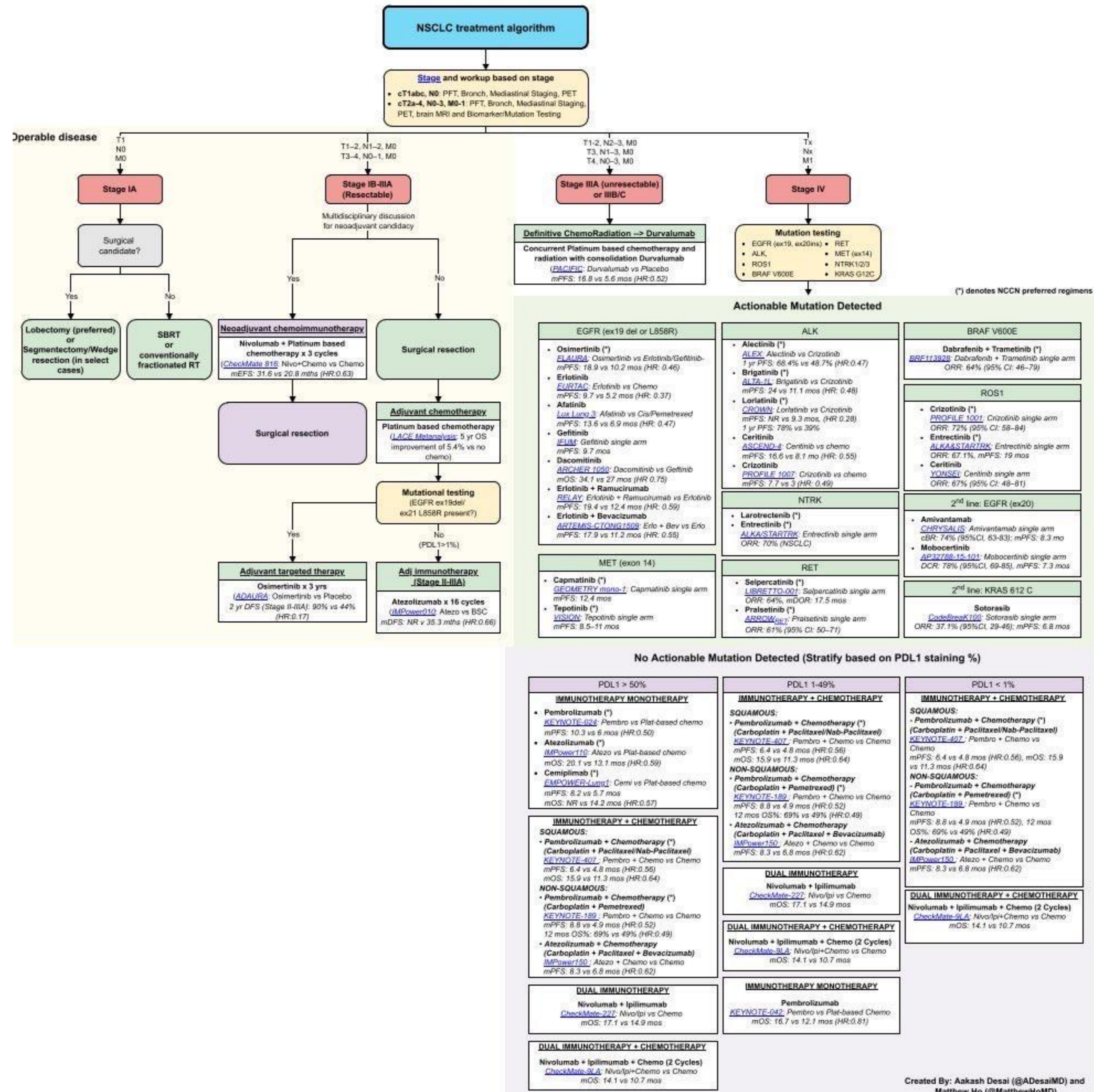
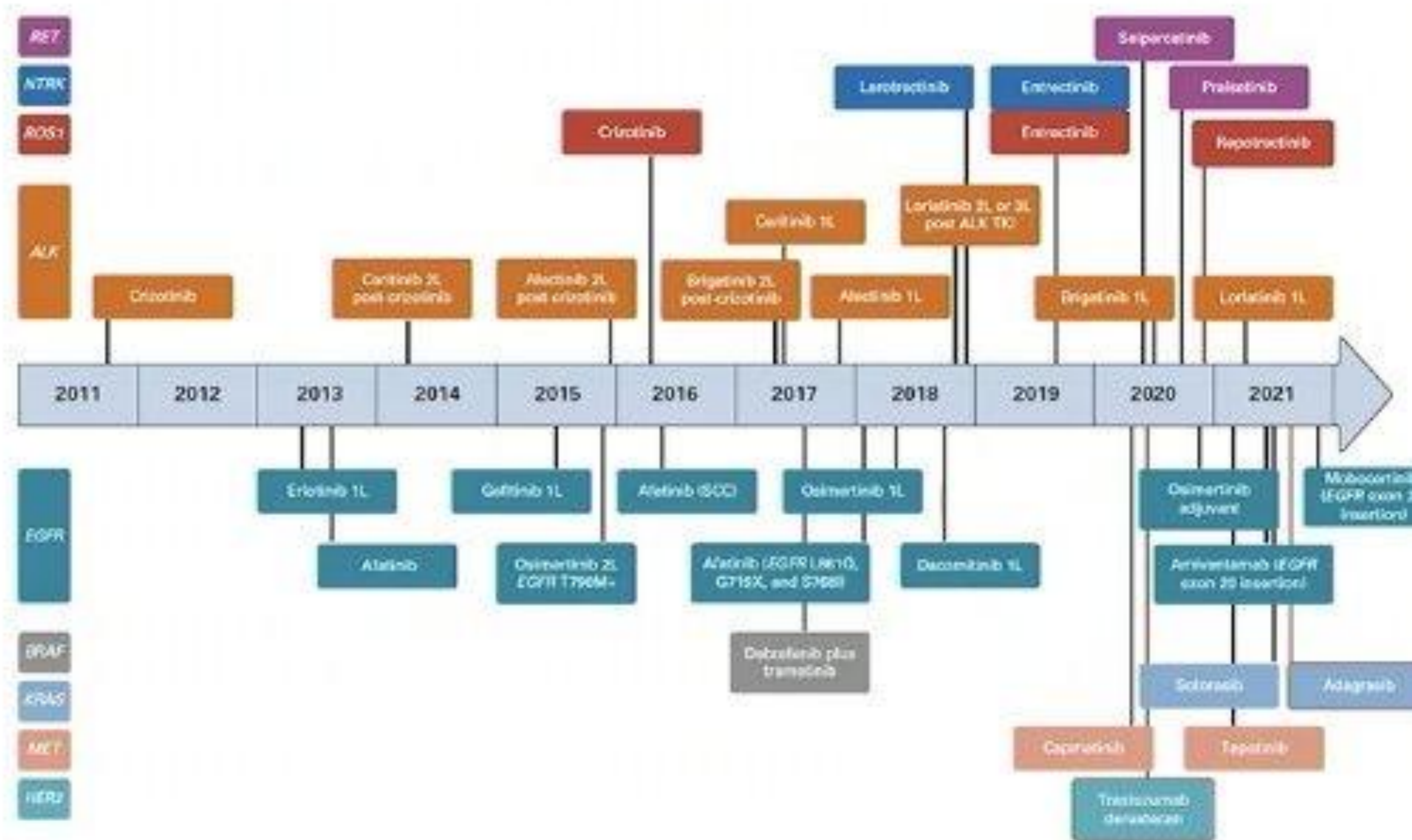
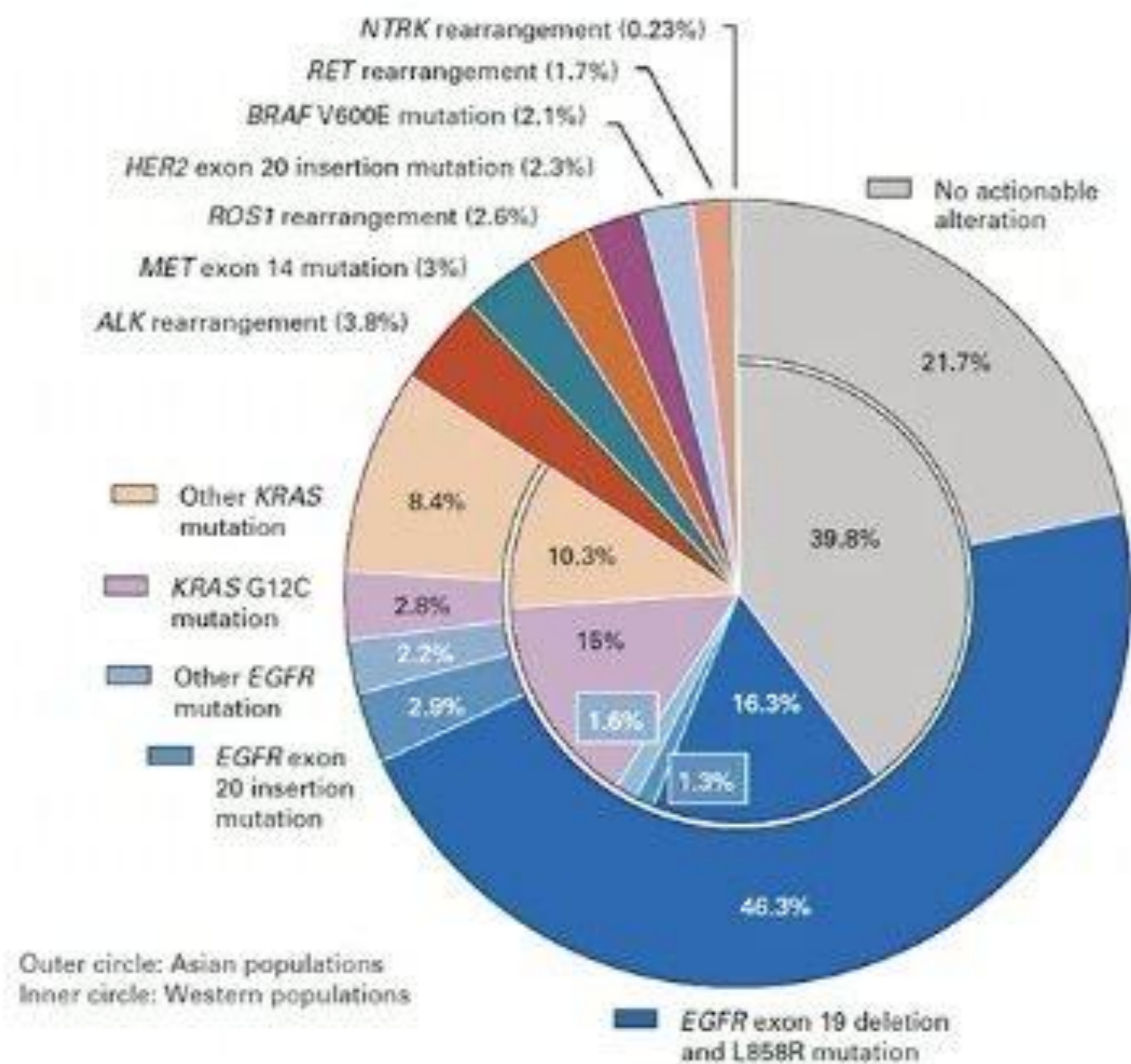


Panel discussion

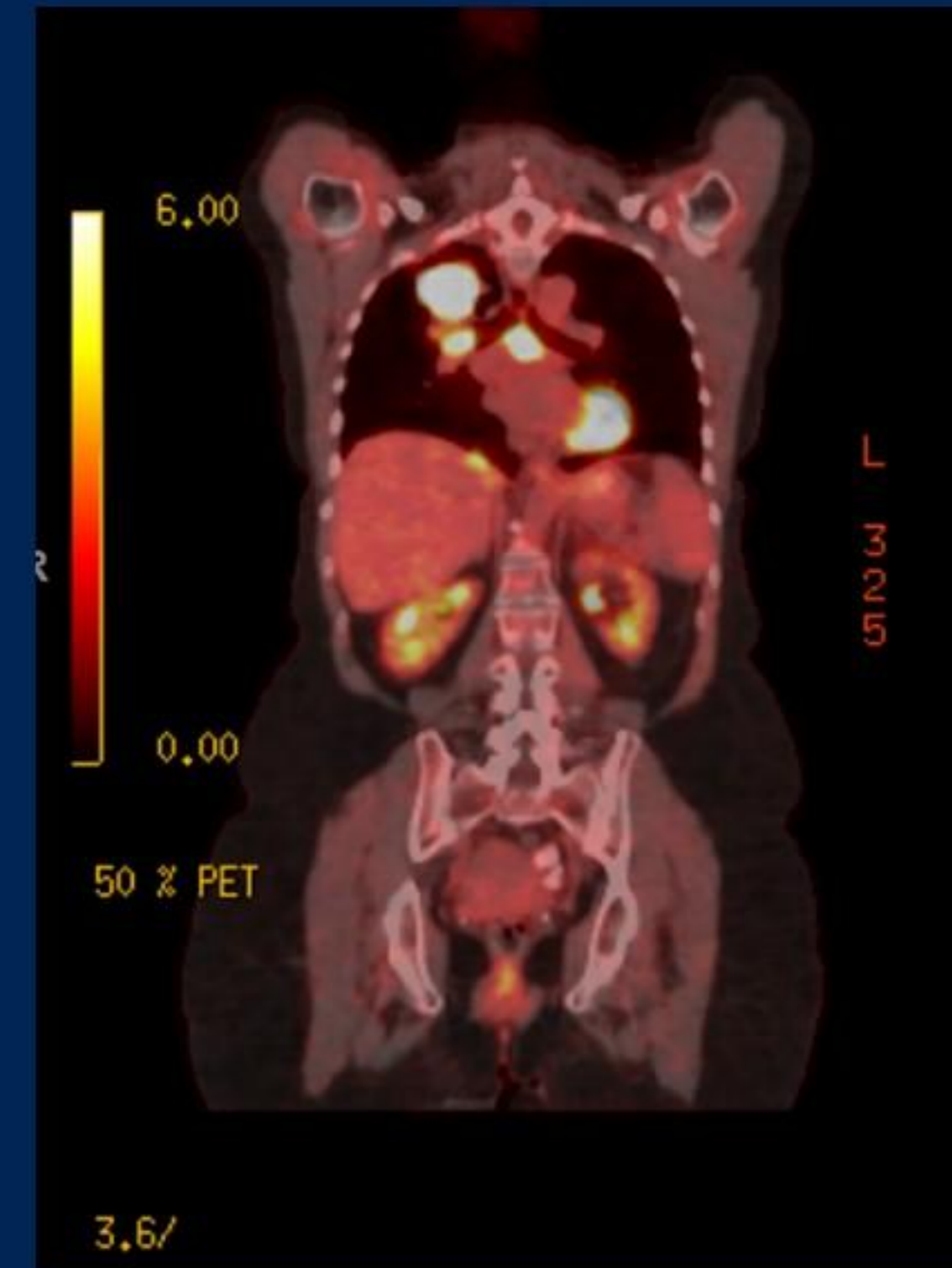
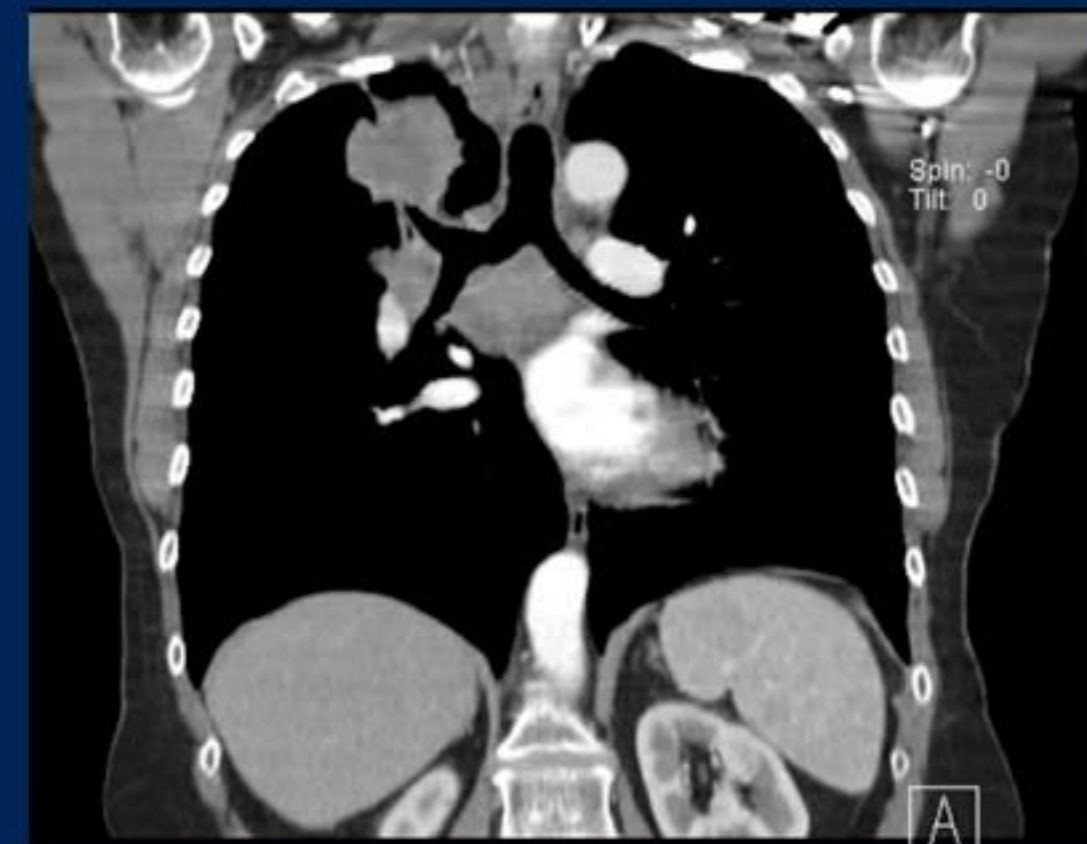
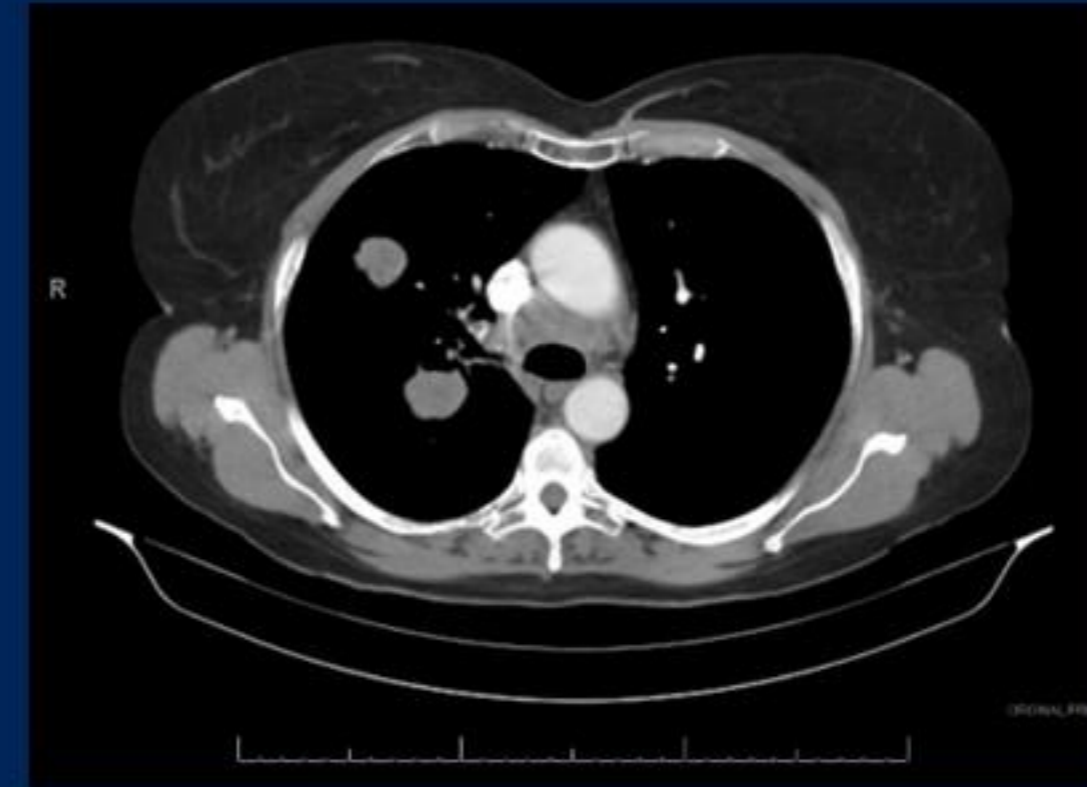


