CALGB 80403 (Alliance)/E1206: A Randomized Phase II Study of Three Chemotherapy Regimens Plus Cetuximab in Metastatic Esophageal and Gastroesophageal Junction Cancers

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ABSTRACT

Purpose

To determine the optimal chemotherapy backbone for testing in future US cooperative group studies for metastatic esophageal and gastroesophageal junction cancers. Cetuximab was added to each treatment arm based on promising preclinical data.

Patients and Methods

Patients with previously untreated metastatic esophageal or gastroesophageal junction cancer were randomly assigned at a one-to-one-to-one ratio to epirubicin, cisplatin, and continuous-infusion fluorouracil (ECF), irinotecan plus cisplatin (IC), or FOLFOX (oxaliplatin, leucovorin, and bolus and infusional fluorouracil). All treatment programs included cetuximab once per week. The primary end point was response rate. Secondary outcomes included overall survival, progression-free survival, time to treatment failure, and safety. As prespecified, primary and secondary analyses were conducted only among patients with adenocarcinoma.

Results

This study randomly assigned 245 patients, including 222 with adenocarcinoma. Among patients with adenocarcinoma, response rate was 60.9% (95% CI, 47.9 to 72.8) for ECF plus cetuximab, 45.0% (95% CI, 33.0 to 57.0) for IC plus cetuximab, and 54.3% (95% CI, 42.0 to 66.2) for FOLFOX plus cetuximab. Median overall survival was 11.6, 8.6, and 11.8 months; median progression-free survival was 7.1, 4.9, and 6.8 months; and median time to treatment failure was 5.6, 4.3, and 6.7 months for each of these arms, respectively. FOLFOX plus cetuximab required fewer treatment modifications compared with ECF plus cetuximab and IC plus cetuximab ($P = .013$), and fewer patients were removed from treatment because of an adverse event or experienced treatment-related death.

Conclusion

In combination with cetuximab, ECF and FOLFOX had similar efficacy, but FOLFOX was better tolerated. Although differences were nonsignificant, IC plus cetuximab seemed to be the least effective and most toxic of the three regimens tested.

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INTRODUCTION

Although esophageal cancer is the sixth leading cause of death resulting from cancer worldwide,¹ few large randomized trials have evaluated treatment of patients with advanced-stage esophageal cancer.^{2,3} In the absence of such data, treatment guidelines for metastatic esophageal cancer have been extrapolated from trials of gastric and gastroesophageal junction (GEJ)

cancers, which seem to respond similarly to standard chemotherapy.

Various chemotherapy regimens have shown activity against advanced esophagogastric cancer, but no regimen has shown clear superiority. Combinations of cisplatin and fluorouracil were among the first to show promise for metastatic esophagogastric cancer, yielding response rates of 25% to 30% and median survivals of 8 to 9 months.⁴⁻⁷ The addition of epirubicin to cisplatin and fluorouracil (ECF) has generated

response rates of 42% to 45% and similar survivals.⁸⁻¹⁰ Newer regimens include irinotecan and cisplatin (IC) once per week and combinations of oxaliplatin, fluorouracil, and leucovorin (FOLFOX); these have demonstrated encouraging response rates and survivals in phase II studies.¹¹⁻¹⁹

Cetuximab is a monoclonal antibody that blocks the ligand-binding site of the epidermal growth factor receptor (EGFR). EGFR expression is found in 71% to 83% of squamous cell carcinomas and in 64% of adenocarcinomas of the esophagus.²⁰⁻²² Increased expression has been a marker of poor prognosis in both malignancies in US and Asian series.²¹⁻²³

In 2005, the National Cancer Institute–sponsored GI Intergroup endorsed a randomized multicenter phase II clinical trial to evaluate the efficacy and safety of three promising chemotherapy combinations for the treatment of metastatic esophageal and GEJ cancers: ECF, IC, and FOLFOX. On the basis of the potential importance of the EGFR pathway in esophageal cancer, cetuximab was added to each regimen. This trial was conducted and completed before publication of two other randomized studies demonstrating a lack of benefit for EGFR inhibitors in molecularly unselected patients with advanced esophagogastric cancer.^{24,25}

