Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial

Jean-Yves Douillard, Rafael Rosell, Mario De Lena, Francesco Carpagnano, Rodryg Ramlau, Jose Luis Gonzáles-Larriba, Tomasz Grodzki, Jose Rodrigues Pereira, Alain Le Groumellec, Vito Lorusso, Claude Clary, Antonio J Torres, Jabrail Dahabreh, Pierre-Jean Souquet, Julio Astudillo, Pierre Fournel, Angel Artal-Cortes, Jacek Jassem, Leona Koubkova, Patricia His, Marcello Riggi, Patrick Hurteloup

Summary

Background **Whether adjuvant chemotherapy improves survival of patients with non-small-cell lung cancer (NSCLC) is not known. We aimed to compare the effect of adjuvant vinorelbine plus cisplatin versus observation on survival in patients with completely resected NSCLC.**

Methods **840 patients with stage IB–IIIA NSCLC from 101 centres in 14 countries were randomly assigned to observation (n=433) or to 30 mg/m^2 vinorelbine plus 100 mg/m^2 cisplatin (n=407). Postoperative radiotherapy was not mandatory and was undertaken according to every centre's policy. The primary endpoint was overall survival. Analysis was by intention to treat. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN95053737.**

Findings **367 patients in the chemotherapy group and 431 in the control group received their assigned treatment. 301 (36%) patients had stage IB disease, 203 (24%) had stage II disease, and 325 (39%) had stage IIIA disease. Tolerance to chemotherapy mainly included neutropenia in 335 (92%) patients and febrile neutropenia in 34 (9%); seven (2%) toxic deaths were also recorded. Compliance was greater with cisplatin than with vinorelbine (median dose intensity 89% [range 17–108] *vs* 59% [17–100]). After a median follow-up of 76 months (range 43–116), median survival was 65·7 months (95% CI 47·9–88·5) in the chemotherapy group and 43·7 (35·7–52·3) months in the observation group. Adjusted risk for death was significantly reduced in patients assigned chemotherapy compared with controls (hazard ratio 0·80 [95% CI 0·66–0·96]; p=0·017). Overall survival at 5 years with chemotherapy improved by 8·6%, which was maintained at 7 years (8·4%).**

Interpretation **Adjuvant vinorelbine plus cisplatin extends survival in patients with completely resected NSCLC, better defining indication of adjuvant chemotherapy.**

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Centre René Gauducheau, Nantes, France (Prof J-Y Douillard MD); **Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain** (Prof R Rosell MD); **IRCCS Oncologico, Bari, Italy** (M De Lena MD); **Ospedale San Paolo, Bari, Italy** (F Carpagnano MD); **Chorob Pluc I Gruzlicy, Poznan, Poland** (R Ramlau MD); **Hospital San Carlos, Madrid, Spain** (J L Gonzáles-Larriba MD); **Regional Hospital for Lung Disease, Thoracic Surgery, Szczecin, Poland** (T Grodzki MD); **Instituto do Cancer Arnaldo Vieira de Carvalho, Sao Paulo, Brazil** (J R Pereira MD); **Centre Hospitalier P Chubert, Vannes, France** (A Le Groumellec MD); **Ospedale "A Cardarelli", Naples, Italy** (Prof V Lorusso MD); **Centre Hospitalier Regional Pasteur, Nice, France** (C Clary MD); **Hospital San Carlos, Madrid, Spain** (A J Torres MD); **Sismanoglio General Hospital, Athens, Greece** (J Dahabreh MD); **Centre Hospitalier Lyon Sud, Pierre-Benite, France** (P-J Souquet MD); **Hospital Germans Trias i Pujol, Badalona, Spain** (J Astudillo MD); **Hôpital Nord, Saint-Etienne, France** (P Fournel MD); **Hospital Miguel Servet, Zaragoza, Spain** (A Artal-Cortes MD); **Academy of Medicine, Gdansk, Poland** (Prof J Jassem MD); **Nem Kladno, Kladno, Czech Republic** (L Koubkova MD); **Institut de Recherche Pierre Fabre, Paris, France** (P His, M Riggi MD, P Hurteloup MD)

Introduction

The International Agency for Research on Cancer reported 1·2 million cases of lung cancer worldwide in 2000, with 1·1 million deaths.[1] Despite surgery, about 40% of patients with stage I non-small-cell lung cancer (NSCLC), 60% of patients with stage II disease, and 75% of patients with stage IIIA disease die within 5 years.[2,3] In 1995, a meta-analysis[4] showed a non-significant 5% survival advantage at 5 years with cisplatin-based adjuvant chemotherapy in resected NSCLC compared with surgery alone. This finding prompted the planning of additional randomised trials.[5] The International Adjuvant Lung Trial (IALT)[6] showed a significant 4% benefit at 5 years for cisplatin-based chemotherapy in combination with various agents after curative surgery in stage I–III NSCLC. The Adjuvant Lung Cancer Project Italy (ALPI)[7] did not find a survival benefit for chemotherapy, although the study used a toxic regimen. Subset analysis by stage showed that the hazard ratio of death was 0·80 (95% CI 0·60–1·06) for stage II versus 0·97 (0·71–1·33) and 1·06 (0·82–1·38) for stages I and III, respectively. The Cancer and Leukemia Group B (CALGB) 9633 study[8] reported a 12% reduction in mortality at 4 years with adjuvant carboplatin plus paclitaxel in stage IB NSCLC, and an update[8] with extended follow-up (54 *vs* 34 months) showed that improvement in survival was no longer significant. The National Cancer Institute of Canada JBR.10 trial[9] showed a 15% improvement in overall survival for stage IB–II NSCLC treated with vinorelbine plus cisplatin. The subset analysis by stage showed a greater benefit at 5 years for stage II (20%) than for stage I (7%); at 6 years, the benefit for stage I disappeared, and survival was greater in the control group. In 1994, the Adjuvant Navelbine International Trialist Association (ANITA) initiated a randomised phase III trial in patients with completely resected stage IB, II, and IIIA NSCLC, to assess the survival benefit of adjuvant vinorelbine plus cisplatin versus control.

