Supplementary Table 1: Summary of trial sites and recruitment.

Trial site ID	Trial site	Principal investigator	Recruitment (incl. screening failures)
CH-22	Universitätsspital Basel, Basel, Switzerland	Sacha Rothschild	0
DE-07	Evangelic Lung Clinics Berlin, Berlin, Germany	Christian Grohé	2
DE-08	University Hospital of Frankfurt, Frankfurt, Germany	Martin Sebastian	7
DE-10	LungenClinic Grosshansdorf, Grosshansdorf, Germany	Martin Reck	3
DE-11	Thoraxklinik Heidelberg, Heidelberg, Germany	Helge Bischoff	2
DE-12	University Hospital of Cologne, Cologne, Germany	Jürgen Wolf	11
DE-23	University Hospital of Tübingen, Tübingen, Germany	Hans-Georg Kopp	0
DE-24	Hospital of the Ludwig-Maximilians-University Munich, Munich, Germany	Rudolf M. Huber	0
ES-01	Hospital Teresa Herrera, A Coruna, Spain	Charo Garcia Campelo	0
ES-02	Hospital General Universitario de Alicante, Alicante, Spain	Bartomeu Massuti	2
ES-04	Hospital Germans Trias I Pujol, Badalona, Spain	Enric Carcereny	1
ES-05	Institut Català D'Oncologia L'Hospitalet - Hospital Duran i Reynals	Ernest Nadal	0
ES-06	Hospital Universitario Vall D'Hebron, Barcelona, Spain	Enriqueta Felip	2
ES-13	Hospital Universitario Materno-Infantil de Canaris, Las Palmas de Gran Canaria, Spain	Delvys Rodriguez Abreu	1
ES-15	Hospital Universitari de la Princesa, Madrid, Spain	Jose Miguel Sánchez	0
ES-16	Hospital Universitario Puerta de Hierro de Majadahonda, Majadahonda, Spain	Mariano Provencio	1
ES-17	Hospital Carlos Haya, Malaga, Spain	Manuel Cobo	0
ES-18	Hospital Son Llatzer, Palma de Mallorca, Spain	Juan Coves Sarto	0
ES-19	Hospital Universitario Virgen del Rocío, Sevilla, Spain	Jesús Corral/Reyes Benabé	2
ES-20	Hospital Clínico Universitario de Valencia, Valencia, Spain	Amelia Insa	1
	Total		35

Supplementary Table 2: Summary of genes tested by „NEOplus“ DNA sequencing (NEO New Oncology, Cologne, Germany)

ALK, ARAF, ATM, ATR, BRAF, BRCA1/2, CDK4, CDKN2A, CDKN2B, CTNNB1, DDR2, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, HRAS, IDH1/2, KEAP1, KIT, KRAS, MAPK2K1, MDM2, MET, MTOR, NFE2L2, NRAS, PDGFRA, PIK3CA, PTEN, RB1, RET, ROS1, STK11, TP53, TSC1/2.

Supplementary Table 3: Summary of patients excluded from efficacy analyses

Number	Reason
1	Protocol violation: no adequate baseline imaging (scans were performed after the start of the treatment)
2	Violation of eligibility criteria: carcinomatous meningtitis and active CNS metastases
3	Violation of eligibility criteria: no central *ROS1* FISH performed
4	Violation of eligibilty criteria: previous treatment with crizotinib and no central *ROS1* FISH performed

Supplementary Table 4: Overall survival in the response-evaluable population (*N*=30).

Overall survival (OS)	
Median OS (months (95% CI))	NR (17.1–not reached)
Events censored (*N* (%))	21 (70%)
OS at 12 months (% (95% CI))	83 (69–97)
OS at 24 months (% (95% CI))	63 (42–84)

Supplementary Table 5: Summary of response assessment of the intention-to-treat (ITT) population (*N*=34).

		Local radiologic assessment		Independent radiologic assessment	
		% (*N*)	**95% CI**	**% (*N*)**	**95% CI**
ITT population (*N*=34)	**Objective response rate (ORR)**	71 (24)	53-85	74 (25)	56-87
	Complete response	0 (0)		0 (0)	
	Partial response	71 (24)		74 (25)	
	Disease control rate (DCR)	88 (30)	73-97	82 (28)	66-93
	Stable disease	18 (6)		6 (2)	

Supplementary Table 6: Time-to-event outcomes of the intention-to-treat (ITT) population (*N*=34).

