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

Key Takeaways

SRK-181 (linavonkibart) is a selective latent TGFβ1 inhibitor

- Designed to have improved safety profile and therapeutical window vs non-selective TGFβ inhibitor

Ongoing Phase 1 study shows:

- Anti-tumor activity in anti-PD1 resistant patients across multiple cancer types
- Proof of mechanism and potential patient selection strategy from biomarker analysis
- Manageable safety profile of the combination treatment of SRK-181 and pembrolizumab

PD-1, programmed cell death protein 1; TGFβ1, transforming growth factor beta-1.

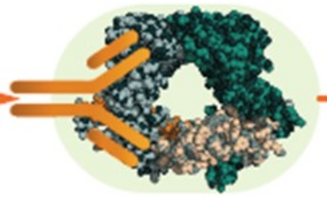
Mechanism of Action

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

TGFβ1 → Drives tumor immune escape that enables tumor survival[1] → Key driver of tumor resistance to CPIs[1] → Present in multiple compartments of the tumor microenvironment[1]

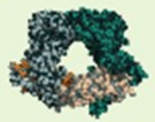
SRK-181 overcomes immune suppression and enhances tumor cell killing

Fully human IgG4 monoclonal antibody



Complete inhibition of TGFβ1

Inhibits activation of latent TGFβ-1 across ALL tumor compartments



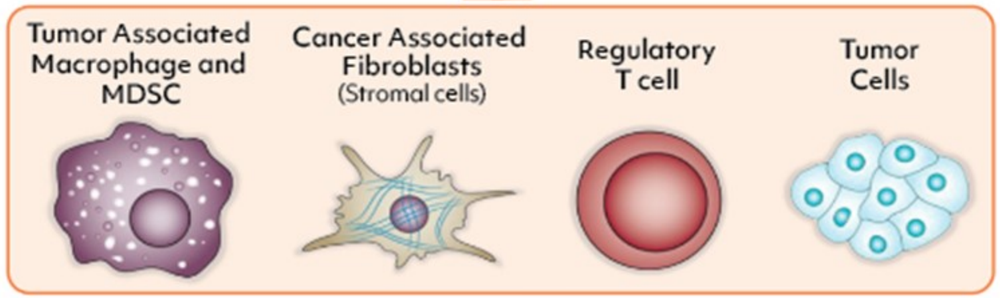
Latent TGFβ1

Mature TGFβ1

SRK-181 Targets latent TGFβ1 inhibiting growth factor before it gets activated

High selectivity to TGFβ1 vs TGFβ2/3

Increases therapeutic window and demonstrates an improved safety profile in GLP nonclinical toxicology studies, with no cardiotoxicities



Overcome immune suppression and enhance tumor cell killing

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.

Phase 1 Clinical Trial Overview

Dose Escalation (3+3)

Part A1: SRK-181 Single Agent
(80-3000 mg q3w/2000 mg q2w)

All advanced solid tumor
n=19

Part A2: SRK-181 + anti-PD-(L)1
(SRK-181: 240-2400mg q3w)

Advanced solid tumor non-responders to prior anti-PD-(L)1
n= 15

Dose Expansion

Part B: SRK-181 (1500mg q3w) + Pembrolizumab
n=up to 40/cohort

Key Eligibility Criteria

- ≥18-year-old and ECOG 0-1
- Measurable disease per RECIST v1.1
- At least 1 prior line of anti-PD-1 antibody
- Part B Cohort **ccRCC** and **HNSCC**:
  - Must have had PD on the most recent prior anti-PD-1
- Part B Cohorts **NSCLC**, **UC** and **MEL**:
  - Non-responders to all prior anti-PD-1

Cohort ccRCC
Cohort HNSCC
Cohort MEL
Cohort UC
Cohort NSCLC
Cohort Any Other*

Study Endpoints

Primary:
- Safety and tolerability

Secondary:
- Anti-tumor activity (BOR, ORR, DoR, and DCR)
- PK and ADA

Exploratory:
- Biomarker
- PFS, OS, etc.

*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.

