original reports

Randomized, Phase II Study Prospectively Evaluating Treatment of Metastatic Esophageal, Gastric, or Gastroesophageal Cancer by Gene Expression of *ERCC1*: SWOG S1201

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abstract

PURPOSE Platinum-based therapy is the standard of care in patients who have HER2-negative, advanced esophagogastric cancer (AEGC). Retrospective data suggest that intratumoral *ERCC1* levels may determine platinum sensitivity. A randomized, phase II study was performed in patients with AEGC to explore whether the efficacy of a platinum-based therapy with fluorouracil, leucovorin, and oxaliplatin (FOLFOX) versus a non–platinum-containing regimen of irinotecan and docetaxel (IT) differed according to *ERCC1* levels.

PATIENTS AND METHODS Overall, 202 untreated patients with HER2-negative AEGC and a Zubrod performance status of 0-1 were evaluated prospectively for mRNA expression of *ERCC1* level and then randomly assigned to FOLFOX or IT, stratified by the intratumoral statuses of *ERCC1* low (< 1.7) or high (≥ 1.7). Objectives were to assess progression-free survival (PFS) and overall survival (OS) in all patients treated with FOLFOX compared with IT, stratified by low and high *ERCC1* levels, and to assess for interactive effects between *ERCC1* expression and treatment arm.

RESULTS Eighty-six percent of patients had *ERCC1* values < 1.7. Thus, evaluation of the *ERCC1*-high subgroup was limited. Grade ≥ 3 anemia, dehydration, diarrhea, and fatigue were greater in patients with IT. Occurrences of grade ≥ 3 neuropathy and decreased neutrophils were greater in patients with FOLFOX. In all patients, FOLFOX had a statistically superior median PFS compared with IT (5.7 *v* 2.9 months; hazard ratio, 0.68; $P = .02$). In patients with *ERCC1* levels < 1.7 receiving FOLFOX, PFS and response rate were statistically superior to IT, with no significant difference in OS.

CONCLUSION The evaluation of *ERCC1* in patients with upper GI tumors was thwarted by an overwhelming predominance of low *ERCC1* mRNA expression. Nonetheless, distribution of treatment effects on PFS did not vary with expression. For all patients and for those with low *ERCC1* expression, FOLFOX was superior in efficacy to IT.

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INTRODUCTION

In 2019, there will be more than 43,500 occurrences of esophagogastric cancer diagnosed in the United States and more than 26,650 deaths.[1] The majority of patients who present have a high risk of recurrence. Many chemotherapeutic drugs, including fluoropyrimidines, platinums, irinotecan, taxanes, TAS 102, the anti-VEGFR antibody ramucirumab, and immunotherapy, have demonstrated activity in this cancer.[2-11] Generally, the combination of fluoropyrimidines and platinums is used as front-line therapy. Although response rates with cytotoxic combinations range from 30%-50%, there can be significant toxicity associated with these regimens, and median overall survival (OS) remains largely between 6 and 9 months, with progression-free survival (PFS) in the 4- to 5-month range.

Doublets of fluorouracil (FU) and leucovorin plus oxaliplatin (FOLFOX) or irinotecan combined with docetaxel (IT) have demonstrated similar efficacy. FOLFOX has a reported response rate of 45%, a time to progression of 6.2 months, and an OS of 8.6 months; IT has reported response rates of 45%, a time to progression of 4.5 months, and an OS of 8.2 months.[12,13] These regimens, FOLFOX and IT, have not been compared yet. Generally, most combination chemotherapy in HER2-negative, advanced esophagogastric cancer has demonstrated a PFS of 4-6 months and an OS of 9-12 months.[2-4,14,15] Identifying predictive markers of outcome and response to

ASSOCIATED CONTENT

Appendix

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

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chemotherapy could help tailor treatment to allow patients to have exposure to drugs that may show maximum benefit.

ERCC1

The nucleotide excision repair pathway is a DNA repair pathway involved in repair of bulky, helix-distorting DNA lesions caused by ultraviolet light or chemicals, including platinum compounds. The cytotoxic effect of platinum compounds is based on the formation of these bulky, intrastrand, platinum-DNA adducts, and removal of these adducts from genomic DNA is mediated by the nucleotide excision repair pathway.[16] Recognition and repair of the platinum-induced damage results in platinum resistance. Critical in this pathway is the *ERCC1* gene (and protein); its low expression has been associated with platinum sensitivity. Several studies across tumor types have evaluated *ERCC1* mRNA expression and its potential to predict treatment response to platinum compounds.

