

Paclitaxel–bevacizumab combination in advanced non-squamous non-small-cell lung cancer (NSCLC): AVATAX, a retrospective multicentric study

Geoffroy Bilger¹, Anne-Claire Toffart, Marie Darrason, Michaël Duruisseaux, Lucie Ulmer, Pascal Wang, Etienne Giroux Leprieur, Nicolas Girard, Marie Ange Massiani, Paul Bore, Renaud Descourt, Julian Pinsolle, Solene Valery, Isabelle Monnet, Aurélie Swalduz, Claire Tissot, Pierre Fournel, Anne Baranzelli, Alexis B. Cortot and Chantal Decroisette

Abstract

Introduction: Compared with docetaxel, the phase-III trial, ULTIMATE, showed a significant improvement of progression-free survival (PFS) with paclitaxel–bevacizumab combination (PB) as second- or third-line treatment in advanced non-small cell lung cancer (NSCLC). With the increase of immunotherapy treatment in first-line settings, the optimal treatment after first-line failure must be redefined.

Methods: This multicentric retrospective study identified all advanced NSCLC patients treated with PB as second-line therapy and beyond. The main efficacy outcomes assessed were objective response rate (ORR), disease control rate (DCR), PFS, and overall survival (OS). The adverse events were reported according to Common Terminology Criteria for Adverse Events (CTCAE).

Results: From January 2010 to February 2020, 314 patients in 16 centers received the PB combination. Most patients were male (55%), with a median age of 60 years (19–82), 95% had adenocarcinoma, 27% had a performance status ≥ 2 , 45% had brain metastases at the time of inclusion. They mostly received the PB combination either in second (20%) or in third-line (39%), and 28% were treated just after ICI failure. ORR and DCR were 40% and 77%, respectively; median PFS and OS were 5.7 [interquartile range (IQR): 3.2–9.6] and 10.8 [IQR: 5.3–19.6] months, respectively. All grade adverse events concerned 82% of patients, including 53% asthenia and 39% neurotoxicity, and 25% of patients continued monotherapy (mostly with bevacizumab) alone due to toxicity. Median PFS for patients treated after ICI failure (ICI+) was significantly superior compared with those not previously treated with ICI (ICI–): 7.0 [IQR: 4.2–11.0] versus 5.2 [IQR: 2.9–8.8] months, $p=0.01$, without statistically significant difference for OS between these two groups. In multivariate analysis, factors associated with superior PFS were previous ICI treatment and performance status of 0–1. Only a performance status of 0–1 was associated with superior OS.

Conclusion: PB combination as second-line treatment or beyond for advanced non-squamous NSCLC had acceptable toxicity and a clinically relevant efficacy and is an option as salvage treatment for these patients, more particularly after ICI progression.

Keywords: bevacizumab, chemotherapy, immunotherapy, non-small cell lung cancer, NSCLC, paclitaxel

Received: 27 February 2022; revised manuscript accepted: 21 April 2022.

Ther Adv Med Oncol

2022, Vol. 14: 1–16

DOI: 10.1177/
17588359221099399

© The Author(s), 2022.
Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:

Geoffroy Bilger
Centre Hospitalier
Universitaire de Grenoble,
38700 Grenoble, France.
Oncology, Grenoble
University Hospital,
Grenoble, France
bilger.geoffroy@gmail.com

Anne-Claire Toffart
Centre Hospitalier
Universitaire de Grenoble,
Grenoble, France

Oncology, Grenoble
University Hospital,
Grenoble, France

Marie Darrason
Service de Pneumologie
Aigue Spécialisée et
Cancérologie Thoracique,
Hôpital Lyon-Sud, CHU
Lyon, Pierre-Bénite,
France

Department of
Pneumology and Thoracic
Oncology, University
Hospital of Lyon, Pierre-
Bénite, France

Institut de Recherches
Philosophiques de Lyon,
Université Lyon 3, Lyon,
France

Lyon Institute of
Philosophical Research,
Lyon 3 University, Lyon,
France

Michaël Duruisseaux
URCOT, Institut de
Cancérologie des Hospices
Civils de Lyon, Lyon,
France

Lucie Ulmer
Alexis B. Cortot
Thoracic Oncology
Department, Hospital
Albert Calmette, Lille,
France

Pascal Wang
Solene Valery
Thoracic Oncology, APHP,
Paris, France

Etienne Giroux Leprieur
APHP Hospital Ambroise
Pare and Université
Paris-Saclay, Boulogne-
Billancourt, France

Nicolas Girard

Institut Curie, Paris,
France

Marie Ange Massiani

Oncology Hospital Rene
Huguenin, Saint-Cloud,
France

Paul Bore

Renaud Descourt
Thoracic Oncology
Department, Hospital
Morvan, Brest, France

Julian Pinsolle

Anne Baranzelli
Unité de pneumologie,
Centre Hospitalier
Métropole Savoie,
Chambéry, France

Isabelle Monnet

Pneumology Department,
CHI Creteil, Creteil, France

Aurélien Swalduz

Department of Thoracic
Oncology, Centre Léon
Bérard, Lyon, France

Claire Tissot

Pneumology Department,
Institut de Cancérologie de
la Loire Lucien Neuwirth,
Saint-Priest-en-Jarez,
France

Pierre Fournel

Service d'Oncologie
Médicale, Institut de
Cancérologie, CHU de
Saint-Etienne, Saint-
Etienne Cedex 2, France

Chantal Decroisette

CH Annecy Genevois,
Epagny Metz-Tessy,
France

Highlights

- This real-life study has evaluated paclitaxel–bevacizumab (PB) combination in pretreated advanced non-squamous non-small cell lung cancer (NSCLC).
- The results confirmed the efficiency of PB with an objective response rate (ORR) of 40% and a median progression-free survival (PFS) of 5.7 months
- PB was particularly efficient following progression on immune checkpoint inhibitors.

Introduction

Lung cancer has become the most widespread cancer and the main cause of cancer deaths worldwide, accounting for nearly a quarter of all cancer deaths, with the most common histological form being non-squamous non-small cell lung cancer (NSCLC).¹ Despite recent progress and an increase in the number of patients who are candidates for second-line treatment or more,² prognostic remains poor.¹

Until 2015 when immunotherapy was implemented in NSCLC, the second-line reference chemotherapies were docetaxel or pemetrexed monotherapy yielding poor results with an objective response rate (ORR) between 5% and 10%, median progression-free survival (PFS) of 1.5–3 months, and median overall survival (OS) of 4.6–12.8 months.^{3–6} Alternative strategies combining mono-chemotherapy with anti-angiogenic agents have been studied to improve treatment beyond failure of platinum-based chemotherapy. Following promising results in phase-II and several retrospective studies,^{7–9} phase-III studies were conducted with the association of docetaxel with ramucirumab¹⁰ and nintedanib,¹¹ leading to a European authorization for these combinations.

