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Original Research

Efficacy of lorlatinib in lung carcinomas carrying distinct ALK translocation variants: The results of a single-center study

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ABSTRACT

Background: Lorlatinib is a novel potent *ALK* inhibitor, with only a few studies reporting the results of its clinical use.

Methods: This study describes the outcomes of lorlatinib treatment for 35 non-small cell lung cancer patients with *ALK* rearrangements, who had 2 ($n = 5$), 1 ($n = 26$) or none ($n = 4$) prior tyrosine kinase inhibitors and received lorlatinib mainly within the compassionate use program.

Results: Objective tumor response (OR) and disease control (DC) were registered in 15/35 (43%) and 33/35 (94%) patients, respectively; brain metastases were particularly responsive to the treatment (OR: 22/27 (81%); DC: 27/27 (100%)). Median progression free survival (PFS) was estimated to be 21.8 months, and median overall survival (OS) approached to 70.1 months. Only 4 out of 35 patients experienced no adverse effects; two of them were the only subjects who had no clinical benefit from lorlatinib. PFS and OS in the no-adverse-events lorlatinib users were strikingly lower as compared to the remaining patients (1.1 months vs. 23.7 months and 10.5 months vs. not reached, respectively; $p < 0.0001$ for both comparisons). *ALK* translocation variants were known for 28 patients; there was no statistical difference between patients with V.1 and V.3 rearrangements with regard to the OS or PFS.

Conclusion: Use of lorlatinib results in excellent disease outcomes, however caution must be taken for patients experiencing no adverse effects from this drug.

Introduction

ALK and *ROS1* gene fusions account for 5–8% and 1–2% of non-small cell lung carcinomas (NSCLCs), respectively [1,2]. The invention of crizotinib led to a breakthrough in the treatment of these categories of patients, given that virtually all subjects with *ALK/ROS1*-rearranged NSCLC derive clinical benefit from this drug [3,4]. However, the efficacy of crizotinib, which was originally developed as a MET kinase inhibitor, is compromised by several factors [1,2,5]. Crizotinib is somewhat less potent as compared to newer *ALK/ROS1*-targeted drugs. Some of the tumors, which are exposed to crizotinib, escape from the therapy by developing secondary mutations in the *ALK* or *ROS1* genes. Furthermore, crizotinib poorly penetrates through blood-brain barrier, therefore a significant portion of crizotinib-treated patients develop brain metastases. There is a number of novel tyrosine kinase inhibitors (TKIs), which were designed to address these disadvantages. In particular, studies on *ALK*-driven cancers demonstrated significant activity of ceritinib, alectinib, brigatinib and lorlatinib in crizotinib-treated and TKI-naïve NSCLCs [6–12]. *ROS*1-rearranged NSCLCs showed sensitivity to ceritinib, lorlatinib, entrectinib and some other TKIs in several clinical trials [1,12,13–15].

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Lorlatinib (PF-06463922) is a potent *ALK/ROS1*-selective inhibitor, which retains activity against some *ALK/ROS1* resistance mutations acquired during prior TKI therapy and is characterized by good penetration into the brain. Several studies demonstrated high efficacy of lorlatinib in both heavily pretreated and TKI-naïve NSCLCs [12,16–20]. Lin et al. [21] reported that lorlatinib renders significantly longer progression-free survival for patients, whose NSCLCs carry the variant 3 (V.3) of the *ALK* rearrangement; this phenomenon was explained by the property of *ALK* V.3 associated carcinomas to develop secondary *ALK* G1202R mutations, which are resistant to the majority of conventional TKIs, but are sensitive to lorlatinib [21]. Lorlatinib was accessible in Russia within years 2017–2019 mainly within the compassionate use program. Here we report a single-center experience of the use of lorlatinib in *ALK*-rearranged NSCLC with the emphasis on *ALK* variant-specific disease outcomes.

