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Gastrointestinal Cancer

Regorafenib in Combination with First-Line Chemotherapy for Metastatic Esophagogastric Cancer

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Key Words. Regorafenib • Esophagogastric cancer • Angiogenesis • Targeted therapy

Abstract

Background. Angiogenesis is critical to gastroesophageal adenocarcinoma growth and metastasis. Regorafenib is a multikinase inhibitor targeting angiogenic and stromal receptor tyrosine kinases. We evaluated whether regorafenib augments the antitumor effect of first-line chemotherapy in metastatic esophagogastric cancer.

Materials and Methods. Patients with previously untreated metastatic gastroesophageal adenocarcinoma received 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) every 14 days and regorafenib 160 mg daily on days 4 to 10 of each 14-day cycle. The primary endpoint was 6-month progression-free survival (PFS). To identify predictive biomarkers of outcome, we examined correlations between genomic characteristics of sequenced pretreatment tumors and PFS.

Results. Between August 2013 and November 2014, 36 patients with metastatic esophagogastric cancer were accrued to this single-center phase II study (NCT01913639). The most common grade 3–4 treatment-related adverse events were neutropenia (36%), leucopenia (11%) and hypertension (8%). The 6-month PFS was 53% (95% confidence interval [CI], 38%–71%), the objective response rate was 54% (95% CI, 37%–70%), and the disease control rate was 77% (95% CI, 67%–94%). Next-generation sequencing did not identify any genomic alterations significantly correlated with response, and there was no association between homologous recombination deficiency and PFS with platinum-based chemotherapy.

Conclusion. Regorafenib (one week on–one week off schedule) is well tolerated in combination with first-line FOLFOX but does not improve 6-month PFS relative to historical control. ***The Oncologist*** 2020;25:e68–e74

Implications for Practice: Prognosis for metastatic esophagogastric cancer remains poor despite modern systemic therapy regimens. This phase II trial indicates that the combination of regorafenib and FOLFOX is well tolerated but does not add to the efficacy of first-line chemotherapy in metastatic esophagogastric cancer. Notably, recently reported data suggest potential synergy between regorafenib and the PD-1 inhibitor nivolumab. As this study demonstrates that regorafenib plus FOLFOX is safe, and combined chemotherapy and immunotherapy show favorable toxicity profiles, future studies combining immunotherapy with regorafenib and chemotherapy may be feasible.

Introduction

Esophageal and gastric (EG) cancers represent a significant global health burden, with a combined incidence of 1.4 million cases yearly [1]. For patients with metastatic disease, 5-fluorouracil with oxaliplatin (FOLFOX) is an accepted first-line regimen, with oxaliplatin being as effective and less toxic than cisplatin when combined with 5-fluorouracil (5-FU) [2]. Unfortunately, despite initial benefit from palliative therapy, the prognosis of patients remains poor, with median overall survival (OS) of less than a year.

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Biologically, EG adenocarcinomas are characterized by activation of the receptor tyrosine kinases (RTKs) human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor, and Ras [3–5]. The HER2-directed antibody trastuzumab is approved in combination with first-line chemotherapy for patients with HER2-positive tumors [6]. Furthermore, pathologic angiogenesis and extracellular matrix remodeling through tumor vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2) signaling potentiates EG cancer growth and metastasis [7]. The VEGFR2-directed antibody ramucirumab is approved in the second-line setting as monotherapy [8] and in combination with paclitaxel [9]. Similarly, the VEGFR2 tyrosine kinase inhibitor apatinib improved survival in the third-line chemotherapy-refractory setting [10]. In the first-line setting, however, antiangiogenics have failed to meaningfully improve survival over fluorouracil/platinum chemotherapy [11–14].

