# Deep Insights, Impactful Medicines

November 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 apitegromab, SRK-181, and other product candidates and indication selection and development timing, its cash runway, the ability of any product candidate to perform in humans in a manner consistent with earlier nonclinical, preclinical or clinical trial data, and the potential of its product candidates and proprietary platform. The use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify such forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. All such forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include preclinical and clinical data, including the results from the Phase 2 trial of apitegromab or Part A of the Phase 1 trial of SRK-181, are not predictive of, are inconsistent with, or more favorable than, data generated from future clinical trials of the same product candidate, including the planned Phase 3 trial of apitegromab in SMA and Part B of the Phase 1 trial of SRK-181, respectively, Scholar Rock’s ability to provide the financial support, resources and expertise necessary to identify and develop product candidates on the expected timeline, the data generated from Scholar Rock’s nonclinical and preclinical studies and clinical trials, information provided or decisions made by regulatory authorities, competition from third parties that are developing products for similar uses, Scholar Rock’s ability to obtain, maintain and protect its intellectual property, the success of Scholar Rock’s current and potential future collaborations, including its collaboration with Gilead, Scholar Rock’s dependence on third parties for development and manufacture of product candidates including to supply any clinical trials, 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, and the impacts of public health pandemics such as COVID-19 on business operations and expectations, as well as those risks more fully discussed in the section entitled "Risk Factors" in Scholar Rock’s Quarterly Report on Form 10-Q for the quarter ended September 30, 2021, 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. All information in this press release is as of the date of the release, and Scholar Rock undertakes no duty to update this information unless required by law.



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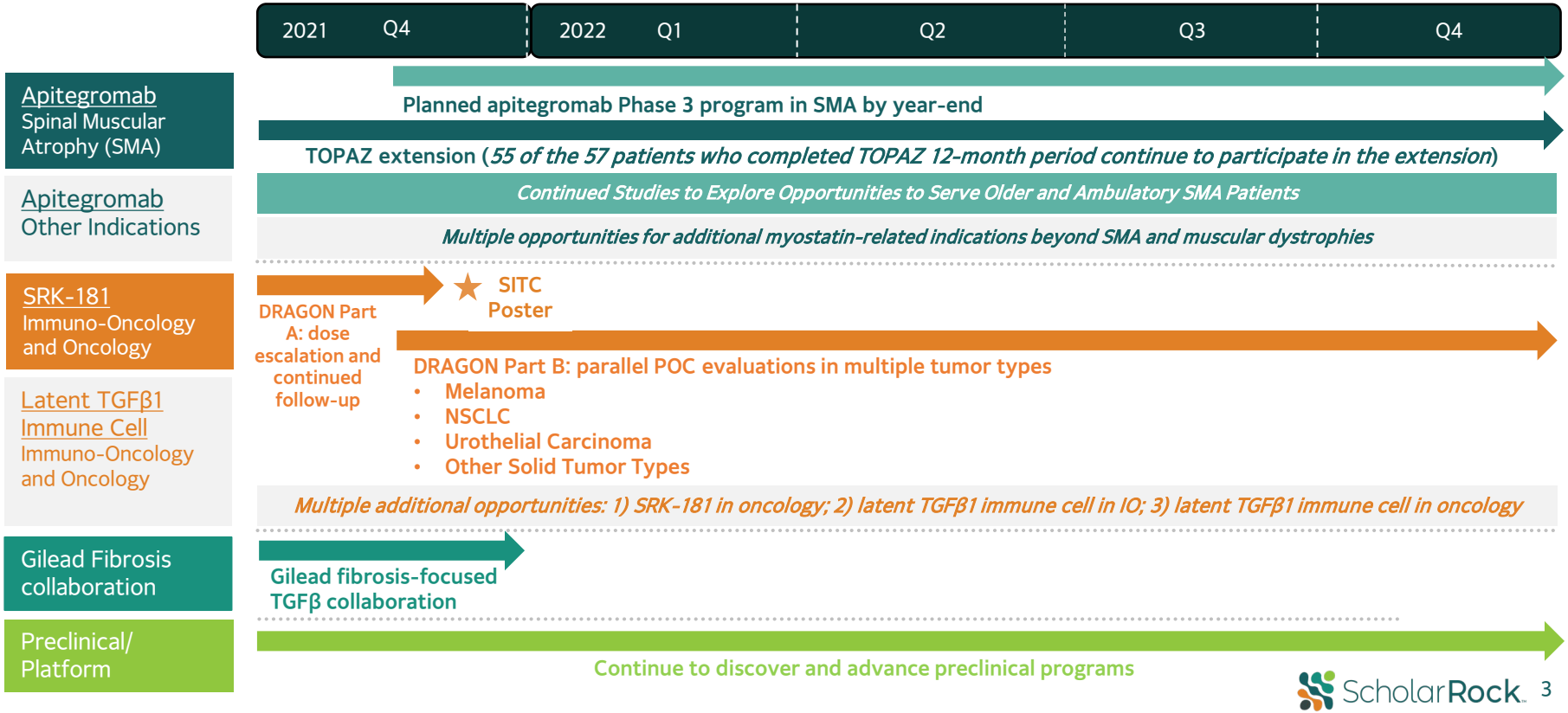
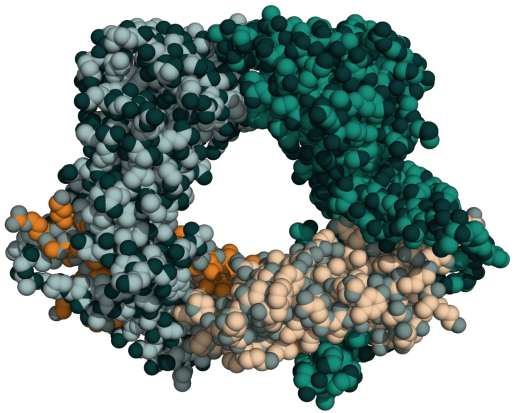
# 2021 Momentum to Carry into 2022 Across Portfolio



# 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 to deliver differentiated therapeutic profiles (i.e. exquisite selectivity)

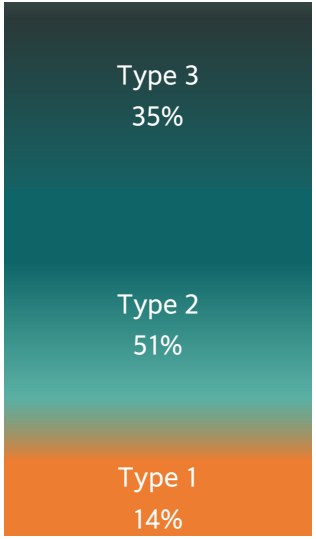
**TOPAZ demonstrated the therapeutic potential of inhibiting the latent forms of growth factors**

# Apitegromab Positioned to be Next Potential Transformative Therapy for Patients with SMA

# Spinal Muscular Atrophy Overview

**Global disease with 30,000-35,000 affected in U.S. and Europe alone**

- Significant, progressive motor function impairment; many lose ambulation
- Severe, progressive disabilities and unable to walk independently
- Infantile onset; unable to sit up independently




TOPAZ* 12-month results showed transformative potential in non-ambulatory Type 2 and 3 patients

Represents ~2/3 of overall patient population

**Motor neuron impairment and loss due to SMN genetic deficiency, leading to muscle atrophy and weakness**

**TOPAZ Phase 2 trial evaluated patients with Type 2 and 3 SMA (did not include Type 1)*
*Lallyet al, OrphanetJournal of Rare Diseases, 2017*

