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Original Research

Atezolizumab with or without bevacizumab and platinum-pemetrexed in patients with stage IIIB/IV non-squamous non-small cell lung cancer with *EGFR* mutation, *ALK* rearrangement or *ROS1* fusion progressing after targeted therapies: A multicentre phase II open-label non-randomised study GFPC 06-2018

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KEYWORDS
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Abstract ***Background:*** Previous reports showed limited efficacy of immune checkpoint inhibitors as single-agent treatment for non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) mutation or *ALK*/*ROS1* fusion. We aimed at evaluating the efficacy and safety of immune checkpoint inhibitor combined with chemotherapy and bevacizumab (when eligible) in this patient subgroup.
Methods: We conducted a French national open-label multicentre non-randomised non-comparative phase II study in patients with stage IIIB/IV NSCLC, oncogenic addiction (*EGFR* mutation or *ALK*/*ROS1* fusion), with disease progression after tyrosine kinase inhibitor and no prior chemotherapy. Patients received platinum, pemetrexed, atezolizumab, bevacizumab (PPAB cohort) or, if not eligible to bevacizumab, platinum−pemetrexed −atezolizumab (PPA cohort). The primary end-point was the objective response rate (RECIST v1.1) after 12 weeks, evaluated by blind independent central review.
Results: 71 patients were included in PPAB cohort and 78 in PPA cohort (mean age, 60.4/66.1 years; women 69.0%/51.3%; *EGFR* mutation, 87.3%/89.7%; *ALK* rearrangement, 12.7%/5.1%; *ROS1* fusion, 0%/6.4%, respectively). After 12 weeks, objective response rate was 58.2% (90% confidence interval [CI], 47.4−68.4) in PPAB cohort and 46.5% (90% CI, 36.3−56.9) in PPA cohort. Median progression-free survival and overall survival were 7.3 (95% CI 6.9−9.0) months and 17.2 (95% CI 13.7−NA) months in PPAB cohort and 7.2 (95% CI 5.7−9.2) months and 16.8 (95% CI 13.5−NA) months in PPA cohort, respectively. Grade 3−4 adverse events occurred in 69.1% of patients in PPAB cohort and 51.4% in PPA cohort; Grade 3−4 atezolizumab-related adverse events occurred in 27.9% and 15.3%, respectively.
Conclusion: Combination approach with atezolizumab with or without bevacizumab and platinum-pemetrexed achieved promising activity in metastatic *EGFR*-mutated or *ALK*/*ROS1*-rearranged NSCLC after tyrosine kinase inhibitor failure, with acceptable safety profile.

1. Introduction

For patients with stage IIIB/IV non-small cell lung cancer (NSCLC) without oncogenic addiction, immune checkpoint inhibitors (ICIs) have emerged as a first-line treatment [1−3]. For patients with epidermal growth factor receptor (*EGFR*) mutation, several phase III trials comparing EGFR tyrosine kinase inhibitors (TKIs) with chemotherapy showed a benefit of TKIs versus chemotherapy, but with no proven benefit on overall survival (OS) [4]. Similarly, TKIs demonstrated efficacy in patients with *ALK* or *ROS1* rearrangements compared to chemotherapy [4]. Nowadays, the standard of care in first-line setting is TKIs in patients with common *EGFR*, *ALK* or *ROS* mutations. Depending on the therapeutic sequence, patients with oncogenic mutations may receive between one to three lines of TKIs. But at some point, in the absence of a targetable resistance mechanism, chemotherapy will be the preferred option [5]. Resistance to third-generation EGFR or ALK TKIs can be mediated by acquired *EGFR* or *ALK* kinase-domain mutations, respectively. However, mutations are found in up to 40−50% of patients and only half of these resistance mechanisms are druggable targets [6]. The majority of patients need a non-targeted therapy such as chemotherapy.

Despite these major advances, most patients experience tumour progression after targeted therapies and chemotherapy, raising the issue of anti-PD-1/PD-L1 monotherapy. Several phase III trials on monotherapy anti-PD1/PD-L1 showed benefits for patients with advanced non-squamous NSCLC [7−9]. However, previous reports showed limited efficacy of ICI as single-agent treatment for NSCLC with *EGFR* mutation or

ALK/*ROS1* fusion [10,11]. It was, therefore, hypothesised that the addition of chemotherapy to immunotherapy could improve the outcomes in these subgroups of patients. The IMpower150 study showed that the addition of ICI (atezolizumab) to vascular endothelial growth factor (VEGF) inhibitor (bevacizumab) plus platinum-based chemotherapy (carboplatin plus paclitaxel) improved progression-free survival (PFS) and OS in first-line treatment of patients with metastatic non-squamous NSCLC, regardless of PD-L1 expression and *EGFR* or *ALK* genetic alteration status [1]. In the IMpower150 randomised phase III study, a subgroup analysis was performed for patients with sensitising *EGFR* mutation. A total of 123 of 1202 patients had an *EGFR* mutation [12]. In this subgroup of patients, median OS was longer in the atezolizumab–bevacizumab–carboplatin–paclitaxel arm (29.4 months) than in the bevacizumab–carboplatin–paclitaxel arm (18.1 months; hazard ratio 0.60, 95% confidence interval [CI] 0.31–1.14). Data on the subgroup of patients with *EGFR* mutation or *ALK* rearrangement were, however, limited and questionable due to a small sample size and unbalanced distribution of baseline characteristics between randomisation groups [13].