ERCC1 and Gastric Cancer

In largely retrospective evaluations, *ERCC1* has been shown to predict response to platinum-based therapy. There has been evaluation by immunohistochemistry (IHC), mRNA levels by reverse transcriptase polymerase chain reaction, and single nucleotide polymorphisms. There has been no correlation between the methodologies assessed. Generally, IHC is an accessible technique although often criticized for potential variability in interpretation. Thereby, use of reverse transcriptase polymerase chain reaction allows for semiquantitative assessment of *ERCC1*, potentially allowing for consistency in evaluation. In gastric cancer, several retrospective evaluations have shown that *ERCC1* has a statistically significant relationship to response and survival in the advanced, perioperative and adjuvant setting.[17-21] A study of preoperative cisplatin and infusional FU in patients with gastric cancer assessed *ERCC1* retrospectively and demonstrated higher response rates and OS in patients with low *ERCC1* mRNA levels. Another trial, SWOG S0356, tested preoperative oxaliplatin combined with protracted-infusion FU and 4,500 cGy of external-beam radiation for esophageal cancer. Of the 90 patients evaluable for this trial, 53 (58.8%) had specimens analyzed for *ERCC1*. *ERCC1* mRNA levels within the primary tumor had a statistically significant inverse relationship to 2-year OS (37% *v* 72%; $P = .04$) and 2-year PFS (17% *v* 67%; $P < .0004$). The cutoff level was 1.66×10^{-3} in relation to expression of the *β-actin* gene, consistent with the previously reported cutpoint of 1.7×10^{-3}.[22,23] Further support that *ERCC1* expression predicts platinum sensitivity came from an evaluation of patients receiving S1 with cisplatin, in whom low *ERCC1* expression was associated with a higher response rate.[21] In another trial of patients with gastric cancer treated with FOLFOX, the median survival time was significantly longer for patients with low compared with high *ERCC1* expression (15.8 *v* 6.2 months; $P < .0001$).[20]

The relationship between *ERCC1* and platinum sensitivity has been demonstrated across tumor types; data in NSCLC, colon cancer, and ovarian cancer corroborate the inverse relationship of *ERCC1* and platinum sensitivity. Further, given that these have largely been retrospective evaluations, it has been difficult to discern whether *ERCC1* is a predictive or prognostic marker. Prospective treatment assignment based on the presence of *ERCC1* by IHC or gene expression has had mixed results.[24,25]

PATIENTS AND METHODS

Patients

Eligibility criteria included patients with unresectable advanced or metastatic HER2-negative adenocarcinoma of the esophagus, stomach, or gastroesophageal junction who were treatment naive or had completed adjuvant therapy at least 180 days before registration. If HER2 status was not known, tissue specimen submission was required for testing. Tumor tissue submission also was required to assess *ERCC1*. Patients must have had a Zubrod performance status of 0-1 with adequate organ function, defined as follows: hemoglobin $\geq$ 9 g/dL; ANC $\geq$ 1,500/μL; platelets $>$ 100,000/μL, total bilirubin $\leq$ 1.5 mg/dL (regardless of whether patients had liver involvement secondary to tumor); AST and ALT both $\leq$ 3 times the institutional upper limit of normal (unless the liver was involved with tumor, in which case both AST and ALT must be $\leq$ 5 times the institutional upper limit of normal), serum creatinine $<$ 1.5 mg/dL or creatinine clearance $>$ 60 mL/min; and no sensory neuropathy $>$ grade 1. Patients may have had measurable and/or nonmeasurable disease as assessed by computed tomography scans or magnetic resonance imaging 28 days or 42 days before registration, accordingly.

The study was approved by the local institutional review boards, and informed consent was obtained from all participants. All eligible patients were randomly assigned irrespective of *ERCC1* status. If *ERCC1* expression or HER2 status could not be determined, or if the patient had HER2-positive status, the patient was ineligible.

mRNA Quantification

Samples were to be fixed in formalin for 8-24 hours and then paraffin embedded according to institutional procedures. All gene expression levels were measured at a Clinical Laboratory Improvement Amendments–approved laboratory (Response Genetics, Los Angeles, CA); microdissection was performed on all formalin-fixed, paraffin-embedded tumor samples to ensure that only tumor cells were dissected. Details about the procedure for microdissection, mRNA isolation, and quantification are provided.[26] Results were to be provided in 7-10 days.

