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Phase 1b Results of Bemarituzumab+mFOLFOX6+Nivolumab for Advanced Gastric/Gastroesophageal Junction Cancer: FORTITUDE-102 Part 1

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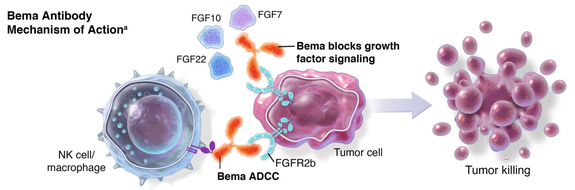
BACKGROUND

- Fibroblast growth factor receptor 2b (FGFR2b), which is encoded by the splice isoform IIIb, has been observed in approximately 20%–30% of patients with newly diagnosed advanced gastric or gastroesophageal junction carcinoma (G/GEJC) not known to be human epidermal growth factor receptor 2 (HER2) positive[1]

Figure 1. Relationship Between FGFR2b and Tumor Cell Proliferation



[a]This figure depicts the proposed mechanism of action and is not meant to imply clinical efficacy. Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; bema, bemarituzumab; FGF, fibroblast growth factor; FGFR2b, FGF receptor 2 isoform IIIb; Ig, immunoglobulin; NK, natural killer. Image adapted from Catenacci D, et al. Presented at: ASCO Annual Meeting; June 4-8, 2021; Online Virtual Scientific Program.

- Bemarituzumab is a first-in-class, humanized, immunoglobulin G1 monoclonal antibody that selectively inhibits FGFR2b signaling and enhances antibody-dependent cellular cytotoxicity against tumor cells expressing FGFR2b[2]
- In the final analysis of the FIGHT study, bemarituzumab + m FOLFOX6 (5-fluorouracil, leucovorin, and oxaliplatin) (mFOLFOX6) prolonged median progression-free survival (PFS) and median overall survival [OS] compared with placebo + mFOLFOX6 in patients with FGFR2b overexpression (2+/3+) in at least 10% of tumor cells by IHC were as follows:[3]
  - PFS: Bemarituzumab, 14.0 mo; placebo, 7.3 mo; hazard ratio (HR) (95% confidence interval [CI]), 0.43 (0.26–0.73)
  - OS: Bemarituzumab, 24.7 mo; placebo,11.1 mo; HR (95% CI), 0.52 (0.31–0.85)
- Nivolumab added to standard first-line chemotherapy increased median OS from 11.1 mo to 14.4 mo (OS HR = 0.71, 98.4% CI: 0.59–0.86) in patients with tumors that were not HER2 positive[4]
- Here, we present an ad hoc, interim analysis from Part 1 (open-label phase 1b) of the FORTITUDE-102 study (NCT05111626), which evaluated the safety and tolerability of bemarituzumab + mFOLFOX6 + nivolumab

METHODS

Study design

- FORTITUDE-102 is designed to evaluate the safety, tolerability, efficacy, and pharmacokinetics (PK) of bemarituzumab added to chemotherapy + nivolumab in subjects with advanced G/GEJC unselected for FGFR2b overexpression (Figure 2)
  - Part 1 (data presented in this poster): Phase 1 safety lead-in of bemarituzumab+mFOLFOX6+nivolumab advanced G/GEJC
  - Part 2 (in progress): Phase 3 randomized efficacy of bemarituzumab or placebo added to chemotherapy+nivolumab with FGFR2b-overexpressing, previously untreated, advanced G/GEJC
- Dosing in Part 1
  - Bemarituzumab 15 mg/kg every 2 weeks with one additional 7.5 mg/kg dose on cycle 1, day 8, with a 28-day dose-limiting toxicity (DLT) threshold of 28 days
  - mFOLFOX6
  - Nivolumab 240 mg every 2 weeks
- Tumor samples were assessed by centralized immunohistochemistry for FGFR2b overexpression (any tumor cells with moderate [2+] to strong [3+] membrane staining) during screening; data were collected and summarized, but the results did not affect eligibility for enrollment
- The protocol was approved by ethics committees at all sites, and all patients provided informed consent

STUDY DESIGN

Figure 2. FORTITUDE-102 Part 1 Study Design

FORTITUDE-102 Part 1
Open-label, phase 1b study (Up to ~20 patients)

Key eligibility criteria
- Unresectable, locally advanced, or metastatic G/GEJC, unselected for FGFR2b overexpression
- RECIST version 1.1 evaluable disease
- ECOG performance status of 0 or 1
- Not known to be HER2 positive
- No evidence or history of corneal abnormalities

Bema 15 mg/kg IV Q2W with one 7.5 mg/kg on C1D8 + Nivo + mFOLFOX6

Primary endpoint
- Incidence of DLTs

Secondary endpoints
- OR, DoR, DCR, PFS, OS
- PK parameters

Abbreviations: Bema, bemarituzumab; C1D8, cycle 1 day 8; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; FGFR2, fibroblast growth factor receptor 2; FGFR2b, IIIb splice isoform of FGFR2; G/GEJC, gastric or gastroesophageal junction carcinoma; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified FOLFOX (infusional 5-fluorouracil, leucovorin, and oxaliplatin); Nivo, nivolumab; PK, pharmacokinetics; Q2W, once every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

RESULTS

Patient characteristics

- Eight pts (50-71 y) were enrolled and evaluated for DLTs: 6 pts were men, 4 patients were Asian, and 4 patients were White (Table 1)
- No patients' tumor samples had FGFR2b overexpression

