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Phase II Study of Cisplatin-combined Schedules as Second-line Chemotherapy in Patients with Non-Small Cell Lung Cancer

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Abstract. *Background: The aim of this study was to evaluate the effectiveness of cisplatin- (CDDP) combined chemotherapy in non-cisplatin pretreated patients with non-small-cell lung cancer (NSCLC). The second cytotoxic drug administered was either etoposide or gemcitabine. First-line treatment was based on paclitaxel combined with either carboplatin or vinorelbine. Patients and Methods: Seventy-eight patients with histologically- or cytologically- confirmed NSCLC, having failed front-line treatment, were enrolled. All patients received 80 mg/m^2 of cisplatin as second-line treatment, on day 1, repeated every 3 weeks; in 48 patients the second agent was etoposide (120 mg/m^2) on days 1, 2 and 3, repeated every 3 weeks and in 30 patients 1 g/m^2 of gemcitabine on day 1, repeated every 3 weeks. Results: All patients were evaluable for response and toxicity. No complete responses were observed. Thirteen (16.67%) patients achieved partial response, 42 (53.85%) stable disease and 23 (29.49%) had disease progression. The median duration of response was 4 months (range 2-8+ months), median time to tumor progression (TTP) 5 months (range 2-9 months) and median survival time after starting second-line chemotherapy, 6 months (range 2-9+ months). Toxicity was acceptable: 9 patients presented with nephrotoxicity (11.54%) and 13 (16.67%) with grade 3-4 neutropenia. Conclusion: The cisplatin combination as second-line treatment in patients with NSCLC exhibited a notable degree of activity and tumor growth control was evidenced by the 16.67% partial response and 53.85% disease stability.*

Treatment of advanced non-small cell lung cancer (NSCLC) with newer cytotoxic agents, *versus* previous cytotoxic combinations including cisplatin, does not appear to have increased response rate and survival. Chemotherapy has rendered an improvement in survival in metastatic NSCLC, as reported in a meta-analysis of relevant studies (1). Large randomized trials related to the treatment of stages IIIB and IV are indicative of this (2, 3). There is a high percentage of non-responders and also of responders who relapse within a short time period. After first-line chemotherapy, patients may still have a reasonably good performance status, thus inspiring the need for further management in order to increase survival and improve the quality of life. Second-line chemotherapy treatment trials, chiefly with the recent pool of cytotoxic agents, have been carried out. Older agents such as etoposide, vindesine, epirubicin or even cisplatin have not shown a response rate of over 10% (4). Similar or higher responses have been produced by agents such as gemcitabine, vinorelbine and paclitaxel (5-11) and by docetaxel, as single-agent therapy (12-14). Cisplatin has only infrequently been applied as second-line treatment in pretreated patients with NSCLC. The existing cisplatin trials mainly utilize new agents (15). The majority of second-line chemotherapy schedules are related either to combinations of newer agents (10, 16-22) or single-agent chemotherapy (23-26) in patients pretreated with cisplatin-combined schedules.

In the present trial, cisplatin-based second-line chemotherapy was administered in combination with other agents considered to be first-line cytotoxic drugs for NSCLC, to patients who had had a non-cisplatin front-line combination. Our main objective was to determine the response rate and, secondly, to evaluate tolerance and survival.

Patients and Methods

Statistical design. In this two-step phase II study, 30 patients were to be initially enrolled and, if an objective response rate of <10% were observed, the treatment would have been abandoned; otherwise at least 20 more patients were to be enrolled. The primary end-point was the efficacy of the regimen and the secondary end-point was duration of response calculated from the

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Table I. *Second-line chemotherapy schedules.*

No. of patients	Drug	Dosage		
48	Cisplatin	80 mg/m^2	day 1	every 3 weeks
	Etoposide	120 mg/m^2	days 1,2,3	every 3 weeks
30	Cisplatin	80 mg/m^2	day 1	every 3 weeks
	Gemcitabine	1 g/m^2	day 1	every 3 weeks

day of the first demonstration of response until progressive disease. Time to progression (TTP) was calculated from the day of entry into the study until documented progressive disease. The median probability of survival and the median TTP were estimated by the Kaplan-Meier method. All reported *p* values are two-sided. A *p* value of <0.05 was considered significant.

