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Real-world treatment outcomes with brigatinib in patients with pretreated ALK+ metastatic non-small cell lung cancer

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ABSTRACT

Background: The next-generation ALK inhibitor brigatinib is approved for use in patients with ALK inhibitor-naïve ALK-positive advanced NSCLC and in patients previously treated with crizotinib. A phase II trial showed that brigatinib is active in patients with ALK-positive metastatic NSCLC (mNSCLC) who had progressed on prior crizotinib (response rate 56 %, median PFS 16.7 months, median OS 34.1 months). We report final data from the UVEA-Brig study of brigatinib in ALK inhibitor-pretreated ALK-positive mNSCLC in clinical practice.

Methods: UVEA-Brig was a retrospective chart review of patients treated with brigatinib in Italy, Norway, Spain and the UK in an expanded access program. Adults with ALK-positive mNSCLC, including those with brain lesions, resistant to or intolerant of ≥1 prior ALK inhibitor and ECOG performance status ≤3 were eligible. Patients received brigatinib 180 mg once daily with a 7-day lead-in at 90 mg. The objectives were to describe patient characteristics, clinical disease presentation, treatment regimens used and clinical outcomes.

Results: Data for 104 patients (male: 43 %; median age: 53 [29–80] years; ECOG performance status 0/1/2/3: 41/41/10/5 %; brain/CNS metastases: 63 %) were analyzed. Patients had received a median of 2 (1–6) lines of

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; BIRC, blinded independent review committee; CI, confidence interval; CNS, central nervous system; CR, complete response; CT, chemotherapy; DoR, duration of response; DoT, duration of treatment; EAP, expanded access program; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; EOPE, early-onset pulmonary event; GPP, Good Pharmacoepidemiology Practice; IO, immunotherapy; ISPE, International Society for Pharmacoepidemiology; mNSCLC, metastatic non-small cell lung cancer; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; ROS1, c-ros oncogene 1; SD, stable disease; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; UVEA-Brig, Use Via Expanded Access to Brigatinib.

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systemic therapy prior to brigatinib (37.5 % received ≥3) and a median of 1 (1–5) lines of prior ALK inhibitor-containing therapy (crizotinib 83.6 %; ceritinib 50.0 %; alectinib 6.7 %; lorlatinib 4.8 %). At the time of analysis, 77 patients had discontinued brigatinib. Overall, the response rate was 39.8 %, median PFS was 11.3 (95 % CI:8.6–12.9) months and median OS was 23.3 (95 % CI: 16.0–NR) months. Four patients discontinued brigatinib treatment due to adverse events. 53 patients received systemic therapy after brigatinib, 42 with an ALK inhibitor (lorlatinib, n = 34).
Conclusions: These real-world data indicate the activity and tolerability of brigatinib in patients with ALK-positive mNSCLC who were more heavily pretreated than patients included in clinical trials.

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85 % of diagnosed lung cancers [1]. Anaplastic lymphoma kinase (*ALK*) gene rearrangements occur in approximately 3–5 % of patients with NSCLC [2,3]. Historically, the prognosis of patients with ALK + advanced NSCLC was poor; for example, in a phase III trial the objective response rate in patients with ALK + NSCLC treated with chemotherapy was 45 % (95 % CI: 37–53) and median progression-free survival (PFS) was 7.0 months (95 % CI: 6.8–8.2) [4]. Furthermore, patients with ALK + NSCLC are at high risk of metastasis to the central nervous system (CNS); rates of CNS metastasis of 60–90 % during the course of the disease have been reported [5,6].

Treatment for ALK + NSCLC has evolved rapidly. Crizotinib, a first-generation ALK tyrosine kinase inhibitor (TKI), was the first agent approved specifically for this patient population having been shown to significantly improve response rate and PFS compared to chemotherapy [7,8]. However, resistance develops in most patients treated with crizotinib, and its limited capability to penetrate the brain means that many patients progress with brain metastases [9–12]. A series of more potent second-generation ALK TKIs with better CNS penetration and different resistance profiles has been developed and approved for use in the treatment of ALK + NSCLC; these include ceritinib, alectinib, and brigatinib [10,13–16]. These agents are approved or recommended for first and/or second-line treatment of ALK + NSCLC [17]. A fifth ALK TKI, lorlatinib, is recommended for use in patients who progress after a second-generation ALK TKI [17] and has also been reported to be more effective in the first-line setting than crizotinib [18]. However, its tolerability profile is different to those of the other ALK TKIs [19,20]. A sixth ALK TKI, ensartinib, has also been recently reported as being more effective than crizotinib in patients with advanced ALK + NSCLC not previously treated with an ALK inhibitor [21]. The use of sequential ALK TKIs has had a significant impact on the outcomes of patients with ALK + metastatic NSCLC: median overall survival (OS) of up to 89 months has been reported in retrospective studies of first-line crizotinib followed by at least one other ALK TKI [22–24].

