Oral vinorelbine and cisplatin as first-line therapy for advanced squamous NSCLC patients: a prospective randomized international phase II study (NAVoTrial 03)

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Abstract

Objective: The study investigated the efficacy and safety of oral vinorelbine-cisplatin (OV-CDDP) and gemcitabine-cisplatin (GEM-CDDP) in patients with squamous non-small cell lung cancer (sq-NSCLC).

Patients and methods: This was an open-label, prospective, multicenter, international phase II study that enrolled untreated patients with advanced sq-NSCLC. Patients were randomized to receive 3-week cycles of either 60–80 mg/m^2 OV days 1 and 8 in combination with 80 mg/m^2 CDDP day 1 (arm A) or 1250 mg/m^2 GEM days 1 and 8 in combination with 75 mg/m^2 CDDP day 1 (arm B). After four cycles, patients without disease progression continued maintenance dose of OV or GEM until progression or unacceptable toxicity. The primary objective was disease control rate (DCR). Secondary objectives included progression-free survival (PFS), time to treatment failure (TTF), overall survival (OS), safety, and quality of life (QoL).

Results: A total of 114 patients with sq-NSCLC were randomized, and 113 were treated (57 in arm A and 56 in arm B). DCR was high in both arms: 73.7% (95%CI: 62.4–100.0) in arm A and 75.0% (95%CI: 63.7–100.0) in arm B. Median PFS and TTF were similar in arm A and B 4.2 and 2.8 months, and 4.3 and 3.1 months, respectively. Even though the difference was not significant, the OS was 10.2 for arm A and 8.4 months for arm B. The safety profiles were consistent with the current knowledge of adverse events. QoL results revealed an improvement in patients under OV treatment.

Conclusion: The OV-CDDP combination showed comparable efficacy to GEM-CDDP with acceptable safety profile and enhanced patients' QoL.

Trial registration: The study was registered under EudraCT number 2012-003531-40.

Keywords: cisplatin, gemcitabine, non-small cell lung cancer, oral vinorelbine, quality of life, squamous cell carcinoma

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Introduction

Lung cancer (LC) is one of the most commonly diagnosed forms of cancer, and continues to be the leading cause of cancer-related deaths, worldwide.[1–3] In 2018, 2.1 million new cases of LC, and 1.8 million related deaths were estimated in both genders globally.[2]

Non-small cell lung cancer (NSCLC) accounts for 85% of total LC cases and presents a 5-year survival rate of about 15%.[4,5] Squamous cell carcinoma represents 25–30% of total LC cases, and has been associated typically with smoking.[6,7] The treatment decisions should consider several parameters including molecular markers, histology,

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performance status (PS), and comorbidities. The immune checkpoint inhibitors' discovery brought a therapeutic option. The use of immunotherapy (e.g. pembrolizumab) has been recommended in first-line therapy for patients with programmed death ligand 1 (PD-L1 expression) ⩾50%, and without actionable driver mutation (epidermal growth factor receptor, anaplastic lymphoma kinase). There is also a possibility to use a combination of immunotherapy and platinum-based chemotherapy in selected patients with a PS score of 0–1. Currently, according to the international guidelines, in patients without actionable oncogenic driver, with contra-indication to the use of immunotherapy, the combination of chemotherapy is a recommended treatment option.[5] In addition, the platinum doublets with either gemcitabine, taxanes, pemetrexed or vinorelbine are considered as reference treatment regimens.[8–10]

Vinorelbine (third-generation cytotoxic agent) in combination with cisplatin (CDDP) is a well-acknowledged and successful regimen for patients with advanced NSCLC.[11–13] Oral vinorelbine (OV) has demonstrated its efficacy with a favorable safety profile, and along with the added convenience of an oral administration.[14–19]

Histology is an important prognostic factor, and treatment decisions should consider histology. Nevertheless, the regimen gemcitabine and cisplatin (GEM-CDDP) is commonly administered to squamous NSCLC (sq-NSCLC) patients.[8]

In 2008 Scagliotti *et al.*[20] demonstrated that the GEM-CDDP combination was more effective on squamous cell carcinomas than that of pemetrexed-CDDP, strengthening the role of histology-driven chemotherapy with advanced NSCLC. However, at the time of the study, limited data were available with OV in squamous histology. There was no direct comparison between OV and GEM in this setting.

Currently, there are no specific data available on the use of OV combined with cisplatin in patients with squamous histology. Thus, these findings warranted further research into this drug as a treatment option. As OV-CDDP is considered effective, the aim of this study was to investigate the efficacy and safety of OV-CDDP and GEM-CDDP in patients with sq-NSCLC. The primary objective of the study was to evaluate the disease control rate (DCR) during the whole study treatment period (WSTP) in the two treatment arms. The secondary objectives included the time to event parameters, progression-free survival (PFS), overall survival (OS), time to treatment failure (TTF), toxicity, and quality of life (QoL).

