications

- Antibodies against the latent forms of additional well-validated targets in oncology (e.g. SRK-181 program) and fibrosis

- Discovery platform to generate mAbs against other latent growth factors

SRK-181: Potential Transformative Backbone for a New Era of Cancer Immunotherapy

Significant Recent 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 Castiglioni[1], Kobe Yuen[1], Yulei Wang[1], Edward E. Kadel III[1], Hartmut Koeppen[1], Jillian L. Astarita[1], Rafael Cubas[1], Suchit Jhunjhunwala[1], Romain Banchereau[1], Yagai Yang[1], Yinghui Guan[1], Cecile Chalouni[1], James Ziai[1], Yasin Şenbabaoğlu[1], Stephen Santoro[1], Daniel Sheinson[1], Jeffrey Hung[1], Jennifer M. Giltnane[1], Andrew A. Pierce[1], Kathryn Mesh[1], Steve Lianoglou[1], Johannes Riegler[1], Richard A. D. Carano[1], Pontus Eriksson[2], Mattias Höglund[2], Loan Somarriba[3], Daniel L. Halligan[3], Michiel S. van der Heijden[4], Yohann Loriot[5], Jonathan E. Rosenberg[6], Lawrence Fong[7], Ira Mellman[1], Daniel S. Chen[1], Marjorie Green[1], Christina Derleth[1], Gregg D. Fine[1], Priti S. Hegde[1], Richard Bourgon[1] & Thomas Powles[8]

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

Article

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

NATURE REVIEWS | CLINICAL ONCOLOGY
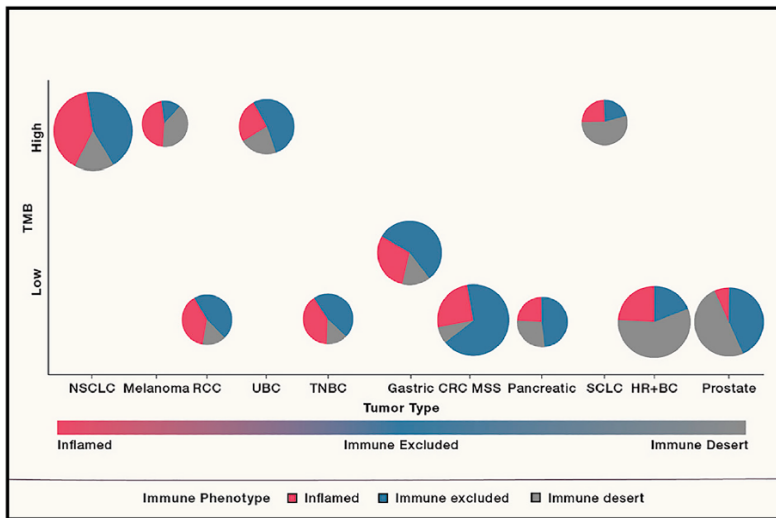
TGFβ biology in cancer progression and immunotherapy

Rik Derynck[1,2,3] ✉, Shannon J. Turley[4] ✉ and Rosemary J. Akhurst[2,3] ✉
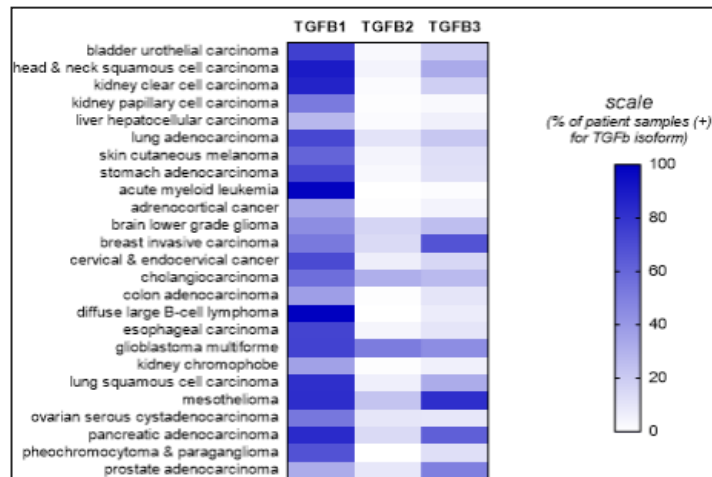
August 2020: *"Bristol Myers Squibb Enters Agreement to Acquire Forbius TGF-beta Program"*

