



# Deep Insights, Impactful Medicines

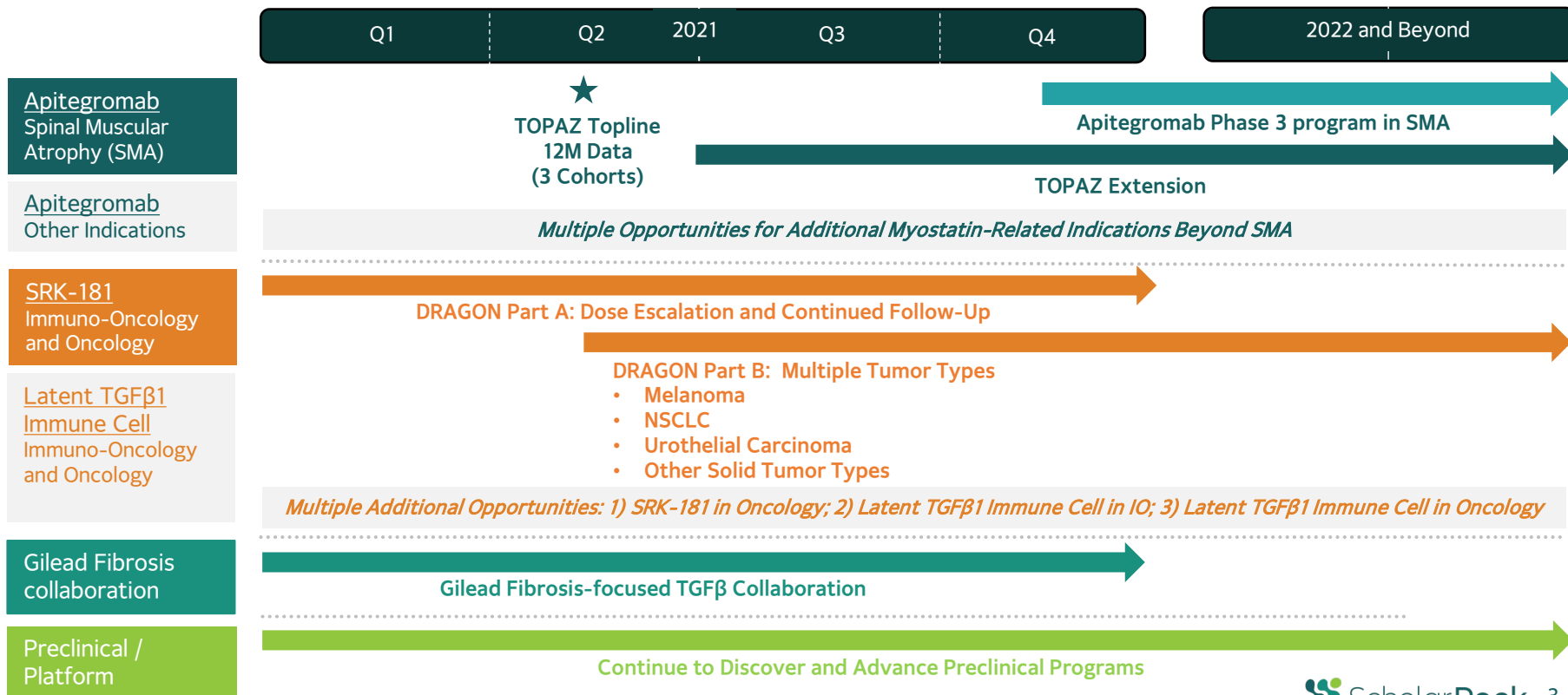
March 2021



# Disclaimers

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.

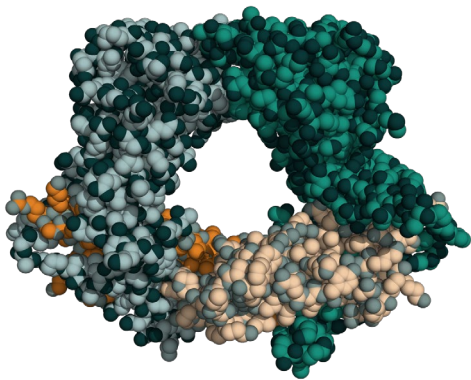
# 2021: Potential for Another Transformative Year



# 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: Potential First Muscle-Directed Therapy for Spinal Muscular Atrophy



# 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*



(nusinersen) injection  
12 mg/5 mL

(\$2B+ LTM sales)



(FDA approved  
August 2020)

**Genentech**

A Member of the Roche Group



suspension for intravenous infusion  
(\$900M+ LTM sales)



**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

**Apitegromab  
(SRK-015)\*\***

SMN = survival motor neuron.

\*Also referred to as SMN correctors.

\*\*apitegromab is an investigational therapy  
under development.

