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Oral maintenance metronomic vinorelbine versus best supportive care in advanced non-small-cell lung cancer after platinum-based chemotherapy: The MA.NI.LA. multicenter, randomized, controlled, phase II trial

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ABSTRACT

Background: Oral vinorelbine administered at the maximum tolerated dose has already showed activity and a good safety profile in advanced non-small-cell lung cancer (NSCLC). The MA.NI.LA study was a phase II, multicenter, randomized, controlled trial that aimed to assess the effects of a 'switched maintenance' regimen with

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oral metronomic vinorelbine (OMV) in patients with NSCLC who had not progressed after first-line platinum-based chemotherapy.

Patients and methods: Patients were randomly assigned in a 1:1 ratio to either OMV (50 mg three-times weekly) as maintenance treatment or best supportive care (BSC). The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective disease control rate (DCR, CR + PR + SD), safety and quality of life.

Results: In total, 61 and 59 patients were assigned to OMV and BSC, respectively. At a median follow-up of 23.9 (IQR 10.2–38.2) months, patients treated with OMV reported a significantly lower progression rate compared to patient in the BSC arm (89% [54/61] vs 96% [56/58]; HR 0.73; 90% CI 0.53-0.999, p = 0.049). Median PFS for patients treated with vinorelbine was 4.3 months (95% CI 2.8–5.6) vs 2.8 months (95% CI 1.9–4.5) for patients receiving BSC. This benefit was specifically evident in patients aged ≥70 years, in current smokers, and in those who reported disease stabilization as best response to induction chemotherapy. OS and response rate and quality of life were similar in the two arms. Drop-out rate for major toxicity with OMV was unexpectedly high (25%, 14/61) mainly due to grade 3–4 neutropenia (11%, 7/61).

Conclusions In patients with unselected NSCLC achieving disease control after platinum-based chemotherapy switch maintenance therapy with OMV prolonged PFS compared to BSC; however, the optimal dose of OMV requires further investigation.

Key message

The MA.NI.LA study evaluated a 'switched maintenance' regimen with oral metronomic vinorelbine (OMV) in patients with NSCLC who did not progress after first-line Pt-based chemotherapy.

In patients with NSCLC achieving disease control after Pt-based chemotherapy switch maintenance therapy with OMV prolonged PFS compared to BSC; however, the optimal dose of OMV requires further investigation.

1. Introduction

Maintenance treatment is a suitable option following first-line chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC) [1,2]. The ESMO guidelines [2] suggested the use of pemetrexed as 'continuous' or 'switched-maintenance' therapy in patients with adenocarcinoma NSCLC and a Performance Status (PS) 0–1 not progressing after four cycles of platinum-based chemotherapy. However, no optimal maintenance therapy has been defined; the impact of maintenance therapy on quality of life (QoL), the best approach to frail patients and those with histology other than adenocarcinoma are not well-established [3].

A favorable toxicity profile and a good QoL are crucial when opting for a maintenance strategy. Furthermore, a 'continuous' approach might be beneficial in patients responding to first-line treatment, while a 'switched' strategy seems beneficial in those achieving stable disease.

Metronomic chemotherapy (mCT) differs from conventional schedules - which are based on the administration of the maximum tolerated dose (MTD) [4]. It consists of frequent or continuous administration of low-dose chemotherapeutic drugs, with no extended intervals between courses. mCT presents multiple mechanisms of action, and shows both a cytostatic effect, thanks to its antiangiogenic action, and an immunomodulatory activity [4]. The rationale behind mCT is improving the therapeutic index by balancing drug activity and treatment-associated toxicities, allowing prolonged duration of treatment and improvement in QoL.

Vinorelbine is a microtubule-targeting agent with promising results when administered orally within mCT regimens, especially in frail patients with advanced disease [5–9]. Oral vinorelbine has been also evaluated as 'continuous maintenance' therapy at MTD in patients with advanced NSCLC [10–12].