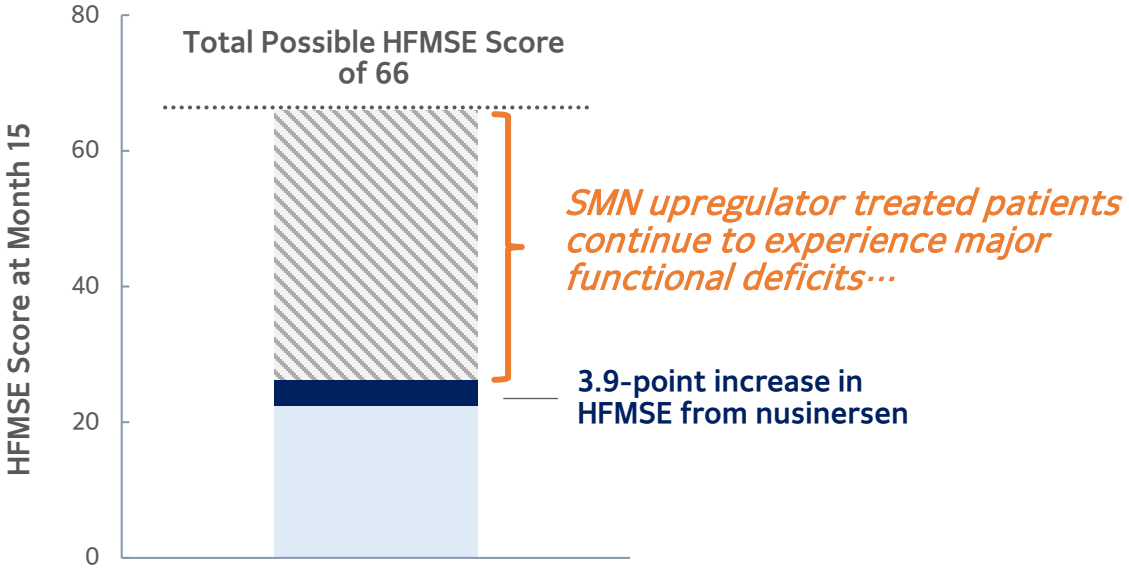
# Potential to Pioneer a New Treatment Era: Opportunity for Muscle-Directed Therapy to Complement SMN Upregulators

| | SPINRAZA® (nusinersen) injection 12 mg/5 mL | Evrysdi™ risdiplam 60 mg powder for oral solution | zolgensma® (onasemnogene abeparvovec-xioi) suspension for intravenous infusion |
|---|---|---|---|
| Phase 3 Trial Design | • Non-ambulatory Type 2/3<br>• 2-12 years of age<br>• **Primary endpoint:** Mean change from baseline in HFMSE at 15 months | • Non-ambulatory Type 2/3<br>• 2-25 years of age<br>• **Primary endpoint:** Mean change from baseline in MFM-32 at 12 months | • Infantile-onset Type 1<br>• <6 months of age<br>• **Primary endpoints:** Ability to sit independently and event-free survival |
| Indication | • Type 1, 2, and 3 SMA in pediatric and adult patients | • Type 1, 2, 3 SMA in patients 2 months of age and older | • SMA in patients less than 2 years of age |
| Market Penetration | • >11,000* patients treated WW<br>• $2+ billion in revenues (LTM) | • ~4,000** patients treated WW<br>• ~CHF243 million in revenues (1H21) | • ~1,200*** patients treated WW<br>• ~$1.2 billion in revenues (LTM) |

**Patients continue to experience major functional impairments despite utilization of SMN upregulators**

*As of Biogen 2Q21 financial update on 7/22/21; includes patients treated worldwide in post-marketing setting, expanded access program, and clinical trials.
**As of Roche 1H21 financial update on 7/22/21; includes patients treated worldwide between clinical trials, commercial, and compassionate use program.
***As of Novartis 2Q21 financial update on 7/21/21; commercially, via managed access programs and in clinical trials
HFMSE = Hammersmith Functional Motor Scale Expanded; MFM-32 = Motor Function Measure – 32 items

# Patients with Type 2 and 3 SMA Continue to Experience Major Functional Deficits Despite Improvement from Nusinersen

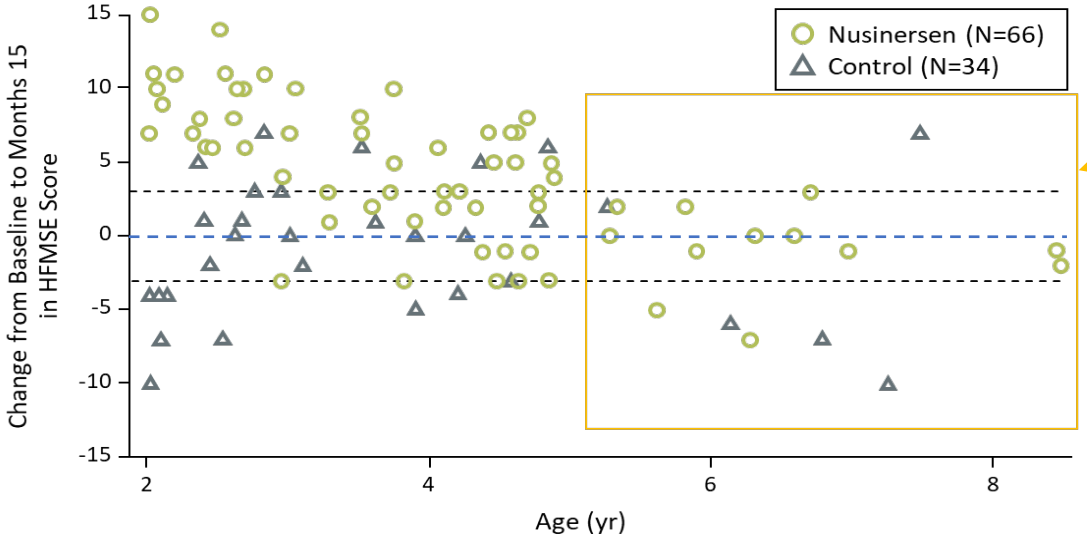



*Mean improvement in HFMSE experienced by patients with non-ambulatory Type 2/3 SMA in nusinersen Phase 3 CHERISH trial*

Darras, B., et.al. Nusinersen in later-onset spinal muscular atrophy. *Neurology.* May 2019; 92 (21) e2492-e2506.
This third-party information is provided for background only and is not intended to convey or imply a comparison to the TOPAZ clinical trial results.

# Nusinersen Does Not Increase HFMSE on Average in Children Who Initiate Treatment After the Age of 5 Years

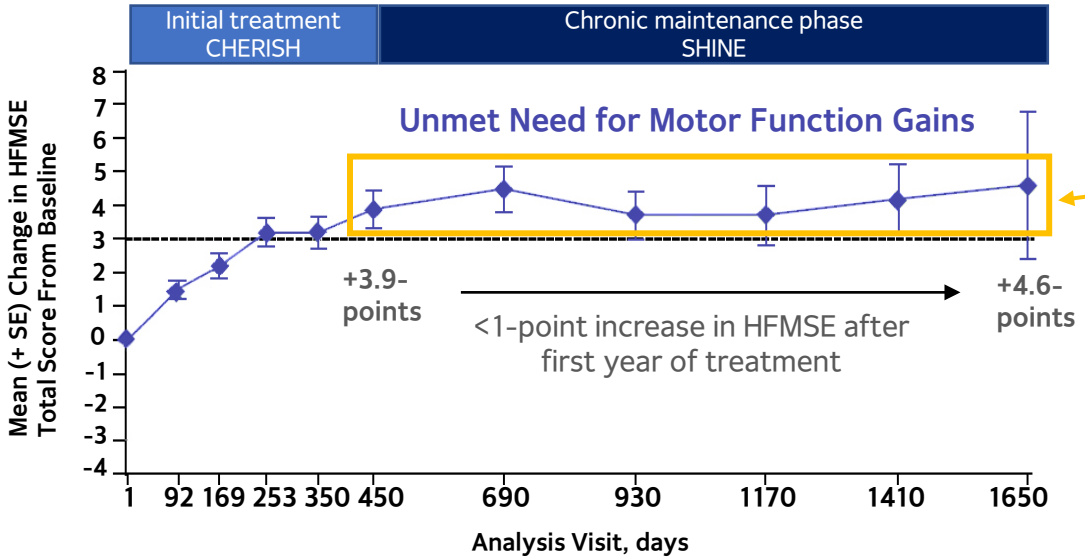
## CHERISH Trial in Non-Ambulatory Type 2/3 SMA†




Majority of patients treated with nusinersen after the age of 5 did not observe an improvement

†Mercuri E, et.al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018;378:625-635.
This third-party information is provided for background only and is not intended to convey or imply a comparison to the TOPAZ clinical trial results.

