UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event Reported): June 3, 2024

Scholar Rock Holding Corporation
(Exact Name of Registrant as Specified in Charter)

Delaware	**001-38501**	**82-3750435**
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(I.R.S. Employer Identification Number)

301 Binney Street, 3rd Floor, Cambridge, MA 02142
(Address of Principal Executive Offices) (Zip Code)

(857) 259-3860
(Registrant's telephone number, including area code)

(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.001 per share	SRRK	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (17 CFR §230.405) or Rule 12b-2 of the Securities Exchange Act of 1934 (17 CFR §240.12b-2). Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01. Regulation FD Disclosure.

On June 3, 2024, Scholar Rock Holding Corporation (the "Company") presented new data from its Phase 1 DRAGON proof-of-concept trial of SRK-181 in combination with pembrolizumab in patients with advanced solid tumors in an oral presentation during the American Society of Clinical Oncology (ASCO) 2024 Annual Meeting.

A copy of the press release relating to the ASCO presentation is attached hereto as Exhibit 99.1 and a copy of the ASCO presentation slides are attached hereto as Exhibit 99.2.

On June 4, 2024, the Company will host a conference call at 8:00 am ET to discuss the new data from its Phase 1 DRAGON proof-of-concept trial of SRK-181 in combination with pembrolizumab in patients with advanced solid tumors. The audio of the conference call can be accessed by registering in advance at the following link: https://register.vevent.com/register/BIca0060fe57734207b3fc21ce38d84a63 and a recording of the call and related presentation may be accessed by visiting the Investors & Media section of the Company's website at http://investors.scholarrock.com.

The information in this report furnished pursuant to Item 7.01 and Exhibits 99.1 and 99.2 shall not be deemed "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section nor shall such information be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, regardless of the general incorporation language of such filing, except as shall be expressly set forth by specific reference in such filing. It may only be incorporated by reference in another filing under the Exchange Act or the Securities Act of 1933, as amended, if such subsequent filing specifically references the information furnished pursuant to Item 7.01 and Exhibits 99.1 and 99.2 of this report.

Item 8.01. Other Events.

On June 3, 2024, the Company presented new data from its Phase 1 DRAGON proof-of-concept trial of SRK-181 in combination with pembrolizumab in patients with advanced solid tumors which included the following:

Safety data from all cohorts in the dose expansion phase (Part B; n=78 patients; 1500 mg q3w) continued to show SRK-181 was generally well tolerated when used in combination with pembrolizumab. One Grade 4 treatment-related adverse event (AE) of generalized dermatitis exfoliative was observed in one patient. No Grade 5 treatment-related AEs occurred. The only treatment-related serious adverse event related to SRK-181 or pembrolizumab that occurred in at least 2% of patients was pemphigoid. The most common AEs were rash, pruritis, fatigue, and diarrhea.

Encouraging responses were observed in multiple tumor types, continuing to support proof-of-concept for SRK-181. The response was assessed by principal investigators based on RECIST 1.1 for patients across five cohorts: clear cell renal cell carcinoma (ccRCC), head and neck squamous cell carcinoma (HNSCC), melanoma (MEL), urothelial carcinoma (UC), and non-small cell lung cancer (NSCLC). A summary of anti-tumor activity is presented in the table below; results for NSCLC (n=11) are not included because no response was observed.

Summary of Response Rate in Multiple Tumor Types

	ccRCC (n=30)	HNSCC (n=11)	MEL (n=11)	UC (n=11)
Objective response rate (ORR)	7 (23.3%)	2 (18.2%)	3 (27.3%)	1 (9.1%)
Durability of response (DoR); median (range), months	7.7+ (2.5+, 20.9+)	2.2+ (0.1, 4.3+)	4.9 (1.8, 7.1)	12.9 (12.9, 12.9)

Tumor infiltration by CD8+ T-cells was measured in multiple tumor types for which paired biopsy samples (i.e., samples before and after treatment for individual patients) were available. The analysis included patients with ccRCC, melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC) or urothelial carcinoma (UC). In 6 out of 9 paired biopsies analyzed, the combination of SRK-181 and pembrolizumab was associated with an enhanced

proinflammatory microenvironment, with activated CD8+ T-cells in responding patients across multiple cohorts and the number of activated T-cells correlating with tumor shrinkage.

Notably, the baseline immune contexture unique to ccRCC amongst the cohorts examined has been identified, predictive of clinical response.

An analysis in ccRCC patients showed a positive correlation between baseline CD8+ infiltration status and response rate, with an increase in ORR from 23.3 to 40%, and an improvement in median durability of response (mDoR) from 7.7 to 9.3 months if enrollment had been limited to patients whose tumors were infiltrated by CD8+ T-cells at baseline.

