



ELSEVIER

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

GLASS: Global Lorlatinib for ALK(+) and ROS1(+) retrospective Study: real world data of 123 NSCLC patients

Nir Peled^{a,b,*}, Roni Gillis^{a,b}, Saadettin Kilickap^c, Patrizia Froesch^d, Sergei Orlov^e, Elena Filippova^e, Umut Demirci^f, Petros Christopoulos^g, Irfan Cicin^h, Fatma Bugdayci Basalⁱ, Cengiz Yilmaz^j, Moiseenko Fedor^{k,l}, Taner Korkmaz^m, Semra Paydasⁿ, Oliver Gautschi^o, Alisan Zirtiloglu^p, Yesim Eralp^m, Havva Yesil Cinkir^r, Ahmet Sezer^s, Mustafa Erman^c, Deniz Tural^p, Hande Turna^t, Julien Mazieres^u, Elizabeth Dudnik^v, Noemi Reguart^w, David Ross Camidge^x, Terry L. Ng^y, Filiz Çay Şenler^z, İsmail Beypınar^A, Doğan Yazılıtaş^B, Ahmet Demirkazık^z, Aziz Karaoğlu^C, Kerem Okutur^D, Hasan Şenol Coşkun^E, Mehmet Ali Nahit Şendur^B, Abdurrahman Isikdogan^E, Devrim Cabuk^I, Perran Fulden Yumuk^F, Ibrahim Yıldız^m, M. Ali Kaplan^E, Özgür Özyılkan^S, İlhan Öztop^C, Omer Fatih Olmez^G, Kübra Aydin^J, Adnan Aydinler^q, Nezi Meydan^H, Roxana Denisa Grinberg^{a,b}, Laila C. Roisman^{a,b}

^a The Legacy Heritage Oncology Center & Dr. Larry Norton Institute, Soroka Medical Center, Beer-Sheva, Israel

^b Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, Israel

^c Department of Preventive Oncology, Hacettepe University Cancer Institute, Ankara, Turkey

^d Oncology Institute of the Southern Switzerland, Bellinzona, Switzerland

^e Pavlov First Saint Petersburg State Medical University, St Petersburg, Russia

^f Uskudar University, Faculty of Medicine, Department of Medical Oncology, Turkey

^g Department of Thoracic Oncology, Thoraxklinik at Heidelberg University Hospital, and Translational Lung Research Heidelberg, Member of the German Center for Lung Research (DZL), Germany

^h Trakya University, Faculty of Medicine, Department of Medical Oncology, Turkey

ⁱ University of Health Sciences, Dr. A.Y. Ankara Oncology Hospital, Department of Medical Oncology, Turkey

^j Ege University, Faculty of Medicine, Department of Medical Oncology, İzmir, Turkey

^k N.N. Petrov National Medical Research Center of Oncology, St. Petersburg, 197798, Russian Federation

^l St. Petersburg Clinical Research and Practical Center for Specialized Types of Medical Care (Oncologic), St. Petersburg, 197758, Russian Federation

^m Acibadem MAA University Hospital, School of Medicine, Department of Medical Oncology, Maslak Hospital, İstanbul, Turkey

ⁿ Department of Oncology, Cukurova University Faculty of Medicine, Adana, Turkey

^o University of Berne and Cantonal Hospital of Lucerne, Switzerland

^p Department of Medical Oncology, Bakirkoy Sadi Konuk Training and Research Hospital, İstanbul, Turkey

^q İstanbul University Institute of Cancer, Department of Medical Oncology, İstanbul, Turkey

^r Gaziantep University, Faculty of Medicine, Department of Medical Oncology, Gaziantep, Turkey

^s Adana Baskent University, Faculty of Medicine, Department of Medical Oncology, Adana, Turkey

^t Cerrahpasa University, Faculty of Medicine Department of Medical Oncology, İstanbul, Turkey

^u Centre Hospitalier Universitaire de Toulouse, Université Paul Sabatier, Toulouse, France

^v Thoracic Cancer Service, Davidoff Cancer Center, Rabin Medical Center, Beilinson Campus, Petah Tikva, 49100, Israel

^w Division of Medical Oncology, Hospital Clínic, Barcelona, Spain; Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain

^x Division of Medical Oncology, Department of Medicine, University of Colorado School of Medicine, 1665 North Aurora Court, Aurora, CO, 80045, USA

^y Ankara University Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey

^z Department of Medical Oncology, Faculty of Medicine, Afyon Kocatepe University, Afyon, Turkey

^A Yildirim Beyazit University Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey

^B Dokuz Eylül University Faculty of Medicine, Department of Medical Oncology, İzmir, Turkey

^C Medicalpark Bahçelievler Hospital, Department of Medical Oncology, İstanbul, Turkey

^D Akdeniz University Faculty of Medicine, Department of Medical Oncology, Antalya, Turkey

* Corresponding author at: Head of Oncology, The Legacy Heritage Oncology Center & Dr. Larry Norton Institute, Soroka Medical Center & Ben-Gurion University, Beer-Sheva, Israel.

E-mail address: peled.nir@gmail.com (N. Peled).

<https://doi.org/10.1016/j.lungcan.2020.07.022>

^E Dicle University Faculty of Medicine, Department of Medical Oncology, Diyarbakir, Turkey

^F Marmara University Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkey

^G Medipol University Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkey

^H Adnan Menderes University Faculty of Medicine, Turkey

^I Kocaeli University, Division of Medical Oncology, Kocaeli, Turkey

^J Memorial Ankara Hospital, Ankara, Turkey

ARTICLE INFO

Keywords:

Lorlatinib

Real-world data

ALK

ROS1

ABSTRACT

Lorlatinib is a third-generation tyrosine-kinases inhibitor (TKI) targeting *ALK/ROS1* fusions. The FDA has approved lorlatinib for TKI-pretreated *ALK*(+) NSCLC, while its approval for *ROS1*(+) is still pending. Here we present the largest real-world data of NSCLC patients harboring *ALK/ROS1* rearrangements treated with lorlatinib.