The combination of paclitaxel and bevacizumab (PB) was evaluated in three retrospective studies with limited numbers of patients but with encouraging results. The response rate ranged from 33–44%, median PFS from 4.6–6.4 months, and median OS reported in one study was 9.6 months.^{12–14} Based on these promising results, the phase-III trial IFCT-1103 ULTIMATE evaluated the efficacy of the PB combination compared with standard docetaxel as second- or third-line treatment in 166 patients with advanced non-squamous NSCLC.¹⁵ Compared with docetaxel, PB combination yielded a significant increase of PFS (5.4 *versus* 3.9 months, $p = 0.005$)

without difference in OS, although this may be due to the crossover that was allowed in this study. Adverse events were different between arms with an increase in hematological toxicity with docetaxel compared with PB. These results supported the use of the PB doublet in second line and beyond, and since 2016 it has been included as an option for the management of advanced non-squamous NSCLC in French guidelines.¹⁶

Among recent therapeutic advances, immunotherapy has been a turning point in the management of NSCLC especially more recently in first-line treatment. As monotherapy for patients with a PDL1 tumor expression $\geq 50\%$ or in combination with chemotherapy, anti-PD1 agents are now part of the first line for most patients.^{17,18} Although the first-line treatment has changed, the options for second-line treatment (for those who received chemo-immunotherapy combination) or third-line treatment (for those who received immunotherapy then platinum-based chemotherapy) remain the same, while pursuit or rechallenge with immunotherapy has not yet proven efficacy.^{19,20} Thus, chemotherapy is still the standard of care in this setting and the PB doublet could be an option.

While data on the efficacy of chemotherapy administered after progression under immunotherapy seemed particularly interesting,^{21–23} the efficacy of the combination of chemotherapy (docetaxel) with an anti-angiogenic molecule (nintedanib or ramucirumab) in post-immunotherapy setting has been the subject of a few studies.^{24–32}

The objective of this study was to evaluate the efficacy and toxicity of the PB combination in clinical practice in second line and beyond in advanced non-squamous NSCLC.

Methods

Study design and patients

We conducted a multicenter retrospective study among 16 hospitals including all advanced NSCLC patients treated with PB as second-line therapy and beyond in routine practice, between January 2010 and January 2020. Patients should have received at least one dose of the combination. Patients who received PB with another treatment drug were excluded.

The primary objective was to describe the median real-world PFS (rwPFS) in patients treated by PB. The secondary objectives included comparison of PFS between patients who previously received immunotherapy and those who did not, objective response rate (ORR) according to RECIST 1.1, disease control rate (DCR), OS, and toxicity. ICI+ subgroup was defined by patients treated with PB immediately after progression under immune checkpoint inhibitors (ICI) therapy, regardless of the line of treatment with ICI.

ICI- subgroup was defined by patients treated with PB without previous ICI therapy just before. Those patients could have received ICI in their previous line of treatment, but not at the line just before PB.

As one of our main objectives was to describe the efficacy of ICI followed immediately by PB, and as we still do not know the accurate duration of the effect of ICI after its discontinuation, this exact sequence of treatment was important to constitute a homogeneous group of patients to avoid bias in the analyses.

Data collection

Patients' electronic medical records, in each center, were reviewed for collecting data. Details are provided in the flow chart.

At the time of PB prescription, variables related to characteristics of patients, lung cancer (age, ECOG-PS, histology subtype, metastatic site), and previous lines of treatment were recorded. Line of treatment of PB combination, dosing of both drugs, number of cycles, toxicity, and reason for discontinuing were recorded.

Objective response criteria, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), were evaluated according to the RECIST 1.1 guidelines (very few according to RECIST 1.0). Similarly, DCR was calculated by adding CR, PR, and SD. The rhythm of the scanner's evaluation varied from center to center. Tolerance was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, assessed by reviewing the patients' medical histories and laboratory records.

Statistical analysis

Data were expressed as number (and percentage) for qualitative variables and median (and (IQR)

for quantitative variables and were using chi-square (or Fisher-exact) or Mann-Whitney tests, as appropriate.

The rwPFS was defined as the time from the first dose of treatment with PB to the first occurrence of disease progression or death from any cause during the study. The date of cancer progression was defined as the date of the first source evidence for progression referenced by the clinician – for example, radiology report, pathology, or exam – or the clinician note date when no evidence sources were documented. Similarly, OS was calculated from the start of PB therapy to death from any cause. The date of data cutoff was 1 August 2020. Survival curves were obtained using the Kaplan-Meier method and compared using log-rank testing. Sensitivity analyses were performed in the following subgroups of patients: patients previously treated with immunotherapy (ICI+), patients with oncogenic addiction and patients previously treated with taxanes or anti-angiogenic agents.

Univariate and multivariate analyses for survival outcomes were analyzed using the Cox proportional hazards model. All clinically significant variables were entered in the multivariate model if they were not collinear. Missing data were indicated in the population description and imputed elsewhere by the variable median value (for quantitative variables) or the most common level (for qualitative variables) in the Cox models.

All tests were two-sided, and p -values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient's characteristics at the initiation of PB

From the 16 participating centers, 314 non-squamous advanced NSCLC patients were included. Patients' characteristics at the time of PB initiation are listed in Table 1.

The median age was 60 years (range 19–82); 141 (45%) were male; 219 (72%) had an ECOG PS score of 0–1; 63 (21%) patients received the combination as second-line treatment, 124 (39%) patients as third-line, and 127 (40%) patients as fourth-line and above. Ninety-eight patients (31%) harbored a *KRAS* mutation and 46 (15%)

patients had an *EGFR* mutation (29 had an activating mutation, that is, deletion in exon 19 or L858R in exon 21; 13 had another known activating or non-activating mutation; and 4 had an *EGFR* mutation with no details found). At the time of initiation of the PB, 140 (45%) patients had brain metastasis and 82 (26%) liver metastasis (Table 1).

The median duration of follow-up since initiation of PB therapy was 15.5 months (IQR: 25–75%, 9.3–30.5). At the end of the follow-up period, 50 (16%) patients were alive and 3 (1%) patients were still treated with PB.

PB administration

The treatment regimen received was in the majority of cases paclitaxel (90 mg/m² on days 1, 8, and 15) and bevacizumab (10 mg/kg on days 1 and 15), of each 28-day cycle (Appendix 1). The median duration of paclitaxel was 3.5 months (IQR: 25–75%, 2.1–5.3) and the median duration of bevacizumab was 4.2 months (IQR: 25–75%, 2.1–8.1) as shown in Appendix 2.

