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The Percentage of ALK-Positive Cells and the Efficacy of First-Line Alectinib in Advanced Non-small Cell Lung Cancer: Is it a novel factor for stratification? (Turkish Oncology Group Study)

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Abstract

Introduction: Alectinib is an effective second-generation ALK tyrosine kinase inhibitor (TKI) used in the first-line treatment of patients with advanced ALK-positive NSCLC. Recent studies demonstrated that the percentage of ALK-positive tumor cells in patient groups receiving crizotinib might affect outcomes. This study aimed to investigate whether the percentage of ALK-positive cells had a predictive effect in patients with advanced NSCLC who received first-line Alectinib as ALK-TKI.

Materials and Methods: This retrospective study included patients with advanced-stage NSCLC who received alectinib as a first-line ALK-TKI and whose percentage of ALK-positive cells was determined by FISH at 27 different centers. Patients who received any ALK-TKI before alectinib were not included in the study. Patients were separated into two groups according to the median (40%) value of the percentage of ALK-positive cells (high-positive group ≥40% and low-positive group <40%). The primary endpoint was PFS, and the secondary endpoints were OS, ORR, and PFS of the subgroups based on different threshold values for the percentage of ALK-positive cells.

Results: 211 patients were enrolled (48.3% female, 51.7% male) to study. 37% (n=78) of the patients had received chemotherapy previously. After a median of 19.4 months of follow-up, the median PFS was not reached in the high-positive group (n=113) but it was 10.8 months in the low-positive group (n=98) (HR: 0.39; 95% CI, 0.25-0.60, p<0.001). The median OS in the high positive group was not reached, whereas it was 22.8 months in the low positive group (HR: 0.37; 95% CI, 0.22-0.63, p<0.001). ORR was significantly higher in the high-positive group (87.2 vs. 68.5%; p=0.002). According to the cutoff values of <20%, 20-39%, 40-59%, and ≥60%, the median PFS was 4.5, 17.1, and 26 months, respectively, and could not be reached in the ≥60% group.

Conclusion: Our study demonstrated that the efficacy of alectinib varies significantly across patient subgroups with different percentages of ALK-positive cells. If these findings are prospectively validated, the percentage of ALK-positive cells may be used as a stratification factor in randomized trials comparing different ALK-TKIs.

Introduction

Targeted therapies have revolutionized the field of cancer treatment. There have been no dramatic changes in the management of each type of cancer. However, remarkable results were obtained in patients with non-small cell lung cancer (NSCLC) that directed treatment from the initial presentation and forced the treatment guidelines to modify. The anaplastic lymphoma kinase (ALK) mutation is one of the most significant of these targets, being found in 4–7% of individuals with NSCLC. The development of more effective treatment agents targeting this driver mutation was crucial in achieving these results.

Alectinib is an effective second-generation tyrosine kinase inhibitor (TKI) that demonstrated a survival benefit over crizotinib in ALK-positive (by immunohistochemical assay) NSCLC patients in the randomized phase 3 ALEX study (1). Regarding the conclusion of this study, alectinib has been one of the

most important agents preferred in first-line treatment. Following that, the study's updated results showed a median progression-free survival (PFS) of 34.8 months (vs. 10.8 months in the crizotinib arm) and a 62.5% of 5-year overall survival (OS) rate (2). The PFS difference was impressive. However, there was no difference in disease control rate (DCR) between alectinib and crizotinib (1). In both arms, approximately 10% of patients had the best response to treatment as progressive disease (PD) or death. Additionally, PFS curves demonstrated a remarkably similar course up to 6 months (1). Response to treatment could not be achieved in approximately 10% of the patients, regardless of the potency of the ALK-TKI they received. This might suggest the possibility that there were additional factors influencing the treatment response despite the presence of a driver mutation causing oncogene addiction.

