AB680 Limits CD73 Activity and Enhances the Activity of α-PD-1 in B16F10 Melanoma Model

Figure 2. (A) AMPlase activity was assessed on B16F10 melanoma tumor sections using a modified form of the Warburg-Meisel method of enzyme histochemistry. Yellow arrows indicate regions with active AMPase activity. The effects of AB680 on syngeneic tumor volumes were assessed in propylactic and therapeutic settings. The PK properties of AB680 were evaluated in multiple preclinical species and a projected human dosing schedule for AB680 was determined via in-life study.

AB680 Mouse Pharmacokinetics

Figure 3. (A) AB680 was dosed once daily in life. Tumor volumes were measured using LC-MS/MS. Dashed lines refer to the potency of AB680 against CD73 in mouse plasma. (B) Plasma to tumor partitioning of AB680 (10 mg/kg dose) was calculated using AUC from t = 0 to t = 72 hrs. Comparative ratios were obtained from AUC. Analysis of mouse PK/PD suggests that the effective dose of AB680 is associated with plasma levels ≥ 30,000 ng/mL. These plasma levels provide >50% coverage of plasma and an estimated 95% coverage in B16F10 tumors. Adjusting for interspecies potency differences, the corresponding human plasma concentrations would be ~270 ng/mL. This target exposure may represent the upper end of the range where we expect to see CD73-related biological effects in humans.

Correlation Between Serum CD73 Concentration and Activity

Figure 5. (A) Soluble CD73 (sCD73) levels in human serum were quantified using our in-house developed ELISA. AMP-deaminase activity was measured using AMP-Glo assay. Each dot represents one independent donor. (B) Total AMP hydrolysis in serum from cancer patients (1-5) was measured. Black bars represent sCD73-mediated hydrolysis while white bars represent TNAP-mediated hydrolysis.

AB680 Limits the Inhibitory Effect of AMP on CD4+ and CD8+ T cells

Figure 6: Human CD4+ T cells (A) and CD8+ T cells (B) were isolated and activated in the presence of AMP with ENA (adenosine deaminase inhibitor). Dose-dependent rescue of CD4+ and CD8+ T cell activation was observed in the presence of exogenous AB680. CD4+ and CD8+ T cell activation was measured by cytokine bead array for IFN-γ and IL-2 and IFN-γ and granzyme B, respectively.

Conclusions

AB680 is a highly potent and selective small-molecule inhibitor of CD73 which can mitigate AMP and ADO-mediated tumor immunosuppression by potentially blocking the production of ADO. AB680 retains high potency when tested in human serum (potency reflects both plasma protein binding and binding to soluble CD73). AB680 exhibits a unique projected human PK profile (including a long projected half-life) amenable to intravenous dosing schedules.

In vivo mouse studies with AB680 in B16F10 tumors suggest that >95% intra-tumoral CD73 inhibition results in increased efficacy in combination with anti-PD-1, additional models to be tested. AB680 is expected to enter clinical development in 4Q2018.