The second-generation ALK TKI brigatinib is a highly selective and potent agent with activity against a broad range of *ALK* mutations and *c-ros* oncogene (ROS1) fusions [25]. It has also been shown to have activity against a broader range of *ALK* resistance mutations than crizotinib and some other ALK TKIs [25]. In the phase II ALTA trial, which formed the basis for the approval of brigatinib for use post-crizotinib, patients with ALK + NSCLC who had progressed on prior crizotinib had a response rate of 56 %, median PFS of 16.7 months and median OS of 34.1 months [26,27]. Patients with CNS metastases had an intracranial response rate of 67 % and median intracranial PFS of 18.4 months [27]. The subsequent phase III ALTA-1 L trial demonstrated that brigatinib significantly improved outcomes compared to crizotinib in patients with ALK + NSCLC who had not received prior ALK inhibitor therapy: blinded independent review committee (BIRC)-assessed median PFS 24.0 versus 11.0 months (HR = 0.49, 95 % CI: 0.35–0.68; log rank $p < 0.0001$) [14,28]. In this trial, the intracranial response rate was 78 % [28]. Brigatinib is currently approved as monotherapy for the treatment of patients with advanced ALK + NSCLC not previously treated with an ALK inhibitor and those who have received prior crizotinib [26,29].

A global expanded access program (EAP) for brigatinib was initiated in 2016 with the participation of 9 countries in Europe, prior to its approval by the European Medicines Agency (EMA) [29]. However, analysis of brigatinib efficacy was not within the scope of the EAP, because data collection encompassed only brigatinib treatment duration, which was reported as a proxy for tolerability and effectiveness. Therefore, the UVEA-Brig (Use Via Expanded Access to Brigatinib) study was designed to capture detailed information about brigatinib therapy for patients treated in the global EAP in Europe, thus providing insight into the use and effectiveness of brigatinib in a real-world clinical practice setting.

2. Methods

2.1. Selection of EAP countries and study sites

As of December 2017, 352 patients had been included in the EAP at 98 sites in nine European countries (Austria, France, Germany, Ireland, Italy, Norway, Spain, Switzerland, and the UK). Sites eligible for inclusion in the UVEA-Brig study were those at which at least two patients were treated with brigatinib in the EAP, local rules and regulations allowed data capture of EAP patients, and no other competing study was going on.

2.2. Study design

UVEA-Brig was a retrospective chart review, with no comparator, designed to collect clinical data reflective of patients with ALK + locally advanced and/or metastatic NSCLC who had received at least one prior ALK TKI and were subsequently treated with brigatinib. Data were extracted retrospectively from patient medical records using electronic case report forms.

2.3. Study population

Patients who started brigatinib treatment in the EAP between June 2016 and December 2017, prior to initiation of this study in January 2018, were eligible. Adults with histologically or cytologically confirmed locally advanced or metastatic NSCLC with ALK fusion diagnosed locally, including those with brain lesions, were included. Additional inclusion criteria included resistance to or intolerance of at least one prior ALK TKI and Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 3.

2.4. Study objectives

The primary objective of this study was to describe patient characteristics, clinical disease presentation, treatment regimens used, and clinical outcomes in patients treated with brigatinib for ALK + locally advanced or metastatic NSCLC in the scope of the EAP. Secondary objectives included describing patient characteristics, clinical disease presentation, treatment regimens used, and clinical outcomes by line of brigatinib therapy.

