Safety, Efficacy, and Biomarker Results of SRK-181, a Latent TGFβ1 Inhibitor, in Anti-PD-1 Resistant Metastatic ccRCC Patients

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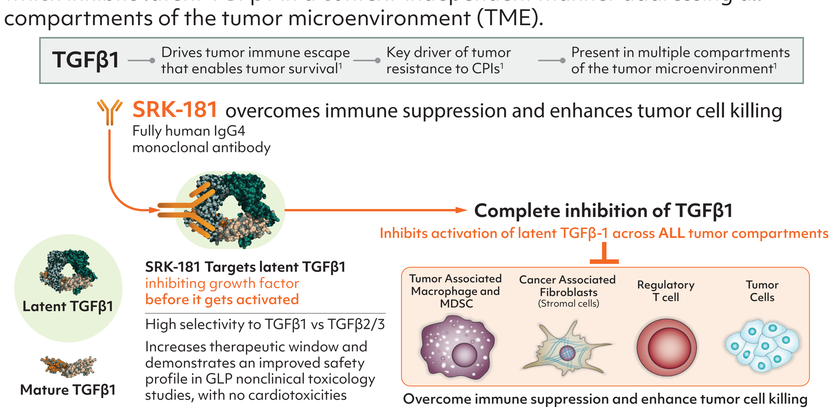
Background

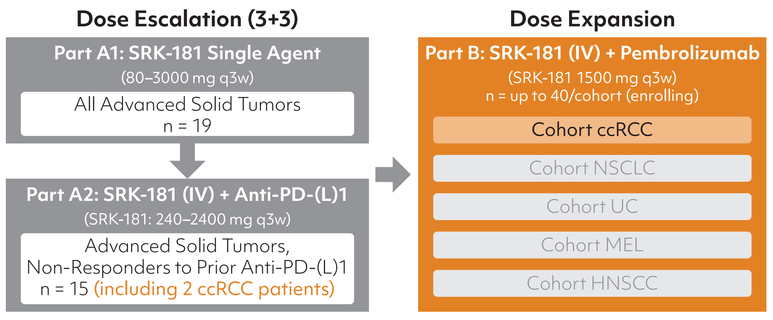
- SRK-181 is an investigational, fully human, selective, IgG4 monoclonal antibody, which inhibits latent TGFβ1 in a context-independent manner addressing all compartments of the tumor microenvironment (TME).



- In mouse tumor models (bladder, melanoma, and breast cancer), SRK-181 in combination with anti-PD-1 therapy overcame primary anti-PD-1 resistance and demonstrated anti-tumor activity.[2]
- MDSC have immune suppressive functions and promote tumor growth and contribute to resistance to immunotherapy. Preclinical results demonstrate that SRK-181 + anti-PD-1 combination therapy significantly reduces myeloid-derived suppressor cell (MDSC) levels within the TME and circulation, which correlates with improved anti-tumor responses.[1-4]
- In the dose escalation part of the DRAGON study, SRK-181 has been generally well-tolerated by patients as a monotherapy and in combination with an anti-PD-(L)1.[5]
  - » No DLTs were observed up to 3000 mg q3w and 2000 mg q2w in SRK-181 monotherapy and up to 2400 mg q3w in combination treatment of SRK-181 + anti-PD-(L)1.
  - » The recommended expansion dose of SRK-181 is 1500mg q3w + anti-PD-(L)1.

Phase 1 Clinical Trial Overview

DRAGON (NCT04291079) is an ongoing, open-label, Phase 1 study. This poster focuses on data from all ccRCC patients in Part A2 and Part B, as enrollment of this cohort was the fastest to achieve enrollment goals.



Eligibility for ccRCC Patients

- >18 years old and ECOG 0–1
- Measurable disease per RECIST v1.1
- At least 1 prior line of anti-PD-1 antibody
- Part A2:
  - Non-responsive to prior anti-PD-1 with a best response of PD or SD
- Part B:
  - Must have had PD on the most recent prior anti-PD-1 treatment
  - Up to 3 lines of treatment are allowed between the last dose of prior anti-PD-1 treatment

