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## ORIGINAL ARTICLE

### Lorlatinib for advanced ALK+ Non-Small Cell Lung Cancer: results of the IFCT-1803 LORLATU cohort

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**Short title: Lorlatinib in ALK+ NSCLC**

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## ABSTRACT

### Background

*ALK-rearranged (ALK+)* Non-Small Cell Lung Cancer (NSCLC) represents a rare subset of lung cancer, with specific presentation, and multiple treatment options, including selective tyrosine kinase inhibitors (TKIs). Real-world evidence is insufficient regarding the actual real-life treatment sequences in the late line setting and available clinical trials may not reflect real-world situation. Here, we took advantage of the French Expanded Access Program (EAP) of lorlatinib, a third-generation TKI targeting ALK and ROS1, to assess treatment sequencing, and lorlatinib efficacy and safety, in patients with *ALK+* NSCLC.

### Methods

All consecutive patients with advanced *ALK+* NSCLC treated between October 2015 and June 2019 with lorlatinib as part of EAP were included. Data were collected and reviewed from medical records by independent research staff of the French Thoracic Cancer Intergroup. Primary endpoint was progression-free survival (PFS).

### Results

Out of the 208 patients included, 117(56%) were female, 142(69%) were never smokers, and 180(87%) had stage IV NSCLC at diagnosis. The most frequent histology was adenocarcinoma (94%) and the median age was 60.9 years. At the time of lorlatinib initiation, 160(77%) patients had brain metastases and 125(72%) were PS 0/1. Lorlatinib was delivered as 2nd/3rd/4th/5th+ line in 4%/17%/30%/49% of patients. 162(78%) patients had previously been treated with chemotherapy, 194(93%) with a 1<sup>st</sup> generation ALK-TKI, 195(94%) with a 2<sup>nd</sup> generation ALK-TKI. Median follow up from lorlatinib initiation was 23.3 months. Median PFS, median overall survival (OS) from lorlatinib initiation, and median OS from advanced NSCLC diagnosis were 9.9 months (95%CI 6-12.3 months), 32.9 months (95%CI 18.7 months-NR), and 97.3 months (95%CI 75.7-152.8 months), respectively. The median duration of treatment with lorlatinib was 11.8 months (95%CI 8.5-18.8 months). Overall response and disease control rate were 49% and 86%, respectively. Central nervous system ORR was 56%. Treatment was stopped due to toxicity in 28 patients (14%). The safety profile of lorlatinib was consistent with previously published data.

### Conclusions

Real-world evidence indicates that lorlatinib offers a significant clinical benefit and high intracerebral antitumor activity in heavily pretreated patients with *ALK+* NSCLC.

**Keywords: Non-small cell lung cancer; ALK; Tyrosine kinase inhibitor, Lorlatinib; Resistance.**

**Highlights:**

Real-world data are lacking regarding lorlatinib efficacy in refractory *ALK+* NSCLC.

In this real-world study lorlatinib PFS and ORR were 9.9 months and 49%.

Lorlatinib represents a major treatment option after failure of *ALK*-TKI.

## INTRODUCTION

Three to 5% of non-small cell lung cancers (NSCLC) display a rearrangement of the *ALK* gene<sup>1,2</sup>. This alteration leads to the synthesis of a chimeric protein encompassing the ALK tyrosine kinase domain and driving the oncogenic process. *ALK* positive (*ALK+*) NSCLCs represent a distinct subset of patients with aggressive disease that has a propensity towards central nervous system (CNS) involvement<sup>3,4</sup>. Based on current ESMO and NCCN guidelines, the treatment strategy for metastatic *ALK+* NSCLC mainly relies on ALK tyrosine kinase inhibitors (TKIs)<sup>5,6</sup>. Crizotinib has been the first *ALK*-TKI to demonstrate superiority over platinum-based chemotherapy as first-line treatment<sup>7</sup>. Subsequently, the so-called 2nd generation *ALK*-TKI such as ceritinib, alectinib or brigatinib showed superior efficacy in front line setting compared to chemotherapy or crizotinib<sup>8-10</sup>. However, all patients eventually develop tumor progression due to resistance mechanisms such as alternative signaling pathway activation or emergence of mutations within the *ALK* kinase domain, or pharmacodynamic patterns<sup>11,12</sup>.

