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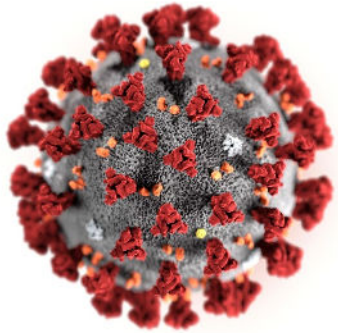

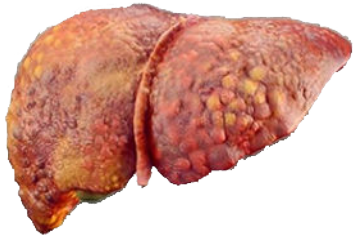

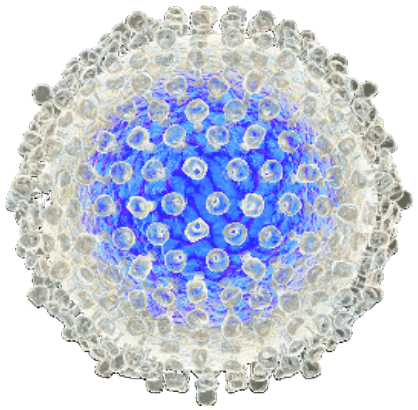

Discovery of Liver-targeted Oral PD-L1 Small Molecule Inhibitors for the Treatment of Chronic Hepatitis B and Liver Cancers

Tongfei Wu

On behalf of the Aligos PD-L1 Project Team

Disclosures

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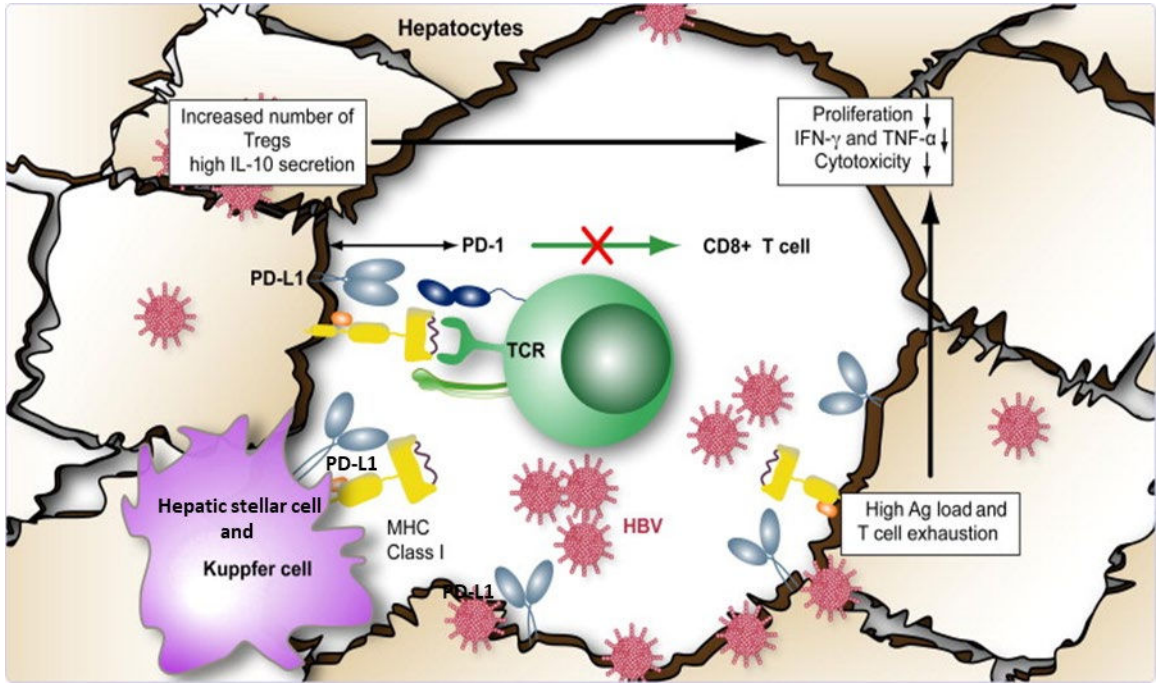
Except where otherwise indicated, the information contained in this presentation speaks as of the date hereof or as of the date at which such information is expressed to be stated, as applicable, and such information may express preliminary estimated, unaudited results which shall be subject to audit or other year-end adjustments and such audited or adjusted results may materially differ from those contained in this presentation.