ccRCC Demographics and Baseline Characteristics

Category	All
N	30*
Age, median (range)	57 (43-80)
Gender (F/M), n (%)	6 (20) / 24 (80)
Ethnicity, n (%)	
Hispanic or Latino	7 (23.3)
Not Hispanic or Latino	21 (70.0)
Not Reported	2 (6.7)
Race, n (%)	
Asian	1 (3.3)
African American	2 (6.7)
White	24 (80.0)
Not Reported	3 (10.0)
Site of Metastases at Baseline, n (%)	
Bone	12 (40.0)
Liver	9 (30.0)
Lung	24 (80.0)
Had Prior Cancer Surgery (Nephrectomy), n (%)	20 (66.7)
IMDC Score at Baseline, n (%)	
Favorable (0)	1 (3.3)
Intermediate (1-2)	18 (60.0)
Poor (≥3)	11 (36.7)
Prior Lines of Therapy, median (range), n (%)	2.5 (1-9)
1	5 (16.7)
2	10 (33.3)
≥3	15 (50)
Received At Least 1 Prior Line of Anti-PD-(L)1 and TKI, n (%)	29 (96.7)
Disease Progressed from the Last Line of Prior Anti-PD-1, n (%)	30 (100)
Best Response of the Last Prior Anti-PD-1	
Stable Disease	14 (46.7)
Progressive Disease	14 (46.7)
Unknown	2 (6.7)
Lines of Prior Anti-PD-(L)1, n (%)	
1	16 (53.3)
2	10 (33.3)
3	3 (10.0)
4	1 (3.3)
Immediate Prior Line of Treatment, n (%)**	
TKI	20 (66.7)
Anti-PD-1	16 (53.3)
Other	12 (40.0)

*2 patients were dosed at 800mg q3w and 1600mg q3w in Part A2. All others were dosed at 1500mg q3w in Part B. **A subject could receive combination treatment. Therefore, the sum is more than 100%.

Clinical cutoff date: August 29, 2023

ccRCC Patient Disposition

Category	All
Enrolled	30
On Study, n (%)	11 (36.7)
Stopped Treatment, n (%)	19 (63.3)
Reason for Completion/Discontinuation, n (%)	
Adverse Event	2 (6.7)*
Clinical Progression	2 (6.7)
Disease Progression based on RECIST v1.1	12 (40.0)
Withdrawal of Consent	3 (10.0)

*2 patients discontinued from the study due to treatment-related AE of stomatitis (Grade 3) and dermatitis exfoliative generalized (Grade 4) respectively.

Clinical cutoff date: August 29, 2023

Safety in ccRCC

Treatment-Emergent AEs Related to SRK-181 or Anti-PD-1 and Immune-Related AE (irAE), All Grades >5%, n (%)

Adverse Event, n (%)	All Grades (n = 30)	Grade 3 (n = 30)	irAE (n = 30)	irAE Grade 3 (n = 30)
Rash*	7 (23.3)	5 (16.7)	7 (23.3)	5 (16.7)
Pruritus	3 (10.0)	0 (0)	3 (10.0)	0
ALT increased	3 (10.0)	1 (3.3)	0	0
AST increased	3 (10.0)	1 (3.3)	0	0
Dyspnoea	2 (6.7)	0 (0)	0	0
Fatigue	2 (6.7)	0 (0)	0	0
Stomatitis	2 (6.7)	1 (3.3)	0	0

*Rash includes rash, rash maculo-papular and rash erythematous

Clinical cutoff date: August 29, 2023

- Only one Grade 4 treatment-related AE was observed, which was dermatitis exfoliative generalized (irAE).
- No Grade 5 treatment-related AE occurred.
- Treatment-related SAEs were dermatitis exfoliative generalized (1 patient, irAE), pemphigoid and rash (both in 1 patient, irAEs); immune-mediated hepatitis (1 patient, irAE); diarrhea, nausea and vomiting (all three AEs in 1 patient).

Preliminary Efficacy in ccRCC

- Twenty-eight (28) patients are response-evaluable, 6 patients had confirmed partial response (PR) based on RECIST1.1 criteria by PI assessment (ORR=21.4%).
  - » The 6 PR patients were heavily treated with median prior lines of therapy of 3.5 (range: 2-5).
    - These patients received at least one line of anti-PD-1 and one line of TKI
    - Had best response of SD or PD on prior anti-PD-1
    - Disease progressed on the last line of prior anti-PD-1
  - » The 6 PR patients achieved a best tumor reduction of -33% to -93%, and remained on study for 2.8+ to 16.3+ months (5 patients > 6.5+ months).
  - » Four PR patients are still on study.
- Ten additional patients had stable disease (SD), five of them are still on study.

