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ORIGINAL RESEARCH

# Metronomic oral vinorelbine in previously untreated advanced non-small-cell lung cancer patients unfit for platinum-based chemotherapy: results of the randomized phase II Tempo Lung trial☆

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**Background:** To assess the efficacy and safety of a metronomic schedule of oral vinorelbine (mVNR) in advanced non-small-cell lung cancer (NSCLC) in patients unfit for platinum-based combination chemotherapy.

**Patients and methods:** This was a multicenter, prospective, randomized, open-label phase II study in treatment-naive patients with TNM stage IIIB/IV NSCLC. Patients received mVNR at a fixed dose of 50 mg × 3 or standard schedule 60-80 mg/m$^2$ weekly until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) without grade 4 toxicity (G4PFS; NCI-CTC v4). Main secondary objectives were safety, disease control rate (DCR) without grade 4 toxicity (G4DCR), DCR, PFS, overall survival (OS) and quality of life (QoL).

**Results:** A total of 167 patients were included, 83 and 84 patients in the mVNR and standard arms, respectively. The median G4PFS was 4.0 months [95% confidence interval (CI): 2.6-4.3] and 2.2 months (95% CI: 1.5-2.9), hazard ration (HR) = 0.63 (95% CI: 0.45-0.88), $P = 0.0068$ in favor of metronomic arm; G4DCR was 45.8% and 26.8% in the mVNR and standard arms, respectively. Grade 3-4 treatment-related adverse events were less frequent in the mVNR arm (25.3% versus 54.4%) mainly owing to a reduction in all grades (15.7% versus 51.9%) and grade 3-4 neutropenia (10.8% versus 42%). PFS was 4.3 (95% CI: 3.3-5.1) and 3.9 months (95% CI: 2.8-5.2) in mVNR and standard arms, respectively. No difference in median OS was observed. QoL was comparable between arms.

**Conclusions:** Metronomic oral vinorelbine significantly prolonged median G4PFS in advanced NSCLC patients unfit for platinum combinations as first-line treatment. It was associated with a clear reduction in toxicity and may be considered as an important option in this challenging population.

**Key words:** vinorelbine, carcinoma non-small-cell lung, administration and dosage, randomized controlled trial, frail

## INTRODUCTION

Non-small-cell lung cancer (NSCLC) remains the most frequent cancer diagnosed and the leading cause of death in males worldwide.[1] Platinum doublets and immunotherapy or immunotherapy alone are the standard palliative treatments for advanced disease but not all patients are fit for such treatments.[2-4]

The definition of unfit patients varies among clinicians; nevertheless, the definition is grounded by two terms: 'elderly' and 'poor performance status'. The criteria established by an Italian panel of experts in 2015 include age, performance status, renal function, heart failure, previous cerebrovascular events, uncontrolled hypertension, neuropathy, hearing loss, symptomatic brain metastases, severe psychiatric disorders and absence of caregiver support. The cut-off of each item depends on the drug administered. The patients could be unfit for cisplatin or carboplatin combined

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chemotherapy.[5] For these unfit patients, single-agent chemotherapy is more suitable. Several drugs showed activity as monotherapy in NSCLC like vinorelbine, gemcitabine, pemetrexed and taxanes.

Vinorelbine (VNR), a third-generation microtubule-targeting agent, was approved in the treatment of breast cancer and NSCLC alone or in combination. The main mechanism of action consists of inhibiting tubulin polymerization during mitosis leading to cell death. Oral VNR was assessed at a starting dose of 60 mg/m$^2$/week for the first three administrations and then increased to 80 mg/m$^2$/week in the absence of severe hematological toxicity. In first-line treatment of NSCLC, oral VNR showed a good efficacy and safety profile, even in elderly patients.[6]

The metronomic concept emerged more than 20 years ago, however, a significant development in various solid tumors was noticed in the past 10 years.[7,8] There are potentially several mechanisms of actions against tumor cells including inhibition of angiogenesis.[9,10]

Metronomic chemotherapy schedule is defined as frequently close or continuous administration of a low dose of a drug and its use was made easier with the advent of oral forms.

The mechanisms of action are different from standard administration and the direct toxic effect on tumor cells is not the main target. When administered with a metronomic schedule, the drug acts mainly by inhibiting angiogenesis and modulating the immune system.[8,11-14]

The mechanisms of action of metronomic VNR (mVNR) are different in inhibiting the formation and maintenance of the tumor vasculature.[13] Oral mVNR has been tested in three phase I trials, setting 50-mg fixed dose three times a week (Monday-Wednesday-Friday) as the reference dose. Results of these phase I studies showed activity associated with a good safety profile.[15-17] A phase II study was conducted in elderly chemo-naive patients with NSCLC with an overall disease control rate (DCR) of 58%, overall survival (OS) of 9 months and good tolerance and no worsening of quality of life (QoL).[18]

The aim of this prospective, multicentric, randomized study was to assess the efficacy and the safety of a metronomic schedule of oral VNR in a homogeneous population of NSCLC patients unfit for platinum-based combination chemotherapy. The control arm was a weekly schedule with oral vinorelbine (OV) as approved worldwide.

