Preliminary Population Pharmacokinetic Modeling of SRK-181 from Phase 1 Dose Escalation Study

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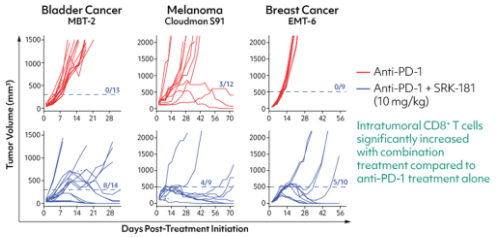
Background

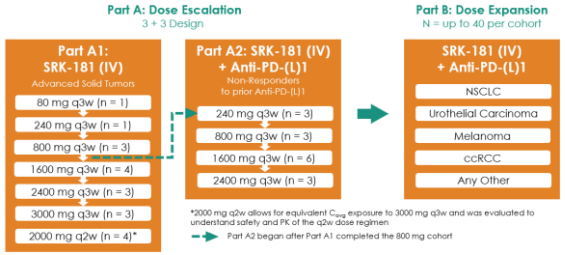
- Despite clinical advances made with check point inhibitor (CPI) therapy, resistance to CPI treatment in cancer patients remains an unmet medical need.[1]
- TGFβ plays an important role in driving immune exclusion and primary resistance to CPIs.[2,3]
- Human data indicate that tumor-associated TGFβ signaling is mainly driven by TGFβ1 in most tumor types.[4]
- SRK-181* is a fully human, IgG4 monoclonal antibody that selectively inhibits latent TGFβ1 activation.[4]

TGFβ Blockade with SRK-181 Rendered Preclinical Tumor Models Susceptible to Anti-PD-1 Therapy[4]



- SRK-181 showed an improved safety profile (including no cardiotoxicities) in 4-week GLP nonclinical toxicology studies compared to nonselective TGFβ inhibitors.[4,5]
- SRK-181 may potentially decrease PD-(L)1 inhibitor resistance and avoid toxicities associated with nonselective TGFβ inhibition approaches in human cancer patients.
- In preclinical mouse tumor models, the average serum concentration observed at a therapeutically relevant dose was ~80 μg/mL[4], this average serum concentration has been targeted when selecting the expansion doses in the DRAGON study (see "Preliminary Population PK Model Simulations").

DRAGON Study Overview



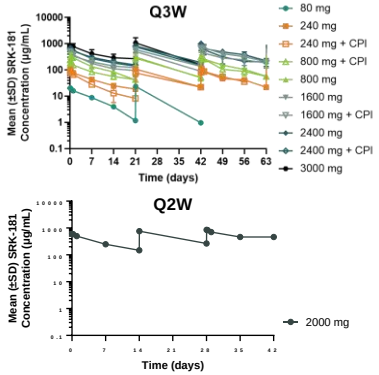
- SRK-181 is currently being studied in the ongoing DRAGON trial (NCT04291079 or SRK-181-001), a multicenter, open-label, Phase 1, FIH, dose escalation and dose expansion study, to evaluate the safety, tolerability, PK, PD, and efficacy, of SRK-181 administered every 2 or 3 weeks (q2w or q3w) as a single agent and in combination with checkpoint inhibitor therapy in patients with locally advanced or metastatic solid tumors.

Clinical PK Data Collection

- Full PK profiles were generated from samples collected from patients in Cycle 1 and 3 at the following timepoints:
  - Pre-dose (0-hour), 1, 6, 24, 168, 336, and 504-hours post-dose for the q3w regimen.
  - The q2w regimen included all the above listed timepoints except 504-hours post-dose.
- In Cycles 2, 4, 5, and 6 only 1-hour and 504-hour (q3w) or 336-hour (q2w) timepoints are collected, and for Cycles 9, 12, 16, 24, and 30 only pre-dose samples are collected.

Summary PK of SRK-181 from DRAGON Trial

Average Observed Serum Concentrations of SRK-181 in DRAGON Trial Administered Q3W (Top) and Q2W (Bottom)



- SRK-181 demonstrates minimal non-linear kinetics at the lowest doses resulting from target-mediated drug disposition (TMDD).
  - TMDD can be overcome with saturation of the target occurring between 240 and 800 mg.
- Minimal accumulation of SRK-181 has been observed after successive dosing in the clinic.
- No significant difference in exposure has been observed between Part A1 (single agent) and Part A2 (combination with CPI).