In their previous lines of treatment, 97 (31%) patients were already treated with taxane-containing chemotherapy, and 91 (29%) patients already received bevacizumab as shown in Table 1. Also, 114 (36%) patients received ICI therapy in their previous lines of treatment. Among them, 88 (28%) patients were treated by PB immediately after ICI progression (ICI+ subgroup): 2 (1%) patients in second line after ICI in first line (ICI monotherapy), 62 (70%) patients in third line after ICI in second line (all ICI monotherapy), 25 (28%) patients in fourth line or more after ICI immediately before (all ICI monotherapy). The median duration of ICI treatment before PB (ICI+ subgroup) was 4.2 months (range 0.5–19) and the median duration between the last infusion of ICI and the first infusion of PB was 27.6 days (range 1–150). Among the *EGFR*+ mut population with activating mutation, all but one received targeted anti-*EGFR* therapy, and all were treated with chemotherapy other than PB in their different treatment lines, each time before PB. Four *EGFR*mut+ patients were in the ICI+ group, that is, treated with ICI just before PB.

Data on possible treatment with radiotherapy were not available.

Efficacy

For the 314 patients included, the median PFS was 5.7 months (IQR: 25–75% 3.2–9.6), 7.0 months (IQR: 25–75% 4.2–11.0) in the ICI+ group versus 5.2 months (IQR 25–75% 2.9–8.8) in the ICI– group, *p*-value=0.01, and hazard ratio (HR)=0.74 [95% confidence interval (CI): 0.56–0.94]. Median PFS was 5.2 months (IQR: 2.9–9.5) for patients harboring *EGFR* pathway mutation, 5.5 months (IQR: 3.3–9.7) for patients previously treated with taxane-based chemotherapy, and 5.3 months (IQR: 2.7–8.7) for patients previously treated with bevacizumab (Figures 1 and 2).

The median OS was 10.8 months (IQR: 25–75% 5.3–19.6), 13.0 months (IQR: 25–75% 6.5–25.3) in the ICI+ group and 10.3 months in the ICI– group (IQR: 25–75% 4.9–18.0), *p*-value=0.06. In subgroup analysis, median OS was 12.8 months (IQR: 5.6–19.5) for patients harboring *EGFR* pathway mutation, 10.3 months (IQR: 5.5–21.3) for patients previously treated with taxane-based chemotherapy, and 11.6 months (IQR: 5.9–20.2) for patients previously treated with bevacizumab (Figures 1 and 2).

On the 308 of the 314 evaluable patients, 122 (40%) achieved a PR, 115 (37%) had SD, and 71 (23%) progressed at first follow-up. None of the patients had a CR. The ORR was, therefore, 40% and DCR 77%. In the subgroup of ICI+ patients, the ORR was 51% versus 35% in the ICI– group (225/314) as shown in Table 2.

A total of 193 (63%) patients were treated with subsequent treatment after progression with PB (8 missing data): 51% (*n*=97) with immunotherapy, 26% (*n*=49) with PB rechallenge, 23% (*n*=45) with chemotherapy, and 1% (*n*=1) with tyrosine kinase inhibitor.

Multivariate analysis demonstrated that the only independent factors positively impacting PFS were ICI+ treatment and an ECOG PS score of 0–1. For the OS, the only independent factor was an ECOG PS score of 0–1 (Tables 3 and 4).

Duration of treatment and toxicity

A total of 257 (82%) patients experienced adverse events of all grades during the administration of PB.

Table 1. Patients' characteristics at the beginning of paclitaxel–bevacizumab (PB).

	Total patients (n = 314)	ICI–, 226 (72%)	ICI+, 88 (28%)	p-value
Patients' characteristics				
Age, years	60 [54–68]	59 [54–67]	62 [56–69]	0.08
Male sex	141 (55%)	132 (58)	41 (47)	0.06
Smoker (MD=8)	249 (81%)	175 (80)	74 (86)	0.19
ECOG PS score (MD= 12)				0.13
0	63 (21%)	44 (20)	19 (22)	
1	156 (52%)	105 (49)	51 (59)	
≥2	83 (27%)	66 (31)	17 (20)	
Cancer characteristics				
Histology				1
Adenocarcinoma	299 (95%)	215 (95)	84 (95)	
Others	15 (5%)	22 (5)	4 (5)	
Brain metastasis	140 (45%)	107 (47)	33 (38)	0.12
Molecular status				<10 ⁻⁴
<i>KRAS</i> mutation	98 (31%)	58 (26)	40 (45)	
<i>EGFR</i> mutation	46 (15%)	42 (19)	4 (5)	
<i>ALK</i> rearrangement	9 (3%)	7 (3)	1 (2)	
Wild type	161 (51%)	119 (53)	42 (48)	
Treatment characteristics				
Treatment previously received				
Taxane-based chemotherapy	97 (31%)	89 (39)	8 (9)	<10 ⁻⁴
Bevacizumab	91 (29%)	61 (27)	30 (34)	0.21
Line of treatment of PB combination				
Second line	63 (21%)	62 (27)	1 (1)	
Third line	124 (39%)	62 (27)	62 (70)	
Fourth line	66 (21%)	48 (22)	17 (19)	
Fifth line or more	61 (19%)	53 (23)	8 (9)	
<p><i>ALK</i>, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; <i>EGFR</i>, epidermal growth factor receptor; ICI, immune checkpoint inhibitors; MD, missing data; PB, paclitaxel and bevacizumab.</p> <p>ICI+ subgroup is defined by patients treated with PB immediately after progression under immune checkpoint inhibitors (ICI) therapy.</p> <p>ICI– subgroup is defined by patients treated with PB without previous ICI therapy just before.</p> <p>Qualitative variables are expressed as n (%) and quantitative variables as median (IQR: 25–75%).</p>				

