CONDITIONALLY ACTIVATABLE INTERFERON-ALPHA 2B IMPROVES TOLERABILITY AND EXHIBITS PREFERENTIAL ACTIVITY IN TUMORS

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Background Despite its potential, the toxicity of interferon alpha has limited its clinical use. CytomX proprietary Probody® Therapeutics (Pb-Tx) technology allowed us to create a conditionally active IFN-a2b (Pb-IFN-a2b) with minimal activity in its prodrug form. The prodrug is activated in the tumor microenvironment (TME), leading to preferential activity in the TME but not in healthy tissues. Pb-IFN-a2b demonstrated a substantially enhanced tolerability profile compared to standard IFN therapy without compromising its antitumor effects.

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 linker between the molecule and the mask by tumor associated proteases.

Results Pb-IFN-a2b demonstrated considerable reduction (1000-fold or more) of interferon signaling in vitro and significantly reduced immune cell activation. Exposure to viable tumor tissues or tumor-associated proteases in vitro fully restored its bioactivity, including the ability of Pb-IFN to stimulate tumor-infiltrating immune cells.

Antitumor activity of the Pb-IFN-a2b in xenograft studies is equal to or greater than Peg-IFN-a2b. In syngeneic mouse tumor models, Pb-IFN demonstrated significant antitumor activity that was further enhanced by PD-(L)1 blockade. Activation of lymphocytes by the molecule was observed in tumors but not in secondary lymphoid organs.

Toxicology studies performed in hamsters demonstrated enhanced tolerability of the molecule compared to its unmasked control. In addition, Pb-IFN-a2b suppressed growth of hamster melanoma tumor model RPMI1846 at dose levels that were above the tolerated dose of the unmasked control.

Biomarkers of IFN signaling were greatly attenuated in non-human primates compared to the unmasked control. In cynomolgus monkey, Pb-IFN-a2b demonstrated linear pharmacokinetics, extended half-life, and was well tolerated at weekly doses up to 60 mg/kg.

Conclusions Pb-IFN-a2b shows improved tolerability and antitumor activity in preclinical studies compared to traditional IFN treatment. These data support Probody cytokine therapeutics as a promising addition to current immunotherapy regimens, potentially expanding their benefits to patients with typically unresponsive tumors.

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