S0356: A Phase II Clinical and Prospective Molecular Trial With Oxaliplatin, Fluorouracil, and External-Beam Radiation Therapy Before Surgery for Patients With Esophageal Adenocarcinoma

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ABSTRACT

Purpose

Pathologic complete response (pCR) after neoadjuvant therapy for locally advanced esophageal adenocarcinoma is associated with improved survival. The Southwest Oncology Group designed a trimodality, phase II, single-arm trial with objectives of achieving a pCR rate of 40% with prospective exploratory analyses of intratumoral molecular markers postulated to affect response and survival.

Patients and Methods

Patients with clinically staged II or III esophageal adenocarcinoma received oxaliplatin 85 mg/m² on days 1, 15, and 29; protracted-infusion fluorouracil (PI-FU) 180 mg/m²/d on days 8 through 43; and external-beam radiation therapy (EBRT) 5 days a week at 1.8 Gy/d for 25 fractions; surgery was performed 28 to 42 days after neoadjuvant therapy. Chemotherapy was planned after surgery. Tumors were analyzed for mRNA expression and polymorphisms in genes involved in drug metabolism and DNA repair.

Results

Ninety-three patients were evaluable. Two deaths (2.2%) were attributable to preoperative therapy, and two deaths (2.2%) were attributable to surgery. Grade 3 and 4 toxicities were recorded for 47.3% and 19.4% of patients, respectively. Seventy-nine patients (84.9%) underwent surgery; 67.7% of patients had R0 resections. Twenty-six patients (28.0%) had confirmed pCR (95% CI, 19.1% to 38.2%). At a median follow-up of 39.2 months, estimates of median and 3-year overall survival (OS) were 28.3 months and 45.1%, respectively. Intratumoral *ERCC-1* gene expression was inversely related to progression-free survival and OS.

Conclusion

Neoadjuvant oxaliplatin, PI-FU, and EBRT for esophageal adenocarcinoma is active and tolerable. Because the regimen failed to meet the primary end point, it does not define a new standard. However, future trials can be built on this platform to validate the role of *ERCC-1* in determining the best systemic regimen for individual patients.

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INTRODUCTION

Long-term survival and cure are elusive for the majority of patients with locally advanced esophageal adenocarcinoma.¹ Although randomized trials conducted in the United States and Europe indicate that neoadjuvant chemotherapy and radiation for esophageal cancer lead to improved survival over surgery alone,^{2,3} the failure of radiation therapy and systemic chemotherapy to eradicate all local disease and undetectable foci of metastatic cancer, respectively, is a major impediment to improved survival and cure.⁴⁻⁶

Identification of intratumoral molecular parameters predictive for response and overall survival (OS) should enable selection of the optimal therapy for each patient.⁷ Because platinum compounds function by binding to DNA, targeting the nucleotide excision repair pathway to prevent repair of bulky, helix-distorting DNA lesions is attractive. The excision repair cross-complementing 1 (ERCC-1) protein is recognized as the rate-limiting enzyme in the nucleotide excision repair pathway, with its gene expression correlating with DNA repair capacity.⁸ Relatively low intratumoral expression levels of ERCC-1 have been associated with improved response and

survival for patients with lung, gastric, and colorectal cancer treated with platinum compounds.⁹⁻¹¹ Similarly, low expression levels of thymidylate synthase (TS) have been associated with both response and survival for patients treated with cisplatin and protracted-infusion fluorouracil (PI-FU).¹² It remains to be established whether either of these influences response or survival when platinum compounds and fluoropyrimidines are combined with radiation and surgery.

