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Tumour Review

FGFR2b protein overexpression: An emerging biomarker in gastric and gastroesophageal junction adenocarcinoma

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ABSTRACT

Gastric and gastroesophageal junction cancer (G/GEJC) is a heterogeneous and complex disease characterized by histologic and molecular subtypes. Although a growing number of treatments have improved survival outcomes in the advanced setting, the greatest therapeutic benefits are observed among patient populations eligible for biomarker-directed therapies. Fibroblast growth factor receptor 2 isoform IIIb (FGFR2b) is an emerging biomarker under phase 3 clinical investigation for G/GEJC with the novel monoclonal antibody bemarituzumab. FGFR2b protein overexpression in gastric cancer, together with its function in various oncogenic signaling pathways, makes it an attractive target for precision medicine and thereby has gained clinical interest for its potential prognostic role in G/GEJC. Thus, to explore the potential role of FGFR2b, this narrative review summarizes the role and mechanism of FGFR2b in advanced G/GEJC, describes appropriate detection methodology for FGFR2b protein overexpression, and discusses future considerations for precision treatment in advanced G/GEJC with respect to FGFR2b protein overexpression and the emergence of other biomarkers.

Introduction

Gastric cancer is the fifth leading cause of cancer-related mortality worldwide, accounting for an estimated 660,000 deaths annually with disease prevalence two-fold higher in men than in women [1]. Geographical incidence varies considerably, with the highest rates observed in Eastern Asia and Eastern Europe relative to Western regions [1]. Disease development may be the result of cellular changes from chronic gastritis, with *Helicobacter pylori* and gastroesophageal reflux disease being implicated as key risk factors for gastric and gastroesophageal junction tumors, respectively [2,3]. Although survival rates have improved over the past few decades owing to earlier diagnosis and treatment, the prognosis for patients with advanced disease remains poor, with 5-year relative survival for distant metastatic disease ranging from approximately 3% to 7% depending on geographic location [4–6].

Gastric cancer is predominately classified as adenocarcinoma (95%) by histopathology and possesses distinct histologic subtypes according to the Lauren (intestinal or diffuse) and World Health Organization classifications [2,7,8]. Four molecular subtypes of gastric cancers—chromosomal instability (CIN), Epstein-Barr virus (EBV) positive, genomically stable (GS), and microsatellite instability (MSI)—have been identified by The Cancer Genome Atlas (TCGA) Research Network, and the Asian Cancer Research Group offers a further classification with 4 subgroups, including MSI high (MSI-H), epithelial mesenchymal transition (EMT), epithelial/tumor protein 53 (TP53) active, and epithelial/TP53 inactive; however, with the exception of MSI, these groups have limited clinical use [9,10].

Until more recently, therapy advancements in advanced gastric and gastroesophageal junction cancer (G/GEJC) have been challenging owing to the inherent complex and heterogeneous nature of the disease [11]. Systemic chemotherapy remains the standard of care (SOC) for the first-line treatment of G/GEJC, with regional preferences in chemotherapeutic choice [12–15]; however, clinical studies evaluating specific G/GEJC subpopulations have led to the inclusion of precision therapies

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in SOC regimens (Supplemental Table 1) [16–21]. In general, G/GEJC treatment guidelines recommend fluoropyrimidine plus platinum-based chemotherapy backbones for most patients regardless of biomarker status; however, precision therapies may be added depending on the patient's biomarker profile [13–15]. For patients with human epidermal growth factor receptor 2 (HER2)–positive disease, trastuzumab with pembrolizumab in combination with fluoropyrimidine- and oxaliplatin-based chemotherapy is recommended; whereas, for HER2-negative disease, nivolumab or pembrolizumab may be added to chemotherapy [13–15,17,19–21]. More recently, Claudin 18.2 (CLDN18.2) has emerged as a targetable biomarker with a variety of monoclonal antibodies, bispecific antibodies, antibody-drug conjugates (ADCs), and chimeric antigen receptor T-cell (CAR T) therapies being investigated in clinical trials [22–24]. Phase 3 evaluations of the monoclonal antibody zolbetuximab have demonstrated clinical benefit in combination with chemotherapy in patients with locally advanced unresectable or metastatic HER2-negative CLDN18.2-positive G/GEJC, leading to recent regulatory approvals [22,23,25,26].

The addition of precision therapies to SOC chemotherapy regimens are based on positive biomarker detection of predictive markers, such as HER2, programmed cell death ligand 1 (PD-L1), CLDN18.2, and MSI-H/mismatch repair deficient (MSI-H/dMMR) [12–15,22,23]. Although inclusion of these therapies into the SOC has improved survival outcomes in the advanced setting [16,17,20,21] therapeutic benefit is currently confined to limited patient populations that are positive for routinely tested predictive markers: HER2 (20%–22% prevalence), PD-L1 (30%–60%), MSI-H (6%–23%), and CLDN18.2 (33%–38%; Supplemental Table 2) [9,10,12,13,22,23,27–33].

Fibroblast growth factor receptor 2 isoform IIIb (FGFR2b) is a tyrosine kinase receptor that has emerged as a targetable biomarker of interest, observed in approximately 38% of patients with advanced G/GEJC (Supplemental Table 2) [34]. Ligand-specific binding to FGFR2b can initiate downstream activation of oncogenic signaling pathways, leading to cellular proliferation and tumor growth, angiogenesis, and dissemination, including within G/GEJC tissue [35,36]. FGFR2b as a transmembrane protein is also a distinct target from FGFR2 aberrations (fusions, rearrangements, and mutations) which are established predictive biomarkers for cholangiocarcinoma and urothelial cancer [35,37,38]. In G/GEJC, *FGFR2* gene amplification is uncommon and is present in a subset of patients with FGFR2b protein overexpression; however, it is not always observed in the presence of FGFR2b protein overexpression [39]. Overexpression of an oncogene not associated with detectable gene amplification has been observed in other cancer types and may be due to overactivation of the paternally and or maternally derived alleles of the gene [40]. Together, these features have supported FGFR2b as a potential therapeutic target in G/GEJC.

