Lung Cancer 136 (2019) 109–114

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Brigatinib in patients with ALK-positive advanced non-small-cell lung cancer pretreated with sequential ALK inhibitors: A multicentric real-world study (BRIGALK study)

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ARTICLE INFO

Keywords:
Advanced non-small cell lung cancer
ALK rearrangement
Brigatinib
Crizotinib
ALK inhibitor
Early access program

ABSTRACT

Objectives: Brigatinib is a next-generation ALK inhibitor initially developed in ALK-positive NSCLC pretreated with crizotinib.

Materials and Methods: This retrospective multicentric study analyzed ALK-positive advanced NSCLC patients pretreated with at least one tyrosine-kinase inhibitor, including crizotinib, and enrolled in the brigatinib French early access program. The primary endpoint was investigator-assessed progression-free survival (PFS).

Results: 104 patients were included (mean age, 56.6 years; never smokers, 61.5%; adenocarcinoma, 98.1%). Patients had received a median of 3 previous treatment lines, including at least 2 ALK inhibitors (mainly crizotinib then ceritinib). At brigatinib initiation, 59.1% had performance status 0–1, 51.9% had ≥ 3 metastatic sites, 74.5% had central nervous system metastases (CNS) and 8.8% had carcinomatous meningitis. Median duration of brigatinib treatment was 6.7 (95% CI, 0.06–20.7) months. Median PFS was 6.6 (4.8–9.9) months for the entire population. For patients who received 2, 3–4 and > 4 lines of treatment before brigatinib, PFS was 4.3 (2.5–8.9), 10.4 (5.9–13.9) and 3.8 (0.8–7.4) months, respectively. In the 91 evaluable patients, disease control rate was 78.2%. From brigatinib start, median overall survival was 17.2 (11.0–not reached) months. Among the 68 patients with progressive disease after brigatinib, CNS was involved in 29.4% of cases. Median OS from the diagnosis of NSCLC was 75.3 (38.2–174.6) months.

Conclusion: These real-world results confirm the efficacy of brigatinib in a cohort of patients heavily pretreated for ALK-positive advanced NSCLC.

1. Introduction

Rearrangements of anaplastic lymphoma kinase gene (*ALK*) are an oncogenic driver reported in 3–5% of patients with non-small cell lung cancers (NSCLC) [1]. Patients with *ALK* rearrangement (ALK-positive) NSCLC are generally younger, are never or light smokers, with a histology of adenocarcinoma and a high risk of central nervous system (CNS) metastases at diagnosis and progression [2,3].

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https://doi.org/10.1016/j.lungcan.2019.08.010
Received 13 May 2019; Received in revised form 17 July 2019; Accepted 13 August 2019

Crizotinib was the first ALK tyrosine-kinase inhibitor (TKI) approved for ALK-positive NSCLC. In first-line treatment, crizotinib achieved objective responses rates from 61 to 74% with a median progression-free survival (PFS) of 8–11 months [4–6]. Mechanisms of acquired resistance to crizotinib (alterations in *ALK* gene or activation of signaling pathways bypassing *ALK*) explain disease progression in most patients treated with crizotinib [7]. The limited CNS penetration of crizotinib is also responsible for intracranial disease progression, which is the most frequent site of relapse. Second-generation ALK inhibitors, namely ceritinib and alectinib, achieved median PFS of 5.7–6.9 months and 8.1–8.9 months, respectively, in patients pretreated with crizotinib [8–12]. However, due to secondary ALK kinase domain resistance mutations (e.g., G1202R mutation) in patients treated by ceritinib or alectinib and previously treated with crizotinib, new ALK inhibitors are required.