2.5. Data analyses

Patient characteristics, as well as treatment patterns prior to the initiation of brigatinib and subsequent to the discontinuation of brigatinib, were examined. Tumor assessments and clinical parameters were evaluated by treating physicians during treatment with brigatinib, and after each line of therapy prior to and subsequent to treatment with brigatinib. Outcomes evaluated included OS (time from brigatinib initiation to death), PFS (time from brigatinib initiation to first disease progression/recurrence or death; patients who did not progress or die were censored at date of last assessment/scan), duration of response (DoR; time from best response to brigatinib to progression, discontinuation or death), time to discontinuation (TTD; time from brigatinib initiation to discontinuation or death, whichever occurs first; patients who did not experience an events were censored), duration of brigatinib treatment (DoT; time from brigatinib initiation to brigatinib discontinuation, last follow up or death, with no censoring) and discontinuation due to adverse events (AEs).

2.6. Statistical analyses

The UVEA-Brig study was observational and epidemiological methods were applied for data analyses, which were performed using the SAS software. Descriptive statistics were used to present the patient characteristics and treatment patterns. OS, PFS, DoR, TTD, and DoT were determined using Kaplan-Meier analysis for each line of brigatinib therapy. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) rates were calculated as proportions by line of brigatinib therapy initiation. Response to therapy was defined as tumor shrinkage or disappearance, where possible assessed using RECIST v1.1.

2.7. Ethics

The study was conducted in accordance with the protocol, the current version of the Declaration of Helsinki International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline, Good Pharmacoepidemiology Practice (GPP), International Society for Pharmacoepidemiology (ISPE) GPP guidelines, and all applicable laws and regulations. Signed informed consent forms were required in Italy, Spain, and Norway if patients were living, but were not mandatory in the UK. Signed informed consent forms were not required for medical chart data collection for deceased patients except in Norway where signed consent from the patient's parent or legal guardian was required by some Ethics Committees.

3. Results

3.1. Patients

Data collection started in January 2018 and database lock was in September 2019. Patients were included from centers meeting the defined eligibility criteria in Italy (n = 56; 13 centers), Norway (n = 13; 2 centers), Spain (n = 14; 5 centers) and the UK (n = 21; 4 centers) between May 2018 and July 2019. Median follow-up was 16.5 months.

3.2. Patient and disease characteristics

Patient and disease characteristics are shown in Table 1. Median age at diagnosis was 53 (range 29–80) years; 59 patients (57 %) were female. The percentage of patients with ECOG performance status 1, 2 and 3 was 41 %, 10 % and 5 %, respectively; 63 % of patients had brain/CNS metastases.

Table 1
Patient and disease characteristics*.

	N = 104
Gender, male/female, %	43/57
Median age, years (range)	53 (29–80)
ECOG performance status, %	
0	41
1	41
2	10
3	5
Unknown	3
Never/former/current smoker, %	49/33/3
Adenocarcinoma, %	95
Stage III/IV at diagnosis, %	24/64
ALK positive,† %	100
Median number of metastatic sites (range)	3 (1–9)
Metastatic sites, %	
Lymph node	66
Brain/CNS	63
Lung	43
Bone	39
Pleura	27
Liver	23

Abbreviations: ALK: Anaplastic lymphoma kinase. CNS: Central nervous system. ECOG: Eastern Cooperative Oncology Group. NSCLC: Non-small cell lung cancer.

* Median age, disease stage and diagnosis of adenocarcinoma are based on assessments at diagnosis of NSCLC; other characteristics are based on assessments at initiation of brigatinib therapy.

† Immunohistochemistry, n = 40; fluorescence in situ hybridization, n = 73; other, n = 4; unknown, n = 17 (status was assessed using more than one technique in 28 patients).

3.3. Prior therapy and outcomes

Prior to receiving brigatinib, patients had received up to 6 lines of systemic therapy (median 2 lines). A total of 41 (39.4 %) patients had received ≥ 3 prior lines of therapy (Table 2). Patients had received up to 5 prior lines of ALK TKI therapy (median 1 line); 87 (83.6 %) patients had received prior crizotinib as one of these lines of therapy, 52 (50.0 %) ceritinib, 7 (6.7 %) alectinib, 5 (4.8 %) lorlatinib and 1 (1.0 %) entrectinib.

Of the 104 patients enrolled, all of whom had received prior first-line therapy, 34 (33 %) had received a first-line ALK TKI (crizotinib 21, ceritinib 11, alectinib 1, and entrectinib 1); the majority of the patients who did not receive a first-line ALK TKI received first-line chemotherapy (Table 2). A total of 102 of the 104 patients had an assessment of response to first-line therapy available, with 1 (1.0 %), 35 (34.3 %) and 34 (33.3 %) patients achieving a CR, PR, and SD, respectively (disease control rate 67.3 %).