PATIENTS AND METHODS

Patients

Patients were eligible if they were age 18 years or older, had metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or GEJ (type I or II by Siewert classification²⁶) with measurable disease according to RECIST version 1.0 had Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and had life expectancy of more than 12 weeks. No prior chemotherapy, radiotherapy, or anti-EGFR therapy was permitted. Individuals were ineligible if they had CNS metastases, presence of grade 2 or greater peripheral neuropathy or grade 2 or greater diarrhea, Gilbert's syndrome, allergy to monoclonal antibodies, major surgery within 4 weeks, second malignancy, or uncontrolled comorbid medical condition.

Trial Design

This study was conducted jointly by Cancer and Leukemia Group B (CALGB), now part of the Alliance for Clinical Trials in Oncology, and the ECOG, now part of the ECOG–American College of Radiology Imaging Network Cancer Research Group. CALGB 80403/E1206 was approved by the institutional review boards of the participating centers, the executive committees of both cooperative groups, and the Cancer Therapy Evaluation Program of the National Cancer Institute.

After signing informed written consent, eligible patients were randomly assigned at a one-to-one-to-one ratio to one of three treatment arms: ECF plus cetuximab (ECF-C; arm A), IC plus cetuximab (IC-C; arm B), or FOLFOX plus cetuximab (FOLFOX-C; arm C). Random assignment was stratified by histology (squamous cell carcinoma *v* adenocarcinoma) and ECOG performance status (0 or 1 *v* 2).

This randomized phase II study was conducted to evaluate the efficacy and safety of these three chemotherapies in combination with cetuximab and identify the most promising chemotherapy backbone for future testing. The primary outcome was tumor response rate (RR) among patients who received at least one dose of chemotherapy. Secondary end points included overall survival (OS), progression-free survival (PFS), time to treatment failure (TTF), and toxicity. All primary and secondary outcomes were calculated among patients with adenocarcinoma only. Analyses of patients with squamous cell cancer were conducted separately and considered exploratory.

Treatment Protocols

After premedication, all patients received cetuximab 400 mg/m² intravenously (IV) over 120 minutes on day 1 of the first cycle and then 250 mg/m² IV over 60 minutes once per week. Patients enrolled in arm A subsequently received on day 1 of each 3-week cycle epirubicin 50 mg/m² IV followed by cisplatin 60 mg/m² IV over 60 minutes and fluorouracil 200 mg/m² continuous IV infusion once per day for 21 days. Patients enrolled in arm B subsequently received on days 1 and 8 of each 3-week cycle cisplatin 30 mg/m² IV over 30 minutes followed by irinotecan 65 mg/m² IV over 90 minutes. Participants enrolled in arm C subsequently received on day 1 of each 2-week cycle oxaliplatin 85 mg/m² IV and leucovorin 400 mg/m² IV, both over 120 minutes, followed by fluorouracil 400 mg/m² IV bolus injection and then fluorouracil 2,400 mg/m² IV infusion over 46 to 48 hours.

To receive full-dose therapy in this trial, patients were required to have an absolute neutrophil count of 1,000/μL or greater, platelets of 75,000/μL or greater, and no other grade 2 or higher treatment-related toxicity. Toxicities in this trial were classified according to the Common Terminology Criteria for Adverse Events (version 3). Dose modifications in this study were cumulative and permanent. Chemotherapy was held for hematologic toxicity until blood counts were acceptable, after which the appropriate chemotherapy agents were dose reduced in 25% increments.