Therefore, we proposed to prospectively evaluate this combination approach in patients with *EGFR* mutation, *ALK* rearrangement or *ROS1* fusion, after tumour progression with optimal targeted therapies. Pemetrexed plus platinum was chosen as chemotherapy backbone since it is the standard of care in first-line treatment of adenocarcinoma NSCLC. Moreover, this combination is in line with the findings from the large retrospective study of Yang *et al.* that investigated treatment strategies in patients with stage IV lung adenocarcinoma with *EGFR* sensitive mutations who developed resistance after first-line TKI treatment (gefitinib). Among patients receiving a platinum-based doublet, pemetrexed appeared to have better clinical efficacy than other cytotoxic drugs [14]. According to their eligibility to bevacizumab treatment, patients were enrolled in two parallel cohorts: platinum, pemetrexed, atezolizumab and bevacizumab (PPAB) cohort or platinum, pemetrexed, atezolizumab (PPA) cohort.

2. Materials and methods

2.1. Type of study

This trial (GFPC 06-2018) was a multicentre open-label non-randomised phase II study with two parallel cohorts, performed in patients having stage IIIB/IV non-squamous NSCLC and *EGFR* mutation or *ALK*/*ROS1* fusion.

The objective was to assess the activity in term of objective response rate (ORR) at 12 weeks evaluated by blind independent central review of the combination of PPA with or without bevacizumab in patients with tumour progression following optimal targeted therapies. The secondary objectives were PFS, OS and safety profile.

The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. It was approved by an independent Ethics Committee ('CPP Ouest V'; 22nd July 2019). A written signed informed consent was obtained from all patients before entering any study procedure. The trial was registered with ClinicalTrials.gov, number NCT04042558 and EudraCT, number 2019-000727-41.

2.2. Patients

The main inclusion criteria were age ≥18 years; histologically or cytologically confirmed stage IIIB/IV non-squamous NSCLC; sensitising mutation in the *EGFR* gene, *ALK* fusion oncogene or *ROS1* fusion oncogene (confirmed in local laboratory) with disease progression during or after treatment with one or more EGFR, ALK or ROS1 TKIs; no prior chemotherapy treatment for stage IV non-squamous NSCLC (except if less than 3 cycles, with treatment free-interval of at least 1 year since last chemotherapy); measurable disease (RECIST v1.1); ECOG performance status of 0 or 1; adequate haematologic and organ function; adequate method of contraception. Patients with non-active CNS metastases were eligible. Patients with stage IIIB non-squamous NSCLC had to be assessed with non-resectable cancer and as not eligible for chemoradiotherapy by investigator. The main exclusion criteria were active CNS metastases, spinal cord compression (not definitely treated), leptomeningeal disease, history of autoimmune disease, history of idiopathic pulmonary fibrosis, organising pneumonia (e.g. bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis or evidence of active pneumonitis on screening chest computed tomography (CT) scan, prior treatment with CD137 agonists or immune checkpoint blockade therapies including anti-PD-1 and anti-PD-L1 therapeutic antibodies, treatment with systemic immunostimulatory agents or systemic immunosuppressive medications (the use of corticosteroids ≤10 mg oral prednisone or equivalent for chronic obstructive pulmonary disease was allowed). Patients with great vessel invasion could be included in both study cohorts (PPAB and PPA).

Patients were not eligible to bevacizumab in case of medically uncontrolled hypertension, prior history of hypertensive crisis or hypertensive encephalopathy, clinically significant cardiovascular disease uncontrolled by medication, recent arterial thrombosis, haemoptysis, history of documented haemorrhagic diathesis or coagulopathy, minor surgical procedure within 7 days or major surgery within 28 days.

2.3. Treatments

In the PPA cohort, patients underwent 4 cycles of induction every 3 weeks with carboplatin AUC 6 mg/mL/min or cisplatin 75 mg/m^2, pemetrexed 500 mg/m^2 and atezolizumab 1200 mg. In the PPAB cohort, patients received also bevacizumab 15 mg/kg, every 3 weeks. The choice of the treatment cohort was left to the discretion of the investigator according to the eligibility criteria, notably related to bevacizumab.

For patients without disease progression or intolerable toxicity, induction treatment was followed by maintenance therapy: atezolizumab plus pemetrexed and bevacizumab administered at the same dosage on 3-week cycles in PPAB cohort; atezolizumab plus pemetrexed administered at the same dosage on 3-week cycles in PPA cohort. Maintenance was continued until tumour progression, intolerable toxicity or death, whichever occurred first.

2.4. Data collected

Data collected from patient medical records using electronic case report forms included sociodemographic data, medical and surgical history, previous oncological treatments, histology, somatic genetic alterations (*EGFR* mutations, *ALK* rearrangement, *ROS1* fusion and other relevant alterations), number and localisation of metastatic sites, concomitant treatments, biological examinations, oxygen saturation, 12-lead electrocardiogram (ECG) and tumour imaging evaluation (thoracic and abdominal-pelvis CT-scan, pelvic magnetic resonance imaging in case of pelvic disease, brain CT or magnetic resonance imaging, bone scan and neck CT if clinically indicated). For patients withdrawn from treatment due to progression, survival was assessed every 6 months.

Tumour imaging was performed every 6 weeks until 36 weeks, then every 9 weeks until progression, death or loss to follow-up and assessed by a masked independent central review per RECIST v1.1. Adverse events (AEs) were collected according to NCI CTCAE v5.0 criteria, and including a causality assessment. In addition, adverse events of special interest (AESI) were also collected, including notably immune-related toxicities, and AEs described in the tolerance profile of bevacizumab.

2.5. Statistical analysis

The primary end-point was the ORR, defined as the proportion of patients with complete response or partial response at 12 weeks according to RECIST v1.1, assessed by independent central review. The primary analysis was performed on the efficacy population, defined as eligible patients who received at least one dose of study treatments. Non-evaluable patients (death or poor health status) were considered as non-responders. Patients with progression (clinical or radiologic) after 6 weeks (2 cycles) were considered as non-responders at 12 weeks. A sensitivity analysis was performed without non-evaluable patients. The two cohorts with and without bevacizumab were analysed separately.

