Cancer Treatment and Research Communications 43 (2025) 100905

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

Efficacy and safety of lorlatinib in patients with ALK- and ROS1-rearranged metastatic non-small cell lung cancer treated within the compassionate use program in Spain

Antonio Calles [a,*], Mirian Alonso [b], Paloma Martín-Martorell [c], Ana Gómez [d], Javier de Castro [e], Maite Martínez-Aguillo [f], Anna Estival [g], Joaquin Mosquera [h], Natividad Martínez-Banaclocha [i], Margarita Majem [j], Roxana Reyes [k], Eider Azkona [l], Ana Laura Ortega [m], Santiago Aguin [n], Ana Santos [o], Andrés Aguilar [p], Marc Cucurull [q], Ana Blasco [r], Virginia Calvo [s], Dolores Isla [t], Ernest Nadal [u], Carlos Aguado [v], Elia Sais [w], Oscar Juan-Vidal [x], MPilar Diz-Taín [y], Álvaro Taus [z], Noemí Villanueva [aa], Cristina Bayona [bb], Margarita Amenedo [cc], Xabier Mielgo [dd], Esperanza Arriola [ee], Javier Baena [ff], on behalf of the Spanish Lung Cancer Group

[a] *Medical Oncology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[b] *Medical Oncology Department, Hospital Virgen del Rocío, Sevilla, Spain*
[c] *Medical Oncology Department, H. Clínico Universitario de Valencia, Spain*
[d] *Medical Oncology Department, H. Ramón y Cajal, Madrid, Spain*
[e] *Medical Oncology Department, H. La Paz, Madrid, Spain*
[f] *Medical Oncology Department, C.H. Navarra, Pamplona, Spain*
[g] *Medical Oncology Department, H. U. Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain*
[h] *Medical Oncology Department, Hospital Teresa Herrera, A Coruña, Spain*
[i] *Medical Oncology Department, Hospital General Universitario Dr. Balmis, Alicante, Spain*
[j] *Medical Oncology Department, H. Santa Creu i Sant Pau, Barcelona, Spain*
[k] *Medical Oncology Department, H. Clínic Barcelona, Barcelona, Spain*
[l] *Medical Oncology Department, Hospital Universitario Cruces, Baracaldo, Spain*
[m] *Medical Oncology Department, Complejo H. de Jaén, Jaén, Spain*
[n] *Medical Oncology Department, H. Santiago, Santiago de Compostela, Spain*
[o] *Medical Oncology Department, Complejo H. de Toledo, Toledo, Spain*
[p] *Medical Oncology Department, H. Quirón-Dexeus, Barcelona, Spain*
[q] *Medical Oncology Department, ICO Badalona, Badalona, Spain*
[r] *Medical Oncology Department, H. General de Valencia, Valencia, Spain*
[s] *Medical Oncology Department, H. Puerta de Hierro, Majadahonda, Spain*
[t] *Medical Oncology Department, H. Lozano Blesa, Zaragoza, Spain*
[u] *Medical Oncology Department, Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL) L'Hospitalet, Barcelona, Spain*
[v] *Medical Oncology Department, Hospital Clínico San Carlos, Madrid, Spain*
[w] *Medical Oncology Department, ICO Girona, Girona, Spain*
[x] *Medical Oncology Department, H. La Fe, Valencia, Spain*
[y] *Medical Oncology Department, Complejo Asistencial Universitario de León, Spain*
[z] *Medical Oncology Department, Hospital del Mar, Barcelona, Spain*
[aa] *Medical Oncology Department, H. Central Asturias, Oviedo, Spain*
[bb] *Medical Oncology Department, H. Burgos, Burgos, Spain*
[cc] *Medical Oncology Department, Centro Onc. Reg. Galicia, A Coruña, Spain*
[dd] *Medical Oncology Department, H. U. Alcorcón, Alcorcón, Madrid, Spain*
[ee] *Medical Oncology Department, Hospital Puerta del Mar, Cádiz, Spain*
[ff] *Medical Oncology Department, H. 12 de Octubre, Madrid, Spain*

Abbreviations: NGS, next-generation sequencing; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry.

* Corresponding author at: Medical Oncology, Hospital General Universitario Gregorio Marañon, 28007, Madrid, Spain.
E-mail address: antonio.calles@live.com (A. Calles).

https://doi.org/10.1016/j.ctarc.2025.100905

Available online 22 March 2025

ARTICLE INFO

Keywords:
Lorlatinib
ALK
ROS1
Non-small-cell lung cancer
Targeted therapy
Tyrosine-kinase inhibitor
Anaplastic lymphoma kinase
Brain metastasis

ABSTRACT

Background: Lorlatinib, a third-generation tyrosine kinase inhibitor (TKI), targets both ALK and ROS1 rearrangements in non-small cell lung cancer (NSCLC). It is approved for ALK-positive patients after progression on prior TKIs but lacks FDA or EMA approval for ROS1-positive NSCLC. This study evaluates lorlatinib's efficacy and safety in both ALK- and ROS1-positive patients through a compassionate use program in Spain.

Methods: We analyzed ALK-positive patients treated from November 2016 to February 2019 and ROS1-positive patients treated from November 2016 to March 2021. Eligible patients had Stage IV NSCLC with confirmed ALK or ROS1 rearrangements and prior TKI therapy. For ALK-positive patients, at least two prior TKIs were required if crizotinib was used first. For ROS1-positive patients, prior crizotinib was required.

Results: In 61 ALK-positive patients, 59 % had brain metastasis, and 85.2 % received at least two prior ALK TKIs. The overall response rate (ORR) was 32.8 %, with a median progression-free survival (PFS) of 11.2 months. Intracranial ORR was 47.6 %, with higher efficacy in patients with evaluable brain metastasis. In patients with 1, 2, or $\geq$3 lines of previous TKIs, we observed a median PFS of 15.1, 11.1 and 7.6 months, respectively. Among 42 ROS1-positive patients, 59 % had brain metastasis, and 61.9 % received $\geq$2 prior therapies. The confirmed ORR was 47.6 %, with 16.7 % complete responses. Median PFS was 10 months. Patients receiving crizotinib alone had a median PFS of 10 months, while those with two prior TKIs had a median PFS of 8.5 months. Intracranial response was 44.4 %, rising to 57.1 % in patients evaluable with brain metastasis. No new safety signals were observed.

Conclusion: Lorlatinib demonstrated consistent efficacy and manageable safety in both ALK- and ROS1-positive NSCLC patients treated under the compassionate use program in Spain. These real-world findings support its use as an effective treatment option in heavily pretreated patients.

MicroAbstract: We evaluated the efficacy and safety of lorlatinib in *ALK*- and *ROS1*-positive NSCLC patients within a compassionate use program in Spain. Among 61 *ALK*-positive patients, including 59 % with brain metastasis and 85.2 % treated with at least 2 prior ALK TKIs, lorlatinib achieved a confirmed overall response rate (ORR) of 32.8 % and a median progression-free survival (PFS) of 11.2 months. In 42 *ROS1*-positive patients previously treated with crizotinib, lorlatinib showed an ORR of 47.6 % and a median PFS of 10 months, confirming its clinical activity despite the lack of FDA or EMA approval for this indication.

Introduction

Rearrangements in the anaplastic lymphoma kinase (*ALK*) and c-ros oncogene 1 (*ROS1*) genes occur in 3–5 % and 1 % of non-small cell lung cancers (NSCLC), respectively, representing distinct molecular subtypes sensitive to targeted tyrosine kinase inhibitors (TKIs) [1,2]. First-line treatment for *ALK*-positive NSCLC includes crizotinib and second-generation ALK inhibitors like alectinib, brigatinib, and ceritinib, while crizotinib and entrectinib are approved for *ROS1*-positive NSCLC [3–7]. Despite initial responses, resistance often emerges due to secondary mutations (such as *ALK* G1202R and *ROS1* G2032R) or disease progression, particularly in the central nervous system (CNS).

Lorlatinib, a third-generation ALK/ROS1 inhibitor, was designed to penetrate the blood-brain barrier and retain activity against these mutations [8]. Lorlatinib demonstrated clinical activity in a non-randomized, multi-cohort, multicenter study (study B7461001; NCT01970865). In the subgroup of 215 patients with *ALK*-positive metastatic NSCLC previously treated with one or more ALK TKI, lorlatinib achieved a 48 % overall response rate (ORR) with a 60 % intracranial ORR. The ORR was 39 % in those patients who received 2 or more TKIs and 31 % in those who received alectinib as the only ALK inhibitor [9,10]. More recently, lorlatinib demonstrated superiority over crizotinib in the randomized phase 3 CROWN clinical trial in treatment-naïve *ALK*-positive advanced NSCLC, showing a significant improvement in progression-free survival (PFS) and central nervous system (CNS) activity [11,12]. In a phase 1/2 trial of lorlatinib involving 69 patients with advanced *ROS1*-positive NSCLC, the ORR was 62 % in the subgroup of 21 patients who were TKI-naïve, and 35 % in the subgroup of 40 patients previously treated with crizotinib [10,13]. Based on these results, lorlatinib was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for *ALK*-positive NSCLC both in the first line and subsequent lines but remains under compassionate use for *ROS1*-positive patients in Spain. Given the rarity of these genetic alterations and the absence of registry data, it is crucial to evaluate lorlatinib's real-world efficacy and safety in clinical practice. We aimed to evaluate the efficacy and safety of lorlatinib under the compassionate use program in Spain in patients with advanced *ALK*+ or *ROS1*+ NSCLC who have received previous treatments.

