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Safety and efficacy of second-line metronomic oral vinorelbine-atezolizumab combination in stage IV non-small-cell lung cancer: An open-label phase II trial (VinMetAtezo)

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ABSTRACT

Objective: To evaluate the safety and efficacy of second-line metronomic oral vinorelbine–atezolizumab combination for stage IV non-small-cell lung cancer.
Methods: This was a multicenter, open-label, single-arm Phase II study performed in patients with advanced NSCLC without activating *EGFR* mutation or *ALK* rearrangement who progressed after first-line platinum-doublet chemotherapy. Combination treatment was atezolizumab (1200 mg IV day 1, every 3 weeks) and oral vinorelbine (40 mg, 3 times by week). The primary outcome was progression-free survival (PFS) during the 4-month follow-up from the first dose of treatment. Statistical analysis was based on the exact single-stage Phase II design defined by A'Hern. Based on literature data, the Phase III trial threshold was set at 36 successes in 71 patients.
Results: 71 patients were analyzed (median age, 64 years; male, 66.2%; ex-smokers/active smokers, 85.9%; ECOG performance status 0–1, 90.2%; non-squamous NSCLC, 83.1%; PD-L1 $\geq$ 50%, 4.4%). After a median follow-up of 8.1 months from treatment initiation, 4-month PFS rate was 32% (95% CI, 22–44), i.e. 23 successes out 71 patients. OS rate was 73.2% at 4 months and 24.3% at 24 months. Median PFS and OS were 2.2 (95% CI, 1.5–3.0) months and 7.9 (95% CI, 4.8–11.4) months, respectively. Overall response rate and disease control rate at 4 months were 11% (95% CI, 5–21) and 32% (95% CI, 22–44), respectively. No safety signal was evidenced.
Conclusion: Metronomic oral vinorelbine-atezolizumab in the second-line setting did not achieve the predefined PFS threshold. No new safety signal was reported for vinorelbine-atezolizumab combination.

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1. Introduction

Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers and is most commonly diagnosed with local or metastatic disease [1]. The majority of patients with advanced or metastatic NSCLC are treated with platinum-doublet chemotherapy regimens, with the exception of those with specific oncogenic factors such as epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements. Indeed, although pembrolizumab (anti-PD-1) was recently approved as first-line treatment for patients with PD-L1 $\geq$ 50% of their NSCLC cells expressing PD-L1, many patients are still not benefiting from this first-line agent [2].

For patients without oncogenic drivers who progress after first-line chemotherapy, immunotherapy is a possible second-line choice [2]. Nivolumab and pembrolizumab (anti-PD-1) or atezolizumab (anti-PD-L1) are checkpoint inhibitors that have been approved in this setting [3]. However, despite the improvements associated with immunotherapy, objective response rates (ORR) remain low and median survival rarely exceeds 10 months [4]. Therefore, other options have been considered such as the combination of immunotherapy and chemotherapy [5].

For patients who progressed after first-line chemotherapy, atezolizumab improved survival compared to docetaxel in the Phase II POPLAR and Phase III OAK trials [6,7]. In addition, new concepts of synergic action between immunotherapy and other drugs such as chemotherapy have been proposed [8]. Indeed, there is evidence that cytotoxic drugs modulate the immune microenvironment of NSCLC by increasing the immunogenicity of cancer cells, increasing cytotoxicity of T-cells and NK cells, increasing release of interferon-γ and necrosis factor-α, decreasing immunosuppressive immune cells, such as Tregs, and consequently reducing inhibitory cytokines such as TGF-β [9]. Immunomodulatory properties have been reported for platinum-based cytotoxic drugs, taxanes and vinca alkaloids such as vinorelbine [10].

