

Figure S1 Flow diagram of the study design. NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4; TKI, tyrosine kinase inhibitor.

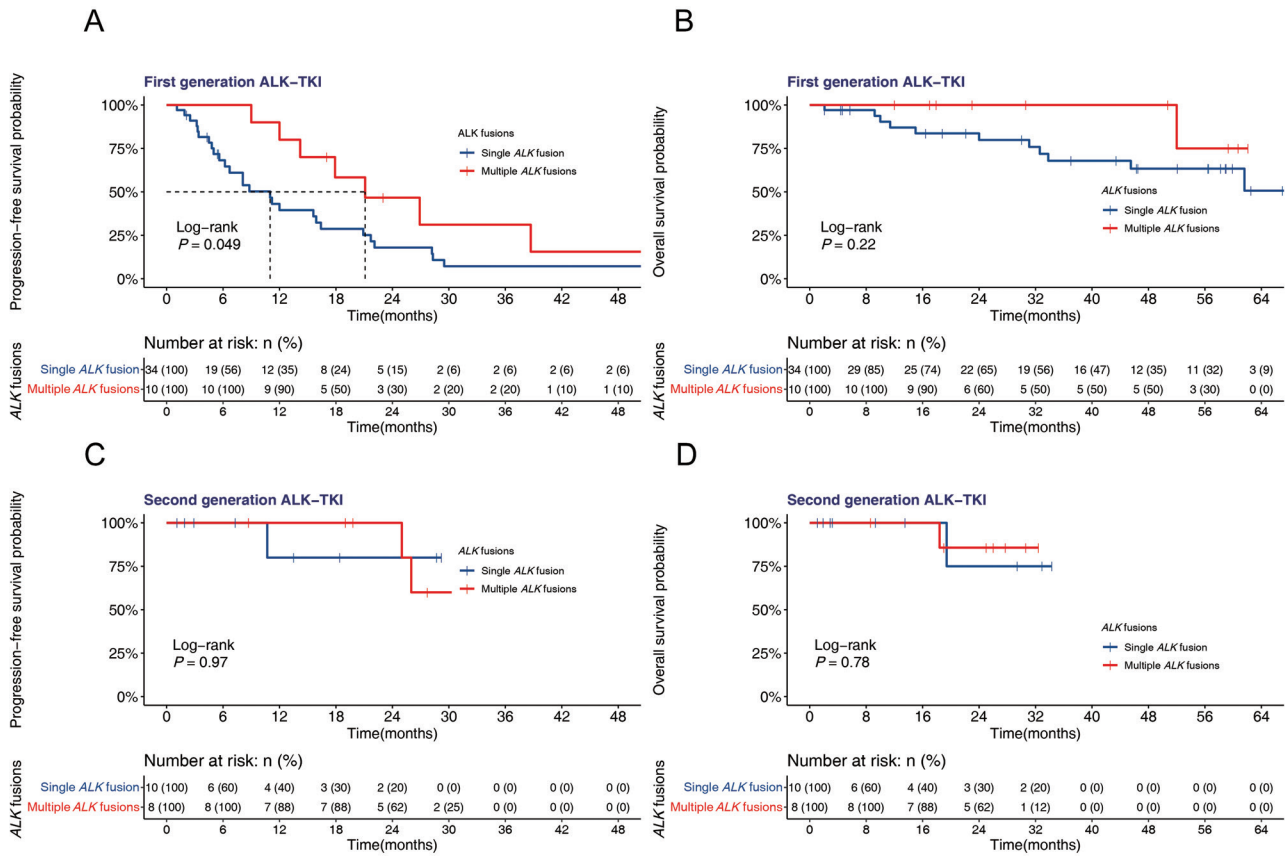


Figure S2 Clinical outcome comparisons in the multiple *ALK* fusion group and single *ALK* fusion group in patients received different generation of ALK-TKIs. (A) Kaplan-Meier curve of the PFS for ALK-TKI treatment in different groups of patients received first generation. (B) Kaplan-Meier curve of OS for ALK-TKI treatment in the different groups of patients received first generation. (C) Kaplan-Meier curve of PFS for ALK-TKI treatment in the different groups of patients received second generation. (D) Kaplan-Meier curve for OS of ALK-TKI treatment in the different groups of patients received second generation. *ALK*, anaplastic lymphoma kinase; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; OS, overall survival.

