# Randomized Phase II Study of Paclitaxel and Carboplatin or Vinorelbine in Advanced Non-small Cell Lung Cancer

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**Abstract.** *Background: A randomized phase II trial was conducted to determine if two non-platinum protocols are able to yield a similar efficacy and toxicity profile as compared to two platinum-based doublets in advanced non-small cell lung cancer (NSCLC). Patients and Methods: A total of 61 patients were randomly assigned to a reference regimen of carboplatin and paclitaxel (repeated every 3 weeks) or to one of three experimental regimens: paclitaxel plus vinorelbine (repeated every 3 or 4 weeks) and carboplatin plus paclitaxel (repeated every 4 weeks). Results: The objective remission rate for all the patients was 34.1%. The median progression-free survival for all the patients was 3 months. The median overall survival and one-year overall survival were 6 months and 21.5%, respectively. Toxicity was moderate and manageable. Response, survival and toxicity did not significantly differ between the four treatment groups. Conclusion: The efficacy and toxicity profile of platinum-free combinations is comparable to that of platinum-based doublets.*

Data from randomized prospective trials have indicated that quality of life can be improved and median overall survival (OS) prolonged by about 10 weeks in stage IIIB with malignant pleural effusion and stage IV non-small cell lung cancer (NSCLC) by platinum-containing palliative chemotherapy (1). Due to similar efficacy, but a more favorable toxicity profile, carboplatin is preferred over cisplatin in the first-line treatment of advanced NSCLC by many groups (2).

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Over the past years, novel cytostatics, *e.g.*, vinorelbine, paclitaxel, docetaxel, gemcitabine and pemetrexed have been shown to be effective in NSCLC. In combination with cisplatin or carboplatin, remission rates up to 50% have been reported (3).

In a prospective randomized study, four platinum-containing regimens were compared in the first-line treatment of NSCLC. Response rates and overall survival did not show statistically significant differences. However, the rate of high-grade toxicities in the carboplatin plus paclitaxel arm was significantly less than that of the other treatment groups. Consequently, the combination of carboplatin and paclitaxel was generally accepted as the new standard regimen in the first-line palliative treatment of advanced NSCLC in North America in 2002 (4).

Since single-agent paclitaxel yields remission rates of 15-40% and vinorelbine is an established option in the palliative treatment of advanced NSCLC (5), the question of whether a platinum-free protocol consisting of paclitaxel and vinorelbine is able to achieve equal efficacy compared with the standard regimen consisting of paclitaxel and carboplatin is of interest. Furthermore, the possible reduction of platinum-associated toxicities (*e.g.*, nausea, emesis, hematotoxicity, nephrotoxicity, ototoxicity) in the platinum-free combinations is of clinical relevance.

In the presented study, a platinum-containing and a platinum-free protocol were compared regarding efficacy and toxicity. In both regimens, two different dose intervals were evaluated, resulting in a randomized phase II trial with four arms.

## Patients and Methods

*Eligibility criteria.* Patients with newly diagnosed and histologically proven Union for International Cancer Control (UICC) stage IIIB (with malignant pleural or pericardial effusion) or stage IV NSCLC without the option of curative surgery or radiotherapy were included. Other inclusion criteria were: age ≥18 years, WHO performance status ≤3, life expectancy >3 months, no prior cytostatic treatment, evaluable tumor manifestations, leukocytes

≥3.0/nl, platelets ≥100/nl, absolute neutrophil count ≥1.0/nl, serum creatinine ≤1.5-fold of normal value, transaminases ≤3-fold of normal value with the exception of tumor-associated elevations, and negative pregnancy test in women with child-bearing potential. Patients were excluded from the study for the following reasons: curative therapeutic option, cerebral metastasis with clinical symptoms, pregnancy and breast feeding, women with child-bearing potential without effective contraception during treatment, inability to give informed consent, second malignancy with the exception of carcinoma *in situ* of the uterine cervix or the skin, basalioma or curatively treated malignant melanoma with relapse-free interval of ≥5 years, unstable or crescendo angina pectoris, malignant cardiac arrhythmias, acute myocardial infarction, stage III or IV heart failure according to the New York Heart Association (NYHA) classification, preexisting neurotoxicity National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade ≥2, concomitant application of other cytostatic agents or immune-modulating agents, concomitant application of large-volume radiation therapy with the possibility of hematological toxicity, allergies or other contraindications to carboplatin, paclitaxel and/or vinorelbine and active infections.

