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## DNA Repair by ERCC1 in Non–Small-Cell Lung Cancer and Cisplatin-Based Adjuvant Chemotherapy

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### ABSTRACT

#### BACKGROUND

Adjuvant cisplatin-based chemotherapy improves survival among patients with completely resected non–small-cell lung cancer, but there is no validated clinical or biologic predictor of the benefit of chemotherapy.

#### METHODS

We used immunohistochemical analysis to determine the expression of the excision repair cross-complementation group 1 (ERCC1) protein in operative specimens of non–small-cell lung cancer. The patients had been enrolled in the International Adjuvant Lung Cancer Trial, thereby allowing a comparison of the effect of adjuvant cisplatin-based chemotherapy on survival, according to ERCC1 expression. Overall survival was analyzed with a Cox model adjusted for clinical and pathological factors.

#### RESULTS

Among 761 tumors, ERCC1 expression was positive in 335 (44%) and negative in 426 (56%). A benefit from cisplatin-based adjuvant chemotherapy was associated with the absence of ERCC1 (test for interaction,  $P=0.009$ ). Adjuvant chemotherapy, as compared with observation, significantly prolonged survival among patients with ERCC1-negative tumors (adjusted hazard ratio for death, 0.65; 95% confidence interval [CI], 0.50 to 0.86;  $P=0.002$ ) but not among patients with ERCC1-positive tumors (adjusted hazard ratio for death, 1.14; 95% CI, 0.84 to 1.55;  $P=0.40$ ). Among patients who did not receive adjuvant chemotherapy, those with ERCC1-positive tumors survived longer than those with ERCC1-negative tumors (adjusted hazard ratio for death, 0.66; 95% CI, 0.49 to 0.90;  $P=0.009$ ).

#### CONCLUSIONS

Patients with completely resected non–small-cell lung cancer and ERCC1-negative tumors appear to benefit from adjuvant cisplatin-based chemotherapy, whereas patients with ERCC1-positive tumors do not.

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LUNG CANCER IS A LEADING CAUSE OF death from cancer in most industrialized countries.<sup>1</sup> Despite undergoing complete resection of non–small-cell lung cancer, 33% of patients with pathological stage IA die within 5 years, as do 77% of those with pathological stage IIIA.<sup>2</sup> Clinical trials have tested the ability of adjuvant chemotherapy to improve survival after complete resection of non–small-cell lung cancer. The International Adjuvant Lung Cancer Trial (IALT) demonstrated an absolute benefit of 4.1% in 5-year overall survival among 1867 patients who were treated with adjuvant cisplatin-based chemotherapy.<sup>3</sup> Several other randomized studies have confirmed the benefit of postoperative platinum-based therapy in non–small-cell lung cancer.<sup>4–7</sup> However, adjuvant chemotherapy has only a modest effect in prolonging survival, with an absolute improvement in 5-year overall survival ranging from 4 to 15%, whereas such treatment is associated with serious adverse effects.<sup>4–7</sup> The main objective of our study, which was termed the IALT Biology (IALT Bio) study, was to identify factors that can predict a benefit from adjuvant cisplatin-based chemotherapy.

DNA repair mechanisms are important in the resistance to cisplatin. The destruction of cells by cisplatin requires the binding of the drug to DNA and the creation of platinum–DNA adducts. Some of these adducts establish covalent cross-linking between DNA strands, thereby inhibiting DNA replication. Nucleotide excision repair has a central role in DNA repair and is associated with resistance to platinum-based chemotherapy.<sup>8</sup> The excision repair cross-complementation group 1 (ERCC1) enzyme plays a rate-limiting role in the nucleotide excision repair pathway that recognizes and removes cisplatin-induced DNA adducts.<sup>9–11</sup> ERCC1 is also important in the repair of inter-strand cross-links in DNA and in recombination processes.<sup>12–14</sup> In vitro studies have linked platinum resistance to the expression of *ERCC1* messenger RNA (mRNA) in cell lines involved in ovarian, cervical, testicular, bladder, and non–small-cell lung cancers.<sup>15</sup> The relation between the expression of *ERCC1* mRNA and resistance to platinum compounds has been corroborated by small, retrospective clinical studies in patients with advanced gastric, ovarian, colorectal, esophageal, or non–small-cell lung cancer.<sup>15–25</sup> These data led us to hypothesize that expression of ERCC1 by

the tumor could predict a survival benefit from cisplatin-based adjuvant chemotherapy in non–small-cell lung cancer.