Based on data from phase III clinical trials [15,16], the null hypothesis was ORR $\leq$35% (p0 = 35%) for PPAB cohort and ORR $\leq$30% (p0 = 30%) for PPA cohort. ORR of 50% for PPAB cohort (p1 = 50%) and 45% for PPA cohort (p1 = 45%) were expected. For each cohort, sample size was based on a one-stage design and the exact binomial distribution [17]. With a one-sided type-1 error rate of 5%, a power of 80% and 10% of non-assessable patients, 75 patients had to be included in PPAB cohort and 74 patients in PPA cohort. Clinical results were to be declared positive for the primary end-point if the lower boundary of the 90% two-sided CI was higher than 35% in the PPAB cohort and 30% in the PPA cohort.

PFS and OS were estimated with the Kaplan–Meier method in each cohort. PFS was defined as the time from inclusion to disease progression (according to RECIST v1.1 as assessed by independent central review) or death from any cause, whichever occurs first. OS was defined as the time from the date of inclusion to death from any cause. For the safety analyses, all AEs occurring during or after the first study drug dose were collected by treatment cohort and NCI CTCAE v5.0 grade and imputability to study agents.

3. Results

3.1. Patient disposition and characteristics at inclusion

A total of 168 patients were screened from September 2019 to October 2021 in 27 centres and 150 were included: 72 in the cohort with bevacizumab (PPAB cohort) and 78 in the cohort without bevacizumab (PPA cohort) (Fig. 1). The mean (SD) age of patients was 60.4 (10.2) and 66.1 (10.2) years, 69.0% and 51.3% were female, 49.3% and 53.8% were non-smokers in PPAB and PPA cohorts, respectively. Performance status was 0–1 for all patients. Clinical stage at inclusion was IIIB/IV for all patients and in almost all of them the histological type was adenocarcinoma (100% and 97.4%, respectively). Mean delay between stage IIIb/IV NSCLC diagnosis and inclusion was 2.5 and 2.2 years, respectively.

EGFR mutation was reported in 87.3% and 89.7% of patients, *ALK* rearrangement in 12.7% and 5.1% and *ROS1* fusion in 0% and 6.4% in PPAB and PPA cohorts, respectively (Table 1). PD-L1 status was positive in 49.3% and 50.0% of patients, respectively, with PD-L1 $\geq$50% in 19.7% and 16.7% of patients, respectively.

3.2. TKI treatment before inclusion

Before inclusion, all patients had received at least one line of TKI treatment (Table 2). The TKI treatment

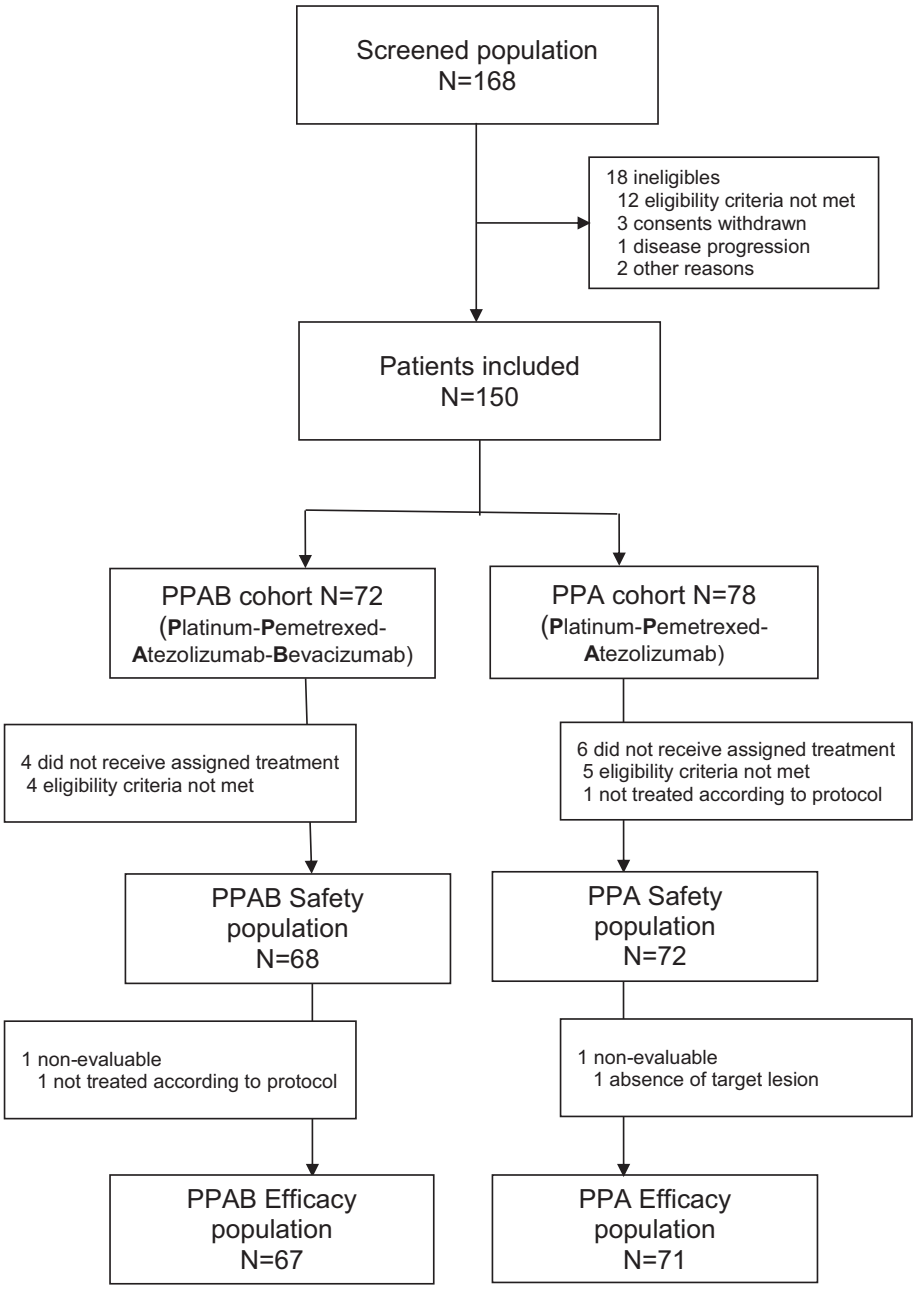

Fig. 1. Flow chart.

