



Original research

Efficacy of alectinib for ALK-positive NSCLC according to tumor burden and body mass index: A pooled analysis of the randomized phase III trials ALEX and J-ALEX

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ABSTRACT

Background: Although first-line alectinib is highly effective, outcomes in ALK-positive NSCLC remain variable. **Methods:** We conducted an individual patient-level pooled analysis of the phase III ALEX (NCT02075840) and J-ALEX (JapicCTI-132316) trials to explore new prognostic and predictive factors. The primary endpoint was PFS. Multivariate Cox and random effects models accounted for trials independence. Baseline characteristics analyzed included high vs. low tumor burden (sum of target lesions by RECIST v1.1 above/below the median) and body mass index (BMI).

Results: 500 patients were included (alectinib n = 249, crizotinib n = 251). Baseline characteristics were balanced between the two arms. Median follow-up was 17.1 months. Alectinib compared to crizotinib improved PFS (HR 0.41, 95%CI 0.31–0.55, p < 0.001) but not OS (HR 0.80, 95%CI 0.50–1.28, p = 0.353). In the whole population, high tumor burden correlated with shorter PFS (HR 1.88, 95%CI 1.44–2.45, log-rank p < 0.001) and OS (HR 2.24, 95%CI 1.40–3.58, log-rank p < 0.001), confirmed in multivariate analysis (PFS HR 1.66, 95%CI 1.26–2.20, p < 0.001). Significant interaction was found between treatment and tumor burden in PFS cox model (p for interaction=0.002). The PFS benefit of alectinib vs. crizotinib was greater in low tumor burden (HR 0.25, 95%CI 0.16–0.41, p < 0.001) than in high tumor burden (HR 0.52, 95%CI 0.36–0.76, p = 0.001). In multivariate analysis, BMI > 25 kg/m² (n = 144) did not correlate with PFS (HR 0.92, 95%CI 0.68–1.25, p = 0.375) but was associated with longer OS (HR 0.50, 95%CI 0.29–0.88, p = 0.025). No significant BMI-treatment interaction was observed.

Conclusions: Tumor burden was prognostic and predictive in ALK-positive NSCLC. Treatment intensification may benefit patients with high tumor burden.

1. Introduction

Anaplastic lymphoma kinase (ALK) gene rearrangements are found

in approximately 5% of non-small cell lung cancers (NSCLC). The standard first-line treatment for advanced ALK-positive NSCLC consists of next-generation tyrosine kinase inhibitors (TKIs). [1] Alectinib, a

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second-generation TKI, was compared with crizotinib in the randomized phase III ALEX and J-ALEX trials involving patients with advanced NSCLC who had not previously received an ALK-TKI. [2,3] Results from these studies established alectinib as a preferred frontline therapy based on prolonged progression-free survival (PFS) compared with crizotinib, although no clear overall survival (OS) advantage has been demonstrated to date, even at longer follow-up. [4–6] Similarly, brigatinib, lorlatinib, and ensartinib have become additional first-line treatment options, providing superior outcomes relative to crizotinib. [7–9] Despite the high rate of disease control achieved, most patients eventually experience disease progression. Several factors may influence the choice of first-line therapy, including the presence of central nervous system (CNS) metastases, ALK variant type, and TP53 mutations. [10, 11] However, there are currently no clinical trial data directly comparing approved next-generation inhibitors in this setting. Moreover, there may be subgroups of patients—based on yet unexplored but easily measurable disease or patient characteristics—for whom treatment efficacy differs. In particular, factors such as tumor burden and body mass index (BMI), which are simple to assess, could contribute to this variability and warrant further investigation.

Tumor burden, or tumor load, refers to the total amount or size of cancer present in the body. It can be assessed through various methods but is most frequently evaluated using imaging techniques or simple biological correlates. Tumor burden is generally considered a prognostic indicator in onco-hematology. [12] However, a standardized definition and quantification of high versus low tumor burden are currently lacking, particularly in the context of NSCLC, [13,14] and few clinical trials incorporate it as a stratification factor or in subgroup analyses.