The immunological effects of chemotherapy could facilitate synergy between cytotoxic drugs and immunotherapy and improve clinical efficacy. However, chemotherapy and immunotherapy treatments are administered for different durations. Typically, chemotherapy is given for a short duration (rarely more than 6 cycles) and immunotherapy can be administered for several months until progression. The use of the oral vinca alkaloid vinorelbine for metronomic chemotherapy – defined as low-dose and frequent administration – has been considered because this microtubule-targeting molecule has potent anti-angiogenic and pro-immune properties at low doses [11,12]. In addition, this mode of administration reduces toxicity and avoids treatment breaks that could promote tumor growth [13]. Metronomic vinorelbine has been used both in first line [14] and second line and beyond [15–20]. In particular, metronomic vinorelbine showed interesting activity in patients progressing after platinum-based treatment in first line and immunotherapy in second line [15–17]. In a multi-institutional retrospective analysis including 30 patients with metastatic NSCLC, a partial response was achieved in 13.3% of cases for an overall disease control rate of 46.7%; median PFS and OS were 3.9 and 8.1 months, respectively, with a 12-month survival rate of 22% [15].

Therefore, a new approach combining immunotherapy and metronomic chemotherapy has emerged for patients who progressed after first-line chemotherapy, based on the hypothesis that immunotherapy could be potentialized by metronomic chemotherapy [14,21,22].

The safety and efficacy of the combination of metronomic oral vinorelbine and atezolizumab have not been previously assessed. In this multicenter, Phase II, open-label, single-arm study, we evaluated the combination of metronomic oral vinorelbine and atezolizumab in second-line treatment of stage IV NSCLC.

2. Patients and methods

2.1. Type of study

The VinMetAtezo (Vinorelbine-Metronomic-Atezolizumab) trial was a multicenter, open-label, single-arm Phase II study performed in patients with advanced NSCLC. The study protocol has been published [23]. The objective was to evaluate safety and efficacy of second-line metronomic oral vinorelbine–atezolizumab combination in stage IV non-small-cell lung cancer.

The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Institutional Review Board of each participating center has approved the protocol. The regulatory authority approved the protocol on October 24, 2018 and the Ethics Committee on 22 November 2018. Written informed consent was obtained from each patient before inclusion. The trial was registered with ClinicalTrials.gov, number NCT03801304 and EudraCT, number: 2018-000164-28.

2.2. Patients

Patients were included if they met the following criteria: advanced NSCLC or relapsed locally advanced NSCLC without *EGFR* activating mutation or *ALK* rearrangement who progressed (RECIST v1.1) after first-line platinum-doublet chemotherapy; measurable lesion (RECIST v1.1); age $\geq$ 18 years; ECOG performance status $<$ 3; life expectancy $>$12 weeks; adequate organ-function results documented by laboratory tests within 3 weeks prior to study inclusion; effective contraception for women of childbearing age. No active brain metastases were allowed.

The main exclusion criteria were: small cell lung cancer, bronchioalveolar or neuroendocrine cancer; known hypersensitivity to immunotherapy; radiation therapy (except for bone or brain) within 3 months prior to baseline imaging; persistent clinical adverse events attributed to prior treatment; active or untreated metastases of central nervous system detected during screening and prior radiographic assessments; uncontrolled pleural effusion; pericardial effusion; ascites requiring recurrent drainage procedures; uncontrolled/symptomatic hypercalcemia requiring continued bisphosphonate or denosumab use; prior autoimmune disease; HIV infection; active HBV or HBC infection; use of systemic corticosteroids up to 10 mg/day or other systemic immunosuppressants within 2 weeks prior to study enrollment or anticipated need for systemic immunosuppressant during the trial.

2.3. Procedures and treatments

The study included a safety run-in phase in 12 patients who received metronomic oral vinorelbine doses (40 mg, 3 times per week) in combination with a fixed dose of atezolizumab (1200 mg IV on day 1, every 21 days). Patients were closely monitored for adverse events. After all 12 patients received study treatment and completed at least one cycle of treatment (21 days), enrollment was interrupted and an independent Data Safety Monitoring Board (DSMB) reviewed the available data and made recommendations regarding study continuation.

After validation of the run-in phase, the next patients received the same treatment regimen until disease progression. In the case of progression as defined by the RECIST criteria, oral vinorelbine and atezolizumab were discontinued. However, if the patient had a major clinical benefit at the time of disease progression, the investigator could decide to continue study treatment.

2.4. Statistical analysis

The primary outcome was PFS during the 4-month period of follow-up from the first dose of treatment. The primary analysis was performed with the intent-to-treat population defined as all included patients. Secondary outcomes were median PFS, median OS, safety according to

CTAE, objective response rate (ORR) and disease-control rate.

