V SIMPOSIO GETHI | 18/19 noviembre de 2019

Ilustre Colegio Oficial de Médicos de Madrid. Aula Jiménez Díaz. Madrid

Alteraciones de ROS y ALK en subtipos infrecuentes de cáncer de pulmón y otros tumores raros

IdiPAZ Instituto de Investigación Hospital Universitario La Paz

Dr. Javier de Castro

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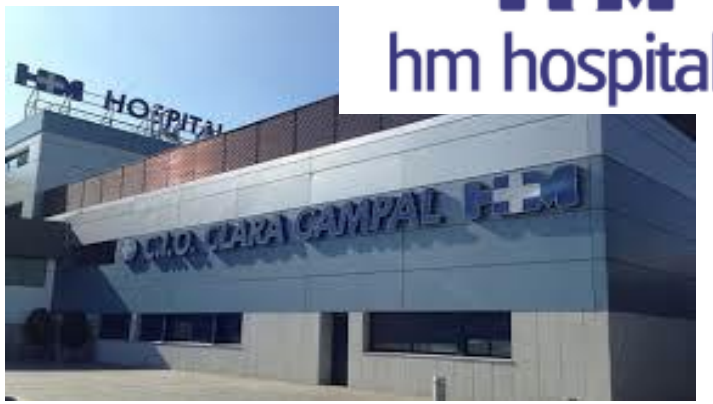


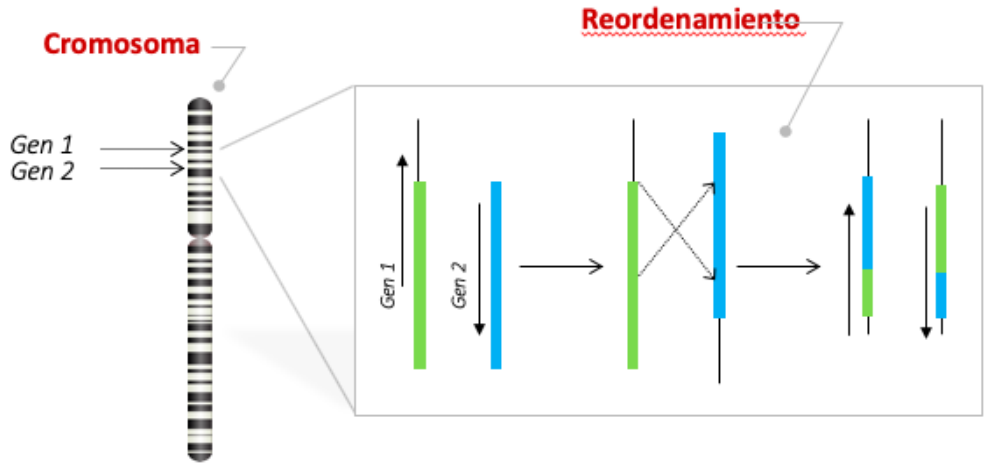
hm hospitales

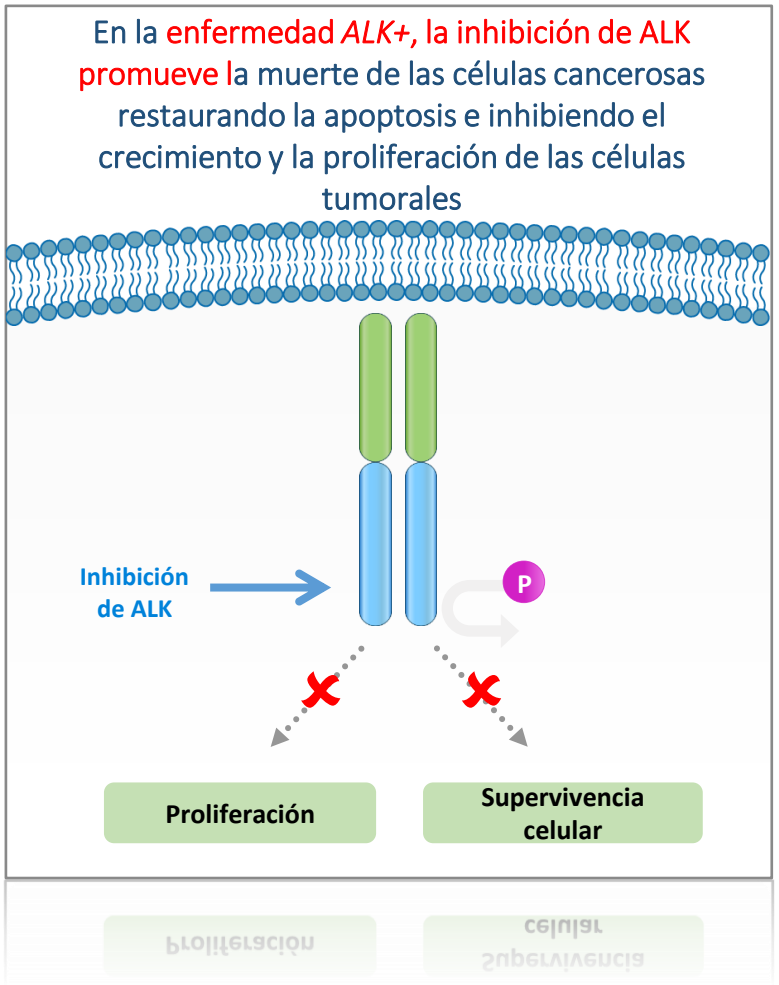
Madrid, 18 de Noviembre 2019

Disclosure

- Educational/travel fees: Astra Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharp and Dohme, Novartis, Pierre Fabre y Roche.
- Advisory board: Astra Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharp and Dohme, Novartis, Pfizer, Roche y Takeda.

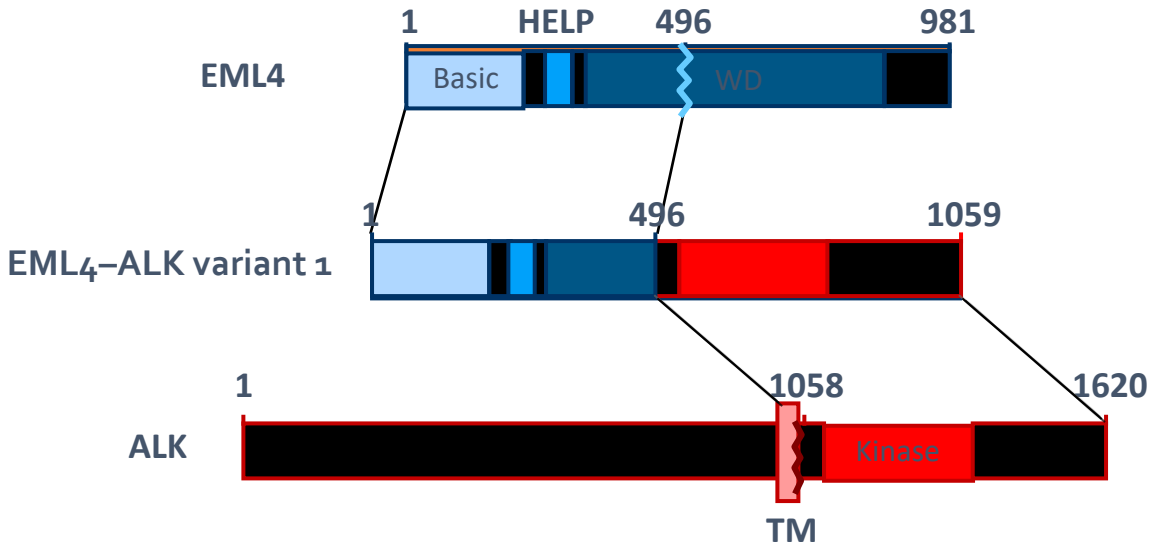
Reordenamiento de ALK





1. Torti & Trusolino. EMBO Mol Med 2011;
2. McDermott, et al. Cancer Res 2008;
3. Takezawa, et al. Clin Cancer Res 2011

EML4-ALK in NSCLC



Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

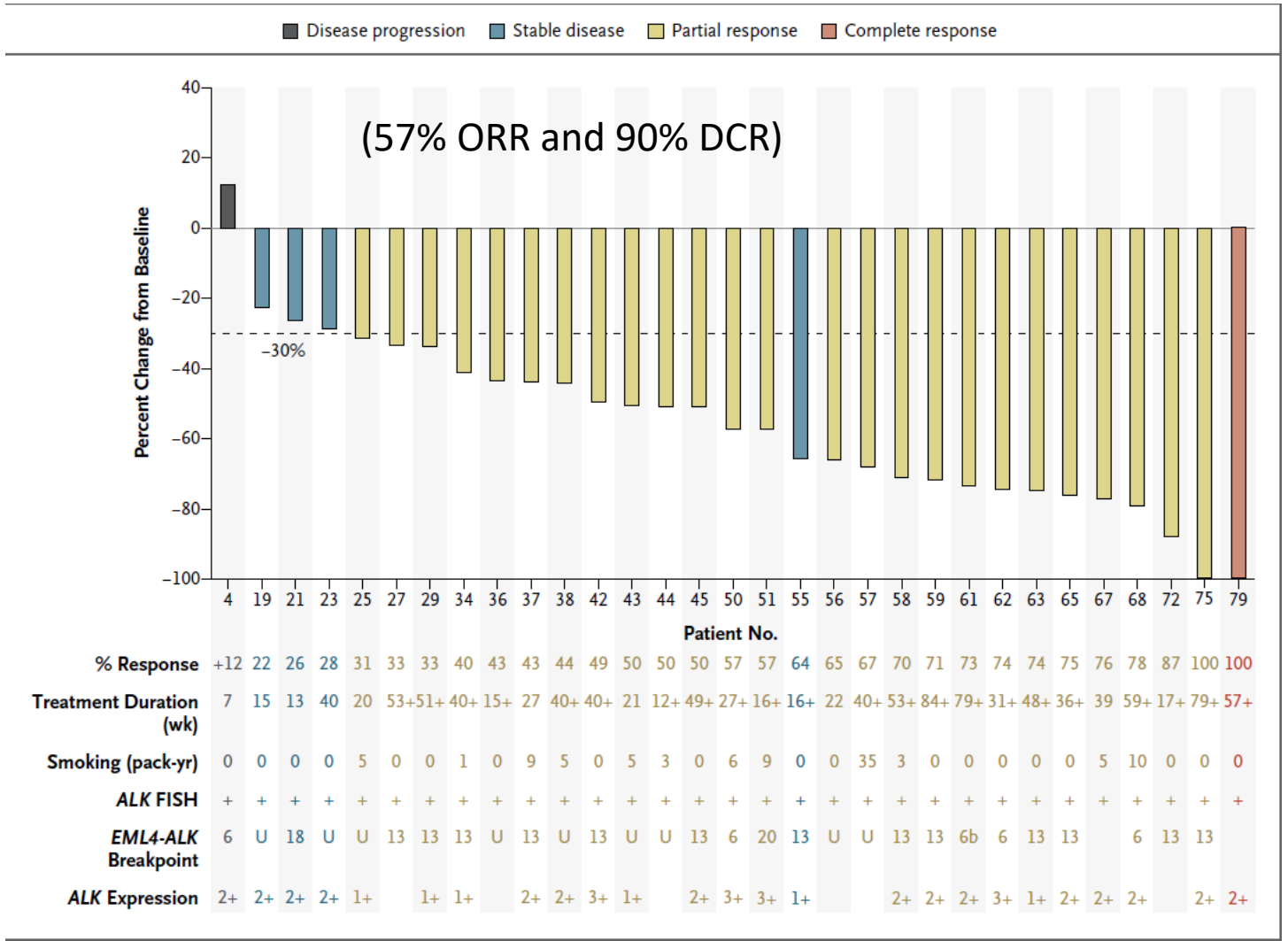
Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]

Soda et al., *Nature* 2007; 448:561-567

The NEW ENGLAND JOURNAL of MEDICINE

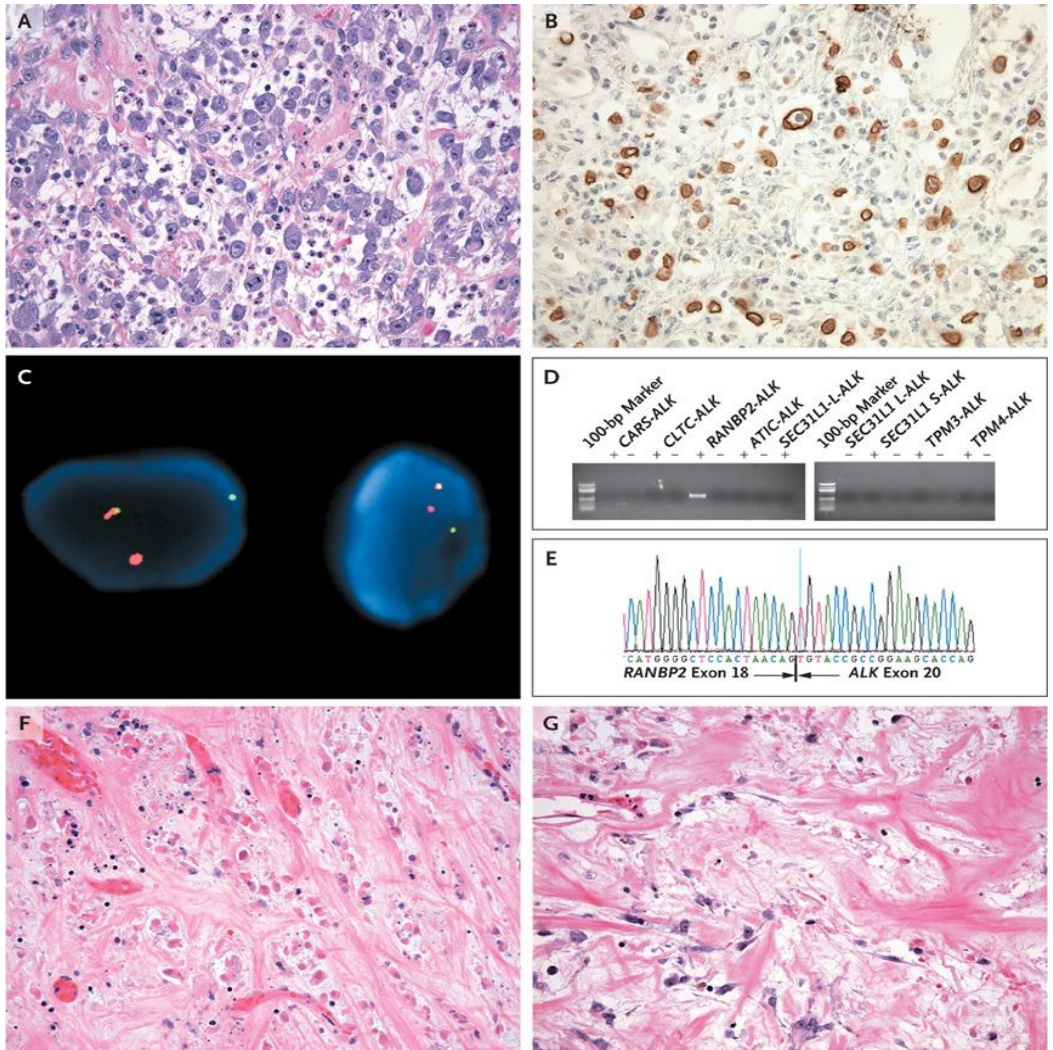
ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer



Crizotinib en el tumor miofibroblástico inflamatorio reordenado *ALK*

James E. Butrynski, MD, David R. D'Adamo, MD, Ph.D., Jason L. Hornick, MD, Ph.D., Paola Dal Cin, Ph.D., Cristina R. Antonescu, MD, Suresh C. Jhanwar, Ph.D., Marc Ladanyi, MD, Marzia Capelletti, Ph.D., Scott J. Rodig, MD, Ph.D., Nikhil Ramaiya, MD, Eunice L. Kwak, MD, Jeffrey W. Clark, MD, et al.



28 de octubre de 2010
N Engl J Med 2010; 363: 1727-1733

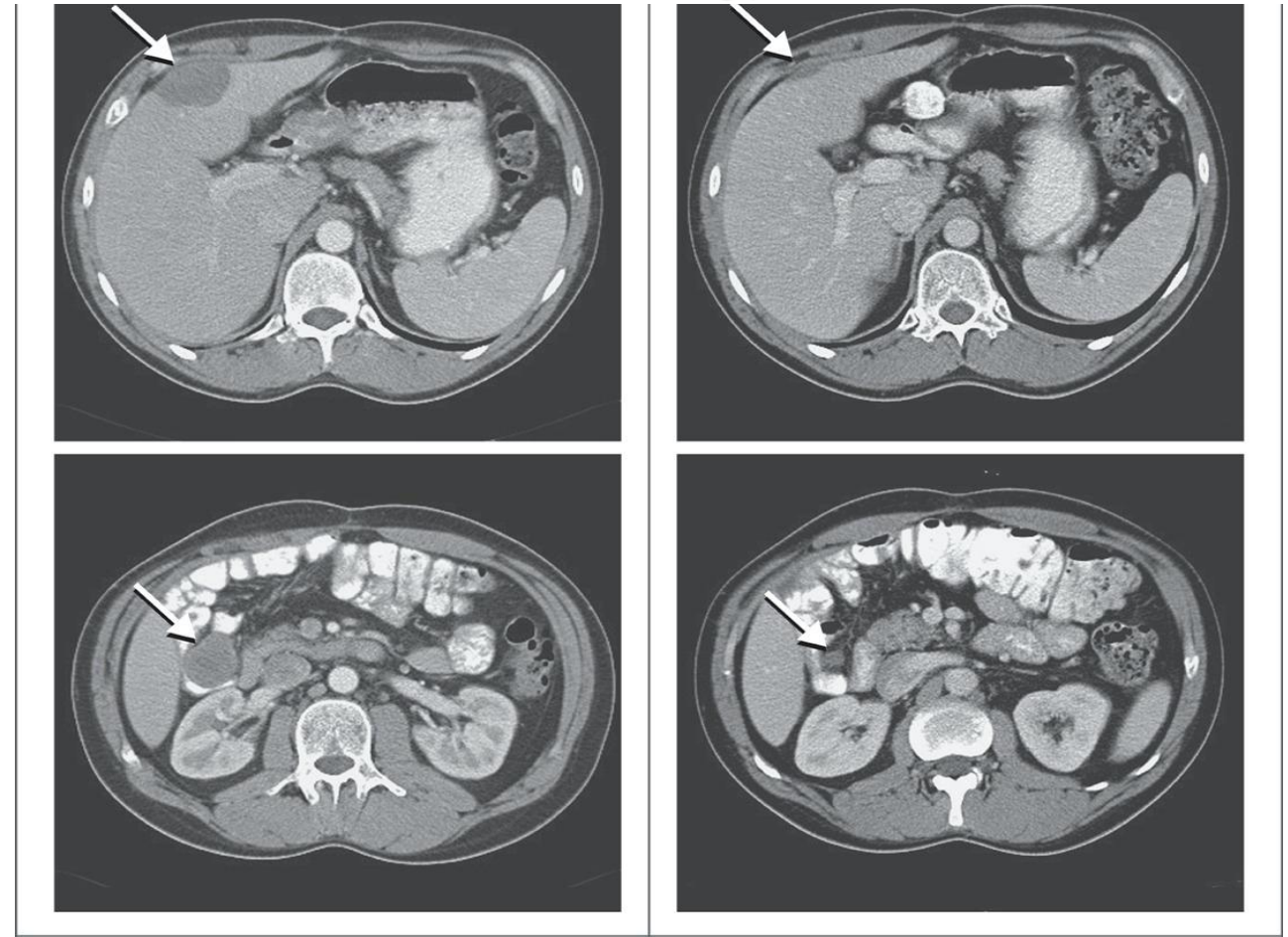
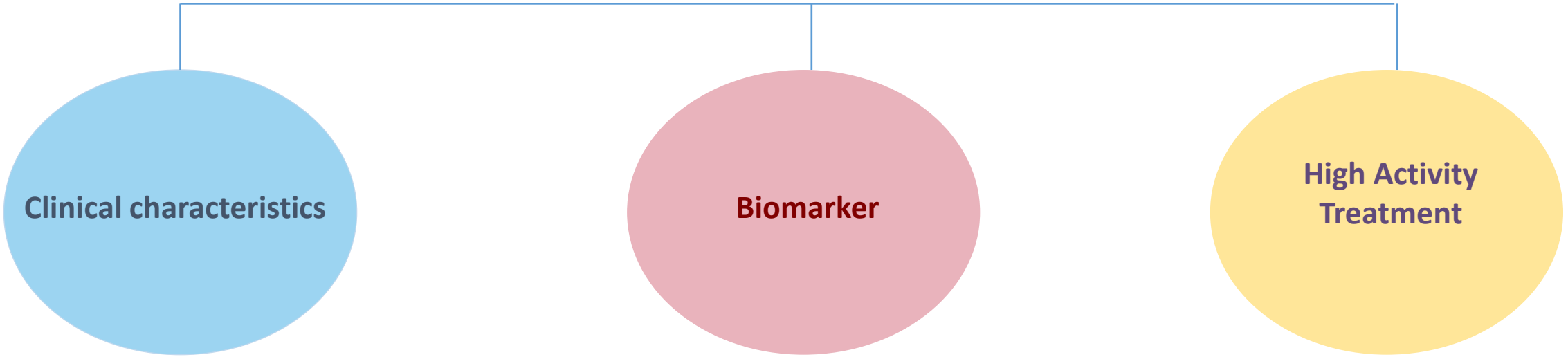


Table 1. ALK gene abnormalities in cancer

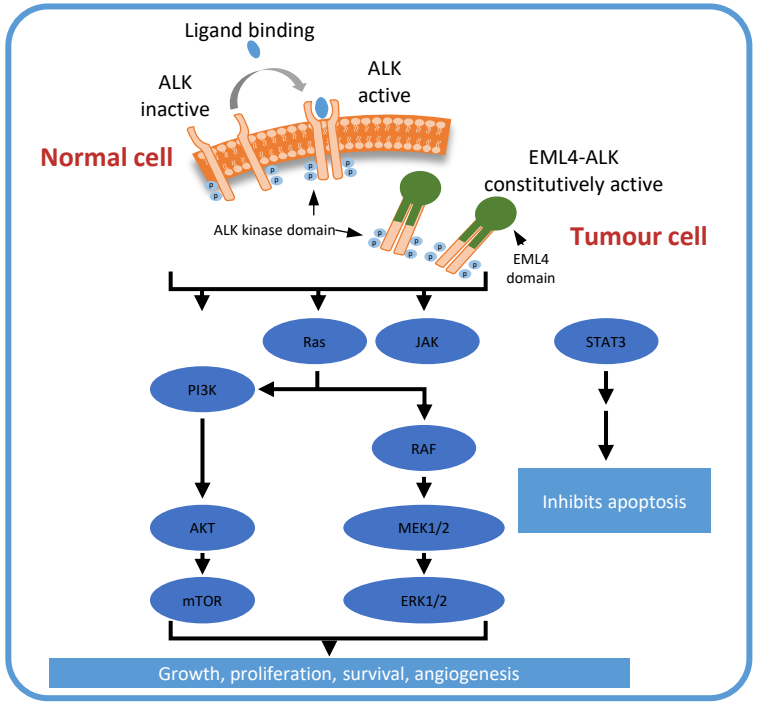
Disease	ALK alteration	Chromosomal abnormality	References
ALCL	NPM–ALK	t(2;5)(p23;q35)	[2]
	TPM3–ALK	t(1;2)(q25;p23)	[11]
	TPM4–ALK	t(2;19)(p23;p13)	[12]
	TFG–ALK	t(2;3)(p23;q21)	[10]
	ATIC–ALK	inv(2)(p23;q35)	[125-127]
	CLTC–ALK	t(2;17)(p23;q23)	[14]
	MSN–ALK	t(2;X)(p32;q11–12)	[128]
	ALO17–ALK	t(2;17)(p23;q25)	[9]
	MYH9–ALK	t(2;22)(p23;q11.2)	[13]
DLBCL	NPM–ALK	t(2;5)(p23;q35)	[129, 130]
	CLTC–ALK	t(2;17)(p23;q23)	[69, 131]
	Unknown	ins(3'ALK)(4q22–24)	[132]
	SQSTM1–ALK	t(2;5)(p23.1;q35.3)	[66]
	SEC31A–ALK	ins(4)(2;4)(?;q21) t(2;4)(p24;q21)	[133, 134]
	Unknown	t(X;2)(q21;p23) and t(2;12)(p23;q24)	[68]
Plasmacytoma	CLTC–ALK	t(2;17)(p23;q23)	[71]
IMT	TPM3–ALK	t(1;2)(q25;p23)	[135]
	TPM4–ALK	t(1;19)(p23;p13)	[135]
	CLTC–ALK	t(2;17)(p23;q23)	[136]
	CARS–ALK	t(2;11;2)(p23;p15;q31)	[9, 137]
	ATIC–ALK	inv(2)(p23;q35)	[138]
	RANBP2–ALK	t(2;2)(p23;q13) inv(2)(p23;p15;q31)	[139]
	SEC31L1–ALK	t(2;4)(p23;q21)	[140]
NSCLC	EML4–ALK	inv(2)(p21;p23)	[85, 97]
	TFG–ALK	t(2;3)(p23;q21)	[97]
	KIF5B–ALK	t(2;10)(p23;p11)	[95, 96]
Esophageal cancer	TPM4–ALK	t(2;19)(p23;p13)	[109, 110]
Renal cell carcinoma	VCL–ALK	t(2;10)(p23;q22)	[111]
Renal medullary carcinoma	VCL–ALK	t(2;10)(p23;q22)	[112]
Breast cancer	EML4–ALK	inv(2)(p21;p23)	[92]
Colon cancer	EML4–ALK	inv(2)(p21;p23)	[92]
Neuroblastoma	Point mutations or amplification		[21-25]
Thyroid carcinoma	Point mutations		[26]

NSCLC ALK +
A targeted therapy model



NSCLC ALK+

Molecular



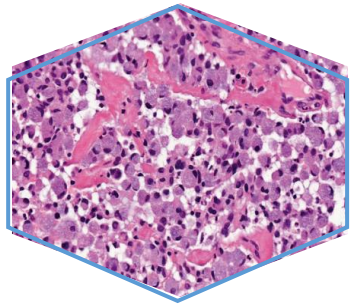
Clínical characteritics

Young patients
55 y

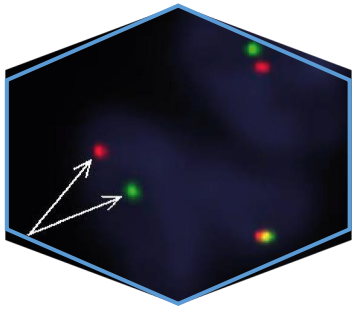
Never-Light smokers
~70% never smokers

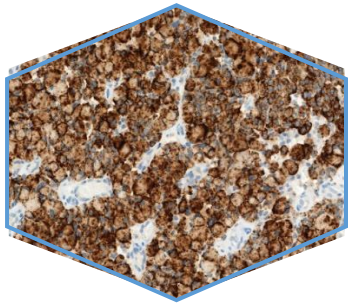
Advanced disease
- pleural/pericardial efusion
- Multiple metastatic locations
- CNS involvement

Pathology



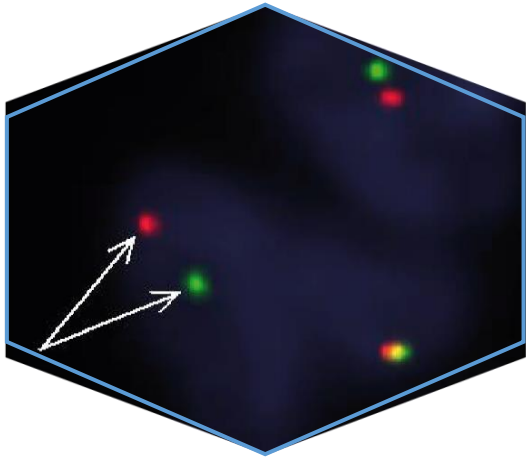
Biomarker



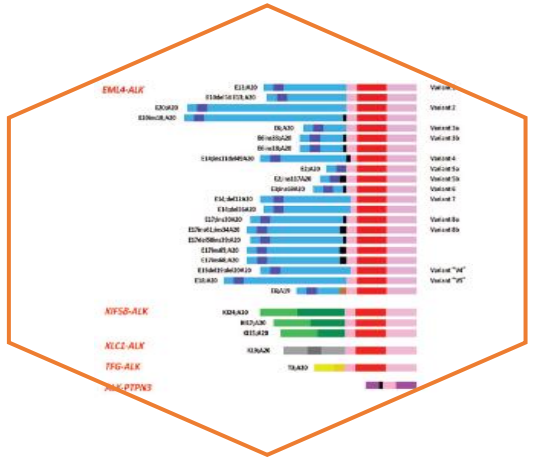


Solomon B et al. NEJM 2014; Soria J-C et al. Lancet 2017
Peters S et al. NEJM 2017; Holla R et al. Cold Spring Harb Mol Case Stud 2017; Tao, et al. Thorac Cancer 2017; Kayaniyil, et al. Curr Oncol 2016
Camidge, et al. Lancet 2012; Chia, et al. Clin Epidemiol 2014

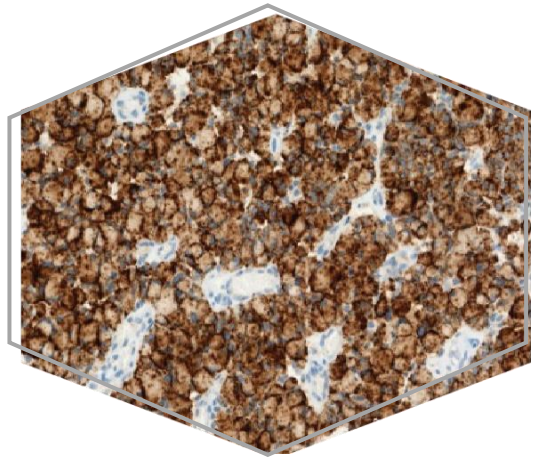
ALK testing?



