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ORIGINAL REPORT

Randomized Phase III Trial of Vinorelbine Plus Cisplatin Compared With Observation in Completely Resected Stage IB and II Non–Small-Cell Lung Cancer: Updated Survival Analysis of JBR-10

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ABSTRACT

Purpose
Adjuvant cisplatin-based chemotherapy (ACT) is now an accepted standard for completely resected stage II and III A non–small-cell lung cancer (NSCLC). Long-term follow-up is important to document persistent benefit and late toxicity. We report here updated overall survival (OS) and disease-specific survival (DSS) data.

Patients and Methods
Patients with completely resected stage IB (T2N0, n = 219) or II (T1-2N1, n = 263) NSCLC were randomly assigned to receive 4 cycles of vinorelbine/cisplatin or observation. All efficacy analyses were performed on an intention-to-treat basis.

Results
Median follow-up was 9.3 years (range, 5.8 to 13.8; 33 lost to follow-up); there were 271 deaths in 482 randomly assigned patients. ACT continues to show a benefit (hazard ratio [HR], 0.78; 95% CI, 0.61 to 0.99; $P = .04$). There was a trend for interaction with disease stage ($P = .09$; HR for stage II, 0.68; 95% CI, 0.5 to 0.92; $P = .01$; stage IB, HR, 1.03; 95% CI, 0.7 to 1.52; $P = .87$). ACT resulted in significantly prolonged DSS (HR, 0.73; 95% CI, 0.55 to 0.97; $P = .03$). Observation was associated with significantly higher risk of death from lung cancer ($P = .02$), with no difference in rates of death from other causes or second primary malignancies between the arms.

Conclusion
Prolonged follow-up of patients from the JBR.10 trial continues to show a benefit in survival for adjuvant chemotherapy. This benefit appears to be confined to N1 patients. There was no increase in death from other causes in the chemotherapy arm.

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INTRODUCTION

Early-stage non–small-cell lung cancer (NSCLC) is best managed with surgical resection with curative intent. Even with complete resection, patients are at significant risk of relapse and death from NSCLC.[1] Recently, three randomized phase III[2-4] trials and the Lung Adjuvant Cisplatin Evaluation meta-analysis[5] have shown a significant survival benefit for adjuvant cisplatin-based chemotherapy for selected patients with completely resected stage II and IIIA NSCLC. Based on this evidence, postoperative adjuvant cisplatin-based chemotherapy now represents the standard of care for the management of stage II to IIIA NSCLC.

While this represents a significant advantage in the management of early-stage NSCLC, it is important that long-term follow-up of these trials be reported. Cisplatin-based chemotherapy regimens have been associated with late toxicities, particularly vascular disease that might negate early survival benefits.[6] This may be particularly so in patients with lung cancer who are older, and have high rates of comorbidity,[7] particularly smoking-related vascular disease.

The International Adjuvant Lung Cancer Trial (IALT)[2] reported a significant survival benefit for

adjuvant cisplatin-based chemotherapy after a median follow-up of 56 months (HR, 0.86; 95% CI, 0.76 to 0.98; $P < .03$). A subsequent report with median follow-up of 90 months no longer showed a survival benefit (HR, 0.91; 95% CI, 0.81 to 1.02; $P = .10$).[8,9] In Cancer and Leukemia Group B (CALGB) trial 9633, a trial of adjuvant carboplatin plus paclitaxel in stage IB patients, the initial report was positive (HR, 0.62; 95% CI, 0.44 to 0.89; $P = .014$) with median follow-up of only 2.8 years.[10] Final publication of the mature results with follow-up of 6.1 years reported that no survival benefit (HR, 0.83; 95% CI, 0.64 to 1.08; $P = .12$) was seen.[11]

JBR.10 was the North American Intergroup phase III trial of adjuvant cisplatin plus vinorelbine that reported the largest survival benefit for adjuvant therapy in early-stage NSCLC.[3] With a median follow-up more than 5 years, a significant improvement in median recurrence-free survival, median overall survival (OS), and a 15% absolute improvement in 5-year survival were reported in the chemotherapy arm. In a subgroup analysis, no benefit for adjuvant chemotherapy was seen in the stage IB patients. Given concerns regarding the potential late effects of cisplatin-based regimens and the loss of benefit with longer follow-up reported in other adjuvant trials, it is important to update survival results and to report any late effects seen in patients on JBR.10.