# Plateauing of HFMSE Increases Observed After First 15 Months of Nusinersen Treatment in Type 2 and 3 SMA



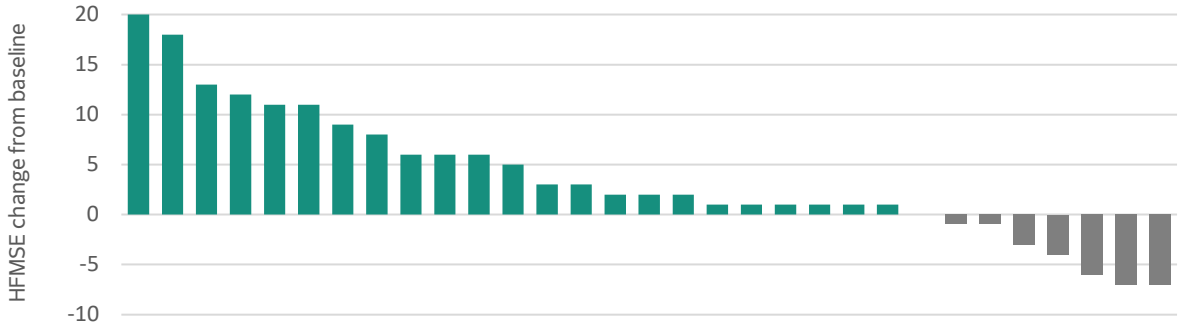

Nusinersen observed plateauing of improvement during chronic maintenance phase…

Most nusinersen-treated patients in CHERISH were <5 years of age at therapy initiation

"Longer-term treatment with nusinersen: results in later-onset spinal muscular atrophy from the SHINE study" P.257, World Muscle Society Congress 2020
This third-party information is provided for background only and is not intended to convey or imply a comparison to the TOPAZ clinical trial results.

# TOPAZ Top-Line Data Showed Apitegromab's Transformative Potential in Patients with Type 2/3 SMA

✓ **Majority of non-ambulatory patients observed a clinical improvement in HFMSE***




✓ **Apitegromab treatment (as add-on to background nusinersen) led to improvements in HFMSE in both non-ambulatory cohorts**

| At 12 months | Mean HFMSE increase | ≥1-point increase | ≥3-point increase |
|---|---|---|---|
| Initiated background nusinersen age <5** | +7.1 points | 88% (7/8) of patients | 63% (5/8) of patients |
| Initiated background nusinersen age ≥5 | +0.6 points | 64% (9/14) of patients | 29% (4/14) of patients |

** Pooled cohorts of non-ambulatory patients treated with apitegromab 20 mg/kg and 2 mg/kg*
***Non-ambulatory patients who initiated background nusinersen at a young age of <5 years and treated with apitegromab 20 mg/kg dose*

# Non-Ambulatory Type 2 Cohort:
## Initiated nusinersen age <5

| Apitegromab (20 mg/kg) + nusinersen | n=8 |
|---|---|
| Mean change from baseline in HFMSE (95% CI) | +7.1 (1.8, 12.5) |
| # (%) patients achieving: | |
| ≥1-pt increase in HFMSE | 7/8 (88%) |
| ≥3-pt increase in HFMSE | 5/8 (63%) |
| ≥5-pt increase in HFMSE | 5/8 (63%) |
| Baseline characteristics: mean (min, max) | n=10 |
| Age | 3.8 (2, 6) |
| HFMSE score | 23.5 (14, 42) |
| # of nusinersen maintenance doses | 5.4 (3, 8) |

Sizable increases in HFMSE observed in patients already treated with chronic maintenance nusinersen

- 88% (7/8) improved
- 63% (5/8) with ≥5-point increase
- 38% (3/8) with >10-point increase
- Continuous and durable improvements observed through 12-months of treatment

*Data on file. Scholar Rock, Inc. Cambridge, MA*

# Non-Ambulatory Type 2/3 Cohort:
## Initiated nusinersen age ≥5

TOPAZ

| Apitegromab (20 mg/kg) + nusinersen | Per Protocol Population* (n=13) | Intent-to-Treat Population (n=14) |
|---|---|---|
| Mean change from baseline in HFMSE (95% CI) | +1.2 (-0.5, 2.9) | +0.6 (-1.4, 2.7) |
| # (%) patients achieving: | | |
| ≥1-pt increase in HFMSE | 9/13 (69%) | 9/14 (64%) |
| ≥3-pt increase in HFMSE | 4/13 (31%) | 4/14 (29%) |
| ≥5-pt increase in HFMSE | 2/13 (15%) | 2/14 (14%) |
| Baseline characteristics: mean (min, max) | n=15 | |
| Age | 11.7 (8, 19) | |
| HFMSE score | 22.7 (13, 39) | |
| # of nusinersen maintenance doses | 5.1 (2, 9) | |

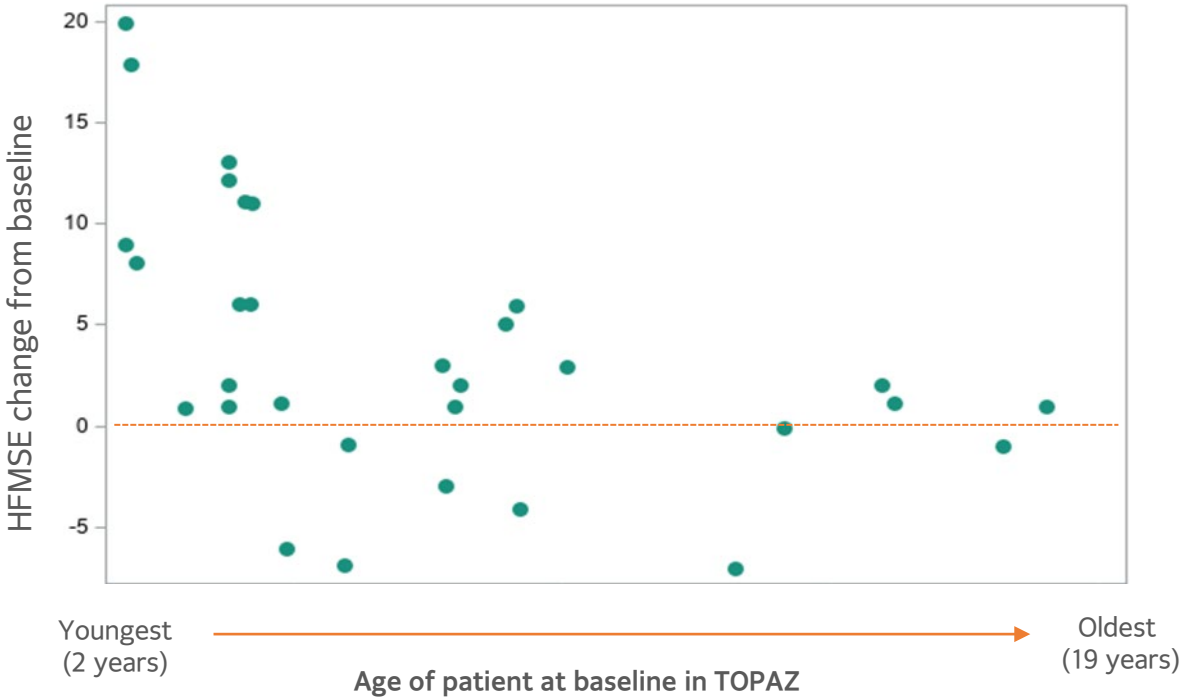
Majority of patients improved in HFMSE (despite initiating background nusinersen age ≥5)

- ~2/3 with ≥1-point increase
- ~30% with ≥3-point increase
- Durability of effect observed through 12-months of treatment

**Patient had concomitant exposure to an acetylcholinesterase inhibitor, which was not permitted per the TOPAZ trial protocol*