Brigatinib is a new ALK inhibitor with a potent activity on many ALK resistance mutations including G1202R mutation, which is inhibitable *in vitro* and in some patients but perhaps not in all [13]. A phase II randomized trial included patients with ALK-positive advanced NSCLC and disease progression after crizotinib treatment (69% with brain metastases and 74% with prior chemotherapy) and compared brigatinib 90 or 180 mg/day after a first week at 90 mg/day [14]. Brigatinib yielded confirmed objective response rates (ORRs) of 51% in arm A (112 patients treated at 90 mg daily) and 55% in arm B (110 patients treated at 180 mg daily with a 7-day lead-in at 90 mg, the recommended dosing regimen) per independent review committee (IRC). Median progression-free survival (PFS) was 9.2 months in arm A and 16.7 months in arm B, per IRC respectively [15]. In patients with measurable brain metastases at baseline, ORR was 42% in 90-mg group and 67% in 180-mg group. Based on the results of the phase II study, the US Food and Drug Administration granted in April 2017 accelerated approval to brigatinib in patients with locally-advanced or metastatic ALK-positive NSCLC who have progressed on or are intolerant to crizotinib. In France, brigatinib was available through an early access program since August 2016 for patients with ALK-positive NSCLC refractory to crizotinib and ceritinib. This program closed on January 21st, 2018 after the approval of brigatinib by the European Medicines Agency. The primary objective of the BRIGALK study was to assess the efficacy of brigatinib after at least two ALK inhibitors in patients who benefited from this early access program.

2. Patients and methods

2.1. Study design and patients

The BRIGALK study (GFPC 07–2017) was a national retrospective non-interventional study that included patients treated with brigatinib in the French early access program. The objective was to describe in real-world setting the efficacy of brigatinib in patients with advanced NSCLC harboring *ALK* rearrangement.

The inclusion criteria were the followings: at least 18 years old; advanced NSCLC; ALK-positive NSCLC assessed with *in situ* hybridization (FISH) and/or immunohistochemistry; previous treatment with at least one ALK inhibitor including crizotinib; treatment with brigatinib in the setting of the early access program from September 1st, 2016 to January 1st, 2018.

The primary objective was to evaluate the investigator-assessed PFS from brigatinib initiation, defined as the time from first dose of brigatinib to first documentation of objective disease progression or to death from any cause. The main secondary objectives were the followings: ORR to brigatinib, overall survival (OS) from brigatinib initiation and from diagnosis of NSCLC; treatment duration and reasons for discontinuation of brigatinib treatment.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the French Advisory Committee on Information Processing in Health Research (CCTIRS). If patients were alive, they received a written information on the study. For deceased patients, an exemption of information was obtained from CCTIRS.

2.2. Data collection

Patient data were obtained retrospectively from medical files and included demographics, characteristics of NSCLC, number and localization of metastatic sites, previous treatments, tumor response to brigatinib, resistance mutation before brigatinib initiation or after progression and treatments after progression. Patients were included consecutively in each center according to inclusion criteria without selection.

2.3. Statistical analysis

The Kaplan-Meier method was used to estimate PFS and OS for the entire cohort and in defined subgroups according to the number of lines of treatments. Best response to treatment was assessed according to RECIST 1.1 criteria [16]. The statistical analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of patients at diagnosis of NSCLC

A total of 104 patients were included in 42 centers. Their mean (SD) age was 56.6 (11.5) years and 61.5% were never-smokers (Table 1). NSCLC was adenocarcinoma in 98.1% of patients with stage IV disease in 88.5%. At diagnosis, there was a mean of 3.3 (1.3) metastatic sites; CNS metastases were reported in 28.9% of patients. Overall, patients were in good condition with performance status at 0–1 for 91.6%.

The median time from NSCLC diagnosis and result of *ALK* translocation test was 21 (range, 0–515) days. Diagnosis of *ALK* translocation was based in 16% of cases on a positive immunohistochemistry with score 3+, on FISH in 84% of cases (78% of these patients had also positive immunohistochemistry with score 2+/3+). Diagnosis was established mainly on biopsy of the primary tumor (62.0%), mediastinal lymph nodes (11.5%), pleural metastases (9.6%) or extra-thoracic metastases (16.9%).

