# ALK & ROS1: First-Line and Mechanisms of Resistance

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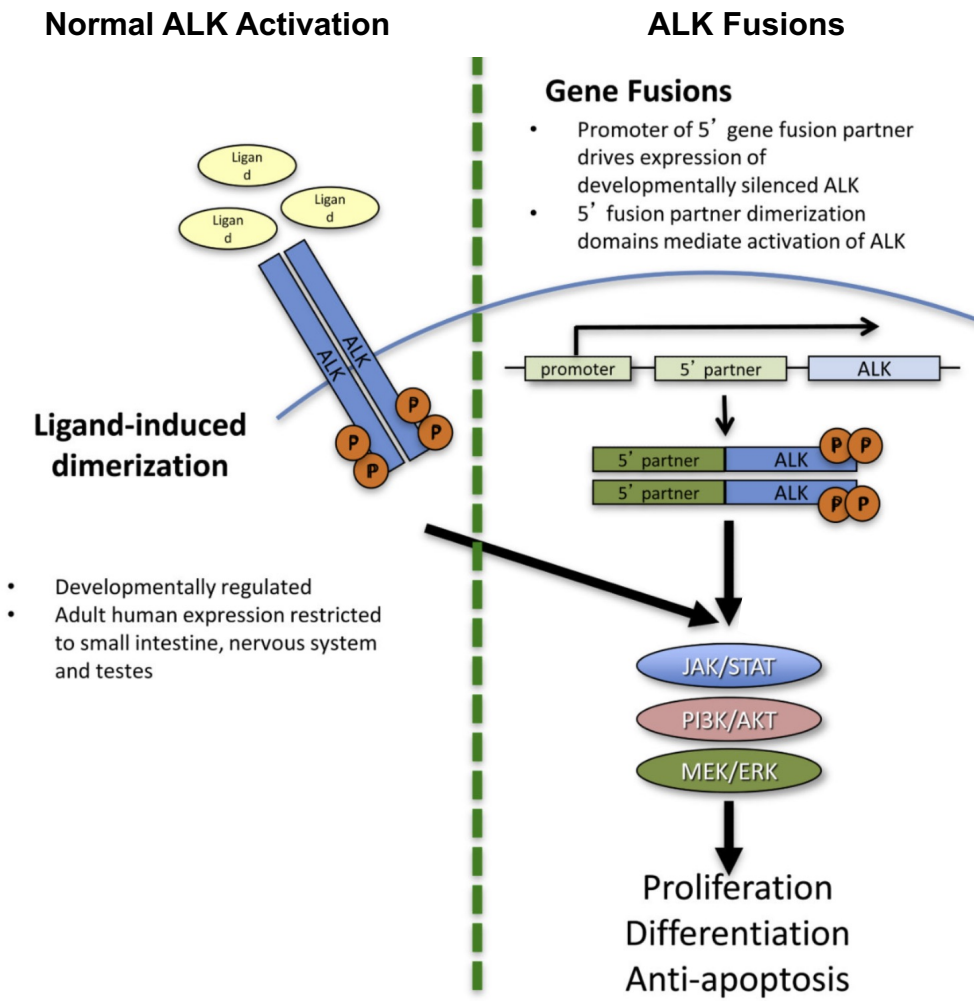
The Miami Cancer Meeting, April 2023

Dana-Farber
Cancer Institute

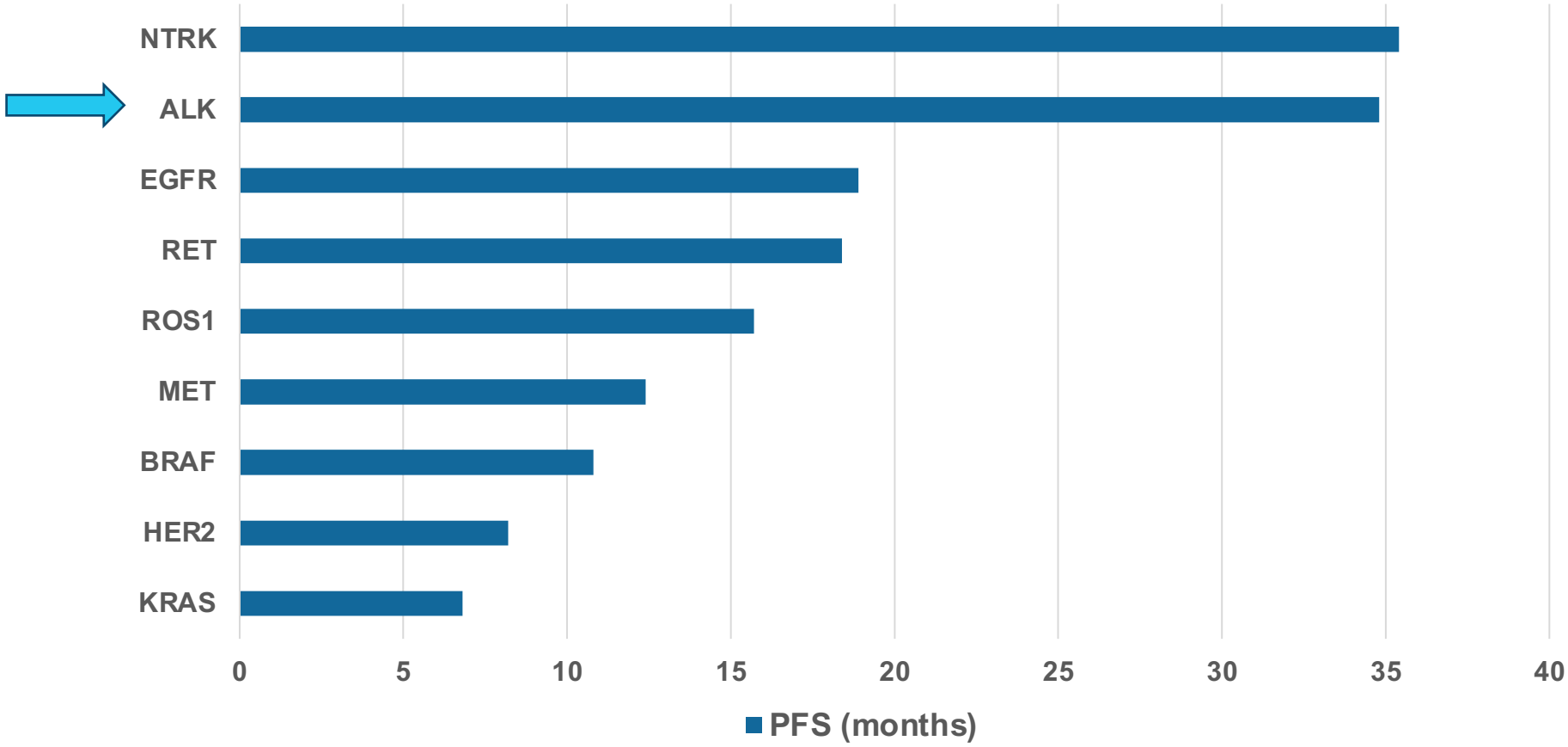
# ALK Fusion+ NSCLC




- 4% of lung adenocarcinomas will be ALK fusion positive
- Majority are the EML4-ALK fusion
- Associated with absent history of tobacco use
- Percent ALK+ increases to nearly 20% in patients <40 years old at diagnosis

*Camidge and Doebele. Nature Reviews Clinical Oncology. 2012; 9(268); Sacher et al. JAMA Oncology. 2016;2(3):313-320*

# Median PFS is variable for actionable targets




**Median OS for ALK+ NSCLC is now > 5 years**

Soria et al 2018, Wolf et al 2021, Mok et al 2020, Drilon et al 2020, Drilon et al 2022, Planchard et al 2022, Drilon et al 2022, Li et al 2022, Skoulidis et al 2021

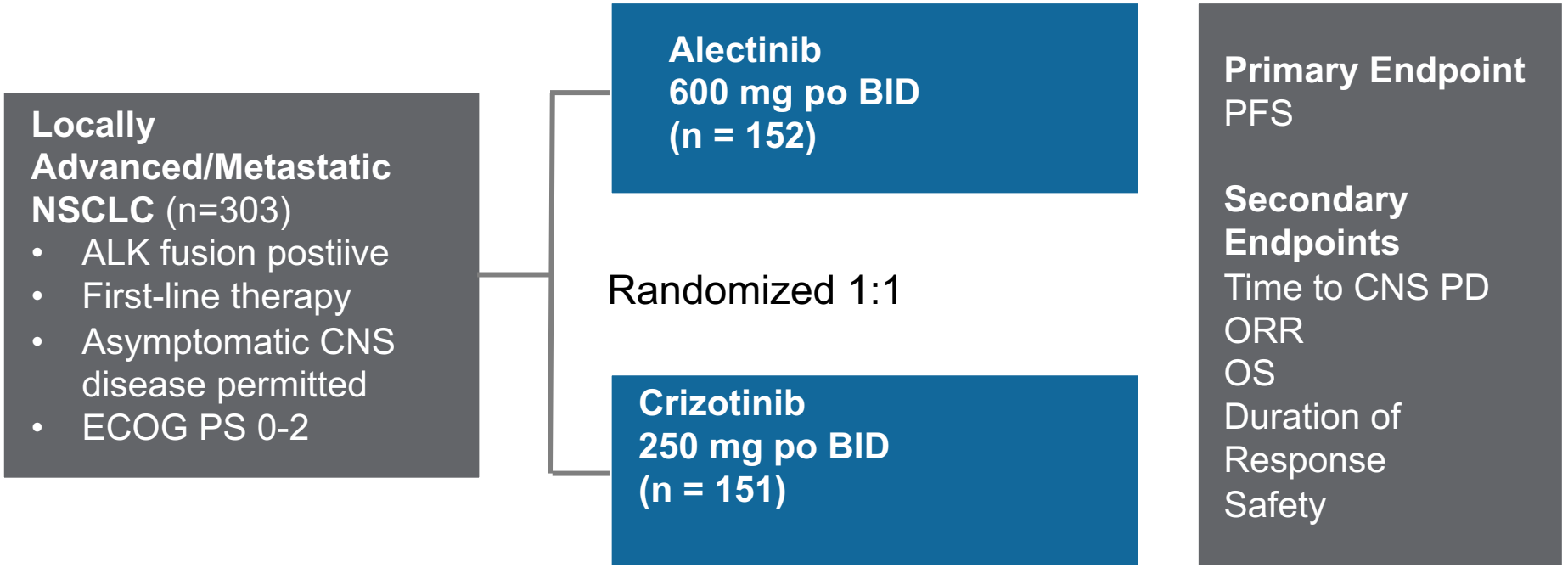
# First-line TKIs for ALK+ NSCLC

| Drug | Trial Name | Median PFS |
|---|---|---|
| ~~Crizotinib >> Chemotherapy 1L~~ | ~~PROFILE 1014~~ | ~~10.9 vs 7.0 mo~~ |
| ~~Ceritinib >> Chemotherapy 1L~~ | ~~ASCEND-4~~ | ~~16.6 vs 8.1 mo~~ |
| Alectinib >> Crizotinib 1L | ALEX | 34.8 vs 10.9 mo |
| ~~Brigatinib >> Crizotinib 1L~~ | ~~ALTA-1L~~ | ~~24.0 vs 11.1 mo~~ |
| Lorlatinib >> Crizotinib 1L | CROWN | 3 yr PFS 64% vs 19% |

Peters et al. NEJM. 2017;377(9):829-838; Solomon et al. Lancet Respiratory Medicine. 2023. 11(4):354-366; Soria et al Lancet 2017; Solomon et al. J Clin Oncol. 2018;36(22):2251-2258; Camidge et al. NEJM;379(21):2027-2039.