	Local radiologic assessment	Independent radiologic assessment
Progression-free survival (PFS)		
Median PFS (months (95% CI))	20.0 (9.6-NR)	20.0 (9.6-NR)
Events censored (*N* (%))	16 (47%)	17 (50%)
PFS at 12 months (% (95% CI))	56 (39-73)	59 (42-75)
PFS at 24 months (% (95% CI))	46 (28-65)	46 (28-65)
Overall survival (OS)		
Median OS (months (95% CI))	NR (20.3-NR)	
Events censored (*N* (%))	23 (68%)	
OS at 12 months (% (95% CI))	82 (69-95)	
OS at 24 months (% (95% CI))	60 (40-80)	

Supplementary Tables 7: (A) ORR and (B) summary of PFS (C) by *TP53* mutation status.

(A)

***TP53*-mutant**	**Responses (*N*)**	**ORR (%)**	**95% CI**	***P*-value (Fisher exact)**
No (*N*=13)	12	92	64-100	1.000
Yes (*N*=5)	4	80	28-100	
All (*N*=18)	16	89	65-99	

(B)

***TP53*-mutant**	**Censored (*N*; %)**	**Median (months)**	**95% CI**	**HR (95% CI)**	***P*-value (log-rank test)**
No (*N*=13)	7; 53.8	24.1	10.1-NR	3.89 (1.12-13.6)	0.022
Yes (*N*=5)	0; 0.0	7.0	1.7–20.0		
All (*N*=18)	7; 38.9	16.8	4.5–29.1		

Supplementary Table 8: Summary of response assessment stratified by therapy line and baseline status of brain metastases.

		Local radiologic assessment		Independent radiologic assessment	
		% (n)	95% CI	% (n)	95% CI
Response by therapy line	**Objective response rate (ORR)**				
	0-1 prior lines of therapy (n=16)	68.8 (11)	41.3-89.0	62.5 (10)	35.4-84.8
	≥2 prior lines of therapy (n=14)	71.4 (10)	41.9-91.6	85.7 (12)	57.2-98.2
	P (Fisher exact)	1.0		0.226	
	Disease control rate (DCR)				
	0-1 prior lines of therapy (n=16)	87.5 (14)	61.7-98.5	75.0 (12)	47.6-92.7
	≥2 prior lines of therapy (n=14)	92.9 (13)	66.1-99.8	92.9 (13)	66.1-99.8
	P (Fisher exact)	1.0		0.336	
Response by brain metastases	**Objective response rate (ORR)**				
	No brain metastases at baseline (n=23)	69.6 (16)	47.1-86.8	69.6 (16)	47.1-86.8
	Brain metastases at baseline (n=6)	66.7 (4)	22.3-95.7	83.3 (5)	35.9-99.6
	P (Fisher exact)	1.0		0.647	
	Disease control rate (DCR)				
	No brain metastases at baseline (n=23)	91.3 (21)	72.0-98.9	82.6 (19)	61.1-95.1
	Brain metastases at baseline (n=6)	83.3 (5)	35.9-99.6	83.3 (5)	35.9-99.6
	P (Fisher exact)	0.515		1.0	

Supplementary Table 9: Summary of time-to-event outcomes stratified by therapy line and baseline status of brain metastases.

