Prevalence of FGFR2b Protein Overexpression in Advanced Gastric Cancers During Prescreening for the Phase III FORTITUDE-101 Trial

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ABSTRACT

PURPOSE Fibroblast growth factor receptor 2 isoform IIIb (FGFR2b) protein overexpression is an emerging biomarker in gastric cancer and gastroesophageal junction cancer (GC). We assessed FGFR2b protein overexpression prevalence in nearly 3,800 tumor samples as part of the prescreening process for a global phase III study in patients with newly diagnosed advanced or metastatic GC.

METHODS As of June 28, 2024, 3,782 tumor samples from prescreened patients from 37 countries for the phase III FORTITUDE-101 trial (ClinicalTrials.gov identifier: NCT05052801) were centrally tested for FGFR2b protein overexpression by immunohistochemistry (IHC) and had evaluable results. FGFR2b positivity was defined as both any % tumor cells (TC) and ≥10% TC exhibiting moderate-to-strong (2+/3+) membranous FGFR2b staining. Prevalence was analyzed across patient and sample characteristics.

RESULTS FGFR2b protein overexpression at any % and ≥10%, 2+/3+ TC positivity was 37.8% (1,428/3,782 [95% CI, 36.2 to 39.3]) and 16.2% (612/3,782 [95% CI, 15 to 17.4]), respectively. Of any %, 2+/3+ TC–positive tumors, 42.9% (612/1,428 [95% CI, 40.3 to 45.4]) were FGFR2b ≥10%, 2+/3+ TC positive. FGFR2b prevalence was not notably different within multiple patient and sample characteristics examined (age, sex, collection method [biopsy *v* resection], collection site, location of primary tumor, and geographic region).

CONCLUSION As of the data cutoff date, we report the largest prevalence assessment of FGFR2b protein overexpression in GC with more than one third (37.8%) of patients with GC exhibiting FGFR2b protein overexpression (any % TC, 2+/3+) by a validated IHC assay. Approximately 16% of patients had FGFR2b protein overexpression in ≥10% of TC. FGFR2b prevalence was similar across geographic regions and within defined patient and sample variables regardless of the level of expression.

ACCOMPANYING CONTENT

Data Sharing Statement

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INTRODUCTION

According to a recent estimate, gastric cancer (GC) has one of the highest incidence and mortality worldwide.[1] Patients with GC, which includes gastroesophageal junction cancer (GEJC), are often diagnosed at advanced stages and have low survival rates.[2] GC is a histologically and molecularly heterogeneous disease, which contributes to the poor outcomes.[3] The identification of biomarkers such as human epidermal growth factor receptor 2 (HER2), mismatch repair (MMR)/microsatellite instability (MSI) status, and PD-L1 have expanded treatment options and resulted in improved response to treatments in patients with advanced GC.[4] Patients with HER2-positive disease, a key immunohistochemistry (IHC)-defined population, are commonly treated with trastuzumab, an anti-HER2 antibody, combined with chemotherapy with or without an anti–PD-1 antibody on the basis of phase III clinical trials.[4-7] Patients with advanced HER2-negative and PD-L1–positive tumors show improved efficacy when treated with the anti–PD-1 antibody nivolumab (combined positive score [CPS] ≥5) in combination with chemotherapy or with pembrolizumab (CPS ≥1).[8-10] Although

CONTEXT

Key Objective

To study the prevalence of fibroblast growth factor receptor 2 isoform IIIb (FGFR2b) protein overexpression in tumors from patients with newly diagnosed advanced or metastatic gastric and gastroesophageal junction cancers and its consistency across various patient demographics and specimen characteristics.

Knowledge Generated

Approximately 38% of patients with gastric cancers who were prescreened for the FORTITUDE-101 trial (ClinicalTrials.gov identifier: NCT05052801) exhibited some level (any % 2+/3+ tumor cells) of FGFR2b protein overexpression by a validated immunohistochemistry assay. At a cutoff of ≥10% 2+/3+ tumor cells staining, approximately 16% of patients had FGFR2b protein overexpression. FGFR2b prevalence did not seem to be affected by age, sex, collection method, collection site, location of primary tumor, or geographic region.

Relevance

This is the largest global assessment of the prevalence of FGFR2b protein overexpression in gastric cancers with potential clinical implications as an emerging target for gastric cancer.

these treatments improve patient outcomes, median overall survival remains low, at approximately 13-20 months in global studies.[5,6,9,10]

