ORAL SMALL-MOLECULE LIVER-TROPIC PD-L1 INHIBITOR PHARMACOKINETICS FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a global challenge due to its high morbidity and mortality rate. The standard of care for advanced HCC in front line and second line therapy consists of two distinct systemic approaches: tyrosine-kinase (TK) and immune checkpoint inhibitors (ICI); however, relapses and dose-limiting tolerability associated with systemic adverse events following treatment with either therapy have been observed[1]. Development of orally bioavailable, tissue-tropic immune checkpoint small-molecule inhibitors that could facilitate ease of administration, exhibit better tissue penetration, and reduce systemic exposure may potentially result in improved efficacy for advanced HCC with reduced systemic toxicity.

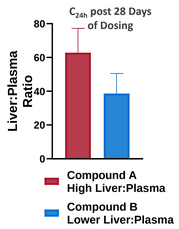
As a preclinical proof-of-concept, small-molecule PD-L1 inhibitors with differential liver and plasma pharmacokinetic profiles were evaluated in a novel orthotopic syngeneic immunocompetent HCC model to evaluate the correlation between pharmacokinetics and anti-tumor efficacy.

OBJECTIVES

- Assess anti-tumor efficacy of small-molecule PD-L1 inhibitors with differential liver and plasma pharmacokinetic profiles in a novel orthotopic syngeneic immunocompetent HCC model

BACKGROUND & METHODS

- Treatment with PD-1/PD-L1 monoclonal antibodies combined with anti-angiogenic VEGF/R inhibitors shows significant benefit in better overall and progression-free survival outcomes than sorafenib in HCC[2-4]
- Regorafenib is an anti-angiogenic VEGFR2-TIE2 tyrosine kinase inhibitor
- Anti-tumor efficacy of small-molecule PD-L1 inhibitors with different Liver:Plasma ratios was assessed in an HCC orthotopic syngeneic model to determine contribution of liver tropism to efficacy
- Combination treatment of small-molecule PD-L1 inhibitor with regorafenib was assessed as proof-of-concept for an all-oral treatment strategy for HCC



Generation of Orthotopic Syngeneic Immunocompetent HCC Mouse Model

- Multiple clones were screened to generate H22 mouse hepatoma cell line expressing human PD-L1 (hPD-L1) and luciferase (Luc)
- H22-hPD-L1-Luc cells were surgically inoculated into the liver of BALB/cJGpt-Pdcd1$^{em1Cin(hPDCD1)}$Cd274$^{tm1(hCD274)}$/Gpt double knock-In transgenic animals[5]

Study Design to Assess Oral Small-Molecule PD-L1 Inhibitors

H22-hPD-L1-Luc cells engrafted in the liver

hPD-1/hPD-L1 KI Balb/c mouse

Dose 28 days *q.d. p.o. (n=7-8/group)*

1. *Vehicle*
2. *Compound A 10 mg/kg*
3. *Compound A 10 mg/kg + Regorafenib 10 mg/kg*
4. *Compound B 10 mg/kg*

In-life tumor growth monitored *via* luciferase measurement

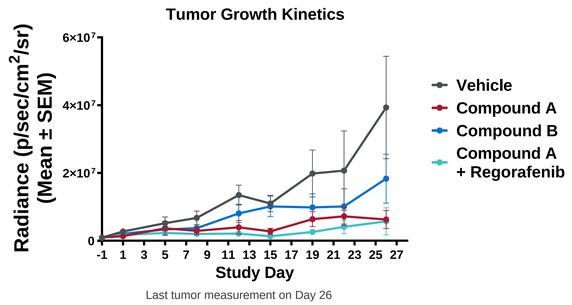
Endpoint Readouts:

Flow cytometry (terminal tumor and blood)

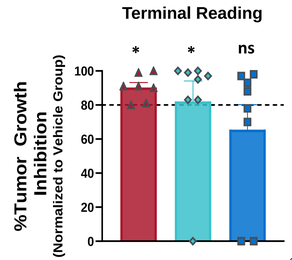
Bioanalysis of plasma, tumor & liver

RESULTS

1. Oral PD-L1 Inhibitor with Higher Liver: Plasma Ratio Mediated Better Anti-tumor Activity in HCC Orthotopic Model



Last tumor measurement on Day 26

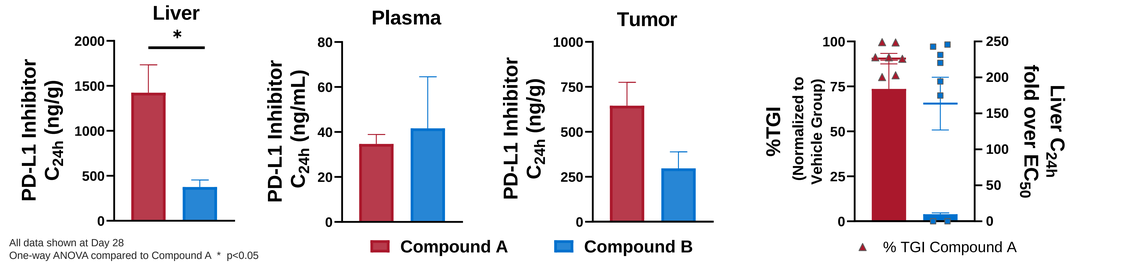


Treatment	% of Animals ≥ 80% TGI
Vehicle	13
Compound A	100
Compound A + Regorafenib	88
Compound B	50

