Liver Selective Acetyl-CoA Carboxylase Inhibitor ND-654 Improves Sorafenib Efficacy in the Treatment of Hepatocellular Carcinoma in Cirrhotic Rats

OVERVIEW

- Current treatment options for HCC are limited, and as such, prognosis is extremely poor with a 5-year survival less than 12%.
- Metabolic attenuation is a promising approach to cancer therapy, and rate-limiting steps in key biosynthetic pathways are particularly attractive.
- Hepatoselective ND-654 is a potent allosteric inhibitor of the lipid master regulator Acetyl CoA Carboxylase (ACC).

ND-654 demonstrates excellent PK/PD relationships in the target tissue, the liver (exposure vs Malonyl CoA reduction) and is effective at modifying Cirrhosis and HCC relevant endpoints in the DEN model. Herein, we report on three DEN studies: A 18 week fixed end point study utilizing 10 mg/kg ND-654 PO, QD, a survival study utilizing 10 & 30 mg/kg ND-654 PO, QD, and a 18 week fixed end point study utilizing 10 mg/kg ND-654 and 10 mg/kg sorafenib PO, QD.

1. ACC: Emerging Tumor Metabolism Target: Tumors Up-regulate ACC to Fuel Cell Growth
   - ACC Oncology Validation
   - NGLC: Targeted opportunity vs LKB1-AMPK-ACC axis
   - LKB1: activated in Peutz–Jeghers syndrome
   - Breast Cancer: ACC1 knock down causes apoptosis in tumor cells
   - ACC2 up-regulates mitotic spindle/cytokinesis
   - ACC2 also acts as a potential pro-cancer gene
   - HCC: ACC overexpression
   - Associated with worse survival in clear cell Renal Cell Carcinoma
   - HCC, ACC overexpression
   - Associated with worse survival in clear cell breast and renal cell carcinomas

2. ND-654: Hepato-Selective ACC Inhibitor
   - ND-654 is well tolerated in rats administered DEN Animals on Drug
   - ND-654 is administered orally to DEN treated rats once a day (5/7 days per week)
   - Drug is well tolerated, no change in body weights, ALT and AST

3. ND-654 Demonstrates Liver Tissue Specific Target Engagement and Pharmacology
   - Liver vs Muscle
   - HepG2 vs Normal Rat
   - ND-654 reduces serum triglycerides and total bilirubin

4. ND-654 is Well Tolerated in Rats Administered DEN Animals on Drug
   - 10 mg/kg ND-654 PO, QD is effective at modifying Cirrhosis and HCC relevant endpoints in the DEN model

5. Liver Directed ND-654 Improves Markers of Liver Health in DEN Treated Rats
   - ND-654 decreased serum triglycerides and total bilirubin

6. Treatment with 10 mg/kg ND-654 QD Results in Marked Reduction of Tumor Nodules
   - ND-654 is administered orally to DEN treated rats once a day (5/7 days per week)

7. ND-654 Decreases PCNA Expression in Tumors and Results in Tumor Necrosis
   - ND-654 decreases markers of inflammation and fibrosis and improves overall survival in the DEN rat model

8. ND-654 Significantly Improved Survival in the Aggressive DEN HCC Model
   - ND-654 increases survival in the DEN rat model

9. ND-654 Shows Improvements in Fibrosis, Stellate Cell Activation and Inflammation Markers in the Rat Liver
   - ND-654 improves the efficacy of Sorafenib in reducing tumor burden

10. Quantitative Liver Adipokine Array From ND-654 Treated DEN Rats Demonstrates Modulation of Fibrosis, Inflammation and Tumor Markers in the Liver

CONCLUSION

- ND-654 preferentially bio-distributes to the liver where it inhibited ACC1/2 activity but did not increase liver toxicity.
- ND-654 inhibits HCC development by decreasing tumor proliferation and causing tumor necrosis.
- ND-654 reduces markers of inflammation and fibrosis and improves overall survival in the DEN rat model.
- ND-654 complements the efficacy of sorafenib in reducing tumor burden.
- Our results therefore provide further evidence that de novo lipogenesis is an important mediator of hepatic carcinogenesis.
- Selective inhibition of hepatic ACC1/2 is a potential therapeutic strategy for HCC.