Fibroblast Growth Factor Receptor 2 Isoform IIIb (FGFR2b) Protein Overexpression and Biomarker Overlap in Patients With Advanced Gastric or Gastroesophageal Junction Cancer (GC/GEJC)

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BACKGROUND

- In GC, targeted therapeutic agents added to chemotherapy have been found to extend survival, including agents directed at human epidermal growth factor receptor 2 (HER2), programmed cell death protein (PD-1), and claudin 18 isoform 2 (CLDN18.2).[1-4]
- Despite these advancements, the prognosis for advanced GC/GEJC adenocarcinoma remains poor, necessitating further treatment strategies to improve outcomes.
- Fibroblast growth factor receptor (FGFR), crucial in tissue formation, angiogenesis, and cell proliferation, exhibits gene amplification in a small subset of GC patients.[5-8] Moreover, FGFR2 protein overexpression, particularly the FGFR2b splice variant, is reported in GC/GEJC tumor tissue, most recently in the randomized phase 2 FIGHT study, at a prevalence of 20%–30%.[9]
- Bemarituzumab, a recombinant humanized IgG1 monoclonal antibody targeting FGFR2b, has shown promise in the FIGHT study:
  - There were clinically meaningful improvements in progression free survival (PFS; median 9.5 vs. 7.4 months; HR 0.72, 95% CI, 0.49–1.08) and overall survival (OS; median 19.2 vs. 13.5 months; HR 0.77, 0.52–1.14) with bemarituzumab plus chemotherapy when compared to placebo plus chemotherapy.[9,10]
  - Building upon these findings, ongoing phase III trials (NCT05052801, NCT05111626) aim to further evaluate the efficacy of chemotherapy combined with bemarituzumab in advanced GC/GEJC.[11,12]
- We sought to provide clinical and molecular characterization of FGFR2b expression in advanced GC/GEJC and its overlap with other biomarkers of interest such as HER2, programmed death-ligand 1 (PD-L1), mismatch repair (MMR) and CLDN18.2.

METHODS

Study design

- We collected patient, treatment, and tumor characteristics from electronic medical records at a single Japanese cancer center
- The eligibility criteria included:
  - unresectable locally advanced, metastatic, or recurrent GC/GEJC;
  - histologically documented adenocarcinoma;
  - no systemic chemotherapy for advanced disease prior to tumor tissue collection;
  - initiation of systemic chemotherapy for advanced disease no more than 5.5 years before study initiation;
  - archival tissue specimen for tissue analysis; and
  - written informed consent for secondary research
- Formalin-fixed paraffin-embedded (FFPE) samples collected before first line therapy (1L) were tested via immunohistochemistry (IHC) for FGFR2b [clone FPR2-D] and PD-L1 [clone 28-8]
- FGFR2b overexpression was defined as any percentage of tumor cells exhibiting moderate (2+) to strong (3+) membranous staining (FGFR2b any 2+/3+)
- Based on the FIGHT final analysis,[10] a pre-specified alternate definition for FGFR2b overexpression of ≥10% of tumor cells exhibiting moderate to strong membranous staining (≥10% 2+/3+) was also evaluated
- PD-L1 stratification (combined positive score [CPS] ≥ 5 or CPS <5) aligns with the stratification in registration studies of bemarituzumab in advanced GC/GEJC, which aids in understanding the potential addressable population
- HER2, MMR and CLDN18.2 [clone 43-14A] were assessed as previously reported,[13,14] and CLDN18.2 positive was defined as ≥75% of tumor cells expressing 2+ or 3+ staining intensity
- The study protocol was approved by the Research Ethics Board at the National Cancer Center Japan