Informed consent was obtained from all the patients before study entry, and the study was approved by the Institutional Ethics Committee.

*Study design*. The patients were randomly assigned to one of four treatment arms (A-D), as shown in Table I. Mandatory supportive treatment included a 5-$HT_3$ receptor antagonist (*e.g.*, ondansetron or tropisetron) before all the cytostatics and dexamethasone, clemastine and ranitidine before paclitaxel application. Additional supportive treatment was allowed and administered at the treating physician's discretion. Arm A was chosen as the reference arm due to its favorable efficacy-toxicity relationship as previously reported by Schiller *et al*. (4). After initial staging procedures (computed tomography (CT) scans of chest and/or abdomen, serum tumor markers), treatment response was monitored with CT scans of involved areas (every 8 weeks during treatment and every 12 weeks thereafter) and the respective serum tumor markers, if applicable. The patients were evaluated for treatment-related toxicity with weekly complete blood counts as well as interval history, physical examination, serum creatinine, serum electrolytes and liver function tests before every chemotherapy administration. Treatment was stopped after six treatment cycles, at disease progression or for the following reasons: unacceptable treatment-related toxicity (*i.e.*, NCI CTC grade IV except for hematotoxicity), neurotoxicity ≥ NCI CTC grade 3, or nephrotoxicity ≥NCI CTC grade 2. Dose modifications due to hematotoxicity were performed as follows:

a) Leukocytes <3/nl and/or thrombocytes <100/nl before day 1 of the respective treatment cycle: treatment was delayed by one week and dose reductions of 30% were mandatory in all following treatments and for all the chemotherapeutics.

b) Leukocytes <1.5/nl and/or thrombocytes <80/nl before days 8 or 15 of the respective treatment cycle: dose reductions of 30% in all the following treatments and for all the chemotherapeutics, treatment was given regularly on days 8 and 15.

*Statistical considerations*. The enrollment goal for this randomized, multicenter, prospective phase II study was 80 patients (20 patients per treatment arm). The primary endpoints were disease control rate (*i.e.*, stable disease (SD) plus partial (PR) or complete remission (CR)) and toxicity (evaluated using the NCI CTC v2.0). Secondary endpoints were remission rate, progression-free survival (PFS) and one-year overall survival (OS) rate. Only the patients who received more than one treatment course were evaluable for response. Tumor size measurement was performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (6). Survival was evaluated using the Kaplan-Meier method and the log-rank test. PFS was measured from the start of treatment to disease progression or death as a result of NSCLC progression. Survival was measured from the first treatment to death or last follow-up. The four treatment arms were evaluated for statistically significant differences in response rate and toxicity using the Chi-square and Fisher's exact test. All the analyses had a significance level of 0.05 and were performed using the software package SPSSWIN, release 17.0 (IBM, Munich, Germany).

## Results

*Patient and treatment characteristics*. A total of 64 patients (of whom 61 were evaluable) from two participating centers were enrolled between 2003 and 2005. The study had to be closed prematurely prior to the enrollment goal of 80 patients due to slow patient accrual. The patients' characteristics are provided in Table I and were similar in the four treatment groups.

A total of 189 treatment courses were administered. Eleven (18%) of all the patients received the predefined maximum treatment of 6 cycles. The rate of patients who were given the maximum of 6 cycles was highest in arm A (n=5; 31.5%), whereas the highest percentages of patients who received only one treatment course were noted in arms B (n=5; 33.4%) and D (n=7; 46.7%). The median number of treatment cycles was 3 for all the patients, 3.5 in arm A, 3 in arms B and C and 2 in arm D.

*Response and survival*. Detailed response data are given in Table II. Only 41 out of the 61 patients (67.2%) were evaluable for response, 20 patients were lost to follow-up or received fewer than 2 treatment cycles and were therefore not evaluable per protocol. The objective remission rate (CR and PR) for all the patients was 34.1%. Eight patients (19.5%) had SD and 19 (46.3%) showed progressive disease (PD). Statistical testing did not show any significant differences in response between the four treatment arms using the Chi-square ($p$=0.192) and Fisher's exact test ($p$=0.120).

The survival data are reported in Table III. The Kaplan-Meier plots of PFS for all four treatment arms are shown in Figure 1. A total of 51 (83.6%) patients progressed during treatment or follow-up. The median PFS for all the patients was 3 (95% confidence interval (CI), 1.9-4.1) months, and the one-year PFS was 13.5% (95% CI, 3.6-23.4%). After 18 months, 10.2% (95% CI, 1.0-19.4%) of the patients were progression-free. PFS did not show statistically significant differences between the treatment groups using the log-rank test ($p$=0.583).

