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ORIGINAL RESEARCH ARTICLE

Compassionate Access to Brigatinib for Patients with Non-small-cell Lung Cancer Harboring a *ROS1* Rearrangement: Results from the BRIGAROS Study

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Abstract

Background *ROS1* chromosomic rearrangement is a rare oncogenic driver, and patients with this rearrangement benefit from specific targeted treatments in the first-line setting. However, therapeutic options are limited in pretreated patients. Brigatinib is a validated drug for *ALK* rearrangements, and also has an in vitro activity against ROS1. In vivo efficacy is also suggested in some clinical series.

Objective We aimed to specifically study brigatinib in patients with pretreated advanced non-small-cell lung cancer (NSCLC).

Methods We retrospectively collected data from 20 centers in France. Brigatinib was delivered through a compassionate use program in France between 2018 and 2020. The primary endpoint was progression-free survival. Secondary endpoints were the objective response rate, overall survival, and tolerance.

Results Twenty-five patients treated with brigatinib were included in our study. All patients were pretreated, and all of them previously received crizotinib. Median progression-free survival was 3.8 months (95% confidence interval 2.8–7.1). The objective response rate was 32%, with a disease control rate of 48%. Three patients had a prolonged response of more than 18 months at the end of data collection. We did not identify factors predictive of prolonged response. There were no grade 4 or 5 toxicities.

Conclusion Brigatinib may represent an interesting therapeutic option for patients who have progressed after standard treatments.

Key Points

Limited clinical series suggest an in vivo efficacy of brigatinib against *ROS1*-rearranged non-small-cell lung cancer (NSCLC).

We studied the efficacy of brigatinib given through a compassionate program in pretreated advanced NSCLC patients.

The objective response rate was 32%, and the disease control rate was 48%, with the median progression-free survival being 3.8 months (95% confidence interval 2.8–7.1), with response in some previously heavily treated patients.

Brigatinib is an interesting therapeutic option for patients who progressed after standard treatments.

1 Background

Chromosomic rearrangements of *ROS proto-oncogene 1* (*ROS1*), a tyrosine-kinase receptor coding gene, results in the activation of cellular pathways responsible for tumoral mutation of cells, and thus represent an oncogenic addiction [1, 2]. *ROS1* rearrangements account for 1–2% of patients with a non-small-cell lung cancer (NSCLC) and are commonly found in young never-smoker patients with

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advanced adenocarcinoma [3]. This molecular alteration is identified through fluorescence in situ hybridization (FISH) or next-generation sequencing [4].

ROS1-rearranged NSCLC is sensitive to tyrosine kinase inhibitors (TKIs). Crizotinib showed an objective response rate (ORR) of 47–72%, a median progression-free survival (mPFS) of 5.5–20 months, and a median overall survival of 17.2–51.4 months in large studies [5–9], and is currently the standard of care. Other treatments have showed potential efficacy in crizotinib-naïve patients, including ceritinib [10], entrectinib [11], repotrectinib [12], and lorlatinib [13]. Most of them are not approved in a majority of countries.

Brigatinib is currently approved in *ALK*-positive patients, but it is also known to be an effective ROS1 inhibitor in vitro [15]. Furthermore, an interesting activity against some resistance mutations driving crizotinib resistance has been reported [16–18]. Nevertheless, the G2032R mutation is not sensitive to brigatinib.

Studies of brigatinib following crizotinib resistance have been recently reported, including a limited number of patients and having response rates ranging from 26% to 29% [19, 20].

We report herein a national multicentric study assessing the effect of brigatinib in 25 patients with a *ROS1*-rearranged NSCLC in the context of compassionate access.

Objective We aimed to assess the efficacy of brigatinib after crizotinib resistance in patients with *ROS1*-rearranged NSCLC.

2 Patients and Methods

2.1 Study Description

BRIGAROS is an observational retrospective multicentric national study. Brigatinib was accessible through a nationwide compassionate access program sponsored by Takeda. All patients enrolled in the program were analyzed for this study. Inclusion criteria were patients with a *ROS1* rearrangement previously treated with at least crizotinib and who had access to brigatinib after making a request to Takeda through the compassionate access program. Brigatinib was delivered in a 90-mg daily dose for the first week, followed by a 180-mg daily dose until toxicity or progression.