Beyond the VEGF pathway, several other growth factors regulate pathologic angiogenesis and the tumor microenvironment. Preclinical studies suggest that the platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) pathways provide escape mechanisms to VEGF-VEGFR2 blockade [15, 16]. Thus, inhibiting these pathways may overcome resistance and prolong the benefit of antiangiogenic therapy. Regorafenib is a small-molecule inhibitor of VEGFR2, FGFR2, and PDGFR that improved survival in metastatic colorectal and hepatocellular carcinoma [17, 18]. In a phase III study in chemotherapy-refractory gastric cancer, regorafenib improved progression-free survival (PFS), suggesting that regorafenib also has activity in EG cancer [19]. However, there are no reported studies of regorafenib in the first-line setting in EG cancer. Therefore, we conducted a phase II trial to determine the activity of regorafenib combined with FOLFOX in chemotherapy-naïve patients with EG cancer.

Materials and Methods

Study Design and Treatment

This was a single-institution, open-label, nonrandomized, single-arm phase II study. Regorafenib was administered on days 4 to 10 of a 14-day cycle as four 40-mg tablets, with mFOLFOX6 (oxaliplatin 85 mg/m^2 intravenously [IV], leucovorin 400 mg mg/m^2 IV, 5-FU 400 mg/m^2 IV bolus, 5-FU 2,400 mg/m^2/day continuous IV infusion over 48 h) on day 1. Treatment was continued until intolerable adverse events (AEs), progressive disease, or death. On the first and second occurrence of a grade 3 AE, regorafenib was reduced to 120 mg daily and 80 mg daily, respectively. The protocol was approved by the institutional review board at Memorial Sloan Kettering Cancer Center. All patients provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

Patients

Eligible patients were at least 18 years old with histologically confirmed metastatic or unresectable esophageal, gastric, or gastroesophageal junction (GEJ) adenocarcinoma. Patients were required to have radiographically evaluable disease, whether measurable by RECIST 1.1 [20] or not. Patients were not allowed to have had prior chemotherapy for metastatic or unresectable EG adenocarcinoma but may have received adjuvant therapy (chemotherapy or chemoradiation) if more than 6 months had elapsed prior to recurrence. Other eligibility criteria included adequate hematologic, renal, and hepatic function, Karnofsky performance status ≥70%, and the ability to swallow oral medication. Exclusion criteria included uncontrolled hypertension, clinically significant cardiac disease, and history of bleeding diathesis or coagulopathy.

Study Endpoints and Tumor Assessments

The primary endpoint was 6-month PFS. Secondary endpoints included best overall clinical benefit defined as RECIST 1.1 stable disease (SD), complete response (CR), or partial response (PR), as well as OS and safety. Tumor response was assessed using computed tomography or magnetic resonance imaging every 8 weeks. AEs were graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical Analysis

All patients who received regorafenib and FOLFOX were included in the description of baseline characteristics, efficacy, and safety analysis. Using an exact single-stage binomial design, we planned to accrue 36 patients, providing 80% power to detect an improvement in 6-month PFS from a historical control of 40% to 61%, with a 5% risk of type I error. If 20 or more patients were progression free at 6 months, regorafenib and FOLFOX would be considered worthy of further investigation. PFS was measured from the start of the treatment to the date of either documentation of disease progression or death, whichever occurred first. Patients who came off study before 6 months (lost to follow-up or withdrew consent) without documented progression were considered as events for the primary endpoint of 6-month PFS. Patients who came off study because of toxicity before 6 months without documented progression were scanned to obtain 6-month assessment of progression. OS was calculated from start of treatment until date of death or follow-up. PFS and OS were estimated using Kaplan-Meier methodology. Objective response rate (ORR) was summarized using binomial proportions and exact 95% confidence intervals (CIs). Descriptive statistics were used to characterize patient characteristics and safety. For genomic analysis, distributions of PFS between patients whose tumors carried alterations in each gene were compared with patients whose tumors did not using permutation log-rank test. A Cox proportional hazards model was used for univariate analysis to evaluate the association between large-scale state transitions (LST) score and PFS, and the Wilcoxon test was used to compare LST scores between responders and nonresponders. All p values were two-sided, and p values less than .05 were considered to indicate statistical significance. All analyses were done in SAS version 9.3 (SAS Institute, Cary, NC) or R version 3.5.1. The data-lock date was October 2018.

