State of the Art: Oncogene Driven Non-Small Cell Lung Cancer

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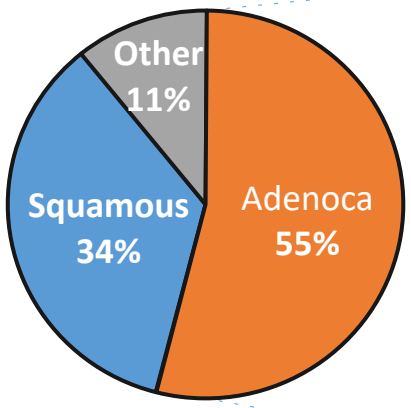
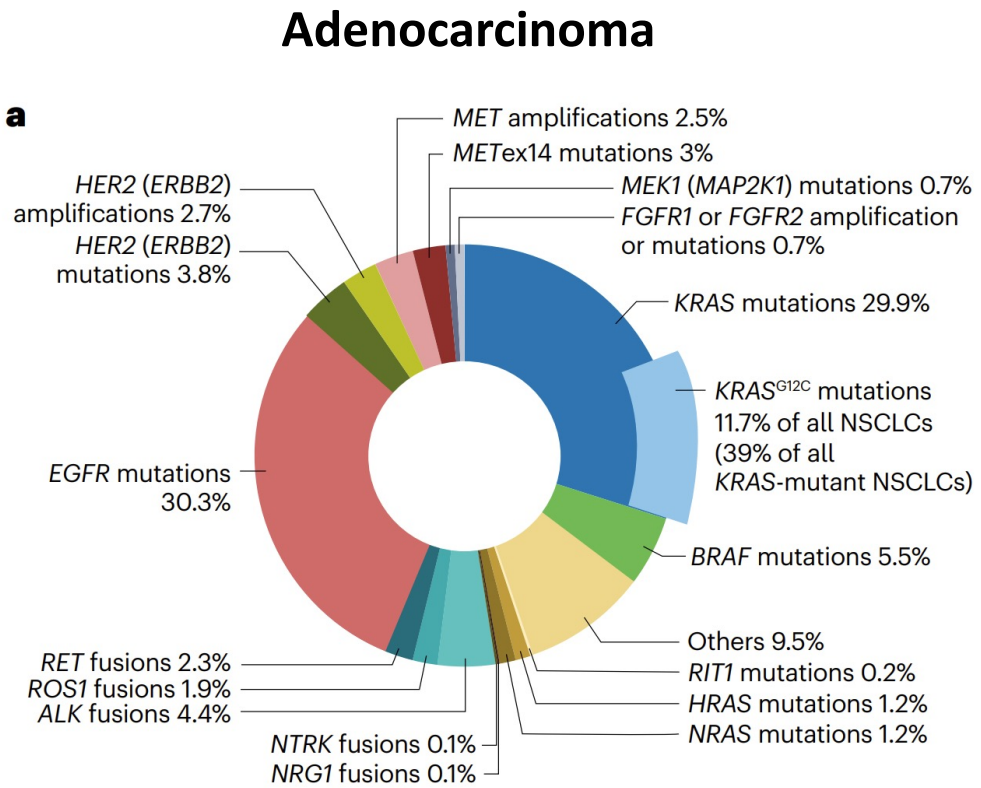
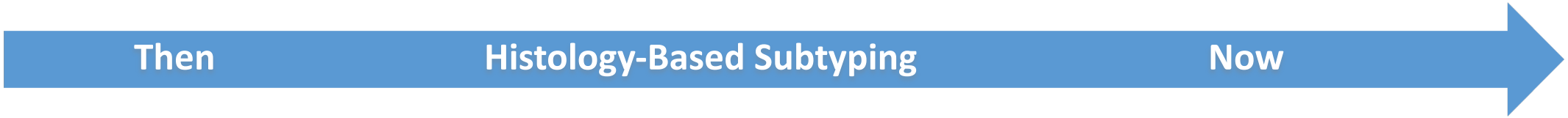
Dissecting NSCLC: Revealing its Many Molecular Subtypes







Nature Reviews Clinical Oncology volume 20, pages143–159 (2023)

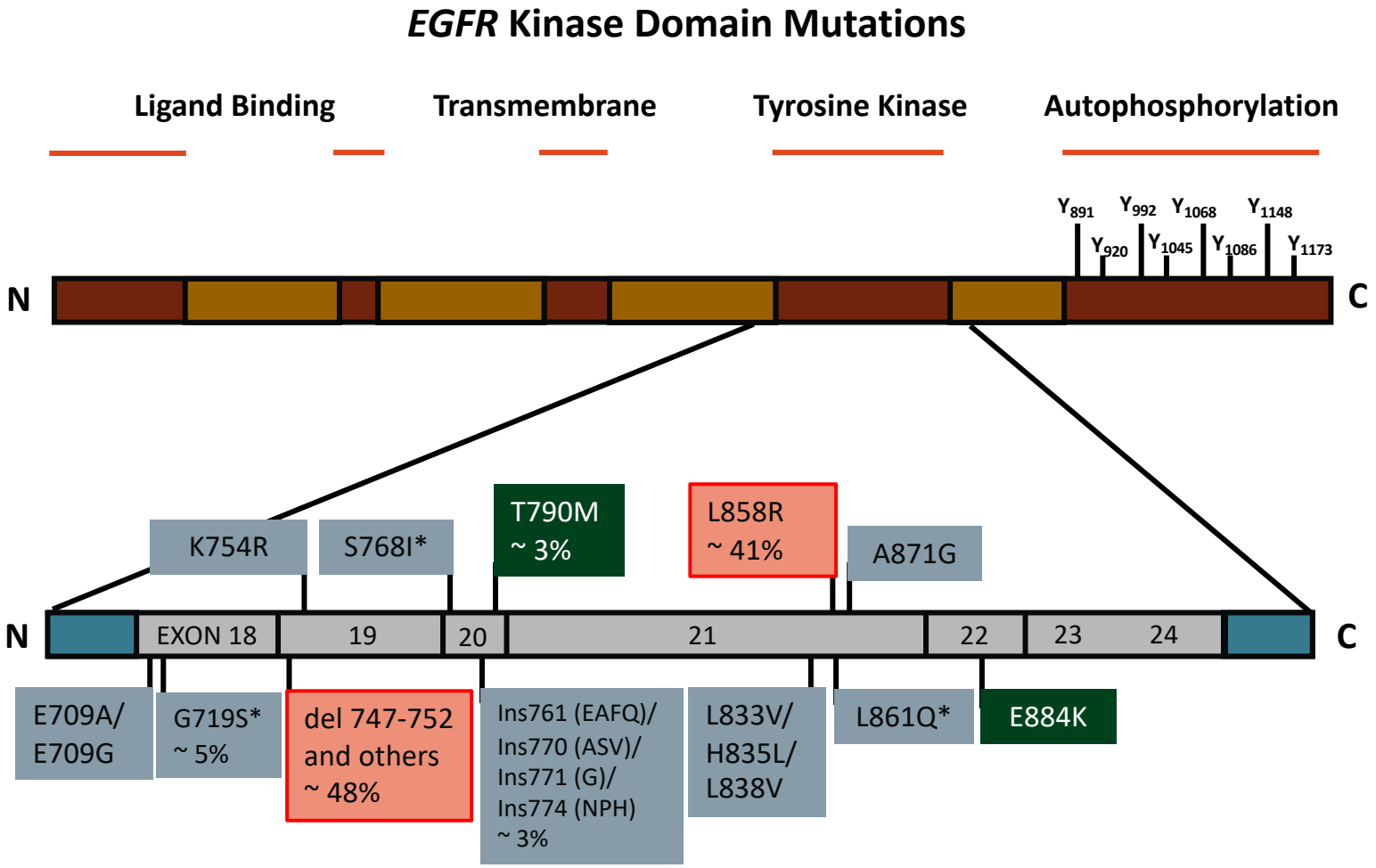
From Diagnosis to Biomarker Testing: Complexity of Morphologic and Molecular Classification

- Histologic subtyping: squamous or nonsquamous?
- **Test for *EGFR, ALK, ROS1, BRAF* V600E, *NTRK*, *RET*, HER2 and *MET*ex14 in all nonsquamous NSCLC**
  - Use broad NGS testing to detect most mutations using least amount of tissue
  - For squamous NSCLC, consider testing in young, never/light smokers or if biopsy specimen is of mixed histology
- **Test for PD-L1 expression in all NSCLC**
- **Wait for results of NGS before acting on PD-L1 results**

EGFR Mutations in NSCLC

EGFR Mutational Epidemiology

- ~ 10% of NSCLC patients in the US
- More common in never-smokers, adenocarcinomas, females, Asians
- Predominantly located in *EGFR* exons 18-21
- The specific *EGFR* mutation identified is important: sensitive mutations, primary resistance mutations, and de novo and acquired resistance mutations



*Noncanonical *EGFR* mutations.

Pao. J Clin Oncol. 2005;23:2556.

First-line Therapy in *EGFR*-Mutated NSCLC

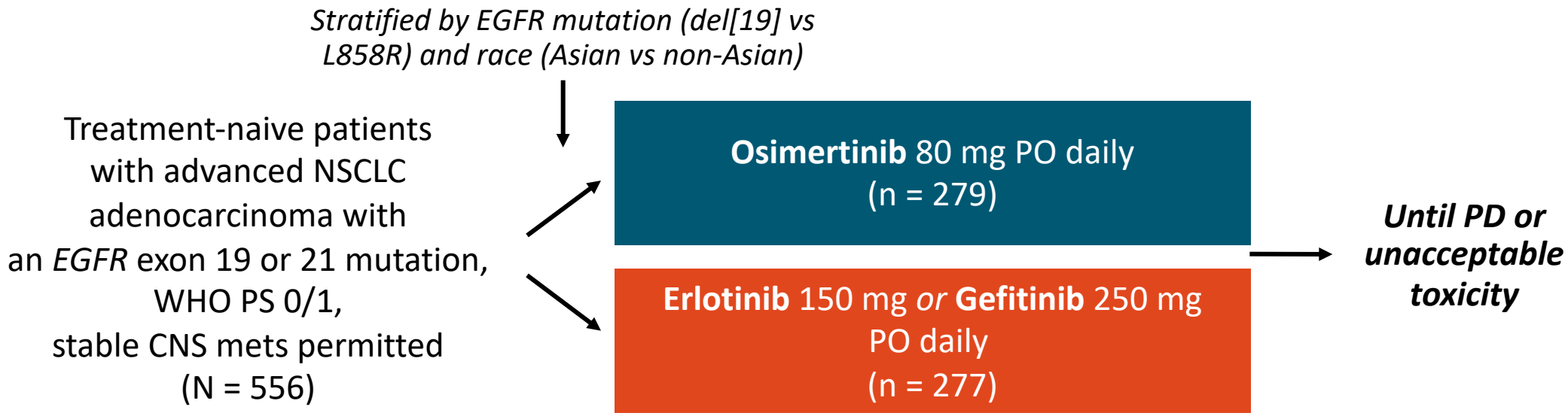
First-line EGFR TKIs vs Chemotherapy in *EGFR* Mutation–Positive NSCLC: A Clear Pattern

Study	N	Treatment	ORR, %	Median PFS, Mos	Median OS, Mos
NEJ002[1]	230	Gefitinib vs carboplatin/paclitaxel	74 vs 31	10.8 vs 5.4 (*P* < .001)	30.5 vs 23.6 (HR: 0.89)
WJTOG 3405[2,3]	172	Gefitinib vs cisplatin/docetaxel	62 vs 32	9.6 vs 6.6 (*P* < .001)	34.8 vs 37.3 (HR: 1.25)
OPTIMAL[4,5]	165	Erlotinib vs carboplatin/gemcitabine	83 vs 36	13.1 vs 4.6 (*P* < .0001)	22.8 vs 27.2 (HR: 1.19)
EURTAC[6,7]	174	Erlotinib vs platinum-based chemotherapy	58 vs 15	9.7 vs 5.2 (*P* < .0001)	22.9 vs 19.5 (HR: 0.93)
LUX-Lung 3[8,9]	345	Afatanib vs cisplatin/pemetrexed	56 vs 23	11.1 vs 6.9 (*P* = .001)	28.2 vs 28.2 (HR: 0.88)
LUX-Lung 6[9,10]	364	Afatinib vs cisplatin/gemcitabine	67 vs 23	11.0 vs 5.6 (*P* < .0001)	23.1 vs 23.5 (HR: 0.93)

1. Maemondo. NEJM. 2010;362:2380. 2. Mitsudomi. Lancet Oncol. 2010;11:121. 3. Yoshioka. ASCO 2014. Abstr 8117. 4. Zhou. Lancet Oncol. 2011;12:735-. 5. Zhou. Ann Oncol. 2015;26:1877. 6. Rosell. Lancet Oncol. 2012;13:239. 7. Khozin. Oncologist. 2014;19:774. 8. Sequist. J Clin Oncol. 2013;31:3327. 9. Yang. Lancet Oncol. 2015;16:141. 10. Wu. Lancet Oncol. 2014;15:213.

FLAURA: First-line Osimertinib vs SoC for *EGFR*-Mutated Advanced NSCLC

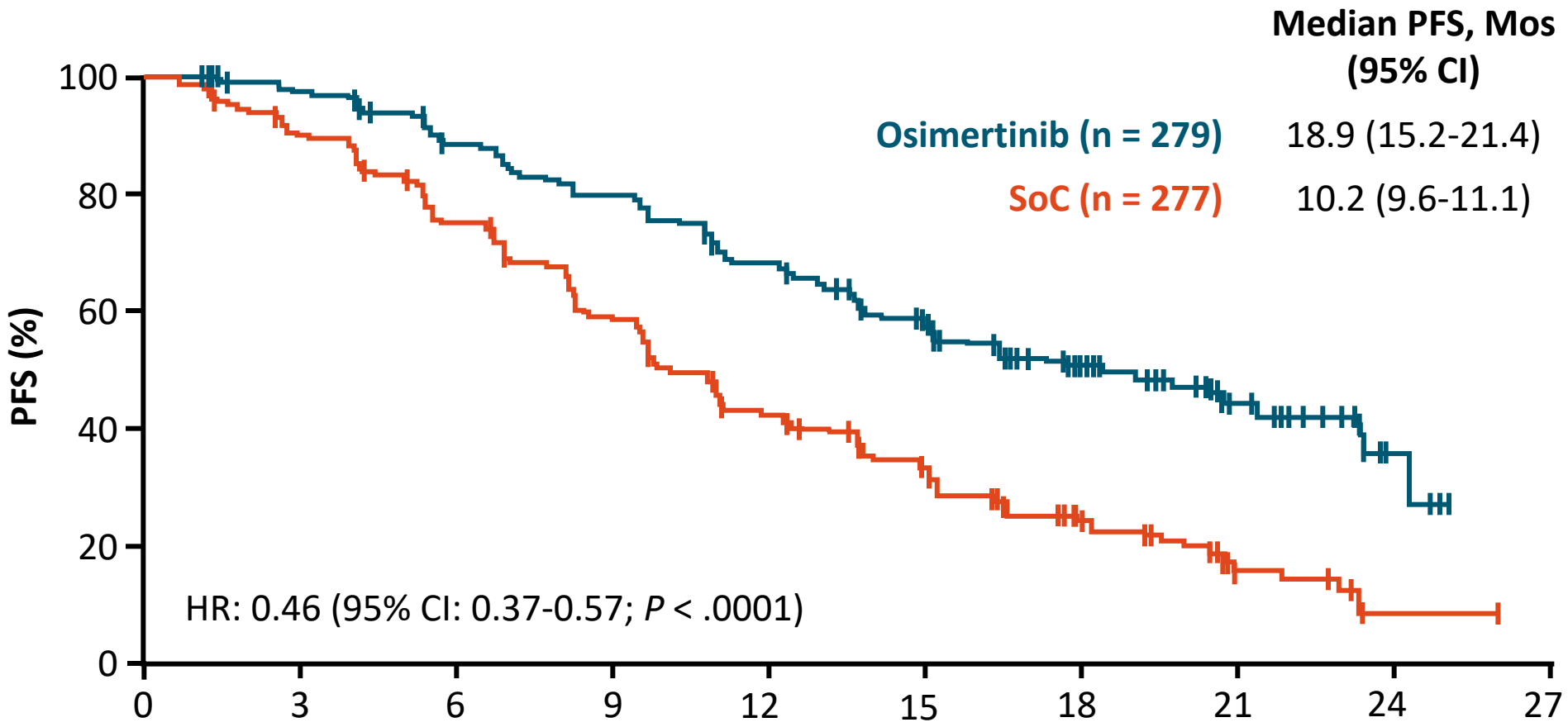
- Double-blind phase III study



- Primary endpoint: PFS
- Secondary endpoints including ORR, DoR, OS, safety

Soria. NEJM. 2018;378:113.

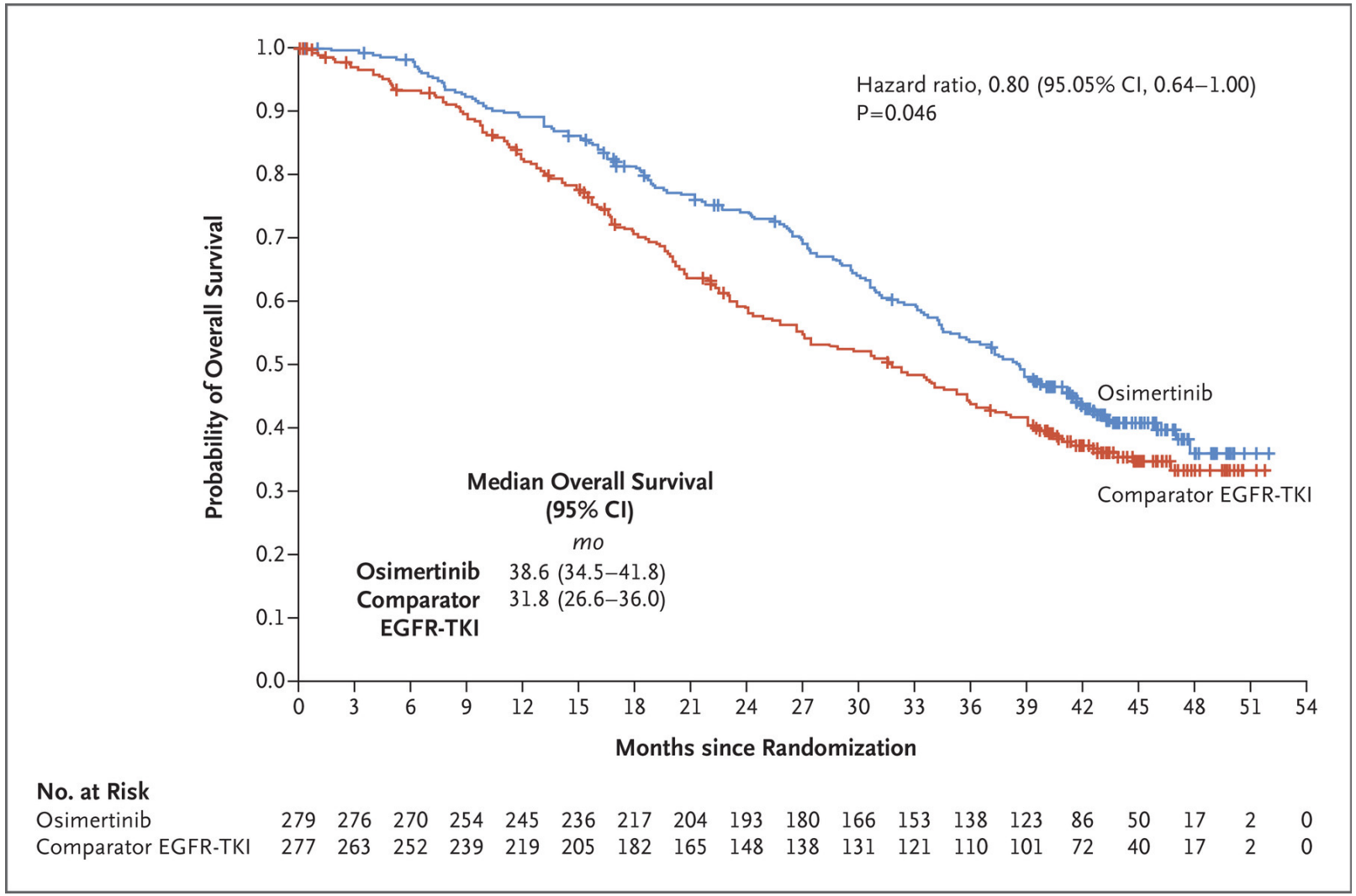
FLAURA: PFS



Patients at Risk, n									
Osimertinib	279	262	233	210	178	139	71	26	4	0
SoC	277	239	197	152	107	78	37	10	2	0