Of the 81 patients who had received at least 2 lines of systemic therapy prior to brigatinib, 69 (85 %) had received a second-line ALK TKI (crizotinib 57, ceritinib 11, lorlatinib 1) (Table 2). Of the 77 patients who had an assessment of response to second-line therapy available, 1 (1.3 %), 33 (42.9 %), and 21 (27.3 %) patients had a CR, PR, and SD, respectively (disease control rate 71.4 %).

In addition, 74 of 104 patients (71 %) had received prior radiotherapy. The most frequent site of radiotherapy was the brain/CNS (59 % of all courses of radiotherapy administered). Stereotactic radiotherapy was used in 45 % of all courses of radiotherapy.

3.4. Brigatinib therapy and outcomes

Of the 104 patients, 93 (89.4 %) received brigatinib at the standard dose of 180 mg once daily following a 7-day lead-in at 90 mg once daily. Of the other 11 patients: eight patients (7.7 %) received brigatinib 90 mg once daily throughout treatment; one patient received brigatinib 180 mg once daily throughout treatment; and one patient received brigatinib 90 mg once daily for 2 days, followed by a reduction to 30 mg once daily for

Table 2
Prior therapy.

		Type of therapy received (n)							
			ALK TKI						
Line	n	CT	Crizotinib	Ceritinib	Alectinib	Lorlatinib	Entrectinib	IO	Targeted*d
1	104	70	21	11	1	0	1	1	1
2	81	8	57	11	0	1	0	2	3
3	41	6	6	21	4	2	0	2	2
4	17	4	3	8	0	1	0	1	0
5	5	1	0	1	1	1	0	2	0
6	3	1	1	0	1	1	0	0	0

Abbreviations: ALK: Anaplastic lymphoma kinase. CT: Chemotherapy. IO: Immunotherapy. TKI: Tyrosine kinase inhibitor.
* Targeted therapies consisted of bevacizumab (combined with chemotherapy) first line; erlotinib, gefitinib and nintedanib (combined with chemotherapy) second line; and erlotinib and nintedanib third line.

5 days, 90 mg once daily for 12 days and 180 mg once daily thereafter. Information was missing for one patient.

The overall median duration of brigatinib therapy was 16.5 (95 % CI: 12.9–18.5) months; 27 patients remained on brigatinib therapy at the time of data cut-off. Duration of brigatinib therapy by line is shown in Table 3.

Best response to brigatinib was evaluated in 93 patients, with a response rate of 39.8 % and a disease control rate of 55.9 % (Table 4). Assessments were made by the investigator using RECIST version 1.1 (42 % of assessments), investigator assessment (33 %), and clinical assessment (20 %). The overall median duration of response was not reached (n = 37) (Table 3). Median PFS in the 104 patients enrolled was 11.3 (95 % CI:8.6–12.9) months and median OS was 23.3 (95 % CI: 16.0–not reached [NR]) months (Table 3; Fig. 1). Progression events were observed in 77 patients, with 17 deaths and 60 patients with progression of disease. Of the 60 patients with progression events, 46 (76.7 %) patients had progression at existing lesions, 3 (5.0 %) developed new lesions only, and 11 (18.3 %) progressed at existing lesions and developed new lesions. Progression of existing lesions occurred most commonly in the brain/CNS (25.9 % of 85 lesions), lungs (18.8 %), liver (12.9 %), lymph nodes (12.9 %) and bone (10.6 %). Median PFS and OS generally decreased with the line of therapy in which brigatinib was used (Fig. 1).

Response data were available for 57 of 65 patients with brain/CNS metastases. Of these 57 patients, 23 (40.4 %) had a best response of partial response and 8 (14.0 %) had stable disease. Median PFS and OS for these patients were 10.4 (95 % CI: 6.6–12.4) months and 21.3 (95 % CI: 13.1–NR) months, respectively. Best responses for patients without

Table 3
Time to event outcomes.

