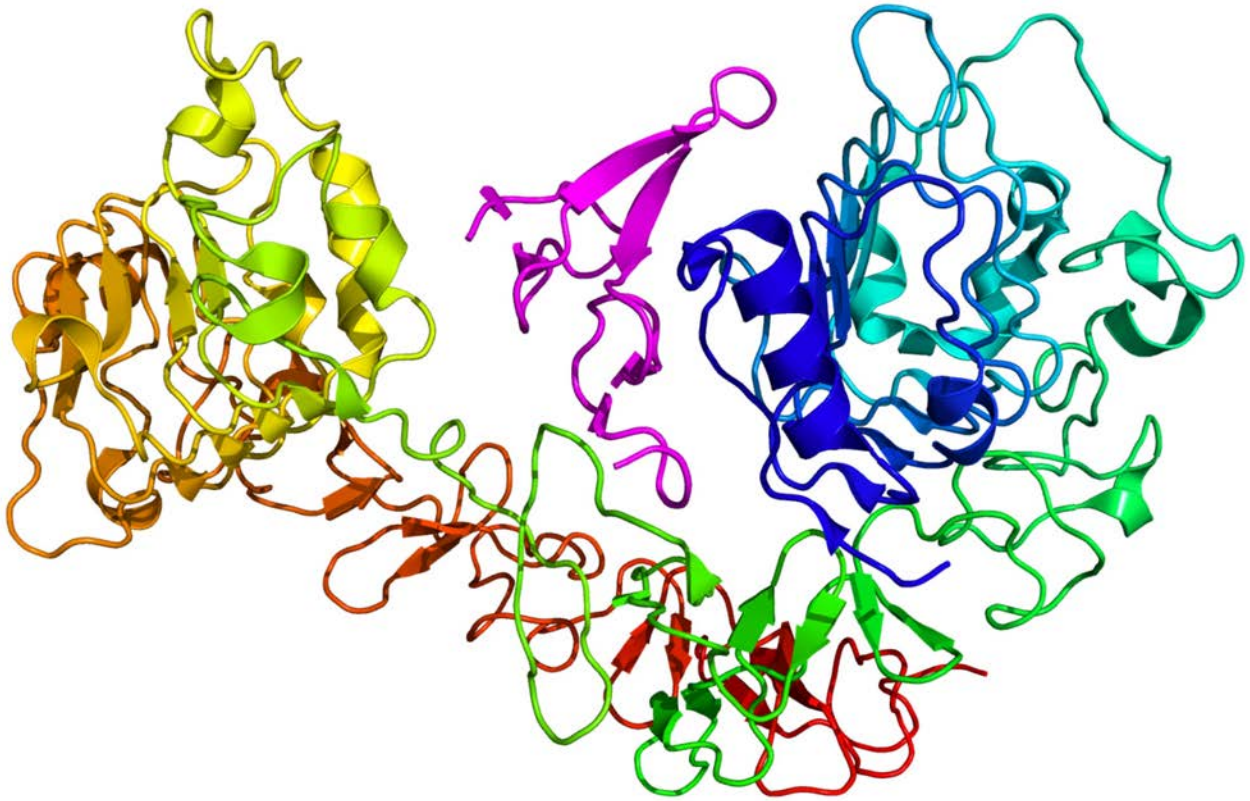
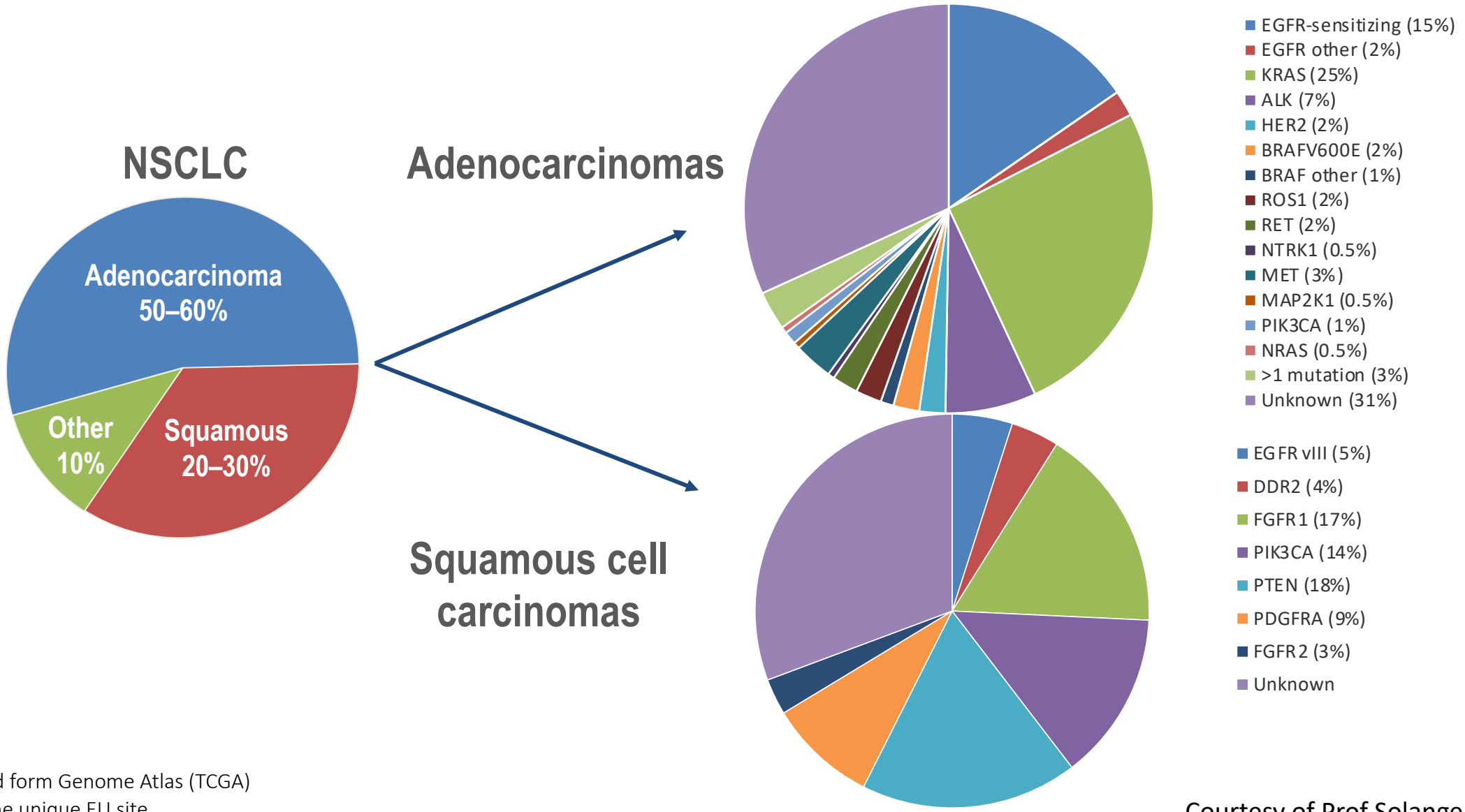


Shaping the Current and Future Treatment of NSCLC with ALK and ROS1 Rearrangements

Prof. Solange Peters, MD-PhD
Chair Medical Oncology
Lausanne University Hospital
Switzerland

Driver alterations in NSCLC



Adapted form Genome Atlas (TCGA)
Lausanne unique EU site

Courtesy of Prof Solange Peters, MD, PhD

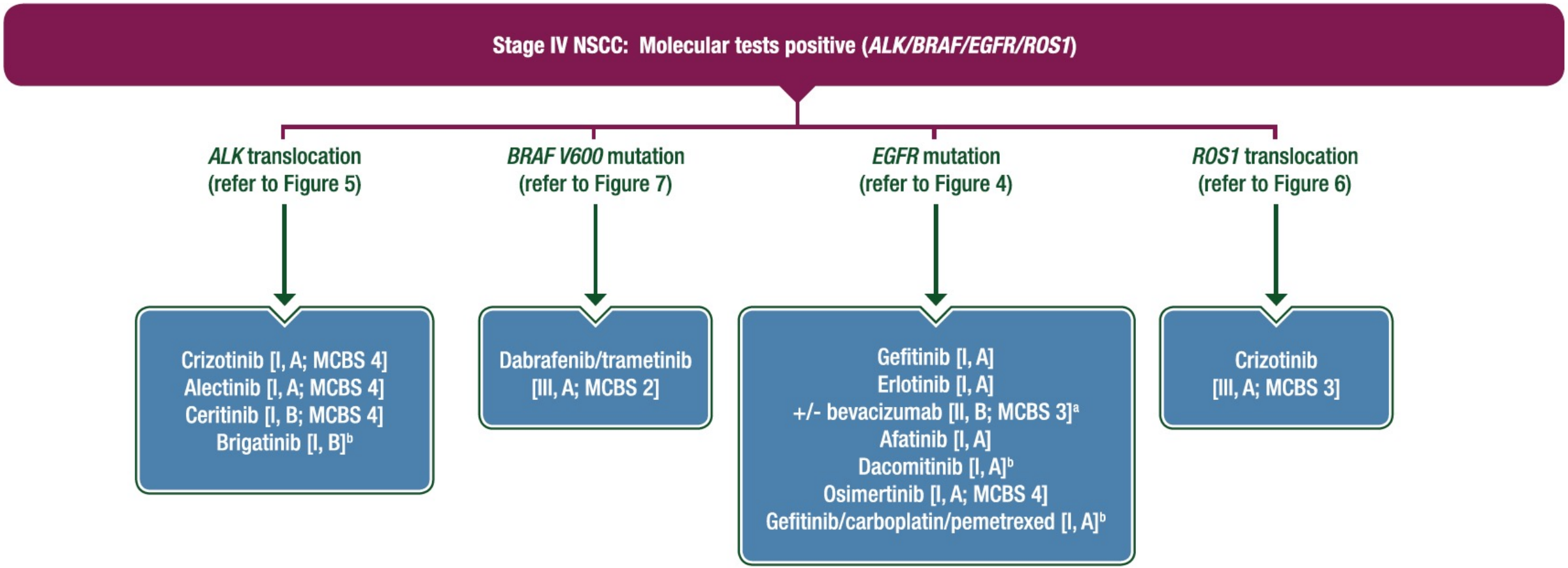
A population of young never smokers NSCLC patients

Patient, age (years)	ALK+	ROS+	ALK/ROS+	EGFR
<30	4/6 (67%)	2/6 (33%)	6/6 (100%)	0/6
31–40	3/17 (18%)	2/16 (13%)	5/17 (29%)	4/17 (23%)
41–50	6/46 (13%)	0/24 (0)	6/46 (13%)	6/55 (11%)
>50	34/568 (6.0%)	4/330 (1%)	38/568 (7.0%)	116/711 (16%)
Total	47/637 (7.4%)	8/376 (2.1%)	55/637 (8.6%)	126/789 (16.0%)

- Adenocarcinoma histology
- Never/light smoking history

Courtesy of Prof Solange Peters, MD, PhD

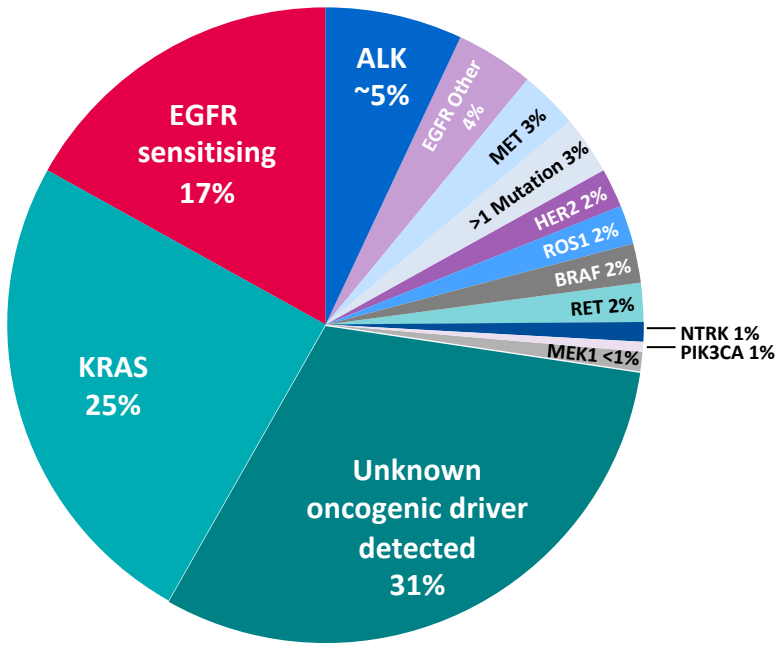
Gobbini E, et al. Lung Cancer 2017 111:30–37
Scarpino S, et al. Lung Cancer 2016 97:95–98



Courtesy of Prof Solange Peters, MD, PhD

Identification of actionable mutations and development of targeted therapies for precision medicine

Common mutations in lung cancer



Treatment is selected by genomic profiling

EGFR sensitising
- Afatinib
- Erlotinib
- Erlotinib + bevacizumab
- Gefitinib
- Necitumumab
- Osimertinib
- Amivantamab JNJ-372
- Patritumab-deruxtecan U3-1402

BRAF
- Dabrafenib
- Dabra/Trametinib
- Vemurafenib
- Binimetinib/Encorafenib

HER2
- Afatinib
- Dacomitinib
- Emtansine
- Pertuzumab
- Trastuzumab
- Mobocertinib TAK-778
- Poziotinib
- Trastuzumab-deruxtecan

ALK
- Alectinib
- Brigatinib
- Ceritinib
- Crizotinib
- Ensartinib
- Lorlatinib

RET
- Apatinib
- Cabozantinib
- Lenvatinib
- Selpercatinib LOXO-292
- Ponatinib
- Vandetanib
- Pralsetinib BLU-667

ROS1
- Ceritinib
- Crizotinib
- DS-6051b
- Entrectinib
- Lorlatinib
- Repotrectinib

MET
- Cabozantinib
- Crizotinib
- Capmatinib
- Savolitinib
- Reprotrectnib
- Tepotinib

NTRK
- DS-6051b
- Entrectinib
- Larotrectinib
- Selitrectinib
- Cabozantinib
- LOXO-101

PIK3CA
- LY3023414

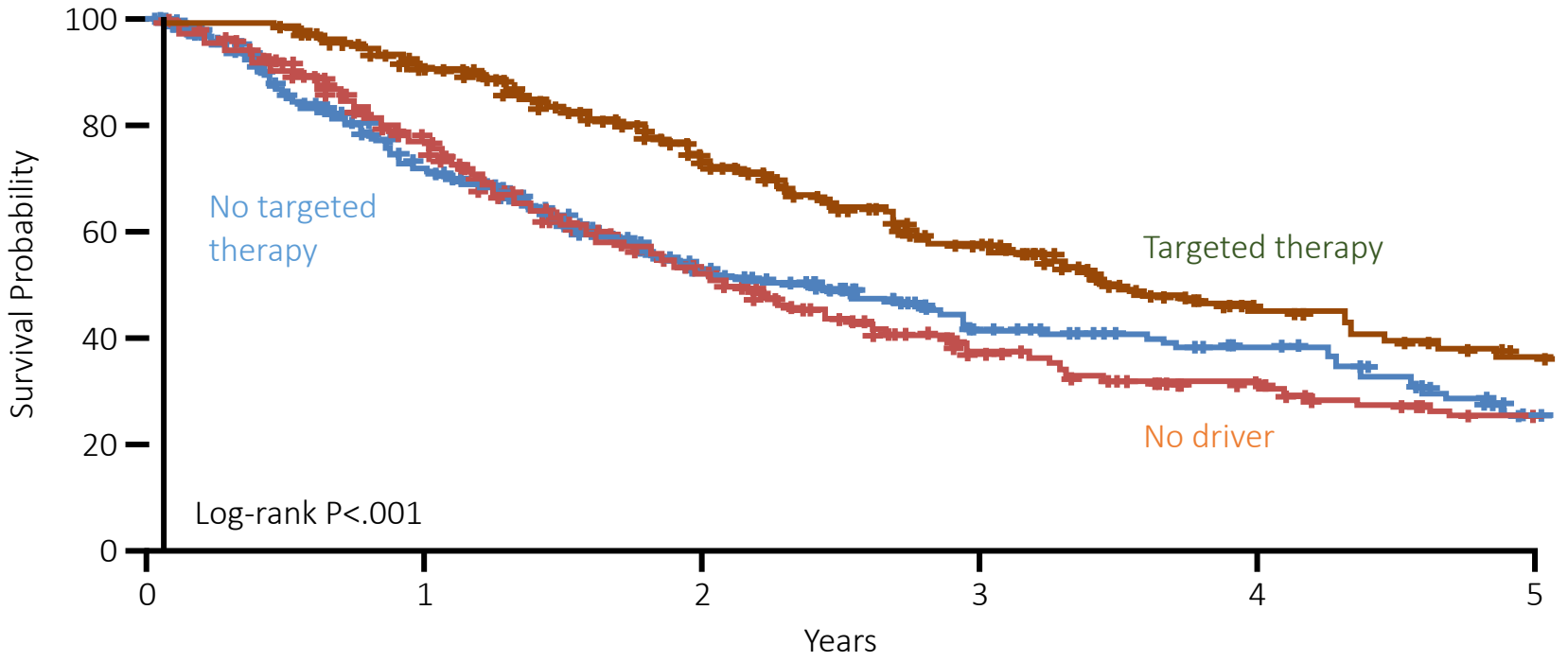
MEK1
- Cobimetinib
- Selumetinib
- Trametinib

KRAS
- Sotorasib AMG 510
- Adagrasib MRTX849

Adapted from Tsao, et al. J Thorac Oncol 2016; Dearden, et al. Ann Oncol 2013
Bevacizumab SmPC 2018; clinicaltrials.gov

Courtesy of Prof Solange Peters, MD, PhD

Oncogene addiction defines targeted opportunities



No. at risk						
Patients with oncogenic driver	318	205	110	64	43	20
No targeted therapy	260	225	143	72	36	23
Targeted therapy	360	250	122	59	36	23
Patients with no driver						