This presentation concerns drug candidates, some of which are undergoing nonclinical studies and others of which are under clinical investigation, and all of which have not yet been approved for marketing by the U.S. Food and Drug Administration. These drug candidates are currently limited by federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

PD-1/PD-L1 is a Major Pathway of Immune Tolerance to HBV

- PD-1/PD-L1 is the major co-inhibitory axis mediating T cell exhaustion in chronic hepatitis B
  - Intrahepatic HBV-specific T cells express PD-1
  - PD-L1 is present on hepatocytes and non-parenchymal cells



PD-L1 inhibitors can potentially reactivate exhausted HBV specific T cells

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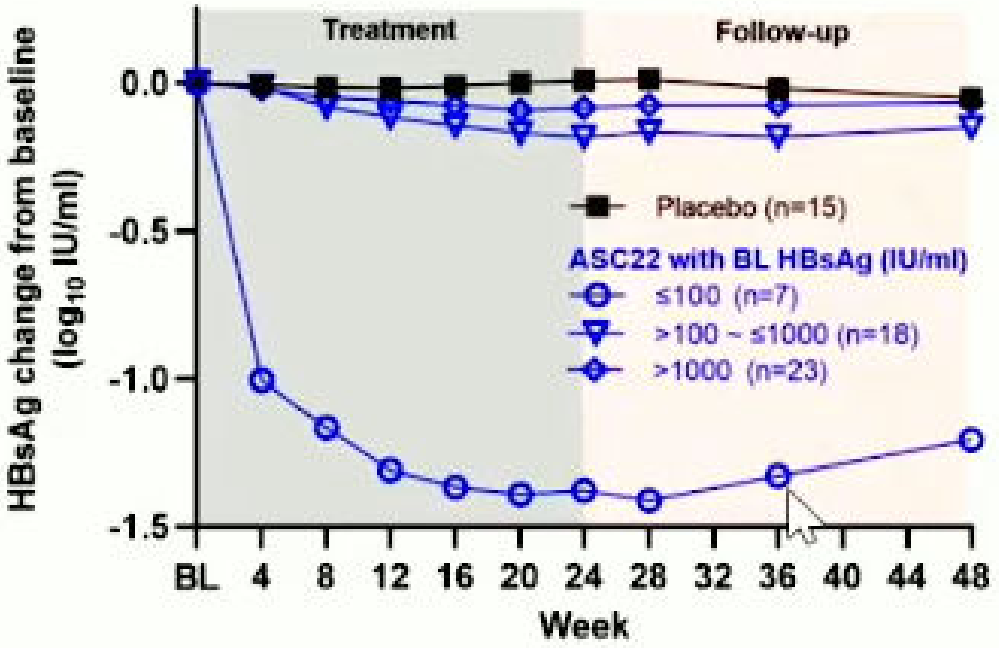
Michel ML et. Al J Hepatol, **2011**, *54*, 1286–1296.

PD-L1 is a Promising Drug Target for Treating Chronic Hepatitis B

- ASC22:
  - PD-L1 antibody, envafolimab, in clinical trials for treatment of chronic hepatitis B (CHB)
  - Envafolimab has been approved in China for advanced solid tumors, SC, 300 mg, Q4W

- ASC22 Phase 2b interim results for CHB :
  - 1.0 mg/kg ASC22 (PD-L1 antibody) Q2W + nucleos(t)ide analogs (NA) for 24-weeks (n=60)
  - 42.9% patients with baseline HBsAg ≤100 IU/mL (n=7) obtained sustained HBsAg loss

Phase 2b Study of ASC22 with NA (EASL, 2022)*



Anti-PD-L1 antibody + NA treatment shows potential functional cure of chronic hepatitis B

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*Guiqiang Wang et. al, Abstract #OS091, The International Liver Congress™ EASL - European Association for the Study of the Liver, June 22-26, 2022

ALG-093702 is a Potent PD-L1 Small Molecule Inhibitor

		Nivolumab PD-1 antibody	Durvalumab PD-L1 antibody	ALG-093702 PD-L1 SMi
Biochemical Activity	**Human PD-1/PD-L1 Interaction** IC_{50} (nM)	**0.159** (n=2)	**0.025** (n=2)	**0.048** (n=2)
	Human PD-L1 Dimerization EC_{50} (nM)	**No dimerization**	**No dimerization**	**5.5** (n=2)
Cellular Activity	**Jurkat PD-1/PD-L1 Blockade** EC_{50} (nM)	**3.3** (n=2)	**0.3** (n=4)	**5.9** (n=8)