Patient selection. All of the 78 patients enrolled had a histologically- or cytologically- confirmed diagnosis of NSCLC and bidimentionally measurable disease, normal renal function and all had been pretreated with non-cisplatin combination chemotherapy. Occasionally, mandatory unidimensional measurable disease was acceptable. Staging by objective imaging methods was performed. All patients had been pretreated with a paclitaxel-based combination: 41 with carboplatin and 37 with vinorelbine. Other eligibility criteria included: World Health Organization (WHO) performance status 0-2, a life expectancy of at least 3 months, inoperable stage IIIA-B and IV, adequate hematological parameters (absolute granulocyte count >1,500/dl, hemoglobin level >9 g/dl, and platelet count >100,000/dl), adequate hepatic (serum bilirubin <1.5 mg/dl, transaminase twice the upper limit of normal) and renal (serum creatine <1.5 mg/dl) function. Patients with brain metastases were included, if after radiation the brain lesions were improved or remained stable with clinical improvement. The lower age limit for enrollment was 18 years. Patients with a secondary malignancy were excluded unless it had been ≥10 years prior and treatment had only been surgical. The study was conducted with the approval of our Institutional Review Boards. All patients gave their informed consent before enrollment.

Treatment. All patients received cisplatin at a dose of 80 mg/m^2 for a 3-hour infusion. This was a multicenter study and the physicians at each institution were allowed to give a second agent of their choice for NSCLC. Thus, two different schedules were applied: (a) 48 patients: 80 mg/m^2 of cisplatin with 2 litres hydration the same day (day 1) and 120 mg/m^2 of etoposide infused for 20 min per day on days 1, 2 and 3, repeated every 3 weeks and (b) 30 patients: cisplatin, as in schedule (a) and 1 g/m^2 of gemcitabine infused for 60 minutes on day one, repeated every 3 weeks. A repeat of gemcitabine on day 8 was avoided because of toxicity, since the patients had undergone chemotherapy pretreatment. Second-line chemotherapy schedules are shown in Table I. Premedication included 8 mg of ondansetron *i.v.* and 8 mg of dexamethasone *i.v.* These 2 drugs were administered 1 hour before starting chemotherapy and 4 and 8 hours thereafter. Patients with response or stable disease were scheduled to undergo 6 courses. In cases of disease progression or unacceptable toxicity, treatment was abandoned. The total number of courses was 231, median 3, range 2-6.

Table II. *Patients' characteristics at start of second-line chemotherapy*.*

		No.	%
No. of patients enrolled		78	100
No. of patients evaluable		78	100
Gender			
Male		69	88.46
Female		9	11.54
Age (yr)			
Median	62		
Range	42-75		
Performance status (WHO)			
0		2	2.56
1		31	39.74
2		45	57.69
Histology			
Adenocarcinoma		43	55.13
Squamous cell		24	30.77
Undifferentiated		9	11.54
Large cell		2	2.56
Stage			
IIIA		9	11.54
IIIB		30	38.46
IV		39	50.00

*Prior treatment: paclitaxel with carboplatin or vinorelbine

Evaluation of patients. Baseline evaluation included medical history, physical examination, tumor measurement or evaluation, WHO performance status, ECG, full blood count, liver and renal function tests, urinalysis, chest and abdominal computed tomography, bone scan and occasional magnetic resonance imaging. Blood count, blood urea and serum creatine were examined before each treatment administration and 7 days after each course. Radiological tests were conducted after 2 courses of treatment or if the clinical signs were indicative of disease progression. Response and toxicity were assessed using standard WHO criteria, as follows: complete response (CR), the disappearance of any sign of demonstrable disease; partial response (PR), ≥50% reduction of measurable disease; and stable disease (SD) <50% decrease of measurable disease or up to 25% increase. The duration of response was measured from the time of documentation of response (CR or PR) to progressive disease. Time to disease progression was measured from the time of the first dose administration to disease progression. The determination of objective response on computed tomography was performed by two independent radiologists and two experienced oncologists.