In addition, an independent analysis showed a positive correlation between elevated regulatory T-cell (Treg) levels in ccRCC patients pre-treatment and response rate, with an increase in ORR from 23.3 to 50% and improvement in mDoR from 7.7 to 9.8 months if enrollment had been limited to patients whose tumors had elevated Treg levels at baseline. Together, these results suggest that baseline CD8+ status and Treg levels should be further investigated as a potential future patient selection strategy, aimed to predict ccRCC patients who are likely to respond to SRK-181 and anti-PD-(L)1 combination therapy.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release issued by the Company on June 3, 2024, furnished hereto.
99.2	Presentation Slides, furnished hereto.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Scholar Rock Holding Corporation

Date: June 3, 2024

By: /s/ Junlin Ho
Junlin Ho
General Counsel and Corporate Secretary

Scholar Rock Presents New Data from SRK-181 Phase 1 DRAGON Trial at ASCO 2024 Annual Meeting

- *Promising objective response rates (ORR) were observed in multiple tumor types in anti-PD-(L)1 resistant patients*
- *Analysis of baseline biomarker data in clear cell renal cell carcinoma (ccRCC) patients reveals a doubling of the ORR highlighting a potential patient selection strategy*
- *SRK-181 combination with pembrolizumab was generally well tolerated*
- *Company holding conference call to discuss data with Dr. Toni Choueiri on Tuesday, June 4th at 7 a.m. CDT/8 a.m. EST*

CAMBRIDGE, Mass.—June 3, 2024—Scholar Rock (NASDAQ: SRRK), a late-stage biopharmaceutical company focused on advancing innovative treatments for spinal muscular atrophy (SMA), cardiometabolic disorders, and other serious diseases where protein growth factors play a fundamental role, today announced encouraging data from its Phase 1 DRAGON proof-of-concept trial of SRK-181, a selective inhibitor of latent TGFβ1 activation, in combination with pembrolizumab in patients with advanced solid tumors. The results show encouraging responses in heavily pretreated and anti-PD-(L)1 resistant patients across multiple tumor types. Data were shared in an oral presentation during the American Society of Clinical Oncology (ASCO) Annual Meeting on June 3 in Chicago.

“These new data from our SRK-181 program show promising response to treatment with SRK-181 across multiple tumor types and represent further evidence of the value of our highly selective TGFβ platform,” said Jay Backstrom, M.D., MPH, President and Chief Executive Officer of Scholar Rock. “The anti-tumor activity we observed in heavily pretreated cancer patients, most notably in ccRCC and melanoma gives us confidence that SRK-181 could be part of a treatment strategy to overcome immune checkpoint inhibitor-associated resistance. In addition, our new finding that baseline CD8+ infiltration status and elevated baseline regulatory T-cell levels in ccRCC correspond with the twofold increase in response rate has the potential to inform a patient selection strategy. We are very encouraged by these new data and are committed to engaging with the FDA in an end of Phase 1 meeting, while also continuing to evaluate opportunities to partner this important program.”

Safety data continued to show SRK-181 was generally well tolerated
Safety data from all cohorts in the dose expansion phase (Part B; n=78 patients; 1500 mg q3w) continued to show SRK-181 was generally well tolerated when used in combination with pembrolizumab. One Grade 4 treatment-related adverse event (AE) of generalized dermatitis exfoliative was observed in one patient. No Grade 5 treatment-related AEs occurred. The only treatment-related serious adverse event related to SRK-181 or pembrolizumab that occurred in at least 2% of patients was pemphigoid. The most common AEs were rash, pruritis, fatigue, and diarrhea.

Data presented continues to provide objective evidence of anti-tumor activity
Encouraging responses were observed in multiple tumor types, continuing to support proof-of-concept for SRK-181. The response was assessed by principal investigators based on RECIST 1.1 for patients across five cohorts: clear cell renal cell carcinoma (ccRCC), head and neck squamous cell carcinoma (HNSCC), melanoma (MEL), urothelial carcinoma (UC), and non-small cell lung cancer (NSCLC). A summary of anti-tumor activity is presented in the table below; results for NSCLC (n=11) are not included because no response was observed.

Summary of Response Rate in Multiple Tumor Types

	ccRCC (n=30)	HNSCC (n=11)	MEL (n=11)	UC (n=11)
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Biomarker findings continue to support proof of mechanism
Tumor infiltration by CD8+ T-cells was measured in multiple tumor types for which paired biopsy samples (i.e., samples before and after treatment for individual patients) were available. The analysis included patients with ccRCC, melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC) or urothelial carcinoma (UC). In 6 out of 9 paired biopsies analyzed, the combination of SRK-181 and pembrolizumab was associated with an enhanced proinflammatory microenvironment, with activated CD8+ T-cells in responding patients across multiple cohorts and the number of activated T-cells correlating with tumor shrinkage.

New biomarker findings in ccRCC could inform patient selection strategy
Notably, the baseline immune contexture unique to ccRCC amongst the cohorts examined has been identified, predictive of clinical response.

An analysis in ccRCC patients showed a positive correlation between baseline CD8+ infiltration status and response rate, with an increase in ORR from 23.3 to 40%, and an improvement in median durability of response (mDoR) from 7.7 to 9.3 months if enrollment had been limited to patients whose tumors were infiltrated by CD8+ T-cells at baseline.

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The presentation is available in the Publications & Posters section of Scholar Rock's website.
For conference information, visit https://conferences.asco.org/.

Conference Call Information
Scholar Rock will host a conference call on June 4 at 8 a.m. EST that can be accessed from Events and Presentations page of Scholar Rock's website. Members of Scholar Rock's executive management team will be joined by Dr. Toni Choueiri, M.D., Director of the Lank Center for Genitourinary (GU) Oncology at Dana-Farber Cancer Institute (DFCI). The audio of the conference call can be accessed by registering in advance at the following link:
https://register.vevent.com/register/BIca0060fe57734207b3fc21ce38d84a63

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, as well as suppressing T cell activity, thereby inhibiting anti-tumor immunity.

