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**Efficacité de la combinaison paclitaxel
hebdomadaire-bevacizumab pour les patients avec un
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épidermoïdes (CBNPC) : AVATAX, une étude
rétrospective multicentrique**

Geoffroy Bilger

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SALVAGE THERAPY WITH PACLITAXEL-BEVACIZUMAB COMBINATION
IN ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER
(NSCLC) : AVATAX, A RETROSPECTIVE MULTICENTRIC STUDY

THÈSE
POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE
SPÉCIALITÉ : ONCOLOGIE MÉDICALE

Par M. Geoffroy BILGER

[Données à caractère personnel]

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE MÉDECINE DE GRENOBLE

Le : 17/09/2021

DEVANT LE JURY COMPOSÉ DE

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Madame le Docteur Anne Claire TOFFART

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A Monsieur Le Professeur Denis MORO-SIBILOT,

Vous me faites l'honneur de juger ce travail. Je vous remercie d'avoir accepté de participer au jury de cette thèse. Veuillez trouver ici l'expression de mes sentiments très respectueux.

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A ma famille

A mes parents,

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A toute ma famille,

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A Paulin,

Ou « Popo » pour les intimes, merci d'avoir été le chat de compagnie parfait, même si tu restes une petite saloperie de temps à autre. Miaou.

A Hélène,

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A mes amis, si nombreux et si fidèles...Ni voyez pas ici un classement hiérarchique par pitié, la rédaction de cette partie a été à la fois délicieuse et éprouvante.

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Le serment d'Hippocrate

Texte revu par l'Ordre des médecins en 2012

“ **Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.**

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

”

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PU-PH	ROUSTIT Matthieu	Pharmacologie fondamentale ; pharmacologie clinique ; addictologie
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Abbreviations :

ALK : Anaplastic Lymphoma Kinase

CR : Complete response

CTCAE : Common Terminology Criteria for Adverse Events

DCR : Disease control rate

ECOG PS : Eastern Cooperative Oncology Group – Performance Status

EGFR : Epidermal Growth Factor Receptor

ICI : Immune checkpoint inhibitors

IQR : Interquartile range

KRAS : Kirsten Rat Sarcoma Viral Oncogene

MDSCs : Myeloid-derived suppressor cells

MD : Missing data

NSCLC : Non-small-cell lung cancer

ORR : Objective response rate

OS : Overall survival

PFS : Progression-free survival

PB : Paclitaxel Bevacizumab

PR : Partial response

PD-L1 : Programmed cell death-ligand 1

PD-1 : Programmed cell death 1

SD : Stable disease

Tregs : Regulatory T cells

VEGF : Vascular Endothelial Growth Factor

Efficacité de la combinaison paclitaxel hebdomadaire - bevacizumab pour les patients avec un cancer bronchopulmonaire non à petites cellule non épidermoïde (CBNPC) : AVATAX, une étude rétrospective multicentrique.

Introduction : L'utilisation de l'immunothérapie en première ligne de traitement des CBNPC de stade avancé nécessite de redéfinir les lignes ultérieures. La combinaison paclitaxel- bevacizumab avait montré son efficacité dans l'essai ULTIMATE en seconde et troisième ligne. AVATAX est une étude française évaluant cette combinaison en vie réelle.

Méthodes : Il s'agit d'une étude rétrospective multicentrique. L'objectif principal était d'évaluer la tolérance et l'efficacité de l'association paclitaxel-bevacizumab pour les CBNPC non épidermoïdes en seconde ligne et plus, avec un intérêt plus particulier pour le sous-groupe des patients traités juste après progression sous inhibiteurs des points de contrôle immunitaire (ICI).

Résultats : Entre janvier 2010 et février 2020, 314 patients ont débuté la combinaison : 55% d'hommes, avec âge médian au diagnostic de 60 ans, 27% avaient un statut PS \geq 2, 45% avec des métastases cérébrales. Une majorité de patients étaient traités en deuxième (20%) et en troisième (39%) ligne et 28% avaient reçu un ICI à la ligne précédente. Le nombre de cures médian a été de 4 [interquartiles (IQ) [3-6]. Le taux de réponse objective était de 40% et le taux de contrôle de la maladie de 77%. Les médianes de survie sans progression (SSP) et de survie globale (SG) étaient de 5,7 mois [IQ,3,2-9,6] et 10,8 mois [IQ,5,3-19,6] respectivement. Les effets secondaires tous grades confondus ont concerné 82% des patients : 53% d'asthénie et 39% de neurotoxicité. La combinaison est devenue une monothérapie pour 25% des patients en raison de toxicité. La SSP médiane des patients traités juste après ICI était significativement supérieure par rapport à celle des patients non préalablement traités par ICI : 7,0 mois [IQ,4,2-11,0] vs 5,2 mois [IQ,2,9-8,8] p (log-rank)=0,01. En revanche, il n'y avait pas de différence significative en termes de SG médiane entre ces 2 groupes. En analyse multivariée, les facteurs associés à une meilleure SSP étaient un traitement par ICI la ligne précédente et l'indice de performance. Seul l'indice de performance était associé à la SG.