		Local radiologic assessment	Independent radiologic assessment
		Median (95% CI)	**Median (95% CI)**
Time-to-event by treatment lines (n=30)	**Progression-free survival (PFS)**		
	0-1 prior lines of therapy (*N*=16)	17.8 (7.0-NR)	NR (7.0-NR)
	≥2 prior lines of therapy (*N*=14)	20.0 (6.9-NR)	20.0 (6.9-NR)
	HR (95% CI)	0.833 (0.328-2.37)	0.955 (0.346-2.64)
	P (log-rank)	0.805	0.930
	Overall survival (OS)		
	0-1 prior lines of therapy (*N*=16)	NR (16.4-NR)	
	≥2 prior lines of therapy (*N*=14)	NR (13.0-NR)	
	HR (95% CI)	1.27 (0.34-4.73)	
	P (log-rank)	0.7234	
Time-to-event by brain metastases (n=29)	**Progression-free survival (PFS)**		
	No brain metastases at baseline (*N*=23)	20.0 (10.1-NR)	20.0 (10.1-NR)
	Brain metastases at baseline (*N*=6)	9.4 (1.7-NR)	7.3 (1.7-NR)
	HR (95% CI)	1.53 (0.488-4.77)	1.93 (0.607-6.15)
	P (log-rank)	0.464	0.257
	Overall survival (OS)		
	No brain metastases at baseline (*N*=23)	NR (17.1-NR)	
	Brain metastases at baseline (*N*=6)	NR (1.7-NR)	
	HR (95% CI)	2.38 (0.588-9.62)	
	P (log-rank)	0.211	

Supplementary Table 10: Summary of acquired co-occurring aberrations detected progression to crizotinib. AR, acquired resistance

Patient	AR mechanisms identified	Gene	DNA seq.	Protein seq.	Genomic fraction	Present at baseline	Comment
1	yes	*TP53*	c.524G>A	p.R175H	93,4	yes	
		PIK3CA	c.1633G>A	p.E545K	36,1	no	
2	yes	*ROS1*	c.6076C>A	p.L2026M	20,5	no	No ROS1 fusion, but ROS1 mutation detected
		TP53	c.833C>A	p.P278H	18,9	no	
3	no	-	-	-	-	-	
4	no	-	-	-	-	-	No ROS1 fusion detected

Supplementary Table 11: Line listing of all dose reductions.

Number of patients	Reason for first dose reduction(s) and grading	Reduced dose (mg)
1	Visual disorder grade 1	200 BID
2	Dysgeusia grade 3	200 BID
3	Vomiting grade 2	200 BID
4	Vomiting grade 3	200 BID
5	Neutropenia grade 3	200 BID
6	Neutropenia grade 3	200 BID
7	Neutropenia grade 3	200 BID
8	Edema peripheral grade 2	200 BID
9	Edema peripheral grade 2	200 BID
10	Persistent edema peripheral grade 1 and headache grade 1	200 BID
11	Asthenia grade 3 and bradycardia grade 2	200 BID
12	Bradycardia grade 2	200 BID
13	Bradycardia grade 2	200 BID
14	Bradycardia grade 2	200 BID
15	Palpitations grade 1	200 BID
16	Renal cyst grade 3	200 BID
Total: n=16		

Supplementary Table 12: Summary of the most common adverse events (≥10%), irrespective of the relatedness to crizotinib.

