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Multicenter phase II trial of nintedanib plus docetaxel in second-line treatment in advanced non-squamous non-small cell lung cancer patients refractory to first-line platin-based chemotherapy (REFRACT GFPC 02–15 study)

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ABSTRACT

Introduction: Advanced non-squamous non-small cell lung cancer (NsqNSCLC) progressing at the induction of a first-line of platin-based chemotherapy is a subgroup of patients with poor prognosis and few second-line treatment options.

Materials and Methods: This single-stage phase II prospective multicenter open-label trial performed in platin-based refractory (i.e. progressing during induction phase of first-line platin-based chemotherapy) advanced NsqNSCLC assessed the efficacy of the nintedanib-docetaxel combination in second-line treatment. The primary endpoint was progression-free survival (PFS) rates at 12 weeks with a cut-off at 30% for ineffectiveness and 50% for minimal efficacy.

Results: A total of 59 patients from 23 centers were included (mean age, 58.5 years; male gender, 73.6%; performance status 0–1, 100%; former/current smokers, 92.5%; adenocarcinoma, 92.5%, median platin-based first-line chemotherapy, 2). Nintedanib-docetaxel combination was administered for a median of 4 cycles. The rate of PFS at 12 weeks was 39.6% (95% CI, 28.2–56.8). Median PFS was 2.7 (95% CI, 1.4–4.1) months and one-year PFS was 11.8% (95% CI, 4.8–22.2). Median overall survival (OS) was 6.9 (95% CI, 4.3–8.2) months and 12-month OS was 32.1% (95% CI, 19.8–45.0); 18-month OS was 27.6% (95% CI, 16,1–40.4). Twenty-nine (53.7%) patients reported at least one serious treatment-related adverse events leading to permanent discontinuation of at least one study drug in 12 (22.2%) patients.

Conclusion: The predefined minimal efficacy was not demonstrated. However, a number of NsqNSCLC patients refractory to first-line platin-based chemotherapy appeared to benefit from this combination.

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1. Introduction

The management of patients with non-small cell lung cancer (NSCLC) has considerably changed with the discovery of oncogenic driver mutations (e.g., EGFR, ALK, BRAF, ROS 1), which are potential targets for therapy [1]. Another major breakthrough was the advent of PD-1/PD-L1 immunotherapy allowing patients with PD-L1 > 50% to be treated with pembrolizumab monotherapy and more recently, regardless of the level of PDL1, to be treated with a combination of pembrolizumab and chemotherapy [2,3]. However, most of these patients with advanced NSCLC receive platin-based chemotherapy associated or not to pembrolizumab as first-line treatment [2,3]. Approximately 15–30% of these patients show an early progression at the induction phase (i.e. during the first 4 cycles without pembrolizumab). Recently, a real-life study confirmed these results with a rate of refractory patients at 38.5% [4]. These patients refractory to platin-based chemotherapy have a poor prognosis, rapid deterioration of general condition and less frequent access to a second line of treatment [5,6].

Nintedanib is an oral triple angiokinase inhibitor that blocks vascular endothelial growth factor receptors (VEGFR 1–3), platelet-derived growth factor receptors (PDGFR-alpha and -beta) and fibroblast growth factor receptors (FGFR 1–3) [7,8]. These three receptors play a major role in tumor growth and spread by forming and maintaining new blood vessels [9,10].

Phase III studies pointed out the efficacy of the combination of an anti-angiogenic agent with a taxane compared to chemotherapy alone in second-line treatment, particularly in first line platin refractory patients. The phase III LUME-Lung 1 study compared nintedanib plus docetaxel vs. docetaxel alone in patients with stage IIIB/IV NSCLC after first-line therapy. In an exploratory analysis performed in the subset of refractory adenocarcinoma patients, median OS was longer in the docetaxel plus nintedanib group compared to the docetaxel group (9.8 vs. 6.3 months; HR, 0.62; p = 0.0246); median PFS was 4.2 vs. 1.6 months, respectively [11]. Comparable results were reported in the REVEL study that evaluated ramucirumab, a VEGFR-2 antagonist, in combination with docetaxel in refractory patients [12]. In the subgroup analysis of refractory patients, median OS was 8.3 vs. 6.3 months, median PFS was 4.0 vs. 2.5 months and overall response rate was 22.5% vs. 12.6% in ramucirumab-docetaxel group compared to docetaxel group, respectively. These two retrospective exploratory analyses provided the rationale for a prospective study in the population of patients refractory to first-line platinum-based chemotherapy.