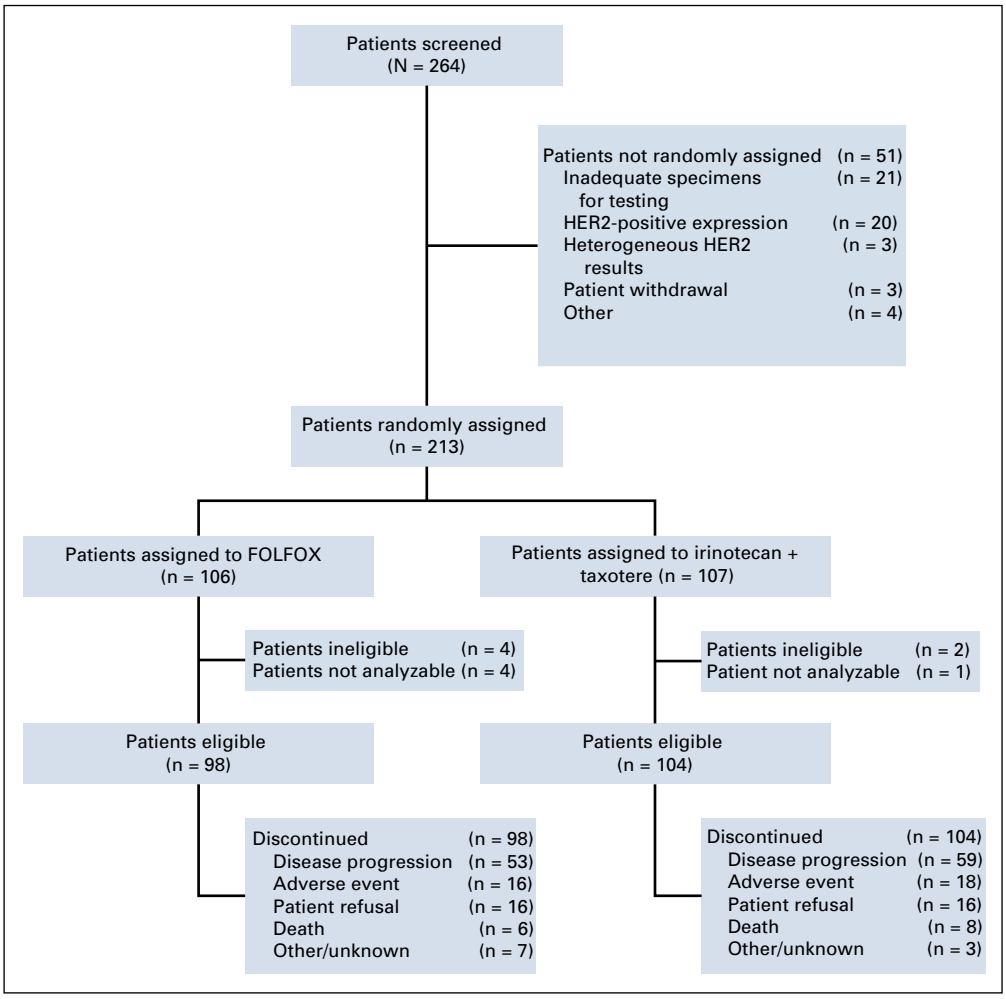

FIG 1. CONSORT flow diagram. FOLFOX, fluorouracil, leucovorin, and oxaliplatin.

Treatment

Treatment consisted of random assignment to either a platinum- or a non–platinum-containing arm with stratification for *ERCC1* level. The regimens were as follows: Arm 1 was FOLFOX, specifically oxaliplatin 85 mg/m^2 intravenously (IV) over 2 hours on day 1, leucovorin 400 mg/m^2 IV over 2 hours on day 1, FU 400 mg/m^2 IV bolus over 1 hour on day 1, and FU 2,400 mg/m^2 IV over 46-48 hours via CADD pump on days 1 and 2. Each cycle was to be administered every 14 days. Arm 2 was IT, specifically irinotecan 65 mg/m^2 IV over 90 minutes with docetaxel 30 mg/m^2 IV over 30 minutes on days 1 and 8. Each cycle was to be administered every 21 days. Dose adjustments of all agents were made according to toxicity experienced during the preceding cycle, using National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) for toxicity grading and serious adverse event reporting. The maximum dose delay for any reason was 4 weeks; omitted doses were not made up, and patients were taken off protocol treatment for dose delays of more than 4 weeks or dose adjustments of 2 or more levels.

Patients underwent disease assessment (by computed tomography or magnetic resonance imaging) every 6 weeks and were treated until disease progression occurred or until symptomatic deterioration, unacceptable toxicity, or treatment delay for any reason lasted longer than 4 weeks. Patients were observed until death or 3 years after registration, whichever occurred first.

Study Endpoints

The primary endpoint of this phase II study was PFS. Secondary endpoints included OS, toxicities, and overall response rate (ORR; confirmed and unconfirmed complete and partial response).