Working with the dual hypotheses that pathologic complete response (pCR) rate after neoadjuvant therapy meaningfully affects progression-free survival (PFS) and OS and that mRNA quantitation of genes and genetic polymorphisms of interest predict for pCR and OS in patients with esophageal adenocarcinoma treated with oxaliplatin, PI-FU, radiation, and surgery, S0356 was designed as a single-arm phase II trial (ClinicalTrials.gov identifier: NCT00086996). The goal chosen for pCR rate was 40%. The clinical trial results and the translational data serving as background to S0356 have been previously published.^{13,14}

PATIENTS AND METHODS

Eligibility

Chemotherapy- and radiation-naïve patients age 18 years or older with histologically documented esophageal adenocarcinomas starting at least 26 cm from the incisors and invading no more than 2 cm into gastric cardia were eligible. A Zubrod performance status of 0 to 2 was required. Tumors had to be clinical stage II or III according to the American Joint Commission on Cancer staging system (sixth edition). It was assumed that patients with a mass in the esophagus visualized by either computed tomography (CT) or magnetic resonance imaging (MRI) had at least a primary T2 tumor. Patients without an esophageal mass or enlarged lymph nodes documented by CT scan or MRI were required to undergo endoscopic ultrasonography (EUS) to demonstrate primary tumor invasion into the muscularis propria (stage IIA). A positron emission tomography (PET) scan was required before eligibility confirmation. Thus, staging was performed noninvasively by CT or MRI, PET scan, and, in selected cases, EUS. Before registration, all patients were to be evaluated by their medical oncologist, radiation oncologist, and surgeon.

Within 28 days of registration, patients were required to have granulocytes $\geq 1,500/\text{mL}$, platelets $\geq 100,000/\text{mL}$, and hemoglobin $\geq 10.0 \text{ g/dL}$. Eligibility required serum creatinine $\leq 1.5\times$ institutional limits of normal, and serum albumin and direct bilirubin had to be within the institutional limits of normal. Patients with peripheral neuropathy $\geq$ grade 2 and/or patients with any inflammatory process in the lungs were ineligible.

Within 14 days of registration, one hematoxylin and eosin slide, 10 unstained slides, 20 formalin-fixed paraffin-embedded (FFPE) tumor tissue sections 10 μm thick of the patient's esophageal tumor biopsy (alternatively, a paraffin block could be substituted), and one purple-top tube of blood for genetic polymorphism analysis were to be sent to the Southwest Oncology Group (SWOG) Tumor Bank to be stored at -80°C . After esophagectomy, similar tissue specimens were sent for central pathology review. This study was conducted adhering to the Reporting Recommendations for Tumor Marker Prognostic Studies as applicable. All trial patients signed an informed consent to the clinical protocol and consented to giving an adequate pretreatment blood sample for genotyping and for permission to use their paraffin-embedded tumor tissue to quantitate the genes of interest.

Genotyping and mRNA Quantification

Details about DNA extraction from blood and single nucleotide polymorphism genotyping are provided in the Appendix (online only). The genes, reference identification numbers, location, function, primers, and restriction enzymes are listed in Appendix Table A1 (online only). All gene expression levels were measured at a Clinical Laboratory Improvement Amendments–approved laboratory, Response Genetics (Los Angeles, CA); microdissection was performed on all FFPE tumor samples to

ensure that only tumor cells were dissected. Details about microdissection, mRNA isolation technique, and the procedure for quantitation of genes of interest are summarized in the Appendix.

Treatment

Treatment consisted of preoperative chemotherapy and radiation, surgery, and postoperative chemotherapy. Oxaliplatin 85 mg/m^2 as a 2-hour intravenous infusion was given on days 1, 15, and 29. On day 8, PI-FU was administered through a central venous catheter at 180 mg/m^2 over 24 hours continuously through day 43. Dose escalations were not permitted. Dose reductions for clinical toxicities (peripheral neuropathy, nausea/vomiting, diarrhea, oral mucositis, esophagitis, and skin and cardiac toxicities) were outlined in the protocol and specified for each agent or, when appropriate, for both. Guidelines for dose reductions for hematologic toxicities were outlined for each agent. Patients requiring more than two dose reductions were taken off the trial.

External-beam radiation therapy (EBRT) was initiated on day 8, concurrent with start of PI-FU. Intensity-modulated radiation therapy was not allowed. EBRT with megavoltage linear accelerators ($\geq 6 \text{ MV}$) delivered radiation to multiple fields. Patients were treated 5 days a week at 1.8 Gy/d for 25 fractions to a total dose of 45 Gy. At least two fields were treated daily; if a three-field technique was used, all three fields were treated daily. The target volume was defined as the primary tumor and regional lymph node basin that would ordinarily be resected at surgery. If the primary tumor was in the distal third of the esophagus, the target volume was enlarged to include celiac lymph nodes. All clinically involved lymph nodes were given at least a 2-cm margin. Dosage was prescribed at the isocenter. No modifications in radiation treatment were allowed.

