INHIBITION OF FIBROBLAST GROWTH FACTOR RECEPTOR 4 (FGFR4) SIGNALING ACTIVATES TUMOR INTERFERON (IFN) SIGNALING IN HEPATOCELLULAR CARCINOMA (HCC)

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Background Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Deregulation of FGF19-FGFR4 signaling has been found in HCC and several FGFR4 inhibitors have shown preliminary efficacy in patients with FGF19 overexpression. The combination of FGFR4 inhibitors with anti-PD-(L)1 antibodies is also under clinical investigation. However, the role of FGFR4 inhibition in tumor microenvironment (TME) remains to be elucidated. ABSK011 is a potent, selective FGFR4 inhibitor that has demonstrated strong antitumor activity in preclinical models and advanced into phase 1b clinical trials. In this study, we investigated the role of ABSK011 in TME of FGF19 overexpressed HCC models, and especially its crosstalk with interferon (IFN) pathway and antitumor immunity 

Methods We evaluated the effects of ABSK011 in multiple FGF19 overexpressed HCC cell lines and in vivo models by RNA sequencing, quantitative PCR, flow cytometry and immunohistochemistry (IHC).

Results RNA sequencing revealed that IFN pathway was consistently enriched after treatment with ABSK011 across various HCC models. Quantitative PCR analysis showed that ABSK011 upregulated mRNA expression of several key genes related to IFN pathway, including IRF1, IFIT1 and CXCL10, both in cell lines and tumor models. Furthermore, expression of surface PD-L1 on HCC cells were significantly increased and reached the plateau with the treatment of ABSK011 at the concentration higher than 0.1μM. In addition, we found that ABSK011 increased CD8+ T cell infiltration in humanized HCC mouse models.

Conclusions These preclinical data demonstrated that ABSK011 treatment increased IFN related response as well as CD8+ T cell infiltration in FGF19 overexpressed HCC models, supporting the combination of FGFR4 inhibitor and immune checkpoint molecules such as anti-PD-(L)1 antibodies to achieve enhanced antitumor activity.