Title

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Epidermal Growth Factor Receptor Inhibition in Epidermal Growth Factor Receptor–Amplified Gastroesophageal Cancer: Retrospective Global Experience

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abstract

PURPOSE Subset analyses from phase III evaluation of epidermal growth factor receptor inhibition (EGFRi) suggest improved outcomes in patients with *EGFR*-amplified gastroesophageal adenocarcinoma (GEA), but large-scale analyses are lacking. This multi-institutional analysis sought to determine the role of EGFRi in the largest cohort of patients with *EGFR*-amplified GEA to date.

PATIENTS AND METHODS A total of 60 patients from 15 tertiary cancer centers in six countries met the inclusion criteria. These criteria required histologically confirmed GEA in the metastatic or unresectable setting with *EGFR* amplification identified by using a Clinical Laboratory Improvement Amendments–approved assay, and who received on- or off-protocol EGFRi. Testing could be by tissue next-generation sequencing, plasma circulating tumor DNA next-generation sequencing, and/or fluorescence in situ hybridization performed by a Clinical Laboratory Improvement Amendments approved laboratory. Treatment patterns and outcomes analysis was also performed using a deidentified clinicogenomic database (CGDB).

RESULTS Sixty patients with *EGFR*-amplified GEA received EGFRi, including 31 of 60 patients (52%) with concurrent chemotherapy. Across treatment lines, patients achieved a 43% objective response rate with a median progression-free survival of 4.6 months (95% CI, 3.5 to 6.4). Patients receiving EGFRi in first-, second-, and third-line therapy achieved a median overall survival of 20.6 months (95% CI, 13.5 to not reached [NR]), 9 months (95% CI, 7.9 to NR), and 8.4 months (7.6 to NR), respectively. This survival far exceeded the 11.2-month (95% CI, 8.7 to 14.2) median overall survival from first-line initiation of non-EGFRi therapy in patients with *EGFR*-amplified GEA in the CGDB. Despite this benefit, analysis of the CGDB (January 2011-December 2020) suggests that only 5% of patients with *EGFR*-amplified GEA received EGFRi.

CONCLUSION Patients with *EGFR*-amplified GEA derive significant benefit from EGFRi. Further prospective investigation of EGFRi in a well-selected patient population is ongoing in an upcoming trial of amivantamab in *EGFR* and/or *MET* amplified GEA.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Gastroesophageal adenocarcinoma (GEA), comprising adenocarcinoma of the distal esophagus, gastroesophageal junction, and stomach, portends the second highest cancer-related mortality and therefore remains a significant global health threat.[1] The majority of patients are diagnosed with metastatic disease, and in this setting, median overall survival (mOS) remains at 12.4-13.8 months in human epidermal growth factor receptor 2 (HER2)–negative GEA,[2-4] despite US Food and Drug Administration approvals for therapies targeting vascular endothelial growth factor receptor 2 (ramucirumab), programmed cell death protein 1 (PD-1) (nivolumab and pembrolizumab), and HER2 (trastuzumab, trastuzumab-deruxtecan).[4-7] Of these approvals, only those targeting HER2-expressing and microsatellite instability-high are approved for molecularly selected populations.

The Cancer Genome Atlas identified that approximately 62% of patients with GEA exhibit chromosomal instability, which is associated with frequent gene

CONTEXT

Key Objective

There is an unmet need for effective therapies for patients with *EGFR*-amplified gastroesophageal adenocarcinoma (GEA). This study retrospectively evaluates the efficacy of epidermal growth factor receptor (EGFR) inhibition in a genomically selected global patient population.

Knowledge Generated

Of the 60 patients with *EGFR*-amplified GEA treated with EGFR inhibitors, 43% achieved an objective response, and overall survival stratified by treatment line exceeded that seen in an EGFR nontargeted historical control cohort.

Relevance

These findings suggest a role for *EGFR* inhibitors with or without concurrent chemotherapy in patients with *EGFR*-amplified GEA.

amplification of receptor tyrosine kinases including HER2, EGFR, mesenchymal-epithelial transition factor (MET), and fibroblast growth factor receptor 2.[8] Epidermal growth factor receptor (EGFR) is overexpressed in up to half of patients and amplified in approximately 6% of patients with GEA and is associated with a poor prognosis.[9-13] EGFRi was explored in unselected patients in three phase III GEA trials—EXPAND (first-line chemotherapy with or without cetuximab), REAL-3 (first-line chemotherapy with or without panitumumab), and COG (second-line gefitinib *v* placebo).[14-16] Although all three of these trials failed to reach their primary end points, post hoc biomarker analyses in EXPAND and COG demonstrated that patients with highly EGFR-expressing or amplified tumors derive a significant survival benefit from EGFRi.[17-19] Subsequent publications supporting the premise of EGFR inhibition in *EGFR*-amplified GEA have led to many patients around the world being treated on clinical trials or off label with EGFRi.[9,20-22] Therefore, we sought to retrospectively summarize the global experience in this setting, in support of future use guided by appropriate genomic biomarker testing.

PATIENTS AND METHODS

Patient Inclusion

Patients with metastatic or unresectable *EGFR*-amplified GEA by tissue-next-generation sequencing (NGS), plasma circulating tumor DNA (ctDNA)-NGS, or fluorescence in situ hybridization (FISH) who received on- or off-protocol EGFRi at 15 tertiary medical centers in the United States, the United Kingdom, Italy, Korea, Japan, and Turkey were identified. All patients were treated in accordance with the Declaration of Helsinki, and this retrospective review was approved by the respective local institutional review board. All clinicopathologic characteristics were prespecified and abstracted a priori per prior publication.[9] Adverse events were graded using Common Terminology Criteria for Adverse Events version 5.0. HER2, programmed death ligand 1 (PD-L1), and mismatch repair testing was performed locally per ASCO/College of American Pathologists (CAP) guidelines. Where possible, PD-L1 status was determined using the Food and Drug Administration–approved pharmDx (Agilent, Santa Clara, CA) immunohistochemical (IHC) assay (PD-L1 IHC 22C3) combined positive score, although alternative antibodies were used by some sites.