An emerging biomarker is fibroblast growth factor receptor 2 isoform IIIb (FGFR2b). Dysregulation of FGFR2 signaling promotes tumorigenesis and progression in GC.[11] Although there are two major isoforms of FGFR2 (FGFR2b and FGFR2c), the isoform more frequently overexpressed in GC is FGFR2b.[12] Its overexpression has been shown to be associated with both the diffuse subtype of GC and poor outcomes.[13-15] Bemarituzumab, an anti-FGFR2b antibody, combined with chemotherapy suggested improved survival compared with chemotherapy alone in patients with advanced FGFR2b-positive, HER2-negative GC in the randomized, double-blind, international, phase II FIGHT trial (ClinicalTrials.gov identifier: NCT03694522); this benefit was more pronounced in patients with FGFR2b protein overexpression in ≥10% of tumor cells (TC).[16,17] These results informed the design of the confirmatory phase III FORTITUDE-101 trial (ClinicalTrials.gov identifier: NCT05052801), an active, fully enrolled, randomized, double-blind trial investigating bemarituzumab combined with chemotherapy in patients with advanced GC and overexpression of FGFR2b.[18]

Prior retrospective studies have reported lower FGFR2b prevalence estimates of approximately 2.5%, 3.7%, and 4.9%.[12-14] The variation in prevalence among these reports and the FIGHT trial may be due to differences in study designs (eg, single center *v* multicenter), age of tumor sample since collection, antibody selection, and IHC scoring approach.[12-14,16] By contrast, the prevalence of FGFR2b protein overexpression was substantially higher in a previously estimated global sample of 910 patients with advanced GC who were prescreened for the FIGHT trial. This analysis assessed tissue samples from an international patient population and central laboratory testing of FGFR2b IHC status using a validated assay to determine FGFR2b protein overexpression in any percentage of TC with moderate-to-strong (2+/3+) membranous FGFR2b staining; however, FGFR2b protein overexpression in ≥10% of TC was estimated after the study was completed. The FIGHT study reported a prevalence of FGFR2b protein overexpression in any percentage of TC in 29% of prescreened patients.[16] Determining the prevalence of FGFR2b protein overexpression in a large, international patient population with GC using an analytically validated IHC assay is important for understanding the subset of patients who may benefit from targeted FGFR2b therapies. In this study, we present the prevalence estimates of FGFR2b protein overexpression (any % and ≥10% of TC, 2+/3+) on the basis of analysis of evaluable prescreening data from 3,782 patients with advanced GC who were prescreened as part of determining eligibility for the large, global, randomized, phase III FORTITUDE-101 trial.

METHODS

Study Design and Patients

FORTITUDE-101 is a randomized, placebo-controlled, phase III trial designed to assess the efficacy of bemarituzumab in combination with chemotherapy (modified fluorouracil, leucovorin, and oxaliplatin) in locally advanced, unresectable, or metastatic GC where tumors were FGFR2b positive as assessed by IHC in patients known to not be HER2 positive (hereafter, referred to as "HER2 negative"). Patients with any TC exhibiting 2+/3+ (moderate-to-strong) membranous FGFR2b staining were eligible for formal trial screening for FORTITUDE-101, but eligibility was amended on November 18, 2022, to include only patients with ≥10% of

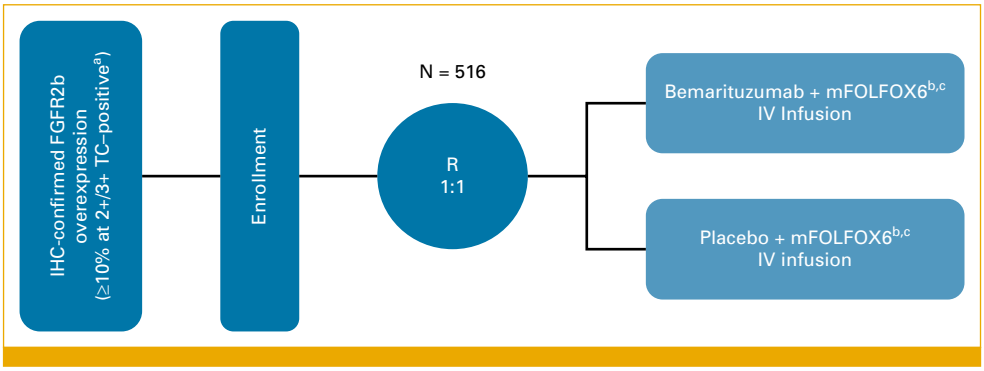

FIG 1. Study design of FORTITUDE-101. [a]At least 10% of TC with moderate (2+) to strong (3+) membrane staining. Patients were initially eligible with any % of TCs with moderate (2+) to strong (3+) membrane staining; on November 18, 2022, the eligibility criteria were amended to require at least 10% of TC with moderate (2+) to strong (3+) staining. [b]mFOLFOX6 is administered as a combination of oxaliplatin and leucovorin IV infusions. FU is administered as bolus, followed by additional administration as IV infusion. [c]Treatment is until progression. FGFR2b, fibroblast growth factor receptor 2 isoform IIIb; FU, fluorouracil; IHC, immunohistochemistry; IV, intravenous; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; R, random assignment; TC, tumor cells.