Conclusion : Ces données confirment en vie réelle les résultats d'efficacité et de tolérance de l'essai ULTIMATE. La combinaison paclitaxel-bevacizumab est particulièrement efficace après progression sous ICI.

Salvage therapy with paclitaxel-bevacizumab combination in advanced non-squamous non-small cell lung cancer (NSCLC): AVATAX, a retrospective multicentric study.

Introduction : With the growing role of immunotherapy (ICI) as first-line setting for advanced NSCLC, strategies must be redefined after failure. The combination paclitaxel-bevacizumab showed in the ULTIMATE trial a significant superiority versus docetaxel as second or third-line treatment. Limited retrospective studies have demonstrated unexpected efficacy of chemotherapy after prior progression on ICI. This combination could be used as salvage treatment following ICI.

Methods : This multi-centric retrospective study identified patients treated with the combination paclitaxel-bevacizumab in metastatic non-squamous NSCLC as second-line therapy or beyond. Main objectives were to describe safety and efficacy of this combination, with special attention to the sub-group treated just after ICI.

Results : From January 2010 to February 2020, 314 patients started the paclitaxel-bevacizumab combination: 55% male, with a median age of 60 years, 27% with a performance status ≥ 2 , 45% with brain metastases. A majority of patients were treated in second (20%) and third-line (39%), and 28% were treated just after ICI failure (88/314). Objective response rate (ORR) was 40% and disease control rate was 77 %. Median progression-free survival (PFS) and overall survival (OS) were 5,7 months [IQ,3,2–9,6] and 10,8 months [IQ,5,3–19,6] respectively. All grade adverse events concerned 82% of patients, including 53% asthenia and 39% neurotoxicity, and 25% of patients continued a monotherapy alone due to toxicity. Median PFS for patients treated after ICI failure (ICI+) was significantly superior compared to those not previously treated with ICI (ICI-): 7,0 months [IQ,4,2–11,0] vs 5,2 months [IQ,2,9–8,8] p (log-rank)=0,01. There was no statistically significant difference in terms of OS between these two groups. In multivariate analysis, factors associated with superior PFS were previous ICI treatment (ICI+) and performance status.

Conclusion : This study confirms an acceptable toxicity profile associated with interesting efficacy of the combination paclitaxel-bevacizumab as second-line treatment or beyond for non-squamous NSCLC patients, particularly after progression with ICI.

Salvage therapy with paclitaxel-bevacizumab combination in advanced non-squamous non-small cell lung cancer (NSCLC): AVATAX, a retrospective multicentric study.

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Highlights:

- Real-world data on the efficacy and safety of the combination Paclitaxel and Bevacizumab in advanced NSCLC remain rare.
- This combination is efficient and well-tolerated in advanced nonsquamous NSCLC in second-line and above.
- This combination is particularly efficient after progression with checkpoint inhibitors.

Keywords: Immunotherapy; Chemotherapy; Non– small cell lung cancer; NSCLC; Paclitaxel; Bevacizumab

Introduction: Compare to docetaxel, the phase III trial, ULTIMATE, showed a significant improvement of progression-free survival (PFS) 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, strategies must be redefined after failure. Here we describe the efficacy and safety of PB combination in advanced non-squamous NSCLC as second-line therapy or beyond.

Methods This multi-centric retrospective study identifies patients, treated with PB, with special attention to the sub-group treated with this salvage combination after progression with immune checkpoint inhibitors (ICI). 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 CTAE.

Results: From January 2010 to February 2020, 314 patients, in 16 centers, started the PB combination: 55% male, median age 60 years (19-82), performance status ≥ 2 27%, brain metastases 45%. A majority of patients were treated in second (20%) or 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 [IQ,3,2–9,6] and 10,8 [IQ,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 to those not previously treated with ICI (ICI-): 7,0 [IQ,4,2–11,0] vs 5,2 [IQ,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. Only the performance status was associated with superior OS.

Conclusions: 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.

1. INTRODUCTION

Lung cancer has become the most widespread cancer and the main cause of cancer deaths in France and 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) [1,2]. Despite recent progress and an increase in the number of patients who are candidates for second-line treatment or more [3,4], prognosis remains poor with relapse remaining almost inevitable [2].