# Apitegromab Phase 2 Trial Design



|                           | Ambulatory Patients<br>(Revised Hammersmith Scale)                                                                                                                                                                                              | Non-Ambulatory Patients<br>(Hammersmith Functional Motor Scale Expanded)                                                                                                   |                                                                                                                                                                                                        |
|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                           | Cohort 1                                                                                                                                                                                                                                        | Cohort 2                                                                                                                                                                   | Cohort 3                                                                                                                                                                                               |
| <b>Design</b>             | <ul style="list-style-type: none"> <li>N= 23; ages 5-21</li> <li>Open-label, single-arm</li> <li>20 mg/kg apitegromab IV Q4W</li> <li>12-month treatment period</li> </ul>                                                                      | <ul style="list-style-type: none"> <li>N= 15; ages 5-21</li> <li>Open-label, single-arm</li> <li>20 mg/kg apitegromab IV Q4W</li> <li>12-month treatment period</li> </ul> | <ul style="list-style-type: none"> <li>N= 20; ages <math>\geq 2</math></li> <li>Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg apitegromab IV Q4W</li> <li>12-month treatment period</li> </ul> |
| <b>Patients</b>           | <ul style="list-style-type: none"> <li>Ambulatory Type 3 SMA</li> <li>Two subgroups:                             <ol style="list-style-type: none"> <li>Receiving background nusinersen</li> <li>Apitegromab monotherapy</li> </ol> </li> </ul> | <ul style="list-style-type: none"> <li>Type 2 or non-ambulatory Type 3 SMA</li> <li>Receiving background nusinersen</li> </ul>                                             | <ul style="list-style-type: none"> <li>Type 2 SMA</li> <li>Receiving background nusinersen (initiated before age 5)</li> </ul>                                                                         |
| <b>Primary Objectives</b> | <ul style="list-style-type: none"> <li>Safety</li> <li>Mean change from baseline in RHS</li> </ul>                                                                                                                                              | <ul style="list-style-type: none"> <li>Safety</li> <li>Mean change from baseline in HFMSE</li> </ul>                                                                       | <ul style="list-style-type: none"> <li>Safety</li> <li>Mean change from baseline in HFMSE</li> </ul>                                                                                                   |

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

# Baseline Characteristics



|                                        | 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

# TOPAZ Interim Analysis Results Demonstrate Proof-of-Concept

*Multiple lines of evidence supporting the potential clinical effect of apitegromab*

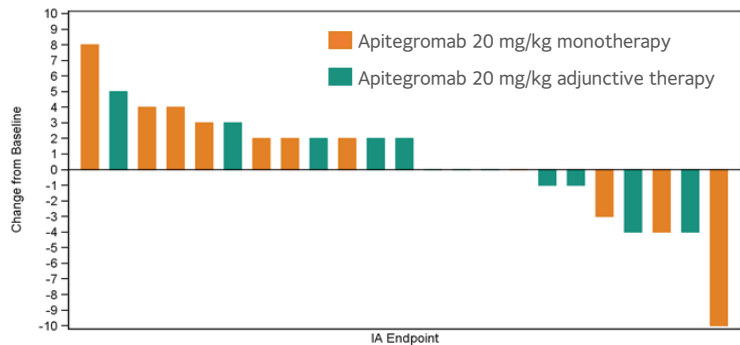
|                                                | Ambulatory Patients<br>(Revised Hammersmith Scale) |                                   |                                   | Non-Ambulatory Patients<br>(Hammersmith Functional Motor Scale Expanded) |                                 |                                  |
|------------------------------------------------|----------------------------------------------------|-----------------------------------|-----------------------------------|--------------------------------------------------------------------------|---------------------------------|----------------------------------|
|                                                | Cohort 1                                           |                                   |                                   | Cohort 2*                                                                | Cohort 3*                       |                                  |
|                                                | 20 mg/kg<br>pooled<br>(n=23)                       | 20 mg/kg<br>monotherapy<br>(n=11) | 20 mg/kg<br>+nusinersen<br>(n=12) | 20 mg/kg<br>+nusinersen<br>(n=14)                                        | 2 mg/kg<br>+nusinersen<br>(n=9) | 20 mg/kg<br>+nusinersen<br>(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 $\geq 1$ -pt increase | 12/23 (52%)                                        | 7/11 (64%)                        | 5/12 (42%)                        | 10/14 (71%)                                                              | 6/9 (67%)                       | 9/9 (100%)                       |
| # (%) patients achieving $\geq 3$ -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  $\geq 1$ -point improvement in Hammersmith scores
- ✓ **Substantial proportion of patients in each cohort attained  $\geq 3$ -point improvement in HFMSE/RHS**
  - High bar and uncommon to observe in any given patient
  - 35% of total patients achieved  $\geq 3$ -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

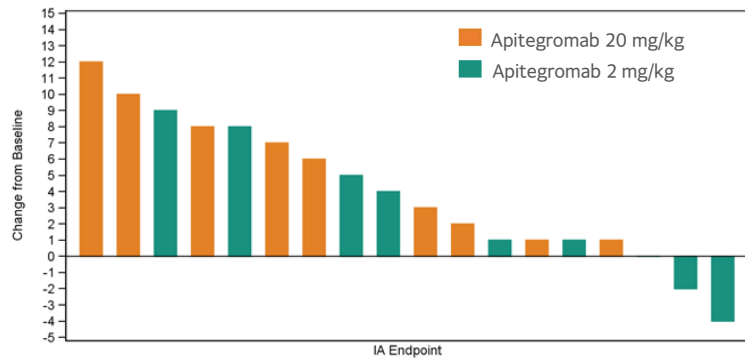
\*3 patients (1 in Cohort 2 and 2 in Cohort 3) each missed 3 doses of apitegromab and the 6-month interim analysis timepoint due to COVID-19-related site access restrictions; the six-month timepoint from these patients was not included in the interim analysis.  
Data on file. Scholar Rock, Inc. Cambridge,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

## Improvements in Hammersmith Scores Observed Across All 3 Cohorts

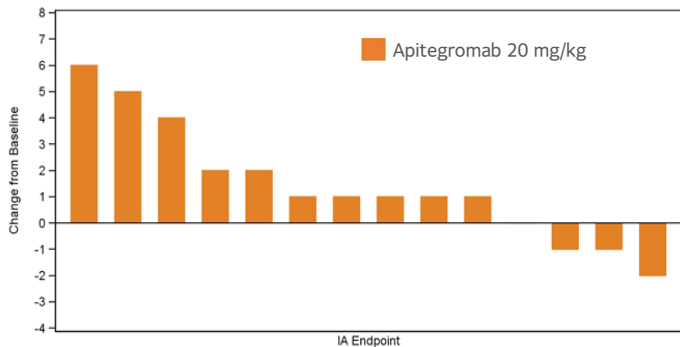
### Cohort 1 (ambulatory Type 3) individual RHS responses



