2023 ESMO TAT

Targeted Anticancer Therapies

SAFETY AND EFFICACY RESULTS OF SRK-181, A LATENT TGFβ1 INHIBITOR, FROM A PHASE 1 TRIAL (DRAGON TRIAL)

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Declaration of Interests

Dr. Timothy A. Yap

- **Employment:** University of Texas MD Anderson Cancer Center, where I am Medical Director of the Institute for Applied Cancer Science, which has a commercial interest in DDR and other inhibitors (IACS30380/ART0380 was licensed to Artios)
- **Advisory/Consulting:** AbbVie, AstraZeneca, Acrivon, Adagene, Almac, Aduro, Amphista, Artios, Athena, Atrin, Avoro, Axiom, Baptist Health Systems, Bayer, Beigene, Boxer, Bristol Myers Squibb, C4 Therapeutics, Calithera, Cancer Research UK, Clovis, Cybrexa, Diffusion, EMD Serono, F-Star, Genmab, Glenmark, GLG, Globe Life Sciences, GSK, Guidepoint, Idience, Ignyta, I-Mab, ImmuneSensor, Institut Gustave Roussy, Intellisphere, Jansen, Kyn, MEI pharma, Mereo, Merck, Natera, Nexys, Novocure, OHSU, OncoSec, Ono Pharma, Pegascy, PER, Pfizer, Piper-Sandler, Prolynx, Repare, resTORbio, Roche, Schrodinger, Theragnostics, Varian, Versant, Vibliome, Xinthera, Zai Labs and ZielBio
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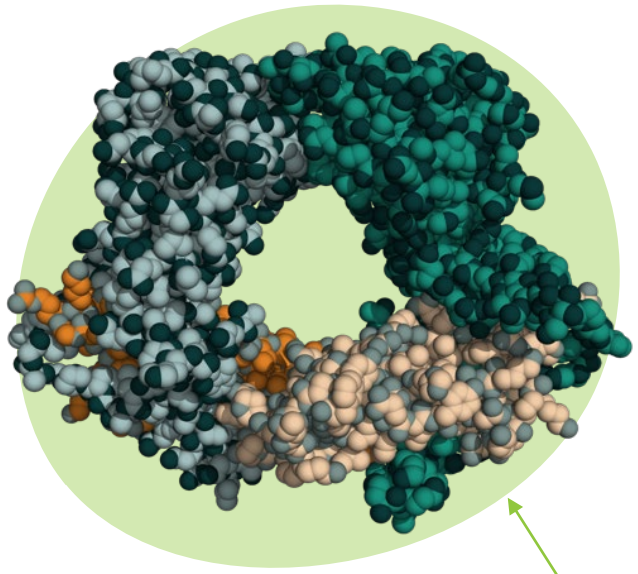
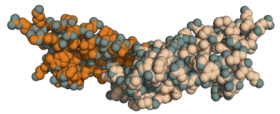
- **Stockholder**: Seagen
- **Travel Expenses to ESMO TAT:** Scholar Rock

SRK-181: Unique Latent TGFβ1 Selective Approach to Overcoming Checkpoint Inhibitor Resistance





Traditional Target
"Mature" growth factor

SRK-181: Latent TGFβ1 Inhibitor

Targets TGFβ1	**Potential to overcome CPI resistance**	SRK-181 inhibits the TGFβ1 implicated in check point inhibitor resistance	
Selective to β1 isoform	**Highly selective to β1 isoform vs. 2 and 3**	Increases therapeutic window and potentially avoids toxicities associated with non-selective TGFβ inhibition	Other programs target multiple isoforms of TGFβ
Targets the latent form of TGFβ1	**Increases opportunity to inhibit TGFβ1**	Selectively targeting the latent form shuts off the growth factor before activation	Most other programs target the mature form of TGFβ1
Context-independent	**Inhibits all sources of TGFβ1**	SRK-181 targets all TGFβ1 sources (LRRC33, GARP and LTBP1 and 3)	Some programs only target one source

Wakefield LM, Winokur TS, Hollands RS, Christopherson K, Levinson AD, Sporn MB. Recombinant latent transforming growth factor beta 1 has a longer plasma half-life in rats than active transforming growth factor beta 1, and a different tissue distribution. *J Clin Invest*. 1990 Dec;86(6):1976-84. doi: 10.1172/JCI114932. PMID: 2254455; PMCID: PMC329834.