Material and methods

LORLAPULM study (GECP 21/04) was an observational, non-interventional, retrospective, multicentre and nationwide study. The study included patients with metastatic NSCLC treated with lorlatinib who were included in the compassionate use program in Spain between November 2016 and February 2019 for *ALK*+ NSCLC and from November 2016 to March 2021 for *ROS1*+ NSCLC. The main inclusion/exclusion criteria to access this program were similar to B7461001 and phase 1/2 study that lead to FDA approval of lorlatinib: evidence of histologically or cytologically confirmed diagnosis of metastatic NSCLC (Stage IV, AJCC v7.0) that carried either a) an ALK rearrangement and prior treatment with at least one ALK TKI; if the prior ALK TKI was crizotinib, additional prior treatment was required with at least one second- generation ALK TKI, such as ceritinib, alectinib, or brigatinib, or b) *ROS1* rearrangement with prior treatment with at least crizotinib. Patients could receive approved chemotherapy regimens or immunotherapy agents in addition to the treatment requirements with ALK/ROS1 TKIs. Adequate organ function and no recent (i.e. within previous 6 months) or active suicidal ideation or behaviour. Patients must have been treated with at least one cycle of lorlatinib. The recommended dose of lorlatinib was 100 mg taken orally once daily. Treatment with lorlatinib was recommended as long as the patient was deriving clinical benefit from therapy without unacceptable toxicity as per physician discretion. Dosing interruption or dose reduction was allowed based on individual safety and tolerability; the first dose reduction consisted of lorlatinib 75 mg taken orally once daily, and the second dose reduction was to 50 mg taken orally once daily. Lorlatinib was permanently discontinued if the patient was unable to tolerate the 50 mg dose taken orally once daily.

Main clinical-pathological variables were collected to describe the

profile of the patients under study. Tumor evaluations were performed by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. For patients with brain metastasis, intracranial tumor response was assessed using modified RECIST 1.1 criteria. Efficacy outcomes included objective tumor response, duration of the response (defined from the first documentation of tumor response to the first documentation of tumor progression or death from any cause), PFS (defined as time from the first dose of treatment to the first documentation of progression or death from any cause), time to treatment failure (TTF, defined as time from the first dose of treatment to the moment of discontinuation of treatment for any cause, including tumor progression, toxicity or death), overall survival (OS, defined as time from diagnosis of metastatic disease to death or last follow-up), and overall survival from lorlatinib (defined as time from the start of treatment until death or last follow- up). Adverse events (AEs) included in the study database were coded according to CTCAE v5.0.

Alive patients must have signed, dated an IRB/EC-approved written informed consent form in accordance with regulatory and institutional guidelines. Only deidentified and anonymized data was collected from the patients by means of electronic case report forms (e-CRFs). Personal data has been treated in accordance with all applicable regulations: according to the Regulation (EU) 2016/679 of the European Parliament and the Council of April 27th, 2016, on Data Protection (GDPR). In Spain, it is regulated by the Organic Law 3/2018, 5th of December, on Personal data protection and digital rights guarantee.

Sample size calculation

Based on the retrospective and observational nature of the study, all statistical analysis were descriptive, and no hypothesis definition or sample size estimation were necessary. All patients with metastatic lung cancer treated with lorlatinib who were included in the compassionate use program in Spain between November 2016 and February 2019 for *ALK*+ and from November 2016 to March 2021 for *ROS1*+ that met all eligibility criteria were included for analysis.

Statistical plan

Descriptive analyses were carried out to evaluate the objectives of the study. In order to describe the profile of the patients under study, a descriptive statistical analysis of each and every one of the variables included in the notebook was carried out for this purpose. Categorical variables are described by their absolute and relative frequency. Continuous variables are described with total n, valid n, n unavailable, means, standard deviation, median, quartiles, minimum and maximum.

Kaplan-Meier curves were utilized for survival analyses, with the median follow-up time calculated using the reverse Kaplan-Meier method. Time-to-event outcomes were determined by defining the initiation of lorlatinib treatment as the starting point for follow-up. The endpoints varied based on the specific outcome: for PFS, the endpoint was the date of first progression; for OS, it was the date of death or last follow-up; for TTF, the endpoint was the date of definitive treatment discontinuation; and for time to intracranial progression (TPP), the endpoint was the date of documented intracranial tumour progression.

All statistical analyses were performed using Stata/MP 18.0 software. Survival probabilities at specific time points, along with their corresponding confidence intervals, were calculated using the *sts list* command, which applies Greenwood's formula. This approach accounts for the variance in the survival function at designated time points, providing reliable estimates of confidence intervals.

Although a significance level of 0.05 was considered for all statistical tests, no hypothesis testing was performed due to the small sample size and low number of events. Consequently, all survival analyses are presented descriptively, and hazard ratios (HRs) were not calculated.

The safety assessment was based primarily on the frequency and severity of AE. AEs were summarized by presenting the number and percentage of these figures in the total number of patients. The absolute and variable frequencies of each AE with respect to the total number of reported AEs were also presented.

Results

Descriptive analysis of the patient population

We included a total of 103 patients (61 *ALK*+ and 42 *ROS1*+) (Table 1). Patients were predominantly female and Caucasian, with a median age of 59.4-year-old (range 39–86) for *ALK*+ pts, and 62.7-year-old (range 40–87) for *ROS1*+ pts. A significant proportion were never-smokers, with 46 % of *ALK*+ and 67 % of *ROS1*+. For *ALK*+ patients, diagnostic methods included FISH (54.4 %), IHC (31.1 %), NGS (3 %), and other RNA/DNA sequencing methods (2.9 %). Among *ROS1*+ patients, FISH (38/32 cases) was the most frequent diagnostic method, followed by IHC (14 cases), NGS (4/42), and RNASeq/Nanostring (1 case each).

At lorlatinib initiation, only 13.1 % of *ALK*+ and 26.2 % of *ROS1*+ patients had an ECOG performance status of 0. Brain metastases were present in 59 % of *ALK*+ and 57.1 % of *ROS1*+ patients. Common sites of metastasis for *ALK*+ included bone (41 %), lung (32.8 %), and liver (19.7 %), while in *ROS1*+ patients, the lung (52.4 %) and bone (35.7 %) were predominant, with liver metastasis in 11.9 %.

Prior therapies

For *ALK*+ patients, 96.7 % had prior TKI treatment, and 85.2 % had received at least two lines of ALK TKIs, with crizotinib being the most commonly used (90.9 %). Second-generation TKIs were frequently used beyond first-line, with 41.8 % treated with alectinib, 38.2 % with brigatinib, and 36.4 % with ceritinib. Chemotherapy was used in 54.1 %, and immunotherapy in 6.6 %. Patients had received a median of 3 prior lines of systemic therapy before lorlatinib, with 31 % having received at least four lines (Table 1 **and Suppl_Figure 1**).

Among *ROS1*+ patients, all had been treated with crizotinib, which was preferentially used in the second line of therapy. First-line therapies included platinum-based chemotherapy (42.9 %), with 7.1 % receiving chemo-immunotherapy or immunotherapy alone. Only 7 % of *ROS1*+ patients received another TKI besides crizotinib. Chemotherapy was used in 54.8 %, and immunotherapy in 16.7 % (Table 1).

Lorlatinib outcomes and survival

For *ALK*+ patients, the confirmed ORR was 32.8 %, with a complete response (CR) in 8.2 % of patients and 34.4 % achieving stable disease (SD). The best response by number of previous lines of TKI is summarized in Table 2. The median PFS was 11.2 months (P25th – P75th: 3.3 – 35.8 months), with PFS rates of 59.0 % (95 %CI 45.7 % - 70.1 %) at 6 months, 49.2 % (95 %CI 36.2 % - 60.9 %) at 12 months, and 29.5 % (95 %CI 18.7 % - 41.1 %) at 24 months (Fig. 1**A**). Median PFS decreased with increasing prior lines of ALK TKIs, with 15.1 months for patients treated with 1 prior TKI, 11.1 months for 2 TKIs, and 7.6 months for ≥3 TKIs (Fig. 1**E**). Intracranial ORR was 47.6 %, rising to 58.8 % in patients with evaluable brain metastases. Intracranial tumor PFS was 56.5 months (P25th – P75th: 20.2 – 67.0 months), with an intracranial tumor PFS at 6, 12 and 24 months after treatment initiation of 92.8 % (95 %CI 79.0 % - 97.6 %), 86.2 % (95 %CI 69.6 % - 94.1 %) and 73.2 % (95 %CI 52.3 % - 86.1 %), respectively (**Figure Sup2**).

In *ALK*+ patients, progression to lorlatinib occurred at a similar rate in intrathoracic and extra-thoracic sites (**SuppTable_1**). Brain progression was documented in 10/30 patients (33.3 %). Only 3 patients (4.9 %) had a tumor re-biopsy at the time of progression, and in 2 patients (3.3 %) a liquid biopsy was obtained. Up to 60 % of the patients received further treatment with lorlatinib, most commonly chemotherapy (44 %), another ALK TKI (33.3 %), and chemo-immunotherapy (11 %). Detailed

Table 1
Clinical and pathological characteristics of patients with ALK and ROS1-positive NSCLC ($n = 103$). All results are shown as n (%), unless otherwise stated.