Biomarker Analysis

Thirty samples obtained prior to first-line therapy were of adequate quality for molecular analysis by MSK-IMPACT, an

on-site cancer-associated gene-bait capture, next-generation sequencing (NGS) assay initially using a panel of 341 and, more recently, 410 and 468 genes. The assay detects mutations, small insertions and deletions, copy number alterations, and select structural rearrangements [21]. Tumors from primary tumors (21 patients) or metastases (9 patients) were sequenced at a mean sequencing coverage of 619× and assigned tumors to consensus molecular subtypes from The Cancer Genome Atlas (TCGA): chromosomal instability (CIN), genomically stable (GS), or microsatellite instability (MSI)-high (MSI-H); testing for the Epstein-Barr virus–positive subtype was not performed. Tumors were classified as GS if the fraction of the autosomal genome affected by DNA copy number alterations was less than 5%. MSI status was inferred using a clinically validated algorithm [22, 23], with MSI-H defined as an MSI sensor score ≥10.

Results

Patient Characteristics

Between August 2013 and November 2014, 42 patients were screened for participation, and 36 patients were enrolled. Three patients were excluded per the eligibility criteria, and three patients withdrew consent before allocation. All patients had histologically confirmed adenocarcinoma: 10 patients had esophageal tumors (28%), 10 patients had GEJ tumors (28%), and 16 patients had gastric tumors (44%). Table 1 summarizes baseline patient demographics and disease characteristics.

Table 1. Baseline patient characteristics (n = 36)

Patient characteristics	*n* (%)
Gender	
Women	5 (14)
Men	31 (86)
Race	
Asian	3 (8)
Black	1 (3)
Hispanic	3 (8)
White	29 (81)
Median age (range)	59 (24–77)
Median KPS (range)	80 (80–100)
Anatomic tumor location	
Gastroesophageal junction	10 (28)
Esophagus	10 (28)
Stomach	16 (44)
Evaluable disease	
Measurable disease by RECIST 1.1	29 (81)
Nonmeasurable	7 (19)
HER2 status	
HER2 IHC 3+	4 (11)
HER2 IHC 0/1 or FISH <2	27 (75)
HER2 not tested	5 (14)

Abbreviations: FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; KPS, Karnofsky performance status; IHC, immunohistochemistry.

Treatment and Outcomes

With median follow-up among survivors of 33 months, we observed 33 deaths at the time of analysis; 19 patients were progression free at 6 months, resulting in a 6-month PFS of 53% (95% CI, 38%–71%). Although this rate is higher than the historical control of 41% with standard chemotherapy, the confidence interval contains 41% and the trial did not meet its prespecified decision rule to declare the combination worthy of further investigation. Median OS was 14.2 months (95% CI, 8.1–20.7 months; Fig. 1A), and median PFS was 7.1 months (95% CI, 4.5–11 months; Fig. 1B).

Thirty-five patients were evaluable for response. One patient had a CR that lasted 48.2 months, 18 patients (51%) had a PR, and 8 patients (23%) had SD (Fig. 1C). The ORR (CR + PR) was 54% (95% CI, 37%–70%), and the disease control rate (CR + PR + SD) was 77% (95% CI, 63%–91%).

The majority of patients who progressed received subsequent therapy, with 24 patients (67%) receiving second-line treatment and 16 patients (44%) receiving third-line treatment (Table 2). Five patients (14%) were treated with immune checkpoint inhibitors, and 15 patients (42%) patients received ramucirumab in combination with chemotherapy. Five patients (14%) with *ERBB2*-amplified tumors received trastuzumab with chemotherapy as second- or third-line treatment.

Toxicity

The most common grade 3–4 treatment-related AEs were neutropenia (36%), leucopenia (11%), and hypertension (8%; Table 3). One patient with a gastric body tumor had grade 5 hematemesis during the third treatment cycle. Twelve patients required regorafenib dose reduction: seven patients were reduced to 120 mg daily, and five patients required two dose reductions to 80 mg daily. The mean relative dose intensities during the first 6 months of treatment for regorafenib, oxaliplatin, bolus 5-FU, and infusional 5-FU were 95.8%, 80%, 83.4%, and 88.4%, respectively.

