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ORIGINAL REPORT

Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses

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See accompanying editorial on page 3082 and article on page 3085

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ABSTRACT

Purpose
The Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial tested whether the addition of radiotherapy to adjuvant chemotherapy improved disease-free survival (DFS) in patients with D2-resected gastric cancer (GC).

Patients and Methods
Between November 2004 and April 2008, 458 patients with GC who received gastrectomy with D2 lymph node dissection were randomly assigned to either six cycles of adjuvant chemotherapy with capecitabine and cisplatin (XP) or to two cycles of XP followed by chemoradiotherapy and then two additional cycles of XP (XPRT). This final update contains the first publication of overall survival (OS), together with updated DFS and subset analyses.

Results
With 7 years of follow-up, DFS remained similar between treatment arms (hazard ratio [HR], 0.740; 95% CI, 0.520 to 1.050; $P = .0922$). OS also was similar (HR, 1.130; 95% CI, 0.775 to 1.647; $P = .5272$). The effect of the addition of radiotherapy on DFS and OS differed by Lauren classification (interaction $P = .04$ for DFS; interaction $P = .03$ for OS) and lymph node ratio (interaction $P < .01$ for DFS; interaction $P < .01$ for OS). Subgroup analyses also showed that chemoradiotherapy significantly improved DFS in patients with node-positive disease and with intestinal-type GC. There was a similar trend for DFS and OS by stage of disease.

Conclusion
In D2-resected GC, both adjuvant chemotherapy and chemoradiotherapy are tolerated and equally beneficial in preventing relapse. Because results suggest a significant DFS effect of chemoradiotherapy in subsets of patients, the ARTIST 2 trial evaluating adjuvant chemotherapy and chemoradiotherapy in patients with node-positive, D2-resected GC is under way.

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INTRODUCTION

The results from the Intergroup 0116 trial,[1,2] along with a meta-analysis of three randomized trials,[3] showed that adjuvant radiotherapy added to fluoropyrimidine-based chemotherapy significantly improved overall survival (OS) of patients with gastric cancer (GC) and established radiotherapy as part of the standard of care for the adjuvant treatment of GC. Controversy remains, however, because the Intergroup 0116 trial has been criticized for suboptimal surgery, with only 10% of patients receiving D2 lymph node dissection.[1] D2 dissection is the most widely recommended surgical procedure for resectable GC,[4,5] because it is considered feasible at high-volume centers by experienced surgeons, leading to a reduction in GC-specific deaths. In Japan and Korea, where gastrectomy with D2 dissection has already been the standard treatment, two randomized phase III trials, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC)[6] and the Adjuvant Capecitabine and

Oxaliplatin for Gastric Cancer After D2 Gastrectomy (CLASSIC)[7] trial, have demonstrated that adjuvant chemotherapy with S-1 or capecitabine plus oxaliplatin reduced the risk of relapse and death in patients with GC.

The Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial was unique in that it included patients with D2-resected, pathologic stage IB to IV (M0) GC and compared adjuvant chemotherapy using capecitabine and cisplatin (XP) with XP plus concurrent chemoradiotherapy (XPRT).[8] The 3-year disease-free survival (DFS) showed no statistically significant difference (74% for XP *v* 78% for XPRT; $P = .0862$), and given these results, the addition of radiotherapy to adjuvant XP chemotherapy could not be routinely advised in patients with GC treated with D2 surgery. The median duration of follow-up of the patients in the ARTIST trial at the time of the initial report was 4 years, and uncertainties remained regarding the OS results and subgroups of patients who may benefit from adjuvant chemoradiotherapy. Therefore, the purpose of the current report was to present the OS results of the ARTIST trial, to update our DFS results after a median of 7 years of follow-up, and to perform multivariable analysis to determine whether the effect of radiotherapy on these end points seems to vary in selected patient subsets. We also performed exploratory biomarker analyses to determine possible prognostic and/or predictive markers of outcomes. An update on the safety results was not performed, given that all patients had already completed their study treatment at the time of the initial report, and therefore, no changes were to be expected from an updated analysis.

PATIENTS AND METHODS

The ARTIST trial was approved by the Samsung Medical Center Institutional Review Board (Seoul, South Korea) in accordance with the ethical principles of the Declaration of Helsinki and local guidelines. Written informed consent was obtained from all participating patients before random assignment.