Patients and methods

Patients

The inclusion criteria included chemo-naïve adult patients with histologically/cytologically proven stage IIIB or stage IV (seventh lung cancer TNM) sq-NSCLC or in relapse (local or distant) after a loco-regional treatment, with a Karnofsky Performance Score (KPS) ⩾70%, and a life expectancy >12 weeks. Other eligibility criteria included presence of at least one measurable non-irradiated lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 guidelines,[21] adequate bone marrow, hepatic and renal functions (neutrophils $\geqslant 2.0 \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L, hemoglobin ⩾10 g/dL, total bilirubin ⩽1.5 × upper limit of normal (ULN), transaminases <2.5 × ULN, alkaline phosphatases <5 × ULN and creatinine <ULN (if limit of value, creatinine clearance 60 ml/min), and at least a 4 week interval since the last radiotherapy. The patients must not have had an active central nervous system disorder and brain metastasis and/or have received systemic immunotherapy. The main reasons for exclusion from the study were known hypersensitivity to the study drug (s) or to drug with similar chemical structures, a presence of factor likely to modify drug absorption (e.g., surgery of the gastrointestinal tract, significant malabsorption), the patients with symptomatic neuropathy (sensory) ⩾ grade 2 according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC, version 2). Written consent was collected for all patients. The institutional review board of each participating institution approved the study (supplemental file 1) which was conducted in accordance with the principles stated in the Declaration of Helsinki and Good Clinical Practice (CPMP/ICH/135/95).

Study design

The study was an open-label, prospective, multicenter, and international phase II study conducted in six countries and registered under the EudraCT number 2012-003531-40. The study was divided in four periods: pre-study screening, combination period, maintenance period, and follow-up. After

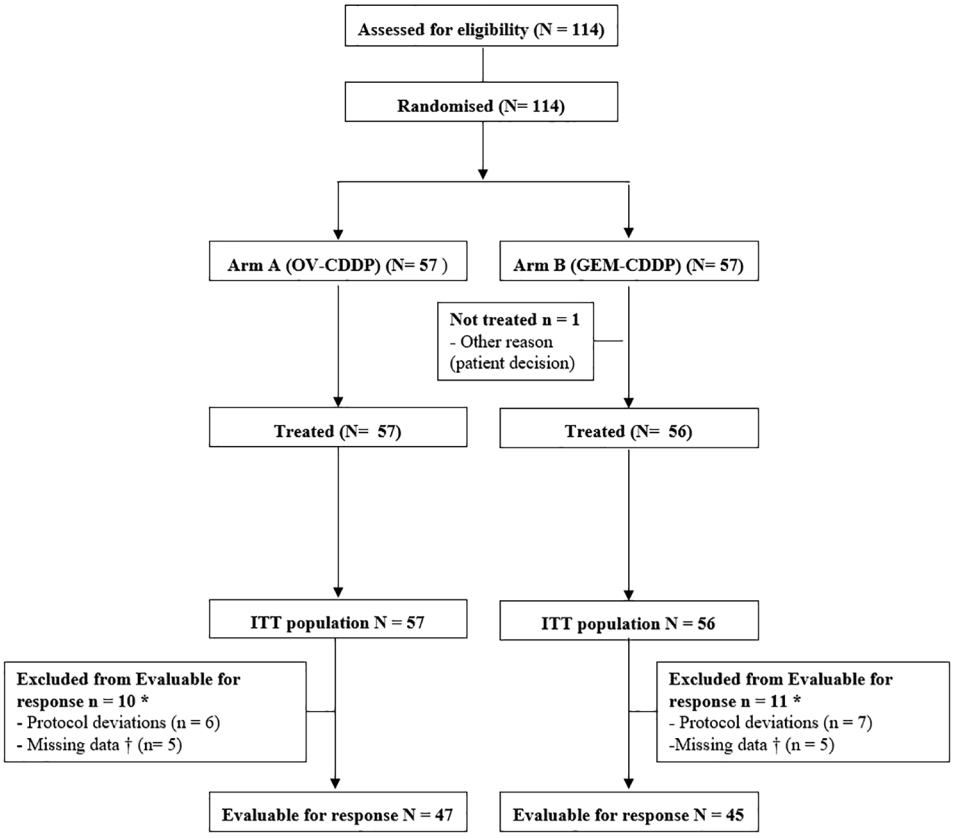


Figure 1. Consort diagram.
*One patient in each arm was excluded from the Evaluable for response population for both protocol deviation and missing data.
†Missing data for tumor response.
Arm A: oral vinorelbine-cisplatin; Arm B: gemcitabine-cisplatin.
AE, adverse event; CDDP, cisplatin; GEM, gemcitabine; ITT, intention-to-treat; OV, oral vinorelbine; PD, progressive disease.

obtaining written informed consent, the patient's eligibility was assessed during the pre-screening period and a randomization form was sent to the study sponsor. Patients were randomized (1:1) according to stage IIIB/IV or relapsing after a local treatment, smoker or non-smoker, center.