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 immunosuppressive tumor microenvironment and induce tumor regression when administered in combination with anti-PD-(L)1 therapy while potentially avoiding toxicities associated with non-selective TGFβ inhibition. Enrollment of the DRAGON Phase 1 proof-of-concept clinical trial (NCT04291079) was completed in December 2023, and patients who remain on the study continue to be treated. The trial enrolled 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.

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, Scholar Rock 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 our 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.

Scholar Rock® is a registered trademark of Scholar Rock, Inc.

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, progress and timing of its clinical trials for SRK-181, and indication selection and development timing, including the therapeutic potential, clinical benefits and safety thereof, expectations regarding timing, success and data announcements of current ongoing clinical trials, 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 preclinical and clinical data, including the results from the Phase 1 clinical trial of SRK-181, are not predictive of, may be inconsistent with, or more favorable than, data generated from future or ongoing 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; 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; Scholar Rock's dependence on third parties for development and manufacture of product candidates including, without limitation, 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 Scholar Rock's Quarterly Report on Form 10-Q for the quarter ended March 31, 2024, 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.

Scholar Rock:

Investors
Rushmie Nofsinger
Scholar Rock
rnofsinger@scholarrock.com
ir@scholarrock.com
857-259-5573

Media
Molly MacLeod
Scholar Rock
mmacleod@scholarrock.com
media@scholarrock.com
802-579-5995

2024 ASCO ANNUAL MEETING

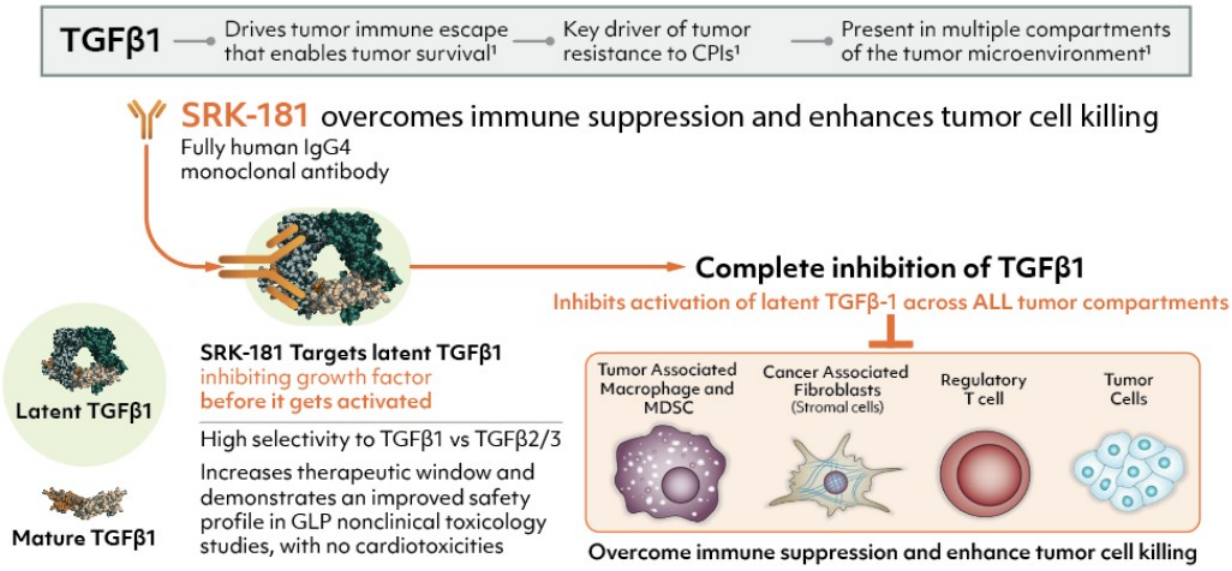
Phase 1 study (DRAGON) of SRK-181 (linavonkibart), a latent TGFβ1 inhibitor, combined with pembrolizumab in anti-PD1 resistant patients with advanced solid tumors: Updated results of expansion phase

Ulka Vaishampayan[1], Randy F. Sweis[2], Deepak Kilari[3], Ahmad Tarhini[4], Justin F. Gainor[5], Minal Barve[6], Guru Sonpavde[7], Meredith Mckean[8], David Park[9], Sunil Babu[10], Yawen Ju[11], Lan Liu[11], Susan Henry[11], Lu Gan[11], Timothy A. Yap[12]

[1]University of Michigan, Ann Arbor, MI; [2]University of Chicago, Chicago, IL; [3]Medical College of Wisconsin, Milwaukee, WI; [4]Moffitt Cancer Center Magnolia Campus, Tampa, FL; [5]Massachusetts General Hospital Harvard Medical School, Boston, MA; [6]Mary Crowley Cancer Research, Dallas, TX; [7]AdventHealth Medical Group, Orlando, FL; [8]Sarah Cannon Research Institute, Nashville, TN; [9]St Jude Crosson Cancer Institute/Providence Medical Foundation, Fullerton, CA; [10]Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN; [11]Scholar Rock, Inc., Cambridge, MA; [12]The University of Texas MD Anderson Cancer Center, Houston, TX

