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ORIGINAL REPORT

Randomized Prospective Biomarker Trial of ERCC1 for Comparing Platinum and Nonplatinum Therapy in Advanced Non–Small-Cell Lung Cancer: ERCC1 Trial (ET)

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ABSTRACT

Purpose

Retrospective studies indicate that expression of excision repair cross complementing group 1 (ERCC1) protein is associated with platinum resistance and survival in non–small-cell lung cancer (NSCLC). We conducted the first randomized trial, to our knowledge, to evaluate ERCC1 prospectively and to assess the superiority of nonplatinum therapy over platinum doublet therapy for ERCC1-positive NSCLC as well as noninferiority for ERCC1-negative NSCLC.

Patients and Methods

This trial had a marker-by-treatment interaction phase III design, with ERCC1 (8F1 antibody) status as a randomization stratification factor. Chemonaïve patients with NSCLC (stage IIIB and IV) were eligible. Patients with squamous histology were randomly assigned to cisplatin and gemcitabine or paclitaxel and gemcitabine; nonsquamous patients received cisplatin and pemetrexed or paclitaxel and pemetrexed. Primary end point was overall survival (OS). We also evaluated an antibody specific for XPF (clone 3F2). The target hazard ratio (HR) for patients with ERCC1-positive NSCLC was ≤ 0.78.

Results

Of patients, 648 were recruited (177 squamous, 471 nonsquamous). ERCC1-positive rates were 54.5% and 76.7% in nonsquamous and squamous patients, respectively, and the corresponding XPF-positive rates were 70.5% and 68.5%. Accrual stopped early in 2012 for squamous patients because OS for nonplatinum therapy was inferior to platinum therapy (median OS, 7.6 months [paclitaxel and gemcitabine] *v* 10.7 months [cisplatin and gemcitabine]; HR, 1.46; $P = .02$). Accrual for nonsquamous patients halted in 2013. Median OS was 8.0 (paclitaxel and pemetrexed) versus 9.6 (cisplatin and pemetrexed) months for ERCC1-positive patients (HR, 1.11; 95% CI, 0.85 to 1.44), and 10.3 (paclitaxel and pemetrexed) versus 11.6 (cisplatin and pemetrexed) months for ERCC1-negative patients (HR, 0.99; 95% CI, 0.73 to 1.33; interaction $P = .64$). OS HR was 1.09 (95% CI, 0.83 to 1.44) for XPF-positive patients, and 1.39 (95% CI, 0.90 to 2.15) for XPF-negative patients (interaction $P = .35$). Neither ERCC1 nor XPF were prognostic: among nonsquamous patients, OS HRs for positive versus negative were ERCC1, 1.11 ($P = .32$), and XPF, 1.08 ($P = .55$).

Conclusion

Superior outcomes were observed for patients with squamous histology who received platinum therapy compared with nonplatinum chemotherapy; however, selecting chemotherapy by using commercially available ERCC1 or XPF antibodies did not confer any extra survival benefit.

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ASSOCIATED CONTENT

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Data Supplement
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INTRODUCTION

Little progress has been made in managing wild-type non–small-cell lung (NSCLC) cancer in the last decade compared with advances that have been made in treating the small subpopulations of epidermal growth factor receptor (EGFR)–positive and anaplastic lymphoma kinase–positive tumors with tyrosine kinase inhibitor therapy. Most patients with advanced NSCLC are treated with a platinum doublet. An effective predictive biomarker is required to direct treatment to improve outcomes.

One of the most promising biomarkers is excision repair cross complementing group 1 (ERCC1) protein, which is involved in the repair of cytotoxic platinum DNA adducts.[1-4] These adducts establish covalent cross-linking within and between DNA strands, which inhibits DNA replication and leads to cell death. ERCC1 binds to XPF protein, forming a heterodimer complex that cleaves DNA structures near the platinum adduct and allows for removal of the cytotoxic DNA lesion.

ERCC1 has been examined as a prognostic or predictive marker in several cancers that are treated with platinum chemotherapy. Increased ERCC1 expression is thought to be associated with platinum resistance in retrospective NSCLC studies.[5] In a meta-analysis of these studies of patients with advanced NSCLC who were treated with platinum therapy, mortality was higher in ERCC1-positive patients than in those with low expression (overall survival [OS] hazard ratio [HR], 1.48).[6] Recent studies similarly conclude that ERCC1 is prognostic,[7] but others do not.[8,9] ERCC1 gene polymorphisms have also been investigated, but results are inconsistent for NSCLC, again often on the basis of retrospective studies.[10-12]

Analyses of stored samples from 761 resected patients with early-stage NSCLC (International Adjuvant Lung Cancer Trial [IALT]) suggested that platinum chemotherapy versus no chemotherapy had a different effect among ERCC1-negative patients (HR, 0.65) than among ERCC1-positive patients (HR, 1.14; $P = .006$).[13] Consequently, several centers use ERCC1 to customize treatment. Review articles and the Centre for Comparative Effectiveness Research in Cancer Genomics identified ERCC1 as a top research priority because its use lacked high-quality evidence, with current evidence on the basis of retrospective studies.[14,15]

We conducted the first—to our knowledge—large, phase III study to prospectively evaluate ERCC1 in any tumor type as a predictive and prognostic biomarker.

PATIENTS AND METHODS

Study Design and Participants

The ERCC1 trial (ET) was a phase III randomized trial conducted across 85 UK hospitals to determine whether nonplatinum therapy is superior to platinum therapy for patients with NSCLC with ERCC1-positive tumors, but noninferior for patients with ERCC1-negative tumors. Inclusion criteria were age ≥ 18 years with histologic confirmation of advanced NSCLC (stage IIIb or IV), no prior chemotherapy, one or more measurable lesions (Response Evaluation Criteria in Solid Tumors v1.1 [RECIST v1.1]), Eastern Cooperative Oncology Group performance status of 0 to 1, and stable brain metastases (if present). Centers that routinely performed EGFR testing did not refer EGFR-positive patients to ET.

The trial had ethics approval and was conducted according to the Declaration of Helsinki.

Random Assignment

Registered patients had their tumor sample sent for central ERCC1 testing and were only randomly assigned after the result was known. Random assignment was performed by telephoning the Trials Center, where a computer program allocated patients by using minimization, stratified by ERCC1 status (positive *v* negative), disease stage (IIIb *v* IV), smoking history (never, former, or current), and hospital. This was done separately for nonsquamous (includes adenocarcinoma, large cell, and not otherwise specified) and squamous patients because of the different treatments.

Procedures

Small biopsied specimens that were obtained mainly from primary tumors (formalin fixed and paraffin embedded) were sent to University College London Advanced Diagnostics—a Clinical Pathology Accredited and Host Laboratory for the UK National External Quality Assessment Service—for centralized ERCC1 testing (immunohistochemistry).

We used an approved 8F1 ERCC1 antibody (Neomarkers, Fisher Scientific, Loughborough, UK) and clone Ab-2 (8F1; 1/300 dilution) and fully automated Leica Biosystems Bond III. Two expert pathologists (M.F. and A.C.) scored each sample blindly, classifying ERCC1 positive as moderate expression in ≥ 50% of tumor cells, or strong expression in ≥ 10% of tumor cells.[13] The quality control validation process involved testing each new antibody batch against established controls from both normal tonsil and tumors with known ERCC1 expression to ensure reproducibility and accurate interpretation.

From April 2013, after new information about the ERCC1-8F1 antibody,[16] the Independent Data Monitoring Committee (IDMC) and investigators added anti–XPF clone 3F2/3 (AbCam, Cambridge, UK), which is specific for the XPF-ERCC1 protein complex,[17] because XPF is also involved in the repair of the cytotoxic platinum DNA adduct. Thirty-four patient samples were measured prospectively and 614 retrospectively. Random assignment was still based on the ERCC1-8F1 antibody. XPF was scored by using QuickScore (familiar to many pathologists)[18] as the sum of staining intensity (score 1 to 3) and proportion of cells stained (score 1 to 5), with a score of ≥ 6 signifying positive staining for the ERCC1-XPF complex.

Doublet chemotherapy was administered once every three weeks, up to 6 cycles (using standard regimens). Squamous patients were randomly assigned to cisplatin 75 mg/m^2 day 1 plus gemcitabine 1,250 mg/m^2 days 1 and 8, or to paclitaxel 175 mg/m^2 day 1 plus gemcitabine. Nonsquamous patients were randomly assigned to cisplatin plus pemetrexed 500mg/m^2 day 1, or to paclitaxel plus pemetrexed. Paclitaxel was used because it is more cost effective than docetaxel, with little association between ERCC1 expression and sensitivities to paclitaxel (regimens used from prior phase II studies).[19]

Clinical examinations, biochemistry, and chest x-rays were performed at baseline, before each chemotherapy cycle, and monthly until 1 year from the start of the first chemotherapy cycle, then every 2 months thereafter. Chest and abdomen computed tomography scans were performed after cycles 2, 4, and 6, or when clinically indicated thereafter.

Statistical Considerations

The primary end point was OS. Secondary end points were progression-free survival (PFS), tumor response, adverse events, chemotherapy adherence, and health-related quality of life (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and LC13).[20]

For ERCC1-negative patients, the expected median OS was 9 months (United Kingdom audit data), with a noninferiority margin of 1.5 months (HR should not be ≥ 1.2), which required 669 deaths (80% power, 5% one-sided statistical significance). For ERCC1-positive patients, we aimed to increase OS from 9 months (platinum) to 11.5 months (nonplatinum), a minimum clinically important benefit (target HR ≤ 0.78, which required 511 deaths; 80% power, 5% two-sided statistical significance. Total target was 1,272 patients.

Analyses were by intention-to-treat. Time-to-event end points were analyzed by using the log rank test and Cox proportional hazards regression model, measured from the random assignment date. For OS, surviving patients were censored at the date last seen alive, and for PFS, an event was RECIST progression or death from any cause and those without an event were censored when last seen alive. ERCC1 and XPF were each examined as predictive—that is, whether the marker status influenced the OS or PFS HR for nonplatinum versus platinum, using an interaction test—and prognostic—that is, whether marker status is correlated with OS or PFS, using multivariable Cox proportional hazards regression. Toxicities were based on the maximum National Cancer Institute Common Terminology Criteria for Adverse Events toxicity grade for each patient and event. Quality of life was analyzed by using mixed modeling for repeated measures.

Early Stopping

Since September 2012, we excluded squamous patients after the IDMC observed that OS and PFS were significantly better with platinum therapy. Squamous histology patients who were still taking nonplatinum treatment and their clinicians were informed and recommended to switch to platinum therapy, unless there was benefit. In July 2013, the IDMC recommended closing the trial for two reasons: reanalysis of the IALT[16] indicated that the 8F1-ERCC1 antibody was questionable, with updated results showing it to not be predictive, and our observed ET data were consistent with these findings (OS HR, 1.08 among ERCC1-positive patients, and the 0.78 target was unlikely to be achieved if ET continued).

RESULTS

Of patients, 648 were randomly assigned between October 2009 and July 2013 (Fig 1). Baseline characteristics were similar between groups (Table 1).

