ORIGINAL ARTICLE

Three-Year Follow-Up of a Randomized Phase II Trial on Refinement of Early-Stage NSCLC Adjuvant Chemotherapy with Cisplatin and Pemetrexed versus Cisplatin and Vinorelbine (the TREAT Study)

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ABSTRACT

Introduction: Adjuvant chemotherapy in non–small cell lung cancer (NSCLC) improves survival but is associated with significant toxicity. The Randomized Phase II Trial on Refinement of Early-Stage NSCLC Adjuvant Chemotherapy with Cisplatin and Pemetrexed versus Cisplatin and Vinorelbine (TREAT study) was designed to test the hypothesis that a protocol with reduced toxicity might improve feasibility of postoperative delivery of adjuvant chemotherapy drugs to patients with NSCLC, thereby improving compliance and, potentially, survival.

Methods: Two adjuvant regimens were evaluated for feasibility in 132 patients with NSCLC: the standard

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regimen of cisplatin and vinorelbine (CVb) (cisplatin 50 mg/m^2 on day 1 and day 8 and vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 every 4 weeks) and a regimen consisting of cisplatin and pemetrexed (CPx) (cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 on day 1 every 3 weeks). The primary end-point analysis showing that CPx is safe and feasible with dose delivery superior to that of CVb has already been published. Here we report the 3-year follow-up results of the secondary efficacy end points—overall, relapse-free, distant metastasis–free, and local relapse–free survival—also with regard to histologic diagnosis.

Results: After a median of 39 months, no significant differences in any of the outcome parameters between CVb and CPx were observed. Also, histologic diagnosis and tumor size in stage IB did not influence survival in the CPx-treated patients. Yet, Cox regression analyses showed that overall survival at 3 years was significantly correlated with feasibility and the occurrence of dose-limiting toxicity.

Conclusions: Although adjuvant chemotherapy with CPx is safe and characterized by less toxicity and better dose delivery than CVb, overall survival was not influenced by treatment arm in the context of this phase II trial.

Keywords: Non–small cell lung cancer; Adjuvant chemotherapy; Pemetrexed; Outcome; Toxicity

Introduction

More than half of patients with non–small cell lung cancer (NSCLC) experience recurrence after resection.[1,2] The goal of postoperative adjuvant chemotherapy (ACT) is to reduce the risk for disease recurrence by eliminating residual disease that may persist after surgical resection, thereby increasing overall survival (OS).[3] Indeed, evidence from phase III studies and several meta-analyses demonstrates that adjuvant cisplatin-based chemotherapy (primarily cisplatin and vinorelbine [CVb]) confers a clear benefit in terms of OS in patients with early-stage, R0-resected NSCLC.[4–14] These results are consistent with findings in a real-life setting from a large, retrospective population-based study that was conducted between 2001 and 2008 and monitored 14,306 veterans with stages IB to IIIA NSCLC. In that study, significantly improved OS was associated with increased use of an adjuvant platinum doublet in patients with resected NSCLC.[3]

ACT is the current standard of care and CVb is the most reported chemotherapy combination option.[14] However, cisplatin-based protocols, particularly CVb, are limited by grade 3 or 4 hematologic toxicity, mainly neutropenia, which can occur in up to 85% of patients, and febrile neutropenia, which can occur in up to 9%, thus resulting in incomplete treatment delivery, therapy delay, dose reductions, or even therapy-related deaths.[5,7,8,15]