The statistical analysis was based on the exact single-stage Phase II design defined by A'Hern [24]. The sample size was based on an exact binomial distribution. The target efficacy hypothesis p1 was set at 55% for 4-month PFS; p0 (indicating that the strategy was clearly ineffective) was set at 40% for 4-month PFS, based on the OAK study where 4-month PFS was 43% [7]. With an alpha-risk of 5% (one-sided) and a beta-risk of 20%, the number of evaluable patients was set at 71. The threshold for the Phase III trial was 36 successes for 71 patients, with success defined as patient without progression or death at 4 months. The 95% confidence interval (CI) of the percentage of successes at 4 months was estimated by the exact method. Statistical significance was defined as $p < 0.05$.

Median PFS and OS were calculated using the Kaplan-Meier method on the entire population and according to PD-L1 level.

The statistical analysis was conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

3. Results

3.1. Patient disposition and characteristics

After the run-in phase, patients were screened in 16 centers from April 17, 2019 to February 5, 2020. A total of 80 patients, including the 12 patients of the run-in phase, were included. Nine patients were excluded (screening failure, n = 7; no study treatment administration, n = 2). Overall, 71 patients were analyzed for the primary outcome.

At inclusion, patients had a median age of 64 years and 47 (66.2%) were male (Table 1). They were generally ex- or active smokers (85.9%). ECOG performance status was 0–1 for 64 (90.2%) patients. PD-L1 level was < 1% for 36 (52.9%) patients and [1%–50%] for 29 (42.6%). NSCLC was non-squamous for 59 (83.1%) patients and squamous for 12 (16.9%). The main metastatic sites were lung (63.4%), bone (35.2%), liver (22.5%), brain (15.5%) and adrenal gland (12.7%). At inclusion, 52 (73.2%) patients had a least two metastatic sites.

For first-line treatment, the best response was complete response for 1 (1.4%) patient, partial response for 31 (43.7%), stabilization for 18 (25.4%) and progression for 21 (29.6%). Mean (SD) duration of treatment was 7.5 (5.8) months.

Table 1
Patient characteristics at inclusion.

	N = 71
Age, years, median (range)	64 (42; 84)
Male gender, n (%)	47 (66.2)
Smoking, n (%)	
Non-smoker	10 (14.1)
Ex-smoker	43 (60.6)
Active smoker	18 (25.3)
ECOG performance status, n (%)	
0	20 (28.2)
1	44 (62.0)
2	7 (9.9)
PD-L1 status, n (%)	
<1%	36 (52.9)
[1%–50%[	29 (42.6)
≥50%	3 (4.4)
Missing	2 (2.8)
Histology, n (%)	
Non-squamous	59 (83.1)
Squamous	12 (16.9)
Metastases, n (%)	
Lung	45 (63.4)
Bone	25 (35.2)
Liver	16 (22.5)
Brain	11 (15.5)
Adrenal gland	9 (12.7)
Others	15 (21.1)
Number of metastases	
≤1	19 (26.8)
≥2	52 (73.2)

3.2. Outcomes

After a median follow-up of 8.1 (95% CI, 5.1–11.7) months from initiation of metronomic oral vinorelbine-atezolizumab combination, the 4-month PFS rate was 32% (95% CI, 22–44). Therefore, the number of successes was 23 out 71 patients, which was below the Phase III trial threshold (36 successes for 71 patients). Median PFS was 2.2 (95% CI, 1.5–3.0) months (Fig. 1).

OS rate was 73.2% (95% CI, 0.61–0.83) at 4 months and 24.3% (95% CI, 0.15–0.36) at 24 months; median OS was 7.9 (95% CI, 4.8–11.4) months (Fig. 2).

Analysis of Kaplan-Meier according to PD-L1 status suggested a tendency for more favorable PFS in patients with PD-L1 level ≥ 1% (Fig. 3 and Fig. 4). ORR and disease control rate at 4 months were 11% (95% CI, 5–21) and 32% (95% CI, 22–44), respectively.

