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ORIGINAL ARTICLE

Clinical characterization of FGFR2b expression in patients with advanced gastric or gastroesophageal junction adenocarcinoma

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Available online xxx

Background: Fibroblast growth factor receptor 2b (FGFR2b) is a novel protein biomarker expressed in gastric and gastroesophageal junction tumors (GC/GEJC). Phase III trials are evaluating the efficacy and safety of FGFR2b-targeting therapies. However, features of FGFR2b-expressing tumors and co-occurrence of FGFR2b expression with currently actionable biomarkers in gastric cancer remain unclear.

Materials and methods: We carried out a single-institution retrospective cohort study of patients who initiated systemic therapy for GC/GEJC to evaluate features of FGFR2b-positive tumors, first-line (1L) treatments received, and co-occurrence with select actionable biomarkers [human epidermal growth factor receptor 2 (HER2), mismatch repair, programmed death-ligand 1 (PD-L1), claudin-18 isoform 2]. A sample was deemed FGFR2b-positive when any (>0%) tumor cells exhibiting moderate (2+) or strong (3+) membrane staining were detected ('any 2+/3+'). Other biomarkers were assessed based on current clinical guidelines. FGFR2b-stratified real-world overall survival (OS) was estimated using the Kaplan—Meier and Cox proportional regression models.

Results: Of 547 GC/GEJC patients identified, 492 (89.9%) met inclusion/exclusion criteria, had evaluable FGFR2b staining, and had complete clinical data. Estimated prevalence of FGFR2b any 2+/3+ was 15.4% [95% confidence interval (CI) 12.4% to 19.0%] in the full cohort of patients and 29.8% (95% CI 22.0% to 38.7%) in patients with samples collected within 1.5 years of study initiation. The majority (53.9%; 95% CI 42.1% to 65.5%) of FGFR2b any 2+/3+ tumor specimens were negative for other assessed biomarkers at a PD-L1 cut-off of combined positive score ≥5. In HER2-negative patients treated in 1L with chemotherapy alone, median OS was 11.5 months (95% CI 10.0-16.3 months) and 15.3 months (95% CI 13.0-16.8 months) for FGFR2b any 2+/3+ and FGFR2b 0/1+, respectively. There was no association between FGFR2b overexpression level and OS [adjusted hazard ratio (HR) 1.14, 95% CI 0.84-1.55].

Conclusions: This study revealed limited overlap of FGFR2b overexpression with currently actionable biomarkers, suggesting FGFR2b is a novel biomarker that identifies a distinct GC/GEJC patient population who may benefit most from an FGFR2b-targeting therapy.

Key words: gastric cancer, FGFR2b, biomarker, bemarituzumab, prevalence, overall survival

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer in both incidence and mortality globally.[1] The preferred first-line (1L) backbone chemotherapy for unresectable or recurrent GC or gastroesophageal junction cancer (GEJC) typically involves a doublet combination of fluoropyrimidine and platinum agents.[2-4] In cases negative for human epidermal

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growth factor receptor 2 (HER2), an anti-programmed cell death protein 1 (anti-PD-1) agent like nivolumab or pembrolizumab is included, particularly for patients with tumors expressing programmed death-ligand 1 (PD-L1) protein or with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors.[5,6] For HER2-positive cases, chemotherapy plus trastuzumab is the standard, with pembrolizumab being included for patients with HER2 and PD-L1 positivity.[7,8] More recently, zolbetuximab, a monoclonal antibody targeting claudin-18 isoform 2 (CLDN18.2), in combination with chemotherapy, has shown improved overall survival (OS) in patients with ≥75% of tumor cells showing moderate (2+) or strong (3+) membranous staining by immunohistochemistry (IHC),[9-11] and is now approved in many countries including Japan. Despite these advancements in care, the prognosis for unresectable GC/GEJC adenocarcinoma remains poor with a 5-year relative survival of only 10% for patients with advanced disease,[12] 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.[13-16] FGFR2 protein overexpression, specifically the FGFR2b splice variant, has also been reported in GC tumor tissue.[13,14] Prevalence of FGFR2b protein overexpression has varied widely and been reported in 2.7%-38% of patients.[14,17-19]

Bemarituzumab, a recombinant humanized IgG1 monoclonal antibody targeting FGFR2b, has shown promise by inhibiting ligand-induced FGFR2b signaling as well as enhanced antibody-dependent cellular cytotoxicity.[20] It exhibits single-agent activity in chemotherapy-refractory GC cases with FGFR2 amplification or FGFR2b overexpression.[21] Encouraging results from the randomized phase II FIGHT study suggest clinically meaningful improvements in progression-free survival [median 9.5 versus 7.4 months; hazard ratio (HR) 0.72] and OS (median 19.2 versus 13.5 months; HR 0.77) with bemarituzumab plus chemotherapy when compared with placebo plus chemotherapy.[17,22] Building upon these findings, ongoing phase III trials (NCT05052801, NCT05111626) aim to further evaluate the efficacy and safety of chemotherapy alone or with nivolumab combined with bemarituzumab in advanced GC/GEJC.[23,24]

However, the clinicopathological features of FGFR2b-expressing tumors and the co-occurrence of FGFR2b protein expression with currently actionable biomarkers in GC, including HER2, MMR, PD-L1, and CLDN18.2, remain unclear. Therefore, our study aims to provide a comprehensive clinical and molecular characterization of FGFR2b expression in advanced GC/GEJC patients, addressing this gap in current knowledge.

MATERIALS AND METHODS

Patients

We carried out a single-institution retrospective cohort study. Individuals receiving care from the National Cancer Center Japan were identified for study inclusion if he/she met the following eligibility criteria including having (i) unresectable, locally advanced, metastatic, or recurrent GC/GEJC; (ii) histologically documented adenocarcinoma; (iii) adequate bone marrow, hepatic, and renal function; (iv) initiated systemic chemotherapy for advanced disease between April 2017 and October 2022; (v) no prior systemic chemotherapy for advanced GC/GEJC; and (vi) archival tissue specimen available for tissue analysis. Inclusion was further restricted to those with FGFR2b-evaluable samples and who had complete clinical data. All patients provided written informed consent for secondary research. The study protocol (#2022-093) was approved by the Institutional Review Board at the National Cancer Center Japan on 22 July 2022.

Clinical and biomarker characteristics

Patient, treatment, and tumor characteristics were collected from existing electronic medical records. Biomarkers HER2, MMR, PD-L1, CLDN18.2, and FGFR2b were assessed using formalin-fixed paraffin-embedded primary tumor tissue specimens collected before initiation of systemic therapy.