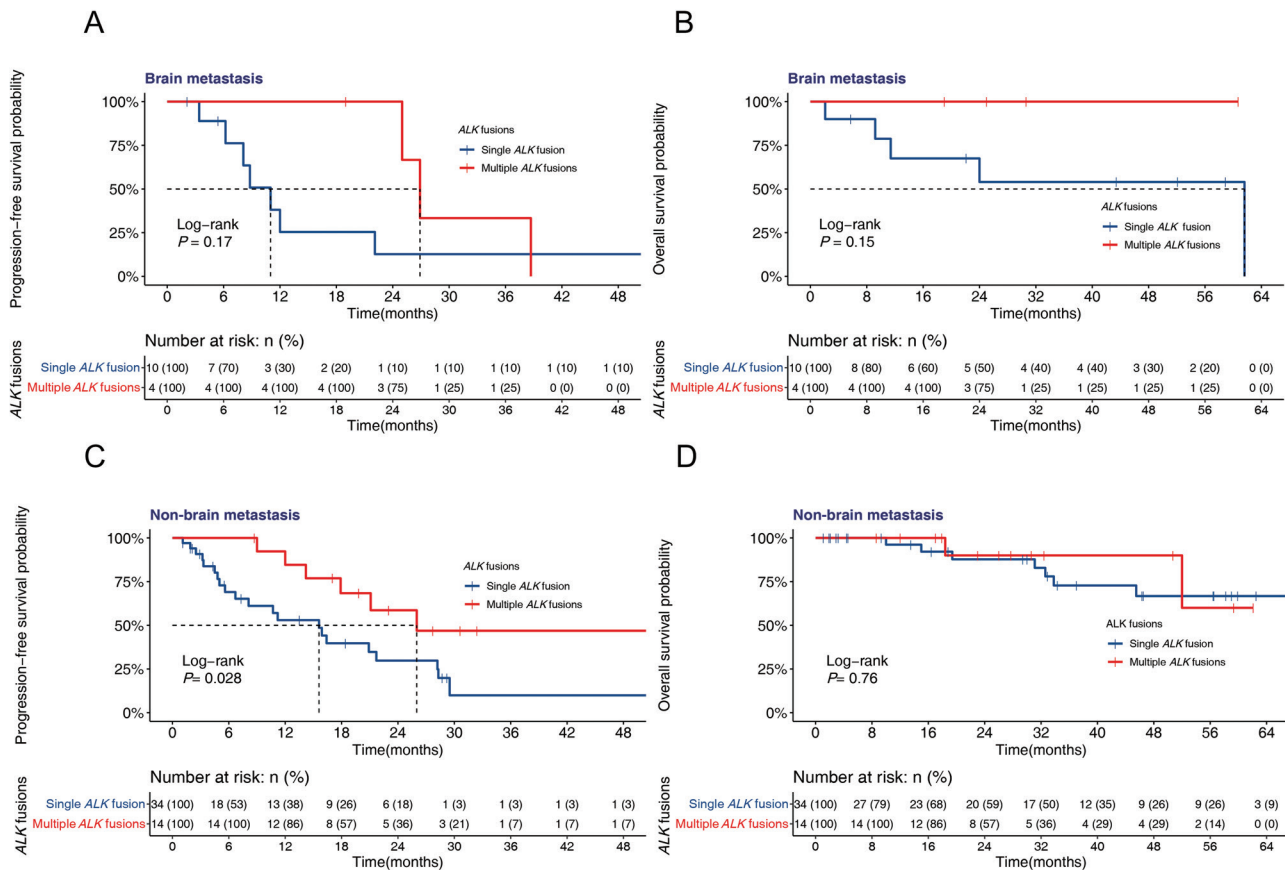


Figure S3 Clinical outcome comparisons in the multiple *ALK* fusion group and single *ALK* fusion group in patients with or without brain metastases. (A) Kaplan-Meier curve of the PFS for ALK-TKI treatment in different groups of patients with brain metastases. (B) Kaplan-Meier curve of OS for ALK-TKI treatment in the different groups of patients with brain metastases. (C) Kaplan-Meier curve of PFS for ALK-TKI treatment in the different groups of patients without brain metastases. (D) Kaplan-Meier curve for OS of ALK-TKI treatment in the different groups of patients without brain metastases. *ALK*, anaplastic lymphoma kinase; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; OS, overall survival.