3.3. Safety

A total of 412 adverse events were reported in 70/71 (98.5%) patients, including 55 (13.3%) Grade 3–4 adverse events; 21 (5.1%) Grade 3–4 adverse events were related to study treatment (related to atezolizumab only, n = 7; to vinorelbine only, n = 10; to both atezolizumab and vinorelbine, n = 4).

The most frequent adverse events were diarrhea, vomiting, anemia and nausea (Table 2); they were most frequently Grade 1–2. One Grade 5 (death) adverse event was reported (pneumonia).

4. Discussion

In this single-arm Phase II study in patients with advanced NSCLC without oncogenic drivers who progressed after first-line platinum-doublet chemotherapy, there was no benefit in terms of PFS for metronomic oral vinorelbine plus atezolizumab compared to preset objectives based on literature data. The Phase III trial threshold was 36 successes for 71 patients at 4 months and only 23 patients did not progress during this period.

The 71 analyzed patients had the expected profile for this setting: median age was 64 years, 66.2% of patients were male, 85.9% were ex-smokers or active smokers, 90.2% had a performance status 0–1 and lung cancer was non-squamous for 83.1%.

Previous studies have assessed the efficacy of atezolizumab alone in patients with advanced NSCLC previously treated with chemotherapy. The open-label, randomized controlled Phase II POPLAR study included patients with squamous or non-squamous NSCLC who progressed after platinum-based chemotherapy [6]. A total of 144 patients were randomized in the atezolizumab group and 143 in the docetaxel group. Median OS was 12.6 (95% CI, 9.7–16.4) months for atezolizumab versus 9.7 (95% CI, 8.6–12.0) months for docetaxel (hazard ratio 0.73; 95% CI, 0.53–0.99; p = 0.04). Of note, OS improvement was correlated with immunohistochemical expression of PD-L1, suggesting that PD-L1 expression was predictive for atezolizumab benefit.

The randomized, open-label, Phase III OAK study included squamous or non-squamous stage IIIB or IV NSCLC with previous platinum-based therapies [7,25]. A total of 425 patients received atezolizumab and 425 received docetaxel. Median OS was improved with atezolizumab compared with docetaxel: 13.8 (95% CI, 11.8–15.7) months vs. 9.6 (95% CI, 8.6–11.2) months; hazard ratio 0.73 (95% CI, 0.62–0.87; p = 0.0003). Patients with tumors expressing high levels of PD-L1 (≥50% on tumor cells or ≥ 10% on tumor-infiltrating immune cells) had the greatest benefit from atezolizumab. Nevertheless, survival was also improved in patients with low PD-L1 expression. In our study, the combination of metronomic oral vinorelbine and atezolizumab did not improve median OS (7.9 months; 95% CI, 4.8–11.4) compared with the