Emerging Evidence Implicates TGFβ1 as Driving Primary Resistance to Checkpoint Inhibitors

Substantial % of solid tumors exhibit immune exclusion

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

Human Tumor Analyses Reveal TGFβ1 as Most Likely Driver of TGFβ Signaling Pathway in Cancers

SRK-181: Unique TGFβ1-Selective Approach to Overcoming Checkpoint Inhibitor Resistance

Scholar Rock's Target
SRK-181: Latent TGFβ1 Inhibitor
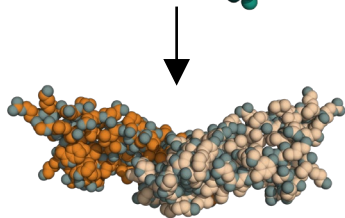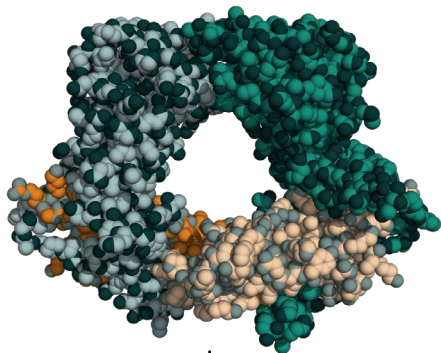
Traditional target:
"Mature" growth factor

✓ **Inhibits TGFβ1 pathway** - implicated in CPI resistance

✓ **Highly selective targeting** - avoids inhibiting latent TGFβ2 and TGFβ3 isoforms

✓ **Aimed at increasing therapeutic window** – potentially avoids toxicities associated with non-selective TGFβ inhibition

✓ **Therapeutic flexibility** - pair with any CPI and optimize dosing of each component of combination therapy

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

SRK-181 is a potent and highly selective inhibitor of latent TGFβ1 activation

Part A

Part B

Part A1:
- SRK-181 as a single agent
- Modified 3+3 dose escalation
- Assess SRK-181 dose range of 80-2400 mg

Part A2:
- SRK-181 with approved anti-PD-(L)1
- 3+3 dose escalation
- Treat with an anti-PD-(L)1 therapy approved for tumor

- SRK-181 in combination 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

- As of January 8, 2021:
  - Part A1: Highest planned dose of 2400 mg being evaluated
  - Part A2: 800 mg dose being evaluated
- Part B initiation planned for 2Q21
- Initial clinical response and safety data expected in 2H21

DRAGON

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2020 Momentum Carrying into 2021:
Continued Execution and Advancements

Strengthened leadership team

Positive TOPAZ interim data in SMA; first demonstration of therapeutic potential of scientific platform

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Initiated DRAGON Phase 1 trial in cancer immunotherapy

Ended 2020 with ~$340M in cash and cash equivalents

2021 Priorities

- ❑ 12-month TOPAZ data for apitegromab in SMA

- ❑ Development and regulatory path for apitegromab in SMA

- ❑ Additional myostatin-related disorders

- ❑ DRAGON trial to evaluate SRK-181's ability to overcome checkpoint resistance

- ❑ Advance scientific platform

Appendix

Apitegromab: Pairing the latent form with important translational insights

Scholar Rock's Guiding Principles for Neuromuscular Indication Selection

Key Characteristics of Spinal Muscular Atrophy (SMA)

Scholar Rock's Guiding Principles	Key Characteristics of SMA
Younger population	Genetic disorder with onset in childhood
At least partially intact innervation and no structural muscle abnormalities	Partial neural connectivity and atrophied muscles that largely retain structural integrity
Need for increase in fast-twitch muscle fibers	Substantial deficit in fast-twitch fibers
Clinical trial endpoint driven by fast-twitch fiber function	Fast-twitch fiber function has a prominent role in SMA outcome measures

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Next Era of SMA Treatment: Muscle-Directed Therapy

Overall Prevalence of 30,000–35,000 in U.S. and Europe

Type 1:
- Infant-onset
- Usually fatal without treatment

Type 2 and non-ambulatory Type 3:
- Later-onset but still early childhood
- Severe deficits in motor function
- SMN upregulators appear to primarily stabilize disease course