## PATIENTS AND METHODS

### *Study design*

This was an open-label, prospective, multicenter, randomized phase II study (EudraCT number: 2014-003859-61). Randomized allocation was 1 : 1 with stratification on stage IIIB/IV (TNM 7th edition 2009) at study entry, age $<$70 years or $\geq$70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1 versus 2 and center. Randomization was carried out by investigators using the Interactive Web Response System. The system allocates a randomization number. Three amendments were implemented to add a supplementary interim safety analysis, to clarify definitions of febrile neutropenia and progression-free survival (PFS) without grade 4 toxicity (G4PFS), to proceed to earlier analysis and to modify the definition of the end of the study (30 days after the last treatment administration of the last patient) with no change of eligibility criteria.

This study was carried out in accordance with the principles stated in the Declaration of Helsinki and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95). All patients provided written informed consent before start of any procedure.

Eligibility criteria included written informed consent, age $\geq$18 years, histologically or cytologically confirmed NSCLC, ECOG PS of 0-1 or 2, stage IIIB/IV or relapsing (locally or distant) after a local treatment. Patients unfit to receive platinum-based chemotherapy had at least one (or more) of the following criteria: previous adjuvant platinum-based chemotherapy, creatinine clearance $<$60 ml/min, heart failure New York Heart Association class II-III, hearing loss $>$grade 2 and medical condition impairing platinum-based chemotherapy according to physician's opinion. No previous systemic chemotherapy for advanced NSCLC was allowed. Patients who might have been treated with surgery, previous targeted therapy or immunotherapy, previous adjuvant chemotherapy or previous palliative radiotherapy on non-target lesions were allowed provided a minimum interval of 2 weeks from the end of radiotherapy and the start of study treatment.

Adequate organ function criteria were bone marrow {[neutrophils $\geq 2.0 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, hemoglobin $\geq$10.0 g/dL], hepatic total bilirubin $\leq 1.5 \times$ upper limit of normal [ULN], transaminases [ALT, AST] $<2.5 \times$ ULN, alkaline phosphatase $<5 \times$ ULN, and renal functions [calculated creatinine clearance $\geq$30 ml/min (Cockcroft and Gault formula)]}. Patients had to have at least one measurable lesion that had not been previously irradiated and a life expectancy of $>$12 weeks. Main non-inclusion criteria were known hypersensitivity to the study drug or to drug with similar chemical structures, any important factor likely to modify drug absorption, inability to swallow, symptomatic brain metastases, sensory neuropathy $\geq$ grade 2, weight loss $>$10% within the previous 3 months, long term oxygen therapy, concomitant/uncontrolled medical disorder, symptomatic ascites or pericardial effusion, history of another malignancy within the past 5 years, except basal cell carcinoma of the skin or carcinoma in situ of the cervix and concomitant treatment with another anticancer therapy.

### *Treatment*

A cycle was 3 weeks of treatment. First, study drug administration had to begin within 7 days after randomization and the treatment had to be continued until disease progression, unacceptable toxicity, patient's refusal or investigator's decision.

**Arm A.** OV was administered 50 mg three times weekly, continuously. Patients received OV on days 1, 3 and 5 of each week continuously according to hematological tolerance (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100051).

In case of grade 3-4 hematological toxicity or grade 2 toxicity, lasting more than 3 weeks with potential clinical consequences, the dose was reduced to 30 mg three times weekly. In case of non-hematological toxicity or persistent grade 2 toxicity with impact on daily activities or grade 3 diarrhea that occurred at any time during the cycle, dose administration was delayed or canceled. If grade $\geq$3 of any other adverse event (AE) occurred, chemotherapy was to be held for a maximum of 3 weeks.

**Arm B.** In the first cycle, the starting dose of OV was 60 mg/m$^2$, then based on hematological tolerance, the dose could be escalated to 80 mg/m$^2$ at cycle 2 and subsequent cycles. Dose could be adjusted in case of toxicity. No re-escalation was allowed after a dose reduction. Primary prophylaxis with oral ondansetron was recommended before each OV administration according to the institutional rules of each center.

Corrective and/or palliative treatment including anti-infectious prophylaxis in high-risk patients were administered as needed in agreement with institutional guidelines.

After disease progression, further second-line treatment was dependent on the investigator's decision.

During the protocol, in case of need of radiotherapy, the patient was to be considered in progression and was to be withdrawn from the trial.

### *Endpoints and assessments*

The main endpoint was G4PFS defined as the first occurrence of either grade 4 toxicity or disease progression or death. Main secondary objectives were tolerance, disease control (complete response [CR] + partial response [PR] + stable disease [SD]) rate, disease control without grade 4 toxicity, DCR and duration, objective response (CR + PR) rate without grade 4 toxicity, objective response rate (ORR), time to first response, PFS, OS and QoL.

