# Discovery and development of BLU-554: a potent, highly selective covalent inhibitor of fibroblast growth factor receptor 4 (FGFR4) in development for the targeted treatment of advanced hepatocellular carcinoma (HCC) patients with amplified and overexpressed FGF19

Liver cancer is the second leading cause of cancer-related deaths worldwide, with HCC accounting for most liver cancers. There is a significant need for more effective and targeted therapies to treat HCC. FGF19 regulates bile acid synthesis and hepatocyte proliferation in normal liver through activation of its receptor FGFR4. Activation of the FGF19 signaling pathway is observed in up to 30% of patients with HCC and has been shown to induce liver cancer in genetic mouse models. Selective inhibition of FGFR4 thus represents a targeted strategy to treat this genetically defined sub-group of HCC. BLU-554 is a potent, highly selective covalent inhibitor of FGFR4 currently being evaluated by Blueprint Medicines in a Phase 1 clinical trial for the treatment of patients with advanced HCC. Herein, we will describe the discovery of BLU-554 utilizing iterative structure-based drug design. This presentation will also include the characterization of the mechanistic details of covalent inhibition of FGFR4 and the structure-activity relationships (SAR) development toward the optimization of overall drug properties for BLU-554. The pharmacokinetics and pharmacological activity of BLU-554 in tumor models with genomically amplified and overexpressed FGF19 will also be described.