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Original Research

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

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Abstract ***Purpose:*** Second-line chemotherapy regimens have demonstrated poor benefit after failure of platinum-based chemotherapy in advanced non-squamous non–small-cell lung cancer (nsNSCLC).
Methods: In this multicentre, open-label phase III trial, patients with advanced nsNSCLC treated with one or two prior lines, including one platinum-based doublet, were centrally randomised to receive 90 mg/m^2 of paclitaxel (D1, D8, D15) plus 10 mg/kg of bevacizumab (D1, D15) every 28 days or docetaxel (75 mg/m^2) every 21 days; crossover was allowed after disease progression. Primary end-point was progression-free survival (PFS). ClinicalTrials.gov registration number: NCT01763671.
Results: One hundred sixty six patients were randomised (paclitaxel plus bevacizumab: 111, docetaxel: 55). The median PFS was longer in patients receiving paclitaxel plus bevacizumab than in patients receveing docetaxel [5·4 months versus 3·9 months, adjusted hazard ratio (HR) 0·61 (95% confidence interval [CI]: 0·44–0·86); p = 0·005]. Objective response rates (ORRs) were 22·5% (95% CI: 14·8–30·3) and 5·5% (95% CI: 0·0–11·5) (p = 0·006), respectively. Median overall survivals were similar (adjusted HR 1·17; p = 0·50). Crossover occurred in 21 of 55 (38·2%) docetaxel-treated patients. Grade III-IV adverse events (AEs) were reported in 45·9% and 54·5% of patients treated with paclitaxel and bevacizumab or docetaxel, respectively (p = NS), including neutropenia (19·3% versus 45·4%), neuropathy (8·3% versus 0·0%) and hypertension (7·3% versus 0·0%). Three patients died due to treatment-related AEs (1·8% in each group).
Conclusion: Weekly paclitaxel plus bevacizumab as second- or third-line improves PFS and ORR compared with docetaxel in patients with nsNSCLC, with an acceptable safety profile. These results place weekly paclitaxel plus bevacizumab as a valid option in this population.
Clinical trials registration number: ClinicalTrials.gov Identifier: NCT01763671.

1. Research in context (PANEL)

1.1. Evidence before this study

- Limited efficacy of systemic treatments for patients with advanced non–small-cell lung cancer (NSCLC) beyond first-line therapy
- Bevacizumab has activity in non-squamous NSCLC (nsNSCLC) and was approved in first-line therapy combined with chemotherapy by Food and Drug Administration (FDA) and European Medicines Agency (EMA)
- Bevacizumab add-on to weekly paclitaxel first-line therapy has almost doubled the response rate and the progression-free survival (PFS), with a favourable safety profile in metastatic breast cancer.

1.2. Added value of this study

The IFCT-1103 ULTIMATE study demonstrated the efficacy of a weekly paclitaxel plus bevacizumab (wPAC-BEV) regimen compared with docetaxel monotherapy in terms of PFS and objective response rate (ORR), with manageable adverse events (AEs) and preserved quality of life. Owing to its crossover design, the study did not demonstrate improvement in overall survival.

1.3. Implications of all the available evidence

Weekly paclitaxel and bevacizumab is an effective treatment option for second- or third-line treatment of nsNSCLC.

2. Background

During the last decades, new combined therapies have contributed to improve outcomes in patients with advanced NSCLC in the first-line setting. More recently, immune checkpoint inhibitors (ICIs) given alone or in combination with chemotherapy have been shown to

prolong survival compared with chemotherapy given alone in selected patients [1–5]. However, the vast majority of patients experience further disease progression which requires subsequent therapy [6]. Drugs usually used after failure of platinum-based chemotherapy in patients with NSCLC without any tumour addictive mutation or after failure of tyrosine kinase inhibitors in case of addictive mutation include docetaxel, pemetrexed (only for non-squamous histology) and erlotinib [7,8]. Combination of docetaxel with anti-angiogenic agents such as nintedanib and ramucirumab has demonstrated modest survival benefit in patients with NSCLC but is not widely used due to limited access [9,10]. In patients with nsNSCLC, bevacizumab, a humanised anti-VEGF monoclonal antibody, has proven its efficacy in combination with paclitaxel and carboplatin as first-line therapy [11]. In metastatic breast cancer, bevacizumab add-on to weekly paclitaxel first-line therapy has almost doubled the response rate and the median PFS [12–14]. The same regimen yielded encouraging results in metastatic nsNSCLC beyond first-line therapy in two small retrospective studies with response rates of 40% and 44% and median PFSs of 6·4 months and 4·6 months, respectively [15,16]. In this context, the IFCT-1103 ULTIMATE study compared wPAC-BEV combination therapy with docetaxel monotherapy as second- or third-line treatment in patients with pre-treated advanced nsNSCLC.