PATIENTS AND METHODS

Study Design

JBR.10 was a phase III randomized trial of adjuvant cisplatin and vinorelbine versus observation in completely resected stage IB or II NSCLC. Postoperative radiation was not permitted. The primary objective was to determine whether postoperative chemotherapy conferred a survival benefit. Accrual began in the National Cancer Institute of Canada Clinical Trials Group (CTG) in 1994, and the study was joined by the Eastern Cooperative Oncology Group (ECOG), Cancer and Leukemia Group B (CALGB), and Southwest Oncology Group (SWOG) in 1998. Accrual ended in 2001. The final analysis was conducted in April 2004 with median follow-up of 5.1 years in the chemotherapy arm and 5.3 years for the observation arm. The full details of the JBR.10 trial are reported elsewhere.[3] For this updated survival analysis, the data cutoff was July 2008. The objectives of this update are to report on the primary survival end point with longer follow-up and causes of late deaths.

Statistical Methods

Analysis of pretreatment characteristics and efficacy analysis such as overall and disease-specific survival (DSS) were with all randomly assigned patients on an intention-to-treat basis. Overall survival was calculated in years from the date of random assignment to the date of death. DSS was calculated from the date of random assignment to the date of death due to lung cancer or lung cancer and complications of its treatment (protocol or nonprotocol treatments).

For OS, Kaplan-Meier curves were used to summarize the distribution of patients on the two treatment arms. A log-rank test, stratified for disease stage (IB or II) and *RAS* mutation status, was used to compare survival between arms. For DSS, the log-rank test was used to test the cause-specific survival hazard. Gray's test was used to test the difference in cumulative cause-specific incidences of death from lung cancer and its treatment or from nondisease-related death. A Cox regression model was used to test for homogeneity of treatment effect and to build the prognostic model of the trial population. All *P* values are two sided. Reported CIs are 95%.

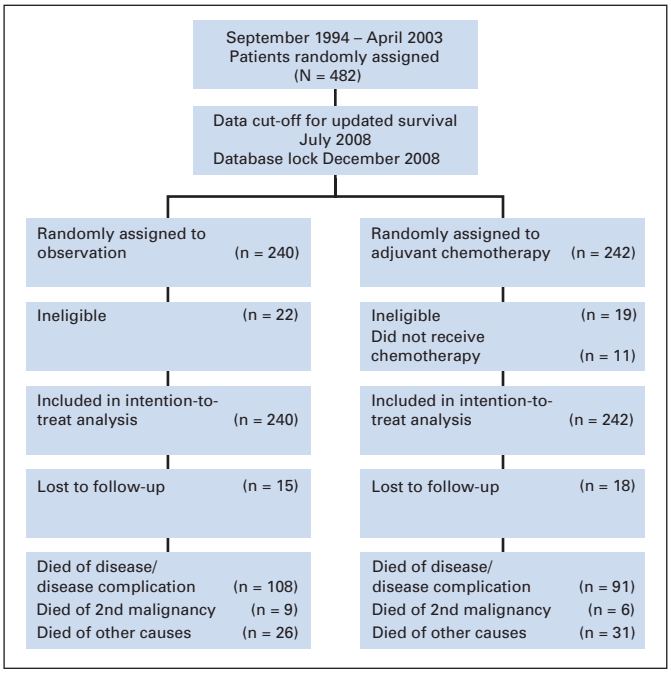

Fig 1. CONSORT diagram. Distribution of all patients.