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

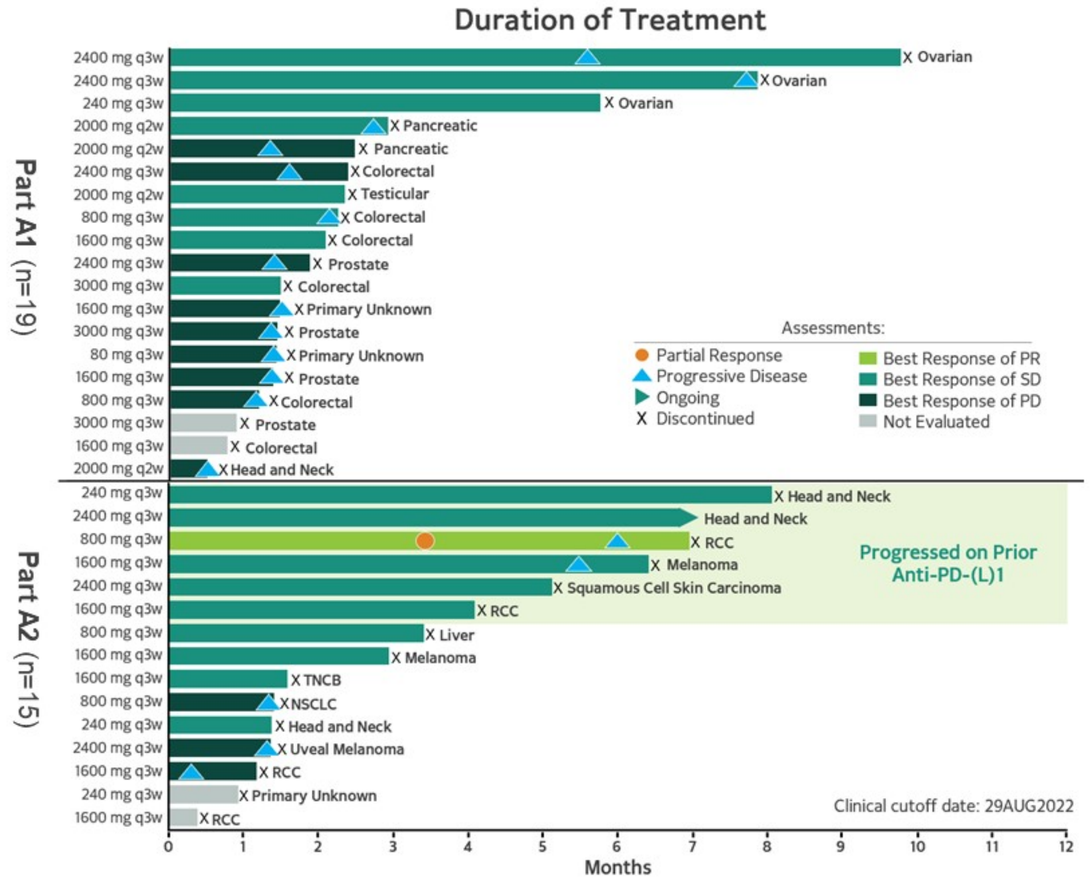
- **MAD:** 3000mg q3w and 2000mg q2w for single SRK-181 and 2400mg q3w for SRK-181 in combination with anti-PD-1
- **MTD not reached; recommended Part B dose** at 1500 mg q3w or 1000 mg q2w

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.

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%)

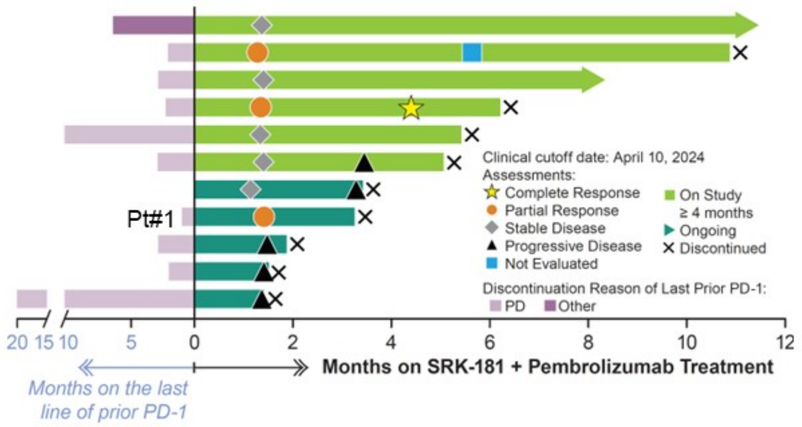
#Rash includes rash, rash macular, rash maculo-papular, rash erythematous, and rash pruritic.
*Treatment-related irAE.