TC exhibiting 2+/3+ membranous FGFR2b staining. The study design for the FORTITUDE-101 trial is shown in Figure 1. Prescreening samples to assess FGFR2b status were obtained from patients at 287 sites globally across 37 countries. There was no particular sample selection methodology for this protocol. All samples were centrally tested

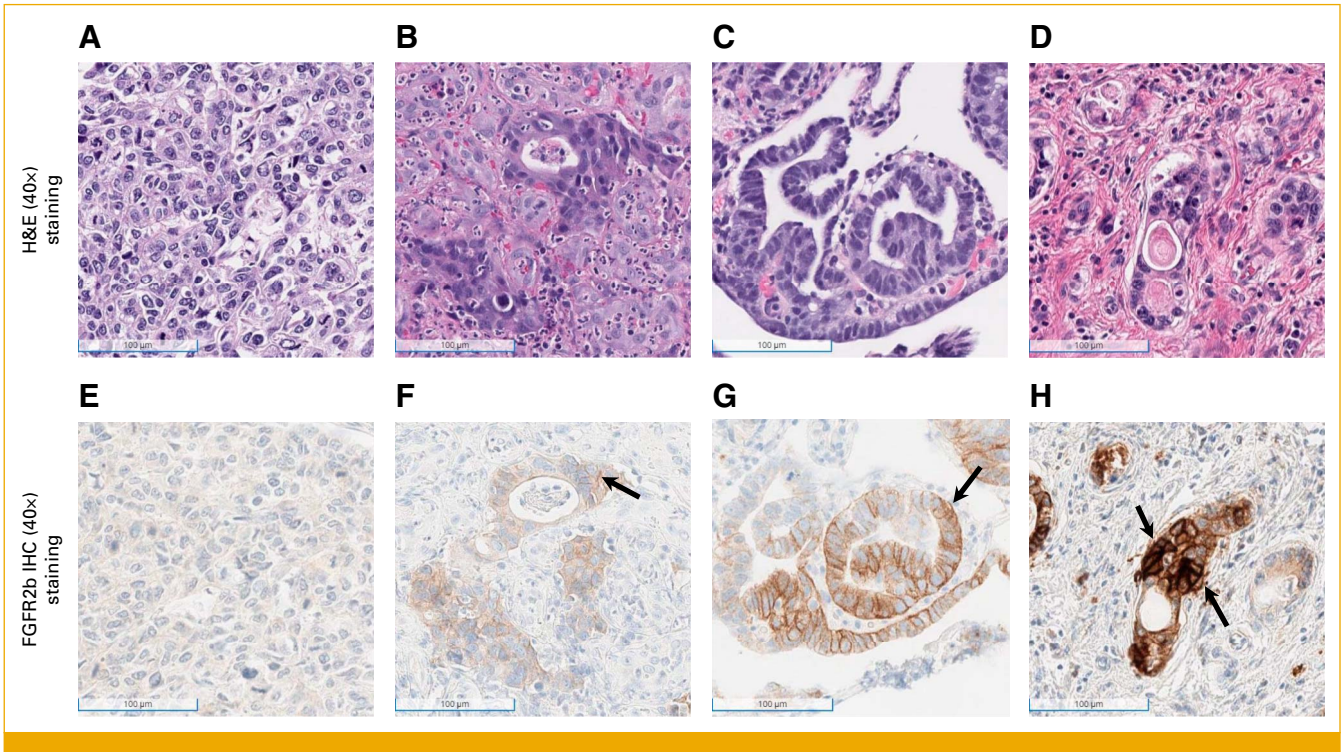

FIG 2. Representative FGFR2b membranous staining at different intensities. Gastric cancers. (A) Gastric adenocarcinoma, surgical resection from primary lesion. (B) Tumor cells are negative for FGFR2b. (C) Gastric adenocarcinoma, biopsy from the stomach. (D) Cancer cells show partial membrane staining with weak (1+) intensity (arrow). (E) Gastric adenocarcinoma, biopsy from the 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 staining (arrows) with FGFR2b. FGFR2b, fibroblast growth factor receptor 2 isoform IIIb; H&E, hematoxylin and eosin; IHC, immunohistochemistry.

