An ELCWP Phase III Trial Comparing Ifosfamide and Cisplatin Regimens in Advanced NSCLC

THIERRY BERGHMANS[1], JEAN-JACQUES LAFITTE[2], ARNAUD SCHERPEREEL[2], MARIANNE PAESMANS[3], JACQUES LECOMTE[4], VICENTE GINER MARCO[5], ANNE-PASCALE MEERT[1], NATHALIE LECLERCQ[1] and JEAN-PAUL SCULIER[1]
for the European Lung Cancer Working Party

[1]Department of Intensive care and Thoracic Oncology and
[3]Data centre, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium;
[2]Department of Pneumology, CHU Lille, Lille, France;
[4]Department of Pneumology, CHU Charleroi, Charleroi, Belgium;
[5]Department of Medical Oncology, Hospital de Sagunto, Valencia, Spain

Abstract. *Aim: While meta-analyses and clinical trials show improved survival in advanced NSCLC treated with platinum-containing chemotherapy, there are few data concerning front-line platinum-free ifosfamide-based regimens. We aimed to compare cisplatin-based chemotherapy to ifosfamide-gemcitabine (IG) with pre-defined second-line docetaxel. Patients and Methods: 693 Untreated advanced inoperable NSCLC cases were randomised to either GIP (gemcitabine, ifosfamide, cisplatin), DP (docetaxel, cisplatin) or IG. Primary outcome was overall survival. Results: Median age of the patients was 58 years with a predominance of males (75%), adenocarcinoma (56%), Karnofsky PS 80-100 (77%) and stage-IV disease (81%). Median survival times were 8.7, 8.8 and 8.3 months for IG, GIP and DP (p=0.79). GIP presented with (p<0.05) greater neutropenia, thrombopenia, vomiting, while greater cardiotoxicity, diarrhea, peripheral neuropathy were observed for DP and encephalopathy for IG. Conclusion: In advanced NSCLC, cisplatin-based CT is not superior to a platinum-free regimen (ifosfamide-gemcitabine) with a favourable toxicity profile.*

Over the last decades, chemotherapy, mainly with regimens including cisplatin, led to survival improvement over best supportive care in advanced and locoregional diseases (1). However, cisplatin has many adverse events that impact on quality of life. Phase III trials published at the time we designed our trial (2-9) did not show any survival advantage of platinum-based regimens over platinum-free ones. As salvage chemotherapy was generally not pre-defined, it is possible that a huge number of patients received further platinum derivatives, giving a possible explanation for the absence of survival differences.

The European Lung Cancer Working Party (ELCWP) conducted a three-arms phase-III trial (3), comparing ifosfamide-gemcitabine (IG) to cisplatin-based regimens. There was no advantage from cisplatin combinations considering survival, response rate and response duration. Based on these results, IG could be considered as a standard therapeutic option and a valuable alternative to cisplatin. In the present phase-III trial, we aimed to determine if the addition of cisplatin to IG could improve for survival, considering that platinum combinations including third-generation agents could show better efficacy than IG, as further supported by a 2006 meta-analysis (10).

When designing the study, there were controversies on the use of triplets instead of doublets platinum-based regimens, when the last are combined with third-generation drugs. The cisplatin-docetaxel (DP) combination appeared interesting allowing increased survival rates (11). As docetaxel was the reference salvage chemotherapy based on the results of randomised trials (12), we designed a 3-arms phase III trial pre-defining the second-line chemotherapy in order to have a platinum-free arm, at least for the two first chemotherapy lines so that received drugs during first and second lines will only differ by cisplatin.

The primary aim of our study was to determine if cisplatin-based chemotherapy including platinum and third

The study was presented at the European Respiratory Society Annual Congress, Amsterdam, The Netherlands, 2011.