Methods

Patients

This open-label study was done in 101 centres in 14 countries. It was approved by the ethics committee of

Correspondence to:
Dr Jean-Yves Douillard,
Department of Medical Oncology,
Centre René Gauducheau,
University of Nantes,
44805 St Herblain, Nantes, France
jy-douillard@nantes.fnclcc.fr

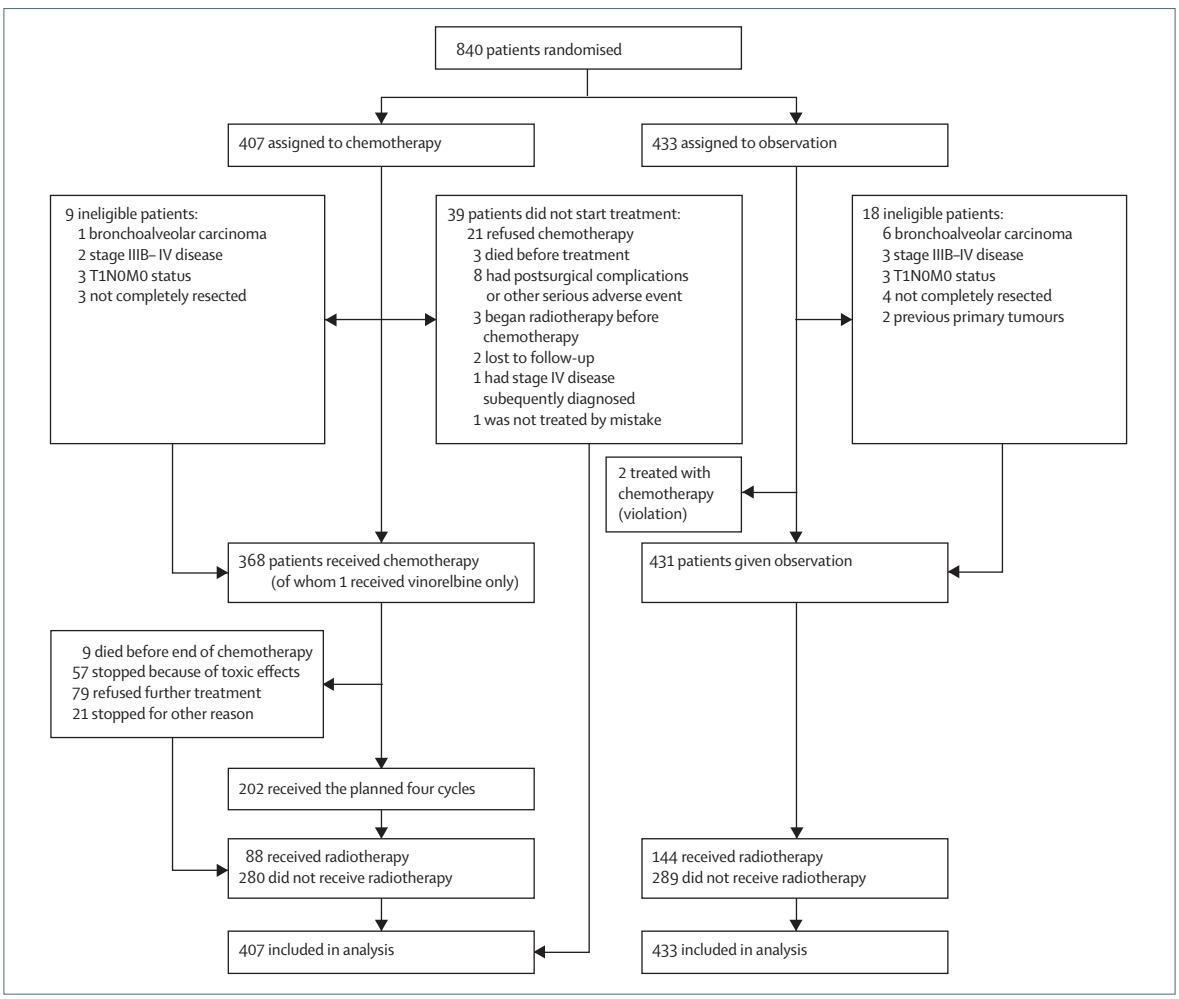

Figure 1: **ANITA trial profile**
Chemotherapy refers to four cycles of intravenous vinorelbine and cisplatin.

every centre and undertaken according to the Declaration of Helsinki. Written informed consent was obtained for all patients. Eligibility criteria included: histologically proven primary NSCLC (apart from bronchoalveolar carcinoma) after examination of the resected tumour by institution pathologist, and pathological TNM (tumour, node, metastasis) staging. Patients were eligible if they had stage I (T2N0 only), stage II, and stage IIIA NSCLC according to the 1986 TNM classification; complete resection of the primary tumour (all margins free of disease: R0); age 18–75 years; WHO performance status 2 or less; and adequate biological functions. Patients with a history of concurrent malignant disease (apart from adequately treated non-melanoma skin cancer or in-situ cervical cancer) or other previous primary tumours were excluded.

Procedures

Patients stratified by centre, stage, and histology (squamous *vs* other) were randomly assigned to vinorelbine plus cisplatin or to observation (control). Patients in the chemotherapy group received 30 mg/m^2 vinorelbine (Navelbine®; Pierre Fabre Médicament Production, Pau, France) on days 1, 8, 15, and 22 (cycles repeated every 4 weeks) for a maximum of 16 doses; and 100 mg/m^2 cisplatin on days 1, 29, 57, and 85 (Cisplatyl commercially available from SANOFI Paris, France). Patients in both groups received the same assessments with respect to clinical examination, haematological analysis, and tumour investigation.

Postoperative radiotherapy was not mandatory or randomised in the ANITA trial. The procedure was optional, was left to the decision of every participating centre, and was to be decided before patients were included into the trial. Radiotherapy was eventually recommended for patients with node-positive disease, at doses ranging from 45 to 60 Gy, 2 Gy per fraction, five fractions a week, which was to be started 2 weeks after the end of chemotherapy or within 2 weeks after randomisation in the control group.

