Kinase Inhibitor Demonstrates Efficacy in a Patient-Derived Xenograft Model of Fibrolamellar Hepatocellular Carcinoma featuring DNAJB1-PRKACA Fusion

Abstract No.4203

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INTRODUCTION

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare and distinct primary hepatic malignancy that has conventionally been considered a histologic variant of HCC. However, it has more recently been recognized as a distinct clinical entity with respect to its epidemiology and prognosis. FL-HCC etiology is unclear and there is no clinical or histological evidence for association with chronic liver disease. Recent genetic studies have identified the gene fusion DNAJB1-PRKACA as a recurrent genetic lesion in the disease. Molecular pathogenesis of FL-HCC however, is not well understood and has been reported to occur in association with focal nodular hyperplasia. Overexpression of genes in the PIK3, MAPK, and RAS pathways is observed in FL-HCC, and in contrast to viral-associated HCC, epigenetic instability in FL-HCC is rare.

Here we describe the development of LI5132, a novel FL-HCC patient-derived xenograft (PDX) model. RNAseq analysis revealed the presence of the DNAJB1-PRKACA gene fusion on chromosome 19, a molecular signature of FL-HCC. Clinical diagnosis as HCC of the fibrolamellar type was confirmed by H&E staining of the PDX tumor. The PDX tumor has a distinctive intratumoral fibrosis with a lamellar pattern. The PDX model was established by inoculating patient tumor cells subcutaneously in NOD-SCID mice, with >90% take rate and robust tumor growth. To evaluate the translational relevance of this model towards therapeutic development, the efficacy of a novel multi-targeted Aurora kinase A and angiokinase inhibitor, ENMD-2076, was evaluated in a therapeutic mode in this model. ENMD-2076 showed significant efficacy in suppressing tumor growth in NOD-SCID mice at the 200mg/kg dose evaluated in this study. Weight loss observed during the treatment period could not be attributed to ENMD-2076 as it was similar to weight loss observed with vehicle treatment. ENMD-2076 has now progressed into Phase II clinical trials for treatment of FL-HCC. This demonstrates the translational utility of this FL-HCC PDX model in development of anticancer therapeutic agents.

STUDY DESIGN

LI5132 tumor cell slurry was inoculated subcutaneously in the rear flank of NOD-SCID mice. Tumor volume and body weight were measured 3 times per week. For the efficacy study, mice were randomized when the average tumor volume was between 200-250mm^3 and mice were treated with vehicle or 200mg/kg ENMD-2076, p.o., q.d. for 31 days.

MODEL INFORMATION

Fig 1. The HuPrime® model

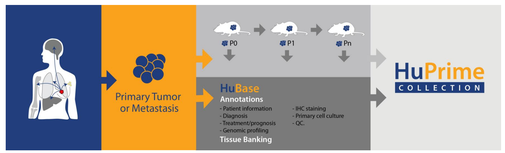


Table 1. LI5132 PDX model information

Model	LI5132
Cancer type	Liver cancer
Subtype	HCC, fibrolamellar type
Ethnicity	Caucasian
Gender	Female
Age	27
Pathology diagnosis	Hepatocellular carcinoma, metastatic hepatocellular carcinoma, fibrolamellar type
Biopsy site	Left chest mass
RNAseq	Available. DNAJB1-PRKACA fusion positive
HLA	
A1	A*02:01
A2	A*01:01
B1	B*40:01
B2	B*40:01
C1	C*07:01
C2	C*03:04

RESULTS

Fig 2. Growth curves and histology of FL-HCC PDX model LI5132

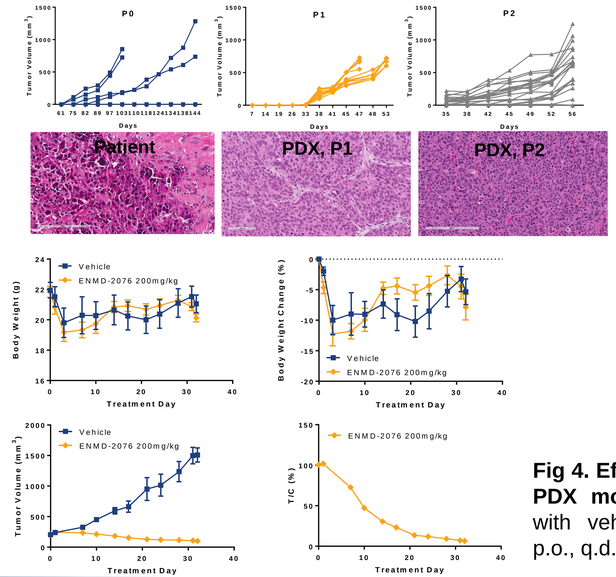
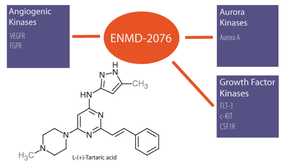


Fig 3. ENMD-2076



ENMD-2076 is a multi-kinase inhibitor with selective activity against Aurora A and Flt3: IC_{50}s of 14nM and 1.86nM, respectively. 25-fold selectivity for Aurora A over Aurora B and less potent for VEGFR2/KDR and VEGFR3, FGFR1 and FGFR2, and PDGFRα

Fig 4. Efficacy of ENMD-2076 in FL-HCC PDX model LI5132. Mice were treated with vehicle or 200mg/kg ENMD-2076, p.o., q.d. for 31 days.

SUMMARY

- ENMD-2076 showed significant efficacy in suppressing FL-HCC PDX model LI5132 tumor growth in NOD-SCID mice at the 200mg/kg dose evaluated in this preclinical study. Transient weight loss observed during the treatment period could not be attributed to ENMD-2076 as it was similar to weight loss observed with vehicle treatment.
- ENMD-2076 is now in clinical development, demonstrating the translational utility of this FL-HCC PDX model.