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DOI:

[10.1200/JCO.2016.68.1841](https://doi.org/10.1200/JCO.2016.68.1841)

Document Version

Publisher's PDF, also known as Version of record

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Citation for published version (APA):

Lee, S. M., Falzon, M., Blackhall, F., Spicer, J., Nicolson, M., Chaudhuri, A., Middleton, G., Ahmed, S., Hicks, J., Crosse, B., Napier, M., Singer, J. M., Ferry, D., Lewanski, C., Forster, M., Rolls, S-A., Capitanio, A., Rudd, R., Iles, N., ... Hackshaw, A. (2017). Randomized Prospective Biomarker Trial of ERCC1 for Comparing Platinum and Nonplatinum Therapy in Advanced Non-Small-Cell Lung Cancer: ERCC1 Trial (ET). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 35(4), 402-411.
<https://doi.org/10.1200/JCO.2016.68.1841>

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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 (ET)

Siow Ming Lee, Mary Falzon, Fiona Blackhall, James Spicer, Marianne Nicolson, Abhro Chaudhuri, Gary Middleton, Samreen Ahmed, Jonathan Hicks, Barbara Crosse, Mark Napier, Julian M. Singer, David Ferry, Conrad Lewanski, Martin Forster, Sally-Ann Rolls, Arrigo Capitanio, Robin Rudd, Natasha Iles, Yenting Ngai, Michael Gandy, Rachel Lillywhite, and Allan Hackshaw

Author affiliations appear at the end of this article.

Published at ascopubs.org/journal/jco on November 28, 2016.

Support information appears at the end of this article.

S.M.L. and A.H. contributed equally to this article.

Presented at the European Society for Medical Oncology 2014 Congress, Madrid, Spain, September 26-30, 2014.

Clinical trial information: ISRCTN02370070.

Corresponding author: Siow Ming Lee, MD, PhD, Department of Oncology, University College London Hospitals, 250 Euston Rd, London NW1 2PG, United Kingdom; e-mail: sm.lee@uclh.nhs.uk.

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0732-183X/17/3504w-402w/\$20.00

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.

J Clin Oncol 35:402-411. © 2016 by American Society of Clinical Oncology

ASSOCIATED CONTENT

See accompanying Editorial on page 384

Appendix
DOI: 10.1200/JCO.2016.68.1841

Data Supplement
DOI: 10.1200/JCO.2016.68.1841

DOI: 10.1200/JCO.2016.68.1841

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 ν negative), disease stage (IIIB ν 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 $\geq 50\%$ of tumor cells, or strong expression in $\geq 10\%$ 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/m² day 1 plus gemcitabine 1,250 mg/m² days 1 and 8, or to paclitaxel 175 mg/m² day 1 plus gemcitabine. Nonsquamous patients were randomly assigned to cisplatin plus pemetrexed 500mg/m² 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 IALT¹⁶ 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 non-squamous 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 $HR \geq 1.20$ 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 $HR \geq 1.20$ 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

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

AUTHOR CONTRIBUTIONS

Conception and design: Siow Ming Lee, Allan Hackshaw

Collection and assembly of data: Fiona Blackhall, James Spicer, Marianne Nicolson, Abhro Chaudhuri, Gary Middleton, Samreen Ahmed, Jonathan Hicks, Barbara Crosse, Mark Napier, Julian M. Singer, David Ferry, Conrad Lewanski, Martin Forster, Sally-Ann Rolls, Arrigo Capitanio, Natasha Iles, Yenting Ngai, Michael Gandy, Rachel Lillywhite, Allan Hackshaw

Data analysis and interpretation: Siow Ming Lee, Mary Falzon, Fiona Blackhall, James Spicer, Marianne Nicolson, Robin Rudd, Allan Hackshaw