Lorlatinib is a 3rd generation, reversible ATP competitive TKI of *ALK* and *ROS1* covering most *ALK*-TKI resistance mutations including the G1202R frequently found after 2nd generation TKI resistance<sup>11,13</sup>. In addition, lorlatinib has a significant penetration in the CNS, a frequent site of recurrence under *ALK*-TKI. Its efficacy in TKI-pretreated *ALK+* NSCLC was evaluated in a uncontrolled, multi-cohort phase I/II clinical trial<sup>14</sup>. This trial led to its approval in Europe in metastatic *ALK+* NSCLC after failure of ceritinib or alectinib or after receiving crizotinib and at least one other *ALK*-TKI.

Few real-world evidence is available regarding treatment sequences and outcomes<sup>15</sup>. Here, we took advantage of the French Expanded Access Program (EAP) of lorlatinib, to assess treatment sequencing, and lorlatinib efficacy and safety, in patients with *ALK+* NSCLC.

## MATERIALS AND METHODS

### Study population and data collection

Consecutive adult patients, from 74 centers, with an advanced or metastatic *ALK+* NSCLC, treated from October 2015 to June 2019 as part of the EAP with lorlatinib, 100mg once daily for at least 7 days, were included in the present study. Patients were eligible for lorlatinib EAP if they had failed at least one line of *ALK*-TKI. The EAP database allowing patient identification were provided by Pfizer.

Data and survival follow-up were extracted from medical records by investigators in each center and documented in a standard case report form. Database is hosted by the French Collaborative Thoracic Intergroup (IFCT) that ensured the quality of the data collected by monitoring the centers with periodic visits of IFCT clinical research associates.

### **Study oversight**

This non-interventional study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, approved by a national ethics committee, French Advisory Committee on Information Processing in Material Research in the Field of Health, and France's national data protection authority (CNIL) in accordance with General Data Protection Regulation. All participating departments approved the study protocol and all included patients still alive received information from their referring physician, with an opportunity not to participate.

### **Study endpoints**

The primary endpoint was progression free survival (PFS) measured from the date of first lorlatinib dose to the date of disease progression according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or death from any cause. Secondary endpoints included : objective response rate (ORR) defined as the percentage of patients with partial or complete response to lorlatinib according to RECIST 1.1 evaluated by investigators ; disease control rate (DCR) defined as the percentage of patients with partial or complete response or stable disease to lorlatinib according to RECIST 1.1 evaluated by investigators ; overall survival (OS) calculated from the date of the lorlatinib first dose to the date of death from any cause ; overall survival (OS) calculated from the date of advanced or metastatic NSCLC diagnosis ; duration of treatment (DOT) measured from the date of lorlatinib first dose to the date of treatment discontinuation or death from any cause during the study ; duration of treatment response measured from the date of first lorlatinib RECIST 1.1 tumor response to the date of disease progression or death from any cause ; CNS response rate defined as the rate of intracranial tumor response to lorlatinib according to RECIST 1.1 evaluated by investigators among patients with brain metastasis ; duration of CNS response, defined as the time from the first documentation of objective cerebral response to the first documentation of cerebral progression or to death from any cause. ORR, PFS, DOT were also collected for subsequent treatments after lorlatinib failure. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events version 5.0. Only grade 3 to 5 adverse events were recorded.

### **Statistical analysis**

Categorical variables are expressed as frequencies and percentages. Quantitative variables are expressed as medians (range). The Kaplan-Meier method was used to estimate PFS and OS endpoints. The cut-off date for survival analysis was February 2<sup>nd</sup> 2020. All analyses were performed using SAS software, Version 9.4 (SAS Institute).