sequence is summarised in Table 2. A majority of patients had received osimertinib (69.0% and 73.1% in PPAB and PPA cohorts, respectively). Best response to targeted therapy was complete response for 8.4% and 1.3% of patients and partial response for 71.8% and 64.1%, respectively. Median number of treatment lines before inclusion was 2 (IQR 1–3) in patients having *EGFR*-mutation NSCLC and 2 (IQR 1–3) in patients having *ALK*/*ROS1*-rearranged NSCLC .

At inclusion in the study, all patients had disease progression. Progression was mainly metastatic (85.9% and 79.5%, respectively) and the main disease progression site was bone (33.8% and 38.5%).

3.3. Evaluation of study treatment

In the intent-to-treat population, a total of 60 (84.5%) patients in PPAB cohort and 63 (80.8%) patients in PPA cohort received 4 cycles of induction therapy. The main reasons for treatment discontinuation before 4 cycles were toxicity (4 patients in PPAB cohort and 3 in PPA cohort), death (2 and 5, respectively, none of them related to treatment toxicity) and disease progression (2 and 3, respectively).

After induction treatment, ORR was 58.2% (90% CI, 47.4–68.4) in PPAB cohort and 46.5% (90% CI, 36.3–56.9) in PPA cohort (Table 3). The primary

Table 1
Patient characteristics (PPAB: platinum, pemetrexed, atezolizumab and bevacizumab; PPA: platinum, pemetrexed, atezolizumab).

	PPAB cohort N = 71	PPA cohort N = 78
Age, years, mean (SD)	60.4 (10.2)	66.1 (10.2)
Female gender, n (%)	49 (69.0)	40 (51.3)
ECOG performance status, n (%)		
0	41 (57.7)	30 (38.5)
1	30 (42.3)	48 (61.5)
Smoking status, n (%)		
Former	32 (45.1)	34 (43.6)
Current	4 (5.6)	2 (2.6)
Never-smoker	35 (49.3)	42 (53.8)
Delay between diagnosis and inclusion, years, mean (SD)	2.5 (1.6)	2.2 (2.2)
Histology, n (%)		
Adenocarcinoma	71 (100)	76 (97.4)
Other	0	2 (2.6)
EGFR mutation, n (%)	62 (87.3)	70 (89.7)
Exon 19	43 (60.6)	40 (51.3)
L858R	14 (19.7)	19 (24.4)
Exon 18	5 (7.0)	5 (7.1)
Ins Exon 20	0 (0.0)	4 (5.7)
Others	0 (0.0)	2 (2.8)
T790M (rebiopsy)	9 (12.7)	8 (10.3)
ALK rearrangement, n (%)	9 (12.7)	4 (5.1)
ROS1 fusion, n (%)	0	5 (6.4)
PD-L1 status, n (%)		
Positive	35 (49.3)	39 (50.0)
≥50%	14 (19.7)	13 (16.7)
Not done	14 (19.7)	10 (12.8)
Clinical stage at inclusion, n (%)		
IIIB	2 (2.8)	5 (6.4)
IV	69 (97.2)	73 (93.6)
Metastasis sites, n (%)		
Bone	42 (59.2)	43 (55.1)
Lung	25 (35.2)	28 (35.9)
Brain	25 (35.2)	19 (24.4)
Lymph nodes	13 (18.3)	32 (41.0)
Liver	15 (21.1)	17 (21.8)
Adrenal gland	11 (15.5)	10 (12.8)
Other	23 (32.4)	23 (29.5)
Previous radiotherapy, n (%)	38 (53.5)	30 (38.5)

Table 2
Characteristics of disease progression prior to study treatment.

	PPAB cohort N = 71	PPA cohort N = 78
EGFR-TKI sequence, n	62	70
Frontline 1st/2nd-generation EGFR TKI	13 (21.0.)	13 (18.5)
Frontline osimertinib (one line)	26 (42.0)	31 (44.3)
1st/2nd-generation EGFR TKI followed by osimertinib (2 lines)	22 (35.5)	22 (31.5)
Other sequence	1 (1.6)	4 (5.7)
EGFR-TKI sequence, n	62	70
ALK/ROS-TKI sequence n	9	4
1 line	1 (11.1)	2 (50)
2 lines	6 (66.7)	2 (50)
≥3 lines	2 (22.2)	0
Disease progression type, n (%)		
Primary tumour	10 (14.1)	16 (20.5)
Metastatic	61 (85.9)	62 (79.5)
Disease progression sites, n (%)		
Bone	24 (33.8)	30 (38.5)
Lung	33 (46.4)	28 (35.9)
Liver	16 (22.5)	16 (20.5)
Central nervous system	14 (19.7)	7 (9.0)
Adrenal gland	11 (15.5)	7 (9.0)
Others	28 (39.4)	27 (34.6)
Number of progression sites, n (%)		
0	9 (12.7)	13 (16.7)
1	24 (33.8)	28 (35.9)
2	23 (32.4)	27 (34.6)
≥3	15 (21.1)	10 (12.8)

TKI, tyrosine kinase inhibitor.

outcome was statistically significant ($p < 0.01$) in both groups since the lower boundary of the 90% two-sided CI was higher than 35% in PPAB cohort and 30% in PPA cohort. Sensitivity analysis excluding non-evaluable patients confirmed the statistical significance of ORR in both cohorts; ORR was 60.9% (90% CI, 49.9–71.2) in PPAB cohort and 52.4% (90% CI, 41.3–63.3) in PPA cohort.