Cetuximab was held and attenuated in 50-mg/m² increments for grade 1 to 2 dermatologic toxicity and discontinued for severe hypersensitivity reaction, interstitial lung disease, or severe or persistent dermatologic toxicity. Epirubicin was attenuated for bilirubin 1.6 to 2.0 mg/dL and discontinued for bilirubin more than 2.0 mg/dL, grade 3 or 4 cardiac toxicity, or echocardiographic evidence of left ventricular ejection fraction less than 40%.

Cisplatin was held and attenuated for grade 3 to 4 nausea or vomiting, grade 2 neurotoxicity, ototoxicity, or creatinine clearance of 60 to 79 mL/min. Cisplatin was permanently discontinued for grade 3 to 4 peripheral neuropathy, severe ototoxicity, or creatinine clearance of less than 60 mL/min. Fluorouracil was held and attenuated for grade 2 or greater mucositis, esophagitis or diarrhea, or grade 3 to 4 hand-foot syndrome. Irinotecan was held and attenuated for bilirubin 1.6 to 2.0 mg/dL, grade 3 to 4 nausea or vomiting, grade 2 or greater mucositis, esophagitis, or diarrhea. Irinotecan was discontinued for bilirubin more than 2.0 mg/dL. Oxaliplatin was held and attenuated for grade 2 neuropathy or grade 3 to 4 nausea or vomiting and discontinued for grade 3 to 4 peripheral neuropathy or cardiac dysfunction.

Assessments

Patients were evaluated on day 1 of each cycle with an interval history, toxicity assessment, physical examination, performance status, and serum chemistries. CBC with differential was obtained once per week. Radiographic response to therapy was assessed every 6 weeks, using RECIST (version 1.0) criteria.

Statistical Plan

Within each treatment arm, a Simon two-stage design was used to test the hypothesis that the proportion (*p*) of patients achieving a complete (CR) or partial response (PR) was equal to 0.25 (*H*₀: *P* = .25) versus the alternative that this proportion was equal to 0.40 (*H*_A: *P* = .40). Under this design, a regimen would be declared efficacious if the null hypothesis were rejected at stage two.²⁷ A selection strategy was specified to determine the most efficacious treatment regimen based on RR.²⁸ The proportion of patients achieving tumor response was estimated based on the actual numbers of patients enrolled under the two-stage design as proposed by Jung et al.²⁹ CIs, adjusted for the two-stage test, were constructed according to the method proposed by Jennison and Turnbull.³⁰

Time-to-event end points included OS, PFS, and TTF. OS was measured from study entry until death resulting from any cause. PFS was measured from study entry until documented progression or death resulting from any cause. TTF was measured from study entry until

documented progression, death resulting from any cause, or end of protocol therapy because of unacceptable toxicity. Duration of response was measured from documented CR or PR until progression or death resulting from any cause among patients with measurable disease. Unplanned pairwise comparisons of OS, PFS, and TTF were conducted among the three regimens using the log-rank test; family-wise significance was determined using the Holm's sequential Bonferroni method.^{31,32} The Kaplan-Meier estimate was used to obtain the survival curves, and CIs were constructed using Greenwood's formula^{33,34}; 95% CI estimates are provided for OS, PFS, and TTF at 1 year from study entry (Appendix Table A1, online only).

In unplanned analyses, toxicity end points were compared across the three treatment regimens using the χ^2 test. As a secondary end point, the proportion of patients with squamous cell carcinoma achieving a CR or PR was estimated based on a single binomial proportion. All analyses among patients with squamous cell carcinoma are exploratory. Follow-up is shown as of September 27, 2014.

RESULTS

Patient Characteristics

From September 2006 to May 2009, 245 patients with esophageal or GEJ cancer were enrolled (Fig 1). Median follow-up time was 38.6 months. Two hundred twenty-two patients had adenocarcinoma (91%), and 23 patients had squamous cell carcinoma (9%). Seventy-four patients with adenocarcinoma were allocated to each treatment arm, and 213 (96%) of 222 patients received at least one cycle of chemotherapy and were evaluable for efficacy and safety analysis.