Genomic Analysis

To explore genomic predictors of response, we prospectively profiled tumor samples from 30 patients with evaluable tissue using the MSK-IMPACT NGS platform [21]. All tumors harbored at least one genomic alteration, and the median mutational burden and copy number alterations were 5.1 mutations per megabase and 0.19, respectively. Oncogenic alterations—characterized by amplifications, homozygous deletions, or somatic mutations—were most frequently observed in *TP53* (87%), *KRAS* (23%), *ERBB2* (20%), *ERBB3* (10%) and cell cycle pathway genes: *CDKN2A* (13%), *CCND1* (10%), *CCNE1* (10%), and *RB1* (10%; Fig. 2). We assigned tumors to consensus TCGA molecular subtypes. The majority of tumors were CIN (24 patients), characterized by a high degree of copy number alterations and low mutational burden; only six patients were considered GS. We observed no MSI-H patients in our study.

To determine whether any genomic alterations were associated with response to regorafenib plus FOLFOX, we evaluated the correlation of PFS with each one (Fig. 2). We did not identify any genomic alteration significantly associated with

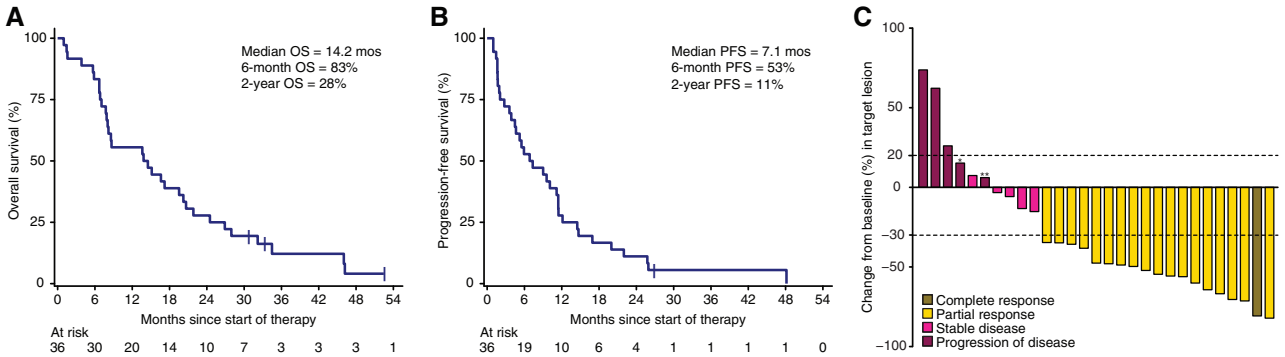

Figure 1. Kaplan-Meier curves and treatment response in patients treated with regorafenib plus FOLFOX. **(A):** OS in months since start of therapy. **(B):** PFS in months since start of therapy. **(C):** The reduction in maximum percentage change from baseline size in tumors. Seven patients evaluable for toxicity only were excluded. *Patient exhibited increase of nontarget lesions; **patient developed new lesions.
Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 2. Subsequent therapies

Subsequent therapy	*n*	+ Ram, *n*	+ Tras, *n*
Second line			
Irinotecan-based	11	5	1
Taxane-based	9	6	1
Checkpoint inhibitors	3	0	0
5-FU-cisplatin	1	0	1
Third line			
Irinotecan-based	2	0	0
Taxane-based	12	4	2
Checkpoint inhibitors	2	0	0

Abbreviations: 5-FU, 5-fluorouracil; Ram, ramucirumab; Tras, trastuzumab.

