Targeting Molecular Fusions in Advanced NSCLC in 2021: ALK, ROS1, NTRK

Corey J. Langer, MD, FACP

Director of Thoracic Oncology

Abramson Cancer Center

Professor of Medicine

University of Pennsylvania

Philadlephia, PA 19104

Disclosures: past 10 yrs

- **Institutional Grant/Research Support**:
  - Pfizer, Lilly, Advantagene, Inovio, Celgene, Vertex, Ariad (Takeda), Merck, Stemcentrex, Genentech/Roche, AstraZeneca, Trizell, GSK, Guardant
- **Scientific Advisor:**
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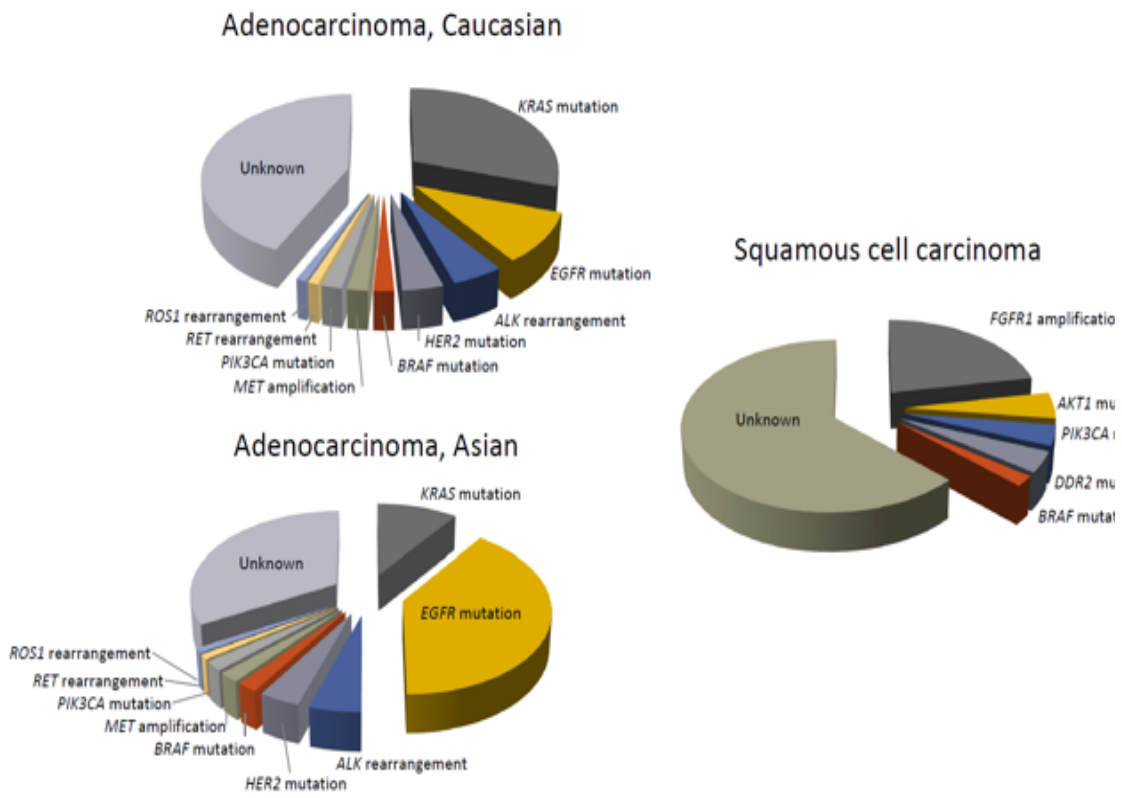
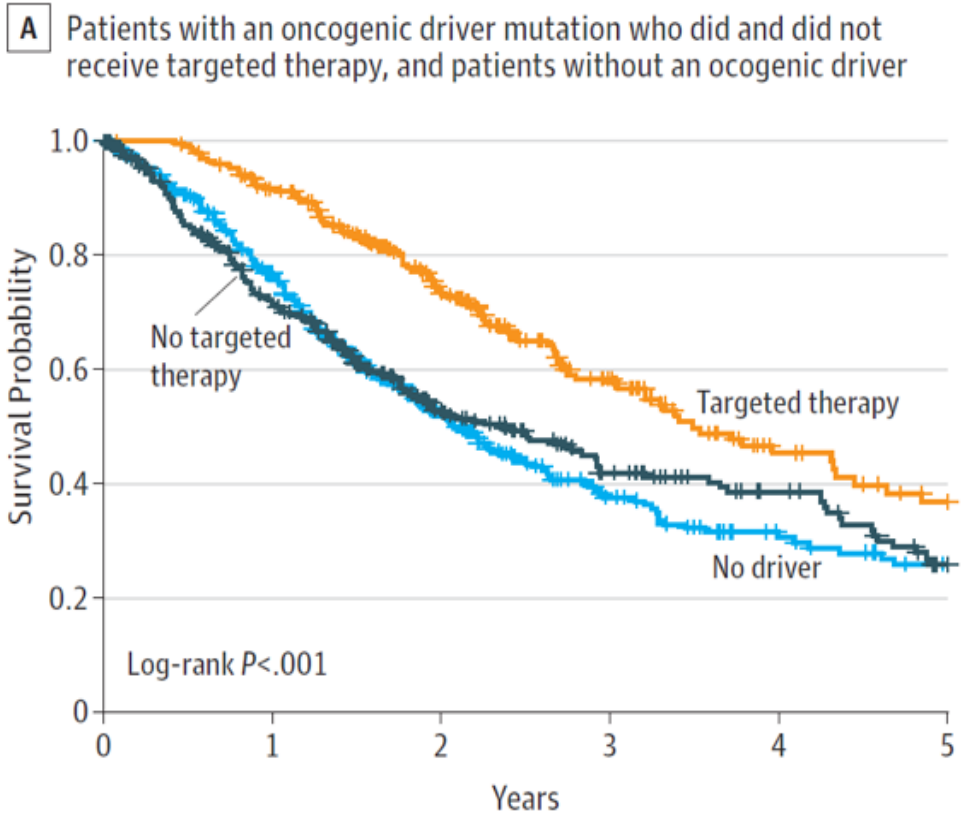
- **Data Safety Monitoring Committees:**
  - Lilly, Amgen, Peregrine, Incyte, SWOG, Oncocyte

Objectives

- Describe guideline-directed recommendations for ALK, ROS1, and NTRK
- Review toxicities of Indicated TKIs
- Delineate Mechanisms of Resistance

Target Directed Therapy Improves OS

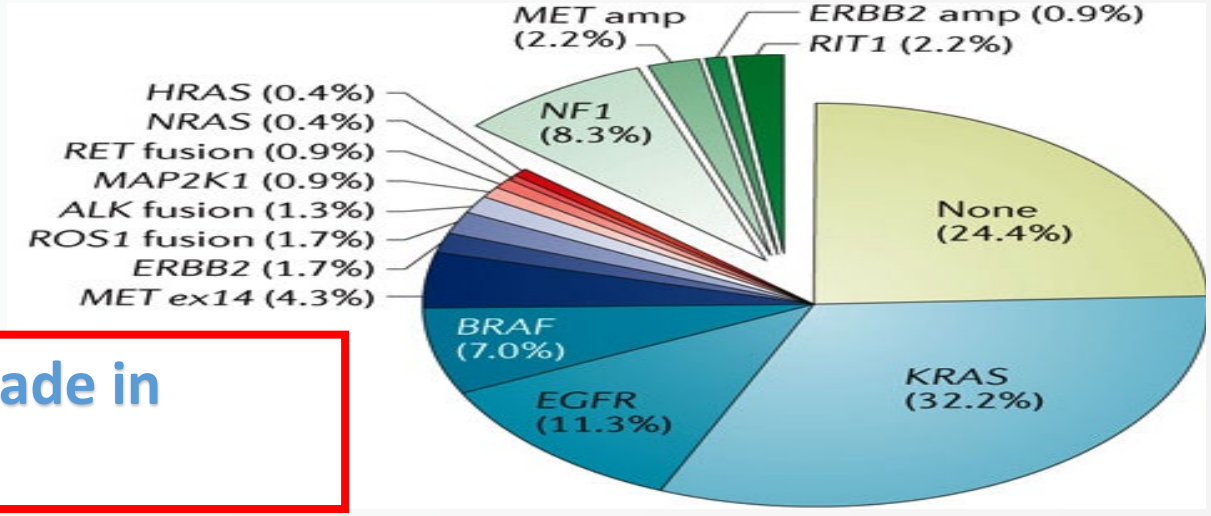




- Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs.
- Kris MG[1], Johnson BE[2], Berry LD[3], Kwiatkowski DJ[4], Iafrate AJ[5], Wistuba II[6], Varella-Garcia M[7], Franklin WA[7], Aronson SL[8], Su PF[3], Shyr Y[3], Camidge DR[7], Sequist LV[5], Glisson BS[6], Khuri FR[9], Garon EB[10], Pao W[3], Rudin C[11], Schiller J[12], Haura EB[13], Socinski M[14], Shirai K[15], Chen H[3], Giaccone G[16], Ladanyi M[1], Kugler K[7], Minna JD[12], Bunn PA[7].
- JAMA. 2014 May 21;311(19):1998-2006. doi: 10.1001/jama.2014.3741.

Targeted Therapy in NSCLC: FDA approvals

Lung Cancer is COMPLEX

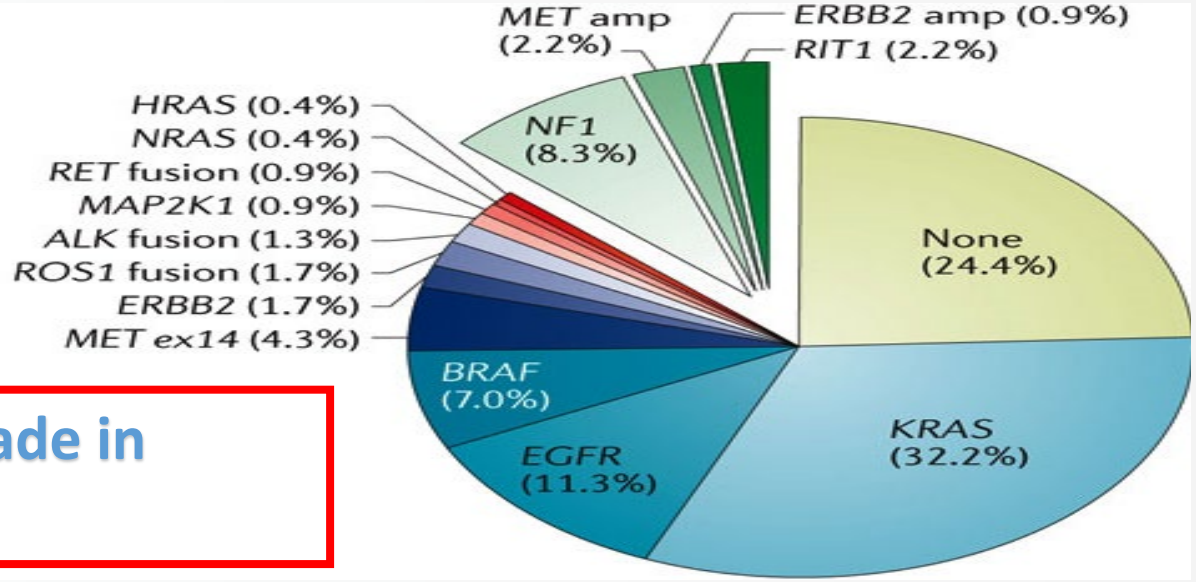


Tremendous progress has been made in personalized therapy

EGFR	ALK	ROS1	BRAF	MET	RET	TRK	KRAS G12C
Erlotinib	Crizotinib	Crizotinib	Dabrafenib	Crizotinib	Vandetanib	**Larotrectinib**	**Sotoroasib**
Gefitinib	Ceritinib	**Entrectinib**	Vemurafenib	**Tepotinib**	Cabozantinib	**Entrectinib**	
Afatinib	Brigatinib		Trametinib	**Capmatinib**	**Selpercatinib**		
Osimertinib	Alectinib				**Pralsetinib**		
Dacomitinib	**Lorlatinib**						
Ramu + Erl							
Amivantamab							
Mobocertinib							

Targeted Therapy in NSCLC: FDA approvals

Lung Cancer is COMPLEX



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Erlotinib	Crizotinib	Crizotinib	Dabrafenib	Crizotinib	Vandetanib	**Larotrectinib**	**Sotoroasib**
Gefitinib	Ceritinib	**Entrectinib**	Vemurafenib	**Tepotinib**	Cabozantinib	**Entrectinib**	
Afatinib	Brigatinib		Trametinib	**Capmatinib**	**Selpercatinib**		
Osimertinib	Alectinib				**Pralsetinib**		
Dacomitinib	**Lorlatinib**						
Ramu + Erl							
Amivantamab							

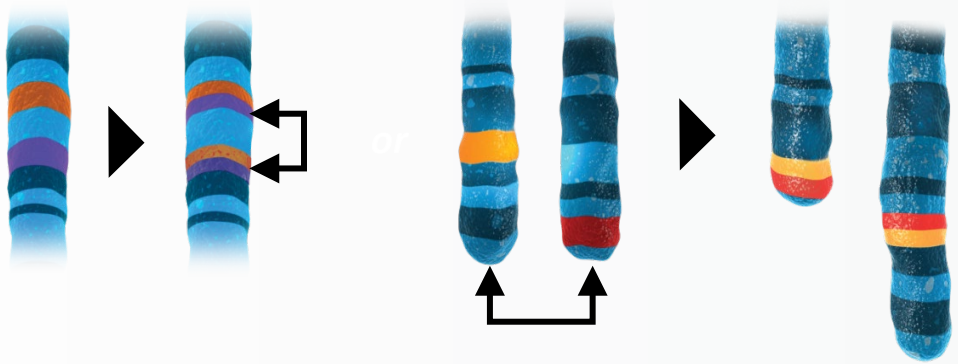
ALK-Rearranged Lung Cancer

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]

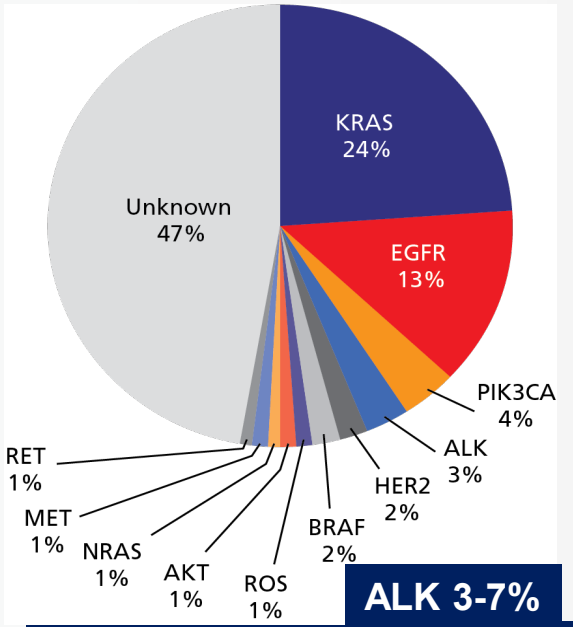
Inversion

Translocation



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

Lung Cancer

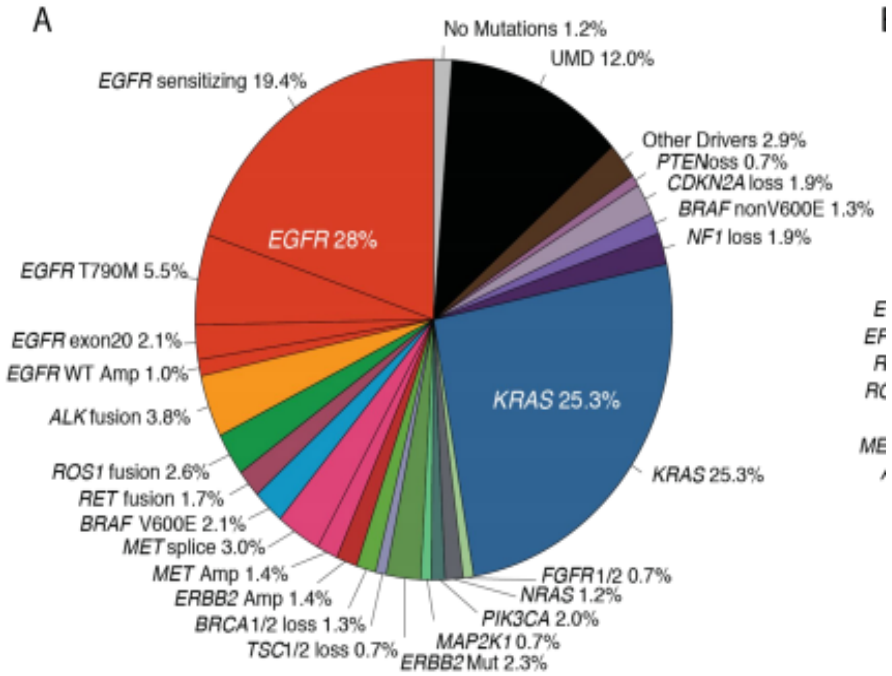


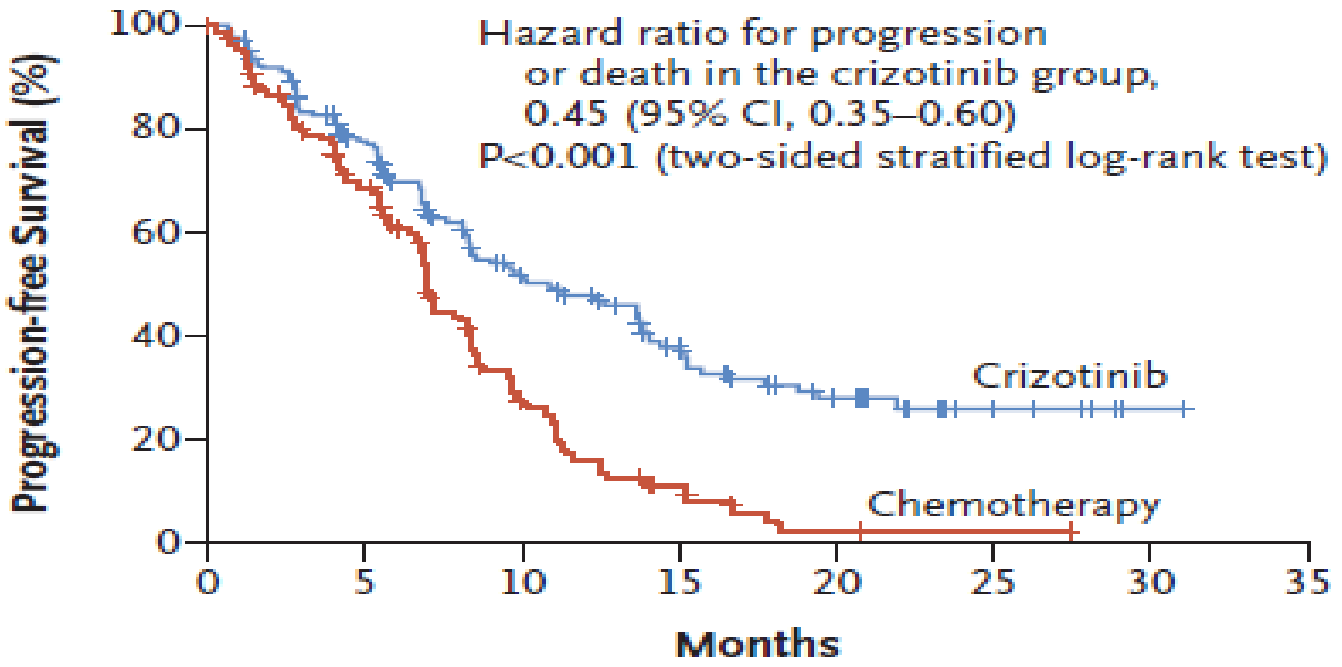
ALK 3-7%

ALK-positive patients:

- Never or minimal smokers
- Young (average age 50 y)
- Adenocarcinoma type (signet ring morphology)
- Poor prognosis without Tx

Targeted Therapy Consistently Superior to Chemotherapy



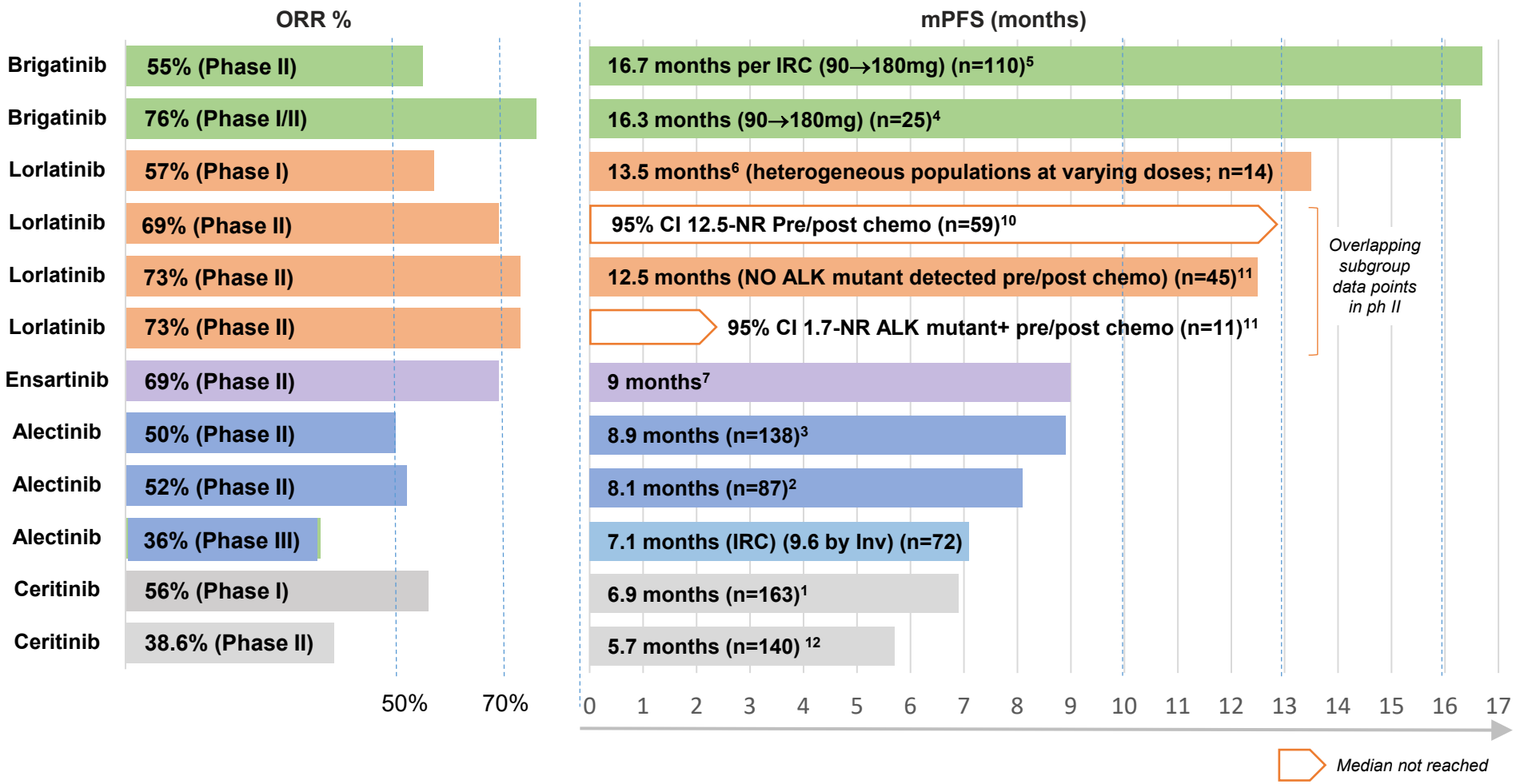


- Jordan Ca Disc 2017
- Shaw NEJM 2013

Next-generation ALK TKI efficacy: Indirect comparison* post-crizotinib (+/- prior chemo)

PFS REMARKABLY consistent across trials for same drug but differs by drug, despite 'similar' ORR

Differ in control of CNS? Differ in suppression of acquired resistance not dominant at baseline? **Including non-ALK mechanisms?**



*Cross-trial comparisons are potentially confounded by differences in trial design and study populations.