EGFR Diagnostic Assays

As patients from multiple centers were included, tissue-NGS and ctDNA-NGS were performed on multiple platforms. All Clinical Laboratory Improvement Amendments–approved commercial NGS assays used in clinical care were accepted for this cohort, including FoundationOne CDx (Foundation Medicine, Cambridge, MA), MSK-IMPACT (Memorial Sloan Kettering, New York, NY), Ashion GEMExTra (Ashion, Phoenix, AZ), Strata NGS (Strata, Ann Arbor, MI), TempuslxT (Tempus, Chicago, IL), Caris Life Sciences, Phoenix, AZ, and DFCI Oncopanel (Dana Farber Cancer Center, Boston, MA). Similarly, ctDNA-NGS was performed using Guardant 360 (Guardant Health, Redwood City, CA), TempuslxF (Tempus, Chicago, IL), or FoundationOne Liquid (Foundation Medicine, Cambridge, MA) and reported using their clinical thresholds. FISH amplification was defined as *EGFR/CEP7* ratio $\geq$ 2.1[23] or a ratio $\geq$ 2 with tight gene clustering in $\geq$ 10% of analyzed cells.[24]

Flatiron Health-Foundation Medicine Clinicogenomic Database

This study used the nationwide (US-based) deidentified advanced Flatiron Health-Foundation Medicine clinicogenomic database (FH-FMI CGDB). Retrospective longitudinal clinical data were derived from electronic health records, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction, and were linked to genomic data derived from FMI comprehensive genomic profiling tests by deidentified, deterministic matching.[25] During the study period, the deidentified data originated from approximately 280 US cancer clinics (approximately 800 sites of care). The study included 2,724 patients who had a diagnosis of advanced GEA, received care within the FH network between

January 2011 and December 2020, and underwent tissue comprehensive genomic profiling (FoundationOne, FoundationOne CDx or FoundationOneLiquid CDx).[26,27] Institutional Review Board approval with waiver of informed consent was obtained before study conduct.

Statistical Analyses

Progression-free survival (PFS) was calculated from the start of initial EGFRi-containing therapy to disease progression or death. OS was calculated from the date of initiation of initial EGFR inhibitor-containing therapy to death. Because of the retrospective nature of this cohort, progression was defined as radiographic or clinical progression as determined by the treating investigator. OS and PFS were estimated using the Kaplan-Meier method and compared between groups using log-rank. A Cox regression model was used to analyze the association between a set of prespecified patient and treatment characteristics (performance status [PS] at EGFR treatment, concurrent chemotherapy, EGFR diagnostic assay, number of prior treatment lines, and primary tumor location and PFS).[9] Multivariable PFS analysis was constructed by including variables that correlated with PFS on univariate analysis with $P \leq .2$. The proportional hazards assumption was confirmed using the Schoenfeld test and graphical diagnostic-based testing on the scaled Schoenfeld residuals.[28] Multivariable OS was not constructed as it would be less informative because of treatment line heterogeneity. All inferential analyses used two-sided methods ($\alpha = .05$), and statistical significance was defined as P value $< .05$. All statistical analyses were conducted using R version 4.0.5.

RESULTS

Patient Population

From 2014 to 2021, a total of 60 patients with *EGFR*-amplified GEA who had received an EGFRi in the metastatic setting at one of 15 tertiary medical centers (Global cohort) were identified with a median follow-up of 7.7 months. Baseline demographics and pathologic features for the Global cohort are shown in Table 1 and the Data Supplement (online only). As this was a retrospective cohort, 12 of the 60 (20%) patients had an Eastern Cooperative Oncology Group (ECOG) PS of 2 at the time of EGFRi initiation. Administered treatments included monoclonal antibodies (mAb: cetuximab, ABT-806, panitumumab) in 50 patients, small molecule tyrosine kinase inhibitors (TKI: gefitinib, erlotinib, afatinib) in eight patients, or both mAb and TKI in two patients. Thirty-one patients (52%) received EGFRi in conjunction with chemotherapy, and six (10%) patients also received concurrent PD-1 inhibition (Table 2). Nine (15%) patients went on to receive subsequent lines of EGFRi.

Efficacy

At the time of censoring, five of 60 (8%) patients remain on therapy. For the entire Global cohort, median progression-free survival (mPFS) was 4.6 months (95% CI, 3.5 to 6.4), which corresponded to a mPFS of 6.0 months (95% CI, 4.6 to 9.0) in patients receiving concurrent chemotherapy, and 3.0 months (95% CI, 2.2 to 6.0) without concurrent chemotherapy (Appendix Fig A1, online only).

Twenty-two (37%) patients achieved a 6-month PFS, including seven of 28 (25%) patients who did not receive chemotherapy (Fig 1A). Among the cohort, 24 of 56 evaluable patients (43%) achieved a radiographic response including 16 of 28 (57%) patients treated with concurrent

TABLE 1. Patient Demographics (Global cohort)

Characteristic	N = 60
Median age, years (range)	58 (22-85)
Male sex, No. (%)	48 (80)
Ethnicity, No. (%)	
Caucasian	49 (82)
Asian	6 (10)
Hispanic	3 (5)
Other/unknown	2 (3)
Location, No. (%)	
Esophageal/GEJ	40 (67)
Gastric	20 (33)
Grade, No. (%)	
Well	1 (2)
Moderate	16 (27)
Poor	42 (70)
Unknown	1 (2)
HER2, No. (%)	
Negative	54 (90)
Positive[a]	6 (10)
PD-L1 CPS, No. (%)	
Negative	12 (28)
1-4	16 (37)
≥ 5	15 (35)
Unknown	17 (–)
MSI, No. (%)	
MSS	55 (100)
MSI-H[b]	0 (0)
Unknown	5

Abbreviations: CPS, combined positive score; FISH, fluorescence in situ hybridization; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSS, microsatellite stable; NGS, next-generation sequencing; PD-L1, programmed death ligand 1.