We identified 25 eligible patients from 20 centers across France between January 2018 and June 2020. Each investigating center was in charge of fulfilling a computerized data collection form designed by the team of the Inter Communal Hospital Center of Créteil, which was the principal investigator. The ethics committee of the *Société de Pneumologie de Langue Française* approved the study (number: CEPRO 2021-002).

The primary endpoint of this study was progression-free survival (PFS). Secondary endpoints included overall survival, ORR, and potential side effects associated with brigatinib.

2.2 Statistical Analysis

Data collection was censured initially at the date of 1 July 2021 for patients who had not progressed to this date, then a data update was done at the start of 2025. An anonymized sheet was created, compiling all of demographic, biologic, and medical data. Quantitative variables were presented using the median and rank, and qualitative variables with frequencies and percentages. All statistical analysis was done with R-studio software, version 4.0.3, in the *Centre Hospitalier Universitaire de Toulouse*.

3 Results

3.1 Characteristics

From the 20 centers in France, 25 patients with a *ROS1*-rearranged NSCLC who received brigatinib via the compassionate access program were identified and included in the study. The main patient characteristics are presented in Table 1. The majority of patients had a good performance status (PS) (92% PS 0 or 1), and 19 (76%) had brain metastasis. The median age was 52, and more were women (60% of patients). The vast majority were previous smokers or never-smokers. All histologic types were adenocarcinoma.

Regarding tumor biology, three patients (12%) had a ROS1-CD74 fusion partner, and two (8%) presented a SDC4-ROS1 rearrangement. Other fusion partners were not specified.

Before receiving brigatinib, patients received an average of three lines of treatment, and all displayed progression following crizotinib. In addition, four previously received lorlatinib and five immunotherapy. Of interest, nine (36%) had a new biopsy before introducing brigatinib. In these patients, no resistant mutations were found, one was negative for *ROS1*, and a *KRAS* mutation was identified. No other resistance mechanism was identified.

One patient could not be evaluated, due to cerebral thrombophlebitis complicated with intracranial hemorrhage before tumor assessment. This patient had brain metastases and a history of pulmonary embolism before treatment. This patient was included in the analysis with a censure correcting factor.

3.2 Outcome

All patients presented with progression on brigatinib at the end of data collection. Eight patients (32%) had a response

on treatment, including one complete response and seven partial responses. Moreover, four patients (16%) had stable disease as best response, leading to a disease control rate of 48%.

Amongst the seven patients with a partial response, all had a treatment duration of over 1 year. The patient with complete response did not progress after nearly 5 years of treatment. There were no clinical or biological characteristic shared by responding patients that could be found in our study. Three of them received lorlatinib before brigatinib, and four had brain metastasis before treatment.

For the 25 patients included in the analysis, the mPFS on brigatinib was 3.8 months (95% confidence interval [CI] 2.8–7.1) (Fig. 1). In the 19 patients with brain metastasis before treatment, 12 progressed in the brain, either via an increase of an already existing metastasis or via the appearance of new lesions, or a combination of these two patterns. The mPFS in the patients with brain metastasis before introducing brigatinib was 3.1 months (95% CI 2.3–7.1) (Fig. 1).

Table 1 Baseline patient characteristics in the intention-to-treat population

	Intention-to-treat population ($n = 25$)
Mean age at diagnosis—years	52 (30–78)
Sex—*n* (%)	
Women	15 (60)
Men	10 (40)
ECOG performance-status—*n* (%)*	
0	12 (48)
1	11 (44)
Not available	2 (8)
Smoking status—*n* (%)	
Never-smoker	12 (48)
Previous smoker	10 (40)
Current smoker	3 (12)
Histologic type—n (%)	
Adenocarcinoma	25 (100)
Others	0
Patients with brain metastasis at diagnosis—*n* (%)	4 (16)
Patients with brain metastasis before starting brigatinib –*n* (%)	19 (76)
Use of previous anticancer drug therapy—*n* (%)	
1	7 (28)
2	5 (20)
3	4 (16)
4	5 (20)
5 or more	4 (16)

ECOG Eastern Cooperative Oncology Group

* ECOG scores range from 0 to 5, with higher scores indicating greater disability

The median overall survival between the introduction of brigatinib and end of data collection was not reached in our study with a 24-month follow-up (Fig. 2). At the end of first data collection, 14 of the 25 patients (56%) were still alive.

