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Advanced-stage ALK-positive non–small-cell lung cancer (NSCLC) patients: Real-world treatment patterns and outcomes from the Italian biomarker ATLAS database

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ABSTRACT

Background: Treatment of advanced *ALK* + NSCLC has improved with increasingly effective ALK tyrosine-kinase inhibitors (TKIs). We report *real-world* treatment patterns and outcomes from the Italian ATLAS registry.
Methods: Clinical-pathological and treatment data were retrospectively and prospectively collected from 37 Italian centers.
Results: 463 *ALK* + advanced NSCLC patients treated from 2019 to 2024 were included. 431 (93 %) patients received 1st line (1L) ALK TKIs, mostly alectinib (82.5 %). 1L treatment choice, reported in 142 cases, was driven by drug access as first (31 %) or subsequent lines (40.1 %) and by safety (21.8 %). Among 382 patients receiving 1L alectinib overall survival (OS) rate was 88.7 % and 73.3 % at 24 and 60 months, respectively. Median progression-free survival (mPFS) was 43.1 months (95 %CI: 29.5–57.0). Brain was a new site of progression in 11 (3.6 %) patients. Intracranial PFS rate was 73.1 % and 59.1 % at 24 and 36 months with a 64.7 % intracranial response rate. Grade $\geq$ 3 adverse events occurred in 41 (10.7 %) patients, mainly hepatic toxicity (13, 3.4 %) and asthenia (5, 1.3 %). At progression tissue and/or liquid biopsy were performed in 28 (23.5 %) and 20 (16.8 %) cases, respectively. Out of 80 patients receiving 2nd line therapy after alectinib, 67 (83.8 %) received lorlatinib achieving mPFS 7.5 (95 % CI: 6.2–8.8) and mOS 26.4 months (95 % CI: 19.1–33.7). 17 (15.5 %) patients died without second line therapy.
Conclusions: Real-world data confirm the effectiveness and safety of alectinib, used as preferred upfront ALK-TKI. The recent 1L lorlatinib approval might change this scenario. Tissue/liquid biopsy at disease progression are underperformed in clinical practice.

1. Background

Lung cancer represents the leading cause of cancer-related death worldwide [1]. Anaplastic lymphoma kinase (*ALK*) gene rearrangements have been identified for the first time in 2007 and the most common *ALK* partner is the echinoderm microtubule-associated protein-like 4 (*EML4*) whose rearrangement generates the EML4-ALK fusion protein [2]. *ALK* rearrangements could be detected in 5–7 % of Non-Small Cell Lung Cancer (NSCLC) patients [2], more frequently in youngers and never smokers, adenocarcinomas, with solid pattern and signet ring cell type tumors and a higher incidence of brain metastases [3,4].

In the last decades many improvements have been made in the treatment landscape of patients with advanced oncogene addicted NSCLC. Crizotinib was the first-in-class ALK tyrosine kinase inhibitor (TKI) approved for the treatment of patients with ALK-positive metastatic NSCLC. Crizotinib is an oral competitive ATP inhibitor of ALK, MET and ROS1 tyrosine kinases that showed an improved objective response rate (ORR) and median progression free survival (mPFS) compared to chemotherapy in both pretreated and treatment-naïve patients [5–7]. In order to overcome resistance mechanisms to crizotinib, more potent second-generation ALK TKIs, such as alectinib, brigatinib and ceritinib, have been developed and approved for the second-line treatment after failure to crizotinib [8–10]. Alectinib, brigatinib, ceritinib and ensartinib (the last one not approved by European Medicines Agency) showed to be effective also as first-line therapy, compared to crizotinib [11–14]. In particular, the global phase 3 ALEX trial showed the superiority of first-line alectinib versus crizotinib, with a prolonged mPFS of 34.8 versus 10.9 months (hazard ratio −HR- 0.43, 95 % confidence interval −CI- 0.32–0.58), a 5-year median overall survival (mOS) rate of 62.5 % (95 % CI 54.3–70.8) with alectinib vs 45.5 % (95 % CI 33.6–57.4) with crizotinib and a higher central nervous system (CNS) activity [15]. The efficacy of alectinib was confirmed also in Asiatic patients population thanks to the results of the J-ALEX and ALESIA trials [16,17]. Alectinib has also been recently introduced in early stage NSCLC treatment as adjuvant therapy for 24 months after surgery thanks to the results of the phase 3 study ALINA [18]. Furthermore, in the ALTA-1L trial patients treated with brigatinib performed a better outcome compared to crizotinib treated patients and brigatinib showed a higher intracranial activity (4-year intracranial PFS of 46 % vs 33 %) [19].