## RESULTS

### *Clinico-pathological characteristics*

Among the 343 patients identified in the lorlatinib EAP database, 208 met the pre-defined inclusion criteria (Supplementary Figure 1). Patient characteristics are summarized in Table 1. Most patients were women (56%), never-smokers (69%) and displayed a stage IV disease at diagnosis (87%). The median age was 60.9 years (range 20.7-83.8). The most frequent histology was adenocarcinoma (94%). At lorlatinib initiation, most of the patients had a good performance status (PS0-1: 72% of patients) and had brain metastases (77%). Patients were heavily pretreated since 79% of them had previously received at least 3 lines of systemic treatment, and 46% also had been treated with brain radiation therapy. Moreover, all patients had been previously treated with at least one ALK-TKI and 93% had received a 1st generation ALK-TKI – crizotinib -, 94 % a 2nd generation ALK-TKI – ceritinib, alectinib, or brigatinib. At lorlatinib initiation, the number of patients that had previously received 1/2/3 or more lines of ALK-TKI were respectively 20 (9%)/120 (58%)/68 (33%).

### *Clinical outcomes*

The median of follow up from lorlatinib initiation was 23.3 months (Interquartile range: 16.5-29.5) (Table 2). Median PFS and median OS from lorlatinib initiation were respectively 9.9 months (95%CI 6.0-12.3 months) and 32.9 months (95%CI 18.7 months-NR) (Figures 1 and 2). Median OS from advanced or metastatic NSCLC diagnosis was 97.3 months (95%CI 75.7-152.8 months). Out of the 208 patients, 191 were assessable for response. Among these patients, ORR and DCR to lorlatinib treatment were respectively 49% and 86%. The median duration of response was 14.9 months (95%CI 10.1 months-NR). CNS response rate was 56% and the median duration of CNS response was 16.7 months (95%CI 10.12 months-NR). The CNS response rate and the median duration of CNS response were respectively 46% and 17.9 months among patients who received brain radiotherapy prior lorlatinib, and 69% and 13.4 months among patients who did not receive this treatment. Overall, 107 patients experienced tumor progression and the two main sites of relapse were the thorax and the brain (Supplementary Figure 2). Median duration of lorlatinib treatment was 11.8 months (95%CI 8.5-18.8 months). When lorlatinib was continued beyond progression (n=89), median



duration of treatment was 1.6 months (IC95% 0.8-4.0 months). Among the patients who had received before lorlatinib initiation only 1 previous ALK TKI, 2 previous ALK-TKIs, and 3 or more ALK-TKIs, median PFS and OS were 10.3 months (95%CI 2.3 months-NR) and NR, 11.8 months (95%CI 7.3-14.6 months) and 32.9 months (95%CI 17.6 months-NR), 5.8 months (95%CI 3.7-10.2 months) and 18.7 months (95%CI 11.6 months-NR), respectively. The ORR depending on whether patients had received 1 previous ALK-TKI, 2 previous ALK-TKI, and 3 or more previous ALK-TKI before lorlatinib initiation were 63%, 47% and 47%, respectively.

### *Safety*

Grade 3 to 5 adverse events occurred in 30% of the patients (Table 3). The most common grade 3 or more adverse events were elevated cholesterol levels (12%), cognitive effects (5%), elevated triglyceride levels (4%), peripheral neuropathies (2%), oedema (2%), left ventricular ejection fraction decreases (2%), and mood effects (1%). Fatal adverse events occurred in 1 patient who died from hypercapnic acute respiratory failure. Adverse events leading to treatment discontinuation occurred in 14% of the patients included in the study. They were mainly represented by cognitive effects, arthralgia, left ventricular ejection fraction decreased, mood effects, oedema, pulmonary hypertension (Supplementary Table S1).