Given the promising results obtained with MTD oral vinorelbine, the phase II MA.NI.LA trial was designed to investigate the efficacy and safety of oral metronomic vinorelbine (OMV) as switch maintenance treatment of advanced NSCLC patients whose disease was controlled by platinum-based induction chemotherapy.

2. Patients and methods

2.1. Study design and procedures

This was a multicenter, open label, randomized, controlled phase II study conducted at 19 Italian referral centers between February 2013 and April 2017 (study ID: NCT02176369).

The study was conducted in accordance with the Helsinki declaration and was approved by each local Ethical Committee. All patients signed an informed consent before inclusion.

2.2. Patients

Inclusion criteria were: age ≥18 years, estimated life expectancy ≥12 months, Eastern Cooperative Oncology Group PS 0–2, histological or cytological diagnosis of stage IIIb or stage IV NSCLC (7th TNM edition), measurable disease according to Response Evaluation Criteria in Solid Tumors 1.0. Patients must not have progressed during four or six 21-day cycles of platinum-based induction therapy with adequate organ function and no residual toxicity at the study entry. Induction regimens were at discretion choice but should not include vinorelbine.

Exclusion criteria were: addicted NSCLC (*EGFR* mutation or *ALK*+ or *ROS1*+ disease), previous malignancy other than NSCLC within the previous 5 years, inability to take oral therapy, progressive brain metastases. Minor eligibility criteria are reported in the Supplementary Material.

2.3. Treatment assignment

Patients were randomly assigned in a 1:1 ratio by using an interactive voice/web-response system to either OMV (Navelbine®, Pierre Fabre, Italy) plus BSC (according to standard practice) as maintenance treatment or best supportive care (BSC) only. Randomization was stratified by center. For each center, it was applied a minimization technique taking into consideration the following factors: ECOG PS (0–1 vs 2), histology (adenocarcinoma vs other), and number of performed platinum-based induction chemotherapy cycles.

2.4. Study drug

Patients received OMV (50 mg three-times weekly, Monday, Wednesday, Friday) until progression, decision to discontinue or unacceptable toxicity (grade 3–4 hematological or non-hematological toxicity excluding alopecia, and not recovered to grade 1 within 3 weeks). Conventionally, 3 consecutive weeks of therapy were considered as one cycle. This schedule was selected in line with previous experiences [5,6,13,14].

Following a planned interim analysis and the recommendation of the Independent Data & Safety Monitoring Committee, an amendment was introduced allowing a dose reduction to 30 mg after the first episode of severe hematological toxicities or grade 3–4 adverse events. In this case, the patient had to continue on the reduced dosage and permanently discontinue in case of new inacceptable toxicity.

2.5. Endpoints

The primary endpoint was progression-free survival (PFS; time from randomization to first documentation of progression or death due to any cause, whichever occurred first). In case of patient alive and progression-free at the last contact, data were censored. Secondary endpoints were: (i) overall survival (OS; time from randomization to death from any cause or, in case of censored data, the last date the patient was known to be alive); (ii) objective disease control rate (DCR; proportion of patients with measurable disease at baseline achieving complete or partial overall best response or stable disease); (iii) post-progression survival (PPS; time from first documentation of objective tumor progression to death from any cause or, in case of censored data, the last date the patient was known to be alive); (iv) QoL according to EORTC QLC30, EORTC QOL-LC13 (version 3); (v) Safety profile (according to Common Terminology Criteria for Adverse Events Version 4.0), timing and relationship to study therapy of adverse events and laboratory abnormalities.

In an explorative fashion, we tested the prognostic and predictive role of different potential biomarkers involved in cancer detection and progression as a previous validated plasma micro RNA signature classifier (MSC) and in tumor angiogenesis consisting in vascular endothelial growth factor A (VEGF-A) and Trombospondin (TSP1) (Supplementary material) [15,16].