Fluorescence in-situ hybridization (FISH) is one of the most important methods to detect ALK-positivity in NSCLC patients. The pioneering studies recommended a cut-off value of 15% or greater for ALK rearrangement positivity as determined by FISH (3, 4). Following that, the FISH method was used to determine inclusion in phase studies of the first ALK-TKI crizotinib, and ≥ 15% was accepted as the global threshold value in clinical practice (5, 6).

Studies have demonstrated that the percentage of ALK-positive tumor cells in patient groups receiving crizotinib may also affect outcomes quantitatively (7, 8). Soria et al. reported that an increase in the percentage of ALK-positive cells in patients receiving crizotinib may be associated with improved PFS and ORR in a pooled analysis of PROFILE studies (8). This study aimed to investigate whether the percentage of ALK-positive cells had a predictive effect in patients with advanced NSCLC who received first-line Alectinib as ALK-TKI.

Materials And Methods

Pathologically confirmed advanced-stage NSCLC patients with ALK translocations were included in this multicenter, retrospective trial. ALK translocation was analyzed by the local laboratories of each center. Only patients diagnosed using the FISH method and whose percentage of ALK-positive cells were given quantitatively in the pathology report were included in the study, as required by the hypothesis tested. No cases were included in the study if the percentage of ALK-positive cells was not specified or if ALK-positivity was demonstrated using a method other than FISH (Immunohistochemistry (IHC), reverse transcriptase-PCR (RT-PCR), and next-generation sequencing (NGS)).

The study group was treated with alectinib as a first-line ALK-TKI, between January 2015 and July 2021. Inclusion criteria allowed to enroll treatment-naïve patients as well as patients who received chemotherapy before alectinib. Patients who received any ALK-TKI prior to alectinib were not included in the study. With the collaboration of the Turkish Oncology Group, the study was conducted in 27 different centers in Turkey. Patients' demographic and clinical characteristics, radiologic evaluations, and pathology reports were collected from patient files and electronic hospital databases.

Patients were separated into two groups according to the median (40%) value of the percentage of ALK-positive cells (high-positive group ≥ 40% and low-positive group < 40%). Due to the lack of a prospectively

established reference value for the percentage of ALK-positive cells, the median value was utilized to ensure that the groups had comparable patient numbers and to reduce heterogeneity between groups.

The primary endpoint was PFS, which was defined as the period from the start of alectinib treatment to the documentation of disease progression (PD, as defined by the investigator using RECIST criteria) or death. Secondary endpoints were OS, ORR, and PFS of the subgroups based on different threshold values for the percentage of ALK-positive cells. Overall survival was defined as the time from initiation of alectinib to death from any cause. The ORR was defined as the percentage of patients who achieved a complete response (CR) or a partial response (PR) as determined by the investigator using RECIST version 1.1.

All statistical procedures were performed with SPSS 22.0 (SPSS Inc, Chicago, Illinois). Variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Categorical variables were compared using the Chi-square or Fisher's exact test, where appropriate. Differences in continuous values between the two groups were assessed with Student's *t*-test for normally distributed variables and non-parametric Mann-Whitney *U* tests for non-normally distributed variables as appropriate. Survival curves were obtained by the Kaplan–Meier method, and the log-rank test was used to compare survival differences. The treatment effect was estimated using a stratified Cox proportional-hazards analysis and expressed as hazard ratios with corresponding 95% confidence intervals. A p-value < 0.05 was considered to be statistically significant. A 5% type-1 error level was used to infer statistical significance.

The local Clinical Research Ethics Committee's approval was obtained.

Results

Patient Characteristics

A total of 211 patients were enrolled in the study. The median age was 57 (min-max:26–90 years). 48.3% of the participants were female (n = 102), 51.7% (n = 109) were male. The non-smoker rate was 52.6%. While 63% (n = 133) of the patients received alectinib in first-line, 37% (n = 78) had previous chemotherapy exposure.