Patients and methods

The patients were receiving lorlatinib therapy in the I.P. Pavlov Medical University (St.-Petersburg, Russia). The study included 35 subjects with *ALK*-rearranged NSCLC, with the first patients starting to receive this drug in March 2017 and the last person included in the lorlatinib treatment in December 2019. The mean age of the patients was 46.7 ± 2.3 years (range: 24–80 years). The median follow-up time, defined as the interval between the start of the therapy and the death or the date of the data cut-off (June 15, 2020), was equal to 17.5 months. Thirteen of these cases were submitted previously to the study of Peled et al. [22], with the data cut-off for these subjects being January 2019. In 12 out of 35 cases, lorlatinib dose reduction to 75 mg ($n = 4$) or 50 mg ($n = 8$) was required due to toxicity of the drug. Twenty eight patients provided to the study tumor samples; these tissues were subjected to *ALK* translocation variant genotyping by RT-PCR-based method as described by Iyevleva et al. [23]. Seven patients failed to preserve relevant biological material for *ALK* genetic testing, therefore they were included in the study based on the data from medical records (*ALK* fusion identified by FISH ($n = 5$) or IHC ($n = 2$)).

Treatment efficacy was evaluated using commonly accepted criteria for tumor response (RECIST), progression-free survival (PFS) and overall survival (OS). Adverse events were documented and graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Statistical analysis was done using MedCalc Statistical Software version 19.1.3. PFS (defined as the time from the start of lorlatinib therapy to disease progression or death) and OS (defined as the time from the diagnosis to death) were analyzed by Kaplan-Meier method and log-rank test. For PFS and OS analysis, patients without progression on lorlatinib or being alive at the end of the study were censored at the date of data cut-off. Duration of therapy, defined as the time interval between the start of lorlatinib treatment and the discontinuation of its use, was analyzed by Kaplan-Meier method.

Results

Characteristics of included patients are given in Table 1. Objective tumor response was observed in 15/35 patients (43%); the disease control was registered in 33/35 (94%) cases (Fig. 1). Twenty seven patients presented with intracranial metastases at the time of lorlatinib treatment; 22 (81%) showed objective response for brain metastatic lesions. Median PFS was estimated to be 21.8 months, and median OS was equal to 70.1 months (Fig. 2). Adverse events were observed in 31/35 (89%) patients; the most frequent adverse events were hypercholesterolemia (20 cases) and edema (13 cases).

Only 4 patients experienced no adverse effects while being on lorlatinib therapy. It is of interest, that the only 2 patients, who showed progressive disease as the best response to lorlatinib, belonged to this group of subjects. PFS and OS in the no-adverse-events lorlatinib users were strikingly lower as compared to the remaining patients (1.1 months vs. 23.7 months and 10.5 months vs. not reached, respectively; $p < 0.0001$ for both comparisons) (Fig. 3a,b). PFS was higher in patients with brain metastases as compared to subjects without CNS involvement (23.5 months vs. 11.1 months; see also Fig. 3c). While comparison of PFS produced p values far below the statistical threshold, the presence of metastases in CNS correlated with statistically better overall survival ($p = 0.030$; Fig. 3d).

The information regarding the variant of the *ALK* translocation was available for the majority of patients included in the study (Table 1). There was no statistical difference between patients with V.1 and V.3 rearrangements with regard to the rate of objective response or PFS. Interestingly, PFS in patients with common *ALK* translocation variants (V1, V2 or V3; 23.7 months) was higher as compared to subjects with rare *ALK* variants (5.6 months) or unknown type of *ALK* rearrangement (13.1 months); however, this difference did not reach the level of statistical significance ($p = 0.188$ and $p = 0.299$, respectively).

The majority of included patients (26/35, 74%) received one TKI therapy prior lorlatinib treatment. Patients receiving prior crizotinib tended to have higher response rate (7/12, 58%) and PFS (23.7 months) as compared to subjects treated by ceritinib (4/14 (29%) and 15.0 months, respectively). However, the statistical tests did not confirm the significance of these observations ($p = 0.233$ and $p = 0.586$, respectively).

