Scholar Rock Presents Additional Preclinical Data Demonstrating a Highly Specific Inhibitor of TGFβ1 Activation Can Render Resistant Solid Tumors Vulnerable to PD1 Blockade and Drive Tumor Regression with Combination Therapy

April 2, 2019

- *Preclinical data presented at the American Association for Cancer Research annual meeting provide further support for the potential of SRK-181 to overcome primary resistance to checkpoint blockade therapy (CBT)*
- *TGFβ1-specific inhibition by SRK-181-mIgG1 was sufficient to render both TGFβ1-expressing and TGFβ1/TGFβ3 co-expressing mouse tumor models sensitive to anti-PD1 immunotherapy, suggesting TGFβ1 is the key isoform contributing to CBT resistance*
- *Combination of SRK-181-mIgG1 and anti-PD1 in preclinical tumor models increased immune cell infiltration and reduced immunosuppressive myeloid cells leading to tumor regression and survival benefit*
- *Company declared SRK-181 as first product candidate in cancer immunotherapy program, with plans to initiate a Phase 1 trial in patients with solid tumors in mid-2020*

CAMBRIDGE, Mass., April 02, 2019 (GLOBE NEWSWIRE) -- Scholar Rock Holding Corporation (NASDAQ: SRRK), a clinical-stage biopharmaceutical company focused on the treatment of serious diseases in which protein growth factors play a fundamental role, today announced additional data that further elucidate the mechanism of action of a highly specific inhibitor of TGFβ1 activation in syngeneic mouse tumor models that emulate clinically-observed primary resistance to checkpoint blockade therapy (CBT). Detailed preclinical results are being presented at the American Association for Cancer Research (AACR) annual meeting in Atlanta, GA on April 2, 2019.

The preclinical data demonstrate that treatment with SRK-181-mIgG1, a highly specific inhibitor of TGFβ1 activation, in combination with an anti-PD1 immunotherapy, can drive tumor regression or control, resulting in significant survival benefit compared to anti-PD1 monotherapy. This was shown across multiple tumor models, including the EMT6 breast cancer mouse model, which expresses both TGFβ1 and TGFβ3 isoforms. In addition, newly presented immune response data show that combination treatment leads to infiltration and expansion of CD8+ T cells and a reduction of immunosuppressive myeloid cells, suggesting TGFβ1's multiple contributions to primary resistance to CBT.

“These new preclinical results reinforce our belief that a highly specific inhibitor of TGFβ1 activation can enable the immune response to overcome a key mechanism of primary resistance to checkpoint blockade therapy, even in tumors that express other TGFβ isoforms, and could meaningfully expand the number of patients who could benefit from checkpoint blockade therapies,” said Nagesh Mahanthappa, Ph.D., President and CEO of Scholar Rock. “With the recently announced nomination of SRK-181 as the first product candidate in our cancer immunotherapy program, we are eagerly working towards initiating a Phase 1 trial in patients with solid tumors in mid-2020.”

Highlights from the preclinical data being presented at AACR for the poster titled “Defeating primary checkpoint resistance: SRK-181 is a first-in-class, fully human antibody that renders resistant tumors sensitive to anti-PD-1” (Poster #4090), include:

- SRK-181-mIgG1 (the murine version of SRK-181) binds to and inhibits the activation of latent TGFβ1 in multiple presentation contexts with high selectivity, high affinity and minimal or no binding to latent TGFβ2 and latent TGFβ3 isoforms.
- In syngeneic mouse tumor models that reflect human primary resistance to CBT, treatment with SRK-181-mIgG1 rendered EMT6 (breast cancer), MBT-2 (bladder cancer), and Cloudman S91 (melanoma) tumors vulnerable to anti-PD1 therapy.
- Combination treatment with SRK-181-mIgG1 and an anti-PD1 antibody resulted in tumor regression or tumor control across multiple cancer models.

	EMT6 breast cancer model (Response*: %, N)	**MBT-2 bladder cancer model (Response**: %, N)**	**Cloudman S91 melanoma model (Response***: %, N)**
Control	0% (0/9)	0% (0/13)	0% (0/11)
Anti-PD1 monotherapy	0% (0/9)	0% (0/13)	17% (2/12)
SRK-181-mIgG1 monotherapy	0% (0/10)	0% (0/12)	0% (0/12)
Anti-PD1/SRK-181-mIgG1, 3 mg/kg	NT	29% (4/14)	83% (10/12)
Anti-PD1/SRK-181-mIgG1, 10 mg/kg	50% (5/10)	57% (8/14)	78% (7/9)
Anti-PD1/SRK-181-mIgG1, 30 mg/kg	NT	NT	73% (8/11)

* For EMT6: Response is defined as animals that achieved a tumor volume at study end of less than 25% of the 2,000mm^3 survival threshold.