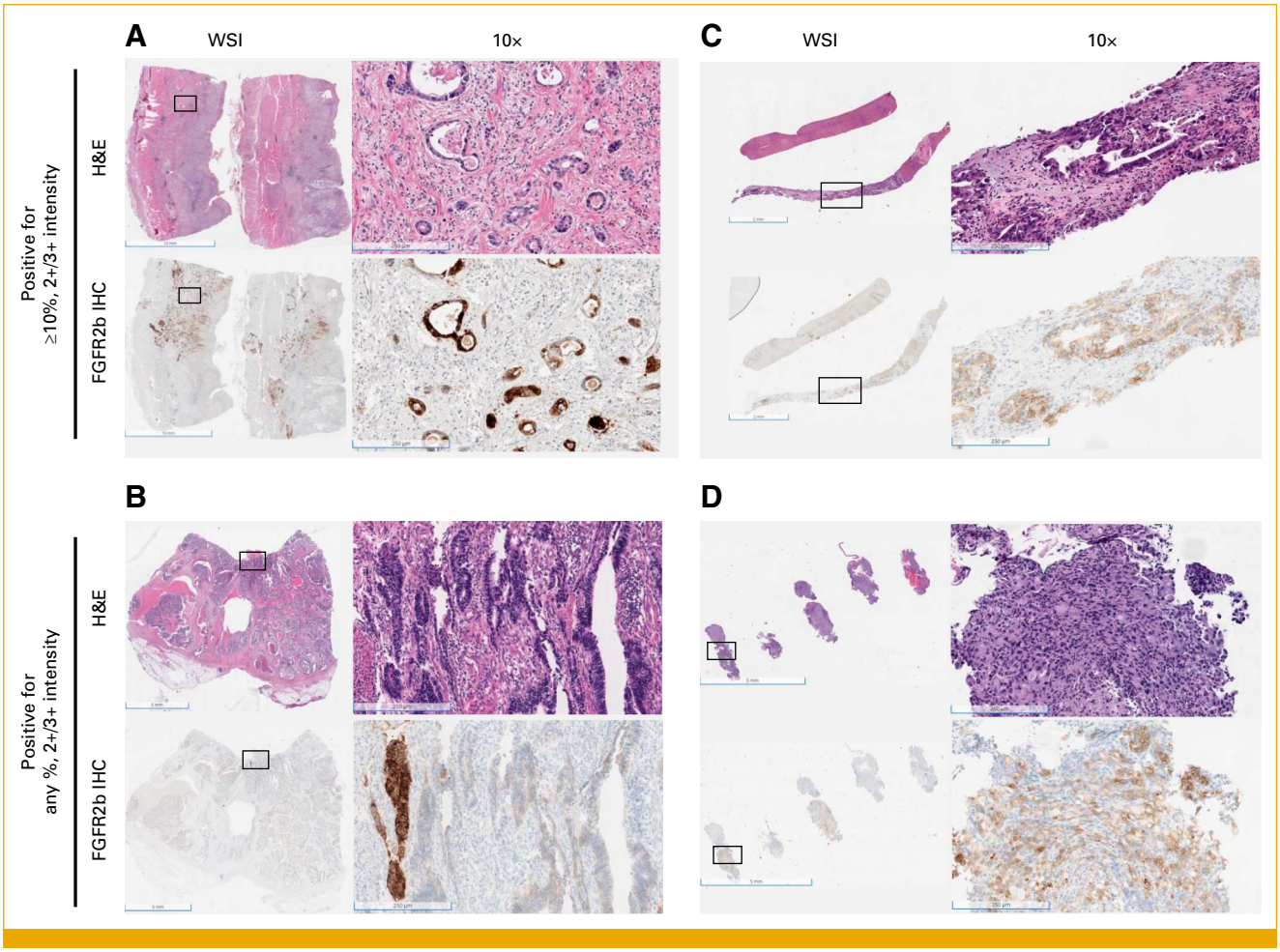

FIG 3. Examples of FGFR2b IHC staining with different collection methods. H&E and FGFR2b IHC staining in WSI and 10× magnification. (A) Surgically resected gastric adenocarcinoma. This patient case is positive for FGFR2b with ≥10% of TC with 2+ to 3+ intensity membranous staining. (B) Surgically resected gastric adenocarcinoma. A positive case for any percentage of TC with 2+ to 3+ intensity membranous staining. (C) Liver core-needle biopsies, metastatic gastric adenocarcinoma. More than 10% of TC show moderate (2+) membranous staining and are positive for ≥10%, 2+/3+ FGFR2b protein overexpression. (D) Gastric mucosal biopsies from primary gastric cancer. Some TC show moderate-to-strong membrane staining. This patient case exhibits FGFR2b protein overexpression at any % TC, 2+/3+ while <10% of TC were positive for FGFR2b protein overexpression. FGFR2b, fibroblast growth factor receptor 2 isoform IIIb; H&E, hematoxylin and eosin; IHC, immunohistochemistry; TC, tumor cells; WSI, whole-slide image.

and scored by trained pathologists. This study was conducted in accordance with the Declaration of Helsinki. All human investigations described in this study were conducted after obtaining approval from each clinical site's local institutional review board or ethics committee, and all procedures adhered to ethical guidelines regarding research involving human subjects.

FGFR2b IHC

Patients were prescreened for FGFR2b protein overexpression status by centralized testing performed through a standardized IHC assay of formalin-fixed, paraffin-embedded (FFPE) tissue using the VENTANA FGFR2b (FPR2-D) RxDx Assay (for investigational use only) and interpreted by a qualified pathologist. Tissue specimens were fresh or archived FFPE tissue; archived tissue specimens must have been collected within 180 days before the patient signing a prescreening consent form at a central laboratory (Q2 Solutions). FGFR2b protein expression was determined by an automated IHC test developed by Roche/Ventana Medical Systems, Inc, using the anti-FGFR2b clone FPR2-D (which is specific for the IIIb isoform of the FGFR2 protein[19]) on a BenchMark ULTRA automated staining platform. Percentages of membranous tumor cell staining at each intensity (0 to 3+) were determined by board-certified pathologists. A sample is considered to exhibit FGFR2b protein overexpression and is deemed positive when any moderate (2+) or strong (3+) membrane staining in tumor cells is detected. Representative images of membranous staining intensity and percentage of tumor cells exhibiting staining are shown in Figures 2 and 3. FGFR2b protein