The patients receiving OV-CDDP were allocated to arm A while those receiving GEM-CDDP were allocated to arm B (CONSORT Diagram, Figure 1, and Supplemental File 2). During the combination period starting with the first treatment intake, four treatment cycles were administered (each cycle corresponding to a treatment period of 3 weeks) unless involving progressive disease (PD), unacceptable toxicity, patient refusal, or an investigator's decision. Patients in arm A received 60 mg/m^2 OV in cycle 1 which was increased to 80 mg/m^2 at cycle 2 according to hematological tolerance (on day 1 and day 8 of each cycle), and 80 mg/m^2 intravenous (i.v.) CDDP (on day 1 of each cycle). For patients who experienced grade 3/4 neutropenia, the OV dose was maintained at 60 mg/m^2. The patients allocated to arm B received 1250 mg/m^2 i.v. GEM (on day 1 and day 8 of each cycle) followed by 75 mg/m^2 CDDP on day 1 of each cycle, every 3 weeks. The GEM dose was adjusted in case patients presented with neutropenia and thrombocytopenia. The patients having objective response or a stable disease (SD) at the end of the combination period could continue receiving a maintenance therapy with OV (arm A) or GEM (arm B), administered at the same doses as cycle 4 (on day 1 and day 8 of each subsequent cycle) until PD, unacceptable toxicity, patient's refusal, or an investigator's decision. The second-line chemotherapy after PD was allowed at discretion of the investigator. After the maintenance therapy, patients were followed-up for 30 days after the last study treatment administration until death or the decision for closure of the study or last contact.

During the study, the doses were adjusted according to dose-limiting hematological and/or non-hematological toxicity. After dose reductions, no further escalation was allowed. Moreover, the participation in the study was discontinued if the total overall cycle duration exceeded 5 weeks. CDDP was administered after a saline hydration following OV or GEM. Anti-emetics were administered to prevent nausea and vomiting. Erythropoietin and growth factors were recommended in the event of grade 3/4 anemia, febrile neutropenia, grade 4 asymptomatic neutropenia lasting more than 7 days, or neutropenic infection. The patients receiving under opiates received prophylactic treatment for constipation.

Evaluation

The tumor assessment was performed according to RECIST 1.1 guidelines.[21] Assessment of measurable, evaluable or non-evaluable disease was carried out at baseline and every 6 weeks using the same methods of assessment and techniques (computed tomography scan or magnetic resonance imaging on thorax/pelvis/abdomen). The stage classification used was the seventh lung cancer TNM (edition 2009). Additionally, imaging of the brain was performed if clinically indicated. Bone scintigraphy performed at the baseline was repeated to record an overall complete response (CR) or to preclude the presence of bone lesions. All assessments were performed and reviewed by the study investigators. An electrocardiogram test was performed in case of abnormality at the baseline. The safety was assessed by reporting of adverse events (AEs) and these were graded according to NCI-CTC v. 2.0. Other assessments included physical examination, complete blood cell count, and QoL assessed with lung cancer symptom scale (LCSS), and a satisfaction questionnaire.[22,23] The end of study was defined by the date of the last progression.

Statistical analysis

The one-sample multiple testing procedure for phase II clinical trials was used, as described by Fleming.[24] The null hypothesis (H0) was that the true DCR $\leqslant$45% was tested against a one-sided alternative. Based on this assumption, an alternative hypothesis (H1) was that the true DCR $\geqslant$66%. A one-sided testing with an alpha level (probability of type I error) $\leqslant$0.05 and beta level (probability of type II error) $\leqslant$0.10 was employed. The total sample size was 50 evaluable patients in each arm. Considering approximately 10% of the patients could be non-evaluable for response, the final estimated number was 110 patients, with 55 patients in each arm.

The primary objective of the study was to evaluate the DCR defined as the rate of CR, partial response (PR), and SD for both arms. The secondary objectives were the estimation of the DCR in the combination period, objective response rate (ORR), duration of disease control, duration of response, duration of SD, PFS, TTF, OS, tolerance, and QoL using the LCSS and satisfaction questionnaire.

Unless otherwise specified, all reported analyses referred to the intention-to-treat population (ITT), comprising all randomized and treated patients with a confirmed diagnosis of sq-NSCLC. The population evaluable for response was defined as the patients included in the ITT, eligible, treated in the assigned arm, who underwent a complete evaluation of target and non-target lesions and had received at least two treatment cycles. The duration of disease control, SD and response was analyzed in the subset of patients with disease control, SD and objective response in the WSTP, respectively. The time-related endpoints were estimated using the Kaplan–Meier method and medians were reported at 95% confidence interval (CI). The analyses were carried out with SAS® for Windows®, version 9.4.

