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

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BeiGene

# Disclosure Information

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## Yibin Xu

I am an employee of BeiGene and have no other financial relationships to disclose.

# FGFR2b is an attractive tumor associated antigen

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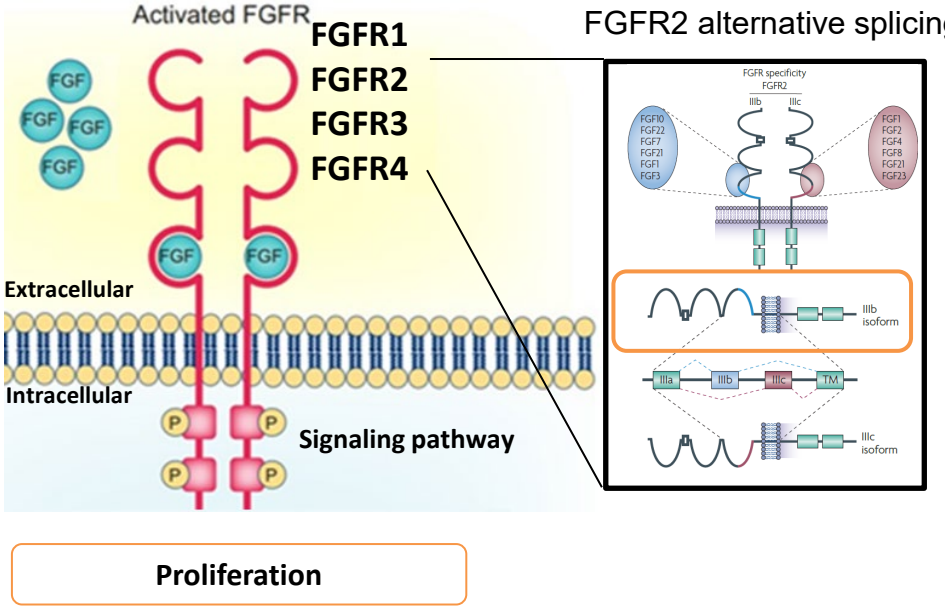
## FGFR2b is both growth factor receptor and tumor associated antigen




**Proliferation**

- The fibroblast growth factor receptors (FGFR) are a family of transmembrane proteins activating multiple downstream pathways
- FGFR2b antibody (Bemarituzumab) under late development for solid tumors, is the only active asset specifically for FGFR2b
- FGF7/10-mediated FGFR2b signaling is essential in corneal development and maintenance
- FGFR2b is an attractive tumor associated antigen, with overexpression in multiple tumor types including GC (37.8%), NSCLC-squamous (21%), TNBC (13%), Ovarian (40%) and Cholangiocarcinoma (22%) while minimal expression in normal tissues

Lancet Oncol 2022; 23: 1430–40; ESMO Asia, Singapore, 2022 Poster 384P JCO Precis Oncol 9:e2400710

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# Highlights of BG-C137

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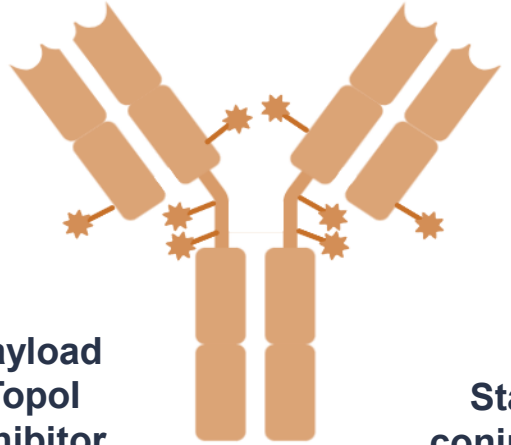
DAR 8



Payload
Topol
inhibitor

Stable
conjugator

**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-C137 Brings Multiple Layers of Benefit

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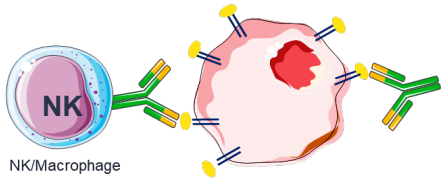
- The MoA of BG-C137 highlights toxin-directed killing without total ligand blockade
- Stronger bystander effect to mitigate the heterogeneity of FGFR2b expression in tumors