More recently, the third-generation ALK-TKI lorlatinib has been introduced in the treatment landscape of ALK-positive NSCLC patients for its major potency, its higher coverage of *ALK* mutations including the most common ALK G1202R resistance mutation, and its better permeability of the blood brain barrier. In the phase 3 CROWN trial, with a median follow-up of 60.2 months in the lorlatinib group and of 55.1 in the crizotinib group, the mPFS was not reached (NR) (95 % CI, 64.3 to NR) with lorlatinib versus 9.1 months (95 % CI, 7.4 to 10.9) with crizotinib [20]. Time to intracranial progression was significantly longer with lorlatinib compared with crizotinib (median NR vs 16.4 months; HR 0.06, 95 % CI 0.03, 0.12). At about 60 months, 92 % of patients treated with lorlatinib were free from intracranial progression, compared with 21 % of patients in the crizotinib arm [20].

In Italy, the regulatory agency Agenzia Italiana del Farmaco (AIFA) initially restricted lorlatinib prescription to those patients progressed to first-line alectinib or ceritinib or after progression to crizotinib and almost another ALK-TKI. Only recently, since December 2023, lorlatinib

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approval for naïve patients has been extended by AIFA [21].

Here we report the treatment patterns and outcomes of ALK-positive advanced NSCLC from the Italian real-world registry ATLAS.

2. Methods

2.1. Study design

This is a multicenter retrospective and prospective observational real-world study conducted on patients with advanced-stage NSCLC harboring *ALK* rearrangements included in the ATLAS Italian real-world registry. Eligible patients were adult (age ≥ 18 years), with histologically or cytologically confirmed diagnosis of advanced NSCLC (stage IIIB/C or IV according to the 8th version of the American Joint Committee on Cancer/International Association for the Study of Lung Cancer TNM Staging System) positive for *ALK* translocations, as determined by validated assays performed in certified local laboratories. All the enrolled patients were included in the ATLAS real-world registry and signed and dated the ATLAS Informed Consent & privacy Form (ICF) in accordance with Italian requirements. We collected clinical, pathological, and molecular data as well as treatment effectiveness and safety. Data were extracted from patients' medical charts and/or electronic healthcare records across 37 Italian Centers participating to the ATLAS real-world registry and were subsequently archived by using a specific electronic case report form (eCRF) available at the investigators' sites. Details about physician's reason for the choice of the specific ALK-TKI drug were collected, as well as the treatment choice in second or further lines. Tumor response according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and data about treatment-related adverse events (TRAEs) with their grade, according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, and their relationship with ALK-TKIs treatment were recorded. The study was conducted in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice and the Declaration of Helsinki. The ATLAS protocol was previously approved by the Independent Ethic Committee of the coordinating center at University of Turin (ethics approval number: 0006981) and then at the local Ethic Committees of all the participating centers.

2.2. Study objectives

The primary objective of this study was to describe the clinical-pathological and molecular baseline characteristics of patients with ALK-positive NSCLC and to depict the therapeutic pathway and physicians' reasons for the choice of the ALK-TKIs sequence.

The secondary objectives of the study included the assessment of the effectiveness of the most frequently used first-line treatment in ALK-positive advanced NSCLC patients (alectinib). The treatment outcomes observed were the ORR, the disease control rate (DCR), the intracranial ORR (icORR), the intracranial DCR (icDCR), the mPFS, and the mOS.

Other secondary objectives included the assessment of the safety profile of alectinib, the assessment of the pattern of disease progression to alectinib, as well as the post-progression diagnostic-therapeutic pathway.

2.3. Statistical analyses

The baseline clinical-pathological and molecular patients' characteristics, as well as the treatments administered, the progression pattern and the loco-regional treatments performed have been summarized by descriptive analysis, including means, standard deviations, medians, quartiles, and absolute or relative frequencies (with their respective two-sided 95 % CI limits, where relevant), according to the specific variables.

Statistical analysis was performed through SPSS Statistics software version 20 (IBM, Armonk, New York, USA). The ORR has been defined as the proportion of participants having either complete response (CR) or partial responses (PR) as best overall response assessed by investigators according to RECIST v1.1, whereas the DCR has been defined as the proportion of participants having CR, PR or stable disease (SD) as best response. Similarly, icORR and icDCR have been described for the intracranial best response to ALK-TKIs according to RANO criteria. The mPFS has been defined as the time from the date of treatment start until either disease progression or death due to any cause, whichever occurs first, whereas the OS has been defined as the time from the date of treatment start to death due to any cause. The mPFS and mOS were estimated using the Kaplan-Meier method. Medians and two-sided 95 % CI have been calculated, and Kaplan-Meier plots for both mPFS and mOS have been provided as appropriate, with the use of the log-rank test for comparisons and a p-value < 0.05 set as threshold for statistical significance. The χ^2, Mann-Whitney, or Fisher exact test and multiple logistic regression were used for correlation analysis. The log-rank test and Cox proportional hazard model were applied to identify the impact of each clinical-pathological features on outcome.

Finally, we reported AEs with their grade according to the CTCAE version 5.0. Descriptive analysis about patients experiencing dose reductions or interruptions have also been collected reporting their percentages.