The median value of the percentage of ALK-positive cells was 40%. Patients were divided into low-positive (< 40%) and high-positive (≥ 40%) groups according to this value. A significant difference was found between the baseline characteristics of the two groups only in terms of age. Although there was no statistically significant difference, female gender (54%) and non-smoker (58%) rates were higher among patients in the high-positive group. It should be noted that the rates of patients who had received prior chemotherapy were 43.9% and 31.9% in the low-positive and high-positive groups, respectively (p = 0.06). The baseline characteristics of the groups are shown in Table 1.

Table 1
Demographic and Clinical Features of the Patients

Feature	Percentage of ALK-Positive Cells < 40% (n = 98)	Percentage of ALK-Positive Cells ≥ 40% (n = 113)	p
Percentage of ALK(+) Cells (median, min-max)	22 (15–38)	60 (40–92)	**< 0.001**
Age (median, min-max)	60 (28–90)	56 (26–80)	**0.023**
Sex (%)			0.09
Female	41.8	54	
Male	58.2	46	
Smoking (%)			0.12
Non-smokers	46.9	58	
Former or Active	53.1	42	
Comorbidity (%)			0.32
Present	44.9	38.1	
Absent	55.1	61.9	
ECOG Performance (%)			0.13
0–1	86.3	93.4	
2–3	13.8	6.6	
Metastatic Sites (%)			
Brain	36.7	31	0.38
Liver	22.4	23.9	0.87
Bone	41.8	43.4	0.88
Surrenal	18.4	12.4	0.25
Pleural Effusion	42.9	44.2	0.89
Treatment Line			0.06
Previous chemo	43.9	31	
First-line	56.1	69	
No of Chemo. Cycles (median, min-max)	3 (1–12)	3 (1–12)	0.58

Efficacy Outcomes According to Break-Apart Ratio

After a median of 19.4 months of follow-up, 36 and 55 patients had progressed or died in the high-positive (n = 113) and low-positive (n = 98) groups, respectively. The median PFS could not be reached in the high-positive group, and it was 10.8 months (95% CI, 4.4–17.2) in the low-positive group (HR: 0.39; 95% CI, 0.25–0.60, p < 0.001). (Fig. 1) The 18-month PFS rate was 68% and 37% in the high- and low-positive groups, respectively.

PFS outcomes of patients who received first-line alectinib were also similar. There were 78 and 55 patients who received first-line alectinib in high-positive and low-positive groups, respectively. Among these patients, the median PFS could not be reached in the high-positive group, and it was 9.6 months (95% CI, 3.4–15.9) in the low-positive group (HR: 0.35; 95% CI, 0.21–0.61, p < 0.001).

Also, the median OS could not be reached in the high-positive group, and it was 22.8 months (95% CI, 10.9–34.7) in the low-positive group (HR: 0.37; 95% CI, 0.22–0.63, p < 0.001). (Fig. 2) The 18-month OS rate was 79% and 57% in the high-positive and low-positive groups, respectively.

Thirteen patients had no response assessment. The ORR was significantly different in favor of the high-positive group (87.2% vs. 68.5%; p = 0.002). Patients with 'progressive disease' as the best response to treatment had a rate of 5.5% and 18% in the high-positive and low-positive groups, respectively. (Table 2)

Table 2
Response Assessment to Alectinib Treatment

Treatment Response	Percentage of ALK-Positive Cells < 40% (n = 89)	Percentage of ALK-Positive Cells ≥ 40% (n = 109)	p
CR	13.5%	21.1%	
PR	55.1%	66.1%	
ORR	**68.5%**	**87.2%**	**0.002**
SD	13.5%	7.3%	
PD	18%	5.5%	

The CNS response assessment was obtained from 36 and 34 patients in the high-positive and low-positive groups, respectively. The objective CNS response rates were quite similar (66.7% vs. 64.7%). However, it should be noted that approximately half of the patients in both groups (44% and 52%, in high- and low-positive groups, respectively) received radiotherapy. CNS progression was seen in 8.3% and 15.3% of the patients in the high-positive and low-positive groups while receiving alectinib.