Ambulatory Type 3:
- Typically childhood-onset
- Wide range of motor function deficits; limited mobility and substantial morbidity
- SMN upregulators appear to primarily stabilize disease course

Relative Prevalence Among Patients Living With SMA

Type 1 14%
Type 3 35%
Type 2 51%
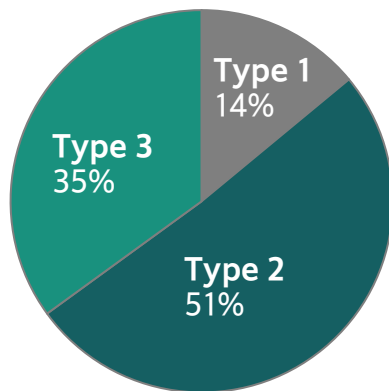
TOPAZ trial focuses on Type 2 and Type 3 SMA

Unmet need would be served by a therapy that:

- Improves motor function
- Safety profile that enables chronic dosing, including in the pediatric population
- Low drug administration burden
- Applicable across SMA types

HFMSE = Hammersmith Functional Motor Scale Expanded

Baseline Characteristics

TOPAZ

	Ambulatory Patients			Non-Ambulatory Patients		
	Cohort 1			Cohort 2	Cohort 3	
	20 mg/kg pooled	20 mg/kg monotherapy	20 mg/kg +nusinersen	20 mg/kg +nusinersen	2 mg/kg +nusinersen	20 mg/kg +nusinersen
N	23	11	12	15	10	10
Mean age (min, max)	12.6 (7, 21)	12.1 (7, 19)	13.1 (7, 21)	11.7 (8, 19)	4.1 (2, 6)	3.8 (2, 6)
Female (%)	65%	73%	58%	53%	30%	50%
SMN2 Gene Copy* (#, %)						
2	1 (4%)	1 (9%)	0 (0%)		1 (10%)	1 (10%)
3	13 (57%)	4 (36%)	9 (75%)	11 (73%)	8 (80%)	8 (80%)
4	5 (22%)	4 (36%)	1 (8%)	2 (13%)	1 (10%)	0 (0%)
Mean # of nusinersen maintenance doses	N/A	N/A	5.6	5.1	5.5	5.4
Discontinuation(s)	1**	0	1**	0	0	0
Mean RHS score (min, max)	49.6 (26, 63)	47.6 (26, 63)	51.3 (43, 62)			
Mean HFMSE score (min, max)				22.7 (13, 39)	26.1 (12, 44)	23.5 (14, 42)

*data not available for all patients
**patient who discontinued study for reasons unrelated to study drug

HFMSE=Hammersmith Functional Motor Scale Expanded; RHS=Revised Hammersmith Scale
*Data on file. Scholar Rock, Inc. Cambridge, MA*

Cohort 1: Improvement in RHS Observed with Both Apitegromab Monotherapy and as Add-on to Background Nusinersen

Ambulatory Type 3 SMA	Apitegromab (20 mg/kg) pooled (n=23)	Apitegromab (20 mg/kg) monotherapy (n=11)	Apitegromab (20 mg/kg) +nusinersen (n=12)
Mean change from baseline in RHS (95% CI)	0.5 (−1.1, 2.2)	0.7 (−2.5, 4.0)	0.3 (−1.4, 2.0)
# (%) patients achieving ≥1-pt increase in RHS	12/23 (52%)	7/11 (64%)	5/12 (42%)
# (%) patients achieving ≥3-pt increase in RHS	6/23 (26%)	4/11 (36%)	2/12 (17%)
# (%) patients achieving ≥5-pt increase in RHS	2/23 (9%)	1/11 (9%)	1/12 (8%)

