Scholar Rock Presents New Data from Phase 1 DRAGON Trial Showing Promising Anti-Tumor Activity in Anti-PD-1 Resistant Metastatic ccRCC Patients and Supporting SRK-181 Continued Tolerability

November 3, 2023

- *Promising anti-tumor activity in heavily pretreated clear cell renal cell carcinoma (ccRCC) patients*
  - *Objective response rate (ORR) of 21.4% and disease control rate of 57%*
  - *Biomarker data supports proof of mechanism across multiple tumor types*
- *Combination therapy of SRK-181 and pembrolizumab was generally well tolerated*
- *Company to discuss SRK-181 program during conference call on third quarter 2023 financial results and business updates, Tuesday, November 7th at 8 a.m. EST*

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 3, 2023-- Scholar Rock (NASDAQ: SRRK), a Phase 3, clinical-stage biopharmaceutical company focused on the treatment of serious diseases in which protein growth factors play a fundamental role, today announced new data from its Phase 1 DRAGON proof-of-concept trial of SRK-181, a selective inhibitor of latent TGFβ1 activation being developed with the aim of overcoming resistance to checkpoint inhibitor therapy in patients with advanced cancer. These data will be presented in two poster presentations during the Society for Immunotherapy of Cancer's (SITC) 38th Annual Meeting & Pre-Conference being held November 1 – 5th in San Diego.

The first poster focuses on the safety, efficacy, and preliminary biomarker data in patients with anti-PD-1 resistant clear cell renal cell carcinoma (ccRCC) in Part A2 (dose escalation) and Part B (dose expansion) of the Phase 1 DRAGON trial. The ccRCC cohort was the focus for that poster, as it was the fastest cohort to achieve enrollment goals. The second poster focuses on preliminary biomarker data from part B of the trial in patients with multiple tumor types.

Data presented continues to support proof of concept for SRK-181 in 28 heavily pretreated patients with ccRCC resistant to anti-PD-1. SRK-181 was generally well tolerated and showed promising anti-tumor activity in this patient population. Of 28 evaluable patients in the ccRCC cohort, six patients treated with SRK-181 in combination with pembrolizumab had confirmed partial responses (PRs) and achieved a best tumor reduction of 33% to 93%, with an objective response rate (ORR) of 21.4%. In the biomarker analysis for ccRCC, levels of circulating granulocytic myeloid-derived suppressor cells (gMDSC) correlated with clinical activity in ccRCC patients treated with SRK-181 in combination with pembrolizumab. The data cutoff for all analyses was August 29, 2023.

“The DRAGON trial has successfully delivered on its objective of demonstrating proof of concept for SRK-181 by showing promising anti-tumor activity. These data, along with biomarker results that support proof of mechanism, highlight the immunosuppressive role of TGFβ as a mechanism of anti-PD-1 resistance in patients,” said Jay Backstrom, M.D., M.P.H., President and Chief Executive Officer of Scholar Rock. “We are particularly encouraged by the responses observed in patients with ccRCC who had been treated with multiple lines of therapy before receiving SRK-181.”

Safety data from ccRCC cohort continue to show SRK-181 is generally well tolerated

Safety data from the ccRCC cohort (n=30 patients; part A2: 1 patient on 800mg q3w and 1 patient on 1600mg q3w and Part B: 28 patients on 1500 mg q3w) continue to show SRK-181 has been generally well tolerated when used in combination with pembrolizumab. No dose-limiting toxicities were observed at any dose level, including at 1500 mg q3w in combination with pembrolizumab, the recommended dose selected for Part B.

One Grade 4 treatment-related adverse event (AE) was observed, dermatitis exfoliative generalized. No Grade 5 treatment-related AEs occurred. Treatment-related serious adverse events were dermatitis exfoliative generalized (1 patient), pemphigoid and rash (both in 1 patient), immune-related hepatitis (1 patient), and diarrhea, nausea, and vomiting (all three in 1 patient).

Preliminary results of SRK-181 in ccRCC patients show promising anti-tumor activity

The response was assessed by principal investigators based on RECIST 1.1. Out of the 28 ccRCC patients with evaluable responses (defined as all enrolled patients except those who are still on study, but pending post-treatment radiographic evaluation):

- Six patients had confirmed PRs (defined as at least a 30% tumor reduction), with best tumor reduction of 33% to 93%, and remained on study for 2.8+ to 16.3+ months (5 of the 6 patients remained on for over 6.5 months).
- Ten patients had stable disease (SD) (defined as tumors with neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD). Five of these patients continued in the study.
- The objective response rate (ORR), defined as the percentage of patients with a partial or complete response to therapy, was 21.4% and the disease control rate (DCR), defined as the percentage of patients whose disease shrinks or remains stable over a certain time period, was 57%. In this difficult to treat population, anti-PD-1 retreatment is generally associated with single-digit ORR or no response.[1]

Biomarker data support proof of mechanism in multiple tumor types

The biomarker strategy includes measuring effects of SRK-181 on both circulating and tumor immune cells, such as tumor infiltration by CD8+ T cells and reductions in myeloid-derived suppressor cell (MDSC) populations. The analysis included patients from Part B with ccRCC, melanoma, non-small cell lung cancer (NSCLC), or urothelial carcinoma (UC).

