Efficacy of Alectinib in ALK-Positive Non-Small Cell Lung Cancer with Leptomeningeal Metastases Pretreated with Crizotinib

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Research Article

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Abstract

Purpose

Leptomeningeal metastases is a fatal complication of advanced non-small cell lung cancer (NSCLC). This study aimed to assess the clinical efficacy of alectinib in ALK-positive NSCLC with LM patients previously treated with crizotinib.

Methods

Retrospective study of NSCLC patients with alectinib-treated ALK- positive NSCLC and LM.

Results

Fourteen patients (mean age, 55 years; 50% women) with adenocarcinoma NSCLC were included in the study. Before starting alectinib, all patients were treated with crizotinib. When LM was diagnosed, all patients had clinical symptoms. Sixteen (50%) patients had a performance status>2. Of 14 total patients, 85.7% (12/14) of the patients had a clinical and radiological responses. From the start of alectinib, median OS and PFS were 17.4 (95% CI, 8.9–25.9) and 11.6 months (95% CI: 8.4–14.8), respectively, one-year survival rate was 57.1%.

Conclusion

Alectinib had significant efficacy against NSCLC with LM, this efficacy was rapid in several patients, even some with poor performance status. Alectinib might be a suitable option for specific patient populations with advanced ALK-positive NSCLC with LM.

1. Introduction

Central nervous system (CNS) metastases, including brain metastases (BM) and leptomeningeal metastases (LM), are frequent causes of disease progression and death in patients with non-small cell lung cancer (NSCLC)[1].The incidence of CNS metastases is around 30–50% in patients with anaplastic lymphoma kinase (ALK)- positive NSCLC, whereas LM is found in about 5% of ALK-positive cases and usually presents as a late complication [2-4]. However, its incidence has increased in subgroups of patients with targetable mutations largely due to the improved outcomes from new molecular therapies. The prognosis of NSCLC patients with LM is poor but has improved, from a historical median survival of 1–3 months to 3–11 months with novel therapies and the integration of local and systemic treatments[2, 4-6]. However, LM is still a thorny clinical problem because of its critical condition, rapid progress, poor prognosis and short survival time, which seriously affects the quality of life of the patients.

Previously, crizotinib was the standard of care first-line therapy for ALK-positive NSCLC[7], but in patients treated with crizotinib, CNS progression occurs in up to 70% of patients[8, 9]. The binding and specificity of Crizotinib to ALK are limited, and the CNS permeability is also low, so it has limited efficacy in patients

with CNS. Alectinib is a second-generation highly selective ALK inhibitor that has proven clinical activity against CNS metastases in patients with ALK-positive NSCLC who were resistant to crizotinib[10, 11]. LM development is generally associated with poor prognosis and worsened performance status[4]. Patients with LM have been routinely excluded from clinical trials, so information on the treatment of ALK-positive LM remains scarce.

In this study, we retrospectively collected data on LM patients at our institute. We sought to investigate the efficacy of alectinib in ALK-positive NSCLC with LM patients previously treated with crizotinib.

2. Material And Methods

2.1 Patients

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Second Affiliated Hospital of Nanchang University. Written informed consent was not required due to the retrospective nature of the study. Patients with advanced NSCLC and LM at the Second Affiliated Hospital of Nanchang University from September 2017 to September 2020 were included. Inclusion criteria were ALK-positive NSCLC, patient age≥18 years with LM (confirmed by magnetic resonance imaging (MR) scans and/or positive cerebrospinal fluid (CSF) cytology), treated with alectinib (600mg bid) after having received crizotinib. Patients who were not diagnosed with NSCLC or patients with NSCLC who presented with LM at the time of diagnosis or who developed LM after progression on alectinib were excluded.

2.2 Statistical analysis

Demographics and clinical characteristics, tumour characteristics, treatment modalities, and outcome were collected from our medical records. LM response assessment was based on the modified RANO LM radiological criteria; CNS and extra-CNS response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Progression-free survival (PFS) was calculated from the date of alectinib administration to the time of disease progression (obvious symptom deterioration when brain imaging was not performed); Overall survival (OS) was calculated from the date of alectinib administration until the date of death or the last follow-up. Survival analyses were performed according to the Kaplan-Meier method, and confidence interval (CI) were calculated at a 95% confidence level. IBM SPSS version 24.0 and GraphPad Prism version 8.0 were used for all statistical analyses and to prepare graphs, respectively.