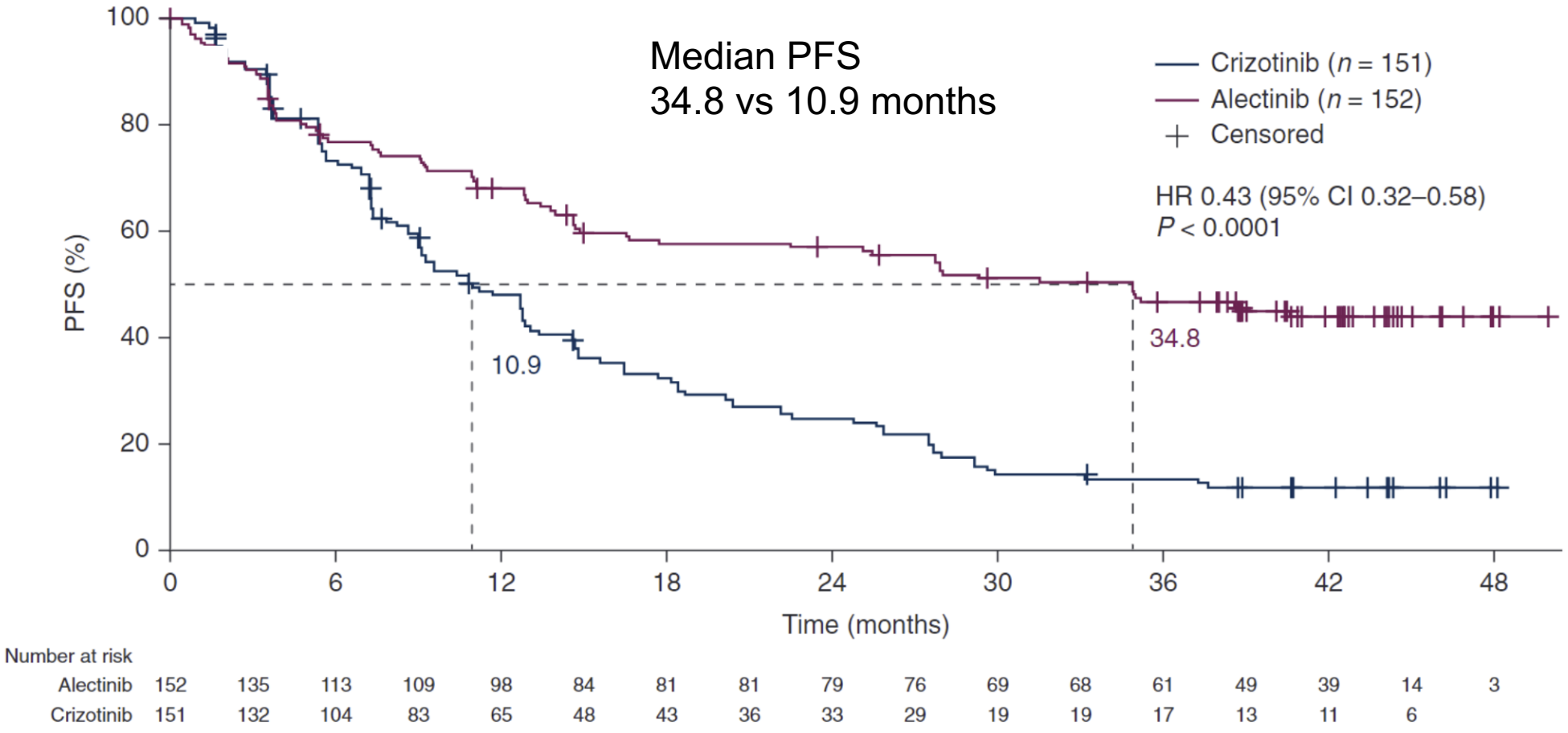
# Study Schema – ALEX

## A randomized, open-label, phase 3 study




Post-progression crossover not allowed on study
Local therapy to asymptomatic CNS progression allowed on study
CNS and systemic serially in all patients

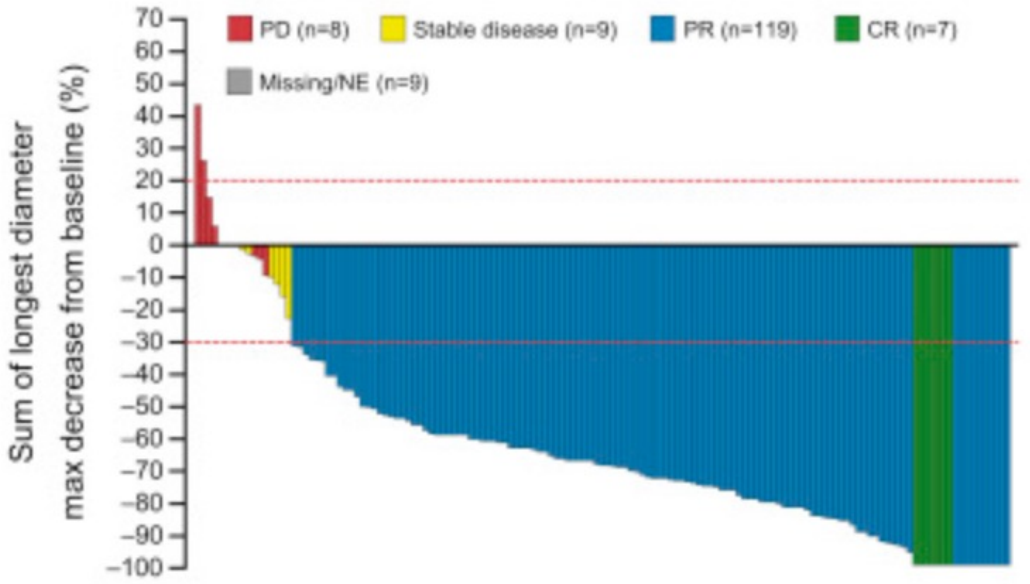
# ALEX Study
# Investigator Assessed PFS