## Bemarituzumab

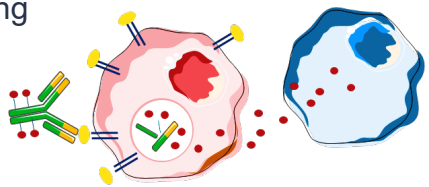
ADCC function
*Hard to overcome heterogeneity*




Sustained signaling blockade
*Related to AE and discontinuation*

## BG-C137

① Direct toxin killing
**Superior efficacy**



② Strong by-stander killing
**Overcome heterogeneity**

③ Partial ligand blockade
**Sparing on-target toxicity related to ligand blockade**

FGFR2b Fc-enhanced Ab
FGFR2b
FGFR2b-positive Cell
FGFR2b-negative Cell
FGFR2b ADC

# BG-C137 demonstrated reasonable internalization and killing in cell lines with diverse FGFR2b expression

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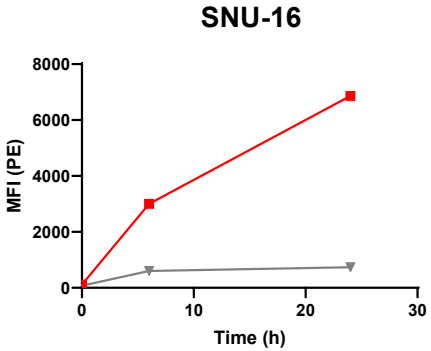
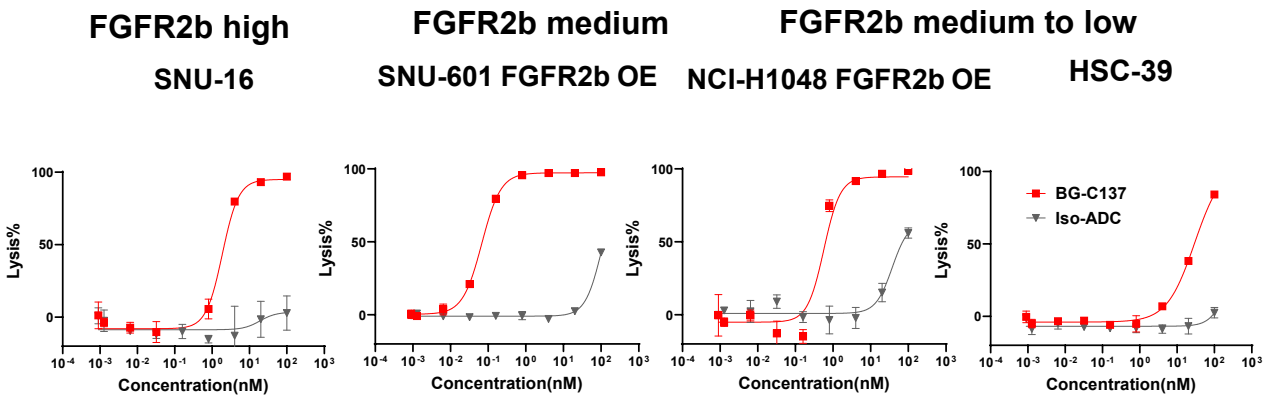
## Reasonable internalization




## Potent cellular killing



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

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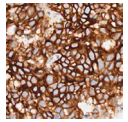
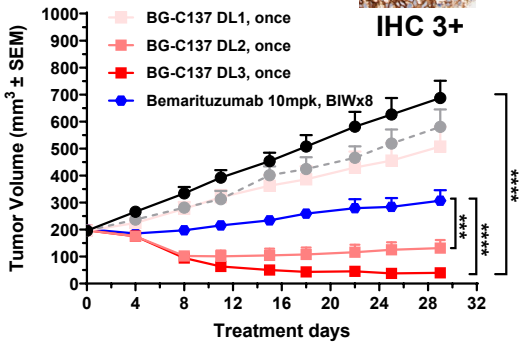
## FGFR2b$^{high}$ SNU-16