Methods: 123 patients were enrolled retrospectively (data cut-off 1/1/2019). Lorlatinib was administered through an early access program for patients with no other available therapy. Outcome and response were defined by each investigator upon RECIST 1.1 criteria.

Results: 106 *ALK*(+) and 17 *ROS1*(+) patients recruited from 8 different countries. The *ALK*(+) cohort included 50 % males, 73 % never-smokers and 68 % with brain metastases. Extracranial (EC) and intracranial (IC) response rates (RR) were 60 % and 62 %, with disease control rates (DCR) of 91 % and 88 % respectively. Mean duration of therapy (DoT) was 23.9 ± 1.6 months and median overall survival (mOS) was 89.1 ± 19.6 months. *ROS1* cohort enrolled 53 % males, 65 % never-smokers and 65 % had brain metastases. EC and IC RR were 62 % and 67 % with DCR of 92 % and 78 % respectively. Median DoT was 18.1 ± 2.5 months and mOS of 90.3 ± 24.4 months. OS and DoT in both cohorts were not significantly correlated with line of therapy nor other parameters.

The most common adverse events of any grade were peripheral edema (48 %), hyperlipidemia (47 %), weight gain (25 %) and fatigue (30 %). CNS adverse events such as cognitive effect of grade 1–2 were reported in 18 % of patients.

Conclusion: Lorlatinib shows outstanding EC/IC efficacy in *ALK/ROS1*(+) NSCLC. The observed mOS of 89 ± 19 months in *ALK*(+) NSCLC supports previous reports, while mOS from of 90 ± 24 months is unprecedented for *ROS1*(+) NSCLC.

1. Introduction

The treatment strategy in anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC) is shifting toward newer agents in the first line setting, while the existing roadmap in *ROS1*(+) NSCLC is not mature yet. The current NCCN recommendations categories alectinib as the preferred 1st line therapy for *ALK*(+) and crizotinib for *ROS1*(+) NSCLC. The ALEX [1–3] and the ALTA [4] studies indicates better progression free survival (PFS) when choosing second generation *ALK* tyrosine kinase inhibitors (TKI) as first line therapy compared with crizotinib. No randomized trial was conducted for *ROS1*.

ALK gene rearrangements occur in approximately 5% of non-squamous patients with NSCLC [5,6]. *ALK* fusion proteins are constitutively active and involved in the proliferation and survival of tumor cells. ⁷ Independent of ligand binding, *EML4* or the partner protein facilitates dimerization of the fusion protein, resulting in the constitutive activation of the *ALK* kinase domain [8,9]. *ALK* fusions are more commonly found in light smokers (< 10 pack years) and/or never-smokers. *ALK* fusions are also associated with younger age and adenocarcinomas with acinar histology or signet-ring cells [10].

ROS1 oncogenic fusions are reported in 1%–2% of non-squamous NSCLC patients and defines a special molecular disease sub-group. The kinase domains of *ALK* and *ROS1* share a significant homology in amino acid identity and most of the differences that exist occur in conservative regions. The *ROS1* locus is located on chromosome 6 and encodes for an orphan tyrosine kinase receptor with no known ligand and biologic function in humans [11]. *ROS1* rearrangements/translocations lead to fusions of an intact *ROS1* tyrosine kinase domain with partner genes, which are usually present on another chromosome [12,13]. *ALK* and *ROS1* rearrangements may be detected by fluorescence *in situ* hybridization (FISH), real-time polymerase chain reaction (RT-PCR) or immunohistochemistry (IHC) and next-generation sequencing (NGS) [14]. Hybrid-capture NGS is the most accurate technique to detect these aberrations with an advantage of recognizing the fusion partner

[15–19].

Recent reviews, such as from Friedlaender A et al. [20] and Tessa A. Morris et al. [21,22] summarized treatment options harboring NSCLC *ALK*(+) and *ROS1*(+) rearrangements.

Acquired resistance to *ALK/ROS1* TKIs is generally inevitable and independent of therapy, and is mediated mainly through a secondary point mutation in tumor driver *ALK* or *ROS1* genes [23,24] The acquired resistance mutation mechanism may influence the probability of response to further lines of treatment, emphasizing the importance of liquid or tissue re-biopsy upon progression in order to identify and target the molecular mechanism of TKI resistance.

Lorlatinib is a potent, brain-penetrant third generation *ALK/ROS1* TKI with a broad mutational coverage including *ALK* G1202R, F1174X, L1196M, G1269A, and I1171 × . It has shown clinical activity in patients with *ALK*(+) and *ROS1*(+) advanced NSCLC, most of whom had central nervous system (CNS) metastases and had received prior crizotinib [25]. Lorlatinib evoked responses in treatment-naïve patients or those resistant to prior *ROS1* TKIs [26].

The safety and efficacy of lorlatinib were evaluated and reported earlier in advanced *ALK/ROS1* NSCLC [27–30]. In crizotinib treated patients the ORR was 73 % (95 % CI 60–84) and median progression-free survival (PFS) of 11.1 (95 % CI 8.2–NR) while in patients who had failed one or more *ALK* TKIs the ORR was 40 % (95 % CI 32–49) with a median PFS of 6.9 (95 % CI 5.4–8.2) months. Based on these results, lorlatinib was recently approved in many countries for previously treated, advanced *ALK*(+) NSCLC. However, there is a lack of data on the activity and tolerability of lorlatinib in the real-world setting.

Here, we report the first major global retrospective study with lorlatinib in previously treated patients with *ALK/ROS1*(+) NSCLC.

2. Methods

This is an international, multicenter, retrospective study, which aimed to describe the efficacy and safety of lorlatinib in previously

treated *ALK/ROS1*(+) NSCLC. All patients were treated through an early access program, when no other targeted therapy was available.

The countries that participated in this study were Turkey, Switzerland, Russia, Israel, Germany, France and the USA, between March 2015 to January 2019 (date of data cutoff). Inclusion criteria were *ALK/ROS1*(+) NSCLC who were previously treated and responded to *ALK/ROS1* TKI and received lorlatinib for at least one month. All cases were treated by lorlatinib outside of clinical trials and have not been previously reported. 123 eligible patients had a pathologic diagnosis of NSCLC at any stage out of which 106 had *ALK* rearrangement and 17 had *ROS1* rearrangement. Accepted test methods for molecular profiling were fluorescence in situ hybridization (FISH), immunohistochemistry (IHC) real time polymerase chain reaction (RT-PCR) or next generation sequencing (NGS) in certified laboratories.