The molecular landscape of NSCLC



Case #1

- 64 yo female
- CC: persistent cough
- PMH/PSH: HLD, no prior history of smoking
- **Imaging:**
 - Chest CT: right apical mass, hilar/mediastinal LAD, supraclavicular LAD, and bilateral lung metastases
 - PET/CT and brain MRI negative for extrathoracic metastatic disease
- **Path:** moderately-differentiated adenocarcinoma
 - Biomarker testing: Local PD-L1 (22C3) negative; Mayo Clinic: EGFR exon 21 L858R
- **Treatment:** first-line osimertinib started April 2018 with early PR



Tumor Type	Carcinoma, Mucoepidermoid	Date and Time of Report	16 th July 2022 22:38 PM	Affiliation	Vellore, Vellore
Clinical Diagnosis	Bronchial lesion bx Ca intracellular mucin deposit possible Mucoepidermoid Ca or lung adeno Ca				

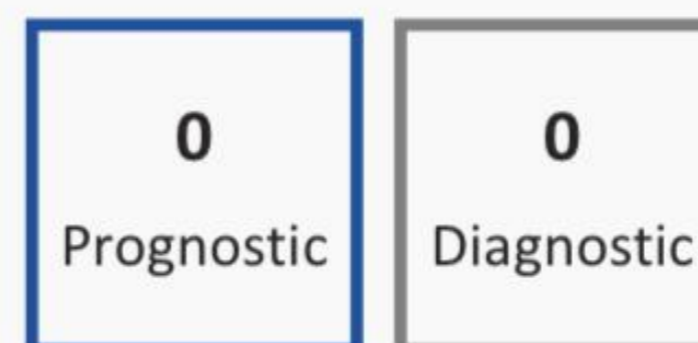
*The test was performed on 19516/22 (A2) block and tumor content was sufficient (>10%) for analysis.

Test Result Summary

Potential treatment impacts



Prognostic and Diagnostic findings



Clinical trials



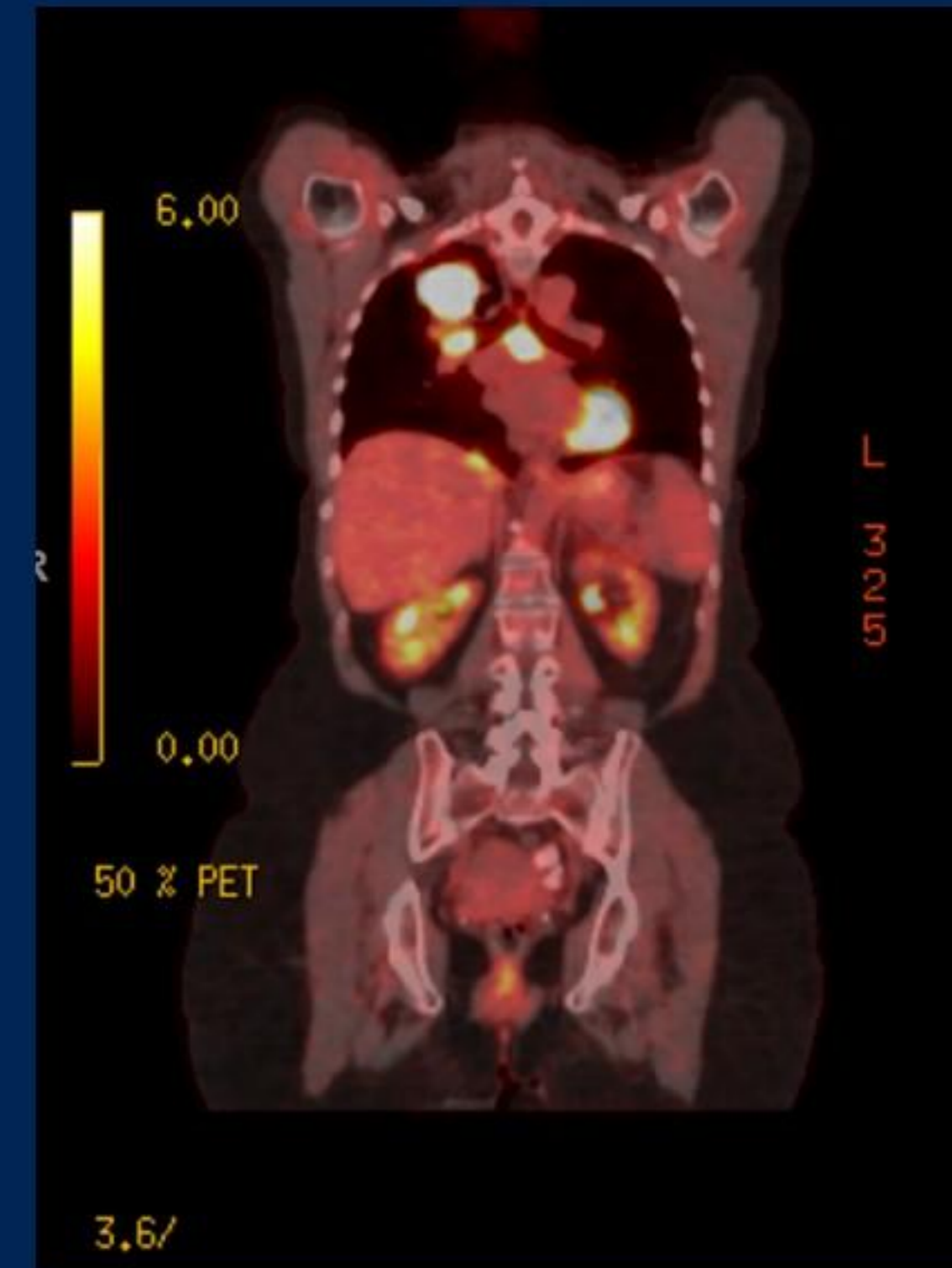
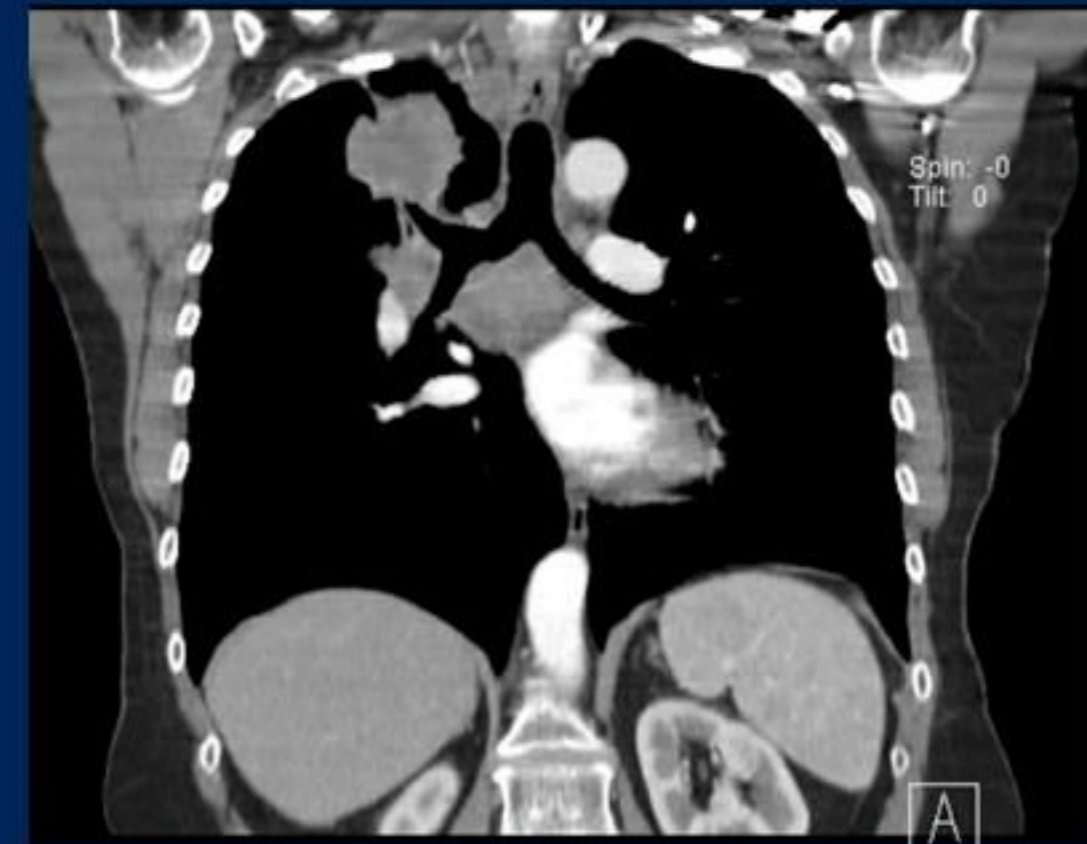
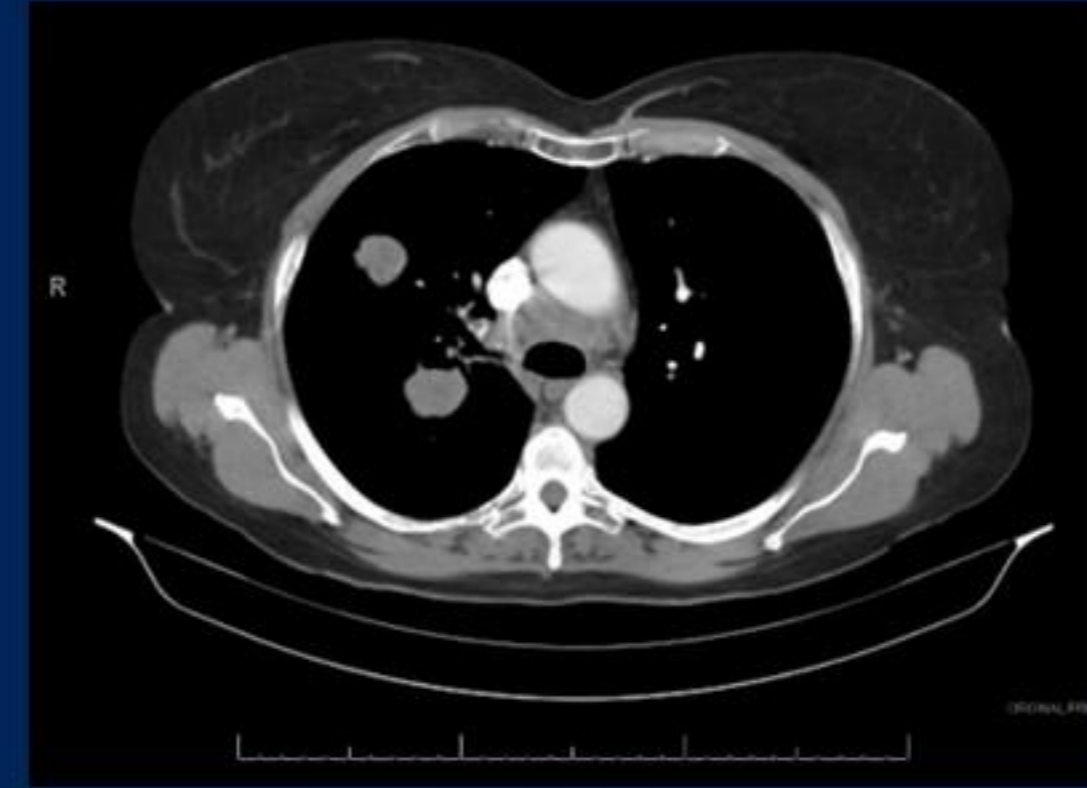
AMP Classification [^]	Evidence Level [^]	Treatment	Treatment Benefit	Drug Approval [^] \$	Clinical Trials
--	------------------------------------	------------------	--------------------------	--------------------------------------	------------------------

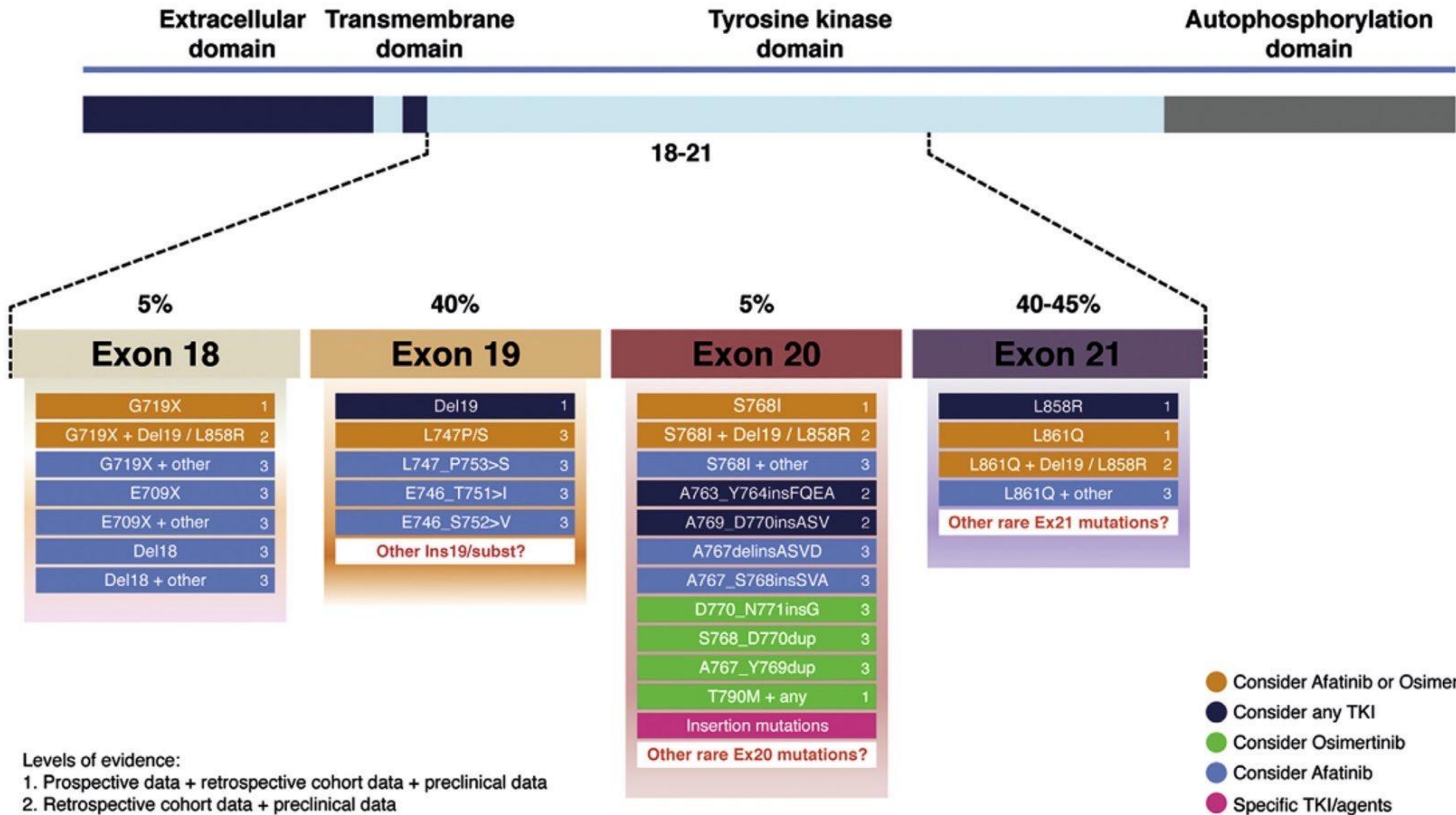
Genomic variants

EGFR p.Leu747_Pro753delinsSer (DEL) Variant Allele Frequency - 1%

Case #1

- 64 yo female
- CC: persistent cough
- PMH/PSH: HLD, no prior history of smoking
- **Imaging:**
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- **Treatment:** first-line osimertinib started April 2018 with early PR





- Consider Afatinib or Osimertinib
- Consider any TKI
- Consider Osimertinib
- Consider Afatinib
- Specific TKI/agents

Levels of evidence:

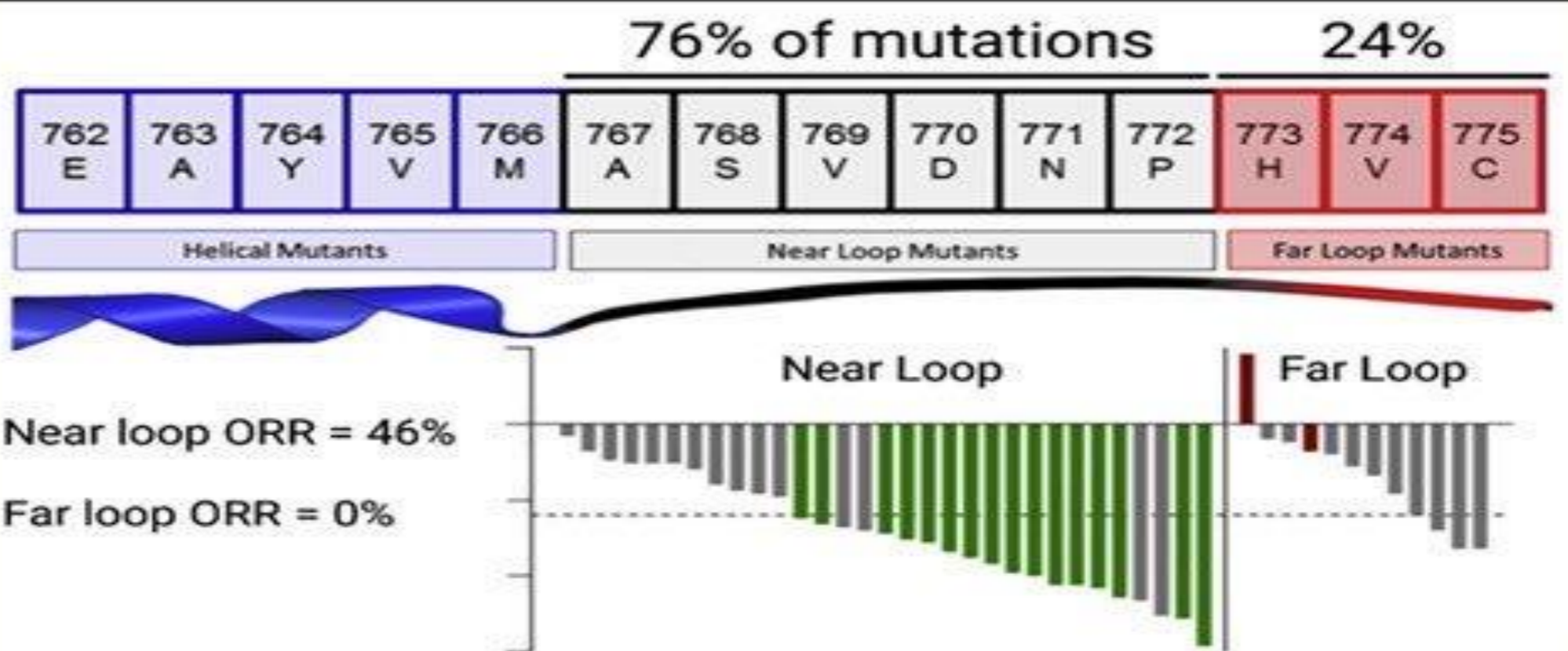
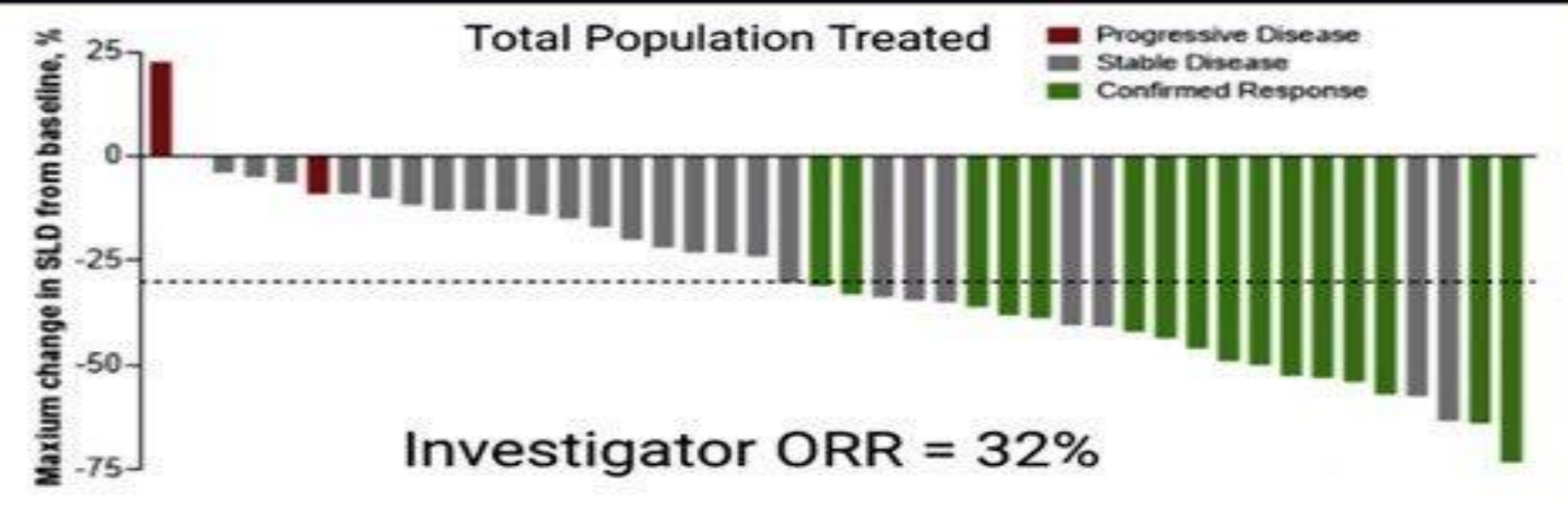
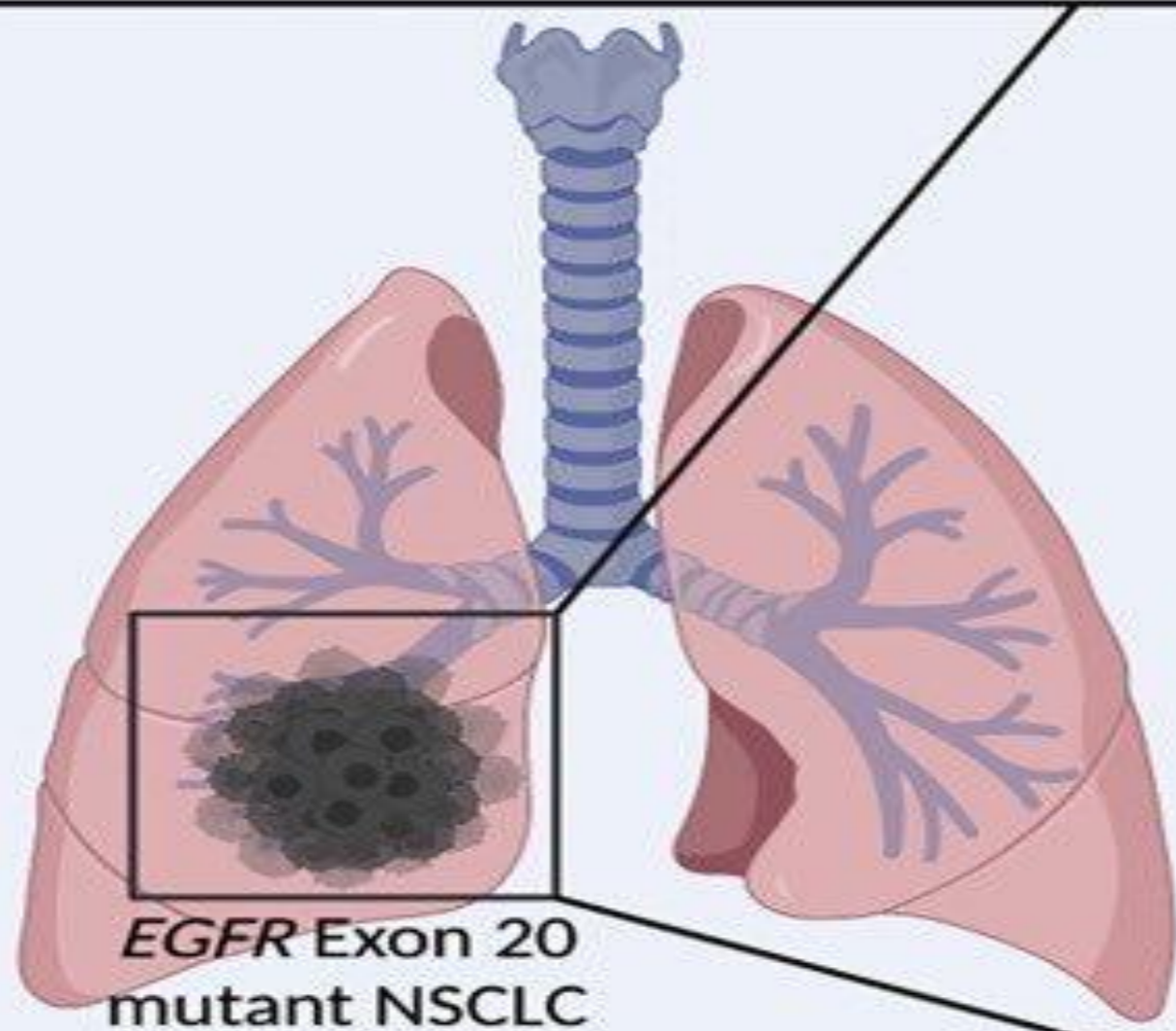
1. Prospective data + retrospective cohort data + preclinical data
2. Retrospective cohort data + preclinical data
3. Individual case studies + preclinical data

Poziotinib in EGFR Exon 20 Mutant Advanced NSCLC



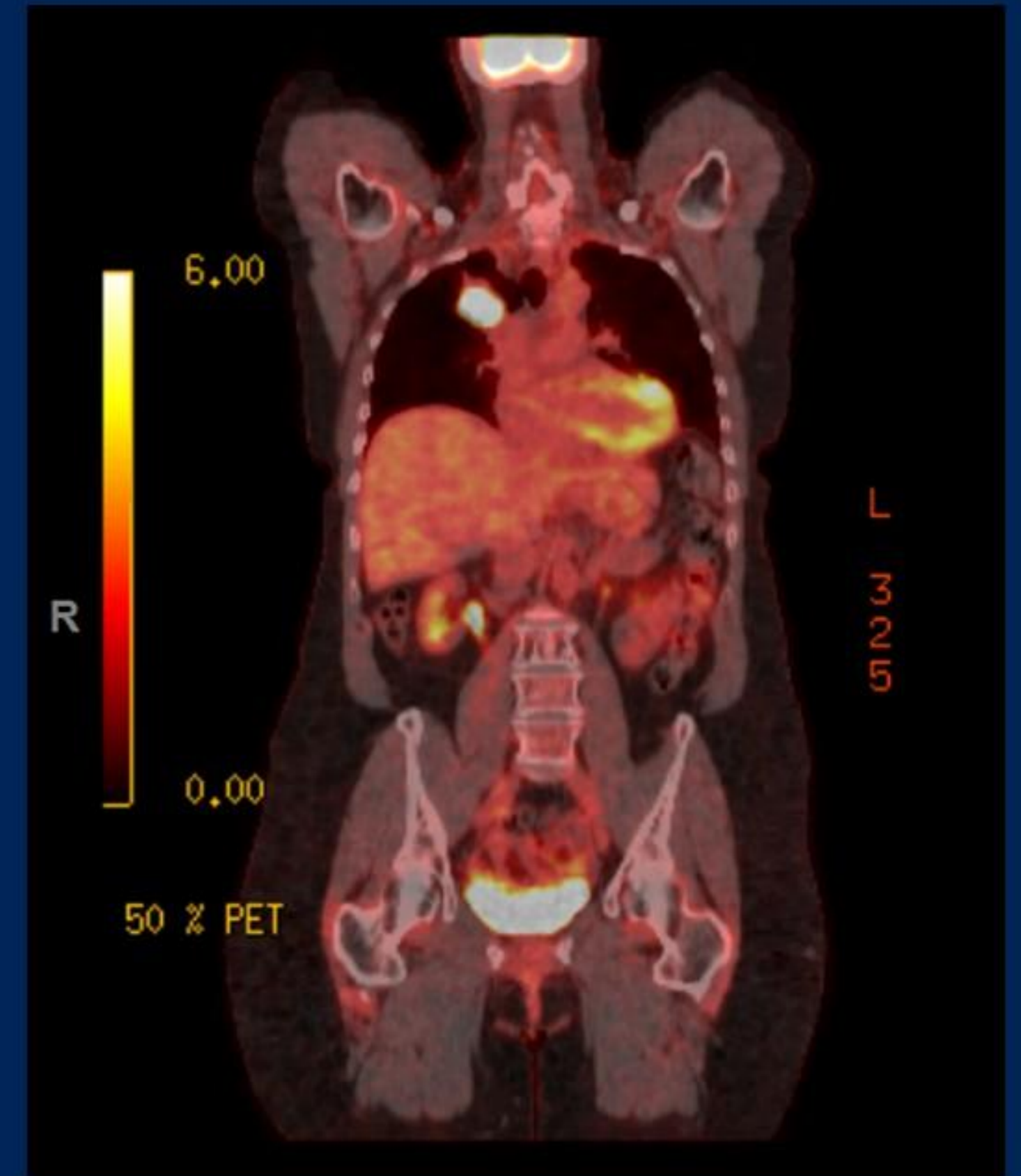
16mg Poziotinib (daily)

NCT03066206 n = 50



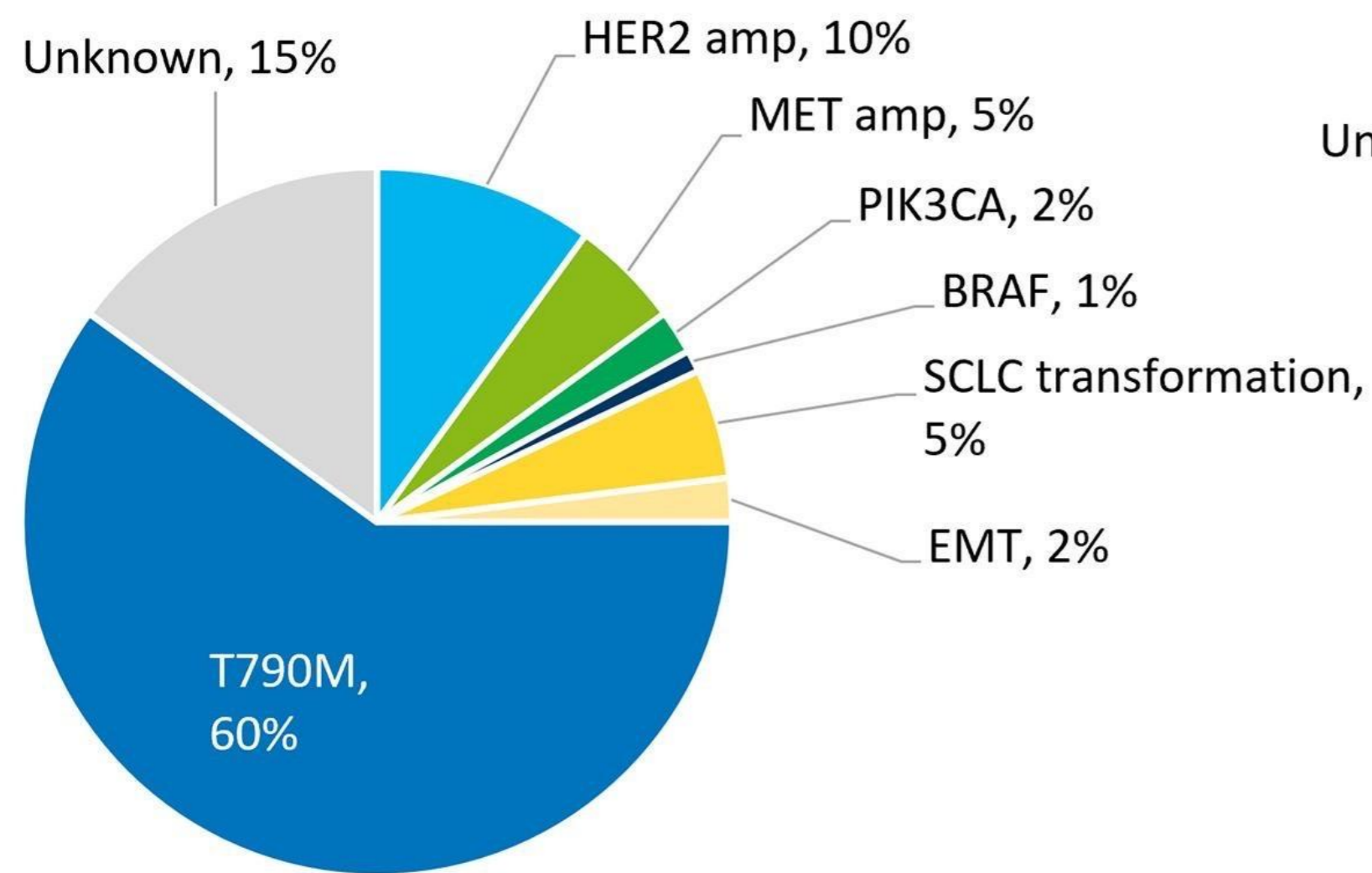
Case 1 Cont'd

- November 2019: solitary progression of right upper lobe mass (17 months after initiation of Osimertinib)
 - PET/CT: FDG avid RUL mass with resolution of LAD and bilateral pulmonary metastases. No extrathoracic disease.

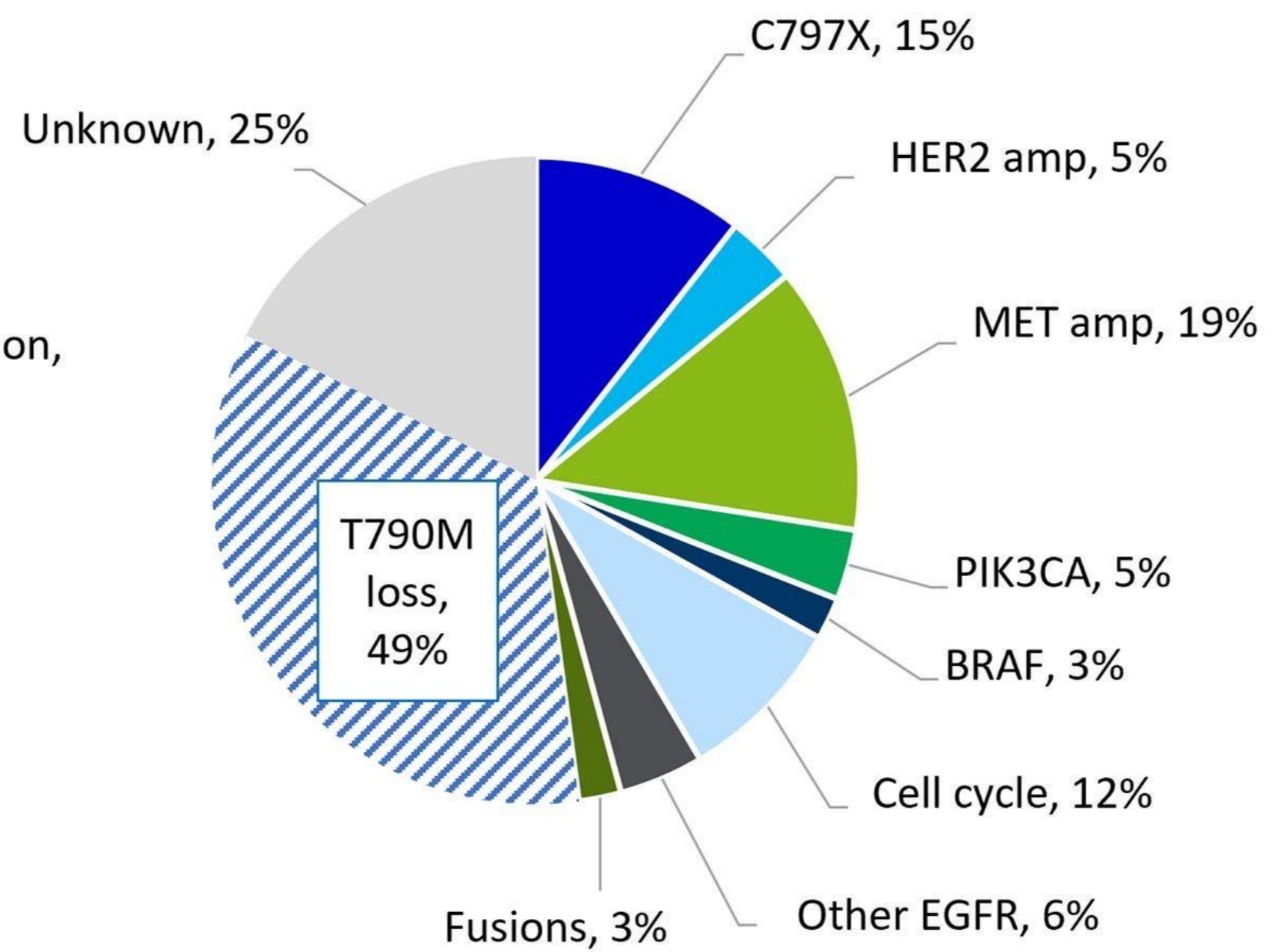


Likely Scale: How Likely Are You To Recommend Biopsy For This Patient?

