# Lung Cancer Case


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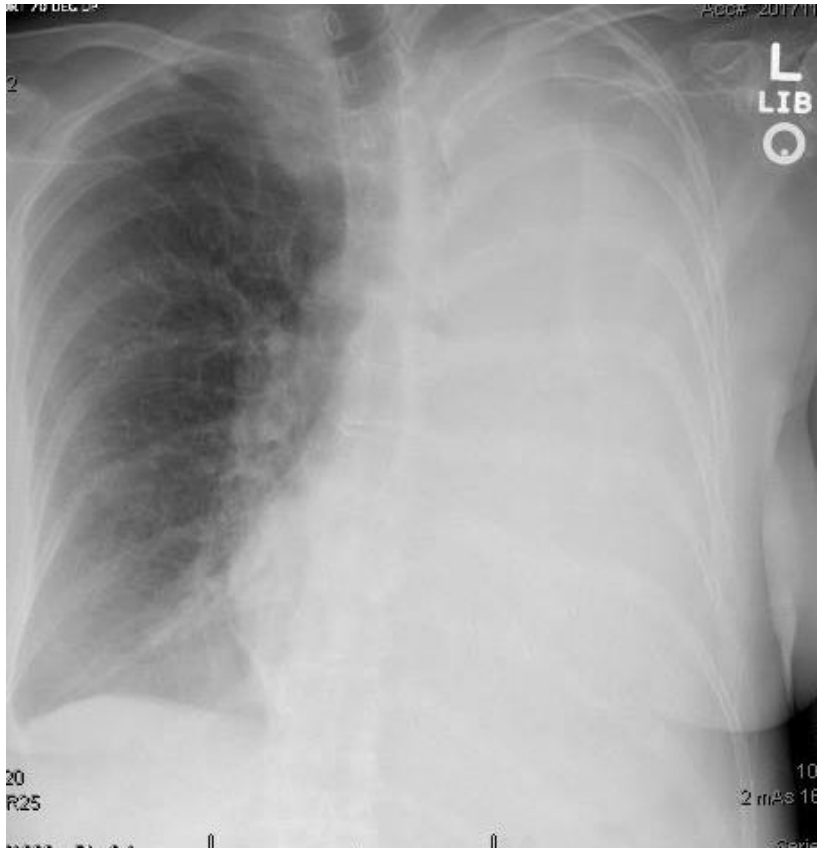
UCDAVIS COMPREHENSIVE CANCER CENTER

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

# Lung Cancer Case

- 63 year-old woman, never smoker, presents with shortness of breath to the emergency department.
- Found to be hypotensive with oxygen saturation of 89%.
- Chest x-ray with large pleural effusion
- Bedside echocardiogram with pericardial tamponade



# Lung Cancer Case

- Patient undergoes pericardiocentesis and thoracentesis with improvement of symptoms, oxygen saturation and blood pressure.
- Cell block reveals lung adenocarcinoma (CK7+, TTF1+, PD-L1 expression 20% (22C3))
- MRI brain with three 3-5 mm brain lesions
- PET CT with metastatic disease to lung, lymph nodes, bone, pleura and adrenal gland

# Lung Cancer Case

Question 1: The patient has Stage IV NSCLC-adenocarcinoma. Her symptoms have improved and she is discharged from hospital. She still has some dyspnea on exertions (PS=1). She has small asymptomatic brain metastasis.

What is your next step?

1. Send molecular testing (NGS panel for > 300 genes (turnaround time 2-3 weeks)?
2. Sent targeted panel (EGFR-mut PCR, ALK FISH, ROS1 FISH, BRAF PCR) with turnaround time for FISH 48 hours and PCR 1 week?
3. Start carboplatin-pemetrexed-pembrolizumab.
4. Start carboplatin-pemetrexed
5. Start erlotinib
6. Start whole brain radiation

# Lung Cancer Case

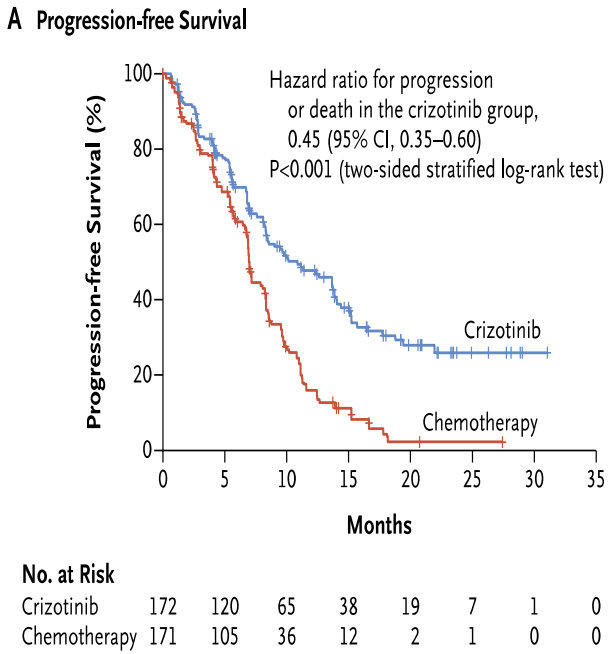
Since the patient was symptomatic, a targeted panel was sent. ALK FISH returned in 2 days and was positive.

Question 2: What ALK TKI do you start?