3. Results

3.1. Patients' characteristics

From July 2019 to March 2024 a total of 463 advanced ALK positive NSCLC patients were considered eligible and included in the analysis across 37 Italian centers. Patients' and disease's characteristics are summarized in Table 1. Median age at diagnosis was 61 (range 21–89) years. Most patients were females (n = 264, 57.0 %) and never smokers (n = 267, 57.7 %). The percentage of patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1 and ≥ 2 was 51.8 %, 35.0 % and 6.7 %, respectively. Lung was the most common metastatic site (43.6 %), followed by bone (39.7 %) and pleura (38.2 %). 121 (26.1 %) patients had brain/central nervous system (CNS) metastases at

Table 1
Patients' and disease's characteristics of the ITT population (N = 463).

Patients' Characteristics	
Age in years: median (range)	61 (21–89)
Age group, years, No (%)	
<70 years	355 (76.7)
≥70 years	108 (23.3)
Gender – N (%)	
Male	199 (43.0 %)
Female	264 (57.0 %)
History of smoking use – N (%)	
Never	267 (57.7 %)
Ex or current	162 (35.0 %)
Not available	34 (7.3 %)
ECOG-Performance Status – N (%)	
0	240 (51.8 %)
1	162 (35 %)
2	25 (5.4 %)
3	6 (1.3 %)
Not available	30 (6.5 %)
Histology, N (%)	
Adenocarcinoma	447 (96.5 %)
Squamous cell carcinoma	6 (1.3 %)
Other	4 (0.9 %)
Metastatic sites at diagnosis, N (%)	
Lung	202 (43.6 %)
Pleura	177 (38.2 %)
Brain	121 (26.1 %)
Liver	79 (17.1 %)
Bone	184 (39.7 %)
Adrenal gland	44 (9.5 %)

baseline. The most frequent histological subtype was adenocarcinoma (96.5 %). Tumor tissue biopsy was the most commonly used specimen type (n = 379, 81.9 %). For determining the ALK status DNA/RNA next-generation sequencing (NGS) was the most common testing method (n = 201, 43.4 %), followed by polymerase chain reaction (PCR) (n = 141, 30.5 %), immunohistochemistry (IHC) (n = 65, 14.0 %), and fluorescence in situ hybridization (FISH) (n = 51, 11.0 %). In 36 cases (7.8 %), more than one method was used and in 44 cases (9.5 %), the testing method was not reported. Concomitant molecular alterations were detected in 25 (5.4 %) cases with *TP53* mutations identified in 7 (1.5 %) patients. Tumor PD-L1 expression was ≥ 50 %, 1–49 %, <1% in 27.0 %, 36.1 %, 21.0 % of cases, respectively.

3.2. Anticancer treatments and outcomes in the intention-to-treat population

All the patients received at least one line of systemic anticancer therapy; treatment patterns are described in Fig. 1A. Most of them received 1st line ALK TKI: alectinib (n = 382, 82.5 %), crizotinib (n = 30, 6.5 %), brigatinib (n = 16, 3.5 %), lorlatinib (n = 2, 0.4 %), ceritinib (n = 1, 0.2 %). First-line chemotherapy +/- immunotherapy was administered in 30 (6.4 %) patients and 2 (0.4 %) patients were treated within clinical trials. Factors driving 1st line treatment choice were reported in 142 cases and were mainly related to drug access as first (31.0 %) or subsequent lines (40.1 %) according to regulatory indications, and safety profile (21.8 %) (Fig. 1B). Median follow-up was 26 months. With 181 events, the mPFS was 33.3 months in the entire population (95 %CI: 26.7–40.0). At the time of analysis mOS was not reached, with 65 events; OS rate was 88.4 % and 74.8 % at 24 and 60 months, respectively (Fig. 2A). The HR for PFS and death in patients with ECOG PS 1, compared to those with ECOG PS 0, was 1.99 (95 % CI, 1.46–2.73) and 2.34 (95 % CI, 1.37–4.01), respectively; HR for PFS and death was 1.79 (95 % CI, 1.10–2.93) and 2.67 (95 % CI, 1.30–5.46) in patients with baseline liver metastases (Supplementary Table 1).

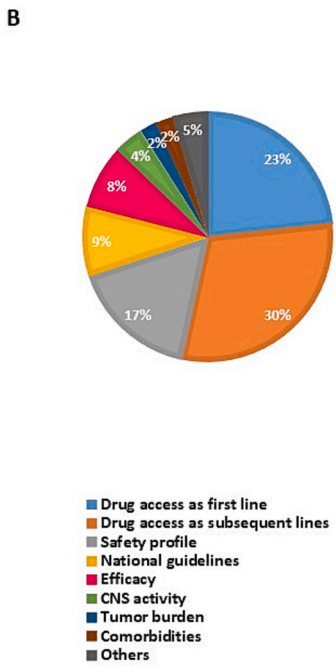

Fig. 1b. Factors driving first line treatment choice (N = 142) (B).

