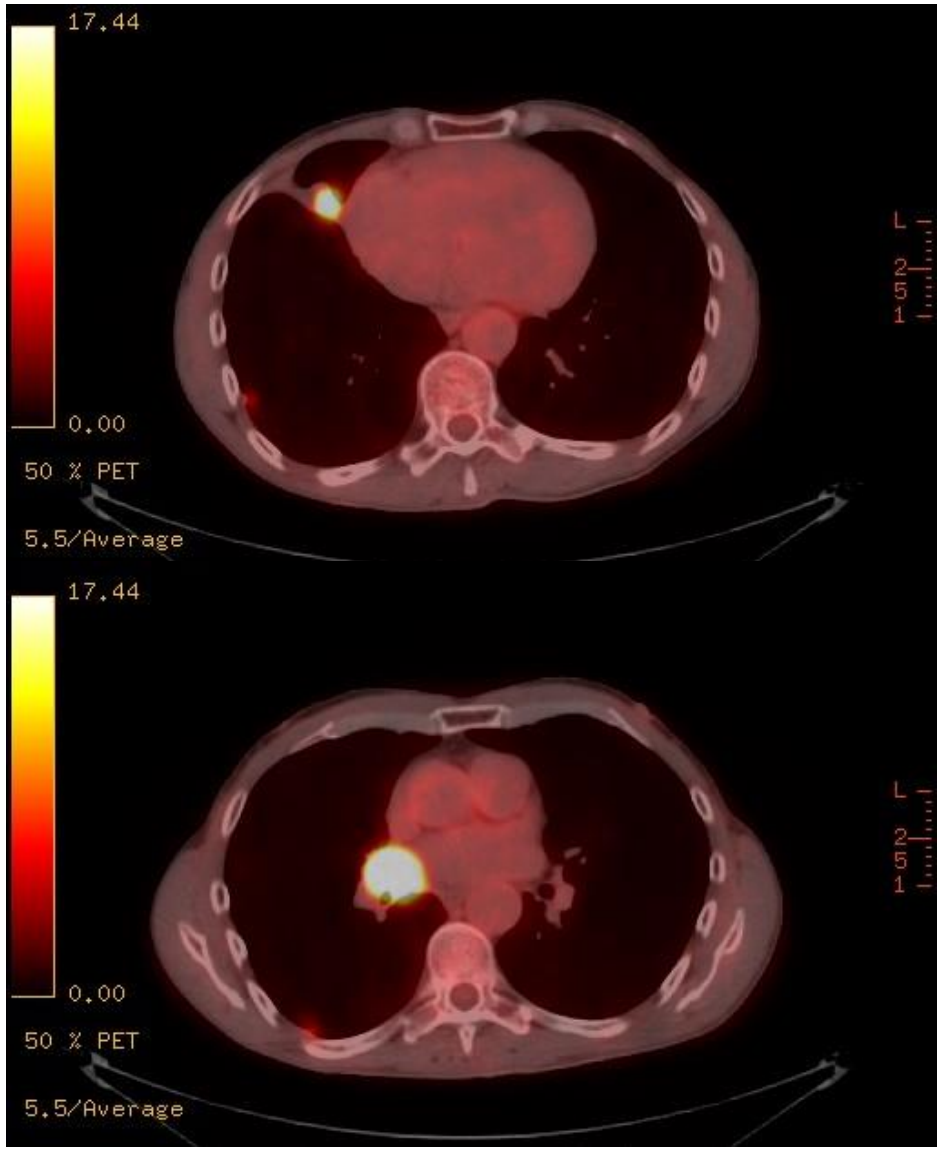
ALK, ROS1-Rearranged NSCLC, Advanced Stage

Initial Presentation: Case 2C-ALK*

57-year-old Caucasian man, with limited smoking history (1 ppd for 5 years) presented with shortness of breath while jogging (in 2010). ECOG PS = 0. He is a marathon runner and in excellent health otherwise

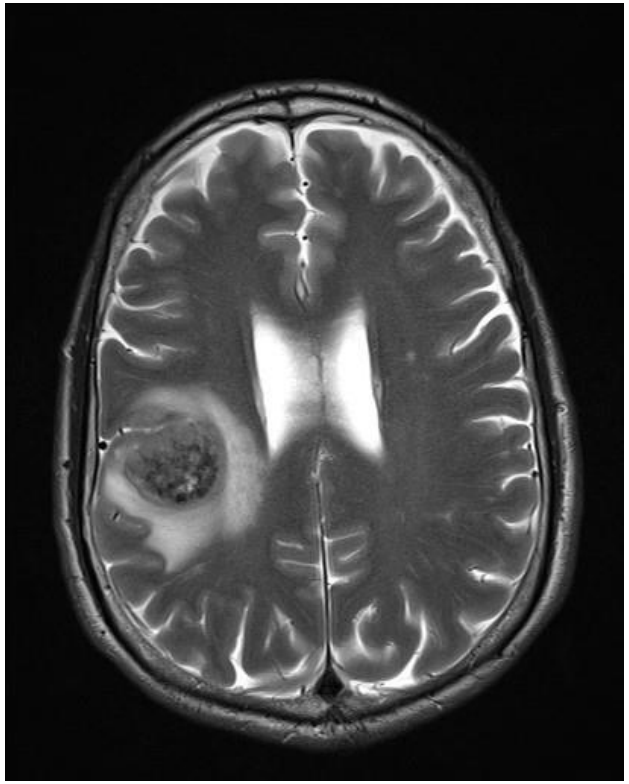
- Presented to his PCP for SOB and a CXR reveals a 2.9 x 3 cm right hilar mass
- PET/CT confirms the right mass (3 x 1.8 cm), which was intensely hypermetabolic and small pleural lung nodules; suspicious lesion in right mid renal cortex and rightt posterior acetabulum
- A bronchoscopic biopsy of right lung mucosal mass shows: NSCLC, Adenocarcinoma, CK20 neg, TTF-1+, CK7+