Results

Patient disposition

A total of 114 patients were enrolled in 25 centers from March 2013 to August 2015. One patient in arm B was not treated (patient decision) resulting in 113 patients in the ITT population (Figure 1). The reasons for treatment discontinuation in both arms were displayed in supplemental file (Supplemental File 3A, B).

Baseline characteristics

The patients presented similar demographic and tumor characteristics (Table 1). The median age was 61 years and 64.5 years in each arm (arm A and arm B), respectively. All the patients had squamous cell carcinoma; 94.7% of patients developed a metastatic disease. Overall, 82.3% of patients (evenly distributed between the two

Table 1. Patient characteristics – ITT population.

Characteristic	Arm A (OV-CDDP)	Arm B (GEM-CDDP)
	***N*=57**	***N*=56**
Age (years)		
Median age	61	64.5
Sex *n* (%)		
Male	40 (70.2)	45 (80.4)
Performance status *n* (%)		
70	2 (3.5)	3 (5.4)
80	22 (38.6)	22 (39.3)
90	23 (40.4)	21 (37.5)
100	10 (17.5)	10 (17.9)
Smoker history *n* (%)		
Never smokers	1 (1.8)	–
Smokers	26 (45.6)	23 (41.1)
Former smokers	30 (52.6)	33 (58.9)
Stage at study entry *n* (%)		
IIIB	2 (3.5)	4 (7.1)
IV	55 (96.5)	51 (91.1)
Relapse	–	1 (1.8)
Metastatic disease *n* (%)		
0	2 (3.5)	4 (7.1)
1	8 (14.0)	11 (19.6)
2	25 (43.9)	18 (32.1)
⩾3	22 (38.6)	23 (41.1)
Metastases localization *n* (%)		
Lymph nodes	29 (50.9)	29 (51.8)
Pulmonary	28 (49.1)	25 (44.6)
Osseous	24 (42.1)	18 (32.1)
Adrenals + Renals	19 (33.3)	15 (26.8)
Pleural node or effusion	17 (29.8)	17 (30.4)
Hepatic	10 (17.5)	12 (21.4)
Skin	1 (1.8)	–
Other	3 (5.3)	12 (21.4)
Prior surgery *n* (%)	4 (7.0)	3 (5.4)
Prior radiotherapy *n* (%)	2 (3.5)	2 (3.6)

Arm A, oral vinorelbine-cisplatin; Arm B, gemcitabine-cisplatin.
CDDP, cisplatin; GEM, gemcitabine; ITT, intention-to-treat; OV, oral vinorelbine.

arms) presented with comorbidities including respiratory, thoracic, and mediastinal disorders (43.9%), vascular disorders (43.0%), and metabolism and nutrition disorders (33.3%).

Drug delivery

The mean duration of the treatment was 15.21 weeks and 16.77 weeks for patients in arm A and arm B, respectively. The mean duration of follow-up was 11.52 months and 11.09 months in the two arms, respectively. During the combination period, 53 patients (93.0%) in arm A continued to cycle two and 36 patients (67.9%) had their OV dose escalated. A summary of dose modifications for OV and GEM during combination and maintenance was displayed in (Table 2A, B). In the combination period, main reasons for dose reduction in both arms were hematological toxicity and patient's convenience/administrative reason. During the maintenance period, on day 1, OV and GEM doses were reduced in only two patients. On day 8, no OV doses were reduced, while 17.9% of patients had GEM dose reduction; at day 8, 50% of patients in arm B did not receive GEM.

Efficacy

Efficacy–ITT population. The primary endpoint, DCR was high and controlled disease was observed in 42 patients (73.7%, one-sided 95%CI: 62.4–100) and 42 patients (75.0%, one-sided 95%CI: 63.7–100.0) in arm A and arm B, respectively (Table 3). ORR was observed in 14 patients (24.6%, 95%CI: 14.1–37.8) and 17 patients (30.4%, 95%CI: 18.8–44.1), in arm A and B, respectively (Table 3). With regards to the Best Overall Confirmed Response during the WSTP, in arm A, 14 patients (24.6%) presented with PR, 28 patients (49.1%) with SD, and 11 patients (19.3%) with PD. In arm B, 17 patients (30.4%) presented with PR, 25 patients (44.6%) with SD, and nine patients (16.1%) with PD.

The estimated median duration of SD was 4.2 months (95%CI: 2.6–4.8) in arm A and 3.8 months (95%CI: 3.1–5.1) in arm B. Similar ORR during the combination period was observed in both arms. No differences in PFS, TTF, and OS were observed between the two arms (Table 3). The estimated median PFS was 4.2 months (95%CI: 2.8–4.9) in arm A and 4.3 months (95%CI: 3.1–5.5) in arm B. Although the difference was not significant, the estimated median OS was 10.2 months for arm A and 8.4 months for arm B (Figure 2).