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

1. Reed E: Nucleotide excision repair and anti-cancer chemotherapy. *Cytotechnology* 27:187-201, 1998
2. Sancar A: Mechanisms of DNA excision repair. *Science* 266:1954-1956, 1994
3. Zamble DB, Mu D, Reardon JT, et al: Repair of cisplatin-DNA adducts by the mammalian excision nuclease. *Biochemistry* 35:10004-10013, 1996
4. McNeil EM, Melton DW: DNA repair endonuclease ERCC1-XPF as a novel therapeutic target to overcome chemoresistance in cancer therapy. *Nucleic Acids Res* 40:9990-10004, 2012
5. Altaia R, Liang X, Yu JJ, et al: Excision repair cross complementing-group 1: Gene expression and platinum resistance. *Int J Mol Med* 14:959-970, 2004
6. Hubner RA, Riley RD, Billingham LJ, et al: Excision repair cross-complementation group 1 (ERCC1) status and lung cancer outcomes: A meta-analysis of published studies and recommendations. *PLoS One* 6:e25164, 2011
7. Huang ZL, Cao X, Luo RZ, et al: Analysis of ERCC1, BRCA1, RRM1 and TUBB3 as predictors of prognosis in patients with non-small cell lung cancer who received cisplatin-based adjuvant chemotherapy: A prospective study. *Oncol Lett* 11:299-305, 2016
8. Lafuente-Sanchis A, Zúñiga Á, Galbis JM, et al: Prognostic value of ERCC1, RRM1, BRCA1 and SETDB1 in early stage of non-small cell lung cancer. *Clin Transl Oncol* 18:798-804, 2016
9. He YW, Zhao ML, Yang XY, et al: Prognostic value of ERCC1, RRM1, and TS proteins in patients with resected non-small cell lung cancer. *Cancer Chemother Pharmacol* 75:861-867, 2015
10. Tiseo M, Bardi P, Bortesi B, et al: ERCC1/BRCA1 expression and gene polymorphisms as prognostic and predictive factors in advanced NSCLC treated with or without cisplatin. *Br J Cancer* 108:1695-1703, 2013
11. Xie F, Sun Q, Wu S, et al: Nucleotide excision repair gene ERCC1 19007T>C polymorphism contributes to lung cancer susceptibility: A meta-analysis. *Genet Test Mol Biomarkers* 18:591-595, 2014
12. Han Y, Liu J, Sun M, et al: A significant statistical advancement on the predictive values of ERCC1 polymorphisms for clinical outcomes of platinum-based chemotherapy in non-small cell lung cancer: An updated meta-analysis. *Dis Markers* 2016:7643981, 2016
13. Olausson KA, Dunant A, Fouret P, et al: DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med* 355:983-991, 2006
14. Thariani R, Wong W, Carlson JJ, et al: Prioritization in comparative effectiveness research: The CANCERGEN Experience. *Med Care* 50:388-393, 2012
15. Macerelli M, Ganzinelli M, Gouedard C, et al: Can the response to a platinum-based therapy be predicted by the DNA repair status in non-small cell lung cancer? *Cancer Treat Rev* 48:8-19, 2016
16. Friboulet L, Olausson KA, Pignon JP, et al: ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. *N Engl J Med* 368:1101-1110, 2013
17. Bhagwat NR, Roginskaya VY, Acquafondata MB, et al: Immunodetection of DNA repair endonuclease ERCC1-XPF in human tissue. *Cancer Res* 69:6831-6838, 2009
18. Detre S, Saclani Jotti G, Dowsett M: A "quickscore" method for immunohistochemical semiquantitation: Validation for oestrogen receptor in breast carcinomas. *J Clin Pathol* 48:876-878, 1995
19. Takenaka T, Yoshino I, Kouso H, et al: Combined evaluation of Rad51 and ERCC1 expressions for sensitivity to platinum agents in non-small cell lung cancer. *Int J Cancer* 121:895-900, 2007
20. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 85:365-376, 1993
21. Pierceall WE, Olausson KA, Rousseau V, et al: Cisplatin benefit is predicted by immunohistochemical analysis of DNA repair proteins in squamous cell carcinoma but not adenocarcinoma: Theranostic modeling by NSCLC constituent histological subtypes. *Ann Oncol* 23:2245-2252, 2012
22. Lee SM, Rudd R, Woll PJ, et al: Randomized double-blind placebo-controlled trial of thalidomide in combination with gemcitabine and carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol* 27:5248-5254, 2009
23. Scagliotti GV, Parikh P, von Pawel J, et al: Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 26:3543-3551, 2008
24. Cobo M, Isla D, Massuti B, et al: Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression: A phase III trial in non-small-cell lung cancer. *J Clin Oncol* 25:2747-2754, 2007
25. Mazzoni F, Cecere FL, Meoni G, et al: Phase II trial of customized first line chemotherapy according to ERCC1 and RRM1 SNPs in patients with advanced non-small-cell lung cancer. *Lung Cancer* 82:288-293, 2013
26. Heo SJ, Jung I, Lee CK, et al: A randomized phase II trial of ERCC1 and RRM1 mRNA expression-based chemotherapy versus docetaxel/carboplatin in advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* 77:539-548, 2016
27. Sargent DJ, Conley BA, Allegra C, et al: Clinical trial designs for predictive marker validation in cancer treatment trials. *J Clin Oncol* 23:2020-2027, 2005
28. Niedernhofer LJ, Bhagwat N, Wood RD: ERCC1 and non-small-cell lung cancer. *N Engl J Med* 356:2538-2540, author reply 2540-2541, 2007
29. Olausson KA, Fouret P, Kroemer G: ERCC1-specific immunostaining in non-small-cell lung cancer. *N Engl J Med* 357:1559-1561, 2007
30. Olausson KA, Soria JC: Validation of ERCC1-XPF immunodetection—Letter. *Cancer Res* 70:3851-3852, author reply 3852, 2010