FGFR2b protein expression was determined by an automated immunohistochemistry (IHC) test developed by Ventana Medical Systems, Inc. (Oro Valley, AZ) using the anti-FGFR2b clone FPR2-D (which is specific for the 'IIIb' isoform of the FGFR2 protein) on a BenchMark ULTRA staining system. Percentages of membranous tumor cell staining at each intensity (0 to 3+) were estimated by board-certified pathologists. A sample is considered to exhibit FGFR2b overexpression and is deemed positive when any moderate (2+) or strong (3+) membrane staining in tumor cells is detected (any 2+/3+). An alternate cut-off at ≥10% of tumor cells at a 2+ or 3+ membrane staining intensity (≥10% 2+/3+) was evaluated. IHC staining for FGFR2b was carried out at Roche Tissue Diagnostics (Oro Valley, AZ). Representative images of membranous staining intensity and percentage of tumor cells exhibiting staining are shown in Figure 1.

PD-L1 expression was assessed by IHC using the PD-L1 assay (Clone 28.8 pharmDx kit; Dako, Agilent Technologies Inc., Santa Clara, CA) and reviewed by trained pathologists from Mosaic Laboratories (CellCarta, Montreal, Canada). PD-L1 expression was quantified using the combined positive score (CPS), defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. Although the result of the calculation can exceed 100, the maximum CPS is defined as 100. Overexpression of PD-L1 was defined as a CPS ≥5 with alternate cut-offs of CPS ≥1 and CPS ≥10 considered in *post hoc* analyses.

Biomarkers collected during routine clinical care followed testing procedures as specified by current treatment guidelines. This included assessment using the following: HER2 [PATHWAY anti-HER2/neu (4B5) rabbit monoclonal antibody (Ventana)] and MMR [anti-mutL homolog 1 (MLH1; ES05) monoclonal antibody, anti-mutS homolog 2 (MSH2; FE11) monoclonal antibody, anti-postmeiotic

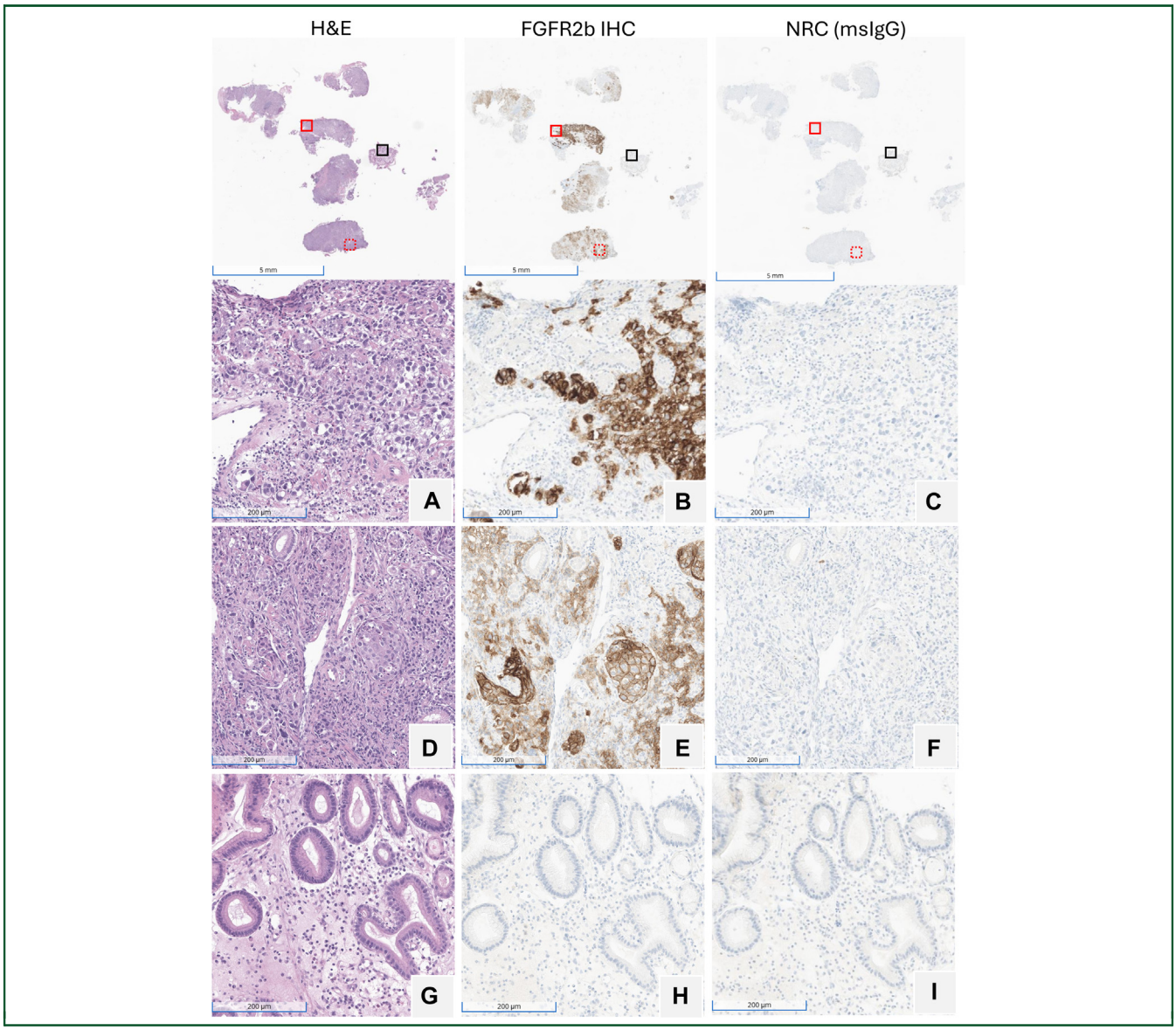

Figure 1. Representative FGFR2b staining of biopsy tissue taken from patients with gastric cancer. The top row displays images at low magnification evaluated with H&E, FGFR2b IHC, and a negative reagent control (mouse IgG). These low-magnification images highlight regions of interest that are further magnified ×40 in images A-I. (A—C). Magnified images from the solid red box. Tumor cells are infiltrating the non-neoplastic gastric body mucosa (A). Tumor cells exhibit moderate to high FGFR2b staining in the membrane and cytoplasm (B). (D—F). Magnified images from the dotted red box. Tumor cells are infiltrating both diffusely and solidly (D). The tumor cells display varying intensities of FGFR2b staining (E). (G—I). Magnified images from the black box. Non-neoplastic gastric mucosa is shown (G), which shows no evidence of staining with FGFR2b (H). FGFR2b, fibroblast growth factor receptor 2b; H&E, hematoxylin—eosin; mIgG, mouse immunoglobulin G; IHC, immunohistochemistry; NRC, negative reagent control.

segregation increased 2 (PMS2; EP51) monoclonal antibody, and anti-mutS homolog 6 (MSH6; EP49) monoclonal antibody (Dako)]. CLDN18.2 [CLDN18 Clone 43-14A (Ventana)] was assessed as previously reported.[25] CLDN positivity was defined as moderate (2+) or strong (3+) staining in ≥75% of tumor cells.