TABLE 1. Patient and Sample Characteristics

Characteristics	Patients (N = 3,782), No. (%)
Sex	
Female	1,217 (32)
Male	2,565 (68)
Region	
APAC	1,988 (53)
EMEA	1,360 (36)
Latin America	362 (10)
United States/Canada	72 (2)
Age, years	
<65	2,023 (53)
≥65	1,759 (47)
Tissue collection site	
Metastatic site	548 (14)
Primary site	3,234 (86)
Tissue collection method	
Biopsy	3,396 (90)
Resection	364 (10)
Unknown	22 (1)
Location of primary tumor	
GC	2,512 (66)
GEJC	455 (12)
Unspecified[a]	815 (22)

Abbreviations: APAC, Asia-Pacific; EMEA, Europe, Middle East, and Africa; GC, gastric cancer; GEJC, gastroesophageal junction cancer.
[a]Unspecified includes both GC and GEJC.

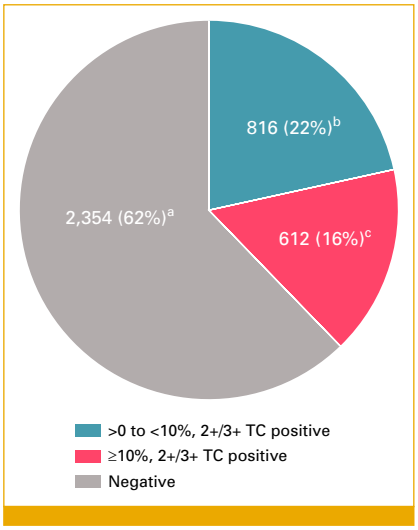

FIG 4. Prevalence of FGFR2b protein overexpression. [a]95% CI, 60.7 to 63.8. [b]95% CI, 20.3 to 22.9. [c]95% CI, 15.0 to 17.4. FGFR2b, fibroblast growth factor receptor 2 isoform IIIb; TC, tumor cells.

overexpression was defined as FGFR2b 2+ or 3+ staining in any percentage of tumor cells (any %, 2+/3+ TC–positive); the FGFR2b ≥10% TC subgroup includes tumor samples that exhibited FGFR2b 2+ or 3+ staining in ≥10% of tumor cells (≥10%, 2+/3+ TC positive).

FGFR2b prevalence was summarized by the evaluable sample size (N), number of positive patient cases (n), and point estimate of prevalence (n/N). Two-sided 95% CI was calculated using the Wald method. Post hoc analyses using Pearson χ^2 test were performed to compare FGFR2b prevalence across patient groups on the basis of age, sex, collection site, collection method, indication, and region, with a significance threshold of $P < .05$. To adjust for multiple comparisons, the P values were corrected using the Benjamini-Hochberg method. All analyses were performed using R version 4.2.3.

RESULTS

Patients

A total of 3,938 tumor samples were prescreened for FGFR2b protein overexpression at any % and ≥10%, 2+/3+ TC positivity using the VENTANA FGFR2b (FPR2-D) RxDx Assay (for investigational use only) through central testing as of the data cutoff date, June 28, 2024, with 3,782 patients having evaluable results. The primary reasons for sample rejection were insufficient viable tumor per pathologist assessment or no tumor available, and there were no clinically meaningful differences in the sample rejection rates across geographic regions. Baseline demographics for evaluable prescreened patients are presented in Table 1; 67.8% were male, and the majority were from Asia-Pacific (52.6%) or Europe, the Middle East, and Africa (36.0%), with the remainder from Latin America (9.6%) or the United States/Canada (1.9%). Imbalances between geographic regions reflect the countries' prescreening activity for the study. The proportion of patients aged younger than 65 years (53.5%) and 65 years and older (46.5%) were similar. Most of the tumor samples were biopsies (89.8%), most were collected from the primary tumor (85.5%), and a majority were GC (66.4%) rather than GEJC.

Prevalence of FGFR2b Protein Overexpression

A total of 1,428 of 3,782 samples (37.8%; 95% CI, 36.2 to 39.3) from patients tested positive for FGFR2b at any %, 2+/3+ TC (Fig 4). The subset of patients whose tumors displayed FGFR2b ≥10%, 2+/3+ TC positivity accounted for 612 of the 3,782 patients in the total evaluable population (16.2%; 95% CI, 15.0 to 17.4), which represents 42.9% of the 1,428 patients who tested positive for FGFR2b at any percentage of TC (Fig 4). The prevalence of FGFR2b with any %, 2+/3+ TC positivity was similar within most defined patient and sample characteristic subgroups (age, sex, collection site, collection method [biopsy *v* resection], location of primary tumor, and region; Fig 5A). The subset of patients