The aim of the present phase II study was to determine the efficacy in terms of PFS of the nintedanib-docetaxel combination as second-line treatment in non-squamous NSCLC patients refractory to a first-line platin-based chemotherapy.

2. Materials and methods

2.1. Type of study and design

This was a single-stage phase II multicenter national open-label trial performed in patients with histologically documented stage IV non-squamous NSCLC refractory (progression as the best response) to first-line platin-based chemotherapy. The objective was to determine the efficacy in terms of PFS of the nintedanib plus docetaxel combination in this refractory population.

The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. It was approved by a local independent Ethics Committee ("CPP Sud Ouest Outre Mer IV": n°15-008/2015-000475-27). Patients gave their consent to participate in the study and for the use of their medical data for research purposes. A written informed consent was obtained from all patients before entering any study procedures. The trial is registered with ClinicalTrials.gov, number NCT02531737.

2.2. Patients

The key inclusion criteria were the followings: histologically confirmed non-squamous stage IV NSCLC; no activating EGFR mutation; no ALK translocation or unknown status; at least one measurable lesion (RECIST 1.1); refractory disease defined by documented progression during first-line chemotherapy based on a platinum-doublet and third-generation drug for ≤ 4 cycles; age ≥ 18 years and < 75 years; performance status 0 or 1; no history of other malignancy within the last 5 years; normal hepatic, renal function and hematological functions.

The key exclusion criteria were the followings: controlled disease by first-line treatment; previous treatment with docetaxel; previous therapy with VEGF inhibitors except bevacizumab; radiographic evidence of cavitary or necrotic tumors at screening; centrally located tumor with radiographic evidence of invasion of blood vessels; chemotherapy, hormonotherapy, immunotherapy or tyrosine kinase inhibitor treatment within the past 4 weeks; radiotherapy (except for brain and extremities); symptomatic brain metastases (dexamethasone therapy was allowed if administered at stable dose within at least one month); severe organic, psychiatric or neurological disorders; Grade ≥ 1 peripheral neuropathy; uncontrolled infection; superior vena cava syndrome; malabsorption syndrome; pregnancy and breast-feeding; surgery less than two months before study entry.

2.3. Treatments

Patients received oral nintedanib (Vargatef®) 400 mg/day on Days 2 to 21 of a 3-week cycle including docetaxel 75 mg/m^2 by intravenous infusion on Day 1. Monotherapy with nintedanib or docetaxel was possible after 4 cycles of dual therapy. As well as a reduction in the dose of docetaxel to 60 mg/m^2 and/or nintedanib to 300 mg/day or 200 mg/day depending on the toxicities.

2.4. Data collection

Data obtained at inclusion visit were age, gender, smoking status, ECOG performance status, weight loss, date of NSCLC diagnosis, histology, tests for EGFR mutation or other mutations, number and localization of metastatic sites, first-line treatments and number of cycles. Data obtained at follow-up visits (each 3 weeks) included characteristics of study treatments, clinical exam, ECOG performance status, chest radiotherapy and biological tests. Tumor response (RECIST 1.1) was assessed using computed tomography or magnetic resonance imaging scan every 6 weeks. Adverse events were assessed from the first dose of study therapy throughout the treatment period and for 30 days after the end of treatment and graded according to the National Cancer Institute Common Toxicity Criteria, version 4.03. Safety data included also adverse events of special interest: perforations (gastrointestinal or not), leakages, fistulas, abscesses, thromboembolic events and drug-induced liver injuries.

A central review of patient evaluations was performed by an expert panel of clinicians in the setting of GFPC (French Lung Cancer Group). The role of this panel was to validate objective responses to treatment and to evaluate the relationship between study drugs and serious adverse events or adverse events of special interest.

2.5. Statistical analysis

The primary endpoint was the rate of PFS at 12 weeks after inclusion in the study (RECIST 1.1 criteria) [13]. Deaths whatever the cause and missing data for primary endpoint were considered as progression. The analyses were performed in patients who received the study treatment ("As treated" population).