Seventeen patients, which were included in the study and benefited from lorlatinib treatment, progressed during the follow-up. The systemic progression, manifested by the enlargement of multiple metastatic lesions, was observed in 14 of these cases; 12 had treatment failure confined to visceral organs, while 2 patients experienced growth of both extracranial and intracranial tumor lesions. Three patients had oligometastatic progressive disease in the brain ($n = 2$) or lung ($n = 1$).

Discussion

NSCLC studies involving lorlatinib treatment are summarized in Table 2. Given the rarity of *ALK* rearrangements and the availability of several *ALK* inhibitors, clinical testing of novel *ALK*-targeted drugs presents a challenge. Published lorlatinib trials demonstrate significant variations with regard to the selection criteria for the patients, clinical characteristics of included subjects, prior treatment history etc., therefore their comparison is complicated.

While the present study did not differ from other repots with regard to response rates, it produced strikingly higher PFS (21.8 months) when compared to majority of similar investigations. The mere fact of observing high PFS for *ALK*-targeted drugs is not surprising: for example, the first-line alectinib trial resulted in PFS equal to 34.8 months [25]. However, most of previous lorlatinib trials produced somewhat lower PFS as compared to the current study. Several factors may play a role with regard to this difference. Interobserver variability may contribute to some extent to the estimation of PFS, especially given that the tumor progression upon continuing TKI treatment may be slow in some circumstances [26,27]. It is of notice, that our series of patients included apparently less pretreated subjects as compared to studies of Shaw et al. [12], Solomon et al. [17], Zhu et al. [24], and Hochmair et al. [20]; only a minority of included subjects experienced alectinib treatment and none received brigatinib prior to lorlatinib (Table 2). It appears that the TKI treatment history may dramatically influence PFS on lorlatinib. Indeed, recent first-line lorlatinib trial revealed that as many as 78% patients remained progression-free at 12 months; median PFS was not reached at the time of the data analysis, but it is very likely to significantly exceed historical estimates obtained on TKI-pretreated patients [19]. Absence of patients with experience of brigatinib therapy in our data set may also be of potential importance: recent real-world study suggested that prior treatment by brigatinib may compromise the efficacy of lorlatinib to a higher extent as compared to the use of other ALK-targeted TKIs [20]. The invitation of patients to the expanded access programs is often highly influenced by the preferences of primary

Table 1
Characteristics of NSCLC patients treated by lorlatinib and the treatment outcome.