Finally, as far as the number of patients allowed, we divided the patients into more detailed subgroups based on the percentage of ALK-positive cells. The percentage thresholds for the groups were < 20%, 20–39%, 40–59%, ≥ 60%, and the median PFS was 4.5, 17.1, 26 months, and not reached, respectively. Among the patients who had response assessment, the ORR was 53.8%, 74.6%, 86.8%, and 87.5%, respectively. (Table 3 and Fig. 3)

Table 3
Efficacy Outcomes According to Different Percentages of ALK-Positive Cells

Percentage of ALK-Positive Cells	No of event / N	ORR (%)	Median PFS (95% CI)
< 20%	21/31	53.8%	4.5 months (0.6–8.3)
20–39%	34/67	74.6%	17.1 months (11.9–22.3)
40–59%	22/55	86.8%	26.0 months (9.9–42)
≥ 60%	14/58	87.5%	NE; 24-month rate: 63%

Discussion

The study's findings indicated that the percentage of ALK-positive cells may be a predictor of treatment efficacy in patients with advanced NSCLC receiving first-line alectinib. The outcomes demonstrated significantly better PFS, OS, and ORR in the high-positive group. Furthermore, there was no other study that included a larger number of patients and investigated the effect of this factor in patients who had received first-line alectinib.

ALK-positivity can be detected by different methods such as IHC, FISH, and NGS. Unlike other approaches, the FISH method allows for the quantification of the percentage of cells with ALK gene rearrangement. Although 15% was established as the threshold for ALK positivity, no widely accepted reference value was shown to be predictive for different ALK-TKIs (9). Due to this limitation, which can only be addressed by a prospective study, we classified patients according to the median value. There was no substantial difference in the patients' baseline characteristics between the low and high groups. Although there was a statistically significant age difference between the groups, the range and median values of both groups were consistent with previously defined values in ALK-positive patient cohorts (3, 10). Although not statistically significant, the high rate of nonsmokers and low rate of patients with prior chemotherapy exposure in the high-positive group may emphasize the disease's driver-mutation dependence. Consistent with this, the PFS values obtained among the treatment-naive patients were quite similar to the results obtained across the entire study group.

The study's primary endpoint was the PFS and it was significantly better in the high-positive group. The ALEX study's updated survival analysis reported a median PFS of 34.8 months vs 10.9 months (HR 0.43, 95% CI 0.32–0.58) in alectinib and crizotinib arms, respectively (2). Also, the 1-year PFS was 67.8% with

alectinib (2). In our study, the median PFS of the low-positive group was 10.8 months, which was dramatically below the expectations for a patient group receiving alectinib. However, in the high-group, the median PFS could not be reached, and the 18-month PFS rate was 68%, which was higher than expected. This PFS difference, which represents a risk reduction of nearly 60%, is rarely achieved even in other studies where the two groups were treated with different drugs.

One of the most important reasons for this efficacy difference was the significant difference in ORR between the high and low-positive groups, which was also a secondary endpoint. In the ALEX study, the ORR was 75.5% in the crizotinib arm and 82.9% in the alectinib arm (1). The ORR achieved in our study was lower in the low-positive group (68.5%) than in the ALEX study, but greater in the high-positive group (87.2%). Another significant finding that demonstrates the predictive effect is that the PD was the best response to alectinib in 18% of the low-positive group and 5.5 percent of the high-positive group. The low-positive group's high number of primary non-responders to alectinib may have contributed to the PFS difference. Because we did not measure it in our study, we could only speculate that duration of response and depth of response may be the other factors that contributed to the PFS difference. Although ORR was obtained in more than half of patients with positive cells less than 20% in the subgroup analysis, the fact that the median PFS was as short as 4.5 months in this subgroup enhanced the possibility that this speculation might be true.