Line of brigatinib therapy	Median DoT, months (95 % CI)	Median overall TTD, months (95 % CI)	Median DoR, months (95 % CI)	Median PFS, months (95 % CI)	Median OS, months (95 % CI)
Overall (n = 104)	16.5 (12.9–18.5)	8.9 (6.4–12.6)	NR (19.9–NR) (n = 37)	11.3 (8.6–12.9)	23.3 (16.0–NR)
Second (n = 23)	19.0 (9.5–22.0)	16.1 (7.8–25.7)	NR (6.8–NR) (n = 9)	15.3 (6.4–25.1)	NR (16.5–NR)
Third (n = 42)	16.8 (13.1–18.6)	11.0 (6.4–17.3)	19.9 (13.1–NR) (n = 17)	11.4 (8.3–15.5)	23.3 (15.0–NR)
Fourth (n = 22)	9.7 (2.6–16.6)	3.1 (1.1–8.0)	17.4 (4.1–NR) (n = 3)	11.2 (5.6–14.3)	12.1 (5.6–21.3)
Fifth or later (n = 17)	17.4 (6.0–23.1)	9.2 (2.7–NR)	NR (6.1–NR) (n = 8)	8.3 (4.4–12.1)	NR (6.0–NR)

Abbreviations: CI: Confidence interval. DoR: Duration of response. DoT: Duration of treatment. NR: Not reached. OS: Overall survival. PFS: Progression-free survival. TTD: time to discontinuation.

Table 4
Best response to brigatinib therapy.

	N = 93
CR	2 (2.2 %)
PR	35 (37.6 %)
SD	15 (16.1 %)
PD	39 (41.9 %)
Not evaluable	2 (2.2 %)
CR + PR	37 (39.8 %)
CR + PR + SD	52 (55.9 %)

Abbreviations: CI: Confidence interval. CR: Complete response. NR: Not reached. PR: Partial response. SD: Stable disease.

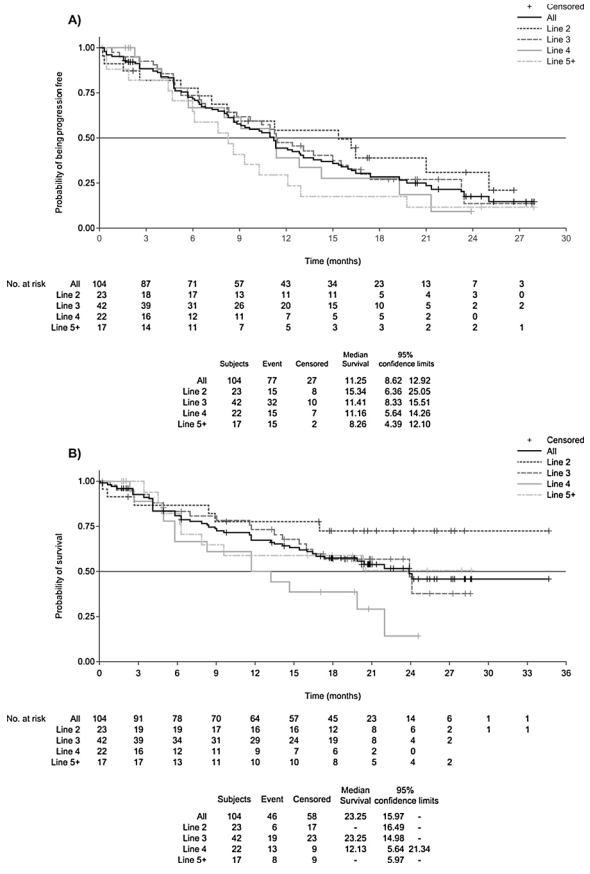

Fig. 1. A) Kaplan-Meier Plot – PFS by line of brigatinib therapy initiation and B) Kaplan-Meier Plot – OS by line of brigatinib therapy initiation.
Abbreviations: CL: Confidence limit. OS: Overall survival. PFS: Progression-free survival.

brain/CNS metastases (n = 39) were partial response 33.3 % and stable disease 19.4 %, while median PFS and median OS 11.4 (95 % CI: 8.3–16.5) months and 23.4 (95 % CI: 14.5–NR) months, respectively.

An analysis of the 15 patients with ECOG performance status of 2 or 3 was also performed. Of the 10 patients with response assessments, 4 (40 %) and 2 (20 %) had a best response of partial response and stable disease, respectively. Median PFS and OS for these patients were 5.6 (95 % CI: 0.5–6.4) months and 5.6 (95 % CI: 0.8–7.6) months, respectively. Best responses for patients with ECOG performance status 0/1 (n = 86) were complete response 2.5 %, partial response 37.5 % and stable disease 16.3 %; median PFS and OS were 12.4 (95 % CI: 11.0–15.5) months and NR (95 % CI: 19.3–NR) months, respectively.