Individual RHS responses
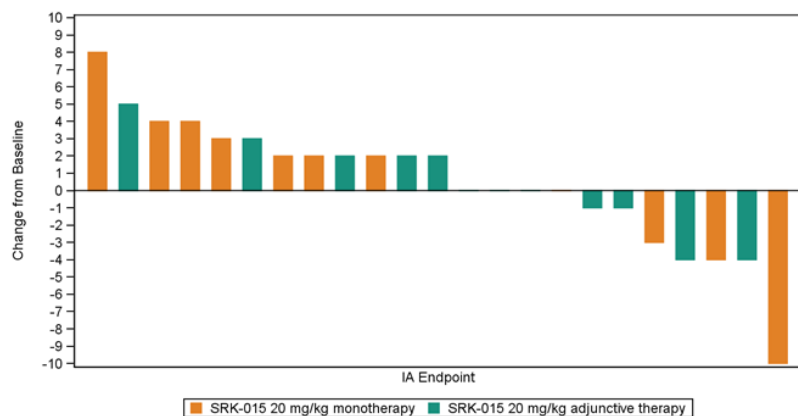
Mean (±SEM) change from baseline in RHS scores
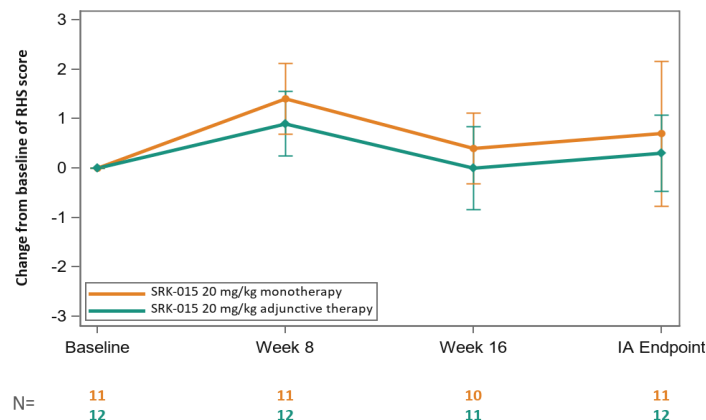
Cohort 2: Meaningful and Consistent Improvements in HFMSE Observed in Type 2 and Non-Ambulatory Type 3 SMA

Type 2 and Non-Ambulatory Type 3 SMA	Apitegromab (20 mg/kg) + nusinersen (n=14)
Mean change from baseline in HFMSE (95% CI)	1.4 (0.1, 2.7)
# (%) patients achieving ≥1-pt increase in HFMSE	10/14 (71%)
# (%) patients achieving ≥3-pt increase in HFMSE	3/14 (21%)
# (%) patients achieving ≥5-pt increase in HFMSE	2/14 (14%)

Individual HFMSE responses

Mean (±SEM) change from baseline in HFMSE scores

Apitegromab = non-proprietary name for SRK-015
Data on file. Scholar Rock, Inc. Cambridge, MA

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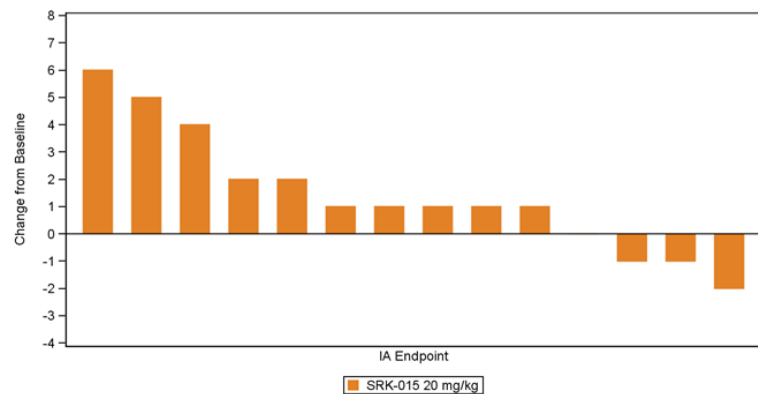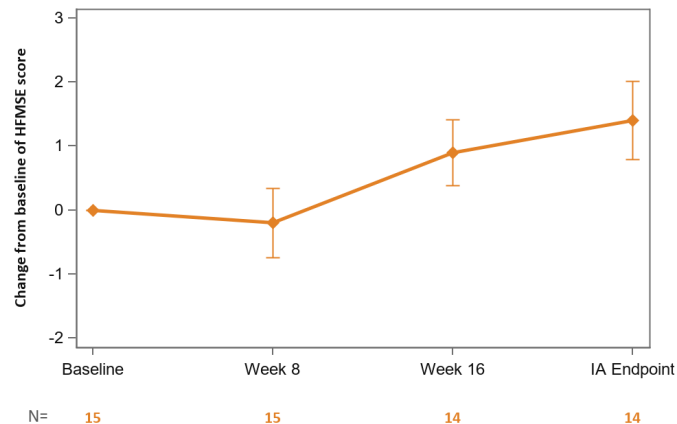
# Cohort 3: Apitegromab High Dose Showed Substantially Greater Improvements in HFMSE scores Than Low Dose