Statistical Considerations

The primary study hypothesis was that patients with high-*ERCC1* status who were treated with IT would have superior PFS compared with those treated with FOLFOX. It was anticipated that roughly 50% of patients would fall into each of the high or low *ERCC1* subgroups according to observed data in colorectal and esophageal cancer studies.[27] One hundred eligible patients in each *ERCC1* subgroup provided at least 80% power to detect hazard ratios (HRs) of 1.55 or greater across a range of potential median PFS

TABLE 1. Patient Characteristics

Characteristic	FOLFOX (n = 98)		Irinotecan + Docetaxel (n = 104)	
	No.	%	No.	%
Age, years				
Median	62.5		62.4	
Minimum	21.5		33.7	
Maximum	85.6		84.8	
Sex				
Male	78	80	83	80
Female	20	20	21	20
Hispanic				
Yes	12	12	19	18
No	83	85	83	80
Unknown	3	3	2	2
Race/ethnicity				
White	83	85	80	77
Black	7	7	6	6
Asian	5	5	8	8
Native American	1	1	0	0
Unknown	2	2	10	10
ERCC1				
High (≥ 1.7)	13	13	15	14
Low (< 1.7)	85	87	89	86
Site of disease				
Esophageal	33	34	36	35
Gastric/GEJ	65	66	68	65

Abbreviations: FOLFOX, fluorouracil, leucovorin, and oxaliplatin; GEJ, gastroesophageal junction.

values (3.0-5.5 months in the inferior arm and 4.7-9.9 months in the superior arm) according to a 10% one-sided log-rank test, 3 years of accrual, and 2 years of follow-up. The total accrual goal was 200 eligible patients. Patients were randomly assigned to treatment with FOLFOX or IT with stratification by *ERCC1* level (high *v* low, ≥ 1.7 *v* < 1.7, respectively) and disease site (esophageal *v* gastric/gastroesophageal junction).

The observed data did not align with our *ERCC1* distributional assumption, in that approximately 86% of the patients had *ERCC1* values lower than 1.7. Thus, the primary objective of assessing PFS in patients with high *ERCC1* by treatment arm was limited by low statistical power, and the interaction analysis of treatment effect by the a priori *ERCC1* threshold was not feasible. Thus, the analysis consisted of the following: (1) assessments of PFS, OS, and ORR in all patients treated with FOLFOX compared with those treated with IT, (2) assessments of PFS, OS, and ORR in patients with low-*ERCC1* status treated with FOLFOX compared with those treated with IT, (3) an assessment of PFS in patients with high-*ERCC1* status treated with FOLFOX compared with those treated with IT, and (4) an investigation into whether differences in PFS between the two treatment arms varied by *ERCC1* levels. The analysis plan also included estimation of *ERCC1* threshold(s) that defined categories of differential treatment effects on PFS given observed evidence of an interaction between *ERCC1* expression and treatment arm.

All eligible patients were included in the analyses by randomized treatment assignment regardless of actual treatments received according to the intent-to-treat principle. Probabilities of OS and PFS were estimated using the Kaplan-Meier method. Statistical differences in event rates between treatment arms were assessed via Cox regression model with stratification for *ERCC1* level (high *v* low) and disease site. Rates of ORR in the subset of patients with measurable disease were compared via the Fisher's exact test or χ^2 test as appropriate. A series of plotted Kaplan-Meier estimates was used to assess variation of treatment arm differences in PFS according to *ERCC1* levels (quartiles).

RESULTS

The study was activated on March 1, 2012, and closed to accrual on April 1, 2015, after meeting the accrual goal with 264 patients registered to the initial screening. The median time from screening to random assignment was 8.73 days (range, 3-20 days). Fifty-one patients were not randomly assigned, most commonly because of inadequate specimens for testing or HER2-positive expression. Two-hundred thirteen patients were randomly assigned. Six patients were deemed ineligible, and five additional patients were excluded from analyses because of death or withdrawal before random assignment; thus, 202 patients were included in the primary analysis (Fig 1). Patient characteristics are listed in Table 1.

Safety

One hundred eighty-nine patients were assessed for adverse events, because 14 patients did not receive protocol therapy. Among the 91 patients assessed for adverse events on the FOLFOX arm, three treatment-related deaths were reported (lung infection and oral mucositis, each n = 1, and a sudden death of unknown cause). Nine additional patients experienced grade 4 adverse events. In 98 patients assessed for adverse events on the IT arm, three treatment-related deaths were reported (multiorgan failure, n = 2; respiratory failure, n = 1). Fourteen additional patients experienced grade 4 adverse events (primarily hematologic events; Table 2).