Table 1. Patient Characteristics at Baseline

Parameter	Observation No.	Observation %	Chemotherapy No.	Chemotherapy %	Total No.	Total %
Patients	240		242		482	
Lost to follow-up	15		18		33	
Median age, years	61		60.5		60.9	
< 65	163	68.0	162	67	325	67
≥ 65	77	32	80	33	157	33
Sex						
Female	86	36	82	34	168	35
Male	154	64	160	66	314	65
PS						
0	116		120		236	
1	123		122		245	
Smoking status						
Ever smoked	218	91	233	96	451	94
No longer smoking	204	85	203	84	407	84
Postsurgical stage						
T2N0	108	45	111	46	219	45
T1N1	32	13	38	16	70	15
T2N1	100	42	93	38	193	40
Histology						
Adenocarcinoma	128	53	128	53	256	53
Squamous	90	38	89	37	179	37
Other	22	9	25	10	47	10
Comorbidity*						
None	185	77	161	66.5	346	72
Present	55	23	81	33.5	136	28
RAS mutation						
Absent	170	71	164	68	334	69.3
Present	58	24	59	24	117	24.3
Unknown	12	5	19	8	31	6.4
Tumor diameter (stage IB), cm						
< 4	54		45		99	
≥ 4	54		66		120	

Abbreviation: PS, Eastern cooperative Oncology Group Performance Status.
*The Charlson Comorbidity Index: None score is equal to 0; Present score is ≥ 1.

Subgroup analyses were conducted to assess chemotherapy effect based on the stratification factors of *RAS* mutation status and disease stage.

Median survival for each level of stratification factor according to the Kaplan-Meier method and log-rank testing was used to test the difference between the two treatment arms. To test for interaction by treatment with those stratification factors, proportional hazard models were used with interaction terms.

RESULTS

Patient Characteristics

A total of 482 patients were randomly assigned, 242 to chemotherapy and 240 to observation (Fig 1). At the time of data cutoff, 33 patients were lost to follow-up, a median of 4.7 years from random assignment (range, 0.9 to 10.4 years). Baseline patient characteristics were well balanced between the arms (Table 1).

Survival

With a median follow-up for this report of 9.3 years (range, 3.2 to 13.8 years), 271 of the 482 randomly assigned patients have died (143 on observation and 128 on chemotherapy). The causes of death for all patients are presented in Table 2 and include 73% who died of disease or complications of treatment of their NSCLC and 27% who died of other causes.

As shown in Figure 2A, patients in the chemotherapy arm continue to experience a significant survival advantage compared with observation. (HR, 0.78; 95% CI, 0.61 to 0.99; $P = .04$). The absolute improvement in 5-year survival is now 11% (67% chemotherapy *v* 56% observation). A Cox regression analysis adjusting for the following prognostic factors potentially correlating with OS was conducted: sex, age, performance status (0 *v* 1 or missing), histology (adenocarcinoma *v* squamous *v* other) and surgery (pneumonectomy *v* lesser resection). The adjusted HR was 0.79 (95% CI, 0.62 to 1.00; $P = .05$).

A Cox regression model with disease stage, chemotherapy, and their interaction was performed. The interaction term for stage was of borderline significance (interaction $P = .09$). Patients with stage II NSCLC had a significant benefit in survival from chemotherapy (HR, 0.68; 95% CI, 0.50 to 0.92; $P = .01$; Fig 2B). The median survival was

Table 2. Cause of Death

Parameter	Observation		Chemotherapy		Total	
	No.	%	No.	%	No.	%
No. of patients	240		242		482	
Patients who died	143	59.6	128	52.9	271	56.2
Disease related	105	43.8	88	36.4	193	40
Disease/nonprotocol or	3	1.1	1	0.4	4	0.8
Protocol treatment			2	0.8	2	0.4
Other primary malignancy	9	3.8	6	2.5	15	3.1
Other cause	26	10.8	31	12.8	57	11.8
COPD/respiratory	4		5		9	
Cardiac*	7		8		15	
Vascular†	7		2		9	
Infection	2		5		7	
Unknown	5		6		11	
Other						
Herniation splenic flexure	1				6	
GI bleed			1			
Ethanol abuse			3			
Alzheimer's			1			

Abbreviation: COPD, chronic obstructive pulmonary disease.
*Cardiac causes include myocardial infarction, chronic heart failure, cardiac arrest, and arrhythmias.
†Vascular causes include stroke, pulmonary embolus, subarrachnoid hemorrhage, and aneurysms.