The association between BMI and survival in patients with lung cancer has been investigated, although findings have been inconsistent. [15] BMI has been recognized as a factor that may influence the pharmacokinetics and pharmacodynamics of cancer treatments, including ALK TKIs. [16–18]

Here, we present the results of a post hoc, patient-level pooled analysis at the primary data cutoff from the randomized phase III ALEX and J-ALEX trials, reporting survival outcomes within the pooled treatment groups. We conducted novel subgroup analyses examining baseline tumor burden and patient BMI as potential prognostic and predictive factors for alectinib therapy.

2. Methods

2.1. Study design and treatment

ALEX (NCT02075840) [2] and J-ALEX (JapicCTI–132316) [3] were both randomized, open-label, phase 3 trials that recruited patients with ALK-positive advanced NSCLC treatment-naïve to ALK inhibitors. Patients were randomly assigned (in a 1:1 ratio) to receive either oral alectinib (at a dose of 600 mg twice daily in the ALEX trial and 300 mg twice daily in the J-ALEX trial) or oral crizotinib (at a dose of 250 mg twice daily). Treatment was continued until disease progression, unacceptable toxic effects, withdrawal of consent, or death.

2.2. Eligibility criteria

Both trials included male and female patients 18 years of age or older with histologically or cytologically confirmed stage IIIB or stage IV ALK-positive NSCLC, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and who had measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The J-ALEX trial enrolled only Japanese patients. Only patients who did not receive previous systemic treatment for advanced NSCLC were enrolled in the ALEX trial, while the J-ALEX trial did allow the inclusion of patients who had received one previous chemotherapy regimen. Key exclusion criteria in both trials were a previous treatment with an ALK inhibitor and the presence of symptomatic brain or leptomeningeal

metastases. Per protocol, treatment crossover after disease progression was allowed in the J-ALEX trial. Both studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and written informed consent was obtained from all patients. The full methods for each study have been previously published. [2,3]

2.3. Outcomes

The objectives of this pooled analysis were to compare survival outcomes (in terms of PFS and OS) of patients treated with first line alectinib vs. crizotinib in the pooled patient population from the two trials and to explore the prognostic and predictive effect of tumor burden and BMI regarding PFS and OS in the pooled patient population.

2.4. Statistical analysis

PFS was defined as the time from the randomization to imaging-confirmed progressive disease on the basis of RECIST 1.1 or death from any cause, whichever occurred first. OS was defined as the time from randomization to death from any cause. Tumor burden was defined as the sum of the diameter of baseline target lesions by RECIST 1.1. [14] BMI categories were defined based on weight and height according to WHO definitions as follows: underweight (BMI < 18.50 kg/m²), normal (BMI: 18.50 – 24.99 kg/m²), overweight (BMI 25.00–29.99 kg/m²), and obese (BMI ≥30 kg/m²).

Patients with missing information about tumor burden and BMI were necessarily excluded from the analysis. RECIST assessment values used in this analysis were those reported in clinical trial databases to evaluate treatment response. Only the baseline assessment was considered, non-target lesions were not taken into account.

Continuous variables were assessed using the Wilcoxon test. Categorical variables were compared using chi-square or Fisher Exact test. Time-to-event data (PFS, OS) were estimated by Kaplan-Meier analysis. The Cox's proportional hazards model was used to calculate the Hazard Ratio and 95% Confidence Interval (95% CI) of the pooled populations. The evaluation of the prognostic role of the tumor burden was done based on a dichotomous division of patients with a baseline sum above (i.e., high tumor burden - highTB) or below (i.e., low tumor burden - lowTB) the median value, while for the BMI the threshold was set at 25 kg/m² (<25, normal-underweight vs. ≥25 overweight/obese). Also, multivariate analysis was performed using Cox's model adjusting for the characteristics that differed between patient by key explored subgroups. Final adjustment included age, BMI, gender, ethnicity, treatment arm, performance status (PS), smoking habit, stage, histology and brain metastases. Random effects models were performed to take into account the independence of the two trial data sets.

