ALK and ROS1 Fusions and BRAF Mutations in NSCLC

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UCDAVIS COMPREHENSIVE CANCER CENTER

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A Comprehensive Cancer Center Designated by the National Cancer Institute

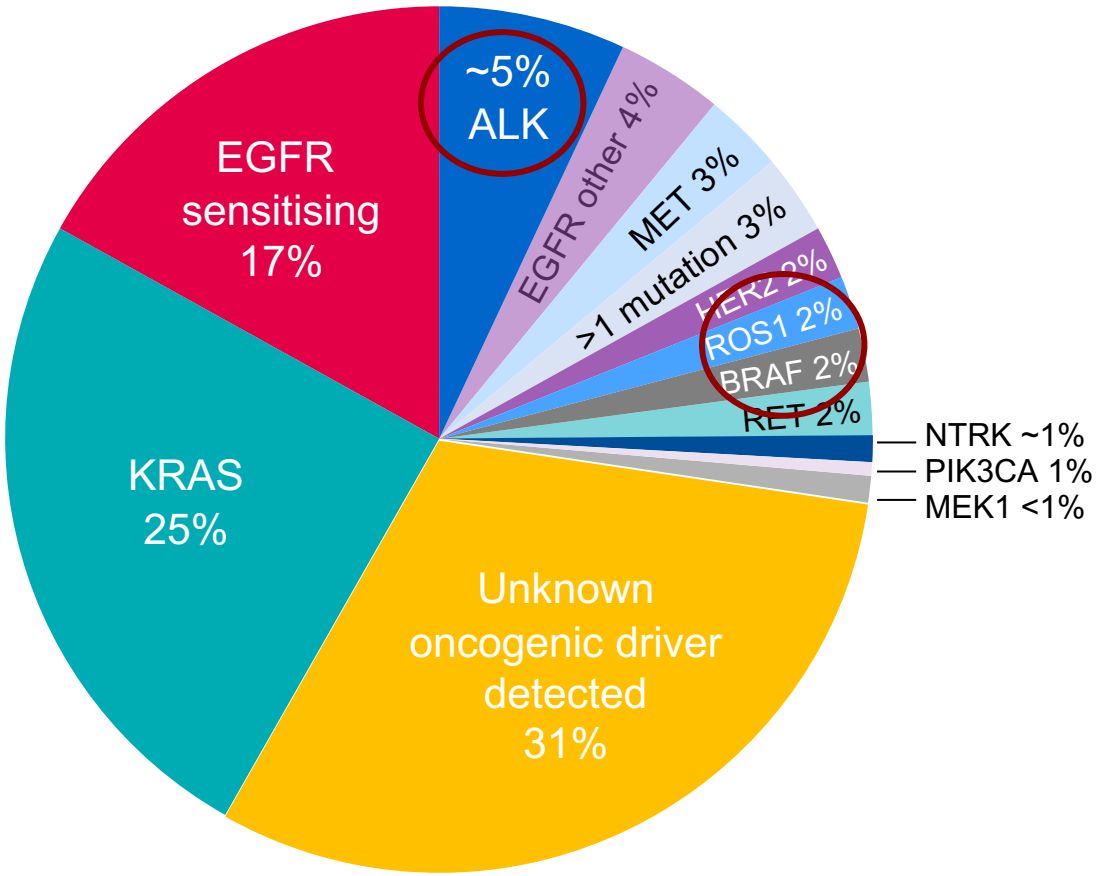
Disclosures

- Consulting/Advisory Board: Blueprint, Beigene, Daiichi Sankyo, EMD Serano, Janssen, Regeneron, Turning Point, Bristol Myers Squibb, Jazz Pharmaceuticals, Novartis, Roche/Genentech, Boehringer Ingelheim

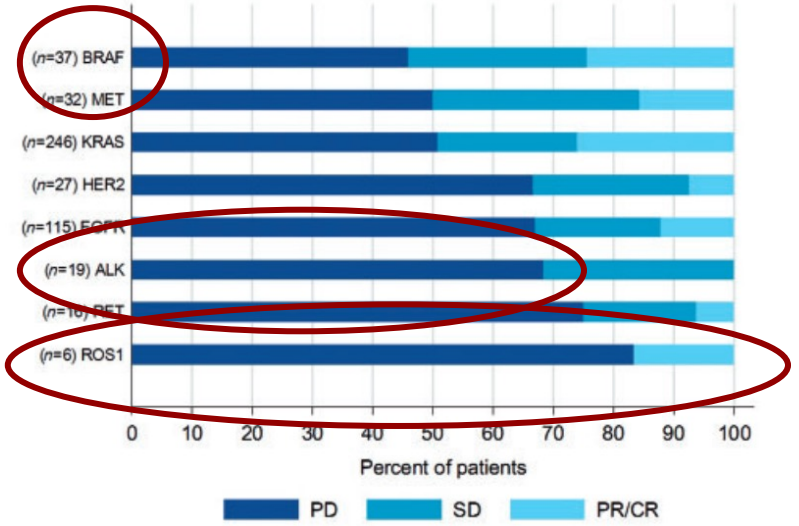
- Research Funding: Merck, Boehringer Ingelheim, Novartis, AstraZeneca, Spectrum, Revolution Medicines

ALK and ROS1 Fusions and BRAF mutations in NSCLC

Driver mutations in lung cancer



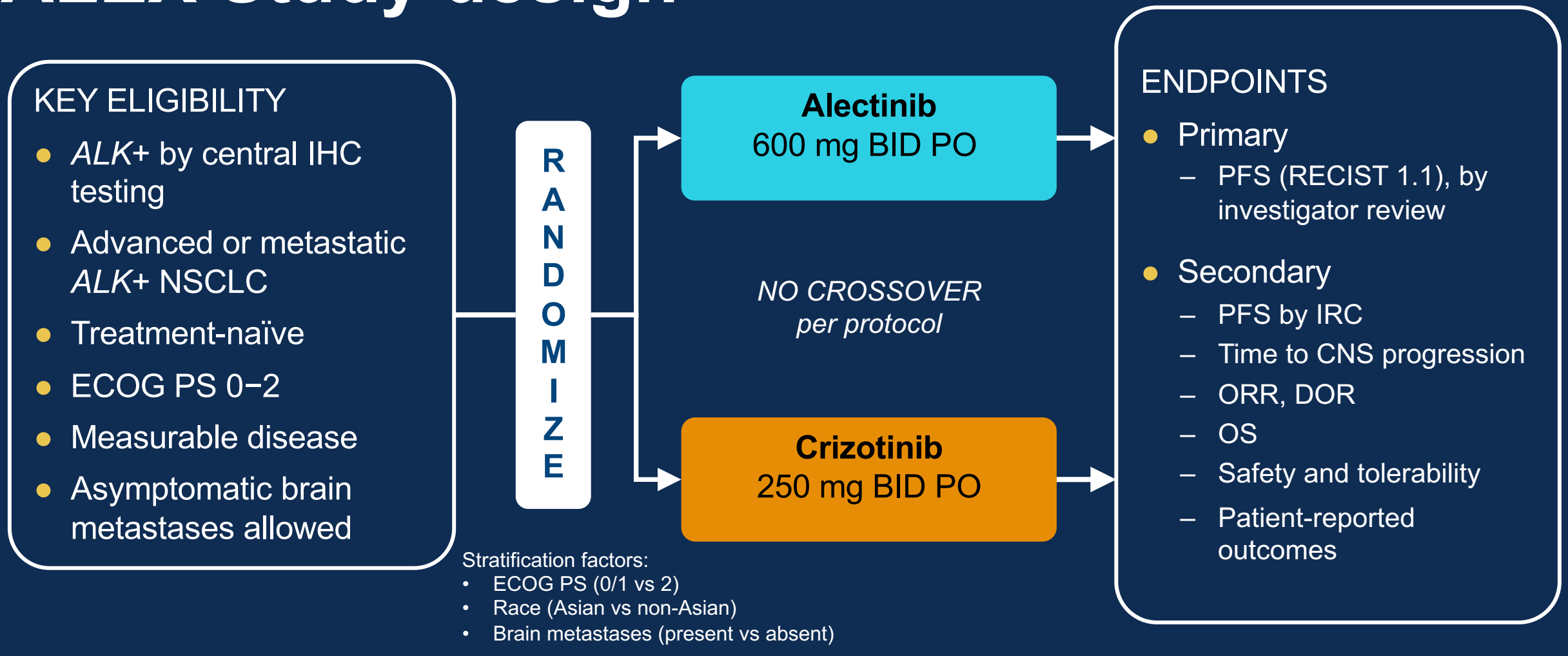
Driver mutations and Response to PD(L)1



- **ALK and ROS1 Fusions and BRAF Muations in total represent ~10% of NSCLC-adenocarcinoma**
- **ALK and ROS1 fusions mainly never/light smoking history**
- **BRAF mutations- maybe older, more likely than ALK or ROS1 Have a smoking history.**
- **BRAF mutant NSCLC may benefit from ICI. ALK and ROS1 no clear benefit to PD-(L)1**

Tsao et al JTO 2016. J. Mazieres et al. Annals of Oncology 2019

ALEX Study design



ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PO, by mouth; PFS, progression-free survival; IRC, independent review committee; CNS, central nervous system; ORR, objective response rate; DOR, duration of response; OS, overall survival

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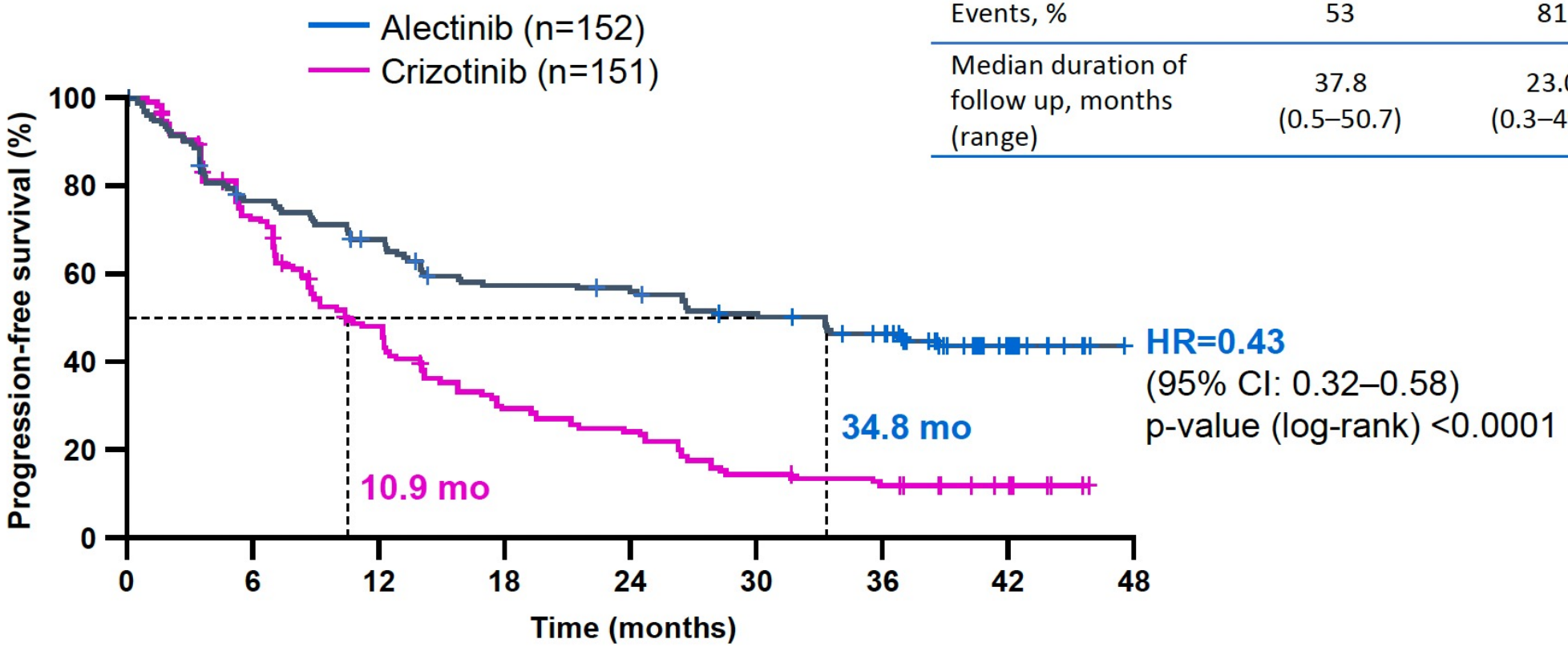
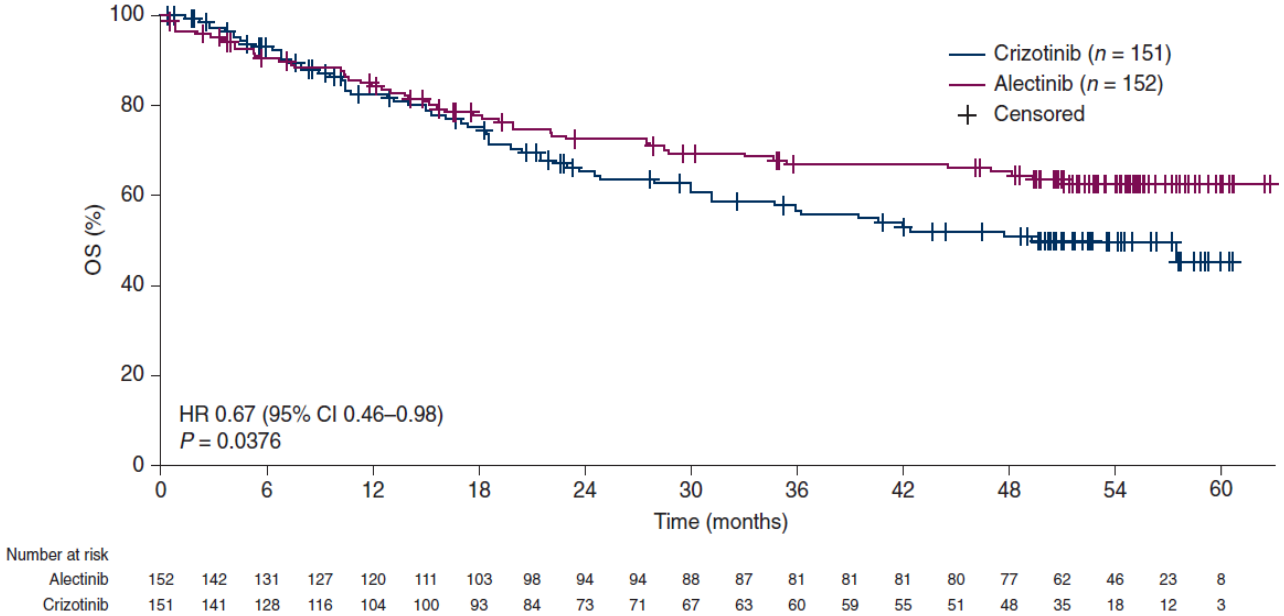
Updated Results: ALEX Trial