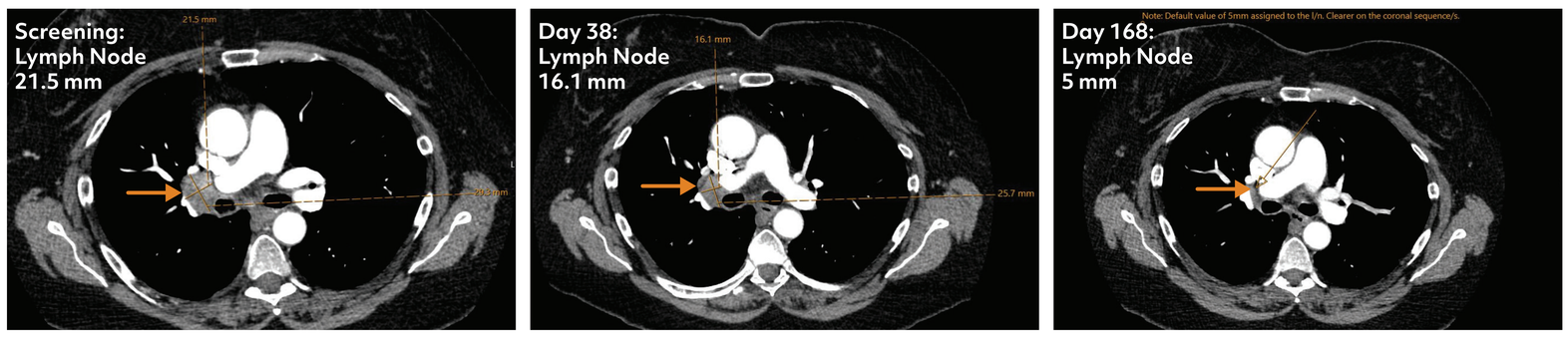
Efficacy in Response-Evaluable ccRCC Patients, n (%)*	N = 28
Best Response	
Complete Response (CR)	0
Partial Response (PR)	6 (21.4)
Stable Disease (SD)	10 (35.7)
Progressive Disease (PD)	9 (32.1)
Objective Response Rate (ORR)	6 (21.4)
Disease Control Rate (DCR)	16 (57.1)

*Response-evaluable patients are all enrolled patients except those who are still on study, but pending post-treatment radiographic evaluation. (2 out of 30 patients are pending post-treatment radiographic evaluation)