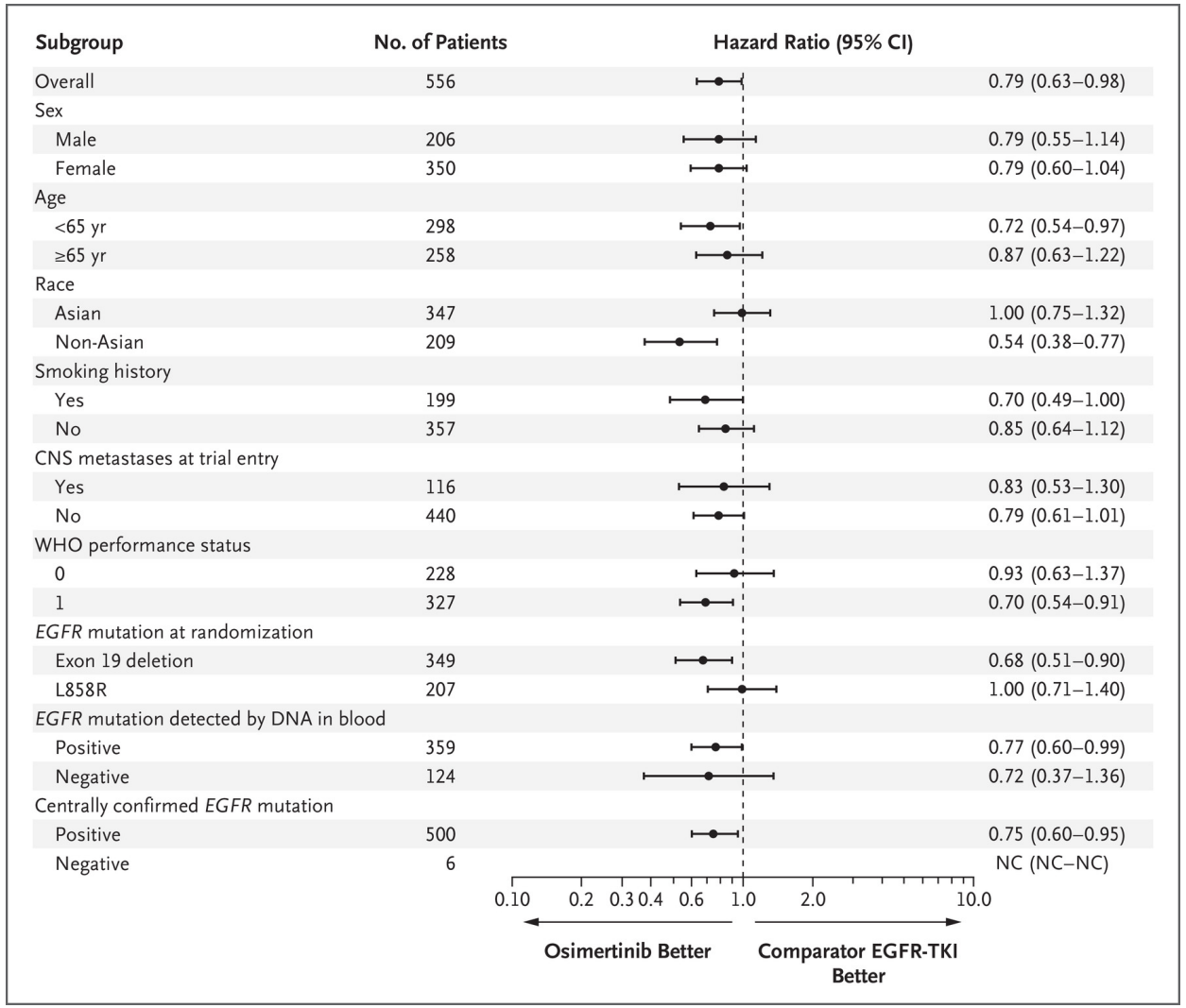
Soria. NEJM. 2018;378:113.

FLAURA: Overall Survival



N Engl J Med 2020; 382:41-50

FLAURA: OS by Subgroup



N Engl J Med 2020; 382:41-50

FLAURA: Adverse Events

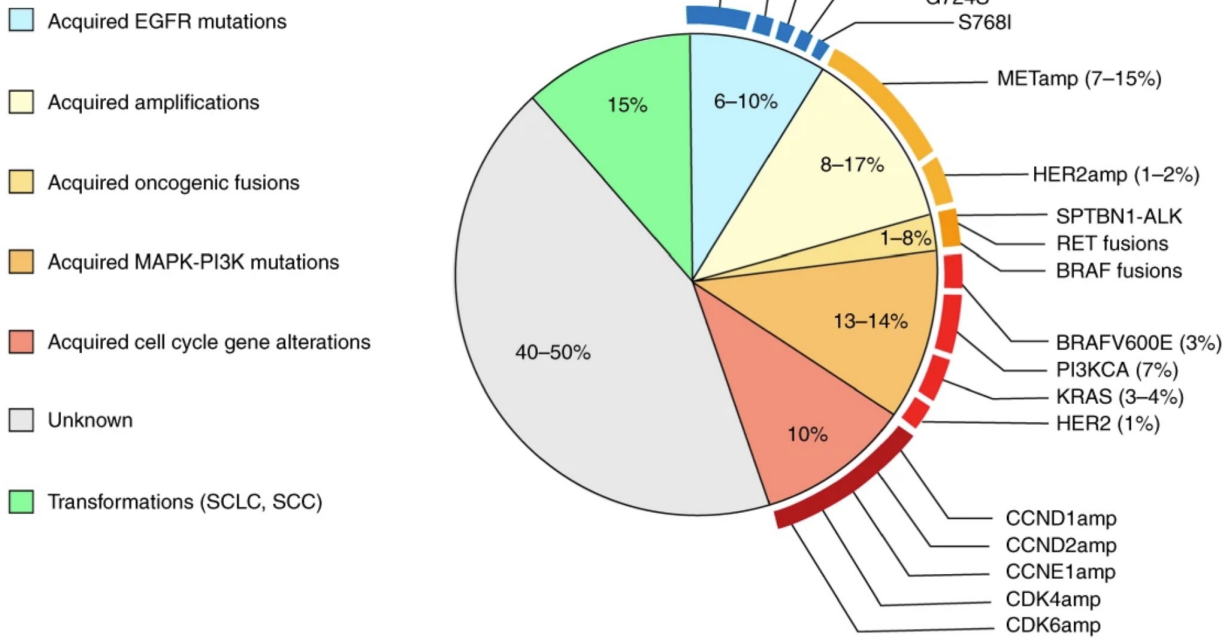
AE, n (%)	Osimertinib (n = 279)			SoC (n = 277)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Diarrhea	120 (43)	35 (13)	6 (2)	116 (42)	35 (13)	6 (2)
Dry skin	76 (27)	11 (4)	1 (< 1)	70 (25)	17 (6)	3 (1)
Paronychia	37 (13)	43 (15)	1 (< 1)	46 (17)	32 (12)	2 (1)
Stomatitis	65 (23)	13 (5)	1 (< 1)	47 (17)	8 (3)	1 (< 1)
Dermatitis acneiform	61 (22)	10 (4)	0	71 (26)	50 (18)	13 (5)
Decreased appetite	27 (10)	22 (8)	7 (3)	24 (9)	22 (8)	5 (2)
Pruritus	40 (14)	7 (3)	1 (< 1)	30 (11)	13 (5)	0
Cough	34 (12)	12 (4)	0	25 (9)	16 (6)	1 (< 1)
Constipation	33 (12)	9 (3)	0	28 (10)	7 (3)	0
AST increased	18 (6)	6 (2)	2 (1)	38 (14)	18 (6)	12 (4)
ALT increased	11 (4)	6 (2)	1 (< 1)	31 (11)	19 (7)	21 (8)

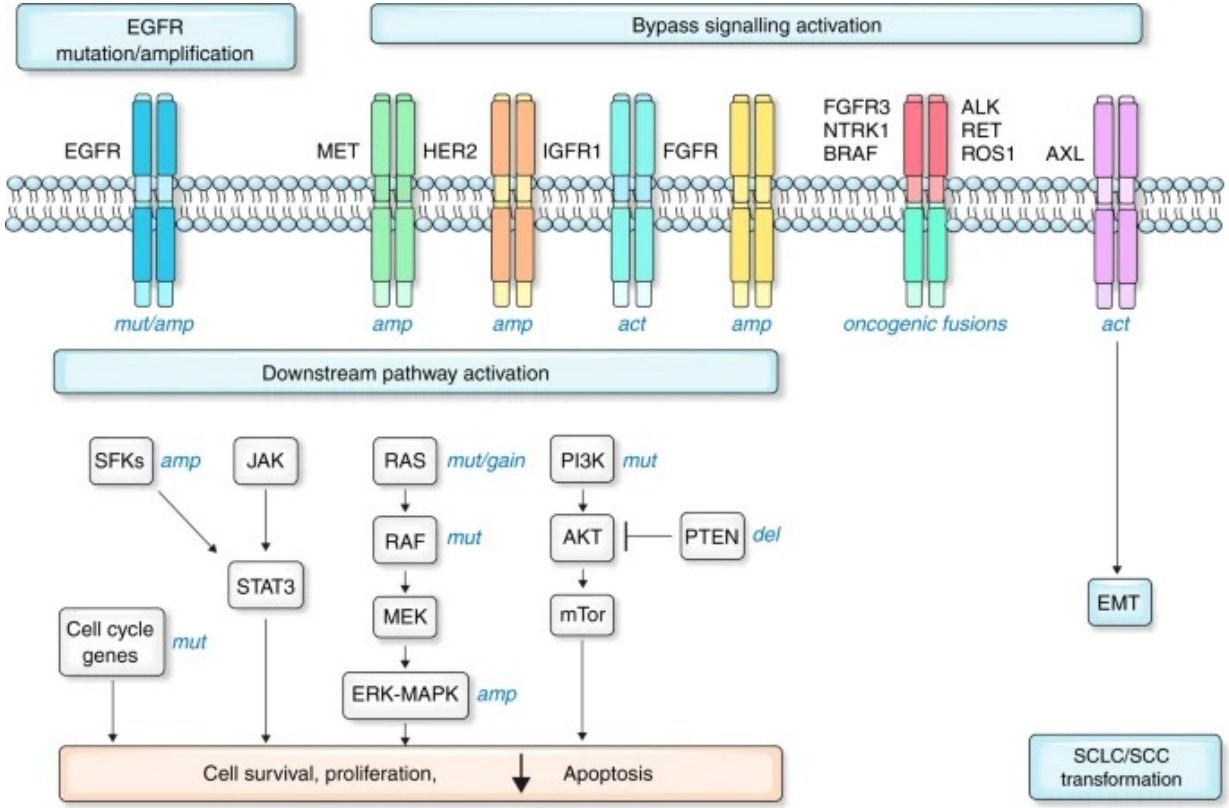
Grade 4 AEs: osimertinib, n = 1 stomatitis; SoC, n = 4 ALT increased.

- Mean duration of exposure: 16.2 mos (range: 0.1-27.4) with osimertinib; 11.5 mos (range: 0-26.2) with SoC

Soria. NEJM. 2018;378:113. Ramalingam. ESMO 2017. Abstr LBA2_PR.

Need for Repeat Testing: Mechanisms of Acquired Resistance After Osimertinib





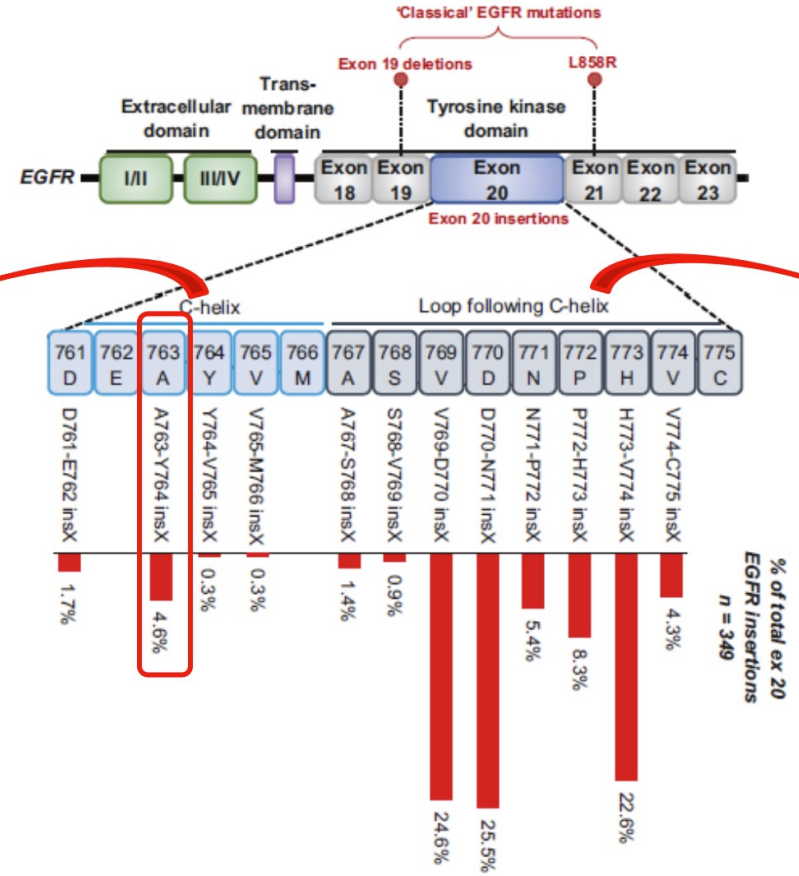
1. Piotrowska. ASCO 2017. Abstr 9020. 2. Oxnard. JAMA Oncol. 2018;4:1527. 3. Leonetti A et al. British Journal of Cancer volume 121, pages725–737 (2019)

EGFR-Mutated NSCLC: Special Populations

Large and Highly Heterogeneous Family of EGFR Exon 20 Insertion Mutations

Exon 20 of EGFR encompasses AAs 762-823 and contains 2 important regions:

- Regulatory C-helix domain (AA762-766)
- Adjacent loop that follows (AA767-774)



Mutations in C-helix may confer some sensitivity to earlier generation TKIs

Majority of exon 20 insertion mutations are found in the loop following the C-helix

Meador et al. Cancer Discov (2021)

Noncanonical *EGFR* Mutations: L861Q, G719X, S768I

- Afatinib: FDA approval in 2018 based on pooled analysis of LUX-Lung 2, 3, 6 (N = 32)[1]
  - ORR: 66% (95% CI: 47% to 81%)
  - DoR at ≥ 12 mos: 52%
  - DoR at ≥ 18 mos: 33%
- Osimertinib?
  - Phase II study in NSCLC with uncommon *EGFR* mutations (N = 36)[2]
  - ORR: 50%,
  - Median PFS: 9.5 mos

1. Afatinib PI. 2. Ahn. ASCO 2018. Abstr 9050.

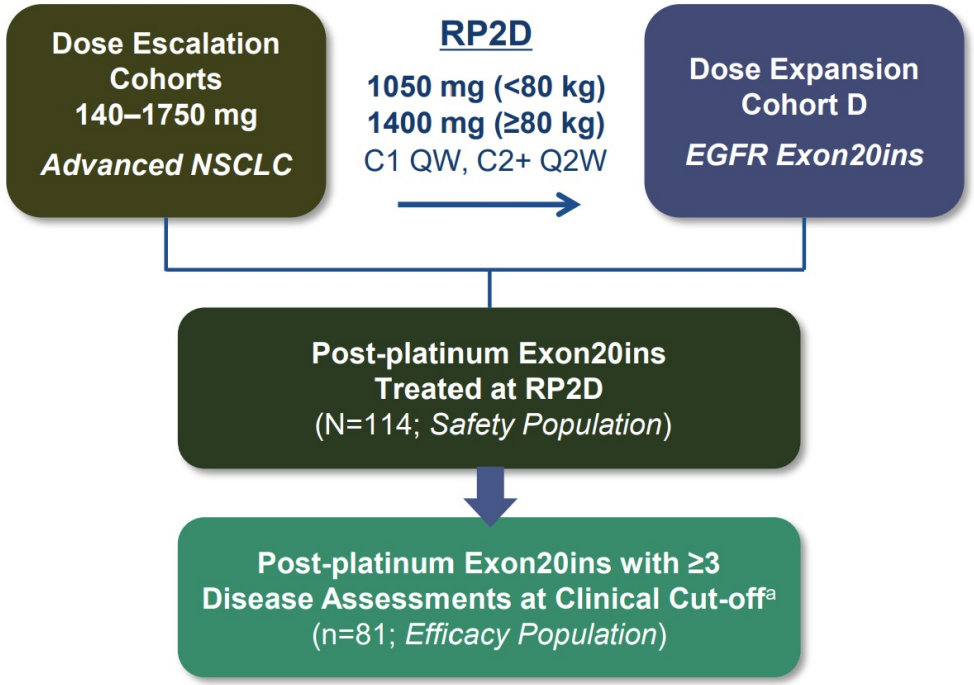
AMIVANTAMAB: CHRYSALIS STUDY DESIGN (POST-PLATINUM EXON20INS POPULATION)

Key Objectives

- Dose escalation: Establish RP2D
- Dose expansion: Assess safety and efficacy at RP2D

Key Eligibility Criteria for Post-platinum Population

- Metastatic/unresectable NSCLC
- EGFR Exon20ins mutation
- Progressed on platinum-based chemotherapy
- Previously-treated and asymptomatic brain metastasis



Efficacy End Points

Primary

- Overall response rate per RECIST v1.1

Key Secondary

- Clinical benefit rate
- Duration of response
- Progression-free survival
- Overall survival

Abbreviations: C, cycle; Q2W, every other week; QW, weekly; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose

References: 1. Sabari JK, et al. WCLC Annual Meeting 2021 Abstract #3031; 2. Park K et al. J Clin Oncol 2021, 39 (30): p3391-3402

[a]Post-platinum patients treated at the RP2D and had ≥3 scheduled disease assessments or discontinued, progressed, or died prior to the 3rd postbaseline assessment at the time of clinical cut-off (June 8, 2020). By October 8, 2020, all responders in the efficacy population had ≥6 months of follow-up from their first disease assessment.

Park K et al. J Clin Oncol 2021, 39 (30): p3391-3402

AMIVANTAMAB: CHRYSALIS STUDY DESIGN (POST-PLATINUM EXON20INS POPULATION)

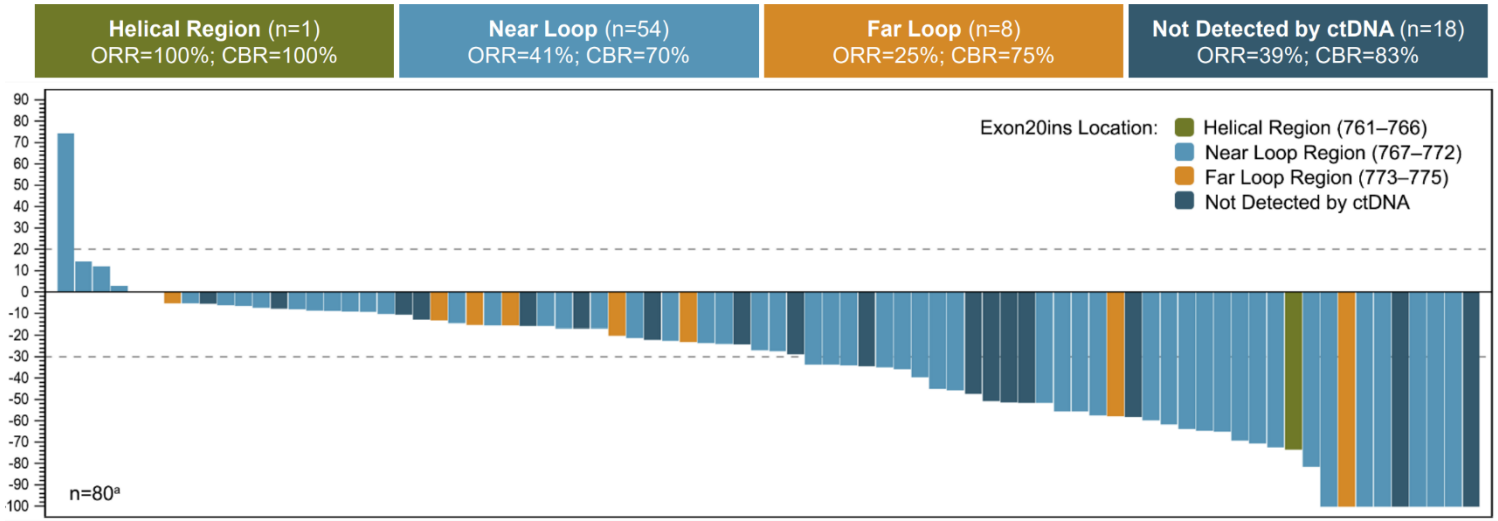
Characteristic, n (%)	Efficacy Population (n=81)
Median age, years (range)	62 (42–84)
Male / Female	33 (41) / 48 (59)
Race	
Asian	40 (49)
White	30 (37)
Black	2 (2)
Not reported/multiple	9 (11)
Smoking history	
Non-smoker	43 (53)
Smoker	38 (47)
Median time from initial diagnosis, months (range)	17 (1–130)
ECOG PS No. (%) 0/1/2	26 (32) / 54 (67) / 1(1)

Characteristic, n (%)	Efficacy Population (n=81)
History of brain metastases	18 (22)
Median number of prior lines (range)	2 (1–7)
Prior systemic therapy	81 (100)
Platinum-based doublet chemotherapy	81 (100)
Immuno-oncology therapy	37 (46)
EGFR TKI	20 (25)
1st-gen TKI	7 (9)
2nd-gen TKI	6 (7)
3rd-gen TKI	6 (7)
Poziotinib	1 (1)

Abbreviations: Gen, generation; TKI, tyrosine kinase inhibitor.