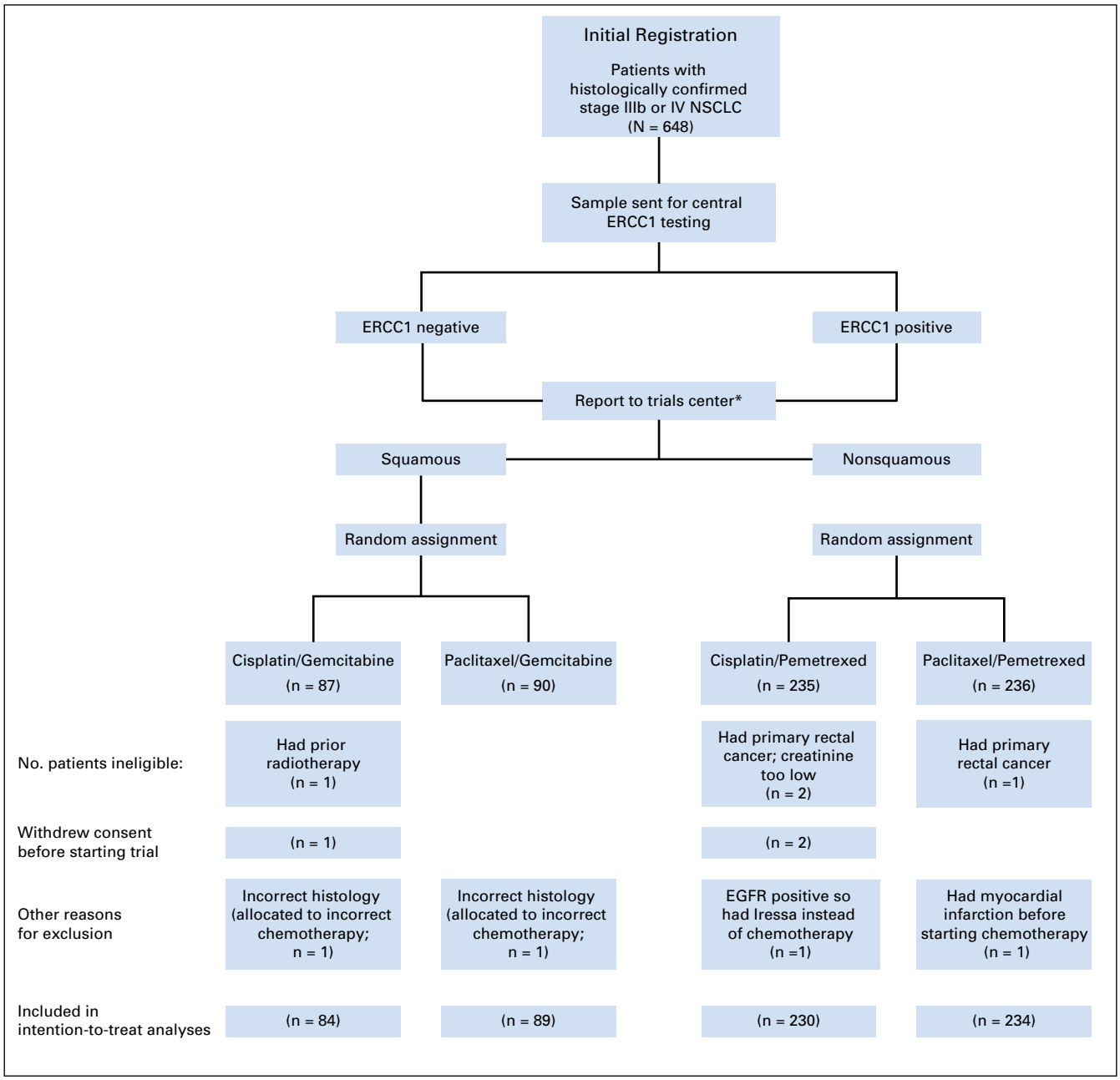

Fig 1. CONSORT diagram. When the urgent safety measure was implemented (September 2012), four patients with squamous histology switched from paclitaxel to cisplatin and carboplatin, 13 stopped trial treatment, two died shortly after stopping paclitaxel and gemcitabine, and one continued with platinum therapy. All other squamous patients had already finished their chemotherapy or had died previously. *Minimization was used to randomly assign patients, but only after excision repair cross complementing group 1 (ERCC1) status and histology were known. Squamous patients were then randomly assigned between each treatment arm using stratification factors ERCC1, smoking, stage, and center. This process ensured balance between the arms for each of these factors, such that they do not differ between the groups (and hence would not act as confounders). The same was done separately for nonsquamous patients. EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer.

Table 1. Baseline Characteristics of 637 Patients Included in the Analyses

Characteristic	Squamous Histology		Nonsquamous Histology	
	Cisplatin and Gemcitabine (n = 84)	Paclitaxel and Gemcitabine (n = 89)	Cisplatin and Pemetrexed (n = 230)	Paclitaxel and Pemetrexed (n = 234)
Median age, years (range)	67 (48-76)	66 (37-84)	63 (39-79)	64 (35-79)
Sex				
Male	79 (66)	71 (63)	58 (133)	56 (131)
Female	21 (18)	29 (26)	42 (97)	44 (103)
ECOG PS				
0	44 (37)	34 (30)	44 (101)	46 (107)
1	56 (47)	66 (59)	56 (129)	54 (127)
Stage				
IIIb	29 (24)	34 (30)	20 (45)	21 (49)
IV	71 (60)	66 (59)	80 (185)	79 (185)
Smoking				
Never	4 (3)	4 (4)	9 (22)	10 (23)
Former	40 (34)	45 (40)	43 (98)	42 (98)
Current	56 (47)	51 (45)	48 (110)	48 (113)
ERCC1				
Negative	23 (19)	24 (21)	46 (105)	45 (106)
Positive	77 (65)	76 (68)	54 (125)	55 (128)
XPF				
Negative	24 (21)	27 (24)	22 (51)	20 (47)
Positive	55 (45)	60 (53)	52 (120)	49 (114)
Unavailable*	21 (18)	13 (12)	26 (59)	31 (73)

NOTE. Data are given as % (No.) unless otherwise noted.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ERCC1, excision repair cross complementing group 1; PS, performance score.
*Insufficient sample.

ERCC1 results were available for 95% of patients within 3 days after the central laboratory received samples (Appendix Table A1, online only). The ERCC1-positive rate for all patients was 60.6% (386 of 637 patients) or 69.9% (332 of 475 patients) using the 8F1 or anti-XPF antibodies, respectively. Corresponding positive rates were 54.5% (253 of 464 patients) and 70.5% (234 of 332 patients) for nonsquamous histology, and 76.7% (133 of 173 patients) and 68.5% (98 of 143 patients) for squamous histology. Appendix Table A2 (online only) lists the concordance between ERCC1 and XPF.

Chemotherapy Adherence

Thirty two patients did not start trial chemotherapy after random assignment (Appendix Table A3, online only). Among those who started treatment, the percentage of patients who completed at least four cycles was 67.9% (platinum) versus 60.2% (nonplatinum) for those with nonsquamous histology ($P = .11$), and 58.7 versus 54.2% ($P = .64$) for those with squamous histology. Appendix Table A4 (online only) lists reasons for nonadherence.

There was no material difference in the number of cycles ($P = .09$, nonsquamous; and $P = .25$, squamous histology). The proportions with dose reductions were broadly similar, but more patients seemed to have dose delays in the platinum therapy groups (both histologies). Median drug dose administered was as expected, without differences between groups (Appendix Table A5, online only). Additional treatments after trial chemotherapy are listed in Appendix Table A6 (online only).

ERCC1 and XPF as Predictive Biomarkers

Among evaluable patients with squamous histology, the partial or complete tumor response rate was 51.6% (platinum) versus 26.5% (nonplatinum; $P = .004$), and was similar for ERCC1-positive patients (50.0 *v* 27.4%) and ERCC1-negative patients (57.1 *v* 23.5%; Appendix Table A7, online only). Among those with nonsquamous histology, the response rate was higher for platinum therapy versus nonplatinum therapy (48.4 *v* 33.0%; $P = .04$) in patients who were ERCC1 positive and similar in patients who were ERCC1 negatives (32.9 *v* 39.0%; $P = .51$). Appendix Table A8 (online only) lists odds ratios for ERCC1 as a predictive marker of response, with no evidence of an association among squamous histology patients (interaction $P = .58$). Although the interaction P value was of borderline statistical significance for nonsquamous subtypes ($P = .04$), results for ERCC1-positive patients contrasted with our hypothesis.

Median follow-up was 30 months; there were 563 deaths (511 from lung cancer) and 594 PFS events. OS and PFS were similar between nonsquamous histology patients who received platinum therapy and nonplatinum therapy (Fig 2). For squamous histology patients, OS and PFS were significantly better with platinum therapy compared with nonplatinum treatment (Fig 2).

Baseline characteristics were similar between ERCC1-positive patients and ERCC1-negative patients (Appendix Table A9, online only). Appendix Fig A1 (online only) shows Kaplan-Meier curves comparing platinum treatment and nonplatinum treatment according to ERCC1 status (8F1 antibody) in all patients (HRs are for nonplatinum *v* platinum therapy). There was no evidence of superiority for nonplatinum therapy (OS or PFS) among ERCC1-positive patients; however, because the effects differed between squamous and nonsquamous subtypes, results are presented separately hereafter. Figure 3 and Appendix Fig A2 (online only) show no evidence for a treatment-by-ERCC1 interaction for either OS ($P = .64$ nonsquamous; $P = .51$ squamous histology) or PFS ($P = .84$

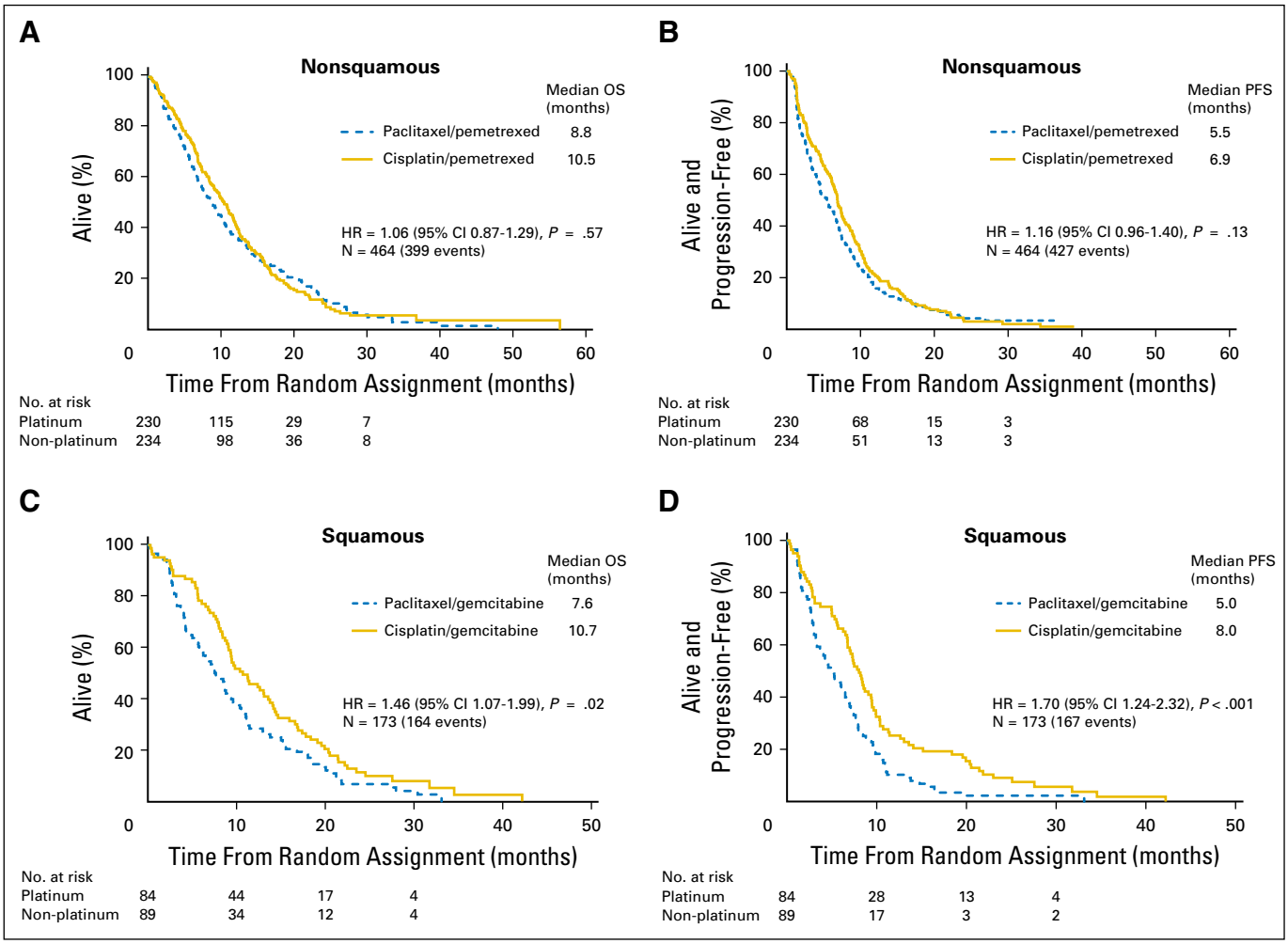

Fig 2. Overall survival (OS) and progression-free survival (PFS) curves according to histology. Unadjusted hazard ratios (HRs) are shown (HRs are for nonplatinum *v* platinum). HR (95% CI) adjusted for the random assignment stratification factors are 1.17 (0.92 to 1.47). 1.22 (0.98 to 1.54), 1.38 (0.89 to 2.13), and 1.44 (0.93 to 2.23) for nonsquamous OS and PFS and squamous OS and PFS, respectively.

nonsquamous; $P = .12$ squamous). Among patients with nonsquamous histology, although the observed OS HR of 0.99 was within the noninferiority limit of 1.20 in ERCC1-negative patients, the HR in positive patients (1.11) was not lower than the target effect of 0.78, and the median OS was higher with platinum therapy (9.6 months *v* 8.0 months; Fig 3). Among patients with squamous histology, all HRs exceeded 1.0 regardless of ERCC1 status (Appendix Fig A2).