To explore the potentially predictive effect of tumor burden and BMI on the efficacy of ALK TKI treatment, we checked the quantitative interaction of these biomarkers on treatment effect. [19] We ran survival cox models with treatment and subgroup (tumor burden or BMI) interaction terms. To investigate the heterogeneity of treatment effects (HR for PFS and OS) across values of tumor burden we performed a Subpopulation Treatment Effect Pattern Plot (STEPP) analysis. [20–22]

Stata software version 17.1 was used for statistical analyses. Given that none of the present analyses were preplanned, they should be considered as exploratory. All statistical tests were two-sided, and a P-value < 0.05 was considered as statistically significant.

3. Results

3.1. Patients

Out of 510 patients included in the two trials, the pooled data set included 500 pts (249 treated with alectinib, 251 treated with crizotinib) with data made available for survival and safety analysis. Baseline

patient characteristics were well balanced in alectinib and crizotinib groups in terms of median age at randomization (58 vs. 56 years), sex distribution (female sex 58% vs. 59%), Asian ethnicity (67% vs. 67%), ECOG PS ≥ 1 (61% vs. 59%), histologic disease subtype (adenocarcinoma 92% vs. 96%) and presence of brain metastases (29 vs. 34%) (Table 1). Median BMI was also similar in patient receiving alectinib or crizotinib (23 vs. 23.1 kg/m²), with 70% vs. 67% of patients having a BMI < 25 kg/m², respectively. In the overall population, the baseline median sum of diameters of target lesions by RECIST criteria was 55 millimeters (mm). Patients with highTB disease (>55 mm) were 47% and 51% in alectinib and crizotinib arms, respectively.

3.2. Overall survival outcomes

After median follow-up for the pooled data set of 17.1 months, in the pooled population alectinib resulted in a significantly longer PFS compared with crizotinib (median not reached vs. 10.2 months, Log-Rank test P-value<0.001). The risk of disease progression or death was significantly reduced with alectinib over crizotinib (HR 0.41, 95% CI 0.31–0.55, $p < 0.001$) (Supplementary Figure 1A). Median OS was not reached in any arm (Log-Rank test P-value<0.587), and no statistical difference was observed in the risk of death between both treatment arms (HR 0.80, 95% 0.50–1.28, $p = 0.353$) (Supplementary Figure 1B).

3.3. Survival outcomes according to tumor burden

In the pooled analysis, 247 patients were classified as lowTB at baseline, of whom 117 (47%) treated with alectinib and 130 (53%)

treated with crizotinib, whereas 244 as highTB, of whom 128 (53%) received alectinib and 116 (48%) received crizotinib, respectively ($p = 0.279$).

According to baseline tumor burden, patients with highTB were more frequently of non-Asian ethnicity (41% vs. 24%), had more frequently ECOG PS ≥ 1 (68% vs. 52%) and had higher prevalence of brain metastases at baseline (41% vs. 23%). No differences were observed between highTB and lowTB groups in terms of median age, gender, BMI, tobacco smoke and histology (Table 2).

3.3.1. Prognostic effect

Patients with highTB had a significant shorter median PFS (HR 1.88, 95% CI 1.44–2.45, Log-Rank test $p < 0.001$) and OS HR (2.24, 95% CI 1.40–3.58, Log-Rank test $p < 0.001$) as compared to patients with LowTB (Figure 1 A and B), irrespective of treatment received.

After adjusting for patients' and disease's characteristics (including the presence of brain metastases) and type of ALK TKI treatment received, in multivariate analysis, patients with highTB had a significant

Table 2

Patient and disease characteristics distribution according to baseline tumor burden.