Cohort 3 has a randomized, double-blind, parallel arm design embedded within TOPAZ

Type 2 SMA	Apitegromab low dose (2 mg/kg) +nusinersen (n=9)	Apitegromab high dose (20 mg/kg) +nusinersen (n=9)
Mean change from baseline in HFMSE (95% CI)	2.4 (-0.9, 5.8)	5.6 (2.5, 8.7)
# (%) patients achieving ≥1-pt increase in HFMSE	6/9 (67%)	9/9 (100%)
# (%) patients achieving ≥3-pt increase in HFMSE	4/9 (44%)	6/9 (67%)
# (%) patients achieving ≥5-pt increase in HFMSE	3/9 (33%)	5/9 (56%)

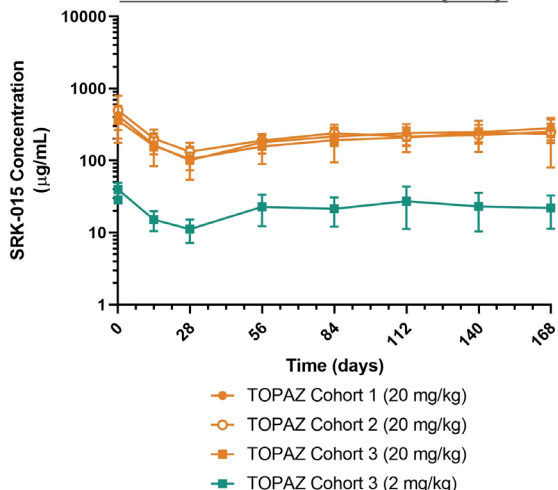### Individual HFMSE responses
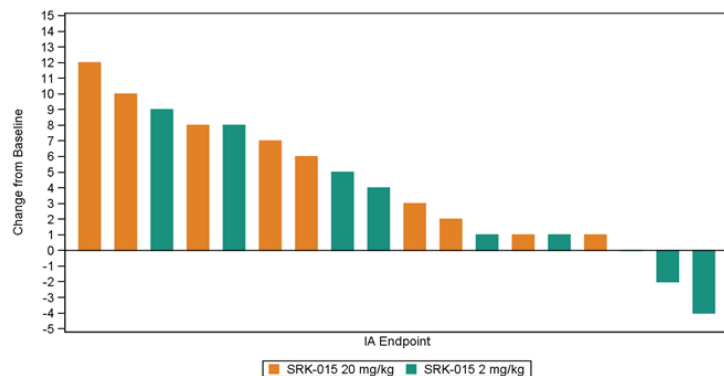
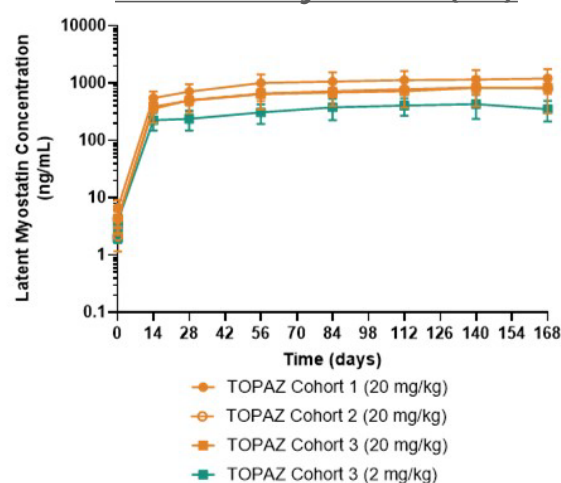### Mean (±SEM) change from baseline in HFMSE scores
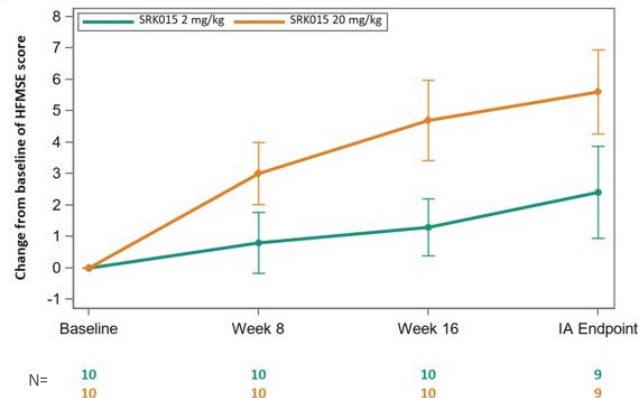
Pharmacokinetic and Pharmacodynamic Data are Supportive of Clinically Observed Dose Response