After completion of preoperative radiation and chemotherapy, restaging scans and endoscopic evaluation were repeated. Responding or stable patients were operated on 4 to 6 weeks after completion of radiation and chemotherapy. Patients who experienced progression to inoperability for cure were removed from study but were observed for survival.

Acceptable surgical approaches to esophagectomy included transhiatal and transthoracic routes, with either a high intrathoracic or cervical anastomosis. Gastrectomy with esophagojejunostomy was not permitted. An extensive thoracic lymphadenectomy was encouraged, including subcarinal (station 7), paraesophageal (station 8), and inferior pulmonary ligament (station 9) lymph nodes. In the abdomen, the lymphadenectomy included all parahiatal and upper paraesophageal lymph nodes, extending to the base of the left gastric pedicle (stations 15 to 17). A resection was considered potentially curative (R0) when all visible tumor was removed with negative margins.

Postoperative chemotherapy commenced between 4 and 10 weeks after surgery. Postoperative chemotherapy consisted of oxaliplatin 85 mg/m^2 on days 1, 15, and 29 and PI-FU 180 mg/m^2 over 24 hours on days 1 through 29.

Definition of Response

Pathologic postoperative stage was the only response recorded. A pCR was defined by the pathologist if no cancer could be identified in the resected esophagus and lymph nodes (ypT0N0M0). Staging was not final until a single-pathologist central review was conducted. PFS was measured from time of study registration to the time of documented disease progression, symptomatic global deterioration, or death from any cause. OS was measured from the date of registration to the date of death from any cause.

Statistical Considerations

The primary goal of this trial was to evaluate pCR probability (based on surgery and central pathology review) for patients with potentially curable esophageal adenocarcinoma. The trial was designed to test the null hypothesis that this combination therapy would result in a true pCR probability of 25% or less against the alternative hypothesis of a true pCR probability of 40% or greater. A two-stage design was used. After the first 45 patients were enrolled, the pCR rate was to be evaluated. If 11 or more patients achieved a pCR, the trial would be allowed to accrue to completion. If 29 of 85 eligible patients achieved a pCR, this would be considered evidence that this regimen would be of interest for future study, regardless of the translational outcome. All treated and eligible patients were considered in the pCR rate. The trial was designed to

have power of 89% when the true pCR probability is 40% and a significance level of $P = .04$.

The correlative hypothesis for S0356 was that tumor expressions less than 1.7 for *ERCC-1* and less than 4.0 for *TS* would be associated with pCR, PFS, and OS. For other genes, median expression levels were explored as the threshold between low and high expression. For each of the polymorphisms included in this analysis, dominant, recessive, codominant, and additive models were explored. No P value adjustments for multiple comparisons were made.

Because of sample size limitations, the primary analyses consisted of univariate models. Multivariate models adjusting for age and disease site (esophageal v gastroesophageal junction) were also explored. For all analyses, results from models adjusting for baseline factors were nearly identical to those from the corresponding univariate models.

Recursive partitioning models were fit to the expression level data to explore whether the categorization of patients into biomarker-based risk groups could be optimized,¹⁵ and a permutation-based resampling method¹⁶ was used to adjust the P values associated with outcome differences between subgroups identified by this method. The rpart library for R statistical software was used for this portion of the analysis.¹⁷

In accordance with SWOG procedure, toxicity and accrual monitoring for this trial were the responsibility of the study coordinator, study statisticians, and the SWOG Disease Committee Chair. Adverse events and toxicities were monitored on an ongoing basis, with formal reports every 6 months.