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## METHODS

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### PATIENTS AND STUDY DESIGN

All patients had participated in the IALT, which compared adjuvant cisplatin-based chemotherapy with observation among patients with non–small-cell lung cancer. Inclusion criteria and the results of the IALT have been reported previously.<sup>3</sup> In brief, we randomly assigned 1867 patients with completely resected non–small-cell lung cancer in stages I through III to receive either cisplatin (at a total dose of 300 to 400 mg per square meter of body-surface area) plus an additional drug (etoposide or a vinca alkaloid) or to be observed only (the control group). The median follow-up was 56 months.

The IALT Bio study was subsequently designed by a steering committee to examine whether tumor markers assessed by immunohistochemical analysis could be used to predict a survival benefit from chemotherapy. The study was conducted according to a detailed protocol and monitored by the steering committee. The protocol stressed the importance of collecting all samples within the participating centers, required a large number of tumor samples to ensure adequate power for prognostic and predictive analyses, and imposed a plan for statistical analysis. To study whether the effect of chemotherapy varied between patients with a positive marker and an equal number of patients with a negative marker, the estimated power to detect a 20% difference in the survival benefit at 5 years, given the enrollment of 800 patients, was 66% (with a two-sided alpha level of 0.01). Such a design has the ability to address the predictive value of 25 markers.

Paraffin-embedded tumor samples were collected from patients at centers that had recruited more than 10 patients. Twenty-eight centers in 14 countries contributed specimens (see the Appendix). Approval was obtained from the local institutional review boards, according to the legal regulations in each participating country. All tumors were reviewed centrally at the Centre Hospitalier Universitaire Albert Michallon, according to the histopathological classification system ad-

opted by the World Health Organization (WHO) in 2004.<sup>26</sup> Immunostaining was performed and evaluated at Institut Gustave Roussy. Representatives of Eli Lilly had access to an early draft of the manuscript for information but otherwise had no input into the manuscript. Members of the steering committee were responsible for the decision to publish the manuscript.

#### IMMUNOSTAINING FOR ERCC1

We used a standard protocol for the immunostaining of the samples. In brief, for epitope retrieval, specimens were exposed to 10 mM citrate buffer (pH 6.0) and heated for 30 minutes in a water bath. Tumor sections were incubated for 60 minutes with a monoclonal antibody specific against the full-length human ERCC1 protein at a 1:300 dilution (mouse, clone 8F1, Neomarkers).<sup>27-30</sup> Antibody binding was detected by means of an ABC kit with NovaRED as the substrate (Vectastain Elite, Vector Laboratories) and Mayers hematoxylin as the counterstain. Sections of normal tonsil tissues were included as external positive controls, and stromal cells surrounding the tumor area served as internal positive controls.

#### MICROSCOPICAL ANALYSIS

Two investigators who were unaware of clinical data independently evaluated ERCC1 staining under a light microscope at a magnification of 400 $\times$ . They recorded whether tumor or stromal cells expressed ERCC1. The staining intensity was graded on a scale of 0 to 3 (with a higher number indicating a higher intensity and with endothelial cells in tonsil control tissue used as a reference and assigned an intensity of 2). Discordant cases were reviewed. Cases without valid internal controls were excluded. Five images of representative areas were acquired at a magnification of 400 $\times$  for each specimen. A total of 500 to 1500 positive or negative tumor nuclei per specimen were manually counted on a computer screen with the use of ImageJ freeware from the National Institutes of Health (<http://rsb.info.nih.gov/ij>). The percentage of positive tumor nuclei was calculated for each specimen, and a proportion score was assigned (0 if 0%, 0.1 if 1% to 9%, 0.5 if 10% to 49%, and 1.0 if 50% or more), as previously described.<sup>31,32</sup> This proportion score was multiplied by the staining intensity of nuclei to obtain a final semiquantitative H score. The median value

of all the H scores was a priori chosen as the cutoff point for separating ERCC1-positive tumors from ERCC1-negative tumors.