*FGFR2b-amplified*

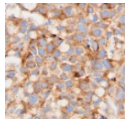


IHC 3+

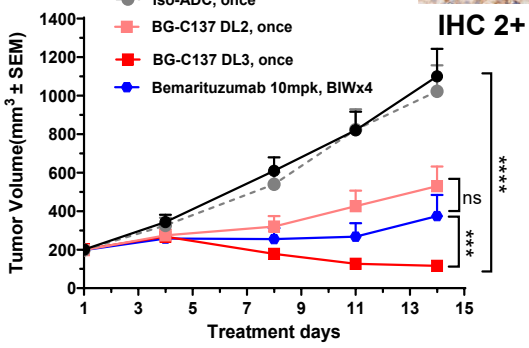



## FGFR2b$^{medium}$ HSC-39

*FGFR2b-amplified*

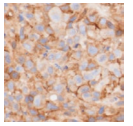


IHC 2+

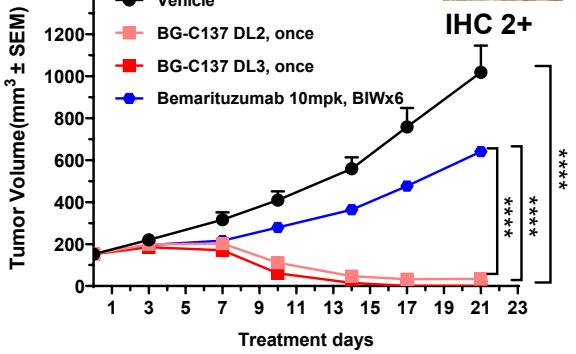



## FGFR2b$^{medium}$ GC PDX

*No FGFR2b amplification*



IHC 2+




- BG-C137 demonstrated efficacy in gastric cancer models with diverse FGFR2b expression (IHC2+ and IHC3+) regardless of FGFR2b amplification status
- No body weight loss observed in efficacy studies

# BG-C137 showed bystander killing effect *in vitro* and anti-tumor efficacy in co-inoculation model

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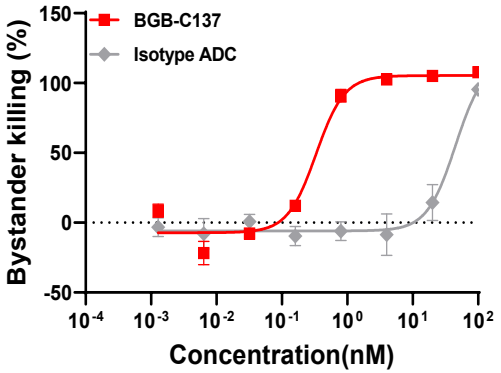
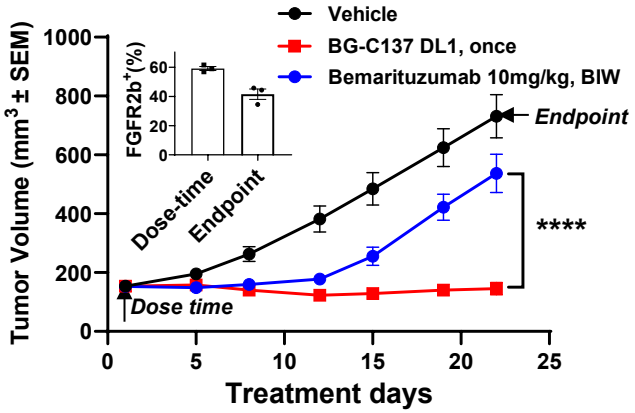
## By-stander killing *in vitro*

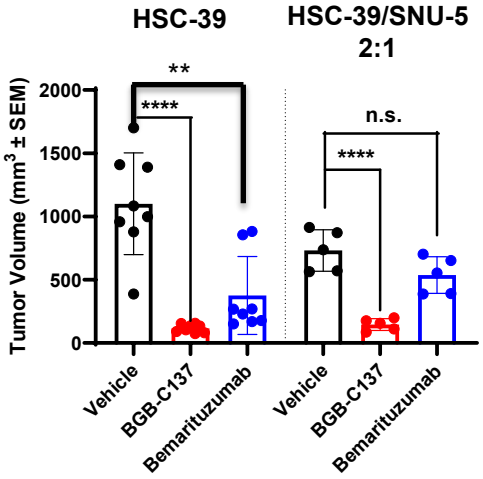
SNU16 (Positive) : Hutu80 (Negative) =1:1