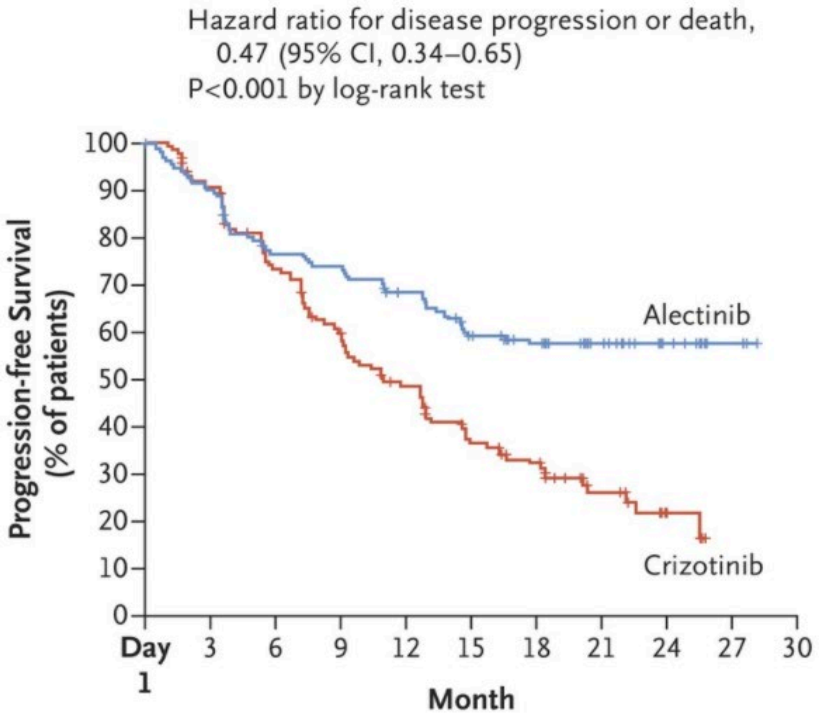
ALK, anaplastic lymphoma kinase; CNS, central nervous system; mPFS, median PFS; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

1. Gadgeel S et al. ESMO 2017 abstract 12990. and associated presentation. 2. Shaw AT, et al. Lancet Oncol. 2016;17:234–242.. 3. Ou S-HI, et al. J Clin Oncol. 2015;34:661–668. 4. Bazehnova LA, et al. Annals of Oncology. 2017;28(suppl_5):479-480. 5. Ahn MJ, et al. Journal of Thoracic Oncology. 2017;12(11S2):S1755-S1756. 6. Shaw et al, TLO 2017 ('1 previous TKI'); 7. Crino et al, JCO 2016 ASCEND 2; 8. ALUR Novello, ESMO 2017; 9. Shaw et al, AACR 2018; 10. Solomon et al, WCLC 2017; 11. Horn et al CCR 2018; 11. Shaw et al, AACR 2018 12. Crino L et al. J Clin Oncol 2016; 34: 2866-73

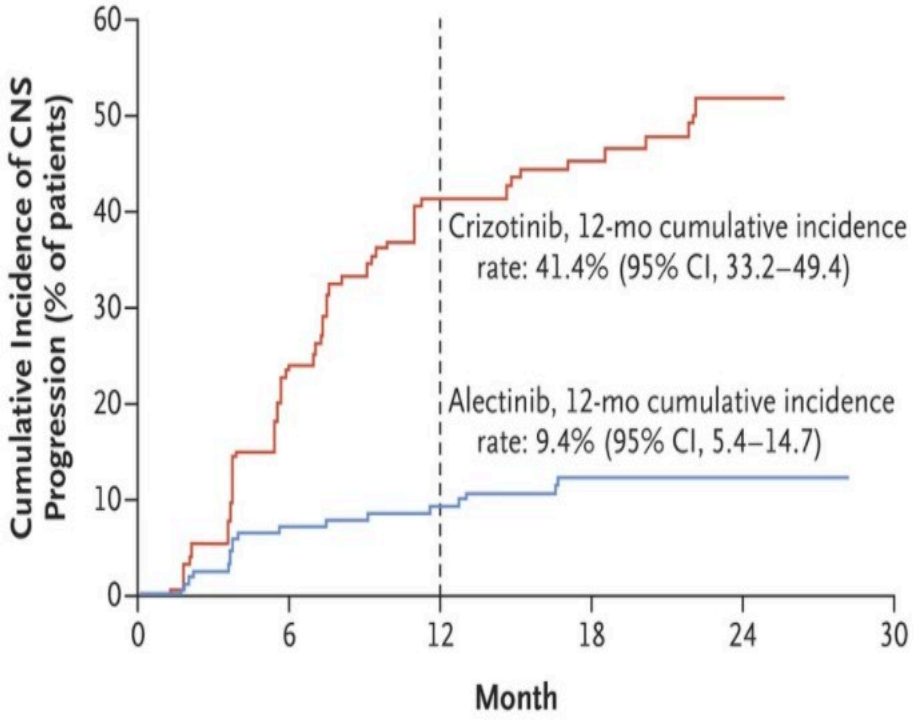
Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Shirish Gadgeel, M.D., Jin S. Ahn, M.D., Dong-Wan Kim, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Maurice Pérol, M.D., Rafal Dziadziuszko, M.D., Rafael Rosell, M.D., Ph.D., Ali Zeaiter, M.D., Emmanuel Mitry, M.D., Ph.D., et al., for the ALEX Trial Investigators*

A Progression-free Survival



C Cumulative Incidence of CNS Progression

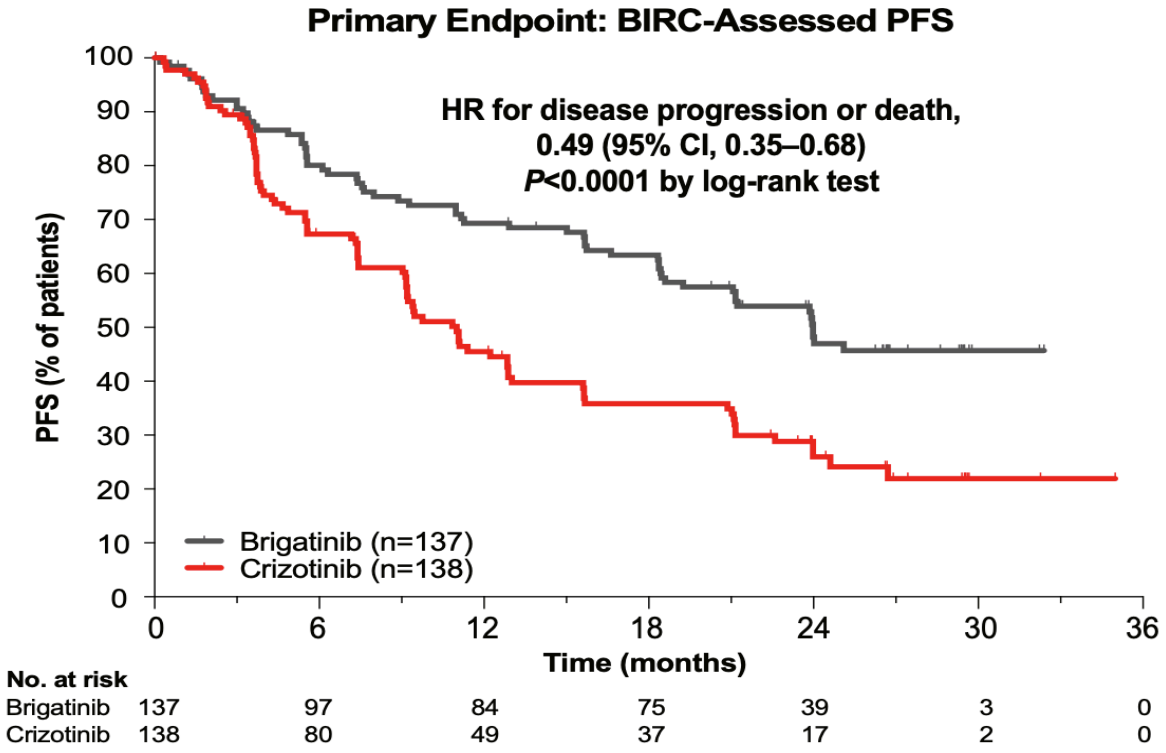


Peters et al, ESMO 2020

Presentation ID 1300P

Efficacy of brigatinib (BRG) vs crizotinib (CRZ): Updated results from the ALTA-1L trial

Figure 2. Updated Overall BIRC-Assessed PFS



Treatment	No. (%) of Patients With Events		Median PFS, mo (95% CI)
	Progression	Death	
Brigatinib (n=137)	56 (41)	7 (5)	24.0 (18.5–NR)
Crizotinib (n=138)	82 (59)	5 (4)	11.0 (9.2–12.9)

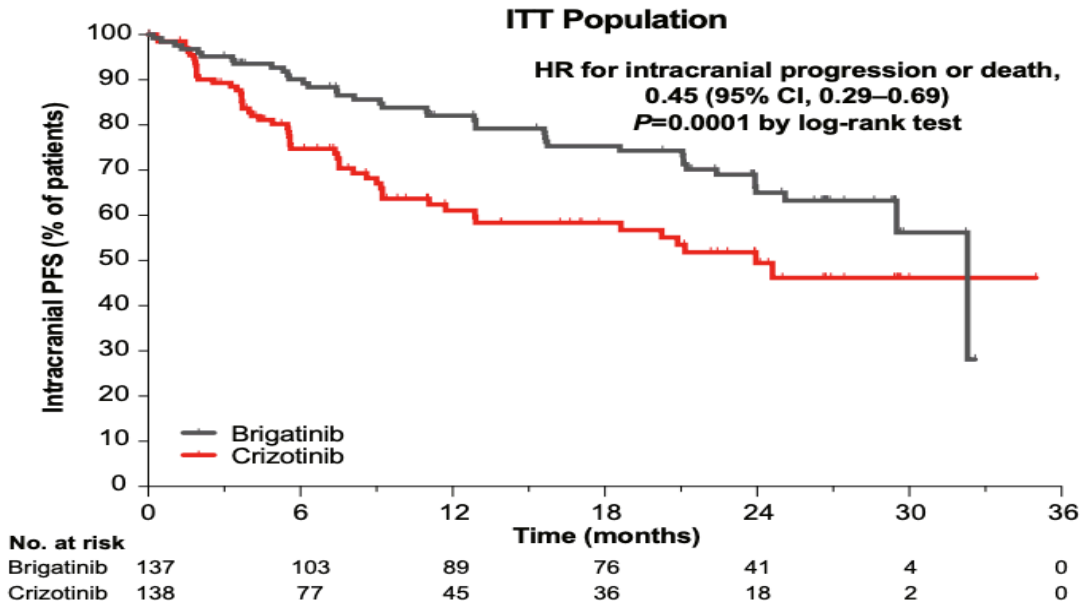
BIRC-Assessed PFS Event-Free Rate		
ITT Population, % (95% CI)	Brigatinib n=137	Crizotinib n=138
2 months	93 (87–96)	91 (85–95)
4 months	87 (79–91)	75 (66–81)
6 months	80 (72–86)	67 (58–75)
12 months	69 (60–77)	46 (36–54)
18 months	63 (54–71)	36 (27–45)
24 months	48 (39–57)	26 (18–35)

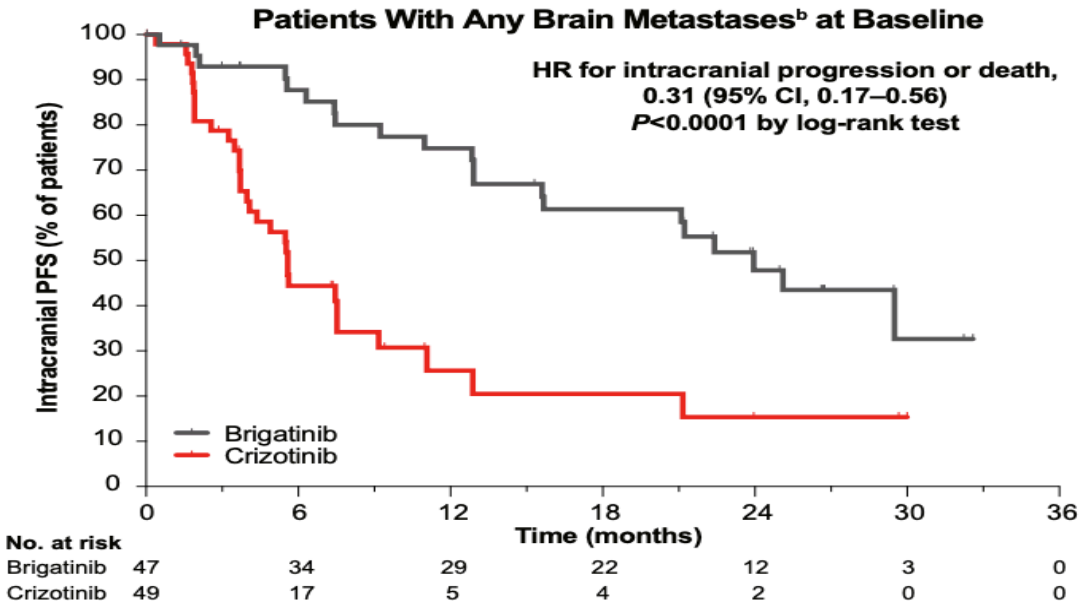
Popat et al, ESMO 2020

Presentation ID 1300P

Intracranial efficacy of brigatinib (BRG) vs crizotinib (CRZ): Updated results from the ALTA-1L trial

Figure 4. Updated BIRC[a]-Assessed Intracranial PFS





Treatment	No. (%) of Patients With Events		Median Intracranial PFS, mo (95% CI)	2-Year PFS, % (95% CI)
	Intracranial Progression	Death		
Brigatinib (n=137)	30 (22)[c]	10 (7)	32.3 (29.5–NR)	65 (55–73)
Crizotinib (n=138)	45 (33)[d]	6 (4)	24.0 (12.9–NR)	50 (38–60)

Treatment	No. (%) of Patients With Events		Median Intracranial PFS, mo (95% CI)	2-Year PFS, % (95% CI)
	Intracranial Progression	Death		
Brigatinib (n=47)	21 (45)[c]	0	24.0 (12.9–NR)	48 (30–63)
Crizotinib (n=49)	29 (59)[e]	3 (6)	5.6 (3.7–7.5)	15 (5–32)

[a] Intracranial reviewers were independent from systemic reviewers. Only brain lesions were reviewed. Patients were counted as having an event if there was radiologic progression, radiotherapy to the brain, or death. [b] Per BIRC assessment. [c] Includes 1 patient with radiotherapy to the brain. [d] Includes 5 patients with radiotherapy to the brain. [e] Includes 2 patients with radiotherapy to the brain

Popat et al, ESMO 2020

Presentation ID LBA2
Lorlatinib vs Crizotinib in the First-line Treatment of Patients with Advanced ALK-Positive NSCLC: Results of the Phase 3 CROWN Study

VIRTUAL 2020 ESMO congress

CROWN Study Design

Key Eligibility
- Stage IIIB/IV *ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST v1.1) with no prior radiation required

Randomized 1:1

Lorlatinib 100 mg QD n=149

Crizotinib 250 mg BID n=147

Stratified by
- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

Primary endpoint
- PFS* by BICR

Secondary endpoints
- PFS by investigator
- ORR by BICR and investigator
- IC-ORR, DR and IC-DR by BICR
- IC-time to progression by BICR
- OS
- Safety
- QoL

No crossover between treatment arms was permitted

*Defined as the time from randomization to RECIST-defined progression or death due to any cause.

BICR, blinded independent central review; DR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.
ClinicalTrials.gov number, NCT03052608

Solomon et al, ESMO 2020

Presentation ID LBA2
Lorlatinib vs Crizotinib in the First-line Treatment of Patients with Advanced ALK-Positive NSCLC: Results of the Phase 3 CROWN Study

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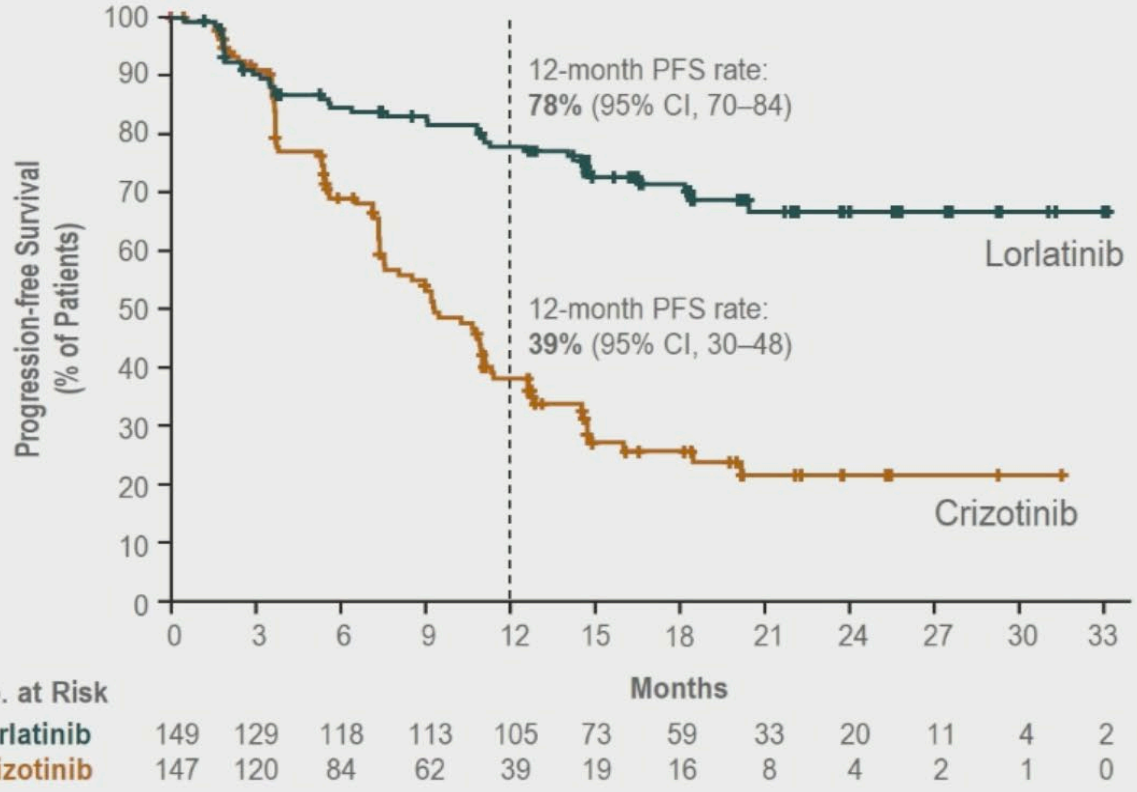
Primary Endpoint: PFS by BICR



	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.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival

Solomon et al, ESMO 2020

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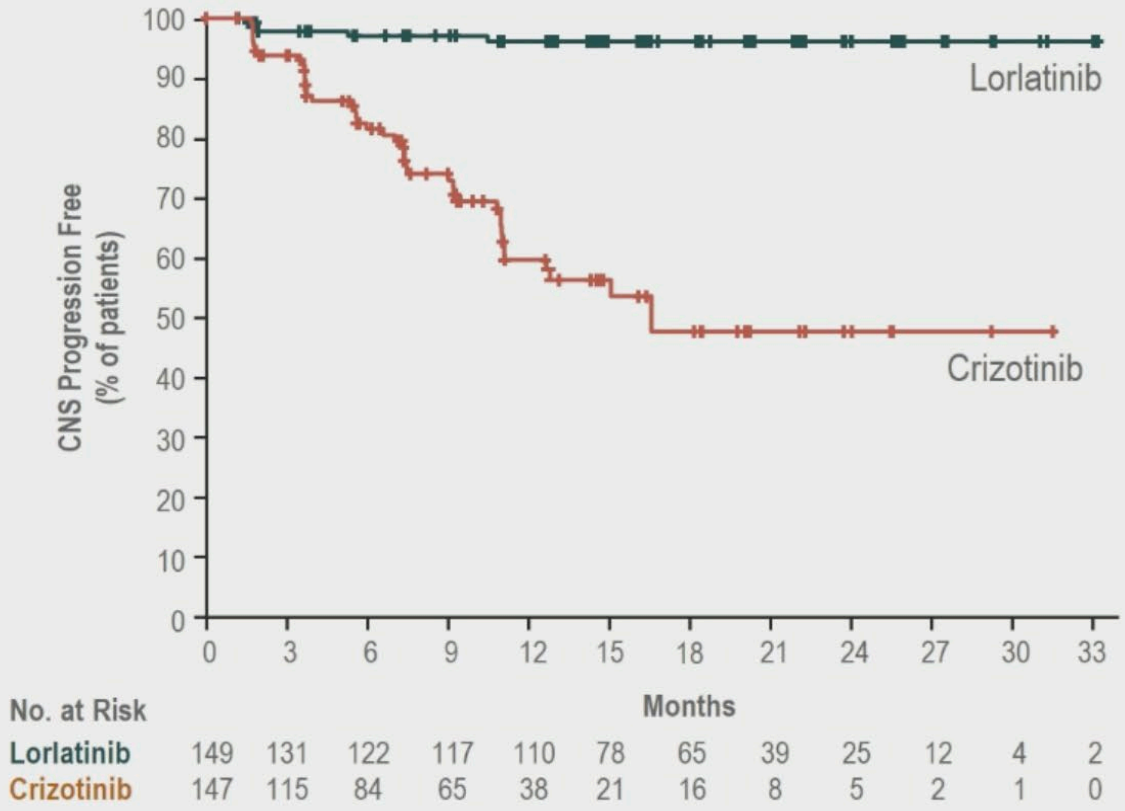
Intracranial Time to Progression by BICR



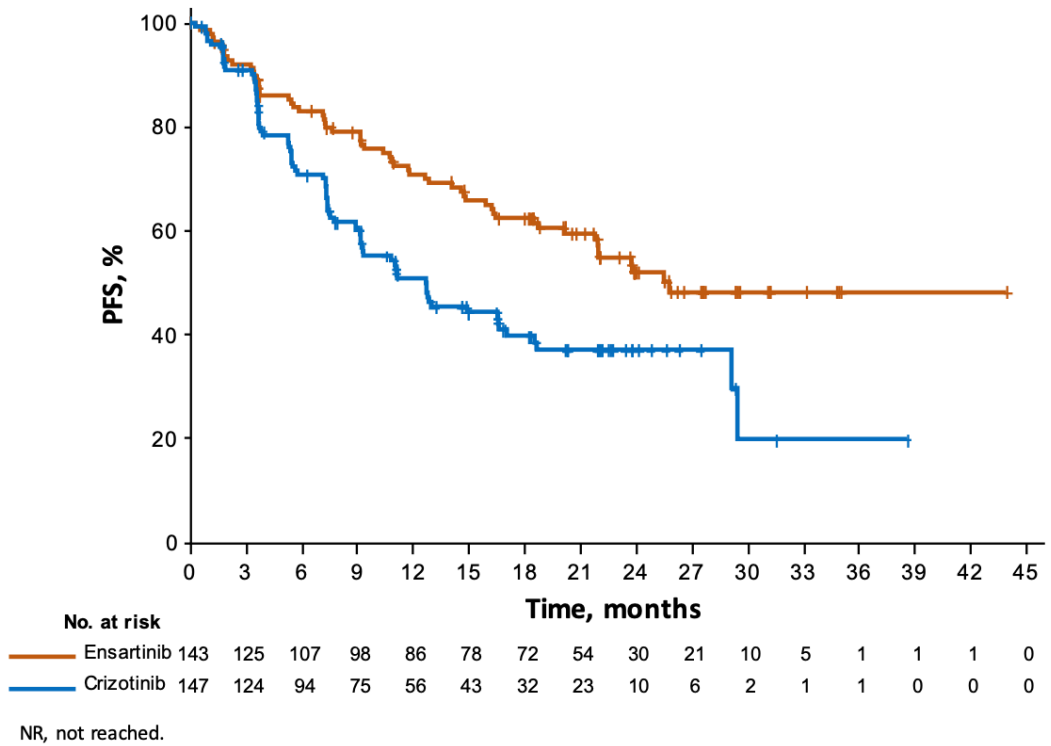
	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	5 (3)	45 (31)
Median time to CNS progression, months (95% CI)	NE (NE–NE)	16.6 (11.1-NE)
HR (95% CI) 1-sided P value*	0.07 (0.03-0.17) <0.001	

*By stratified log-rank test.