ALG-093702 but not the PD-1 or PD-L1 antibodies, induce PD-L1 dimerization

ALG-093702 shows similar potency to the FDA-approved PD-1 antibody nivolumab

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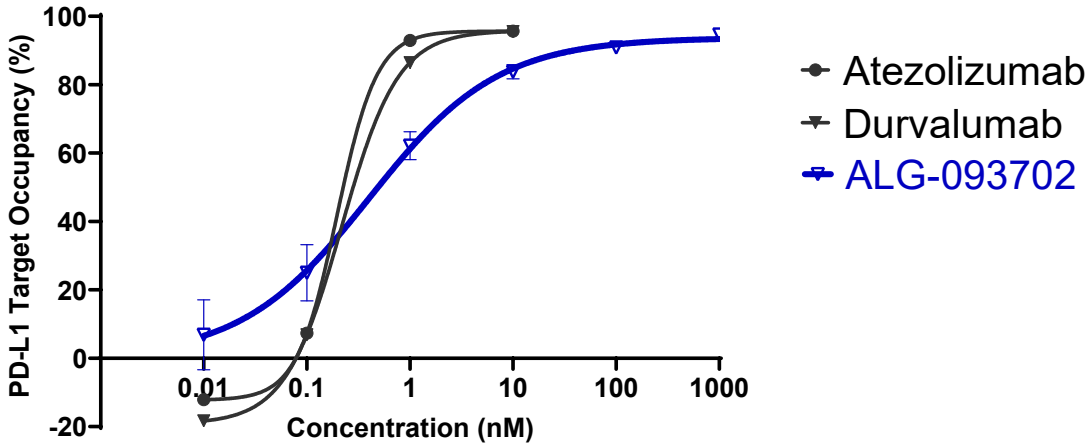
ALG-093702 Has a Different Mechanism of Action of PD-1/PD-L1 Blockade vs. PD-L1 Antibodies

A. Cellular PD-L1 Target Occupancy

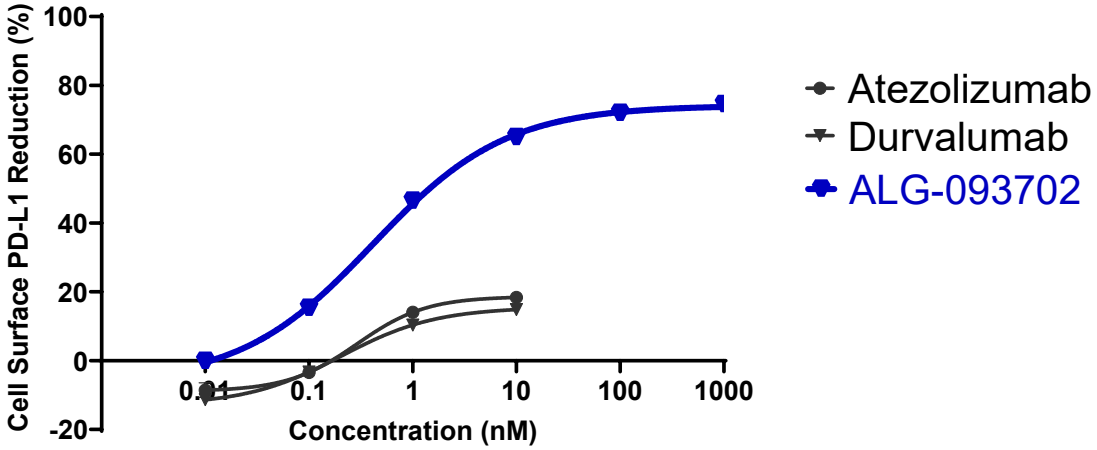
FACS using MIHI PD-L1antibody which competes with PD-L1 inhibitors



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

B. Cellular Surface PD-L1 Reduction

FACS using Abcam 28.8 PD-L1antibody which cannot compete with PD-L1 inhibitors



	Atezolizumab	Durvalumab	ALG-093702
PD-L1 reduction EC_{50} (nM)	No effect	No effect	1.5