Characteristics of the patients	Treatment outcome								
	Number of patients within a subgroup	CR	PR	SD	PD	Objective response (CR + PR)	Clinical benefit (CR + PR + SD)	Median PFS [95% CI]	Median OS [95% CI]
Gender	*N* = 35								
Male	16	1	4	10	1	5 (31%)	15 (94%)	21.5 [6.2–23.7]	NR
Female	19	0	10	8	1	10 (53%)	18 (95%)	23.5 [11.2–31.6]	70.1 [26.0–70.1]
ALK fusion variant	*N* = 35								
EML4ex13/ALKex20 (V.1)	13	0	7	5	1	7 (54%)	12 (92%)	21.8 [8.2–23.7]	NR
EML4ex20/ALKex20 (V.2)	4	1	1	2	0	2 (50%)	4 (100%)	NR	NR
EML4ex6/ALKex20 (V.3)	8	0	3	5	0	3 (38%)	8 (100%)	NR	54.0 [30.3–54.0]
Rare variants	2	0	1	1	0	1 (50%)	2 (100%)	5.6 [5.6–23.5]	51.2 [51.2–70.1]
Unknown	8	0	2	5	1	2 (25%)	7 (88%)	13.1 [1.1–31.6]	NR
Treatment line	*N* = 35								
1st line	2	0	1	1	0	1 (50%)	2 (100%)	NR	NR
2nd line	16	1	6	8	1	7 (44%)	15 (94%)	15.0 [8.2–23.7]	51.2 [25.8–51.2]
3rd line	12	0	5	7	0	5 (42%)	12 (100%)	31.6 [11.1–31.6]	NR
4th line	5	0	2	2	1	2 (40%)	4 (80%)	21.5 [1.1–21.8]	NR
Number of prior TKIs	*N* = 35								
None	4	1	1	2	0	2 (50%)	4 (100%)	NR	NR
1 TKI	26	0	11	14	1	11 (42%)	25 (96%)	21.5 [11.1–23.7]	NR
2 TKIs	5	0	2	2	1	2 (40%)	4 (80%)	23.5 [1.1–31.6]	70.1 [10.5–70.1]
Prior TKI treatment	*N* = 35								
None	4	1	1	2	0	2 (50%)	4 (100%)	NR	NR
Crizotinib only	12	0	7	4	1	7 (58%)	11 (92%)	23.7 [8.2–23.7]	NR
Ceritinib only	14	0	4	10	0	4 (29%)	14 (100%)	15.0 [6.2–21.8]	NR
Crizotinib and other TKIs[a]	5	0	2	2	1	2 (40%)	4 (80%)	23.5 [1.1–31.6]	70.1 [10.5–70.1]
Prior chemotherapy	*N* = 35								
No	20	0	9	10	1	9 (45%)	19 (95%)	14.9 [10.6–31.6]	70.1 [26.0–70.1]
Yes	15	1	5	8	1	6 (40%)	14 (93%)	NR	NR
Prior therapy	*N* = 35								
None	2	0	1	1	0	1 (50%)	2 (100%)	NR	NR
Chemotherapy only	2	1	0	1	0	1 (50%)	2 (100%)	NR	NR
Crizotinib (with or without chemotherapy)	12	0	7	4	1	7 (58%)	11 (92%)	23.7 [8.2–23.7]	NR
Ceritinib (with or without chemotherapy)	14	0	4	10	0	4 (29%)	14 (100%)	15.0 [6.2–21.8]	NR
Crizotinib and ceritinib (with or without chemotherapy)	3	0	2	1	0	2 (67%)	3 (100%)	23.5 [1.1–31.6]	70.1 [12.8–70.1]
Crizotinib and alectinib (with or without chemotherapy)	2	0	0	1	1	0 (0%)	1 (50%)	1.1 [1.1–1.1]	10.5 [10.5–10.5]
CNS metastases	*N* = 35								
Absent	8	1	2	3	2	3 (33%)	6 (75%)	11.1 [1.1–11.1]	23.2 [10.5–23.2]
Present	27	0	12	15	0	12 (44%)	27 (100%)	23.5 [13.1–31.6]	NR
Adverse events	*N* = 35								
Absent	4[b]	0	1	1	2[b]	1 (25%)	2 (50%)	1.1 [1.1–8.2]	10.5 [10.5–25.7]
Present	31	1	13	17	0	14 (45%)	31 (100%)	23.7 [15.0–31.6]	NR
Types of adverse events	*N* = 35								
Hypercholesterolemia	20	0	7	13	0	7 (35%)	20 (100%)	31.6 [11.4–31.6]	NR
Edema	13	1	6	6	0	7 (54%)	13 (100%)	23.5 [11.1–23.5]	70.1 [23.8–70.1]
Weight gain	4	0	4	0	0	4 (100%)	4 (100%)	31.6 [nd]	NR
Peripheral neuropathy	2	0	0	2	0	0 (0%)	2 (100%)	11.1 [11.1–11.1]	23.2 [23.2–23.2]
Psychosis	2	0	2	0	0	2 (100%)	2 (100%)	21.8 [21.8–23.7]	NR
Hypercreatinemia	1	0	1	0	0	1 (100%)	1 (100%)	–	–
Pleuritis	1	0	1	0	0	1 (100%)	1 (100%)	–	–
Tumor response by RECIST (total)	*N* = 35	1 (3%)	14 (40%)	18 (51%)	2 (6%)	15 (43%)	33 (94%)	21.8 [11.4–31.6]	70.1 [38.2–70.1]
CNS response	*N* = 27	7 (26%)	15 (56%)	5 (19%)	0 (0%)	22 (81%)	27 (100%)	23.5 [13.1–31.6]	NR

Abbreviations: CR – complete response; NR - not reached; OS – overall survival; PD – progressive disease; PFS – progression-free survival; PR – partial response; SD – stable disease.