Safety

Overall, 86% of patients died during the study, mainly due to PD (73.7%) (Supplemental File 4A to C). A total of 57 and 56 patients evaluable for safety. Two treatment-related deaths were reported (one patient from arm A died of respiratory failure, and one patient died of septic shock from arm B). Overall, most of the related AEs of any grade that occurred were related to gastrointestinal, general, metabolism, and hematological disorders, and were mainly of grade 1/2 in both arms. During the WSTP, respectively 87.7% and 92.9% of patients developed treatment-related AEs (r-AEs) of any grade in arm A and arm B. During the combination period, fatigue was the main r-AEs grade 3/4 in both arms (Table 4A). The rates of nausea/vomiting of any grade were similar in both arms; however, there was a trend for more grade 3/4 nausea/vomiting in arm B. During the combination period, febrile neutropenia grade 3/4 of was 10.5% in arm A while it was less frequent (1.8%) in arm B. During the maintenance period, fewer patients experienced r-AEs of any grade and of grade 3/4 in both arms. (Table 4B). Most of the serious hematological grade 3/4 AEs resolved with adequate curative treatments.

Quality of life: LCSS and satisfaction questionnaires

An improvement in the overall QoL and decrease in disease symptom burden was observed during the study (Supplemental File 5). Patients in OV arm had a total LCSS score that generally decreased with a mean change from baseline: −0.68 (standard deviation or StD: 2.06) from the baseline to the end of the study treatment period, with a peak improvement at the end of the fourth cycle (Supplemental File 5A). A similar trend was observed for the average symptom burden index, that is a mean decrease from the baseline of −0.64 (StD: 1.90) at the end of fourth cycle (Supplemental File 5B), mainly due to improvements in symptoms such as cough, hemoptysis, and pain. This was also reflected by the total symptom distress scale (Supplemental File 5C) and overall QoL scale (Supplemental File 5E), which had peak improvements from the baseline at the end of the fourth cycle.

Conversely, in arm B, the total LCSS score, average symptom burden index and total symptom

Table 2. Drug delivery – ITT population.

A.

Variable	Combination period		Maintenance period	
	Arm A (OV-CDDP)	Arm B (GEM-CDDP)	Arm A (OV-CDDP)	Arm B (GEM-CDDP)
	***N*= 57**	***N*= 56**	***N*=29**	***N*=28**
Mean number of cycles (StD)	3.4 (1.0)	3.3 (1.1)	4.1 (4.4)	5.5 (4.2)
Escalation dose *n* (%)	36 (67.9)	NA	NA	NA
Dose reduction *n* (%)				
Oral vinorelbine d1/8	7 (12.3)/2 (3.5)	NA	2 (6.9)/0 (0.0)	NA
Cisplatin d1	4 (7.0)	5 (8.9)	NA	NA
Gemcitabine d1/8	NA	5 (8.9)/6 (10.7)	NA	2 (7.1)/5 (17.9)
Dose canceled *n* (%)				
Oral vinorelbine d1/8	0 (0.0)/25 (43.9)	NA	0 (0.0)/8 (27.6)	NA
Cisplatin d1	1 (1.8)	1 (1.8)	NA	NA
Gemcitabine d1/8	NA	0 (0.0)/29 (51.8)	NA	0 (0.0)/14 (50.0)
RDI (%) per patient*				
Oral vinorelbine	80.8 (17.0)	NA	90.6 (15.5)	NA
Cisplatin	92.2 (10.1)	91.5 (10.4)	NA	NA
Gemcitabine	NA	78.5 (16.9)	NA	84.9 (19.0)

B.

Variable	Combination period		Maintenance period	
	Arm A (OV-CDDP)	Arm B (GEM-CDDP)	Arm A (OV-CDDP)	Arm B (GEM-CDDP)
	***N*=192 cycles**	***N*=184 cycles**	***N*=118 cycles**	***N*=153 cycles**
% of dose reduced				
Oral vinorelbine d1/8	3.6/1.0	NA	1.7/0.0	NA
Cisplatin d1	2.1	3.3	NA	NA
Gemcitabine d1/8	NA	2.7/3.3	NA	1.3/3.3
% of dose canceled				
Oral vinorelbine d1/8	0.0/15.6	NA	0.0/11.9	NA
Cisplatin d1	0.5	0.5	NA	NA
Gemcitabine d1/8	NA	0.0/21.2	NA	0.0/22.2

A.Number and percentage of patients with at least one dose modified.
B.Proportion of doses modified by cycles during combination and maintenance period – ITT population.
*Values are presented as mean (StD).
Arm A, oral vinorelbine-cisplatin; Arm B, gemcitabine-cisplatin.
d1, day 1; d1/8, day 1 and day 8 respectively.
CDDP, cisplatin; GEM, gemcitabine; ITT, intention-to-treat; NA, not applicable; OV, oral vinorelbine; RDI, relative dose intensity; StD, standard deviation.

