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Non-small cell lung cancer recurrence following surgery and perioperative chemotherapy: Comparison of two chemotherapy regimens (IFCT-0702: A randomized phase 3 final results study)

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ABSTRACT

Introduction: This study compared the efficacy of docetaxel alone *vs.* docetaxel plus cisplatin/carboplatin in resected NSCLC patients relapsing after preoperative, adjuvant, or perioperative platinum-based chemotherapy.
Materials and methods: Patients were randomly assigned to receive docetaxel plus cisplatin/carboplatin (Arm A) or docetaxel alone (Arm B). Primary endpoint was progression-free survival (PFS). Secondary endpoints were response rate at 6 weeks, toxicity, quality of life, and overall survival (OS).
Results: From November 2007 to August 2012, 88 patients were enrolled. Due to an unexpectedly slow accrual, the trial was prematurely stopped. Adding platinum to docetaxel caused a non-significant increase in PFS. Median PFS was 8.0 months (95% CI: 5.3–10.4) for Arm A *vs.* 5.6 months (95% CI: 4.0–7.3) for Arm B (HR: 0.71, 95% CI: 0.45–1.1, $p = 0.15$). Median OS was 16.0 months (95% CI: 10.1–23.9) for Arm A *vs.* 12.4 months (95% CI: 8.2–19.6) for Arm B. In pre-planned subgroup analyses, a time to recurrence $\geq$12 months and non-squamous histology favorably influenced OS (HR: 0.51, 95% CI: 0.29–0.91, $p = 0.02$ and HR: 0.54, 95% CI: 0.33–0.91, $p = 0.02$, respectively). There were no unexpected adverse events, and Grade 3–4 toxicity was comparable in both groups.
Conclusions: Our study failed to demonstrate significant PFS improvement with the docetaxel-platinum doublet compared to single-agent docetaxel. The 3.6-month improvement in OS with the cisplatin-based doublet proves, however, appealing and merits further investigation.

1. Introduction

While surgery is indicated for early-stage disease, several trials conducted since 1995 have demonstrated the benefits of adjuvant chemotherapy in non-small cell lung cancer (NSCLC) [1–7],

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which has become the standard treatment for Stage II or III disease. Neoadjuvant chemotherapy has also been studied, with significant response rates [8–10], though only marginally improved survival. Meta-analyses have demonstrated the potential benefits of neoadjuvant chemotherapy, which is still prescribed primarily in Stage IIIA (N2) [3]. The adjuvant/neoadjuvant chemotherapy regimens demonstrating the best efficacy to toxicity ratio are platinum-based doublets.

Given that chemotherapy has gained wider acceptance for early-stage NSCLC, physicians are facing growing relapse incidence in good performance status (PS) patients. Most recurrences after perioperative chemotherapy–surgery are typically non-surgical: locally advanced relapses or metastatic diseases. Patients who eventually relapse are candidates for further systemic anticancer treatment. The advantage of second-line chemotherapy following an initial platinum-based regimen is largely debated. Some physicians advocate re-challenge with a platinum-based doublet, whereas others recommend standard second-line monotherapy [11–13].

Randomized studies comparing platinum-based doublets *vs.* single-agent chemotherapy in second-line chemotherapy for Stage IV NSCLC have reported improved response rates and progression free survival (PFS), yet not overall survival (OS) [14,15]. So far there have been no trials addressing the role of platinum agents for patients pretreated with chemotherapy–surgery.

This randomized Phase 3 trial sought to compare, in terms of PFS, docetaxel alone with a platinum-based docetaxel combination in NSCLC patients who relapsed following initial surgery–chemotherapy.