## Profound efficacy in heterogenous model

HSC-39 (IHC 2+) :SNU-5 (Negative) = 2:1




- BG-C137 maintained significant tumor inhibition in co-inoculation model while Bemarituzumab showed weaker anti-tumor effect compared with homogeneous model

# BG-C137 inhibited tumors in PDX models with high heterogeneous FGFR2b expression

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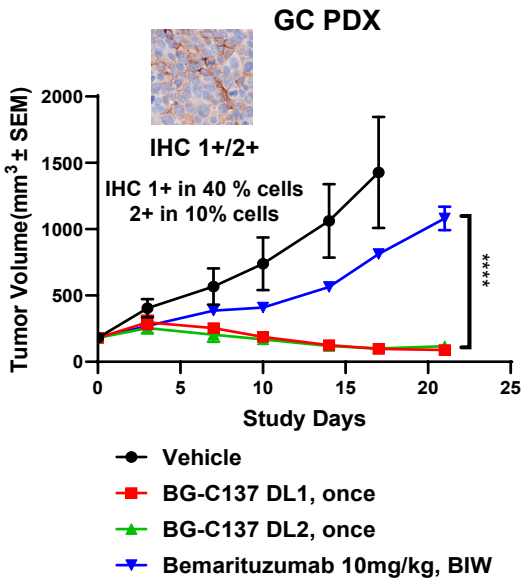
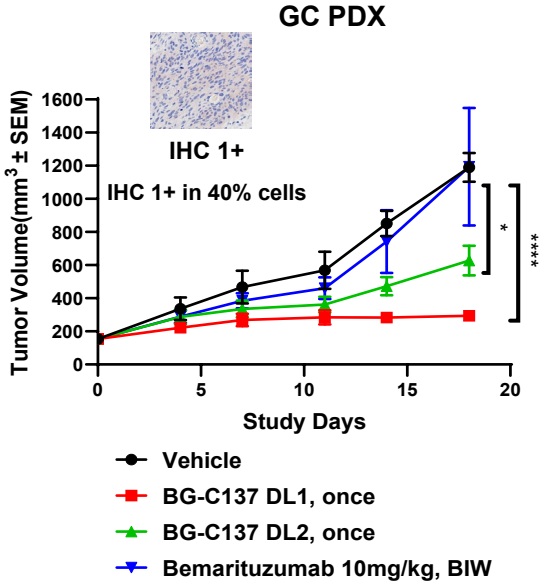
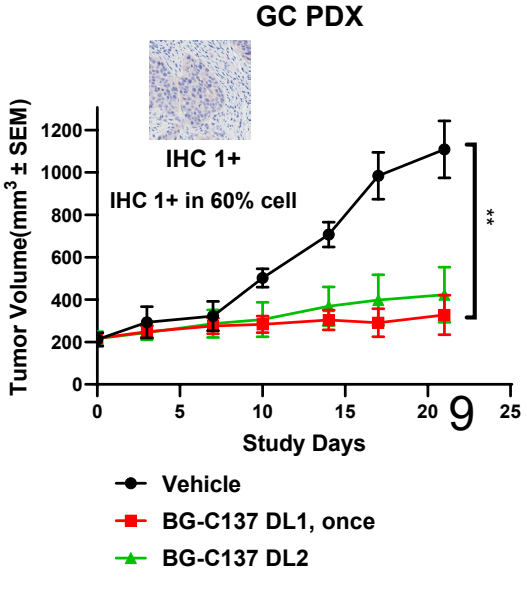
## BG-C137 demonstrated efficacy in PDX models with highly heterogeneous FGFR2b expression