2.6. Assessments

All patients were assessed at baseline (after the completion of induction therapy and within 4 weeks from randomization), then after every two cycles (6 weeks ± 1) until disease progression or new therapy initiation. Baseline tumor measurements were carried out by imaging (CT scan or MRI) and response was assessed using the RECIST 1.0 criteria applying the same method of tumor assessment throughout the study. Response confirmation occurred 4 weeks or more after the initial measurement. Clinical assessment with clinical examination, complete blood cell count and serum chemistry analysis were performed every cycle (3 weeks ± 1). Patients were assessed for adverse events before every cycle, and rated their QoL on day 1 of every other cycle (6 weeks ± 1) and at 30 days after the discontinuation visit.

Blood sampling to measure biomarkers (VEGF-A, TSP1, MSC) was performed at baseline and then repeated every 6 weeks for VEGF-A and TSP1 but for the purpose of the present paper only results obtained at baseline are reported. Circulating biomarkers were measured as previously described (see supplementary material) [7,17].

2.7. Statistical Analysis (see also Supplementary Material for a full description)

The study design provided 80% power to detect a 67% improvement in median PFS from 3.0 to 5.0 months (hazard ratio [HR]: 0.60) for the comparison of OMV arm with BSC arm. Assuming 12 months of uniform accrual, a follow-up of further 18 months, an attrition rate between 5% and 10%, and using a one-sided log-rank test with a 5% α level, 100

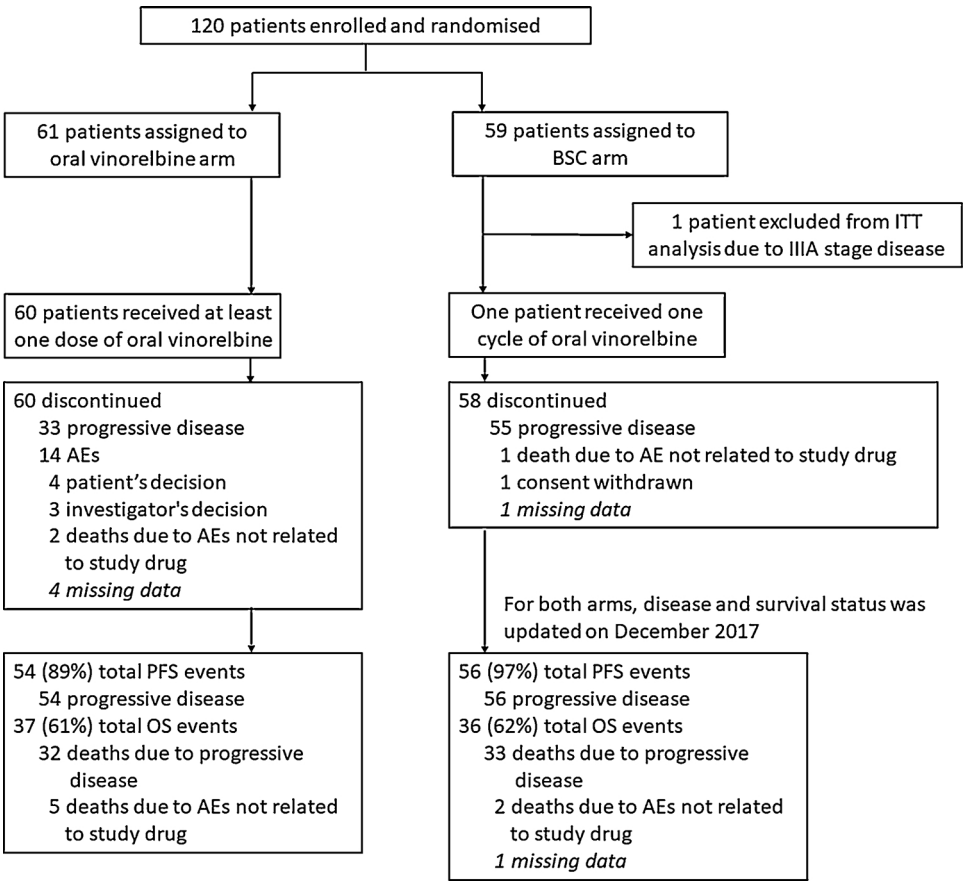

Fig. 1. Patients' disposition.
BSC, best supportive care; AE, Adverse Event; PFS, Progression-Free Survival; OS, Overall Survival.

