

Prospective, Randomized, Multicenter, Phase III Study of Fluorouracil, Leucovorin, and Irinotecan Versus Epirubicin, Cisplatin, and Capecitabine in Advanced Gastric Adenocarcinoma: A French Intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) Study

Rosine Guimbaud, Christophe Louvet, Pauline Ries, Marc Ychou, Emilie Maillard, Thierry André, Jean-Marc Gornet, Thomas Aparicio, Suzanne Nguyen, Ahmed Azzedine, Pierre-Luc Etienne, Eveline Boucher, Christine Rebischung, Pascal Hammel, Philippe Rougier, Laurent Bedenne, and Olivier Bouché

ABSTRACT

Purpose

To compare epirubicin, cisplatin, and capecitabine (ECX) with fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatments in patients with advanced gastric or esophagogastric junction (EGJ) adenocarcinoma.

Patients and Methods

This open, randomized, phase III study was carried out in 71 centers. Patients with locally advanced or metastatic gastric or EGJ cancer were randomly assigned to receive either ECX as first-line treatment (ECX arm) or FOLFIRI (FOLFIRI arm). Second-line treatment was predefined (FOLFIRI for the ECX arm and ECX for the FOLFIRI arm). The primary criterion was time-to-treatment failure (TTF) of the first-line therapy. Secondary criteria were progression-free survival (PFS), overall survival (OS), toxicity, and quality of life.

Results

In all, 416 patients were included (median age, 61.4 years; 74% male). After a median follow-up of 31 months, median TTF was significantly longer with FOLFIRI than with ECX (5.1 v 4.2 months; $P = .008$). There was no significant difference between the two groups in median PFS (5.3 v 5.8 months; $P = .96$), median OS (9.5 v 9.7 months; $P = .95$), or response rate (39.2% v 37.8%). First-line FOLFIRI was better tolerated (overall rate of grade 3 to 4 toxicity, 69% v 84%; $P < .001$; hematologic adverse events [AEs], 38% v 64.5%; $P < .001$; nonhematologic AEs: 53% v 53.5%; $P = .81$).

Conclusion

FOLFIRI as first-line treatment for advanced gastric and EGJ cancer demonstrated significantly better TTF than did ECX. Other outcome results indicate that FOLFIRI is an acceptable first-line regimen in this setting and should be explored as a backbone regimen for targeted agents.

J Clin Oncol 32:3520-3526. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Advanced gastric adenocarcinoma has a poor prognosis with a spontaneous median survival of 3 to 6 months.¹ Chemotherapy is the standard palliative treatment in patients with an acceptable clinical status because it provides better survival and quality of life than supportive care. Many chemotherapy regimens have demonstrated efficacy in advanced gas-

tric cancer (AGC). Combinations of cisplatin and fluorouracil (CF) and combinations of epirubicin, cisplatin, and fluorouracil (ECF) are old standards that are still active and widely used today. In the past decade, more drugs, including oral fluorouracil, docetaxel, oxaliplatin, and irinotecan, have proved to be effective for this indication. New first-line regimens demonstrated equivalence (epirubicin, cisplatin, and capecitabine [ECX]; epirubicin, oxaliplatin,

Rosine Guimbaud, Centre Hospitalier Universitaire Toulouse, Toulouse; Christophe Louvet, Institut Mutualiste Montsouris; Thierry André, Hôpital Saint Antoine; Jean-Marc Gornet, Centre Hospitalier Universitaire Saint Louis (Assistance Publique-Hôpitaux de Paris); Pascal Hammel, Hôpital Beaujon; Philippe Rougier, Hôpital Européen Georges Pompidou, Paris; Pauline Ries, Institut Paoli Calmettes, Marseille; Marc Ychou, Institut Régional du Cancer Val d'Aurelle, Montpellier; Emilie Maillard, Fédération Francophone de Cancérologie Digestive; Laurent Bedenne, Centre Hospitalier Universitaire, Dijon; Thomas Aparicio, Hôpital Avicenne, Bobigny; Suzanne Nguyen, Hôpital Général, Beauvais; Ahmed Azzedine, Hôpital Général, Montélimard; Pierre-Luc Etienne, Clinique Armorica, Saint-Brieuc; Eveline Boucher, Centre Eugène Marquis, Rennes; Christine Rebischung, Hôpital A. Michallon, Grenoble; Olivier Bouché, Centre Hospitalier Universitaire Robert Debré, Reims, France.

Published online ahead of print at www.jco.org on October 6, 2014.

Support information appears at the end of this article.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00374036.

Corresponding author: Rosine Guimbaud, PhD, Centre Hospitalier Universitaire Toulouse, Hôpital Rangueil, 1 av. du Pr Jean Poulhes, TSA50032 Toulouse Cedex 9, France; e-mail: guimbaud.r@chu-toulouse.fr.

