1381 DISCOVERY OF ALG-093989, A HIGHLY POTENT AND ORALLY BIOAVAILABLE SMALL MOLECULE PD-L1 INHIBITOR FOR THE TREATMENT OF CANCERS

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Background PD-1/PD-L1 antibody-based therapies have demonstrated tremendous success in the treatment of a variety of cancers. However, these antibody drugs are associated with several disadvantages, such as weak tumor penetration, immune-related adverse events (irAEs) due to their long half-life and development of anti-drug antibodies. Here, we report the discovery of ALG-093989, a highly potent and orally bioavailable PD-L1 small molecule inhibitor, that may overcome the limitation of PD-1/PD-L1 antibodies.

Methods The biochemical interaction of PD-1/PD-L1 and PD-L1 dimerization was assessed by AlphaLISA®. Cellular activity was measured using a co-culture assay of PD-1 expressing Jurkat NFAT luciferase T cells with PD-L1 expressing CHO cells. Pharmacokinetic (PK) studies were performed in rat. *In vivo* PD-L1 target occupancy was assessed at 6 hours following a single oral dose in a humanized-PD-L1 MC38 subcutaneous mouse model.

Results ALG-093989 inhibits PD-1/PD-L1 interaction with an IC_{50} of 14 pM and induces PD-L1 dimerization with an EC_{50} of 13 nM. ALG-093989 has similar T-cell activation potency as durvalumab, and approximately 10-fold improved T-cell activation potency vs. INCB086550, a PD-L1 small molecule inhibitor that demonstrated clinical response in a phase I study. Oral bioavailability of ALG-093989 in rat following a single dose at 15 mg/kg dosing was 40%. In the *in vivo* humanized-PD-L1 MC38 mouse model, a single oral dose of ALG-093989 at 5 mg/kg demonstrated similar PD-L1 target occupancy to that of 150 mg/kg orally-administered INCB086550 and 5 mg/kg intravenously-administered durvalumab.

Conclusions We have discovered ALG-093989, a highly potent PD-L1 small molecule inhibitor, which shows similar T-cell activation potency as durvalumab, and ~ 10-fold improved T-cell activation potency vs. INCB086550. ALG-093989 has the same target occupancy in mice following oral dosing at a 30-fold lower dose than INCB03989. The properties of ALG-093989 warrant further evaluation as a potential candidate for drug development.

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