Park K et al. J Clin Oncol 2021, 39 (30): p3391-3402

AMIVANTAMAB: CHRYSALIS STUDY DESIGN (POST-PLATINUM EXON20INS POPULATION)



25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

BICR-assessed Response	Efficacy Population (n=81)
Overall response rate	**40%** (95% CI, 29–51)
Median duration of response	**11.1 months** (95% CI, 6.9–NR)
Best response, n (%)	
Complete response	3 (4)
Partial response	29 (36)
Stable disease	39 (48)
Progressive disease	8 (10)
Not evaluable	2 (2)
Clinical benefit rate[a]	74% (95% CI, 63–83)
Median follow-up	9.7 months (1.1 – 29.3 months)

References: 1. Sabari JK, et al. WCLC Annual Meeting 2021 Abstract #3031;
2. Park K et al. J Clin Oncol 2021, 39 (30): p3391-3402

Park K et al. J Clin Oncol 2021, 39 (30): p3391-3402

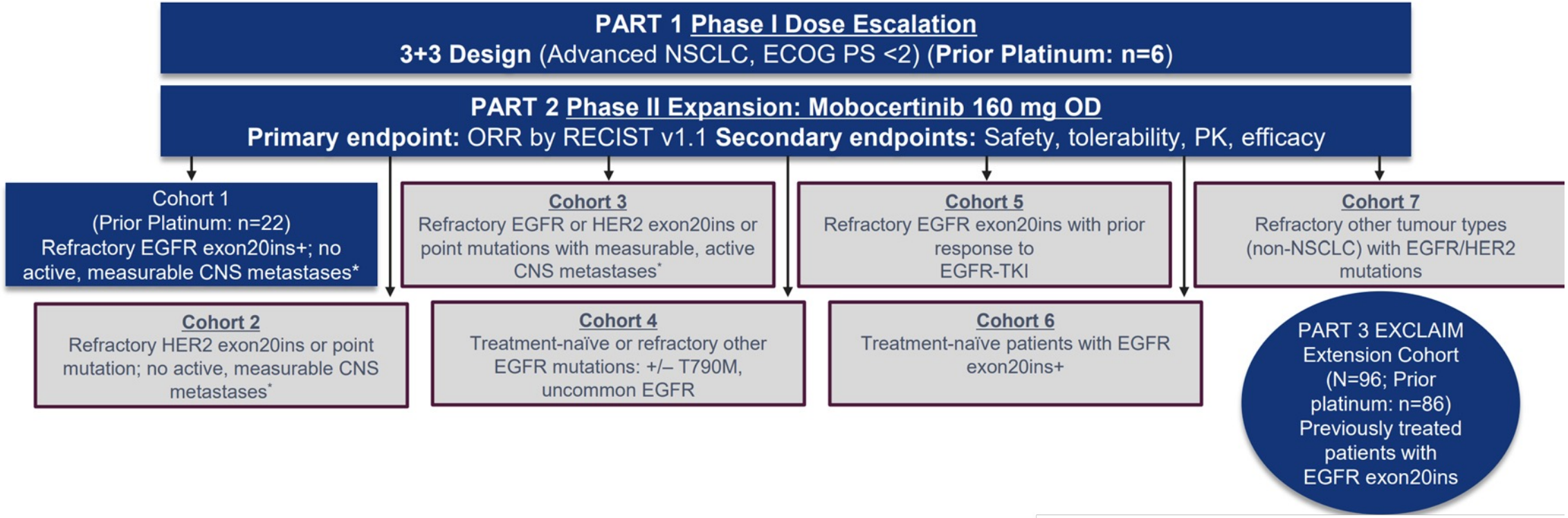
AMIVANTAMAB: CHRYSALIS STUDY DESIGN (POST-PLATINUM EXON20INS POPULATION)

Adverse Event, n (%)	Safety Population (N=114)	
	Treatment-emergent AE	Treatment-related AE
Any AE	113 (99)	112 (98)
Grade ≥3 AE	40 (35)	18 (16)
Serious AE	34 (30)	10 (9)
AE leading to death	8 (7)	0
AE leading to discontinuation	11 (10)	5 (4)
AE leading to dose reduction	15 (13)	15 (13)
AE leading to dose interruption[a]	40 (35)	24 (21)

AE (≥15% of Treatment-emergent AEs), n (%)	Safety Population (N=114)			
	Treatment-emergent AE		Treatment-related AE	
	Total	Grade ≥3	Total	Grade ≥3
EGFR-related				
Rash[b]	98 (86)	4 (4)	98 (86)	4 (4)
Paronychia	51 (45)	1 (1)	48 (42)	1 (1)
Stomatitis	24 (21)	0	21 (18)	0
Pruritus	19 (17)	0	19 (17)	0
MET-related				
Hypoalbuminemia	31 (27)	3 (3)	17 (15)	2 (2)
Peripheral edema	21 (18)	0	11 (10)	0
Other				
Infusion related reaction	75 (66)	3 (3)	75 (66)	3 (3)
Constipation	27 (24)	0	7 (6)	0
Nausea	22 (19)	0	13 (11)	0
Dyspnea	22 (19)	2 (2)	6 (5)	0
Fatigue	21 (18)	2 (2)	14 (12)	1 (1)
Increased ALT	17 (15)	1 (1)	14 (12)	1 (1)

Park K et al. J Clin Oncol 2021, 39 (30): p3391-3402

MOBOCERTINIB: PPP AND EXCLAIM COHORTS



Ramalingam SS, et al. ASCO Annual Meeting 2021 Abstract #9014;
Zhou C, et al. 2021 JAMA Oncol, doi:10.1001/jamaoncol.2021.4761

MOBOCERTINIB: PPP AND EXCLAIM COHORTS

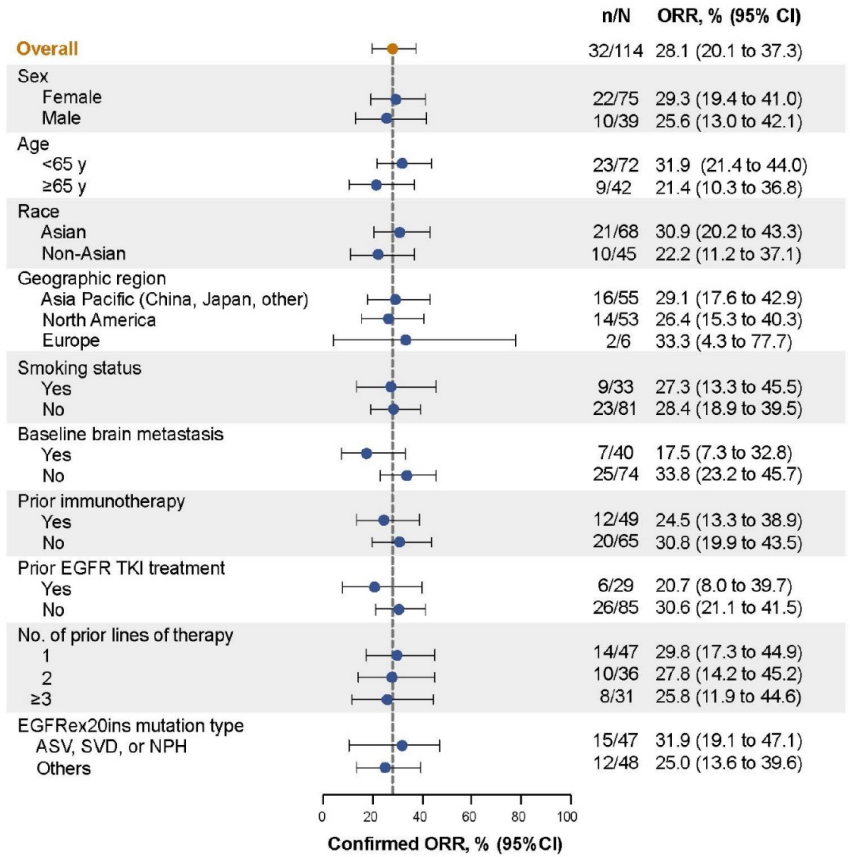
Characteristic	PPP Cohort (N=114)	EXCLAIM Cohort (N=96)
Median age, years (range)	60 (27–84)	59 (27–80)
Female, %	66	65
Race: Asian/White/Black/Other, %	60/37/3/1	69/29/2/0
Histology: Adenocarcinoma/Squamous/Large cell, %	98/1/1	99/1/0
ECOG PS 0/1, %	25/75	29/71
History of smoking: Never/Current/Former, %	71/2/27	73/2/25
Median no. prior systemic anticancer regimens (range)	2 (1–7)	1 (1–4)
Prior systemic anticancer regimens: 1/2/≥3, %	41/32/27	51/31/18
Prior platinum therapy, %	100	90
Prior EGFR TKI therapy, %	25	31
Prior immunotherapy, %	43	34
Baseline brain metastases, %	35	34

- Ramalingam SS, et al. ASCO Annual Meeting 2021 Abstract #9014; Zhou C, et al. 2021 JAMA Oncol, doi:10.1001/jamaoncol.2021.4761

MOBOCERTINIB: PPP AND EXCLAIM COHORTS

	PPP cohort (n=114)	EXCLAIM cohort (n=96)
IRC assessments		
Confirmed ORR, % (95% CI)	28 (20–37)	25 (17–35)
CR, %	0	0
PR, %	28	25
Median DoR, months (95% CI)*	17.5 (7.4–20.3)	NE (5.6–NE)
Confirmed DCR, % (95% CI)†	78 (69–85)	76 (66–84)
Investigator assessments		
Confirmed ORR, % (95% CI)	35 (26–45)	32 (23–43)
CR, %	<1	1
PR, %	34	31
Median DoR, months (95% CI)*	11.2 (5.6–NE)	11.2 (7.0–NE)
Confirmed DCR, % (95% CI)†	78 (69–85)	75 (65–83)
Median follow up, months	14.2 (0.7 – 35.8)	13.0 (0.7 – 18.8)

Data cutoff dale November 1, 2020
*DoR per Kaplan-Meier estimates, †DCR defined as confirmed CR or PR , or best response of stable disease for at least 6 weeks alter initiation of study drug

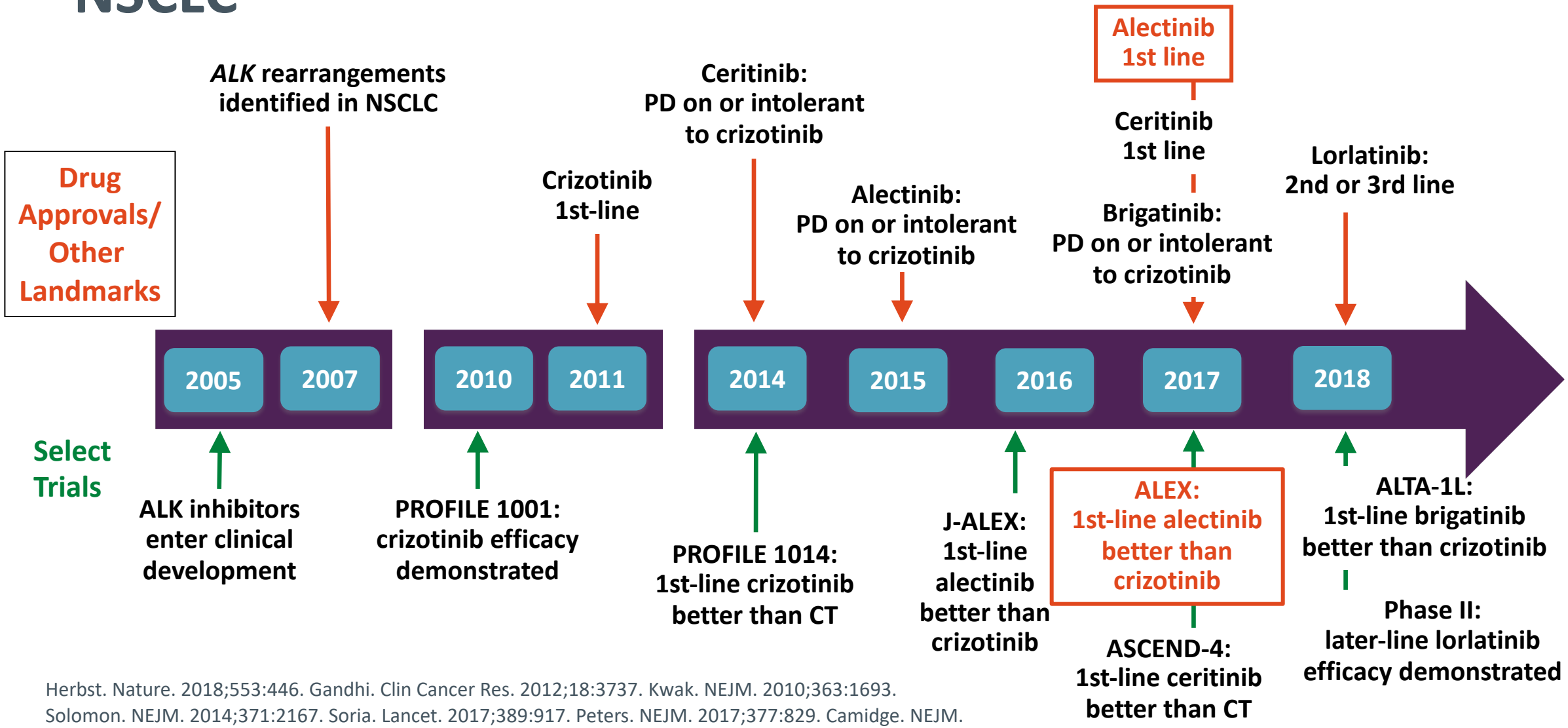


Ramalingam SS, et al. ASCO Annual Meeting 2021 Abstract #9014;
Zhou C, et al. 2021 JAMA Oncol, doi:10.1001/jamaoncol.2021.4761

ALK- Oncogenic Translocation

First-line *ALK* Translocation–Positive NSCLC

Evolution of Care: *ALK* Translocation–Positive Advanced NSCLC



Herbst. Nature. 2018;553:446. Gandhi. Clin Cancer Res. 2012;18:3737. Kwak. NEJM. 2010;363:1693. Solomon. NEJM. 2014;371:2167. Soria. Lancet. 2017;389:917. Peters. NEJM. 2017;377:829. Camidge. NEJM. 2018;379:2027. Solomon. Lancet Oncol. 2018;19:1654. Hida. Lancet. 2017;390.29.

ALEX: Alectinib vs Crizotinib in Untreated *ALK*-Positive NSCLC

- Randomized, open-label phase III trial

Stratified by ECOG PS (0/1 vs 2), race (Asian vs non-Asian), CNS mets (yes vs no)

Patients with advanced* *ALK*-positive NSCLC, ECOG PS 0-2, no prior systemic tx for advanced NSCLC, measurable disease, asymptomatic brain or leptomeningeal mets permitted, CNS RT permitted if ≥ 14 days before enrollment (N = 303)

Alectinib 600 mg BID PO (n = 152)

Crizotinib 250 mg BID PO (n = 151)

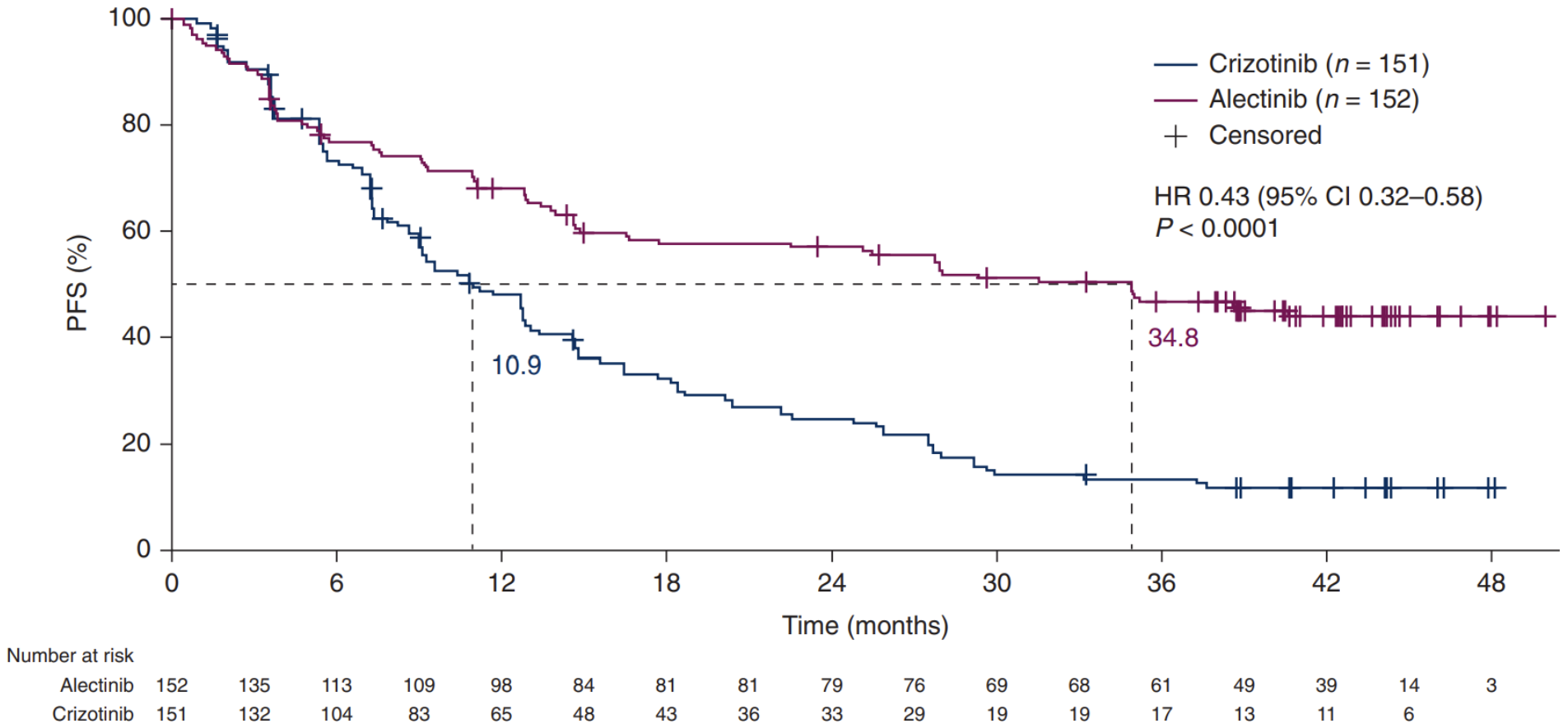
Until PD, unacceptable toxicity, or withdrawal; no crossover permitted†

*Stage IIIB/IV. †Patients in crizotinib arm may have received alectinib after PD in countries where alectinib available.