Efficacy

The median PFS was significantly longer in the FOLFOX arm (n = 98) than in the IT arm (n = 104): 5.7 months (95% CI, 4.4 to 7.1 months) versus 2.9 months (95% CI, 1.9-4.1 months). The HR was 0.71 (95% CI, 0.53 to 0.95; *P* = .02;

TABLE 2. Treatment-Related Toxicities With Grades 3 to 5 Adverse Events Occurring in at Least 10% of Patients

	No. of Patients by Treatment Arm and Event Grade							
	FOLFOX (n = 91)				Irinotecan + Docetaxel (n = 98)			
Adverse Event	≤ 2	3	4	5	≤ 2	3	4	5
Anemia	85	6	0	0	84	14	0	0
Dehydration	89	2	0	0	79	18	1	0
Diarrhea	87	4	0	0	70	25	3	0
Fatigue	84	7	0	0	84	14	0	0
Nausea	84	7	0	0	86	12	0	0
Neutrophil count decreased	62	23	6	0	79	10	9	0
White blood cell decreased	82	8	1	0	84	7	7	0
Maximum grade any adverse event	33	46	9	3	36	45	14	3

Abbreviation: FOLFOX, fluorouracil, leucovorin, and oxaliplatin.

Fig 2). The median OS was greater with FOLFOX than IT, but this difference did not reach statistical significance: 11.4 months (95% CI, 9.8 to 13.5 months) versus 8.7 months (95% CI, 6.0 to 10.1 months); the HR was 0.82 (95% CI, 0.61 to 1.11; $P = .20$; Fig 3). A higher ORR was observed in the FOLFOX arm than in the IT arm, although this difference was not statistically significant: 33 of 79 evaluable patients (42%; 95% CI, 31% to 53%) versus 26 of 88 evaluable patients (30%; 95% CI, 20% to 39%; $P = .10$). Twenty patients (25%) in the FOLFOX arm and 21 patients (24%) in the IT arm had stable disease.

Similar to the total cohort, in the *ERCC1*-low subgroup, the median PFS was improved in the FOLFOX arm compared with the IT arm: 5.9 months (n = 85; 95% CI, 4.1 to 7.1 months) versus 2.8 months (n = 89; 95% CI, 1.7 to 4.1 months), respectively. The HR was 0.68 (95% CI, 0.50 to

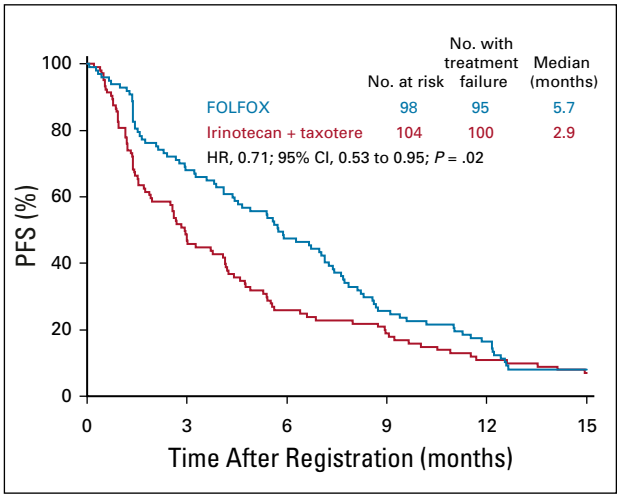

FIG 2. Progression-free survival (PFS) in all patients. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio.

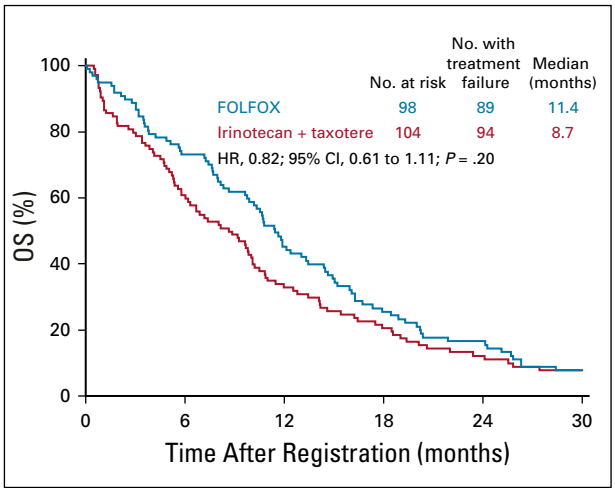

FIG 3. Overall survival (OS) in all patients. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio.

0.93; $P = .02$; Fig 4). The median OS for the *ERCC1*-low subgroup was 11.4 months (95% CI, 8.7 to 13.0 months) in the FOLFOX arm and was 8.0 months (95% CI, 5.8 to 10.0 months) in the IT arm; the HR was 0.83 (95% CI, 0.60 to 1.13; $P = .24$; Fig 5). Of the 70 and 76 evaluable patients with measurable disease in the FOLFOX and IT arms, 31 (44%; 95% CI, 32% to 57%) versus 21 (28%; 95% CI, 18% to 39%) responses were seen ($P = .04$; Appendix Table A2, online only). In the FOLFOX versus in the IT arm, there were 17 patients (24%) versus 20 patients (26%) with stable disease.