events were required for demonstrating superiority of the vinorelbine arm, needing an accrual of 120 patients. Efficacy and activity analyses were performed on the Intention-to-Treat (ITT) population (i.e., all randomized patients meeting all major eligibility criteria, regardless of the treatment actually received, withdrawal, or protocol deviation). These patients were analyzed according to the treatment group allocated by the randomization procedure. Safety analysis was performed on all patients who received at least one cycle of the study drug. Survival and disease status of enrolled patients was updated on December 2017. A full detail of the statistical procedures is provided in the Supplementary Material.

3. Results

3.1. Patient population

In total, 120 patients were enrolled: 61 and 59 were assigned to OMV and BSC arm, respectively (Fig. 1). One patient assigned to BSC was excluded from ITT population due to violation of major eligibility criteria (stage IIIA). The two arms were well-balanced in terms of baseline characteristics, with the exception of a higher number of patients with brain metastasis and subjects receiving six cycles of induction CT in the OMV arm (Table 1). One patient in the BSC arm actually received vinorelbine, and as such was considered for the safety analysis.

Patients on OMV underwent a median (IQR) of 4 (2–7) treatment cycles (range: 1–54). Vinorelbine therapy was interrupted mainly because of disease progression (n = 33, 58.9%) and occurrence of adverse events (n = 14, 25.0%); other causes were lack of compliance (n = 2, 3.6%), death during treatment (n = 2, 3.6%), lack of compliance with protocol requirements (n = 2, 3.6%), patient's decision (n = 4, 7.1%) or investigator's decision (n = 1, 1.8%). Reason of OMV discontinuation was missing for 5 patients.

3.2. Progression-free survival

Median follow-up was 23.9 (IQR: 10.2–38.2) months. Disease progression occurred in 92.4% (110/119) of patients; those on OMV reported a significantly lower progression rate compared with patients in the BSC arm (OMV: 89% [54/61]; BSC: 96% [56/58]; HR: 0.73; 90% CI: 0.53–0.999; one-sided p = 0.049). Median PFS for patients on OMV was 4.3 months (95% CI 2.8–5.6) vs 2.8 months (95% CI 1.9–4.5) for those receiving BSC (Fig. 2A). At subgroup analysis, the advantage for OMV was still reported in patients ≥70 years, current smokers, and those with disease stabilization as best response to induction CT (Fig. 2B).

3.3. Overall survival

Seventy-three/119 (61.3%) patients died during the study. The OS rate was similar between the two arms (OMV: 61% [37/61]; BSC: 62% [36/58]; HR 1.07; 90% CI 0.72–1.57, two-sided p = 0.784). Median OS for patients on OMV was 11.8 months (95% CI: 8.4–19.6) vs 14.2 months (95% CI: 10.7–21.6) for patients receiving BSC (Fig. 2C). This finding was consistent regardless of the subgroups analyzed (Fig. 2D).

Most patients in both arms eventually died due to disease progression (32 for vinorelbine and 33 for BSC); a minor percentage of patients suffered fatal adverse events such as stroke, acute event, emottisis, ictus cerebral and atrial fibrillation (five cases, two during treatment), among patients treated with OMV, and spontaneous pneumothorax and a possible cardiovascular event in the BSC group. Reason of death was missing for one patient in BSC arm. No fatal adverse event related to therapy was observed by clinicians.