Our findings are consistent with prior studies and extend these findings. Almost all previous studies examined crizotinib-treated patients. Because it was the first ALK-TKI and PROFILE studies to detect ALK positivity using the FISH method, in contrast to the ALEX study, which used the IHC (1, 6). Soria et al. reported efficacy data according to the percentage of ALK-positive cells in a pooled analysis of PROFILE 1005, 1007, and 1014 studies, in 2018 (8). While the overall ORR was 55% in patients receiving crizotinib in this study, the lowest ORR was 38% in patients with an ALK positivity of between 15–20%. In the patient group above 20%, the median PFS was 9.5 months, while the patient group below 20% had a PFS of 4.3 months. The results of the group with less than 20% are consistent with our findings. However, when the threshold percentage was increased (25, 35, and 55 percent), the median PFS did not change at 9.6 months, contrary to our findings. This fact could be attributed to the difference in efficacy between the two ALK-TKIs, and the 9.5 months of PFS might represent the natural efficacy limit for crizotinib treatment, in which patients mostly experience CNS progression (8). When other real-world data, including patients taking crizotinib, is examined, the cut-off value is generally accepted to be 50% (11–13). Jiang et al. demonstrated in one of these studies that crizotinib was significantly more effective in patients with ALK-positive cells greater than 50% versus patients with low ALK-positive cells (ORR 83.8 vs. 60.9% and mPFS 13.5 vs. 8.7 months, respectively) (14). In another study involving crizotinib patients, we reported a significant increase in PFS in those with a high percentage (cut-off: 50%) compared to those with a low percentage (mPFS was 17.9 vs. 7.06 months, HR: 0.43, 95% CI 0.24–0.76, p = 0.004) (11). In the study of Toruner et al., 10 of 66 patients were treated with alectinib. When the threshold value was accepted as 50%, the mPFS was better in high-positive patients than in low-positive patients (16 vs 4 months, HR 2.89, 95% CI 1.34–6.24, p = 0.0068) (12).

Our study had a relatively short median follow-up period, but there was a significant difference in OS between the two groups. The significant difference in ORR and PFS could simply be attributed to the OS difference. In the ALEX study, the alectinib arm had a 1-year OS of 84.3% and a 2-year OS of 72.5%. The high-positive group obtained 79% of the 18-month OS, which was consistent with the pivotal phase study (2). The median OS in the low group was 22.8 months, far below the expected survival for ALK-positive disease. Even in the ALEX study's crizotinib arm, the median OS was reported as 57.4 months (2). It should be noted that the study included real-world patients with poor performance and comorbidities. Additionally, approximately one in three patients received chemotherapy during the ALK test. One could argue that many of these patients presented with symptoms necessitating immediate treatment. Another important factor influencing the OS outcome was the previously unavailability of other ALK-TKI agents (lorlatinib, brigatinib, etc.) in our country that could be used following progression on alectinib.

Another critical point is that tumor biopsy is not always a complete representation of the tumor's molecular characteristics because of the intratumoral heterogeneity (15). This possibility may have had a greater impact on the patients with a lower percentage. The clinical significance of the numerical difference in ORR and PFS values was obvious, especially between the patient groups whose percentages were < 20, 20–39, and 40–59. At values greater than 40%, one could argue that this difference was closed. However, it should be kept in mind that even ALK positivity below 20% resulted in an ORR that was incomparable to that of conventional cytotoxic treatments, and the depth and duration of response may vary significantly between individuals. Another important question that future research can answer is whether drug resistance mutations, which are the most serious problem for ALK-TKI treatments, develop differently in groups with low or high ALK-positive cells.

In conclusion, our findings showed that the efficacy of alectinib varies significantly across patient groups with different percentages of ALK-positive cells. This difference may not be explained only by factors such as the retrospective nature of the study, group heterogeneity, and a lack of standardization of pathological evaluation in different centers, all of which are weaknesses of our study. Furthermore, if our findings are prospectively validated, the percentage of ALK-positive cells may be used as a stratification factor in randomized trials comparing different ALK-TKIs.