Subsequently, the predictive capacity of FGFR2b protein overexpression using immunohistochemistry (IHC) is being investigated for targeted therapy with the humanized FGFR2b monoclonal antibody bemarituzumab. Evaluation of bemarituzumab in the FGFR2b biomarker-based phase 2 randomized, double-blind, placebo-controlled FIGHT trial [41] and ongoing phase 3 FORTITUDE studies (NCT05052801 and NCT05111626) looks to expand treatment options for patients with advanced G/GEJC. As clinical development progresses, there is a growing interest among clinicians and pathologists alike to further understand FGFR2b as an emerging biomarker. To this end, in this narrative review we summarize the role and mechanism of disease of FGFR2b in advanced G/GEJC, including the mechanistic pathway, prevalence, clinicopathologic characteristics, and prognostic understanding. Appropriate detection methodology for FGFR2b protein overexpression is also described, as well as future considerations for precision treatment in the evolving G/GEJC landscape.

Structure and function of FGFR2b

The FGF/FGFR intracellular pathway plays an important role in controlling cell growth, proliferation, differentiation, angiogenesis, and survival [42]. During embryonic development, this pathway is associated with morphogenesis; whereas, in adults, its role is focused on nervous system control, tissue repair, wound healing, and tumor angiogenesis [42]. Within the FGFR family, four distinct genes (*FGFR1–4*) give rise to tyrosine kinase receptors that are activated upon binding of one of 23 different ligands and stabilized by heparan sulfate proteoglycan [36,42,43]. Ligand-induced FGFR dimerization then leads to fibroblast growth factor receptor substrate 2 (FRS2) phosphorylation within the intracellular tyrosine kinase domain, resulting in downstream activation of the mitogen-activated protein kinase and the phosphoinositide-3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway (Fig. 1**A**) [36,42].

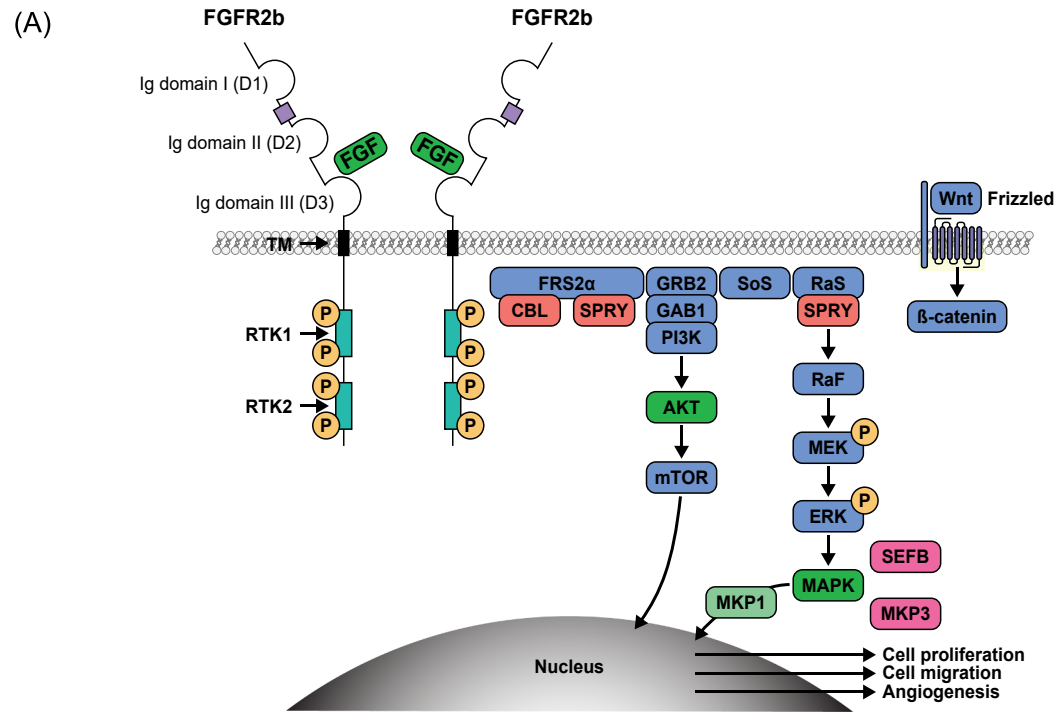
FGFRs comprise a cytoplasmic domain, a single transmembrane domain, and an extracellular ligand-binding domain, which is composed of three immunoglobulin-like domains (D1–D3). FGFR isoforms are generated by alternative splicing of exons 8 and 9 on D3 of the *FGFR2* gene. Encoding of the C-terminal of D3 by exon 8 gives rise to the IIIb isoform (FGFR2b), whereas encoding by exon 9 gives rise to the IIIc isoform (FGFR2c) **(**Fig. 1**B)** [35,42]. FGFR isoforms exhibit various binding specificities for different FGF ligands. While other FGFRs and their isoforms bind to an array of FGF ligands, FGFR2b binds to a uniquely restricted subset of keratinocyte growth factor (KGF) ligands (FGFs 3, 7, 10, 22; Fig. 1**C**) [35,36,42,44–46].

