Establishing Proof of Mechanism in Patients: Preliminary Biomarker Data of SRK-181 (a latent TGFβ1 inhibitor) from DRAGON Study

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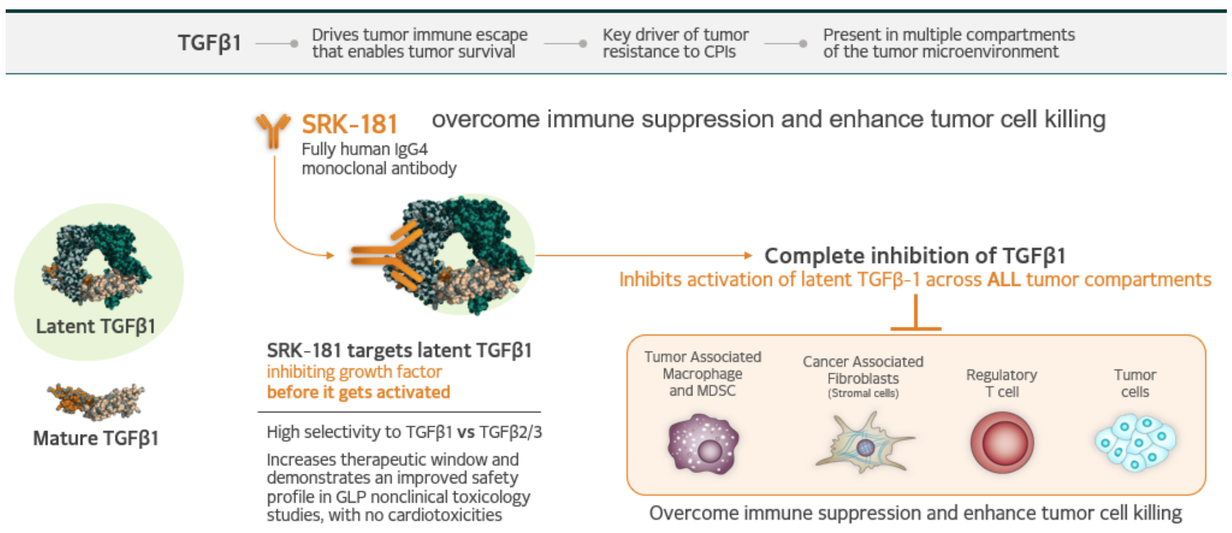
Background

- TGFβ drives tumor immune escape by promoting an immunosuppressive tumor microenvironment that enables tumor survival. [1]
- TGFβ mediates resistance to anti-PD-1/PD-(L)1 CPIs by decreasing antigen presentation and T-cell infiltration, leading to reduced tumor cell killing. [1]
- Human data implicate that TGFβ signaling is mainly driven by TGFβ1 in most tumor types. [2]
- 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).



- Preclinical data revealed that combination of SRK-181 and anti-PD1 overcame immune exclusion in the TME leading to an influx of effector T cells into tumors which correlated with tumor regression and significant survival benefits.[2]
- A biomarker strategy to validate SRK-181's mechanism in patients and evaluate treatment response was based on our proof of concept for SRK-181 in preclinical models. Here we present biomarker data evaluating SRK-181's mechanism of action in patients.

Dragon - Protocol overview

Dose Escalation (3+3)

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

All advanced solid tumor n=19

Part A2: SRK-181 (IV) + 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 (IV) + Pembrolizumab (SRK-181: 1500mg q3w) n=up to 40/ cohort (enrolling)