Declarations

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Conflict of interest: The authors declare no conflicts of interest

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Figures

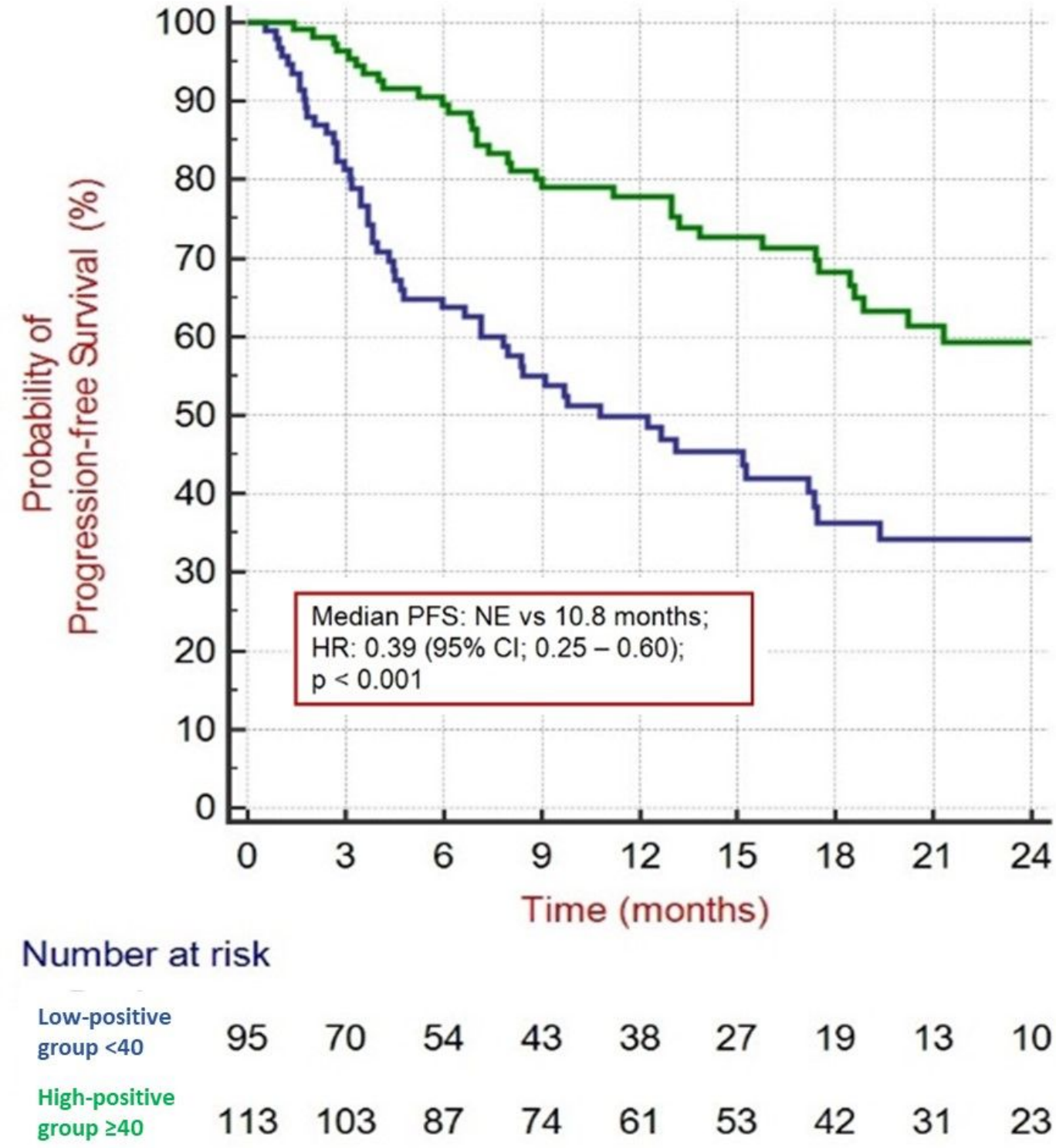


Figure 1

Progression-free Survival