RESULTS

Between February 5, 2005, and August 1, 2008, a total of 98 patients were registered. Interim analysis confirmed the requisite pCR rate and safety profile to complete accrual. One patient withdrew consent before therapy could be administered; four patients were ineligible on the basis of histology ($n = 1$) and issues of timing for biopsies and scans ($n = 3$). Demographics and clinical characteristics are listed in Table 1 for the 93 patients evaluable for response, survival, and toxicity. The evaluable patients included 87 men (93.5%) and six women.

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	No. of Patients (N = 93)	%
Age, years		
Median	62.2	
Range	41.6-83.1	
Sex		
Male	87	94
Female	6	6
Race		
White	86	96
Other	4	4
Missing	3	
Performance status		
0	54	59
1	38	41
Missing	1	
Primary site		
Esophagus	55	60
Gastroesophageal junction	36	40
Missing	2	
Disease stage		
II	39	42
III	54	58

Table 2. Maximum Grade of Adverse Events Experienced by Patients

Toxicity	Grade 3		Grade 4		Grade 5	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Blood/bone marrow	9	9.7	7	7.5	0	0
Constitutional (fatigue/anorexia)	24	25.8	0	0	0	0
GI (diarrhea/nausea/mucositis)	37	39.8	1	1.1	0	0
Infection	9	9.7	3	3.2	0	0
Metabolic (hypokalemia/hyponatremia/renal)	10	10.8	2	2.2	0	0
Neurologic	2	2.2	1*	1.1	0	0
Pulmonary	11	11.8	6	6.4	2†	2.2

*One patient had a cerebrovascular accident.

†Two patients had acute respiratory distress syndrome.

Race was reported for 90 patients, of whom 86 (95.5%) were white. Primary disease site was the esophagus in 55 patients (60.4%), gastroesophageal junction in 36 patients (39.6%), and not classified in two patients. Preclinical staging by CT scans, EUS, and/or PET scan defined 54 patients (58.1%) as having stage III and 39 patients (41.9%) as having stage II disease. With the exception of one patient whose data are missing, all eligible patients had a performance status of 0 (59.0%) or 1 (41.0%).

Seventy-nine patients (84.9%) underwent esophagectomy. Eight patients had either R1 or R2 resections; the operative data on eight patients are not available; 63 patients underwent an R0 resection. Two patients (2.2%) died postoperatively. Thirty-six patients (38.7%) completed postoperative therapy.

Forty-four patients (47.3%) and 18 patients (19.4%) had grade 3 or grade 4 treatment-related toxicities, respectively. The most common grade 3 toxicities were GI in 37 patients (39.8%) and flu-like symptoms in 24 patients (25.8%). The most common grade 4 toxicities were hematologic (7.5%) and pulmonary (6.5%). Two patients (2.2%) died of pulmonary infections before surgery. Table 2 lists the most common toxicities reported in this trial.

Twenty-seven patients (29.0%) had pathology reports stating no cancer could be found in the resected specimen. Central review of these specimens found residual disease in one patient. Hence, 26 patients (28.0%; 95% CI, 19.1% to 38.2%) had central pathology

Fig 1. Kaplan-Meier curve of overall survival in the Southwest Oncology Group S0356 trial.

Table 3. Univariate Analysis of the Association Between mRNA Expression and the Number of Patients Having Specific Gene Quantitation With Median Expressions Levels, OS, PFS, and pCR

Genes	OS			PFS			pCR			No. of Patients	Expression Level	
	HR	95% CI	P	HR	95% CI	P	OR	95% CI	P		Median	Range
<i>GSTP-1</i>	0.75	0.38 to 1.46	.39	1.02	0.54 to 1.92	.96	1.40	0.41 to 4.76	.59	55	1.61	0.52-8.73
<i>ERCC-1</i>	2.72	1.21 to 6.10	.015	2.77	1.32 to 5.80	.0070	0.93	0.27 to 3.19	.91	53	1.92	0.33-5.29
<i>TP</i>	0.90	0.45 to 1.81	.77	0.78	0.40 to 1.51	.46	1.48	0.43 to 5.10	.53	52	8.93	1.36-38.45
<i>TS</i>	0.81	0.40 to 1.66	.56	0.84	0.42 to 1.65	.60	1.01	0.28 to 3.58	.99	50	3.32	0.92-8.62
<i>DPD</i>	0.72	0.33 to 1.60	.42	0.65	0.31 to 1.37	.26	2.02	0.48 to 8.49	.92	39	0.57	0-2.22
<i>RRM1</i>	1.06	0.41 to 2.75	.91	1.15	0.46 to 2.86	.76	1.00	0.19 to 5.29	1.00	26	1.75	0.35-5.81
<i>XPD</i>	0.41	0.11 to 1.53	.18	0.46	0.14 to 1.49	.19	2.33	0.31 to 17.55	.41	19	1.88	0.76-3.60