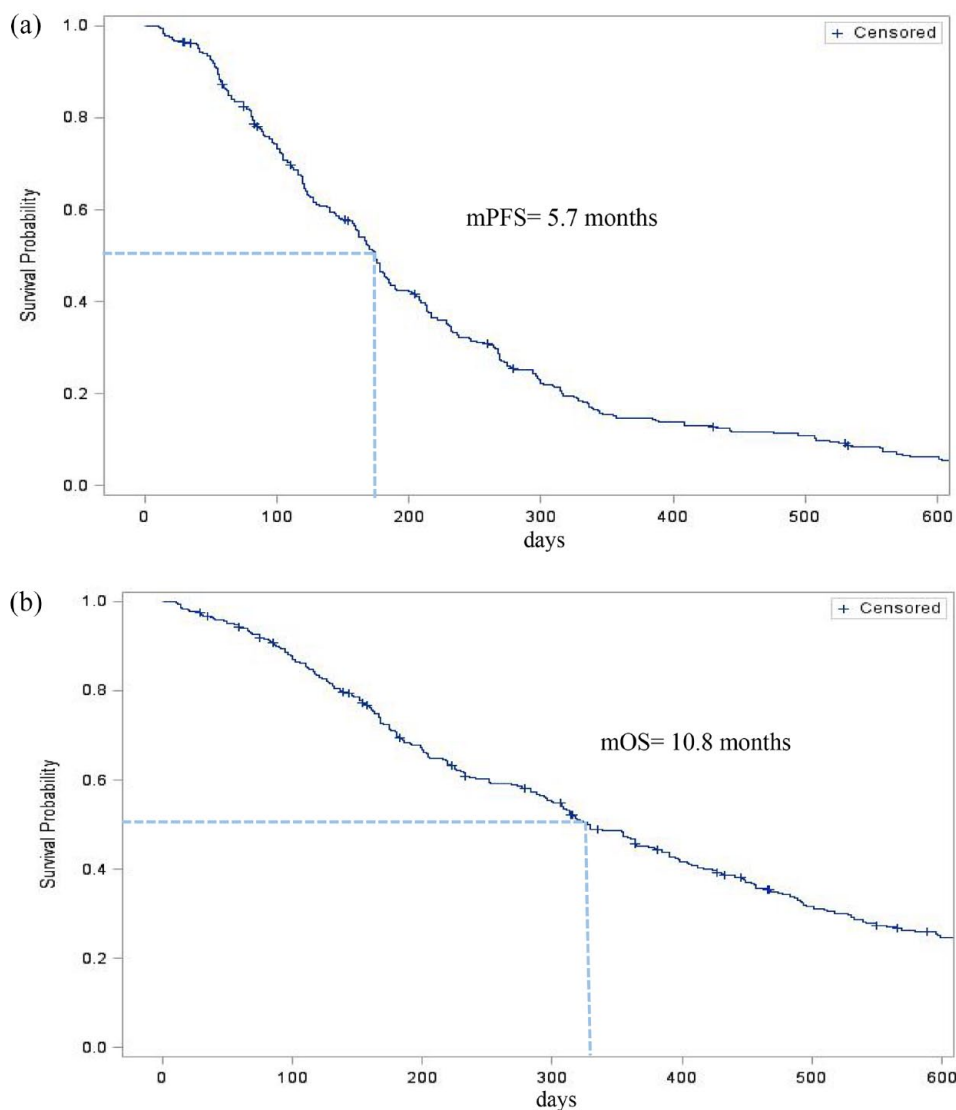


Figure 1. Kaplan–Meier estimates of the (a) progression-free survival (PFS) and (b) overall survival (OS) of patients with advanced non-small cell lung cancer receiving paclitaxel–bevacizumab treatment.

The most common adverse events were asthenia (53%), neurotoxicity (39%), gastrointestinal toxicity (21%), hematotoxicity (18%), proteinuria (17%), bleeding events (15%), hypertension (11%), and ungual toxicity (9%) as shown in Table 5.

One hundred and four patients (33%) discontinued the combination for monotherapy with either molecule from whom 77 patients (25%) due to toxicity: paclitaxel was discontinued in 30 (10%) patients due to neurological toxicity, bevacizumab in 11 (4%) patients due to toxicity, particularly hemorrhagic toxicity (Appendix 2).

No treatment-related deaths were observed.

Discussion

In this large real-world analysis of non-squamous advanced NSCLC patients treated with the PB combination, median PFS was 5.7 months and ORR was 40%. These results compare favorably with regimens of chemotherapy usually used following failure of platinum-based chemotherapy,^{3–6} in France being docetaxel or pemetrexed. The results of AVATAX are in line with those found in the phase-III ULTIMATE,¹⁵ REVEL¹⁰ and LUME-Lung 1¹¹ studies. However, in contrast to the above-mentioned studies, our population better reflects real-world practice, with 27% of patients with an ECOG PS score ≥ 2 , and 40% treated in fourth line or more. The reported

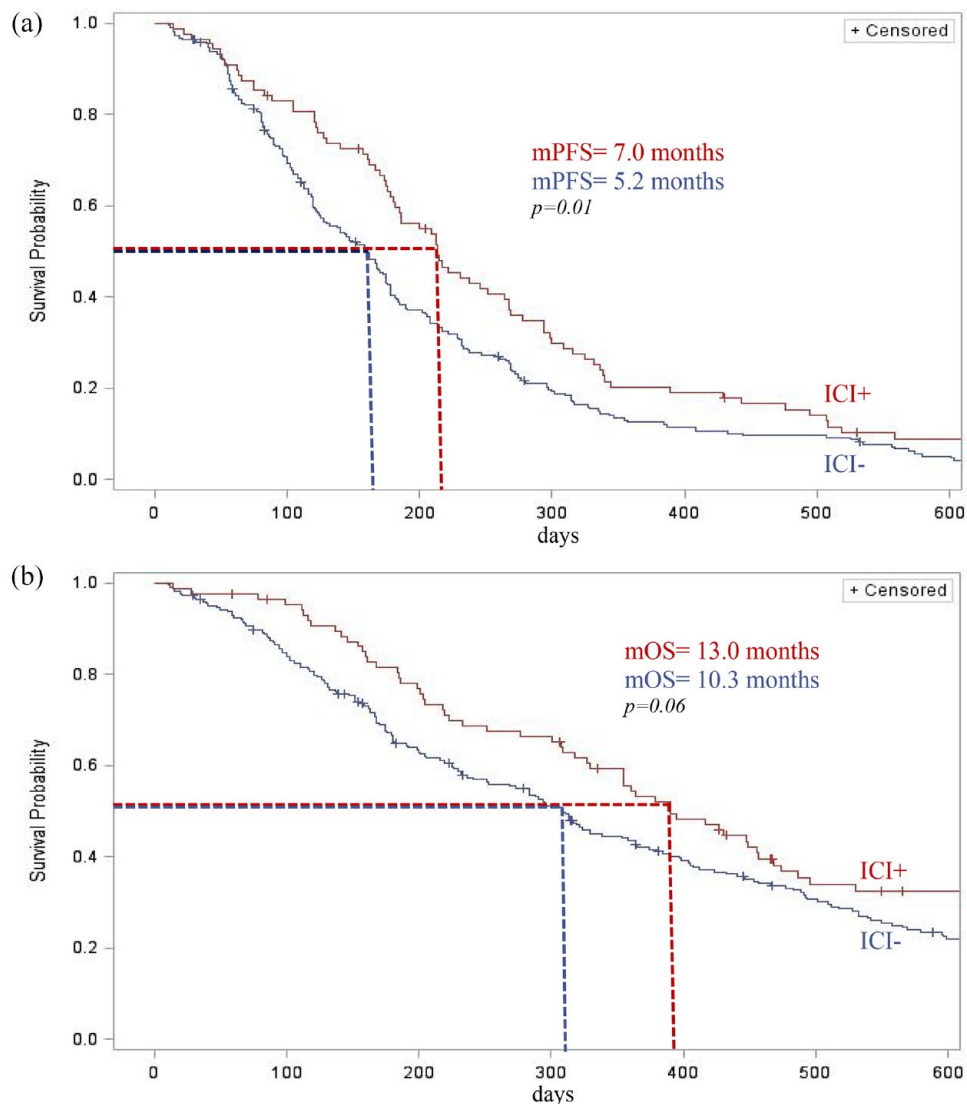


Figure 2. Kaplan–Meier estimates of the (a) progression-free survival (PFS) and (b) overall survival (OS) of patients according to prior treatment with immunotherapy (ICI).