*Cases may have been modified for educational purposes

Question

- MRI brain shows a 2.6 x 2.3 x 2.6 mass in the right parietal lobe
- Tissue testing reveals no actionable mutations (limited tissue, only EGFR/KRAS testing was done)



Question 1: What treatment would you recommend as a next step (as of 10 years ago)?

- **WBRT + chemotherapy**
- **Carboplatin/pemetrexed alone**
- **Immunotherapy**
- **SRS + chemotherapy**

Question

- Patient completes SRS, 4 cycles of carboplatin/pemetrexed, and 12 cycles of maintenance pemetrexed before experiencing disease progression in the lung
- MRI remains stable

Question 2: What do you recommend for this patient with stage IV NSCLC with no actionable mutations and progression on SOC (as of 10 years ago)?

- **Clinical trial + Biopsy to repeat molecular testing**
- **Immunotherapy**
- **Radiation therapy**
- **None of the above**

Case

- At the time, patient was initiated on clinical trial with docetaxel and ramucirumab
- Although he demonstrated a response, the patient was discontinued after 6 cycles due to grade 3 AEs
- Patient took brief treatment holiday and his disease progressed
- Repeated molecular testing demonstrated ALK rearrangement

FISH Study Only

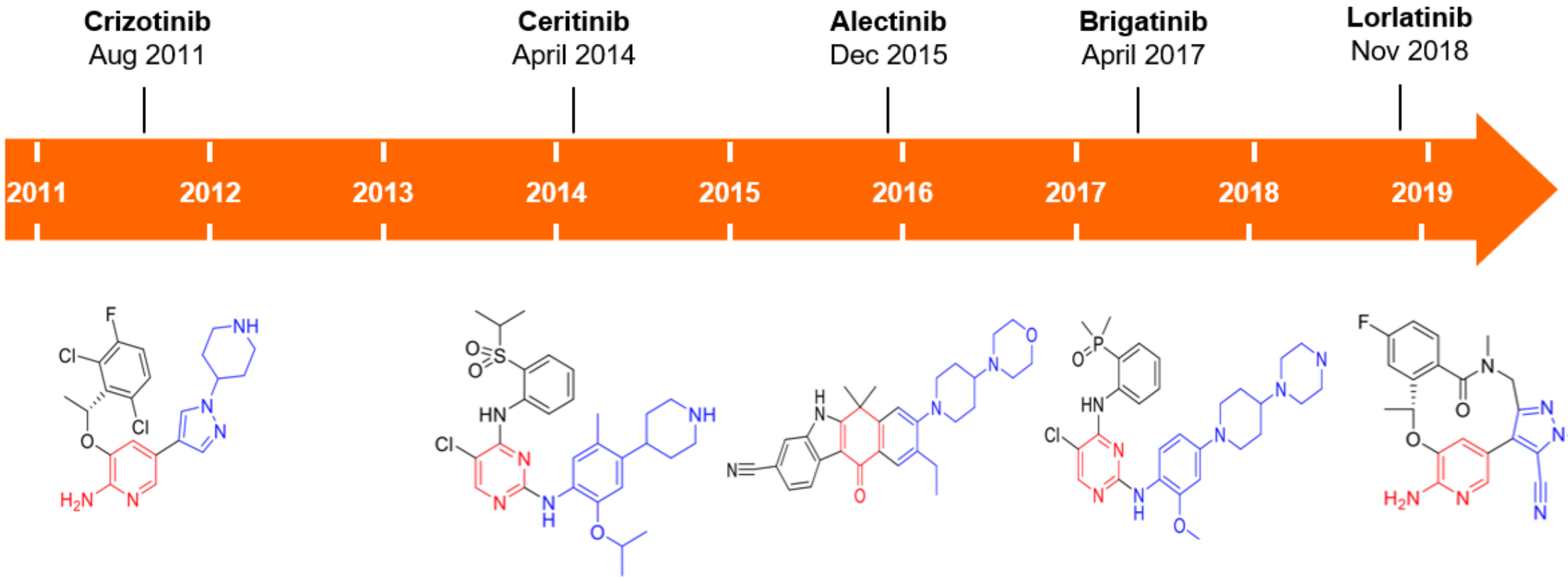
ALK FISH Studies [LSI ALK Dual Color Break Apart FISH Probe, Vysis, Inc.]:

POSITIVE SIGNAL PATTERNS:
nuc ish(ALKx2)(5'ALK sep 3'ALKx1): 2 of 50 cells = 4.0% ALK Rearrangement
nuc ish(5'ALKx1,3'ALKx2-3)(5'ALK con 3'ALKx1-2): 32 of 50 cells = 64.0% Intact ALK and ALK Rearrangement with 5'Loss

NEGATIVE SIGNAL PATTERNS:
nuc ish(ALKx2): 9 of 50 cells = 18.0% Normal
nuc ish(ALKx1): 6 of 50 cells = 12.0% Loss of intact ALK signal
nuc ish(ALKx3): 1 of 50 cells = 2.0% Gain of intact ALK signals

Impression:
Positive for an ALK rearrangement by FFPE interphase FISH analysis

Timeline for FDA Accelerated Approval of TKIs Targeting ALK



Question

Question 3: What would you recommend as his next treatment (as of ~8 years ago)?

- **Alectinib**
- **Crizotinib**
- **Lorlatinib**
- **Brigatinib**

Question

- Patient was on crizotinib for ~1 year before progression of disease
- Patient was initiated on HSP-90 inhibitor clinical trial
- Unfortunately, patient progressed in ~ 6 months and was started on ceritinib, for which he maintained for approximately 2 years until MRI brain demonstrated progression of disease in the brain (two lesions in the left occipital lobe)

Question 4: With progression of brain metastases, what next line of therapy would you recommend?

- **Brigatinib**
- **Lorlatinib**
- **Alectinib**
- **Crizotinib again**

Question

- Patient was on alectinib for ~2 years before showing minimal progression of disease in the lungs
- Liquid biopsy was ordered and demonstrated a FGFR2 mutation

Question 5: With no other actionable mutations, what next line of therapy would you recommend?

- **Continue alectinib**
- **Lorlatinib**
- **Brigatinib**
- **Crizotinib**

Global ALEX: Study Design & Progression Free Survival

KEY ELIGIBILITY

- Advanced or metastatic *ALK*+ NSCLC
- *ALK*+ by central IHC testing
- Treatment-naïve
- ECOG PS 0−2
- Measurable disease
- Asymptomatic brain metastases allowed

RANDOMIZE

N=286

Alectinib
600 mg BID PO

NO CROSSOVER
per protocol

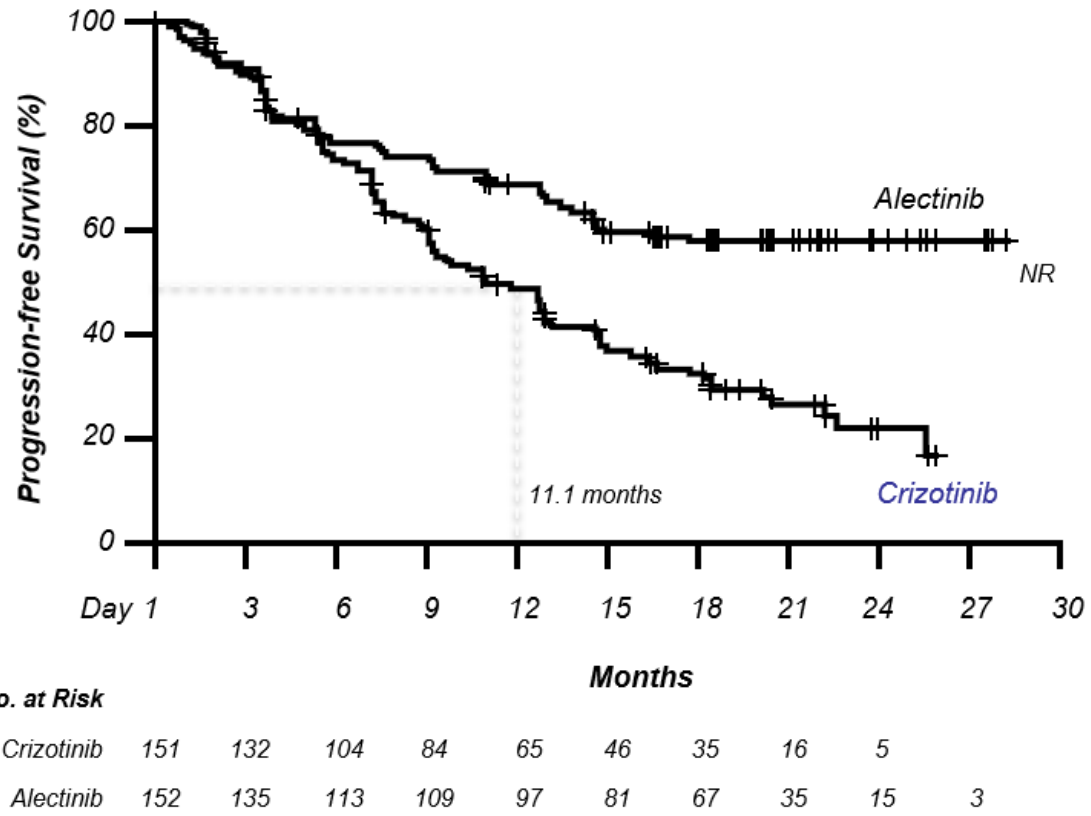
Crizotinib
250 mg BID PO

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

ENDPOINTS

- Primary
  - PFS (RECIST 1.1), by investigator review
- Secondary
  - PFS by IRC
  - Time to CNS progression
  - ORR, DOR
  - OS
  - Safety and tolerability
  - Patient-reported outcomes