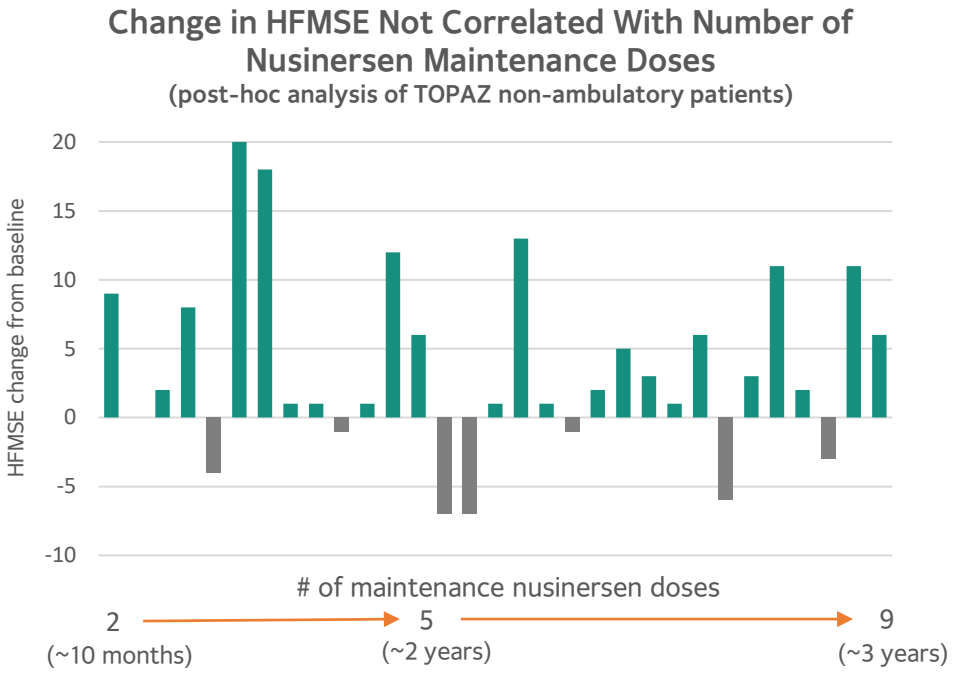
*Data on file. Scholar Rock, Inc. Cambridge, MA*

# HFMSE Improvements Observed Across Age Range of Non-Ambulatory Patients with Relatively Larger Gains from Earlier Treatment




**Pooled cohorts of non-ambulatory patients treated with apitegromab 20 mg/kg and 2 mg/kg; excludes 4 patients who each missed 3 doses of apitegromab due to COVID-19-related site access restrictions and were not included in the primary (intent-to-treat) analysis.*
*Data on file. Scholar Rock, Inc. Cambridge, MA*

# Increases in HFMSE Not Correlated with Duration of Prior Nusinersen Treatment




## Further data suggesting increases in HFMSE may be attributable to apitegromab

- No correlation between duration of prior nusinersen treatment and change in HFMSE
- Patients in TOPAZ were already in chronic maintenance phase of nusinersen (mean of ~2 years at enrollment)

*Data on file. Scholar Rock, Inc. Cambridge, MA*

# WHO Motor Development Milestone Achievements Further Support Apitegromab's Potential to Improve Motor Function

| Non-ambulatory Type 2/3 Patients | Pooled | Initiated nusinersen age <5 | Initiated nusinersen age ≥5 |
|---|---|---|---|
| # of patients gaining ≥1 WHO motor milestone(s) | 7/35 | 4/20 | 3/15 |

*Following 12 months of apitegromab treatment…*

Sitting without support

Hands & knees crawling

Standing with assistance

Walking with assistance

Standing alone

Walking alone

WHO motor milestone analysis included all patients who completed the 12-month treatment period, including 4 patients who missed 3 doses of apitegromab due to COVID-19-related site access restrictions. Median baseline score for both non-ambulatory cohorts was 1.0.

1 patient (initiated nusinersen age ≥5) gained 2 new motor milestones and 1 patient (initiated nusinersen age <5, 20 mg/kg) gained 3 new motor milestones

*Pictures are not of patients with SMA and are not meant to be representative of patients with SMA. Data on file. Scholar Rock, Inc. Cambridge, MA.*

# Safety Results from TOPAZ 12-Month Top-Line Analysis Support Evaluation of Apitegromab in Phase 3 Trial

| Treatment-emergent adverse events (TEAEs) | Apitegromab 2 mg/kg (n=10) | Apitegromab 20 mg/kg (n=48) | Total (n=58) |
|---|---|---|---|
| Any TEAE | 9 (90.0%) | 44 (91.7%) | 53 (91.4%) |
| Any Serious TEAE | 1 (10.0%) | 4 (8.3%) | 5 (8.6%) |
| 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%) | 3 (6.2%) | 3 (5.2%) |

- **Five most frequently reported TEAEs*:** Headache (24%), pyrexia (22%), upper respiratory tract infection (22%), cough (22%), and nasopharyngitis (21%).
- SAEs, Grade 3 AEs and AE leading to early study discontinuation were all assessed by investigators as unrelated to study drug
- **Anti-drug antibodies (ADA)** were present at low titers following apitegromab treatment in 3 out of 58 enrolled patients. No apparent impact on drug exposure was observed and was not associated with any hypersensitivity reactions.

**Incidence and severity of AEs were consistent with the 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.*
**TEAE rates are across all patients in TOPAZ trial*
*Data on file. Scholar Rock, Inc. Cambridge, MA*

# Preliminary Thoughts on Apitegromab Phase 3 Trial Design

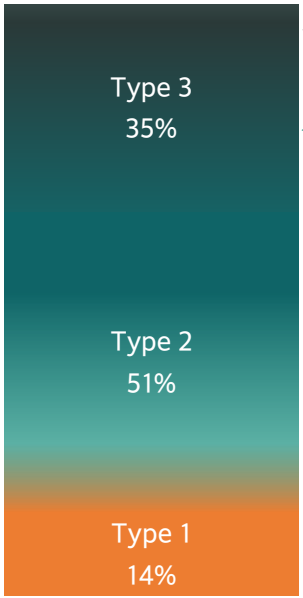
Apitegromab recently received Fast Track (FDA) and PRIME (EMA) designations, recognizing unmet medical needs in SMA

*Phase 3 trial design subject to regulator interactions and feedback*

| | |
|---|---|
| **Design** | • Randomized, double-blind, placebo-controlled<br>• 12-month treatment period<br>• Apitegromab IV Q4W as add-on to nusinersen or risdiplam<br>• TOPAZ data support investigation of up to 20 mg/kg |
| **Subjects** | • Non-ambulatory Type 2 and Type 3 SMA<br>• Pediatric population in chronic maintenance phase of SMN therapy |
| **Key Objectives** | • HFMSE<br>• Safety |
| **Timeline** | • Aim to initiate by end of 2021 |

# Additional Opportunities May Be Pursued With Separate Development Strategies

**Global disease with 30,000-35,000 affected in U.S. and Europe alone**




C

Ambulatory patients

- Smaller population but high unmet need as benefits of SMN regulators not well-established
- TOPAZ suggests potential clinical benefit in a subset of patients

A

Apitegromab in non-ambulatory Type 2 and 3 with background SMN upregulators

- Represents 2/3 of overall patients
- Patients already treated with or eligible for SMN upregulator therapy
- Improvements in motor function on top of SMN upregulators observed in TOPAZ

B

Type 1 patients, including those treated with gene therapy

- Highest incidence population and growing prevalence due to SMN upregulator treatment
- TOPAZ showed benefits of early treatment suggesting potential in Type 1 patients

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

# 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 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]

Article

*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

**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

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]✉*

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

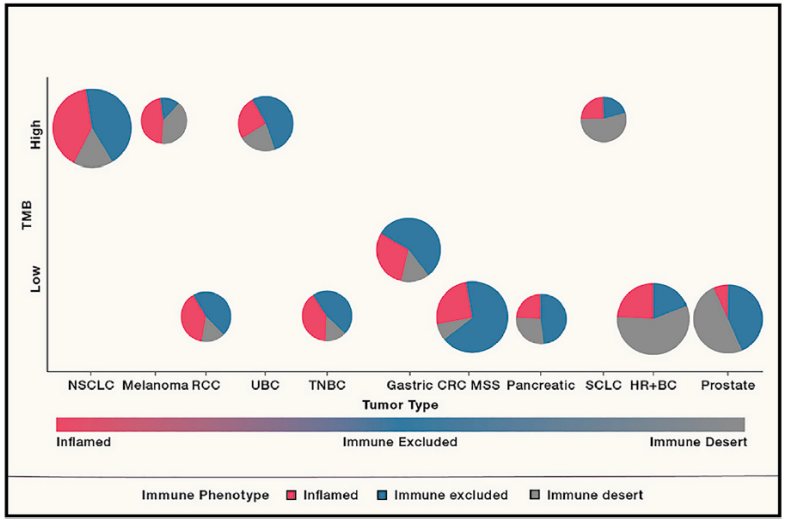
**June 2019:** *"Merck to Acquire Tilos Therapeutics: Merck Gains Portfolio of Investigational Antibodies Modulating TGFβ"*