ALG-093702 can reach similar PD-L1 target occupancy as FDA approved PD-L1 antibodies

ALG-093702 but not the PD-1 or PD-L1 antibodies, reduces cell surface PD-L1

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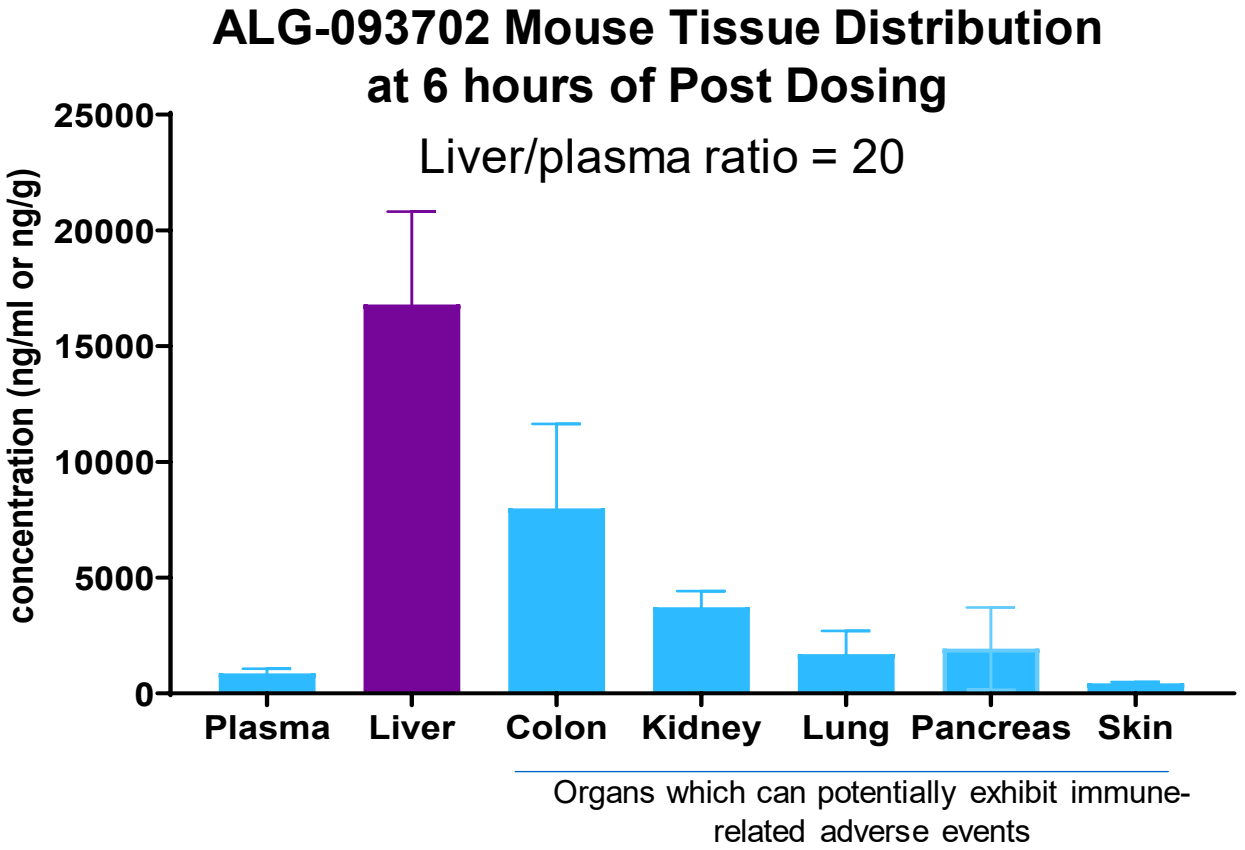
ALG-093702 Exhibits Liver Targeted Tissue Distribution

	ALG-093702 Mouse PK
PO Dose (mg/kg)	52 (Prodrug ALG-093701)
T_{max} (hr)	2.0
C_{max} (ng/mL)	1807
$AUC_{0\text{-}inf}$ (ng.h/mL)	8913
Oral bioavailability	41%