2.1. Data collection and response assessment

Anonymized demographic and clinical characteristics were documented by the investigators including age; gender; ethnicity; smoking habits, tumor stage; date of diagnosis; *ALK/ROS1* detection; brain metastasis at disease diagnosis, previous therapies; extracranial and intracranial best response to each line of treatment, brain radiation; type of progression for each line and date of death. Specifically, lorlatinib therapy was recorded including dose modifications, treatment duration, reasons for final drug discontinuation and adverse events. Extracranial and intracranial responses were assessed by each investigator upon complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) (RECIST 1.1) [31–33].

The data was collected centrally by the corresponding author at Soroka University Medical Center, Israel; under the IRB approval number 0058-19-SOR.

2.2. Outcomes

Several clinical endpoints were assessed. Objective response rate (ORR) was defined by the investigator using RECIST 1.1 as the proportion of patients achieving a best clinical response to lorlatinib of either CR or PR. Disease control rate (DCR) was defined as the patients achieved a best clinical response of CR + PR + SD. Duration of therapy (DoT) was defined as time from lorlatinib treatment initiation until treatment termination, including treatment beyond progression. Patients without a progression event were censored at the earlier of initiation of a new therapy or last available medical record. Finally, overall survival (OS) was calculated from initial diagnosis of metastatic disease with a data cut-off at January 2019. Patients who were still alive at the time of data cut off were censored at the date of the last available medical record.

2.3. Statistical analysis

Statistical analysis was performed by SPSS (version 23, IBM Corporation) and RStudio (Version 1.2.1335, RStudio, Inc.). Analysis variables as well as ORR and DCR were summarized and stratified by line of therapy (Table 1) and by the extracranial versus intracranial response (Tables 3A and 3B). DoT and OS were analyzed using the Kaplan-Meier method P-values < 0.05 were considered as significant.

3. Results

From March 2015 to January 2019, a total of 123 *ALK* or *ROS1* positive NSCLC patients were enrolled from 8 countries (Table 1).

3.1. *ALK* positive patients

One hundred and sixteen patients with *ALK*-positive NSCLC had a mean age of 53 ± 12.7 years old (ranging from 19 to 85 years old) and

50 % (53/106) were males. Most of patients 73 % (77/106) were never smokers. Lung adenocarcinoma was the predominant histology 97 % (103/106) and the vast majority was diagnosed with advanced disease 96 % (102/106). Molecular testing for *ALK* rearrangement were performed locally via FISH, IHC, NGS and RT-PCR (76 %, 31 %, 8% and 13 % respectively) whilst 23/106 patients were diagnosed with more than one method and 72/106 (68 %) patients had brain metastases at the time of diagnosis.

Lorlatinib was 2nd line in 16/106 patients (15 %), 3rd line in 40/106 patients (38 %), 4th line in 33/106 patients (31 %) and ≥ 5 th line in 17/106 patients (16 %). Most patients initiated lorlatinib therapy with ECOG score of 0–1 (65/106 patients, 61 %). Previous last therapies prior to lorlatinib were crizotinib (40/106, 38 %), ceritinib (25/106, 24 %), alectinib (15/106, 14 %), Brigatinib (13/106, 12 %) and chemotherapy (13/106, 12 %; Table 2).

Investigator assessed RECIST 1.1 objective response rate (ORR) were 60 % (52/87) extracranial and 62 % (40/65) intracranial, while disease control rate (DCR) were 91 % (79/87) and 88 % (57/65) respectively (Tables 3A and 3B). ORR showed a non-significant trend of a higher ORR correlated to the line of treatment (Table 3A). Interestingly CR was achieved in 10 % (9/87). The median duration of therapy (DoT) was not reached with a mean DoT of 23.9 ± 1.6 months (95 % CI 20.9–27) (Fig. 1). Median overall survival (OS) was 89.1 ± 19.6 months (95 % CI 50.7–127.5) (Fig. 2). OS and DoT were not significantly correlated with neither line of therapy nor with the previous type of therapy. Molecular profiling before lorlatinib initiation was not available.

3.2. *ROS1* positive patients

Seventeen patients with *ROS1*-positive NSCLC had a mean age of 51 ± 10.7 years (range, 22–70 years), 53 % (9/17) males, 65 % (11/

Table 1

Baseline characteristics and patient demographics. Data are in (%) in *ALK/ROS1* group, unless indicated otherwise. ECOG = Eastern Cooperative Oncology Group.

Characteristics	<i>ALK</i> (+) patients	<i>ROS1</i> (+) patients
Age at diagnosis, Y		
Median	53	49
Mean (SD)	53 (12.7)	51 (10.7)
Range	19–84	22–70
Sex		
Male	53 (50%)	9 (53%)
Female	53 (50%)	8 (47%)
Smoking history		
Never	77 (73%)	11 (65%)
Current	5 (5%)	1 (6%)
Former	23 (21%)	5 (29%)
Unknown	1 (1%)	0 (%)
Histology		
Adenocarcinoma	103 (97%)	16 (94%)
Other NSCLC	3 (3%)	1 (6%)
Stage of disease at diagnosis		
Early	4 (4%)	1 (6%)
3–4	102 (96%)	16 (94%)
ECOG performance status at diagnosis		
0–1	65 (61%)	11 (65%)
2	15 (14%)	3 (18%)
NA	26 (25%)	3 (18%)
Brain metastasis at diagnosis		
Present	72 (68%)	11 (65%)
Absent	34 (32%)	6 (35%)
Method of diagnosis [†]		
FISH	81 (76%)	12 (71%)
IHC	33 (31%)	2 (12%)
NGS	8 (8%)	2 (12%)
PCR	14 (13%)	2 (12%)

[†] Few patients have been diagnosed by more than one method.

