If You have Lungs, You are at risk for Lung Cancer.

Discussion of Lung Cancer Cases in Non-smokers

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Disclosure

- Mohamed K Mohamed, MD, PhD

Honoraria for speaker engagements for BMS, Astra Zeneca, Regeneron and G1 Therapeutics.

CASE 1
56 YOM, Never Smoker Fitness Trainer

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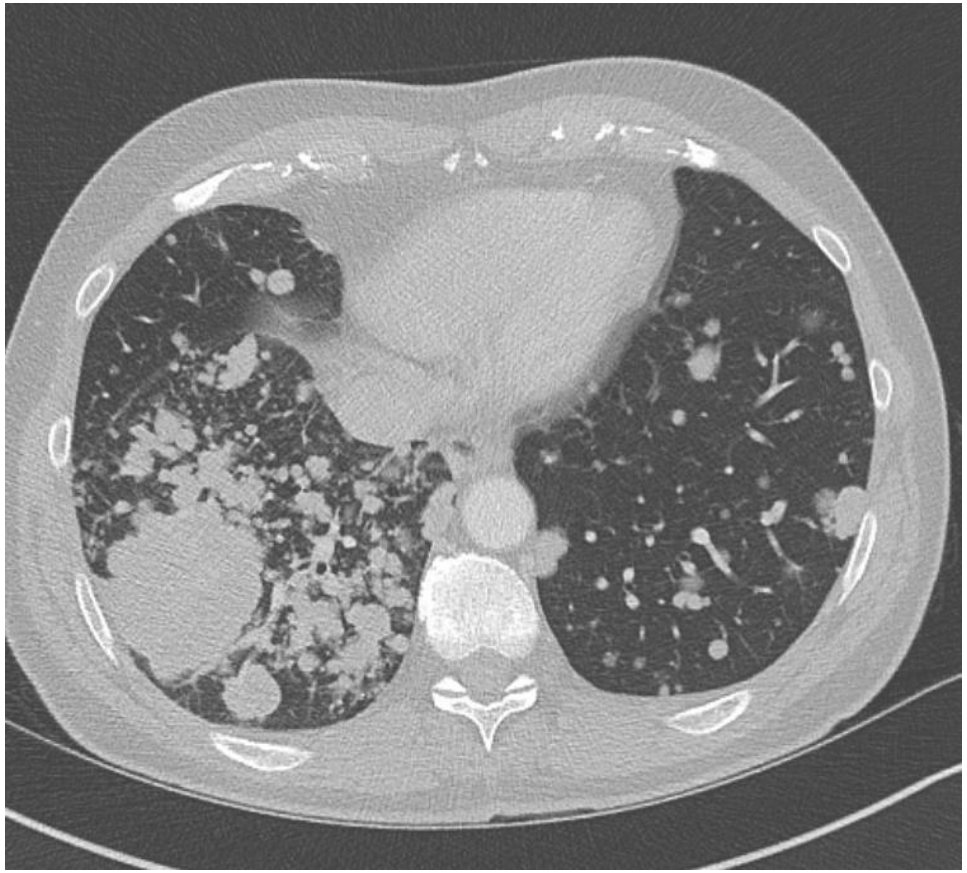
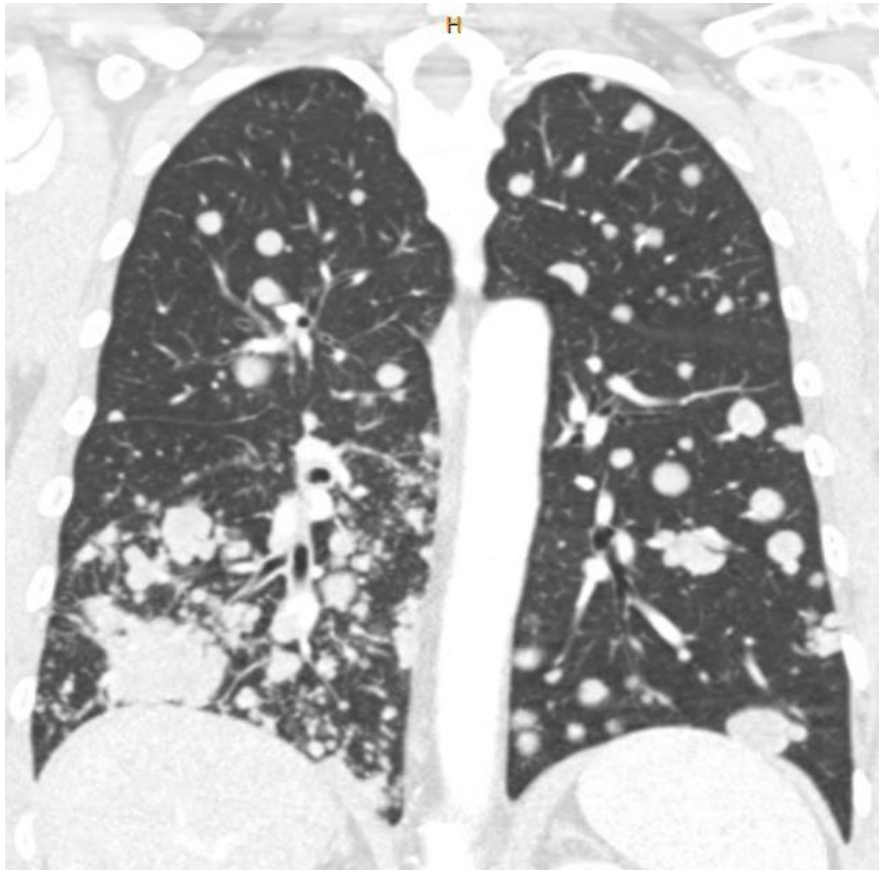
- This patient has history of ulcerative colitis and stage I Melanoma, treated with wide excision 11 years ago presented with cough and chest congestion during Christmas.
- Many family members were sick at that time. All recovered but him. He continues to have persistent cough with low-grade fever and worsening shortness of breath.
- PCP treated him for sinus infection with no improvement. Six weeks later, his symptoms were getting worse. He was seen at one of the urgent care center and chest x-ray was suspicious for pneumonia. He was referred to a pulmonologist.
- CT Chest showed widespread pulmonary metastatic disease with mediastinal and right hilar and cervical adenopathy. With history of melanoma, the radiologist thought it is most concerning for melanoma metastases but with a dominant mass and greatest involvement in the right lower lobe. PET scan and MRI brain with no new findings.
- Bronchoscopy with EBUS were performed and the pathology was consistent with Primary Lung Adenocarcinoma. (tumor cells are positive for CK7, TTF-1 while they are negative for CK20, CDX2, p63, CK5/6, GATA3 and S100).

56 YOM with stage IV NSCLC, Adenocarcinoma





Discussion Questions

- The patient is symptomatic from his disease. What do you do?

  a) Start treatment with systemic Chemotherapy +/- Immunotherapy?.

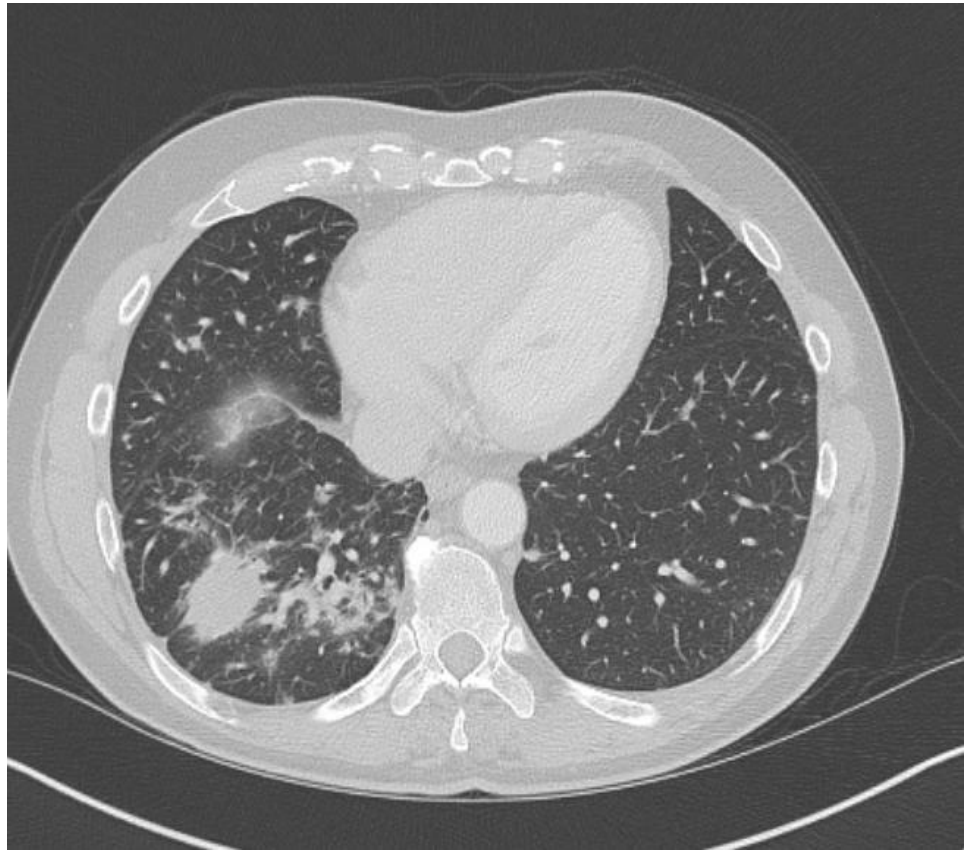
  b) Send Tissue to Molecular studies and wait for results 2-3 weeks? What Platform would you use?

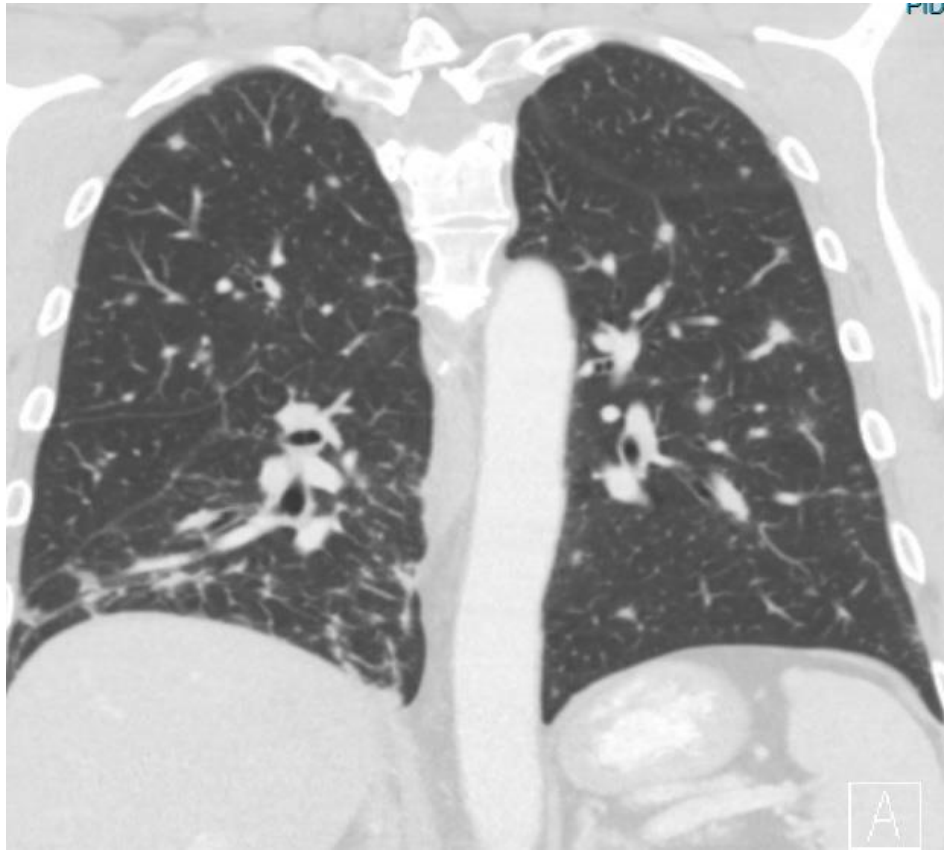
  Sequential PCR tests, NGS tissue, NGS liquid, or concurrent NGS Tissue and liquid?

  c) If his Molecular studies are negative for actionable mutation, What treatment do you use?