3. Patients and methods

3.1. Study design

This double-arm, randomised, open-label, multicentre, phase III clinical trial was conducted in patients with pre-treated advanced nsNSCLC. Patients were allowed to crossover to the other arm after disease progression over the study. This study was approved by a local ethics committee (CPP Nord-Ouest III, France) and complied with French legislation, Good Clinical Practices and the principles outlined in the latest version of the Declaration of Helsinki. After approvals, the study was implemented in 36 hospitals and cancer centres in France.

3.2. Patients

Adult patients with confirmed stage III nsNSCLC not amenable to local treatment or stage IV nsNSCLC, and progressing after 1 or 2 lines of treatment, were eligible to the IFCT-1103 ULTIMATE study after written informed consent. At inclusion (baseline), patients had to present with documented disease progression and good World Health Organization (WHO) performance status (PS) (PS$\leq$2), and they must have been previously treated with platinum-based chemotherapy and with pemetrexed treatment. Prior treatment with bevacizumab was allowed but not with taxanes. In addition, patients with active epidermal growth factor receptor (EGFR) mutation had to be treated with at least one previous line of EGFR tyrosine kinase inhibitor and those with anaplastic lymphoma kinase (ALK) rearrangement had to previously receive crizotinib. Patients should not present with symptomatic brain metastasis, neither history of haemoptysis and major blood vessel infiltration. Peri-operative chemotherapy or chemoradiotherapy was not allowed unless it ended at least six months before trial inclusion.

3.3. Randomisation

The patients were randomised (2:1) to receive wPAC-BEV therapy or docetaxel (DOC) treatment. Central computer randomisation was performed using a minimisation method (random factor of 0·8). Patients were stratified by centre, WHO-PS (0–1 versus 2), number of prior lines of treatment (1 versus 2) and prior exposure to bevacizumab (yes versus no).

3.4. Procedures

Within 28 days after selection, patients were randomised to receive either 90 mg/m^2 of paclitaxel (D1, D8, D15) and 10 mg/kg of bevacizumab (D1, D15) every four weeks or 75 mg/m^2 of docetaxel every three weeks, until disease progression or unacceptable toxicity. Dose reductions were allowed for paclitaxel and docetaxel, but not bevacizumab, up to a maximum of two. (Supplement T1).

3.5. Outcomes

The primary end-point was the PFS, defined as the time between randomisation and disease progression (as assessed by the investigator using response evaluation criteria in solid tumors (RECIST) 1.1) or death from any cause, whatever came first. The secondary end-points included the objective response rate (ORR) at eight weeks, the overall survival (OS, defined as the time between baseline and death from any cause), post-discontinuation OS (defined as the time between the first progression and death from any cause), PFS in patients who crossed over to the other arm (defined as the time between day 1 of post-discontinuation treatment and disease progression (as assessed by the investigator using RECIST 1.1) or death from any cause), safety and quality of life using the Lung Cancer Symptom Scale (LCSS).The LCSS was evaluated at baseline, treatment initiation and then every 8 weeks. For each item, a linear transformation was applied to standardise the raw score to a range from 0 to 100, with 100 representing the worst quality of life. A ten-point change in an item was considered to be clinically meaningful. Thus, an improvement in Quality of Life (QoL) was

defined as a ten point reduction or greater between the baseline and 8- or 16-week assessments.

3.6. Statistics

All randomised patients were included in the intention-to-treat (ITT) population that was used for efficacy analyses. All patients who received at least one cycle of study treatment were included in the safety population (safety analysis).