Disease control rate was 93.8% (60/64) of patients in PPAB cohort and 93.8% (61/65) of patients in PPA cohort at 6 weeks; 98.4% (60/61) and 93.5% (58/62) of patients at 12 weeks (Table 3).

Median follow-up of patients was 14.8 (95% CI, 13.0–17.7) months in PPAB cohort and 13.1 (95% CI, 9.6–15.8) in PPA cohort. Median PFS according to Kaplan–Meier analysis was 7.3 (95% CI, 6.9–9.0) months in PPAB cohort and 7.2 (95% CI, 5.7–9.2) months in PPA cohort. Median PFS was similar in the EFGR or ALK/ROS1 subgroups (Fig. 2).

Median OS was 17.2 (13.7–NA) months in PPAB cohort and 16.8 (13.5–NA) months in PPA cohort (Fig. 3).

3.4. Safety

The most frequent AEs reported in PPAB and PPA cohorts were asthenia (69.1% and 55.6% of patients, respectively), anaemia (41.2% and 48.6%) and nausea/vomiting (48.5% and 41.7%) (Table 4). Vascular hypertensive disorders of any grade were reported in 22.1% of patients of PPAB cohort and 1.4% of patients of PPA cohort.

Grade 3–4 AEs occurred in 69.1% of patients in PPAB cohort and 51.4% in PPA cohort; Grade 3–4 atezolizumab-related AEs occurred in 27.9% and 15.3%, respectively. No toxicity-related death was observed.

A total of 22 AESIs were reported in PPAB cohort (including 13 of Grade 3–4) and 10 in PPA cohort (including 3 of Grade 3–4). Among AESIs of any grade, thyroid disorders were reported in Grade 3 (4.4%) and 1 (1.4%), hepatocellular damage/hepatitis in Grade 1 (1.5%) and 2 (2.8%) and non-infectious myocarditis in Grade 1 (1.5%) and zero. Among Grade 3–4 AESIs, only vascular hypertensive disorders were reported in

Table 3
Activity outcomes.

	PPAB cohort	PPA cohort
Objective response rate[a] (ORR)	N = 67	N = 71
n (%)	39 (58.2)	33 (46.5)
90% CI	47.4–68.4	36.3–56.9
P-value	<0.01[b]	<0.01[c]
Responses at 6 weeks, n (%)	n = 64	n = 65
Complete response	0	0
Partial response	26 (40.6)	23 (35.4)
Stable disease	34 (53.1)	38 (58.5)
Progressive disease	3 (4.7)	3 (4.6)
Not evaluable	1 (1.6)	1 (1.5)
Responses at 12 weeks, n (%)	n = 64	n = 65
Complete response	1 (1.6)	0
Partial response	38 (59.3)	33 (50.7)
Stable disease	21 (32.8)	25 (38.5)
Progressive disease	4 (6.2)	6 (9.2)
Not evaluable	0	1 (1.5)

[a] Complete response plus partial response rates after 4 cycles of induction treatment.
[b] Test versus 35%.
[c] Test versus 30%.

more than one patient (6 patients, all in PPAB cohort; 8.8%).

4. Discussion

The present study included patients with stage IIIB/IV non-squamous NSCLC, *EGFR* mutation or *ALK*/*ROS1* fusion, progression after at least one optimal TKI and no prior chemotherapy. The two cohorts appear to be representative of patients with actionable genomic alteration progressing after targeted treatment. A majority of patients were female, half were non-smokers and almost all had adenocarcinoma. PD-L1 expression at diagnosis was ≥50% in 19.7% and 16.7% of patients, respectively. The most frequent *EGFR* mutations at diagnosis were Exon 19 deletion (60.6% and 51.3% in PPAB/PPA cohorts, respectively) and L858R mutation (19.7% and 24.4% in PPAB/PPA cohorts, respectively). Dealing with ALK rearrangement and ROS translocation, they respectively concerned 13 and 5 patients