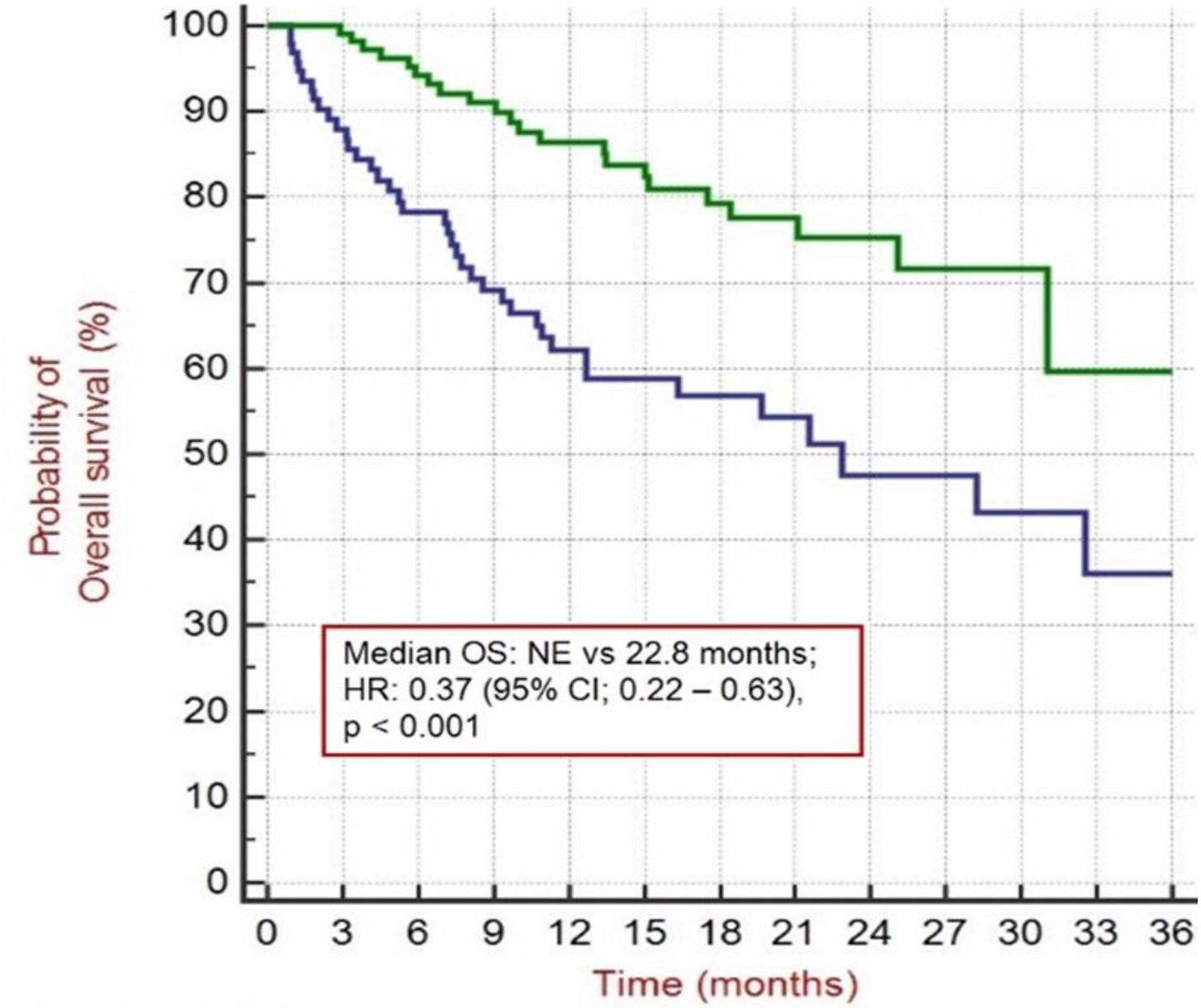


Figure 2

Overall Survival

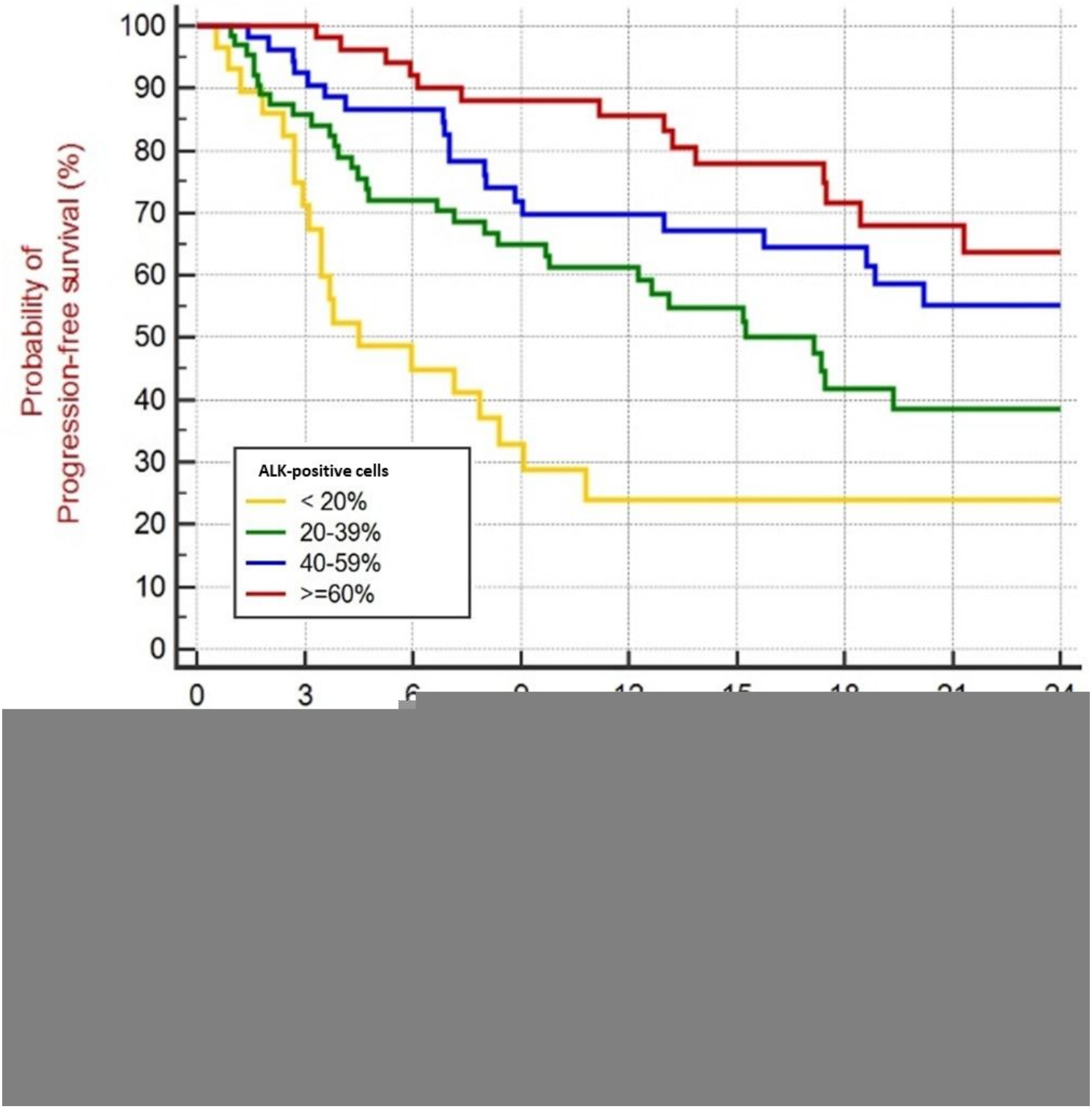


Figure 3

Progression-free Survival of the Subgroups