	ALK + $N = 61$	ROS1 + $N = 42$
Gender		
Male	23 (37.7)	15 (35.7)
Female	38 (62.3)	27 (64.3)
Race		
Caucasian	61 (100.0)	38 (90.5)
Latin	0	1 (2.4)
Asian	0	2 (4.8)
Black, African	0	1 (2.4)
Age, mean (SD)	59.4 (11.7)	62.7 (13.2)
Min. – max.	39 – 86	40 – 87
Smoking History		
Smoking status		
Never smoker (≤ 100 cigarettes/lifetime)	28 (45.9)	28 (66.7)
Former smoker (≥ 1 year)	22 (36.1)	9 (21.4)
Active smoker	9 (14.7)	4 (9.5)
Unknown	2 (3.3)	1 (2.4)
Pack/year, median [IQR]	15 [10, 25]	10 [1.8, 34]
Min. – max.	5 – 520	1.6 – 40
Cigarettes/day, mean (SD)	20 [10, 20]	8 [2, 15]
Min. – max.	10 – 40	2 – 20
Comorbidities		
None	27 (44.3)	13 (31.0)
Asthma	3 (4.9)	2 (4.8)
Heart disease	2 (3.3)	4 (9.5)
Mellitus diabetes	5 (8.2)	3 (7.1)
Dyslipemia	3 (4.9)	7 (16.7)
COPD	0 (0.0)	1 (2.4)
Ex-Alcoholism	2 (3.3)	0 (0.0)
Active Alcoholism	1 (1.6)	0 (0.0)
Hypercholesterolemia	1 (1.6)	4 (9.5)
Hypertension	10 (16.4)	11 (26.2)
Nephropathy	1 (1.6)	1 (2.4)
Obesity	0 (0.0)	0 (0.0)
Depressive syndrome/Anxiety	4 (6.6)	4 (9.5)
Vasculopathy	0 (0.0)	1 (2.4)
Others	22 (36.1)	20 (47.6)
Charlson Index Score, median [IQR]	7 [6, 8]	7.5 [7, 8]
Min. – max.	0 – 8	7 – 12
Previous History of Thromboembolic Disease		
Thromboembolic disease	4 (6.6)	14 (33.3)
Anticoagulant treatment	4 (6.6)	12 (28.6)
Performance Status		
0	8 (13.1)	11 (26.2)
1	36 (59.0)	23 (54.8)
2	7 (11.5)	5 (11.9)
3	1 (1.6)	1 (2.4)
Unknown	9 (14.7)	2 (4.8)
Disease stage at diagnosis		
IB	1 (1.6)	0 (0.0)
IIA	0 (0.0)	3 (7.3)
IIIA	6 (9.8)	1 (2.4)
IIIB	7 (11.5)	4 (9.8)
IVA	16 (26.2)	16 (39.0)
IVB	31 (50.8)	17 (41.5)
Unknown	1 (1.6)	0
Histology subtype		
Adenocarcinoma	56 (91.8)	42 (100.0)
Adenosquamous	1 (1.6)	0 (0.0)
Squamous	1 (1.6)	0 (0.0)
NOS/Undifferentiated	1 (1.6)	0 (0.0)
Other	2 (3.3)	0 (0.0)
Histology grade		
Not specified	43 (70.5)	30 (71.4)
Well differentiated	2 (3.3)	2 (4.8)
Moderately differentiated	6 (9.8)	2 (4.8)
Poorly differentiated	8 (13.1)	6 (14.3)
Undifferentiated	1 (1.6)	2 (4.8)
Unknown	1 (1.6)	0 (0.0)
Brain metastasis at diagnosis		
No	36 (59.0)	31 (73.8)
Yes	21 (34.4)	9 (21.4)
Unknown	3 (4.9)	2 (4.8)
Brain metastases before Lorlatinib initiation		
No	22 (36.1)	17 (40.5)
Yes	36 (59.0)	24 (57.1)
Unknown	3 (4.9)	1 (2.4)
Brain Imaging Method		
None	8 (13.1)	2 (4.8)
CT	15 (24.6)	17 (40.5)
PET	3 (4.9)	3 (7.1)
MRI	22 (36.1)	10 (23.8)
Unknown	13 (21.3)	10 (23.8)
Concomitant steroid treatment	14 (23)	12 (28.36)
Previous treatments for brain metastasis		
Surgery	5 (8.2)	1 (2.4)
Whole brain radiation	15 (24.6)	6 (14.3)
SRS/radiosurgery	9 (14.8)	5 (11.9)
Other metastasis location		
Lung	20 (32.8)	22 (52.4)
Lymphangitis	2 (3.3)	4 (9.5)
Pulmonary Lymph Nodes	18 (29.5)	14 (33.3)
Pleural Nodes	6 (9.8)	7 (16.7)
Pleural Effusion	10 (16.4)	13 (31.0)
Meningeal Carcinomatosis	1 (1.6)	0 (0.0)
Bone	25 (41.0)	15 (35.7)
Liver	12 (19.7)	5 (11.9)
Adrenal Gland	8 (13.1)	4 (9.5)
Soft Tissue	2 (3.3)	0 (0.0)
Other	11 (18.0)	9 (21.4)
Prior systemic treatment	60 (98.4)	42 (100.0)
Chemotherapy	33 (54.1)	23 (54.8)
Immunotherapy	4 (6.6)	7 (16.7)
Radiotherapy	32 (52.5)	12 (28.6)
Oral Tyrosine Kinase Inhibitor	59 (96.7)	42 (100.0)
Previous lines of treatment before Lorlatinib		
1	4 (6.6)	16 (38.1)
2	24 (39.3)	20 (47.6)
3	11 (18.0)	3 (7.1)
4	9 (14.8)	0 (0.0)
5	10 (16.4)	3 (7.1)
Unknown	3 (4.9)	0
Previous ALK TKIs received before Lorlatinib		
1	3 (5.3)	–
2	21 (36.8)	–
3	11 (19.3)	–
≥4	20 (35.1)	–

information of post-progression therapies can be found in **SuppTable_2**. With a median follow-up time of 55.2 months (P25th – P75th: 48.1 - 59.2), the median OS was 13.5 months (P25th – P75th: 5.3 – 52.6 months), with 6-month, 12-month, and 24-month OS rates of 72.1 % (95 %CI 59.1 % - 81.7 %), 54.1 % 54.1 % (95 %CI 40.9 % - 65.6 %), and 36.1 % (95 %CI 24.3 % - 47.9 %), respectively (Fig. 1**C**). Median OS from the time of stage IV diagnosis was 45.8 months (P25th – P75th: 20.1 – 81.1). OS according to previous lines of ALK TKI therapy is shown in Fig. 1**D**

For *ROS1*+ patients, the confirmed ORR was 47.6 %, with a CR in 16.7 % of patients and SD in 38.1 % (Table 2). Responses were seen regardless of the number of previous TKIs received, with 46.2 % ORR in the 39 patients with crizotinib as the only previous TKI versus 66.6 % ORR in the 3 patients who received 2 previous TKIs. Intracranial ORR was 44.4 %, increasing to 57.1 % in patients with evaluable brain metastases. The median PFS was 10 months (P25th – P75th: 5.2 – Not reached (NR) months), with PFS rates of 72.7 % (95 %CI 56.2 % - 83.9 %) at 6 months, 47.7 % (95 %CI 31.7 % - 62.0 %) at 12 months, and 40.1 % (95 %CI 25.1 % - 54.7 %) at 24 months (Fig. 2**A**). Patients who had only received crizotinib had a median PFS of 10 months, while those treated with 2 prior TKIs had a median PFS of 8.5 months (Fig. 2**E**).

In *ROS1*+ patients, progression to lorlatinib occurred preferentially intrathoracically: 47.4 % in the lung, 5.3 % as lymphangitic spread, 15.8 % in lymph nodes, and 40 % as pleural nodes/effusion (**SuppTable_1**). Brain progression was documented only in 4 patients (9.5 %,

Table 2
Overall response rate (ORR) of lorlatinib in ALK+ and ROS1+ patients. All results are shown as n (%), unless otherwise stated.

	ALK + *N* = 61	ROS1 + *N* = 42
Best response to the treatment ORR (CR + PR)	20 (32.8)	20 (47.6)
CR	5 (8.2)	7 (16.7)
PR	15 (24.6)	13 (31.0)
SD	21 (34.4)	16 (38.1)
PD	16 (26.2)	3 (7.1)
Unknown	4 (6.6)	3 (7.1)
Intracranial tumour response (in patients with previous brain metastasis)		
No	7 (33.3)	3 (33.4)
Yes	10 (47.6)	4 (44.4)
Not documented/evaluable	4 (19.1)	2 (22.2)
Intracranial tumour response (in patients with evaluable brain metastasis)		
No	7 (41.2)	3 (42.9)
Yes	10 (58.8)	4 (57.1)
Best response to the treatment according to number of previous TKI therapy		
1 TKI (n = 14)	4 (28.6)	18 (46.2)
CR	2 (14.3)	6 (15.8)
PR	2 (14.3)	12 (31.6)
SD	7 (50.0)	15 (39.5)
PD	3 (21.4)	3 (7.9)
Unknown	0 (0.0)	3 (7.6)
2 TKIs (n = 28)	12 (42.9)	2 (66.9)
CR	3 (10.7)	1 (33.3)
PR	9 (32.1)	1 (33.3)
SD	5 (17.9)	1 (33.3)
PD	8 (28.6)	0 (0.0)
Unknown	3 (10.7)	0 (0.0)
≥3 TKIs (n = 16)	3 (18.7)	–
CR	0 (0.0)	–
PR	3 (18.7)	–
SD	8 (50.0)	–
PD	4 (25.0)	–
Unknown	0 (0.0)	–

CR, complete response; PR, partial response; SD, stable disease; PD, progresssive disease; TKI, tyrosine kinase inhibitor.

Figure Sup2). In 61.5 % of the cases, patients received subsequent treatment after lorlatinib, including chemotherapy (87.5 %), immunotherapy (37.5 %), and ROS1 TKI (only one patient). The median OS was 38.3 months (P25th – P75th: 9.7 – NR months), with OS rates of 85.4 % (95 %CI 70.4 % - 93.2 %) at 6 months, 65.4 % (95 %CI 48.6 % - 77.8 %) at 12 months, and 57.5 % (95 %CI 40.7 % - 71.1 %) at 24 months (Fig. 2**C**). Patients treated with crizotinib alone had a median OS of 39.8 months, compared to 9.7 months in those who received an additional ROS1 TKI. Median OS from the time of stage IV diagnosis was 82.7 months (P25th – P75th: 39.0 – NR months). OS according to previous lines of ROS1 TKI therapy is shown in Fig. 2**F**.

Safety

In *ALK*+ patients, the median exposure to lorlatinib was 8.5 months (range 0.4–56.5 months), while for *ROS1*+ patients, the median was 7 months (range 1.2–41.1 months). Dose reductions occurred in 23 % of *ALK*+ patients (14/61) and 23.8 % of *ROS1*+ patients (10/42). For *ALK*+ patients, 6 were reduced to 75 mg/day, 7 to 50 mg/day, and 1 to 25 mg/day, with re-escalation in 7 patients (11.5 %). For *ROS1*+ patients, 7 were reduced to 75 mg/day, 2 to 50 mg/day, and 1 to 25 mg/day. Lorlatinib discontinuation due to adverse events occurred in 13.1 % (*ALK*+) and 9.5 % (*ROS1*+), with disease progression being the most common reason for discontinuation.

