Original Study

Oral Vinorelbine Plus Cisplatin as First-Line Chemotherapy in Nonsquamous Non–Small-Cell Lung Cancer: Final Results of an International Randomized Phase II Study (NAVotrial 01)

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Abstract

Two cisplatin-based doublets with either oral vinorelbine or pemetrexed were tested in patients with Nonsquamous Non–Small-Cell Lung Cancer in a randomized Phase II study involving 153 patients (1:2 ratio): 51 pemetrexed/cisplatin and 102 oral vinorelbine/cisplatin. Single agent maintenance was also included. Oral vinorelbine and cisplatin reported an efficacy in line with what can be achieved with a standard treatment.

Background: The combination of oral vinorelbine plus cisplatin has been studied in numerous trials as first-line treatment of patients with non–small cell lung cancer (NSCLC) regardless of histologic subtype. NAVoTrial 01 is the first study that explores this combination specifically in nonsquamous (NS) NSCLC by assessing the feasibility of this doublet (ratio 1:2) in an investigational approach. A reference arm with pemetrexed plus cisplatin was included. Maintenance therapy with single-agent therapy after 4 cycles of combination therapy was included in the study schedules because it reflected a trend in first-line treatment of NSCLC. **Patients and Methods:** Stage IIIB/IV untreated/relapsed patients with NS NSCLC received a 3-week cycle of pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 on day 1 (arm A) or oral vinorelbine 80 mg/m^2 on days 1 and 8 (first cycle 60 mg/m^2) and cisplatin 80 mg/m^2 on day 1 (arm B). After 4 cycles, patients without disease progression received single-agent maintenance treatment with pemetrexed or oral vinorelbine. **Results:** Overall, 153 patients were randomized (arm A/arm B: 51/102). Disease control rate (%) for arm A was 76.5 (95% confidence interval [CI], 62.5-87.2) and for arm B it was 75.0 (95% CI, 65.3-83.1), Response rates for arm A were 31.4% (95% CI, 19.1-45.9) and for arm B were 24.0% (95% CI, 16.0-33.6). Median progression-free survival for arm A was 4.3 months (95% CI, 3.8-5.6) and for arm B it was 4.2 months (95% CI,

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3.6-4.7). Median survival for arm A was 10.8 months (95% CI, 7.0-16.4) and for arm B it was 10.2 months (95% CI, 7.8-11.9). Main grade 3/4 hematologic toxicities were neutropenia 18.3% (arm A) and 44.0% (arm B), whereas febrile neutropenia was reported in 2% of patients in each arm. **Conclusion:** Oral vinorelbine and cisplatin had an efficacy in line with that achieved with a standard treatment such as pemetrexed and cisplatin, coupled with an acceptable safety profile.

