A Randomized Phase II Trial Assessing in Advanced Non-small Cell Lung Cancer Patients with Stable Disease after Two Courses of Cisplatin-Gemcitabine an Early Modification of Chemotherapy Doublet with Paclitaxel-Gemcitabine Versus Continuation of Cisplatin-Gemcitabine Chemotherapy (GFPC 03-01 Study)

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Background: There is no consensus on the optimal treatment for patients with advanced non-small cell lung cancer and stable disease after cisplatin-based chemotherapy. The objective of the trial was to evaluate a switch to a different dual-agent chemotherapy.

Methods: Patients with stage IV non-small cell lung cancer and stable disease after two cycles of cisplatin (P) and gemcitabine (G) (P day1 (d_1): 75 mg/m^2, G: 1250 mg/m^2 d_1 and d_8 every 3 weeks) were randomized to receive either two further cycles of PG (arm A) or paclitaxel (100 mg/m^2 d_1, d_8, d_{15}) plus gemcitabine (1250 mg/m^2 d_1 and d_8, every 4 weeks) (arm B).

Results: Two-hundred-twenty-eight patients were enrolled between October 2003 and August 2006. After two cycles of PG, 98 patients (43%) had stable disease; 87 were randomized: 45 to arm A and 42 to arm B. The objective response rates were 15.6% (6.5–29.4) and 21.4% (10.3–36.8) in arms A and B. Overall survival after randomization was 9.6 months (7.0–13.8) in arm A and 9.3 months (7.4–13.3) in arm B. Adverse events were similar in the two arms for hematological and non hematological toxicities.

Conclusions: Sequential first-line chemotherapy in these patients is feasible with no difference in response rates. These results do not warrant a phase III trial.

Key Words: NSCLC, Stage IV, Sequential chemotherapy.

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The first-line treatment generally recommended for patients with stage IV non-small cell lung cancer (NSCLC) who are in good general condition (performance status 0 or 1) consists of four to six cycles of doublet chemotherapy with a platinum salt plus a third-generation drug. The drugs usually combined with platinum are docetaxel, paclitaxel, vinorelbine, and gemcitabine, all of which have similar efficacy.[1–3] Most responses occur early after two cycles of chemotherapy.[4] Responder patients show a symptomatic improvement in 61% of cases after 1 course of chemotherapy and in 96% of cases after 2 courses.[5] Given the cumulative toxicity of platinum salts, these data support early assessment of the treatment response, after only two courses. The choice of treatment is then fairly simple for responders (the same treatment should be continued) and also for patients who progress (second-line treatment, depending on their general condition). More problematic in clinical practice is the case of patients with stable disease after two courses of cisplatin-based therapy. Indeed, stabilization depends on the growth kinetics of the tumor, its cellular heterogeneity, and treatment efficacy. The RECIST criteria[6] define patients with stable disease as those with responses below 30% and progression below 20%. However, these patients are heterogeneous, some having an early response and others progressing. In addition, tumor stabilization on treatment can provide a survival benefit.[7] This is clearly the case of second-line treatments, where the rate of disease control and the time to progression both correlate with survival.[8,9] Evaluation of the clinical benefit possibly associated with tumor stabilization can contribute to the

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choice of subsequent therapy. In clinical practice, disease stabilization during chemotherapy, especially after early assessment, raises the choice between continuing with the same drugs and switching to a different chemotherapy regimen. Switching treatment allows other active drugs to be introduced, while at the same time avoiding cross-resistance[10,11] and cumulative toxicity. Alternative chemotherapies have already been used,[12,13] but no survival benefit has so far been demonstrated. The use of a platinum-free doublet could reduce toxicity[14] while preserving efficacy.[15] Alternating paclitaxel and gemcitabine administration has been proposed as first-line treatment,[16] based on synergistic effects.[17] The present study (the Groupe Français de Pneumo-Cancérologie [GFPC] 03-01 trial) was designed to evaluate the consequences of replacing a platinum salt by paclitaxel in patients with stable NSCLC after two courses of cisplatin-gemcitabine combination therapy. We postulated that the sequential treatment might yield better response rates, longer survival, and less toxicity. The choice of the weekly regimen was based on previous studies,[16,18] which showed that weekly infusions yielded better dose intensity with less toxicity.