Until 2015, the standard of care for second-line NSCLC was docetaxel or pemetrexed monotherapy with modest results: an objective response rate (ORR) between 5-10%, a median progression-free survival (PFS) of 1.5 to 3 months, and median overall survival (OS) of 4.6 to 12.8 months [5-9]. Because of these poor results, alternative strategies combining mono-chemotherapy with anti-angiogenic agents have been studied. After promising results in phase II and several retrospective studies [10-15], phase III studies were conducted with the association of docetaxel with aflibercept [16], ramucirumab [17]) and nintedanib [18,19], leading to a European authorization for these combinations.

The combination of paclitaxel and bevacizumab (PB) was evaluated in 3 retrospective studies with limited numbers of patients but with encouraging results. The response rate ranged from 33% to 44%, median PFS from 4.6 to 6.4 months, and median OS, reported in one study was 9.6 months [20-22]. Based on these promising results, the French phase III trial (IFCT-1103 ULTIMATE) evaluated the efficacy of the PB combination in 166 patients compared to standard docetaxel as second or third-line treatment in patients with advanced non-squamous NSCLC [23]. Compared to docetaxel, the PB combination allowed a significant increase of PFS (5.4 vs. 3.9 months, $p=0.005$) without difference in OS. Toxicities were different between arms but are expected to be in favor of the PB arm. These results

supported the use of the PB doublet in the 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 [24].

Among recent therapeutic advances, immunotherapy has been a turning point in the management of NSCLC especially more recently in first-line treatment. As monotherapy or in combination with chemotherapy, these indications are increasingly broad from the first line with demonstrated superiority over previous reference treatments [25-33]. Post-immunotherapy treatment lines are thus modified, while pursuit or rechallenge with immunotherapy has not yet proved efficacy [34-36]. Chemotherapy has become once again the standard of care in these further lines. In this context, the PB doublet could be an option.

While data on the efficacy of chemotherapy administered after progressions under immunotherapy seemed particularly interesting [37-39], 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 [40-48].

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.

2. METHODS

Study design and Patients

We conducted a multicenter retrospective study among 16 hospitals of French academic clinical research groups GFPC (Pneumo-Cancerology French Group) and IFCT (French Cooperative Thoracic Intergroup) including all advanced NSCLC treated by PB as second-line therapy and beyond in standard practice, between January 2010 and January 2020. They 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 PFS in patients treated by PB. The secondary objectives included objective response rate (ORR) according to RECIST 1.1, disease control rate (DCR), overall survival (OS), and toxicity.

Ethics approval was obtained on 09 October 2019 (Observational Research Protocol Review Committee) of the French Society of Pneumology (SPLF), (IRB CEPRO 2019-033). An information letter was sent to each living patient providing him the opportunity to refuse study participation.

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) and partial response (PR), stable disease (SD), and progressive disease (PD), were evaluated according to the

RECIST 1.1 guidelines. Disease control rate (DCR) was calculated by adding CR, PR, and SD. 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 interquartile range [IQR]) for quantitative variables and were using chi-squared (or Fisher-exact) or Mann-Whitney tests, as appropriate.

PFS was calculated from the start of PB therapy to progression or death. 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 clearly 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).

3. RESULTS

Patients' 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 an EGFR mutation. At the time of initiation of the PB, 140 (45%) patients had brain metastasis, and 82 (26%) liver metastasis.

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.

Paclitaxel-bevacizumab 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. 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).

Previous regimen treatments before PB

In their previous lines of treatment, 97 (31%) patients were already treated with taxane-containing chemotherapy, and 91 (29%) patients already received bevacizumab.

Eighty-eight (28%) patients were treated with PB immediately after ICI progression (defined as ICI+ group): 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).

Efficacy

On the 308/314 evaluable patients: 122 (40%) achieved a PR, 115 (37%) had SD and 71 (23%) progressed. None of the patients had a complete response. The ORR was therefore 40% and DCR 77%. In the subgroup of ICI+ patients, (88/314), the ORR was 51% vs 35% in the ICI- group (225/314).

For the 314 patients included, the median PFS was 5.7 months [IQ 25%-75% 3.2-9.6], 7.0 months [IQ 25%-75% 4.2-11.0] in the ICI+ group vs 5.2 months [IQ 25%-75% 2.9-8.8] in the ICI- group, P -value=0,01. Median PFS was 5.2 months [IQ range 2.9-9.5] for patients harboring EGFR pathway mutation, 5.5 months [IQ range 3.3-9.7] for patients previously treated with taxane-based chemotherapy, and 5.3 months [IQ range 2.7-8.7] for patients previously treated with bevacizumab.