Based on the literature, the expected median PFS was 2·5 months in the docetaxel group. A sample size of 109 assessable patients in the wPAC-BEV group and 55 in the DOC group (randomisation ratio of 2:1) was required to demonstrate a gain of 1·5 months of PFS in median in the wPAC-BEV group with an alpha error of 5% (two-sided) and a power of 80%.

Patient and disease characteristics were described for all the patients ITT population and compared between treatment groups. The relative dose intensity, defined as the ratio between 'delivered' and 'planned' dose intensities, was calculated for each study treatment.

The efficacy analysis was carried out on the ITT population. The median PFS (primary efficacy criterion) was estimated using the Kaplan-Meier method, and a log-rank test was carried out for PFS comparison between treatment groups. The follow-up was censored on December 31, 2016. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from a Cox model, adjusting for stratification variables. Similar analyses were carried out for the OS. The ORR at eight weeks after baseline was described and compared between groups. In patients who crossed over to the other arm, the median PFS and OS were calculated.

Safety data were only described over the first sequence of randomised treatment for the safety population (patients who received at least one cycle of randomised treatment), with a focus on randomised treatment-related AEs.

Statistical analyses were performed using SAS® software, version 9·4 (SAS Institute Inc., Cary, NC, USA), and two-sided tests with type I error $\alpha = 0{\cdot}05$ were applied for all analyses.This trial is registered with ClinicalTrials.gov, number NCT01763671.

4. Results

4.1. Patients' disposal and characteristics

A total of 166 randomised patients [wPAC-BEV group: 111 (67%), DOC group: 55 (33%)] were included between May 31, 2013 and August 13, 2014. Among this ITT population, two patients withdrew before their first wPAC-BEV cycle, leading to a safety population based on 164 patients (Fig. 1).

Patients' characteristics were balanced between treatment groups (Table 1). The majority of patients (69%) received only one previous line of chemotherapy and 31% had been previously exposed to bevacizumab (median: 8 prior cycles; range: 1.47). There were more never smokers and patients >70 years in the DOC group (16.4% and 18.2%, respectively) than in the wPAC-BEV group (8.1% and 9%, respectively). Patients were administered a median of five cycles of randomised therapy in both groups (range: 1.40 for the DOC group and 1.35 for the wPAC-BEV group). The RDI mean was 91·4% for the 333 docetaxel cycles administered over the study, while for the 637 paclitaxel and bevacizumab cycles administered, it was 85·6% and 90·8%, respectively (Supplementary Table 2). Crossover occurred in 21 of 55 (38·2%) docetaxel-treated patients and in 9 of 109 (8·3%) wPAC-BEV–treated patients. In patients who did not cross over (n = 134, 82%), the first administered anticancer drug within 60 days after discontinuation was erlotinib (8/16 patients in the DOC group; 8/48 patient from the wPAC-BEV group; Supplementary Table 3).

4.2. Efficacy

The PFS significantly improved in patients receiving wPAC-BEV over DOC [median, 5·4 months versus 3·9 months; adjusted HR: 0·61, 95% CI = 0·44–0·86; p = 0·005] (Fig. 2). Subgroup analysis favouredwPAC-BEV in most subgroups (Fig. 3), except in patients with prior exposure to bevacizumab (HR: 1.18 (95% CI = 0·63–2·22)) and performance status equal 2 (HR: 1.38 (95% CI = 0·30–6·43)). The benefit associated with wPAC-BEV tended to decrease with the number of previous bevacizumab cycles: for patients with eight or less previous cycles (n = 27), the HR was 0·60 (95% CI = 0·24–1·48; p = 0·26) compared with 1.86 (95% CI = 0·66–5·24; p = 0·24) for those with at least nine previous bevacizumab cycles (n = 24) (data not shown). The time from diagnosis to baseline did not impact PFS.