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Introduction

Current guidelines report that chemotherapy for locally advanced and metastatic NSCLC is the reference treatment for patients who do not have a molecular target.[1,2] The standard first-line chemotherapy remains a combination of cisplatin or carboplatin with third-generation agents including vinorelbine, gemcitabine, paclitaxel, or docetaxel.[3-5] The use of bevacizumab in addition to chemotherapy in standard management is not accepted everywhere, but it may be offered for some subsets of patients with NSCLC.[6] The choice of third-generation agents is generally driven by patient comorbidities, cost, dose schedule, and expected toxicities, because the efficacy of different platinum-based combinations are comparable.[7] In the absence of other specific markers, histologic subtype may drive the selection of platinum doublet, and pemetrexed in combination with cisplatin has reported better results than gemcitabine and cisplatin in nonsquamous (NS) NSCLC.[8] To our knowledge, this trial was the first prospective study in NSCLC to report survival differences by histologic subtype with different chemotherapy regimens. Among third-generation doublets, vinorelbine plus cisplatin is a well-acknowledged regimen in advanced NSCLC. In addition, in the adjuvant setting, vinorelbine is the third-generation anticancer drug that in combination with cisplatin has allowed cure in patients.[9-11] An oral formulation of vinorelbine was developed as a line extension of the injectable form for the indications for which intravenous vinorelbine was approved worldwide. The efficacy of oral vinorelbine in combination with platinum has been confirmed in randomized phase II and phase III studies, and this combination is an alternative therapy for advanced NSCLC, with the convenience of oral administration.[12-16] Currently, there are no specific studies reporting the use of oral vinorelbine and cisplatin in NS NSCLC. Conversely, a non–preplanned subset analysis in the phase III GLOB 3 (Global Lung Oncology Branch trial 3) study, comparing oral vinorelbine and docetaxel in a platinum-based combination as first-line chemotherapy in squamous and NS NSCLC, confirmed an increased chemosensitivity of adenocarcinoma when compared with that of squamous NSCLC.[15] These findings warranted consideration of the impact of a platinum-based combination with oral vinorelbine in a specific subset of patients with NS NSCLC. This randomized phase II trial aimed to assess the feasibility of a platinum-based doublet with oral vinorelbine (ratio 1:2) in an investigational approach as first-line treatment in patients with NS NSCLC. A reference arm was included with a platinum doublet including pemetrexed to evaluate whether the final results should be confirmed by a phase III trial. The primary objective was disease control rate (DCR), including patients with stable disease, partial response, and complete response. A maintenance treatment with either pemetrexed or oral vinorelbine was delivered to patients with nonprogressive disease.

Patients and Methods

Patients

Chemotherapy-naive patients with histologically/cytologically proven NS NSCLC, with disease classified as stage IIIB/IV (2009 TNM classification)[17] or relapsing (locally or distantly) after local treatment that was not suitable for locoregional treatment, with a Karnofsky performance score $\geq$ 80%,[18] and age from 18 to 75 years were eligible. Patients had to have at least 1 unidimensionally measurable indicator lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[19] that had not been previously irradiated, a life expectancy longer than 12 weeks; neutrophil levels $\geq 2.0 \times 10^9$/L, platelet levels $\geq 100 \times 10^9$/L, hemoglobin value $>$ 11 g/dL; total bilirubin levels $\leq 1.5 \times$ the upper limit of normal (ULN), transaminase levels $< 2.5 \times$ the ULN, alkaline phosphatase levels $< 5 \times$ the ULN; serum creatinine levels $\leq$ the ULN, if limit value, and creatinine clearance $\geq$ 60 mL/min.

Exclusion criteria included radiotherapy within the previous 4 weeks, pregnancy, brain metastasis or leptomeningeal involvement, symptomatic peripheral neuropathy $>$ grade 1 according to the National Cancer Institute Common Toxicity Criteria, version 2.0.[20] Women of childbearing potential had to use a medically accepted method of contraception during the 2 months preceding the beginning of the study, throughout the study period, and for up to 3 months after the last dose of study treatment.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines[21] and was approved by each participating institution's ethics committee. All patients signed written informed consent before starting the study.

Study Design

The study was sponsored by Pierre Fabre Médicament Laboratories, which supplied the project design, monitoring, data analysis, and study investigational products. The study protocol received the Eudract study number 2009-012001. Patients were randomized on a 1:2 basis, according to a minimization procedure by investigational center, sex (male vs. female), smoker status (yes vs. no), microscopic diagnostic method (cytologic vs. histologic) and stage (IIIB vs. IV vs. relapsing).[22] Patients received either cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 on day 1 (arm A) or cisplatin 80 mg/m^2 on day 1 plus oral vinorelbine 80 mg/m^2 on day 1 and day 8 (arm B) after the first cycle at 60 mg/m^2 to test hematologic tolerance. Chemotherapy was administered every 3 weeks for

4 cycles until documented disease progression, unacceptable toxicity, or patient refusal. In case of objective response or disease stabilization, treatment was continued in each arm until disease progression or toxicity with either single-agent pemetrexed or oral vinorelbine at the same doses and schedules as cycle 4, every 3 weeks. No dose reescalation was permitted after dose reduction of pemetrexed, oral vinorelbine or cisplatin. Dose reductions and omissions were allowed within cycles (day 8) for oral vinorelbine. Treatment was discontinued if it could not be administered after an additional 2 weeks' delay (cycle duration $>$ 5 weeks) related to any toxicity. When disease progressed, further second-line treatment was dependent on the investigator's decision.