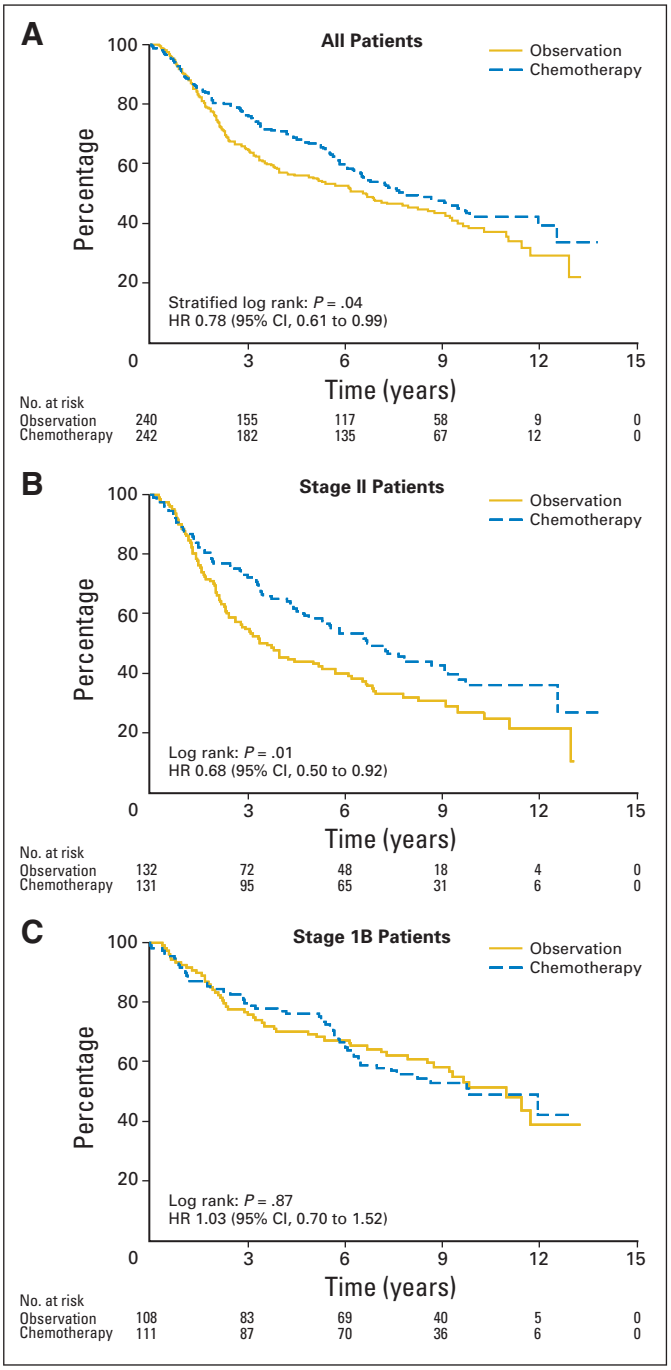

Fig 2. Overall survival comparisons by treatment arm: (A) for all randomly assigned patients; (B) for patients with stage II disease; (C) for patients with stage IB (T2N0) disease. HR, hazard ratio.

3.6 years for patients on observation versus 6.8 years for those receiving chemotherapy. In contrast, there was no survival benefit for chemotherapy in stage IB patients (Fig 2C; HR, 1.03; 95% CI, 0.70 to 1.52; $P = .87$). The median survival was 11 years for the patients in observation arm versus 9.8 years for patients receiving chemotherapy. Within stage IB, however, tumor size was predictive of chemotherapy effect (interaction $P = .02$ for chemotherapy effect by tumor size 4 cm or larger). Patients with tumors 4 cm or larger in size derived clinically meaningful benefit from chemotherapy (HR, 0.66; 95% CI, 0.39 to 1.14; $P = .13$; Fig 3B), while those with tumors smaller than 4 cm did not (HR, 1.73; 95% CI, 0.98 to 3.04; $P = .06$; Fig 3A). The 5-year survival for patients with tumors 4 cm or larger was 59% on observation versus 79% with chemotherapy.