Only one biopsy was performed after progression in one patient, which found the G2032R resistance mutation, potentially explaining the therapeutic failure.

3.3 Tolerance

All patients received a 90-mg daily dose of brigatinib for 1 week without any major side effect, followed by an increase to 180 mg daily. Brigatinib was well tolerated in the majority of patients. Two side effects of importance were reported. An increase of a known renal amylosis was reported in one patient, without clear imputability and without treatment discontinuation. A dilated cardiopathy found in another patient led to brigatinib interruption, with possible imputability after investigation and declaration to the pharmacovigilance department.

4 Discussion

In this retrospective multicentric analysis done on a "real life" patient population, we showed that brigatinib has an inconstant efficacy in *ROS1* patients. Nevertheless, it appears that some heavily pretreated patients can derive prolonged benefit from the drug. Despite a limited number of patients, our study represents the largest cohort in the setting of this rare population of pretreated *ROS1* patients.

The mPFS of our study is 3.8 months, however, with a wide gap between patients, ranging from 2 months to more than 5 years. This could be explained on one hand by the compassionate access of our study, with "real life" patients, the majority of them being treated with multiples lines of treatment with an increased risk of intrinsic tumoral resistance.

Few studies have reported the use of brigatinib in patients who have progressed following crizotinib treatment. One retrospective study evaluating seven patients with crizotinib-resistant *ROS1* NSCLC reported an ORR of 29%, for a disease control rate of 43%. PFS was not evaluable [19].

In a phase II multicentric basket study, called the Barossa cohort, brigatinib was used in three patient cohorts with a *ROS1*-positive tumor. In 19 crizotinib-resistant *ROS1* NSCLC patients, the ORR was 31.6%, with a disease control rate of 57.9%. The mPFS was 7.3 months in this population [20], which is higher than our study, but patients had only received crizotinib, whereas in our population, some patients were heavily pretreated with more options than crizotinib only.