Table 2
Last therapy before Lorlatinib treatment.

Last Therapy before Lorlatinib	Summary of cases	Lorlatinib as 2 nd Line	Lorlatinib as 3 rd Line	Lorlatinib as 4 th Line	Lorlatinib as 5 th Line	Lorlatinib as 6 th Line	Lorlatinib as 7 th Line	Lorlatinib as 8 th Line
ALK(+) Patients								
Crizotinib	40 (38%)	12 (75%)	22 (55%)	4 (13%)	2 (18%)			
Alectinib	15 (14%)	1 (6%)	2 (5%)	8 (24%)	1 (9%)	1 (50%)		2 (67%)
Brigatinib	13 (12%)		1 (2%)	6 (18%)	4 (36%)		1 (100%)	1 (33%)
Ceritinib	25 (24%)	3 (19%)	9 (22%)	10 (30%)	2 (18%)	1 (50%)		
Chemotherapy	13 (12%)		6 (16%)	5 (15%)	2 (18%)			
Total ALK(+) cases	106 (100%)	16 (100%)	40 (100%)	33 (100%)	11 (100%)	2 (100%)	1 (100%)	3 (100%)
ROS1(+) Patients								
Crizotinib	12 (71%)	5 (83%)	5 (83%)				1 (100%)	1 (100%)
Ceritinib	2 (12%)	1 (17%)	1 (17%)					
Chemotherapy	3 (18%)			3 (100%)				
Total ROS1(+) cases	17 (100%)	6 (100%)	6 (100%)	3 (100%)			1 (100%)	1 (100%)

N (% from summary of line of treatment).

Table 3A
Extracranial best response to Lorlatinib treatment.

Extracranial Best response to Lorlatinib treatment	Summary of cases	2nd Line	3rd Line	4th Line	5th Line	6th Line	7th Line	8th Line
ALK(+) Patients								
Objective Response Rate	<u>52 (60%)</u>	7 (64%)	21 (63%)	15 (54%)	7 (70%)	0 (0%)	0 (0%)	2 (67%)
Disease Control Rate	<u>79 (91%)</u>	11 (100%)	28 (88%)	24 (86%)	10 (100%)	2 (100%)	1 (100%)	3 (100%)
Complete Response	9 (10%)	2 (18%)	4 (13%)	1 (4%)	2 (20%)			
Partial Response	43 (50%)	5 (46%)	17 (53%)	14 (50%)	5 (50%)			2 (67%)
Stable Disease	27 (31%)	4 (36%)	7 (22%)	9 (32%)	3 (30%)	2 (100%)	1 (100%)	1 (33%)
Progressive Disease	8 (9%)	0 (0%)	4 (12%)	4 (14%)				
Summary of available data	<u>87 (100%)</u>	<u>11 (100%)</u>	<u>32 (100%)</u>	<u>28 (100%)</u>	<u>10 (100%)</u>	<u>2 (100%)</u>	<u>1 (100%)</u>	<u>3 (100%)</u>
Indeterminate/ Missing Data	19	5	8	5	1			
Total ALK(+) cases	106	16	40	33	11	2	1	3
ROS1(+) Patients								
Objective Response Rate	<u>8 (62%)</u>	1 (25%)	4 (100%)	1 (33%)			1 (100%)	1 (100%)
Disease Control Rate	<u>12 (92%)</u>	4 (100%)	4 (100%)	2 (67%)			1 (100%)	1 (100%)
Complete Response	0 (0%)							
Partial Response	8 (61%)	1 (25%)	4 (100%)	1 (33%)			1 (100%)	1 (100%)
Stable Disease	4 (31%)	3 (75%)		1 (33%)				
Progressive Disease	1 (8%)			1 (33%)				
Summary of available data	<u>13 (100%)</u>	<u>4 (100%)</u>	<u>4 (100%)</u>	<u>3 (100%)</u>			<u>1 (100%)</u>	<u>1 (100%)</u>
Indeterminate/ Missing Data	4	2	2					
Total ROS1(+) cases	17	6	6	3			1	1

All percentage calculations are from the total of patients with available evaluable data.

N (% from summary of line treatment).

17) were never smokers. Lung adenocarcinoma was the predominant histology in 94 % and 94 % had advanced disease. Molecular testing for ROS1 rearrangement was performed locally via FISH, IHC, NGS and RT-PCR (71 %, 12 %, 12 % and 12 % respectively). 11/17 patients (65 %) had brain metastases before lorlatinib initiation.

Lorlatinib was 2nd line in 6/17 patients (35 %), 3rd line in 6/17 patients (35 %) and ≥4th line in 5/17 (30 %). ECOG score was 0–1 in 11/17 (65 %) of the patients upon lorlatinib initiation. Last previous line prior to lorlatinib was crizotinib in 12/17 (71 %), ceritinib in 2/17 (12 %) and chemotherapy in 3/17 (18 %; Table 2).

Extracranial and intracranial ORR were 62 % (8/13) and 67 % (6/9), while DCR were 92 % (12/13) and 78 % (7/9) respectively (Tables 3A and 3B). Median DoT was 18.1 ± 2.5 months (95 % CI 13.2–23.1) (Fig. 1) and median OS was 90.3 ± 24.4 months (95 % CI 42.5–138.1) (Fig. 2). OS and DoT were not significantly correlated with lorlatinib line of therapy.

3.3. Adverse events

The most common lorlatinib treatment-related adverse events of any grade among all patients were hypercholesterolemia 46 % (56/123), hypertriglyceridemia 43 % (53/123), peripheral edema 47 % (58/123), weight gain 24 % (30/123) and fatigue 24 % (30/123). CNS adverse events such as cognitive effect of grade 1–2 were reported in 18 % (22/123) of patients.

4. Discussion

This report confirms the activity of lorlatinib in ALK and ROS1 positive NSCLC both extracranial and intracranial as well as the overall survival of 89 ± 19 months for ALK(+) NSCLC patients treated with next generation TKIs, and it is the first report showing a median OS of 90.3 ± 24.4 months for patients with ROS1(+) NSCLC.