© 2014 by American Society of Clinical Oncology

0732-183X/14/3231w-3520w/\$20.00

DOI: 10.1200/JCO.2013.54.1011

and capecitabine [EOX]; and mFOLFOX) or superiority (docetaxel, cisplatin, and fluorouracil [DCF]) to CF or ECF.²⁻⁴ Their long-term benefit remains poor with overall survival still less than 1 year (7 to 9 months in most studies). Second-line chemotherapy has recently been validated in randomized studies⁵⁻⁷ in patients with a functional status capable of tolerating it.

Recently, anti-human epidermal growth factor receptor 2 (HER2; Herceptin) was the first targeted therapy to show efficacy. This drug was beneficial in a subgroup representing no more than 25% of all patients with gastric cancer with overexpression of HER2.⁸ No other targeted therapy is currently available for the first-line treatment of AGC because anti-epidermal growth factor receptor and anti-vascular endothelial growth factor approaches failed to demonstrate efficacy in recent phase III studies.⁹⁻¹¹ Finally, for AGC without overexpression of HER2, several first-line chemotherapy regimens that combine two or three cytotoxic agents (including fluorouracil, anthracycline, platinum, and derived taxanes) are available.¹² These regimens are characterized by similar efficacy but different levels of toxicity. In this palliative setting, toxicity profiles are particularly important and have to be considered before choosing a treatment.

Irinotecan has demonstrated activity in AGC as both a first- and second-line treatment in several phase II studies and in one phase III trial.¹³⁻¹⁵ In the Dank et al¹⁴ phase III trial, the combination of irinotecan with once per week 22-hour infusions of fluorouracil was not inferior to CF and demonstrated a more favorable safety profile and a trend toward a better quality of life.^{14,16} Despite favorable data from these prior studies, the combination of irinotecan and fluorouracil has not gained acceptance as a therapeutic option in the first-line treatment of AGC.

Our study compared fluorouracil, leucovorin, and irinotecan (FOLFIRI), the usual combination of irinotecan and fluorouracil widely used in colon cancer treatment, and ECX as first-line treatment for patients with gastric or esophagogastric junction (EGJ) adenocarcinoma.

PATIENTS AND METHODS

Study Population

This prospective, open, randomized, phase III study was performed in 71 French centers and was a collaborative study conducted by the Fédération Francophone de Cancérologie Digestive, the Fédération Nationale des Centres de Lutte Contre le Cancer, and the Groupe Cooperateur Multidisciplinaire en Oncologie (FFCD-Unicancer-GERCOR).

Patients with histologically confirmed, unresectable, locally advanced or metastatic gastric or EGJ adenocarcinoma were eligible. Other inclusion criteria were age 18 years or older, measurable and/or assessable lesions according to RECIST criteria,¹⁷ WHO performance score (PS) ≤ 2 , ability to take oral medications, no previous palliative chemotherapy (≥ 6 months from adjuvant chemotherapy was allowed), ≥ 3 weeks from previous radiotherapy, sufficient bone marrow function, creatinemia ≤ 110 $\mu\text{mol/L}$, and bilirubinemia ≤ 35 $\mu\text{mol/L}$.

Exclusion criteria were history of fluorouracil or anthracycline cardiotoxicity, cardiac or coronary deficiency; known cerebral or meningeal metastasis; other life-threatening cancer; being pregnant or breast-feeding; inability to complete the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) questionnaire; or unable to plan regular follow-up for any reason. All participants gave their written informed consent before inclusion. The study was approved by relevant ethics committees.

Study Design, Patient Stratification, and Treatment

Patients were randomly assigned (1:1) to receive either ECX as the first-line treatment (ECX arm) or FOLFIRI (FOLFIRI arm). Stratification criteria were WHO PS (0 v 1 to 2), measurable or assessable lesions, center, history of adjuvant chemotherapy or radiochemotherapy, tumor localization (gastric v EGJ), and pathologic type (linitis plastica or not). The second-line treatment was predetermined to reduce discrepancies in practices between the arms: second-line FOLFIRI for patients in the ECX arm and second-line ECX for patients in the FOLFIRI arm.

The ECX regimen consisted of epirubicin 50 mg/m² (15-minute intravenous [IV] infusion) plus cisplatin 60 mg/m² (1-hour IV infusion) on day 1 followed by oral capecitabine 1 g/m² twice per day from day 2 to day 15 every 3 weeks¹⁸; the maximum cumulative dose of epirubicin authorized was 900 mg/m².

The FOLFIRI regimen consisted of irinotecan 180 mg/m² (90-minute IV infusion) and leucovorin 400 mg/m² (2-hour IV infusion) followed by a fluorouracil 400 mg/m² IV bolus and then fluorouracil 2,400 mg/m² as a 46-hour continuous infusion every 2 weeks. Dose modifications, appropriate hydration, and premedication were predefined in the study protocol.

The first-line treatment was dispensed until disease progression, unacceptable toxicity, patient's request to stop treatment, or death. The second-line treatment was given after a minimum treatment-free interval of 3 weeks and biologic and clinical recovery.

Before each chemotherapy cycle, a clinical examination and complete laboratory assessments were performed. Every 8 weeks from random assignment to progression, an electrocardiogram, a thoracoabdominal computed tomography (CT) scan, and complete laboratory and quality-of-life (QoL) assessments were performed.