Mechanism of Action

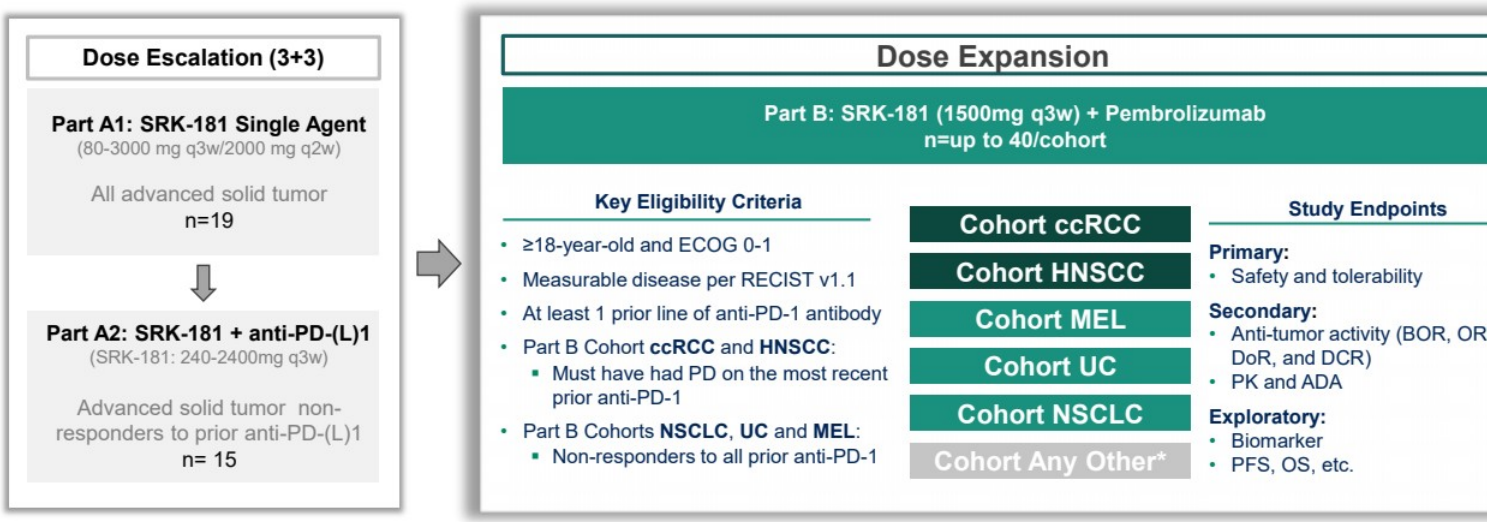
SRK-181, a Selective Anti-TGFβ1 Antibody, Overcomes CPIs Resistance



1.Batlle E, et al. *Immunity*. 2019; 50(4):924-940.
CPI, checkpoint inhibitor; GLP, good laboratory practice; MDSC, myeloid derived suppressor cells; TGFβ1, transforming growth factor beta-1.

PRESENTED BY: Ulka Vaishampayan, MD

Phase 1 Clinical Trial Overview



*Cohort Any Other was terminated early and HNSCC was added.

ADA, anti drug antibody; BOR, best overall response; ccRCC, clear cell renal cell carcinoma; DCR, disease control rate; DoR, duration of response; ECOG, eastern cooperative oncology group; HNSCC, head and neck squamous cell carcinoma; MEL, melanoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PD-(L)1, PD-1/PD-L1; PFS, progression-free survival; PK, Pharmacokinetic; q2w, every 2 weeks; q3w, every 3 weeks; RECIST, response evaluation criteria in solid tumors; UC, urothelial carcinoma.

PRESENTED BY: Ulka Vaishampayan, MD

Preliminary Safety and Efficacy

Phase 1 *Dose Escalation Phase*

Safety

- **SRK-181 was well tolerated:** No DLTs observed; no Grade 4 or 5 treatment-related AEs

MAD/MTD

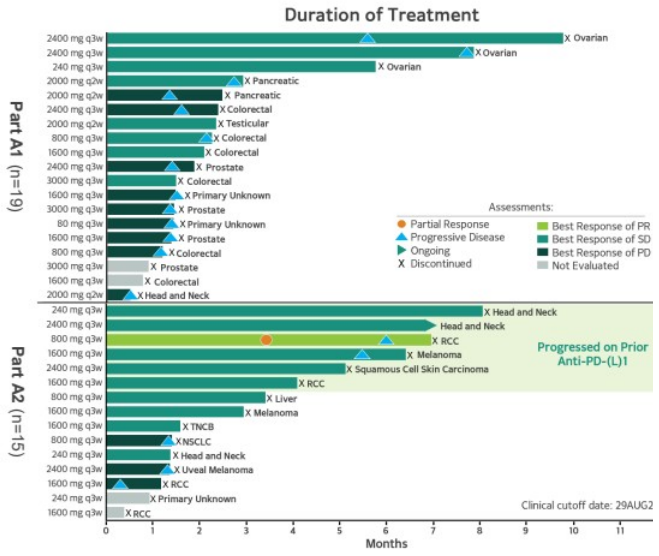
- **MAD:** 3000mg q3w and 2000mg q2w for single SRK-181 and 2400mg q3w for SRK-181 in combination with anti-PD-1
- **MTD not reached; recommended Part B dose** at 1500 mg q3w or 1000 mg q2w

PK

- Exposure was similar between monotherapy and combination
- Approximately dose proportional exposure over 240 mg q3w
- Minimal to no accumulation was observed after multiple doses

Efficacy

- **Part A1, Single-Agent Dose Escalation**
  - All 3 ovarian cancer patients were stable beyond ~ 6-month cutoff
- **Part A2, Combination Treatment Dose Escalation**
  - 1 PR in anti-PD-1 resistant ccRCC patient
  - 5 (33%) patients had SD for 4+ months
    - 1 HNSCC patient had a 29.4% tumor reduction



Martin CJ, et al. *Sci Transl Med*. 2020;12:eaay8456.
Yap T, et al. *J ImmunoTherapy of Cancer* 2022;10:doi: 10.1136/jitc-2022-SITC2022.0780.