*Mok et al. Annals of Oncology. 2020;31(8):1056*

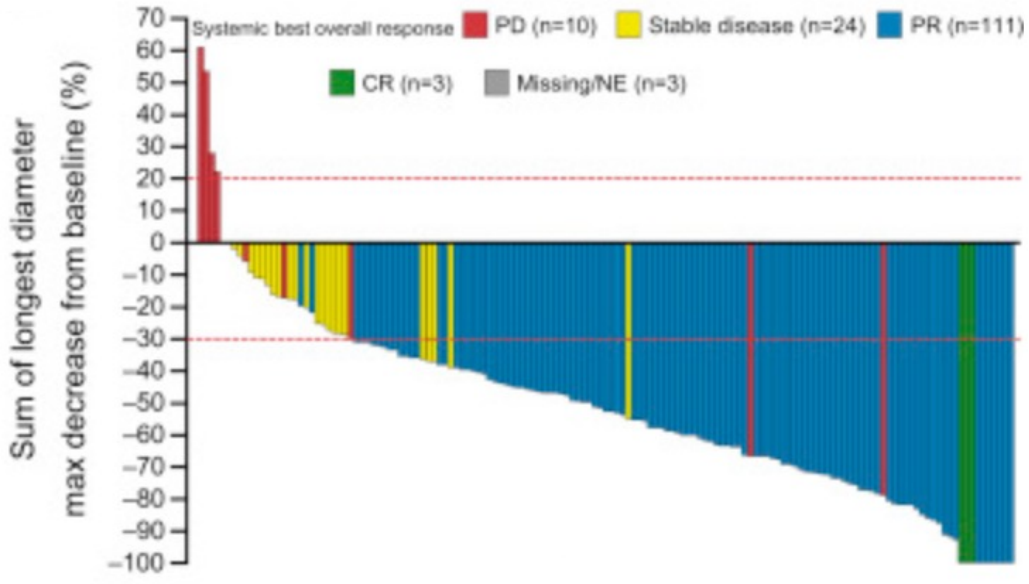
# ALEX Study – Best Response

**Alectinib**




ORR 82.9%
CR 4%
PR 79%

**Crizotinib**

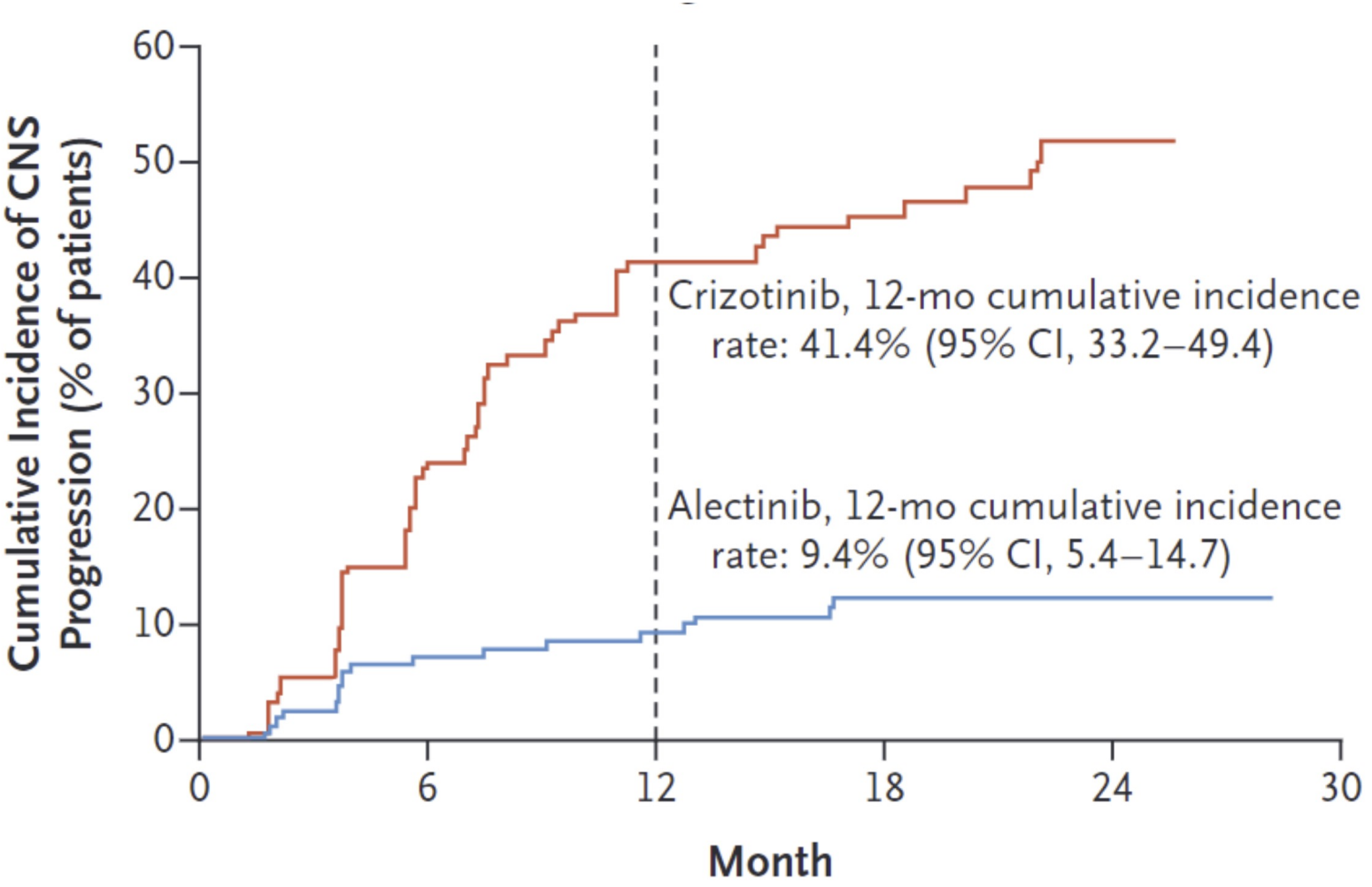



ORR 75.5%
CR 1%
PR 74%



*Peters et al 2017; Camidge et al. JTO. 2019*

# ALEX Study – CNS Activity

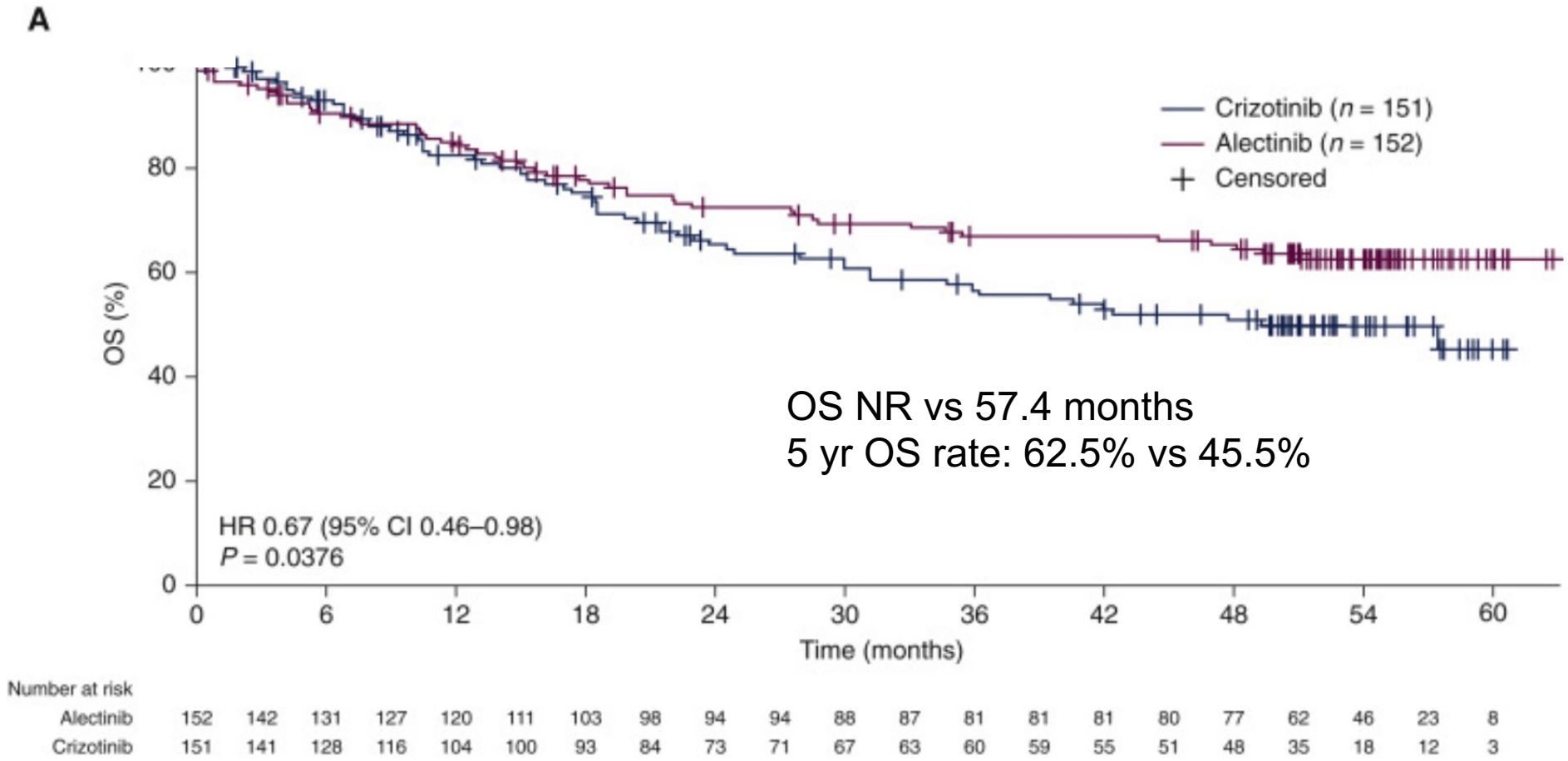



**Alectinib CNS ORR:** 78.6%
CNS CR rate: 20%

**Crizotinib CNS ORR:** 40%

Peters et al. NEJM. 2017.

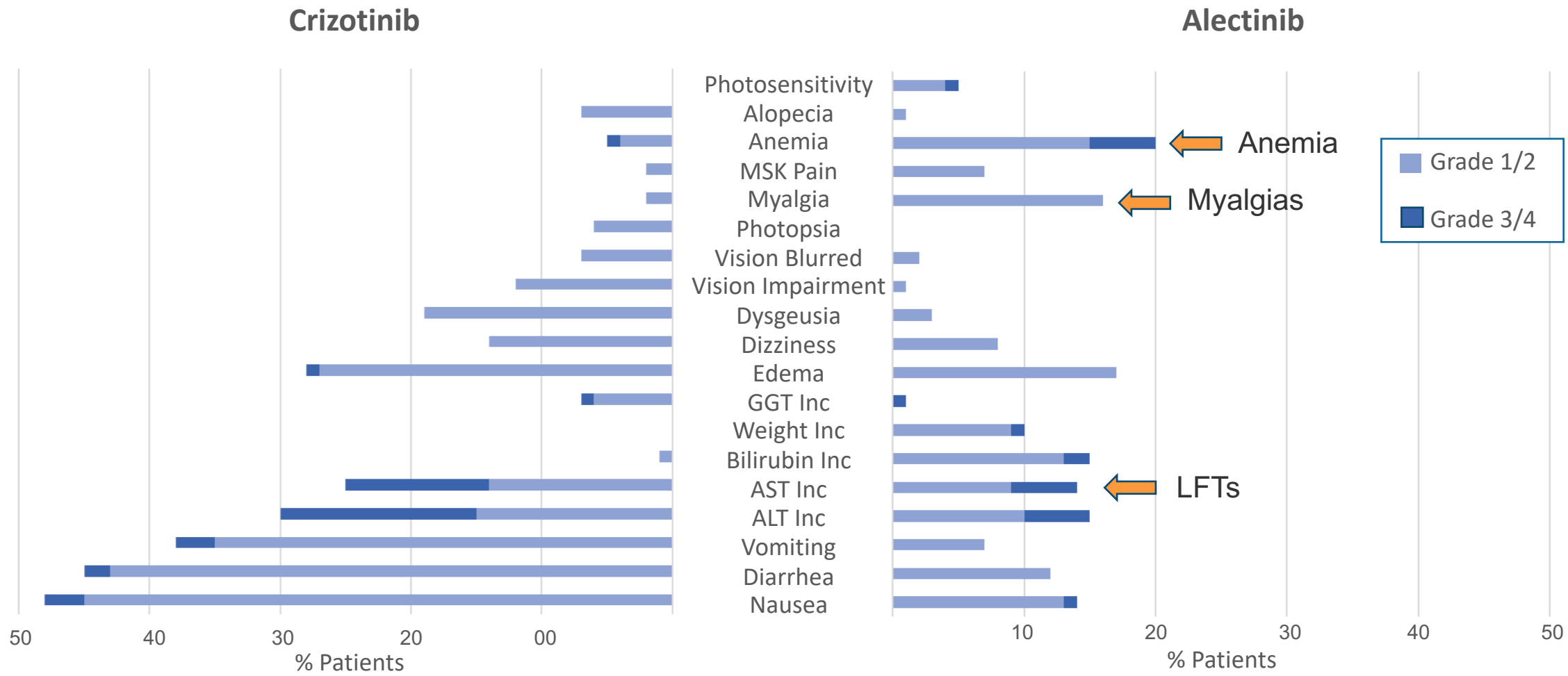
# ALEX: Overall Survival Analysis




OS NR vs 57.4 months
5 yr OS rate: 62.5% vs 45.5%

*Mok et al. Annals of Oncology. 2020;31(8):1056*

# ALEX Safety



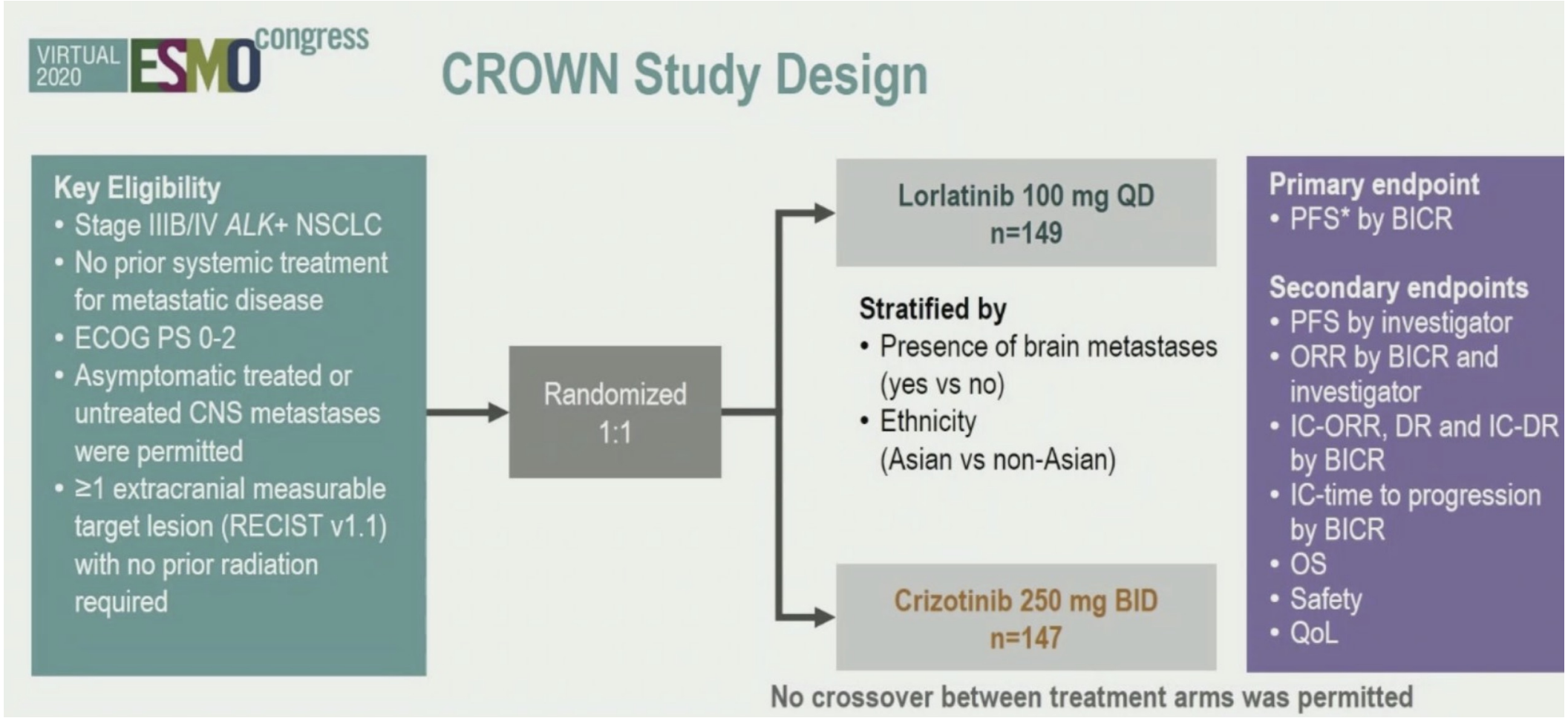

***13% d/c rate for adverse effects***
***21% dose reduction rate***

***11% d/c rate for adverse effects***
***16% dose reduction rate***



Peters et al. NEJM. 2017.