Demographic and clinical characteristics are listed in Table 1. Median age was 59 years; a majority were male (88%) and white

(96%) with an ECOG performance status of either 0 (48%) or 1 (49%). Fifty-six percent of patients had esophageal tumors, and 43% had tumors of the GEJ.

Treatment and Response Characteristics

Patients with adenocarcinoma received a median of 18 weeks of chemotherapy. There was no statistically significant difference among treatment arms in the number of treatment weeks received (Kruskal Wallis $P = .39$), and there was no significant difference in the total dose of cetuximab received (F-test $P = .11$). More than half (58%) of all patients stopped treatment because of disease progression, followed by adverse events (13%) and withdrawal of consent (11%).

Response was assessed in two stages among eligible patients with measurable adenocarcinoma receiving at least one cycle of chemotherapy (Table 2). Overall, 200 patients met these criteria. Of the 63 patients receiving ECF-C, one patient had a CR and 37 had a PR, for an objective RR (ORR) of 60.9% (95% CI, 47.9 to 72.8). Of the 71 patients receiving IC-C, one patient had a CR and 31 had a PR, for an ORR of 45.0% (95% CI, 33.0 to 57.0). Of the 66 patients receiving FOLFOX-C, two patients had a CR and 33 had a PR, for an ORR of 54.3% (95% CI, 42.0 to 66.2). Thus, the null hypothesis ($p \text{ v } H_0 \leq 0.25$) was rejected in all three arms, and all three treatments were defined as efficacious, with $P < .001$ for each treatment arm. Median duration of response was 7.1 months with ECF-C, 6.5 months with IC-C, and 6.6 months with FOLFOX-C.

All 213 patients who received at least one dose of chemotherapy were evaluable for OS, PFS, and TTF. For the ECF-C, IC-C, and FOLFOX-C arms, median OS was 11.6 (95% CI, 8.1 to 13.4),

Fig 1. CONSORT diagram. ECF-C, epirubicin, cisplatin, and fluorouracil plus cetuximab; FOLFOX-C, oxaliplatin, leucovorin, and fluorouracil plus cetuximab; IC-C, irinotecan and cisplatin plus cetuximab; OS, overall survival; TTF, time to treatment failure.

Table 1. Demographic and Clinical Characteristics of Patients With Adenocarcinoma Who Received $\geq$ One Cycle of Chemotherapy

Characteristic	No. (%)			Total (N = 213)
	ECF-C (n = 67)	IC-C (n = 73)	FOLFOX-C (n = 73)	
Age, years				
30-39	2 (3)	2 (3)	2 (3)	6 (3)
40-49	14 (21)	11 (15)	11 (15)	36 (17)
50-59	27 (40)	23 (31)	27 (37)	77 (36)
60-69	15 (22)	24 (33)	20 (27)	59 (28)
70-79	8 (12)	11 (15)	11 (15)	30 (14)
$\geq$ 80	1 (1)	2 (3)	2 (3)	5 (2)
Mean	57.7	59.9	59.6	59.1
Median	57.7	60.3	59.2	59.2
Range	33-87	34-81	30-83	30-87
Sex				
Male	59 (88)	60 (82)	68 (93)	187 (88)
Female	8 (12)	13 (18)	5 (7)	26 (12)
Race				
White	65 (97)	69 (94)	71 (97)	205 (96)
Black	1 (1)	2 (3)	2 (3)	5 (2)
Asian	0	1 (1)	0	1 (< 1)
Unknown	1 (1)	1 (1)	0	2 (1)
ECOG PS				
0	31 (46)	36 (49)	35 (48)	102 (48)
1	33 (49)	35 (48)	36 (49)	104 (49)
2	3 (4)	2 (3)	2 (3)	7 (3)
Primary site				
Esophagus	44 (66)	33 (45)	42 (58)	119 (56)
GEJ	23 (34)	40 (55)	28 (38)	91 (43)
Unknown	0	0	3 (4)	3 (1)
Disease type				
Measurable	65 (97)	72 (99)	70 (96)	207 (97)
Nonmeasurable	1 (1)	1 (1)	2 (3)	4 (2)
Unknown	1 (1)	0	1 (1)	2 (1)
Tumor grade				
I	0	1 (1)	4 (6)	5 (2)
II	22 (33)	31 (42)	28 (38)	81 (38)
III	37 (55)	35 (48)	33 (45)	105 (49)
IV	2 (3)	2 (3)	4 (6)	8 (4)
Unknown	6 (9)	4 (5)	4 (6)	14 (7)
Involved site				
Esophagus	41 (61)	35 (48)	36 (49)	112 (53)
Stomach	9 (13)	5 (7)	6 (8)	20 (9)
GEJ	26 (39)	37 (51)	28 (38)	91 (43)
Abdomen/pelvis	9 (13)	7 (10)	4 (5)	20 (9)
Liver	43 (64)	46 (63)	39 (53)	128 (60)
Lung/pleura	12 (18)	20 (27)	15 (21)	47 (22)
Bone	5 (7)	6 (8)	7 (10)	18 (8)
Lymph nodes	50 (75)	48 (66)	53 (73)	151 (71)
Other	18 (27)	12 (16)	17 (23)	47 (22)