In the *ERCC1*-high subgroup, the median PFS was similar in the FOLFOX and IT arms: 4.7 months (n = 13; 95% CI, 2.1 to 8.7 months) versus 5.3 months (n = 15; 95% CI, 0.9 to 11.5 months); the HR was 0.91 (95% CI, 0.4 to 2.0; $P = .83$; Fig 6). Of the nine and 12 evaluable patients with measurable disease in the FOLFOX and IT arms, two (22%; 95% CI, 0% to 60%) versus five (42%; 95% CI, 15% to 72%) responses were seen ($P = .64$; Appendix Table A1).

The PFS by treatment arm was plotted within *ERCC1* quartiles: 0.20-0.80, ≥ 0.81-0.1.10, ≥ 1.11-1.42, and ≥ 1.43-5.71. These plots showed a consistent pattern of improved PFS in the FOLFOX versus the IT arm and, thus, little evidence of differential treatment effects on PFS across *ERCC1* levels in this population (Appendix Figs A1, A2, A3, and A4, online only). Thus, no statistical tests for interactions were performed.

DISCUSSION

To our knowledge, this was the first study to prospectively validate intratumoral gene expression of *ERCC1* as a potential marker of response to platinum-based chemotherapy. This randomized, phase II trial in patients with advanced esophagogastric cancer did not demonstrate a differential treatment effect on PFS on the basis of *ERCC1*

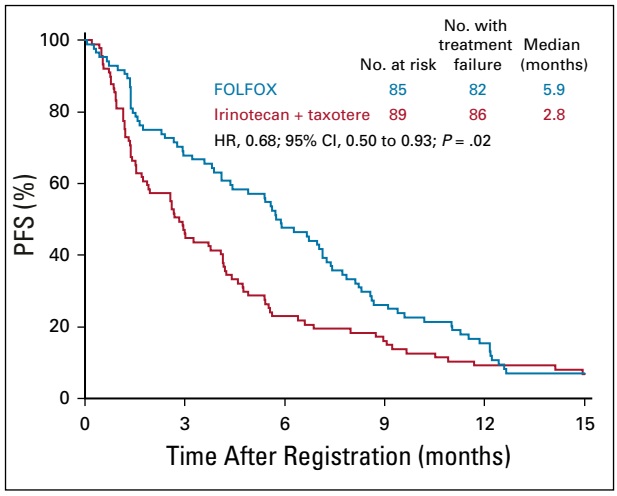

FIG 4. Progression-free survival (PFS) in patients with *ERCC1*-low status. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio.

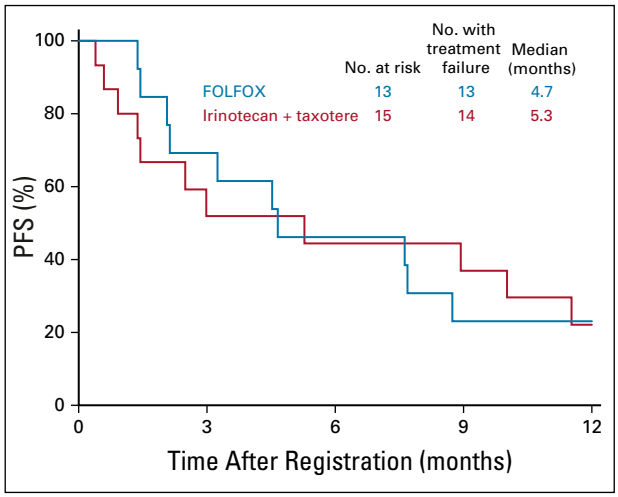

FIG 6. Progression-free survival (PFS) in patients with *ERCC1*-high status. FOLFOX, fluorouracil, leucovorin, and oxaliplatin.

levels. Despite the retrospective data reported across various tumor types, evaluated by IHC or gene expression, which have shown an inverse relationship of *ERCC1* and platinum sensitivity, this prospective evaluation did not confirm those results.

Our proposed assumption, based on several retrospective studies, was that the number of patients with *ERCC1*-high and *ERCC1*-low statuses would be split 50/50. The interim evaluation revealed that the statistical value of *ERCC1*-high/-low statuses was approximately 20/80 and not 50/50, as had been hypothesized. As such, we adjusted our objectives, because there was not enough statistical power to assess treatment effects in the group of patients with *ERCC1*-high status. The variation in the prospective evaluation of the *ERCC1*-high/-low distribution differed from that reported in prior studies. We have not identified the cause of this difference in distribution of *ERCC1* expression.