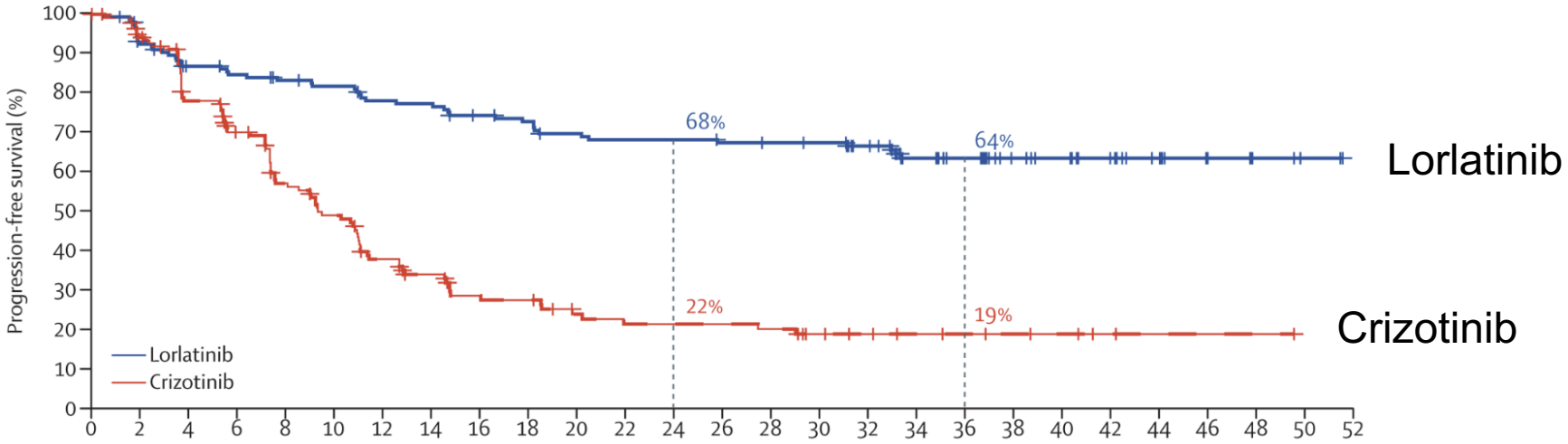
# CROWN Trial – 1L Lorlatinib vs Crizotinib




Presented by Benjamin Solomon. ESMO 2020. LBA2_PR

# CROWN: 1L Lorlatinib vs Crizotinib, Three-year Update

## Progression Free Survival




Lorlatinib

Crizotinib

| | 3 year PFS | vs Crizotinib |
|---|---|---|
| Alectinib (ALEX) | 46.5% | 13.5% |
| Lorlatinib (CROWN) | 64% | 19% |

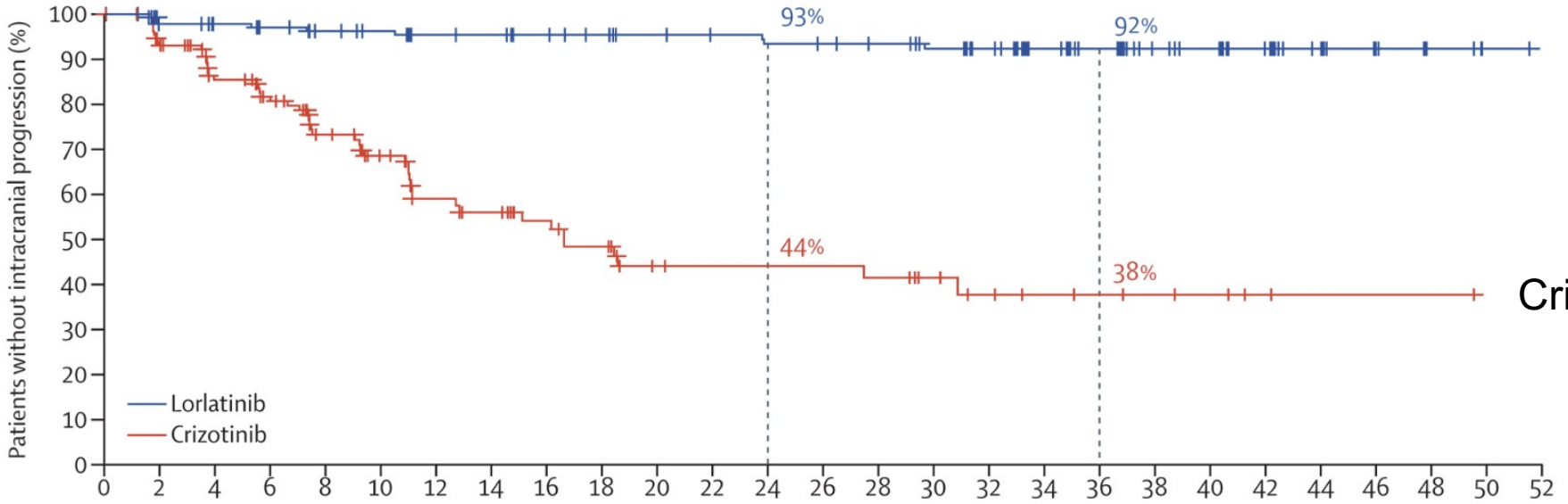
*Alectinib and Lorlatinib have not been compared in a study*



*Solomon et al. Lancet Resp Med. 2022; Mok et al. Ann Oncol. 2020.*

# CROWN: 1L Lorlatinib vs Crizotinib

## CNS Progression Free Survival




Lorlatinib

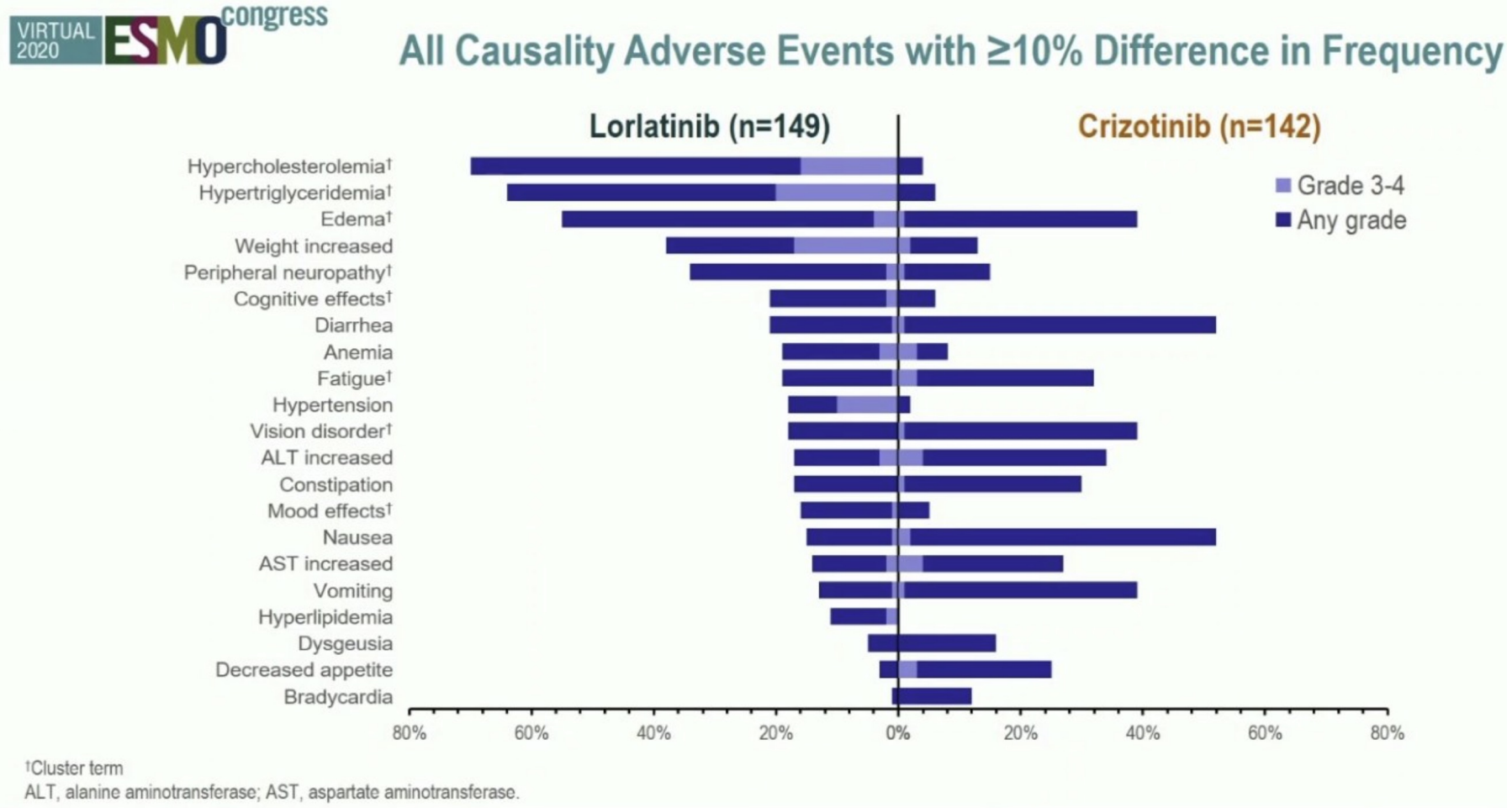
**71% CNS CR Rate**

Crizotinib

| Number at risk (number censored) | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lorlatinib | 149 | 131 | 127 | 122 | 117 | 114 | 109 | 108 | 105 | 102 | 98 | 96 | 94 | 93 | 90 | 86 | 75 | 62 | 54 | 39 | 34 | 25 | 17 | 8 | 4 | 1 | 0 |
| | (0) | (15) | (19) | (23) | (27) | (30) | (34) | (35) | (38) | (41) | (45) | (47) | (47) | (48) | (51) | (54) | (65) | (78) | (86) | (101) | (106) | (115) | (123) | (132) | (136) | (139) | (140) |
| Crizotinib | 147 | 118 | 97 | 83 | 65 | 54 | 39 | 35 | 29 | 25 | 18 | 17 | 17 | 17 | 16 | 12 | 9 | 7 | 6 | 5 | 4 | 2 | 1 | 1 | 1 | 0 | 0 |
| | (0) | (20) | (32) | (41) | (52) | (59) | (67) | (69) | (74) | (75) | (80) | (81) | (81) | (81) | (81) | (85) | (87) | (89) | (90) | (91) | (92) | (94) | (95) | (95) | (95) | (96) | .. |