2. Materials and methods

2.1. Eligibility criteria

Inclusion criteria were: age ≥18 years and ≤75 years; Eastern Cooperative Oncology Group performance status (ECOG-PS) 0 to 1; NSCLC histologically or cytologically confirmed as inoperable and not eligible for curative radiotherapy; previous adjuvant/neoadjuvant chemotherapy consisting of at least two full cycles of a platinum-containing regimen, with a maximum cisplatin dose of 320 mg/m^2 and no fixed maximum carboplatin dose; pathological tumor-node-metastasis (pTNM) stage of pT1N0 to pT3N2 [16]. Patients exhibiting T4 tumors graded as N0-2 that had been completely resected could be included; following a 2009 protocol amendment, patients surgically treated for multiple nodules in the same lung (M1) could be enrolled as well. Patients exhibiting complete histological response (pT0N0) following neoadjuvant chemotherapy were eligible. Patients were to display at least one unidimensionally measurable lesion (RECIST 1.0 criteria) [17], with adequate hematological, hepatic, and renal function. Exclusion criteria were: prior neoadjuvant chemotherapy with progressive disease as best response; prior treatment with docetaxel, stable disease following neoadjuvant chemotherapy with no necrosis or tumor modification on pathological tumor specimen; relapse <6 months post-surgery. The protocol was approved by an institutional review board (CPP V Sud Est); the study was endorsed by the regulatory authorities and registered in the French Trial Registry (EudraCT number 2007-001997-97) and ClinicalTrials.gov Registry (NCT00535275).

2.2. Trial design and drug administration

Patients were randomly assigned (1:1) to two groups. One received docetaxel 75 mg/m^2 intravenously on Day 1 (21-day cycle), followed by either cisplatin 75 mg/m^2 or carboplatin area under concentration (AUC) 5 (based on the Calvert formula, if patient previously tretaed with cisplatin at >320 mg/m^2) on Day 1 (21-day cycle) (Arm A, the experimental arm). The control group received docetaxel 75 mg/m^2 alone (Arm B, the control arm). Treatment was repeated over four cycles, except for progressive disease, unacceptable toxicity, or patient refusal. Patients with stable disease or response were given two additional cycles of docetaxel alone (75 mg/m^2) in both arms. Patients were assigned *via* a centralized Web-based system (https://extranet.ifct.fr/) using the following stratification factors: center, time to recurrence (<12 months or ≥12 months), initial chemotherapy type (adjuvant or neoadjuvant), and initial chemotherapy (taxanes *vs.* others). For dose modification, see online Appendix. Tumor response was assessed every two cycles using systematic CT scan of thorax and upper abdomen and other tests, as well as at chemotherapy end or on occurrence of symptoms suggesting disease progression. Following treatment completion, patients were assessed every 6 weeks using CT scans. Regular data reviews were performed by a safety monitoring board.

2.3. Statistical considerations

Analyses were performed on an intent-to-treat basis. The study's primary endpoint was PFS, defined as the time from the randomization date to the date of disease progression or death from any cause. Secondary endpoints were: tumor response rate at 6 weeks (RECIST 1.0); toxicity using National Cancer Institute Common Toxicity Criteria (NCI CTC) (Version 3.0); quality of life (EORTC QLQ C30 LC13 module); OS defined as the time from the randomization date to the date of death from any cause. Living patients were censored on December 31, 2012. Overall 263 events were required to achieve 90% power, at a significance level of 5%, to detect an increased PFS from 3 months in the control arm to 4.5 months in the experimental arm, using two-sided log-rank test. Thus 300 patients (150 in each arm), enrolled over 36 months and observed for at least 12 months, would be required. Two interim analyses were scheduled at the 100 and 200 event markers, according to the O'Brien and Fleming method. Grade 3 and 4 adverse events were reported. Proportion comparisons were performed *via* the Chi-squared test for heterogeneity or Fisher's exact test.