The Randomized Phase II Trial on Refinement of Early-Stage NSCLC Adjuvant Chemotherapy with Cisplatin and Pemetrexed versus Cisplatin and Vinorelbine (the TREAT study) was designed to test the hypothesis that a protocol with reduced toxicity might improve the feasibility of ACT drug delivery, compliance, and (potentially) survival.[16] Trials in patients with advanced NSCLC and mesothelioma using a combination of cisplatin and pemetrexed (CPx) have shown that CPx is characterized by promising efficacy and a favorable safety profile coupled with convenient once-every-3-weeks administration.[17–20] CPx was therefore chosen for comparison with CVb from the standpoints of side effects and dose delivery in the adjuvant setting.[21] Clinical feasibility was the primary end point; it was defined as (1) no death due to cancer, toxicity, or comorbidity; (2) no nonacceptance by the patient leading to premature withdrawal; and (3) no dose-limiting toxicity (DLT), which in turn was defined as grade 4 neutropenia lasting longer than 7 days, febrile grade 3 or 4 neutropenia, grade 4 thrombocytopenia lasting longer than 7 days or any grade with bleeding, or grade 3 or 4 nonhematologic toxicity (except nausea, vomiting, and hair loss).[21]

The primary and secondary end points, which were analyzed after approximately a mean follow-up of 4 months, were reported previously.[21] For the primary end point, CPx was demonstrated to be safe and feasible. The feasibility rate of the CPx regimen was 95.5% versus 75.4% for CVb ($p < 0.001$). The secondary end points included dose delivery, which differed significantly between treatment arms: 74.6% for CPx versus 20% for CVb ($p < 0.0001$), and toxicity, which was apparent in significantly fewer grade 3 or 4 hematologic events in the CPx group (10.5% versus 76.5% in the CVb group; $p < 0.0001$) and a similar incidence of nonhematologic grade 3 or 4 toxicity (33% versus 31% in the CPx and CVb groups, respectively). Time to treatment failure delivery was 3.6 months in the CVb group, whereas failure of treatment delivery was not reached in the CPx group ($p < 0.001$).[21]

Potential limitations of these results are the predictive information that has emerged since initiation of the trial (questioning the use of pemetrexed with a histologic diagnosis of squamous cell carcinoma) and the stage information (questioning the benefit of ACT in patients with smaller stage IB tumors[22]). After achievement of the primary end point, we now report the longer-term results of the TREAT study and key secondary outcomes after a 3-year follow-up period.

Methods

The full details of the TREAT trial's design, treatment plan, end points, eligibility criteria, toxicity management, and follow-up modalities were reported previously.[16,21] The trial was approved by the ethics committees of every center, conducted according to good clinical practice and the Declaration of Helsinki, and registered at clinicaltrials.gov (identifier NCT00349089). Briefly, the trial was a prospective, multicenter open label, randomized phase II study that included patients who had fully recovered after complete resection of pathologically confirmed NSCLC stages IB, IIA, IIB, and T3N1 (according to the Tumor, Node, Metastasis [TNM] staging system, version 6).[23] Eligible tumor types were squamous cell carcinoma, adenocarcinoma (including bronchoalveolar differentiation), and large cell and mixed cell carcinoma without a small cell fraction.

Patients were randomly assigned to either four cycles of CPx (cisplatin 75 mg/m^2 on day 1 and pemetrexed 500 mg/m^2 on day 1) with vitamin supplementation every 3 weeks or CVb (cisplatin 50 mg/m^2 on day 1 and day 8 and vinorelbine 25 mg/m^2 on days 8, 15, and 22) every 4 weeks. Patients were stratified according to center, nodal status (N0 versus N1), and surgical procedure (lobectomy versus pneumonectomy). Postoperative radiotherapy was not allowed.

The key secondary end points analyzed were relapse-free survival (RFS) and OS. RFS was defined as the interval between day of surgery and date of death (from any cause) or relapse, whichever occurred first. OS was defined as time from surgery to death from any cause. Additional secondary end-point parameters were local RFS and distant metastasis–free survival. Follow-up visits occurred at 3- to 6-month intervals for 3 years and consisted of clinical and laboratory examination, chest radiography complemented by computed tomography in cases of clinically or radiologically suspected relapse, and (optionally) abdominal ultrasonography.