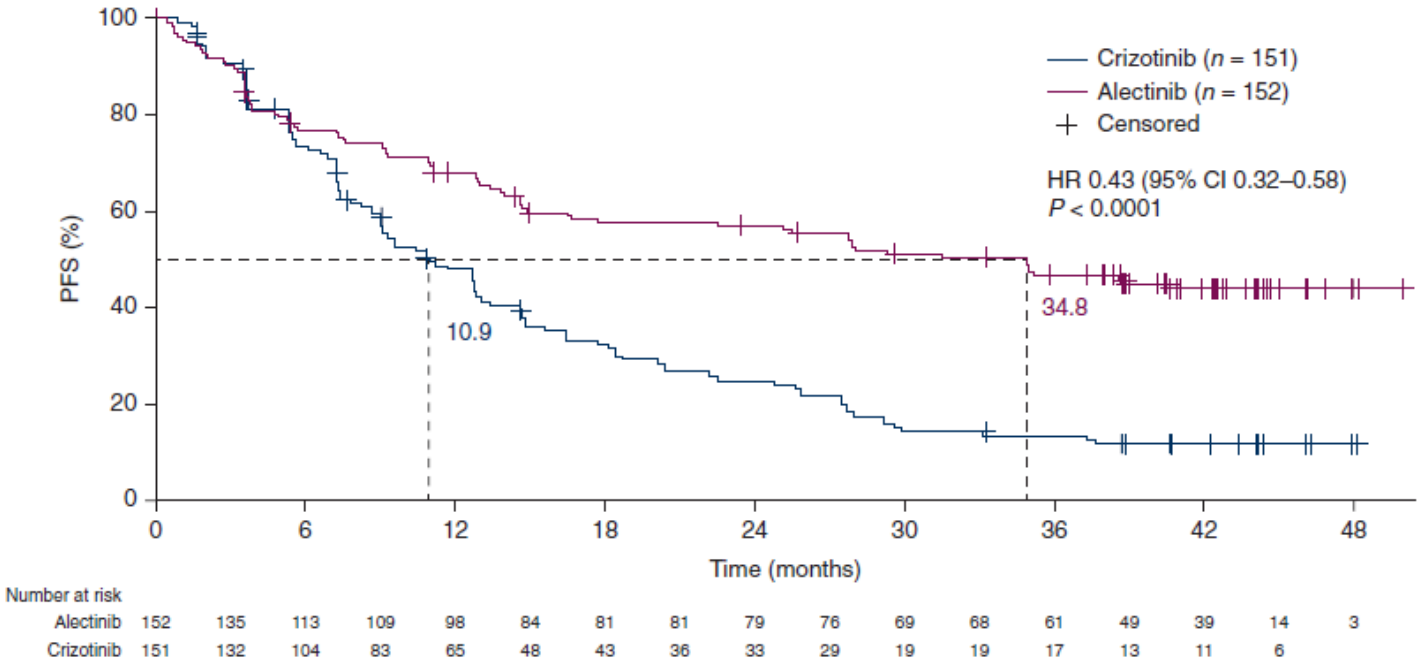
	Crizotinib (N=151)	Alectinib (N=152)
Patients with events, n (%)	102 (68)	62 (41)
Median PFS, months (95% CI)	**11.1** (9.1–13.1)	**NR** (17.7–NR)
HR (95% CI) P-value (log-rank test)	**0.47** (0.34–0.65) P<0.0001	

