724 A Phase I Study of HCW9218, a Bifunctional TGF-β Antagonist/IL-15 Protein Complex, in Advanced Solid Tumors

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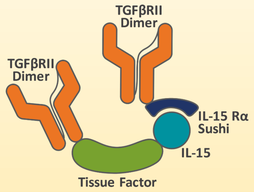
BACKGROUND

- HCW9218 is a bifunctional protein complex comprised of dimeric extracellular domains of the human transforming growth factor beta (TGF-β) receptor II (2*TGFβRII) and human interleukin-15 (IL-15) (Liu *et al.*, Mol Ther 2021; Chaturvedi *et al.*, Mol Ther 2022).



HCW9218

- The mechanisms of action of HCW9218 are to 1) activate immune effector cells and 2) sequester soluble immunosuppressive TGF-β.

PRIMARY OBJECTIVE

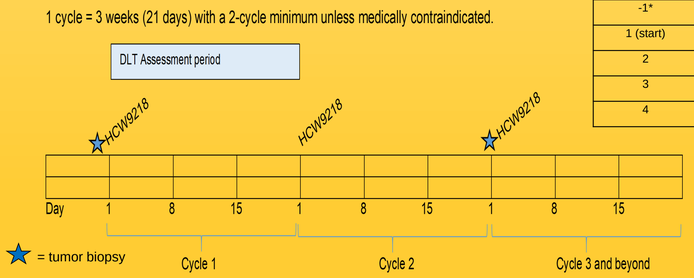
- The primary objective of this Phase I first-in-human clinical trial is to determine the maximum tolerated dose (MTD) of HCW9218 in patients with chemo-refractory/resistant advanced solid tumors.

METHODS

- HCW9218 is administered subcutaneously in the outpatient setting once every 3 weeks for a minimum of 2 cycles (**Fig 1**).
- HCW9218 dose ranges are from 0.25 mg/kg (DL1) to 1.2 mg/kg (DL4).
- Correlative objectives include immunogenicity, pharmacokinetic (PK) profiles of HCW9218, lymphocyte number, phenotype and function by flow cytometry analysis.

SCHEMA/DOSE LEVELS

Fig 1.



Phase I HCW9218 Dose Levels	
Dose Level (DL)	**HCW9218 dose**
-1*	0.1 mg/kg
1 (start)	0.25 mg/kg
2	0.5 mg/kg
3	0.8 mg/kg
4	1.2 mg/kg

Fig 2.

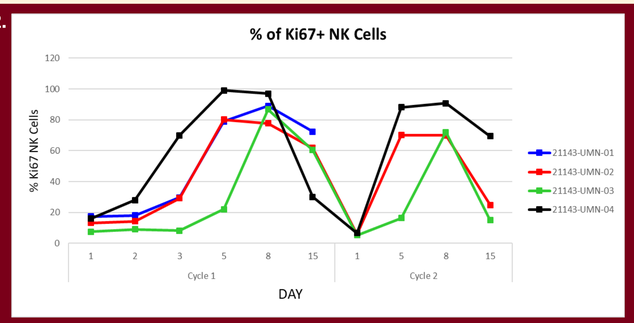


Fig 3.

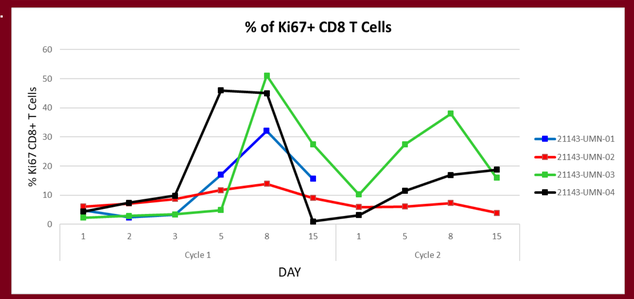


Fig 4.