#### STATISTICAL ANALYSIS

As in the IALT study, the primary end point was overall survival after randomization. Disease-free survival was analyzed as a secondary end point. To identify any selection bias within the participating centers, the baseline characteristics of the two groups of patients (with or without blocks of tumor tissue) were compared with the use of chi-square tests stratified according to center, and the overall rates of survival were compared with the use of a Cox model. Baseline data according to ERCC1 status were compared in univariate analyses with the use of chi-square tests and in a multivariate logistic model including all variables with P values of less than 0.05.

Survival rates were estimated with the use of the Kaplan–Meier method. The prognostic values of the ERCC1 status and chemotherapy were studied with the use of a Cox model, which was stratified according to center and adjusted for significant prognostic factors for survival (sex and the stage of disease) and factors associated with ERCC1 (age, revised histopathological type, and the presence or absence of pleural invasion). The predictive value of ERCC1 was studied by testing the interaction between the ERCC1 status and the attributed treatment (chemotherapy or no chemotherapy) in the same Cox model. We performed sensitivity analyses using Cox models with a variety of adjustment factors, and the results were similar. Therefore, we report only results that corresponded to the model we previously described. All reported P values are two-sided. P values of less than 0.01 were a priori considered to indicate statistical significance to limit the risk of false positive results. All analyses were performed with the use of SAS software, version 8.2 (SAS Institute).

## RESULTS

#### CHARACTERISTICS OF THE PATIENTS

As a group, the 28 centers that participated in our study were able to provide one tumor block for 867 of the 1045 patients (83%) who had enrolled in the original IALT study. These 867 patients and the remaining 178 had similar base-

Table 1. Characteristics of the Patients.\*

Characteristic	All Patients (N=761)	Patients with ERCC1-Positive Tumors (N=335) <i>number (percent)</i>	Patients with ERCC1-Negative Tumors (N=426)	P Value†‡
Age				0.002‡
<55 yr	231 (30)	80 (24)	151 (35)	
55–64 yr	330 (43)	161 (48)	169 (40)	
>64 yr	200 (26)	94 (28)	106 (25)	
Sex				<0.001
Male	621 (82)	292 (87)	329 (77)	
Female	140 (18)	43 (13)	97 (23)	
Pathological TNM stage				0.97
Stage I	267 (35)	119 (36)	148 (35)	
Stage II	175 (23)	76 (23)	99 (23)	
Stage III	319 (42)	140 (42)	179 (42)	
Tumor				0.10
T1	118 (16)	60 (18)	58 (14)	
T2	452 (59)	188 (56)	264 (62)	
T3	181 (24)	85 (25)	96 (23)	
T4	10 (1)	2 (1)	8 (2)	
Histologic type				<0.001
Squamous-cell carcinoma	426 (56)	236 (70)	190 (45)	
Adenocarcinoma	242 (32)	71 (21)	171 (40)	
Other	93 (12)	28 (8)	65 (15)	
Performance-status score§				0.06
0	426 (56)	188 (56)	238 (56)	
1	276 (36)	113 (34)	163 (38)	
2	59 (8)	34 (10)	25 (6)	
Pleural invasion				0.007
Yes	61 (8)	37 (11)	24 (6)	
No	700 (92)	298 (89)	402 (94)	
Vascular invasion				0.04
Yes	222 (29)	85 (25)	137 (32)	
No	539 (71)	250 (75)	289 (68)	
Surgery				0.35
Pneumonectomy	306 (40)	141 (42)	165 (39)	
Lobectomy or segmentectomy	455 (60)	194 (58)	261 (61)	
Radiotherapy				0.35
Yes	199 (26)	82 (24)	117 (27)	
No	562 (74)	253 (76)	309 (73)	
Planned dose of cisplatin				0.67
80 mg/m <sup>2</sup> per cycle	139 (18)	58 (17)	81 (19)	
100 mg/m <sup>2</sup> per cycle	544 (71)	245 (73)	299 (70)	
120 mg/m <sup>2</sup> per cycle	78 (10)	32 (10)	46 (11)	

\* TNM denotes tumor–node–metastasis. Percentages may not total 100 because of rounding.

