A novel, potent and selective FGFR4 inhibitor, HM18422 in hepatocellular carcinoma with FGFR4-driven pathway activation

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Abstract

Introduction: Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and the second most frequent cause of cancer-related death, however, treatment options are very limited. In recent studies, aberrant signaling through FGFR4 and its ligand, FGF19 has been identified as the oncogenic driver in a subset of HCCs and reported to be associated with poor prognosis. About 30% of HCC patients have altered FGF19/FGFR4 signaling pathway, therefore, the treatment with FGFR4 inhibitor may produce benefit.

Materials and Methods: Using the structure-based design, we have generated a novel, potent and selective FGFR inhibitor, HM18422 with irreversible-covalent binding mode, and evaluated its anti-tumor activity in a variety of HCC cell lines, HCC cell line xenografts and orthotopic grafts.

Results: Biochemical selectivity assays demonstrated that HM18422 is highly selective towards FGFR4 compared to other FGFR isotypes as well as a panel of several kinases. The treatment of HM18422 to FGFR1b amplified and overexpressed HCC cell lines led to suppression of FGFR1b/FGFR signaling pathway and concomitant reduction in cell viability in a dose-dependent manner. Oral administration of HM18422 to mice bearing FGFR1b altered HCC cells showed a dose-dependent pharmacokinetics, pharmacodynamic modulation of FGFR signaling and antitumor efficacy in xenograft models. And HM18422 demonstrated inhibition of tumor growth in an orthotopic liver xenograft model of FGFR1b altered HCC in nude mice.

Conclusion: In conclusion, the treatment of HCC patients with a potent and selective FGFR4 inhibitor, HM18422, can be an attractive approach targeting approximately 30% of HCC patients by inhibiting altered FGFR4-mediated signaling cascade. Further preclinical studies with HM18422 will be performed and reported soon.

Keywords: FGFR4, Hepatocellular carcinoma, FGFR1b, Pharmacokinetics, Pharmacodynamics, Antitumor Efficacy

B. Representative bioluminescence images

C. Induction of caspase 9-dependent apoptosis

References

2. BMCCancer 2012, 7, 12.

Author Disclosures

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