3.3. First line alectinib

3.3.1. Patients and outcomes

382 (82.5 %) patients received 1st line alectinib. Median age was 60 (range 21–89) years, 222 patients (58.1 %) were female and 221 (57.9 %) never smokers. The percentage of patients with ECOG PS 0, 1 and ≥ 2 was 51.0 %, 35.1 % and 7.1 %, respectively; 93 (24.3 %) patients had brain/CNS metastases at baseline. Concomitant molecular alterations were detected in 22 cases (5.8 %), with *TP53* mutations identified in 7

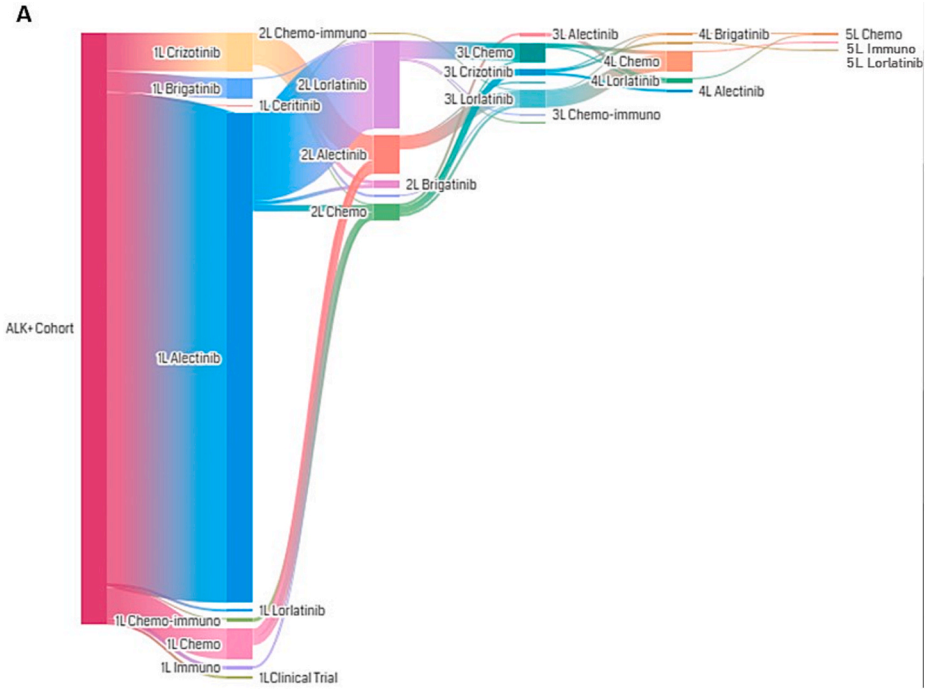

Fig. 1a. Treatment patterns in the analyzed population (A). Sankey diagram showing treatment sequences for 463 patients with ALK-positive aNSCLC. From left to right shows flow of patients from first-line of treatment (1L), second-line (2L), third-line (3L), fourth-line (4L), and fifth line (5L). ALK, anaplastic lymphoma kinase; aNSCLC, advanced NSCLC; Chemo, chemotherapy; Immuno, immunotherapy;

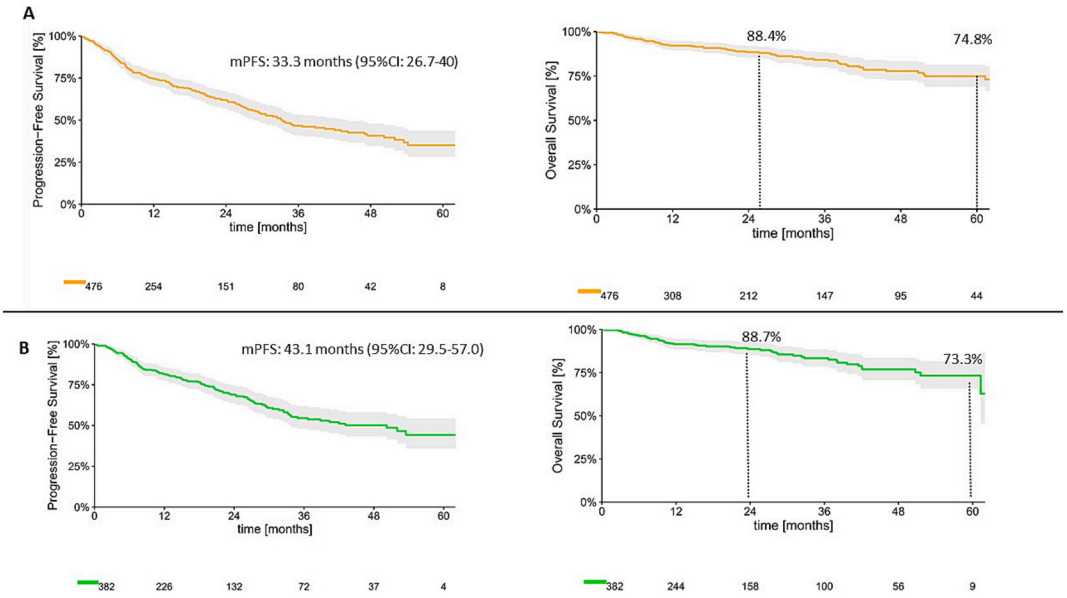

Fig. 2. Kaplan Meier curves for PFS and OS in the overall analyzed population (N = 463) (**A**) and in patients receiving 1st line alectinib (n = 382) (**B**). PFS and OS were measured in months from the start of treatment.

