

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 immune-suppressive adenosine in the tumor microenvironment. Herein, we describe CBO421, a CD73 targeting DFC, 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 targeting CD73 that are currently in clinical development, with potential best-in-class activity.

Methods

Inhibition of CD73 by CBO421 was evaluated in cell-free and cell-based assays. Functional activity was measured in a PBMC rescue assay in the presence of AMP. Binding to cancer cells was measured in the presence and absence of AMP or small molecule CD73 inhibitors by flow cytometry. CD73 internalization was measured in MDA-MB-231 cancer cells. Pharmacokinetic (PK) studies were conducted in Balb/c mice. Plasma concentrations were measured using an anti-human IgG Fc in combination with CD73 capture ELISA. Efficacy of CBO421 was evaluated in syngeneic mouse models.

Results

CBO421 is a potent, AMP-competitive inhibitor of CD73. In cell-free and cell-anchored CD73 inhibition assays (on tumors and immune cells), CBO421 demonstrated potent activity, comparable or superior to small molecule inhibitors and anti-CD73 mAbs in clinical development. Unlike most anti-CD73 mAbs, CBO421 demonstrated complete enzyme inhibition against soluble and cell-anchored CD73. In a functional PBMC rescue assay, CBO421 demonstrated potent reactivation of CD8⁺ T cells as measured by CD25⁺ and granzyme B⁺, which was comparable to small molecule controls and more potent by up to 2-logs than anti-CD73 mAb comparators. As described with some anti-CD73 mAbs, CBO421 triggered CD73 receptor internalization as a second mechanism to reduce CD73 mediated adenosine production. CBO421 is biologically stable with an antibody-like PK profile in mice. CBO421 demonstrated tumor growth inhibition in multiple syngeneic mouse models injected with either CD73-negative or CD73-expressing cancer cells. Combination therapy of CBO421 with an anti-PD-1 mAb resulted in significant increases in tumor regression and complete responses when compared with the respective monotherapy cohorts. All mice with complete responses demonstrated immunologic memory upon tumor rechallenge.

Conclusions

CBO421 demonstrated high potency in functional cell-based assays. This in vitro potency and favorable PK profile of CBO421 translated to antitumor efficacy 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.