3. Results

3.1. Patient characteristics

A total of 153 lung cancer patients diagnosed with LM were hospitalized at our center from September 2017 and September 2020, ultimately, 14 patients were included, the flow chart of the screened patients is

summarized in Fig. 1. Patient and tumor characteristics are listed in Table 1. The median age was 55 years (range 41-68 years). 7 were female (50.0%). 21.4% (3/14) were former or current smokers. All tumor histological analyses indicated lung adenocarcinoma. All patients had LM-related clinical symptoms, 57.1% (8/14) of patients were diagnosed with LM by cytology, and 42.9% (6/14) were diagnosed by MRI scan and cerebrospinal fluid (CSF) cytopathology. Performance status was >2 for 50.0% (7/14) of patients. There were11 patients who had concomitant BM, and 35.7% (5/14) of patients had received brain radiotherapy before LM. Three of the patients received whole-brain radiotherapy (WBRT), two patient received SRS for brain parenchymal metastasis. All patients were treated with crizotinib before LM.

Table1 Patients Characteristics

Characteristics		No (%)
Total case		14
Median age years (range, year)		55(41-68)
Gender	Male	7（50.0）
	Female	7（50.0）
Smoking history	Former or current	3（21.4）
	Never	11 (78.6)
Histology	Adenocarcinoma	14 (100)
LM after crizotinib treatment	Yes	14 (100)
BM before LM	Yes	7（50.0）
	No	7（40.0）
Brain radiotherapy before LM	Yes	5（35.7）
	No	9（64.3）
Number of treatment lines before LM	1	5（35.7）
	2	7（50.0）
	4	2（14.3）
Neurological symptoms	Yes	14 (100)
ECOG performance status score	≤2	7（50.0）
	＞2	7（50.0）
Concomitant BM	Yes	11(78.6)
	No	3（21.4）
CSF cytopathology	Yes	8（57.1）
	No	6（42.9)
Diagnosis of LM by MRI scan	Yes	10 (71.4)
	No	4（28.6)

BM, brain metastasis; ECOG, Eastern Cooperative Oncology Group; LM, leptomeningeal metastasis; CSF, cerebrospinal fluid;

3.2 CSF analysis

All patients with LM underwent lumbar puncture, and CSF cytopathology was positive in 8 patients. Of 14 total patients, CSF pressure was increased (>20 cmH2O) in 6 patients, increased total protein CSF levels (>0.45 g/L) were present in 85.7% of patients with LM, and decreased glucose was present in 21.4% of patients. The average value of CSF chloride was 121.4 (120.1, 124.4) mmol/L, and CSF glucose was 2.6 (2.2, 3.4) mmol/L. (Table 2)

Table 2 CSF analysis

CSF analysis	No%/M（P25, P75）
cytopathology positive	8 (57.1)
protein Elevated	12(85.7)
Protein (mg/L)	899.2 (524.8, 2263.9)
chloride (mmol/L)	121.4 (120.1, 124.4)
glucose (mmol/L)	2.6 (2.2, 3.4)

CSF, cerebrospinal fluid

3.3 Clinical Responses of LM

At the time of the analysis of this study, ten patients deaths (71.43%) had died, mean follow-up after LM was 12.2 months. The median time from the date of initial diagnosis with lung cancer to the occurrence of LM was 12.9 months. Of 14 total patients, 85.7% (12/14) of the patients had a clinical and radiological responses. Individual survival of this 14-patient series is reported in Fig. 2. From NSCLC diagnosis, median OS was 29.3 (95% CI: 19.5–39.1 months) (Fig. 3). From alectinib initiation, median OS and PFS were 17.4 (95% CI, 8.9–25.9) and 11.6 months (95% CI: 8.4–14.8), respectively (Fig. 4), one-year survival rate was 57.1%. No grade-3/4 toxicity was reported. Bevacizumab was given to 6 patients with disease progression after alectinib treatment, intrathecal chemotherapy was given to 6 patients with severe LM-related clinical symptoms.

4. Discussion

As scarce data have been reported on the efficacy of alectinib in LM patients, our study showed a possible role of alectinib in treating LM. To the best of our knowledge, this is the first retrospective study to assess the efficacy of alectinib in ALK-positive NSCLC with LM patients previously treated with crizotinib. We concluded that a number of LM patients benefited from alectinib with dramatically relieving symptoms and long OS. From alectinib initiation, median OS was 17.4 (95% CI, 8.9–25.9), one-year survival rate was 57.1%.