cases (1.8 %). ORR was 74.6 % and DCR was 88.7 % (Table 2). With 119 events, mPFS was 43.1 months (95 %CI: 29.5–57.0). At the time of analysis mOS was not reached with 51 events occurred; OS rate was 88.7 % and 73.3 % at 24 and 60 months, respectively (Fig. 2B). The HR for PFS was 2.21 (95 % CI, 1.50–3.26) in patients with ECOG PS 1 and 1.97 (95 % CI, 1.10–3.53) in the presence of baseline liver metastases (Supplementary Table 2).

Intracranial activity data were available for 85 out of 93 patients with brain metastases. The CNS response rate was 59.1 %, with 30 (32.2 %) patients experiencing an intracranial CR and 25 (26.9 %) a PR. The icDCR was 86.0 % (Table 2). A total of 8 patients (8.6 %) had received prior local CNS treatment [surgery and radiotherapy were carried out in three (3.2 %) and five (5.4 %) cases respectively, with whole brain radiotherapy performed only in two cases (2.2 %)]. The intracranial mPFS has not been reached; PFS rate was 73.1 % and 59.1 % at 24 and 36 months, respectively. In the group of 289 patients without baseline CNS metastases, brain was recorded as a new site of progression in 11 (3.8 %) cases.

3.3.2. *Safety analysis*

The incidence of treatment-related toxicities is summarized in Table 2. Any grade TRAEs with alectinib were reported in 58.6 % of cases, whereas 41 (10.7 %) patients experienced grade 3 or higher TRAEs, mostly hepatic toxicity (13, 3.4 %) and asthenia (5, 1.3 %). A grade 5 (fatal) sepsis was reported in one patient and was considered to be related to treatment by the investigator. TRAEs led to a dose reduction in 63 (16.5 %) of patients. Six patients (1.6 %) permanently discontinued treatment with alectinib because of toxicity, with pneumonitis and hepatic injury occurring in 3 (0.8 %) and 2 (0.5 %) patients, respectively.

3.3.3. *Patterns of disease progression and subsequent treatments*

At the time of data analysis 110 (28.8 %) patients progressed to first line alectinib. 42 (38.2 %) received alectinib beyond progression. 25 of them (22.7 %) were treated with radiotherapy as local therapy on the site of disease progression with alectinib continuation (Supplementary Table 3).

80 (72.7 %) patients switched to a second line systemic treatment. 13 (11.8 %) patients who received alectinib beyond progression were still on first-line treatment at the time of data analysis. 17 (15.5 %) patients died without receiving any second line therapy. The most common sites of disease progression were lung (32.8 %), brain (24.4 %) and lymphnodes (17.6 %). Tissue rebiopsy was performed in 28 (23.5 %) and liquid biopsy in 20 (16.8 %) cases, with 5 patients undergoing both tissue and liquid biopsy; *ALK* G1202R mutation was the most frequent mechanism of resistance identified on tissue rebiopsies (15 %) (Fig. 3). Further treatment was received by 23 out of 40 patients (57.5 %) who progressed to second-line therapy.

In 67 (83.8 %) cases, lorlatinib was the subsequent treatment after alectinib failure. Best response was available for 50 patients, with a CR in one patient (2.0 %), a PR in 20 patients (40.0 %), SD in 21 patients (42.0 %), and disease progression in 8 patients (16.0 %); 17 patients were non-evaluable. mPFS to second line lorlatinib was 7.5 months (95 % CI: 6.2–8.8) and mOS, calculated from the start of second line lorlatinib, was 26.4 (95 % CI: 19.1–33.7) months.

Among the 13 (16.3 %) patients receiving second line therapy other than lorlatinib, mPFS was 7.3 months (95 % CI: 2.8–11.8) and mOS 26.5 months (95 % CI: 2.1–50.8).

4. Discussion

ALK TKIs have transformed the natural history of ALK-positive NSCLC since the crizotinib era. Subsequently, alectinib, brigatinib, ensartinib, and lorlatinib have demonstrated improved responses, better CNS outcomes, and prolonged PFS and OS, thus representing effective frontline treatment options [5–17,19–20].

In this evolving scenario, our study describes real-world treatment patterns and outcomes of patients with advanced/metastatic NSCLC harboring *ALK* rearrangements within the Italian ATLAS registry. The baseline characteristics of patients were consistent with the known profile reported in literature, with more than half being female (57.0 %), mostly never smoker (57.7 %) and with adenocarcinoma histology (96.5 %). The percentage of patients with ECOG PS 0–1 was 87 %. The median age was 61 years, slightly higher than that reported in randomized trials, and a lower percentage of patients (26.1 %) presented brain metastases at diagnosis. This reflects a less selected population and highlights the potential underdiagnosis of brain metastases due to the non-systematic execution of baseline brain magnetic resonance imaging (MRI) [22,23].