PATIENTS AND METHODS

Patients

Patients were eligible if they had never-treated, histologically or cytologically proven stage IV or pleural stage IIIB NSCLC (adenocarcinoma, squamous cell carcinoma, large-cell carcinoma), a performance status <2, age between 18 and 70 years, a measurable target lesion according to the RECIST criteria,[6] satisfactory renal, hematologic and cardiac function, no peripheral neuropathy and no other chronic progressive disease. The patients' written informed consent was required. Patients were ineligible if they had other histologic types, brain metastases, a superior vena cava syndrome, any severe organic disorder, a history of cancer, or concurrent radiotherapy. Exclusion criteria included contraindications to steroid therapy and allergy to Polysorbate 80. The initial evaluation comprised a physical examination, hematological, hepatic and renal tests, tumor assessment based on radiography, cerebral, thoracic and subdiaphragmatic computed tomography, bone scintigraphy, and a cardiac and neurologic work-up. The protocol was approved by the ethics committee of Limoges Hospital on July 29, 2003.

Treatment Protocol

We chose a phase II randomized trial format because it allowed us to assess the effectiveness of the experimental arm with a small number of patients, before possibly proceeding with a phase III trial (which needed more patients). The inclusion of a standard treatment arm helped to avoid a selection bias served to control the response rate with the usual treatment. Randomization was stratified according to performance status (0 versus 1), and the number of metastatic sites (≤ 1 versus >1). The patients received two 21-day courses of cisplatin-gemcitabine (cisplatin 75 mg/m^2 day 1 (d_1), gemcitabine 1250 mg/m^2, d_1, d_8) with dose adjustment according to hematological status. If the nadir polymorphonuclear cell count was below 500 for 7 days and/or the platelet count was below 25,000, the gemcitabine and cisplatin doses were reduced by 20%. The patient left the trial if a new episode occurred after this first dose reduction. If the blood cell counts before each course showed a polymorphonuclear neutrophil count below 1500 and/or a platelet count below 100,000, treatment was postponed for a week. If treatment had to be postponed for more than 2 weeks, the patient left the trial. The doses were also adjusted in case of peripheral neurotoxicity and renal or hepatic impairment. After these two treatment courses, patients who were not assessable, patients who were in progression and patients who had objective responses left the study and were treated as decided by the investigator. Patients with stable disease in the RECIST system were randomized between two new 21-day courses of cisplatin-gemcitabine (arm A, control) or two 21-day courses of paclitaxel-gemcitabine, as described by De Pas,[18] consisting of paclitaxel 100 mg/m^2 on d_1, d_8, and d_{15}; and gemcitabine 1250 mg/m^2 on d_1 and d_8 (arm B, experimental). In case of hematological toxicity (polymorphonuclear neutrophils <1500 and/or platelets $<100{,}000$), treatment with paclitaxel and gemcitabine was postponed for a week and the doses of the two drugs were reduced by 20%. If treatment had to be postponed more than twice for a week, the patient left the trial. Regardless of the treatment arm, after completing the four courses the patients were simply monitored until they progressed. The choice of treatment after disease progression was left to the investigator.

Endpoints

The response to treatment was evaluated every two courses (with the repetition of the initial examination to evaluate the target was done systematically). Supplementary investigations were performed if clinical signs of disease progression were present. Responses were defined according to RECIST criteria.[6] Toxicity was assessed with National Cancer Institute-Common Toxicity Criteria (version 2.0).[19] Treatment was halted in case of toxicity, progression, study completion, or refusal to continue. All objective responses were confirmed 4 weeks later. All evaluations were reviewed blindly by the GFPC panel of investigators. Grade $\geq$III toxicity was also reviewed by the panel, together with the potential responsibility of the study treatments.

Statistical Analysis

The main end point was rate of objective responses after four courses (two courses after randomization) in the intention-to-treat analysis. The required number of patients for the experimental arm was calculated with Simon's two-step method.[20] For a type 1 error of 5%, a type 2 error of 20%, the required number of subjects was 18 for stage 1 and 43 for stage 2, with the above hypotheses: the experimental strategy had to be rejected at the first stage if the response rate was $<10\%$ (2 responses or less/18); passage to phase III would be recommended if the response rate was $>25\%$ (8 responses or more/43), with sufficient efficacy. A secondary end point was the response duration in patients with objective responses. Progression free survival (PFS) and overall survival (OS) were studied in all the patients (from an intent to treat perspective). Tolerability was analyzed per course and per patient in all the patients. Quantitative variables were expressed as means or medians and standard deviations or interquartiles ranges. Qualitative variables