Table 3. Treatment-related adverse events occurring in >10% of patients (*n* = 36)

Toxicity	Any, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Grade 5, *n* (%)
ALT/AST/AP elevation	26 (72)	2 (5)	0	0
Fatigue	22 (61)	2 (5)	0	0
Thrombocytopenia	19 (53)	0	2 (5)	0
Leukopenia	18 (50)	4 (11)	0	0
Nausea	17 (47)	0	0	0
Neuropathy	17 (47)	0	0	0
Neutropenia	14 (39)	7 (19)	6 (17)	0
Hypertension	14 (39)	3 (8)	0	0
Anorexia	10 (27)	0	0	0
Mucositis	8 (22)	2 (6)	0	0
Anemia	8 (22)	0	0	0
Hand-foot syndrome	7 (19)	0	0	0
Vomiting	7 (19)	0	0	0
Diarrhea	4 (11)	1 (3)	0	0
Hematemesis	0	0	0	1 (3)

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase.

outcome (OS or PFS). Notably, all six *ERBB2*-amplified patients derived clinical benefit, including one CR, four PRs, and one SD. Of these, three patients were classified as HER2-positive per standard criteria [6] and received trastuzumab combined with chemotherapy as second-line treatment, resulting in two SDs and one PR, who survived 14.4, 26.0, and 35.7 months, respectively.

Lastly, we assessed for associations between response and homologous recombination deficiency (HRD), as defects in HR have been associated with response to platinum-based chemotherapy [24, 25]. The only patient with a somatic loss-of-function HR mutation (in *BRCA2*) did not respond to treatment. In addition, we determined the LST score, a surrogate marker for HRD based on copy number data [26]. We found no association with PFS (p = .23) and no difference in LST score between responders and nonresponders (p = .80).

Discussion

In this phase II trial evaluating regorafenib with first-line chemotherapy for patients with metastatic EG adenocarcinoma, the combination demonstrated a manageable safety profile and showed clinical activity with a 6-month PFS of 53% (95% CI, 38%–71%). Although this PFS is higher than that of historical controls receiving chemotherapy alone, the trial did not meet its prespecified endpoint to be considered for further investigation.

Preclinical and clinical data suggest that several growth factors regulate angiogenesis to promote cancer cell growth and metastasis, and antiangiogenic agents including ramucirumab and regorafenib have demonstrated efficacy as second- or third-line treatment for EG cancer [8, 9, 19]. However, our study adds to the growing body of work showing a lack of survival benefit for the addition of antiangiogenic therapy to first-line chemotherapy. In the phase III AVAGAST trial, bevacizumab plus chemotherapy produced small improvements in PFS and ORR but no survival benefit compared with chemotherapy alone [12]. Likewise, the recently reported randomized, placebo-controlled phase III RAINFALL trial found that adding ramucirumab to cisplatin/