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Patients were registered and randomised by the Biometric Department of the Institut de Recherche Pierre Fabre (IRPF, Paris, France), which was also responsible for the statistical analysis. Treatment was allocated through listings issued from computer by blocks of four patients and then faxed to the centre, not masked. Eligibility criteria were checked directly on the registration form faxed by the investigator to IRPF within 42 days of surgery.

Patients were followed up every 3 months during the first 2 years, and then every 6 months until death. Investigators assessed local or distant relapse clinically or with conventional imaging consisting of chest radiographs, abdominal ultrasonography, bone scans, CT scans, and MRI. Second primary lung cancer was not regarded as a relapse. Local relapse was defined as ipsilateral mediastinal relapse, and all other relapses were regarded as distant relapses, including those in the contralateral mediastinum or in other organs.

All study centres were monitored. During visits, study procedures, protocol compliance, and informed consent procedures were reviewed. An independent data monitoring committee was appointed.

The primary endpoint was to compare overall survival in the two groups. Secondary endpoints were disease-free survival and safety. Overall survival was defined as the time elapsed from the date of randomisation to death from any cause or to last follow-up. Patients who were alive at the cutoff date or lost to follow-up were censored at the date of last contact. We defined disease-free survival as the time elapsed from the date of randomisation to relapse or to death from any cause. Patients without relapse at cutoff were censored at the date of last contact. Maximum WHO grade (or severity) was reported by cycle and by patient for haematological and non-haematological toxic effects.

Statistical analysis

By assuming a 2-year survival of 30% in the control group, an absolute improvement of 10% indicating a benefit of adjuvant chemotherapy, a power of 90%, and a one-sided type I error of 5%, we calculated that 466 deaths were needed by using a 1:1 randomisation procedure and a log-rank test to compare the groups. With these assumptions, an accrual period of 2 years, 1 additional year of follow-up, and the accommodation for an anticipated 10% loss to follow-up, the planned sample size for the study was 400 patients per treatment group.

Time-dependent variables were described by Kaplan-Meier curves and life tables by treatment group. Overall survival and disease-free survival were compared by a stratified log-rank test. We did a multivariate analysis to identify the prognostic factors for overall survival. All variables reaching a significant level of 10% in univariate analyses were tested in a Cox proportional hazards model. Subgroup analyses were not planned; however, exploratory analyses were undertaken to generate hypotheses.

We did an interim analysis of safety at 6 months, at 12 months, and when 600 patients had been enrolled, to allow study termination if treatment tolerability was unacceptable (ie, toxic deaths exceeding 5%). At the time of these analyses, the stopping rules were not activated, allowing completion of the recruitment. All analyses were done in the intention-to-treat population. Data were analysed with SAS system software (version 8.2 for Windows). This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN95053737.

	Chemotherapy (n=407)	Observation (n=433)
Age (years)		
Median (range)	59 (32–75)	59 (18–75)
<55 years	134 (33%)	152 (35%)
≥55 years	273 (67%)	281 (65%)
Sex		
Male	346 (85%)	375 (87%)
Female	59 (14%)	56 (13%)
Missing	2 (<1%)	2 (<1%)
Time from surgery to randomisation (days)		
Median (range)	34 (6–54)	33 (7–52)
Type of surgery		
Pneumonectomy	155 (38%)	155 (36%)
Lobectomy	233 (57%)	253 (58%)
Other	16 (4%)	23 (5%)
Missing	3 (1%)	2 (<1%)
Postoperative stage		
I	146 (36%)	155 (36%)
II	89 (22%)	114 (26%)
IIIA	166 (41%)	159 (37%)
IIIB–IV	2 (<1%)	2 (<1%)
Missing	4 (1%)	3 (1%)
Lymph nodal status		
N0	179 (44%)	188 (43%)
N1	107 (26%)	136 (31%)
N2	118 (29%)	106 (24%)
Missing	3 (1%)	3 (1%)
Histology		
Squamous-cell carcinoma	240 (59%)	253 (58%)
Non squamous-cell carcinoma	163 (40%)	175 (41%)
Mixed squamous and non-squamous	1 (<1%)	3 (1%)
Missing	3 (1%)	2 (<1%)
WHO performance status		
0	196 (48%)	225 (52%)
1	192 (47%)	189 (44%)
2	14 (3%)	14 (3%)
Missing	5 (1%)	5 (1%)

Data are number of patients (%) unless stated otherwise.

Table 1: **Patient demographic and baseline characteristics**

Role of the funding source

The sponsor of the study participated in the data collection, data analysis, and patient monitoring, while the executive steering committee (J-YD, MDL, and RR)

	Vinorelbine (n=407)	Cisplatin (n=407)
Patients never treated	39	40
Patients who completed cycles (% of treated patients)		
Cycle 1	368 (90%)	367 (90%)
Cycle 2	296 (73%)	295 (72%)
Cycle 3	248 (61%)	247 (61%)
Cycle 4	202 (50%)	201 (49%)
Planned dose (mg/m^2)	480	400
Cumulative dose (mg/m^2)	270 (20–515)	304 (50–418)
Dose intensity (mg/m^2 per week)	18 (5–30)	22 (4–27)
Relative dose intensity (%)	59% (17–100)	89% (17–108)
Number of doses	10 (1–17)	4 (1–4)

Data are number of patients (%) or median (range) unless stated otherwise.

Table 2: **Chemotherapy compliance**

handled all questions regarding the management of the study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From December, 1994, to December, 2000, 840 patients were enrolled in the trial: 407 were assigned to chemotherapy and 433 to observation (figure 1). On Aug 1, 2004, median potential follow-up was 76 months (range 43–113) in the chemotherapy group and 77 months (43–116) in the observation group.

Table 1 shows the patients' characteristics. Overall, 486 (58%) patients had a lobectomy and 310 (37%) a pneumonectomy; 325 (39%) had postoperative stage IIIA disease, 203 (24%) had stage II disease, and 301 (36%) had stage I (T2N0) disease. Biological variables, medical and surgical history, tobacco and alcohol consumption, and clinical characteristics at baseline did not differ between the two groups.