NOTE. HRs are for the comparison between high and low expression. For *ERCC-1* and *TS*, the thresholds between high and low expression were 1.7 and 4.0, respectively, based on prior results. For all other genes, the median expression level was used as the threshold value.

Abbreviations: *DPD*, dihydropyrimidine dehydrogenase; *ERCC-1*, excision repair cross-complementing; *GSTP-1*, glutathione S-transferase pi 1; HR, hazard ratio; OR, odds ratio; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; *RRM1*, ribonucleotide reductase 1; *TP*, thymidine phosphorylase; *TS*, thymidylate synthase; *XPD*, xeroderma pigmentosum D.

confirmation of T0N0 esophageal lesions after treatment. Among all resected patients, 22 (27.8%) had cancer in lymph nodes (stage III).

With a median follow-up time of 39.2 months, 53 patients (57.0%) have died. The current Kaplan-Meier estimates of median and 3-year OS are 28.3 months (95% CI, 22.4 to 52.4 months) and 45.1% (95% CI, 34.8% to 55.4%), respectively. Current estimates of median and 3-year PFS are 19.7 months (95% CI, 14.7 to 28.3 months) and 36.8% (95% CI, 26.9% to 46.6%), respectively. The Kaplan-Meier plot for OS is shown in Figure 1. Patients achieving pCR had a statistically significant survival advantage over patients who did not ($P = .01$).

Germline DNA was extracted for analysis from all 91 available blood samples. Of the 91 FFPE tissue samples submitted, sufficient tumor tissue was obtained to perform gene expression of at least one gene in 55 patients. Outcomes and demographic characteristics of patients evaluable for gene expression analysis ($n = 55$) were not significantly different from those of the study population as a whole.

The median *ERCC-1* mRNA expression in relation to the β -actin gene was 1.92 (range, 0.33 to 5.29), and median *TS* mRNA expression in relation to the β -actin gene was 3.32 (range, 0.92 to 8.62). Twenty-two (41.5%) of 53 patients had *ERCC-1* mRNA levels below the

predefined cutoff of 1.7. Twenty-seven (54.0%) of 50 patients had *TS* mRNA levels below the predefined cutoff of 4.0. Gene expression data are listed in Table 3. Using the established cutoff values for *ERCC-1* and *TS*, no significant association with baseline characteristics was found, including pretherapy stage.

Patients with an *ERCC-1* gene expression level greater than 1.7 had significantly worse PFS (hazard ratio [HR], 2.77; 95% CI, 1.32 to 5.80; $P = .0070$) and OS (HR, 2.72; 95% CI, 1.21 to 6.10; $P = .015$) than patients with *ERCC-1* mRNA expression levels ≤ 1.7 . Kaplan-Meier plots of PFS and OS by *ERCC-1* expression are shown in Figures 2 and 3, respectively. *ERCC-1* gene expression did not influence pCR. The predefined *TS* gene expression cutoff of 4.0 was not associated with survival or pCR. None of the other tested genes were associated with survival or pCR, using the median mRNA expression levels as cutoff points (Table 3).

A recursive partitioning analysis explored whether optimization of expression level cut point selection might yield improved marker-based risk group identification. Only PFS was analyzed with this method, because there were inadequate events for the OS analysis and too few responders for the pCR analysis. Among all genes listed in Table 3, only *ERCC-1* entered the recursive-partitioning model. The

Fig 2. Progression-free survival by *ERCC-1* mRNA levels in 53 patients treated with oxaliplatin-based chemoradiotherapy within the Southwest Oncology Group S0356 trial.