- $773 million total potential deal value

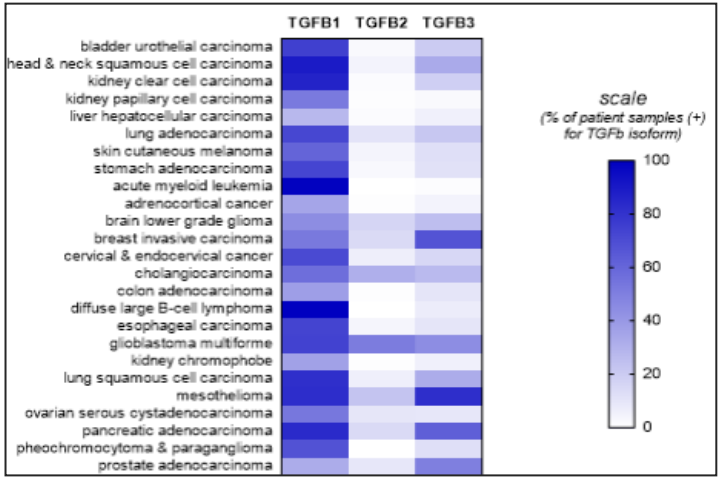
**August 2020:** *"Bristol Myers Squibb Enters Agreement to Acquire Forbius TGF-beta Program"*

# 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*

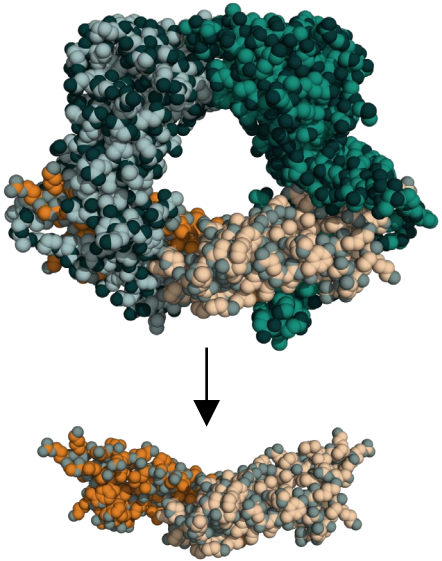



## Human Tumor Analyses Reveal TGFβ1 as Most Likely Driver of TGFβ Signaling Pathway in Cancers

†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 TGFβ1-Selective Approach to Overcoming Checkpoint Inhibitor Resistance

## Scholar Rock's Target
### SRK-181: Latent TGFβ1 Inhibitor



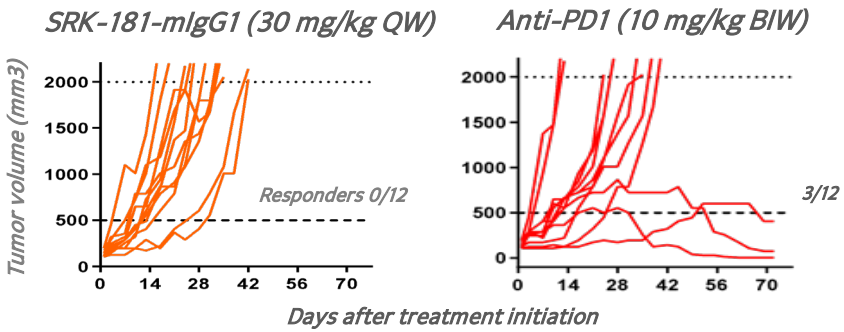
**Traditional target:**
"Mature" growth factor

- ✓ **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

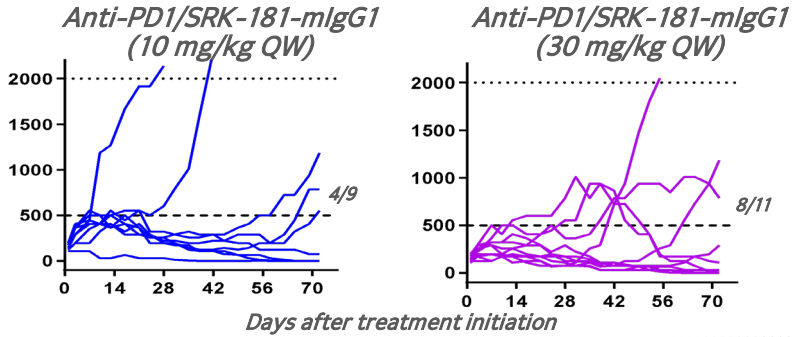
# TGFβ1 Blockade with SRK-181-mIgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

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

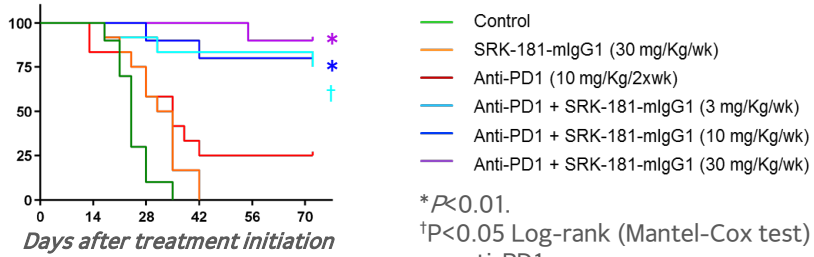
### Tumor Regression: Monotherapy




### Tumor Regression: Combination Therapy



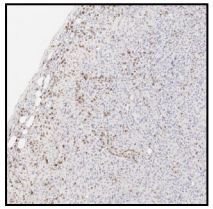

### Survival Benefit



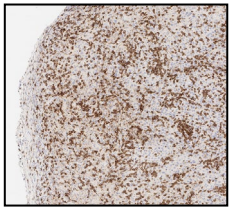

*$P$<0.01.
†P<0.05 Log-rank (Mantel-Cox test) vs anti-PD1.

### *Overcoming immune exclusion*

Anti-PD1



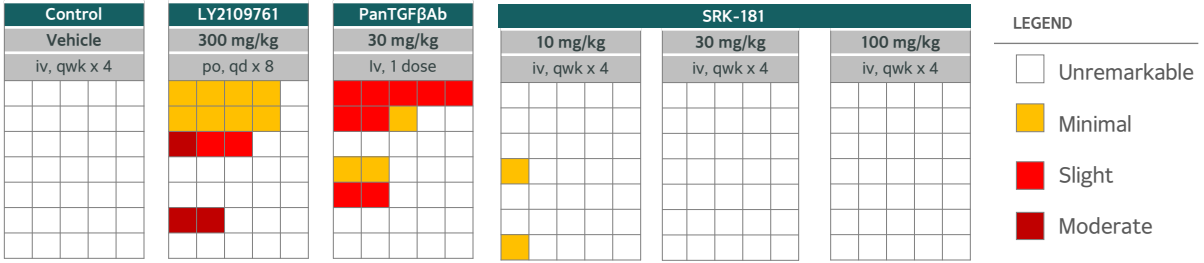
Anti-PD1/ SRK-181-mIgG1 led to influx of CD8+ cells in preclinical bladder tumor model



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.