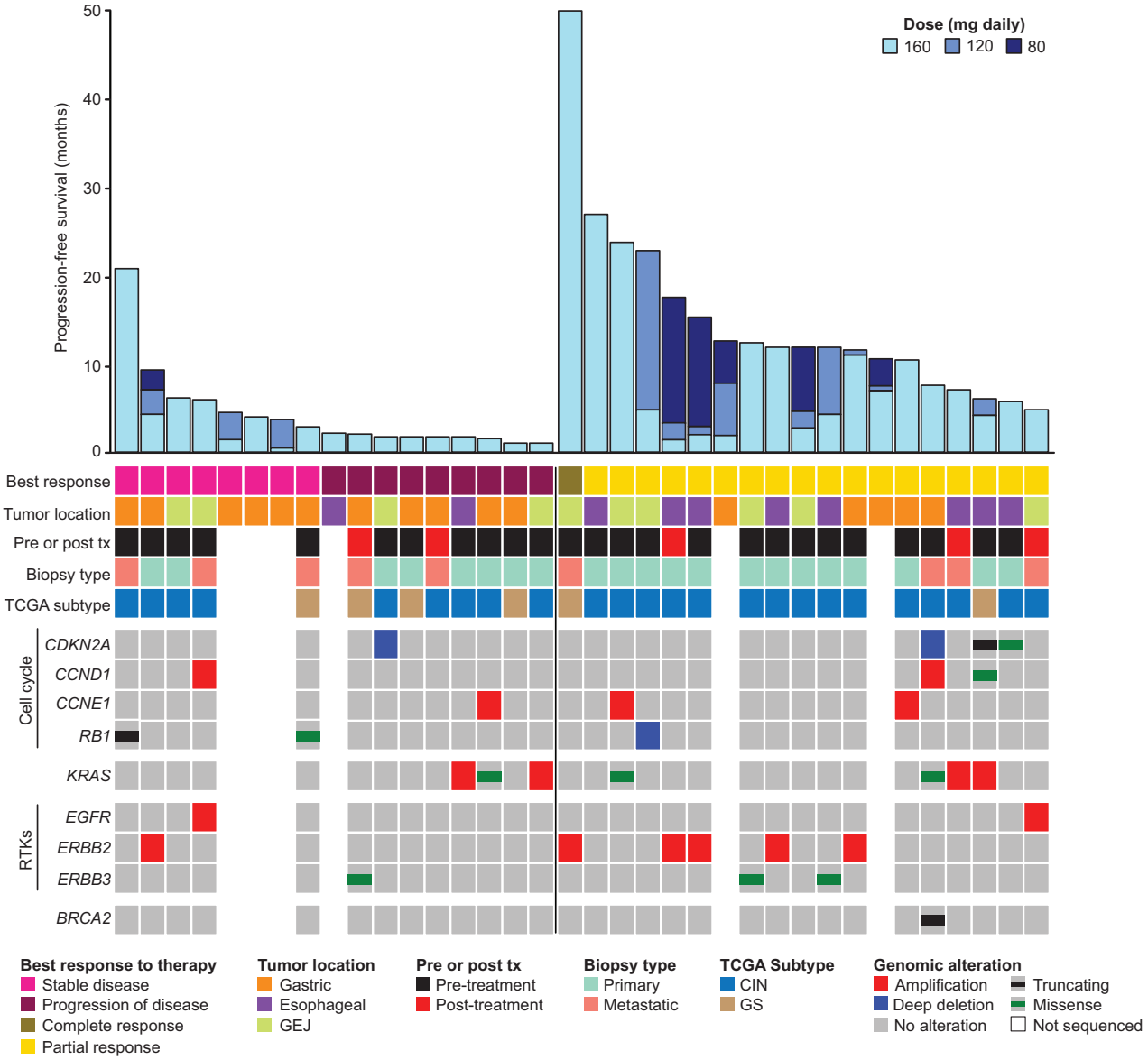

Figure 2. Genomic alterations and response to regorafenib plus FOLFOX. Relevant clinical features and key genomic alterations in 30 sequenced patients. Bar plot shows progression-free survival on treatment colored proportionally by time on treatment dosage. Best response to treatment, tumor location, pre- or posttreatment sequencing, metastatic status, and TCGA molecular subtype of the tumors are also annotated.
Abbreviations: CIN, chromosome instability; GEJ, gastroesophageal junction; GS, genomically stable; RTK, receptor tyrosine kinase; TCGA, The Cancer Genome Atlas; tx, treatment.

fluoropyrimidine did not improve OS [27]. Phase II studies also did not find a benefit when adding ramucirumab to either FOLFOX or S1 plus oxaliplatin [11, 14]. Although regorafenib targets multiple kinases in addition to VEGFR2, this broader activity does not seem to translate to better clinical activity. Therefore, a definitive benefit of anti-angiogenic agents as first-line treatment for EG cancer has yet to be demonstrated.

The molecular basis for this lack of efficacy in frontline EG cancer treatment is unclear. One potential explanation is that first-line chemotherapy selects for tumors that are more susceptible to angiogenesis inhibitors. Consistent with this notion, there are preclinical data in several tumor types suggesting that platinum resistance enhances secretion of or dependence on angiogenic factors like VEGF [28–30]. In addition, the chemotherapy backbone may modulate the effect of angiogenesis blockade, as ramucirumab has shown clinical benefit in combination with paclitaxel in EG cancer but not with platinum-based regimens. Several studies have demonstrated that paclitaxel has antiangiogenic properties [31], and in vivo animal data indicate that paclitaxel strongly mobilizes endothelial precursors whereas cisplatin does not [32]. Lastly, patients receiving second-line treatment are likely to be chemotherapy refractory, and therefore we may observe a larger effect with angiogenesis blockade compared with first-line treatment. Detailed exploratory analysis may help elucidate mechanisms of response and resistance to angiogenesis inhibition.