The design of this single-stage phase II design trial was done according to the approach of A'Hern [14]. Based on previous studies, a minimum level of efficacy at 12 weeks was set at 50% (p_1) and the value

Table 1
Characteristics of study patients at inclusion in all patients of "As treated" population) and in subgroups (patients with PFS < 6 months and ≥ 6 months).

	All patientsN = 53	PFS < 6 months N = 39	PFS ≥ 6 months N = 14	
Age (years)				
Mean (SD)	58.5 (8.5)	57.6 (8.9)	61.3	NS
Median (range)	61.0 (35; 73)	59 (35; 73)	62.5 (44; 67)	
Male gender, n (%)	39 (73.6)	29 (74)	10 (71)	NS
Smoking, n (%)				
Former smoker	23 (43.4)	16 (41)	7 (50)	NS
Current smoker	26 (49.1)	22 (56)	4 (28.5)	
Never-smoker	4 (7.5)	1 (2)	3 (21)	
Performance status, n (%)				
0	13 (24.5)	10 (25)	3 (21)	NS
1	40 (75.5)	29 (74)	11 (78.5)	
Adenocarcinoma, n (%)	49 (92.5)	35 (90)	14 (100)	NS
Presence of metastases at inclusion, n (%)	52 (98.1)	38 (97)	14 (100)	NS
Number of metastatic sites, n (%)				
1	12 (22)	9 (23)	3 (21)	NS
2	20 (37)	13 (33)	7 (50)	
3	10 (19)	8 (20)	2 (14)	
≥ 4	10(19)	8 (20)	2 (14)	
Missing	1	1	0	
Metastatic sites, n (%)				
Bone	24 (45.3)	20 (51)	4 (28.5)	NS
Lung	23 (43.4)	14 (36)	9 (64)	NS
Liver	22 (41.5)	19 (48)	3 (21)	NS
Brain	19 (35.8)	15 (38)	4 (28.5)	NS
Adrenal gland	14 (26.4)	12 (30)	2 (14)	NS
Cervical and supraclavicular lymph nodes	6 (11.3)	3 (7)	3 (21)	NS
Other	11 (20.8)	5 (13)	6 (42)	NS
Cancer-related symptoms, n (%)	40 (75.5)	26 (66)	14 (100)	NS
First-line treatment, n (%)				
Platin-based dual therapy	53 (100)	39 (100)	14 (100)	NS
Cisplatin	26 (49.1)	20 (51)	6 (43)	NS
Carboplatin	27 (50.9)	19 (49)	8 (57)	NS
Pemetrexed	53 (100)	39 (100)	14 (100)	NS
Bevacizumab	12 (22.6)	10 (26)	2 (14)	NS
Number of cycles of first-line treatment, n (%)				
1	1 (1.9)	1 (2.5)	0	NS
2	29 (54.7)	20 (51)	9 (64)	NS
3	10 (18.9)	9 (23)	1 (7)	NS
4	13 (24.5)	9 (23)	4 (28.5)	NS
First-line treatment duration (days), mean (SD)	53.3 (19.4)	58.6 (48)	54.7 (21.2)	NS

NS, not significant.

for a clearly ineffective treatment was set at 30% (p_0); the null hypothesis H_0: $P \leq p_0$ was tested against the alternative hypothesis H_1: $P \geq p_1$. The sample size determination of this single-stage phase II trial was based on exact binomial distribution with alpha risk 0.05 and beta risk 0.10. With 10% of non-evaluable subjects at 12 weeks, the number of patients to be included was 59. With 53 analyzable patients, the threshold of success was 22 patients. The secondary endpoints were OS, overall response rate and safety profile. Median PFS and median OS after treatment initiation were estimated using Kaplan-Meier method. An exploratory analysis was performed in patients with PFS ≥ 6 months.

The statistical analyses were performed with SAS 9.2 software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient disposition and characteristics at inclusion

A total of 59 patients in 23 centers were enrolled and followed from December 7, 2015 to December 24, 2019. Six patients did not receive the study combination and were excluded from the analysis (hepatitis, hemoptysis, no progression, superior vena cava syndrome, death, performance status > 1); 53 patients received at least one dose of one study drug and were included in the "As treated" population and in safety analysis.