Table I. *Patient characteristics and treatment regimens*.

| Variable | N (%) | | | | |
|---|---|---|---|---|---|
| | All patients N=61 | Arm A N=16 (26%) | Arm B N=15 (25%) | Arm C N=15 (25%) | Arm D N=15 (25%) |
| | (100%) | Carboplatin AUC 5 *i.v.* day 1 + paclitaxel 175 mg/m$^2$ *i.v.* day 1 (repeat day 22) | Paclitaxel 175 mg/m$^2$ *i.v.* day 1 + vinorelbine 20 mg/m$^2$ *i.v.* days 1 and 8 (repeat day 22) | Carboplatin AUC 5 *i.v.* day 1 + paclitaxel 100 mg/m$^2$ *i.v.* days 1, 8 and 15 (repeat day 29) | Paclitaxel 100 mg/m$^2$ *i.v.* days 1, 8 and 15 + vinorelbine 15 mg/m$^2$ *i.v.* days 1, 8 and 15 (repeat day 29) |
| Gender | | | | | |
| Female | 24 (39.3) | 9 (56.2) | 8 (53.3) | 2 (13.3) | 5 (33.3) |
| Male | 37 (60.7) | 7 (43.7) | 7 (46.6) | 13 (86.6) | 10 (66.7) |
| Median age (years) | 59 (range, 34-85) | 58.5 (range, 44-79) | 62 (range, 48-85) | 56 (range, 43-74) | 59 (range, 34-73) |
| Karnofsky performance status (%) | | | | | |
| 100 | 5 (8.2) | 2 (12.5) | 1 (6.6) | 0 | 2 (13.3) |
| 80-90 | 50 (82.0) | 11 (68.7) | 13 (86.6) | 13 (86.6) | 13 (86.6) |
| 60-70 | 5 (8.2) | 2 (12.5) | 1 (6.6) | 2 (13.3) | 0 |
| 50 | 1 (1.6) | 1 (6.2) | 0 | 0 | 0 |
| Stage | | | | | |
| IIIB | 5 (8.2) | 2 (12.5) | 0 | 2 (13.3) | 0 |
| IV | 56 (91.8) | 14 (87.5) | 15 (100) | 13 (86.6) | 14 (93.3) |
| Histology | | | | | |
| Adenocarcinoma | 36 (59.0) | 9 (56.2) | 9 (60.0) | 10 (66.7) | 8 (53.3) |
| NSCLC, not otherwise specified | 9 (14.8) | 1 (6.2) | 2 (13.3) | 1 (6.6) | 5 (33.3) |
| Squamous cell carcinoma | 8 (13.1) | 4 (25.0) | 2 (13.3) | 0 | 2 (13.3) |
| Large-cell carcinoma | 6 (9.8) | 1 (6.2) | 1 (6.6) | 4 (26.6) | 0 |
| Adenosquamous carcinoma | 2 (3.3) | 1 (6.2) | 1 (6.6) | 0 | 0 |

Table II. *Response data*.

| Variable | N (% of all patients) | N (% of patients in treatment arm) | | | |
|---|---|---|---|---|---|
| | All patients N=41 (100%) | Arm A N=11 (26.8%) | Arm B N=9 (22%) | Arm C N=13 (31.7%) | Arm D N=8 (19.5%) |
| Complete remission | 2 (4.9) | 0 | 0 | 1 (7.7) | 1 (12.5) |
| Partial remission | 12 (29.3) | 4 (36.4) | 2 (22.2) | 4 (30.8) | 2 (25.0) |
| Stable disease | 8 (19.5) | 1 (9.1) | 4 (44.4) | 0 | 3 (37.5) |
| Progressive disease | 19 (46.3) | 6 (54.5) | 3 (33.3) | 8 (61.5) | 2 (25.0) |

The Kaplan-Meier plots of OS for the four treatment arms are shown in Figure 2. The median OS for all the patients was 6 (95% CI, 3.4-8.6) months. The one-year OS was 21.5% (95% CI, 10.0-33.0%) and two-year OS 9.8% (95% CI, 0.1-19.5%). The median OS was not significantly different between the four treatment groups using the log-rank test ($p$=0.188). A total of 48 (78.7%) out of all the patients died during treatment or follow-up: 44 due to disease progression, one due to neutropenic sepsis (treatment arm A), and in three patients, the cause of death was unknown.