3.2. Treatments before brigatinib initiation

Before brigatinib, patients received a median of 3 lines of treatment. Among the different therapeutic sequences presented in Table 2, the most frequent were two (n = 29) or three lines (n = 43). For the 29 patients who received two lines of treatment before brigatinib, the most frequent sequence was crizotinib-ceritinib (n = 24; 82.7%); for the 43 patients who received 3 lines before brigatinib, the most frequent sequence was chemotherapy-crizotinib-ceritinib (n = 32; 74.4%). Almost all patients received at least two anti-ALK TKIs before brigatinib (97/104; 93.3%).

First-line treatment was chemotherapy for 62.5% of patients or crizotinib for 36.5% (Table 3). All patients with chemotherapy treatment received a platinum/pemetrexed combination. Median duration of chemotherapy was 5.8 (range, 0.1–29.6) months and median duration of crizotinib treatment was 9.2 (range, 0.1–22.2) months.

Second-line treatment was chemotherapy (platinum/pemetrexed) for 18.3% of patients and TKI for the others (crizotinib for 52.9% and ceritinib for 26.9%). Median duration of post-chemotherapy treatment was 11.5 months for crizotinib and median duration of post-crizotinib treatment was 3.0 months for ceritinib.

A total of 75 patients received a 3rd line of treatment (chemotherapy, 13.3%; crizotinib, 8.0% and ceritinib, 77.3%); 32, 18 and 11 patients received a 4th, 5th, and 6th line of treatment, respectively (Table 2).

Radiotherapy was administered before brigatinib to 56.7% (59/

Table 1
Characteristics of patients at diagnosis of NSCLC.

		N = 104
Mean age, years (SD)		56.6 (11.5)
Range		23–85
Female gender, n (%)		63 (60.6)
Performance status, n (%)		
0		43 (51.8)
1		33 (39.8)
≥ 2		7 (8.4)
Missing		21
Smoking, n (%)		
Current smoker		8 (7.7)
Former smoker		32 (30.8)
Never-smoker		64 (61.5)
Concomitant diseases, n (%)		
Cardiovascular disease		22 (21.2)
Hypercholesterolemia		13 (12.5)
Cancer		10 (9.6)
Diabetes		6 (6.2)
Chronic obstructive pulmonary disease		3 (2.9)
Others		6 (6.2)
Histology, n (%)		
Adenocarcinoma		102 (98.1)
Large-cell carcinoma		2 (1.9)
Stage, n (%)		
Localized		2 (1.9)
Locally advanced		10 (9.6)
Metastatic		92 (88.5)
Metastatic sites [a]		
Number, mean (SD)	3.3 (1.3)	
Localization, n (%)		
Bone	48 (53.3)	
Liver	39 (43.3)	
Lung	28 (31.1)	
Adrenal gland	28 (31.1)	
Central nervous system	26 (28.9)	
Pleura	21 (23.3)	
Lymph nodes	18 (20.0)	
Pericardium	8 (8.9)	
Others	6 (6.7)	
Peritoneum	3 (3.3)	
Missing	2	

[a] For the 92 patients with metastatic stage.

Table 2
Therapeutic sequences before brigatinib.

Sequences 2 lines	N = 29
Crizotini**b-c**eritinib	24
Crizotini**b-c**hemotherapy	1
Chemotherapy-crizotinib	4
3 lines	**N = 43**
Chemotherapy-crizotini**b-c**eritinib	32
Chemotherapy-crizotini**b-a**lectinib	1
Chemotherapy-chemotherapy-crizotinib	2
Crizotini**b-c**hemotherapy-ceritinib	3
Crizotini**b-ceritinib-c**hemotherapy	4
Alectini**b-crizotinib-c**eritinib	1
4 lines	**N = 14**
Chemotherapy-chemotherapy-crizotini**b-c**eritinib	3
Chemotherapy-crizotini**b-ceritinib-c**hemo/immunotherapy	3
Chemotherapy-crizotini**b-ceritinib-l**orlatinib	3
Chemotherapy-crizotini**b-c**hemotherapy-ceritinib	2
Crizotini**b-ceritinib-c**hemotherapy-chemotherapy	2
Crizotini**b-chemotherapy-ceritinib-c**hemotherapy	1
5 lines and more	**N = 18**
Chemotherapy-crizotini**b-ceritinib-c**hemotherapy-other	4
Chemotherapy-crizotini**b-ceritinib-c**hemotherapy-other	5
Chemotherapy-chemotherapy-ceritini**b-c**hemotherapy-alectinib	1
Chemotherapy-chemotherapy-ceritini**b-c**hemotherapy-ceritinib	5
Crizotini**b-c**hemotherapy-chemotherapy-crizotini**b-other**	2
Crizotini**b-i**mmunotherapy-crizotini**b-ceritinib-o**ther	1

Table 3
Systemic treatments before brigatinib.