- Primary endpoint: PFS (investigator-assessed)
- Secondary: ORR, DoR, OS, PFS (IRC assessed), CNS ORR, time to CNS progression (IRC-assessed), safety

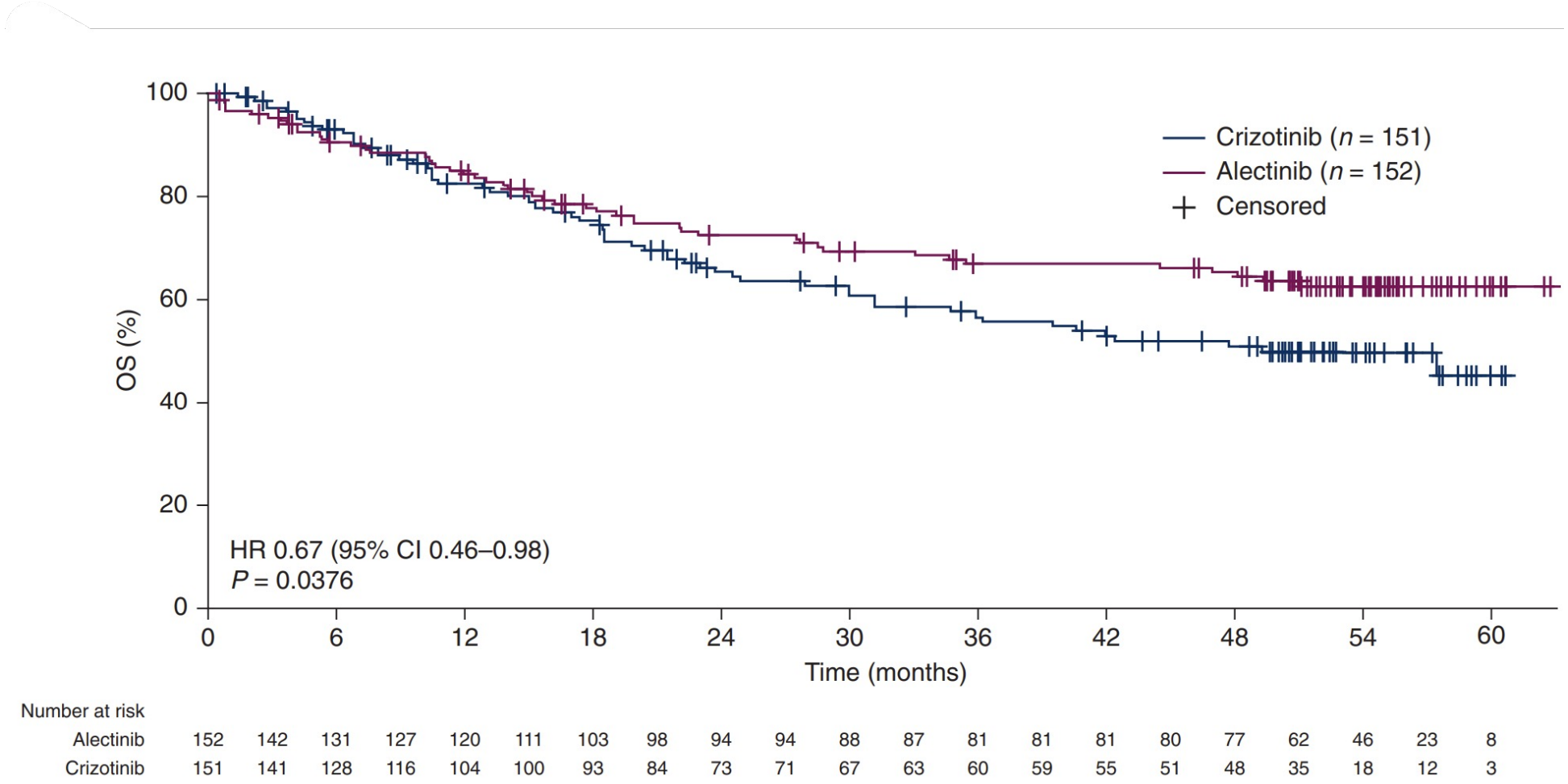
Peters. NEJM. 2017;377:829. Camidge. ASCO 2018. Abstr 9043.

ALEX: Investigator-Assessed PFS



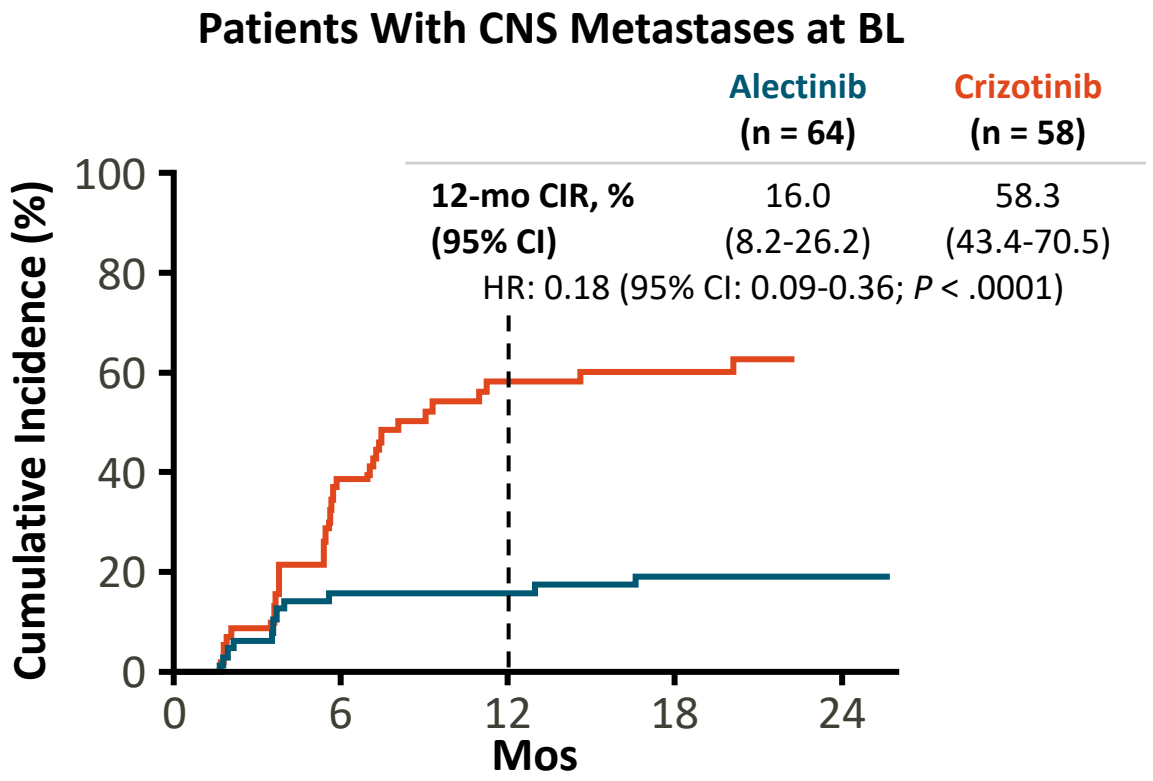
Mok T. et al Ann Oncol . 2020 Aug;31(8):1056-1064

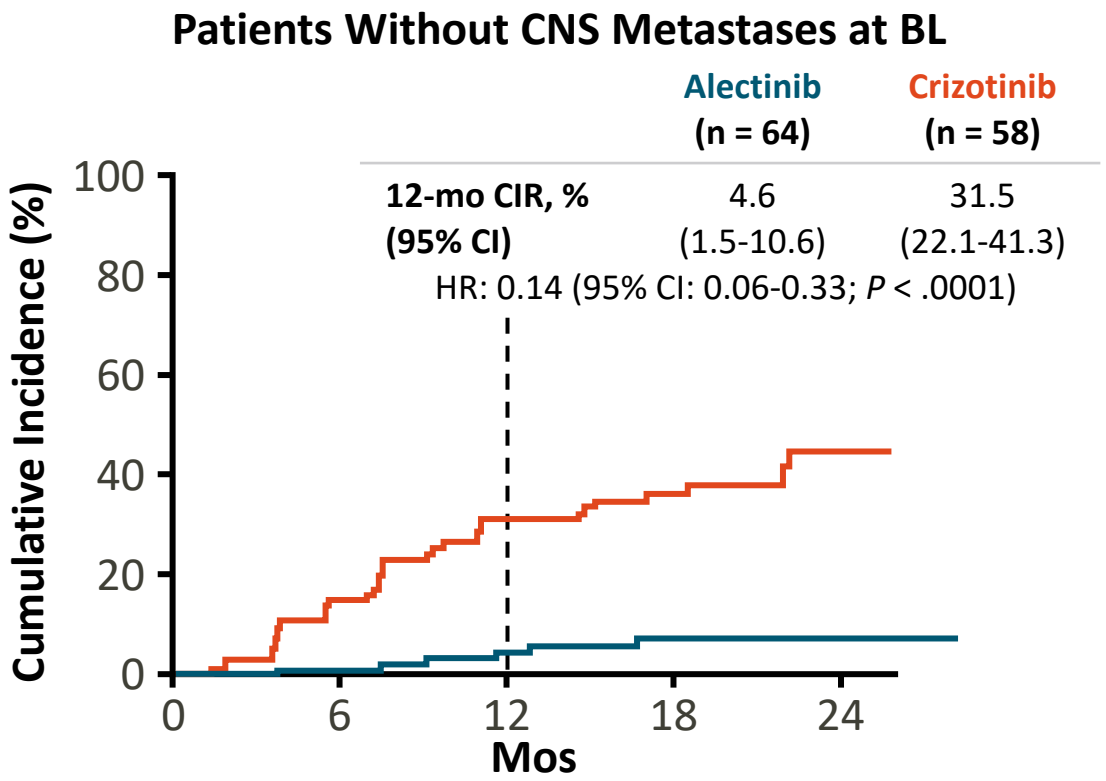
ALEX: OS



Mok T. et al Ann Oncol . 2020 Aug;31(8):1056-1064

ALEX: Time to CNS Progression by CNS Metastases at Baseline





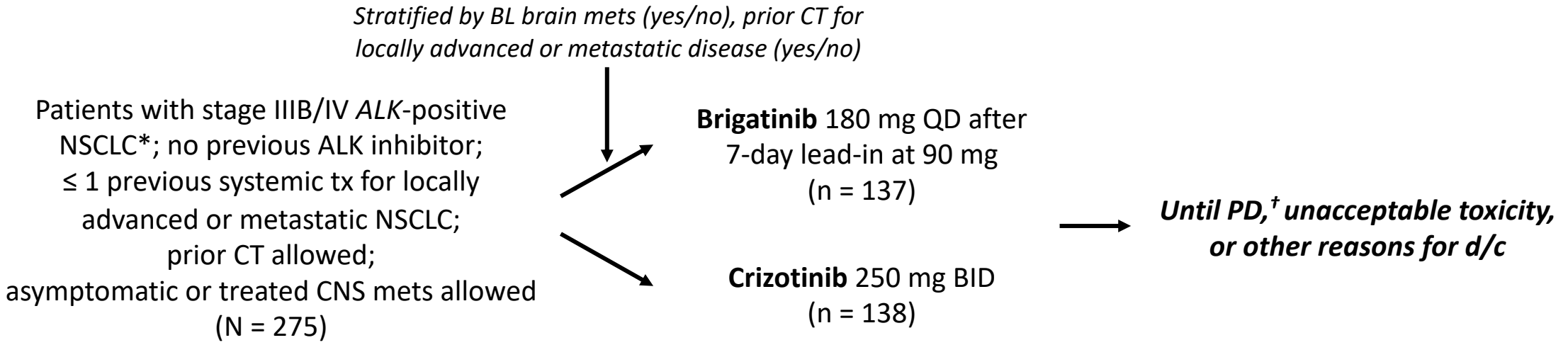
In a competing risk analysis of CNS progression, non-CNS progression, and death, the first event of CNS progression, non-CNS progression, or death was counted for each patient

- Alectinib delayed time to CNS progression in patients with and without CNS metastases at BL compared with crizotinib

Gadgeel. Ann Oncol. 2018;29:2214.

ALTA-1L: Brigatinib vs Crizotinib in Untreated *ALK*-Positive NSCLC

- Multicenter, randomized, open-label phase III trial

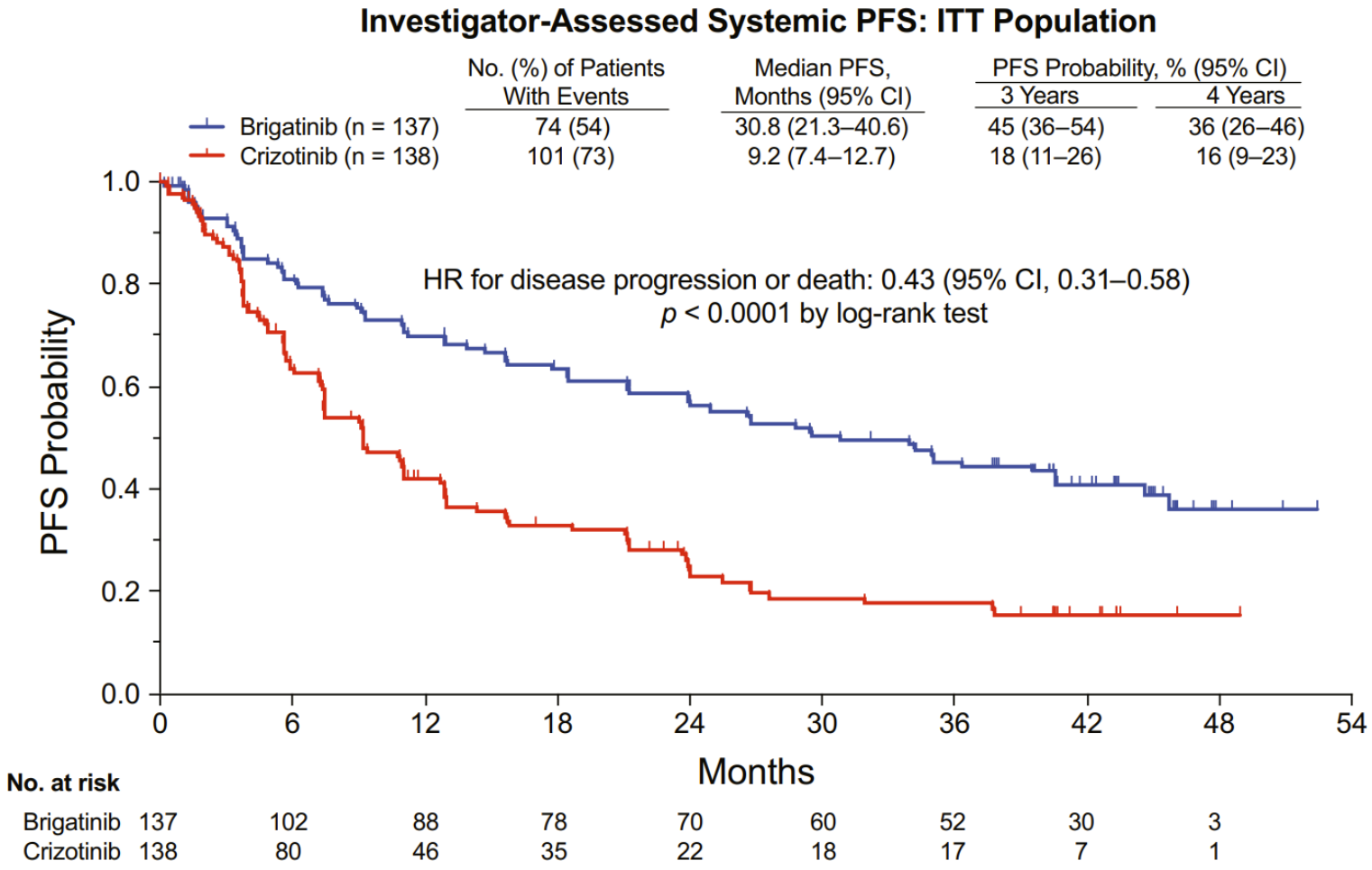


*Local testing allowed. †Crossover from crizotinib to brigatinib permitted on PD. CNS surveillance in all patients at same frequency as body imaging.

- Primary endpoint: BIRC-assessed PFS (RECIST v1.1)
- Secondary endpoints: confirmed ORR, confirmed intracranial ORR, intracranial PFS, OS, safety

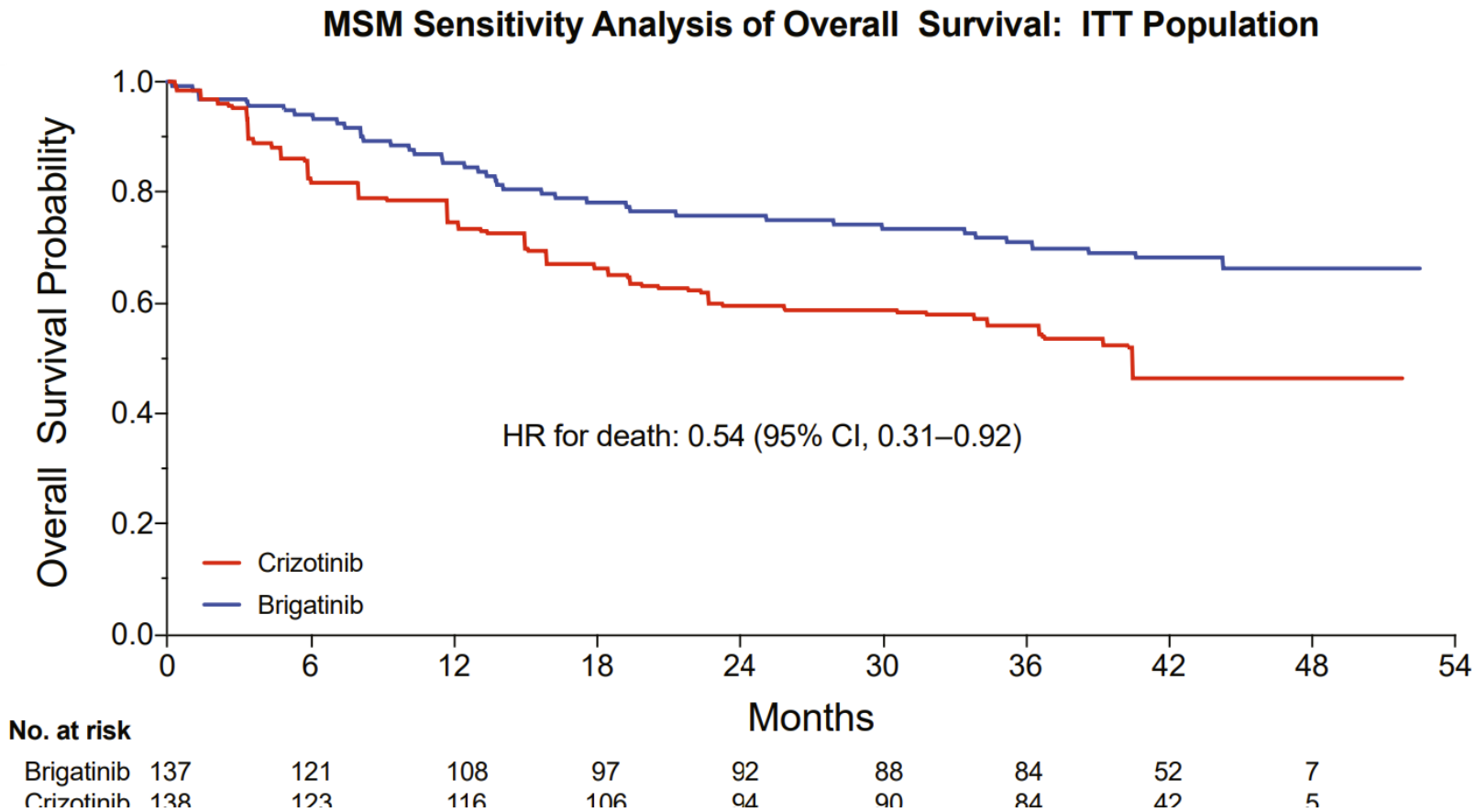
Camidge. NEJM. 2018;379:2027.