G4PFS was calculated from the date of randomization until the date of progression or the date of grade 4 toxicity or the date of death due to any cause, whichever occurred first. Overall response of the patient is defined as the best response designation (CR and PR had to be confirmed no less than 4 weeks apart) recorded from the date of randomization until the end of the study treatment period (Supplementary Figure S2). Duration of disease control without grade 4 toxicity was calculated among the responders and stable patients from the date of randomization until the documentation of progression or grade 4 toxicity or death due to any cause, whichever occurred first. Time to first response was calculated among the responders (i.e. confirmed CR and PR) from the date of randomization up to the first report of documented response. PFS was calculated from the date of randomization until the date of progression or the date of death due to any cause if no progression was recorded before. Patients who were lost to follow-up or reach the time point of analysis without a known record of progression or death had the PFS censored at the date of last tumor assessment or last contact of a follow-up showing no progression, whichever occurred last. Survival was measured from the date of randomization up to death or last follow-up. For patients who had not died, survival time was censored at the date of last news.

Assessment of measurable disease was to be carried out every 6 weeks until disease progression and evaluated according to RECIST 1.1. Spiral computed tomography (CT) scan and magnetic resonance imaging (MRI) were preferred. Safety was assessed by the investigator on day 1 of each cycle by physical examination including vital signs, body weight and PS, complete blood cell count and serum biochemistry (days 1, 8 and 15), reporting AEs using the NCI-CTC version 4.0 grading and the QoL questionnaire (EORTC QLQ C30). The safety assessment was graded on the NCI-CTC classification version 4.0. Worse grades were reported by cycle and by patient. All safety analyses were carried out regardless of the relationship to treatment and related to treatment. All serious adverse events (SAEs) and treatment-related SAEs were counted and presented in tables. QoL was evaluated through the EORTC QLQ C30 that was to be completed before randomization, before cycle 2 and then every two cycles and at the end of treatment evaluation. The QLQ-C30 includes five functional scales, three symptom scales, a global health status/QoL scale and six single items. All the scales and single items measures range in score from 0 to 100. A high score represents a higher response level. Changes of the scores from baseline of the parameters are provided.

### *Statistical analyses*

Based on a median G4PFS of 2.0 months in the standard arm and 3.2 months in mVNR arm, 143 events were needed at least according to a two-sided log-rank test at $\alpha = 0.05$ significance level and 80% power to show a statistically significant difference. Assuming a 10% dropout rate and study duration of 30 months, 166 patients were planned to be enrolled.

All registered and treated patients were included in the intent-to-treat (ITT) population. Evaluable population for response included all patients that were eligible, evaluable, randomized and treated in the arm assigned by randomization. The study periods were divided into screening, treatment and follow-up periods. All treated patients were included in the analysis of safety unless a patient was lost to follow-up. Patients were considered evaluable for health-related QoL analysis if they had completed at least two questionnaires (including the questionnaire completed before randomization). The first interim analysis (IA) was carried out when 40 patients had been randomized. Upon request of the data monitoring committee (DMC) during this first IA, a second IA was carried out after 40 additional patients had been randomized. Time-related endpoints were estimated using the Kaplan—Meier method. Confidence intervals (CIs) on the median were calculated using