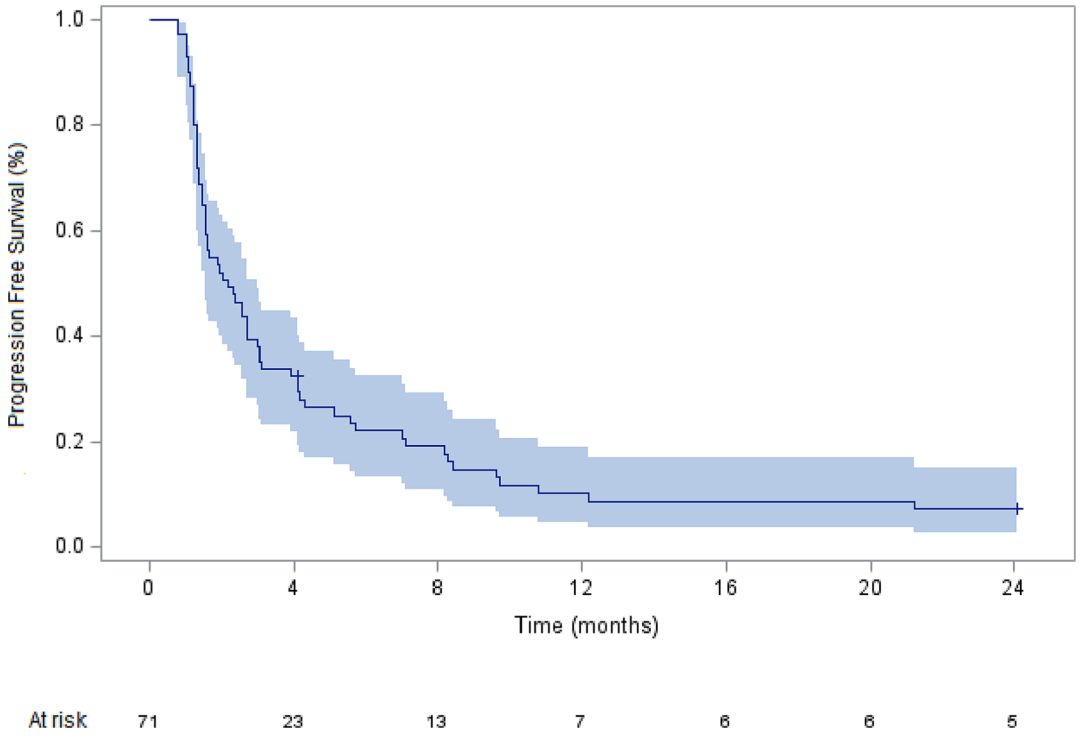

Fig. 1. Progression-free survival.

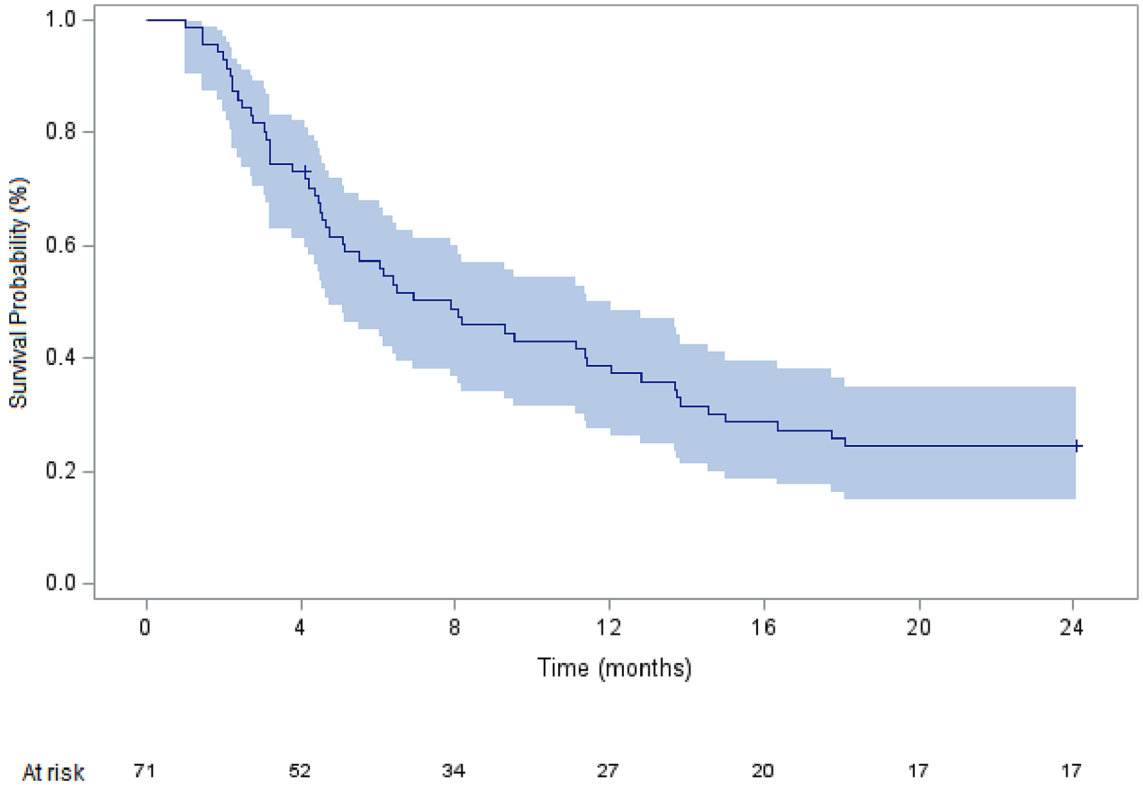

Fig. 2. Overall survival.

median OS reported in the respective atezolizumab arm of the POPLAR and OAK studies.