Solomon et al, ESMO 2020

Phase 3 Randomized Study of Ensartinib vs Crizotinib in Anaplastic Lymphoma Kinase (ALK)–Positive NSCLC Patients: eXalt3

BIRC-Assessed mPFS (ITT)



NR, not reached.

	Ensartinib (n = 143)	Crizotinib (n = 147)
mPFS (95% CI), mo	**25.8** (21.8-NR)	**12.7** (9.2-6.6)
Hazard ratio (95% CI)	**0.51** (0.35-0.72)	
P value (log-rank test)	**.0001**	

	Median follow-up (range), mo
Ensartinib	23.8 (0-44)
Crizotinib	20.2 (0-38)

Horn et al, ESMO 2020

Phase III ALK Studies to date

	ASCEND-4	J ALEX	ALEX	ALESIA	ALTA-1	CROWN	EXALT-3
DRUG	CERITINIB	ALECTINIB	ALECTINIB	ALECTINIB	BRIGATINIB	LORLATINIB	ENSARTINIB
CONTROL ARM	CHEMO	CRIZOTINIB	CRIZOTINIB	CRIZOTINIB	CRIZOTINIB	CRIZOTINIB	CRIZOTINIB
mPFS (mo)	16.6	25.9	34.8	NR	24.0	NR	25.8
Control (mo)	8.1	10.2	10.9	11.1	11.1	9.3	12.7
HR (PFS)	0.55	0.38	0.43	0.22	0.49	0.28	0.51
ORR	72.5	92	83	91	71		

Phase III ALK Studies to date

	ASCEND-4	J ALEX	ALEX	ALESIA	ALTA-1	CROWN	EXALT-3
DRUG	CERITINIB	ALECTINIB	ALECTINIB	ALECTINIB	BRIGATINIB	LORLATINIB	ENSARTINIB
CONTROL ARM	CHEMO	CRIZOTINIB	CRIZOTINIB	CRIZOTINIB	CRIZOTINIB	CRIZOTINIB	CRIZOTINIB
mPFS (mo)	16.6	25.9	34.8	NR	24.0	NR	25.8
Control (mo)	8.1	10.2	10.9	11.1	11.1	9.3	12.7
HR (PFS)	0.55	0.38	0.43	0.22	0.49	0.28	0.51
ORR	72.5	92	83	91	71		

Does PFS benefit translate into improved OS?

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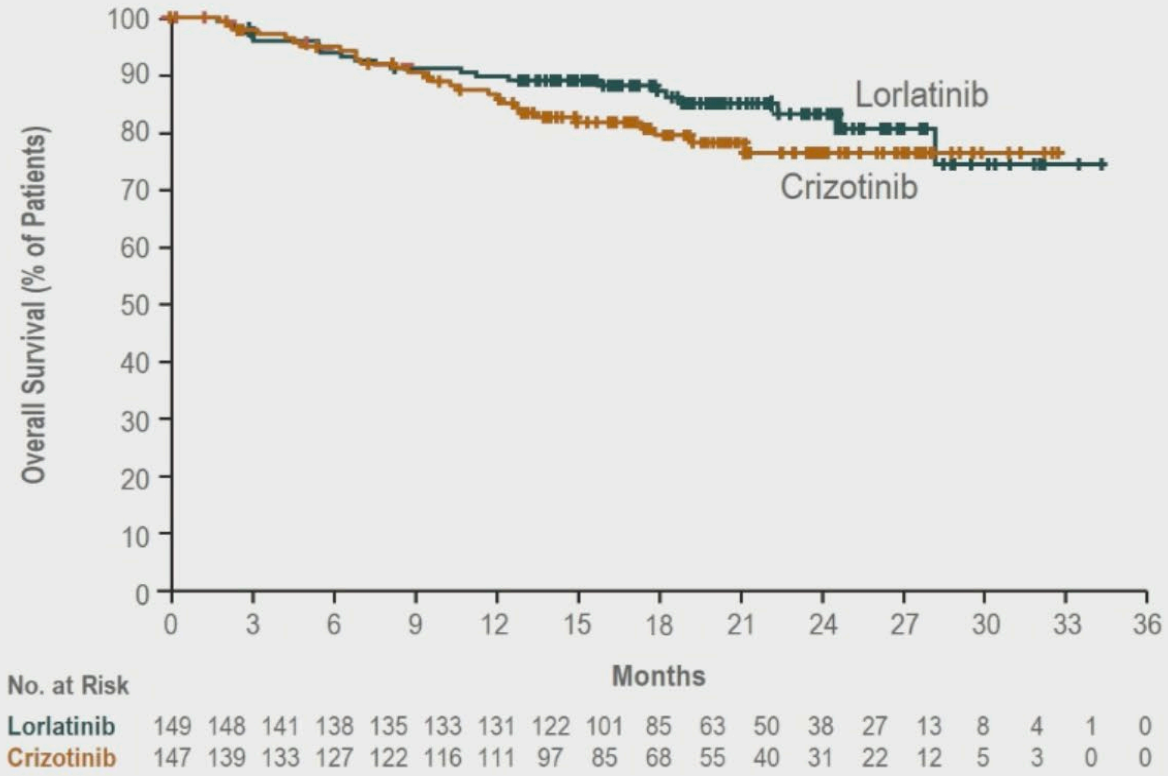
Overall Survival

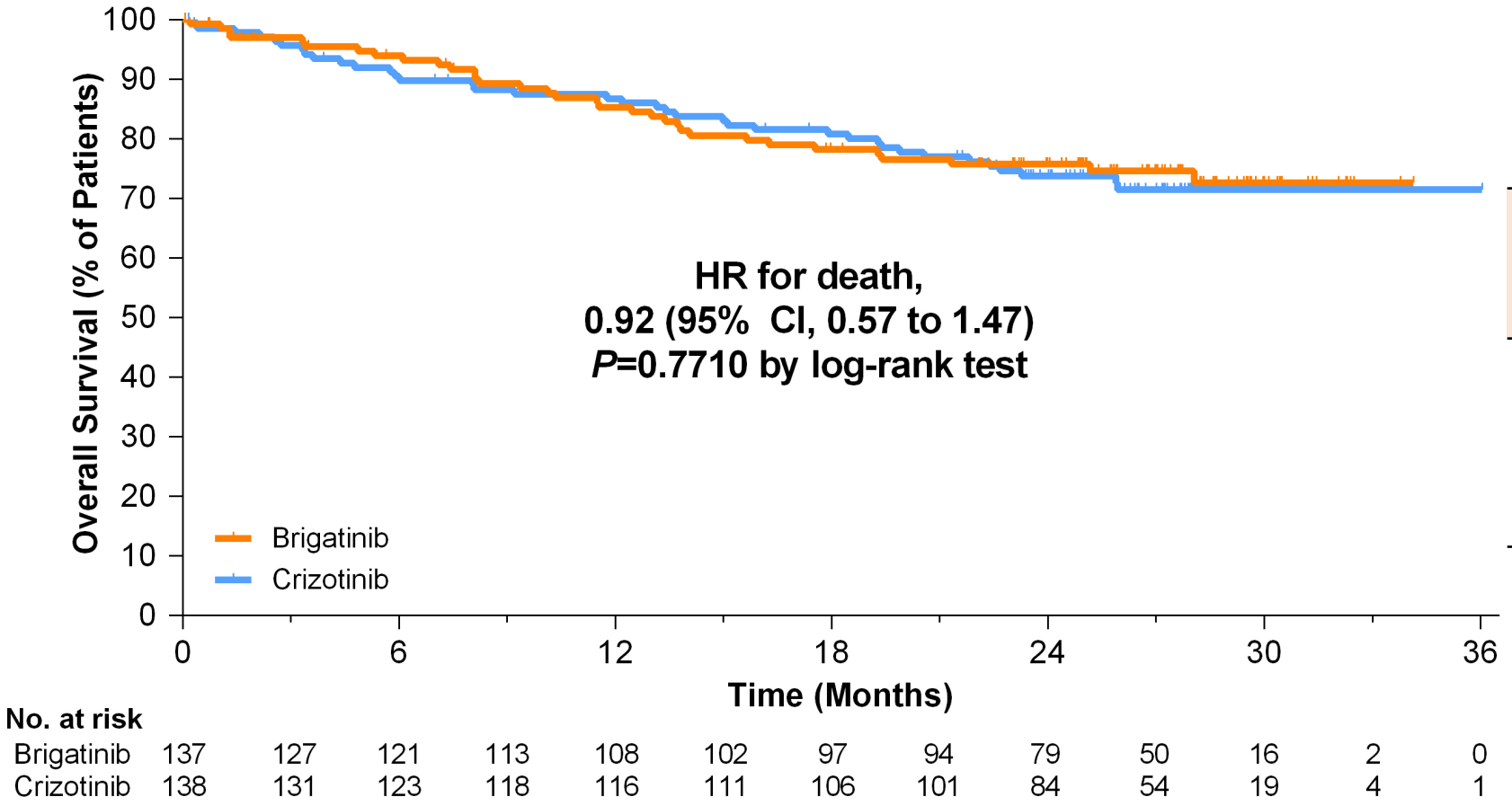


	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	23 (15)	28 (19)
Median OS, months (95% CI)	NE (NE–NE)	NE (NE–NE)
HR (95% CI)	0.72 (0.41-1.25)	

P value for OS was not provided since this is an interim analysis for OS and the efficacy boundary for OS was not crossed
CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival

Solomon et al, ESMO 2020

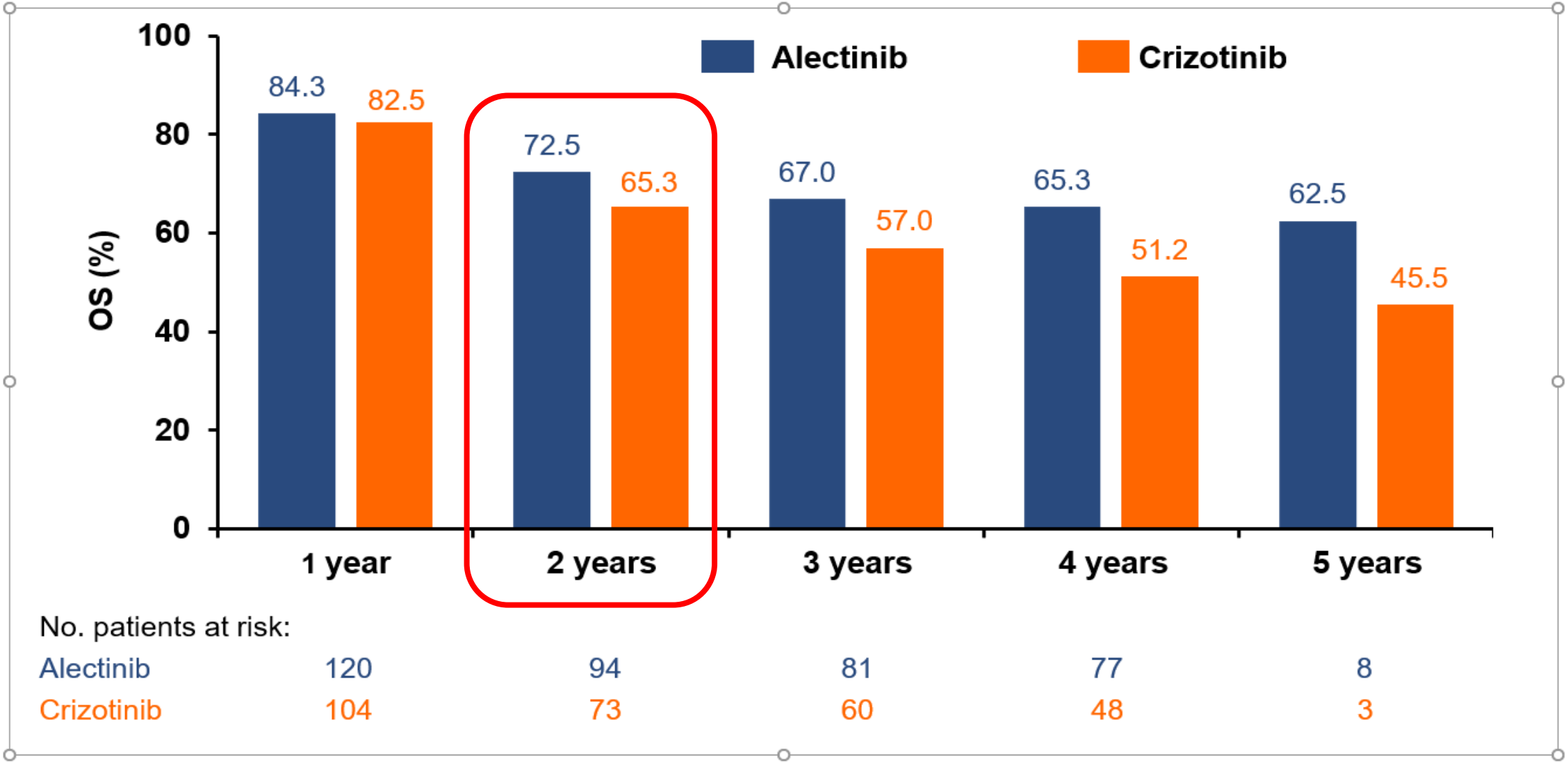
Overall Survival: ALTA-1L ESMO ASIA 2019: Crossover included



Treatment	Deaths, No. (%) of Patients	2-Year Overall Survival, % (95% CI)
Brigatinib (n=137)	33 (24)	76 (67–82)
Crizotinib (n=138)	37 (27)	74 (65–80)

Camidge et al, ESMO 2019

Figure 2. OS-event free rate in the ITT population

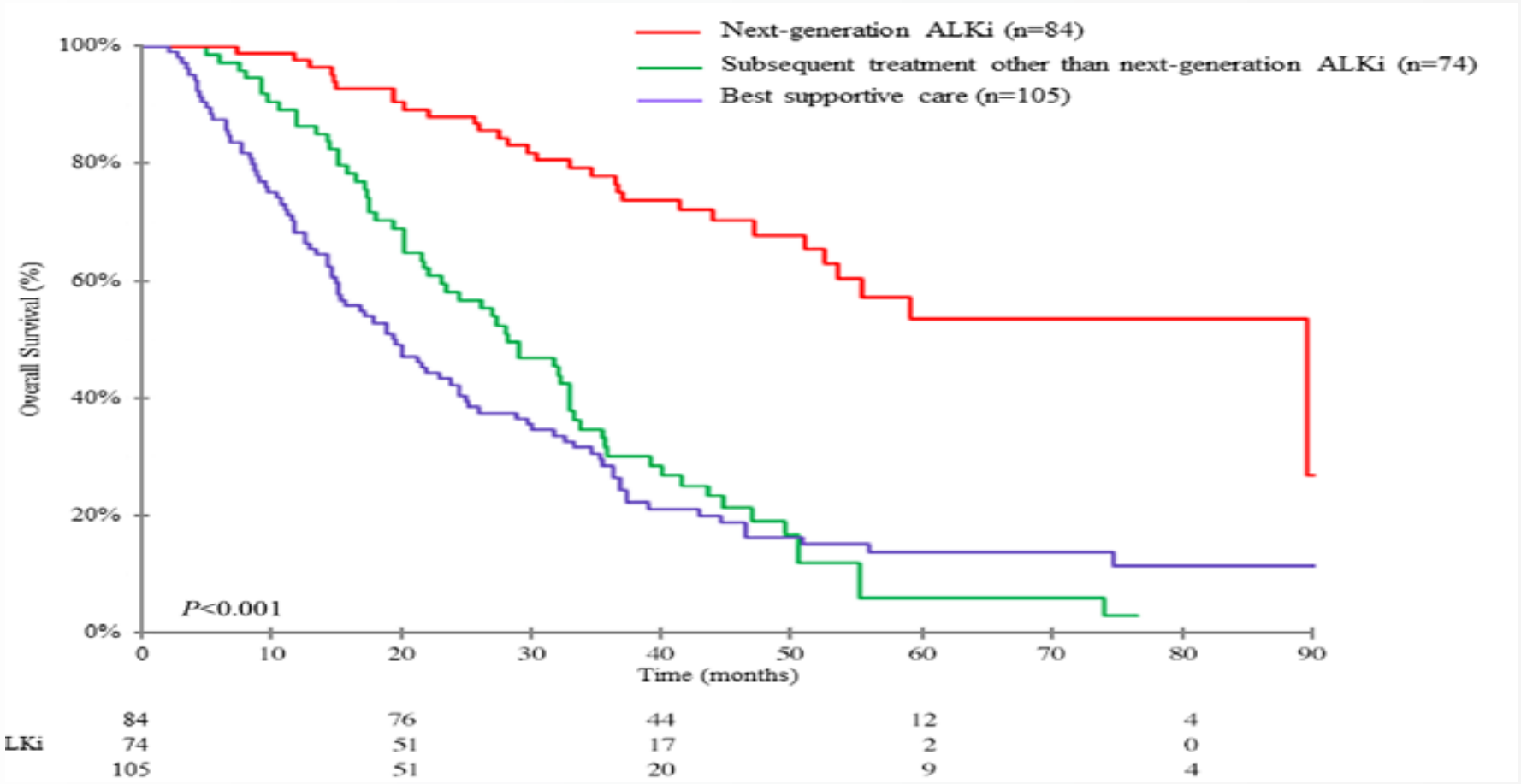


No. patients at risk:

Alectinib	120	94	81	77	8
Crizotinib	104	73	60	48	3

Peters et al, ASCO 2020

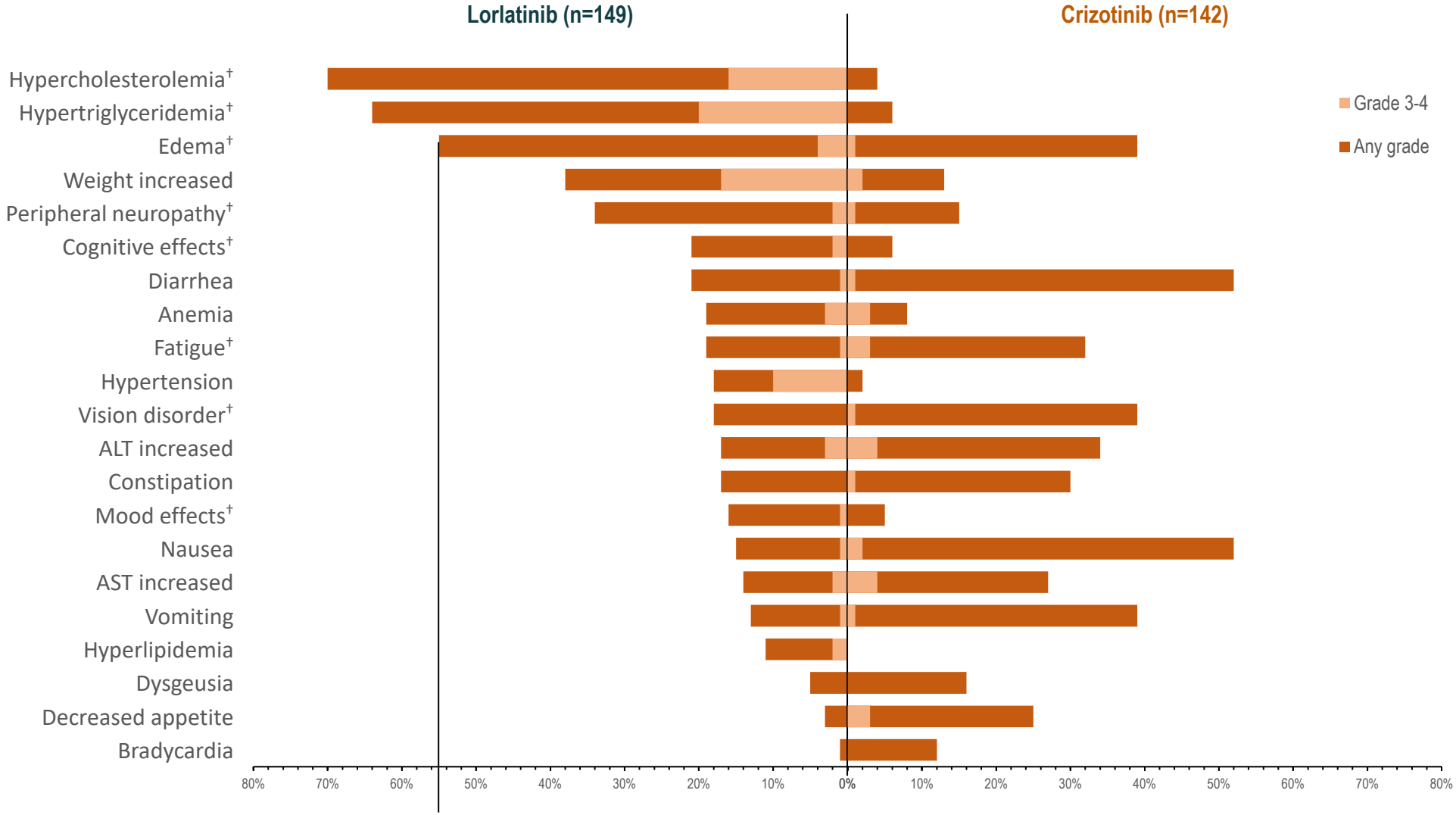
Long survival of *ALK+* NSCLC patients post CRIZ if Tx'd with Next Gen ALK TKI



Next Gen ALK TKI post-criz	mOS 89.6m (53.3 – NR)
Rx but no next gen ALK TKI post-criz	mOS 28.2m (22.1 – 33.0)
BSC post-criz	mOS 19.6m (15.1 – 24.5)

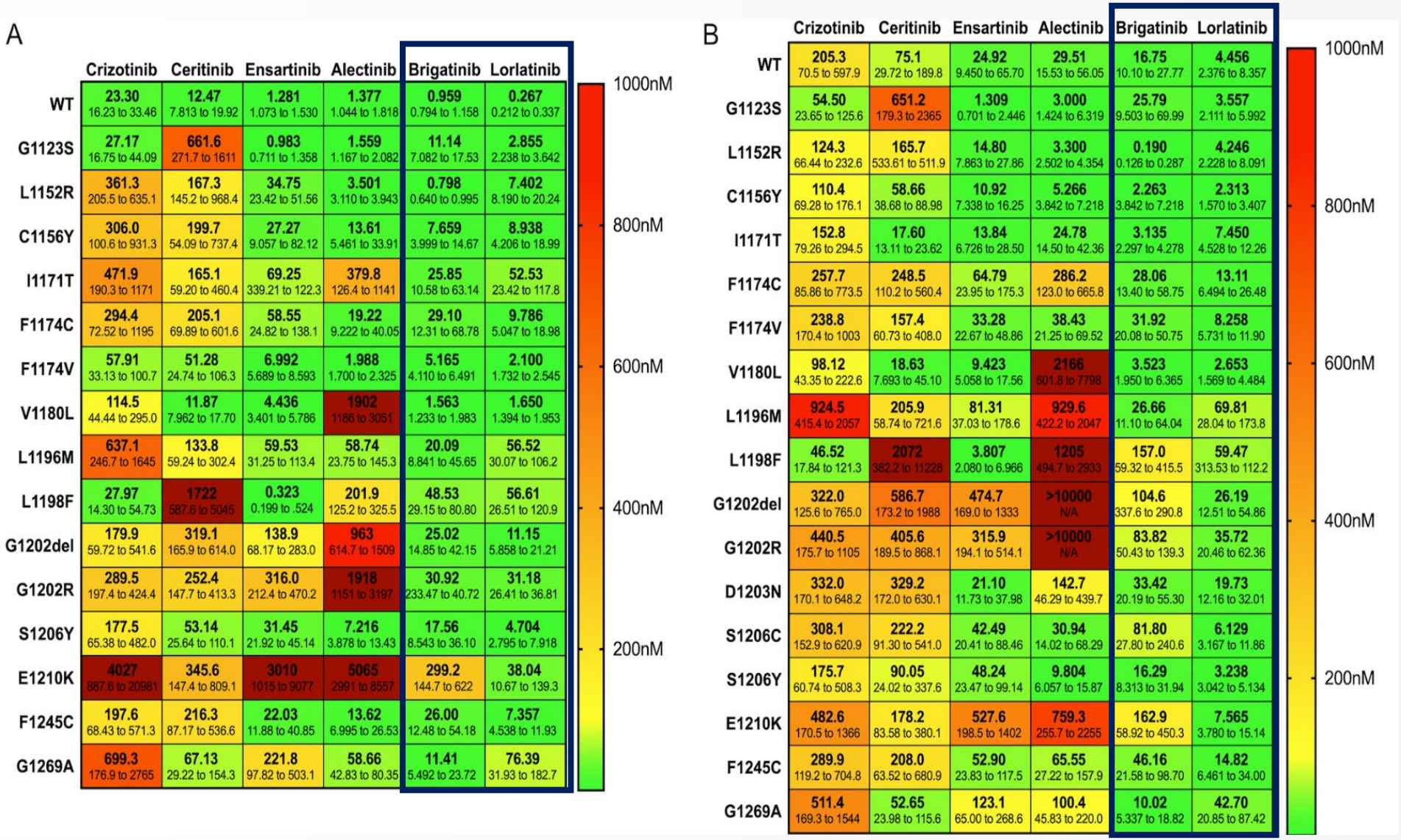
•All Causality Adverse Events with ≥10% Difference in Frequency

