Pharmacokinetics of Hu5F9-G4, a first-in-class anti-CD47 antibody, in patients with solid tumors and lymphomas

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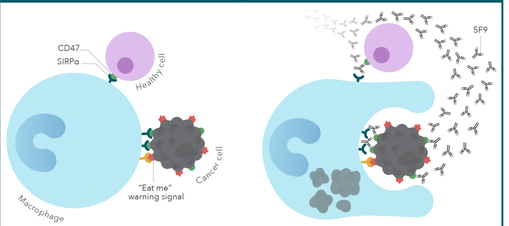
Background



- CD47 is a "don't eat me" signal that is over-expressed on cancer cells and enables cancer cells to escape macrophage phagocytosis
- 5F9 binding to CD47 enables tumor cell phagocytosis and activates an anti-tumor T-cell response in vitro and in vivo
- 5F9 is being evaluated as an anti-cancer therapy in multiple clinical trials both as a mono- and combination therapy

Objectives

- Characterize the pharmacokinetics (PK) and anti-drug antibody (ADA) incidence after single and multiple doses of 5F9 in patients with solid tumors and lymphomas
- Identify the recommended phase 2 dosing regimen (RP2D) by combining all available PK data using population PK modelling methodologies

Methods

Identifier	Summary of design	Number of patients	Number of samples
SCI-CD47-001	Phase 1/2 dose escalation and expansion study in adult solid tumors and lymphoma patients	55	1052
5F9 Dose Levels	Part A: 0.1-3 mg/kg Part B: Prime/maintenance: 1/1-30 mg/kg QW Part C: Prime/Load/Maintenance: 1/20-30 mg/kg Q@W/20-30 mg/kg QW		
5F9003	Phase 1/2 study in adult non-Hodgkin's lymphoma patients in combination with rituximab	22	336
5F9 Dose Levels	Prime/maintenance: 1/10-30 mg/kg weekly Prime/Load/maintenance: 1/20-30 mg/kg Q2W/20-30 mg/kg QW		
5F9004	Phase 1/2 study in adult solid tumor and colorectal cancer patients in combination with cetuximab	21	161
5F9 Dose Levels	Prime/maintenance: 1/10-30 mg/kg weekly Prime/Load/maintenance: 1/20-30 mg/kg Q2W/20-30 mg/kg QW		

- Noncompartmental analysis (NCA) was performed using NCA for R software package[2]
- Population PK analysis was performed using NONMEM v7.0 (v. 7.3, ICON Development Solutions, Hanover, MD)

Results

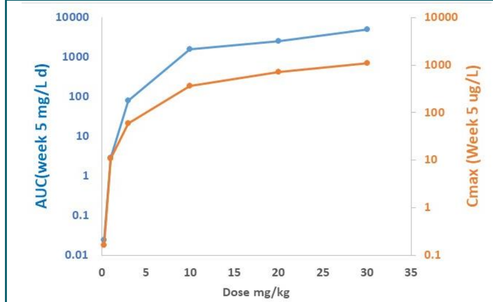
PK parameters after 1st, 2nd, and 5th doses

SCI-CD47-001

	Week 1[a]		Week 2			Week 5		
Dose (mg/kg)	Number of patients	C_{max} (mg/L)	Number of subjects	AUC_{last} mg/L/d	C_{max} (mg/L)	Number of patients	AUC_{last} mg/L/d	C_{max} (mg/L)
0.1[b]	1	NC	NC	NC	NC	NC	NC	NC
0.3	2	0.138 [NC]	1	0.00665 [NC]	0.170 [NC]	1	0.0246 [NC]	0.161 [NC]
1	6	0.682 [121]	6	0.141 [48.0]	5.83 [48.0]	6	2.89 [112]	10.6 [52.3]
3	6	0.637 [1830]	3	33.7 [29.9]	45.3 [27.9]	2	80.0 [23.6]	58.7 [1.67]
10	3	0.573 [54.3]	3	577 [9.36]	177 [16.9]	3	1560 [12.7]	368 [22.4]
20	35	0.758 [235]	35	898 [112]	411 [27.3]	33	2560 [60.9]	728 [23.4]
30	3	0.776 [7.01]	2	724 [37.7]	586 [42.9]	2	5080 [54.2]	1090 [45.0]

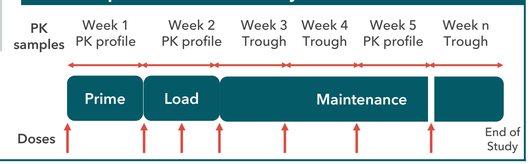
Abbreviations: AUC_{last} = area under concentration curve till last time point above limit of quantification; reported as geometric mean [geometric CV%]; C_{max}: maximum serum concentration; reported as geometric mean [geometric CV%] ; NA: Not applicable; NC: Not calculable.[a]All subjects in parts B and C of study SCI-CD47-001 and all subjects in study 5F9003 got a priming dose of 1 mg/kg. AUC was not calculable in any subject during Week 1.