PFS and OS were analyzed using the Cox proportional hazards regression model, presented as Kaplan–Meier estimates with hazard ratio (HR) and 95% confidence intervals (CI). Survival estimate differences between the two arms were assessed using two-sided log-rank test. Planned exploratory subgroup analyses of PFS and OS were conducted using stratification and predefined prognostic variables (*i.e.*, time to recurrence <12 months or ≥12 months after the end of the last treatment either surgery (patients treated with neoadjuvant chemotherapy and surgery) or chemotherapy (patients treated with perioperative or post operative chemotherapy)). All statistical tests were two-sided; p values of ≤0.05 were considered statistically significant.

3. Results

3.1. Patients

From November 2007 to August 2012, 88 patients were enrolled by 33 institutions and randomly assigned, with 44 patients to each arm (Fig. 1). All exhibited tumor recurrence not amenable to local radiotherapy or surgery. Due to slow accrual rates, the study was discontinued earlier than expected, with the final analysis conducted in January 2013. Primary patient characteristics were well-balanced between the two arms (Table 1). Time

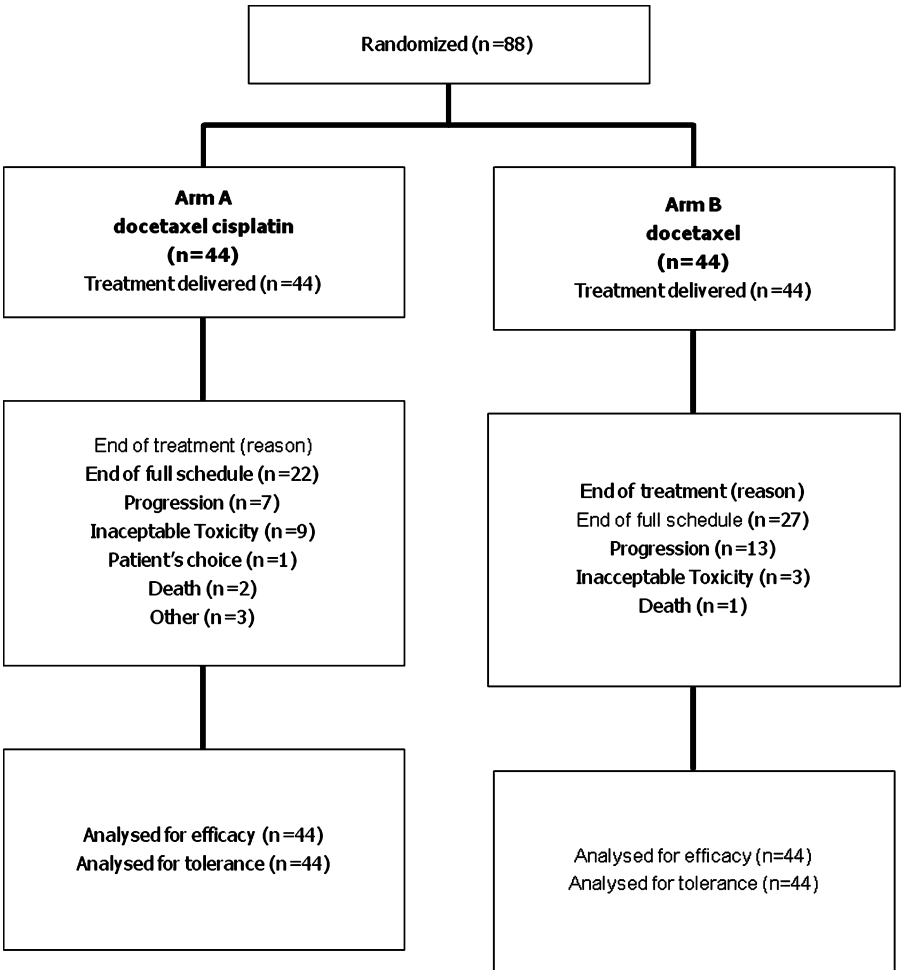

Fig. 1. CONSORT chart.

from the combined treatment (surgery preceded or followed by chemotherapy) end to tumor relapse was >12 months in 61/88 cases (69.3%).