FISH test

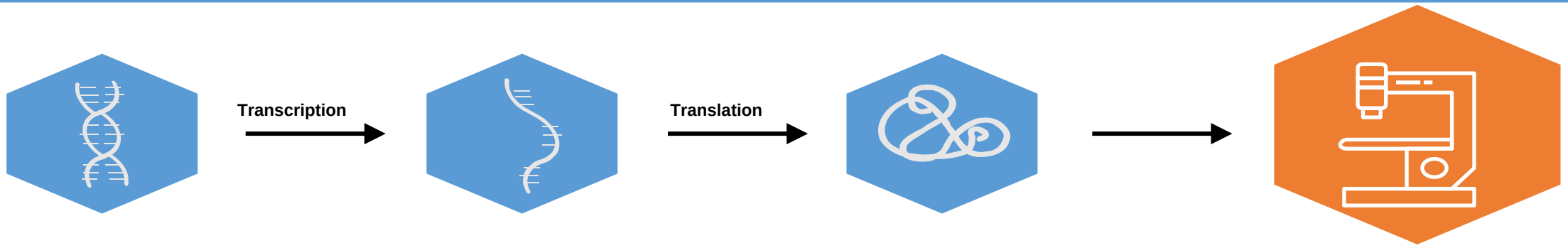


NGS
Multiplex PCR



Inmunohistochemistry

Elige la mejor opción para tu hospital



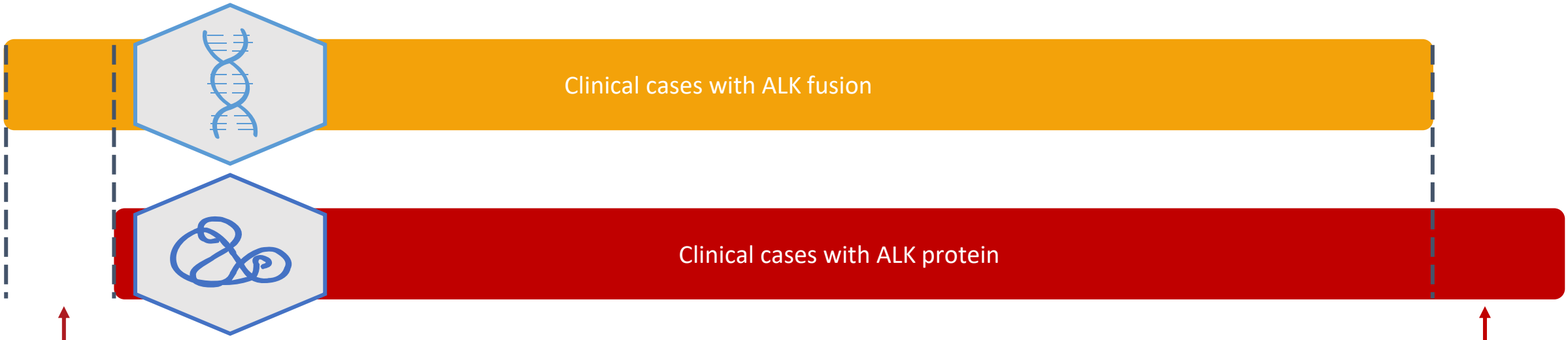
ALK rearrengement

mARN transcription
Fusion gene ALK

ALK protein

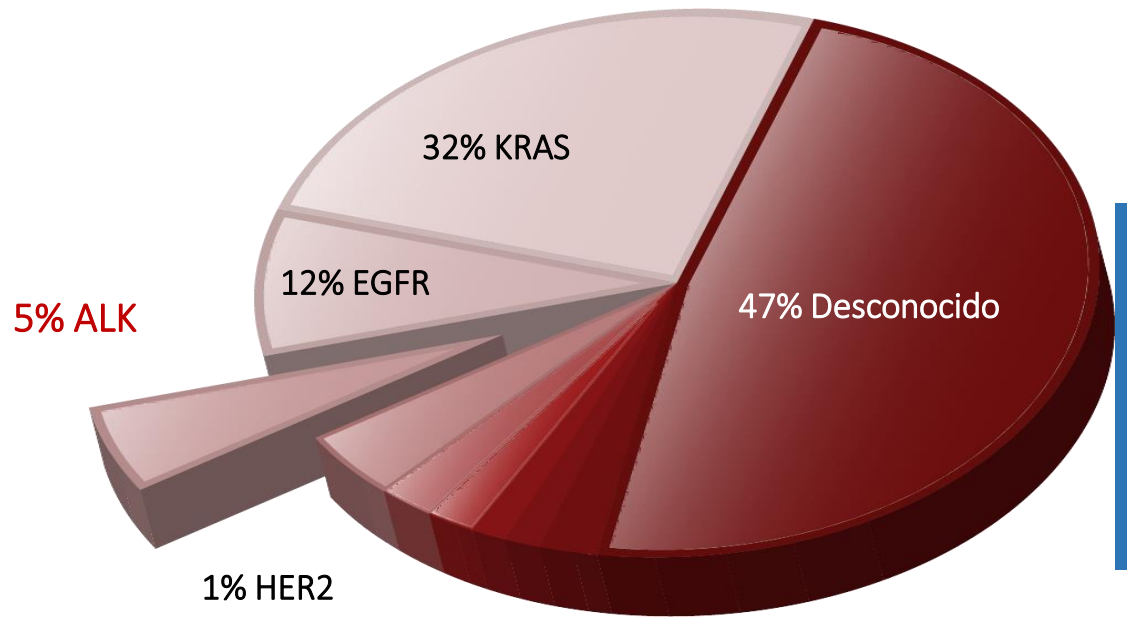
Oncogenic activity
Potential target

Protein is the target



Adaptado de K. Kerr

Diagnóstico de enfermedad ALK+ en CPNM



28.000 pacientes fueron diagnosticados con CP en España en 2017

Unos 500 pacientes fueron ALK-positivos [6]

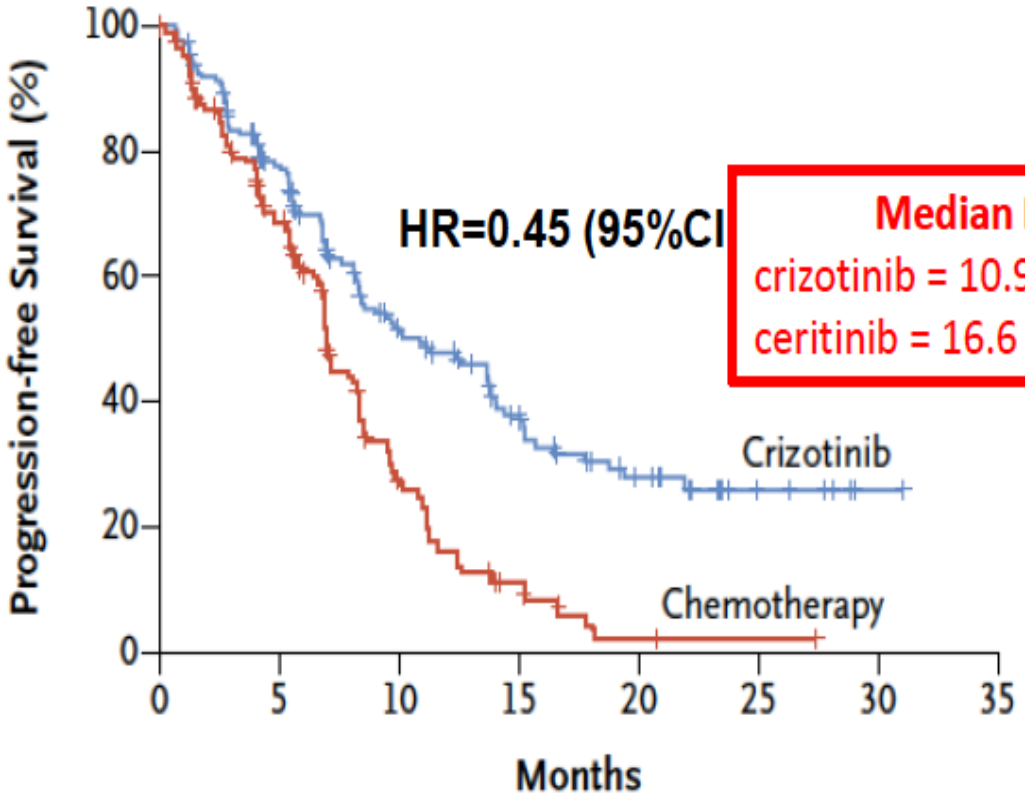
La enfermedad ALK+ aparece en aproximadamente el 5% de los pacientes con CPNM avanzado[1-5]

ALK = quinasa del linfoma anaplásico; EGFR = receptor del factor de crecimiento epidérmico; HER2 = receptor del factor de crecimiento epidérmico humano 2
KRAS = K-ras

1. Dearden, et al. Ann Oncol 2013; 3. Hallberg, et al. Nat Rev Cancer 2013; 4. Pao & Girard. Lancet Oncol 2011; 5. Rikova, et al. Cell 2007; 6 SEOM evaluation report 2018

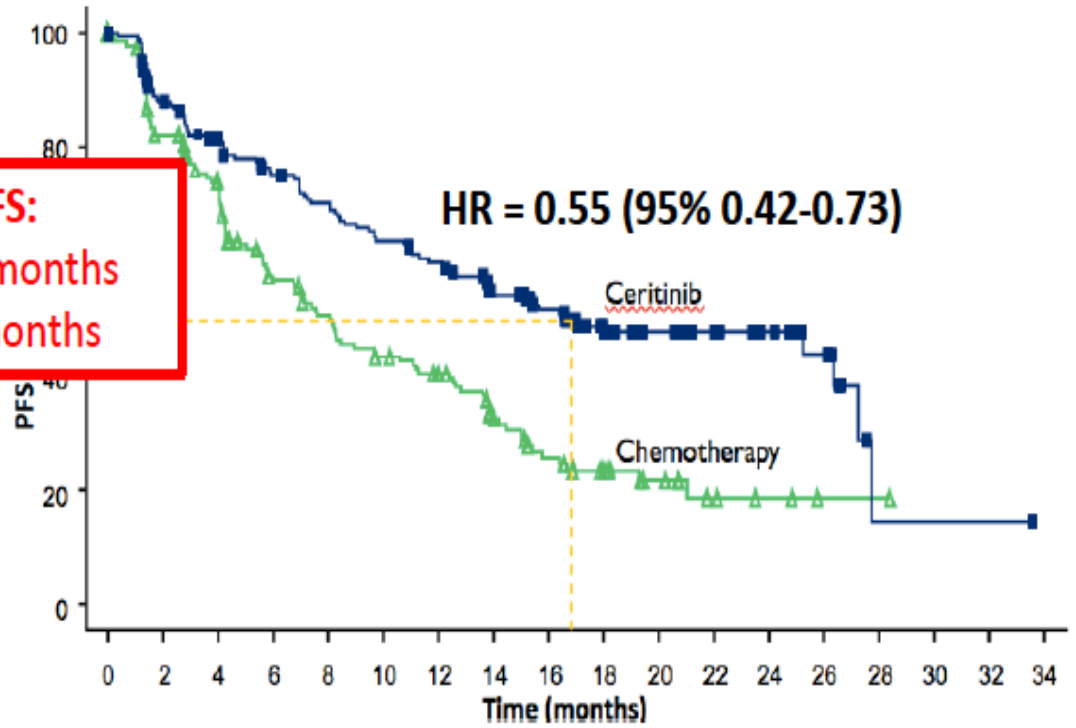
Crizotinib and Ceritinib in first line

Crizotinib: PROFILE 1014 confirmatory Phase 3 trial vs 1st line chemotherapy[1]



Median PFS:
crizotinib = 10.9 months
ceritinib = 16.6 months

Ceritinib: ASCEND 4 Phase 3 trial vs 1st line chemotherapy[2]



1. Solomon et al. New Engl J Med 2014

2. De Castro G et al. WCLC 2016

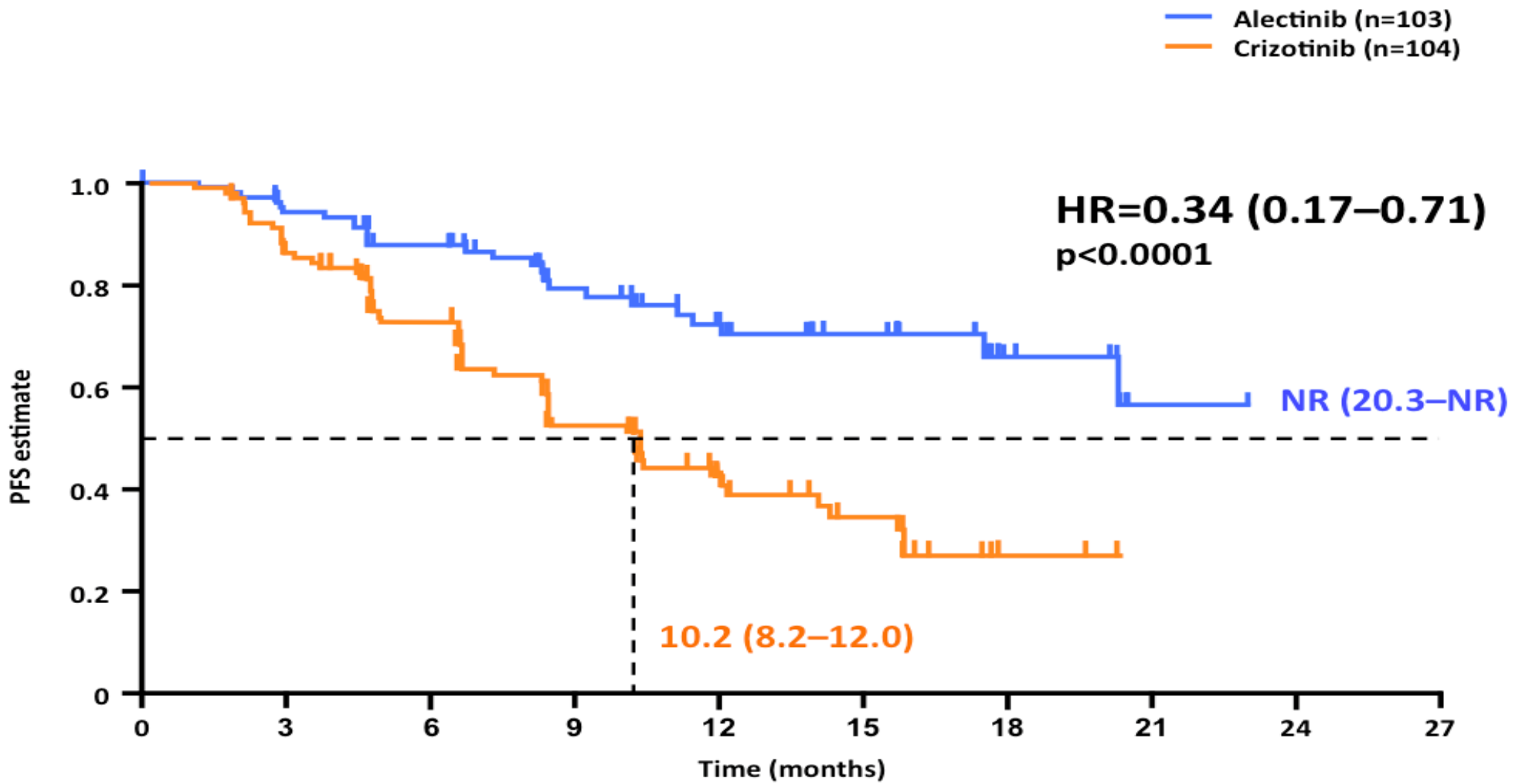
Alectinib vs Crizotinib in 1L

- J-ALEX — Japan
- ALEX — Western countries
- ALESIA — Asia

Brigatinib vs Crizotinib in 1L

- ALTA 1L

J-ALEX primary endpoint: PFS by IRF (ITT)



Nokihara, et al, ASCO 2016 (Abs. 9008)

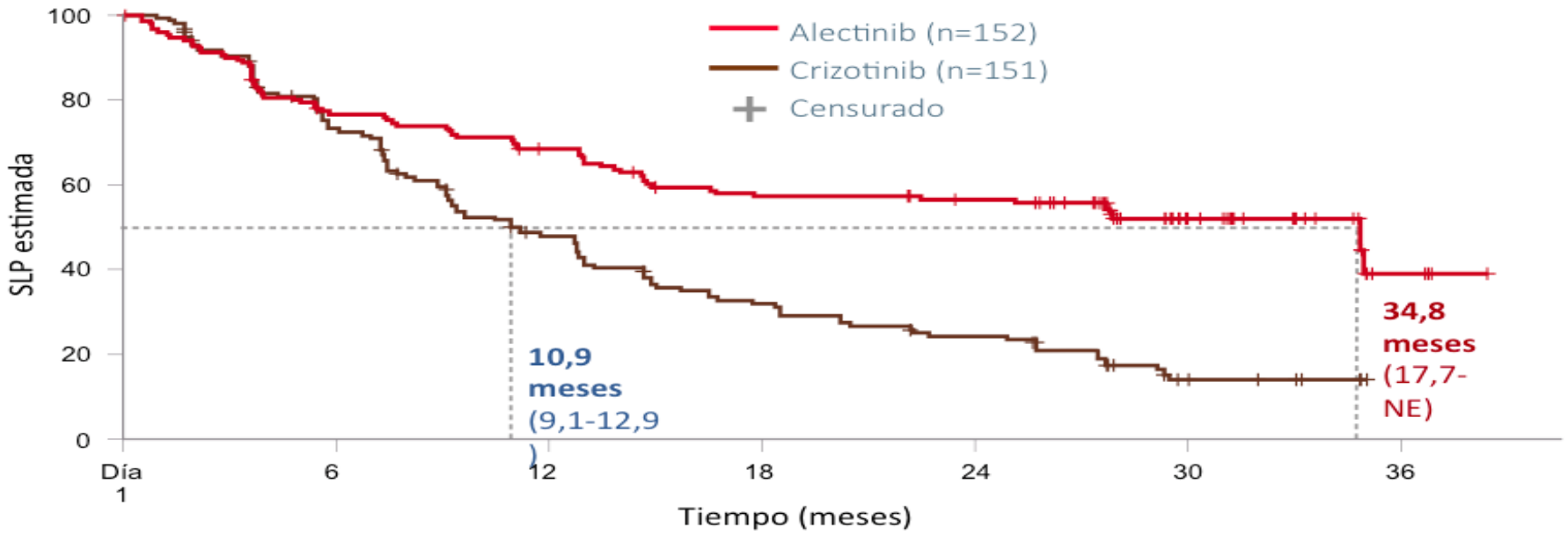
ALEX
Response rate and response duration

* 33.1 months (95% CI: 31.3–NE) with alectinib versus 11.1 months (95% CI: 7.5–13.0) with crizotinib

	Crizotinib (n=151)	Alectinib (n=152)
Pacientes que responden, n (%) (IC 95%)	114 (75,5) (67,8–82,1)	126 (82,9) (76,0–88,5)
Valor p	0,09 (No estadísticamente significativo)	
RC, n (%)	3 (2)	7 (5)
RP, n (%)	111 (73,5)	119 (78)
EE, n (%)	24 (16)	9 (6)

Shaw, et al. ASCO 2017; Peters, et al. N Engl J Med 2017; Camigde, et al. ASCO 2018

ALEX
Progression Free Survival

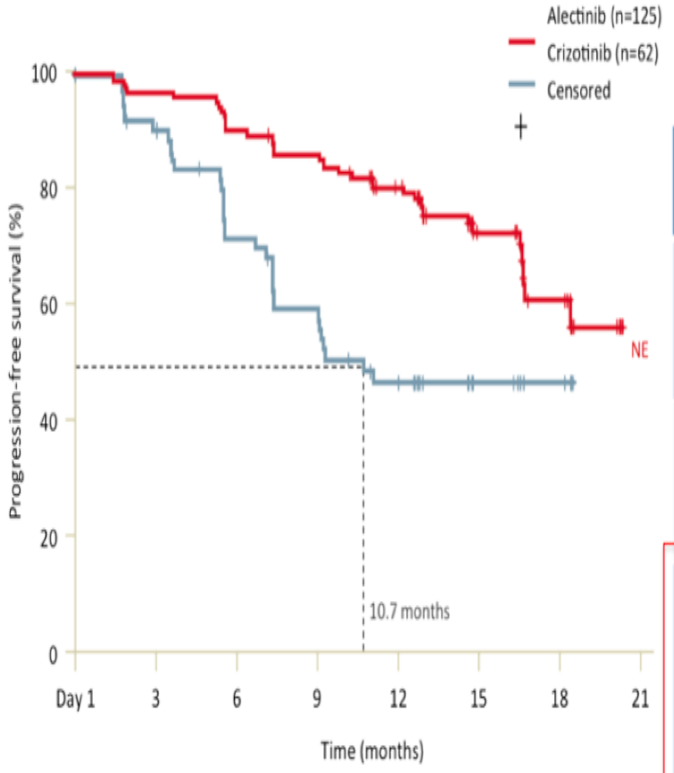


No. pacientes en riesgo

Alectinib	152	135	113	109	99	84	81	81	77	69	33	19	4
Crizotinib	151	132	104	83	64	47	42	25	31	24	10	8	0

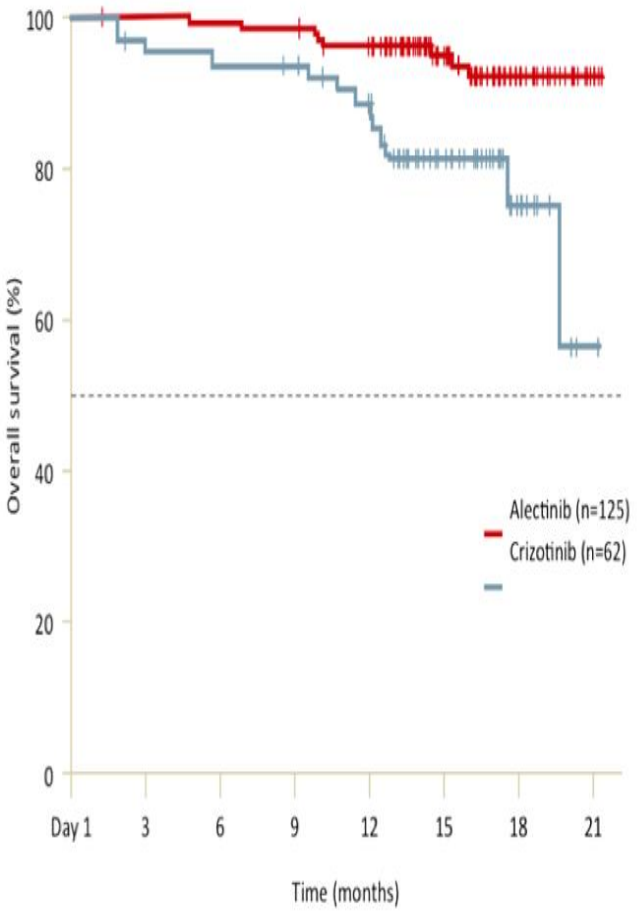
Camidge DR, et al. Updated efficacy and safety data from the global phase III ALEX study of alectinib (AL) versus crizotinib (CZ) in untreated advanced ALK+ NSCLC . J Clin Oncol 36, 2018 (suppl; abstr 9043). Póster #9043 presentado en ASCO 2018 Annual Meeting

ALESIA: PFS and Overall Survival



Secondary endpoint
IRC assessed

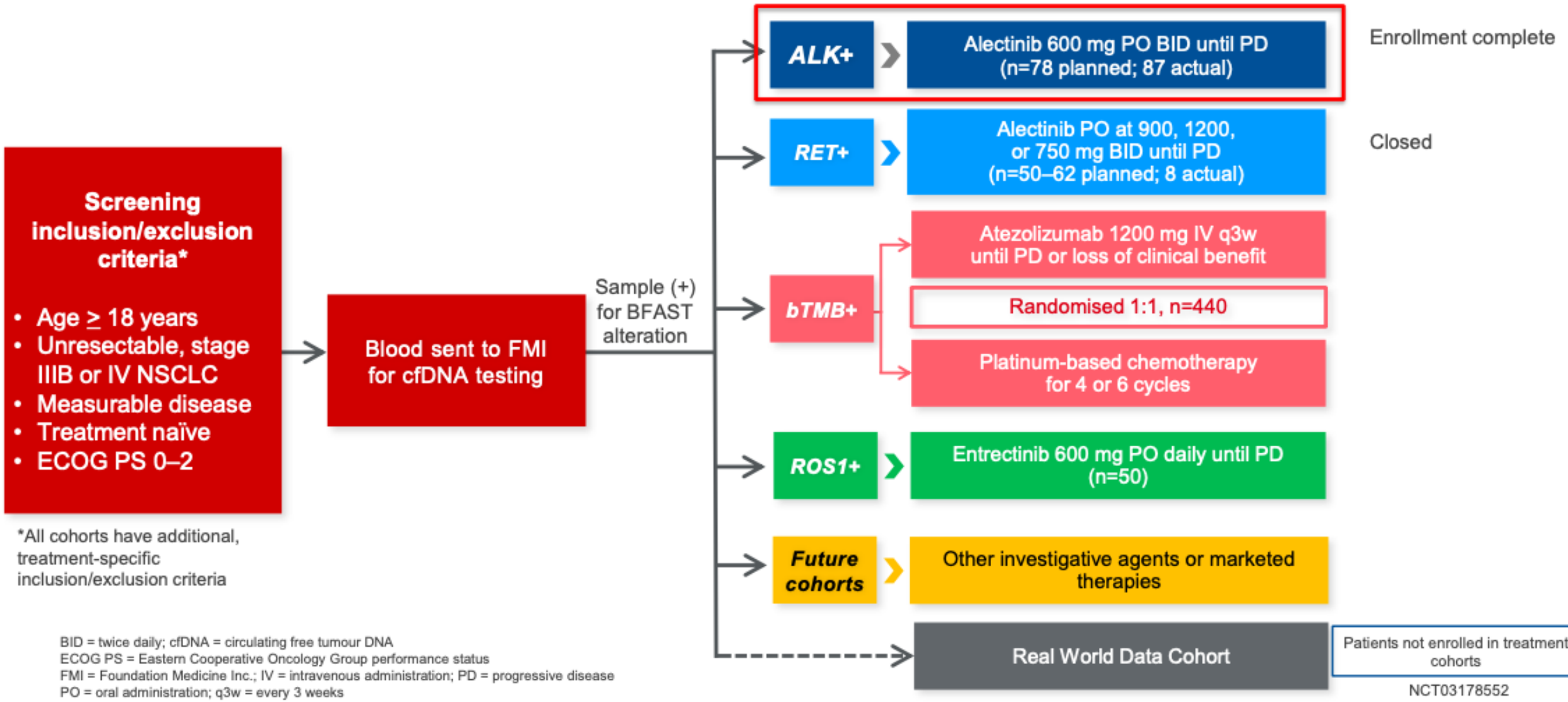
	Alectinib n=125	Crizotinib n=62
Patients with event, n (%)	36 (28.8)	31 (50.0)
Median PFS, months (95% CI)	**NE** (16.7–NE)	**10.7** (7.4–NE)
HR (95% CI) P-value (log-rank test)	**0.37** (0.22–0.61) P<0.0001	



	Alectinib n=125	Crizotinib n=62
Patients with event, n (%)	8 (6.4)	13 (21.0)
Median PFS, months (95% CI)	NE	NE (19.8-NE)
HR (95% CI) P-value (log-rank test)	**0.28** (0.12–0.68) P=0.0027	