	Grade, number (%) of patients					
AE term	**Any**	**1**	**2**	**3**	**4**	**5**
Any AE	33 (97)	33 (97)	30 (88)	19 (56)	0 (0)	6 (18)
In ≥ 10% of patients						
Oedema	22 (65)	44 (15)	7 (21)	-	-	-
Visual disturbances	22 (65)	22 (65)	-	-	-	-
Diarrhoea	21 (62)	16 (47)	5 (15)	-	-	-
Bradycardia	17 (50)	12 (35)	5 (15)	-	-	-
Nausea	15 (44)	9 (26)	5 (15)	1 (3)	-	-
Musculosceletal pain	13 (38)	9 (26)	4 (12)	-	-	-
ALT* increased	12 (35)	10 (29)	1 (3)	1 (3)	-	-
Vomiting	12 (35)	7 (21)	4 (12)	1 (3)	-	-
Asthenia/fatigue	11 (32)	7 (21)	4 (12)	-	-	-
Leukopenia/neutropenia	11 (32)	6 (18)	2 (6)	3 (9)	-	-
Dizziness	10 (29)	7 (21)	2 (6)	1 (3)	-	-
Anaemia	9 (26)	8 (24)	-	1 (3)	-	-
AST* increased	9 (26)	9 (26)	-	-	-	-
Constipation	8 (24)	6 (18)	2 (6)	-	-	-
Blood creatinine increased	7 (21)	6 (18)	1 (3)	-	-	-
Cough	7 (21)	4 (12)	3 (9)	-	-	-
Dyspnea	7 (21)	4 (12)	1 (3)	2 (6)	-	-
Respiratory tract infection	7 (21)	3 (9)	4 (12)	-	-	-
Viral infection, not specified	7 (21)	5 (15)	2 (6)	-	-	-
Urinary tract infection	6 (18)	2 (6)	4 (12)	-	-	-
Abdominal pain	6 (18)	5 (15)	1 (3)	-	-	-
Dyspepsia	5 (15)	4 (12)	1 (3)	-	-	-
Headache	5 (15)	4 (12)	1 (3)	-	-	-
Hypophosphataemia	5 (15)	3 (9)	1 (3)	1 (3)	-	-
Muscle cramps	5 (15)	4 (12)	1 (3)	-	-	-
Pulmonary embolism/ venous thrombosis	5 (15)	1 (3)	-	2 (6)	-	2 (6)
AP* increased	4 (12)	4 (12)	-	-	-	-
Decreased appetite	4 (12)	2 (6)	2 (6)	-	-	-
Dysgeusia	4 (12)	3 (9)	1 (3)	-	-	-
Hypoalbuminaemia	4 (12)	4 (12)	-	-	-	-
Hyponatriaemia	4 (12)	4 (12)	-	-	-	-
Peripheral neuropathy	4 (12)	3 (9)	1 (3)	-	-	-
Pleural effusion	4 (12)		2 (6)	2 (6)	-	-
Rash	4 (12)	4 (12)	-	-	-	-
Thrombocytopenia	4 (12)	3 (9)	-	1 (3)	-	-

*ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase

Supplementary Table 13: Line listing of all treatment-related serious adverse events (SAE).

Description of event	Grade	Seriousness criteria
Visual disturbance	1	Important medical condition
Diarrhoea	1	Important medical condition
Diarrhoea	2	Hospital stay over night
Vomiting	3	Hospital stay over night
Pulmonary embolism	5	Death, hospital stay over night
Deep vein thrombosis	3	Hospital stay over night
Pneumonitis	2	Hospital stay over night
Complicated renal cyst	3	Hospital stay over night

Supplementary Table 14: Changes in heart rate (A), systolic blood pressure (B) and diastolic blood pressure (C) during study treatment (*N*=34).

(A)

	Heartrate (bpm)				
Study phase or visit	**Number of records**	**Mean**	**Median**	**Minimum**	**Maximum**
Screening	33	84·5	82	60	142
During treatment	619	65·5	63	44	115
End of treatment visit	8	81·3	80·5	57	100
Safety follow-up visit	6	82·8	81·5	66	106
Unscheduled visit	48	60·9	56	46	125

(B)

	Systolic blood pressure (mmHg)				
Study phase or visit	**Number of records**	**Mean**	**Median**	**Minimum**	**Maximum**
Screening	33	128·6	128	101	165
During treatment	619	123·4	122	70	189
End of treatment visit	9	131·1	124	97	170
Safety follow-up visit	6	127	131	100	150
Unscheduled visit	62	122·1	120	87	162

(C)

	Diastolic blood pressure (mmHg)				
Study phase or visit	**Number of records**	**Mean**	**Median**	**Minimum**	**Maximum**
Screening	33	83	80	60	106
During treatment	619	74·7	74	48	113
End of treatment visit	9	76·8	78	56	100
Safety follow-up visit	6	83·8	83·5	65	100
Unscheduled visit	62	73·7	70	60	100

Supplementary Table 15: Tabulation of results of multiple imputations of QLQ-C30. HSQOL, global quality of life; EF, emotional functioning; CF, cognitive functioning; PF, physical functioning; RF, role functioning.