The mean (SD) age of patients was 58.5 (8.5) years and 73.6% were male, 92.5%. were former/current smokers; 18.9% had a weight loss > 5%. (Table 1). Histology of tumor was adenocarcinoma in 92.5% of patients.

In first line, all patients received platinum-pemetrexed combination, associated with bevacizumab in 22.6% of cases, for a median of 2 cycles.

Table 2
Efficacy results in "As treated" population and in patient with PFS ≥ 6 months).

	All patients N = 53	95% CI	PFS ≥ 6 months N = 14
Progression-free survival at 12 weeks, n (%)	21 (39.6)	26.5–54.0	14 (100)
Death at 12 weeks, n (%)	9 (17.0)	–	0
Kaplan-Meir analysis			
Progression-free survival			
1 year, %	11.8	4.8–22.2	
Median (months)	2.7	1.4–4.1	8.4
Overall survival			
1 year, %	32.1	19.8–45.0	64
Median (months)	6.9	4.3–8.2	
Best observed response (12-month follow-up), n (%)			
Complete response (CR)	0	–	0
Partial response (PR)	10 (18.9)	–	4 (28.5)
Stable disease (SD)	19 (35.8)	–	10 (71.5)
Progressive disease (PD)	24 (45.3)	–	0

3.2. Study treatments

The median number of cycles with the combination was 4 (IQR 2–6); there was a dose modification in 25 (47.2%) patients for docetaxel and in 18 (34.0%) for nintedanib. After progression, 36/53 (68%) patients received a third-line treatment (including immunotherapy in 83% [30/36] of cases). For patients receiving immunotherapy, 42.9% had duration of treatment of>4 months and the rates of complete, partial response and stabilization were 0%, 25% and 21.5%, respectively.

3.3. Efficacy

At 12 weeks, 21 (39.6%) patients were not progressive, and the primary endpoint was therefore not achieved (Table 2).

Best observed response was partial response for 18.9%, stable disease for 35.8% and progressive disease for 45.3% (no patient had complete response) (Table 2). Among the 12 patients who received bevacizumab as first-line treatment, 33.4% had no progression at 12 weeks and best observed response was partial response for 8.3%, stable disease for 58.3% and progressive disease for 33.4%.

Median PFS was 2.7 (95% CI, 1.4–4.1) months (Fig. 1) and one-year PFS was 11.8% (95% CI, 4.8–22.2); median OS was 6.9 (95% CI, 4.3–8.2) months (Fig. 2) and 12 and 18-months OS were 32.1% (95% CI, 19.8–45.0) and 27.6% (95% CI, 16.1–40.4), respectively.

Fourteen (26%) of the 53 patients showed specific outcomes: they had a PFS ≥ 6 months. These long responders did not seem to present any particular clinical characteristics (Table 1), except for a lower number of metastases (71% with 1 or 2 metastases), in particular visceral metastases (liver, adrenal gland, bone). They were well refractory to first-line treatment with 64% progression after the first 2 cycles and only a small percentage (14%) had received bevacizumab as first-line treatment.

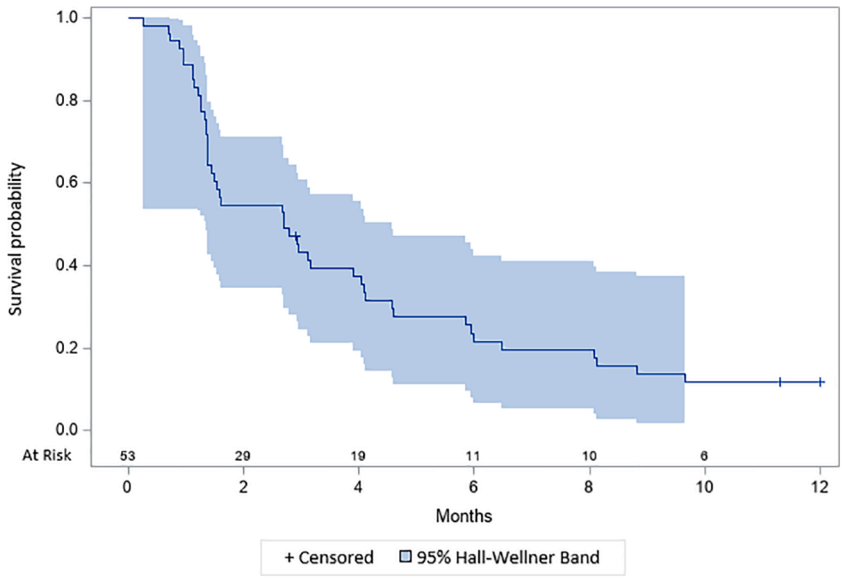

Fig. 1. Progression-free survival ("As treated" population).