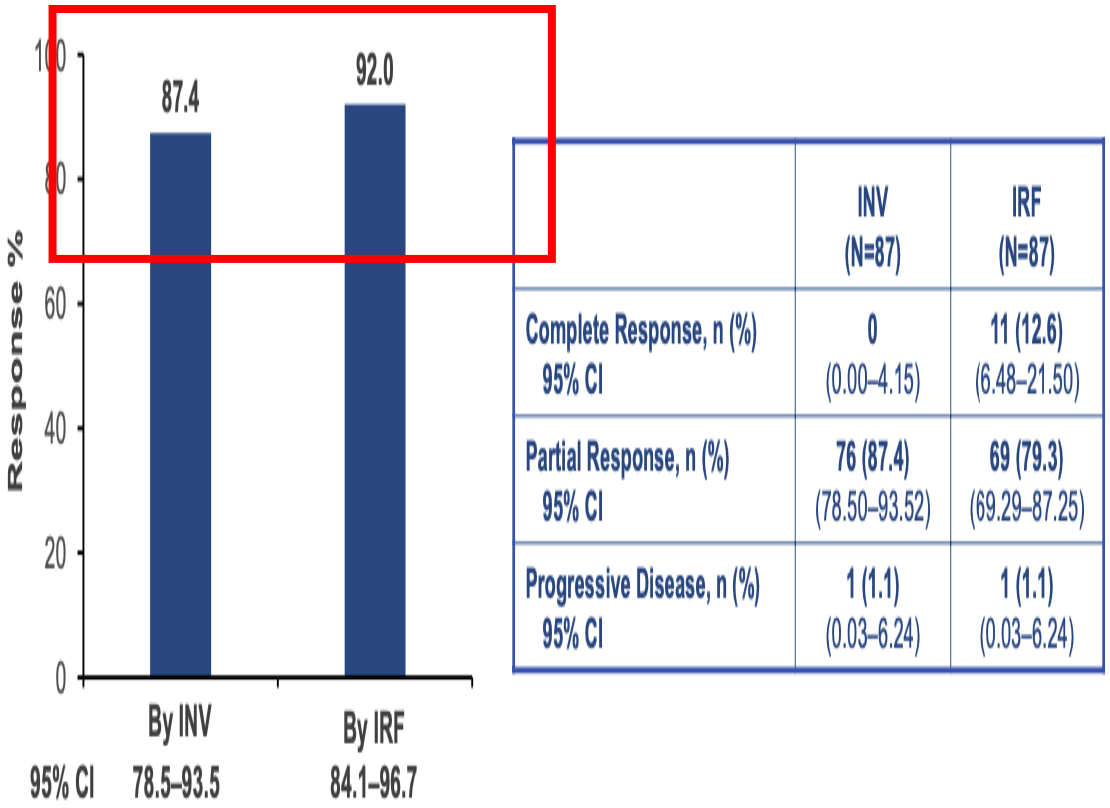
Primary data cut-off: 31 May, 2018 IRC: Independent Committee Revisor
Median duration of follow up (alectinib vs crizotinib): 16.2 vs 15.0 months
The p-values presented for the efficacy endpoints are descriptive only

Study design



BID = twice daily; cfDNA = circulating free tumour DNA
ECOG PS = Eastern Cooperative Oncology Group performance status
FMI = Foundation Medicine Inc.; IV = intravenous administration; PD = progressive disease
PO = oral administration; q3w = every 3 weeks

Results: Confirmed response (INV vs IRF)



	INV (N=87)	IRF (N=87)
Complete Response, n (%) 95% CI	0 (0.00–4.15)	11 (12.6) (6.48–21.50)
Partial Response, n (%) 95% CI	76 (87.4) (78.50–93.52)	69 (79.3) (69.29–87.25)
Progressive Disease, n (%) 95% CI	1 (1.1) (0.03–6.24)	1 (1.1) (0.03–6.24)

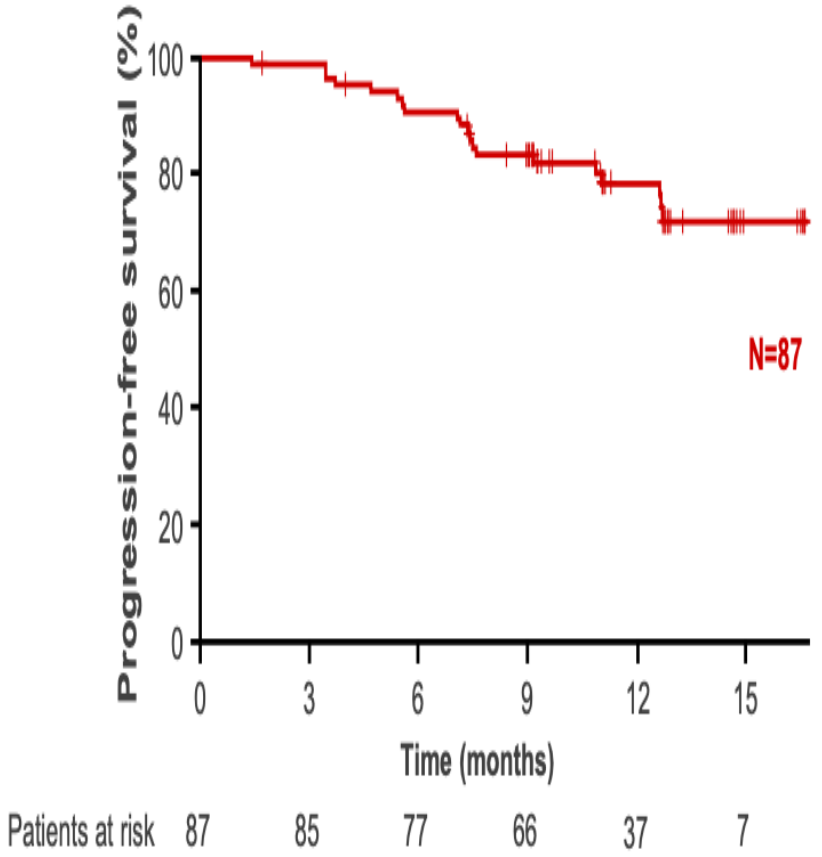
Median duration of follow-up: 12.58 months

ALEX confirmed ORR = 71.7% (95% 63.8–78.7)[1]

INV = investigator-assessed; IRF = independent review facility-assessed

1. Mok, et al. ESMO 2019

Results: PFS by investigator



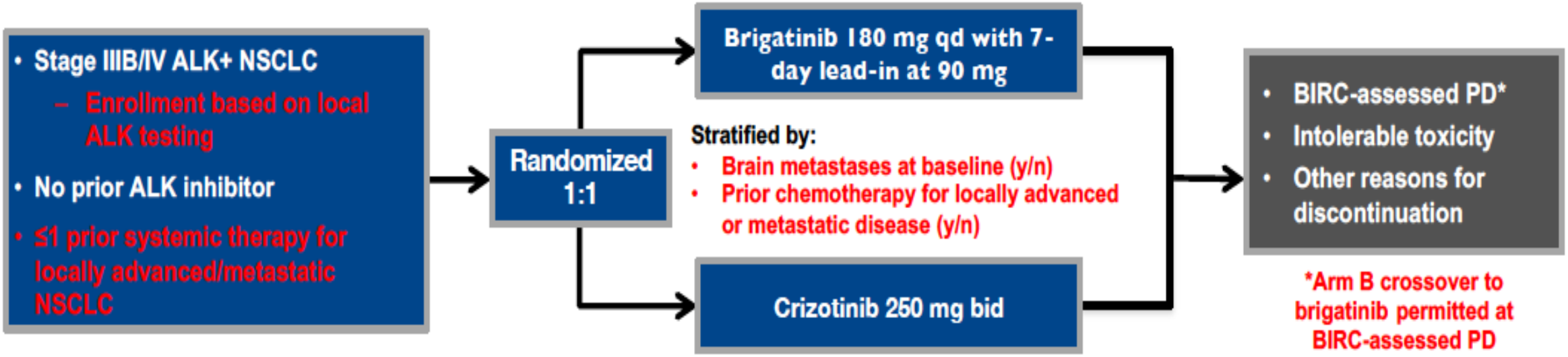
Patients with event, n (%)	20 (23)
Median PFS, months (95% CI)	NE (NE)
12-month PFS, % (95% CI)	78.38 (69.07–87.69)
ALEX[1]	N=152
12-month PFS, % (95% CI)	68.4 (61.0–75.9)

Median duration of follow-up: 12.6 months

PFS = progression-free survival; NE = non-estimable

1. Peters, et al. NEJM 2017

ALTA-1L: Phase 3, Open-label, Randomized, Multicenter, Study (NCT02737501)



Disease assessment every 8 weeks, including brain MRI for all patients

- Primary endpoint: Blinded independent review committee (BIRC)–assessed PFS per RECIST v1.1
- Key secondary endpoints: Confirmed ORR, confirmed intracranial ORR, intracranial PFS, OS, safety, and tolerability
- Statistical considerations: ~270 total patients (198 events); 135 in each arm to detect a 6-month improvement in PFS (HR=0.625), assuming:
  - 10-month PFS in crizotinib arm
  - 2 planned interim analyses at 99 (50%) and 149 (75%) total expected events

Trial fully accrued in August 2017 (N=275)

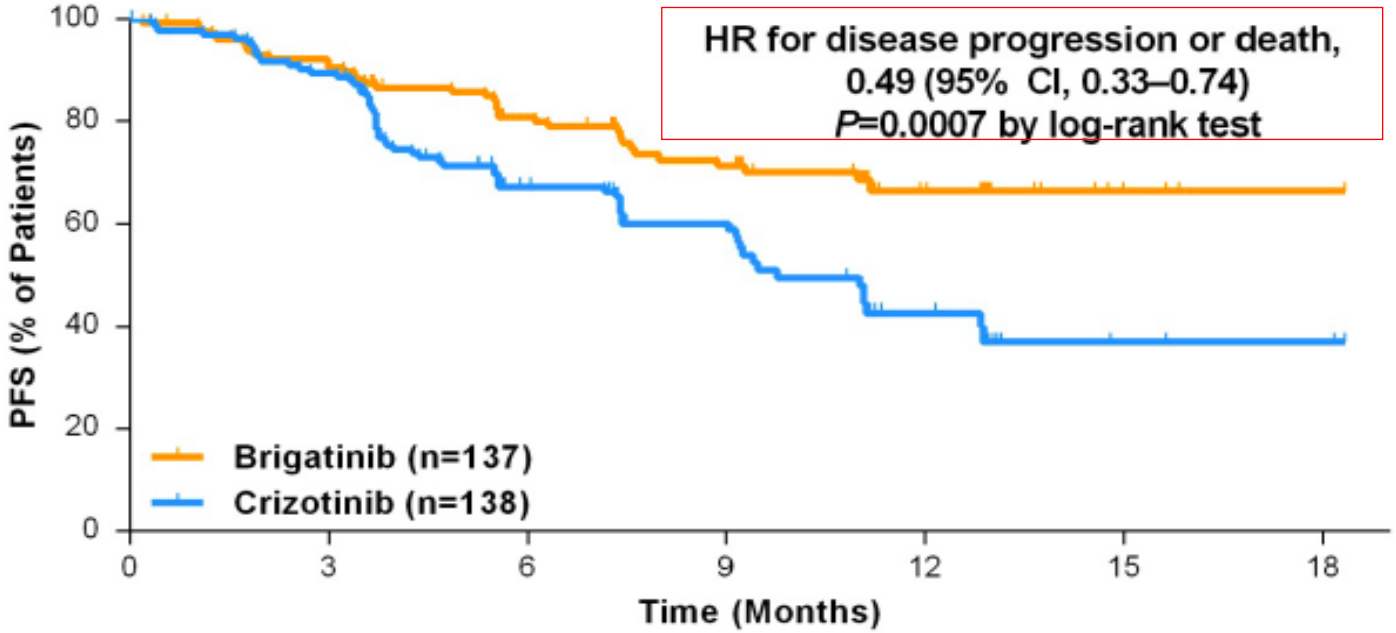
First interim analysis:
- A total of 99 PFS events are included
- According to the prespecified O'Brien-Fleming Lan-DeMets alpha spending function, a 2-sided *P* value of 0.0031 was used to define the threshold for significance

WCLC 2018

ALTA-1L: Phase 3, Open-label, Randomized, Multicenter, Study (NCT02737501)

Primary Endpoint: BIRC-Assessed PFS

- **Brigatinib met the prespecified threshold for statistical superiority vs crizotinib**



Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=137)	36 (26)	NR (NR–NR)	67 (56–75)
Crizotinib (n=138)	63 (46)	9.8 months (9.0–12.9)	43 (32–53)

- **Investigator-assessed median PFS was NR (95% CI, NR–NR) in the brigatinib arm and 9.2 months (95% CI, 7.4–12.9 months) in the crizotinib arm (HR, 0.45 [95% CI, 0.30–0.68]; log-rank *P*=0.0001)**
- **1-year OS probability: brigatinib, 85% (95% CI, 76%–91%); crizotinib, 86% (77%–91%)**

WCLC 2018

PFS

PROFILE 1014
mPFS: 10.9 m

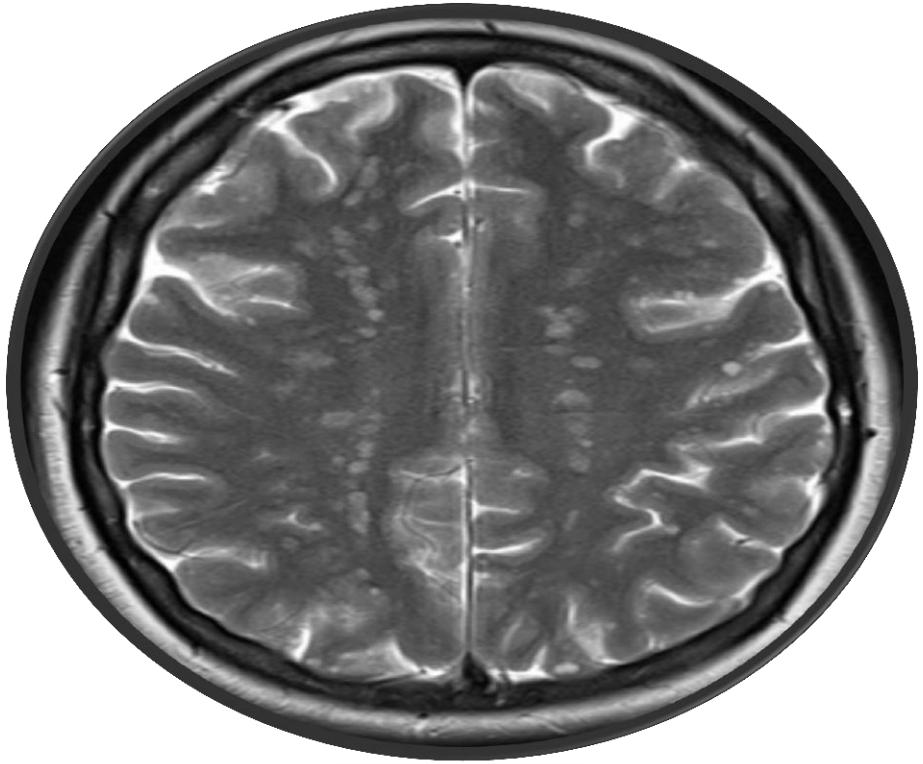
ASCEND-4
mPFS: 16.6 m

ALEX
mPFS 34.8 m

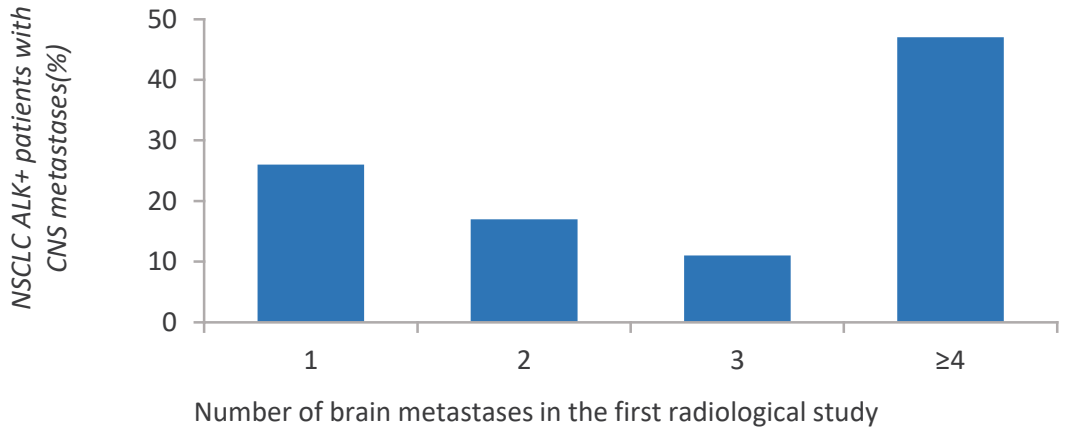
ALTA
mPFS NR m

Solomon B et al. NEJM 2014; Soria J-C et al. Lancet 2017; Camidge R et al. ASCO 2018 (Abst. 9043), Camidge R et al, NEJM 2018

High incidence of CNS involvement in NSCLC ALK patients



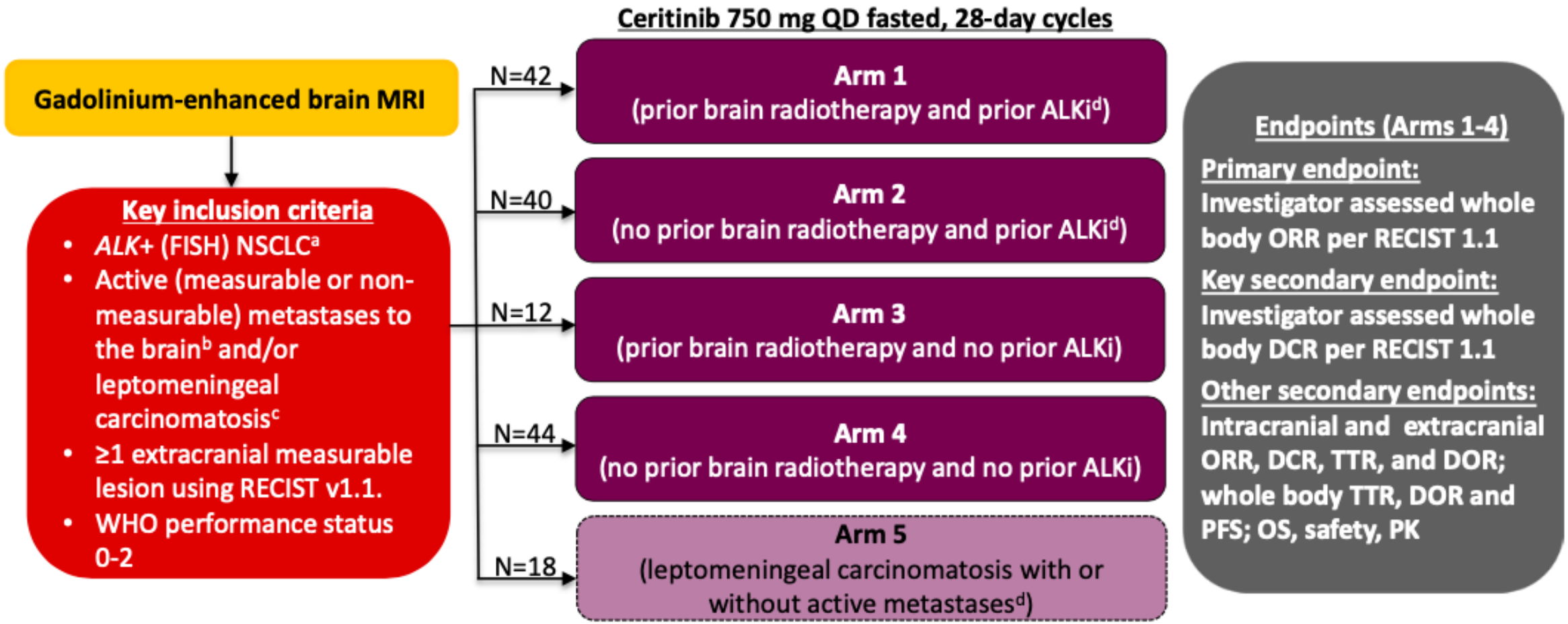
35% of ALK + have CNS involvement at diagnosis



Most patients have multiple CNS metastasis

1. Guerin, et al. J Med Econ 2015
2. Johung, et al. J Clin Oncol 2016;
3. Weickhardt, et al. J Thorac Oncol 2012

ASCEND-7 STUDY DESIGN



- Intracranial and extracranial responses were assessed using modified RECIST 1.1 and RECIST 1.1, respectively.
  - As per modified RECIST, the usual criteria to select target lesions were used but maximum five target lesions located in the brain could be selected at baseline and evaluated at each assessment time point.

[a] according to 7th edition of the American Joint Committee on Cancer
[b] Lesion free of local treatment (stereotactic or WBRT) or lesions in unequivocal progression after radiotherapy
[c] diagnosis requires either documentation of the presence of malignant cells detected at the cytological examination of CSF or serious suspicion of LC supported by imaging findings
[d] Previous treatment with ALKi other than crizotinib was not allowed

WHOLE BODY BEST OVERALL RESPONSE PER INVESTIGATOR ASSESSMENT

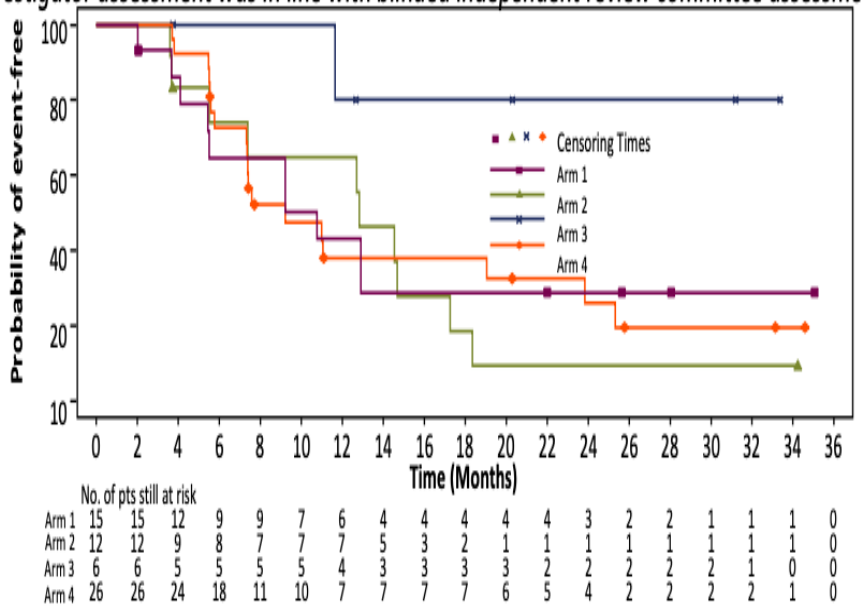
Rapid response with a high DCR was seen across all 4 arms
Investigator assessed response was consistent with blinded independent review committee assessment

	ARM 1 Prior brain RT/ prior ALKi N=42	ARM 2 No prior brain RT/ prior ALKi N=40	ARM 3 Prior brain RT/ No prior ALKi N=12	ARM 4 No prior brain RT or ALKi N=44
Best overall response, n (%)				
Partial response (PR)	15 (35.7)	12 (30.0)	6 (50.0)	26 (59.1)
Stable disease (SD)	13 (31.0)	21 (52.5)	2 (16.7)	5 (11.4)
Progressive disease (PD)	7 (16.7)	6 (15.0)	1 (8.3)	7 (15.9)
Unknown	7 (16.7)	1 (2.5)	3 (25.0)	6 (13.6)
Overall response rate (CR+PR), % (95% CI)	**35.7** (21.6, 52.0)	**30.0** (16.6, 46.5)	**50.0** (21.1, 78.9)	**59.1** (43.2, 73.7)
Disease control rate (CR+PR+SD), % (95% CI)	**66.7** (50.5, 80.4)	**82.5** (67.2, 92.7)	**66.7** (34.9, 90.1)	**70.5** (54.8, 83.2)

WHOLE BODY DURATION OF RESPONSE PER INVESTIGATOR ASSESSMENT

Clinically meaningful DOR

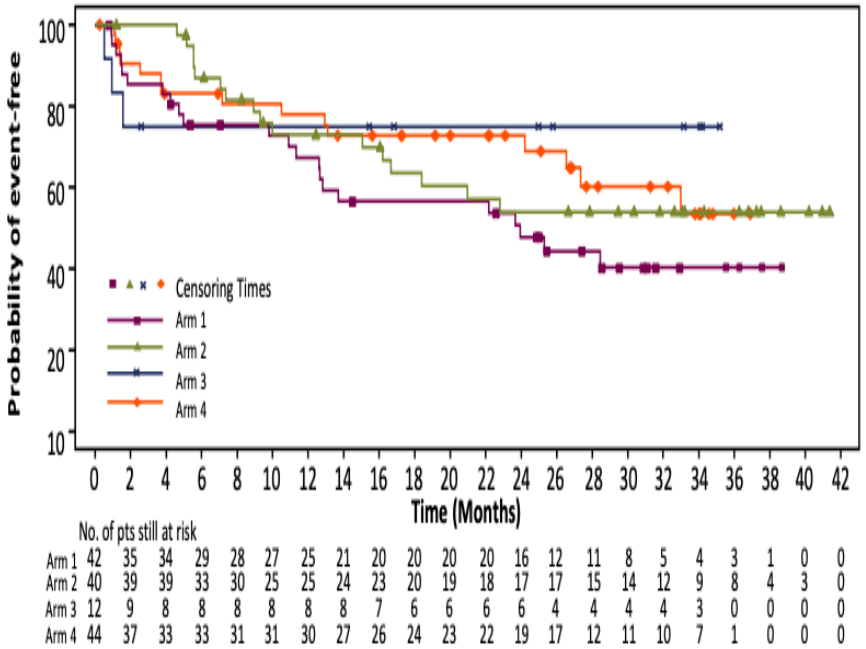
Investigator assessment was in line with blinded independent review committee assessment



	ARM 1 Prior brain RT/ prior ALKi M=15	ARM 2 No prior brain RT/ prior ALKi M=12	ARM 3 Prior brain RT/ No prior ALKi M=6	ARM 4 No prior brain RT or ALKi M=26
Duration of response (DOR)				
Median DOR, months (95% CI)	**10.8** (4.1, NE)	**12.8** (3.7, 17.3)	**NE** (11.7, NE)	**9.2** (7.3, 23.9)
Estimated 6-month event-free probability, % (95% CI)	64.6 (34.7, 83.5)	74.1 (39.1, 90.9)	100 (100, 100)	72.7 (51.1, 86.0)
Events, n/M (%)	10/15 (66.7)	10/12 (83.3)	1/6 (16.7)	18/26 (69.2)

M is the number of patients included in the DOR analysis

OVERALL SURVIVAL



	ARM 1 Prior brain RT/ prior ALKi N=42	ARM 2 No prior brain RT/ prior ALKi N=40	ARM 3 Prior brain RT/ No prior ALKi N=12	ARM 4 No prior brain RT or ALKi N=44
Overall survival (OS)				
Median OS, months (95% CI)	**24.0** (12.6, NE)	**NE** (16.2, NE)	**NE** (1.0, NE)	**NE** (26.5, NE)
Estimated 12-month event-free probability, % (95% CI)	67.4 (50.4, 79.6)	72.9 (55.5, 84.5)	75.0 (40.8, 91.2)	77.9 (61.8, 87.9)
Events n/N (%)	22/42 (52.4)	16/40 (40.0)	3/12 (25.0)	15/44 (34.1)

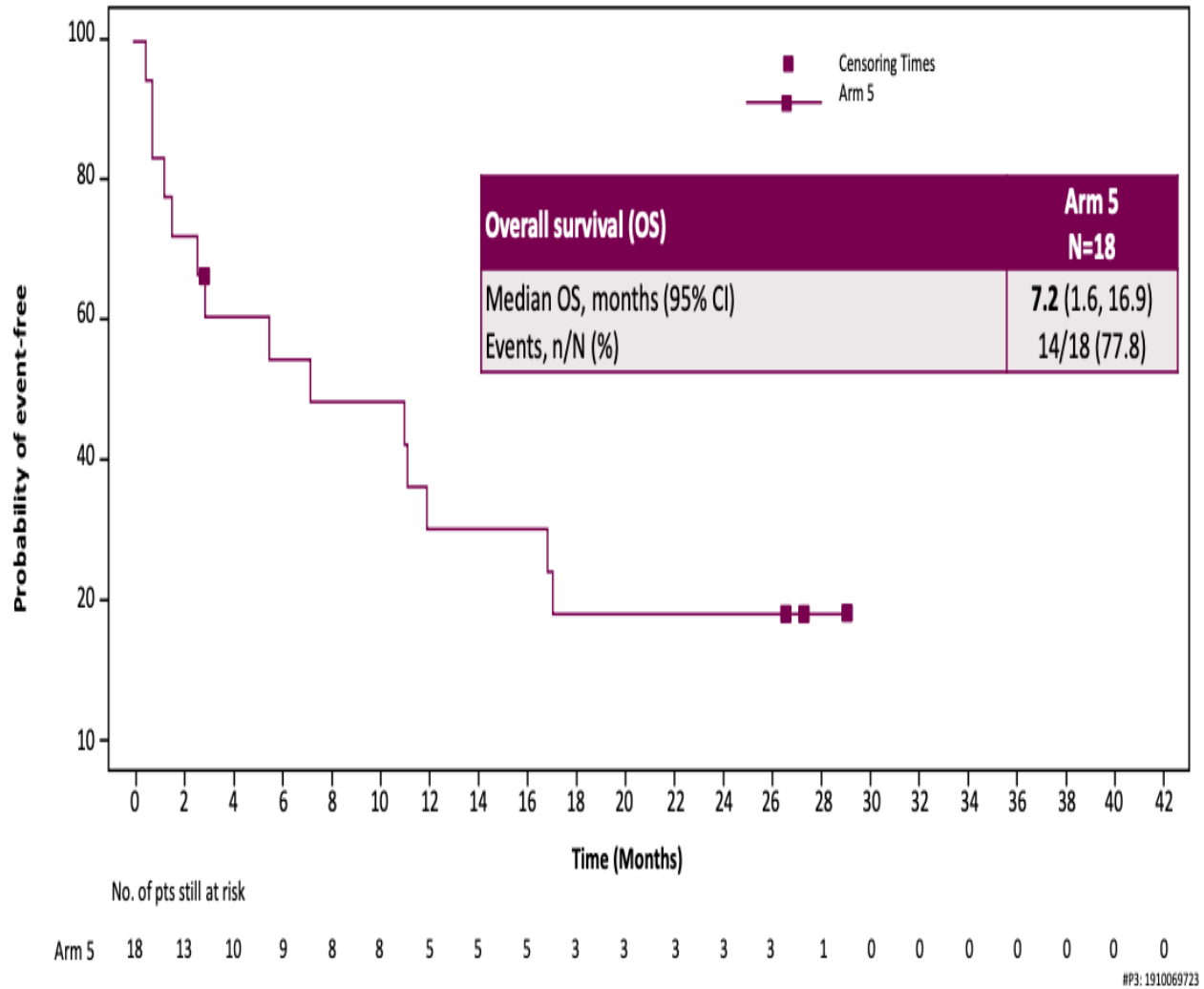
OVERALL RESPONSE RATE *(PER INVESTIGATOR ASSESSMENT)*

	Arm 5 N=18
Best overall response, n (%)	
Partial response (PR)	3 (16.7)
Stable disease (SD)	9 (50.0)
Progressive disease (PD)	1 (5.6)
Unknown	5 (27.8)
Overall response rate (CR+PR), % (95% CI)	**16.7** (3.6, 41.4)
Disease control rate (CR+PR+SD), % (95% CI)	**66.7** (41.0, 86.7)
Duration of response (DOR)	M=3
Median DOR, months (95% CI)	**5.5** (3.7, 9.9)
Events n/M (%)	3/3 (100)