toxicities are also very acceptable and consistent with the known safety profile of this combination, the majority of treatment discontinuation being related to fatigue or limiting neurotoxicity. Adverse events were, however, less frequent and severe than in the studies that evaluated the association docetaxel and nintedanib or ramucirumab in the same indication, which may be due to the retrospective design that may lead to underreporting of adverse events.^{11,12,24–32} Interestingly, we found that patients previously treated with bevacizumab still benefit from PB combination, in contrast with previous results of the ULTIMATE study.¹⁵ However, bevacizumab tends to be less and less given in first-line regimens, as most chemo-immunotherapy regimens

do not include it. Another interesting finding from our results is the effectiveness of the PB combination in patients with *EGFR* mutation.

Nowadays, immunotherapy can be used in all lines of treatment in advanced NSCLC and several retrospective studies reported an improved efficacy of rescue chemotherapy after failure of ICI.^{21–23} In published studies, the combination of docetaxel and an antiangiogenic agent as salvage treatment directly after ICI yielded an ORR of 18–60%, a DCR of 80–90%, a median PFS of 3.2–6.8 months and a median OS of 8.8–20.9 months.^{24–32} In line with these results, our study shows a longer PFS on PB for patients who previously received immunotherapy compared with those who did not.

Table 2. Efficacy of the paclitaxel–bevacizumab combination.

Patients evaluable for therapeutic response	N= 314	ICI– 226 (72%)	ICI+ 88 (28%)	p-value
For patients with evaluable response	308			
Best overall response				0.03
Partial response	122 (40%)	77 (35)	45 (51)	
Stable disease	115 (37%)	88 (40)	27 (31)	
Progressive disease	71 (23%)	55 (25)	16 (18)	
Overall response rate	122 (40%)	77 (35)	45 (51)	9×10^{-3}
Disease control rate	237 (77%)	165 (75)	72 (82)	0.20

ICI, immune checkpoint inhibitors.
 ICI+ subgroup is defined by patients treated with PB immediately after progression under immune checkpoint inhibitors (ICI) therapy.
 ICI– subgroup is defined by patients treated with PB without previous ICI therapy just before.
 Qualitative variables are expressed as n (%).
 Of the 314 patients included, 308 were evaluable for therapeutic response: 3 patients stopped treatment early without prior evaluation due to infectious complications, 2 patients were lost to follow-up without prior evaluation, and 1 patient died early from an intercurrent event without prior evaluation.

The hypothesis of possible chemosensitization after prior exposure to immunotherapy is supported by synergistic activity in both preclinical and clinical models.^{33,34} Also, mechanisms positively enhancing the immunomodulatory effect of chemotherapy include the elimination of suppressor myeloid cells (MDSCs) and regulatory T cells (Tregs), increased antigen-specific immune response, improved antigen presentation, increased death receptors in tumor cells, and increased PD1–PDL1 expression.^{35,36} Finally, it has also been reported that the therapeutic level of anti-PD1/PDL1 immune checkpoint inhibitors was maintained during chemotherapy administration due to the long half-life of the antibody,³⁷ producing a residual effect on immune memory cells, which could be stimulated by successive chemotherapy with its immunological effects. Although the positive effects of PD1/PDL1 inhibitors can affect the initial response to salvage treatment, these effects are likely not persistent.

Parallel to all this, it is known that antiangiogenic agents stimulate the immune system. The VEGF plays a crucial role in modulating the tumor immune microenvironment with an immunosuppressive role. Inhibition of VEGF significantly increases infiltration of CD4-positive and CD8-positive T cells and reduces the number of Tregs and MDSCs in tumor tissue, facilitates dendritic cells maturation, and reduces tumoral expression

of PDL1.^{38–40} Some recent studies indicated that ICI resistance could be alleviated with a combination of ICI with anti-angiogenesis treatment by reprogramming the tumor immune microenvironment that was the cause of immunotherapy failure. Interestingly, Tozuka *et al.*³¹ showed in patients with advanced NSCLC that the addition of ramucirumab enhanced docetaxel efficacy only in patients previously treated with ICI, with no difference in the case of absence of ICI pretreatment, suggesting a real synergy between antiangiogenic agents and immunotherapy.

With the growing role of immunotherapy and antiangiogenics agents from the first line in advanced NSCLC, one important question remains the optimal treatment sequencing strategies and the choice of the optimal treatment when initial therapy failed.

A growing body of evidence suggests the importance of the use of ICI and antiangiogenic therapy in the therapeutic pathway, leading to the best chance of survival.⁴¹ Since the first current treatment line has changed compared with when studies such as ULTIMATE, LUME-Lung 1, and REVEL were designed, the place of the PB combination remains to be defined in the new treatment sequence used nowadays. To date, there have been no prospective, randomized controlled trials demonstrating the optimal

Table 3. Univariate and multivariate analysis of factors associated with PFS from the initiation of paclitaxel–bevacizumab therapy.

	Median PFS (IQR, 25–75%)	Univariate analysis		Multivariate analysis	
	in months	HR [95% CI]	<i>p</i> -value	HR [95% CI]	<i>p</i> -value
Patients' characteristics					
Sex			0.72		0.89
Male (<i>n</i> = 141)	5.8 (3.4–9.7)	1		1	
Female (<i>n</i> = 173)	5.4 (2.8–8.9)	10.43 [0.83–1.31]		1.02 [0.80–1.30]	
Age			0.71		0.43
< 68 years (<i>n</i> = 220)	5.7 (0.9–9.6)	1		1	
≥ 68 years (<i>n</i> = 94)	5.8 (3.9–8.6)	0.95 [0.73–1.23]		1.12 [0.84–1.49]	
ECOG PS score			10 ⁻³		5 × 10 ⁻³
0 (<i>n</i> = 63)	5.8 (3.6–9.0)	1		1	
1 (<i>n</i> = 156)	6.5 (3.9–10.1)	0.99 [0.73–1.33]		1.01 [0.74–1.39]	
≥ 2 (<i>n</i> = 83)	3.8 (1.8–7.6)	1.625 [1.153–2.291]		1.58 [1.12–2.24]	
Cancer characteristics					
Histology			0.71	–	
Adenocarcinoma	5.8 (3.2–9.2)	1			
Other	4.3 (2.9–12.7)	1.10 [0.66–1.86]			
Brain metastasis			0.09		0.23
No	6.0 (3.7–10.1)	1		1	
Yes	5.0 (2.8–8.7)	1.22 [0.97–1.54]		1.16 [0.91–1.49]	
Molecular status			0.05		0.02
Wild type	6.5 (3.4–10.3)	1		1	
<i>KRAS</i> mutation	5.3 (2.8–8.6)	1.62 [0.96–1.80]		1.47 [1.12–1.94]	
<i>EGFR/ALK</i>	5.2 (2.9–8.8)	1.34 [1.03–1.94]		1.23 [0.90–1.69]	
Anticancer treatment characteristics					
Line of treatment of the PB combination			0.82		0.86
Second line	5.4 (2.6–9.9)	1		1	
Third line	5.8 (3.4–9.7)	0.94 [0.69–1.29]		1.15 [0.81–1.64]	
Fourth line	5.7 (2.9–8.7)	1.10 [0.77–1.57]		1.11 [0.77–1.61]	
Fifth line or more	6 (3.5–8.9)	0.99 [0.69–1.42]		1.03 [0.71–1.48]	
Treatment previously received					
Taxane			0.67	–	