The median PFS obtained in our study for the combination of atezolizumab with metronomic oral vinorelbine (2.2 months; 95% CI, 1.5–3.0) was comparable to median PFS in the arm atezolizumab of the POPLAR study (2.7 months; 95% CI, 2.0–4.1) [6] and in the arm atezolizumab of the OAK study (2.8 months; 95% CI, 2.6–3.0) [7]. It should be noted that if our study population was comparable in terms of age and sex ratio to the patients of the OAK study [7], we also included nearly 10% of patients with performance status 2 and<5% of patients with high

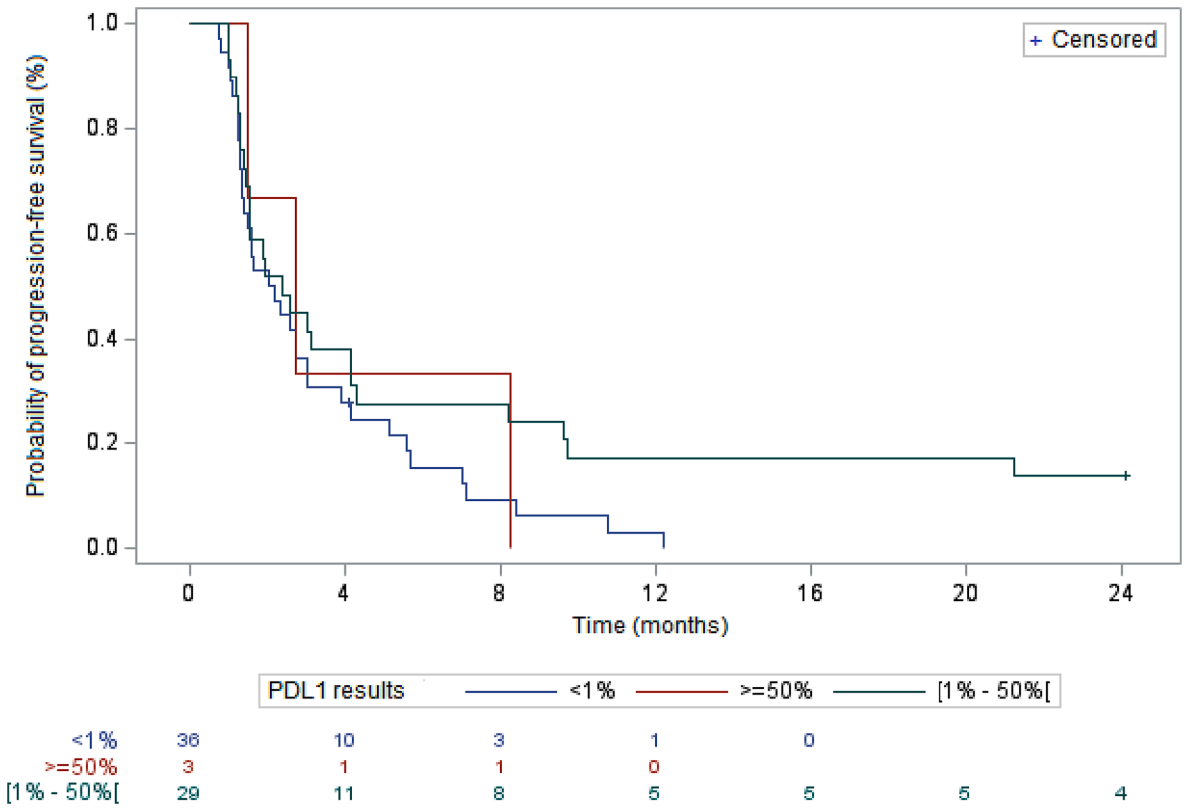

Fig. 3. PFS according to PD-L1 level.