Dose reduction rate:
Lorlatinib 21%



†Cluster term
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

In vitro sensitivity to ALKi in BA/F3 cell lines with different resistance mutations: IC50 ranking



A

	Crizotinib	Ceritinib	Ensartinib	Alectinib	Brigatinib	Lorlatinib
WT	23.30 16.23 to 33.46	12.47 7.813 to 19.92	1.281 1.073 to 1.530	1.377 1.044 to 1.818	0.959 0.794 to 1.158	0.267 0.212 to 0.337
G1123S	27.17 16.75 to 44.09	661.6 271.7 to 1611	0.983 0.711 to 1.358	1.559 1.167 to 2.082	11.14 7.082 to 17.53	2.855 2.238 to 3.642
L1152R	361.3 205.5 to 635.1	167.3 145.2 to 968.4	34.75 23.42 to 51.56	3.501 3.110 to 3.943	0.798 0.640 to 0.995	7.402 8.190 to 20.24
C1156Y	306.0 100.6 to 931.3	199.7 54.09 to 737.4	27.27 9.057 to 82.12	13.61 5.461 to 33.91	7.659 3.999 to 14.67	8.938 4.206 to 18.99
I1171T	471.9 190.3 to 1171	165.1 59.20 to 460.4	69.25 339.21 to 122.3	379.8 126.4 to 1141	25.85 10.58 to 63.14	52.53 23.42 to 117.8
F1174C	294.4 72.52 to 1195	205.1 69.89 to 601.6	58.55 24.82 to 138.1	19.22 9.222 to 40.05	29.10 12.31 to 68.78	9.786 5.047 to 18.98
F1174V	57.91 33.13 to 100.7	51.28 24.74 to 106.3	6.992 5.689 to 8.593	1.988 1.700 to 2.325	5.165 4.110 to 6.491	2.100 1.732 to 2.545
V1180L	114.5 44.44 to 295.0	11.87 7.962 to 17.70	4.436 3.401 to 5.786	1902 1186 to 3051	1.563 1.233 to 1.983	1.650 1.394 to 1.953
L1196M	637.1 246.7 to 1645	133.8 59.24 to 302.4	59.53 31.25 to 113.4	58.74 23.75 to 145.3	20.09 8.841 to 45.65	56.52 30.07 to 106.2
L1198F	27.97 14.30 to 54.73	1722 587.6 to 5045	0.323 0.199 to .524	201.9 125.2 to 325.5	48.53 29.15 to 80.80	56.61 26.51 to 120.9
G1202del	179.9 59.72 to 541.6	319.1 165.9 to 614.0	138.9 68.17 to 283.0	963 614.7 to 1509	25.02 14.85 to 42.15	11.15 5.858 to 21.21
G1202R	289.5 197.4 to 424.4	252.4 147.7 to 413.3	316.0 212.4 to 470.2	1918 1151 to 3197	30.92 233.47 to 40.72	31.18 26.41 to 36.81
S1206Y	177.5 65.38 to 482.0	53.14 25.64 to 110.1	31.45 21.92 to 45.14	7.216 3.878 to 13.43	17.56 8.543 to 36.10	4.704 2.795 to 7.918
E1210K	4027 887.6 to 20981	345.6 147.4 to 809.1	3010 1015 to 9077	5065 2991 to 8557	299.2 144.7 to 622	38.04 10.67 to 139.3
F1245C	197.6 68.43 to 571.3	216.3 87.17 to 536.6	22.03 11.88 to 40.85	13.62 6.995 to 26.53	26.00 12.48 to 54.18	7.357 4.538 to 11.93
G1269A	699.3 176.9 to 2765	67.13 29.22 to 154.3	221.8 97.82 to 503.1	58.66 42.83 to 80.35	11.41 5.492 to 23.72	76.39 31.93 to 182.7

1000nM
800nM
600nM
400nM
200nM

B

	Crizotinib	Ceritinib	Ensartinib	Alectinib	Brigatinib	Lorlatinib
WT	205.3 70.5 to 597.9	75.1 29.72 to 189.8	24.92 9.450 to 65.70	29.51 15.53 to 56.05	16.75 10.10 to 27.77	4.456 2.376 to 8.357
G1123S	54.50 23.65 to 125.6	651.2 179.3 to 2365	1.309 0.701 to 2.446	3.000 1.424 to 6.319	25.79 9.503 to 69.99	3.557 2.111 to 5.992
L1152R	124.3 66.44 to 232.6	165.7 533.61 to 511.9	14.80 7.863 to 27.86	3.300 2.502 to 4.354	0.190 0.126 to 0.287	4.246 2.228 to 8.091
C1156Y	110.4 69.28 to 176.1	58.66 38.68 to 88.98	10.92 7.338 to 16.25	5.266 3.842 to 7.218	2.263 3.842 to 7.218	2.313 1.570 to 3.407
I1171T	152.8 79.26 to 294.5	17.60 13.11 to 23.62	13.84 6.726 to 28.50	24.78 14.50 to 42.36	3.135 2.297 to 4.278	7.450 4.528 to 12.26
F1174C	257.7 85.86 to 773.5	248.5 110.2 to 560.4	64.79 23.95 to 175.3	286.2 123.0 to 665.8	28.06 13.40 to 58.75	13.11 6.494 to 26.48
F1174V	238.8 170.4 to 1003	157.4 60.73 to 408.0	33.28 22.67 to 48.86	38.43 21.25 to 69.52	31.92 20.08 to 50.75	8.258 5.731 to 11.90
V1180L	98.12 43.35 to 222.6	18.63 7.693 to 45.10	9.423 5.058 to 17.56	2166 601.8 to 7798	3.523 1.950 to 6.365	2.653 1.569 to 4.484
L1196M	924.5 415.4 to 2057	205.9 58.74 to 721.6	81.31 37.03 to 178.6	929.6 422.2 to 2047	26.66 11.10 to 64.04	69.81 28.04 to 173.8
L1198F	46.52 17.84 to 121.3	2072 382.2 to 11228	3.807 2.080 to 6.966	1205 494.7 to 2933	157.0 59.32 to 415.5	59.47 313.53 to 112.2
G1202del	322.0 125.6 to 765.0	586.7 173.2 to 1988	474.7 169.0 to 1333	>10000 N/A	104.6 337.6 to 290.8	26.19 12.51 to 54.86
G1202R	440.5 175.7 to 1105	405.6 189.5 to 868.1	315.9 194.1 to 514.1	>10000 N/A	83.82 50.43 to 139.3	35.72 20.46 to 62.36
D1203N	332.0 170.1 to 648.2	329.2 172.0 to 630.1	21.10 11.73 to 37.98	142.7 46.29 to 439.7	33.42 20.19 to 55.30	19.73 12.16 to 32.01
S1206C	308.1 152.9 to 620.9	222.2 91.30 to 541.0	42.49 20.41 to 88.46	30.94 14.02 to 68.29	81.80 27.80 to 240.6	6.129 3.167 to 11.86
S1206Y	175.7 60.74 to 508.3	90.05 24.02 to 337.6	48.24 23.47 to 99.14	9.804 6.057 to 15.87	16.29 8.313 to 31.94	3.238 3.042 to 5.134
E1210K	482.6 170.5 to 1366	178.2 83.58 to 380.1	527.6 198.5 to 1402	759.3 255.7 to 2255	162.9 58.92 to 450.3	7.565 3.780 to 15.14
F1245C	289.9 119.2 to 704.8	208.0 63.52 to 680.9	52.90 23.83 to 117.5	65.55 27.22 to 157.9	46.16 21.58 to 98.70	14.82 6.461 to 34.00
G1269A	511.4 169.3 to 1544	52.65 23.98 to 115.6	123.1 65.00 to 268.6	100.4 45.83 to 220.0	10.02 5.337 to 18.82	42.70 20.85 to 87.42

1000nM
800nM
600nM
400nM
200nM

Horn et al, J Thorac Oncol 2019; 14:1901-1911In

Efficacy Non-Head to Head Comparison: Post Next-Gen Gen ALK TKI

ALK TKI Trial	Post 2nd Gen ALK TKI Population	N	ORR	PFS	Baseline Brain Mets	ECOG PS	Median Prior Therapies	Source
Lorlatinib Phase 2	Non-crizotinib ALK TKI	28	43%	5.5 months	46%	≥2 0%	NA	Besse et al ASCO 2018
	Alectinib	62	40%	5.5 months	NR	NR		
	≥ 2 ALK TKIs	111	40%	6.9 months	73%	≥2 5.4%		

This tells us some but definitely not all cases are still addicted just to ALK and can respond to the right next ALK TKI if that mechanism is covered by a different ALK TKI

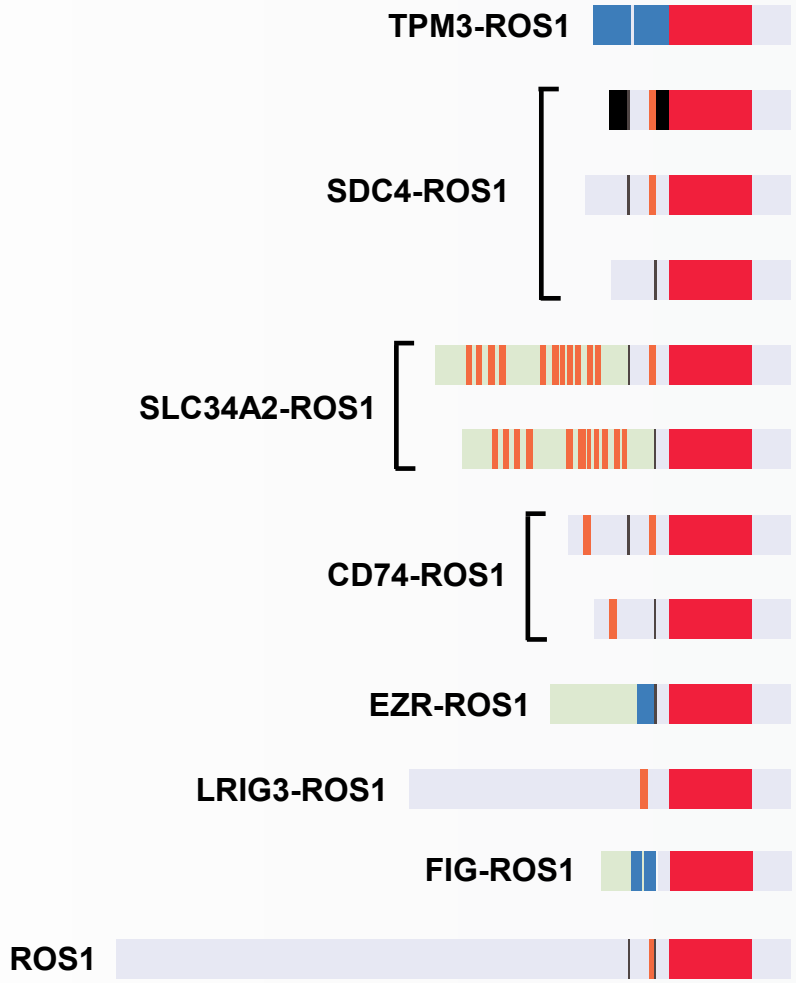
Efficacy Non-Head to Head Comparison: Post Next-Gen Gen ALK TKI (off label trial data))

ALK TKI Trial	Post 2nd Gen ALK TKI Population	N	ORR	PFS	Baseline Brain Mets	ECOG PS	Median Prior Therapies	Source
Ensartinib Phase 1/ 2	≥ 2 ALK TKIs	21	23%	NR	NR	NR	NR	Horn et al NACLC 2017
	Crizotinib + ≥1 2nd Gen ALK TKI	16	25%	1.9 months	NR	NR	NR	Horn et al CCR 2018
Ceritinib ASCEND-9	Alectinib	20	25%	3.7 months	60%	WHO PS 1 45%	70% patients had ≥2 prior lines any therapy	Horinouchi et al WCLC 2017
Brigatinib case series (retrospective)	Alectinib	22	17%	4.4 months	82%	NR	59% 2 prior TKIs	Lin et al JTO 2018
Brigatinib Austrian EAP	2nd Gen TKI (12 patients prior ceritinib as 2G TKI only)	18	77%	NR	31% (all patients including prior criz only)	NR	NR	Hochmair et al WCLC 2018
Brigatinib, Stinchcombe IISR	Next-Gen ALK TKIs	20	40%	6.4 months	60%	NR	Median= 3 (includes chemo)	Stinchcombe et al ASCO 2019
BRIGALK- French EAP (retrospective)	≥ 2 ALK TKIs (93% crizotinib-ceritinib)	104	50%	6.6 months	75%	≥2 41%	Median= 3 (includes chemo)	Descourt et al ASCO 2019
Brigatinib 2001	Alectinib	9	57%	N/A	44%	≥2 0%	NR	Murakami et al WCLC 2019
UVEA- Brigatinib	1 prior ALK TKI	50	35%	5.7 months	60%	NR	Median= 1 ALK TKI	Novello et al ESMO 2019

Summary: ALK

- Start with a next generation ALK TKI – choose based on safety, tolerability, efficacy, cost, convenience
- At extra-CNS progression consider rebiopsy and reanalysis for ALK mutations AND for emerging 2nd drivers for rational choice of next ALK TKI (regardless of line of therapy in label) or rational combination
- If no actionable change – pemetrexed-based chemo (add in vs swap out) +/- local ablative therapy
- At CNS progression consider dose escalation/drug change
- The future – 4th gen for compound mutations, actionable second driver identification, other drugs – degraders, ADCs
- CPIs – 3rd or 4th line

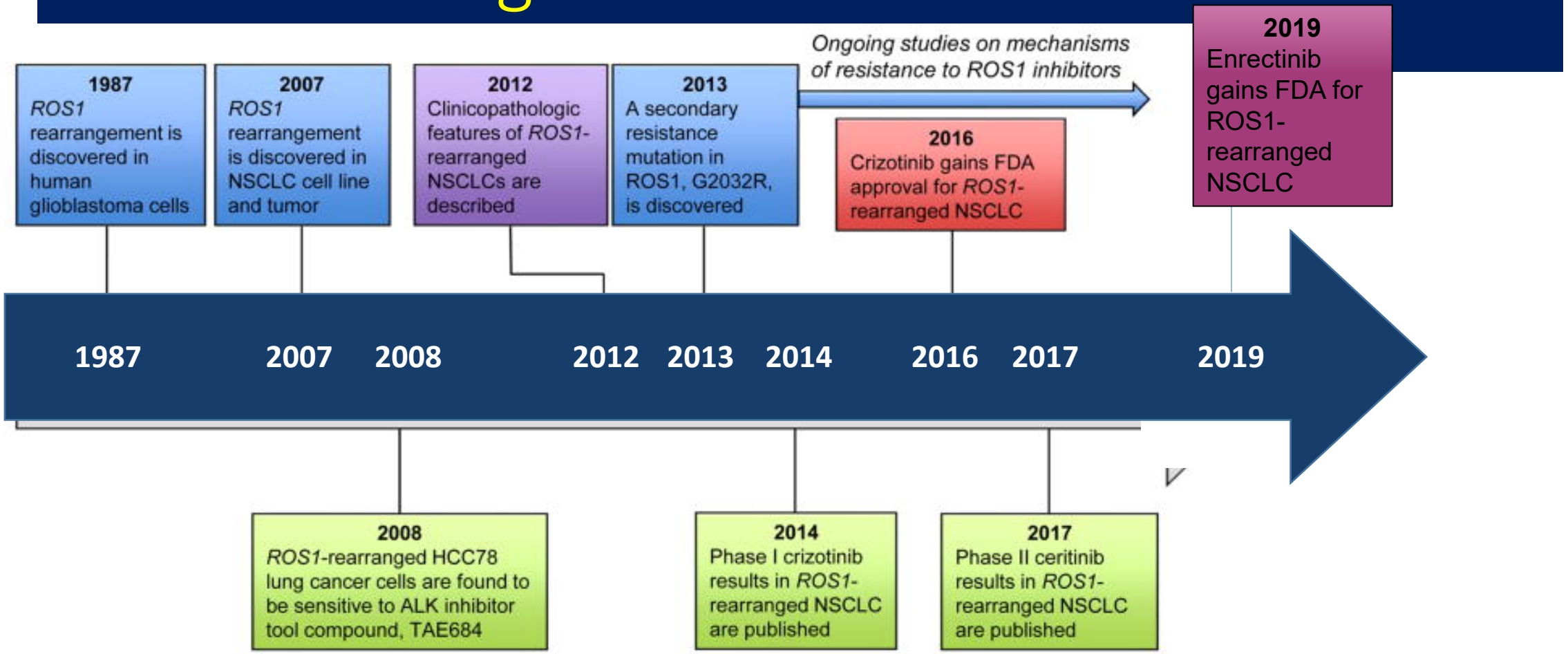
ROS1 Rearrangements in NSCLC



- Identified in ~1% of NSCLC
- Also found in some GBMs, cholangiocarcinomas, and other tumor types
- Activated by chromosomal rearrangement, leading to constitutive kinase activation and oncogene addiction
- No overlap with ALK

Bergethon et al., JCO 30(8): 863-70, 2012; Takeuchi et al., Nat Med 18(3): 378-81, 2012; Rimkunas et al., CCR 18(16): 4449-57, 2012

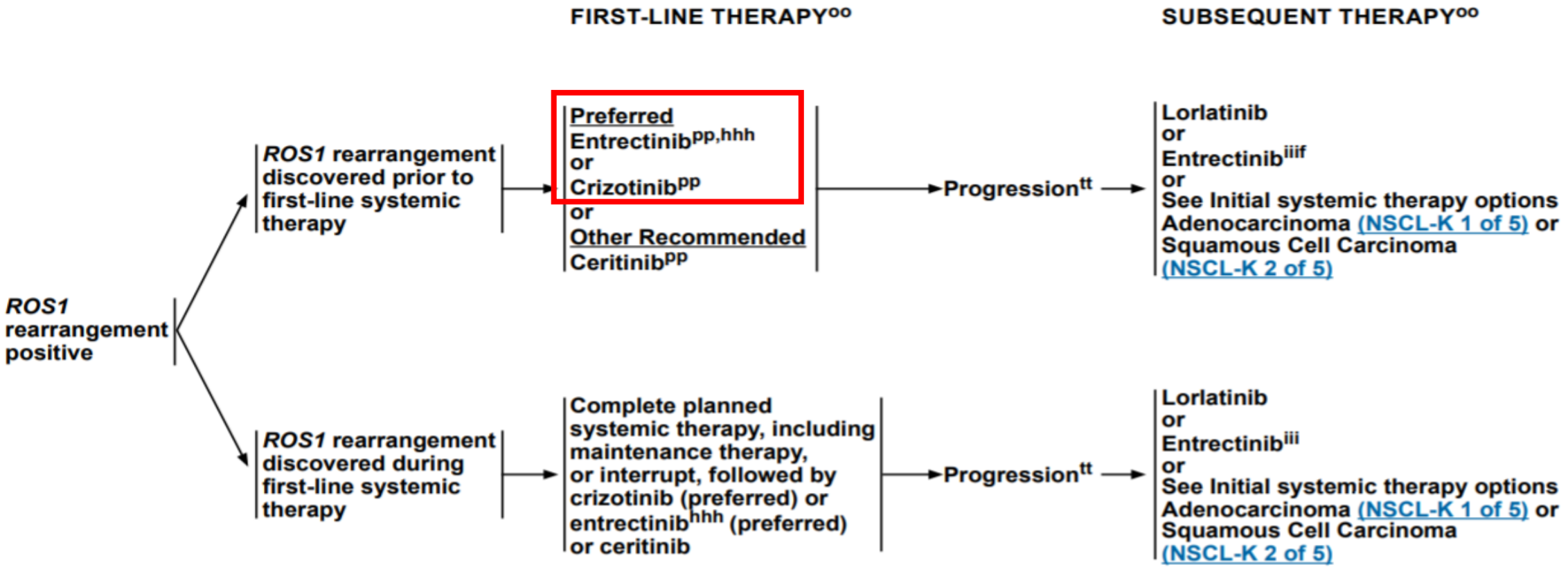
ROS1 Rearrangements in NSCLC



- 1% to 2% of NSCLC adenocarcinoma

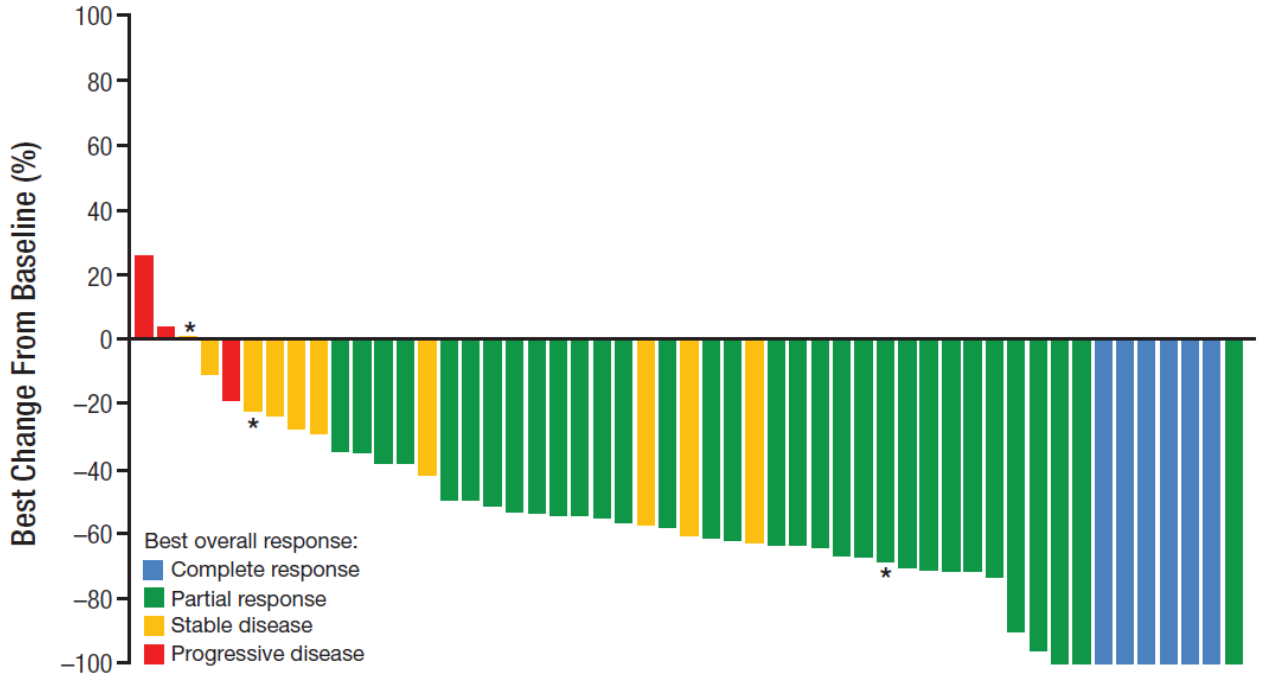
Bergethon, et al. *J Clin Oncol*. 2012. Riess, et al. *CLC* 2013. Shan, et al. *PLOS One*. 2015. Sehgal K, et al. *Precis Cancer Med*. 2020 Jun;3:17. Lin JL, et al. *J Thorac Oncol*. 2017;12(11):1611–1625.