The median OS was 10.8 months [IQ 25%-75% 5.3-19.6], 13.0 months [IQ 25%-75% 6.5-25.3] in the ICI+ group vs 10.3 in the ICI- group [IQ 25%-75% 4.9-18.0], P -value=0,06. In subgroup analysis, median OS was 12.8 months [IQ range 5.6-19.5] for patients harboring EGFR pathway mutation, 10.3 months [IQ range 5.5-21.3] for patients previously treated with taxane-based chemotherapy, and 11.6 months [IQ range 5.9-20.2] for patients previously treated with bevacizumab.

A total of 193 (63%) patients were treated with subsequent treatment after progression with PB (8 missing data): 51% (n=98) with immunotherapy, 26% (n=49) with paclitaxel bevacizumab 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.

Duration of treatment and toxicity

A total of 257 (82%) patients experienced adverse events of all grades during the administration of PB (Table 2). 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%).

One hundred and four patients (33%) discontinued the combination for monotherapy with either molecule from whom seventy-seven 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.

No treatment-related deaths were observed.

4. DISCUSSION

In this large retrospective analysis of non-selected advanced NSCLC patients treated with the PB combination, median PFS and OS were 5.7 and 10.8 months respectively, with a 40% ORR. These results seem better than the outcomes of monotherapy in second-line therapy [5-9] and are in line with those found in the phase III ULTIMATE [23], REVEL [17], and LUME-Lung 1 [18] studies. However, in contrast to the above-mentioned studies, our population was not selected, with 27% of patients with an ECOG PS score ≥ 2 , and 40% treated in fourth line or more. The reported 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 [17-19,40-48].

The efficacy of the PB doublet may be explained by the synergistic action of bevacizumab and the direct antiangiogenic effect of paclitaxel [49-51]. In our study patients previously treated with bevacizumab still benefit from PB combination; These results are consistent with other studies [52], but not with the ULTIMATE study [23]. Our results also show the effectiveness of the PB combination in patients with EGFR mutation, although this population is under-represented in the cohort.

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 [37-39]. In published studies, the combination of docetaxel and an antiangiogenic agent as salvage treatment directly after ICI allowed an ORR of 18 to 60%, a DCR of 80 to 90%, a median PFS of 3.2 to 6.8 months, and a median OS of 8.8 to 20.9 months [40-48]. In line with these results, our study shows in the ICI+ group a median PFS

for PB significantly superior compare to ICI- group: 7.0 vs 5.2 months $p=0,01$, but without statistical benefit in OS (13.0 vs 10.3 months $p=0.06$). These data further highlight the potential for an antiangiogenic agent plus chemotherapy in the post-ICI setting.

The hypothesis of possible chemosensitization after prior exposure to immunotherapy is supported by synergistic activity in both preclinical and clinical models [55,56]. 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 [57,58]. 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 [59-60], producing a residual effect on immune memory cells, which could be stimulated by successive chemotherapy with its own immunological effects. Although the positive effects of PD-1/PD-L1 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 vascular endothelial growth factor (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 [61-66]. 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 [47] 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 [67]. Since the first current treatment line has changed compare to ULTIMATE, LUME-Lung 1, and REVEL studies, the place of the PB combination remains to be defined, although probably in second-line after immunotherapy alone or after chemo-immunotherapy. Indeed, after progression with ICI, pursuit or rechallenge with immunotherapy has not yet proved efficacy [34-36], and until more data to be available, the treatment of choice remains chemotherapy. To date, there have been no prospective, randomized controlled trials demonstrating the optimal 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 physician's choices.

In addition, despite the absence of predictive markers of sensitivity to antiangiogenic treatment available in clinical practice today, previous data suggest particular effectiveness of chemotherapy with antiangiogenic therapy for patients with aggressive and refractory disease [15,19] and clinically relevant intracranial activity of bevacizumab in case of recurrent brain metastasis [69].

Our study has several limitations. First, it is retrospective, with possibly some underreporting of potential side effects and a lack of verification on imagery response data. Second, all patients in the cohort were French. Third, patients treated with PB in the ICI+

group were mostly treated in third-line therapy after immunotherapy failure in second-line (n=62/88) and therefore could have shown better clinical outcomes compare to the ICI- group who received PB later (n=101/226 treated with PB in fourth-line or more). Fourth, our study was conducted at a time when ICI was mainly used in second line, recommendations have since changed with most patients treated with ICI in first line. Thus, our results with PB treatment should be interpreted with caution in patients treated in first-line with immunotherapy alone or immunotherapy combined with chemotherapy. Moreover, 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.