[a]HER2-positive defined as IHC 3+ or 2+/FISH+.

[b]MSI testing included clinical MMR IHC, MMR polymerase chain reaction, or NGS.

TABLE 2. Patient Treatment Characteristics (Global cohort)

Characteristic	N = 60
Treatment line, No. (%)	
1	19 (32)
2	15 (25)
3	8 (13)
4+	18 (30)
Treatment category, No. (%)	
Chemotherapy plus mAb	29 (48)
mAb	16 (27)
TKI	7 (12)
mAb plus PD-1i	4 (7)
Chemotherapy plus mAb plus PD-1i	1 (2)
mAb plus PD-1i plus TKI	1 (2)
mAb plus TKI	1 (2)
Chemotherapy plus TKI	1 (2)
EGFR inhibitor, No. (%)	
Cetuximab	27 (45)
ABT-806	13 (22)
Panitumumab	10 (17)
Gefitinib	5 (8)
Erlotinib	3 (5)
Cetuximab plus afatinib	1 (2)
Cetuximab plus erlotinib	1 (2)

Abbreviations: EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-1i, PD-1 inhibitor; TKI, tyrosine kinase inhibitor.

chemotherapy and eight of 28 (29%) patients who received EGFRi alone (Fig 1B). The median duration of response was 3.6 months (range 0.1-18.1 months). Because of the retrospective nature of this study, PS, treatment line, and therapies were heterogeneous. Multivariable PFS analysis demonstrated that patients benefited regardless of EGFR inhibitor used. However, patients selected using FISH (hazard ratio [HR], 6.58; 95% CI, 2.02 to 21.2) or ctDNA (HR, 3.73; 95% CI, 1.28 to 10.9) were significantly associated with increased risk of progression or death. There was also at least a two-fold increased risk of progression or death for patients with an ECOG PS of 2 (HR, 2.4; 95% CI, 0.97 to 5.83) or treatment line ≥ 4 (HR, 2.0; 95% CI, 0.71 to 5.70), but these associations did not reach statistical significance (Table 3).

These benefits translated into 20.6-month (95% CI, 13.5 to not reached [NR] mOS with first-line therapy, which compares favorably with 11.2-month (95% CI, 8.7 to 14.2) real-world OS observed for patients with *EGFR*-amplified GEA selected from the Foundation Medicine FH-FMI CGDB, who had not received EGFR inhibition (Figs 2A and 2B). Patients who received EGFRi in the second- and third-line therapies achieved 9-month (95% CI, 7.9 to NR) and 8.4-month (7.6 to NR) mOS, respectively. Similarly, patients achieved mPFS of 6.9 (6.0 to 14.3), 5.2 (3.5 to NR), and 6.6 (2.0 to NR) months in the first, second, and third treatment lines (Fig 2C), respectively. PFS and OS met or exceeded expected survival with standard-of-care therapies in HER2-negative patients in all three treatment lines.

Biomarkers and Resistance

We then evaluated the *EGFR* amplification detection method in 28 patients who had undergone both tissue and ctDNA testing pretreatment. Patients with *EGFR*-amplified tissue and ctDNA, tissue only, or ctDNA only had median PFS of 6.7 (n = 18; 95% CI, 4.6 to 14.1), 6.4 (n = 7; 95% CI, 6.0 to NR), and 1.7 (n = 3; 95% CI, 1.6 to NR) months, respectively, among the 28 patients who underwent sequencing by both assays. Previous evaluation of EGFR inhibition identified *MET*/*ERBB2* amplification or activation of the mitogen-activated protein kinase or RAS-phosphatidylinositol 3-kinase (PI3K) pathways as common resistance mechanisms.[29-35] Alterations at any time point in *MET*, *ERBB2*, RAF (*RAF1/BRAF*), RAS (*KRAS/NRAS*), and PI3K (*PIK3CA/B/G/PIK3R1*) were identified in 14%, 16%, 16%, 16%, and 14% of patients who underwent tissue or ctDNA sequencing at any time point (n = 51), respectively, which was overall reflective of that seen across the FH-FMI CGDB (Appendix Fig A2, online only). Within our cohort of 60 EGFRi-treated patients, *MET* and *RAS* alterations were nearly mutually exclusive, although *RAS* and *ERBB2* were frequently coaltered (Fig 3A). No correlation was identified between *EGFR* tissue copy number (Appendix Fig A3, online only) or aggregated pretreatment alterations (RAS, PI3K, RAF, *ERBB2*, and *MET*; data not shown) and PFS. However, patients with *MET* coamplification at any time point trended toward inferior PFS (P = .1; Fig 3B).

Of note, six PD-1 inhibitor naive patients received concurrent EGFR and PD-1 inhibition. Despite PD-L1 combined positive score ≥ 1, their mPFS was only 2.0 (95% CI, 0.6 to NR) versus 5.0 (95% CI, 3.6 to 6.6) months in those without concurrent PD-1 inhibition (P = .04; Appendix Fig A4, online only). Although concerning, prospective validation is needed to confirm these findings.