AE, adverse event; ccRCC, clear cell renal cell carcinoma; DLT, dose-limiting toxicity; HNSCC, head and neck squamous cell carcinoma; MAD, maximum administered dose; MTD, maximum tolerated does; PK, Pharmacokinetic; PD, progressive disease; PR, partial response; q2w, every 2 weeks; q3w, every 3 weeks; SD, stable disease.

PRESENTED BY: Ulka Vaishampayan, MD

Patient Demographics and Disposition

Phase 1 Dose Expansion Phase

Category	All[#]
N	78
Age, median (range)	65y (32-81y)
Gender, M, n (%)	56 (71.8)
Prior Lines of Therapy, median (range)	3 (1-9)
Number of Lines of Prior Anti-PD-(L)1, n (%)	
1	48 (61.5)
2	23 (29.5)
3	6 (7.7)
4	1 (1.3)
Best Response to Prior Anti-PD-(L)1, n (%)	
Partial Response	1 (1.3)^
Stable Disease	40 (51.3)
Progressive Disease	37 (47.4)
Disease Progressed from the Last Prior Anti-PD-1, n (%)	76 (97.4)*

Category	All
Enrolled	78
On Study, n (%)	10 (12.8)
Stopped Treatment, n (%)	68 (87.2)
Reason for Completion/Discontinuation, n (%)	
Disease Progression Based on RECIST 1.1	40 (51.3)
Clinical Progression	6 (7.7)
Adverse Event[&]	17 (21.8)
Investigator Decision	1 (1.3)
Withdrawal of Consent	4 (5.1)

[&]10 patients (12.8%) discontinued from the study due to treatment-related AEs: rash maculo popular and pneumonitis (2 patients), bullous pemphigoid, colitis, erythroderma, generalized erythematous rash, invasive squamous cell carcinoma, mucositis oral (1 patient each).

[#]Includes patients of 30 ccRCC, 11 HNSCC, 11 MEL, 11 UC, 11 NSCLC and 4 Any Other Cohorts.
^1 HNSCC patient had best response of PR to prior anti-PD-(L)1.
*2 MEL patients discontinued the last prior anti-PD-(L)1 due to other reason instead of disease progression.

AE, adverse event; ccRCC, clear cell renal cell carcinoma; HNSCC, head and neck squamous cell carcinoma; MEL, melanoma; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PD-(L)1, PD-1/PD-L1; RECIST, response evaluation criteria in solid tumors; UC, urothelial carcinoma.

Manageable Safety Profile

Phase 1 Dose Expansion Phase

Treatment-Emergent AEs Related to SRK-181 or Anti-PD(L)1

Adverse Event	All Grades (>5%) N=78	≥Grade 3 N= 78
Rash#	25 (32.1%)*	10 (12.8%)*
Pruritus	20 (25.6%)*	1 (1.3%)*
Fatigue	16 (20.5%)	1 (1.3%)
Diarrhoea	11 (14.1%)	0 (0%)
Nausea	5 (6.4%)	1 (1.3%)
ALT increased	4 (5.1%)	2 (2.6%)
AST increased	4 (5.1%)	1 (1.3%)
Arthralgia	4 (5.1%)	0 (0%)
Vomiting	4 (5.1%)	0 (0%)

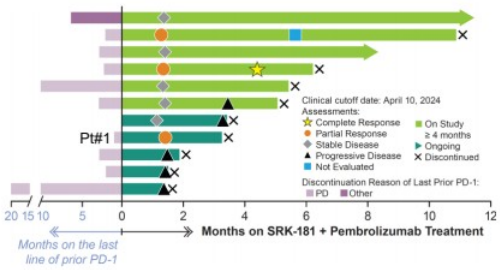
#Rash includes rash, rash macular, rash maculo-papular, rash erythematous, and rash pruritic.
*Treatment-related irAE.

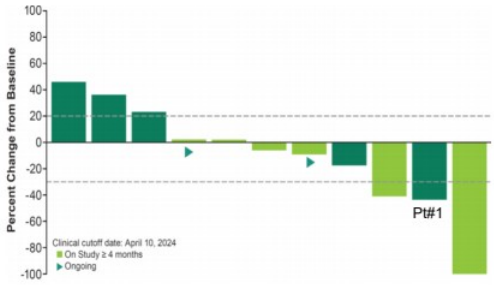
- There was 1 treatment-related Grade 4 AE (Dermatitis exfoliative generalised)
- There was no treatment-related Grade 5 AE
- Treatment-related SAE >2% (2 patients) were Pemphigoid (irAE)