At eight weeks, the ORR was four folds higher in the wPAC-BEV group (22·5%, 95% CI = 14·8–30·3) than in the DOC group (5·5%, 95% CI = 0·0–11·5; p = 0·006) (Supplementary Table 1), with 72% and 58% of patients achieving disease control, respectively. At study closure, there was no patient on treatment either with paclitaxel plus bevacizumab or with docetaxel (Fig. 1). In the DOC group, 37 patients (67·3%) received a further cancer treatment less than 60 days after treatment discontinuation, including 21 patients (38·2%) who crossed over to wPAC-BEV (Fig. 1). In the wPAC-BEV group, 57 patients (52·3%) received further cancer treatment after treatment discontinuation, including nine patients (8·3%) who crossed over to DOC. After a median follow-up of 36·2 months (range: 28·6; 43·0), no OS difference was observed between treatment groups (medians: 9.9 versus. 11.4 months, HR: 1·17, 95% CI = 0.82–1·65; p = 0·50) (Supplementary Fig. 1).

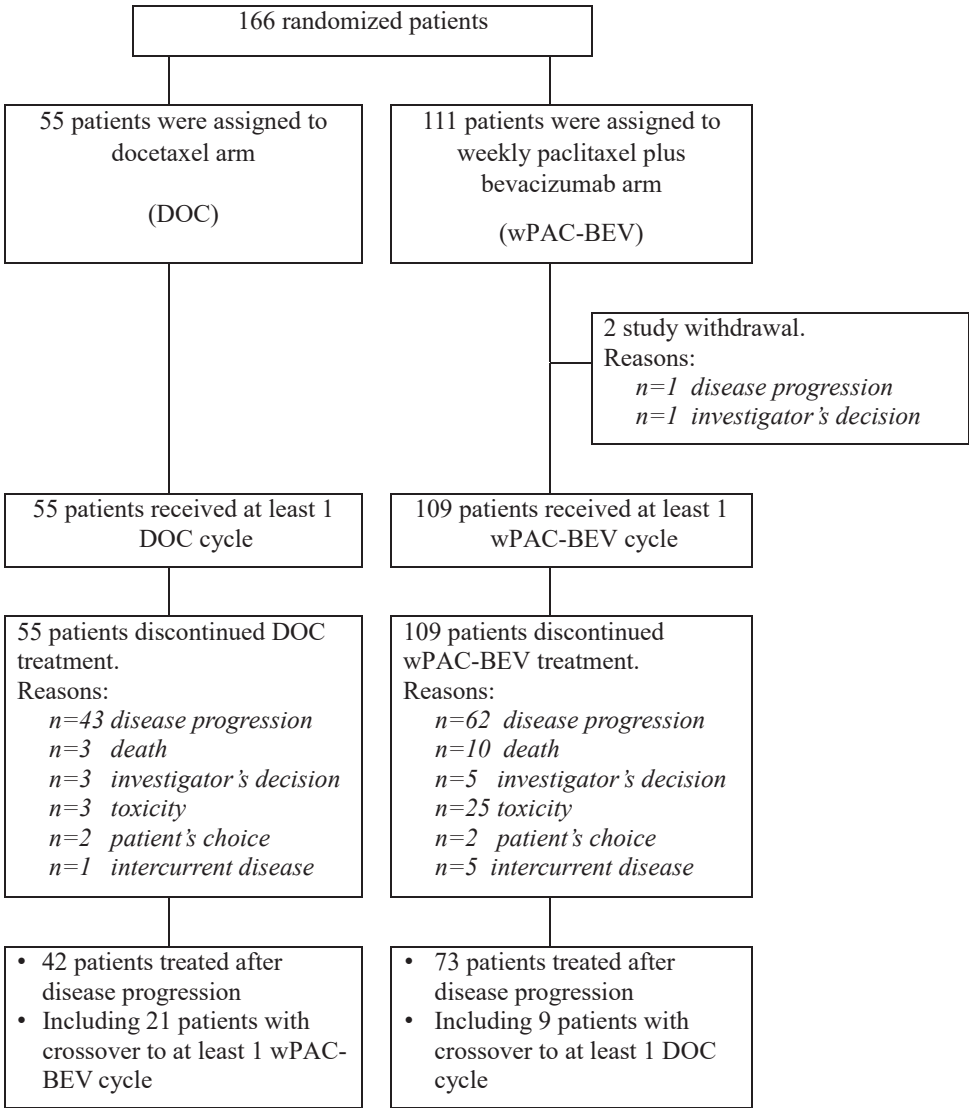

Fig. 1. Disposition of patients. DOC = docetaxel. wPAC-BEV = weekly paclitaxel plus bevacizumab.