31. Ma D, Baruch D, Shu Y, et al: Using protein microarray technology to screen anti-ERCC1 monoclonal antibodies for specificity and applications in pathology. *BMC Biotechnol* 12:88, 2012
32. Friboulet L, Postel-Vinay S, Sourisseau T, et al: ERCC1 function in nuclear excision and interstrand crosslink repair pathways is mediated exclusively by the ERCC1-202 isoform. *Cell Cycle* 12:3298-3306, 2013
33. Malottki K, Popat S, Deeks JJ, et al: Problems of variable biomarker evaluation in stratified medicine research—A case study of ERCC1 in non-small-cell lung cancer. *Lung Cancer* 92:1-7, 2016
34. Tsodikov OV, Enzlin JH, Schärer OD, et al: Crystal structure and DNA binding functions of ERCC1, a subunit of the DNA structure-specific endonuclease XPF-ERCC1. *Proc Natl Acad Sci USA* 102:11236-11241, 2005
35. Biggerstaff M, Szymkowski DE, Wood RD: Co-correction of the ERCC1, ERCC4 and xeroderma pigmentosum group F DNA repair defects in vitro. *EMBO J* 12:3685-3692, 1993
36. Vaezi A, Wang X, Buch S, et al: XPF expression correlates with clinical outcome in squamous cell carcinoma of the head and neck. *Clin Cancer Res* 17: 5513-5522, 2011
37. Arora S, Kothandapani A, Tillison K, et al: Downregulation of XPF-ERCC1 enhances cisplatin efficacy in cancer cells. *DNA Repair (Amst)* 9: 745-753, 2010
38. Liu C, Zhou S, Begum S, et al: Increased expression and activity of repair genes TDP1 and XPF in non-small cell lung cancer. *Lung Cancer* 55:303-311, 2007