ALTA-1L: PFS (Primary Endpoint)



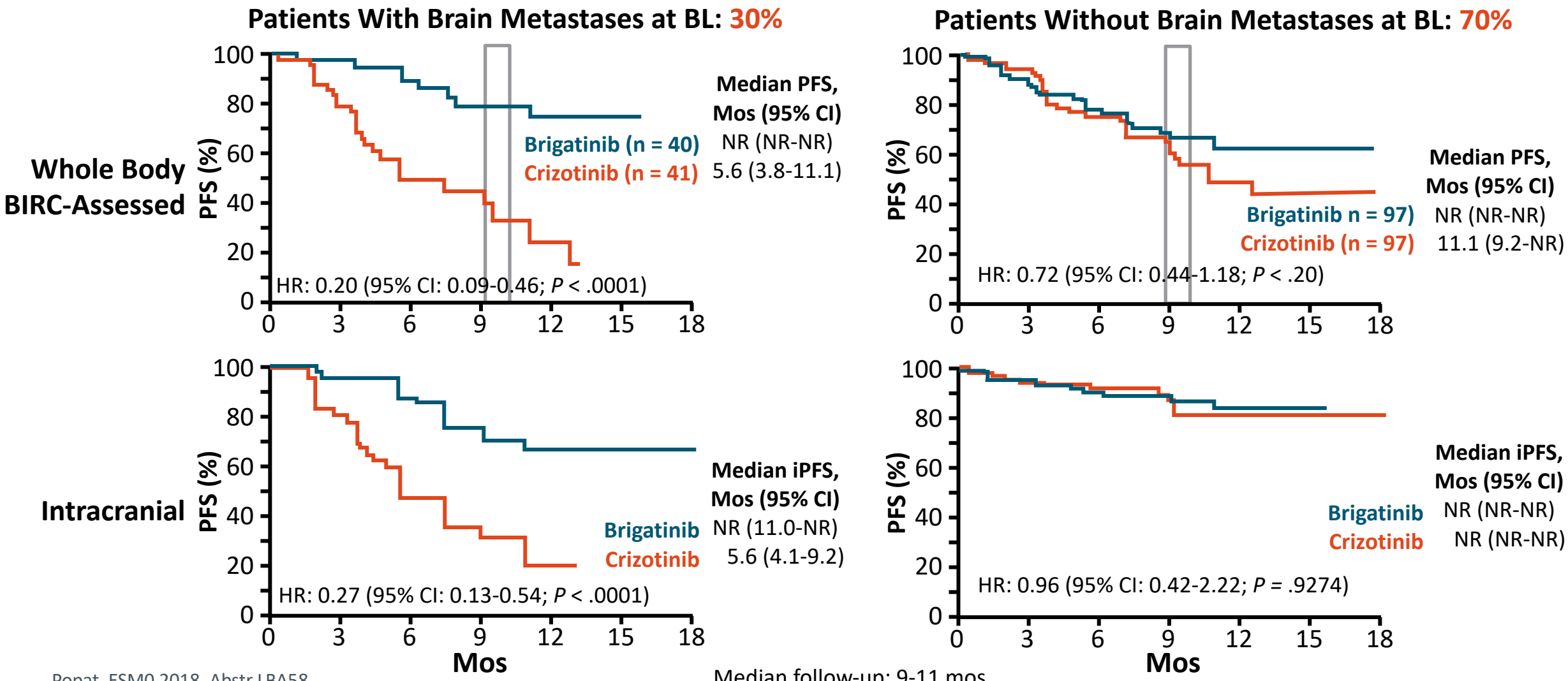
Camidge R. et al J Thorac Oncol . 2021 Dec;16(12):2091-2108.

ALTA-1L: Overall Survival



Camidge R. et al J Thorac Oncol . 2021 Dec;16(12):2091-2108.

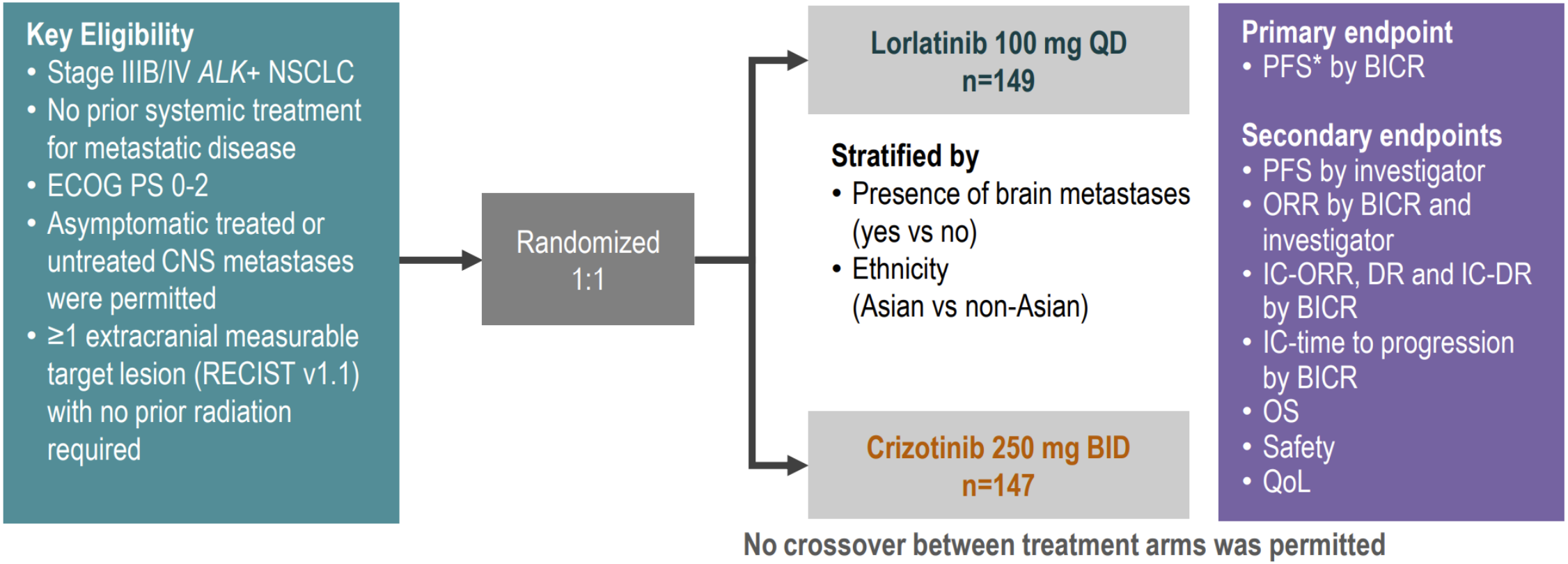
ALTA-1L: PFS by CNS Metastases at BL



Median follow-up: 9-11 mos.

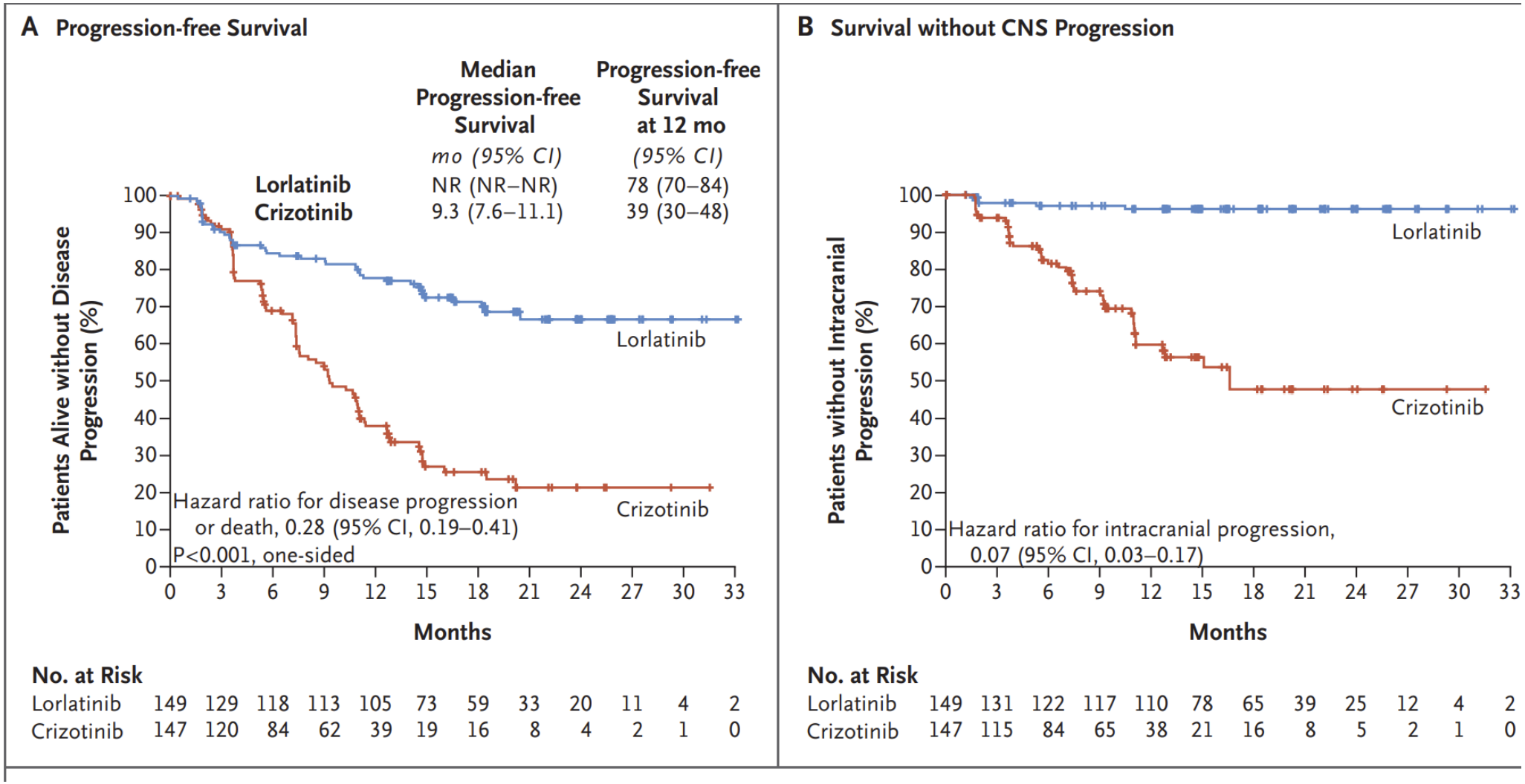
Popat. ESM0 2018. Abstr LBA58.

Crown Study: Lorlatinib vs Crizotinib in Untreated *ALK*-Positive NSCLC



Shaw A. et al N Engl J Med 2020; 383:2018-2029

Crown Study: Lorlatinib vs Crizotinib in Untreated *ALK*-Positive NSCLC



Shaw A. et al N Engl J Med 2020; 383:2018-2029

Is there a 'best' next generation ALK inhibitor ?

Drug	Study	Response Rate (ORR)	PFS months (Hazard Ratio)	CNS mets at BL Drug/comparator	IC RR
*Ceritinib**	*ASCEND-4*	*72.5%*	*16.6 (0.55)*	*32% / 31 %*	*73%*
Alectinib	ALEX	82.9%	25.7 (34.8) (0.5)	38 % / 42%	81%
Brigatinib	ALTA-1L	71%	24 (29) (0.49)	29% / 30%	78%
Ensartinib	eXalt-3	75%	25.8 (0.51)	33% / 39%	64%
Lorlatinib	CROWN	76%	NR (0.28)	26 %/ 27%	82%

*Comparator for ceritinib /ASCEND-4 is platinum doublet chemotherapy
PFS for crizotinib : 9.3 – 12.7 months ; ORR 58 – 75.5%; IC RR 21 – 50%
Updated analyses of PFS Mok ESMO 2019, Camidge ESMO Asia 2019

Peters et al. NEJM 2017, Camidge et al NEJM 2018, Horn et al IASLC WCLC 2020, Solomon ESMO 2020

Is there a ‘best’ next generation ALK inhibitor ?

Drug	Study	Serious TRAEs	Dose reduction	Dose Discontinuation	Treatment Related Adverse Effects (TRAEs) more common than crizotinib
Alectinib	ALEX	28%	16%	11%	Anaemia, Mylagia, Raised bilirubin, weight gain, musculoskeletal pain, photosensitivity reaction
Brigatinib	ALTA-1L	28%	28%	12%	Raised Creatine Kinase, Cough, Hypertension, Raised lipase, Early onset pneumonitis
Ensartinib	eXalt-3	24%	24%	9%	Rash (70%), pruritis, pyrexia
Lorlatinib	CROWN	35%	49%	7 %	Hypercholesterolaemia, hypertriglyceridaemia, weight increase, peripheral neuropathy, cognitive effects
Entrectinib	STARTRK	No randomised data; commonest : fatigue, constipation, dysgeusia, oedema, dizziness, dysaesthesia			

Peters et al. NEJM 2017, Camidge et al NEJM 2018, Horn et al IASLC WCLC 2020, Solomon ESMO 2020

Is there a ‘best’ next generation ALK inhibitor ?

Cellular ALK Phosphorylation Mean IC50 (nM)

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

IC50 ≤ 50 nM

IC50 > 50 <200 nM

IC50 ≥ 200 nM

Is there a best ALK TKI for first line treatment ?

Is there a benefit from sequencing TKIs ?

Cancer Discov
. 2016 Oct;6(10):1118-1133.

Newly Available and Emerging Biomarkers for Targeted Therapy in NSCLC

New Kids on the block: Beyond *EGFR/ALK*

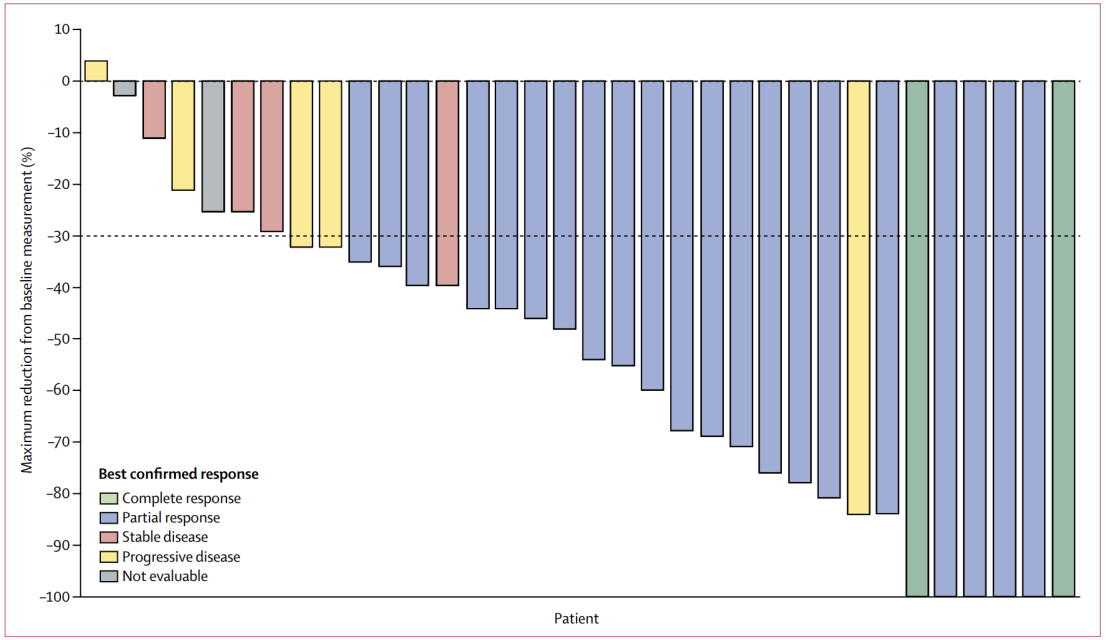
- New
  - *BRAF V600E*
  - *ROS Gene Fusions*
  - *NTRK* fusions
  - *MET*ex14–skipping mutations
  - *RET* gene fusions
  - KRAS G12C
  - HER2
- A little farther out
  - *Non KRAS* G12C mutations
  - KEAP1/STK11

BRAF V600E Mutations

Tumor Agnostic FDA Indication for Dabrafenib + Trametinib

- Adult and pediatric patients age ≥6 yr with unresectable or metastatic ***BRAF* V600E–mutated solid tumors** with PD after previous treatment with no satisfactory alternative treatment options
  - Accelerated approval based on BRF117019, NCI-MATCH, and CTMT212X2101 trials
  - Supported by COMBI-d, COMBI-v, and BRF113928 trials
- Tumor-specific approvals in *BRAF* V600E/K–positive melanoma and *BRAF* V600E–positive anaplastic thyroid cancer, NSCLC, and pediatric low-grade glioma

Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial



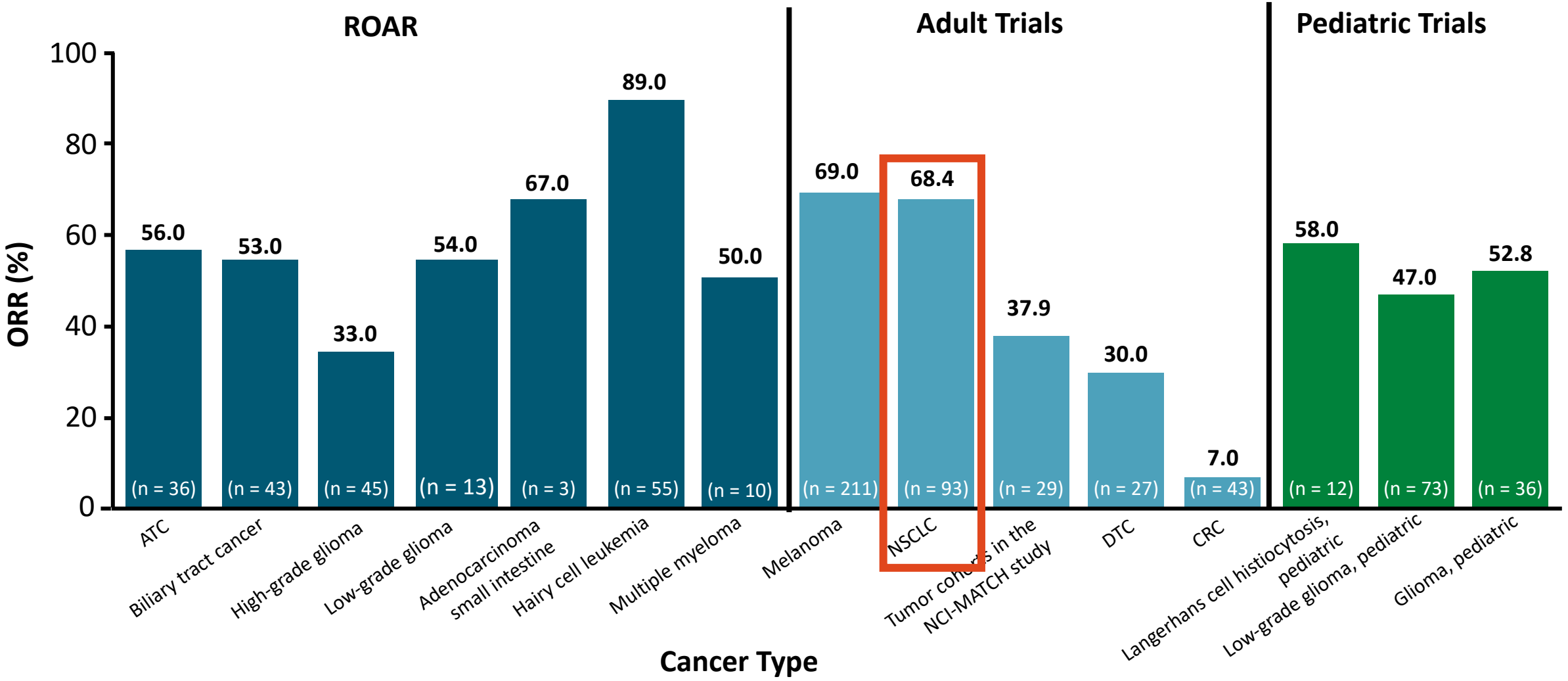
	Investigator assessed (n=36)	Independent review committee assessed (n=36)
Overall response (complete and partial responses)	23 (64%; 46–79)	23 (64%; 46–79)
Disease control (complete responses, partial responses, and stable disease)	27 (75%; 58–88)	26 (72%; 55–86)
Complete response	2 (6%)	2 (6%)
Partial response	21 (58%)	21 (58%)
Stable disease	4 (11%)	3 (8%)
Progressive disease	5 (14%)	7 (19%)
Not evaluable	4 (11%)	3 (8%)

Data are n (%; 95% CI) or n (%).