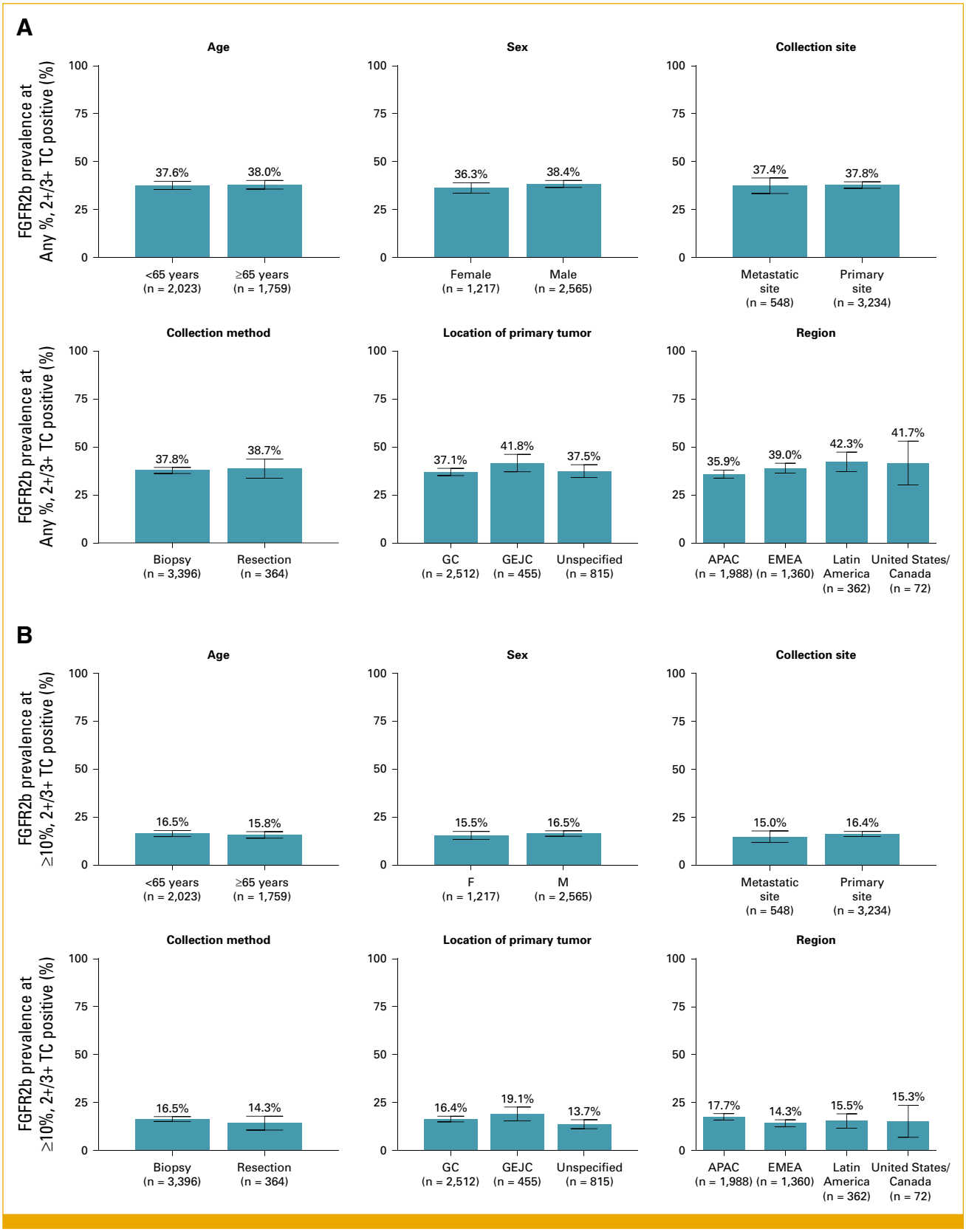

FIG 5. Prevalence of FGFR2b (any %, 2+/3+ TC positive and ≥10%, 2+/3+ TC positive) by patient and sample characteristic subgroups. (A) FGFR2b protein overexpression prevalence for any %, 2+/3+ TC positivity by patient and sample characteristic subgroups. (B) FGFR2b protein overexpression prevalence for ≥10%, 2+/3+ TC positivity by patient and (continued on following page)

FIG 5. (Continued). sample characteristic subgroups. With post hoc analyses using Pearson χ^2 test, FGFR2b prevalence was comparable (adjusted *P* value > .05) in subgroups on the basis of the examined factors for patient characteristics. Error bars represent 95% CIs. APAC, Asia-Pacific; EMEA, Europe, Middle East, and Africa; FGFR2b, fibroblast growth factor receptor 2 isoform IIIb; GC, gastric cancer; GEJC, gastroesophageal junction cancer; TC, tumor cells.

exhibiting FGFR2b ≥10%, 2+/3+ TC positivity was also analyzed for prevalence across these subgroups, and no notable differences were observed (Fig 5B).