Correspondence to: Thierry Berghmans, MD, Ph.D., Institut Jules Bordet, Rue Héger-Bordet, 1, B-1000 Brussels, Belgium. Tel: +32 25413191, Fax: +32 25343756, e-mail: thierry.berghmans@bordet.be

Key Words: Non-small cell lung cancer, cisplatin, ifosfamide, docetaxel, survival, phase III trial.

generation drugs will improve survival in comparison to a platinum-free combination (ifosfamide-gemcitabine with docetaxel as salvage chemotherapy) in patients with advanced NSCLC.

Patients and Methods

Eligibility criteria. Eligible patients had an initially advanced (unresectable or functionally-inoperable) stage III (stage IIB patients with inoperable lesions were deemed eligible) or stage IV pathologically-confirmed NSCLC, based on the 5th TNM classification. Other eligibility criteria as well as the study protocol are freely-available at www.elcwp.org. The protocol was approved by the ethical committees of the Institutions. This academic trial was designed and opened for accrual before the implementation of the European directive on EUDRACT number. The ClinicalTrials.gov identifier is NCT00622349. Patients from the following institutions were randomized: Institut Jules Bordet, Brussels, Belgium (J.P. Sculier, T. Berghmans, A.P. Meert, I CsToth, P. Van Houtte, M. Paesmans, N. Leclercq); Centre Hospitalier Etterbeek-Ixelles-Molière, Brussels, Belgium (G. Plat, S. Bensliman); Hôpital Warquignies, Boussu, Belgium (M. Richez); CHU, Charleroi, Belgium (J. Lecomte); Cliniques Saint-Luc, Bouges, Belgium (O Van Cutsem); CHU Saint-Pierre, Brussels, Belgium (V. Ninane); CHU André Vésale, Montignies-le-Tilleul, Belgium (D. Brohée); Hôpital Ambroise Paré, Mons, Belgium (P. Wackenier, S. Holbrechts); RHMS Baudour, Tournai-Ath, Belgium (P. Ravez, V. Richard); CH Peltzer-la-Tourelle, Verviers, Belgium (J.L. Corhay, Y. Bonduelle, I. Louviaux); CH Hornu-Frameries, Hornu-Frameries, Belgium (C. El Khawand); Clinique St-Joseph, Gilly, Belgium (B. Colinet); Hospital de Sagunto, Valencia, Spain (V. Giner); CHU Calmette, Lille, France (J.J Lafitte, A. Scherpereel); CH Douai, Douai, France (M.C. Florin, E. Maetz, S Desurmont); Hôpital de Hayange, Hayange, France (M.C. Berchier, P. Botrus); Cabinet Médical Dampierre, Anzin, France (B. Stach, J.P. Roux); Clinique Médico-Chirurgicale Tessier, Valenciennes, France (G. Demarcq, F. Radenne); CHI, Le Raincy-Montfermeil, France (T. Collon); CH Tourcoing, Tourcoing, France (X. Ficheroulle); CH du Dr Schaffner, Lens, France (J. Amourette, C. Bergoin); Hellenic Cancer Institute, Athens, Greece (A. Efremidis, G. Koumakis); Evangelismos General Hospital, Athens, Greece (C.G. Alexopoulos, M. Vaslamatzis).

Chemotherapy. Patients were randomised on a 1:1:1 ratio between GIP (gemcitabine 1 g/m^2 days 1+8; ifosfamide 3 g/m^2 day 1; cisplatin 50 mg/m^2 day 1), DP (docetaxel 75 mg/m^2 plus cisplatin 50 mg/m^2, both on day 1) and IG (ifosfamide 3 g/m^2 day 1; gemcitabine 1g/m^2 days 1+8). Central randomization using a minimization algorithm was performed by calling the ELCWP central office. Complete staging was performed after 3 courses. Non-progressing patients received 3 further courses of the same chemotherapy. In case of response, patients were treated until best response. In case of non-metastatic disease, if chest tumor was an indication for irradiation, chest radiotherapy could be administered after 3 courses of chemotherapy according to local protocols four weeks after the administration of the last dose of chemotherapy.