### *Subsequent therapy*

After lorlatinib treatment, 66 patients received at least one subsequent systemic therapy mainly represented by chemotherapy and second generation ALK-TKI (Supplementary Table S2 and Supplementary Figure 3). Apart from a higher proportion of women, the characteristics of patients who received subsequent systemic therapy were broadly similar to those who did not receive any systemic therapy after lorlatinib (Supplementary Table S3). Among the subsequent treatments given as first or second line after discontinuation of lorlatinib, ALK-TKI had the longest median duration of treatment followed by platinum-doublet chemotherapy, immunotherapy, and non-platinum-based chemotherapy (Supplementary Table S2). For the 33 patients that received an ALK-TKI as the first subsequent line after the lorlatinib the ORR and the median PFS were 24% and 4 months (CI95% 2.8-8.7 months) (Supplementary Table S4). The OS from the initiation of ALK-TKI as the first subsequent line after the lorlatinib was 21.9 months (95%CI 16-21.9 months).

## **DISCUSSION**

LORLATU cohort represents the largest real-life study describing the efficacy and safety of lorlatinib after the failure of at least one ALK-TKI in *ALK+* NSCLC. This study confirms the efficacy of

lorlatinib in this setting. Indeed, we observed an ORR of 49% and a median PFS of 9.9 months with lorlatinib, close to the ORR of 47% and median PFS of 7.3 months reported among the 198 patients pretreated with at least one ALK-TKI in the pivotal phase II study<sup>14</sup>. In our cohort, The CNS response rate of 56.4%, and the median duration of the CNS response of 16.7 months were also close to the 63% of intracranial objective response and the 14.5 months of median duration of intracranial response described in Solomon *et al.* In addition, the CNS response rate was 69% in patients who were naive of cerebral radiation with a median duration of intracranial response of 13.4 months. These results were indicative of significant intracerebral antitumor activity. As expected, we found a decrease in the lorlatinib efficacy with the number of lines of previous ALK-TKIs received; this was also observed in the phase II clinical trial and in a real-life study<sup>14,16</sup>. In our study, for instance, the PFS decreased from 11.7 months to 5.8 months depending on whether patients had received two or more previous ALK-TKIs. These results suggest a benefit of using lorlatinib early in the patient's management and highlight the need for further analysis of treatment sequences. However, the question of where to place lorlatinib in the treatment sequence has recently become more complex with the results of the phase 3 CROWN trial showing the superiority first-line setting of lorlatinib over crizotinib in terms of PFS<sup>17</sup>. In the absence of a direct comparison of first-line lorlatinib with second-generation ALK-TKIs, it is difficult to provide a definitive answer.

The safety profile of lorlatinib was consistent with previously published data<sup>14,16-18</sup>. The most common serious adverse events were metabolic disorders such as hypercholesterolemia or hypertriglyceridemia, neurological disorders such as cognitive impairment, peripheral neuropathy or mood disorders, and edema. Although the median duration of treatment between our study and the pivotal phase 2 trial was comparable (7.6 months vs. 8.3 months), the frequency of grade 3 or higher hypercholesterolemia and hypertriglyceridemia was lower in our study compared to the pivotal phase 2 trial (12% vs. 15% and 4% vs. 16%, respectively). However, these frequencies were comparable to those obtained in other real-life studies<sup>16,18</sup>. These discrepancies could be related to the fact that patient follow-up is probably less protocolized and less rigorous in real-life situations. Interestingly, the frequency of discontinuation of treatment due to toxicity was higher in our study than in the Salomon *et al.* trial (14% vs 3%). In both cases the main cause of discontinuation was cognitive effects, highlighting the difficulty of managing this kind of adverse events.

Most patients in our study received at least one additional line of systemic therapy after stopping lorlatinib, mainly chemotherapy or ALK-TKIs. There are very few data on the use of ALK-TKIs after progression on lorlatinib. A real-life study reported a PFS of 7.5 months with brigatinib in 37 patients pretreated with lorlatinib<sup>19</sup>. Here we observed a median PFS of 4.0 months and an ORR of 24% among 33 patients treated with an ALK-TKI as the first subsequent therapy after lorlatinib. Moreover,

ALK-TKI had the longest median duration of treatment among sub-sequent therapies after discontinuation of lorlatinib. Further investigation, including an exhaustive description of the mechanisms of resistance to lorlatinib, is needed to address this question of the ALK-TKI therapy after lorlatinib failure.