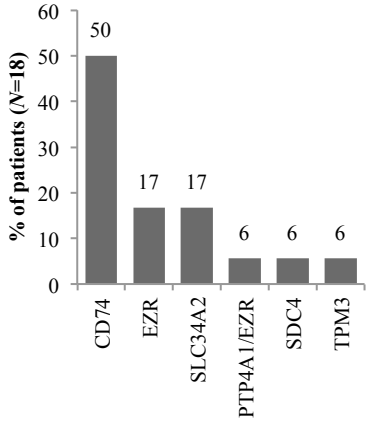
Score	Method (n=5 imputations unless otherwise stated)	Time intervals	Transform-ation	Linear slope (b)	SE(b)	P	Rel. var. increase
HSQOL	Mixed model (no imputation)	All	No	0.0206	0.0081	0.011	--
HSQOL	Mixed model (no imputation)	0-9	No	0.0287	0.0114	0.012	--
HSQOL	MI of mixed model using FCS	0-9	No	0.0186	0.0130	0.16	0.35
HSQOL	MI of mixed model using FCS, n=10 imput.	0-9	No	0.0183	0.0127	0.15	0.28
HSQOL	MI of mixed model using FCS	0-9	Logit	0.0159	0.0110	0.24	0.49
HSQOL	MI of mixed model, Monotone Reg	0-9	No	0.0207	0.0120	0.087	0.23
HSQOL	MI of mixed model, Monotone Reg	0-9	Logit	0.0178	0.0121	0.15	0.36
HSQOL	MI of mixed model using FCS	0-11	No	-0.0088	0.0114	0.44	0.20
HSQOL	MI of mixed model using FCS	0-11	Logit	-0.0036	0.0131	0.79	0.68
HSQOL	MI of mixed model, Monotone Reg	0-11	No	-0.0032	0.0116	0.78	0.39
HSQOL	MI of mixed model, Monotone Reg	0-11	Logit	-0.0048	0.0107	0.66	0.27
EF	Mixed model (no imputation)	0-9	no	0.0148	0.0074	0.045	--
EF	MI of mixed model using FCS	0-9	no	0.0092	0.0141	0.52	0.73
EF	MI of mixed model using FCS	0-9	Logit	0.0095	0.0124	0.45	0.43
EF	MI of mixed model, Monotone Reg	0-9	no	0.0152	0.0125	0.23	0.43
EF	MI of mixed model, Monotone Reg	0-9	Logit	0.0132	0.0122	0.29	0.54
CF	Mixed model (no imputation)	All	no	-0.0041	0.0062	0.51	
CF	MI of mixed model using FCS	0-9	no	-0.0106	0.0098	0.28	0.27
CF	MI of mixed model using FCS	0-9	Logit	-0.0121	0.0154	0.45	1.97
CF	MI of mixed model , Monotone Reg	0-9	no	-0.0065	0.0097	0.50	0.34
CF	MI of mixed model, Monotone Reg	0-9	Logit	-0.0054	0.0093	0.56	0.53
PF	Mixed model (no imputation)	All	no	0.0156	0.0076	0.042	--
PF	MI of mixed model using FCS	0-9	no	0.0172	0.0142	0.26	0.59
PF	MI of mixed model using FCS	0-9	Logit	0.0100	0.0134	0.47	0.83
PF	MI of mixed model , Monotone Reg	0-9	no	0.0113	0.0008	0.21	0.44
PF	MI of mixed model , Monotone Reg	0-9	Logit	0.0132	0.0111	0.24	0.36
PF	MI of mixed model using FCS	0-11	No	-0.0027	0.0157	0.86	1.63
PF	MI of mixed model using FCS	0-11	Logit	-0.0382	0.0207	0.86	3.64
PF	MI of mixed model , Monotone Reg	0-11	No	0.0036	0.0162	0.83	2.45
PF	MI of mixed model , Monotone Reg	0-11	Logit	0.0124	0.0132	0.37	1.44
SF	Mixed model (no imputation)	All	no	0.0164	0.0100	0.10	--
SF	MI of mixed model using FCS	0-9	No	-0.0003	0.0167	0.99	0.82
SF	MI of mixed model using FCS	0-9	Logit	0.0049	0.0174	0.78	1.17
SF	MI of mixed model , Monotone Reg	0-9	No	0.0043	0.0132	0.74	0.22
SF	MI of mixed model , Monotone Reg	0-9	Logit	0.0054	0.0122	0.66	0.23
RF	Mixed model (no imputation)	All	no	0.0140	0.0102	0.17	--
RF	MI of mixed model using FCS	0-9	No	0.0141	0.0171	0.25	0.53
RF	MI of mixed model using FCS	0-9	Logit	0.0186	0.0158	0.62	0.49
RF	MI of mixed model , Monotone Reg	0-9	No	0.0097	0.0192	0.62	0.83
RF	MI of mixed model , Monotone Reg	0-9	Logit	0.0077	0.0153	0.62	0.42