*Solomon et al. Lancet Resp Med. 2022*

# Lorlatinib Adverse Effects

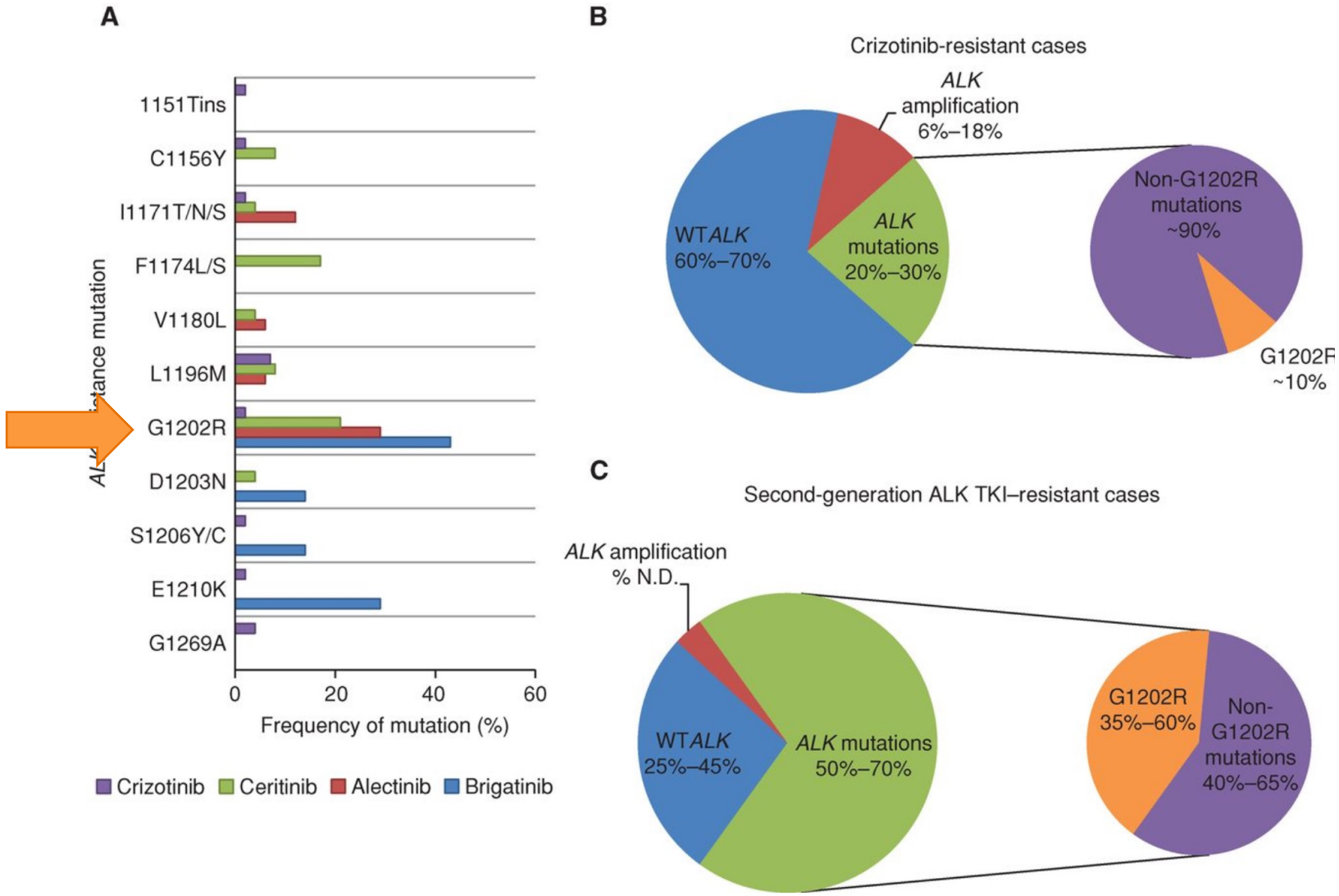



Discontinuation Rate 7%
Dose Reduction Rate 21%

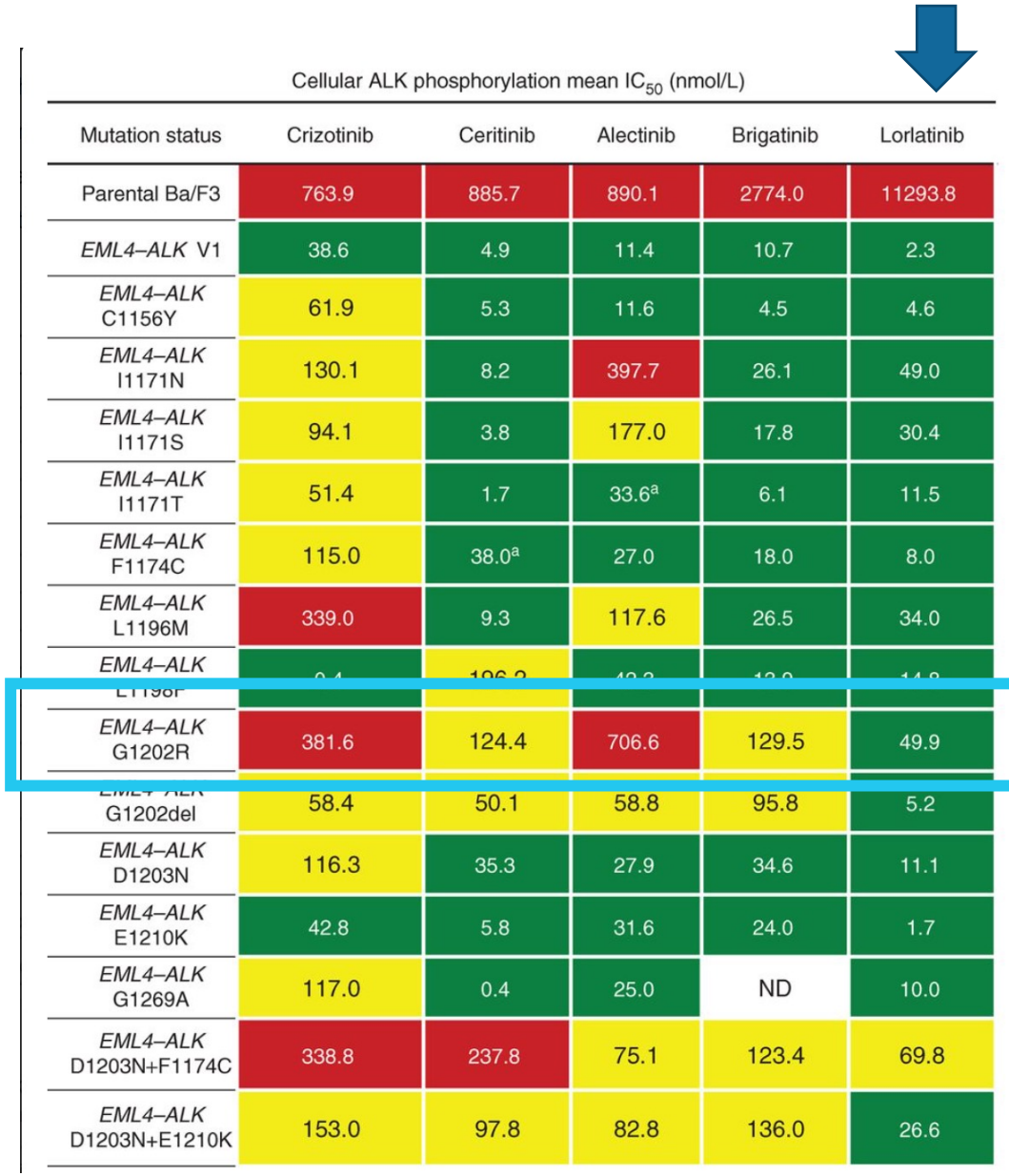
Discontinuation Rate 10%
Dose Reduction Rate 15%

*Solomon et al. ESMO 2020. LBA2*

# Resistance to 1st and 2nd Generation ALK TKIs




*Lin et al. Cancer Discov. 2017; 7(2):137*



Cellular ALK phosphorylation mean $IC_{50}$ (nmol/L)

| 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 | | | | | |
| *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 |