*Toxicity*. Selected severe (NCI CTC grade III and IV) toxicity data are reported in Table IV. Sixty out of 61 the patients were evaluable. Leukopenia grade I-IV was significantly more frequent in the platinum-free treatment arms B and D ($p$=0.036) as opposed to arms A and C. However, there was no significant difference in grade III and IV leukopenia. Nevertheless, there was a trend ($p$=0.066) towards a higher rate of grade III and IV infections in arm D, and the rate of grade I-IV infections was significantly higher ($p$=0.022) as compared to arms A-

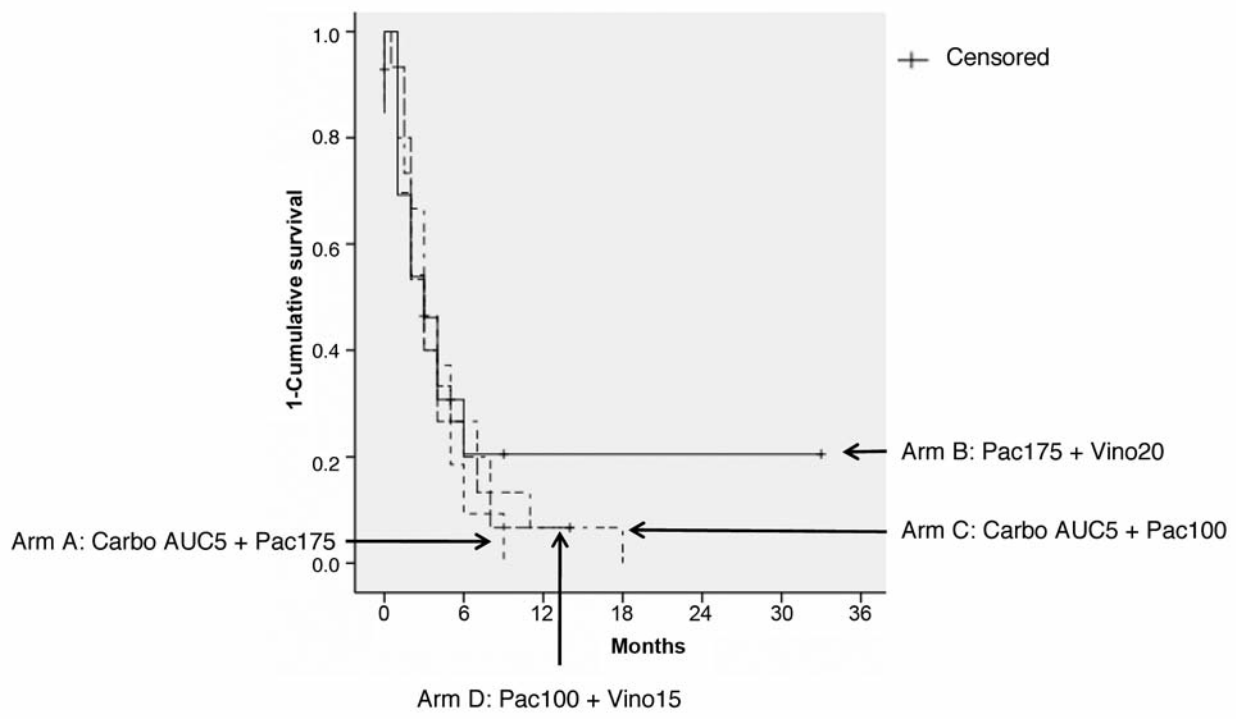


Figure 1. *Kaplan-Meier plots of progression-free survival for the four treatment arms.*

Table III. *Survival data.*

| Variable | All patients N=61 (100%) | Arm A N=16 (26%) | Arm B N=15 (25%) | Arm C N=15 (25%) | Arm D N=15 (25%) |
|---|---|---|---|---|---|
| Median progression-free survival, months (95% confidence interval) | 3 (1.9-4.1) | 3 (1.1-4.9) | 4 (1.5-6.5) | 3 (2.1-3.9) | 4 (1.0-7.4) |
| Median overall survival, months (95% confidence interval) | 6 (3.4-8.6) | 9 (5.8-12.2) | 12 (2.1-21.9) | 4 (2.1-5.9) | 5 (1.5-8.5) |
| One-year overall survival, % (95% confidence interval) | 21.5 (10.0-33.0) | 8.8 (7.4-25.0) | 43.2 (16.6-69.8) | 20 (0.7-40.7) | 10.2 (8.4-28.8) |

C. Grade III and IV anemia and thrombocytopenia tended to be more frequent in the platinum-containing arms A and C. One treatment-related death occurred in arm A as a result of neutropenic sepsis. Non-hematological toxicity (polyneuropathy and nausea/vomiting) was infrequent and manageable in all the arms.