Selectivity of SRK-181 Offers Potential to Avoid Toxicity and Dose-limiting Challenges of Non-selective TGFβ Inhibition

Toxicology:

- Unremarkable
- Minimal
- Slight
- Moderate

Microscopic Observations in Heart	CONTROL Vehicle iv, qwk x 4	LY2109761 300 mg/kg po, qd x 8	PanTGFβAb 30 mg/kg Iv, 1 dose	SRK-181 10 mg/kg iv, qwk x 4	SRK-181 30 mg/kg iv, qwk x 4	SRK-181 100 mg/kg iv, qwk x 4
Valvulopathy						
Atrium—Mixed cell infiltrate						
Myocardium—Degeneration/necrosis						
Myocardium—Hemorrhage						
Myocardium—Mixed cell infiltrate, base						
Coronary artery—Necrosis with inflammation						
Cardiomyocyte—Necrosis/inflammatory cell infiltrate				*		

Non-selective TGFβ Inhibitors

Toxicity: Minimal, slight and moderate

Selective TGFβ1 Inhibitor

Toxicity: Minimal

* findings consistent with normal variation, not test article-related

Repeat Dose Pilot Toxicology Study

Adult female Sprague Dawley rats

Cardiac findings were exhibited
in animals dosed with pan-TGFβ antibody or LY2109761 (inhibitor of ALK5, common TGFβ receptor kinase) **as expected based on published data†**

NO CARDIOTOXICITIES (valvulopathy) were noted with SRK-181
NOAEL for SRK-181: 100 mg/kg QW
(highest dose evaluated)

4-week GLP toxicology studies

RATS
NOAEL for SRK-181: 200 mg/kg QW
(highest dose evaluated)

NON-HUMAN PRIMATES
NOAEL for SRK-181: 300 mg/kg
(highest dose evaluated)

Preclinical data published in *Science Translational Medicine*. Martin CJ, et al. *Sci Transl Med* 2020 Mar 25;12(536): eaay8456.

† Source: Anderton MJ, et al. Induction of heart valve lesions by small-molecule ALK5 inhibitors. *Toxicol Pathol*. 2011;39: 916-924.; and Stauber AJ, et al. Nonclinical safety evaluation of a transforming growth factor β Receptor I kinase inhibitor in Fischer 344 rats and beagle dogs. *J Clin Pract*. 2014: 4:3.

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DRAGON Phase 1 POC Trial to Evaluate SRK-181's Ability to Overcome Primary/Acquired Resistance to Checkpoint Inhibitors

Part A: Dose Escalation (3+3 Design)

Part A1: SRK-181(IV)

Advanced solid tumors that failed SOC treatment (completed)

- SRK-181 80 mg q3w (n=1)
- SRK-181 240 mg q3w (n=1)
- SRK-181 800 mg q3w (n=3)
- SRK-181 1600 mg q3w (n=4)
- SRK-181 2400 mg q3w (n=3)
- SRK-181 3000 mg q3w (n=3)
- SRK-181 2000 mg q2w (n=4)*

Part A2 began

Part A2: SRK-181(IV) + Anti-PD-(L)1

Non-Responders to prior Anti-PD-(L)1; Best response of SD/PD after 3 cycles (completed)

- SRK-181 240 mg q3w (n=3)
- SRK-181 800 mg q3w (n=3)
- SRK-181 1600 mg q3w (n=6)
- SRK-181 2400 mg q3w (n=3)

*2000 mg q2w allows for equivalent C_{ave} exposure to 3000 mg q3w and is being evaluated to understand safety and PK of the q2w dose regimen

Part B: Dose Expansion (n= up to 40 per cohort)

Part B: SRK-181(IV) 1500mg q3w + Anti-PD-(L)1 (enrolling)

- Cohort NSCLC (non-responders to prior anti-PD-1)
- Cohort UC (non-responders to prior anti-PD-1)
- Cohort MEL (non-responders to prior anti-PD-1)
- Cohort ccRCC (disease progressed on the most recent prior anti-PD-1)
- Cohort HNSCC (disease progressed on the most recent prior anti-PD-1)

Part A Endpoints

Primary:
- Safety and tolerability (incidence/severity of AEs and SAEs)
- MTD or MAD
- Recommended dose for Part B

Secondary:
- PK
- ADA

Exploratory:
- Anti-tumor activity (ORR, DOR)
- Biomarker

Part B Endpoints

Primary:
- Safety and tolerability (incidence/severity of AEs and SAEs)

Secondary:
- Anti-tumor activity (ORR, DOR)
- PK
- ADA

Exploratory:
- Survival outcomes (PFS, OS)
- Biomarker

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NCT04291079 on www.clinicaltrials.gov.

