Preclinical evaluation of BG-C137, a potential first-in-class FGFR2b targeting ADC, for the treatment of FGFR2b-expressing cancer

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Abstract

Fibroblast growth factor receptor 2b（FGFR2b， FGFR2IIIb), an alternative splicing isoform of FGFR2, is a receptor tyrosine kinases that activates multiple signaling cascades upon binding of FGFs, promoting cancer cell proliferation.. It also a tumor associated antigen being overexpressed in multiple solid tumor types, especially gastric cancer (GC). Indeed, the clinical benefit of targeting FGFR2b has been demonstrated by Bemarituzumab, an Fc-enhanced monoclonal antibody in combination with chemotherapy in first line FGFR2b-expressing gastric cancer. Here, we report the preclinical characterization of BG-C137, a first-in-class FGFR2b antibody conjugated with topoisomerase inhibitor.

In contrast to Bemarituzumab, which functions through antibody dependent cellular phagocytosis/cytotoxicity and sustained signaling blocking function, BG-C137 introduced direct toxin killing to enhance the tumor inhibition with strong by-stander effect to overcome the heterogeneity of FGFR2b expression. Upon antigen engagement, BG-C137 was fast internalized and potently killed tumor cells with diverse FGFR2b expression level. Single dose of BG-C137 showed strong anti-tumor efficacy in vivo, including FGFR2b amplified and non-amplified models. It also demonstrated strong bystander killing effect in vitro and maintained strong anti-tumor efficacy in models with heterogeneous FGFR2b expression. Besides, we showed that corneal dystrophy, which might correlate with corneal toxicity of Bemarituzumab in the clinic, was caused by its complete signaling blocking function. Whereas BG-C137 with weaker blocking function antibody spared corneal dystrophy in mice as well as in non-human private, even at high doses. With differentiated targeting strategy, BG-C137 is not only a first-in-class FGFR2b ADC, but also holds the potential to pursue the best-in-class opportunity in FGFR2b targeting treatments. Together, these observations support the clinical development of BG-C137 for the treatment of FGFR2b-expressing tumors (ClinicalTrials.gov ID NCT06625593).