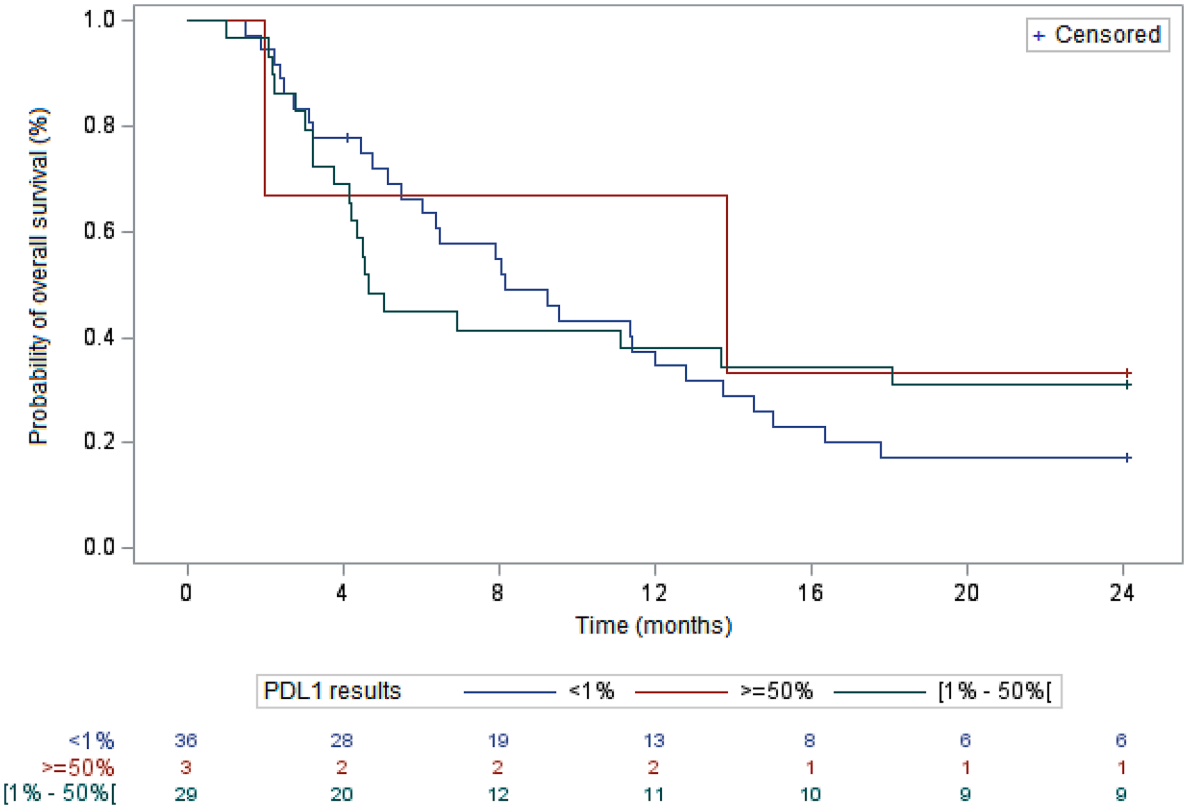

Fig. 4. OS according to PD-L1 level.

Table 2
Adverse events.

	n = 71 Grade 1–2	Grade 3–4
Diarrhea	23 (32)	8 (12)
Vomiting	17 (24)	2 (3)
Anemia	12 (17)	3 (4.5)
Nausea	15 (21)	–
Neutropenia	7 (9.8)	2 (3)
Arthralgia	9 (12.7)	–
Myalgia	6 (8.5)	–
Hyperthyroidism	5 (7)	–
Hypothyroidism	4 (6)	–
Paresthesia	5 (7)	–
Colitis	1 (1.5)	2 (3)
Cholangitis	1 (1.5)	–
Pneumonia	1 (1.5)	–

Results are presented as n (%).

PD-L1 expression (not included and 17% in the OAK study, respectively). The high percentage of patients with performance status 2 could be responsible, at least in part, for the reduced activity due to fast progressors related to low performance status [26]. It should also be noted that the present cohort included 22.5% of patients with liver metastasis, for whom a pooled analysis based on 10 randomized controlled trials showed a decreased efficacy of atezolizumab in second line compared to patients without liver metastasis [19].