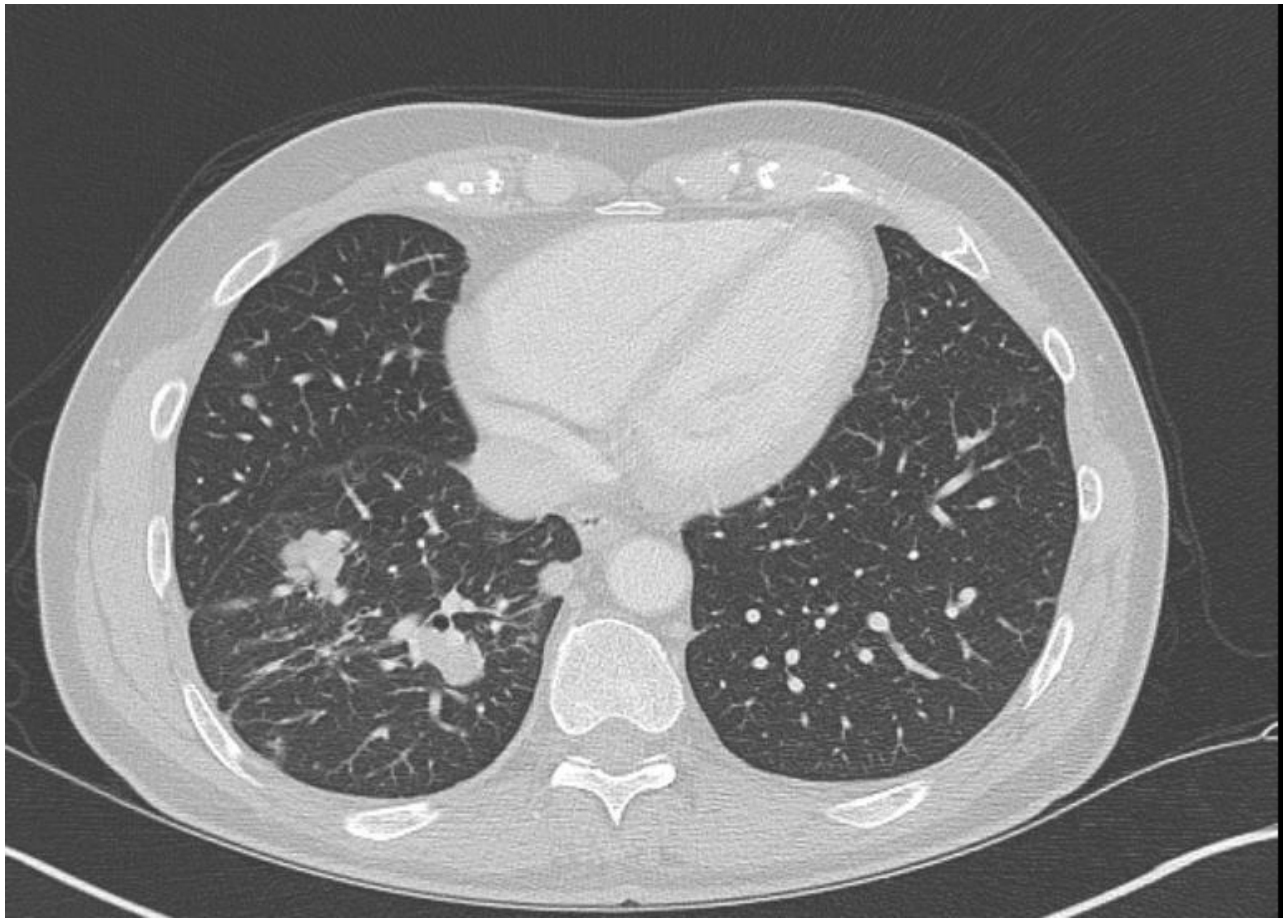
- Molecular studies were done with Concurrent NGS Tissue and liquid.
- The Liquid results were reported 5 days later and showed **Positive EGFR Exon 19 deletion**. PDL1 was 20%. Tissue NGS Results 2 weeks later confirmed the EGFR mutation.
- Questions:
- 1) Based on the above finding how would you treat this patient 16 months ago vs today?
- 2) If he has brain metastases or EGFR (L858R) mutations, would you treat him differently?
- 3) What are the current and potential future treatment options for Patients with Positive EGFR mutations?

56 YOM with stage IV NSCLC, Adenocarcinoma and EGFR mutation at 6 wks after Osimeritinib



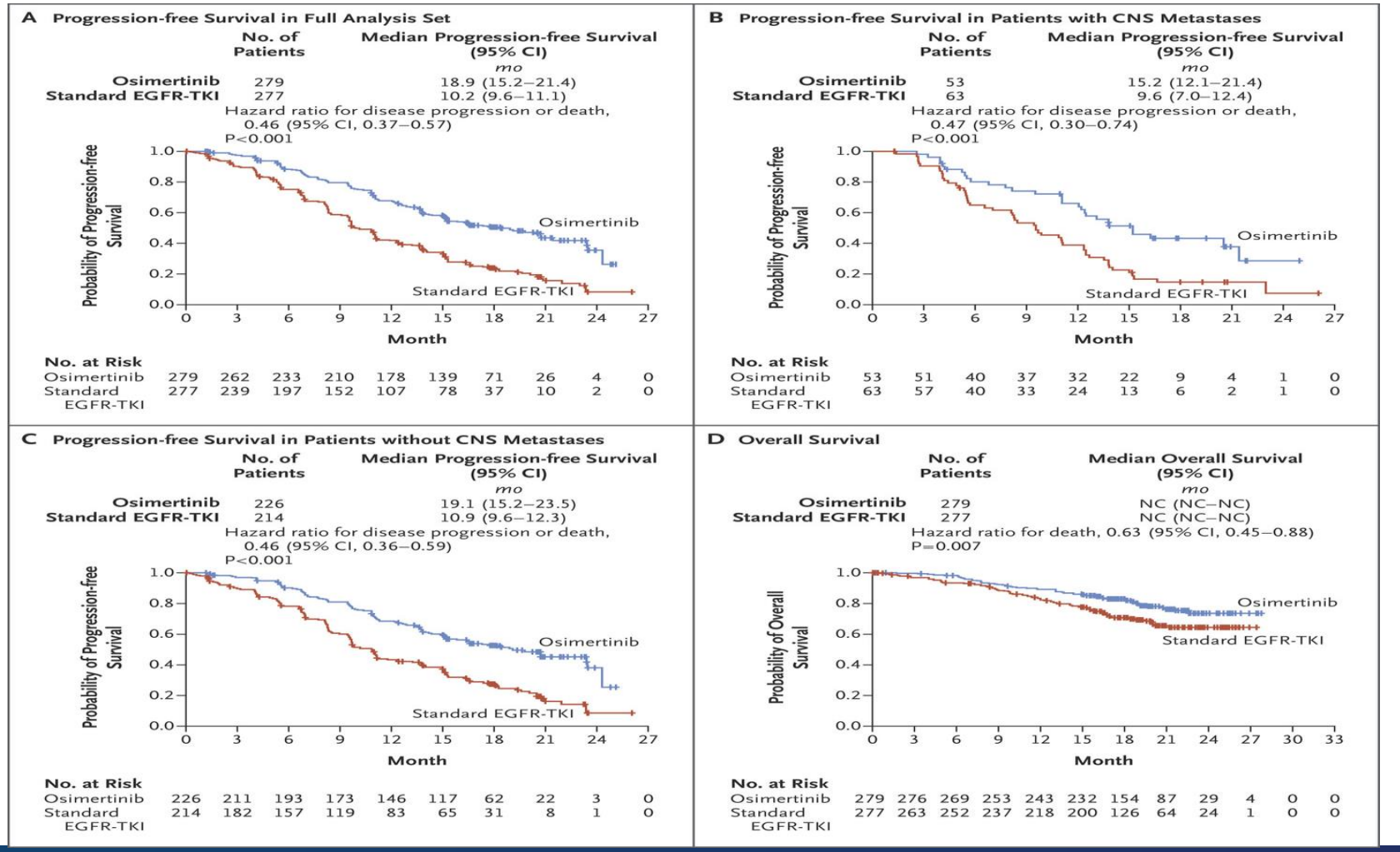


After 14 Months of Treatment with Osimertinib, the patient has 2 enlarging Nodules in the right lung.
What would you do next?



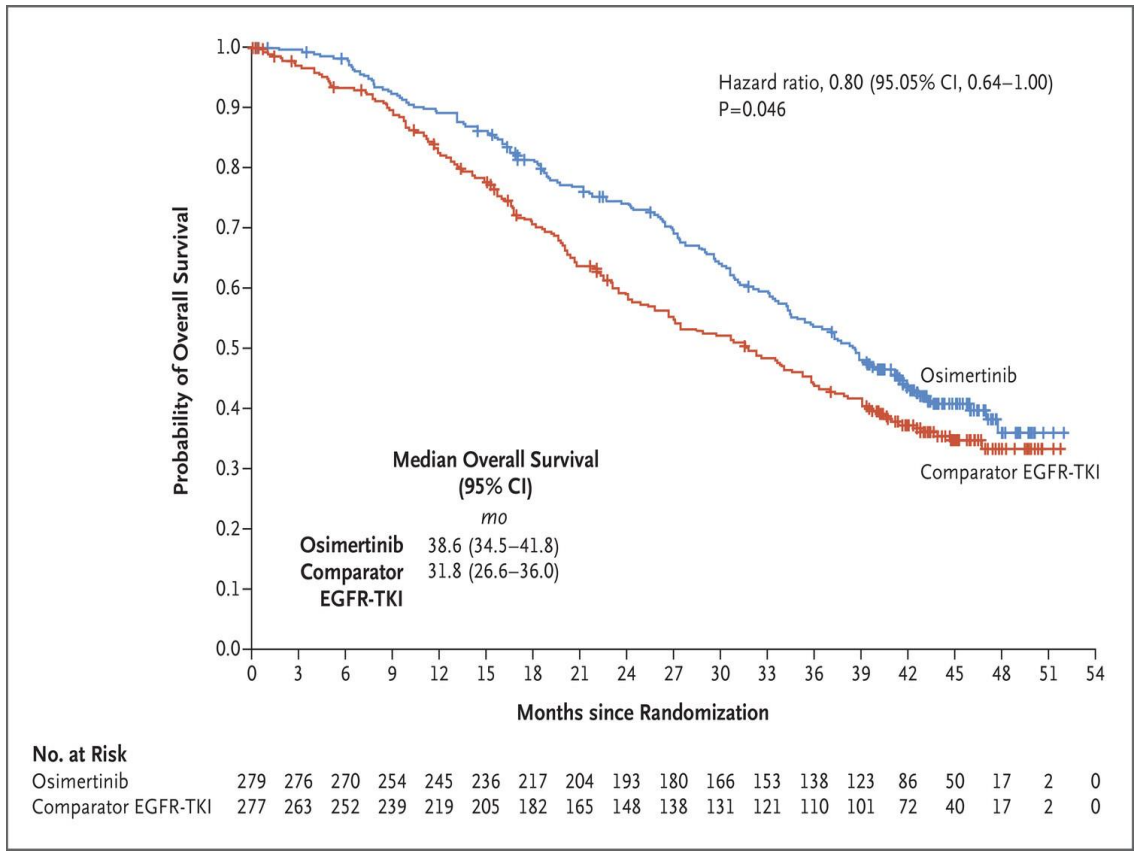
FLAURA: Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