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

| Microscopic observations in heart |
|---|
| Valvulopathy |
| Atrium—Mixed cell infiltrate |
| 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**

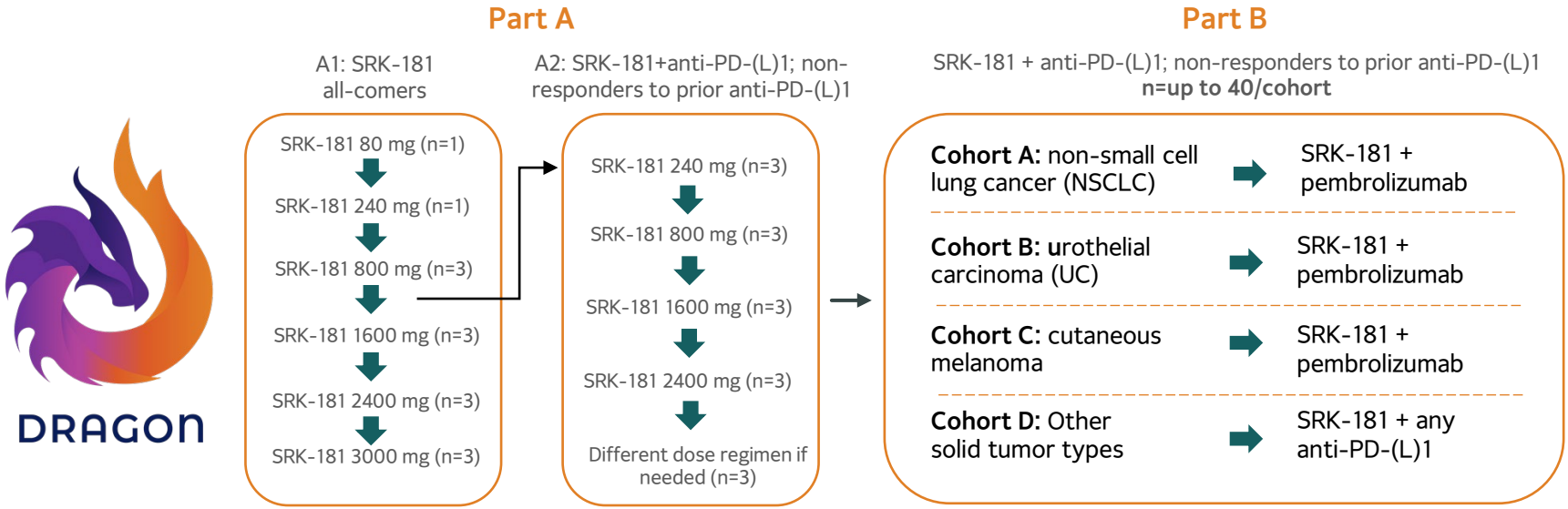
Preclinical data published in *Science Translational Medicine*. Martin CJ, et al. *Sci Transl Med* 2020 Mar 25;12(536): eaay8456.
*Source: Anderton MJ, et al. Induction of heart valve lesions by small-molecule ALK5 inhibitors. *Toxicol Pathol*. 2011;39: 916-924.; and Stauber AJ, et al. Nonclinical safety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

# SRK-181 Therapeutic Hypothesis: Potential Advantages of Latent TGFβ1 Inhibitor

| | SRK-181* | Bifunctional TGFβ/CPI | ALK5 Inhibitor | Nonselective TGFβ antibody |
|---|---|---|---|---|
| Selectivity for TGFβ1: potential for wider therapeutic window and improved safety | ✓ | X | X | X |
| Ability to combine with any anti-PD-(L)1 | ✓ | X | ✓ | ✓ |
| Ability to optimize dosing of each component of combination therapy | ✓ | X | ✓ | ✓ |
| Activity spatially distinct from anti-PD-(L)1 in tissue | ✓ | X | ✓ | ✓ |

SRK-181 is an investigational product candidate currently being evaluated in DRAGON phase 1 clinical trial. The efficacy and safety of SRK-181 have not been established.

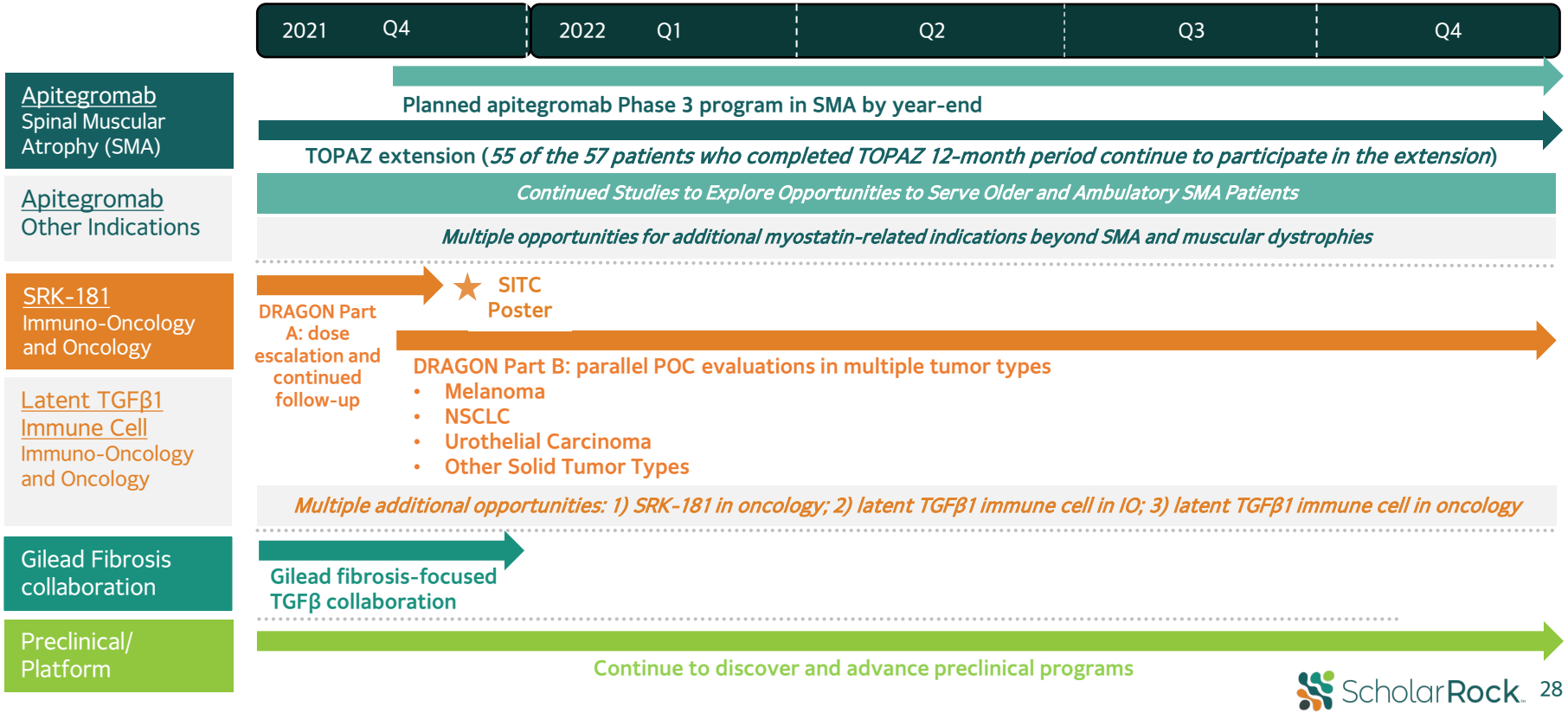
# DRAGON Phase 1 POC Trial to Evaluate SRK-181's Ability to Overcome Primary Resistance to Checkpoint Inhibitors




*Part B Initiated in October 2021*

NCT04291079 on www.clinicaltrials.gov.