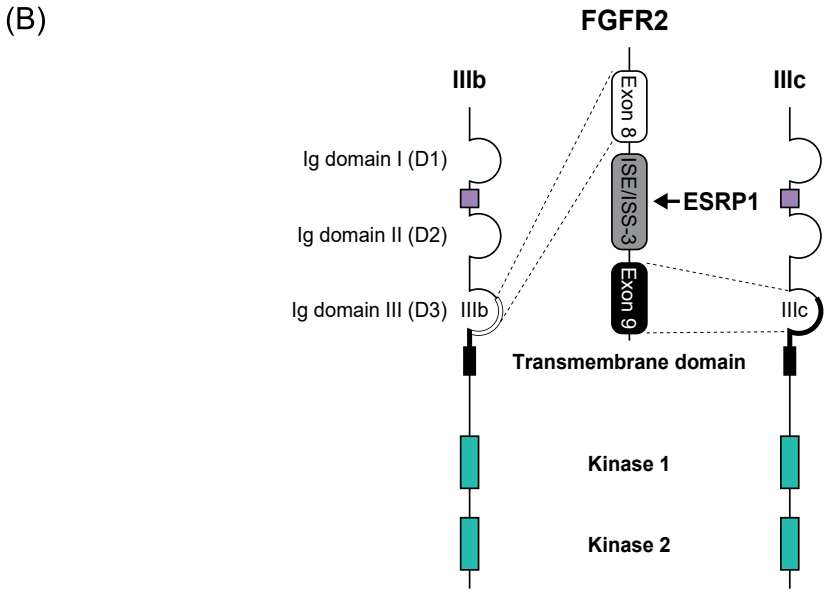
Activation of FGF7 results in FGFR2b degradation and cell proliferation, whereas that of FGF10 promotes cell migration and receptor recycling [47]. FGF10–induced intracellular phosphorylation of tyrosine (Y) 734 on FGFR2b leads to PI3K and SH3 domain-binding protein 4 (SH3BP4) recruitment, a complex important for FGFR2b recycling and response. Thus, aberrations in FGFR2b signaling and endocytosis may be associated with cancer migration and invasion in response to FGF10 ligand binding [47].

FGFR2b and role in disease

Dysregulated FGF/FGFR signaling is involved in the development and progression of many cancer types, driven by genomic alterations in FGFRs, including gene amplification, mutation, chromosomal translocation/fusion, and receptor protein overexpression [45,48,49]. FGFR2 signaling specifically has been shown to promote cell proliferation, invasion, migration, and disease progression through the down regulation of thrombospondin4 via the PI3K/AKT/mTOR pathway [50]. Receptor gene amplification can lead to supraphysiologic receptor protein overexpression, and FGFR2 overexpression is associated with altered C-terminal splicing, which may promote receptor accumulation [45].

Selective disruption of the FGFR2b isoform leads to lethal effects in the lung, limbs, and other organs during embryo development [42] and to disruptions in the maintenance of alveolar epithelial type 2 cells in the lung during homeostasis and delays lacrimal gland regeneration in adults. [51,52]. Deregulation of FGFR2b is also associated with skeletal disorders during development and with ligand-induced FGFR2b signaling in tumor cells [47]. Selectively targeting the FGFR2b protein presents an opportunity to interrupt cancer cell proliferation while minimizing potential adverse effects, such as phosphate imbalances, fatigue, diarrhea, and various ocular or dermatologic toxicities associated with the disruption of signaling via other members of the FGFR family [43,53]. FGFR2b is primarily expressed in epithelial cells within normal gastric mucosa at low levels, whereas overexpression is observed in approximately 38% of G/GEJCs [34,35,42,54]. The FGFR2c isoform is primarily expressed in mesenchymal cells [35,42,54]. Activation of EMT is associated with loss of FGFR2b expression in FGFR-resistant SNU-16 gastric cell lines in which the FGFR2b isoform dominates [55]. It has been suggested that loss of FGFR2b expression is associated with the activation of FGFR2c expression in prostate and bladder cancer and potentially metastatic disease [35,56,57]. It also has been suggested that the switch from FGFR2b to FGFR2c owing to EMT increases the risk