3.2. Study treatment

The median treatment cycle number delivered was four (Table A, available online). Two patients underwent treatment with carboplatin in Cycle 1 and onwards, and a further four patients switched from cisplatin to carboplatin during the following chemotherapy cycles, according to protocol adaptation rules.

After four cycles, a comparable number of patients received Cycles 5 and 6. There were two protocol violations, with two patients receiving Cycle 5 with docetaxel and cisplatin and one Cycle 6 with docetaxel and cisplatin.

After progression 23 patients received post progression therapy in Arm A and 31 in Arm B (Table B available online). This difference was not statistically significant (p: 0.08).

3.3. Efficacy

Median follow-up was 34.3 months (range: 5.0–61.3). At final analysis, 68 patients had died: 32 in Arm A and 36 in Arm B ($p = 0.31$). Primary death cause was cancer progression (91.3% Arm A and 87% Arm B). A clinically non-significant increase in PFS with the combined chemotherapy regimen was observed, with an HR of 0.71 (HR: 0.71, 95% CI: 0.45–1.1, $p = 0.15$) and median PFS of 8.0 months in the experimental arm (95% CI: 5.3–10.4) *vs*. 5.6 months for the control arm (95% CI: 4.0–7.3) (Fig. 2).

The 6-week response rates have been compiled in Table 2. An increased objective response rate was observed in the platinum-based arm ($p < 0.0001$). The median OS was 12.6 months (95% CI: 10.9–18.8). By adding platinum to docetaxel, median OS improved achieving 16.0 months (95% CI: 10.1–23.9) in the experimental arm *vs.* 12.4 months (95% CI: 8.2–19.6) in the control arm. The HR for death was 0.87 (95% CI: 0.53–1.42; $p = 0.58$) (Fig. 3).

Pre-planned subset analysis (Tables C, D available online) revealed non-squamous histology to significantly influence PFS (HR: 0.56; 95% CI: 0.35–0.91, $p = 0.02$) and OS on multivariate analyses (HR: 0.54; 95% CI: 0.33–0.91, $p = 0.02$). Time to recurrence $\geq$12 months proved also influential on OS (HR: 0.51; 95% CI: 0.29–0.91, $p = 0.02$) but not on PFS.

3.4. Patient-reported assessments

Compliance rates with Patient-Reported Assessments for each treatment arm are presented in Table E (available online). High compliance rates were observed (65–100%) up to week 12 and were comparable across both treatment arms. Lower compliance rates were observed during the first follow-up visit (45–56%). At baseline, mean EORTC scores were generally low, ranging from 5

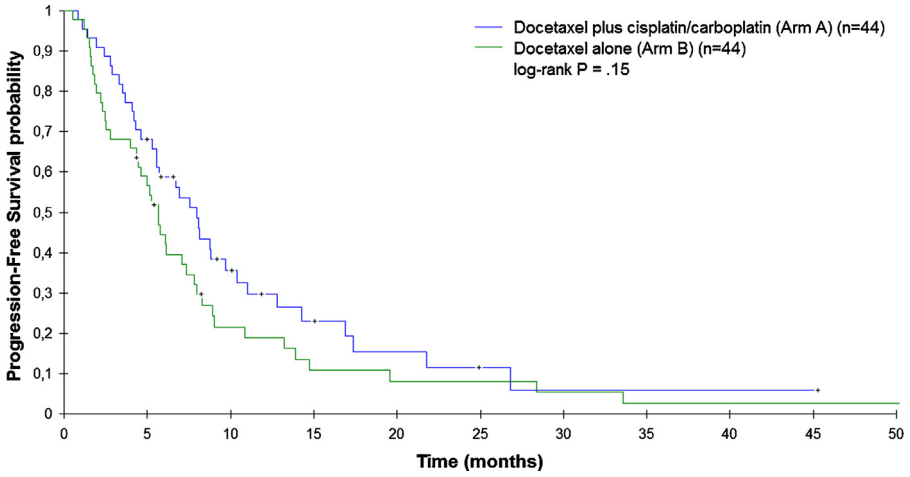

Fig. 2. Primary objective: progression-free survival.

to 44 (Table F available online), suggesting that patients had moderate symptom levels. This finding was consistent with good ECOG Performance Status at baseline.