were expressed as frequency and percentages with 95% confidence intervals. Percentages were compared between groups by using the χ^2 test or Fisher's exact test as appropriate. Quantitative variables were compared with Student *t* test or Wilcoxon's test for unpaired series when the variable was not normally distributed. OS, PFS, and time under observation were analyzed with the Kaplan-Meier method. Given the objective of the study, the two treatment arms were not compared with each other. SAS software version 8 (SAS Inc., Cary, NC) and Epi-Info V6.04 (CDC, Atlanta) were used for statistical analysis.

RESULTS

Between October 2003 and August 2006, 228 patients were enrolled in the study by 30 centers (Appendix). Their characteristics are shown in Table 1. Most of the patients

TABLE 1. Characteristics of the Overall Population and of the Two Treatment Subgroups ($n = 87$)

	All Patients ($n = 228$)		Arm A ($n = 45$)		Arm B ($n = 42$)		
	N	%	N	%	N	%	
Age[a] (yr)							$p = 0.004$[b]
Median	57		59		56		
Range	(52–62)		(55.9–60.3)		(52.6–57.2)		
Sex[c]							$p = 0.54$[b]
Male	182	79.8	34	75.6	34	81	
Female	46	20.2	11	24.4	8	19	
Performance status[c]							$p = 0.76$[b]
0	110	48.2	21	46.7	21	50	
1	118	51.8	24	53.3	21	50	
Histological type[c]							$p = 0.48$
Squamous cell	54	23.7	28	62.2	26	62	
Adenocarcinoma	139	61.3	12	26.7	8	19	
Large cell	35	15.3	5	11.1	8	19	
Metastatic sites[c]							$p = 0.54$[b]
≤1	89	39.0	20	44.4	16	38	
>1	139	61.0	25	55.6	26	62	
Stage[c]							$p = 0.53$[b]
IIIB	7	3.1	2	4.4	1	2.4	
IV	221	96.9	43	95.6	41	97.6	

[a] Student *t* test.
[b] Comparison between arm A and B.
[c] χ^2 or Fisher's exact test.

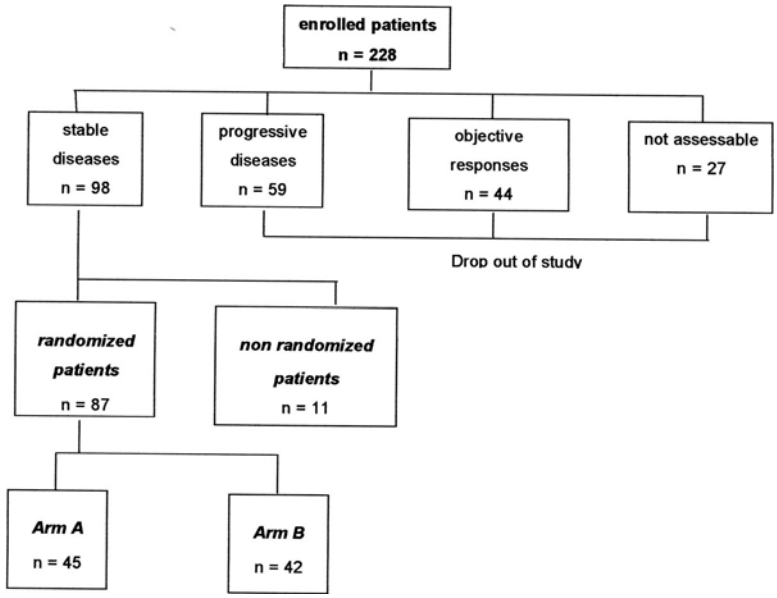

FIGURE 1. Flow chart of the study.