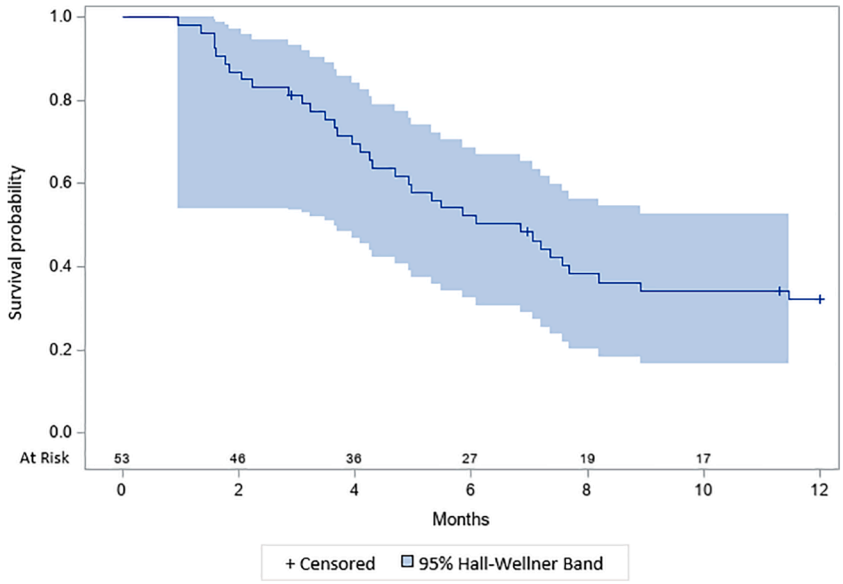

Fig. 2. Overall survival ("As treated" population).

3.4. Safety

Fifty-two (96.3%) out of the 53 patients who received at least one dose of study treatments reported 397 TEAE. Twenty-nine (53.7%) patients reported at least one serious TEAE. Twelve (22.2%) patients had at least one TEAE that led to permanent discontinuation of at least one study drug. TEAE were considered to be related to study treatment in 69.3% (275/397) of cases.

The most frequent TEAE were gastrointestinal disorders (n = 32; 59.3%), neutropenia (n = 26, 48.1%), fatigue/asthenia/general physical health deterioration (n = 28; 51.9%) and paresthesia/ peripheral neuropathy (n = 15, 27.8%) (Table 3).

Most adverse events (75.3%; 299/397) were Grade 1–2. Thirty-three (61.1%) patients reported at least one Grade 3–4 TEAE; 5 patients had Grade 5 TEAE: 4 were not related to study drugs (pericarditis, disease progression, deterioration of general condition, meningeal metastases) and one TEAE was considered to be related (hemoptysis).

Adverse events of special interest were reported in 5 patients: thromboembolic events (n = 2), elevation of liver enzymes (n = 2) and abscess of port (n = 1).

4. Discussion

In this open-label phase II study in advanced non-oncogene-addicted NsqNSCLC patients refractory to first-line platin-based chemotherapy, the primary study objective for efficacy of the nintedanib-docetaxel combination (12-week PFS for 50% of the patients) was not achieved. Indeed, 21 (39.6%; 95% CI, 26.5–54.0) patients had PFS at 12 weeks with a median PFS and OS of 2.7 and 6.9 months, respectively. Nevertheless, a subpopulation of these patients with extremely severe prognosis seems to benefit from this combination with a 1-year PFS of 11.8% and 12 and 18-month OS of 32.1% and 27.6%, respectively.

In the exploratory analysis in the subset of first-line refractory adenocarcinoma patients of the LUME-Lung 1, median PFS in the nintedanib plus docetaxel group was 4.2 months and median OS was 9.8 months [11]. Comparable results were reported in the exploratory

Table 3
Treatment-emergent adverse events according to System Organ Classes (Safety population).