† P values were calculated by the chi-square test and univariate analysis.

‡ P=0.007 for trend.

§ World Health Organization scores for performance status range from 0 to 2, with a score of 0 indicating no symptoms, 1 mild symptoms, and 2 moderate symptoms.

line characteristics and overall rates of survival. The amount and quality of 824 of the 867 blocks were adequate for serial sectioning. Among these blocks, 783 contained tumor material corresponding to non-small-cell lung cancer and were included in our study. After exclusion of blocks without valid positive internal controls, ERCC1 expression was evaluated in a total of 761 patients. All further statistical analyses were performed on this population.

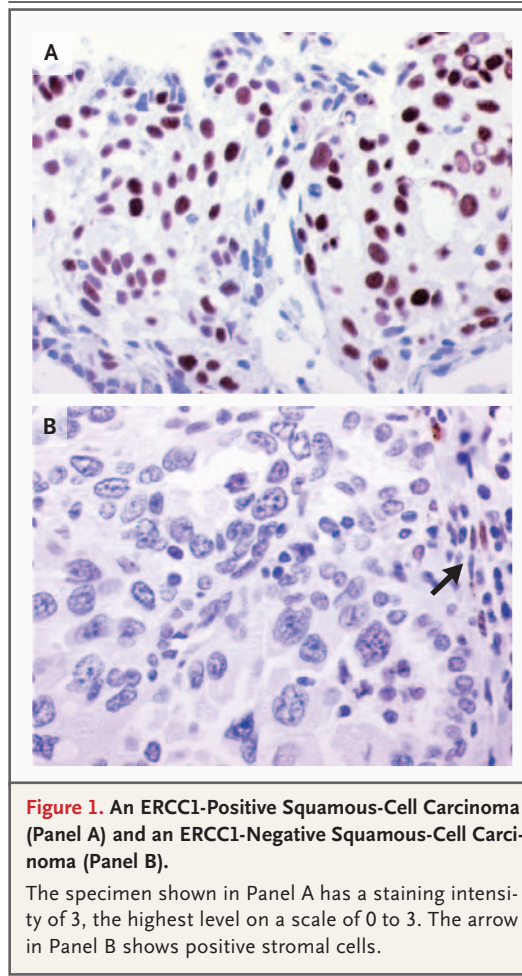
Table 1 summarizes the characteristics of the study population. A total of 426 patients had squamous-cell carcinomas (56%), 242 had adenocarcinomas (32%), and 93 had another histologic type (12%). The median age of the patients was 58 years (range, 27 to 77), and 82% were men. Of the 761 patients, 389 (51%) received adjuvant cisplatin-based chemotherapy and 372 (49%) were in the control group.

#### IMMUNOHISTOCHEMICAL ASSESSMENT OF ERCC1 EXPRESSION

Figure 1 shows that ERCC1 was localized to the nucleus. The median percentage of cells with nuclei that stained with the monoclonal antibody was 24% (range, 0 to 100), whereas the median value of H scores was 1.0. Tumors with an H score exceeding 1.0 (i.e., tumors with a staining intensity score of 2 and with 50% or more positive nuclei or with a staining intensity score of 3 and 10% or more positive nuclei) were deemed to be ERCC1-positive. Of the 761 tumors, 335 (44%) were ERCC1-positive. Table 1 compares the demographic characteristics, tumor characteristics, and treatments according to ERCC1 expression in a univariate analysis. A multivariate logistic model showed that the expression of ERCC1 was significantly correlated with age ( $P=0.03$ ; less common in patients younger than 55 years of age than in patients 55 to 64 years of age), histologic type ( $P<0.001$ ; less common in adenocarcinomas than in squamous-cell carcinomas), and pleural invasion ( $P=0.01$ ; less common in the absence than in the presence of pleural invasion).