Conclusion

Paclitaxel bevacizumab combination in patients with advanced NSCLC in second-line and above is efficient and well-tolerated. Perspectives trials are needed to address the question of the best chemotherapy association after first-line ICI combined or not with chemotherapy.

Flow chart of the study population.

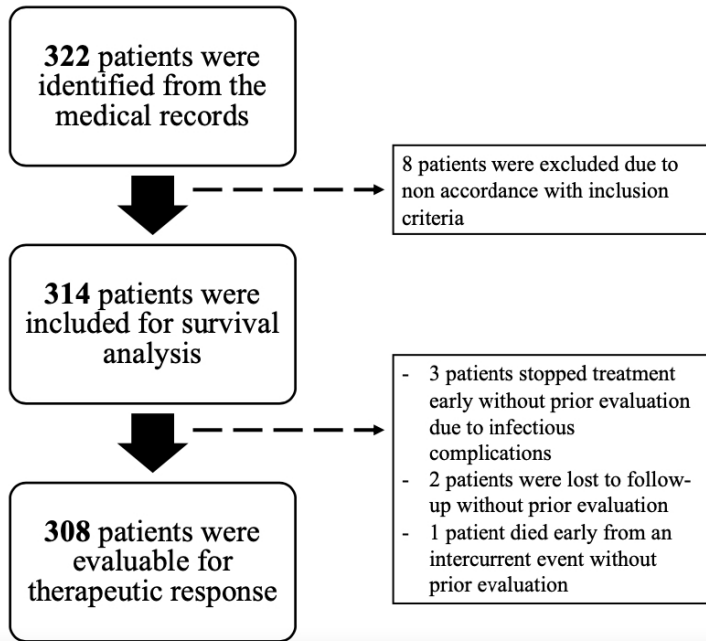


Table 1. Patients' characteristics at the beginning of paclitaxel-bevacizumab (PB).

	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 (26%)	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
KRAS mutation	98 (31%)	58 (26)	40 (45)	
EGFR mutation	46 (15%)	42 (19)	4 (5)	
ALK 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				<10 ⁻⁴
2 nd line	63 (21%)	62 (27)	1 (1)	
3 rd line	124 (39%)	62 (27)	62 (70)	
4 th line	66 (21%)	48 (22)	17 (19)	
5 th line or more	61 (19%)	53 (23)	8 (9)	

*ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; MD, missing data.

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 (%) and quantitative variables as median (IQR, 25%-75%).

Annexe 1. Schedule of the paclitaxel-bevacizumab combination

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

Table 2. 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 (%).

Annexe 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%)
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.

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), ungueal 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.

Table 3. Efficacy of the paclitaxel-bevacizumab combination

Patients evaluable for therapeutic response	N=314	ICI- 226 (72%)	ICI+ 88 (28%)	<i>p</i> -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+ 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.

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

	Median PFS (IQR, 25%-75%) in months	Univariate analysis		Multivariate analysis	
		HR [95% CI]	<i>p</i> -value	HR [95% CI]	<i>p</i> -value
Patients' characteristics					
Sex			0.72		0.89
- Male (n=141)	5.8 (3.4-9.7)	1		1	
- Female (n=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 (n=220)	5.7 (0.9-9.6)	1		1	
- ≥68 years (n=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 (n=63)	5.8 (3.6-9.0)	1		1	
- 1 (n=156)	6.5 (3.9-10.1)	0.99 [0.73-1.33]		1.01 [0.74-1.39]	
- ≥2 (n=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	
- KRAS mutation	5.3 (2.8-8.6)	1.62 [0.96-1.80]		1.47 [1.12-1.94]	
- EGFR / ALK	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
- 2 nd line	5.4 (2.6-9.9)	1		1	
- 3 rd line	5.8 (3.4-9.7)	0.94 [0.69-1.29]		1.15 [0.81-1.64]	
- 4 th line	5.7 (2.9-8.7)	1.10 [0.77-1.57]		1.11 [0.77-1.61]	
- 5 th 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	...	
- 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]	

*ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; MD, missing data; HR, hazard ratio ; CI, confidence interval ; 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 (%) and quantitative variables as median (IQR, 25%-75%).

Table 5. Univariate and multivariate analysis of factors associated with OS from the initiation of paclitaxel bevacizumab therapy.