The most frequent treatment-related adverse events (TRAEs) for *ALK*+ patients were dyslipidemia (68 %) and edema (32.7 %), with nervous system disorders affecting 4.5 % (1 case of grade ≥3 peripheral sensory neuropathy). Psychiatric disorders were reported in 5.1 %, with two grade 3–4 cases (delirium and depression). No lorlatinib-related deaths occurred in *ALK*+ patients (Table 3).

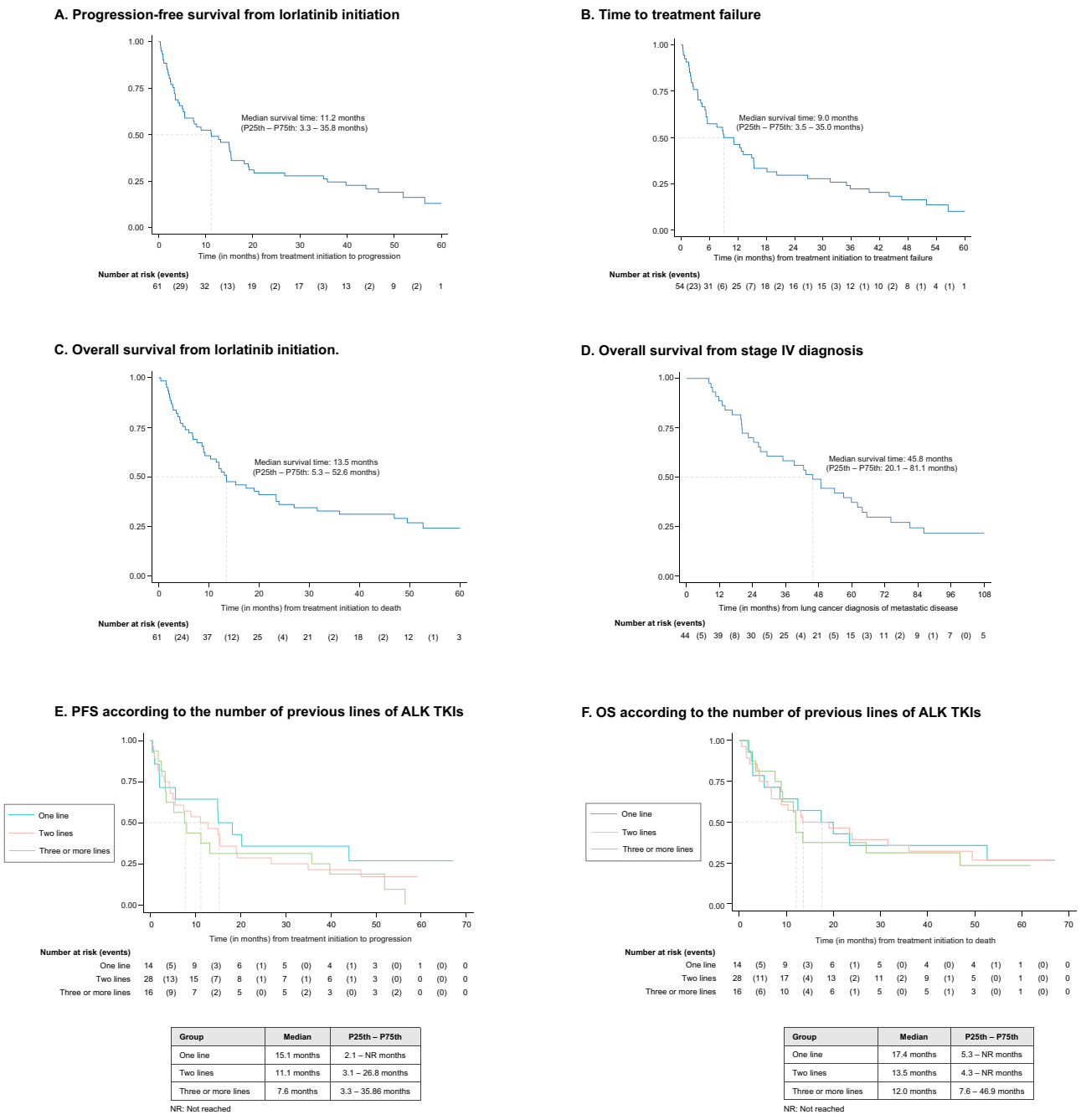
For *ROS1*+ patients, dyslipidemia (48 %) and edema (31 %) were the most frequent TRAEs (Table 3). Hypertriglyceridemia was grade 3–4 in 4 % of cases, and hypercholesterolemia was grade 3–4 in 5 %. Nervous system disorders were reported in 29 %, mostly grade 1–2, with two grade ≥3 cognitive disturbance cases. Psychiatric disorders were observed in 7 %, including one grade 3 agitation case. No lorlatinib-related deaths were reported in *ROS1*+ patients.

Discussion

This study provides valuable insights into the real-world application of lorlatinib in patients with previously treated *ALK*+ and *ROS1*+ NSCLC. With 61 patients in the *ALK*+ cohort and 42 in the *ROS1*+cohort, this series represents one of the largest collections of lorlatinib-treated NSCLC patients in Spain, offering detailed outcomes on efficacy, safety, and survival in heavily pretreated populations. The post-progression TKI setting for patients with *ALK*- and *ROS1*-rearranged NSCLC remains challenging due to limited treatment options available and the paucity of randomized clinical trials. Most of the evidence, including supporting regulatory approvals, is derived from single-arm studies, limiting direct comparisons between treatment options. Current NCCN guidelines (v3.2025) recommend lorlatinib or systemic therapy after progression on second-generation ALK TKI (alectinib, brigatinib, ceritinib, or ensartinib) in ALK-positive NSCLC. In the case of ROS1-positive NSCLC, lorlatinib (preferred), entrectinib, or repotrectinib are recommended after progression on a ROS1 TKI [14]. Overall, systemic therapy (chemotherapy or immunotherapy) offers limited efficacy in *ALK*/ROS1 NSCLC after TKI progression [15]. For instance, in the ALUR trial, chemotherapy for previously treated *ALK*+ patients demonstrated poor outcomes, with a median PFS of only 1.4 months and no CNS tumor responses in patients with measurable CNS metastases at baseline, in stark contrast to alectinib [16]. In addition, PD-1/PD-L1 inhibitor monotherapy is generally ineffective in this population, irrespective of PD-L1 expression levels [14].

In the *ALK*+ cohort of our study, the ORR of 32.8 % and median PFS of 11.2 months align with previous results from phase 1 and phase 2 pivotal trials of lorlatinib [9,17]. Specifically, in the phase 2 trial, the ORR was 38.7 % (95 %CI, 29.6–48.5) and the PFS 6.9 months in the cohort of 111 patients who received two or more previous ALK TKIs [17]. In our study, lorlatinib also demonstrated significant intracranial efficacy, with a 47.6 % response rate, which rose to 58.8 % in patients with measurable brain metastases—a population known for poorer prognosis due to the high rate of CNS involvement (59 %) [18]. In the phase 2 trial, the intracranial activity was 54.2 % in the 48 evaluable patients included. Overall, these efficacy outcomes are consistent with other real-world studies of lorlatinib and emphasize lorlatinib's reproducibility in a more heterogeneous population [19–26].

Emerging therapies expanding options in the post-TKI setting for *ALK*-positive NSCLC includes NVL-655, a fourth-generation, selective, brain-penetrant ALK inhibitor with granted breakthrough therapy designation by the FDA for the treatment of patients with metastatic *ROS1*-NSCLC who previously received at least 2 ROS1 TKIs. NVL-655 is being evaluated in the phase 1/2, open label, single arm ALKOVE-1 trial [27]. The phase 1 part enrolled 131 patients with pretreated *ALK*+ NSCLC. In those patients with lorlatinib-naive disease ($n = 17$), the ORR



Group	Median	P25th – P75th
One line	15.1 months	2.1 – NR months
Two lines	11.1 months	3.1 – 26.8 months
Three or more lines	7.6 months	3.3 – 35.86 months

NR: Not reached

Group	Median	P25th – P75th
One line	17.4 months	5.3 – NR months
Two lines	13.5 months	4.3 – NR months
Three or more lines	12.0 months	7.6 – 46.9 months