Courtesy of Prof Solange Peters, MD, PhD

Kris M, et al. JAMA 2014 311:1998–2006

Where advances are

1) Frontline strategy for advanced NSCLC

- The best compound first
- Protecting the brain
- (A higher specificity to reduce side effects)

2) Resistance mechanisms to frontline strategies

- Current knowledge
- Innovative treatment approaches

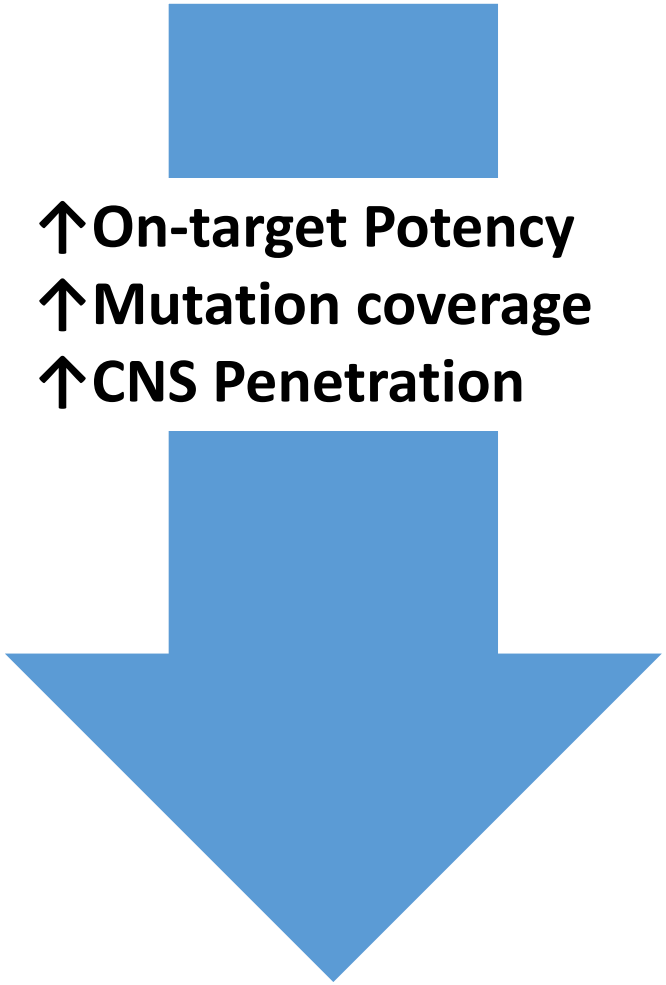
3) Early disease perspectives

Courtesy of Prof Solange Peters, MD, PhD

ALK REARRANGEMENT

Courtesy of Prof Solange Peters, MD, PhD

Landscape of ALK inhibitors in clinical use



ALK TKI		STATUS
1st generation	Crizotinib	▪ FDA-approved, EMA-approved
2nd generation	Ceritinib	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line
	Alectinb	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line
	Brigatinib	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line
	Ensartinib	▪ *Investigational*
3rd generation	Lorlatinib	▪ FDA / EMA approved, in patients who have received 1 or more ALK inhibitors

Courtesy of Prof Solange Peters, MD, PhD

Currently approved first-line treatments for advanced *ALK*+ NSCLC

Key trial: PROFILE 1014[1]
FDA approval in 1L: Aug 2011
EMA approval in 1L: Nov 2015

mPFS 10.9 months[1†]

Key trial: ASCEND-4[2]
FDA approval in 1L: May 2017
EMA approval in 1L: Jun 2017

mPFS 16.6 months[2‡]

Key trial: ALEX[3–5]
FDA approval in 1L: Nov 2017
EMA approval in 1L: Dec 2017

mPFS 34.8 months[5§]

Key trial: ALTA-1L[6,7]
FDA approval in 1L: May 2020
EMA approval in 1L: Apr 2020

mPFS 29.4 months[7§,¶]

1. Solomon, et al. N Engl J Med 2014
2. Soria, et al. Lancet 2017; 3. Peters, et al. N Engl J Med 2017
4. Camidge, et al. J Thorac Oncol 2019; 5. Mok, et al. Ann Oncol 2020
6. Camidge, et al. N Engl J Med 2018; 7. Camidge, et al. ESMO Asia 2019

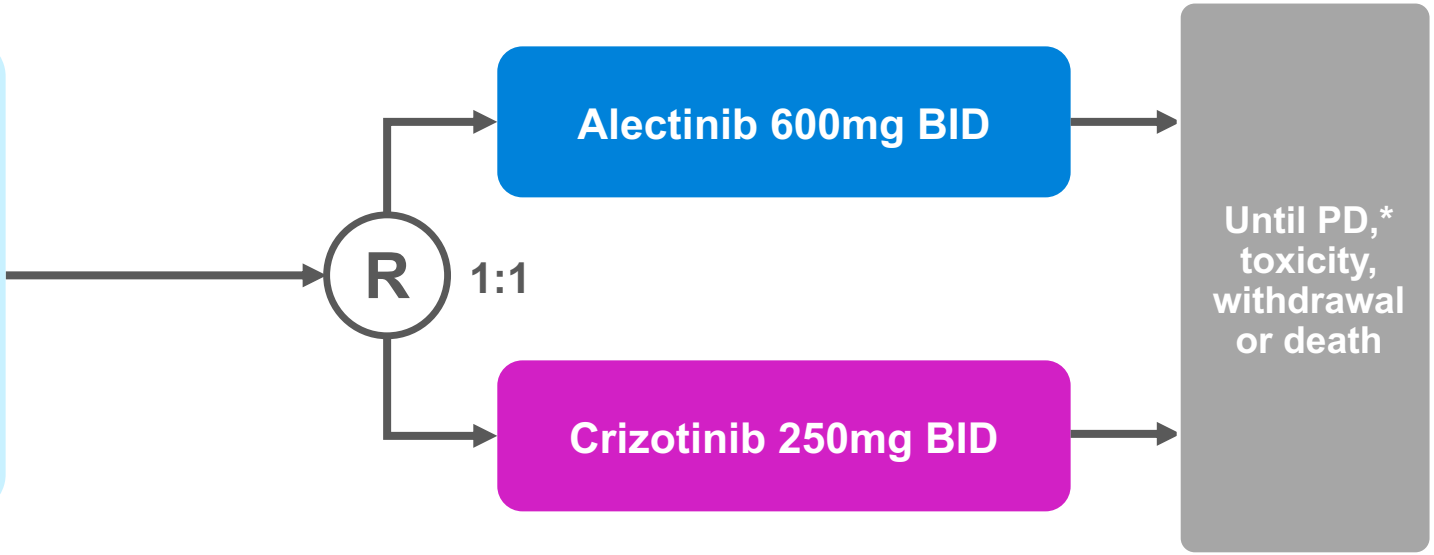
†Median PFS by IRC; ‡Median PFS by BIRC; §Median PFS by INV
¶INV-assessed, however the 1° endpoint of ALTA-1L is PFS by BIRC assessment (**24.0 months**)[7]

Courtesy of Prof Solange Peters, MD, PhD

ALEX: Randomised, multicentre, phase III, open-label study of alectinib versus crizotinib in treatment-naïve ALK+ NSCLC

- Stage IIIB/IV NSCLC
- *ALK*+ disease according to IHC test
- Treatment naïve
- ECOG PS 0–2

(N=303)



Stratification factors

- ECOG PS (0/1 vs 2)
- Ethnicity (Asian vs non-Asian)
- CNS metastases at baseline (presence vs absence)

Primary endpoint

- PFS (investigator-assessed)

Secondary endpoints

- PFS by IRC
- Time to CNS progression
- ORR
- DoR
- OS
- CNS ORR
- CNS DoR
- QoL
- Safety

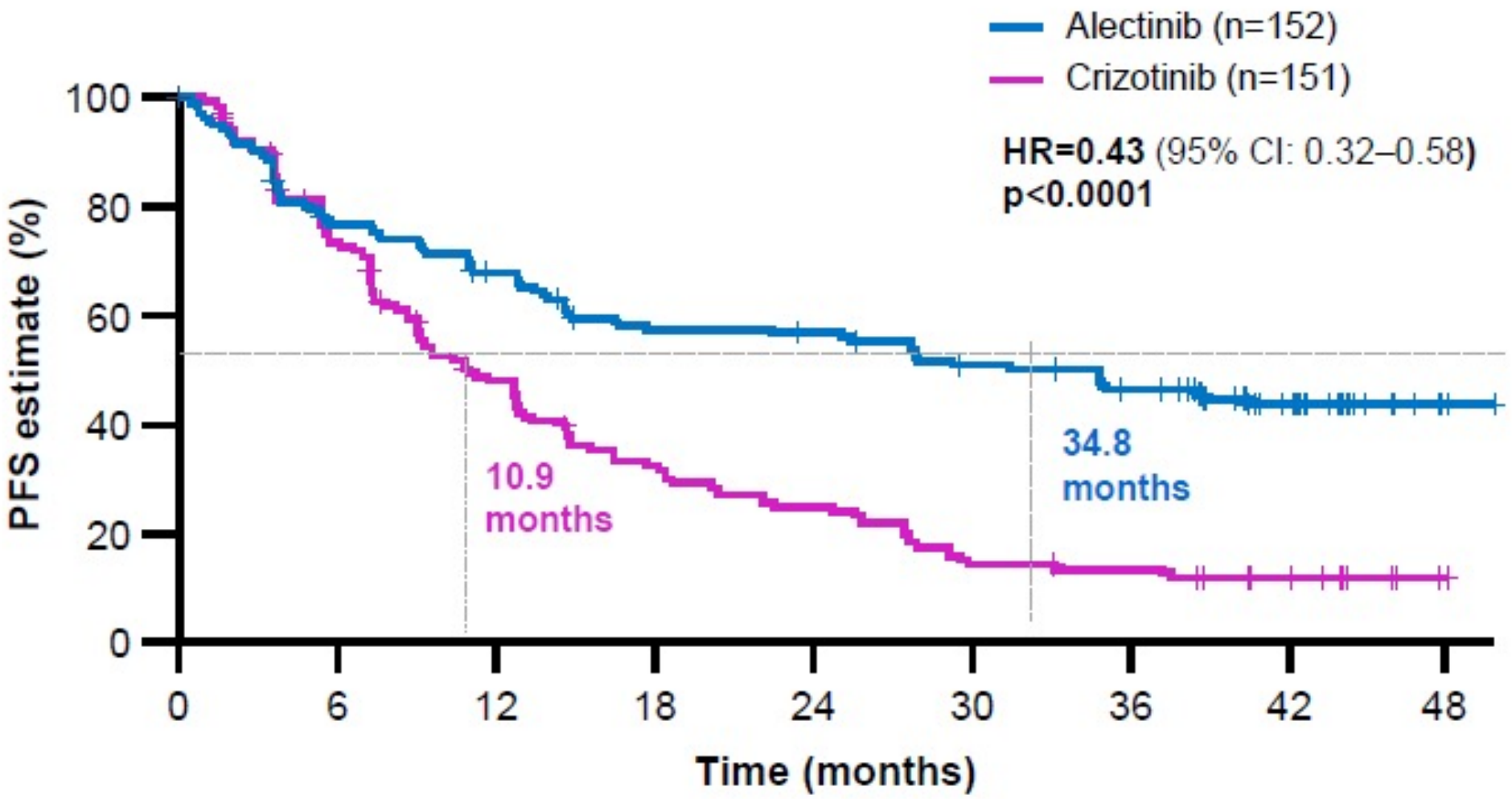
The first patient was enrolled in August 2014.
*Isolated asymptomatic CNS progression; treatment until systemic or symptomatic CNS PD allowed. Crossover between treatment arms was not permitted before PD. Further lines of therapy after PD were at the physician's discretion and based on treatment availability.
ALK = anaplastic lymphoma kinase; BID = twice daily; CNS = central nervous system; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; FISH = fluorescence in-situ hybridisation; IHC = immunohistochemistry; IRC = independent review committee
NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival
QoL = quality of life

Peters, et al. N Engl J Med 2017

Courtesy of Prof Solange Peters, MD, PhD

ALEX: Final investigator assessed PFS

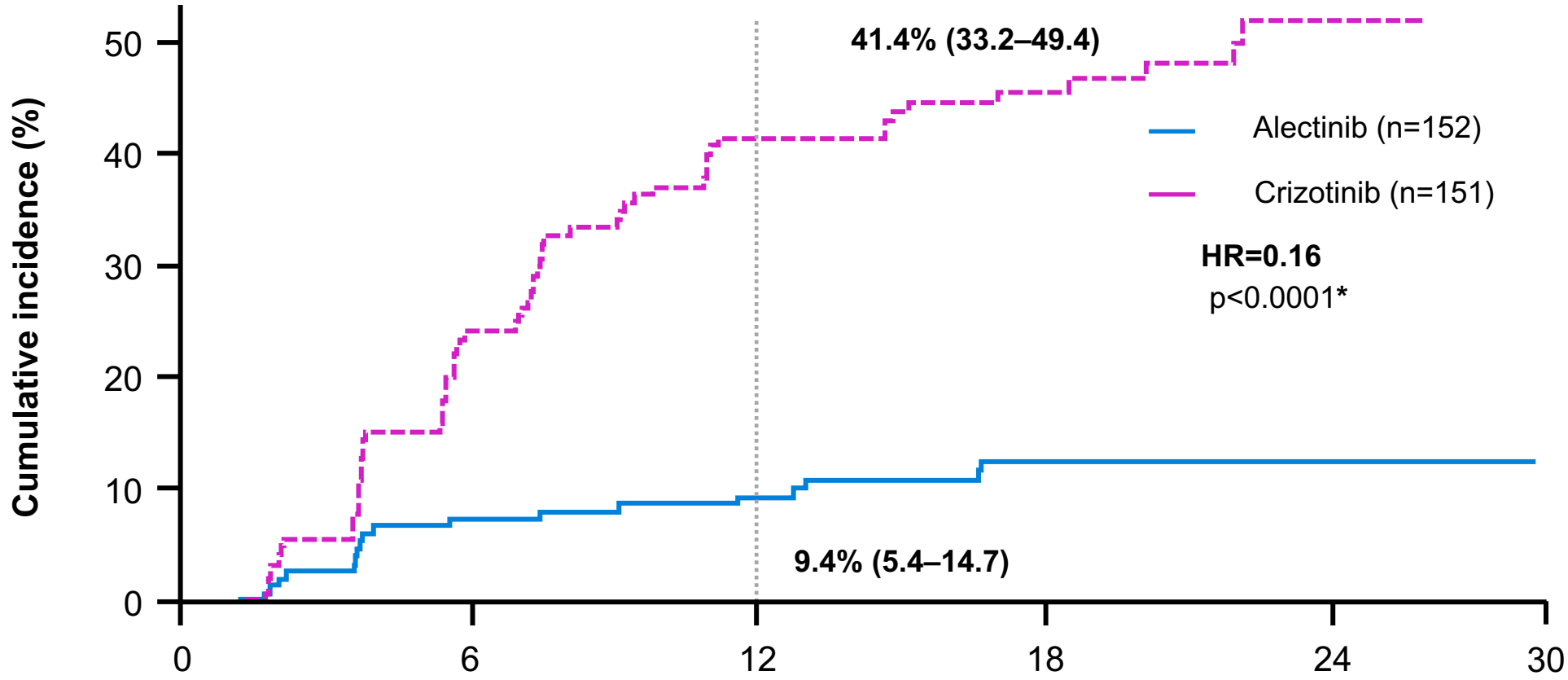
57% reduction in risk to progression vs. crizotinib



Courtesy of Prof Solange Peters, MD, PhD

Mok T. et al. ESMO 2019. Poster 1484 PD

ALEX: Time to CNS progression in ITT



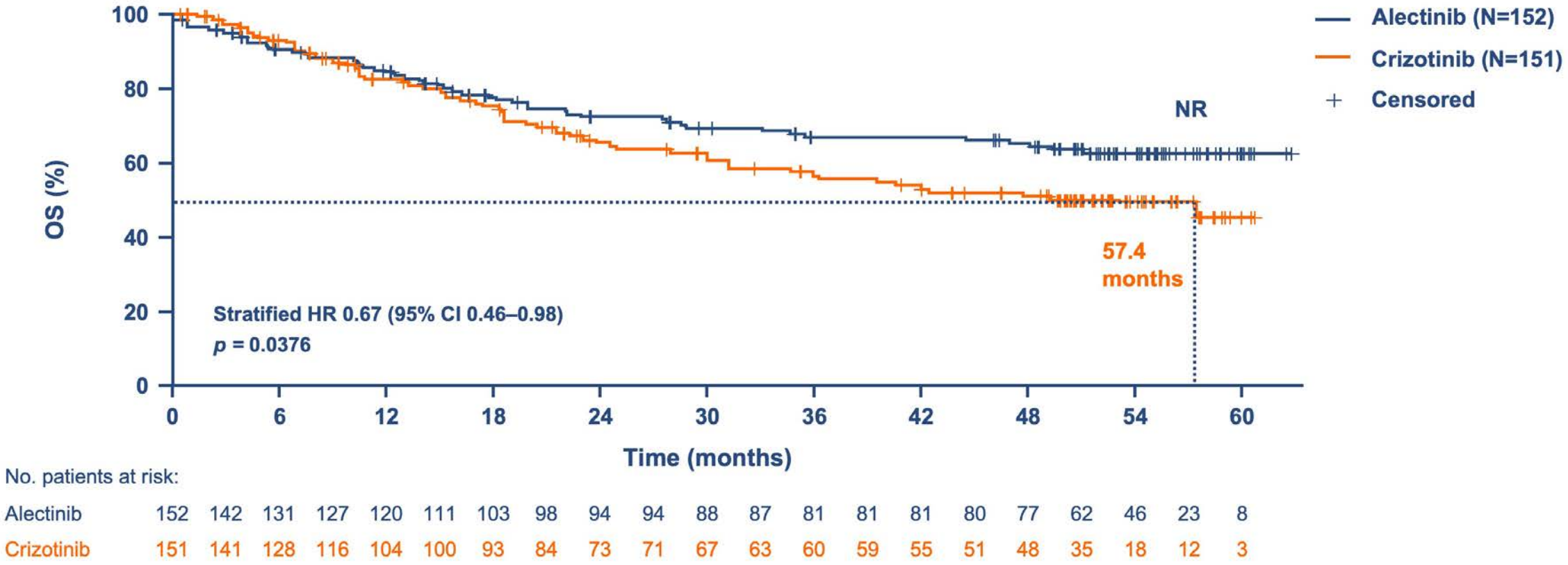
Alectinib reduced the risk of CNS progression by 84% (HR=0.16, p<0.0001)