Statistical methods

Calculation of sample size was based on the assumption that the experimental therapy arm would be rated as unacceptable if the actual feasibility rate (1 – withdrawal/DLT rate) was 65% or lower but the therapy would be considered a promising candidate for further development if the true feasibility rate reached 80% or more. The calculated total sample size was 134 patients for a type I error of 5% and a power of 80%. Times to events were estimated by the product limit method and compared using the log-rank test. For analysis of potential prognostic factors, univariate and multivariate analyses were performed by using a proportional hazard regression model. The following potential prognostic factors were included: treatment, age ($<$65 versus $\geq$65 years), sex, performance status at baseline, resection type, tumor stage, tumor status (pT), size of primary tumor ($<$4 cm or $\geq$4 cm), nodal status (pN), tumor grading and histologic diagnosis, "dose delivery," occurrence of DLT, and feasibility. Results were presented as adjusted hazard ratios (HRs). The chi-square test and Cochran-Armitage test for trend in cases of more than two categories were used to compare categorical variables. Continuous variables were compared by the *t*-test, and *p* values less than 0.05 were considered significant in two-sided tests. No adjustment of the error probability for multiple testing was performed. SAS Release 9.2 software (SAS Institute Inc., Cary, NC) was used in the analysis.

Results

Patient characteristics

As described before, 132 patients were randomized, with 67 patients treated in the CPx arm and 65 patients in the CVb arm. The mean follow-up time was 34.1 months (range 1.2–58.3) in the overall group, with 33.9 months for those in the CPx group and 34.3 months for those in the CVb group. The patients' baseline characteristics were evenly distributed with respect to age, sex, smoking status, performance status, tumor stage, histologic diagnosis, and surgical procedures[21] (Table 1). Notably, 38% of patients had stage IB disease (CPx arm 37%, CVb arm 38%) with a tumor diameter less than 4 cm in 14% (CPx arm 16%, CVb arm 12%) and 24% had a tumor diameter larger than 4 cm (CPx arm 21%, CVb arm 26%). Squamous cell carcinoma was present in 43% of all patients with 45% in the CPx arm and 42% in the CVb arm.

Relapses and RFS

Tumor relapse occurred in 31% of all patients: in 36% of patients receiving CPx versus 26% of patients receiving CVb, respectively. RFS did not differ significantly ($p = 0.813$) with medians not reached, and very similar 3-year RFS rates (Fig. 1). In a multivariate Cox regression analysis (Supplemental Table 1), RFS was not significantly influenced by chemotherapy type (HR = 0.831, 95% confidence interval [CI]: 0.317–2.177, $p = 0.707$), but occurrence of DLT and feasibility significantly influenced RFS ($p = 0.024$ each).

More patients in the CPx group than in the CVb group experienced local relapses (18% versus 5%), with most being mediastinal lymph node metastases in the CPx group, whereas the rates of distant relapse in both groups were similar (20.9% versus 18.5%). Brain metastases occurred more frequently in the CVb arm (75% of distant metastases) than in the CPx treatment arm (21% of distant metastases). Local RFS and distant

Table 1. Patients' baseline characteristics

Characteristics	CPx (n = 67)	CVb (n = 65)	Total (N = 132)
Age (range), y	58 (40-73)	60 (38-74)	59 (38-74)
Sex (%)			
Male	72	77	74
Female	28	23	26
Stage (%)[a]			
IB	37	38	38
<4 cm	16	12	14
≥4 cm	21	26	24
IIA	12	8	10
IIB	46	48	47
T3N1	5	6	5
Surgical procedures (%)			
Lobectomy	84	82	83
Pneumonectomy	12	15	14
Complex resections	4	3	3
Histologic diagnosis (%)			
Squamous cell carcinoma	45	42	43
Nonsquamous cell carcinoma	55	58	57
• Adenocarcinoma	• 37	• 44	• 41
• Large cell carcinoma	• 9	• 9	• 9
• Mixed cell carcinoma	• 9	• 5	• 7

[a]According to the TNM staging system, version 6.
CPx, patients who received chemotherapy with cisplatin and pemetrexed; CVb, patients who received chemotherapy with cisplatin and vinorelbine; TNM, tumor, node, metastasis.

metastasis–free survival, however, did not differ between treatment arms ($p = 0.877$ and $p = 0.813$, respectively).