All patients had received crizotinib before developing LM, mostly as first-line treatment. Patients with LM exhibit a dismal prognosis and severe symptoms, at the time of LM diagnosis, all patients had

neurological symptoms and 7 of the 14 had performance status ≥2. A positive CSF cytology remains the gold standard for the diagnosis of LM, but CSF cytology was considered positive in 66%–90% of patients. CSF cytology studies are commonly qualitative and sensitivity is low, although specificity is high[4]. Studies showed that CSF cytology positive in 57.1% of patients, by MRI/CT scan for 71.4% and by both methods for 28.5%; positivity rates comparable to those found in other studies[12, 13]. Non-diagnostic pathological findings upon routine CSF analysis are observed in more than 90% of LM patients and include increased opening pressure (>200 mm H2O) in 21%–42%, elevated protein (>50 mg/dL) 56%–91%, and decreased glucose (<60 mg/dL) in 22%–63% [14]. Our study find CSF pressure was increased (>20 cmH2O) in 6 patients, increased total protein CSF levels (>0.45 g/L) were present in 85.7% of patients with LM, and decreased glucose was present in 21.4% of patients, which is roughly consistent with our studies.

LM in ALK-positive NSCLC tends to as a late complication after a median time of 9 months from the diagnosis of the NSCLC[3]. LM is usually accompanied by a poor prognosis, with a median OS of several months if patients receive conventional treatments. However, tyrosine kinase inhibitor (TKI) therapy after LM diagnosis is an independent predictive factor for extended survival. Although the benefit from ALK inhibitors has been established in BM, data regarding the activity in LM are limited to case-reports. The first-generation ALK, ROS1, and MET inhibitor crizotinib has demonstrated remarkable CNS disease control rate (55% and 65% at 12 and 24 weeks, respectively) in patients with BM[8]. PROFILE 1014 study has shown that crizotinib has better CNS disease control than standard chemotherapy[15]. Regardless, the CNS is a frequent relapse site for patients treated with crizotinib. Alectinib, which is a second-generation ALK inhibitor with excellent CNS penetration, has impressive systemic and CNS efficacy in patients with ALK-positive NSCLC both following crizotinib and as a front-line therapy[16-18]. Unlike crizotinib, alectinib displays an increased ability to cross the blood-brain barrier (BBB), and also not a substrate for P-glycoprotein, which promotes efflux at the BBB, reaching significant CSF concentrations[19]. Different case series on LM have reported significant and durable radiological responses with standard (600 mg twice daily)[11, 20]. The ALEX (NCT02075840) study has compared the efficacy of alectinib or crizotinib as first line-treatment in BM and asymptomatic LM, however, results for the last subgroup have not been reported, we are looking forward to the results announced. The second-generation ALK/ROS1 inhibitor ceritinib displayed significant systemic and intracranial activity in patients with ALK positive who were pretreated with crizotinib[21, 22]. The phase II ASCEND- 7 study published by the European Society of Medical Oncology (ESMO) in 2019 showed that ceritinib led to a median PFS of 5.2 months and a median OS of 7.2 months in patients with LM from NSCLC. All 18 enrolled patients had been pretreated with multiline therapy, including radiotherapy, chemotherapy and crizotinib[23]. Brigatinib, a potent ALK/ROS/EGFR inhibitor, had an impressive intracranial ORR of 53%-67% with a median PFS > 12 months when used in BM. A patient with ALK- positive NSCLC and LM pretreated with crizotinib and ceritinib was successfully treated with brigatinib and achieved an intracranial response for more than 14 months[24]. The phase 3 ALTA-1L trial includes patients with any CNS recurrence. Preliminarly, the intracranial ORR was 67% with a median PFS of 11 months, but response of LM was not analyzed separately from that of BM[25]. Overall, the efficacy of brigatinib in LM needs to be further investigated.

Lorlatinib has been shown to elicit impressive intracranial responses in patients with ALK-positive NSCLC[16]. But their role against LM has not been established. Second- generation ALK- TKIs have a higher rate of intracranial response and can be positioned as front- line drugs in NSCLC with LM. However, the sequence in which ALK-TKIs are administered for effective disease control requires further evaluation.

