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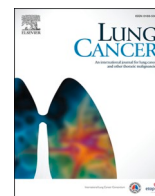
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Research Paper

Safety and Patient-Reported outcomes of atezolizumab plus chemotherapy with or without bevacizumab in stage IIIB/IV non-squamous non-small cell lung cancer with EGFR mutation, ALK rearrangement or ROS1 fusion progressing after targeted therapies (GFPC 06–2018 study)



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ABSTRACT

Background: In an open-label multicenter non-randomized non-comparative phase II study in patients with stage IIIB/IV non-squamous non-small cell lung cancer (NSCLC), oncogenic addiction (EGFR mutation or ALK/ROS1 fusion), with disease progression after tyrosine-kinase inhibitor and no prior chemotherapy (NCT04042558), atezolizumab, carboplatin, pemetrexed with or without bevacizumab showed some promising result. Beyond the clinical evaluation, we assessed safety and patient-reported outcomes (PROs) to provide additional information on the relative impact of adding atezolizumab to chemotherapy with and without bevacizumab in this population.

Materials: Patients received platinum-pemetrexed-atezolizumab-bevacizumab (PPAB cohort) or, if not eligible, platinum-pemetrexed-atezolizumab (PPA cohort). The incidence, nature, and severity of adverse events (AEs) were assessed. PROs were evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-Core 30 and EORTC QLQ-Lung Cancer 13).

Result: Overall, 68 (PPAB) and 72 (PPA) patients were evaluable for safety. Grade 3–4 AEs occurred in 83.8% (PPAB) and 63.9% (PPA). Grade 3–4 atezolizumab-related AEs occurred in 29.4% and 19.4%, respectively. Grade 3–4 bevacizumab-related AEs occurred in 36.8% (PPAB). Most frequent grade 3–4 AEs were neutropenia (19.1%

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in PPAB; 23.6% in PPA) and asthenia (16.2% in PPAB; 9.7% in PPA). In PPAB, we observed a global stability in global health security (GHS) score, fatigue and dyspnea with a constant tendency of improvement, and a significant improvement in cough. In PPA, we observed a significant improvement in GHS score with a significant improvement in fatigue, dyspnea and cough. At week 54, we observed an improvement from baseline in GHS score for 49.2% of patients. In both cohorts, patients reported on average no clinically significant worsening in their overall health or physical functioning scores.

Conclusion: PPAB and PPA combinations seem tolerable and manageable in patients with stage IIIB/IV non-squamous NSCLC with oncogenic addiction (EGFR mutation or ALK/ROS1 fusion) after targeted therapies.

1. Introduction

For patients with stage IIIB/IV Non-Small-Cell-Lung-Cancer (NSCLC) with common *EGFR* mutation, the standard of care is based on the use of EGFR tyrosine kinase inhibitors (TKIs) with osimertinib as first choice [1,2]. 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 [3]. Resistance to third-generation EGFR or ALK TKIs can be mediated by acquired *EGFR* or *ALK* kinase-domain mutations, respectively. However, such mutations are found in only 40–50 % of patients and only half of these resistance mechanisms are druggable targets [4]. Most patients therefore need a non-targeted therapy such as chemotherapy.

The use of immune checkpoint inhibitor (ICI) as PD-L1 or PD-1 inhibitor is systematic in first or second line of treatment in NSCLC without addiction, but, for patients with oncogenic addiction, clinical trials data have shown a lack of efficacy, particularly in case of ALK rearrangement [5–9].

Although multiple randomized phase 3 trials have found that chemotherapy combined with immunotherapy improves outcomes for patients with advanced NSCLC, it is to notice that patients with *EGFR* mutations were excluded from most trials [8,9]. Subsequently, the phase III IMpower150 study showed that the addition of ICI (atezolizumab) to VEGF inhibitor (bevacizumab) plus platinum-based chemotherapy (carboplatin plus paclitaxel) improved progression-free survival (PFS) and overall survival (OS) in first-line treatment of patients with metastatic non-squamous NSCLC, regardless of PD-L1 including patients with *EGFR* or *ALK* genetic alteration status [10–15].

The non-randomized phase II GFPC 06–2018 study, one of the first study which evaluated the combination of immunotherapy plus chemotherapy with or without VEGF inhibitor in metastatic *EGFR*-mutated or *ALK/ROS1*-rearranged NSCLC after TKI failure achieved promising efficacy [16].