3.5. Brigatinib safety

At the time of this analysis, brigatinib therapy had been discontinued in 77 patients, with a median time to discontinuation of 8.9 (95 % CI: 6.4–12.6) months (Table 3). Treatment was discontinued in four patients (5.2 %) due to AEs, whereas the majority of patients discontinued due to disease progression or lack of response (n = 55, [71.4 %]; other reasons, n = 18 [23.4 %]). The AEs resulting in brigatinib discontinuation were: one grade 2 pneumonitis occurring at 7.7 months of second-line brigatinib treatment (not early-onset pulmonary event [EOPE]); one grade 3 pneumonitis occurring 4 days after the first dose of brigatinib in a patient treated fourth-line, 5 months after completion of prior therapy (only reported case of EOPE based on published definitions [30,31]); one grade 2 asthenia/fatigue at 0.7 months of fourth-line treatment; and one grade 3 amylase and creatinine kinase increase after 10.4 months of third-line treatment. Results were similar for patients with and without brain/CNS metastases, although fewer patients with brain/CNS metastases discontinued therapy due to disease progression/lack of response (67.3 % vs 78.6 %). Two patients with brain/CNS metastases withdrew due to adverse events (grade 2 pneumonitis and grade 2 asthenia/fatigue, as described above).

Of the 15 patients with ECOG performance status of 2/3, one discontinued due to an AE (grade 2 pneumonitis as described above) and 7 due to disease progression or lack of response.

3.6. Therapy post-brigatinib

After brigatinib discontinuation, 53 patients received subsequent systematic therapy, with patients receiving one (44 patients), two (8 patients) or three (1 patient) lines of further therapy. As their first line of therapy after brigatinib, 42 patients received an ALK TKI (lorlatinib, 34; alectinib, 7; ceritinib, 1); two patients received two lines of ALK TKI-containing therapy following brigatinib (lorlatinib followed by alectinib and alectinib followed by lorlatinib). In addition, one patient received a further three lines of therapy, consisting of cisplatin + pemetrexed, then lorlatinib, followed by carboplatin + gemcitabine.

Best response to subsequent lines of therapy was available for 31 patients, with a PR in eight patients, SD in eight patients, and disease progression in 13 patients; two patients were non-evaluable. The mean treatment duration of the first line of therapy after brigatinib was 2.57 (SD = 1.19) months for patients receiving lorlatinib, 1.58 (SD = 2.29) months for alectinib, 1.52 (SD = not applicable) months for ceritinib and 2.17 months (SD = 2.04) for chemotherapy.

4. Discussion

The UVEA-Brig study, a retrospective analysis of patients with ALK + metastatic NSCLC who were treated with brigatinib in an EAP in four European countries, has provided real-world data indicating that brigatinib has substantial activity and is generally well tolerated when used in daily clinical practice to treat patients with ALK + metastatic NSCLC who had been considerably more heavily pretreated than those enrolled into clinical trials [14,27,28,31]; in addition, patients with poorer ECOG performance status were enrolled, although the incidence of brain metastases was similar to that in the ALTA trial of second-line brigatinib [27]. The study adds to evidence from previous studies indicating the efficacy and safety of brigatinib in real-world clinical practice [32–34].

In the largest of these studies, the global EAP covering 21 countries including Italy, Spain, Norway and the UK, brigatinib treatment duration was used as a proxy for tolerability and effectiveness and analyzed in 604 patients with ALK + locally advanced or metastatic NSCLC previously treated with an ALK TKI [32]. Median brigatinib TTD was dependent on the number of prior TKIs received: 11.8 months (95 % CI: 8.7–NE) for one prior ALK TKI; 10.8 months (95 % CI: 8.2–14.1) for two prior ALK TKIs; and 7.7 months (95 % CI: 6.1–14.9) for three or more ALK TKIs [32]. This led the authors to conclude that brigatinib was effective in clinical practice, regardless of previous ALK TKI treatment [32]. The overall TTD in UVEA-Brig, which included a subset of patients from the global EAP, was in line with these data.