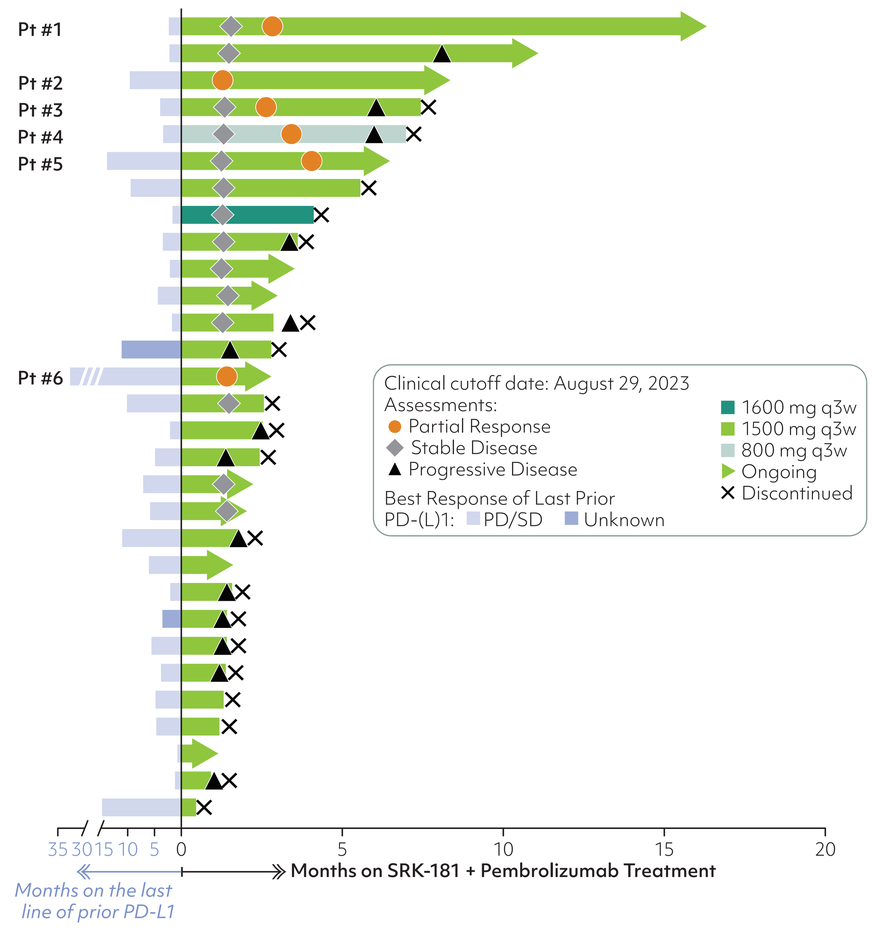
Clinical cutoff date: August 29, 2023

Patients with PR	SRK-181 Dose (mg, Q3W)	Age (yrs) / Gender	Lines of Prior Therapy	IMDC Score at Screening	Metastatic Sites at Screening	Pt Status	Treatment Duration (months)	Best % Change in SOD from Baseline
Pt #1	Part B, 1500	58/M	1. Nivolumab/Ipilimumab 2. Cabozantinib	3 (Poor risk)	Liver, Lung, Lymph Nodes, Kidney	Ongoing	16.3+	-82%
Pt #2	Part B, 1500	58/F	1. Nivolumab/Ipilimumab 2. Belzutifan 3. Cabozantinib	1 (Intermediate risk)	Bone, Lung, Lymph Nodes, Kidney	Ongoing	8.3+	-93%
Pt #3	Part B, 1500	63/M	1. Nivolumab/Ipilimumab 2. Nivolumab 3. Cabozantinib	2 (Intermediate risk)	Lung, Lymph Nodes	Off study	7.4	-50%
Pt #4	Part A2, 800	56/M	1. Sunitinib 2. Nivolumab/Ipilimumab 3. Cabozantinib 4. Lenvatinib/Everolimus 5. Pembrolizumab/Axitinib	3 (Poor risk)	Bone, Lung, Lymph Nodes, Pleural, Pancreas	Off study	7	-57%
Pt #5	Part B, 1500	69/F	1. Sunitinib 2. Sunitinib 3. Nivolumab/Ipilimumab 4. Axitinib 5. Pembrolizumab/Lenvatinib	2 (Intermediate risk)	Bone, Liver, Lung, Genitalia	Ongoing	6.5+	-55%
Pt #6	Part B, 1500	51/M	1. Nivolumab/Ipilimumab 2. Nivolumab 3. Pembrolizumab/Axitinib 4. Other (clinical trial, anti-CD3 & ENPP3)	3 (Poor risk)	Lymph Nodes	Ongoing	2.8+	-33%