Efficacy Criteria

The primary end point was time-to-treatment failure (TTF) for the first-line therapy in the two treatment arms. TTF was defined as the time between random assignment and disease progression, treatment discontinuation, or death.

The secondary end points were progression-free survival (PFS) defined as the time between random assignment and disease progression or death and overall survival (OS) defined as the time between random assignment and death. Toxicity was evaluated by National Cancer Institute Common Toxicity Criteria version 2.0 and QoL.

Tumor response was evaluated by investigators and classified according to RECIST criteria.¹⁷ CT scans were performed before the start of treatment and then every 8 weeks until disease progression for each treatment line and in each arm. QoL was collected by using the EORTC QLQ-C30 (15 dimensions) and the EORTC QLQ-STO22 (22 questions; the gastric cancer module) questionnaires.¹⁹

Selection of Population Size

To detect an expected improvement in median TTF during first-line treatment from 3.45 months with ECX to 4.60 months with FOLFIRI (two-sided $\alpha = 5\%$, $\beta = 20\%$), it was necessary to include 416 patients over 48 months to observe 379 events, taking into account a planned interim analysis at 190 events. This interim analysis to test the superiority of FOLFIRI was done when 349 patients had been included and 252 events had been observed (67% of events required). Superiority could not be reached ($P = .78$), so the study continued.²⁰

Statistical Analyses

All efficacy analyses were performed on an intent-to-treat principle. The safety population was defined as all patients receiving at least one dose of study treatment. Qualitative variables are described as numbers and percentages, and quantitative variables are described as means, standard deviations, and medians and ranges (minimum-maximum). On-treatment variables (response, duration of treatment) were compared by using the χ^2 test, Fisher's exact test, or a nonparametric Wilcoxon test, depending on the type and distribution of the variables.

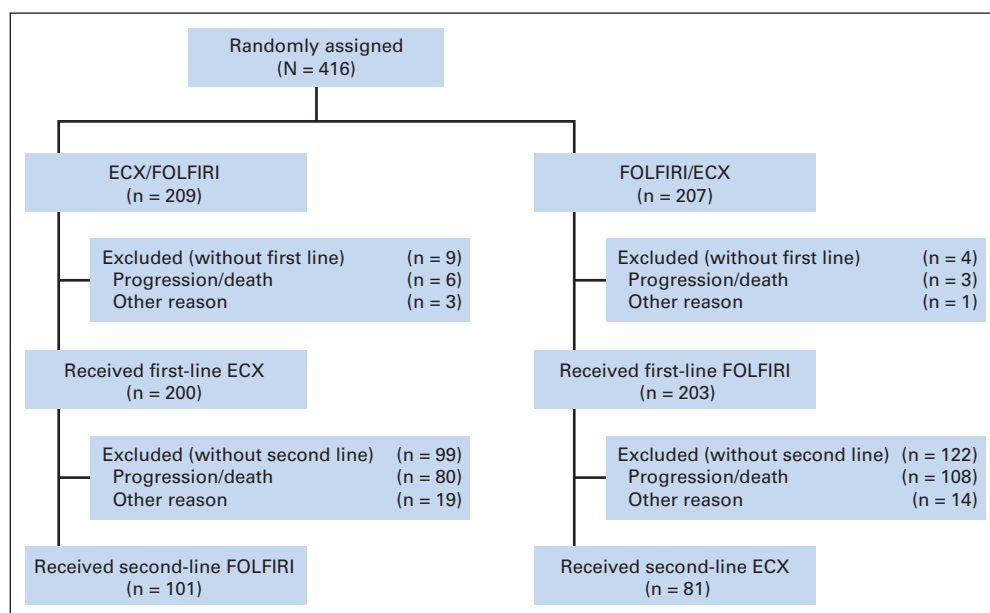


Fig 1. CONSORT diagram. ECX, epirubicin, cisplatin, and capecitabine; FOLFIRI, irinotecan, leucovorin, fluorouracil bolus, and continuous infusion.

Median follow-up was calculated according to reverse Kaplan-Meier estimates. Survival curves were plotted by using Kaplan-Meier estimates and were compared by using the log-rank test. Univariate Cox models were used to calculate the hazard ratio (HRs) with 95% CIs. To assess the assumption of proportional hazards of Cox models, Schöenfeld residuals were plotted. QoL scores were calculated according procedures defined in the EORTC QLQ-C30 scoring manual. An analysis of time until definitive deterioration of QoL (decrease in QLQ-C30 score of five or more points without any improvement) was performed. All analyses were performed by using SAS software version 9.1 (SAS Institute, Cary, NC). The level of statistical significance was $P < .05$.

RESULTS

Study Population

A total of 416 patients (ECX, $n = 209$; FOLFIRI, $n = 207$) were randomly assigned to receive the study treatment between June 2005 and May 2008 (Fig 1). The two groups were balanced for demographic and clinical characteristics (Table 1). Median age was 61.4 years, 74% of patients were male, and 82% had a WHO PS of 0 to 1.