Patients with advanced NSCLC have frequently symptoms such as fatigue, cough, dyspnea, anorexia, weight loss, and pain that can have a substantial negative effect on health-related quality of life (HRQOL) [17,18]. These symptoms can also be increased by symptomatic treatment-related adverse events. In this context, the effects of the combination of multiple treatments on symptoms and HRQOL need to be considered alongside disease control and survival outcomes because therapy remains palliative rather than curative in this setting. We herein report safety profile and HRQOL in each treatment arm of the GFPC 06–2018 study.

2. Material and methods

2.1. Study design

The GFPC 06–2018 trial is a multicenter open-label non-randomized phase II study, performed in stage IIIB/IV non-squamous NSCLC patients with *EGFR* mutation or *ALK/ROS1* fusion progressing after targeted therapies, with two parallel cohorts: one cohort (PPA) of patients treated with atezolizumab and platinum-pemetrexed, and one cohort (PPAB) of patients treated by atezolizumab, platinum-pemetrexed and

bevacizumab [16]. In each cohort, the primary endpoint was the objective response rate (ORR) at 12 weeks and the secondary objectives were PFS and OS. Details of the trial design, patient population, treatments, and efficacy results were previously published [16].

2.2. Ethical approval and consent to participate

The GFPC 06–2018 trial was conducted in accordance with Good Clinical Practices recommendations and the principles of the Declaration of Helsinki. The protocol approval was obtained from an independent ethics committee (“CPP Ouest V”; July 22, 2019, 2019–000727-41). All patients provided written informed consent. An independent data monitoring committee reviewed safety data during the study. The trial was registered with [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT04042558 and EudraCT, number 2019–000727-41.

2.3. Objectives

The objectives of this analysis were to assess, in each cohort, the safety of the combined treatments as reported per standardized safety procedures over the participation of the patients, and patient-reported outcomes (PROs) and HRQOL benefits.

2.4. Patients and procedures

For induction treatment (4 cycles), patients were treated with combination atezolizumab (1200 mg), bevacizumab (7.5 mg/kg), pemetrexed (500 mg/m²) and carboplatin (AUC 5) or cisplatin (70 mg/m²) given once every 3 weeks until progression or atezolizumab (1200 mg), pemetrexed (500 mg/m²) and carboplatin (AUC 5) or cisplatin (70 mg/m²) at the same frequency. 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 tumor progression, intolerable toxicity or death, whichever occurred first.

The main inclusion criteria were: age \geq 18 years; histologically or cytologically confirmed stage IIIB/IV non-squamous NSCLC; sensitizing mutation in the *EGFR* gene, *ALK* fusion oncogene or *ROS1* fusion oncogene 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; measurable disease (RECIST v1.1); ECOG performance status of 0 or 1; adequate hematologic and organ function. Patients with non-active central nervous system (CNS) metastases were eligible. The main exclusion criteria were active CNS metastases, spinal cord compression (not definitely treated), leptomeningeal disease, history of auto-immune disease, history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan, treatment with systemic immunostimulatory agents or systemic immunosuppressive medications, prior treatment with CD137 agonists or immune checkpoint blockade therapies including anti-PD-1 and anti-PD-L1 therapeutic antibodies.

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, hemoptysis, history of documented hemorrhagic diathesis or coagulopathy, minor surgical procedure within 7 days or major surgery within 28 days.

2.5. Safety evaluation

Safety was assessed through toxicities that occurred either in the induction treatment or the maintenance treatment. Toxicities were evaluated by protocol planned physical exam, laboratory assays, monitoring of adverse events (AEs). All-cause AEs, atezolizumab-related AEs and bevacizumab-related AEs were assessed and graded using the NCI-CTCAE (National Cancer Institute Common Terminology Criteria for AEs) version 5.0 criteria and were coded using the MEDRA (Medical Dictionary for Regulatory Activities) version 26.0.

2.6. Pros assessment

PROs were predefined secondary endpoints, assessed for all included patients at baseline, every 6 weeks (2 cycles) until 36 weeks, then every 9 weeks until progression, death or lost. They were based on the use of the standardized validated EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Quality of Life Questionnaire-Core) and EORTC QLQ-Lung cancer 13 (LC13) self-administered questionnaires to assess health-related quality of life [19,20]. The EORTC QLQ-C30 questionnaire comprises 30 questions across five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), a global health status (GHS) scale, and various single items (e.g., dyspnea, diarrhea) [19]. The EORTC QLQ-LC13 module comprises questions on disease-specific symptoms, 13 questions across one multi-item scale to assess dyspnea and various other single items (e.g., chest pain, cough, sore mouth) [20].

