DUAL-SPECIFIC ANTIBODIES BLOCKING BOTH PD-L1 AND PD-L2 ENGAGEMENT OF PD-1 RESTORE ANTI-TUMOR IMMUNITY

¹Coline Couillault*, ¹Anupallavi Srinivasamani, ¹Shweta Hedge, ²Qinying Liu, ³Ashwin Jaiswal, ¹Dongxing Zha, ¹Michael Curran. ¹MD Anderson Cancer Center, Houston, TX, USA; ²Fudan University, Shanghai, China; ³Astrazeneca, Gaithersburg, MD, USA

Background Inhibition of T cell activation and effector function via engagement of the co-inhibitory receptor PD-1 is a critical mechanism enabling tumors to evade host immunity. The two ligands for PD-1, PD-L1 and PD-L2, can be expressed by a variety of immunosuppressive stromal cells, particularly of the myeloid lineage, endothelial cells, and by tumors themselves. In addition to PD-1, PD-L1 engages B7-1 in an additional co-inhibitory interaction. Blocking only PD-1 or only PD-L1 thus does not relieve all inhibitory components of this pathway. We hypothesized that bispecific antibodies blocking both PD-L1 and PD-L2 could more fully restore tumor-specific T cell activation and potentiate anti-cancer immunotherapy. Furthermore, we speculated that enhancing the cytotoxic effector function of these antibodies might further enhance their efficacy through the depletion of tumor cells and supportive stroma.

Methods We investigated the capacity of monoclonal antibodies capable of bivalent binding to both PD-L1 and PD-L2 to restore the function of PD-1-suppressed T cells in vitro. To assess the in vivo therapeutic efficiency of bispecific PD-Ligand antibodies with ADCC capacities, mouse IgG2a and modified human IgG1 versions were generated. We assessed their ADCC activity in vitro using a bioluminescent reporter assay, and their therapeutic efficiency in vivo in syngeneic or human-cell derived tumors.

Results The bispecific antibodies we generated restore the function of PD-1-suppressed T cells in vitro with equivalent efficiency to the FDA approved PD-1 antibody Pembrolizumab. Moreover, our modified human bispecific antibodies lead to significantly higher FcγRIIIa activation than FDA-approved clinical human IgG1 PD-L1 antibodies in vitro. In vivo, ADCC-capable PD-Ligand bispecific antibodies suppress the growth of U2940 lymphoma in immunodeficient mice more efficiently than Rituximab, and in a syngeneic model of PD-L1/PD-L2 double positive colon carcinoma, these antibodies demonstrate superiority to PD-1 blocking antibodies to limit tumor growth and increase survival. Furthermore, treatment with our bispecific antibodies increases T cell proliferation and reduces density of immunosuppressive myeloid stroma in vivo.

Conclusions ADCC-capable PD-Ligand bispecific antibodies display higher therapeutic potential than existing anti-PD-1 antibodies and represent a new class of PD-1 pathway therapeutics with significant potential for the treatment of a variety of human cancers.

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