Deaths and OS

The rate of death did not differ significantly between treatment arms, with a total rate of 27% (27% for the CPx arm versus 26% for the CVb arm). Reasons for death were also comparable between groups, with 17% attributed to tumor relapse (18% in the CPx arm and 15% in the CVb arm), 5% unrelated to therapy or tumor (5% in each arm), and 5% unknown. Also, death by resection type did not differ between arms: 83% of the patients received a lobectomy, with death rates of 22% in both arms, and 14% of patients received a pneumonectomy, with a death rate of 4% for the overall cohort (5% in the CPx arm and 3% in the CVb arm).

OS did not differ between treatment arms, with the median not reached in the CPx arm and an OS of 59 months in the CVb arm ($p = 0.858$) (Fig. 2). In a multivariate Cox regression analysis (Supplemental Table 2), OS was not significantly influenced by treatment arm (HR = 0.594, 95% CI: 0.165–2.131, $p = 0.424$); once again, however, occurrence of DLT ($p = 0.002$) and feasibility ($p = 0.002$) were significant.

Influence of tumor size in stage IB and histologic diagnosis on survival parameters

Tumor size in stage IB had no significant impact on RFS (HR = 0.405, 95% CI: 0.038–4.277) or OS (HR = 1.187, 95% CI: 0.063–22.473).

OS was not influenced by whether the histologic diagnosis was squamous cell carcinoma or adenocarcinoma (HR = 1.362, 95% CI: 0.433–4.288); the results for comparisons of squamous cell and nonsquamous cell carcinoma were similar (HR = 1.359). Also, RFS was not influenced by histologic diagnosis: HR = 1.550 (95% CI 0.632–3.802) and HR = 1.721, respectively. Neither RFS ($p = 0.4183$) nor OS ($p = 0.3634$) differed significantly in patients with squamous cell carcinoma with regard to chemotherapy arm (Fig. 3). Similar results were obtained for patients with nonsquamous cell carcinoma, in which case neither RFS ($p = 0.249$) nor OS ($p = 0.309$) differed significantly between treatment arms (Fig. 4).

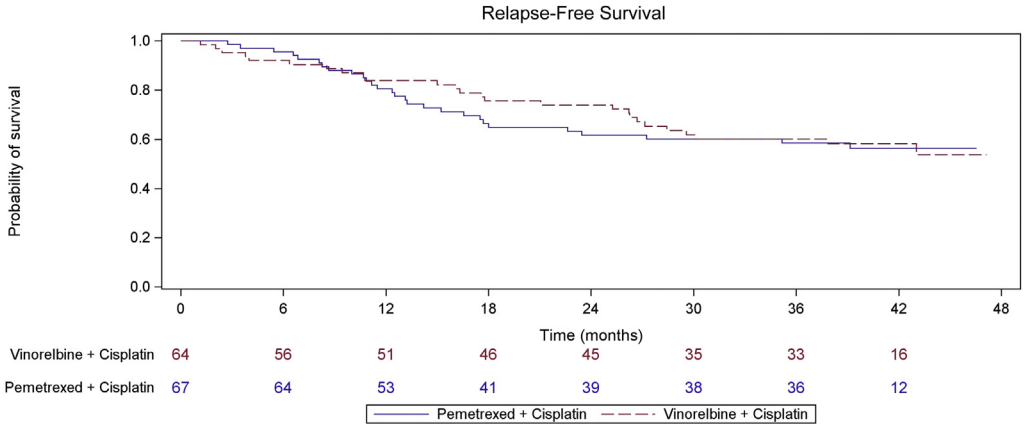

Figure 1. Relapse-free survival did not differ between the cisplatin plus pemetrexed and cisplatin plus vinorelbine arms, with the medians not reached and similar 3-year relapse-free survival rates of 59% and 60%, respectively ($p = 0.813$).