Table 3. Efficacy parameters – ITT population.

Outcome	Arm A (OV-CDDP)	Arm B (GEM-CDDP)
	N = 57	*N* = 56
Whole study treatment period: combination and maintenance period		
DCR *n* (%)		
CR + PR + SD	42 (73.7)	42 (75.0)
ORR *n* (%)		
Responders	14 (24.6)	17 (30.4)
Duration of disease control		
Median (95%CI)	4.8 (4.1–5.7)	5.2 (4.3–6.6)
PFS		
Median (95%CI)	4.2 (2.8–4.9)	4.3 (3.1–5.5)
TTF		
Median (95%CI)	2.8 (2.1–4.0)	3.1 (2.3–4.4)
OS		
Median (95%CI)	10.2 (6.9–12.9)	8.4 (5.3–11.9)
Combination period		
DCR *n* (%)		
CR + PR + SD	42 (73.7)	42 (75.0)
ORR *n* (%)		
Responders	14 (24.6)	16 (28.6)

Arm A, oral vinorelbine-cisplatin; Arm B, gemcitabine-cisplatin.
CDDP, cisplatin; CI, confidence interval; DCR, disease control rate; GEM, gemcitabine; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; OV, oral vinorelbine; PFS, progression-free-survival; SD, stable disease; TTF, time to treatment failure.

distress scale decreased from the baseline to the second cycle, but gradually increased toward the end of the treatment period. A similar trend was observed for the overall QoL scale with minimal improvement from the baseline at the end of the treatment period (mean change from baseline: −0.09; StD: 3.75).

The treatment constraint in terms of impact on normal activities was mainly reported for i.v. dosage forms.

Discussion

Several randomized trials have shown similar efficacy in different platinum-based therapies for the treatment of advanced NSCLC regardless of the histology data.[25,26] Therefore, the choice of chemotherapy has relied on the safety profile of the drug and mode of administration. Scagliotti *et al.*[20] reported the superiority of a combination (GEM-CDDP) over another (pemetrexed-CDDP).[27] These results confirmed the role that plays histology when choosing treatments. In the present study, we reported the results of the NAVoTrial 03, the first international randomized study comparing OV and GEM in a homogeneous cohort of patients with sq-NSCLC.

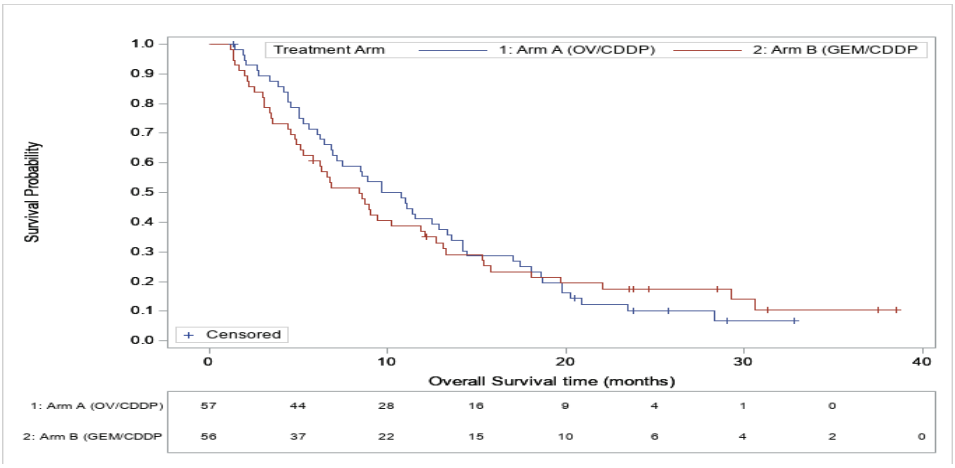
The efficacy profile of OV has been previously documented in pivotal phase II/III studies.[28,29] A prospective multicenter international randomized study was conducted in patients with non-squamous NSCLC patients for a comparison of pemetrexed-CDDP *versus* a combination of OV-CDDP (NAVotrial 01).[30] The primary goal was achieved, and the results showed comparable DCR between both arms. The DCR in the OV-CDDP arm was 75.0% and the median PFS was 4.2 months. NAVotrial 01 study also showed the importance of maintenance therapy with OV without an increased toxicity. A cost-analysis study[31] was performed across 12 European countries to measure cost savings from treatments. The calculation included total number of chemotherapy administrations, AEs and the rate of hospitalizations due to AEs. The authors concluded that the OV-CDDP regimen could be potentially cost-effective. Farhat et *al.*[18] reported similar results for a phase II single arm. Despite the small sample size, the combination of OV-CDDP followed by maintenance was effective with no toxic deaths.[18]

The maintenance therapy with various combinations of agents including targeted therapies and/or immunotherapy has been investigated.[32] Maintenance may be delivered after induction treatment in patients eligible to receive it with the same single agent or with a different agent ("switch maintenance").[33,34]

Several phase III studies had previously shown the contribution of maintenance therapy in terms of PFS or OS.[35] In our study, DCR after induction and maintenance was similar in the two arms. PFS and TTF were also comparable in both arms, with a slightly higher OS in arm A.