Table 1. Patients' Demographic and Clinical Characteristics at Baseline

Characteristic	ECX Arm (n = 209)		FOLFIRI Arm (n = 207)		Total (N = 416)	
	No.	%	No.	%	No.	%
Age, years						
Median	61.4		61.4		61.4	
Range	27.9-83.8		28.8-81.0		27.9-83.8	
Male sex	154	73.7	155	74.9	309	74.3
WHO PS						
0	61	29.2	71	34.3	132	31.7
1	108	51.7	102	49.3	210	50.5
2	36	17.2	27	13.0	63	15.1
Missing	4	1.9	7	3.4	11	2.6
Tumor location						
EGJ	73	34.9	63	30.4	136	32.7
Gastric	133	63.6	138	66.7	271	65.1
Missing	3	1.4	6	2.9	9	2.2
Primary site resected	54	25.8	48	23.2	102	24.5
Linitis plastica	45	21.5	53	25.6	98	23.6
Metastatic disease	173	82.8	176	85.0	349	83.9
Previous treatment	23	11.0	20	9.7	43	10.3
Type of previous treatment						
Chemotherapy plus radiotherapy	12	52.2	13	65.0	25	58.1
Chemotherapy alone	4	17.4	5	25.0	9	20.9
Other	7	30.4	2	10.0	9	20.9

Abbreviations: ECX, epirubicin, cisplatin, and capecitabine; EGJ, esophagogastric junction; FOLFIRI, fluorouracil, leucovorin, and irinotecan; PS, performance status.

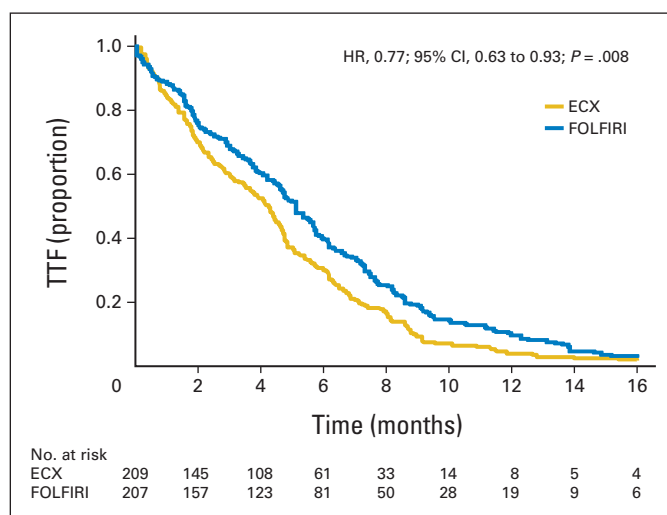


Fig 2. Time-to-treatment failure (TTF) according to treatment arm (Kaplan-Meier estimation). ECX arm: epirubicin, cisplatin, and capecitabine as the first-line treatment; FOLFIRI arm: irinotecan, leucovorin, fluorouracil bolus, and continuous infusion as the first-line treatment. HR, hazard ratio.

The location of the primary tumor was gastric in 65% of the patients and EGJ in 33%; the primary site was resected for 25%. Linitis plastica was present in 24% of the patients. Most of the patients (84%) had metastatic disease (synchronous in 83% of the patients). Only 43 patients (10.3%) had received previous anticancer treatment in an adjuvant or neoadjuvant setting (Table 1).

A CONSORT flow diagram for the patients is provided in Figure 1. Nine patients in the ECX arm and four in FOLFIRI arm did not receive any study treatment because of rapid disease progression, death before treatment initiation, or for other reasons. These patients were excluded from the safety analysis. All randomly assigned patients ($n = 416$) were eligible for the efficacy analysis on an intent-to-treat basis, and 403 patients (ECX arm: 200; FOLFIRI arm: 203) were eligible for the safety analysis.

Treatment Administered

First-line chemotherapy. The median number of cycles received was six (range, three to 21) in the ECX arm and 12 (range, four to 72) in the FOLFIRI arm.

Second-line chemotherapy. In all, 48% of patients in the ECX arm and 39% in the FOLFIRI arm received second-line chemotherapy ($P = .06$). The median number of cycles received was three (range, three to 15) in the ECX arm and eight (range, four to 44) in the FOLFIRI arm. Approximately 19% of patients received third-line treatment (at the discretion of the investigator).

Primary End Point

After a median follow-up of 31 months, the median TTF for the first-line therapy was significantly shorter in the ECX arm (4.24 months; 95% CI, 3.48 to 4.65 months) than in the FOLFIRI arm (5.08 months; 95% CI, 4.53 to 5.68 months; log-rank $P = .008$; HR, 0.77; 95% CI, 0.63 to 0.93; Fig 2).

Disease progression was the major cause of treatment discontinuation in both arms; it was less frequent in the ECX arm (48%) than in the FOLFIRI arm (61%). Other causes of treatment discontinuation were toxicity (14.5% [ECX] v 3.9% [FOLFIRI]), patient's request to stop (9.8% [ECX] v 6.4% [FOLFIRI]), change in general status (15% in each arm), and death (6.5% [ECX] v 10% [FOLFIRI]).