were men (80%) and 61% had adenocarcinomas. After 2 courses of cisplatin-gemcitabine, 59 patients [25.9%; 20.3–32.1] were in progression, 44 [19.3%; 14.4–25.0] had objective responses, and 27 [11.8%; 7.9–16.8] were not assessable. The investigators considered that 98 patients [43%; 36.9–49.7] had stable disease, but panel review subsequently excluded 4 patients (1 in progression and 3 with objective responses). Furthermore, one patient refused to continue the protocol and six had a deterioration of their performance status that prevented them from continuing in the study (Figure 1). Thus, 87 patients were randomized, 45 to arm A and 42 to arm B. As shown in Table 1, the characteristics of the patients were similar in the two arms, although mean age was slightly higher in arm A. The first stage, focusing on 18 patients, showed 3 objective responses in arm B (paclitaxel-gemcitabine), with acceptable toxicity, authorizing the study to continue. Six patients were not assessable in the final analysis (three in each arm). At the end of the two stages, among the randomized patients, the objective response rate was 15.6% [6.5–29.4] (7 patients) in arm A (continued cisplatin + gemcitabine) and 21.4% [10.3–36.8] (9 patients) in arm B (paclitaxel–gemcitabine). The rate of disease control was 68.9% in arm A and 80.9% in arm B. Numerically, there were more progressions in arm A and more cases of stable disease and responses in arm B (Table 2, Figure 2). Among the non randomized patients, the relative dose intensity was 0.98 for cisplatin and 0.97 for gemcitabine after 2 courses. For patients randomized to arm B, after 4 courses the relative dose intensity was 0.99 for cisplatin, 0.99 for paclitaxel, and 0.97 for gemcitabine. For patients randomized to arm A, it was 0.98 for cisplatin and 0.96 for gemcitabine. Progression-free survival and OS, calculated from the randomization date, were similar in the two arms, (Figure 3). The median PFS, also calculated from randomization was 7.4 months [5.4–11.4] in arm A and 6.9 months [5.0–9.0] in arm B. The median survival time from the date of diagnosis was 11.0 months [8.6–15.4] in arm A and 10.7 months [8.7–14.9] in arm B. Among the non randomized patients, the median survival time after inclusion was 13.8 months for responders and 4.7 months for patients who were in progression after two courses. The dynamics of the responses differed in the two arms. In arm A (control), the response rate was the same after four courses as after two courses. In arm B (experimental), some new responses were obtained after the full four courses compared with the first two courses (Figure 2). Toxicity was acceptable in both arms (Table 3). No grade 3–4 nausea-vomiting or grade III/IV neurologic toxicity occurred in arm B.

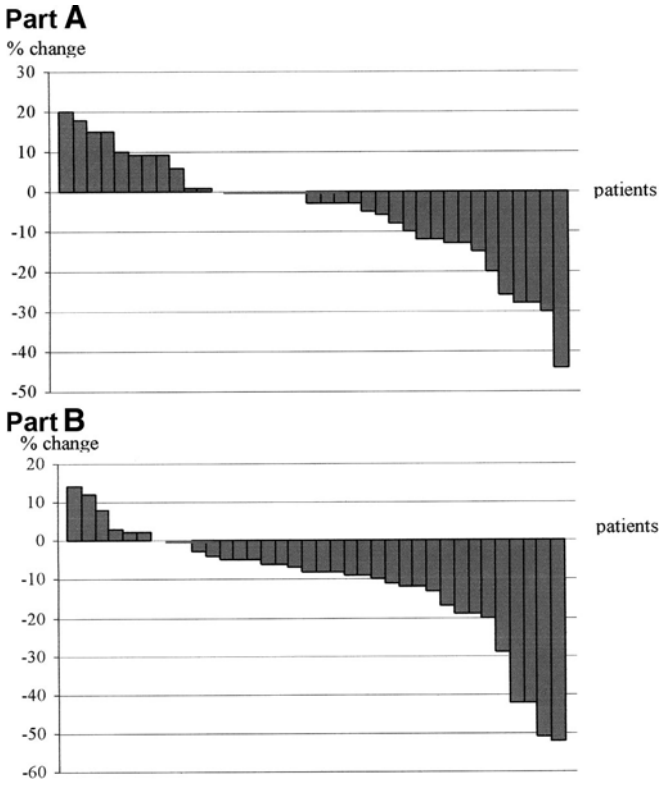

FIGURE 2. *Part A,* Percentage change in tumor volume between evaluation two (four courses) and evaluation one (two courses) in arm A (45 patients). *Part B,* Percentage change in tumor volume between evaluation two (four courses) and evaluation one (two courses) in arm B (42 patients).