Per IRC

Courtesy of Prof Solange Peters, MD, PhD

Peters, et al. NEJM 2017; Shaw et al. ASCO 2017

ALEX: median OS > 5 years



OS data remain immature, with 37% of events recorded (stratified HR 0.67, 95% CI 0.46-0.98)

Median OS was not reached with alectinib vs 57.4 months with crizotinib (95% CI 34.6-NR)

Peters, ASCO 2020, Mok, Annals Oncol 2020

Courtesy of Prof Solange Peters, MD, PhD

ALTA-1L: randomised, multicentre, phase III, open-label study of first-line brigatinib versus crizotinib in ALK-TKI naïve advanced *ALK*+ NSCLC

- Stage IIIB or IV NSCLC
- *ALK*+ disease
- No previous ALK inhibitor
- ≤1 prior systemic therapy for advanced NSCLC
- ≥1 measurable lesion as defined by RECIST 1.1

(N=275)

R 1:1

Brigatinib 180mg QD (with 90mg QD 7-day lead-in)

Crizotinib 250mg BID

1 Primary endpoint

- PFS (assessed by BIRC)

2 Secondary endpoints*

- ORR
- Intracranial ORR
- Intracranial PFS
- OS
- HRQoL
- Safety and tolerability
- DCR

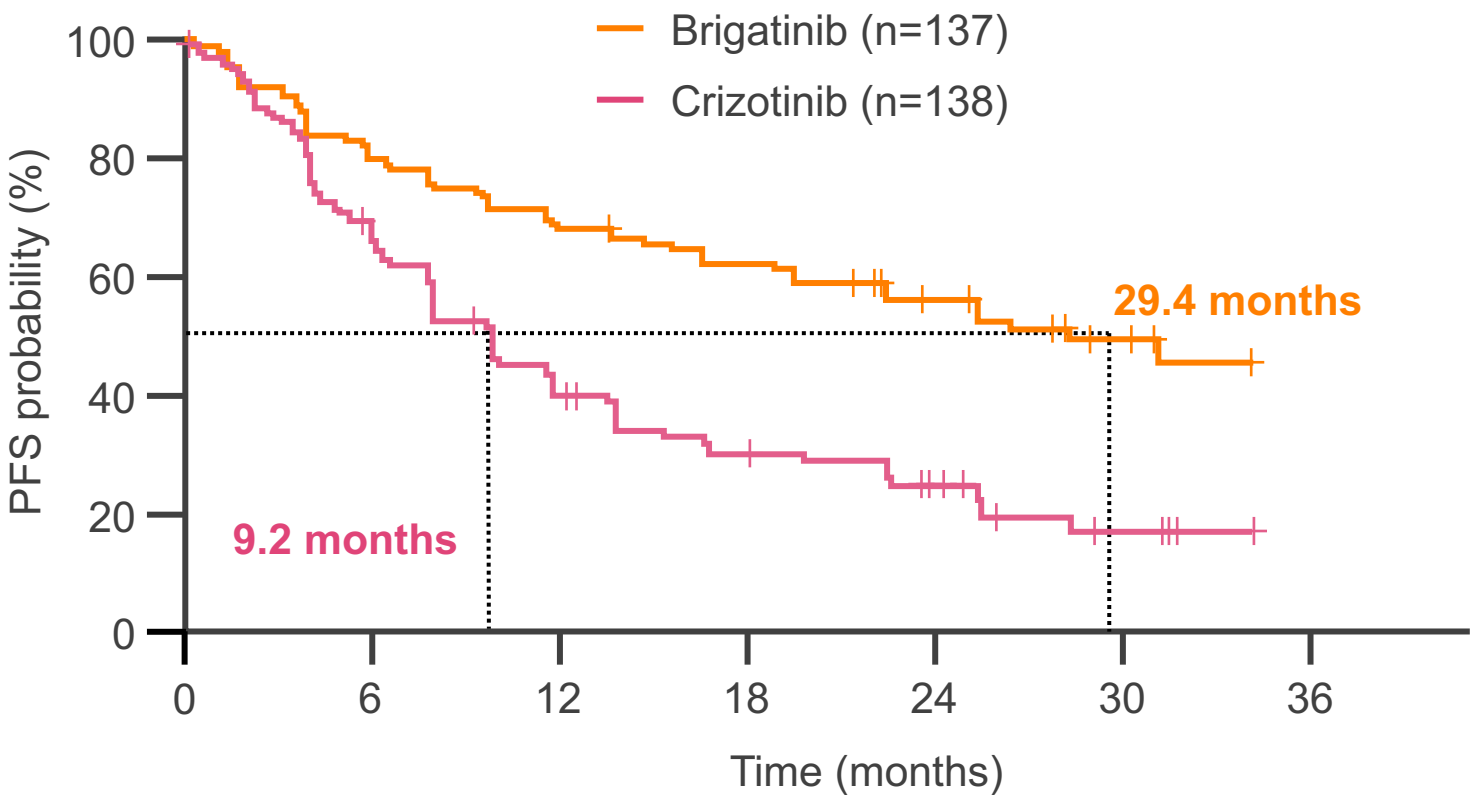
Camidge, et al. N Engl J Med 2018

*ORR, intracranial ORR, intracranial PFS and DCR were BIRC-assessed
BID = twice daily; QD = once daily

Courtesy of Prof Solange Peters, MD, PhD

ALTA-1L: brigatinib demonstrated a median PFS benefit versus crizotinib

Endpoint: PFS
(investigator-assessed [ITT population])*



	Brigatinib (n=137)	Crizotinib (n=138)
ORR, %	74	62
Median DoR, months (95% CI)	NR (19.4–NR)	13.8 (9.3–20.8)

HR = 0.43 (95% CI: 0.31–0.61)
Log-rank p<0.0001

Data cut-off: 28 June 2019
*The primary endpoint was PFS by BIRC assessment (**24.0 months** for brigatinib and 11.0 months with crizotinib; HR 0.49)
NR = not reached

Camidge, et al. ESMO Asia 2019

Courtesy of Prof Solange Peters, MD, PhD

ALTA-1L: treatment with brigatinib resulted in longer PFS versus crizotinib in patients with and without CNS metastases at baseline

Patients **with** CNS metastases at baseline

	Brigatinib (n=40)	Crizotinib (n=41)
Median PFS	24.0	5.6
Hazard ratio (95% CI)	0.25 (95% CI: 0.14–0.46)	

Patients **without** CNS metastases at baseline

	Brigatinib (n=97)	Crizotinib (n=97)
Median PFS	24.0	13.0
Hazard ratio (95% CI)	0.65 (95% CI: 0.44–0.97)	

Data cut-off: 28 June 2019
Assessed by BIRC

Camidge, et al. ESMO Asia 2019

Courtesy of Prof Solange Peters, MD, PhD

Investigational ALK inhibitors in development and not yet approved for first-line treatment of advanced *ALK*+ NSCLC

Lorlatinib

Key trial: CROWN[1]
mPFS not reached

Ensartinib

Key trial: eXalt3[2,3]
Investigational
(not yet approved)

LORLATINIB IS NOT EMA-APPPROVED IN FIRST LINE – ONLY IN LATER LINES

ENSARTINIB IS NOT EMA-APPPROVED

1. Shaw, et al. WCLC 2018; 2. Wu, et al. WCLC 2017
3.Horn, et al. WCLC 2020

Courtesy of Prof Solange Peters, MD, PhD

CROWN: randomised, multicentre, phase III, open-label study of first-line lorlatinib versus crizotinib in advanced *ALK*+ NSCLC

- Locally advanced or metastatic *ALK*+ NSCLC
- ≥1 extracranial measurable target lesion not previously irradiated
- No prior systemic NSCLC treatment
- Includes patients with asymptomatic CNS metastases
- ECOG PS 0–2

(N=280)

R 1:1

Lorlatinib 100mg QD

Crizotinib 250mg BID

1 Primary endpoint

- PFS (assessed by BIRC)

2 Secondary endpoints

- OS
- PFS (investigator)
- ORR (BIRC)
- Intracranial ORR
- Intracranial TTP
- DoR
- Intracranial DoR
- Time to response
- Intracranial time to response
- Safety
- PROs

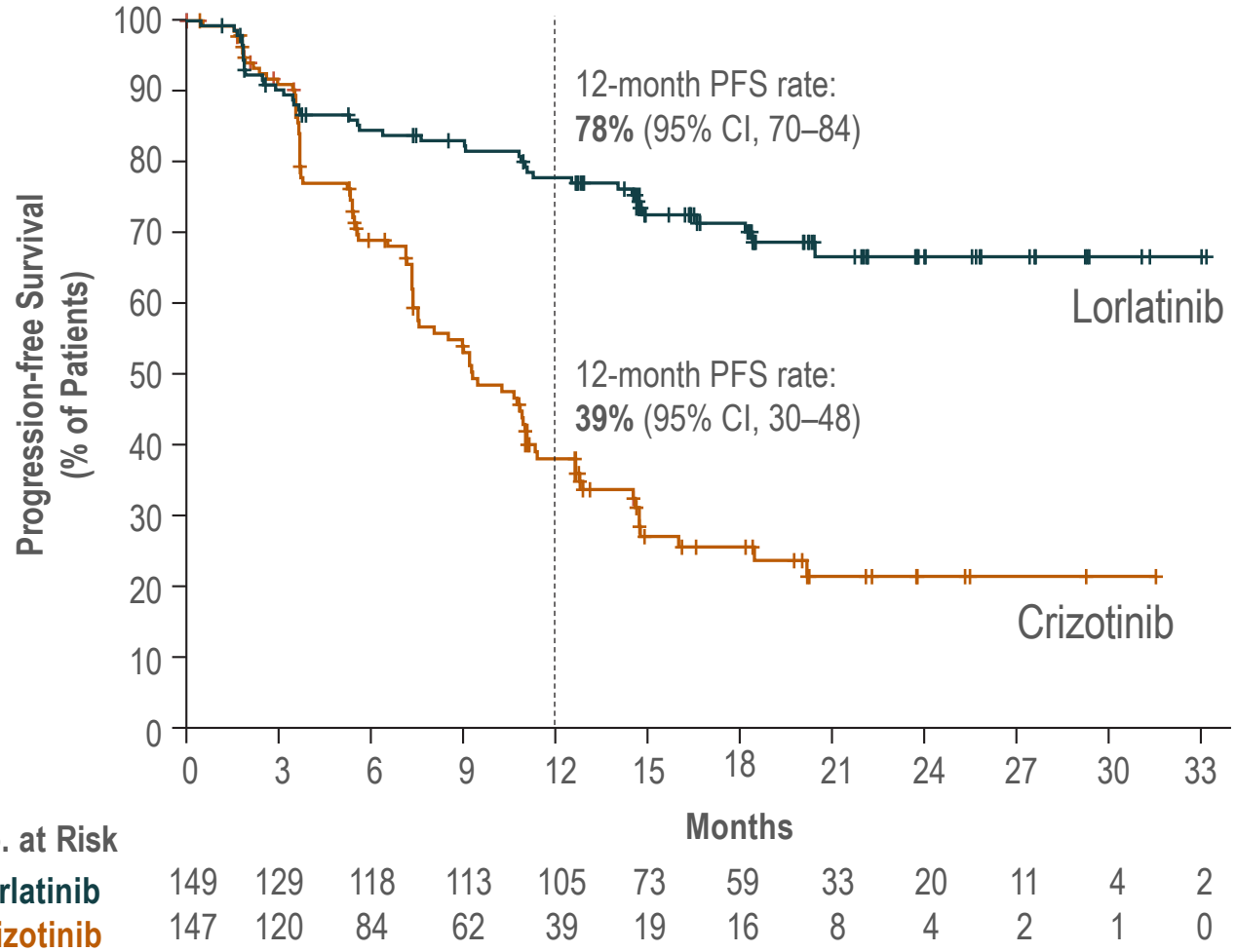
Shaw, et al. WCLC 2018

LORLATINIB IS NOT EMA-APPPROVED IN FIRST LINE – ONLY IN LATER LINES

BID = twice daily; QD = once daily

Courtesy of Prof Solange Peters, MD, PhD

Primary Endpoint: PFS by BICR



	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	41 (28)	86 (59)
Median PFS, months (95% CI)	NE (NE–NE)	9.3 (7.6-11.1)
HR (95% CI) 1-sided P value*	**0.28** (0.19-0.41) <0.001	

*By stratified log-rank test.

LORLATINIB IS NOT EMA-APPPROVED IN FIRST LINE – ONLY IN LATER LINES

BICR, blinded independent central review; Solomon B, ESMO 2020

Courtesy of Prof Solange Peters, MD, PhD

Intracranial-OR across new-generation ALK TKIs

Intra-cranial response	Measurable and non-measurable	Measurable
Alectinib (RR)	59%	81%
Alectinib (CR)	45%	38%
Brigatinib (RR)	67%	78%
Brigatinib (CR)	37%	11%

	Patients with measurable or non-measurable brain metastases at baseline		Patients with measurable brain metastases at baseline	
	Lorlatinib (n=38)	Crizotinib (n=40)	Lorlatinib (n=17)	Crizotinib (n=13)
IC-responders, n (%)	**25 (66)**	**8 (20)**	**14 (82)**	**3 (23)**
(95% CI)	(49-80)	(9-36)	(57-96)	(5-54)
Odds ratio (95% CI)	8.41 (2.59-27.23)		16.83 (1.95-163.23)	
IC-CR, n (%)	**23 (61)**	**6 (15)**	**12 (71)**	**1 (8)**
Median DR, months (95% CI)	NE (NE–NE)	9.4 (6.0-11.1)	NE (NE–NE)	10.2 (9.4-11.1)

LORLATINIB IS NOT EMA-APPPROVED IN FIRST LINE – ONLY IN LATER LINES

Odds ratio >1 indicates better outcome for lorlatinib relative to crizotinib
CR, complete response; DR, duration of response; IC, intracranial; NE, not evaluable; OR, objective response

Courtesy of Prof Solange Peters, MD, PhD

PFS with or without brain mets with new-generation ALK TKIs

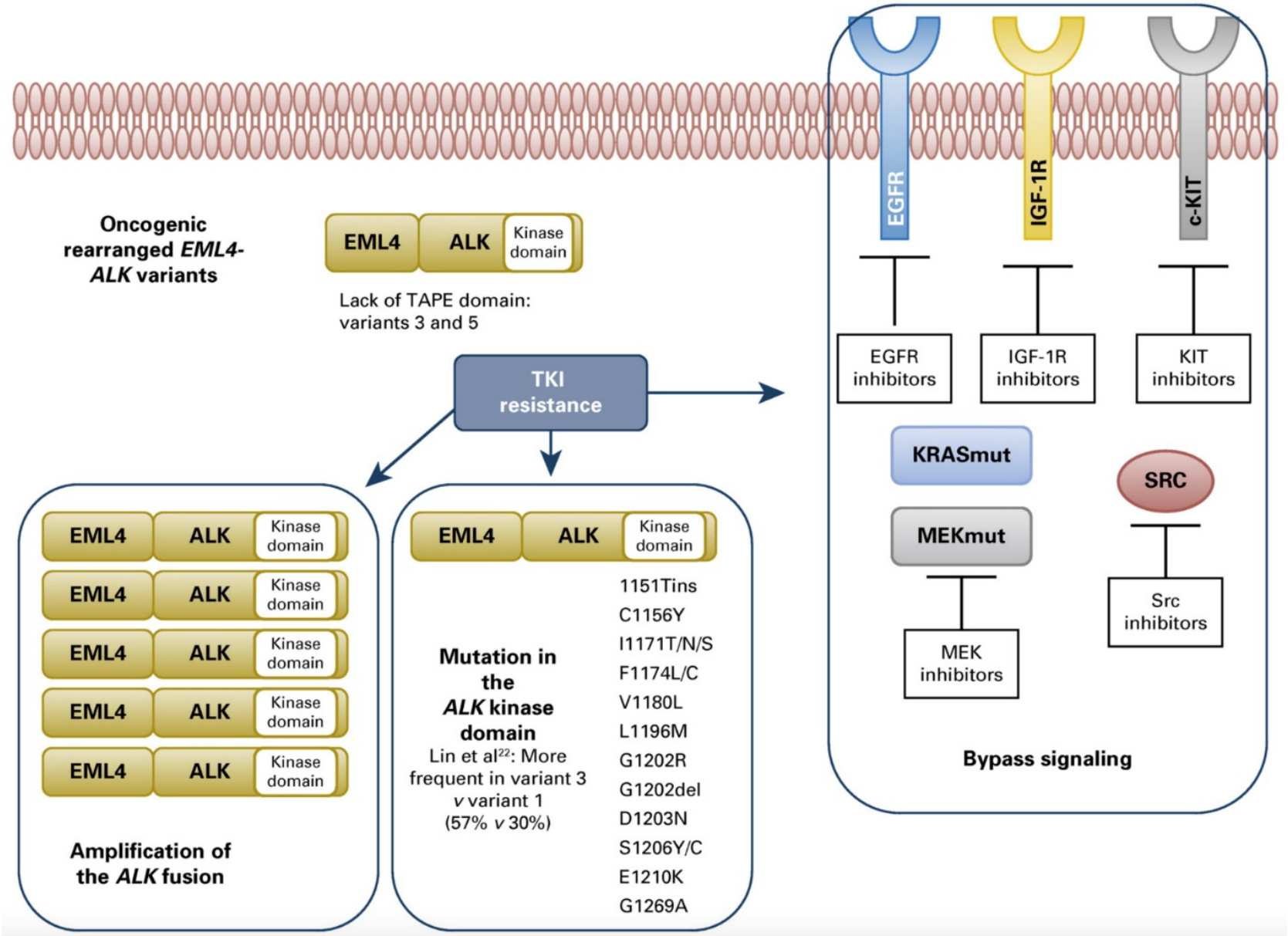
	ALTA-1L[1]		ALEX[2-4]		CROWN[5]		eXalt3[6]	
	Brigatinib (n=137)	Crizotinib (n=138)	Alectinib (n=152)	Crizotinib (n=151)	Lorlatinib (n=149)	Crizotinib (n=147)	Ensartinib (n=143)	Crizotinib (n=147)
IRC median PFS, months (95% CI)	24.0 (18.5-NE)	11.0 (9.2-12.9)	25.7 (19.9-NE)	10.4 (7.7-14.6)	NE (NE-NE)	9.3 (7.6-11.1)	31.3 (20.2 – NR)	12.7 (9.2 – 16.6)
HR (95% CI)	0.489 (0.35-0.68)		0.50 (0.36-0.70)		0.28 (0.19-0.41)		0.50 (0.36 – 0.71)	
Median OS, HR (95% CI)	0.92 (0.57-1.47)*		0.67 (0.46-0.98)		0.72 (0.41-1.25)		0.90 (0.55 – 1.49)†	

		ALTA-1L[1]		ALEX[2-4]		CROWN[5]		eXalt3[6]	
		Brigatinib (n=137)	Crizotinib (n=138)	Alectinib (n=152)	Crizotinib (n=151)	Lorlatinib (n=149)	Crizotinib (n=147)	Ensartinib (n=81)	Crizotinib (n=76)
Efficacy	PFS WITH baseline brain mets (INV-assessed), HR (95% CI)	0.24 (0.12-0.45)		0.37 (0.23-0.58)		IRC-assessed 0.20 (0.10-0.43)		NR	
	PFS WITHOUT baseline brain mets (INV-assessed), HR (95% CI)	0.57 (0.38-0.84)		0.46 (0.31-0.68)		IRC-assessed 0.32 (0.2-0.49)		BIRC-assessed (mITT population) 0.40 (0.23-0.70)	

1. Camidge DR, et al. J Clin Oncol. 2020 [Published online ahead of print] doi: 10.1200/JCO.20.00505. 2. Peters S, et al. *New Engl J Med.* 2017;377:829-838. 3Gadgeel S, et al. Ann Oncol. 2018;29:2214-2222. 4. Mok T, et al. *Ann Oncol.* 2020;31(8):1056-1064. 5. Solomon B, et al. Presented at the 2020 European Society for Medical Oncology (ESMO) Virtual Congress; September 19-21, 2020. 6. Wu Y, et al. Presented at the 2020 World Conference on Lung Cancer (WCLC) Annual Meeting. January 27-31, 2021; Singapore.