Median PFS in patients receiving DOC who crossed over to wPAC-BEV was 4·9 months (95% CI = 2·9–6·4). For patients receiving wPAC-BEV, the median PFS was 1·9 month (95% CI = 0·7–3·6) for patients who crossed over to DOC. Interestingly, the median post-discontinuation OS was 12.5 months (95% CI = 7·0–19·4) in patients receiving DOC crossed over to wPAC-BEV and 5·2 months (95% CI = 2·1–7·0) in patients receiving other further treatments. The median post-discontinuation OS in patients receiving wPAC-BEV was 5.0 months (95% CI = 3·3–9·0).

4.3. Safety and quality of life

Treatment-related grade III-IV AEs occurring during the first sequence (e.g. before any disease progression) of treatment were similar in the wPAC-BEV group and in the DOC group (in 45·9% and 54·5% of patients, respectively; Table 2). Overall treatment-related AEs were more frequent in patients receiving wPAC-BEV (in 98·2% and 90·2% of patients, respectively). Patients receiving DOC experienced more grade III–IV haematological treatment-related AEs, mainly due to higher rates of neutropenia (45·5% versus 19·3%) and febrile neutropenia (7·3% versus 0·9%). Conversely, patients receiving wPAC-BEV experienced more related grade III–IV non-haematological toxicity (27·5% versus 9·1%) and more specifically neuropathy (8·3% versus 0·0%), hypertension (7·3% versus 0·0%) and thromboembolic events in a lesser extent (4·6% versus 0·0%). Two deaths (1·8% of patients) were related to wPAC-BEV therapy (oesophagobronchial fistula and ischaemic stroke) and one patient receiving DOC (1·8%) died from drug-related pneumonitis. There was no new safety signal during the sequence 2 (Supplementary Table 4). At 8 and 16 weeks after first study drug administration,

Table 1
Patient and disease characteristics at baseline – Analysis population (N = 166).

Characteristics	Docetaxel (n = 55)	Paclitaxel plus bevacizumab (n = 111)	Total (n = 166)
Male	42 (76·4%)	78 (70·3%)	120 (72·3%)
Age, years	59·7 (35·8;78·9)	59·6 (18·6;81·8)	59·7 (18·6;81·8)
≥70 years	10 (18·2%)	10 (9·0%)	20 (12·0%)
Smoking status			
Never smokers	9 (16·4%)	9 (8·1%)	18 (10·8%)
WHO performance status[a]			
0-1	51 (92·8%)	103 (92·8%)	154 (92·8%)
Pathological type			
Adenocarcinoma	51 (92·7%)	100 (90·1%)	151 (91·0%)
Number of previous lines			
1	39 (70·9%)	76 (68·5%)	115 (69·3%)
2	14 (25·5%)	34 (30·6%)	48 (28·9%)
3	2 (3·6%)	1 (0·9%)	3 (1·8%)
Prior exposure to bevacizumab			
Yes	17 (30·9%)	34 (30·6%)	51 (30·7%)
Time from advanced NSCLC diagnosis			
≤9 months	20 (36·4%)	52 (46·8%)	72 (43·4%)

Data are median (range) for age or n (%).
WHO = World Health Organisation; NSCLC = non–small-cell lung cancer.
No significant difference ($p < 0.05$) in characteristics was observed between treatment groups.

improved score of quality of life (using the LCSS) compared with baseline was observed in 16.7% and 15% of patients receiving DOC, respectively, and 24.1% and 26.3% of patients receiving wPAC-BEV, respectively. Patients' worsened score of quality of life was similar between treatment groups (18·5% of patients receiving wPAC-BEV versus 33·3% of patients receiving DOC and 26·3% versus 20·0%, respectively; Supplementary Fig. 2).