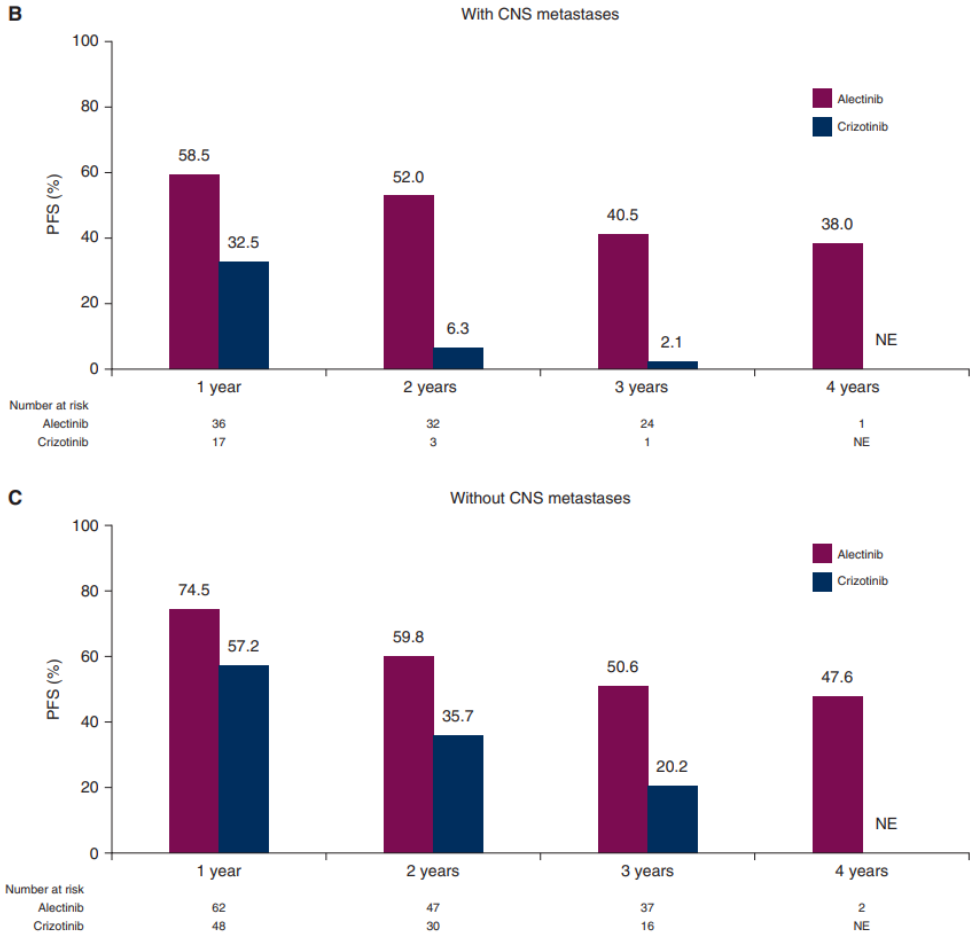


Peters et al NEJM 2017

Global ALEX: Updated Results

Alectinib is Superior to Crizotinib as First-Line Therapy





Peters et al NEJM 2017; Mok T et al Annals of Oncology 2020

Case

- Patient continued on alectinib for another ~1.5 years before PET/CT indicated increased FDG intensity within mid esophagus
- EUS Bx was performed which showed malignant cells that are consistent with metastatic adenocarcinoma of lung origin
- NGS testing was ordered and showed EML4-ALK fusion present and new ALK p.G1202R resistance mutation present

Genomic Sequencing Findings	Allele Frequency	FDA-Approved Therapies in patient's tumor*	FDA-Approved Therapies in other tumor type*
AKT3 Amplification	N/A	None	None
ALK (c.3604G>A, **p.G1202R**)	42%	None	None
EML4-ALK Fusion	N/A	Brigatinib, Crizotinib, Lorlatinib, Alectinib, Ceritinib	Crizotinib
EGFR Amplification	N/A	None	None
MDM4 Amplification	N/A	None	None
TUMOR MUTATIONAL BURDEN STATUS (TMB)			
Cannot be determined			
MICROSATELLITE STATUS (MSI)			
Stable			
PD-L1 22C3 FDA (KEYTRUDA) for NSCLC STATUS			
Expressed			
Tumor Proportion Score: 3%			
Intensity: 1+			

Question

Question 6: With the new information gathered from the patient's molecular testing, what therapy would you recommend?

- **Continue alectinib**
- **Lorlatinib**
- **Brigatinib**
- **Ceritinib**

Case

- Patient was initiated on lorlatinib 100 mg daily and has continued with stable disease since (for ~2 years)
- Brain metastases stable since SRS to occipital lesion
- Lorlatinib has been shown to have therapeutic efficacy in ALK resistance mutations including G1202R

Mutations and ALK Inhibitors

Clinical benefit
% of patients with only this mutation achieving clinical benefit or sensitivity on sequential treatment

Relapsing
% of patients relapsing on this inhibitor harboring only this mutation

Three or more patients with treatment results

Relapsing \ Clinical benefit	>66%	33-66%	<33%
<5%	Likely beneficial	Possibly beneficial	No benefit expected
5-9%	Possibly beneficial	Conflicting evidence	No benefit expected
≥10%	Conflicting evidence	No benefit expected	No benefit expected

Two or less patients with treatment results

Relapsing \ Clinical benefit	100%	50%	0%	No patients treated
<5%	Possibly benefidial	Insufficient evidence	No benefit expected	Insufficient evidence
5-9%	Possibly beneficial	No benefit expected	No benefit expected	No benefit expected
≥10%	No benefit expected	No benefit expected	No benefit expected	No benefit expected