	Alectinib	Crizotinib
Events, %	53	81
Median duration of follow up, months (range)	37.8 (0.5–50.7)	23.0 (0.3–49.8)



T. Mok et al. ESMO 2019

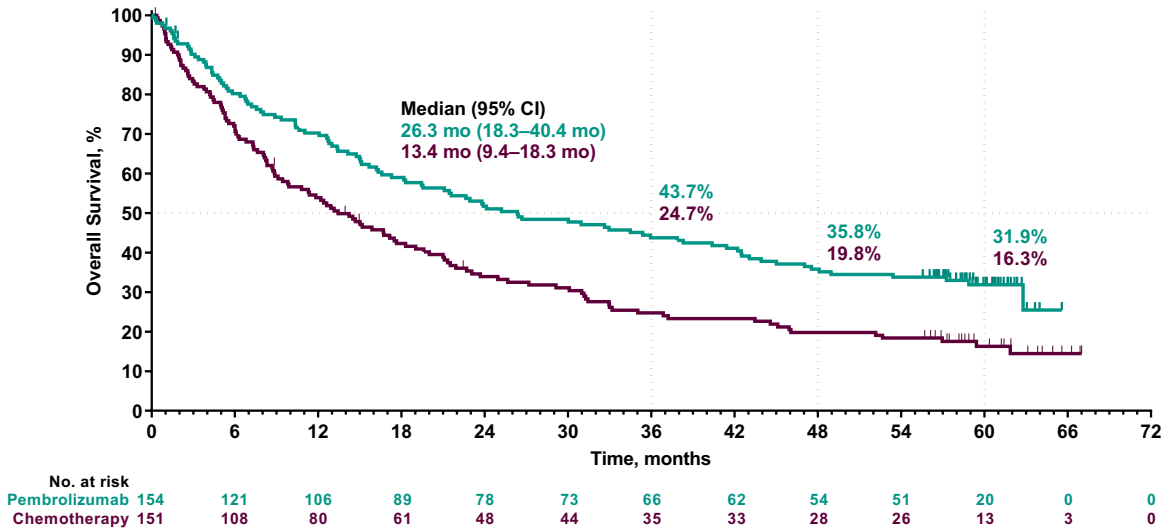
ALEX: Secondary Endpoint: OS (Updated)



	Alectinib	Crizotinib
Median OS	Not reached	57.4 months
5-year OS	62.5%	45.5%

Mok et al. *Ann Oncol*. 2020;31(8):1056

KN024 Pembrolizumab 5-yr OS PD-L1 High

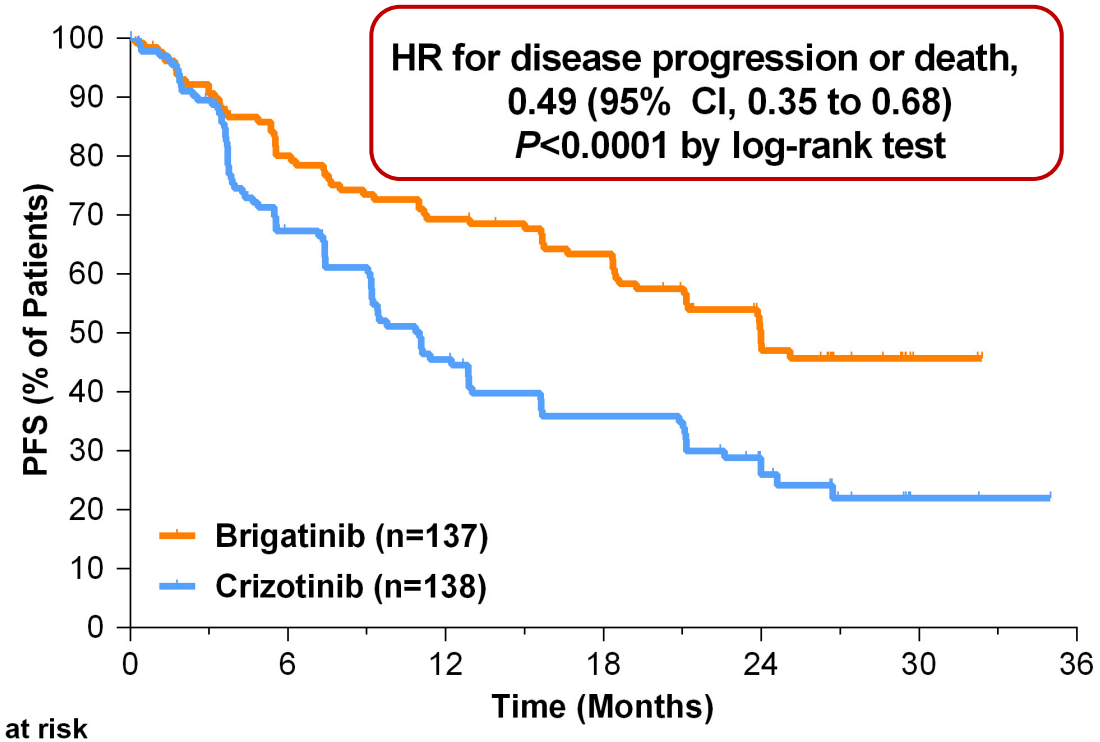


J. Brahmer et al. ESMO 2020

Note: J-ALEX did not show OS benefit compared to criz likely d/t crossover

Updated PFS ALTA 1L Brigatinib

Primary Endpoint: BIRC-Assessed PFS

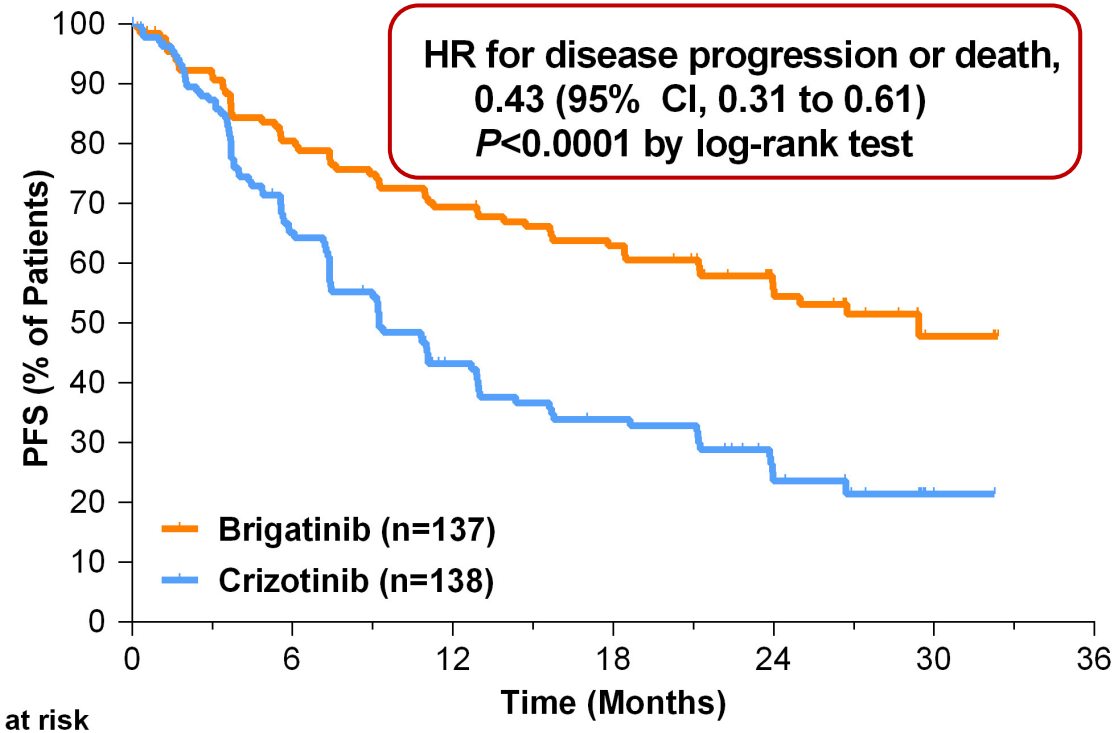


No. at risk

Brigatinib	137	97	84	75	39	3	0
Crizotinib	138	80	49	37	17	2	0

Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=137)	63 (46)	24.0 mo (18.5–NR)	48 (39–57)
Crizotinib (n=138)	87 (63)	11.0 mo (9.2–12.9)	26 (18–35)

Investigator-Assessed PFS



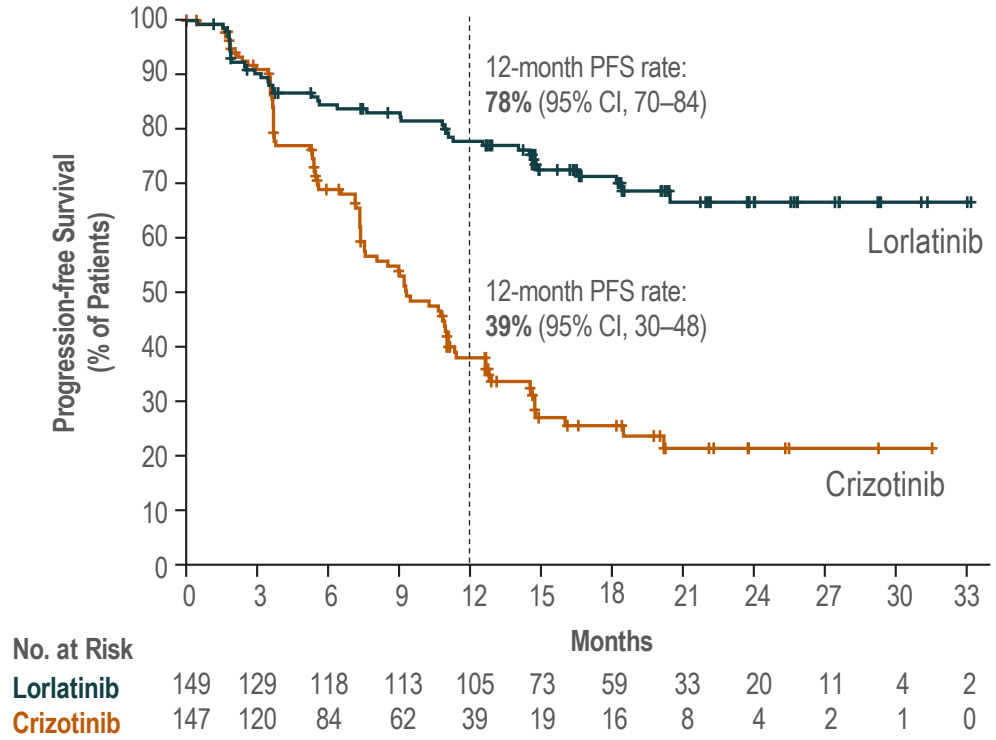
No. at risk

Brigatinib	137	102	88	78	46	4	0
Crizotinib	138	82	46	35	14	1	0

Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=137)	59 (43)	29.4 mo (21.2–NR)	56 (46–64)
Crizotinib (n=138)	92 (67)	9.2 mo (7.4–12.9)	24 (16–32)

Lorlatinib > Crizotinib

Crown 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.