The extracranial ORR of 60 % and 62 % respectively and the intracranial ORR of 62 % and 67 % respectively are as expected and in similarity with previous reports for lorlatinib both in the ALK and the

Table 3B
Intracranial best response to Lorlatinib treatment.

Intracranial Best response to Lorlatinib treatment	Summary of cases	2nd Line	3rd Line	4th Line	5th Line	6th Line	7th Line	8th Line
ALK(+) Patients								
Objective Response Rate	40 (62%)	5 (50%)	12 (71%)	13 (52%)	7 (78%)	1 (50%)	1 (100%)	2 (67%)
Disease Control Rate	57 (88%)	10 (100%)	14 (83%)	20 (80%)	9 (100%)	2 (100%)	1 (100%)	3 (100%)
Best Overall Response								
Complete Response	10 (16%)	2 (25%)	2 (12%)	5 (20%)	1 (11%)			
Partial Response	30 (46%)	2 (25%)	10 (59%)	8 (32%)	6 (67%)	1 (50%)	1 (100%)	2 (67%)
Stable Disease	17 (26%)	4 (50%)	2 (12%)	7 (28%)	2 (22%)	1 (50%)		1 (33%)
Progressive Disease	8 (12%)		3 (17%)	5 (20%)				
Summary of available data	65 (100%)	8 (100%)	17 (100%)	25 (100%)	9 (100%)	2 (100%)	1 (100%)	3 (100%)
Indeterminate/ Missing Data	41	8	23	8	2			
Total ALK(+) cases	106	16	40	33	11	2	1	3
ROS1(+) Patients								
Objective Response Rate	6 (67%)	2 (67%)	2 (100%)	1 (33%)			1 (100%)	
Disease Control Rate	7 (78%)	3 (100%)	2 (100%)	1 (33%)			1 (100%)	
Best Overall Response								
Complete Response	1 (11%)		1 (50%)					
Partial Response	5 (56%)	2 (67%)	1 (50%)	1 (33%)			1 (100%)	
Stable Disease	1 (11%)	1 (33%)						
Progressive Disease	2 (22%)			2 (67%)				
Summary of available data	9 (100%)	3 (100%)	2 (100%)	3 (100%)			1 (100%)	
Indeterminate/ Missing Data	8	3	4				1	
Total ROS1(+) cases	17	6	6	3			2	

All percentage calculations are from the total of patients with available evaluable data. N (% from summary of line treatment).

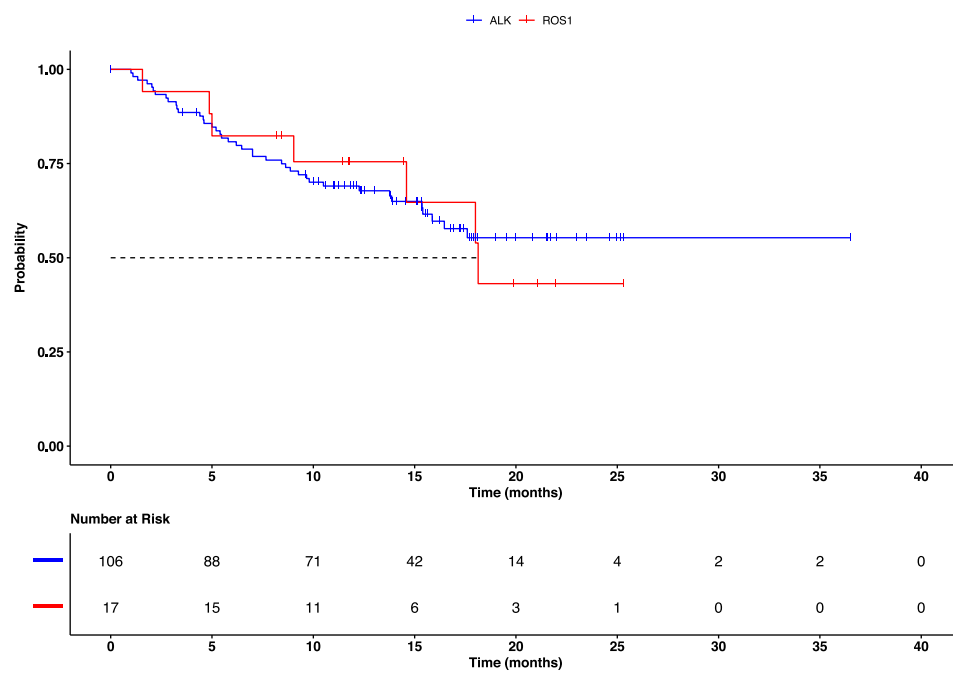


Fig. 1. Duration of Therapy (DoT) of Lorlatinib in ALK and ROS1 NSCLC patients.

ROS1 positive NSCLC [34] ROS1 median DoT of 18.1 ± 2.5 months (95 % CI 13.2–23.1) showed in this cohort (Fig. 1) while previously reported 21.1 months (IQR 15.2–30.3) [35].

The intracranial ORR of lorlatinib in this cohort was similar to the extracranial ORR with a range of 50 %–70 %. This is in line with the previous report of Camidge R et al. who reported an intracranial response of 45.8–66.7 % [36]. Lorlatinib was reported recently to overcome leptomeningeal disease [37].

The median OS of 89.1 ± 19 and 90.3 ± 24 months in ALK and ROS1 positive NSCLC presented in this study (Fig. 2), where crizotinib was used first in most patients, challenges the new recommendation for a preferred 2nd generation ALK TKI in the ALK(+) population. The

updated ALEX data shows a median PFS of 34.8 months for alectinib vs. 10.9 months for crizotinib and overall survival benefit for alectinib arm HR 0.67 (CI 0.46–0.98) [38,39]. Therefore, the current report may emphasize the importance of preserving numerous therapeutic alternatives, particularly in countries with limited access to newer agents. Treatment strategy should be taken in caution and after considering all factors including existence of brain disease, mechanism of resistant and drug availability.