Results were similar after excluding 32 patients who did not start trial chemotherapy and censoring four patients with squamous histology when they switched from nonplatinum therapy to platinum therapy after the IDMC recommendation, or after excluding patients randomly assigned to platinum therapy who later received a taxane (docetaxel) as well as those randomly assigned to paclitaxel who later received platinum therapy (Appendix Table A10, online only).

We conducted similar analyses for XPF. Baseline characteristics were similar between XPF-negative patients and XPF-positive patients (Appendix Table A11, online only). Kaplan-Meier curves are shown in Fig 4 (nonsquamous) and Appendix Fig A3 (online only; squamous). OS seemed to be better for platinum treatment than for nonplatinum treatment among patients with nonsquamous histology who were XPF negative, though not statistically significant at the 0.05 level (median 11.6 months *v* 8.9 months; HR, 1.39; $P = 1.14$), but given the OS HR (1.09) among XPF-positive patients, interaction *P* value was .35. This was in contrast to an apparent survival benefit for platinum therapy in squamous histology patients who were XPF positive (OS HR, 1.65; $P = .02$; PFS HR, 1.88; $P = .003$), with no effect among XPF-negative patients (OS HR, 1.06; $P = .86$; PFS HR, 1.30; $P = .39$; interaction $P = .21$ for OS). Using higher scores to categorize patients as XPF positive produced similar results (Appendix Table A12, online only).

Analyses that examined the predictive effects of ERCC1 or XPF according to sex, disease stage, and smoking did not show any subgroup effects (Appendix Table A13, online only).

We combined ERCC1 and XPF and still found no evidence that they were predictive. OS HR among patients with nonsquamous subtypes who were positive for both markers was 1.09 (95% CI, 0.78 to 1.51) compared with 1.16 (95% CI, 0.67 to 1.99)

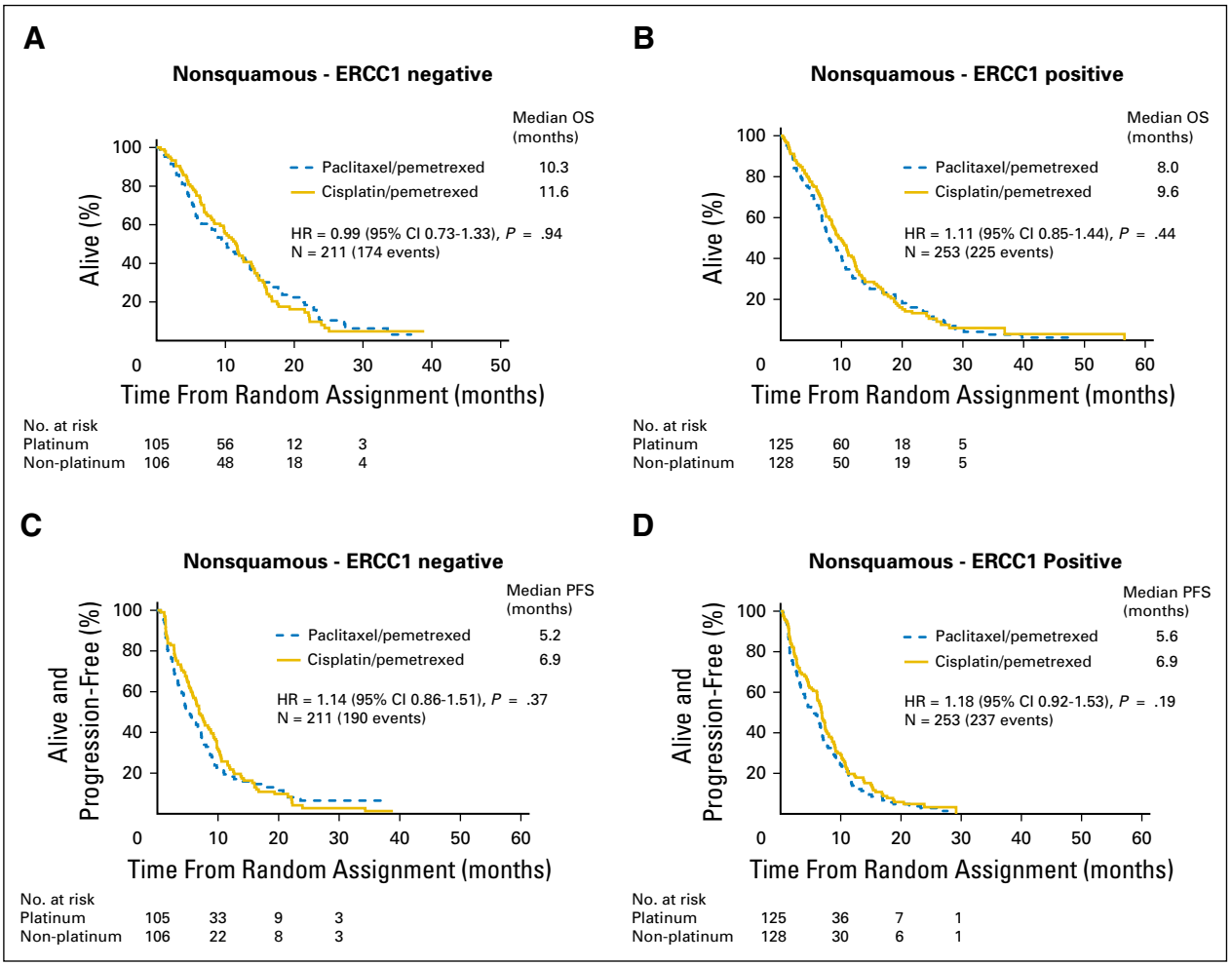

Fig 3. Overall survival (OS) and progression-free survival (PFS) curves by excision repair cross complementing group 1 (ERCC1) status (8F1 antibody), among nonsquamous histology. Unadjusted hazard ratios (HRs) are shown (HRs are for nonplatinum *v* platinum). HR (95% CI) adjusted for the random assignment stratification factors are 1.20 (0.81 to 1.78), 1.41 (0.96 to 2.08), 1.11 (0.79 to 1.56), and 1.32 (0.94 to 1.85) for ERCC1-negative patients OS and PFS, and ERCC1-positive patients OS and PFS, respectively. Test for interaction (between ERCC1 and treatment) was $P = .64$ (OS) and $P = .84$ (PFS). Two-tailed $P = .94$ (OS in ERCC1-negative patients) applies to the null hypothesis of HR, 1.0. One-tailed P value for the null hypothesis of HR ≥ 1.20 versus alternative HR < 1.20 (ie, the prespecified noninferiority margin) is 0.09 where $P < .05$ is evidence for noninferiority.

for patients who were negative for both markers, that is, not materially different. The corresponding HRs for squamous histology were 1.56 (95% CI, 1.00 to 2.43) and 1.82 (95% CI, 0.64 to 5.17), respectively.

ERCC1 and XPF As Prognostic Biomarkers

Unlike many retrospective studies,[6] neither ERCC1 nor XPF were prognostic markers for OS or PFS (Table 2 and Appendix Fig A4, online only; HRs are for marker positive *v* negative). All but one of the associations indicated that ERCC1-positive patients or XPF-positive patients had outcomes that were similar to patients who were negative, overall or within each treatment group (the association [PFS HR, 1.86 in squamous histology] had a P value of .03, possibly as a result of multiple testing and only 84 patients). Similar conclusions were made after combining ERCC1 and XPF: the adjusted OS HR comparing patients who were positive for both markers with those who were negative for both was 1.08 (95% CI, 0.79 to 1.44) for nonsquamous histology, and 0.87 (95% CI, 0.51 to 1.47) for squamous histology.

Adverse Events and Quality of Life

The proportion of patients who experienced any grade 3 to 5 adverse events was similar between platinum and nonplatinum groups: 66.7% versus 70.8% (squamous, $P = .56$), and 69.1% versus 72.2% (nonsquamous, $P = .46$; Appendix Tables A14 and A15, online only). Health-related quality of life was also broadly similar (Appendix Table A16, online only).

DISCUSSION

ET is the first randomized phase III study in advanced NSCLC specifically designed to evaluate prospective testing of ERCC1 as a predictive biomarker. Neither tumor ERCC1 nor XPF protein

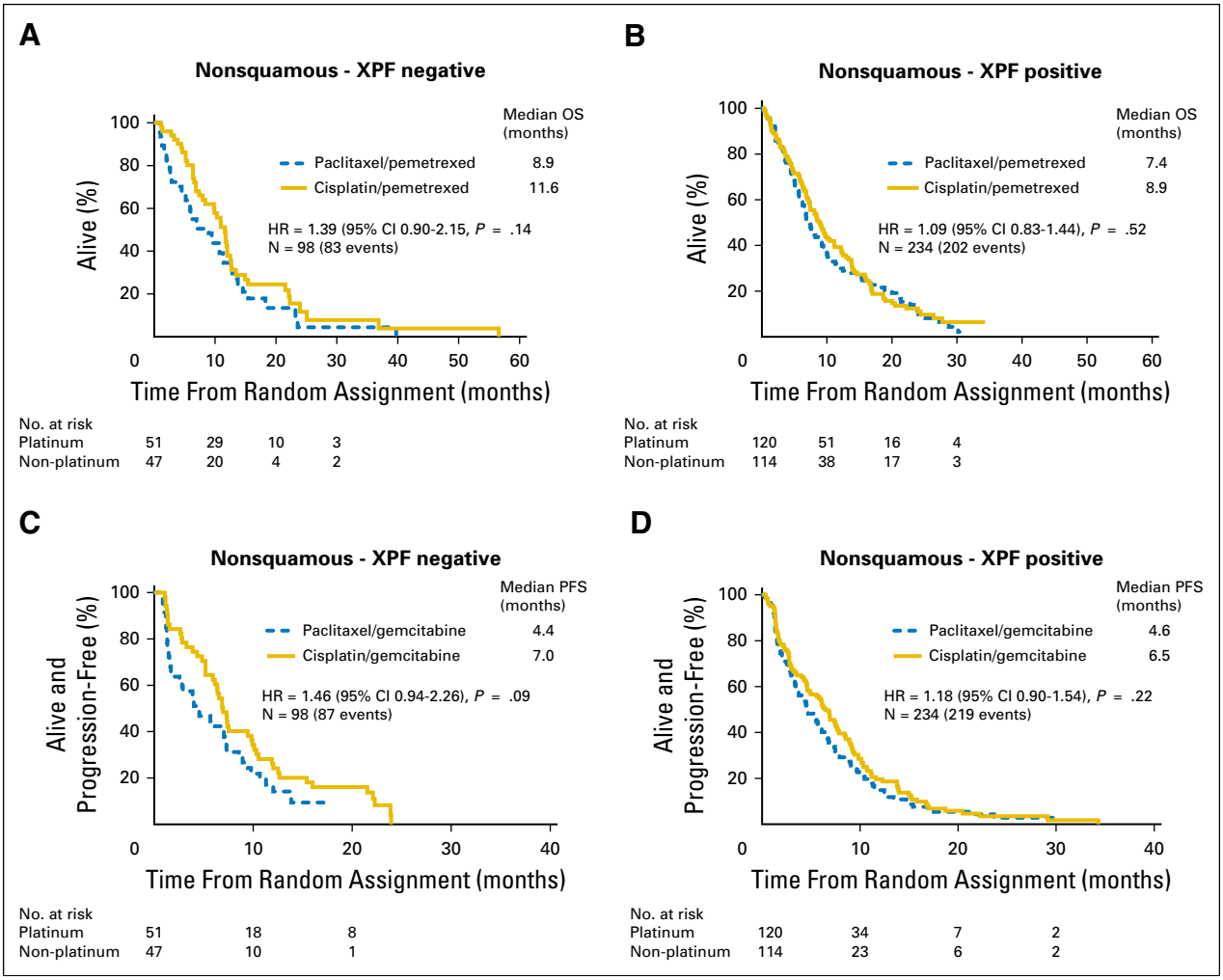

Fig 4. Overall survival (OS) and progression-free survival (PFS) curves by XPF status, among nonsquamous histology. Test for interaction (between excision repair cross complementing group 1 [ERCC1] and treatment) was $P = .35$ (OS) and $P = .40$ (PFS). Two-tailed $P = .14$ (OS in XPF-negative patients) applies to the null hypothesis of hazard ratio (HR), 1.0. One-tailed P value for the null hypothesis of HR ≥ 1.20 versus alternative HR < 1.20 (ie, the prespecified noninferiority margin) is 0.74 where $P < .05$ is evidence for noninferiority (HRs are for nonplatinum *v* platinum).

expression using commercially available antibodies predicted outcomes for platinum therapy or nonplatinum chemotherapy.