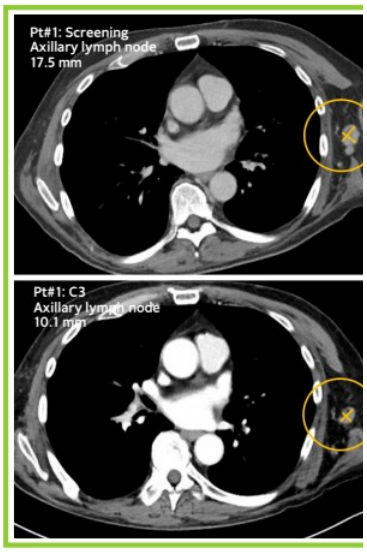
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAE, immune-related adverse event; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PD-(L)1, PD-1/PD-L1; SAE, serious adverse event

Efficacy in Cohort MEL

Clinical Responses in Anti-PD-1 Non-responders







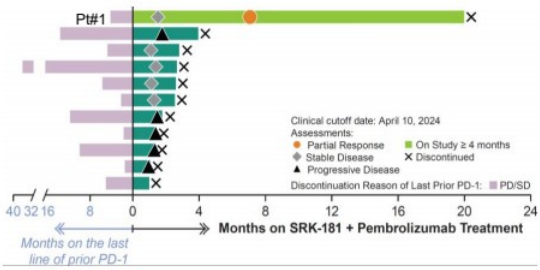
Efficacy	Intent To Treat N=11
ORR	**3 (27.3%)**
Confirmed CR	**1 (9.1%)**
Confirmed PR	**1 (9.1%)**
mDoR (Months)	**4.9 (1.8, 7.1)**
DCR	**8 (72.7%)**

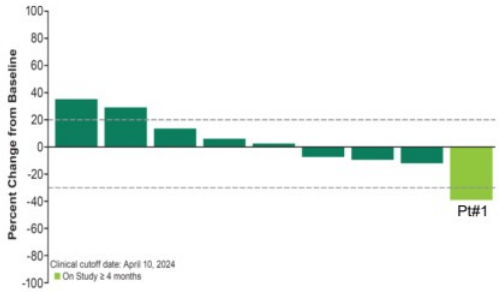
- **Median lines of prior cancer therapy: 3 (range 1 – 7)**
  - All have SD or PD as BOR to the last prior anti-PD-1
  - 9 (82%) had PD from the last prior anti-PD-1

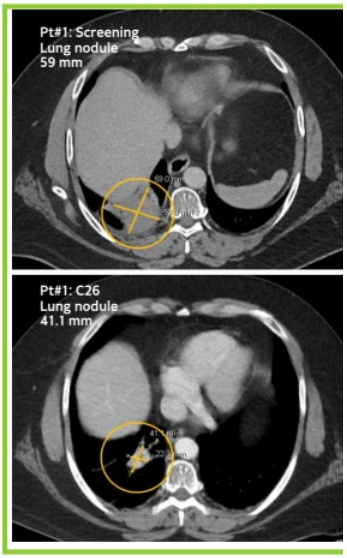
BOR, best overall response; CR, complete response; DCR, disease control rate; mDoR, median duration of response; MEL, melanoma; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response.

Efficacy in Cohort UC

Clinical Responses in Anti-PD-1 Non-responders







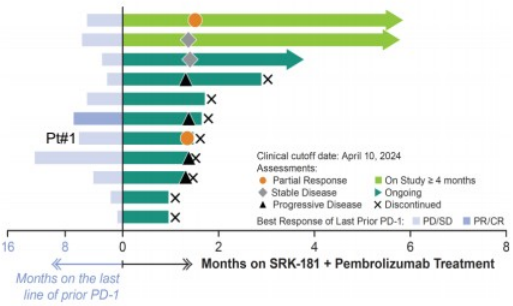
Efficacy	Intent To Treat N=11
ORR	1 (9.1%)
Confirmed PR	1 (9.1%)
mDoR (Months)	12.9 (12.9, 12.9)
DCR	5 (45.5%)

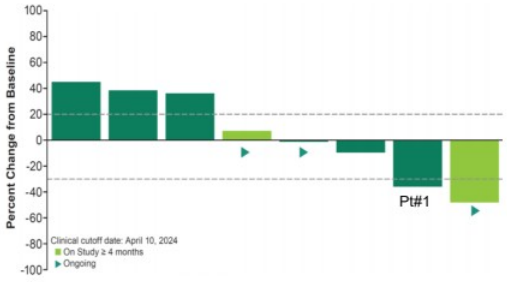
- **Median lines of prior cancer therapy: 4 (range 2 – 5)**
  - All have SD or PD as BOR to the last prior anti-PD-1
  - All had PD from the last prior anti-PD-1

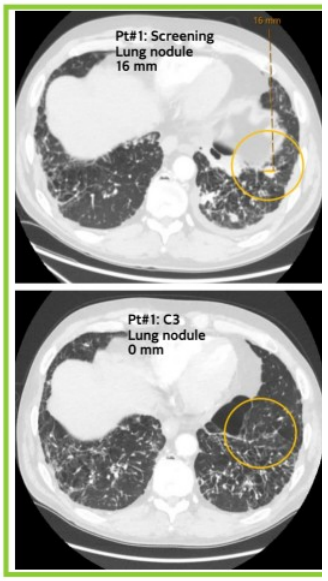
BOR, best overall response; DCR, disease control rate; mDoR, median duration of response; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease; UC, urothelial carcinoma.