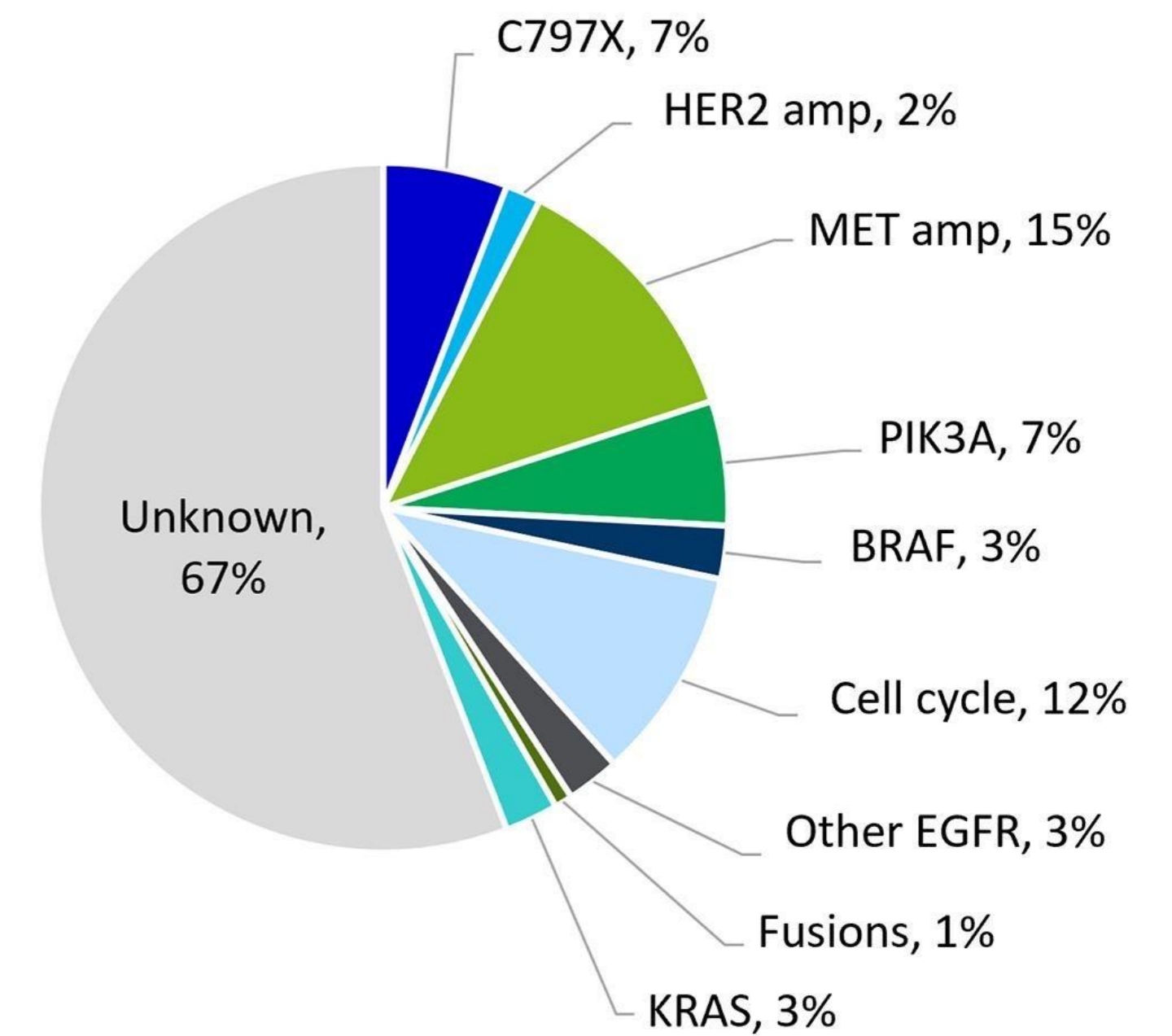
First-line erlotinib, gefitinib, afatinib



Second-line osimertinib



First-line osimertinib

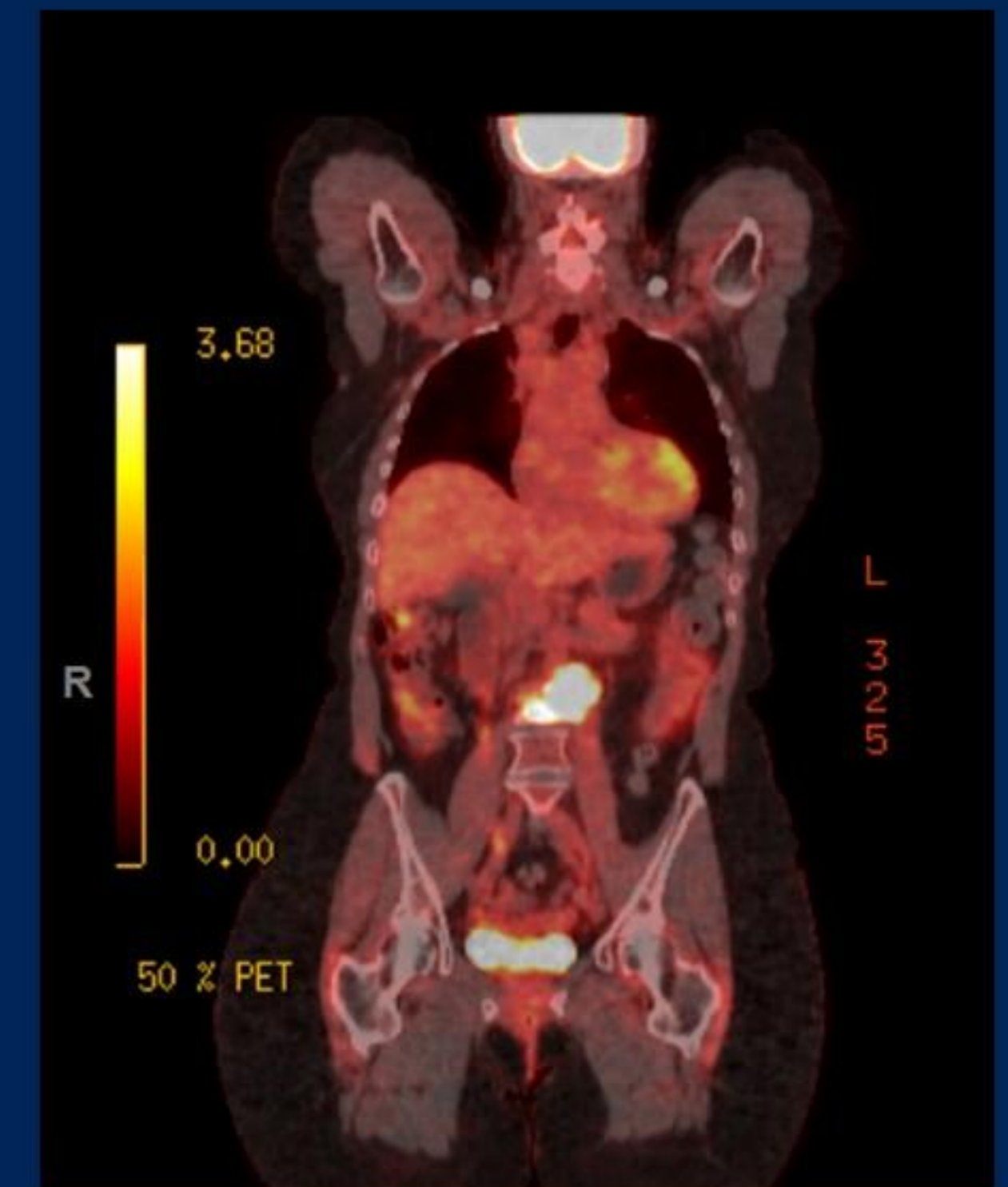
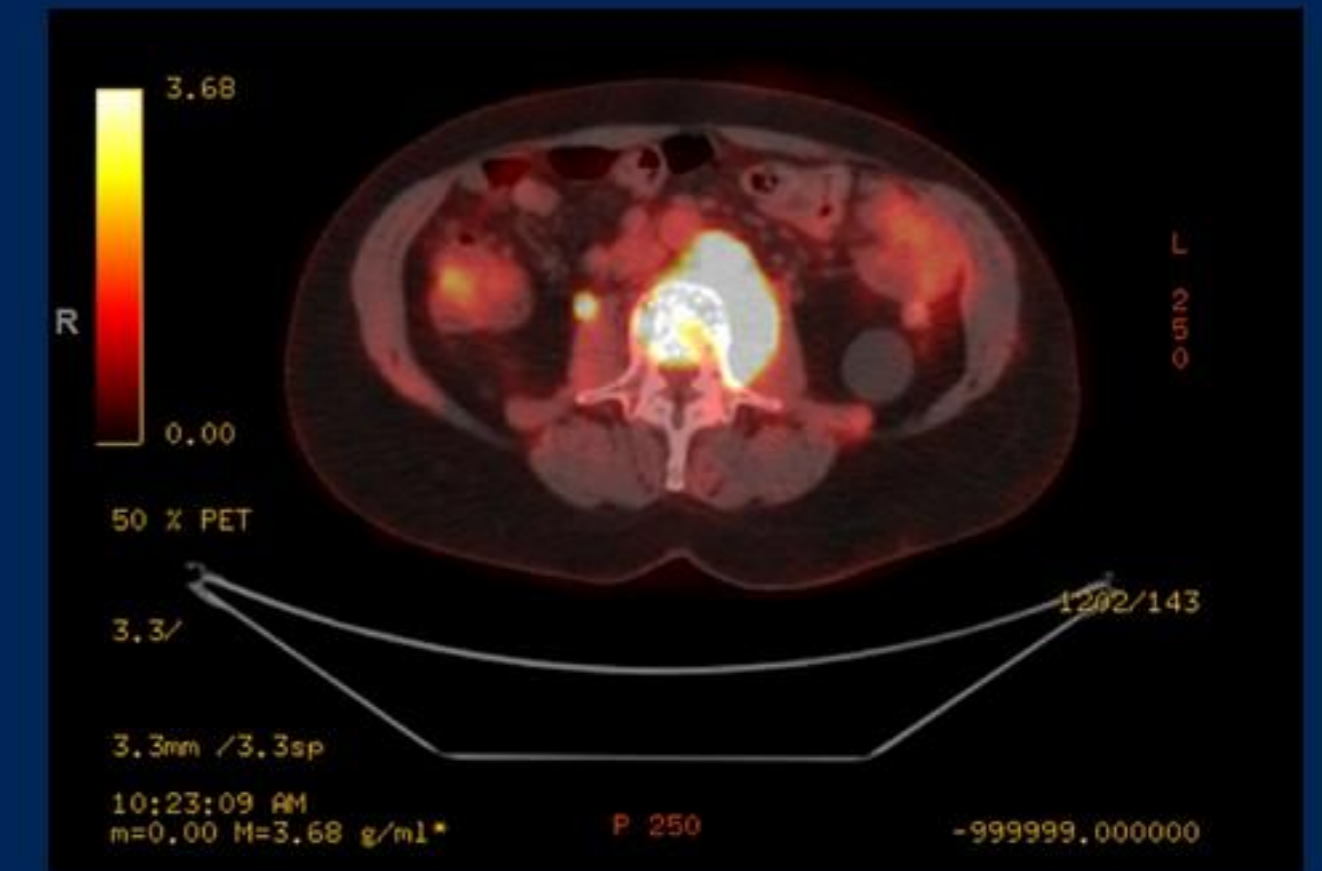


Multiple Choice Question: What would you do next?

- A. Switch to platinum doublet +/- immunotherapy
- B. Switch to monotherapy immunotherapy
- C. Radiate progressing site and continue on Osimertinib
- D. Radiate progressing site and switch to a different systemic therapy

Case 1 continued

- November 2019
 - SBRT (6000 cGy in 8 Fx) to RUL mass
 - Continuation of Osimertinib
- January 2021 : solitary progression to paraspinal soft tissue mass
 - PET/CT: excellent PR to SBRT with new 6.2 cm paraspinal ST mass
 - MRI brain: negative



Case continued

- Biopsy: adenocarcinoma with admixed small cell histologic component
- Biomarker testing:
 - PD-L1 negative
 - EGFR exon 21 L858R

Multiple Choice Question: Which Treatment Are You Likely To Recommend For This Patient

- A. Platinum-Etoposide
- B. Platinum-Etoposide plus osimertinib
- C. Platinum-Etoposide plus RT
- D. Platinum-Etoposide + immune checkpoint inhibitor

Case 1 continued

- March 2021 – June 2021: Treatment
 - carboplatin and etoposide x 4 cycles plus osimertinib with PR
 - RT to residual paraspinal mass
 - Osimertinib continued

Take Home Messages: EGFR mutated NSCLC with SCLC transformation

- Histologic transformation to SCLC is a mechanism of resistance to EGFR TKI
- ~ 3-10 % of EGFR-mut NSCLC will undergo SCLC transformation following EGFR TKI
- The median time to SCLC transformation is approximately 17-18 months
- Biopsy is needed to diagnose SCLC transformation
- SCLC transformation is seen with Rb1, TP53, and PIK3CA mutations plus retention of original EGFR mutation
- Inactivation of TP53 and Rb1 may be present at initial NSCLC diagnosis
- Platinum-etoposide is the preferred regimen for transformed SCLC
 - Taxanes have shown clinical benefit while ICI lacked benefit
- The role of continuing EGFR TKI with chemotherapy remains unclear in this setting

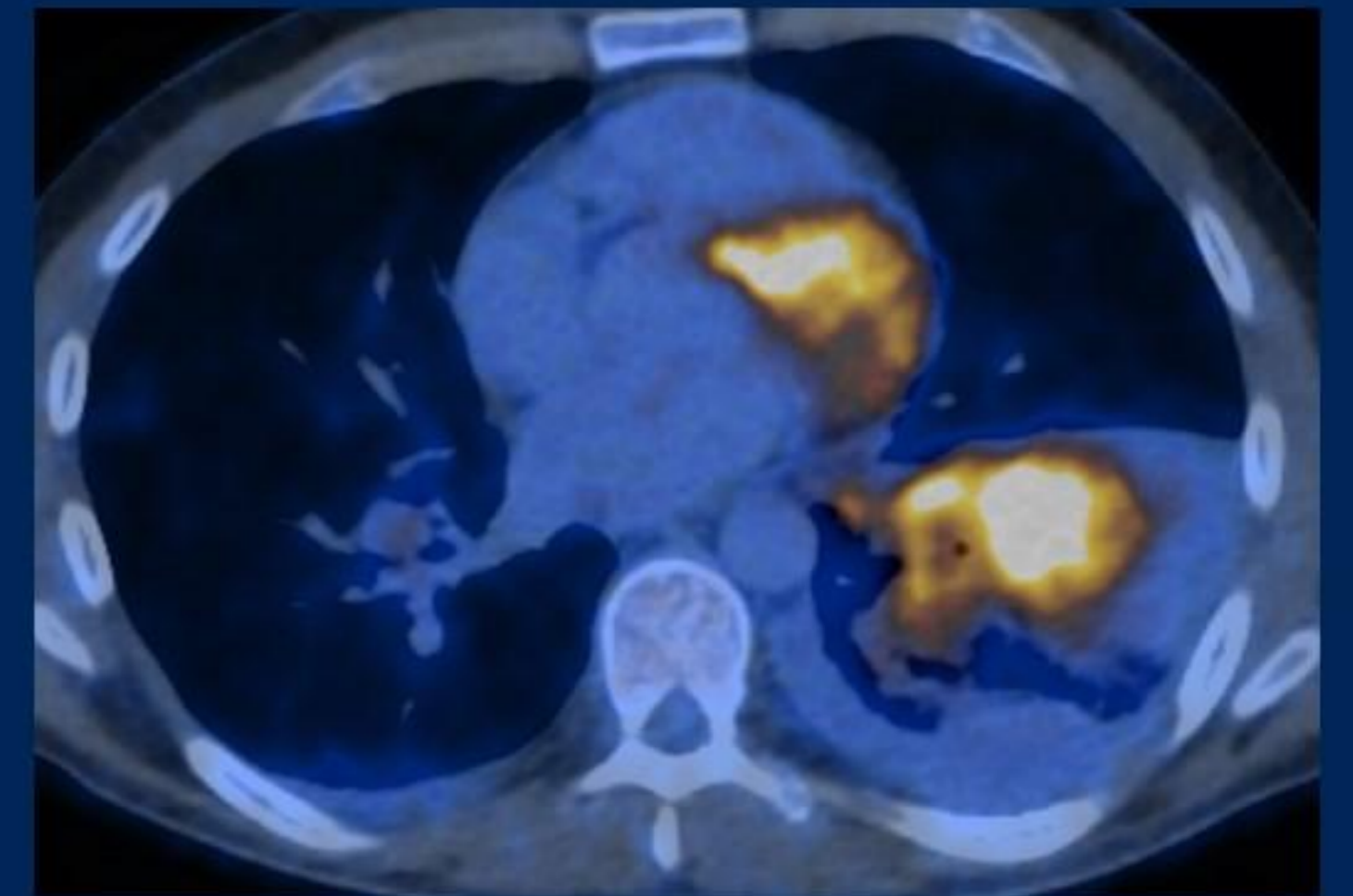
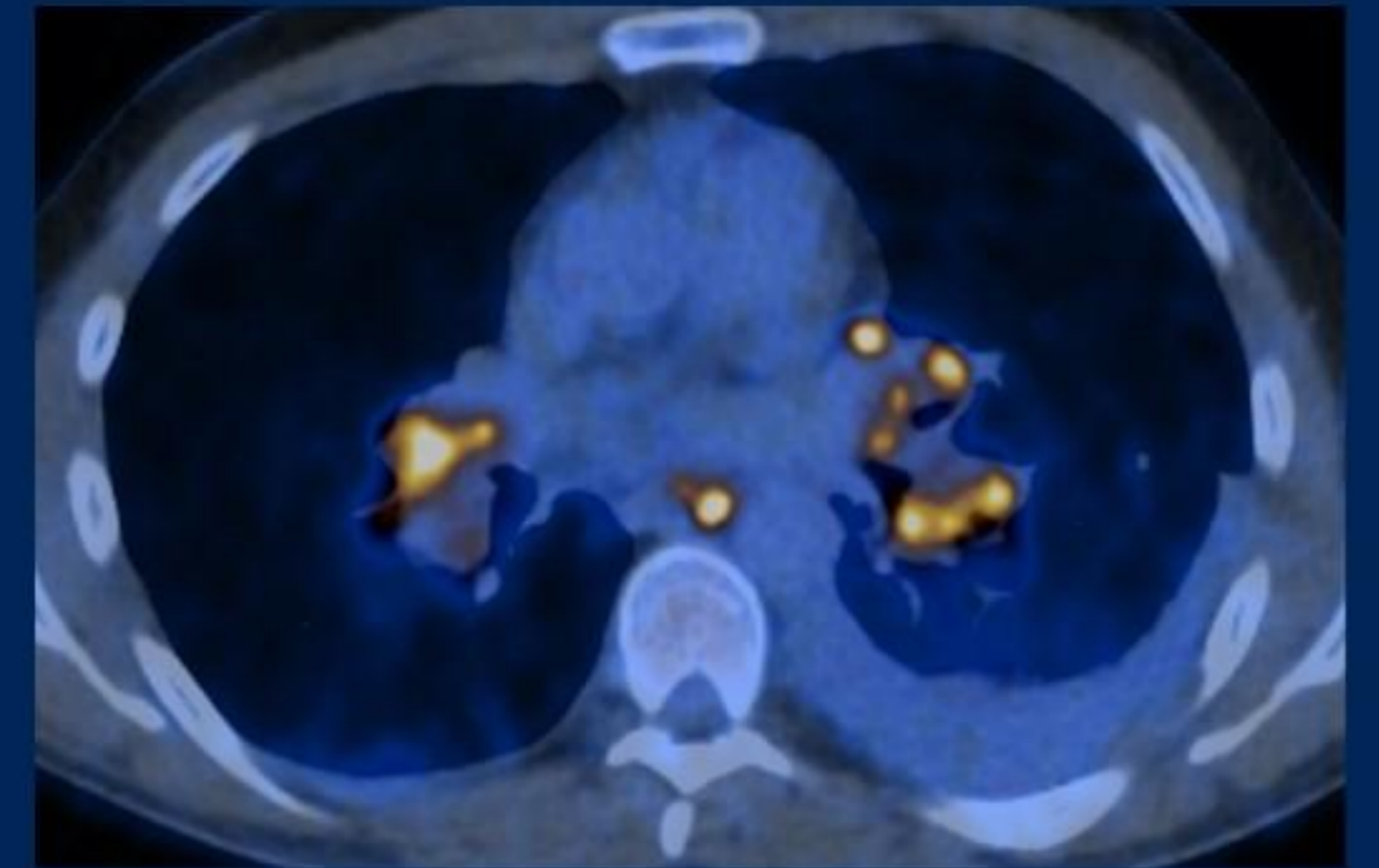
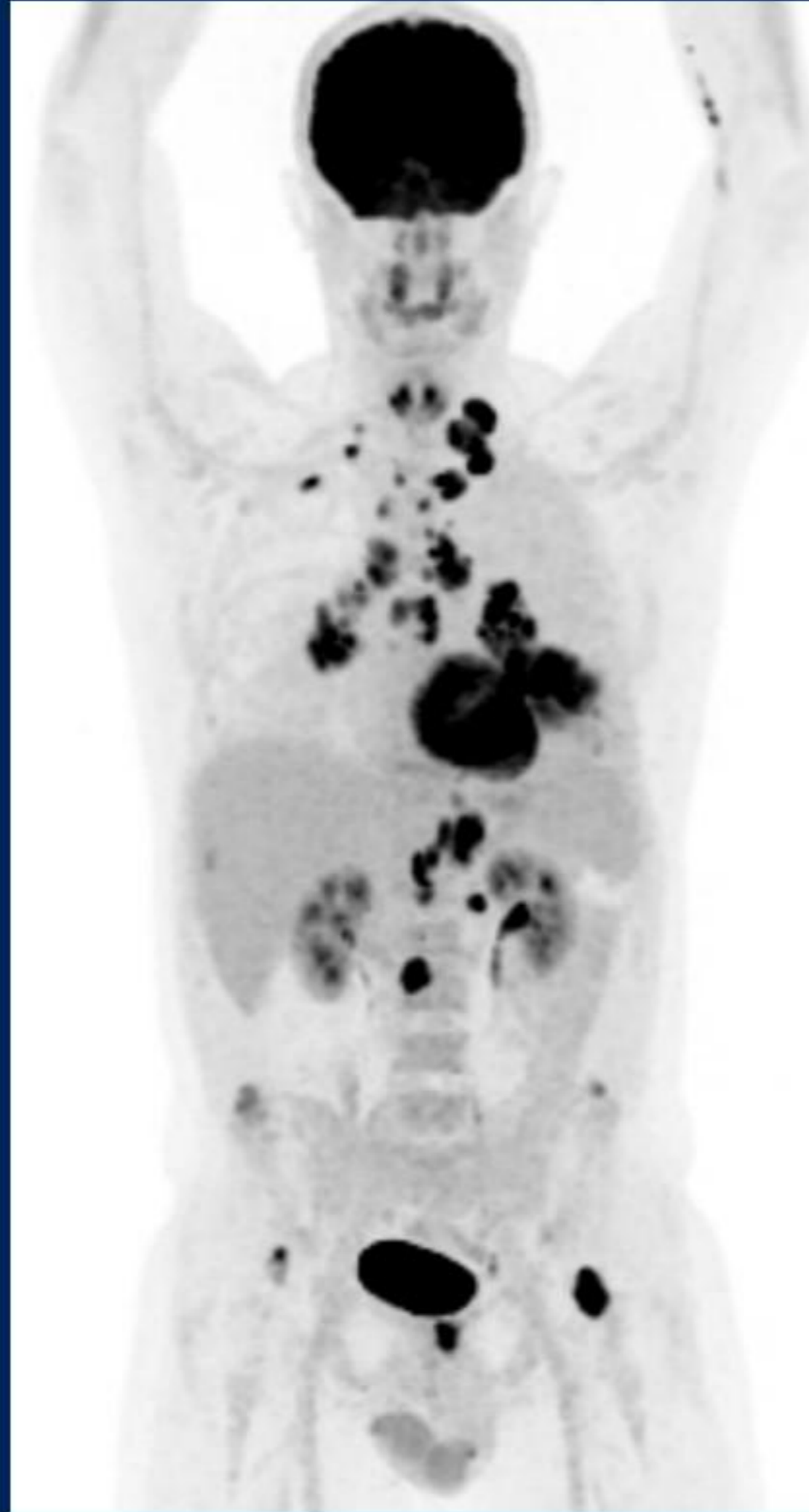
Case 2