***Table 2*: Overall response as assessed by investigator and independent review committee**

Planchard D et. Al Lancet Oncol . 2017 Oct;18(10):1307-1316.

Response Rates With Dabrafenib + Trametinib Across *BRAF* V600E–Mutated Cancers



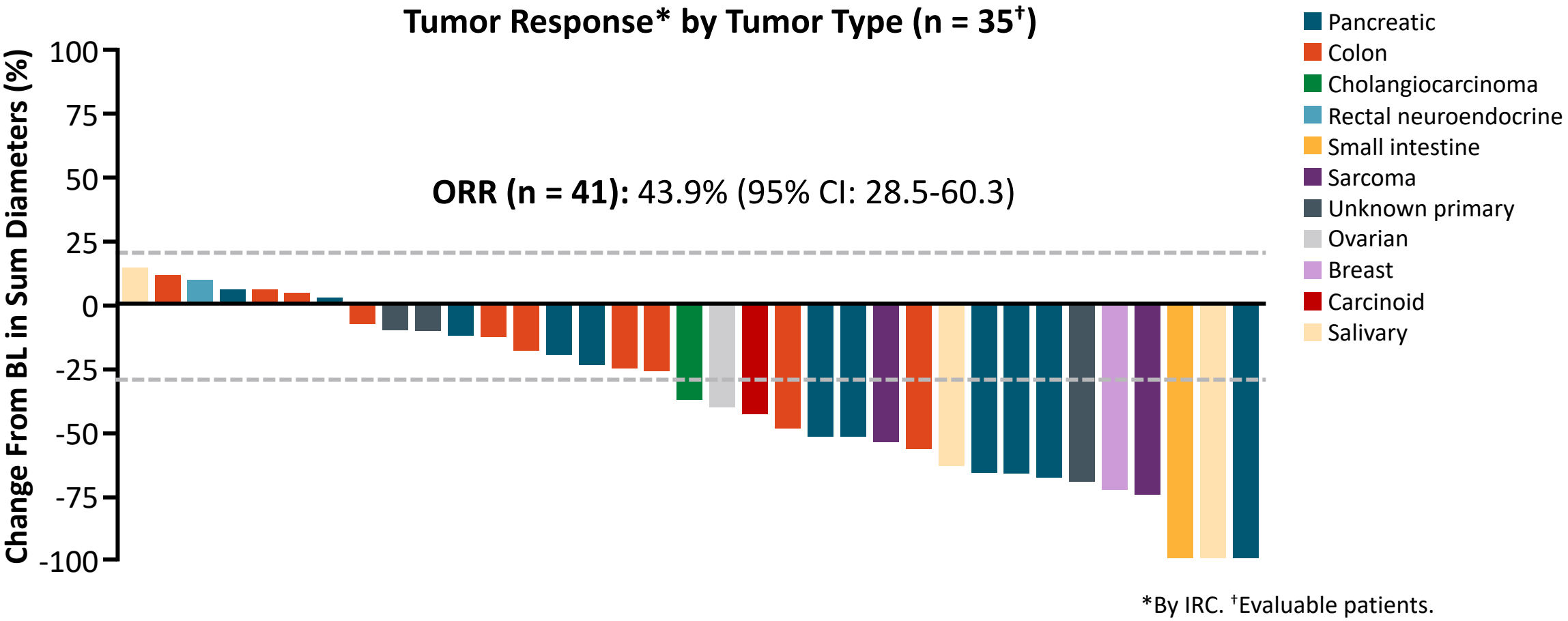
Subbiah. Nat Med. 2023;29:1103. NCT02034110. NCT02124772. NCT02684058.

RET Gene Fusion–Positive NSCLC

Tumor Agnostic FDA Indication for Selpercatinib

- Locally advanced or metastatic solid tumors with a ***RET* fusion** and PD on or after previous systemic treatment or no satisfactory alternative treatment options
  - Accelerated approval based on LIBRETTO-001
- Tumor-specific approvals
  - Locally advanced or metastatic NSCLC with a *RET* fusion
  - Advanced or metastatic MTC with a *RET* mutation requiring systemic therapy
  - Advanced or metastatic RAI-refractory thyroid cancer with a *RET* fusion requiring systemic therapy

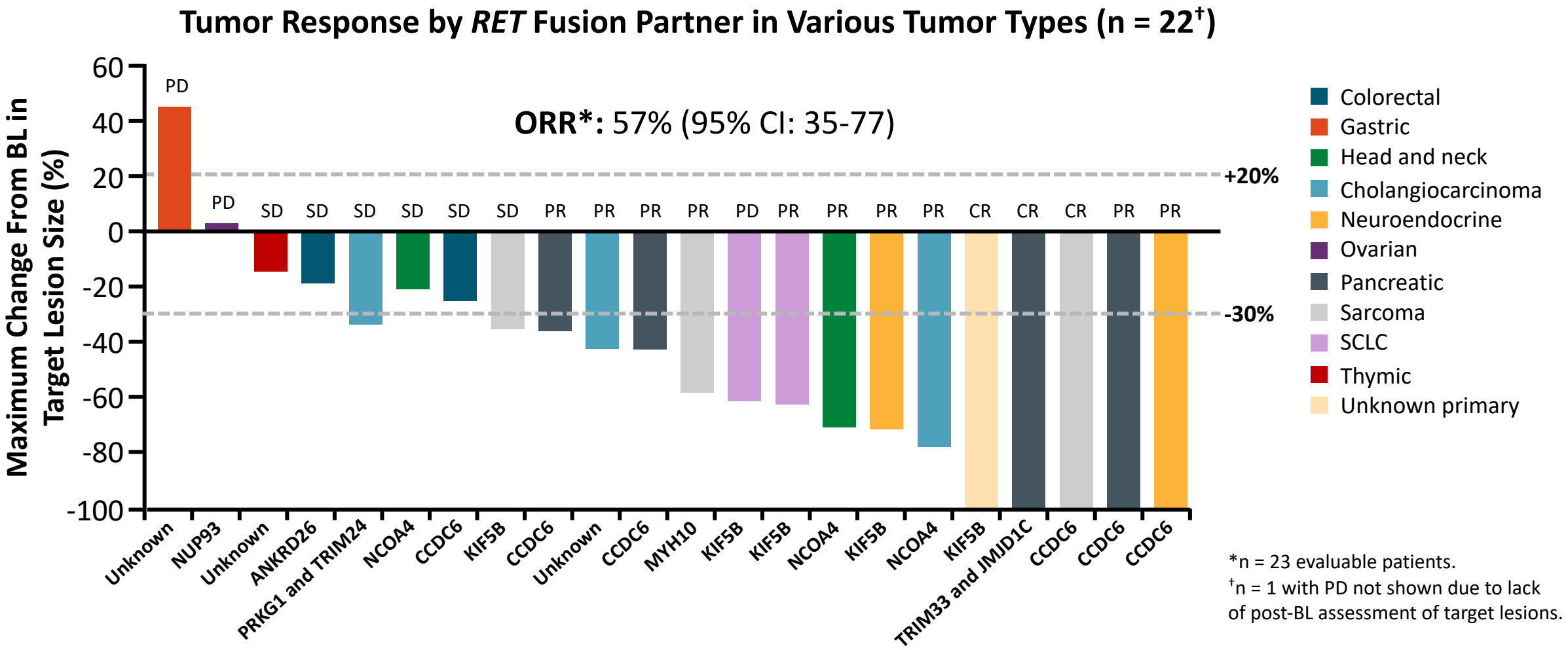
LIBRETTO-001: Selpercatinib Is Active in *RET* Fusion–Positive Cancers



*By IRC. †Evaluable patients.

Subbiah. Lancet Oncol. 2022;23:1261.

ARROW: Pralsetinib Is Active in *RET* Fusion–Positive Cancers (Investigational)



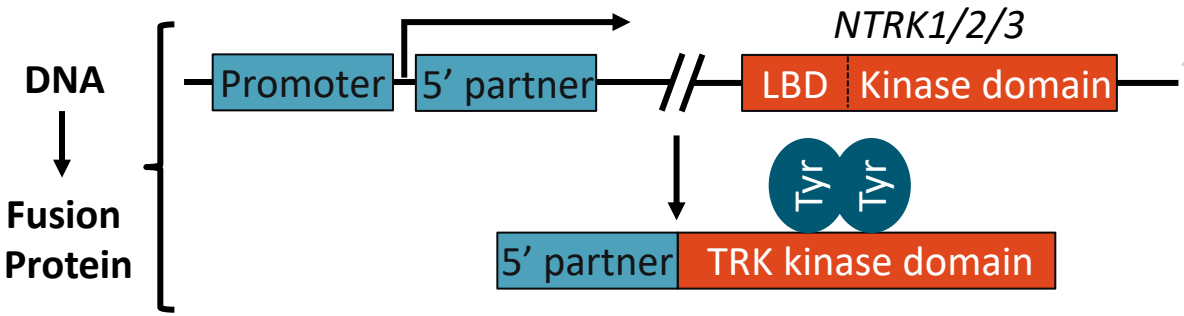
*n = 23 evaluable patients.
†n = 1 with PD not shown due to lack of post-BL assessment of target lesions.

Subbiah. Nat Med. 2022;28:1640.

NTRK Fusion–Positive NSCLC

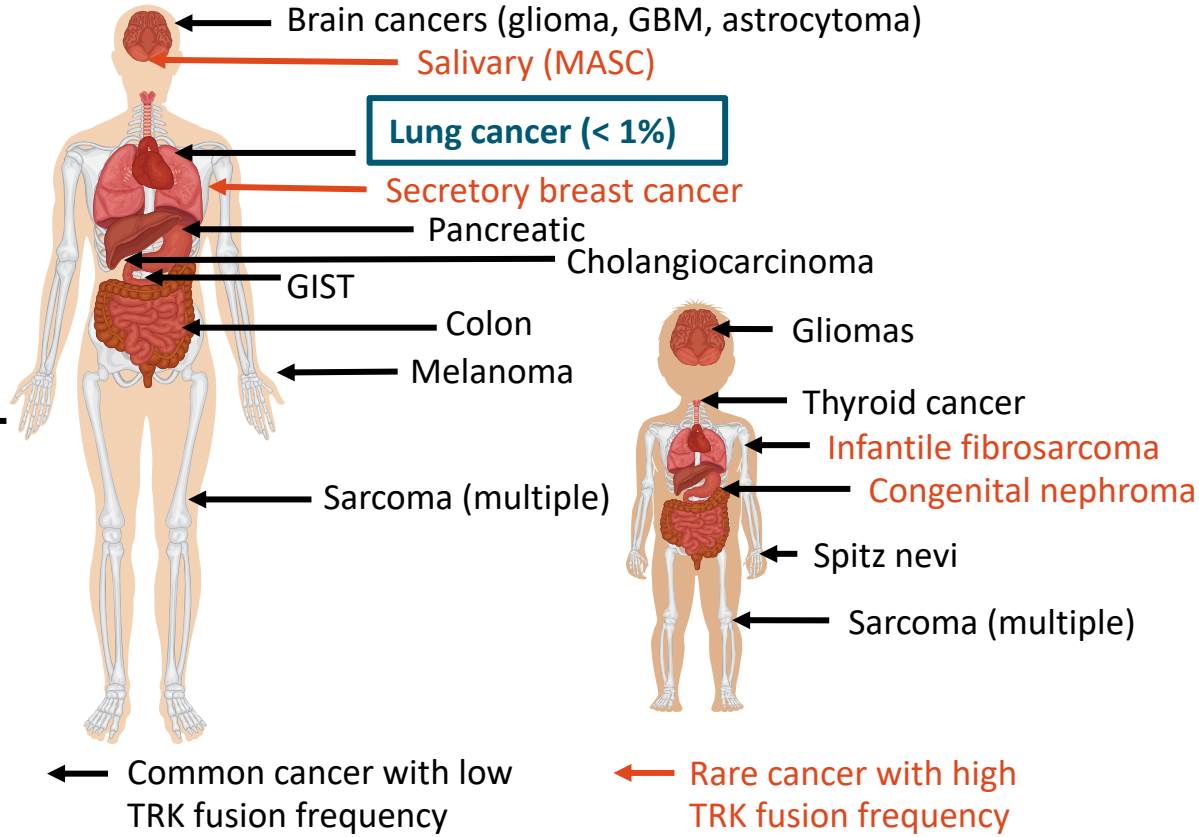
NTRK Rearrangements and TRK Fusions in Cancer

- Normal role in neuronal development in utero and postnatal neuronal differentiation, survival, function; expression limited to CNS
- In cancer, rearrangement of *NTRK* gene couples TK domain with a 5’ fusion partner to generate a chimeric TRK protein lacking LBD



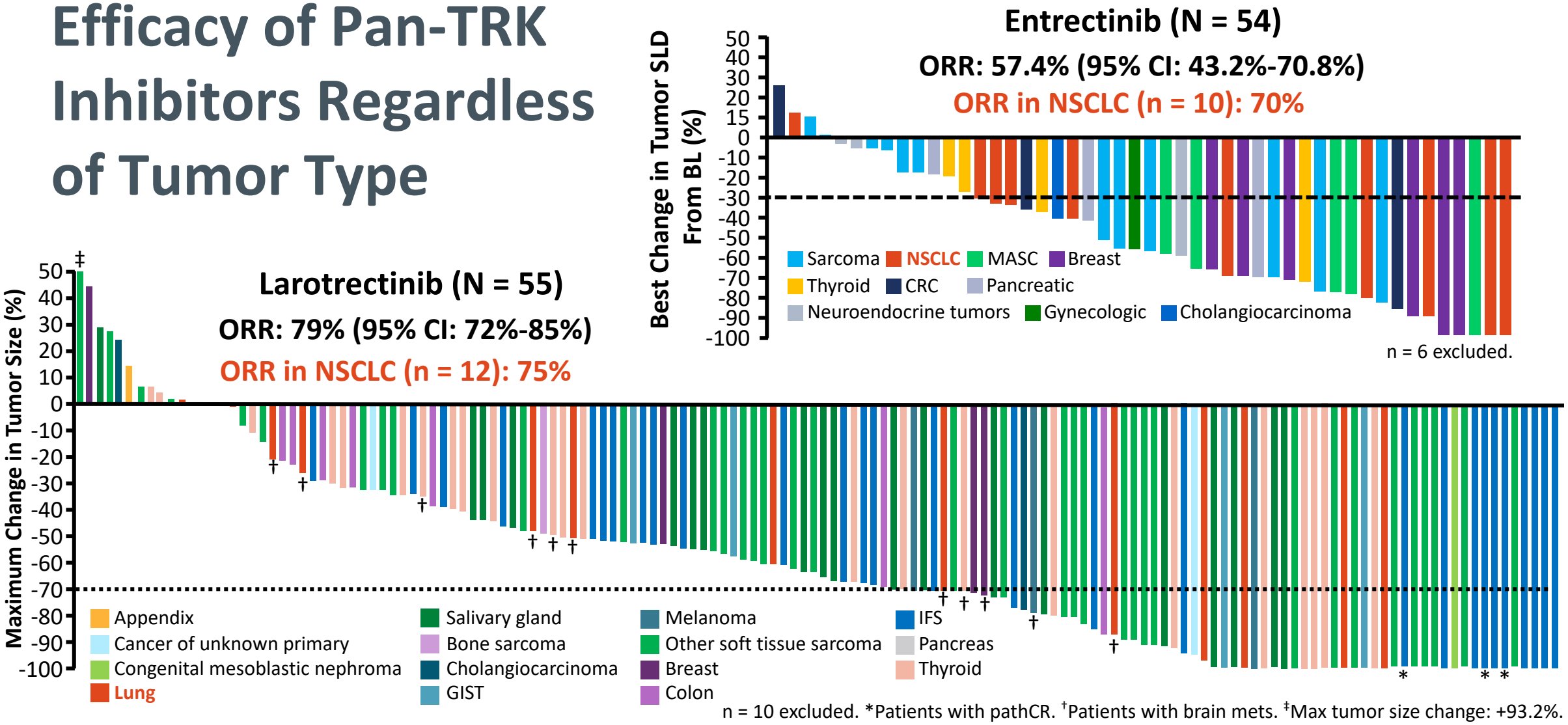
Leads to overexpression or constitutive activation of kinase domain

NTRK Fusions Are Rare Events:
0.21% Across 11,116 Patients With Tumors of All Types



Cocco. Nat Rev Clin Oncol. 2018;15:731. Hyman. ASCO 2017. Abstr LBA2501. Gatalica. AACR-NCI-EORTC 2017. Abstr A047.

Efficacy of Pan-TRK Inhibitors Regardless of Tumor Type



- DoR: 10.4 mos with entrectinib (n = 31); 35.2 mos with larotrectinib (n = 44)

Hong. Lancet Oncol. 2020;21:531. Doebele. Lancet Oncol. 2020;21:271.

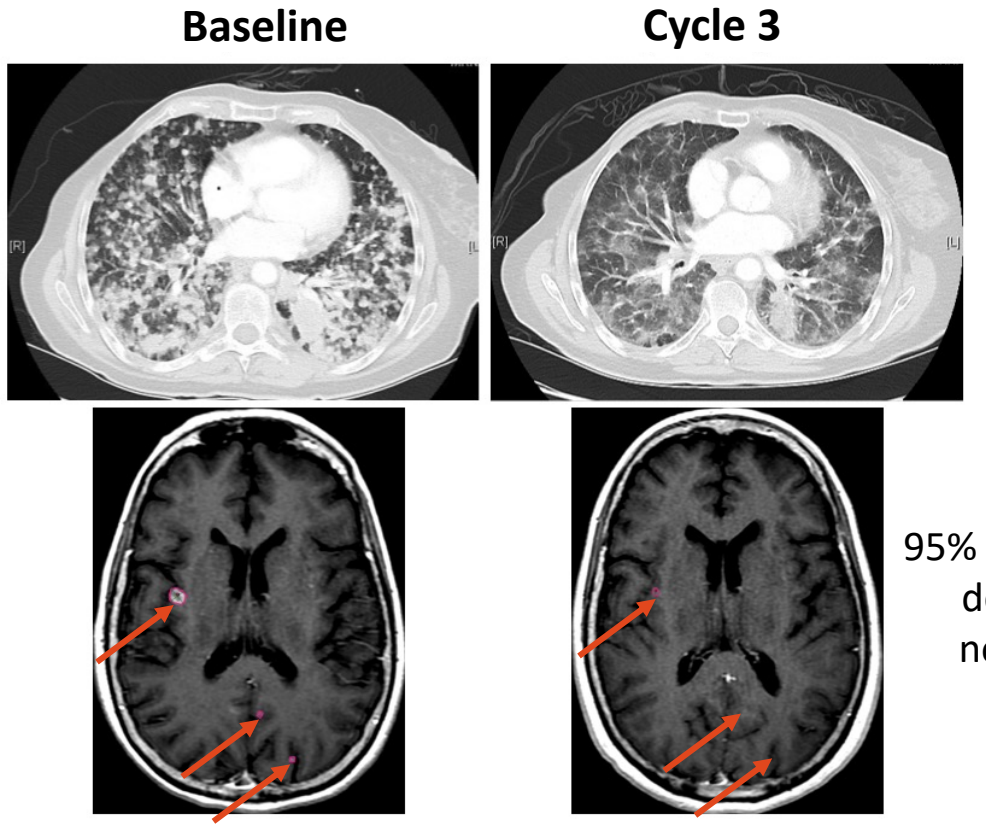
Intracranial ORR With Pan-TRK Inhibition in *NTRK* Fusion–Positive Solid Tumors and CNS Metastases

CNS Activity of Entrectinib

Intracranial Response by BICR, n (%)	Entrectinib[1] (n = 11)
Intracranial ORR	6 (54.5)
▪ CR	3 (27.3)
▪ PR	3 (27.3)
▪ SD	1 (9.1)
▪ PD	3 (27.3)
▪ Non-CR/PD, missing or unevaluable	NE

Data cutoff: May 31, 2018.

