INTRODUCTION
CD73 catalyzes the extracellular generation of adenosine (ADO) from adenosine monophosphate (AMP). ADO suppresses immune responses, including tumor infiltration, by activation of A2A and A2B receptors. Expressed on T cells and NK cells, the presence of adenosine in the extracellular milieu can result in the blockade of immune responses. Various efforts have been made to increase the effects of ADO by using inhibitors of CD73. Inhibitors of CD73 (CD73i) used in this presentation include AB680, A00830, A001421.

RESULTS AND CONCLUSIONS

c) CD73 is expressed across a wide range of tumor types, including those with limited response to anti-PD-1 therapy. CD73 completely reversed AMP-mediated inhibition of T cell proliferation and effectors as well as NK cell cytolytic function. AMP abrogated the enhanced allogeneic CD4+ T cell stimulation and IFNγ production mediated by blocking PD-1/PD-L1 and TIM3, an effect that was reversed by CD73. Mechanistically, addition of AMP in MLRs represented expression of activation markers and immune checkpoint proteins. Thus, activation of the adenosineergic pathway may limit the efficacy of ICIs. TCGA data from anti-PD-1-treated melanoma patients identified CD73 expression as a negative prognostic factor. Finally, co-administration of a CD73i with an anti-PD-1 mAb resulted in significant reduction of tumor volume associated with increases in immune cell infiltration.

CD73 inhibitors, alone or in combination with anti-PD-1 and anti-TIM3 antibodies, translates into potent enhancement of immune cell activation and expansion of effector cells. These data provide a rationale for clinical evaluation of CD73i + ICIs combinations.

CD73i Enhances the Activity of αPD-1 in B16.F10 Melanoma Model

Figure 6: In-house generated CD73 inhibitor, A00830 or AB680, together with αPD-1 antibody (RMP1-14) were dosed by intraperitoneal injection each day for a week. Tumors reached a volume of 50 mm³. Change in tumor volume (A) associated with clinical change in the animal was shown. Similar to A00830, AB680 also increased efficacy of αPD-1 antibody (B) as measured by tumor volume (C) and survival curves (D). Mice bearing tumors > 1000 mm³ were sacrificed as per protocol. Pink circles indicate days when αPD-1 antibody dosing occurred.

Figure 7: Lymphokine-activated killer cells (LAKs) were generated from C57BL/6 splenocytes cultured in LPS. Expression of adenosine receptors were assessed by qPCR. LAK cells pre-incubated with αPD-1 and cultured with LLC target cells loaded with caspase detection reagent (B). Cytoytic activity of LAKs were depicted as percent casapse-positive LLCs.