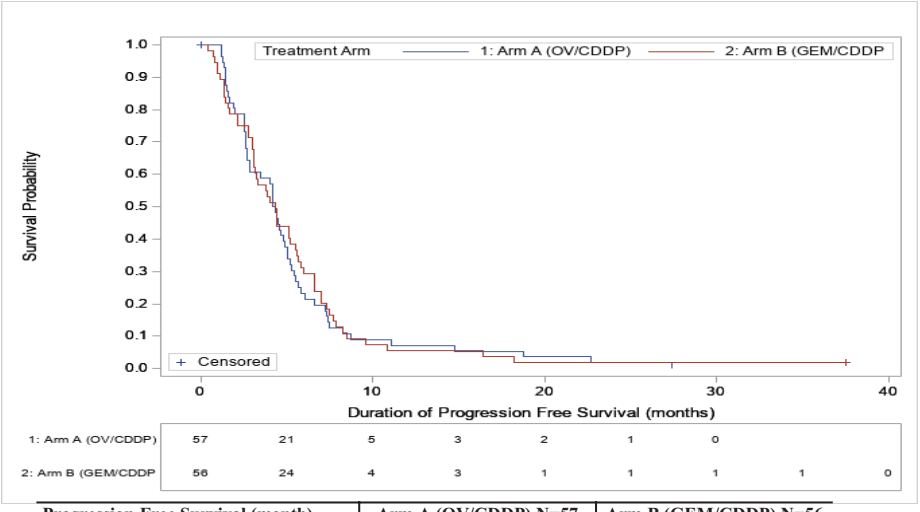
Overall, the safety profile in both arms was consistent considering the current state of understanding of the two doublets. Despite a greater

(a)



Overall survival (month)	Arm A (OV/CDDP) N=57	Arm B (GEM/CDDP) N=56
N of event (%)	51 (89.5%)	47 (83.9%)
N of censored observations (%)	6 (10.5%)	9 (16.1%)
Median [95%CI]	10.2 [6.9-12.9]	8.4 [5.3-11.9]
Patients alive at 9 months	30 (53.6%)	23 (42.3%)
Patients alive at 12 months	23 (41.1%)	20 (36.8)

(b)



Progression Free Survival (month)	Arm A (OV/CDDP) N=57	Arm B (GEM/CDDP) N=56
N of event (%)	56 (98.2%)	54 (96.4%)
N of censored observations (%)	1 (1.8%)	2 (3.6%)
Median [95%CI]	4.2 [2.8-4.9]	4.3 [3.1-5.5]
Patients without progression at 9 months	5 (8.9%)	5 (9.1%)
Patients without progression at 12 months	4 (7.1%)	3 (5.5)

Figure 2. Kaplan–Meier analysis on overall survival (a) and progression-free survival (b) – ITT.
Estimation of medians survival was performed with Kaplan–Meier analysis. 95% CI for median duration of disease control were calculated using the Brookmeyer and Crowley method.
Probability estimates were based upon Kaplan–Meier estimates and 95% CI use the log-log transformation.
Arm A, oral vinorelbine-cisplatin; Arm B, gemcitabine-cisplatin.
CDDP, cisplatin; CI, confidence interval; GEM, gemcitabine; ITT, intention-to-treat population; OV, oral vinorelbine.

rate of hematological AEs observed in the arm A, the safety profile of OV was acceptable. Most AEs were of grade 1/2 with non-serious AEs in both arms. A trend for lesser grade 3/4 renal disorders and skin toxicities of grade 1/2 were reported in OV-CDDP arm than in GEM-CDDP arm.

During the maintenance period, the rate of dose reduction in OV-CDDP arm was low and the AEs were manageable.

Finally, the perception of OV treatment was well received, showing benefits in the overall QoL of

Table 4. Number and percentage of patients with at least one grade 3/4 treatment-related AEs during the combination and maintenance period – ITT population.

A.