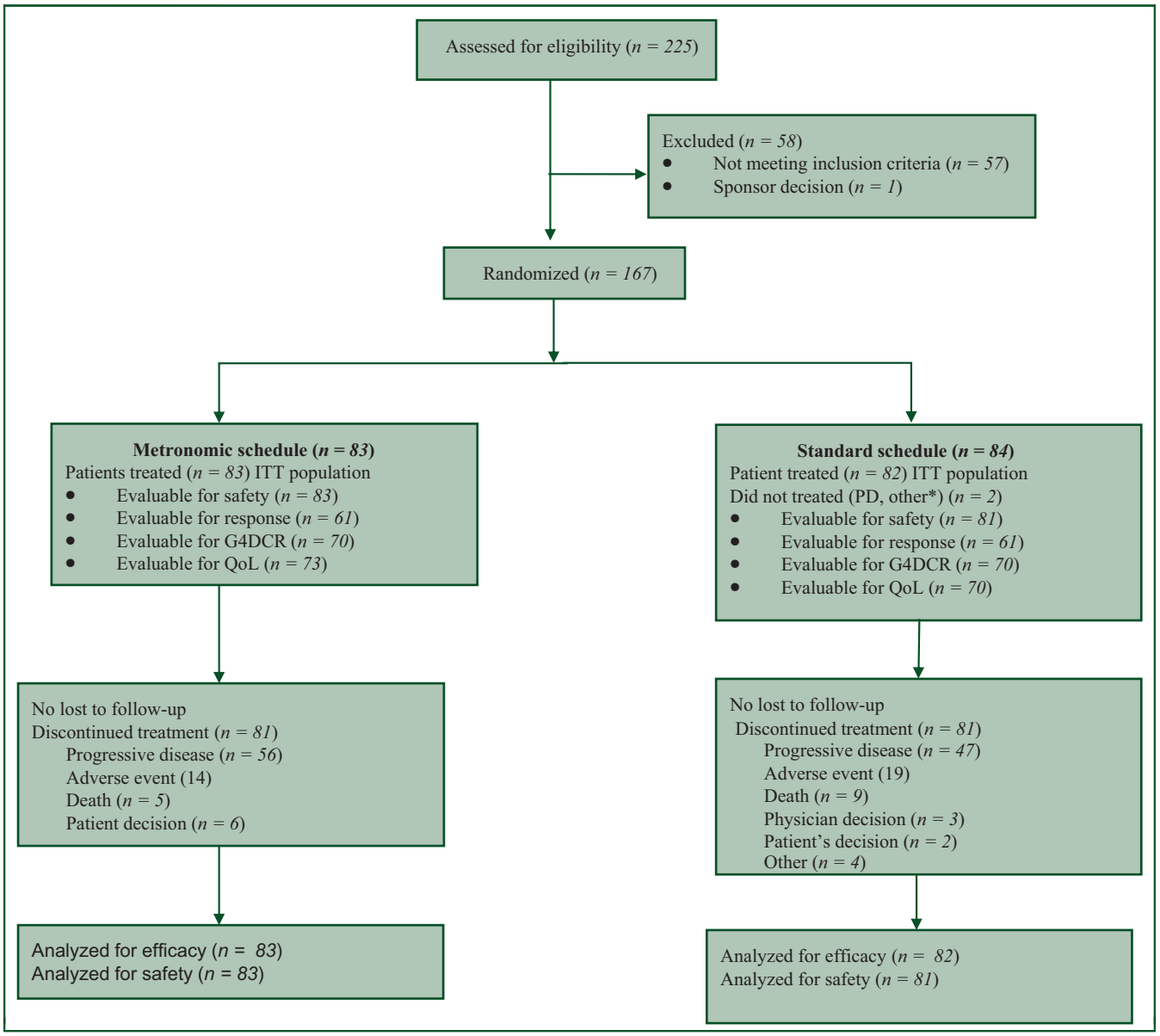


**Figure 1. CONSORT flow diagram.**
G4DCR, duration of disease control without grade 4 toxicity; ITT, intent to treat; other, delay starting treatment; PD, progressive disease; QoL, quality of life.

the Brookmeyer and Crowley method. The patients who received any new anticancer therapy before disease progression were censored at the start of the new therapy. The data cut-off date for final analysis was on the 15 October 2018.

Data were analyzed using the SAS® system software (version 9.3 or higher).

## RESULTS

### *Patient characteristics*

From October 2015 to October 2017, 29 centers in 8 European countries included 167 patients. The ITT population included 165 patients; 2 patients were not treated. At the cut-off date, 9.6% patients in the mVNR arm and 11.9% patients in the standard arm were alive (Figure 1 consort diagram). The majority of patients were male (75.8%), aged ≥70 years (84.2%), with ECOG PS 0-1 (64.2%), clinical stage IV (90.9%) with three or more organs involved (59.4%). Two patients in the mVNR arm and five patients in the standard arm were previously treated with VNR as part of adjuvant therapy. Patient characteristics at baseline were well balanced between the arms (Table 1).

### *Dose delivery*

A total of 482 and 418 cycles were administered in the mVNR and the standard arms, respectively. The median number of cycles received was four cycles in the mVNR arm (range: 1-44) and four cycles in the standard arm (range: 1-18). The median dose intensity per cycle was 80 mg/m$^2$/week in the mVNR arm and 57.75 mg/m$^2$/week in the standard arm. The median relative dose intensity (RDI) per patient was 85% and 68.7% in the mVNR and the standard

**Table 1. Patient characteristics at baseline in both arms: intent to treat population**

| | Metronomic arm | Standard arm |
|---|---|---|
| | *n* (%) | *n* (%) |
| Number of patients | 83 (100) | 82 (100) |
| Age (years) | | |
| Median | 77.0 | 77.0 |
| <70 | 14 (16.9) | 12 (14.6) |
| ≥70 | 69 (83.1) | 70 (85.4) |
| Gender | | |
| Male | 62 (74.7) | 63 (76.8) |
| Smoking history | | |
| Never/past smoker | 7 (8.4)/66 (79.5) | 6 (7.3)/61 (74.3) |
| Current smoker | 10 (12.0) | 15 (18.3) |
| ECOG PS | | |
| 0-1/2 | 55 (66.3)/28 (33.7) | 51 (62.2)/31 (37.8) |
| Clinical stage at entry | | |
| IIIB/IV | 9 (10.8)/72 (86.7) | 4 (4.9)/77 (93.9) |
| Relapse non-IIIB/IV | 2 (2.4) | 1 (1.2) |
| Histology | | |
| Squamous/adenocarcinoma | 30 (36.1)/45 (54.2) | 33 (40.2)/40 (48.8) |
| Others | 8 (9.7) | 9 (11.0) |
| Number of organs involved | | |
| 1-2 | 6 (7.2)/28 (33.7) | 4 (4.9)/29 (35.4) |
| ≥3 | 49 (59.0) | 49 (59.8) |
| Most frequent type of organs involved (≥20%) | | |
| Lung | 78 (94.0) | 80 (97.6) |
| Lymph node | 64 (77.1) | 62 (75.6) |
| Pleural effusion | 24 (28.9) | 24 (29.3) |
| Bone | 14 (16.9) | 19 (23.2) |
| Adrenal gland | 17 (20.5) | 13 (15.9) |

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

arms, respectively. The median relative dose intensity per cycle was 100% and 74.5% in the mVNR and the standard arms, respectively. More patients received 90% to >100% of the planned dose in the mVNR than in the standard arm. Dose modifications were more frequent in the standard arm than in the mVNR arm: 47.7% and 24.0% of cycles. The main reason for dose modification was the occurrence of an AE, 36.0% in the standard arm and 17.4% in the mVNR arm (Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2021.100051).