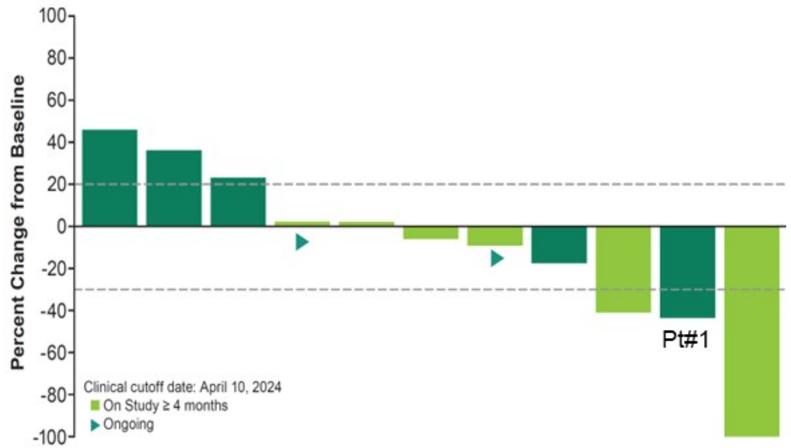
- There was 1 treatment-related Grade 4 AE (Dermatitis exfoliative generalised)
- There was no treatment-related Grade 5 AE
- Treatment-related SAE >2% (2 patients) were Pemphigoid (irAE)

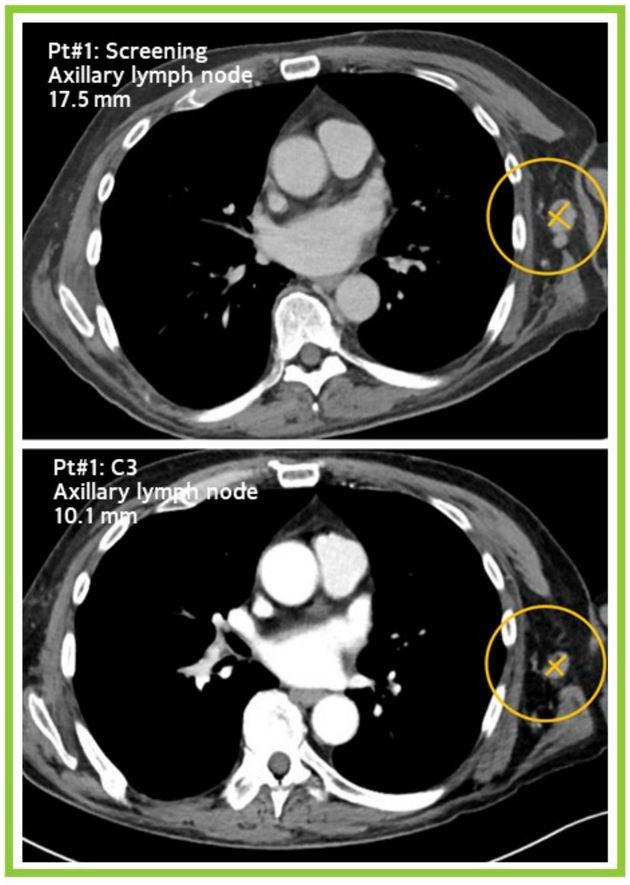
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAE, immune-related adverse event; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PD-(L)1, PD-1/PD-L1; SAE, serious adverse event

Efficacy in Cohort MEL

Clinical Responses in Anti-PD-1 Non-responders







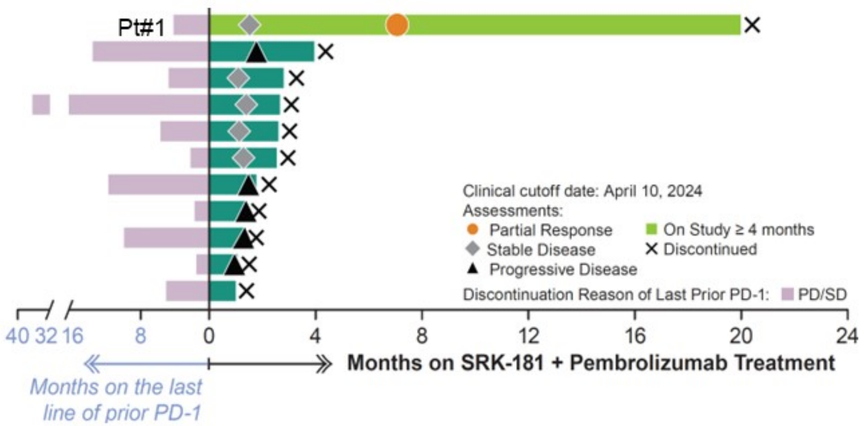
Efficacy	Intent To Treat N=11
ORR	3 (27.3%)
Confirmed CR	1 (9.1%)
Confirmed PR	1 (9.1%)
mDoR (Months)	4.9 (1.8, 7.1)
DCR	8 (72.7%)