Abbreviations: ECF-C, epirubicin, cisplatin, and fluorouracil plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX-C, oxaliplatin, leucovorin, and fluorouracil plus cetuximab; GEJ, gastroesophageal junction; IC-C, irinotecan and cisplatin plus cetuximab.

Table 2. Response Among All Eligible Patients With Measurable Adenocarcinoma Receiving $\geq$ One Cycle of Chemotherapy (N = 200)

Response	No. (%)		
	ECF-C (n = 63)	IC-C (n = 71)	FOLFOX-C (n = 66)
CR	1 (1.5)	1 (1.4)	2 (3.0)
PR	37 (58.7)	31 (43.6)	33 (50.0)
SD	14 (22.2)	23 (32.4)	18 (27.2)
PD	5 (7.9)	11 (15.5)	8 (12.1)
Not assessed	2 (3.2)	2 (2.8)	4 (6.0)
Unknown	4 (6.3)	3 (4.2)	1 (1.5)
ORR, %	60.3	45.1	53.0
95% CI	47.2 to 72.4	33.2 to 57.3	42.5 to 68.1
Response duration, months			
Median	7.1	6.5	6.6
Range	1.1-65.8	0.5-26.5	2.4-60.1

Abbreviations: CR, complete response; ECF-C, epirubicin, cisplatin, and fluorouracil plus cetuximab; FOLFOX-C, oxaliplatin, leucovorin, and fluorouracil plus cetuximab; IC-C, irinotecan and cisplatin plus cetuximab; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Adverse Effects

Overall, FOLFOX-C seemed to be the least toxic of the three chemotherapy regimens. Treatment modifications occurred less commonly with FOLFOX-C (73%) than with IC-C (85%) or ECF-C (91%; $\chi^2 P = .013$). Fewer patients randomly assigned to FOLFOX-C discontinued treatment because of an adverse event or experienced treatment-related death (11%) as compared with ECF-C (19%) or IC-C (26%; $\chi^2 P = .17$). Appendix Figure A1 (online only) depicts the median percentage of expected dose administered for each drug by cycle within each treatment regimen. A subgroup of patients receiving FOLFOX-C continued treatment for more weeks compared with those receiving ECF-C or IC-C.

Composite grade 3 to 5 hematologic toxicity was similar among the three treatment arms ($\chi^2 P = .32$; Table 3). However,

Fig 2. Overall survival for patients with adenocarcinoma by treatment arm. ECF-C, epirubicin, cisplatin, and fluorouracil plus cetuximab; FOLFOX-C, oxaliplatin, leucovorin, and fluorouracil plus cetuximab; IC-C, irinotecan and cisplatin plus cetuximab.

