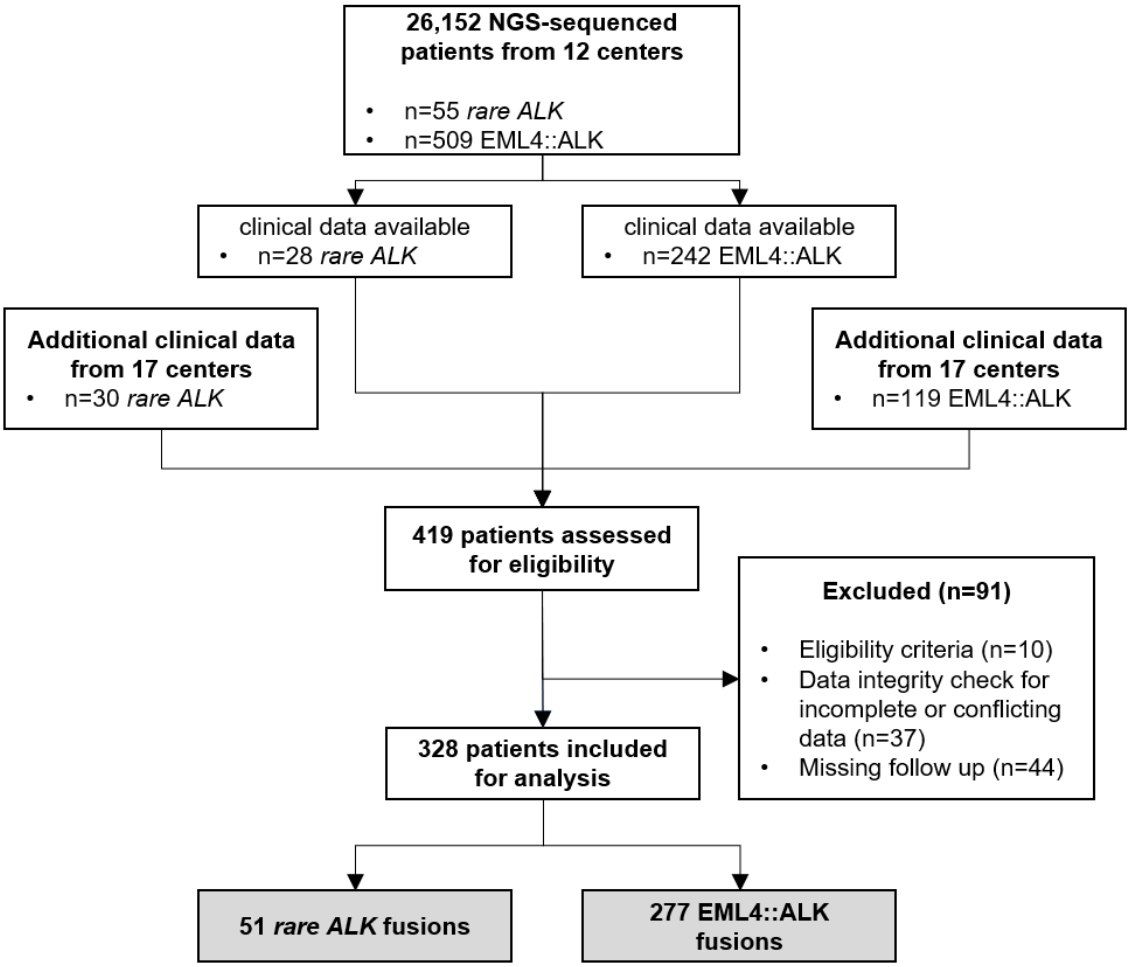
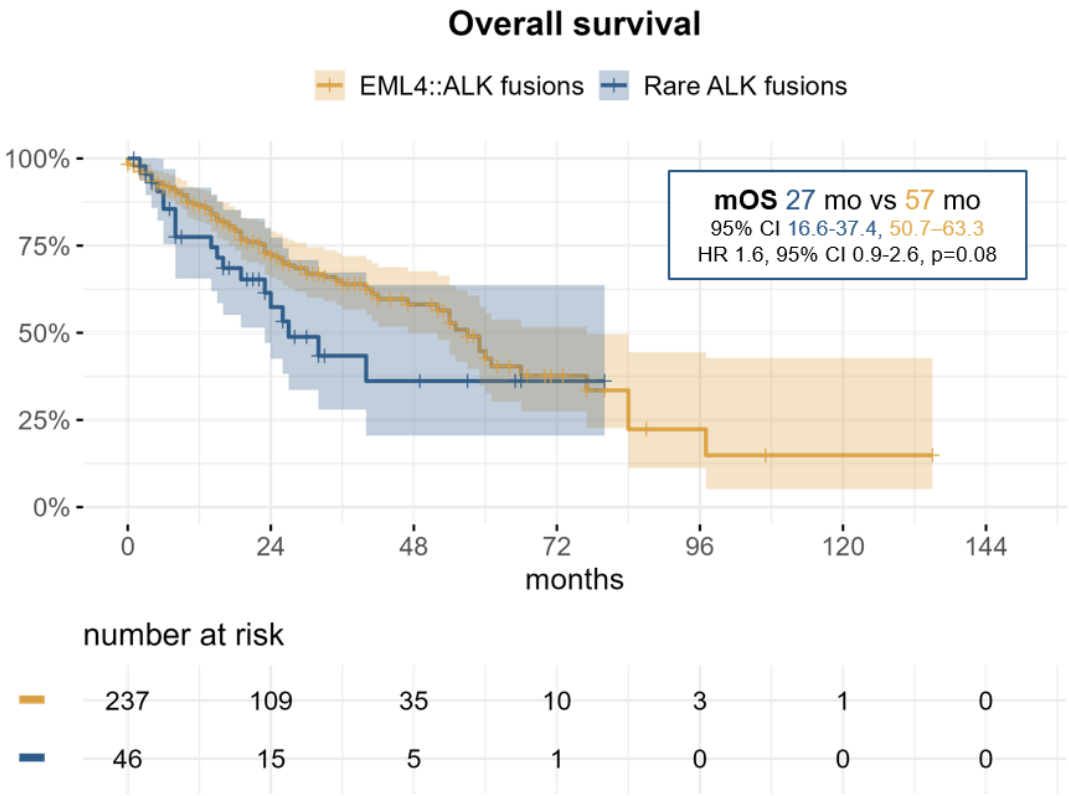
SUPPLEMENTS