Patients and Study Procedures

Full details of the ARTIST trial have been published previously.[8] In brief, patients eligible for this trial had stage IB to IV (M0) GC, according to the American Joint Committee on Cancer 2002 staging system, and had undergone curative D2 surgery with no residual malignant disease. Patients were stratified according to pathologic stage (IB or II *v* III or IV) and the type of surgery (total *v* subtotal gastrectomy). They were then randomly assigned to receive adjuvant XP or XPRT. In the XP arm, treatment included six cycles of capecitabine 1,000 mg/m^2 twice a day on days 1 to 14 and cisplatin 60 mg/m^2 on day 1. XP chemotherapy was repeated every 3 weeks for up to six cycles. In patients assigned to the XPRT arm, radiotherapy 45 Gy concurrently with capecitabine 825 mg/m^2 twice a day was given after the completion of two cycles of XP, followed by two additional cycles of XP. Radiotherapy was fractionated to 1.8 Gy daily, 5 days a weeks, over 5 weeks.

All 458 patients adhered to the same schedule of follow-up visits after completion of study treatment, which required recording of symptoms, adverse events graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 2), and laboratory and imaging studies. These assessments were scheduled to occur every 6 months for up to 5 years.

Biomarker Studies

Primary tumor tissues from 415 surgical specimens were readily available for tissue microarray. All slides were reviewed by a pathologist (K.-M.K.) who was blinded to study treatment and clinical data, and the representative areas were carefully selected and marked on paraffin blocks. Four GC tissue cores (0.6 mm in diameter) were obtained from a single paraffin block, and the immunohistochemical stains for MET, HER2, EGFR, p53, FGFR2, MLH1, and E-cadherin were performed according to the protocols. Three independent pathologists with no prior knowledge of clinicopathologic or molecular results evaluated the results, and in all cases, HER2, MET, EGFR, and E-cadherin overexpression was graded as 0, 1+, 2+, or 3+ but ultimately classified as positive (2+ or 3+) or negative (0 or 1+) for statistical purposes. FGFR2 and MLH1 expression also was classified as positive or negative. The presence of Epstein-Barr virus (EBV) was detected by EBV-encoded RNA in situ hybridization as previously described,[9] and only cases with strong signal within almost all of the tumor cell nuclei were considered EBV positive.

Statistical Considerations

The primary end point of the ARTIST trial was DFS, and secondary end points included OS, relapse patterns, and safety. DFS was measured from the date of surgery until death, relapse, or second primary tumor, whichever occurred first. Comparisons of DFS and OS between arms according to the intent-to-treat principle were performed using a two-sided log-rank test. Analyses adjusted by disease stage and the type of surgery were performed using the Cox regression model. Hazard ratios (HRs) with 95% CIs were calculated using the Cox proportional hazards model. Survival curves were presented according to the Kaplan-Meier method. DFS benefit, if any, was analyzed according to baseline characteristics including age, sex, stage, type of surgery, Lauren classification, and lymph node status. Variables used to identify prognostic factors for DFS and OS included age ($< v \geq 56$ years); sex (male *v* female); Eastern Cooperative Oncology Group performance status (0 *v* 1); Lauren classification (intestinal *v* diffuse *v* mixed); tumor location (proximal/body *v* antrum *v* multiple/diffuse); type of surgery (subtotal *v* total gastrectomy); lymph node status (negative *v* positive) and ratio ($< v \geq 0.083$); stage (I/II *v* III/IV); p53, EGFR, HER2, and MET status; and MLH1 and E-cadherin expression. Interactions were represented by products of the corresponding variables. Nonsignificant variables were dropped one at a time, beginning with the least significant. The cutoff date for this final analysis was September 1, 2013.

RESULTS

Between November 2004 and April 2008, 458 patients were entered onto the study. All patients were randomly assigned, 228 patients to the XP arm and 230 patients to the XPRT arm (Fig 1). Baseline patient and tumor characteristics were generally well balanced across treatment arms (Table 1). In both arms, 22% and 37% of patients had stage IB and stage II disease, respectively. Intestinal-type GC was present in 163 patients (36%), and 274 patients (60%) had diffuse-type GC. At least one cycle of study treatment was received by 453 patients. The planned six cycles of XP chemotherapy and XPRT chemoradiotherapy were completed in 75% and 82% of patients, respectively.