Outcomes and statistical analysis

Analyses were conducted for three groups: (i) all patients meeting inclusion/exclusion criteria with evaluable FGFR2b protein expression ('full cohort') and as *post hoc* analytic subgroups; (ii) all patients from the full cohort with metastatic or unresectable GC/GEJC and tumor samples collected in 2021 or later, i.e. within 1.5 years of study initiation ('subgroup 1'); and (iii) all patients from the full cohort with tumor samples collected >1.5 years from study initiation ('subgroup 2').

Descriptive analyses were carried out to summarize clinical and biomarker characteristics and 1L treatment regimens by FGFR2b status. Real-world OS was calculated as the time from 1L treatment initiation to death, loss to follow-up, or end of study period, whichever occurred first. Patients without a death event were censored at last contact or the end of the study period. OS curves were estimated using the Kaplan—Meier method and evaluated for homogeneity of cohorts using the log-rank test. Univariate and multivariate Cox proportional regression models were

used to estimate HRs and 95% confidence intervals (CIs) for OS. Pre-specified covariates for the multivariable analysis included age (≥70 versus <70 years), sex (male versus female), Eastern Cooperative Oncology Group performance score (PS; ≥1 versus <1), number of metastatic organ sites (≥2 versus <2), prior gastrectomy (yes versus no), alkaline phosphatase [ALP; ≥ upper limit of normal (ULN) versus <ULN], Lauren's classification (diffuse versus intestinal/indeterminant), and type of systemic therapy in 1L (chemotherapy with immunotherapy versus chemotherapy alone, and trastuzumab or other therapy versus chemotherapy alone). Statistical analyses were carried out using SAS Enterprise Guide Version 8.2 (SAS Institute Inc., Cary, NC).

RESULTS

FGFR2b prevalence and biomarker co-expression

A total of 547 GC/GEJC patients who received systematic anticancer therapy between April 2017 and October 2022 were identified for the study. Primary tumor specimens were obtained for these patients through resection ($n = 25$) or biopsy ($n = 522$). The full cohort consisted of 492 patients (89.9%) who met the inclusion/exclusion criteria, had evaluable FGFR2b samples, and had complete clinical data. Of these patients, 15.4% (76/492; 95% CI 12.4% to 19.0%) overexpressed FGFR2b at any 2+/3+ and 4.1% (20/492; 95% CI 2.5% to 6.2%) overexpressed FGFR2b at ≥10% 2+/3+. Of the tumor samples with FGFR2b any 2+/3+, 26.3% (20/76; 95% CI 16.9% to 37.7%) were FGFR2b ≥10% 2+/3+.

There were no differences in patient or tumor characteristics between the FGFR2b any 2+/3+ stratum and the stratum of patients demonstrating FGFR2b protein membranous staining at less than 2+/3+ intensity, i.e. staining at a 1+ intensity or no FGFR2b membranous staining ('FGFR2b 0/1+'), except for time of specimen collection and specimen collection method (Table 1, Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.10532). The estimated prevalence of FGFR2b any 2+/3+ expression was 29.8% (37/124; 95% CI 22.0% to 38.7%) in subgroup 1 (patients with metastatic or unresectable GC/GEJC and specimens collected within 1.5 years of study initiation) compared with 10.4% (38/365; 95% CI 7.6% to 14.2%) in subgroup 2 (patients with specimens collected >1.5 years from study initiation). These trends were similar when stratifying by the alternate cut-off of FGFR2b ≥10% 2+/3+ [11.3% for subgroup 1 (14/124; 95% CI 6.3% to 18.2%) versus 1.6% for subgroup 2 (6/365; 95% CI 0.6% to 3.5%)]. In patients with HER2-negative tumor specimens, the estimated prevalence of FGFR2b any 2+/3+ was 33.0% ($n = 33/100$; 95% CI 23.9% to 43.1%) in subgroup 1 compared with 11.8% (38/321; 95% CI 8.5% to 15.9%) in subgroup 2. These trends were similar when stratifying by the alternate cut-off of FGFR2b ≥10% 2+/3+ [14.0% (14/100; 95% CI 7.9% to 22.4%) versus 1.9% (6/315; 95% CI 0.7% to 4.1%)]. This trend was also observed for PD-L1 and CLDN18.2, with estimated prevalences of 33.1% (41/124) compared with 13.2% (48/365) for PD-L1 CPS ≥5 and 33.9% (42/124) compared with 17.5% (64/365) for CLDN18.2-positive in subgroups 1 and 2, respectively.

The estimated prevalences of actionable biomarkers among patients with FGFR2b any 2+/3+ in the full cohort were 6.6% (5/76) for HER2-positive, 1.3% (1/76) for dMMR, 61.8% (47/76) for CPS ≥1, 11.8% (9/76) for PD-L1 CPS ≥5, 7.9% (6/76) for CPS ≥10, and 25.0% (19/76) for CLDN18.2-positive (Table 1). Of these tumor specimens with FGFR2b any 2+/3+ expression, 53.9% (41/76; 95% CI 42.1% to 65.5%) were negative for the assessed actionable biomarkers using a PD-L1 cut-off of CPS ≥5 (Table 2). Results were similar when removing patients with recurrent disease from the cohort. For the cut-offs of CPS ≥1 and CPS ≥10, 21.1% (16/76; 95% CI 12.5% to 31.9%) and 56.6% (43/76; 95% CI 44.7% to 67.9%) of tumors were negative for the assessed actionable biomarkers (Supplementary Table S2A and B, available at https://doi.org/10.1016/j.esmoop.2025.105322). The estimated prevalences of actionable biomarkers among patients with FGFR2b any 2+/3+ in subgroup 1 were 10.8% (4/37) for HER2-positive, 0% (0/37) for dMMR, 62.2% (23/37) for CPS ≥1, 13.5% (5/37) for PD-L1 CPS ≥5, 10.8% (4/37) for CPS ≥10, and 35.1% (13/37) for CLDN18.2-positive (Table 1). Of these tumor specimens in subgroup 1 with FGFR2b any 2+/3+ expression, 43.2% (16/37; 95% CI 27.1% to 60.5%) were negative for the assessed actionable biomarkers using a PD-L1 cut-off of CPS ≥5 (Table 2). For the cut-offs of CPS ≥1 and CPS ≥10, 18.9% (7/37; 95% CI 8.0% to 35.2%) and 45.9% (17/37; 95% CI 29.5% to 63.1%) of tumors were negative for the assessed actionable biomarkers (Supplementary Table S2A and B, available at https://doi.org/10.1016/j.esmoop.2025.105322).

