

Adenosine Signaling Through A2AR Limits The Efficacy of Anti-CTLA4 and Chemotherapy in Preclinical Models.

Ho P, Hsieh M-Y, Hotson A, Miller R, McCaffery I, Willingham S
Corvus Pharmaceuticals, Burlingame, CA 94010, USA.

Elevated levels of extracellular adenosine within the tumor microenvironment create an immunosuppressive niche that promotes tumor growth and metastasis. Adenosine signaling via the A2A receptor (A2AR) on immune cells suppresses anti-tumor immunity and has been shown to limit the efficacy of immunotherapies such as anti-PD-L1 or anti-PD-1 monoclonal antibodies (mAbs).

CPI-444 is a potent and selective oral A2AR antagonist that is currently being investigated in Phase 1/1b clinical trials alone and in combination with an anti-PD-L1 antibody (Atezolizumab) in selected solid tumors. New preclinical data suggests that combining CPI-444 with anti-CTLA-4 mAbs as well as chemotherapy treatment are also promising therapeutic strategies in solid tumors, suggesting a broad role for adenosine as an immune suppressive mechanism.

The efficacy of CPI-444 + anti-CTLA-4 mAb treatment was evaluated in MC38 and CT26 syngeneic mouse tumor models. In CT26, combination treatment eliminated established tumors in up to 90% of mice approximately 2 weeks after treatment was initiated. In MC38, combination CPI-444 and anti-CTLA-4 mAb treatment prolonged survival of 80% of mice compared to only 40% of mice that received CPI-444 or anti-CTLA-4 mAbs alone. The effect of CPI-444 + anti-CTLA-4 treatment on T-cell proliferation, T cell activation, and T_{REG} function will be discussed.

Chemotherapy releases adenosine and ATP into the tumor microenvironment (TME). Multiple chemotherapies have also been shown to up-regulate the ecto-enzymes CD39

and CD73 that produce adenosine and further suppress immune function. In the MC38 model, CPI-444 treatment synergized with doxorubicin and eliminated established tumors 80% of treated mice. CPI-444 treatment was also synergistic with cyclophosphamide, inhibiting the growth of RENCA tumors, a model that is considered resistant to chemotherapy. Ongoing studies are evaluating the effect of CPI-444 + chemotherapy on tumor infiltrating lymphocyte localization, activation, and expression of CD73 and CD39.

These results suggest that blockade of the adenosine signaling pathway may be vital for enhancing anti-tumor responses in solid tumors that show an incomplete response to anti-CTLA4 therapy or chemotherapy.