2.7. Statistical analysis

Population for safety analysis included all enrolled patients who met all eligibility criteria and received at least one dose of one drug or more of the combined treatment. The total number of cycles was described.

The percentage of patients with at least one AE (overall serious, leading to study drug discontinuation, interruption, or death) was described, with AE categorization (any cause, related to atezolizumab, to bevacizumab). We also focused on AEs (any grade) occurring for at least in 10 % of patients.

Patients considered for PRO analysis were patients included in the efficacy analysis population (met all eligibility criteria and received at least one full dose of treatment) who completed EORTC QLQ-C30 and QLQ-LC13 questionnaires at inclusion and at least once on an on-study time point thereafter. PRO analysis was restricted to the GHS, the fatigue and cough scales from the QLQ-C30 questionnaire, and the dyspnea scale from the QLQ-LC13 because we wished to focus on the most frequent and relevant symptoms altering the HRQOL in lung cancer. HRQOL scores were calculated according to the developers' scoring guidelines.

Completion was defined by number (percentage) of patients with questionnaires fulfilled at the different follow-up time points. Compliance was defined by number (percentage) of patients with questionnaires fulfilled at the different follow-up time points among patients that should have a questionnaire (alive, without progression, and not lost to follow-up).

The time to deterioration was defined as the delay between inclusion to a variation of at least 10 points from baseline in symptom/functioning scales (increase for symptoms, decrease for functioning scale), which corresponds to the minimal threshold for a moderate change [21]. Patients without deterioration during the follow-up were censored at the

last available HRQOL assessment or at 54 weeks otherwise. Patients with baseline scores symptoms above 90 (or patients with baseline functions scores below 10) were censored at 0 day. During the whole follow-up, percentage of patients with improvement (decrease of 10 points for symptoms, increase of 10 points for functioning scales), stability (changes less than 10 points), or deterioration compared with baseline value were calculated.

The HRQOL results were modeled using a linear mixed effect model, including the time as fixed effect, as well as a random intercept and slope by patient. For cough, the results were binarized (symptom present is at least little cough), and analyzed using a logistic mixed effect model. Predictions from models were displayed with the associated 95 % confidence interval obtained using 500 bootstrapped samples.

The time to deterioration was described using Kaplan-Meier curves and summarized using the median time to deterioration with the associated 95 % confidence interval.

For overall improvement, stability or deterioration, if the patient was still followed at 54 weeks without progression but without HRQOL assessment, single imputation was performed using the aforementioned mixed models.

Statistical analyses were performed using R software version 4.0.2.

3. Results

3.1. Patients and treatment

A total of 149 patients were enrolled, 71 and 78 patients were respectively assigned to receive PPAB and PPA. 18 patients were treated with cisplatin (investigator's choice), 15 in the PPAB cohort and 3 in the PPA cohort, the other patients received carboplatin. The median duration of follow-up was 14.8 months (min–max 0.9–32.5) for cohort PPAB, and 13.1 months for cohort PPA (min–max 0.4–32.7). 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. *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. PD-L1 status was positive in 49.3 % and 50.0 % of patients, with PD-L1 \geq 50 % in 19.7 % and 16.7 % of patients, in PPAB and PPA cohorts, respectively. For the safety analysis, 68 and 72 patients were considered in the PPAB and PPA groups; for PRO analysis, 67 and 71 patients were considered. The mean number of cycles achieved was 11.6 (PPAB) and 10.3 (PPA), a mean of 3.6 cycles in the induction phase in both cohorts and a mean of 9.8 (PPAB) and 8.6 (PPA) cycles in the maintenance phase (Table 1).

3.2. Efficacy

Detailed results about efficacy in the two cohorts of the GFCP 06–2018 study have been published previously. Briefly, at 12 weeks, ORR was 58.2 % (90 % CI, 47.4–68.4, $p < 0.01$) in PPAB cohort and 46.5 % (90 % CI, 36.3–56.9, $p < 0.01$) in PPA cohort [16].

3.3. Safety

Data are reported in Table 2. Almost all patients experienced at least one AE: 100 % (68/68) and 97.2 % (70/72) reported at least one AE during follow-up, in PPAB and PPA cohorts, respectively. The most frequent AEs reported in PPAB and PPA cohorts were asthenia (70.6 % and 63.9 %), anemia (42.6 % and 58.3 %), nausea/vomiting (60.3 % and 50.0 %). Grade 3–4 AEs occurred for 83.8 % of patients in PPAB cohort and 63.9 % in PPA cohort: most frequent grade 3–4 AEs were neutropenia (19.1 % in PPAB and 23.6 % in PPA) and asthenia (16.2 % in PPAB and 9.7 % in PPA).

