Discovery of a Liver-Targeted PD-L1 Small Molecule Inhibitor for the Treatment of Chronic Hepatitis B and Liver Cancer

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Background
The PD-1/PD-L1 immune checkpoint pathway has emerged as an attractive target to reverse immune tolerance in chronic hepatitis B (CHB). However, due to systemic immune related adverse events associated with antibodies, lower doses of PD-1/PD-L1 antibodies have been used in clinical trials for CHB patients compared to cancer patients. Here, we report the discovery of a liver-targeted PD-L1 small molecule inhibitor that preferentially and significantly partitions into the liver and thereby may potentially mitigate extra-hepatic on target related toxicity.

Methods
Biochemical interaction of PD-1/PD-L1 and PD-L1 dimerization were 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. HBV-specific T cell activation assays were performed with PBMCs from an HBV-infected patient. Pharmacokinetic studies were performed in C57Bl/6 mice. In vivo PD-L1 target occupancy and tumor growth inhibition was assessed using either a MC38 humanized-PD-L1 subcutaneous mouse model or a liver metastasis mouse model.

Results 1 - In Vitro Biochemical and Cellular Potency

A. Cellular PD-L1 Target Occupancy
FACS using MH1 PD-L1 antibody which competes with PD-L1 inhibitors

B. Cellular Surface PD-L1 Reduction
FACS using Abcam 28.8 PD-L1 antibody which cannot compete with PD-L1 inhibitors

Results 2 - Mechanism of Action of PD-1/PD-L1 Blockade

A. Cellular PD-L1 Target Occupancy
FACS using MH1 PD-L1 antibody which competes with PD-L1 inhibitors

B. Cellular Surface PD-L1 Reduction
FACS using Abcam 28.8 PD-L1 antibody which cannot compete with PD-L1 inhibitors

Results 3 - ALG-093702 Exhibits Liver Targeted Tissue Distribution

A. Mouse PK Parameters

B. Mouse Tissue Distribution at 6 hours of Post Dosing

Results 4 - 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

Results 5 - 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

B. In vivo PD-L1 Target Occupancy in a MC38-human-PD-L1 Liver Metastasis Model

Results 6 - ALG-093702 Reactivates HBV-specific T-cells from an HBV-infected Patient

Conclusions:
We discovered a liver-targeted PD-L1 small molecule inhibitor, ALG-093702, with a different mechanism of action of PD-1/PD-L1 blockade compared to PD-L1 antibodies. The compound blocked PD-1/PD-L1 interaction while also reducing cell surface PD-L1. ALG-093702 had similar in vivo and ex vivo potency to a PD-L1 antibody drug, durvalumab. Overall, these data suggest that ALG-093702 has the potential to mitigate immune related systemic toxicity and could potentially be used for the treatment of chronic hepatitis B, hepatocellular carcinoma and liver metastatic patients.

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