	Lesion diameter ≤ 55 (N = 247)	Lesion diameter > 55 (N = 244)	Lesion diameter unknown (N = 9)	
	Median (IQR)	Median (IQR)	Median (IQR)	Wilcoxon test P-value
AGE	58 (48–67)	57 (46–66)	51 (43–56)	0.236
BMI	22.8 (20.5–25.2)	23.3 (20.7–25.5)	21.5 (21.5–28.0)	0.410
	n (%)	n (%)	n (%)	Fisher's exact test P-value
BMI				0.952
< 18.50	21 (8.5%)	17 (7.0%)	0 (0.0%)	
18.50–24.99	151 (61.1%)	149 (61.1%)	6 (66.7%)	
25.00–29.99	58 (23.5%)	58 (23.8%)	2 (22.2%)	
≥ 30.00	13 (5.3%)	12 (4.9%)	1 (11.1%)	
Unknown	4 (1.6%)	8 (3.3%)	0 (0.0%)	
GENDER				0.028
Male	89 (36.0%)	112 (45.9%)	6 (66.7%)	
Female	158 (64.0%)	132 (54.1%)	3 (33.3%)	
ETHNICITY				< 0.001
Asian	185 (74.4%)	143 (58.6%)	7 (77.8%)	
Non-Asian	59 (23.9%)	100 (41.0%)	2 (22.2%)	
Unknown	3 (1.2%)	1 (0.4%)	0 (0.0%)	
ECOG PS				0.001
0	119 (48.2%)	79 (32.4%)	1 (11.1%)	
1	119 (48.2%)	151 (61.9%)	8 (88.9%)	
2	9 (3.6%)	14 (5.7%)	0 (0.0%)	
SMOKE				0.103
Never smoked	154 (62.3%)	140 (57.4%)	5 (55.6%)	
Past smoker	87 (35.2%)	89 (36.5%)	3 (33.3%)	
Current smoker	6 (2.4%)	15 (6.1%)	1 (11.1%)	
STAGE				0.447
IIIB	10 (4.0%)	6 (2.5%)	0 (0.0%)	
IV	237 (96.0%)	238 (97.50%)	9 (100.0%)	
HISTOLOGY				0.087
Adenocarcinoma	238 (96.4%)	224 (91.8%)	9 (100.0%)	
Squamous cell carcinoma	4 (1.6%)	5 (2.0%)	0 (0.0%)	
Large cell carcinoma	0 (0.0%)	3 (1.2%)	0 (0.0%)	
Others	5 (2.0%)	12 (4.9%)	0 (0.0%)	
CNS				< 0.001
METASTASES				
No	191 (77.3%)	144 (59.0%)	9 (100.0%)	
Yes	56 (22.7%)	100 (41.0%)	0 (0.0%)	
TREATMENT				0.279
Alectinib	117 (47.4%)	128 (52.5%)	6 (66.7%)	
Crizotinib	130 (52.6%)	116 (47.5%)	3 (33.3%)	