M is the no of pts included in DOR analysis; Investigator assessed response was in line with BIRC assessment

#P3: 1910069

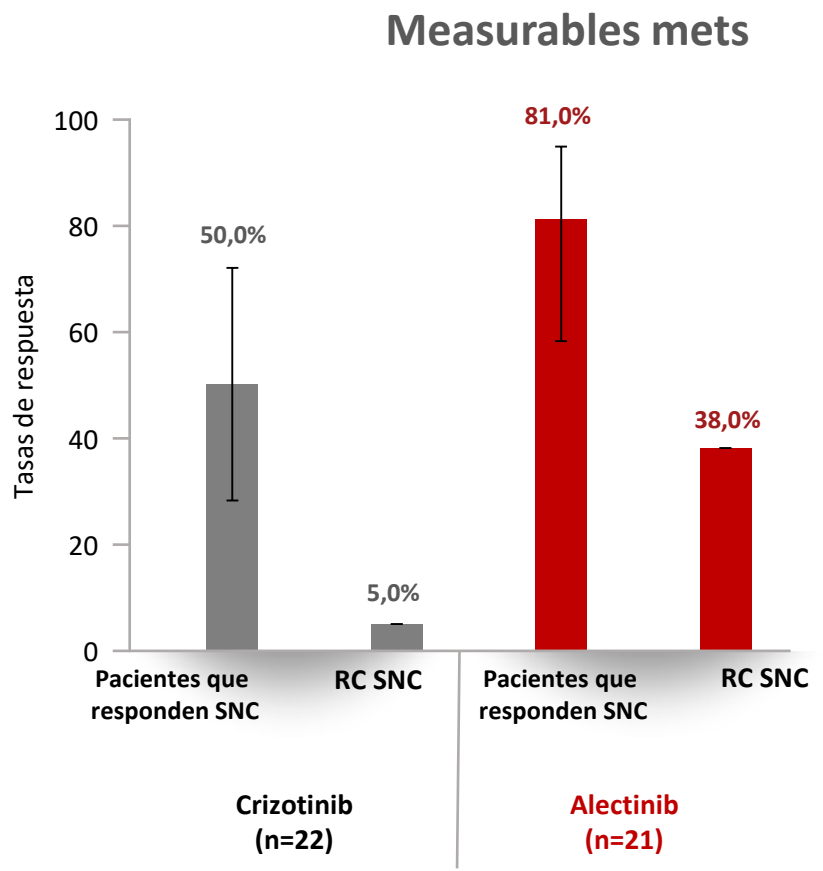
OVERALL SURVIVAL *(PER INVESTIGATOR ASSESSMENT)*

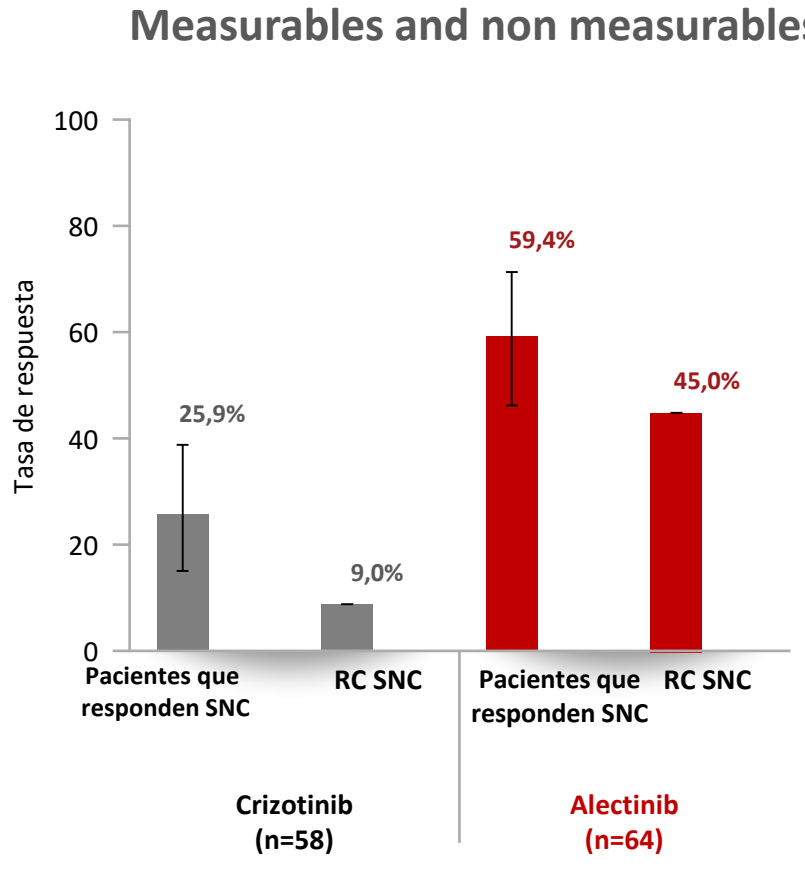


Overall survival (OS)	Arm 5 N=18
Median OS, months (95% CI)	**7.2** (1.6, 16.9)
Events, n/N (%)	14/18 (77.8)

#P3: 1910069723

Alectinib showed high CNS activity 81% and 38% of measurables metastases

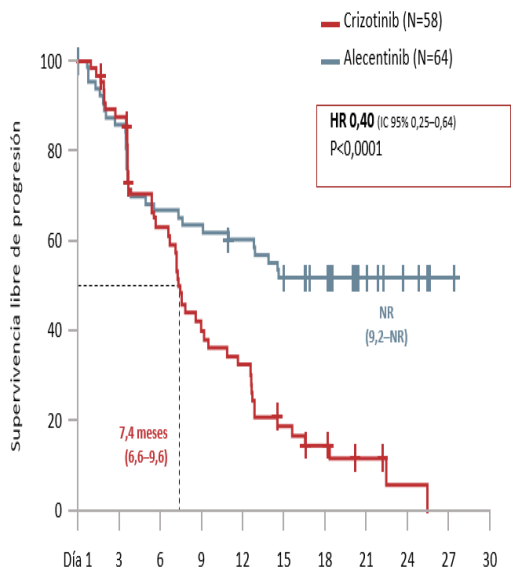




1. Peters, et al. N Engl J Med 2017
2. Shaw, et al. ASCO 2017

PFS
(CNS involvement at diagnosis)*

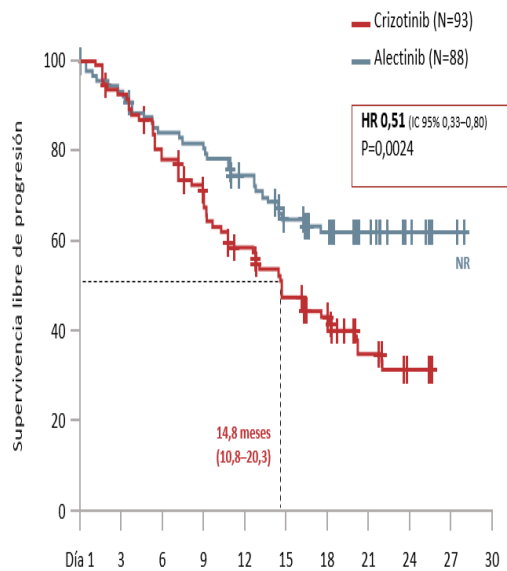
Patients with CNS involvement at diagnosis†



Pacientes en riesgo

Crizotinib	58	48	66	22	17	9	6	3	1
Alectinib	64	54	41	39	36	31	24	10	4	1

Patients without CNS involvement at diagnosis†



Pacientes en riesgo

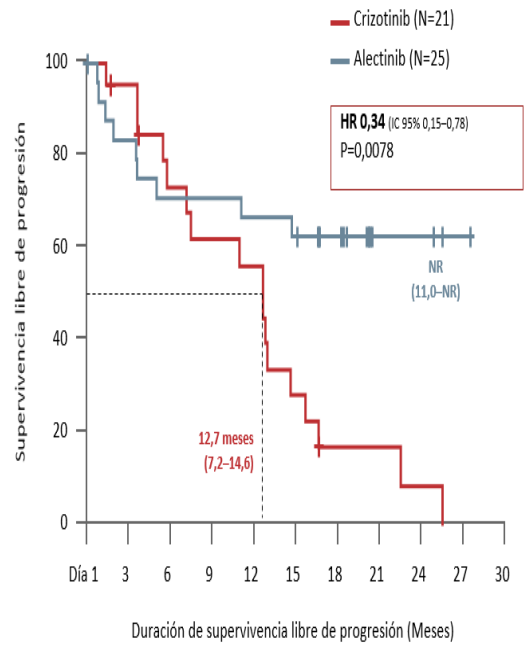
Crizotinib	93	84	71	62	48	37	29	13	4
Alectinib	88	81	72	70	61	50	43	25	11	2

*Valorada por el investigador; †Todos los pacientes con metástasis en SNC en situación inicial, independientemente de la radioterapia
NR = no alcanzado.

Shaw, et al. ASCO 2017

PFS in patients with CNS involvement and previous RT*

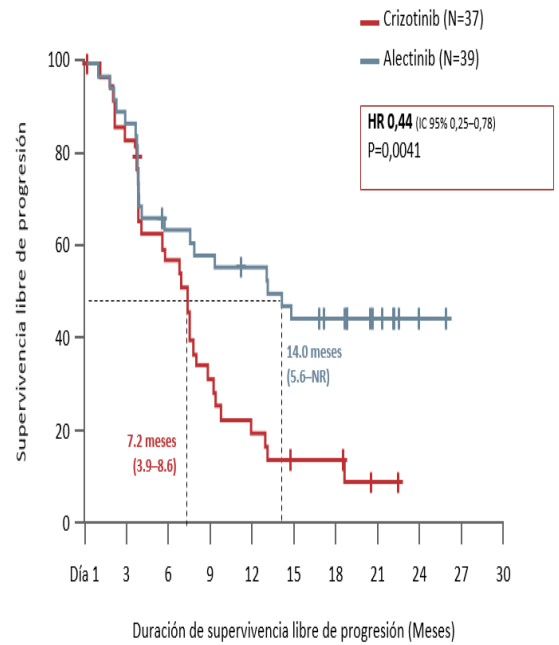
Patients with previous RT



Pacientes en riesgo

Crizotinib	21	18	13	11	10	5	2	2	1	
Alectinib	25	20	17	17	16	15	11	3	3	1

Patients without previous RT



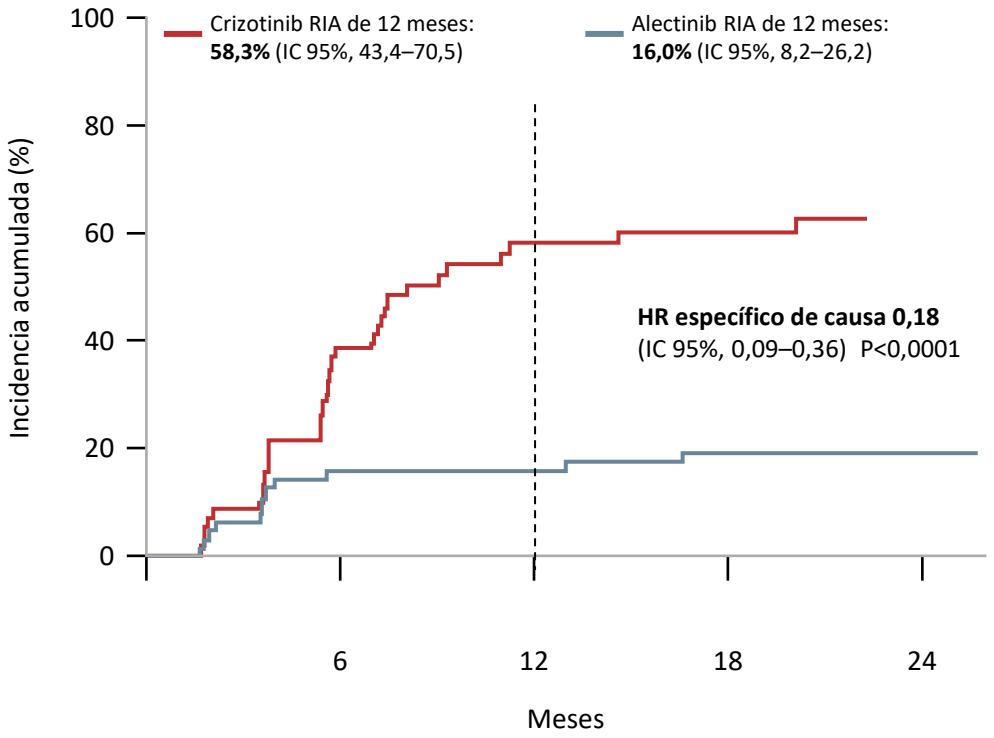
Pacientes en riesgo

Crizotinib	37	30	20	11	7	4	4	1	
Alectinib	39	34	24	22	20	16	13	7	1

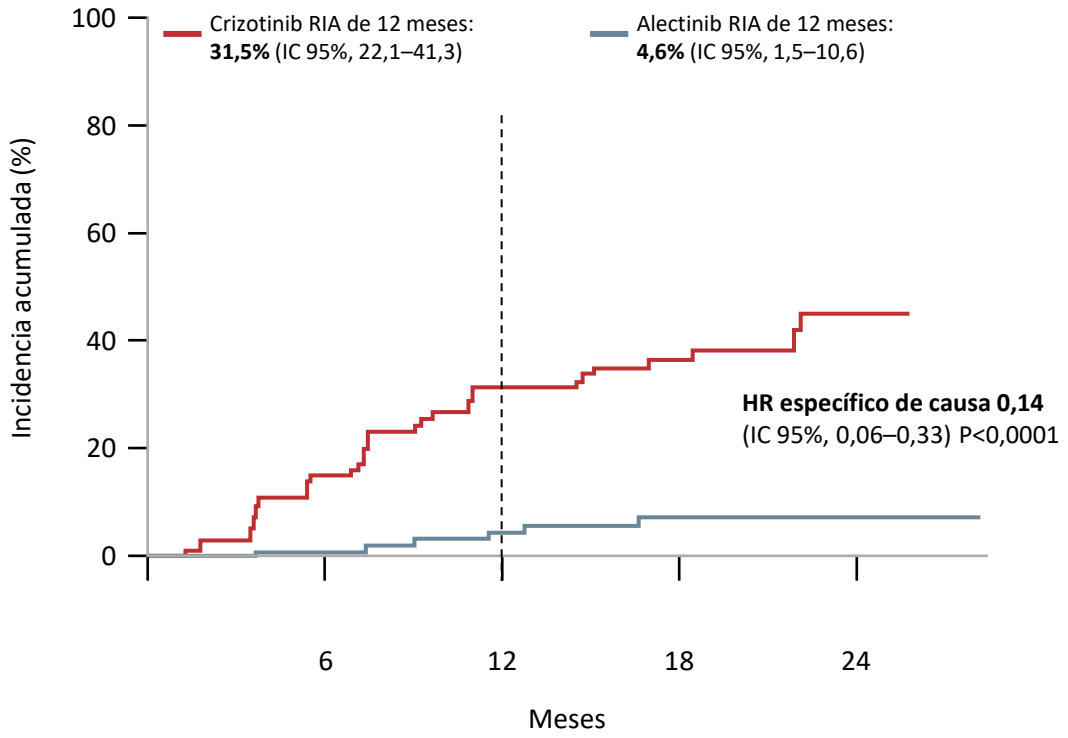
*CRI, pacientes con metástasis cerebral en situación inicial; §Un paciente del grupo de Alecensa con nometástasis en SNC por CRI había recibido RT previa, pero se excluyó aquí
RT= radioterapia (incluye radiocirugía estereotáctica y radioterapia holocraneal adelantada)

IRC-assessed cumulative incidence of CNS progression (CRI, ITT)

Patients with CNS involvement at diagnosis†



Patients without CNS involvement at diagnosis†



*Para cada paciente, se contabilizó el primer acontecimeinto de progresión en SNC, progresión fuera de SNC o muerte.
RIA = Razón de incidencia acumulada.

Brigatinib activity in CNS involvement (ALTA 1L)

Systemic Objective Response[a] (ITT Population)

	Brigatinib n=137	Crizotinib n=138	OR (95% CI)
Confirmed ORR, % (95% CI)	71 (62–78)	60 (51–68)	1.59 (0.96–2.62) P=0.0678
Confirmed CR, %	4	5	
Confirmed PR, %	67	55	
ORR at ≥1 assessment, % (95% CI)	76 (68–83)	73 (65–80)	1.13 (0.66–1.97) P=0.6512
CR, %	7	8	
PR, %	69	65	
Median DoR in confirmed responders, mo (95% CI)	NR (NR–NR)	11.1 (9.2–NR)	
12-month probability of maintaining response, % (95% CI)	75 (63–83)	41 (26–54)	

[a]Assessed by the BIRC.

Intracranial Objective Response[a] in Patients with Brain Metastases at Baseline

Measurable[b] brain metastases at baseline	Brigatinib n=18	Crizotinib n=21	OR (95% CI)
Confirmed intracranial ORR, % (95% CI)	78 (52–94)	29 (11–52)	10.42 (1.90–57.05) P=0.0028
CR, %	11	0	
PR, %	67	29	
Intracranial ORR at ≥1 assessment, % (95% CI)	83 (59–96)	33 (15–57)	9.29 (1.88–45.85) P=0.0023
Any brain metastases at baseline	**n=43**	**n=47**	
Confirmed intracranial ORR, % (95% CI)	67 (51–81)	17 (8–31)	13.00 (4.38–38.61) P<0.0001
CR, %	37	4	
PR, %	30	13	
Intracranial ORR at ≥1 assessment, % (95% CI)	79 (64–90)	23 (12–38)	16.30 (5.32–49.92) P<0.0001

[a]Assessed by the BIRC.
[b]≥10 mm in diameter.

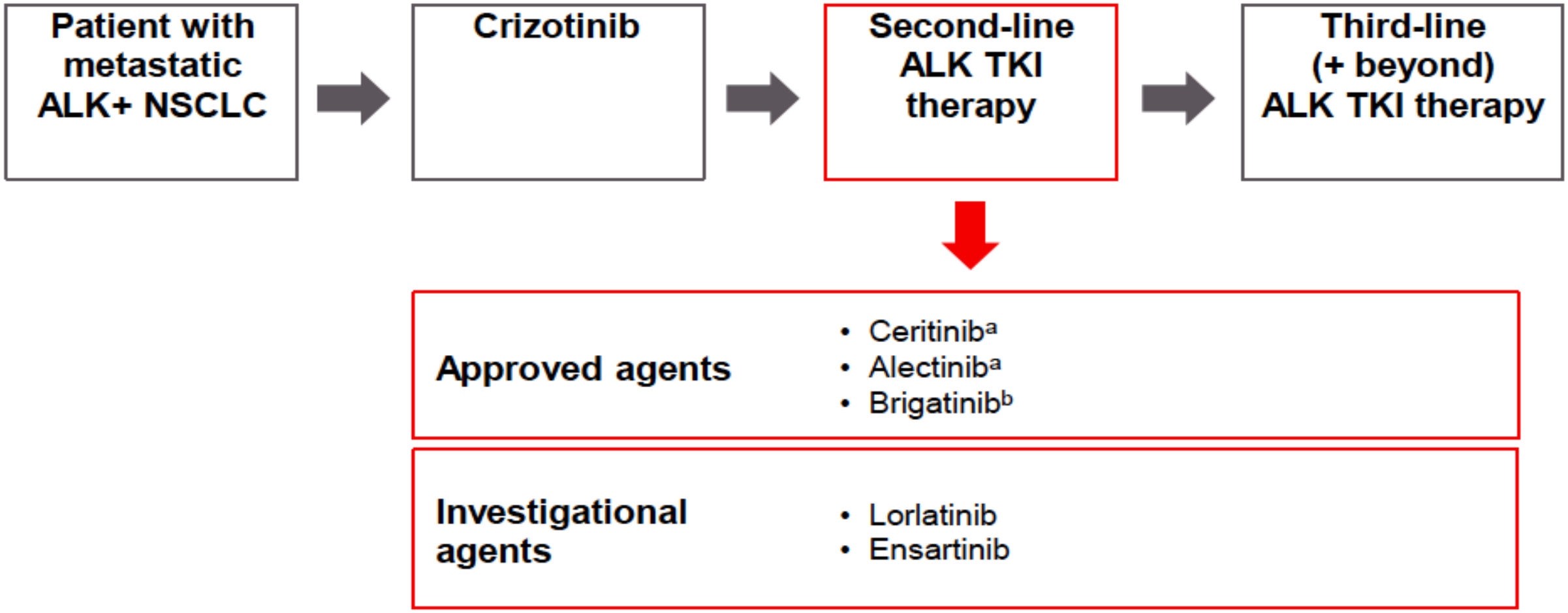
ALK TKIs TOXICITY PROFILES

	Crizotinib[1]	Ceritinib[a,2]	Alectinib[3]	Brigatinib[b,4]
Common AEs: All grades	Vision disorder 71% ↑ALT 79% ↑AST 66% Diarrhea 61% Nausea 56% Edema 49% Vomiting 46% Constipation 43% Upper respiratory infection 32% ↓Appetite 30% Fatigue 29% Neuropathy 21% Dizziness 18%	Diarrhea 85% Nausea 69% Vomiting 67% Fatigue 45% Abdominal pain 40% ↓Appetite 34% Weight loss 24%	Anemia 62% Constipation 34% Fatigue 26% Myalgia 23% Edema 22%	Nausea 40% Diarrhea 38% Fatigue 36% Cough 34% Headache 27%
Grade 3/4 AEs/ laboratory abnormalities (≥3%)	Neutropenia 11% Lymphopenia 7% Hypophosphatemia 10% ↑ALT 15% ↑AST 8%	Fatigue 7% Vomiting 5% Diarrhea 4.8% Anemia 4.2% Abdominal pain 3.7% Weight loss 3.7% ↑GGT 49% ↑ALT 34% ↑AST 21% ↑ALP 12% Hyperglycemia 10% ↑Amylase 8% ↑Lipase 6% ↑Creatinine 4.2% ↓Phosphate 3.7%	Anemia 7% ↑ALT 6% ↑AST 6% Hyperbilirubinemia 5% ↑Creatinine 4.1%	↑CPK 12% Hypertension 6.4% Pneumonia 5.5%[c] ↑Lipase 5.5% Lymphopenia 4.5% Hyperglycemia 3.6% ↓Phosphorus 3.6% Rash 3.6%

Indirect comparison for illustration only; clinical significance is not implied. Cross-trial comparisons are potentially confounded by differences in trial design and study population.

[a]Values reported for 750 mg fasted; [b]180 mg once daily with a 7-day lead in at 90 mg; [c]Includes one grade 5 event.
AE, adverse event; ALK, anaplastic lymphoma kinase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma-glutamyl transferase; TKI, tyrosine kinase inhibitor.
1. Xalkori (crizotinib) [package insert]. New York, NY: Pfizer Inc; 2018. 2. Zykadia (ceritinib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017. 3. Alecensa (alectinib) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2017. 4. Alunbrig (brigatinib) [package insert]. Cambridge, MA: Takeda Pharmaceutical Company Limited, USA; 2018.

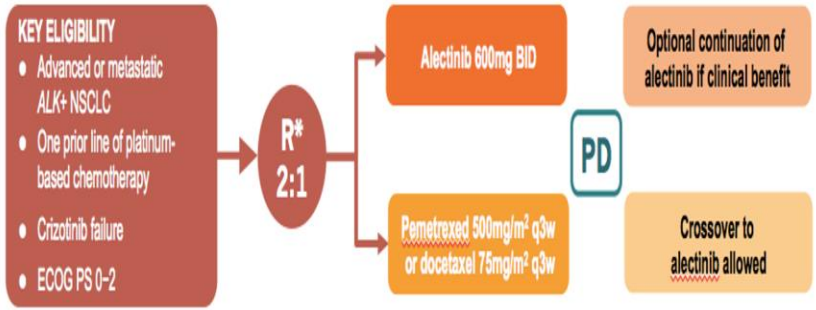
Second-line therapy for ALK+ NSCLC



[a]Approved in Canada, the European Union, and the United States; [b]Approved in Canada and the United States.
ALK, anaplastic lymphoma kinase; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.