In the chemotherapy group, 368 (90%) patients received vinorelbine and 367 concurrently received cisplatin (figure 1). Of these patients, 141 (38%) patients received more than 66% of the total planned dose of vinorelbine and 233 (63%) received more than 66% of the total planned dose of cisplatin; 202 (50%) patients completed the planned four cycles (table 2). Compliance to chemotherapy showed no difference according to type of surgery. Fewer patients undergoing pneumonectomy received more than 66% of the planned chemotherapy doses than those undergoing lobectomy (49 [35%] *vs* 85 [40%] for vinorelbine, p=0·35; 83 [59%] *vs* 142 [67%] for cisplatin, p=0·16).

The most frequent haematological grade 3–4 toxic effects in the chemotherapy group were neutropenia, anaemia, and febrile neutropenia. Other common non-haematological toxic effects included asthenia, nausea or vomiting, anorexia, and infection (table 3). Overall, 458 patients died during the study or during follow-up to the cutoff date (206 chemotherapy, 252 observation). 36 of these patients died within 20 weeks after randomisation: 16 in the chemotherapy group, including seven (2%) treatment-related deaths; and 20 deaths in the observation group. Treatment-related fatal toxic effects included four patients with septic shock, one with pneumonia, one with cardiac arrest, and one with renal failure in the chemotherapy group, compared with one with pneumonia, two with cardiac failure, and one with lethal haemoptysis in the observation group.

At the time of analysis (Aug 1, 2004), 201 (49%) patients in the chemotherapy group and 181 (42%) in the observation group were still alive. Median survival was 65·7 months (95% CI 47·9–88·5) for patients assigned chemotherapy and 43·7 months (35·7–52·3) for controls (hazard ratio 0·80 [0·66–0·96], p=0·017; figure 2A). The absolute overall survival benefit for patients assigned chemotherapy compared with controls was 2·8% at

	Chemotherapy		Observation	
	WHO grade >0	WHO grade 3–4	WHO grade >0	WHO grade 3–4
Neutropenia	335 (92%)	308 (85%)	13 (4%)	1 (<1%)
Anaemia	283 (78%)	50 (14%)	23 (6%)	0
Thrombocytopenia	52 (14%)	11 (3%)	2 (1%)	0
Febrile neutropenia	34 (9%)	34 (9%)	0	0
Infection	110 (32%)	39 (11%)	39 (10%)	6 (2%)
Nausea or vomiting	278 (80%)	95 (27%)	25 (7%)	1 (<1%)
Diarrhoea	54 (16%)	8 (2%)	8 (2%)	1 (<1%)
Constipation	156 (45%)	17 (5%)	18 (5%)	1 (<1%)
Anorexia	247 (71%)	52 (15%)	66 (17%)	6 (2%)
Asthenia	286 (82%)	97 (28%)	121 (32%)	10 (3%)
Peripheral neuropathy	99 (28%)	11 (3%)	4 (1%)	0
Alopecia	200 (57%)	18 (5%)	0	0

Data are number of patients (%). n/a=not applicable.

Table 3: **Worst WHO grade by patient**

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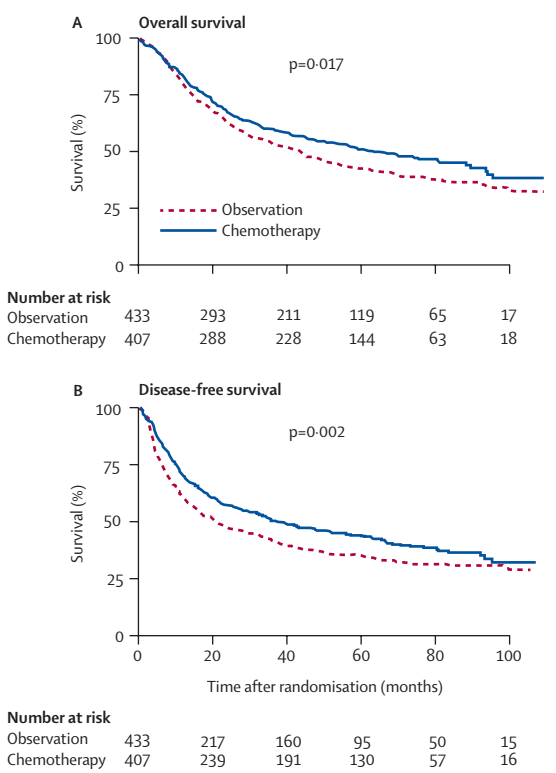

Figure 2: **Disease-free survival and overall survival**

	Univariate		Multivariate (backward)	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age				
≥55 years *vs* <55 years	0·82 (0·67–1·00)	0·05	0·76 (0·63–0·94)	<0·001
Sex*				
Male *vs* female	0·86 (0·65–1·15)	0·3	..	..
WHO performance status†				
0 *vs* 0–2	1·26 (1·05–1·51)	0·02	..	0·2
Type of surgery†				
Pneumonectomy *vs* other	0·73 (0·60–0·88)	<0·001	..	0·1
Radiotherapy†				
No *vs* yes	1·34 (1·10–1·63)	0·003	..	0·7
Tumour stage				
IIIA *vs* I–II	0·54 (0·45–0·65)	<0·001	0·64 (0·52–0·78)	<0·001
Lymph nodal status				
≥N1 *vs* N0	0·53 (0·44–0·64)	<0·001	0·61 (0·49–0·75)	<0·001
Histological type*				
Squamous *vs* non-squamous	1·04 (0·86–1·25)	0·7	..	..

Table 4: **Cox analyses of potential prognostic factors on survival**

	Variable estimate	Wald χ2	p χ2	Hazard ratio (95% CI)
Treatment group				
Chemotherapy *vs* observation	–0·279	8·605	0·003	0·76 (0·63–0·91)
Age				
<55 years *vs* ≥55 years	–0·273	7·090	0·008	0·76 (0·62–0·93)
Disease stage				
I–II *vs* IIIA	–0·467	21·09	<0·0001	0·63 (0·51–0·77)
Nodal status				
N0 *vs* N>0	–0·515	22·98	<0·001	0·60 (0·48–0·74)

Table 5: **Cox analysis of prognostic factors on survival, with addition of treatment group**

1 year, 4·7% at 2 years, 8·6% at 5 years, and 8·4% at 7 years. In the univariate analysis, we identified age younger than 55 years, performance status 0, type of surgery, no radiotherapy, tumour stage I and II, and no lymph node involvement as significant predictors of survival (table 4). When these variables were included in the Cox proportional hazard model with the addition of treatment group, we found treatment group, age, tumour stage, and lymph node status to have significant hazard ratios (table 5).