Patients with progressive disease received docetaxel (75 mg/m^2 every 3 weeks) after GIP and IG, and IG after DP. Assessment of response was done every 3 courses. Non-progressing patients were treated by 3 further courses. In case of response, patients were treated until best response.

Table I. *Eligible patients' characteristics at randomization*.

	IG n=229	GIP n=231	DP n=233
Age median, years (range)	59 (30-84)	58 (29-78)	58 (28-81)
Gender			
Male	172 (75%)	174 (75%)	177 (76%)
Female	57 (25%)	57 (25%)	56 (24%)
Karnofsky PS			
60-70	51 (22%)	52 (23%)	54 (23%)
80-90-100	178 (78%)	179 (78%)	179 (77%)
Histology			
Squamous	53 (23%)	45 (20%)	55 (24%)
Adenocarcinoma	128 (56%)	133 (58%)	125 (54%)
Large cell	12 (5%)	21 (9%)	16 (7%)
Other NSCLC	36 (16%)	32 (14%)	37 (16%)
Stage*			
IIB	3 (1%)	2 (1%)	1 (<1%)
IIIA	12 (5%)	7 (3%)	14 (6%)
IIIB	27 (12%)	30 (13%)	31 (13%)
IV	186 (81%)	191 (83%)	187 (80%)
Unknown	1 (<1%)	1 (<1%)	-
Weight loss			
≤5%	123 (54%)	139 (60%)	124 (53%)
>5%	79 (34%)	69 (30%)	77 (33%)
unknown	27 (12%)	23 (10%)	32 (14%)
Neutrophil count			
≤7500/mm^3	129 (56%)	143(62%)	140 (60%)
>7500/mm^3	99 (43%)	83 (36%)	91 (39%)
unknown	1 (<1%)	5 (2%)	2 (1%)

GIP, Gemcitabine-ifosfamide-cisplatin; IG, ifosfamide-gemcitabine; DP, docetaxel-cisplatin; PS, performance status; NSCLC, non-small cell lung carcinoma. *according to the 5th International Staging System.

Methods of evaluation. Treatment plan with mode of administration, dose adaptation plan, initial work-up and follow-up procedures are detailed in the protocol at www.elcwp.org. Response and toxicity were assessed using the WHO criteria (13). Progression-free survival was the period between the day of registration and the date of first progression or death. Survival was dated from the day of registration.

Statistical design and methods. The primary end-point of this unblinded superiority trial was to determine if cisplatin-based chemotherapy, GIP or DP, would improve survival in comparison to IG. According to the ELCWP experience, it was expected to reach a 35% 1-year survival rate in the control arm (IG). An increase of this 1-year survival to 50% in the two experimental arms (GIP and DP), judged clinically relevant, should be detected with a power of 80% using a two-sided log-rank test and a 5% level for significance. With these assumptions, it was required to overall observe approximately 360 events (deaths). We anticipated reaching this number of events with randomization of at least 620 eligible patients.

Survival curves were estimated using the Kaplan-Meier method. The log rank test was used to compare survival curves. *p*-Values for testing differences between proportions were calculated with chi-square tests or with Fischer's exact tests. A multivariate