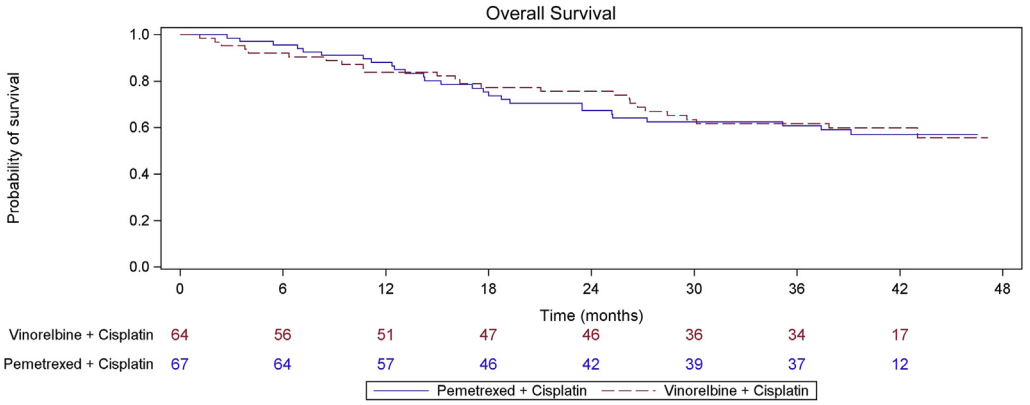

Figure 2. Overall survival did not differ between the cisplatin plus pemetrexed and cisplatin plus vinorelbine arms, with the median survival not reached in the cisplatin plus pemetrexed arm, a rate of 59% in the cisplatin plus vinorelbine arm, and similar 3-year overall survival rates of 75% and 77%, respectively ($p = 0.858$).

Discussion

This is the first study to provide survival data on CPx as ACT for NSCLC after complete tumor resection.

After a 3-year follow-up period, no significant survival differences between the CPx and CVb arms (the most frequently reported chemotherapy combination for ACT) have been demonstrated. An important and, to our knowledge, not previously reported finding emerging from the multivariate Cox regression analysis is that occurrence of DLT and feasibility had a significant impact on survival.

This finding suggests that lowered toxicity and therefore improved feasibility and drug delivery may improve OS. Although a recent Cochrane review[24] reported that ACT in NSCLC is generally considered tolerable, exposure to the current "standard" regimen leads to significant early toxicity. The impact of the perception of acute toxicity by patients is a topic of discussion; however, its true incidence and consequence are still unknown, and it may lower drug delivery to a significant extent.[25] In this context, our finding that OS may be related to feasibility, which included "no nonacceptance by the patient leading to premature withdrawal" in its definition, adds to this discussion and may be regarded as a relevant patient-related factor favoring a more feasible regimen. In addition to early side