### *Primary endpoint*

Overall, disease progression, AE with grade 4 toxicity or death was reported in 74 (89.2%) patients in arm A and 78 (95.1%) in arm B at the cut-off date. The median time to disease progression, AE with grade 4 toxicity or death or the median time to G4PFS was 4.0 months (95% CI: 2.6-4.3) and 2.2 months (95% CI: 1.5-2.9), hazard ration (HR) = 0.63 (95% CI: 0.45-0.88), $P = 0.0068$, in the mVNR and standard arms, respectively (Figure 2; Table 2). An estimated 37% risk reduction in disease progression, AE with grade 4 toxicity or death (increase in G4PFS) was observed for patients in arm A compared with those in arm B (HR 0.63; 95% CI: 0.45-0.88).

### *Safety*

Globally, treatment-related AEs were more frequently experienced by patients included in the standard arm (84.0%) compared with mVNR (61.4%). Grade 3 and 4 AEs were more frequently observed in the standard arm (54.4%) compared with the mVNR arm (25.3%). Any-grade neutropenia was experienced by 15.7% of patients in the mVNR arm versus 51.9% in the standard arm and 32.1% of patients in the standard arm versus 3.6% of patients in the mVNR arm had grade 4 event. Rates of grade 4 treatment-related, non-hematological AEs were low in both arms. Any grade of treatment-related gastro-intestinal disorders were 41% and 51.9% in the mVNR and standard arms, respectively. There was a trend for less treatment-related nausea of any grade in the mVNR arm (24.1%) compared with the standard arm (35.8%). Conversely, there was a trend for less any-grade stomatitis in the standard arm (7.4%) compared with the mVNR arm (13.3%). The incidence of grade 3-4 stomatitis was low in both arms, 0% and 1.2% in the standard and mVNR arms, respectively (Table 3). Overall grades of treatment-related general disorders were 26.5% in the mVNR arm versus 40.7% in the standard arm, respectively.

Treatment-related SAEs were experienced by eight patients in the mVNR arm and seven patients in the standard arm. One patient experienced grade 5 febrile neutropenia in the experimental arm and one patient in the standard arm experienced grade 5 neutropenic sepsis.

### *Efficacy results*

Overall, PFS was 4.3 months (95% CI: 3.3-5.1) and 3.9 months (95% CI: 2.8-5.2), HR = 0.98 (95% CI: 0.70-1.38), in the mVNR and standard arms, respectively.

There was no complete response. A partial response was observed in five patients in both arms. A partial response without grade 4 toxicity was observed in four and two patients in the mVNR and standard arms, respectively.

Time to first response was 1.6 months (95% CI: 1.4-7.1) and 2.6 months (95% CI: 1.1-4.1), HR = 1.32 (95% CI: 0.17-10.49) in the mVNR and standard arms, respectively. Stable disease was observed in 57.8% patients in the mVNR arm and 57.3% patients in the standard arm. Stable disease without grade 4 toxicity was noted in 41.0% of patients in the mVNR arm and 24.4% of patients in the standard arm. The median duration of stable disease was similar between both arms.

Overall, 63.9% and 63.4% of patients had disease control in mVNR and standard arms, respectively. The median duration of disease control was 5.4 months (95% CI: 4.5-7.0) and 5.8 months (95% CI: 4.3-6.8) in the mVNR and standard arms, respectively. Disease control without grade 4 toxicity was observed in 45.8% patients in the mVNR arm and 26.8% patients in the standard arm. The median duration of disease control without grade 4 toxicity was 4.8 months (95% CI: 4.2-6.5) and 3.3 months (95% CI: 2.5-3.8) in the mVNR and standard arms, respectively. In total, 12 and 15 patients in the mVNR arm and 6 and 9 patients in the standard arm had disease progression without grade 4 toxicity and DCR (ITT) where 15 patients had PD in metronomic arm and 9 patients had PD in the standard arm,