Our study was not designed to compare the outcomes according to the PD-L1 expression (in particular only 4.4% of patients had PD-L1 $\geq$ 50%). Nevertheless, there was a trend in Kaplan-Meier analysis for a more favorable PFS in patients with PD-L1 level $\geq$ 1%, as reported in the OAK and POPLAR studies [6,7]. Moreover, survival curves were long-tailed with nearly 30% of patients surviving to 2 years, suggesting clinical efficacy of the combination, most likely in patients with high PD-L1 expression.

We report an ORR equal to 11% (95% CI, 5–21) for the combination of metronomic oral vinorelbine and atezolizumab, which is comparable to the ORR reported in the atezolizumab arms in the POPLAR study (14.6%) [6] and in the OAK study (14%) [7].

The safety data show that the combination of metronomic oral vinorelbine plus atezolizumab was feasible without unacceptable toxicity.

Our study has some limitations. The study was open-label and tumor measurement was not centralized. The absence of a comparative group is the main limitation. We used a single-stage Phase II design to evaluate the combination of metronomic oral vinorelbine and atezolizumab. This method allows the evaluation of a new treatment in comparison to historical data before designing a Phase 3 study. The definition of the preset threshold for inefficiency and minimum level for efficiency is somehow arbitrary and is dependent on literature data. One could say also that these results are no longer relevant since pembrolizumab, with or without chemotherapy, is now the standard of first-line treatment in patients with advanced NSCLC. Nevertheless, a substantial number of patients, such as patients with contraindications to immunotherapy, receiving high-dose corticosteroids or with untreated symptomatic brain metastases are treated with chemotherapy alone in the first line and remain eligible to immunotherapy in second-line setting. The benefit of this sequential approach is the subject of recent studies [20]. Furthermore, even in patients who have received a combination of chemo-immunotherapy, there is probably a profile of patients who may benefit from this combination, in particular patients with low PD-L1 expression, and elderly or performance status 2 patients.

The concept of synergic action of metronomic chemotherapy dosing plus immunotherapy in advanced NSCLC is not invalidated by our study and the metronomic approach remains an attractive alternative to maximum tolerated dose therapy [14]. Preventing tumor growth indirectly by targeting the tumor microenvironment with daily low-dose chemotherapy has the potential to improve immune checkpoint efficacy and minimize therapeutic resistance [8]. Thus, promising results were reported recently on the effects of metronomic administration of an oral gemcitabine prodrug with anti-PD-1 in animal models of NSCLC [21]. Clinical trials, generally Phase 2 studies, which evaluate combination strategies with various ICIs and chemotherapy treatments are ongoing [8].

The safety of the second-line metronomic oral vinorelbine-atezolizumab combination should be noted, with only 5.1% of grade 3–4 adverse events related to study treatment, even though 9.9% of patients had a performance status 2.

In conclusion, metronomic oral vinorelbine-atezolizumab in the second-line setting did not achieve the predefined PFS threshold. No new safety signal was reported for vinorelbine-atezolizumab combination and the type and severity of adverse events reported were consistent with what was expected for each product.

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Alain Vergnenegre: Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Validation, Writing – review & editing. **Isabelle Monnet:** Data curation, Investigation, Validation, Writing – review & editing. **Charles Ricordel:** Validation, Writing – review & editing. **Acya Bizieux:** Data curation, Investigation, Validation, Writing – review & editing. **Hubert Curcio:** Data curation, Investigation, Validation, Writing – review & editing. **Marie Bernardi:** Data curation, Investigation, Validation, Writing – review & editing. **Romain Corre:** Data curation, Investigation, Validation, Writing – review & editing. **Florian Guisier:** Data curation, Funding acquisition, Investigation, Project administration, Resources, Validation, Writing – review & editing. **Stéphane Hominal:** Data curation, Investigation, Validation, Writing – review & editing. **Gwenaelle Le Garff:** Data curation, Investigation, Validation, Writing – review & editing. **Olivier Bylicki:** Data curation, Funding acquisition, Investigation, Project administration, Resources, Validation, Writing – review & editing. **Chrystèle Locher:** Data curation, Investigation, Validation, Writing – review & editing. **Margaux Geier:** Conceptualization, Formal analysis, Methodology, Validation, Writing – review & editing. **Christos Chouaïd:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Validation, Writing – original draft, Writing – review & editing. **Gilles Robinet:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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