Long-Term DFS and OS

At the time of our initial report,[8] 127 patients had experienced relapse or died (XP arm, n = 72; XPRT arm, n = 55), producing a censoring rate of 72%. In this updated report, 141 patients had experienced relapse or died (XP arm, n = 79; XPRT arm, n = 62), producing a censoring rate of 69%. The HR for DFS was 0.740 (95% CI, 0.520 to 1.050; $P = .0922$) as shown in Figure 2, which is consistent with the original report of the ARTIST trial.[8]

After median follow-up duration of 7 years, the probabilities of surviving at 5 years were 73% and 75% in the XP and XPRT arms, respectively (log-rank $P = .484$; Fig 3). The HR for OS was 1.130 (95% CI, 0.775 to 1.647; $P = .5272$). Among 141 patients with relapse, the median time from relapse to death was 8 months (9.7 months in XP arm *v* 7.2 months in XPRT arm; $P = .076$).

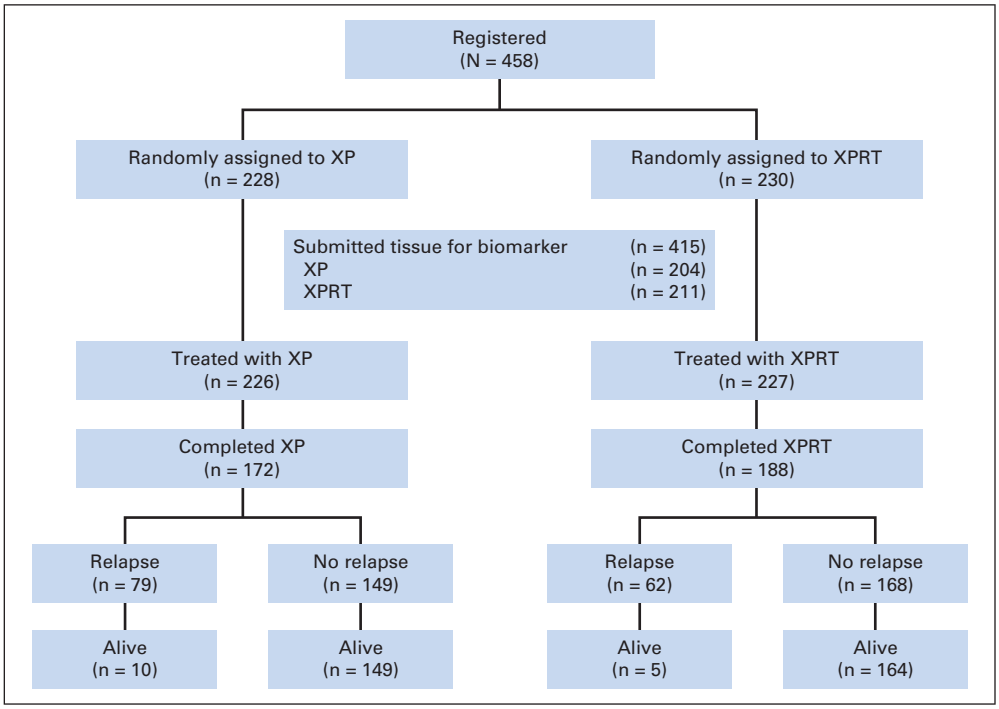

Fig 1. Flow diagram of all registered patients. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

Pattern of Relapse

Locoregional relapse was defined as relapse at anastomosis site, duodenal stump, tumor bed, remnant stomach, or regional lymph nodes within the radiation field. Lymph node relapse outside the radiation field, peritoneal seeding, liver metastasis, and metastasis to extra-abdominal sites were regarded as distant relapse. We found a clinically relevant difference in the pattern of relapse, where locoregional relapse was more frequent in the XP arm (13%) than in the XPRT arm (7%; $P = .0033$). Distant metastases were observed in 27% and 24% of patients in the XP and XPRT arms, respectively ($P = .5568$). More detailed evaluation of the pattern of relapse, as well as the long-term safety concerns, for the whole study population and for patients who were treated with chemoradiotherapy will be presented in another publication.

Biomarker Analyses

Primary tumor tissue samples from 415 patients were submitted for analysis, corresponding to 90% of patients enrolled. Table 2 lists the results of laboratory testing of tumor tissue using immunohistochemistry for EGFR, HER2, MET, p53, FGFR2, MLH1, and E-cadherin. EBV positivity was found in 25 specimens (6%). Only 30 and 53 specimens evaluated had HER2 2+/3+ and EGFR 2+/3+, respectively. There was no association between HER2 overexpression and DFS (HR, 1.003; 95% CI, 0.443 to 2.273; $P = .994$) or between EGFR expression and DFS (HR, 0.867; 95% CI, 0.520 to 1.448; $P = .586$). Similarly, MET expression (HR, 0.433; 95% CI, 0.160 to 1.170; $P = .099$) and FGFR2 expression (HR, 1.053; 95% CI, 0.566 to 1.960; $P = .870$) had no significant impact on DFS.