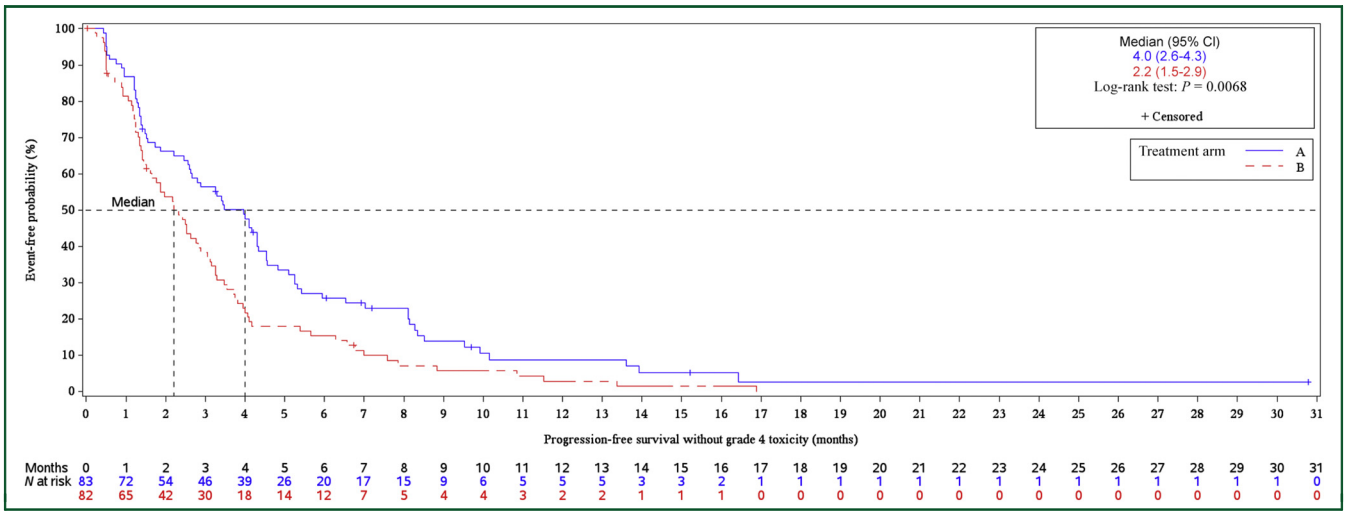


**Figure 2. Progression-free survival without grade 4 toxicity: intention to treat population.**
Log-rank test *P* value based on stratified approach including the stratification factors [stage at study entry (III/IV), age at study entry (<70/≥70 years) and ECOG performance (0-1/2)].
1 month = 30.4375 days.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

**Table 2. Efficacy results: intent to treat population**

| | Metronomic arm | Standard arm | Log-rank test *P* value HR (95% CI) |
|---|---|---|---|
| Number of patients *n* (%) | 83 (100) | 82 (100) | |
| PFS without G4 toxicity (months) Median (range) | 4 (2.6-4.3) | 2.2 (1.5-2.9) | 0.0068 0.63 (0.45; 0.88) |
| PFS (months) Median (range) | 4.3 (3.3-5.1) | 3.9 (2.8-5.2) | |
| OS (months) Median (range) | 7.1 (5.3-8.5) | 7.6 (5.2-8.8) | |
| DCR without grade 4 toxicity % (95% CI) | 45.8 (34.8-57.1) | 26.8 (17.6-37.8) | |
| DCR | 63.9 (52.6-74.1) | 63.4 (52.0-73.8) | |
| ORR without grade 4 toxicity % (95% CI) | 4.8 (1.3-11.9) | 2.4 (0.3-8.5) | |
| ORR % (95% CI) | 6.0 (2.0-13.5) | 6.1 (2.0-13.7) | |

CI, confidence interval; DCR, disease control rate; HR, hazard ration; ORR, overall response; OS, overall survival; PFS, progression-free survival.

respectively. Overall, the median time to disease progression was 4.3 months (95% CI: 3.3-5.1) (Figure 3).

The median OS was 7.1 months (95% CI: 5.3-8.5) and 7.6 months (95% CI: 5.2-8.8), HR = 1.02 (95% CI: 0.72-1.45), in the mVNR and standard arms, respectively.

### *QoL*

In the ITT and evaluable populations, changes observed from baseline with the EORTC QLQ C30 questionnaire were similar in both arms with no worsening of QoL scores. QoL data were available for 85.6% of patients.

## DISCUSSION

The Tempo Lung randomized phase II trial evaluated the activity of first-line mVNR in advanced NSCLC patients not eligible to receive a platinum-based chemotherapy combination in first-line approach. The study met its primary endpoint showing a statistically significant ($P = 0.0068$) and clinically relevant increase in G4PFS in the metronomic arm in ITT analysis. PFS without grade 4 toxicity was longer in the mVNR arm. A statistically significant 37% risk reduction in disease progression, grade 4 toxicity or death (primary endpoint of the study) was observed for patients in the mVNR arm compared with those in the standard arm.

Moreover, DCR without grade 4 toxicity was reported in more patients included in the metronomic schedule arm compared with those included in the standard arm. There was also a trend of the median duration of disease control without grade 4 in favor of the metronomic arm. The same trend is observed in the median PFS without grade 2, 3, 4 toxicity between both arms. PFS without grade 2, 3, 4 toxicity was longer in patients who received treatment on an mVNR compared with patients in the standard arm.

Accordingly, the median RDI by cycle of OV was higher in the metronomic arm (100%) compared with those of the standard arm (74.5%). This was owing to better tolerance of the metronomic regimen with less dose modification for AEs (36% of cycles with at least one dose modification in the standard arm versus 17.4% of cycles in the metronomic arm). The median duration of disease control of 6 months and the median OS of 7 months are in line with other mVNR and weekly schedule phase II studies in a population of unfit patients.[19,20] A large international retrospective study reached the same conclusions.[21]

A metronomic treatment was associated with a clear reduction in AE incidences so perfectly fitting the needs of unfit NSCLC patients. Severe (grade 3 and 4) toxicity of any system or organ dropped from 54.4% with standard schedule to 25.3% with mVNR. Similarly, all grade toxicity rates decreased from 84% to 61.4%. Focusing on