3.4. Overall response rate

One patient in the OMV arm showed partial response, versus no patient in the BSC group. Stabilization of disease was reported by 31 patients (51.7%) with OMV and 25 patients (44.6%) with BSC. DCR was therefore 53.3% (32/60) with OMV and 44.6% (25/56) with BSC (OR: 1.42; 95% CI: 0.68–2.94) (Table S1).

3.5. Further therapy and post-progression survival

On disease progression, the choice of further therapy was at the investigator's discretion (Table S2). Vinorelbine MTD was prescribed to five patients in each arm. Mean PPS at 9 months for patients on OMV was 2.61 months (90% CI: 1.78–3.43) vs 4.02 months (90% CI: 3.27–4.76) for those in the BSC arm (two-sided p = 0.037, Table S3).

Table 1
Baseline characteristics.

Baseline characteristics	Vinorelbine (n = 61)	Best supportive care (n = 58)	Overall (n = 119)
Age, median (range); years	70.2(45.1–83.9)	67 (46.4–82.8)	68.8 (45.1–83.9)
Males, number (%)	40 (65.6)	39 (67.2)	79 (66.4)
Smoking status; n (%):			
Never smoker	18 (30.0)	7 (13.7)	25 (22.5)
Current smoker	12 (20.0)	15 (29.4)	27 (24.3)
Former smoker	30 (50.0)	29 (56.9)	59 (53.2)
Missing data	*1 (1.6)*	*7 (12.1)*	*8 (6.7)*
BMI, median (IQR); kg/m^2	25.6 (22.7–27.8)	25.7 (22.8–29.0)	25.7 (22.7–29.0)
Missing data	*8 (13.1)*	*7 (12.1)*	*15 (12.6)*
ECOG PS; n (%):			
0	41 (67.2)	33 (56.9)	74 (62.2)
1	19 (31.1)	25 (43.1)	44 (37.0)
2	1 (1.6)	0 (0)	1 (0.8)
Histological type at primary diagnosis:			
Adenocarcinoma	37 (64.9)	36 (72.0)	73 (68.2)
Squamous cell carcinoma	17 (29.8)	11 (22.0)	28 (26.2)
Large cell carcinoma	2 (3.5)	0 (0)	2 (1.9)
Adenosquamous carcinoma	0 (0)	2 (4.0)	2 (1.9)
Other	1 (1.8)	1 (2.0)	2 (1.9)
NSCLC not otherwise specified	*4 (6.6)*	*8 (13.8)*	*12 (10.1)*
Tumor stage, n (%):			
IIIB	9 (14.8)	5 (8.6)	14 (11.8)
IV	52 (85.2)	53 (91.4)	105 (88.2)
Metastasis*, n (%):			
Liver	6 (9.8)	3 (5.3)	9 (7.6)
Lung	30 (49.2)	32 (56.1)	62 (52.5)
Bone	19 (31.1)	10 (17.5)	29 (24.6)
Lymph nodes	27 (44.3)	21 (36.8)	48 (40.7)
Brain	12 (19.7)	5 (8.8)	17 (14.4)
Other	13 (21.3)	14 (24.6)	27 (22.9)
Induction chemotherapy, patients (%):			
4 cycles	15 (24.6)	20 (35.7)	35 (29.9)
6 cycles	46 (75.4)	36 (64.3)	82 (70.1)
Missing data	*0 (0)*	*2 (3.4)*	*2 (1.7)*
Type of induction chemotherapy, n (%):			
Cisplatin + pemetrexed	13 (21.3)	15 (25.8)	28 (23.6)
Carboplatin + pemetrexed	15 (25.6)	11 (18.9)	26 (21.8)
Cisplatin + gemcitabine	19 (31.1)	15 (25.7)	34 (28.6)
Carboplatin + gemcitabine	11 (18.0)	14 (24.1)	25 (21.0)
Cisplatin + taxotere	1 (1.6)	1 (1.7)	2 (1.7)
Carboplatin + taxol	2 (3.3)	3 (5.1)	5 (4.2)
Cisplatin-based	33 (54.1)	31 (53.4)	64 (53.8)
Carboplatin-based	28 (45.9)	28 (48.2)	56 (47.0)
Best response to induction chemotherapy, patients (%)			
CR	1 (1.6)	0 (0)	1 (0.9)
PR	15 (24.6)	7 (13.0)	22 (19.1)
SD	45 (73.8)	47 (87.0)	92 (80.0)
Missing data	*0 (0)*	*4 (3.4)*	*4 (3.4)*

* Missing data about metastatic site for one patient in BSC arm.