More patients with squamous histology had high ERCC1 expression (77%) than did nonsquamous patients (55%), which is similar to other reports.[13,21] Despite this higher rate, which was thought to be associated with platinum resistance, platinum therapy was significantly better (response rate, PFS, and OS) than nonplatinum therapy in patients with squamous histology. Results for squamous histology patients indicated that OS (10.7 months *v* 7.6 months), PFS (8.0 months *v* 5.0 months), and response rate (51.6% *v* 26.5%) after platinum therapy were all better than expected, even though the patient group seemed similar to those reported in practice and studies (Appendix Table A17, online only).[22,23] Squamous NSCLC might have different DNA repair profiles for platinum and nonplatinum therapy compared with nonsquamous subtypes, thus warranting further investigation. To our knowledge, this is the first time any randomized trial has shown superior outcomes among squamous NSCLC treated with platinum versus nonplatinum therapy, and these patients should continue to have this.

For nonsquamous tumors, although nonplatinum therapy was noninferior to platinum therapy among ERCC1-negative patients (OS HR, 0.99), we could not demonstrate that nonplatinum was superior among ERCC1-positive patients (OS HR, 1.11; superiority $P = 0.60$; target HR, 0.78).

We also did not find a correlation between ERCC1 and OS and PFS, unlike that reported in retrospective studies. OS among nonsquamous histology patients with ERCC1-positive tumors was similar to those who were negative (median, 9.6 months *v* 11.6 months; HR, 1.05).

Our study strengths were as follows: evaluation of both the 8F1-ERCC1 and 3F2-XPF antibodies assessed centrally by two consultant pathologists which increased the accuracy and reliability of the analysis; the ability to examine each marker as predictive or prognostic; and ERCC1 was measured prospectively in all patients in real time, with ERCC1 stratification incorporated into the randomization to ensure balance between treatment groups.

Only three previous trials have measured ERCC1 prospectively, but all used it to direct treatment and so they could not

Table 2. ERCC1 or XPF As a Prognostic Marker: Association With OS or PFS

	OS			PFS		
	No. of Patients (events)	HR (95% CI)	*P*	No. of Patients (events)	HR (95% CI)	*P*
Nonsquamous histology						
ERCC1						
Cisplatin and pemetrexed	230 (198)	1.05 (0.80 to 1.40)	.72	230 (215)	1.12 (0.85 to 1.46)	.43
Paclitaxel and pemetrexed	234 (201)	1.14 (0.86 to 1.51)	.36	234 (212)	1.14 (0.86 to 1.49)	.36
Combined*	464 (399)	1.11 (0.91 to 1.35)	.32	464 (427)	1.13 (0.93 to 1.37)	.22
XPF						
Cisplatin and pemetrexed	171 (147)	1.20 (0.83 to 1.72)	.33	171 (160)	1.22 (0.87 to 1.73)	.25
Paclitaxel and pemetrexed	161 (138)	0.96 (0.66 to 1.39)	.82	161 (146)	1.00 (0.69 to 1.44)	.99
Combined*	332 (285)	1.08 (0.83 to 1.40)	.55	332 (306)	1.10 (0.86 to 1.42)	.44
Squamous histology						
ERCC1						
Cisplatin and gemcitabine†	84 (78)	1.49 (0.85 to 2.60)	.16	84 (80)	1.86 (1.06 to 3.26)	.03
Paclitaxel and gemcitabine†	89 (86)	0.94 (0.56 to 1.56)	.80	89 (87)	0.76 (0.45 to 1.28)	.30
Combined*†	173 (164)	1.12 (0.77 to 1.63)	.55	173 (167)	1.12 (0.77 to 1.64)	.52
XPF						
Cisplatin and gemcitabine	66 (62)	0.72 (0.42 to 1.23)	.23	66 (64)	0.73 (0.43 to 1.25)	.26
Paclitaxel and gemcitabine	77 (74)	1.11 (0.68 to 1.83)	.67	77 (75)	1.18 (0.72 to 1.93)	.52
Combined*	143 (136)	0.91 (0.63 to 1.31)	.61	143 (139)	0.92 (0.64 to 1.33)	.67

NOTE. HRs are for positive versus negative ERCC1 or XPF status (Appendix Fig A4).
Abbreviations: ERCC1, excision repair cross complementing group 1; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*HRs are adjusted for treatment group.
†HRs are adjusted for stage and smoking status because, from Appendix Table A8, they were not far from statistical significance.

allow for any prognostic interaction effect of ERCC1,[24-26] and there was no comparator group without directed treatment. Two trials considered ERCC1 to influence response rates,[24,25] whereas the other found no effect.[26] ET has the only design that is able to compare platinum therapy with nonplatinum therapy in each ERCC1-positive and ERCC1-negative group, that is, a marker-by-treatment interaction design.[27]

We encountered some challenges: introduction of routine local EGFR mutation testing at hospitals competed with ET for tissue blocks of eligible patients; 25% of samples received were small and were just enough for ERCC1 testing; and 70 patients were not randomly assigned because of insufficient sample. ET was designed and set up in 2008 when the 8F1-assay for ERCC1 was in common use, but after accumulating evidence, the reliability of this assay was questioned. It would be difficult to switch to another biomarker in the prospective randomization process, which is an important potential problem for future biomarker-driven trials.

Several reasons might explain our findings. First, lack of specificity of ERCC1 immunohistochemistry testing, despite using the recommended 8F1 antibody when our trial was launched.[17,28-31] Second, although the 55% observed ERCC1-positive rate for nonsquamous histology patients in our trial is within the range reported from other studies (31% to 65%), some variability may be a result of different fixation methods, newer antibody batches, and different thresholds for classifying positivity.[6] Of interest, within the IALT, the rate was 44% in 2006 but 77% in the subsequent reanalyses of the same samples using a different antibody batch.[13,16] During ET, the ERCC1-positive rate did not change noticeably over time, despite using different antibody batches.

In the 2006 IALT report,[13] the OS HR for chemotherapy versus no therapy was 0.65 among ERCC1-negative patients, but 1.14 in ERCC1-positive patients, with a strong treatment-by-ERCC1 interaction ($P = .009$). However, reanalyses of the same samples using a different batch produced corresponding HRs of 0.81 and 0.96, respectively, with no evidence that ERCC1 was predictive (interaction $P = .53$).[16] Analyses of two other trials with the later batch showed similar inconsistent results.[16] The authors concluded that only one of four ERCC1 protein isoforms (202) had full capacity for nucleotide excision repair and cisplatin resistance, but none of the 16 commercially available antibodies distinguishes between them.[16,32] Processing issues associated with ERCC1 testing requires a validated standard procedure to be developed for future studies.[6,33]

After reports on the specificity of the 8F1 antibody to detect functional ERCC1 during ET (first raised by Bhagwat et al,[17] who found it cross-reacted with an unrelated protein), we revised our protocol to also examine the obligate XPF partner protein expression by using an anti-XPF antibody.[17] Repair of the cytotoxic platinum DNA adducts involve the ERCC1-XPF heterodimer complex.[34,35] XPF expression using 3F2 anti-XPF antibody could be a better predictive biomarker than 8F1-ERCC1 for platinum therapy,[17,36] and targeting XPF-ERCC1 by RNA interference increases cisplatin efficacy.[37] Several studies suggest a role of XPF in platinum resistance.[37,38] In ET, we observed that patients with nonsquamous histology who were XPF negative derived some benefit from platinum therapy (HR, 1.39; $P = .14$), but this is inconclusive and there was little association in XPF-positive patients (HR, 1.09; $P = .52$).

Because the active ERCC1 202 isoform is associated with XPF to form the only functional heterodimer,[32] such that a coexpression between ERCC1 and XPF dimers might have a stronger predictive value than either marker alone, we analyzed our data for patients who were positive for both ERCC1 and XPF (compared with those who were negative for both). We

again found no evidence for them to be either prognostic or predictive.

Although the IDMC stopped ET early, it was not underpowered. The primary objective was to show that nonplatinum therapy is more effective than platinum therapy among ERCC1-positive patients. Conditional power is the chance of obtaining the target OS HR of ≤ 0.78 if the trial had continued to the planned end (target 511 deaths), given the observed number of deaths and observed HR. It would have been futile to continue because conditional power was small: $< 0.01\%$ among all patients (352 deaths), and 7% among nonsquamous subtypes (225 deaths).

In conclusion, patients with advanced squamous NSCLC who were treated with nonplatinum chemotherapy had significantly worse outcomes than did those who were treated with platinum chemotherapy. Prospectively selecting the type of chemotherapy using the 8F1 or XPF antibody for ERCC1 did not predict OS or PFS for either histologic subtype. Furthermore, ERCC1 and XPF were not prognostic markers for advanced NCSLC. Neither ERCC1 nor XPF, using current commercial tests, should be used in routine practice without further investigation. Future studies could focus on developing assays that target the functional ERCC1 202 protein, which may be associated with cisplatin resistance.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Randomized Prospective Biomarker Trial of ERCC1 for Comparing Platinum and Nonplatinum Therapy in Advanced Non–Small-Cell Lung Cancer (ERCC1 Trial)

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Gloucestershire Hospitals NHS Foundation Trust: David Farrugia, MD
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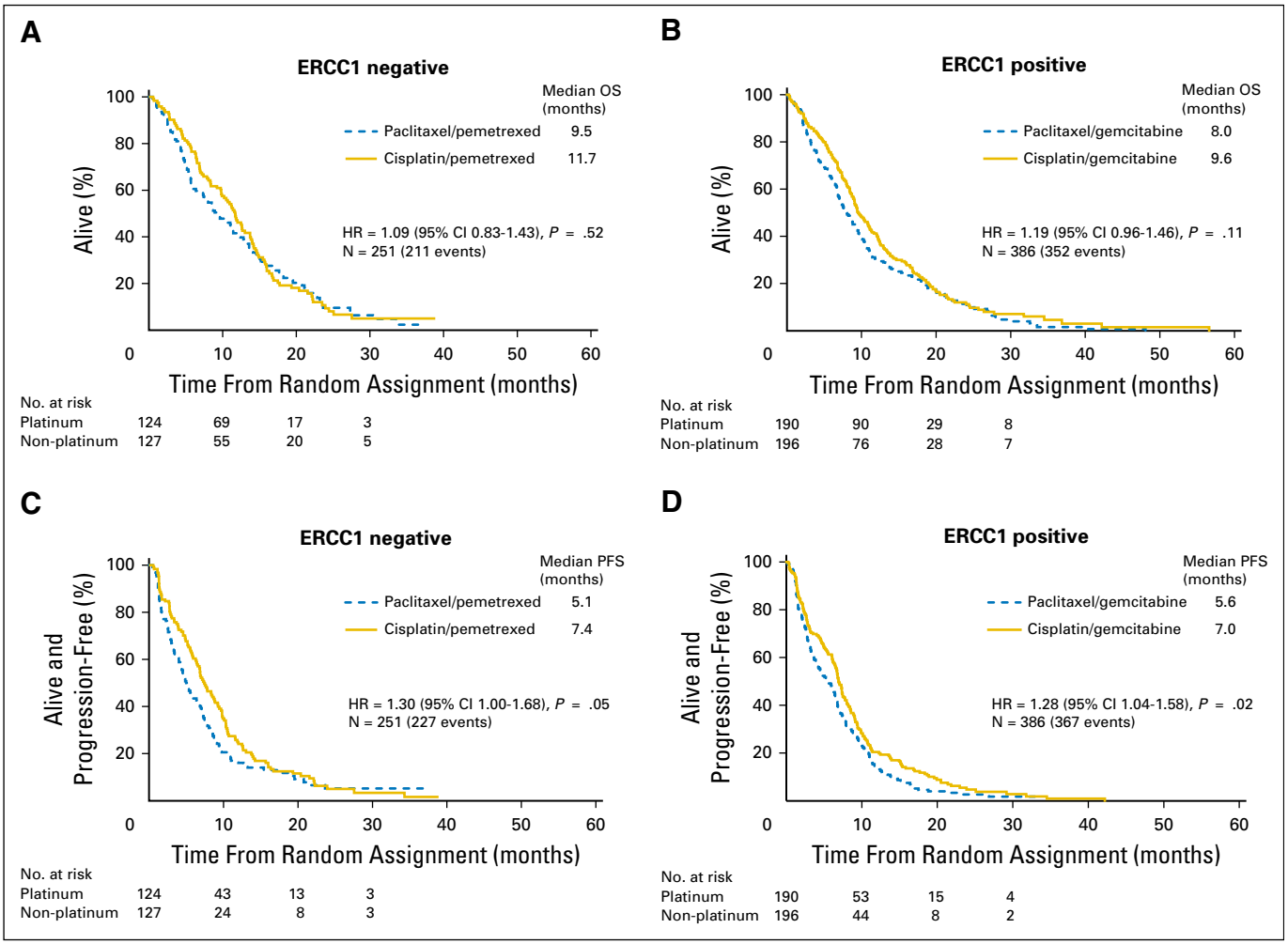