Safety data reported in this study is presented in Table 4 and the results are similar to previously reported data [40], no unexpected adverse effects and no treatment related deaths were noted by our investigators. The existence of cognitive changes was reported in this

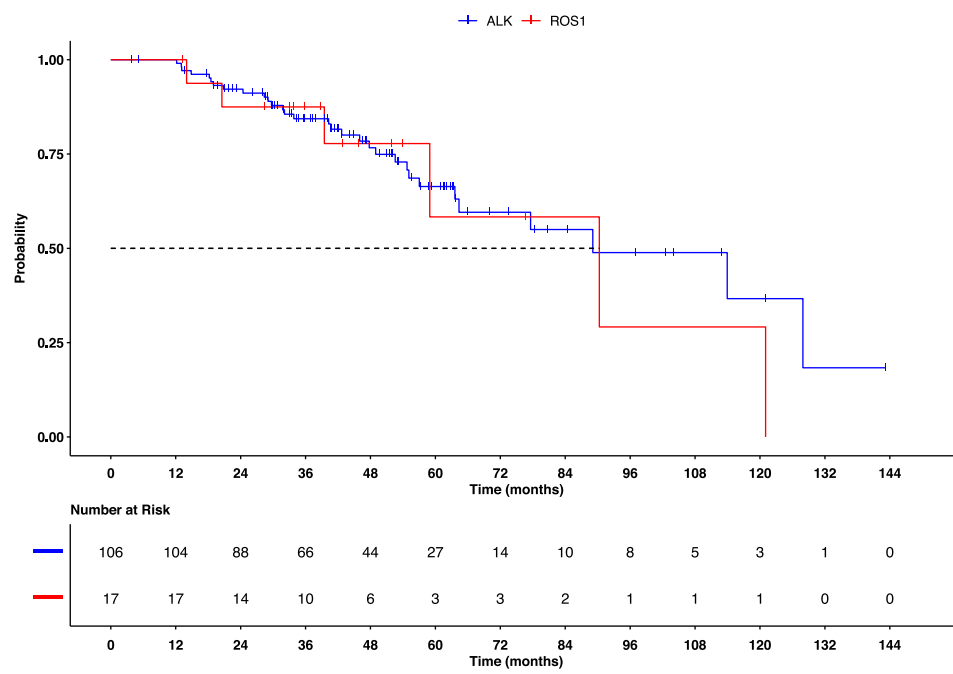


Fig. 2. Overall Survival (OS) since first diagnosis, all cohorts (ALK and ROS1 subgroups).

Table 4
Lorlatinib's adverse events.

Adverse effect N = 123	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Hyperlipidemia	13 (11%)	35 (28%)	8 (6%)	3 (3%)
Hypercholesterolemia	12 (10%)	34 (28%)	7 (6%)	3 (3%)
Hypertriglyceridemia	25 (20%)	24 (20%)	2 (2%)	2 (2%)
Peripheral edema	27 (22%)	29 (24%)	2 (2%)	
Weight increased	23 (19%)	5 (4%)	2 (2%)	
Fatigue	23 (19%)	6 (5%)	1 (1%)	
Peripheral neuropathy	9 (7%)	4 (3%)	2 (2%)	
Cognitive effects	16 (13%)	6 (5%)		
Mood effects	16 (13%)	3 (2%)		
Diarrhea	6 (5%)	1 (1%)		
Arthralgia	6 (5%)	3 (2%)		
Increased AST	8 (6%)	2 (2%)		
Bronchial pain while breathing deeply	2 (2%)			
QTc prolongation		2 (2%)		
Creatinine elevation		1 (1%)		
Pleural and pericardial effusion		1 (1%)		
Systemema	1 (1%)			
Rash	2 (2%)			
Anemia	1 (1%)			
Dyspnea	1 (1%)			
Exanthema	1 (1%)			
Formication left arm	1 (1%)			
Ischemia	1 (1%)			
Dry skin	1 (1%)			
Double vision	1 (1%)			
Fever	1 (1%)			

registry, while was not reported in this incidence previously.

Our study has several limitations. First, it is retrospective and therefore imaging routine and standardization of previous lines were not feasible. Likewise, the exact time of RECIST progression is limited, and therefore we discussed duration of therapy and not PFS, moreover there is a high degree of censoring which might reflect an over-estimation of the median DoT. Survival data may overcome this limitation. Molecular profiling on progression was not available in most cases, and centrally assessed molecular testing or RECIST evaluation was not feasible. Moreover, adverse events were collected and graded

retrospectively.

Credit author statement

All authors reviewed manuscript and participated in the writing and editing and worked in the data collection and analysis.

Conflict of interest were provided in ICMJE forms attached to the submission.

Acknowledgment

We grateful to Pfizer for the funding of the grant IIS 53234545.