[a] Crizotinib and ceritinib: 3; crizotinib and alectinib: 2.

[b] Among 4 patients with the absence of adverse events, 3 subjects had *ALK* V.1 translocation variant, and one patient had *ALK* rearrangement determined only by IHC; the latter NSCLC and one NSCLC with *ALK* V.1 fusion showed the disease progression upon lorlatinib treatment.

physicians. Our patient series had remarkably high number of subjects with intracranial involvement. Lorlatinib is known to be particularly effective towards CNS metastases, therefore preferential recruitment of subjects with brain involvement could have led to some bias with regard to PFS. Indeed, patients with visceral-only tumor lesions fared surprisingly worse in this study as compared to NSCLC cases with brain metastases (Table 1); this could be explained by distinct biological properties and prior drug exposure of visceral cancer lesions. Furthermore, in contrast to earlier studies (Table 2), our report considered the pattern of the disease progression followed by the initial response to lorlatinib; as mentioned above, visceral systemic progression was more characteristic than the growth of brain lesions. Most of published lorlatinib trials involved NSCLCs, which were *ALK*-tested using FISH or IHC (Table 2). Our patient series is the only lorlatinib study, where the majority of *ALK* translocations were validated by genotyping. It is of interest, that patients with unknown variants of *ALK* rearrangements had numerically lower PFS as compared to subjects with common *ALK* translocations (Table 1). FISH and IHC generally produce concordant results with *ALK*

Table 2
Lorlatinib clinical studies involving patients with ALK-rearranged NSCLC.