5. Discussion

Weekly paclitaxel combined with bevacizumab as second- or third-line therapy demonstrated superiority over docetaxel in terms of PFS, the primary end-point, with a 38% risk reduction in disease progression, and ORR (22·5% and 5·5%, respectively) in a population of patients with advanced nsNSCLC. No superiority of paclitaxel plus bevacizumab was observed on OS. However, the optional crossover design of the study may have impacted this result as more docetaxel-treated patients crossed over after disease progression. These efficacy outcomes were associated with a manageable safety profile, although more patients in the wPAC-BEV arm withdrew their treatment because of AEs. As a consequence of the increased PFS, the duration of treatment in the experimental arm was higher and led to higher cumulative AEs. Part of the increased toxicity of wPAC-BEV was linked to cumulative toxicities of taxanes such as neurotoxicity. Importantly, quality of life was found to be preserved in patients treated with wPAC-BEV.

The efficacy of combining docetaxel with anti-angiogenic agents in NSCLC has been previously reported with two other drugs: nintedanib, an angiokinase inhibitor that targets the pro-angiogenic pathways mediated by vascular endothelial growth factor

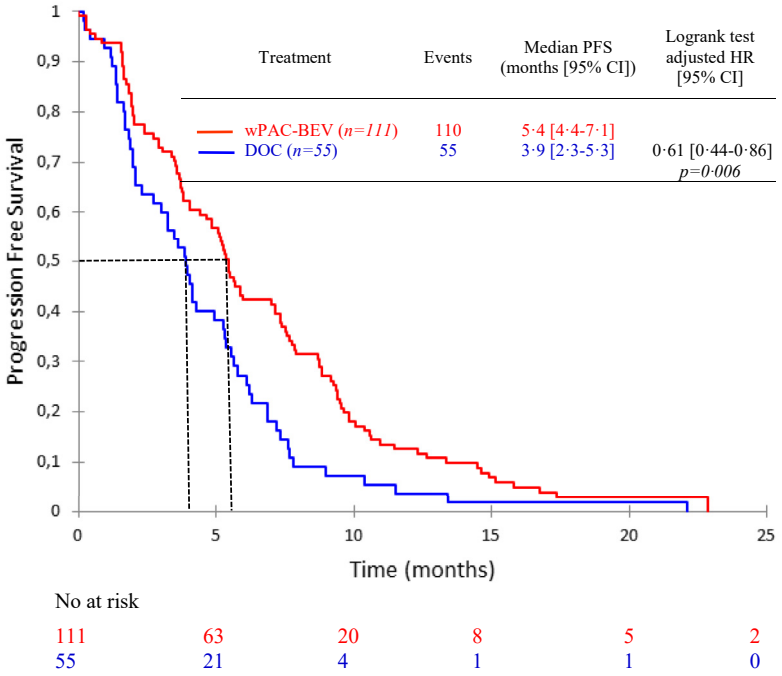

Fig. 2. Progression-free survival (Kaplan Meier curves). CI = confidence interval. DOC = docetaxel. HR = hazard ratio. PFS = progression-free survival. wPAC-BEV = weekly paclitaxel plus bevacizumab.