Affiliations

Siow Ming Lee, Mary Falzon, Martin Forster, Arrigo Capitanio, Robin Rudd, Natasha Iles, Yenting Ngai, Michael Gandy, Rachel Lillywhite, and Allan Hackshaw, University College London, University College London Hospitals; **James Spicer**, Guy's and St Thomas's NHS Foundation Trust; **Conrad Lewanski**, Charing Cross Hospital, London; **Fiona Blackhall**, The Christie NHS Foundation Trust, Manchester; **Marianne Nicolson**, Aberdeen Royal Infirmary, Aberdeen; **Abhiro Chaudhuri**, Lincoln County Hospital, Lincoln; **Gary Middleton**, University of Birmingham, Birmingham; **Samreen Ahmed**, Leicester Royal Infirmary, Leicester; **Jonathan Hicks**, New Victoria Hospital, Kingston Upon Thames; **Barbara Crosse**, Calderdale and Huddersfield NHS Foundation Trust, Huddersfield; **Mark Napier**, North Devon District Hospital, Barnstaple; **Julian M. Singer**, Princess Alexandra Hospital NHS Foundation Trust, Harlow; **David Ferry**, New Cross Hospital, Wolverhampton; and **Sally-Ann Rolls**, Withybush General Hospital, Haverfordwest, United Kingdom.

Support

Supported by Eli Lilly and sponsored by University College London (endorsed by Cancer Research UK, C1438/A9947, with S.M.L. supported by the University College London/University College London Hospitals Biomedical Research Centre). Eli Lilly also provided free pemetrexed. Aprepitant (Emend) was provided by Merck Sharpe & Dohme. Eli Lilly and Merck Sharpe & Dohme had no role in the study design, data collection, data analysis, data interpretation, or report writing, although they saw a draft of the paper.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/iffc.

Siow Ming Lee

Consulting or Advisory Role: Roche, Bristol-Myers Squibb

Mary Falzon

No relationship to disclose

Fiona Blackhall

Honoraria: Medivation, AstraZeneca

Consulting or Advisory Role: Medivation, AstraZeneca

Speakers' Bureau: Pfizer

Research Funding: Pfizer (Inst), AstraZeneca (Inst), Boehringer Ingelheim (Inst), Novartis (Inst)

James Spicer

Consulting or Advisory Role: Merck Sharp & Dohme, Roche, AstraZeneca, Boehringer Ingelheim

Travel, Accommodations, Expenses: Merck Sharp & Dohme

Marianne Nicolson

Honoraria: Eli Lilly

Consulting or Advisory Role: Eli Lilly

Speakers' Bureau: Eli Lilly

Research Funding: Eli Lilly

Travel, Accommodations, Expenses: Eli Lilly

Abhro Chaudhuri

No relationship to disclose

Gary Middleton

Honoraria: Bristol-Myers Squibb, Pierre Fabre, Merck Serono

Consulting or Advisory Role: Eli Lilly, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, GemVax & KAEL, Merck Serono

Research Funding: GemVax & KAEL, Merck Sharp & Dohme

Travel, Accommodations, Expenses: Merck Sharp & Dohme

Samreen Ahmed

Consulting or Advisory Role: Novartis, Pfizer, Genentech, Bristol-Myers Squibb, Eisai

Travel, Accommodations, Expenses: Merck, Bristol-Myers Squibb

Jonathan Hicks

Stock or Other Ownership: Roche

Consulting or Advisory Role: AstraZeneca, Boehringer Ingelheim

Travel, Accommodations, Expenses: Eli Lilly

Barbara Crosse

No relationship to disclose

Mark Napier

No relationship to disclose

Julian M. Singer

No relationship to disclose

David Ferry

Employment: Eli Lilly

Stock or Other Ownership: Eli Lilly

Conrad Lewanski

Honoraria: Eli Lilly, Merck, Roche

Consulting or Advisory Role: Eli Lilly

Martin Forster

Honoraria: Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca

Consulting or Advisory Role: Merck Sharp & Dohme Oncology, Bristol-Myers Squibb, Pfizer, Novartis, AstraZeneca, Merck Serono

Research Funding: Boehringer Ingelheim (Inst), AstraZeneca (Inst)

Travel, Accommodations, Expenses: Merck Sharp & Dohme Oncology, Merck Serono, Pfizer, Boehringer Ingelheim

