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Open-label Phase II trial to evaluate safety and efficacy of second-line metronomic oral vinorelbine–atezolizumab combination for stage-IV non-small-cell lung cancer – VinMetAtezo trial, (GFPC[‡] 04-2017)

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Metronomic chemotherapy is defined as frequent low-dose administration without prolonged drug-free breaks. Combining immune-checkpoint inhibitors and metronomic chemotherapy is a new approach to improve responses and delay onset of resistance to immune-checkpoint inhibitors. This multicenter, Phase II, open-label, single-arm study was designed to assess the safety and efficacy of metronomic oral vinorelbine in combination with immune-checkpoint inhibitors in advanced non-small-cell lung cancers progressing after first-line platinum-based chemotherapy. The recommended metronomic oral vinorelbine dose will be determined during a safety run-in period including 12 patients; the main study will include 59 additional patients. The primary outcome is progression-free survival at 4 months. Secondary outcomes are safety of the combination, median overall survival, objective response rate, disease-control rate at 4 months and quality of life (NCT03801304).

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Lung cancer is the leading cause of cancer deaths in USA, with 5-year survival at ~16%. Representing >85% of lung cancers, non-small-cell lung cancer (NSCLC) is the most common type. Unfortunately, most of these patients are diagnosed with locally advanced or metastatic disease [1–4].

Immunotherapy enhanced a paradigmatic shift in NSCLC treatment, especially through the anti-PD1 or its ligand's (PD-1/PD-L1) pathway. PD-1 [3] is an immune-checkpoint receptor expressed by activated T cells. Upon binding to its ligands, PD-L1 and PD-L2, PD-1 normally moderates ongoing immune responses and prevents autoimmunity [3]. Several compounds have been used as second-or-more-line agents [4]. For first-line, chemotherapy-treated patients, immunotherapy is a second-line option. In this setting, nivolumab and pembrolizumab (anti-PD-1) and atezolizumab (anti-PD-L1) monoclonal antibodies were approved and have gradually been introduced into clinical management of advanced NSCLCs [5,6].

Despite these notable advances, persistently low objective response rates (ORRs) to second-line immune-checkpoint inhibitors NSCLC treatment [7] have led to new second-line options, especially immunotherapy–chemotherapy combinations [2]. Second-line immune-checkpoint inhibitors therapy might be combined with chemotherapy to improve immunotherapy efficacy for regimens without major toxicity. Currently, many drugs

are combined with immunotherapy as first- or second-line regimens. Oral vinorelbine has been used for many years to treat NSCLCs [8,9]. Metronomic chemotherapy is defined as frequent low-dose administration without prolonged drug-free breaks to reduce toxic effects and prevent rapid revascularization that can promote tumor growth during therapy breaks [9]. The immunostimulatory effects of metronomic chemotherapy are: induced immunogenic cancer-cell death [10]; enhanced antigen presentation through dendritic cell modulation [11] and increased cancer-cell immunogenicity [12]; preferential regulatory T-cell depletion [13]; modulation of myeloid-derived suppressor cells [14]; and heightened immune-effector-cell cytotoxic activity, for example, of tumor-specific T cells [15]. Metronomic chemotherapy-immunotherapy synergism has been reported [16].

Using oral vinca alkaloid vinorelbine for metronomic therapy has been accorded considerable attention, especially because of its potent anti-angiogenic and pro-immune and microtubule-targeting properties at low dose [17,18]. Activity was reported in elderly patients against metastatic breast cancer, advanced refractory NSCLCs [19,20] and advanced NSCLCs [21]. Barlesi *et al.* [22] recently published the usefulness of a mathematical model to determine the optimal metronomic vinorelbine dose for NSCLC and mesothelioma patients. In most studies, the recommended metronomic oral vinorelbine (MOV) dose alone is 50 mg/day, thrice weekly [19,20,23]. The MOVE trial, prescribing first-line MOV alone for elderly patients, achieved 18.6% ORR [23]. Sutiman *et al* recently comparing two MOV doses combined with erlotinib for NSCLC patients obtained good disease control (~50%) [24]. Safety of MOV combined with sorafenib for advanced NSCLC patients was described previously [25]. More recently the safety of MOV was also confirmed by a retrospective multicentric analysis including 270 advanced NSCLC [26] and an individual patient-data meta-analysis including 9 studies and 418 patients [27].