#### SURVIVAL AND ERCC1 EXPRESSION

The 5-year overall survival rate was 43% (95% confidence interval [CI], 39% to 47%) for the total study population (Table 2). In the Cox model, adjusted for the multivariate predictors of survival, ERCC1 expression, as compared with the absence of expression of ERCC1, had no prognos-



**Figure 1. An ERCC1-Positive Squamous-Cell Carcinoma (Panel A) and an ERCC1-Negative Squamous-Cell Carcinoma (Panel B).**

The specimen shown in Panel A has a staining intensity of 3, the highest level on a scale of 0 to 3. The arrow in Panel B shows positive stromal cells.

tic value for the entire study population (adjusted hazard ratio for death, 0.88; 95% CI, 0.71 to 1.10;  $P=0.26$ ).

#### SURVIVAL AND ADJUVANT CHEMOTHERAPY

The 5-year overall survival rates were 44% in the chemotherapy group (95% CI, 39% to 50%) and 42% in the control group (95% CI, 37% to 48%) (Table 2). In the Cox model, the adjusted hazard ratio for death was 0.84 (95% CI, 0.68 to 1.03;  $P=0.09$ ) in favor of chemotherapy (Table 2 and Fig. 2A).

#### SURVIVAL, ERCC1 EXPRESSION, AND CHEMOTHERAPY

Among patients with ERCC1-negative tumors, overall survival was significantly longer in the chemotherapy group than in the control group (adjusted hazard ratio for death, 0.65; 95% CI, 0.50 to 0.86;  $P=0.002$ ) (Table 2). The 5-year overall survival rates among patients with ERCC1-negative

**Table 2.** Overall Survival According to Attributed Treatment and ERCC1 Status.

Group	All Patients	Chemotherapy Group	Control Group	Hazard Ratio for Death (95% CI)*	P Value
<b>Patients with ERCC1-negative tumors</b>				0.65 (0.50–0.86)	0.002
Deaths — no./total no. of patients	218/426	105/224	113/202		
Rate of survival at 5 yr — % (95% CI)	44 (38–49)	47 (40–55)	39 (32–47)		
Median survival — mo	48	56	42		
<b>Patients with ERCC1-positive tumors</b>				1.14 (0.84–1.55)	0.40
Deaths — no./total no. of patients	172/335	92/165	80/170		
Rate of survival at 5 yr — % (95% CI)	43 (37–49)	40 (32–49)	46 (37–55)		
Median survival — mo	52	50	55		
<b>All patients</b>				0.84 (0.68–1.03)	
Deaths — no./total no. of patients	390/761	197/389	193/372		
Rate of survival at 5 yr — % (95% CI)	43 (39–47)	44 (39–50)	42 (37–48)		
Median survival — mo	50	53	48		
<b>Hazard ratio for death (95% CI)†</b>	0.88 (0.71–1.10)	1.16 (0.86–1.56)	0.66 (0.49–0.90)	—	—
<b>P value</b>	0.26	0.34	0.009	—	0.009‡

\* Hazard ratios are for the comparison of the chemotherapy group with the control group. All hazard ratios were adjusted for sex, age, tumor stage, histologic type, and the presence or absence of pleural invasion, stratified according to center.

† Hazard ratios are for the comparison of patients with ERCC1-positive tumors with those with ERCC1-negative tumors.

‡ The P value is for the interaction between ERCC1 expression and treatment.

tumors were 47% (95% CI, 40% to 55%) in the chemotherapy group and 39% (95% CI, 32% to 47%) in the control group. Median overall survival was 14 months longer in the adjuvant chemotherapy group (56 months) than in the control group (42 months) (Fig. 2B). Disease-free survival among patients with ERCC1-negative tumors was also longer in the chemotherapy group than in the control group (adjusted hazard ratio for recurrence or death, 0.65; 95% CI, 0.50 to 0.85;  $P=0.001$ ) (Fig. 2C).

Among patients with ERCC1-positive tumors, there was no significant difference in survival between the adjuvant chemotherapy group and the control group (adjusted hazard ratio for death, 1.14; 95% CI, 0.84 to 1.55;  $P=0.40$ ) (Table 2 and Fig. 2D).

Overall, the interaction terms between ERCC1 expression and treatment were significant for overall survival ( $P=0.009$ ) and for disease-free survival ( $P=0.008$ ).