Supplement 1. Study flowchart. Data was collected from 29 international centers and manually checked for eligibility, data quality and follow up (at least 3 months follow-up were required).

Rare ALK fusion variant	5' fusion Exon	3' fusion Exon	number
CLIP1::ALK	**13**	**20**	**1**
CLIP1::ALK	**12**	**20**	**2**
DCTN1::ALK	**5**	**2**	**1**
DCTN1::ALK	**26**	**20**	**3**
KIF5B::ALK	**NR**	**NR**	**1**
KIF5B::ALK	**15**	**20**	**1**
KIF5B::ALK	**24**	**20**	**5**
KIF5B::ALK	**17**	**20**	**5**
ALK::KLC1	**20**	**9**	**1**
KLC1::ALK	**9**	**20**	**5**
HIP1::ALK	**21**	**20**	**3**
HIP1::ALK	**28**	**20**	**1**
HIP1::ALK	**30**	**20**	**1**
GCC2::ALK	**19**	**20**	**2**
GCC2::ALK	**13**	**20**	**1**
GCC2::ALK	**6**	**20**	**2**
ETV6::ALK	**NR**	**20**	**1**
KIF13A::ALK	**NR**	**20**	**1**
SDC::ALK	**10**	**1**	**1**
SFTB::ALK	**18**	**6**	**1**
COL6A3::ALK	**13**	**20**	**1**
LCLAT1::ALK	**1**	**2**	**1**
MPRIP::ALK	**NR**	**NR**	**1**
BCL11A::ALK	**3**	**20**	**1**
SFTPB::ALK	**6**	**18**	**1**
EZR::ALK	**12**	**18**	**1**
PRKAB1 :: ALK	**16**	**5**	**1**
CLIP4::ALK	**2**	**4**	**1**
FNDCA3::ALK	**19**	**20**	**1**
WDR43::ALK	**1**	**2**	**1**
PRKAR1A::ALK	**9**	**20**	**1**

Supplement 2. Subgroups of *rare ALK* fusions sorted by fusion partner and exonic breakpoint.



Supplement 3. Kaplan-Meier plot with 95% confidence intervals for overall survival in patients with *rare ALK* fusions as compared to EML4::ALK fusions during first-line therapy irrespective of treatment choice in advanced NSCLC.