Alectinib in 2nd line: ALUR STUDY

STUDY DESIGN



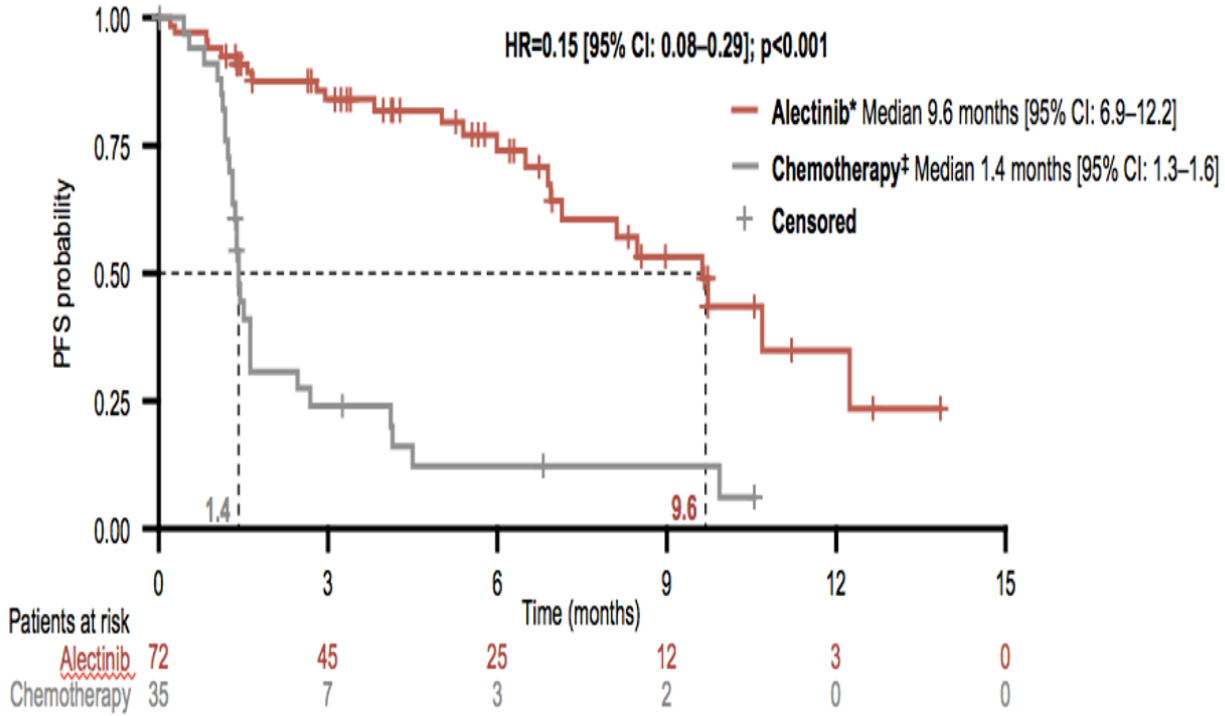
Primary endpoint	**Investigator-assessed PFS in the ITT population**
Secondary endpoints	**CNS ORR in patients with measurable CNS disease at baseline as assessed by an IRC (key secondary endpoint)**; IRC-assessed PFS; systemic ORR; DCR and DOR per RECIST v1.1 (investigator and IRC assessed); PFS in patients with CNS metastases at baseline (investigator and IRC assessed); time to CNS progression by baseline CNS disease status (IRC assessed); CNS DCR and CNS DOR in patients with CNS metastases at baseline (IRC assessed); OS; safety

*Randomisation was stratified by ECOG PS (0/1 vs 2); CNS metastases at baseline (yes vs no); history of radiotherapy to the brain (yes vs no) for patients with CNS metastases at baseline; BID, twice daily; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, Independent Review Committee; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours

Novello et al. ESMO 2017

Alectinib in 2nd line: ALUR STUDY

PRIMARY ENDPOINT: PFS, INVESTIGATOR-ASSESSED



- At data cut-off (26.01.17), median follow-up was 6.5 months with alectinib and 5.8 months with chemotherapy
- Median time on treatment was 20 weeks (range: 0.4–62.1) in the alectinib arm and 6 weeks (range: 1.9–47.1) in the chemotherapy arm

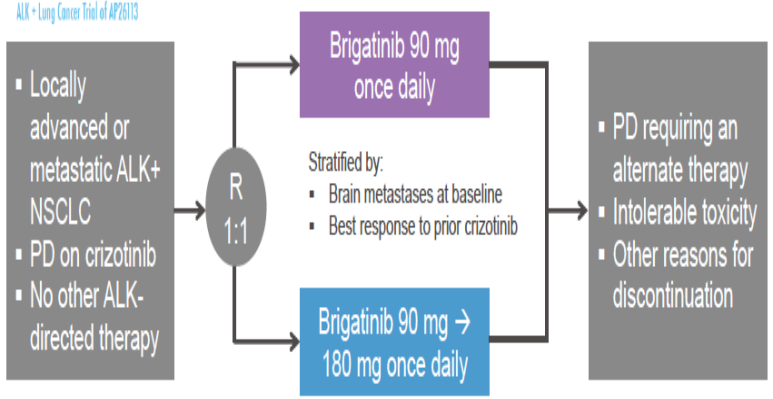
CI, confidence interval; *Events: 24 (33.3%); Censored: 48 (66.7%); ‡Events: 28 (80%); Censored: 7 (20%)

Novello et al. ESMO 2017

Second-line brigatinib (ALTA): systemic efficacy and safety

ALTA
ALK + Lung Cancer Trial of AP26113

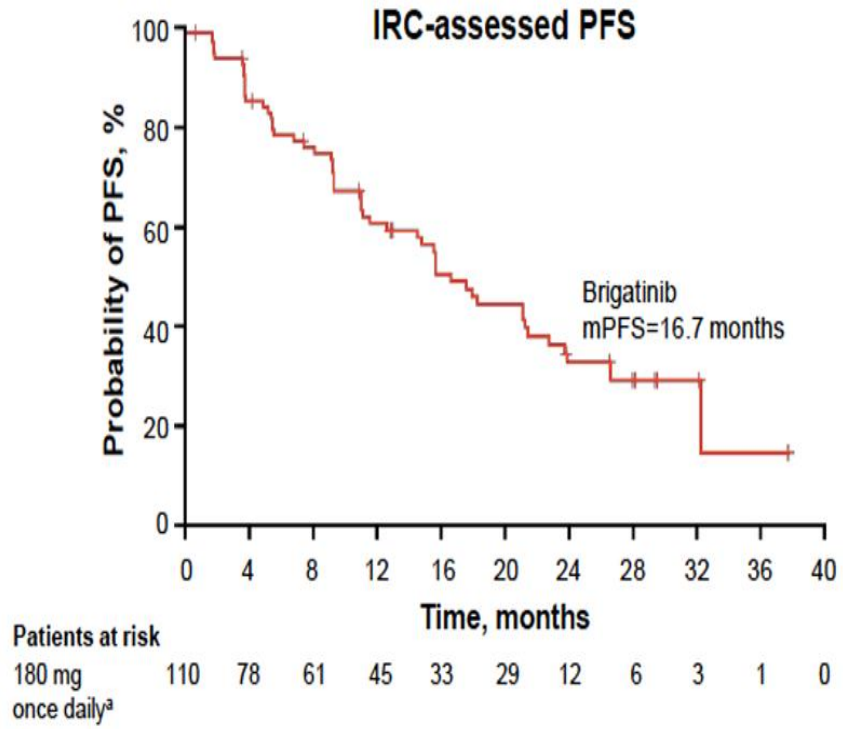
Phase 2, open-label, multicenter, international study (NCT02094573)



Primary endpoint: confirmed ORR per RECIST v1.1 (assessed by investigator)

Key secondary endpoints: confirmed ORR (assessed by IRC), CNS response (IRC-assessed intracranial ORR and PFS in patients with active brain metastases[a]), DOR, PFS, OS, safety, and tolerability

Randomized phase 2 design not intended for statistical comparisons between arms; however, post hoc comparisons were performed on PFS and OS to support dose selection

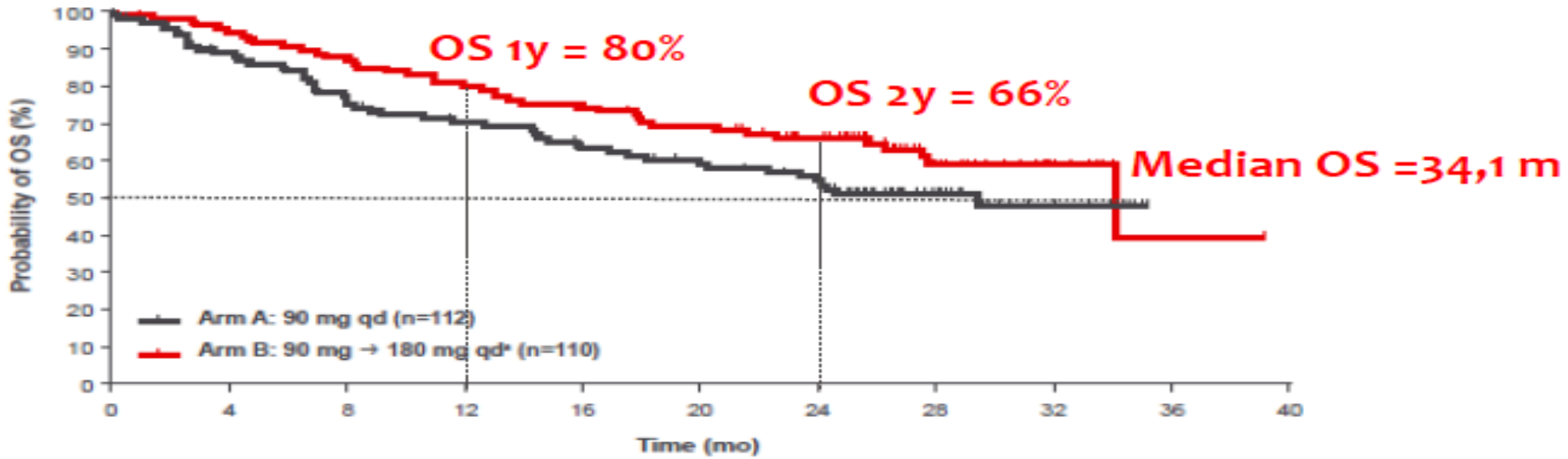


	Brigatinib 180 mg once daily[a] (n=110)
ORR,[b] % (95% CI)	56 (47-66)
Median PFS,[b] months (95% CI)	16.7 (11.6-21.4)
Median OS, months (95% CI)	34.1 (27.7-NR)

- The most common treatment-related AEs of any grade in the brigatinib 180 mg arm were diarrhea (35%), nausea (33%), and increased blood creatine phosphokinase (32%). The most common grade ≥3 treatment-related AEs were increased blood creatine phosphokinase (13%), hypertension (5%), and increased lipase (5%)
- Treatment discontinuation attributable to AEs: 11%
- Dose interruption attributable to any AE: 62%

Data reported as of September 29, 2017.
[a]180 mg once daily with 7-day lead in at 90 mg once daily; [b]IRC assessed.
AE, adverse event; CI, confidence interval; IRC, independent review committee; NR, not reached; OS, overall survival; PFS, progression-free survival.
With permission from Huber RM, et al. Poster. ASCO. 2018 (abstr 9061).

OS results in ALTA trial



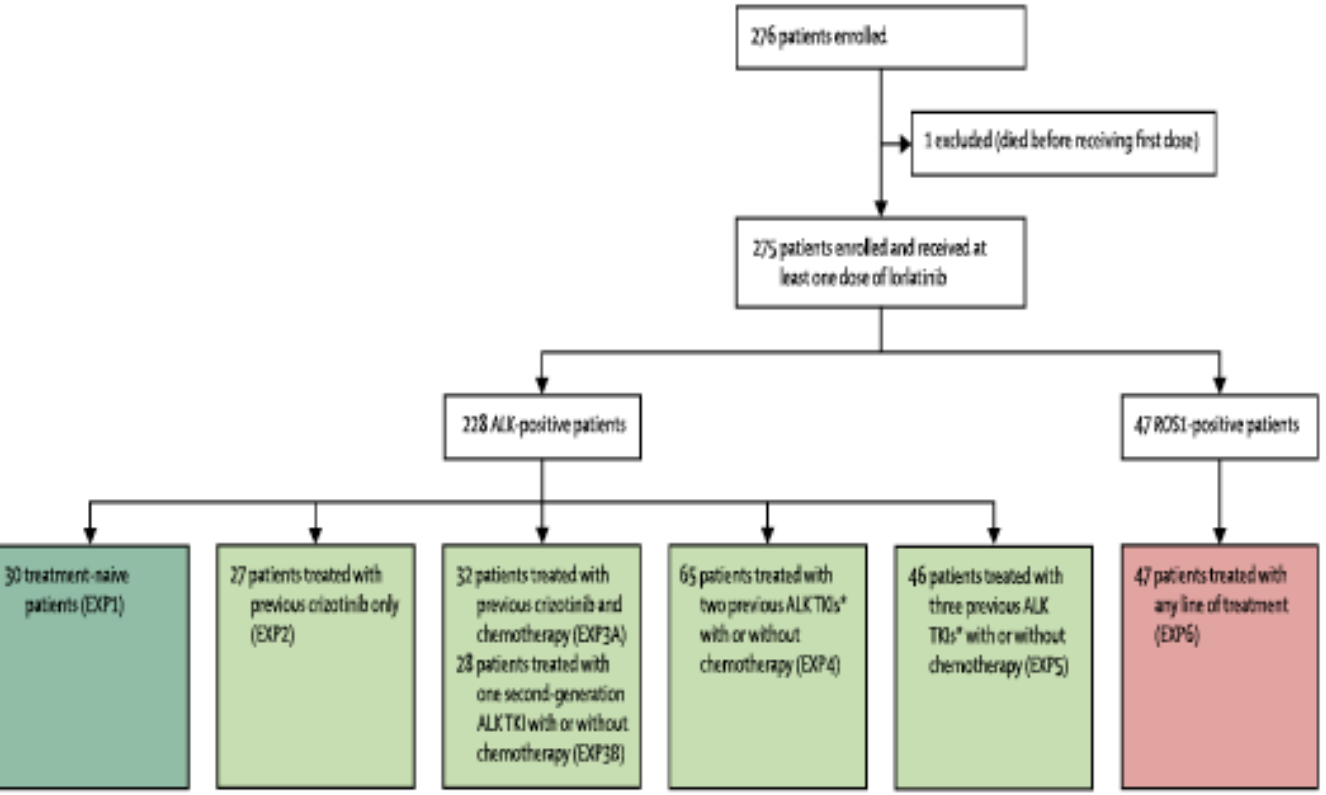
No. at risk:											
Arm A: 90 mg qd	112	92	77	70	61	55	49	23	9	0	0
Arm B: 90 mg → 180 mg qd*	110	100	91	83	77	68	56	25	10	1	0

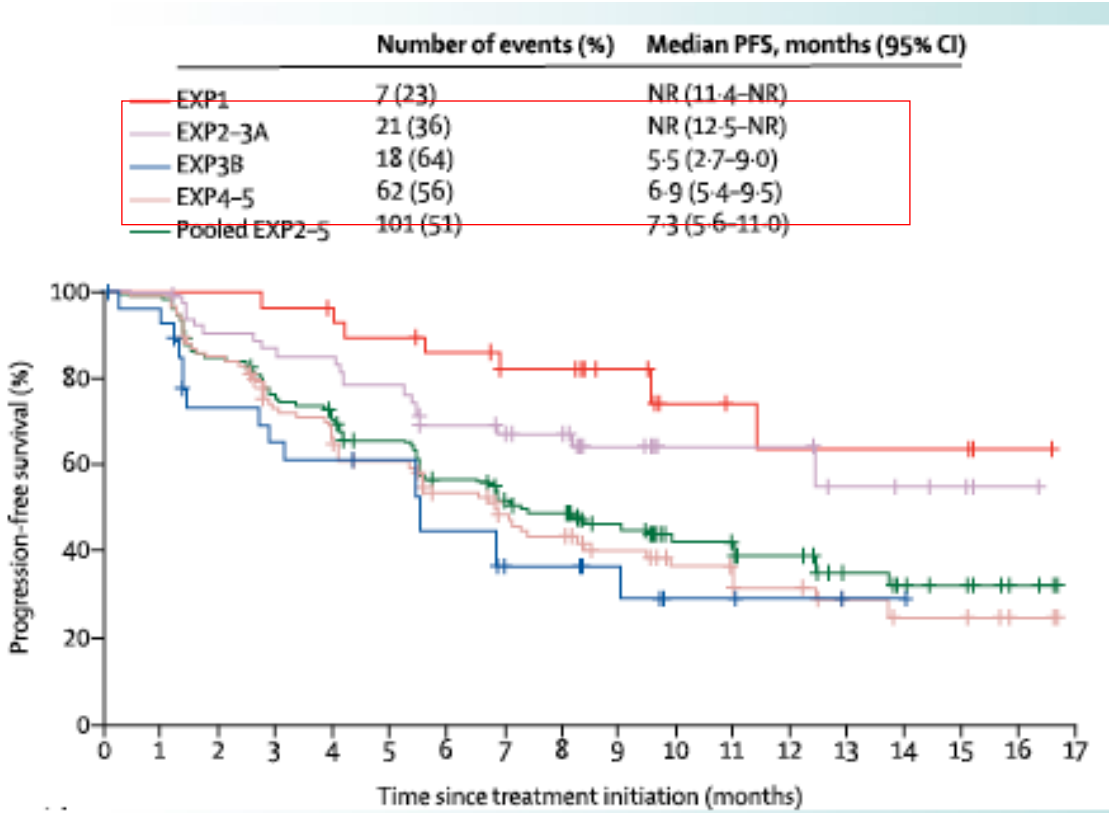
	Arm A: 90 mg qd	Arm B: 90 mg → 180 mg qd*
Median OS, months (95% CI)	29.5 (18.2–NR)	34.1 (27.7–NR)
1-year OS probability, % (95% CI)	70 (61–78)	80 (71–87)
2-year OS probability, % (95% CI)	55 (44–64)	66 (56–74)

* 180 mg qd with 7-day lead-in at 90 mg

Huber et al, ASCO 2018

Lorlatinib: fase II trial





Solomon B Lancet 2018

Phase 1/2 lorlatinib study: efficacy and safety

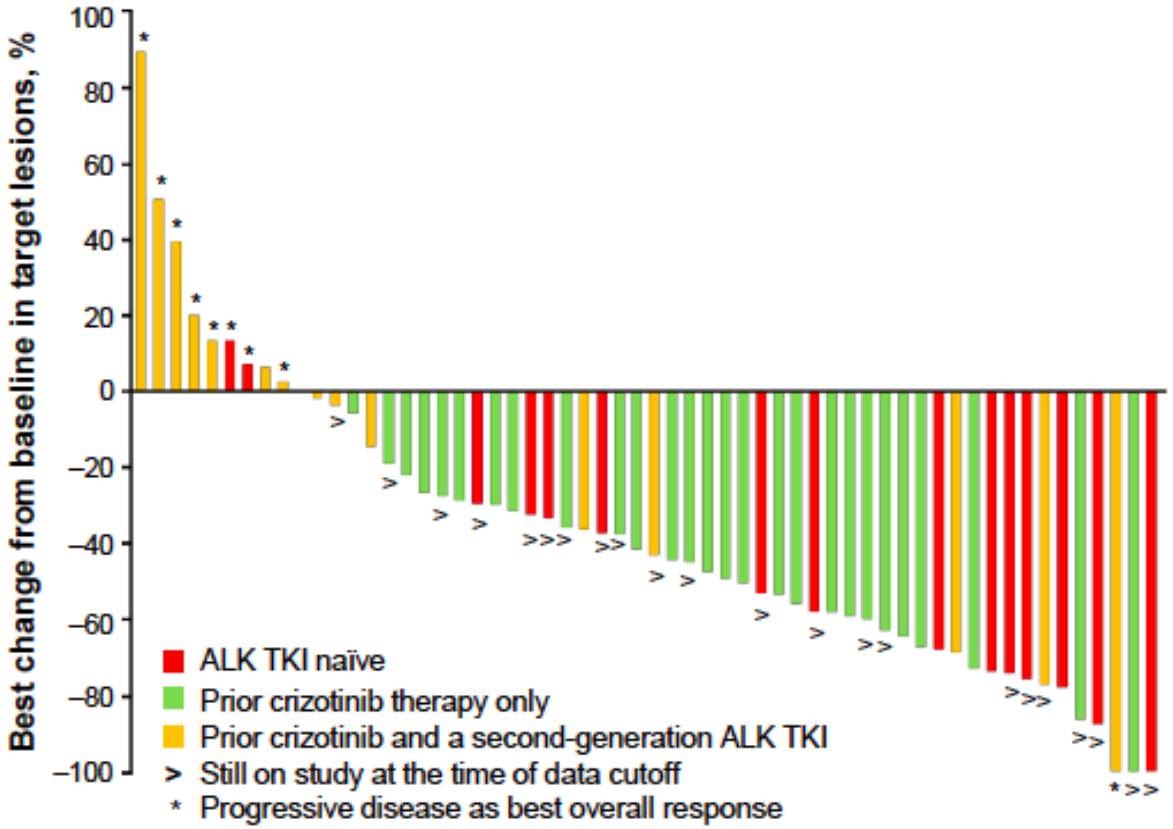
Lorlatinib efficacy in later lines of ALK TKI treatment

	EXP2-3A Prior crizotinib ± CT (n=59)	EXP3B Prior non-crizotinib ALK TKI ± CT (n=28)	EXP4-5 ≥2 prior ALK TKIs ± CT (n=111)
ORR,[a,b] % (95% CI)	72.9 (59.7-83.6)	42.9 (24.5-62.8)	39.6 (30.5-49.4)
Median PFS,[a,b] months (95% CI)	11.1 (8.2-NR)	5.5 (2.9-8.2)	6.9 (5.4-9.5)

- Most common treatment-related AEs (any grade, and grade 3/4) were hypercholesterolemia (84%, 16%) and hypertriglyceridemia (67%, 17%), which were managed with standard medical therapy and/or lorlatinib dose modifications
- Nine patients (3.3%) permanently discontinued lorlatinib due to a treatment-related AE

[a]Data cutoff February 2, 2018; [b]Independent review committee assessed.
ALK, anaplastic lymphoma kinase; ALKi, ALK inhibitor; CI, confidence interval; CT, chemotherapy; NR, not reported; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
Besse B, et al. *J Clin Oncol*. 2018;36(15 suppl; abstr 9032).

Phase 1/2 ensartinib (X-396): systemic efficacy and safety



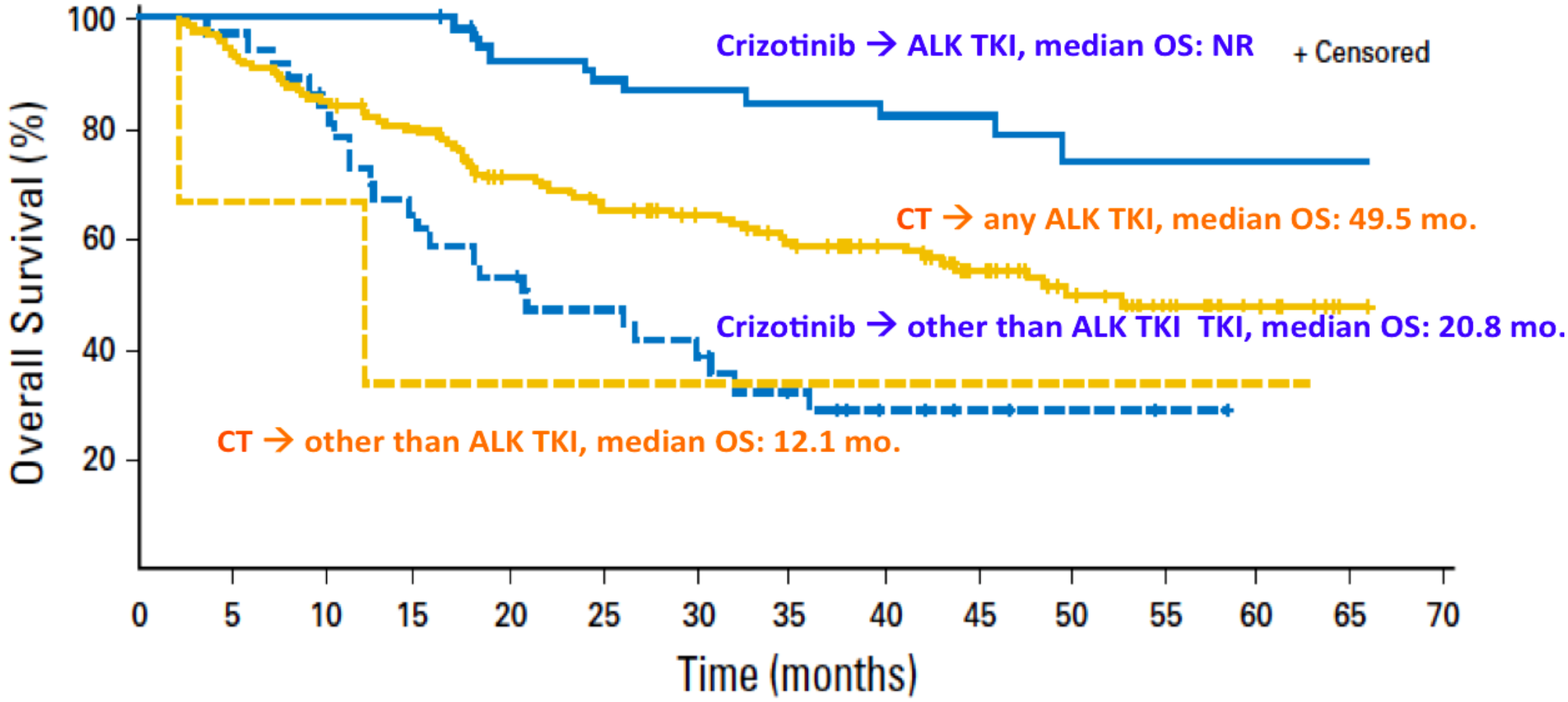
	Prior crizotinib only (n=29)	Prior crizotinib and prior second-generation ALK TKI[b] (n=16)
RR,[a] % (95% CI)	69 (50.8-2.7)	25 (10.2-49.5)
Median PFS, months (95% CI)	9.0 (5.6-11.7)	1.9 (1.7-5.7)

- The most common ensartinib-related AEs were rash (56%), nausea (36%), pruritus (28%), vomiting (26%), and fatigue (22%)
- Treatment discontinuation and dose interruption attributable to ensartinib-related toxicity were 5.2% and 15%, respectively

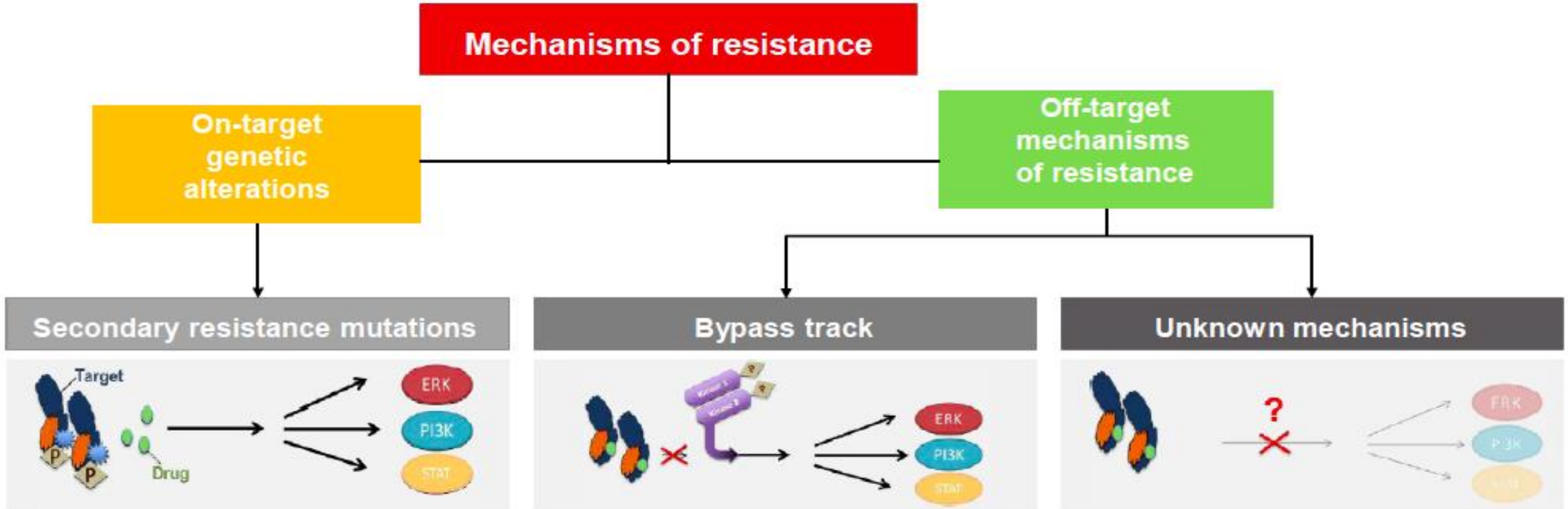
Note: ALK+ evaluable patients at ≥200 mg who completed ≥1 cycle and had a postbaseline response assessment
23% of patients experienced a treatment-related grade 3/4 toxicity (primarily rash and pruritus)

Data cutoff: February 15, 2017.
[a]Based on partial response; [b]Included ceritinib, alectinib, or brigatinib.
AE, adverse event; ALK, anaplastic lymphoma kinase; CI, confidence interval; PFS, progression-free survival; RR, response rate; TKI, tyrosine kinase inhibitor.
Adapted from Horn L, et al. Ensartinib (X-396) in ALK-positive non-small cell lung cancer: results from a first-in-human phase I/II, multicenter study. *Clin Cancer Res*. 2018;24:2771-2779 with permission from AACR.

After Progression continuation with TKI is preferable

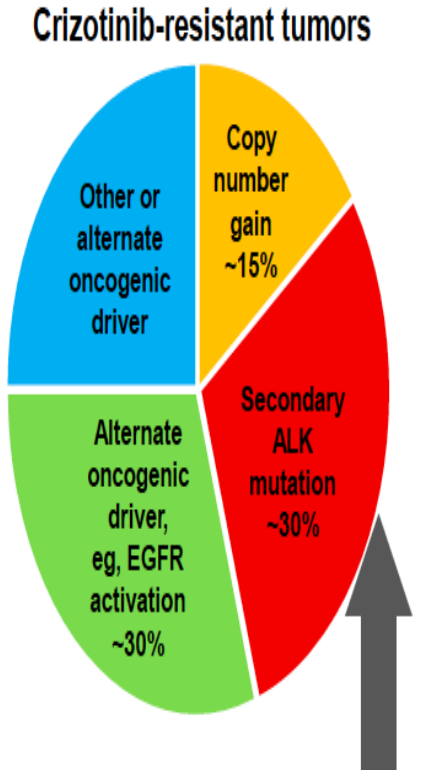


Solomon- JCO 2018



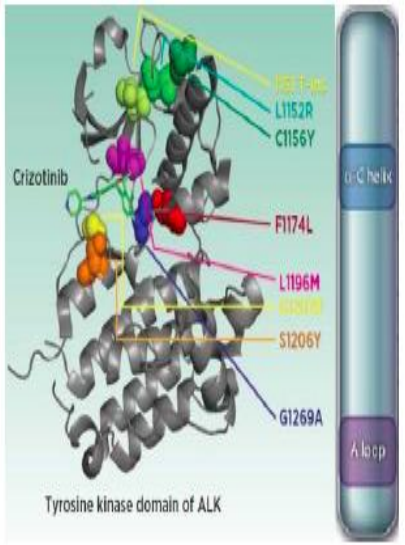
ERK, extracellular regulated kinase; PI3K, phosphoinositide 3-kinase; STAT, signal transducer and activator of transcription; TKI, tyrosine kinase inhibitor.
Lin JJ, et al. *Cancer Discov*. 2017;7:137-155. Niu X, et al. *Transl Cancer Res*. 2017;6(suppl 2):S239-S245.