RAS mutation status (*H-RAS, K-RAS, N-RAS*) was known for 451 of the 482 randomly assigned patients. *RAS* mutation was absent in 334 patients (69.3%) and present in 117 patients (24.3%). *RAS* mutation status was not associated with a differential effect of chemotherapy either for survival (interaction $P = .97$) or DSS (interaction $P = .2$). For patients with wild-type *RAS*, median survival was 6.6 years with observation versus 7.8 years in the chemotherapy arm (HR, 0.84; 95% CI, 0.63 to 1.12; $P = .24$; Appendix Figs A1 and A2, online only). For patients with *RAS* mutations, median survival was 7.8 years for observation versus 9.7 years for chemotherapy (HR, 0.82; 95% CI, 0.50 to 1.35; $P = .44$). Although the interaction term was nonsignificant for DSS, *RAS* wild type patients did appear to have more benefit from chemotherapy (HR, 0.72; 95% CI, 0.51 to 1.02; $P = .06$) compared with *RAS* mutation–positive patients (HR, 1.07; 95% CI, 0.61 to 1.88; $P = .82$).

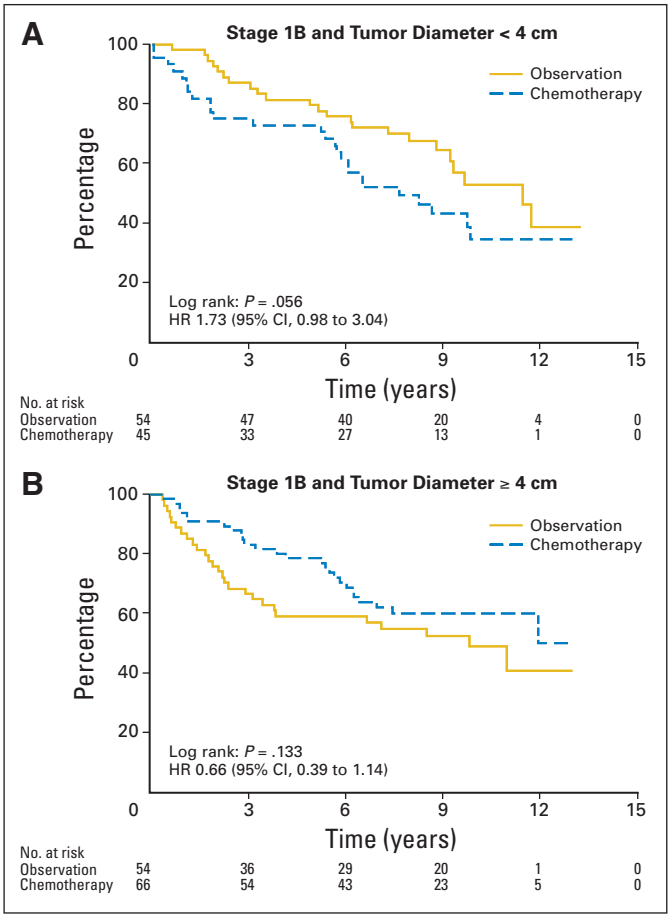

Fig 3. (A) Survival comparison for stage IB patients with primary tumor less than 4 cm by treatment arm. (B) Survival comparison for stage IB patients with primary tumor 4 cm or greater by treatment arm. Interaction, $P = .022$. HR, hazard ratio.

DSS and Competing Risk Analysis

Of the 482 randomly assigned patients, 199 died of disease or complications of treatment (73% of all deaths). Adjuvant chemotherapy resulted in a significantly reduced risk of dying of lung cancer (HR, 0.73; 95% CI, 0.55 to 0.97; $P = .03$). Chemotherapy retained its significant beneficial effect on DSS after adjusting for other prognostic factors (HR, 0.73; 95% CI, 0.55 to 0.96; $P = .03$).

A competing risks analysis was performed to assess the probability of death from lung cancer versus death from other causes. Causes of death for all patients are presented in Table 2 and cumulative incidence plots for those who died of disease or complications of treatment and those who died of nondisease-related causes are shown in Figure 4.

The Gray test was used to test the difference in the cumulative cause-specific incidences. Patients on observation had a significantly higher chance of death due to lung cancer ($P = .02$), whereas there was no significant difference in death from other causes ($P = .62$).