Supportive treatments, such as antiemetic agents, transfusion of blood products, analgesics, antibiotics, antidiarrheal agents, granulocyte colony-stimulating factors (except for primary prophylactic use), and erythropoietic agents were allowed according to evidence-based recommendations. Patients treated with pemetrexed received oral folic acid 400 μg daily and a vitamin B_{12} injection every 9 weeks from 1 to 2 weeks before the first dose of treatment until 3 weeks after the last dose.

Evaluation

Patients underwent physical examination and tumor measurements by imaging techniques (computed tomography and magnetic resonance imaging). The same methods of assessment and the same techniques were used at baseline, during the prescreening study period, from day −21 to day −1, and throughout the study to ensure comparability. Evaluation of tumor response was performed every 2 cycles (6 weeks) according to Response Evaluation Criteria in Solid Tumors, version 1.1. After completion of 4 cycles, in the case of maintenance treatment, assessment was performed every 2 cycles (every 6 weeks). Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria, version 2.0 grading[20] (white blood cell and biochemical evaluation on day 1 and day 8 of every cycle in both arms) and febrile neutropenia was diagnosed according to Pizzo's definition.[23]

The main end point of the study was DCR. Secondary end points included overall response rate (ORR), progression-free survival (PFS, defined as the time elapsed from randomization until disease progression or death from any cause, whichever occurred first), overall survival (OS), time to treatment failure (TTF, defined as time elapsed from randomization until failure: disease progression, relapse, death, withdrawal because of an adverse event, patient refusal, loss to follow-up, start of a new anticancer therapy), and safety.

Statistical Analysis

The 1-sample multiple-testing procedure for phase II clinical trials described by Fleming[24] was used with 2 prespecified analyses. The null hypothesis (H_0) assumed a true DCR of 55% with an alternative hypothesis (H_1) of 70%, a type I error $\alpha \leq 0.05$, and a type II error $\beta \leq 0.15$. All treated patients were included in the ITT analysis[22] and were analyzed for safety. The evaluable population was defined as all patients eligible for the trial who underwent a full evaluation of target and nontarget lesions and had received at least 2 cycles of study treatment (including patients with progressive disease documented before the second cycle). DCR and ORR were tabulated together with 95% confidence interval (CI), following the exact method. The Kaplan-Meier method was applied to PFS, TTF, and OS. Subset analysis, according to stratification factors, was performed for DCR, ORR, PFS, and OS. Statistical analysis was performed using SAS software, version 8.2 for Windows (SAS Institute, Cary, NC).