Supplementary Table 16: Tabulation of results of multiple imputations of QLQ-LC13. CO, coughing; DY, dyspnoea; HA, haemoptysis; PC, chest pain.

Score	Method (n=5 imputations unless otherwise stated)	time intervals	Transform-ation	Linear slope (b)	SE(b)	P	Rel. var. increase
CO	Mixed model (no imputation)	All	No	-0.0298	0.0077	0.0001	
	MI of mixed model using FCS	0-9	No	-0.0380	0.0153	0.021	0.77
	MI of mixed model using FCS	0-9	Logit	-0.0442	0.0154	0.0063	0.44
	MI of mixed model, Monotone Reg	0-9	No	-0.0419	0.0123	0.0013	0.39
	MI of mixed model, Monotone Reg	0-9	Logit	-0.0379	0.0184	0.062	0.64
DY	Mixed model (no imputation)	0-9	no	0.0143	0.0082	0.082	
	MI of mixed model using FCS	0-9	no	-0.0073	0.0159	0.65	0.99
	MI of mixed model using FCS	0-9	Logit	-0.0134	0.0113	0.24	0.13
	MI of mixed model, Monotone Reg	0-9	no	-0.0064	0.0143	0.66	0.88
	MI of mixed model, Monotone Reg	0-9	Logit	-0.0106	0.0125	0.40	0.45
HA	Mixed model (no imputation)	All	no	-0.0040	0.0032	0.22	
	MI of mixed model using FCS	0-9	no	-0.0079	0.0044	0.073	0.05
	MI of mixed model using FCS	0-9	Logit	-0.0108	0.0112	0.35	0.97
	MI of mixed model , Monotone Reg	0-9	no	-0.0081	0.0043	0.060	0.01
	MI of mixed model, Monotone Reg	0-9	Logit	-0.0062	0.0088	0.49	0.48
PC	Mixed model (no imputation)	All	no	-0.0081	0.0046	0.082	
	MI of mixed model using FCS	0-9	no	-0.0098	0.0069	0.16	0.03
	MI of mixed model using FCS	0-9	Logit	-0.0250	0.0145	0.089	0.30
	MI of mixed model , Monotone Reg	0-9	no	-0.0093	0.0072	0.20	0.22
	MI of mixed model , Monotone Reg	0-9	Logit	-0.0137	0.0205	0.52	1.78

Supplementary Figure 1: (A) Distribution of ROS1 fusion types and (B) ORR by *ROS1* fusion type (investigator-assessed; *N*=18).

(A)