### Cohort 3 (Type 2) individual HFMSE responses



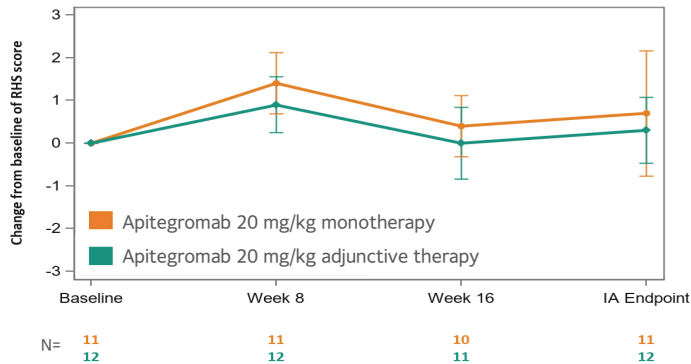
### Cohort 2 (Type 2 & non-amb. Type 3) individual HFMSE responses



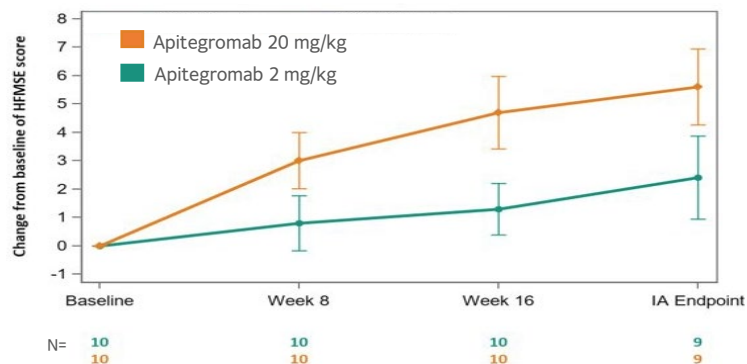
- Most patients experienced an improvement
  - 67% of total patients achieved  $\geq 1$ -pt increase in Hammersmith scores
- Dose response demonstrated in Cohort 3 (randomized, double-blind, parallel arm design)
  - High-dose arm showed greater improvements; supported by PK/PD results

# Effects on Hammersmith Scores Observed Through 6 Months of Treatment

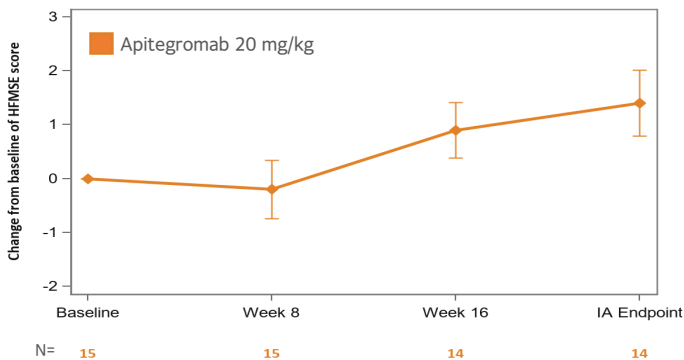
**Cohort 1: Mean ( $\pm$ SEM) change from baseline in RHS scores**



**Cohort 3: Mean ( $\pm$ SEM) change from baseline in HFMSE scores**



**Cohort 2: Mean ( $\pm$ SEM) change from baseline in HFMSE scores**



- 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%)     |

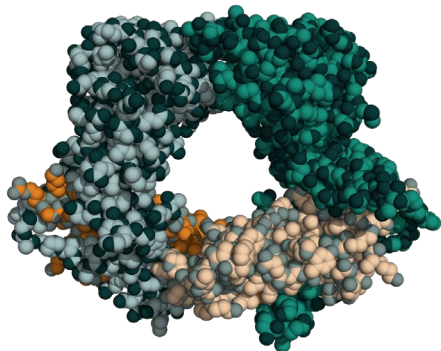
- **Five most frequently reported TEAEs:** Headache, upper respiratory tract infection, pyrexia, nasopharyngitis, and cough.
- **1 serious TEAE (Cohort 1):** Assessed by trial investigator as unrelated to apitegromab. Grade 2 viral upper respiratory infection (prior history) and was hospitalized. Event 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

# Unlocking the Potential of the Scholar Rock R&D Engine

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

**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

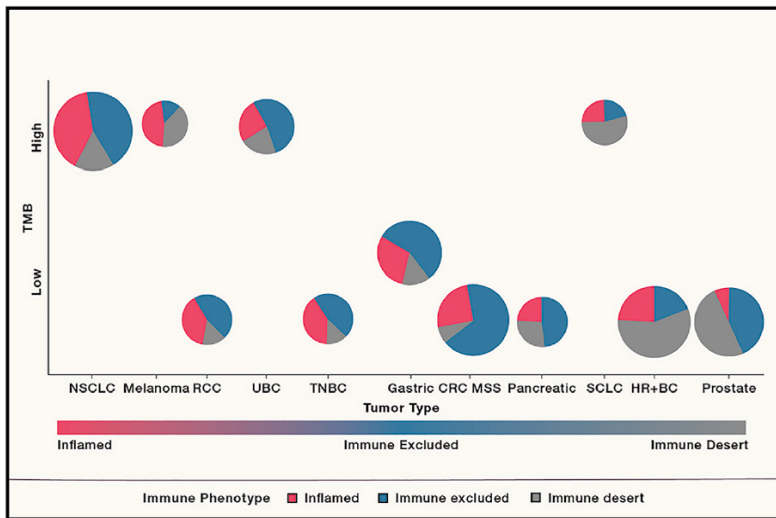
Rik Derynck<sup>1,2,3</sup>✉, Shannon J. Turley<sup>4</sup>✉ and Rosemary J. Akhurst<sup>5,6,7</sup>✉

