

Figure S1 Kaplan-Meier curve with longer OS for ALK-positive NSCLC patients receiving at least three ALK inhibitors compared to one or two. ALK, anaplastic lymphoma kinase; mOS, median overall survival; TKI, tyrosine kinase inhibitor; OS, overall survival; NSCLC, non-small cell lung cancer.

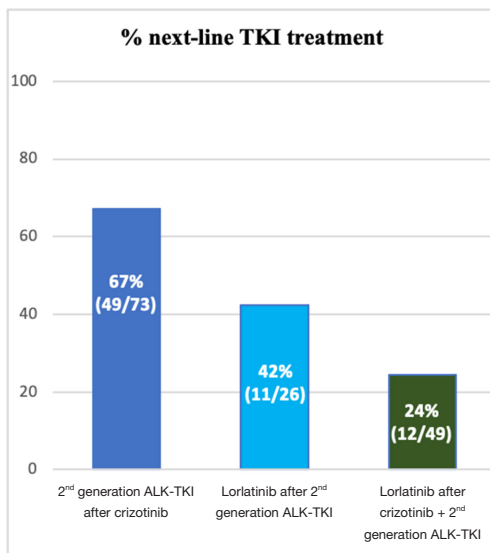


Figure S2 Histogram showing subsequent therapy after progression on initial ALK-TKI. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.

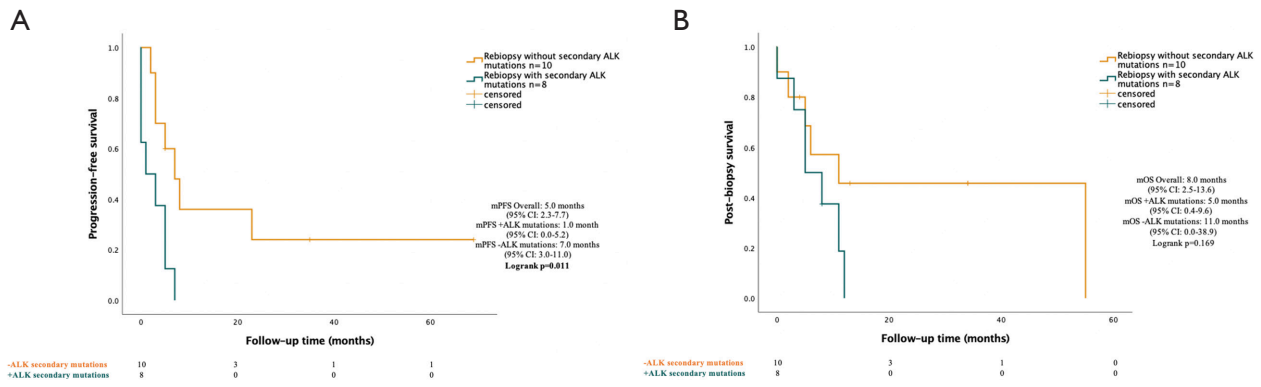


Figure S3 Impact of secondary *ALK* mutations on outcome. Kaplan-Meier curves showing PFS on next-line treatment (A) and post-biopsy survival (B) for patients with and without secondary *ALK* mutations. *ALK*, anaplastic lymphoma kinase; mPFS, median progression-free survival; CI, confidence interval; mOS, median overall survival; PFS, progression-free survival.

