

Novel antibody targeting soluble and tumor-bound NKG2D ligand MIC reshapes tumor immune ecosystem and is ready for clinical evaluation in mCRPC under an approved IND

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Background: In response to genotoxic insults, stressed epithelial cells express MHC I-chain related molecule (MIC) on the surface as a consequence of activating the ATM pathway. MIC itself has no known direct impact on tumor survival or growth. Within immune microenvironment, initial tumor cell surface MIC can activate NK cells and co-stimulate CD8 T cells through engagement of the activating receptor NKG2D, thereby promoting immune surveillance and limiting early tumorigenesis. In established malignancies, particularly metastatic diseases, tumor cells shed surface MIC and release the soluble form MIC (sMIC). Although chronic engagement of either soluble or membrane MIC can contribute to NK or CD8 T cell dysfunction, sMIC is highly immune suppressive. It disrupts NK cell homeostasis and function, , impairs antigen-specific CD8 T cell function, and promotes immune suppressive activity of MDSCs and TAMs in tumor microenvironment. We have demonstrated that MIC/sMIC is widely expressed by prostate tumor cells and is significantly upregulated in mCRPC tumors. We have also shown significantly elevated levels of serum sMIC in prostate cancer patients with metastatic diseases.

Methods and Results: To target this pathway, we have developed a novel class of B10G5 with a unique mechanism of action. Pre-clinical studies in syngeneic mouse models demonstrated that B10G5 targets both sMIC and cell-surface MIC to re-invigorate both NK and CD8 T cell immunity by promoting intratumoral stem-memory-like NK and CD8 T populations while preventing intratumoral effector NK and CD8 from terminal exhaustion. CZX-11, a humanized B10G5 clinical drug candidate, induced 100% long-term complete tumor regression (CR) at the dose as low as 1.0 mg/kg in preclinical models. These animals were fully protected from tumor re-challenge. We are initiating a First-in-Human trial of CZX-11 to treat patients in patients with metastatic prostate cancer or metastatic Ewing Sarcoma under an approved IND.

Conclusions: Pre-clinical studies support the novel mechanism of action of CZX-11, supporting the potential clinical activity of CZX-11 in mCRPC patients.

Funding Acknowledgements: This work was supported by NIH/NCI grant R01CA284640 and R01CA290719 to JW and Chicago Prostate SPORE P50CA180995. This work was also previously funded by PCF First-in-Field Challenging Award.

Conflict of Interest Statement: J. Wu is the inventor of the B10G5 antibody and has internationally granted patents. B10G5 was licensed to CanCure LLC. J. Wu has ownership of CanCure LLC who is the provider of CZX-11.