Table S1 Distribution of *ALK* rearrangements identified from the 125 patients

<i>ALK</i> fusions detected from the cohort	Patients (%)
<i>EML4-ALK</i> fusions (n=82)	
<i>EML4-ALK</i> (E6:A19)	1 (0.8)
<i>EML4-ALK</i> (E13:A19)	2 (1.6)
<i>EML4-ALK</i> (E18:A19)	1 (0.8)
<i>EML4-ALK</i> (E19:A14)	1 (0.8)
<i>EML4-ALK</i> (E19:A20)	2 (1.6)
<i>EML4-ALK</i> (E21:A20)	2 (1.6)
<i>EML4-ALK</i> (E2:A19)	1 (0.8)
<i>EML4-ALK</i> (E6:A19)	3 (2.4)
<i>EML4-ALK</i> (V1)	27 (21.6)
<i>EML4-ALK</i> (V2)	6 (4.8)
<i>EML4-ALK</i> (V3)	31 (24.8)
<i>EML4-ALK</i> (V5)	2 (1.6)
<i>EML4-ALK</i> (V5a)	2 (1.6)
<i>EML4-ALK</i> (V8)	1 (0.8)
Multiple <i>ALK</i> fusions (n=26)	
<i>COX7A2L-ALK</i> (Cintragenic:A20), <i>LINC01210-ALK</i> (Lintergenic:A20), <i>ATP13A4-ALK</i> (A9:A19)	1 (0.8)
<i>DYSF-ALK</i> (Dintergenic:A20), <i>ITGAV-ALK</i> (I2:A20)	1 (0.8)
<i>EML4-ALK</i> (V3), <i>CTNNA2-ALK</i> (C8:A19)	1 (0.8)
<i>EML4-ALK</i> (E13:A19), <i>ALK-RBKS</i> (A19:R7)	1 (0.8)
<i>EML4-ALK</i> (V1), <i>ALK-ACTN1</i> (A19:A18)	1 (0.8)
<i>EML4-ALK</i> (V1), <i>ALKQPCT-ALK</i> (Qintergenic:A20)	1 (0.8)
<i>EML4-ALK</i> (V1), <i>CNTNAP5-ALK</i> (Cintergenic:A20)	1 (0.8)
<i>EML4-ALK</i> (V1), <i>FSHR-ALK</i> (Fintergenic:A20)	1 (0.8)
<i>EML4-ALK</i> (V1), <i>MGST2-ALK</i> (Mintergenic:A20)	1 (0.8)
<i>EML4-ALK</i> (V1), <i>RAB10-ALK</i> (Rintergenic:A20)	1 (0.8)
<i>EML4-ALK</i> (V1), <i>SOS1-ALK</i> (S10:A20)	1 (0.8)
<i>EML4-ALK</i> (V1), <i>STK17B-ALK</i> (SNA:A20)	1 (0.8)
<i>EML4-ALK</i> (V2), <i>LINC01121-ALK</i> (L1:A20)	1 (0.8)
<i>EML4-ALK</i> (V2), <i>VTA1-ALK</i> (Vintergenic:A20)	1 (0.8)
<i>EML4-ALK</i> (V3), <i>ALK-intergenic</i> (A19:Intergenic)	1 (0.8)
<i>EML4-ALK</i> (V3), <i>CDH2-ALK</i> (Cintergenic:A20)	1 (0.8)
<i>EML4-ALK</i> (V3), <i>CELF4-ALK</i> (Cintergenic:A20)	1 (0.8)
<i>EML4-ALK</i> (V3), <i>EML4-ALK</i> (E6:A19), <i>ALK-intergenic</i> (A19:Intergenic)	1 (0.8)
<i>EML4-ALK</i> (V3), <i>LOC388942-ALK</i> (Lintergenic:A20)	1 (0.8)
<i>EML4-ALK</i> (V3), <i>LYPD1-ALK</i> (Lintron3:A20)	1 (0.8)
<i>EML4-ALK</i> (V3), <i>SLC8A1-ALK</i> (Sintergenic:A19)	1 (0.8)
<i>EML4-ALK</i> (V3), <i>SMPD4-ALK</i> (S1:A20)	1 (0.8)
<i>EML4-ALK</i> (V5), <i>RBM20-ALK</i> (R1:A20)	1 (0.8)
<i>EML4-ALK</i> (V7), <i>LINC00327-ALK</i> (L2:A20), <i>GJB6-ALK</i> (Gintergenic:A20)	1 (0.8)
<i>MIR548AD-ALK</i> (Mintergenic:A20), <i>CAMKMT-ALK</i> (C3:A20)	1 (0.8)
<i>STRN-ALK</i> (S3:A20), <i>PDK1-ALK</i> (P7:A20)	1 (0.8)
Non- <i>EML4-ALK</i> fusions with 3'- <i>ALK</i> (n=17)	
<i>ARHGAP15-ALK</i> (A6:A20)	1 (0.8)
<i>C12orf75-ALK</i> (C1:A20)	1 (0.8)
<i>CENPA-ALK</i> (Cintergenic:A20)	1 (0.8)
<i>CHRNA7-ALK</i> (Cintergenic:A20)	1 (0.8)
<i>EPAS1-ALK</i> (E1:A20)	1 (0.8)
<i>FAM179A-ALK</i> (F1:A20)	1 (0.8)
<i>HIP1-ALK</i> (H22:A21)	1 (0.8)
<i>KIF5B-ALK</i> (K20:A20)	1 (0.8)
<i>KLC1-ALK</i> (K9:A20)	1 (0.8)
<i>LOC349160-ALK</i> (L1:A20)	1 (0.8)
<i>MEMO1-ALK</i> (Mintergenic:A20)	1 (0.8)
<i>PDCL3-ALK</i> (Pintergenic:A20)	1 (0.8)
<i>SORCS1-ALK</i> (S10:A20)	1 (0.8)
<i>STRN-ALK</i> (S3:A20)	1 (0.8)
<i>TACR1-ALK</i> (T1:A20)	1 (0.8)
<i>TANC1-ALK</i> (T3:A20)	1 (0.8)
<i>TUBB8-ALK</i> (T3:A20)	1 (0.8)