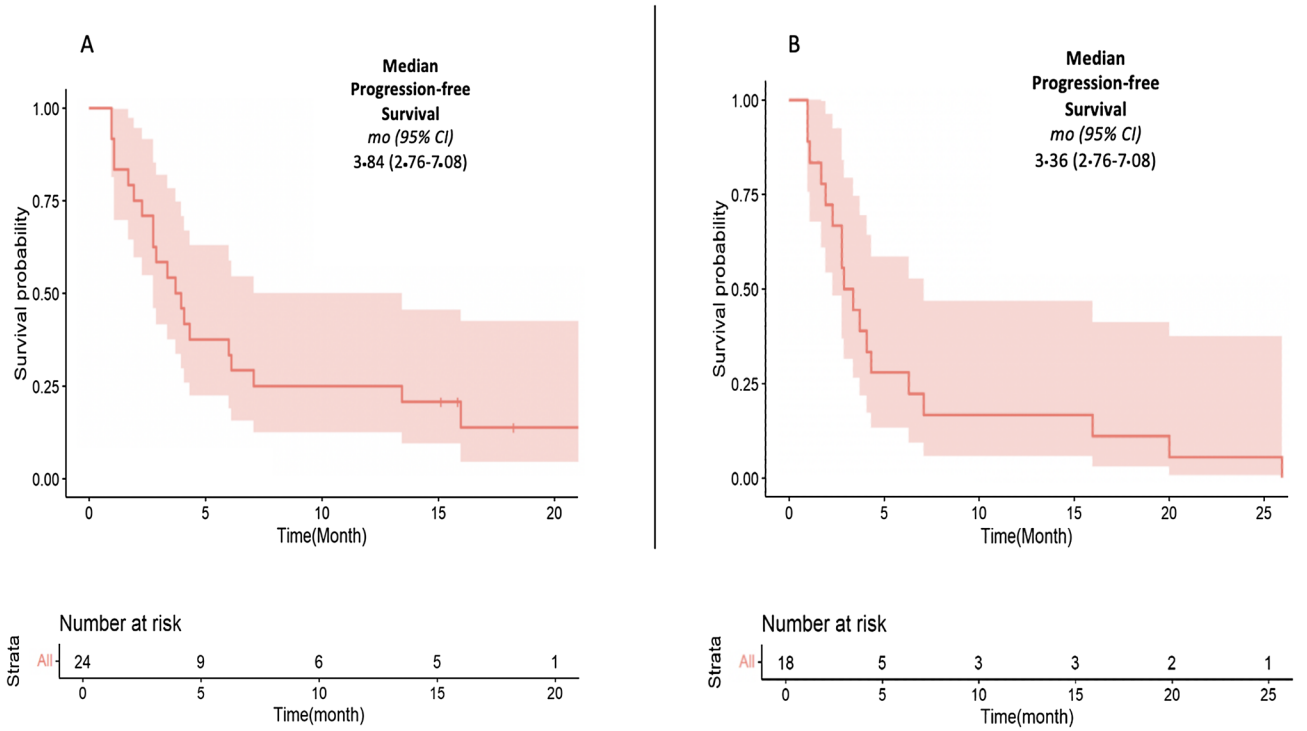

Fig. 1 Progression-free survival with brigatinib for all patients (**A**) and for patients with brain metastasis before introducing brigatinib (**B**). *CI* confidence interval, *mo* months

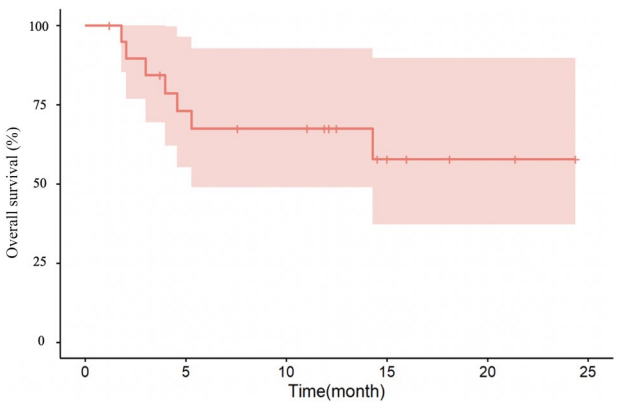

Fig. 2 Overall survival with brigatinib in all patients since brigatinib introduction

These two studies compared with our study are shown in Fig. 3.

Other therapeutic options in *ROS1*-rearranged NSCLC have been tested. Ceritinib showed an ORR of 62%, and mPFS was 9.3 months for all patients and 19.3 months for crizotinib-naïve patients in a multicentric phase II study [10]. Entrectinib, a neurotrophic tyrosine receptor kinase (NTRK) inhibitor, active on ROS1, was associated with a 77% ORR and a median duration of response of 24.6 months in a pooled-analysis on 56 patients [11]. Repotrectinib is also an NTRK and ROS1 inhibitor; it demonstrated potent activity, with an ORR of 79% and an mPFS of 35.7 months [12]. Finally, lorlatinib showed an interesting ORR of 62% and an mPFS of 21 months in TKI-naïve patients. Following crizotinib resistance, lorlatinib is a preferred option due to its central nervous system diffusion, with an ORR of 35% and an mPFS of 8.5 months [13].

ROS1 therapeutic resistance mechanisms are insufficiently analyzed in practice. Only one rebiopsy following brigatinib resistance was performed in our study, and found a G2032R resistance mutation, conferring potential resistance to this treatment. These mutations were probably not investigated enough in this study, as systematic biopsies were not mandatory.

Few serious side effects were reported in our study, supporting the favorable safety profile of brigatinib, which is concordant with preexisting data. However, this study did not include the systematic collection on all side effects with brigatinib, such as diarrhea or asthenia.