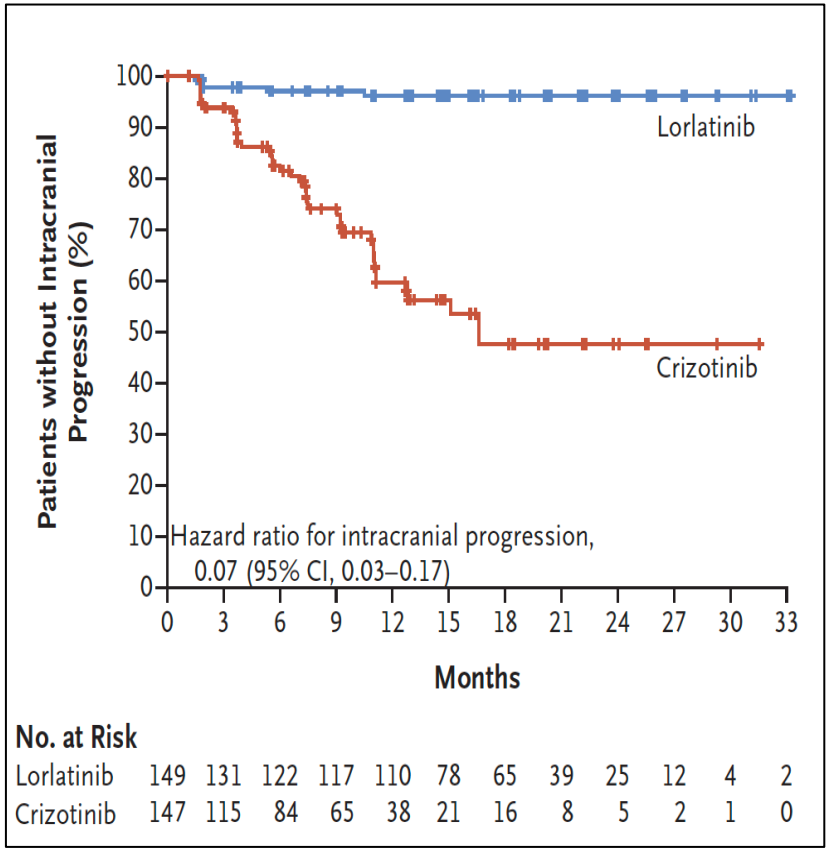
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival

Solomon LBA#2, ESMO 2020

Comparing ALK Inhibitors By CNS Activity

Trial	Therapy	iORR[a] (Measurable Disease)	iORR (Measurable or Non-measurable)	iPFS at 12- or 24-months[b]	Cumulative Incidence of CNS Progression[c]
ALEX[58,59]	Alectinib	81%	59%	-	9%
ALTA-1L[60,61]	Brigatinib	78%	67%	48% (24 mos)	-
CROWN[62]	Lorlatinib	82%	66%	-	3%

[a]iORR, intracranial objective response rate.
[b]iPFS, intracranial progression-free survival.
[c]Assessed at 12-months.



Myall et al, *Neurooncol Adv*, 2021
Shaw et al, *NEJM*, 2020

How to Choose? FDA Approved Next Generation ALK inhibitors for 1L Therapy: Efficacy and Toxicity

	Alectinib	Brigatinib	Lorlatinib
ORR	79%	71%	76%
Med PFS by ICR	25.7 mo	24 mo	NR
Med PFS by IR	34.8	30.8	NR
Med OS	>5 yr	NR	NR
Toxicity	Fatigue, constipation, myalgia (CPK), edema, transaminitis (moderate) Weight gain	Nausea, diarrhea, fatigue, HA, HTN, pulm tox, transaminitis	Edema, neuropathy, cognitive changes (mood), lipids, weight gain

Yun & Bazhenova, *Cancer Manag Res*, 2022

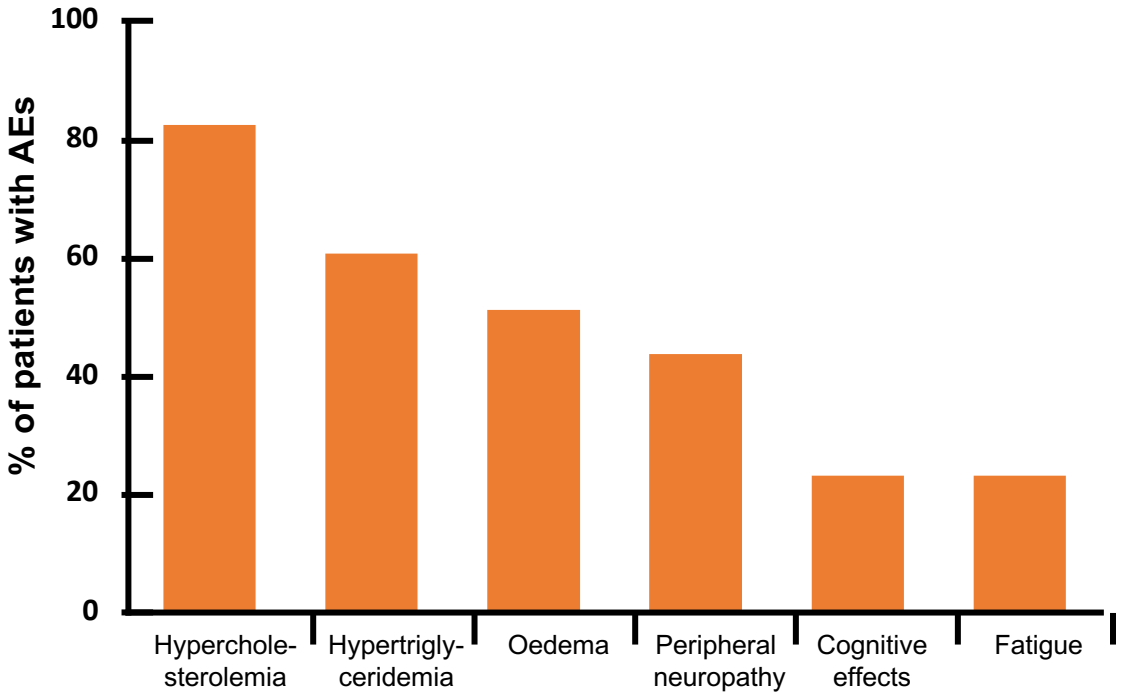
What to do for Second Line Treatment:
Data from the phase 1/2 study of lorlatinib supported its approval in the ≥2L setting

Efficacy[1]

Response to lorlatinib	Non-crizotinib TKI±CT (n=28)	2 ALK TKIs±CT or 3 ALK TKIs±CT (n=111)
ORR,% (95% CI)	42.9 (24.5–62.8)	39.6 (30.5–49.4)
Median PFS,* months (95% CI)	5.5 (2.9–8.2)	6.9 (5.4–9.5)
Intracranial ORR, % (95% CI)	46.2 (19.2–74.9)	48.1 (36.9–59.5)

ORR for patients treated with 1L alectinib was 31%[2]

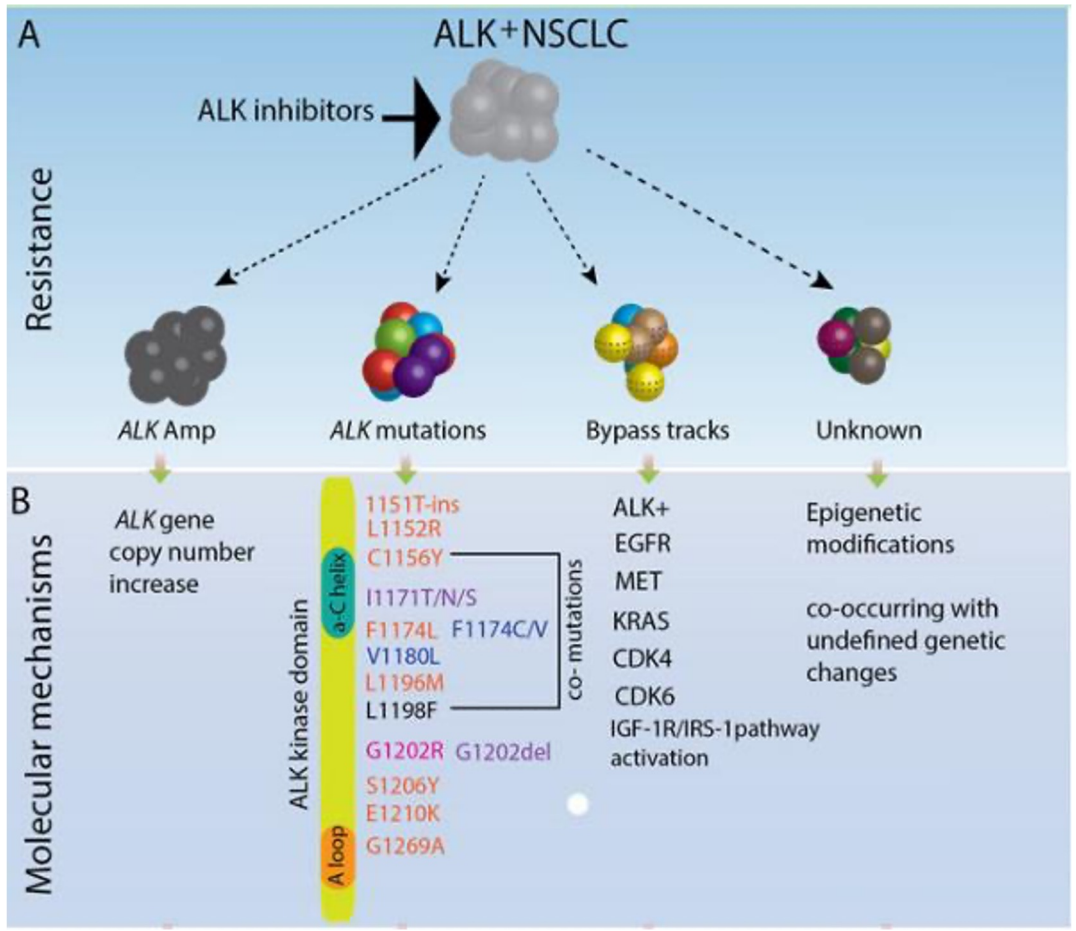
Safety‡[3]



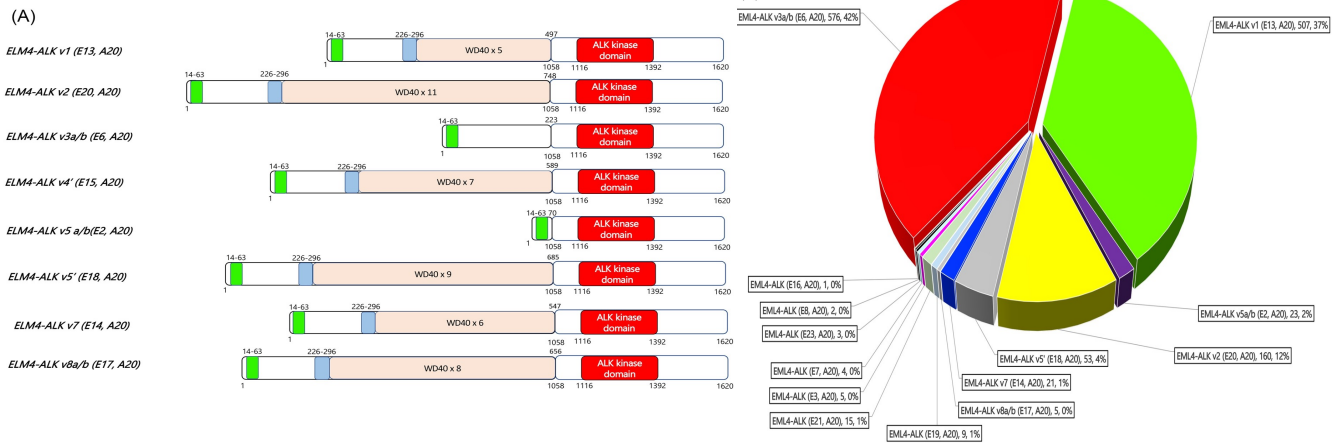
Data cut-off: 2 February 2018
*Kaplan-Meier estimate
†Data are from all patients treated in the phase 1/2 study (n=295)

1. Besse, et al. ASCO 2018; 2. Lorlatinib US PI; 3. Bauer, et al. Oncologist 2019

EML4-ALK Variants and Resistance Mechanisms in ALK+ NSCLC



Wu, W et al. (2017). Cancers. 9. 164. 10.3390/cancers9120164.