- 36 years old male
 - Husband and father of two kids
 - Founder and CEO of a start-up company
 - Active in all kinds of outdoor sports
 - Smoking history with 10 pack years
-
- History of productive cough for 7 weeks
 - Intermittent fever
 - Reduction of activity and fitness level. Patient denies any other symptoms

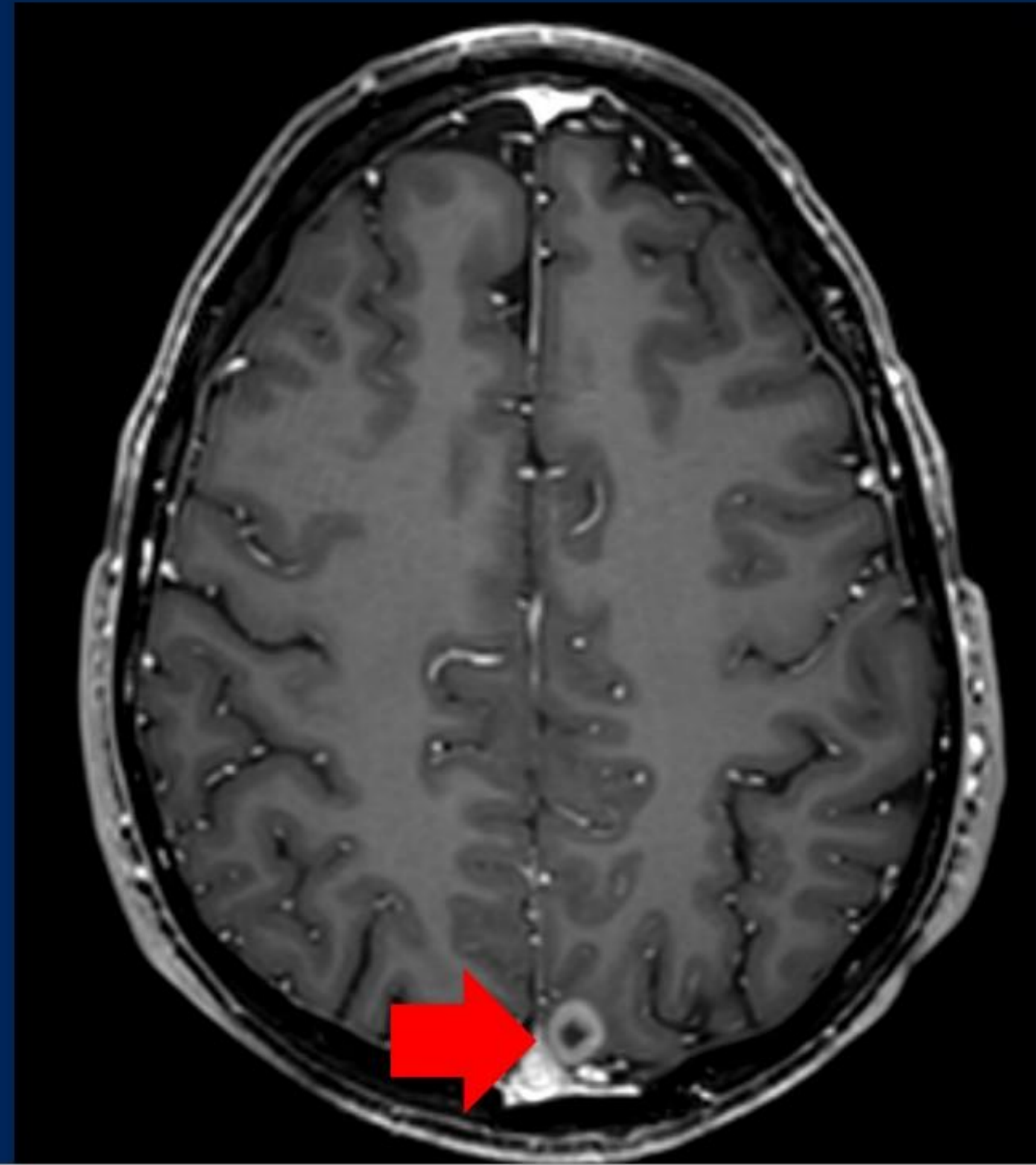
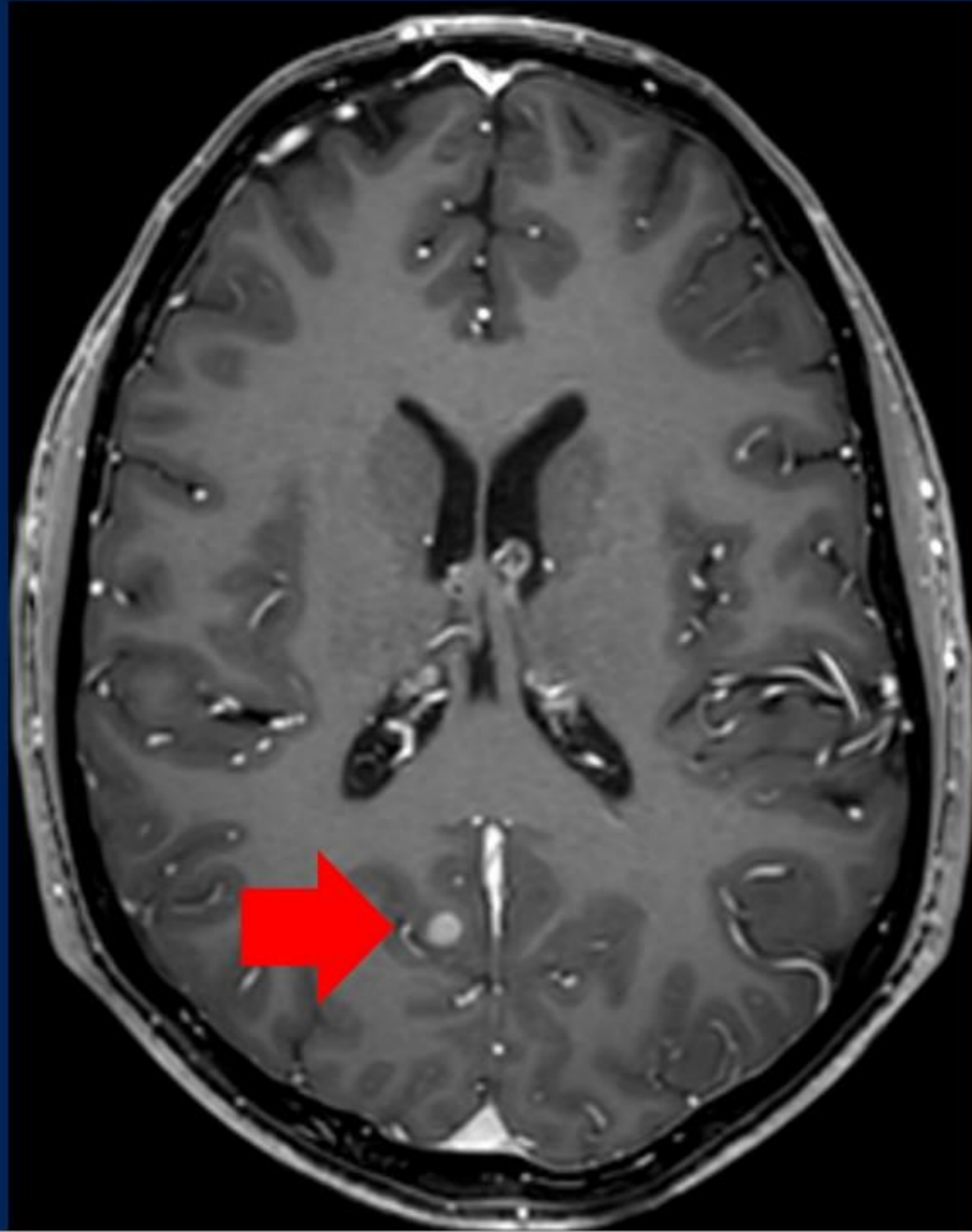
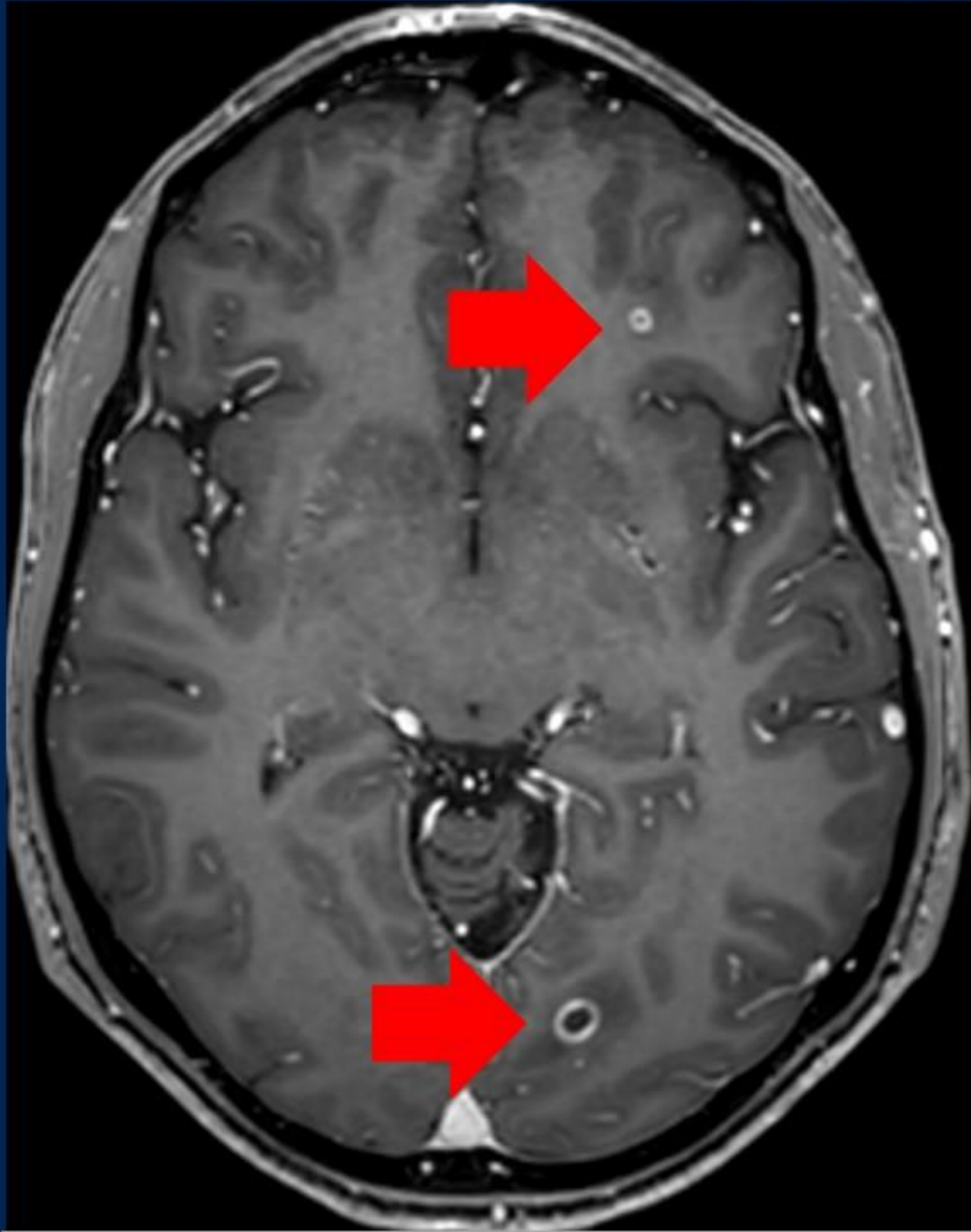
Case 2 Continued

Work-up

- 10/2021: CT thorax
- 10/2021: EBUS
- 10/2021: FDG-PET
- 10/2021: c-MRI



Case 2 continued



➤ n=10 supra- and infratentorial brain metastases, max 11mm

Case 2 continued

Pathology:

- Mediastinal LN & pleura
- Malignant cells in pleural effusion
- All LN stations (11R, 4R, 7, 4L, 11L) positive for adenocarcinoma, TTF-1+

Foundation one:

- EGFR amplification, rearrangement exon 25
- PD-L1 (tumor cells) > 50%
- MSI stable
- TMB 8Muts/Mb

Case 2 continued

10/2021: Interdisciplinary tumor board

- Systemic therapy with Osimertinib
- Radiotherapy of painful femur metastasis

Multiple Choice Question:
How would you manage brain metastases?