All patients received at least one line of systemic anticancer therapy, with the majority (93.6 %) receiving a first-line ALK TKI. In 30 cases (6.4 %), ALK TKI was administered in subsequent lines due to delays in

Table 2
1st line alectinib: objective responses and safety.

Objective responses to 1st line alectinib (N = 382)	
ORR	285 (74.6 %)
DCR	339 (88.7 %)
Best response	
CR	33 (8.6 %)
PR	252 (66 %)
SD	54 (14.1 %)
PD	17 (4.5 %)
NE	26 (6.8 %)
CNS activity (N = 93)	
icORR	55 (59.1 %)
icDCR	80 (86 %)
Intracranial best response	
CR	30 (32.2 %)
PR	25 (26.9 %)
SD	25 (26.9 %)
PD	5 (5.4 %)
NE	8 (8.6 %)
Treatment-Related Adverse Events (TRAEs)[a] with 1L alectinib (N = 382)	
Any grade TRAEs[a]	
Grade 1	117 (30.6 %)
Grade 2	66 (17.3 %)
Grade 3	38 (9.9 %)
Grade 4	2 (0.5 %)
Grade 5	1 (0.3 %)
Grade 3 TRAEs[a]	
Blood bilirubin increased	7 (1.8 %)
Transaminases increased	6 (1.6 %)
Fatigue	5 (1.3 %)
Anemia	4 (1 %)
Edema	4 (1 %)
Blood creatine phosphokinase increased	2 (0.5 %)
Skin disorders	2 (0.5 %)
Pneumonitis	2 (0.5 %)
Neutrophil count decreased	1 (0.3 %)
Creatinine increased	1 (0.3 %)
Hypokalemia	1 (0.3 %)
Hyponatremia	1 (0.3 %)
Diarrhea	1 (0.3 %)
Electrocardiogram QT corrected interval prolonged	1 (0.3 %)
Weight gain	1 (0.3 %)
Grade 4 TRAEs	
Creatinine increased	1 (0.3 %)
Pneumonitis	1 (0.3 %)
Grade 5 TRAEs	
Sepsis	1 (0.3 %)
TRAEs leading to dose reduction	63 (16.5 %)
TRAE leading to definitive discontinuation of therapy[a]	6 (1.6 %)
Pneumonitis	3 (0.8 %)
Hepatic toxicity	2 (0.5 %)
Electrocardiogram QT corrected interval prolonged	1 (0.3 %)
Edema	1 (0.3 %)

ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluated; CNS, central nervous system; ic, intracranial.

[a] Some patients reported multiple TRAEs.

molecular reporting or missed detection of *ALK* rearrangements at diagnosis. Efficacy data from our real-world study align with literature, confirming the favorable outcomes of this subgroup compared to patients with non-oncogene addicted NSCLC. With a median follow-up of 26 months, the mPFS in the overall analyzed population was 33.3 months (95 % CI: 26.7–40.0), while the mOS was not reached. The overall survival rates were 88.4 % and 74.8 % at 24 and 60 months, respectively. Liver involvement and ECOG PS emerged as the only reliable clinical predictor of survival outcomes. Patients with liver metastases at baseline or ECOG PS 1 had significantly lower mPFS and mOS, consistent with previously reported data [24]. Unfortunately, the prognostic and predictive impact of concomitant molecular alterations could not be evaluated due to the small sample size.

Alectinib was the most commonly preferred first-line treatment (82.5 %), followed by second-line lorlatinib (83.8 %), consistent with recent real-world analyses [25]. Factors influencing first-line treatment choice were reported in 142 cases and were primarily related to drug access, either as a first-line (31 %) or subsequent-line (40.1 %), according to regulatory indications, as well as to safety profile (17 %). It is important to highlight that in Italy, AIFA initially restricted the use of lorlatinib to patients who had progressed on first-line alectinib or ceritinib, or after progression on crizotinib followed by at least one other ALK-TKI. Moreover, the use of lorlatinib as a first-line treatment was authorized only in December 2023 [21]. In this context, considering that patients were enrolled between July 2019 and March 2024, the predominance of alectinib as first-line therapy in our cohort likely reflects both the regulatory limitations on lorlatinib use and physicians' greater familiarity with alectinib at the time. However, the mPFS with first line alectinib in this real-world study is 43.1 months and is consistent with findings from other real-world analyses and higher than that observed in the ALEX trial, which reported median PFS of 34.8 months [95 % CI 17.7-not evaluable (NE)] (ALEX) [12,15] This difference may be attributed to less standardized imaging and follow-up schedules in real-world settings, as well as to the potential variability in radiologic assessments across institutions.