The estimated prevalences of actionable biomarkers among patients with FGFR2b ≥10% 2+/3+ in the full cohort were 0% (0/20) for HER2-positive, 0% (0/20) for dMMR, 55.0% (11/20) for CPS ≥1, 10.0% (2/20) for PD-L1 CPS ≥5, 10.0% (2/20) for CPS ≥10, and 45.0% (9/20) for CLDN18.2-positive (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105322). Of these tumor samples with FGFR2b ≥10% 2+/3+ expression, 50.0% (10/20; 95% CI 27.2% to 72.8%) were negative for the assessed actionable biomarkers using a PD-L1 cut-off of CPS ≥5 (Table 2; Figure 2A). Results were similar when removing patients with recurrent disease from the cohort. For the cut-offs of CPS ≥1 and CPS ≥10, 35.0% (7/20; 95% CI 15.4% to 59.2%) and 50.0% (10/20; 95% CI 27.2% to 72.8%) of tumors were negative for the assessed actionable biomarkers (Supplementary Table S2A and B, available at https://doi.org/10.1016/j.esmoop.2025.105322). The estimated prevalences of actionable biomarkers among patients with FGFR2b ≥10% 2+/3+ in subgroup 1 were 0% (0/14) for HER2-positive, 0% (0/14) for dMMR, 57.1% (8/14) for CPS ≥1, 14.3% (2/14) for PD-L1 CPS ≥5, 14.3% (2/14) for CPS ≥10, and 42.9% (6/14) for CLDN18.2-positive (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105322). Of these tumor samples with FGFR2b ≥10% 2+/3+ expression in subgroup 1, 50.0% (7/14; 95% CI 23.0% to 77.0%) were

Table 1. Cohort characteristics and actionable biomarkers stratified by FGFR2b status, full cohort and subgroup 1

	Full cohort *N* = 492		Subgroup 1 cohort *N* = 124	
	FGFR2b any 2+/3+ (*n* = 76, 15.4)	FGFR2b 0/1+ (*n* = 416, 84.6)	FGFR2b any 2+/3+ (*n* = 37, 29.8)	FGFR2b 0/1+ (*n* = 87, 70.2)
Sex, male	54 (71.1)	295 (70.9)	26 (70.3)	60 (69.0)
Age at start of 1L, years, mean (SD)	68.0 (12.1)	65.9 (12.5)	67.6 (12.1)	66.2 (13.4)
<70	37 (48.7)	217 (52.2)	17 (45.9)	41 (47.1)
≥70	39 (51.3)	199 (47.8)	20 (54.1)	46 (52.9)
ECOG PS				
0	42 (55.3)	279 (67.1)	15 (40.5)	50 (57.5)
1	27 (35.5)	112 (26.9)	17 (45.9)	25 (28.7)
≥2	7 (9.2)	25 (6.0)	5 (13.5)	12 (13.8)
Primary tumor site				
Stomach	64 (84.2)	362 (87.0)	30 (81.1)	78 (89.7)
GEJ	12 (15.8)	54 (13.0)	7 (18.9)	9 (10.3)
Year of primary tumor specimen collection				
Pre-2018	6 (7.9)	92 (22.1)	0 (0.0)	0 (0.0)
2018	11 (14.5)	80 (19.2)	0 (0.0)	0 (0.0)
2019	8 (10.5)	78 (18.8)	0 (0.0)	0 (0.0)
2020	13 (17.1)	77 (18.5)	0 (0.0)	0 (0.0)
2021	23 (30.3)	51 (12.3)	22 (59.5)	49 (56.3)
2022	15 (19.7)	38 (9.1)	15 (40.5)	38 (43.7)
Primary tumor specimen collection method				
Biopsy	67 (88.2)	400 (96.2)	37 (100.0)	87 (100.0)
Resection	9 (11.8)	16 (3.8)	0 (0.0)	0 (0.0)
Disease status				
Metastatic	62 (81.6)	362 (87.0)	37 (100.0)	86 (98.9)
Unresectable locally advanced	0 (0.0)	11 (2.6)	0 (0.0)	1 (1.1)
Recurrent	14 (18.4)	43 (10.3)	0 (0.0)	0 (0.0)
Number of metastatic organ sites at advanced diagnosis				
0	1 (1.3)	11 (2.6)	0 (0.0)	1 (1.1)
1	54 (71.1)	303 (72.8)	27 (73.0)	65 (74.7)
2	17 (22.4)	85 (20.4)	8 (21.6)	16 (18.4)
≥3	4 (5.3)	17 (4.1)	2 (5.4)	5 (5.7)
Metastatic organs				
Lymph node	45 (59.2)	266 (63.9)	28 (75.7)	61 (70.1)
Peritoneal	35 (46.1)	196 (47.1)	16 (43.2)	44 (50.6)
Liver	28 (36.8)	122 (29.3)	15 (40.5)	24 (27.6)
Lung	6 (7.9)	31 (7.5)	2 (5.4)	6 (6.9)
Bone	3 (3.9)	19 (4.6)	2 (5.4)	4 (4.6)
Other	10 (13.2)	29 (7.0)	4 (10.8)	4 (4.6)
Primary tumor Lauren's classification				
Intestinal	32 (42.1)	158 (38.0)	18 (48.6)	38 (43.7)
Diffuse	41 (53.9)	222 (53.4)	19 (51.4)	44 (50.6)
Indeterminate/unknown	3 (3.9)	36 (8.7)	0 (0.0)	5 (5.7)
Primary tumor Borrmann's classification				
Type 4	16 (21.1)	89 (21.4)	10 (27.0)	23 (26.4)
Non-type 4	60 (78.9)	325 (78.1)	27 (73.0)	64 (73.6)
Type 3	42 (55.3)	202 (48.6)	23 (62.2)	50 (57.5)
Type 2	11 (14.5)	97 (23.3)	3 (8.1)	13 (14.9)
Type 1	1 (1.3)	7 (1.7)	0 (0.0)	1 (1.1)
Type 0	5 (6.6)	17 (4.1)	0 (0.0)	0 (0.0)
Unclassifiable	1 (1.3)	2 (0.5)	1 (2.7)	0 (0.0)
Unknown	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)
Prior surgery for GC/GEJC				
No	62 (81.6)	360 (86.5)	37 (100.0)	86 (98.9)
Yes	14 (18.4)	56 (13.5)	0 (0.0)	1 (1.1)
Perioperative chemotherapy				
No	66 (86.8)	386 (92.8)	37 (100.0)	87 (100.0)
Yes	10 (13.2)	30 (7.2)	0 (0.0)	0 (0.0)
Alkaline phosphatase at initiation of 1L				
ALP < ULN[a]	42 (55.3)	297 (71.4)	19 (51.4)	64 (73.6)
ALP ≥ ULN[a]	34 (44.7)	119 (28.6)	18 (48.6)	23 (26.4)