ALG-093702 exhibits significantly higher liver exposure vs. other tested tissues

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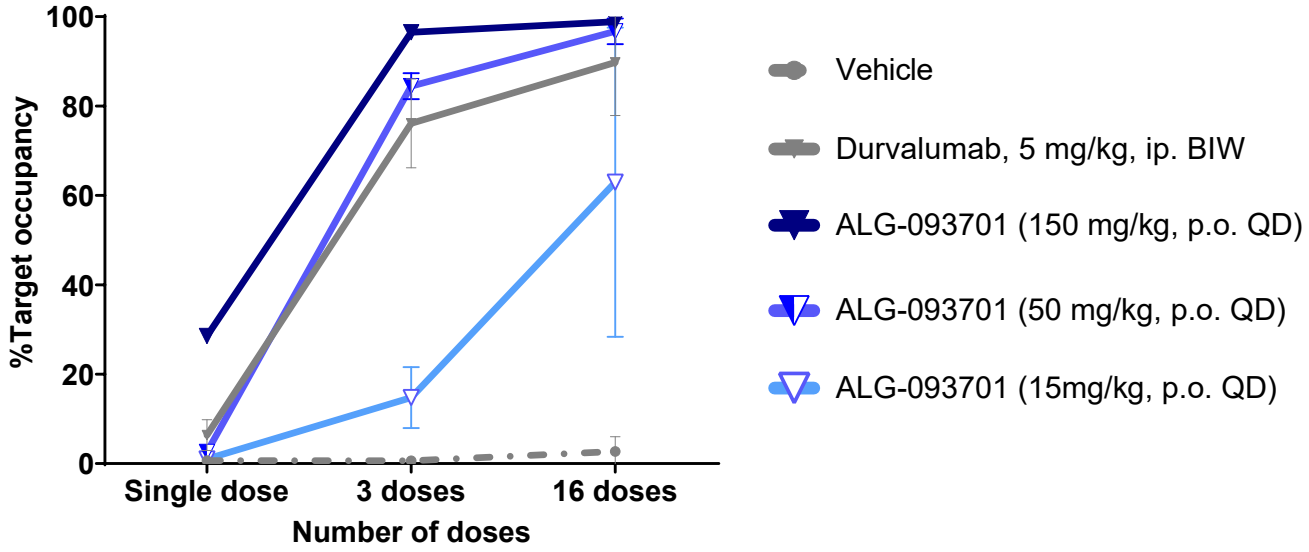
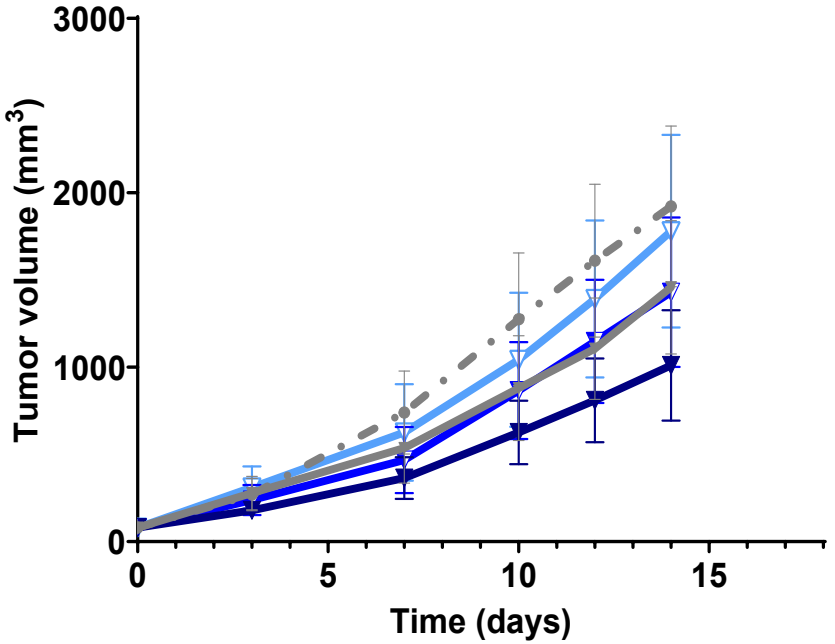
ALG-093702 Demonstrated Target Occupancy and Efficacy in a Mouse Sub-Q Tumor Model

A. In vivo PD-L1 Target Occupancy in a MC38-human-PD-L1 Sub-Q model*



B. In vivo Tumor Growth Inhibition (TGI) in a MC38-human-PD-L1 Sub-Q model



ALG-093702 prodrug (50 mg/kg; PO) can reach similar PD-L1 target occupancy and TGI as durvalumab