Fig A1. Overall survival (OS) and progression-free survival (PFS) curves according to excision repair cross complementing group 1 (ERCC1) status (8F1 antibody), nonsquamous and squamous histologies combined. Unadjusted hazard ratios (HRs) are shown (for nonplatinum *v* platinum). HR (95% CI) adjusted for random assignment stratitification factors are 1.28 (0.89 to 1.83), 1.53 (1.07 to 2.18), 1.22 (0.94 to 1.59), and 1.30 (1.00 to 1.69) for ERCC1-negative patients OS and PFS and ERCC1-positive patients OS and PFS, respectively. Two-tailed $P = .52$ (OS in ERCC1-negative patients) applies to the null hypothesis of HR, 1.0. One-tailed P value for the null hypothesis of HR $\geq$ 1.20 versus alternative HR $<$ 1.20 (ie, the prespecified noninferiority margin) is 0.25.

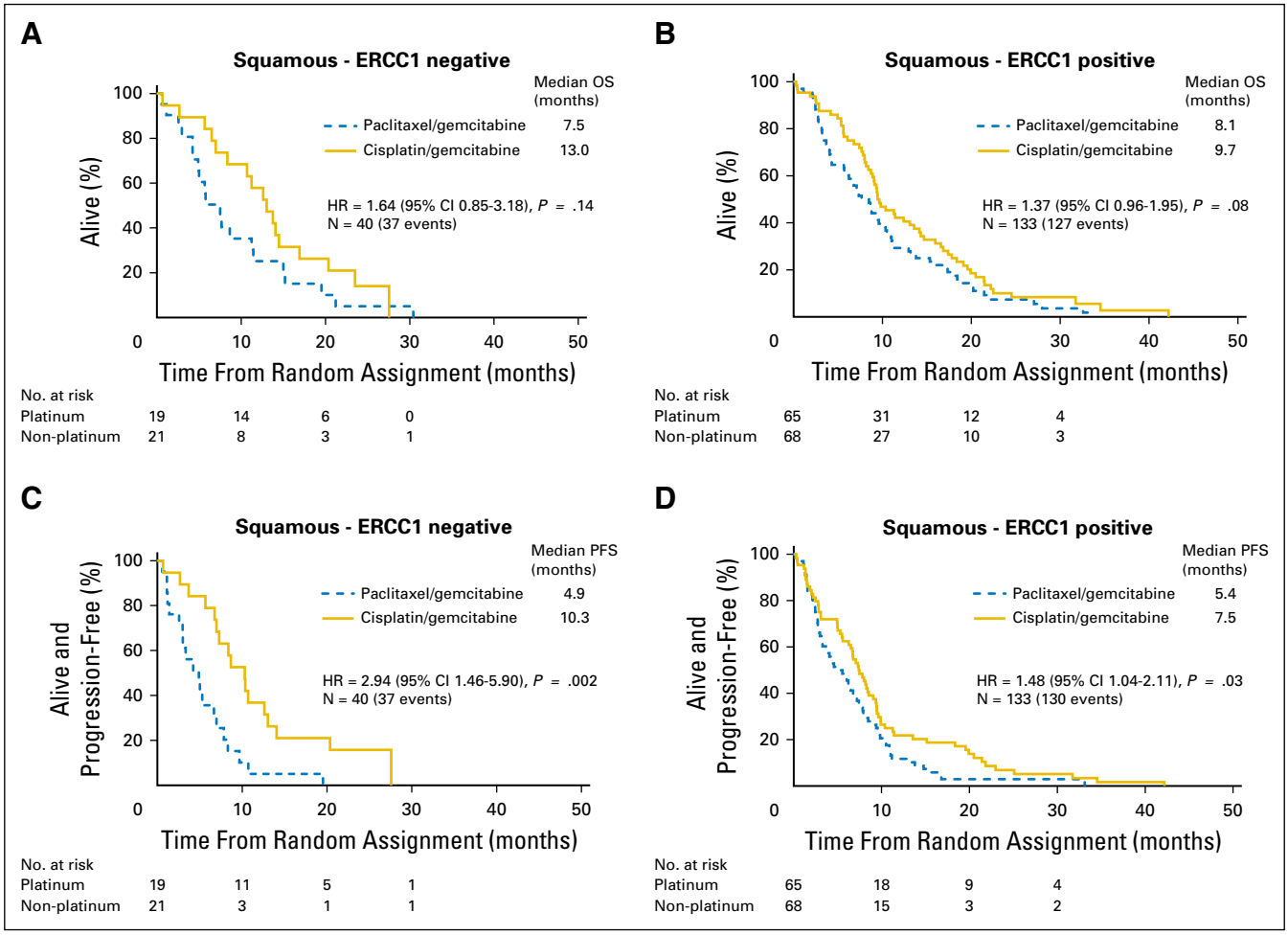

Fig A2. Overall survival (OS) and progression-free survival (PFS) curves by excision repair cross complementing group 1 (ERCC1) status (8F1 antibody), among squamous histology. Unadjusted hazard ratios (HRs) are shown (for nonplatinum *v* platinum). HR (95% CI) adjusted for random assignment stratitification factors are 2.20 (1.08 to 4.48), 5.21 (2.23 to 12.18), 1.61 (0.94 to 2.76), and 1.48 (0.87 to 2.53) for ERCC1-negative patients OS and PFS and ERCC1-positive patients OS and PFS, respectively. Test for interaction (between ERCC1 and treatment) was $P = .51$ (OS) and $P = .12$ (PFS). Two-tailed $P = .14$ (OS in ERCC1-negative patients) applies to the null hypothesis of HR, 1.0. One-tailed P value for the null hypothesis of HR ≥ 1.20 versus alternative HR < 1.20 (ie, the prespecified noninferiority margin) is 0.76 where $P < .05$ is evidence for noninferiority.

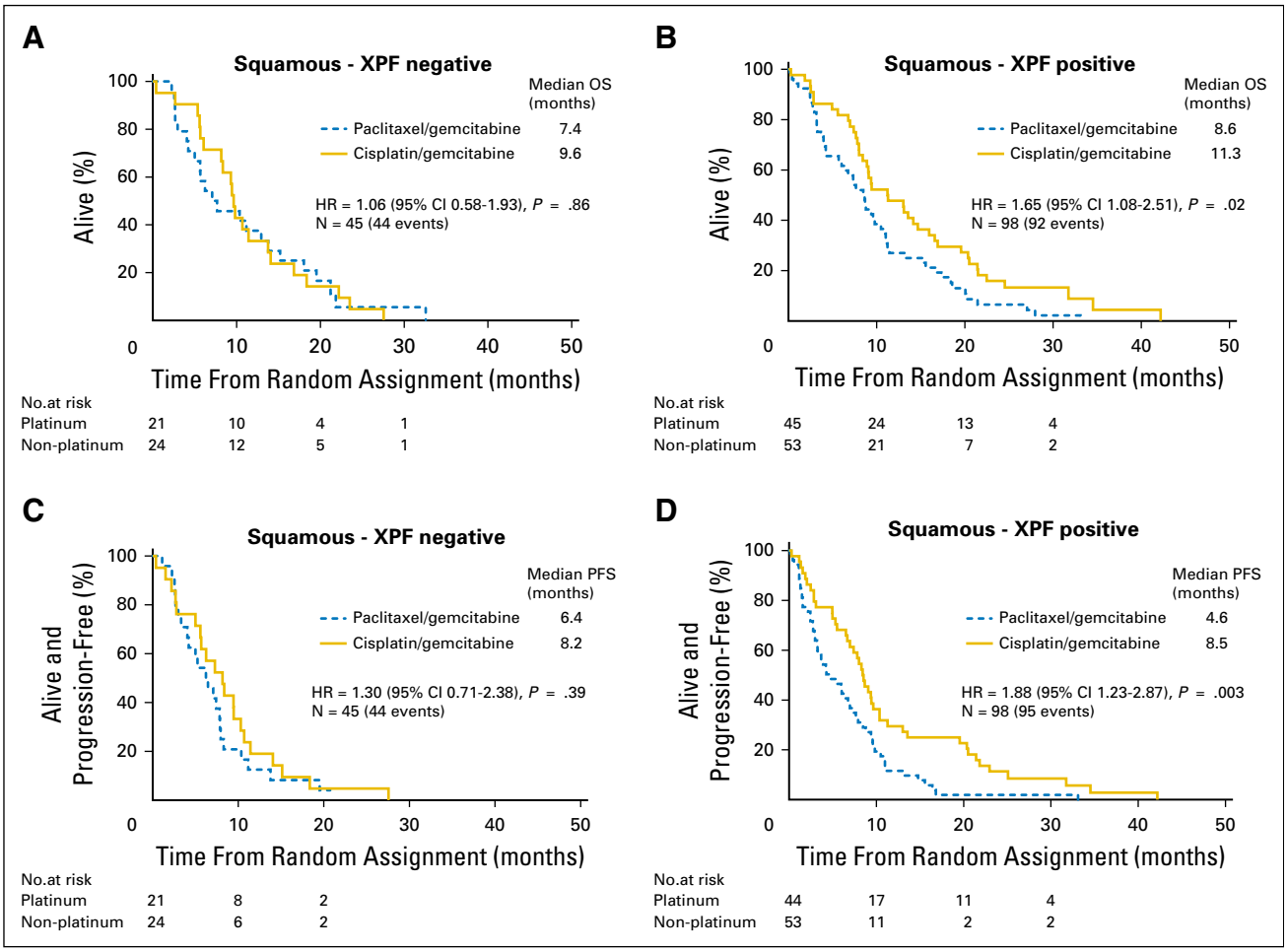

Fig A3. Overall survival (OS) and progression-free survival (PFS) curves by XPF status, among squamous histology. Test for interaction (between excision repair cross complementing group 1 [ERCC1] and treatment) was $P = .21$ (OS) and $P = .24$ (PFS). Two-tailed $P = .86$ (OS in XPF-negative patientss) applies to the null hypothesis of hazard ratio (HR), 1.0. One-tailed P value for the null hypothesis of HR ≥ 1.20 versus alternative HR < 1.20 (ie, the prespecified noninferiority margin) is 0.34 where $P < .05$ is evidence for noninferiority. HRs for nonplatinum versus platinum therapy.