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

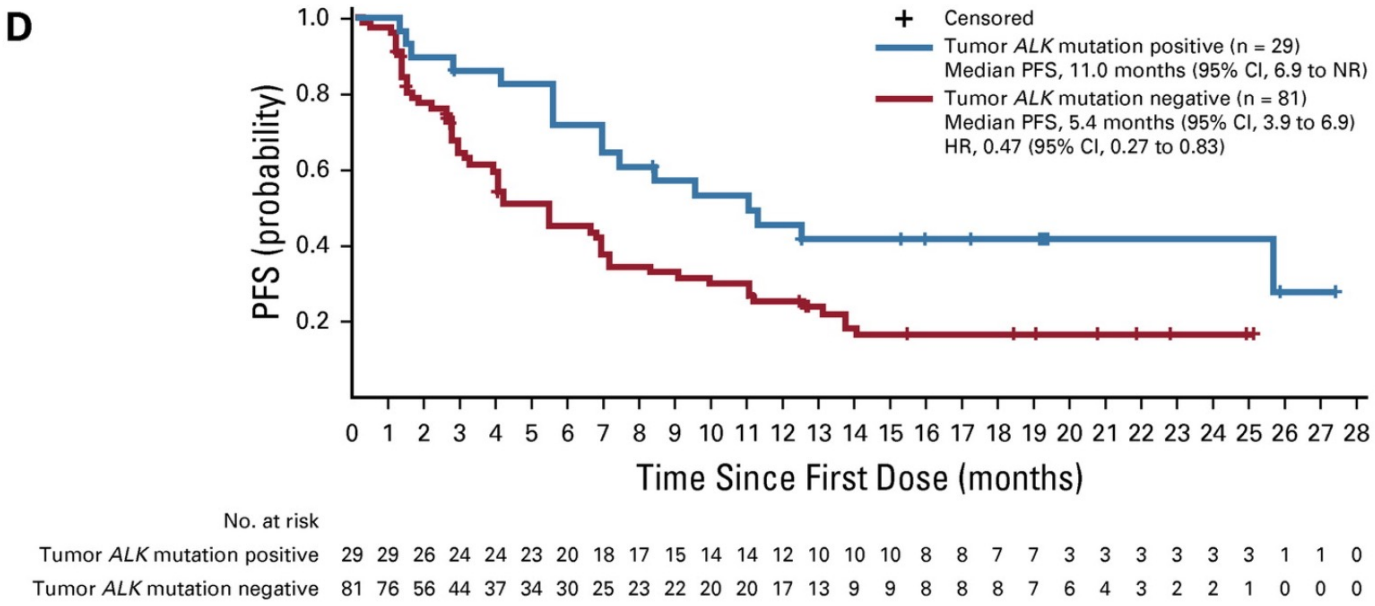
B

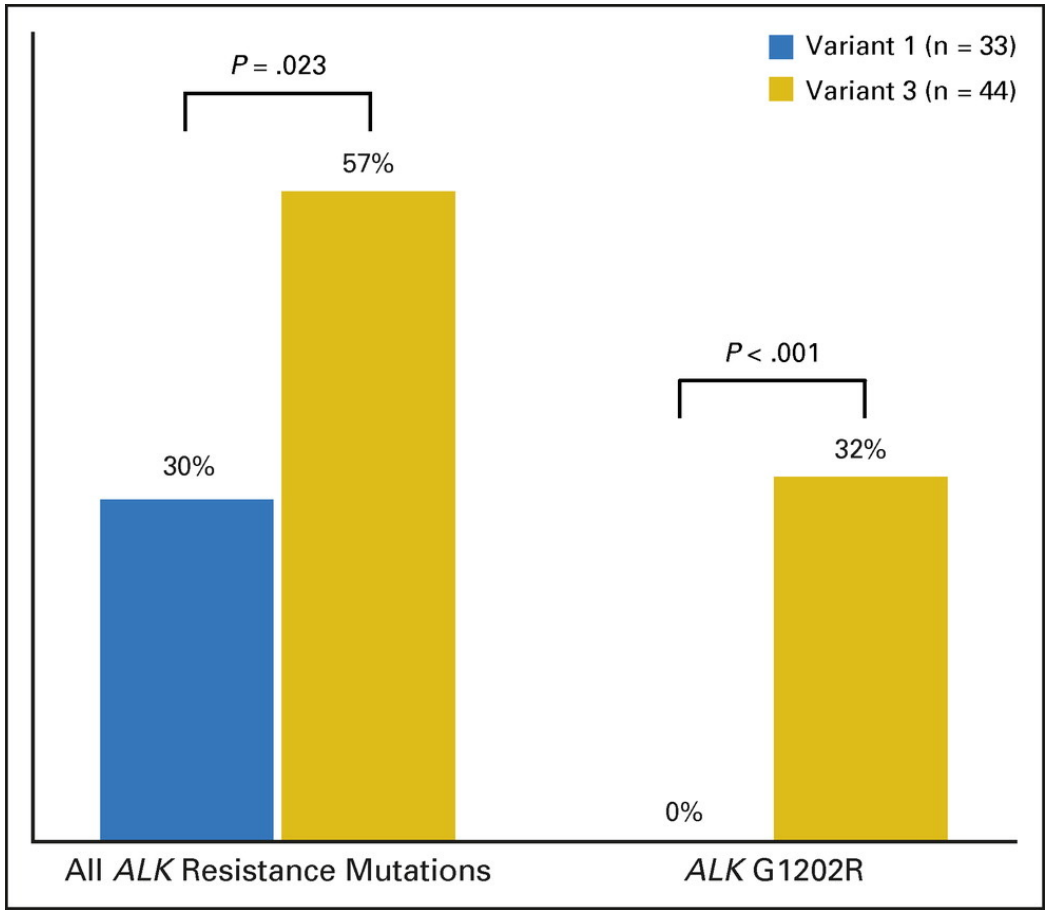
	Crizotinib	Ceritinib	Ensartinib	Alectinib	Brigatinib	Lorlatinib
WT	205.3 70.5 to 597.9	75.1 29.72 to 189.8	24.92 9.450 to 65.70	29.51 15.53 to 56.05	16.75 10.10 to 27.77	4.456 2.376 to 8.357
G1123S	54.50 23.65 to 125.6	651.2 179.3 to 2365	1.309 0.701 to 2.446	3.000 1.424 to 6.319	25.79 9.503 to 69.99	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
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

Zhang et al. Lung Cancer 2019. Lin et al JCO 2018, Horn et al JTO 2019

ALK mutation status / variants and efficacy of Lorlatinib





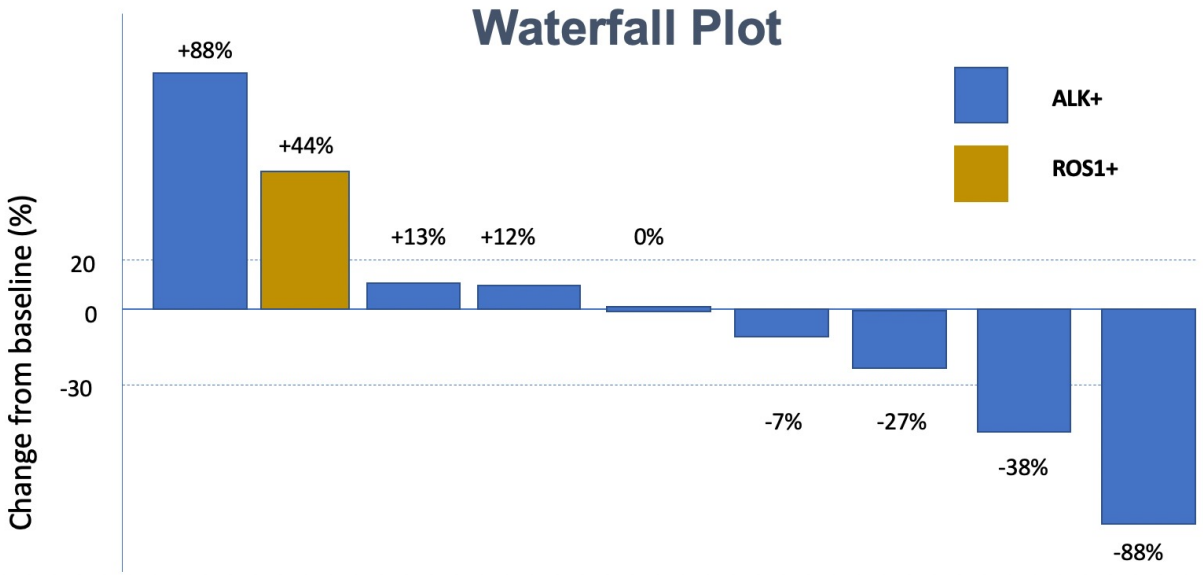
Lorlatinib had longer PFS in v3 patients (n= 17) compared to v1 patients (n= 12).

All patients were previously treated with crizotinib and another ALK inhibitor

Lin et al JCO 2018. Shaw JCO 2019

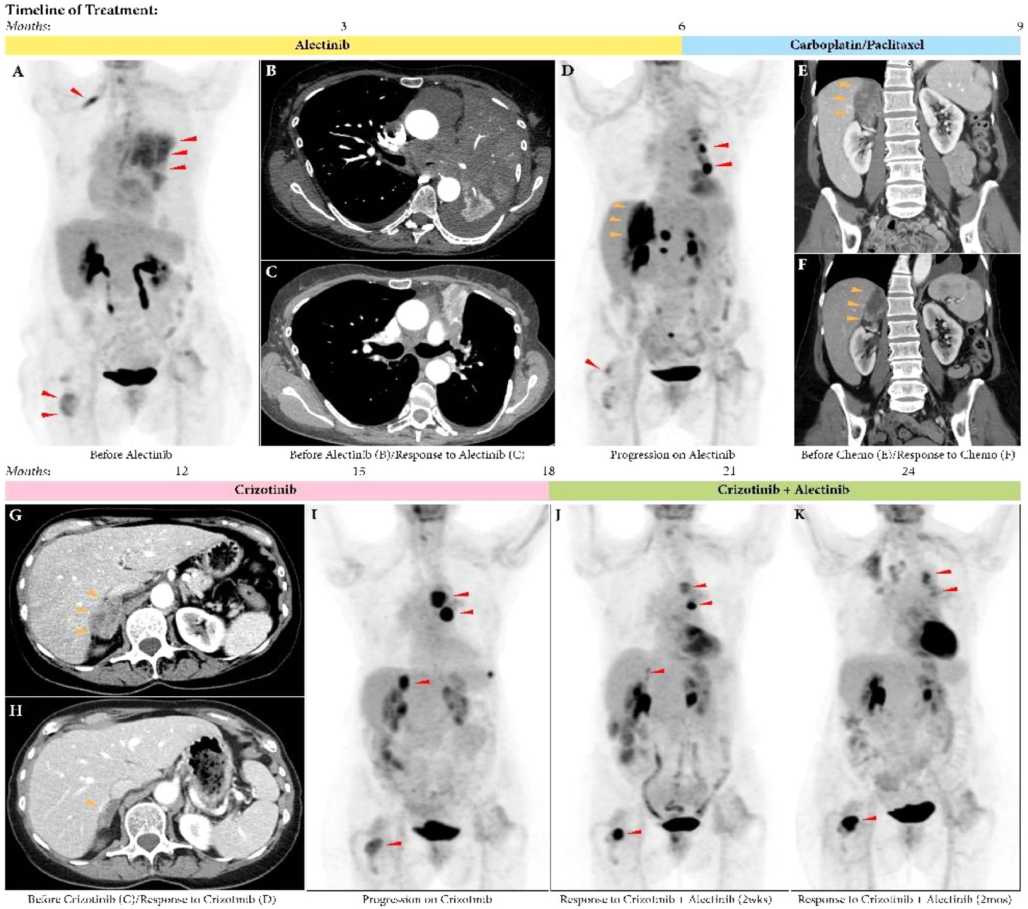
Bypass Tracts Also Matter in ALK TKI Resistance and are Actionable

A Phase 1 Study of Ceritinib and Trametinib



M. Lara, JW Riess, C. Blakely. WCLC 2021

Early Progression on Alectinib with MET amplification and Response to Crizotinib and Alectinib/Crizotinib



J. Jiang, R. Camidge, JW Riess. CLC 2021

4th Generation ALK Inhibitors in Development

TPX-0131: cellular potency against WT, single and compound mutant ALK

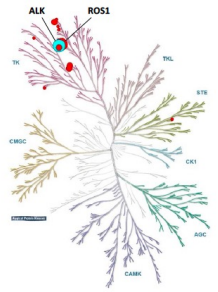
- Potent against the *ALK* solvent front (e.g., G1202R) and hinge region (e.g., L1198F) resistance mutations
- Reduced potency against I1171X and G1269S mutations
- Potent against a range of *EML4-ALK* compound mutations refractory to approved ALK TKIs, including G1202R-based compound mutations

Cui JJ et al., AACR 2020; Brion WM et al., Mol Cancer Ther 2021

Cell proliferation IC_{50} values (nM)						
EML4-ALK	**TPX-0131**	**Crizotinib**	**Alectinib**	**Brigatinib**	**Ceritinib**	**Lorlatinib**
WT	**0.4**	**50**	**7.4**	**12**	**3.9**	**0.8**
I1171N	516	254	4310	49	72	48
I1171S	189	188	306	31	27	31
I1171T	316	232	210	33	29	25
L1196M	**0.5**	**274**	**50**	**21**	**5.4**	**38**
L1198F	<0.2	18	397	74	618	30
G1202R	**0.2**	**434**	**2690**	**188**	**329**	**52**
G1269A	13	451	197	20	15	49
G1269S	701	1390	671	46	97	191
L1196M/L1198F	<0.2	252	2250	253	1410	1310
L1198F/C1156Y	<0.2	19.3	776	102	1310	140
L1198F/I1171N	1.6	626	236	55.1	64.1	78.7
G1202R/C1156Y	0.2	745	2420	810	1300	521
G1202R/L1196M	0.7	808	>10000	1100	1260	4780
G1202R/L1198F	<0.2	188	3000	2040	2010	1710
G1202R/G1269A	9.9	705	7200	164	303	636
G1202R/G1269A/L1204V	14.9	634	6740	176	345	673
G1202R/G1269A/L1198F	0.2	596	>10000	907	1670	6330

NVL-655: a selective, potent 4G ALK TKI

Kinase selectivity screen



Fold ALK IC_{50}	Kinase
1x	ALK, ROS1
1 – 10x	LTK, PYK2, TRKB, FAK
10 – 50x	SLK, TRKA, FER, MUSK, EPHA6, TRKC
>50x	323 other kinases

IC_{50} of NVL-655 and other ALK TKIs in Ba/F3 cell proliferation assays

	Cell expressing ALK fusion	NVL-655	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
No kinase domain mutations	NCI-H3122 (EML4-ALK v1)	2.3	180	36	23	21	3.5
	NCI-H2228 (EML4-ALK v3)	0.70	90	55	13	13	< 1.1
	Karpas299 (NPM1-ALK)	2.0	59	25	18	7.8	3.5
	Ba/F3 EML4-ALK v1	1.6	270	90	25	42	< 3.6
G1202R+ mutations	Ba/F3, G1202R	< 0.73	950	570	1600	400	87
	Ba/F3, G1202R/L1196M	7.0	1500	1400	2200	820	3600
	Ba/F3, G1202R/G1269A	3.0	1100	350	1300	240	970
Non-G1202R+ mutations	Ba/F3, L1196M	29	1100	79	120	100	86
	Ba/F3, I1171N	27	320	140	570	30	59
	Ba/F3, I1171S	29	350	140	390	18	59
	Ba/F3, I1171T	35	400	140	260	16	51