- Cohort UC
- Cohort ccRCC
- Cohort melanoma
- Cohort NSCLC
- Cohort HNSCC

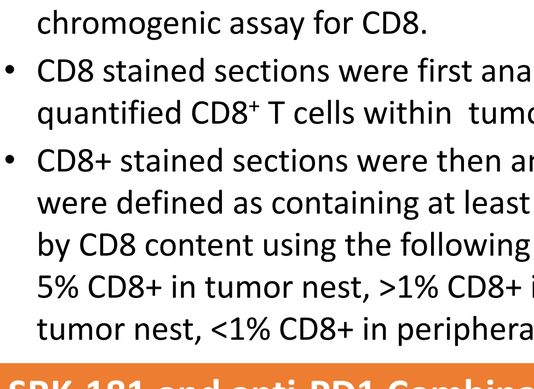
Methods

- Blood for flow cytometry analysis of myeloid derived suppressor cells (MDSC) was originally collected at baseline and pre-infusion C2D1 (cycle 2 day 1). After protocol amendment, blood was collected every Cycle Day 1 pre-infusion and EoT.
- Biopsies were collected at baseline and post-treatment between day 21 - 45. As of Aug 29, 2023, 8 paired biopsies of sufficient quality were collected and stained for CD8. Biopsies were formalin-fixed paraffin embedded and stained using a chromogenic assay for CD8.
- CD8 stained sections were first analyzed in a primary compartmental analysis[3] that quantified $CD8^+$ T cells within tumor, tumor margin and stromal compartments.
- CD8+ stained sections were then analyzed using tumor nest analysis[4]. Tumor nests were defined as containing at least ≥250 cells and 500µm^2. Nest were characterized by CD8 content using the following criteria: >5% CD8+ in tumor nest (Infiltrated), < 5% CD8+ in tumor nest, >1% CD8+ in peripheral interface (Excluded), < 5% CD8+ in tumor nest, <1% CD8+ in peripheral interface (Desert).

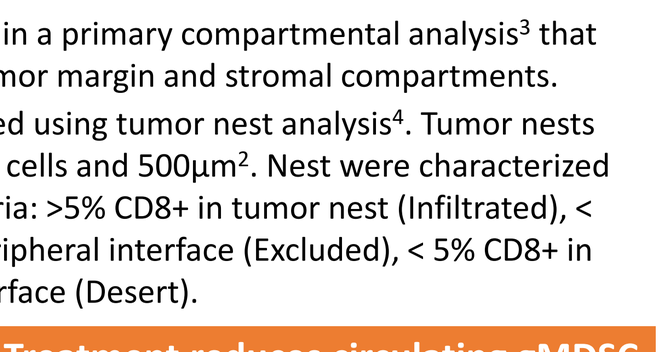
SRK-181 and anti-PD1 Combination Treatment reduces circulating gMDSC (granulocytic Myeloid-Derived Suppressor Cells) in PR patients

- Myeloid-derived suppressor cells (MDSC) have immune suppressive functions and promote tumor growth and contribute to resistance to immunotherapy[5]
- Preclinical studies suggest MDSC plays a critical role in tumor development [2]
- Level of circulating MDSC may correlate with clinical response[6]
- In preclinical studies, SRK-181 and anti-PD1 combination reduced levels of tumor MDSCs[2]
- For patients in Part B with the BOR of PR, treatment decreased circulatory gMDSC below baseline. An analysis of gMDSC in ccRCC patients is reported in poster #666.
- Similar data was generated for mMDSC; however, there was no correlation between clinical activity and mMDSC levels.

gMDSC over time – Overall Trend Mean Value (All patients)



gMDSC over time – Patients with BOR of PR



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

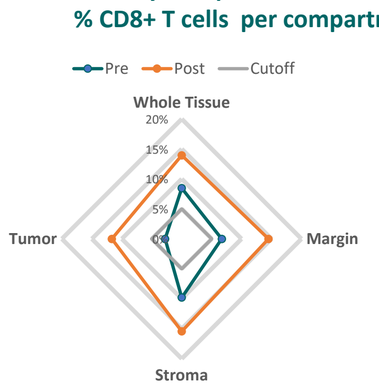
Abbreviations: Anti-PD-(L)1, programmed death ligand-1 antibody/programmed cell death protein-1 antibody; BOR, best overall response; ccRCC, clear cell renal cell carcinoma; CPI, checkpoint inhibitor; gMDSC, granulocytic myeloid derived suppressor cell; HNSCC, head and neck squamous cell carcinoma, EoT, end of treatment; mMDSC, monocytic myeloid derived suppressor cell; MDSC, myeloid derived suppressor cell; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; q3w, every 3 weeks; SD, stable disease; TGFβ1, transforming growth factor beta-1; 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)**. Lee-Hoeflich, S. 12th Annual World Biomarker & CDx Conference 2022 4.) Caldwell, C et al AACR 2021 #3137 5) Law, et Cells, 2020. **9**(3). **6)** Meyer, et al.,. Cancer Immunol Immunother, 2014. **63**(3): p. 247-57.