1. Crizotinib
2. Alectinib
3. Ceritinib

# Crizotinib (1st generation ALK inhibitor)

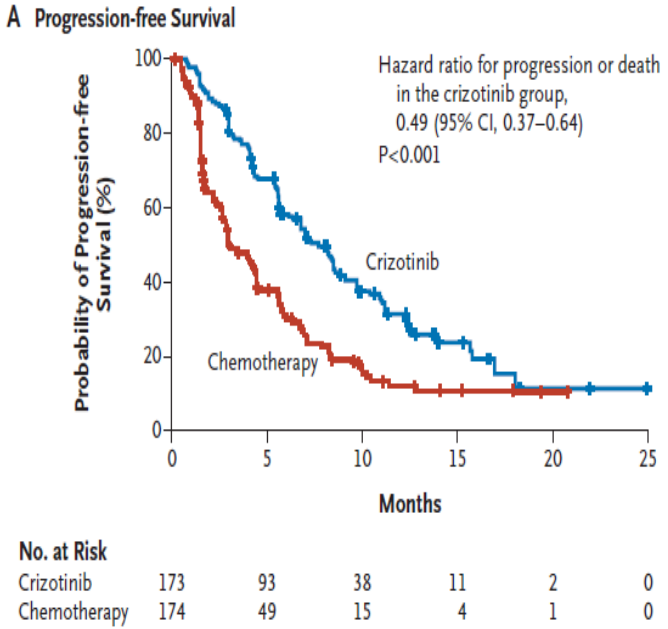
## PROFILE 1014




| Endpoint | |
|---|---|
| ORR % | 74% |
| Median PFS | 10.9 months |
| Median Duration of Response | 11.3 months |

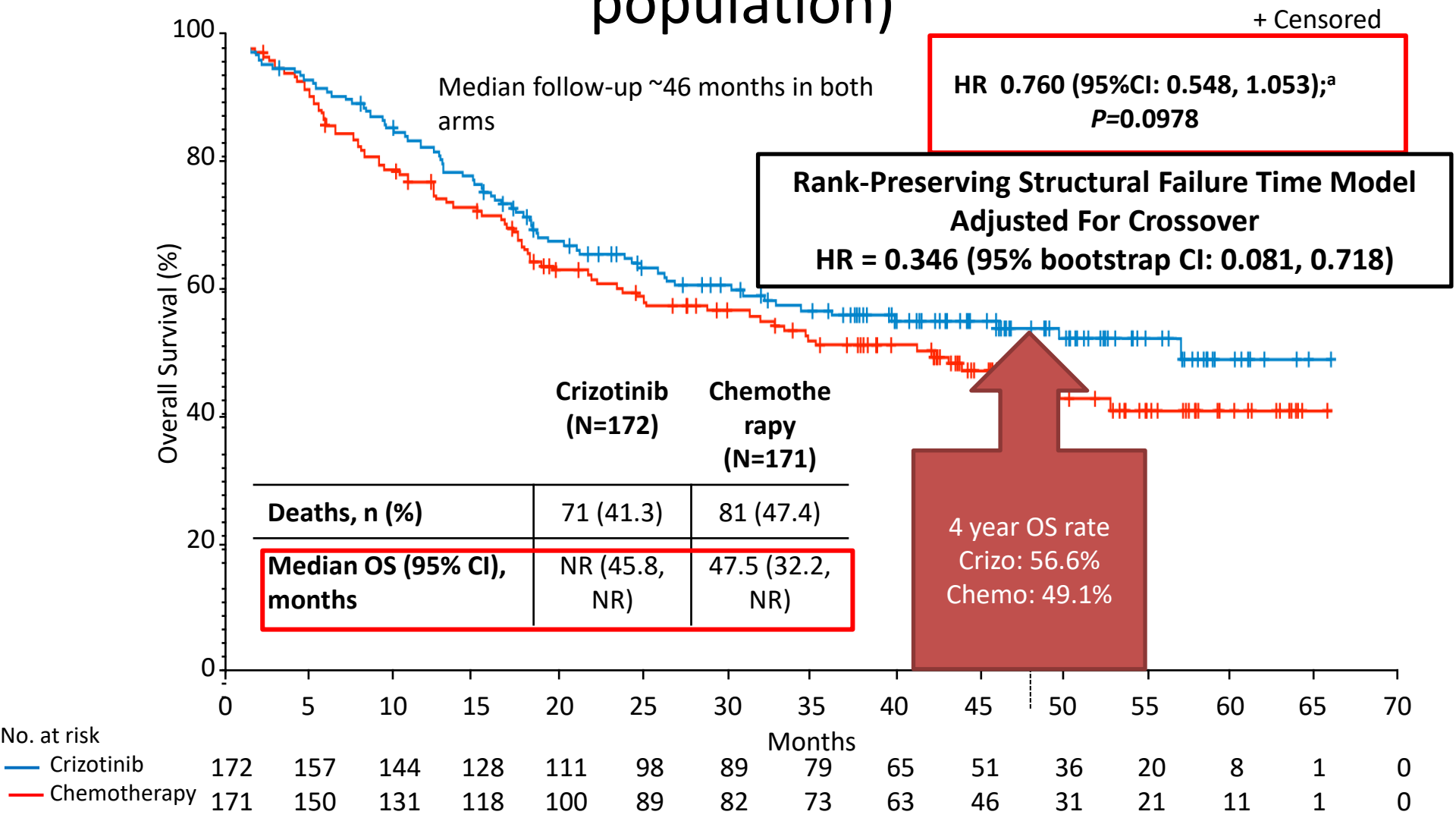
Solomon BJ, et al. NEJM 2014

## PROFILE 1007




| Endpoint | |
|---|---|
| ORR % | 65% |
| Median PFS | 7.7 months |
| Median Duration of Response | 8 months |

# PROFILE 1014: Final primary OS analysis (ITT population)




[a]2-sided p-value from the log-rank test stratified by ECOG PS, race, brain metastases

Mok T, et al. ESMO 2017. Abstract LBA50.