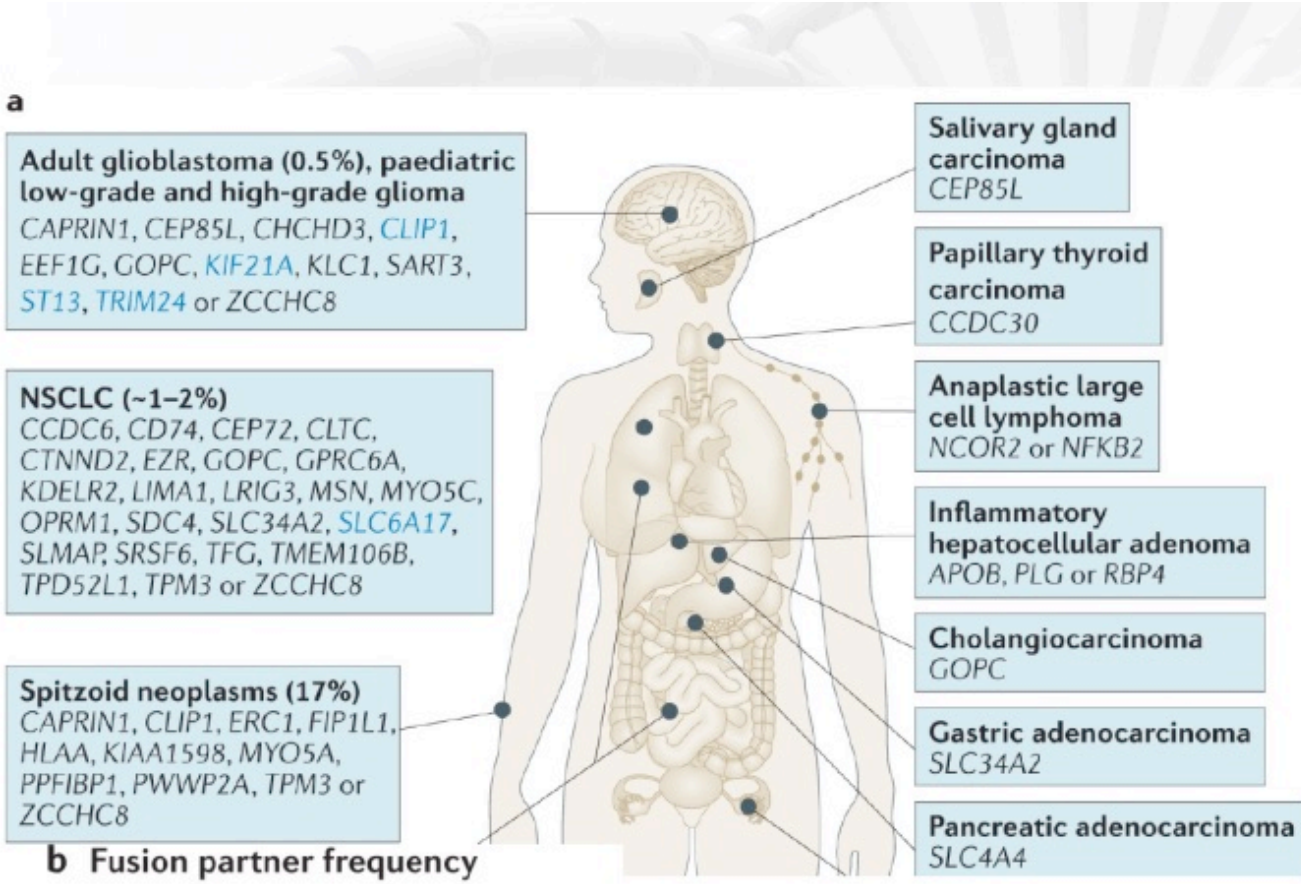
- Potent WT ALK and ALK G1202R
- Potent against G1202R-based compound mutations

Potency color legend
IC_{50} < 10 nM
10 nM ≤ IC_{50} < 100 nM
IC_{50} ≥ 100 nM

Preclinical Activity against many compound mutations/G1202R

ROS-1 NSCLC

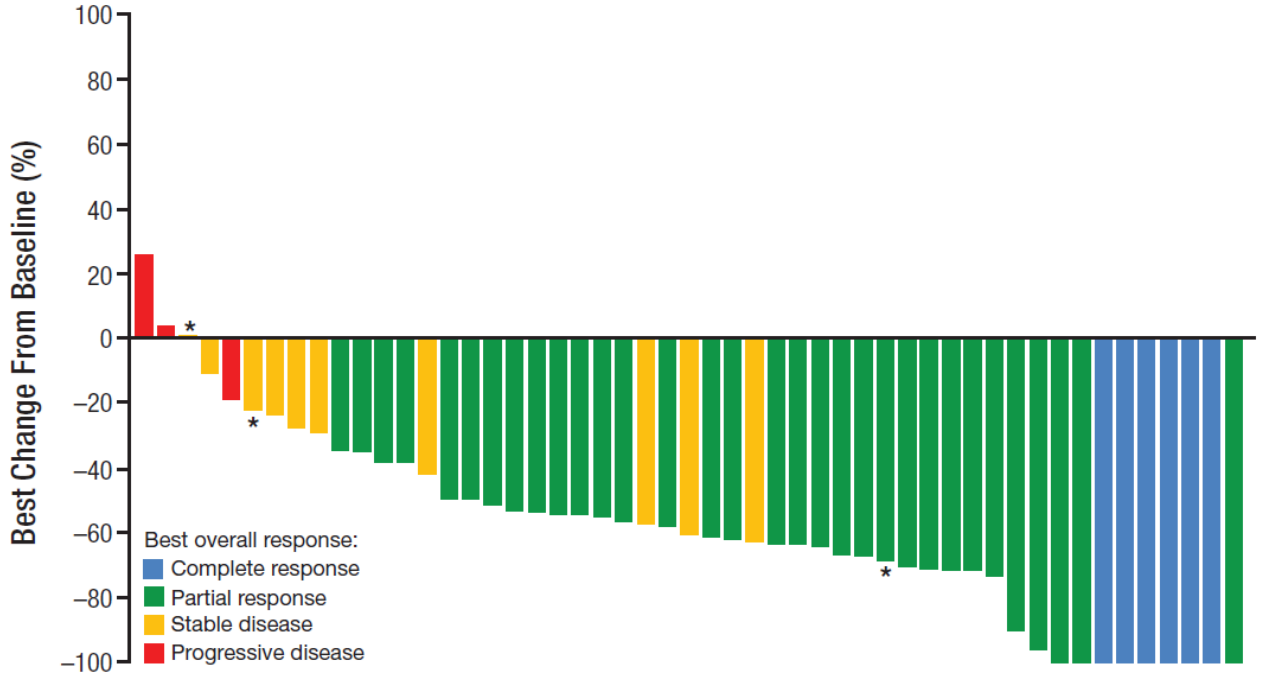
- Unknown physiologic role
- Fusions seen in 1-2% NSCLC
- Typically, adenocarcinoma, occasional large cell and squamous histologies
- Seen in younger, light/never smokers
- ~70% homology with ALK kinase domain



Drilon et al. *Nat Rev Clin Oncol* **18,** 35–55 (2021
https://doi.org/10.1038/s41571-020-0408-9

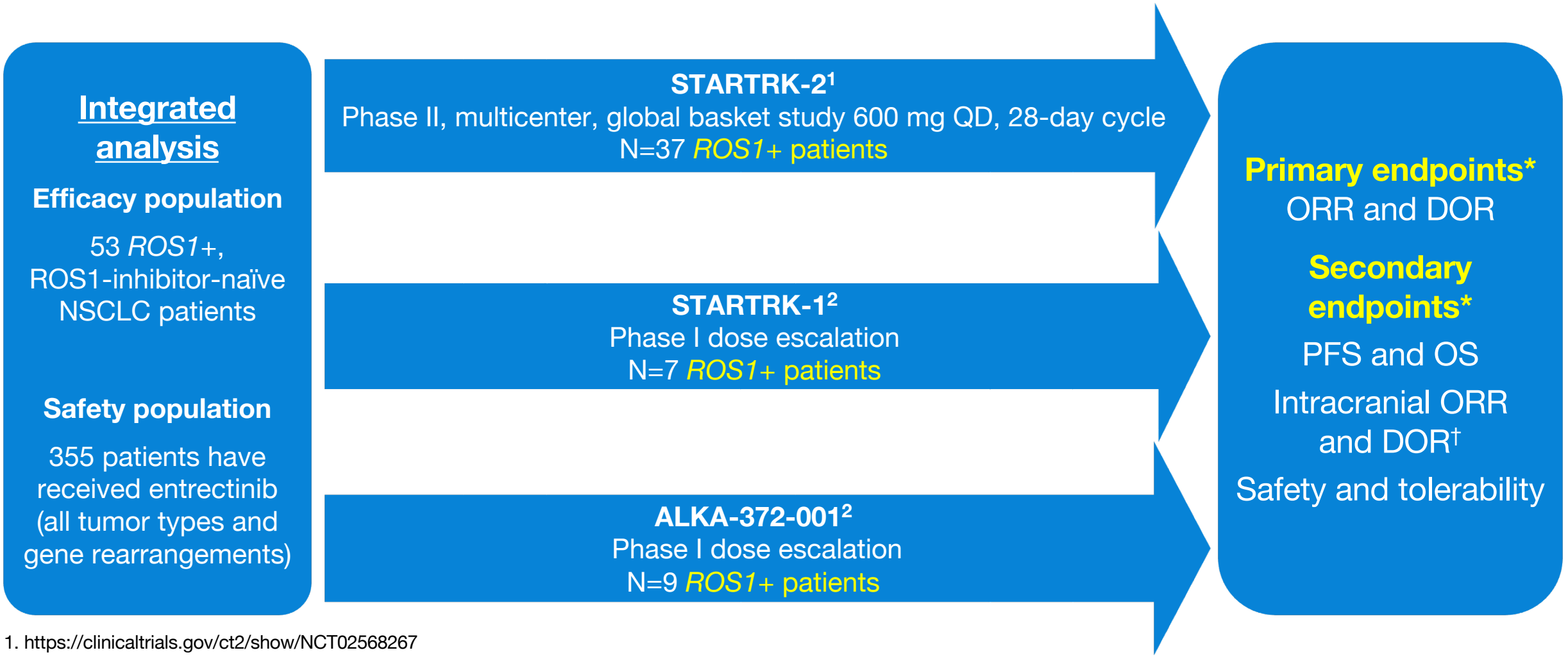
Phase 1 PROFILE 1001 Study: Crizotinib in *ROS1*-Rearranged NSCLC—Updated Analysis

- 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
- ORR- 72% (58-83)
- mPFS- 19.3 (15.2-39.1)



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

Integrated Analysis of 3 Studies: Entrectinib in *ROS1*+ NSCLC

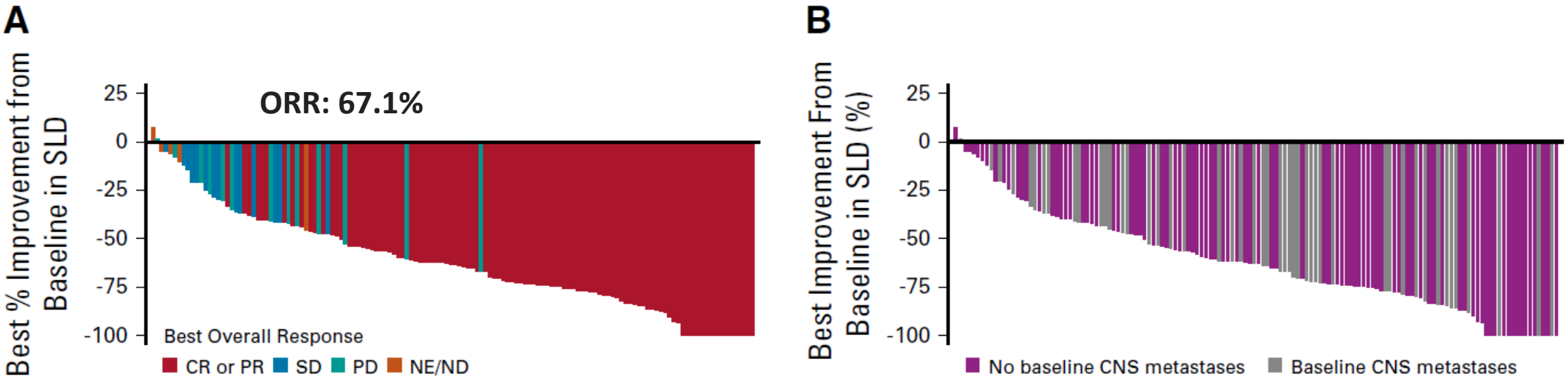


1. https://clinicaltrials.gov/ct2/show/NCT02568267
2. Drilon, et al. Cancer Discov 2017