- A. Systemic therapy
- B. Radiosurgery of all brain metastases
- C. Whole brain irradiation
- D. Radiosurgery followed by whole brain irradiation
- E. Whole brain irradiation with integrated boost

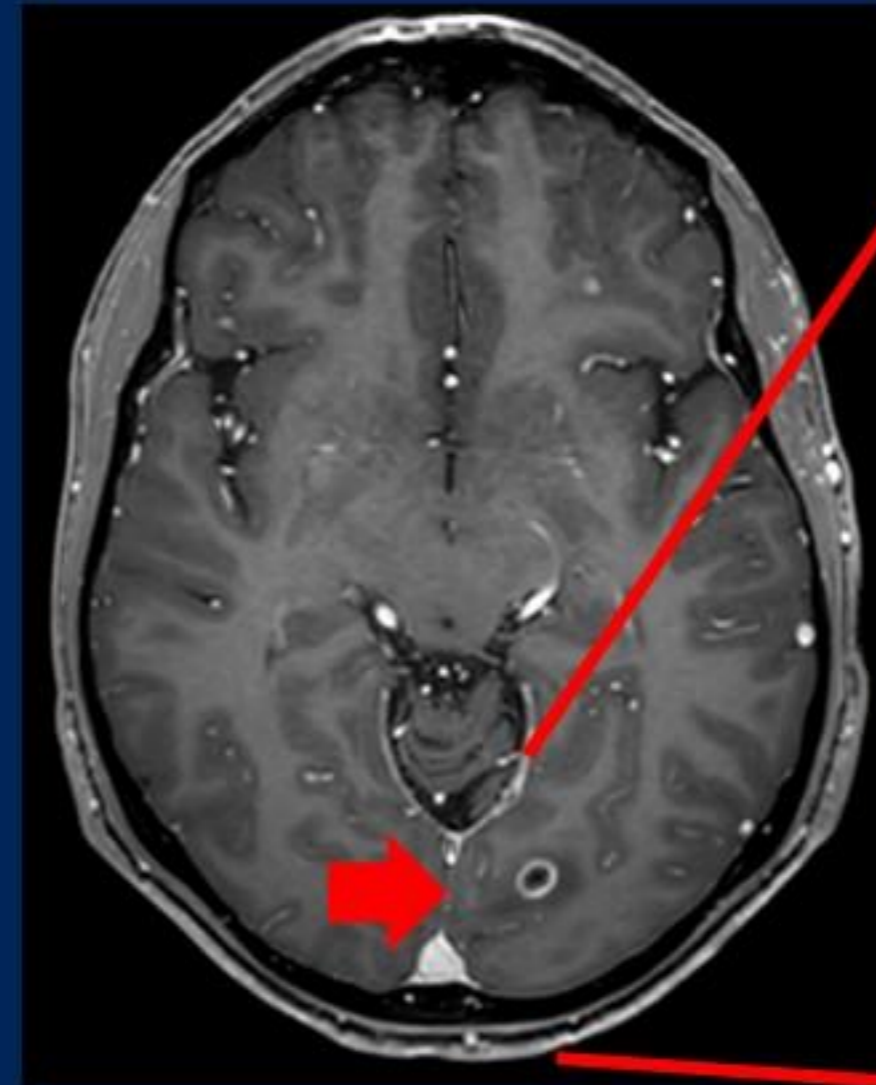
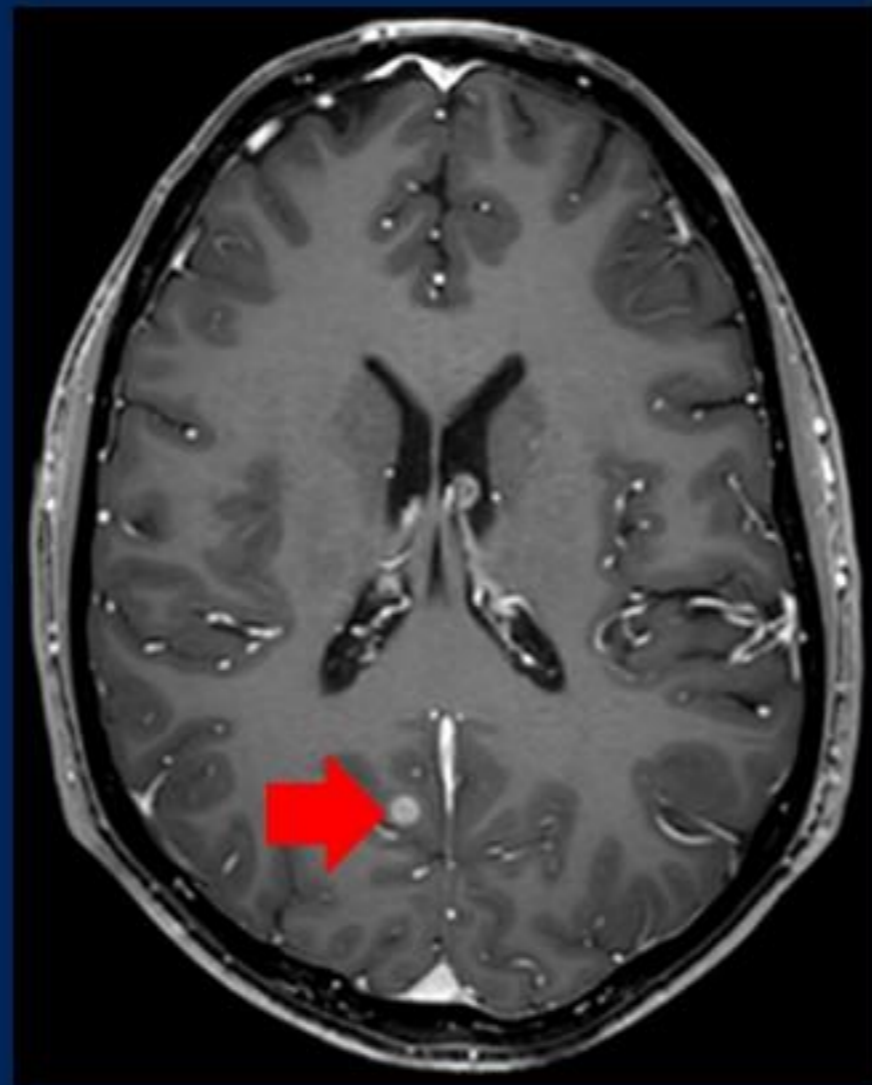
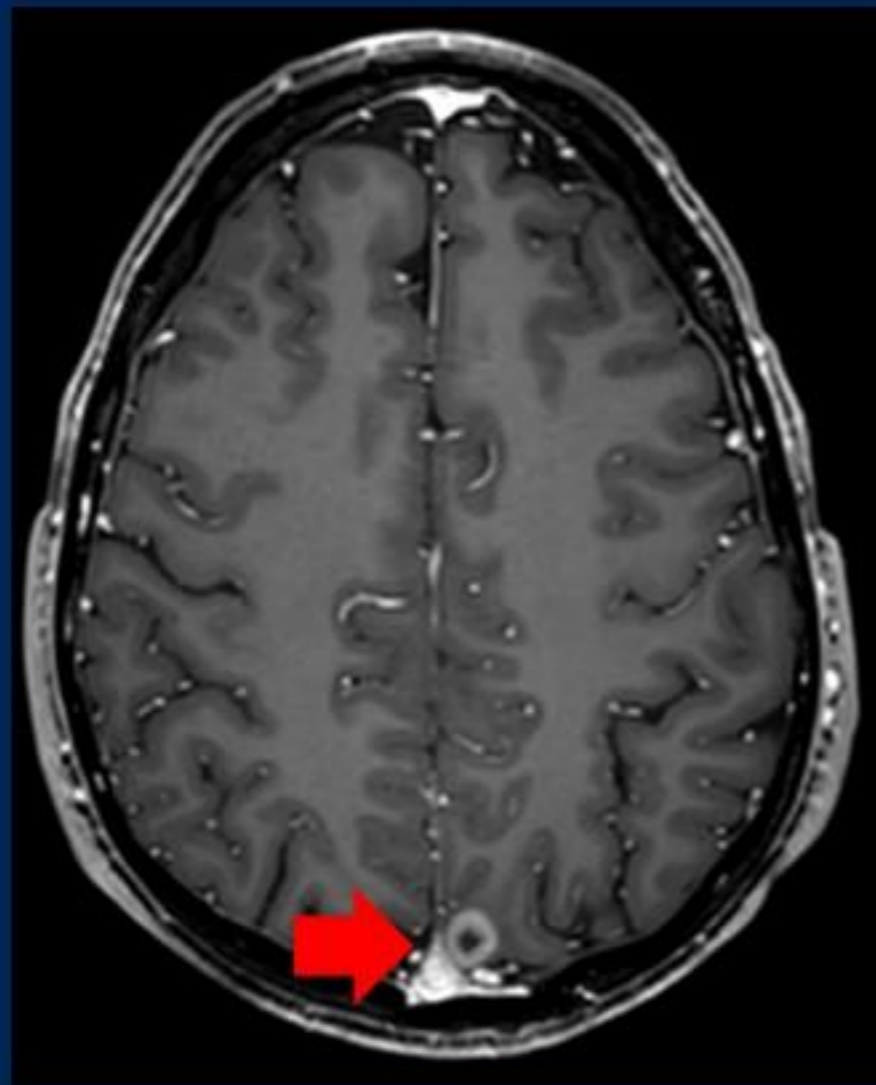
Case 2 continued

Discussion with patient:

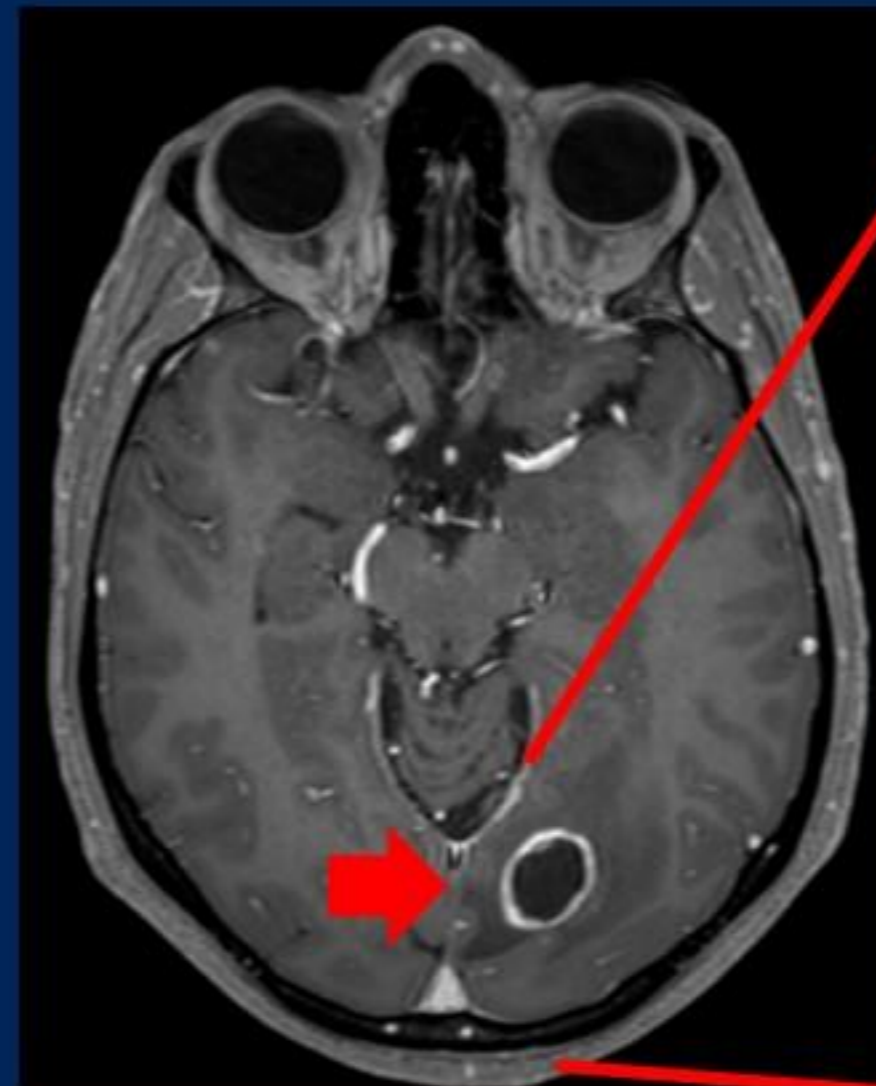
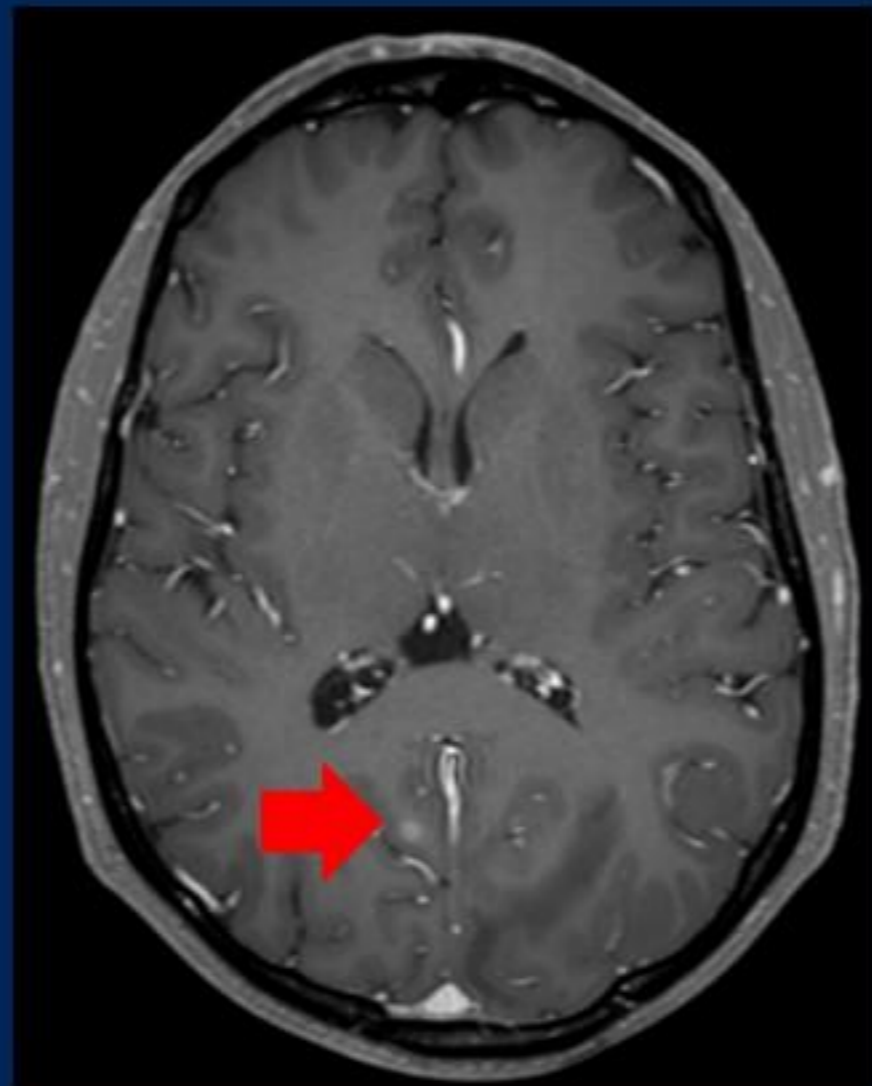
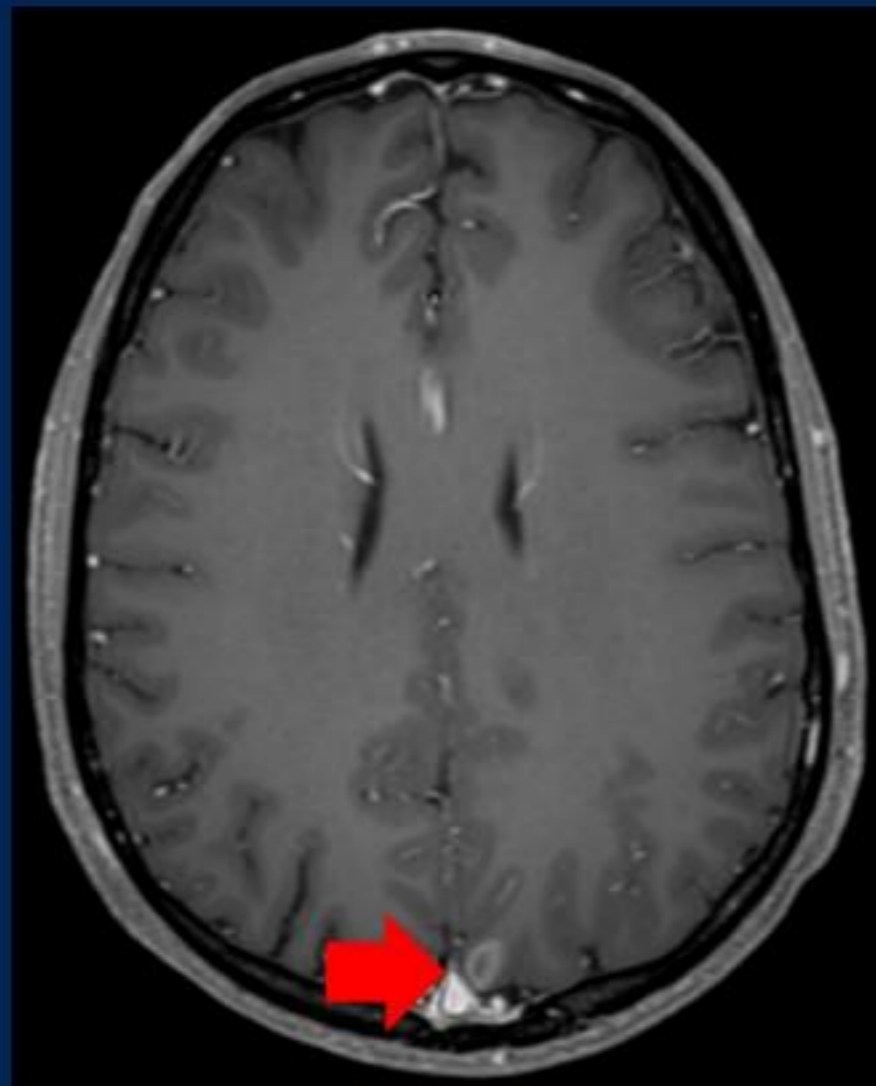
- Decision against up-front SRS or other forms of brain radiation
- Early follow-up c-MRI after 4 weeks of Osimertinib

Case 2 continued

10/2021



11/2021



Multiple Choice Question:

What would you do next?