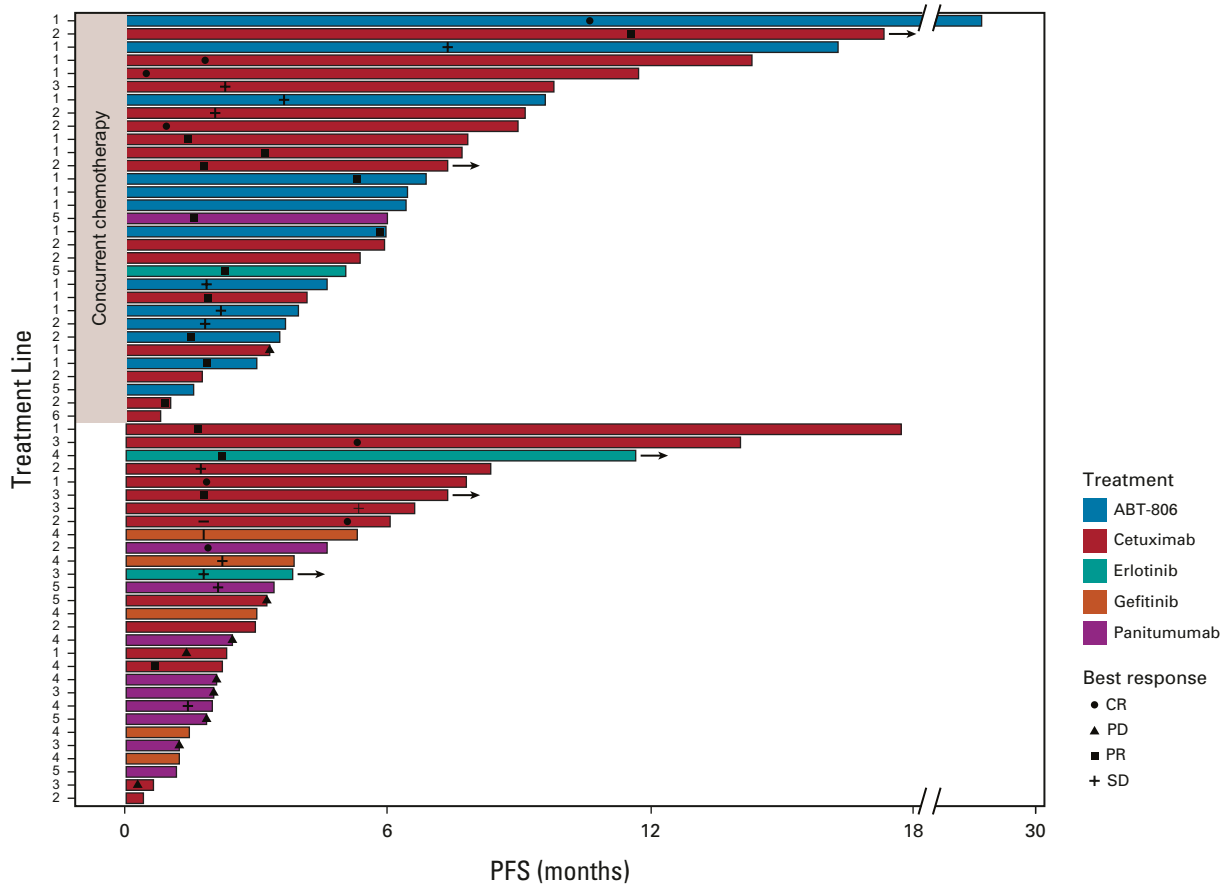
Safety

Thirty-one (52%) patients developed dermatologic toxicity while on therapy, including one grade 3 rash. Five patients (8%) developed grade 1-2 diarrhea. Other low frequency treatment-related toxicities included fatigue and hypomagnesemia. Only one patient required an EGFR inhibitor dose-reduction.

Real-World Biomarker Prevalence

We queried the Foundation Medicine FH-FMI CGDB database for patients with *EGFR*-amplified GEA to select the population who may benefit from EGFR inhibition. In this cohort, 182 of 2,662 patients (6.8%) had GEA tissue

A



B

Treatment Line	1	2	3	4+	Any Line
Overall	11/17 (65%)	7/15 (43%)	2/8 (25%)	4/16 (25%)	24/56 (43%)
EGFRi plus chemotherapy	9/14 (64%)	5/10 (50%)a	0/1 (0%)	2/3 (67%)	16/28 (57%)
EGFRi	2/3 (67%)a	2/5 (40%)a	2/7 (29%)a	2/13 (15%)	8/28 (29%)

FIG 1. (A) Swimmer's plot for patients treated at one of 15 tertiary cancer centers stratified by concurrent chemotherapy administration demonstrating PFS exceeding 6 months in 21 patients, including many receiving EGFR blockade without chemotherapy. Many responses were deep and durable. (B) Radiographic objective response stratified by treatment line and EGFR inhibition with or without concurrent chemotherapy. [a]Concurrent PD-1 inhibition in six patients is included. CR, complete response; EGFR, epidermal growth factor receptor; EGFRi, EGFR inhibition; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; PR, partial response; SD, stable disease.

samples with *EGFR* amplifications with a copy number ≥ 8 (Appendix Table A1, online only). Within this cohort, only 5% of evaluable patients with *EGFR*-amplified GEA received EGFRi. This suggests a sizable remaining population who may benefit from access to EGFRi in this setting.

DISCUSSION

To our knowledge, this is the largest pooled analysis in the literature of patients with *EGFR*-amplified GEA who received EGFR inhibitors—nearly triple the size of the largest subset presented in phase III trial analysis.[19] We demonstrated that EGFRi, alone or in combination with chemotherapy led to higher objective response rate, PFS, and OS than expected with standard of care in biomarker-selected patients. Given previous findings from multiple cohorts that *EGFR* amplification is not prognostic of survival,[13,36] the results of this global collaboration further support the clinical benefit of EGFRi in patients with EGFR-amplified GEA.