Lines of treatment [a]	N (%)
1st line	**N = 104**
Chemotherapy	65 (62.5)
Crizotinib	38 (36.5)
Alectinib	1 (1.0)
2nd line	**N = 104**
Chemotherapy	19 (18.3)
Crizotinib	55 (52.9)
Ceritinib	28 (26.9)
Alectinib	1 (1.0)
Immunotherapy	1 (1.0)
3rd line	**N = 75**
Chemotherapy	10 (13.3)
Crizotinib	6 (8.0)
Ceritinib	58 (77.3)
Immunotherapy	1 (1.3)
4th line	**N = 32**
Chemotherapy	19 (59.4)
Crizotinib	2 (6.3)
Ceritinib	6 (18.8)
Lorlatinib	3 (9.4)
Alectinib	1 (3.1)
Immunotherapy	1 (3.1)
5th line	**N = 18**
Chemotherapy	6 (33.3)
Crizotinib	6 (33.3)
Ceritinib	5 (27.8)
Alectinib	1 (5.6)
6th line	**N = 11**
Chemotherapy	3 (27.3)
Crizotinib	5 (45.4)
Ceritinib	3 (27.3)

Results are presented as n (%).
[a] 2 lines for n = 29 patients; 3 lines for n = 43; 4 lines for n = 14, 5 lines for n = 7 and 6 lines for n = 11.

104) of patients, most frequently during the first treatment line (47.5%; 28/59). Brain was the main target for radiotherapy (64%; 38/59).

3.3. Clinical characteristics at brigatinib initiation

At initiation of brigatinib treatment, performance status was 0–1 for 59.1% of patients (Table 4). More than 40% of them had a PS ≥ 2 and general symptoms (asthenia or weight loss) for 72%; 51.9% of patients had ≥ 3 metastatic sites and 74.5% and 8.8% had CNS metastases and carcinomatous meningitis, respectively. CNS metastases were active in the majority of cases (51.8%).

A tissue rebiopsy was performed for 33.7% (35/104) of patients (Table 3). Detection of resistance mutations was carried out in 18 cases and G1202R mutation was identified in 4 patients; other mutations found are reported in Table 4.

Almost all patients (95.2%; 99/104) received brigatinib at 90 mg/day for 7 days and then 180 mg/day. The 180-mg dose was reduced to 90 mg for 9 (8.8%) patients and 10 (9.6%) had permanent treatment discontinuation due to intolerance or patient request.

3.4. Efficacy of brigatinib in entire population

The date of primary data cut-off was June 30, 2018. Median PFS from initiation of brigatinib was 6.6 (95% CI, 4.8–9.9) months with a median OS of 17.2 (95% CI, 11.0–not reached) months (Fig. 1).

For patients who received 2, 3–4 and > 4 lines of treatment, median PFS was 4.3 (95% CI, 2.5–8.9), 10.4 (95% CI, 5.9–13.9) and 3.8 (95% CI, 0.8–7.4) months, respectively (Fig. 2).

For the 91 evaluable patients, the disease control rate was 78.2% (stable disease, 28.2%; partial response, 45.7%; complete response, 4.3%). Median duration of brigatinib treatment was 6.7 (range, 0.06–20.7) months.

Table 4
Clinical characteristics of patients before brigatinib treatment.