Grade 3–4 atezolizumab-related AEs occurred in 29.4 % and 19.4 %, in PPAB and PPA cohorts, respectively. The adverse event with special interest included notably 6 thyroid disorders (3 hyperthyroiditis and 3

Table 1
Patient characteristics at inclusion (N = 149).

	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)
ALK rearrangement, n (%)	9 (12.7)	4 (5.1)
ROSI 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)
Systemic treatmentTotal number of cycles (mean ± SD)	11.6 (8.1)3.7 (0.8)9.8	10.3 (8.5)3.6 (0.9)8.5
In the induction phase	(7.4)	(8.4)
In the maintenance phase		

PPAB: platinum-pemetrexed-atezolizumab-bevacizumab, PPA: platinum-pemetrexed-atezolizumab.

hypothyroiditis), five hepatic cytolysis, one non-infectious myocarditis, one nephritis and, one immune-mediated pneumonitis.

In the PPAB cohort, the main AE related to bevacizumab was vascular hypertensive disorders, reported for 11 (16.2 %) patients. Grade 3–4 bevacizumab-related AEs occurred in 36.8 % of patients, notably three central nervous system hemorrhages, one optic disorders in addition to hypertension.

Apart from treatment discontinuations due to tumor progression or death, toxicity required definitive discontinuation for 10 patients in PPAB and 8 patients in PPA. As for AEs that lead to deaths (3 respiratory distress, 2 septic shock and 1 sudden death), they were reported for 2 patients in PPA cohort, and 4 patients in PPAB cohort, none of them attributed to bevacizumab; 3 deaths were attributed to atezolizumab.

3.4. Quality of life

The completion and compliance for the PRO instruments over time/study duration are shown in Table 3, description was ended at week 54 due to very low number of patients after. Compliance at baseline was 100 % in both treatment groups, and decreased, but was always higher than 50 %.

The evolution of GHS and functional symptoms during the follow up is illustrated by Fig. 1. The median time to deterioration for GHS was 37.4 and 31.3 weeks in PPAB and PPA cohorts, respectively; for fatigue it was 8.3 weeks in PPAB and 13.1 weeks in PPA; for dyspnea, the median time to deterioration was 24 weeks in PPAB and 34.7 weeks in PPA; for cough, the median time to deterioration was not reached.

Table 2
Adverse events (AEs).

	PPAB cohort n = 68		PPA cohort n = 72	
	Any grade	Grade3-4	Any grade	Grade 3-4
AEs of any cause				
All	68 (100)	57 (83.8)	70 (97.2)	46 (63.9)
Leading to study drug discontinuation	47 (69.1)	47 (69.1)	25 (34.7)	24 (33.3)
Leading to study drug interruption	43 (63.2)	42 (61.8)	37 (51.4)	34 (47.2)
Serious	35 (51.5)	31 (45.6)	30 (41.7)	19 (26.4)
Death	4 (5.8)	4 (5.8)	2 (2.8)	2 (2.8)
AEs related to atezolizumab				
All	50 (73.5)	20 (29.4)	45 (62.5)	14 (19.4)
Serious	6 (8.8)	5 (7.4)	4 (5.6)	2 (2.8)
Death	2 (2.9)	2 (2.9)	1 (1.4)	1 (1.4)
AEs related to bevacizumab				
All	50 (73.5)	25 (36.8)	2 (2.8)	0
Serious	1 (1.5)	0	0	0
Death	0	0	0	0
AEs of any grade in ≥ 10 % of patients				
Asthenia	48 (70.6)	11 (16.2)	46 (63.9)	7 (9.7)
Anemia	29 (42.6)	6 (8.8)	42 (58.3)	10 (13.9)
Nausea and vomiting	41 (60.3)	2 (2.9)	36 (50.0)	3 (4.2)
Neutropenia	22 (32.4)	13 (19.1)	25 (34.7)	17 (23.6)
Appetite disorders	24 (35.3)	4 (5.9)	18 (25.0)	2 (2.8)
Constipation	19 (27.9)	0	18 (25.0)	1 (1.4)
Breathing abnormalities	16 (23.5)	3 (4.4)	22 (30.6)	5 (6.9)
Musculoskeletal and connective tissue pain and discomfort	19 (27.9)	0	18 (25.0)	1 (1.4)
Thrombocytopenia	10 (14.7)	5 (7.4)	15 (20.8)	6 (8.3)
Diarrhea	12 (17.6)	0	12 (16.7)	0
Hepatocellular damage and hepatitis	14 (20.6)	7 (10.3)	10 (13.9)	2 (2.8)
Liver function analyses	22 (32.4)	3 (4.4)	9 (12.5)	2 (2.8)
White bloodcell analyses	10 (14.7)	5 (7.4)	6 (8.3)	2 (2.8)
Coughing and associated symptoms	18 (26.5)	0	12 (16.7)	0
Vascular hypertensive disorders	20 (29.4)	11 (16.2)	3 (4.2)	1 (1.4)
Headaches	15 (22.1)	0	8 (11.1)	0
Pain and discomfort	14 (20.6)	2 (2.9)	8 (11.1)	1 (1.4)
Renal failure and impairment	16 (23.5)	3 (4.4)	6 (8.3)	0
Rashes, eruptions and exanthems	5 (7.4)	0	10 (13.9)	0
Gastrointestinal and abdominal pain	15 (22.1)	1 (1.5)	5 (6.9)	0
Febrile disorders	11 (16.2)	0	4 (5.6)	0
Nasal disorders	14 (20.6)	1 (1.5)	2 (2.8)	0