	Alectinib	Brigatinib	Ceritinib	Crizotinib	Lorlatinib
C1156Y	**Likely beneficial** Relapsing: **1/82 (1%)** Sensitivity: **5/5 (100%)**	Possibly beneficial Relapsing: **0/32 (0%)** Sensitivity: **1/1 (100%)**	Possibly beneficial Relapsing: **3/53 (6%)** Sensitivity: **2/3 (67%)**	No benefit expected Relapsing: **22/220 (10%)** No patients treated	Insufficient evidence Relapsing: 1/34 (3%) Sensitivity: 1/2 (50%)
I1171N	No benefit expected Relapsing: **17/82 (21%)** No cases treated	No benefit expected Relapsing: **1/32 (3%)** Sensitivity: **0/3 (0%)**	**Likely beneficial** Relapsing: **0/53 (0%)** Sensitivity: **6/6 (100%)**	Insufficient evidence Relapsing: 0/220 (0%) No patients treated	Possibly beneficial Relapsing: **1/34 (3%)** Sensitivity: **1/1 (100%)**
I1171S	No benefit expected Relapsing: **6/82 (7%)** No cases treated	Possibly beneficial Relapsing: **0/32 (0%)** Sensitivity: **1/1 (100%)**	Insufficient evidence Relapsing: 0/53 (0%) No patients treated	Insufficient evidence Relapsing: 1/220 (0.5%) No patients treated	Insufficient evidence Relapsing: 0/34 (0%) No patients treated
I1171T	Possibly beneficial Relapsing: **4/82 (5%)** Sensitivity: **2/2 (100%)**	No benefit expected Relapsing: **0/32 (0%)** Sensitivity: **0/1 (0%)**	**Likely beneficial** Relapsing: **0/53 (0%)** Sensitivity: **3/3 (100%)**	Insufficient evidence Relapsing: 10/220 (4%) No patients treated	Insufficient evidence Relapsing: 0/34 (0%) No patients treated
F1174C	Possibly beneficial Relapsing: **0/82 (0%)** Sensitivity: **1/1 (100%)**	Insufficient evidence Relapsing: 0/32 (0%) No patients treated	Possibly beneficial Relapsing: **3/53 (6%)** Sensitivity: **1/1 (100%)**	No benefit expected Relapsing: **2/220 (0.9%)** Sensitivity: **0/1 (0%)**	Possibly beneficial Relapsing: **0/34 (0%)** Sensitivity: **1/1 (100%)**
F1174L	Possibly beneficial Relapsing: **0/82 (0%)** Sensitivity: **1/1 (100%)**	Possibly beneficial Relapsing: **1/32 (3%)** Sensitivity: **1/1 (100%)**	No benefit expected Relapsing: **3/53 (6%)** Sensitivity: **0/1 (0%)**	Insufficient evidence Relapsing: 9/220 (4%) No patients treated	Insufficient evidence Relapsing: 0/34 (0%) No patients treated
F1174V	Possibly beneficial Relapsing: **0/82 (0%)** Sensitivity: **1/1 (100%)**	Insufficient evidence Relapsing: 1/32 (3%) No patients treated	Insufficient evidence Relapsing: 2/53 (4%) No patients treated	Insufficient evidence Relapsing: 4/220 (2%) No patients treated	Possibly beneficial Relapsing: **0/34 (0%)** Sensitivity: **2/2 (100%)**
L1196M	Conflicting evidence Relapsing: **9/82 (11%)** Sensitivity: **9/11 (82%)**	No benefit expected Relapsing: **2/32 (6%)** Sensitivity: **1/2 (50%)**	Possibly beneficial Relapsing: **3/53 (6%)** Sensitivity: **10/10 (100%)**	No benefit expected Relapsing: **55/220 (25%)** No cases treated	**Likely beneficial** Relapsing: **1/34 (3%)** Sensitivity: **7/10 (70%)**
G1202R	Conflicting evidence Relapsing: **26/82 (32%)** Sensitivity: **4/6 (67%)**	No benefit expected Relapsing: **10/32 (31%)** Sensitivity: **2/4 (50%)**	No benefit expected Relapsing: **19/53 (36%)** Sensitivity: **1/2 (50%)**	No benefit expected Relapsing: **16/220 (7%)** No cases treated	**Likely beneficial** Relapsing: **1/34 (3%)** Sensitivity: **17/22 (77%)**
G1269A	**Likely beneficial** Relapsing: **0/82 (0%)** Sensitivity: **2/3 (67%)**	Insufficient evidence Relapsing: 0/32 (0%) Sensitivity: 1/2 (50%)	**Likely beneficial** Relapsing: **0/53 (0%)** Sensitivity: **2/3 (67%)**	No benefit expected Relapsing: **34/220 (16%)** No cases treated	**Likely beneficial** Relapsing: **1/34 (3%)** Sensitivity: **5/5 (100%)**
L1196M G1202R	Insufficient evidence Relapsing: 2/82 (2%) No patients treated	Insufficient evidence Relapsing: 1/32 (3%) No patients treated	Insufficient evidence Relapsing: 0/53 (0%) No patients treated	Insufficient evidence Relapsing: 0/220 (0%) No patients treated	No benefit expected Relapsing: **4/34 (12%)** Sensitivity: **0/1 (0%)**