# 2021 Momentum to Carry into 2022 Across Portfolio



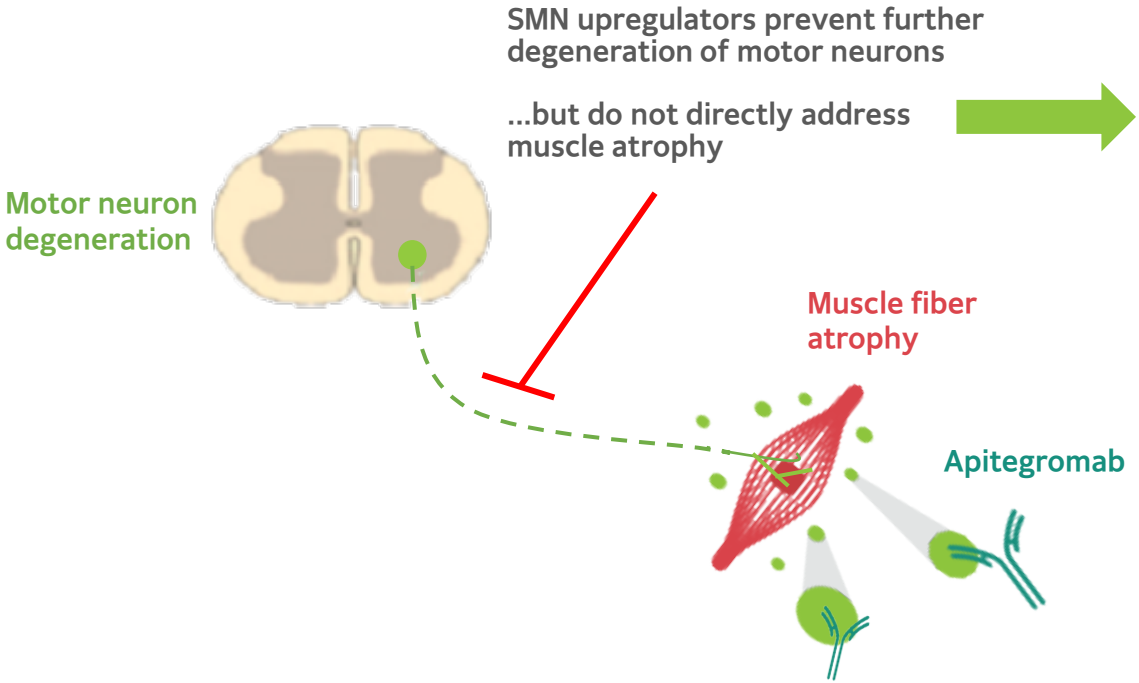
# Appendix

ScholarRock™

# 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) |
|---|---|
| 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 |

# Apitegromab: Muscle-Directed Therapy Aimed at Complementing SMN Upregulators

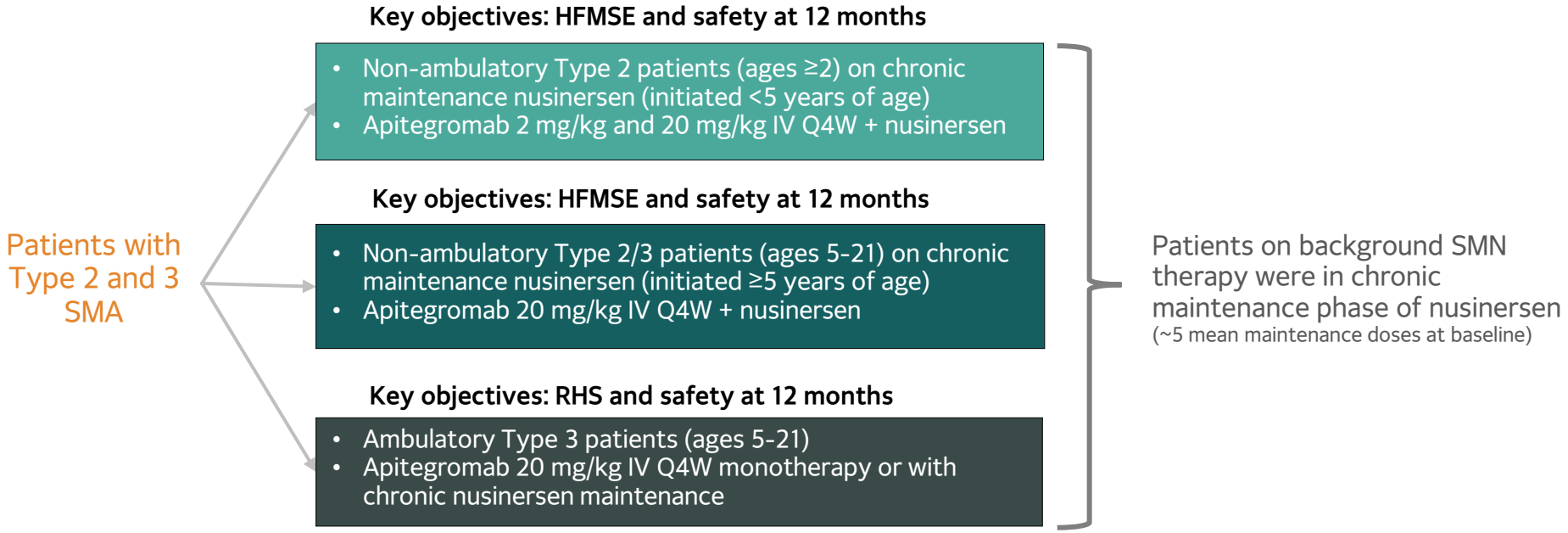



## Apitegromab is a muscle-directed approach aimed at improving motor function

- Myostatin is a negative regulator of skeletal muscle growth
- Apitegromab is a fully human, mAb that specifically binds to proforms of myostatin and inhibits myostatin activation

*Adapted from images courtesy of the SMA Foundation*

# Apitegromab Phase 2 Trial Design




**55 of the 57* patients who completed TOPAZ 12-month period continue to participate in the extension**

**Excludes one patient from Cohort 1 that discontinued from the trial*

# Baseline Characteristics

*Nusinersen-treated patients well into chronic maintenance phase*

TOPAZ

| | Non-Ambulatory, Ages ≥2 and initiated nusinersen <5 years | | | Non-Ambulatory, Ages 5-21 | Ambulatory, Ages 5-21 | | |
|---|---|---|---|---|---|---|---|
| | 20 mg/kg +nusinersen | 2 mg/kg +nusinersen | Pooled | 20 mg/kg +nusinersen | 20 mg/kg monotherapy | 20 mg/kg +nusinersen | Pooled |
| N | 10 | 10 | 20 | 15 | 11 | 12 | 23 |
| Mean age at baseline (min, max) | 3.8 (2, 6) | 4.1 (2, 6) | 4.0 (2, 6) | 11.7 (8, 19) | 12.1 (7, 19) | 13.1 (7, 21) | 12.6 (7, 21) |
| Mean RHS score (min, max) | | | | | 47.6 (26, 63) | 51.3 (43, 62) | 49.6 (26, 63) |
| Mean HFMSE score (min, max) | 23.5 (14, 42) | 26.1 (12, 44) | 24.8 (12, 44) | 22.7 (13, 39) | | | |
| **Mean # of nusinersen maintenance doses (min, max)** | **5.4 (3, 8)** | **5.5 (2, 9)** | **5.5 (2, 9)** | **5.1 (2, 9)** | **N/A** | **5.6 (2, 8)** | **N/A** |
| SMN2 Gene Copy* (#, %) | | | | | | | |
| 2 | 1 (10%) | 1 (10%) | 2 (10%) | | 1 (9%) | 0 (0%) | 1 (4%) |
| 3 | 8 (80%) | 8 (80%) | 16 (80%) | 11 (73%) | 4 (36%) | 9 (75%) | 13 (57%) |
| 4 | 0 (0%) | 1 (10%) | 1 (5%) | 2 (13%) | 4 (36%) | 1 (8%) | 5 (22%) |
| Discontinuation(s) | 0 | 0 | 0 | 0 | 0 | 1** | 1** |

*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*

# Majority of Ambulatory Patients Maintained or Improved in RHS Score from Baseline

| | Apitegromab 20 mg/kg monotherapy | Apitegromab 20 mg/kg + nusinersen |
|---|---|---|
| Mean change from baseline in RHS (95% CI) | -0.4 (-3.9, 3.1) | -0.3 (-2.0, 1.4) |
| # (%) patients achieving: | | |
| ≥0-pt increase in RHS | 6/11 (55%) | 7/12 (58%) |
| ≥1-pt increase in RHS | 4/11 (36%) | 5/12 (42%) |
| ≥3-pt increase in RHS | 3/11 (27%) | 2/12 (17%) |
| Baseline characteristics: mean (min, max) | n=11 | n=12 |
| Age | 12.1 (7, 19) | 13.1 (7, 21) |
| HFMSE score | 47.6 (26, 63) | 51.3 (43, 62) |
| # of nusinersen maintenance doses | n/a | 5.6 (2, 8) |