DLTs, safety, tolerability, and response

- No DLTs were reported and no new safety signals were identified during the 28-day dose evaluation period
- An ad-hoc review was performed 13 mo after the DLT period, showing median treatment of ~29.6 weeks (range, 7.9–55.1) (Table 2)
  - 7 patients had 11 serious TEAEs (hyponatremia [n = 1] and corneal infection [n = 1] considered bemarituzumab-related)
  - 8 patients had 26 grade ≥ 3 TEAEs
  - 4 patients reported 11 TEAEs considered bemarituzumab-related comprising 8 preferred terms (conjunctival hyperemia, corneal disorder, corneal infection, delirium, hyponatremia, hypopyon, mucosal inflammation, and visual acuity reduced)
  - 6 patients reported 25 ocular TEAEs of grades ≤ 2, with a median time to onset of ~18 weeks
- 1 patient had TEAE leading to bemarituzumab discontinuation (corneal disorder)
- Treatment was interrupted in 6 patients due to bemarituzumab-related AEs (3 pts due to ocular AEs)
- The recommended phase 3 dose was 15 mg/kg every 2 weeks with one 7.5 mg/kg dose on cycle 1 day 8
- At the ad-hoc review, 3 patients experienced partial response, 4 experienced stable disease, and 1 experienced disease progression

PK outcomes

- Mean exposures (C_{max} and C_{trough}) achieved during the first 3 cycles are consistent with FIGHT study (same bemarituzumab dosing regimen). No meaningful exposure changes with the addition of nivolumab, indicating no drug interactions (Figure 3)
- Estimated terminal elimination half-life ranges from 7 to 11 days, consistent with historical data
- Mean target coverage for projected minimum efficacious exposure based on FIGHT trial (60 µg/mL) achieved during the first 2 cycles

RESULTS (Continued)

Table 1. Patient Characteristics

Characteristics	Patients (N = 8)
Age, y, min–max	50–71
Gender, n/N patients	
Male	6/8
Female	2/8
Race, n/N patients	
Asian	4/8
White	4/8
Had 1 or more prior treatments, n/N patients	3/8
Baseline ECOG status, n/N patients	
0	3/8
1	5/8

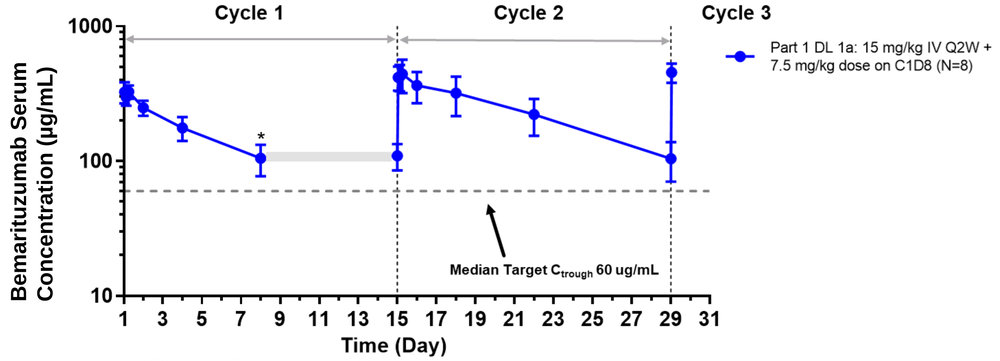
Abbreviations: ECOG, Eastern Collaborative Oncology Group.

Table 2. Safety Outcomes at 13-mo Ad Hoc Review (Median Treatment 29.6 Weeks)

Type of Event	Patients (N = 8) with ≥1 Event
Any TEAE, n/N patients	
Serious	7/8
Grade ≥ 3	8/8
Any TRAE, n/N patients	
Serious	2/8
Grade ≥ 3	4/8
Leading to bemarituzumab discontinuation	2/8
Leading to bemarituzumab interruption	6/8
Ocular TEAE, n/N patients	
Serious	1/8
Grade ≥ 3	2/8
Leading to bemarituzumab discontinuation	1/8
Leading to bemarituzumab interruption	3/8

Abbreviations: TEAE, treatment emergent adverse event; TRAE, treatment related adverse event. Database lock date 3 August 2023.

Figure 3. Mean Pharmacokinetic Profiles for Bemarituzumab (Cycles 1, 2, 3)



*C1D8 post dose samples were not available from sites. Abbreviations: C1D8, cycle 1 day 8; DL, dose level; IV, intravenous; Q2W, once every 2 weeks.

CONCLUSIONS

- FORTITUDE-102 is the first time a combination of bemarituzumab, mFOLFOX6, and nivolumab is assessed
- There were no new safety signals after 13 mo of follow-up
- Absence of DLTs and safety/PK profiles consistent with those observed in the FIGHT phase 2 study suggested no drug interactions with nivolumab; accordingly, Part 2 was initiated at a dose of bemarituzumab 15 mg/kg every 2 weeks with a single 7.5 mg/kg dose on day 8 of the first cycle
- In the phase 3 FORTITUDE-102 Part 2 (NCT05111626; actively recruiting), bemarituzumab or placebo added to chemotherapy + nivolumab is being studied in G/GEJC pts with FGFR2b overexpression of ≥ 10% tumor cells with moderate (2+) to strong (3+) membrane staining

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