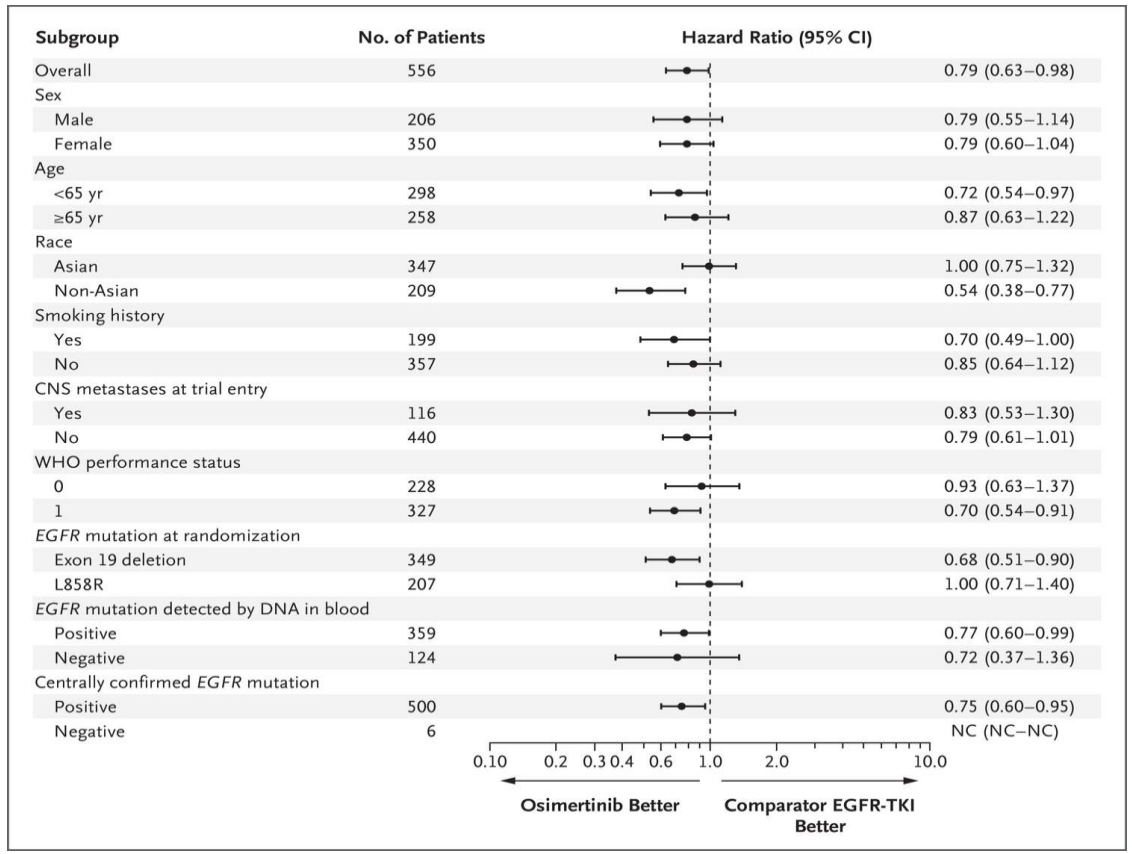
Soria et al N Engl J Med 2018;378:113-125



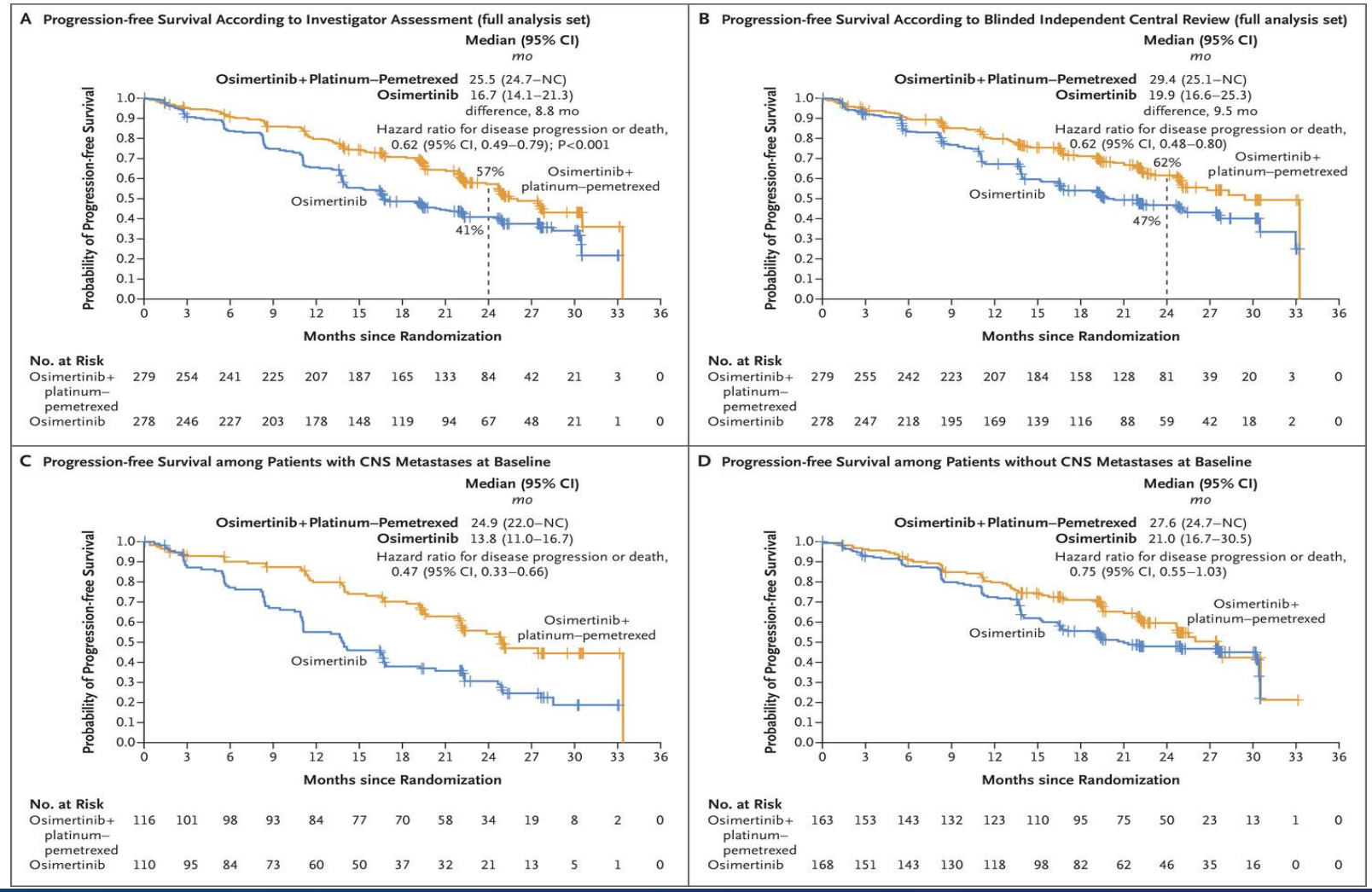
FLAURA: Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

Ramalingam etal, N Engl J Med 2020;382:41-50





FLAURA 2: Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC. Planchard et al. N Engl J Med 2023;389:1935-1948



MARIPOSA: Can Amivantamab and Lazertinib Replace Osimertinib in the Front-Line Setting?

Danielle Brazel and Misako Nagasaka, Lung Cancer (Auckl).2024; 15: 41-47.

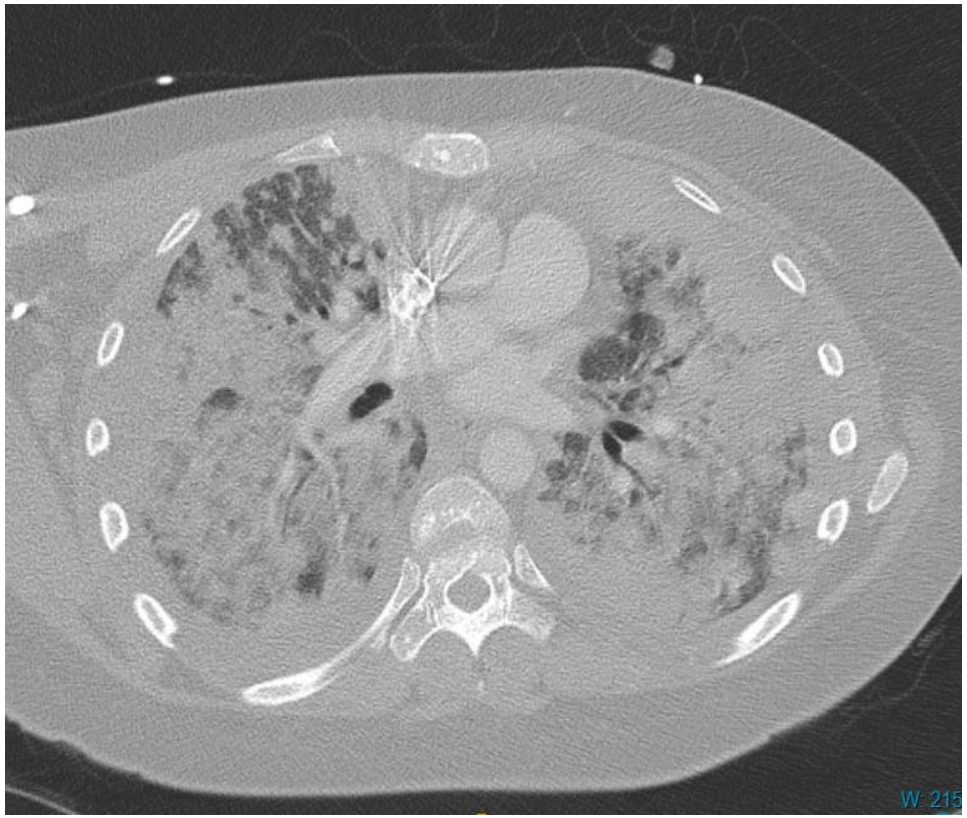
- Amivantamab is a bispecific antibody against EGFR and MET alterations. Lazertinib is a tyrosine kinase inhibitor active against EGFR mutations including common resistance mutations.
- The MARIPOSA trial was designed to study if the combination of amivantamab plus lazertinib in untreated epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) patients would provide improved progression-free survival.
- Amivantamab plus lazertinib reduced the risk of progression or death by 30% (95% CI 0.58–0.85, p<0.001).[26] The combination improved median PFS by 7.1 months (23.7 months on combination therapy; 95% CI 19.1–27.7 vs osimertinib 16.6 months; 95% CI 14.8–18.5) with HR 0.70 (95% CI 0.58–0.85).
- The PFS benefit in patients with brain metastases with amivantamab plus lazertinib was 18.3 months (95% CI 16.6–23.7) versus osimertinib 13.0 months (95% CI 12.2–16.4). Combination amivantamab plus lazertinib improved median DOR by 9 months (25.8 vs 16.8).