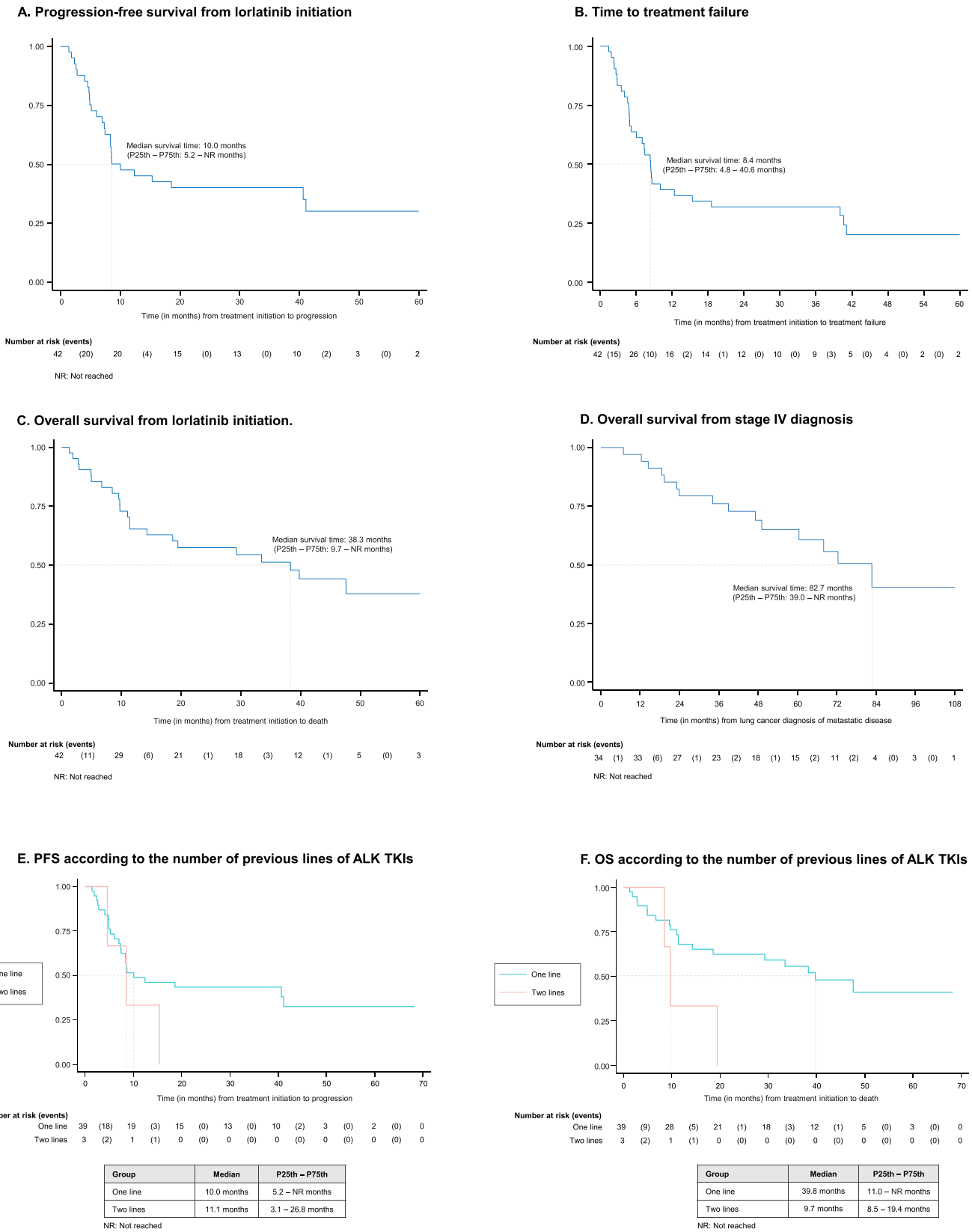
NR: Not reached

Fig. 1. Survival curves in *ALK*+ NSCLC patients treated with lorlatinib estimated by the Kaplan-Meier method. A, Progression-free survival. B, Time to treatment failure. C, Overall survival from lorlatinib initiation. D, Overall survival from stage IV diagnosis. E, Progression-free survival according to the number of previous lines of ALK TKIs. D, Overall survival from lorlatinib according to the number of previous lines of ALK TKIs.

was 53 % across all doses (9 of 17 patients), and the intracranial ORR was seen in 50 % of those who were lorlatinib naive (one out two patients) [28].

Similarly, in the *ROS1*+ cohort of our study, lorlatinib displayed remarkable efficacy, with an ORR of 48 % and median PFS of 10 months. The intracranial response rate was 57 %, particularly important given that 57 % of these patients had brain metastases at baseline. In addition, brain progression was documented only in 4 patients, with a long time to intracranial progression (Suppl Fig 2). This is consistent with previously published real-world data and pivotal trials, further establishing lorlatinib as an effective option for *ROS1*+ NSCLC, particularly in controlling CNS disease [13,19,23,25,26,29]. The median OS of 38.3 months and an extraordinary 82.7-month OS from metastatic diagnosis in *ROS1*+ patients emphasize the long-term benefit of active targeted therapies in this population [6,30,31]. However, our study reveals a significant unmet need for the access to newer-generation TKIs in *ROS1*+ patients, as very few patients in our study received another ROS1 TKI post-lorlatinib. Increasing access to clinical trials and reducing restrictive eligibility criteria could expand treatment options and improve outcomes for this relatively small but critical patient population.

There are several new agents recently available or under investigation for *ROS1*-positive NSCLC. Repotrectinib, a next-generation ROS1 inhibitor, was evaluated in the single arm, open-label TRIDENT-1 trial. In the cohort of patients previously treated with a ROS1 TKI but without prior chemotherapy or immunotherapy ($n = 56$), repotrectinib achieved an ORR of 38 %, with a 38 % intracranial ORR in patients with



Group	Median	P25th – P75th
One line	10.0 months	5.2 – NR months
Two lines	11.1 months	3.1 – 26.8 months

NR: Not reached

Group	Median	P25th – P75th
One line	39.8 months	11.0 – NR months
Two lines	9.7 months	8.5 – 19.4 months

NR: Not reached

Fig. 2. Survival curves in *ROS1*+ NSCLC patients treated with lorlatinib estimated by the Kaplan-Meier method. A, Progression-free survival. B, Time to treatment failure. C, Overall survival from lorlatinib initiation. D, Overall survival from stage IV diagnosis. E, Progression-free survival according to the number of previous lines of *ROS1* TKIs. F, Overall survival from lorlatinib according to the number of previous lines of ROS1 TKIs.

Table 3
Adverse events in ALK+ and ROS1+ patients ($n = 103$). All results are shown as n (%), unless otherwise stated. [§]Two observations have lost value in the grade.

	ALK					ROS1				
Grade	1 - 2 $N = 143$	3 $N = 29$	4 $N = 1$	5 $N = 1$	Total[§] $N = 176$	1 $N = 29$	2 $N = 37$	3 $N = 15$	4 $N = 3$	Total[§] $N = 85$
Blood and lymphatic system disorders	1 (0.7)	3 (10.3)	0 (0.0)	0 (0.0)	4 (2.3)	2 (6.9)	2 (5.4)	0 (0.0)	0 (0.0)	4 (4.7)
Anemia	1 (0.7)	2 (6.9)	0 (0.0)	0 (0.0)	3 (1.7)	2 (6.9)	1 (2.7)	0 (0.0)	0 (0.0)	3 (3.5)
Leukocytosis	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophil count decreased	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.2)
Platelet count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.7)	0 (0.0)	0 (0.0)	2 (2.4)
Others	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.2)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.2)
Pericardial effusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.2)
Endocrine disorders	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cushingoid	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Blurred vision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Others	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	14 (9.8)	1 (3.4)	1 (25.0)	0 (0.0)	16 (9.1)	3 (10.3)	2 (5.4)	0 (0.0)	0 (0.0)	5 (5.9)
Abdominal distension	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	6 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Diarrhea	1 (0.7)	1 (3.4)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysphagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.2)
Dysphagia	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.2)
Mucositis oral	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)
Nausea	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oral hemorrhage	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	33 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	33 (18.7)	5 (17.2)	7 (18.9)	2 (13.3)	0 (0.0)	14 (16.5)
Edema face	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema limbs	12 (8.4)	0 (0.0)	0 (0.0)	0 (0.0)	12 (6.8)	5 (17.2)	6 (16.2)	1 (6.7)	0 (0.0)	12 (14.1)
Fatigue	5 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.8)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.2)
Fever	6 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Generalized edema	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.2)
Localized edema	4 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	4 (13.8)	0 (0.0)	0 (0.0)	4 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic failure	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others	0 (0.0)	3 (10.3)	0 (0.0)	3 (1.7)	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	4 (2.8)	1 (3.4)	1 (25.0)	3 (1.7)	6 (3.4)	0 (0.0)	1 (2.7)	1 (6.7)	0 (0.0)	2 (2.4)
Bronchial infection	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gum infection	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Folliculitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.2)
Lung infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (1.2)
Others	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	20 (14.0)	3 (10.3)	0 (0.0)	0 (0.0)	23 (13.1)	5 (17.2)	5 (13.5)	4 (26.7)	1 (33.3)	15 (17.6)
Alanine aminotransferase increased	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholesterol high	17 (11.9)	1 (3.4)	0 (0.0)	0 (0.0)	18 (10.2)	2 (6.9)	2 (5.4)	3 (20.0)	1 (33.3)	8 (9.4)
Lipase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Weight gain	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (3.4)	1 (2.7)	1 (6.7)	0 (0.0)	3 (3.5)
Metabolism and nutrition disorders	30 (21.0)	6 (20.7)	1 (25.0)	0 (0.0)	37 (21.0)	2 (6.9)	6 (16.2)	5 (33.3)	1 (33.3)	14 (16.5)
Anorexia	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypercalcemia	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalemia	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperlipidemia	1 (0.7)	0 (0.0)	1 (25.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (5.4)	1 (6.7)	0 (0.0)	3 (3.5)
Hypertriglyceridemia	23 (16.1)	5 (17.2)	0 (0.0)	0 (0.0)	23 (13.1)	2 (6.9)	3 (8.1)	3 (20.0)	1 (33.3)	9 (10.6)
Others	3 (2.1)	1 (3.4)	0 (0.0)	0 (0.0)	4 (2.3)	0 (0.0)	1 (2.7)	1 (6.7)	0 (0.0)	2 (2.4)
Musculoskeletal and connective tissue disorders	7 (4.9)	1 (3.4)	0 (0.0)	0 (0.0)	8 (4.5)	0 (0.0)	3 (8.1)	0 (0.0)	0 (0.0)	4 (4.7)
Arthralgia	5 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.8)	0 (0.0)	2 (5.4)	0 (0.0)	0 (0.0)	3 (3.5)
Arthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.2)
Back pain	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bone pain	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	7 (4.9)	1 (3.4)	0 (0.0)	0 (0.0)	8 (4.5)	5 (17.2)	5 (13.5)	2 (13.3)	0 (0.0)	12 (14.1)
Amnesia	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aphonia	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cognitive disturbance	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (3.4)	0 (0.0)	2 (13.3)	0 (0.0)	3 (3.5)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)

(*continued on next page*)

Table 3 (*continued*)