8.6 (95% CI, 6.0 to 12.4), and 11.8 months (95% CI, 8.8 to 13.9), respectively (Fig 2). Corresponding median PFS (Fig 3) was 7.1 (95% CI, 4.5 to 8.4), 4.9 (95% CI, 3.9 to 6.0), and 6.8 months (95% CI, 5.4 to 8.1), and median TTF (Fig 4) was 5.6 (95% CI, 3.9 to 7.2), 4.3 (95% CI, 3.6 to 5.5), and 6.7 months (95% CI, 4.8 to 7.4), respectively. Pairwise comparisons for each time-to-event end point resulted in one significant difference in TTF between IC-C and FOLFOX-C ($P = .012$) after applying the Holm's sequential Bonferroni adjustment for multiple comparisons.

Fig 3. Progression-free survival for patients with adenocarcinoma by treatment arm. ECF-C, epirubicin, cisplatin, and fluorouracil plus cetuximab; FOLFOX-C, oxaliplatin, leucovorin, and fluorouracil plus cetuximab; IC-C, irinotecan and cisplatin plus cetuximab.

IC-C was observed to have higher rates of grade 3 to 5 GI toxicity as compared with ECF-C or FOLFOX-C: 41%, 31%, and 22%, respectively ($\chi^2 P = .04$). IC-C was also noted to have higher rates of grade 3 to 5 metabolic toxicity: 34%, 18%, and 26%, respectively ($\chi^2 P = .09$). ECF-C and FOLFOX-C had higher rates of neurologic toxicity than IC-C: 15% and 16% versus 3%, respectively ($\chi^2 P = .02$).

Seventeen patients died within 30 days of receiving protocol therapy: five patients (7.5%) receiving ECF-C, six patients (8.2%) receiving IC-C, and six patients (8.2%) receiving FOLFOX-C. In the ECF-C arm, three patients experienced sudden death, one died as a result of complications from acute renal failure, and one died

Fig 4. Time to treatment failure for patients with adenocarcinoma by treatment arm. ECF-C, epirubicin, cisplatin, and fluorouracil plus cetuximab; FOLFOX-C, oxaliplatin, leucovorin, and fluorouracil plus cetuximab; IC-C, irinotecan and cisplatin plus cetuximab.

Table 3. Grade 3 to 5 AEs at Least Possibly Related to Treatment in Treated Patients Using CTCAE (version 3) Criteria

AE	No. (%)		
	ECF-C (n = 67 evaluable)	IC-C (n = 73 evaluable)	FOLFOX-C (n = 73 evaluable)
Hematologic	36 (53)	43 (59)	34 (46)
Neutropenia	33 (49)	37 (51)	31 (43)
Leukocytopenia	9 (13)	16 (22)	12 (16)
Anemia	5 (7)	10 (13)	5 (7)
Thrombocytopenia	3 (4)	6 (8)	2 (3)
Lymphopenia	5 (7)	8 (11)	2 (3)
Nonhematologic	49 (73)	56 (77)	48 (66)
Constitutional symptoms	9 (13)	15 (21)	12 (16)
Dermatologic	12 (17)	8 (11)	16 (22)
GI	21 (31)	30 (41)	16 (22)
Infection	9 (12)	6 (7)	5 (7)
Metabolic	12 (18)	25 (34)	19 (26)
Neurologic	10 (15)	2 (3)	12 (16)
Pain	6 (8)	2 (3)	2 (3)
Pulmonary	3 (4)	2 (3)	0 (0)
Vascular	5 (7)	7 (9)	3 (4)
Death (not CTCAE defined)	3 (4)	0 (0)	0 (0)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECF-C, epirubicin, cisplatin, and fluorouracil plus cetuximab; FOLFOX-C, oxaliplatin, leucovorin, and fluorouracil plus cetuximab; IC-C, irinotecan and cisplatin plus cetuximab.