ALK fusion gene	5' fusion partner	3' fusion partner	ALK IHC	ALK FISH	1st targeted treatment	Best response
CLIP1::ALK	12	20	p	n	Lorlatinib	PR
DCTN1::ALK	26	20	p	n	Alectinib	PR
DCTN1::ALK	26	20	p		Crizotinib	SD
KIF5B::ALK	17	20	p	n	Alectinib	PD
KIF5B::ALK	17	20	p		Lorlatinib	SD
KLC1::ALK	9	20	p	n	Lorlatinib	PR
HIP1::ALK	30	20	p		Alectinib	PR
ETV6::ALK		20	n	p	Alectinib	SD
KLC1::ALK	9	20	p		Alectinib	PR
GCC2:ALK	6	20	p		Alectinib	PD
KIF5B::ALK	17	20	p		Lorlatinib	PR
HIP1::ALK	21	20	p		Brigatinib	PR
SFTB::ALK	18	6	n		Crizotinib	SD
KIF5B::ALK	24	20	p		Crizotinib	PR
KLC1::ALK	9	20	p	p	Crizotinib	SD
KIF5B::ALK	24	20			Crizotinib	PR
HIP1::ALK	21	20			Alectinib	PR
HIP1::ALK	28	20	p		Alectinib	SD
COL6A3::ALK	13	20			Crizotinib	PR
LCLAT1::ALK	1	2			Alectinib	PR
KIF5B::ALK	17	20			Alectinib	PR
KIF5B::ALK	24	20	p		Alectinib	PR
KIF5B::ALK	17	20	p		Alectinib	PR
GCC2::ALK	19	20	p		Alectinib	PR
KLC1::ALK	9	20	p		Alectinib	PR
DCTN1::ALK	26	20	p		Brigatinib	PR
HIP1::ALK	30	20		p	Brigatinib	PR
MPRIP::ALK			p	p	Alectinib	PR
KIF5B::ALK			p	p	Crizotinib	SD
KIF5B::ALK	15	20			Alectinib	PR
GCC2::ALK	13	20	p		Alectinib	PD

ALK::KLC1	20	9			Alectinib	PR
SFTPB::ALK	6	18			Crizotinib	PR
HIP1::ALK	21	20			Alectinib	PR
CLIP1::ALK	13	20	p		Alectinib	CR
KIF5B::ALK	24	20			Alectinib	PR
EZR::ALK	12	18	p	p	Alectinib	PR
DCTN1::ALK	5	2	p	p	Alectinib	PD
GCC2::ALK	6	20	n	p	Alectinib	PD
PRKAR1A::ALK	9	20	p		Alectinib	PR
GCC2::ALK	19	20	p		Alectinib	PR
CLIP1::ALK	12	20	p		Lorlatinib	PR

Supplement 4. *Rare ALK* cohort with information on fusion partner, break points, IHC and FISH. Best responses to first treatment with TKI, irrespective of treatment line. ORR data for first treatment with TKI available for 42/51 *rare ALK* patients (CR 1/42, PR 29/42, SD 7/42, PD 5/42). p: positive, n: negative.

	Responder (N = 30)	Non-responder (N = 12)
IHC positive	**19**	**9**
IHC negative	**0**	**3**
IHC not available	**11**	**0**
IHC positivity in tested patients	**100%**	**75%**

Supplement 5. ALK expression by immunohistochemistry (IHC) in patients with *rare ALK* fusions with or without objective tumor response to first ALK inhibitor. FISH: fluorescence in situ hybridization.

Variable	Availability of Data	Median PFS (95% CI)	Proportional hazards assumption	Hazard Ratio (95% CI)	P-value for Cox regression
Sex (female vs male)	**N = 51/51 (100%)**	**11 (0-23.6) vs 22 (0-24.8) mo**	**Not True**	**/**	**/**
Age (>65 years vs ≤65 years)	**N = 51/51 (100%)**	**14 (6.2-21.8) vs 30 (0-62.5) mo**	**Not True**	**/**	**/**
ECOG (PS 2-3 vs PS 0-1)	**N = 49 / 51 (96%)**	**8 (5.1-10.9) vs 16 (0-32.5) mo**	**True**	**2.1 (0.4-2.4)**	**0.1**
Histology (Other vs Adeno)	**N = 51/51 (100%)**	**3 (2.2-3.8) vs 16 (2.4-29.6) mo**	**True**	**9.6 (2.6-36.3)**	**<0.01**
Smoker (never vs ever)	**N = 49 / 51 (96%)**	**23 (2.4-43.6) vs 8 (0.2-15.8) mo**	**True**	**0.6 (0.3-1.4)**	**0.3**
Brain metastasis at first diagnosis (yes vs no)	**N = 49 / 51 (96%)**	**14 (7.0-21) vs 16 (0-37) mo**	**Not True**	**/**	**/**
TP53 Mutation (yes vs no)	**N = 43 / 51 (84%)**	**23 (6.3-30.7) vs 8 (2-14) mo**	**Borderline**	**/**	**/**
First-line Therapy (Platin vs TKI)	**N = 51 / 51 (100%)**	**5 (1.3-2.4) vs 23 (7.1-38.9) mo**	**True**	**3.1 (1.2-8)**	**0.02**

Supplement 6. Univariate Cox regression analysis for first-line PFS in patients with *rare ALK* fusions.