Larotrectinib Efficacy in Patient With EPS15-NTRK1 Lung Cancer and CNS Metastases[2]



PR in lung target lesions

95% aggregate volume decrease in CNS nontarget lesion

1. Doebele. AACR 2019. Abstr CT131. 2. Lassen. ESMO 2018. Abstr 409O.

NTRK Fusion: Summary

- Very rare (0.3% of NSCLC) but actionable if identified
- Larotrectinib and entrectinib both show significant clinical activity in patients with *NTRK* fusion–positive disease
- On November 26, 2018, larotrectinib was approved by the FDA for treatment of any solid tumor with *NTRK* gene fusions, followed by approval of entrectinib on August 15, 2019

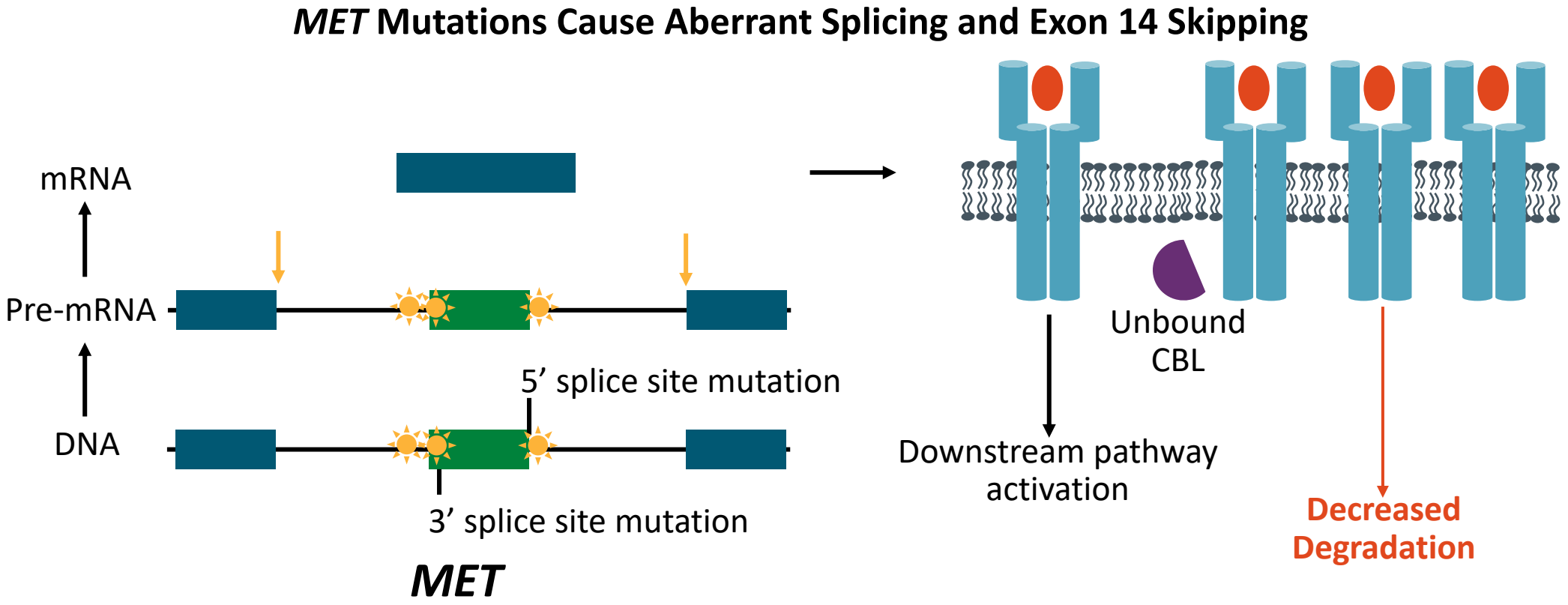
Larotrectinib PI. Entrectinib PI.

*MET*ex14 Mutation–Positive NSCLC

MET: A New Target in NSCLC

- ***MET* exon 14 skipping mutations**
- *MET* fusions
- *MET* amplification
  - *MET* amplification as primary oncogenic event
  - *MET* amplification in the context of an *EGFR* mutation (or other mutation)

*MET*ex14 Splice Site Alterations: Alternative Splicing Can Be Oncogenic

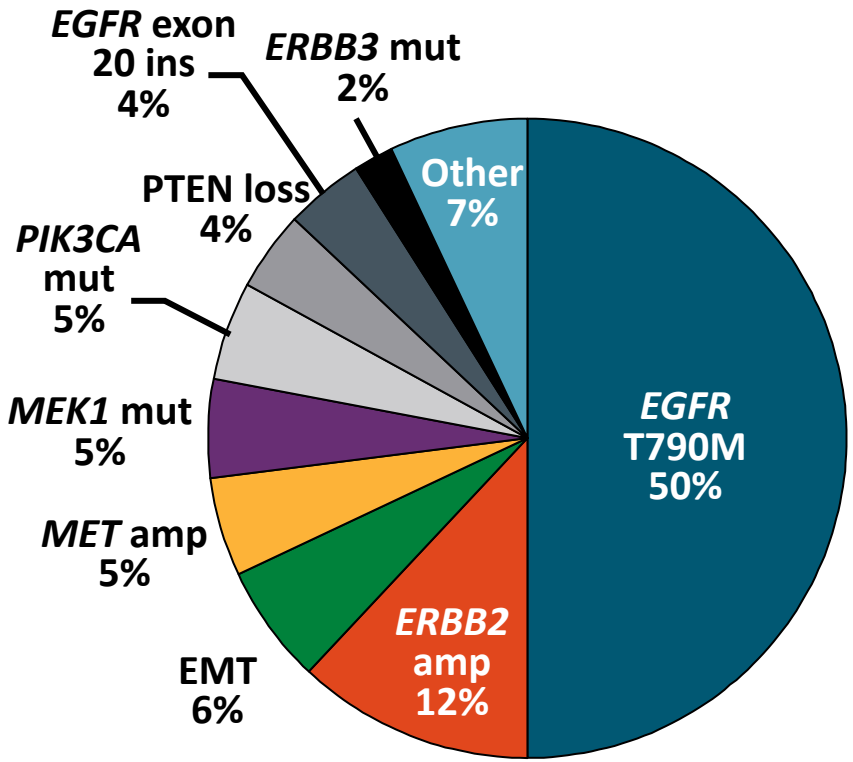


Multiple different specific mutations result in the same exon 14 splice effect;
~ 20% to 30% of exon 14 mutations have coincident *MET* amplification

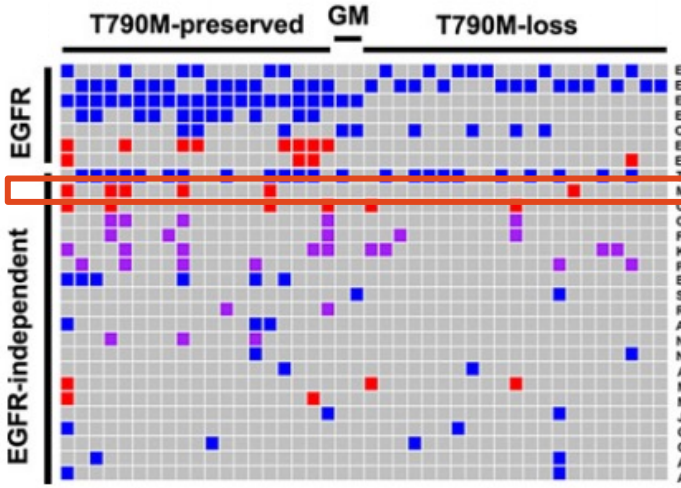
Drilon. Clin Cancer Res. 2016;22:2832. Awad. J Clin Oncol. 2016;34:721.

MET Amp Reported in NSCLC With Acquired Resistance to EGFR TKIs Using Cell-Free DNA Analysis

First- and Second-Generation EGFR Inhibitor Resistance Mechanisms[1]



Third-Generation EGFR Inhibitor Resistance Mechanisms[2]



Blue box: mut
Red box: amp
Purple box: mut and/or amp

41 Patients with progression tumor NGS

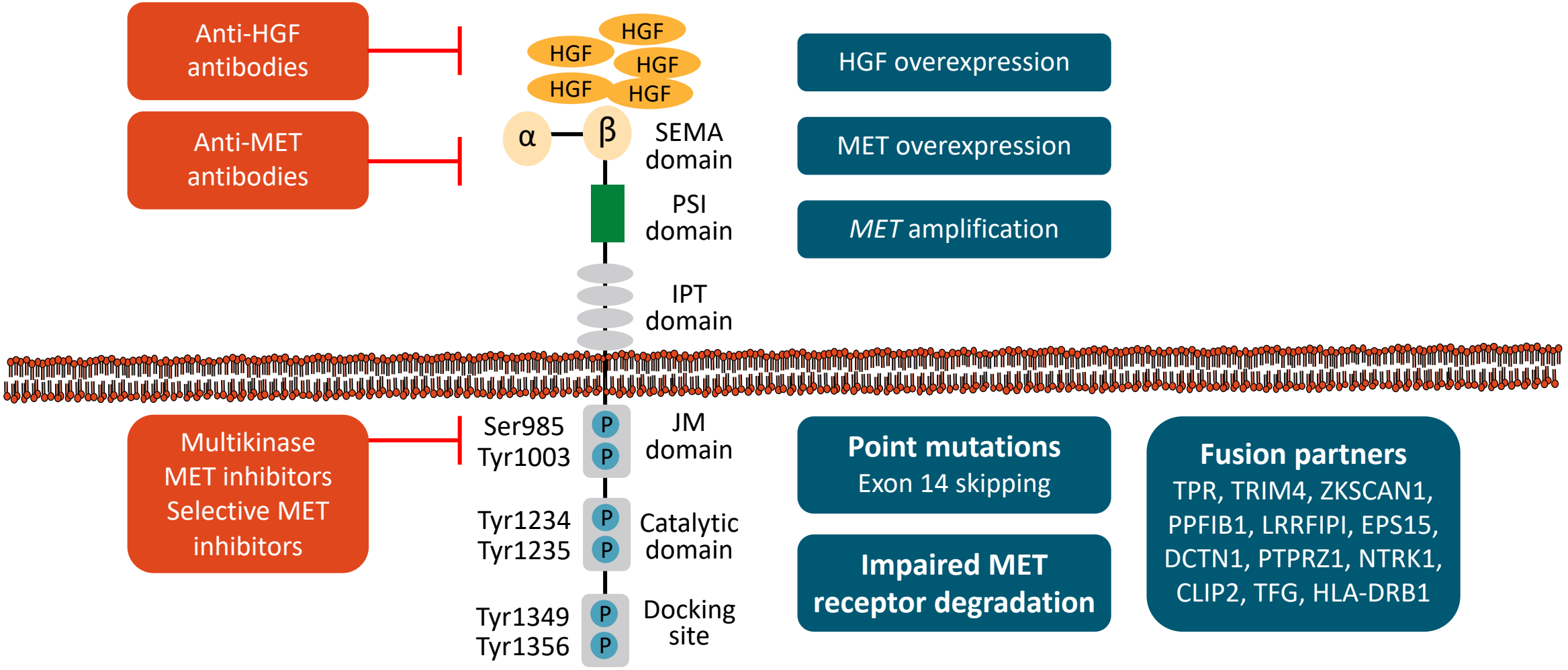
13 Maintained T790M
9 C797S
2 *PIK3CA* mutation

28 Lost T790M
6 SCLC transformation
4 *MET* amplification — 10%
2 *BRAF* mutation
2 *PIK3CA* mutation
1 *KRAS* Q61K
1 *CCDC6-RET* fusion
1 *FGFR3-TACC3* fusion
1 *ESYT2-BRAF* fusion

Patient flowchart of multi-institutional cohort (N = 143) with acquired resistance to osimertinib[3]

1. Camidge. Nat Rev Clin Oncol. 2014;11:473. 2. Le. Clin Cancer Res. 2018;24:6195. 3. Oxnard. JAMA Oncol. 2018;4:1.

MET Alterations Targetable Through 3 Approaches: Selective TKIs Appear to Be the Most Effective



Liang. Onco Targets Ther. 2020;13:2491.

MET TKIs: Types

- Type I: ATP competitors that bind to the ATP-binding pocket of the active form (DFG-in)
  - Type Ia: more interaction with G1163
    - Crizotinib
  - Type Ib: more interaction with Y1230 (more specific)
    - Capmatinib, tepotinib, and savolitinib
- Type II: ATP competitors that bind to the inactive state (DFG-out)
  - Cabozantinib, merestinib, and glesatinib
- Type III: allosteric inhibition
  - Tivantinib

Rehman. EMJ. 2018;4:100. Reungwetwattana. Lung Cancer. 2017;103:27.
Huang. Curr Treat Options Oncol. 2020;21:33. Kufareva. J Med Chem. 2008;51:7921.

MET TK Inhibitors – Activity According to *MET* Mutations

Mutations		Type Ia	Type Ib			Type II		
		Crizotinib	Capmatinib	Tepotinib	Savolitinib	Cabozantinib	Merestinib	Glesatinib
Exon 14 skipping (parental)		22	0.6	3.0	2.1	7.8	8.1	21
1090	G1090A	176	7.3	145	69	0.3	0.8	1.7
	G1090S	41	3.0	42	24	0.7	1.3	6.7
1092	V1092I	292	2.8	2.6	2.9	16	13	5.7
	V1092L	223	2.5	2.3	13	1.8	10	6.5
1133	D1133V	30	0.9	2.6	7.3	88	29	62
1155	V1155M	89	3.4	23	16	17	5.6	22
1159	Y1159H	181	0.9	22	8.1	107	28	46
1163	G1163E	91	0.9	10	3.3	49	9.3	89
	G1163R	> 1000	2.5	70	8.5	62	14	66
1164	D1164G	213	7.2	74	28	25	9.7	24
1195	L1195F	23	0.3	2.6	1.8	> 1000	83	90
	L1195V	235	8.1	55	22	118	44	236
1200	F1200I	199	6.1	45	30	694	212	275
	F1200L	23	0.8	8.0	7.7	229	109	111
1211	M1211T	26	2.8	24	11	22	7.5	18

Mutations		Type Ia	Type Ib			Type II		
		Crizotinib	Capmatinib	Tepotinib	Savolitinib	Cabozantinib	Merestinib	Glesatinib
1228	D1228A	> 1000	> 1000	> 1000	> 1000	200	89	216
	D1228E	690	137	> 1000	573	37	19	30
	D1228G	319	697	> 1000	431	72	23	46
	D1228H	665	> 1000	> 1000	> 1000	79	25	38
	D1228N	> 1000	> 1000	> 1000	> 1000	36	26	22
	D1228Y	> 1000	477	> 1000	> 1000	539	149	74
1230	Y1230C	645	> 1000	> 1000	> 1000	8.4	7.4	12
	Y1230D	698	> 1000	> 1000	> 1000	16	5.5	11
	Y1230S	811	> 1000	> 1000	> 1000	23	12	14
	Y1230H	216	401	> 1000	> 1000	20	8.2	19
	Y1230N	> 1000	> 1000	> 1000	> 1000	19	4.1	14

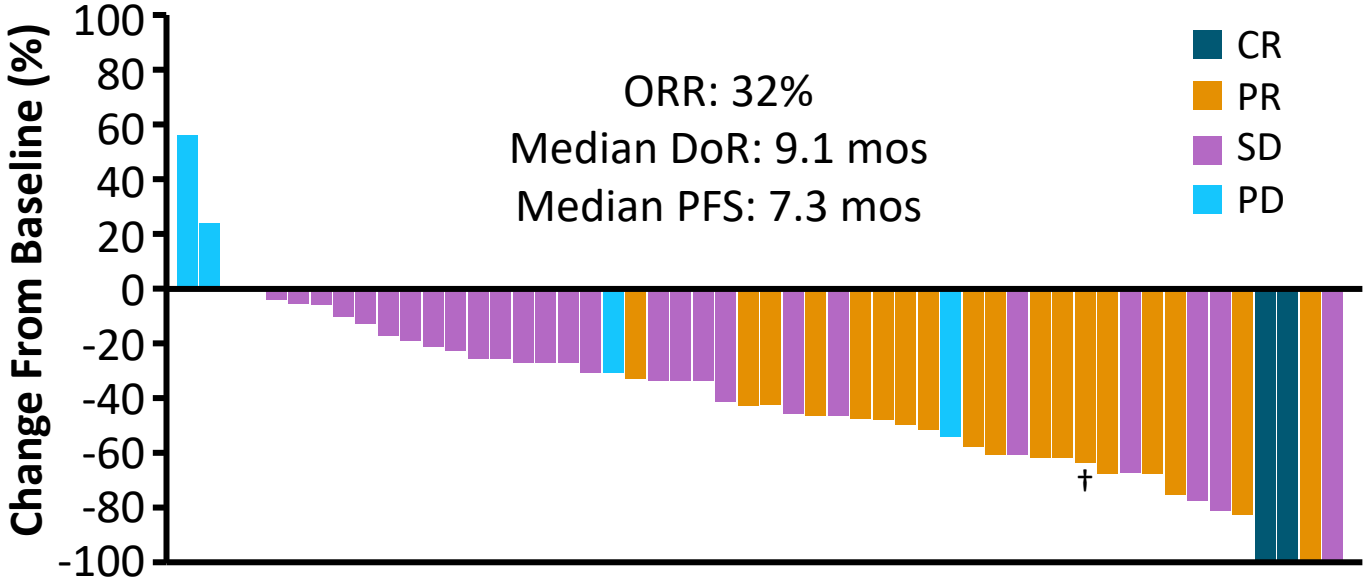
$IC_{50} \leq 50$ nM | $50 < IC_{50} < 200$ nM | $IC_{50} \geq 200$ nM

Fujino. J Thorac Oncol. 2019;14:1753.

PROFILE 1001: Crizotinib in *MET* Exon 14–Altered NSCLC

- Crizotinib: multikinase TKI approved for treatment of *ALK*+ and *ROS*+ NSCLC
- Open-label, multicohort phase I study evaluating efficacy, safety of crizotinib in NSCLC, including a *MET*ex14 expansion cohort (n = 69)
- MET inhibition with crizotinib a viable off-label option for patients with *MET* exon 14–altered NSCLC but has limited CNS penetration

Best % Change in Target Lesion Size from Baseline (n = 52*)



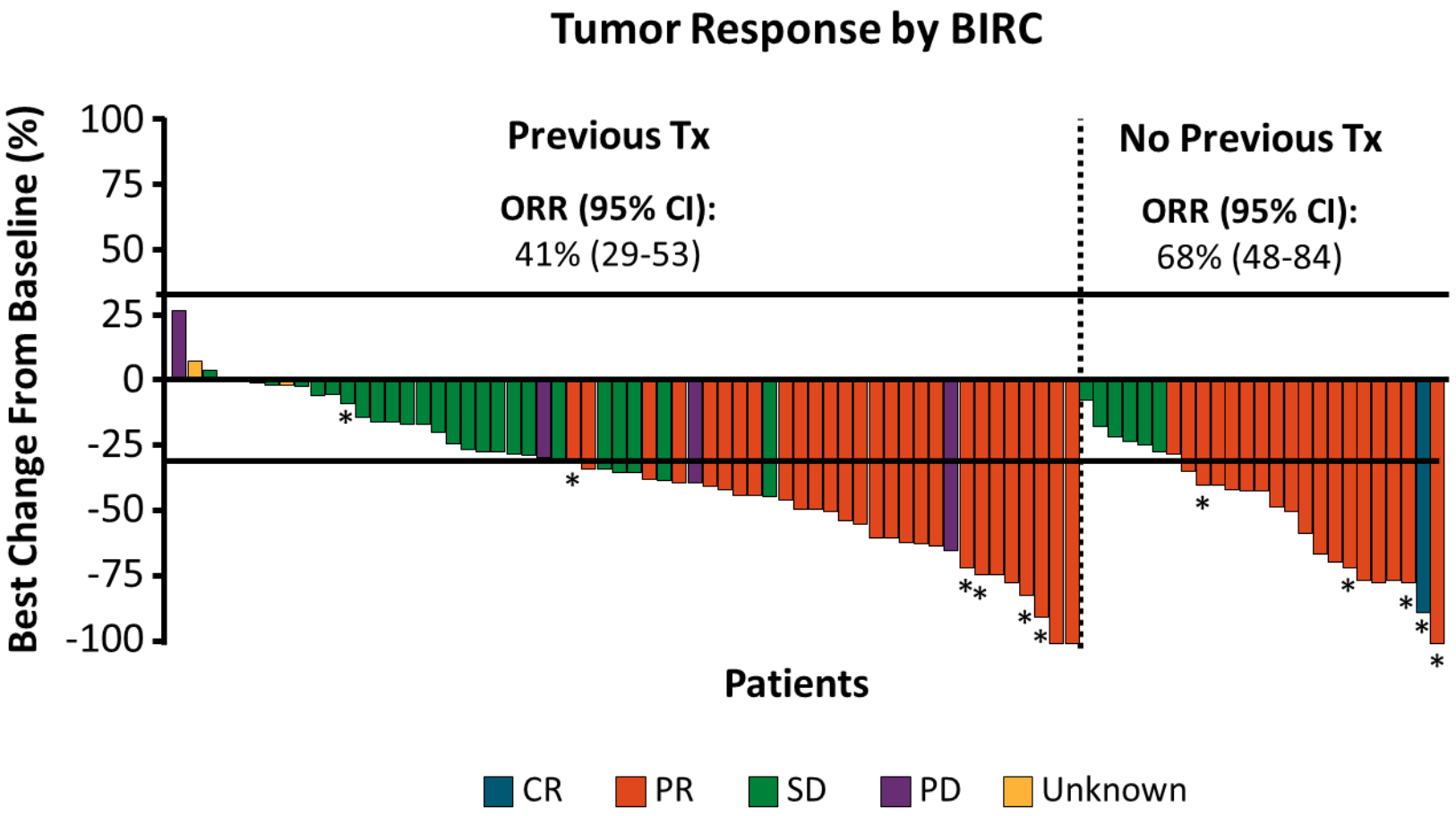
*Of 65 response-evaluable patients, 13 excluded from waterfall plot.
†*MET*ex14 alteration by local testing; *ROS1*+, WT *MET* by central testing.