Dose modifications due to treatment-related toxicity were implemented in 13 (21.3%) of the patients, and in 10 of these, dose reduction was performed over only one treatment cycle. The dose modifications were necessary almost exclusively due to hematological toxicity. Due to the overall infrequent need for dose reductions, statistical tests for possible differences between the treatment arms could not be performed.

## Discussion

Kosmidis *et al.* (7) found no difference in efficacy and toxicity comparing carboplatin plus paclitaxel *versus* paclitaxel and gemcitabine which was in accordance with the present findings. However, another study (8) found a statistically significant difference in efficacy and toxicity in favor of vinorelbine and gemcitabine as compared to carboplatin and vinorelbine. The present study confirmed that platinum-free combinations represent a viable option in the treatment of advanced NSCLC and expand the arsenal of therapeutic options.

The disease control rates in this study were similar to published data. The objective response rates (CR and PR) of

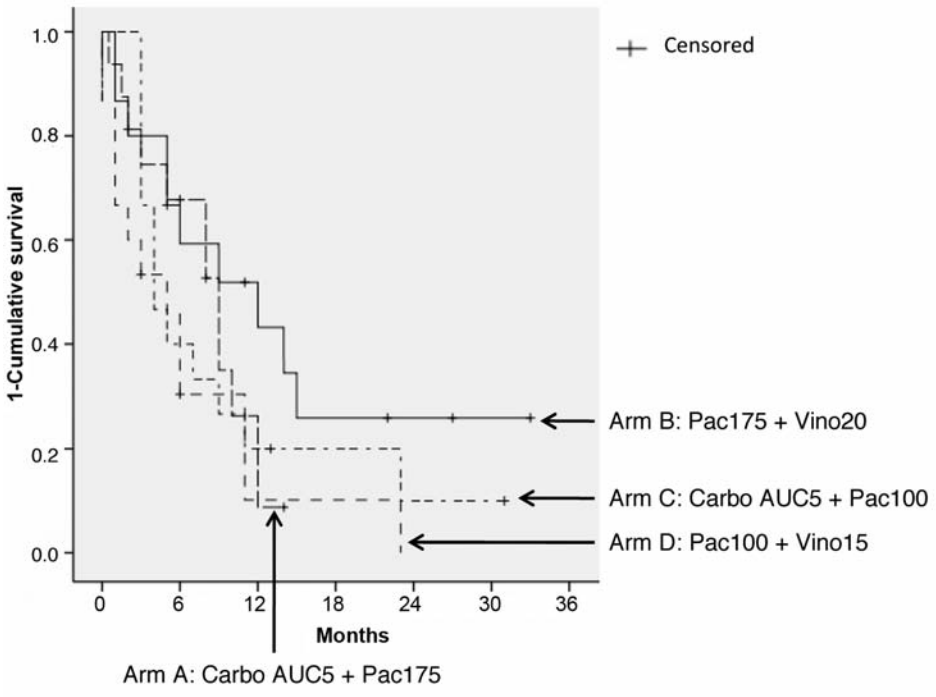


Figure 2. *Kaplan-Meier plots of overall survival for the four treatment arms*.

Table IV. *Selected grade III and IV toxicity (grading according to the National Cancer Institute Common Toxicity Criteria) and p-values*.