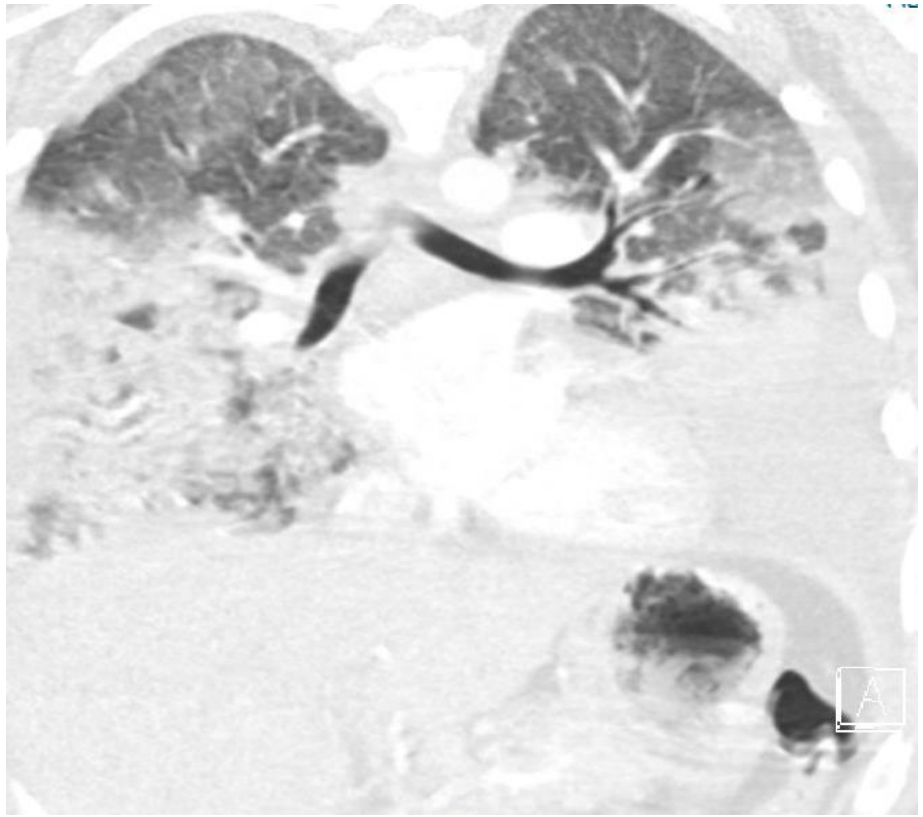
CASE 2
32 YOF Never Smoker Artist

32 YOF Never Smoker Artist

- The patient was admitted to the hospital on January 29, 2021 complaining of tachycardia, shortness of breath with exertion and intolerance to exercises started since October 2020. She was seen by her primary care physician but she was found to have significant tachycardia with heart rate of 154 and she was transferred to the hospital for evaluation.
- CTA of the chest showed no PE but there was extensive peripheral predominant areas of patchy consolidated airspace disease throughout both lungs was suspicious for multifocal pneumonia. The patient was treated for community-acquired pneumonia and IV fluid.
- March 24, 2021 presented again to the ED with worsening dyspnea and now requiring Oxygen 4-6L/min to keep her O2 sat above 90%.
- Repeat CTA showed progression of the multifocal bilateral airspace disease that was seen previously on the previous scan. The persistent appearance was favoring atypical bacterial or fungal pneumonia and bronchoscopy was recommended.
- Bronchoscopy showed poorly differentiated carcinoma with signet ring features. By immunohistochemistry, the neoplastic cells are positive for cytokeratin 7 and TTF-1 but negative for cytokeratin 20 and CDX2 consistent with Lung Primary.

32 YOF Artist with stage IV NSCLC, Adenocarcinoma.





Case Discussion

- Now this patient is very symptomatic and condition is worsening on high O2 demand close to intubation, What do you do?
- PET scan showed additional Bone metastases and MRI brain showed 4 small lesions.
- Immediate Concurrent Tissue NGS and liquid NGS were sent to 2 different vendors at that time.
- Liquid biopsy results were available in 7 days and was negative for any actionable mutation. (No tumor-related somatic alterations were detected in this patient's sample. This may be due to either absence of detectable mutations in the tumor itself or, more commonly, low levels of circulating tumor-derived cell-free DNA (ctDNA). Low ctDNA levels are most often encountered in patients with early stage or low volume disease, patients responding to therapy, and/or patients with stable disease).
- What would be the best course of action at this point?

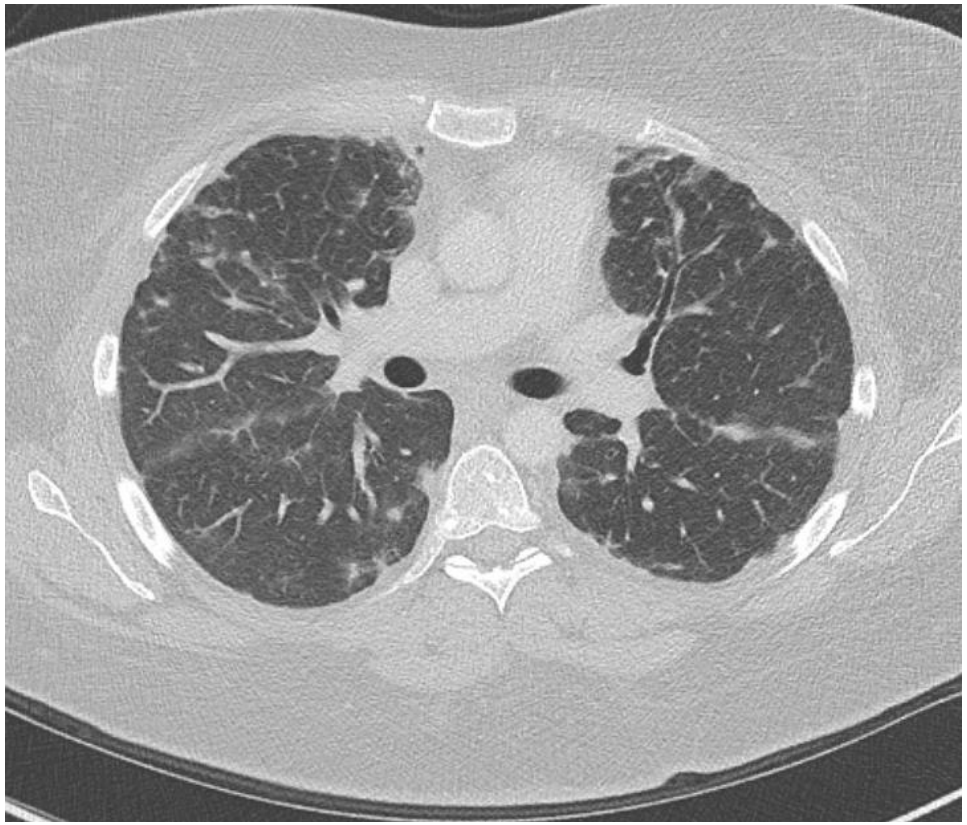
  a) Wait for the tissue biopsy

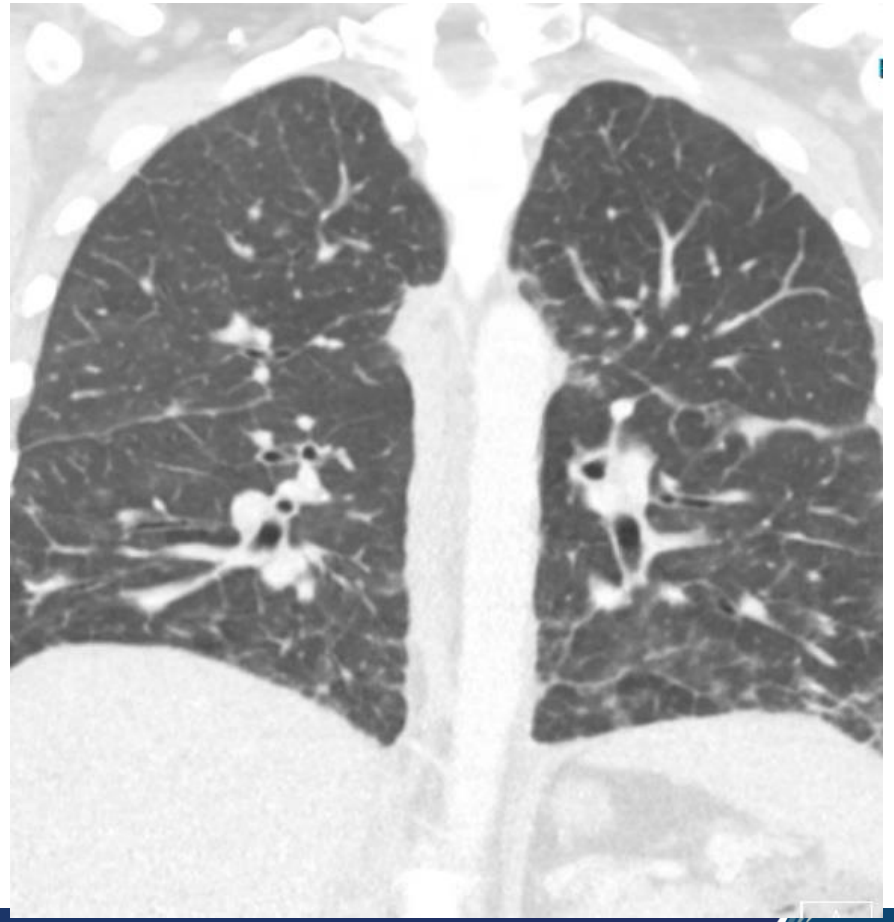
  b) Start Chemotherapy +/- Immunotherapy

  c) Call the palliative care/hospice team

- Fortunately, the Tissue NGS was reported with 10 days and it showed EML4-ALK fusion.
- The patient started treatment with Alectinib during her hospitalization and discharged home 5 days later with no O2 requirement.
- Follow up CT scan in 6 weeks shown next.