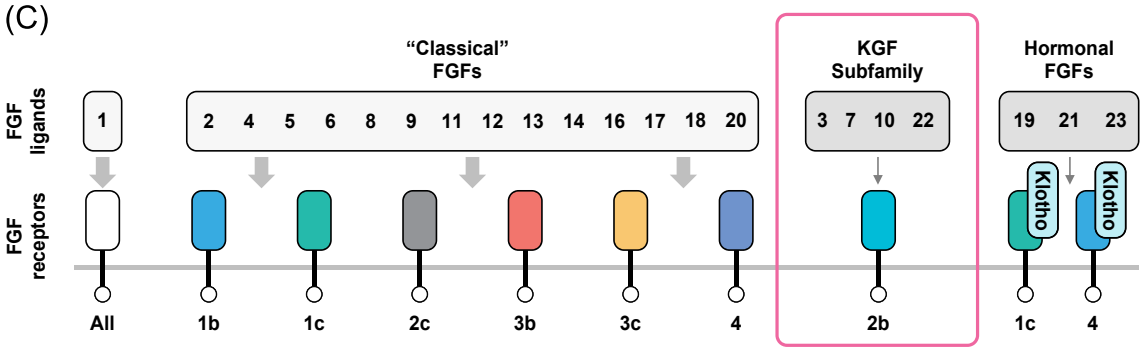


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Fig. 1. FGFR2b signaling pathway, isoforms, and specificity. (A) Ligand binding and homodimerization activate downstream signaling cascades, including the PI3K/AKT/mTOR, RAS/MAPK, and Wnt/β-catenin pathways that function in cell proliferation, migration, and angiogenesis [36,42,44]. (B) Alternative splicing of the C-terminal of the Ig domain III of FGFR2 determines the specific ligands for each FGFR2 variant.[35] The two major isoforms include the FGFR2 IIIb and IIIc isoforms [42]. (Reproduced from Ishiwata T. Role of fibroblast growth factor receptor-2 splicing in normal and cancer cells. Front Biosci 2018;23:626–639. Copyright (1997–2018) IMR Press.) (C) FGF ligands bind select FGFRs with strong activation. FGFR2b is selectively bound by the KGF subfamily with strong activation [35,46]. AKT, protein kinase B; CBL, Casitas B lineage lymphoma; D, domain; ERK, extracellular signal-regulated kinase; ESRP1, epithelial splicing regulatory protein 1; FGF, fibroblast growth factor; FGFR2, FGF receptor 2; FGFR2b, FGFR2 isoform IIIb; FRS2α, FGFR substrate 2α; GAB1, growth factor receptor bound protein-2 – associated-binding protein 1; GRB2, growth factor receptor bound protein-2; Ig, immunoglobulin; ISE/ISS-3, intronic splicing enhancer/intronic splicing silencer-3; KGF, keratinocyte growth factor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; MKP1, mitogen-activated protein kinase phosphatase 1; MKP3, mitogen-activated protein kinase phosphatase 3; mTOR, mammalian target of rapamycin; P, phosphate; PI3K, phosphoinositide 3-kinase; RaF, rapidly accelerated fibrosarcoma proto-oncogene, serine/threonine kinase; RaS, rat sarcoma; RTK, receptor tyrosine kinase; SEFB, SAM-dependent methyltransferase; SoS, son of sevenless; SPRY, sprouty protein; TM, transmembrane; Wnt, wingless-related integration site.

of resistance to anti-FGFR2b antibody [58]; however, further research is needed to elucidate the potential mechanism.

Clinical characteristics and prognostic utility of FGFR2b in gastric cancer

Limited evidence suggests that FGFR2b protein expression is a marker of poor prognosis and clinicopathologic features (Supplemental Table 3) [59–63]. In other cases, protein overexpression was not a significant independent prognostic factor for disease-specific survival in gastric cancer despite observed associations with less favorable clinicopathologic features, such as diffuse gastric cancer subtype [60,64]. Further studies found no association with poor outcomes and in one instance, observed an association with positive outcomes [61,62,65,66].

Interpretation of study findings has been complicated by the absence of standardized IHC detection methodology (eg, use of various antibodies possessing different specificities) and variability in IHC scoring approaches (eg, membranous versus cytoplasmic staining) and protein expression cutoffs [39,59,60,62,67,68]. Additionally, due to tissue sample quality (eg, age of tissue, number of tissue samples per patient case) and scoring methodology, the frequency of FGFR2b in the studied patient populations can vary widely (range, 3%–38%), and the total number of FGFR2b overexpressors available for analysis in historical studies has been low [34,54,59,60]. Progress to address this gap was published in the largest global assessment to date evaluating the prevalence of FGFR2b protein overexpression in gastric cancers, wherein 3782 fresh or recently obtained (<180 days) tumor samples collected from patients across 37 countries were centrally tested using a validated assay [34]. In this study, global prevalence of FGFR2b protein overexpression (any 2+/3+ tumor cell staining) was observed in approximately 38% of patients; with a cutoff of ≥10% 2+/3+ tumor cell staining, prevalence was approximately 16%. Prevalence remained consistent across geographic regions and key patient and sample characteristics [34].

Previous studies indicate that the correlation of high FGFR2 protein expression with poor survival was specific in only diffuse gastric cancer and was associated with peritoneal metastasis [61,64,69]. In a meta-analysis of 10 studies of Asian patients with advanced gastric cancer, FGFR2 protein overexpression (detected by either FGFR2b-specific or pan-FGFR2 antibodies) correlated with tumor invasion (odds ratio [OR]=2.63, $P<0.0001$), higher rates of lymph node metastasis (OR=1.87, $P<0.0001$), advanced stage (OR=1.78, $P<0.03$), worse survival outcomes (hazard ratio=1.40, $P<0.00001$), and poor prognoses [70]. Similarly, data from Ahn et al found FGFR2b overexpression to be significantly more frequent with the diffuse type (77%, $P=0.01$) and advanced-stage disease (37%, $P=0.006$) [59]. Conversely, in a study of patients with G/GEJC from central Europe, FGFR2 protein overexpression did not correlate with patient survival except in the diffuse type [71]. In this study, intestinal type gastric cancer (62%) was more prevalent than the diffuse type (25%). In summary, limited evidence suggests FGFR2b protein overexpression as a prognostic biomarker in advanced gastric cancer and warrants further investigation across international cohorts.

Clinical utility of FGFR2b biomarker detection

Bemarituzumab is a first-in-class, humanized, afucosylated IgG1 monoclonal antibody that blocks FGFR2b signaling via competitive binding inhibition of FGF ligands and evokes increased antibody-dependent cell-mediated cytotoxicity against FGFR2b-overexpressing gastric tumor cells [41,72]. The potential clinical benefit of bemarituzumab in patients with FGFR2b-selected G/GEJC has been demonstrated in phase 1 and 2 studies [39,41,53], and confirmatory phase 3 studies are currently underway (NCT05052801, NCT05111626).