Courtesy of Prof Solange Peters, MD, PhD

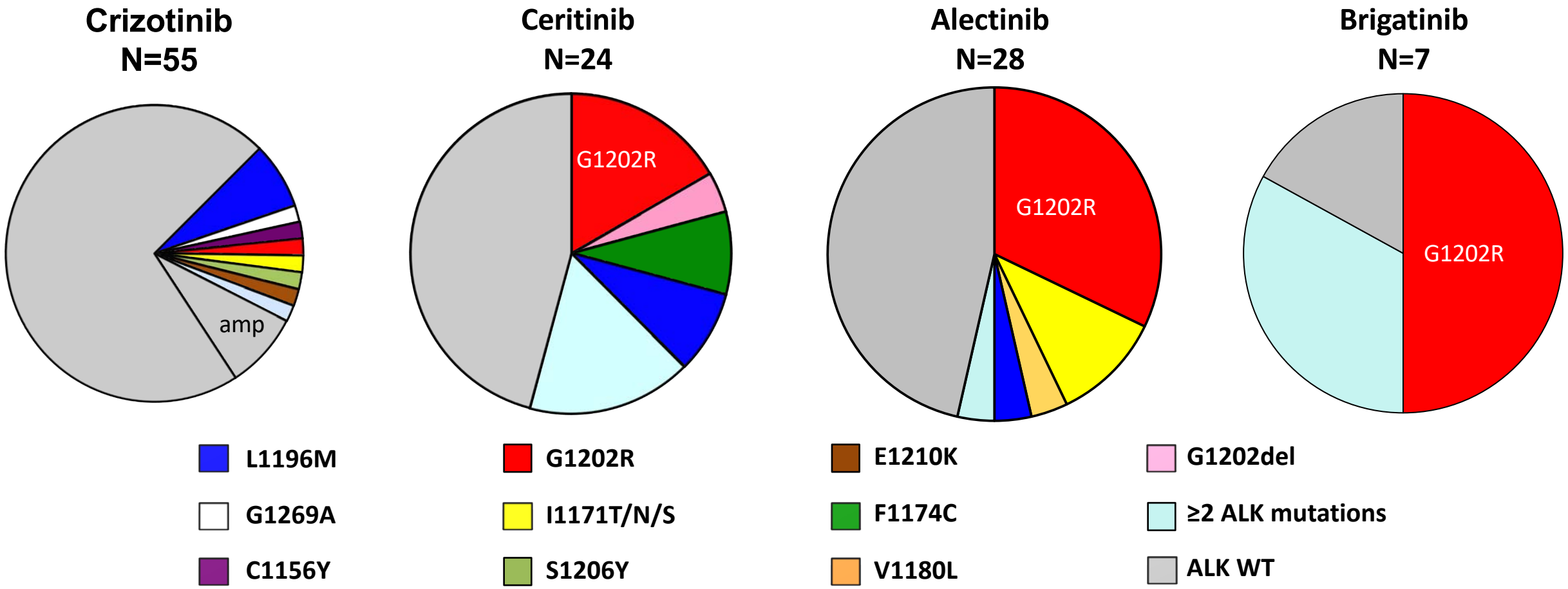
ALK TKI resistance



Lin, JCO 2018
Frueh and Peters, JCO 2018

Courtesy of Prof Solange Peters, MD, PhD

ALK G1202R Is the Most Common Resistance Mutation Emerging on 2nd-Generation ALK TKIs



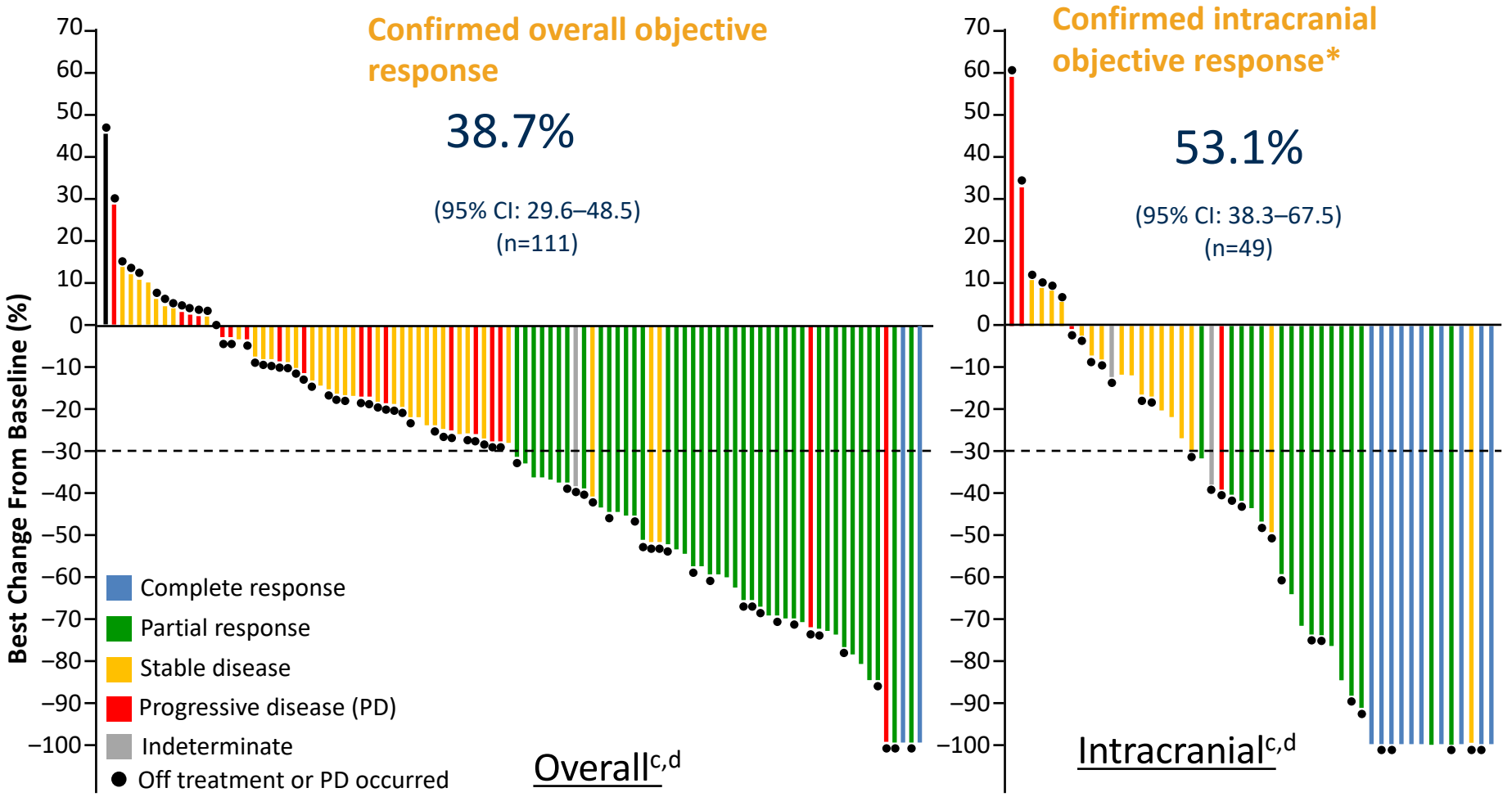
TKI: tyrosine kinase inhibitor.

Updated from Gainor JF, et al. *Cancer Discov*. 2016;6:1118–1133.

Courtesy of Prof Solange Peters, MD, PhD

Pooled efficacy in EXP4[a] and EXP5[b] cohorts (ALK-positive, 2–3 prior ALK TKI ± chemotherapy)

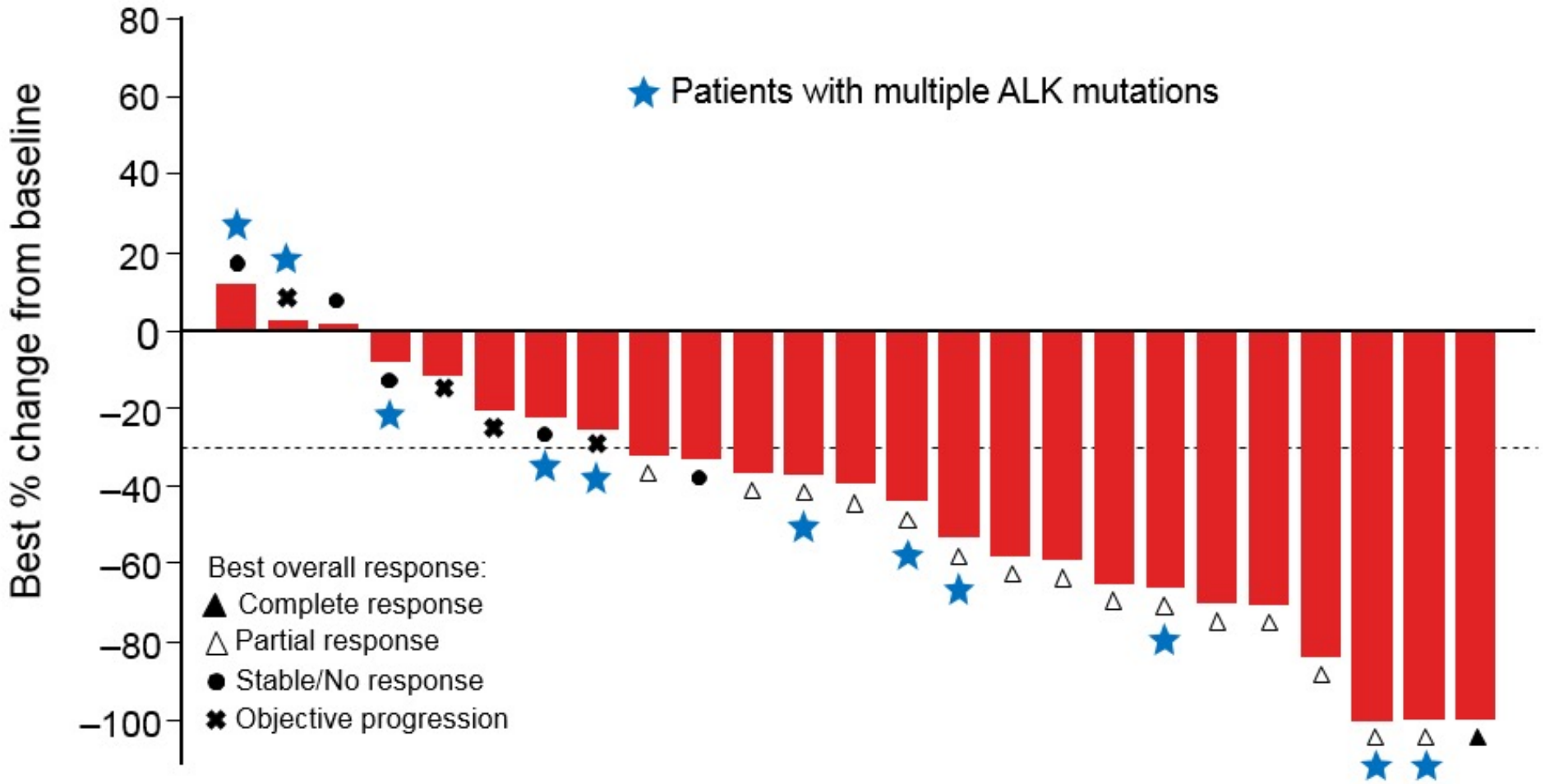
	EXP4+5 (n=111)
ORR, n/N (%) (95% CI)	43/111 (39) (30, 49)
IC ORR, n/N (%) (95% CI)	40/83 (48) (37, 59)
Median DOR, months (95% CI)	NR (5.5, NR)
DOR ≥6 months, n%/n (%)	20/43 (47)
Median PFS, months (95% CI)	6.9 (5.4, 9.5)



Courtesy of Prof Solange Peters, MD, PhD

Solomon *et al* Lancet Oncology 2018

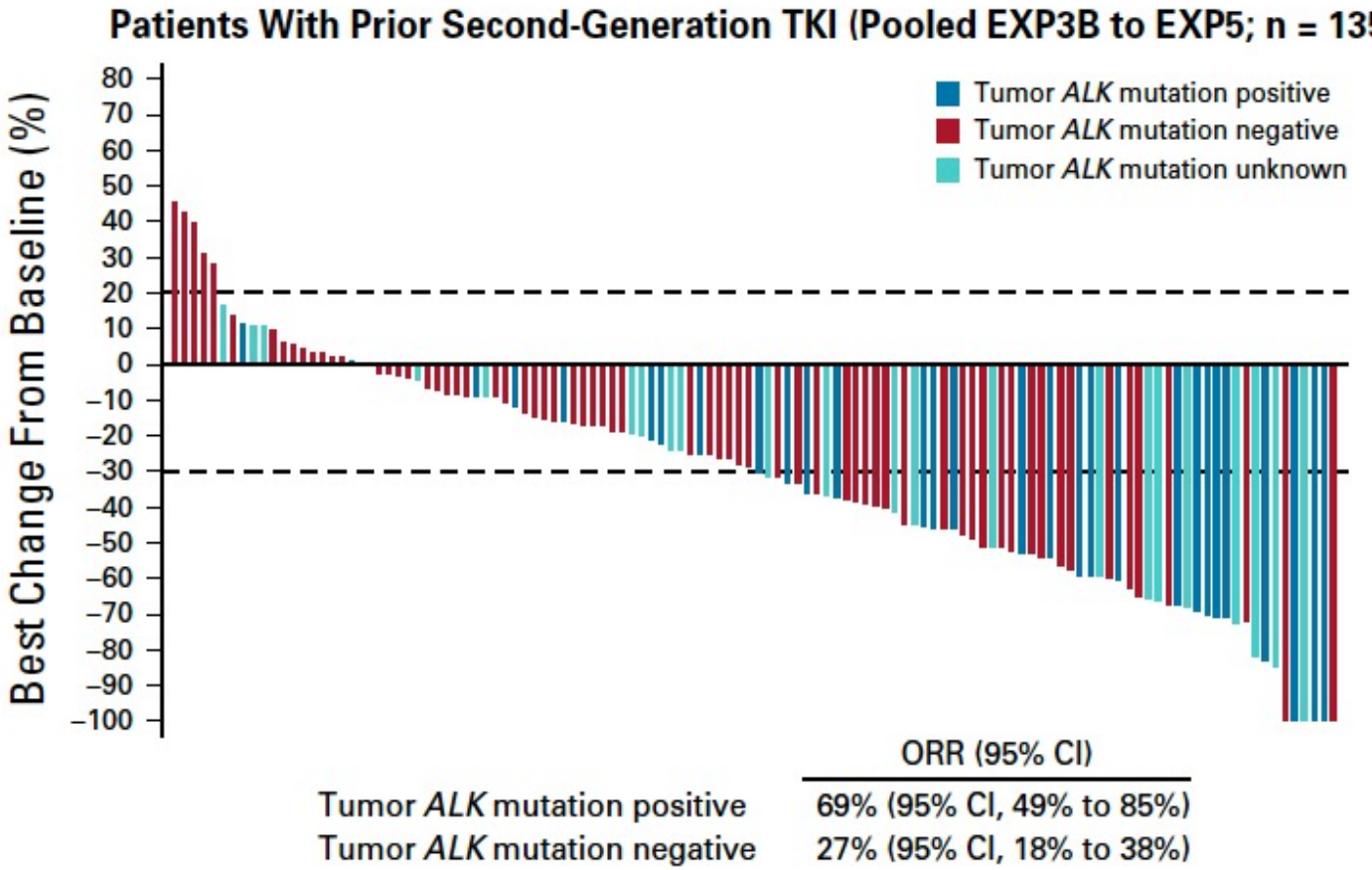
Best response in patients harboring the ALK G1202R mutation (EXP2–5)