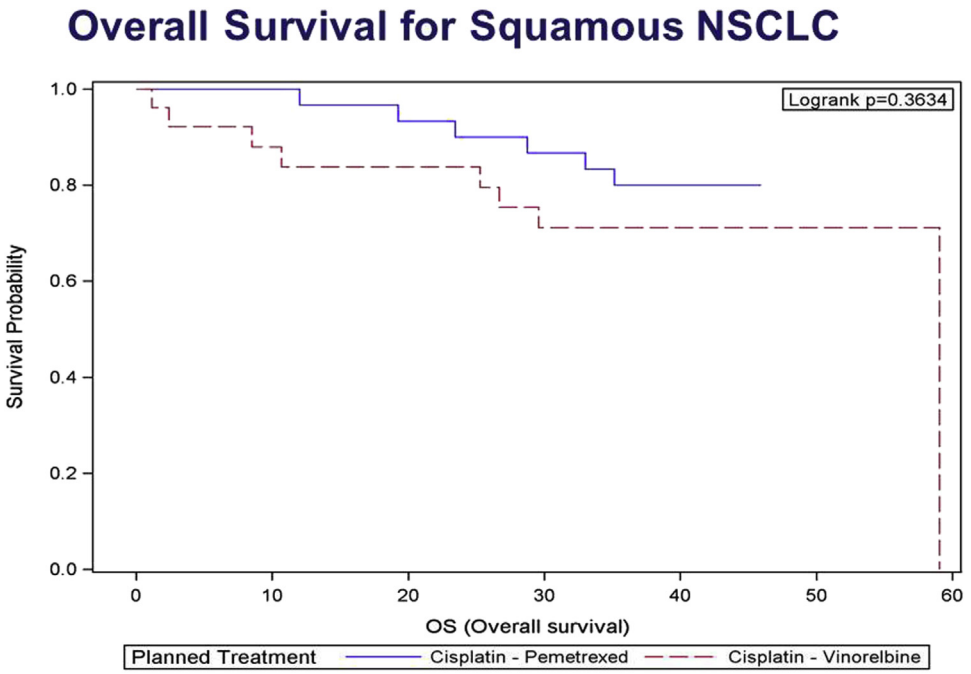

Figure 3. Overall survival for squamous non-small cell lung cancer did not differ between the cisplatin plus pemetrexed and cisplatin plus vinorelbine arms ($p = 0.363$).

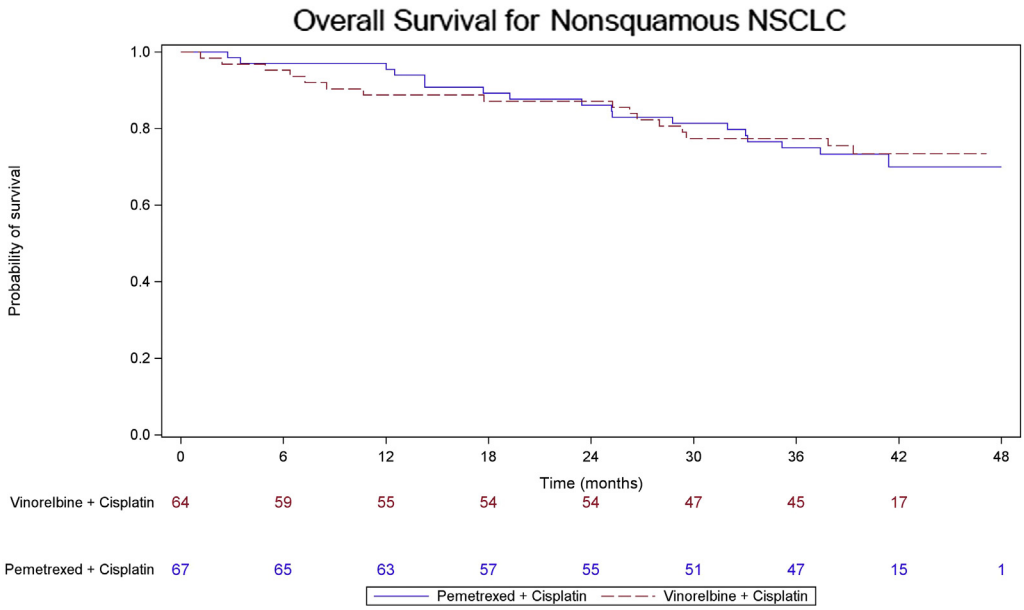

Figure 4. Overall survival for nonsquamous non-small cell lung cancer did not differ between the cisplatin plus pemetrexed and cisplatin plus vinorelbine arms ($p = 0.309$).

effects, ACT in NSCLC may also lead to significant late toxicity. A recent analysis of the International Adjuvant Lung Trial (IALT)[26] reported on a higher risk of non–cancer-related mortality after 5 years. Therefore, the correlation of dose limiting toxicity to survival as seen in our trial may also be related to less late toxicity; however, this correlation is still speculative, and the low number of patients and the short-follow-up period have to be taken into account. Moreover, even though our previous analysis clearly demonstrated that CPx lowers DLT and improves feasibility compared with CVb, the current analysis of efficacy end points has not revealed survival differences. Still, lowering acute toxicity may reduce delayed toxic treatment effects and thereby affect long-term survival and should therefore be explored in further trials.