Data cut-off 31 May 2018

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

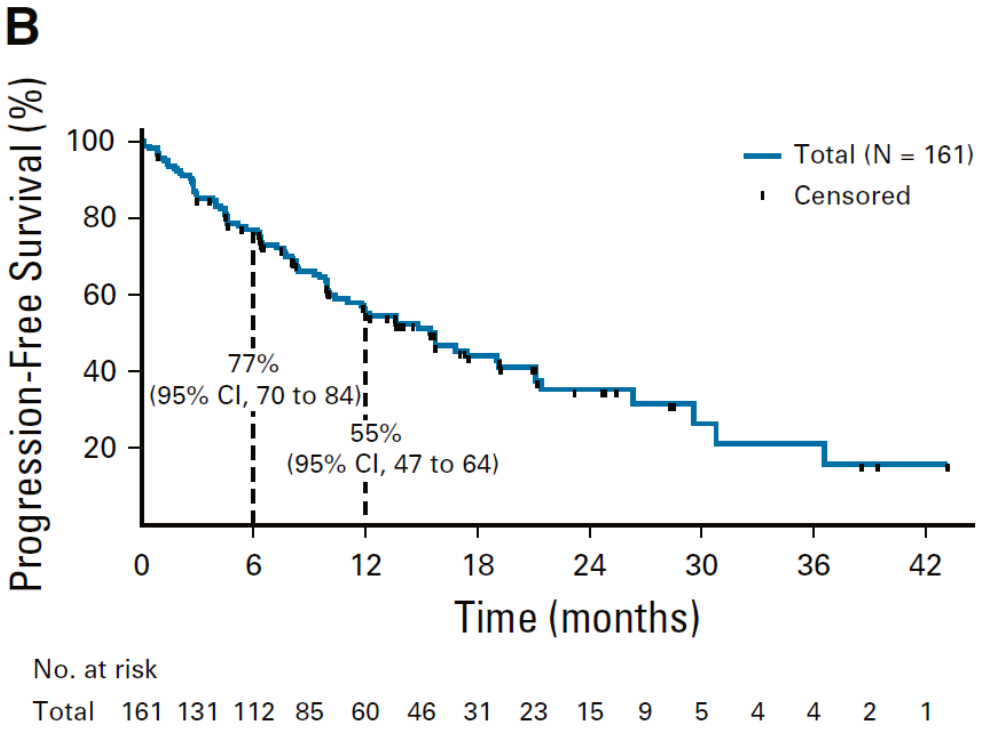
- Updated integrated analysis of 3 phase I/II clinical trials (ALKA-372-001, STARTRK-1, and STARTRK-2) of entrectinib, in *ROS1* fusion-positive NSCLC
- 161 patients with a follow-up of ≥ 6 months were evaluable
- Median duration of follow-up, 15.8 months
- Median treatment duration was 10.7 months



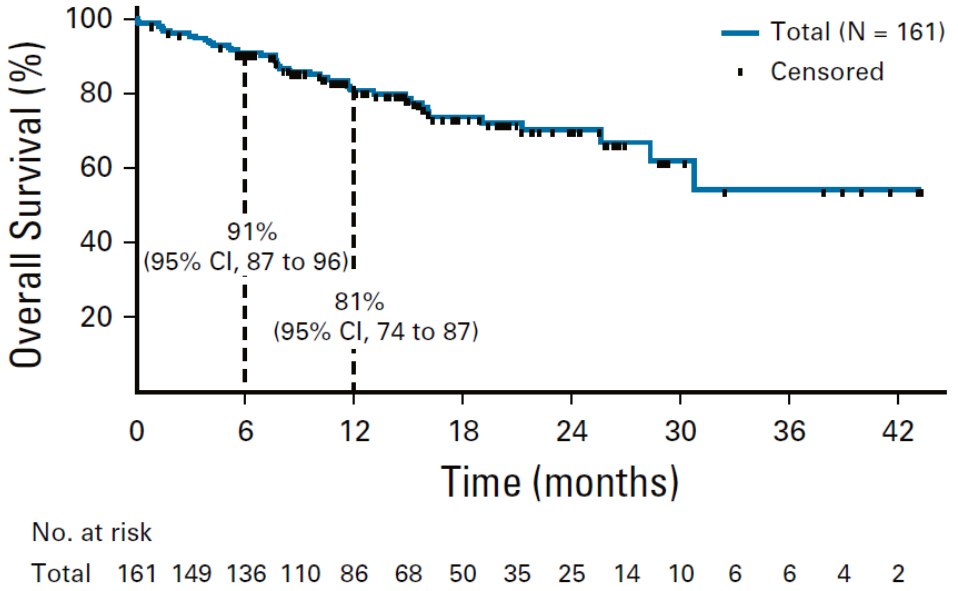
Intracranial ORR: 79.2% (n = 19/24)[b]; median intracranial DoR: 12.9 months (12-mo rate, 55%)

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

Entrectinib in *ROS1*-Fusion-Positive NSCLC: PFS and OS—Updated Analysis



Median PFS: 15.7 months
12-month PFS: 55%



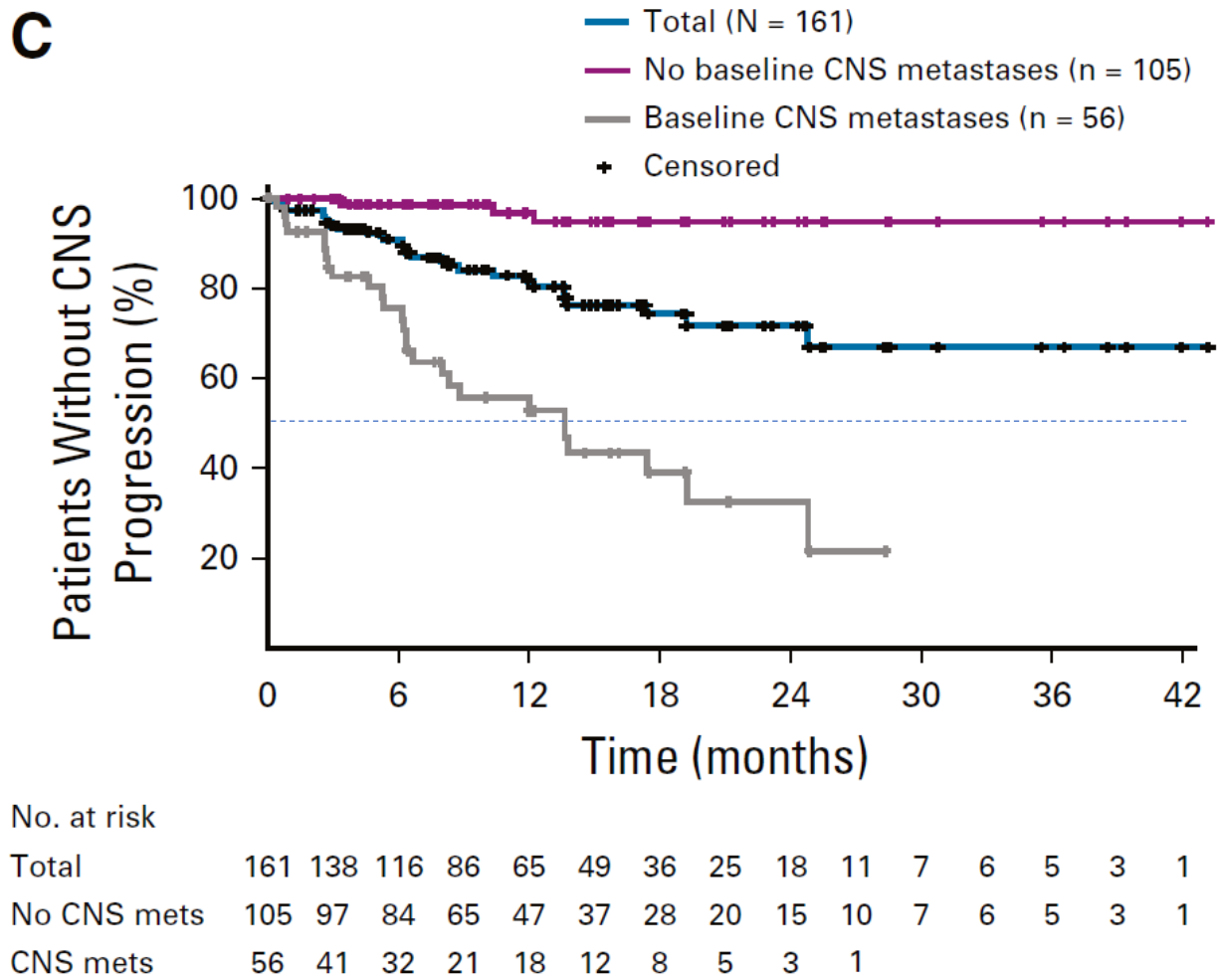
Median OS: NE
12-month PFS: 81%

Side effects: hyperuricemia, weight gain, dizziness/CNS taste changes, edema, GI side effects, AST/ALT evlevation

Median duration of follow-up, 15.8 months
Dsziadziuszko R, et al. *J Clin Oncol*. 2021;39(11):1253-1263.

Median Time to CNS Progression With Entrectinib

- Overall population: NE (exploratory) progression (exploratory end point;
- Scan-confirmed CNS progression
  - No baseline CNS mets: 3/105 (2.9%)
  - Baseline CNS mets: 27/56 (48.2%)



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

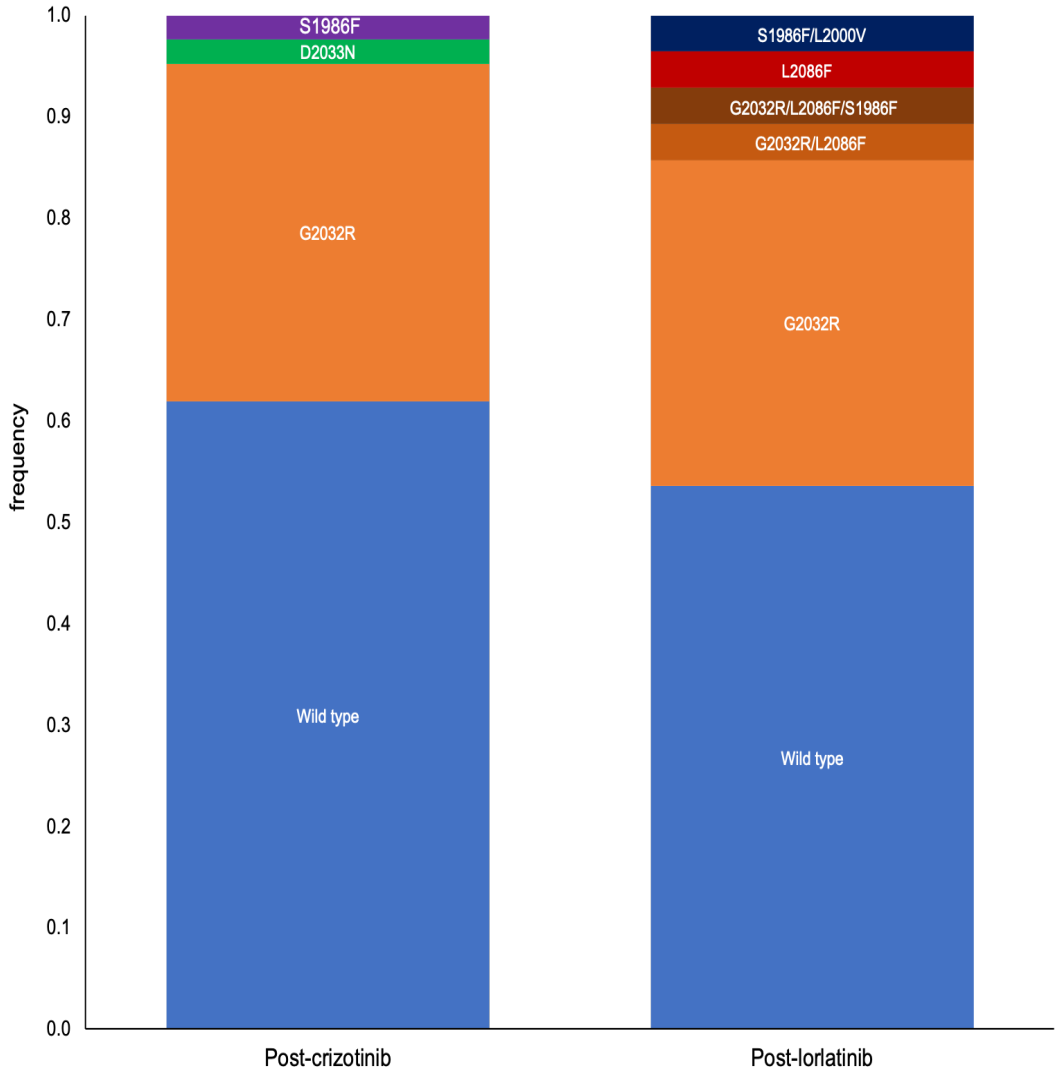
Summary of ROS1 TKIs in TKI-Naïve ROS1+ NSCLC

	Crizotinib* (PROFILE 1001)	Entrectinib* (ALKA-372-001, STARTRK-1, STARTRK-2)	Ceritinib (Korean Phase 2)	Taletrectinib (Chinese Phase 2)	Lorlatinib (Phase 1/2)	Repotrectinib# (TRIDENT-1 Phase 1/2)
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