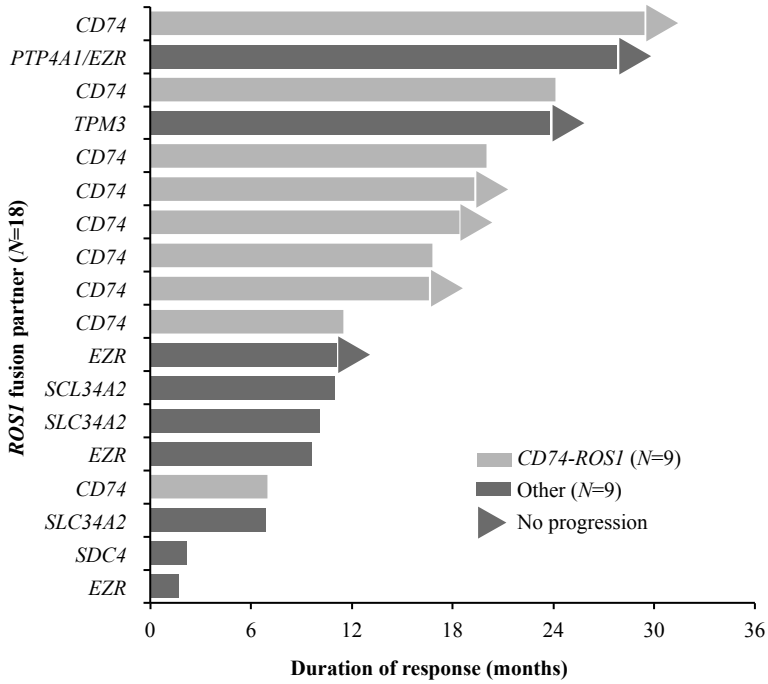


(B)

Fusion partner	Responses (*N*)	ORR (%)	95% CI	*P*-value (Fisher exact)
CD74 (*N*=9)	9	100	66-100	0.473
Other (*N*=9)	7	78	40-97	
All	16	89	65-99	

Supplementary Figure 2: (A) Swimmer plot of PFS and (C) summary of PFS by *ROS1* fusion type (investigator-assessed; *N*=18).

(A)

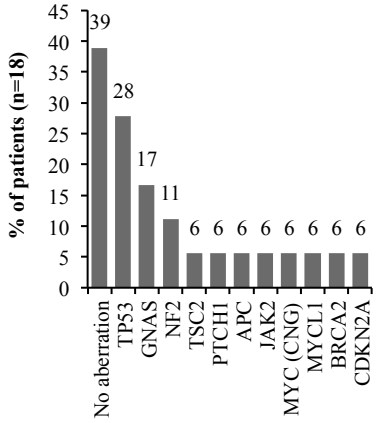


(B)

Fusion partner	Censored (n,%)	Median (months)	95% CI	HR (95% CI)	*P*-value (log-rank test)
CD74 (*N*=9)	4, 44.4	20.0	7.0-NR	0.490 (0.146-1.64)	0.239
Other (*N*=9)	3, 33.3	10.1	1.7-NR		
All	7, 38.9	16.8	4.5-29.1		

Supplementary Figure 3: (A) Distribution of co-occurring aberrations, (B) ORR, (C) swimmer plot of PFS, and (D) PFS by status of co-aberration (investigator-assessed; *N*=18). CNG, copy number gain

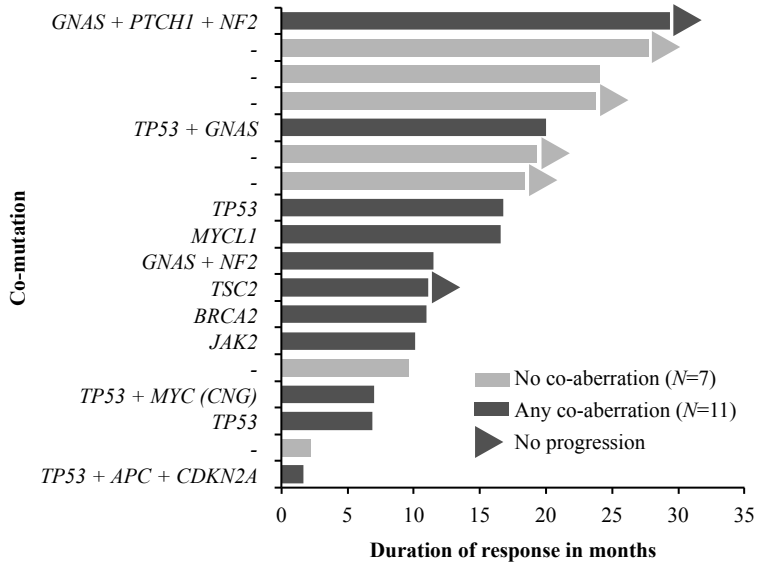
(A)



(B)

Co-aberrations	Responses (*N*)	ORR (%)	95% CI	*P*-value (Fisher exact)
No (*N*=7)	6	86	42-100	0.641
Any (*N*=11)	10	91	59-100	
All (*N*=18)	16	89	65-99	