	Median OS (IQR, 25%-75%) in months	Univariate analysis		Multivariate analysis	
		HR [95% CI]	<i>p</i> -value	HR [95% CI]	<i>p</i> -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
- 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	
- KRAS mutation	9.6 (5.3-15.0)	1.28 [0.97-1.69]		1.49 [1.11-1.98]	
- EGFR / ALK	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
- 2 nd line	10.1 (4.5-21.5)	1		1	
- 3 rd line	11.8 (5.3-21.1)	0.92 [0.66-1.28]		1.11 [0.76-1.60]	
- 4 th line	10.4 (4.9-17.8)	1.02 [0.71-1.48]		1.02 [0.69-1.50]	
- 5 th 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]	

*ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; MD, missing data; HR, hazard ratio ; CI, confidence interval ; ICI : immune checkpoint inhibitors.

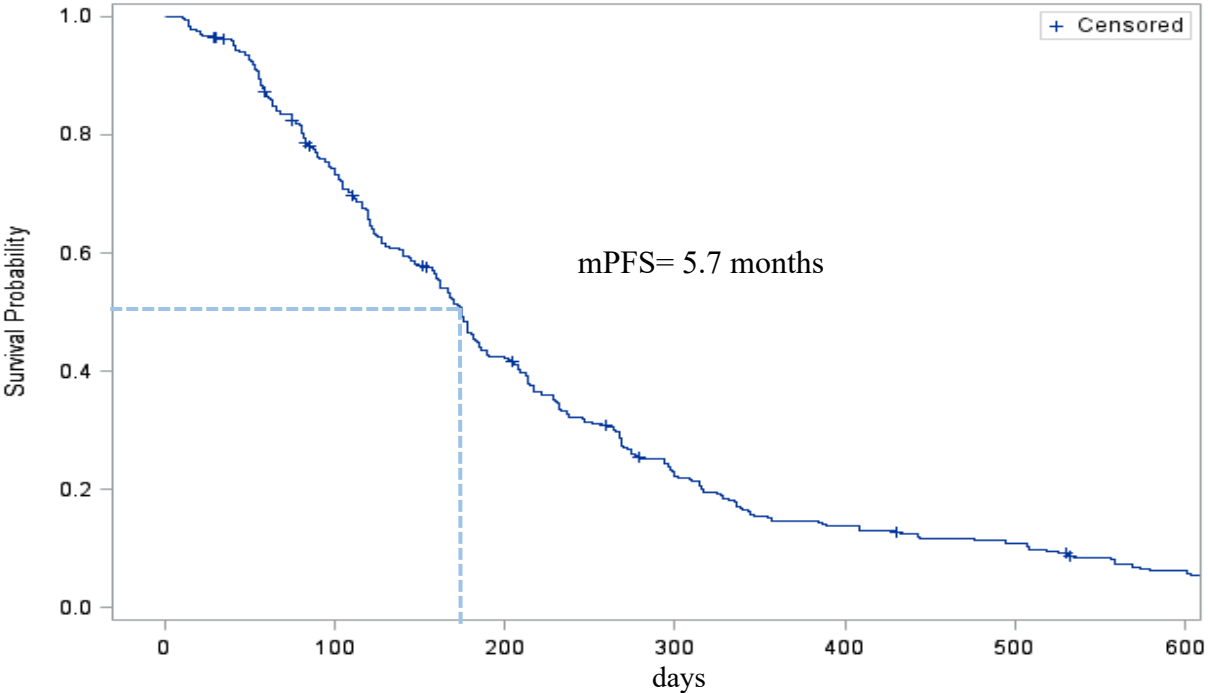
ICI+ subgroup is defined by patients treated with PB immediately after progression under immune checkpoint inhibitors (ICI) therapy.

ICI- subgroup is defined by patients treated with PB without previous ICI therapy just before.

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

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.

(a)



(b)