TABLE 3. Univariate and Multivariate PFS Analysis (Global cohort)

	Univariate PFS			Multivariable PFS		
Characteristic	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Pre-EGFRi ECOG PS						
0	—	—		—	—	
1	1.22	0.65 to 2.29	.54	1.13	0.55 to 2.30	.7
2	2.31	1.04 to 5.11	.039	2.38	0.97 to 5.83	.058
Concurrent chemotherapy						
No chemotherapy	—	—		—	—	
Chemotherapy	0.6	0.35 to 1.03	.062	1.3	0.58 to 2.88	.5
EGFR-amplified assay						
Tissue	—	—		—	—	
Both	1.11	0.57 to 2.16	.76	1.52	0.71 to 3.29	.3
ctDNA	4.19	1.65 to 10.6	.003	3.73	1.28 to 10.9	.016
FISH	6.84	2.89 to 16.2	< .001	6.58	2.04 to 21.2	.002
Treatment line						
1	—	—		—	—	
2	1.50	0.72 to 3.11	.28	1.25	0.56 to 2.80	.6
3	1.26	0.49 to 3.22	.63	1.17	0.38 to 3.67	.8
4+	3.54	1.72 to 7.26	< .001	2.01	0.71 to 5.70	.2
Primary site						
Esophageal/GEJ	—	—				
Gastric	1.2	0.67 to 2.12	.54			
EGFRi						
mAb	—	—				
mAb + TKI	0.55	0.13 to 2.41	.43			
TKI	1.19	0.50 to 2.83	.69			

Abbreviations: ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor inhibitor; FISH, fluorescence in situ hybridization; GEJ, gastroesophageal junction; HR, hazard ratio; mAb, monoclonal antibody; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Our study has several limitations, including retrospective nature, lack of central radiologic assessment, and patient and molecular diagnostic heterogeneity. It is also important to note that 20% of patients had an ECOG PS of 2, and 30% received EGFRi in the fourth line or later. Therefore, this represented a sicker population than would be studied in a prospective trial. Despite this limitation, patients who received first-, second-, or third-line EGFRi exceeded the objective response rate, PFS, and OS reported in contemporary studies, respectively.[2-5,37] Of note, many patients developed oligometastatic progression after initial treatment response yet went on to have extended OS. This presumably reflects intrapatient heterogeneity, and in many cases, this was driven by co-occurring HER2 expression, with the receipt of subsequent HER2-directed therapies.

These findings mirror those seen in the recent FIGHT trial that demonstrated a survival benefit when adding bemarituzumab to first-line chemotherapy in patients with FGFR2-expressing GEA. In a well-selected population, patients achieved a median OS of 19.2 months with bemarituzumab plus chemotherapy versus 13.5 months in patients receiving chemotherapy alone.[38]

Although there was no clear difference in efficacy between EGFRi used, patients with detection of *EGFR* amplification by tissue-NGS had superior PFS compared with those with *EGFR* amplification detected by FISH or only by plasma-NGS. This likely relates to intrapatient EGFR heterogeneity leading to therapeutic resistance.[39-41] We previously demonstrated that patients with high tumor burden shed more ctDNA, and therefore, subclonal amplifications may be detected in the ctDNA. Conversely, low disease burden may lead to false absence of *EGFR* amplification from plasma, and so further biomarker development is needed.[36,42] In addition to *EGFR* heterogeneity, we identified *KRAS*, *NRAS*, *MET*, and *ERBB2* as frequently coaltered resistance mechanisms, which potentially contributed to resistance and support a role for combination therapy approaches.

