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

Yibin Xu, Xiaolin Su, Qiming Xu, Mengran Qian, Taichang Zhang, Mei-Hsuan Tsai, Ruyue Ji, Junna Jiang, Bin Shao, Yuan Zhuang, Jiyuan Zhang, Xiaomin Song, Zhitao Wan, Xiaoyan Tang, Yue Wu, Charng-Sheng Tsai, Chichi Huang, Lai Wang, Zhirong Shen

Authors' Affiliation: BeiGene Global Research, P.R. China; #Correspondence: yibin.xu@beigene.com, zhirong.shen@beigene.com

BeiGene

#abstract No 3778

Abstract

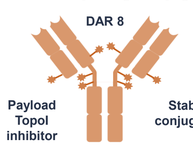
Fibroblast growth factor receptor 2b (FGFR2b, FGFR2IIIb), an alternative splicing isoform of FGFR2, is a receptor tyrosine kinase that activates multiple signaling cascades upon binding of FGFs, promoting cancer cell proliferation. It is also a tumor associated antigen overexpressed in multiple solid 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 a topoisomerase inhibitor.

In contrast to Bemarituzumab, which functions through antibody dependent cellular phagocytosis/cytotoxicity and sustained signaling blocking function, BG-C137 introduces direct toxin killing to enhance the tumor inhibition with strong bystander effect to overcome the heterogeneity of FGFR2b expression. Upon antigen engagement, BG-C137 was rapidly internalized and potently killed tumor cells with diverse FGFR2b expression levels. A single dose of BG-C137 showed superior anti-tumor efficacy compared to multiple doses of Bemarituzumab in vivo, including in FGFR2b amplified and non-amplified models. It also demonstrated a strong bystander killing effect in vitro and maintained strong anti-tumor efficacy in models with heterogeneous FGFR2b expression. Additionally, we showed that corneal dystrophy, which might correlate with corneal toxicity of Bemarituzumab in the clinic, was caused by its complete signaling blocking function. In contrast, BG-C137, with a weaker blocking function antibody, spared corneal dystrophy in mice as well as in non-human primates, even at high doses. With a 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).

Molecule Design

BG-C137 is a FGFR2b-targeted ADC composed of a humanized anti-FGFR2b mAb and a cleavable linker with a TOP1i payload.

Figure 1. Antibody drug conjugate design



FGFR2b Ab

Potent binding with strong selectivity toward FGFR2b
Partial ligand blockage

Payload

Topoisomerase I inhibitor, clinically-validated for FGFR2b expressing tumors
Stronger bystander effect

Linker

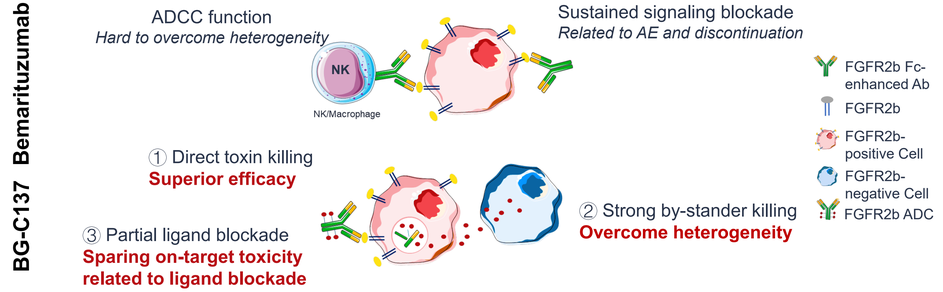
Stable conjugation to improve stability

DAR

Optimal DAR to achieve maximum potency

Differentiated MoA of BG FGFR2b ADC Brings Multiple Layers of Benefit

Figure 2. The MoA of BG-C137 highlights toxin-directed killing without total ligand blockade. Stronger bystander effect is also a great fit for FGFR2b, which is heterogeneously expressed in tumors.



Reasonable Internalization and Potent Cellular Killing in Cell Lines with Diverse FGFR2b Expression

Figure 3. Reasonable internalization

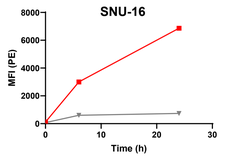
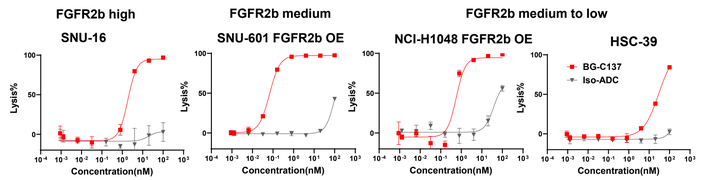


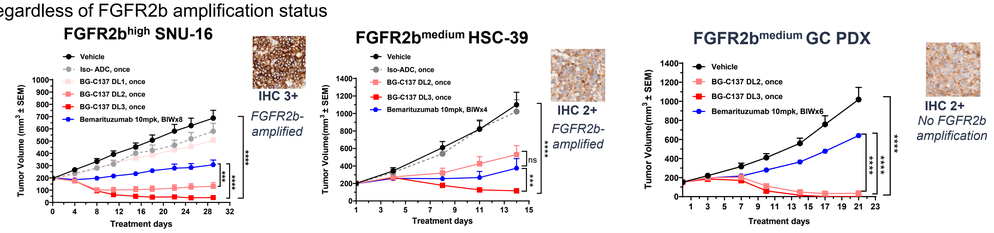
Figure 4. BG-C137 demonstrated nanomolar-range killing in cell lines with diverse FGFR2b expression