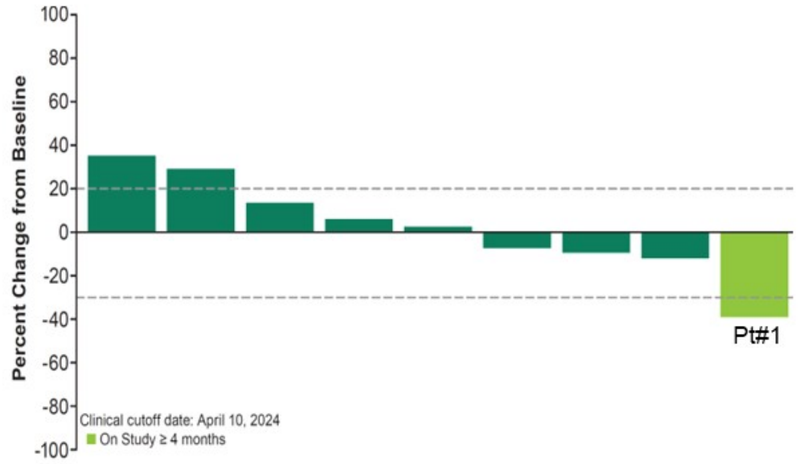
- **Median lines of prior cancer therapy: 3 (range 1 – 7)**
  - All have SD or PD as BOR to the last prior anti-PD-1
  - 9 (82%) had PD from the last prior anti-PD-1

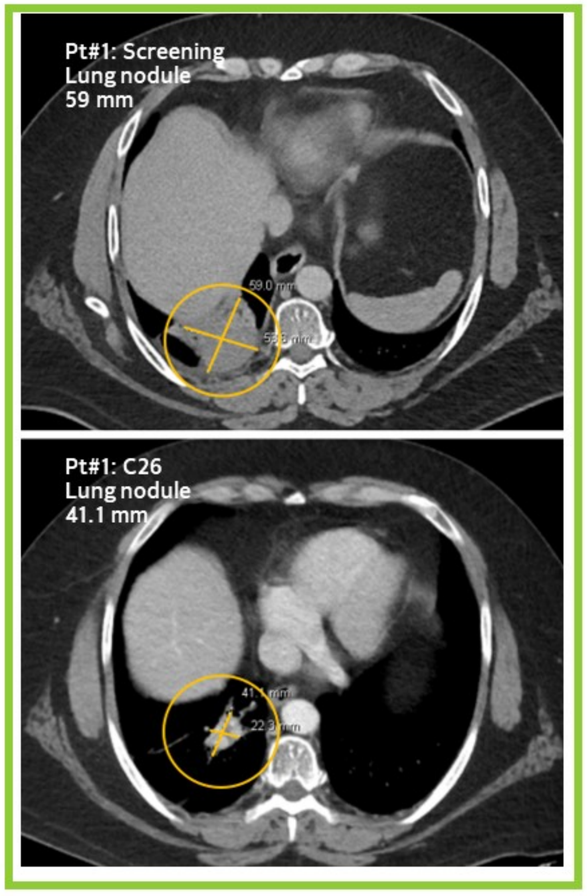
BOR, best overall response; CR, complete response; DCR, disease control rate; mDoR, median duration of response; MEL, melanoma; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response.