An interesting finding in our results is the nonsignificant differences between local and distant relapses. Although the rate of local relapses was higher in the CPx arm, differences for distant relapse rates were absent. This result might be interpreted as reflecting the effects of the different treatment modalities. Hypothetically, local relapses might be influenced mainly by the efficacy of surgical therapy, whereas ACT should also be targeted toward eradicating micrometastases and thus reducing the rate of distant metastases. Therefore, one might argue that the nonsignificant differences seen in local relapse may be due to imbalances in surgical therapy in a trial of this size, which is emphasized by the high numbers of mediastinal lymph node relapse in the CPx arm. On the other hand, the recent analysis of the International Adjuvant Lung Trial speaks against this assumption because the trial's authors reported that ACT also reduced the risk of local relapse.[26] Thus, this finding is still unexplained and warrants further attention in future studies.

There are potential limitations of a phase II study and uncertainties regarding the degree to which they might account for the results. Interpretation of the efficacy results of our study must be placed in the context of the limitations inherent in a phase II study not powered to analyze survival implications, as well as the inclusion of a high proportion of patients with either stage IB tumors (38% total: 14% <4 cm and 24% >4 cm) or tumors with histologic findings of squamous cell carcinoma (43% squamous cell versus 57% nonsquamous cell). The correlative data on smaller tumor diameter and/or histologic findings of squamous cells[17,22] emerged when the trial was already more than half recruited. It was therefore decided to not amend the protocol—which may have jeopardized the trial—and instead continue to leave the inclusion of patients with stage IB or histologically diagnosed squamous cell carcinoma to the discretion of the trial centers. Although there is some evidence to suggest that these two factors may have a negative effect on survival outcomes, the data presented here in both cases are insufficient to provide a rationale for or against the use of ACT in such patients and must be interpreted in the context of the small sample size, the follow-up time of only 3 years, and other factors. Thus, only a prospective phase III trial with a long follow-up of at least 5 years might address these points sufficiently,

although whether so long a follow-up time is ever going to be in place is questionable.

The first study to establish the correlation between tumor diameter and survival advantage was the Cancer and Leukemia Group B study B-9633.[22] An unplanned subanalysis showed that patients with tumors larger than 4 cm had a significant survival advantage when treated with ACT (HR = 0.69, 95% CI: 0.48–0.99, p = 0.043). In a similar exploratory subgroup analysis from the JBR.10 trial, patients with tumors smaller than 4 cm demonstrated no significant advantage from ACT (HR = 1.73, 95% CI: 0.98–3.04, $p = 0.06$), whereas the patients with larger tumors experienced more potentially meaningful therapeutic benefits (HR = 0.66, 95% CI: 0.39–1.14, $p = 0.13$).[6] However, given that both of these analyses were post hoc analyses, their results must interpreted with caution and similarly should have been confirmed in a prospective setting. Other analyses also failed to provide conclusive results. In the Lung Adjuvant Cisplatin Evaluation study meta-analysis, stage IB disease showed only a trend toward an OS benefit (HR = 0.93, 95% CI: 0.78–1.10) compared with an HR of 0.83 for stages II through IIIA.[7] The subgroup analysis according to stage from the updated NSCLC meta-analysis revealed a consistent 5-year improvement in OS for stage IB through stage IIIA.[9] A pooled exploratory analysis performed on 538 eligible patients from the JBR.10 and CALG B-9633 trials also examined the effect of tumor size on survival benefit from adjuvant platinum-based chemotherapy. In this multivariable analysis, tumor size emerged as being prognostic for disease-free survival ($p = 0.003$) but having borderline prognostic value for OS ($p = 0.1$). A nonsignificant trend ($p = 0.24$) for increasing effect of chemotherapy on OS with advancing tumor size was also noted.[27]