There is no standard regimen for LM several therapeutic options, including intrathecal chemotherapy and radiotherapy, have been applied to manage LM[4, 26]. Although intrathecal chemotherapy is a fairly effective treatment for patients with LM from NSCLC, the optimal agent, dosing, and schedule are yet to be defined. The most commonly used intrathecal chemotherapeutic agents are methotrexate, cytarabine, and thiotepa[4]. Wu and colleagues have conducted a pooled analysis, which included patients with NSCLC treated with intrathecal chemotherapy alone or in combination with other interventions (intrathecal chemotherapy, WBRT, Epidermal growth factor receptor (EGFR)-TKIs, traditional chemotherapy, and supportive care), the clinical response was 64%, the cytological response to intrathecal chemotherapy was 55%, and the radiographic response was 53%, the median survival duration was 3.0–4.3months[27].In our study, intrathecal chemotherapy was given to 6 patients with severe LM-related clinical symptoms, and the symptoms were relieved quickly after treatment. There is no consensus on whether whole-brain radiotherapy (WBRT) is a beneficial treatment for patients with LM. A retrospective review of 125 patients with NSCLC and LM reported that survival was not improved by WBRT[28]. In contrast, another retrospective study showed that patients who underwent WBRT for LM survived longer (8.4 months vs 1.8 months, $p < 0.001$)[29]. However, a retrospective study demonstrated that WBRT has clear survival advantages for patients with wild-type EGFR, and molecular biological stratification of LM patients for WBRT is highly recommended[30]. The US National Comprehensive Cancer Network (NCCN) 2020 guidelines for management of LM recommend focal RT in association with intrathecal chemotherapy in patients with favorable prognostic factors (KPS $\geq$ 60, mild neurologic deficits, stable systemic disease, available therapeutic options for systemic disease)[31].

The development of therapeutic agents with greater CNS penetration is vital for the management of CNS metastases from NSCLC. However, their further effectiveness is limited by inadequate BBB penetration and acquired drug resistance. Further studies are needed to further understand the mechanisms underlying resistance to treatment.

There were some limitations to our study. Firstly, it was a retrospective study; secondly, small samples from LM were collected because the incidence of ALK-positive was low and included only a single institution; thirdly, LM occurred after the treatment of crizotinib, and we did not perform fluid biopsy of CSF to explore the mechanism of drug resistance in order to select more accurate targeted drugs.

In conclusion, alectinib had significant efficacy against NSCLC with LM, this efficacy was rapid in several patients, even some with poor performance status. Therefore, alectinib might be a suitable option for specific patient populations with advanced ALK-positive NSCLC with LM. However, additional studies are needed to confirm these findings.

Declarations

Declarations

Not applicable

Funding

Not applicable

Conflicts of interest/Competing interests

Authors report no conflict of interest

Availability of data and material

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Authors' contributions

LZL and YLY performed the statistical analysis and participated in drafting and wrote the manuscript; XW and ZMZ made useful comments and participated in revising the manuscript; XW and CYZ collected the clinical data; AWL was the principal investigator for this study and was involved in project oversight and organization. All authors approved the final version of the manuscript.

Ethics approval

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Second Affiliated Hospital of Nanchang University. Written informed consent was not required due to the retrospective nature of the study.

