AB801 is a Highly Potent and Selective AXL Kinase Inhibitor that Demonstrates Significant Anti-Tumor Activity

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Overview

The tyrosine kinase receptor AXL is highly expressed in a variety of cancer, stromal, and immune cells in tumors, and has been implicated in resistance to chemotherapy, targeted therapies, and immunotherapies. Our team has discovered and characterized AB801, a novel highly potent and selective small molecule AXL inhibitor.

This poster describes the preclinical evaluation of AB801 in vitro & in vivo models.

AXL Signaling Supports Therapeutic Resistance in Tumors

High expression of AXL results in drug resistance and altered immune responses. Activation of AXL can occur in a ligand-dependent manner via ligand-induced growth arrest or protein–protein interaction (PPI).

AXL phosphorylation initiates signaling cascades that promote cancer cell proliferation, survival, migration, and an immunosuppressive microenvironment.

Pan-Kinase Selectivity of AB801

AB801 exhibits excellent potency and selectivity in functional and immunofluorescence assays.

In functional assays, AB801 improves profile over previous AXL inhibitors.

审议

AB801 was tested against a broad non-AXL panel of kinase targets (excluding PI3Kγ). Using a qPCR-based competition binding experiment, AB801 showed <35% of control activity (indicating stronger binding) against 7 other kinase targets, excluding AXL.

AB801 was tested against a broad non-AXL panel of kinase targets (excluding PI3Kγ) using a pAXL ELISA in HEK293T cells transiently transfected with Nanoluc-tagged AXL. pAXL levels were evaluated by western blot after 72h of drug exposure. AB801 showed >100-fold selectivity over PI3Kγ, with all other kinases being >100-fold

Using a DRAK1 (47-kDa) phospho- specific antibody, AB801 dose-dependently attenuated pDRAK1 in HEK293T cells with IC50 of 0.3 μM

Figure 3: AB801 inhibits ligand-dependent & ligand-independent AXL Phosphorylation

Figure 4: AXL expression is present in cancer cells and in the myocardial compartment in MC38 tumors. Tumors (100-450 mm3) were used to characterize AXL expression in cancer cells. AXL was also analyzed in higher tumor volumes and functional analyses.

MC38 Tumors Are Infiltrated by TCF+ CD8 T Cells

Increasing DNA Damage

Figure 5: AXL expression in combination with Oxaliplatin and anti-PD-1 significantly decreases tumor volume and increases survival in the MC38 model

AXL Pathway Is Activated in MC38 Tumors

AXL is Expressed in Cancer and Myocardial Cells in MC38 Tumors

SUMMARY

AB801 exhibits excellent potency and selectivity in functional and cellular-based assays. AB801 possesses an improved profile over previous AXL inhibitors.

AB801 displays excellent pharmacokinetics in preclinical development profiles, thus limiting off-target liabilities. The lowest Km is for DRAK1 (47-kDa), with all other kinases being >100-fold.

The AXL pathway is activated in MC38 tumors with AXL detectable on both tumor cells and in the myocardial compartment.

AB801 in combination with Oxaliplatin and anti-PD-1 significantly decreases tumor volume and increases survival in the MC38 tumor model.

AB801 enhances lymphocyte function through multiple cancer cell lines in 2D and 3D cultures by increasing DNA damage.

References


Data generated by Acura, Biomedical Informatics from Synovar.