Study	Patients	Method of ALK testing	Prior TKIs (number of patients)	Main outcomes		
				Tumor responses by RECIST[a]	Duration of the effect	Overall survival
Shaw et al., 2017, phase 1 study [17]	Dose-finding study involving 41 patients, who received prior TKI therapy (n = 40) or was TKI-naïve (n = 1)	FISH or IHC	Crizotinib: 36 Ceritinib: >/= 20 Alectinib: >/= 9 Brigatinib: 2	OR: 19 (46%; 3 CR and 16 PR); SD: 8 (20%); PD: 11 (27%) OR in patients who received 1 TKI: 8/14 (57%); 2 or more TKIs: 11/26 (42%) Intracranial response: 8/19 (42%)	PFS: 9.6 months 1 prior TKI: 13.5 months; 2 or more prior TKIs: 9.2 months	
Solomon et al., 2018, phase 2 study [12]	30 treatment-naïve patients	FISH or IHC	–	OR: 27 (90%; 1 CR and 26 PR); SD: 2 (7%); PD: 1 (3%)	PFS: not reached Duration of response: not reached	
	59 patients who received previous crizotinib, with or without chemotherapy	FISH or IHC	Crizotinib: 59	OR: 41 (69%; 1 CR and 40 PR); SD: 10 (17%); PD: 6 (10%) Intracranial response: 20/23 (87%)	PFS: not reached[b] Duration of response: not reached	
	28 patients who received one previous non-crizotinib ALK tyrosine kinase inhibitor, with or without chemotherapy	FISH or IHC	Last TKI received: Alectinib: 13 Ceritinib: 13 Brigatinib: 1 Other: 1	OR: 9 (32%; 1 CR and 8 PR); SD: 10 (36%); PD: 7 (25%)	PFS: 5.5 months Duration of response: not reached	
	111 patients with two or three previous ALK tyrosine kinase inhibitors, with or without chemotherapy	FISH or IHC	Last TKI received: Crizotinib: 18 Ceritinib: 34 Alectinib: 49 Brigatinib: 7 Other: 3	OR: 43 (39%; 2 CR and 41 PR); SD: 38 (34%); PD: 20 (18%)	PFS: 6.9 months Duration of response: not reached	
Zhu et al., 2020, international real-world analysis (early access program) [24]	76 patients, who failed all available ALK inhibitors (or had secondary ALK mutations rendering resistance to available inhibitors); some of these patients were also required to receive standard chemotherapy	Not indicated	Crizotinib: 66 Ceritinib: 46 Alectinib: 43 Brigatinib: 10 Other: 1	OR: 21 (78%; 2 CR and 19 PR); SD: 30 (39%); PD: 13 (17%)	PFS: 9.3 months 1 prior TKI: 9.3 months; 2 previous TKI: not reached; > 2 previous TKI: 11.2 months	Not reached
Peled et al., 2020, international real-world analysis (early access program) [22]	106 patients, who received prior TKI therapy	FISH (76%), IHC (31%), NGS (8%) or PCR (13%); 23 patients were tested by more than one method	Last therapy received: Crizotinib: 40 Ceritinib: 25 Alectinib: 15 Brigatinib: 13	Extracranial response: 52/87 (62%); intracranial response: 40/65 (62%)	Median duration of therapy: not reached; mean duration of therapy: 23.9 months	89.1 months
Hochmair et al., 2020, multicenter real-world analysis (early access program, Austria) [20]	37 patients, who received prior TKI therapy (1 line: 10; 2 lines: 13; 3 lines: 13; 4 lines: 1)	FISH (46%), IHC (35%), NGS (3%) or more than one method (16%)	Crizotinib: 25 Ceritinib: 21 Alectinib: 14 Brigatinib: 27	OR: 16 (43%; 1 CR and 15 PR); SD: 5 (14%); PD: 16 (43%)	Median duration of therapy: 4.4 months	41.8 months
Shaw et al., 2020, phase 3 study [19]	149 treatment-naïve patients	IHC	–	OR: 113 (76%; 4 CR and 109 PR); SD: 19 (13%); PD: 10 (7%) Intracranial response: 14/17 (82%)	Proportion of patients without disease progression at 12 months: 78% PFS: not reached	
Present study, single-center real-world analysis (mainly patients included in the early access program, Russia)	35 patients, who received prior TKI therapy (n = 31) or was TKI-naïve (n = 4)	PCR (28 patients) FISH (5 patients) OR IHC (2 patients)	Crizotinib: 17 Ceritinib: 17 Alectinib: 2	OR: 15 (43%; 1 CR and 14 PR); SD: 18 (51%); PD: 2 (6%) Intracranial response: 22/27 (81%)	PFS: 21.8 months; median duration of therapy: not reached; mean duration of therapy: 24.9 months	70.1 months

Abbreviations: CR – complete response; OR – objective response; OS – overall survival; PD – progressive disease; PFS – progression-free survival; PR – partial response; SD – stable disease.

[a] The rate of tumor responses was calculated towards the total number of included patients, irrespective of the number of cases evaluable for response by the RECIST criteria.

[b] 11.1 months, as reported in the follow-up study [16].