Efficacy in Cohort UC

Clinical Responses in Anti-PD-1 Non-responders







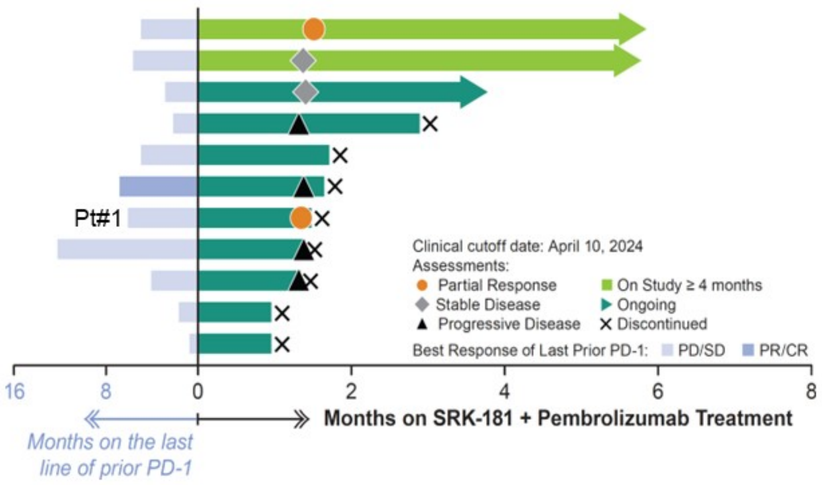
Efficacy	Intent To Treat N=11
ORR	1 (9.1%)
Confirmed PR	1 (9.1%)
mDoR (Months)	12.9 (12.9, 12.9)
DCR	5 (45.5%)

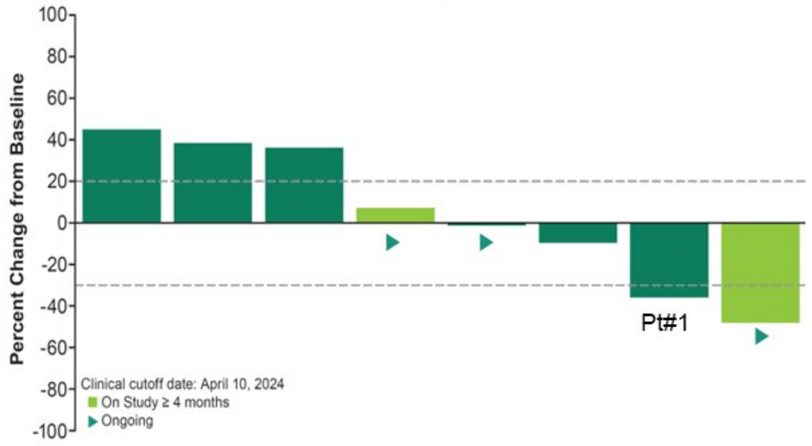
- **Median lines of prior cancer therapy: 4 (range 2 – 5)**
  - All have SD or PD as BOR to the last prior anti-PD-1
  - All had PD from the last prior anti-PD-1

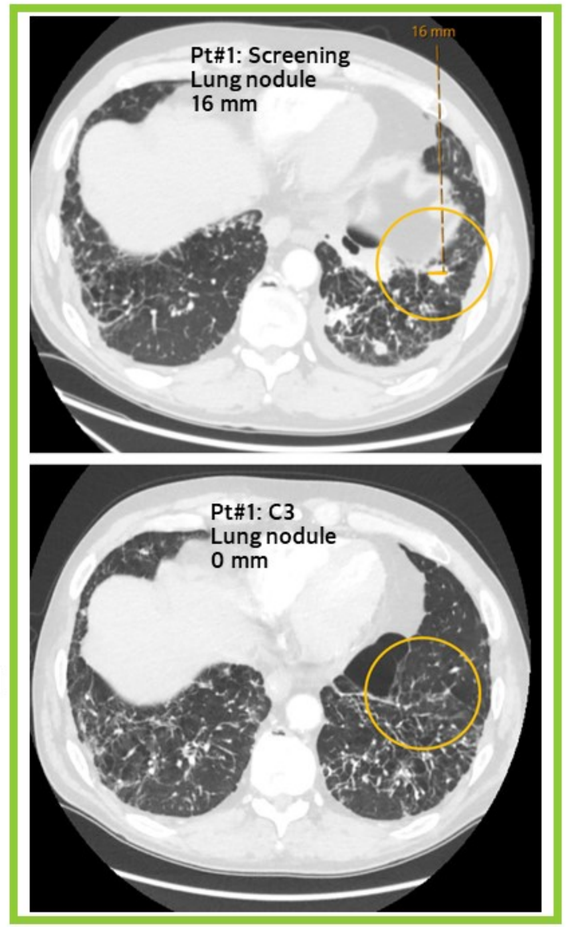
BOR, best overall response; DCR, disease control rate; mDoR, median duration of response; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease; UC, urothelial carcinoma.