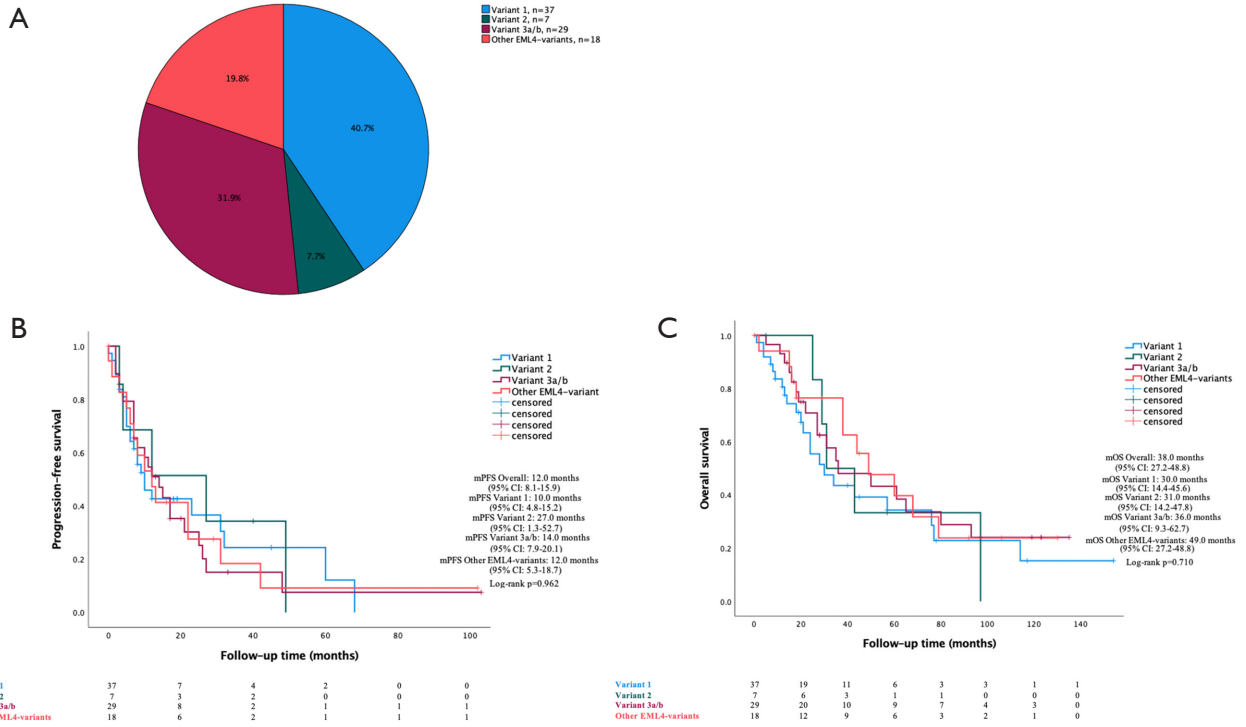


Figure S4 Impact of *EML4*-fusion variants on outcome. Pie chart showing the distribution of the different *EML4*-fusion variants (A). Kaplan-Meier curves for PFS (B) and OS (C) showed no statistically significant difference between the different *EML4*-fusion variants. *EML4*, echinoderm microtubule-associated protein-like 4; mPFS, median progression-free survival; CI, confidence interval; mOS, median overall survival.

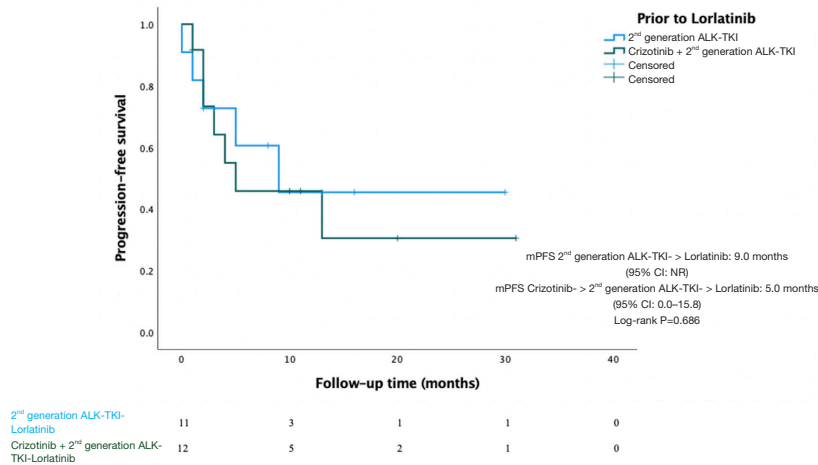


Figure S5 Kaplan-Meier curve demonstrating PFS regarding treatment prior to lorlatinib. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; mPFS, median progression-free survival; NR, not reached.