(continued on next page)

Table 2 (continued)

	PPAB cohort n = 68		PPA cohort n = 72	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Oedema	12 (17.6)	0	15 (20.8)	0
Lacrimation disorders	12 (17.6)	0	10 (13.9)	0
Joint related signs and symptoms	12 (17.6)	2 (2.9)	4 (5.6)	0
Upper respiratory tract infections	10 (14.7)	0	6 (8.3)	0
Stomatitis and ulceration	9 (13.2)	1 (1.5)	3 (4.2)	0
General signs and symptoms	9 (10.2)	4 (5.9)	8 (11.1)	3 (4.2)
Mucosal findings abnormal	8 (11.8)	0	5 (6.9)	1 (1.4)
Pruritus	4 (5.9)	0	10 (13.9)	0
Anxiety symptoms	6 (8.8)	0	6 (8.8)	0
Cholestasis and jaundice	6 (8.8)	2 (2.9)	4 (5.6)	0
Leukopenia	9 (13.2)	1 (1.5)	1 (1.4)	1 (1.4)
Eye and eyelid infections	7 (10.3)	0	4 (5.6)	0
Paraesthesia and dysaesthesia	9 (13.2)	0	2 (2.8)	0
Urinary abnormalities	8 (11.8)	0	3 (4.2)	0

Results are given as n (%).

PPAB: platinum-pemetrexed-atezolizumab-bevacizumab, PPA: platinum-pemetrexed-atezolizumab.

Table 3

Compliance and completion for the PRO instruments (QLQ-C30 and QLQ-LC13).

	PPAB cohort (n = 67)	PPA cohort (n = 71)
Baseline Compliance	67 (100%)67/67 (100 %)	71 (100%)71/71 (100 %)
Week 6 Completion	51 (76 %)51/63 (81 %)	53 (75 %)53/66 (80 %)
Week 12 Compliance	48 (72 %)48/60 (80 %)	50 (70 %)50/62 (81 %)
Week 18 Compliance	40 (60 %)40/58 (69 %)	37 (52 %)37/55 (67 %)
Week 24 Compliance	36 (54 %)36/50 (72 %)	31 (44 %)31/45 (69 %)
Week 30 Compliance	30 (45 %)30/42 (71 %)	23 (32 %)23/35 (66 %)
Week 36 Compliance	20 (30 %)20/32 (62 %)	16 (23 %)16/24 (67 %)
Week 45 Compliance	13 (19 %)13/18 (72 %)	12 (17 %)12/15 (80 %)
Week 54 Compliance	7 (10 %)7/14 (50 %)	6 (8 %)6/10 (60 %)

PPAB: platinum-pemetrexed-atezolizumab-bevacizumab, PPA: platinum-pemetrexed-atezolizumab.

In the PPAB group, we observed, during the follow up, a global stability in GHS score, fatigue and dyspnea with a constant tendency of improvement, and a significant and constant improvement in cough. In the PPA group, we observed, during the follow up, a significant improvement in GHS score with a significant and constant improvement in fatigue, dyspnea and cough.

