Clinical Pharmacology Characterization of Bemarituzumab in Gastric Cancer (GC) and Gastroesophageal Junction Cancer (GEJC) Patients Supports the Interchangeability of Q2W and Q3W Dosing Regimens

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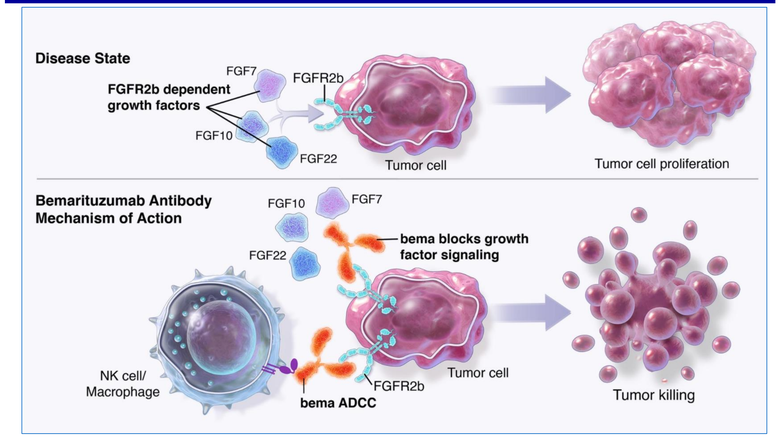
BACKGROUND



- Fibroblast growth factor receptor 2b (FGFR2b) is an isoform of FGFR2 that is overexpressed in gastric cancer and other solid tumors
- Bemarituzumab (Bema) is an FGFR2b-specific monoclonal antibody with a dual mechanism of action designed to 1) block FGF ligand binding, thereby inhibiting the downstream signaling pathways leading to cell proliferation, and 2) enhance ADCC, promoting tumor cell death.
- Bema is being explored in first-line GC and GEJC in two registrational trials: FORTITUDE-101 (NCT05052801) and FORTITUDE-102 (NCT05111626)
- Bema dosing regimen in the registrational trials is 15 mg/kg Q2W + 7.5 mg/kg on cycle 1 day 8, same as the first line GC/GEJC Ph2 FIGHT study
- While mFOLFOX6 Q2W is given as chemo backbone in US, Asian and some EU investigators prefer CAPOX Q3W due to convenience of oral administration and local standard of care
- Objective is to evaluate the interchangeability of the current trial Q2W dosing regimen with an alternate Q3W dosing regimen of 22 mg/kg and 11 mg/kg on cycle 1 day 8, enabling investigator choice of mFOLFOX6 or CAPOX in the FORTITUDE-102 trial design

METHODS

Population PK Model

Two compartment PK model used to best describe Bema concentration vs. time course. Model was used to select Q3W doses that achieve similar trough concentration to Q2W dosing

Exposure Metric

Through ROC analysis, C_{trough} selected as the most relevant exposure metric to characterize ORR and grade ≥ 2 corneal AEs

Exposure Response (ER) Analysis

Exposure-ORR and exposure- grade ≥ 2 corneal AEs analysis performed to demonstrate interchangeability between Q2W and Q3W regimens

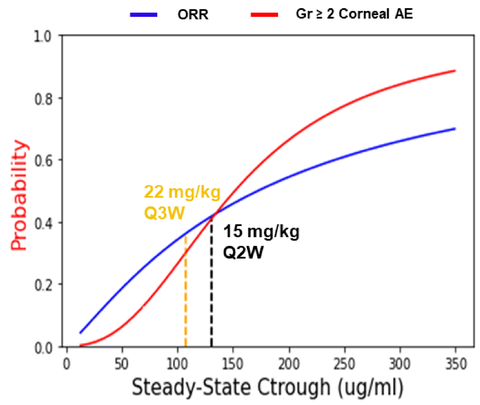
Ph1b Data and PBPK Model

Data from ongoing Ph1b studies and PBPK modeling used to support the findings from ER analysis