as a result of progressive disease. In the IC-C arm, three patients died as a result of severe diarrhea and dehydration, one experienced sudden death, one died as a result of catheter-related sepsis, and one died as a result of respiratory failure caused by aspiration pneumonia. Among patients randomly assigned to FOLFOX-C, four patients died as a result of progressive disease, one as a result of postoperative complications, and one as a result of a GI bleed. Treatment-related deaths (defined as deaths occurring during treatment not attributed to disease progression) occurred in six patients (8.2%) randomly assigned to IC-C, four patients (6.0%) randomly assigned to ECF-C, and two patients (2.7%) randomly assigned to FOLFOX-C.

Second-Line Therapy

Of 213 patients, 121 (56%) reported receiving second-line therapy for their cancer, with no difference observed among treatment arms. Treatments prescribed in five or more patients were: (chemo)radiotherapy (n = 28), docetaxel (n = 11), irinotecan plus cisplatin (n = 8), carboplatin plus paclitaxel (n = 8), FOLFOX (n = 6), ECF (n = 6), irinotecan (n = 5), FOLFIRI (fluorouracil, leucovorin, and irinotecan; n = 5), docetaxel plus capecitabine (n = 5), fluorouracil plus leucovorin (n = 5), and capecitabine (n = 5).

Patients With Squamous Cell Carcinoma

Patients with squamous cell carcinoma were permitted to enroll in this clinical trial as part of an exploratory analysis. Only 23 patients with this histology enrolled, far fewer than the 64 patients expected.

A total of 19 patients were evaluable for response. Among patients randomly assigned to IC-C, the RR was only 12.5%, but it seemed higher for those assigned to ECF-C (67%) and FOLFOX-C (60%).

Median OS among 22 evaluable patients with squamous cell carcinoma was 8.2 months, primarily driven by the short median OS of patients randomly assigned to IC-C (6.5 months). Median OS was 10.6 months for patients randomly assigned to ECF-C and 12.4 months for patients randomly assigned to FOLFOX-C.

DISCUSSION

In this randomized phase II trial of cetuximab plus chemotherapy (ECF, IC, or FOLFOX), we demonstrated that each of the three combinations tested had a superior RR to the historic RR for the combination of cisplatin and fluorouracil, with ECF-C leading the group, followed by FOLFOX-C and IC-C. OS seemed promising for ECF-C and FOLFOX-C, especially considering that no patients with locally advanced disease were included in our trial. On the basis of the rates of required treatment modifications, treatment-related deaths, adverse events requiring discontinuation of therapy, and TTE, FOLFOX-C seemed to be the best tolerated of the three regimens. In contrast, IC-C seemed to be least efficacious, and IC-C was poorly tolerated in combination with cetuximab. Overall, these data suggest that FOLFOX may be the preferred chemotherapy backbone for further development.

Since the completion of our study, two large randomized trials have been published evaluating the efficacy of EGFR antibodies in unselected chemotherapy-naïve patients with esophagogastric adenocarcinoma. The REAL 3 (Randomized Open-Labelled Multicenter Trial of the Efficacy of Epirubicin, Oxaliplatin, and Capecitabine [EOX] With or Without Panitumumab in Previously Untreated Advanced Esophagogastric Cancer) study compared the combination of epirubicin, oxaliplatin, and capecitabine (EOC) with attenuated EOC plus panitumumab in 553 patients with advanced esophagogastric adenocarcinoma.²⁴ The EXPAND (Erbix in Combination With Xeloda and Cisplatin in Advanced Esophagogastric Cancer) study randomly assigned 904 patients with advanced gastric or GEJ adenocarcinoma to capecitabine and cisplatin with or without cetuximab.²⁵ Neither study showed an efficacy advantage for the addition of an EGFR antibody; RRs were nearly identical in both studies, and survival was inferior for the experimental arm in the REAL 3 study²⁴ and similar in EXPAND.²⁵ Therefore, it seems unlikely that cetuximab inflated the RRs or the survival of the platinum/fluorouracil-based regimens tested in our study. The possibility that molecular characteristics may predict resistance to or benefit from cetuximab is currently being explored in a correlative analysis of samples from our trial.