DISCUSSION

FGFR2b is a compelling new target for GC therapy, which underscores the need for a comprehensive evaluation of FGFR2b prevalence to inform the use of FGFR2b selective therapies.[15] Bemarituzumab showed promising efficacy in patients with FGFR2b-positive advanced GC, particularly in patients with protein overexpression of FGFR2b in ≥10% of TC.[16,17] In this study, we report that approximately 38% (95% CI, 36.2 to 39.3) of patients with advanced GC who were prescreened for the FORTITUDE-101 trial and had evaluable results were positive for FGFR2b protein overexpression. The subset of patients whose tumors displayed FGFR2b ≥10%, 2+/3+ TC positivity corresponded to approximately 16% (95% CI, 15.0 to 17.4) of the total evaluable population and approximately 43% of the FGFR2b any %, 2+/3+ TC–positive population. The FGFR2b prevalence estimate for any %, 2+/3+ TC positivity from the FORTITUDE-101 prescreening data is more similar to that reported in the FIGHT prescreening data[16] than previous estimates that ranged from approximately 2.5% to 4.9%.[12-14] To date, this study represents the largest global sample of patients with advanced GC to be assessed for FGFR2b status using a validated IHC assay through centralized testing.[12-14,16] Thus, the results of this study are likely to provide the most robust estimates of FGFR2b protein overexpression prevalence in the general population of patients with advanced GC. Although the incidence or risk of GC is known to vary by age, sex, and geographic location,[1,20] FGFR2b protein overexpression prevalence within defined baseline characteristics analyzed for tumors with any % or ≥10%, 2+/3+ TC positivity was similar. Overall, the similarity in FGFR2b protein overexpression prevalence at any % or ≥10%, 2+/3+ TC positivity among patients with different age, sex, tumor collection site, collection method (biopsy *v* resection), location of primary tumor, and geographic region suggests that these factors do not affect FGFR2b prevalence. This has important clinical implications for diagnostic intention and for determining the proportion of patients who may benefit from FGFR2b targeted therapies.

The lower prevalence reported in previous studies was based on retrospective analyses that used a variety of antibodies, preanalytic variables, differences in sample adequacy, IHC protocols, and scoring algorithms to define FGFR2b positivity, possibly leading to variability in results.[12-14,16] Furthermore, many of these studies used tissue microarrays, which are not directly comparable with the sample types evaluated in the FORTITUDE-101 study.

A strength of this study is that it reports on the prevalence of FGFR2b protein overexpression in the largest sample analyzed with a validated assay from many study centers with global representation. This study also assessed FGFR2b in fresh or recent archival tissue samples with central testing using a robust, validated IHC assay that is being developed as the candidate companion diagnostic for bemarituzumab. Although multiple other predictive biomarkers have been reported in GC with varying prevalence—including HER2 positivity (generally reported as approximately 15%),[21-26] PD-L1 (CPS ≥5, approximately 29%-60%),[8,27] MSI-high/MMR-deficient (approximately 3%-7%),[9,28] and claudin-18.2 (38.4%)[29]—this study was designed only to prescreen for FGFR2b protein overexpression. Future studies should examine the extent of overlap of FGFR2b protein overexpression with other biomarkers, as this may suggest additional potential treatment regimens. Additionally, it will be important to further elucidate if there are differences in prevalence in certain subgroups, such as histological subtype and other disease characteristics, as FGFR2b protein overexpression may be more prevalent in patients with poorly differentiated and diffuse-type GC.[14] Additionally, although this study did not evaluate concordance in FGFR2b protein overexpression prevalence between paired primary and metastatic tumor samples, this is an area that warrants further research. Whether FGFR2b prevalence is different among metastatic sites is an open question. One study has observed that FGFR2b protein overexpression correlates with lymph node metastasis and another that FGFR2b protein overexpression occurs more frequently in lymph node metastases compared with matched primary GC samples.[12,14] However, a third study did not observe significant differences in FGFR2b protein overexpression status with lymph nodes and distant metastases.[13]

This study is one of the largest prevalence assessments in the field of unresectable or metastatic GC, examining more than 3,700 evaluable patients. Nearly 40% of evaluable prescreened tumor samples from patients with locally advanced, unresectable, or metastatic GC exhibited FGFR2b protein overexpression at any %, 2+/3+ TC positivity and approximately 16% at FGFR2b ≥10%, 2+/3+ TC positivity. FGFR2b protein overexpression at any %, 2+/3+ TC positivity has previously been associated with a survival benefit with bemarituzumab; a more pronounced benefit was observed with FGFR2b ≥10%, 2+/3+ TC positivity. There were no notable differences in FGFR2b protein overexpression at any % or ≥10%, 2+/3+ TC positivity