Continued

Table 1. Continued

	Full cohort N = 492		Subgroup 1 cohort N = 124	
	FGFR2b any 2+/3+ (n = 76, 15.4)	FGFR2b 0/1+ (n = 416, 84.6)	FGFR2b any 2+/3+ (n = 37, 29.8)	FGFR2b 0/1+ (n = 87, 70.2)
Systemic anticancer therapy in 1L				
Chemotherapy with or without platinum agent	65 (85.5)	317 (76.2)	31 (83.8)	55 (63.2)
Chemotherapy with platinum agent and immunotherapy	4 (5.3)	36 (8.7)	2 (5.4)	13 (14.9)
HER2-targeting agents with or without chemotherapy or immunotherapy	5 (6.6)	56 (13.5)	4 (10.8)	19 (21.8)
Other treatment combinations	2 (2.6)	7 (1.7)	0 (0.0)	0 (0.0)
HER2 status				
Positive	5 (6.6)	56 (13.5)	4 (10.8)	20 (23.0)
Negative	71 (93.4)	351 (84.4)	33 (89.2)	67 (77.0)
Missing	0 (0.0)	9 (2.2)	0 (0.0)	0 (0.0)
MMR status				
Deficient	1 (1.3)	15 (3.6)	0 (0.0)	3 (3.4)
Proficient	73 (96.1)	391 (94.0)	37 (100.0)	84 (96.6)
Missing	2 (2.6)	10 (2.4)	0 (0.0)	0 (0.0)
PD-L1 status				
CPS ≥10	6 (7.9)	47 (11.3)	4 (10.8)	20 (23.0)
CPS ≥5	9 (11.8)	81 (19.5)	5 (13.5)	36 (41.4)
CPS ≥1	47 (61.8)	227 (54.6)	23 (62.2)	66 (75.9)
CPS <1	27 (35.5)	186 (44.7)	13 (35.1)	21 (24.1)
Missing	2 (2.6)	3 (0.7)	1 (2.7)	0 (0.0)
CLDN18.2 status				
Positive	19 (25.0)	88 (21.2)	13 (35.1)	29 (33.3)
Negative	55 (72.4)	316 (76.0)	24 (64.9)	57 (65.5)
Missing	2 (2.6)	12 (2.9)	0 (0.0)	1 (1.1)

All values are number of patients or patients' specimen samples (%) unless otherwise indicated. Percentages are calculated based on column totals, i.e. include patients with missing data. Subgroup 1 includes all patients from the full cohort with metastatic or unresectable GC/GEJC and tumor samples collected in 2021 or later, i.e. within 1.5 years of study initiation.

1L, first-line therapy; ALP, alkaline phosphatase; CLDN18.2, claudin 18 isoform 2; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; FGFR2b, fibroblast growth factor receptor 2b; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; PD-L1, programmed death-ligand 1; PS, performance score; SD, standard deviation; ULN, upper limit of normal.

[a]ULN is defined as 322 IU/l if the assay was carried out on or before 15 January 2021 and ULN is defined as 113 mg/dl if the assay was carried out after 15 January 2021.

negative for the assessed actionable biomarkers using a PD-L1 cut-off of CPS ≥5 (Table 2; Figure 2B). For the cut-offs of CPS ≥1 and CPS ≥10, 35.7% (5/14; 95% CI 12.8% to 64.9%) and 50.0% (7/14; 95% CI 23.0% to 77.0%) of tumors were negative for the assessed actionable biomarkers (Supplementary Table S2A and B, available at https://doi.org/10.1016/j.esmoop.2025.105322).

Clinical outcomes by FGFR2b expression

Most patients in the full cohort (382/492) received 1L chemotherapy alone (fluoropyrimidine with or without a platinum agent). Patients with HER2-negative tumors who received chemotherapy alone in 1L (n = 371) had a median follow-up time of 13.0 months with a median OS of 11.5 months (95%

Table 2. Actionable biomarkers in patients with FGFR2b-overexpressing tumors, primary and alternate FGFR2b cut-off values, and PD-L1 cut-off of CPS ≥5, full cohort and subgroup 1

	FGFR2b any 2+/3+		FGFR2b ≥10% 2+/3+	
	Full cohort, n = 76	Subgroup 1, n = 37	Full cohort, n = 20	Subgroup 1, n = 14
HER2+	5 (6.6)	4 (10.8)	0 (0.0)	0 (0.0)
HER2− and dMMR or PD-L1 CPS ≥5	9 (11.8)	5 (13.5)	2 (10.0)	2 (14.3)
HER2−, pMMR or PD-L1 CPS <5, and CLDN18.2-positive	17 (22.4)	11 (29.7)	8 (40.0)	5 (35.7)
Negative for all currently actionable biomarkers	41 (53.9)	16 (43.2)	10 (50.0)	7 (50.0)
Missing one or more actionable biomarkers	4 (5.3)	1 (2.7)	0 (0.0)	0 (0.0)

All values are number of patients or patients' specimen samples (%) unless otherwise indicated. Percentages are calculated based on column totals, i.e. include patients with missing data. Subgroup 1 includes all patients from the full cohort with metastatic or unresectable GC/GEJC and tumor samples collected in 2021 or later, i.e. within 1.5 years of study initiation.

CLDN18.2, claudin 18 isoform 2; CPS, combined positive score; dMMR, mismatch repair deficient; FGFR2b, fibroblast growth factor receptor 2b; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1; pMMR, proficient mismatch repair.