Figure 1 Consort Diagram

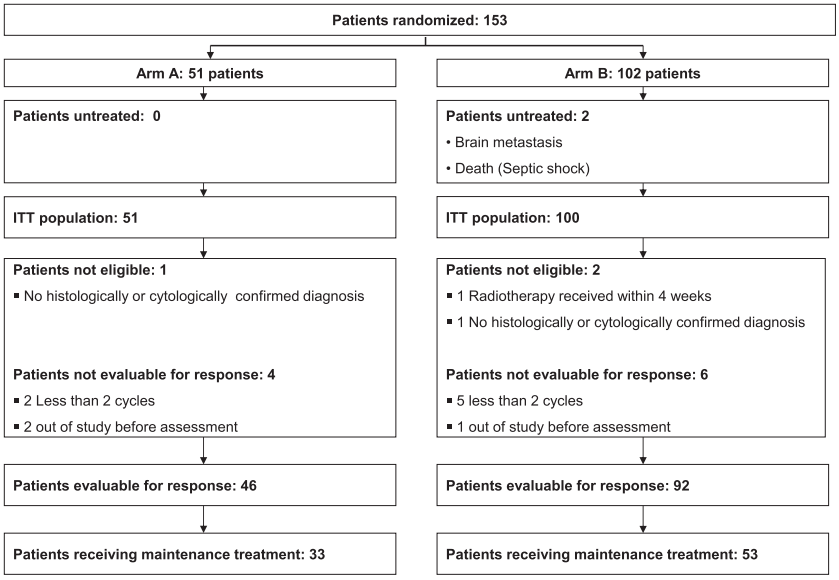


Table 1 Main Patients Characteristics

Characteristic	Arm A (n = 51)	Arm B (n = 100)
Sex, No. of Patients (%)		
Male	33 (64.7)	62 (62.0)
Median age, years (range)	63.8 (40.3-75.5)	61.0 (38.4-75.1)
<65 (%)	60.8	71.0
≥65 (%)	39.2	29.0
Performance Status at Baseline (%)		
80%	41.2	42.0
90%	35.3	25.0
100%	23.5	33.0
Smoker at Randomization (%)	37.3	40.0
Histologic Subtype (%)		
Squamous cell carcinoma	–	1.0
Adenocarcinoma	82.4	88.0
Large cell carcinoma	7.8	10.0
Others	9.8	1.0
Stage at Randomization (%)		
IIIB	9.8	8.0
IV	88.2	88.0
Relapsed disease	2.0	4.0
Median Delay Between Diagnosis and Study Entry, mo (range)	0.9 (0.2-75.2)	0.7 (0.2-48.6)
Histopathologic Diagnosis		
Cytologic (%)	25.5	26.0
Histologic (%)	74.5	74.0
Number of Organs Involved (%)		
1	5.9	7.0
2	35.3	28.0
≥3	58.8	65.0

Table 2 Drug Delivery

Variable	Arm A	Arm B
Median Cycles in Combination and Maintenance Periods (range)	6 (1-23)	5 (1-29)
Cycles Delayed in Combination Period (%)	n = 176	n = 333
Vinorelbine oral d 1/8	–	15.9/1.8
Pemetrexed	6.3	–
Cisplatin	5.7	15.3
Dose Canceled in Combination Period (%)		
Vinorelbine oral d 1/8	–	0/12.3
Pemetrexed	0	–
Cisplatin[a]	0.6	1.5
Cycles Delayed in Maintenance Period (%)	n = 180	n = 272
Vinorelbine oral d 1/8	–	19.5/1.5
Pemetrexed	13.3	–
Dose Canceled in Maintenance Period (%)		
Vinorelbine oral d 1/8	–	0.3[b]/3.3
Pemetrexed	0	–
Relative Dose Intensity Per Patient in Combination Period (%)	n = 51	n = 100
Vinorelbine oral (range)	–	87.4 (38.4-109.4)
Pemetrexed (range)	99.3 (72.6-149.9)	–
Cisplatin (range)	99.0 (42.0-119.8)	93.8 (20.4-147.9)
Relative Dose Intensity Per Patient in Maintenance Period (%)	n = 33	n = 53
Vinorelbine oral (range)	–	88.0 (38.6-106.9)
Pemetrexed (range)	98.6 (65.0-104.0)	–
Dose Reduction Overall Period (%)	n = 356	n = 605
Vinorelbine oral d 1/8	–	1.6/0.5
Pemetrexed	1.6	–
Cisplatin	4.5	2.7

[a]175 and 328 cycles for arm A and arm B, respectively.
[b]Unknown for 1 patient.

Results

Patient Characteristics

From November 2009 to February 2011, 153 patients were enrolled in 31 centers (51 patients in arm A and 102 patients in arm B). In arm A, 51 patients (100.0%) were treated and 46 (90.2%) were evaluable for tumor response. In arm B, 100 patients (98.0%) were treated and 92 (92.0%) were evaluable for tumor response (Fig. 1). Baseline patient and disease characteristics were similar in the 2 arms (Table 1).