In the chemotherapy group, 186 (46%) patients had disease progression and 55 (14%) died without progression; corresponding numbers for the observation group were 252 (58%) and 34 (8%), respectively. Median disease-free survival was 36·3 months (95% CI 28·0–52·1) in the chemotherapy group and 20·7 months (16·1–28·6) in the observation group (hazard ratio 0·76 [95% CI 0·64–0·91], p=0·002; figure 2B). The absolute benefit of chemotherapy on disease-free survival was 9% at 6 months, 9·5% at 1 year, 9·6% at 2 years, 8·7% at 5 years, and 5·5% at 7 years.

Relapse was lower in the chemotherapy group than in the observation group (local relapse, 49 [12%] patients *vs* 76 [18%] patients, p=0·025; distant relapse, 101 [25%] *vs* 122 [28%], p=0·27). In both groups, the lung was the most common site of relapse (chemotherapy, 91 [22%] *vs* control, 123 [28%]; p=0·004). Bone metastasis were almost three times lower in patients assigned chemotherapy than in those assigned observation (15 [4%] *vs* 46 [11%]; p=0·0001), whereas brain metastases were more frequent in the chemotherapy group than in the observation group (53 [13%] *vs* 43 [10%]; p=0·16); the brain was the only metastatic site in 38 (9%) patients assigned chemotherapy and in 34 (8%) assigned observation.

In patients with stage IB disease (T2N0), 5-year survival was 62% (95% CI 54–70) in the chemotherapy group and 64% (56–71) in the control group (hazard ratio 1·10 [0·76–1·57]). Corresponding values were 52% (41–63) and 39% (30–49) for patients with stage II disease (0·71 [0·49–1·03]), and 42% (34–50) and 26% (18–33) for those with stage IIIA disease (0·69 [0·53–0·90]). These results did not allow a definite conclusion, because the test of interaction between tumour stage and chemotherapy on survival was not significant (p=0·07).

The test of interaction on survival detected a heterogeneous effect of chemotherapy according to nodal status (p=0·004), but did not warrant conclusion because

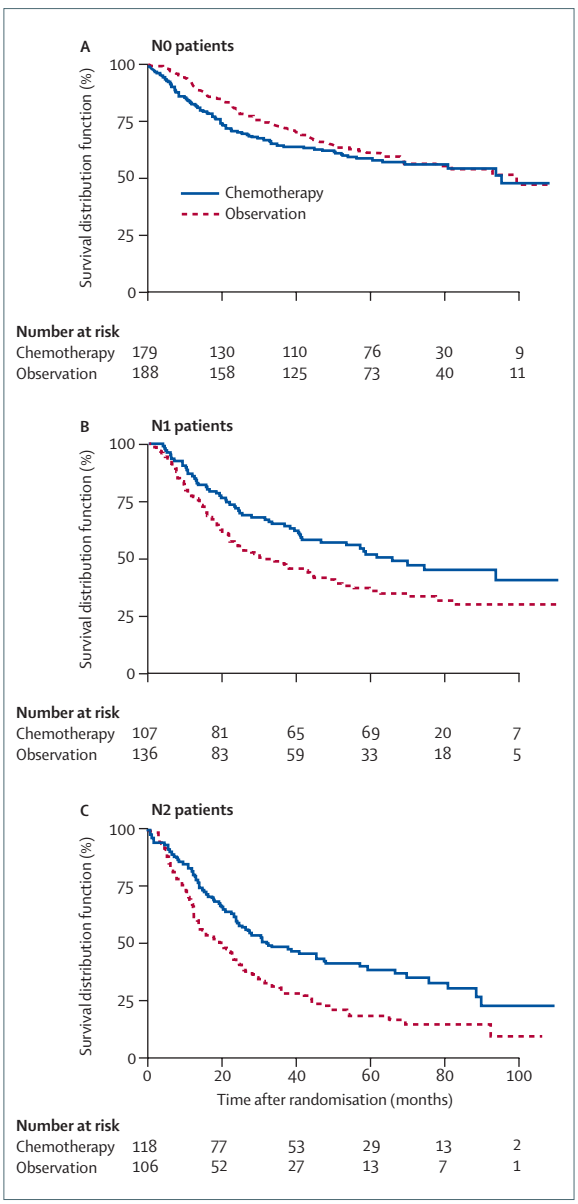

Figure 3: **Survival according to lymph node status**

the number of patients was too low in each subgroup. For patients with N0 status, 5 year-survival was 58% (95% CI 51–66) in the chemotherapy group and 61% (53–68) in the observation group (hazard ratio 1·14, [0·83–1·57]). However, corresponding values for 5 year-survival were 52% (42–62) versus 36% (28–45) for patients with N1 status (0·67 [0·47–0·94]), and 40% (30–49) versus 19% (11–27) for patients with N2 status (0·60 [0·44–0·82]; figure 3).

Overall, postoperative radiotherapy was delivered to 232 (28%) patients (>N0). More patients in the observation group than in the chemotherapy group received postoperative radiotherapy (144 [33%] *vs* 88 [22%], p=0·0002). Of patients receiving radiotherapy, 116 (50%) had N2 status, whereas only 31 (13%) had N0 status. In 243 (29%) patients with N1 status, 5 year-survival was improved in patients assigned chemotherapy who did not have radiotherapy, whereas individuals in the observation group who received radiotherapy had improved survival at 5 years (table 6). Conversely, radiotherapy improved 5-year survival in patients with N2 status from both groups (table 6). No association was detected between chemotherapy and postoperative radiotherapy (p=0·5).

Discussion

In this trial, we showed that the combination of vinorelbine and cisplatin significantly improved overall survival in patients with stages IB–IIIA NSCLC. However, our subgroup analysis indicated that the benefit is seen mainly in patients with stage II and IIIA disease.

