Discovery of CBO421, a first-in-class Drug Fc-Conjugate (DFC), targeting CD73 in Cancer

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Background

CD73 (NT5E) contributes to immune evasion in solid tumors by producing immuno-suppressive adenosine. Herein, we describe CBO421, a CD73 targeting DFC, that is a multivalent conjugate of a novel small molecule inhibitor stably linked to a proprietary immune-silent human IgG1 Fc. CBO421 combines the strengths of small molecule inhibitors and monoclonal antibodies (mAbs) targeting CD73 that are in clinical development, with potential best-in-class activity.

Methods

CD73 inhibition was evaluated and functional activity measured in a PBMC rescue assay with AMP. Binding to cancer cells and CD73 internalization was measured by flow cytometry. Tumor spheroid penetration was measured with $CD73^+$ cancer cells. Efficacy of CBO421 was evaluated in syngeneic mouse models.

Results

CBO421 is a potent, AMP-competitive inhibitor of CD73. CD73 inhibition by CBO421 was comparable or superior to small molecules and anti-CD73 mAbs. Unlike most anti-CD73 mAbs, CBO421 demonstrated complete CD73 enzyme inhibition. CBO421 demonstrated potent reactivation of $CD8^+$ T cells as measured by $CD25^+$ and granzyme B^+, that was comparable to small molecules and significantly more potent than anti-CD73 mAbs. Differentiated from small molecules, CBO421 triggered CD73 internalization as a second mechanism to reduce CD73 mediated adenosine production. The 2.3-fold smaller size and hydrodynamic radius of CBO421 compared to mAbs significantly improved tumor spheroid penetration. CBO421 demonstrated significant tumor growth inhibition (TGI) in multiple syngeneic mouse models with $CD73^-$ or $CD73^+$ cancer cells. Combination therapy of CBO421 with an anti-PD-1 mAb resulted in significant increases in TGI and complete responses when compared with the respective monotherapy. Immunologic memory was demonstrated in complete responders by rejection of tumor upon re-challenge.

Conclusions

CBO421 demonstrated high potency, combined with multiple, distinct mechanisms of action that translated to potent antitumor activity as a monotherapy in syngeneic mouse models that was further improved in combination with PD-1 therapy. Based on these results and other emerging data, CBO421 is being advanced as a clinical development candidate for the treatment of solid cancers.