	Patients with at least on TEAE n (%) N = 54	Number of TEAE all grade) n (%) N = 397	Number of patients with Grade 3–4 TEAE	Number of patients with Grade 5 TEAE
General disorders and administration site conditions	33 (61.1)	50 (12.6)	2	2
Fatigue, asthenia, general physical health deterioration	28 (51.9)	36 (9.1)	3	0
Gastrointestinal disorders	32 (59.3)	83 (20.9)	5	0
Nausea	18 (33.3)	21 (5.3)	1	0
Vomiting	9 (16.7)	10 (2.5)	1	0
Abdominal pain	5 (9.3)	10 (2.5)	0	0
Diarrhea	24 (44.4)	33 (8.3)	3	0
Blood and lymphatic system disorders	29 (53.7)	78 (19.6)	0	0
Anemia	12 (22.2)	12 (3.0)	1	0
Febrile neutropenia	6 (11.2)	6(1.6)	6	0
Leukopenia	6 (11.2)	6(1.6)	4	0
Neutropenia	26 (48.1)	52 (13.1)	6	0
Respiratory, thoracic and mediastinal disorders	16 (29.6)	24 (6.0)	0	0
Dyspnea	7 (13)	7 (1.8)	2	0
Hemoptysis	3 (5.6)	3 (0.8)	0	1
Pulmonary embolism	2 (3.7)	2 (0.5)	2	0
Metabolism and nutrition disorders	15 (27.8)	18 (4.5)	0	0
Decreased appetite	11 (20.4)	13 (3.3)	1	0
Nervous system disorders	15 (27.8)	21 (5.3)	1	1
Paresthesia, peripheral neuropathy	9 (16.7)	10 (2.5)	1	0
Infections and infestations	15 (27.8)	20 (5.0)	2 [a]	0
Bronchitis	5 (9.3)	5 (1.3)	0	0
Device-related infection	1 (1.9)	2 (0.5)	1	0
Investigations	13 (24.1)	44 (11.1)	0	0
Alanine aminotransferase/ alanine aminotransferase increased	7 (13.1)	20 (5.0)	0	0
Skin and subcutaneous tissue disorders	13 (24.1)	19 (4.8)	0	0
Alopecia	8 (14.8)	8 (2.0)	0	0
Musculoskeletal and connective tissue disorders	9 (16.7)	13 (3.3)	0	0
Cardiac disorders	5 (9.3)	5 (1.3)	0	1
Eye disorders	4 (7.4)	5 (1.3)	0	0
Hepatobiliary disorders	3 (5.6)	4 (1.0)	0	0
Endocrine disorders	2 (3.7)	2 (0.5)	1 [b]	0
Injury, poisoning and procedural complications	2 (3.7)	2 (0.5)	2	0
Ear and labyrinth disorders	2 (3.7)	2 (0.5)	0	0
Renal and urinary disorders	2 (3.7)	2 (0.5)	1	0
Psychiatric disorders	2 (3.7)	2 (0.5)	0	0
Congenital, familial and genetic disorders	1 (1.9)	1 (0.3)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1(1.9)	1 (0.3)	0	0
Reproductive system and breast disorders	1 (1.9)	1 (0.3)	0	0

Only most frequent or of interest Preferred Terms are reported in each System Organ Class.
Results are presented as n (%).
[a] Including one patient with sepsis.
[b] Adrenal insufficiency.

analysis of the REVEL study of refractory patients receiving ramucirumab plus docetaxel with a median PFS of 4.0 months, median OS of 8.3 months and disease control rate of 52.2% [12]. Our results were comparable in terms of disease control rate (54.7%), but median PFS (2.7 months) and median OS (6.9 months) were slightly shorter. In fact, apart from exploratory subgroup analyses, few prospective studies are dedicated to patients refractory to a first line of platin-based chemotherapy. Thus, our results are closer to those of the TITAN study. In this phase III prospective randomized study, refractory NSCLC patients received erlotinib or standard chemotherapy as second line [5]. Median PFS was 6.3 and 8.6 weeks, median OS was 5.3 and 5.5 months and disease control rate was 34.5% and 43.0% in erlotinib group and chemotherapy group, respectively.