Table II. *Highest documented toxicities per patient during treatment*

	IG (n=229)		GIP (n=231)		DP (n=233)		*p*-Value
Grade	I-II	III-IV	I-II	III-IV	I-II	III-IV	
Leucopoenia	36.3%	41.3%	30.0%	61.2%	46.9%	26.3%	<0.001
Neutropenia	27.4%	43.9%	14.2%	73.0%	22.4%	53.5%	<0.001
Febrile neutropenia	-	6.1%	-	10.4%	-	11.6%	0.11
Infection	10.5%	14.4%	8.7%	16.0%	11.2%	19.3%	0.35
Thrombopenia	19.7%	9.0%	26.0%	31.3%	2.6%	3.5%	<0.001
Bleeding	5.7%	-	6.9%	1.3%	7.7%	2.1%	0.09
Alopecia	41.5%	21.4%	38.5%	30.7%	42.1%	27.5%	0.04
Cardiotoxicity	3.1%	1.3%	2.6%	0.9%	6.4%	2.1%	ND
Constipation	12.7%	0.9%	9.5%	0.9%	11.2%	0.4%	ND
Diarrhea	9.6%	0.4%	15.6%	0.9%	22.3%	1.3%	ND
Genito-urinary	3.0%	-	3.0%	-	0.4%	-	ND
Hear loss	3.9%	0.4%	3.9%	-	6.4%	-	0.37
Nausea/vomiting	46.7%	3.1%	57.6%	3.9%	45.5%	6.9%	0.12
Neuropathy	6.1%	1.3%	3.9%	1.3%	0.9%	0.4%	ND
Peripheral neuropathy	12.2%	0.9%	13.0%	0.9%	19.7%	0.4%	ND
Renal	3.1%	-	4.3%	-	5.6%	1.7%	0.02
Respiratory	14.0%	3.5%	16.9%	3.9%	14.2%	2.6%	0.71
Skin	19.2%	0.9%	18.6%	0.9%	11.6%	1.7%	0.62
Stomatitis	14.0%	0.4%	19.0%	0.9%	18.9%	2.1%	0.20

For descriptive purposes, rates of patients experienced grades I-II and grades III-IV have been presented in the Table. The *p*-values reported are however for comparing rates of grades III and IV. ND, Statistical test not done due to small number f events; GIP, gemcitabine-ifosfamide-cisplatin; IG, ifosfamide-gemcitabine; DP, docetaxel-cisplatin.

analysis for adjustment of the treatment effect taking into account prognostic factors was performed by fitting the data with a Cox model for duration of survival and a logistic regression model for objective response. The result of a statistical test was considered significant when $p<0.05$. All reported *p*-values are two-sided. Chemotherapy dose-intensity was calculated as the ratio of the cumulative dose to the actual duration of treatment (expressed in mg/m^2 and per week). Relative dose intensity (DI) was the ratio of the achieved DI divided by the planned DI. Non-parametric tests (Kruskal-Wallis) were used to detect for differences between treatment arms (overall and paired comparisons).

Results

Between 12/2003 and 03/2009, 707 patients were randomized out of whom 14 were ineligible. Eligible patients' characteristics are described in Table I.

The median number of delivered chemotherapy cycles was 3 in each arm. The median treatment duration was 75 days, 86 days and 70 days for IG, GIP and DP, respectively. The relative dose-intensity (RDI) of cisplatin, ifosfamide and gemcitabine were significantly reduced within GIP in comparison to IG and DP ($p<0.001$ for all pair's comparisons).

In an intent-to-treat analysis (including unassessable patients), response rates (RR) at first assessment were 24% (95%CI: 18%-30%), 30% (95%CI: 24%-36%) and 24% (95%CI: 19%-30%) for IG, GIP and DP, respectively ($p=0.23$). Respectively, 5, 6 and 3 patients had an improved response at the second evaluation. Best RR are 26% (95%CI: 21%-32%), 33% (95%CI: 27%-39%) and 26% (95%CI: 20%-31%) for IG, GIP and DP. Three statistically independent predictive factors for objective response were identified in multivariate analysis: good performance status (Odds ratio [OR] 1.63, $p=0.05$), normal white blood cell count (OR 0.93, $p=0.002$) and normal haemoglobinemia (OR:1.18, $p=0.001$). No statistically significant difference in progression-free survival (PFS) was observed among the three arms ($p=0.80$). The median and 1-year PFS are 3.2 months and 10%, 4.1 months and 13%, 3.0 months and12% for IG, GIP and DP, respectively.