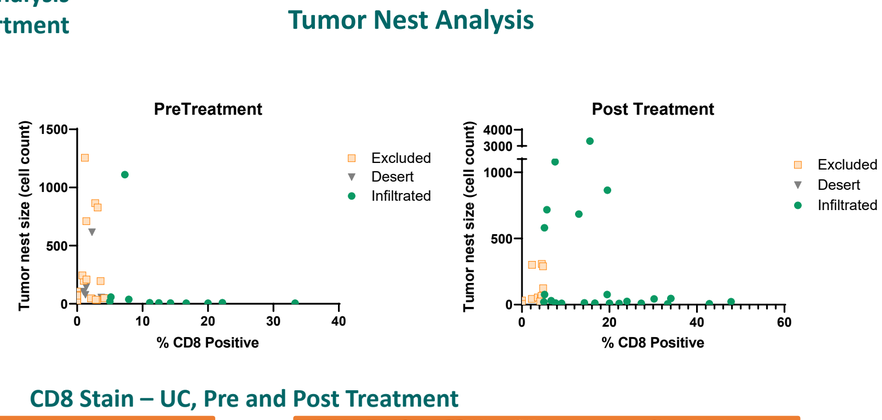
SRK-181 and anti-PD1 Combination Treatment Increases Cytotoxic CD8+ Cells Tumor Infiltration in Urothelial Carcinoma (UC)

- Paired biopsies from 2 UC patients were analyzed for CD8 content.
- An increase in CD8+ T-cell infiltration was observed in both biopsy pairs, overcoming an initially excluded or desert phenotype and resulting in more infiltrated tumor.
- Shown here is the representative quantification and images from 1 UC patient.

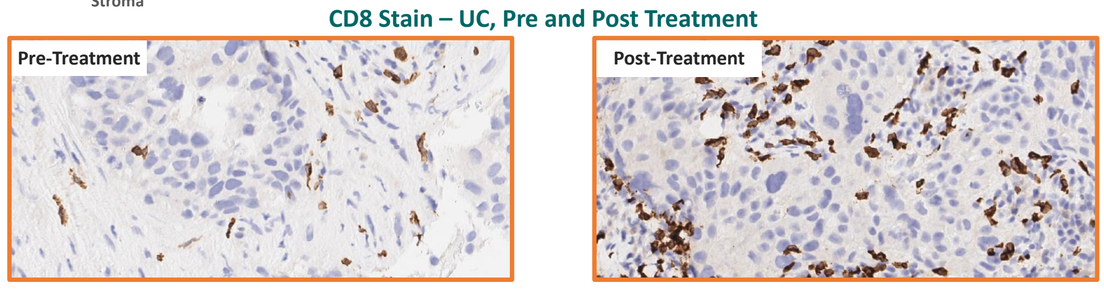
Primary Compartmental Analysis % CD8+ T cells per compartment