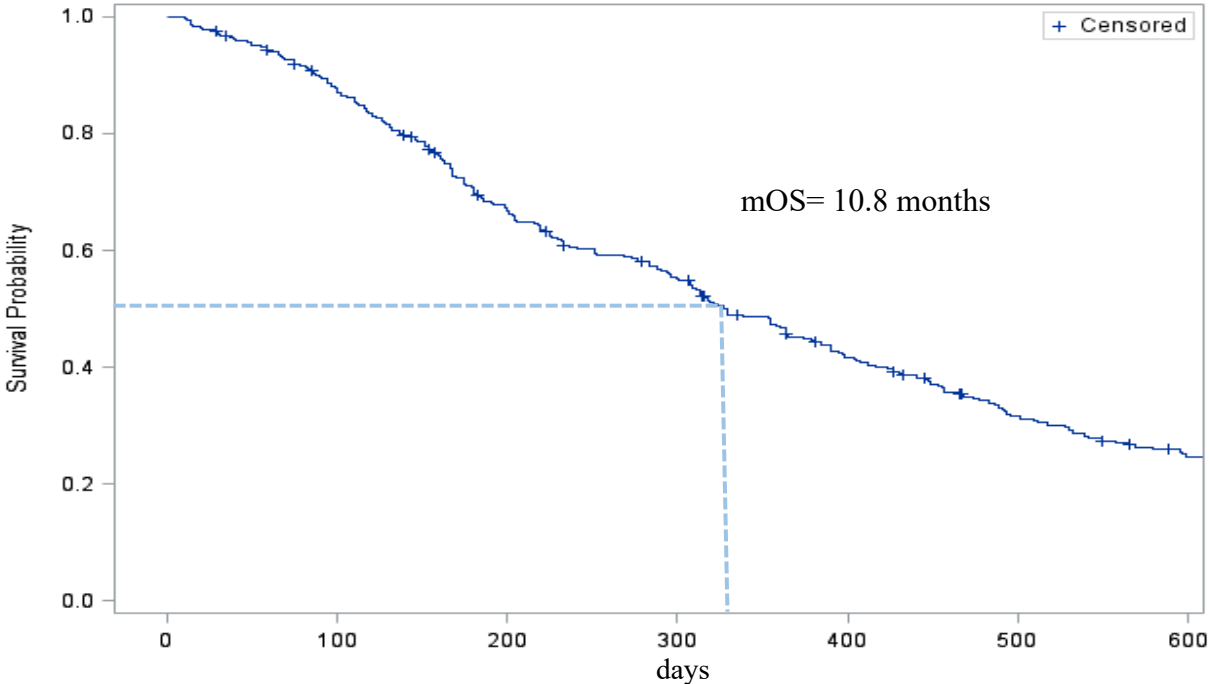
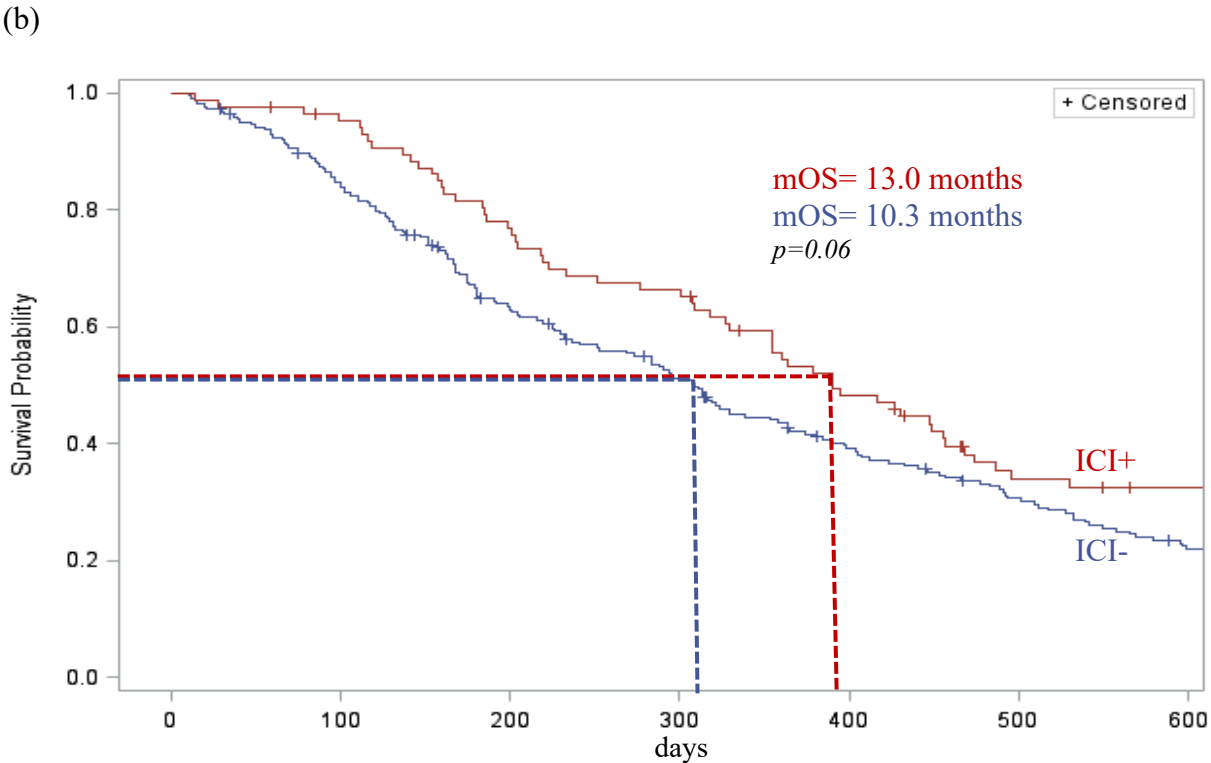
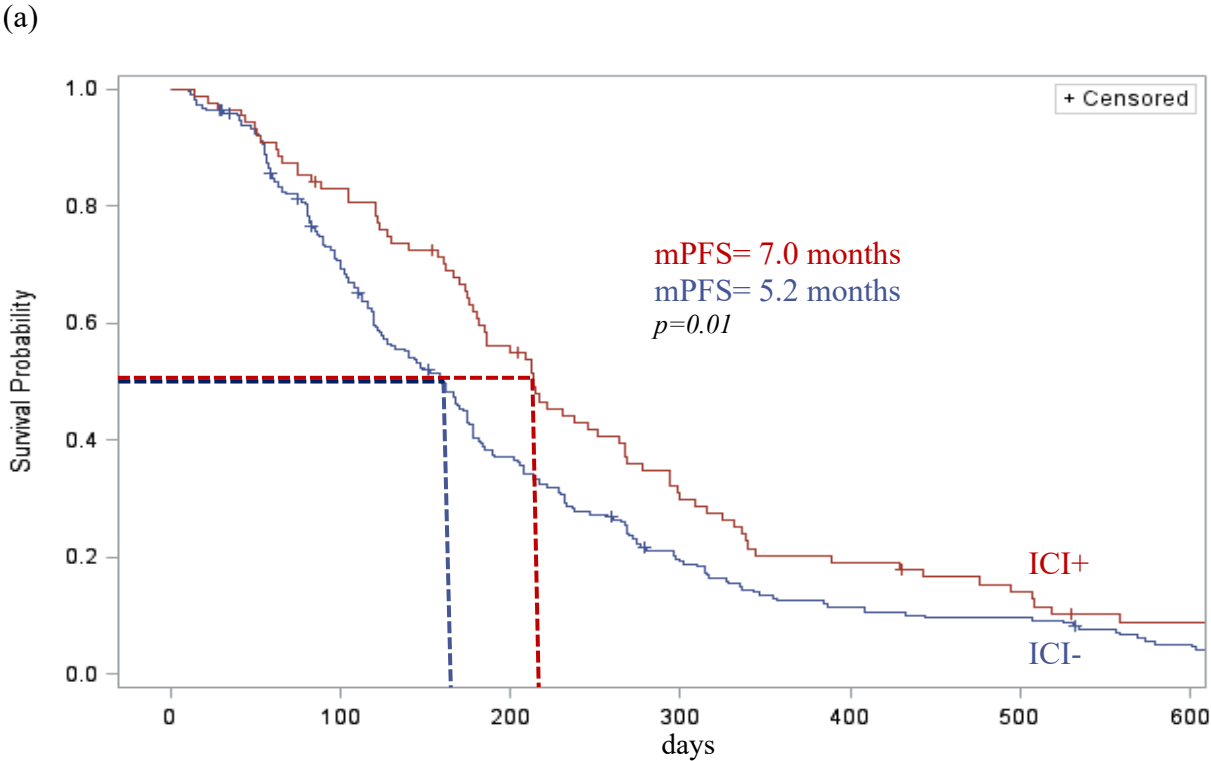