Correlation of histologic finding of squamous cells with outcome of adjuvant therapy has been equally inconclusive. A differential efficacy of pemetrexed according to histologic findings was reported in a phase III trial by Scagliotti et al. in patients with advanced NSCLC in 2008.[17] In the early-stage NSCLC trials, however, no prospective trial or meta-analysis demonstrated any correlation between histologic diagnosis and outcomes. JBR.10 actually demonstrated an advantage for a histologic finding of squamous cells, and poor outcomes in adenocarcinoma were reported in the Adjuvant Navelbine International Trialist Association trial.[4,6,7,9,28,29] Similarly, tumor histology had no significant effect on chemotherapy outcomes in either the Lung Adjuvant Cisplatin Evaluation study's vinorelbine subgroub analysis[8] or in the NSCLC meta-analysis.[9]

Another limitation of our study was the brevity of its follow-up period, which was prespecified at the time of the trial's setup. We selected an analysis time point of 3 years rather than the customary 5 years or longer needed to establish OS data; hence, we can only report at 3 years follow-up. Mauguen et al.[30] recognized the limitations of using OS as the accepted standard end point in clinical trials of chemotherapy and radiotherapy for lung cancer. Although the end point is reliable and simple to measure, it takes years to observe in the nonmetastatic NSCLC setting. Surrogate end points that enable earlier assessment of treatment effects would be helpful. Their analysis of patient data from 60 randomized trials concluded that disease-free survival is a valid surrogate end point for OS and one that should be explored in studies of ACT in patients with NSCLC. As for the question of whether the time between surgery and initiation of ACT affects OS (because it does in colon and breast cancer), the current literature suggests this is not the case with ACT for NSCLC. In a multivariable analysis of 1032 patients, the interval between surgery and ACT was not associated with survival.[14]

Interest in finding more feasible regimens or schedules providing an alternative to CVb therapy continues to be high, and many research initiatives exist. This search is encouraged by the results of our phase II trial, which might be interpreted as evident that reduction or, even better, avoidance of DLT and improvement of feasibility by applying less toxic regimens might improve survival. A series of trials have focused on this direction. Carboplatin plus paclitaxel showed promising results in an exploratory analysis in patients with large tumors, although no benefit has been shown in the overall result of the stage IB trial.[31] Hirai et al. recently demonstrated that a split regimen of CVb is well tolerated for patients with resected NSCLC.[32] Further results of adjuvant CPx are expected from the International Tailored Adjuvant Chemotherapy trial (EudraCT#: 2008-001764-36) and the Eastern Cooperative Oncology Group E1505 (NCT00324805) trials. Despite a lack of level 1 data regarding the utility of CPx in an adjuvant setting, the National Comprehensive Cancer Network guidelines recommend it as an option for ACT for histologic diagnosis of nonsquamous NSCLC.[33] In addition to CVb and CPx, other regimens were included in the E1505 trial, which closed to accrual in September 2013. The regimens included cisplatin plus gemcitabine and cisplatin plus docetaxel, which are also named as options by the National Comprehensive Cancer Network. In interim data presented on E1505, all four options have been selected on a fairly equal basis for patients enrolled in the trial.[34]

In conclusion, we were able to demonstrate that ACT with CPx is safe and associated with less toxicity

than is CVb and that in this randomized phase II study, survival is influenced not by treatment arm but rather by DLT and feasibility. The interpretation of efficacy data in our study needs to be weighed against the limitations of a phase II trial, and one should be cautious in transferring these results to the clinical routine and, in particular, to patients with squamous carcinoma and patients with stage IB disease. It is important that we continue to investigate the effects of less toxic regimens because the survival benefit with current ACT is limited. Our challenge is to decrease toxicity and improve survival by integrating the new drugs established as being effective in metastatic disease into the adjuvant setting. The use of longer follow-up times or surrogate survival end points would provide a significant advance in trials of ACT and would provide more accurate insight as to whether less toxic regimens may have an impact on lower rates of long-term complications such as secondary cancers. Given the promising efficacy results shown for CPx in three trials in later-stage NSCLC tumors[17] and its demonstrated reduced toxicity profile in this trial, further study of the effects of this regimen on survival in early-stage NSCLC seems warranted.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2015.09.014.

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