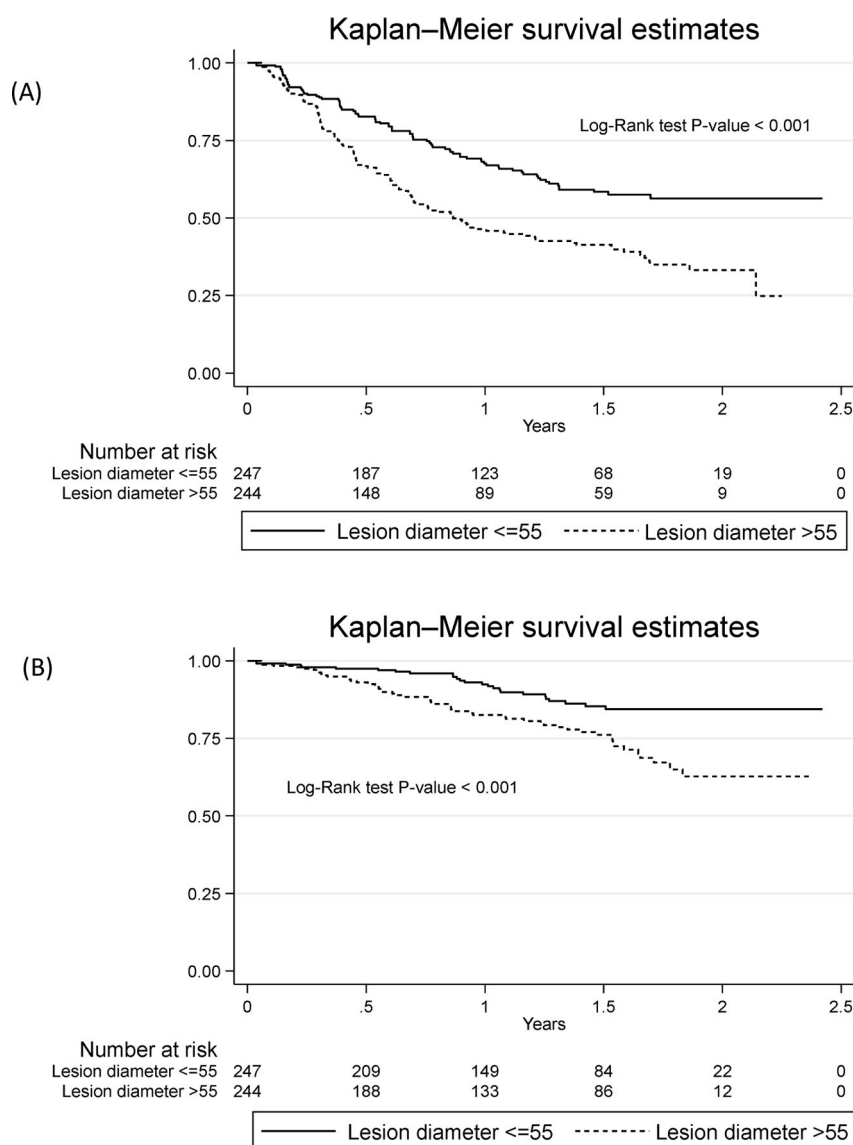


Fig. 1. KM estimated for PFS (A) and OS (B) of patients with baseline high and low tumor burden.

increased risk of disease progression or death as compared with patients with lowTB (HR 1.66, 95% CI 1.26–2.20, $p < 0.001$) (Supplementary Table 1). No statistically significant effect of tumor burden was observed on OS (HR 1.57, 95% CI 0.96–2.57) (Supplementary Table 2).

3.3.2. Predictive effect

In the PFS cox model, a significant interaction was found between treatment and tumor burden ($p_{\text{for interaction}} = 0.002$). In patients with lowTB, alectinib conferred a 75% relative reduction in the risk of disease progression or death compared to crizotinib (HR 0.25, 95% CI 0.16–0.41, $p < 0.001$), while in patients with highTB the relative benefit of alectinib over crizotinib was less (HR 0.52, 95% CI 0.36–0.76, $p = 0.001$).

In the OS cox model, no significant interaction was found between treatment and tumor burden ($p_{\text{for interaction}} = 0.439$). Alectinib conferred a similar relative reduction in the risk of death compared to crizotinib in patients with lowTB (HR 0.79, 95% CI 0.35–1.80, $p = 0.572$) than in patients with highTB (HR 0.87, 95% CI 0.48–1.55, $p = 0.645$).

The Subpopulation Treatment Effect Pattern Plot (STEPP) analysis investigating the heterogeneity of treatment effects (HR for PFS and OS) across values of tumor burden considered as continuous variable is shown in Fig 2 A and B. Particularly, increasing efficacy of alectinib

over crizotinib was observed at the lowering of tumor burden for PFS, while similar efficacy was observed in OS.

3.4. Survival outcomes according to patient's BMI

Overall, out of 344 patients with BMI < 25, 169 (49%) and 175 (51%) were treated with alectinib and crizotinib, respectively, whereas 74 (51%) and 70 (49%) of the 144 patients with BMI ≥ 25 received alectinib and crizotinib, respectively ($p = 0.692$). For 12 patients the BMI was not known. Patient's characteristics were well balanced between BMI subgroups, except for ethnicity (Supplementary Table 3).

3.4.1. Prognostic effect

Patients with baseline BMI ≥ 25 had similar median PFS (HR 0.91, 95% CI 0.69–1.21, $p = 0.523$) and OS (HR 0.73, 95% CI 0.44–1.21, $p = 0.219$) as compared to patients with BMI < 25 (Supplementary Figure 2 A and B).

