A POTENT AND SELECTIVE SMALL MOLECULE ANTAGONIST OF CD73 ABSK051 REVERSES IMMUNOSUPPRESSION THROUGH REDUCTION OF ADENOSINE PRODUCTION

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Background CD73, an ecto-5-nucleotidase involved in ATP metabolism, converts AMP into adenosine, thereby plays a critical role in immunosuppression in tumor microenvironment. Overexpression of CD73 has been observed across cancer types and correlated with poor prognosis. Therefore, targeting CD73 enzymatic activity can potentially rescue the immunosuppression induced by adenosine and bring clinical benefits to cancer patients. Unlike antibodies, small molecule modulators may offer potential advantages in dosing regimen, tumor penetration, and others. In this study, we investigated the in vitro and in vivo function of ABSK051, a novel small molecule antagonist of CD73 discovered by Abbisko, and also its anti-tumor efficacy as a potent immune modulator.

Methods The effects of ABSK051 on adenosine production were evaluated using cell based luciferase assay. Its function in rescuing AMP induced immunosuppression was investigated by monitoring activation levels of CD8+ T cells. For in vivo studies, tumor-bearing syngeneic mice were treated with ABSK051 and its inhibition on plasma CD73 activity and tumor growth were measured. In addition, humanized tumor models were also developed using several human cancer cell lines and utilized to evaluate the efficacy of ABSK051.

Results ABSK051 demonstrated strong in vitro inhibition of CD73 enzymatic activity, thereby effectively rescued the immune inhibition induced by adenosine. It also demonstrated in vivo anti-tumor efficacy as a single agent in various preclinical tumor models and in combination with other immunoncology agents.

Conclusions Taken together, these data demonstrated desirable preclinical biological profile of ABSK051 against CD73 and in regulating tumor growth, paving the road for further development of it as a preclinical drug candidate and potential clinical evaluation as an immune agent for cancer patients.