767 PRE-CLINICAL AND FIRST-IN-HUMAN STUDIES OF HCW9218, A BIFUNCTIONAL TGF-β ANTAGONIST/IL-15 PROTEIN COMPLEX, IN ADVANCED SOLID TUMORS

[1]Melissa A Geller*, [2]Manish Patel, [3]Hing C Wong, [3]Peter R Rhode, [3]Philip M Arlen, [3]Danieska Sandino, [3]Karen L Kage, [3]Delsy G Gaetano, [3]Jack O Egan, [3]Giles M Leclerc, [3]Pallavi Chaturvedi, [3]Niraj Shrestha, [3]Zhu Xiaoyun, [4]Martin Felices, [4]Shannon Lunn, [4]Bethany Hanke, [4]Kelsey Mullen, [4]Deepa Kolaseri Krishnadas, [1]Rose Wangen, [1]Jeffrey S Miller. *[1]University of Minnesota, Minneapolis, MN, USA; [2]University of Minnesota Medical Center, Minneapolis, MN, USA; [3]HCW Biologics Inc., Miramar, FL, USA; [4]University of Minnesota, Minneapolis, MN, USA*

Background HCW9218 is a bifunctional protein complex comprising dimeric extracellular domains of human transforming growth factor beta (TGF-β) receptor II and interleukin-15 (IL-15). HCW9218 1) stimulates immune effector cells and 2) sequesters soluble immunosuppressive TGF-β.[1 2] The objectives of our pre-clinical and first-in-human studies are to explore the antitumor mechanism of action (MOA) and determine the RP2D.

Methods Two syngeneic mouse tumor models were used to explore the MOA of HCW9218. A phase I dose escalation study (NCT05322408) of HCW9218 monotherapy (Q3W, subcutaneous) has been completed in adult patients (n=12) with refractory advanced/metastatic solid tumors and is expanding at the highest dose level (1.2mg/kg).[3] Correlative analyses included pharmacokinetics, serum cytokines, blood lymphocytes, and cellular/molecular profiling of tumors.

Results In B16F10 melanoma and 4T1 breast cancer murine models, HCW9218 promotes proliferation and activation of progenitor exhausted (Tpex) and exhausted transitory effector (Tem) $CD8^+$ T cells in draining lymph nodes, and $CD8^+$ memory T cells and NK cells in peripheral blood. HCW9218 increases tumor infiltrating Tpex, Tem, and memory $CD8^+$ T cells and enhances antitumor potency of immune checkpoint blockade therapy, likely due to stimulation of Tpex and Tem cells. HCW9218 protein localizes in tumors and significantly lowers TGF-β levels and increases proinflammatory cytokines. In the first-in-human clinical trial, there were no dose limiting toxicities. The most common adverse events are grade 1–2 injection site reactions and transient lymphopenia. Patients receiving ≥0.25 mg/kg HCW9218 exhibit robust NK cell and $CD8^+$ T cell proliferation through day 15 and recurred with each treatment cycle, a biologic effect beyond what has been previously observed with other IL-15 agonists. At ≥0.5 mg/kg HCW9218, serum TGF-β1 levels decrease to baseline through day 8. Immunofluorescent staining of patients' tumors show that HCW9218 increases $CD8^+$ T cell infiltration with elevated tumor Tpex and/or fully differentiated memory $CD8^+$ T cells correlating with disease stabilization. Single-cell RNA-seq tumor analysis demonstrates that HCW9218 reduces expression of genes associated with tumor invasion, immunosuppression, and inflammation and upregulates genes involved in differentiation of Tpex, TCR signaling, and inflammatory response, while downregulating proinflammatory response genes of tumor lymphocytes. HCW9218 has a serum half-life of ~25h in patients.

Conclusions Repeated HCW9218 administration at ≥0.5 mg/kg in heavily pretreated advanced solid tumor patients resulted in immune cell activation, proliferation, and infiltration into the tumor microenvironment without causing unacceptable toxicity. HCW treatment presents a promising approach to enhancing the antitumor activity of immune checkpoint inhibitors in patients with solid tumors.

Trial Registration NCT05322408

REFERENCES

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Ethics Approval This study was approved by the University of Minnesota's Institutional Review Board; approval number: 00015102.

Consent Written informed consent was obtained from the patients included in the clinical trial for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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