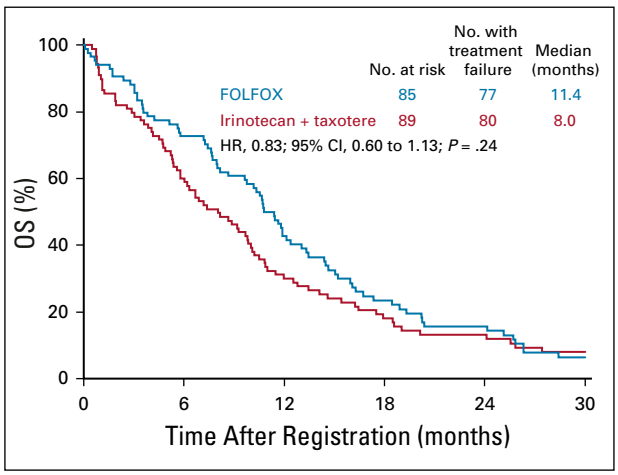

FIG 5. Overall survival (OS) in patients with *ERCC1*-low status. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio.

We conducted an investigation and validation of the tissue handling, laboratory techniques, and data. Further evidence that there was not an issue with the procedure of evaluation of *ERCC1* derives from a contemporaneous trial evaluating *ERCC1* in colorectal cancer, the MAVERICC trial.[28] This study was designed to prospectively evaluate *ERCC1* in patients with metastatic colorectal cancer randomly assigned to FOLFOX with bevacizumab versus fluorouracil, leucovorin, irinotecan with bevacizumab (ie, platinum- and non–platinum-containing regimens). This study also assumed a 50/50 split for *ERCC1*-high/-low statuses, and the interim data analysis also found a similar 20/80 distribution, consistent with our observations.

Another consideration is that the cutoff level of 1.7, which had been identified previously in other studies, may not have been accurate. To assess this more, a series of Kaplan-Meier curves were done to show if there was a differential treatment effect on PFS across varying levels (Figs 5 and 6, Appendix Figs A1 through A4), and this effect was not found. The curves demonstrate a similar pattern in each, suggesting that the treatment effects on PFS do not significantly vary by *ERCC1* mRNA level.

Other techniques have been used to assess *ERCC1*, including evaluation by IHC and evaluation of *ERCC1* polymorphisms. Validated quantitative immunofluorescence assays have been plagued by variability in antibody performance, and none has been reproducibly used in a study of prospective treatment assignment.[29] However, given the well-documented impact of post-translational modification of *ERCC1* on DNA repair, one limitation of our study may have been reliance on *ERCC1* mRNA levels for patient categorization.[30] Unfortunately, there has not been prospective validation of any technique used to evaluate *ERCC1*.

Overall, there was a statistically significant improvement in PFS for FOLFOX compared with IT, a finding that was

consistent across *ERCC1* levels. In the *ERCC1*-low group, there was a statistically significant improvement in PFS and ORR but not OS, although there was a numeric improvement noted. This result may have been due to the smaller numbers in each of the subgroups. To our knowledge, there have not been any prior randomized trials comparing FOLFOX to IT. This significant improvement with FOLFOX may suggest that the addition of a platinum as well as FU is important in the first-line treatment of advanced gastric cancer.

This study was the first, to our knowledge, to prospectively analyze the use of *ERCC1* expression as a predictive biomarker with real-time measurement and treatment assignment. Unfortunately, this study did not validate or identify *ERCC1* as a predictive marker of platinum sensitivity in upper GI tumors. It did support the use of FOLFOX, a platinum-containing regimen, as a standard and superior front-line regimen compared with the non–platinum-containing IT.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized, Phase II Study Prospectively Evaluating Treatment of Metastatic Esophageal, Gastric, or Gastroesophageal Cancer by Gene Expression of *ERCC1*: SWOG S1201

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APPENDIX

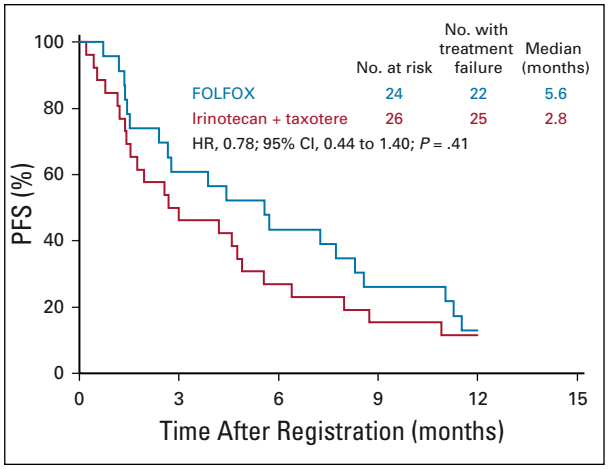

FIG A1. Progression-free survival (PFS) across *ERCC1* levels: first quartile. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio.