(Continued)

Table 3. (Continued)

	Median PFS (IQR, 25–75%)	Univariate analysis		Multivariate analysis	
	in months	HR [95% CI]	p-value	HR [95% CI]	p-value
No	5.7 (3.1–8.8)	1			
Yes	5.5 (3.3–9.7)	0.95 [0.74–1.21]			
Bevacizumab			0.53	–	
No	5.8 (3.3–9.7)	1			
Yes	5.3 (2.7–8.7)	1.084 [0.84–1.40]			
ICI			0.01		6×10^{-3}
No	5.2 (2.8–8.8)	1		1	
Yes	7.0 (4.2–11.0)	0.74 [0.56–0.94]		0.65 [0.48–0.89]	

ALK, anaplastic lymphoma kinase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; ICI, immune checkpoint inhibitors; IQR, interquartile range; PB, paclitaxel–bevacizumab; PFS, progression-free survival.
ICI+ subgroup is defined by patients treated with PB immediately after progression under immune checkpoint inhibitors (ICI) therapy.
ICI– subgroup is defined by patients treated with PB without previous ICI therapy just before.

Table 4. Univariate and multivariate analysis of factors associated with OS from the initiation of paclitaxel–bevacizumab therapy.

	Median OS (IQR, 25–75%)	Univariate analysis		Multivariate analysis	
	in months	HR [95% CI]	p-value	HR [95% CI]	p-value
Patients' characteristics					
Sex			0.50		0.47
Male	11.6 (5.5–19.5)	1		1	
Female	10.4 (5.3–20.1)	0.92 [0.72–1.17]		0.91 [0.70–1.18]	
Age			0.73		0.28
<68 years	11.1 (5.3–19.5)	1		1	
≥68 years	10.4 (5.5–21.1)	1.05 [0.90–1.38]		1.17 [0.88–1.57]	
ECOG PS score			<10 ⁻⁴		<10 ⁻⁴
0	13.0 (6.3–24.2)	1		1	
1	12.6 (6.6–23.2)	1.17 [0.84–1.63]		1.22 [0.87–1.71]	
≥2	6.1 (2.8–15.0)			2.14 [1.48–3.10]	
Cancer characteristics					
Histology			0.90	–	
Adenocarcinoma	10.8 (5.3–19.5)	1			
Other	11.9 (5.5–24.3)	0.96 [0.54–1.72]			
Brain metastasis			0.05		0.04

(Continued)

Table 4. (Continued)

	Median OS (IQR, 25–75%)	Univariate analysis		Multivariate analysis	
	in months	HR [95% CI]	<i>p</i> -value	HR [95% CI]	<i>p</i> -value
No	12.0 (5.5–22.6)	1		1	
Yes	9.7 (5.2–16.7)	1.27 [1.00–1.62]		1.31 [1.00–1.71]	
Molecular status			0.21		0.02
Wild type	11.6 (5.3–23.2)	1		1	
<i>KRAS</i> mutation	9.6 (5.3–15.0)	1.28 [0.97–1.69]		1.49 [1.11–1.98]	
<i>EGFR/ALK</i>	12.8 (5.6–19.5)	1.11 [0.79–1.54]		1.01 [0.74–1.42]	
Anticancer treatment characteristics					
Line of treatment of the PB combination			0.92		0.95
Second line	10.1 (4.5–21.5)	1		1	
Third line	11.8 (5.3–21.1)	0.92 [0.66–1.28]		1.11 [0.76–1.60]	
Fourth line	10.4 (4.9–17.8)	1.02 [0.71–1.48]		1.02 [0.69–1.50]	
Fifth line or more	10.4 (5.9–17.4)	0.96 [0.66–1.40]		1.07 [0.72–1.57]	
Treatment previously received					
Taxane			0.57	–	
No	11.6 (5.5–21.3)	1			
Yes	10.3 (5.1–18.0)	1.08 [0.83–1.40]			
Bevacizumab			0.55	–	
No	10.6 (5.3–19.6)	1			
Yes	11.6 (5.9–20.2)	0.92 [0.70–1.21]			
ICI			0.03		0.02
No	10.1 (4.9–18.3)	1		1	
Yes	12.8 (6.6–25.7)	0.74 [0.56–0.97]		0.68 [0.49–0.94]	

ALK, anaplastic lymphoma kinase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; ICI, immune checkpoint inhibitors; IQR, interquartile range; OS, overall survival; PB, paclitaxel and bevacizumab.
ICI+ subgroup is defined by patients treated with PB immediately after progression under immune checkpoint inhibitors (ICI) therapy.
ICI- subgroup is defined by patients treated with PB without previous ICI therapy just before.

treatment choice for patients with advanced NSCLC following failure of ICI treatment. Thus, analyses of real-world data from clinical practice are essential to help physicians' choices. While pursuit or rechallenge with immunotherapy has not yet proved efficacy,^{19,20} our results suggest the efficacy of the PB combination following failure of immunotherapy.

Our study has several limitations. First, the design is retrospective, with possibly some underreporting of potential side effects and a lack of central review of the radiological response. Second, patients treated with PB in the ICI+ group were mostly treated in third-line therapy after immunotherapy failure ($n = 62/88$) and, therefore, may have a better clinical outcome compared with the

Table 5. Tolerance of the paclitaxel–bevacizumab combination.

	Total patients (n=314)
Adverse events of any grade	257 (82%)
Asthenia	165 (53%)
Neurological disorders	121 (39%)
Gastrointestinal disorders	66 (21%)
Blood disorders	55 (18%)
Proteinuria	52 (17%)
Bleeding events	48 (15%)
Hypertension	33 (11%)
Ungueal disorders	28 (9%)
Qualitative variables are expressed as n (%).	