The mPFS with second-line lorlatinib was 7.5 months, which is slightly longer than data from other analyses where patients had received one or more prior systemic treatment lines.[27] It should be noted that the duration of this sequential therapy appears shorter than the mPFS observed with first-line lorlatinib. Furthermore, the mPFS with second line lorlatinib is remarkably modest compared to the first-line results of the CROWN trial, where mPFS remained unreached after 5 years of follow-up, with the longest reported PFS in advanced NSCLC to date, confirming lorlatinib as the most effective upfront therapy for patients with ALK-positive disease. [20] In the absence of clinical trials directly comparing first-line lorlatinib with the alectinib–lorlatinib sequence, it remains speculative, but plausible, that the greatest clinical benefit may be achieved when lorlatinib is used upfront. This is supported by the prolonged mPFS observed in the CROWN trial, suggesting that the earlier use of lorlatinib, before the emergence of compound ALK resistance mutations or more aggressive disease biology, might maximize its therapeutic potential.

Indeed, among patients who progressed on first-line alectinib in this study, 15.5 % died without receiving any second-line therapy. These findings confirm the high attrition rate observed in other studies of ALK-positive advanced NSCLC and further underscore the importance of using the most effective ALK TKI as upfront therapy.[24,28] This approach, rather than a sequential treatment strategy—where the benefit may be lost in few patients who are still eligible for further active treatment—could maximize the opportunity to achieve durable disease control for the largest number of patients with ALK-positive advanced NSCLC. Considering that differences in safety profiles and clinicians' greater familiarity with alectinib may continue to influence its preferential use in the first-line setting in the near future, improvements in the learning curve of safety management and the observation of long-term effectiveness in real-world practice will gradually position lorlatinib as the preferred first-line option.

Ideally, second- and subsequent-line therapies should be guided by the identification of acquired resistance mechanisms. However, our study found that tissue rebiopsy was performed in only 23.5 % of cases and liquid biopsy in 16.8 % of cases among patients who progressed on first-line alectinib, with ALK G1202R emerging as the most frequent resistance mechanism, as expected.[29] The underperformed tissue or liquid biopsy at the time of progression has also been reported in other recent real world analyses.[26] This trend likely reflects several challenges, including limited rebiopsy access, the current lack of standardized treatment strategies based on resistance mechanisms in ALK-positive NSCLC and the different drug development compared to other targeted therapies, such as EGFR TKIs, where the presence of specific resistance mutations—like EGFR T790M (in earlier-generation TKIs) or MET amplification—guides subsequent treatment decisions, including

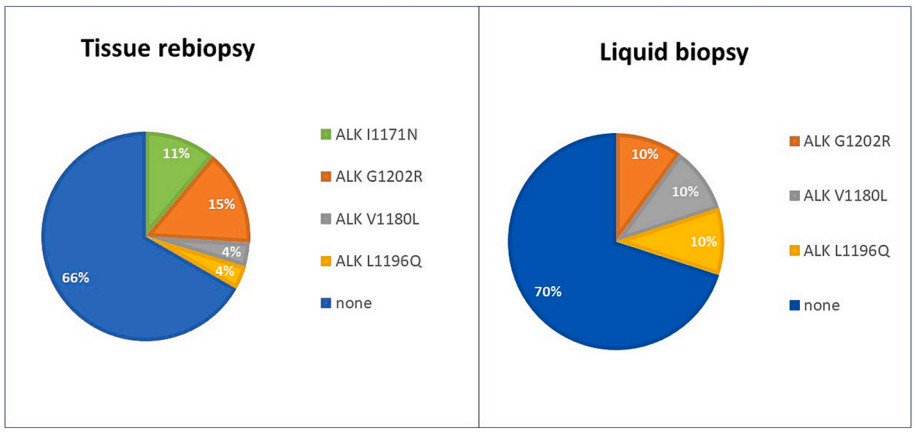

Fig. 3. Resistance mutations on rebiopsy/liquid biopsy in patients progressing on first-line alectinib. Tissue rebiopsy was performed in 28 (23.5%) and liquid biopsy in 20 (16.8%) cases.

switching to third-generation TKIs like osimertinib or exploring combination therapies.[30] Nonetheless, rebiopsy remains important for several reasons. First, the presence of specific resistance mutations, such as ALK G1202R, may inform the use of next-generation ALK TKIs like lorlatinib, which has shown activity against a broad spectrum of ALK resistance mutations, including G1202R. [31] Second, the comprehensive genomic profiling (CGP) can reveal off-target resistance mechanisms (e.g., MET or EGFR alterations, KRAS mutations, or histologic transformation), which might open the door to targeted therapies or enrollment in biomarker-driven clinical trials.[32] It is important to underline that in ALK-positive disease, multiple ALK resistance mutations or complex mechanisms may coexist, not always leading to actionable mutations.[29] However, while data are still emerging, the identification of actionable alterations at progression could offer therapeutic opportunities beyond empiric treatment switches. Therefore, promoting molecular reassessment at progression, even if not yet fully standardized, could help tailor treatment strategies and improve outcomes in selected patients.