ROS1 REARRANGEMENT POSITIVE[ll]



Phase 1 PROFILE 1001 Study: Crizotinib in *ROS1*-Rearranged NSCLC—Updated Analysis

- 53 patients received crizotinib; median duration of treatment: 22.4 mo
- ROS1 status determined by FISH or RT-PCR
- All patients received crizotinib 250 mg BID starting dose
- Median follow up: 62.6 mo



Shaw AT, et al. *Ann Oncol*. 2019; 30(7):1121–1126.

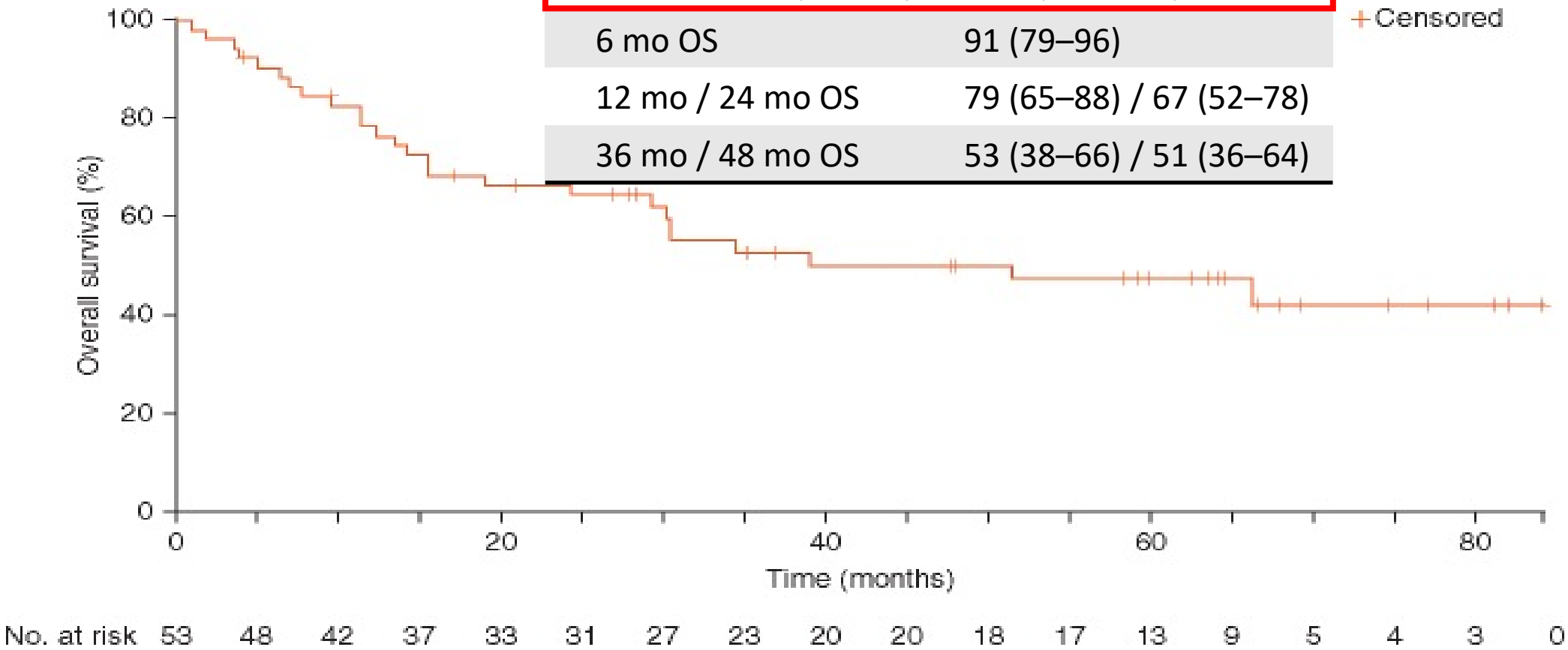
Phase 1 Crizotinib Study: Antitumor Activity End Points—Updated Analysis

End points	ROS1-rearranged NSCLC (N = 53)
ORR, % (95% CI)[a]	72 (58–83)
CR, n (%)	6 (11)
PR, n (%)	32 (60)
SD (≥6 weeks), n (%)	10 (19)
PD, n (%)	3 (6)
Not evaluated[b]	2 (4)
Median time to first tumor response, weeks (range)[c]	7.9 (4.3–103.6)
Median duration of response, months (95% CI)[d,e]	24.7 (15.2–45.3)
Median PFS, months (95% CI)[d,f]	19.3 (15.2–39.1)

Shaw AT, et al. *Ann Oncol*. 2019; 30(7):1121–1126.

Phase 1 Crizotinib Study: Overall Survival—Updated Analysis

Deaths, n (%)	26 (49)
Median OS, mo (95% CI)[b]	51.4 (29.3–NR)
6 mo OS	91 (79–96)
12 mo / 24 mo OS	79 (65–88) / 67 (52–78)
36 mo / 48 mo OS	53 (38–66) / 51 (36–64)



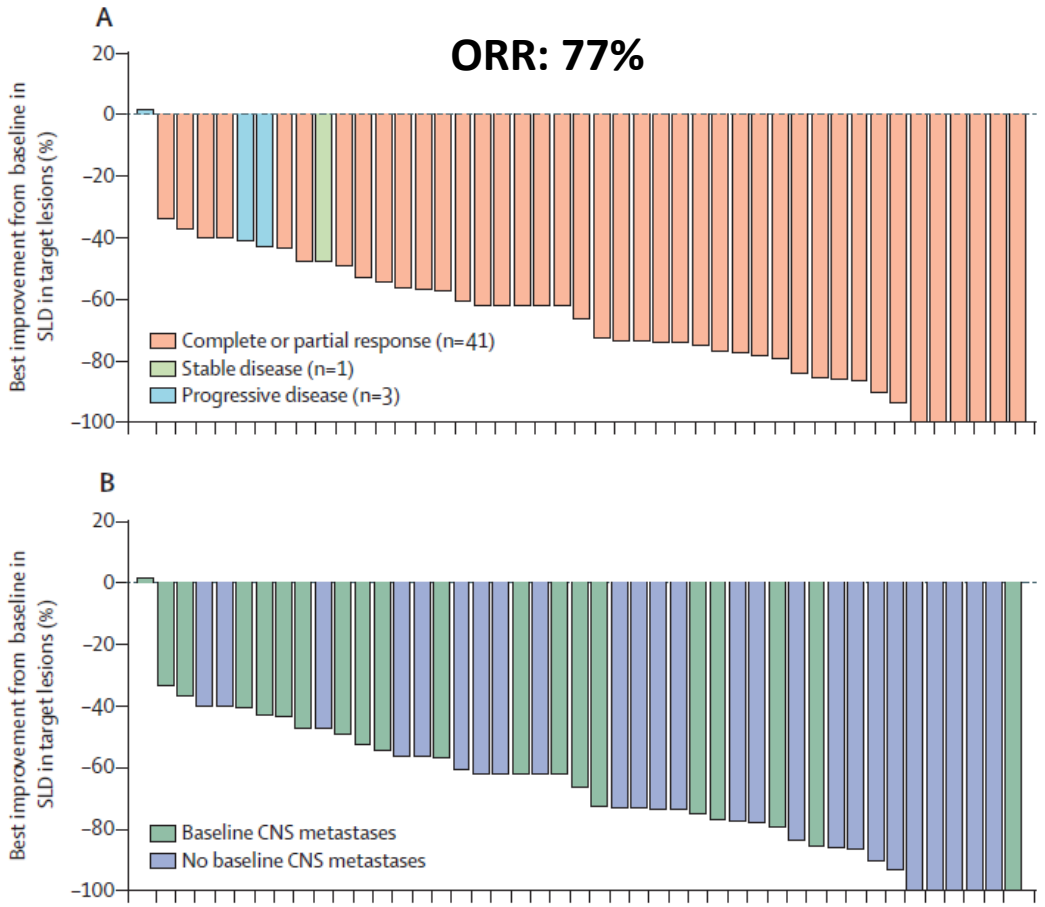
Median duration of follow up: 62.6 mo

Shaw AT, et al. *Ann Oncol*. 2019; 30(7):1121–1126.

ROS1: Crizotinib Activity

Trial	#	Region	Pretreated Pts	*ROS1* test	ORR	mPFS, months	mOS, months	1y-S
Profile, ph. I	53	World	86%	FISH/rtPCR	72%	19.3	51.4	79%
OxOnc, ph. II	127	East Asia	81%	rtPCR	72%	15.9	32.5	83%
EUROS1, pooled	32	Europe	97%	FISH/IHC/NGS	80%	9.1	NR	NR
AcSè, basket	37	France	97%	IHC/FISH	54%	5.5	17.2	NR
EUCROSS, ph. II	34	Spain/Germany	79%	FISH	73%	20.0	NR	83%
METROS*, Ph.II	64	Italy	94%	FISH	67%	16.5	40.0	75%

Entrectinib in *ROS1*-Fusion-Positive NSCLC

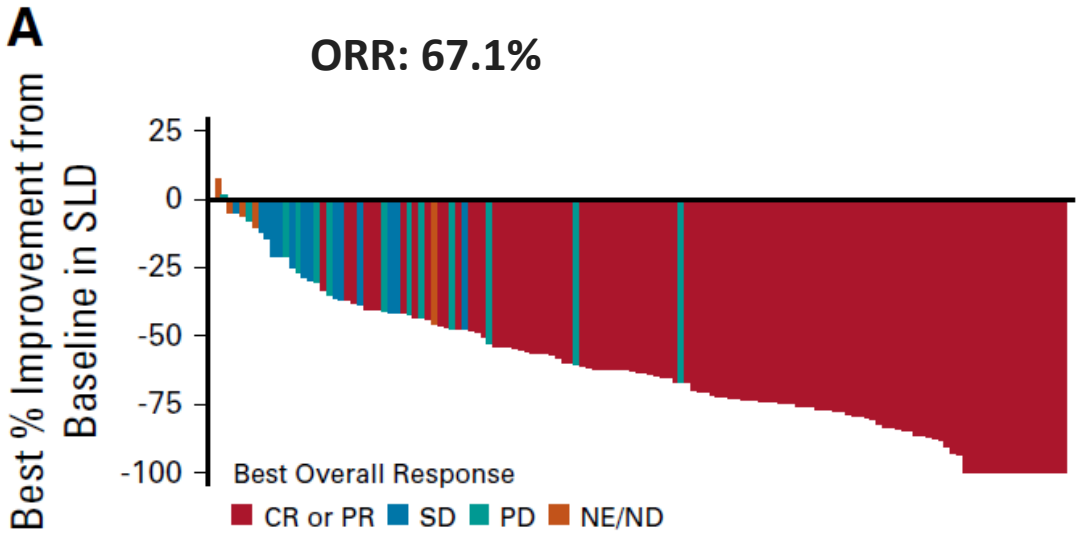


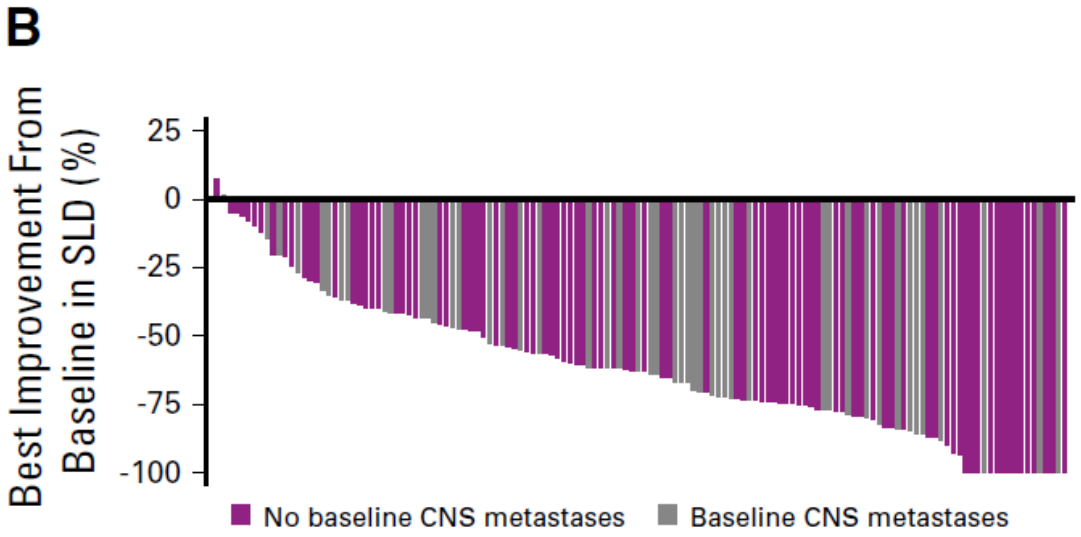
	Integrated efficacy-evaluable population (n=53)	Patients with baseline CNS disease (n=23)*	Patients with no baseline CNS disease (n=30)*
Objective responses, n; % (95% CI)	41; 77% (64–88)	17; 74% (52–90)	24; 80% (61–92)
Best overall response			
Complete response, n (%)	3 (6%)†	0	3 (10%)
Partial response, n (%)	38 (72%)†	17 (74%)	21 (70%)
Stable disease, n (%)	1 (2%)	0	1 (3%)
Progressive disease, n (%)	4 (8%)	4 (17%)	0
Non-complete response or non-progressive disease, n (%)	3 (6%)	0	3 (10%)
Missing or unevaluable, n (%)‡	4 (8%)	2 (9%)	2 (7%)
Duration of response			
Median, months (95% CI)	24·6 (11·4–34·8)	12·6 (6·5–NE)	24·6 (11·4–34·8)
Progression-free survival			
Median, months (95% CI)	19·0 (12·2–36·6)	13·6 (4·5–NE)	26·3 (15·7–36·6)
Intracranial activity	..	20·0‡	..
Overall response, n; % (95% CI)	..	11; 55% (32–77)	..
Best intracranial response			
Complete response, n (%)	..	4 (20%)	..
Partial response, n (%)	..	7 (35%)	..
Stable disease, n (%)	..	0	..
Progressive disease, n (%)	..	3 (15%)	..
Non-complete response or non-progressive disease, n (%)	..	4 (20%)	..
Missing or unevaluable, n (%)§	..	2 (10%)	..

Shaw AT, et al. *Lancet Oncol*. 2019; Drilon A, et al. *Lancet Oncol*. 2020.

Entrectinib in *ROS1*-Fusion-Positive NSCLC: Updated Analysis

- Updated integrated analysis of 3 phase I/II clinical trials (ALKA-372-001, STARTRK-1, and STARTRK-2) of entrectinib, in *ROS1* fusion-positive NSCLC
- 161 patients with a follow-up of ≥ 6 months were evaluable
- Median duration of follow-up, 15.8 months
- Median treatment duration was 10.7 months





Dziadziuszko R, et al. *J Clin Oncol*. 2021;39(11):1253-1263.

Entrectinib in *ROS1*-Fusion-Positive NSCLC: Response—Updated Analysis[a]

Efficacy Parameter	*ROS1* Fusion–Positive NSCLC		
	Efficacy-Evaluable Population (N = 161)	Baseline CNS Metastases[a] (n = 56)	No Baseline CNS Metastases[a] (n = 105)
Objective response, n (%, 95% CI)	108 (67.1, 59.3 to 74.3)	35 (62.5, 48.6 to 75.1)	73 (69.5, 59.8 to 78.1)
Best overall response, n (%)			
CR	14 (8.7)	4 (7.1)	10 (9.5)
PR	94 (58.4)	31 (55.4)	63 (60.0)
SD	14 (8.7)	4 (7.1)	10 (9.5)
PD	15 (9.3)	9 (16.1)	6 (5.7)
Non-CR or non-PD	10 (6.2)	2 (3.6)	8 (7.6)
Missing or unevaluable[b]	14 (8.7)	6 (10.7)	8 (7.6)
DoR			
Median, months (95% CI)	15.7 (13.9 to 28.6)	14.9 (9.6 to 20.5)	24.6 (13.9 to 34.8)
Range, months	1.8-42.3[c]	1.8-25.7[c]	1.9-42.3[c]
Patients with events, n (%)	48 (44.4)	17 (48.6)	31 (42.5)
6-month durable response, % (95% CI)	83 (76 to 90)	84 (70 to 97)	83 (74 to 92)
9-month durable response, % (95% CI)	75 (67 to 84)	73 (57 to 89)	76 (66 to 86)
12-month durable response, % (95% CI)	63 (53 to 73)	62 (44 to 80)	63 (51 to 75)

Intracranial ORR: 79.2% (n = 19/24)[b]; median intracranial DoR: 12.9 months (12-mo rate, 55%)

a Median duration of follow-up, 15.8 months. b 24 pts w/ measurable baseline CNS mets by BICR

Dziadziuszko R, et al. *J Clin Oncol*. 2021;39(11):1253-1263.

Cross-Trial Side Effect Comparison: Crizotinib and Entrectinib

	Crizotinib		*Entrectinib*	
	All grades (%)	Grade 3 (%)	All grades (%)	Grade 3-4 (%)
Vision disorder	87	0	NR	NR
Nausea	51	2	17	0
Edema	47	0	16	0
Diarrhea	45	0	26	2
Vomiting	38	4	14	0
Elevated transaminases	36	4	10/10	2/2
Constipation	34	0	33	0
Bradycardia	21	0	NR	NR
Fatigue	21	0	24	0
Dizziness	19	0	32	<1
Dysgeusia	19	0	42	<1
Hypophosphatemia	17	15	1	<1
Decreased appetite	15	2	NR	NR
Neutropenia	15	9	4	4
Rash	13	0	7	1
Weight increase	NR	NR	19	7
Paresthesia	NR	NR	17	0
Myalgia	NR	NR	14	2
Blood creatinine increase	NR	NR	13	<1

Shaw AT et al., Ann Oncol 2019; 30:1121-26; Drilon A et al., Lancet Oncol 2020;21:261-70

Summary of ROS1 TKIs in TKI-Naïve ROS1+ NSCLC

	Crizotinib*	Entrectinib*	Ceritinib	Taletrectinib	Lorlatinib	Repotrectinib#
N	53	161	20	15	21	22
ORR	72%	67% (n=108)	67%	93%	62%	91%
Median PFS	19.3 months	15.7 months	19.3 months	N/A	21.0 months	Not available
CNS activity	N/A	19/24 (79%) patients with measurable intracranial disease	2/5 (40%) patients with measurable or nonmeasurable intracranial disease	N/A	7/11 (64%) patients with measurable or nonmeasurable intracranial disease	3/3 (100%) patients with measurable intracranial disease
Reference	Shaw et al. Ann Oncol 2019	Dziadziuszko et al. JCO 2021	Lim et al. JCO 2017	Zhou C et al., ASCO 2021	Shaw et al. Lancet Oncol 2019	Cho et al. WCLC 2020; ASCO 2019

**FDA-approved; #granted FDA breakthrough therapy designation in 2020 for ROS1 TKI-naïve NSCLC*

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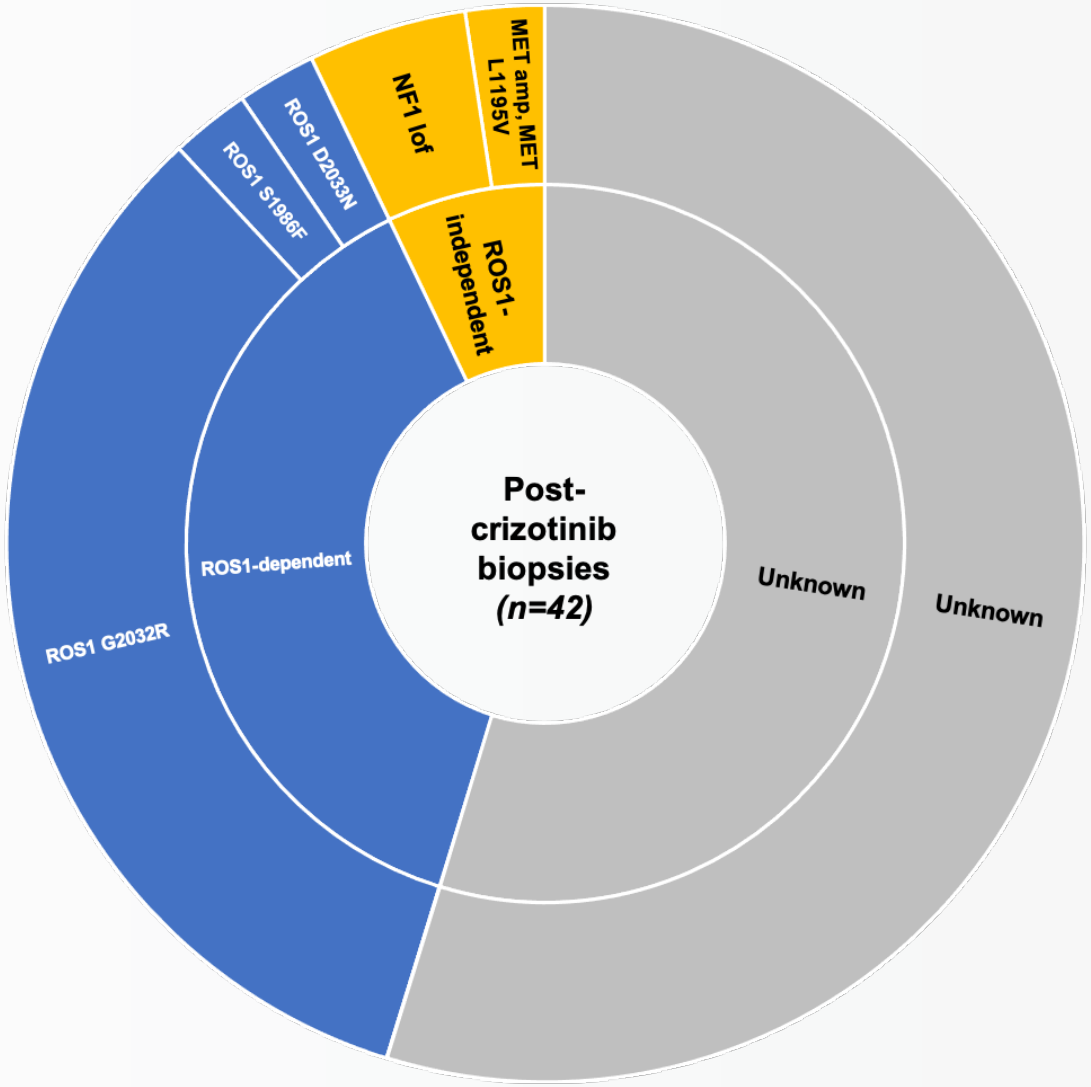
Median PFS	19.3 months	15.7 months	19.3 months	N/A	21.0 months	Not available
CNS activity	N/A	19/24 (79%) patients with measurable intracranial disease	2/5 (40%) patients with measurable or nonmeasurable intracranial disease	N/A	7/11 (64%) patients with measurable or nonmeasurable intracranial disease	3/3 (100%) patients with measurable intracranial disease
Reference	Shaw et al. Ann Oncol 2019	Dziadziuszko et al. JCO 2021	Lim et al. JCO 2017	Zhou C et al., ASCO 2021	Shaw et al. Lancet Oncol 2019	Cho et al. WCLC 2020; ASCO 2019