Fig 3. Overall survival by *ERCC-1* mRNA levels in 53 patients treated with oxaliplatin-based chemoradiotherapy within the Southwest Oncology Group S0356 trial.

optimal split for *ERCC-1* mRNA expression using recursive partitioning was 1.66 (adjusted $P = .032$).

In the univariate analysis, nominally significant associations were observed between OS and the following two polymorphisms: *TS* 5'-UTR (2R/3R ν 2R/2R; HR, 2.39; 95% CI, 0.98 to 5.80; $P = .055$) and *XPB* Lys751Gln (AC ν AA; HR, 1.84; 95% CI, 1.00 to 3.36; $P = .049$). However, comparison of homozygous patients for these polymorphisms did not yield a significant result.

DISCUSSION

The hypothesis behind S0356 was that pCR rate derived from neoadjuvant therapy of the esophagus drives PFS and OS. The failure to hit the target of 40% for pCR and the resulting PFS and OS suggest the hypothesis was correct, because the pCR rate of 28.0% did not lead to a striking advantage in either PFS or OS over recent single-arm trials for patients with esophageal adenocarcinoma. Indeed, the pCR rate observed in this trial was not high enough to reject the null hypothesis. Nevertheless, this is an active preoperative regimen that can be administered safely without increasing surgical morbidity and mortality. The fact that less than 40% of our patients could be treated postoperatively suggests that consideration be given to a second course of chemotherapy before surgery so that all systemic therapy is completed before surgery.

In perspective, the pCR rate and the median survival time of 28.3 months reported here are similar to recent single-arm trial results reported for patients with esophageal adenocarcinoma in North America and Europe.¹⁸⁻²¹ The Cancer and Leukemia Group B (CALGB) 9781 trial, which was terminated early, is a remarkable exception and justified the goal of investing the S0356 trial with a goal of 40% pCR. The CALGB study reported a pCR rate of 40% and a 4.5-year median survival. Unfortunately, CALGB 9781 enrolled only 30 patients in the treatment arm.² A recent report of a phase III randomized trial from the Netherlands is also noteworthy because it reports a median survival time of approximately 4 years for patients with esophageal cancer treated preoperatively with carboplatin, paclitaxel, radiation, and surgery. However, the inclusion of squamous cell esophageal tumors may have influenced these results.³

Our data demonstrate that patients with *ERCC-1* mRNA levels greater than the predefined cutoff of 1.7 had significantly worse PFS and OS when compared with patients with levels below this cutoff, including dramatic differences in terms of 2-year PFS (39% ν 72%, respectively) and 2-year OS (16% ν 62%, respectively). These results provide strong arguments that *ERCC-1* mRNA expression is associated with PFS and OS in locally advanced esophageal adenocarcinoma treated with this regimen. To the best of our knowledge, this is the first report demonstrating in a prospective fashion that *ERCC-1* mRNA expression is associated with survival in patients with adenocarcinoma of the esophagus or gastroesophageal junction treated with a potentially curable trimodality strategy. *ERCC-1* mRNA expression was not associated with pCR. It is possible that the few patients with pCR and

evaluable *ERCC-1* mRNA quantitations led to this finding. It is also possible that *ERCC-1* selectively affects micrometastasis rather than the primary tumor.

We were unable to confirm the results of Joshi et al²² in regard to the association between *TS* mRNA expression and outcome for patients with esophageal cancer with adenocarcinomas and squamous cell tumors treated with trimodality therapy. Furthermore, the results of S0356 do not provide associations between outcome and polymorphisms in genes involved in DNA repair, platinum detoxification, and fluorouracil metabolism.

By treating all patients in this trial with the same regimen, it cannot be stated whether *ERCC-1* is truly a predictive marker to be used in selecting patients for treatment with this regimen or is simply prognostic. However, the trial validated that the predetermined cutoff level for *ERCC-1* has a statistically significant association with PFS and OS for patients treated with oxaliplatin, PI-FU, radiation, and surgery. Given these results, SWOG is planning a prospective biomarker-driven clinical trial for patients with advanced but potentially curable esophageal adenocarcinomas.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(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.

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