We describe here the design of a multicenter, Phase II, open-label, single-arm study designed to assess the safety and efficacy of MOV in combination with atezolizumab and the result of a running safety phase. The study hypothesis is based on immunotherapy potentialization by metronomic chemotherapy, herein the atezolizumab-MOV combination, whose safety and efficacy have not been assessed previously.

Materials & Methods

This multicenter, Phase II, open-label, single-arm study was designed to assess atezolizumab-MOV safety and efficacy in patients with advanced NSCLCs.

Eligibility criteria for inclusion were: advanced NSCLC or relapsed locally advanced NSCLC, without activating *EGFR* mutation or *ALK* rearrangement, progressing after first-line platinum-doublet-based chemotherapy, according to RECIST v1.1; a measurable lesion (RECIST v1.1); age ≥ 18 years, with ECOG PS < 3 and life expectancy > 12 weeks; adequate laboratory-test-documented organ-function results during the 3 weeks preceding study enrollment; effective contraception for women of child-bearing potential; national healthcare insurance and written informed consent to participate.

The main noneligibility criteria were: small cell lung, bronchioalveolar or neuroendocrine cancer; known hypersensitivity to immunotherapy; radiotherapy (except for bone or brain) within the 3 months preceding baseline imaging; persistent clinical adverse events (AEs) attributed to prior treatment; active or untreated computed tomography or magnetic resonance imaging detected CNS metastases 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; human immunodeficiency virus or active hepatitis B- or C-positivity; systemic corticosteroid up to 10 mg/day or other systemic immunosuppressant use during the 2 weeks preceding study enrollment; or anticipated need for systemic immunosuppressant(s) during the trial.

Study design

A run-in phase aimed to ensure the safety of the fixed-dose atezolizumab (1200 mg iv. on day 1, every 21 days)-MOV (40-mg dose, thrice weekly for 3 weeks) combination; the latter was chosen based on the literature [23,25,26]. To assess tolerance, the numbers (%) of AEs, according to National Cancer Institute CTCAE, will be recorded. Toxicity will be determined by the number (%) of grade- ≥ 3 AEs in the first 12 patients during the first cycle, with $> 20\%$ grade- ≥ 3 specific immune-related or oral vinorelbine-related AEs defining dose toxicity. A ≤ 6 -week trial interruption will allow Data Safety Monitoring Board (DSMB) case review.

In the case of toxicity, the dose will be decreased to 30 mg, thrice weekly. The same AE-assessment procedure will be applied to the following 12 patients.

Table 1. Adverse events during the run-in phase (n = 12).

Adverse event	Grades ≤2			Grades >2
	1	2	3	4
Hematologic	1	1	–	–
Infectious	1			
Neurologic	–	1		
Vascular thrombus	–	2		
Fatigue		2		
Digestive	5	3		
General disorders	–	3	2 [†]	–
Pain	–	1	1 [†]	–
Cutaneous	1	1		

[†]Not drug related.

The main study

Once the safety run-in phase has been completed and the regimen validated, the study design will be as follows: MOV (40 or 30 mg, thrice weekly for 3 weeks) in combination with fixed atezolizumab infusions (1200 mg iv. on day 1, every 21 days). Patients will be treated until disease progression. When progression according to RECIST criteria occurs, MOV will be stopped. Atezolizumab will be continued until clinical progression. Overall, 71 patients will be enrolled in this Phase II study, including the 12 safety run-in-phase participants.

Cross-sectional analyses will attempt to identify relevant biomarkers and evaluate their relationship(s) to clinical outcomes. The specific analysis will be based on PD-L1 expression, but other biomarkers would be tested.