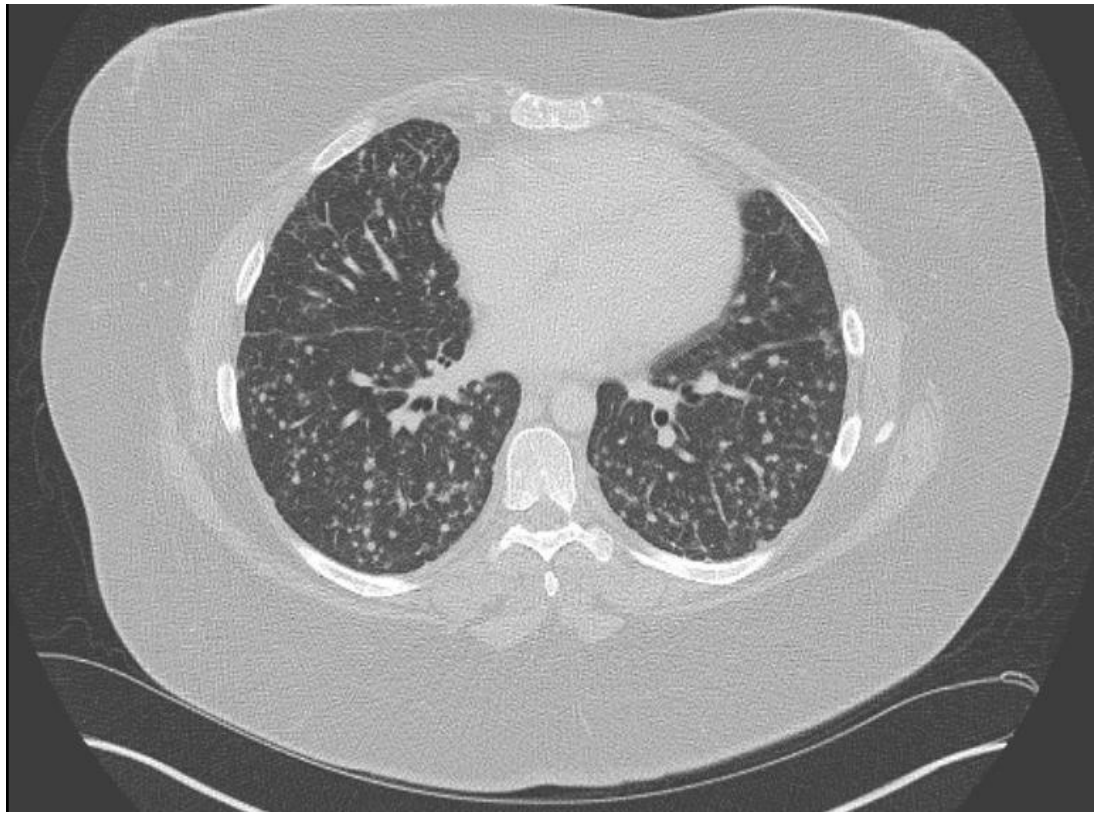
32 YOF Artist with stage IV NSCLC, Adenocarcinoma and ALK Gene Translocation 6 wks after Alectinib treatment





32 YOF Artist with ALK Positive Lung Adenocarcinoma

- After 29 of treatment with Alectinib, her scan showed disease progression with enlarging pulmonary nodules and Worsening bone metastases.
- Treatment was changed to Lorlatinib and responded to it. Has been on treatment for 12 months

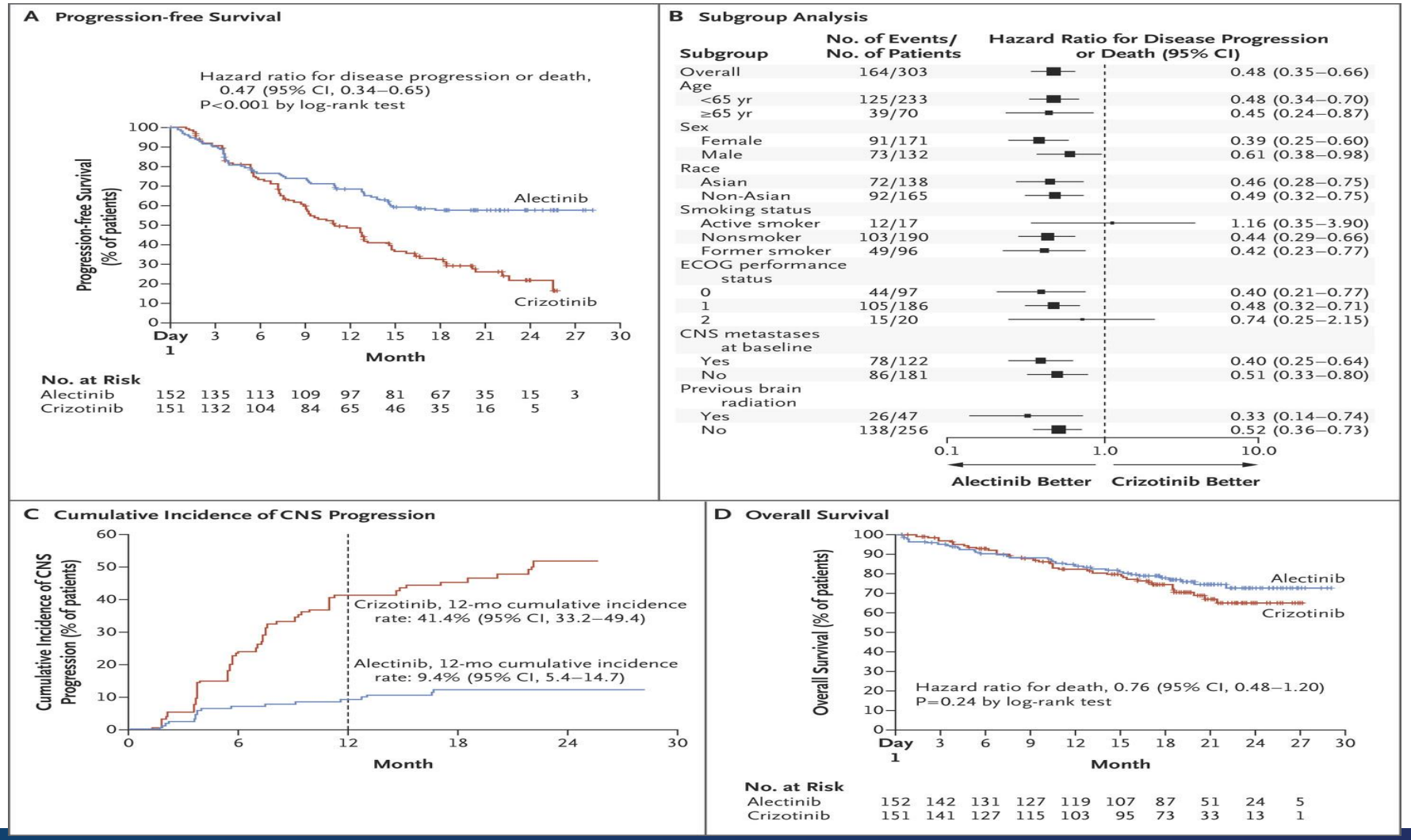


Case Discussion

- What are the limitations for Molecular testing with Liquid or Tissue NGS. Would this case support the concurrent testing?
- If You see this patient today, Would you consider the same treatment options starting with Alectinib followed by Lorlatinib after progression or start with Lorlatinib as first line based on the Crown data presented at ASCO 2024.
- What are the main concerning adverse effects for these products and what monitoring is needed?

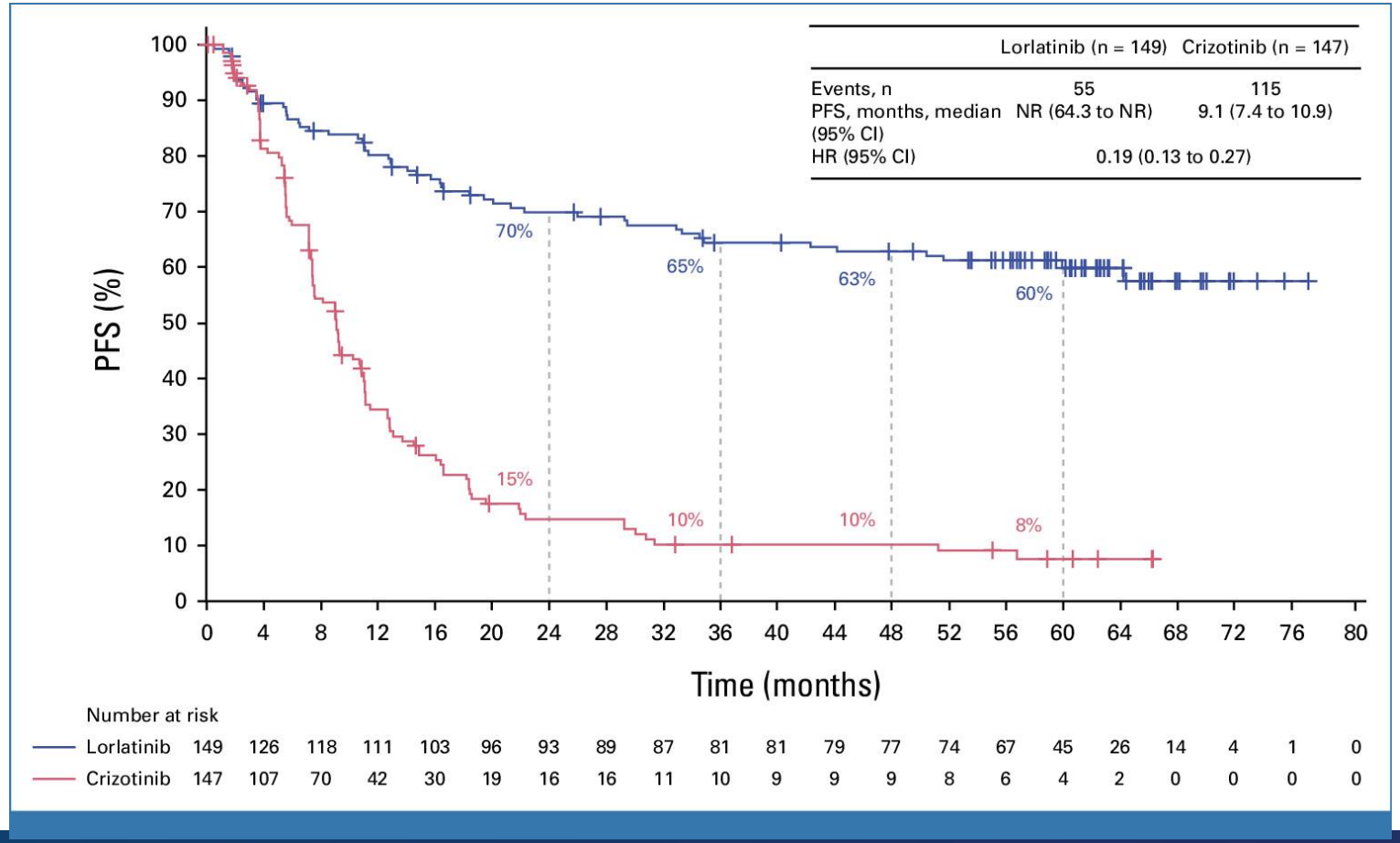
Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

Peters et al N Engl J Med 2017;377:829-838



Lorlatinib Versus Crizotinib in Patients With Advanced *ALK*-Positive Non–Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study