The number of deaths attributed to cardiac, vascular, and respiratory causes was small and similar in both arms.

A second malignancy developed in 51 patients (10.6%; Table 3). Slightly more second malignancies were seen in the observation arm (11.9% *v* 9.5%). Median time to second malignancy was 3.0 years in the observation arm and 5.2 years in the chemotherapy arm. Second primary lung cancers were infrequent with only six (five NSCLC and one small cell) in the observation arm and two (one NSCLC and one small cell) in the chemotherapy arm.

DISCUSSION

The demonstration that adjuvant cisplatin-based chemotherapy significantly improves survival for patients with resected stage II and IIIA NSCLC represents an important advance in the management of this malignancy. The randomized, phase III trials showing a survival benefit for adjuvant chemotherapy were initially reported with median-follow-up times of 56 months, 5.1 years and 76 months for IALT,

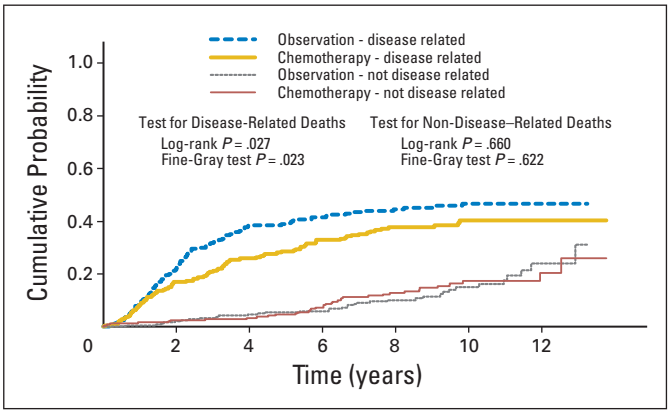

Fig 4. Cumulative incidence plots for death due to non–small-cell lung cancer or other causes by treatment arm.

Table 3. Second Primary Malignancies

Parameter	Observation (n = 240)	Vinorelbine (n = 242)	Total (N = 482)
Second malignancies			
No	212	219	431
%	88.3	90.5	89.4
Yes	28	23	51
%	11.7	9.5	10.6
Site of malignancy			
Bladder	0	3	3
Brain	0	1	1
Colon	2	1	3
Head and neck	6	1	7
Kidney	1	1	2
Liver	1	0	1
Melanoma	1	1	2
Non–small-lung cancer	5	1	6
Small-cell lung cancer	1	1	2
Prostate	2	5	7
Sarcoma	1	0	1
Thyroid	1	0	1
Other	4	3	7
Unknown	3	5	8

JBR.10, and Adjuvant Navelbine International Trialist Association, respectively. Long-term follow-up of patients in these trials is critical to assess whether chemotherapy is associated with a sustained survival benefit and to identify any late toxicities that may be attributable to adjuvant therapy. For example, in trials of adjuvant therapy for breast cancer the survival benefit is maintained or amplified over time.[12]

The data reported here from the updated survival analysis of patients on JBR.10 represents the longest reported follow-up data from any of the recent adjuvant NSCLC trials. Most importantly, with median follow-up of longer than 9 years, a significant survival benefit for adjuvant cisplatin and vinorelbine is maintained with an absolute improvement in 5-year survival of 11%. Furthermore, no significant increase in death from other causes or from other primary malignancies was observed in the patients receiving adjuvant chemotherapy.

These results differ from recent survival updates from other NSCLC adjuvant trials. CALGB 9633 initially reported a survival advantage for adjuvant carboplatin and paclitaxel in stage IB patients with median follow-up of only 2.8 years. Mature results of this study with follow-up of 74 months no longer show a survival benefit for adjuvant chemotherapy. However, there was a trend for longer OS with a HR of 0.83 and so the lack of significance may be related to a lack of statistical power for this study to detect a survival advantage in this relatively good risk population with only 344 patients and 155 events.