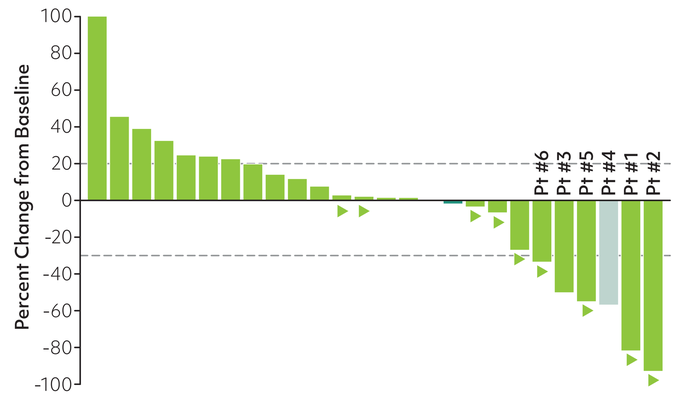
ccRCC Patient #2 with Ongoing PR



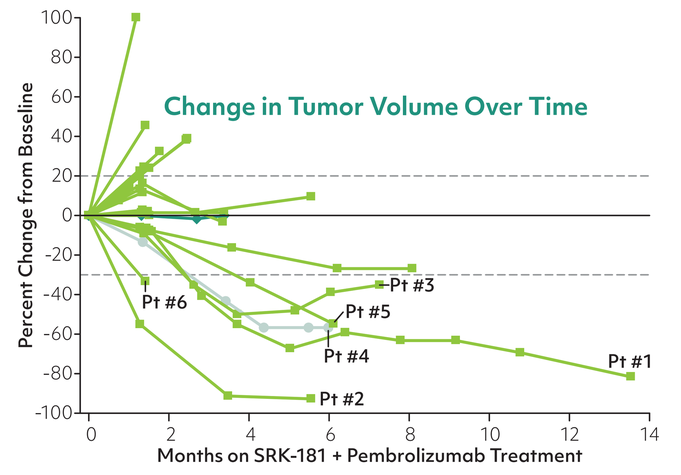
Duration of Treatment



Best Response in Target Lesions



Change in Tumor Volume Over Time

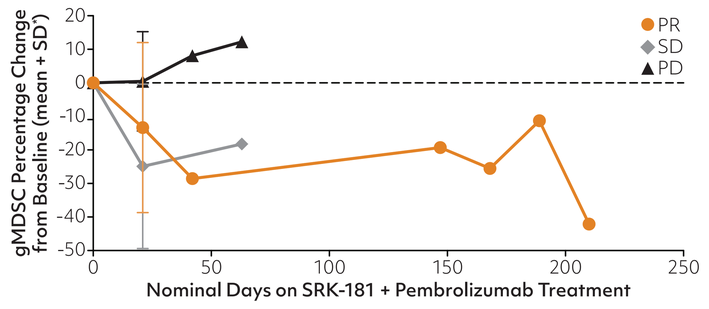


Preliminary Biomarker Summary of SRK-181 in ccRCC

- For ccRCC patients with best response of PR or SD, SRK-181 + pembrolizumab treatment was associated with decreased circulatory gMDSC below baseline.
- For most of the ccRCC patients with best response of PD, gMDSC levels increased above baseline.
- Similar data was generated for mMDSC; however, achieving PR was not associated with decreased circulatory mMDSC below baseline. For patients with the best response of PD, mMDSC levels increased above baseline. A comprehensive analysis of biomarkers in the Dragon study is reported in Poster #726.

The level of gMDSC cells were assessed in patient blood samples using flow cytometry (MDSCV Assay, Labcorp, Burlington, NC). *Multiple patient samples were collected on Day 21, while a single sample was collected at other time points because the protocol was amended to add sample collections on the first day of each subsequent cycle.

Deeper Suppression of gMDSC Correlates with Better Response in SRK-181 + Pembrolizumab-Treated ccRCC



Summary

- In heavily pretreated patients with ccRCC resistant to anti-PD-1, combination therapy of SRK-181 and pembrolizumab demonstrated promising anti-tumor activity with ORR of 21.4%, disease control rate of 57%, and durability of responses. By contrast, anti-PD-1 retreatment is generally associated with single-digit ORR or no response.[6]
- The combination treatment was generally well tolerated as of the data cutoff (Aug 29, 2023) with predominant skin toxicities of rash and pruritus (irAE).
- Circulating gMDSC levels correlate with better clinical responsiveness in ccRCC patients treated with SRK-181 + pembrolizumab.
- Our data highlights the immunosuppressive role of TGFβ as a mechanism of anti-PD-1 resistance in patients and warrants further investigation of SRK-181.

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Abbreviations: AE, adverse event; ALT, alanine aminotransferase; Anti-PD-(L)1, programmed death ligand-1 antibody/programmed cell death protein-1 antibody; AST, aspartate aminotransferase; ccRCC, clear cell renal cell carcinoma; CPI, checkpoint inhibitor; CR, complete response; DCR, disease control rate; DLT, dose-limiting toxicity; gMDSC, granulocytic myeloid derived suppressor cell; irAE, immune-related adverse event; MBT-2, Mouse Bladder Tumor line-2; mMDSC, monocytic myeloid derived suppressor cell; MDSC, myeloid derived suppressor cell; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, progressive disease; PI, principal investigator; PR, partial response; q2w, every 2 weeks; q3w, every 3 weeks; RCC, renal cell carcinoma; SAE, serious adverse event; SD, stable disease; TGFβ1, transforming growth factor beta-1; TKI, tyrosine kinase inhibitor; TME, tumor microenvironment; UC, urothelial carcinoma.

References: 1) Batlle, et al. *Immunity.* 2019; 50(4):924-940. 2) Martin, et al. *Sci Transl Med.* 2020;12:eaay8456. 3) Law, et al. *Cells*, 2020. 9(3). 4) Meyer, et al. *Cancer Immunol Immunother*, 2014. 63(3): p. 247-57. 5) Yap, et al. *Journal for ImmunoTherapy of Cancer*, 2022;10:doi: 10.1136/jitc-2022-SITC2022.0780 6) Pal, et al. *The Lancet.* 2023; 15;402(10397):185-195.