Analysis took place after 458 patients had died instead of the planned 466; the steering committee allowed the analysis at this point, judging that the difference of eight deaths would not affect the results. Because of simulation with 466 deaths, a significant improvement in survival was still recorded with chemotherapy. Survival was much higher than originally anticipated (trial design took place before publication of the meta-analysis),[4] because we initially expected a larger proportion of patients with stage IIIA disease on the basis of data available at this time.[10]

Median age of patients in ANITA also did not differ from other trials, including JBR.10,[9] CALGB 9633,[8] and the LACE (Lung Adjuvant Cisplatin Evaluation) meta-analysis.[11] We included more male patients than female patients and more squamous-cell carcinomas in our trial than in US trials,[8,9] indicating differences in tobacco smoking; but histology was not a prognostic factor in univariate or multivariate analyses.

Furthermore, the frequency of adverse events in the chemotherapy group were similar to those already reported in trials with vinorelbine in the adjuvant setting.[9] Although this regimen was feasible, 2% of patients died from toxic effects, which is higher than that reported in other adjuvant trials (none in CALGB 9633,[8] two [0·8%] in JBR.10,[9] and seven [0·8%] in IALT[6]). This toxicity could have been due to the high doses of cisplatin and vinorelbine, and these doses might need to be altered to a less toxic regimen of 50 mg/m^2 cisplatin on days 1 and 8 and 25 mg/m^2 vinorelbine per week (as in the JBR.10 trial),[9] or to the every 3-week regimen described by Gebbia in general practice[12] that would provide a similar median dose of both drugs to that used in ANITA.

Three trials of adjuvant chemotherapy in NCSLC have shown improved survival with chemotherapy: IALT[6] (four cycles of cisplatin-based chemotherapy *vs* observation; hazard ratio 0·86 [95% CI 0·76–0·98], p=0·03), JBR.10[9] (vinorelbine and cisplatin *vs* observation; 0·69 [0·52–0·91], p=0·0009), and the Japan Lung Cancer Research Group[12] (uracil-tegafur *vs* no treatment; 0·71

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[0·52–0·98], p=0·04). These results accorded with the meta-analysis on adjuvant chemotherapy for NSCLC.[4,14,15] However, another three trials showed no survival benefit from adjuvant chemotherapy: the Big Lung Trial,[16] which had a small sample size, various cisplatin-based combinations, a short follow-up of 29 months, and 15% of patients with incomplete resected disease; ALPI,[7] which used a regimen of mitomycin, vindesine, and cisplatin, and had a high frequency of early death and poor compliance; and CALGB 9633,[8] which used a paclitaxel-carboplatin regimen in patients with stage IB only, and was updated in 2006 to show no survival benefit despite promising results shown previously after a short follow-up.

None of the trials showed a survival advantage in stage IA–IB NSCLC apart from with the use of uracil-tegafur (hazard ratio 0·48 [0·29–0·81]).[13] Neither IALT[6] nor JBR.10[9] showed a benefit from chemotherapy in stage IB disease, similar to our results. IALT[6] did not show a survival benefit in stage II disease (hazard ratio 0·94, [0·80–1·11]; p=0·51). However, improvement in survival on stage II disease was significant in JBR.10[9] (0·59 [0·42–0·85]; p=0·004), and stage II disease benefited from adjuvant chemotherapy in our trial (absolute benefit of 13% at 5 years). The discrepancy between these trials could be related to a reduced efficacy of the first and second generations of drugs, combined with cisplatin in most of the patients in the IALT trial.[6] Neither ALPI[7] nor the Big Lung Trial[16] showed any survival benefit of chemotherapy in stage III disease, by contrast with the positive results recorded in IALT (0·89 [0·80–0·99]) and our ANITA trial.

The effect of adjuvant chemotherapy has been further analysed in the LACE meta-analysis,[11] showing that cisplatin-based adjuvant chemotherapy in resected NSCLC provides a 5% benefit in survival at 5 years, which is not clinically different from the 1995 meta-analysis.[4] Subgroup analysis by stage confirmed that patients with stages IA and IB did not benefit from chemotherapy whereas those with stage II and stage IIIA did (both 0·83 [0·73–0·95]). According to LACE,[11] the inclusion of cisplatin in chemotherapy schedules is crucial. With analysis of the vinorelbine-cisplatin combination as a separate subgroup, the hazard ratio was 0·80 (0·70–0·91; p=0·04) compared with doublet or triplet combinations of first and second-hand generation drugs with cisplatin (doublets, 0·93 [0·80–1·07]; triplets, 0·93 [0·84–1·14]).[11] Our findings on the benefits of the vinorelbine-cisplatin combination confirms the JBR.10 findings[9] in patients with stage II disease, and provide new data for patients with stage IIIA.

We did not plan to analyse the effect of postoperative radiotherapy in ANITA. Although every centre defined its policy on radiotherapy before the beginning of the trial, more patients in the observation group than in the chemotherapy group received radiotherapy. Although the reason for this difference is unclear, investigators might have chosen to give radiotherapy to patients receiving no adjuvant treatment, or patients might have refused to undergo additional radiotherapy after chemotherapy. Since the decision to give postoperative radiotherapy was not randomised, any conclusions should be drawn cautiously. Nevertheless, the descriptive analysis showed that radiotherapy could benefit patients with N2 status and could be harmful when combined with chemotherapy in patients with N1 status. By contrast, the Eastern Cooperative Oncology Group[17] reported no benefit from concurrent use of cisplatin-etoposide and radiotherapy in patients with stage II and IIIA disease, possibly because 42% of the patients had stage II. The effect of postoperative radiotherapy in patients with N0 disease in our study cannot be assessed since only a few patients received the treatment. No data are available to support the use of postoperative radiotherapy in node-positive disease. Based on our non-randomised results, we cannot recommend postoperative radiotherapy for N1 status, although it could be considered for N2 status. A randomised trial initiated in France (LungART IFCT 0503) for N2 disease is in progress.