Overall, the majority of patients reported improvement between baseline and week 54 in the four dimensions assessed by the QOL questionnaires (Table 4): we observed an improvement in fatigue for 50.4 %, in dyspnea for 50.4 % and in cough for 41.4 % of patients. Conversely, deterioration was observed in 45 % of patients for fatigue, 31.5 % of patients for dyspnea, and 20.3 % of patients for cough. As for GHS score, it was improved for 49.2 % of all patients but deteriorated in 33.1 % of patients. Evolutions between baseline and week 54 were imputed for 51.4 % of patients for GHS score, 53.6 % of patients for fatigue, 54.3 % of patients for dyspnea and 55.8 % of patients for coughing.

4. Discussion

The GFPC 06–2018 study suggested an efficacy for the combination of anti PD-L1 and platinum-pemetrexed with or without bevacizumab in metastatic *EGFR*-mutated or *ALK/ROS1*-rearranged NSCLC after TKI. In this study, the two/these two treatment combinations seemed to be safe and tolerable. No significant risk was identified with PPAB, which suggested that the four-drug regimen had no additive toxicities compared with the three-drug treatment. The combination of immunotherapy and chemotherapy with or without bevacizumab decreased time to deterioration of QOL and functional symptoms and contributed to improve fatigue and dyspnea for most patients.

The safety data (grade 3–4 AEs in 83.8 % and 63.9 % of patients in PPAB and PPA cohorts, and 6 treatment-related deaths) are similar as those observed in other studies [10,22–24].

In the IMPOWER150 study, which evaluated the efficacy of atezolizumab-bevacizumab-carboplatin-paclitaxel (ABCP) or atezolizumab-carboplatin-paclitaxel (ACP) versus bevacizumab-carboplatin-paclitaxel (BCP) in an all-comer patient population with metastatic non-squamous NSCLC, ABCP versus BCP had statistically significant and clinically meaningful PFS and OS benefits regardless of PD-L1 expression and numerical improvements irrespective of *EGFR* or *ALK* genetic alteration status; with ACP versus BCP, a similar benefit was not observed. The complementary analyses about safety describe 57.3 % of grade 3–4 AEs in the quadritherapy group which is less than in our study (83.8 %). However, the majority of IMPOWER150 population was treated in first line, while our patients were all exposed to at least one TKI prior to be enrolled. Treatment-related death data were comparable to ours, occurring in 1.0 %, 3.1 % and 2.5 % of patients treated by ACP, ABCP, and BCP respectively [10–12].

More recently, the randomized, double-blind, phase 3 KEYNOTE-789 trial assessed efficacy and tolerance of pemetrexed and platinum-based chemotherapy with or without pembrolizumab subsequent therapy for TKI-resistant, *EGFR*-mutant, metastatic non-squamous NSCLC patients. While the HR for OS favored immunotherapy arm (HR 0.84; 95 % CI, 0.69–1.02), it did not reach statistical significance [22]. This trial targeted a population comparable to ours and brought similar safety data about the association of chemotherapy with immunotherapy after TKIs. Toxicity was comparable with our study, with treatment-related AEs for 89.8 % of patients in chemotherapy plus immunotherapy group versus 86.2 % of patients in chemotherapy group, 43.7 % and 38.6 % of severe AEs respectively. Few immune related severe AEs were observed (4.5 %).

The phase III CHECKMATE 722 trial compared nivolumab plus chemotherapy versus chemotherapy in patients with *EGFR*-mutated metastatic NSCLC after *EGFR* TKIs. AEs occurred in 85 % in the chemotherapy plus atezolizumab arm of which 45 % of grade 3–4 AEs [23,24].

Beyond tolerance, HRQOL under treatment and symptomatic evolution are important criteria when therapeutic pressure increases. The PRO instruments have previously been well validated for advanced NSCLC and are now widely used [22,23] but few studies have systematically assessed the HRQOL of ICIs in patients with NSCLC and even less in patients with oncogenic driver. Prospective assessment PROs with the appropriate hypothesis and instruments is essential, particularly in clinical trials that evaluate new therapeutics in incurable cancers [25,26]. Benefit in terms of PROs may be expected if a drug is efficacious and has a good tolerability profile. By contrast, if a new treatment is found to be efficient but highly toxic, it is impossible to evaluate the trade-off of efficacy versus toxicity without collecting prospective PRO data. Our analysis was based on an improvement cut-off score of 10 points from baseline to determine clinical relevance [21,27,28].