- A. Continue Osimertinib in asymptomatic patient
- B. Continue Osimertinib and SRS to a single progressive brain metastasis only
- C. Continue Osimertinib SRS to progressive and all residual brain metastases

Case 2 continued

11/2021:

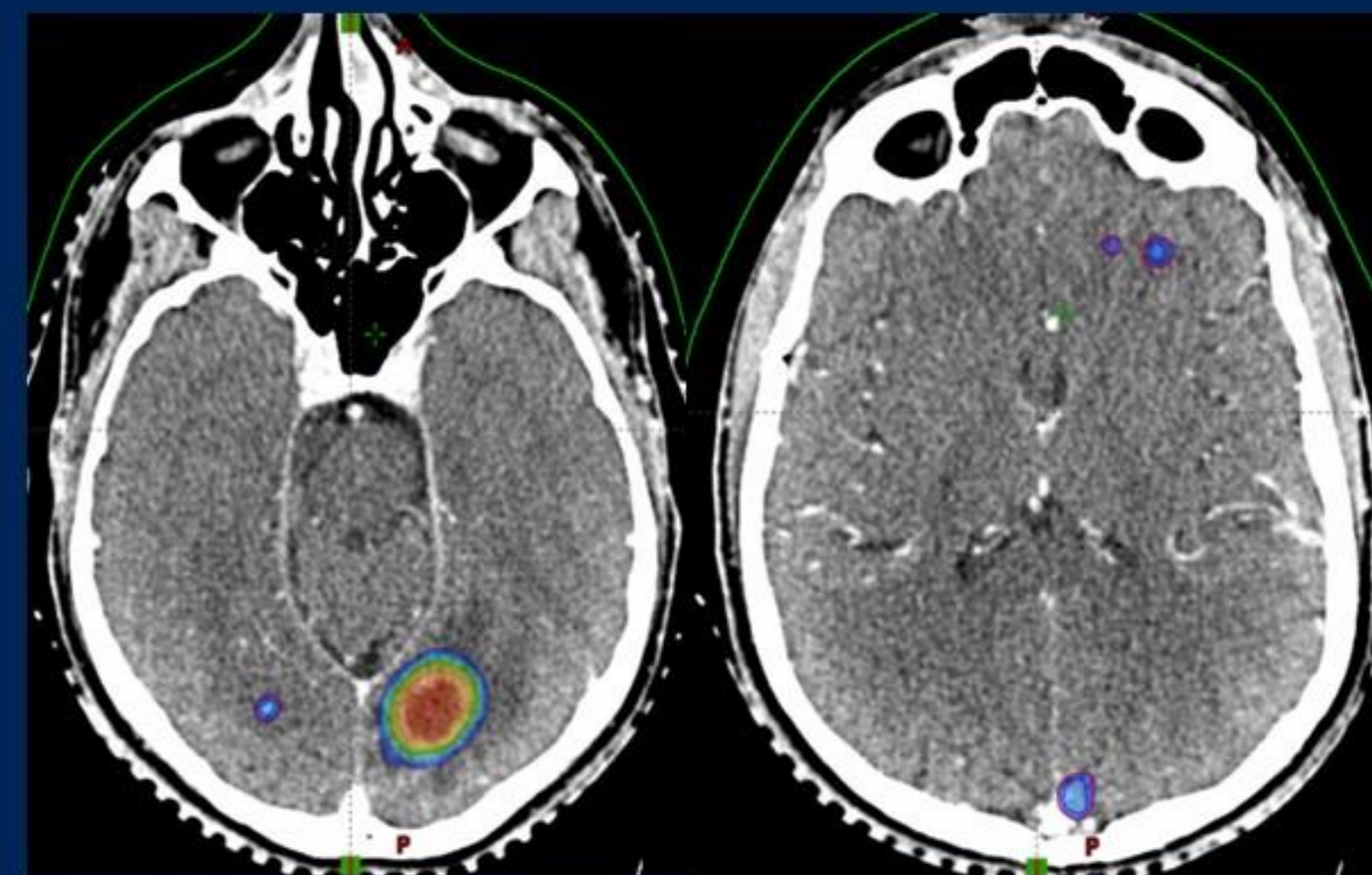
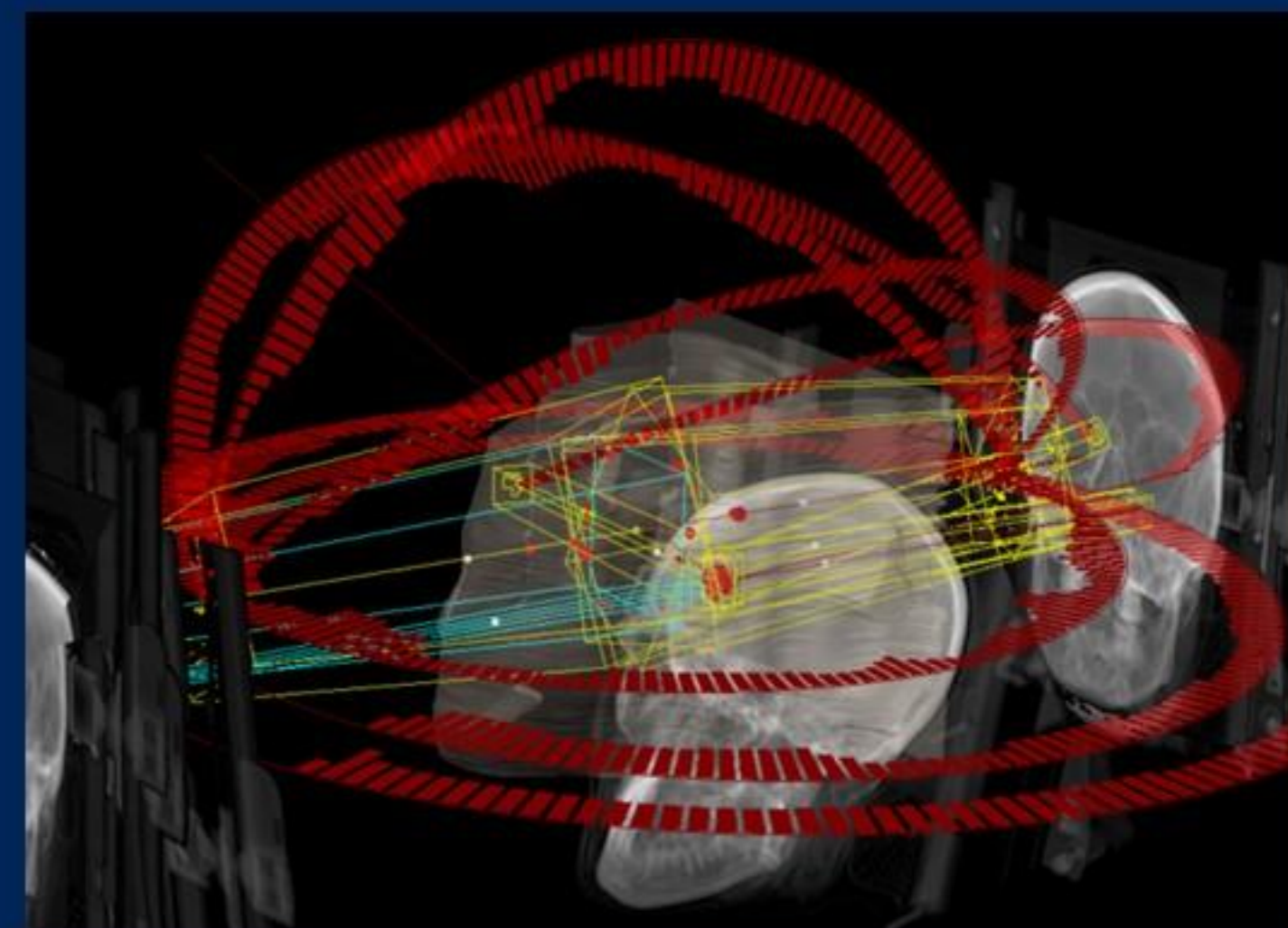
N=9 residual brain mets:

➤ SRS with 1 x 20Gy, single-isocenter

N=1 progressive brain met:

➤ SRT with 6 x 5Gy

➤ Continuation of Osimertinib



Case 2 continued

02/2022: Follow-up imaging FDG-PET and c-MRI

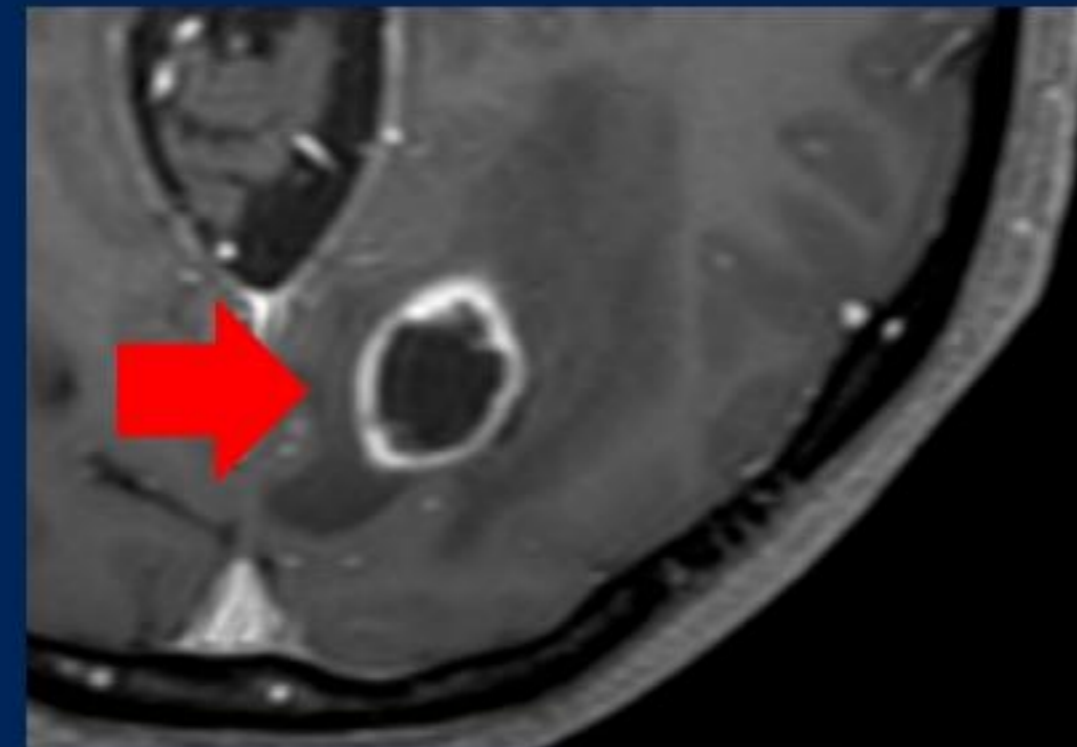
10/2021



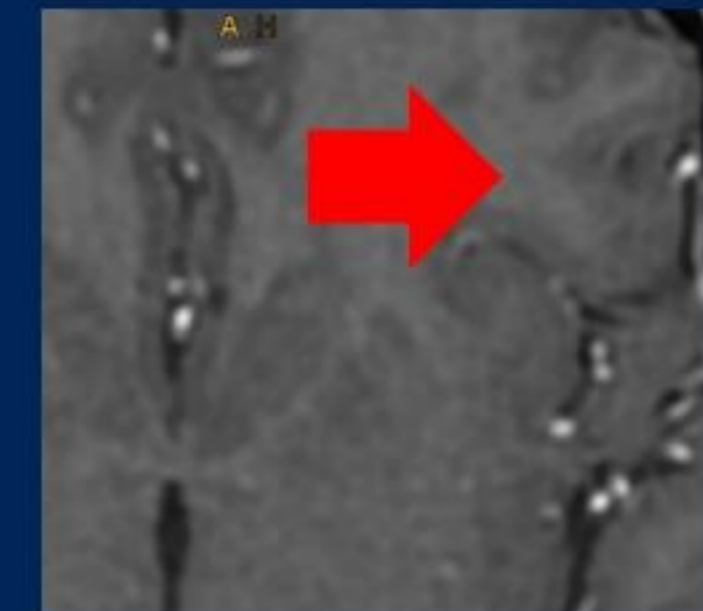
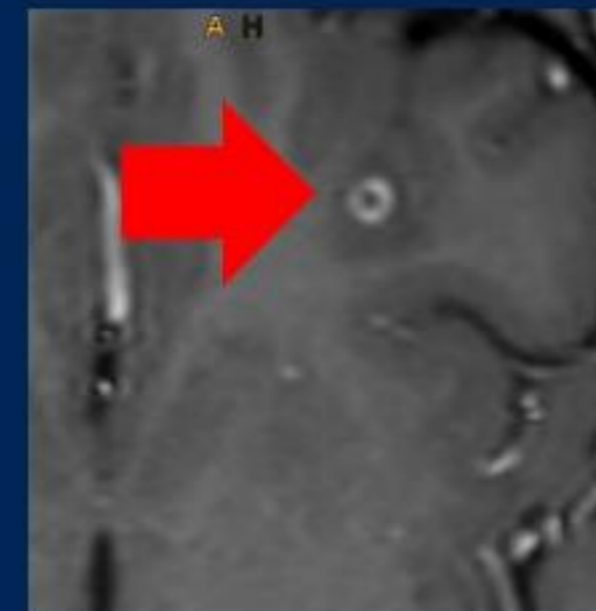
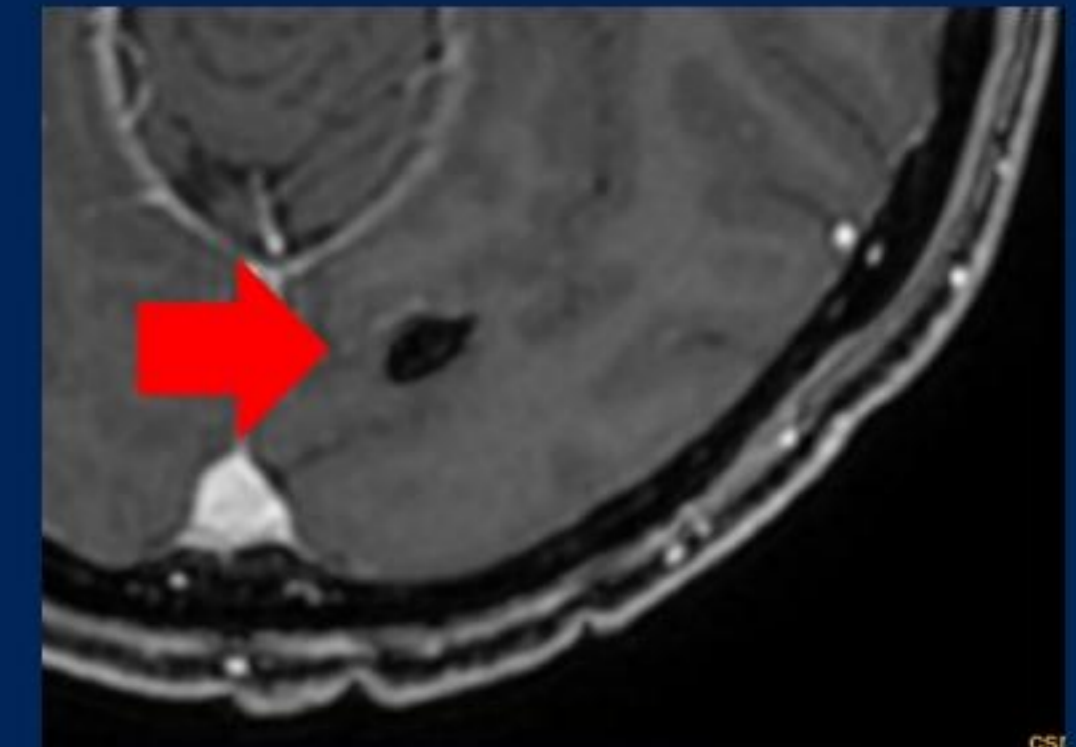
02/2022



11/2021



02/2022



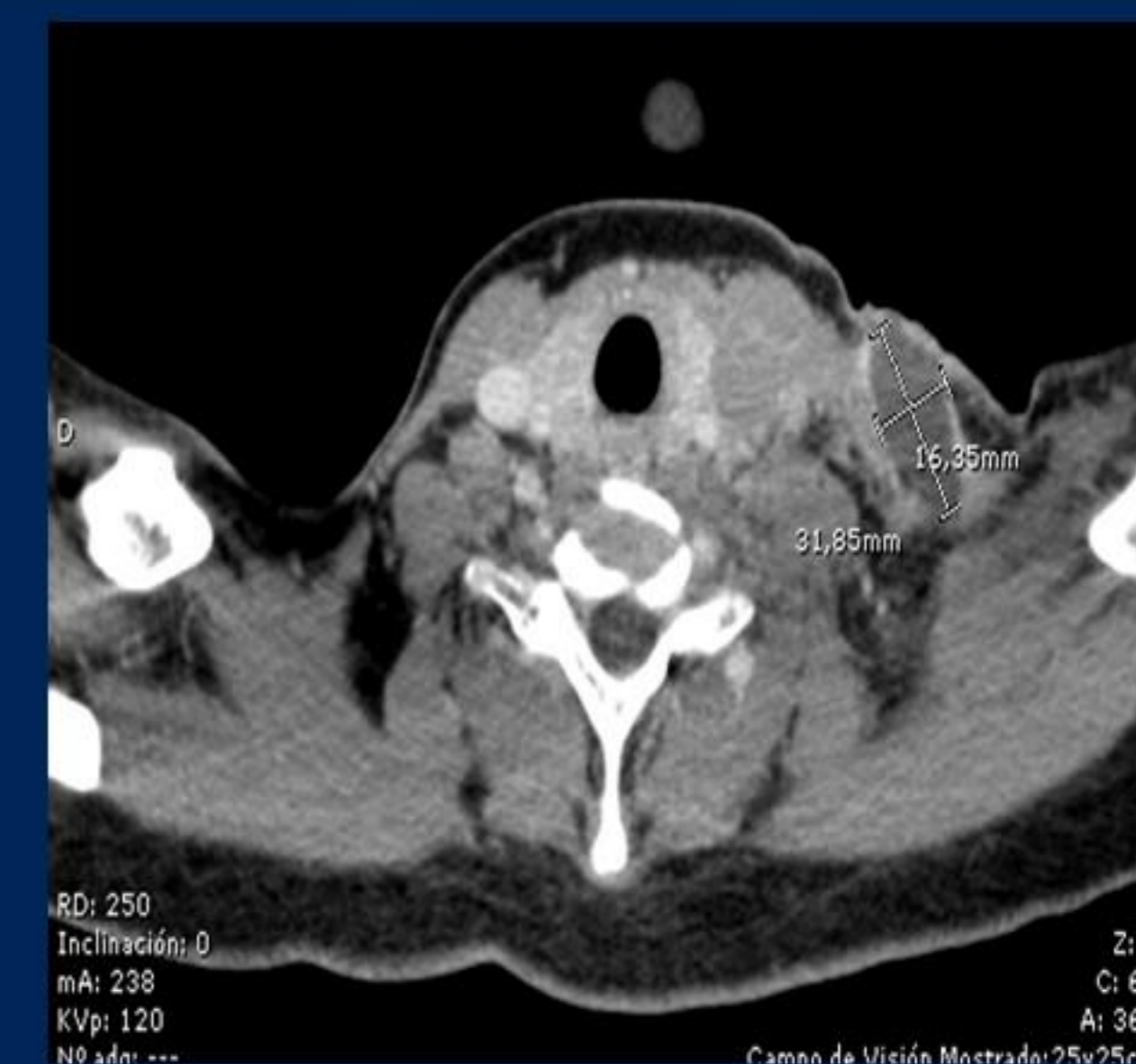
➤ Patient being in CR and free from any symptoms

Take Home messages

- EGFR kinase domain duplication is rare with 0.2% of all NSCLC pts
- Limited clinical evidence suggest sensitivity to targeted EGFRi
- No data about prevalence of brain metastases and efficacy of EGFRi
- Overall, no prospective randomized evidence about the sequencing of systemic therapy and local radiotherapy in asymptomatic patients
- If decision is made against up-front local radiotherapy, early c-MRI restaging is recommended to identify non-responders