| Variable | N (% of all patients) | N (% of patients in treatment arm) | | | | *P*-value |
|---|---|---|---|---|---|---|
| | All patients N=60 (100%) | Arm A N=15 (25%) | Arm B N=15 (25%) | Arm C N=15 (25%) | Arm D N=15 (25%) | |
| Anemia | 6 (10.0) | | | | | 0.513 |
| Grade III | | 1 (6.6) | 0 | 1 (6.6) | 1 (6.6) | |
| Grade IV | | 2 (13.3) | 0 | 1 (6.6) | 0 | |
| Leukopenia | 20 (33.3) | | | | | 0.220 |
| Grade III | | 2 (13.3) | 4 (26.6) | 2 (13.3) | 1 (6.6) | |
| Grade IV | | 1 (6.6) | 2 (13.3) | 2 (13.3) | 6 (40.0) | |
| Thrombopenia | 7 (11.6) | | | | | 0.525 |
| Grade III | | 2 (13.3) | 0 | 1 (6.6) | 0 | |
| Grade IV | | 1 (6.6) | 1 (6.6) | 1 (6.6) | 1 (6.6) | |
| Neutropenia | 14/51 (27.5) | | | | | 0.496 |
| Grade III | | 2 (14.3) | 4 (33.3) | 0 | 3 (27.3) | |
| Grade IV | | 1 (7.1) | 1 (8.3) | 1 (7.1) | 2 (18.2) | |
| Febrile neutropenia | 5 (8.3) | | | | | 0.542 |
| Grade III | 0 | 1 (6.6) | 1 (6.6) | 2 (13.3) | | |
| Grade IV | 1 (6.6) | 0 | 0 | 0 | | |
| Infections | 12 (20) | | | | | 0.066 |
| Grade III | | 1 (6.6) | 2 (13.3) | 1 (6.6) | 6 (40) | |
| Grade IV | | 2 (13.3) | 0 | 0 | 0 | |
| Polyneuropathy | 5 (8.3) | | | | | |
| Grade III | | 0 | 3 (20) | 2 (13.3) | 0 | 0.120 |
| Grade IV | | 0 | 0 | 0 | 0 | |
| Nausea | 5 (8.3) | | | | | 0.699 |
| Grade III | | 1 (6.6) | 1 (6.6) | 3 (20) | 0 | |
| Grade IV | | 0 | 0 | 0 | 0 | |
| Vomiting | 3 (5) | | | | | 0.559 |
| Grade III | | 0 | 1 (6.6) | 2 (13.3) | 0 | |
| Grade IV | | 0 | 0 | 0 | 0 | |

36.4% (arm A) and 38.5% (arm C) were comparable to other studies containing platinum agents in which response rates of 35% to 40% have been reported (9-11). Similarly, the response rates of 22.2% (arm B) and 37.5% (arm D) resemble those of other platinum-free protocols with response rates ranging from 21% to 41% (5, 12-18).

The median PFS in arms A and C was approximately 3 months lower than in other studies with platinum-based regimens (9, 19, 20), whereas in the platinum-free arms B and D, the PFS of 4 months was comparable to that of published data (21-23). The median OS in arm A (9 months) was comparable to other platinum-based protocols (8.1-12.3 months), but the median OS in arm C was lower (4 months) (4, 5, 7, 24-26). For non-platinum-based doublets, a median OS of 8.3 to 13.5 months has been reported (4, 14). The median OS of arm B (12 months) fell within that range, whereas that of arm D (5 months) did not. One-year survival rates with platinum-based chemotherapy range from 28% to 47% (5, 7, 9, 20, 26-29). The results of study arms A and C were inferior to that. With regard to platinum-free protocols, the results of arm B were comparable and those of arm D inferior to previously published data, with one-year survival rates being around 40% (7, 30).

Toxicity was generally moderate and manageable with the exception of one therapy-related death due to neutropenic sepsis in arm A. There was no statistically significant difference in toxicity between all four treatment arms. There was a non-significant trend towards higher rates of grade III/IV leukopenia, neutropenia and infections in the platinum-free arms which was in accordance with the literature on combination treatment with taxanes and vinorelbine reporting an incidence of leukopenia of up to 70% (31, 32). Regarding grades I-IV combined, there were significantly more infections in arm D than in the other treatment arms. Vinorelbine-containing chemotherapy is known to carry a high risk of leukopenia, neutropenia and infections (33). The patients treated with carboplatin and paclitaxel tended to have a higher incidence of grade III/IV anemia and thrombopenia, and high rates of both toxicities have been reported for this combination (7, 26, 27). Non-hematological severe toxicity was infrequent and manageable in all the arms.

This study had several limitations. Although the patient characteristics (Table I) were similar to those of other published studies on grade III and IV NSCLC (4, 19, 34-36), the recruitment goal of 20 patients per arm was not reached. The differences in survival in the four treatment arms compared to published data are most likely explained by the low number of patients and selection bias. A considerable number of patients were lost to follow-up and only 41 patients were evaluable for response. Nevertheless, the results confirmed that platinum-containing and platinum-free doublets can be administered safely and with comparable efficacy and toxicity in patients with advanced NSCLC. This represents an important expansion in therapeutic options for these patients with the possibility of a more individualized treatment in NSCLC. Randomized controlled trials with higher numbers of patients are warranted to confirm these results.

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## Conflict of Interest Statement

None declared.

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