Poster No. 497

HX301, a First-in-class ARK5i, Demonstrates Antitumor Activity in Preclinical HCC Models with High ARK5/myc Expression

Zhihua Jiao[1], Jessie Wang[1], Hang Ke[2], Faming Zhang[2], and Henry Li[2]
[1]Crown Bioscience, Inc., 16550 West Bernardo Drive, Building 5, Suite 525, San Diego, CA 92127, USA
[2]Hanx Biopharmaceuticals, Ltd., Oceanside, California, USA

Introduction

Hepatocellular carcinoma (HCC) is an aggressive malignancy of high mortality, the sixth most common worldwide, with few treatment options. Current drug treatments, including chemo-/targeted therapies (*e.g.,* sorafenib), are usually ineffective in the advanced HCC patient population, and come with high toxicity. ARK5, or NUAK1, a novel AMP-activated protein kinase (AMPK) family member 5, is found overexpressed in many malignancies, including HCC, and is usually associated with poor prognosis, as well as drug resistance. For example, doxorubicin, a first-line chemotherapy for TACE (transarterial chemoembolization) for advanced HCC. In addition, ARK5 is found to be vitally involved in oncoprotein Myc-driven oncogenesis (metabolic homeostasis/cell survival), particularly in tumors under nutrition/oxygen-deprivations, including HCC. HX301 is a clinical stage first-in-class (FIC) inhibitor of ARK5 (ARK5i) and other kinase activities (*e.g.,* CDK4/6 and CSF1R). In this study HX301's antitumor activity was evaluated in HCC over-expressing both ARK5 and c-myc.

Methods

A panel of subcutaneous HCC patient-derived xenograft models (PDXs) were genomically profiled by whole transcriptome sequencing (RNA-seq). Selected models, with different expression of ARK5 and c-myc expression, were assessed pharmacologically using daily dosing of 100 mg/kg HX301. Specifically, for LI1035, 10 mg/kg regorafenib and 30 mg/kg sorafenib were applied to assess the comparable anti-tumor efficiency. Subcutaneous tumor responses to HX301 were calculated by tumor growth inhibition (TGI).

Results

HCC-PDX models LI1035 and LI6610 both had high expression of ARK5 and Myc genes, whereas LI6650 had no expression of Myc, and similar expression levels of ARK5 compared to LI1035 and LI6610. LI6652 had no expression of ARK5 and similar expression level of Myc compared to LI1035 and LI6610. The $\log_2$ FPKM values of ARK5 and Myc in model LI1035 were 3.9284 and 4.8177 respectively, in model LI6610 were 3.6629 and 5.3658 respectively, in model LI6650 were 3.1228 and -0.0556 respectively, in model LI6652 were -0.3538 and 6.5785 respectively (**Table 1**). Preliminary results demonstrated that LI1035 responded to HX301, superior to the current SOCs of sorafenib and regorafenib (**Figure 1**). Together, HX301 showed consistent anti-HCC activity (TGI = 62% at Day 20, $p<0.05$) in another HCC preclinical model LI6610 with high expression of ARK5 and Myc (**Figure 2**). Whereas a smaller TGI was observed in the LI6650 model (TGI = 44%, $p<0.05$) and in LI6652 model (TGI = 58%, n.s.). Moreover, HX301 showed good tolerability in the different models tested.

Results cont.

Table 1. RNA expression level of ARK5 and Myc genes in the PDX models of LI1035, LI6610, LI6650, and LI6652.

PDX models	Subtype	Pathology Diagnosis	ARK5 (Log_2[FPKM])	Myc (Log_2[FPKM])
LI1035	HCC	Tumor embolus in individual vessel, fibrous tissues hyperplasia with part of fibrous septum formation.	3.9284	4.8177
LI6610	HCC	Left lobe of liver: grade II-III, peripheral hepatic tissues show nodular cirrhosis G2S4.	3.6629	5.3658
LI6650	HCC	Right lobe of liver: with necrosis, grade II-III. Peripheral hepatic tissues show nodular cirrhosis G2S4.	3.1228	-0.0556
LI6652	HCC	Right lobe of liver: grade II-III.	-0.3538	6.5785