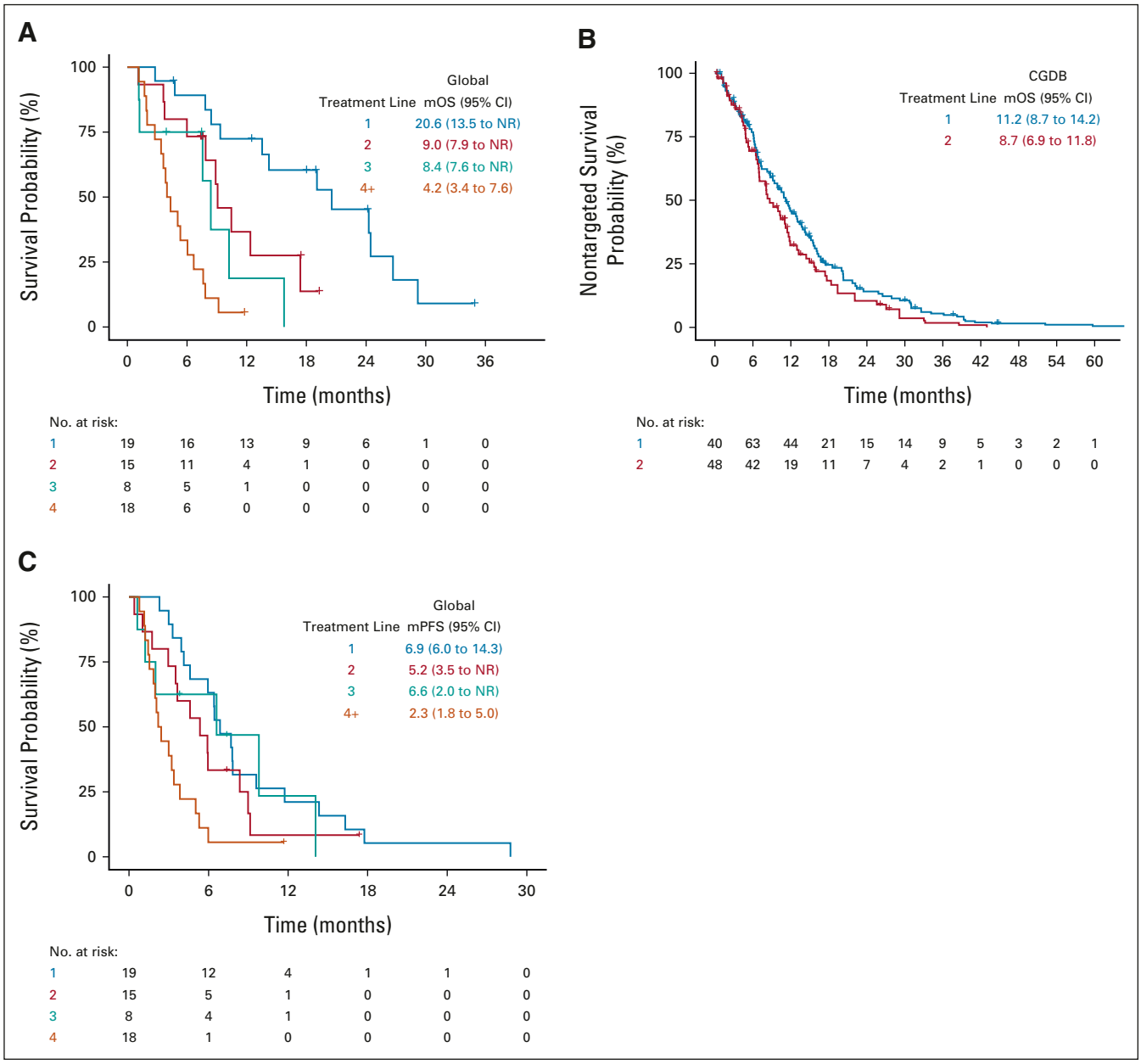


FIG 2. Kaplan-Meier analysis for patients with *EGFR*-amplified GEA demonstrating (A) OS stratified by treatment line for patients treated at one of 15 tertiary cancer centers (Global cohort) and (B) Kaplan-Meier analysis for patients in the FH-FMI CGDB functioning as historic control OS from first-line therapy initiation in patients with *EGFR*-amplified GEA, not receiving an EGFRi. (C) Global cohort PFS stratified by treatment line. EGFR, epidermal growth factor receptor inhibitor; FH-FMI CGDB, Flatiron Health-Foundation Medicine clinicogenomic database; GEA, gastroesophageal adenocarcinoma; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival.

Our data support a role for combination of targeted therapy and chemotherapy to suppress resistance and prolong survival. However, combination of EGFRi and anthracyclines should be avoided, as demonstrated in REAL3.[18] EGFR targeting can also be augmented by using concurrent mAb and TKI[13] or by overcoming resistance using amivantamab, a dual EGFR and MET inhibiting mAb.[43] Although the small subset of patients who received concurrent PD-1 inhibition in this cohort demonstrated inferior survival, the recent approval of first-line trastuzumab, pembrolizumab, and chemotherapy on the basis of KEYNOTE-811 suggests a role for combined PD-1 and receptor tyrosine kinase inhibition in GEA treatment, at least in a subset of patients with PD-L1 expression.[44] Further prospective evaluation is needed to evaluate these combination approaches with EGFRi.

In the real-world FH-FMI CGDB database, we identified that only 5% of patients with GEA harboring *EGFR*-amplification received EGFRi from 2011 to 2020. This global collaboration highlights the difficulty in conducting prospective studies in molecularly selected subpopulations, as well as

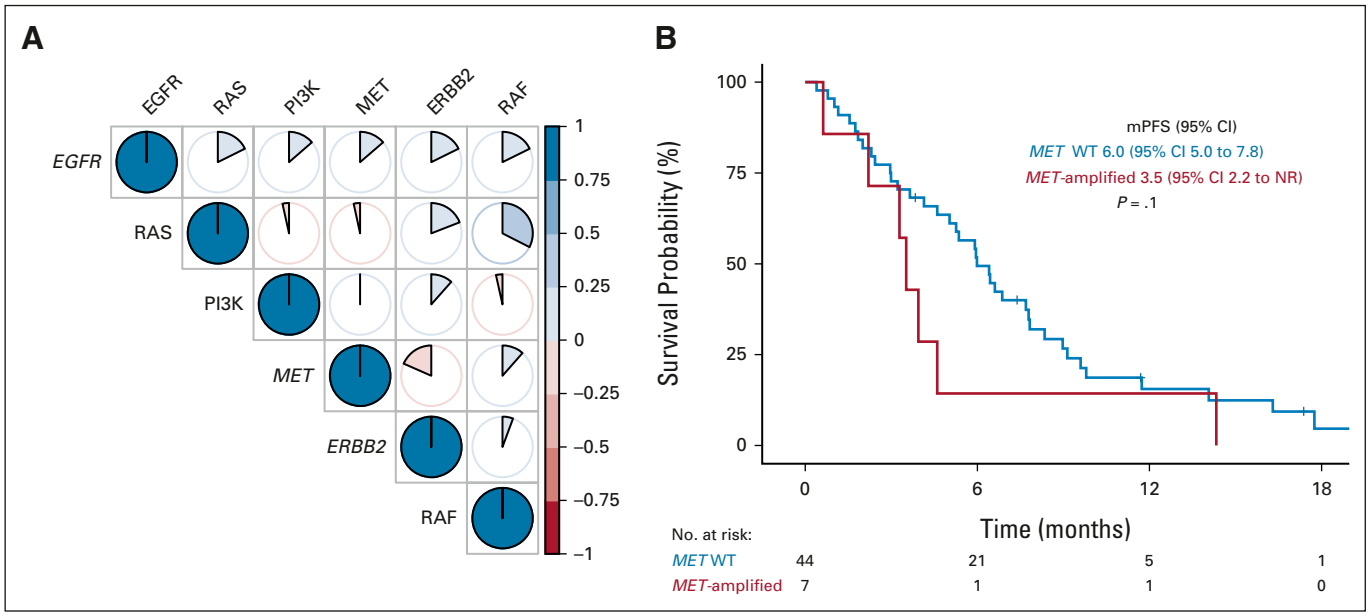


FIG 3. (A) Correlation plot of potential resistance mechanisms identified in each patient demonstrating similar frequencies of alterations in *MET*, *ERBB2*, RAF (*RAF1/BRAF*), RAS (*KRAS/NRAS*), and PI3K (*PIK3CA/B/G/PIK3R1*) pathway genes. Coalteration of *ERBB2* and RAS was common, whereas coalteration of RAS and *MET* was uncommon. (B) Kaplan-Meier analysis stratifying PFS *MET* amplification status as detected by ctDNA or tissue-NGS. ctDNA, circulating tumor DNA; mPFS, median progression-free survival; NGS, next-generation sequencing; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; WT, wild type.

the unmet need for targeted therapy access in a population that can derive dramatic benefit from already-approved agents with ORR, PFS, and OS outperforming historical controls for each line of therapy. Phase II evaluation of amivantamab, a bispecific antibody against EGFR and MET, in patients with *EGFR*- and/or *MET*-amplified GEA is now underway, will prospectively answer this question in a well-selected patient population (ClinicalTrials.gov identifier: NCT05117931). While future trials in this population remain underway, these findings merit consideration for National Comprehensive Cancer Network compendium inclusion of cetuximab and panitumumab, which are already widely used in gastrointestinal malignancies.