**FDA-approved; #granted FDA breakthrough therapy designation in 2020 for ROS1 TKI-naïve NSCLC*

Moving to 2L Options: Resistance to Crizotinib



Lin JJ, et al. Clin Cancer Res 2021;27:2899-909

Second-Line ROS1 TKI Landscape in *ROS1*+ NSCLC

Lorlatinib

Repotrectinib

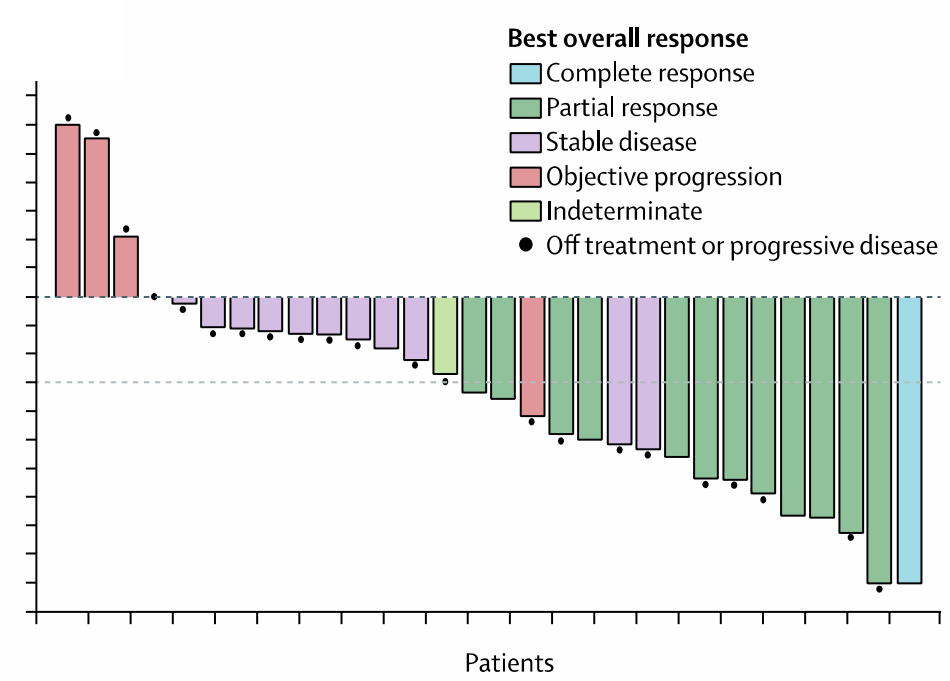
Taletrectinib

Cabozantinib

Duration of response
CNS activity
Spectrum of activity against ROS1 *resistance mutations*

Lorlatinib and Repotrectinib in Crizotinib/ROS1 TKI-Pretreated Cohorts

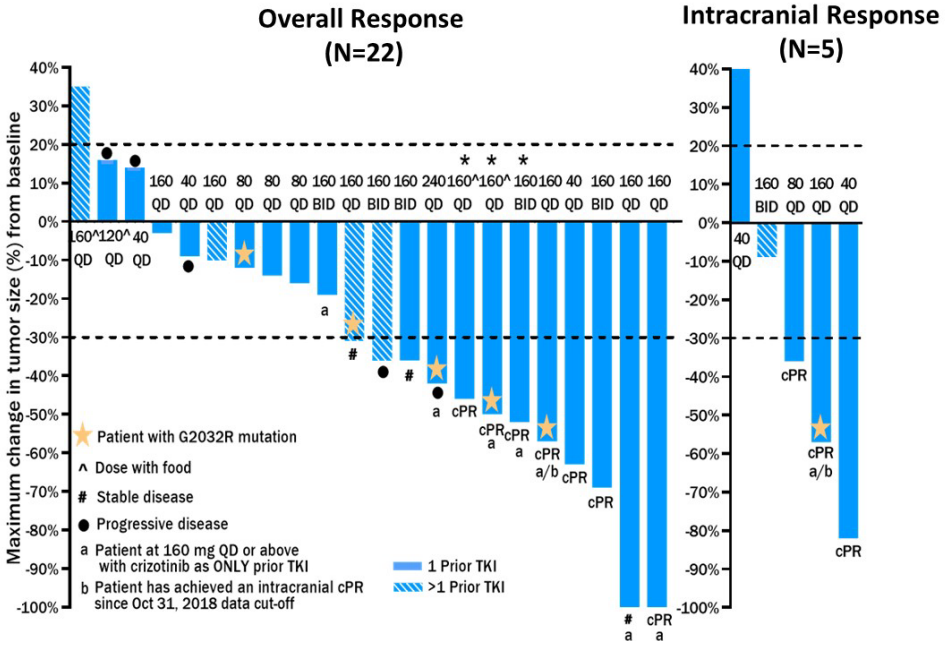
Lorlatinib



- N = 40
- **ORR 35%** (95% CI, 21-52)
- **Median PFS 8.5 months** (95% CI, 4.7 to 15.2)
- **Median duration of response 13.8 months** (95% CI, 9.7-NR)
- **Intracranial ORR 50%** (12/24; 95% CI, 29-71)

Shaw AT et al., Lancet Oncol 2019;20:1691-701

Repotrectinib



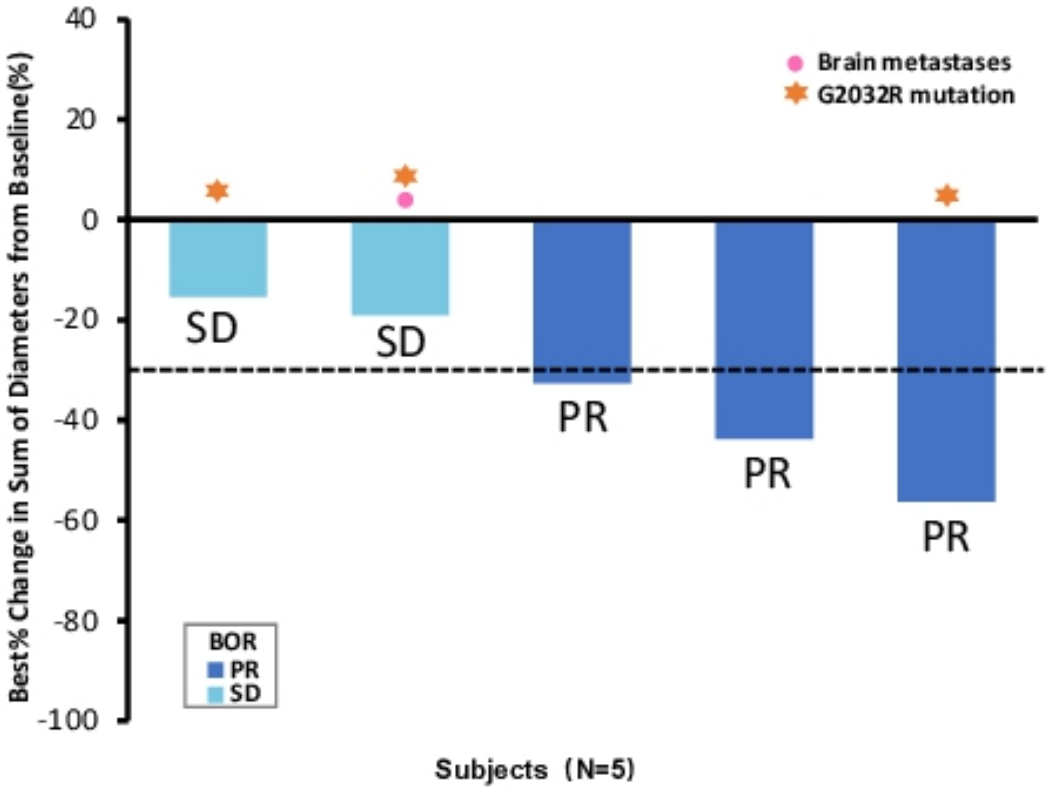
Pretreated with 1 TKI (N=18)**

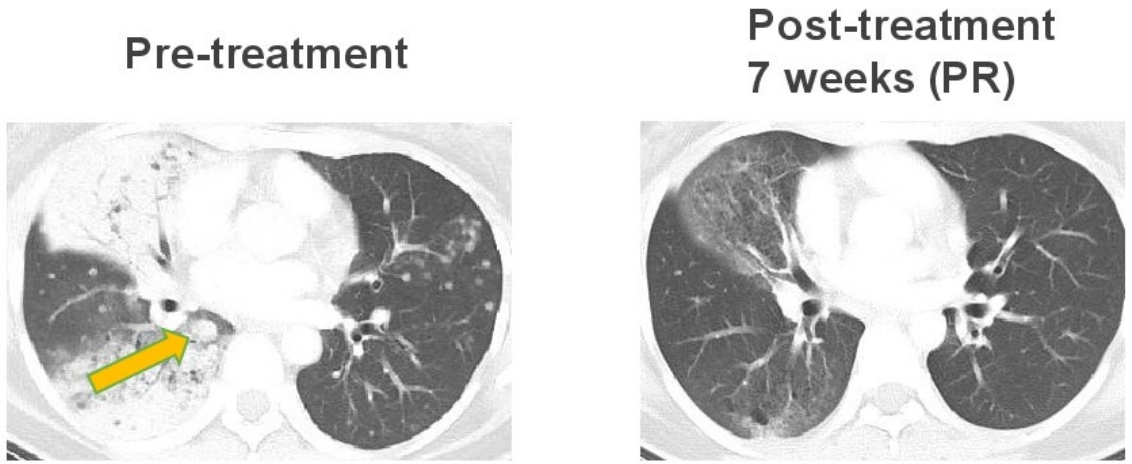
Confirmed ORR, n/N (%) 95% CI (%)	**7/18 (39%)** (17 – 64)
ORR at 160 mg QD or above • **Crizotinib as ONLY prior TKI**	**6/11 (55%)** **4/7 (57%)**
IC-ORR[1], n/N (%) 95% CI (%)	**3/4 (75%)** (19 – 99)
Clinical benefit rate, n/N (%) 95% CI (%)	**14/18 (78%)** (52 – 94)
Median follow-up time, months Range	**14.6** 1.4 – 14.6+

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

Cho BC et al., ASCO 2019

Taletrectinib in Crizotinib-Pretreated *ROS1*+ NSCLC: Preliminary Results from TRUST: Phase II Study in China





- 38-year-old female subject with CD74-ROS1 fusion positive NSCLC
- 2 prior systematic regimens: chemotherapy and crizotinib
- Acquired ROS1 G2032R resistant mutation post-crizotinib therapy
- Received taletrectinib at 600 mg QD
- Achieved PR by investigator evaluation at week 7
- Remains on treatment

Zhou C et al., ASCO 2021

ROS1 TKIs in Crizotinib/TKI-Pretreated *ROS1*+ NSCLC

	Lorlatinib (Phase 1/2)	Repotrectinib (TRIDENT-1 phase 1)	Taletrectinib (Pooled US+Japan phase 1)
Patients	N=40	N=18	N=6
ORR	35%	39% (55% at 160 mg qd or above)	33%
Median PFS	8.5 months	Not available	14.2 months
CNS activity	12/24 (50%) patients with measurable or nonmeasurable intracranial disease	3/4 (75%) patients with measurable intracranial disease	N/A (reported in China TRUST phase II study, Zhou C et al., ASCO 2021)
Clinical ROS1 G2032R activity	Response in 0/6 (0%) patients with a baseline ROS1 G2032R in plasma	Responses in 3/7 (43%) patients with a baseline ROS1 G2032R	N/A (reported in China TRUST phase II study, Zhou C et al., ASCO 2021: 3/5 pts w/ ROS1 G2032R w/ response)
Most common treatment-related or treatment-emergent AEs (all grades)	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, cognitive effects, weight increased, dizziness, mood effects, lipase increased	Dizziness, dysgeusia, dyspnea, fatigue, constipation, paresthesia, anemia, nausea, cough, pyrexia, headache, vomiting, upper respiratory tract infection, ataxia, pain in extremity	ALT increase, AST increase, nausea, diarrhea, vomiting, creatinine increase
Reference	Shaw et al., Lancet Oncol 2019	Cho et al., ASCO 2019	Ou et al, J Thorac Oncol Clin Res Rep 2021

ROS1-Dependent Resistance Following Next-Generation ROS1 TKIs

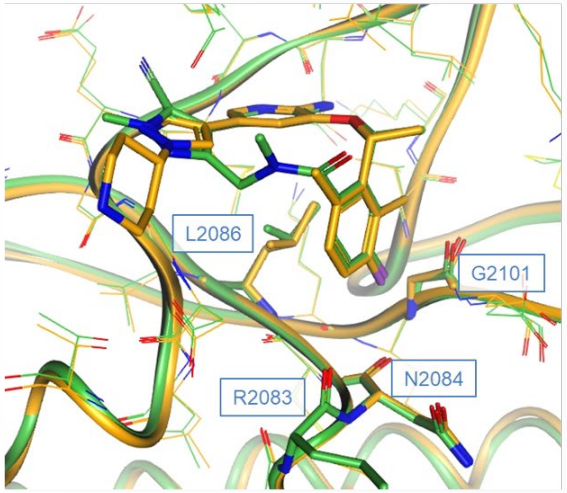
IC_{50} (nmol/L)	Crizotinib	Entrectinib	Lorlatinib	Repotrectinib	Cabozantinib	Ceritinib	Brigatinib	Taletrectinib	Alectinib
Parental	840.5	1801.0	>3000	1218.0	>3000	1117.0	>3000	>3000	1207.0
Non-mutant	5.4	2.7	0.7	2.0	2.8	16.4	9.4	2.6	995.4
G2032R	609.6	436.3	196.6	23.1	17.5	346.4	472.7	53.3	1091.0
L2000V	37.1	25.9	2.5	10.1	7.6	124.9	78.9	29.8	985.0
L2086F	536.8	440.0	>3000	587.9	3.6	226.9	159.3	1265.0	672.5
S1986F/L2000V	159.4	36.1	2.4	7.2	5.1	86.9	62.5	20.3	1080.0
S1986F/L2086F	469.7	344.2	>3000	241.2	1.3	154.8	48.5	662.6	919.9
G2032R/L2086F	498.6	335.4	>3000	248.9	5.0	573.9	450.9	744.2	1254.0
S1986F/G2032R	594.4	718.5	990.6	65.1	70.1	614.7	717.0	105.4	1137.0
S1986F/G2032R/L2086F	562.8	1111.0	2131.0	1178.0	9.4	1116.0	1341.0	2432.0	1150.0

IC_{50} ≤ 50 nmol/L

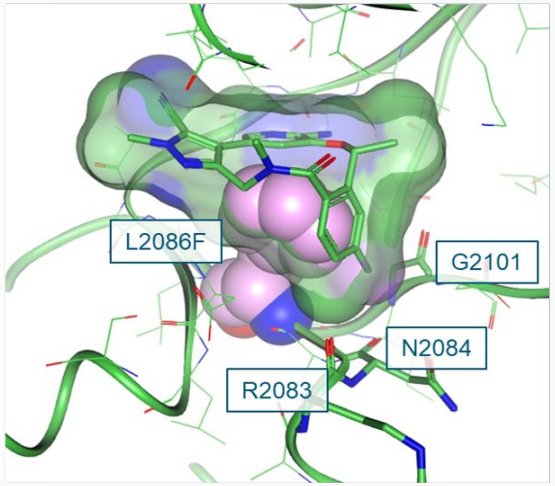
50 nmol/L < IC_{50} <200 nmol/L

IC_{50} ≥ 200 nmol/L

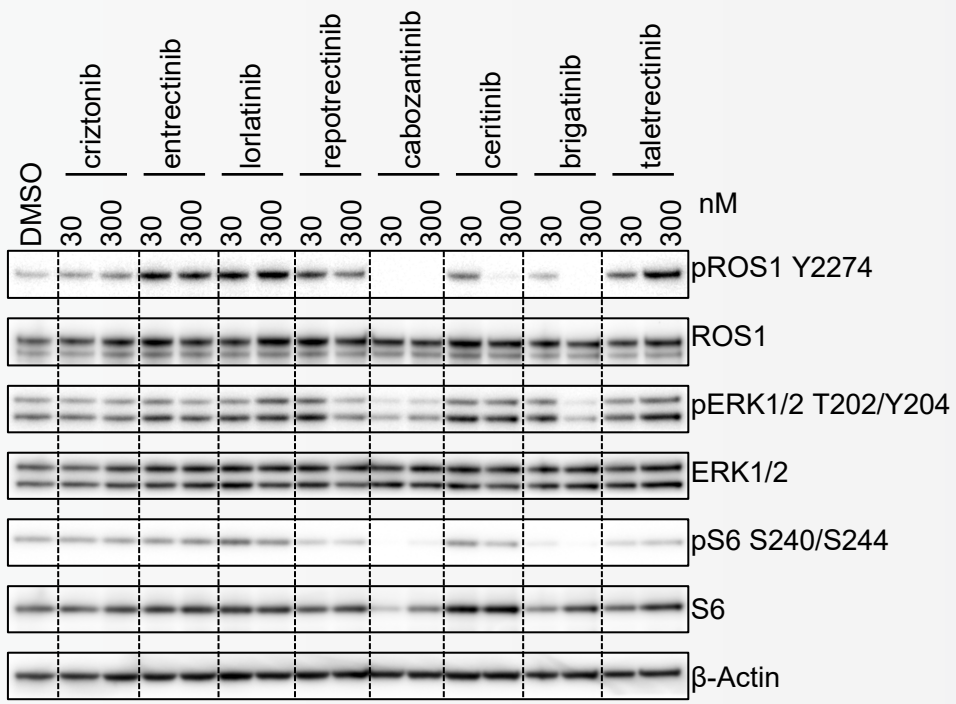
Nonmutant ROS1



ROS1-L2086F



Ba/F3 CD74-ROS1 L2086F



Lin JJ, et al. Clin Cancer Res 2021;27:2899-909

Combination Strategies in *ROS1* Fusion+ NSCLC

MGH
(PI: I. Dagogo-Jack)

KEY ELIGIBILITY
- Stage IV ALK+ or ROS1+ NSCLC
- Prior ≥1 TKI
- Measurable disease
- ECOG PS 0-2

N ~ 9-12 per cohort for dose escalation

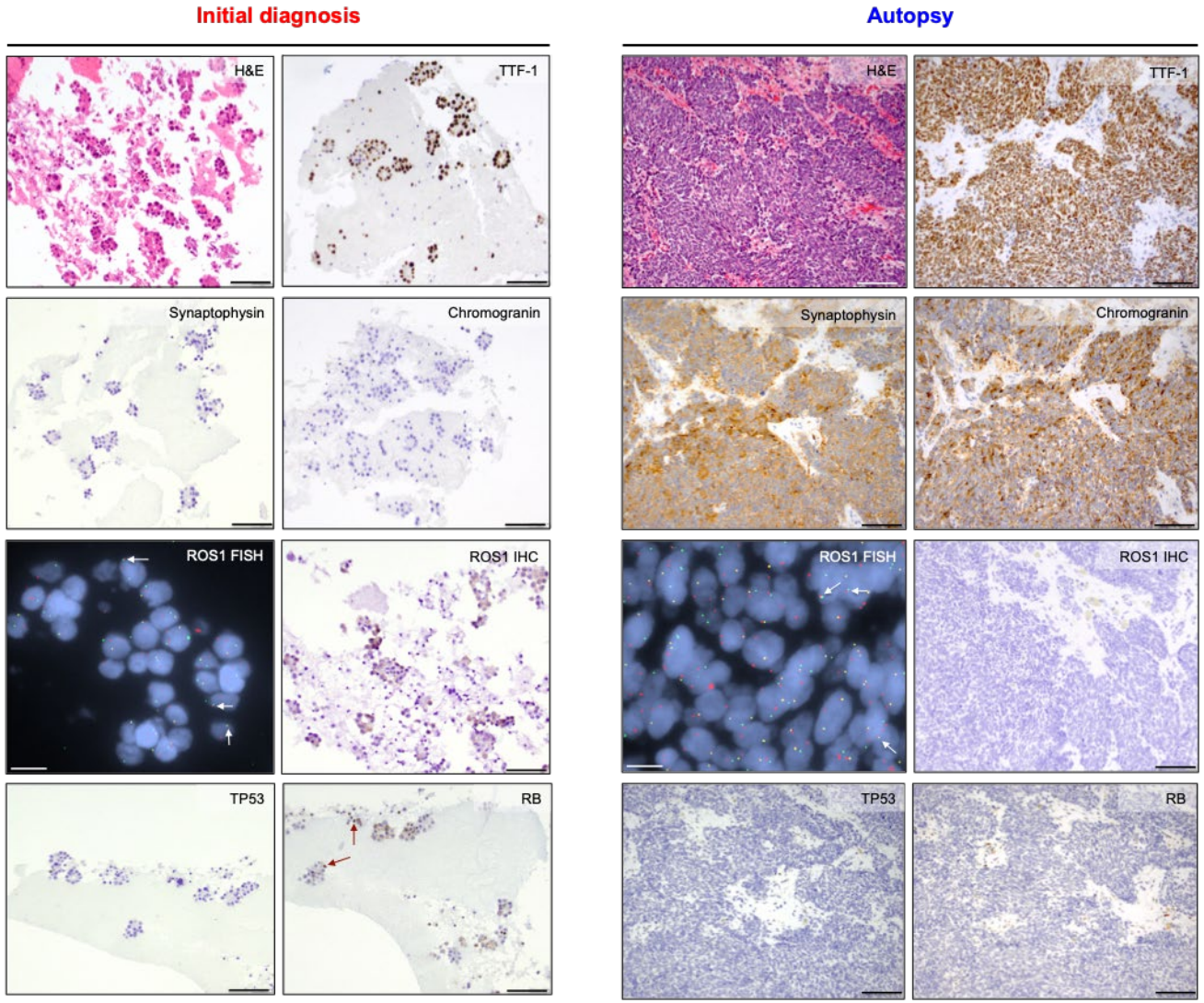
3+3

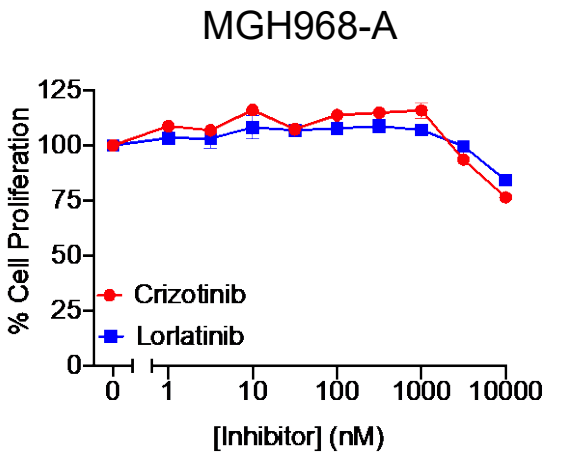
- **Lorlatinib + Crizotinib (ALK/METi)**
- **Lorlatinib + Binimetinib (MEKi)**
- **Lorlatinib + TNO155 (SHP2i)**

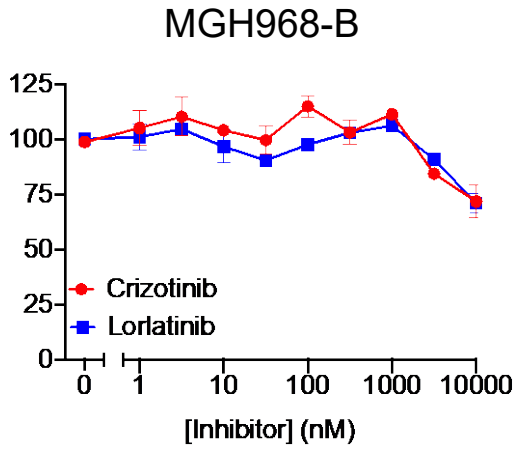
OBJECTIVE/ENDPOINT
Primary
- Safety/tolerability, RPIID and MTD determination