One-way ANOVA compared to vehicle
* p<0.05
ns (non-significant) p>0.05

- Treatment with Compound A alone demonstrated greatest number of animals with 80% or higher % tumor growth inhibition (%TGI) after 26 days of treatment
- Compound A had more animals with %TGI above 80% compared to Compound B
- Combination treatment of Compound A and regorafenib resulted in similar anti-tumor efficacy as Compound A alone, with fewer animals having >80% TGI

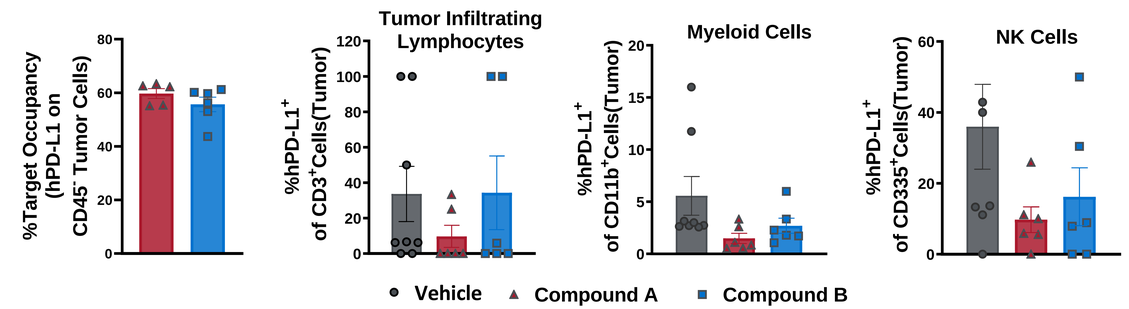
2. Higher Liver Concentrations were Associated with Increased Efficacy in HCC Orthotopic Model



All data shown at Day 28
One-way ANOVA compared to Compound A * p<0.05

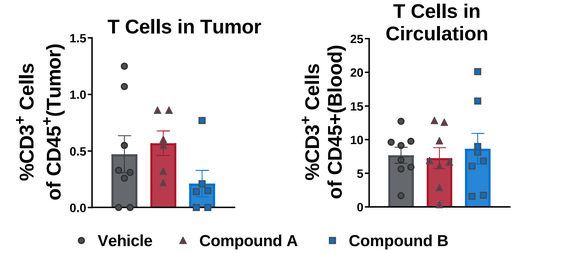
- Compound A demonstrated significantly higher liver tropism than Compound B with higher Liver:Plasma ratio
- Increasing PD-L1 inhibitor liver concentrations and Liver: Plasma ratio were associated with increase in % TGI in this orthotopic model

3. PD-L1 Inhibitor Mediated Reduction in PD-L1 in Tumor and Tumor-Associated Immune Cells



- Target occupancy (44%-63%) in tumor cells was observed after treatment of both compounds
- Reduction in the frequency of hPD-L1+ myeloid and NK cells in tumor was observed upon treatment with both Compounds
- Reduction in the frequency of hPD-L1+ tumor infiltrating lymphocytes was also observed upon treatment with Compound A

4. Higher Tumor T Cell Infiltration with Liver-Tropic PD-L1 Inhibitor



- Higher T cell infiltration in liver tumor observed with treatment of Compound A compared to Compound B
- Similar T cell frequencies observed in circulation

CONCLUSIONS

- A novel orthotopic syngeneic immunocompetent HCC mouse model was generated to evaluate PD-1/PD-L1 inhibitors for HCC
- Treatment with orally bioavailable small-molecule PD-L1 inhibitors possessing liver-tropic pharmacokinetic profiles was associated with increased efficacy and tumor clearance in this model
- Combination treatment of small-molecule PD-L1 and VEGF inhibitor shows similar efficacy as small-molecule PD-L1 inhibitor monotherapy, but further dose exploration needed
- Target engagement was observed upon treatment with oral small-molecule PD-L1 inhibitors both in tumor and immune cells
- These data suggest that development of small-molecule PD-L1 inhibitors with biodistribution to the liver may provide benefit in the treatment of HCC

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