# Ceritinib – ASCEND 4

## ASCEND 4 Study Design

**Key entry criteria**
- ALK-positive by central FISH testing.
- Locally advanced or metastatic NSCLC.
- No prior systemic treatment for advanced disease.
- ECOG 0-2
- Asymptomatic or neurologically stable brain metastases.

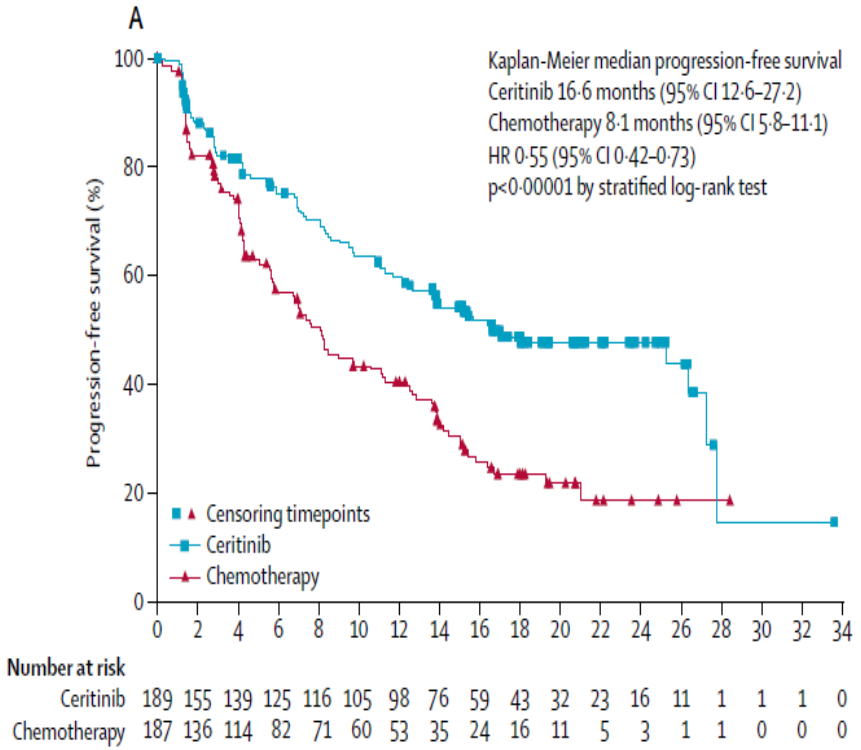
RANDOMIZE

**Ceritinib 750 mg QD** (N=189)

**Pemetrexed + cisplatin or carboplatin x 4*** (N=187)

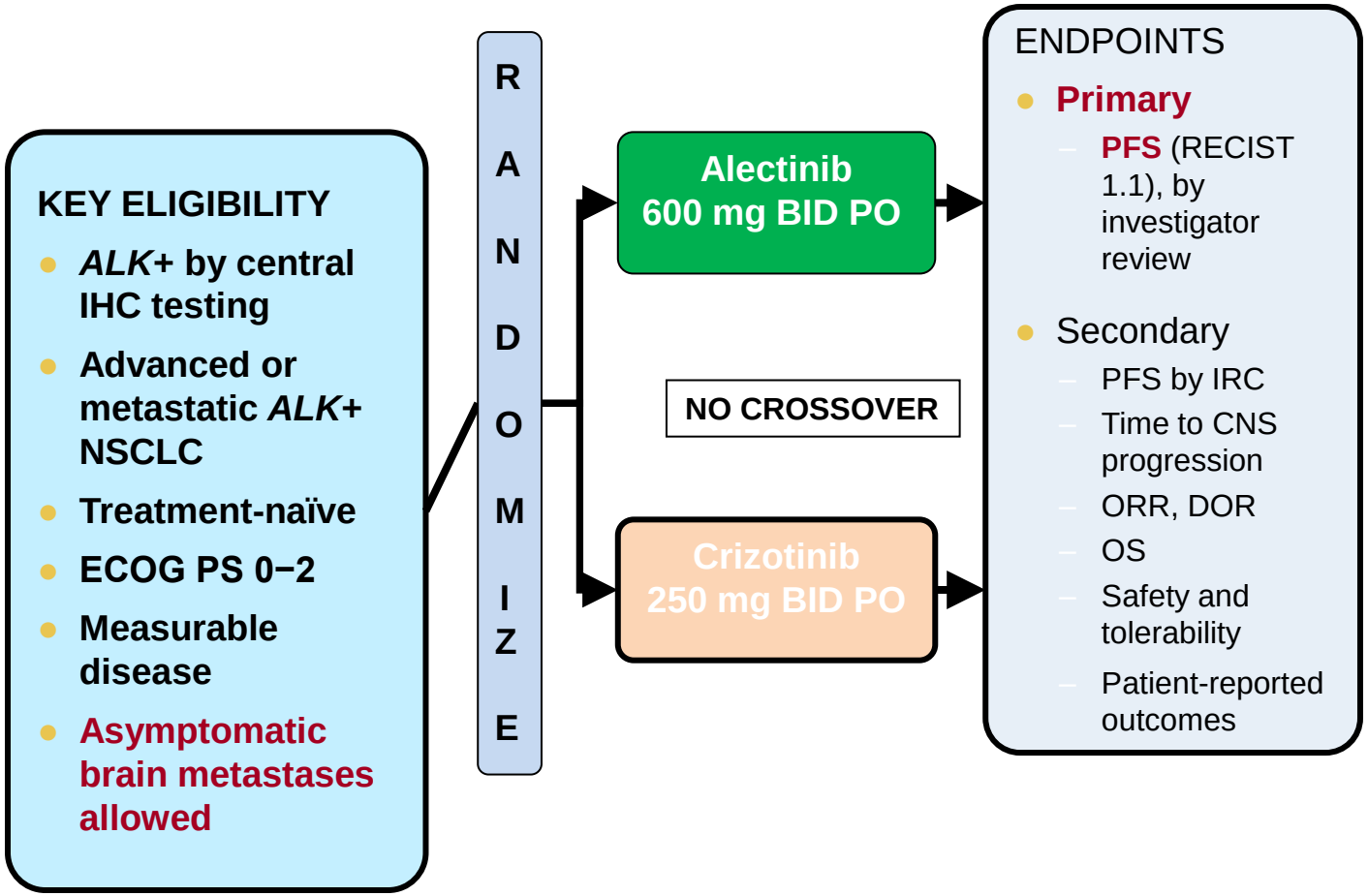
* Maintenance pemetrexed allowed

**CROSSOVER TO CERITINIB PERMITTED AFTER PROGRESSION**




Soria JC, et al. Lancet 2017

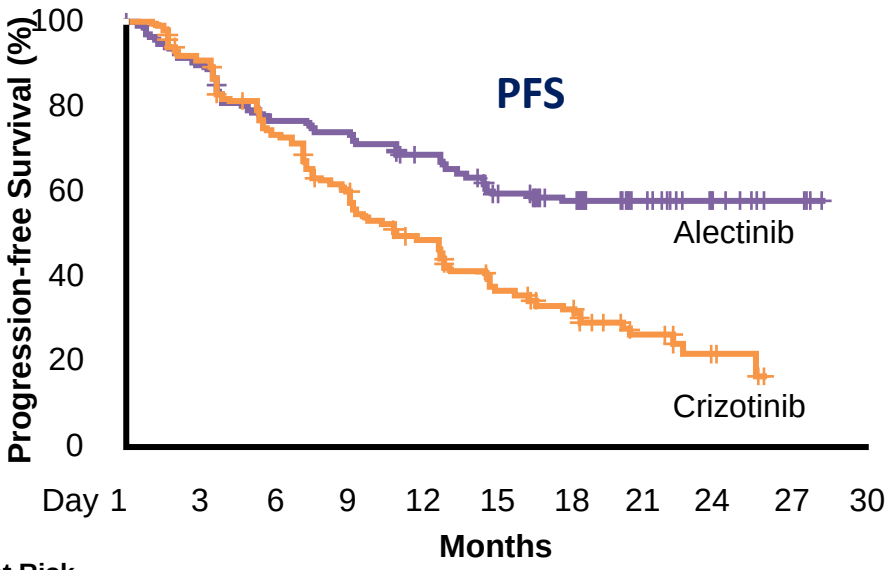
# ALEX Study: Alectinib vs Crizotinib in ALK+ NSCLC




Stratification factors:
- ECOG PS (0/1 vs 2)
- Race (Asian vs non-Asian)
- Brain metastases (present vs absent)

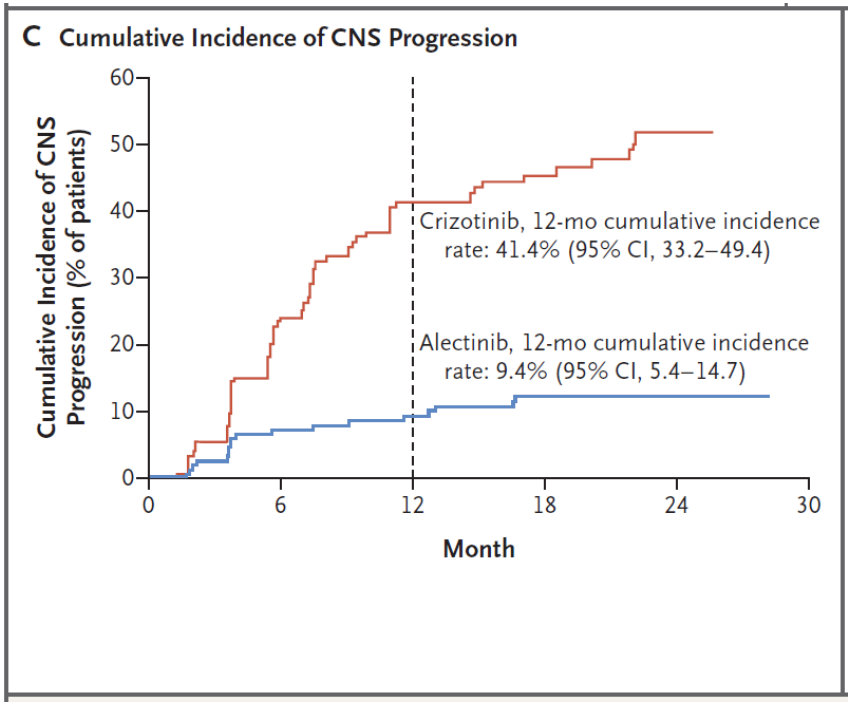
Shaw A et al. Proc. ASCO 2017

# ALEX : Primary end points (PFS) & Activity in CNS Metastases




**No. at Risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Crizotinib | 151 | 132 | 104 | 84 | 65 | 46 | 35 | 16 | 5 | |
| Alectinib | 152 | 135 | 113 | 109 | 97 | 81 | 67 | 35 | 15 | 3 |




| | Crizotinib (N=151) | Alectinib (N=152) |
|---|---|---|
| Patients with events, n (%) | 102 (68) | 62 (41) |
| Median PFS, months (95% CI) | 11.1 (9.1–13.1) | NE (17.7–NE) |
| HR (95% CI) P-value (log-rank test) | 0.47 (0.34–0.65) P<0.0001 | |