In conclusion, this mature study shows a significant survival benefit for adjuvant vinorelbine plus cisplatin in patients with resected stage IB–IIIA NSCLC, although the benefit is mainly in stages II and IIIA. Furthermore, our findings reveal the need for a clearer definition of the role of postoperative radiotherapy in stage IIIA disease. To identify subsets of patients who could have greater benefit from adjuvant chemotherapy, genetic assessment of the patients in this trial is under way.

	Chemotherapy		Control	
	Radiotherapy (n=73)	No radiotherapy (n=152)	Radiotherapy (n=128)	No radiotherapy (n=114)
N1 (n=243)				
1-year survival	92%	85%	83%	73%
2-year survival	76%	70%	61%	52%
5-year survival	40%	56%*	43%	31%
N2 (n=224)				
1-year survival	98%	71%	74%	57%
2-year survival	77%	49%	48%	35%
5-year survival	47%	34%	21%	17%
All (n=467)				
1-year survival	96%	79%	78%	68%
2-year survival	76%	61%	54%	46%
5-year survival	45%	46%*	32%	27%

*42% of patients censored at 5 years.

Table 6: **Overall survival estimates according to radiotherapy and lymph node status**

Contributors

J-Y Douillard, R Rosell, M De Lena, F Carpagnano, R Ramlau, J L Gonzáles-Larriba, T Grodzki, J Rodrigues Pereira, A Le Groumellec, V Lorusso, C Clary, A J Torres, J Dahabreh, P-J Souquet, J Astudillo,

P Fournel, A Artal-Cortes, J Jassem, and L Koubkova, were the main investigators regarding study accrual. P His was the study statistician. M Riggi and P Hurteloup participated in the study design, study monitoring, and acquisition of data.

Conflicts of interest

J-Y Douillard has consulted for Pierre Fabre Médicament. M Riggi, P Hurteloup, and P His are employees of Pierre Fabre Médicament. The other authors declare no conflicts of interest.

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ANITA trial Investigators

Argentina—M Chacon (Instituto de Oncologia Alexander Fleming, Buenos Aires); M Rondidon, E Saad (Hospital Frances, Buenos Aires); M Rosemberg, M Van Kooten (Instituto de Oncologia Alexander Fleming, Buenos Aires).

Austria—A Mohn-Staudner, N Vetter (Otto Wagner Spital Baumgartner Höhe, Wien); R Mutschlechner, S Schmeikal (Landesklinik Hochegg, Grimmenstein).

Brazil—C H Barrios, S Lago, M-H Sostruznik (Hospital Sao Lucas de PUCRS, Porto Alegre); R Caponero, A Malzyner (Hospital E Vasconcelos, Sao Paulo); G Delgado, L A Pires (Hospital, Sorocaba); F Kazumi Ikari, S Mayumi Nikaedo, J Rodrigues Pereira (Instituto do Cancer A Vieira de Carvalho, Sao Paulo); A Trajano (Hospital A Maltez, Salvador); J Vinholes (Hospital Santa Rita, Porto Alegre).

Czech Republic—R Gregar, M Pesek, G Krakorova (Faculty Hospital, Plzen); J Hlusek, (Hospital, Zlin); E Horenkova (Faculty Hospital, Ostrava); I Kisa (Asylum for TB and respiratory diseases, Mesto Albrechtice); V Kolek (University Hospital, Olomouc); L Kouboka (Nem Kladno, Kladno); J Krynska (Hospital, Zlin); M Kucera (Hospital, Breclav); P Reiterer, F Wurst (Masaryk's Hospital, Usti nad Labem); B Skalova (Teaching Hospital Motol, Prague); J Skrickova, S Spelda (Deparment of TB and respiratory diseases and Palliative Care Unit, Brno); P Zatloukal, L Havel, I Spasova (Faculty Hospital Bulovka, Prague).

France—P Astoul, J P Kleisbauer (Hôpital Ste Marguerite, Marseille); P Balmes, E Coste (CHRU Gaston Doumergue, Nîmes); J R Barrière (Centre Hospitalier, Draguigan); P Bellier (Centre Hospitalier, Vienne); H Bérard (HIA Ste Anne, Toulon); F Blanchon (Centre Hospitalier, Meaux); J Bodin, I Bourlaud, M D'Arlhac (Centre Hospitalier Georges Renon, Niort); P Bombaron, C H Emile Muller (Mulhouse); C Boutin (Hôpital de la Conception, Marseille); P Carles (Centre Hospitalier Larrey, Toulouse); D Charpin (CHU Nord, Marseille); J P Chavaillon, C Rotomondo (Hôpital de la Fontonne, Antibes); C Clary (Centre Hospitalier Régional Pasteur, Nice); O Corbion, A Monnier, X S Sun (Hôpital André Boulloche, Montbéliard); G Dabouis (Hôtel Dieu, Nantes); E Dansin (Centre Oscar Lambret, Lille); P Deguiral (Centre Hospitalier Régional, St Nazaire); P Delecluse (Polyclinique du Bois, Lille); V Delecroix (Centre Etienne Dolet, St Nazaire); J-Y Douillard (Centre René Gauducheau Nantes-Saint-Herblain); H Dutau (CHU Nord, Marseille Nord); J P Dutin (Centre Hospitalier St Michel, La Rochelle); M Faraldi (Centre Hospitalier, Compiègne); P Fournel (Hopital Nord, Saint-Etienne); J M Frolet, O Jarry, B Taviot (Clinique Ste Marie, Châlon sur Saone); H Galloux (Centre Hospitalier de Cornouaille, Quimper); A Geraards (Centre Hospitalier, Auxerre); M Grivaux (Hôpital St Faron, Meaux); J Guigay (Institut Gustave Roussy, Villejuif); P Hyvernat (Clinique de la Sauvegarde, Lyon); J Y Jasnot (Cabinet Médical, Nantes); V Jounieaux (Hôpital Sud, Amiens); S Kassayet (Hôpital, Salon de Provence); J J Lafitte (CHRU, Lille); P Leclerc (Centre Hospitalier des Yvelines, St Germain en Laye); A Le Groumellec (Centre Hospitalier P Chubert, Vannes); P Le Lann (Centre Hospitalier Laennec, Creil); E Lemarié (CHR Bretonneau, Tours); P Le Mevel (Centre Hospitalier, Morlaix); G Letanche (Centre Hospitalier, Givors); J Le Treut (Centre Hospitalier, Aix en Provence); E Maetz (Centre Hospitalier, Douai); P Masson, B Maury (Centre Hospitalier, Cholet); G Meunier (Centre Hospitalier, Montluçon); I Migaud (CH de Bretagne-Sud, Lorient); J F Morère (Hôpital Avicennes, Bobigny); C Muller-Aufaure (Hôpital, Senlis); D Paillotin (Centre Hospitalier de Bois Guillaume, Rouen); M Pérol (Hôpital de la Croix Rousse, Lyon); T Pigeanne (CH Côte de Lumière, Sables d'Olonne); M C Pujazon (Centre Hospitalier Larrey, Toulouse); R Riou (Centre Hospitalier, Valence); J P Roux (Centre Hospitalier, Valenciennes); C Ruesch (Centre Hospitalier, St Chamond); P Salze (Centre Hospitalier Louis Pasteur, Colmar); C Simonian (Centre Hospitalier, Martigues); J Soots (CMC, Bruay La Buissière); P J Souquet (Centre Hospitalier Lyon-Sud, Pierre-Bénite); F Varlet (Centre Hospitalier, Dunkerque); F Vaylet (Hôpital Percy, Clamart); A Vergnenègre (CHRU Dupuytren, Limoges); J M Vernejoux (CHU Haut Lévèque, Pessac); A Voloch (Centre Médical PAROT, Lyon); S Vuillermoz (CH St Joseph et St Luc, Lyon).