In multivariate analysis, with correction for patients' and disease's characteristics and type of ALK TKI treatment received, BMI ≥ 25 correlated with better OS compared to BMI < 25 (HR 0.50, 95% CI 0.29–0.88, $p = 0.025$) (Supplementary Table 2), while no statistically significant association was found with PFS (HR 0.92, 95% CI 0.68–1.25,

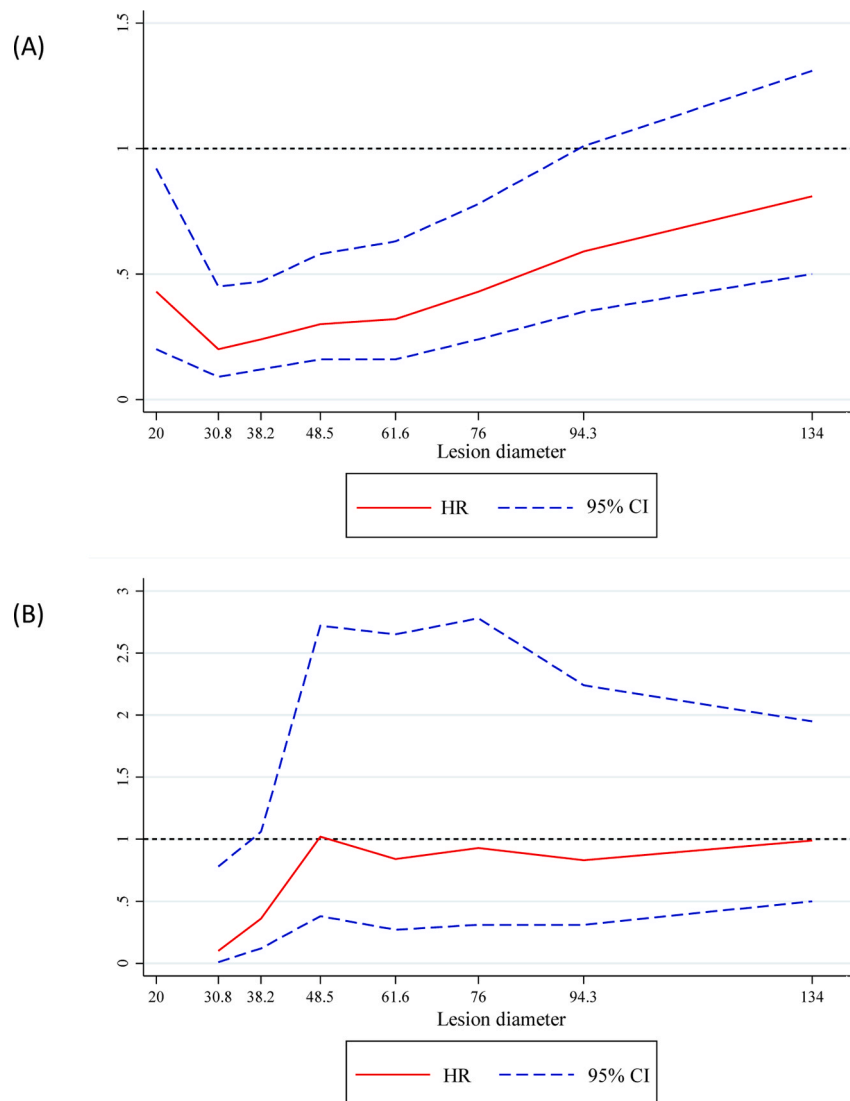


Fig. 2. Graphical representation of STEPP analysis: HR for PFS (A) and OS (B) at increasing values of baseline tumor burden.

$p = 0.375$) (Supplementary Table 1).

3.4.2. Predictive effect

In PFS and OS cox models, there was no significant interaction between BMI and ALK TKI treatment.

In patients with BMI < 25, alectinib conferred a 56% relative reduction in the risk of disease progression or death compared to crizotinib (HR 0.44, 95% CI 0.32–0.62, $p < 0.001$), similarly to what was observed in patients with BMI ≥ 25 (HR 0.35, 95% CI 0.19–0.63, $p = 0.001$).