Bemarituzumab with modified infusional 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) was evaluated in FIGHT, a phase 2 randomized, placebo-controlled trial in patients with advanced HER2-negative G/GEJC [39,41]. In this study, patients were screened and prospectively enrolled based on positive FGFR2b protein overexpression as assessed by IHC (defined as membranous staining of 2+ to 3+ in >0% of tumor cells) or *FGFR2* amplification via next-generation sequencing of plasma circulating tumor DNA (ctDNA). At baseline, 96% of patients had overexpression of FGFR2b; however, only 26 (17%) exhibited *FGFR2* gene amplification [39]. Moreover, in a post hoc analysis of the phase 2 trial, patients with FGFR2b protein overexpression, irrespective of *FGFR2* gene amplification, benefited from bemarituzumab [39]. Together, these phase 2 learnings informed the phase 3 trial decision to base biomarker selection of patients on FGFR2b protein overexpression only [39,41].

The discrepancies in FGFR2b protein overexpression compared with ctDNA-based *FGFR2* amplification levels observed in FIGHT have also been highlighted by other studies using tissue-based in situ hybridization (ISH)/fluorescence in situ hybridization (FISH) methodology for *FGFR2* amplification analyses [54,59,60,73–75]. Yashiro et al reported a greater number of cases positive for FGFR2b overexpression using IHC (2+ or 3+ staining) compared with *FGFR2* gene amplification using FISH [54]. Several other studies compared *FGFR2* amplification using FISH versus IHC and concluded FISH should not be substituted for IHC detection because of the high probability of false negatives due to intratumoral heterogeneity and low Pearson correlation coefficients [73,74]. Among evaluable G/GEJC cases in a study examining the relationship between *FGFR2* amplification and expression, 61% of 176 cases were positive for FGFR2 overexpression via IHC, whereas only 15% of 140 cases were positive for *FGFR2* amplification via FISH [75]. Similarly, Ahn et al observed greater detection of FGFR2b protein overexpression compared with *FGFR2* amplification, although increased IHC staining intensity appeared to correlate with greater levels of amplification via FISH [59]. The evidence therefore demonstrates the evaluation of protein overexpression as an appropriate method to identify patients for FGFR2b-targeted therapy.

An evaluation of a biomarker-enriched subgroup has the potential to further identify select patients with G/GEJC for whom anti-FGFR2b therapy may be of benefit [41]. The phase 2 FIGHT trial also explored trial outcomes for a prespecified subgroup of patients with FGFR2b overexpression in at least 10% of tumor cells [39,41]. In FIGHT, 59.7% of patients treated with bemarituzumab-mFOLFOX6 (n=77) and 66.7% of patients in the placebo arm (n=78) had overexpression of FGFR2b in

≥10% of tumor cells [41]. After a minimum follow-up of 2 years, bemarituzumab-mFOLFOX6 showed a clinically meaningful benefit compared with placebo-mFOLFOX6, with improvements in progression-free survival and overall survival more pronounced in the FGFR2b ≥10% subgroup (Fig. 2). Among the FGFR2b ≥10% subgroup, overall survival for the bemarituzumab-mFOLFOX6 arm (24.7 months) was more than double that of the placebo-mFOLFOX6 arm (11.1 months) [41]. Overall, clinical findings to date support FGFR2b protein overexpression as an important biomarker in predicting response to anti-FGFR2b therapy with bemarituzumab in patients with HER2-negative G/GEJC [41].

FGFR2b IHC detection methodology

In the FIGHT and ongoing FORTITUDE clinical studies in G/GEJC, the FGFR2b selection of patients has been based on IHC via the VENTANA FGFR2b (FPR2-D) RxDx Assay (for investigational use only, Roche Diagnostics Solutions, Tucson, AZ, USA). This assay uses a mouse monoclonal antibody (FPR2-D clone) to detect the FGFR2b protein by binding within the extracellular domain. The IHC assay is performed on formalin-fixed, paraffin-embedded G/GEJC tumoral tissue and exhibits a partial or complete membrane staining pattern. The FPR2-D antibody has demonstrated high sensitivity and specificity in detecting the expression of FGFR2b rather than other isoforms, with the level of FGFR2b expression ranging from 0 to 3+, as classified by staining intensity (Fig. 3) [34,68]. Evaluation of the investigational VENTANA FGFR2b (FPR2-D) RxDx Assay and the highly specific antibody FPR2-D, paired with an established staining protocol, may offer a standardized approach in patient selection for bemarituzumab therapy [34,68].

Future considerations

As the number of clinically relevant biomarkers in G/GEJC continues to grow, comprehensive biomarker profiling provides valuable insight in assessing treatment options and supports the opportunity for further research into the overlap of FGFR2b with other biomarkers in gastric cancer. In a study of 176 Japanese patients with gastric cancer, including 16 with GEJC, no association was observed between FGFR2 and HER2 overexpression status, with approximately one-third of HER2-positive cases also being positive for FGFR2 and vice versa [67]. However, this study used antibodies targeting both FGFR2 IIIb and IIIc isoforms with IHC staining and scoring methodology that differ from the one used in other phase 2 and 3 clinical trials [39,67]. In an IHC analysis, overlap was observed in gastric tumor samples with positive FGFR2b (staining intensity ≥2) and PD-L1 (>1%) expression, such that 60% of patients who were FGFR2b positive were also PD-L1 positive [76]. A Japanese study using the validated Ventana FGFR2b (FPR2-D clone) assay reported FGFR2b protein expression (any 2+/3+ staining) in advanced or metastatic G/GEJC HER2-negative tumor samples to overlap by 16% for PD-L1 combined positive score ≥5 and 36% for CLDN18.2 expressed in ≥75% of tumor cells [77]. In this same study, approximately 40% of FGFR2b-positive tumors did not express other currently actionable biomarkers. Further investigations are required to evaluate the overlap of FGFR2b protein overexpression with other