$IC_{50} \leq 50$ nmol/L

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

$IC_{50} \geq 200$ nmol/L

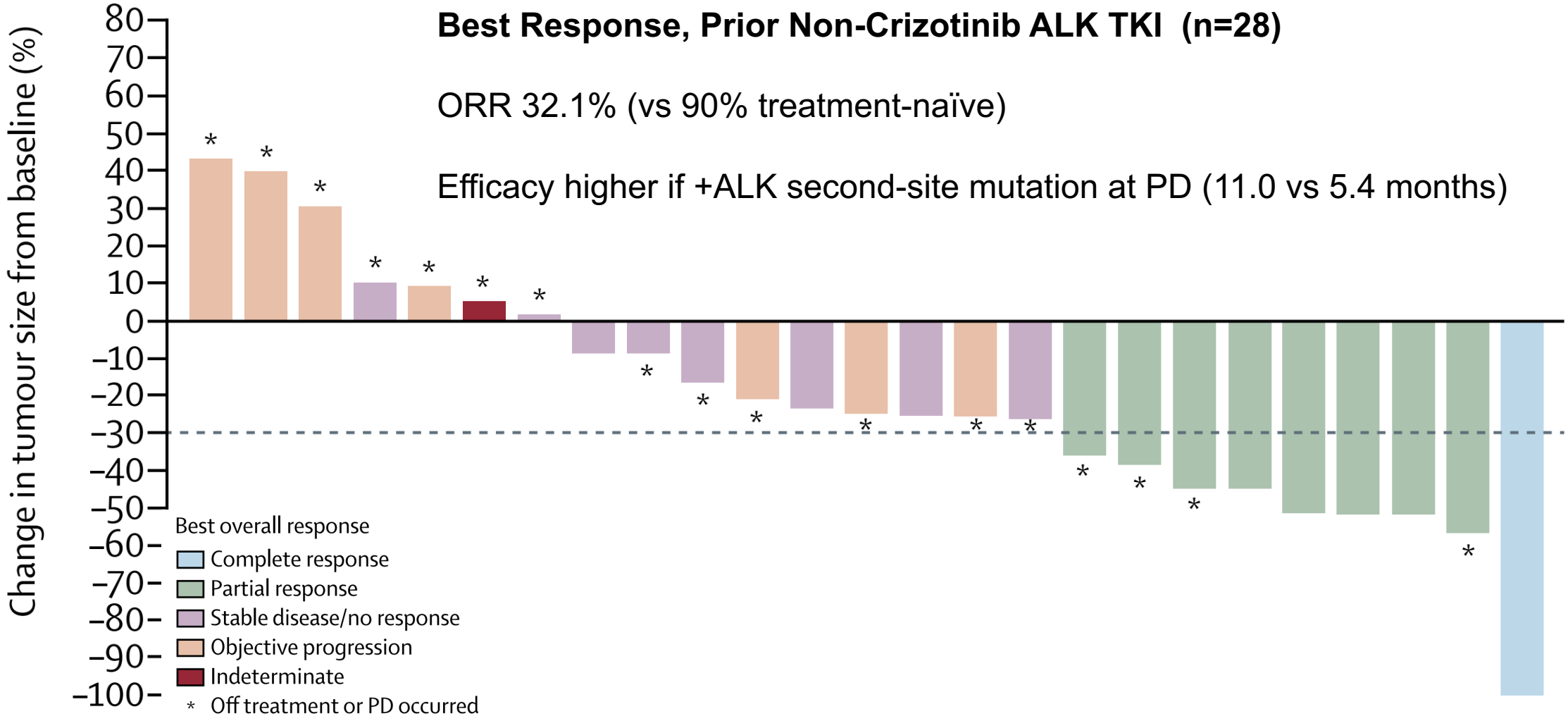
ALK G1202R Mutation

***The ALK inhibitors vary in their activity against acquired ALK mutations***

***The G1202R produces resistance to all approved ALK inhibitors except lorlatinib***

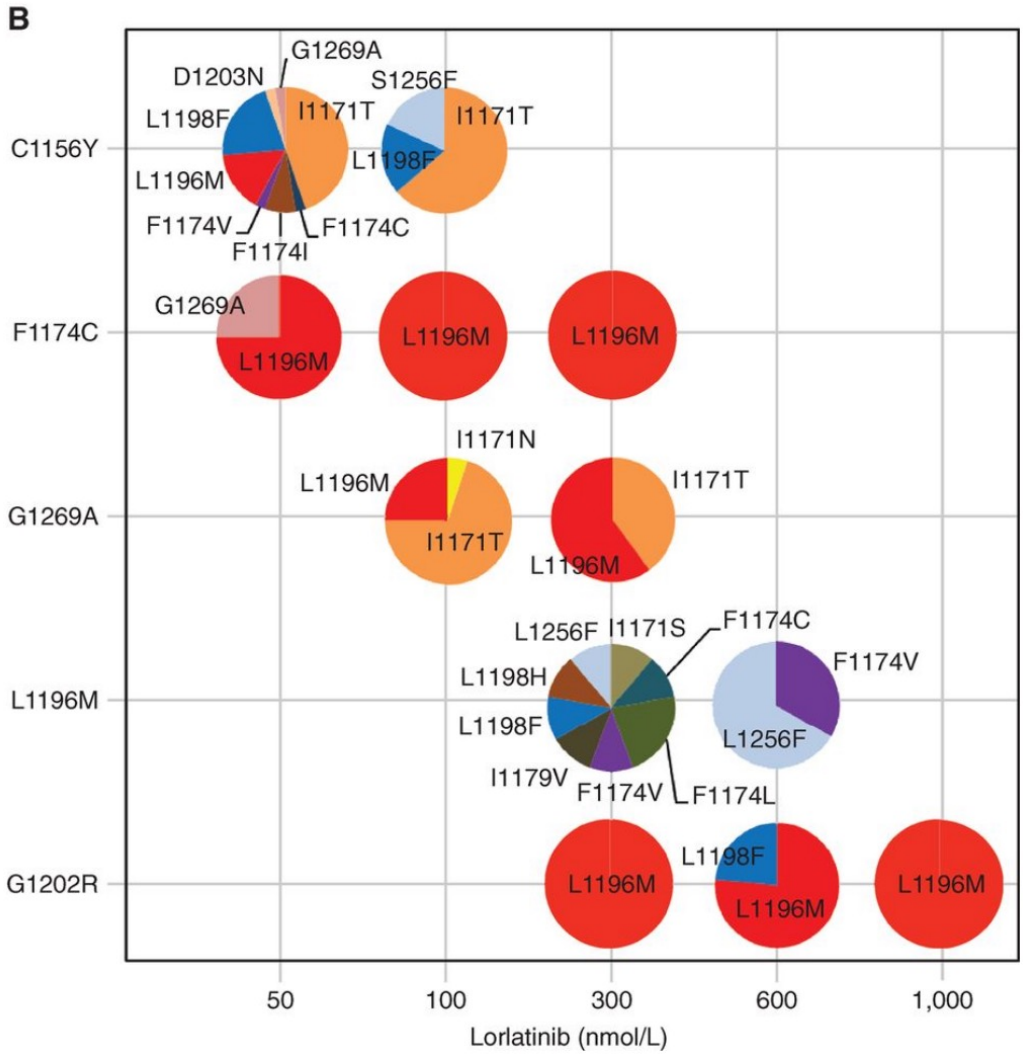
Gainor et al. Cancer Discovery. 2016

# Lorlatinib activity in the 2L+ Setting




*Solomon et al. Lancet Oncol. 2018; 19(120):1654; Shaw et al. J Clin Oncol. 2019; 37(16):1370.*

# Lorlatinib Resistance

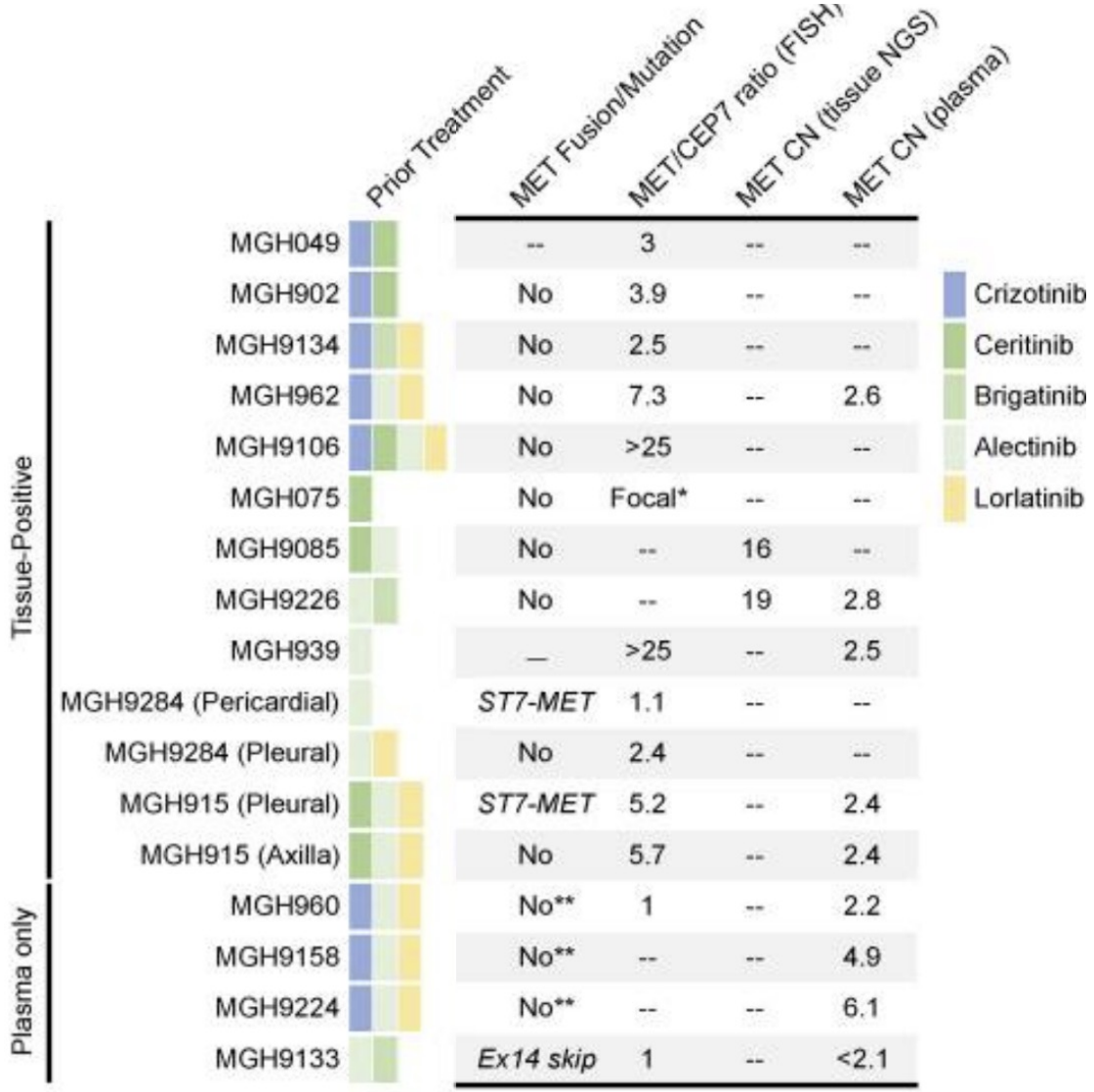



*C1156Y (crizotinib resistance as single mutation)+ L1198F (lorlatinib resistance) resensitizes to crizotinib*

*I1171N compound mutations → Sensitive to the FLT3 inhibitor Gilteritinib in preclinical studies*

*L1196M + G1202R → resistance to all approved ALK TKIs*

*Yoda et al. Cancer Discovery. 2018; 8(6):714-29, Mizuta et al. Nature Communications. 2021;12:1261, Shaw et al. NEJM. 2016;374(1):54-61, Okada et al. EBioMedicine. 2019;41:105-19*