Solomon etal. Journal of Clinical Oncology https://doi.org/10.1200/JCO.24.00581



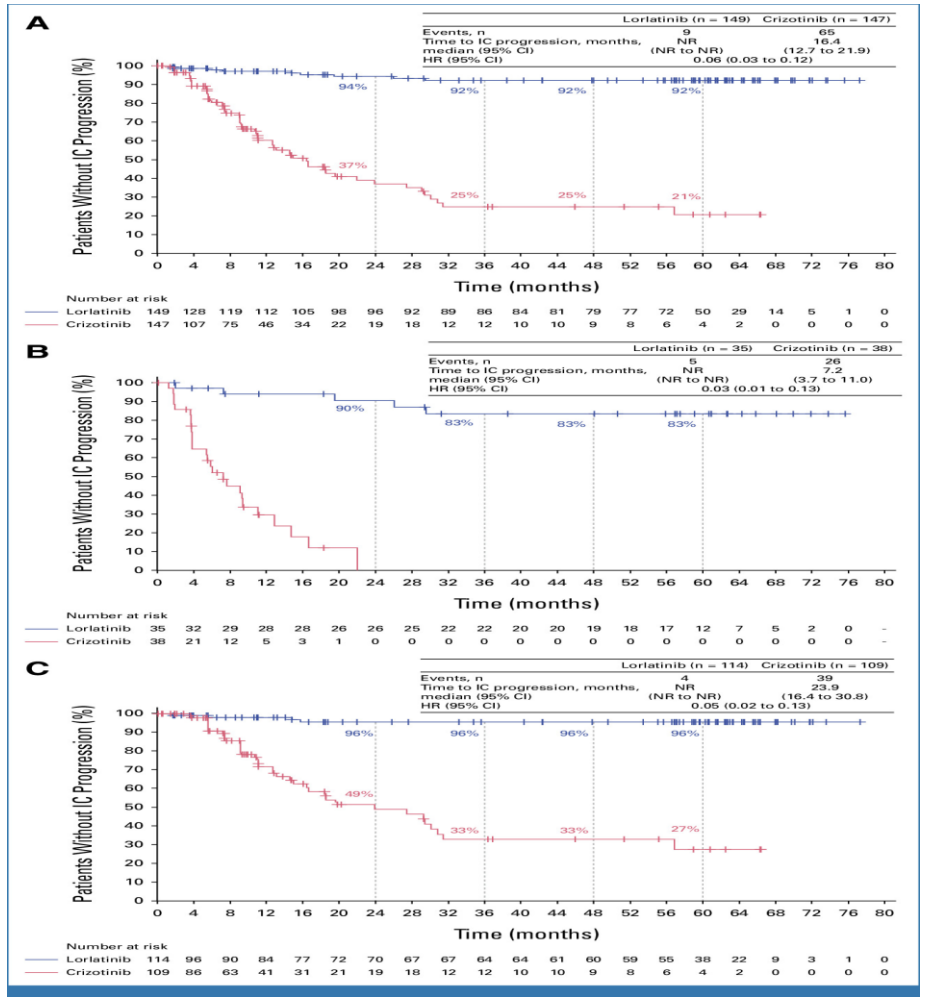
Lorlatinib Versus Crizotinib in Patients With Advanced *ALK*-Positive Non–Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study

Time to intracranial progression by investigator assessment using modified RECIST, version 1.1, in (

A) the intention-to-treat population,

B) (B) patients with baseline brain metastases, and

C) (C) patients without baseline brain metastases. HR, hazard ratio; IC, intracranial; NR, not reached.



CASE 3

35 YOF Never Smoker School Teacher

CASE 3

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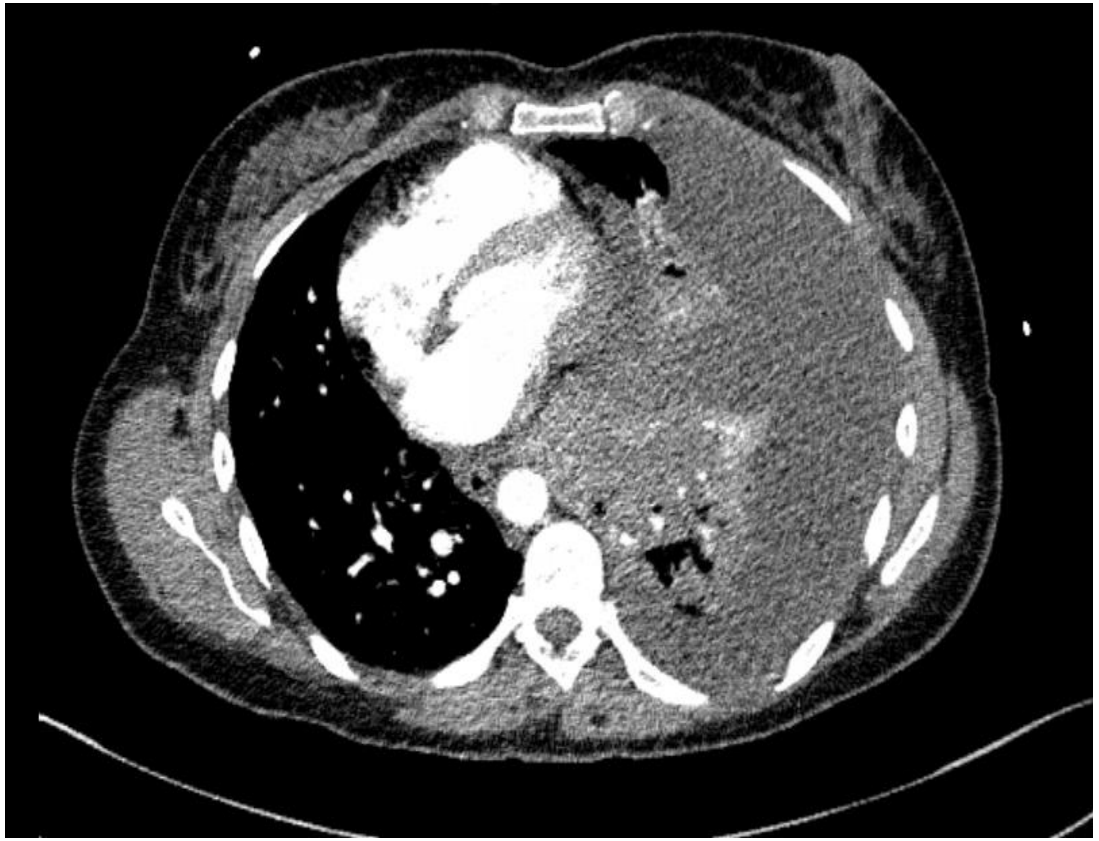
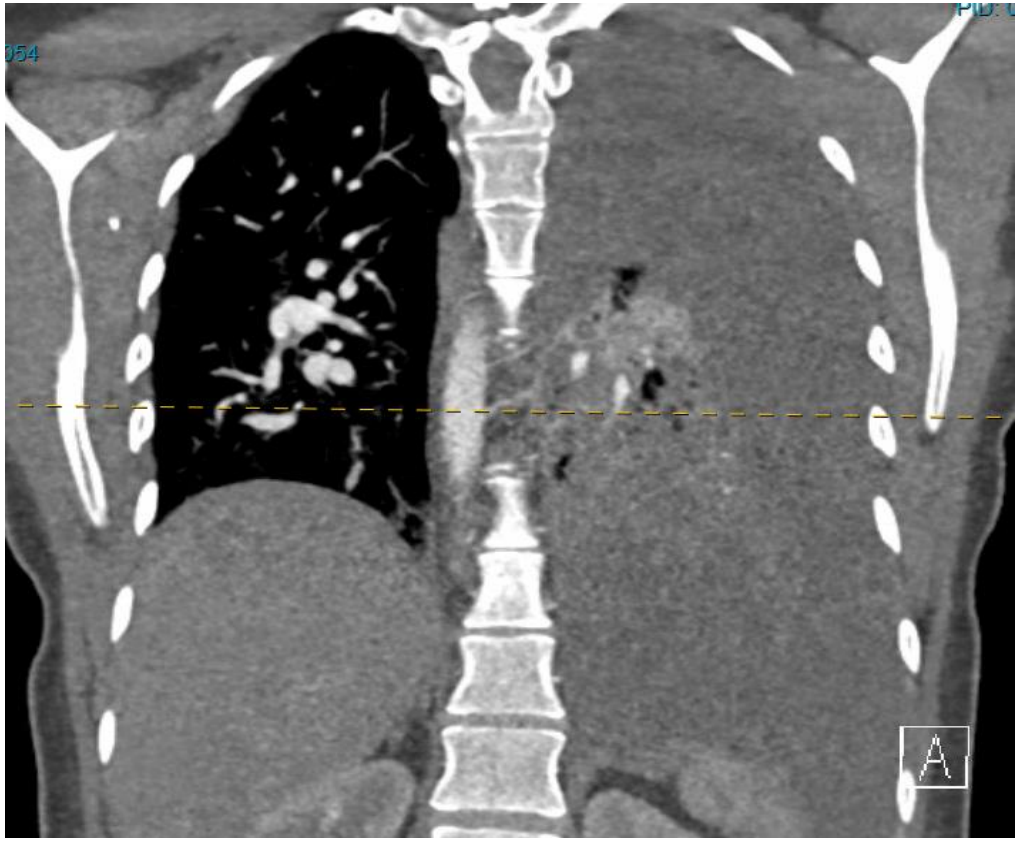
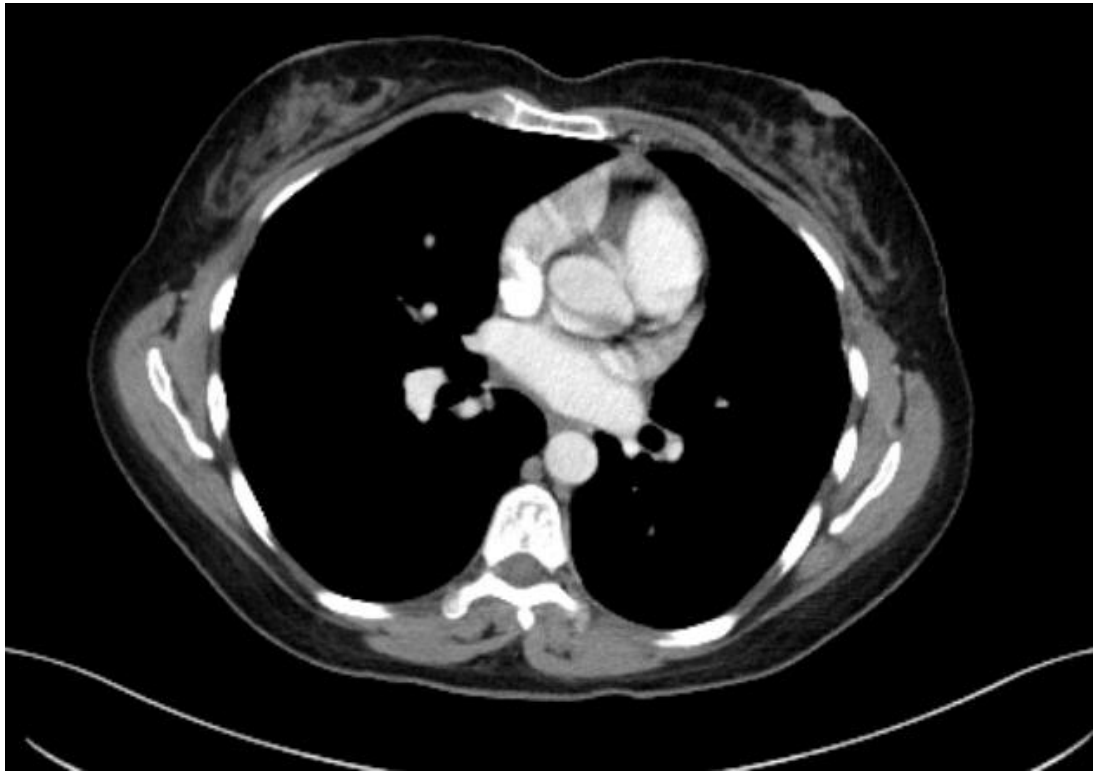
- She has been complaining of persistent cough for 2 months after cold symptoms. She was seen few times at urgent care facilities and treated with courses of antibiotics with no improvement in her condition. Her dyspnea and cough was progressive and she presented to the emergency department.
- CTA of the chest showed no PE but near-complete atelectasis of the lingula and left lower lobe with heterogeneous consolidation resulting in marked narrowing of the left sided airways, likely multifocal pneumonia. Large left pleural effusion.
- The patient underwent US guided left Thoracentesis and the pleural fluid was positive for Primary Lung Adenocarcinoma.
- Concurrent Molecular studies with Liquid and Tissue NGS were performed and both showed Positive EZR-ROS1 fusion. PDL1 was 98%.