Sally-Ann Rolls

No relationship to disclose

Arrigo Capitanio

No relationship to disclose

Robin Rudd

No relationship to disclose

Natasha Iles

No relationship to disclose

Yenting Ngai

No relationship to disclose

Michael Gandy

Employment: The Doctors Laboratory

Rachel Lillywhite

No relationship to disclose

Allan Hackshaw

Stock or Other Ownership: Thermo Fisher Scientific, Illumina

Honoraria: Roche, Boehringer Ingelheim

Consulting or Advisory Role: Roche

Research Funding: Eli Lilly (Inst), Boehringer Ingelheim, AstraZeneca, Roche

Acknowledgment

We gratefully acknowledge the expertise and support of the Independent Data Monitoring Committee: Michael Peak (Chair), Daniel Hochhauser, and Roger A'Hern. We also thank Laura Fulford, who worked on the pilot study for ERCC1 testing, and all the patients who kindly agreed to participate in the trial. Trial Management Group members: Siow Ming Lee (Chair), Mary Falzon, Fiona Blackhall, James Spicer, Marianne Nicolson, Gary Middleton, Sally-Ann Rolls, Robin Rudd, Allan Hacksaw.

Appendix

Clinicians who recruited patients were as follows:

Aberdeen Royal Infirmary: Marianne Nicolson, MD
 Addenbrookes Hospital: Susan Harden, MD
 Aintree University Hospital: John Littler, MD
 Barnet & Chase Farm Hospitals NHS Trust: Girija Anand, MD
 Beatson West of Scotland Cancer Centre: David Dunlop, MD
 Birmingham Heartlands Hospital: Joyce Thompson, MD
 Blackpool Victoria Hospital - Muthiah Sivaramalingham, MD
 Bristol Haematology and Oncology Centre: Adam Dangoor, MD
 Calderdale and Huddersfield NHS Foundation Trust: Barbara Crosse, MD
 Charing Cross Hospital: Conrad Lewanski, MD
 Chelsea & Westminster Hospital: Mark Bower, MD
 Clatterbridge Centre for Oncology: Aisha Tufail, MD
 Conquest Hospital: Timothy Sevitt, MD
 Darent Valley Hospital: Riyaz Shah, MD
 Derriford Hospital: Dennis Yiannakis, MD
 Dorset Cancer Centre (Poole Hospital) : Mike Bayne, MD
 Dorset County Hospital: Mike Bayne, MD
 Essex County Hospital: Dakshinamoorthy Muthukumar, MD
 Forth Valley Royal Hospital: Nicola Steele, MD
 Glan Clwyd Hospital: Angel Garcia Alonso, MD
 Gloucestershire Hospitals NHS Foundation Trust: David Farrugia, MD
 Guys Hospital: James Spicer, MD
 Ipswich Hospital: Jamie Morgan, MD
 Isle of Wight NHS Trust: Judith Cave, MD
 James Paget University Hospitals NHS Foundation Trust: Ulrike Dervedde, MD
 Kent & Canterbury Hospital: Russell Burcombe, MD
 Lanarkshire NHS Trust (Hairmyres, Monklands and Wishaw Hospital) : Clinton Ali, MD
 Leicester Royal Infirmary: Samreen Ahmed, MD
 Lewisham Hospital: Eleni Karapanagiotou, MD
 Lincoln County Hospital: Abhiro Chaudhuri, MD
 Lister Hospital: Andreas Polychronis, MD
 Macclesfield District General Hospital: Hamid Sheikh, MD
 Maidstone Hospital: Riyaz Shah, MD
 Mount Vernon Hospital: Andreas Polychronis, MD
 New Cross Hospital: Simon Grumett, MD
 Norfolk and Norwich Hospital: Thankamma Ajithkumar, MD
 North Devon District Hospital: Mark Napier, MD
 North Middlesex University Hospital NHS Trust: David Chao, MD
 Nottingham University Hospitals NHS Trust: Vanessa Potter, MD
 Peterborough City Hospital: Kate Fife, MD