Cytotoxicity rate (%) is calculated from cell index readout as follows: $Cytotoxicity\ Rate\ (\%) = 100 - \frac{Cell\ Index_{Sample}}{Cell\ Index_{No\ Ab}} \times 100$. Iso-ADC: anti-Covid19 CB6 antibody conjugated to same linker-payload as BG-C137, which acts as a non-relevant ADC

Single dose of BG-C137 showed superior anti-tumor efficacy to Bemarituzumab

Figure 5. BG-C137 demonstrated efficacy in gastric cancer models with diverse FGFR2b expression (IHC2+ and IHC3+) regardless of FGFR2b amplification status



Bystander killing effect in vitro and anti-tumor efficacy in co-inoculation model

Figure 6. By-stander killing in vitro

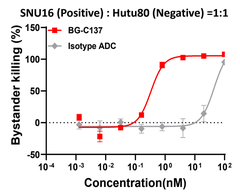
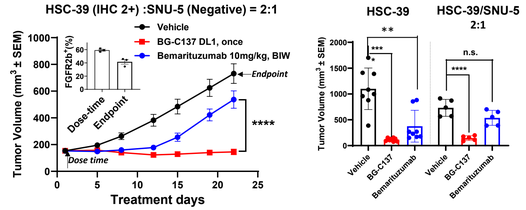
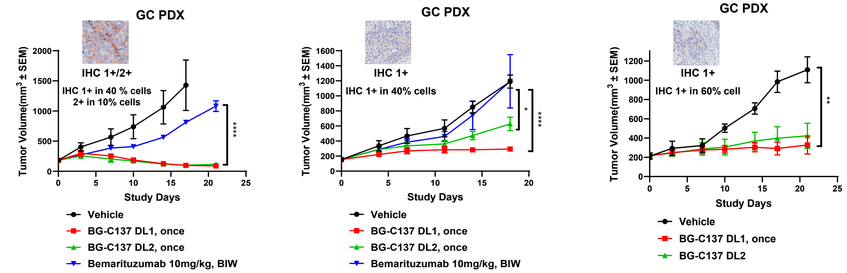


Figure 7. Profound efficacy in co-inoculation model



Potent tumor inhibition in high FGFR2b heterogeneous PDX models

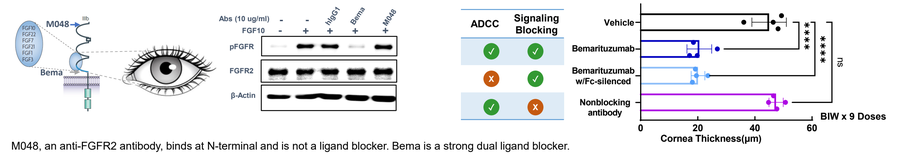
Figure 8. BG-C137 demonstrated efficacy in PDX models with highly heterogeneous FGFR2b expression



Corneal dystrophy is caused by sustained FGFR2b signaling blocking

Bemarituzumab showed corneal dystrophy in mice consistent with clinical findings. Corneal dystrophy signifying the thinning of corneal tissue is caused by sustained signaling blockage.

Figure 9. Corneal dystrophy is caused by sustained FGFR2b signaling blocking



M048, an anti-FGFR2 antibody, binds at N-terminal and is not a ligand blocker. Bema is a strong dual ligand blocker.

With a partial ligand blocker antibody, BG-C137 does not induce corneal dystrophy with repeated dosing in mice or non-human primates

Figure 10. Antibody of BG-C137 is a partial ligand blocker, as it weakly inhibits FGF7-induced signaling and spares FGF10-induced signaling

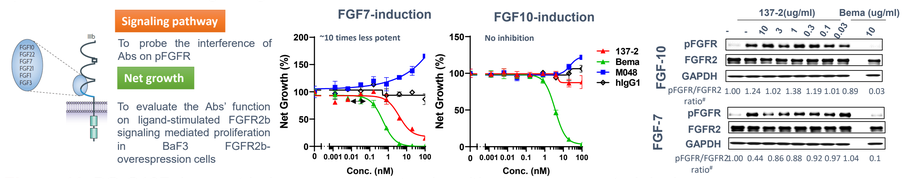
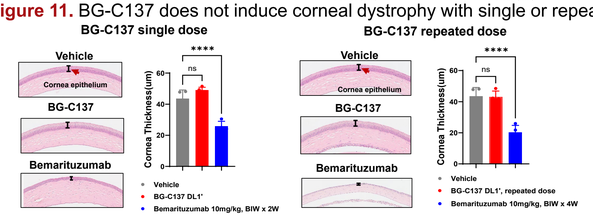


Figure 11. BG-C137 does not induce corneal dystrophy with single or repeated dosing



No observation of corneal dystrophy or any ocular AE in non-human primates at high doses with repeated dosing, suggesting that BG-C137 holds potential in sparing corneal dystrophy in patients

Conclusion

BG-C137 is a FGFR2b-targeted ADC with strong scientific rationale and preclinical proof-of-concept. It demonstrated strong antitumor effects in FGFR2b expressing tumors with diverse expression levels. Additionally, by targeting FGFR2b with a weaker blocking function antibody, BG-C137 spared corneal dystrophy in mice as well as in non-human primates, even at high doses. With a differentiated targeting strategy, BG-C137 is not only a first-in-class FGFR2b ADC but also has the potential to become the best-in-class treatment for FGFR2b-targeting therapies.