Characteristics	N = 104
Stage IV	104 (100)
ECOG performance status	
0	17 (19.3)
1	35 (39.8)
≥ 2	36 (40.9)
Missing	16
Location of metastatic sites	
Central nervous system	76 (74.5)
Bone	54 (52.9)
Lung	44 (43.1)
Pleura	32 (31.4)
Liver	32 (31.4)
Peripheral lymph nodes	32 (31.4)
Adrenal gland	12 (11.8)
Meninges	9 (8.8)
Pericardium	6 (5.9)
Missing	2
Symptoms	
General	74 (72.5)
Neurological or meningeal	32 (31.4)
Missing	2
Weight loss > 5 kg	36 (36.7)
Missing	6
Rebiopsy before brigatinib	35 (33.7)
Metastatic site	14
Primitive tumor	11
Cerebrospinal fluid	6
Pleura	4
Liquid biopsy	9
Result of rebiopsy	
Histological change	2
ALK rearrangement not found	4
Detection of mutation resistance before brigatinib	18
G1202R	4
L861Q	1
C1156Y	1
F1174L	1
Exon 2 KRAS	1
TP53	1
MET amplification	1

Results are presented as n (%).

Among the 68 patients with progressive disease after brigatinib, CNS was involved in 29.4% of cases (including new lesions for 5 and carcinomatous meningitis for 5). Brigatinib treatment was continued beyond disease progression in 25% (17/68) of patients in combination with local treatment in 53% (9/17) of them.

During post-brigatinib progression, 15% (12/68) of patients had a rebiopsy (one mutation G1202R and one mutation D1203 N were reported). A systemic treatment was administered to 52% (35/68) of patients after brigatinib (lorlatinib, n = 25; crizotinib, n = 1; chemotherapy, n = 7) and 13% (9/68) had a second subsequent treatment line after brigatinib (lorlatinib, n = 5, chemotherapy, n = 4). Eight patients benefited from stereotactic brain radiation therapy.

Median OS from the diagnosis of NSCLC was 75.3 months (95% CI, 38.2–174.6) (Fig. 2).

4. Discussion

This retrospective study shows that brigatinib exhibits clinical activity in a cohort of patients heavily pretreated with at least two ALK inhibitors. The median PFS and OS from brigatinib initiation were 6.6 months and 17.2 months, respectively. ORR and disease control rate were 50.0% and 78.2%, respectively, consistently with the results of the 180-mg arm of the phase II study of Kim et al, which included crizotinib-refractory ALK-positive NSCLC patients (ORR, 54%; disease control rate, 84%) [14]. PFS appeared to be lower compared to the 180-mg arm of this clinical trial (6.6 vs. 12.9 months). However, patients in our

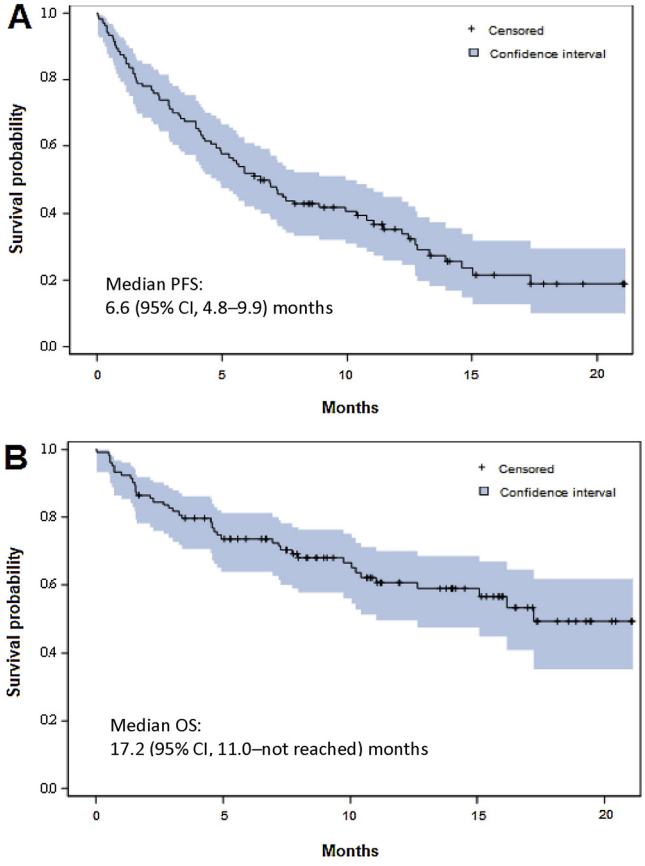

Fig. 1. PFS (A) and OS (B) since initiation of brigatinib treatment.