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

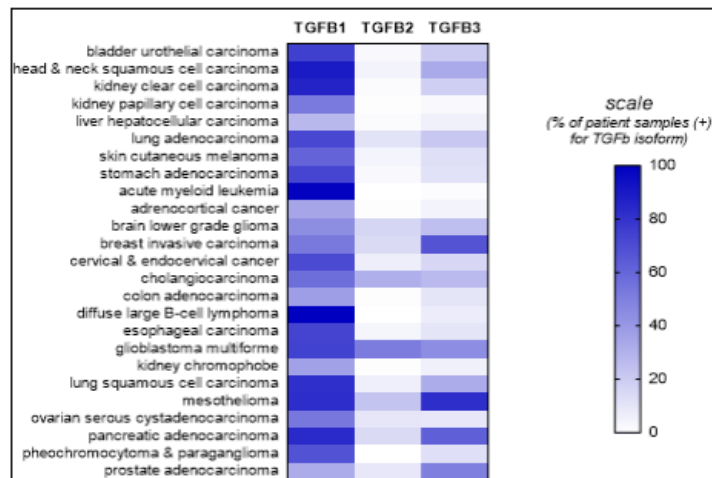
**August 2020:** *“Bristol Myers Squibb Enters Agreement to Acquire Forbius TGF-beta Program”*

# Emerging Evidence Implicates TGF $\beta$ 1 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\*



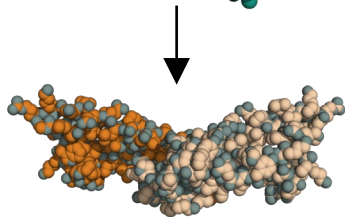
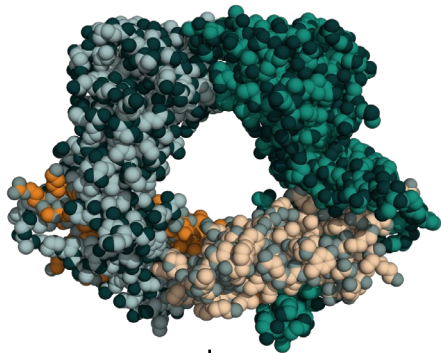
## Human Tumor Analyses Reveal TGF $\beta$ 1 as Most Likely Driver of TGF $\beta$ Signaling Pathway in Cancers

\*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>.

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

# SRK-181: Unique TGF $\beta$ 1-Selective Approach to Overcoming Checkpoint Inhibitor Resistance

## Scholar Rock's Target SRK-181: Latent TGF $\beta$ 1 Inhibitor



Traditional target:  
“Mature” growth factor

- ✓ Inhibits TGF $\beta$ 1 pathway - implicated in CPI resistance
- ✓ Highly selective targeting - avoids inhibiting latent TGF $\beta$ 2 and TGF $\beta$ 3 isoforms
- ✓ Aimed at increasing therapeutic window - potentially avoids toxicities associated with non-selective TGF $\beta$  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

# 2021: *Continued Execution and Advancements*

## *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

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

## Key Characteristics of Spinal Muscular Atrophy (SMA)

# 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

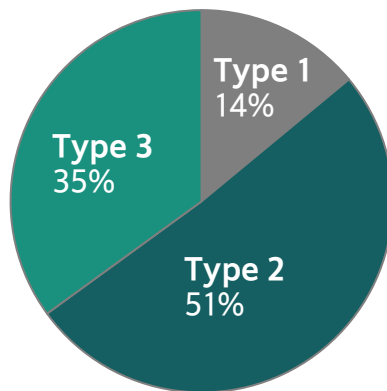
## *Type 2 and non-ambulatory Type 3:*

- 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*



*TOPAZ trial focuses on  
Type 2 and Type 3 SMA*

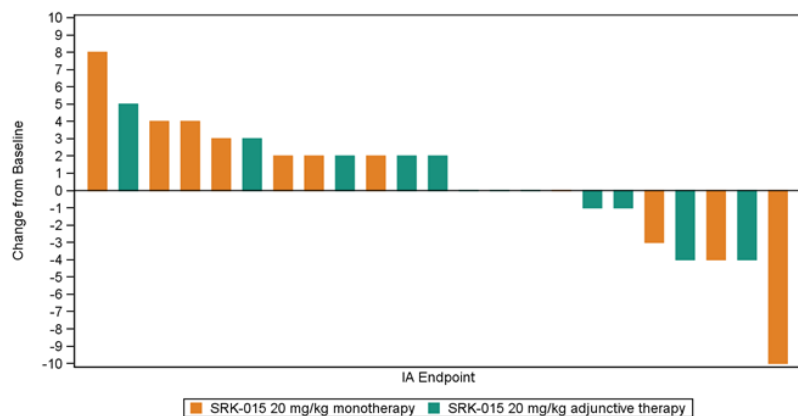
## *Unmet need would be served by a therapy that:*