Results

Demographics. From January 2002 until April 2004, 78 patients were enrolled in the study (Table II). All patients

Table III. *Response.*

	No. of patients	%
Complete response	-	-
Partial response	13	16.67
Stable disease	42	53.85
Disease progression	23	29.49

Table IV. *Hematological and non-hematological toxicities.*

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Neutropenia	6 (7.69)	5 (6.41)	9 (11.54)	4 (5.13)	24 (30.77)
Anemia	8 (10.26)	15 (19.23)	-	-	23 (29.49)
Thrombo-cytopenia	3 (3.85)	1 (1.28)	-	-	4 (5.13)
Nausea/ vomiting	23 (29.49)	2 (2.56)	-	-	25 (32.05)
Mucositis	2 (2.56)	-	-	-	2 (2.56)
Diarrhea	2 (2.56)	-	-	-	2 (2.56)
Neurotoxicity	20 (25.64)	6 (7.69)	-	-	26 (33.33)
Nephrotoxicity	6 (7.69)	3 (3.85)			9 (11.54)
Fatigue	4 (5.13)	6 (7.69)	-	-	10 (12.82)
Allergy	-	-	-	-	-
Cardiotoxicity	-	-	-	-	-

had previously undergone paclitaxel-based front-line chemotherapy.

Response. No CR was achieved. All responders had partial tumor regression: 13 (16.67%) patients showed PR, 42 (53.85%) SD and 23 (29.49%) had disease progression (Table III). The median response duration was 4 months (range 2-8+ months), the TTP was 5 months (range 2-8 months) and the median survival from the beginning of second-line chemotherapy was 6 months (range 2-9+ months). There was no difference in the response rate of those treated with cisplatin-etoposide and those with cisplatin-gemcitabine ($p=0.85$).

Toxicity. The main adverse reactions were nausea/vomiting, myelotoxicity and nephrotoxicity. Generally, toxicity was acceptable; a small percentage (11.7%) had to refrain from treatment due to blood urea and serum creatine increase after the second or third course. Hematological and non-hematological toxicities are shown in Table IV. There was no difference in the toxicity of cisplatin-etoposide *versus* cisplatin-gemcitabine.

Discussion

Many studies related to second-line chemotherapy in NSCLC have been published. This is a justified effort since chemotherapy treatment failure in advanced NSCLC is common, either due to the ineffectiveness of first-line chemotherapy or to recurrence after the initial response. Reviewing the existing data, the great majority of second-line treatments consist of combinations or single-agent chemotherapy of the newer, recent cytotoxic drugs, following first-line therapy with cisplatin combinations. Insistence on treating patients with advanced-stage NSCLC is based on studies indicating that chemotherapy (*versus* supportive care) produces a significant prolongation of survival (27). In a review article (28), some recent agents were considered to be effective when used alone or in combination as second-line treatment. These agents, vinorelbine, paclitaxel, docetaxel, gemcitabine and irinotecan, have also been administered as first-line therapy with effectiveness. The data related to these agents are controversial, rendering either a very low 'negligible' response rate or over 20% in patients pretreated with a cisplatin-combined chemotherapy. In one study, single gemcitabine second-line treatment showed a 6% response rate, which is very low, but the therapy was well-tolerated (8), whereas in another study, the same agent produced a 19% objective response rate (29). This difference in response might have been due to the patients' characteristics: in the latter study, there were more stage III than stage IV patients. Docetaxel, vinorelbine and ifosfamide have been tested, each as single-agent second-line therapy following a cisplatin front-line combination. The objective response rates were quite low: docetaxel at 100 mg/m^2 (10.8%) was the most advantageous *versus* docetaxel at 75 mg/m^2 (6.7%) and *versus* vinorelbine-ifosfamide (0.8%). These researchers concluded that docetaxel does deliver meaningful benefit (24). In another trial with a small number of patients, the response to vinorelbine was 6.5% (19).

In a review related to second-line chemotherapy, such conflicting results were criticized (30). The authors pointed

out: that a more general definition of drug resistance would be appropriate *versus* resistance to platinum only, that selection criteria for second-line treatment for NSCLC patients have not yet been defined, that guidelines for second-line NSCLC treatment based on clinical information on drug sensitivity to first-line therapy need to be developed and that more direct comparisons between well-defined groups of patients should be made (30). The same critical comments might be made with regard to several other studies. The combination of docetaxel with gemcitabine after cisplatin-related treatment was administered in NSCLC patients and the partial response rate was 15.6% with stable disease at 34.4% (31). Another second-line combination of docetaxel, this time with vinorelbine, showed a similar response rate (18%) with stable disease at 41% (22). A low response rate was observed in the application of paclitaxel as a single agent in second-line therapy in NSCLC: only 2 out of 64 patients (3%) had a partial response (9). Another trial, again using paclitaxel on a weekly basis, produced a higher second-line treatment response rate of 21% (32). From all of the different studies related to second-line chemotherapy after cisplatin, the predominating assumption is that docetaxel is the preferable treatment (10,33-35); some authors suggest that docetaxel may be the gold standard in second-line chemotherapy (11, 36).