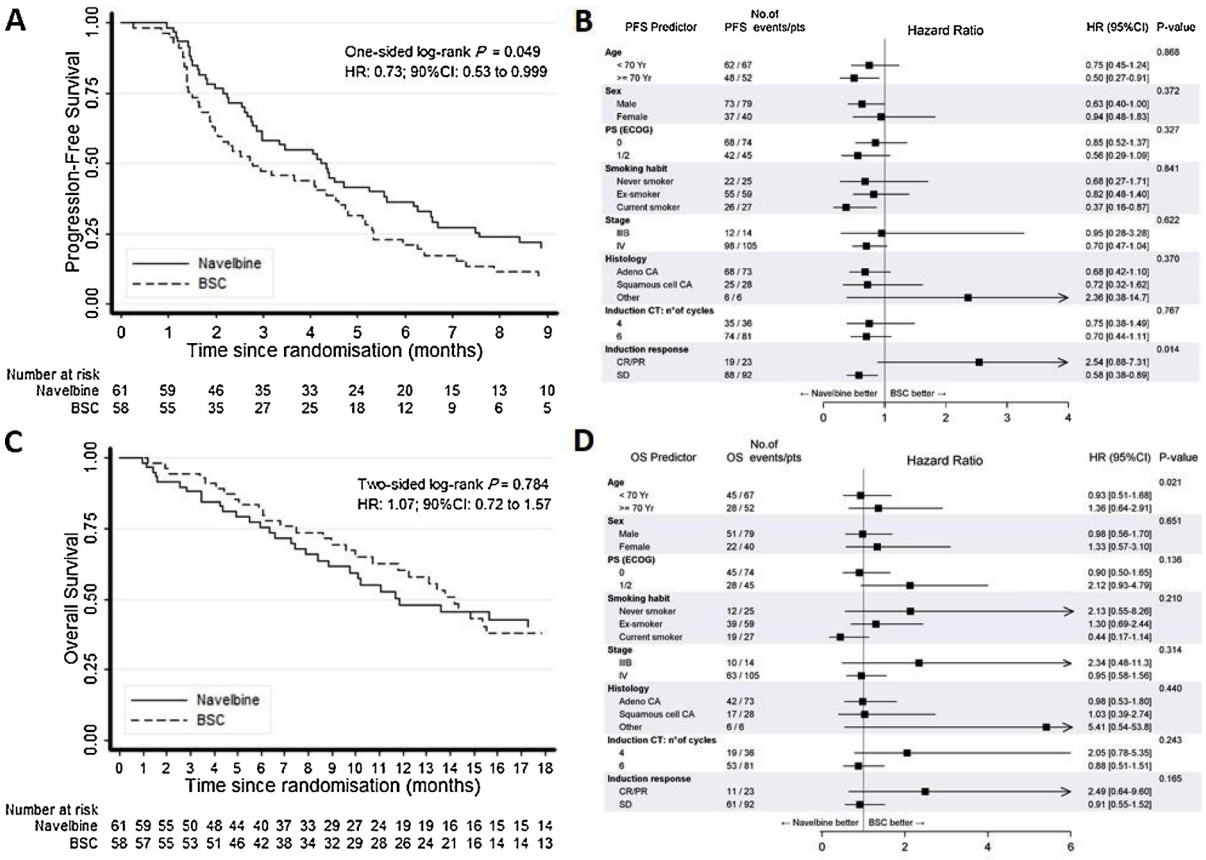

Fig. 2. (A) Progression-free survival (PFS) and (B) PFS subgroup univariate analysis for patients treated with oral vinorelbine maintenance versus best supportive care (BSC), and (C) overall survival (OS) and (D) OS subgroup univariate analysis for patients treated with oral vinorelbine maintenance versus BSC.
p-values for interaction between subgroups are reported in the forest plots. HR, hazard ratio; PS, performance status; CA, carcinoma; CT, chemotherapy; CR, complete response; PR, partial response; SD, stable disease.

3.6. Quality of life

Among patients on OMV, no relevant worsening in QoL was observed during treatment compared with baseline or BSC (Table S4). No association was identified between patients' baseline characteristics and QoL assessment at baseline and during treatment (data not shown).

3.7. Tolerability

The most common adverse drug reactions (ADRs) experienced by patients on OMV (50 mg three times a week) were neutropenia [two (3.3%) G2, three (4.9%) G3 and 11 (18.0%) G4], followed by other hematological alterations such as leukopenia [three (4.9%) G3 and three (4.9%) G4]. Other ADRs recorded for OMV were asthenia, decreased appetite, diarrhea, dysgeusia, febrile neutropenia, nausea and vomiting (Table 2). In ten cases, hospitalization was required due to AEs (neutropenia in seven cases). Discontinuation due to AEs were reported for hematologic toxicities [neutropenia (n = 6), anemia (n = 1), leukopenia (m = 1), thrombocytopenia (n = 1) or non-hematologic symptoms [asthenia (n = 3), diarrhea (n = 2), nausea, vomiting and pain (n = 1); the same patient could have experienced multiple events].

Drop-outs for toxicity occurred mostly within the first two cycles (9/14, 65%). After the protocol amendment for toxicity, 5 patients reduced the doses to 30 mg; in all cases treatment was well-tolerated with only G2 AEs in 2 patients (nausea and neuropathy).