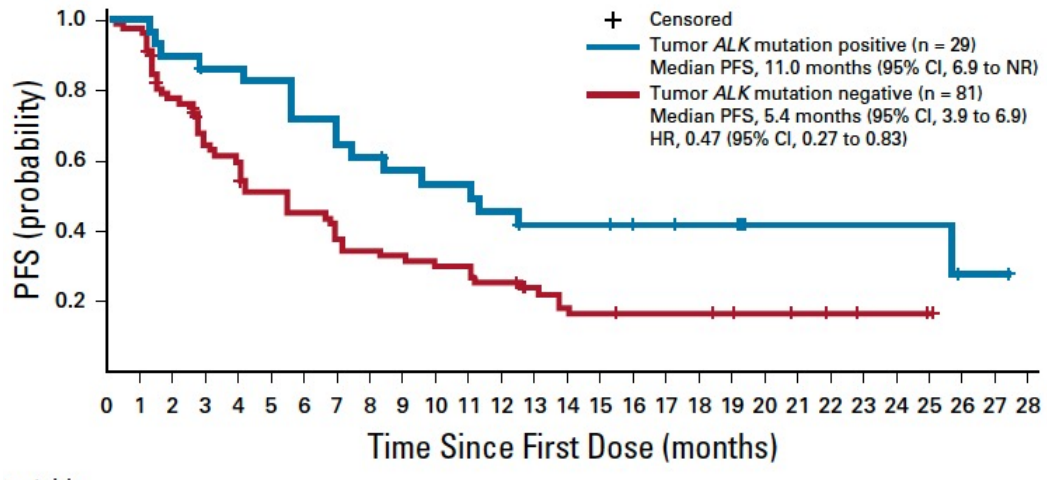
[a]Detected in either cfDNA or tumor tissue (archival or de novo) analysis sets

Courtesy of Prof Solange Peters, MD, PhD

Responses seen in patients with and without ALK mutations detected in tissue



	ORR (95% CI)
Tumor *ALK* mutation positive	69% (95% CI, 49% to 85%)
Tumor *ALK* mutation negative	27% (95% CI, 18% to 38%)



Courtesy of Prof Solange Peters, MD, PhD

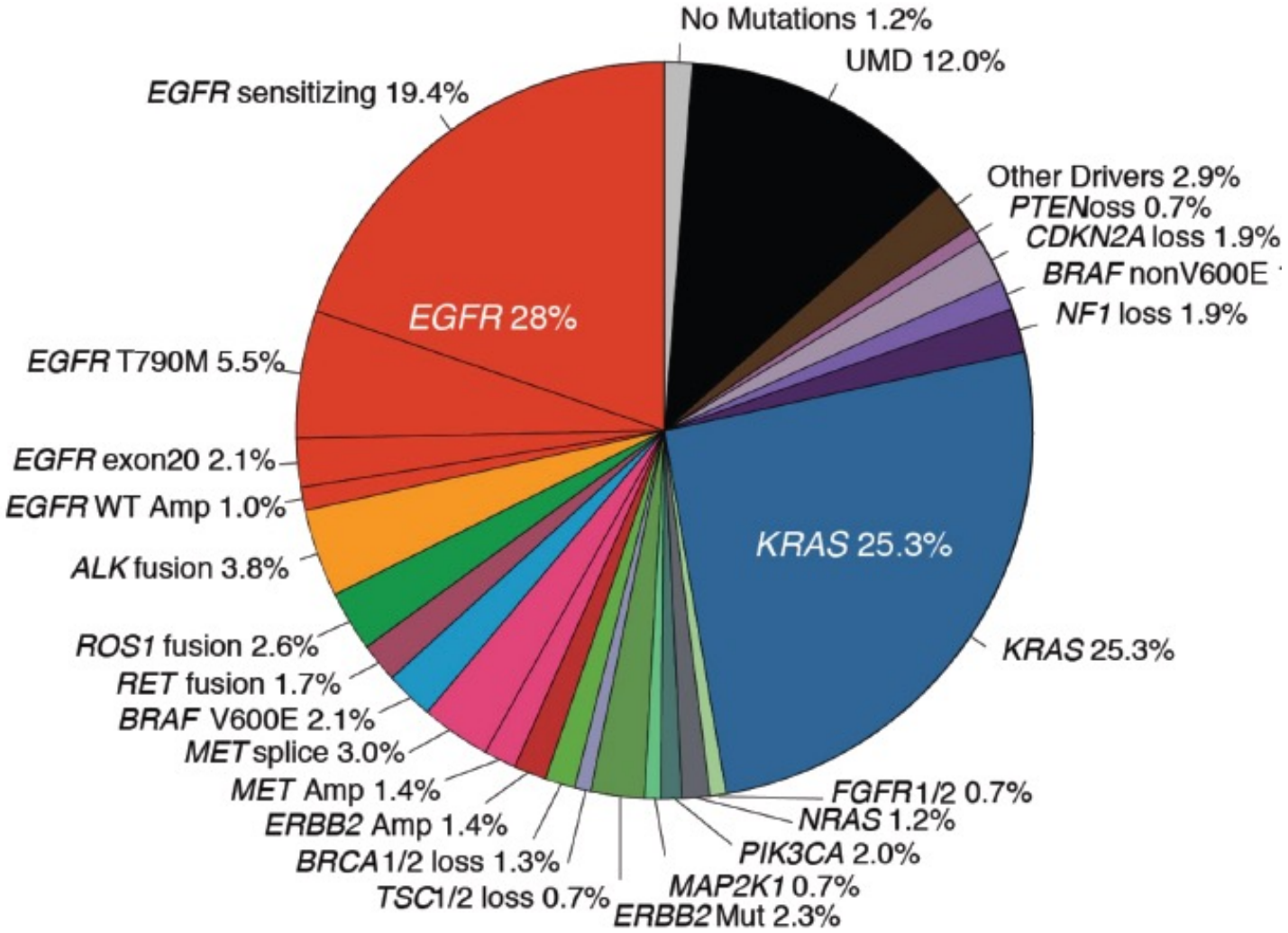
Shaw, Solomon et al JCO 2019

ROS-1 REARRANGEMENT

Courtesy of Prof Solange Peters, MD, PhD

Updates in new targets

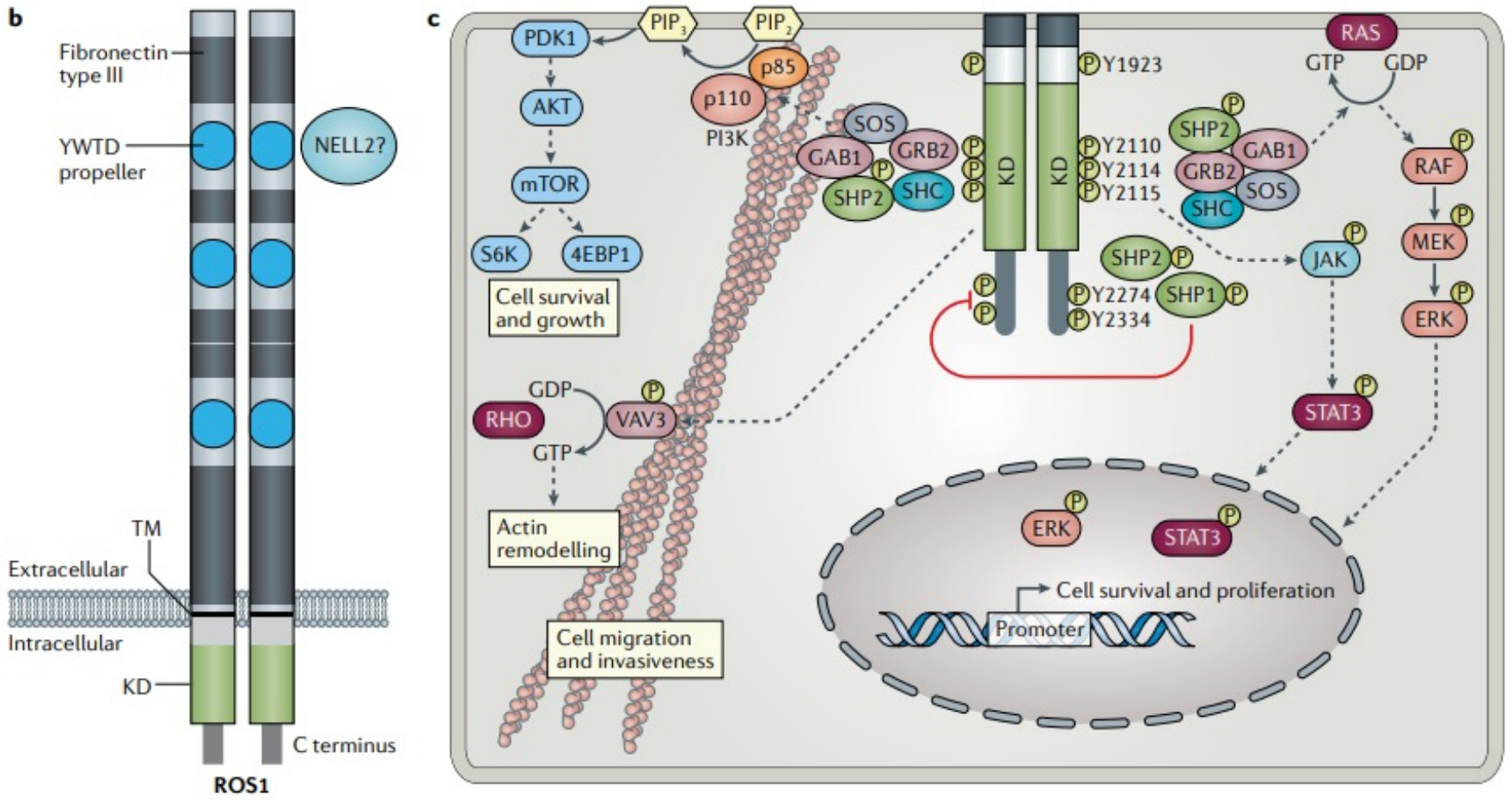
- **ROS1 fusions**
- RET fusions
- NTRK fusions
- MET exon 14 mutations
- BRAF mutations



Courtesy of Prof Solange Peters, MD, PhD

Jordan Cancer Discovery 2018

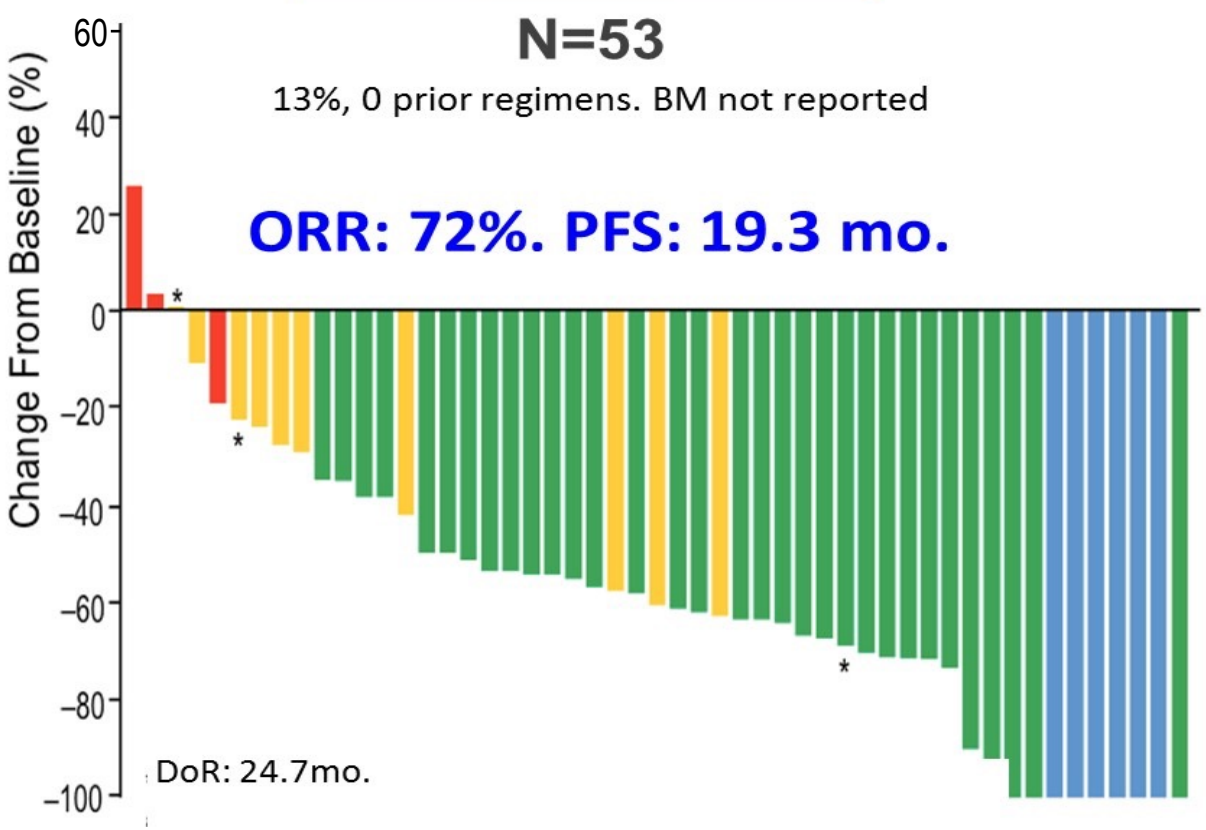
ROS1+ NSCLC

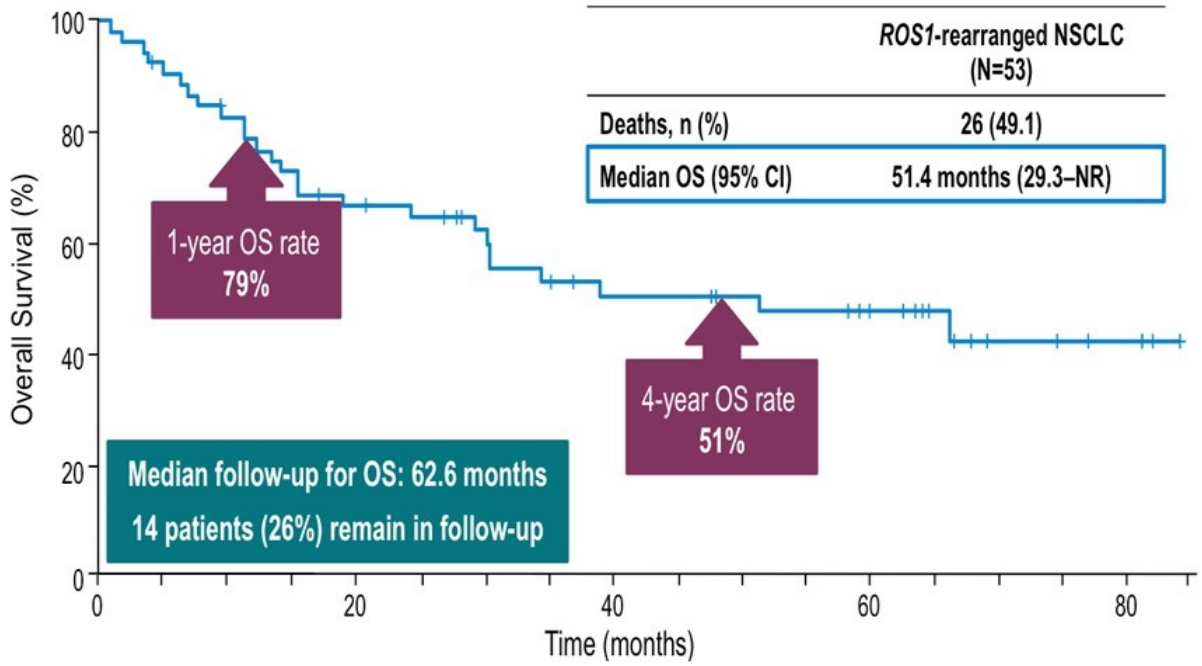


- Cell signalling pathways induced by ROS1 catalytic activity include the RAS–RAF–MEK–ERK (MAPK), PI3K–AKT–mTOR, JAK–STAT3 and VAV3–RHO pathways
- Up to 35-40% of patients with ROS1 fusion-positive NSCLC already have CNS metastases at the time of diagnosis, highlighting the need for alternative treatment options with CNS activity