Following treatment with SRK-181 and pembrolizumab, circulating MDSC levels decreased below baseline in all patients with PRs (n=7), which included those in the ccRCC, melanoma, and UC cohorts. CD8+ T cells were measured in tumor types for which paired biopsy samples (i.e., samples before and after treatment for individual patients) of sufficient quality were available: UC, melanoma, and NSCLC. In those patients (n=8), SRK-181 treatment was associated with an increase in CD8+ T cell infiltration into tumors. These findings were consistent with preclinical data showing that treatment with SRK-181 and anti-PD-(L)1 therapy decreased circulating MDSC levels and increased CD8+ T cell infiltration into tumors, which correlated with tumor response and survival benefit.

The results will be presented at the SITC 38th Annual Meeting in two poster presentations, details of which can be found below. The posters will be made available in the Publications & Posters section of Scholar Rock's website following the conference.

Title: Establishing Proof of Mechanism in Patients: Preliminary Biomarker Data of SRK-181 (a latent TGFβ1 inhibitor) from DRAGON Study
Presentation Type: Poster 726
Presenter: Susan Henry, PhD, Senior Director, Translational Sciences, Scholar Rock, Inc.
Location: Exhibit Halls A and B1, San Diego Convention Center
Date/Time: November 4, 11:55 AM – 1:25 PM PST and 7 – 8:30 PM PST

Title: Safety, Efficacy, and Biomarker Results of SRK-181, a Latent TGFβ1 Inhibitor, in Anti-PD-1 Resistant Metastatic ccRCC Patients
Presentation Type: Poster 666
Presenter: Timothy Yap, MBBS, PhD, FRCP, Medical Oncologist and Physician-Scientist; and Associate Professor, Department of Investigational Cancer Therapeutics, University of Texas MD Anderson Cancer Center
Location: Exhibit Halls A and B1, San Diego Convention Center
Date/Time: November 4, 11:55 AM – 1:25 PM PST and 7 – 8:30 PM PST

For conference information, visit https://www.sitcancer.org/2023/home

(1) Pal, et al. The Lancet. 2023; 15;402(10397):185-195.

About SRK-181

SRK-181 is a selective inhibitor of TGFβ1 activation being developed to overcome primary resistance to checkpoint inhibitor therapy, such as anti-PD-(L)1 antibodies, in advanced cancer. TGFβ1 is the predominant TGFβ isoform expressed in many human tumor types. Based on analyses of various human tumors that are resistant to anti-PD-(L)1 therapy, data suggest that TGFβ1 is a key contributor to the immunosuppressive tumor microenvironment, excluding and preventing entry of cytotoxic T cells into the tumor, thereby inhibiting anti-tumor immunity. (2) SRK-181 specifically targets the latent TGFβ1 isoform in a context-independent manner, designed to enable complete inhibition of TGFβ1 in all compartments within the tumor microenvironment. Scholar Rock believes that SRK-181 has the potential to overcome this immune cell exclusion and induce tumor regression when administered in combination with anti-PD-(L)1 therapy while potentially avoiding toxicities associated with non-selective TGFβ inhibition. The DRAGON Phase 1 proof-of-concept clinical trial (NCT04291079) in patients with locally advanced or metastatic solid tumors is ongoing. The trial is currently enrolling and dosing patients in multiple proof of concept cohorts conducted in parallel, including urothelial carcinoma (UC), cutaneous melanoma (MEL), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), and clear cell renal cell carcinoma (ccRCC). SRK-181 is an investigational product candidate and its efficacy and safety have not been established. SRK-181 has not been approved for any use by the FDA or any other regulatory agency.

2) Martin et al., Sci. Transl. Med. 12: 25 March 2020

About Scholar Rock

Scholar Rock is a biopharmaceutical company that discovers, develops, and delivers life-changing therapies for people with serious diseases that have high unmet need. As a global leader in the biology of the transforming growth factor beta (TGFβ) superfamily of cell proteins and named for the visual resemblance of a scholar rock to protein structures, the clinical-stage company is focused on advancing innovative treatments where protein growth factors are fundamental. Over the past decade, the company has created a pipeline with the potential to advance the standard of care for neuromuscular disease, cardiometabolic disorders, cancer, and other conditions where growth factor-targeted drugs can play a transformational role.

Scholar Rock is the only company to show clinical proof of concept for a muscle-targeted treatment in spinal muscular atrophy (SMA). This commitment to unlocking fundamentally different therapeutic approaches is powered by broad application of a proprietary platform, which has developed novel monoclonal antibodies to modulate protein growth factors with extraordinary selectivity. By harnessing cutting-edge science in disease spaces that are historically under-addressed through traditional therapies, Scholar Rock works every day to create new possibilities for patients. Learn more about the company's approach at ScholarRock.com and follow @ScholarRock and on LinkedIn.

Availability of Other Information About Scholar Rock

Investors and others should note that we communicate with our investors and the public using our company website www.scholarrock.com, including, but not limited to, company disclosures, investor presentations and FAQs, Securities and Exchange Commission filings, press releases, public conference call transcripts and webcast transcripts, as well as on Twitter and LinkedIn. The information that we post on our website or on Twitter or LinkedIn could be deemed to be material information. As a result, we encourage investors, the media and others interested to review the information that we post there on a regular basis. The contents of our website or social media shall not be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended.

Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including, but not

limited to, statements regarding Scholar Rock's future expectations, plans and prospects, including without limitation, Scholar Rock's expectations regarding its growth, strategy, and progress and indication selection and development timing, 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," "could," "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. 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, without limitation, that clinical data, including the results from the Phase 2 clinical trial of apitegromab, or Part B of the Phase 1 clinical trial of SRK-181, and are not predictive of, may be inconsistent with, or more favorable than, data generated from future clinical trials of the same product candidates, 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, and Scholar Rock's ability to manage expenses and to obtain additional funding when needed to support its business activities, 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 June 30, 2023, 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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