Figure 1. The response of HX301 in PDX model of LI1035

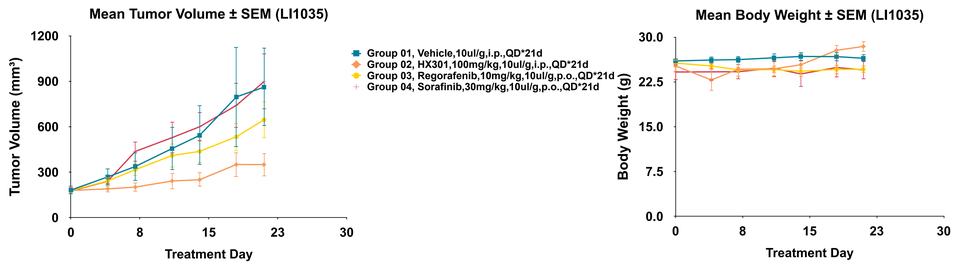


Figure 2. The response of HX301 in PDX models of LI6610, LI6650, LI6652

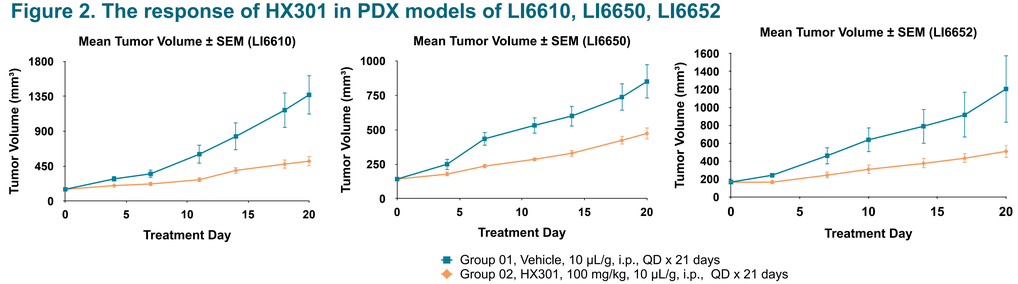
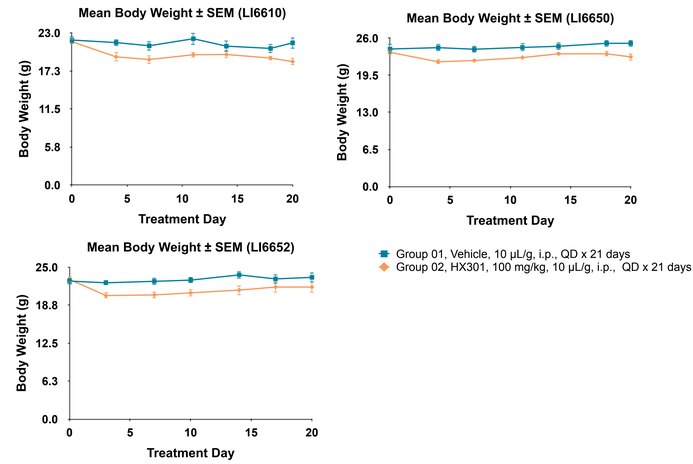


Figure 3. The mean body weight after treatment of HX301 in PDX models of LI6610, LI6650, LI6652



Conclusion

The preliminary data generated demonstrates that HX301 has strong antitumor activity in HCC-PDX models expressing both ARK5 and c-myc. HX301 has the potential to be a first-in-class ARK5i candidate for the treatment of advanced HCC with high expression of c-myc, warranting further clinical investigation.

References

1. Li, Q. X., Feuer, G., Ouyang, X., *et al.* Experimental animal modeling for immuno-oncology[J]. *Pharmacology & Therapeutics*, 2017, 173: 34-46.
2. Papin, A., Tessoulin, B., Bellanger, C., *et al.* CSF1R and BTK inhibitions as novel strategies to disrupt the dialog between mantle cell lymphoma and macrophages[J]. *Leukemia*, 2019, 33(10): 2442-2453.
3. Zhang, X., Lv, H., Zhou, Q., *et al.* Preclinical Pharmacological Evaluation of a Novel Multiple Kinase Inhibitor, ON123300, in Brain Tumor Models Preclinical PK/PD Evaluation of ON123300 in Brain Tumor[J]. *Molecular cancer therapeutics*, 2014, 13(5): 1105-1116.

Download this poster at: crownbio.com/AACR23