3.8. Biomarkers

At baseline, mean VEGF values were 441.2 pg/mL (n = 51; range: 20.0–1684.9) in the OMV group and 382.9 pg/mL (n = 51; range 20.3–3208.3) in the BSC arm. Corresponding figures for TSP1 were 18504.4 ng/mL (n = 51; range 2158.0–53095.2) and 18536.1 ng/mL (n = 50; range 1053.7–36367.8), respectively. Twenty-three/47 (48.9%) patients in the OMV arm and 24/48 (50.0%) of those in the BSC arm were positive for MSC. Analysis of survival according to biomarkers concentration is reported in Table S5 and Figures S1–3. MSC is predictor of PFS and OS. In negative and positive MSC patients, median PFS is 4.8 (95% CI: 2.8–6.4) months and 3.0 (95% CI: 2.0–4.4) months, respectively. In negative and positive MSC patients, median OS is 17.3 (95% CI: 12.3–25.9) months and 9.6 (95% CI: 6.0–14.9) months, respectively. Overall, no interaction between treatment effect and biomarker values was detected (data not shown).

Table 2
Main adverse reaction related to vinorelbine (n = 61). The maximum grade of severity was considered for each patient.

	Grade 1; n (%)	Grade 2; n (%)	Grade 3; n (%)	Grade 4; n (%)
Anemia	0 (0)	3 (4.9)	2 (3.3)	0 (0)
Asthenia	3 (4.9)	6 (9.8)	3 (4.9)	0 (0)
Decreased appetite	2 (3.3)	3 (4.9)	0 (0)	0 (0)
Diarrhea	4 (6.6)	6 (9.8)	1 (1.6)	0 (0)
Dysgeusia	2 (3.3)	1 (1.6)	0 (0)	0 (0)
Febrile neutropenia	0 (0)	0 (0)	2 (3.3)	1 (1.6)
Leukopenia	0 (0)	0 (0)	3 (4.9)	3 (4.9)
Nausea	6 (9.8)	8 (13.1)	0 (0)	0 (0)
Neutropenia	0 (0)	2 (3.3)	3 (4.9)	11 (18.0)
Vomiting	4 (6.6)	3 (4.9)	0 (0)	0 (0)

4. Discussion

To our knowledge, the MA.NI.LA. study is the first randomized, controlled trial to investigate the effects of a 'switched maintenance' regimen with OMV oral metronomic vinorelbine in patients with advanced NSCLC not progressing after first-line platinum-based chemotherapy.