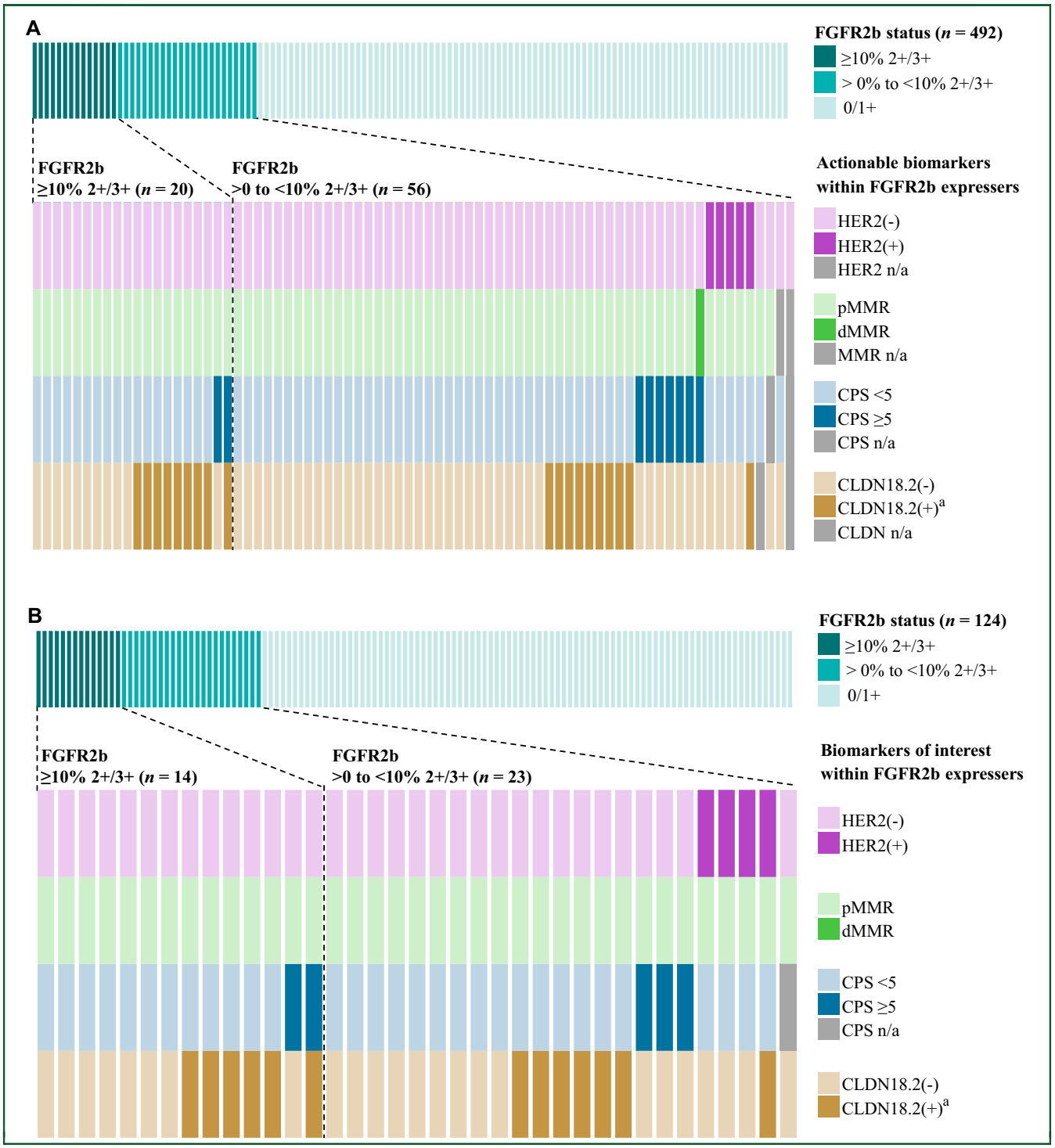

Figure 2. FGFR2b status and FGFR2b any 2+/3+ overlap with actionable biomarkers. Full cohort (A) and subgroup 1 (B). Top row: the vertical bars represent the FGFR2b biomarker status of the primary GC/GEJC tumor for each patient in the cohort. Bottom rows: the vertical stack of bars represents the HER2, MMR, PD-L1, and CLDN18.2 biomarker statuses of the primary GC/GEJC tumor for each patient with FGFR2b expression at any 2+/3+ in the cohort. CLDN, claudin; CPS, combined positive score; dMMR, deficient mismatch repair; FGFR2b, fibroblast growth factor receptor 2 isoform IIIb; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1; pMMR, proficient mismatch repair. [a]Defined as CLDN18.2 ≥75% of tumor cells with 2+ or 3+ staining intensity.

CI 10.0-16.3 months) and 15.3 months (95% CI 13.0-16.8 months) among patients expressing FGFR2b any 2+/3+ (n = 65) and FGFR2b 0/1+ (n = 306), respectively (Figure 3A). Using the alternate cut-off, the median OS were 11.5 months (95% CI 5.9-18.4 months) and 14.8 months (95% CI 12.6-16.5 months) among patients expressing FGFR2b ≥10% 2+/3+ (n = 17) and FGFR2b <10% 2+/3+ or 0/1+ (n = 354), respectively (Supplementary Figure S1A, available at https://doi.org/10.1016/j.esmoop.2025.105322). OS was not estimated for the 39 patients (n = 4 FGFR2b any 2+/3+, n = 35 FGFR2b 0/1+) with HER2-negative tumors who received 1L chemotherapy plus immunotherapy due to the small sample size.

