Preclinical pharmacokinetic, pharmacodynamic and efficacy relationships of ALG-093702, a liver targeted PD-L1 small molecule inhibitor, in different in vivo models

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KEY TAKE HOME MESSAGES

Rationale

PD-1/PD-L1 is a major pathway of T-cell exhaustion in CHB

Problem

Dose-limiting systemic toxicities of PD-1/L1 antibodies

Our Solution

Liver-targeted PD-L1 SMi to localize T-cell activation to the liver

Current Status

- Identified liver targeted PD-L1 SMi (ALG-093702)
- Investigating PK/PD to guide compound selection and dosing strategy

INTRODUCTION AND OBJECTIVES

The PD-1/PD-L1 immune checkpoint pathway is an attractive target to reverse immune tolerance in chronic hepatitis B (CHB). However, due to the systemic immune adverse effects associated with antibodies, a lower dose of PD-1/PD-L1 antibodies has been used in CHB vs. the dose used for cancer. ALG-093702 is a liver-targeted PD-L1 small molecule inhibitor that preferentially partitions into the liver and thereby may potentially mitigate extra-hepatic on-target related toxicity. Characterizing the relationship between pharmacokinetics (PK), pharmacodynamics (PD) and the efficacy of ALG-093702 is critical for selecting the dosing strategy of novel liver targeted PD-L1 inhibitor drugs.

METHODS

Biochemical PD-1/PD-L1 interaction was assessed by AlphaLISA®. Cellular activity was measured using a co-culture reporter assay in which NFAT activity of Jurkat T cells was constitutively inhibited by the engagement of PD-1 by PD-L1-expressing CHO cells. Oral dosing of ALG-093701, a prodrug of ALG-093702, was used for in vivo PK/PD/efficacy studies. In vivo PK/PD/efficacy were assessed in humanized-PD-L1 MC38 subcutaneous tumors and/or a liver metastasis mouse model. Target engagement was assessed by FACS using MIH1 PD-L1 antibody which competes with PD-L1 inhibitors. Percentage target engagement was calculated using median fluorescent intensity compared with an untreated control.

CONCLUSIONS

- ALG-093702 is a liver-targeted PD-L1 small molecule inhibitor with similar in vitro potency, in vivo PD-L1 target occupancy and tumor growth inhibition as durvalumab.
- Increases in target occupancy were dose dependent, with a PK/PD correlation to overall plasma/tumor exposures.
- The preclinical PK/PD/efficacy correlation provides guidance for the efficacious human dose prediction and dosing strategy for clinical studies of oral liver targeted PD-L1 small molecule inhibitors.

RESULTS

Discovery of a Highly Potent PD-L1 Small Molecule Inhibitor

		Nivolumab	Durvalumab	ALG-093702
Biochemical Activity	PD-1/PD-L1 Interaction IC_{50} (nM)	0.159 ± 0.007 (n=2)	0.025 ± 0.009 (n=2)	0.048 ± 0.005 (n=2)
	PD-L1 Dimerization IC_{50} (nM)	*not applicable*	*not applicable*	5.0 ± 1.0 (n=2)
Cellular Activity	Jurkat PD-1/PD-L1 Blockade EC_{50} (nM)	3.3 ± 0.3 (n=2)	0.3 ± 0.1 (n=4)	6.8 ± 2.4 (n=15)

Table 1: Biochemical and Cellular activities of Aligos PD-L1 inhibitor vs. FDA-approved antibodies

ALG-093702 is Orally Bioavailable Through Prodrug and Shows High Liver Tropism in Mice

(A) Mouse PK Parameters

	ALG-093702
PO Dose (mg equiv. of parent/kg)*	50
T_{max} (h)	2.00
C_{max} (nM)	2912
$AUC_{0\text{-}inf}$ (nM.h)	14,364
Oral Bioavailability	41%

*Dose of prodrug ALG-093701 as mg equiv. of parent ALG-093702

(B) ALG-093702 Tissue Distribution at 6h postdose

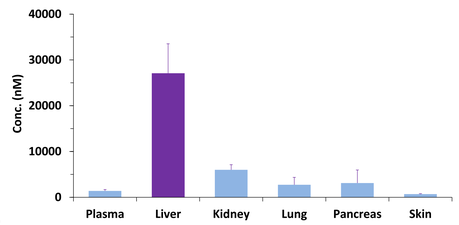
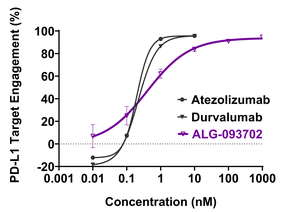


Figure 1: Mean plasma and tissue concentrations of ALG-093702 in C57BL/6 mice
(A) Mouse PK parameters and (B) tissue distribution of ALG-093702 after a single PO dose of prodrug ALG-093701*

ALG-093702 Induces Target Engagement in vitro and in vivo

(A) Cellular PD-L1 Target Engagement



Compound	Atezolizumab	Durvalumab	ALG-093702
Target Occupancy EC_{50} (nM)	0.22	0.28	0.49