Greece—O Anagnostopoulou, G Blazogiannakis, J Dimitroulis, A Gerogianni, M Marinou, F Palamidas, G Pavlakou, A Rapti, M Toumbis, S Tzannes (Hospital of Lung Diseases Sotiria, Athens); N Androulakis, V Georgoulias, N Souglakos (University Hospital, Heraklion); J Dahabre, J Dritsas, G Papagiannakis (Sismanoglio Hospital, Athens).

Italy—M S Aapro (Istituto Europeo di Oncologia, Milan); F Carpagnano, M L Cisternino, G Di Rienzo, G Napoli, S Orlando (Ospedale San Paolo, Bari); G Carteni, F Giampaglia, G Iodice, M P Mannelli (Azienda Ospedaliera Cardarelli, Naples); M De Lena, V Lorusso (Ospedale "A Cardarelli", Naples); A Martoni, B Melotti, (Policlinico S Orsola-Malpighi, Bologna); E Massa (Policlinico Universitario, Cagliari); L Scarcella, T Todisco (Ospedale Silvestrini, Perugia).

Lebanon—G Chahine, M Ghosn, J Kattan, G Khayyat, J Khoury, G Tabet, Z Bacha (Hotel Dieu de France University Hospital, Beirut).

Mexico—G Calderillo, M D Gallardo (Instituto Nacional de Cancerologia, Mexico); O Hernandez Reyes (Hospital Guadalajara, Tijuana).

Poland—J Alchimowicz, M Blachowski, H Janowski, B Kuta, P Serwatowski, G Ziolo, (IMA Sokolowskiego, Szczecin); E Bednaruk, J Jassem, J Madrzak, M Nowaczyk (Academy of Medicine, Gdansk); M Bryl, W Dyszkiewicz, E Nowak, R Razmlau (Wielkopolskie Centrum Chorob Pluc I Gruzlicy, Poznan); A Czech, A Szczesna, A Guzowska, J Krusiewicz, P Maj, B Mirkowicz, A Niedziolka, W Seweryniak (Mazowieckie Centrum Leczenia Chorob Pluc I Gruzlicy, Otwock); G Czyzewicz, H Olechnowicz, T Gil, K. Krawczyk, D Skutecka, J Warmus (Jana Pawla II, Krakow); T Grodzki (FETCS Thoracic Surgery, Szczecin); A Rozmiarek, R Sibilski, D Szklar (Lubuski Osrodek Onkologii, Zielona Gora).

Portugal—M Bernardo, J Gouveia (Hospital de Santo Antonio dos Capuchos, Lisbon).

South Africa—H du Toit (Panorama Medi-Clinic, Cape Town).

Slovakia—I Bakos, J Plutinski (TB and respiratory diseases Institute, Nitra-Zobor); P Kasan (Faculty hospital with Policlinic, Bratislava).

Spain—R Aguilo, C Montero, J Terrasa (H Universitario Son Dureta, Palma de Mallorca); M R Alfonso, A Torres (H Clínico San Carlos, Madrid); A Anton, A Artal-Cortes, F Sánchez (H Universitario Miguel Servet, Zaragoza); R Arrabal, M Benavides, J L Bermudez, M Cobo, A Domenec, A Fernandez de Rota (H Universitario Carlos Haya, Malaga); J Astudillo, R Rosell, J M Sánchez Torres (Hospital Universitario Germans Trias i Pujol, Badalona); E Baeta, I Bover (H Sant Joan de Reus, Reus); E Batiste-Alentron, R M Franquesa, M Gay (H General de Vic, Vic); R Cabeza, C Hernandez, J M Izquierdo, A Paredes (H Universitario Nuestra Sra de Aránzazu, San Sebastian); A Carrato, N Diaz, J García Gómez, M L Gonzalves (H Universitario General de Elche, Elche); C Garcia Giron (H Universitario General Yagüe, Burgos); R García Gómez, F Gonzáles-Aragoneses (H Universitario Gregorio Marañon, Madrid); J Garcia Tirado, D Isla (H Clínico Universitario Lozano Blesa, Zaragoza); J L Gonzales-Larriba (Hospital San Carlois, Madrid); J Lizon (H Universitario San Juan, Alicante); S Morales (H Universitario Arnau Vilanova, Lérida); J Moya (H Universitario Bellvitge, Barcelona); M Nogue, M Segui (H Universitario Parc Taulí, Sabadell); J Ortega (H Universitario Marqués de Valdecilla, Santander).

USA—A Brown, R Castillo, J Cole, R Gralla, C Kardinal, E McElroy (Ochsner Cancer Institute, New Orleans, LA, USA).

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