The BRIGALK study analyzed 184 patients with ALK + advanced NSCLC included in the French EAP for brigatinib, who had previously been treated with at least one ALK TKI; median PFS was 4.8 (3.8–5.6) months [33]. In the UVEA-Brig study, median PFS was 11.3 (95 % CI:8.6–12.9) months overall. It is important to note that patients included in the BRIGALK study had received a median of two prior ALK TKIs and three prior lines of therapy overall, whereas the median number of prior ALK TKIs and lines of prior therapy received in UVEA-Brig were one and two, respectively. This may explain why the median PFS in UVEA-Brig appears to be higher than that in BRIGALK. However, we cannot rule out an effect on PFS of differences in patient or disease characteristics, robustness of PFS evaluation in real-world studies, or differences in clinical practice in France versus the four countries involved in UVEA-Brig. Finally, in a smaller single-center study of 35 patients in Austria with ALK + NSCLC resistant to another ALK TKI, brigatinib was investigated as a second or later line of therapy. The median PFS of 9.9 months in this study aligns with the data from UVEA-Brig [34]. Overall, the data from these studies and UVEA-Brig all suggest that brigatinib is effective in a clinical setting in patients with ALK + advanced NSCLC who have received prior therapy with ALK TKIs and other therapies.

In the phase II ALTA trial, brigatinib produced median PFS of 16.7 (95 % CI: 11.6–21.4) months and median OS of 34.1 (95 % CI: 27.7–NR) months at 2 years of follow-up [27]. While PFS and OS in UVEA-Brig both appear shorter than in ALTA, it is important to note that the patient populations differed in terms of exposure to prior therapy: patients in ALTA had received ALK TKI therapy with prior crizotinib only, although 74 % of patients had received prior chemotherapy [27,31], whereas patients in UVEA-Brig had received a median of 2 and up to 6 lines of prior systemic therapy and a median of 1 and up to 5 lines of prior ALK TKI therapy. Furthermore, UVEA-Brig included patients with ECOG performance status $\geq$ 2 and patients who had been treated with all available treatment options and were unable to participate in a clinical trial. These patients would be expected to have a worse prognosis than those enrolled in ALTA, which is supported by the median PFS and OS of 5.6 months observed in patients with ECOG performance status of 2 or 3 included in UVEA-Brig. For those patients in UVEA-Brig who received brigatinib second line, a group more similar to the patient population in ALTA, median PFS was 15.3 (95 % CI: 6.4–25.1) months, similar to that observed in ALTA, confirming the real-world efficacy of brigatinib.

In the phase II ALTA trial, patients with CNS metastases had an intracranial response rate of 67 % and median intracranial PFS of 18.4 months [27]. In our study, partial responses were observed in 40.4 % of patients with brain/CNS metastases who had assessments available, while median PFS was 10.4 months. While these outcomes appear less positive than those in the ALTA trial, in ALTA, the response and PFS for intracranial lesions was reported, whereas we report a combination of intracranial/CNS response and systemic response. Therefore, the data are not directly comparable; in addition, the difference in patient

populations, particularly the fact that patients in UVEA-Brig had received more prior therapy than those in ALTA, has to be considered.

Data from UVEA-Brig suggest that ALK TKIs used following brigatinib have activity, although our data did not enable us to determine the proportion of this activity due to intracranial and extracranial activity. The most commonly used ALK TKI was lorlatinib, perhaps because it is believed to be more effective than other ALK TKIs (alectinib or ceritinib) or chemotherapy in this setting. [35]. However, further studies to establish the optimal sequence of ALK TKIs in patients with ALK + advanced NSCLC are needed.

In clinical trials, the safety profile of brigatinib has been consistent, with a low incidence of grade ≥ 3 AE; the most significant event noted in these trials was EOPE, the incidence of which is reduced using the approved brigatinib regimen (90 mg/day for 7 days followed by 180 mg/day [14,31,36]. Neither UVEA-Brig nor the other real-world studies provided detailed data regarding the tolerability of brigatinib, and retrospective data collection in these studies means that data are not directly comparable to clinical trial safety data. However, it is notable that the rate of brigatinib discontinuation due to AEs, a more reliable indicator of meaningful toxicity, was low in both UVEA-Brig (3.9 %) and the large EAP (0.7 %) [32]. Furthermore, in UVEA-Brig, there was no indication of an increased rate of discontinuation due to AEs in patients with brain/CNS metastases or those with ECOG performance status of 2/3. Finally, across the UVEA-Brig and large EAP studies [32], a total of only one discontinuation was reported to be due to an EOPE, suggesting that use of the approved dosing regimen of 90 mg/day for 7 days followed by 180 mg/day minimizes the incidence of this event in clinical practice.