Prognostic Factors on Long-Term DFS and OS

Cox proportional hazards model, based on both DFS and OS end points, was considered backward model selection. We began with treatment, predefined prognostic variables, and their first-order interaction terms and removed one prognostic variable at a time. Factors that showed individual prognostic value in univariable models were used to examine their joint prognostic value in a multivariable model. Significant interactions were found between tumor location and type of surgery, between stage and lymph node status, between lymph node status and ratio, and between treatment and some variables. However, the only treatment interaction terms included in the final model were with lymph node ratio and Lauren classification (Table 3), suggesting that the effect of radiotherapy in patients with a high lymph node ratio or intestinal-type GC was different from the effect in patients with a low lymph node ratio or diffuse GC, respectively. Pathologic stage was a significant prognostic factor for both DFS (HR, 2.83; 95% CI, 1.87 to 4.27; $P < .01$) and OS (HR, 2.82; 95% CI, 1.83 to 4.35; $P < .01$), but the interaction of treatment and stage was not significant in this model.

Subgroup analyses were performed to identify patient populations who may benefit from chemoradiotherapy (Fig 4), and calculation of HRs and 95% CIs showed that the potential benefit from the addition of radiotherapy to adjuvant chemotherapy could not be excluded in patients with node-positive disease and intestinal-type GC. In 396 patients with node-positive disease, 3-year DFS was significantly different (72% in XP arm *v* 76% in XPRT arm; $P = .04$). Similarly, in 163 patients with intestinal-type GC, 3-year DFS rates were 83% and 94% in the XP and XPRT arms, respectively ($P = .01$). There also was a trend toward improved DFS in patients with advanced stage.

DISCUSSION

To our knowledge, the ARTIST trial was the first and only study that investigated the role of adjuvant chemoradiotherapy in patients with D2-resected GC and compared it directly with fluoropyrimidine-platinum combination adjuvant chemotherapy. We report here on

Table 1. Baseline Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	XP (n = 228) No. of Patients	XP (n = 228) %	XPRT (n = 230) No. of Patients	XPRT (n = 230) %
Age, years				
Median	56		56	
Range	22-77		28-76	
Sex				
Male	153	67	143	62
Female	75	33	87	38
ECOG performance status				
0	96	42	99	43
1	132	58	131	57
Primary tumor location				
Proximal	9	4	13	6
Body	112	49	107	46
Antrum	87	38	90	39
Multiple/diffuse	20	9	20	9
Pathologic stage*				
IB	50	22	49	21
II	86	38	84	37
III	65	29	71	31
IV (M0)	27	12	26	11
N stage				
N0	35	15	27	12
N1	123	54	130	57
N2	52	23	49	21
N3	18	8	24	10
No. of lymph nodes dissected				
Median	40		40	
Range	13-142		12-84	
No. of involved lymph nodes				
Median	3		3	
Range	0-50		0-51	
Lymph node ratio†				
Mean	0.083		0.084	
SD	0.160		0.159	
Lauren classification				
Intestinal	88	39	75	33
Diffuse	130	57	144	63
Mixed/not specified	10	4	11	4

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.
*According to the Joint Committee on Cancer Staging System, sixth edition (2002).
†No. of positive lymph nodes/No. of lymph nodes dissected.

the 7-year follow-up results of patients comparing adjuvant XP chemotherapy with XPRT in the phase III ARTIST trial. This updated report confirms that patients can achieve long-term DFS and possible cure with both adjuvant chemotherapy and chemoradiotherapy. Treatment compliance and safety profile with chemotherapy and chemoradiotherapy were generally good. These long-term results, together with the results from the ACTS-GC[6] and the CLASSIC[7] trials, provide additional support for adjuvant chemotherapy as a standard of care in patients with D2-resected GC. However, it should be noted that there are subsets of patients who may benefit from the addition of radiotherapy to adjuvant chemotherapy, and the optimal adjuvant chemotherapy regimen has yet to be identified. Thus, adjuvant chemoradiotherapy in node-positive, D2-resected GC should be explored further within the framework of clinical trials.