ALK, anaplastic lymphoma kinase; *EML4*, echinoderm microtubule-associated protein-like 4.

Table S2 Univariate and multivariate Cox regression analysis of 62 patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)	1.012 (0.986, 1.039)	0.363		
Gender				
Male	Ref.			
Female	0.673 (0.352, 1.292)	0.235		
Smoking status		0.366		
Never	Ref.			
Former/current	1.629 (0.758, 3.500)	0.211		
Unknown	0.697 (0.165, 2.953)	0.625		
ECOG PS				
0–1	Ref.			
≥2	1.344 (0.549, 3.289)	0.517		
Unknown	0.621 (0.187, 2.060)	0.436		
Stage				
III	Ref.			
IV	1.058 (0.461, 2.424)	0.895		
Brain metastasis				
No	Ref.			
Yes	1.245 (0.614, 2.522)	0.543		
Bone metastasis				
No	Ref.			
Yes	1.286 (0.669, 2.474)	0.451		
Liver metastasis				
No	Ref.			
Yes	2.005 (0.903, 4.453)	0.087		
Pleural metastasis				
No	Ref.			
Yes	1.153 (0.596, 2.231)	0.673		
Contralateral lung metastasis				
No	Ref.			
Yes	1.287 (0.584, 2.837)	0.531		
Treatment lines				
First-line	Ref.			
Second-line	0.697 (0.270, 1.799)	0.456		
ALK-TKIs				
First generation	Ref.		Ref.	
Second generation	0.174 (0.053, 0.569)	0.004	0.209 (0.063, 0.692)	0.010
ALK fusion				
Single <i>ALK</i> fusion	Ref.		Ref.	
Multiple <i>ALK</i> fusions	0.378 (0.178, 0.804)	0.012	0.490 (0.229, 1.049)	0.066

HR, hazard ratio; CI, confidence interval; ref., reference; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.

Table S3 Baseline characteristics of the 56 patients with ALK-rearranged NSCLC who received ALK-TKI therapy