Drug Delivery

Overall, a median of 6 and 5 cycles of chemotherapy were administered per patient in arm A and arm B, respectively, including the combination and maintenance treatment periods. During the maintenance period, 7 cycles of single-agent chemotherapy were delivered in 8 of 33 (24.2%) patients in arm A and 14 of 53 (26.4%) patients in arm B, with a maximum of 25 cycles of maintenance therapy in 1 patient in arm B. During the combination treatment period, the day 1 doses of pemetrexed and oral vinorelbine were delayed in 6.3% and 15.9% of cycles, respectively, mainly for neutropenia. During the maintenance period, pemetrexed was delayed in 13.3% of cycles, and oral vinorelbine was delayed in 19.5% and 1.5% of cycles on day 1 and day 8, respectively. During the combination treatment period, the relative dose intensity in arm A was 99.3% for pemetrexed and 99.0% for cisplatin; in arm B it was 87.4% for oral vinorelbine and 93.8% for cisplatin. During the maintenance treatment period, the relative dose intensity was 98.6% for pemetrexed and 88.0% for oral vinorelbine (Table 2).

Efficacy

In the ITT population, the DCR in the combination treatment period was 76.5% in arm A (n = 51) and 75.0% in arm B (n = 100). ORR was 23.5% and 21.0%, respectively. Thirty-three

Table 3 Treatment Discontinuation During the Induction Phase

Reason	Arm A		Arm B	
	N	%	N	%
Progressive disease	11	61.1	27	57.4
Adverse event	4	22.2	10	21.3
Protocol deviation	1	5.6	—	—
Death during induction phase	1	5.6	3	6.4
Investigator decision	—	—	4	8.5
Patient refusal	1	5.6	3	6.4
Total	18	100.0	47	100.0

(64.7%) patients in arm A and 53 (53.0%) patients in arm B received maintenance treatment. The main reasons explaining the difference between the 2 arms in the number of patients receiving maintenance treatment were the physician's habit of continuing maintenance therapy more easily with pemetrexed, because it was already registered in this setting in arm A, and the physician's decision not to continue treatment in arm B (Table 3). DCR after combination and maintenance treatment was 76.5% in arm A and 75.0% in arm B. ORR after the combination and maintenance treatment periods was 31.4% and 24.0%, respectively (Table 4). At disease progression, 24 (47.1%) patients in arm A and 63 (63.0%) patients in arm B received second-line chemotherapy. Platinum-based doublets were delivered in 4 (16.7%) patients in arm A and 15 (23.8%) patients in arm B. Single-agent non−platinum-based chemotherapy was delivered in 20 patients in arm A and 48 patients in arm B, with the following percentages in each arm, respectively: docetaxel, 85.0% and 22.9%; gemcitabine, 5.0% and 0%; pemetrexed, 0% and 72.9%; paclitaxel, 5.0% and 0%; vinorelbine, 5.0% and 2.1%; and other antineoplastic agents, 0% and 2.1%.

The median TTF was 4.2 months and 4.1 months in arm A and arm B, respectively. The median PFS was 4.3 months and 4.2 months in arm A and arm B, respectively (Fig. 2), with a respective PFS at 6, 12, and 18 months of 29.4%, 7.8%, 3.9% and 33.0%, 11.0 %, 5.0 %, in arm A and arm B, respectively.

The median OS was 10.8 months and 10.2 months in arm A and arm B, respectively (Fig. 3), with an OS in arm A at 6, 12, and 18 months of 72.5%, 45.1%, and 31.4 %, respectively, and in arm B of 69.0%, 40.0 %, 30.0 %, respectively. Kaplan-Meier PFS and OS were similar in the 2 arms according to the previously mentioned prognostic factors.

Safety

During the combination treatment period, drug-related grade 3/4 leukopenia and neutropenia was reported in 18.3% of patients in arm A and in 44.0% of patients in arm B, with only a 2.0% rate of febrile neutropenia in both arms. Grade 3/4 thrombocytopenia was observed in 6.0% of patients in arm A and in 0% of patients in arm B. Grade 3/4 gastrointestinal disorders were reported by 3.9% of patients in arm A and 11.0% of patients in arm B. Grade 3/4 thoracic disorders occurred in 4% and 0% of patients in arm A and arm B, respectively. During the maintenance period, only 86 patients were evaluable. Among them, 30.3% experienced grade 3/4 neutropenia with pemetrexed and 20.8% with oral vinorelbine, without febrile neutropenia; nonhematologic toxicities were rare and comparable between the 2 arms (Table 5).