Tumor Nest Analysis



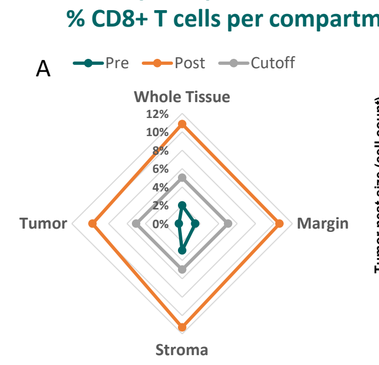
CD8 Stain – UC, Pre and Post Treatment



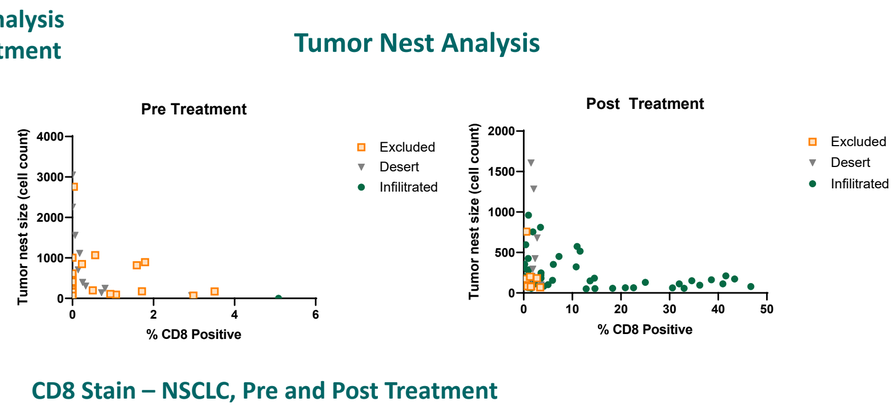
SRK-181 and anti-PD1 Combination Treatment Increases Cytotoxic CD8+ Cells Tumor Infiltration in Non-small cell lung cancer (NSCLC)

- Paired biopsies from 3 NSCLC patients were analyzed for CD8 content.
- An increase in CD8+ T-cell infiltration was observed in 2 out of 3 biopsy pairs.
- Shown here are representative quantification and images from 1 NSCLC patient.

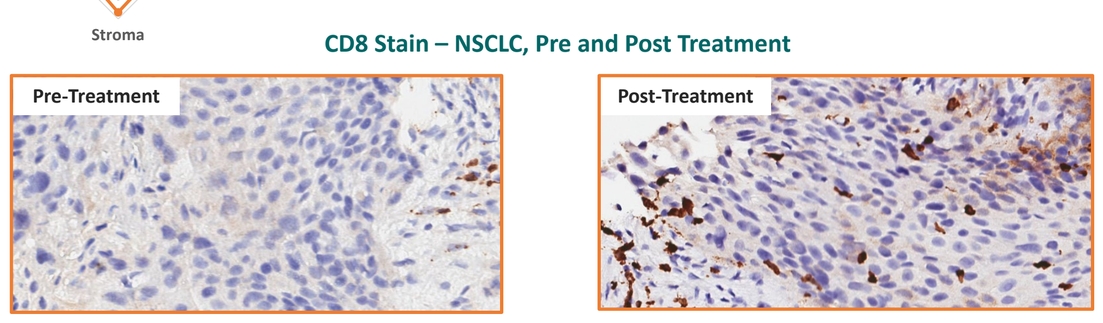
Primary Compartmental Analysis % CD8+ T cells per compartment



Tumor Nest Analysis



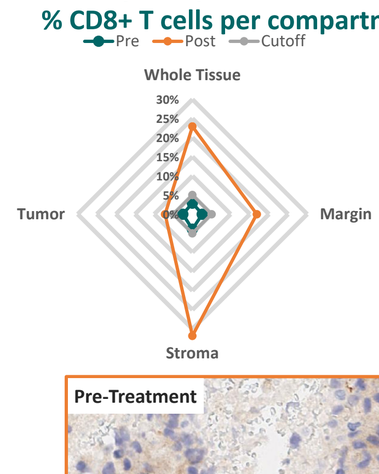
CD8 Stain – NSCLC, Pre and Post Treatment