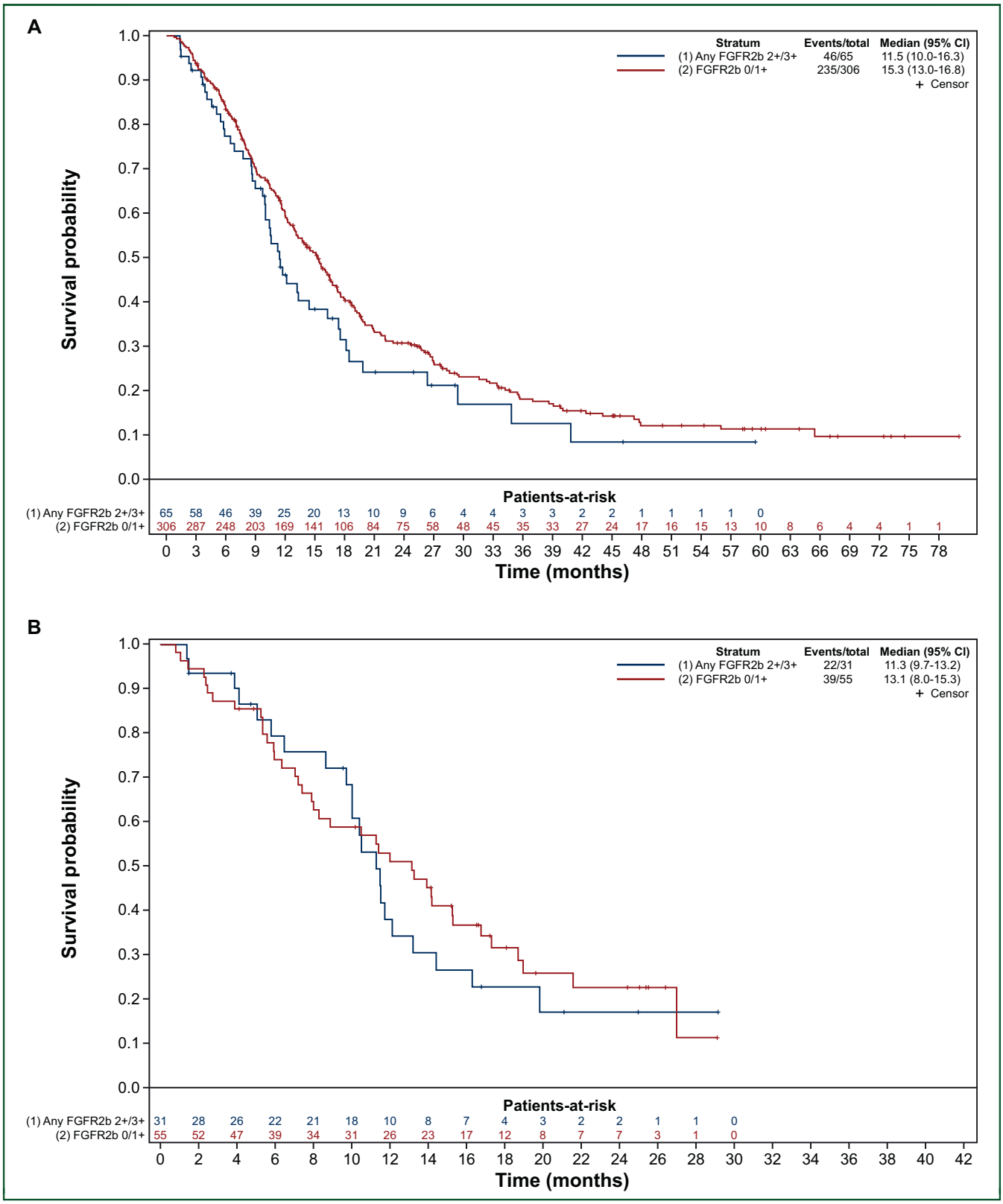

Figure 3. Kaplan–Meier curve for overall survival (OS) by FGFR2b expression status (any 2+/3+ versus 0/1+) in HER2(−) patients who received chemotherapy alone. Full cohort (A) and subgroup 1 (B). Subgroup 1 includes all patients from the full cohort with metastatic or unresectable GC/GEJC and tumor samples collected in 2021 or later, i.e. within 1.5 years of study initiation. CI, confidence interval; FGFR2b, fibroblast growth factor receptor 2b; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2.

In subgroup 1, patients with HER2-negative tumors who received chemotherapy alone in 1L ($n = 86$) had a median follow-up time of 11.4 months with median OS of 11.3 months (95% CI 9.7-13.2 months) and 13.1 months (95% CI 8.0-15.3 months) among patients expressing FGFR2b any 2+/3+ ($n = 31$) and FGFR2b 0/1+ ($n = 55$), respectively (Figure 3B). Using the alternate cut-off, the median OS were 11.5 months (95% CI 4.1-14.4 months) and 11.7 months (95% CI 8.9-14.2 months) among patients expressing FGFR2b ≥10% 2+/3+ ($n = 12$) and FGFR2b <10% 2+/3+ or 0/1+ ($n = 74$), respectively (Supplementary Figure S1B, available at https://doi.org/10.1016/j.esmoop.2025.105322).

No association was seen between FGFR2b overexpression levels and OS in the multivariable regression model (adjusted HR 1.14; 95% CI 0.84-1.55; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105322). Regression results were similar when removing patients with recurrent disease, stratifying by the alternate cut-off of FGFR2b ≥10% 2+/3+, and evaluating subgroup 1 alone.

DISCUSSION

We evaluated the clinicopathological features and clinical outcomes in patients with unresectable, metastatic, or recurrent GC/GEJC by their FGFR2b overexpression status, with FGFR2b positivity defined as any FGFR2b membranous protein expression at a 2+ (moderate) or 3+ (strong) staining intensity. Prevalence of the FGFR2b biomarker at the any 2+/3+ staining intensity in this study was comparable to that seen in the FIGHT phase II clinical trial (NCT03694522),[17] with both studies reporting ∼30% using tissue samples acquired near to study initiation (within 1.5 years and 6 months, respectively), though slightly lower than reported in the FORTITUDE-101 (NCT05052801) prescreening.[19] Many of the patients expressing FGFR2b at any 2+/3+ staining intensity were negative for currently actionable biomarkers assessed and minimal bivariate overlap was seen in the actionable biomarkers. No statistical difference was seen in OS between patients with tumors expressing FGFR2b at any 2+/3+ and those expressing FGFR2b at 0/1+ intensity membranous staining.

A previous study reported that FGFR2b overexpression was associated with histological diffuse type and high N stage,[13] but there were no differences in histological type or lymph node metastasis by FGFR2b status in our cohort. However, we did observe a difference in positivity rate by year of tissue collection. A similar observation has been reported for other biomarkers including HER2[26] and PD-L1.[27] In this cohort, samples collected within 1.5 years of study initiation demonstrated biomarker positivity rates for CLDN18.2 and PD-L1 similar to those in previous reports[9,10,28,29] while specimens collected >1.5 year before study initiation showed lower positivity rates. There may be multiple factors contributing to this phenomenon as well as other variability in biomarker measurements, such as, loss of antigenicity over time,[26] intratumoral biomarker heterogeneity,[30] or other pre-analytical factors unmeasured in this study such as tissue-processing procedures.[31] It is important to note that this was not a study of repeated testing of the same tissue specimens over time, so we cannot determine whether biomarker detection levels change over time or when this phenomenon might begin. However, these and other results suggest that reliable evaluation of biomarkers, including FGFR2b and CLDN18, requires the use of tissue specimens collected within 2 -3 years, as older samples may compromise biomarker detection. This is also aligned with currently ongoing clinical studies which require fresh tumor specimens or archival tissue obtained no >6 months before enrollment for central FGFR2b assessment.[19,23,24]

Importantly, a limited number of tumors with membranous expression of the FGFR2b protein at the 2+ or 3+ staining intensity also express currently actionable biomarkers. The lack of overlap presents an opportunity for including FGFR2b along with other actionable biomarkers in panel testing to best inform treatment options for patients with advanced GC/GEJC. Additionally, the lack of biomarker overlap suggests that an efficacious FGFR2b-targeting therapy may be beneficial for patients who are not eligible for currently available molecular targeting therapies.

We observed no statistical difference in OS by FGFR2b expression. A previous study reported an association between FGFR2b expression, diffuse type histology, and worse prognosis.[13] While diffuse type histology was associated with worse progression in our analysis (adjusted HR 1.43, 95% CI 1.14-1.79; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105322), FGFR2b expression was not (HR 1.14, 95% CI 0.84-1.55). Both estimates were attenuated and had wider CIs in our analysis of patients with tissue collected within 1.5 years of study initiation.

There were some study limitations worth noting. Firstly, the data from this study were obtained from a single-institution, retrospectively, with a limited sample size. Secondly, patients treated with investigational agents, through active clinical trials, in 1L were excluded from the cohort, but patients treated with investigational agents in later lines of therapy were not excluded. This may limit the generalizability of the OS findings. Thirdly, we observed an inverse association between time of specimen collection and estimated prevalences of FGFR2b any 2+/3+, PD-L1 CPS ≥5, and CLDN18.2 positivity. None the less, the tumor specimens collected within 1.5 years of study initiation had prevalence estimates comparable to those previously published, including FGFR2b any 2+/3+ reported in the FIGHT phase II clinical trial,[17] where the tumor tissue collection window was restricted to 6 months before enrollment. Finally, this study only included patients who initiated therapy. If FGFR2b is prognostic of more rapidly progressing disease and worsening health, some FGFR2b-expressing patients might not have been healthy enough to initiate systemic therapy and would not have been included in our study.