Very few studies related to non-cisplatin front-line chemotherapy and a cisplatin combination second-line treatment have been reported. Two studies by Kakolyris *et al.* combined cisplatin with irinotecan as second-line chemotherapy in patients with NSCLC who had undergone previous treatment with a docetaxel-based therapy (with either carboplatin or gemcitabine as the second drug) (15,37). The cisplatin fixed dose was 80 mg/m^2 and that of irinotecan 100 mg/m^2 on day 1 and 110 mg/m^2 on day 8 repeated every 3 weeks. The partial response rate was 20% with a median response duration of 4 months and 20% disease stability, but disease progression was 58%. The authors interpreted the rather high response rate as being due to the lack of complete cross-resistance between the drug combinations. Another study tested second-line chemotherapy with cisplatin and vinorelbine in patients with NSCLC pretreated with paclitaxel and gemcitabine. The dose of CDDP was 80 mg/m^2 on day 1 and that of vinorelbine 25 mg/m^2 on days 1 and 8, both drugs repeated every 3 weeks; the number of patients was small (seventeen) and the responders were 3 (18%) (38). In another trial (39), second-line therapy included carboplatin instead of CDDP, combined with vinorelbine in patients who had failed a taxane-based treatment. Of the 37 treated patients, a 16% response rate was observed. These authors commented on a statistically significant benefit in patients with response and with disease stability over patients with disease progression. The present study, with cisplatin at 80 mg/m^2 combined with etoposide or gemcitabine, showed a PR rate of 16.67% with a median response duration of 4 months; stable disease was observed in 53.85% and 29.49% had disease progression. Minor differences between the previous study and ours might be due to the other cytotoxic drug which was used in combination with cisplatin.

The use of well-established agents (used over a long period of time in combination with cisplatin in front-line therapy) in our second-line chemotherapy trial rendered acceptable toxicity with the main adverse reactions being nausea/vomiting and nephrotoxicity to a mild degree.

Cisplatin combinations as second-line treatment do offer benefit to a minority of patients and the responses are at a similar level to that of non-cisplatin combinations when the latter are also used as second-line treatment.

In conclusion, the use of cisplatin combinations as second-line chemotherapy seems to have a place in the management of patients with advanced NSCLC. Although partial responses are not high, when taking into account the high percentage of disease stability (and since non-cisplatin combinations are generally preferable as front-line treatment), the cisplatin-based chemotherapy could be used in patients with normal renal function.

References

1 Non-Small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small-cell lung cancer, a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Br Med J *311*: 899-909, 1995.

2 Cullen MH, Billingham LJ, Woodroffe CM, Chetyawardana AD, Gower NH, Joshi R *et al*: Mitomycin, ifosfamide and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. J Clin Oncol *17*: 3188-3194, 1999.

3 Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J *et al*: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med *346*: 92-98, 2002.

4 Pronzato P, Landucci M, Vaira F, Vigani A and Bertelli G: Failure of vinorelbine to produce responses in pretreated non-small-cell lung cancer patients. Anticancer Research *14*: 1413-1415, 1994.

5 Hainsworth JD, Thomson DS and Greco FA: Paclitaxel by 1-hour infusion: an active drug in metastatic non-small-cell lung cancer. J Clin Oncol *13*: 1609-1614, 1995.

6 Belani CP: Single agents in the second-line treatment of non-small-cell lung cancer. Semin Oncol *25*: 10-14, 1998.

7 Crino L, Mosconi AM, Scagliotti GV, Selvaggi G, Rinaldi M, Dell GM *et al*: Gemcitabine as second-line treatment for relapsing or refractory advanced non-small-cell lung cancer: a phase II trial. Semin Oncol 25: 23-26, 1998.

8 Scullier JP, Lafitte JJ, Berghmans T, Thiriaux J, Licomte J, Efremidis A *et al*: A phase II trial testing gemcitabine as second-line chemotherapy for non-small-cell lung cancer. Lung Cancer *29*: 67-73, 2000.

9 Scullier JP, Berghmans T, Lafitte JJ, Richez M, Recloux P, Van Cutsem O *et al*: A phase II study testing gemcitabine as second-line single agent treatment for patients with advanced non-small-cell lung cancer failing after a first-line chemotherapy. Lung Cancer *37*: 73-77, 2002.