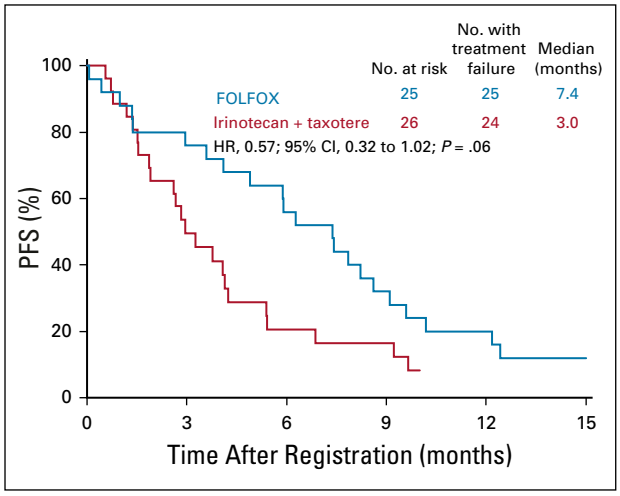

FIG A2. Progression-free survival (PFS) across *ERCC1* levels: second quartile. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio.

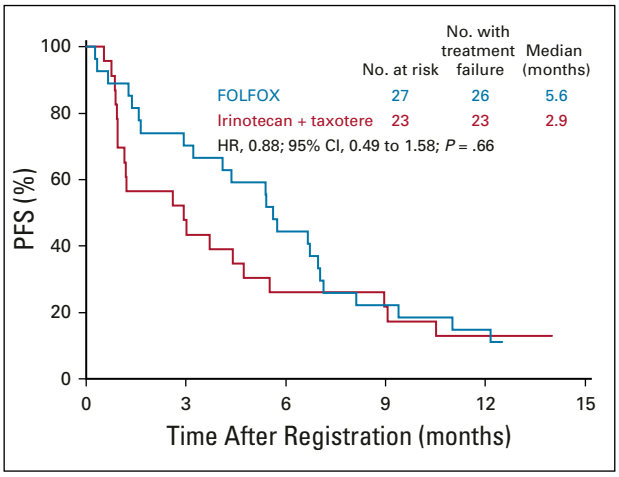

FIG A3. Progression-free survival (PFS) across *ERCC1* levels: third quartile. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio.

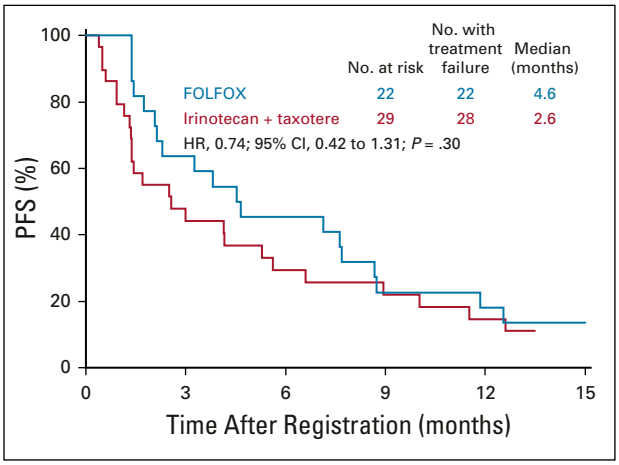

FIG A4. Progression-free survival (PFS) across *ERCC1* levels: fourth quartile. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio.

TABLE A1. Disease Response

	ERCC1 Low				*ERCC1* High			
	FOLFOX		Irinotecan + Docetaxel		FOLFOX		Irinotecan + Docetaxel	
Response Type	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Complete response	2	3	4	5	0	0	2	17
PR	22	31	12	16	2	22	2	17
PR, nonmeasurable disease	0	0	0	0	0	0	0	0
Unconfirmed complete response	0	0	1	1	0	0	0	0
Unconfirmed PR	7	10	4	5	0	0	1	8
Unconfirmed PR, nonmeasurable disease	0	0	0	0	0	0	0	0
Stable/no response	17	24	20	26	3	33	1	8
Increasing disease	12	17	31	41	2	22	3	25
Symptomatic deterioration	1	1	1	1	0	0	1	8
Assessment inadequate	9	13	3	4	2	22	2	17
Total	70	100	76	100	9	100	12	100

NOTE. Data provided as of September 26, 2018.

Abbreviations: FOLFOX, fluorouracil, leucovorin, and oxaliplatin; PR, partial response.