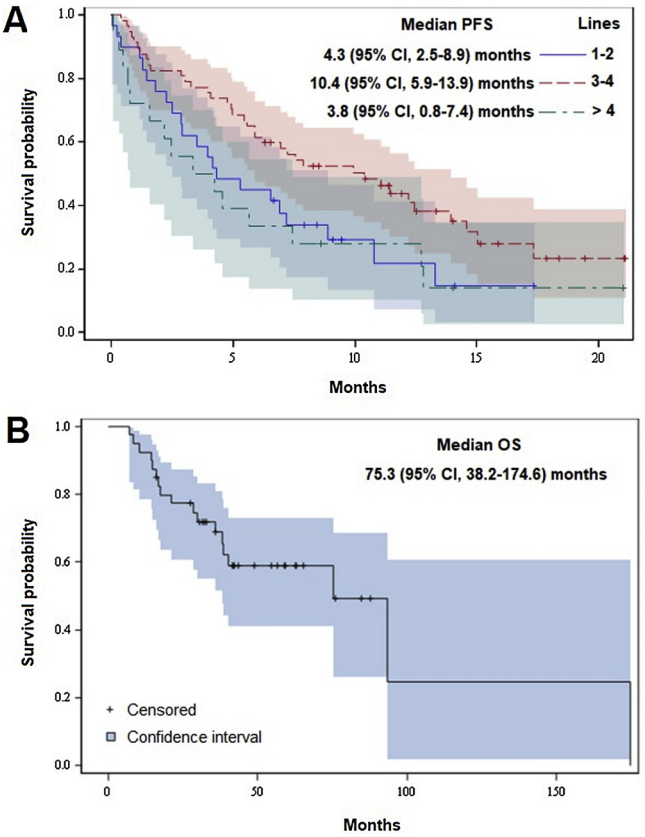

Fig. 2. PFS since initiation of brigatinib according to the number of previous lines of treatment (A) and OS from the diagnosis of NSCLC (B).

cohort were more heavily pretreated and had a poorer condition with 40.9% of patients with PS ≥ 2. In the phase II trial, patients with any prior TKI other than crizotinib were not included and only 6% of the patients enrolled had a PS ≥ 2. In our study, PFS under brigatinib differed not consistently according to the number of pre-brigatinib lines. The retrospective design of the study and the small number (n = 29) in the subgroup of patients who received two previous lines of treatment do not allow conclusions to be drawn about the observed results. This subgroup consisted of patients who predominantly received crizotinib and ceritinib (n = 24). The PFS values should be taken with caution because 5 patients had less than one month of brigatinib and 8 are censored because they were still under treatment at the date of analysis.

CNS metastases are frequent in ALK-positive patients. In this cohort, 28.9% of patients had CNS metastases at diagnosis and 74.5% at brigatinib initiation (8.8% had carcinomatous meningitis). Among the 68 patients with disease progression after brigatinib initiation, CNS location was at the forefront in 29.4% of cases, thus suggesting a high efficacy of brigatinib on CNS metastases. This has been demonstrated in an exploratory analysis of brigatinib efficacy in ALK-positive NSCLC patients with brain metastases included in a phase II trial [17]. In patients with measurable brain metastases treated with 90 mg/day first week followed by 180 mg/day, a confirmed intracranial ORR of 67% (95% CI, 41–87) and a median intracranial PFS of 18.4 months (95% CI, 12.8–not reached) were reported.