Pharmacokinetics* (PK)

Pharmacodynamics (PD)

- Well-behaved PK profile consistent with that commonly observed with monoclonal antibodies
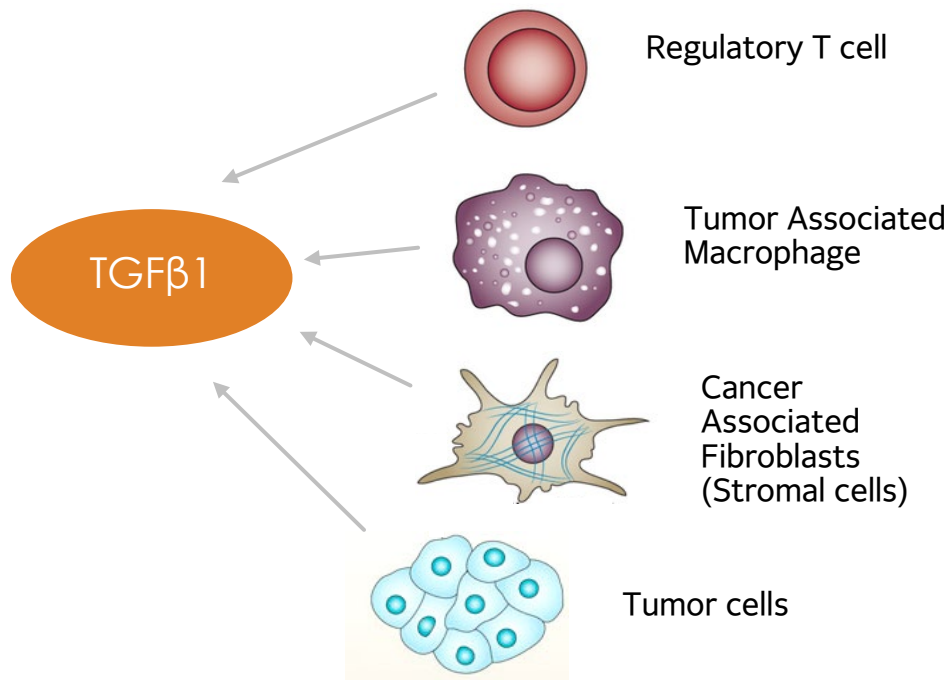- Drug exposure was dose proportional

- Target engagement by apitegromab was confirmed
- Low dose (2 mg/kg) yielded lower level of target engagement and did not achieve full target saturation

High dose (20 mg/kg) yielded higher levels of drug exposure and target engagement than low dose (2 mg/kg)

*Starting at day 28, measures are pre-dose trough levels
Apitegromab = non-proprietary name for SRK-015
Data on file. Scholar Rock, Inc. Cambridge, MA

Inhibition of TGFβ1: Multipronged Approach for Immuno-Oncology

TGFβ1 is a key driver of immune system evasion by cancer cells

Regulatory T cell

Tumor Associated Macrophage

TGFβ1

Cancer Associated Fibroblasts (Stromal cells)