References

- [1] Solange Peters, et al., Alectinib versus crizotinib in untreated ALK-positive non--small-cell lung cancer, *N. Engl. J. Med.* 377.9 (2017) 829–838, <https://doi.org/10.1056/NEJMoa1704795>.
- [2] D. Ross Camidge, et al., Updated efficacy and safety data and impact of the EML4-ALK fusion variant on the efficacy of alectinib in untreated ALK-positive advanced non--small cell lung cancer in the global phase III ALEX study, *J. Thorac. Oncol.* 14.7 (2019) 1233–1243, <https://doi.org/10.1016/j.jtho.2019.03.007>.
- [3] Takashi Seto, et al., Final PFS Analysis and Safety Data From the Phase III J-ALEX Study of Alectinib (ALC) vs. Crizotinib (CRZ) in ALK-Inhibitor Naïve ALK-positive Non-Small Cell Lung Cancer (ALK+ NSCLC), (2019), p. 9092, https://doi.org/10.1200/JCO.2019.37.15_suppl.9092.
- [4] Dong-Wan Kim, et al., Brigatinib (BRG) in Patients (pts) With Crizotinib (CRZ)-Refractory ALK+ Non-Small Cell Lung Cancer (NSCLC): First Report of Efficacy and Safety From a Pivotal Randomized Phase (ph) 2 Trial (ALTA), (2016), p. 9007, https://doi.org/10.1200/JCO.2016.34.15_suppl.9007.
- [5] B. Solomon, K.D. Wilner, A.T. Shaw, Current status of targeted therapy for anaplastic lymphoma kinase-rearranged non-small cell lung cancer, *Clin. Pharmacol. Ther.* 95 (2014) 15–23, <https://doi.org/10.1038/clpt.2013.200>.
- [6] E.L. Kwak, Y.J. Bang, D.R. Camidge, et al., Anaplastic lymphoma kinase inhibition in non--small-cell lung cancer, *N. Engl. J. Med.* 363 (2010) 1693–1703, <https://doi.org/10.1056/NEJMoa1006448>.
- [7] A.T. Shaw, J.A. Engelman, *ALK* in lung cancer: past, present, and future, *J. Clin. Oncol.* 31 (2013) 1105–1111, <https://doi.org/10.1200/JCO.2012.44.5353>.
- [8] J.J. Lin, G.J. Riely, A.T. Shaw, A.L.K. Targeting, Precision medicine takes on drug resistance, *Cancer Discov.* 7 (2017) 137–155, <https://doi.org/10.1158/2159-8290.CD-16-1123>.
- [9] K. Rikova, A. Guo, Q. Zeng, et al., Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer, *Cell* 131 (2007) 1190–1203, <https://doi.org/10.1016/j.cell.2007.11.025>.
- [10] M. Soda, Y.L. Choi, M. Enomoto, et al., Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer, *Nature* 448 (2007) 561–566, <https://doi.org/10.1038/nature06123>.

