706 CONDITIONAL CYTOKINE THERAPEUTICS FOR TUMOR-SELECTIVE BIOLOGICAL ACTIVITY: PRECLINICAL CHARACTERIZATION OF A DUAL-MASKED IFN-A2B

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Background Cytokines have been shown to elicit broad anti-tumor activity in preclinical models. These results have translated into the approval for clinical use of IFN-alpha and IL-2 before the checkpoint therapy era. However, to date, the clinical success of cytokines has been limited by systemic toxicity and poor exposure. CytomX Therapeutics has developed a new class of antibodies called Probody® therapeutics (Pb-Tx), designed to widen the therapeutic window by minimizing binding to targets in healthy tissue while being preferentially activated in the tumor microenvironment (TME) by tumor-associated proteases. CytomX has applied the Pb-Tx platform across multiple modalities including traditional antibodies, antibody-drug conjugates and T-cell engaging bispecifics and has advanced multiple programs into clinical studies. Here we have expanded the Pb-Tx platform with a conditionally activated cytokine version of IFN-α2b that has the potential to improve the therapeutic index of IFN-alpha therapy and allow systemic delivery.

Methods We engineered an IFN-α2b with a dual masking strategy using a cleavable Fc domain at one end of IFN-a2b, and a cleavable affinity peptide mask at the other end. The construct was optimized to both maximize cleavability and minimize IFN-a2b toxicity. All animal experiments were reviewed and approved by CytomX's Institutional Animal Care and Use Committee (IACUC Protocol AP303).

Results The optimized IFN-a2b conditionally activated cytokine strongly reduced IFN-a2b activity in vitro (5,000X) in its dual-masked form. Its activity was fully restored upon protease activation. Transcriptional profiling of in vitro treated PBMC confirmed reduction of interferon-mediated activities of the masked molecule. In vitro studies with dissociated tumors indicated its ability to activate tumor immune infiltrate, that could be further enhanced by concomitant PD-L1 blockade. In mouse xenograft studies, conditionally activated IFN-a2b cytokines induced complete regression at doses as low as 0.1mpk (activity comparable to peginterferon). Surrogate conditionally activated IFN-a2b molecules were also highly potent in syngeneic mice in vivo efficacy studies. Finally, we established an in vivo safety model in hamster which has been shown to be sensitive to IFN-a-mediated toxicity in the liver and bone marrow. In hamster, we showed that conditionally activated IFN-a2b cytokines are well tolerated up to 15mpk and have reduced systemic IFN-a2b mediated toxicity as compared to the unmasked cytokine.

Conclusions Taken together these preclinical data further support the development of conditionally activated IFN-a2b with the potential to improve the therapeutic index of IFN-a therapy and to enable single agent and combination treatment in multiple clinical settings.

Ethics Approval All animal experiments were reviewed and approved by CytomX's Institutional Animal Care and Use Committee (IACUC Protocol AP303).

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