Efficacy in Cohort HNSCC

Clinical Responses in Heavily Pre-treated and Anti-PD-1 Resistant Patients







Efficacy	Intent To Treat N=11
ORR	2 (18.2%)
Confirmed PR	1 (9.1%)
mDoR (Months)	2.2+ (0.1, 4.3+)
DCR	4 (36.4%)

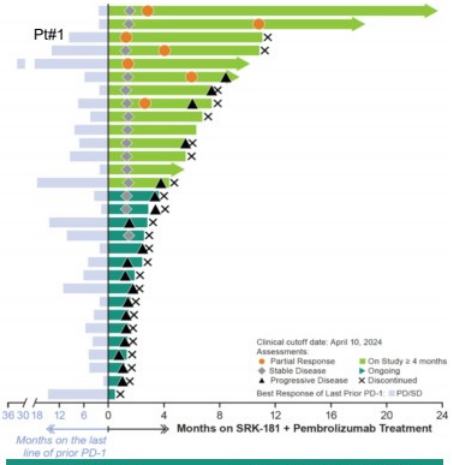
- **Median lines of prior cancer therapy: 3 (range 1 – 7)**
  - 10 (91%) have SD or PD as BOR to the last prior anti-PD-1
  - All had PD from the last prior anti-PD-1

BOR, best overall response; DCR, disease control rate; HNSCC, head and neck squamous cell carcinoma; mDoR, median duration of response; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease.

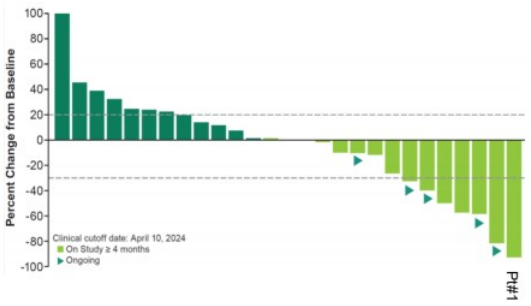
PRESENTED BY: Ulka Vaishampayan, MD

Efficacy in Cohort ccRCC

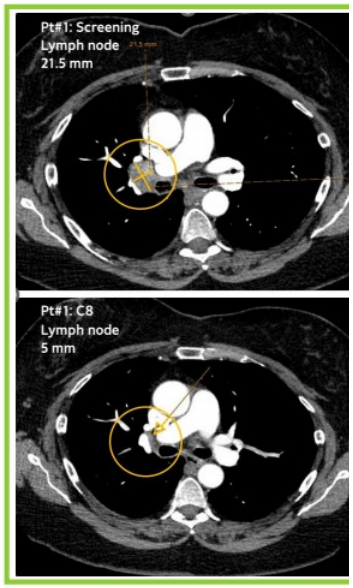
Clinical Responses in Heavily Pre-treated and Anti-PD-1 Resistant Patients



Efficacy	Intent To Treat N=30
ORR	7 (23.3%)
Confirmed PR	6 (20%)
mDoR (Months)	7.7+ (2.5+, 20.9+)
DCR	17 (56.7%)



- **IMDC score: intermediate 67%; poor 30%**
- **Median lines of prior cancer therapy: 2 (range 1 – 9)**
  - 29 (97%) received at least 1 prior anti-PD-1 and TKI
  - All had SD or PD as BOR to the last prior anti-PD-1
  - All had PD from the last prior anti-PD-1



BOR, best overall response; DCR, disease control rate; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mDoR, median duration of resp
ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhib

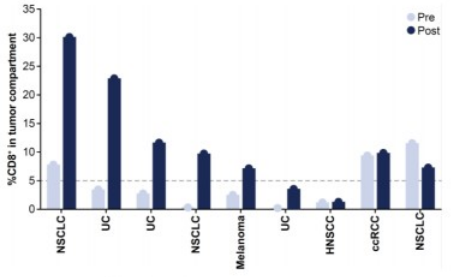
PRESENTED BY: Ulka Vaishampayan, MD

Proof of Mechanism

SRK-181 and Pembrolizumab Treatment Creates a Proinflammatory Microenvironment

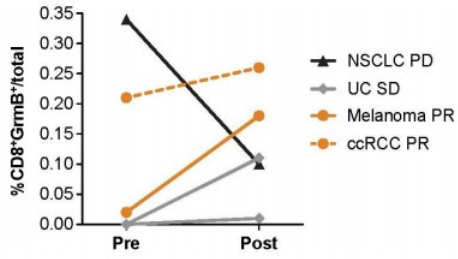
- SRK-181 and pembrolizumab increase CD8+ T-cells infiltration into tumors across multiple tumor types
- CD8+ T-cell were activated (CD8+GrmB+) in responding patients across multiple cohorts
- The number of CD8+GrmB+ cells correlates with tumor shrinkage

SRK-181 and Pembrolizumab Increased CD8+ Infiltration

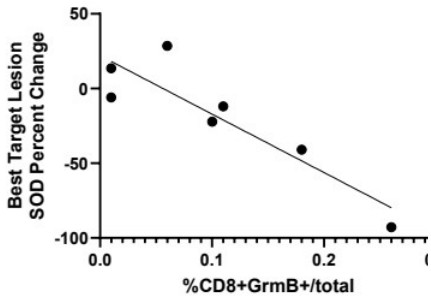


Line indicates cutoff that defines infiltrated status.
Data generated from available paired biopsies that were evaluated using a chromogenic assay.