Symptoms were comparably improved in the 2 arms (Figs. A–C available online). A significant benefit favoring patients treated in arm A was observed between baseline and the first treatment evaluation for the single item of physical functioning (24% *vs.* 0%, $p = 0.002$). A statistically non-significant improvement favoring patients treated in arm A was also observed for the following 2 items: emotional functioning (45% *vs.* 25%, $p = 0.07$) and functional scales (27% *vs.* 11%, $p = 0.09$). Overall, the quality of life scores demonstrated that no detrimental effect was observed in the patients treated with the docetaxel–platinum doublet.

Table 1
Patient demographics and clinical characteristics at study entry by treatment arm.

Characteristics	Arm A $n = 44$ (%)	Arm B $n = 44$ (%)	p-Value
Age, years			
Median (range)	61.9 (48–75)	61.7 (42–75)	0.63
Gender			
Male	36 (81)	32 (72)	0.31
Female	8 (19)	12 (28)	
ECOG PS			
0	24 (54.5)	19 (43.2)	0.40
1	20 (45.5)	24 (54.5)	
2	0 (0)	1 (2.3)	
Clinical stage at surgery			
IA	3 (6.8)	2 (4.55)	0.11
IB	15 (34.1)	10 (22.7)	
IIA	2 (4.5)	1 (2.27)	
IIB	3 (6.8)	9 (20.5)	
IIIA	13 (29.5)	13 (29.5)	
IIIB	7 (15.9)	3 (6.82)	
IV[a]	0 (0)	4 (9.09)	
Histology			
Squamous	13 (29.5)	16 (36.4)	0.50
Non squamous	31 (70.5)	28 (63.6)	
Type of initial CT			
Adjuvant	33 (75)	34 (77)	0.80
Neoadjuvant	11 (25)	10 (23)	
Type of medication			
Taxanes	4 (9)	4 (9)	1
Others	40 (91)	40 (91)	
Time to recurrence			
<12 months	11 (25)	16 (36)	0.62
≥12 months	33 (75)	28 (64)	

[a] Resection of multiple nodules in the same lung.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status.

3.5. Safety

No unexpected adverse events were reported, nor were there drug-related deaths. Grade 3 to 4 hematologic toxicities and relevant non-hematological adverse events have been listed in Table 3. Grade 3–4 gastrointestinal (GI) toxicity, neutropenia, and febrile neutropenia were more common in the combination arm, yet between-group differences were not significant. No increase in Grade 3 to 4 renal toxicity was observed in the combination arm.

4. Discussion

This was the first study to investigate platinum-based chemotherapy in NSCLC patients relapsing following front-line adjuvant/neoadjuvant platinum-doublet chemotherapy combined with surgery. Due to slow accrual rates, this study designed to recruit 300 patients was discontinued after enrolling 88 and is therefore underpowered. Newer trials that were more appealing to patients most likely competed with patient accrual to our study. Nevertheless, our study's founding scientific basis constitutes a real issue in standard patient care. No consensus currently exists that distinguishes between post-chemotherapy and post-surgery recurrence and genuine disease progression following chemotherapy for Stage IV NSCLC. Some trials consider

Table 2
Clinical outcome by treatment arm.

Outcome	Arm A (n (%))	Arm B (n (%))	p-Value
Best overall response			
CR	2 (4.55)	0 (0)	<0.0001
PR	22 (50)	6 (13.6)	
SD	8 (18.2)	23 (52.3)	
PD	2 (4.55)	4 (9.09)	
NE	10 (22.7)	11 (25)	
PFS			
No. of events	35	40	0.15
Median (months)	8.0	5.6	
95% CI	5.3–10.4	4.0–7.3	
OS			
No. of events	31	34	0.58
Median (months)	16.0	12.4	
95% CI	10.1–23.9	8.2–19.6	

CR, complete response; NE, non evaluable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; PFS, progression-free survival.