Koopman B et al, Clinical Lung Cancer 2022

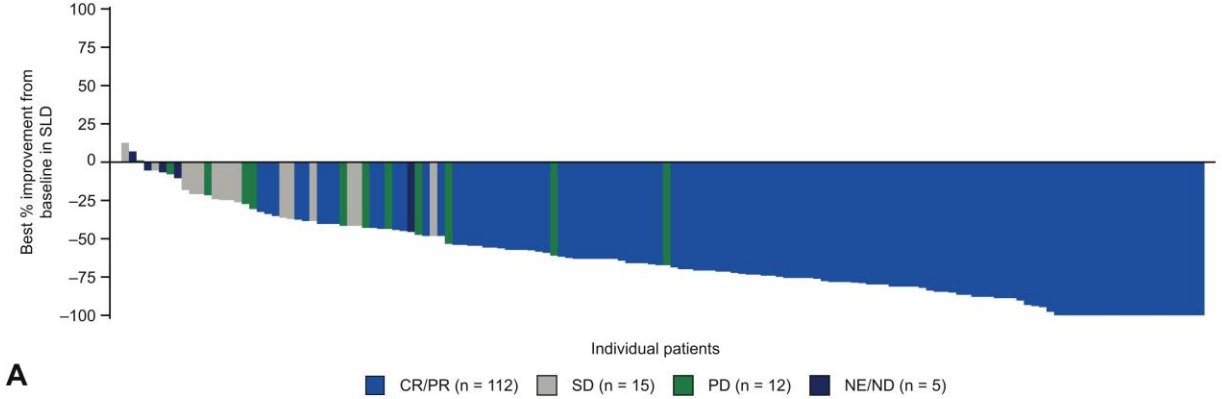
Question

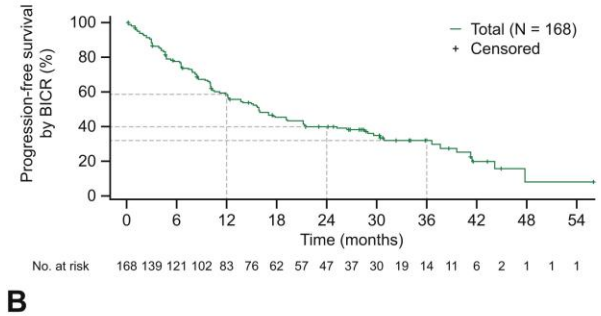
Question 7: If patient had ROS1 fusion and brain metastases, what therapy would you recommend as first line?

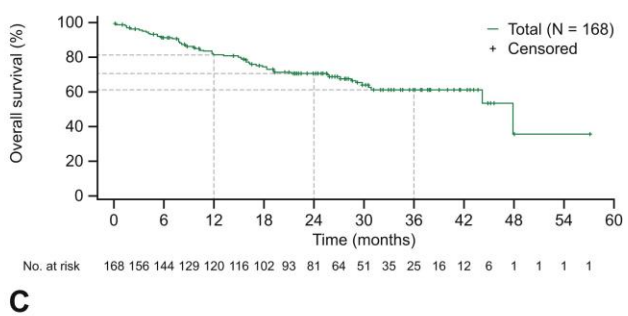
- **Entrectinib**
- **Repotrectinib**
- **Crizotinib**
- **Ceritinib**
- **Either 1 or 2**