Three patients died of drug-related toxicity: 1 in arm A and 1 in arm B.

Discussion

Recent randomized phase III trials suggest that NS NSCLC has a better prognosis when treated with chemotherapy in advanced disease[25] as well as in an adjuvant setting.[26] However, the histologic subtype is not specified in a nonnegligible portion of patients with advanced NSCLC: in the JMBD trial, a generic cytologic diagnosis of NSCLC without further subtype classification was made in 252 of 1669 patients (15.5%), and the OS in this subgroup showed no significant difference between pemetrexed plus cisplatin and gemcitabine plus cisplatin arms (8.6 vs. 9.2 months; hazard ratio, 1.08; 95% CI, 0.81-1.45).[12]

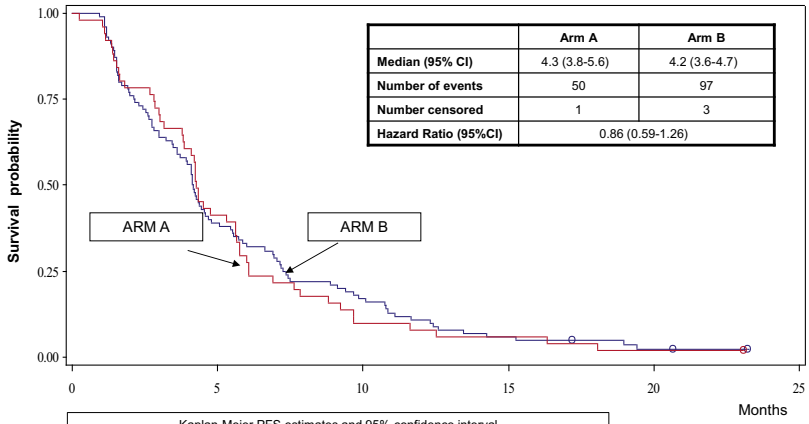
On the basis of new publications on NS NSCLC, several doublets have been reported to have similar results, refueling the issue of whether pemetrexed plus cisplatin remains the best available option as reported in a recent meta-analysis of NS NSCLC.[27] Patel et al. reported that an induction and maintenance regimen based on pemetrexed slightly delayed progression in late-stage NS NSCLC but had no impact on OS, the primary end point, when compared with a paclitaxel-based regimen—the hazard ratio indicated no difference between the 2 regimens ($P = .949$).[28] Other phase III studies compared pemetrexed and other agents in platinum-based

Table 4 Overall Response and DCR (RECIST) According to Investigator (ITT Population)

Outcome	Combination Period				Combination and Maintenance Periods			
	Arm A (n = 51)		Arm B (n = 100)		Arm A (n = 51)		Arm B (n = 100)	
	N	%	N	%	N	%	N	%
PR[a]	12	23.5	21	21.0	16	31.4	24	24.0
SD	27	52.9	54	54.0	23	45.1	51	51.0
DCR	39	76.5	75	75.0	39	76.5	75	75.0
PD	8	15.7	18	18.0	8	15.7	18	18.0
NE	4	7.8	7	7.0	4	7.8	7	7.0

Abbreviations: DCR = disease control rate; ITT = intent to treat; NE = nonevaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
[a]For 4 patients in arm A and 10 patients in arm B, PR was confirmed during maintenance period.