Demographics and Baseline Characteristics

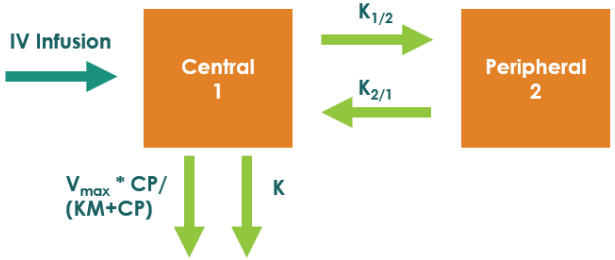
- SRK-181 has been safely administered via IV infusion to 34 patients in Part A as a single-agent (80 – 3000 mg q3w, 2000 q2w) and when combined (240 - 2400 mg q3w) with checkpoint inhibitor therapy (e.g., pembrolizumab)[6].
  - 19 patients (8F/11M) were enrolled in Part A1 and 15 patients (3F/12M) into Part A2.
  - Age for Part A1 ranged from 41 to 79 years with a median age of 66 years.
  - Age for Part A2 ranged from 32 to 75 years with a median age of 65 years.

Preliminary Population PK Model Methods

- A preliminary population PK model was generated to characterize the PK of SRK-181 with non-linear mixed effect modeling and to support the choice of 1000 mg q2w and 1500 mg q3w as the dosing regimen for the Dose Expansion phase.
- Data from 34 patients were evaluated in this model, which was a 2-compartment model with IV infusion to the central compartment followed by first order distribution between the central and peripheral compartments.
- Elimination from the central compartment was described as two competing mechanisms: a saturable non-linear Michaelis-Menten (MM) (V_{max}, K_M) mechanism, and a linear mechanism (K).
- Population PK model parameters were estimated with NONMEM 7.5, PDxPop5.3. using the ADVAN13 subroutine and the first-order conditional estimation method with interaction.
  - The objective function value computed by NONMEM was used in a log-likelihood ratio test for the comparison of hierarchical models.
  - The addition of a structural or variance parameter was considered statistically significant if the objective function reduced by ≥3.84 ($P < 0.05$ for 1 degree of freedom).
- Residual error, the difference between the observed and model-predicted concentrations, was modeled with a combined additive and proportional error models.
- Interindividual variability was modeled with an exponential error model, assuming a log-normal distribution.
- The relationship between the individual parameters and covariates (age, sex, weight, and treatment type) were evaluated graphically by plotting each individual parameter against each covariate.
- The goodness of fit [of the model] was evaluated by visual inspection of diagnostic plots, bootstrap and visual predictive check procedures.

Preliminary Population PK Model Results

Preliminary Population PK Model Structure



- The base model was considered the final model as it provided the best fit and representation of observed data.
- Complete convergence (with covariance step) was achieved. Population model parameters, residual variability, interindividual variability (VC, K), and individual parameters were estimated.
- All residual errors were less than 20%, except for K_M (315%).
- Interindividual variabilities were 20.2% (VC), 26.5% (K) and shrinkage (less than 30% is ideal) based on standard deviations were 2.40% (VC), 6.54% (K).
- At higher doses (800-3000mg), MM clearance is saturated for a longer duration within the dose interval. Therefore, Michaelis-Menten clearance ($CL_{MM} = V_{max}/(K_M+CP)$) dominates elimination while not saturated; and after saturation the linear clearance (CL=VC*K) dominates elimination.
- The SRK-181 population PK parameters appeared similar between single agent SRK-181 and SRK-181 in combination with pembrolizumab therapy.
- Population model and individual parameters are presented in the tables below, individual parameters were consistent with population parameters:

Population PK Parameter:	Estimate:
V_{max} (μg/hr)	65.0
K_M (μg/mL)	0.04
K (hr^{-1})	0.00337
VC (mL)	3340

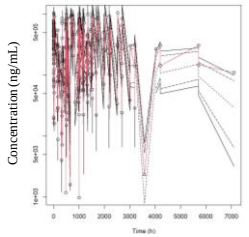
Individual PK Parameter:	Estimate:
CL (mL/hr)	11.7
$T_{1/2}$ (hr)	359
K (hr^{-1})	0.0035
VC (mL)	3393

Goodness of Fit

- Overall, goodness of fit evaluations indicate that the model fits the data reasonably well. There was no evidence to suggest a more complex model would perform better.
- Evaluation via VPC showed less than 10% of the observations outside the 90% confidence interval indicating the model and parameter estimates adequately describe the observed data.

Bootstrap (Left) and Visual Predictive Check (Right) Evaluation of Goodness of Fit

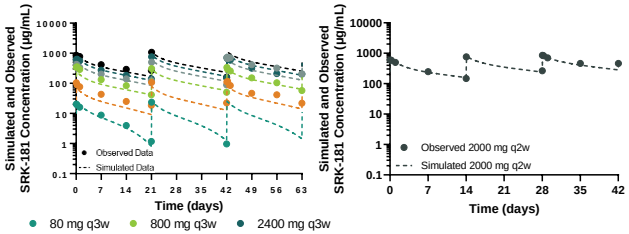
Parameter	NONMEM Parameter Estimates	95% Confidence Intervals (CI) Bootstrap Procedure LowerCI	UpperCI
VC (mL)	3340	3060	3600
K (hr^{-1})	0.00337	0.00301	0.00388
$K_{1/2}$ (hr^{-1})	0.00715	0.00471	0.00964
$K_{2/1}$ (hr^{-1})	0.0121	0.0079	0.0163
V_{max} (μg/hr)	65.0	12.5	179
K_M (μg/mL)	0.04	0.011	7320
WT ADD	1310	409	3970
WT CCV	0.127	0.103	0.141
IIV VC	0.0409	0.0193	0.057
IIV K	0.0703	0.0206	0.0968