A quarter of the patients in this study seem to benefit from the docetaxel-nintedanib combination in terms of PFS. No specific clinical criterion could be evidenced in this population as in the LUME 1 or REVEL studies, except for a lower number of metastases, in particular visceral metastases, which is a known prognostic factor but not predictive of response to treatment [15]. To our knowledge, there are no predictive biomarkers (blood, tissue or standard imaging) of response to antiangiogenic drugs associated with cytotoxic chemotherapy [16]. The population most sensitive to the combination of docetaxel and antiangiogenic drugs appears to be very difficult to target to date.

There are few data on the use of immunotherapy in second line for advanced NSCLC in patients refractory to first-line platin-based treatment. The CHECKMATE 057 study evaluated the PD-1 inhibitor nivolumab vs. docetaxel as second-line treatment in patients who progressed after first-line treatment. Although only refractory patients were enrolled in our study, the median PFS (2.7 months) was comparable to that of the nivolumab arm of CHECKMATE 057 study (2.3 months) [15]. Exploratory analysis of CHECKMATE 057 in the subgroup of patients who started immunotherapy within 3 months after the end of the first line of platin-based chemotherapy did not show benefit of nivolumab vs. docetaxel (HR 0.95; 95% CI, 0.76–1.20). It would be interesting to evaluate immunotherapy in refractory NSCLC patients. The combination of chemotherapy and immune checkpoint inhibitors (PD-L1/PD-1) has become a standard first-line treatment for NsqNSCL (PD-L1 $<$ 50%). With this combination of immunotherapy and chemotherapy, the number of patients progressing in the first 3 months seems to be slightly lower (10–20%) compared to chemotherapy alone.

This study was prospective and multicentric with a number of patients based on statistical assumptions. Therefore, it has good external validity but has also some limitations. The main limitation is the absence of a comparative group. Indeed, it was decided to use a single-stage phase II design to evaluate the study drug combination. This design is frequently used to evaluate if a new treatment is likely to achieve a basic level of efficacy based on historical data before launching a larger comparative randomized phase III trial. As a consequence of the single arm design, the trial was open-label. However, the response rates assessed by each investigator were reassessed and validated by an expert panel of clinicians of GFPC (French Lung Cancer Group). The choice of the predefined thresholds for inefficacy and for minimum level of efficacy was based on literature but was somewhat arbitrary. The statistical hypothesis was a 50% gain for PFS thus leading to a median PFS of 12 weeks rather than 8 weeks according to literature data. Another limitation is the definition of refractory NSCLC patients which can vary according to authors, thus making comparisons across studies difficult [16]: progressive disease as best response to first-line therapy (PD-FLT), time since start of first-line therapy (TSFLT) $\leq$ 5 months and time since end of first-line therapy (TEFLT) $<$ 3 months [12,17,18]. We adopted a

strict definition of the refractory status which is the same as in the TITAN study: progression within the four first cycles of a standard platin-based chemotherapy doublet [5]. Patients selected with this definition were those with the worst prognosis. This could explain the important number of patients with progression at the early times of their management (half had progression within the first two cycles).

It could be argued that with the availability of pembrolizumab, with or without chemotherapy, the standard of first-line treatment has changed in recent years. Nevertheless, a non-negligeable number of patients continue to receive a doublet of chemotherapy alone in the first line, in particular those with contraindications to immunotherapy, untreated symptomatic brain metastases or those with high doses of corticosteroids. In addition, even in patients treated with pembrolizumab-platinum doublet, second-line treatment in those with progressive disease as the best response remains a challenge. Retrospective studies show encouraging results with nintedanib-docetaxel in patients who received immunotherapy-chemotherapy combinations in the first line, even though these studies do not specifically consider refractory patients [19,20]. Therefore, although our results did not achieve the predefined primary endpoint in terms of PFS at 12 weeks, the results for median PFS and OS are encouraging if the poor prognosis of this patient population is considered.

In conclusion, although the PFS rate at 12 weeks was better than ineffectiveness, the predefined minimal efficacy was not demonstrated. However, a number of NsqNSCLC patients refractory to first-line platin-based chemotherapy appeared to benefit from this combination.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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