PD-L1 target occupancy is correlated with tumor growth inhibition

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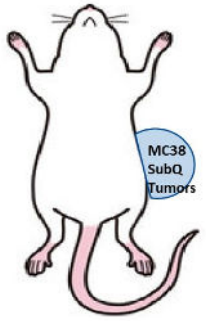
*24 hours of post dosing; FACS of tumor using MIHI PD-L1antibody which compete with PD-L1 inhibitors

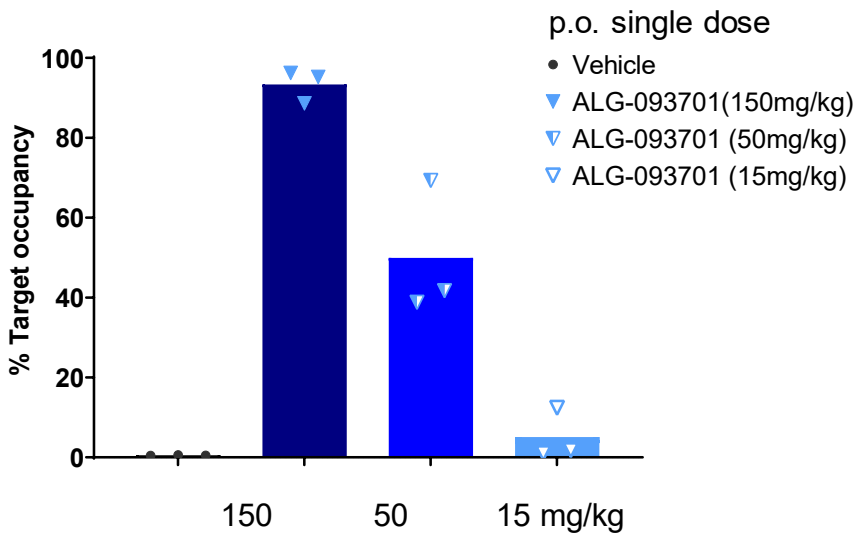
ALG-093701 is a prodrug of ALG-093702

ALG-093702 Requires a Lower Minimum Efficacious Dose in a Liver Metastasis Model vs. a Sub-Q Model

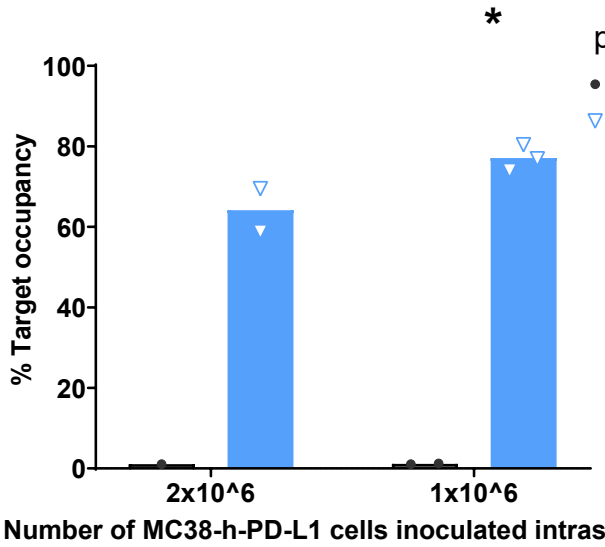
A. In vivo PD-L1 Target Occupancy in a MC38-human-PD-L1 Sub-Q model*

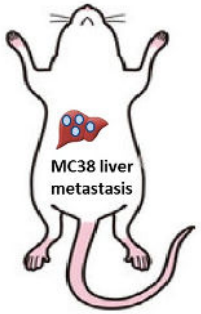


6 hours post dosing
PO 15 -150 mg/kg
Tumor/plasma ratio
= 0.10 – 0.40



B. In vivo PD-L1 Target Occupancy in a MC38-human-PD-L1 liver metastasis model





6 hours post dosing
PO 50 mg/kg
Liver/plasma ratio
= 20

15 mg/kg PO of an ALG-093702 prodrug **cannot** achieve significant PD-L1 target occupancy in Sub-Q tumors

15 mg/kg PO of an ALG-093702 prodrug **can** achieve significant PD-L1 target occupancy in liver metastasis tumors