ICI– group who received PB later ($n=101/226$ treated with PB in fourth line or more). Our results with PB treatment should be interpreted with caution in patients treated in first line with immunotherapy alone as this population was not represented in our study. Fourth, we cannot exclude that some patients in the ICI+ group were treated with PB after ICI cessation for another reason that progression, for example due to toxicity, even if it represents a minority of the case. Finally, as the treatment sequence studied in our cohort was PB following ICI monotherapy, effectiveness after combination ICI and chemotherapy today use in first-line remains unclear.

However, these observations supported that immunotherapy followed by PB is a promising sequential strategy, and further studies are warranted to evaluate our observations. In the case of progression following ICI therapy or combination of ICI chemotherapy, patients should however be encouraged to participate in clinical trials evaluating novel agents.

Conclusion

PB combination in patients with advanced non-squamous NSCLC in second line and beyond was efficient and well-tolerated. Prospective trials are needed to address the question of the best chemotherapy association after first-line ICI combined or not with chemotherapy.

Ethics approval and consent to participate

Ethical approval was obtained on 9 October 2019 (Observational Research Protocol Review Committee) of the French Society of Pneumology (SPLF), [Institutional Review Board (IRB) CEPRO 2019-033]. An information letter was sent to each living patient providing him the opportunity to refuse study participation, as per French law.

Author contribution(s)

Geoffroy Bilger: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Anne-Claire Toffart: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Supervision; Validation; Visualization; Writing – review & editing.

Marie Darrason: Data curation; Formal analysis; Investigation; Writing – review & editing.

Michaël Duruisseaux: Data curation; Investigation; Writing – review & editing.

Lucie Ulmer: Data curation; Investigation; Writing – review & editing.

Pascal Wang: Data curation; Investigation; Writing – review & editing.

Etienne Giroux Leprieur: Data curation; Investigation; Project administration; Supervision; Writing – review & editing.

Nicolas Girard: Data curation; Investigation; Project administration; Supervision; Writing – review & editing.

Marie Ange Massiani: Data curation; Investigation; Writing – review & editing.

Paul Bore: Data curation; Formal analysis; Investigation; Writing – review & editing.

Renaud Descourt: Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision; Writing – review & editing.

Julian Pinsolle: Data curation; Investigation; Writing – review & editing.

Solene Valery: Data curation; Formal analysis; Investigation; Writing – review & editing.

Isabelle Monnet: Data curation; Formal analysis; Investigation; Writing – review & editing.

Aurélié Swalduz: Data curation; Investigation; Writing – review & editing.

Claire Tissot: Data curation; Investigation; Writing – review & editing.

Pierre Fournel: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing – review & editing.

Anne Baranzelli: Data curation; Investigation; Writing – review & editing.

Alexis B. Cortot: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – review & editing.

Chantal Decroisette: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft.

ORCID iD

Geoffroy Bilger  <https://orcid.org/0000-0001-6811-0941>

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

- de Groot PM, Wu CC, Carter BW, *et al.* The epidemiology of lung cancer. *Transl Lung Cancer Res* 2018; 7: 220–233.
- Davies J, Patel M, Gridelli C, *et al.* Real-world treatment patterns for patients receiving second-line and third-line treatment for advanced non-small cell lung cancer: a systematic review of recently published studies. *PLoS ONE* 2017; 12: e0175679.
- Crino L, Mosconi AM, Scagliotti G, *et al.* Gemcitabine as second-line treatment for advanced non-small cell lung cancer: a phase II trial. *J Clin Oncol* 1999; 17: 2081–2085.
- Shepherd FA, Dancey J, Ramlau R, *et al.* Prospective randomized trial of docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; 18: 2095–2103.
- Hanna N, Shepherd FA, Fossella FV, *et al.* Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; 22: 1589–1597.
- Kim ES, Hirsh V, Mok T, *et al.* Gefitinib versus docetaxel in previously treated non-small cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008; 372: 1809–1818.
- Herbst RS, O'Neill VJ, Fehrenbacher L, *et al.* Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer. *J Clin Oncol* 2007; 25: 4743–4750.
- Adjei AA, Mandrekar SJ, Dy GK, *et al.* Phase II trial of pemetrexed plus bevacizumab for second-line therapy of patients with advanced non-small cell lung cancer: NCCTG and SWOG study N0426. *Clin Oncol* 2010; 28: 614–619.
- Hu B, Zhou X, Liu Y, *et al.* Comparison of chemotherapy plus bevacizumab vs. chemotherapy alone as third-line treatment or beyond for advanced non-small cell lung cancer: a propensity score-matched analysis. *Oncol Lett* 2018; 15: 5671–5679.
- Garon EB, Ciuleanu T-E, Arrieta O, *et al.* Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014; 384: 665–673.
- Reck M, Kaiser R, Mellemegaard A, *et al.* Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol* 2014; 15: 143–155.
- Le Moulec S, Hadoux J, Gontier E, *et al.* Combination of paclitaxel and bevacizumab in heavily pre-treated non-small cell lung cancer (NSCLC) patients: a case series study on 15 patients. *Bull Cancer* 2013; 100: 30–37.
- Habib S, Delourme J, Dhalluin X, *et al.* Bevacizumab and weekly paclitaxel for non-squamous non-small cell lung cancer patients: a retrospective study. *Lung Cancer* 2013; 80: 197–202.
- Zarza V, Couraud S, Bosc C, *et al.* Paclitaxel-bevacizumab is a possible alternative as salvage