At time of analysis, death had been documented in 644 patients (92%), 24 are alive (5%) and 25 (3%) were lost to follow-up. Median follow-up is 55 months. The 1-year survival rates are 37% (95%CI: 30%-44%), 35% (95%CI: 29%-41%) and 35% (95%CI: 29%-41%) for IG, GIP and DP ($p=0.79$). The corresponding median survival times (MST) are 8.7, 8.8 and 8.3 months. Female sex (HR 0.80, $p=0.02$), good performance status (HR 0.58, $p<0.001$), minimal weight loss (<5%) (HR 0.73, $p<0.001$), stage III (HR 0.78, $p<0.001$), normal white blood cell count (HR1.05, $p<0.001$), haemoglobinemia (HR 0.92, $p=0.001$) and calcium level (HR 0.57, $p=0.007$) were found to be prognostic factors for survival in a multivariate Cox model.

Highest documented toxicities per patient are reported in Table II. Thrombotic events were observed in 4.8% (IG), 6.5% (GIP) and 4.3% (DP). Twenty-seven deaths possibly not related to cancer were recorded, 7 with GIP and 10 for IG and DP. Nine febrile neutropenias were related to study drugs (2 in IG and GIP each and 5 in DP), while the relationship between the 18 others and chemotherapy remains doubtful. They were mainly due to infectious (n=2) or thromboembolic events (arterial ischemia or pulmonary embolism in 3 cases each); 5 sudden deaths were noted.

Additional anticancer treatments. After induction chemotherapy, 30 patients received a local treatment: Chest irradiation (IG 4, GIP 7, DP 10), surgery (IG 2, DP 4) or surgery followed by chest irradiation (GIP 2, DP 1). At the time of analysis, progression and/or relapse has been documented in 497 patients, 170 in the IG, 165 in the GIP and 162 in the DP. Second-line chemotherapy was given to 135, 130 and 126 patients in the IG, GIP and DP arms. It was performed according to the protocol in 89% (120/135) for IG, 93% (121/130) for GIP and 86% (108/126) for DP arms. Among the initial IG cohort, 30 patients (13·1%) received at any time a platinum derivative, but only 4 (1·7%) in second-line.

Discussion

This phase III trial shows that cisplatin combinations do not offer improved survival in comparison with a platinum-free chemotherapy with ifosfamide and gemcitabine, in the context of a pre-defined second-line regimen without cisplatin in the IG arm. IG appears to be a valuable alternative to cisplatin-based combinations with similar survival times and reduced toxicity.

At least 27 randomized trials comparing for different platinum-free chemotherapy regimens have been published so far. While a meta-analysis (10) published in 2006 suggested a detrimental effect of platinum-free chemotherapy, only two individual trials (14, 15) showed a statistically significant reduced survival associated to first-line chemotherapy without platinum salts, while the opposite was found in one trial (16).

Some potential biases and limitations have to be discussed. In previous trials, platinum was given in 12% to 42% of the initially randomized patients (3, 8, 9, 16-20). When considering only those receiving second-line chemotherapy, it increased to 55-90%. The present trial was designed to overcome this problem by defining the second-line therapy, a design never used in the previous trials, so that the IG arm will be free of platinum salts, at least for the first two lines of treatment. The protocol was applied as initially designed so that only 1.7% of the patients receiving salvage chemotherapy in the IG cohort received platinum derivatives, and a further 11.4% in third or subsequent lines. Three randomized trials (3, 14, 21) compared ifosfamide and cisplatin-based regimens without evident survival difference. Cisplatin and ifosfamide have closely-related mechanisms of action. This could be an explanation to the absence of additive effect when combining ifosfamide and cisplatin and for the similar efficacy of cisplatin and ifosfamide regimens in this trial.