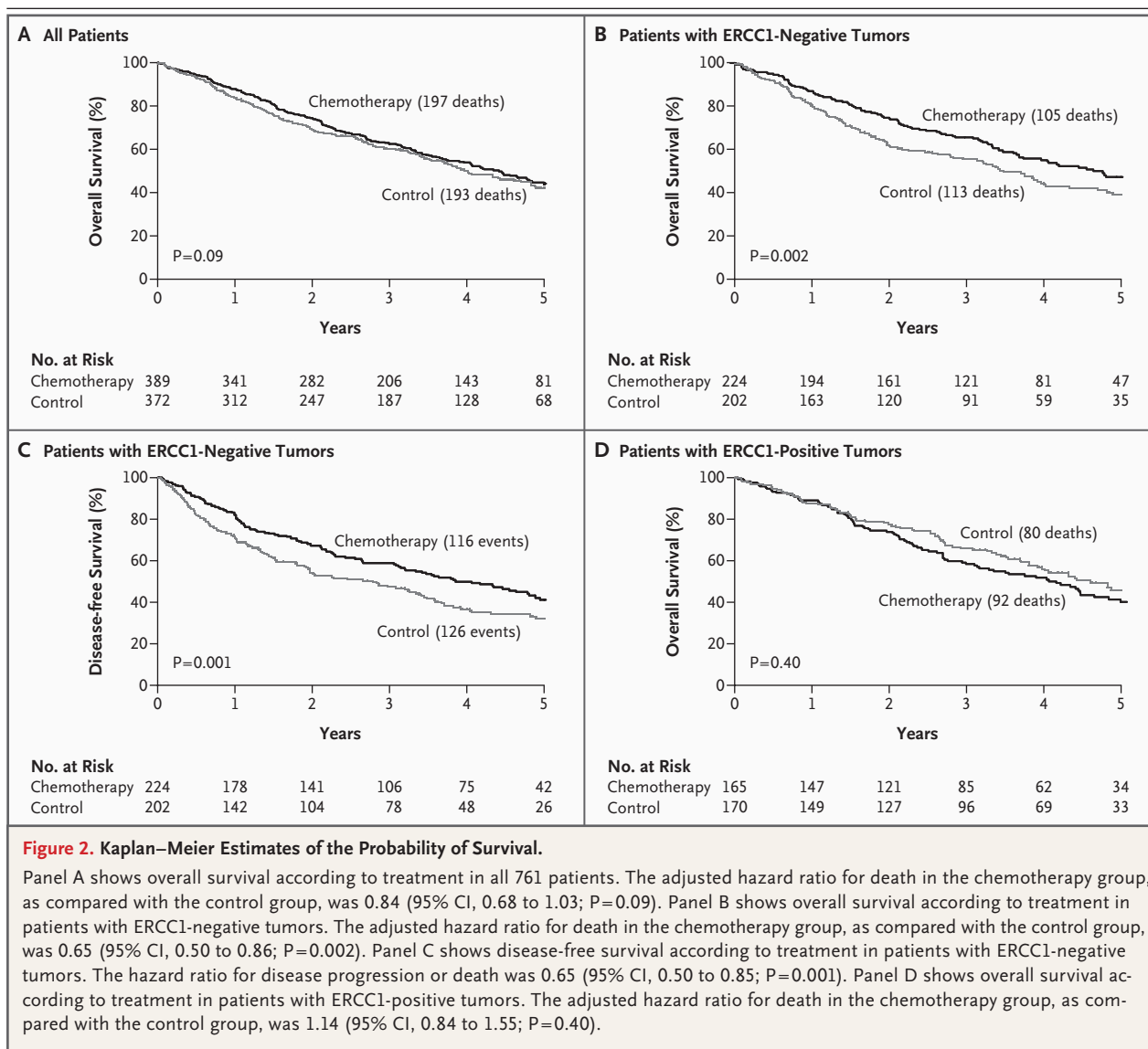
#### SURVIVAL AND ERCC1 EXPRESSION IN THE CONTROL GROUP

When the analysis focused exclusively on patients in the control group, the 5-year overall survival

rate was significantly higher among patients with ERCC1-positive tumors (46%; 95% CI, 37% to 55%) than among patients with ERCC1-negative tumors (39%; 95% CI, 32% to 47%), with an adjusted hazard ratio of 0.66 (95% CI, 0.49 to 0.90;  $P=0.009$ ) (Table 2).