Lin JJ, et al. Clin Cancer Res 2021;27:2899-909

Small Cell Transformation in *ROS1* Fusion+ NSCLC







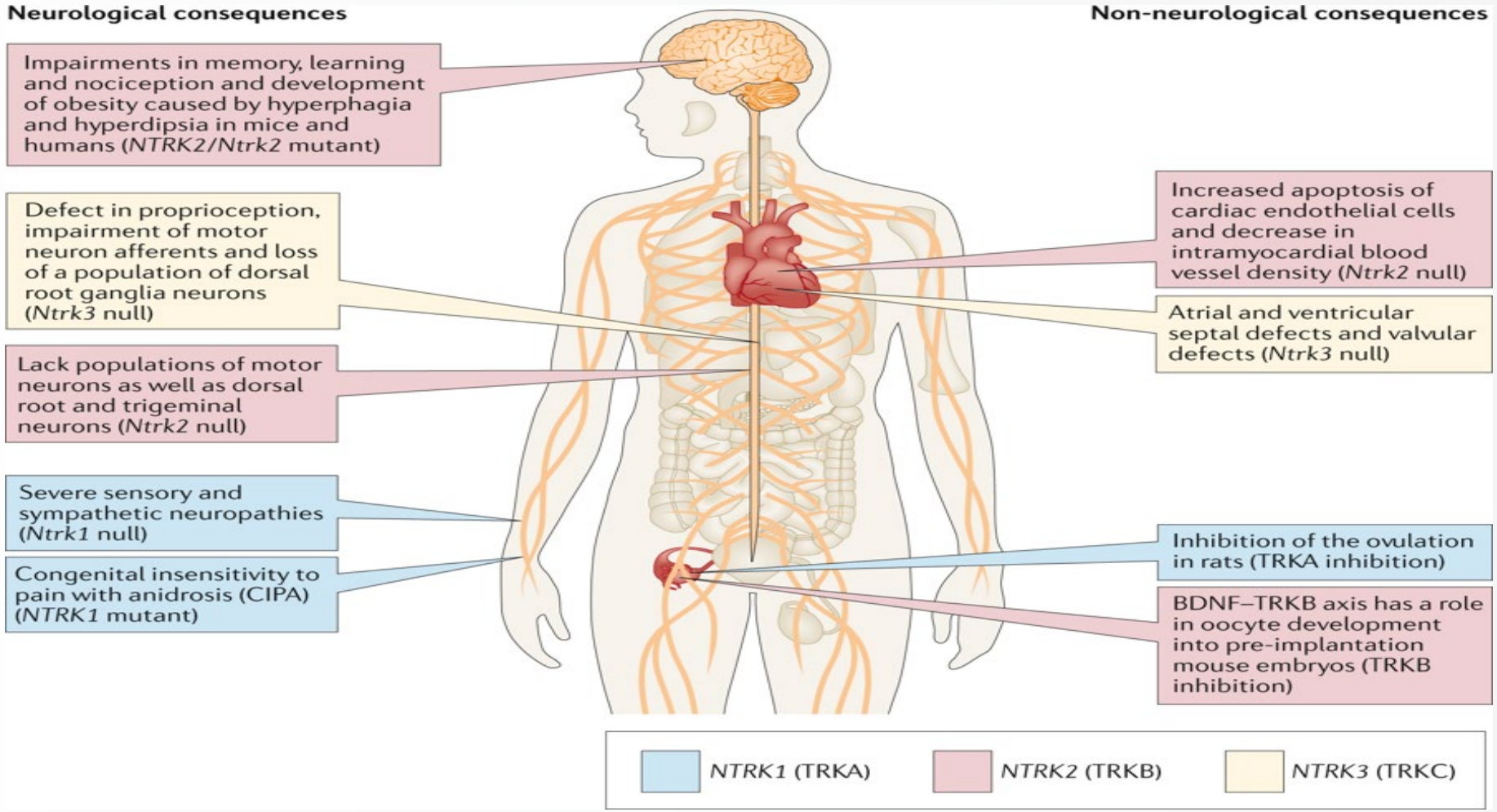
Lin JJ et al., NPJ Precis Oncol 2020;4:21

ROS1 Conclusions

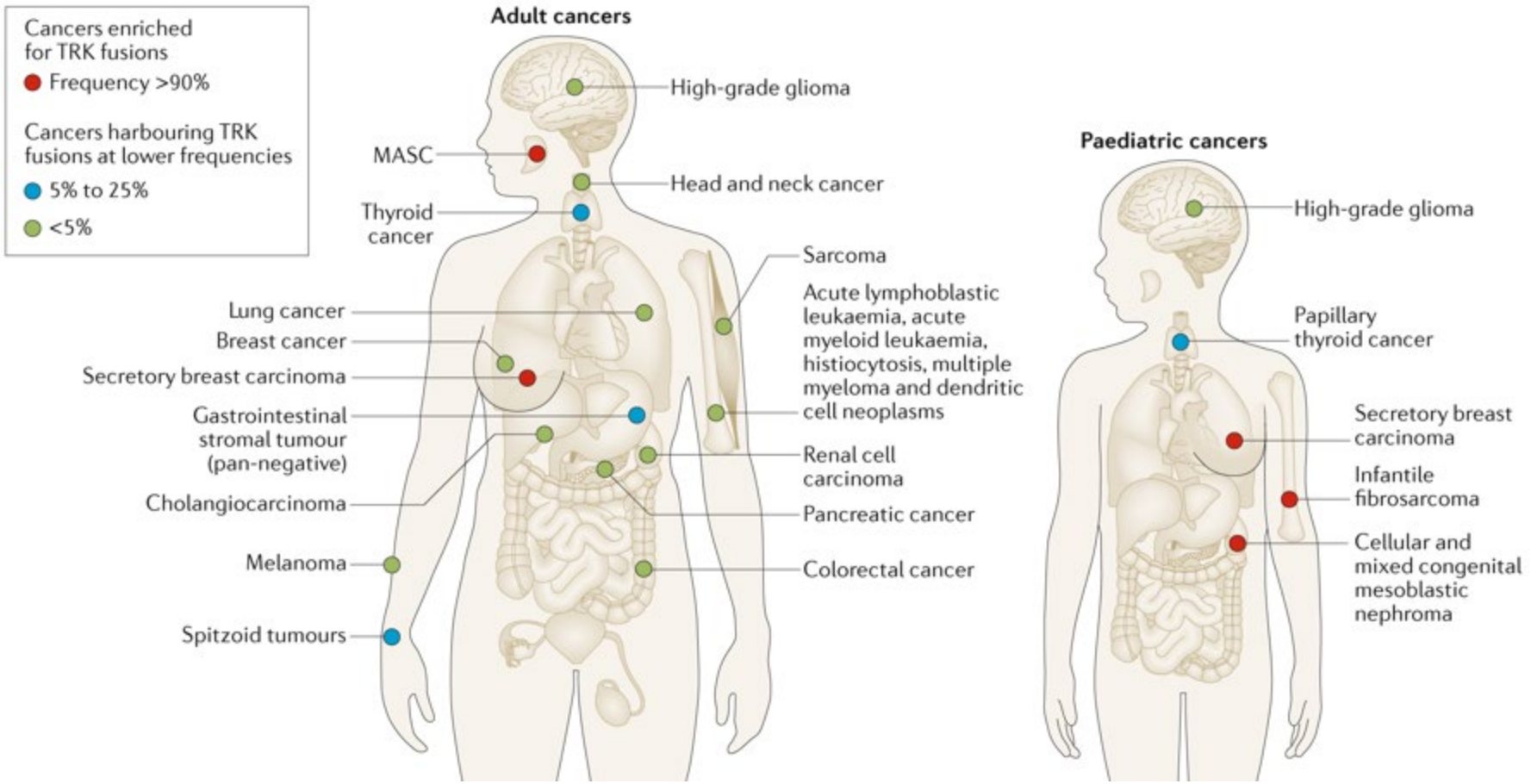
- Account for 1-2% of all Non-sq NSCLC
- Crizotinib and Entrectinib: active agents, with RR% > 65%, PFS 15-20 mos, LTS rates > 4 yrs
- At resistance, R/O other actionable markers, as well as SCLC transformation
  - Lorlatinib, Repotrectinib, Taletrectinib and Cabozantinib all active
  - SOC: Platinum and Pemetrexed +/- Bev

NTRK

The TRK pathway is involved in nervous system development and maintenance



NTRK fusions are found across diverse adult and pediatric cancers



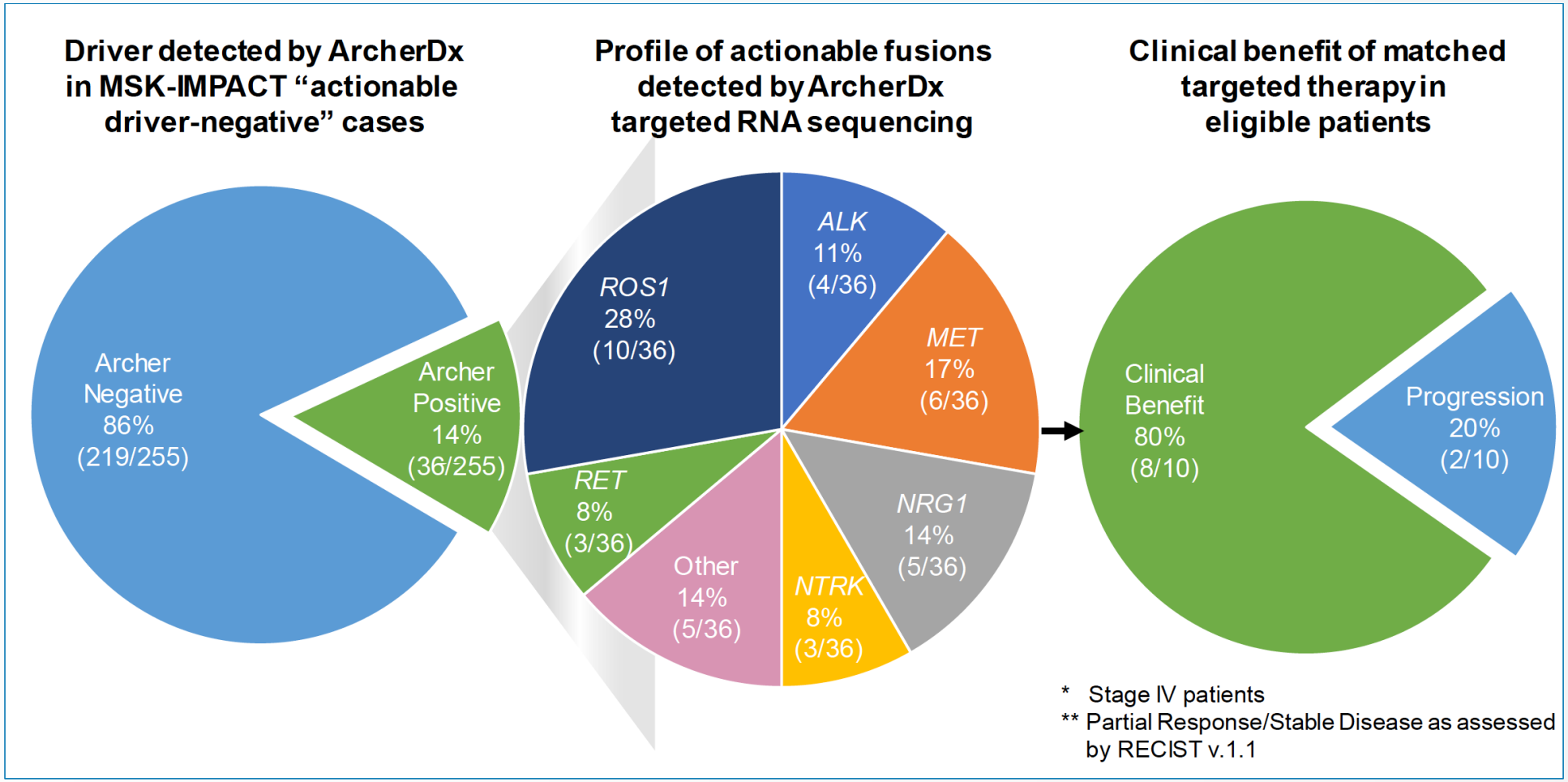
Cocco et al, Nat Rev Clin Oncol 2018

Targeted RNA sequencing can complement DNA-based NGS by increasing NTRK fusion detection

DNA

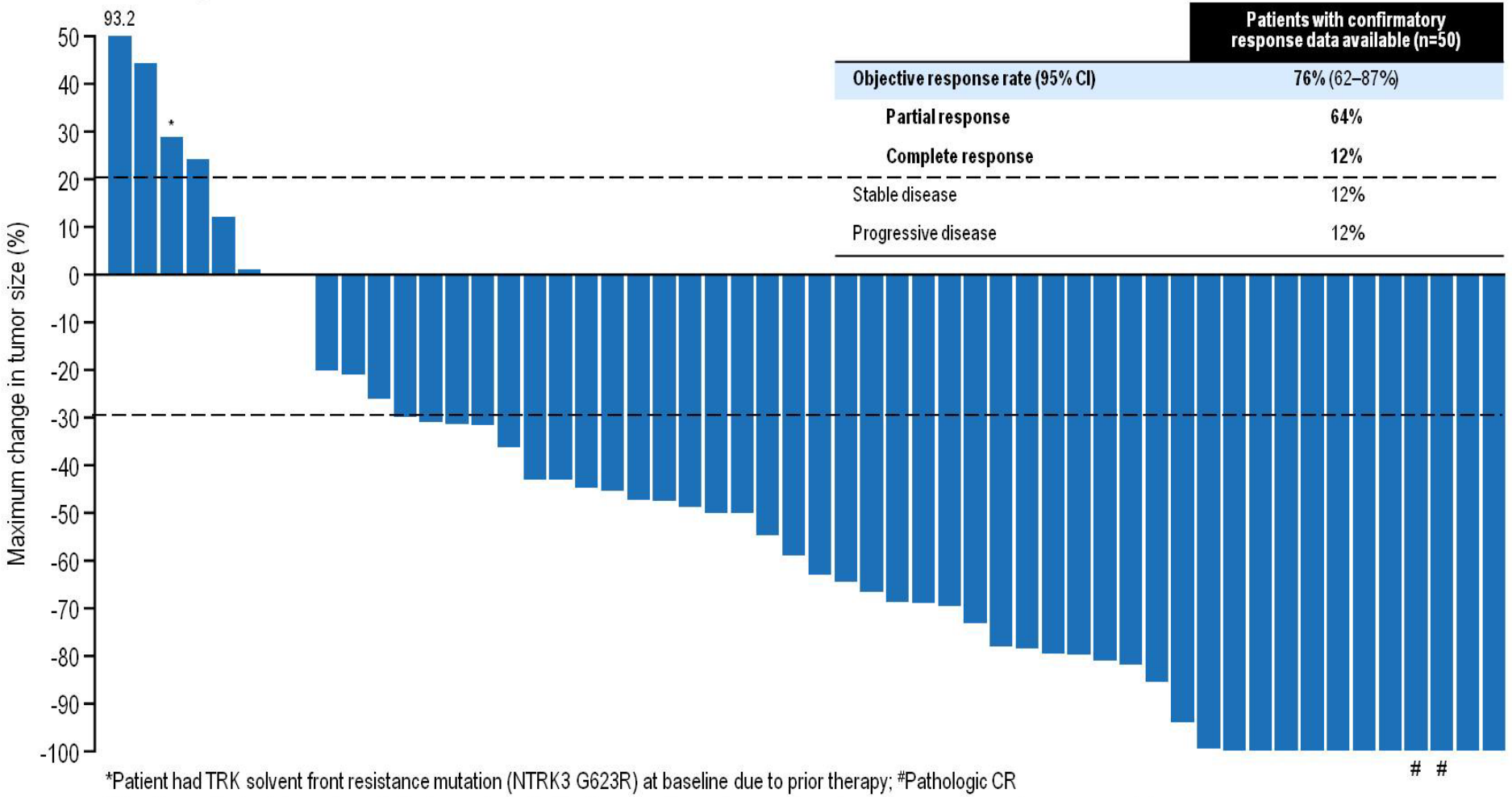
no driver identified

RNA



Benayed et al, Clin Cancer Res 2018

Efficacy of larotrectinib in TRK fusion cancers

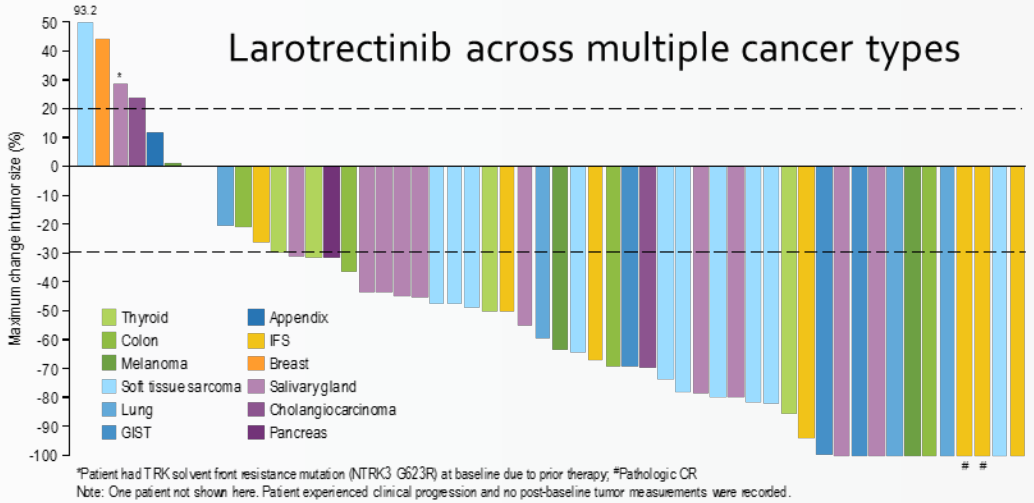


	Patients with confirmatory response data available (n=50)
Objective response rate (95% CI)	**76%** (62–87%)
Partial response	**64%**
Complete response	**12%**
Stable disease	12%
Progressive disease	12%

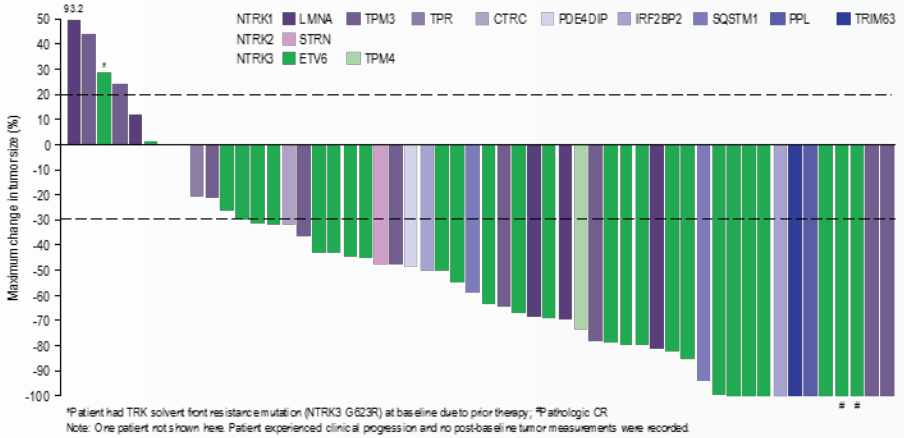
*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

David Hyman at 2017 ASCO Annual Meeting

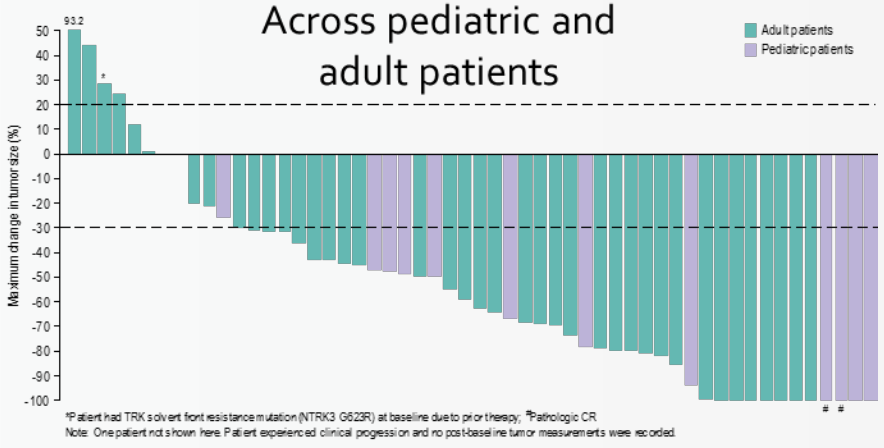
First generation TRK inhibition: active in NTRK fusion (+) adult and pediatric cancers



Across fusion types



Across pediatric and adult patients



Drilon et al, NEJM 2017

Long-term efficacy of larotrectinib in TRK-fusion positive NSCLC

This analysis reports updated long-term efficacy and safety data of patients with TRK fusion-positive lung cancer treated with larotrectinib

Adult phase I (NCT02122913)
- Age ≥18 years
- Advanced solid tumors

n=1

NAVIGATE: adult/adolescent phase II 'basket' trial (NCT02576431)
- Age ≥12 years
- Advanced solid tumors
- TRK fusion cancer

n=19

20 patients with metastatic lung cancer harboring an *NTRK* gene fusion

Endpoints

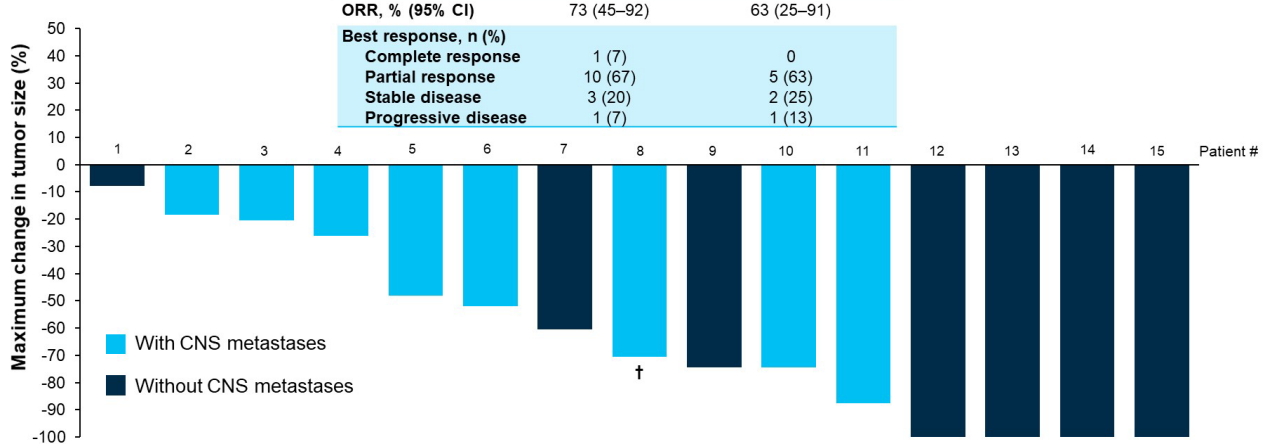
Primary
- **ORR per investigator assessment (RECIST v1.1)**

Secondary
- **DoR**
- **PFS**
- **OS**
- **Safety**

Data cut-off: July 20, 2020 **Dose:** 100 mg BID

	N = 20
Age, median (range), years	48.5 (25.0–76.0)
Sex, n (%)	
Male	10 (50)
Female	10 (50)
CNS metastases at baseline, n (%)	
No	10 (50)
Yes	10 (50)
Previously treated with radiotherapy*	2 (10)
***NTRK* gene fusion**, n (%)	
NTRK1	16 (80)
NTRK2	0
NTRK3	4 (20)
Testing methods, n (%)	
RNA-based anchored multiplex PCR	4 (20)
RNA-based NGS	2 (10)
RNA-based whole transcriptome sequencing	1 (5)
DNA-based NGS	13 (65)
Tumor histology, n (%)	
Adenocarcinoma	19 (95)
Neuroendocrine carcinoma	1 (5)†

	All patients (N = 20)	Patients with CNS metastases (N = 10)
Evaluable patients, n	15	8
ORR, % (95% CI)	73 (45–92)	63 (25–91)
Best response, n (%)		
Complete response	1 (7)	0
Partial response	10 (67)	5 (63)
Stable disease	3 (20)	2 (25)
Progressive disease	1 (7)	1 (13)