As explained in the introduction, we considered that sufficient data were available to justify our choice of IG as a reference treatment and a standard arm. Taking into account the toxicity profile of cisplatin-based regimens and the difficulty to broadly administer them, we thought that a large improvement in survival with GIP was required for clinical relevance. In a previous meta-analysis, 1-year survival with platinum combinations was 34% (22), mostly including second-generation drugs. This led us to think that a combination of cisplatin and a third-generation drug could improve 1-year survival above these values.

A third controversy is with regard to the dosage of cisplatin. Addition of intermediate-dose cisplatin (50 mg/m^2) to a combination of ifosfamide and gemcitabine (GIP) did not improve any of the end-points (response, progression-free survival, survival). Furthermore, the triplet was associated with higher hematological toxicity resulting in a statistically significant reduction in the RDI of each component. In our experience (23), higher cisplatin doses do not result in survival improvement in advanced NSCLC but are associated with significantly more chronic complications. Four other randomized trials (24-27) comparing conventional to high doses of cisplatin did not show any improvement in response rate or survival.

The combination of ifosfamide and gemcitabine is a valuable well-tolerated alternative to cisplatin doublets in patients with advanced NSCLC. A triplet combination (GIP) fails to improve survival and is associated with more hematological toxicity resulting in reduced dose-intensity. The data from other randomized trials are consistent with our study, suggesting that doublet regimens with cisplatin or ifosfamide can be applicable as first-line treatment for advanced and metastatic NSCLC.

Conflicts of Interest

The Authors have no conflicts of interest to declare in respect of this work and this publication.

Acknowledgements

The study was financed by the European Lung Cancer Working Party and by an unrestricted grant from Eli Lilly, Sanofi Aventis and ASTA.

The data management was carried out by the European Lung Cancer Working Party independently. The study was independently designed, conducted, analysed and interpreted by the study coordinators and the authors from the European Lung Cancer Working Party.

References

1 Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol *26*: 4617-4625, 2008.

2 Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, Palamidas P and Vlachonikolis I: Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicentre trial. Lancet *357*: 1478-1484, 2001.

3 Sculier JP, Lafitte JJ, Lecomte J, Berghmans T, Thiriaux J, Florin MC, Efremidis A, Alexopoulos CG, Recloux P, Ninane V, Mommen P, Paesmans M and Klastersky J: A three-arm phase III randomised trial comparing combinations of platinum derivatives, ifosfamide and/or gemcitabine in stage IV non-small-cell lung cancer. Ann Oncol *13*: 874-882, 2002.

4 Kosmidis P, Mylonakis N, Nicolaides C, Kalophonos C, Samantas E, Boukovinas J, Fountzilas G, Skarlos D, Economopoulos T, Tsavdaridis D, Papakostas P, Bacoyiannis C and Dimopoulos M: Paclitaxel plus carboplatin *versus* gemcitabine plus paclitaxel in advanced non-small-cell lung cancer: a phase III randomized trial. J Clin Oncol *20*: 3578-3585, 2002.

5 Greco FA, Gray JR, Jr., Thompson DS, Burris HA, III, Erland JB, Barton JH Jr., Litchy S, Houston GA, Butts JA, Webb C, Scott C and Hainsworth JD: Prospective randomized study of four novel chemotherapy regimens in patients with advanced nonsmall cell lung carcinoma: a minnie pearl cancer research network trial. Cancer *95*: 1279-1285, 2002.

6 Chen YM, Perng RP, Lee YC, Shih JF, Lee CS, Tsai CM and Whang-Peng J: Paclitaxel plus carboplatin, compared with paclitaxel plus gemcitabine, shows similar efficacy while more cost-effective: a randomized phase II study of combination chemotherapy against inoperable non-small-cell lung cancer previously untreated. Ann Oncol *13*: 108-115, 2002.