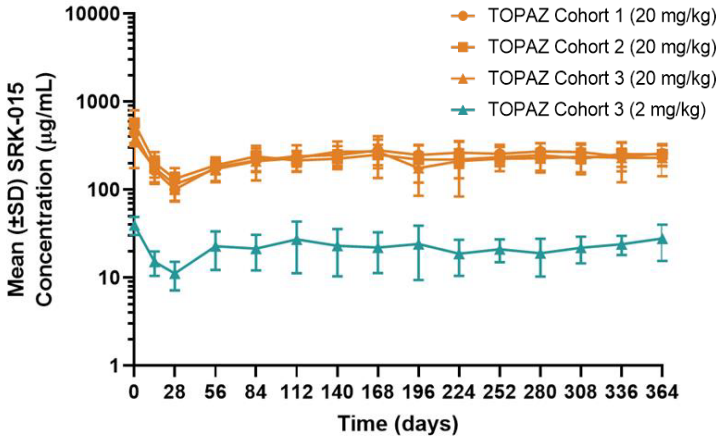
Majority maintained or improved

- 57% (13/23) with ≥0-point increase
- 39% (9/23) with ≥1-point increase
- Up to 8-point increase observed
- Results contrast with declines typically observed with natural history of ambulatory patients

*Data on file. Scholar Rock, Inc. Cambridge, MA*

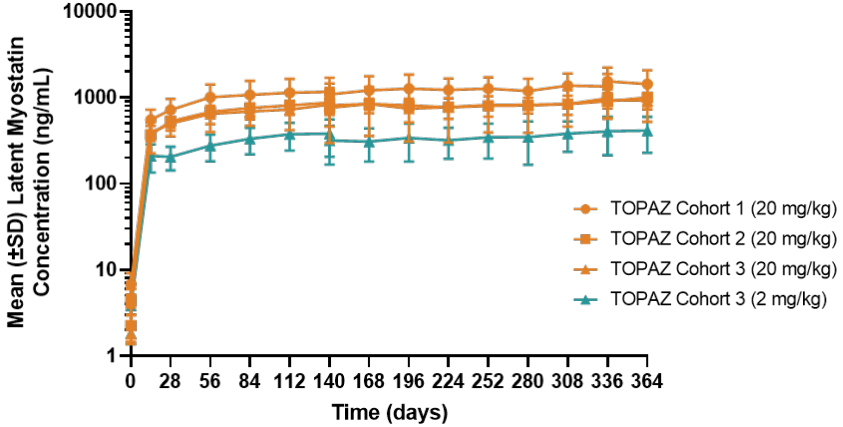
# Pharmacokinetic and Pharmacodynamic Data are Supportive of Clinically Observed Effects

## Pharmacokinetics* (PK)




- Dose-proportional and sustained drug exposure following chronic administration of apitegromab

## Pharmacodynamics (PD)




- Both 2 mg/kg and 20 mg/kg doses yielded high levels of target engagement (>100-fold increase from baseline)
- 20 mg/kg dose offers relatively higher magnitude of target engagement than 2 mg/kg dose

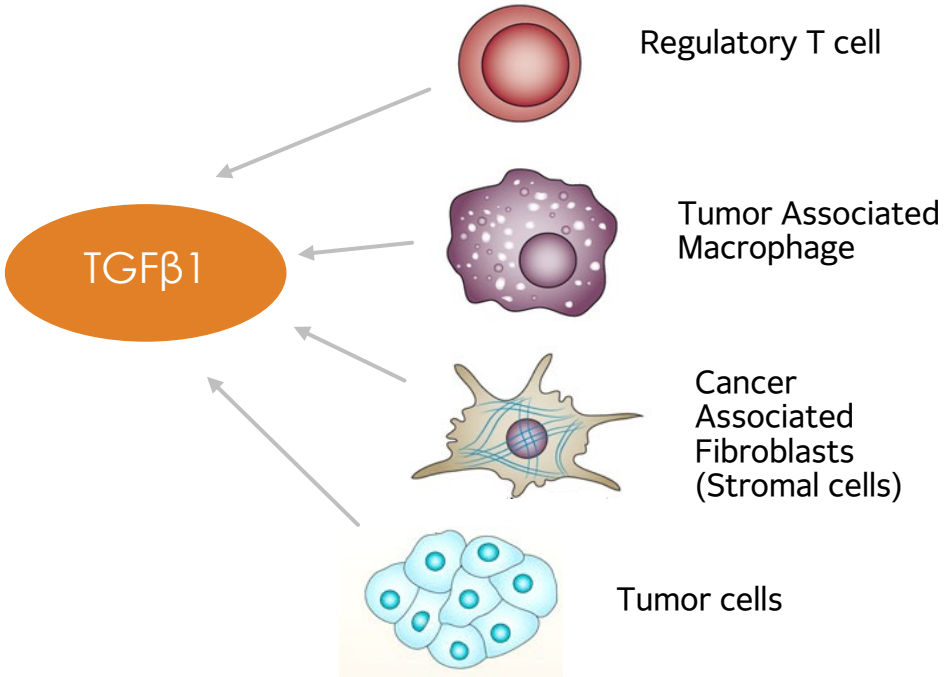
**High levels of target engagement achieved by both doses, with relatively higher absolute levels with high dose**

*Starting at day 28, measures are pre-dose trough levels

Data on file. Scholar Rock, Inc. Cambridge, MA

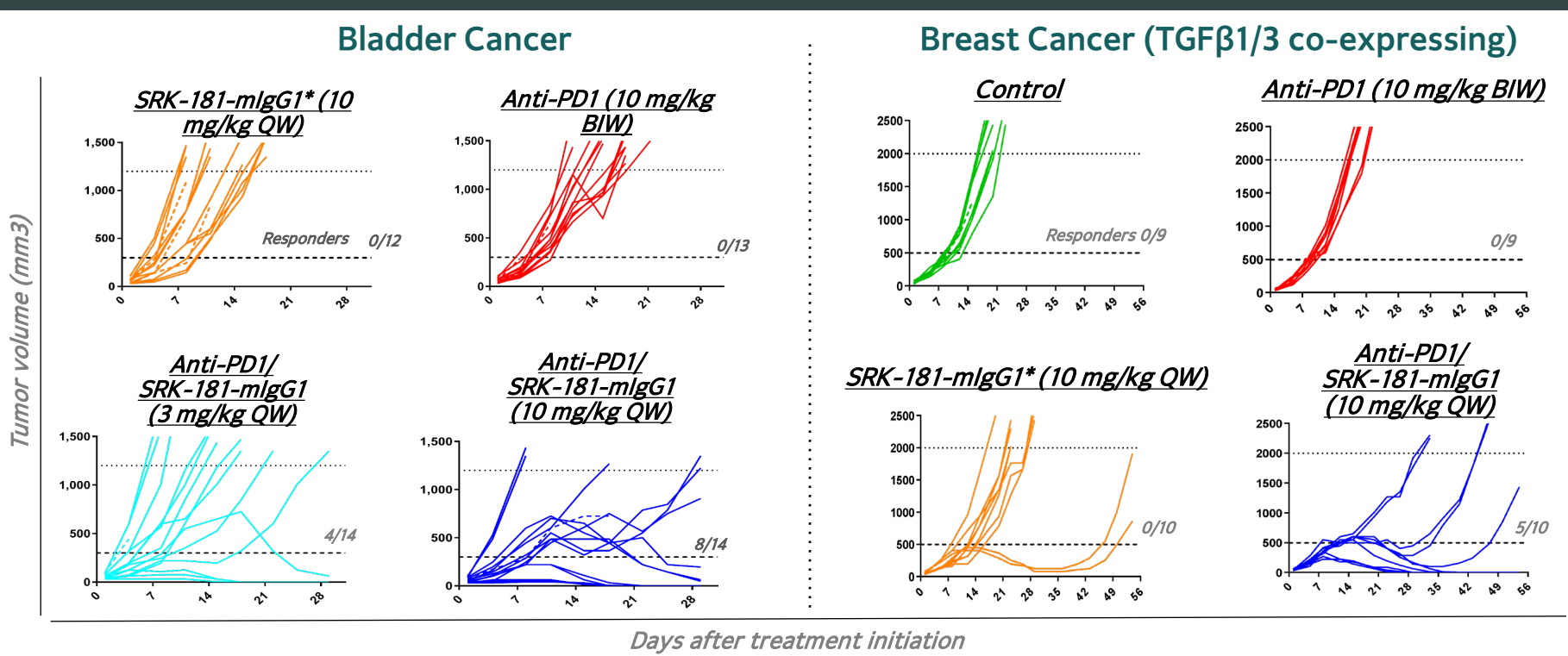
# Inhibition of TGFβ1: Multipronged Approach for Immuno-Oncology

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




- 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




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.*