PT *n* (%)	Combination period			
	Arm A (OV-CDDP)		Arm B (GEM-CDDP)	
	N = 57		*N* = 56	
	Any grade	G3/G4	Any grade	G3/G4
Nausea	25 (43.9)	1 (1.8)	26 (46.4)	5 (8.9)
Vomiting	17 (29.8)	2 (3.5)	13 (23.2)	3 (5.4)
Diarrhea	15 (26.3)	2 (3.5)	8 (14.3)	1 (1.8)
Constipation	7 (12.3)	2 (3.5)	9 (16.1)	0
Stomatitis	2 (3.5)	0	9 (16.1)	1 (1.8)
Subileus	1 (1.8)	1 (1.8)	0	0
Fatigue	32 (56.1)	7 (12.3)	29 (51.8)	8 (14.3)
General physical health deterioration	1 (1.8)	0	1 (1.8)	1 (1.8)
Decreased appetite	10 (17.5)	1 (1.8)	10 (17.9)	2 (3.6)
Anemia*	4 (7.0)	3 (5.3)	4 (7.1)	3 (5.4)
Febrile neutropenia*	6 (10.5)	6 (10.5)	1 (1.8)	1 (1.8)
Neutropenia*	6 (10.5)	6 (10.5)	0	0
Leukopenia*	1 (1.8)	1 (1.8)	0	0
Thrombocytopenia*	0	0	1 (1.8)	1 (1.8)
Deafness	4 (7.0)	1 (1.8)	2 (3.6)	0
Peripheral sensory neuropathy	1 (1.8)	0	2 (3.6)	1 (1.8)
Peripheral motor neuropathy	0	0	1 (1.8)	1 (1.8)
Hemoptysis	0	0	3.6	1.8
Hiccups	2 (3.5)	1 (1.8)	0	0
Pulmonary embolism	1 (1.8)	1 (1.8)	1 (1.8)	1 (1.8)
Acute pulmonary edema	0	0	1 (1.8)	1 (1.8)
Respiratory failure	1 (1.8)	1 (1.8)	0	0
Renal failure	1 (1.8)	1 (1.8)	2 (3.6)	2 (3.6)
Renal failure acute	0	0	1 (1.8)	1 (1.8)
Pneumonia	0	0	1 (1.8)	1.8
Septic shock	0	0	1 (1.8)	1 (1.8)

(continued)

Table 4. (continued)

B.

PT *n* (%)	Maintenance period			
	Arm A (OV-CDDP)		Arm B (GEM-CDDP)	
	N = 29		*N* = 28	
	Any grade	G3/G4	Any grade	G3/G4
Fatigue	12 (41.4)	3 (10.3)	11 (39.3)	2 (7.1)
Asthenia	1 (3.4)	1 (3.4)	2 (7.1)	0
Neuropathy peripheral	0	0	1 (3.6)	1 (3.6)
Febrile neutropenia*	3 (10.3)	3 (10.3)	0	0
Anemia*	1 (3.4)	1 (3.4)	0	0
Neutropenic infection	1 (3.4)	1 (3.4)	0	0

A.Number (%) of patients with at least one grade 3/4 treatment-related AEs during the combination period.
B.Number (%) of patients with at least one grade 3/4 treatment-related AEs during the maintenance period.
Arm A, oral vinorelbine-cisplatin; Arm B, gemcitabine-cisplatin.
*AEs related to laboratory parameters assessed as clinically significant.
AE, adverse event; CDDP, cisplatin; G, grade; GEM, gemcitabine; ITT, intention-to-treat; OV, oral vinorelbine; PT, preferred term.

patients. Indeed, there was evidence suggesting that patients with cancer prefer oral treatments as compared with i.v. therapy.[36] Oral anticancer therapies have been on a steady rise in the last few years mainly due to patients' preferences for easier administration, reduced rates of hospitalizations and saving time/cost-effectiveness owing to fewer hospital visits, access to home-based therapy, and reduced risk of infections resulting from long-term central venous catheters.[37,38] Convenient alternatives and QoL should be considered while assessing the benefit–risk balance. Oral agents allow easy monitoring, dosage adjustments and a safer use after adequate patient education for an improved adherence. Oral chemotherapy also facilitates maintenance strategy to prolong disease control.

Overall, our study confirmed that OV-CDDP followed by OV as single agent in maintenance therapy was well tolerated, and ensured an effective DCR in approximately 74% of patients thus representing a valuable therapeutic option. This study demonstrated the tolerability of the administration of OV on day 1 and day 8. This treatment regimen may be a suitable treatment option for patients with sq-NSCLC who cannot receive immunotherapy. It warrants further research, potential combinations of OV and immunotherapy are under investigation (GFPC‡ 04-2017).

Conclusion

In conclusion, OV showed an efficacy comparable with GEM in a homogenous cohort of patients with sq-NSCLC. The disease control achieved with OV-CDDP was high with a trend for a higher median OS, and the safety was good with an overall improvement of patients' QoL than GEM-CDDP. Therefore, OV is a suitable treatment choice in patients with advanced sq-NSCLC in combination or in maintenance therapy to prolong disease control while offering convenience.

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Conflict of interest statement

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Supplemental material

Supplemental material for this article is available online.

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