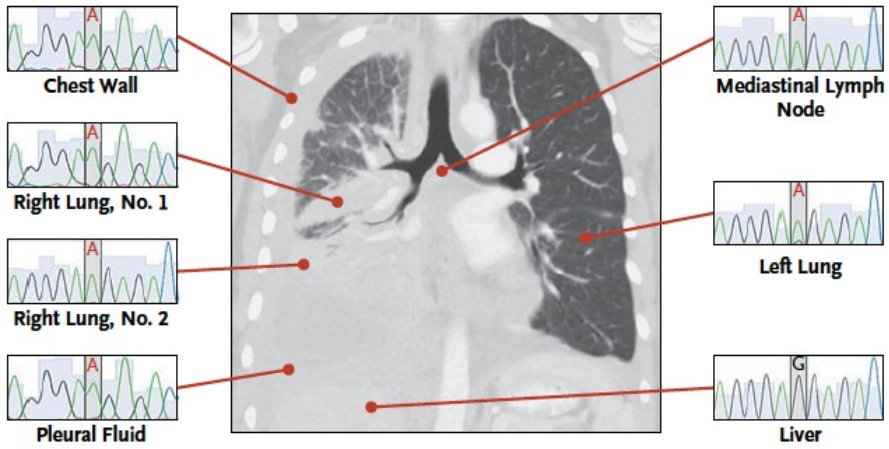
**FDA-approved*

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

ROS1-Dependent Resistance to ROS1 TKIs

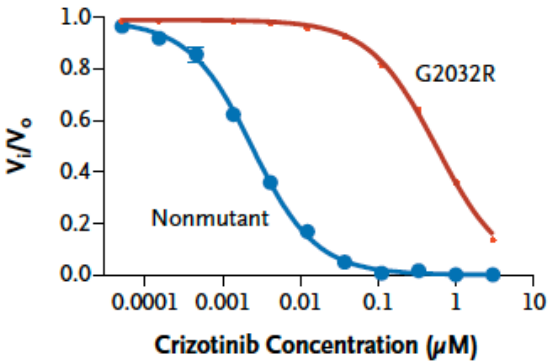


Detection of ROS1 G2032R

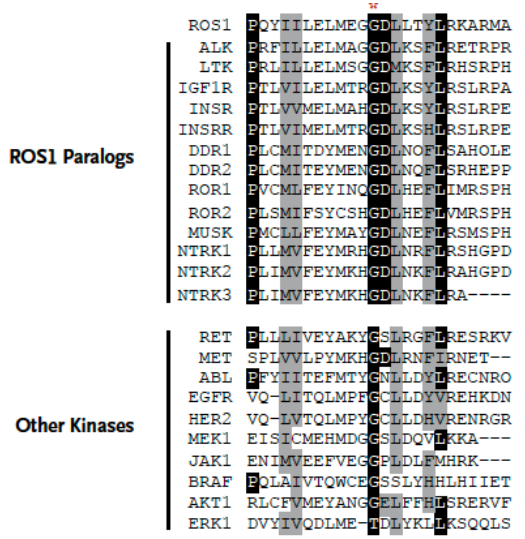


Autopsy Site	G2032R
Liver (normal)	–
Chest wall tumor	+
Right lung tumor no. 1	+
Right lung tumor no. 2	+
Malignant pleural effusion	+
Mediastinal lymph-node tumor	+
Left lung (microscopic disease)	+

ROS1 in vitro *kinase assay*



ROS1 G2032: highly conserved solvent front residue



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

Awad MM et al., N Engl J Med 2013;368:2395-401

Addressing ROS1-Dependent Resistance: ROS1 TKIs in Crizotinib/TKI-Pretreated *ROS1*+ NSCLC

	Lorlatinib (Phase 1/2) / (Real World*)	Repotrectinib (TRIDENT-1 Phase 1/2)	Taletrectinib (Chinese Phase 2)
Patients	N=40/N=80	N=72	N=5
ORR	35%/45%	30-39% (depending on prior Tx history)	60%
Median PFS	8.5 months /(7.1 mo*)	Not available	Not available
CNS activity	12/24 (50%) patients with measurable or nonmeasurable intracranial disease	Reported to have CNS activity in patients with baseline CNS metastases	Reported to have CNS activity in patients with baseline CNS metastases
Clinical ROS1 G2032R activity	Response in 0/6 (0%) patients with a baseline ROS1 G2032R in plasma	Responses in 8/15 (53%) patients with a baseline ROS1 G2032R	Response in 1/3 (33%) patients with a baseline ROS1 G2032R
Reference	Shaw et al., Lancet Oncol 2019/N. Girard et al. ESMO Open 2022	Lin et al., AACR-NCI-EORTC 2021	Zhou C et al., ASCO 2021

* LORLATU Real World Retrospective Cohort. N Girard et al. ESMO Open 2022.

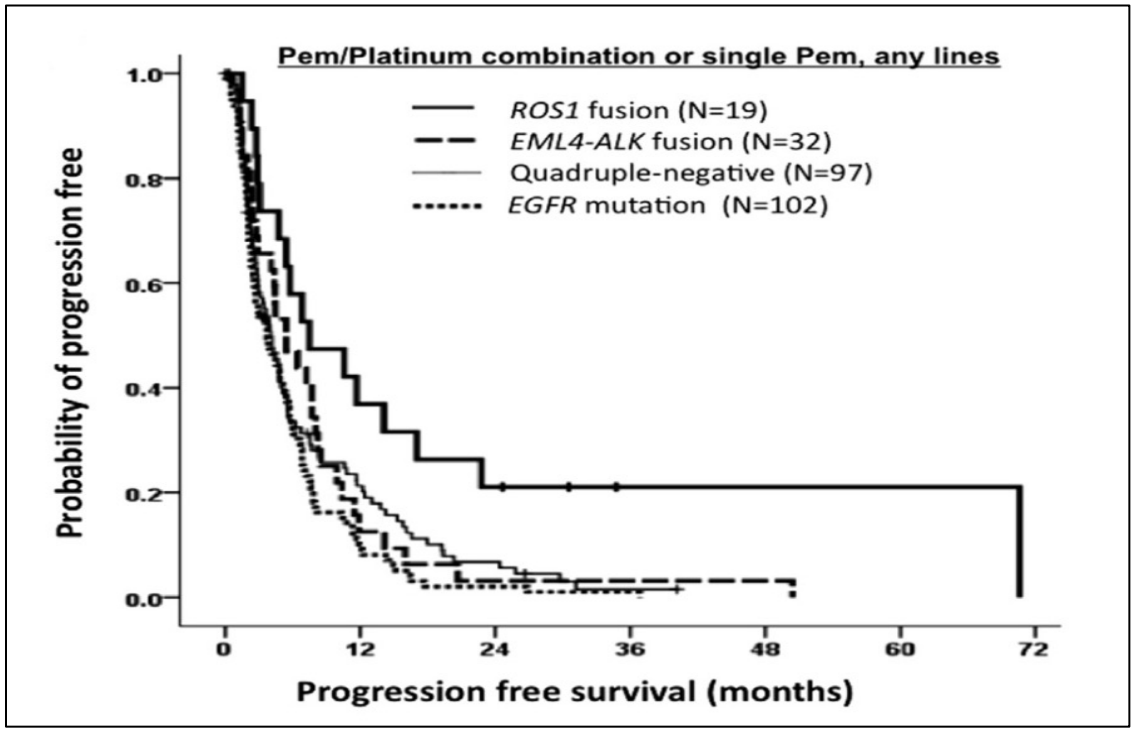
Pemetrexed Based Chemotherapy and in ROS1+ NSCLC

Table 1 Summary of ROS1 Cases

Case	Sex	Age, years	Treatment	PFS During Pemetrexed Treatment (mo)
1	F	35	CPB × 6 → PB × 21 → P × >14[a]	>36
2[b]	M	64	CPB × 6 → PB × 37 → P × >19[c]	>47
3	F	56	CP × 4 → P × 18 → crizotinib	18
4[d]	F	65	C-Pac × 4→ P × 24	24

Abbreviations: B = bevacizumab; C = carboplatin; F = female; M = male; P = pemetrexed; Pac = paclitaxel; PFS = progression-free survival.
[a]Bevacizumab discontinued because of nonspecific neurologic complaints.
[b]Case 2 initially stage IIIB at diagnosis and received concurrent chemoradiation with biopsy proven recurrence 1 year later.
[c]Bevacizumab discontinued because of proteinuria.
[d]Case 4 is the only patient who received pemetrexed as second-line treatment. She died from treatment-related complications, not progression.

JW Riess et al. CLC 2013.

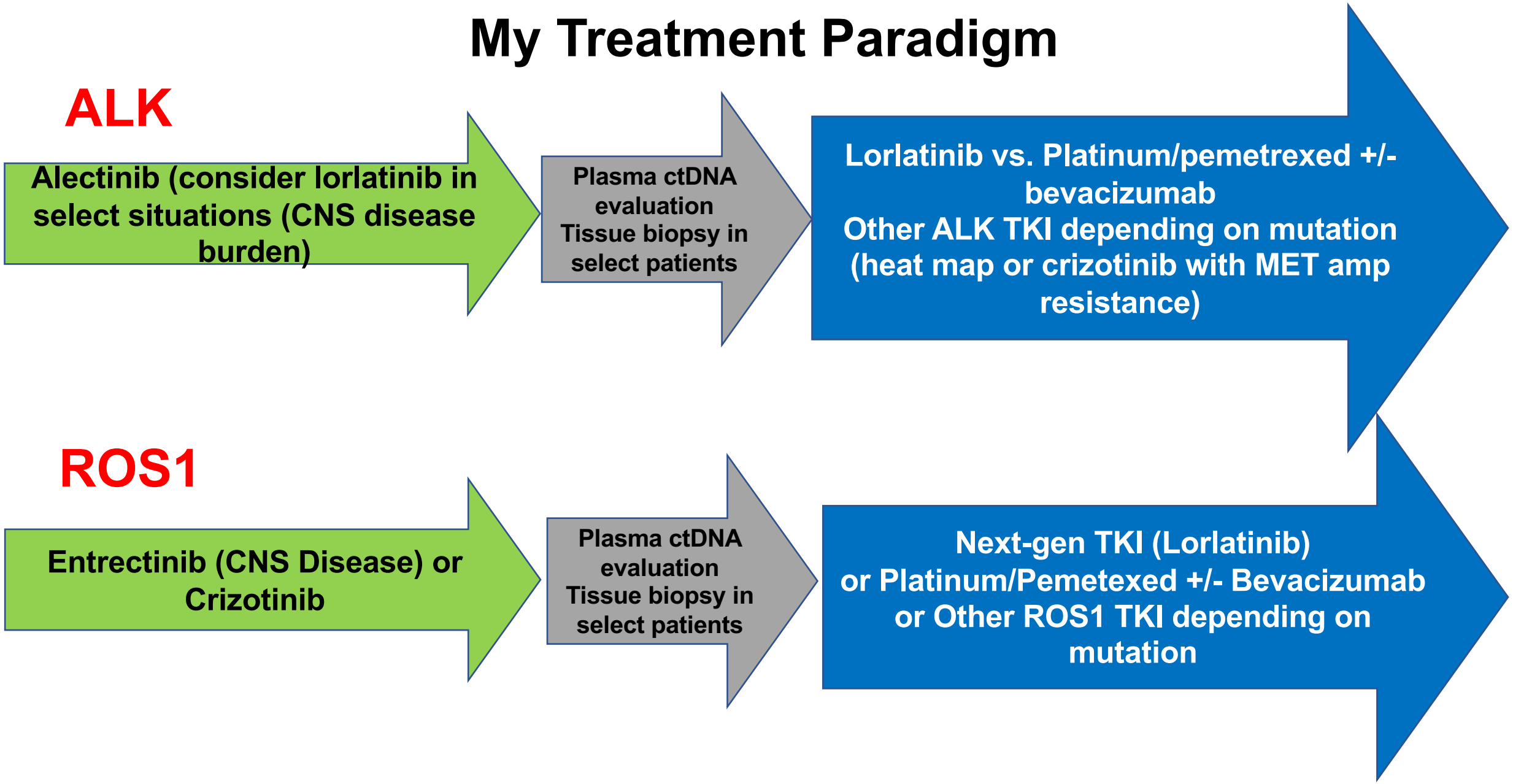


HR (95% CI), compared to quadruple negative cohort:

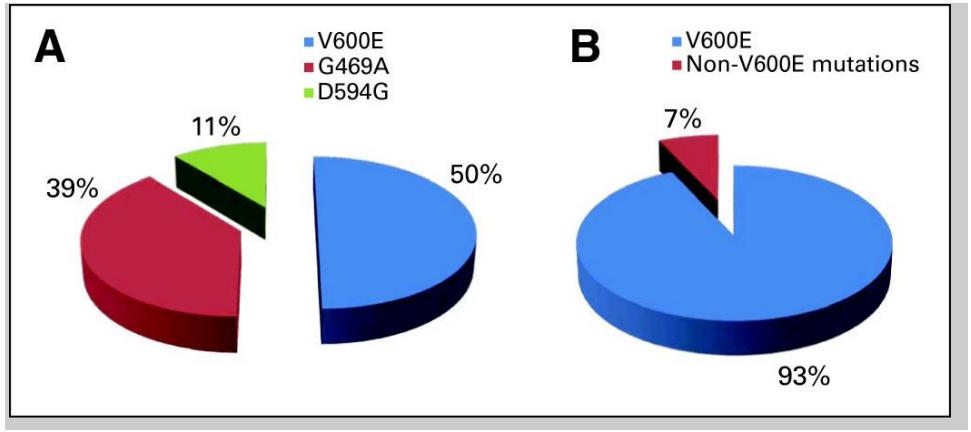
ROS1 fusion	HR 0.48 (0.28 – 0.83), p=0.008
EML4-ALK fusion	HR 0.96 (0.64 – 1.45), p=0.852
EGFR mutation	HR 1.29 (0.96 – 1.72), p=0.083