(B) PD-L1 Target Engagement in vivo humanized PD-L1 Liver metastasis

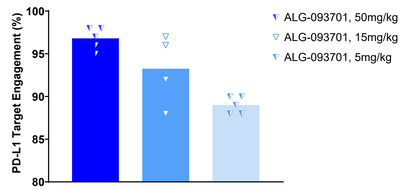


Figure 2: Effect of Aligos PDL1 inhibitor on target engagement
(A) PD-L1-expressing CHO cells were incubated for 24 hours in presence of PD-L1 inhibitors. PD-L1 target engagement was assessed by FACs using MIH1 anti-PD-L1 antibody.
(B) hu-PD-L1 MC38 cells were injected intra-splenic to generate liver metastasis and mice were dosed with ALG-093701 orally (PO) with a single dose. Liver was collected 6 hours post-dosing and target engagement was assessed by FACs using MIH1 anti-PD-L1 antibody.

CONTACT INFORMATION

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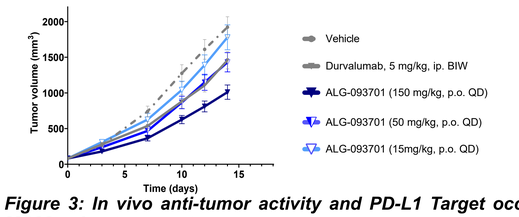
ALG-093702 at 50 mg/kg Shows Similar Efficacy to 5 mg/kg of Durvalumab in an SC Tumor Model

(A) In vivo Tumor Growth Inhibition in a MC38-human-PD-L1 Subcutaneous Model



(B) PD-L1 Target Occupancy at day 3 in MC38-human-PD-L1 Subcutaneous Model

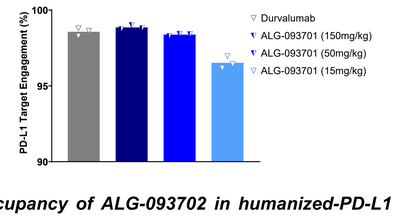
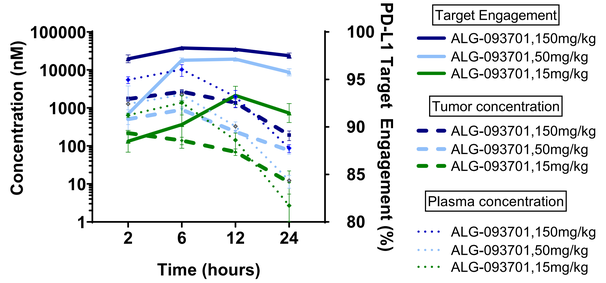


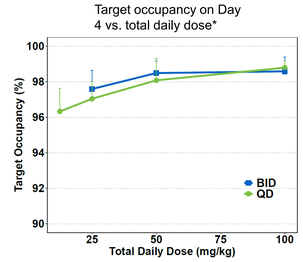
Figure 3: In vivo anti-tumor activity and PD-L1 Target occupancy of ALG-093702 in humanized-PD-L1 MC38 subcutaneous tumor
hu-PD-L1 MC38 cells were implanted subcutaneously, and mice dosed with vehicle or indicated compounds.
(A) Anti-tumor activity of ALG-093702 was assessed by measuring tumor volume.
(B) Target occupancy was measured at 24 hours after 3 days of dosing by FACS.
Dose-dependent increase in anti-tumor and target engagement was observed. At 50 mg/kg ALG-097302 was as efficacious as durvalumab at 5 mg/kg.

ALG-093702 in vivo PK/PD Studies in MC-38 Human PD-L1 Subcutaneous Model

(A) Single dose



(B) Repeat dose (QD and BID)



(C) PK/PD correlation (QD and BID)

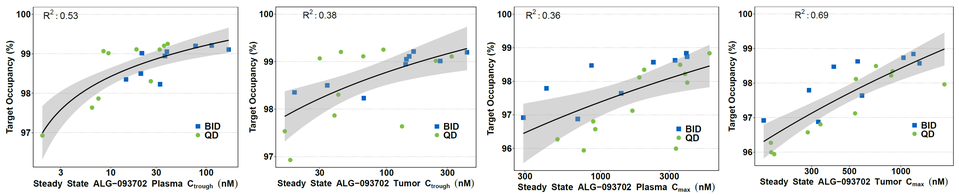


Figure 4: In vivo PK/PD relationship of ALG-093702 in MC-38 human PD-L1 subcutaneous model
hu-PD-L1 MC38 cells were implanted subcutaneously, and mice dosed with vehicle or indicated compounds.
(A) PD-L1 target occupancy vs. plasma and tumor concentration following single doses at 15, 50 and 150 mg/kg.
(B) Dose response and (C) PK-PD correlation on Day 4 following 12.5, 25, and 50 mg/kg QD and BID, 100 mg/kg QD PO administration in MC-38 human PD-L1 subcutaneous mouse model.
Increases in target occupancy following single and repeat doses were dose-dependent. At steady state, plasma and tumor C_{tough} and C_{max} correlated with target occupancy.
The PD correlation with two PK parameters, combined with the observation of similar target occupancy for the same total BID or QD dose each, are suggestive of PK/PD correlation with $AUC_{0\text{-}24}$ at the evaluated doses.