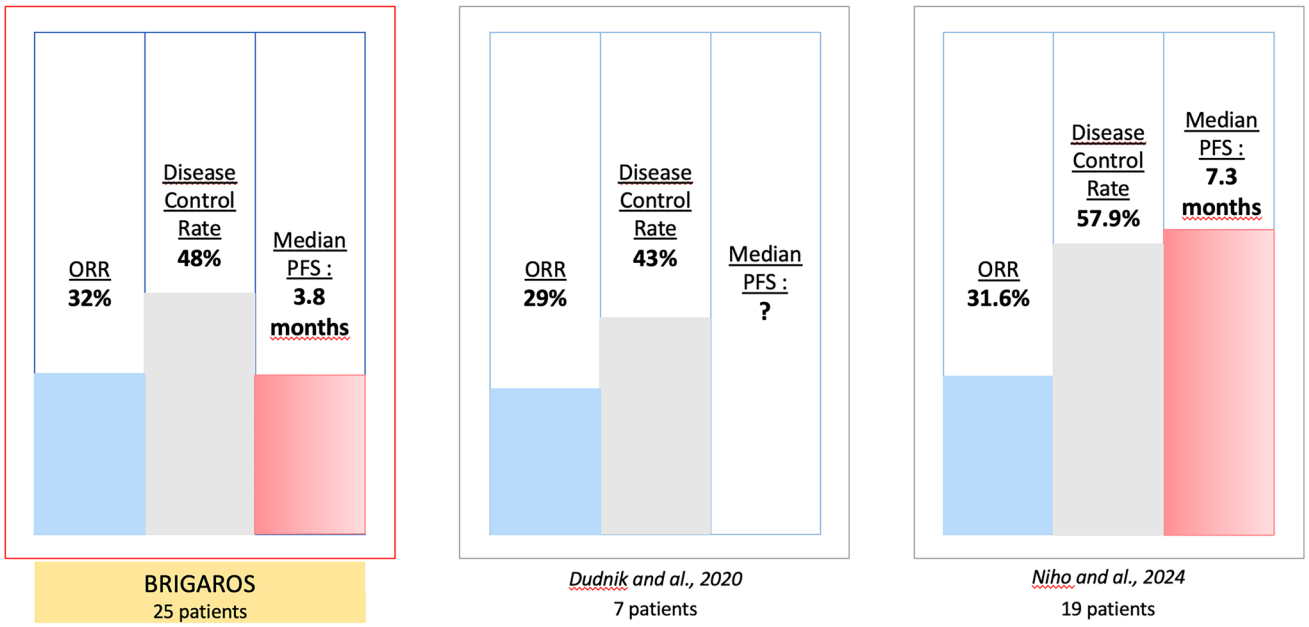

Fig. 3 Comparison of the three largest series performed in patients with *ROS1* metastatic NSCLC under treatment with brigatinib who had crizotinib resistance. *NSCLC* non-small-cell lung cancer, *ORR* objective response rate, *PFS* progression-free survival

The only grade 3 side effect was a dilated heart disease, potentially imputable to brigatinib, although the medical literature does not report this type of severe side effect.

Our study shows some limitations. The retrospective pattern of this study and the limited number of patients are one known limitation, however well described and inherent to the *ROS1* population in NSCLC. Another important limit lies in the compassionate access to brigatinib, which initially specified pretreatment with at least two prior ROS1-targeted therapies and a chemotherapy. However, some patients received brigatinib outside these recommendations, with only one prior line of treatment with crizotinib. In these eight patients, only three patients presented with a partial response and the others did not show any response. This seems consistent with the ORR and disease control rate of the global population.

5 Conclusion

Brigatinib cannot be considered as a standard treatment for *ROS1* patients but might be considered as an option in heavily pretreated patients. Further studies should investigate predictive biomarkers in this setting.

Declarations

Author contribution Jean Mourlanette, Julien Mazieres, and Siham Mallah wrote this article, centered the data in Toulouse, and made statistical analyses. Gaelle Rousseau-Bussac and Christos Chouaid promoted the study, and helped retrieving data. All co authors participated in data collection.

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Ethics Approval The ethics committee of the *Société de Pneumologie de Langue Française* approved the study (number: CEPRO 2021-002).

Consent to Participate Not applicable, a letter of information was given to patients alive.

Consent to Publish Not applicable.

Availability of Data and Materials The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

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