RESULTS

- The $C_{trough,ss}$, ORR and probabilities of corneal AE are predicted to be comparable between the 22 mg/kg Q3W regimen and the 15 mg/kg Q2W regimen (Figure 1)
- PBPK model indicated a slow accumulation of bema in the cornea resulting in delayed achievement of the steady state corneal concentration (Figure 2)
- The predicted delayed achievement of the steady state corneal concentration aligned with the delayed onset of grade ≥ 2 corneal AEs observed from Study FIGHT (Figure 2)
- PBPK model suggested no major differences in the corneal tissue concentration-time profiles between the 22 mg/kg Q3W dosing regimen and the 15 mg/kg Q2W dosing regimen (Figure 2)
- Predicted cornea exposure is not very sensitive to differences between the 22 mg/kg Q3W and the 15 mg/kg Q2W dosing regimen (Figure 2)
- Model predicted and observed C_{trough} at cycles 1 and 2 from Q3W are comparable to Q2W, supported lack of difference in ORR (Figure 3)
- Observed safety data from Q3W regimen demonstrated that bema is safe and tolerated. Supported lack of difference in grade ≥ 2 corneal AEs (Table 1)

Figure 1. Exposure-response analysis (ORR and Grade ≥ 2 corneal AEs) for the Q2W and Q3W regimens



Black dashed line: predicted median $C_{trough,ss}$ for Q2W (130.46 µg/mL; 95% CI: 44.81, 281.33)
Yellow dashed line: predicted median $C_{trough,ss}$ for Q3W (107.01 µg/mL; 95% CI: 25.42, 259.13)

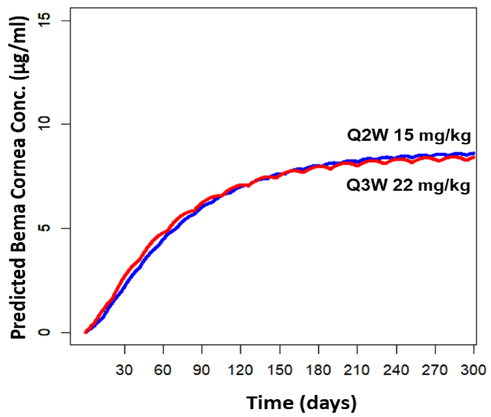


Figure 2. Predicted cornea concentration for Q2W and Q3W dosing regimens based on PBPK modeling

Figure 3. Model predicted and observed C_{trough} for Q2W and Q3W regimens from different studies

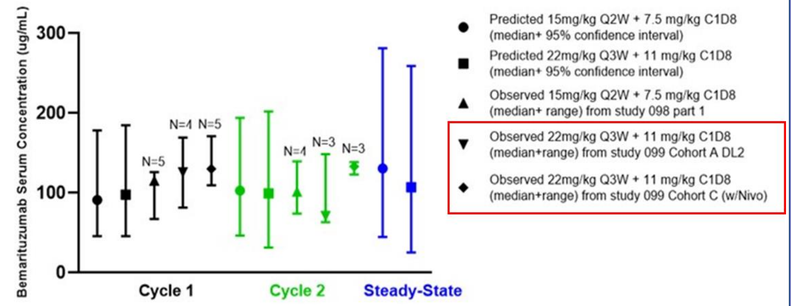


Table 1. Preliminary safety data from an ongoing Ph1b GC study FORTITUDE-103 (NCT05322577) with the Q3W regimen

Q3W regimens

Gastric Cancer	Combo with CAPOX/SOX+Nivo DL2: 22 mg/kg Q3W + 11 mg/kg on C1D8
	Among 10 DLT-evaluable subjects, no DLTs, no AEs leading to discontinuation, no fatal and TE-SAEs during the DLT period.

CONCLUSIONS

- No major difference in ORR and Grade ≥ 2 corneal AEs between the Q3W and Q2W dosing regimens.
- Amgen revised the design of FORTUTUDE-102 study to allow the integration of Q3W dosing regimen based on the results from this analysis
- The interchangeability between the Q2W and Q3W dosing regimen enabled investigator choice of mFOLFOX6 or CAPOX in the FORTITUDE-102 trial design

Abbreviations
PK: Pharmacokinetics. **Q2W:** Every two weeks. **Q3W:** Every three weeks. **$C_{trough,ss}$:** Steady-state minimum concentration. **ADCC**: Antibody dependent cell cytotoxicity. **ROC**: Receiver operating characteristic. **ORR**: Objective response rate. **AE**: Adverse event. **PBPK**: Physiologically based pharmacokinetics. **Nivo**: Nivolumab. **DLT**: Dose limiting toxicity. **TE-SAE**: Treatment emergent severe adverse event

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