# Sustained FGFR2b signaling blocking Contributed to Corneal dystrophy

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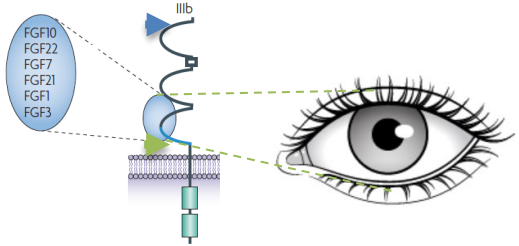
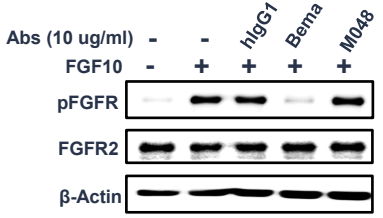
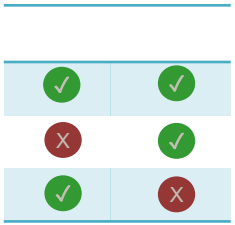


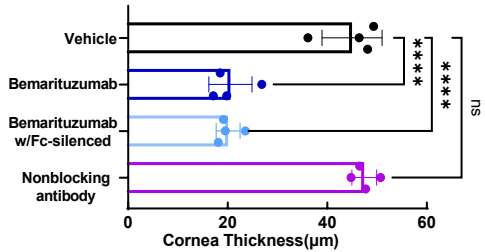

- FGF7/10-mediated FGFR2b signaling is essential in corneal development and maintenance
- Consistent with clinical finding, sustained signaling blockage with Bemarituzumab(Bema) showed corneal dystrophy in mice

- Corneal dystrophy: the thinning of corneal
- M048, anti-FGFR2 antibody, binds at N-terminal and is not a ligand blocker. Bemarituzumab is a strong dual ligand blocker

## Corneal dystrophy is caused by sustained FGFR2b signaling blocking






BIW x 9 Doses

- M048 showed comparable $IC_{50}$ in FGFR2 binding but with lower Emax (backup slides p48)
- 10mpk of M048 BIW was selected for study considering 5mpk of M048 showed sustained *in vivo* PD effect in SNU-16 upon 4 days
- No difference on PK between wildtype and Fc-enhanced Bemarituzumab were reported on monkey

# Antibody of BG-C137 is a partial ligand blocker

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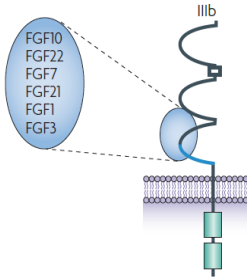


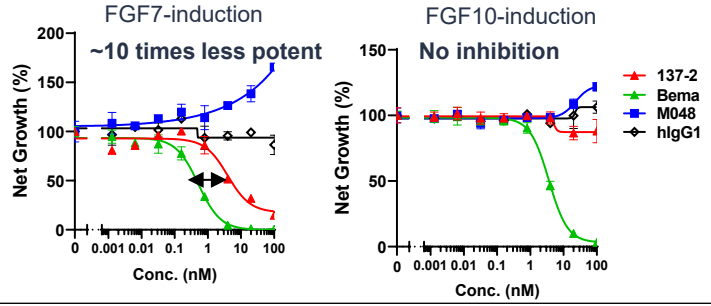

**Signaling pathway**

To probe the interference of Abs on pFGFR

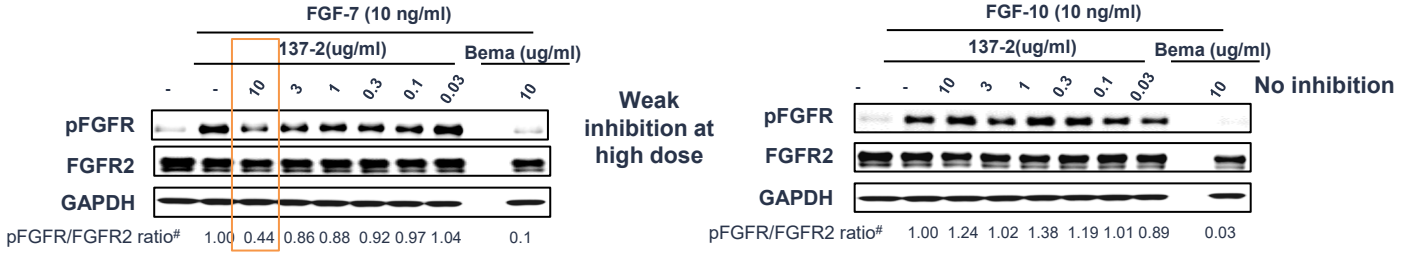
**Net growth**

To evaluate the Abs' function on ligand-stimulated FGFR2b signaling mediated proliferation in BaF3 FGFR2b-overespression cells