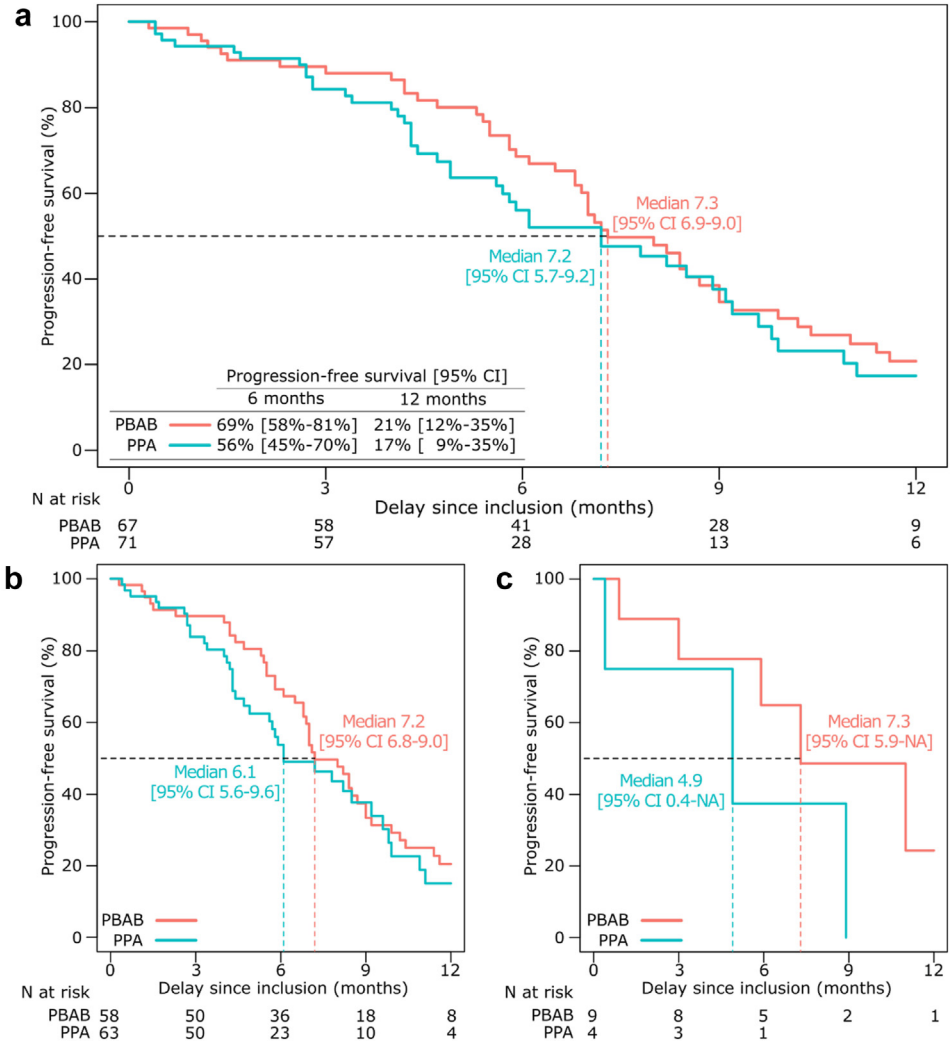

Fig. 2. Progression-free survival in PPAB and PPA cohorts: entire cohorts (**a**), EGFR subgroups (**b**) and ALK/ROS1 subgroups (**c**). EGFR, epidermal growth factor receptor; PPA, platinum, pemetrexed and atezolizumab; PPAB, platinum, pemetrexed, atezolizumab, bevacizumab.

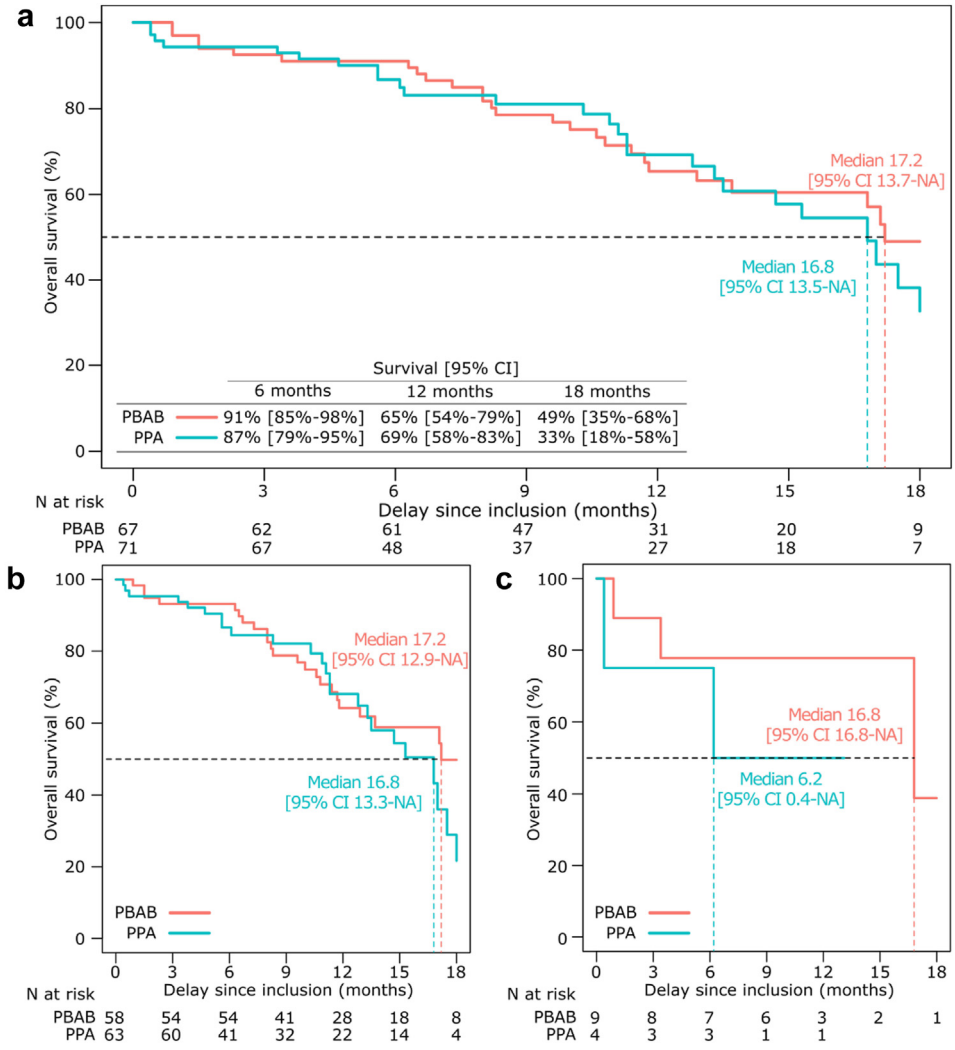

Fig. 3. Overall survival in PPAB and PPA cohorts: entire cohorts (**a**), EGFR subgroups (**b**) and ALK/ROS1 subgroups (**c**). EGFR, epidermal growth factor receptor; PPA, platinum, pemetrexed and atezolizumab; PPAB, platinum, pemetrexed, atezolizumab, bevacizumab.

over the enrolled population. Despite these genomic alterations are rare, we opted to also include patients harbouring such ALK/ROS1 fusion in a study combining chemotherapy and immunotherapy in view of the efficacy of immunotherapy in monotherapy in this subtype of patients [11]. The most frequent TKI treatment before inclusion was osimertinib (69.0% and 73.1% in PPAB/PPA cohorts, respectively) and ORR to TKI was 80.3% and 65.5%, respectively.