- chemotherapy in advanced non-small cell bronchial carcinoma. *Rev Mal Respir* 2014; 31: 601–607.
15. Cortot AB, Audigier Valette C, Molinier O, *et al.* Weekly paclitaxel plus bevacizumab versus docetaxel as second- or third-line treatment in advanced non-squamous non-small-cell lung cancer: results of the IFCT-1103 ULTIMATE study. *Eur J Cancer* 2020; 131: 27–36.
 16. Référentiels Auvergne Rhône-Alpes en oncologie thoracique. 12th ed. 2016. http://referentiels-aristot.com/wp-content/uploads/1_CBNPC_2022b_V2DEF.pdf
 17. Kim J, Cho J, Lee MH, *et al.* Relative efficacy of checkpoint inhibitors for advanced NSCLC according to programmed death-ligand-1 expression: a systematic review and network meta-analysis. *Sci Rep* 2018; 8: 11738.
 18. Dafni U, Tsourti Z, Vervita K, *et al.* Immune checkpoint inhibitors, alone or in combination with chemotherapy, as first-line treatment for advanced non-small cell lung cancer. A systematic review and network meta-analysis. *Lung Cancer* 2019; 134: 127–140.
 19. Gijaj Levra M, Cotté FE, Corre R, *et al.* Immunotherapy rechallenge after nivolumab treatment in advanced non-small cell lung cancer in the real-world setting: a national data base analysis. *Lung Cancer* 2020; 140: 99–106.
 20. Gobbini E, Toffart AC, Pérol M, *et al.* Immune checkpoint inhibitors rechallenge efficacy in non-small-cell lung cancer patients. *Clin Lung Cancer* 2020; 21: e497–e510.
 21. Schvartsman G, Peng SA, Bis G, *et al.* Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer. *Lung Cancer* 2017; 112: 90–95.
 22. Park SE, Lee SH, Ahn JS, *et al.* Increased response rates to salvage chemotherapy administered after PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer. *J Thorac Oncol* 2018; 13: 106–111.
 23. Costantini A, Corny J, Fallet V, *et al.* Efficacy of next treatment received after nivolumab progression in patients with advanced nonsmall cell lung cancer. *ERJ Open Res* 2018; 4: 00120-2017.
 24. Grohe C, Blau W, Gleiber W, *et al.* Nintedanib + docetaxel in lung adenocarcinoma patients (pts) following treatment with immune checkpoint inhibitors (ICIs): updated efficacy and safety results of the ongoing non- interventional study (NIS) VARGADO (NCT02392455). *J Clin Oncol* 2020; 38(Suppl. 15): 9604.
 25. Brueckl WM, Reck M, Rittmeyer A, *et al.* Efficacy of docetaxel plus ramucirumab as palliative third-line therapy following second-line immune-checkpoint-inhibitor treatment in patients with non-small-cell lung cancer stage IV. *Clin Med Insights Oncol* 2020; 14: 1179554920951358.
 26. Corral J, Majem M, Rodríguez-Abreu D, *et al.* Efficacy of nintedanib and docetaxel in patients with advanced lung adenocarcinoma treated with first-line chemotherapy and second-line immunotherapy in the nintedanib NPU program. *Clin Transl Oncol* 2019; 21: 1270–1279.
 27. Reck M, Syrigos K, Miliauskas S, *et al.* Non-interventional LUME-BioNIS study of nintedanib plus docetaxel after chemotherapy in adenocarcinoma non-small cell lung cancer: a subgroup analysis in patients with prior immunotherapy. *Lung Cancer* 2020; 148: 159–165.
 28. Shiono A, Kaira K, Mouri A, *et al.* Improved efficacy of ramucirumab plus docetaxel after nivolumab failure in previously treated non-small cell lung cancer patients. *Thorac Cancer* 2019; 10: 775–781.
 29. Harada D, Takata K, Mori S, *et al.* Previous immune checkpoint inhibitor treatment to increase the efficacy of docetaxel and ramucirumab combination chemotherapy. *Anticancer Res* 2019; 39: 4987–4993.
 30. Yoshimura A, Yamada T, Okuma Y, *et al.* Retrospective analysis of docetaxel in combination with ramucirumab for previously treated non-small cell lung cancer patients. *Transl Lung Cancer Res* 2019; 8: 450–460.
 31. Tozuka T, Kitazono S, Sakamoto H, *et al.* Addition of ramucirumab enhances docetaxel efficacy in patients who had received anti-PD-1/PD-L1 treatment. *Lung Cancer* 2020; 144: 71–75.
 32. Gawri K, Dawar R, Rodriguez E, *et al.* Improved outcomes with ramucirumab & docetaxel in metastatic non- small cell lung cancer after failure of immunotherapy. In: *2020 World conference on lung cancer*, Singapore, 28–31 January 2021, poster P01.09.
 33. Ramakrishnan R, Antonia S and Gabrilovich DI. Combined modality immunotherapy and chemotherapy: a new perspective. *Cancer Immunol Immunother* 2008; 57: 1523–1529.
 34. Radfar S, Wang Y and Khong HT. Activated CD4+ T cells dramatically enhance chemotherapeutic tumor responses in vitro and in vivo. *J Immunol* 2009; 183: 6800–6807.
 35. Chen G and Emens LA. Chemoimmunotherapy: reengineering tumor immunity. *Cancer Immunol Immunother* 2013; 62: 203–216.

36. Emens LA and Middleton G. The interplay of immunotherapy and chemotherapy: harnessing potential synergies. *Cancer Immunol Res* 2015; 3: 436–443.
37. Brahmer JR, Drake CG, Wollner I, *et al.* Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol* 2010; 28: 3167–3175.
38. Li B, Lalani AS, Harding TC, *et al.* Vascular endothelial growth factor blockade reduces intratumoral regulatory T cells and enhances the efficacy of a GM-CSF-secreting cancer immunotherapy. *Clin Cancer Res* 2006; 12: 6808–6816.
39. Shrimali RK, Yu Z, Theoret MR, *et al.* Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. *Cancer Res* 2010; 70: 6171–6180.
40. Fukumura D, Kloepper J, Amoozgar Z, *et al.* Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol* 2018; 15: 325–340.
41. Molife C, Hess LM, Lin Ciu Z, *et al.* Sequential therapy with ramucirumab and/or checkpoint inhibitors for non-small-cell lung cancer in routine practice. *Future Oncol* 2019; 15: 2915–2931.

Appendix 1

Schedule of the paclitaxel-bevacizumab combination.

Total patients (n = 314)	
Initial treatment dose of paclitaxel, MD = 17	
90 mg/m ² , D1 D8 D15, D1 = D28	150 (51%)
80 mg/m ² , D1 D8 D15, D1 = D21	108 (36%)
90 mg/m ² , D1 D8, D1 = D21	39 (13%)
Initial treatment dose of bevacizumab, MD = 31	
10 mg/kg, D1 D15, D1 = D28	212 (75%)
15 mg/kg, D1 D21, D1 = D21	65 (23%)
7.5 mg/kg, D1 D21, D1 = D21	6 (2%)
MD, missing data.	

Appendix 2

Tolerance of the paclitaxel-bevacizumab combination.

Total patients (n = 314)	
Administration of PB	
Duration of paclitaxel (in days)	105 (63–161)
Duration of bevacizumab (in days)	127 (63–245)
Discontinuation of one of the drugs (MD = 4)	104 (34%)
Reason of discontinuation of one of the drugs (n = 104)	
Neuropathy	30 (29%)

(Continued)

Appendix 2 (Continued)

	Total patients (n = 314)
Asthenia	17 (16%)
Bleeding	7 (7%)
Hematological reason	5 (5%)
Other	45 (43%)
Reason of final discontinuation (n=311)	
Progression	230 (74%)
Toxicity	34 (11%)
Therapeutic window	23 (7%)
Death	13 (4%)
Other	11 (4%)

MD, missing data; PB, paclitaxel and bevacizumab.

Qualitative variables are expressed as n (%) and quantitative variables as median (IQR: 25–75%).

Other included: bevacizumab maintenance (n=19), cessation of bevacizumab due to radiotherapy (n=5), ungual disorder (n=4), gastrointestinal disorder (n=2), hypertension (n=2), cessation of bevacizumab due to excavation of pulmonary lesion (n=2), wound healing problem (n=2), infection (n=2), oedematous syndrome (n=1), pulmonary embolism (n=1), discovery of another cancer (n=1), pneumothorax (n=1), proteinuria (n=1), MD=2.