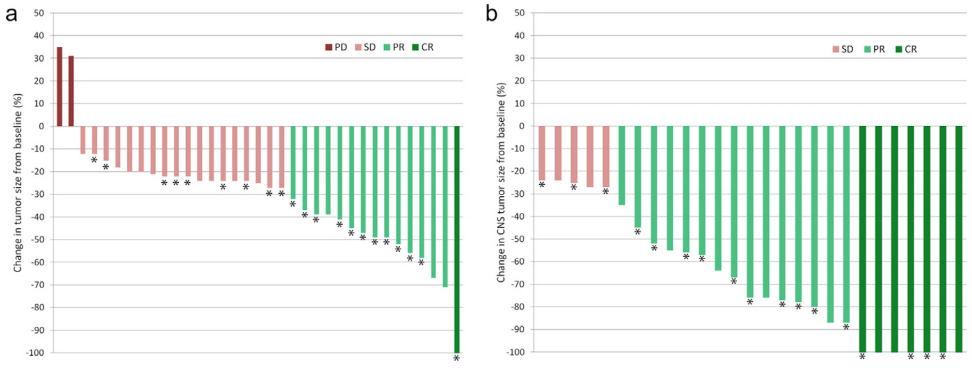

Fig. 1. Best percentage change in tumor size (a) and CNS lesions (b) from baseline. Patients continuing lorlatinib treatment are marked with asterisks.

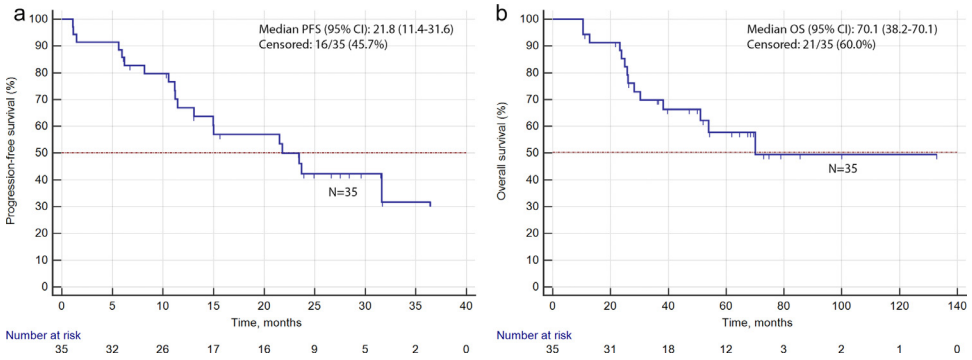

Fig. 2. PFS (a) and OS (b) in 35 patients receiving lorlatinib.

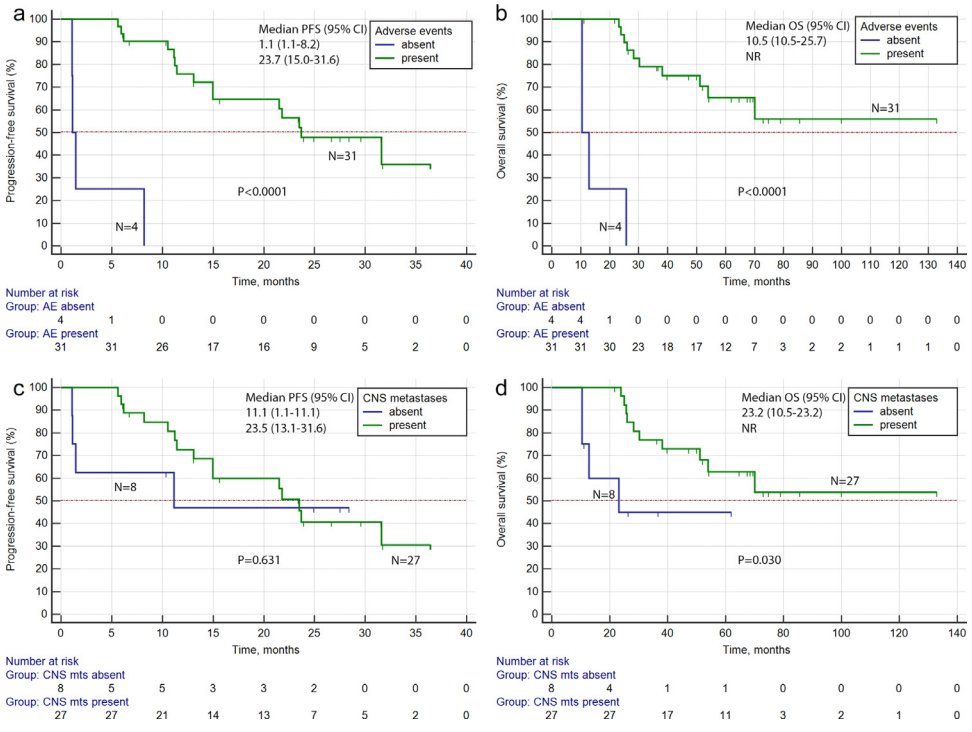

Fig. 3. PFS and OS in patients with or without adverse events (a, b), and in patients with or without CNS metastases (c, d), upon lorlatinib treatment.