Characteristics	All	Single ALK fusion	Multiple ALK fusions	P
No. of patients (%)	56 (100.0)	44 (78.6)	12 (21.4)	–
Age (years), median (range)	51.5 (42.0, 61.0)	51.0 (43.5, 64.3)	53.00 (41.8, 57.5)	0.667
Age, n (%)				0.999
≤40 years	10 (17.9)	8 (18.2)	2 (16.7)	
41–55 years	23 (41.1)	18 (40.9)	5 (41.7)	
56–70 years	18 (32.1)	14 (31.8)	4 (33.3)	
>70 years	5 (8.9)	4 (9.1)	1 (8.3)	
Gender, n (%)				0.642
Male	27 (48.2)	20 (45.5)	7 (58.3)	
Female	29 (51.8)	24 (54.5)	5 (41.7)	
Smoking status, n (%)				0.648
Never	40 (71.4)	31 (70.5)	9 (75.0)	
Former/current	13 (23.2)	10 (22.7)	3 (25.0)	
Unknown	3 (5.4)	3 (6.8)	0 (0.0)	
ECOG PS, n (%)				0.521
0	15 (26.8)	11 (25.0)	4 (33.3)	
1	30 (53.6)	23 (52.3)	7 (58.3)	
≥2	11 (19.6)	10 (22.7)	1 (8.3)	
Pathology, n (%)				0.754
Squamous cell carcinoma	1 (1.8)	1 (2.3)	0 (0.0)	
Adenocarcinoma	54 (96.4)	42 (95.5)	12 (100.0)	
Adenosquamous carcinoma	1 (1.8)	1 (2.3)	0 (0.0)	
Stage, n (%)				0.507
III	12 (21.4)	10 (22.7)	2 (16.7)	
IVA	20 (35.7)	14 (31.8)	6 (50.0)	
IVB	24 (42.9)	20 (45.5)	4 (33.3)	
Brain metastasis, n (%)				0.955
No	44 (78.6)	34 (77.3)	10 (83.3)	
Yes	12 (21.4)	10 (22.7)	2 (16.7)	
Liver metastasis, n (%)				0.482
No	45 (80.4)	34 (77.3)	11 (91.7)	
Yes	11 (19.6)	10 (22.7)	1 (8.3)	
Bone metastasis, n (%)				0.777
No	33 (58.9)	25 (56.8)	8 (66.7)	
Yes	23 (41.1)	19 (43.2)	4 (33.3)	
Adrenal metastasis, n (%)				1.000
No	53 (94.6)	42 (95.5)	11 (91.7)	
Yes	3 (5.4)	2 (4.5)	1 (8.3)	
Pleural metastasis, n (%)				0.178
No	35 (62.5)	30 (68.2)	5 (41.7)	
Yes	21 (37.5)	14 (31.8)	7 (58.3)	
Contralateral lung metastasis, n (%)				0.164
No	40 (71.4)	29 (65.9)	11 (91.7)	
Yes	16 (28.6)	15 (34.1)	1 (8.3)	
Treatment lines, n (%)				0.465
First-line	48 (85.7)	39 (88.6)	9 (75.0)	
Second-line	8 (14.3)	5 (11.4)	3 (25.0)	
Disease progression, n (%)				0.409
No	20 (35.7)	14 (31.8)	6 (50.0)	
Yes	36 (64.3)	30 (68.2)	6 (50.0)	
ALK-TKI, n (%)				0.355
Alectinib	13 (23.2)	8 (18.2)	5 (41.7)	
Ensartinib	1 (1.8)	1 (2.3)	0 (0.0)	
Crizotinib	41 (73.2)	34 (77.3)	7 (58.3)	
Ceritinib	1 (1.8)	1 (2.3)	0 (0.0)	

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table S4 Univariate and multivariate Cox regression analysis of 56 patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)	1.011 (0.984, 1.039)	0.439		
Gender				
Male	Ref.			
Female	0.730 (0.369, 1.444)	0.365		
Smoking status				
Never	Ref.			
Former/current	1.542 (0.711, 3.346)	0.273		
Unknown	0.732 (0.098, 5.454)	0.761		
ECOG PS				
0–1	Ref.			
≥2	1.301 (0.532, 3.181)	0.565		
Stage				
III	Ref.			
IV	1.044 (0.414, 2.218)	0.921		
Brain metastasis				
No	Ref.			
Yes	1.322 (0.631, 2.773)	0.459		
Bone metastasis				
No	Ref.			
Yes	1.204 (0.610, 2.377)	0.593		
Liver metastasis				
No	Ref.			
Yes	1.881 (0.837, 4.229)	0.126		
Pleural metastasis				
No	Ref.			
Yes	1.075 (0.536, 2.154)	0.839		
Contralateral lung metastasis				
No	Ref.			
Yes	1.177 (0.529, 2.623)	0.689		
Treatment lines				
First-line	Ref.			
Second-line	0.792 (0.305, 2.060)	0.633		
ALK-TKIs				
First generation	Ref.		Ref.	
Second generation	0.072 (0.010, 0.529)	0.010	0.084 (0.011, 0.619)	0.015
ALK fusion				
Single ALK fusion	Ref.		Ref.	
Multiple ALK fusions	0.360 (0.148, 0.874)	0.024	0.464 (0.191, 1.130)	0.091

HR, hazard ratio; CI, confidence interval; ref., reference; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.