Figure 2 Progression-Free Survival (PFS) for The Intent-To-Treat (ITT) Population

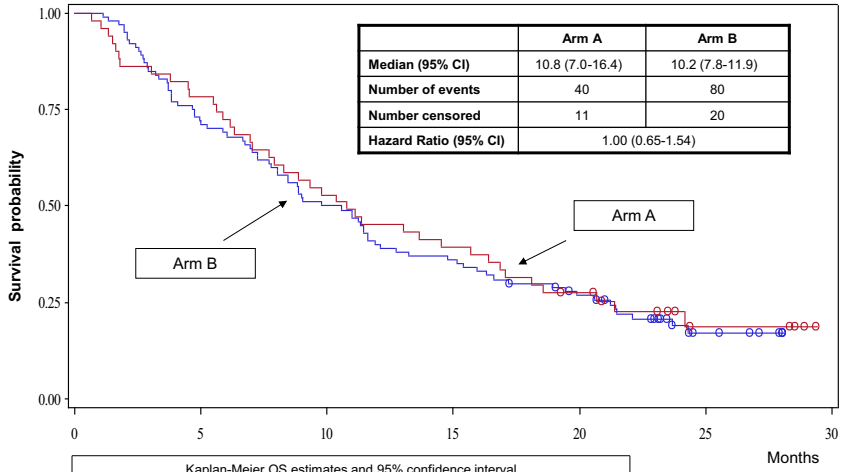


	Arm A	Arm B
Median (95% CI)	4.3 (3.8-5.6)	4.2 (3.6-4.7)
Number of events	50	97
Number censored	1	3
Hazard Ratio (95%CI)	0.86 (0.59-1.26)	

Kaplan-Meier PFS estimates and 95% confidence interval		
Time point	Arm A	Arm B
6 months	29.4% (95% CI = 17.7-42.1)	33.0% (95% CI = 24.0-42.2)
12 months	7.8 % (95% CI = 2.5-17.2)	11.0 % , (95% CI = 5.8-18.0)
18 months	3.9 % (95% CI = 0.7-11.9)	5.0 % , (95% CI = 1.9-10.5)

chemotherapy, reporting similar results in terms of OS, even if this was not the primary end point.[29,30] Therefore, the main issue is in which sequence the currently available treatments should be used and which agents are best used as first- and second-line chemotherapy or in some cases as maintenance therapy. Several factors should be considered. More molecular markers—eg, thymidylate synthase expression levels—may provide a suitable tool for identifying patients more likely to respond to pemetrexed-based chemotherapy.[31-34] Patient convenience and preference should be taken into account. The current generation of chemotherapeutic agents are administered by the intravenous route in combination with cisplatin. Oral vinorelbine may offer more patient convenience than intravenous agents, especially when used as a single agent. It can reduce time spent in the hospital as well as the constraints related to intravenous agents. It can decrease patient anxiety and dispense with venous access difficulties.[35-37] A cost analysis was performed in Italy on the basis of the current phase II study, taking into account the cost of the anticancer drugs, serious adverse events, and

Figure 3 Overall Survival (OS) of The Intent-To-Treat (ITT) Population



	Arm A	Arm B
Median (95% CI)	10.8 (7.0-16.4)	10.2 (7.8-11.9)
Number of events	40	80
Number censored	11	20
Hazard Ratio (95% CI)	1.00 (0.65-1.54)	

Kaplan-Meier OS estimates and 95% confidence interval		
Time point	Arm A	Arm B
6 months	72.5% (95% CI = 58.1-82.7)	69.0% , (95% CI = 58.9-7.1)
12 months	45.1 % (95% CI = 31.2-58.0)	40.0 % , (95% CI = 30.4-49.4)
18 months	31.4 % (95% CI = 19.3-44.2)	30.0 % , (95% CI = 21.4-39.1)