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EQUAL CONTRIBUTION

S.J.K. and D.V.T.C. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Epidermal Growth Factor Receptor Inhibition in Epidermal Growth Factor Receptor–Amplified Gastroesophageal Cancer (GEA): Retrospective Global Experience

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APPENDIX

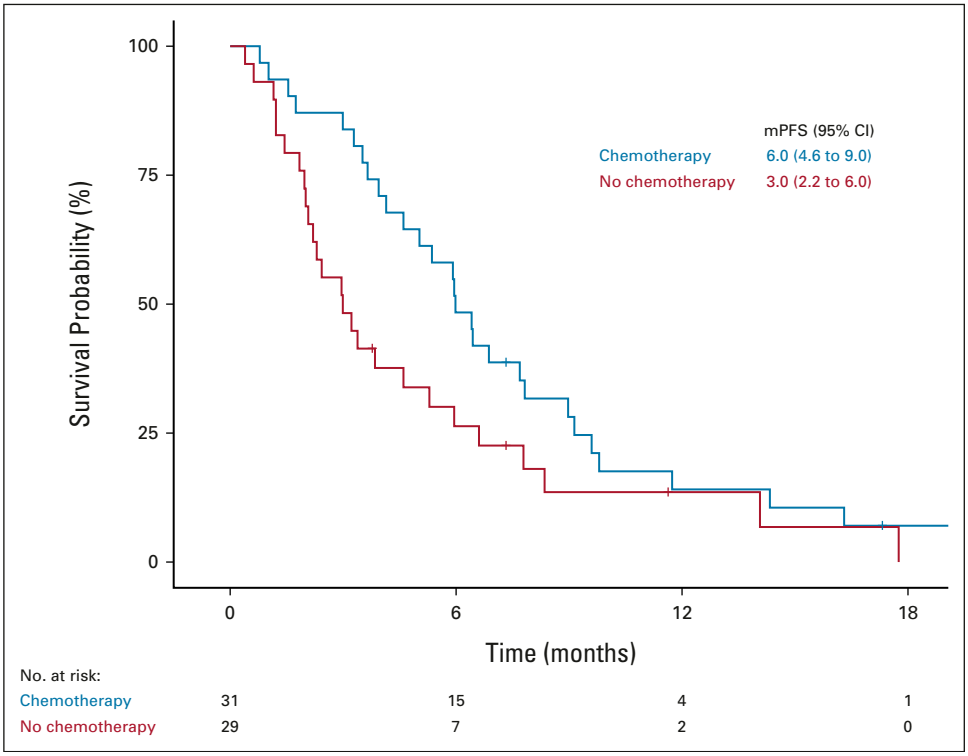

FIG A1. Kaplan-Meier analysis comparing progression-free survival stratified by the receipt of concurrent chemotherapy or not. mPFS, median progression-free survival.

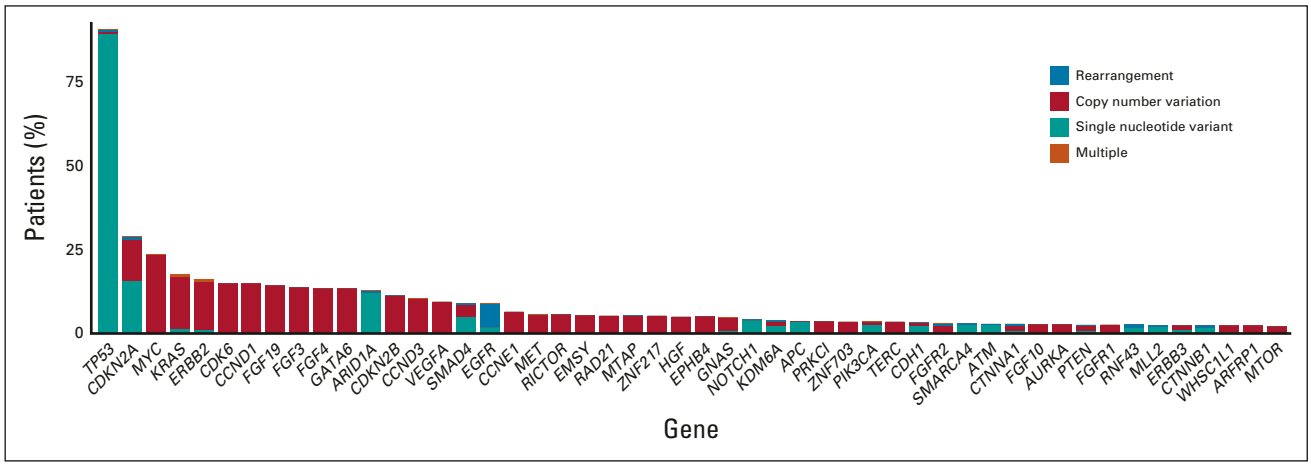

FIG A2. Genomic alterations co-occurring with *EGFR* amplification in the CGDB cohort (n = 182 patients). CGDB, clinicogenomic database.