# MET Amplification at ALK Inhibitor Resistance

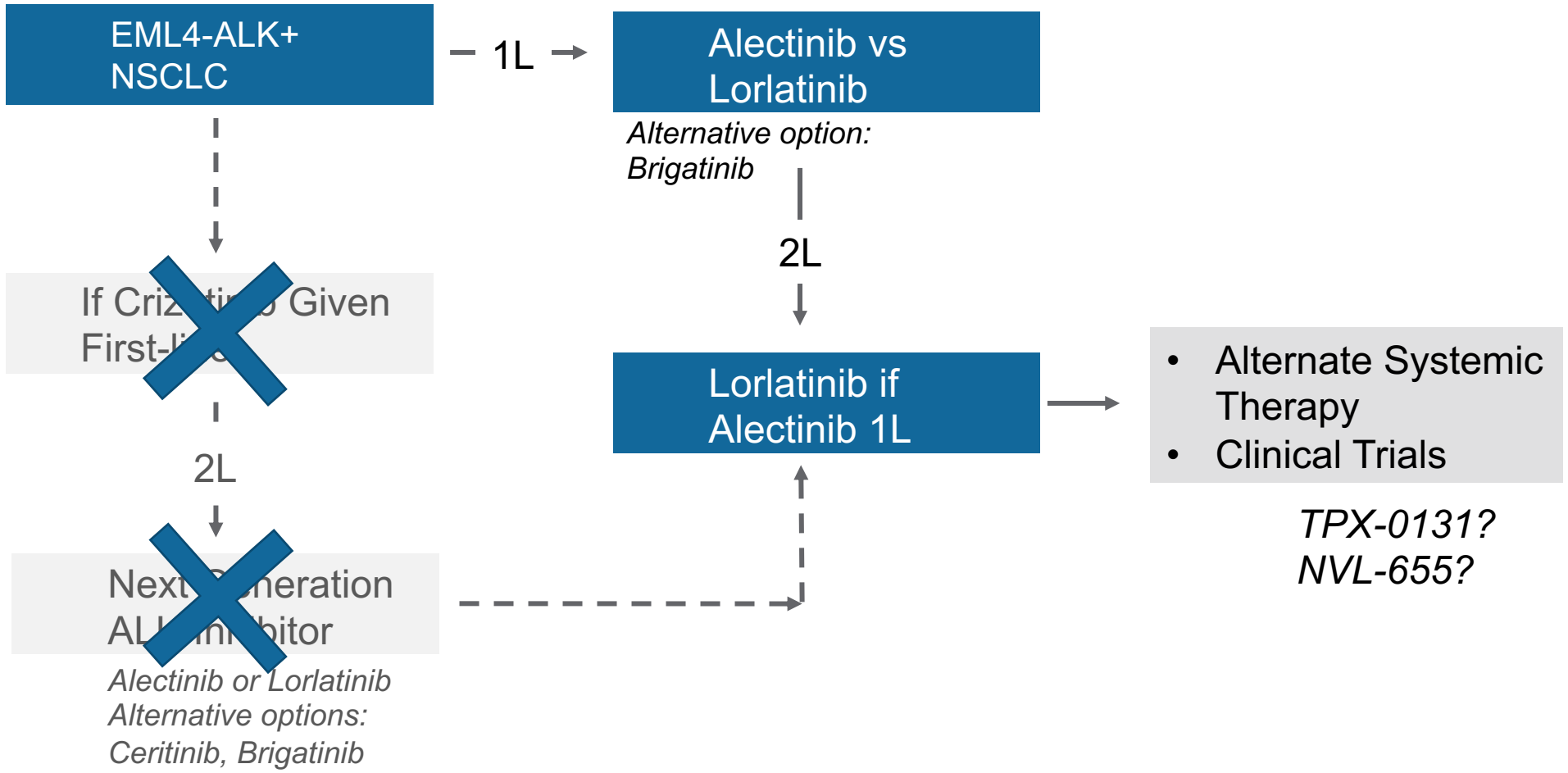
15% Rate of MET amplification

- 12% After 2nd Generation ALK Inhibitors
- 22% After lorlatinib

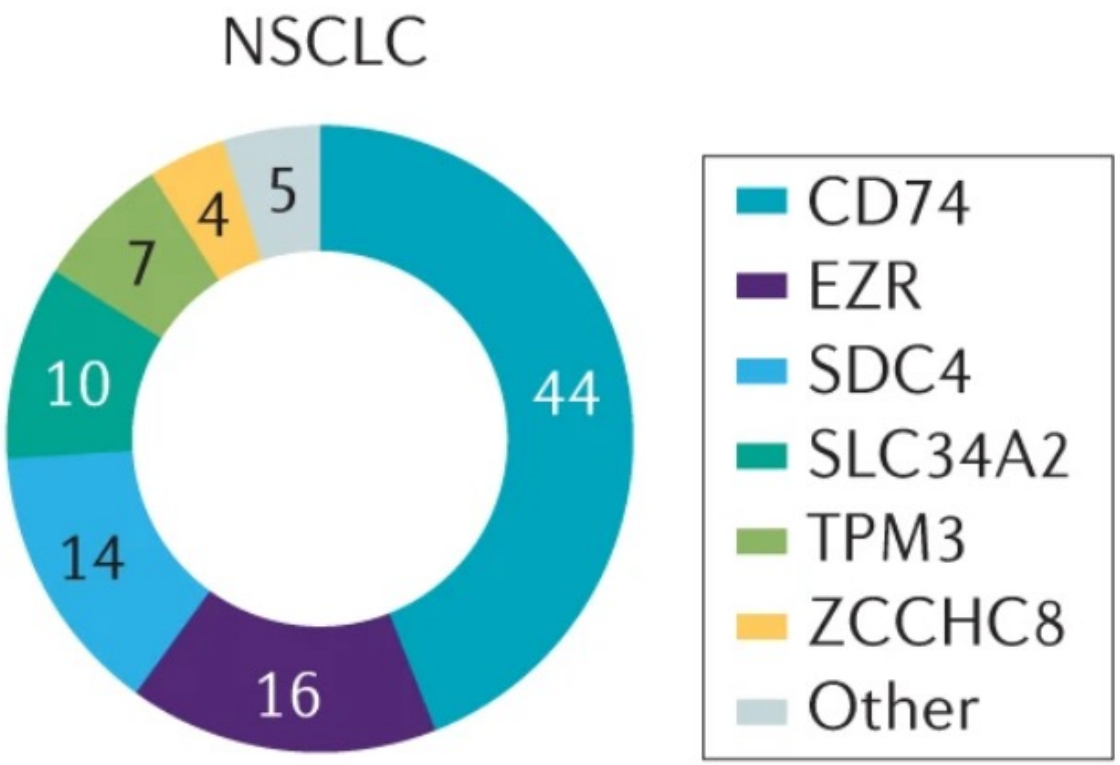
Two-patient case series with short duration responses to MET inhibition

- Crizotinib monotherapy 10 weeks PFS
- Crizotinib + Lorlatinib 3 months PFS

# Management of ALK NSCLC in 2023



# ROS1 Fusions in NSCLC

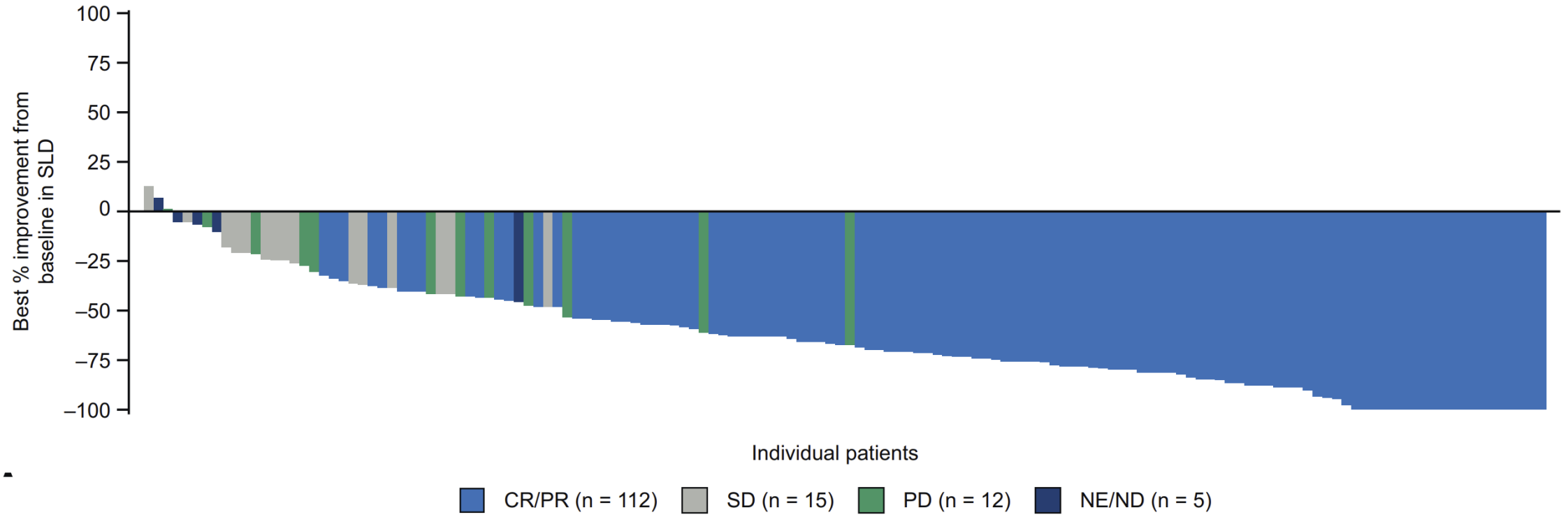



- 1-2% of lung adenocarcinomas
- 80% occur in patients with no history of tobacco use
- Median age 50



*Drilon et al. Nature Reviews Clinical Oncology. 2021.*

# Entrectinib for ROS1+ NSCLC - Preferred if CNS involvement

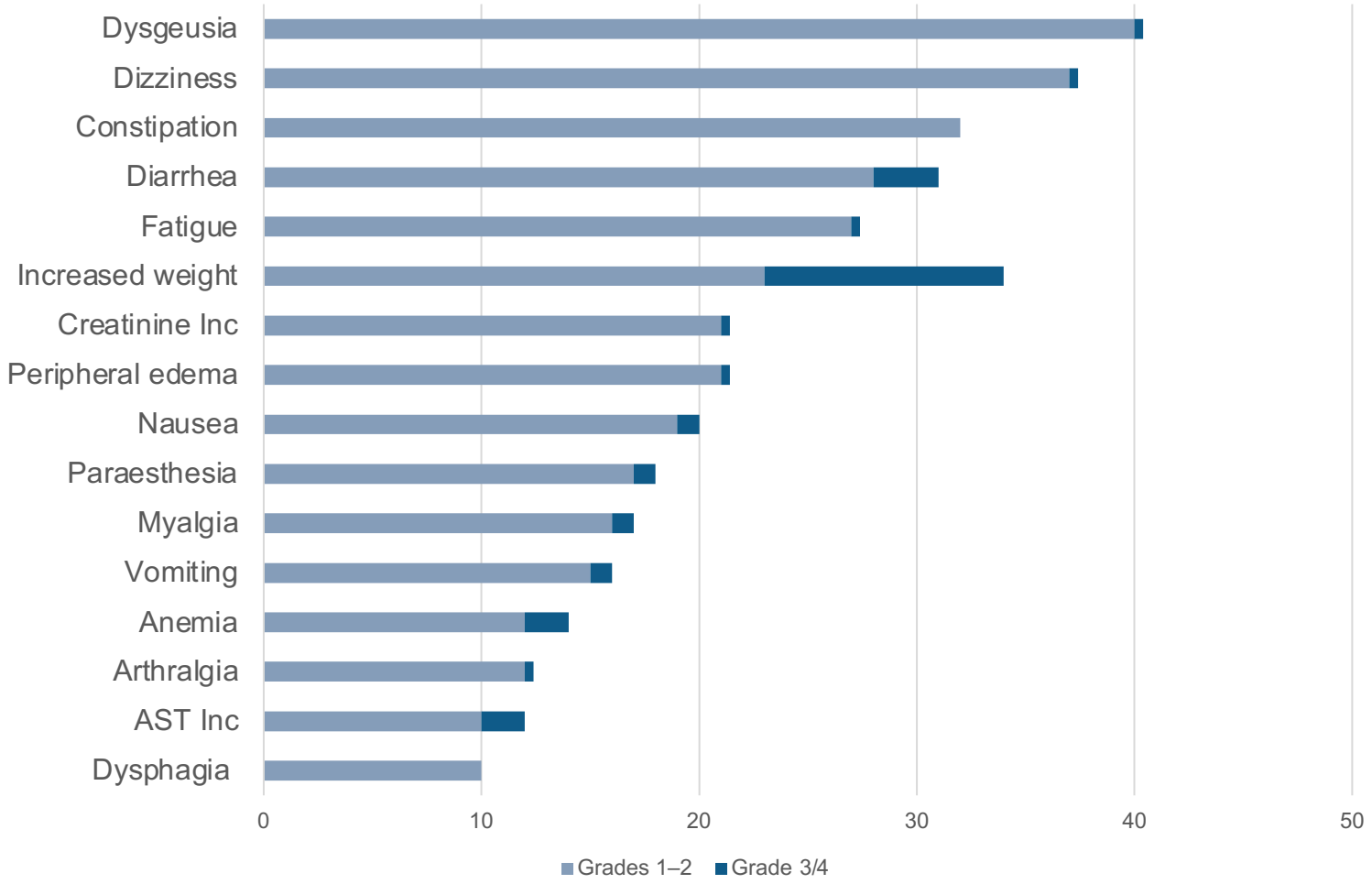



N = 53
ORR 68%, median PFS 15.7 months

**CNS Response Rate 80%**

*Drilon et al. JTO Clinical and Research Reports. 2022;3(6):100332*

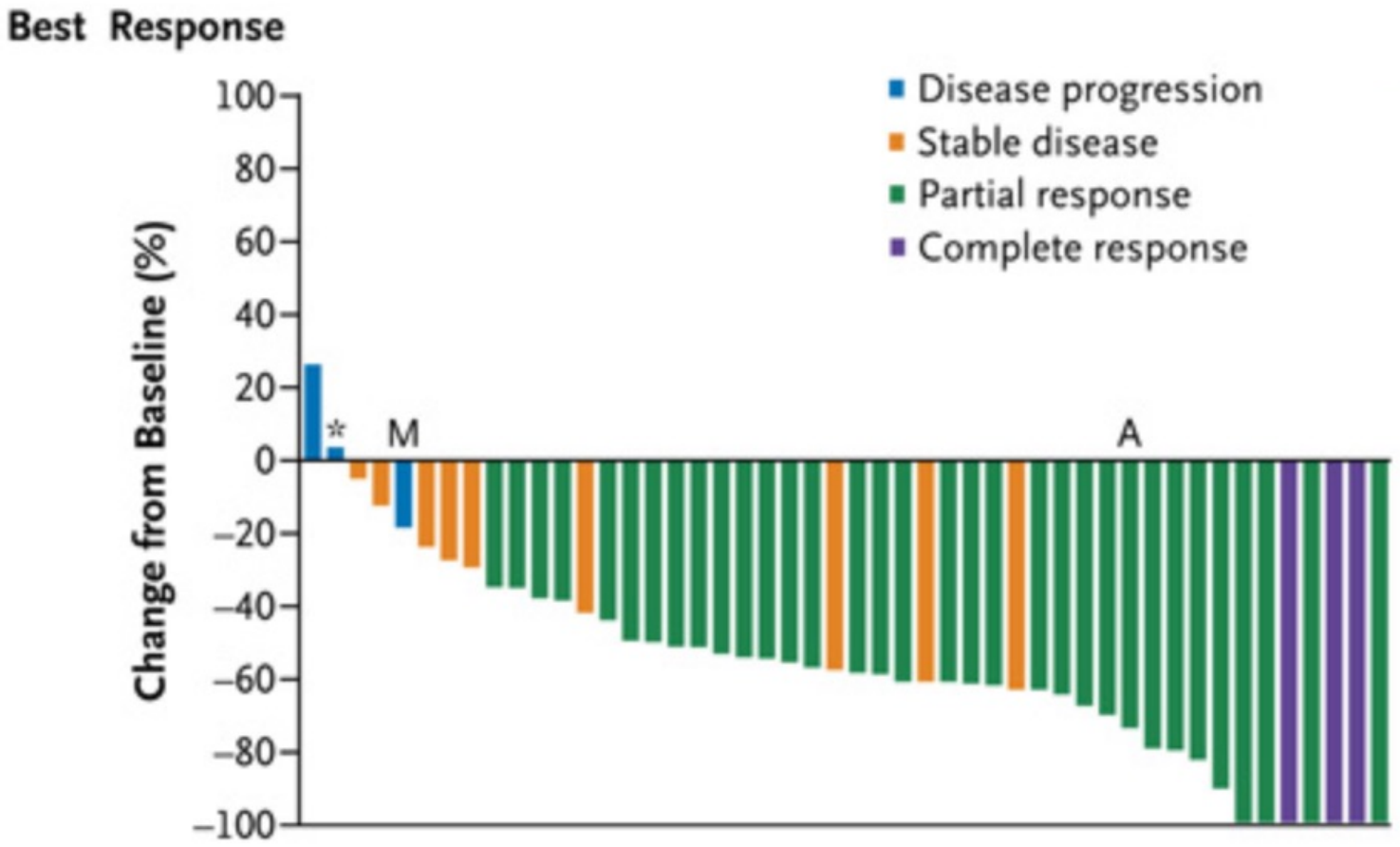
# Entrectinib Treatment-Related Adverse Events