Table 5 Grade 3/4 Toxicity During Combination and Maintenance Periods

	Combination Period		Maintenance Period	
Toxicity Per Patient	**Arm A**	**Arm B**	**Arm A (Pemetrexed)**	**Arm B (Oral Vinorelbine)**
Hematologic (%)	(n = 49)	(n = 100)	(n = 33)	(n = 53)
Anemia	8.2	9.0	6.1	9.4
Leukopenia	10.2	26.0	15.2	3.8
Neutropenia	18.3	44.0	30.3	20.8
Thrombocytopenia	6.1	0	0	0
Febrile neutropenia	2.0	2.0	0	3.8
Nonhematologic (%)	(n = 51)	(n = 100)	(n = 33)	(n = 53)
Fatigue	3.9	7.0	0	3.8
Gastrointestinal disorders	3.9	11.0	3.0	1.9
Nausea	0	5.0	–	–
Vomiting	2.0	7.0	–	–
Stomatitis	2.0	0	3.0	1.9
Constipation	0	1.0	–	–
Respiratory, Thoracic Disorders	4.0	0	–	–
Pulmonary hemorrhage	2.0	0	–	–
Pulmonary embolism	2.0	0	–	–
Deep vein thrombosis	2.0	0	–	–
Renal Failure	2.0	2.0	–	–

administration settings: the average cost per patient is 4077 euros (US$5,580) for oral vinorelbine plus cisplatin and 14,528 euros (US$19,833) for pemetrexed plus cisplatin.[38]

Maintenance therapy in NSCLC can prolong OS in patients who have benefited from platinum-based induction chemotherapy.[39,40] The current study shows that continuous maintenance with single-agent oral vinorelbine or pemetrexed allows continuation of effective treatment with an acceptable safety profile, although the small sample size allows no clear conclusion on the use of maintenance treatment.

In conclusion, this randomized phase II study is the first investigation of a new platinum doublet including oral vinorelbine in the treatment of NS NSCLC. Because, to our knowledge, this combination has never been explored in this subset of patients, a reference arm with pemetrexed and cisplatin, the most widely used doublet in this field, was included. According to the primary and secondary end points (DCR, PFS, and OS), the 2 regimens proved effective, in line with other previously reported studies in advanced NSCLC. The safety profile differed across the 2 doublets, but the incidence and severity of adverse events was acceptable and easily manageable in the 2 arms. More grade 3/4 neutropenia was reported during the combination period in arm B, but with low rates of febrile neutropenia that were similar across the 2 arms. Nonhematologic drug-related grade 3/4 toxicities were reported mainly during the combination treatment period. The incidence of hematologic toxicity was lower during the maintenance period in arm B, probably because of the better dose adaptation of oral vinorelbine. Maintenance treatment allowed effective safe chemotherapy to be delivered, although the small number of patients receiving maintenance treatment in arm B did not allow correct evaluation of its effects.

In summary, the doublet oral vinorelbine plus cisplatin showed an efficacy in NS NSCLC in line with that achieved with a standard treatment such as pemetrexed and cisplatin, coupled with an acceptable safety profile. The treatment sequence should be decided individually based on histologic and molecular parameters as well as patient preference and cost of treatment. The design of the current study allows no comparison between the 2 arms, although there seems to be no need for a comparative phase III study to confirm the role of other platinum-based doublets, such as oral vinorelbine and cisplatin, which has been proved a suitable combination for first-line chemotherapy in advanced NSCLC[14-16] and is already registered in most countries.

Clinical Practice Points

- The combination of oral vinorelbine and cisplatin lacks specific studies in nonsquamous (NS) non small cell lung cancer (NSCLC).
- This randomized phase II trial was aimed to assess the feasibility of two platinum doublets with either pemetrexed or oral vinorelbine in an investigational approach (ratio 1:2) as first-line treatment in NS NSCLC patients.
- Maintenance with single agent pemetrexed or oral vinorelbine after four cycles of combination was included. The platinum-based doublet including oral vinorelbine reported an efficacy in line with what can be achieved with a standard treatment.
- The maintenance treatment with either oral vinorelbine or pemetrexed allowed delivering an effective and safe chemotherapy, although the small number of patients receiving maintenance in both arms did not allow the correct evaluation of its impact on survival.
- This is the first study testing the role of oral vinorelbine and cisplatin in the field of NS NSCLC.
- On the basis of the above results, the authors conclude that there seems to be no need for a comparative phase III study

to confirm the role of other platinum-based doublets, such as oral vinorelbine and cisplatin which has been proven a suitable combination for first-line chemotherapy in advanced NSCLC. Moreover, this combination is already registered in most countries, independently by the histology and the maintenance status.

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