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

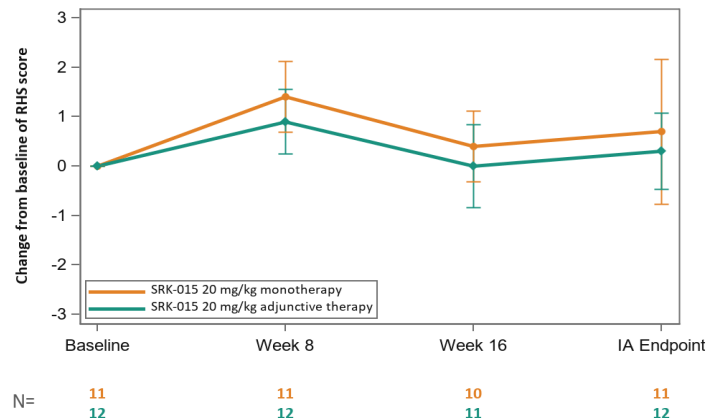
# Cohort 1: Improvement in RHS Observed with Both Apitegromab Monotherapy and as Add-on to Background Nusinersen

| 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 $\geq 1$ -pt increase in RHS | 12/23 (52%)                          | 7/11 (64%)                                | 5/12 (42%)                                |
| # (%) patients achieving $\geq 3$ -pt increase in RHS | 6/23 (26%)                           | 4/11 (36%)                                | 2/12 (17%)                                |
| # (%) patients achieving $\geq 5$ -pt increase in RHS | 2/23 (9%)                            | 1/11 (9%)                                 | 1/12 (8%)                                 |

**Individual RHS responses**



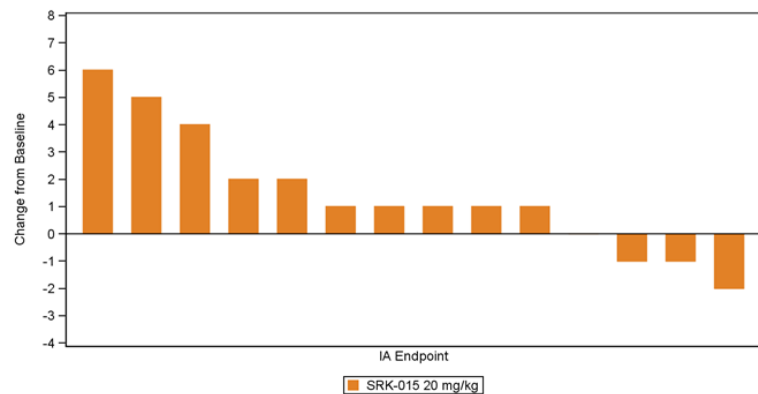
**Mean ( $\pm$ SEM) change from baseline in RHS scores**



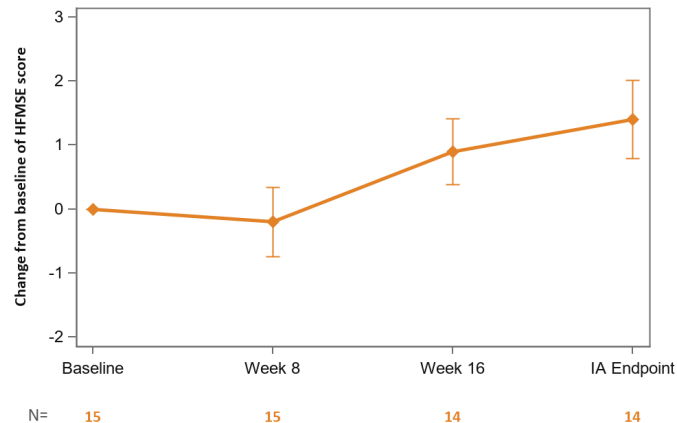
# Cohort 2: Meaningful and Consistent Improvements in HFMSE Observed in Type 2 and Non-Ambulatory Type 3 SMA

| 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 $\geq 1$ -pt increase in HFMSE | 10/14 (71%)                                |
| # (%) patients achieving $\geq 3$ -pt increase in HFMSE | 3/14 (21%)                                 |
| # (%) patients achieving $\geq 5$ -pt increase in HFMSE | 2/14 (14%)                                 |

## Individual HFMSE responses



## Mean ( $\pm$ SEM) change from baseline in HFMSE scores

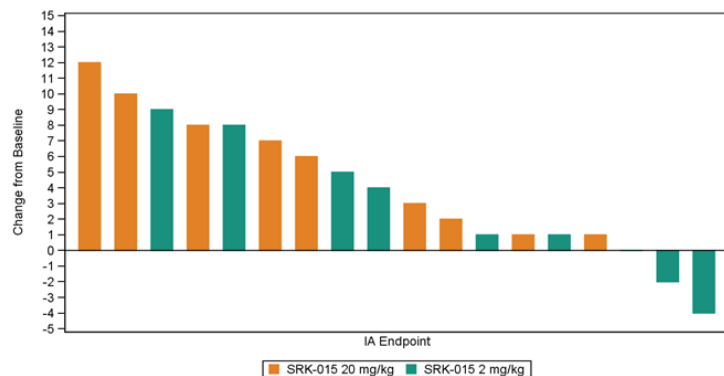


# Cohort 3: Apitegromab High Dose Showed Substantially Greater Improvements in HFMSE scores Than Low Dose

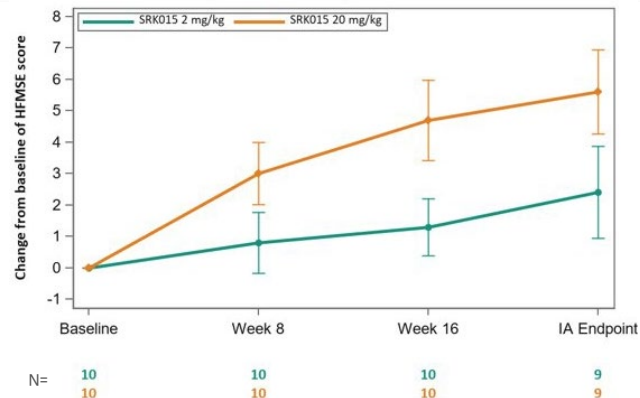
*Cohort 3 has a randomized, double-blind, parallel arm design embedded within TOPAZ*