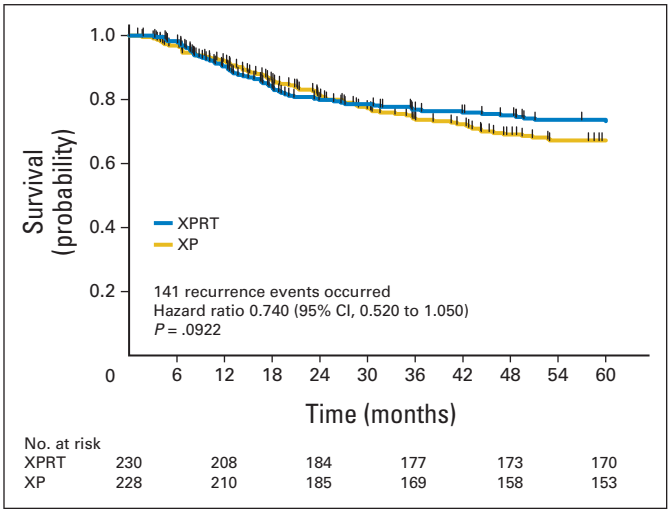

Fig 2. Disease-free survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

There remains controversy surrounding the choice of adjuvant therapy for completely resected GC. After the initial publication of the Intergroup 0116 trial,[1] the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial reported the superiority of perioperative (ie, given before and after surgery) chemotherapy when compared with surgery alone.[10] More recently, the role of adjuvant chemotherapy was examined in the ACTS-GC[6] and CLASSIC[7] trials. In both trials, the surgery-alone arm fared significantly worse when compared with the adjuvant chemotherapy arm in terms of DFS and OS. These trials led to different treatment strategies for patients with GC, including adjuvant chemoradiotherapy, perioperative chemotherapy, or adjuvant chemotherapy. Although chemoradiotherapy and perioperative MAGIC chemotherapy now seem likely to be the recommended adjuvant treatment in the United States and Europe, current practice for treatment of D2-resected GC in Asia has become adjuvant chemotherapy with either S-1 or capecitabine plus

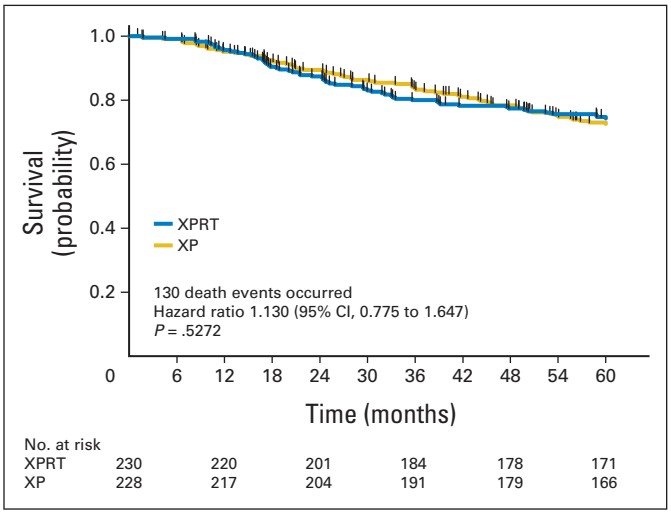

Fig 3. Overall survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

Table 2. Exploratory Biomarker Analyses

Biomarker*	XP (n = 204)		XPRT (n = 211)	
	No. of Patients	%	No. of Patients	%
HER2				
0/1+	190	93	195	93
2+	4	2	5	2
3+	10	5	11	5
MET				
0/1+	153	75	167	79
2+	48	24	40	19
3+	3	1	4	2
EGFR				
0/1+	178	87	184	87
2+/3+	26	13	27	13
p53				
Negative	138	68	151	71
Positive	66	32	60	29
FGFR2				
Negative	174	85	186	88
Weakly positive/positive	30	15	25	12
MLH1 loss				
Negative	27	13	20	10
Positive	177	27	191	90
E-cadherin loss				
Negative	20	10	25	12
Positive	184	90	186	88
Ebstein-Barr virus				
Negative	197	97	191	91
Positive	7	3	18	9

Abbreviations: EGFR, epidermal growth factor receptor; FGFR2, fibroblast growth factor receptor 2; HER2, human epidermal growth factor receptor 2; XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.
*Biomarker analyses were done by immunohistochemical stains in 415 patients in whom tumor blocks were readily available.