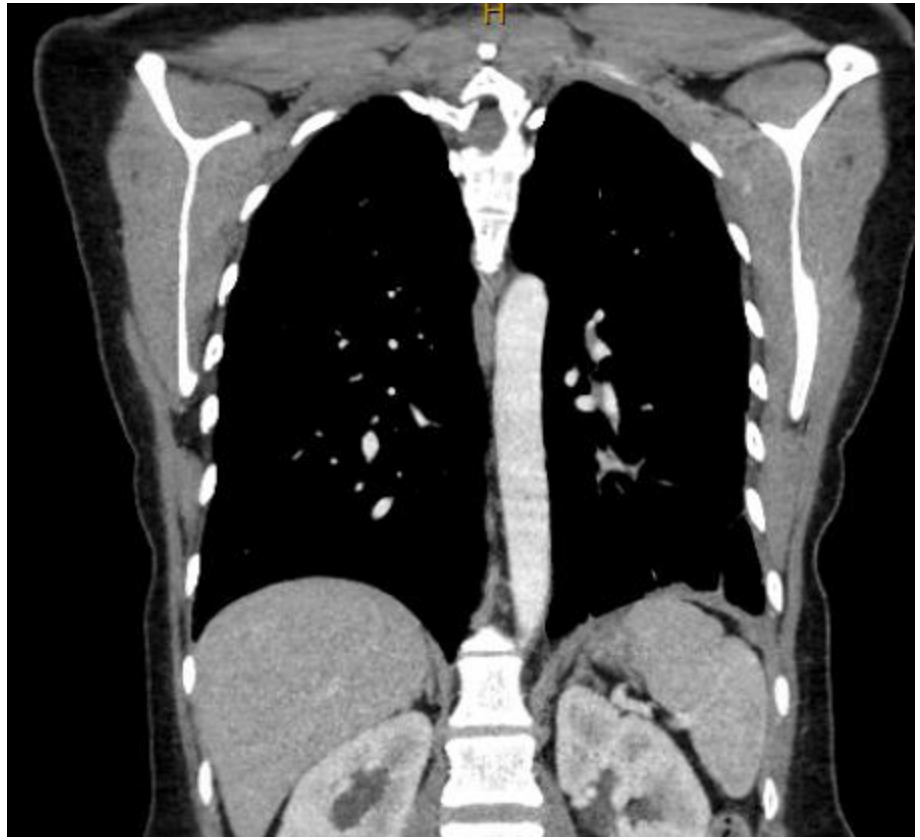
35 YOF Never Smoker School Teacher at presentation





35 YOF Never Smoker School Teacher at presentation with ROS1 fusion after 2 month treatment with Repotrectinib





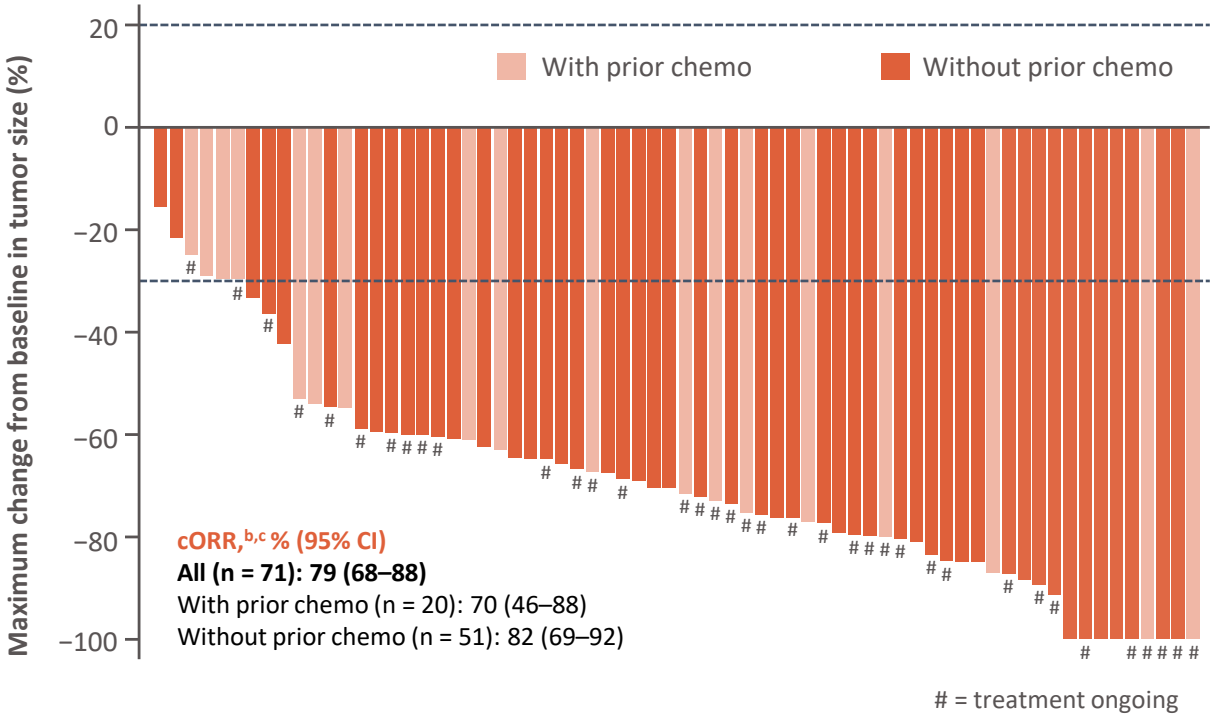
Case Discussion

- How frequently is ROS1 fusion?
- How do you chose between the many options available, Crizotinib, Entrectinib, Repotrectinib or Lorlatinib?
- CNS toxicity especially dizziness is very common. How do you manage it?

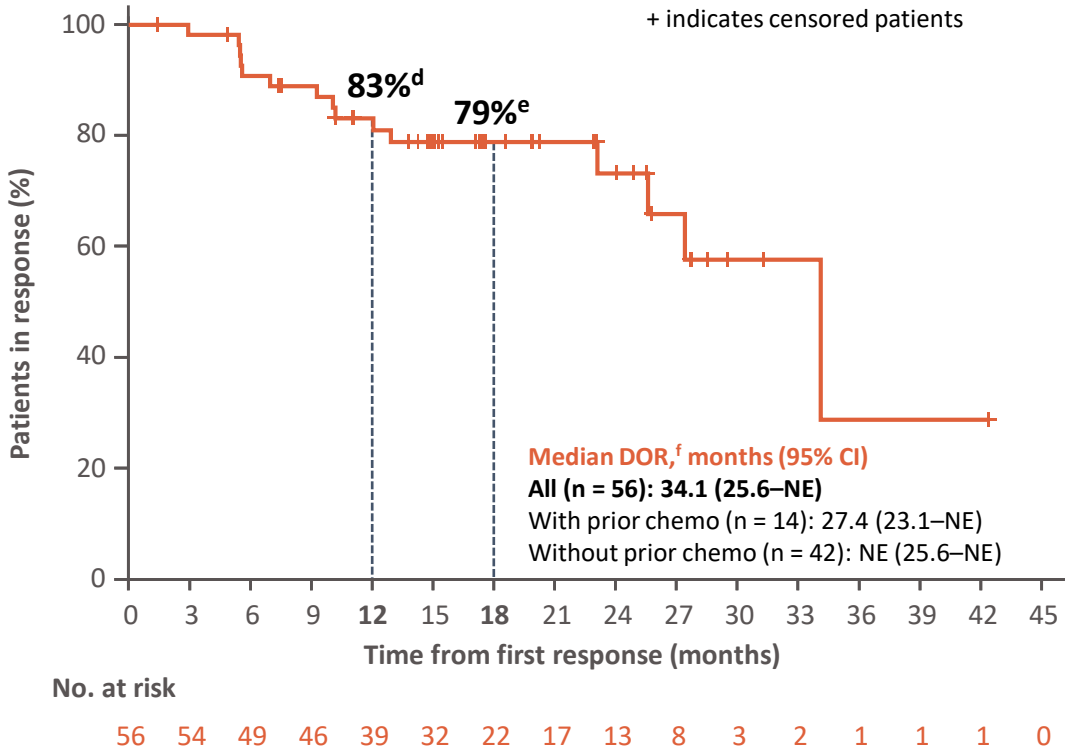
Repotrectinib in *ROS1* Fusion–Positive Non–Small-Cell Lung Cancer

Drilon et al, N Engl J Med 2024;390:118-131

Change in tumor burden per BICR[a]



DOR

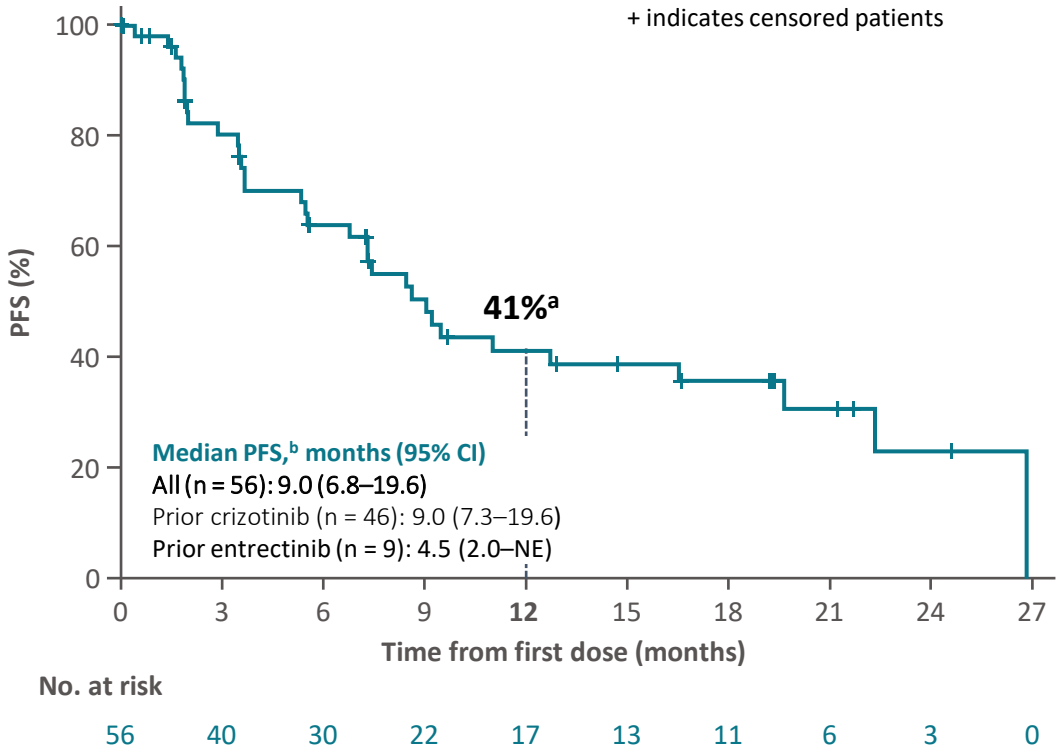


- Of patients in the ROS1 TKI-naïve cohort treated at the RP2D (n = 63), cORR was 78% (95% CI, 66–87) and median DOR was NE (95% CI, 25.6–NE)[g]