- [org/10.1038/nature05945](https://doi.org/10.1038/nature05945).
- [11] J. Acquaviva, R. Wong, A. Charest, The multifaceted roles of the receptor tyrosine kinase ROS in development and cancer, *Biochim. Biophys. Acta* 1795 (2009) 37–52, <https://doi.org/10.1016/j.bbcan.2008.07.006>.
- [12] J.F. Gainor, A.T. Shaw, Novel targets in non-small cell lung cancer: ROS1 and RET fusions, *Oncologist* 18 (2013) 865–875, <https://doi.org/10.1634/theoncologist.2013-0095>.
- [13] K. Takeuchi, M. Soda, Y. Togashi, et al., RET, ROS1 and ALK fusions in lung cancer, *Nat. Med.* 18 (2012) 378–381, <https://doi.org/10.1038/nm.2658>.
- [14] J.J. Lin, A.T. Shaw, Recent advances in targeting ROS1 in lung Cancer, *J. Thorac. Oncol.* 12 (2017) 1611–1625, <https://doi.org/10.1093/annonc/mdw383.06>.
- [15] R. Grinberg, L. Roisman, S. Geva, M. Lefterova, K. Quinn, L.S. Gutman, A. Dvir, R. Yair, R. Lanman, D. Mehta, L. Kiedrowski, P1. 04-47 tumor mutation burden through hybrid capture–circulating tumor DNA may predict response to immunotherapy in NSCLC, *J. Thorac. Oncol.* 14 (10) (2019) S459, <https://doi.org/10.1016/j.jtho.2019.08.950>.
- [16] A.B. Rozenblum, M. Ilouze, E. Dudnik, A. Dvir, L. Soussan-Gutman, S. Geva, N. Peled, Clinical impact of hybrid capture–based next-generation sequencing on changes in treatment decisions in lung cancer, *J. Thorac. Oncol.* 12 (2) (2017) 258–268, <https://doi.org/10.1016/j.jtho.2016.10.021>.
- [17] S.M. Ali, T. Hensing, A.B. Schrock, J. Allen, E. Sanford, K. Gowen, A. Kulkarni, J. He, J.H. Suh, D. Lipson, J.A. Elvin, Comprehensive genomic profiling identifies a subset of crizotinib-responsive ALK-rearranged non-small cell lung cancer not detected by fluorescence in situ hybridization, *Oncologist* 21 (June (6)) (2016) 762, <https://doi.org/10.1634/theoncologist.2015-0497>.
- [18] M. Pekar-Zlotin, F.R. Hirsch, L. Soussan-Gutman, M. Ilouze, A. Dvir, T. Boyle, M. Wynes, V.A. Miller, D. Lipson, G.A. Palmer, S.M. Ali, Fluorescence in situ hybridization, immunohistochemistry, and next-generation sequencing for detection of EML4-ALK rearrangement in lung cancer, *Oncologist* 20 (March (3)) (2015) 316, <https://doi.org/10.1634/theoncologist.2014-0389>.
- [19] N. Peled, G. Palmer, F.R. Hirsch, M.W. Wynes, M. Ilouze, M. Varella-Garcia, L. Soussan-Gutman, G.A. Otto, P.J. Stephens, J.S. Ross, M.T. Cronin, Next-generation sequencing identifies and immunohistochemistry confirms a novel crizotinib-sensitive ALK rearrangement in a patient with metastatic non-small-cell lung cancer, *J. Thorac. Oncol.* 7 (September (9)) (2012) e14–16, <https://doi.org/10.1097/jto.0b013e3182614ab5>.
- [20] A. Friedlaender, G. Banna, S. Patel, A. Addeo, Diagnosis and treatment of ALK aberrations in metastatic NSCLC, *Curr. Treat. Options Oncol.* 20 (October (10)) (2019) 79, <https://doi.org/10.1007/s11864-019-0675-9>.
- [21] Tessa A. Morris, Christine Khoo, Benjamin J. Solomon, Targeting ROS1 rearrangements in non-small cell lung cancer: crizotinib and newer generation tyrosine kinase inhibitors, *Drugs* 79.12 (2019) 1277–1286, <https://doi.org/10.1007/s40265-019-01164-3>.
- [22] D. Killock, Lorlatinib in ROS1-positive NSCLC, *Nat. Rev. Clin. Oncol.* 17 (January (1)) (2020) 7, <https://doi.org/10.1038/s41571-019-0301-6>.
- [23] H. Yasuda, L.L. de Figueiredo-Pontes, S. Kobayashi, D.B. Costa, Pre-clinical rationale for use of the clinically available multitargeted tyrosine kinase inhibitor crizotinib in ROS1-translocated lung cancer, *J. Thorac. Oncol.* 7 (7) (2012) 1086–1090, <https://doi.org/10.1097/JTO.0b013e3182570919>.
- [24] Alice T. Shaw, et al., Crizotinib in ROS1-rearranged non-small-cell lung cancer, *N. Engl. J. Med.* 371.21 (2014) 1963–1971, <https://doi.org/10.1056/NEJMoa1406766>.
- [25] OA02.03 clinical activity of Lorlatinib in patients with ROS1 + advanced non-small cell lung cancer: phase 2 study cohort EXP-6 ou, S. et al, *J. Thorac. Oncol.* 13 (10) (2020) S322–S323, <https://doi.org/10.1016/j.jtho.2018.08.241>.
- [26] B.J. Solomon, J.-F. Martini, S.-H.I. Ou, R. Chiari, R.A. Soo, A. Bearz, S. Li, H. Thurm, C.-C. Lin, G.J. Riely, T.M. Bauer, A.T. Shaw, 1380PD, Efficacy of lorlatinib in patients (pts) with ROS1-positive advanced non-small cell lung cancer (NSCLC) and ROS1 kinase domain mutations, *Ann. Oncol.* 29 (October (suppl.8)) (2018) mdy292.003, <https://doi.org/10.1093/annonc/mdy292.003>.
- [27] A.T. Shaw, E. Felip, T.M. Bauer, et al., Lorlatinib in non-small cell lung cancer with ALK or ROS1 rearrangement: an international, multicenter, open-label, single-arm, first-in-man phase 1 trial, *Lancet Oncol.* 18 (2017) 1590–1599, [https://doi.org/10.1016/S1470-2045\(17\)30680-0](https://doi.org/10.1016/S1470-2045(17)30680-0).
- [28] B.J. Solomon, B. Besse, T.M. Bauer, et al., Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study, *Lancet Oncol.* 19 (2018) 1654–1667, [https://doi.org/10.1016/S1470-2045\(18\)30649-1](https://doi.org/10.1016/S1470-2045(18)30649-1).
- [29] Alice T. Shaw, et al., Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1–2 trial, *Lancet Oncol.* (2019), [https://doi.org/10.1016/S1470-2045\(19\)30655-2](https://doi.org/10.1016/S1470-2045(19)30655-2).
- [30] A.T. Shaw, B.J. Solomon, B. Besse, T.M. Bauer, C.C. Lin, R.A. Soo, G.J. Riely, S.H. Ou, J.S. Clancy, S. Li, A. Abbattista, ALK resistance mutations and efficacy of Lorlatinib in advanced anaplastic lymphoma kinase-positive non-small-cell lung cancer, *J. Clin. Oncol.* 37 (June (16)) (2019) 1370–1379, <https://doi.org/10.1200/jco.18.02236>.
- [31] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), *Eur. J. Cancer* 45 (2009) 228–247, <https://doi.org/10.1016/j.ejca.2008.10.026>.
- [32] Nancy U. Lin, et al., Response assessment criteria for brain metastases: proposal from the RANO group, *Lancet Oncol.* 16.6 (2015) e270–e278 <http://linkinghub.elsevier.com/retrieve/pii/S1470204515700574>.
- [33] Elizabeth A. Eisenhauer, et al., New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1), *Eur. J. Cancer* 45.2 (2009) 228–247 <http://www.ncbi.nlm.nih.gov/pubmed/19097774>.
- [34] A.T. Shaw, E. Felip, T.M. Bauer, et al., Lorlatinib in non-small cell lung cancer with ALK or ROS1 rearrangement: an international, multicenter, open-label, single-arm, first-in-man phase 1 trial, *Lancet Oncol.* 18 (2017) 1590–1599, [https://doi.org/10.1016/S1470-2045\(17\)30680-0](https://doi.org/10.1016/S1470-2045(17)30680-0).
- [35] Alice T. Shaw, et al., Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1–2 trial, *Lancet Oncol.* (2019), [https://doi.org/10.1016/S1470-2045\(19\)30655-2](https://doi.org/10.1016/S1470-2045(19)30655-2).
- [36] D.R. Camidge, B.J. Solomon, E. Felip, B. Besse, A. Bearz, S. Peters, F. Toffalorio, A. Abbattista, H. Thurm, G. Peltz, R. Wiltshire, Intracranial and extracranial efficacy of lorlatinib in the post second-generation ALK tyrosine kinase inhibitor (TKI) setting, *Ann. Oncol.* 30 (October) (2019) v608–609, <https://doi.org/10.1093/annonc/mdz260.009>.
- [37] Z. Li, P. Li, B. Yan, Q. Gao, X. Jiang, Z. Zhan, Q. Yan, A. LiZaso, C. Huang, Sequential ALK inhibitor treatment benefits patient with leptomeningeal metastasis harboring non-EML4-ALK rearrangements detected from cerebrospinal fluid: a case report, *Thorac. Cancer* 11 (January (1)) (2020) 176–180, <https://doi.org/10.1111/1759-7714.13259>.
- [38] Takashi Seto, et al., Final PFS Analysis and Safety Data From the Phase III J-ALEX Study of Alectinib (ALC) vs. Crizotinib (CRZ) in ALK-Inhibitor Naïve ALK-Positive Non-Small Cell Lung Cancer (ALK+ NSCLC), (2019), p. 9092, https://doi.org/10.1200/JCO.2019.37.15_suppl.9092.
- [39] Tony Mok, et al., Updated overall survival and final progression-free survival data for patients with treatment-naïve advanced ALK-positive non-small-cell lung cancer in the ALEX study, *Ann. Oncol.* S0923-7534 (20) (2020) 39796–39799, <https://doi.org/10.1016/j.annonc.2020.04.478>.
- [40] Benjamin J. Solomon, et al., Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study, *Lancet Oncol.* 19 (12) (2018) 1654–1667, [https://doi.org/10.1016/S1470-2045\(18\)30649-1](https://doi.org/10.1016/S1470-2045(18)30649-1).