Courtesy of Prof Solange Peters, MD, PhD

Crizotinib first in class ROS1 targeting TKI for *ROS1*-rearranged NSCLC



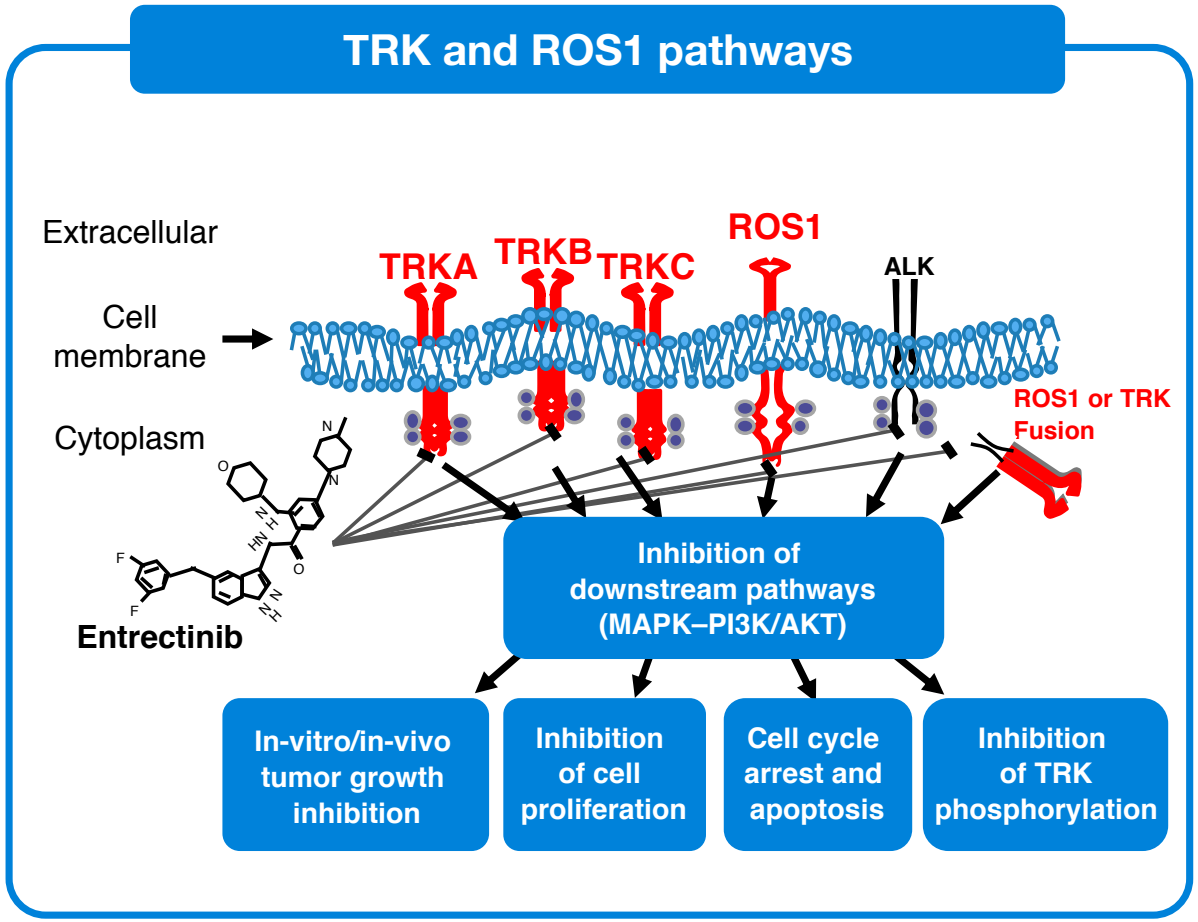


Shaw NEJM 2014

Courtesy of Prof Solange Peters, MD, PhD

Shaw et al. Annals of Oncology 2019

Entrectinib is a potent ROS1 and TRK inhibitor



Target	ROS1	TRKA	TRKB	TRKC
IC_{50} (nM)	0.2	1.7	0.1	0.1

Entrectinib is an oral, potent and selective ROS1/NTRK/ALK tyrosine kinase inhibitor that is CNS active[1,2]

- More potent ROS1 inhibitor than crizotinib in preclinical studies[1]
- Potent pan-TRK inhibitor in clinical development
- Designed to cross the blood–brain barrier and remain within CNS, with demonstrated clinical activity in primary brain tumors and secondary CNS metastases

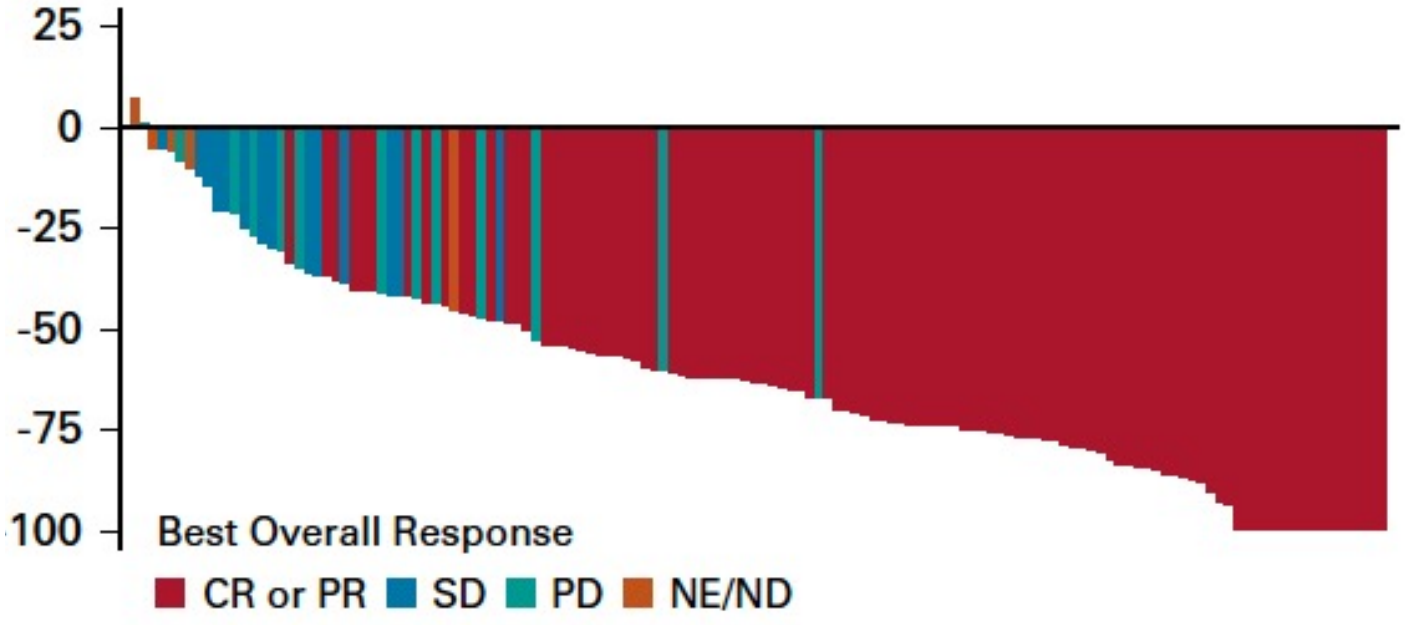
Courtesy of Prof Solange Peters, MD, PhD

Activity of Entrectinib in ROS1 rearranged NSCLC – combined analysis of ALKA-372-001, STARTRK-1, and STARTRK-2 (n=161)

Overall response ITT

ORR = 67.1%

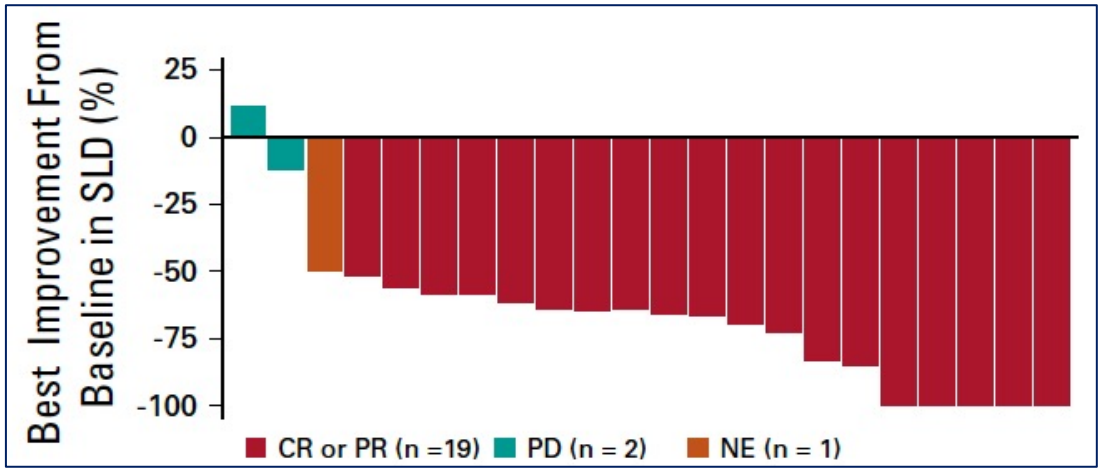
mPFS = 15.7 months



Intracranial Activity

IC ORR: 79.2%

IC PFS: 12 months



Prior lines of systemic therapy, n (%)[a]	
0	60 (37.3)
1	64 (39.8)
≥ 2	37 (23.0)

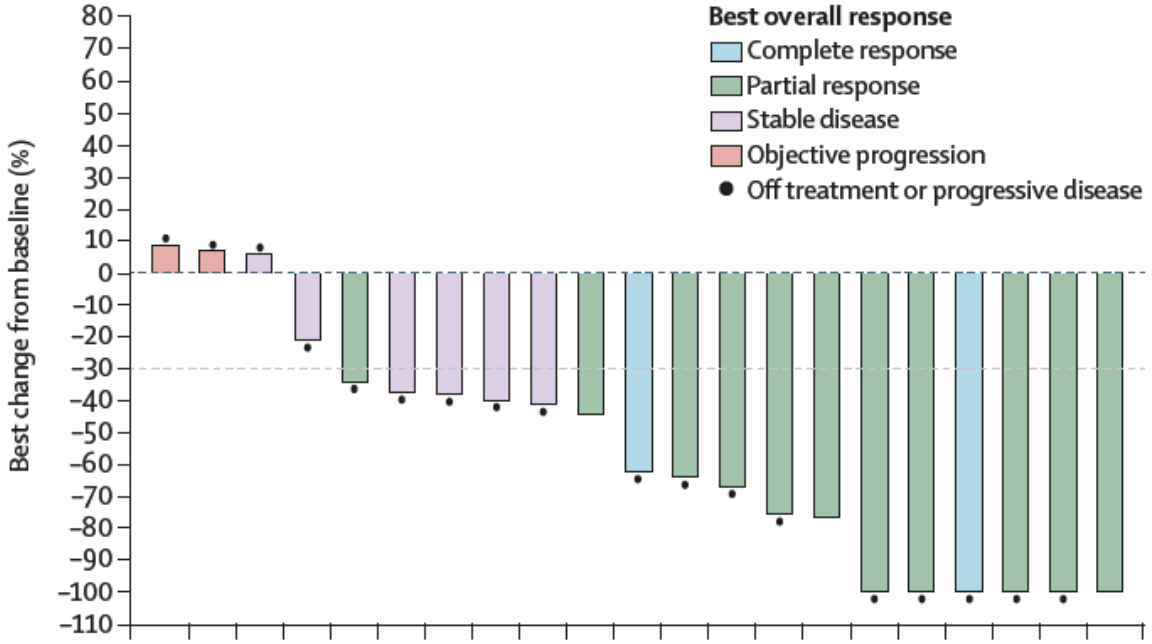
No ROS TKI resistance

Courtesy of Prof Solange Peters, MD, PhD

Dzaidziuszko JCO 2021

Lorlatinib multicenter: open-label, phase 1–2 trial

ROS1-TKI naïve pts (n=21)



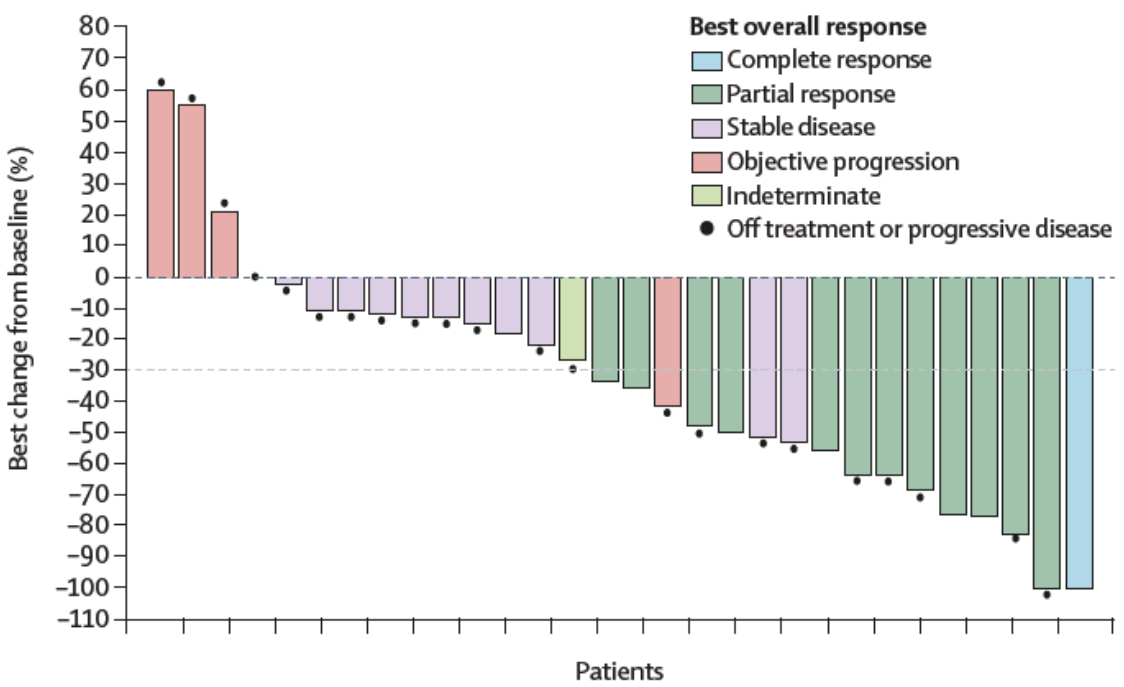
ORR: 62% (38–82)

IC ORR : 64%

mDoR, month: 25.3 (7.5–31.9)

mPFS: 21 (4.2-31.9)

Crizotinib pretreated pts (n=40)



ORR: 35% (21-52)

IC ORR: 50%

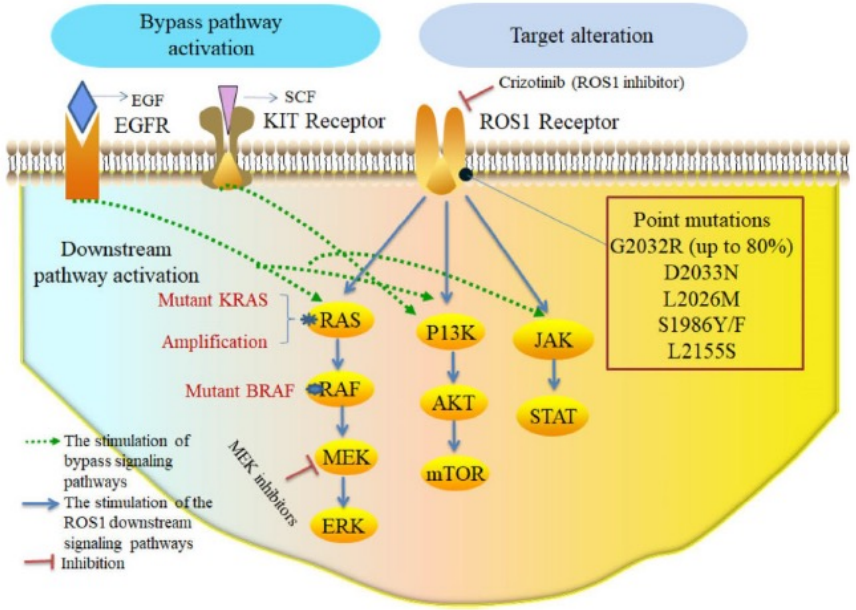
mDoR, month: 13.8 (9.7–NR)

mPFS: 8.5 (4.7-15.2)

Shaw et al 2020 Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1–2 trial Lancet Oncol. 2019 Dec;20(12):1691-1701. doi: 10.1016/S1470-2045(19)30655-2. Epub 2019 Oct 25.

Courtesy of Prof Solange Peters, MD, PhD

Resistance to ROS1 TKIs



Mutation	ROS1 fusion	Location	Mechanism	Potent TKIs
G2032R	CD74-ROS1	Solvent front of the kinase hinge	Glycine-to-arginine substitution at codon 2032 in the ROS1 kinase domain causes resistance to ROS1 kinase inhibition through steric interference with drug binding	Cabozantinib Ropotrectinib
D2033N	CD74-ROS1	Solvent front of the kinase hinge	Aspartic acid-to-asparagine substitution at codon 2033 leads to a modification of electrostatic forces at the exterior surface of the ATP-binding site and reorientation of surrounding residues in front of the ATP-binding pocket	Lorlatinib Cabozantinib Ropotrectinib
L2155S	SLC34A2-ROS1	Not reported yet	Protein malfunction	Lorlatinib Cabozantinib Ropotrectinib
S1986F/Y	EZR-ROS1	Not reported yet	Serine to tyrosine (S1986Y)/serine to phenylalanine (S1986F) substitution leads to an obstruction in the path to the enzyme active site and an increase in kinase activity	Lorlatinib Cabozantinib Ropotrectinib
L2026M	CD74-ROS1	Gatekeeper position of inhibitor-binding pocket	Leucine-to-methionine substitution at codon 2026	Lorlatinib Ceritinib Cabozantinib Ropotrectinib