when analyzed by age, sex, collection site, defined collection method (biopsy *v* resection), location of primary tumor, or geographic region. This suggests that a substantial proportion of patients with GC express the FGFR2b protein biomarker across key patient demographics and specimen characteristics.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Bray F, Laversanne M, Sung H, et al: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74:229-263, 2024
2. Lordick F, Carneiro F, Cascinu S, et al: Gastric cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 33:1005-1020, 2022
3. Gullo I, Carneiro F, Oliveira C, et al: Heterogeneity in gastric cancer: From pure morphology to molecular classifications. Pathobiology 85:50-63, 2017
4. Sato Y, Okamoto K, Kawano Y, et al: Novel biomarkers of gastric cancer: Current research and future perspectives. J Clin Med 12:4646, 2023
5. Bang YJ, Van Cutsem E, Feyereislova A, et al: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 376:687-697, 2010
6. Janjigian YY, Kawazoe A, Bai Y, et al: Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: Interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. Lancet 402:2197-2208, 2023
7. Wang F, Ba Y: Treatment strategies for patients with HER2-positive gastric cancer. Cancer Biol Med 20:934-941, 2024
8. Janjigian YY, Shitara K, Moehler M, et al: First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): A randomised, open-label, phase 3 trial. Lancet 398:27-40, 2021
9. Shitara K, Ajani JA, Moehler M, et al: Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. Nature 603:942-948, 2022
10. Rha SY, Oh DY, Yañez P, et al: Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): A multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 24:1181-1195, 2023
11. Gordon A, Johnston E, Lau DK, et al: Targeting FGFR2 positive gastroesophageal cancer: Current and clinical developments. Onco Targets Ther 15:1183-1196, 2022
12. Yashiro M, Kuroda K, Masuda G, et al: Clinical difference between fibroblast growth factor receptor 2 subclass, type IIIb and type IIIc, in gastric cancer. Sci Rep 11:4698, 2021
13. Han N, Kim MA, Lee HS, et al: Evaluation of fibroblast growth factor receptor 2 expression, heterogeneity and clinical significance in gastric cancer. Pathobiology 82:269-279, 2015
14. Ahn S, Lee J, Hong M, et al: FGFR2 in gastric cancer: Protein overexpression predicts gene amplification and high H-index predicts poor survival. Mod Pathol 29:1095-1103, 2016
15. Tojjari A, Nagdas S, Saeed A, et al: Deciphering the FGFR2 code: Innovative targets in gastric cancer therapy. Curr Oncol 31:4305-4317, 2024
16. Wainberg ZA, Enzinger PC, Kang YK, et al: Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): A randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol 23:1430-1440, 2022
17. Wainberg ZA, Kang YK, Lee KW, 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 27:558-570, 2024
18. Bemarituzumab or placebo plus chemotherapy in gastric cancers with fibroblast growth factor receptor 2b (FGFR2b) overexpression (FORTITUDE-101). 2024. https://clinicaltrials.gov/study/NCT05052801
19. Gemo AT, Deshpande AM, Palencia S, et al: FPA144: A therapeutic antibody for treating patients with gastric cancers bearing FGFR2 gene amplification. Cancer Res 74:5446, 2014 (abstr 5446)
20. Takatsu Y, Hiki N, Nunobe S, et al: Clinicopathological features of gastric cancer in young patients. Gastric Cancer 19:472-478, 2016
21. Kim KC, Koh YW, Chang HM, et al: Evaluation of HER2 protein expression in gastric carcinomas: Comparative analysis of 1414 cases of whole-tissue sections and 595 cases of tissue microarrays. Ann Surg Oncol 18:2833-2840, 2011
22. Cho EY, Park K, Do I, et al: Heterogeneity of ERBB2 in gastric carcinomas: A study of tissue microarray and matched primary and metastatic carcinomas. Mod Pathol 26:677-684, 2013
23. Park DI, Yun JW, Park JH, et al: HER-2/neu amplification is an independent prognostic factor in gastric cancer. Dig Dis Sci 51:1371-1379, 2006
24. Shan L, Ying J, Lu N: HER2 expression and relevant clinicopathological features in gastric and gastroesophageal junction adenocarcinoma in a Chinese population. Diagn Pathol 8:76, 2013
25. Yano T, Doi T, Ohtsu A, et al: Comparison of HER2 gene amplification assessed by fluorescence in situ hybridization and HER2 protein expression assessed by immunohistochemistry in gastric cancer. Oncol Rep 15:65-71, 2006
26. Yoon HH, Shi Q, Sukov WR, et al: Association of HER2/ErbB2 expression and gene amplification with pathologic features and prognosis in esophageal adenocarcinomas. Clin Cancer Res 18:546-554, 2012
27. Schoemig-Markiefka B, Eschbach J, Scheel AH, et al: Optimized PD-L1 scoring of gastric cancer. Gastric Cancer 24:1115-1122, 2021

28. Chao J, Fuchs CS, Shitara K, et al: Assessment of pembrolizumab therapy for the treatment of microsatellite instability–high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials. JAMA Oncol 7:895-902, 2021
29. Shitara K, Xu RH, Ajani JA, et al: Global prevalence of claudin 18 isoform 2 in tumors of patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma. Gastric Cancer 27:1058-1068, 2024