Efficacy in Cohort HNSCC

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







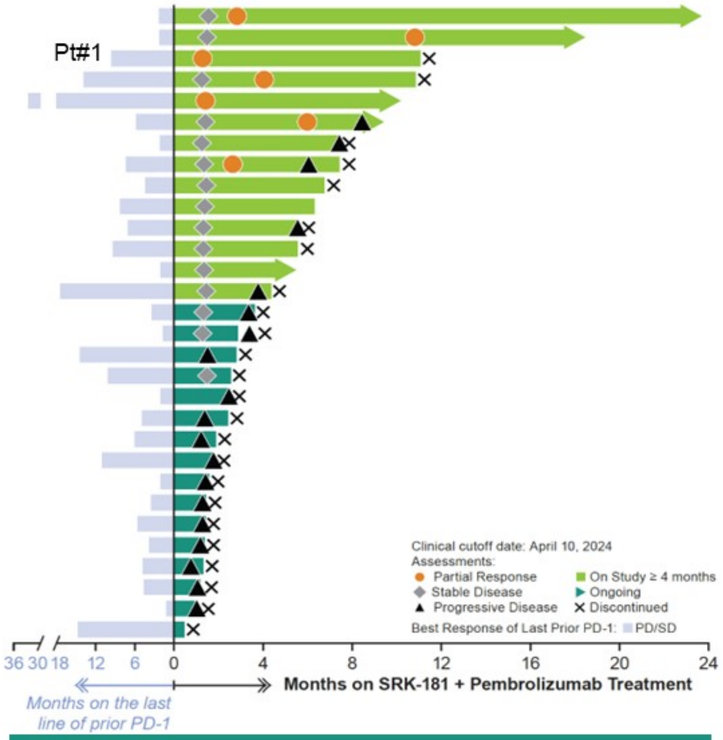
Efficacy	Intent To Treat N=11
ORR	2 (18.2%)
Confirmed PR	1 (9.1%)
mDoR (Months)	2.2+ (0.1, 4.3+)
DCR	4 (36.4%)

- **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

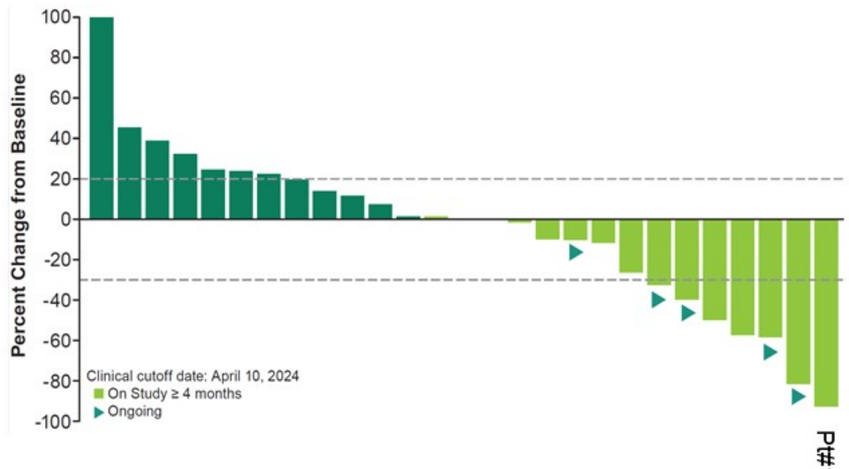
BOR, best overall response; DCR, disease control rate; HNSCC, head and neck squamous cell carcinoma; mDoR, median duration of response; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease.

Efficacy in Cohort ccRCC

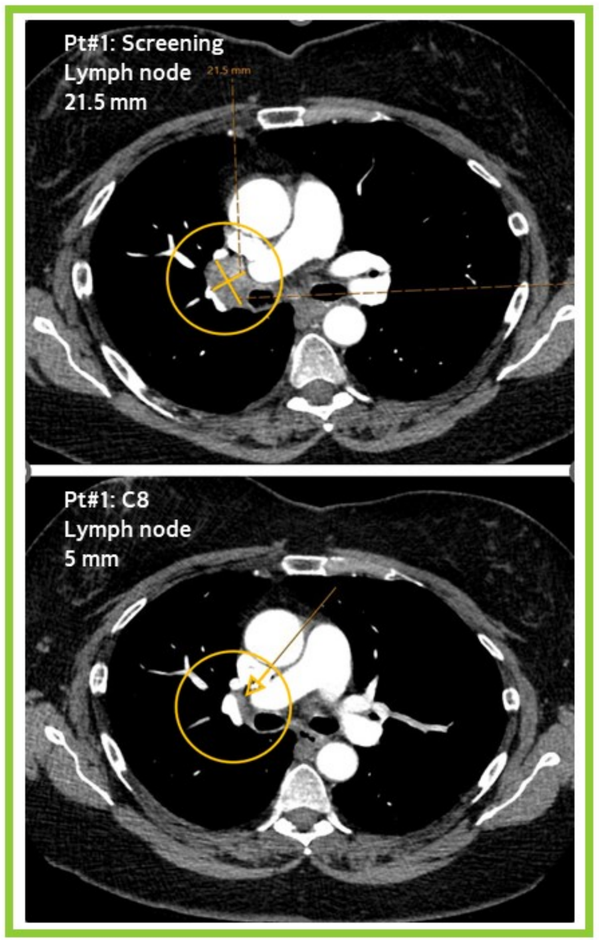
Clinical Responses in Heavily Pre-treated and Anti-PD-1 Resistant Patients