PFS and OS

There was no significant difference in median PFS between the ECX arm and the FOLFIRI arm (5.29 months [95% CI, 4.53 to 6.31 months] v 5.75 months [95% CI, 5.19 to 6.74 months]; log-rank $P = .96$; HR, 0.99; 95% CI, 0.81 to 1.21). Similarly, there was no significant difference in median OS between the two arms (9.49 months [95% CI, 8.77 to 11.14 months] v 9.72 months [95% CI, 8.54 to 11.27 months]; log-rank $P = .95$; HR, 1.01; 95% CI, 0.82 to 1.24; Table 2).

Response Rate

The objective response rate (ORR) for the first-line-treatment was determined in 189 of 209 patients in the ECX arm and 198 of 207 patients in the FOLFIRI arm. There was no significant difference between the two arms (39.2% v 37.8%, respectively, including 3.7% and 4% complete response rate). Similarly, the ORR for the second-line treatment was not statistically different: 13.7% in the ECX arm (receiving FOLFIRI as second-line treatment) versus 10.1% in the FOLFIRI arm (receiving ECX as second-line treatment).

Table 2. Efficacy Results for PFS and OS

Variable	ECX Arm (n = 209)			FOLFIRI Arm (n = 207)			P
	No.	%	95% CI	No.	%	95% CI	
PFS, months							.96*
Median		5.29			5.75		
Range		4.53-6.31			5.19-6.74		
24-month survival		5.03	2.46 to 8.97		2.76	1.01 to 6.03	
OS, months							.95*
Median		9.49			9.72		
Range		8.77-11.14			8.54-11.27		
24-month survival		11.17	7.03 to 16.36		10.71	6.51 to 16.09	

Abbreviations: ECX, epirubicin, cisplatin, and capecitabine; FOLFIRI, fluorouracil, leucovorin, and irinotecan; OS, overall survival; PFS, progression-free survival.
*Log-rank test.

Safety

First-line treatment. The overall rate of grade 3 to 4 toxicity was significantly higher with ECX than with FOLFIRI (84% v 69%, respectively; $P < .001$). High-grade hematologic adverse events were significantly more frequent with ECX than with FOLFIRI (64.5% v 38%, respectively; $P < .001$), but no significant difference was noticed for nonhematologic adverse events (53.5 v 53%, respectively; $P = .81$; Table 3).

Second-line treatment. No significant difference between the two arms was observed (Table 3).

Death as a result of toxicity. A total of 16 treatment-related deaths as a result of toxicity occurred: seven with first-line ECX and two with second-line FOLFIRI in the ECX arm; five with first-line FOLFIRI and two with second-line ECX in the FOLFIRI arm. Six of the 16 events were related to hematologic toxicities, five to global deterioration of the patient, three to sudden death and/or stroke, one to acute renal failure, and one to digestive toxicity.

QoL

More than 85% of patients in each arm completed at least one QLQ-C30 questionnaire. The median number of questionnaires per patient was two (range, one to 11) in the ECX arm and three (range, one to 12) in the FOLFIRI arm. For QLQ-STO22, the median number was two (range, one to 12) in each arm.

Our analysis focused on the QLQ-C30 global health score, physical score, and fatigue. There was no significant difference in any of

these scores between the two arms and no real trend toward a rapid deterioration in QoL. This conclusion was confirmed by the time to definitive deterioration. The median time was 7.6 months (95% CI, 6.1 to 8.9 months) in the ECX arm versus 7.4 months (95% CI, 6.2 to 8.6 months) in the FOLFIRI arm ($P = .64$). Further results for QoL will be presented in a separate publication.

DISCUSSION

Optimal chemotherapy in the first-line treatment of advanced gastric and EGJ adenocarcinoma is still a matter of debate. Several combinations of two or, more commonly, three cytotoxic agents have been validated in this setting. In this phase III trial involving 416 patients, first-line chemotherapy with FOLFIRI demonstrated acceptable response and survival outcomes and was less toxic and better tolerated than ECX. The study achieved the primary end point of superior TTF for FOLFIRI compared with ECX, a key end point that factors in both disease status and therapy toxicity, which lead to treatment discontinuation.

A recent updated meta-analysis provided evidence that irinotecan-containing regimens procured a survival benefit in first-line treatment of AGC.¹⁵ But a clear advantage of regimens that contain irinotecan over those that do not has not been established. In particular, the combination of irinotecan plus cisplatin, as evaluated in Japanese studies, did not improve outcome in AGC,²¹ perhaps because of an unfavorable toxicity profile. Irinotecan plus a fluorinated pyrimidine seems to be preferred. Several trials have indicated that irinotecan plus fluorouracil could be effective and well tolerated²²; in particular, FOLFIRI could be an appropriate combination.