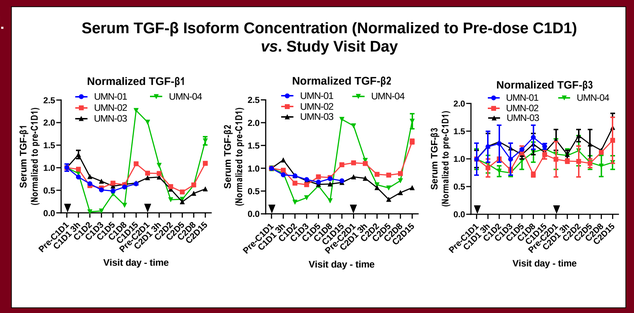
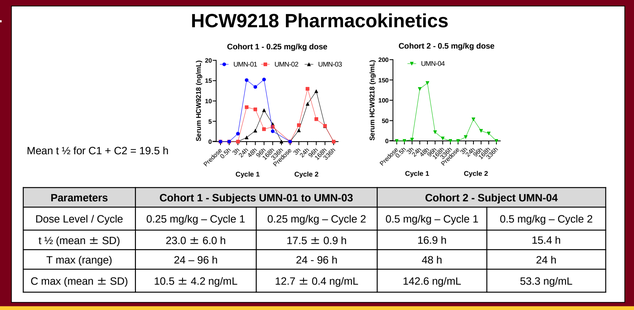


Fig 5.



Parameters	Cohort 1 - Subjects UMN-01 to UMN-03		Cohort 2 - Subject UMN-04	
Dose Level / Cycle	0.25 mg/kg – Cycle 1	0.25 mg/kg – Cycle 2	0.5 mg/kg – Cycle 1	0.5 mg/kg – Cycle 2
t ½ (mean ± SD)	23.0 ± 6.0 h	17.5 ± 0.9 h	16.9 h	15.4 h
T max (range)	24 – 96 h	24 - 96 h	48 h	24 h
C max (mean ± SD)	10.5 ± 4.2 ng/mL	12.7 ± 0.4 ng/mL	142.6 ng/mL	53.3 ng/mL

RESULTS

Demographics/Toxicity

Patient	Age	Gender	Disease	Race	Ethnicity	Dose	Doses Received	Gr3/4 toxicity
UMN-01	46	M	GIST	Unknown	Non-Hispanic	0.25 mg/kg	1	- Gr 3 tumor pain
UMN-02	57	M	Colon	White	Non-Hispanic	0.25 mg/kg	2	- Gr 3 Ascites
UMN-03	71	F	Ovary	White	Non-Hispanic	0.25 mg/kg	2	- Gr 3 Lymphocyte count decreased (n = 2) - Gr 3 hyponatremia - Gr 3 hypokalemia (n = 2) - Gr 3 Anemia - Gr 3 CKD - Gr 3 AKI
UMN-04	60	M	Colon	White	Non-Hispanic	0.5 mg/kg	3	None

*The most common adverse event experienced by all patients were grade 1-2 injection site reactions.

Immune Activity

- All subjects had a robust proliferation of NK cells (**Fig 2**), ranging from 77% to 97% Ki-67$^+$ by day 8 after dosing (7-15% pre-dosing), which corresponded to an increased mean % of NK cells to 31% of the lymphocytes at Day 8 and 37% at day 15 (11% pre-dosing). Responses were sustained through day 15, a biological effect beyond that previously observed for other IL-15 agonists.
- In the 3 patients who received Cycle 2, the proliferation of NK cells by Ki-67$^+$ was again observed, peaking on Day 8. 14 days after one dose, 46% of NK cells were CD56^{bright} (11% pre-dosing).
- A modest increase in Ki-67$^+$ CD8$^+$ T cells was observed on day 8 which was not sustained but was reactivated following Cycle 2 (**Fig 3**).
- There is a 50% reduction of serum TGF-β1 at the 0.25 mg/kg dose (Subjects UMN-01, -02, -03). The 0.5 mg/kg dose is able to almost completely neutralize serum TGF-β1 (Subject UMN-04) (**Fig 4**).
- HCW9218 did not increase serum levels of IL-1α, IL-1β, IL-6, IFN, or TNF.
- HCW9218 pharmacokinetics mimic NK cell Ki67$^+$ levels (**Fig 5**).

CONCLUSIONS

- HCW9218 safely and robustly expands NK cells after a single dose and escalation continues as planned to DL3 (0.8 mg/kg).

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