Grade	ALK					ROS1				
	1 - 2 $N = 143$	3 $N = 29$	4 $N = 1$	5 $N = 1$	Total§ $N = 176$	1 $N = 29$	2 $N = 37$	3 $N = 15$	4 $N = 3$	Total§ $N = 85$
Dysarthria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.2)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Memory impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.2)
Neuralgia	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paresthesia	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy	1 (0.7)	1 (3.4)	0 (0.0)	0 (0.0)	2 (1.1)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Syncope	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	3 (8.1)	0 (0.0)	0 (0.0)	4 (4.7)
Psychiatric disorders	7 (4.9)	2 (6.9)	0 (0.0)	0 (0.0)	9 (5.1)	0 (0.0)	2 (5.4)	1 (6.7)	0 (0.0)	3 (3.5)
Agitation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	1 (1.2)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (1.2)
Confusion	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Delirium	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	1 (0.7)	1 (3.4)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (1.2)
Hallucinations	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Irritability	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nephrotic syndrome	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal colic	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	11 (7.7)	4 (13.8)	0 (0.0)	1 (100.0)	16 (9.1)	3 (10.3)	2 (5.4)	0 (0.0)	1 (33.3)	6 (7.1)
Atelectasis	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea	5 (3.5)	1 (3.4)	0 (0.0)	0 (0.0)	6 (3.4)	0 (0.0)	1 (2.7)	0 (0.0)	1 (33.3)	2 (2.4)
Pleural effusion	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonitis	1 (0.7)	2 (6.9)	0 (0.0)	0 (0.0)	3 (1.7)	3 (10.3)	1 (2.7)	0 (0.0)	0 (0.0)	4 (4.7)
Productive cough	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wheezing	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (1.4)	1 (3.4)	0 (0.0)	0 (0.0)	3 (1.7)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)
Alopecia	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperhidrosis	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Social circumstances	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (0.6)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Others	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (0.6)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)

measurable CNS metastases (5/13) [32]. Taletrectinib, a highly potent, CNS-active, ROS1 TKI, showed compelling efficacy in patients with ROS-1 NSCLC. Pooled analysis from the TRUST-I and TRUST-II trials reported an ORR of 55.8 % in patients previously treated with a ROS1 TKI ($n = 113$). In the subset of patients with measurable CNS metastases ($n = 32$), the intracranial ORR was 65.6 % [33]. NVL-520 is a novel selective, TRK-sparing and brain-penetrant ROS1 inhibitor. The FDA has granted breakthrough therapy designation to NVL-520 for the treatment of patients with metastatic *ROS1*-NSCLC who previously received at least two ROS1 TKIs based on the preliminary activity shown in the currently ongoing phase 1/2 ARROS-1 trial (NCT05118789). Patients with *ROS1 G2032R* mutations ($n = 9$) achieved an ORR of 78 %, while those with CNS metastases ($n = 11$) had an ORR of 73 %. In heavily pretreated patients who received at least two prior ROS1 TKIs and chemotherapy ($n = 17$), NVL-520 achieved an ORR of 53 %. Notably, those previously treated with lorlatinib or repotrectinib ($n = 18$) had an ORR of 50 % [34]. In summary, the consistent efficacy and intracranial activity of lorlatinib, along with emerging data for novel ROS1 inhibitors such as repotrectinib, taletrectinib, and NVL-520, highlight the expanding therapeutic landscape for patients with *ROS1* alterations after progression on prior TKIs.

The slightly superior outcomes in the *ROS1*+ cohort compared to *ALK*+ patients may be attributed to differences in disease biology and patient characteristics. *ROS1*+ NSCLC often arises in younger, healthier, non-smoking individuals with fewer comorbidities, which could contribute to better overall outcomes. In both cohorts, however, patients who had received multiple prior TKIs experienced diminishing returns with lorlatinib, particularly in *ALK*+ cases. This trend was previously observed in the phase II trial of lorlatinib, where response rates and PFS were lower in patients who had been treated with greater number of prior ALK TKIs. This decremental efficacy of lorlatinib could be biologically explained in part, by the acquisition of more complex, compound *ALK* resistant mutations, that are harder to target effectively; lower tyrosine kinase activity dependance in favor of bypass signaling or alternative pathway activation that promote tumor growth and survival in an independent manner than ALK oncoprotein tyrosine kinase activation; or just by the presence of worse clinical prognostic factors, such as a higher prevalence of CNS metastasis and poorer performance status in patients after treatment with multiple lines of therapy.

The high incidence of brain metastases in both *ALK*+ and *ROS1*+ populations underscore the unmet need for CNS-active therapies [35–37]. Lorlatinib's CNS efficacy is particularly striking in previously TKI treated population, with intracranial response rates of 57 % in *ROS1*+ patients and 47.6 % in *ALK*+ patients, consistent with results from prior trials [9,10,12,17]. The prevention and treatment of brain metastases are crucial to improve both quality of life and survival, given that over half of the patients in both cohorts presented with CNS involvement, and lorlatinib offers a key advantage by reducing intracranial progression and impact on patient-reported outcomes (PROs) [38]. For instance, in the *ROS1*+ cohort, the high intracranial response rate in patients receiving steroids for CNS symptoms reflects the critical role of lorlatinib in managing neurologically symptomatic disease. These findings underscore the importance of optimizing treatment sequencing and prioritizing therapies with robust intracranial efficacy, particularly in heavily pretreated populations.

Given the benefits seen in CNS disease control with lorlatinib in *ALK*+ patients from the CROWN trial [11,12], it is reasonable to extrapolate that earlier use of lorlatinib in *ROS1*+ NSCLC could prevent or delay CNS progression. These findings support further exploration of lorlatinib as a first-line option in *ROS1*+ NSCLC to achieve both therapeutic and preventive CNS effects, similar to its established role in *ALK*+ patients.

The safety profile of lorlatinib in both cohorts was consistent with previous reports from prospective clinical trials [9,10,13]. Common adverse events included dyslipidemia, edema, and neurological and psychiatric symptoms. The incidence of grade ≥3 dyslipidemia (11 %) was lower than that reported in clinical trials (16 %), potentially due to differences in retrospective data collection and proactive management strategies. In both *ALK*+ and *ROS1*+ patients, dose modifications, such as reductions and interruptions were common, yet the safety profile remained manageable. Dose modifications are key strategies in managing adverse events while maintaining treatment adherence with lorlatinib as previously described [39]. In addition, supportive care (e.g., lipid-lowering agents for hypercholesterolemia) complements dose modifications, enabling continued treatment without compromising efficacy. Our study was not designed to capture specific management strategies and their impact on treatment adherence but there are ongoing planned studies to evaluate it. The *ROS1*+ cohort, in particular, experienced a higher rate of treatment discontinuation due to AEs (9.5 %), mirroring other real-world studies, which have reported discontinuation rates higher than clinical trials [19,23,26,29]. This highlights the challenges of managing toxicity in routine practice, where patients often present with comorbidities or are on concurrent medications that may exacerbate side effects.

Lorlatinib has also demonstrated a favorable impact on quality of life in patients with *ALK*+ and *ROS1*+ NSCLC. In a prospective series of 59 *ALK*+ patients in Canada whose tumor progressed despite 2nd generation ALK TKI, lorlatinib demonstrated sustained improvement in quality of life [40]. In the phase 1/2 study of lorlatinib (NCT01970865) that included 255 patients with *ALK*+ or *ROS1*+ advanced NSCLC, PROs -including quality of life-, were clinically meaningful improved and maintained over time, with the exception of peripheral neuropathy [38]. Due to the nature of our study, we did not collect any PROs to provide a comprehensive view of lorlatinib's tolerability and quality of life in a heavily pretreated population.

The retrospective design of our study introduces several limitations, including the lack of a control group that prevents comparisons to other therapies and limits control for confounding factors; the varying imaging techniques, the unblinded central review of responses, and timing of assessments that may influence the degree of tumor response and the time to tumor progression; and other bias such as selection bias, as not all patients in the expanded access program (EAP) in Spain could not been included. Given the lack of randomized trials in the post-progression setting, validation of these findings should rely on real-world studies with larger, diverse cohorts. Multicenter registries and matched analyses using real-world evidence could address some limitations. Moreover, consistency in terms of efficacy and safety across retrospective data from different countries has been already mentioned, which helps to enhance generalizability of our data. Additionally, limited access to molecular data, particularly post-progression biopsies, hampers a more thorough understanding of resistance mechanisms to lorlatinib, both in *ALK*+ and *ROS1*+ NSCLC patients [41,42]. Prospective studies, like the ALKALINE trial (NCT04127110), are needed to elucidate predictive biomarkers and optimize patient selection for lorlatinib, particularly in later lines of therapy.

In conclusion, the efficacy and safety profiles of lorlatinib in both *ALK*+ and *ROS1*+ NSCLC patients treated within the compassionate use program in Spain are consistent with previous studies. Lorlatinib shows robust and durable responses, particularly in the CNS, with manageable toxicity. These real-world data support its continued use in heavily pretreated *ALK*+ and *ROS1*+ patients and highlight the potential benefits of its earlier use in both cohorts, particularly for CNS disease control. Further research into predictive biomarkers and access to new ROS1 TKIs is essential to optimize treatment strategies for these patients.

Suppl_Figure 1. Previous therapies by line of treatment and tumor activity in ALK+ NSCLC patients before treatment with lorlatinib. A, Treatment modality received before lorlatinib. B, Best overall response (BOR) by line of therapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. C, Overall response rate (CR + PR) by line of therapy. D, Median duration of treatment by line of therapy (in months).