#### DISCUSSION

The IALT reported a benefit from adjuvant cisplatin-based chemotherapy for patients with completely resected non-small-cell lung cancer (hazard ratio for death, 0.86 in 1867 patients), but no predictor of benefit from chemotherapy was identified.<sup>3</sup> One of the important findings in our study is that a low level of expression of ERCC1 by tumor cells was associated with longer survival after adjuvant treatment with cisplatin-based chemotherapy. In the group of patients with ERCC1-negative tumors who received such treatment, the risk of death was decreased by 35% (hazard ratio, 0.65). By contrast, the risk of death was not decreased among patients with ERCC1-positive tumors who received cisplatin-based adjuvant chemotherapy (hazard ratio, 1.14). Although it was not possible to collect tumor samples from all



patients in centers that participated in our study, the baseline characteristics and survival of the 83% who were included in our study did not differ significantly from those of the 17% who were not included. Furthermore, our findings are strengthened by an adjustment for standard prognostic variables, the requirement of a high level of significance (with a two-sided alpha level of 0.01), and the definition of an a priori cutoff point for an ERCC1-positive tumor.<sup>33</sup>

ERCC1 is the limiting factor in nucleotide excision repair, which removes platinum–DNA adducts. ERCC1 may also be involved in the repair of DNA double-strand breaks, especially those induced by interstrand cross-links.<sup>12</sup> For this rea-

son, the mechanism by which ERCC1 contributes to cisplatin resistance probably involves more than nucleotide excision repair. It is possible that the presence of ERCC1 reflects an inherent biologic characteristic of the tumor. However, as suggested in previous studies,<sup>34</sup> in the control group, patients who had ERCC1-negative tumors had a shorter overall survival than did patients with ERCC1-positive tumors (Table 2). This finding is in contrast to the results observed in patients who received adjuvant chemotherapy and favors the interpretation that the presence or absence of ERCC1 is a determinant of the sensitivity of non-small-cell tumor cells to platinum. Other factors may also contribute to the sensitivity to plati-

num (e.g., tolerance to DNA damage), and the clinical relevance of these factors may depend on the dose of cisplatin that is administered, the combination of cisplatin with other drugs, subsequent radiotherapy, and other aspects of treatment. Consequently, we cannot make a general statement concerning the influence of ERCC1 expression on the outcome of other treatment regimens for non-small-cell lung cancer.

Our results suggest that determination of ERCC1 expression in non-small-cell lung cancer cells before chemotherapy can make a contribution as an independent predictor of the effect of adjuvant chemotherapy. For more than a decade, small studies have repeatedly reported an association between low levels of expression of ERCC1 mRNA in several solid tumors and improved clinical outcomes among patients treated with platinum-containing regimens.<sup>15-18,20,21,24</sup> In particular, it has been reported that the expression of ERCC1 mRNA predicts a response to chemotherapy in advanced non-small-cell lung cancer.<sup>20</sup> Furthermore, two common polymorphisms of the ERCC1 gene<sup>35-38</sup> (codon 118 C/T and C8092A)

have been correlated with the response to platinum-based chemotherapy in colorectal cancer<sup>39</sup> and non-small-cell lung cancer.<sup>40</sup> These polymorphisms are mainly associated with lower rates of translation of the ERCC1 gene, which results in low levels of the protein in nuclei. Since the type of immunohistochemical analysis we used can be applied in almost every pathology laboratory, our findings could be widely applicable if confirmed by independent studies.

In conclusion, patients with completely resected non-small-cell lung cancer and ERCC1-negative tumors derived a substantial benefit from adjuvant cisplatin-based chemotherapy, as compared with patients with ERCC1-positive tumors.