In the OS cox model, the HR between alectinib and crizotinib was 0.99 (95% CI 0.58–1.71, $p = 0.976$) in patients with BMI < 25 and 0.39 (95% CI 0.12–1.21, $p = 0.103$) in patients with BMI ≥ 25 , respectively.

The STEPP analysis for PFS and OS based on baseline BMI value is shown in Supplementary Figure 3 A and B.

4. Discussion

This pooled analysis of the phase III ALEX and J-ALEX trials identifies, for the first time to our knowledge, tumor burden as both a prognostic and predictive factor in patients with ALK-positive advanced NSCLC treated in a randomized setting. Specifically, patients with high TB exhibited poorer outcomes and reduced efficacy of alectinib. In

addition, we identified BMI as a potential prognostic indicator warranting further investigation. These findings underscore the importance of identifying prognostic factors in patients receiving first-line ALK TKIs, particularly to better define subgroups with worse prognoses. This analysis also highlights the relevance of baseline characteristics in guiding treatment decisions, offering a practical opportunity for risk stratification and personalized management of patients with ALK-positive disease. A biomarker is considered predictive when the treatment effect differs between biomarker-positive and biomarker-negative patients, in at least two comparison groups. [19] On this regard, the significant interaction between treatment and tumor burden is particularly noteworthy: even if both groups (low and high TB) derive benefit from alectinib, patients with low TB derive much greater benefit from alectinib compared to crizotinib. The STEPP analysis provided additional insight into the relationship between baseline tumor burden and treatment efficacy by modeling the treatment effect continuously across the spectrum of disease extent, rather than relying solely on an arbitrary dichotomous cutoff. Interestingly, the relative benefit of alectinib over crizotinib in terms of PFS appeared progressively greater in patients with lower tumor burden, while this advantage was attenuated as tumor burden increased. These findings support the hypothesis that baseline disease extent may act not only as a prognostic factor, but also as a modifier of ALK-TKI efficacy. Importantly, the STEPP analysis

strengthens the robustness of the interaction observed in the Cox model and suggests that the effect of tumor burden on treatment effect follows a continuous, even if non-linear, pattern.

On the contrary, the STEPP analysis according to baseline BMI did not show a clear pattern of heterogeneity in treatment effect between alectinib and crizotinib, consistent with the absence of a significant interaction in the Cox models. These findings suggest that BMI may act predominantly as a prognostic rather than predictive factor in ALK-positive NSCLC. The biological mechanisms underlying this association are uncertain. This is still exploratory, and it remains to be clarified whether the prognostic effect of BMI relates to metabolic comorbidities, altered pharmacokinetics, or confounding from patients with very low BMI—potentially reflecting weight loss and cancer cachexia. [15,18,23–25] Recognizing BMI influence may help optimize supportive care strategies and set realistic expectations for outcomes.

Findings from this study could inform more personalized treatment approaches, suggesting that patients with high TB may benefit from intensified therapeutic strategies. Potential strategies might include early introduction of next-generation ALK inhibitors or combination regimens incorporating chemotherapy, antiangiogenic agents, or antibody–drug conjugates. [26–30]

Tumor burden is an important prognostic factor in solid tumors, including lung cancer. Although this concept has been more extensively investigated in the setting of immunotherapy, [31] fewer studies have investigated the prognostic impact of this parameter in oncogene-addicted NSCLC, most of which with a retrospective design and reporting conflicting results. Data on this association in ALK-positive disease are particularly scarce. In EGFR-mutant disease, tumor burden appears to be prognostic rather than predictive of TKIs efficacy. [32–34] Beyond reflecting the extent of disease, tumor burden may represent more aggressive tumor biology, potentially linked to elevated lactate dehydrogenase levels and increased shedding of circulating tumor DNA (ctDNA). [35–38] Indeed, ctDNA shedding largely depends on tumor burden and may itself serve as a marker of poor prognosis. In the phase III ALTA–3 study, only 40% of patients had detectable ALK fusions in ctDNA before alectinib initiation. Median PFS was 22.5 months (95% CI: 19.2–NE) in patients without detectable ALK fusion versus 11.1 months (95% CI: 8.0–19.3) in those with detectable ALK fusion (HR 0.48, 95% CI 0.32–0.71, $p = 0.0002$). [39] Similarly, in our analysis, patients with lowTB across treatment groups had a PFS HR of 0.53 as compared to highTB. The advantage of tumor burden lies in its ease of assessment—it can be evaluated in any clinical setting, independent of technological or economic constraints.