>10% Rate

*Drilon et al. JTO Clinical and Research Reports. 2022;3(6):100332*

# Crizotinib for ROS1+ NSCLC




N=53

ORR 72%
Median PFS 19.3 months

Median OS 51.4 months

**Poor CNS activity**

*Shaw et al. NEJM. 2014; 37(21):1963.* *Shaw et al. Ann Oncol. 2019; 30(7):1121.*

**Table 4. Treatment-related AEs reported in ≥10% of patients**

| Event | *ROS1*-rearranged NSCLC (*N* = 53) | |
|---|---|---|
| | Any grade, *n* (%) | Grade 3, *n* (%) |
| Any AE[a] | 53 (100) | 19 (36) |
| Vision disorder[b] | 46 (87) | 0 (0) |
| Nausea | 27 (51) | 1 (2) |
| Edema[b] | 25 (47) | 0 (0) |
| Diarrhea | 24 (45) | 0 (0) |
| Vomiting | 20 (38) | 2 (4) |
| Elevated transaminases[b] | 19 (36) | 2 (4) |
| Constipation | 18 (34) | 0 (0) |
| Bradycardia[b] | 11 (21) | 0 (0) |
| Fatigue | 11 (21) | 0 (0) |
| Dizziness[b] | 10 (19) | 0 (0) |
| Dysgeusia | 10 (19) | 0 (0) |
| Hypophosphatemia | 9 (17) | 8 (15) |
| Decreased appetite | 8 (15) | 1 (2) |
| Neutropenia[b] | 8 (15) | 5 (9) |
| Rash | 7 (13) | 0 (0) |

[a]Independent of the 10% cut-off used in this table; no grade 4 or 5 treatment-related AEs were reported.
[b]Clustered term comprising AEs that represent similar clinical symptoms/syndromes.
AE, adverse event; NSCLC, non-small-cell lung cancer.

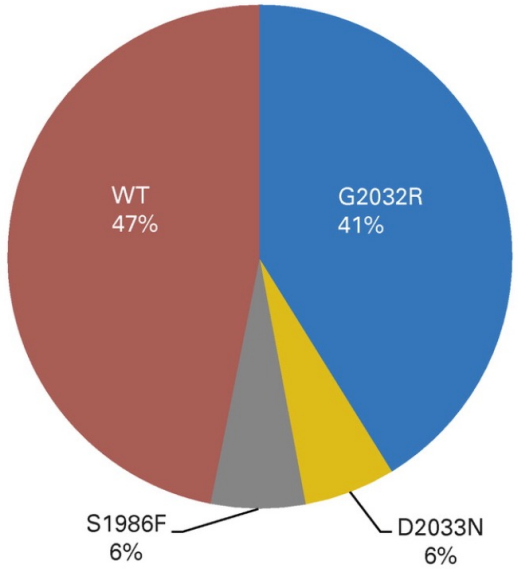
# Crizotinib for ROS1+ NSCLC Adverse Effects

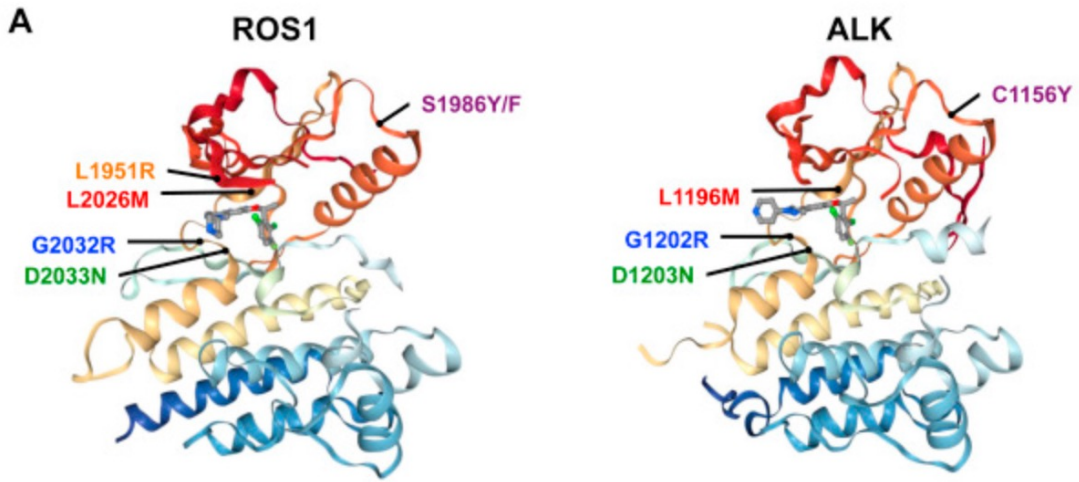
Consisted with known crizotinib safety profile

- 87% Vision disorder
- 51% Nausea
- 47% Edema
- 36% AST or ALT Elevation

*Shaw et al. Ann Oncol. 2019; 30(7):1121.*

# ROS1 TKI Resistance




**G2032R Solvent Front = dominant second site mutation**

Repotrectinib clinical trials ongoing

| $IC_{50}$ (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 |
| G2032R | 609.6 | 436.3 | 196.6 | 23.1 | 17.5 | 346.4 | 472.7 | 53.3 | 1091.0 |
| 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 |

$IC_{50} \leq 50$ nmol/L

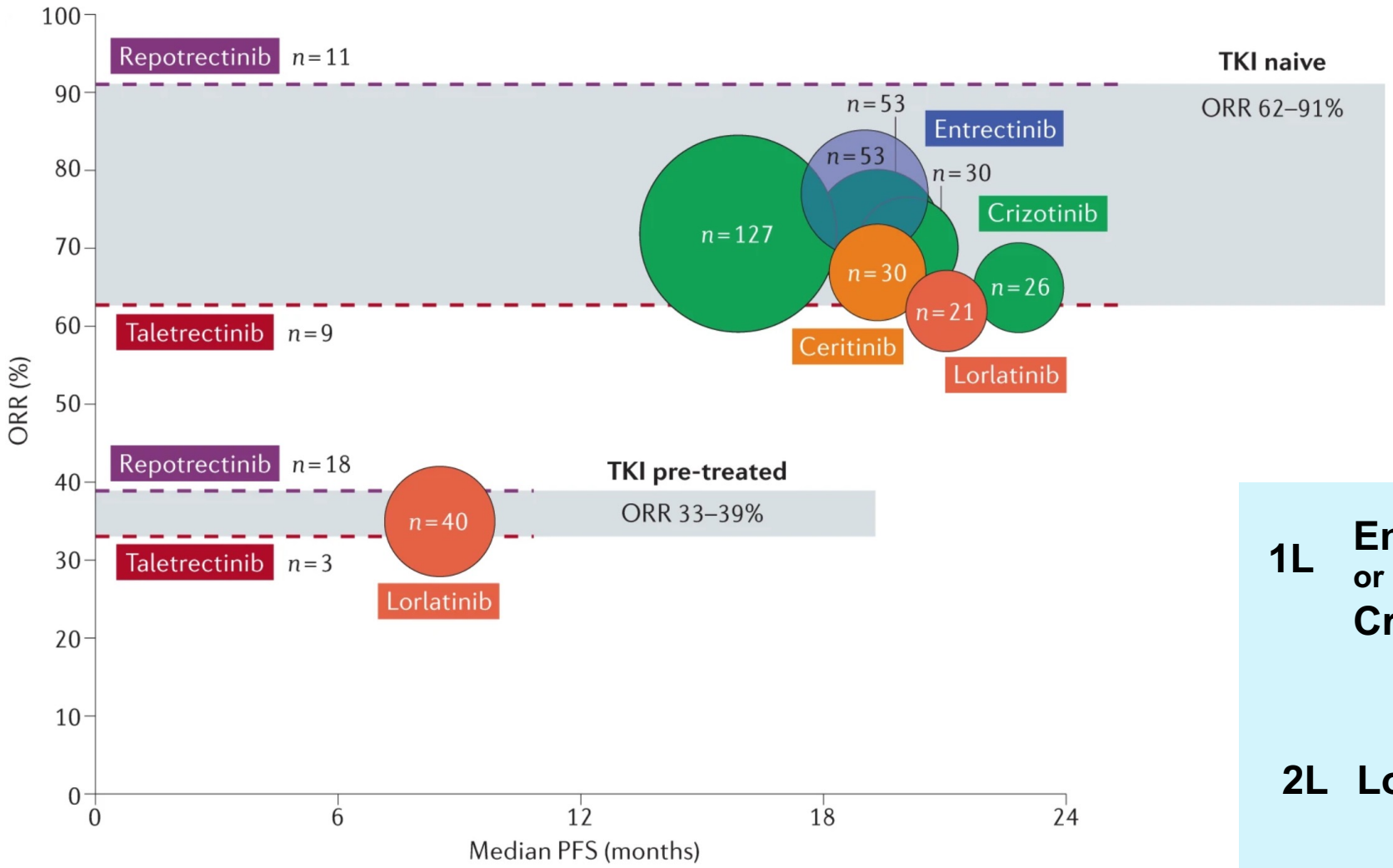
50 nmol/L < $IC_{50}$ <200 nmol/L

$IC_{50} \geq 200$ nmol/L



Lin et al, 2017; Lin et al, 2021; *Gainor et al. JCO Precision Oncology. 2017; Drilon et al. Nature Reviews Clinical Oncology. 2020.*

# So, how do you choose among ROS inhibitors?




**1L** **Entrectinib** or **Crizotinib**

↓

**2L** **Lorlatinib**



*Drilon et al. Nature Reviews Clinical Oncology. 2020.*

- First-line treatment options for ALK+ NSCLC include alectinib and lorlatinib
- Both entrectinib and crizotinib are reasonable first-line treatment options for ROS1+ NSCLC
- Resistance to targeted therapy is heterogenous and includes both on- and off-target mechanisms
- Next-generation TKIs may offer activity at acquired TKI resistance