Our study has several limitations mainly related to its retrospective nature. This type of design prevents standardization of the tumor follow-up and evaluation of adverse events. Moreover, because of this retrospective design, centralization of RECIST evaluations and molecular analyses was not feasible. Due to the lack of systematic molecular analysis at tumor progression with ALK-TKIs, these real-life data do not allow us to evaluate the efficacy of lorlatinib according to the mechanisms of resistance to the ALK-TKI previously received. Indeed, while preclinical data show that lorlatinib is effective against most resistance mutations to first or second generation ALK-TKIs, its efficacy may be reduced in the presence of an off-target resistance mechanism such as *MET* or *HER2* amplification or *KRAS* mutation<sup>11,20-22</sup>. The value of lorlatinib compared with other systemic treatments such as chemotherapy could be questioned in the presence of such alterations. For similar reasons, we were also not able to evaluate the impact of the EML4-ALK fusion variants on lorlatinib efficacy. Finally, due to the absence of systematic molecular analysis at tumor progression, we cannot describe the mechanisms of resistance to lorlatinib. The ongoing IFCT-1902 ORAKLE trial evaluating the efficacy of lorlatinib after a first-line with alectinib or brigatinib has planned to centralize molecular testing and will provide important data on these issues.

In conclusion, this study confirms the position of lorlatinib as an effective rescue treatment after resistance to 1st and 2nd generation ALK-TKIs. The overall safety profile was favorable, although neurological side effects could lead to treatment discontinuation. The recent results from the phase 3 CROWN trial demonstrating the superiority of lorlatinib over crizotinib in the first line setting will complexify treatment sequences for ALK+ NSCLC<sup>17</sup>. However, in ALK+ NSCLC first-line treatment is now based on 2nd generation ALK-TKIs, and the optimal sequencing of ALK-TKIs remain to be further analyzed.

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#### **DECLARATION OF INTERESTS STATEMENT**

Dr Baldacci, Dr Avrillon, Dr Quantin, Dr Duruisseaux, Dr Clément-Duchêne, Dr Cousin, Dr Ricordel, Dr Merle, Dr Otto, Dr Schneider, M Morin, Mrs Langlais, Dr Girard report no conflict of interest.

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## Tables

**Table 1: Demographics of the cohort**

<b>Characteristics</b>	<b><i>n = 208 (%)</i></b>
<b>Gender</b>	
Male	91 (44)
Female	117 (56)
<b>Median age (years, range)</b>	60.9 (20.7-83.8)
<b>Smoking status</b>	
Current or former smokers	64 (31)
Never smokers	142 (69)
Unknown	2
<b>TNM staging at diagnosis</b>	
I-II	4 (2)
III	24 (12)
IV	180 (86)
<b>Brain metastasis at diagnosis</b>	
Present	59 (28)
Absent	149 (72)
<b>Histology</b>	
Adenocarcinoma	195 (94)
Squamous carcinoma	5 (2)
Other	8 (4)
<b>PS at lorlatinib initiation</b>	
0-1	125 (72)
≥ 2	48 (28)
Unknown	35
<b>Previous lines of systemic therapy</b>	
1	8 (4)
2	36 (17)
3	62 (30)
≥ 4	102 (49)
<b>Previous systemic therapy</b>	
Chemotherapy	162 (78)
1 <sup>st</sup> generation ALK TKI	194 (93)
2 <sup>nd</sup> generation ALK TKI	195 (94)
Immune checkpoint inhibitors	10 (5)
<b>Previous lines of ALK TKI</b>	
1	20 (9)
2	120 (58)
≥ 3	68 (33)
<b>Previous brain radiotherapy</b>	95 (46)
<b>Brain metastasis at lorlatinib initiation</b>	
Present	160 (77)
Absent	48 (23)

**Table 2: Lorlatinib therapy clinical outcome (PFS: progression free survival; OS: overall survival; CNS : central nervous system).**