** For MBT-2: Response is defined as animals that achieved a tumor volume at study end of less than 25% of the 1,200mm^3 survival threshold.

*** For Cloudman S91: Response is defined as animals that achieved a tumor volume at study end of less than 25% of the 2,000mm^3 survival

threshold.

NT: Not tested

- In the EMT6 breast cancer mouse model, in which both the TGFβ1 and TGFβ3 isoforms are expressed, treatment with SRK-181-mIgG1 and anti-PD1 resulted in synergistic antitumor efficacy, as evidenced by either complete responders or tumor growth delay compared to no responders with either SRK-181-mIgG1 or anti-PD1 monotherapy. These data indicate that, despite the presence of TGFβ3, blockade of the TGFβ1 isoform is sufficient to sensitize EMT6 tumors to anti-PD1 therapy. Furthermore, these results are consistent with the hypothesis that TGFβ1 is the isoform that drives immunosuppressive TGFβ signaling in the tumor microenvironment, immune exclusion, and primary resistance to CBT.
- Combination treatment with SRK-181-mIgG1 and an anti-PD1 antibody resulted in statistically significant survival benefit when compared to anti-PD1 monotherapy in all three evaluated syngeneic mouse tumor models. Median survival was not reached in the EMT6 study, in the anti-PD1/SRK-181-mIgG1 10 mg/kg combination group of the MBT-2 study, and in any of the combination groups of the Cloudman S91 study.
- As demonstrated in the MBT-2 tumor model, combination treatment with SRK-181-mIgG1 and anti-PD1 led to a significant increase in effector T cells ($p<0.05$) and a significant decrease in intratumoral immunosuppressive myeloid cells ($p<0.05$). Specific examples of tumor immune cells believed to be relevant to the observed anti-tumor response include (as compared to IgG control at day 10 of treatment):
    - An approximately 900% increase in the number of CD8+ T cells (as a percentage of total immune cells) observed with the combination treatment compared to an approximately 100-200% increase with anti-PD1 or SRK-181-mIgG1 alone. The combination of SRK-181-mIgG1 and anti-PD1 resulted in an expansion of the CD8+ population to representing an average of 34% of the tumor's immune cells from a control average of 3.5%.
    - An approximately 70% decrease in the number of tumor-associated macrophages or myeloid-derived suppressor cells (TAMs/MDSCs) was observed with the combination treatment compared to an approximately 35-40% decrease with anti-PD1 or SRK-181-mIgG1 alone. The combination resulted in a reduction in the TAM/MDSC population to 14% of the tumor's immune cells from a control average of 47%.
- Adult rats treated with SRK-181 up to a weekly dose of 100mg/kg for four weeks showed an improved preclinical toxicity profile versus a pan-TGFβ antibody and an ALK5 inhibitor.

The poster can be accessed at: https://scholarrock.com/platform/publications/

About SRK-181
SRK-181 is a highly specific inhibitor of TGFβ1 activation being developed to overcome primary resistance to checkpoint blockade therapies (CBTs). TGFβ1 is the predominant TGFβ isoform expressed in many human tumors, particularly for those tumors where checkpoint therapies are currently approved. Based on analyses of human tumors that are resistant to CBT, TGFβ1 is implicated as a key contributor to exclude immune cell entry into the tumor microenvironment, thereby preventing normal immune function. By overcoming this immune cell exclusion, SRK-181 has the potential to induce tumor regression when administered in conjunction with CBT.

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, fibrosis and anemia. Scholar Rock's newly elucidated understanding of 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.

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 the ability of SRK-181 to render tumors vulnerable to checkpoint blockade therapy, including the inhibitor's ability to affect tumor regression, tumor control or survival; the toxicity profile of SRK-181; and the timeline for and progress in developing SRK-181. 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. 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 the reproducibility of any preclinical data presented; preclinical data and testing of SRK-181 may not be predictive of the results or success of clinical trials; the development of SRK-181 will take longer and/or cost more than planned; SRK-181 will not receive regulatory approval; any data generated from Scholar Rock's future nonclinical studies and clinical trials; and those risks more fully discussed in the section entitled "Risk Factors" in Scholar Rock's Annual Report on Form 10-K for the quarter and full year ended December 31, 2018, 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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