About 5% of non-squamous NSCLC are ALK positive and therefore data from large series are rarely reported. To our knowledge, our cohort is the first one to present real-life data on sequential strategy in patient who received at least three ALK inhibitors even though data were limited. A previous study of Solomon et al reported a phase II trial in different cohorts of patients with ALK-positive or ROS1-positive advanced NSCLC treated with lorlatinib [18]. Thus, the cohort EXP4-5 included 111 ALK-positive patients pretreated with 2 or 3 ALK TKI inhibitors (including the second-generation drugs ceritinib, alectinib and brigatinib) with or without chemotherapy. ORR was 38.7% (intracranial ORR, 48%) and disease control rate was 73%; PFS was 6.9 (95% CI, 5.4–9.5) months [18]. These results are also consistent with those of our study.

ALK inhibitors are now considered as the standard of care in patients with ALK-positive NSCLC. Some questions remain unanswered about the optimal sequential therapy with different ALK inhibitors. The benefit of a sequential strategy has been evidenced in different studies. The PROFILE 1014 phase III study compared first-line crizotinib vs. chemotherapy in ALK-positive NSCLC patients [19]. The longest OS was obtained for crizotinib-treated patients who received a subsequent ALK TKI, thus indicating the benefit of sequential strategy with ALK TKIs. The French retrospective CLINALK study performed in a large population of unselected patients with ALK-positive NSCLC was also in favor of a sequential strategy. After progression on crizotinib treatment, patients received either best supportive care, subsequent drug other than next-generation ALK inhibitors or next-generation ALK inhibitors. Better survival outcomes were reported for patients with next-generation ALK inhibitors: median OS from progression was 25.0 months vs. 6.4 months for drugs other than next-generation ALK inhibitors and 1.5 months for best supportive care [20]. It is also important to underline that about half (51.5%) of patients in our cohort with progression received a systemic treatment post brigatinib (most often lorlatinib).

The recent results of the ALEX and ALTA-1 L studies have challenged the current sequential strategy with ALK inhibitors [21,22]. These studies included TKI untreated patients with advanced ALK-positive NSCLC and compared next-generation frontline ALK TKIs to crizotinib. In the ALEX study, the rate of PFS at 12 months was significantly higher with alectinib than with crizotinib (68.4% vs. 48.7%, respectively); 12% of patients in the alectinib group had an event of CNS progression and 45% in the crizotinib group [22]. In the ALTA-1 L study, the rate of PFS at 12 months was higher with brigatinib than with crizotinib (67% vs. 43%, respectively) [21]. ORR was 71% with brigatinib and 60% with crizotinib; the rates of intracranial response in patients with measurable lesions were 78% and 29%, respectively. Therefore, the strategy with a next generation ALK inhibitor in frontline showed its clear superiority to crizotinib, especially for the risk of CNS progression. However, data from real-world studies and indirect analyses assessing sequential strategy starting with crizotinib and new inhibitors as first line treatment are needed. In this study, only one patient received brigatinib after alectinib and three patients after lorlatinib and at least after three therapeutics sequences. This did not allow definitive conclusions to be drawn about the efficacy of brigatinib after first-line alectinib.

Detection of ALK acquired resistance mutations in patients progressing during ALK TKI treatment is not recommended today in France, outside of clinical trials. For this reason, only a small proportion of patients benefited from tissue rebiopsy or liquid biopsy. However, such information may be valuable in determining the optimal choice of next-generation TKIs, which have different activity against distinct mutations. When rebiopsy of the progressing site is not feasible, comprehensive testing such as a next-generation sequencing panel using circulating tumor DNA can provide information on ALK resistance mutations, but also on other molecular mechanisms of resistance for which the patient may receive treatment either through a clinical trial or expanded access [23]. Given the small number of patients who had a re-biopsy before brigatinib and the low number of mutations highlighted, it is difficult from the data of this study to assess the relevance of this research on the adaptation of anti-ALK treatments.

Our study has some limitations. Data were not recorded prospectively, but were obtained from patient medical records. Therefore, we cannot exclude some selection biases. The efficacy of treatment was assessed by the investigator and there was no independent review committee; a bias associated with investigator assessment cannot be discarded. In this real-life study, it was not always possible to have a complete information from medical records in some patients. This was the case, for example, for patients who had a dose reduction or for those who stopped brigatinib before progression. One of the strengths of the study is the absence of stringent criteria for study inclusion. As a consequence, the study population is representative of real-life patients heavily treated for advanced NSCLC.