A significantly prolonged PFS was reported with OMV, as compared with the BSC arm (4.3 vs 2.8 months), without any worsening in QoL. However, the response rates resulted similar in the two arms, likely due to the predominantly cytostatic mechanism of action of OMV. Similarly, no difference in OS was observed, although a trend to prolonged survival was reported in the BSC arm. The high incidence of drop-out, also due to adverse events, contributes to explain the shorter PPS reported in the OMV arm: indeed, patients withdrawing from OMV likely directly started BSC, thus reducing survival. Moreover, the better PPS reported in the BSC can be attributed to the high number of patients (n = 11, 19%) who received anti-PD1 as second- or third-line therapy.

An unexpected high rate of hematological toxicity was reported with OMV at the full dose (e.g., neutropenia, 18% G4). This finding differs from previous studies reporting 0–10% rate of G3–4 events [7,9,18]. However, our patients were not chemo-naïve, but started OMV after platinum-based induction chemotherapy. The lack of serious toxicity in patients reducing the dose to 30 mg three times weekly suggests this regimen as more indicated for highly-pretreated patients. This is also supported by a recent study showing that at this dose the drug continues to maintain clinical activity [18]. The notion that toxicity occurred early along with the high variability of the number of cycles administered (from 1 to 54), suggests the presence of pharmacodynamic/pharmacogenomic mechanisms contributing to the tolerability of OMV in this setting. For instance, it has been shown that OMV blood concentrations were about 2.5 times higher in patients with toxicities compared with those without toxicity [18].

Interesting insights on the potential use of OMV were reported at the subgroup analysis of PFS. Indeed, OMV was associated with prolonged PFS in some subgroups of patients, i.e. elderly (≥70 years), current smokers, and those who achieved disease stabilization after induction CT. These findings may have clinical relevance, also given that the OMV arm included more patients with brain metastasis and the advantage in PFS was unrelated to tumor histology. On the other hand, a potential detrimental effect of OMV in patients responsive to induction therapy cannot be excluded, suggesting that these patients may benefit more from continuous, rather than "switch" maintenance. Noteworthy, a large number of patients with adenocarcinoma were enrolled before the amendment to the protocol we applied consequently to the results of PARAMOUNT trial, which excluded patient potentially benefitting from maintenance treatment with pemetrexed.

At explorative analysis, among the evaluated biomarkers (VEGF, TSP, MSC), none showed predictive value and only MSC seemed to have prognostic value, in line with previous findings [19]. Conversely to VEGF and TSP that are biomarkers of angiogenesis [16], the MSC rather reflects immunosuppressive phenotypic changes enhancing tumor growth and aggressiveness [20]. Further evaluation of the data is ongoing (manuscript in preparation).

We must acknowledge that the study was planned in the pre-immunotherapy era and therefore PD1 status was not investigated. In the current treatment scenario further elucidations on the potential role of OMV will require a proper correlation of PD1 status with immunotherapy. Noteworthy, OMV may exert immunotherapeutic effects [21], suggesting the possibility of its combination with immunotherapy.

In conclusion this study met its primary endpoint of improving PFS, and showed that OMV may play a role in the maintenance therapy of NSCLC. However, in the platinum-pretreated setting, the lack of OS gain and toxicity prompt for refinement of the schedule.

Conflicts of interest

The authors have no other conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.04.001.

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