Tumor cells
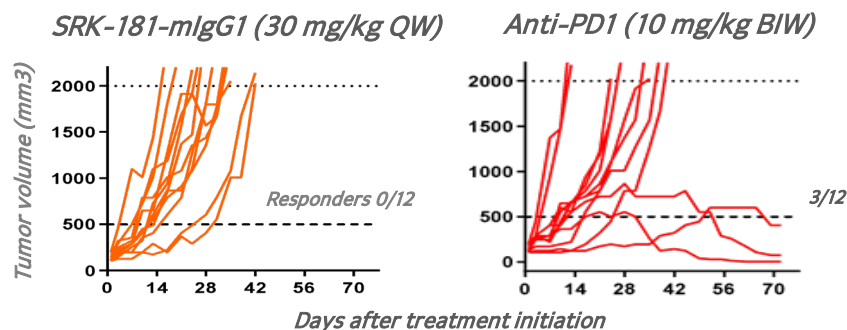
- Pathway analysis in patient tumors points to TGFβ1 as major determinant of primary resistance to anti-PD-(L)1 therapy
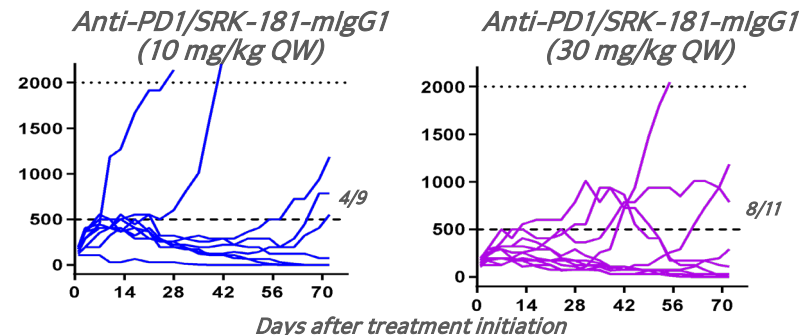
- TGFβ1 creates 'immune excluded' tumor microenvironment

TGFβ1 Blockade with SRK-181-mIgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

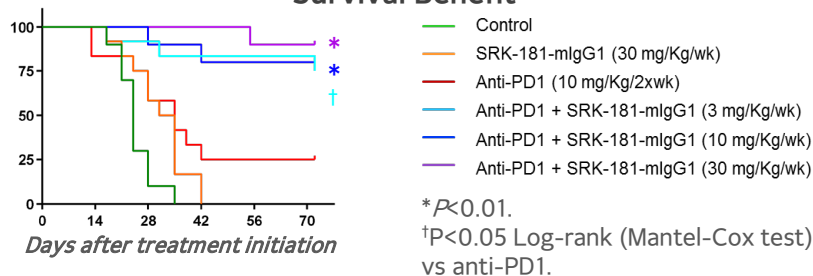## Melanoma (Cloudman S91) model: Combination treatment led to tumor regression and survival benefit

Tumor Regression: Monotherapy

SRK-181-mIgG1 (30 mg/kg QW)

Responders 0/12

Anti-PD1 (10 mg/kg BIW)

3/12

Tumor volume (mm3)
Days after treatment initiation

Tumor Regression: Combination Therapy

Anti-PD1/SRK-181-mIgG1 (10 mg/kg QW)

4/9

Anti-PD1/SRK-181-mIgG1 (30 mg/kg QW)

8/11

Days after treatment initiation

Survival Benefit

- Control
- SRK-181-mIgG1 (30 mg/Kg/wk)
- Anti-PD1 (10 mg/Kg/2xwk)
- Anti-PD1 + SRK-181-mIgG1 (3 mg/Kg/wk)
- Anti-PD1 + SRK-181-mIgG1 (10 mg/Kg/wk)
- Anti-PD1 + SRK-181-mIgG1 (30 mg/Kg/wk)

Days after treatment initiation

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

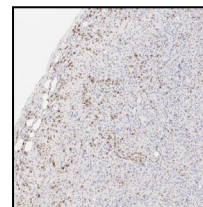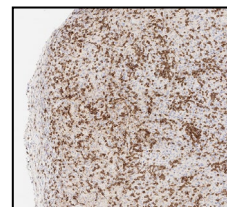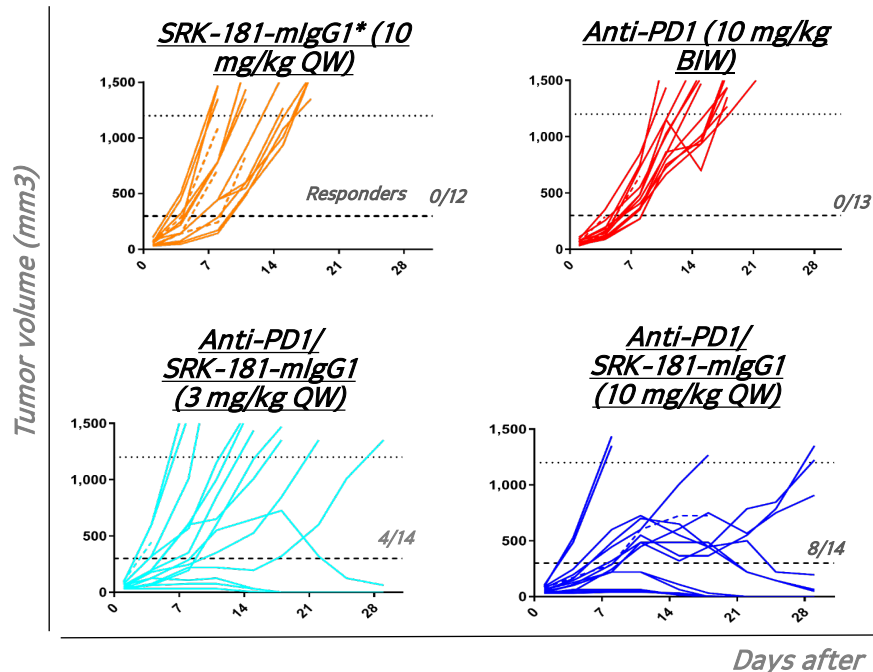### Overcoming immune exclusion