In conclusion, this study confirms the efficacy of brigatinib in a cohort of patients heavily pretreated for ALK-positive advanced NSCLC. These real-life results are consistent with clinical data reported in randomized trials.

Funding

This work was supported by an academic grant of Takeda.

Declaration of Competing Interest

Dr. DESCOURT reports personal fees from TAKEDA, personal fees from PFIZER, personal fees from NOVARTIS, personal fees from ROCHE, outside the submitted work.

Dr. PEROL reports grants and other from ROCHE, other from LILLY, other from PFIZER, other from BOEHRINGER, other from MSD, other from BMS, grants and other from ASTRA ZENECA, grants from CHUGAI, from TAKEDA, other from NOVARTIS, other from PIERRE FABRE, other from CLOVIS, during the conduct of the study.

Dr. PLANCHARD reports personal fees from ASTRAZENECA, personal fees from Boehringer, personal fees from BMS, personal fees from MSD, personal fees from NOVARTIS, personal fees from PFIZER, personal fees from CELGENE, personal fees from ROCHE, personal fees from PRIME ONCOLOGY, personal fees from PEER CME, outside the submitted work.

Dr. MENNECIER reports personal fees from PFIZER, personal fees from ROCHE, personal fees from NOVARTIS, outside the submitted work.

Dr. WISLEZ reports personal fees from BOERINGHER INGELHEIM, personal fees and non-financial support from ROCHE, personal fees and non-financial support from MSD, personal fees from BMS, personal fees from ASTRAZENECA, personal fees from AMGEN, outside the submitted work.

Dr. GUISIER reports personal fees and non-financial support from BMS, personal fees from MSD/MERCK US, personal fees from ASTRAZENECA, personal fees from ROCHE, grants and personal fees from BOEHRINGER INGELHEIM, non-financial support from CHUGAI, non-financial support from PFIZER, outside the submitted work.

Dr. AULIAC reports personal fees and non-financial support from ASTRAZENECA, personal fees and non-financial support from ROCHE, non-financial support from MSD, non-financial support from BOEHRINGER, personal fees and non-financial support from BMS, outside the submitted work.

Dr. CHOUAID reports grants and personal fees from TAKEDA, grants from ROCHE, grants and personal fees from PFIZER, grants and personal fees from NOVARTIS, outside the submitted work.

Dr. ROUSSEAU-BUSSAC, Dr. CORTOT, Dr. GALLAND, Dr. DO, Dr. SCHOTT, Dr. DANSIN and Dr. ARRONDEAU have nothing to disclose.

Acknowledgements

We thank the investigators and staffs of all sites who participated: Cécile Dujon (Le Chesnay), Jeannick Madelaine (Caen), Gaelle Jeannin (Clermont Ferrand), Olivier Bylicki (HIA Percy), Catherine Daniel (Institut Curie, Paris), Dominique Spaeth (Polyclinique de Gentilly, Nancy), Benoît Cloarec (Avignon), Alain Vergnenègre (Limoges), Eric Jauffret (Boulogne-Billancourt), Hannah Ghalloussi (Nice), Patricia Barré (Cahors), Laurent Greillier (Marseille), Pierre Fournel (Saint-Priest-en-Jarez), Olivier Molinier (Le Mans), Guillaume Leveillier (Saint Brieuc), Haitham Oweis (Châlons-en-Champagne), Ahmed Azzedine (Montélimar), Marie Coudurier (Chambéry), Anne-Marie Chiappa (Quimper), Arnaud Bedin (Evreux), Hugues Morel (Orléans), Romain Corre (Rennes), Corinne Lamour (Poitiers), Denis Morot-Sibilot (La Tronche), Bachar Chahine (Rouen), Bruno Taviot (Givors) Violaine Giraud (Boulogne-Billancourt), Olivier Herreman (Romans), Laurence Bigay-Game (Toulouse), Anne-Sophie Bugnet (Thonon-les-Bains) and Soizic Ferlandin (CHU Brest).

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