The combination treatment with PPA with or without bevacizumab appeared to be effective in metastatic non-squamous NSCLC with *EGFR* mutation, *ALK* rearrangement or *ROS1* fusion progressing after targeted therapies. ORR at 12 weeks was 58.2% in PPAB cohort and 46.5% in PPA cohort. These rates achieved statistical significance in both cohorts compared to predefined rates based on literature data. Median PFS was 7.3 months in PPAB cohort and 7.2 months in PPA cohort; median OS were 17.2 and 16.8 months, respectively. Another standard of care in this setting is bevacizumab plus paclitaxel and carboplatin, which is the only bevacizumab-based regimen approved by the United States Food and Drug Administration. However, a Phase III study showed no difference between the combination of pemetrexed and carboplatin and that of bevacizumab plus paclitaxel and carboplatin [18].

Beyond the anti-angiogenic effects of bevacizumab, the inhibition of VEGF has also immunomodulatory effects [19]. In thoracic oncology, the potential advantage of combination approach that associates anti-VEGF and ICI to chemotherapy was evaluated in the Phase III randomised controlled trial IMpower150, which assessed atezolizumab and bevacizumab plus chemotherapy in patients with metastatic non-squamous NSCLC who had not previously received chemotherapy [1,3]. Of interest, this study population included 13% of patients with *EGFR* mutation or *ALK* rearrangement, who had progressed after one or more targeted therapy [3]. In patients with *EGFR* mutations, ORR was 70.6%,

Table 4
Adverse events.

	PPAB cohort n = 68		PPA cohort n = 72	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Adverse event of any cause				
All	68 (100)	47 (69.1)	65 (90.3)	37 (51.4)
Leading to study drug discontinuation	29 (42.6)	18 (26.5)	9 (12.5)	5 (6.9)
Leading to study drug interruption	34 (50.0)	22 (32.4)	26 (36.1)	16 (22.2)
Serious	20 (29.4)	17 (25.0)	26 (36.1)	17 (23.6)
Death	3 (4.4)	0	3 (4.2)	0
Adverse event related to atezolizumab				
All	48 (70.6)	19 (27.9)	40 (55.6)	11 (15.3)
Serious	5 (7.4)	5 (7.4)	3 (4.2)	1 (1.4)
Death	0	0	0	0
Adverse event related to bevacizumab				
All	46 (67.6)	20 (29.4)	0	0
Serious	2 (2.9)	1 (1.5)	0	0
Death	0	0	0	0
Adverse event of any grade in ≥10 of patients				
Asthenia	47 (69.1)	10 (14.7)	40 (55.6)	4 (5.6)
Anaemia	28 (41.2)	6 (8.8)	35 (48.6)	9 (12.5)
Nausea and vomiting	33 (48.5)	1 (1.5)	30 (41.7)	4 (5.6)
Neutropenia	18 (26.5)	11 (16.2)	21 (29.2)	15 (20.8)
Constipation	18 (26.5)	0	14 (19.4)	0
Appetite disorders	18 (26.5)	3 (4.4)	14 (19.4)	1 (1.4)
Breathing abnormalities	11 (16.2)	3 (4.4)	11 (15.3)	3 (4.2)
Thrombocytopenia	9 (13.2)	5 (7.4)	12 (16.7)	6 (8.3)
Musculoskeletal and connective tissue pain and discomfort	8 (11.8)	0	11 (15.3)	0
Diarrhoea	7 (10.3)	0	11 (15.3)	0
Hepatocellular damage and hepatitis	11 (16.2)	7 (10.3)	7 (9.7)	2 (2.8)
Liver function analyses	10 (14.7)	1 (1.5)	7 (9.7)	1 (1.4)
White blood cell analyses	10 (14.7)	4 (5.9)	6 (8.3)	1 (1.4)
Coughing and associated symptoms	10 (14.7)	0	6 (8.3)	0
Vascular hypertensive disorders	15 (22.1)	9 (13.2)	1 (1.4)	1 (1.4)
Headaches	9 (13.2)	0	5 (6.9)	0
Pain and discomfort	8 (11.8)	1 (1.5)	5 (6.9)	1 (1.4)
Renal failure and impairment	9 (13.2)	2 (2.9)	3 (4.2)	0
Rashes, eruptions and exanthems	4 (5.9)	0	8 (11.1)	0
Gastrointestinal and abdominal pain	9 (13.2)	0	2 (2.8)	0
Febrile disorders	8 (11.8)	0	3 (4.2)	0
Nasal disorders	10 (14.7)	1 (1.5)	1 (1.4)	0
Lacrimation disorders	6 (8.8)	0	4 (5.6)	0
Stomatitis and ulceration	8 (11.8)	1 (1.5)	2 (2.8)	0
General signs and symptoms	7 (10.3)	3 (4.4)	4 (5.6)	2 (2.8)

Results are given as n (%).

median PFS was 10.2 months and median OS was 26.3 months in the atezolizumab plus bevacizumab plus chemotherapy group (n = 34) versus 35.6%, 6.9 months and 21.4 months in the atezolizumab plus chemotherapy group (n = 45) versus 41.9%, 6.9 months and 20.1 months in the bevacizumab plus chemotherapy group (n = 44) [13]. However, the small size of the subgroup of patients with *EGFR* mutation and the imbalance of mutation types and previous targeted treatments prevented firm conclusions to be drawn regarding this combination therapy in this subgroup of patients [12,20].