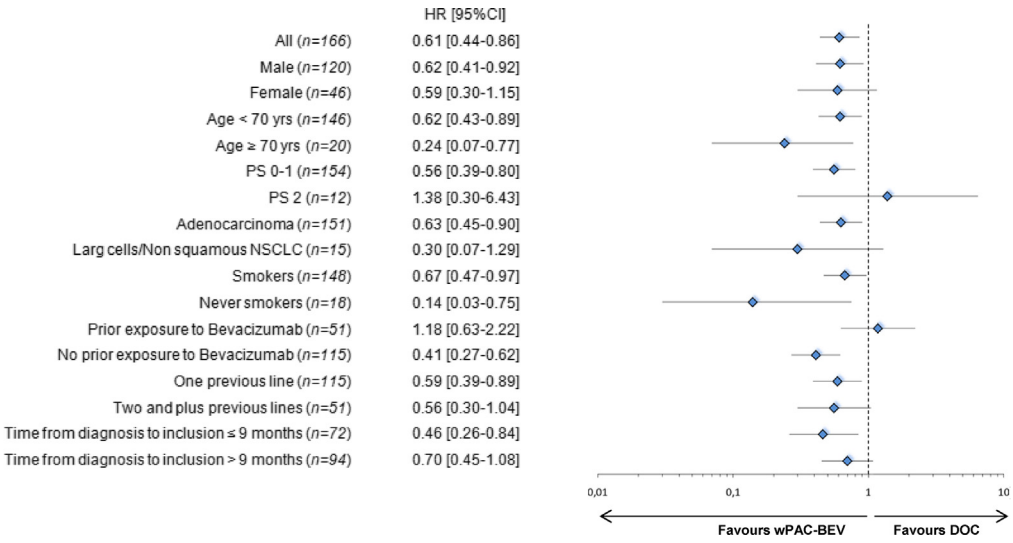

Fig. 3. Forest plot of hazard ratios for progression-free survival in clinically relevant patient subgroups (n = 166). DOC = docetaxel. PS = performance status. NSCLC = non–small-cell lung cancer. wPAC-BEV = weekly paclitaxel plus bevacizumab.

receptors (VEGFR)1–3, fibroblast growth factor receptors 1–3 and platelet-derived growth factor receptors α and β [17] and ramucirumab, a fully human IgG1 monoclonal antibody against VEGFR-2 extracellular domain [18]. Among phase III developments, both drugs have been investigated in combination with docetaxel versus placebo in patients with advanced NSCLC [9,10]. These two studies did not allow any crossover. Nintedanib improved PFS (primary end-point) compared with placebo (median PFS 3.4 versus 2.7 months, HR 0.79 95%CI = 0.68–0.92, p = 0.0019) in the LUME-Lung 1 study. A significant improvement in OS was also observed in the adenocarcinoma subgroup. Ramucirumab improved OS (primary end-point) compared with placebo (10.5 versus 9.1 months, HR 0.86 95%CI = 0.75–0.98, p = 0.032) and PFS (median PFS 4.5 versus 3 months, p < 0.0001). Following these results, EMA approved both ramucirumab and nintedanib, and FDA approved ramucirumab. Both drugs are currently being reimbursed in several countries. European Society for Medical Oncology (ESMO) guidelines have included nintedanib or ramucirumab in combination with docetaxel, along with bevacizumab combined with paclitaxel as treatment options following first-line chemotherapy [19]. The lack of direct comparison between these regimens limits any evidence-based recommendation. In our study, paclitaxel plus bevacizumab appears to be less effective in patients with previous exposure to bevacizumab. This was not the case with ramucirumab; however, only 14% of the population had been exposed to bevacizumab [9]. Although the weekly design of the wPAC-BEV protocol is more constraining than other regimens including anti-angiogenic–based second-line regimens, weekly administration of chemotherapy has been shown to be feasible, especially in frail patients [20]. Moreover, wPAC-BEV was shown to have less hematological toxicity than docetaxel. In addition, bevacizumab is the only anti-angiogenic agent that is not covered anymore under patent protection. Given financial toxicity of recent immunotherapy-based regimens, some countries might find this second-line regimen attractive.

Since the IFCT-1103 ULTIMATE study was designed, new therapeutic opportunities have been offered to patients with NSCLC, thanks to the development of ICI targeting the programmed death-1 and its ligand, the programmed death-ligand 1 [21]. In patients who failed first-line platinum-based therapy, nivolumab, pembrolizumab and atezolizumab demonstrated superiority over docetaxel in both non-squamous and squamous NSCLC [1–3]. More recently, ICIs given in combination with platinum-based chemotherapy have been shown to improve survival compared with chemotherapy alone in the first-line setting of nsNSCLC [4,5]. So far, bevacizumab is the only anti-angiogenic agent approved for first-line treatment of nsNSCLC. Real-world data have reported a rather low use of bevacizumab in first-line setting [22]. However, recent results from the IMPOWER 150 study showing efficacy of a combination of carboplatin, paclitaxel, bevacizumab and atezolizumab may reinforce the role of bevacizumab in this setting [23], although the quadruplet is not yet approved by EMA or FDA. Remaining treatment options after failure of platinum-based chemotherapy and ICIs given sequentially or combined together are extrapolated from studies performed before the era of immunotherapy. They mostly rely on docetaxel, with an objective response rate below 10% [13,14]. Thus, development of new regimens with higher efficacy is eagerly needed. In that context, combination of weekly paclitaxel and bevacizumab may be considered as a new treatment option for patients eligible to

Table 2
Treatment-related adverse events, classified by MedDRA preferred terms according to CTC-AE version 4, occurring during the first sequence of randomised treatment in all patients with a least one dose of study drug.