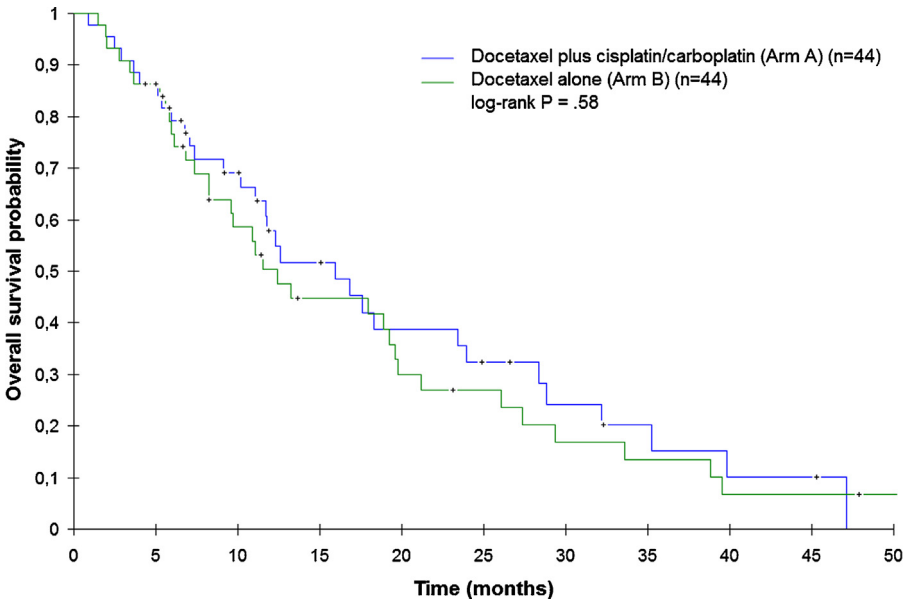

Fig. 3. Secondary objective: overall survival.

these patients as chemotherapy-naïve, treating them with standard first-line platinum-based doublet chemotherapy, while others categorize them as pretreated, administering single-agent therapies.

Several differences exist between post-surgical recurrence and recurrence after standard first-line chemotherapy. The former patients generally exhibit good health (PS 0–1), with disease progression mainly diagnosed in post-surgical follow-up. The chemotherapy dose is lower than that used in first-line treatment for Stage III/IV. The time from first-line treatment to recurrence treatment is typically longer. Most of our relapses occurred after 1 year. In fact, our protocol excluded relapses occurring within the first 6 months post-surgery.

This group's survival characteristics were surprisingly positive, with PFS and OS falling in the range of what is typically reported in chemotherapy-naïve Stage IV. Both arms' outcomes were comparable to a select patient population eligible for bevacizumab administration [18–20] or maintenance chemotherapy [21–23]. Our population could have been subject to bias by selective inclusion criteria. This could account for 24% of patients previously treated with neoadjuvant chemotherapy being responsive or stable at the time of surgery, thereby representing a chemosensitive patient population with good prognosis. This may partially account for our relatively good survival results compared to those observed in maintenance studies with only stable and responding patients included. In our study, the longest survival was noted in patients with recurrence occurring ≥1 year following combined surgery–chemotherapy. We believe that these survival characteristics advocate for a more favorable disease.

Although our patient response rate was significantly improved with the platinum doublet, there was no significant reduction in progression hazard, as compared to that achieved with docetaxel alone. There was also a trend for improved survival with the platinum doublet, which was not statistically significant. Reduced statistical power owing to insufficient accrual could account for this non-significant finding. More over a slight imbalance, however not statistically significant, in post progression therapies with more patients treated in the single-agent docetaxel arm may have favored overall survival results in this arm and thus explains up to a certain extent the lack of survival difference. The

Table 3
Most clinically relevant grade 3 to 4 adverse events as classified by National Cancer Institute Common Toxicity Criteria (NCI CTC) Version 3.0.