<b>Characteristics</b>	<b>n = 208 (%)</b>
<b>Median follow up (IQR, months)</b>	23.3 (16.5-29.5)
<b>Median PFS (95% CI, months)</b>	9.9 (6.0-12.3)
<b>Median OS (95% CI, months)</b>	32.9 (18.7-NR)
<b>Median OS from advanced or metastatic NSCLC diagnosis (95% CI)</b>	97.3 (75.7-152.8)
<b>Best response to lorlatinib (N,%)</b>	
Number of patients with available data	191 (92)
Complete response	8 (4)
Partial response	85 (45)
Objective response	93 (49)
Stable disease	71 (37)
Progression	25 (13)
Not evaluable	2 (1)
<b>Median duration of response (95% CI, months)</b>	14.9 (10.1-NR)
<b>CNS objective response * (available data; %)</b>	84 (/149; 56)
<b>CNS objective response in patients with prior brain radiotherapy * (available data; %)</b>	38 (/82; 46)
<b>CNS objective response in patients without prior brain radiotherapy * (available data; %)</b>	46 (/67; 69)
<b>Median duration of CNS response (95% CI, months)</b>	16.7 (10.1-NR)
<b>Median duration of CNS response in patients with prior brain radiotherapy (95% CI, months)</b>	17.9 (10.1-NR)
<b>Median duration of CNS response in patients without prior brain radiotherapy (95% CI, months)</b>	13.4 (6.4-NR)
<b>Median lorlatinib duration (95% CI, months)</b>	11.8 (8.5-18.8)
<b>Median lorlatinib duration beyond progression (95% CI, months)</b>	1.61 (0.76-4.01)
<b>Treatment discontinuation</b>	112 (54)
<b>Cause of treatment discontinuation</b>	
Disease progression	60 (29)
Toxicity	28 (14)
Death	15 (7)
Investigator's decision	7 (3)
Patient's decision	1 (1)
Intercurrent disease	1 (1)

\* Defined as the rate of intracranial tumor response according RECIST v1.1

**Table 3: Serious adverse events in patients treated with lorlatinib (reported in more than 1% of patients).**

	<b>n = 208 (%)</b>			
	<b>Grade 3-5</b>	<b>Grade 3</b>	<b>Grade 4</b>	<b>Grade 5</b>
<b>Any adverse event</b>	62 (30)	48 (23)	13 (6)	1 (1)
<b>Hypercholesterolemia</b>	24 (12)	17 (8)	7 (3)	0 (0)
<b>Cognitive effect</b>	11 (5)	10 (5)	1 (0.5)	0 (0)
<b>Hypertriglyceridemia</b>	8 (4)	6 (3)	2 (1)	0 (0)
<b>Peripheral neuropathy</b>	5 (2)	5 (2)	0 (0)	0 (0)
<b>Oedema</b>	5 (2)	5 (2)	0 (0)	0 (0)
<b>Ejection fraction decrease</b>	4 (2)	4 (2)	0 (0)	0 (0)
<b>Mood effect</b>	3 (1)	2 (1)	1 (0.5)	0 (0)
<b>Fatigue</b>	3 (1)	2 (1)	1 (0.5)	0 (0)
<b>Arthralgia</b>	2 (1)	2 (1)	0 (0)	0 (0)
<b>Pulmonary hypertension</b>	2 (1)	1 (0.5)	1 (0.5)	0 (0)

## Figure legends

**Figure 1: Progression free survival.** Kaplan-Meier estimate of progression-free survival (PFS). Tick marks on the survival curves indicate censoring of data. CI denotes confidence interval.

**Figure 2: Overall survival.** Kaplan-Meier estimate of overall survival (OS) measured from lorlatinib initiation. Tick marks on the survival curves indicate censoring of data. CI indicates confidence interval. NR denotes not reached.

**Supplementary Figure S1: Flow chart.**

**Supplementary Figure S2: Sites of progression on lorlatinib.**

**Supplementary Figure 3: Lorlatinib treatment duration.** Each line represents duration of the indicated therapy for one patient (red lorlatinib, blue previous therapy, green subsequent therapy).