In our study, the median time for deterioration for GHS was 37.4 weeks in PPAB and 31.3 weeks in PPA; for fatigue it was 8.3 weeks in PPAB and 13.1 weeks in PPA; for dyspnea 24 weeks in PPAB and 34.7 weeks in PPA; for cough 19.3 weeks in PPAB and 25.1 weeks in PPA. At

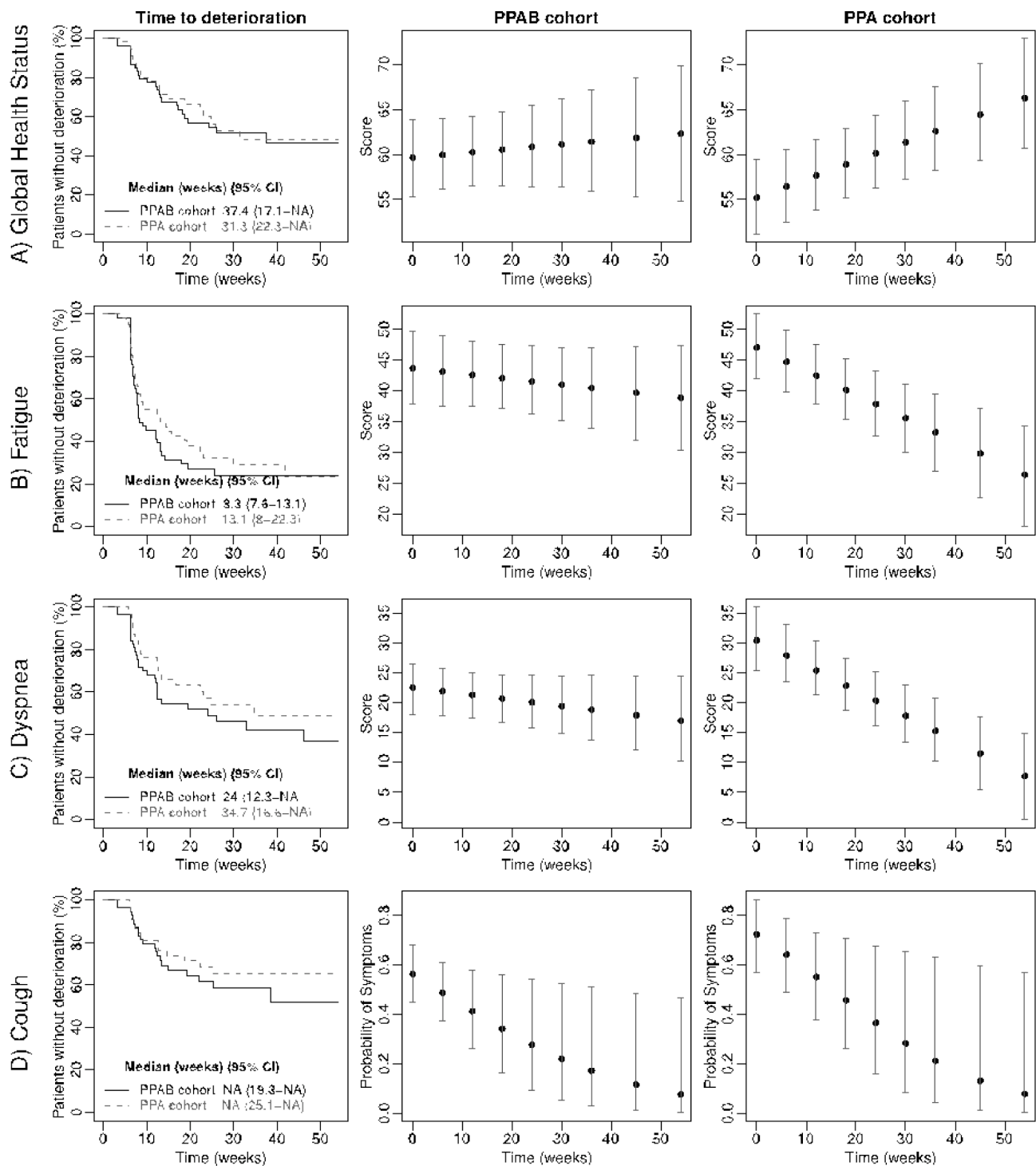


Fig. 1. Time to deterioration and mean change from baseline through 54 weeks in GHS score (A), fatigue (B), dyspnea (C) and cough (D) scores in PPAB cohort and PPA cohort.

week 54, we observed an improvement from baseline for 49.2 % of patients regarding GHS, in fatigue for 50.4 %, in dyspnea for 50.4 % and in cough for 41.4 % of patients. The phase III AURA 3 trial, which validated the superiority of osimertinib over platinum-pemetrexed chemotherapy in patients with confirmed T790M-positive NSCLC that had relapsed after first-line EGFR-TKI therapy, showed that patients treated with chemotherapy after TKI have an improvement in GHS/HRQOL and in physical and functional symptoms: 84 % were improved in cough, 89 % in dyspnea, 100 % in fatigue [29].