| Type 2 SMA                                              | Apitegromab low dose (2 mg/kg)<br>+nusinersen (n=9) | Apitegromab high dose (20 mg/kg)<br>+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 $\geq 1$ -pt increase in HFMSE | 6/9 (67%)                                           | 9/9 (100%)                                            |
| # (%) patients achieving $\geq 3$ -pt increase in HFMSE | 4/9 (44%)                                           | 6/9 (67%)                                             |
| # (%) patients achieving $\geq 5$ -pt increase in HFMSE | 3/9 (33%)                                           | 5/9 (56%)                                             |

## Individual HFMSE responses

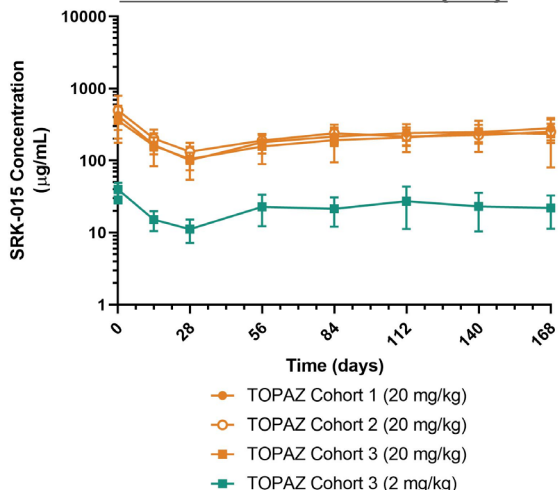


## Mean ( $\pm$ SEM) change from baseline in HFMSE scores



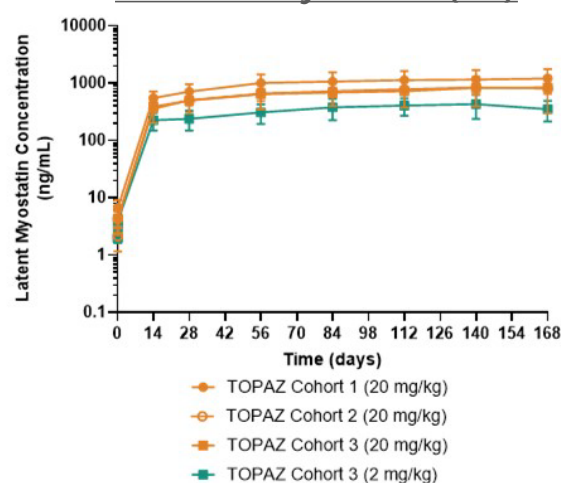
# Pharmacokinetic and Pharmacodynamic Data are Supportive of Clinically Observed Dose Response

## Pharmacokinetics\* (PK)



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

## Pharmacodynamics (PD)

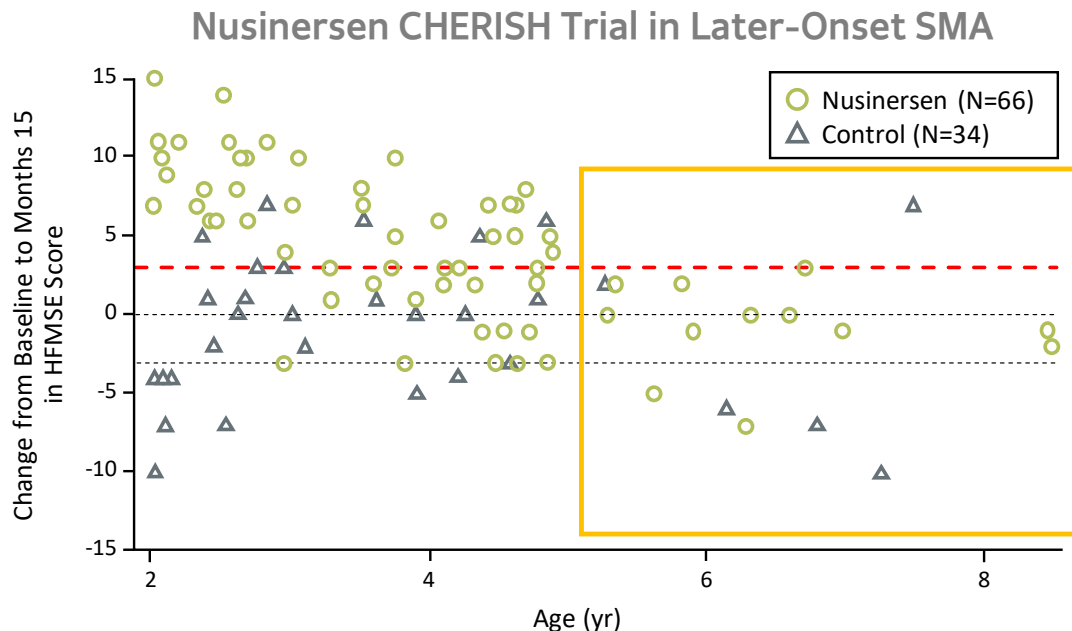


- Target engagement by apitegromab was confirmed
- Low dose (2 mg/kg) yielded lower level of target engagement and did not achieve full target saturation