Figure 1

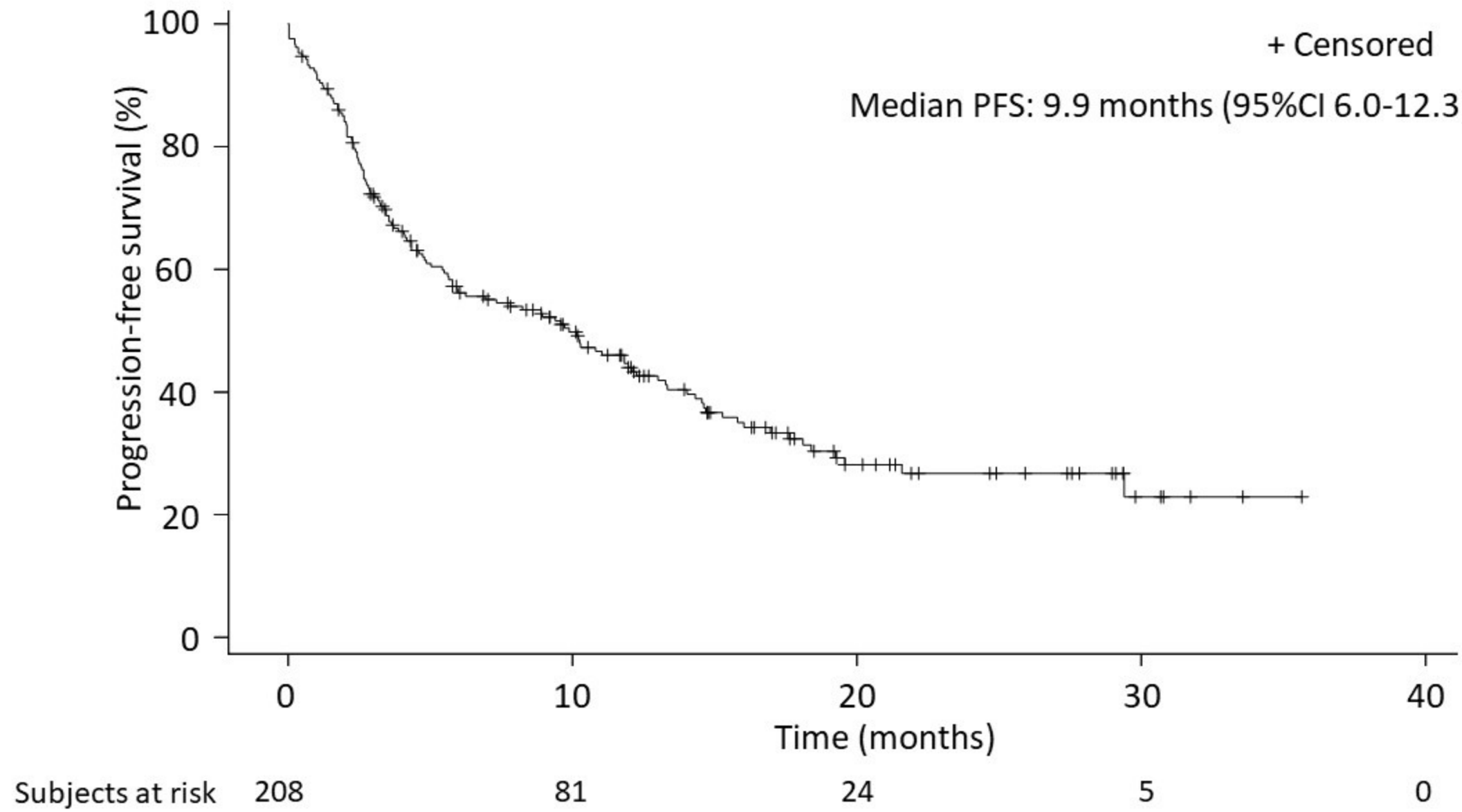


Figure 2