The survival data in our study are similar to those obtained in most phase III studies, which highlights the poor prognosis of AGC.²³ However, compared with the pivotal British REAL-2 trial (Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer), our results with ECX appeared inferior in terms of PFS (6.7 months for REAL-2 and 5.29 months in our study) and ORR (46.4% and 39.2%, respectively). The different schedules of the ECX regimen (14 days of capecitabine every 21 days in our study) probably did not interfere; the dose-intensity was the same, and both regimens were validated in AGC. The lower PFS and ORR are likely explained by the greater rigor in our trial of performing CT scans every 8 weeks, rather than the Medical Research Council practice of performing scans every 3 months, which probably inflated both PFS and ORR. The ToGA study (ToGA Study—A Study of Herceptin [Trastuzumab] in Combination With Chemotherapy Compared With Chemotherapy Alone in Patients With HER2-Positive Advanced Gastric Cancer) is the only recent phase III study to demonstrate a median OS superior to 11 months in both arms. However, it was carried out in patients with HER2-positive AGC and excluded patients with linitis plastica, although our population had a linitis plastica prevalence of 24%.⁸ Because the diagnosis of linitis plastica depended on the investigator's appraisal, it is possible that some of these cases were limited to signet ring cell adenocarcinoma; however, this histologic characteristic is also a potential negative prognostic factor.

Our study revives the important debate that there may be nonplatinum-based chemotherapy alternatives in the first-line treatment of AGC. Here, FOLFIRI clearly appears as an interesting option for patients who are unable to take platinum-containing drugs. The utility of epirubicin is also called into question; many continue to debate whether anthracyclines should be used for therapy, given their toxicity.^{23,24} Our results support abandoning their use.

Table 3. Maximum Severity Grade for Toxicities

Toxicity and Grade	ECX Arm		FOLFIRI Arm		P*
	No.	%	No.	%	
First-line	200		203		
Nonhematologic					.81
Grade 0 to 2	85	42.5	90	44.3	
Grade 3 to 4	107	53.5	108	53.2	
Missing	8	4.0	5	2.5	
Hematologic					< .001
Grade 0 to 2	60	30.0	120	59.1	
Grade 3 to 4	129	64.5	78	38.4	
Missing	11	5.5	5	2.5	
Overall					< .001
Grade 0 to 2	25	12.5	58	28.6	
Grade 3 to 4	167	83.5	140	69.0	
Missing	11	5.5	5	2.5	
Second-line	101		81		
Nonhematologic					.39
Grade 0 to 2	50	49.5	36	44.4	
Grade 3 to 4	47	46.5	44	54.3	
Missing	4	4.0	1	1.2	
Hematologic					.89
Grade 0 to 2	53	52.5	44	54.3	
Grade 3 to 4	44	43.6	35	43.2	
Missing	4	4.00	1	1.2	
Overall					.73
Grade 0 to 2	29	28.7	22	27.2	
Grade 3 to 4	68	67.3	58	71.6	
Missing	4	4.00	1	1.2	

Abbreviations: ECX, epirubicin, cisplatin, and capecitabine; FOLFIRI, fluorouracil, leucovorin, and irinotecan.

*P value from χ^2 test.

Finally, the treatment schedules evaluated in our trial did not include a taxane; this could be criticized because taxanes have demonstrated noticeable activity in AGC.⁴⁻⁶ However, the benefit of DCF was balanced by its substantial toxicity, and median survival in these trials was the same order of magnitude as that observed in European and Western phase III studies and in our trial.

The choice of TTF as the primary end point could be considered. Like PFS, TTF includes not only tumor progression and death but also therapeutic failure. Thus, this end point introduces the idea of tolerance and overall acceptability of treatment, which is more representative of the benefit-risk ratio of palliative treatments. In clinical practice, appreciation of the benefit-risk ratio should help clinicians and guide therapeutic decisions in palliative situations.

Our study showed that first-line FOLFIRI was significantly less toxic and better tolerated than ECX. High rates of overall toxicities, the majority of which are clinically manageable, are common with most of the usual chemotherapy combinations in the AGC setting. In first-line ECX, the total for deaths as a result of toxicity was 3%, and the overall incidence of high-grade toxicities reached 83.5%; in first-line FOLFIRI, the total for deaths as a result of toxicity was 1%, and the overall incidence of high-grade toxicities was 69%. The difference in TTF largely stems from the 10% higher rate of therapy discontinuation as a result of toxicity in the ECX arm. More patients stopped treatment because of progressive disease with first-line FOLFIRI compared with ECX.

Second-line monotherapies based on irinotecan or taxane are now validated in AGC. Three studies have demonstrated a slight survival benefit compared with best supportive care.⁵⁻⁷ Although not all patients are able to receive second-line treatment and because strategic studies are infrequent in AGC, few data are available for estimating the proportion and characteristics of these patients. In our trial, the design included a second-line chemotherapy planned after disease progression under the first-line treatment. Forty-three percent of patients received second-line therapy with no significant difference between arms, suggesting that, although patients were treated for a longer time when FOLFIRI was the first-line therapy than was the case with ECX (4.8 v 3 months), the same proportion of patients had access to second-line treatment.