Figure 2. Kaplan–Meier estimates of the (a) progression-free survival (PFS) and (b) overall survival (OS) of patients according to prior treatment with immunotherapy (ICI).



THÈSE SOUTENUE PAR : BILGER GEOFFROY

TITRE : Salvage therapy with paclitaxel-bevacizumab combination in advanced non-squamous non small cell lung cancer (NSCLC)

CONCLUSION : AVA-AX, a retrospective multicentric study

Introduction: Compare to docetaxel, the phase III trial, ULTIMATE, showed a significant improvement of progression-free survival (PFS) 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, strategies must be redefined after failure. Here we describe the efficacy and safety of PB combination in advanced non-squamous NSCLC as second-line therapy or beyond.

Methods This multi-centric retrospective study identifies patients, treated with PB, with special attention to the sub-group treated with this salvage combination after progression with immune checkpoint inhibitors (ICI). 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 CTAE.

Results: From January 2010 to February 2020, 314 patients, in 16 centers, started the PB combination: 55% male, median age 60 years (19-82), performance status ≥ 2 27%, brain metastases 45%. A majority of patients were treated in second (20%) or 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 [IQ,3,2-9,6] and 10,8 [IQ,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 to those not previously treated with ICI (ICI-): 7,0 [IQ,4,2-11,0] vs 5,2 [IQ,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. Only the performance status 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.

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