**Table 3. Treatment-related adverse events per patient (rate > 5%)**

| Number of patients | Metronomic VNR arm *n* (%) | | | Standard VNR arm *n* (%) | | |
|---|---|---|---|---|---|---|
| | 83 (100) | | | 81 (100) | | |
| | Any grade | Grade 3 | Grade 4 | Any grade | Grade 3 | Grade 4 |
| Any system organ | 51 (61.4) | 17 (20.5) | 4 (4.8) | 68 (84.0) | 19 (23.5) | 25 (30.9) |
| Hematological | | | | | | |
| Neutropenia | 13 (15.7) | 6 (7.2) | 3 (3.6) | 42 (51.9) | 8 (9.9) | 26 (32.1) |
| Anemia | 7 (8.4) | 3 (3.6) | — | 7 (8.6) | 3 (3.7) | — |
| Febrile neutropenia | 3 (3.6) | 1 (1.2) | 1 (1.2) | 5 (6.2) | 3 (3.7) | 2 (2.5) |
| Non-hematological | | | | | | |
| Nausea | 20 (24.1) | 2 (2.4) | — | 29 (35.8) | 1 (1.2) | — |
| Diarrhea | 17 (20.5) | 1 (1.2) | — | 24 (29.6) | 2 (2.5) | — |
| Asthenia | 16 (19.3) | 4 (4.8) | — | 21 (25.9) | 7 (8.6) | — |
| Vomiting | 7 (8.4) | 1 (1.2) | — | 15 (18.5) | 1 (1.2) | |
| Fatigue | 6 (7.2) | 1 (1.2) | — | 12 (14.8) | 4 (4.9) | — |
| Constipation | 3 (3.6) | — | — | 11 (13.6) | — | — |
| Stomatitis | 11 (13.3) | 1 (1.2) | — | 6 (7.4) | — | — |
| Loss appetite | 6 (7.2) | — | — | 9 (11.1) | — | — |

VNR, vinorelbine.

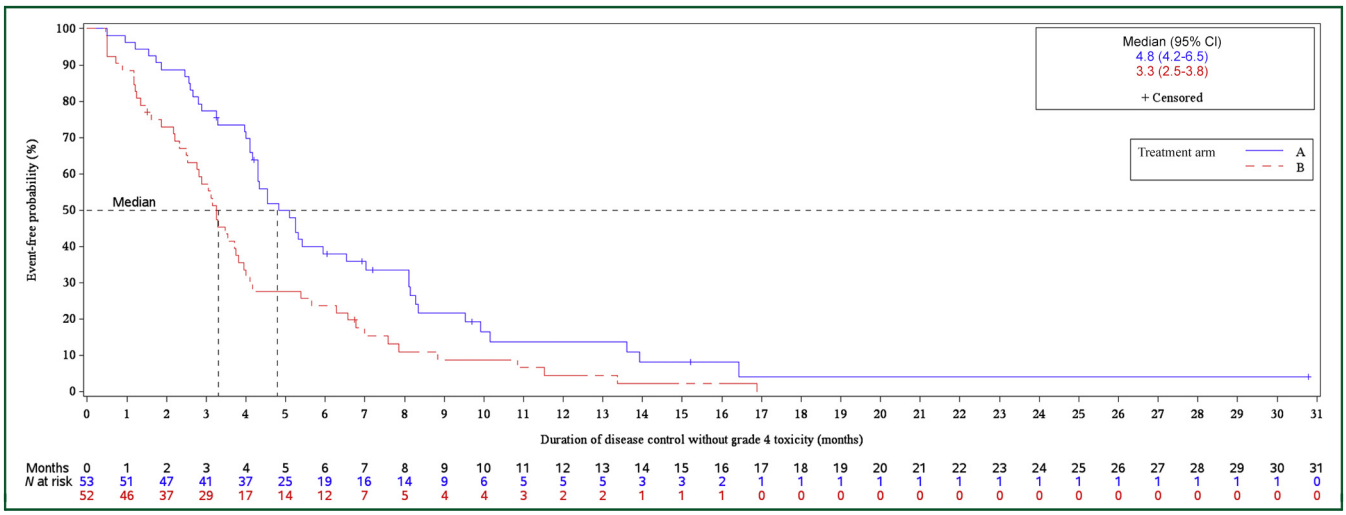


**Figure 3. Duration of disease control without grade 4 toxicity.**
Only responders and stable patients are included in the analysis of duration of disease control.
1 month = 30.4375 days.
CI, confidence interval.

hematological toxicity, in the metronomic arm, there was an impressive difference with a reduction in both all-grade and grade 3-4 neutropenia. Anemia rates were comparable between arms. The potential of metronomic chemotherapy has been assessed in various advanced cancer in preclinical and clinical studies.[8,12,13,22,23] In metastatic breast cancer, metronomic chemotherapy with vinorelbine is a treatment option.[24] Despite the availability of immunotherapy or targeted therapy agents as first-line treatment in advanced NSCLC, there are still NSCLC patients with advanced disease who may not be eligible for these treatments.[2,25,26] These patients are a subset of patients with heterogeneous features such as older age, high tumor burden with metastasis, carrying significant numerous chronic conditions or comorbidities and impaired PS. Therefore, it may be important in this challenging population composed of unfit advanced NSCLC patients to explore the use of oral metronomic chemotherapy over standard oral chemotherapy.[22]