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#### APPENDIX

Members of the steering committee for the IALT Bio study were Fabrice André, Elisabeth Brambilla, Ariane Dunant, Martin Filipits, Thierry Le Chevalier, Jean-Pierre Pignon, Robert Pirker, Helmut Popper, Jean-Charles Soria, and Rolf Stahel. The following investigators and pathologists also participated in this study: *Austria* — R. Pirker, Internal Medicine, Vienna; G. Dekan, Institute of Pathology, Vienna; *Belgium* — J. Vansteenkiste, University Hospital, Leuven; *Brazil* — I. Sathler Pinel, Instituto Nacional de Cancer, Rio de Janeiro; R. Younes, Hospital Antonio Candido Camarco, São Paulo; *France* — A. Kanoui, Centre Physiothérapie du Rouget, Sarcelles; R. Dachez, Laboratoire Claude Levy, Paris; S. Deslignères, Hospital Delafontaine, Saint-Denis; O. Languille-Mimoune, Cabinet Pathologie, Paris; P. Sabatier, Centre Hospitalier Victor Dupouy, Argenteuil; T. Le Chevalier, Institut Gustave-Roussy, Villejuif; P. Boz, Cabinet de Pathologie, Papeete; P. Bruneval, Association Promotion Anatomie Pathologique, Paris; F. Capron, Groupe Hospitalier Pitié-Salpêtrière, Paris; M. Charpentier, Cabinet Pathologie Tolbiac, Paris; B. Chetaille, Hôpital Sainte Marguerite, Marseille; E. Dulmet, Centre Chirurgical Marie-Lannelongue, Le Plessis Robinson; B. Gosselin, Centre Hospitalier Universitaire, Lille; D. Grunenwald, P. Validire, Institut Mutualiste Montsouris, Paris; F. Labrousse, Centre Hospitalier Universitaire, Limoges; D. Petrot, Cabinet d'Anatomie Pathologique, Niort; N. Rouyer, Cabinet de Pathologie Butet-Rouyer, Nice; B. Milleron, M. Antoine, Hôpital Tenon, Paris; J. Morère, M. Kambouchner, Hôpital Avicenne, Bobigny; G. Ozonne, Ceditrac — Centre Médico Chirurgical du Cèdre, Bois Guillaume; T. Ducastelle, Laboratoire d'Anatomie et Cytologie, Rouen; E. Quoix, Hôpital Lyautey, Strasbourg; P. Durand de Grossouvre, Laboratoire d'Anatomie Pathologique, Haguenau; B. Gasser, Centre Hospitalier Universitaire, Strasbourg; A. Rivière, Centre François Baclesse, Caen; F. Galateau-Salle, Centre Hospitalier Universitaire, Caen; C. Tuchais, P. Jallet, G. Bertrand, I. Valo, Centre Paul Papin, Angers; *Germany* — W. Eberhardt, University Hospital, Essen; D. Theegarten, Institute of Pathology, Ruhr-University Bochum, Bochum; *Greece* — P. Christaki, Papanikolaou General Hospital, Pylea; T. Dsosios, V. Kyriakou, Athens University School of Medicine, Athens; E. Papadakis, P. Agelidou, Sotiria Hospital, Athens; K. Zarogoulidis, University Hospital, Thessaloniki; *Italy* — A. Masotti, Azienda Ospedaliera Di Verona, Verona; N. Pericoli, Ospedale Santa Maria Goretti, Latina; *Lithuania* — A. Jackevicius, Institute of Oncology Vilnius University, Vilnius; *Poland* — J. Laudanski, L. Chyczewski, M. Kozłowski, J. Niklinski, Medical School, Białystok; T. Grodzki, J. Pankowski, Regional Hospital for Lung Diseases, Szczecin; T. Orłowski, M. Chabowski, R. Langfort, Institute of Tuberculosis and Lung Disease, Warsaw; B. Muszczynska-Bernhard, Dolnoslaskiego Centrum Chorob Pluc, Wrocław; *Romania* — T. Ciuleanu, Oncological Institute Ion Chiricuta, Cluj-Napoca; *Slovakia* — J. Baumohl, University Teaching Hospital, Kosice; *Spain* — F. Cardenal, Hospital Duran I Reynals, Barcelona; R. Bernat, Hospital de Bellvitge, Barcelona; J. Salinas, J.B. Lopez, Hospital Virgen de Arrixaca, El Palmar Murcia; *Sweden* — B. Bergman, A. Hussein, Sahlgrenska Hospital, Göteborg; *Yugoslavia* — G. Radosavljevic, Institute for Lung Disease, Belgrade.

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