Table S1 Medians for survival time according to treatment status (log-rank test)

Treatment status	Patients, n (%)	mOS (95% CI) (months)	Log-rank P value
2 nd generation ALK-TKI after crizotinib (yes vs. no)	49 (66.2) vs. 25 (33.8)	50.0 (32.1–67.9) vs. 14.0 (7.8–20.2)	<0.001*
First-line ALK-TKI vs. chemotherapy	98 (60.4) vs. 54 (29.6)	65.0 (22.7–107.3) vs. 44.0 (22.8–65.2)	0.76
Subsequent line of any systemic therapy upon progression on initial ALK-TKI (yes vs. no)	70 (71.4) vs. 28 (28.6)	44.0 (24.8–63.2) vs. 13.0 (9.1–16.9)	<0.001*
Subsequent line of 2 nd generation ALK-TKI upon progression on initial ALK-TKI (yes vs. no)	59 (60.2) vs. 39 (39.8)	57.0 (38.0–76.0) vs. 16.0 (11.6–20.4)	<0.001*

*, clinical variables that are statistically significant between the groups. mOS, median overall survival; CI, confidence interval; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.

Table S2 Results of survival analysis for the numbers of treatment with ALK-TKIs with Cox regression analysis and log-rank test

ALK-TKIs	Patients, n (%)	mOS (95% CI) (months)	HR (95% CI)	P value
≥ Three ALK inhibitors	25 (16.7)	79.0 (32.1–125.9)	0.46 (0.25–0.83)	0.008*
One + two ALK inhibitors	125 (83.3)	43.0 (25.4–60.6)	Reference	0.11 (log-rank)
One	85 (56.7)	38.0 (6.7–69.3)		
Two	40 (26.7)	43.0 (25.8–60.2)		
Three	17 (11.3)	NR		
Four	5 (3.3)	79.0 (30.0–128.0)		
Five	2 (1.3)	38.0 (NR)		
Six	1 (0.7)	60.0 (NR)		
Overall	150 (100.0)	49.0 (30.5–67.5)		

*, clinical variables that are statistically significant between the groups. ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; mOS, median overall survival; HR, hazard ratio; CI, confidence interval; NR, not reached.

Table S3 Treatment patterns with ALK-TKI sequences and proportions of patients

Treatment pattern	Overall (n=150), n (%)	Crizotinib (n=74)	2 nd generation ALK-TKI (n=76)
One ALK inhibitor	85 (56.7)		
	25 (16.7)	Crizotinib	
	3 (2.0)		Ceritinib
	56 (37.3)		Alectinib
	1 (0.7)		Brigatinib
Two ALK inhibitors	40 (26.7)		
	14 (9.3)	Crizotinib-ceritinib	
	14 (9.3)	Crizotinib-alectinib	
	1 (0.7)	Crizotinib-brigatinib	
	3 (2.0)		Alectinib-brigatinib
	6 (4.0)		Alectinib-lorlatinib
	1 (0.7)		Ceritinib-brigatinib
	1 (0.7)		Ceritinib-alectinib
Three ALK inhibitors	17 (11.3)		
	2 (1.3)	Crizotinib-alectinib-brigatinib	
	3 (2.0)	Crizotinib-alectinib-lorlatinib	
	4 (2.7)	Crizotinib-brigatinib-lorlatinib	
	2 (1.3)	Crizotinib-ceritinib-alectinib	
	2 (1.3)	Crizotinib-alectinib-ceritinib	
	1 (0.7)	Crizotinib-brigatinib-ceritinib	
	3 (2.0)		Alectinib-brigatinib-lorlatinib
	Four ALK inhibitors	5 (3.3)	
1 (0.7)		Crizotinib-alectinib-lorlatinib-brigatinib	
1 (0.7)		Crizotinib-ceritinib-alectinib-brigatinib	
1 (0.7)		Crizotinib-ceritinib-alectinib-lorlatinib	
2 (1.3)			Ceritinib-alectinib-brigatinib-lorlatinib
Five ALK inhibitors	2 (1.3)		
	2 (1.3)	Crizotinib-ceritinib-alectinib-lorlatinib-brigatinib	
Six ALK inhibitors	1 (0.7)		
	1 (0.7)	Crizotinib-brigatinib-lorlatinib-alectinib-brigatinib-crizotinib	

ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.