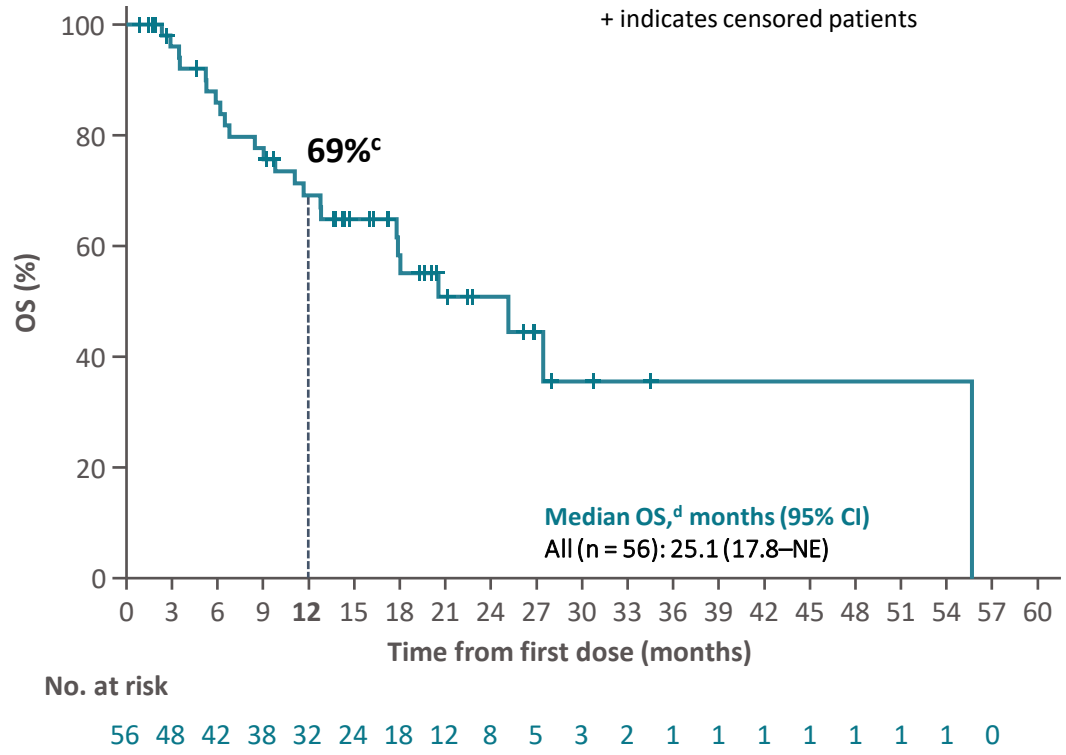
Median follow-up: 24.0 months (range, 14.2–66.6).

[a]Three patients did not have post-baseline tumor size measurement. [b]By RECIST v1.1. [c]10% (n = 7) and 69% (n = 49) of patients had CR and PR, respectively. [d]95% CI, 73–93. [e]95% CI, 68–90. [f]Number of events = 15; number of patients censored (%) = 41 (73). [g]12- and 18-month DOR rates (95% CI) were 85% (75-95) and 80% (69-92), respectively.

PFS



OS

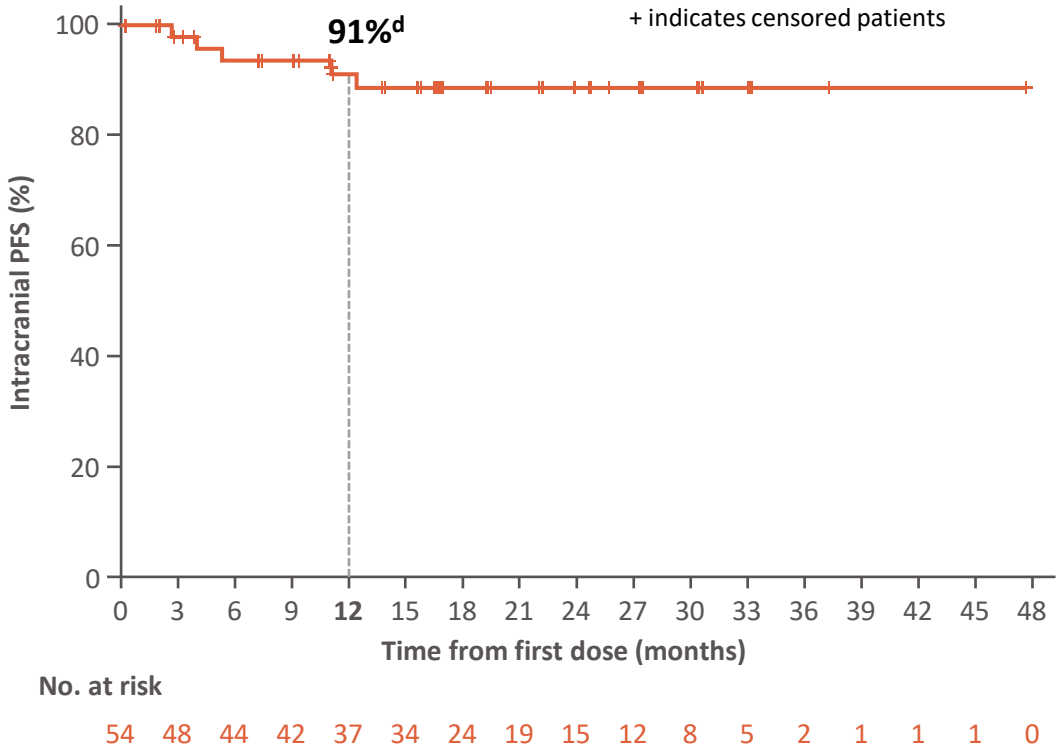


- Of patients in the 1 prior ROS1 TKI and no prior chemo cohort treated at the RP2D (n = 53), median PFS was 9.0 months (95% CI, 6.8–19.6)[e] and median OS was 20.5 months (95% CI, 17.8–NE)[f]

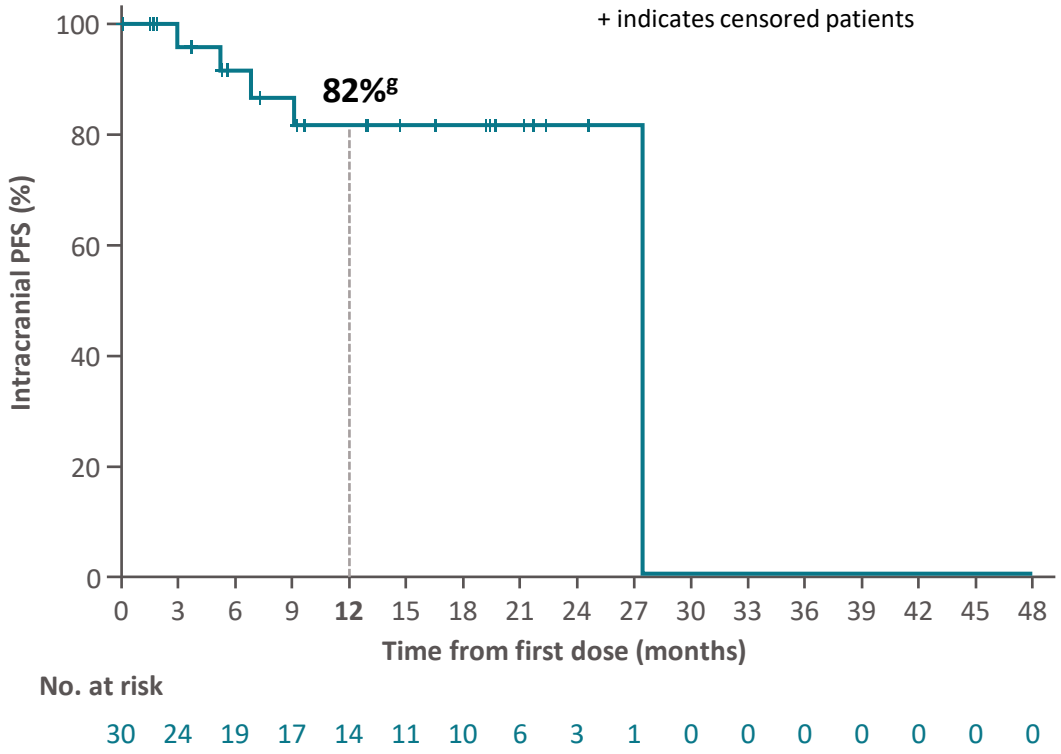
Median follow-up: 21.5 months (range, 14.2–58.6).

[a]95% CI, 27–56. [b]Number of events = 33; number of patients censored (%) = 23 (41). [c]95% CI, 56–82. [d]Number of events = 24; number of patients censored (%) = 32 (57). [e]12-month PFS rate (95% CI) was 42% (28-57). [f]12-month OS rate (95% CI) was 69% (56-83).

ROS1 TKI-naïve[b,c]



1 prior ROS1 TKI and no prior chemo[e,f]



- In an analysis of time to first intracranial progression only,[h] none occurred within 18 months of repotrectinib treatment in both TKI-naïve and TKI-pretreated patients

Median follow-up: ROS1 TKI-naïve, 24.0 months (range, 14.2–66.6); 1 prior ROS1 TKI and no prior chemo, 21.5 months (range, 14.2–58.6).

[a]Exploratory analysis of intracranial PFS based on time of development of new brain lesions as assessed by BICR. [b]Includes patients from phase 1 (n = 6) and phase 2 (n = 48). [c]Number of events = 5. [d]95% CI, 83-100. [e]Includes patients from phase 1 (n = 3) and phase 2 (n = 27). [f]Number of events = 5. [g]95% CI, 65-98. [h]Intracranial PFS censored by non-intracranial progression or death.

Summary

- Lung Cancer in Non Smoker especially young patients is common and should not be missed.
- Unfortunately, there is no screening for these patients, so persistent symptoms should be taken seriously and evaluated in a timely manner.
- Molecular testing with NGS is life saving for many of these patients and should be done as soon as a diagnosis is made. Concurrent testing is valuable.
- Each one of these mutation is a unique disease and must be labeled as such and not being lumped with all the other stage IV Lung Cancer. Example would be ALK fusion positive Adenocarcinoma of the Lung.
- Target Therapy may not curative but has changed the landscape of Lung Cancer treatment with improvement in Survival and quality of life.

THANK YOU