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DRAGON Part A: Demographics and Disposition

Category	Part A1 Monotherapy	Part A2 Combination Treatment
N	19	15
Age, median (range)	66(41 - 79)	65 (32 - 75)
Gender (F/M)	8/11	3/12
Ethnicity Hispanic or Latino Not Hispanic or Latino Not Reported	 0 18 1	 2 13 0
Race White	 19	 15
Prior Lines of Therapy, median (range)	4 (1,10)	3 (2,7)

Category	Part A1 Monotherapy	Part A2 Combination Treatment
Enrolled	19	15
On Study	0	0
Stopped Treatment	19	15
Reason for Completion/Discontinuation Adverse Event Clinical Progression Investigator Decision Disease Progression based on RECIST v1.1 Withdrawal of Consent	 2* 3 2 11 1	 4** 5 0 4 2

*In Part A1, 1 patient discontinued from study due to an AE of road traffic accident that was unrelated to SRK-181 treatment; 1 patient discontinued due to an SRK-181-related AE of rash maculo-papular.

**In Part A2, 2 patients discontinued from the study due to treatment-unrelated AEs of spinal cord compression and ascites; 1 patient discontinued due to an anti-PD-(L)1-related AE of rash maculo-papular; 1 patient discontinued due to an SRK-181-related AE of pemphigoid.

DRAGON Part A: Safety

PART A1 Monotherapy

Treatment-Emergent AEs Related to SRK-181, All Grades >10%

Dose (MG)	80 N=1	240 N=1	800 N=3	1600 N=4	2400 N=3	3000 N=3	2000 N=4	All N=19
Fatigue	0	1	0	0	1	0	1	3 (15.8%)
Decreased Appetite	1	0	1	0	0	0	0	2 (10.5%)
Nausea	1	0	0	0	0	0	1	2 (10.5%)

No DLTs were observed up to 3000 mg q3w and 2000 mg q2w

No Grade 4 or 5 treatment-related AEs occurred

Treatment-related Grade 3 AEs:

- Alanine aminotransferase increased (1 patient)

Treatment-related SAEs:

- None

PART A2 Combination Treatment

Treatment-Emergent AEs Related to SRK-181 or Anti-PD(L)1, All Grades >10%

Dose (MG)	240 N=3	800 N=3	1600 N=6	2400 N=3	All N=15
Rash maculo-papular	1	1	1	2	5 (33.3%)
Pruritus	1	1	1	1	4 (26.7%)
Rash	0	1	0	2	3 (20.0%)
Diarrhea	0	0	2	0	2 (13.3%)
Pemphigoid	0	0	0	2	2 (13.3%)

Clinical cutoff date: December 2, 2022
All dose levels were administered q3w except 2000 mg, which was administered q2w.

No DLTs were observed up to 2400 mg q3w

No Grade 4 or 5 treatment-related AEs occurred

Treatment-related Grade 3 AEs:

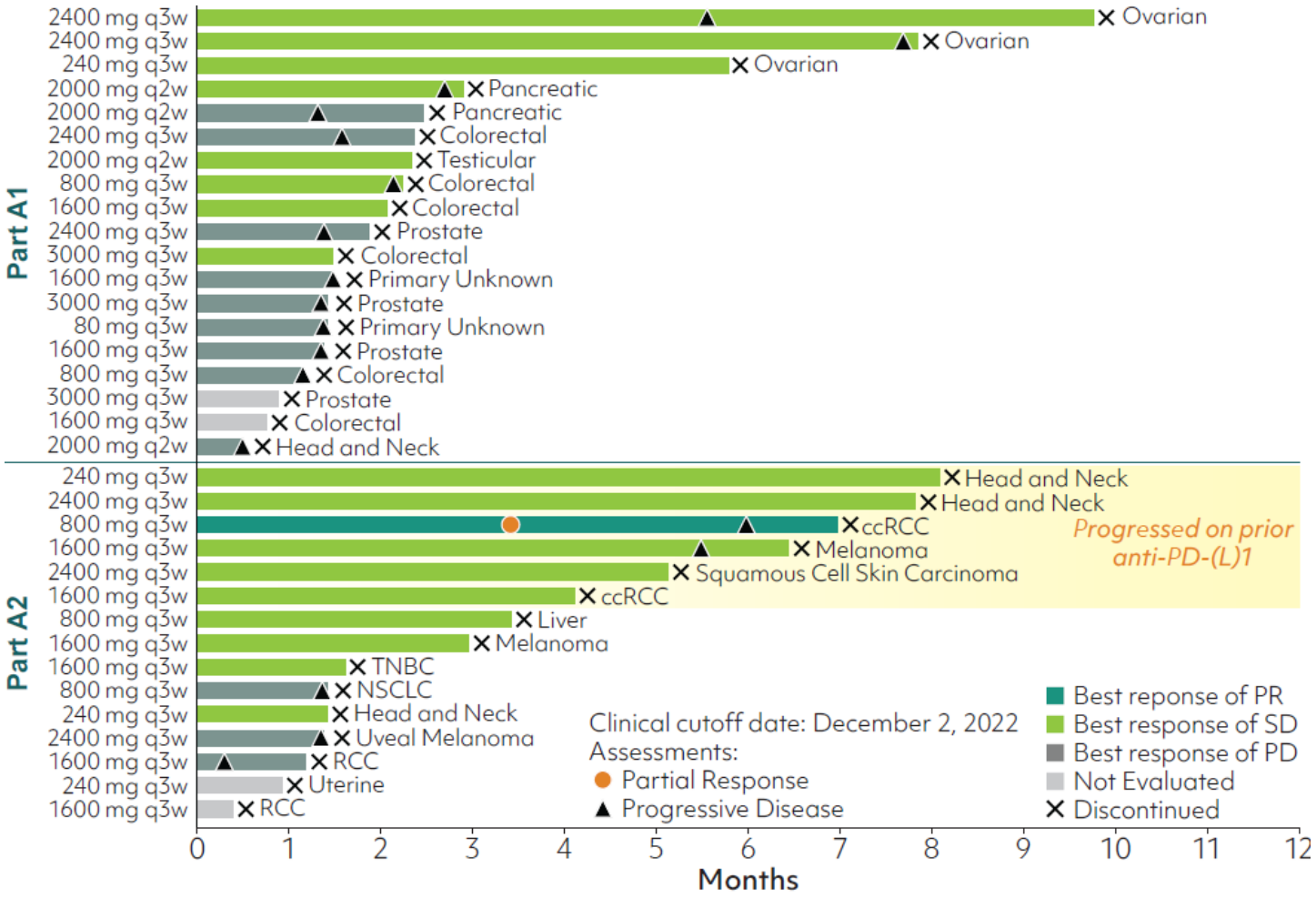
- Puritus (2 patients), blister, immune-mediated lung disease, pemphigoid, rash, rash maculo-popular and rash vesicular (1 patient each)

Treatment-related SAEs:

- Blister, pruritus, and rash (all in 1 patient) and immune-mediated lung disease (1 patient)

Dragon Part A: Preliminary Efficacy Data

Duration of Treatment Part A Duration of Treatment



Part A1 Monotherapy(n=19)

- 8 patients had a best response of stable disease (SD)
  All 3 patients with ovarian cancer were stable for 6-10 month

Ovarian Patient	SRK-181 Dose (q3w)	Age	Lines of Prior Therapy	Duration of Treatment (wks)	Best Tumor Reduction*
Pt #1	A1, 2400mg	73Y	1.Paclitaxel/Carboplatin; 2.Topotecan; 3.Doxil; 4.Gemcitabine; 5.Altretamine; 6.Bevacizumab/Gemcitabine/ Carboplatin; 7.Letrozole	42 (off study)	+4%
Pt #2	A1, 2400mg	48Y	1.Carboplatin/Taxol; 2.Carboplatin/Taxol; 3.Leuprorelin	34 (off study)	-15%
Pt #3	A1, 240mg	66Y	1.Carboplatin/Docetaxel 2.Carboplatin/Docetaxel 3.Carboplatin/Docetaxel/ Bevacizumab 4.Bevacizumab 5.Leuprorelin	25 (off study)	-6%