Despite its strengths, this study has limitations. First, the analyses were exploratory in nature. Second, as the results were based on the primary data cutoff of both trials, definitive conclusions regarding OS benefits are limited, given the short follow up and the immaturity of OS data. Third, although random-effects models were applied to account for trial differences, unaccounted variables—such as crossover—may still have influenced results. Fourth, unmeasured confounding factors may have contributed to observed associations, particularly regarding BMI and other baseline characteristics. Some imbalance in prognostic characteristics between the two groups by tumor burden was observed, including ECOG PS and presence of brain metastases. Nevertheless, this analysis was performed within randomized trials, where residual confounding is attenuated. Moreover, the multivariate analysis took into account all the potential prognostic factors. Finally, no genomic data by next generation sequencing were available to be incorporated in the analyses to better refine the prognostic stratification.

Overall, this is the first study from randomized trials to investigate the prognostic and predictive role of tumor burden and BMI in ALK-positive NSCLC. Further research is warranted to validate the findings, including analyses of trials evaluating different ALK TKIs. Prospective studies incorporating tumor burden as a stratification factor could refine therapeutic strategies and improve outcomes for patients deriving less benefit from current ALK-targeted therapies.

5. Conclusion

In conclusion, while alectinib remains a preferred first-line treatment for ALK-positive advanced NSCLC—offering significant efficacy and safety advantages over crizotinib—the identification of high tumor burden as a negative prognostic and predictive factor further refines our understanding of patient outcomes in this setting. These findings underscore the need to adapt treatment strategies based on baseline disease burden and highlight the importance of personalized approaches to optimize care for patients with advanced ALK-positive NSCLC.

CRedit authorship contribution statement

Marco Tagliamento: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Marco Bruzzone:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Eva Blondeaux:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Filippo Dall’Olio:** Writing – review & editing. **Mihaela Aldea:** Writing – review & editing. **Carlo Genova:** Writing – review & editing. **Arianna Marinello:** Writing – review & editing. **Jordi Remon:** Writing – review & editing. **Lizza E.L. Hendriks:** Writing – review & editing. **Lucia Del Mastro:** Writing – review & editing. **David Planchard:** Writing – review & editing. **Fabrice Barlesi:** Writing – review & editing. **Matteo Lambertini:** Writing – review & editing. **Benjamin Besse:** Writing – review & editing, Supervision.

Data source

This study is based on research using data from data contributor F. Hoffmann–La Roche that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for the contents of this publication.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Tagliamento: Honoraria for consulting from Oncotech, AstraZeneca, Pharmamar; personal honoraria (speaker bureau/advisory board) from Roche, Novartis, Takeda, Sandoz, AstraZeneca, Regeneron, MSD; non-personal financial support (travel-accommodation expenses) from Eli Lilly, Takeda, OSE Immunotherapeutics, Roche, Daiichi Sankyo, Johnson&Johnson; research grants (to institution) from AIRC - Italian Association on Cancer Research, Pfizer.

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the institution) of AstraZeneca, GSK, Novartis, Merck, Roche, Takeda, Blueprint, Mirati, Abbvie, Gilead, MSD, Merck, Amgen, Boehringer Ingelheim, Pfizer, Daiichi, Amgen.

Planchard: Consulting, advisory role or lectures for AstraZeneca, Abbvie, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Janssen, Pfizer, Roche, Pierre-fabre, Takeda, ArriVent, Mirati, Seagen, GSK; Clinical trials research as principal or co-investigator (Institutional financial interests) of AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo, Abbvie, Janssen, Pierre-fabre, Takeda, ArriVent, Mirati, Seagen; Travel, Accommodations, Expenses from AstraZeneca, Roche, Novartis, Pfizer.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2026.116867](https://doi.org/10.1016/j.ejca.2026.116867).

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