7 Gebbia V, Galetta D, Caruso M, Verderame F, Pezzella G, Valdesi M, Borsellino N, Pandolfo G, Durini E, Rinaldi M, Loizzi M, Gebbia N, Valenza R, Tirrito ML, Varvara F and Colucci G: Gemcitabine and cisplatin *versus* vinorelbine and cisplatin *versus* ifosfamide+gemcitabine followed by vinorelbine and cisplatin *versus* vinorelbine and cisplatin followed by ifosfamide and gemcitabine in stage IIIB-IV non small cell lung carcinoma: a prospective randomized phase III trial of the Gruppo Oncologico Italia Meridionale. Lung Cancer *39*: 179-189, 2003.

8 Gridelli C, Gallo C, Shepherd FA, Illiano A, Piantedosi F, Robbiati SF, Manzione L, Barbera S, Frontini L, Veltri E, Findlay B, Cigolari S, Myers R, Ianniello GP, Gebbia V, Gasparini G, Fava S, Hirsh V, Bezjak A, Seymour L and Perrone F: Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small-cell lung cancer: a phase III trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol *21*: 3025-3034, 2003.

9 Alberola V, Camps C, Provencio M, Isla D, Rosell R, Vadell C, Bover I, Ruiz-Casado A, Azagra P, Jimenez U, Gonzalez-Larriba JL, Diz P, Cardenal F, Artal A, Carrato A, Morales S, Sanchez JJ, de las PR, Felip E and Lopez-Vivanco G: Cisplatin plus gemcitabine *versus* a cisplatin-based triplet *versus* nonplatinum sequential doublets in advanced non-small-cell lung cancer: a Spanish Lung Cancer Group phase III randomized trial. J Clin Oncol *21*: 3207-3213, 2003.

10 Pujol JL, Barlesi F and Daures JP: Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials. Lung Cancer *51*: 335-345, 2006.

11 Fossella F, Pereira JR, vonPawel J., Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M and Belani CP: Randomized, multinational, phase III study of docetaxel plus platinum combinations *versus* vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol *21*: 3016-3024, 2003.

12 Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M, Burkes R, Coughlin S, Kim Y and Berille J: Prospective randomized trial of docetaxel *versus* best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol *18*: 2095-2103, 2000.

13 WHO handbook for reporting results of cancer treatment. Geneva, 1979.

14 Boni C, Tiseo M, Boni L, Baldini E, Recchia F, Barone C, Grossi F, Germano D, Matano E, Marini G, Labianca R, Di CF, Bagnulo A, Pennucci C, Caroti C, Mencoboni M, Zanelli F, Prochilo T, Cafferata MA and Ardizzoni A: Triplets *versus* doublets, with or without cisplatin, in the first-line treatment of stage IIIB-IV non-small cell lung cancer (NSCLC) patients: a multicenter randomised factorial trial (FAST). Br J Cancer *106*: 658-665, 2012.

15 Quoix E, Zalcman G, Oster JP, Westeel V, Pichon E, Lavole A, Dauba J, Debieuvre D, Souquet PJ, Bigay-Game L, Dansin E, Poudenx M, Molinier O, Vaylet F, Moro-Sibilot D, Herman D, Bennouna J, Tredaniel J, Ducolone A, Lebitasy MP, Baudrin L, Laporte S and Milleron B: Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet *378*: 1079-1088, 2011.

16 Tan EH, Szczesna A, Krzakowski M, Macha HN, Gatzemeier U, Mattson K, Wernli M, Reiterer P, Hui R, Pawel JV, Bertetto O, Pouget JC, Burillon JP, Parlier Y and Abratt R: Randomized study of vinorelbine – gemcitabine *versus* vinorelbine--carboplatin in patients with advanced non-small cell lung cancer. Lung Cancer *49*: 233-240, 2005.

17 Chen YM, Perng RP, Shih JF, Tsai CM and Whang-Peng J: A randomized phase II study of vinorelbine plus gemcitabine with/without cisplatin against inoperable non-small-cell lung cancer previously untreated. Lung Cancer *47*: 373-380, 2005.