* Best % change in sum of diameters in target lesions from baseline

Part A2 Combination Treatment(n=15)

- At 800 mg q3w, 1 partial response (PR) was observed in patient with anti-PD-1-resistant clear cell renal cell carcinoma (ccRCC)
- 9 patients had best response of SD
- 6 patients (yellow highlight) were stable beyond the 16-week cutoff
  1 patient with head and neck cancer had a 29.4% tumor reduction

Clinical cutoff date: December 2, 2022
Preliminary anti-tumor effects were assessed using RECIST1.1 and reported based upon investigator assessment

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Dragon Part B (Combination Treatment) Update

- **20 patients dosed across multiple cohorts**
  - Cohort ccRCC: 9 patients
  - Cohort NSCLC: 3 patients
  - Cohort UC: 4 patients
  - Cohort Melanoma: 1 patient
  - Cohort Any Other: 3 patients (Enrollment closed)
- **SRK-181 was generally well tolerated in combination with pembrolizumab**
  - Dose: 1500 mg q3w or 1000 mg q2w
- **Two confirmed PRs**
  - Ongoing patients with anti-PD-1 resistant ccRCC

ESMO TAT Clinical cutoff date: December 2, 2022

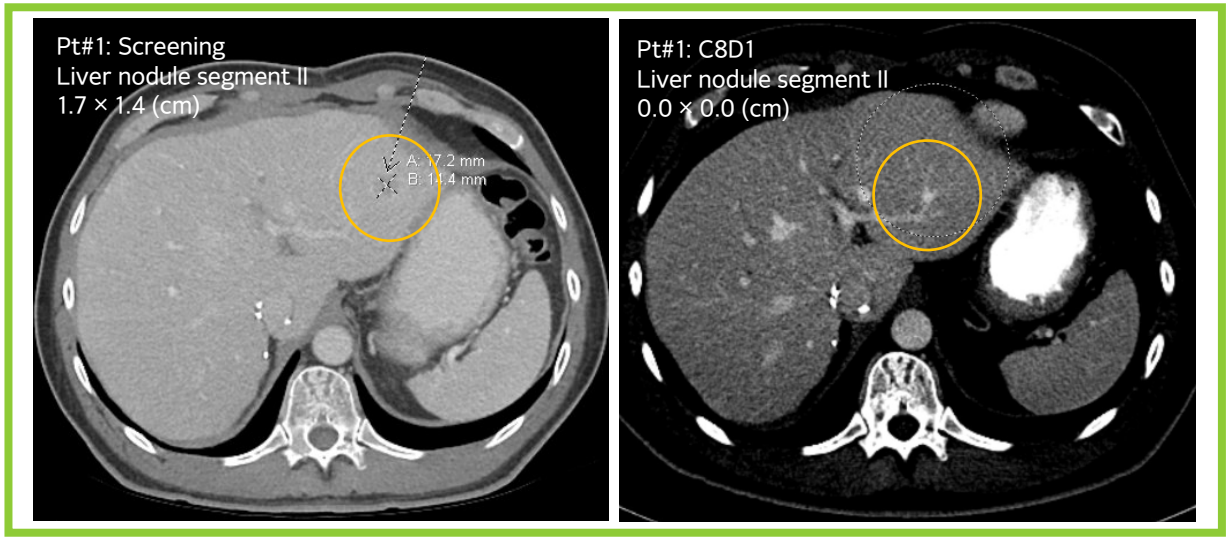
Summary of ccRCC Patients (Part A2 and Part B, Combination Treatment)