oxaliplatin. It is well known that the survival outcomes differ considerably between Western and Asian countries, with overall 5-year survival rates of 10% to 40% in the United States[2] compared with 50% or higher in Japan and Korea.[6-8] Proposed hypotheses to explain this disparity include early detection leading to stage migration, differences in treatment policy, and the possible different tumor biology.[11] When it comes to the extent of lymphadenectomy for curative resections in patients with GC, although Western studies failed to demonstrate OS benefit with D2 surgery,[5,12] extended (D2) lymph node dissection improves the precision of staging and is associated with lower locoregional relapse and GC-related death rates than D1 surgery.[13] In eastern Asian countries where D2 surgery has long been considered standard, some surgeons still consider the OS benefit seen in the Intergroup 0116 trial to be merely a compensation of inadequate surgery.[4] Sasako et al[14], in the ACTS-GC trial, reported 5-year OS rates of 72% in patients receiving adjuvant S-1 and 61% in the surgery-only patients. Their DFS rates at 5 years were 65% in the S-1 patients and 53% in the surgery-only patients. Notably, these survival outcomes are, along with the results from the CLASSIC trial,[7] comparable to those observed in this ARTIST trial directly comparing adjuvant chemotherapy (XP) and chemoradiotherapy and further support the effectiveness of adjuvant chemotherapy in patients with D2-resected GC. However, treatment choice based solely on the extent of lymph node dissection (ie, chemoradiotherapy after less than D2 surgery *v* chemotherapy after D2 surgery) is too simplistic, and the patient subsets that may benefit from the addition of radiotherapy merit additional investigation. In addition, there are other important controversial issues in the adjuvant setting of GC, including the comparison of a single agent versus combination chemotherapy and the importance of therapy duration, that still remain unanswered.

One may argue that the negative result obtained here is, in part, a result of the relatively high proportion of early-stage disease in both arms, where approximately 60% of the patients had stage IB or II GC. In the protocol, this final analysis was scheduled for when 227 events of relapse or death were observed, but only 141 events occurred after a median follow-up of 7 years. Similarly, approximately 15% of patients had lymph node–negative disease. Considering less locoregional recurrence in the XPRT arm than in the XP arm, it seems prudent to avoid these patients in future clinical trials involving adjuvant chemoradiotherapy. Another possible explanation could be the observation of a high percentage of diffuse-type GCs in the ARTIST trial. In the Intergroup 0116 trial, 39% of patients had diffuse-type GC, whereas more than 60% of our patients had diffuse-type GC, which is prone to early relapse and distant metastasis.[15] We cannot exclude that more diffuse GCs in the ARTIST trial was one of the main reason for the negative result. As commented by Brooks et al,[16] if the decreased efficacy of chemoradiotherapy in diffuse GC exists, future clinical trials may consider different adjuvant strategies based on histology. Of note, median time between relapse and death was only 8 months, reflective of a grim prognosis for patients with GC with recurrent or metastatic disease.

In exploratory biomarker analyses, no biomarker was prognostic or emerged as an independent predictive marker for chemoradiotherapy benefit. Although HER2 overexpression was acknowledged to be of value in palliative chemotherapy selection,[17] HER2 positivity in this trial was lower than expected (ie, HER2 3+ in 5% of patients) and was not associated with improved DFS. However, it should be acknowledged that tumor molecular profiles are known to change throughout disease course, and the reported

Table 3. Multivariable Cox Model for Prognostic Analysis

Variable	Disease-Free Survival			Overall Survival		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Stage	2.83	1.87 to 4.27	< .01	2.82	1.83 to 4.35	< .01
Treatment–Lauren classification interaction	2.8	1.03 to 7.63	.04	3.10	1.14 to 8.40	.03
Treatment–lymph node ratio interaction	2.03	1.44 to 2.87	< .01	1.98	1.38 to 2.83	< .01