Other studies, including the present study, addressed this issue by including only patients who had progressed under TKI treatment. The study by Lam *et al.* included 40 patients with *EGFR* mutated NSCLC after TKI failure. Patients received a combination of atezolizumab (1200 mg), bevacizumab (7.5 mg/kg), pemetrexed (500 mg/m^2) and carboplatin (AUC 5) given once every 3 weeks until progression [21]. With a median follow-up of 17.8 months, ORR was 62.5%, median PFS was 9.4 months and median OS was not reached (95% CI: 16.4 months–not reached). These results, obtained in conditions similar to those of this study (except the Asian population and lower dose of bevacizumab) were similar to the results in the PPAB cohort. The recent randomised, double-blind, Phase III ORIENT-31 study evaluated the anti-PD-1 antibody sintilimab with or without a bevacizumab biosimilar plus chemotherapy (cisplatin and pemetrexed) in 444 patients having non-squamous

NSCLC and *EGFR* mutation who progressed after EGFR TKI therapy [22]. In the sintilimab plus bevacizumab and chemotherapy arm, ORR was 43.9% and PFS was 6.9 months, compared to 33.1% and 5.6 months in the sintilimab and chemotherapy arm and 25.2% and 4.3 months in the chemotherapy arm, respectively. This study confirmed that, in this population of *EGFR*-mutated non-squamous NSCLC patients who progressed after EGFR TKIs, immunotherapy combined with bevacizumab and chemotherapy significantly improved PFS compared with chemotherapy alone.

In our study, treatment in both cohorts had tolerable safety profile and AEs were manageable. The rates of Grade 3-4 AEs (69.1% of patients in PPAB cohort and 51.4% in PPA cohort) were similar to those reported in the IMpower150 study (55.8%–66.7%) [12] and ORIENT-31 study (39.3%–55.7%) [23]. There were no deaths related to toxicity in the two cohorts of our study. Severe atezolizumab-related AEs were reported in 27.9% and 15.3% of patients in PPAB and PPA cohorts, respectively, in line with the rates of immune AEs reported in the study of Lam *et al.* (all grades: 37.5%) [21]. The higher rate of vascular hypertensive disorders in the cohort with bevacizumab was expected and underscores the need to carefully select patients eligible for this treatment.

The strengths of our study are a relatively large sample size, a high rate of patients who achieved the four planned cycles for induction treatment and the centralised review board to assess the primary end-point. Conversely, our study has some limitations. The design was open-label and there was no comparator for each cohort. As the choice of treatment cohort was left to the investigators, there is a risk that for the same eligibility criteria, fit patients were included in the PPAB arm and unfit in PPA cohort. In addition, it was difficult to conclude for treatment efficacy in patients with *ALK* rearrangement or *ROS1* fusion because of small sample sizes.

In conclusion, combination approach with atezolizumab with or without bevacizumab and platinum-pemetrexed achieved promising efficacy in metastatic *EGFR*-mutated or *ALK*/*ROS1*-rearranged NSCLC after TKI failure, with acceptable tolerance profile. These data will be further investigated in a comparative trial if possible.

Credit author statement

Olivier Bylicki: Conceptualisation, Investigation, Supervision, Writing - Original Draft, Writing - Review & Editing. Pascale Tomasini: Investigation. Gervais Radj: Conceptualisation, Investigation. Florian Guisier: Investigation and Writing - Review & Editing. Isabelle Monnet: Investigation. Charles Ricordel: Investigation. Laurence Bigay-Game: Investigation. Margaux Geier: Investigation. Christos Chouaid: Investigation. Catherine Daniel: Investigation, Writing - Review & Editing. Aurelie Swalduz: Investigation. Anne-Claire Toffart: Investigation. Helene Doubre: Investigation. Jean-Michel Peloni: Investigation. Diane Moreau: Investigation. Fabien Subtil: Formal analysis, Writing - Review & Editing. Jean-Michel Grellard: Data Curation, Project administration. Marie Castera: Data Curation. Benedicte Clarisse: Data Curation, Project administration, Writing - Review & Editing. Pedro-Henrique. Martins-Lavinas: Formal analysis, Writing - Review & Editing. Chantal Decroisette: Investigation, Writing - Review & Editing. Laurent Greillier: Investigation, Writing - Review & Editing.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

O.B reports adviser and consultant for BMS, AstraZeneca, Roche, MSD, Takeda; P.T reports adviser and consultant for Roche, AstraZeneca, BMS, Amgen, Takeda, Janssen-Cillag and Novartis; F.G reports research support from Takeda and Pfizer, adviser and consultant for Amgen, BMS, AstraZeneca, Roche, MSD, Pfizer and Takeda; C.R reports research support from AstraZeneca, reports adviser and consultant for BMS, AstraZeneca and Takeda; L.B-G reports adviser and consultant for AstraZeneca, MSD, BMS, Amgen, Takeda, Viatris, Ipsen and Pfizer; M.G reports research support from BMS and Roche, adviser and consultant for BMS, AstraZeneca, Pfizer and Sanofi; C.C reports adviser and consultant for AstraZeneca, Roche, Sanofi Aventis, BMS, MSD, Lilly, Novartis, Pfizer, Takeda, Bayer and Amgen; C.Da. reports adviser and consultant for AstraZeneca, BMS and Novartis; A.S. reports adviser and consultant for Roche and Lilly; A-C.T reports adviser and consultant for AstraZeneca, Roche, MSD, BMS, Leo Pharma, Amgen, Nutrician, Pfizer; H.D. reports research support from MSD and Pfizer, adviser and consultant BMS, Amgen, Leo Pharma, Novartis, Roche; C.De. reports adviser and consultant for AstraZeneca, Roche, Sanofi, Janssen-Cilag, Takeda, BMS, Sandoz, Novartis, Lilly and Pfizer; L.G. reports research support from Abbvie, AstraZeneca, BMS, MSD, Novartis, Pfizer, PharmaMar, Roche, Sanofi and

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