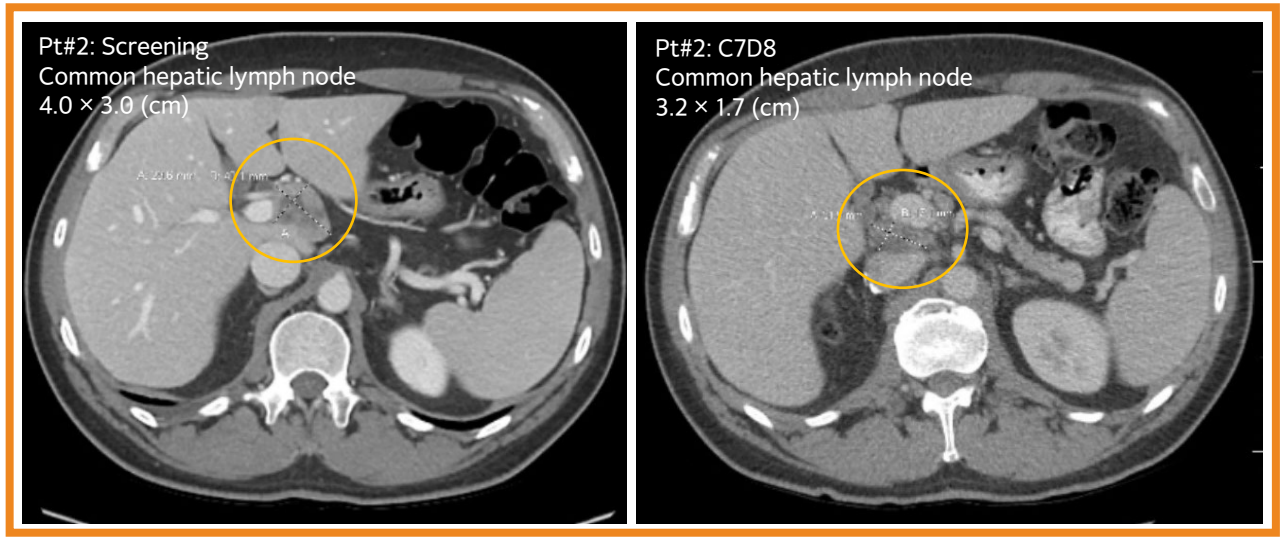
- As of Dec 02, 2022, total 11 ccRCC patients are enrolled in Part A2 and Part B
  - N=2 in Part A2 (all discontinued from study) and N=9 in Part B (5 pts remain on study)
  - Enrollment continues
- 3 confirmed PRs have been observed in ccRCC patients based on investigator assessment
  - Patients are anti-PD-1 resistant patient (no response on prior anti-PD-1 therapy and disease progress on the most recent prior anti-PD-1 therapy)
  - ORR: 27% (3/11)

Clinical cutoff date: December 2, 2022

Summary of ccRCC Patients with PR in Dragon (Part A2 and Part B, Combination Treatment)

Responded Pts	SRK-181 Dose (mg, Q3W)	Age (Year)/ Gender	Lines of Prior Therapy	IMDC Score at Screening	Metastatic Sites at Screening	Pt Status	Duration of Treatment (wks)	Best % Change in SOD* from Baseline
Pt #1	Part A2, 800	56/M	1. Sunitinib **2. Nivolumab/Ipilimumab** 3. Cabozantinib 4. Lenvatinib/Everolimus **5. Pembrolizumab/Axitinib**	3 (Poor risk)	Lung/ Lymph Nodes/ Pleural/ Pancreas/ Bone	Off study	30	-57%
Pt #2	Part B, 1500	58/M	**1. Nivolumab/Ipilimumab** 2. Cabozantinib	3 (Poor risk)	Lung/ Lymph Nodes/Liver	Ongoing	32+ (by Dec 2, 2022)	-67%
Pt #3	Part B, 1500	63/M	**1. Nivolumab/Ipilimumab** **2. Nivolumab** 3. Cabozantinib	2 (Intermediate risk)	Lung/ Lymph Nodes	Ongoing	16+ (by Dec 2, 2022)	-50%





Clinical cutoff date: December 2, 2022

* SOD: Sum of diameters in target lesions

Conclusion

As of Dec 02, 2022

- SRK-181 was generally well tolerated in combination with anti-PD-(L)1 at all doses
- No DLTs were observed up to 3000mg q3w/2000mg q2w as monotherapy and up to 2400mg q3w as combination treatment.
- Three confirmed PR were observed in patients with anti-PD-1 resistant ccRCC (ORR: 3/11=27%; enrollment of this cohort is ongoing)

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