CRediT authorship contribution statement

Antonio Calles: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mirian Alonso:** Writing – review & editing, Resources, Investigation, Data curation. **Paloma Martín-Martorell:** Writing – review & editing, Resources, Investigation, Data curation. **Ana Gómez:** Writing – review & editing, Resources, Investigation, Data curation. **Javier de Castro:** Writing – review & editing, Resources, Investigation, Data curation. **Maite Martínez-Aguillo:** Writing – review & editing, Resources, Investigation, Data curation. **Anna Estival:** Writing – review & editing, Resources, Investigation, Data curation. **Joaquin Mosquera:** Writing – review & editing, Resources, Investigation, Data curation. **Natividad Martínez-Banaclocha:** Writing – review & editing, Resources, Investigation, Data curation. **Margarita Majem:** Writing – review & editing, Resources, Investigation, Data curation. **Roxana Reyes:** Writing – review & editing, Resources, Investigation, Data curation. **Eider Azkona:** Writing – review & editing, Resources, Investigation, Data curation. **Ana Laura Ortega:** Writing – review & editing, Resources, Investigation, Data curation. **Santiago Aguin:** Writing – review & editing, Resources, Investigation, Data curation. **Ana Santos:** Writing – review & editing, Resources, Investigation, Data curation. **Andrés Aguilar:** . **Marc Cucurull:** Writing – review & editing, Resources, Investigation, Data curation. **Ana Blasco:** Writing – review & editing, Resources, Investigation, Data curation. **Virginia Calvo:** Writing – review & editing, Resources, Investigation, Data curation. **Dolores Isla:** Writing – review & editing, Resources, Investigation, Data curation. **Ernest Nadal:** Writing – review & editing, Resources, Investigation, Data curation. **Carlos Aguado:** Writing – review & editing, Resources, Investigation, Data curation. **Elia Sais:** Writing – review & editing, Resources, Investigation, Data curation. **Oscar Juan-Vidal:** Writing – review & editing, Resources, Investigation, Data curation. **MPilar Diz-Taín:** Writing – review & editing, Resources, Investigation, Data curation. **Álvaro Taus:** Writing – review & editing, Validation, Investigation, Data curation. **Noemí Villanueva:** Writing – review & editing, Resources, Investigation, Data curation. **Cristina Bayona:** Writing – review & editing, Resources, Investigation, Data curation. **Margarita Amenedo:** Writing – review & editing, Resources, Investigation, Data curation. **Xabier Mielgo:** Writing – review & editing, Resources, Investigation, Data curation. **Esperanza Arriola:** Writing – review & editing, Resources, Investigation, Data curation. **Javier Baena:** Writing – review & editing, Resources, Investigation, Data curation.

Declaration of competing interest

AC Consulting fees: AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche/Genentech, Eli Lilly and Company, Novartis, Takeda, Merck Sharp & Dohme, and Bristol Myers Squibb; Research funding: Merck Sharp & Dome. Payment or honoraria: AstraZeneca, Boehringer-Ingelheim, Bayer, Pfizer, Roche, Novartis, Merck Sharp & Dohme, and Bristol Myers Squibb. Support for attending meetings and/or travel: Roche, Boehringer-Ingelheim, Pfizer, Merck Sharp & Dohme, and Bristol Myers Squibb. AG Consulting fees: AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche/Genentech, Eli Lilly and Company, Novartis, Takeda, Merck Sharp & Dohme, and Bristol Myers Squibb. Research funding: Merck Sharp & Dome. Payment or honoraria: AstraZeneca, Boehringer-Ingelheim, Bayer, Pfizer, Roche, Novartis, Merck Sharp & Dohme, and Bristol Myers Squibb. Support for attending meetings and/or travel: Roche, Boehringer-Ingelheim, Pfizer, Merck Sharp & Dohme, and Bristol Myers Squibb. MA Support for attending meetings and/or travel:BMS, MSD,Roche. JC Consulting fees: Astra Zeneca, Bristol Myers Squibb,

Hoffmann- La Roche,Merck Sharp and Dohme,Boehringer Ingelheim, Janssen,Lilly,Sanofi,Takeda,Pfizer,Glaxo. Payment or honoraria:Astra Zeneca,Bristol Myers Squibb,Hoffmann- La Roche,Merck Sharp and Dohme,Pfizer,Janssen,Takeda,Sanofi. Support for attending meetings and/or travel: Astra Zaneca,Merck Sharp and Dohme, Hoffmann- La Roche. Advisory Board: Astra Zeneca,Bristol Myers Squibb,Hoffmann-La Roche,Merck Sharp and Dohme,Glaxo,Janssen,Gilead, Sanofi. AA Personal fees: Janssen-Cilag; Takeda Oncology. Support for attending meetings and/or travel: MSD, Janssen-cilag, Roche Farma, BMS AE Payment or honoraria: Pharmamar, GSK, Roche, MSD, AstraZeneca, BMS, Takeda. Support for attending meetings and/or travel: MSD, Pharmamar, Astrazeneca, Boheringer, Takeda. Advisory Board: MSD, Roche, Astrazeneca. SA Consulting fees: Bristol-Myers-Squibb, MERCK, MSD, Grunenthal. Conference payment: Bristol-Myers-Squibb, MERCK. Payment for expert testimony: MERCK. Support for attending meetings and/or travel: MERK, MSD. Advisory Board: MERCK, MSD. AB Consulting fees: Takeda &Sanofi Payment or honoraria: AstraZeneca, Sanofi & Pfizer. Support for attending meetings and/or travel: Takeda, Roche & Janssen. VC Consulting fees: Roche, AstraZeneca, MSD, BMS, Takeda, Sanofi, Amgen. Payment or honoraria: Roche, BMS, MSD, AstraZeneca, Takeda, Pfizer, Janssen. Support for attending meetings and/or travel: AstraZeneca, Roche, MSD, Takeda. EN Grants: Roche, Pfizer, BMS and Merck Serono. Consulting fees: Roche, Bristol Myers Squibb, Merck Sharp Dohme, Merck-Serono, Sanofi, Pfizer, Lilly, Janssen, Amgen, Daiichi-Sankyo, Boehringer-Ingelheim, AstraZeneca, Takeda, Sanofi, Pierre Fabre, Qiagen, and Bayer. Payment or honoraria: Roche, Bristol Myers Squibb, Merck Sharp Dohme, Merck-Serono, Sanofi, Pfizer, Lilly, Janssen, Amgen, Daiichi-Sankyo, Boehringer-Ingelheim, AstraZeneca, Takeda, Sanofi, Pierre Fabre, Qiagen, and Bayer. Support for attending meetings and/or travel: Roche, Takeda, MSD and Pfizer. Advisory Board: Roche, Apollomics and MSD. NV Payment or honoraria: Pfizer & AstraZeneca. CB Payment or honoraria: Sanofi/Regeneron. BMS, AstraZeneca, Pfizer & Roche. Payment for expert testimony: MSD, Roche. Support for attending meetings and/or travel: Roche, MSD, Sanofi/Regeneron, Takeda, Lilly. MA Payment or Honoraria: AZ, Merck, PharmaMar. Support for attending meetings and/or travel: GSK, AZ & MERCK MC Payment or honoraria: Takeda. Support for attending meetings and/or travel: PhamaMar DI Payment or honoraria: Amgen, Janssen, AstraZenecaca, Novartis, BMS, Roche, MSD, Pfizer. Support For Attending Meetings And/Or Travel: AstraZeneca, MSD, Pfizer, Roche, Takeda. Advisory Board: Amgen, AstraZeneca, BMS, Roche, Janssen, Lilly, MSD, Pfizer, Sanofi. CA Payment or honoraria: MSD, Novartis, AstraZeneca, Sanofi, Pfizer. Support for attending meetings and/or travel:Roche, Pierre Fabre, Takeda. Advisory Board: AstraZeneca, BMS, Novartis OJ Consulting fees: Bristol-Myers Squibb, Roche/Genetech, AstraZeneca, Pfizer, Eli Lilly, Takeda, Janssen Payment or honoraria: Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche/Genentech, AstraZeneca, Pfizer, Eli Lilly, Takeda, Janssen. Support for attending meetings and/or travel: Takeda, Roche/Genentech, MSD PD Payment or honoraria: BMS, AstraZeneca, Roche, MSD, Takeda, Pfizer, Amgen. Support for attending meetings and/or travel: BMS, Roche, MSD, Takeda. Advisory Board: BMS, AstraZeneca, Boehringer Ingelheim. Other financial or non-financial interests: AstraZeneca, Roche, Mirati, Pfizer. AT Payment or honoraria: Roche, Pfizer, BMS, GSK, AZ, Sanofi. Support for attending meetings and/or travel: GSK XM Payment or honoraria: Novartis, Roche, Pfizer, Astra Zeneca, MSD. Support for attending meetings and/or travel: Roche, Lilly, MSD. Advisory Board: Pfizer, AstraZeneca. Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: Grupo Español Transversal de Tumores Huérfanos e Infrecuentes (GETTHI), Grupo Español de Terapias Inmuno-biológicas contra el Cancer (GETICA) EA Payment Honoraria: Bristol-Myers Squib, AstraZeneca, Amgem. Support for attending meetings and/or travel: Bristol-Myers Squibb, Pfizer, Roche The rest of the authors declare no competing interests.

Acknowledgments

LORLAPULM study (GECP 21/04) was sponsored by the SLCG Foundation and received funding from Pfizer through an independent research grant.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2025.100905.