Treatment-related adverse events	Any grade		Grade III-IV	
	DOC (n = 55)	wPAC-BEV (n = 109)	DOC (n = 55)	wPAC-BEV (n = 109)
Any adverse event	50 (90·9%)	107 (98·2%)	30 (54·5%)	50 (45·9%)
Haematological toxicity	42 (76·4%)	80 (73·4%)	28 (50·9%)	22 (20·2%)
Febrile neutropenia	4 (7·3%)	1 (0·9%)	4 (7·3%)	1 (0·9%)
Thrombopenia	13 (23·6%)	13 (11·9%)	0	0
Neutropenia	31 (56·4%)	50 (45·9%)	25 (45·5%)	21 (19·3%)
Anemia	33 (60·0%)	62 (56·9%)	4 (7·3%)	2 (1·8%)
Non-haematological toxicity	45 (81·8%)	101 (92·7%)	5 (9·1%)	30 (27·5%)
Bleeding/haemorrhage	1 (1·8%)	49 (45·0%)	0	1 (0·9%)
Hypertension	0	22 (20·2%)	0	8 (7·3%)
Proteinuria	0	23 (21·1%)	0	0
Constipation	0	21 (19·3%)	0	0
Neuropathy	15 (27·3%)	54 (49·5%)	0	9 (8·3%)
Thromboembolic event	0	8 (7·3%)	0	5 (4·6%)
Stomatitis	5 (9·1%)	19 (17·4%)	0	1 (0·9%)
Asthenia	27 (49·1%)	62 (56·9%)	3 (5·5%)	9 (8·3%)
Alopecia	19 (34·5%)	32 (29·4%)	2 (3·6%)	0
Vomiting	6 (10·9%)	15 (13·8%)	0	1 (0·9%)
Anorexia	11 (20·0%)	25 (22·9%)	1 (1·8%)	2 (1·8%)
Diarrhoea	12 (21·8%)	22 (20·2%)	0	0
Nausea	12 (21·8%)	24 (22·0%)	0	1 (0·9%)

Data are the number of patients with at least one adverse event (%).
DOC = docetaxel. wPAC-BEV = weekly paclitaxel plus bevacizumab.
Treatment-related adverse events leading to death: 1 pneumonitis in a DOC patients (1·8%); 2 adverse event in 2 wPAC-BEV patients (1.8%): 1 ischaemic stroke and 1 oesophagobronchial fistula.

anti-angiogenic drugs. Since the study was designed before immunotherapy emerged as a standard treatment in NSCLC, the reproducibility of these results in patients already exposed to ICIs remains to be determined. The same is true for other second-line regimens. Recent data suggest a similar efficacy of the combinations of nintedanib and docetaxel or bevacizumab and paclitaxel in patients already exposed to immunotherapy [24,25].

This study has several limitations. First, although main baseline characteristics between the 2 arms were well balanced, patients included in the DOC arm tended to be older and to be more frequently never smokers than in the wPAC-BEV arm. Second, crossover from one arm to another prevented any definitive conclusion on OS benefit. Allowing crossover in this study was decided to give all patients access to the experimental regimen because treatment options in 3rd line and beyond are very limited and to favour recruitment. Interestingly, allowing crossover provided data on activity of wPAC-BEV in patients previously exposed to DOC, although these patients may represent a selected population.

In conclusion, wPAC-BEV is an effective new second- or third-line therapeutic option for patients with advanced nsNSCLC and previously treated with platinum-based therapy, especially in patients with no or little prior exposure to bevacizumab, with manageable AEs and preserved quality of life. The confirmation of these results in patients already exposed to immunotherapy is warranted.

Contributors

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Role of the funding source

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Conflict of interest statement

A.B.C. has reported receiveing honoraria from Roche, AstraZeneca, Bristol-Myers Squibb, BoehringerIngelheim, MSD, Novartis and Pfizer and travel grants from Roche, AstraZeneca, BoehringerIngelheim,

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Appendix A. Supplementary data

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