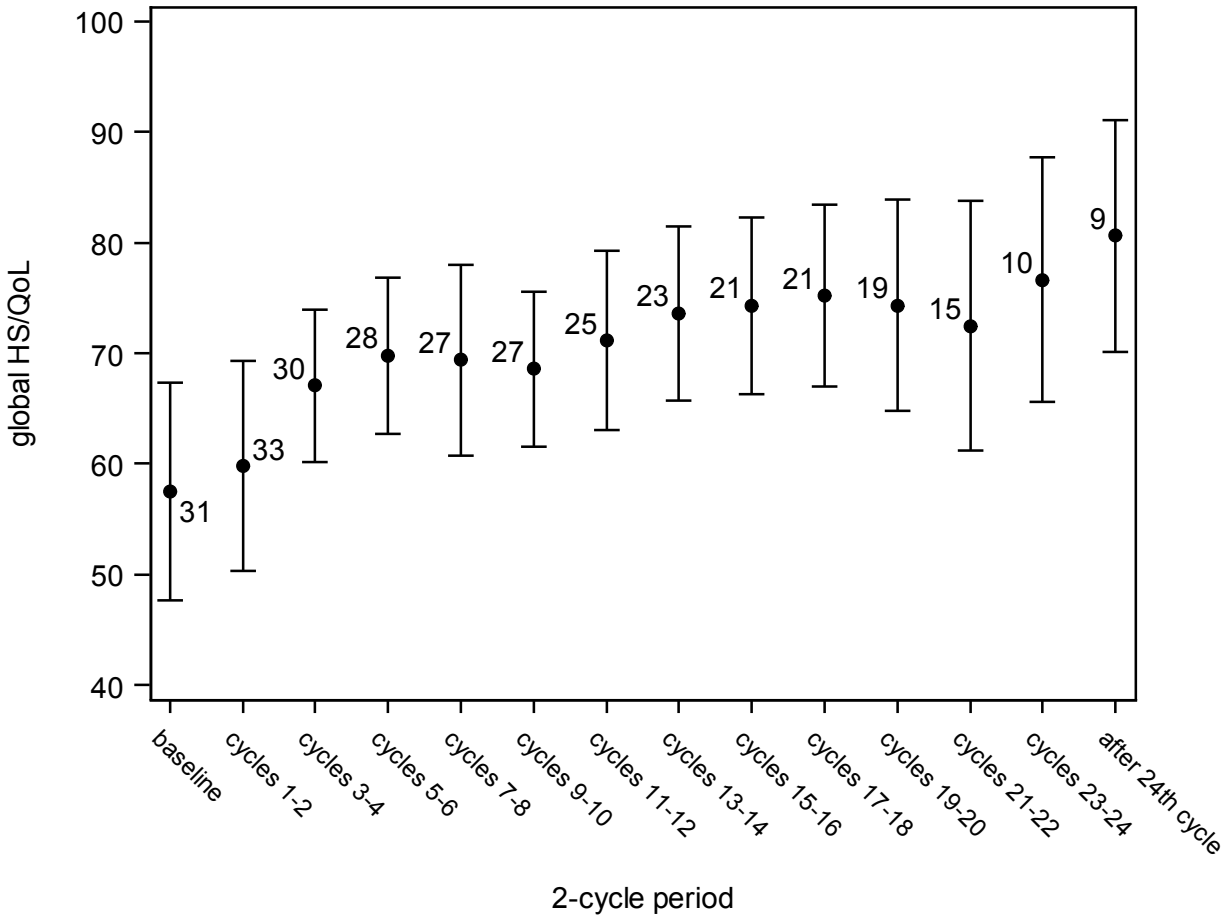
(C)



(D)

Co-aberration	Censored (*N*; %)	Median (months)	95% CI	*P*-value (log-rank test)
No (*N*=7)	4; 57	24.1	2.2-NR	0.175
Any (*N*=11)	3; 27	11.5	6.9-20.0	
All (*N*=18)	7; 39	16.8	4.5-29.1	

Supplementary Figure 4: Change in global quality of life assessed through QLQ-C30.



Supplementary Figure 5: Change in intensity of selected lung cancer-associated symptoms assessed through QLQ-LC13 – coughing (A), haemoptysis (B), chest pain (C), dyspnea (D).