The combination of targeted therapies with cytotoxic chemotherapy is a promising approach to improving the treatment of AGC. Today, only patients with AGC with overexpression of HER2 benefit from targeted therapy.⁸ The other targeted therapies in first-line phase III clinical trials failed. The addition of bevacizumab to fluorouracil-platinum demonstrated no superior efficacy in the AVAGAST trial (A Study of Bevacizumab in Combination With Capecitabine and Cisplatin as First-line Therapy in Patients With Advanced Gastric Cancer [AVAGAST]).¹¹ Likewise, recently published phase III studies that evaluated anti-epidermal growth factor receptors were also negative, such as the REAL 3 (REAL 3: A Randomised Open-labelled Multicentre Trial of the Efficacy of Epirubicin, Oxaliplatin and Capecitabine [EOX] With or Without Panitumumab in Previously Untreated Advanced Oesophago-gastric Cancer) and EXPAND (Eributix [Cetuximab] in Combination With Xe-

loda and Cisplatin in Advanced Oesophago-gastric Cancer) trials.^{9,10} Moreover, a deleterious effect of the association of EOX plus panitumumab was noted, possibly because of the suboptimal cytotoxic chemotherapy regimen. Thus, the choice of the backbone chemotherapy should be a determining factor for the development of targeted therapies in AGC. Given the near universal failure to identify active targeted agents in first-line therapy when using either fluorouracil-platinum or ECF-capecitabine-based chemotherapy regimens, FOLFIRI, which has already been combined with targeted therapies in metastatic colorectal cancer, should be considered a serious option in treating AGC.

In our study, FOLFIRI as the first-line treatment for AGC and EGJ cancer demonstrated significantly better TTF than ECX. The parity of other outcomes, including PFS, tumor response, and OS, indicates that FOLFIRI is an acceptable first-line regimen in this setting and should be explored as a backbone regimen for targeted agents.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Rosine Guimbaud, Roche (C); Christophe Louvet, Pfizer (C), Roche (C); Thierry André, Roche (C); Thomas Aparicio, Pfizer (C); Olivier Bouché, Pfizer (C), Roche (C) **Stock Ownership:** None **Honoraria:** Christophe Louvet, sanofi-aventis, Roche; Thierry André, Baxter, Roche; Thomas Aparicio, Pfizer, Roche; Pierre-Luc Etienne, Roche; Philippe Rougier, Pfizer; Olivier Bouché, Roche, Pfizer **Research Funding:** None **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Rosine Guimbaud, Christophe Louvet, Marc Ychou, Christine Rebeschung, Philippe Rougier, Laurent Bedenne, Olivier Bouché

Administrative support: Laurent Bedenne

Provision of study materials or patients: Christophe Louvet, Thierry André, Suzanne Nguyen, Pierre-Luc Etienne, Eveline Boucher, Olivier Bouché

Collection and assembly of data: Marc Ychou, Thierry André, Jean-Marc Gornet, Thomas Aparicio, Suzanne Nguyen, Ahmed Azzedine, Pierre-Luc Etienne, Eveline Boucher, Pascal Hammel, Laurent Bedenne, Olivier Bouché

Data analysis and interpretation: Pauline Ries, Emilie Maillard, Thierry André

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

1. Wagner AD, Grothe W, Haerting J, et al: Chemotherapy in advanced gastric cancer: A systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 24:2903-2909, 2006

2. Cunningham D, Starling N, Rao S, et al: Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 358:36-46, 2008

3. Al-Batran SE, Hartmann JT, Probst S, et al: Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: A study of the Arbeitsgemein-

schaft Internistische Onkologie. *J Clin Oncol* 26:1435-1442, 2008

4. Van Cutsem E, Moiseyenko VM, Tjulandini S, et al: Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: A report of the V325 Study Group. *J Clin Oncol* 24:4991-4997, 2006

5. Kang JH, Lee SI, Lim do H, et al: Salvage chemotherapy for pretreated gastric cancer: A randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 30:1513-1518, 2012
6. Ford H, Marshall A, Bridgewater JA, et al: Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): An open-label, phase 3 randomised controlled trial. *Lancet Oncol* 15:78-86, 2014
7. Thuss-Patience PC, Kretschmar A, Bichev D, et al: Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer: A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 47:2306-2314, 2011
8. 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
9. Waddell T, Chau I, Cunningham D, et al: Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): A randomised, open-label phase 3 trial. *Lancet Oncol* 14:481-489, 2013
10. Lordick F, Kang YK, Chung HC, et al: Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): A randomised, open-label phase 3 trial. *Lancet Oncol* 14:490-499, 2013
11. Ohtsu A, Shah MA, Van Cutsem E, et al: Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: A ran-

domized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 29:3968-3976, 2011

12. Park SC, Chun HJ: Chemotherapy for advanced gastric cancer: Review and update of current practices. *Gut Liver* 7:385-393, 2013

13. Bouché O, Raoul JL, Bonnetain F, et al: Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: A Federation Francophone de Cancérologie Digestive Group Study—FFCD 9803. *J Clin Oncol* 22:4319-4328, 2004