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

## Later-Onset SMA: High Unmet Need to Improve Motor Function

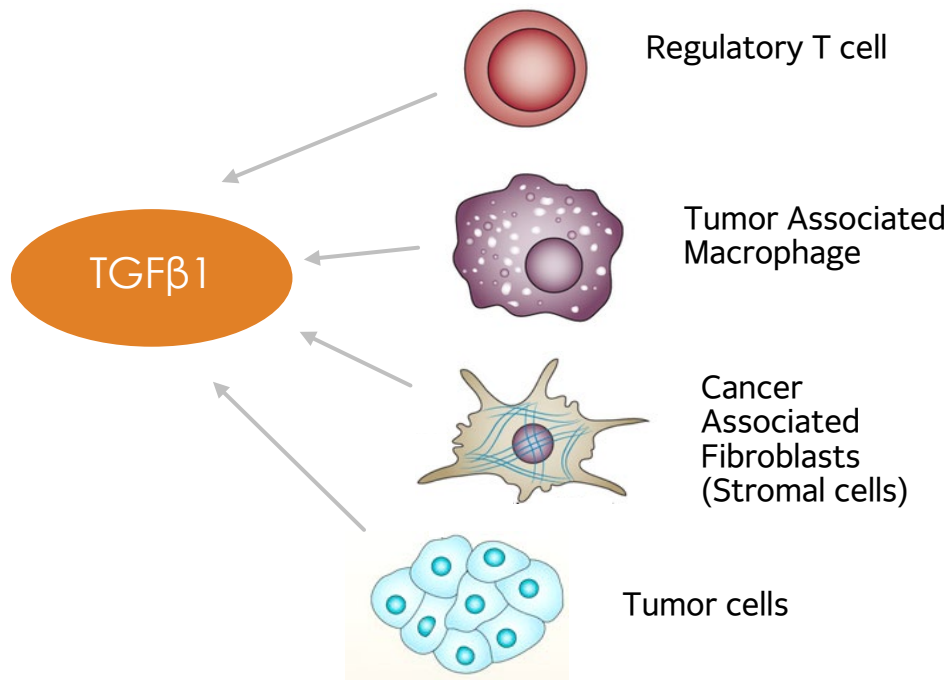


## In patients with later-onset SMA who were age $\geq 5$ at screening...

- Primary benefit of nusinersen appeared to be stabilization of motor function (in HFMSE) rather than improvement from baseline
- Attainment of  $\geq 3$ -point increase was rare (<15% of patients) even with nusinersen treatment

# Inhibition of TGF $\beta$ 1: Multipronged Approach for Immuno-Oncology

*TGF $\beta$ 1 is a key driver of immune system evasion by cancer cells*

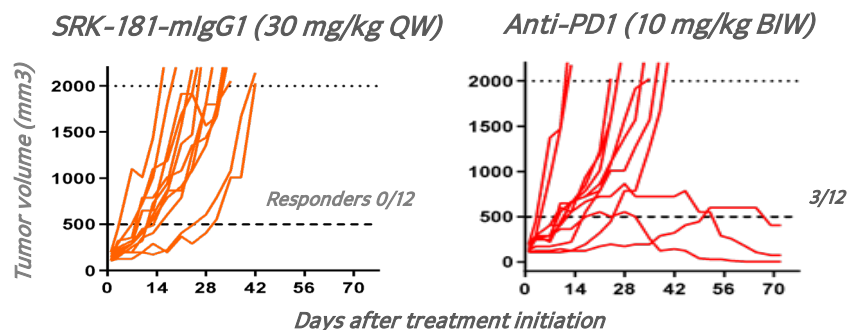


- Pathway analysis in patient tumors points to TGF $\beta$ 1 as major determinant of primary resistance to anti-PD-(L)1 therapy
- TGF $\beta$ 1 creates 'immune excluded' tumor microenvironment

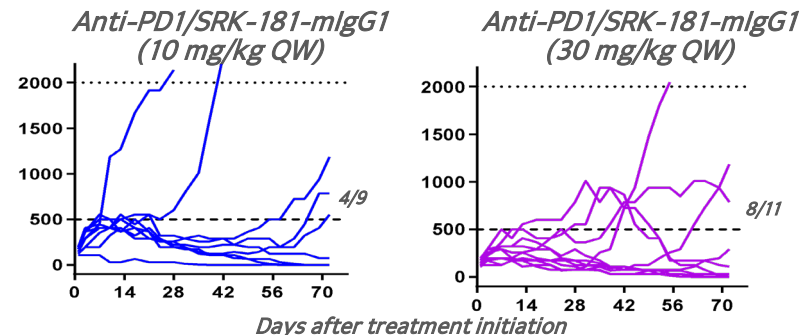
# TGF $\beta$ 1 Blockade with SRK-181-mIgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