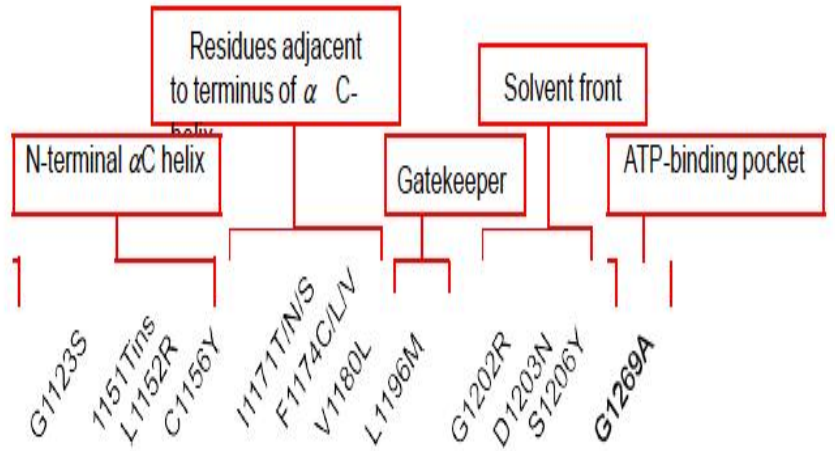
Approximate proportion of resistance mechanisms identified in crizotinib-resistant tumors

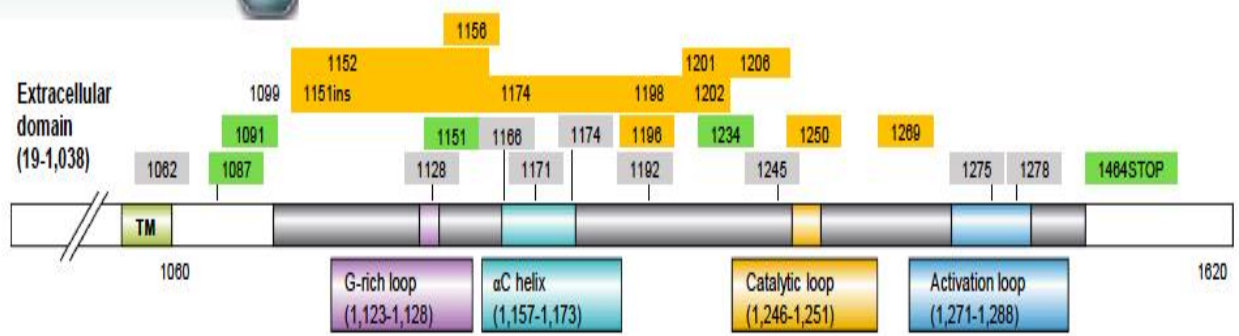


In some patients, more than one resistance mechanism can be detected

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.
Image adapted from Isozaki H, et al. *Cancers*. 2015;7:763-783.







ALK, anaplastic lymphoma kinase; ATP, adenosine triphosphate.
Hallberg B, et al. *Nat Rev Cancer*. 2013;13:685-700. Katayama R, et al. *Clin Cancer Res*. 2015;21:2227-2235.

Cellular ALK Phosphorylation Mean IC50 (nM)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4-ALK V1	38.6	4.9	11.4	10.7	2.3
EML4-ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4-ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4-ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4-ALK I1171T	51.4	1.7	33.6[3]	6.1	11.5
EML4-ALK F1174C	115.0	38.0[3]	27.0	18.0	8.0
EML4-ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4-ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4-ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4-ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4-ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4-ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4-ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4-ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4-ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

IC50 ≤ 50 nM

IC50 > 50 <200 nM

IC50 ≥ 200 nM

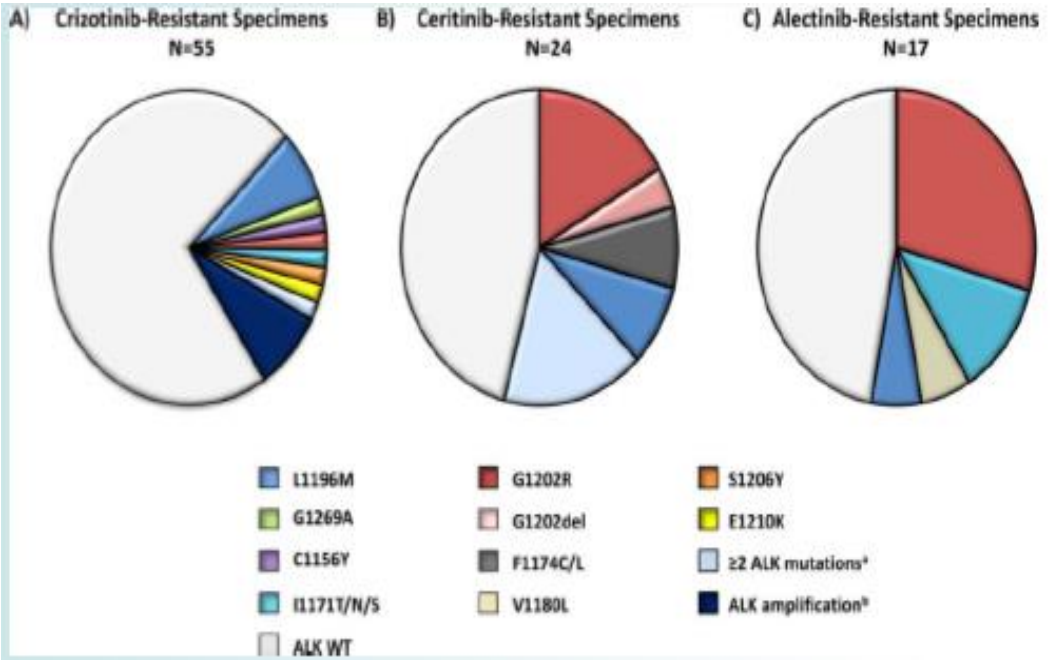


Table 1. Ropotrectinib Potently Inhibited WT and Mutant ALK/ROS1/TRK in Ba/F3 Cell Proliferation IC_{50} (nM

	EML4-ALK V1		CD74-ROS1			LMNA-TRKA		ETV6-TRKB		ETV6-TRKC		
Inhibitor	WT	G1202R	WT	G2032R	D2033N	WT	G595R	WT	G639R	WT	G623R	G623I
Ropotrectinib	27	63.6	<0.2	3.3	1.3	<0.2	0.4	<0.2	0.6	<0.2	3	1.4
Crizotinib	55.7	400	14.6	266.2	200.9							
Ceritinib	7.1	965	42.8	1813	169.2							
Alectinib	11.6	417										
Brigatinib	10.9	190.5	21	1172	128.4							
Lorlatinib	0.5	41.5	0.2	160.7	3.3							
Ensartinib			39.5	371.8	401.9							
Entrectinib			10.5	1813	169.2	0.5	705	<0.5	1384	0.6	1623	1351
Larotrectinib						4	1024	10.9	3000	10.2	3293	742.3

Drilon et al ASCO 2018 ; Gainor et al Cancer discov 2016

Phase 2 study of lorlatinib

	EXP2-3A Post crizotinib[a] (n=59) EXP2: Prior crizotinib only EXP3A: Prior crizotinib + 1-2 regimens of CT	
	No mutation[b] (n=43)	≥1 mutation[b] (n=15)
BOR, n (%)		
CR	1 (2.3)	0
PR	30 (69.8)	11 (73.3)
SD	8 (18.6)	0
PD	4 (9.3)	2 (13.3)
IND	0	2 (13.3)
ORR, n (%)	31 (72.1)	11 (73.3)
95% CI	56.3-84.7	44.9-92.2

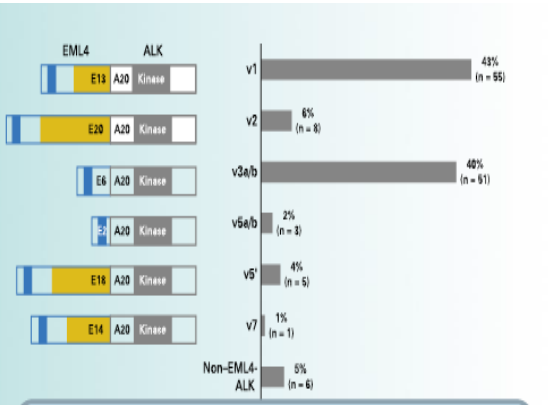
	EXP3B, 4-5: Prior second-generation TKI (n=139)[c] EXP3B: 1 non-crizotinib TKI ± CT EXP4: 2 prior ALK TKIs ± CT EXP5: 3 prior ALK TKIs ± CT	
	No mutation[d] (n=87)	≥1 mutation[d] (n=49)
BOR, n (%)		
CR	2 (2.3)	1 (2.0)
PR	21 (24.1)	29 (59.2)
SD	36 (41.4)	10 (20.4)
PD	21 (24.1)	5 (10.2)
IND	7 (8.0)	4 (8.2)
ORR, n (%)	23 (26.4)	30 (61.2)
95% CI	17.6-37.0	46.2-74.8

[a]1 patient sample was nonanalyzable; [b]Detected in either cell-free DNA or tumor tissue (archival or de novo) analysis sets; [c]Three patient samples were nonanalyzable; [d]Detected in either cell-free DNA or tumor tissue (archival or de novo) analysis sets.

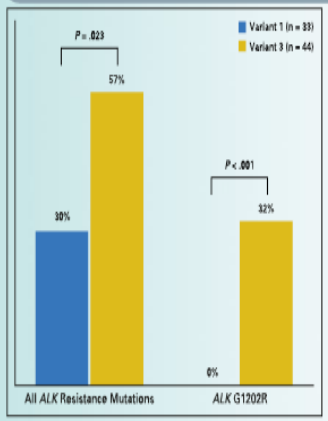
ALK, anaplastic lymphoma kinase; BOR, best overall response; CI, confidence interval; CR, complete response; CT, chemotherapy; IND, indeterminate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Shaw AT, et al. *Cancer Res*. 2018;78(15 suppl; abstr CT044).

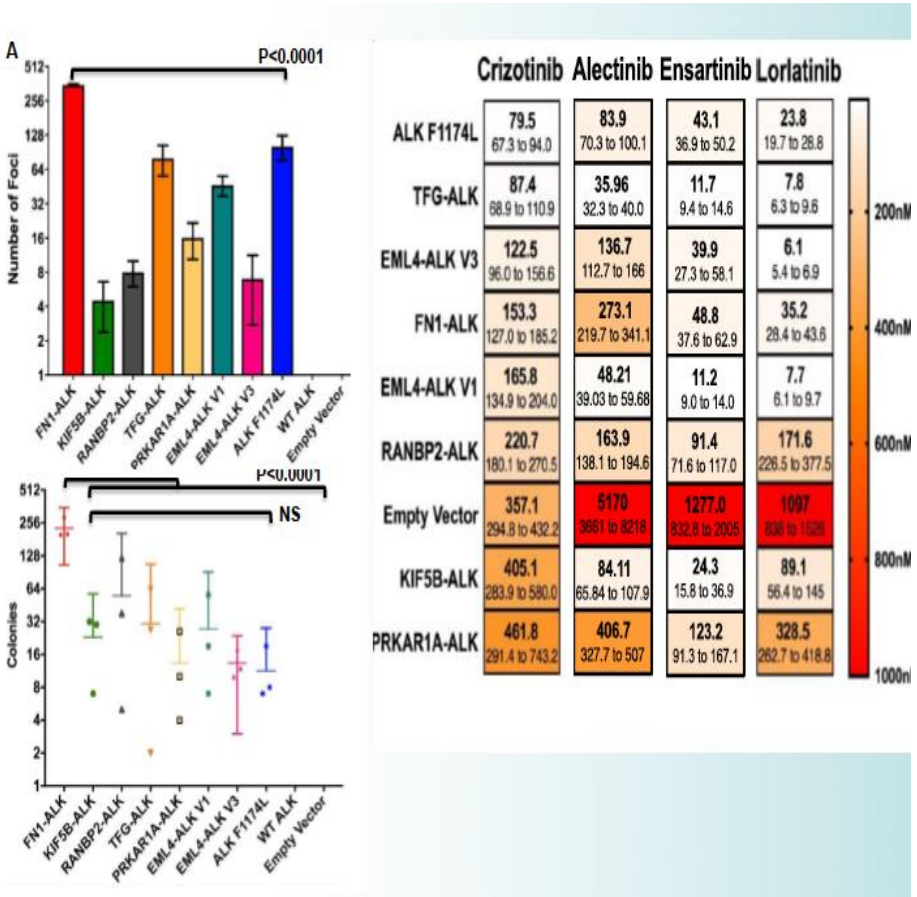
ALK fusion variants



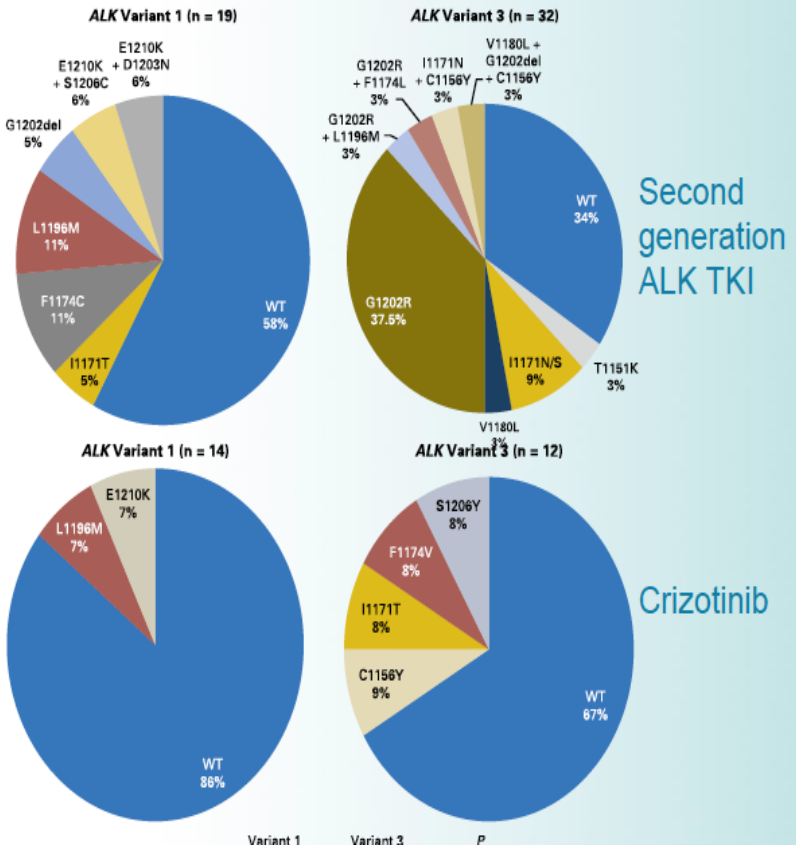
The most frequent ALK variants were EML4-ALK variant 1 in 55 patients (43%) and variant 3 in 51 patients (40%)



ALK resistance mutations were significantly more common in variant 3 than in variant 1 (57% v 30%; P = .023).



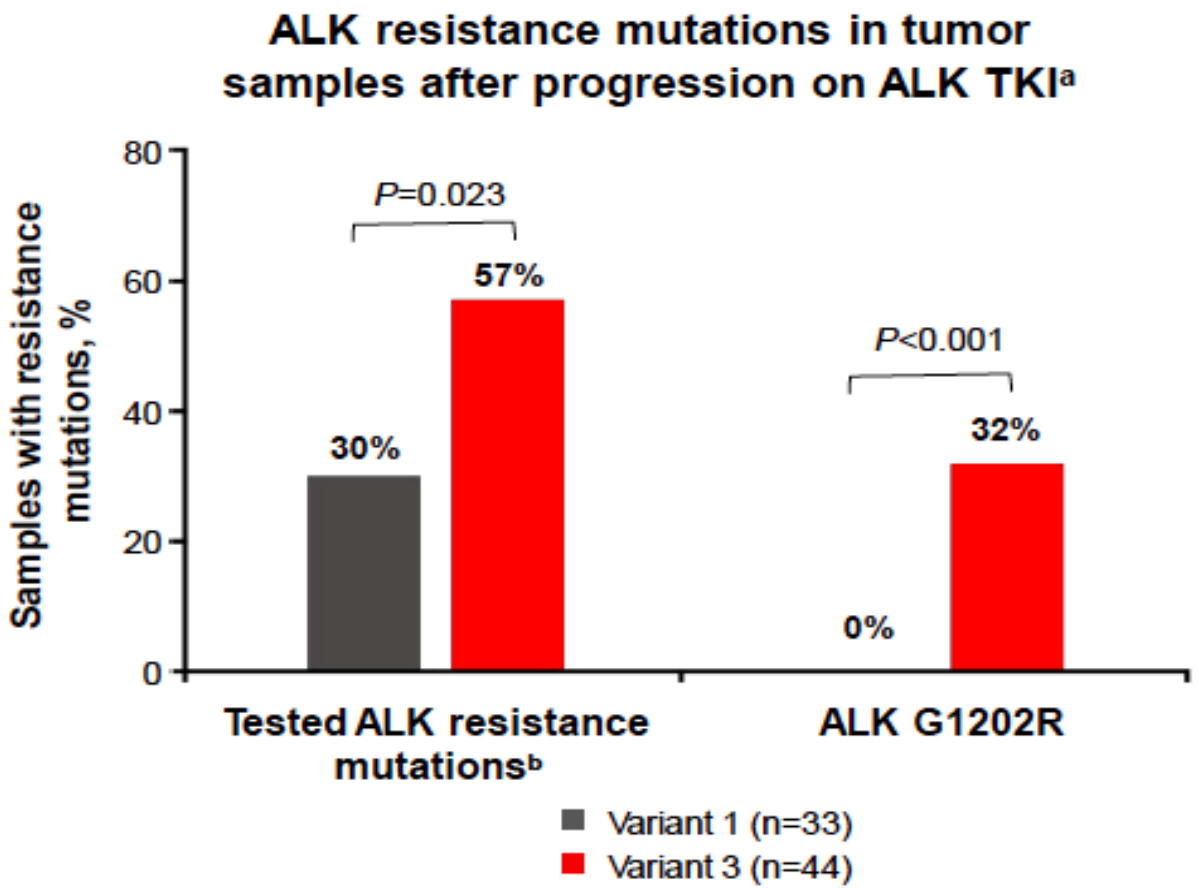
Distribution of ALK resistance mut in tumor biopsy obtained after disease progression

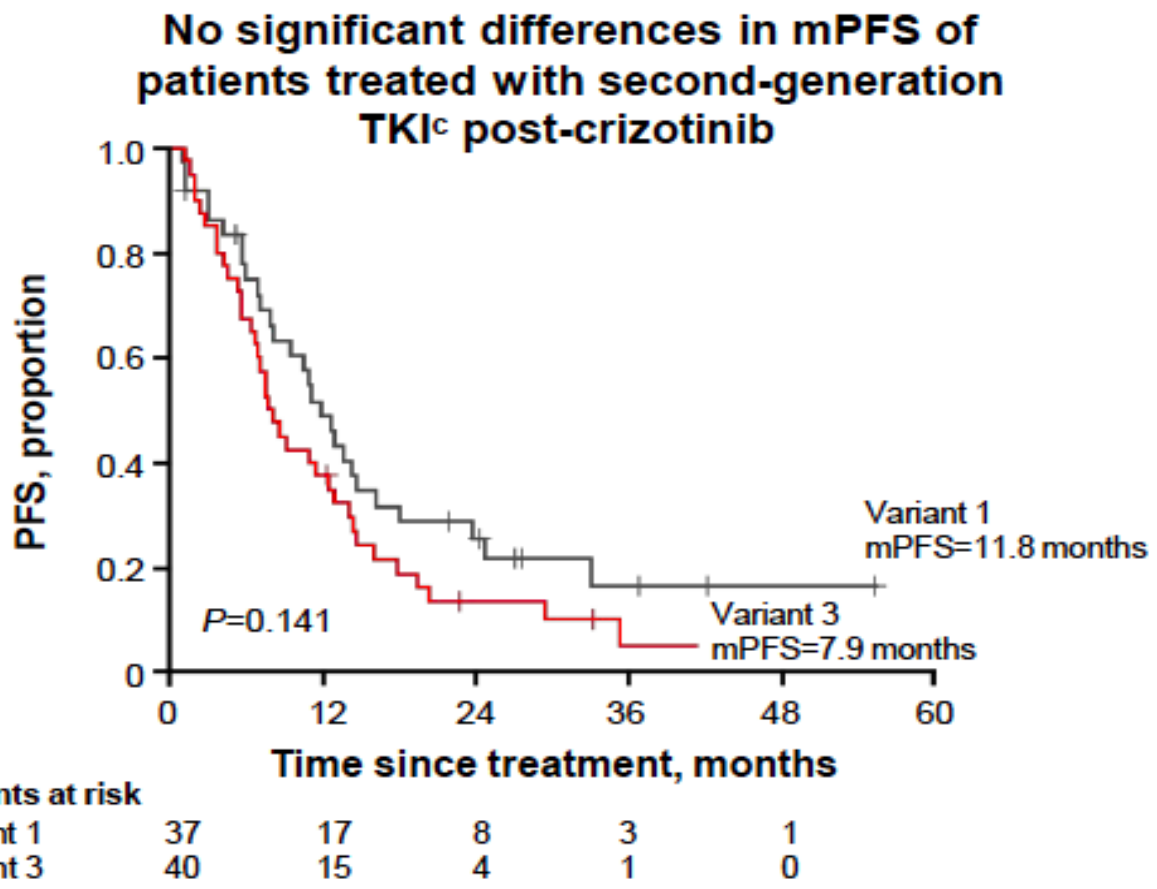


Childress et al. Mol CancerRes 2018

Lin J e tal al JCO 2018

Variants of EML4-ALK are associated with different resistance mechanisms





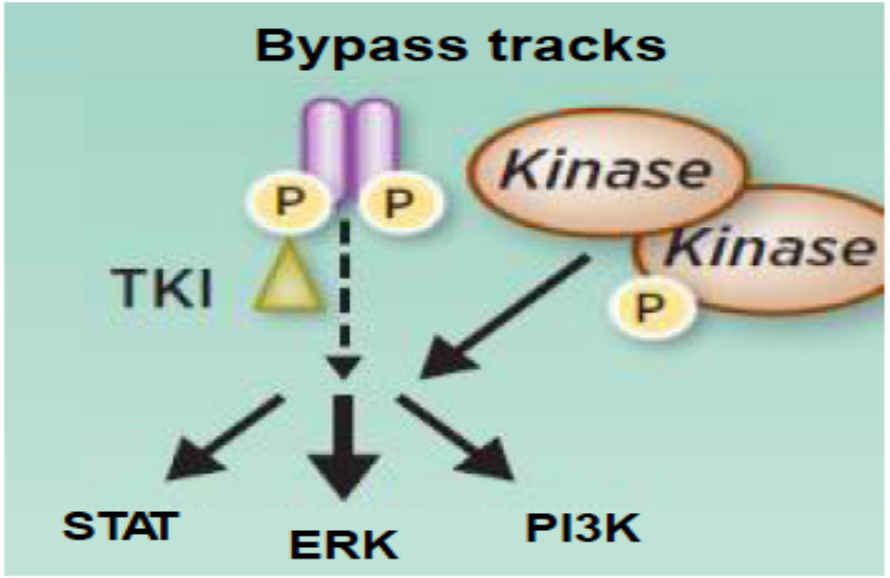
[a]ALK TKI treatment included crizotinib (94%), ceritinib (42%), alectinib (54%), brigatinib (11%), and lorlatinib (30%); [b]ALK resistance mutations evaluated were E1210K, D1203N, S1206Y/C, G1202R, G1202del, L1196M, F1174L/C, C1156Y, I1171T/N/S, F1174L/C, V1180L, and T1151Tins; [c]Second-generation TKI was defined as ceritinib, alectinib, or brigatinib in this study.

ALK, anaplastic lymphoma kinase; EML4-ALK, echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase; mPFS, median progression-free survival; TKI, tyrosine kinase inhibitor.

Lin JJ, et al. *J Clin Oncol*. 2018;36:1199-1206. Reprinted with permission. © 2018 American Society of Oncology. All rights reserved.

Different resistance mechanisms

- Activation of bypass signaling leading to reactivation of downstream pathways
  - Genetic alteration (amplification or mutation)
  - Autocrine signaling or ligand activation
  - Dysregulation of feedback signaling
- Several bypass tracks have been identified
  - EGFR activation
  - NRG1 fusion, HER2, HER3
  - MEK mutation
  - MET amplification (except for crizotinib)
  - KIT amplification, SRC activation, IGF-1R activation



ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ERK, extracellular regulated kinase; HER, human epidermal growth factor receptor; IGF-1R, insulin-like growth factor-1 receptor; KIT, CD117; MEK, mitogen-activated protein kinase (MAPK) kinase; NRG1, neuregulin 1; P, phosphate; PI3K, phosphoinositide 3-kinase; SRC, sarcoma; STAT, signal transducer and activator of transcription; TKI, tyrosine kinase inhibitor.

Reprinted from Katayama R, et al. Therapeutic targeting of anaplastic lymphoma kinase in lung cancer: a paradigm for precision cancer medicine. *Clin Cancer Res*. 2015;21:2227-2235 with permission from AACR.

What is the value of checkpoint inhibitor therapy in ALK+ NSCLC?

Driver	n	RR, %	Median PFS, months	Median OS, months	Impact on PFS of:			
					PD-L1	Smoking	Nb line	Subtype
Total		19	2.8	13.3				
KRAS	271	26	3.2	13.5	✓	⊘	⊘	⊘
EGFR	125	12	2.1	10	✓	⊘	⊘	⊘
BRAF	43	24	3.1	13.6	⊘	✓	⊘	N/A
MET	36	16	3.4	18.4	N/A	⊘	N/A	⊘
HER2	29	7	2.5	20.3	N/A	✓	⊘	N/A
ALK	23	0	2.5	17	⊘	⊘	⊘	N/A
RET	16	6	2.1	21.3	⊘	⊘	⊘	N/A
ROS1	7	17	–	–	⊘	⊘	⊘	N/A

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor 2; N/A, not applicable; Nb line, number of prior lines before immunotherapy; NSCLC, non–small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RET, rearranged during transfection; ROS1, Ros proto-oncogene 1; RR, response rate.