High ALG-093702 liver exposure might be responsible for the lower minimum efficacious dose in the liver metastasis model vs. Sub-Q model

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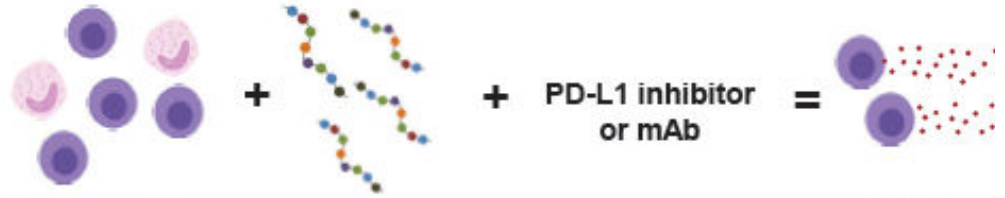
*6 hours post dosing, FACS subQ tumor and liver using MIHI PD-L1antibody which competes with PD-L1 inhibitors

ALG-093701 is a prodrug of ALG-093702

ALG-093702 Reactivates HBV-specific T-cells from an HBV-infected Patient

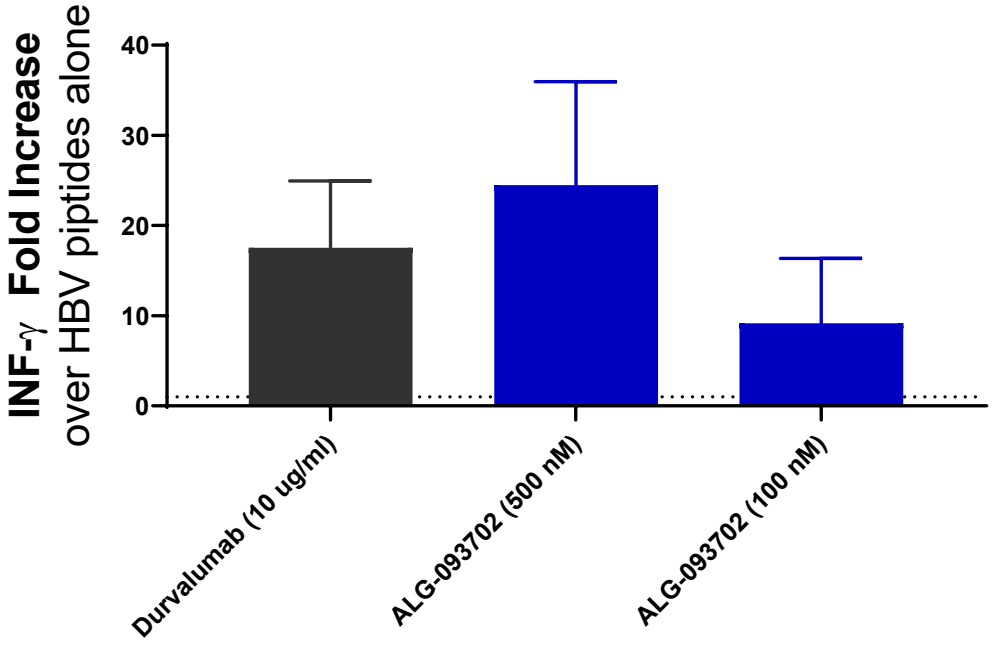
PD-L1 Inhibitor treatment reactivates the HBV-specific T cell response*



Immune cells (PBMC) from an HBV infected patient

HBV surface + Core peptides

Increased IFN-γ production



ALG-093702 reactivates HBV-specific T cells from an HBV-infected patient to a similar extent as durvalumab

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*EP Thi et al. Abstract#1508, The International Liver Congress™ EASL - European Association for the Study of the Liver, June 22-26, 2022

Summary

- Identified a small molecule PD-L1 inhibitor, ALG-093702, with similar *in vitro* and *in vivo* potency to an FDA-approved PD-L1 antibody
- ALG-093702 blocks PD-1/PD-L1 interaction and reduces cell surface PD-L1
- ALG-093702 demonstrates higher liver exposure vs. other tested tissues
- ALG-093702 requires a lower minimum efficacious dose in a liver metastasis model vs. a sub-Q model
- ALG-093702 reactivates HBV-specific T cells from an HBV-infected patient to a similar extent as durvalumab

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