Overall, this is the first study to comprehensively characterize the clinicopathological characteristics, including overlap with actionable biomarkers, in FGFR2b-expressing advanced GC/GEJC Japanese patients using methods and definitions similar to two ongoing FGFR2b-targeting phase III clinical trials (NCT05052801 and NCT05111626).[23,24]

FGFR2b is a novel biomarker that identifies a distinct GC/GEJC patient population who may benefit most from an FGFR2b-targeting therapy. This study identified approximately half of the patients with FGFR2b expression at any 2+/3+ staining intensity not being candidates for currently approved targeted therapies. This presents an opportunity for future efficacious treatment options in patients expressing FGFR2b in advanced GC/GEJC.

FUNDING

This work was supported by research funding from Amgen (no grant number).

DISCLOSURE

YA: speaker payment or honoraria from Guardant Health Inc. IN: other financial/non-financial interests from Ono and Chugai Pharmaceutical Co Ltd, MSD. TH: speaker payment or honoraria from CytoGen Inc. and Takata Pharmaceutical. YN: grants from Seagen Inc., Genomedia Inc., Guardant Health AMEA, Guardant Health Inc., Tempus Labs, Roche Diagnostics KK, Daiichi Sankyo Co Ltd, and Chugai Pharmaceutical Co Ltd; speaker payment or honoraria from Guardant Health Pte Ltd, MSD KK, Eisai Co Ltd, Zeria Pharmaceutical Co Ltd, Miyarisan Pharmaceutical Co Ltd, Merck Biopharma Co Ltd, CareNet Inc., Hisamitsu Pharmaceutical Co Inc., Taiho Pharmaceutical Co Ltd, Daiichi Sankyo Co Ltd, Chugai Pharmaceutical Co Ltd, Becton Dickinson and Company, and Guardant Health Japan Corp; participation on a data safety monitoring board/advisory board from Guardant Health Pte Ltd, Natera Inc., Roche Ltd, Seagen Inc., Premo Partners, Daiichi Sankyo Co Ltd, Takeda Pharmaceutical Co Ltd, Exact Sciences Corporation, and Gilead Sciences Inc. AK: grant or contract from AstraZeneca; consulting fees from Zymeworks and Merck & Co Inc.; speaker payment or honoraria from Daiichi Sankyo, Eli Lilly, Ono Pharmaceutical Co Ltd, Bristol Myers Squibb, Taiho Pharmaceutical Co Ltd, and Merck Serono Biopharma. SM: honoraria from Taiho Pharmaceutical Co Ltd, Chugai Pharmaceutical Co Ltd, Eli Lilly Co Ltd, Merck Biopharma Co Ltd, MSD KK, and Roche Ltd. DK: grants to institution from Ono, MSD, Novartis, Servier, Janssen, IQVIA, Syneoshealth, CIMIC, and Cimicshiftzero; speaker payment or honoraria from Takeda, Chugai, Lilly, MSD, Ono, Seagen, Guardant Health, Eisai, Taiho, Bristol Myers Squibb, Daiichi Sankyo, Pfizer, Merckbiopharma, and Sysmex. YK: grants to institution from Taiho, Astellas, Lilly, Takeda, Daiichi Sankyo, AstraZeneca, Boehringer Ingelheim, Chugai, Genmab, Incyte, AbbVie, Amgen, Merck, Hengrui, Novartis, and Ono Pharmaceutical; consulting fees from Incyte, Takeda, Boehringer Ingelheim, Amgen, and AbbVie; speaker payment or honoraria from Taiho, Lilly, and Takeda. HB: speaker payment or honoraria from Ono Pharmaceutical and Taiho Pharmaceutical. TKo: research grants from Beigene Ltd, AstraZeneca, Chugai Pharmaceutical, Parexel International, Shionogi, Taiho Pharmaceutical, Astellas Amgen BioPharma, MSD, and Ono Pharmaceutical; honoraria for lectures from Ono Pharmaceutical, Covidien Japan, MSD, Boehringer Ingelheim, Kyowa Kirin, EA Pharma, Bristol Myers Squibb, 3H Clinical Trial, AstraZeneca, Taiho Pharmaceutical, LiangYiHui Healthcare | Oncology News China, Japanese Society of Pharmaceutical Health Care and Sciences, Oncolys BioPharma, and BMS; participation in advisory boards for Ono Pharmaceutical, Taiho Pharmaceutical, Japanese Society of Pharmaceutical Health Care and Sciences, and LiangYiHui Healthcare | Oncology News China; participation in data safety monitoring board for NPT Co Ltd. TY: grants to institution from Amgen KK, Bristol Myers Squibb KK, Chugai Pharmaceutical Co Ltd, Daiichi Sankyo Co Ltd, Eisai Co Ltd, FALCO biosystems Ltd, Genomedia Inc., Medical & Biological Laboratories Co Ltd, Merus NV, Molecular Health GmbH, MSD KK, Nippon Boehringer Ingelheim Co Ltd, Ono Pharmaceutical Co Ltd, Pfizer Japan Inc., Roche Diagnostics KK, Sanofi KK, Sysmex Corp, Taiho Pharmaceutical Co Ltd, and Takeda Pharmaceutical Co Ltd; speaker payment or honoraria from Chugai Pharmaceutical Co Ltd, Takeda Pharmaceutical Co Ltd, Merck Biopharma Co Ltd, Bayer Yakuhin Ltd, Ono Pharmaceutical Co Ltd, and MSD KK. KS: research funding to institution from Astellas Pharma, Ono Pharmaceutical, Daiichi Sankyo, Taiho Pharmaceutical, Chugai Pharma, MSD, Amgen, Eisai, PRA Health Sciences, and Syneos Health; consulting fees for advisory roles from Bristol Myers Squibb, Takeda Pharmaceuticals, Ono Pharmaceutical, Novartis, Daiichi Sankyo, Amgen, Boehringer Ingelheim, MSD, Astellas, Guardant Health Japan, Janssen, AstraZeneca, Zymeworks Biopharmaceuticals Inc., ALX Oncology Inc., and Bayer; lecture fees from Bristol Myers Squibb, Ono Pharmaceutical, Janssen, and AstraZeneca; fees for educational edits from Eli Lilly and Astellas. SLR, JH, REY, CHC, SY, SR, HH, EF: employee and stockholder of Amgen Inc.

ACKNOWLEDGEMENTS

Writing support from Tim Peoples, MA, ELS (contractor to Amgen Inc.).

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