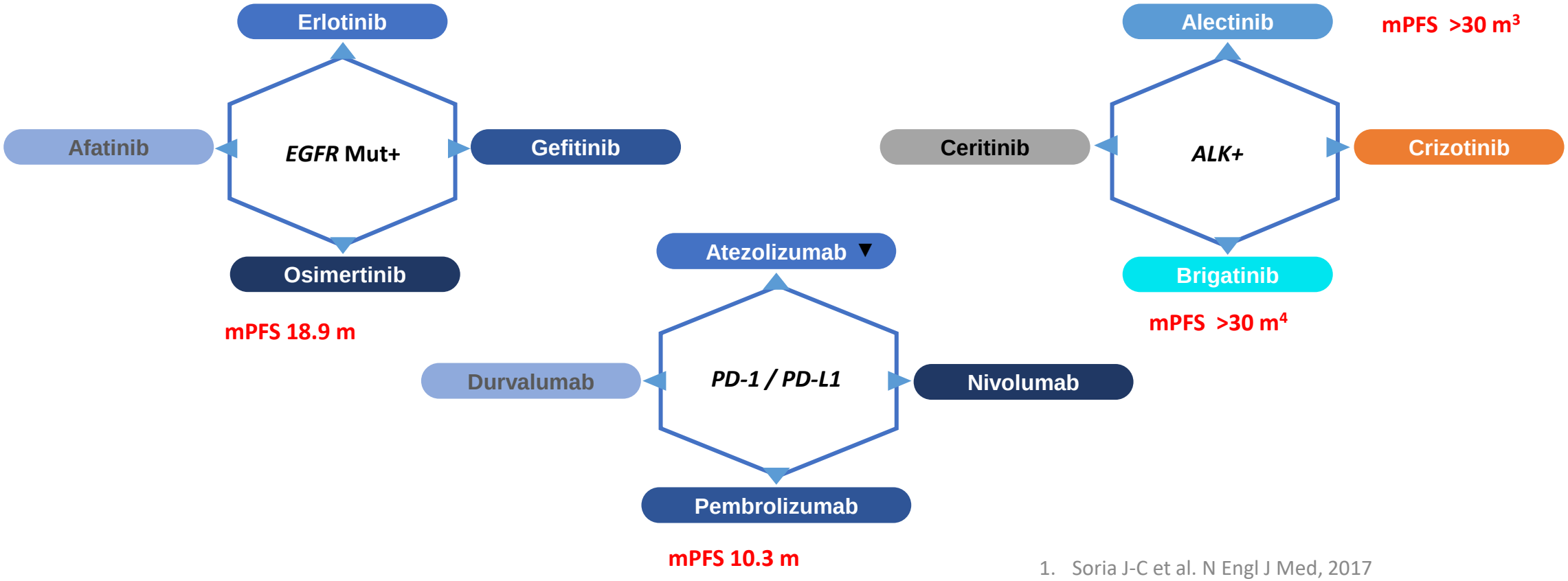
Mazieres, J. et al. Presented at: ASCO 2018 (abstr 9010)

TREATMENT OF NSCLC ALK +

NO MOLECULAR TESTING BEYOND THE PROGRESSION OR G1202R MUTATION

TESTING BEYOND THE PROGRESSION OR NO G1202R MUTATION

The best benefit ever seen in advanced NSCLC



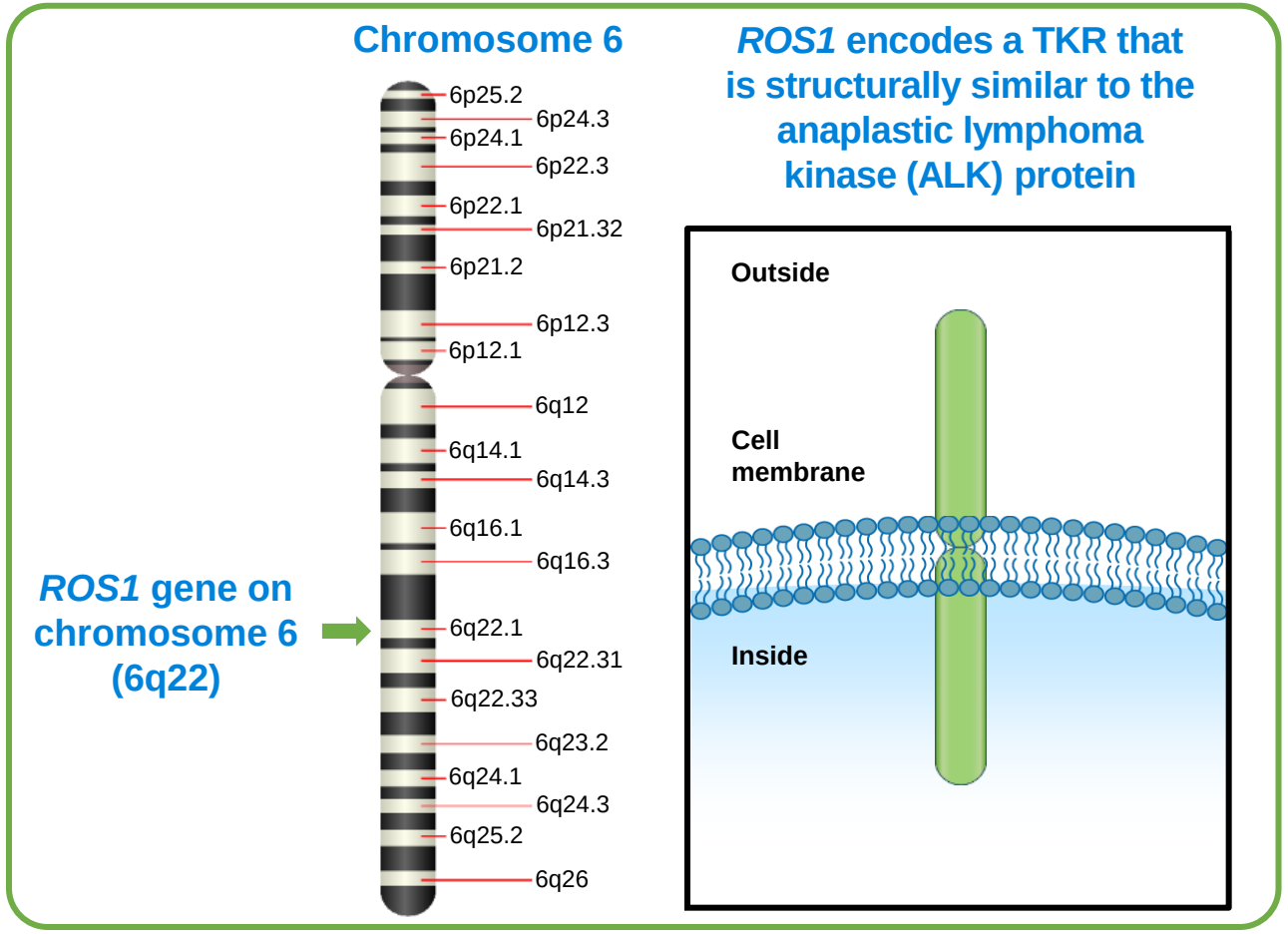
1. Soria J-C et al. N Engl J Med, 2017
2. Reck M et al. N Engl J Med. 2016
3. Peters S et al. NEJM 2017
4. Camidge et al, NEJM 2018

What is *ROS1*?

- The *ROS1* gene encodes a tyrosine kinase receptor (TKR) of unknown function and ligand[1–3]
- Genetic rearrangements leading to constitutive expression of ROS1 have been identified in a number of tumour types, including NSCLC[1–3]

The function of *ROS1* is not clear[3]

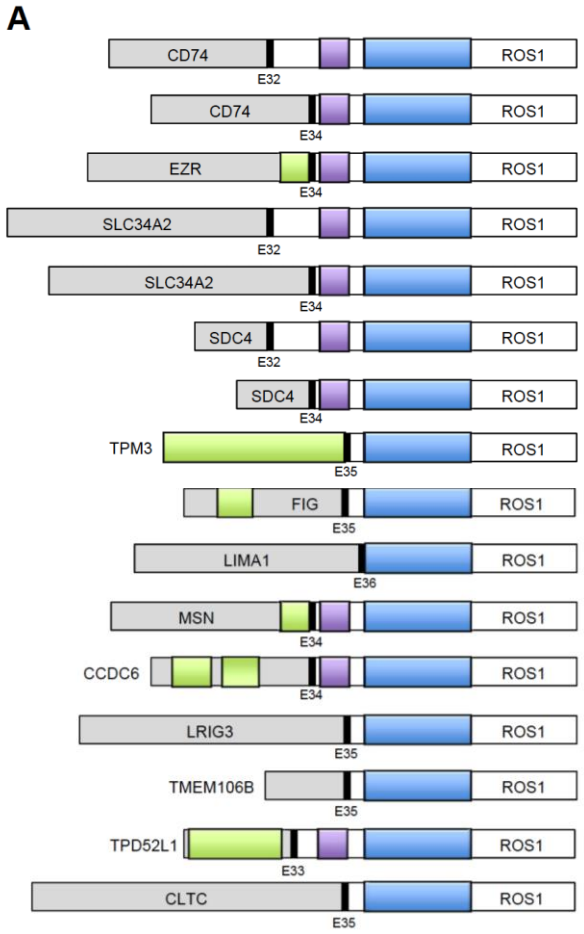
- **No ligands have been identified**
- **Mice lacking wild-type *ROS1* are viable and appear healthy**

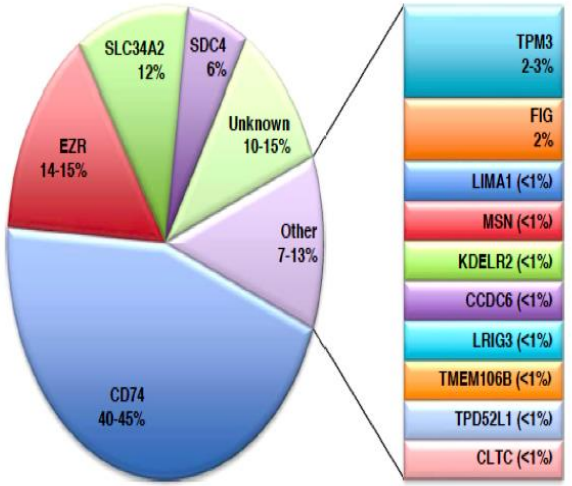


1. Birchmeier, et al. Proc Natl Acad Sci USA 1987; 2. Rikova, et al. Cell 2007; 3. Gainor and Shaw. Oncologist 2013

Ros1 REARRANGEMENTS IN NSCLC

- *ROS1* rearrangements are identified in approximately 1–2% of NSCLC cases.[1–3]
- *ROS1* rearrangements lead to fusion of a portion of ROS1, including its tyrosine kinase domain, to a variety of different partner proteins.[3,4]
- ROS1 fusion kinases are constitutively activated and function as potent oncogenic drivers.[3,4]



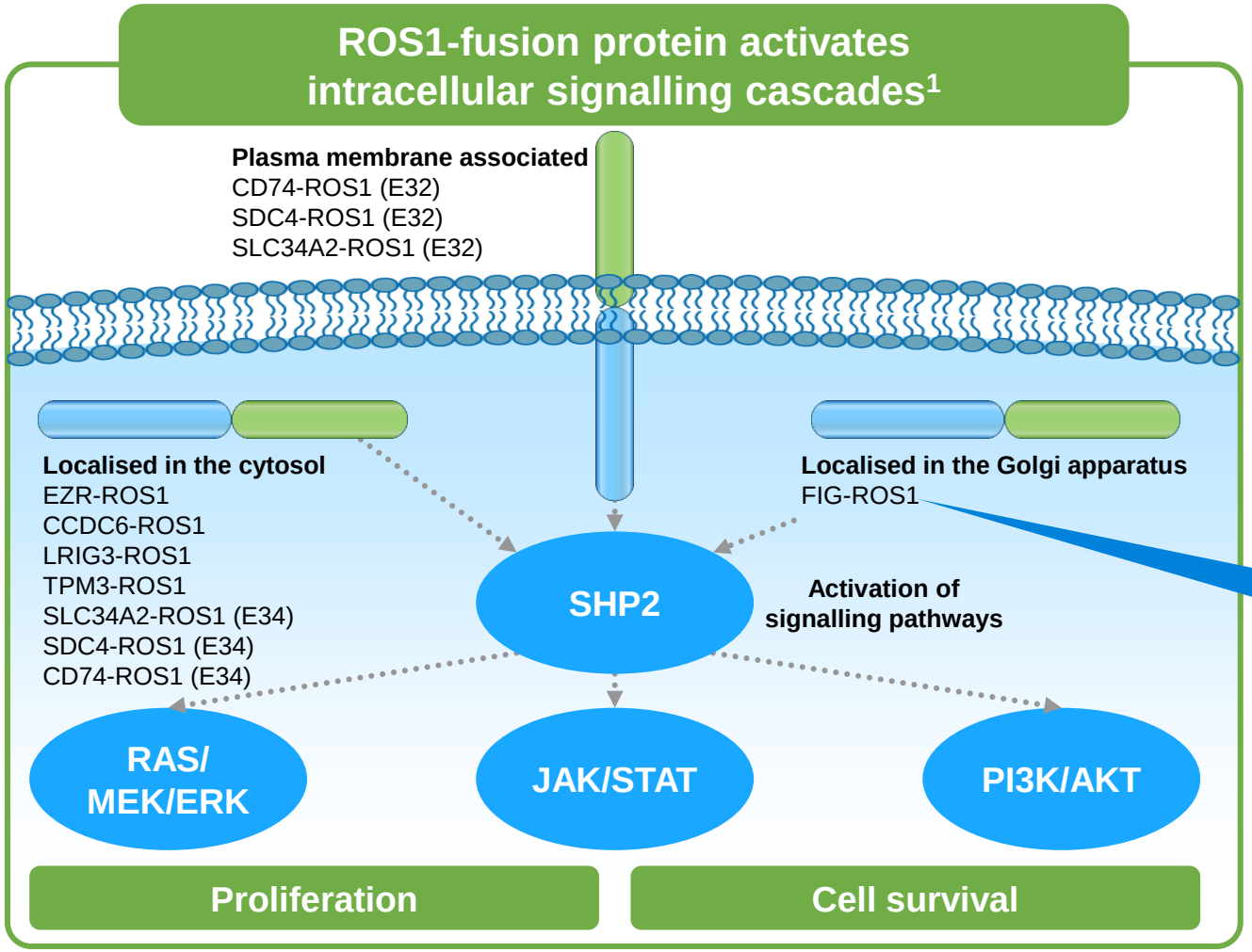


Lin and Shaw. *J Thorac Oncol.* 2017;12:1611–1625.

NSCLC, non-small cell lung cancer.

1. Bergethon K. *J Clin Oncol.* 2012;30:863–870. 2. Dugay F, et al. *Oncotarget.* 2017;8:53336-53351.
3. Davies KD, Doebele RC. *Clin Cancer Res.* 2013;19:4040–4045. 4. Lin JJ and Shaw AT. *J Thorac Oncol.* 2017;12:1611–1625.

The ROS1-fusion protein is constitutively active and drives cell proliferation and survival



The exact mechanism by which ROS1-fusion proteins become constitutively active remains unclear[2]

1. Rossi, et al. Lung Cancer 2017;
2. Gainor and Shaw. Oncologist 2013

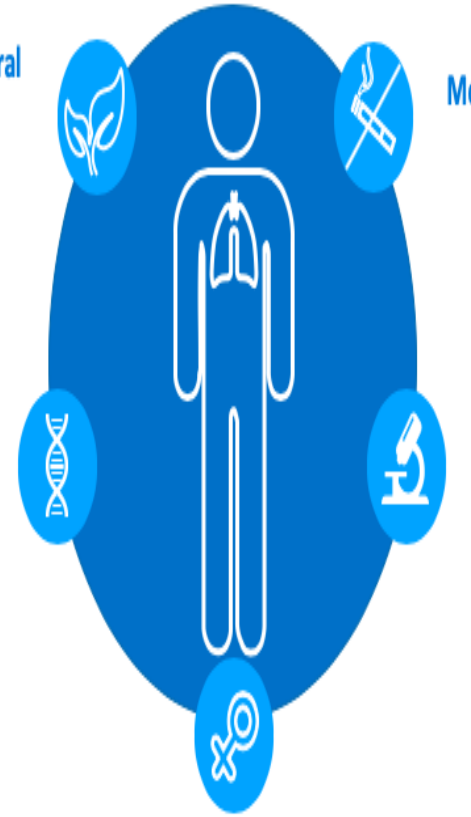
Typical characteristics of patients with *ROS1*+ NSCLC

Younger age compared with the general NSCLC population

Median age ~50 years[1,2]

More commonly never or former smokers

~3/4 never smokers[1,2]



Lack other mutations/rearrangements found in NSCLC (e.g. *EGFR, KRAS, ALK*)

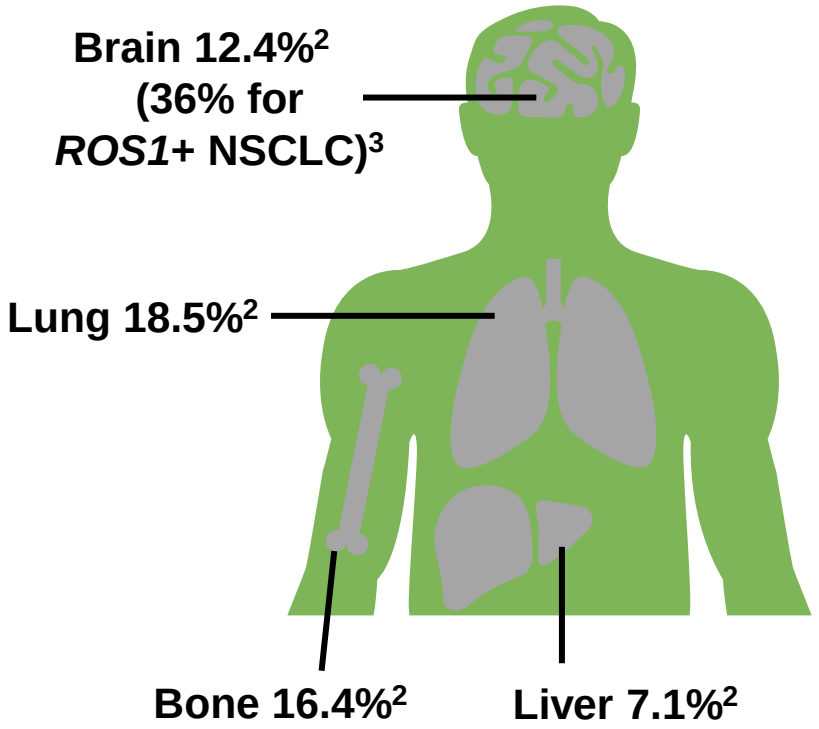
Adenocarcinoma histology

~100%[1,2]

More commonly female

~2/3 female[1,2]

The most common sites of metastases for patients with all types of Stage IV lung cancer[2]

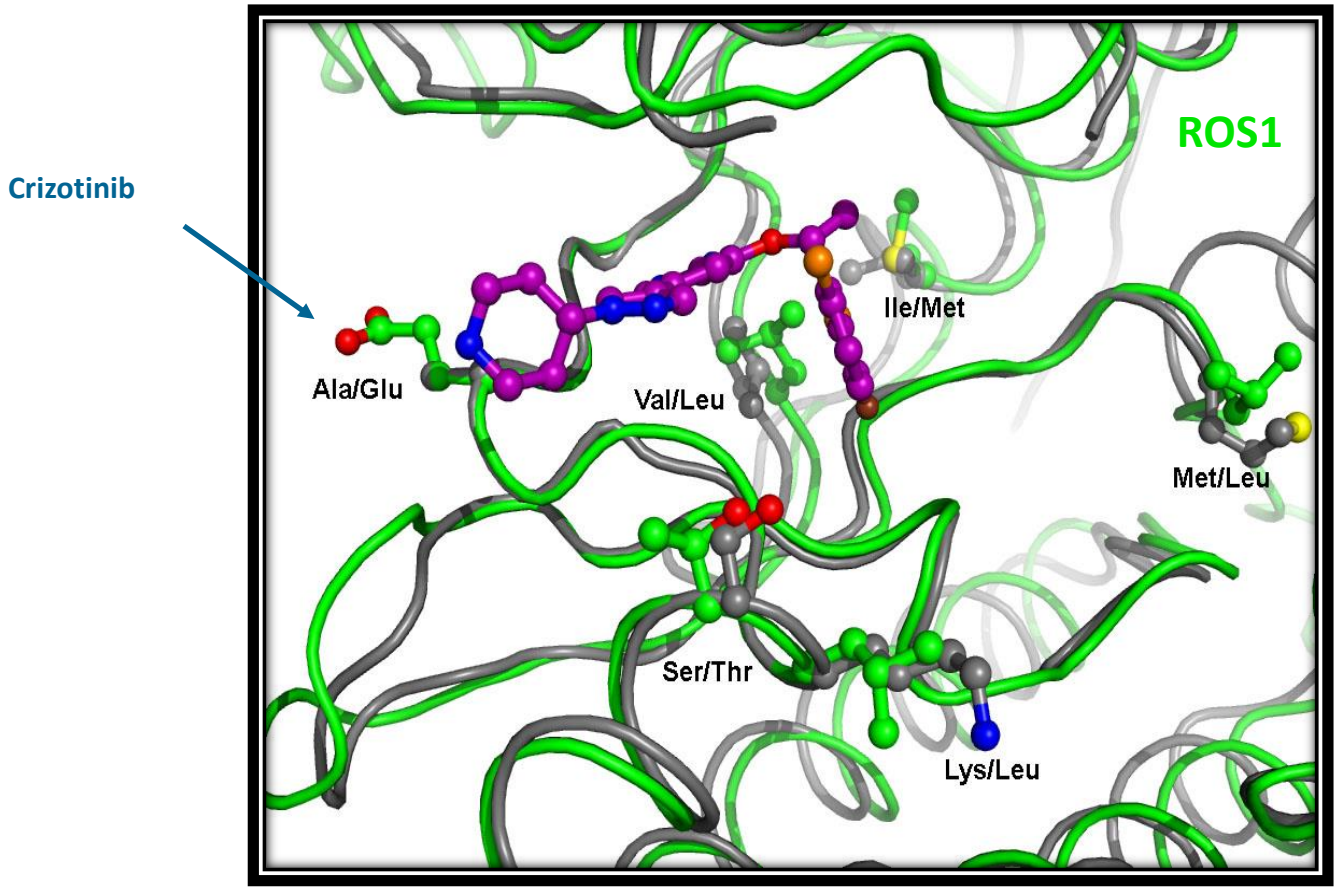


NSCLC subtypes can have distinct patterns and proportions of metastatic spread[4]

1. Detterbeck, et al. Chest 2017; 2. Oikawa, et al. Oncol Lett 2012; 3. Patil, et al. J Thorac Oncol 2018; 4. Doebele, et al. Cancer 2012

Ros1 Receptor tyrosine kinase

- ROS1 is phylogenetically related to ALK, resulting in sensitivity to some ALK tyrosine kinase inhibitors (TKIs).[1]
- Crizotinib is an oral TKI that targets ALK/ROS1/MET.[2–4]
  - ALK kinase K_i : 0.5 nM*
  - ROS1 kinase K_i : 0.6 nM*
  - MET kinase K_i : 0.6 nM*

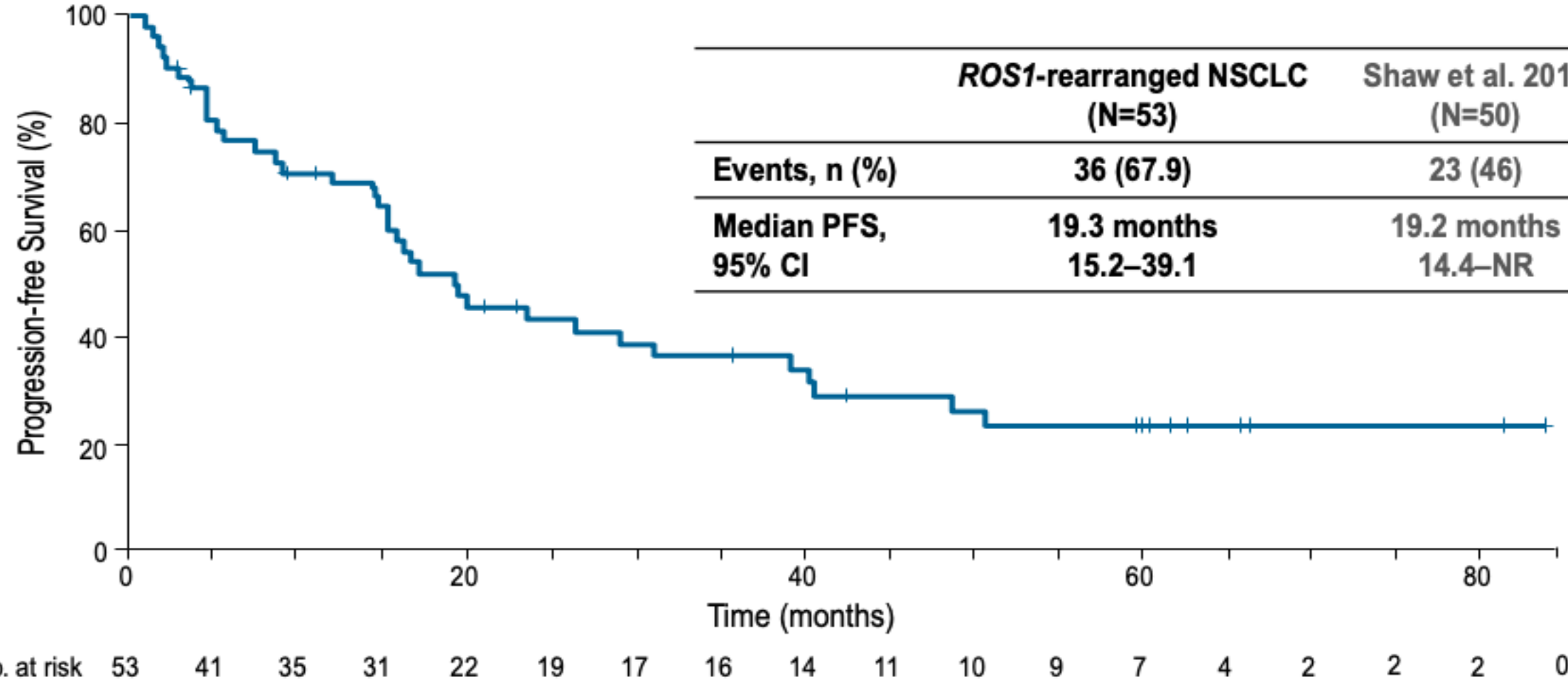


Shaw et al. ASCO 2012:abs7508.

*In biochemical assays using recombinant human enzymes.
ALK, anaplastic lymphoma kinase; K_i, inhibition constant.

1. Shaw AT, et al. *N Engl J Med.* 2014;371:1963–71.
2. Davies KD, et al. *Clin Cancer Res.* 2012;18:4570–4579.
3. Pfizer, data on file.
4. Zou HY, et al. *PNAS.* 2015;112:3493–3498.

Updated Progression-free Survival



	ROS1-rearranged NSCLC (N=53)	Shaw et al. 2014 (N=50)
Events, n (%)	36 (67.9)	23 (46)
Median PFS, 95% CI	19.3 months 15.2–39.1	19.2 months 14.4–NR

elcc

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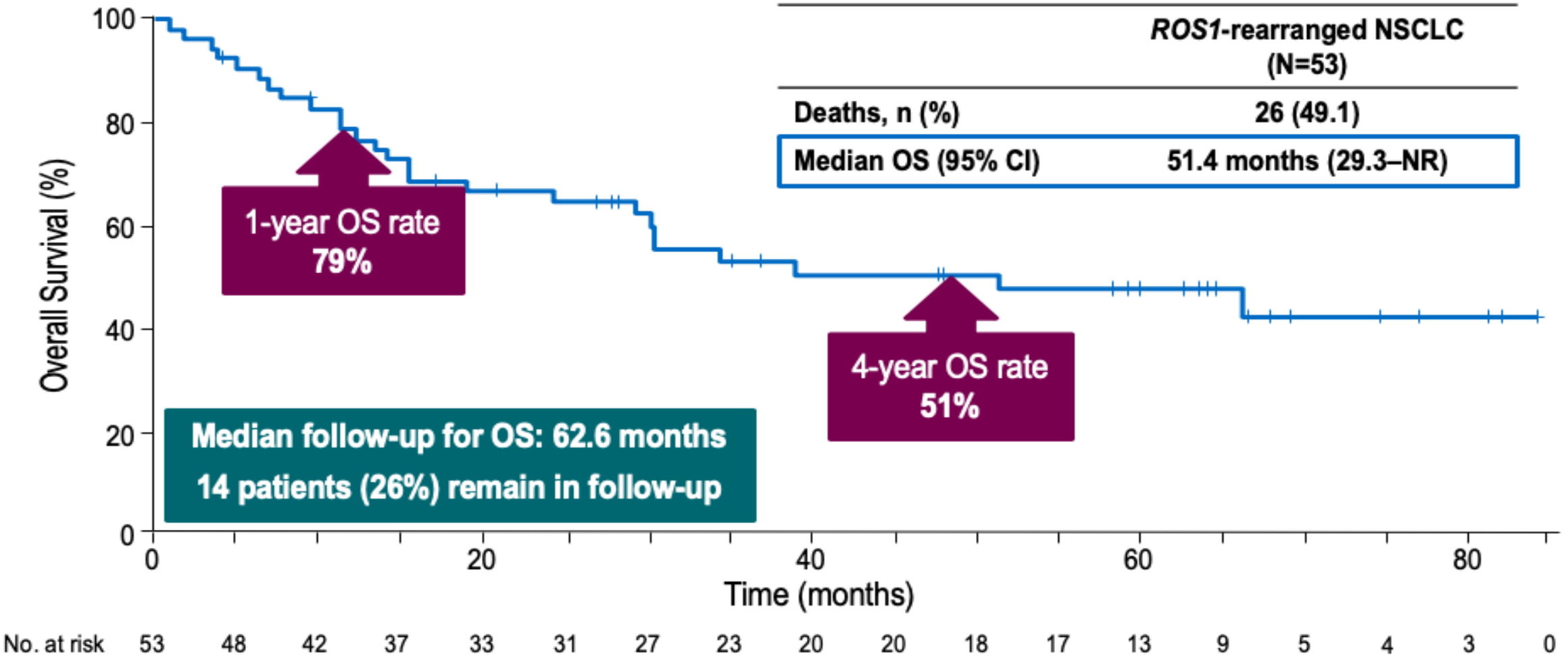
CI, confidence interval; NR, not reached; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

Overall Survival

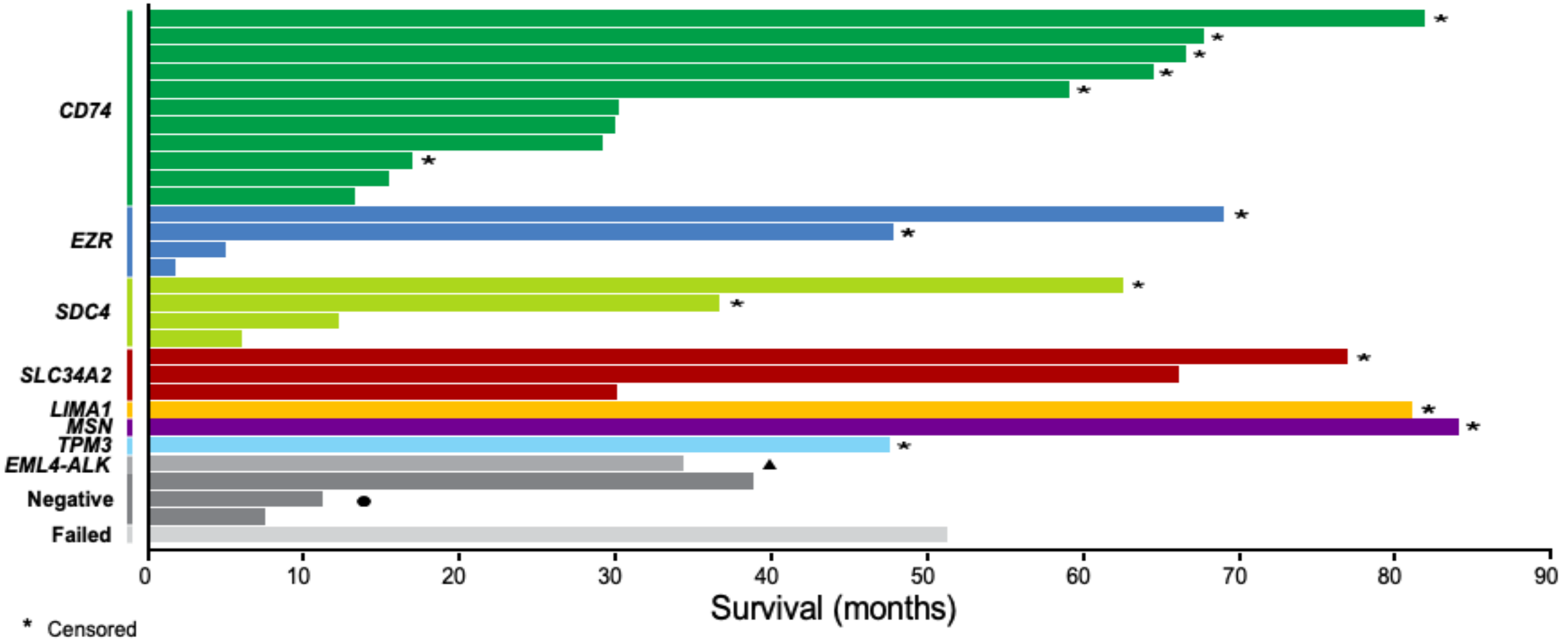


1. Shaw AT, et al. *N Engl J Med.* 2014;371:1963–71.
2. Shaw AT, ELCC 2019

NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival.