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 response; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

PRESENTED BY: Ulka Vaishampayan, MD

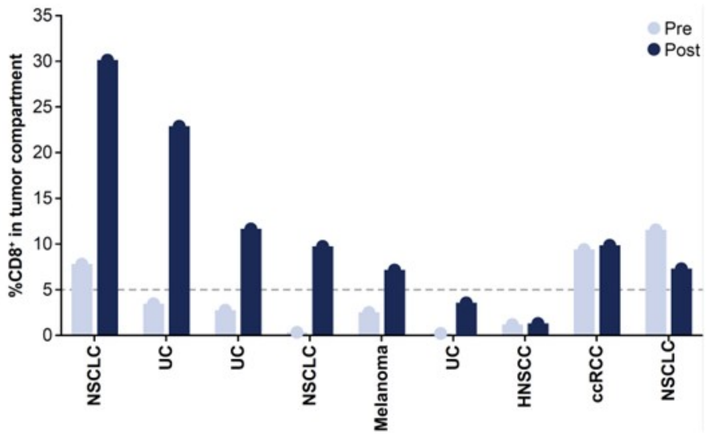
Data cut date: Apr 10, 2024

Proof of Mechanism

SRK-181 and Pembrolizumab Treatment Creates a Proinflammatory Microenvironment

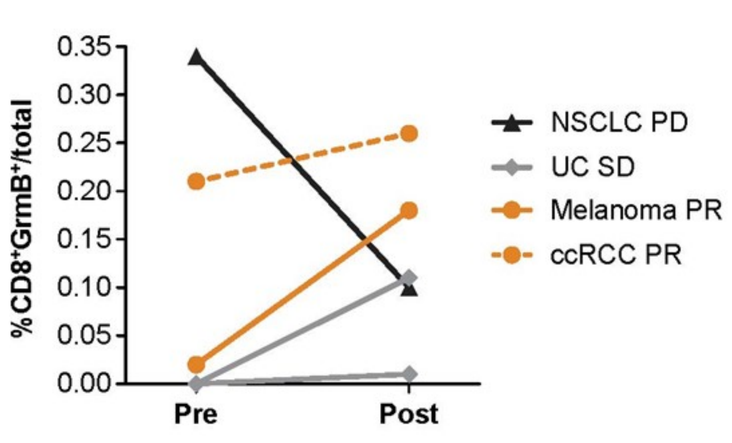
- SRK-181 and pembrolizumab increase CD8+ T-cells infiltration into tumors across multiple tumor types
- CD8+ T-cell were activated (CD8+GrmB+) in responding patients across multiple cohorts
- The number of CD8+GrmB+ cells correlates with tumor shrinkage

SRK-181 and Pembrolizumab Increased CD8+ Infiltration

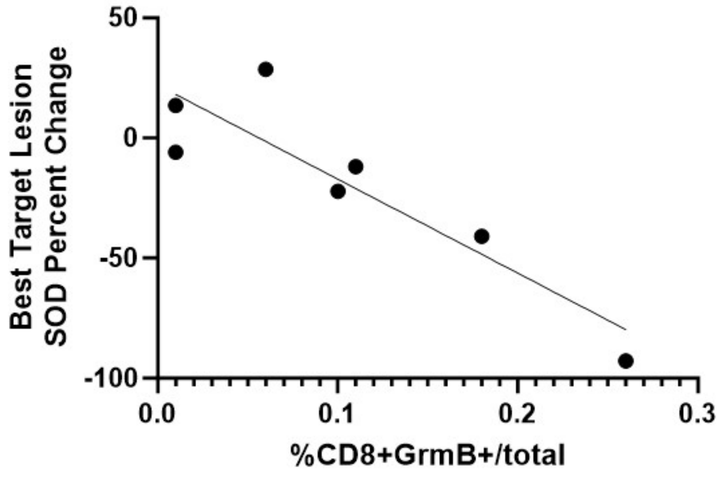


Line indicates cutoff that defines infiltrated status.
Data generated from available paired biopsies that were evaluated using a chromogenic assay.