Furthermore, in our analysis CNS activity was recognized as the most important factor for first line treatment choice by 4 % of clinicians. It is well established that brain metastases cause significant threats to quality of life and survival for patients with advanced NSCLC, especially ALK-positive NSCLC, which appears to have a particular tropism toward CNS.[33] In our analysis we were able to demonstrate the benefit of first line alectinib in terms of CNS activity as well. Alectinib showed an icDCR of 86 % and an icPFS rate of 73.1 % and 59.1 % at 24 and 36 months, respectively, which aligns with CNS activity reported in the ALEX study.[34] It is also worth noting that only the 8.6 % of patients had received prior local CNS treatment before alectinib treatment, in line with the recommended approach of avoiding potentially toxic local treatments when a drug penetrating blood–brain barrier is available. [35] It would be interesting to investigate whether CNS activity would have been more frequently prioritized as the main determinant for first-line treatment choice if clinicians had been surveyed after the first-line approval of lorlatinib, given its remarkable intracranial efficacy demonstrated in the CROWN trial.[20].

In conclusion, our study represents a real snapshot about NSCLC with *ALK* rearrangements in Italy. Our data confirms the favorable outcomes of this molecularly-defined subgroup in a real-world setting, emphasizing the importance of early molecular testing and prompt targeted treatment. This study has several limitations due to its retrospective nature. Potential reporting and information biases must be considered. The heterogeneity of the methodologies used for ALK rearrangement detection, with NGS applied in only 43.34 % of cases and no detailed information available on the specific assays used, impairs the possibility of drawing biological conclusions. The sample size limits comparisons between patients receiving first-line alectinib and those receiving other treatments. Additionally, the described first-line treatment choices may not fully reflect the current ALK treatment landscape, given the recent inclusion of lorlatinib as an upfront treatment option. However, the study is prospectively ongoing, and future updates may help capture how clinicians' treatment preferences evolve in response to the expanding therapeutic landscape for ALK-positive NSCLC. Nevertheless, these data are valuable for contextualizing the current treatment algorithm for ALK-positive NSCLC patients in a rapidly evolving landscape and provide a potential comparator for future approaches in the dynamic and changing treatment patterns of ALK-positive NSCLC.

CRediT authorship contribution statement

Maria Lucia Reale: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Daniela Scattolin:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Antonio Vitale:** Validation, Writing – review & editing. **Francesco Passiglia:** Data curation, Supervision, Validation, Writing – review & editing. **Salvatore Grisanti:** Validation, Writing – review & editing. **Marianna Macerelli:** Validation, Writing – review & editing. **Domenico Galetta:** Supervision, Validation, Writing – review & editing. **Claudio Sini:** Validation, Writing – review & editing. **Gabriele Minuti:** Validation, Writing – review & editing. **Fabrizio Citarella:** Validation, Writing – review & editing. **Elisa Roca:** Validation, Writing – review & editing. **Francesco Agustoni:** Validation, Writing – review & editing. **Alessandra Dodi:** Validation, Writing – review & editing. **Diego Cortinovis:** Validation, Writing – review & editing. **Lorenzo Belluomini:** Validation, Writing – review & editing. **Serena Ricciardi:** Validation, Writing – review & editing. **Antonello Veccia:** Validation, Writing – review & editing. **Elio Gregory Pizzutilo:** Validation, Writing – review & editing. **Vieri Scotti:** Validation, Writing – review & editing. **Greta Alì:** Validation, Writing – review & editing. **Francesca Mazzoni:** Validation, Writing – review & editing. **Alessandro Russo:** Validation, Writing – review & editing. **Daniele Pignataro:** Validation, Writing – review & editing. **Alessandra Bulotta:** Validation, Writing – review & editing. **Pierluigi Piovano:** Validation, Writing – review & editing. **Concetta Sergi:** Validation, Writing – review & editing. **Anna Bettini:** Validation, Writing – review & editing. **Carlo Genova:** Validation, Writing – review & editing. **Alberto Pavan:** Validation, Writing – review & editing. **Hector José Soto Parra:** Visualization, Writing – review & editing. **Cinzia Ortega:** Validation, Writing – review & editing. **Daniele Pozzessere:** Validation, Writing – review & editing. **Tiziana Vavalà:** Validation, Writing – review & editing. **Rita Chiari:** Validation, Writing – review & editing. **Cristina Zannori:** Validation, Writing – review & editing. **Alessandro D'Aveni:**

Validation, Writing – review & editing. **Giulia Meoni:** Validation, Writing – review & editing. **Diana Giannarelli:** Formal analysis, Methodology, Visualization, Writing – review & editing. **Umberto Malapelle:** Conceptualization, Supervision, Validation, Writing – review & editing. **Silvia Novello:** Conceptualization, Supervision, Validation, Writing – review & editing. **Emilio Bria:** Supervision, Validation, Writing – review & editing. **Giulia Pasello:** Conceptualization, Formal analysis, Funding acquisition, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2025.108762.

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