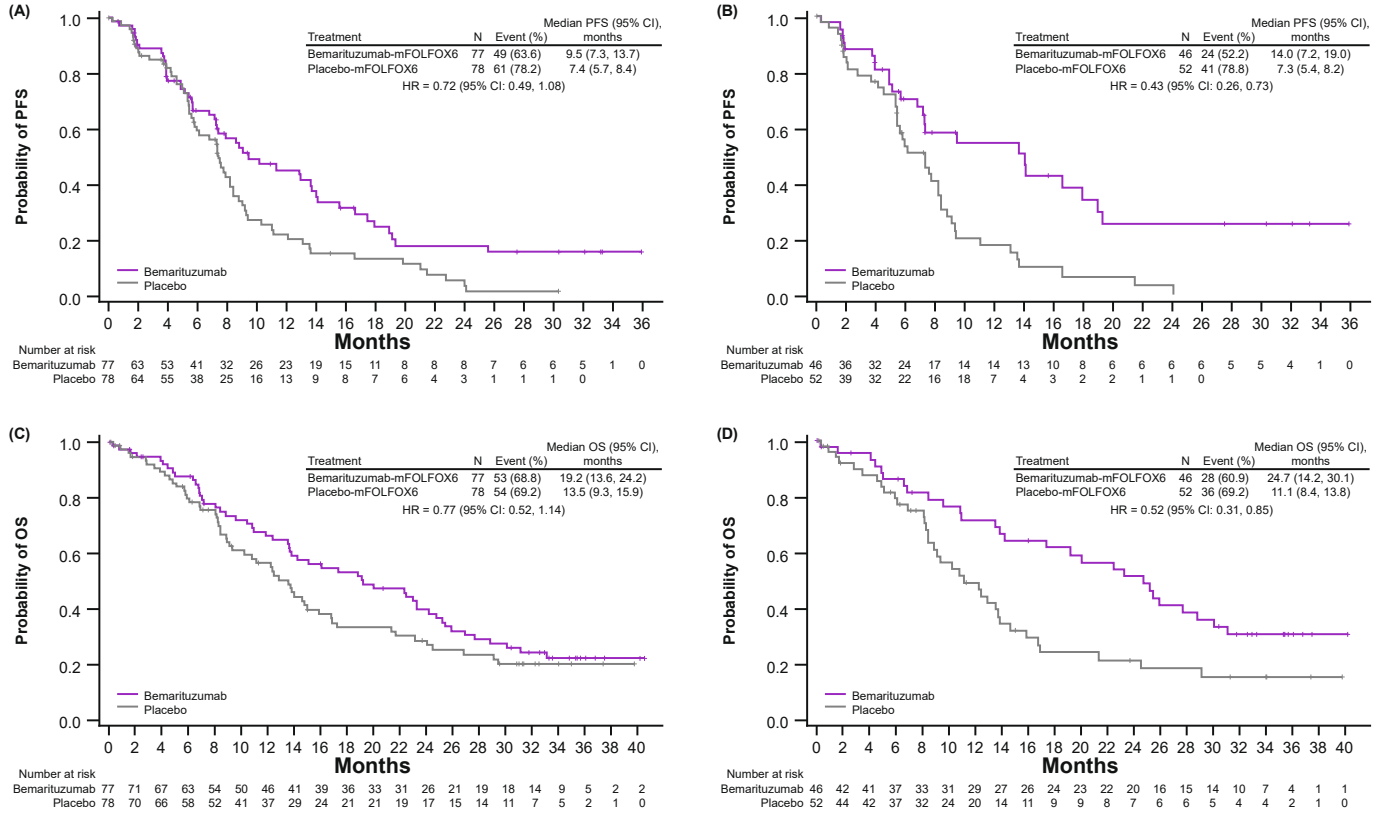

Fig. 2. Survival outcomes in patients with locally advanced/metastatic G/GEJC treated with bemarituzumab-mFOLFOX6 versus placebo-mFOLFOX6. (A) KM curve of PFS in the ITT population.[a] (B) KM curve of PFS in the FGFR2b ≥10% subgroup. (C) KM curve of OS in the ITT population.[a] (D) KM curve of OS in the FGFR2b ≥10% subgroup [41]. FGFR2b, fibroblast growth factor receptor 2 IIIb isoform; G/GEJC, gastric and gastroesophageal junction cancer; HR, hazard ratio; ITT, intention-to-treat; KM, Kaplan-Meier; mFOLFOX6, modified infusional 5-fluorouracil, leucovorin, and oxaliplatin; OS, overall survival; PFS, progression-free survival. [a]The ITT population included all patients who underwent randomization. The Cox proportional hazards model, with adjustment for randomization stratification factors, was used to calculate HRs and 95% CIs. Vertical bars show censoring. (Reproduced from Wainberg ZE, et al. Bemarituzumab as first-line treatment for locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma: final analysis of the randomized phase 2 FIGHT trial. Gastric Cancer 2024;27:558–570. https://creativecommons.org/licenses/by/4.0/).