Shaw A et al. ASCO 2017,
Peters, S. et al NEJM 2017

| Time to CNS Progression | Crizotinib (N=151) | Alectinib (N=152) |
|---|---|---|
| Patients with events, n (%) | 66 (45) | 18 (12) |
| Median PFS, months (95% CI) | 11.1 (9.1–13.1) | NE (17.7–NE) |
| HR (95% CI) P-value (log-rank test) | 0.16 (0.10-0.28) P<0.0001 | |

# Next generation ALK TKIs have distinct side effect profiles

| | Common side effects | Common lab changes | Less common but notable AEs |
|---|---|---|---|
| Ceritinib | Diarrhea (86%)<br>Nausea (80%)<br>Vomiting (60%)<br>Abdominal pain (54%)<br>Fatigue (52%) | ⇧ALT (80%), 27% grade 3/4<br>⇧AST (75%),13% grade 3/4<br>⇧Cr (58%)<br>⇧Glu (49%) | ILD (4%)<br>QTc (3%) |
| Alectinib | Fatigue (41%)<br>Constipation (34%)<br>Edema (30%)<br>Myalgia (29%) | ⇧AST (51%)<br>⇧AP (47%)<br>⇧CPK (43%)<br>⇧Bili (39%)<br>⇧ALT (34%) | ILD (0.4%)<br>Severe myalgia (1.2%)<br>Severe CPK elevation (4.6%) |
| Brigatinib | Nausea (51%)<br>Fatigue (42%)<br>Diarrhea (41%)<br>Headache (34%)<br>Cough (33%) | Increased amylase (21%)<br>Increased AST (18%) | Gr3 hypertension (5%)<br>Early onset pulmonary toxicity (6%) |

*Slide courtesy of Joel Neal MD*

# Ongoing First Line Phase 3 Trials

| Sponsor | Trial | Drug | Comparator | Target | Reporting date | Trial ID |
|---|---|---|---|---|---|---|
| Takeda | ALTA-1L | brigatinib | crizotinib | 270 | April 2019 | NCT02737501 |
| Pfizer | CROWN | lorlatinib | crizotinib | 280 | Dec 2019 | NCT03052608 |
| Xcovery | eXalt3 | ensartinib | crizotinib | 402 | April 2020 | NCT02767804 |

# Lung Cancer Case

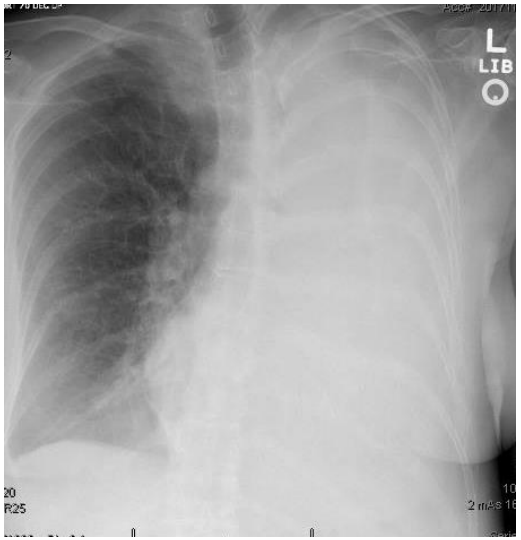
Question 3:

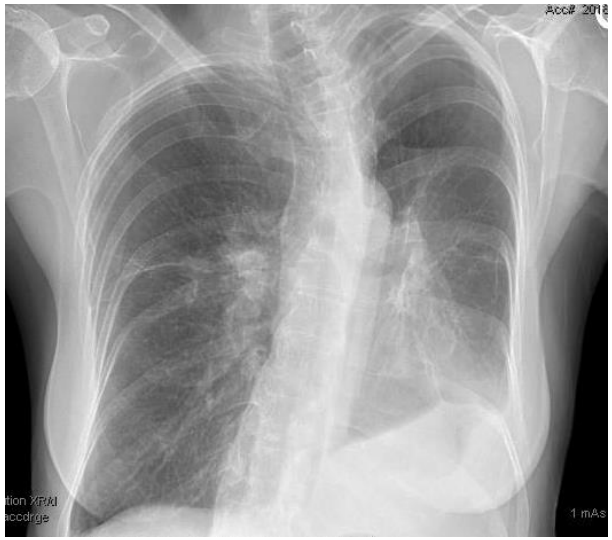
Would you radiate the patient's brain metastases?

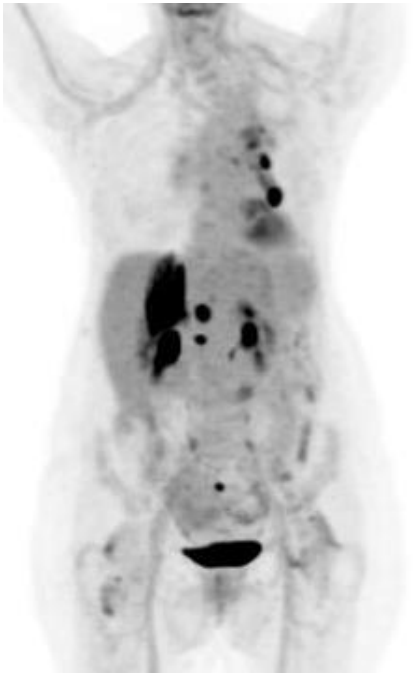
1. Yes
2. No

# Lung Cancer Case Continued

- The patient starts alectinib with rapid improvement of symptoms.
- 6 months later patient develops R sided flank pain. PET CT shows progressive disease