Based on most recent publications highlighting the excellent safety profile of the metronomic approach and considering the distinctive features of such a difficult and high-risk population, the primary endpoint was set on a composite endpoint such as G4PFS.[27] In fact, unfit advanced NSCLC patients represent a unique setting in which the risk/benefit ratio of treatment should be carefully evaluated, and safety issues are of paramount importance. In accordance with unfit characteristics, patients included in the present study were elderly with median age of 77 years; one-third presented with an ECOG PS of 2.[2,28,29]

Previously, Gridelli et al.[6] reported an incidence of 50% of grade 3-4 neutropenia and 70% of all grades of neutropenia with OV used as single agent in elderly, advanced NSCLC patients with comorbidities.[6] Compared with the incidence

of hematological toxicity reported by Gridelli et al.,[6] the incidence observed in the Tempo Lung trial was lower (rate of any hematological toxicity 27.7%; grade 3-4 neutropenia 15.7% in our trial). Regarding the incidences of non-hematological related toxicities, there was a trend favorable in the metronomic arm with fewer rates of general disorders and particularly fatigue of any grade.

Oral chemotherapy in elderly patients may bring potential advantages by reducing side-effects due to the use of intravenous lines and is more convenient, allowing home treatment. Single-agent OV in elderly patients is recommended as a suitable option.[2,29,30] Metronomic chemotherapy is also recommended in elderly patients as it brings a good compromise of efficacy and tolerability. The safety results of Tempo Lung compare favorably with safety outcomes reported in several recent publications with the same dose schedule in first-line advanced NSCLC patients and with favorable disease control.[18,19] There was a trend for longer PFS in the mVNR arm and the disease control without a grade of toxicity was higher as well in the mVNR arm.

Platinum-based chemotherapy and recently platinum-immunotherapy combinations are the most appropriate treatment in first-line treatment of NSCLC, but some patients will not be able to receive the platinum doublet for several reasons. The elderly lung cancer vinorelbine Italian study (ELVIS) demonstrated a significant activity with better survival and good tolerance with i.v. VNR alone compared with best supportive care in elderly patients aged $\geq$70 years with advanced NSCLC.[29] In 2015, an international panel of experts agreed that unfit elderly patients could benefit from single-agent, third-generation chemotherapy.[31] Metronomic VNR was better tolerated than the weekly schedule that makes this schedule particularly suitable in first-line treatment of elderly, suboptimal PS patients with several comorbidities. In this study, QoL was comparable between the arms without worsening over time. Oral chemotherapy is convenient in clinical practice to monitor therapy according to the patient's profile and tolerance while reducing time in clinics.

### *Conclusions*

Metronomic vinorelbine can be considered as a new standard treatment option in unfit advanced NSCLC patients owing to a good balance between efficacy and tolerance even in a frail and high-risk population in relation to the excellent safety profile and the improved efficacy. The 50 mg, thrice a week dosage is well tolerated and effective. The low hematological toxicity could preserve the bone marrow reserve for a possible second line of treatment.

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## DISCLOSURE

AC has disclosed expert testimony (Pierre Fabre), travel accommodations/expenses (Roche, Pierre Fabre). A Morabito has disclosed speaker's bureau (Pfizer, BMS, Boehringer, MSD, Roche, AstraZeneca). FG has disclosed advisory boards/consultations (Eli Lilly, Roche, Boehringer Ingelheim, AstraZeneca, Pierre Fabre, BMS, MSD, Novartis); honoraria: seminar/talks to industry (Eli Lilly, Roche, Boehringer Ingelheim, AstraZeneca, Pierre Fabre, Amgen, Celgene, BMS, MSD); research funding (AstraZeneca, BMS, MSD). RR has disclosed consulting/advisory (Roche, MSD, Pfizer, Novartis, Boehringer Ingelheim). G-LC has disclosed consulting/advisory (Pfizer, Boehringer Ingelheim, Astellas). JB-B reports grants and personal fees from Roche-Genentech, grants from Pfizer, personal fees from MSD, personal fees from BMS, personal fees from AstraZeneca, personal fees from Novartis and grants from Pierre Fabre outside the submitted work. PL is an employee of Pierre Fabre Médicament. CTTM is an employee of Pierre Fabre Médicament. SG, biostatistician, is an employee of Pierre Fabre Médicament (IRPF). DK has disclosed consultancy and advisory board: Pfizer, AstraZeneca, Roche/Genentech, BMS, MSD. T-EC reports consulting/advisory, personal fees from Astellas Pharma, Janssen, BMS, Merck Serono, Amgen, Roche, Pfizer, Boehringer Ingelheim, Servier, A-D Pharm, Lilly, AstraZeneca and Novartis; non-financial support from Pfizer, Sanofi, Boehringer Ingelheim, Merck, Servier, Ipsen, Amgen, Adpharm, AstraZeneca, Roche, BMS, Lilly, Janssen, Novartis and Astellas Pharma. All other authors declare no conflicts of interest.

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