The positive survival advantage reported in IALT with a median follow-up of 56 months was no longer evident after 90 months.[8] This appeared to be related to an increase in noncancer deaths in the chemotherapy arm after 5 years. An important finding of our updated survival analysis of JBR.10 is that deaths due to causes other than NSCLC were not increased in the chemotherapy arm. In particular, the number of deaths from cardiac or vascular causes was low in both arms.

The reasons for the difference seen in the IALT and our results are not obvious. One possibility may be related to the smoking status of the patients in the two trials. In JBR.10, 84% of patients were no longer smoking at the time of random assignment. This information is not reported from IALT. Current smoking has been reported as an independent predictor of survival in patients with NSCLC after surgical resection.[13,14] Alternatively, this may be related to the relatively low incidence of comorbidity in the JBR.10 patients (28%). The Charlson Comorbidity Index score was used to assess comorbidity. Comorbidity has also been reported to be an independent predictor of survival in early-stage NSCLC.[15,16] Information on the comorbidities of the IALT patients is not available. Other explanations might be the difference in chemotherapy used in the two trials or possibly the exclusion of postoperative radiation in JBR.10. Finally, there were 33 patients lost to follow-up in JBR.10, 15 in the observation arm and 18 in the chemotherapy arm. However, the likelihood of this impacting the results is remote.

Similar to our initial report, a survival advantage for adjuvant cisplatin and vinorelbine continues to be seen primarily in stage II patients. Median survival was almost double in the chemotherapy patients (3.6 *v* 6.8 years) with an absolute improvement in 5-year survival of 15%. Overall, patients with IB disease did not benefit (HR, 1.03; $P = .87$).

The analysis of stage IB patients based on primary tumor size was an unplanned analysis testing reports that primary tumor size appeared to be important in CALGB 9633.[17] In JBR.10, IB patients with tumors 4 cm or greater in size did appear to derive a clinically meaningful benefit, with a similar HR of 0.66 (*v* HR 0.68 in stage II patients). The lack of statistical significance may be due to the small sample size, with only 99 and 120 patients in the less than 4 cm and 4 cm or greater subgroups respectively. While this analysis by size within the stage IB subset is only exploratory, the results provide support for a similar exploratory subgroup from CALGB 9633. This study was restricted to stage IB disease and a statistically significant improvement in survival for adjuvant chemotherapy was seen for patients with tumors 4 cm or greater ($P = .043$), with a HR (HR, 0.69) similar to that seen in this JBR.10 updated analysis.

However, both of these analyses were posthoc and caution should be exercised in interpreting their significance.

The original report of JBR.10 suggested a trend toward a differential effect of adjuvant chemotherapy based on the presence or absence of *RAS* mutation, although the interaction term for *RAS* was not significant ($P = .29$).[3] In our current analysis we were not able to demonstrate a significant interaction with chemotherapy for either OS or DSS. Interestingly, the HR for *RAS* wild-type patients did show apparent benefit for chemotherapy on DSS, which was not seen in patients who were *RAS* mutation positive. Two previous adjuvant trials, ECOG 4592[18] and the Adjuvant Lung Project Italy,[19] assessed only *K-RAS* and found no association with treatment effect.

Second primary malignancies (SPM) of any site were seen in 11% of the study population over the 9 years of follow-up and were similar in the two arms. This is similar to previous reports of risk of SPM in lung cancer survivors. Keller et al[20] reported a cumulative SPM risk of 6.1% after 73 months of follow-up of patients in the ECOG 3590 study. In stage I patients surviving longer than 5 years after lobectomy, Kim et al[21] found a 9.5% cumulative risk of SPM. Second primary lung cancers were infrequent, and more often seen in the observation arm of our study. This is lower than the 13% to 20% cumulative risk of second primary lung cancers or smoking-related cancers reported by Johnson[22] in an earlier review of the literature. This may possibly be

explained by the high smoking cessation rate of 84% in our trial, since the development of a second primary lung cancer has been associated with continued exposure to tobacco products in previous reports.[23]

In summary, this updated analysis with more than 9 years of follow-up confirms a significant survival benefit for adjuvant chemotherapy in early-stage NSCLC. The survival benefit is seen in the stage II patients. No evidence of unexpected late toxicity or increase in second malignancies from adjuvant chemotherapy was observed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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