Little is known of the impact of EGFR antibodies on the IC regimen; one small study enrolled 16 patients with IC-refractory esophagogastric cancer and administered the same regimen plus cetuximab.³⁵ Only one patient demonstrated a major response, and the toxicity for IC-C was consistent with the additive toxicity expected for the combination.

In both the REAL 3 and EXPAND studies, higher rates of grade 3 to 5 diarrhea, rash, mucositis, and hypomagnesemia were observed with EGFR antibody treatment, although treatment-related deaths and adverse events leading to treatment discontinuation were nearly identical. Randomized data with FOLFOX and EGFR antibodies in esophagogastric cancer are lacking, but similar results have been noted with the addition of EGFR antibodies to FOLFOX in colorectal cancer.^{36,37} Although cetuximab probably increased the rates of diarrhea, rash, mucositis, and hypomagnesemia when added to the ECF and FOLFOX regimens in a comparable fashion, a differential impact cannot be ruled out. The IC arm may have seen a greater increase in diarrhea than the other arms, and this may have had a negative impact on the efficacy and safety results of this arm. In addition, the greater familiarity of US investigators with the FOLFOX regimen (v ECF or IC) may have skewed the toxicity results in favor of this treatment arm.

One can only speculate how FOLFOX would have compared with the EOC combination. The REAL 2 study demonstrated that EOC had superior OS but similar RR and PFS compared with the ECF regimen.² Toxicity was variable across the three treatment arms. Ultimately, the REAL 2 investigators chose EOC over ECF as their favored chemotherapy backbone, based as much on ease of administration and toxicity profile as on efficacy, a conclusion not dissimilar from that of our study.

In summary, on the basis of the favorable efficacy of ECF-C and FOLFOX-C and the superior tolerability of FOLFOX-C, FOLFOX seems to be the safer and more reliable chemotherapy backbone for future testing in cooperative group studies in advanced esophageal and GEJ cancers. However, selection of future chemotherapy plus targeted agent combinations will ultimately depend on the unique characteristics and interactions of the specific agents involved. Findings of this study suggest that FOLFOX represents an attractive standard of care for treatment of patients with advanced esophageal cancer.

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Disclosures provided by the authors are available with this article at www.jco.org.

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ECF, IC, or FOLFOX Plus Cetuximab for Esophageal and GEJ Cancers

Table A1. Estimates of 1-Year OS, PFS, and TTF and Associated 95% CIs

Treatment Arm	OS (%; 95% CI)	PFS (%; 95% CI)	TTF (95% CI)
Arm A: ECF-C	0.478 (0.355 to 0.591)	0.164 (0.087 to 0.262)	0.134 (0.066 to 0.227)
Arm B: IC-C	0.411 (0.298 to 0.520)	0.110 (0.051 to 0.193)	0.082 (0.034 to 0.159)
Arm C: FOLFOX-C	0.483 (0.363 to 0.593)	0.197 (0.114 to 0.295)	0.183 (0.104 to 0.280)

Abbreviations: ECF-C, epirubicin, cisplatin, and fluorouracil plus cetuximab; FOLFOX-C, oxaliplatin, leucovorin, and fluorouracil plus cetuximab; IC-C, irinotecan and cisplatin plus cetuximab; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

Fig A1. Median percentage of expected dose administered for each regimen by cycle. Cycles with fewer than 10 patients were truncated. (A) Epirubicin, cisplatin, and fluorouracil plus cetuximab; (B) irinotecan and cisplatin plus cetuximab; (C) Oxaliplatin, leucovorin, and fluorouracil plus cetuximab.