Recent Phase 1 DRAGON Data Show SRK-181 Continues to be Well Tolerated with Early Indications of Efficacy

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- All doses were generally well tolerated, no dose limiting toxicities observed including at the Part B dose of 1500 mg

- Biomarker data consistent with target engagement

- Two confirmed partial responses observed in patients with anti-PD-1 resistant clear cell renal cell carcinoma

- Enrollment of DRAGON Part B continues to progress

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 10, 2022-- 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 early 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 therapy in patients with advanced cancer. The data were shared in a poster presentation during the Society for Immunotherapy of Cancer's (SITC) 37th Annual Meeting & Pre-Conference being held November 8-12 in Boston.

“Resistance to checkpoint inhibitor therapy remains a significant challenge in the treatment of advanced cancer. The DRAGON trial is investigating our novel TGFβ1 selective monoclonal antibody, SRK-181, which was designed to address this challenge based on the strong, scientific rationale that TGFβ1 is a driving mechanism of resistance to checkpoint inhibitors. Our preclinical work suggests that SRK-181 may overcome this resistance and avoid the cardiotoxicities that have limited other non-selective approaches,” said Jay Backstrom, M.D., M.P.H., President and Chief Executive Officer of Scholar Rock. “These early DRAGON findings of safety, target engagement and indications of efficacy support our conviction around Scholar Rock’s differentiated approach and the potential role that SRK-181 may play in addressing the existing treatment hurdles. We are excited to continue advancing DRAGON and look forward to sharing additional data next year.”

Data continue to show SRK-181 is generally well tolerated
Safety data from the dose escalation portion of the trial (Part A) continue to show SRK-181 is generally well tolerated when used alone or in combination with anti-PD-(L)1 checkpoint inhibitor therapy. No dose-limiting toxicities were observed in patients receiving SRK-181 as monotherapy (Part A1) when dosed up to 3000 mg once every three weeks (q3w) or 2000 mg once every two weeks (q2w), or in patients receiving SRK-181 in combination with checkpoint inhibitor therapy (Part A2) when dosed up to 2400 mg q3w. All dose levels were generally well tolerated, including the recommended SRK-181 dose of 1500 mg q3w or 1000 mg q2w in combination with anti-PD-(L)1 for the dose expansion portion of the trial (Part B).

No Grade 4 or 5 treatment-related AEs occurred. Treatment-related Grade 3 adverse events were increased levels of alanine aminotransferase (one patient in Part A1); pruritus (two patients in Part A2), blister, immune-mediated lung disease, rash and rash maculo-papular (one patient each in Part A2). A treatment-related serious adverse event of elevated troponin I (one patient) was observed in Part A1; blister, pruritus, and rash (all in one patient) and immune-mediated lung disease (one patient) were observed in Part A2.

Early indications of efficacy
The response was assessed by principal investigators based on RECIST 1.1. Partial response (“PR”) is defined as at least a 30% tumor reduction. As of the data cut-off date (August 29, 2022), 15 patients were enrolled in Part A2 with the following results:

- One confirmed PR in a patient with anti-PD-1 resistant clear cell renal cell carcinoma at 800mg in Part A2 of the trial who remained in the study for 30 weeks.
- One ongoing patient in the 2400 mg dose group of Part A2 with head and neck cancer experienced a 29.4% tumor reduction.
- Nine patients experienced a best response of stable disease. This included six patients whose disease progressed prior to the trial and were stable beyond the 16-week cutoff.

As of the data cut-off date, 14 patients were enrolled in Part B. One ongoing patient with anti-PD-1 resistant clear cell renal cell carcinoma had a confirmed PR.

Biomarker data from Part A consistent with target engagement
The biomarker strategy for DRAGON explores early signs of SRK-181 activity, including target engagement and pathway modulation. It includes measuring effects on both circulating and tumor immune contexture, such as CD8+ T cell infiltration and reductions in myeloid-derived suppressor cell (MDSC) populations, as well as analysis of TGFβ-related pathway signaling.

Following treatment with SRK-181 in Part A, circulatory TGFβ1 levels increased in all dose groups. Given the small number of participants in each dosing cohort, dose-dependent increases in circulatory TGFβ1 levels were not apparent. These findings are consistent with preclinical results from a mouse tumor model (MBT-2) that suggest circulatory TGFβ1 may be a potential pharmacodynamic biomarker of SRK-181. Combination treatment with anti-PD-(L)1 therapy also appears to have similar circulatory TGFβ1 levels as monotherapy.

“At this early stage, the biomarker findings are consistent with the circulating TGFβ1 levels observed in our preclinical studies. We also saw target engagement accompanied by robust efficacy measured through MDSC levels as PD biomarker and immune infiltration into tumors and tumor

regression in our preclinical studies," said Mo Qatanani, Senior Vice President, Research. "We are excited to generate further biomarker analyses from DRAGON, including MDSC levels to reflect PD activity and present them at future scientific meetings."

The poster will be made available in the Publications & Posters section of Scholar Rock's website following the conference.

For conference information, visit https://www.sitcancer.org/2022/home

About SRK-181
SRK-181 is a selective inhibitor of latent 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 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. (1) Scholar Rock believes SRK-181, which specifically targets the latent TGFβ1 isoform, 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) 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.

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

About Scholar Rock
Scholar Rock is a clinical-stage biopharmaceutical company focused on the discovery and development of innovative medicines for the treatment of serious diseases in which signaling by protein growth factors plays a fundamental role. Scholar Rock is creating a pipeline of novel product candidates with the potential to transform the lives of patients suffering from a wide range of serious diseases, including neuromuscular disorders, cancer, and fibrosis. Scholar Rock's approach to targeting the molecular mechanisms of growth factor activation enabled it to develop a proprietary platform for the discovery and development of monoclonal antibodies that locally and selectively target these signaling proteins at the cellular level. By developing product candidates that act in the disease microenvironment, the Company intends to avoid the historical challenges associated with inhibiting growth factors for therapeutic effect. Scholar Rock believes its focus on biologically validated growth factors may facilitate a more efficient development path. For more information, please visit www.ScholarRock.com or follow Scholar Rock on Twitter (@ScholarRock) and LinkedIn (https://www.linkedin.com/company/scholar-rock/).

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.

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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, 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, 2022, 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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