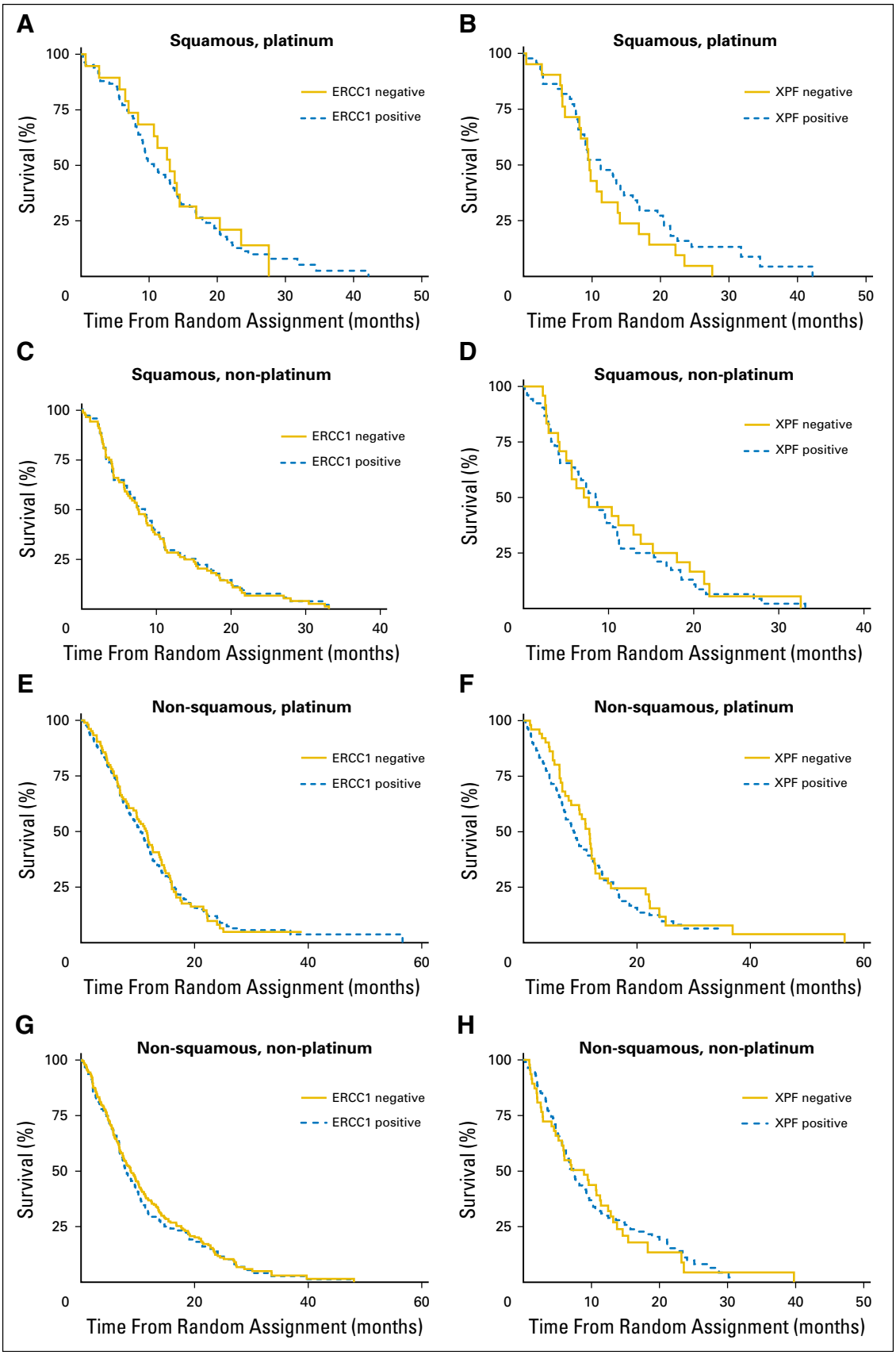

Fig A4. Excision repair cross complementing group 1 (ERCC1) and XPF as prognostic markers for overall survival: Kaplan-Meier curves of marker positive and negative patients, according to histology and whether they received platinum or nonplatinum therapy. Hazard ratios are listed in Table 2.

Table A1. ERCC1 Testing

Working Days, No.	Patients, No. (%)
1	261 (44.2)
2	227 (38.4)
3	72 (12.2)
4	19 (3.2)
5	4 (0.7)
6	2 (0.3)
7	3 (0.5)
8	2 (0.3)
12	1 (0.2)*

NOTE. Number of working days from when the tissue block was received by the central laboratory until the ERCC1 result was reported to the trials center (n = 591; dates were missing for 57 patients). Median time taken was 2 days.
Abbreviation: ERCC1, excision repair cross complementing group 1.
*An incorrect block was sent initially (endometrial tissue), so a second (lung) sample had to be requested, hence the 12 days

Table A2. Concordance Between the 8F1 ERCC1 Antibody and XPF Clone XPF 3F2/3 Antibody Among 637 Patients Analyzed

	ERCC1	
XPF	Negative	Positive
Squamous and nonsquamous patients		
Negative	85 (33.9)	58 (15.0)
Positive	82 (32.7)	250 (64.8)
Insufficient sample	84 (33.5)	78 (20.2)
Nonsquamous patients		
Negative	68 (32.2)	30 (11.9)
Positive	72 (34.1)	162 (64.0)
Insufficient sample	71 (33.7)	61 (24.1)
Squamous patients		
Negative	17 (42.5)	28 (21.0)
Positive	10 (25.0)	88 (66.2)
Insufficient sample	13 (32.5)	17 (12.8)

NOTE. Data are given as No. (%).
Abbreviation: ERCC1, excision repair cross complementing group 1.

Table A3. Adherence to Trial Chemotherapy

Chemotherapy	Squamous Histology		Nonsquamous Histology	
	Cisplatin and Gemcitabine (n = 84)	Paclitaxel and Gemcitabine (n = 89)	Cisplatin and Pemetrexed (n = 230)	Paclitaxel and Pemetrexed (n = 234)
No. of completed cycles				
0 (did not start)	4.8 (4)	6.7 (6)	4.8 (11)	4.7 (11)
1	14.3 (12)	11.2 (10)	10.9 (25)	8.5 (20)
2	9.5 (8)	22.5 (20)	10.4 (24)	20.5 (48)
3	15.5 (13)	9.0 (8)	9.1 (21)	8.5 (20)
4	27.4 (23)	23.6 (21)	20.4 (47)	17.5 (41)
5	7.1 (6)	5.6 (5)	8.7 (20)	6.8 (16)
6	21.4 (18)	21.4 (19)	35.2 (81)	32.5 (76)
Unknown*	—	—	0.4 (1)	0.8 (2)
Dose reductions at cycle				
1	12.5 (10 of 80)	3.6 (3 of 83)	3.2 (7 of 218)	1.8 (4 of 221)
2	17.6 (12 of 68)	24.6 (18 of 73)	17.6 (34 of 193)	13.4 (27 of 201)
3	16.7 (10 of 60)	13.2 (7 of 53)	17.1 (29 of 169)	11.1 (17 of 153)
4	14.9 (7 of 47)	31.1 (14 of 45)	20.3 (30 of 148)	18.0 (24 of 133)
5	16.7 (4 of 24)	20.8 (5 of 24)	15.8 (16 of 101)	12.0 (11 of 92)
6	11.1 (2 of 18)	10.5 (2 of 19)	18.5 (15 of 81)	17.1 (13 of 76)
Dose delays at cycle				
1	11.2 (9 of 80)	7.2 (6 of 83)	5.5 (12 of 218)	4.1 (9 of 221)
2	27.9 (19 of 68)	23.3 (17 of 73)	27.5 (53 of 193)	16.9 (34 of 201)
3	31.7 (19 of 60)	20.8 (11 of 53)	21.9 (37 of 169)	15.0 (23 of 153)
4	34.0 (16 of 47)	20.0 (9 of 45)	23.0 (34 of 148)	12.8 (17 of 133)
5	16.7 (4 of 24)	8.3 (2 of 24)	23.8 (24 of 101)	10.9 (10 of 92)
6	33.3 (6 of 18)	21.0 (4 of 19)	27.2 (22 of 81)	14.5 (11 of 76)
Day 8 gemcitabine not administered				
1	16	9		
2	3	11		
3	4	5		
4	5	8		
5	3	2		
6	1	1		

NOTE. Data are given as % (No.).
*Patients known to have started chemotherapy, but number of cycles are unknown (data not received from site).

Table A4. Reasons Why Patients Did Not Start Chemotherapy After Random Assignment or Why Others Stopped Before Six Cycles (after starting chemotherapy)

	Squamous Histology		Nonsquamous Histology	
	Cisplatin and Gemcitabine	Paclitaxel and Gemcitabine	Cisplatin and Pemetrexed	Paclitaxel and Pemetrexed
Did not start chemotherapy at all, No.				
Total	4	6	11	11
Adverse event	1		3	2
Clinical decision/patient unfit	1	2	5	3
Died	2	1	1	2
Disease progression			2	1
Patient request				1
Had palliative radiotherapy		1		
Urgent safety measure*		1		
Reason not reported		1		2
Started chemotherapy but stopped before six cycles, % (No.)				
Total	62	64	137†	145†
Adverse event	19.4 (12)	21.9 (14)	24.8 (34)	17.9 (26)
Clinical decision/patient unfit	32.3 (20)	26.6 (17)	24.1 (33)	31.7 (46)
Died	3.2 (2)	12.5 (8)	6.6 (9)	6.2 (9)
Disease progression	12.9 (8)	21.9 (14)	20.4 (28)	30.0 (43)
Intercurrent disease	1.6 (1)	—	0.7 (1)	0.7 (1)
Only four cycles were intended			1.5 (2)	0.7 (1)
Patient request	9.7 (6)	6.2 (4)	8.0 (11)	4.8 (7)
Secondary malignancy			0.7 (1)	0.7 (1)
Treatment suspended > 42 days	1.6 (1)	—	0.7 (1)	2.1 (3)
Urgent safety measure*	11.3 (7)‡	9.4 (6)‡		
Withdrew consent			0.7 (1)	—
Reason not reported	8.1 (5)	1.6 (1)	11.7 (16)	5.5 (8)

*That is, after the statement to not use nonplatinum therapy in patients with squamous histology.
†Excluding the three patients from Appendix Table A3 who were known to have started chemotherapy, but number of cycles were not reported.
‡In the nonplatinum group, patients had stopped after one (n = 2), two (n = 2), and four (n = 2) cycles. In the platinum group, patients were recorded as having stopped trial treatment after one (n = 2), two (n = 1), three (n = 2), and four (n = 2) cycles and were treated off-protocol.

Table A5. Summary of Chemotherapy Doses Administered Among Patients Who Started Chemotherapy

	Squamous Histology		Nonsquamous Histology	
Drug Dose According to Cycle	Cisplatin and Gemcitabine	Paclitaxel and Gemcitabine	Cisplatin and Pemetrexed	Paclitaxel and Pemetrexed
Pemetrexed				
1			500 (400, 950)	500 (375, 900)
2			500 (250, 950)	500 (50, 700)
3			500 (250, 930)	500 (250, 850)
4			500 (355, 930)	500 (250, 850)
5			500 (355, 930)	500 (300, 810)
6			500 (350, 930)	500 (300, 640)
Gemcitabine (day 1)				
1	1,250 (1,000, 2,600)	1,250 (938, 2,356)		
2	1,250 (935, 2,500)	1,250 (940, 2,300)		
3	1,250 (935, 2,500)	1,250 (938, 2,300)		
4	1,250 (937, 2,500)	1,250 (938, 2,300)		
5	1,250 (933, 2,166)	1,250 (1,226, 1,292)		
6	1,250 (933, 1,250)	1,250 (1,250, 1,292)		
Cisplatin				
1	75 (50, 160)		75 (56, 170)	
2	75 (50, 150)		75 (53, 170)	
3	75 (48, 150)		75 (53, 155)	
4	75 (41, 150)		75 (38, 140)	
5	75 (48, 125)		75 (38, 140)	
6	75 (48, 75)		75 (38, 140)	
Paclitaxel				
1		175 (173, 350)		175 (131, 342)
2		175 (130, 350)		175 (88, 342)
3		175 (131, 350)		175 (88, 342)
4		175 (130, 350)		175 (88, 342)
5		175 (130, 200)		175 (106, 280)
6		175 (130, 175)		175 (105, 258)

NOTE. Data are given as median (minimum, maximum). Drug doses are mg/m^2.