Clinically significant toxicity	Arm A doublet $n = 44$ (%)	Arm B monotherapy $n = 44$ (%)	Total	p-Value
Anemia	4 (9.09)	0 (0)	4 (4.55)	0.12
Leukopenia	1 (2.27)	2 (4.55)	3 (3.41)	1
Neutropenia	32 (72.7)	26 (59.09)	58 (65.9)	0.26
Febrile neutropenia	8 (18.18)	3 (6.82)	11 (12.5)	0.2
Nausea	3 (6.82)	0 (0)	3 (3.41)	0.24
Vomiting	3 (6.82)	0 (0)	3 (3.41)	0.24
Diarrhea	4 (9.09)	0 (0)	4 (4.55)	0.12
Constipation	1 (2.27)	0 (0)	1 (1.14)	1
Asthenia	4 (9.09)	1 (2.27)	5 (5.68)	0.36
Hypersensitivity	0 (0)	1 (2.27)	1 (1.14)	1
Dehydration	1 (2.27)	0 (0)	1 (1.14)	1
Myalgia	1 (2.27)	0 (0)	1 (1.14)	1
Paresthesia	2 (4.55)	0 (0)	2 (2.27)	0.49
Hyponatremia	1 (2.27)	0 (0)	1 (1.14)	1
Increased gamma glutamyltransferase	0 (0)	1 (2.27)	1 (1.14)	1
Mouth irritation	1 (2.27)	0 (0)	1 (1.14)	1
Nail disorder	0 (0)	1 (2.27)	1 (1.14)	1
Pneumonia	1 (2.27)	0 (0)	1 (1.14)	1
Renal toxicity	0 (0)	0 (0)	0 (0)	–

tolerability profiles of both docetaxel and the docetaxel–platinum doublet were similar to those previously observed. Grade 3/4 toxicities were more common in the doublet arm, the difference being not statistically significant, and there were trends for increased GI toxicity, neutropenia, and febrile neutropenia in the combination arm. Reintroducing cisplatin did not increase Grade 3–4 renal toxicity. It should be emphasized that no detrimental effect on the patient-reported assessments was observed in the doublet arm.

While platinum-doublets have been the backbone of first-line regimens for over 10 years [24], they have failed to improve OS in the second-line setting, despite improving PFS and response rate [14,15]. In a 2009 meta-analysis [25], doublet chemotherapy was compared to single-agent therapy as second-line treatment of advanced NSCLC, with significantly improved response rate and PFS, yet not OS, and all at the cost of increased toxicity.

Our survival results were comparable to those of a very favorable subgroup of first-line patients. In sharp contrast, despite an improved response rate, adding platinum to docetaxel produced no significant effect on either PFS or OS. The only trend observed was a longer PFS and OS in the combined arm. All in all, concerning chemotherapy, this patient population behaved like a typical population of first line patients. We strongly believe that the trend we have observed merits further investigation. Although the choice of chemotherapy and number of agents remain to be determined, we would recommend considering platinum doublets in patients relapsing ≥1 year following initial surgery–chemotherapy.

We must also address the issue of correctly defining to which chemotherapy line we are referring. In clinical trials, these patients are often included into the same category as metastatic patients. Yet based on our data, their surprisingly good prognosis could induce a bias in so-called second-line trials. Based on our data, patients with tumor recurrence >1 year after perioperative treatment could exhibit similar or better survival than Stage IV patients who have not previously been operated on. In our opinion, these patients should be included in first-line rather than second-line trials.

Further investigation must thus be conducted into this patient category. Considering survival data, these patients rather behave like first-line patients, and we suggest that they could be treated as such with a platinum-based doublet or should at least be eligible for new first-line trials.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2015.05.016

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