CD8+ Cytotoxic T-cells were Activated in Responding Patients



Data generated from available paired biopsies that were evaluated using a multiplex fluorescent assay.



Data generated from available post treatment biopsies that were evaluated using a multiplex fluorescent assay.

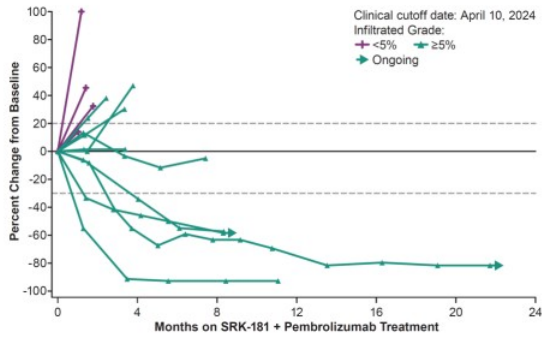
ccRCC, clear cell renal cell carcinoma; CD, cluster of differentiation; GrmB, Granzyme B; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; UC, urothelial carcinoma.

PRESENTED BY: Ulka Vaishampayan, MD

Biomarker Data May Inform Patient Selection Strategy

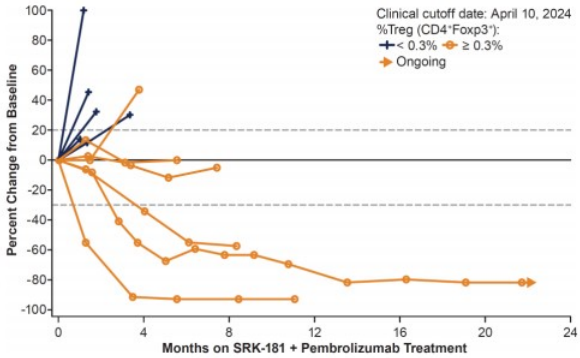
Baseline CD8+ T-cell Infiltration Status and Baseline Treg Levels Suggest a Higher Chance of Clinical Response

Baseline CD8+ Infiltration Status Suggest a Higher Chance of Response in ccRCC Patients



- Baseline data was available from 14 patients and 10 were infiltrated
- If enrollment had been limited to patients who were infiltrated at baseline:
  - ORR is increased from **23.3%** (7/30) to **40%** (4/10)
  - mDoR is improved from **7.7** months to **9.3** months

Elevated Baseline Treg (CD4+Foxp3+) Levels within Tumor Compartmer Suggest a Higher Chance of Response in ccRCC Patients



- Baseline data was available from 11 patients and 6 had elevated Treg leve
- If enrollment had been limited to patients with elevated Treg at baseline
  - ORR is increased from **23.3%** (7/30) to **50%** (3/6)
  - mDoR is improved from **7.7** months to **9.8** months

*1 patient progressed prior to 1st scan, so not represented on spider plot.

ccRCC, clear cell renal cell carcinoma; CD, cluster of differentiation; mDoR, median duration of response; Foxp3, forkhead box p3; ORR, objective response rate; TGFβ1, transforming growth factor beta-1; Treg, T regulatory cells

PRESENTED BY: Ulka Vaishampayan, MD

Summary

Objective evidence of anti-tumor activity across multiple cancer types with duration of response up to 20+ months

- ORR 23.3% in ccRCC, 18.2% in HNSCC, 27.3% in MEL, including 1 CR, and 9.1% in UC
- mDoR were 7.7+m in ccRCC, 2.2+m in HNSCC, 4.9m in MEL and 12.9m in UC

Biomarker findings establish proof of mechanism and inform potential patient selection strategy

- Combination was associated with enhanced proinflammatory microenvironment with activation of CD8+ T-cells in responding patients across multiple cohorts and the number of activated T-cells correlating with tumor shrinkage
- In baseline CD8+ T-cells infiltrated ccRCC patients, ORR increases from **23.3%** to **40%** with mDoR improving from **7.7 months** to **9.3 months**
- In baseline Treg elevated ccRCC patients, ORR increases from **23.3%** to **50%** with mDoR improving from **7.7 months** to **9.8 months**

Safety profile with the combination of SRK-181 and pembrolizumab was manageable

- Treatment-related AEs were primarily skin toxicities with 1 Grade 4 skin event; no Grade 5 event
- Treatment-related G3+ AEs ≥ 5% were rash only and treatment-related SAE ≥ 2% were pemphigoid only

AE, adverse event; ccRCC, clear cell renal cell carcinoma; CD, cluster of differentiation; CR, complete response; HNSCC, head and neck squamous cell carcinoma; mDoR, median duration of response; MEL, melanoma; ORR, objective response rate; PD, progressive disease; PR, partial response; SAE, serious adverse events; SD, stable disease; Treg, T regulatory cells; UC, urothelial carcinoma.

Conclusion

- Anti-tumor activity in anti-PD1 resistant patients across multiple cancer types establishes proof-of-concept for SRK-181, a selective latent TGFβ1 inhibitor
- Biomarker results establish proof of mechanism and inform potential patient selection strategy in ccRCC
- These data warrant further investigation of SRK-181

TGFβ1, transforming growth factor beta-1.

THANK YOU FOR YOUR ATTENTION

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