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Figures

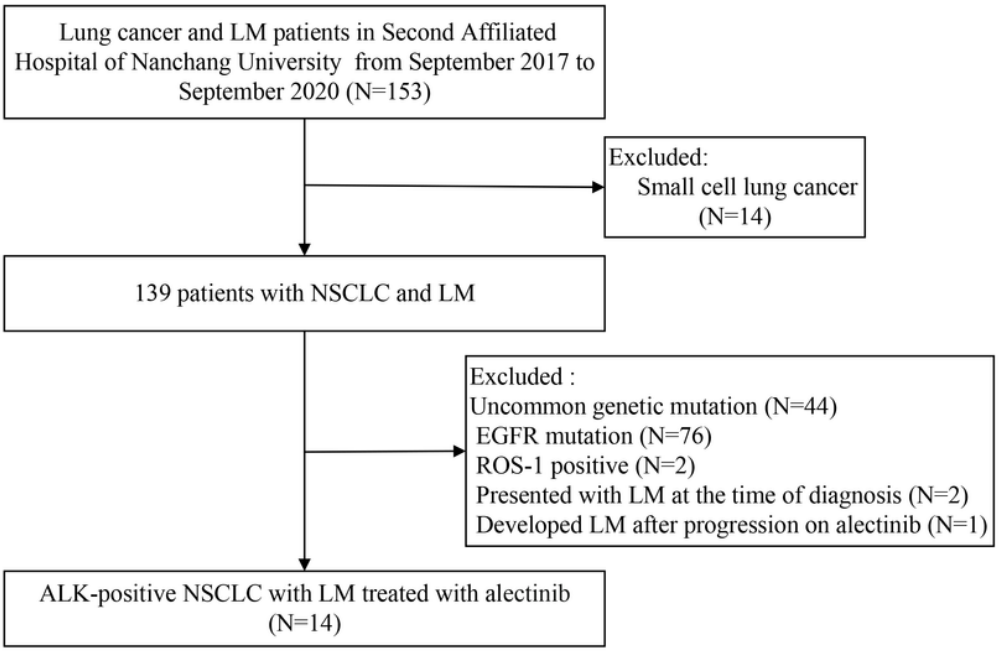

Figure 1

Flow chart of screened patients. NSCLC: non-small cell lung cancer; LM: leptomeningeal metastases; EGFR: epidermal growth factor receptor.

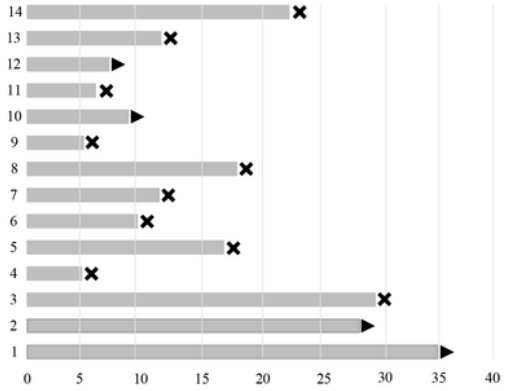

Figure 2

Individual survival for this series of NSCLC patients from the time of alectinib initiation