YF Chen et al JTO 2016

Advanced ALK/*ROS1* Fusion+ NSCLC:
My Treatment Paradigm

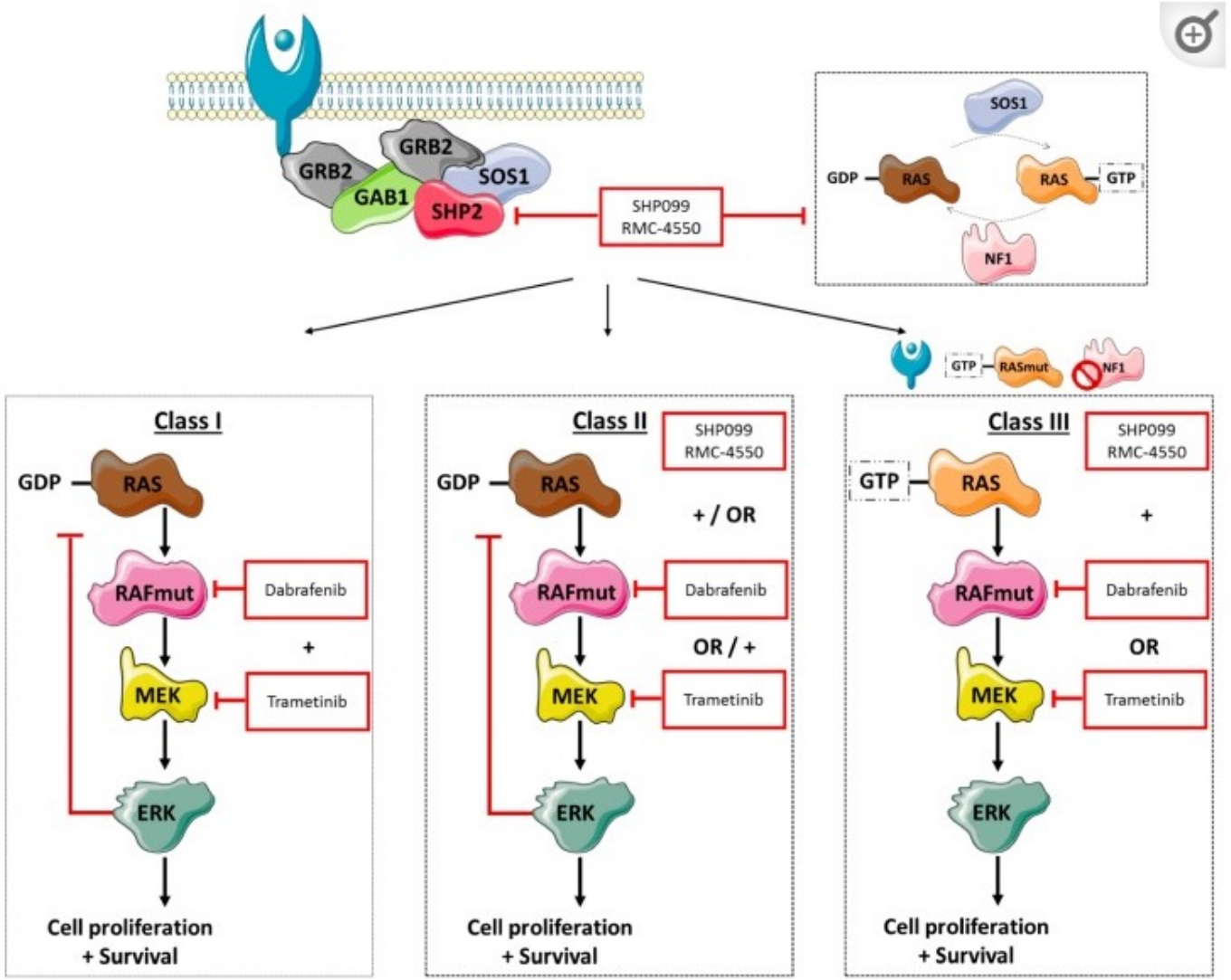


BRAF in NSCLC: It's In a Different Class



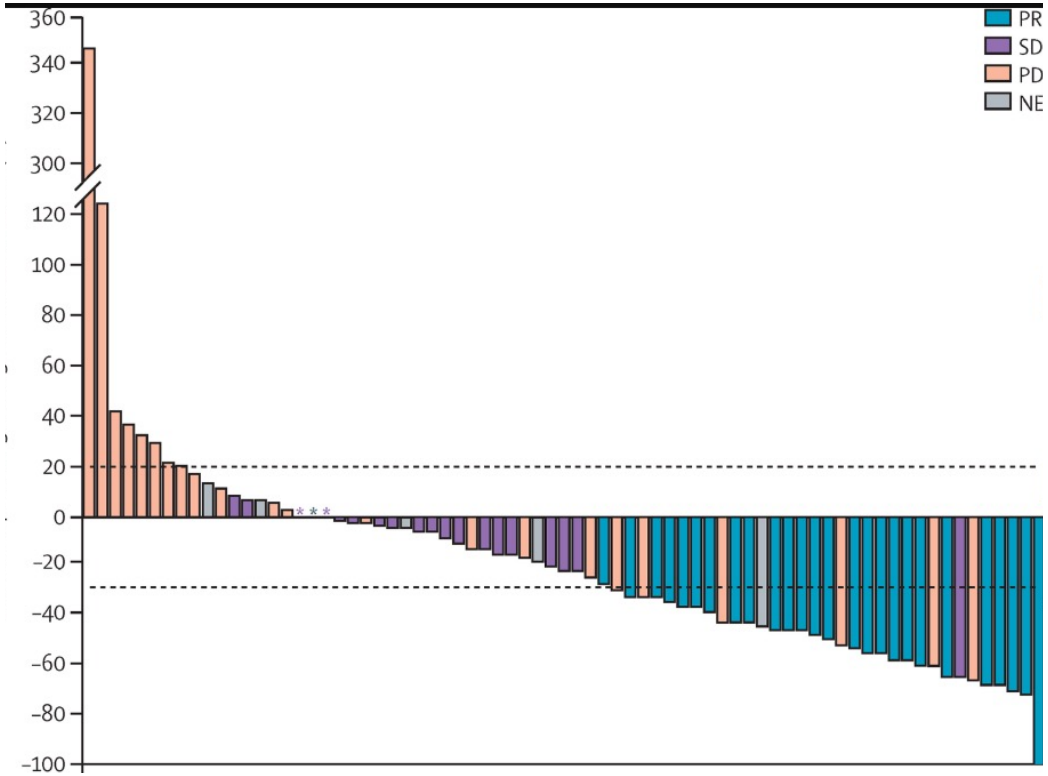
- ~2-3% NSCLC
- More Frequent in Adenocarcinoma
- More likely than EGFR/ALK to have smoking history
- Different distribution than melanoma
- Different Classes of BRAF mutations have therapeutic implications
- Maybe responsive to PD(L)1 ICI

P. Paik et al. JCO 2011
J. Bracht et al Cancers 2019

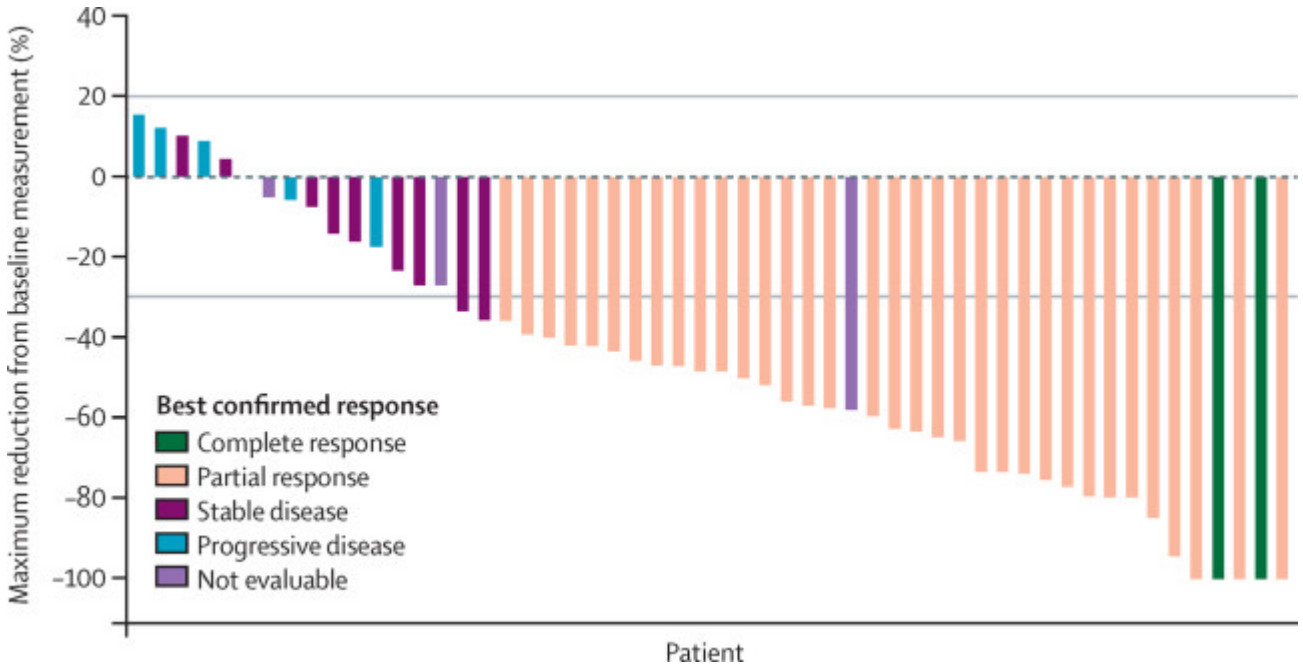


J. Bracht et al Cancers 2019

MEKi Improved Clinical Outcomes When Added to BRAFi in BRAF V600E mutant NSCLC



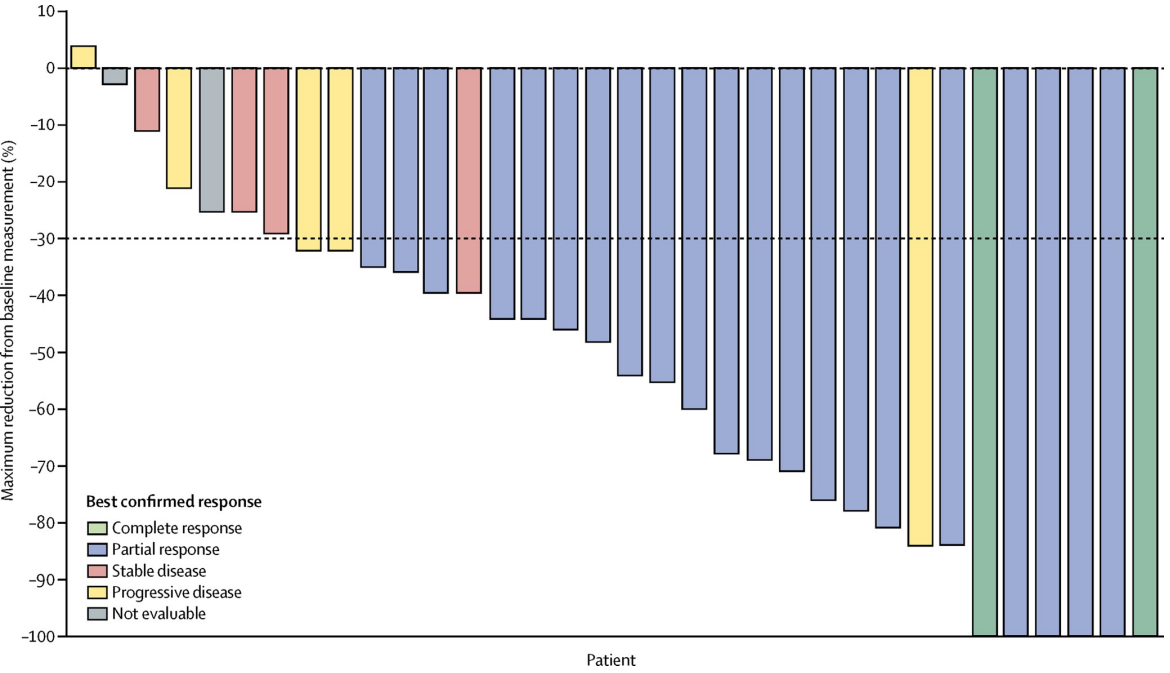
Dabrafenib Alone in Previously Treated BRAF V600E NSCLC
N=78
ORR = 33%
mPFS 5.5 mo
mDoR 9.6 mo



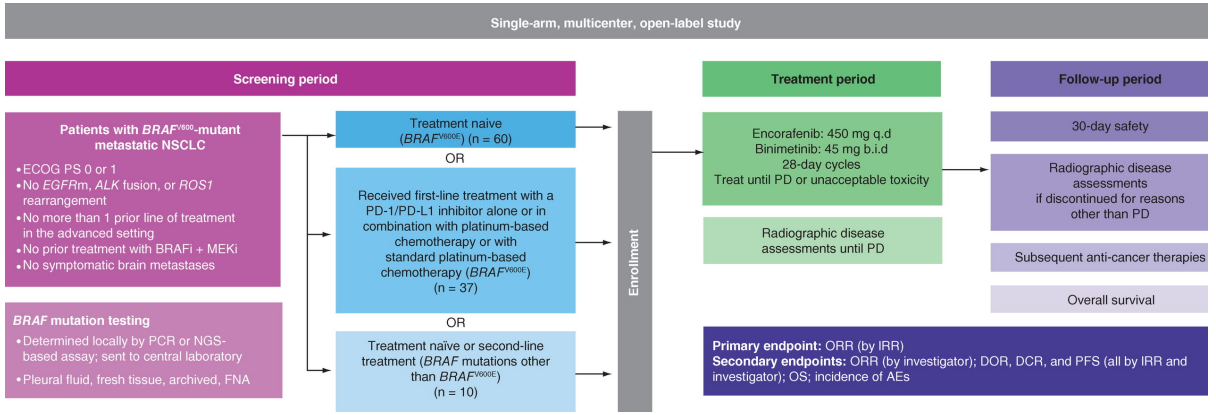
Dabrafenib + Trametinib in Previously Treated BRAF V600E NSCLC
N=57
ORR = 64%
mPFS 9.7 mo
mDoR 9 mo

D. Planchard et al Lancet Onc 2016

BRAFi + MEKi in BRAF V600E NSCLC



Dabrafenib + Trametinib in Untreated BRAF V600E NSCLC
N=39
ORR = 64%
mPFS 10.9 mo
mDoR 10.4 mo



PHAROS Trial – Encorafenib plus binimetinib in BRAF V600E/K NSCLC

D. Planchard et al Lanet Onc 2017. G. Riely et al Fut Onc 2021.


Thank you!