Outcomes

The primary outcome is PFS rate at 4 months. The secondary outcomes are median PFS, median OS, tolerance according to CTAE, ORR, disease-control rate and quality of life during the study using the EORTC QLQ-C30 scale.

Statistical analyses

This open-label, multicenter, Phase II study used the exact single-stage Phase II design defined by A'hern [28]. The sample size is based on an exact binomial distribution.

Minimal efficacy hypothesis (p_1) is set at 55% event-free rate of PFS at 4 months; (p_0), indicating that the strategy is clearly ineffective, is set at 40% PFS at 4 months (based on the OAK study's 43% PFS at 4 months). With a 5% alpha-risk (unilateral perspective) and a 20% β -risk, the number of assessable subjects is set at 71. The Phase III trial threshold is 36 successes/71 subjects, with success defined as a subject without death or progression at 4 months. The percentage of patient successes at 4 months will be described with its 95% confidence interval, estimated by the exact method. $p < 0.05$ will define statistical significance. The intent-to-treat population (all patients included) will be analyzed. The per-protocol population will also be analyzed. The results will be presented according to the CONSORT Statement recommendations.

The statistical analysis plan will be validated by the trial's Scientific Committee.

Ethical considerations

The study will be conducted in compliance with the principles of the Declaration of Helsinki, and each participating institution's Institutional Review Board has approved the protocol. All patients must give written informed consent before any screening or inclusion procedures. The regulatory authority approved the protocol on 24 October 2018 and the Ethics Committee on 22 November 2018 (NCT03801304, EudraCT number: 2018-000164-28).

Results

The trial was opened in four centers for the run-in phase (25 January 2019 to 19 March 2019). 12 patients were included: the DMSB reviewed 25 AEs (Table 1). Three grade-3 AEs occurred: deteriorated general condition attributed to increased size of brain metastases, not treatment-related; metastasis-related bone pain, not treatment-

related, that was rapidly attenuated with specific treatment and without affecting the protocol; loss of appetite and weight loss, possibly treatment-related, leading to protocol interruption for 1 week.

The DMSB recommended transition to the main study at the 40-mg/day, thrice weekly, MOV dose on 16 April 2019, which was validated by the regulatory authority.

Discussion & conclusion

The safety and efficacy study of the atezolizumab–MOV combination will enable us to determine whether metronomic chemotherapy administration can enhance the efficacy of immunotherapy alone with an acceptable tolerance profile. Depending on market-access times, the majority of patients diagnosed with advanced NSCLC are or will be eligible for first-line combination immunotherapy–platinum–doublet chemotherapy regimens, but most of them will progress on them. No management recommendations for second-or-more lines exist for these patients but the possibility of immunotherapy–metronomic chemotherapy reintroduction, after a therapeutic pause or after second-line chemotherapy is an alternative option worth exploring. This Phase II trial will enable safety and efficacy evaluations of the atezolizumab–MOV combination.

Executive summary

Background

- Atezolizumab, a monoclonal antibody targeting PD1-L1, is approved for second-line treatment of non-small-cell lung cancers.
- The concept of metronomic chemotherapy is defined as frequent, low-dose administration without prolonged drug-free breaks.
- New options for second-line therapy of non-small-cell lung cancers are needed.
- Combining immune-checkpoint inhibitors and metronomic chemotherapy is such a new approach to improve responses and retard development of resistance to immune-checkpoint inhibitors.

Trial design

Open-label Phase II trial to evaluate safety and efficacy of second-line metronomic oral vinorelbine–atezolizumab combination for stage-IV non-small-cell lung cancer

Disclaimer

Sponsors were involved in the study design, but not in patient inclusion, collection and interpretation of data, writing the report and the decision to submit the article for publication. This multicenter Phase II, open-label, single-arm study was designed to assess the safety and efficacy of the metronomic oral vinorelbine and atezolizumab combination.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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