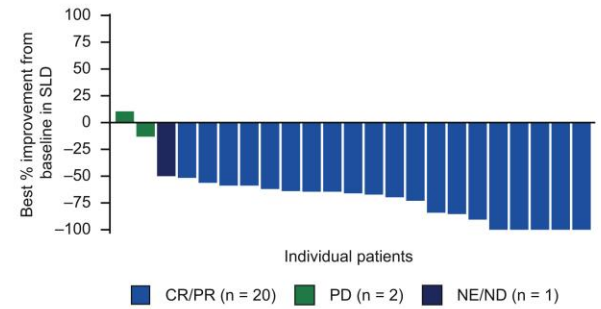
Entrectinib in ROS1-positive patients

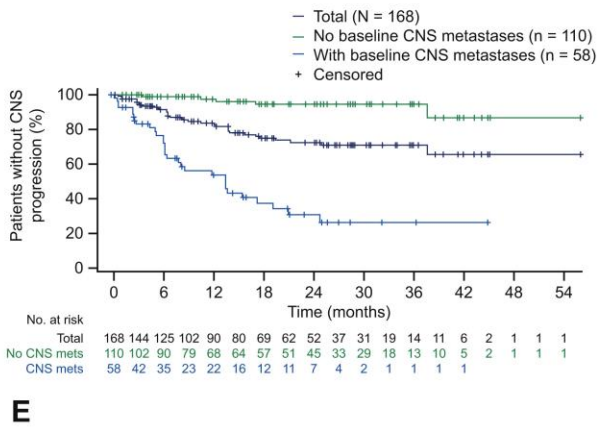
CNS Post-crizotinib

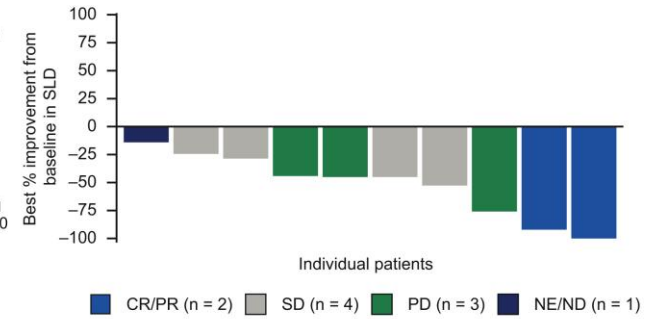


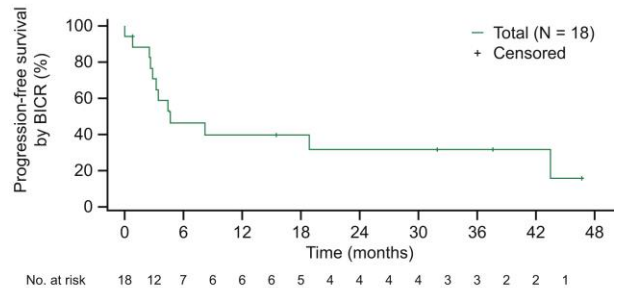


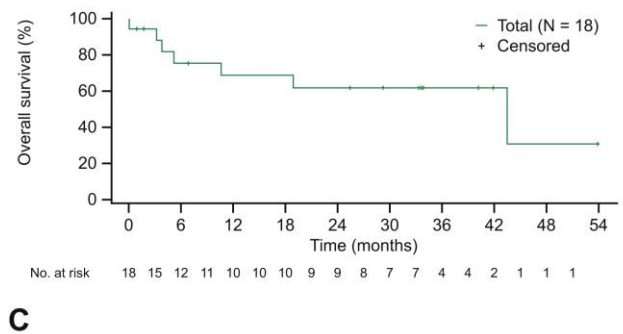


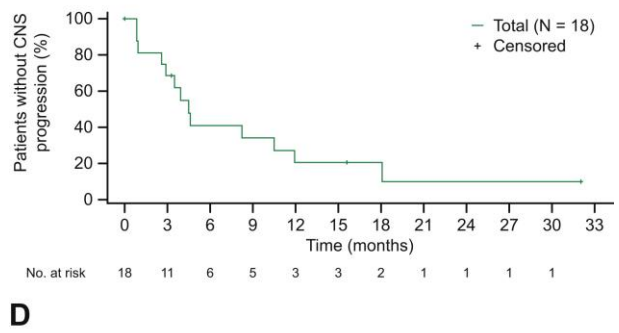












Drilon A. et al, JTO Clinical and Research Reports 2022

RESEARCH SUMMARY

Repotrectinib in *ROS1* Fusion–Positive Non–Small-Cell Lung Cancer

Drilon A et al. DOI: 10.1056/NEJMoa2302299

CLINICAL PROBLEM

ROS1 fusions occur in up to 2% of patients with non–small-cell lung cancer (NSCLC). Early-generation ROS1 tyrosine kinase inhibitors (TKIs) have antitumor activity, but resistance mutations develop in at least half the patients. Repotrectinib is a next-generation ROS1 TKI that has shown preclinical activity against *ROS1* fusion–positive cancers, including those with resistance mutations.

CLINICAL TRIAL

Design: An international, phase 1–2 trial assessed the efficacy and safety of repotrectinib in patients with advanced solid tumors, including *ROS1* fusion–positive NSCLC.

Intervention: 103 patients were treated in the phase 1 dose-escalation trial; 416 were treated in phase 2 and received 160 mg of repotrectinib once daily for 14 days, followed by 160 mg twice daily until disease progression or unacceptable toxic effects had occurred or consent was withdrawn. The primary end point in phase 2 was a confirmed objective response.

RESULTS

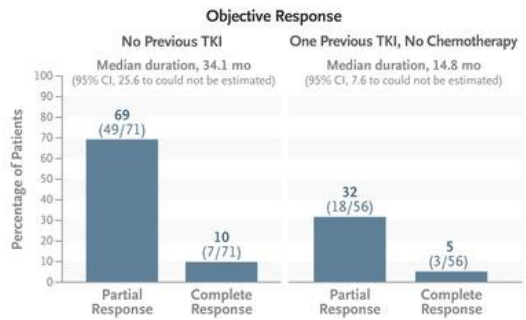
Efficacy: A response occurred in nearly 80% of patients with *ROS1* fusion–positive NSCLC who had not previously received a ROS1 TKI, in 38% of those who had previously received one ROS1 TKI and had never received chemotherapy, and in nearly 60% of those who had previously received at least one ROS1 TKI and had the *ROS1* G2032R resistance mutation at baseline.

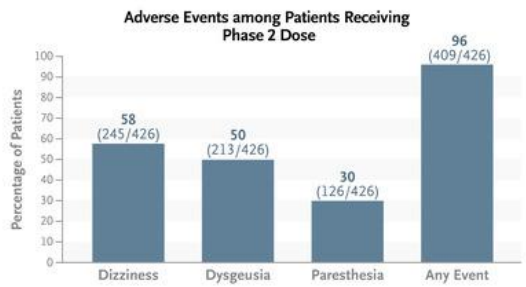
Safety: Among the patients who received the phase 2 dose of repotrectinib, the most common treatment-related adverse events of any grade were dizziness, dysgeusia, and paresthesia. Most adverse events were grade 1 or 2 in severity.

LIMITATIONS AND REMAINING QUESTIONS

- The trial is limited by its single-group design and by its small sample size resulting from the rarity of *ROS1* fusion–positive NSCLC.
- Longer-term data on efficacy and safety are needed.

Links: Full Article | NEJM Quick Take





CONCLUSIONS

Treatment with repotrectinib led to durable responses in a substantial percentage of patients with *ROS1* fusion–positive NSCLC, including patients who had previously received a ROS1 TKI and those who had not previously received a ROS1 TKI.