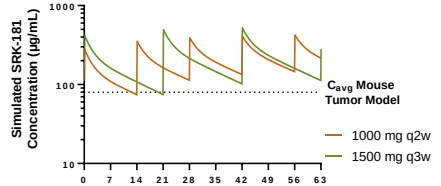
Preliminary Population PK Model Simulations

- The preliminary population PK model was able to adequately capture and predict concentrations of SRK-181 after IV infusion to patients with locally advanced or metastatic solid tumors when administered q2w or q3w.

Overlay of Simulated and Observed SRK-181 PK Concentrations from Doses Utilized in the DRAGON Trial



Simulations of Dose Levels to be Used in Dose Expansion Phase (1000 mg q2w and 1500 mg q3w)



Dose (mg)	Statistic	C_{max} (μg/mL)	T_{max} (hr)	C_{last} (μg/mL)	T_{last} (hr)	$AUC_{0\text{-}336h}$ (hr*μg/mL)	$AUC_{0\text{-}504h}$ (hr*μg/mL)	Cav (μg/mL)
1000 q2w	**Mean**	**434.7**	**3**	**159.7**	**336**	**82168.0**	**NA**	**244.5**
	SD	107.3	-	68.0	-	27262.8	-	81.14
	CV (absolute)	0.2	-	0.4	-	0.3	-	0.3
1500 q3w	**Mean**	**536.0**	**3**	**119.4**	**504**	**NA**	**116251.7**	**230.7**
	SD	100.8	-	51.29	-	-	33398.1	66.27
	CV (absolute)	0.2	-	0.4	-	-	0.3	0.3

- Estimated exposures between the 1500 mg q3w and 1000 mg q2w dosing regimens for SRK-181 were similar. These dosing regimens also achieved steady state trough levels above the C_{avg} observed at a therapeutically relevant dose in mouse tumor models.

Interpretation and Conclusions

- SRK-181 has been safely administered across a dose range in a q3w dosing regimen and at a dose of 2000 mg in a q2w dosing regimen. The preliminary population PK model fit the concentration-time data collected from 34 patients in the DRAGON trial and was used to characterize the PK of SRK-181.
  - TMDD was observed at low doses of SRK-181 but can be overcome at concentrations above the saturation level.
  - There were no observed differences in the PK profile between the single agent and in combination with CPI therapy.
- Overall, goodness of fit evaluations (graphic, VPC and bootstrap analyses) indicated the model fit the observed data reasonably well and was representative of the observed data.
- The chosen expansion doses are based on clinical pharmacokinetics, safety, and the average concentration observed at a therapeutically relevant dose in mouse tumor models (~80 μg/mL).[4]
  - Exposure between the 1000 mg q2w and 1500 mg q3w dosing regimens was similar, as expected.
  - Modeling and simulation with data from the DRAGON trial were used to support 1000 mg IV q2w and 1500 mg IV q3w dosing regimens for dose expansion.

Abbreviations: Anti-PD-(L)1, programmed death ligand-1 antibody/programmed cell death protein-1 antibody; C_{avg} average plasma concentration; CPI, checkpoint inhibitor; CL, clearance; FIH, first in human; GLP, good laboratory practice; IgG4, immunoglobulin G4; IV; intravenous; K, first order elimination rate constant; $K_{1/2}$, first order transfer rate constant (compartment 1 to compartment 2); $K_{2/1}$, first order transfer rate constant (compartment 2 to compartment 1); K_M, Michaelis Menten constant; PD, pharmacodynamic; PK, pharmacokinetic; q2w, every 2 weeks; q3w, every 3 weeks; $T_{1/2}$, half-life; TGFβ1, transforming growth factor beta-1; TMDD, target mediated drug disposition; VC, central compartment volume; V_{max}, Michaelis-Menten maximum elimination rate

References: 1) Carretero-González, et al. *Oncotarget*. 2018;9:8706-8715. 2) Mariathasan, et al. *Nature*. 2018;554:544-548. 3) Hugo, et al. *Cell*. 2017;168:542. 4) Martin, et al. *Sci Transl Med*. 2020;12:eaay8456. 5) Welsh, et al. *Int J Toxicol*. 2021 Mar 19; https://doi.org/10.1177/10915818219898945. 6) Yap, et al. SITC 2021 http://dx.doi.org/10.136/jitc-2021-SITC2021.332

*Disclaimer: SRK-181 is an investigational drug candidate being developed and studied for oncology. The effectiveness and safety of SRK-181 have not been established. SRK-181 has not been approved by the EMA, FDA, or any other regulatory authority.

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