10 Laack E, Dierlamm T, Knuffmann C, Popp J, Scmied B, Durk H *et al*: Docetaxel and carboplatin as second-line chemotherapy for metastatic non-small-cell lung cancer. Lung Cancer 36: 303-307, 2002.

11 Fossella FV, Lynch T and Shepherd FA: Second-line chemotherapy for NSCLC: establishing a gold standard. Lung Cancer *38*: 5-12, 2002.

12 Fossella FV, Lee JS, Shin DM, Calayag M, Huber M, Perez-Soler R *et al*: Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small-cell lung cancer. J Clin Oncol *13*: 645-651, 1995.

13 Gandara DR, Vokes E, Green M, Bonomi P, Devore R, Comis R *et al*: Activity of docetaxel in platinum-treated non-small-cell lung cancer: results of a phase II multicenter trial. J Clin Oncol *18*: 131-135, 2000.

14 Robinet G, Thomas P, Perol M, Vergnenegre A, Lena H, Taytard A *et al*: Efficacy of docetaxel in non-small-cell lung cancer patients previously treated with platinum-containing chemotherapy. French Group of Pneumo-Cancerology. Rev Mal Respir *17*: 83-89, 2000.

15 Kakolyris S, Kouroussis Ch, Souglakos J, Agelakis S, Kalbakis K, Vardakis N, Vamvakas L and Georgoulias V: Cisplatin and irinotecan (CPT-11) as second-line treatment in patients with advanced non-small-cell lung cancer. Lung Cancer *34*: S71-S76, 2001.

16 Georgoulias V, Kouroussis Ch, Agelidou A, Boukovinas I, Palamidas P, Stavrinidis E, Polyzos A, Syrigos K, Veslemes M, Toubis M, Ardavanis A, Tselepatiotis and Vlachonikolis I, for the Lung Cancer Committee of the Hellenic Oncology Research Group (HORG): Irinotecan plus gemcitabine *vs* irinotecan for the second-line treatment of patients with advanced non-small-cell lung cancer pretreated with docetaxel and cisplatin: a multicenter, randomized phase II study. Br J Cancer 1-7, 2004. (in press)

17 Androulakis N, Kouroussis Ch, Kakolyris S, Tzannes S, Papadakis E, Souglakos J, Kotsakis A, Vardakis N, Hatzidaki D and Georgoulias V: Salvage treatment with paclitaxel and gemcitabine for patients with non-small-cell lung cancer after cisplatin- or docetaxel-based chemotherapy: a multicenter phase II study. Ann Oncol *9*: 1127-1130, 1998.

18 Androulakis N, Papadakis E, Bania E, Apostolopoulou P, Tsiafaki X, Kalofonos C, Rapti A, Toubis M, Chainis K, Kouroussis Ch, Sarra E, Vardakis N, Hatzidaki D and Georgoulias V: Second-line treatment with docetaxel (D) and gemcitabine (G) in patients with advanced non-small-cell lung cancer (NSCLC): a multicenter phase II trial. Proc Ann Soc Clin Oncol *18*: 494a, 1999.

19 Herrero CC, Martinez EN and Jaime AB: Second-line treatment with gemcitabine and vinorelbine in non-small-cell lung cancer cisplatin failures: a pilot study. Lung Cancer *27*: 47-53, 2000.

20 Iaffaioli RV, Tortoriello A, Gravina A, Facchini G, Turitto G, Ella S, Griffo S, Gentile M, Praioli G, Frattolillo A, Muto P, Libutti M, De Marino V, Illiano A and Barbarisi A: Phase I-II study of gemcitabine and paclitaxel in pretreated patients with stage IIIb-IV non-small-cell lung cancer. Lung Cancer *30*: 203-210, 2000.

21 Kosmas C, Tsavaris N, Panopoulos C, Vadiaka M, Stavroyianni N, Kourelis T, Malamos N, Antonopoulos M and Kalofonos HP: Gemcitabine and vinorelbine as second-line therapy in non-small-cell lung cancer after prior treatment with taxane+platinum-based regimens. Eur J Cancer *37*: 972-978, 2001.

22 Leu KM, Kim KM, Larson M and Schiller JH: Phase I/II of docetaxel and vinorelbine in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. Lung Cancer *34*: 105-113, 2001.