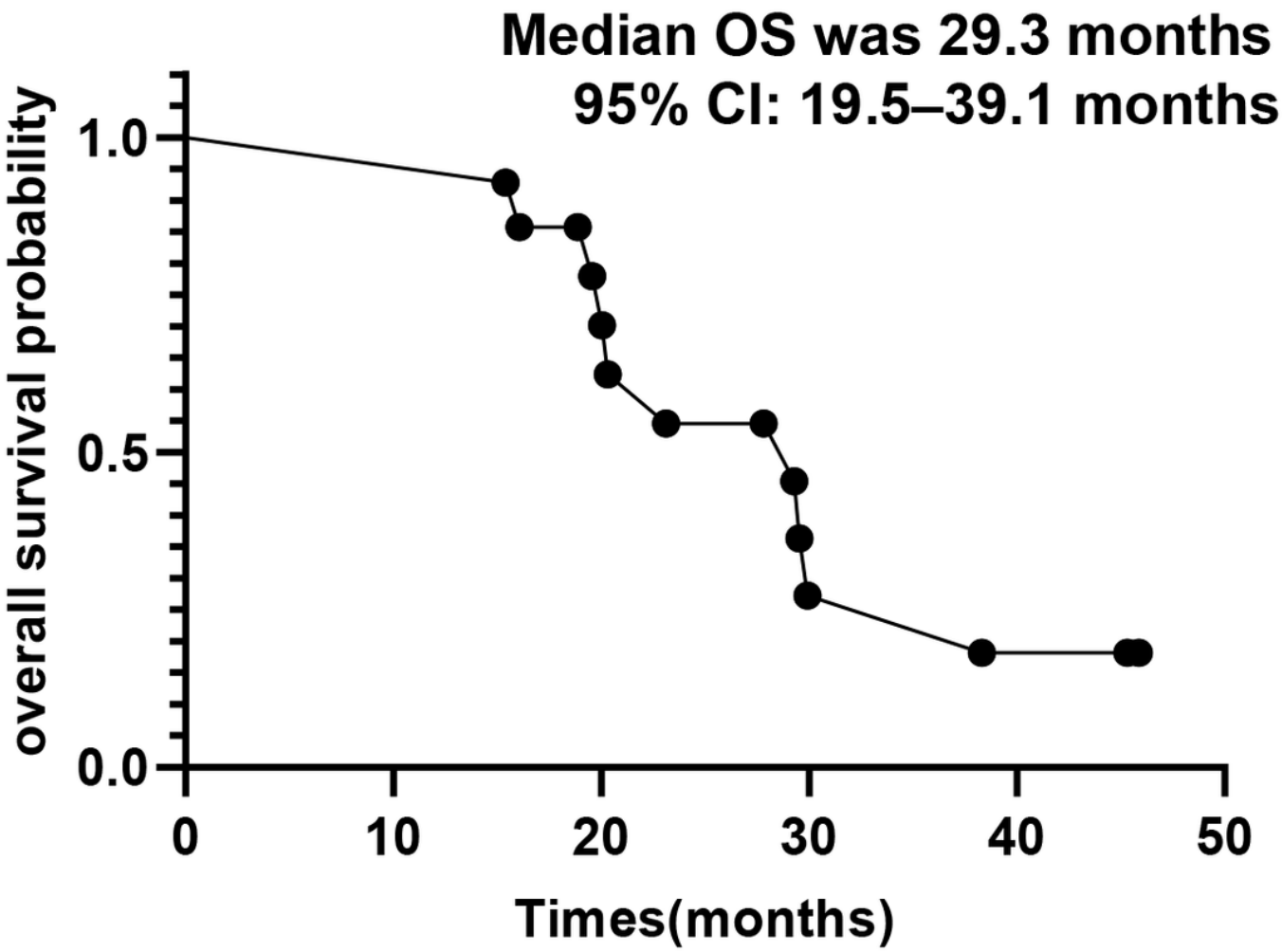

Figure 3

OS from the diagnosis of NSCLC

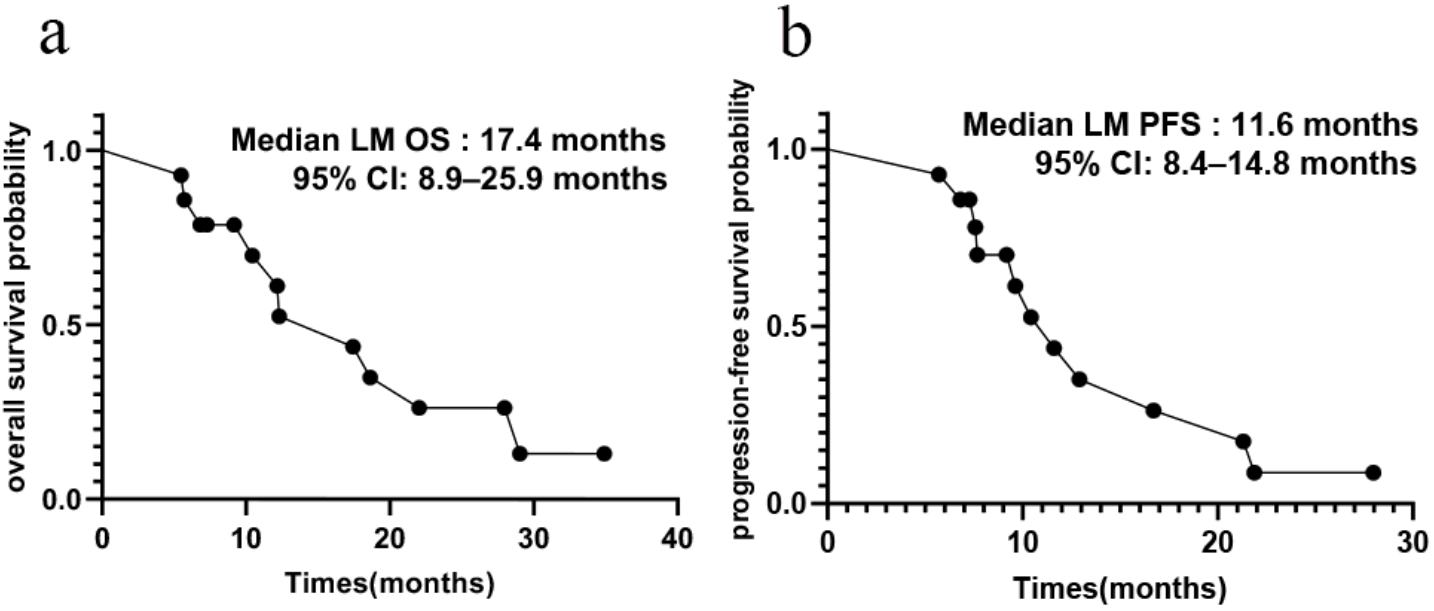

Figure 4

OS (a) and PFS (b) from the initiation of alectinib in patients with ALK-positive NSCLC and LM