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

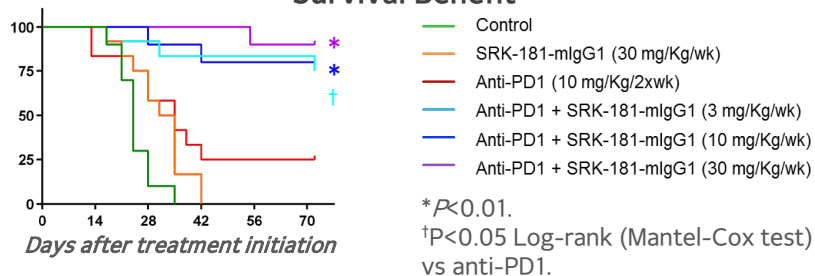
### Tumor Regression: Monotherapy



### Tumor Regression: Combination Therapy

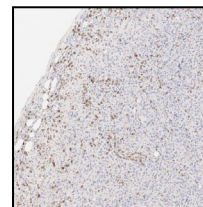


### Survival Benefit

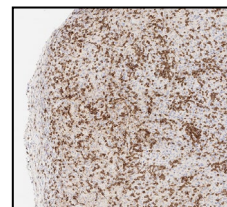


### Overcoming immune exclusion

Anti-PD1

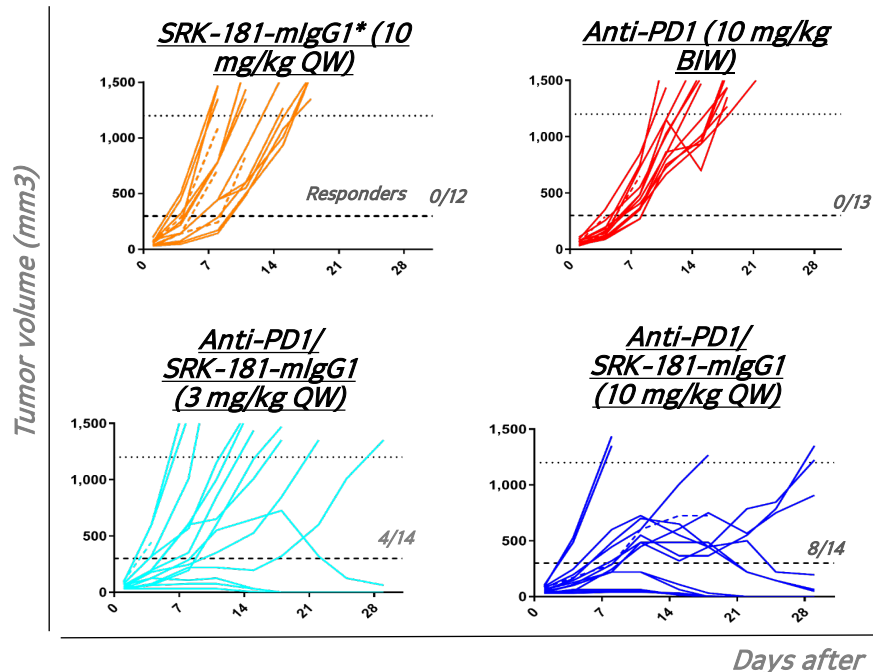


Anti-PD1/ SRK-181-mIgG1 led to influx of CD8+ cells in preclinical bladder tumor model

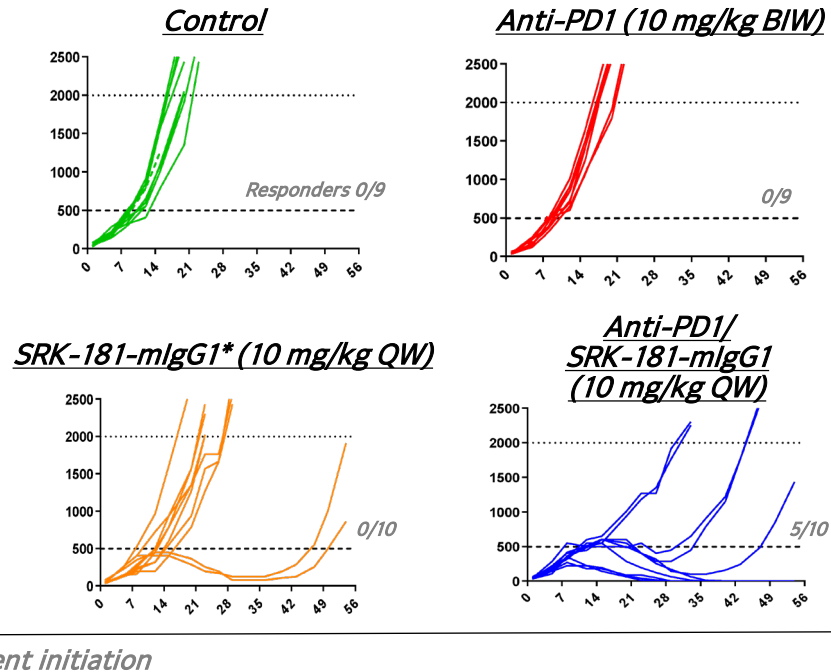


# TGF $\beta$ 1 Blockade with SRK-181-mIgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

## Bladder Cancer



## Breast Cancer (TGF $\beta$ 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.

# TGFβ1 Isoform Specificity of SRK-181 Improved Preclinical Toxicity Profile

| Microscopic observations in heart                   | Control     | LY2109761  | PanTGFβAb  | SRK-181     |             |             | LEGEND                                                                                   |
|-----------------------------------------------------|-------------|------------|------------|-------------|-------------|-------------|------------------------------------------------------------------------------------------|
| Valvulopathy                                        | Vehicle     | 300 mg/kg  | 30 mg/kg   | 10 mg/kg    | 30 mg/kg    | 100 mg/kg   | <div>□ Unremarkable</div> <div>■ Minimal</div> <div>■ Slight</div> <div>■ Moderate</div> |
| Atrium—Mixed cell infiltrate                        | iv, qwk x 4 | po, qd x 8 | iv, 1 dose | iv, qwk x 4 | iv, qwk x 4 | iv, qwk x 4 |                                                                                          |
| Myocardium—Degeneration/necrosis                    |             |            |            |             |             |             |                                                                                          |
| 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 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

### 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

# 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

\* Planning to open eligibility to patients with history of primary resistance to either pembrolizumab or nivolumab NCT04291079 on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).