This analysis has limitations. First, this is a phase II study with a

limited number of patients, with an open-label design which could influence how patients perceive HRQOL [30,31]. The percentage of patients who completed the PRO questionnaires decreased with time from baseline but completion rate during the whole follow-up is in line with that of other NSCLC clinical trials.

In addition, the EORTC QLQ-C30 and –LC13 were developed before the availability of cancer immunotherapy and, therefore, may miss certain immunotherapy-associated symptoms (eg, rash, pruritus, pneumonitis) that could be experienced with such treatments [32].

With the increasing costs of healthcare, we pay more attention to the

Table 4
Evolution from baseline in GHS and functional symptoms.

	PPAB cohort n (%)	PPA cohort n (%)	Total n (%)
Global Health Status	24 (40.7)24	37 (56.9)17	61 (49.2)41
Amelioration	(40.7)11	(26.2)11	(33.1)22
Deterioration	(18.6)	(16.9)	(17.7)
Stability			
Fatigue	26 (41.3)33	39 (59.1)25	65 (50.4)58
Amelioration	(52.4)4	(37.9)2	(45.0)6
Deterioration	(6.3)	(3)	(4.7)
Stability			
Dyspnea	23 (37.7)26	41 (62.1)14	64 (50.4)40
Amelioration	(42.6)12	(21.2)11	(31.5)23
Deterioration	(19.7)	(16.7)	(18.1)
Stability			
Coughing	24 (38.7)16	29 (43.9)10	53 (41.4)26
Amelioration	(25.8)22	(15.2)27	(20.3)49
Deterioration	(35.5)	(40.9)	(38.3)
Stability			

PPAB: platinum-pemetrexed-atezolizumab-bevacizumab, PPA: platinum-pemetrexed-atezolizumab.

value of new cancer treatments [33]. The European Society for Medical Oncology (ESMO) has developed and validated the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) for grading the magnitude of clinically meaningful benefit [34]. The association of immunotherapy and chemotherapy has been shown to improve response rate and PFS; such a benefit would be scored as 3 of the maximum rating of 5 using the ESMO-MCBS. Because the ESMO-MCBS also emphasizes the effect of new treatments on global HRQOL in incurable cancers, improvement in PROs increases the score to 4. Patient-reported outcomes data, as reported in our study, provide a clear contribution to evaluation of the overall clinical benefit.

5. Conclusion

Combination approach with atezolizumab with or without bevacizumab and platinum-pemetrexed in metastatic *EGFR*-mutated or *ALK/ROS1*-rearranged NSCLC after TKI failure seem to be effective with safety and PRO data which support the positive benefit-risk profile without negative impact on HRQOL and durability of disease symptom control. Combined with efficacy data and manageable safety profile, the PRO data suggest that the tritherapy or the quadritherapy could represent a new option for the second-line treatment of metastatic *EGFR*-mutated or *ALK/ROS1*-rearranged NSCLC after TKI failure.

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Data sharing

The data that support the findings of this study are available upon reasonable request to the corresponding author.

CRedit authorship contribution statement

Lyria Amari: Writing – original draft, Formal analysis, Conceptualization. **Pascale Tomasini:** Writing – review & editing, Investigation, Conceptualization. **Emmanuelle Dantony:** Writing – original draft, Software, Methodology, Conceptualization. **Gaëlle Rousseau-Bussac:** Investigation. **Charles Ricordel:** Investigation. **Laurence Bigay-Game:** Investigation. **Dominique Arpin:** Investigation. **Hugues Morel:** Investigation. **Remi Veillon:** Investigation. **Grégoire Justeau:** Investigation. **Eric Huchot:** Investigation. **Pierre Fournel:** Investigation. **Alain**

Vergnègre: Investigation. **Acya Bizeux:** Investigation. **Fabien Subtil:** Writing – original draft, Supervision, Methodology, Formal analysis. **Bénédicte Clarisse:** Project administration, Methodology, Data curation, Conceptualization. **Chantal Decroisette:** Writing – review & editing, Validation, Investigation. **Christos Chouaid:** Writing – review & editing, Writing – original draft, Validation, Data curation. **Laurent Greillier:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Olivier Bylicki:** Conceptualization, Investigation, Writing – original draft.

Declaration of competing interest

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