Overall Survival AND *ROS1* FUSION PARTNERs(N=30)[a]

OS did not differ according to ROS1 fusion partner; however, the number of patients with each type of *ROS1* rearrangement was small, and further studies are needed



* Censored

▲ One patient had negative results per next-generation sequencing, with an *EML4-ALK* fusion detected.

● One patient had an atypical FISH pattern and negative results per next-generation sequencing.

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[a]N is the number of patients who underwent ROS1 fusion partner testing. FISH, fluorescence in situ hybridization.

Crizotinib en CP *ROS1*

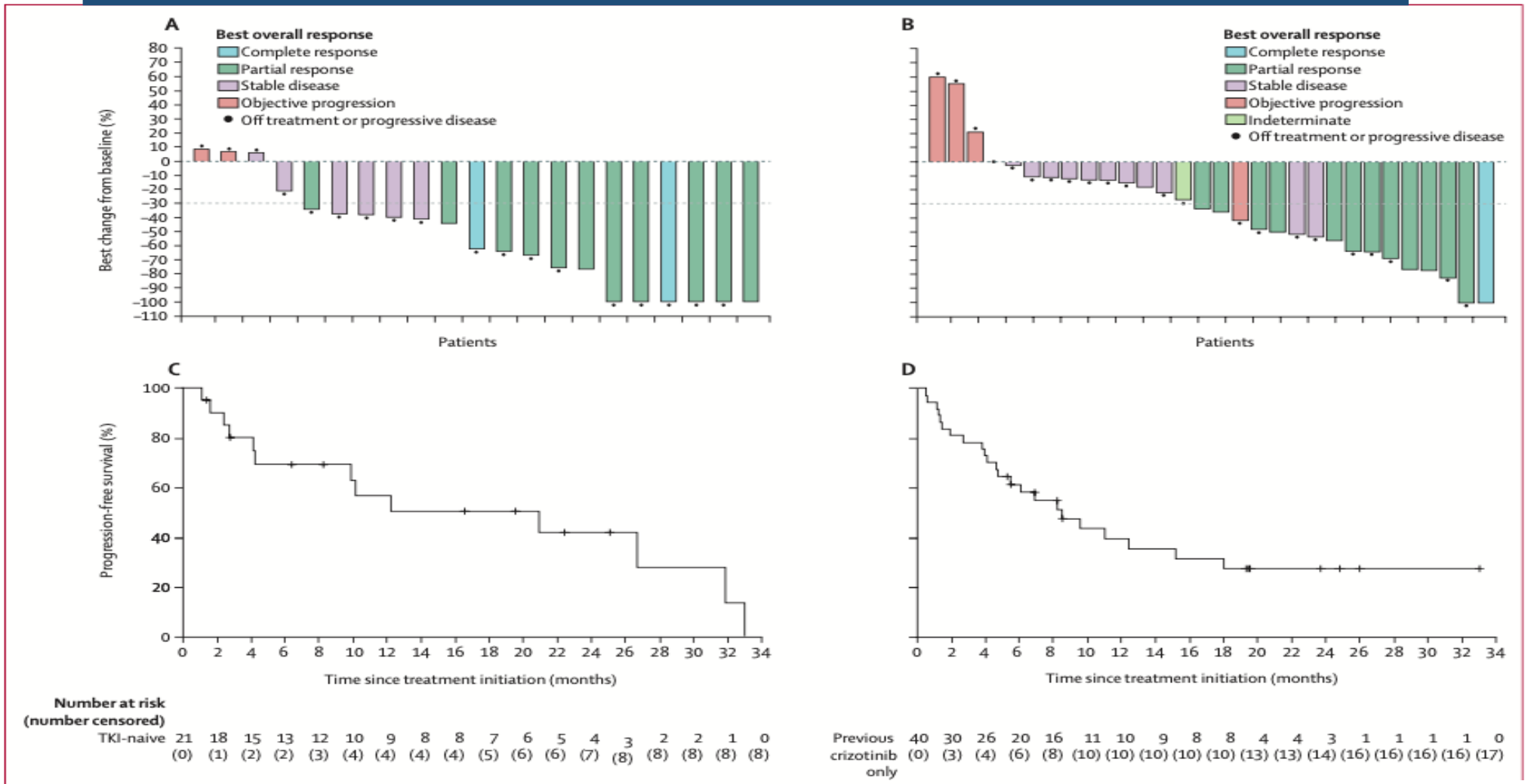
Trial	N	Region	ORR	PFS (mo.)	mOS / 1-year OS
PROFILE 1001, ph I	53	World	72%	19.3	51.4 mo. / 79%
OxOnc, ph II	127	East Asia	72%	15.9	32.5 mo. / 83.1%
EUROS, pooled	32	Europe	80%	9.1	NR
AcSé, basket trial	37	France	54%	5.5	17.2 mo. / NR
EUCROSS, ph II	34	Spain/Germany	73%	20.0	NR / 83%
METROS, ph II	26	Italy	62%	17.2	Not reached

Crizotinib approved by FDA (11 March 2016) and EMA (21 July 2016)

Shaw- NEJM 2014 * Shaw – ESMO 2016 (1206PD) * Wu – JCO 2018 * Mazières – JCO 2015 * Moro-Sibilot – WCLC 2018 * Vassal – ASCO 2018 * Michels – JTO 2019 * Landi – JTO 2017

Lorlatinib in advanced *ROS1*-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1–2 trial

TKI naive | Crizotinib pretreated



Shaw AT, et al. *Lancet Oncol 2019*

Lorlatinib in advanced *ROS1*-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1–2 trial

	TKI-naive*	Any previous ROS1 TKI†	
		No mutations	≥1 mutation
Circulating free DNA			
Number of patients with analysable samples	17	33	6
Best overall response			
Complete response	2 (12%)	1 (3%)	0
Partial response	8 (47%)	8 (24%)	0
Stable disease	5 (29%)	14 (42%)	5 (83%)
Objective progression	2 (12%)	4 (12%)	1 (17%)
Indeterminate‡	0	6 (18%)	0
Responders	10 (59%)	9 (27%)	0
Tumour tissue (de novo)			
Number of patients with analysable samples	7	11	5
Best overall response			
Complete response	1 (14%)	0	0
Partial response	4 (57%)	1 (9%)	2 (40%)
Stable disease	2 (29%)	6 (55%)	3 (60%)
Objective progression	0	2 (18%)	0
Indeterminate‡	0	2 (18%)	0
Responders	5 (71%)	1 (9%)	2 (40%)

Data are n (%) unless otherwise specified. TKI=tyrosine kinase inhibitor. *All TKI-naive patients had no mutations. †Includes patients treated with crizotinib only, patients previously treated with one previous non-crizotinib ROS1 TKI, and patients treated with two or more ROS1 TKIs. ‡Patients defined as indeterminate if (1) only baseline assessment available; (2) tumour assessments incomplete; or (3) first response assessment of stable disease at an interval less than 6 weeks from treatment start and no subsequent disease evaluation.

***Table 3:* Activity by presence or absence of *ROS1* mutations in circulating free DNA or tumour tissue (de-novo)**

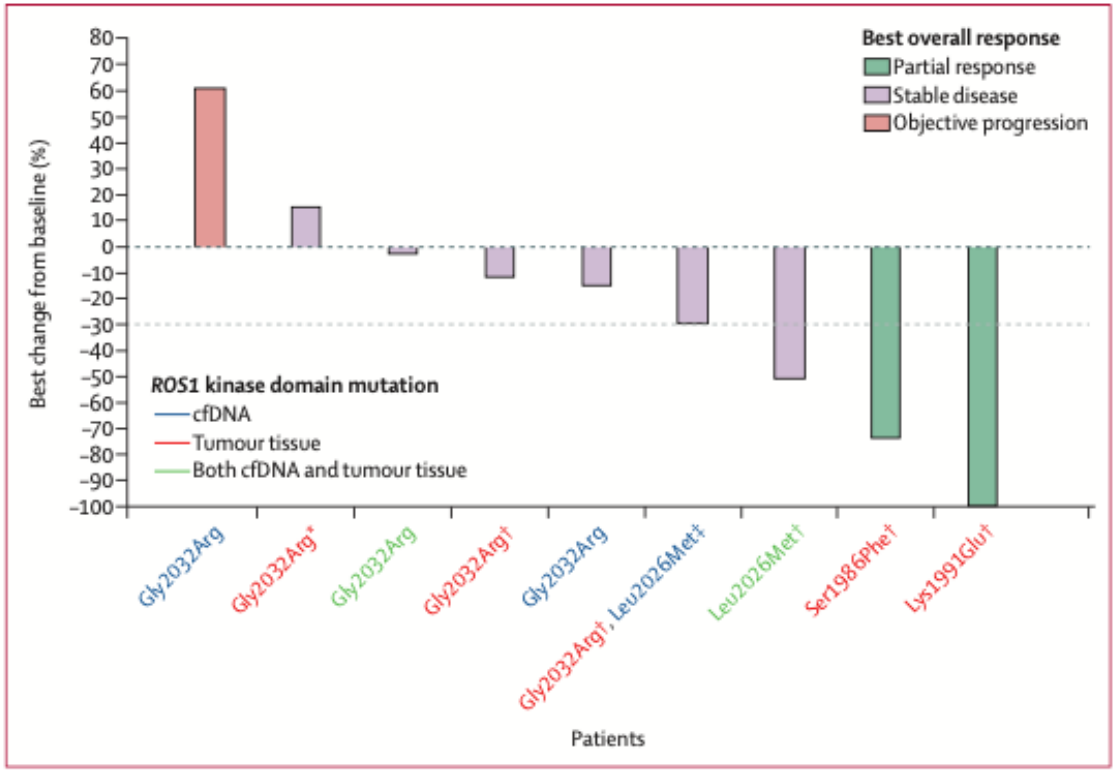
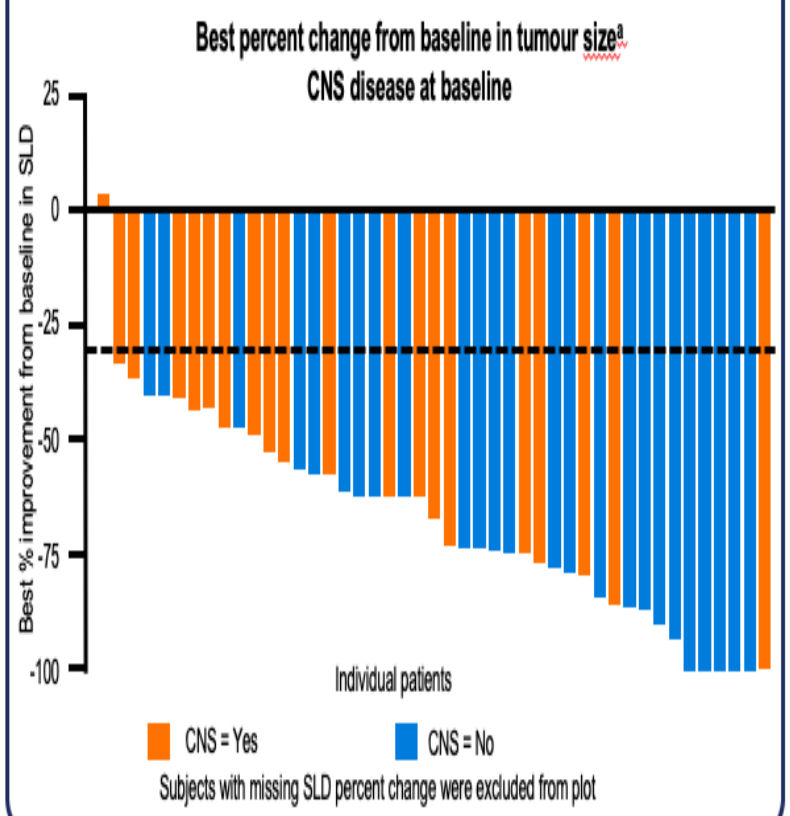


***Figure 2:* Best percentage change in tumour size from baseline in patients with at least one *ROS1* kinase domain mutation in cfDNA or tumour tissue (archival or de-novo)**
All patients had received prior crizotinib. The dashed line shows a 30% reduction in target lesions, which is the threshold for partial response. cfDNA=circulating free DNA. *Patient previously received crizotinib and DS6051B. †ROS1 mutation found in de-novo tumour sample. §Patient previously received crizotinib and ceritinib, and also had the silent Ile2025Ile mutation in cfDNA.

Shaw AT, et al. *Lancet Oncol 2019*

Eficacia de Entrectinib en CP *ROS 1*

Change in tumour size: *ROS1+* NSCLC population

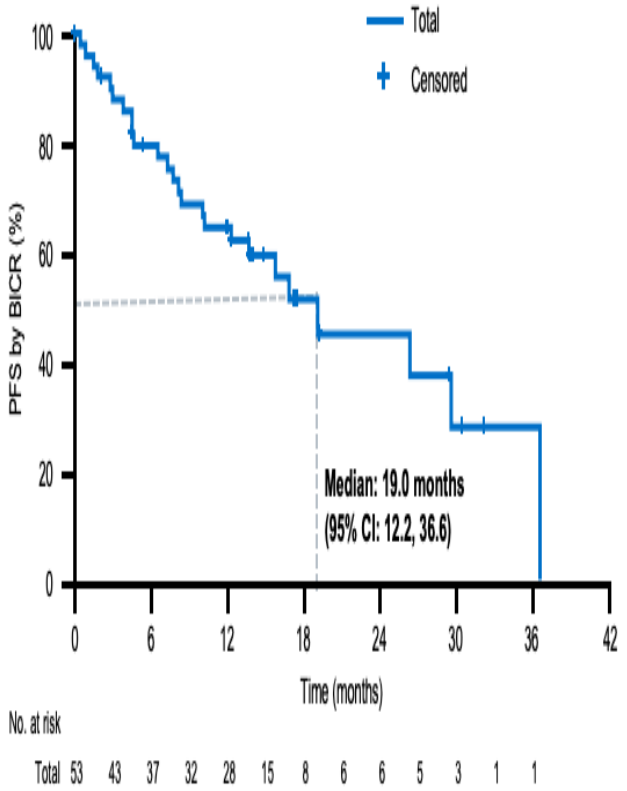


n (%)	Total (n=53)	CNS disease present at baseline† (n=23)	CNS disease absent at baseline† (n=30)
ORR[b‡] (95% CI)	41 (77.4) (63.8, 87.7)	17 (73.9) (51.6, 89.8)	24 (80.0) (61.4, 92.3)
CR	3 (5.7)	0	3 (10.0)
Median DoR,‡ months (95% CI)	24.6 (11.4, 34.8)	12.6 (6.5, NE)	24.6 (11.4, 34.8)
Median PFS,‡ months (95% CI)	19.0 (12.2, 36.6)	13.6 (4.5, NE)	26.3 (15.7, 36.6)
Median OS, months (95% CI)	NE (NE, NE)	-	-
Clinical benefit rate* (95% CI)	41 (77.4) (63.8, 87.7)	-	-

a. Best change at any single timepoint; b. Confirmed responses only
*Includes SD for at least 6 months. †CNS disease status determined by Investigator; ‡By blinded independent central review (RECIST v1.1)
Data cut-off date: 31 May 2018. ROS1 inhibitor-naïve patients with *ROS1+* NSCLC (integrated analysis population)

CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SLD, sum of the longest diameter;

PFS, *ROS1+* NSCLC



	Total n=53	CNS disease present at baseline (n=23)†	CNS disease absent at baseline (n=30)†
Patients with event, n (%)	25 (47.2)	11 (47.8)	14 (46.7)
PD, n	20	8	12
Death, n	5	3	2
Time to event (months)			
Median (95% CI)	19.0 (12.2, 36.6)	13.6 (4.5, NE)	26.3 (15.7, 36.6)

Median PFS 19.0 months
(95% CI 12.2, 36.6)

Median follow up: 15.5 months

Data cut-off date: 31 May 2018. ROS1 inhibitor-naïve patients with *ROS1+* NSCLC (integrated analysis population).
†CNS disease status determined by Investigator.
BICR: blinded independent central review; CI, confidence interval; CNS, central nervous system; NE, not estimable; PD, progressive disease; PFS, progression-free survival

EUROPEAN LUNG CANCER CONGRESS 2019
Barlesi et al. Entrectinib in ROS1 NSCLC

Preliminary Efficacy of Repotrectinib in TKI Naive *ROS1*+ NSCLC by BICR

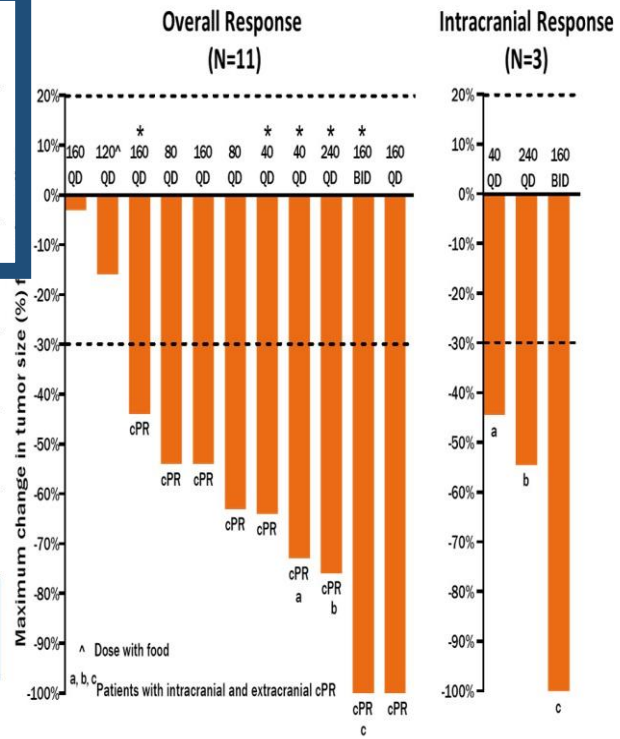
TKI Naive (N=11)	
Confirmed ORR, n/N (%) 95% CI (%)	9/11 (82%) (48 – 98)
ORR at 160mg QD or above	5/6 (83%)
Duration of response (DOR), months	
Median	Not reached
Range	5.6 – 17.7+
Intracranial ORR (IC-ORR)[1], n/N (%) 95% CI (%)	3/3 (100%) (29 – 100)
Clinical benefit rate, n/N (%) 95% CI (%)	11/11 (100%) (72 – 100)
Median follow-up time, months Range	16.4 3.5+ – 19.4+

*5 of 9 patients remain in cPR from 10.9+ to 17.7+ months. 3 patients with IC-ORR remain in cPR for 10.9+, 12.1+, and 17.6+ months.

[1] For patients with CNS measurable disease at baseline

BICR: Blinded Independent Central Review

Clinical Benefit Rate: CR + PR + SD ≥ 2 Cycles



Preliminary Efficacy of Repotrectinib in TKI Pretreated *ROS1*+ NSCLC by BICR

Pretreated with 1 TKI (N=18**)	
Confirmed ORR, n/N (%) 95% CI (%)	7/18 (39%) (17 – 64)
ORR at 160 mg QD or above	6/11 (55%)
IC-ORR[1], n/N (%) 95% CI (%)	3/4 (75%) (19 – 99)
Clinical benefit rate, n/N (%) 95% CI (%)	14/18 (78%) (52 – 94)
Median follow-up time, months Range	14.6 1.4 – 14.6+

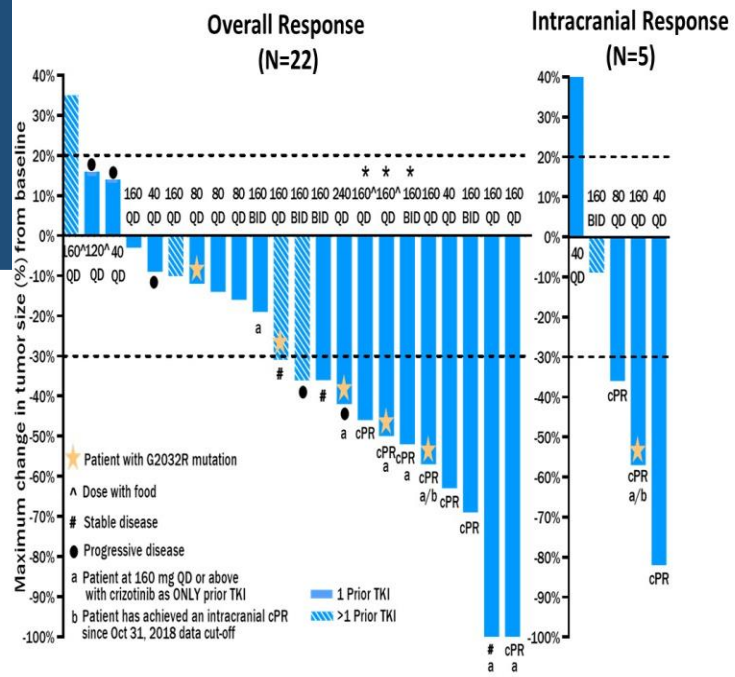
*3 of 7 patients remain in cPR from 1.0+ to 7.6+ months

** 4 patients treated with > 1 prior TKI not included (3 of 4 had tumor regressions)

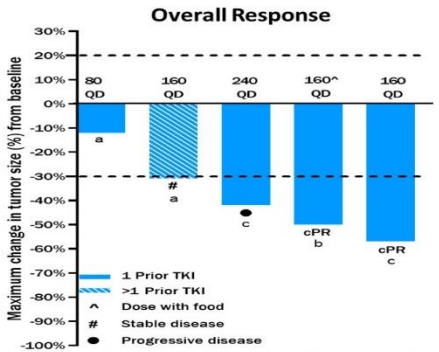
[1] For patients with CNS measurable disease at baseline

BICR: Blinded Independent Central Review

Clinical Benefit Rate: CR + PR + SD ≥ 2 Cycles



Preliminary Clinical Activity of Repotrectinib Against *ROS1* G2032R Solvent Front Mutation



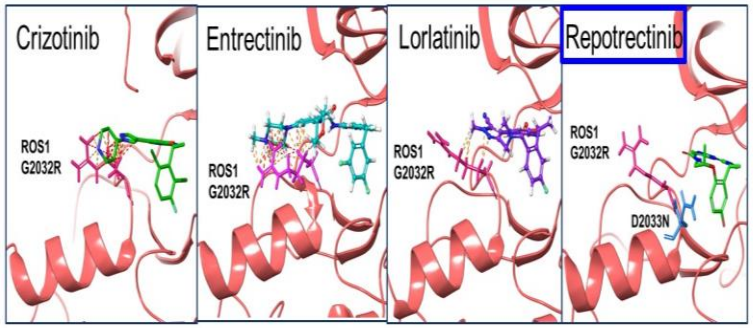
G2032R identified in (a) plasma cfDNA; (b) tumor tissue; (c) plasma cfDNA and tumor tissue

- *ROS1* G2032R identified by plasma cfDNA or tissue NGS test in 5 patients who had prior crizotinib treatment
- All 5 patients experienced tumor regressions on repotrectinib
- **Confirmed ORR: 2/5 (40%)**
  - 2/3 (67%) for 160 mg QD and above with 1 prior TKI
    - 1 cPR at 160 mg QD with food (DOR 1.0+ months and remains on treatment at 3.0+ months)
    - 1 cPR at 160 mg QD (DOR 4.4 months and remains on treatment at 18.6+ months)

Eficacia en CP *ROS 1*

	N	RR (%)	PFS (mo.)	OS (mo.) 1-y OS (%)	Ic-RR (%)	Efficacy pretreated
Crizotinib	53	72	19.3	51.4 / 79	50 (*ALK*)	**NA**
Ceritinib	32	62	19.3	24 / 56	25[a]	**NA**
Entrectinib	53	77	19.0 (26.3 w/o BM)	NR / 85	55*	**NA**
Lorlatinib	13	62	21.0	NR	67[@]	**YES (27%)**
Repotrectinib	10	80	NR	NR	100[#]	**YES (18%)**

Repotrectinib is a Small, Rigid Macrocycle Designed to Overcome the *ROS1* G2032R Solvent Front Mutation



CD74-ROS1 Ba/F3 Cell Proliferation IC_{50} (nM)*

ROS1	Crizotinib	Ceritinib	Cabozantinib	Entrectinib	Lorlatinib	Repotrectinib
WT	14.6	42.8	0.5	10.5	0.2	<0.2
G2032R	266.2	1391	11.3	1813	160.7	3.3

*Data based on evaluation of comparable proxy chemical reagents purchased from commercial sources except repotrectinib

[a]N=8. *N=11. [@]N=6 Crizotinib-naïve. 55% in crizotinib-pretreated. [#]N=6

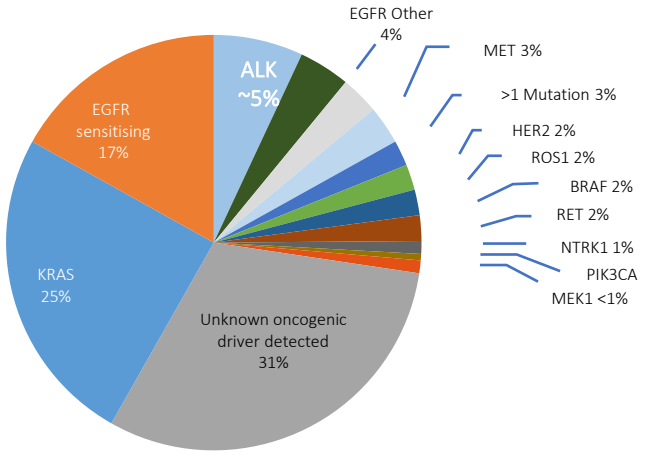
Shaw – NEJM 2014 * Shaw – ESMO 2016 * Peters – NEJM 2018 * Lim – JCO 2018 * Doebele – WCLC 2018 * Ou – WCLC 2018 * Lin – WCLC 2018

ALK y *ROS1*

- Enfermedad poco frecuente (¿o no tanto??
- Necesario diagnóstico
- Tratamiento muy eficaz
- Frecuente afectación SNC controlable
- Tratamiento con TKI secuencial
- Necesidad de identificar molecularmente la progresión
- Papel de la QT / Inmuno en fases tardías

La Oncología actual es el paradigma de la medicina personalizada

Mutaciones comunes en Cáncer de Pulmón



El tratamiento es orientado según el perfil molecular

EGFR sensitising
- Gefitinib
- Erlotinib)
- Erlotinib+ Bevacizumab)
- Afatinib
- Osimertinib
- Necitumumab

ALK
- Crizotinib
- Alectinib
- Certinib
- Lorlatinib
- Brigatinib
- Ensartinib

MET
- Crizotinib
- Cabozantinib
- Tepotinib
- Savolotinib
- Capmatinib

BRAF
- Vemurafenib
- Dabrafenib

RET
- Cabozantinib
- Apatinib
- Vandetanib
- Ponatinib
- Lenvatinib
- LOXO-292

NTRK1
- Entrectinib
- Larotrectinib
- Cabozantinib
- DS-6051b

HER2
- Trastuzumab
- Trastuzumab emtansine
- Pertuzumab
- Afatinib
- Dacomitinib

ROS1
- Entrectinib
- Crizotinib
- Cabozantinib
- Certinib
- Lorlatinib
- DS-6051b

PIK3CA
- LY3023414

MEK1
- Trametinib
- Selumetinib
- Cobimetinib

▼This product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. These should be reported to the regulatory authorities in your country according to your national requirements

Tsao A et al. J Thorac Oncol. 2016; Dearden S et al. Ann Oncol 2013; AVASTIN SmPC 2018; clinicaltrials.gov