TABLE 2. Tumor Responses After Randomization (n = 87)

	Arm A n = 45			Arm B n = 42		
	N	%	95% CI	N	%	95% CI
NA	3	6.7	(1.4–18.3)	3	7.2	(1.5–19.5)
PD	11	24.4	(12.9–39.5)	5	11.9	(4.0–25.6)
SD	24	53.3	(37.9–68.3)	25	59.5	(43.3–74.4)
OR	7	15.6	(6.5–29.5)	9	21.4	(10.3–36.8)

NA, not assessable; PD, progressive disease; SD. stable disease; OR, objective response; CI, confidence interval.

DISCUSSION

This is the first randomized phase II trial of early modification of a chemotherapy cisplatin doublet with paclitaxel in patients who had stable NSCLC after two courses of a platinum-based two-drug regimen. Such patients are highly heterogeneous, some having a reduction in the target tumor and others an increase, but the change is not sufficient to comply with the definition of an objective response or disease progression. Our results showed that sequential chemotherapy is feasible, with no major toxicity. Despite different response rates, however, the OS and TTP were similar in the two arms. Nevertheless, considering our working hypotheses, the response rate obtained in the experimental arm does not warrant a phase III trial of this sequential strategy. Sequential chemotherapy is a controversial topic. It can be based on two or one drugs, as in recent studies,[21,22] but in these two trials the switch was performed later, after four and six cycles. Only progression-free survival was improved. We chose to test an early switch Novello et al.[23] have reported that five courses of a cisplatin-gemcitabine doublet is superior to two courses with both drugs followed by three courses of gemcitabine monotherapy. Finally, it seemed better to switch