References

[1] J.L. Schneider, J.J. Lin, A.T. Shaw, ALK-positive lung cancer: a moving target, Nat. Cancer 4 (3) (2023) 330–343.
[2] J.J. Lin, A.T. Shaw, Recent Advances in Targeting ROS1 in Lung Cancer, J. Thorac. Oncol. 12 (11) (2017) 1611–1625.
[3] L.E. Hendriks, K.M. Kerr, J. Menis, T.S. Mok, U. Nestle, A. Passaro, et al., Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆, Ann. Oncol. 34 (4) (2023) 339–357.
[4] S. Gendarme, O. Bylicki, C. Chouaid, F. Guisier, ROS-1 Fusions in Non-Small-Cell Lung Cancer: evidence to Date, Curr. Oncol. 29 (2) (2022) 641–658.
[5] R. Dziadziuszko, M.G. Krebs, F. De Braud, S. Siena, A. Drilon, R.C. Doebele, et al., Updated Integrated Analysis of the Efficacy and Safety of Entrectinib in Locally Advanced or Metastatic ROS1 Fusion-Positive Non-Small-Cell Lung Cancer, J. Clin. Oncol. 39 (11) (2021) 1253–1263.
[6] A.T. Shaw, G.J. Riely, Y.J. Bang, D.W. Kim, D.R. Camidge, B.J. Solomon, et al., Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001, Ann. Oncol. 30 (7) (2019) 1121–1126.
[7] A.T. Shaw, S.H. Ou, Y.J. Bang, D.R. Camidge, B.J. Solomon, R. Salgia, et al., Crizotinib in ROS1-rearranged non-small-cell lung cancer, N. Engl. J. Med. 371 (21) (2014) 1963–1971.
[8] Y.Y. Syed, Lorlatinib: first Global Approval, Drugs 79 (1) (2019) 93–98.
[9] B.J. Solomon, B. Besse, T.M. Bauer, E. Felip, R.A. Soo, D.R. Camidge, 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.
[10] A.T. Shaw, E. Felip, T.M. Bauer, B. Besse, A. Navarro, S. Postel-Vinay, et al., Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial, Lancet Oncol. 18 (12) (2017) 1590–1599.
[11] B.J. Solomon, T.M. Bauer, T.S.K. Mok, G. Liu, J. Mazieres, F. de Marinis, et al., Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study, The Lancet Respiratory Medicine (Baltimore) 11 (4) (2023) 354–366.
[12] A.T. Shaw, T.M. Bauer, F. de Marinis, E. Felip, Y. Goto, G. Liu, et al., First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer, N. Engl. J. Med. 383 (21) (2020) 2018–2029.
[13] A.T. Shaw, B.J. Solomon, R. Chiari, G.J. Riely, B. Besse, R.A. Soo, et al., Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial, Lancet Oncol. 20 (12) (2019) 1691–1701.
[14] Network NCC. Non-Small Cell Lung Cancer (Version 3.2025) [Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
[15] K. Arnaoutakis, Y. Wan, J. Elliott, M. Young, Y. Yin, K. Leventakos, et al., Real-World Treatment Patterns and Outcomes Across Three Lines of Therapy in Patients with ALK+ NSCLC, Adv. Ther. 41 (8) (2024) 3217–3231.
[16] S. Novello, J. Mazieres, I.J. Oh, J. de Castro, M.R. Migliorino, A. Helland, et al., Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study, Ann. Oncol. 29 (6) (2018) 1409–1416.
[17] E. Felip, A.T. Shaw, A. Bearz, D.R. Camidge, B.J. Solomon, J.R. Bauman, et al., Intracranial and extracranial efficacy of lorlatinib in patients with ALK-positive non-small-cell lung cancer previously treated with second-generation ALK TKIs, Ann. Oncol. 32 (5) (2021) 620–630.
[18] P.W. Sperduto, S. Mesko, J. Li, D. Cagney, A. Aizer, N.U. Lin, et al., Survival in Patients With Brain Metastases: summary Report on the Updated Diagnosis-Specific Graded Prognostic Assessment and Definition of the Eligibility Quotient, J. Clin. Oncol. 38 (32) (2020) 3773–3784.
[19] V.W. Zhu, Y.T. Lin, D.W. Kim, H.H. Loong, M. Nagasaka, H. To, et al., An International Real-World Analysis of the Efficacy and Safety of Lorlatinib Through Early or Expanded Access Programs in Patients With Tyrosine Kinase Inhibitor-Refractory ALK-Positive or ROS1-Positive NSCLC, J. Thorac. Oncol. 15 (9) (2020) 1484–1496.
[20] M. Alexander, J. Wei, S. Parakh, T. John, S. Kao, A. Nagrial, et al., LOREALAUS: LOrlatinib REAL-World AUStralian Experience in Advanced ALK-Rearranged NSCLC, JTo Clin. Res. Rep. 4 (4) (2023) 100490.
[21] S. Baldacci, B. Besse, V. Avrillon, B. Mennecier, J. Mazieres, P. Dubray-Longeras, et al., Lorlatinib for advanced anaplastic lymphoma kinase-positive non-small cell lung cancer: results of the IFCT-1803 LORLATU cohort, Eur. J. Cancer 166 (2022) 51–59.

[22] C. Britschgi, A. Addeo, M. Rechsteiner, R. Delaloye, M. Fruh, G. Metro, et al., Real-World Treatment Patterns and Survival Outcome in Advanced Anaplastic Lymphoma Kinase (ALK) Rearranged Non-Small-Cell Lung Cancer Patients, Front. Oncol. 10 (2020) 1299.
[23] N. Frost, P. Christopoulos, D. Kauffmann-Guerrero, J. Stratmann, R. Riedel, M. Schaefer, et al., Lorlatinib in pretreated ALK- or ROS1-positive lung cancer and impact of TP53 co-mutations: results from the German early access program, Ther. Adv. Med. Oncol. 13 (2021) 1758835920980558.
[24] Y. Goto, T. Shukuya, A. Murata, H. Kikkawa, B. Emir, R. Wiltshire, et al., Real-world therapeutic effectiveness of lorlatinib after alectinib in Japanese patients with ALK-positive non-small-cell lung cancer, Cancer Sci. (2023).
[25] M.J. Hochmair, H. Fabikan, O. Illini, C. Weinlinger, U. Setinek, D. Krenbek, et al., Later-Line Treatment with Lorlatinib in ALK- and ROS1-Rearrangement-Positive NSCLC: a Retrospective, Multicenter Analysis. Pharmaceuticals (Basel). 13 (11) (2020).
[26] N. Peled, R. Gillis, S. Kilickap, P. Froesch, S. Orlov, E. Filippova, et al., GLASS: global Lorlatinib for ALK (+) and ROS1 (+) retrospective Study: real world data of 123 NSCLC patients, Lung Cancer 148 (2020) 48–54.
[27] J.J. Lin, J.C. Horan, A. Tangpeerachaikul, A. Swalduz, A. Valdivia, M.L. Johnson, et al., NVL-655 Is a Selective and Brain-Penetrant Inhibitor of Diverse ALK-Mutant Oncoproteins, Including Lorlatinib-Resistant Compound Mutations, Cancer Discov. 14 (12) (2024) 2367–2386.
[28] A.E. Drilon, J.J. Lin, M.L. Johnson, C.S. Baik, L.G. Paz-Ares, B. Besse, et al., 1253O Phase I/II ALKOVE-1 study of NVL-655 in ALK-positive (ALK+) solid tumours, Annals of Oncology 35 (2024) S802–S8S3.
[29] N. Girard, S. Galland-Girodet, V. Avrillon, B. Besse, M. Duruisseaux, J. Cadranel, et al., Lorlatinib for advanced ROS1+ non-small-cell lung cancer: results of the IFCT-1803 LORLATU study, ESMo Open. 7 (2) (2022) 100418.
[30] A. Drilon, C.H. Chiu, Y. Fan, B.C. Cho, S. Lu, M.J. Ahn, et al., Long-Term Efficacy and Safety of Entrectinib in ROS1 Fusion-Positive NSCLC, JTo Clin. Res. Rep. 3 (6) (2022) 100332.
[31] Y.L. Wu, S. Lu, J.C. Yang, J. Zhou, T. Seto, M.J. Ahn, et al., Final Overall Survival, Safety, and Quality of Life Results From a Phase 2 Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced NSCLC, JTo Clin. Res. Rep. 3 (10) (2022) 100406.
[32] A. Drilon, D.R. Camidge, J.J. Lin, S.W. Kim, B.J. Solomon, R. Dziadziuszko, et al., Repotrectinib in ROS1 Fusion-Positive Non-Small-Cell Lung Cancer, N. Engl. J. Med. 390 (2) (2024) 118–131.
[33] M. Pérol, W. Li, N.A. Pennell, G. Liu, Y. Ohe, F.G.M. De Braud, et al., 1289P Pooled efficacy and safety from 2 pivotal phase II trials of taletrectinib in patients (Pts) with advanced or metastatic ROS1+ non-small cell lung cancer (NSCLC), Annals of Oncology 35 (2024) S821.
[34] B. Besse, A.E. Drilon, B.C. Cho, D.R. Camidge, J. Neal, C.C. Lin, et al., 1256MO Phase I/II ARROS-1 study of zidesamtinib (NVL-520) in ROS1 fusion-positive solid tumours, Annals of Oncology 35 (2024) S804–S8S5.
[35] A. Drilon, C. Jenkins, S. Iyer, A. Schoenfeld, C. Keddy, M.A. Davare, ROS1-dependent cancers - biology, diagnostics and therapeutics, Nat. Rev. Clin. Oncol. 18 (1) (2021) 35–55.
[36] S. Park, B.C. Ahn, S.W. Lim, J.M. Sun, H.R. Kim, M.H. Hong, et al., Characteristics and Outcome of ROS1-Positive Non-Small Cell Lung Cancer Patients in Routine Clinical Practice, J. Thorac. Oncol. 13 (9) (2018) 1373–1382.
[37] T. Patil, D.E. Smith, P.A. Bunn, D.L. Aisner, A.T. Le, M. Hancock, et al., The Incidence of Brain Metastases in Stage IV ROS1-Rearranged Non-Small Cell Lung Cancer and Rate of Central Nervous System Progression on Crizotinib, J. Thorac. Oncol. 13 (11) (2018) 1717–1726.
[38] S. Peters, A.T. Shaw, B. Besse, E. Felip, B.J. Solomon, R.A. Soo, et al., Impact of lorlatinib on patient-reported outcomes in patients with advanced ALK-positive or ROS1-positive non-small cell lung cancer, Lung Cancer 144 (2020) 10–19.
[39] E. Arriola, J. de Castro, R. Garcia-Campelo, B. Bernardez, R. Bernabe, J. Bruna, et al., Expert Consensus on the Management of Adverse Events of Lorlatinib in the Treatment of ALK+ Advanced Non-small Cell Lung Cancer, Clin. Drug Investig. 44 (8) (2024) 553–576.
[40] M. Rupp, F. Fanton-Aita, S. Snow, P. Wheatley-Price, B. Melosky, R.A. Juergens, et al., Lorlatinib Effectiveness and Quality-of-Life in Patients with ALK-Positive NSCLC Who Had Failed Second-Generation ALK Inhibitors: Canadian Real-World Experience, Curr. Oncol. 30 (7) (2023) 6559–6574.
[41] A.T. Shaw, B.J. Solomon, B. Besse, T.M. Bauer, C.C. Lin, R.A. Soo, et al., ALK Resistance Mutations and Efficacy of Lorlatinib in Advanced Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer, J. Clin. Oncol. 37 (16) (2019) 1370–1379.
[42] J.J. Lin, N.J. Choudhury, S. Yoda, V.W. Zhu, T.W. Johnson, R. Sakhtemani, et al., Spectrum of Mechanisms of Resistance to Crizotinib and Lorlatinib in ROS1 Fusion-Positive Lung Cancer, Clin. Cancer Res. 27 (10) (2021) 2899–2909.