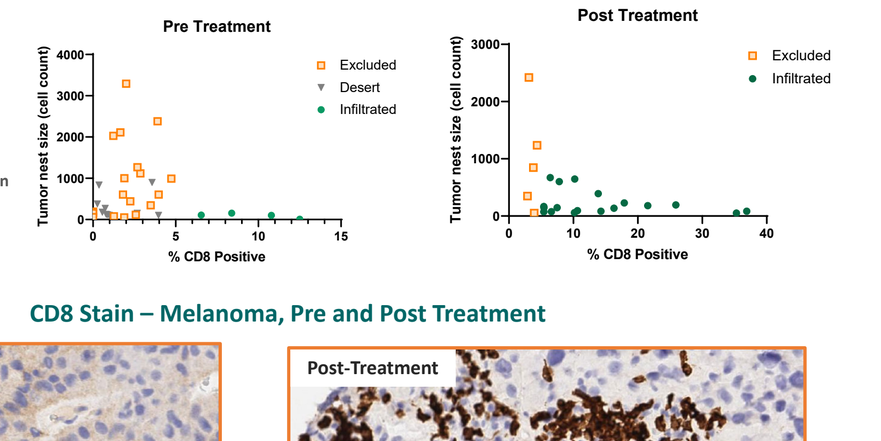
SRK-181 and anti-PD1 Combination Treatment Increases Cytotoxic CD8+ Cells Tumor Infiltration in Melanoma

- Paired biopsies from 2 melanoma patients were analyzed for CD8 content.
- An increase in CD8+ T-cell infiltration was observed in both biopsy pairs, overcoming an initially excluded or desert phenotype and resulting in more infiltrated tumor.
- Shown here is the representative quantification and images from 1 melanoma patient.

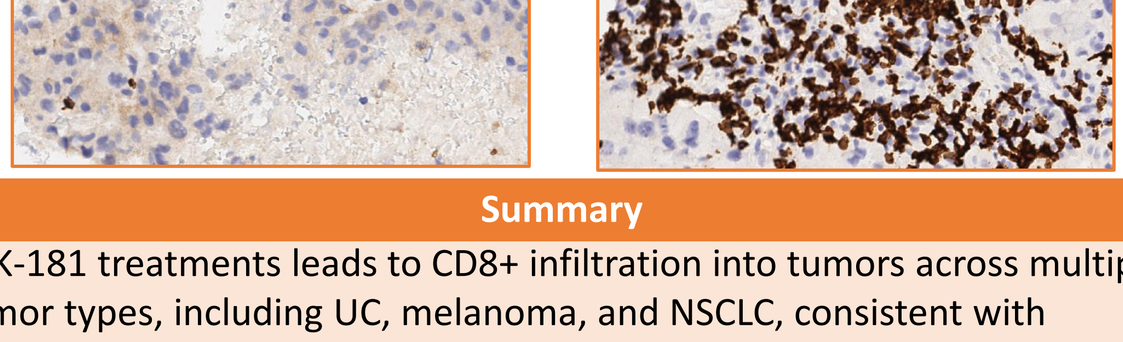
Primary Compartmental Analysis % CD8+ T cells per compartment



Tumor Nest Analysis



CD8 Stain – Melanoma, Pre and Post Treatment



Summary

- SRK-181 treatments leads to CD8+ infiltration into tumors across multiple tumor types, including UC, melanoma, and NSCLC, consistent with established MOA observed in preclinical studies[2] . Patients that experienced tumor shrinkage also experienced CD8+ infiltration into the tumor compartment.
  - Collection of paired biopsies from ccRCC patients has been challenging. Several post treatment biopsies did not contain sufficient viable tumor for analysis.
  - No patients have been enrolled in the head and neck cancer cohort as of cutoff date: Aug 29, 2023
- SRK-181 treatment leads to a decrease in immunosuppressive MDSCs which may be linked to responses. PRs were observed in ccRCC, melanoma and UC patients, all PR patients experienced a decrease in circulating gMDSC. A comprehensive analysis of ccRCC patient data is reported in poster #666.
- Collection and analysis of biomarker data is ongoing
- **Exclusion of CD8+ T cells from the tumor has been proposed as a mechanism underlying immunosuppression contributing to CPI resistance. Consistent with preclinical data, we show that treatment with SRK-181 and pembrolizumab led to an increase in CD8+ T-cell infiltration into the tumor compartment across multiple tumor types.**

***Disclosures:** SRK-181 is an investigational drug candidate that is currently being evaluated in a Phase 1 clinical trial. The safety and efficacy of SRK-181 have not been established. SRK-181 has not been approved by the U.S. Food and Drug Administration or any other health authority for any indication.