14. Dank M, Zalwski J, Barone C, et al: Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. *Ann Oncol* 19:1450-1457, 2008

15. Qi WX, Shen Z, Lin F, et al: Overall survival benefits for irinotecan-containing regimens as first-line treatment for advanced gastric cancer: An updated meta-analysis of ten randomized controlled trials. *Int J Cancer* 132:E66-E73, 2013

16. Curran D, Pozzo C, Zalwski J, et al: Quality of life of palliative chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction treated with irinotecan combined with 5-fluorouracil and folinic acid: Results of a randomised phase III trial. *Qual Life Res* 18:853-861, 2009

17. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer

Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205-216, 2000

18. Cho EK, Lee WK, Im SA, et al: A phase II study of epirubicin, cisplatin and capecitabine combination chemotherapy in patients with metastatic or advanced gastric cancer. *Oncology* 68:333-340, 2005

19. Vickery CW, Blazeby JM, Conroy T, et al: Development of an EORTC disease-specific quality of life module for use in patients with gastric cancer. *Eur J Cancer* 37:966-971, 2001

20. Guimbaud R, Bouché O, Rebischung C, et al: Planned interim analysis of the intergroup FFCD-GERCOR-FNCLCC-AERO phase III study comparing two sequences of chemotherapy in locally advanced or metastatic gastric cancers. *J Clin Oncol* 27:210s, 2009 (suppl 15s; abstr 4533)

21. Boku N, Yamamoto S, Fukuda H, et al: Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: A randomised phase 3 study. *Lancet Oncol* 10:1063-1069, 2009

22. Wang DL, Gu DY, Huang HY, et al: Irinotecan-involved regimens for advanced gastric cancer: A pooled-analysis of clinical trials. *World J Gastroenterol* 16:5889-5894, 2010

23. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Oba K, Paoletti X, et al: Role of chemotherapy for advanced/recurrent gastric cancer: An individual-patient-data meta-analysis. *Eur J Cancer* 49:1565-1577, 2013

24. Enzinger PC, Burtneess B, Hollis D, et al: CALGB 80403/ECOG 1206: A randomized phase II study of three standard chemotherapy regimens (ECF, IC, FOLFOX) plus cetuximab in metastatic esophageal and GE junction cancer. *J Clin Oncol* 28:302s, 2010 (suppl 15s; abstr 4006)

Support

Supported by Laboratoire Roche and Laboratoire Pfizer, Fédération Francophone de Cancérologie Digestive, Dijon, France; Fédération Nationale des Centres de Lutte Contre le Cancer, Paris, France; and Groupe Coopérateur Multidisciplinaire en Oncologie, Paris, France.



Acknowledgment

The authors thank the sponsor of the study (Centre Hospitalier Universitaire Toulouse, Centre Hospitalier de Toulouse, and la Ligue Nationale Contre le Cancer); the patients who participated in this study; all of the investigators (A. Adenis, D. Arsène, P. Artru, Y. Becouarn, M. Belkheir, M. Bennamoun, B. Bensoussan, V. Boige, O. Boulat, G. Breysacher, L. Cany, E. Carola, B. Chauffert, P. Chiappa, T. Conroy, J. Dauba, G. Declety, B. Denis, G. Desguetz, F. Desseigne, F. Di Fiore, S. Dominguez, M. Duluc, A.C. Dupont-Gossard, O. Dupuis, J.L. Dutel, J.L. Faroux, S. Fratté, G. Freyer, M.P. Galais, M. Garcia, D. Gargot, M.H. Gaspard, M. Gatineau, D. Genet, V. Guerin-Meyer, P. Guichard, M. Hebbbar, J. Jacob, P. Jouet, J.L. Jouve, M.C. Kaminsky, A. Khalil, F. Khemissa, P. Kieffer, J.P. Lafargue, B. Landi, S. Lavau-Denes, C. Lecaille, T. Lecomte, A. Ledit, C. Lenoir, C. Lepère, G. Lepeu, G. Lledo, C. Locher, J.P. Lotz, D. Luet, M. Mabro, A. Madroszyk, H. Mahmoud, F. Maindrault, S. Manfredi, T. Mansourbakht, J. Martin, M. Mesières, P. Michel, L. Mineur, E. Mitry, V. Moulin, B. Paillot, A. Patenotte, H. Perrier, J.M. Phelip, C. Platini, L. Poincloux, P. Poudoux, J. Provencal, A.M. Queuniet, J.L. Raoul, K. Richard, O. Romano, E. Samalin, J.F. Seitz, I. Sobhani, N. Stremsdoerfer, J. Taieb, P. Texereau, J. Thauray, A. Thiot-Bidault, A.L. Villing, F. Viret, H. Zerazhi); F. Masskouri (data manager); C. Choine, H. Fattouh, F. Guiliani, A. Kodjo, and N. Le Provost (Clinical Research Assistants); M. Moreau (the project manager of the Fédération Francophone de Cancérologie Digestive [FFCD]); and C. Girault (administrative executive of the FFCD).