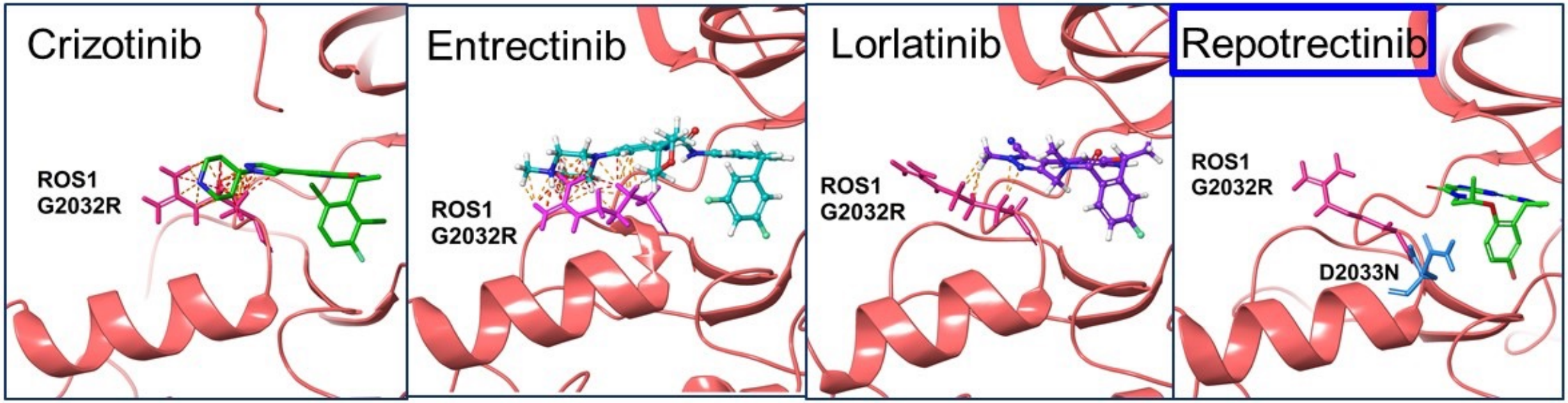
	Crizotinib	Ceritinib	Lorlatinib	Brigatinib	Cabozantinib	Foretinib	Entrectinib	AZD3463	Repotrectinib	Ensartinib
Cthrough (ng/mL)	237 to 800	1400		552	1080	46 to 900				
Cthrough (nM)	530 to 913					70	1330		425	
CSF/plasma conc.	0.001 to 0.003						0.4		0.04	
WT CD74-ROS	2 to 44	11 to 230	0.05 to 1	2.7 to 30	0.5 to 9	1.8 to 14	5.3 to 10	10	0.2	39
WT SLC34A2-ROS1	21	506	1.15			19				
WT FIG-ROS	41 to 60	304 to 488	0.2			6				
E1935G	350					6.6				
L1947R	1420					17.9				
L1951R	8.8 to 97	76.4 to 611		611	0.18 to 20.7					
G1971E	605					8.7				
E1974K	23	42.3		10.3	6.8	6.2		30.9		
V1979A	b	b								
V1979M	b									
1981 Tins[c]	d	d	d							
L1982F	4.7 to 6.9	23 to 27			0.08 to 2.94	15.3				
S1986 Y/F[b]	116 to 125	73 to 99	1 to 1.6							
E1990G	4.0	22.1			0.34					
F1994L	3.3	19.4			0.01					
M2001T[c]	d	d	d							
K2003I	1.4 to 1.5	4.5 to 11.7			0.28 to 0.32					
F2004C	40.5	68.7		20.2	56.8	23.5		19.9		
E2020K	41.1	97.8		24.9	10.5	9.7		53.2		
F2024 C/V[c]	d	d	d							
L2026Ma	22.4 to 259	4.6 to 90	1.1 to 2	3.5 to 200	0.92 to 11	3.2 to 8.6	3500	1800		
L2028-[c]										
G2032Ra	254 to 2700	276 to 2200	160 to 508	170 to 1172	1.4 to 26	39.7 to 90	1813 to 2200		8.4	372
D2033Na	140 to 200	306 to 535	0.38 to 3.3	69.1 to 128	0.2 to 0.65	2.2	169		1.3	402
T2036-[c]										
C2060G	690					13.6				
F2075 V/C	17 to 23	68.7 to 92		9.1 to 14.1	4.9 to 31.4	9.7 to 16		6.2, 41.6		
V2089M	15.6	42.8		6.7	7.5	2.9		16.1		
V2098I	10.9 to 901	44.4		9.0	1.7	2.5 to 9.9		12.5		
G2101Aa	27.1	0.06	d			0.004				
D2113 N/G	25.4 to 29.6	118 to 163		24	15.3 to 41.2	8.5 to 25.4		40 to 42.5		
M2134I	14.2	55.7		11.1	4.3	5.4		15.2		
L2155S	405	185				534				
L2223S	1.13	11.2			0.07					
L2223X		b								

Of note:
The solvent front substitutions ROS1 G2032R, TRKA G595R and TRKC G623R as well as ALK G1202R are paralogous

Roys, Cancer chemo and pharm 2019
Guisier Clin Lung Cancer 2019

Courtesy of Prof Solange Peters, MD, PhD

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



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

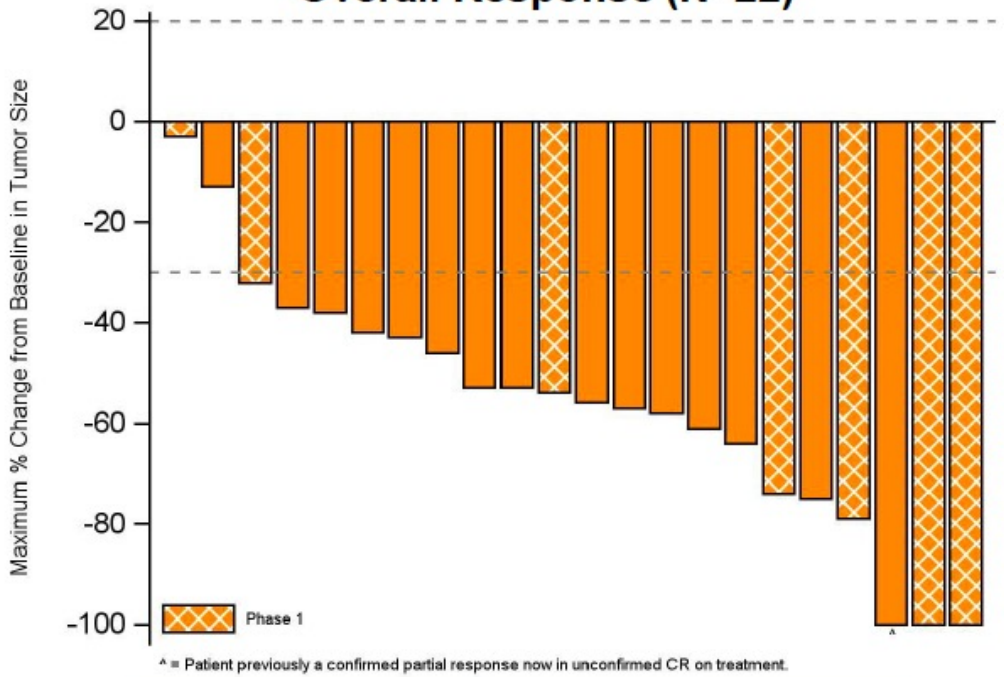
ROS1	Crizotinib	Ceritinib	Cabozantinib	Entrectinib	Lorlatinib	Repotrectinib
WT	14.6	42.8	0.5	10.5	0.2	<0.2
G2032R	266.2	1391	11.3	1813	160.7	3.3

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

Courtesy of Prof Solange Peters, MD, PhD

Repotrectinib (TPX-0005): Clinical activity in TKI-naïve ROS1+ NSCLC (TRIDENT-1)

Overall Response (N=22)



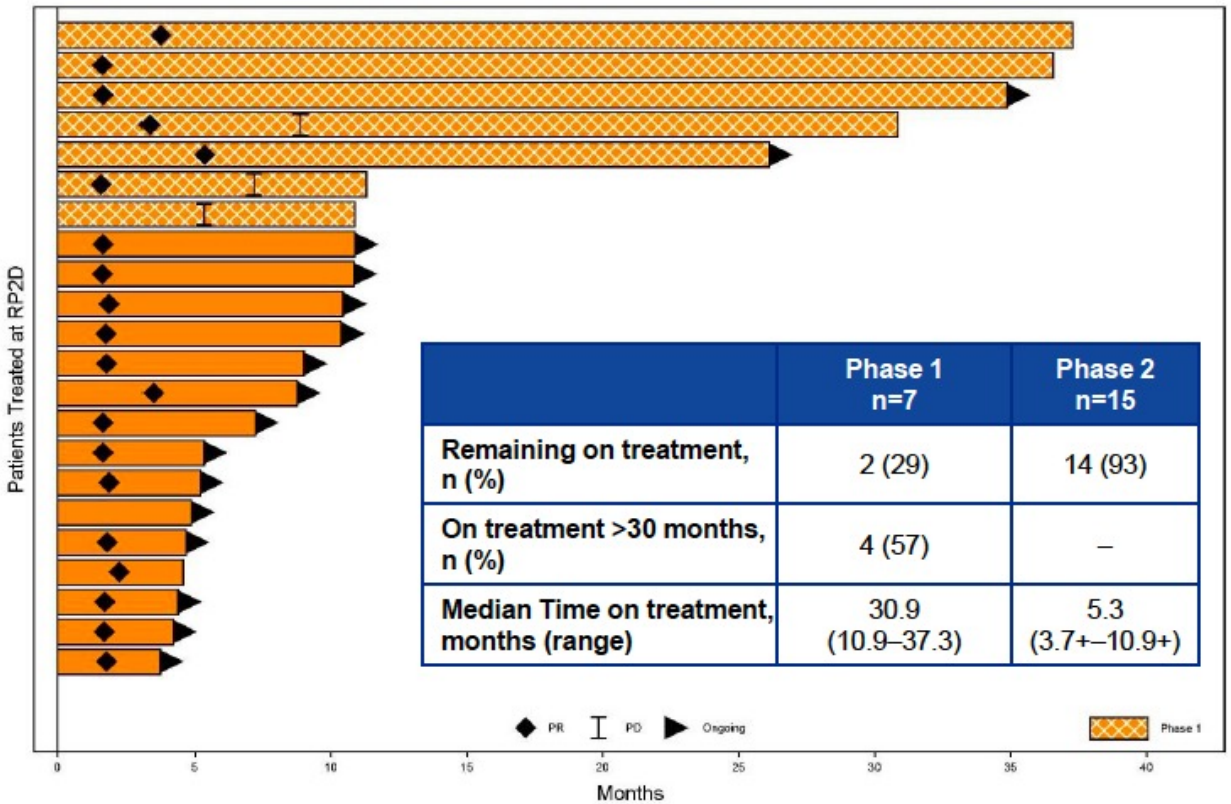
^ = Patient previously a confirmed partial response now in unconfirmed CR on treatment.

	Phase 2 N=15	Phase 1+2 N=22
Confirmed ORR, % (95% CI)	93% (68–100)	91% (71–99)

N=22 patients with baseline and at least two post baseline scans
- *N=15 Phase 2 patients*
- *N=7 Phase 1 patients treated at or above the Phase 2 recommended dose*

As of 31 December 2020, the 16th patient in Phase 2 has an unconfirmed PR and is on treatment awaiting a second post-baseline confirmatory scan.

Duration of Treatment (N=22)



	Phase 1 n=7	Phase 2 n=15
Remaining on treatment, n (%)	2 (29)	14 (93)
On treatment >30 months, n (%)	4 (57)	–
Median Time on treatment, months (range)	30.9 (10.9–37.3)	5.3 (3.7+–10.9+)

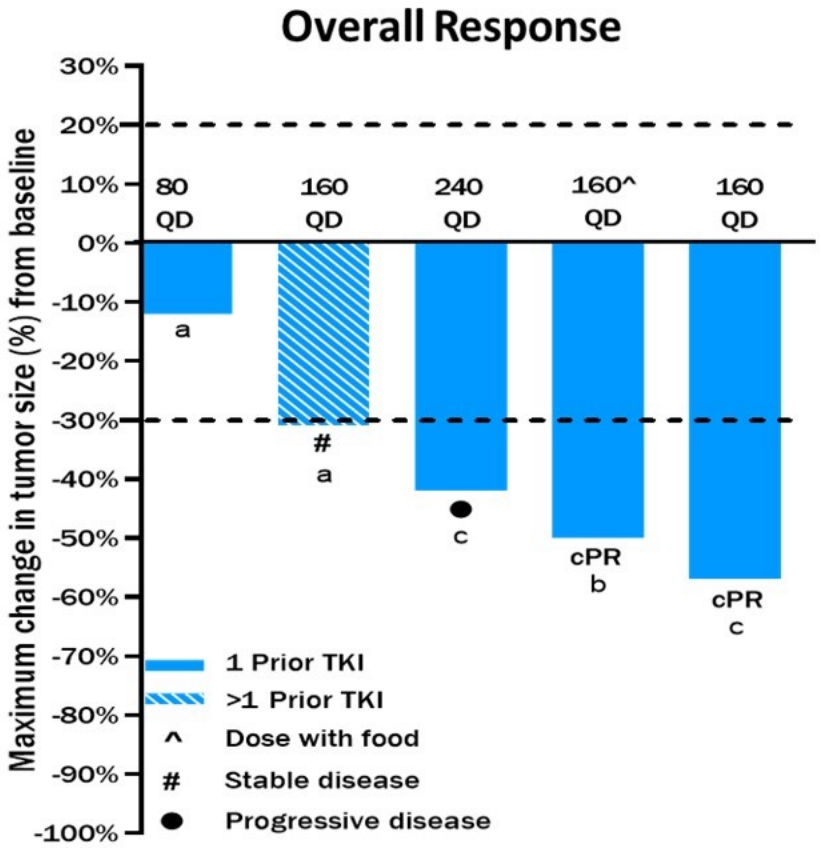
†Includes patients with a baseline and at least two post-baseline scans; Phase 1 data includes only patients treated at or above repotrectinib RP2D.
PD, progressive disease; PR, partial response; RP2D, recommended Phase 2 dose

Equivalent brain activity

Cho BC et al., WCLC 2020

Courtesy of Prof Solange Peters, MD, PhD

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

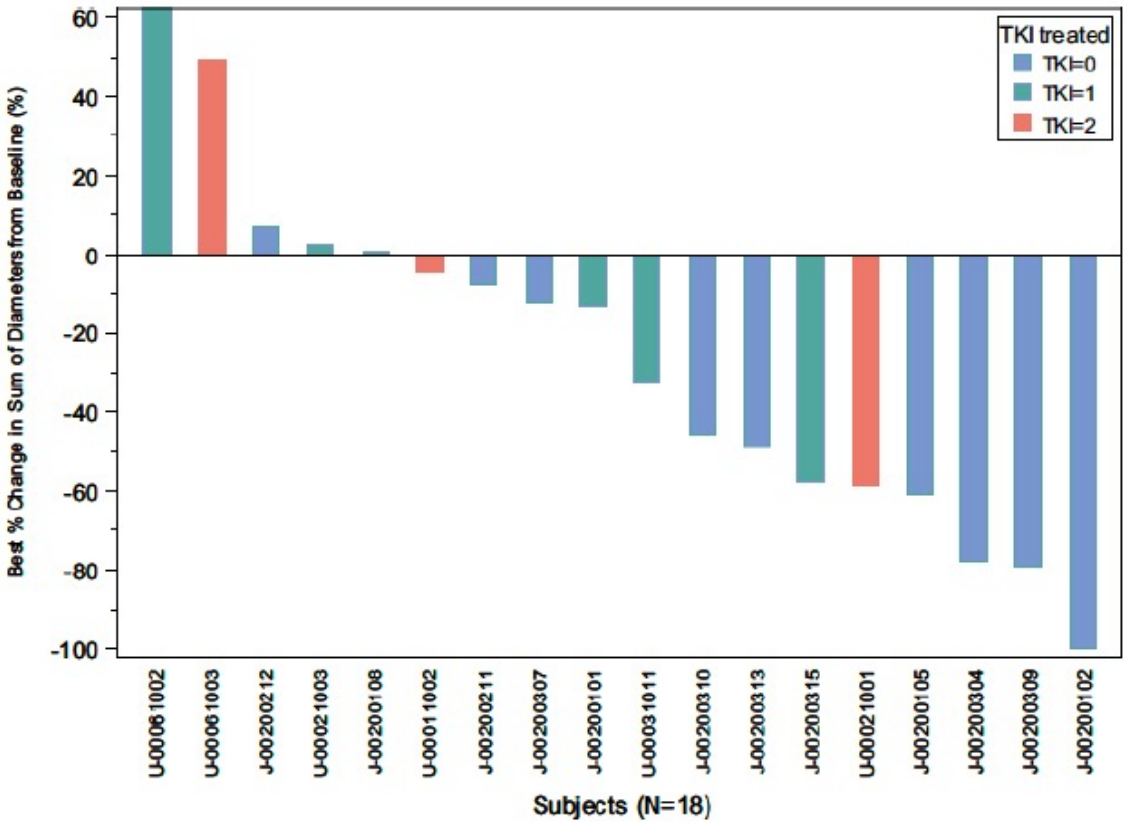
- *ROS1* G2032R identified by plasma cfDNA or tissue NGS test in 5 patients who had prior crizotinib treatment
- All 5 patients experienced tumor regressions on repotrectinib
- **Confirmed ORR: 2/5 (40%)**
  - 2/3 (67%) for 160 mg QD and above with 1 prior TKI
    - 1 cPR at 160 mg QD with food (DOR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

Courtesy of Prof Solange Peters, MD, PhD

Taletrectinib (DS-6051b)

- Taletrectinib is a **ROS1/TRK inhibitor with activity against *ROS1* G2032R SFM** and L2026M gatekeeper mutation **in preclinical studies** (Katayama et al.)
- In the Japanese phase 1 study, among 9 patients with crizotinib-naïve advanced ROS1+ NSCLC, ORR was 66.7% (Fujiwara et al.)
  - ORR 33.3% among 3 crizotinib-pretreated patients
- US phase 1 study results (Papadopoulos et al.):
  - **Crizotinib-refractory ROS1+ NSCLC evaluable for response (n=6): ORR 33%** (95% CI, 9.7-70); **median PFS 4.1 months**

Pooled analysis of US and Japanese pI studies (response by number of prior ROS1 TKIs)



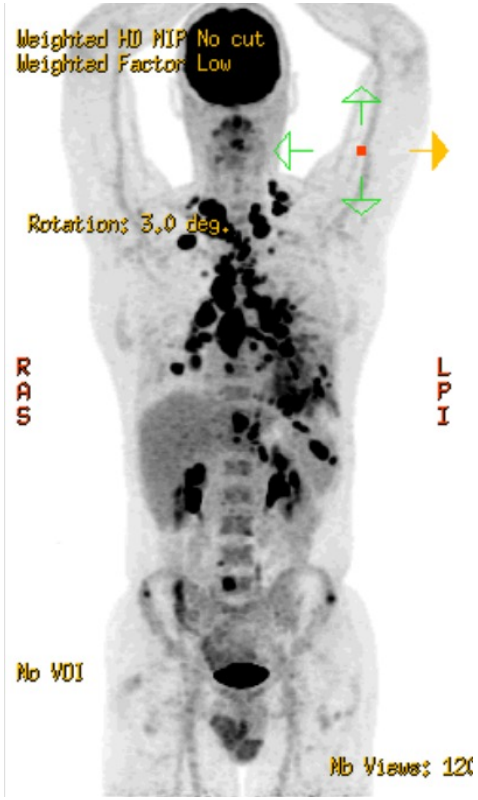
ROS1 TKI-naïve (n=9): cORR 66.7% (95% CI 35.4-87.9)
Crizotinib-refractory (n=6): cORR 33.3% (95% CI 9.7-70.0)
Two prior ROS1 TKIs (n=3): cORR 33.3% (95% CI 6.1-79.2)