RESULTS

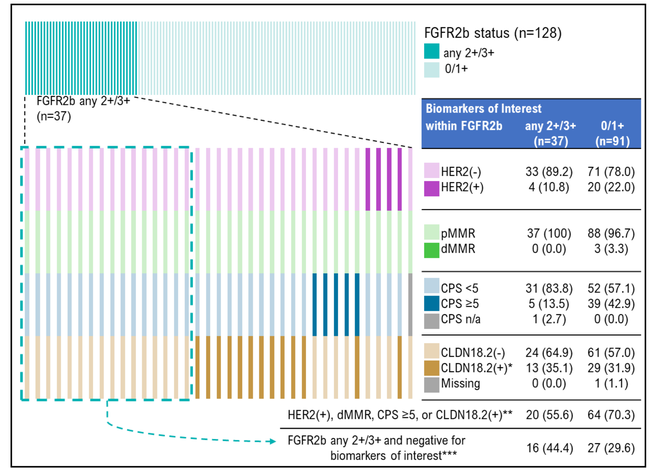
- 547 tumor specimens were identified and tested for FGFR2b and PD-L1 with 500 samples evaluable for FGFR2b
- The subcohort described here consists of the 128 GC/GEJC patients with tumor specimens collected no more than 1.5 years before study initiation
- Estimated prevalence of FGFR2b any 2+/3+ was 28.9% (37/128; 95% CI: 21.2, 37.6) and of FGFR2b ≥10% 2+/3+ was 10.9% (14/128; 95% CI: 6.1-17.7)
- There were no differences between the FGFR2b any 2+/3+ and FGFR2b 0/1+ staining intensity groups in patient or tumor characteristics including the frequency of Borrmann type 4 tumors (27.0% vs. 26.4%) or histological diffuse type (51.4% vs. 49.5%) (Table 1)
- Prevalence of biomarkers of interest are summarized in Figure 1
  - Estimated prevalences of FGFR2b any 2+/3+ among biomarkers of interest were 16.6% (4/24) in HER2 positive, 0% (0/3) in deficient MMR (dMMR), 11.4% (5/44) in PD-L1 CPS ≥5, and 31.0% (13/42) in CLDN18.2 positive
  - In FGFR2b any 2+/3+ tumor samples, 13.5% (5/37) exhibited a PD-L1 CPS ≥ 5 and 35.1% (13/37) were CLDN18.2 positive
  - Of the 37 samples with any FGFR2b 2+/3+ expression, 16 (44.4%) were negative for biomarkers of interest

*Table 1. Patient and Tumor Specimen Characteristics Stratified by FGFR2b Status**

	FGFR2b Any 2+/3+ (N = 37)	FGFR2b 0/1+ (N = 91)
Gender, male	26 (70.3)	64 (70.3)
Age at start of 1L, y, mean (SD)	67.6 (12.1)	66.7 (13.3)
ECOG performance score		
0	15 (40.6)	52 (57.1)
1	17 (45.9)	26 (28.6)
≥2	5 (13.5)	13 (14.3)
Primary tumor site, stomach	30 (81.1)	81 (89.0)
Lauren's classification, diffuse	19 (51.4)	45 (49.5)
Borrmann's Classification Type 4	10 (27.0)	24 (26.4)
Disease status, metastatic	37 (100)	90 (98.9)
Number of metastatic organ sites		
0	0 (0.0)	1 (1.1)
1	28 (75.7)	71 (78)
2	7 (18.9)	14 (15.4)
≥3	2 (5.4)	5 (5.5)
Liver metastasis	15 (40.5)	27 (29.7)
Lung metastasis	2 (5.4)	6 (6.6)
Peritoneal metastasis	16 (43.2)	44 (48.4)
Lymph node metastasis	28 (75.7)	62 (68.1)
Bone metastasis	2 (5.4)	4 (4.4)
Other metastasis	4 (10.8)	4 (4.4)

All values are no. patients or patients' specimens (%) unless otherwise indicated. Abbreviations: 1L, first line; ECOG, Eastern Cooperative Oncology Group; FGFR2b, fibroblast growth factor receptor 2 isoform IIb; SD, standard deviation. *An association between sample collection date and prevalence of tested biomarkers was observed, suggesting possible misclassification of biomarker status in tumor specimens collected more than 1.5 years before study initiation.

Figure 1. Distribution and Overlap of Biomarkers of Interest Stratified by FGFR2b Status



All values are no. patients or patients' specimens (%) unless otherwise indicated. Abbreviations: CLDN, claudin; CPS, combined positive score; dMMR, deficient mismatch repair; FGFR2b, fibroblast growth factor receptor 2 isoform IIIb; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death ligand 1; pMMR, proficient mismatch repair. *Defined as CLDN18.2 ≥75% of tumor cells with 2+ or 3+ staining intensity. **One FGFR2b 0/1+ sample that is missing CLDN18.2 but is positive for HER2 is included in this row. ***One FGFR2b any 2+/3+ sample that is missing PD-L1 CPS is excluded from this row.

CONCLUSIONS

- FGFR2b is a novel protein biomarker detected by IHC that identifies a GC/GEJC patient population who may benefit from FGFR2b targeting therapies (eg, bemarituzumab) currently being tested in clinical trials
- In this single center analysis of 128 tumor samples, ~30% of patients had tumors expressing FGFR2b at any 2+/3+, and among those patients ~40% are not eligible for currently approved targeted therapies
- These results may be useful for interpreting the ongoing phase III trials targeting FGFR2b in GC/GEJC, as well as considering future treatment strategies directed at FGFR2b

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Seiya Sato (sesat2@east.ncc.go.jp) reports no conflicts of interest to disclose.

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