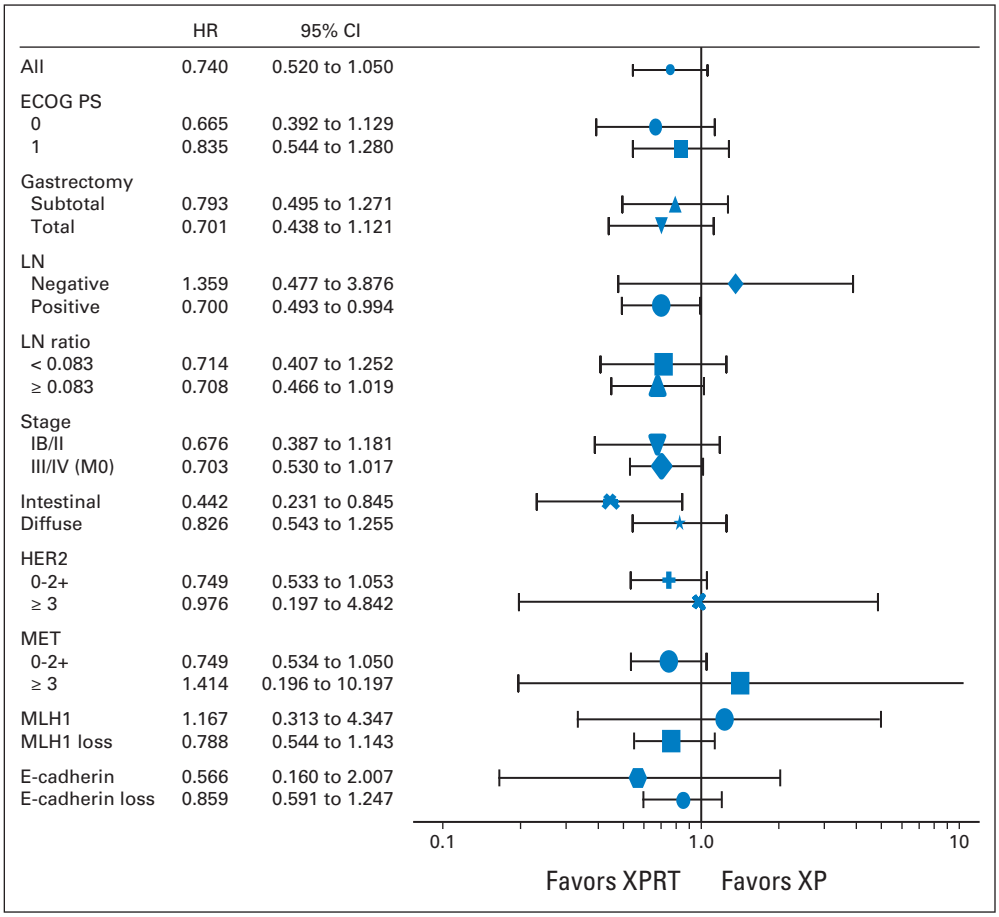

Fig 4. Forest plot of hazard ratios (HRs) and 95% CIs for disease-free survival. ECOG PS, Eastern Cooperative Oncology group performance status; HER2, human epidermal growth factor receptor 2; LN, lymph node; XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

results reflect tumor status at baseline. It should also be acknowledged that the percentages of each biomarker, as well as the sample size, were relatively small.

Perhaps one of the most interesting findings in the current updated report was the observation of an improved outcome obtained by chemoradiotherapy in certain patient subsets. Chemoradiotherapy seems beneficial in patients with node-positive disease or higher lymph node ratio and intestinal-type GC. Although it may be reflective of a random observation of an exploratory subset analysis, a similar finding has been observed in the Intergroup 0116 trial,[2] where there was reduced treatment effect in patients with diffuse GC. At the moment, in making treatment decisions for individual patients, we suggest that advanced stage, lymph node status, and the Lauren classification be the factors taken into account when chemoradiotherapy is being considered. These questions are currently being addressed in our multicenter, larger, three-arm phase III ARTIST 2 trial (ClinicalTrials.gov identifier: NCT0176146), which aims to compare all of the current standards of care in the adjuvant setting of D2-resected, node-positive, stage II or III GC (chemotherapy with S-1 for 1 year *v* combination chemotherapy with S-1 and oxaliplatin [SOX] for 6 months *v* chemoradiotherapy involving two cycles of SOX followed by S-1/radiotherapy and then four additional cycles of SOX). Issues raised by this ARTIST and other contemporary trials in the adjuvant setting of GC should hopefully be answered by ARTIST 2, where the hypothesis is that the addition of a platinum to S-1 and of radiotherapy to adjuvant chemotherapy will improve DFS. A total of 900 patients (ie, 300 per arm) will be registered onto the ARTIST 2 trial, and the stratification factors include stage, type of surgery, and the Lauren classification.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses

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