UVEA-Brig has a number of strengths and limitations. The study reflects clinical practice across four different countries, providing real-world data outside of a clinical trial setting. It has thus helped to provide early data on the effectiveness of brigatinib in clinical practice. Furthermore, the study includes different patient populations treated in different healthcare systems and geographies, providing insight into treatment patterns and outcomes. A further strength is that this study provides insight into brigatinib treatment in both patients who received brigatinib second line as well as in patients with more heavily pretreated, very advanced NSCLC, some of whom had exhausted available treatment options and were unable to participate in clinical trials.

In terms of limitations, the study relied on medical records, and the availability and quality of the information in these records may vary between physicians and countries. Furthermore, the retrospective nature of the study means that some data may be incomplete. In addition, disease assessment was based on evaluations performed by treating physicians, which may have resulted in inconsistences in defining response and disease progression, although a significant proportion of patients were assessed using RECIST. Finally, the study sites at which data were collected may not have been representative of all sites in all of the countries involved in the EAP.

5. Conclusions

The UVEA-Brig study provides real-world data on the use of brigatinib therapy in patients with ALK + advanced NSCLC previously treated with at least one line of ALK TKI-containing therapy in an EAP in Europe. These data indicate the substantial activity and tolerability of brigatinib when used in daily clinical practice to treat patients with ALK + locally advanced or metastatic NSCLC who had been more heavily pretreated than those enrolled into clinical trials. The results are also consistent with other real-world data for brigatinib and support clinical trial data demonstrating the efficacy of brigatinib in patients with ALK + locally advanced or metastatic NSCLC [14,27,28,31].

CRediT authorship contribution statement

Sanjay Popat: conception or design, data acquisition, data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved). **Nawal Bent-Ennakhil:** data analysis, data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved). **Odd Terje Brustugun:** data acquisition, data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved). **Jacques Cadranel:** conception or design, data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved). **Enriqueta Felip:** data acquisition, data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved). **Marina Chiara Garassino:** data acquisition, data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved). **Frank Griesinger:** data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved). **Åslaug Helland:** data acquisition, data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved). **Maximilian Hochmair:** conception or design, data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved). **Christian Kruhl:** conception or design, data acquisition, data analysis, data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved). **Silvia Novello:** data acquisition, data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved). **Maurice Pérol:** data interpretation, drafting the manuscript, revising it critically for important intellectual content and approving the final version to be published, and agrees to be accountable for all aspects of the work (ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved).

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Role of the funder/sponsor

Takeda was involved in the study design, data collection, data analysis, and preparation of the manuscript.

Data statement

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within three months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

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Odd Terje Brustugun: Investigation, Writing – Review & Editing

Jacques Cadranel: Conceptualization, Methodology, Writing – Review & Editing

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Nawal Bent-Ennakhil: Methodology, Validation, Formal analysis, Data curation, Writing – Review & Editing, Visualization

Christian Kruhl: Conceptualization, Methodology, Investigation, Writing – Review & Editing

Silvia Novello: Investigation, Writing – Review & Editing

Declaration of Competing Interest

Sanjay Popat: Honoraria – AbbVie, AstraZeneca, Boehringer Ingelheim, BMS, Chugai, EMD Serono, Guardant Health, Medscape, MSD, Novartis, OncLive, Pfizer, Roche, Takeda and Tesaro, research grant/institutional funding – Bayer, BMS, Ariad, Boehringer Ingelheim, Celgene, Clovis Oncology, Eli Lilly, EMD Serono, Epizyne, MSD, Pfizer, Roche, Synta and Takeda.

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Marina Garassino: advisory/consultancy role – AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Inivita, MSD, Novartis, Pfizer, Roche, Sanofi Aventis, Seattle Genetics, Takeda, speaker – AstraZeneca, BMS, Celgene, Eli Lilly, MSD, Roche, Takeda, institutional funding – AstraZeneca, Blueprint Medicine, Exelixis, GSK, Incyte, Merck KGaA, MSD, Novartis, Roche, Spectrum, Takeda, United Therapeutics.

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