AUC and Cmax increased non-linearly with dose

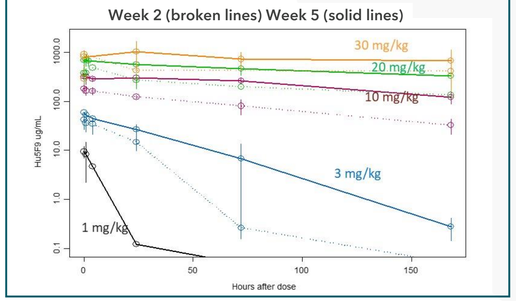


- At doses of 0.1 – 10mg/kg increases in C_{max} and AUC were greater than dose-proportional indicating nonlinearity in PK
- The PK parameters were consistent with the presence of a CD47 antigen sink, which was saturated at doses ≥ 10 mg/kg. Above this dose level, increases in C_{max} and AUC were dose proportional

Noncompartmental PK Analysis



Concentration Profile Over Dose Range



Population PK Analysis

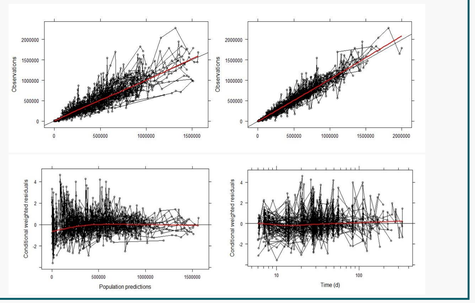
- Final PK model was a two compartment disposition model with linear and nonlinear (Michaelis-Menten) clearance
- Inter-individual variability in PK parameters were described using log-normal distribution
  - $\theta_i = \theta_{TV} e^{\eta_i}$ where θ_i is the parameter for the i^{th} individual, θ_{TV} is the typical parameter value for the population and η_i is the random variable explaining the difference between the individual and the population; η_i was assumed to be normally distributed with a variance of ω^2.
- Among covariates tested (age, gender, body weight, body surface area, ethnicity, and tumor type), only body weight was found to be statistically significant
  - In the final model, the relationship between CL, Vc and weight was:
  - $CL_i = CL_{TV} \left(\frac{BW_i}{70}\right)^{1.17} \exp(\eta_i)$
  - $Vc_i = Vc_{TV} \left(\frac{BW_i}{70}\right)^{0.487} \exp(\eta_i)$

Population PK Parameter Estimates

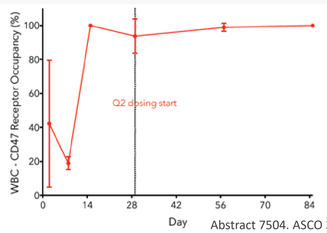
Parameter	Population Estimate	RSE (%)[a]	Parameter	Population Estimate	RSE (%)[a]
CL (L/d)	0.218	9.08	η_{CL}	29.0	13.2
V_c (L)	3.98	4.40	η_{Vc}	32.7	12.7
V_p (L)	2.43	8.97			
Q (L/day)	1.25	12.2			
V_{max} (mg/d)	36.0	19.0	η_{Vmax}	70.9	11.3
K_M (µg/mL)	2.16	23.9			
Weight on CL[a]	1.17	15.4	Residual variability		
Weight on V_c[a]	0.487	23.6	proportional error (%CV)	24.2	5.1

Relative standard error, calculated as standard error of estimate / estimate*100%); RSE was derived from the asymptotic standard errors obtained following a covariance step in NONMEM;
b Expressed as %CV; c Natural exponent

Goodness of fit plots: Final Population PK Model



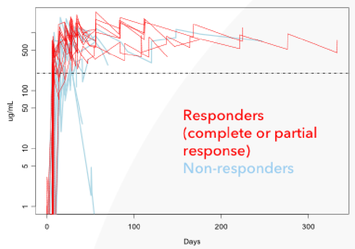
Observed Receptor Occupancy



Abstract 7504. ASCO 2018.

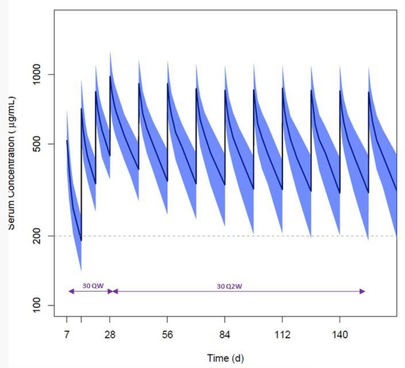
- Measurements confirmed near-maximal receptor occupancy on peripheral white cells at ~ 30 mg/kg
- Model-estimated PK parameters indicate that a concentration of 200 µg/mL is associated with ~99% peripheral receptor occupancy (RO), a level typically associated with optimal efficacy for other (T-cell) checkpoint inhibitors

All responders in 5F9003 had concentration >200 µg/mL



- Efficacy data (5F9003) also indicated all responding patients' PK profiles were above this threshold of 200 µg/mL

Simulations of Recommended Phase 2 Dose (RP2D): Median (interquartile range)



- Simulations identified RP2D (prime 1 mg/kg followed by 30 mg/kg QW for cycle 1 and 30 mg/kg Q2W cycle 2 onwards) that enables majority of patients to rapidly attain and maintain concentrations above 200 µg/mL threshold

Anti-drug Antibodies

- Serum samples from 2/58 patients (3.4%) tested positive for ADA; no impact on PK observed

Conclusions

- PK profile of 5F9 is typical of monoclonal antibodies directed towards cell-surface receptors
  - PK is nonlinear at doses < 10 mg/kg and linear at doses ≥ 10 mg/kg
  - Terminal half-life is approximately 2 weeks
- Population PK parameters indicate the existence of an antigen sink on multiple dosing, similar to other targeted antibodies
- An optimal effective concentration (C_{eff}) of 200 µg/mL was determined
- An RP2D scheme was identified: Prime (1 mg/kg), followed by weekly 30 mg/kg doses of Hu5F9 in cycle 1, and 30 mg/kg doses every other week was predicted to help rapidly attain and maintain concentrations above the C_{eff} in the vast majority of patients
- PK profile of 5F9 is suitable for every other week dosing

References

- Majeti, et al. (2009). "CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells.." Cell 138:2 (23)
- Buckeridge, et al. (2015). "Simple, Automatic Noncompartmental Analysis: The PKNCA R Package." Journal of Pharmacokinetics and Pharmacodynamics, 42(1), pp. 11-107