## Net growth on BaF3




## Signaling pathway in SNU-16




- Antibody of BG-C137 (137-2) weakly inhibits FGF7-induced signaling and spares FGF10-induced signaling

# BG-C137 does not induce corneal dystrophy in preclinical studies

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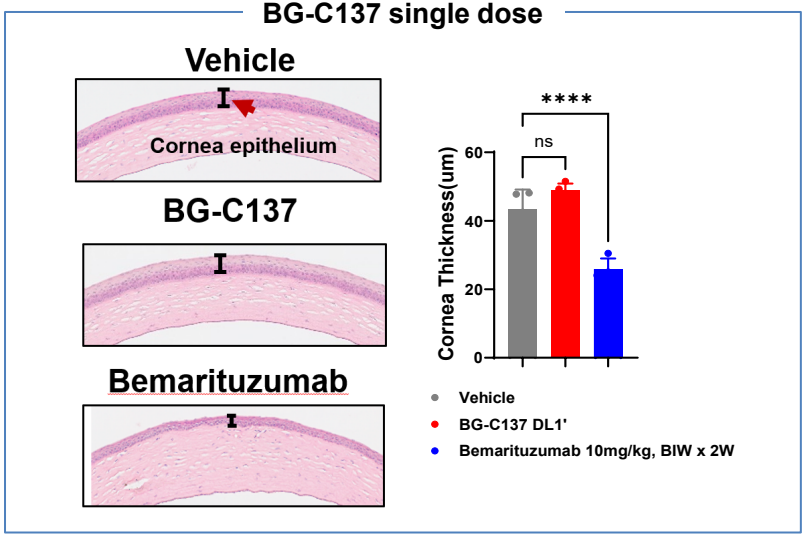


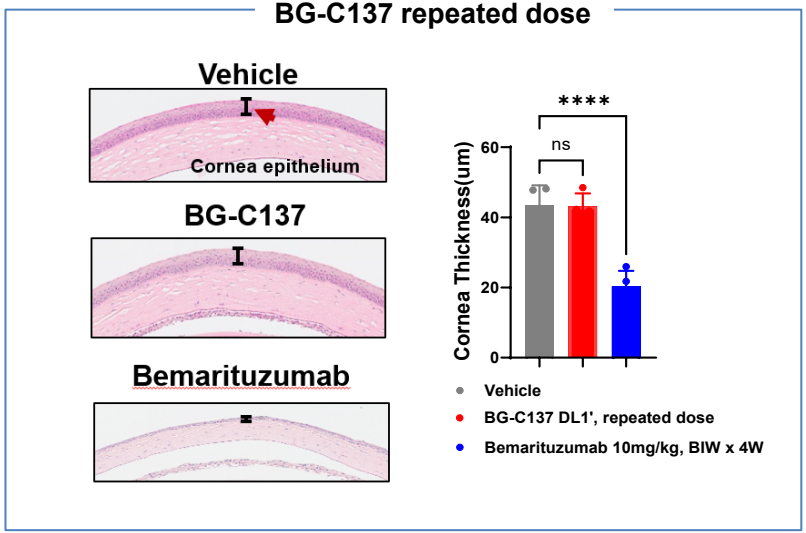


- Consistent with the observation in mouse, Bemarituzumab shows reversible corneal dystrophy in rats and monkeys
- **No observation of corneal dystrophy or any ocular AE in non-human primates at high doses with repeated dosing, suggesting that BG-C137 holds potential in sparing corneal dystrophy in patients**

# Conclusion

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- BG-C137 is a FGFR2b-targeted ADC with strong scientific rationale and preclinical proof-of-concept
- It demonstrates strong antitumor effects in FGFR2b expressing tumors with diverse expression levels
- 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
- Together, these observations support the clinical development of BG-C137 for the treatment of FGFR2b-expressing tumors (ClinicalTrials.gov ID NCT06625593)