Lin JJ, et al. ASCO 2021

TRK inhibitors are active in TRK fusion-positive cancers

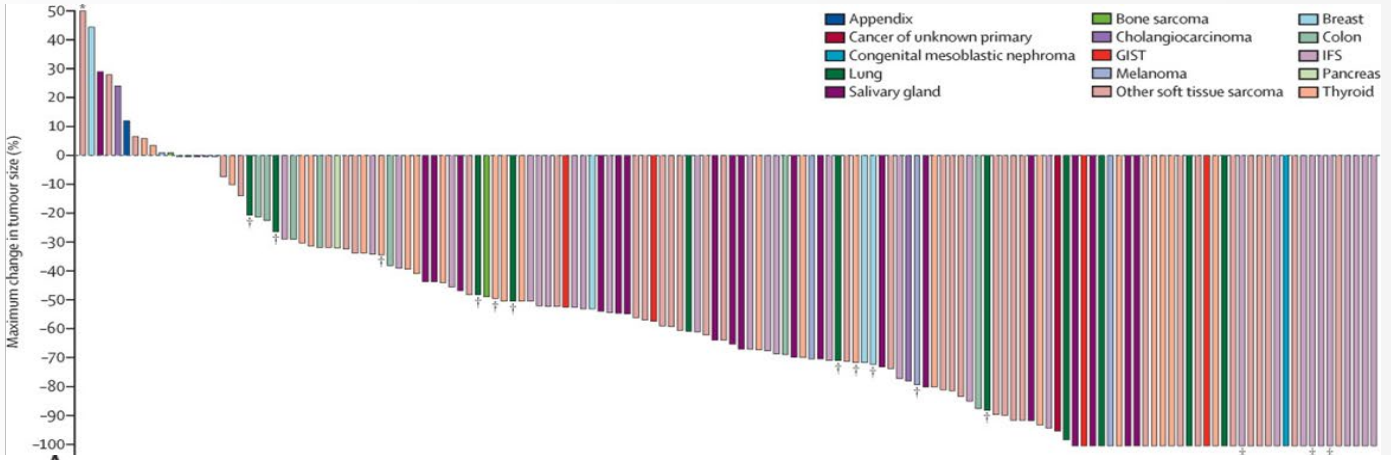
<u>Larotrectinib</u>

ORR 79%

(95% CI 72-85%, n=159)

Median DoR 35.2 months

Median PFS 28.3 months



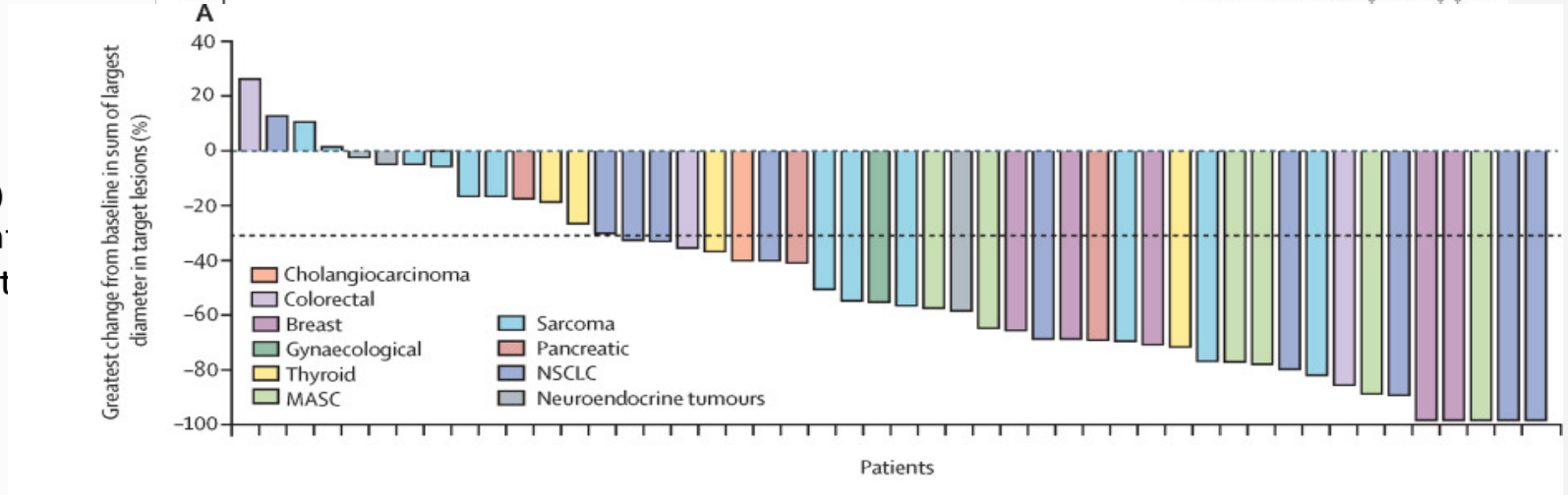
<u>Entrectinib</u>

ORR 57%

(95% CI 43-71%, n=54)

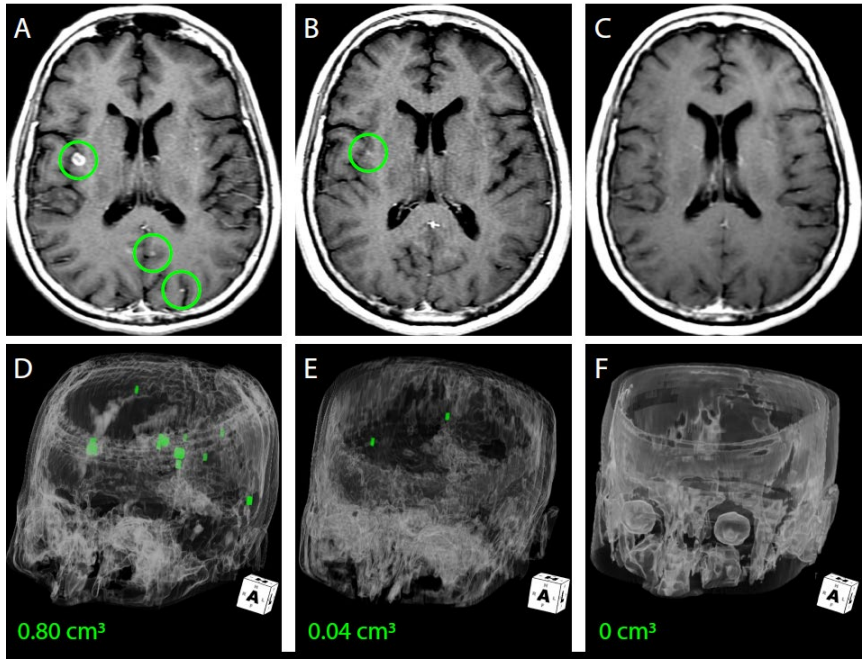
Median DoR 10 mon

Median PFS 11 mont



TRK inhibitors are active in the CNS

Patients with brain metastases	Larotrectinib	Entrectinib
ORR (at all sites)	ORR 60% (n=5)	ORR 50% (n=12)
Intracranial ORR	ORR 66% (n=3)	ORR 55% (n=11)
Intracranial PFS	Not reported	14 months

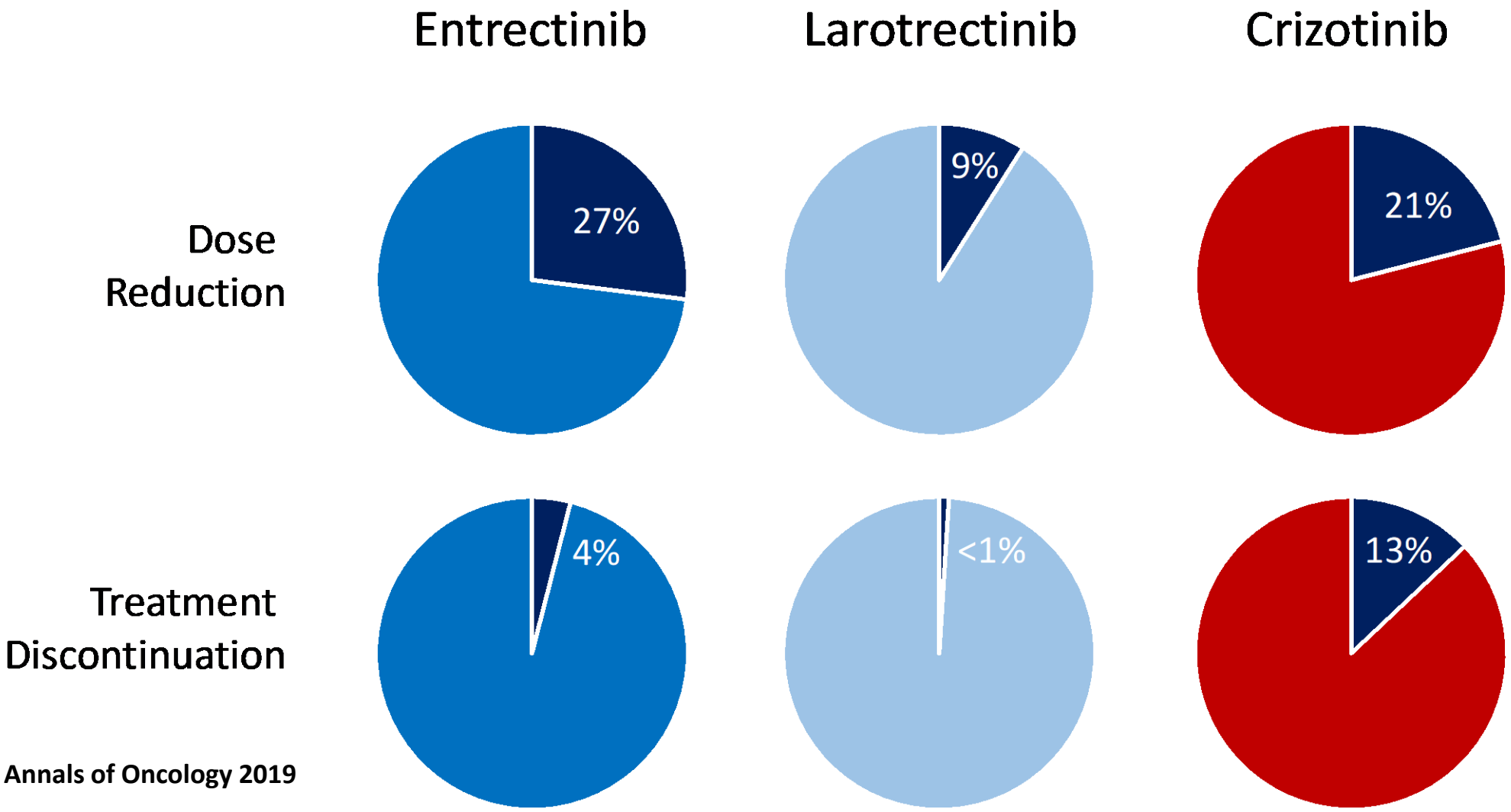


TRK fusion-positive lung cancer with brain metastases treated with larotrectinib

- Confirmed PR (–34%)
- Near intracranial CR (–95%, volumetric)
- Remains on therapy at 6+ months

Drilon et al, ASCO 2019; Demetri et al, ESMO 2018; Rosen et al JCO-PO 2019

TRK inhibitors are well-tolerated

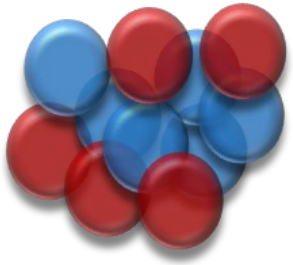


Drilon, Annals of Oncology 2019

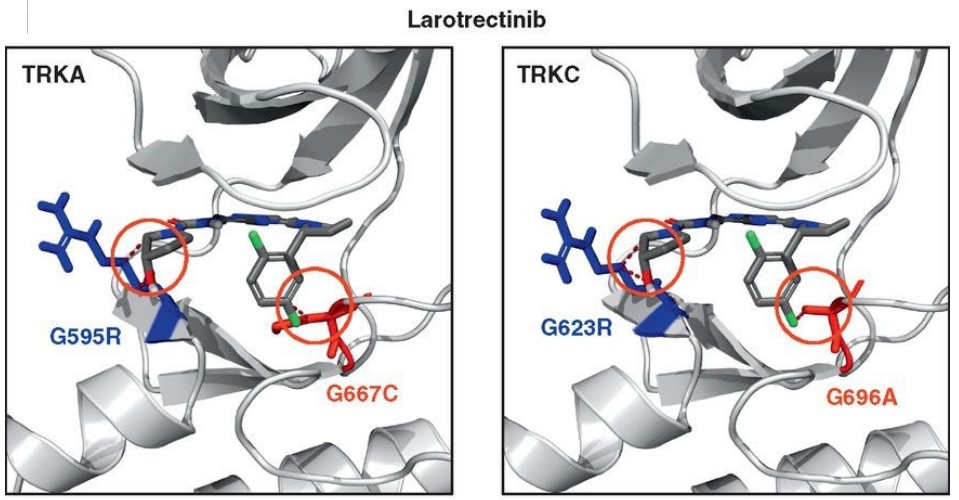
TRK fusion-positive cancers can develop on-target resistance to TRK inhibitor therapy

NTRK fusion

1st-generation TKI



NTRK fusion
NTRK mutation

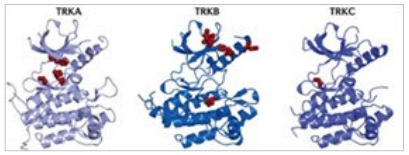


Drilon et al, Cancer Discov 2017

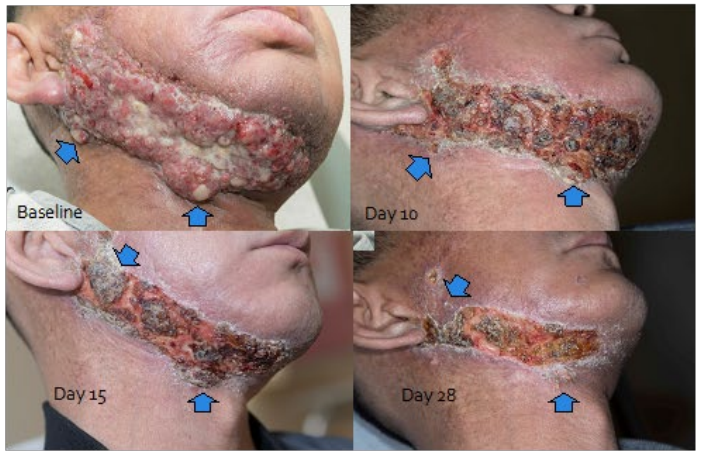
Next-generation TRK TKIs can address on-target resistance to early-generation TRK TKIs

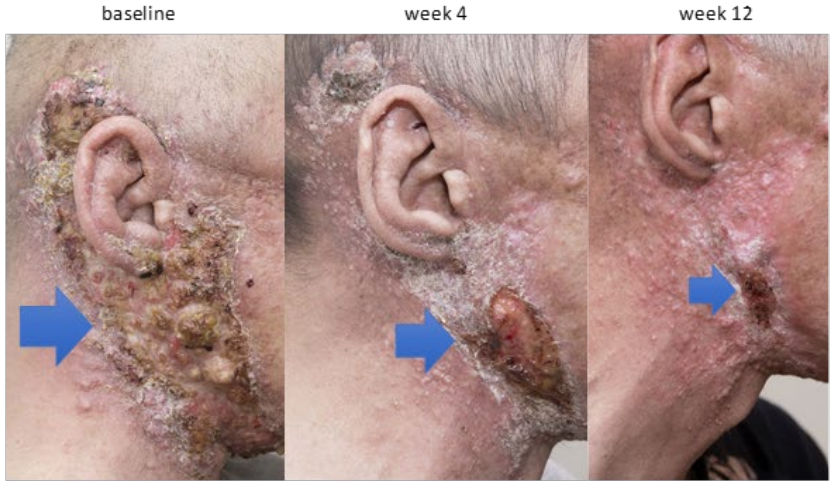
1st gen drug → **2nd gen drug**

Larotrectinib
Entrectinib



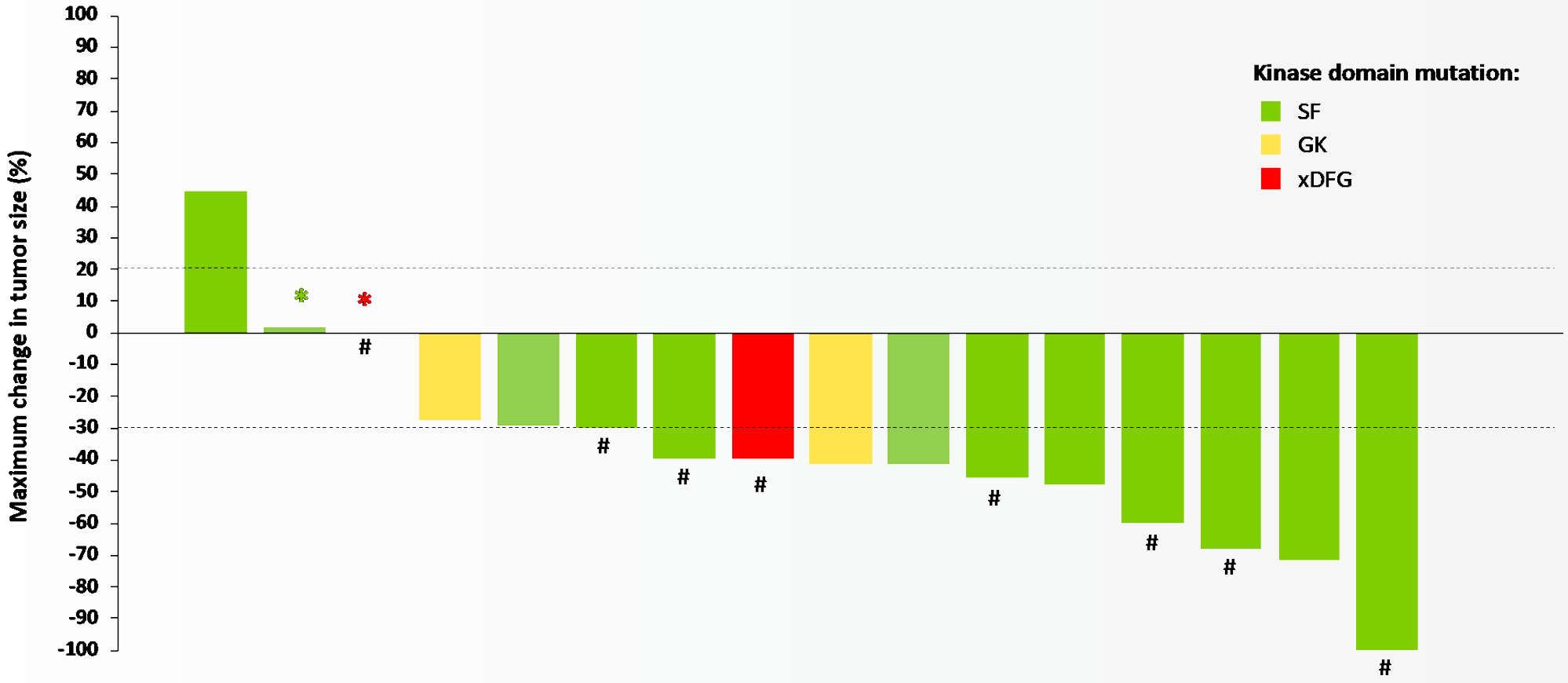
Selitrectinib
Repotrectinib
Taletrectinib
SIM1803-1A
PBI-200





Drilon et al, Cancer Discov 2018

Next-gen TRK TKIs can address on-target resistance to early-generation TRK TKIs



Cocco et al, Nature Med 2019

Conclusions

- **TRK inhibitors are active and results in durable disease control in NTRK fusion-positive cancers.**

- **Resistance to TRK inhibitor therapy can develop**
  - Next-generation TRK TKIs can re-establish disease control
  - Molecular profiling can help direct treatment sequencing

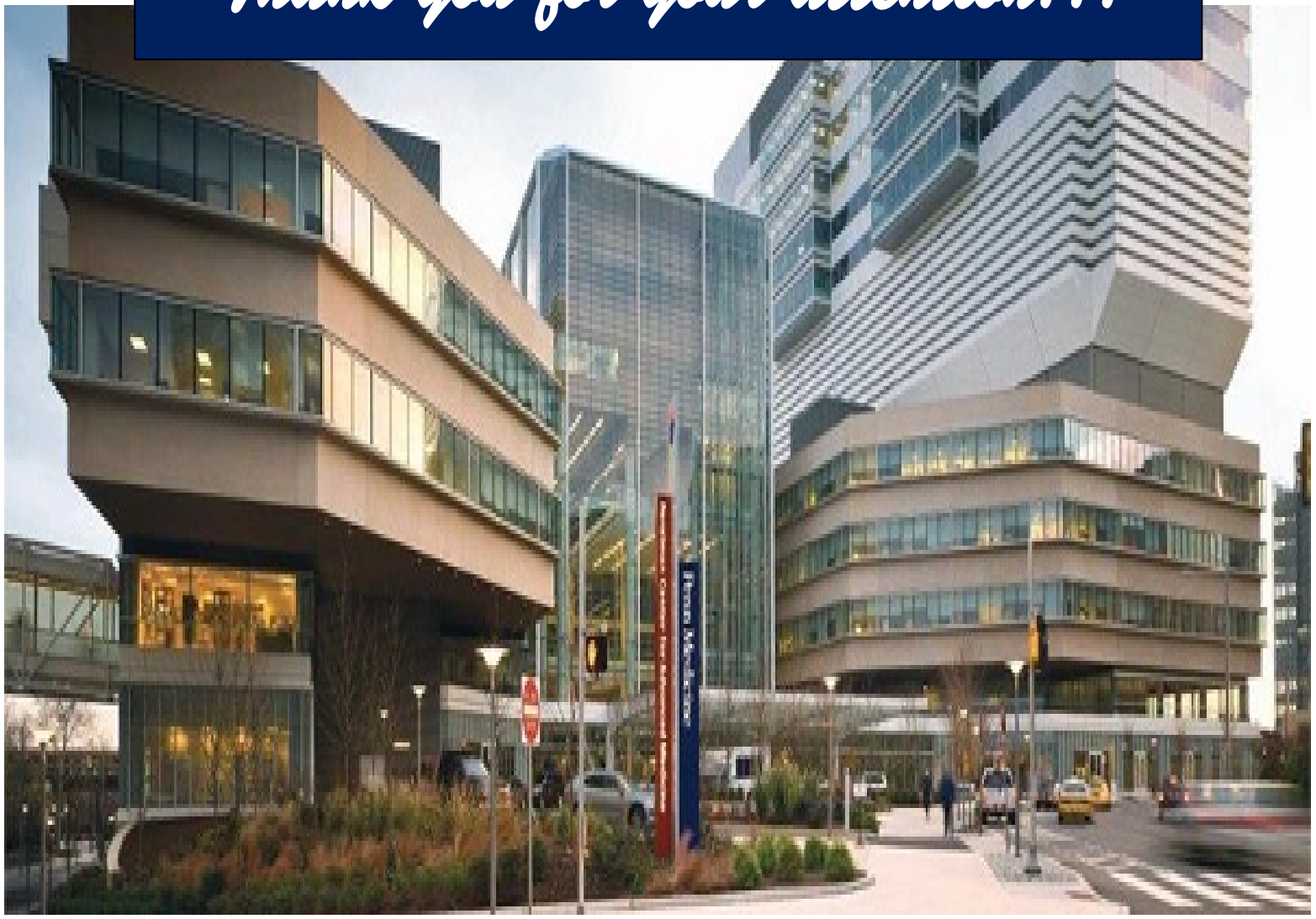
- **TRK inhibitors are well-tolerated**
  - Low rate of dose modification and discontinuation
  - TRK inhibitors have a unique side-effect profile that requires monitoring in the clinic

Lazarus Effect

Actionable Oncogenic Drivers Trump PS

Jean-Baptiste Jouvenet, 1706

Thank you for your attention!!!



Perelman Center for Advanced Medicine
University of Pennsylvania, Philadelphia, PA