Pilgrim Hospital: Abhiro Chaudhuri, MD
 Queen Alexandra Hospital, Portsmouth: Suhail Baluch, MD
 Queen Elizabeth Hospital, Gateshead: Fiona McDonald, MD
 Queen Elizabeth the Queen Mother Hospital, Margate: Russell Burcombe, MD
 Queen's Hospital, Burton Upon Trent: Anula Chetiyawardana, MD
 Raigmore Hospital - Carol Macgregor, MD
 Royal Berkshire Hospital - Joss W. Adams, MD
 Royal Derby Hospital: Manjusha Keni, MD
 Royal Devon & Exeter NHS Foundation Trust: Elizabeth Toy, MD
 Royal Gwent Hospital: Alison Brewster, MD
 Royal Hampshire County Hospital: Luke Nolan, MD
 Royal Preston Hospital: Geraldine Skailes, MD
 Royal Shrewsbury Hospital: Anirban Chatterjee, MD
 Royal Surrey County Hospital: Gary Middleton, MD
 Royal Sussex County Hospital: Sankha Surva Mitra, MD
 Royal United Hospitals, Bath: Emma De Winton, MD
 Russells Hall Hospital: Simon Grumett, MD
 Salisbury NHS Foundation Trust: Adityanarayan Bhatnagar, MD
 Sandwell and West Birmingham Hospitals NHS Trust: Sarah Williams, MD
 Scunthorpe General Hospital: Nabil El-Mahdawi, MD
 Singleton Hospital: Kath Rowley, MD
 Southampton General Hospital: Christian Ottensmeier, MD
 Southport and Formby District General Hospital: Pooja Jain, MD
 St Bartholomew's Hospital: Paula Wells, MD
 St Georges Hospital, Tooting: Tim Benepal, MD
 St Mary's Hospital, London: Conrad Lewanski, MD
 Taunton and Somerset NHS Foundation Trust: Petra Jankowska, MD
 The Christie NHS Foundation Trust: Fiona Blackhall, MD
 The New Victoria Hospital: Jonathan Hicks, MD
 The Princess Alexandra Hospital: Julian Singer, MD
 The Whittington Hospital: Pauline Leonard, MD
 Torbay Hospital: Nicole Dorey, MD
 University College Hospital: Siow Ming Lee, MD, PhD
 University Hospital of South Manchester: Yvonne Summers, MD
 University Hospital, Coventry - Mark Hocking, MD
 University Hospitals of Morecambe Bay NHS Foundation Trust: David Fyfe, MD
 Warrington and Halton Hospitals NHS Foundation Trust: Aisha Tufail, MD
 West Suffolk Hospital: Yvonne Rimmer, MD
 Whiston Hospital: Ernest Marshall, MD
 William Harvey Hospital, Ashford: Russell Burcombe, MD
 Withybush General Hospital: Vallipuram Vigneswaran, MD
 Worcestershire Royal Hospital: David Farrugia, MD
 Wrexham Maelor Hospital: Angel Garcia Alonso, MD
 Yeovil District Hospital NHS Foundation Trust: Matthew Sephton, MD
 Ysbyty Gwynedd Hospital: Nick Stuart

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 stratification 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 stratification 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 $HR \geq 1.20$ 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 patients) applies to the null hypothesis of hazard ratio (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 0.34 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

XPF	ERCC1	
	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).

Randomized Trial of Prospective ERCC1 in Advanced Lung Cancer

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

Drug Dose According to Cycle	Squamous Histology		Nonsquamous Histology	
	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/m².

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.

Randomized Trial of Prospective ERCC1 in Advanced Lung Cancer

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	<i>P</i>	Interaction <i>P</i> *
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)

ERCC1 Status	Nonsquamous			Squamous			Both Combined		
	Negative (n = 211)	Positive (n = 253)	<i>P</i>	Negative (n = 40)	Positive (n = 133)	<i>P</i>	Negative (n = 251)	Positive (n = 386)	<i>P</i>
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.

Randomized Trial of Prospective ERCC1 in Advanced Lung Cancer

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

XPF Status	Nonsquamous			Squamous			Both Combined		
	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.

Randomized Trial of Prospective ERCC1 in Advanced Lung Cancer

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.

Randomized Trial of Prospective ERCC1 in Advanced Lung Cancer

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.