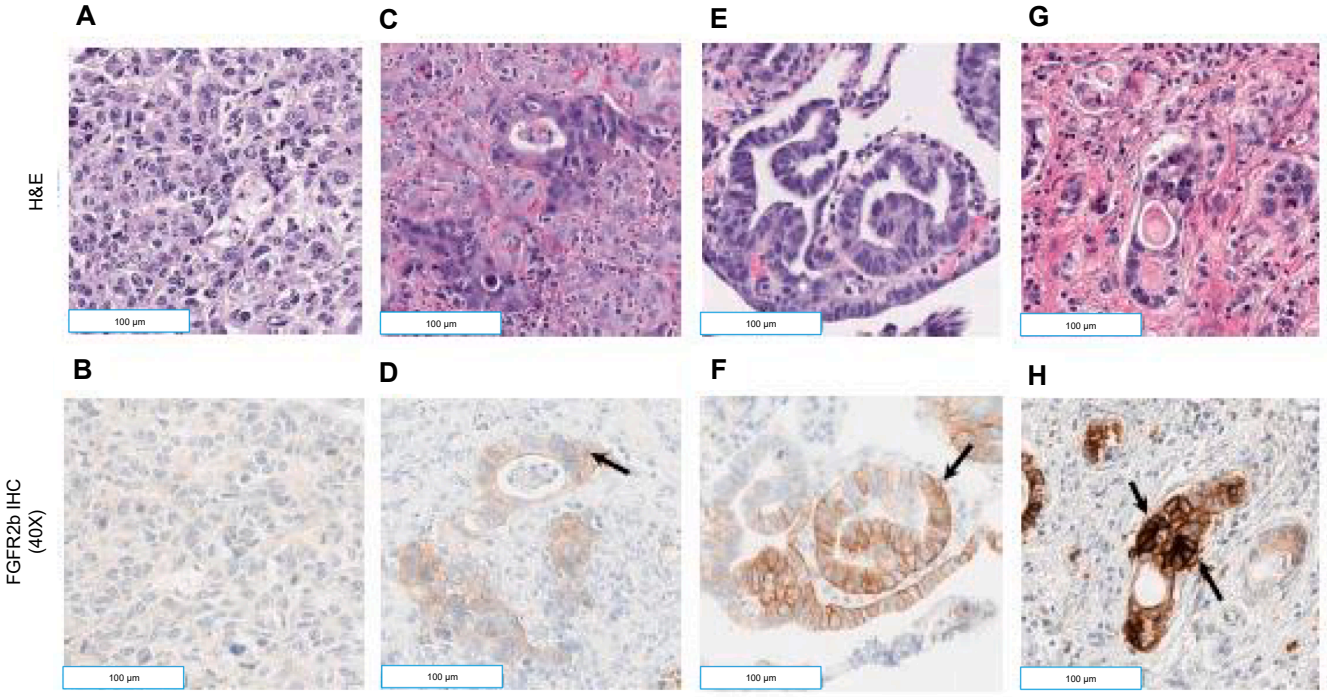

Fig. 3. Gastric adenocarcinomas. A, C, E, and G: H&E staining. B, D, F, and H: FGFR2b IHC staining. (A) Gastric adenocarcinoma, surgical resection from primary lesion. (B) Tumor cells are negative for FGFR2b. (C) Gastric adenocarcinoma, biopsy from stomach. (D) Cancer cells show partial membrane staining with weak (1+) intensity (arrow). (E) Gastric adenocarcinoma, biopsy from stomach. (F) Tumor cells have complete or partial membrane staining with weak (1+) to moderate (2+; arrow) intensity. (G) Gastric adenocarcinoma, surgical resection from primary lesion. (H) Tumor cells show strong (3+) membrane (arrows) staining with FGFR2b [34]. FGFR2b, fibroblast growth factor receptor 2 IIIb isoform; H&E, hematoxylin and eosin; IHC, immunohistochemistry. (Reproduced from Rha SY, et al. Prevalence of FGFR2b protein overexpression in advanced gastric cancers during prescreening for the phase III FORTITUDE-101 trial. JCO Precis Oncol 2025;9:e2400710. Journal link to article).

actionable biomarkers in larger sample sizes.

Although intratumoral heterogeneity is commonly observed for G/GEJC biomarkers, the body of data for FGFR2b heterogeneity has been limited to date [69,78]. One study found FGFR2b overexpression was significantly greater in paired metastatic lesions than in primary tumor (75% vs 47%) [59]. Another study found intratumoral heterogeneity in 56% of cases when evaluating multiple areas of the primary tumor [60]. A biopsy specimen obtained from a small tumor region may not be representative of the whole heterogeneous tumor, thus collection of multiple samples obtained from different regions is likely to be more representative of a patient's FGFR2b protein overexpression status [78]. In clinical practice, evaluation of approximately 6 to 8 tumor biopsies is recommended for G/GEJC tumors and affords the advantage of more accurately characterizing biomarker expression across the whole tumor, potentially reducing the rate of false-negative selection [78,79]. Previous IHC studies with HER2, PD-L1, and CLDN18 biomarkers demonstrated a need to evaluate multiple biopsies for accurate assessment [79–81]. It will be important to understand FGFR2b heterogeneity and the appropriate tissue quantity to assess during analysis of protein overexpression by IHC.