Table A6. Additional Treatments Administered After Trial Chemotherapy Stopped

	Squamous Histology		Nonsquamous Histology*	
	Cisplatin and Gemcitabine (n = 84)	Paclitaxel and Gemcitabine (n = 89)	Cisplatin and Pemetrexed (n = 230)	Paclitaxel and Pemetrexed (n = 234)
Any further chemotherapy	16 (19%)	15 (17%)	35 (15%)	58 (25%)
Platinum (with or without others, but not docetaxel†)	7	11	8	42
Docetaxel† (with or without others, not platinum)	5	1	16	4
Platinum and docetaxel†	2	3	4	4
Pemetrexed maintenance only			4	4
Other	2		3	4
Biologic agents	8 (10%)	11 (12%)	53 (23%)	59 (25%)
Erlotinib	8	11	50	55
Crizotinib				2
Erlotinib and crizotinib			1	
Erlotinib and trial drug			1	
Afatinib and erlotinib				1
Other (eg, trial drugs)			1	1
Radiotherapy	32 (38%)	43 (48%)	73 (32%)	72 (31%)
Surgery	1	4	2	4

*Appendix Table A10 presents an analysis in which the following are excluded when examining the association between ERCC1 and treatment and the effect on overall survival and progression-free survival: 16 + four patients randomly assigned to and started cisplatin and pemetrexed who had any docetaxel therapy later on, and 42 + four patients randomly assigned to and started paclitaxel and pemetrexed who had any platinum therapy later.
†Or any other taxane.

Table A7. Best Tumor Response Up to the End of Chemotherapy Cycle Six

	Squamous Histology		Nonsquamous Histology	
	Cisplatin and Gemcitabine	Paclitaxel and Gemcitabine	Cisplatin and Pemetrexed	Paclitaxel and Pemetrexed
ERCC1 positive				
Total	65	68	125	128
Progressive disease	7	6	8	15
Stable disease	17	31	39	52
Partial response	24	14	43	32
Complete response	0	0	1	1
Not evaluable	2	1	0	1
Not assessed	15	16	34	27
Partial response/complete response rate*	36.9%	20.6%	35.2%	25.8%
	$P = .05$		$P = .13$	
Partial response/complete response rate†	50.0%	27.4%	48.4%	33.0%
	$P = .02$		$P = .04$	
ERCC1 negative				
Total	19	21	105	106
Progressive disease	0	2	8	16
Stable disease	6	11	45	34
Partial response	8	4	25	32
Complete response	0	0	1	0
Not evaluable	2	0	3	2
Not assessed	3	4	23	22
Partial response/complete response rate*	42.1%	19.0%	24.8%	30.2%
	$P = .17$		$P = .44$	
Partial response/complete response rate†	57.1%	23.5%	32.9%	39.0%
	$P = .08$		$P = .51$	
All patients				
Total	84	89	230	234
Progressive disease	7	8	16	31
Stable disease	23	42	84	86
Partial response	32	18	68	64
Complete response	0	0	2	1
Not evaluable	4	1	3	3
Not assessed	18	20	57	49
Partial response/complete response rate*	38.1%	20.2%	30.4%	27.8%
	$P = .01$		$P = .54$	
Partial response/complete response rate†	51.6%	26.5%	41.2%	35.7%
	$P = .004$		$P = .32$	

NOTE. *P* values from Fisher's exact test.
Abbreviation: ERCC1, excision repair cross complementing group 1.
*As a percentage of all randomly assigned patients
†As a percentage of patients with evaluable disease (ie, progressive disease, stable disease, partial response, or complete response).

Table A8. Odds Ratios for ERCC1 Status as a Predictive Marker of Response According to Histology (for those with progressive disease, stable disease, partial response [PR], or complete response [CR])

	OR of Having PR/CR (95% CI) for Nonplatinum *v* Platinum Therapy	*P*	Interaction *P**
Nonsquamous patients			
ERCC1 negative	1.30 (0.68 to 2.49)	.42	.04†
ERCC1 positive	0.53 (0.29 to 0.94)	.03†	
Squamous patients			
ERCC1 negative	0.23 (0.05 to 1.08)	.06	.58
ERCC1 positive	0.38 (0.16 to 0.87)	.02	

NOTE. Interaction *P* values using all patients (where not evaluable/assessed are counted as 'not PR/CR') were *P* = .70 (squamous) and *P* = .08 (nonsquamous).
Abbreviations: ERCC1, excision repair cross complementing group 1; OR, odds ratio.
*Interaction *P* values between ERCC1 status and treatment group (from a logistic regression with PR/CR as the event of interest).
†Although of borderline statistical significance, patients on nonplatinum treatment were less likely (odds ratio 0.53) to have a PR/CR, than those on platinum therapy, but the trial hypothesis was the opposite to this.

Table A9. Baseline Characteristics According to ERCC1 Status (8F1 antibody)

	Nonsquamous			Squamous			Both Combined		
ERCC1 Status	Negative (n = 211)	Positive (n = 253)	*P*	Negative (n = 40)	Positive (n = 133)	*P*	Negative (n = 251)	Positive (n = 386)	*P*
Age, years, median	64	64	.89	68	66	.13	65	65	.94
Sex, %									
Male	55.5	58.1	.57	80.0	72.9	.37	59.4	63.2	.33
Female	44.5	41.9		20.0	27.1		40.6	36.8	
ECOG PS, %									
0	43.6	45.8	.63	45.0	36.8	.35	43.8	42.7	.79
1	56.4	54.2		55.0	63.2		56.2	57.3	
Stage, %									
IIIb	18.5	21.7	.38	20.0	34.6	.08	18.7	26.2	.03
IV	81.5	78.3		80.0	65.4		81.3	73.8	
Smoking, %									
Never	10.0	9.5	.50	2.5	4.5	.10	8.8	7.8	.90
Former	39.3	44.7		57.5	38.4		42.2	42.5	
Current	50.7	45.8		40.0	57.1		49.0	49.7	
Histology, %									
Squamous							15.9	34.5	< .001
Nonsquamous							84.1	65.5	

NOTE. *P* values: Wilcoxon for age, χ^2 for all others.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ERCC1, excision repair cross complementing group 1; PS, performance status.

Table A10. OS and PFS HRs

	OS	PFS
	HR (95% CI)	HR (95% CI)
Nonsquamous		
All patients (as in Fig 3)		
ERCC1 negative	0.99 (0.73 to 1.33)	1.14 (0.86 to 1.51)
ERCC1 positive	1.11 (0.85 to 1.46)	1.18 (0.92 to 1.53)
After excluding patients who did not start trial therapy		
ERCC1 negative	0.99 (0.73 to 1.35)	1.16 (0.86 to 1.56)
ERCC1 positive	1.11 (0.85 to 1.46)	1.20 (0.92 to 1.56)
Excluding patients who had certain additional treatments*		
ERCC1 negative	1.16 (0.82 to 1.58)	1.29 (0.94 to 1.76)
ERCC1 positive	1.21 (0.91 to 1.61)	1.14 (0.86 to 1.50)
Squamous		
All patients (as in Appendix Fig A2)		
ERCC1 negative	1.64 (0.85 to 3.18)	2.94 (1.46 to 5.90)
ERCC1 positive	1.37 (0.96 to 1.95)	1.48 (1.04 to 2.11)
After patients who did not start trial therapy and censoring the four who switched		
ERCC1 negative	1.69 (0.86 to 3.35)	3.15 (1.54 to 6.45)
ERCC1 positive	1.42 (0.98 to 2.05)	1.50 (1.03 to 2.17)

NOTE. OS and PFS HRs before and after excluding the 32 patients who did not start any trial treatment (Appendix Table A4) and censoring the four patients with squamous histology who switched from nonplatinum to platinum therapy at the date of the urgent safety measure. The table also shows the results after excluding nonsquamous patients randomly assigned to platinum therapy only who later had a taxane, and vice versa. HRs are for nonplatinum versus platinum therapy.
Abbreviations: ERCC1, excision repair cross complementing group 1; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Appendix Table A6: The following patients were excluded (acknowledging this will not be based on a full randomized comparison): Patients randomly assigned to and started cisplatin and pemetrexed who had any docetaxel (taxane) therapy later. Patients randomly assigned to and started paclitaxel and pemetrexed who had any platinum therapy later on.

Table A11. Baseline Characteristics According to XPF Status

	Nonsquamous			Squamous			Both Combined		
XPF Status	Negative (n = 98)	Positive (n = 234)	*P*	Negative (n = 45)	Positive (n = 98)	*P*	Negative (n = 143)	Positive (n = 332)	*P*
Age, years, median	63	65	.47	66	63	.38	64	65	.32
Sex, %									
Male	54.1	57.3	.59	77.8	72.4	.50	61.5	61.8	.96
Female	45.9	42.7		22.2	27.6		38.5	38.2	
ECOG PS, %									
0	39.8	43.6	.52	44.4	35.7	.32	41.3	41.3	.99
1	60.2	56.4		55.6	64.3		58.7	58.7	
Stage, %									
IIIb	18.4	23.5	.30	24.4	32.6	.32	20.3	26.2	.17
IV	81.6	76.5		75.6	67.4		79.7	73.8	
Smoking, %									
Never	8.2	9.8	.79	2.2	5.1	.65	6.3	8.4	.57
Former	42.9	44.9		40.0	42.9		42.0	44.3	
Current	49.0	45.3		57.8	52.0		51.8	47.3	
Histology, %									
Squamous							31.5	29.5	.67
Nonsquamous							68.5	70.5	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table A12. Using Higher Scores for XPF to Categorize Patients as Positive Among Those with Nonsquamous Histology

Definition of Positive*	OS HR (95% CI) for Nonplatinum *v* Platinum Therapy	*P* for Interaction Between XPF Status and Treatment
Total score ≥ 6 (as in Fig 4)		
Positive (n = 234; rate 70%)	1.09 (0.83 to 1.44)	.35
Negative (n = 98)	1.39 (0.90 to 2.15)	
Total score ≥ 7	1.05 (0.71 to 1.41)	.35
Positive (n = 204; rate 61%)	1.46 (1.00 to 2.13)	
Negative (n = 128)		
Total score ≥ 8		
Positive (n = 149; rate 45%)	1.04 (0.74 to 1.47)	.36
Negative (n = 183)	1.34 (0.97 to 1.83)	

*On the basis of the percentage of cells stained and level of intensity.

Table A13. Subgroup Analyses of the Predictive Effects of ERCC1 or XPF

	Overall Survival			Progression-Free Survival		
	Marker Negative	Marker Positive	Interaction *P*	Marker Negative	Marker Positive	Interaction *P*
Nonsquamous patients						
ERCC1						
Female	0.73 (0.46 to 1.17)	0.88 (0.58 to 1.33)	.70	0.87 (0.56 to 1.35)	0.98 (0.65 to 1.46)	.64
Male	1.22 (0.82 to 1.80)	1.35 (0.96 to 1.90)	.69	1.38 (0.95 to 2.02)	1.36 (0.96 to 1.91)	.90
Stage IIIb	1.20 (0.58 to 2.46)	1.62 (0.90 to 2.90)	.55	1.72 (0.86 to 3.45)	1.70 (0.96 to 3.00)	.83
Stage IV	0.94 (0.67 to 1.30)	1.01 (0.75 to 1.36)	.82	1.05 (0.77 to 1.44)	1.10 (0.82 to 1.46)	.83
Nonsmoker	0.98 (0.64 to 1.50)	1.09 (0.76 to 1.56)	.79	0.97 (0.65 to 1.46)	1.23 (0.86 to 1.75)	.40
Smoker	0.96 (0.62 to 1.48)	1.13 (0.77 to 1.67)	.59	1.37 (0.91 to 2.05)	1.15 (0.79 to 1.67)	.49
XPF						
Female	0.79 (0.39 to 1.61)	1.08 (0.70 to 1.68)	.42	0.95 (0.47 to 1.92)	1.06 (0.70 to 1.60)	.69
Male	2.01 (1.07 to 3.77)	1.15 (0.80 to 1.65)	.12	2.00 (1.10 to 3.63)	1.27 (0.89 to 1.81)	.16
Stage IIIb	0.88 (0.32 to 2.46)	1.89 (1.03 to 3.46)	.17	1.73 (0.62 to 4.87)	1.50 (0.85 to 2.63)	.98
Stage IV	1.64 (0.99 to 2.69)	0.95 (0.69 to 1.30)	.06	1.44 (0.89 to 2.35)	1.10 (0.81 to 1.49)	.30
Nonsmoker	1.40 (0.76 to 2.58)	1.03 (0.70 to 1.50)	.35	1.52 (0.82 to 2.80)	1.05 (0.73 to 1.51)	.25
Smoker	1.47 (0.78 to 2.77)	1.20 (0.80 to 1.81)	.67	1.43 (0.76 to 2.69)	1.41 (0.95 to 2.09)	.98
Squamous patients						
ERCC1						
Nonsmoker	1.44 (0.63 to 3.29)	1.68 (0.97 to 2.92)	.78	2.20 (0.95 to 5.10)	2.18 (1.26 to 3.79)	.98
Smoker	1.92 (0.63 to 5.81)	1.17 (0.73 to 1.87)	.24	4.44 (1.10 to 17.89)	1.09 (0.68 to 1.74)	.03
XPF						
Nonsmoker	1.18 (0.45 to 3.10)	1.67 (0.92 to 3.04)	.68	1.37 (0.52 to 3.63)	2.31 (1.27 to 4.20)	.35
Smoker	0.90 (0.40 to 2.01)	1.58 (0.84 to 2.97)	.20	1.45 (0.64 to 3.28)	1.57 (0.84 to 2.95)	.45

NOTE. In relation to sex, disease stage, and smoking. Data are given as hazard ratios and 95% CIs for nonplatinum versus platinum therapy, among patients with nonsquamous histology, and smoking status for squamous histology (because of potential correlation with ERCC1). Nonsmoker is defined as never smoker plus former smokers. There are only two interaction *P* values < .05, but only *P* = .03 (weak evidence for interaction), possibly as a result of chance, given the multiple analyses above.
Abbreviation: ERCC1, excision repair cross complementing group 1.