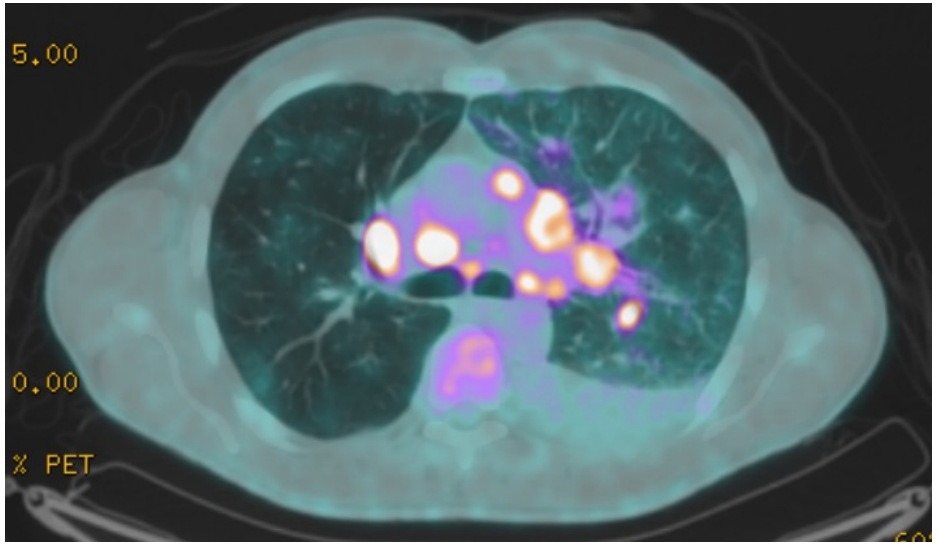
Katayama R et al., Nat Commun 2019; 10:3604
Fujiwara Y et al., Oncotarget 2018; 9:23729-37
Papadopoulos K et al., Clin Cancer Res 2020; 26:4785-94

Courtesy of Prof Solange Peters, MD, PhD

Case Medical history 1971

- Young English teacher, excellent general state, never smoker
- Very sportive – progressive limitations in running performances
- Progressive cough and fatigue
- Family doctor asks for a CT scan then a PET/CT, early 2015

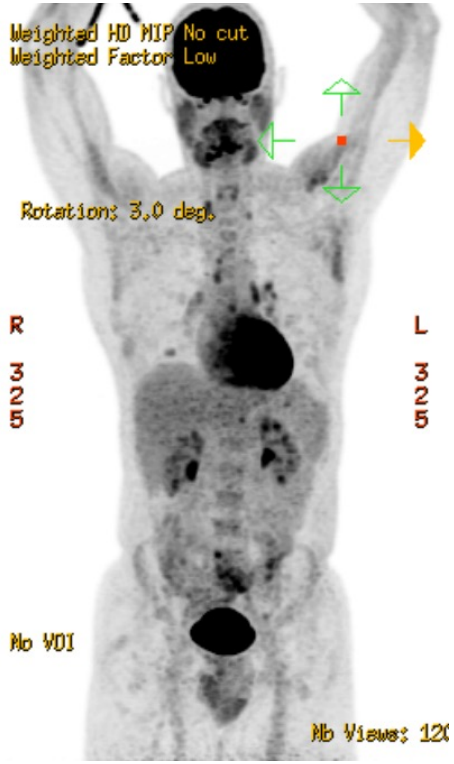


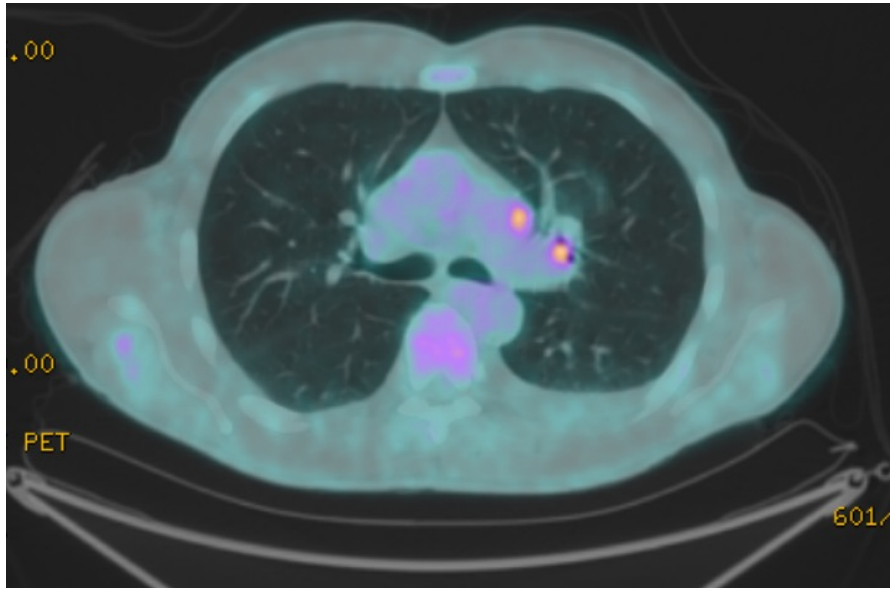


Courtesy of Prof Solange Peters, MD, PhD

Supraclavicial node biopsy

- Adenocarcinoma, solid & acinar, TTF-1 positive, EGFR WT
- IHC positive for ALK
- No brain lesions at MRI
- Emergency crizotinib introduction for rapidly worsening general symptoms. PET-CT after 6 weeks

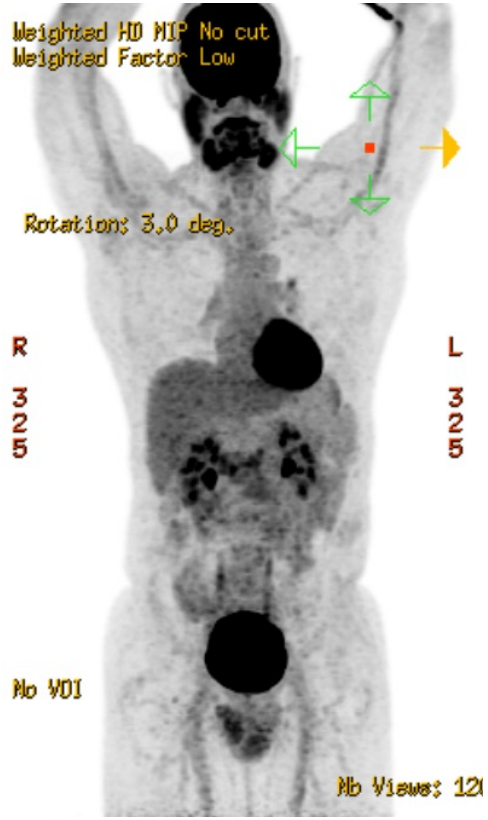


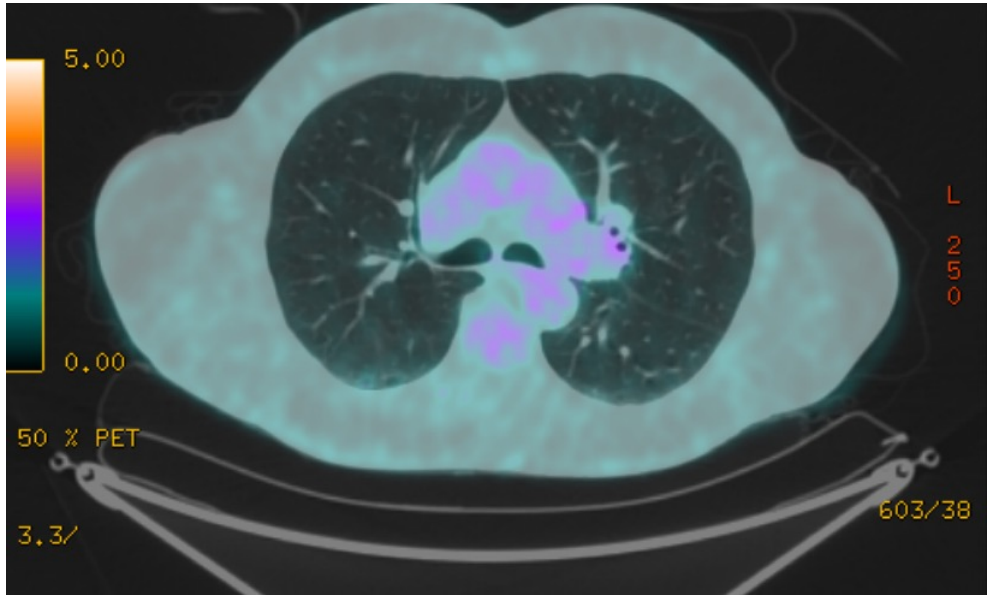


Courtesy of Prof Solange Peters, MD, PhD

After 9 months

- CR, no brain lesion at MRI
- Resuming of a normal life, despite some nausea grade 1 and visual disturbances, running, and working 100%

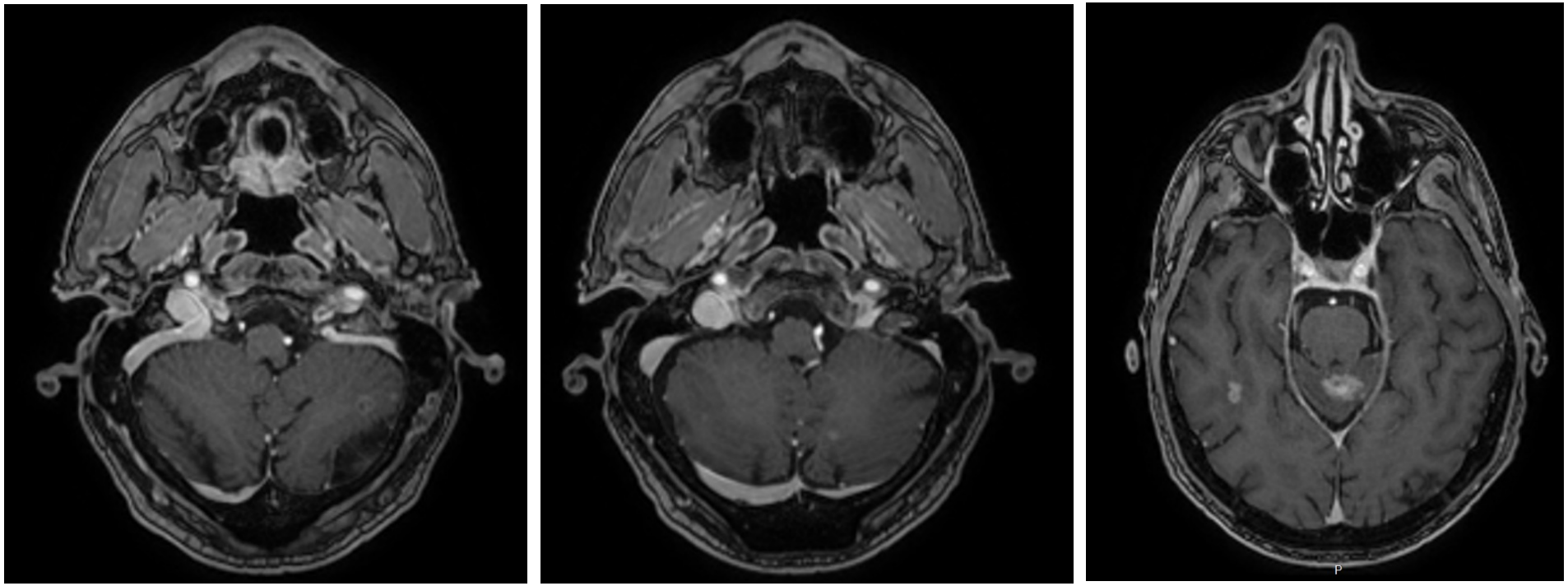




Courtesy of Prof Solange Peters, MD, PhD

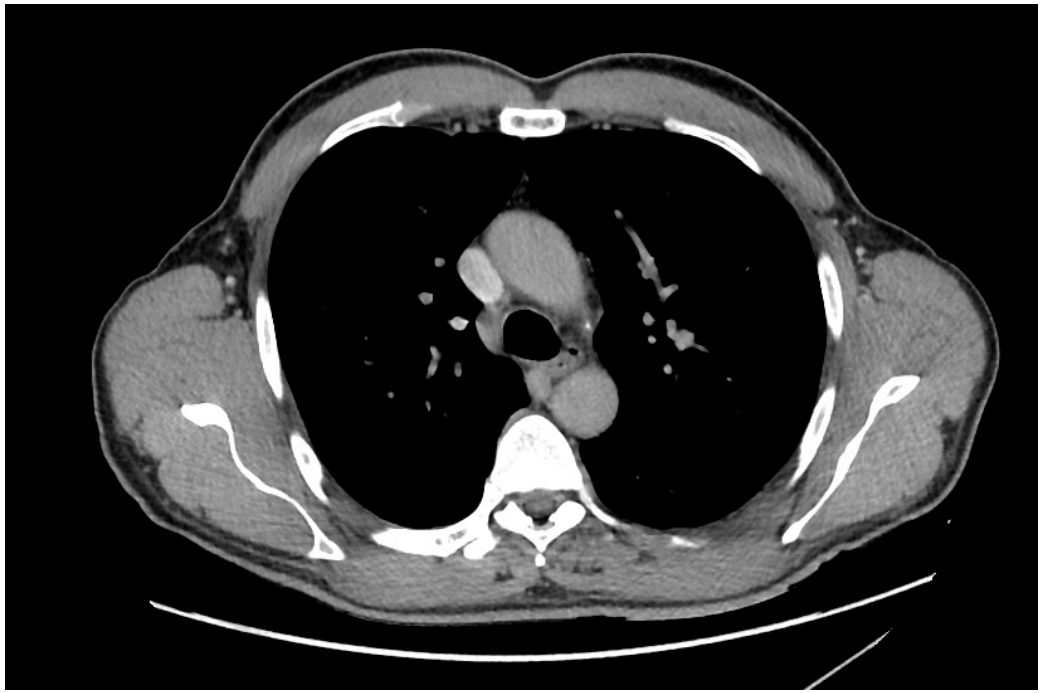
After 18 months

- No significant general symptoms
- Evokes some episodes of dizziness after running
- PET/CT: persistence of a CR.
- But…



Courtesy of Prof Solange Peters, MD, PhD

At Disease Progression

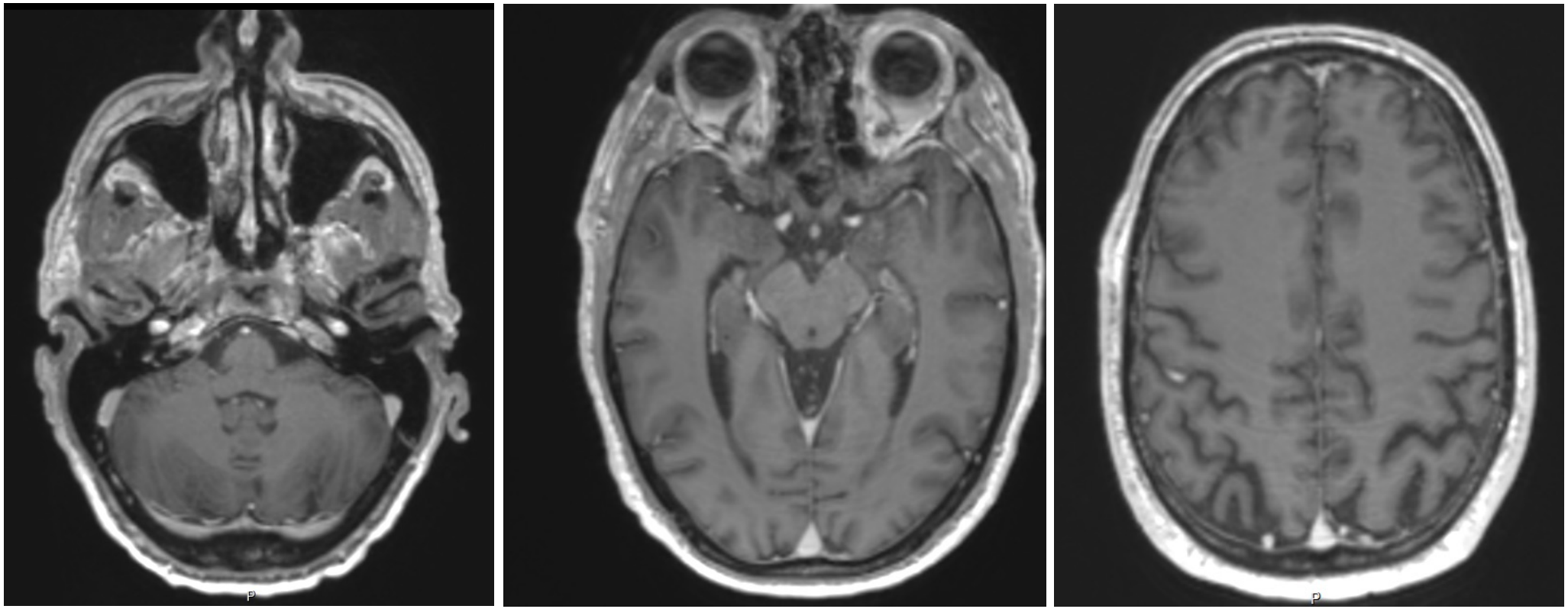


- No systemic relapse
- Introduction of alectinib 600mg bid
- Complete disappearance of dizziness and fatigue in 4 weeks

Courtesy of Prof Solange Peters, MD, PhD

Today, > 5 years later

- Complete remission, working 100%
- Teaching sports again, despite some fluctuating myalgia and significant photosensitivity



Courtesy of Prof Solange Peters, MD, PhD