Anti-PD1

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

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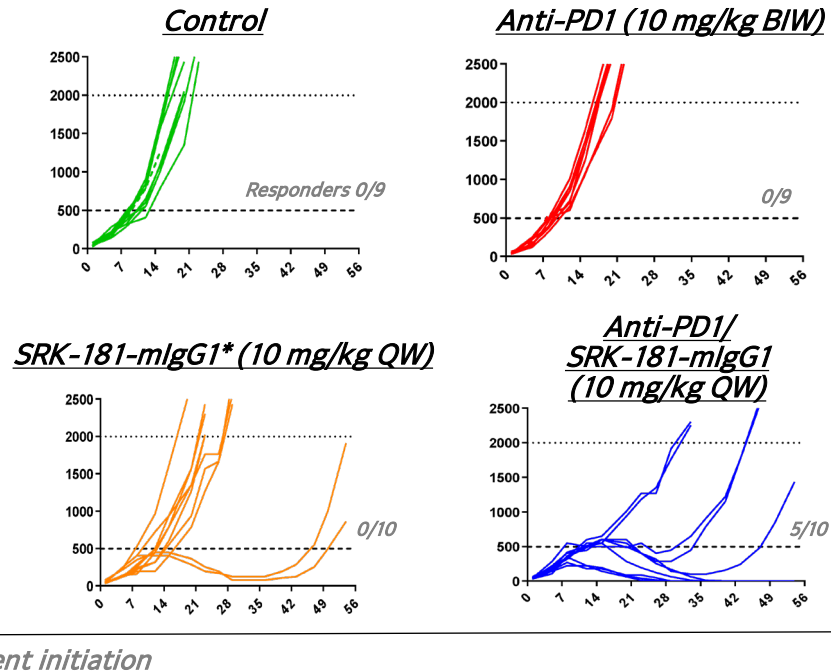# TGFβ1 Blockade with SRK-181-mIgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

TGFβ1 Isoform Specificity of SRK-181 Improved Preclinical Toxicity Profile

Microscopic observations in heart	Control Vehicle (iv, qwk x 4)	LY2109761 300 mg/kg (po, qd x 8)	PanTGFβAb 30 mg/kg (Iv, 1 dose)	SRK-181 10 mg/kg (iv, qwk x 4)	SRK-181 30 mg/kg (iv, qwk x 4)	SRK-181 100 mg/kg (iv, qwk x 4)
Valvulopathy						
Atrium—Mixed cell infiltrate		Minimal	Slight			
Myocardium—Degeneration/necrosis			Minimal			
Myocardium—Hemorrhage		Moderate				
Myocardium—Mixed cell infiltrate, base			Minimal	Minimal		
Coronary artery—Necrosis with inflammation			Slight			
Cardiomyocyte—Necrosis/inflammatory cell infiltrate		Moderate		Minimal		

LEGEND
- Unremarkable
- Minimal
- Slight
- Moderate

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.

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

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

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)

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

Safety and PK Data as Single-Agent

- Enables progression to evaluation of combination treatment

DRAGON Part B: Multiple Opportunities for Efficacy Signals

DRAGON Part B

- Study population focused on patients already shown to have primary resistance to 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 2Q21; initial clinical response and safety data expected in 2H21

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