Table A14. Grade 3 to 5 Adverse Events, Treatment or Disease Related

	Squamous Histology		Nonsquamous Histology	
	Cisplatin and Gemcitabine (n = 84)	Paclitaxel and Gemcitabine (n = 89)	Cisplatin and Pemetrexed (n = 230)	Paclitaxel and Pemetrexed (n = 234)
Any grade 3-5 event	66.7	70.8	69.1	72.2
Events that led to death*	3	5	12 (10)†	8
Any grade 3-4 event	84.3	87.4	66.1	70.9
Grade 3 and 4 events				
Low lymphocytes	2.4	0	0.43	0.85
Low neutrophils‡	15.5	10.1	12.2	15.4
Low platelets‡	9.5	5.6	2.2	1.7
Low red blood cells‡	10.7	3.4	4.8	6.4
Low white cells‡	9.5	3.4	2.6	6.0
Any hematologic event	23.8	14.6	15.6	21.4
Clinical symptoms				
Acute kidney injury‡	0	1.1	0.43	0
Alopecia‡	1.2	2.2	0.43	3.8
Anaphylaxis	0	1.1	0.43	0.85
Appetite (low)	2.4	6.7	2.6	2.6
Chest pain	1.2	2.2	3.5	4.7
Confusion	0	0	0.87	1.7
Constipation‡	3.6	2.2	0.87	0.85
Cough	1.2	1.1	0.87	0.43
Diarrhea‡	0	4.5	3.9	4.7
Dysphagia	3.6	1.1	0.43	0.43
Dyspnea	7.1	11.2	11.7	12.4
Fatigue‡	16.7	16.9	16.1	20.5
Fever‡	0	1.1	1.3	1.7
Fracture	0	0	0.87	1.7
GI (other)	0	0	1.3	0.43
Headache	2.4	0	1.3	1.3
Hearing problems‡	0	1.1	1.3	0.43
Heart problems	3.6	4.5	3.0	4.3
Hypertension	1.2	0	0.43	0.43
Infection‡	16.7	19.1	16.1	19.7
Insomnia	0	0	1.3	0.85
Mucositis (oral)‡	1.2	3.4	2.2	1.7
Nausea‡	4.8	3.4	9.6	3.4
Neuropathy	1.2	7.9	1.3	4.7
Pain	10.7	19.1	7.4	14.1
Peripheral ischemia	1.2	0	0.87	0
Pruritis/itching‡	0	0	0.43	0
Pulmonary embolism	3.6	2.2	6.1	6.8
Rash‡	1.2	0	0.43	1.7
Sepsis	0	2.2	0.43	1.7
Stroke	1.2	0	1.3	0.43
Thrombotic event	3.6	2.2	3.0	4.3
Vomiting‡	2.4	2.2	8.7	4.3
Other	28.6	16.8	16.1	15.0
Any clinical 3 to 4 event	60.7	67.4	63.5	64.5
Laboratory adverse events				
Raised ALT‡	0	1.1	0.87	5.1
Raised AST‡	0	1.1	0	0.43
Raised ALP	0	0	1.3	1.3
Raised GGT	1.2	3.4	0.87	3.0
Hypoalbuminemia	0	2.2	0.43	1.7
Hyponatremia	2.4	3.4	2.6	2.1

NOTE. Data are given as percentages of the total number; where there were five or more occurrences. The differences between the proportions that had any hematologic event were not statistically significant: 23.8% versus 14.6% (squamous patients, $P = .12$), and 15.6% versus 21.4% (nonsquamous patients, $P = .11$). The event rate was slightly higher in the nonplatinum groups for pain (14.1% *v* 7.4% nonsquamous; 19.1% *v* 10.7% squamous).

Abbreviations: ALP, alkaline phosphatase; GGT, γ-glutamyl transferase.

*Appendix Table A15 lists details.

†Patients (n = 2) did not start trial treatments, so effectively, there were n = 10 patients.

‡Toxicity was prespecified as being of interest.

Table A15. Details of Serious Adverse Events That Were Associated With Death

	Squamous Histology		Nonsquamous Histology	
	Cisplatin and Gemcitabine	Paclitaxel and Gemcitabine	Cisplatin and Pemetrexed	Paclitaxel and Pemetrexed
No.	3	5	12 (10)*	8
Cause	2 hemorrhage (pulmonary; lower GI)	2 lung infection†	4 myocardial infarction‡	1 myocardial infarction
	1 collapsed (lung cancer later stated as cause of death)	1 dysphagia	4 lung infection*§	2 lung infection†
		1 cardiac failure	1 stroke	1 pneumonitis†
		1 not reported	1 neutropenic sepsis‖	1 pneumothorax
			1 respiratory failure*	1 neutropenia¶
			1 not reported†	1 perforated bowel†
				1 not specified#
Considered at least possibly treatment related		1	6	5

NOTE. See Appendix Table A14. Serious adverse events were either disease or treatment related.
*n = 1 patient with lung infection and another with respiratory failure did not start any trial chemotherapy; therefore, n = 10 serious adverse events as a result of death among patients who started chemotherapy.
†n = 1 considered possibly treatment related.
‡n = 1 considered possibly treatment related; and n=1 probably treatment-related.
§n = 2 considered possibly treatment related.
‖Considered definitely treatment related.
¶Considered probably treatment related.
#n = 1 considered probably treatment related but lung cancer later stated as cause of death.

Table A16. Quality of Life (EORTC QLQ-C30 and the lung cancer module LC13, version 3.0)

Item	Nonsquamous			Squamous		
	Baseline Mean: Paclitaxel and Pemetrexed	Baseline Mean: Cisplatin and Pemetrexed	Mean Difference During and After Treatment, 99% CI	Baseline Mean: Paclitaxel and Gemcitabine	Baseline Mean: Cisplatin and Gemcitabine	Mean Difference During and After Treatment, 99% CI
Global health status	62.3	63.0	0.8 (−3.6 to 5.3)	59.0	62.1	−4.2 (−10.4 to 2.0)
Functional scales						
Physical	76.8	75.3	0.4 (−4.4 to 5.2)	67.8	75.9	−8.7 (−15.9 to −1.5)
Role	67.4	68.7	−0.9 (−7.5 to 5.6)	59.5	68.4	−8.0 (−18.3 to 2.4)
Emotional	74.0	74.3	−0.3 (-4.9 to 4.4)	71.0	73.0	−4.4 (−11.5 to 2.8)
Cognitive	83.8	85.0	1.4 (−3.3 to 6.0)	79.2	86.8	−2.0 (−9.1 to 5.0)
Social	72.6	75.7	−2.6 (−8.2 to 3.1)	70.6	73.2	−4.2 (−13.7 to 5.4)
Symptom scales						
Fatigue	37.1	34.0	1.1 (-3.9 to 6.1)	41.1	36.2	5.2 (−2.8 to 13.3)
Nausea/vomiting	9.3	10.2	-4.5 (−7.8 to −1.1)*	12.3	6.4	1.2 (−4.1 to 6.6)
Pain	30.0	26.1	0.7 (−4.8 to 6.2)	36.6	25.4	7.1 (−1.8 to 16.1)
Dyspnea	37.3	37.8	2.1 (−3.9 to 8.1)	44.9	40.4	5.5 (−3.5 to 14.6)
Insomnia	36.3	36.5	0.3 (−5.7 to 6.3)	39.1	29.3	5.5 (−4.9 to 15.8)
Appetite loss	26.6	27.0	−0.4 (−6.2 to 5.2)	34.1	19.5	9.0 (−0.6 to 18.6)
Constipation	19.4	17.2	−2.0 (−6.6 to 2.6)	20.2	21.0	0.2 (−8.4 to 8.8)
Diarrhea	6.9	6.3	−0.9 (−3.8 to 1.9)	7.8	7.9	2.2 (−2.5 to 6.9)
Financial problems	19.6	21.7	−0.6 (−6.9 to 5.7)	21.8	22.8	−1.4 (−11.0 to 8.2)
LC13 symptoms						
Dyspnea	27.4	29.0	0.5 (−4.6 to 5.6)	32.4	29.2	5.7 (−2.7 to 14.1)
Coughing	43.3	47.1	−2.6 (−7.7 to 2.5)	48.1	42.2	4.8 (−3.0 to 12.5)
Hemoptysis	3.0	3.4	−0.2 (−1.8 to 1.4)	7.4	7.5	0.4 (−4.1 to 4.9)
Sore mouth	5.8	7.1	−2.7 (−6.4 to 0.9)	10.3	6.2	2.8 (−2.9 to 8.5)
Dysphagia	5.2	5.8	−1.2 (−4.4 to 1.9)	8.6	4.0	4.3 (−1.4 to 10.0)
Peripheral neuropathy	4.0	6.1	8.3 (4.2 to 12.4)*	11.1	8.9	12.7 (4.2 to 21.2)*
Alopecia	2.8	2.3	31.5 (27.3 to 35.7)*	2.9	2.2	27.4 (20.5 to 34.4)*
Pain in chest	19.5	18.1	−1.5 (−5.8 to 2.8)	23.3	19.5	1.0 (−5.7 to 7.7)
Pain arm/shoulder	21.7	17.3	0.5 (−4.3 to 5.2)	28.0	22.1	6.4 (−2.0 to 14.8)
Pain in other parts	23.1	22.9	4.0 (−1.3 to 9.3)	22.4	19.1	1.1 (−7.8 to 10.0)
Help from pain medication†	63.8	63.6	−0.2 (−5.7 to 5.3)	63.5	61.8	4.1 (−3.7 to 11.9)

Scores range from 0 to 100 for each item. For the global health and functional scales, 0 indicates poor health and 100 good health. For all other scales, 0 indicates no symptoms and 100 high level of symptoms. The mean difference is the treatment effect for nonplatinum minus platinum, from a repeated measures mixed model, allowing for the baseline values. For the global health and functional scales, a positive mean difference indicates that nonplatinum was better and a negative difference indicates that platinum was better. For all other scales, a negative mean difference indicates that nonplatinum was better and a positive difference indicates that platinum was better. 99% CIs are shown because there are multiple analyses. As expected, paclitaxel and pemetrexed was associated with fewer patients with nausea and vomiting in nonsquamous patients ($P = .001$). Platinum therapy caused less peripheral neuropathy and alopecia in both squamous and nonsquamous patients ($P < .001$ for both).

*Associations that had P values $\leq .001$.

†For those who took pain medication.

Table A17. Comparison of the Median OS and PFS in Squamous Histology Patients Between the ERCC1 Trial and Other Studies

Median, Months	ERCC1 Trial		Lee et al, 2009[22]	Scagliotti, 2008[23]	UK National Audit Data, (LUCADA)
	Cisplatin and Gemcitabine (n = 84)	Paclitaxel and Gemcitabine (n = 89)	Carboplatin and Gemcitabine (n = 239)	Cisplatin and Gemcitabine (n = 229)	Platinum Therapy
OS	11.4	8.7	9.4	10.8	~9
PFS	8.4	6.0	5.8	5.5	

Abbreviations: OS, overall survival; PFS, progression-free survival.