23 Crino L, Mosconi AM, Scagliotti GV, Selvaggi G, Novell S, Rinaldi M, Della Giulia M, Gridelli C, Rossi A, Calandi C, De Marinis F, Noseda M and Tonato M: Gemcitabine as second-line treatment for advanced non-small-cell lung cancer: a phase II trial. J Clin Oncol *17*: 2081-2085, 1999.

24 Fossella FV, De Vore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, moore M, Candara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F and Hammerahaimb L: Randomized phase III trial of docetaxel *versus* vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. J Clin Oncol *18*: 2354-2362, 2000.

25 Shepherd FA, Fossella FV, Lynch T, Armand JP, Rigas JR and Kris MG: Docetaxel (Taxotere) shows survival and quality-of-life benefits in the second-line treatment of non-small-cell lung cancer: a review of phase III trials. Semin Oncol *28(1 Suppl 2)*: 4-9, 200.

26 Socinski MA, Steagall A and Gillenwater H: Second-line chemotherapy with 96 h infusional paclitaxel in refractory non-small-cell lung cancer: report of a phase II trial. Cancer Invest *17*: 181-188, 1999.

27 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.

28 Ferringo D and Buccheri G: Second-line chemotherapy for recurrent non-small-cell lung cancer: do new agents make a difference? Lung Cancer *29*: 91-104, 2000.

29 Crino L, Mosconi AM, Scagliotti G *et al*: Gemcitabine as second-line treatment for advanced non-small-cell lung cancer: a phase II trial. J Clin Oncol *17*: 2081-2085, 1999.

30 Huisman C, Smit EF, Giaccone G and Postmus PE: Second-line chemotherapy in relapsing or refractory non-small-cell lung cancer: a review. J Clin Oncol *18*: 3722-3730, 2000.

31 Kakolyris S, Papadakis E, Tsiafaki X, Kalofonos C, Rapti A, Toubis M, Bania E, Kouroussis Ch, Chainis K, Androulakis N, Agelaki S, Sarra E, Vardakis N and Georgoulias V: Docetaxel in combination with gemcitabine plus rh G-CSF support as second-line treatment in non-small-cell lung cancer A multicenter phase II study. Lung Cancer *32*: 179-187, 2001.

32 Buccheri G and Ferrigno D: Second-line weekly paclitaxel in patients with inoperable non-small-cell lung cancer who fail combination chemotherapy with cisplatin. Lung Cancer *45*: 227-236, 2004.

33 Massarell E, Andre F, Liu DD, Lee JJ, Wolf M, Fandi A, Ochs J, Le Chevalier T, Fossella F and Herbst RS: A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small-cell lung cancer. Lung Cancer *39*: 55-61, 2003.

34 Dancey J, Shepherd FA, Gralla R and Kim YS: Quality of life assessment of second-line docetaxel *versus* best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial. Lung Cancer *43*: 183-194, 2004.

35 Wachters FM, Van Putten JWG, Boezen HM and Groen HJM: Phase II study of docetaxel and carboplatin as second treatment in NSCLC. Lung Cancer *45*: 255-262, 2004.

36 Georgoulias VA: Second-line chemotherapy in relapsing or refractory patients with non-small-cell lung cancer. Lung Cancer *38*: 61-66, 2002

37 Kakolyris S, Souglakos J, Agelaki S, Kouroussis Ch, Mavroudis D, Sarra E, Malliotakis P and Georgoulias V: A dose-escalation study of irinotecan (CPT-11) in combination with cisplatin in patients with advanced non-small-cell lung cancer previously treated with a docetaxel-based front-line chemotherapy. Lung Cancer *30*: 193-198, 2000.

38 De Pas T, de Braud F, Mandala M, Curigliano G, Catania C, Ferretti G, Sozzi P, Solli P and Goldhirsch A: Cisplatin and vinorelbine as second-line chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC) resistant to taxol plus gemcitabine. Lung Cancer *31*: 267-270, 2001.

39 Agelaki S, Bania H, Kouroussis Ch, Blazoyiannakis G, Souglakos J, Tsiafaki X, Kalbakis K, Rapti A, Androulakis N, Georgoulias V and Papadakis E: Second-line treatment with vinorelbine and carboplatin in patients with advanced non-small-cell lung cancer, A multicenter phase II study. Lung Cancer *34*: 77-80, 2001.

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