Using our NGS panel, we present the first broad genomic characterization of EG cancers from patients treated with

regorafenib. Our cohort was enriched for CIN tumors, whereas the GS and MSI-H subtype were rare or absent, respectively. These data are consistent with the lower frequency of MSI-H tumors in metastatic compared with localized EG cancers, as well as the higher prevalence of CIN GEJ tumors reported in Western populations. We identified six patients with *ERBB2* amplifications, although only three were HER2 positive by clinical criteria (immunohistochemistry [IHC] and/or fluorescence in situ hybridization [FISH] positivity). This HER2 discordance between NGS and IHC/FISH may be partly attributed to tumor heterogeneity, as we have previously demonstrated [5].

We did not identify any genomic alterations associated with response to first-line chemotherapy plus regorafenib, although this analysis is limited by the small sample size. Larger data sets would be necessary to make definitive conclusions regarding the impact of specific alterations on treatment response. It remains likely that tumor genomics may not fully explain the response to first-line chemotherapy or antiangiogenic agents. Rather, a broader assessment of the tumor transcriptome, proteome, metabolome, or other features may be needed to elucidate predictive biomarkers. Of note, we found that all six patients with *ERBB2* amplification benefited from regorafenib plus FOLFOX, with five of six patients demonstrating a PR or CR (83%). By targeting multiple tyrosine kinases, regorafenib may block RTK-RAS-PI3K signaling, which is overactivated in HER2-positive tumors [5].

Conclusion

Although our study suggests that regorafenib does not add to the efficacy of first-line chemotherapy in metastatic EG cancer, the regimen of FOLFOX plus regorafenib is well tolerated and may be amenable to combinations with additional systemic therapies such as immunotherapy. For example, the response rate for single-agent nivolumab in patients with chemotherapy-refractory metastatic gastric cancer was 11% in a phase III trial [33]; impressively, however, a recently reported phase Ib study (NCT03406871) combining regorafenib and nivolumab in previously treated patients with gastric cancer showed a response rate of 44% [34]. Although these data need to be validated in larger cohorts, they suggest that regorafenib may have synergy with immunotherapy. Moreover, checkpoint inhibitors have been safely combined with chemotherapy [35]. Although the recently reported KEYNOTE 62 trial did not find a benefit from the addition of pembrolizumab to first-line chemotherapy in advanced EG cancer, this study used cisplatin plus fluoropyrimidine as the chemotherapy backbone [36]. Importantly, multiple studies have shown that oxaliplatin induces immunologic cell death, whereas cisplatin does not activate immunologic cell death on its own despite the presumably similar mechanism of action [37–39]. Hence, it will be interesting to await results from the phase III CheckMate649 trial (NCT02872116) comparing first-line fluoropyrimidine and oxaliplatin plus nivolumab versus fluoropyrimidine and oxaliplatin. It is possible that oxaliplatin may be a better chemotherapy backbone for combination chemoimmunotherapy regimens compared with cisplatin. Thus, future trials assessing the potential benefit of combining immunotherapy with regorafenib and FOLFOX may be feasible and warranted.

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Disclosures

Gustavo Dos Santos Fernandes: Roche, Merck Sharp & Dohme, AstaZeneca, United, Sanofi, Bayer (SAB); **Michael F. Berger:** Roche (C/A); **David H. Ilson:** Amgen, Bayer, Eli Lilly & Co., Pieris, Roche, AstraZeneca, Bristol-Myers Squibb, Astellas, Merck, Taiho (C/A); **Yelena Y. Janjigian:** Boehringer Ingelheim, Bayer, Genentech/Roche, Bristol-Myers Squibb, Eli Lilly & Co., Merck (RF), Merck Serono, Bristol-Myers Squibb, Eli Lilly & Co., Pfizer, Bayer, Imugene, Merck (SAB). The other authors indicated no financial relationships.

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