18 Smit EF, van Meerbeeck JP, Lianes P, Debruyne C, Legrand C, Schramel F, Smit H, Gaafar R, Biesma B, Manegold C, Neymark N and Giaccone G: Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group – EORTC 08975. J Clin Oncol *21*: 3909-3917, 2003.

19 Wachters FM, Van Putten JW, Kramer H, Erjavec Z, Eppinga P, Strijbos JH, de Leede GP, Boezen HM, de Vries EG and Groen HJ: First-line gemcitabine with cisplatin or epirubicin in advanced non-small-cell lung cancer: a phase III trial. Br J Cancer *89*: 1192-1199, 2003.

20 Yamamoto N, Fukuoka M, Negoro SI, Nakagawa K, Saito H, Matsui K, Kawahara M, Senba H, Takada Y, Kudoh S, Nakano T, Katakami N, Sugiura T, Hoso T, and Ariyoshi Y: Randomised

phase II study of docetaxel/cisplatin vs docetaxel/irinotecan in advanced non-small-cell lung cancer: a West Japan Thoracic Oncology Group Study (WJTOG9803). Br J Cancer *90*: 87-92, 2004.

21 Brocato N, Bruno MF, Araujo CE, Cervellino JC, Pirisi C, Temperley G, Sparrow C, Savulsky C and Balbiani LR: Treatment of non-small cell lung cancer with ifosfamide (IFO)+ 4'-epiadriamycin (EPI)+platinum *vs*. IFO+EPI: a GETLAC Study. Grupo de Estudio y Tratamiento Latinoamericano del Cancer Study. Oncology *52*: 24-31, 1995.

22 D'addario G, Pintilie M, Leighl NB, Feld R, Cerny T, and Shepherd FA: Platinum-based *versus* non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. J Clin Oncol *23*: 2926-2936, 2005.

23 Sculier JP, Lafitte JJ, Paesmans M, Thiriaux J, Alexopoulos CG, Baumohl J, Schmerber J, Koumakis G, Florin MC, Zacharias C, Berghmans T, Mommen P, Ninane V and Klastersky J: Phase III randomized trial comparing moderate-dose cisplatin to combined cisplatin and carboplatin in addition to mitomycin and ifosfamide in patients with stage IV non-small-cell lung cancer. Br J Cancer *83*: 1128-1135, 2000.

24 Gandara DR, Crowley J, Livingston RB, Perez EA, Taylor CW, Weiss G, Neefe JR, Hutchins LF, Roach RW, Grunberg SM *et al*: Evaluation of cisplatin intensity in metastatic non-small-cell lung cancer: a phase III study of the Southwest Oncology Group. J Clin Oncol *11*: 873-878, 1993.

25 Gralla RJ, Casper ES, Kelsen DP, Braun DW Jr., Dukeman ME, Martini N, Young CW and Golbey RB: Cisplatin and vindesine combination chemotherapy for advanced carcinoma of the lung: A randomized trial investigating two dosage schedules. Ann Intern Med *95*: 414-420, 1981.

26 Klastersky J, Sculier JP, Ravez P, Libert P, Michel J, Vandermoten G, Rocmans P, Bonduelle Y, Mairesse M, Michiels T, Thiriaux J, Mommen P and Dalesio O: A randomized study comparing a high and a standard dose of cisplatin in combination with etoposide in the treatment of advanced non-small-cell lung carcinoma. J Clin Oncol *4*: 1780-1786, 1986.

27 Shinkai T, Saijo N, Eguchi K, Sasaki Y, Tominaga K, Sakurai M, Suga J, Miyaoka H, Sano T, Keicho N *et al*: Cisplatin and vindesine combination chemotherapy for non-small cell lung cancer: a randomized trial comparing two dosages of cisplatin. Jpn J Cancer Res *77*: 782-789, 1986.

Received October 25, 2013
Revised November 8, 2013
Accepted November 12, 2013