1064 CHARACTERIZATION OF PRECLINICAL ANTI-TUMOR AND PHARMACODYNAMIC ACTIVITY IN RESPONSE TO CONDITIONALLY ACTIVE IFNA WITH OR WITHOUT CHECKPOINT BLOCKADE

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Background Interferon alpha 2b (IFN) is an approved immunotherapy for treatment of multiple tumors; however, the toxicity of IFNa has limited its clinical use. Using CytomX proprietary Probody® Therapeutics (Pb-Tx) technology, a conditionally active, mouse cross reactive IFN-a (Pb-IFNa-A/D) with minimal activity in its prodrug form, was generated to enable the study of cancer immunobiology in the mouse. Pb-IFNa-A/D is activated by the elevated protease activity associated with the tumor microenvironment (TME), leading to preferential IFN activity in the TME but not in healthy tissues. Pb-IFNa-A/D has displayed robust activity in a range of tumors, including checkpoint non-responsive models.

Methods The Pb-Tx platform technology attenuates activity of a molecule by blocking its active regions through affinity or steric interference. Such blockade, termed masking, is reversed upon proteolytic cleavage of a substrate-containing linker between the molecule and the mask by tumor-associated proteases. To investigate the pharmacodynamic activity and evaluate biomarkers related to response to Pb-IFNa-A/D, we screened 25 syngeneic murine tumor models with both monotherapy and PD-1 checkpoint blockade combination. In addition to monitoring efficacy outcomes, tumor tissue and peripheral blood were collected 48 hours post administration for pharmacodynamic response measurement.

Results Pb-IFNa-A/D monotherapy demonstrated anti-tumor activity in a range of syngeneic tumor models, including some refractory to PD-1 blockade. Combination of Pb-IFNa-A/D and PD-1 blockade demonstrated enhanced antitumor activity in comparison to PD-1 alone. We assayed peripheral blood cytokine levels 48hrs post administration of Pb-IFNa-A/D and observed a significant increase in chemokines including CXCL10, and cytokines including CCL2/3, while PD-1 blockade showed no significant increase. The combination treatment significantly increased CXCL10 in comparison to both monotherapies.

To analyze changes in lymphocyte activation we performed peripheral blood immunophenotyping. Pb-IFNa-A/D and combination treatment demonstrated a significant increase in peripheral blood lymphocyte activation by CD69 and Granzyme B staining and were correlated with response.

To evaluate the on-tumor changes in response to Pb-IFNa-A/D, we performed RNA-seq on tumor tissue. We observed an increase in interferon-stimulated genes with Pb-IFNa-A/D and combination treatment. In agreement with peripheral observations, Pb-IFNa-A/D and combination treatment similarly increased Granzyme-B and CXCL10 expression.

Conclusions Pb-IFNa-A/D demonstrated robust anti-tumor activity in a range of syngeneic tumor models. Pharmacodynamic activity in the periphery and tumor demonstrates an IFN-stimulated immune response.

These data support Pb-IFNa-A/D as a promising clinical candidate as both a single agent and in combination with checkpoint blockade, potentially expanding their benefits to patients with unresponsive tumors.