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.

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PRESENTED BY: Ulka Vaishampayan, MD
Data cut date: Apr 10, 2024
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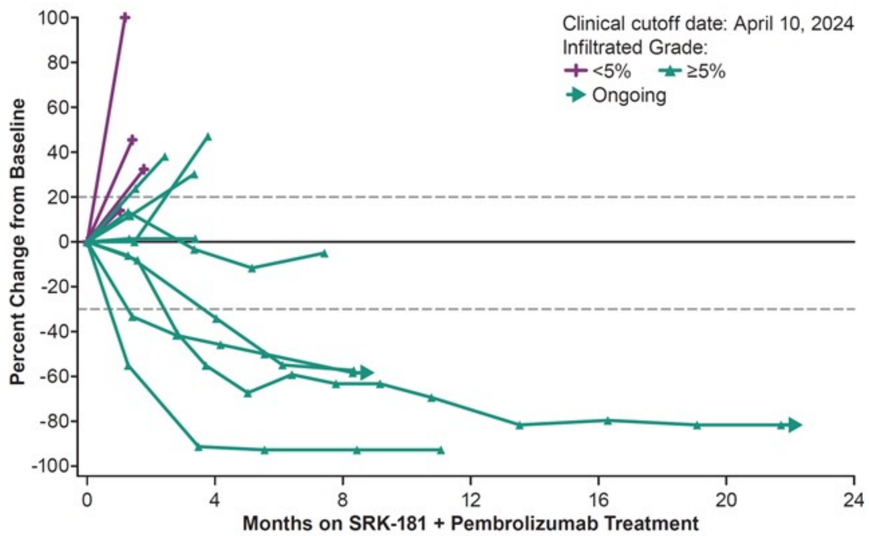
KNOWLEDGE CONQUERS CANCER

Biomarker Data May Inform Patient Selection Strategy

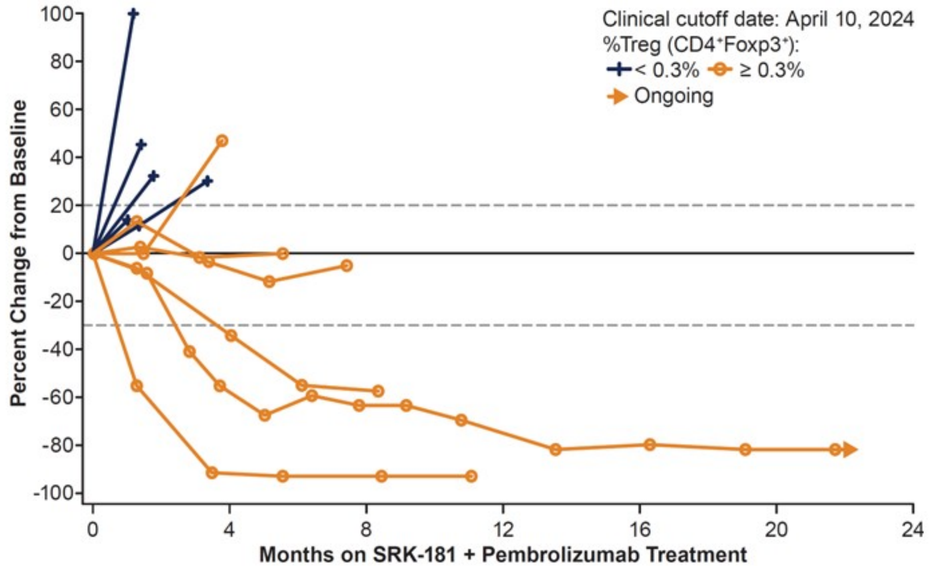
Baseline CD8+ T-cell Infiltration Status and Baseline Treg Levels Suggest a Higher Chance of Clinical Response

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 Compartment Suggest a Higher Chance of Response in ccRCC Patients



- Baseline data was available from 11 patients and 6 had elevated Treg levels
- 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

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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