genotyping procedures, however some occasional failures of these indirect methods may lead to false-positive detection of *ALK* rearrangements [28,29].

The study of Lin et al. [21] included 6 patients with V.1 and 15 subjects with V.3 *ALK* rearrangements, and demonstrated statistically longer PFS for NSCLCs with *ALK* V.3 fusions. Our study had comparable number of observations (13 patients with V.1 and 8 subjects with V.3 rearrangements, respectively), however failed to replicate this difference. Distinct pretreatment history may be a reason for the discrepancy between our observation and the report of Lin et al. [21]. Patients with the lack of adverse events had clearly worse outcomes of lorlatinib treatment as compared to subjects with the detectable toxicity of the drug (Table 1). Previous studies did not consider this type of associations (Table 2). The existence of correlations between the extent of adverse events and the degree of tumor response is not uncommon [30,31]. Our data may potentially call to consider an adjustment of lor-

latinib dosage in patients with poor tumor response and complete lack of the toxicity of the drug. It is of interest that among 4 patients with no adverse event and poor response to lorlatinib 3 subjects had *ALK* V.1 gene fusion and 1 NSCLC carried *ALK* rearrangement detected only by IHC (Table 1). Although no conclusions can be drawn from this small number of observations, one may speculate that some subjects may have ultra-rapid drug turnover due to especial pharmacogenomic constitution or certain lifestyle factors [32], and these individual metabolic characteristics could critically affect the disease outcome only in patients with particular translocation variants.

Recent phase 3 randomized trial comparing lorlatinib and crizotinib resulted in the approval of the former drug for the first-line NSCLC treatment and is likely to be practice-changing. Lorlatinib clearly outperformed crizotinib for all treatment efficacy end-points, while showing more or less similar rate of adverse events. For example, the response rate in the lorlatinib arm was 76%, while only 58% of patients receiving crizotinib achieved objective reduction of tumor size as determined by RECIST criteria. The advantage of lorlatinib was particularly evident when considering patients with CNS involvement (intracranial response: 82% vs. 23%, respectively). Lorlatinib and crizotinib had distinct pattern of adverse events, with hypercholesterolemia, hypertriglyceridemia, increased weight and cognitive and mood disorders being characteristic for the former, and diarrhea, nausea, vomiting, low appetite and mild vision impairment being more frequently observed in the latter arm [19]. Given that lorlatinib demonstrated unprecedented duration of tumor response combined with generally manageable toxicity profile, it is very likely to be increasingly used in the first-line setting. However, the experience of treatment of *ALK*-rearranged NSCLC after the failure of lorlatinib is very limited for the time being. It remains to be seen, what effective options remain for the patients with acquired resistance to this drug. There are several ALK-targeted drugs, and the pattern of their antitumor activity may significantly depend on the type of prior treatment. Consequently, optimal sequencing of ALK-specific agents is critical for achieving maximal overall survival [33].

ALK-driven NSCLCs have high life expectancy, thanks to the availability of multiple treatment options [34]. Our study resulted in overall survival of 70.1 months, which may be regarded as an important advance in the NSCLC management. Further accumulation of the experience related to the clinical use of lorlatinib may help to define its position within the spectrum of *ALK*-targeted drugs.

Ethical approval

The study was approved by the local Ethics Committee. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent

Informed consent was obtained from all patients included in the study.

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Authors' contributions

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Declaration of Competing Interest

All other authors have no relevant financial or non-financial interests to disclose.

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