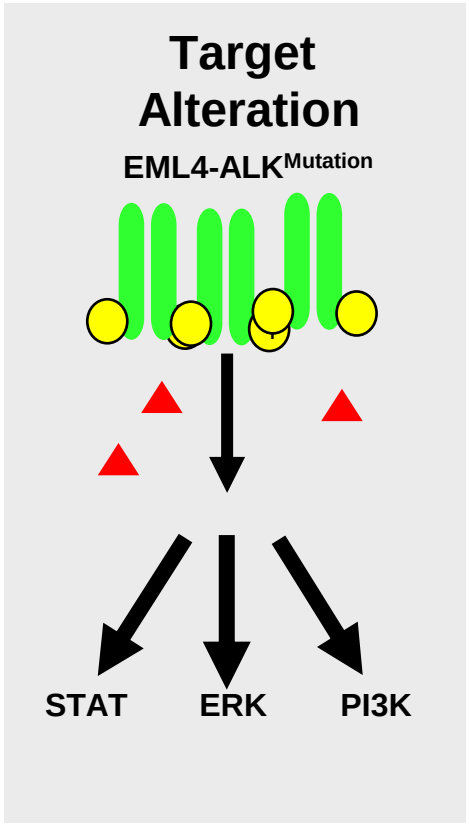


# Lung Cancer Case

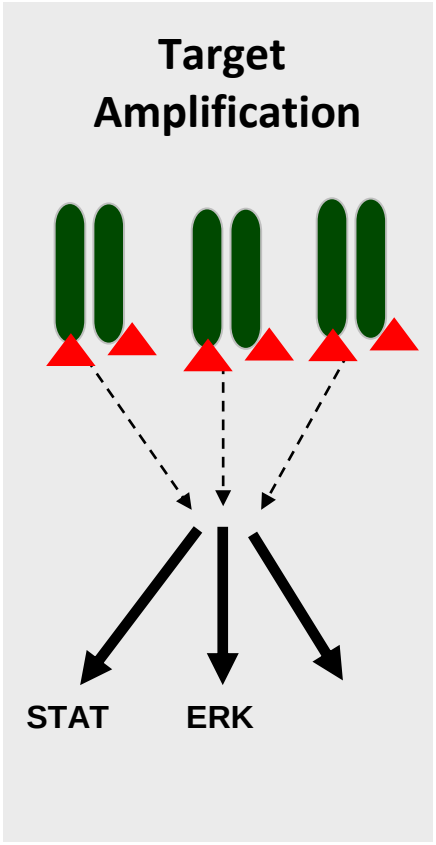
Question 4: Would you rebiopsy (tissue or plasma) this patient with ALK positive NSCLC with progression on alecitinib?

1. Yes
2. No

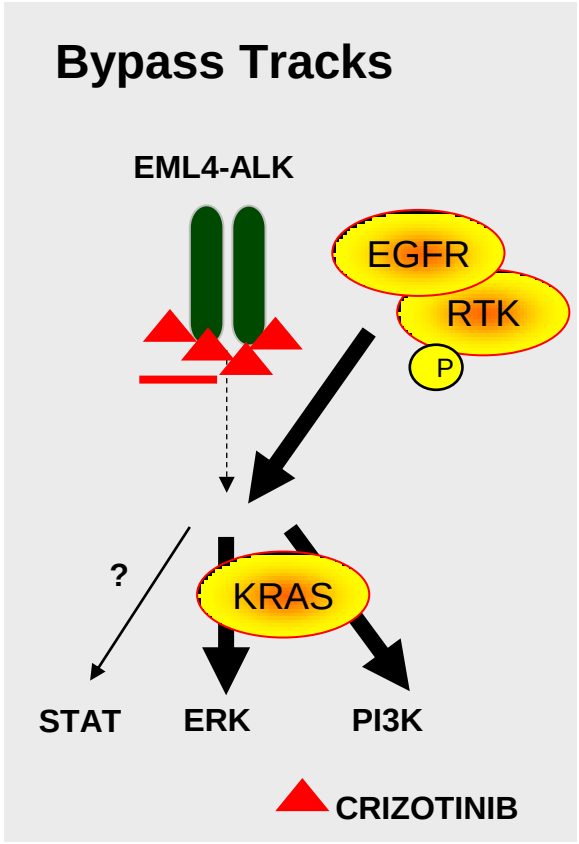
# General Mechanisms of ALK TKI Resistance




Mutations in ALK kinase domain




Amplification of ALK fusion




Bypass Signaling: EGFR, IGF-1R, c-KIT, HER-2/HER3, RAS-RAF-MAPK, SRC

Lovly ASCO Educ Book 2015.

# Selection of ALK TKI Based on Resistance Mutation

**Resistance Mechanisms in ALK-Positive Lung Cancer**

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 | 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 |

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

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

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

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

# ALK patient Rebiopsy At Progression

| BIOMARKER FINDINGS | ACTIONABILITY |
|---|---|
| **Microsatellite status** - MS-Stable | **No therapies or clinical trials.** see Biomarker Findings section |
| **Tumor Mutational Burden** - TMB-Low (5 Muts/Mb) | **No therapies or clinical trials.** see Biomarker Findings section |

| GENOMIC FINDINGS | THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE) |
|---|---|---|
| *MET* - amplification | Crizotinib | Cabozantinib |
| 7 Trials see p. 11 | | |
| *ALK* - EML4-ALK fusion (Variant 1) | Alectinib | none |
| | Brigatinib | |
| | Ceritinib | |
| 10 Trials see p. 19 | Crizotinib | |

**GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS**

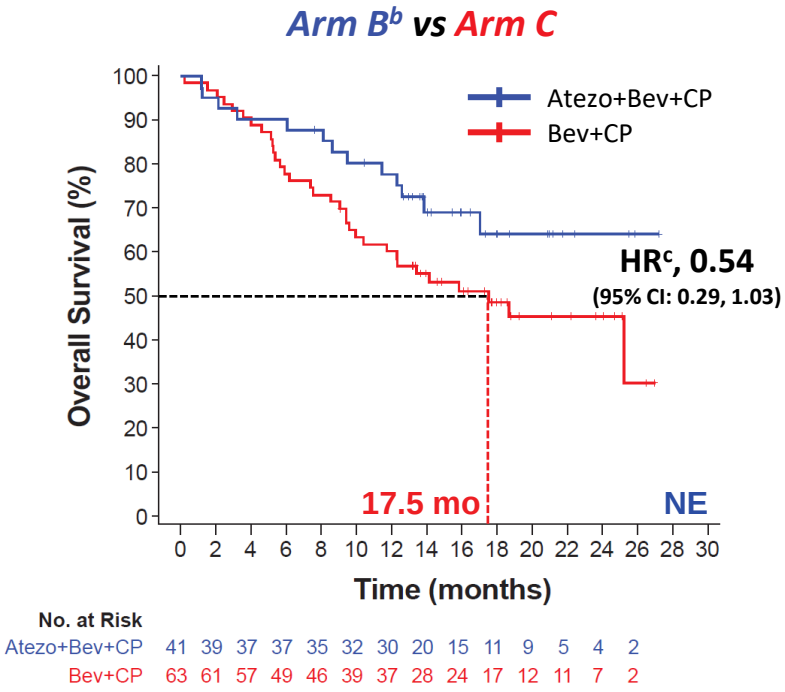
*For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Alterations section.*

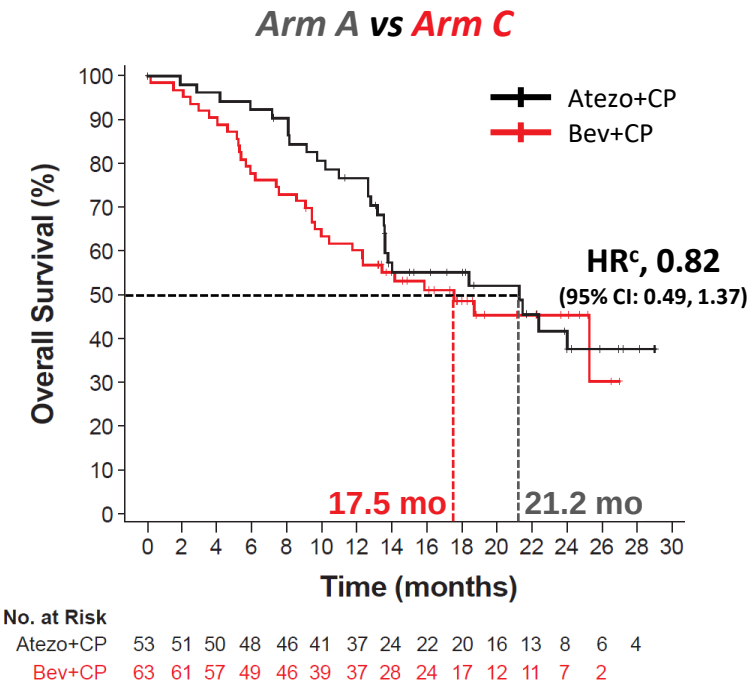
# Lung Cancer Case

Question 5: What would you treat the patient next with?

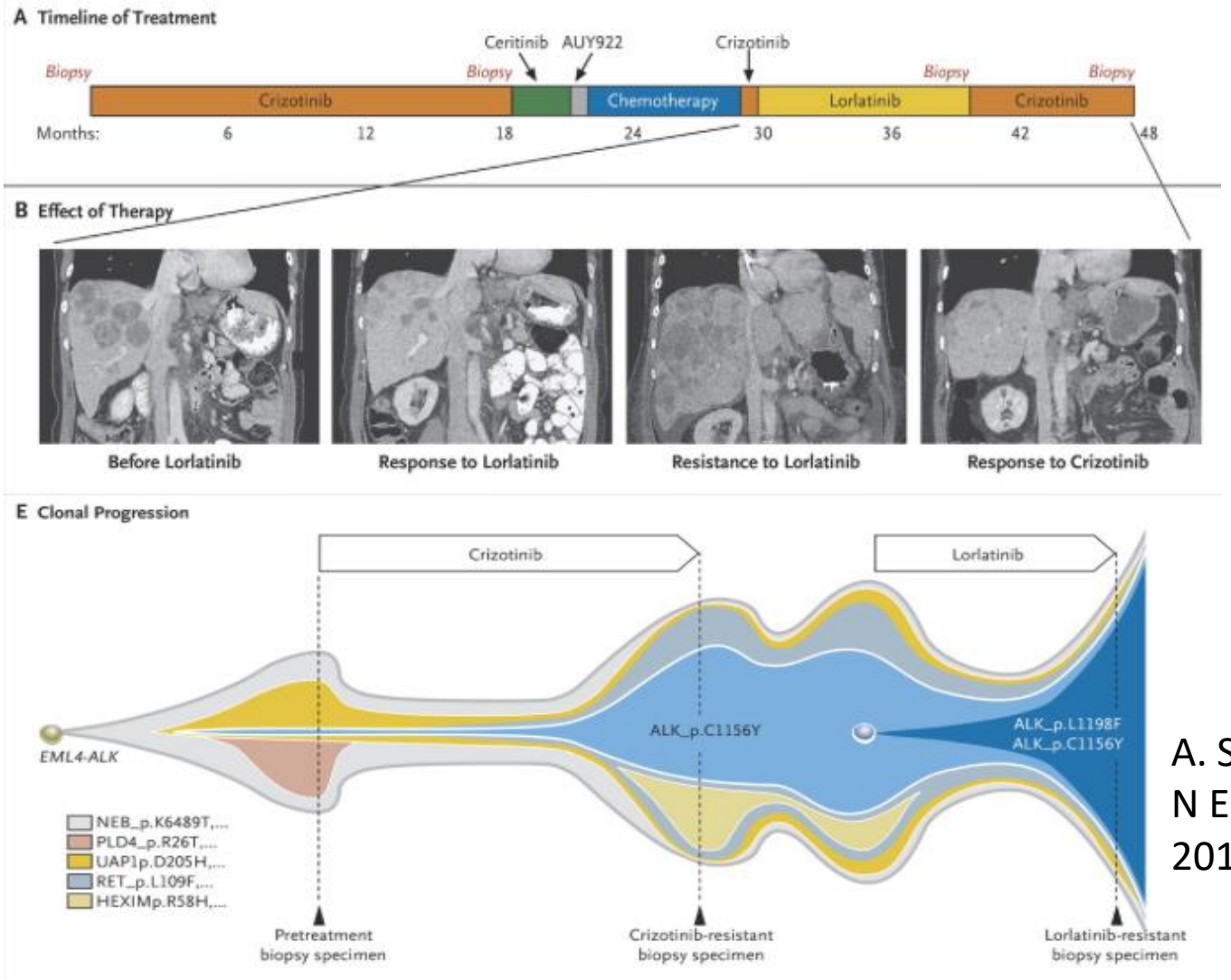
1. Carboplatin-pemetrexed-pembrolizumab
2. Crizotinib
3. Carboplatin-pemetrexed
4. Carboplatin-pemetrexed-bevacizumab
5. Carboplatin-paclitaxel-bevacizumab-atezolizumab

# Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of *EGFR/ALK*+ Patients[a]



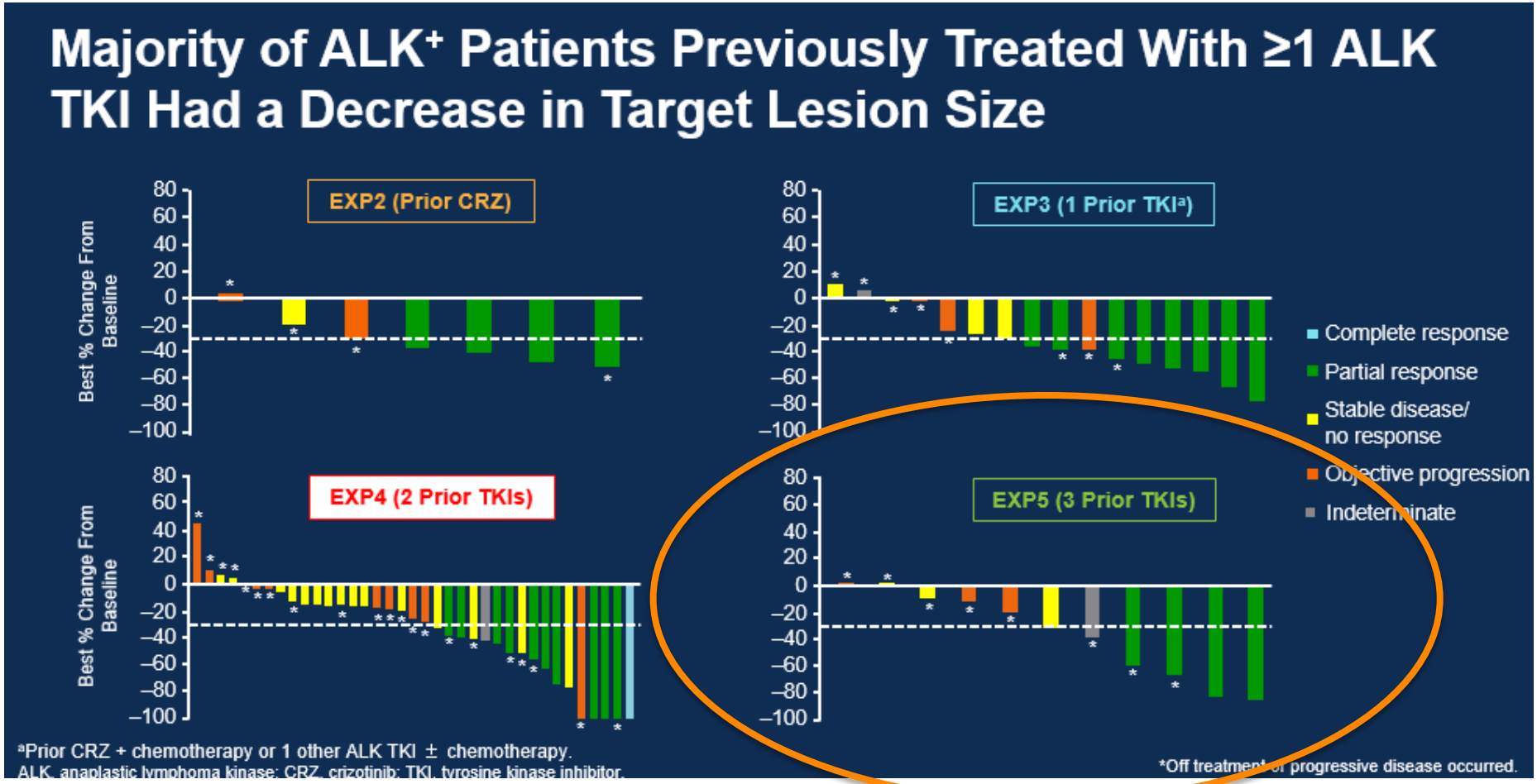



# Re-Sensitization to crizotinib after progression on lorlatinib




A. Shaw et al.
N Engl J Med
2016; 374:54-61

# Third generation ALK inhibitors to overcome ALK-TKI resistance: Lorlatinib as an example




Ou et al., ASCO 2017