Overall, current evidence supports FGFR2b protein overexpression as a clinically relevant biomarker for the anti-FGFR2b antibody bemarituzumab [41,59]. Indeed, study results indicate that a biomarker-enriched subgroup of patients with ≥10% FGFR2b protein overexpression may derive greater clinical benefit compared with the full population [41]. These findings are similar to those observed in the ToGA trial for a subgroup of patients with higher HER2 overexpression who received enhanced benefit from a trastuzumab with chemotherapy combination [16]. Clinical benefit associated with biomarker enrichment for PD-L1 (combined positive score, ≥5) or CLDN18.2 (≥75% of tumor cells) expression in G/GEJC cancer has also been reported in studies evaluating the programmed death receptor-1 inhibitor nivolumab and the CLDN18.2-targeting antibody zolbetuximab in combination with chemotherapy [19,22,23]. Together, these studies reinforce the concept that increased protein expression of an IHC biomarker has the potential to predict greater efficacy. Ongoing FGFR2b biomarker-selected clinical studies include the phase 3 FORTITUDE-101 trial of mFOLFOX6 plus bemarituzumab or placebo and the phase 1b/3 FORTITUDE-102 trial of mFOLFOX6 plus bemarituzumab with or without the anti–programmed death-1 antibody nivolumab, both in previously untreated advanced G/GEJC (NCT05052801 and NCT05111626, respectively).

Although bemarituzumab is currently the only FGFR2b-targeting investigational therapeutic to have attained late-stage clinical development, first-in-human studies of FGFR2b-targeting ADCs have recently been initiated, including BG-C137 (NCT06625593) and ALK201 (NCT06656390). Research interest in targeting FGFR2b beyond the first-line setting is growing with neoadjuvant and later-line settings being investigated for monoclonal antibodies (eg, late-line bemarituzumab in the BEMARA study, NCT06680622) as well as alternative therapeutic modalities (eg, BG-C137 and ALK201).

Identification of novel biomarkers in G/GEJC has the potential to improve diagnostic assessment, leading to effective stratification of patient populations and better precision-based treatment strategies. Future diagnostic evaluation might consider upfront reflex testing of important G/GEJC biomarkers to allow timely treatment decisions and ultimately improve patient outcomes. Within clinical practice, reducing the turnaround time required to access biomarker test results and thereby commencing treatment is critical. Although turnaround times for IHC tests can be relatively short, integrating reflex panel testing of all emerging biomarkers at diagnosis into existing workflows may help further expedite identification of patients who might clinically benefit from a targeted therapy for first-line treatment [16,41]. Multidisciplinary tumor boards and other formal venues can help aid in the

education of biomarker detection strategies as new targeted treatments are approved and guidelines continue to evolve [12,82].

Conclusion

FGFR2b intersects with multiple cellular pathways involved in tumor cell proliferation, and the limited body of evidence to date suggests FGFR2b protein overexpression as detected by IHC may have a prognostic role in G/GEJC. As FGFR2b is overexpressed in a sizeable proportion of patients with advanced G/GEJC, further understanding the clinicopathologic characteristics associated with FGFR2b protein overexpression and the potential predictive and prognostic implications of this emerging biomarker in G/GEJC are areas of ongoing research and clinical interest.

CRediT authorship contribution statement

Elizabeth C. Smyth: Conceptualization, Data curation, Writing – review & editing. **Kyoung-Mee Kim:** Conceptualization, Data curation, Writing – review & editing. **Sun Young Rha:** Conceptualization, Data curation, Writing – review & editing. **Zev A. Wainberg:** Conceptualization, Data curation, Writing – review & editing. **Hayden Honeycutt:** Conceptualization, Data curation, Writing – review & editing, Methodology, Project administration, Writing – original draft. **Erica Sommermann:** Conceptualization, Data curation, Writing – review & editing, Methodology, Project administration, Writing – original draft. **Atsushi Ochiai:** Conceptualization, Data curation, Writing – review & editing.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Elizabeth C. Smyth received research grants from Astra Zeneca and BMS; consulting fees/other remunerations from Amgen Inc., Astra Zeneca, Astellas, BeiGene, BMS, MSD, Pfizer, T-CypherBio, and Zymeworks; and holds nonremunerative positions of influence with EORTC GI Trials Group (Chair), ESMO Guidelines Committee (Chair), and UKIOG Trustee. Elizabeth C. Smyth is supported by the National Institute for Health and Care Research Biomedical Research Centre at Oxford. The views expressed in this review are those of the author's and not necessarily those of the National Health Service, the National Institute for Health and Care Research, or the Department of Health. Kyoung-Mee Kim and Atsushi Ochiai have no disclosures to report within the last 12 months. Sun Young Rha received research grants from ABL Bio, ALX Oncology, Amgen Inc., Arcus Biosciences, Astellas Pharma, AstraZeneca, BeiGene, Bold Therapeutics, Daiichi Sankyo, Eisai, Ipsen, Leap Therapeutics, Ono Pharmaceutical, Macrogenics, MedPacto, Merck KGaA, MSD, Pfizer, Seagen, Taiho Pharmaceutical, and Zymeworks and served on the speakers bureau for Amgen Inc., Astellas, AstraZeneca, Daiichi-Sankyo, Eisai, Ipsen, Lilly, MSD, and Sanofi Aventis. Zev A. Wainberg received research grants from Arcus Biosciences, BMS, and Novartis and consulting fees/other remunerations from Alligator, Arcus Biosciences, Amgen Inc., Astellas, Astra Zeneca, Bayer, BMS, Daiichi, Gilead, Ipsen, Jannsen, Merck, Novartis, Regeneron, and Roche/Genentech. Hayden Honeycutt and Erica Sommermann are employees and shareholders of Amgen Inc.

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Appendix A. Supplementary data

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