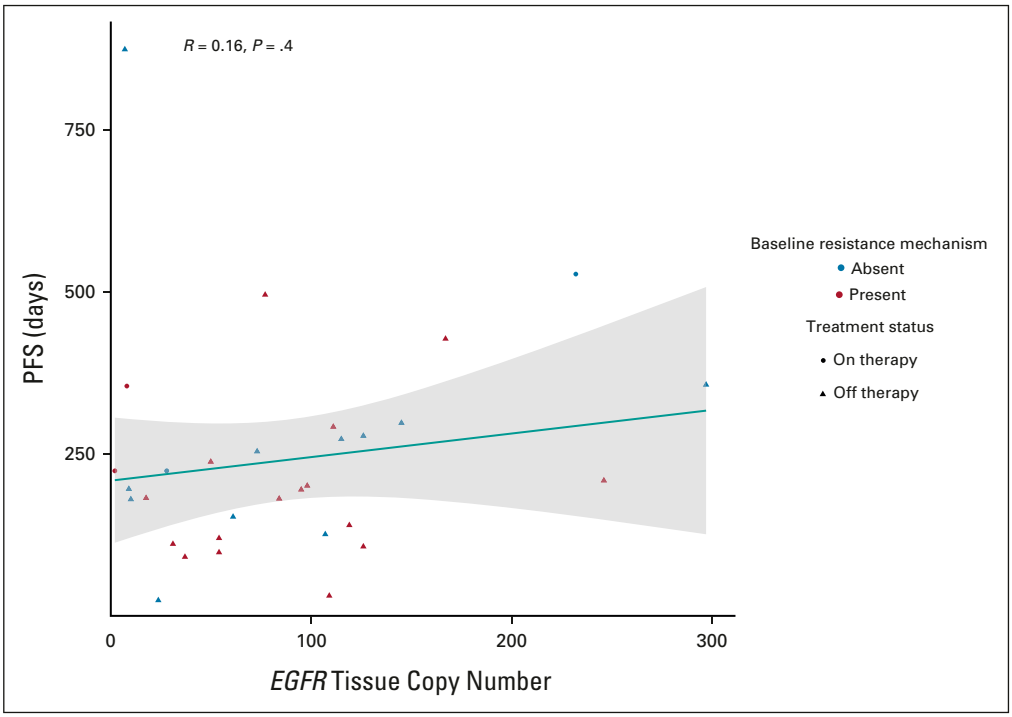

FIG A3. *EGFR* tissue copy number stratified by the presence of baseline resistance mechanisms poorly correlates with PFS. Baseline resistance mechanisms were defined as pathogenic alteration in *MET*, *RAS*, *ERBB2, BRAF*, or PI3K-associated genes present in tissue or plasma ctDNA NGS. ctDNA, circulating tumor DNA; NGS, next-generation sequencing; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase.

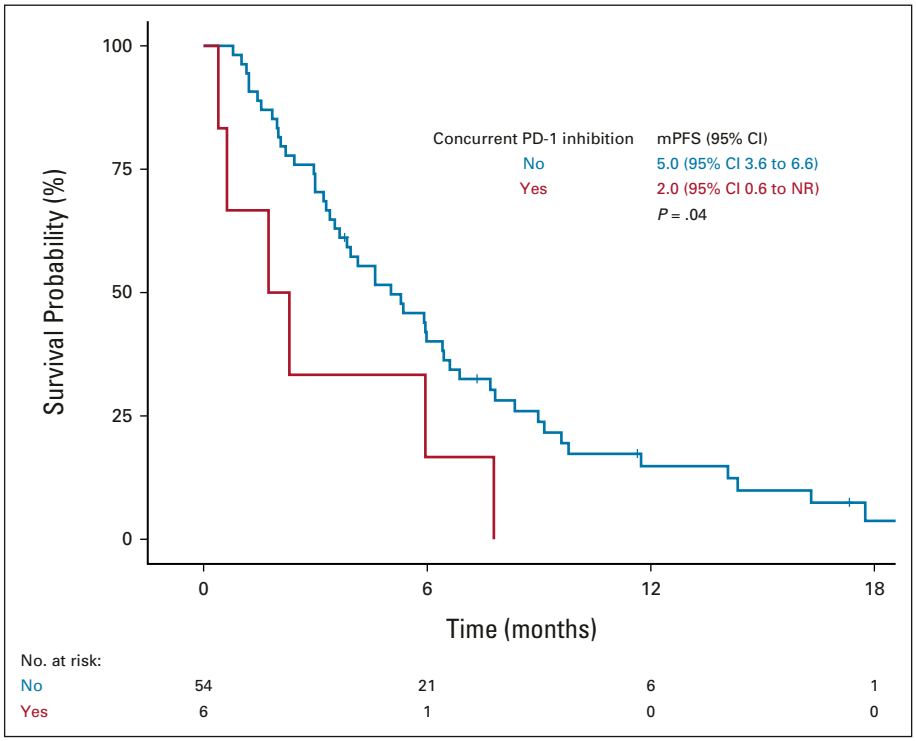

FIG A4. Kaplan-Meier analysis suggesting inferior PFS when using concurrent PD-1 blockade in conjunction with EGFRi. EGFRi, epidermal growth factor receptor inhibitor; mPFS, median progression-free survival; NR, not reached; PD-1, programmed cell death protein 1; PFS, progression-free survival.

TABLE A1. Frequency of EGFR Amplification Stratified by CN (clinicogenomic database cohort)

Primary Site	All Patients, N	All *EGFR*-Amplified, No. (%)	*EGFR* CN, 8-19 (%)	*EGFR* CN, 20-99 (%)	*EGFR* CN, ≥ 100 (%)
All GEA	2,662	182 (6.8)	57 (2.1)	75 (2.8)	50 (1.9)
Esophageal	1,149	100 (8.7)	36 (3.1)	42 (3.7)	22 (1.9)
Gastric	808	23 (2.8)	4 (0.5)	13 (1.6)	6 (0.7)
GEJ	705	59 (8.3)	17 (2.4)	20 (2.8)	22 (3.1)

Abbreviations: CN, copy number; EGFR, epidermal growth factor receptor; GEA, gastroesophageal adenocarcinoma; GEJ, gastroesophageal junction.