Background HCW9218 is a bifunctional protein complex comprising dimeric extracellular domains of the human transforming growth factor beta (TGF-β) receptor II and human interleukin-15 (IL-15). HCW9218 acts to (1) stimulate immune effector cells and (2) sequester soluble immunosuppressive TGF-β. The primary objective of this Phase I first-in-human clinical trial is to determine the maximum tolerated dose of HCW9218 in advanced solid tumors.

Methods HCW9218 is administered subcutaneously in the outpatient setting once every 3 weeks for a minimum of two cycles. HCW9218 dose range was established through extensive nonclinical studies using the MABEL approach. Patients’ assigned dose levels range from 0.25 mg/kg (DL1) to 1.2 mg/kg (DL4). Correlative analyses include HCW9218 immunogenicity and pharmacokinetic profiles, serum cytokine levels and lymphocyte number, phenotype and function.

Results Since 4/2022, three patients have been dosed. Patient #1 had a recurrent GI stromal tumor, received one dose but elected to discontinue due to metastatic bone pain. He experienced an injection site reaction lasting >72 hours requiring dose expansion to 3 subjects. Patient #2 had recurrent colon cancer, received 2 doses and discontinued due to unrelated grade 3 ascites requiring paracentesis and disease progression. Patient #3 had recurrent ovarian cancer and has received 2 doses to date. There has been one grade 3 adverse event (AE). The most common AEs have been grade 1-2 injection site reactions. Unexpectedly, patients at the DL1 level exhibit consistent and robust immune activity for at least 2 weeks after a single dose (figure 1). PBMC and serum were collected prior to dose 1, and at 2 to 15 days after dosing. All subjects had a robust increase in NK cell proliferation (81% Ki-67 by day 8 after dosing vs. 12.6% pre-dosing), which corresponded to an increased mean percent of NK cells to 34% of lymphocytes (12.6% pre-dosing). These responses were sustained through day 15, a biologic effect beyond that previously observed for other IL-15 agonists. By day 14, 44% of NK cells were CD56 bright. Additionally, there was a modest increase in Ki-67 CD8 T cells at day 8. No treatment-mediated effects were seen on serum IL-1α, IL-1β, IL-6, IFN-γ or TNFα, whereas levels of TGF-β1 and TGF-β2 were reduced (as expected) and MCP-1 was elevated. Preliminary pharmacokinetic analysis showed a Cmax at 20–73h post-dosing and half-life of ~78h.

Conclusions HCW9218 safely and robustly expands NK cells after a single dose and escalation continues as planned to DL2 (0.5 mg/kg).

Trial Registration NCT05322408

REFERENCES