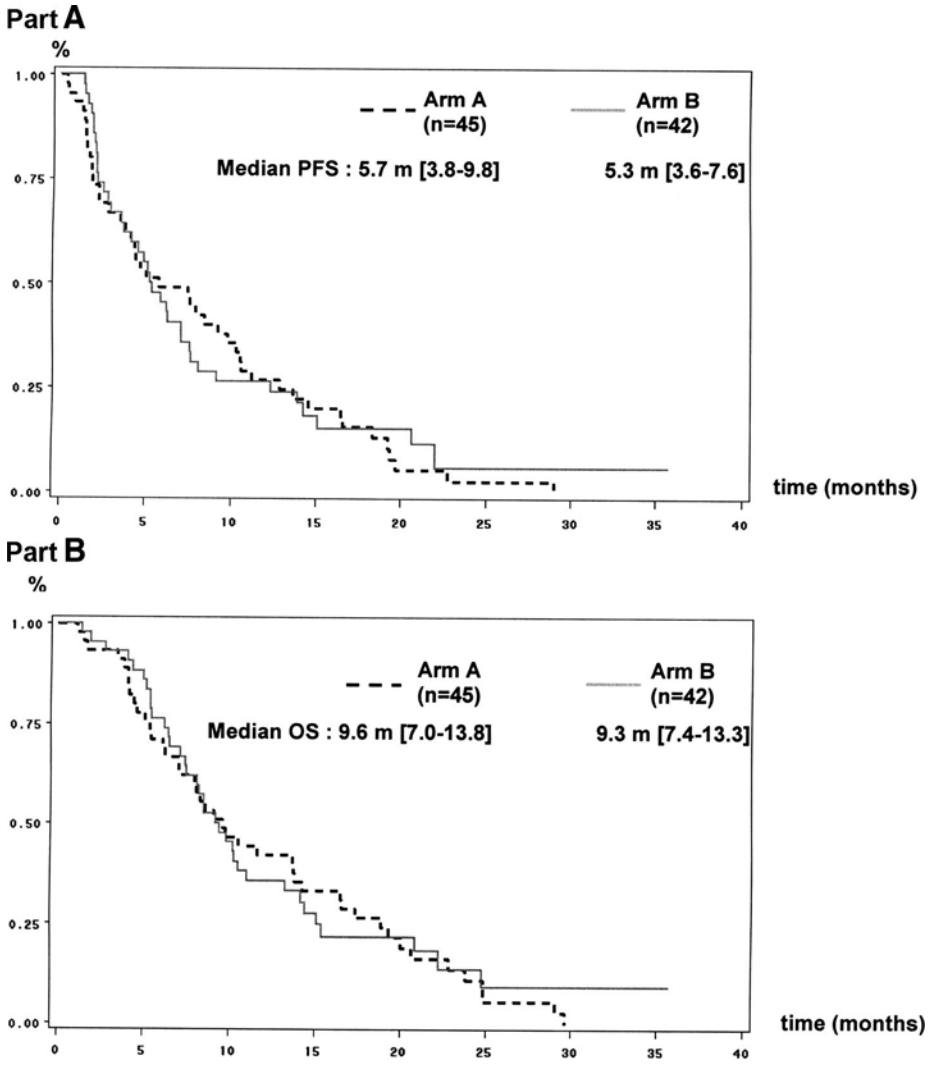

FIGURE 3. *Part A*, Progression-free survival (PFS) in months (m) among randomized patients ($n = 87$) according to the Kaplan Meier method. *Part B*, Overall survival (OS) in months (m) among randomized patients ($n = 87$) according to the Kaplan Meier method.

TABLE 3. Grade III–IV Toxicities and Percentages, According to the Cycle Number

	After Two Cycles $n = 432$		Arm A $n = 84$		Arm B $n = 82$	
	N	%	N	%	N	%
Hematological toxicity						
Neutropenia	64	14.8	14	16.7	8	9.8
Febrile neutropenia	3	0.7	1	1.2	3	3.7
Thrombocytopenia	27	6.2	6	7.1	3	3.7
Anemia	18	4.2	4	4.8	4	4.9
Leucopenia	3	0.7	1	1.2	1	1.2
Non hematological toxicity						
Renal toxicity	7	1.6	—		—	
Fatigue	11	2.5	3	3.6	3	3.6
Nausea vomiting	12	2.8	2	2.4	—	
Unexpected event[a]	21	4.9	2	2.4	3	3.6

[a] Thrombophlebitis, ischemia, alopecia, pulmonary infection, allergy, diarrhea, fever.

early after the chemotherapeutic sequence rather than in case of progression.[24] Our study examined this unresolved question on the use of sequential treatments. Some studies are very similar to ours, but most involved relatively small and heterogeneous populations, ruling out meaningful comparisons. Some studies involved an early switch in chemotherapy for all the patients, regardless of the response after the first two courses,[25–27] while others involved only patients whose disease was controlled after the first two courses.[13,28] In addition, it is not always easy to compare response rates between the different treatments, because some authors only calculated the overall response rate for the two phases. However, our results are compatible with all previous reports. Thus, in the study by Dongiovanni et al.,[27] involving 55 patients receiving 2 courses of cisplatin plus vinorelbine followed by 2 courses of paclitaxel plus gemcitabine, the objective response rate was 27% after the first 2 courses but 42% after 4 courses. Another study[12] showed that alternative drug administration (docetaxel or vinorelbine) in associated with cisplatin did not improve the objective response rate. Finally, in a phase III trial,[13] patients were randomized, after

three courses of cisplatin-ifosfamide-gemcitabine, either to three supplementary courses of cisplatin-ifosfamide-gemcitabine or to paclitaxel. As in our study, this phase III trial showed that a three drug combination followed after three cycles by paclitaxel does not result in better outcome compared with cisplatin based chemotherapy. The type of response (objective or non change) was not a significant prognosis factor. Our study has certain limitations. The response evaluation at 7 weeks, after only two courses of cisplatin-based therapy, may be considered premature. However, almost all the responses in the control arm were obtained after the first two courses, the following two courses increasing the response rate by only 15%. Likewise, the choice of 3-week cycles (meaning that the response had to be evaluated after 7 weeks) may be open to criticism, but early response assessment is now a validated option. The choice of a phase II randomized trial design ruled out certain comparisons but confirmed that there was no loss of chance in the sequential arm with respect to OS or the time to progression. In addition, only 15% more responses were obtained in the cisplatin-gemcitabine arm. One another limit is the study design: the protocol was drawn up in late 2002, before the widespread use of pharmacogenomics in lung cancer patient management.[29] Individual treatment tailoring based on criteria predictive of efficacy or tolerability will help to optimize therapy for patients with stable disease.

CONCLUSION

The GFPC 03-01 trial shows that sequential chemotherapy is feasible in patients who have stable NSCLC after two courses of cisplatin, without major toxicity. This phase II randomized study shows no evidence that switching regimen may results in higher response rates. The response rate in the experimental arm is too low to warrant a phase III study witch the same sequential strategy.

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APPENDIX: INVESTIGATORS' CENTERS

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