MET TKI Potency Comparison

	Crizotinib	Cabozantinib	Savolitinib	Tepotinib	Capmatinib
IC_{50}, nM	22.5	7.8	2.1	~1.7-3.0	0.6

Drilon. Nat Med. 2020;26:47. Paik. ASCO 2019. Abstr 9005. Wolf. ASCO 2019. Abstr 9004.

Phase II GEOMETRY mono-1: Efficacy With Capmatinib in *MET*ex14 Mutation–Positive NSCLC

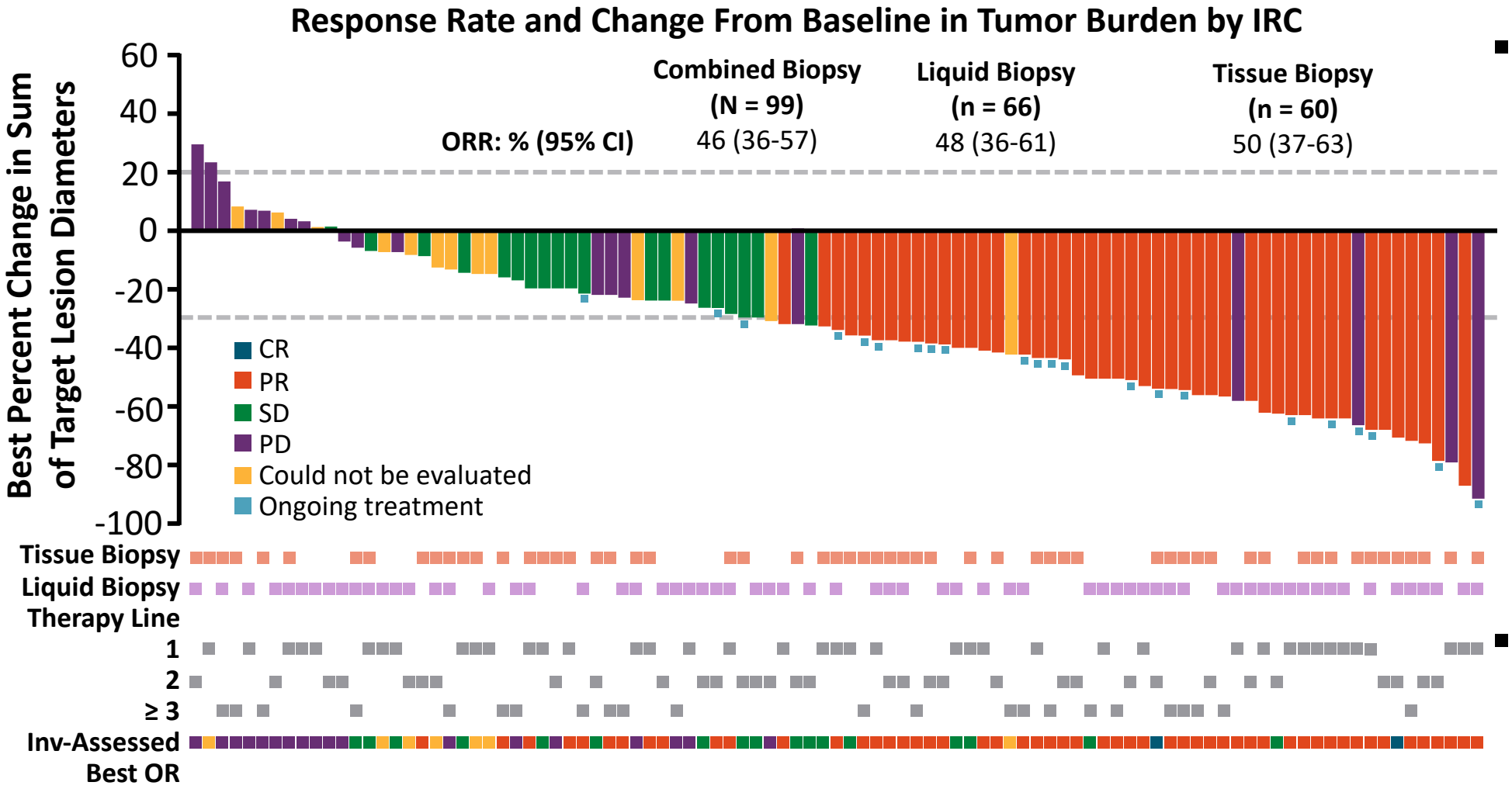


- Durability of response by BICR
  - DoR
    - 1L: 12.6 mos
    - 2L/3L: 9.7 mos
  - PFS
    - 1L: 12.4 mos
    - 2L/3L: 5.4 mos
- 54% (7/13) with intracranial response

*Patients still on treatment.

Wolf. NEJM. 2020;383:944.

Phase II VISION: Efficacy With Tepotinib in *MET*ex14 Mutation–Positive NSCLC



- Durability of response by BIRC
  - DoR: 11.1 mos
    - L: 9.9 mos
    - T: 15.7 mos
  - PFS: 8.5 mos
    - L: 8.5 mos
    - T: 11.0 mos
- Patients with CNS mets also achieved benefit from tx

Median follow-up in efficacy population: 17.4 mos.

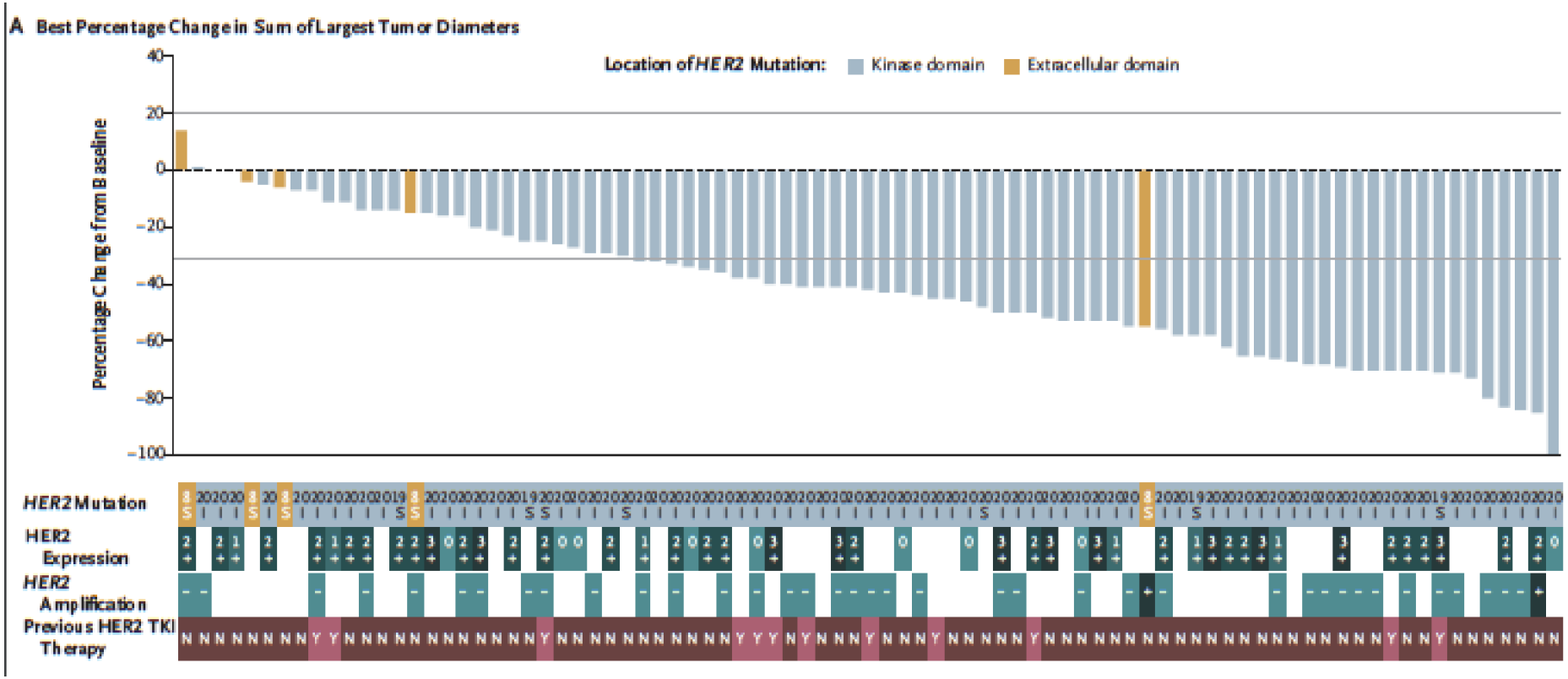
Paik. NEJM. 2020;383:931.

MET Exon 14 Skipping Mutation–Positive NSCLC: Summary

- Crizotinib has activity in *MET*ex14-positive NSCLC but poor CNS penetration
- Next-generation *MET* inhibitors (capmatinib and tepotinib) are also active in *MET*ex14-positive NSCLC but with improved activity in the CNS
- On May 6, 2020, capmatinib was approved by the FDA for treatment of *MET*ex14-positive NSCLC, becoming the optimal first-line therapy in this setting
  - Tepotinib is under priority review by the FDA

HER2 Mutation–Positive NSCLC

Trastuzumab Deruxtecan (T-DXd) in HER2-mutant NSCLC



	Outcome (95% CI) N=91
ORR	55% (44-65)
mDOR	9.3 mos (5.7-14.7)
mPFS	8.2 mos (6.0-11.9)
mOS	17.8 mos (13.8-22.1)

Li BT, NEJM 2022

Trastuzumab Deruxtecan (T-DXd) in HER2-mutant NSCLC

DESTINY-Lung01: Single arm, phase 2 study of T-DXd 6.4mg/kg IV q21 days

Table 3. Most Common Investigator-Reported Drug-Related Adverse Events in the Study Population (91 Patients).

Event	Grade 1–2	Grade 3	Grade 4	Grade 5	Overall
	number of patients (percent)				
Drug-related adverse event	46 (51)	37 (41)	4 (4)	1 (1)*	88 (97)
Drug-related adverse events with ≥20% incidence					
Nausea	58 (64)	8 (9)	0	0	66 (73)
Fatigue†	42 (46)	6 (7)	0	0	48 (53)
Alopecia	42 (46)	0	0	0	42 (46)
Vomiting	33 (36)	3 (3)	0	0	36 (40)
Neutropenia‡	15 (16)	14 (15)	3 (3)	0	32 (35)
Anemia§	21 (23)	9 (10)	0	0	30 (33)
Diarrhea	26 (29)	2 (2)	1 (1)	0	29 (32)
Decreased appetite	27 (30)	0	0	0	27 (30)
Leukopenia¶	17 (19)	4 (4)	0	0	21 (23)
Constipation	20 (22)	0	0	0	20 (22)

Pneumonitis (ILD)

- **Adjudicated drug-related ILD occurred in 24/91 patients (26%)**
  - Grade 1- 3 patients
  - Grade 2- 15 patients
  - Grade 3 – 4 patients
  - Grade 5- 2 patients
- Median duration of onset of ILD – 141 days (range, 14-462)
- 21 patients required corticosteroids

August 11, 2022: US FDA approved T-DXd (5.4mg/kg) for HER-mutant NSCLC after one prior line of therapy

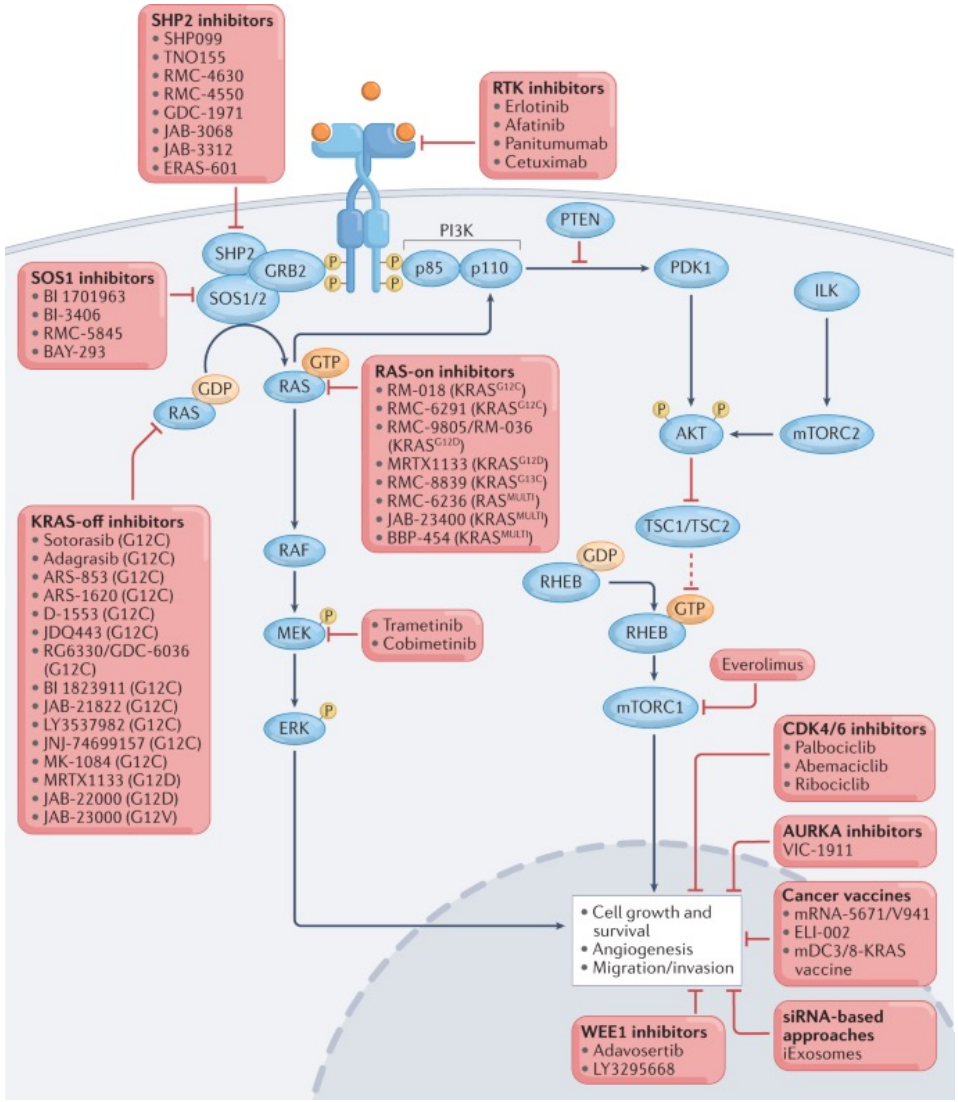
Li BT, NEJM 2022

KRAS G12C Mutation–Positive NSCLC

KRAS Signaling Cascade

KRAS proteins are small GTPases that cycle between GTP-On and GDP-Off state

When KRAS is activated, it transduces the extracellular signal into the intracellular one by switching on downstream signaling pathways such as RAF/ MEK/ERK, PI3K/AKT/mTOR which are important in cell growth, differentiation and survival



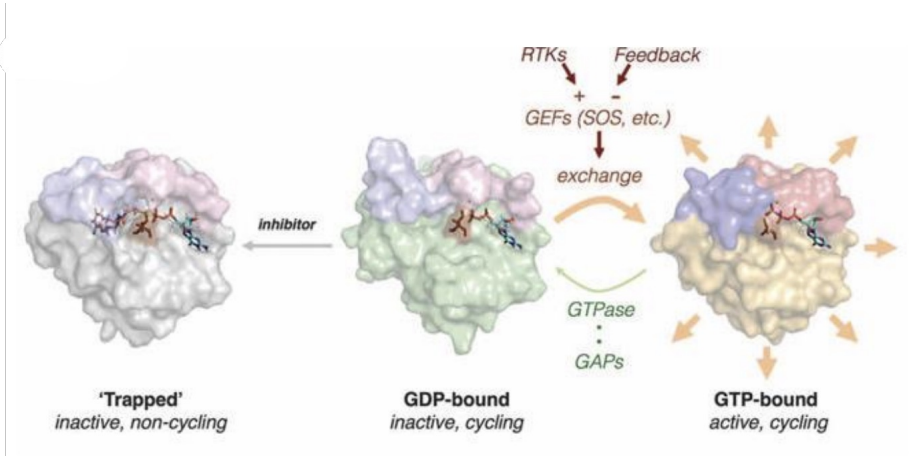
Nature Reviews Clinical Oncology **volume 19**, pages637–655 (2022)

Mechanism of action of KRAS G12C inhibitors

Difficulties in developing direct inhibitors

- Smooth surface with limited binding sites for compounds
- KRAS has high affinity for GTP
- High intracellular concentration of GTP presents challenges in creating direct inhibitors of GPT binding

Downstream targeting had limited efficacy due to the existence of several feedback loops and interactions with other pathways



Development of KRAS G12C inhibitors became possible after crystallographic studies discovered a new pocket beneath the effector binding switch-II region. Cysteine thiols are nucleophilic allowing compounds to bind. KRAS G12C inhibitors inhibit RAS activity by blocking SOS-mediated nucleotide exchange and altering the affinity of KRAS for GDP versus GTP nucleotide

Lito P et al. Science. 2016;351(6273):604-608

Second line. Adagrasib and Sotorasib

	Adagrasib[1, 2]	Sotorasib[3,4]
N efficacy (safety)	112 (116)	172 (174)**
ORR (95% CI)	43 (34.5-52.6)	41 (33.3-48.4)**
mDOR months (95% CI)	8.5 (6.2 to 13.8),	12.3 (7.1-15)**
mPFS months	6.5 (4.7 to 8.4)	6.3 (*5.3 to 8.2)***
mOS months	12.6(9.2 to 19.2)	12.5 (10- 17.8)**
Median follow up, months	15.6	24.9**
icORR (prospective untreated brian mets cohort)	6/19 32%	NR
icDOR*	NR (4.1-NE)	NR
icPFS*	4.2 (3.8-NE)	NR
Approval	FDA	FDA, EU, Canada

1 Janne PA et al NEJM 2022, 2 Sabari et al ASCO 2022 3, Skoulidis et al NEJM 2021 4 Dy et al AACR 2022

Safety Profile

	Adagrasib[1]	Sotorasib[2]
Toxicities (all grades) Regardless of attribution	Diarrhea 71% Nausea 70% Fatigue 60% Vomiting 57% Anemia 36% Dyspnea 35%	Diarrhea 51% Nausea 31% Fatigue 25%
Discontinuation Rate	6.9%	7.1%
Dose reduction	52%	Dose modification (reduction, interruption, modification) 22%
Dose interruptions	71%	

1 Janne PA et al NEJM 2022, 2 Sabari et al ASCO 2022 3, Skoulidis et al NEJM 2021 4 Dy et al AACR 2022

Conclusions

- Because of highly effective targeted therapies (and lack of efficacy with immunotherapy), testing for *EGFR/ALK/ROS1/BRAF/NTRK/MET*ex14*/RET* at diagnosis is mandatory for all patients with nonsquamous NSCLC
- Broad testing with NGS for both required and emerging biomarkers is highly recommended
- Testing rates are far from ideal; collaboration between medical oncology and pathology to design best testing strategy for patients is encouraged