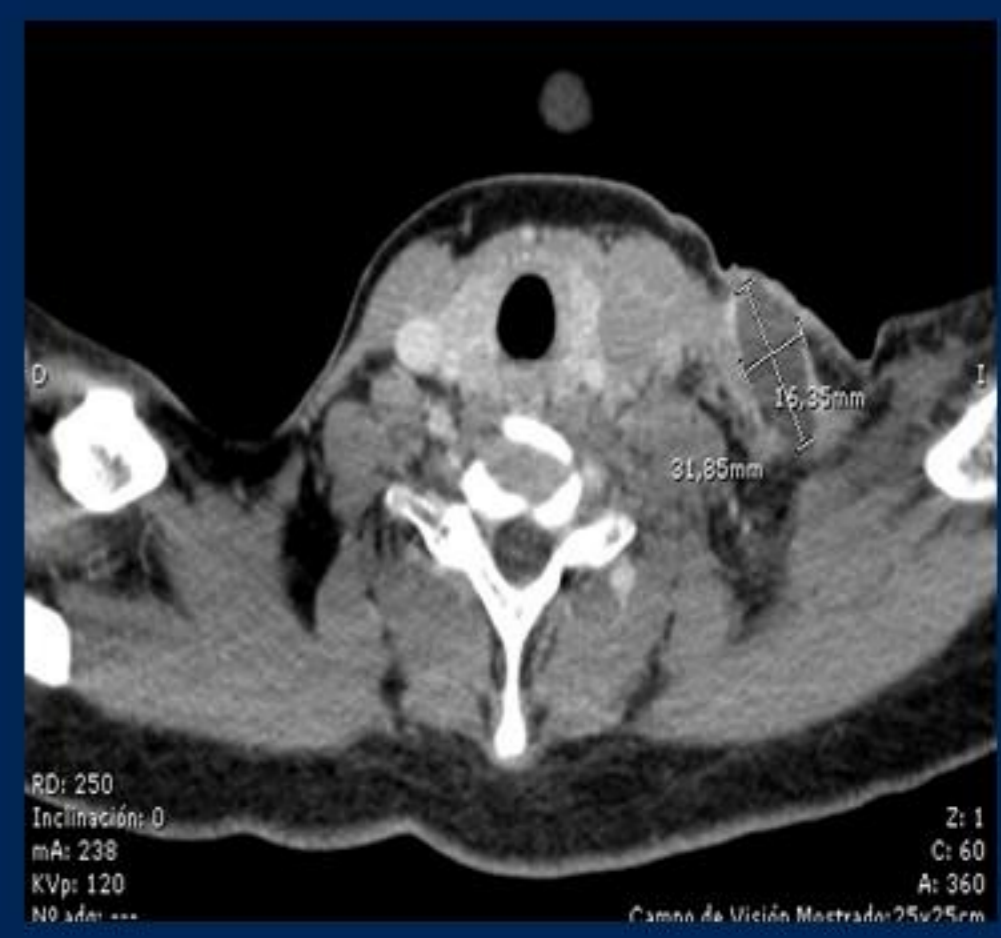
Case 3

- 29-year-old female (2015)
- Non-smoker; presented with 3 weeks of symptoms: dyspnea, cough, and dysphonia
- Findings:
 - Pleural and pericardial effusion
 - Multiple nodal involvement (bilateral cervical and supraclavicular)
 - Small lung nodule. No brain or bone metastasis
- Diagnosis: Stage IV Adenocarcinoma ALK + (FISH) in supraclavicular node biopsy and pericardial cytology
- Treatment (April 2015): Crizotinib 250 mg/12 h

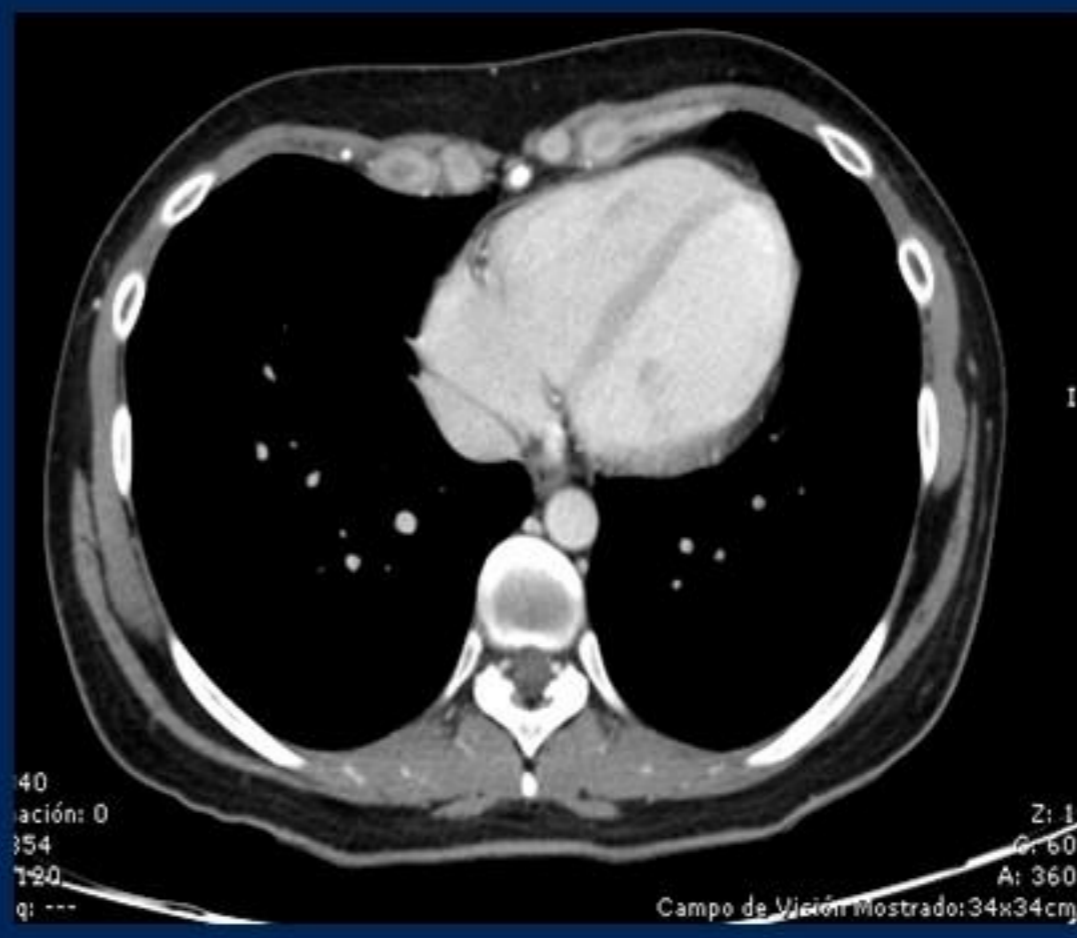


Case 3 continued

- Complete Response at first CT scan
- Treatment well tolerated



April 2015



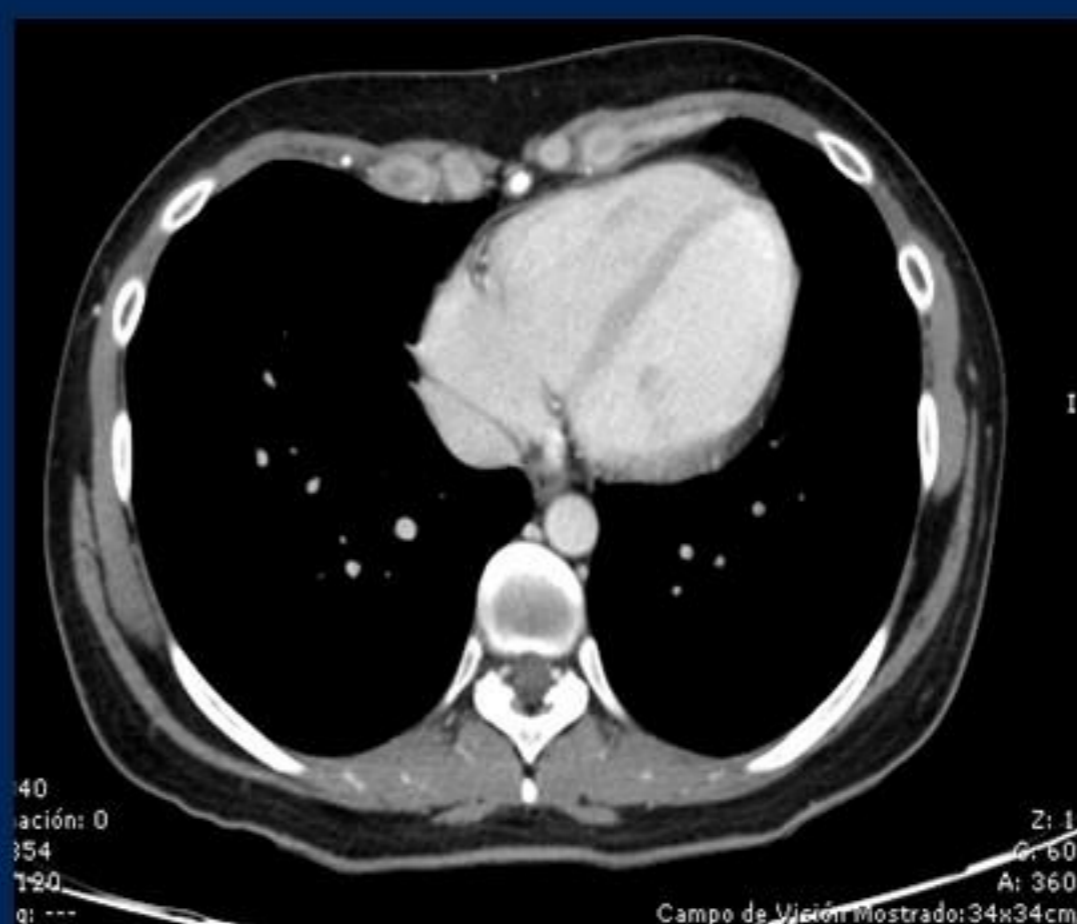
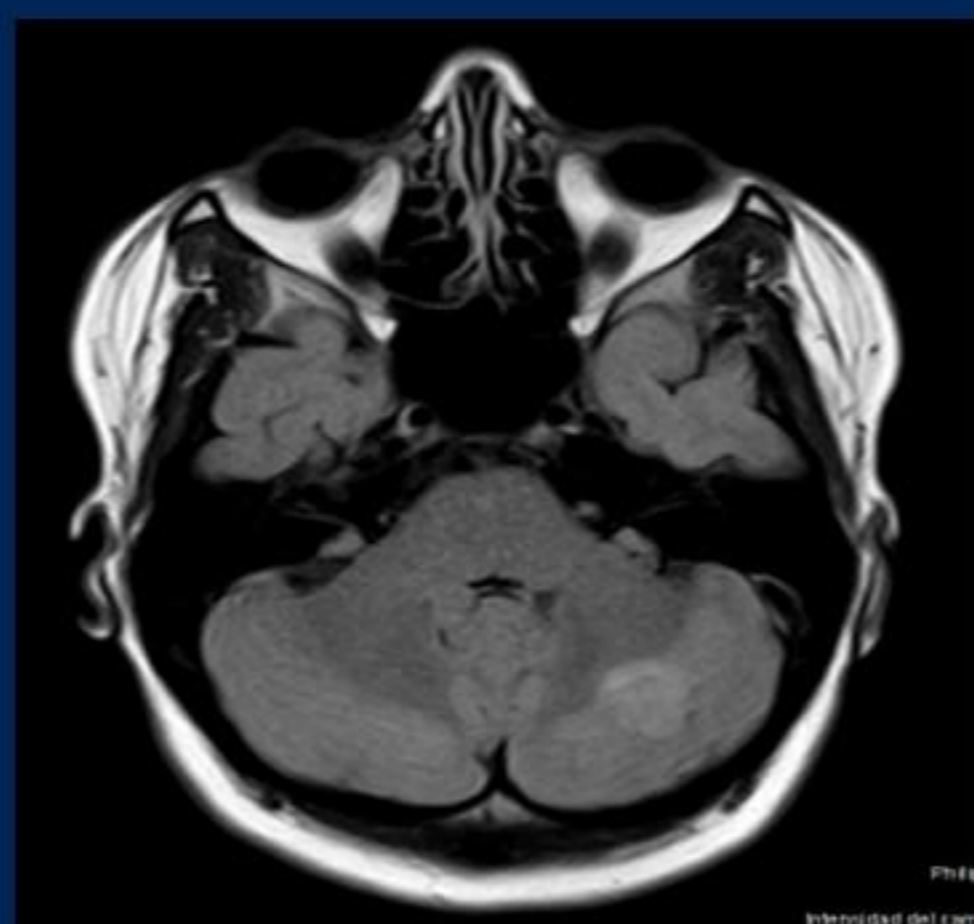
Sept 2015

Case 3 continued

- Complete Response at first CT scan
- Treatment well tolerated
- April 2016 developed brain only progression



April 2015

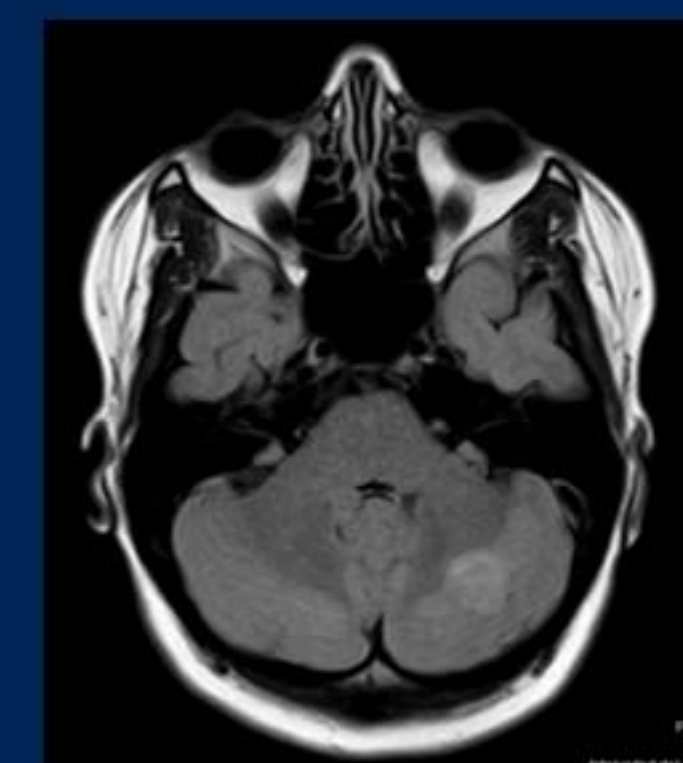


Sept 2015

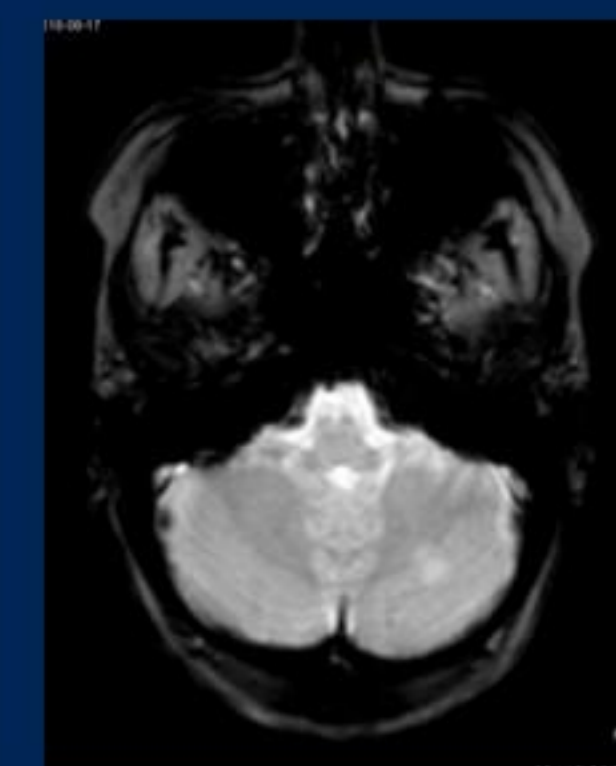
Likely Scale: How Likely Are You To Recommend “liquid biopsy” For This Patient with brain only progression?

Case 3 continued

- The patient was enrolled in ASCEND 7 study¹ (Ceritinib 750 mg/24h)
- Tolerability: Required dose reduction (600 mg/24h) due to GI tox
- Outcome:
 - Partial Response
 - Duration of response 1 year
 - **Once again exclusive brain progression**



April 2016



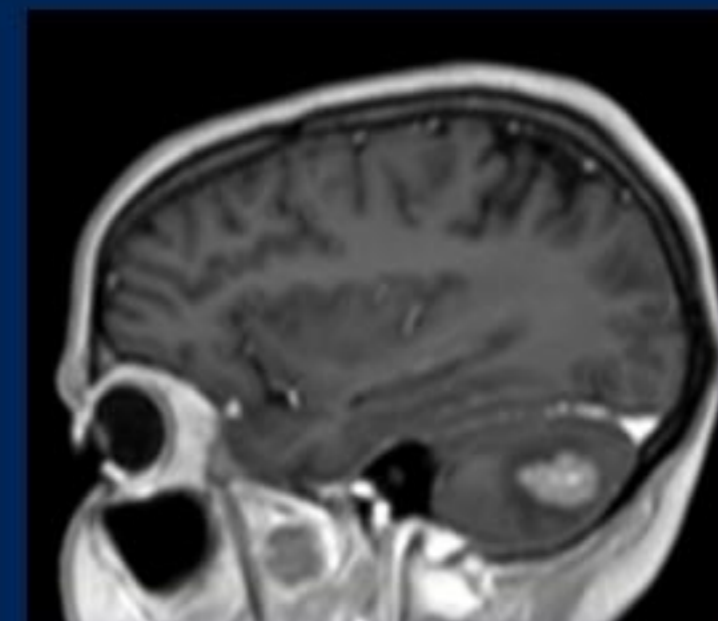
Aug 2016

¹ Chow L, Garrido P. Clin Cancer Research 2022

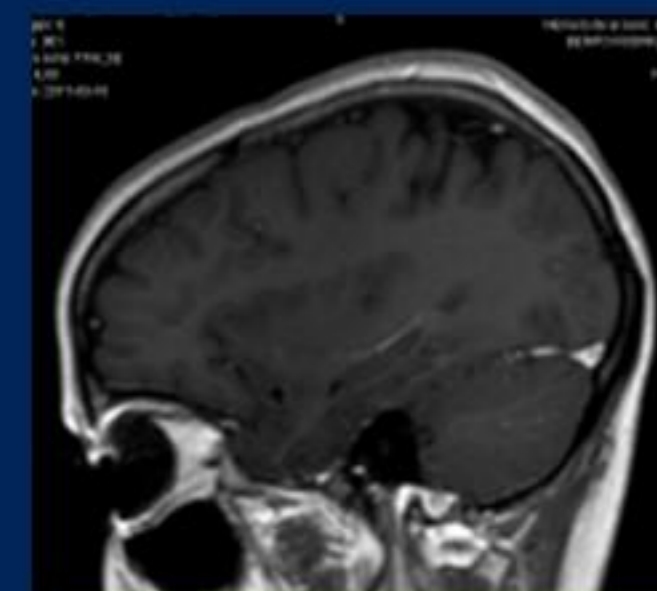
Likely Scale: How Likely Are You To introduce Alectinib And Wait For CNS Efficacy Before Suggesting Radiotherapy?

Case 3 continued

- Patient started Alectinib in Jan 2017
- Treatment well tolerated
- Achieved Complete Response



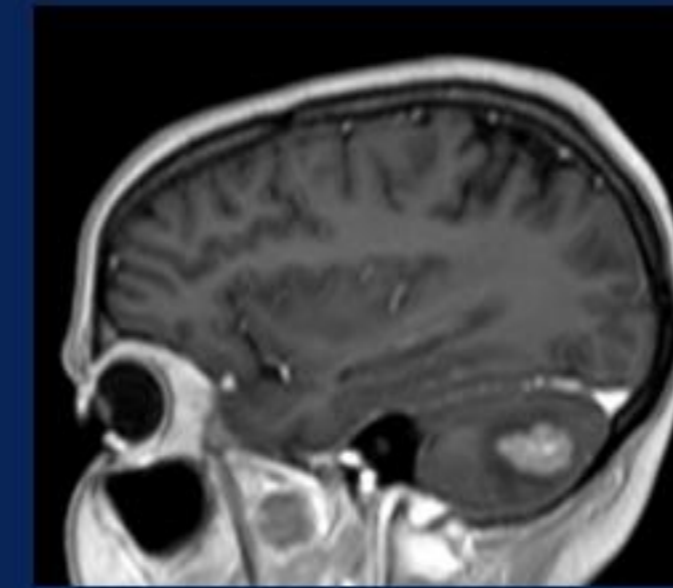
Jan 2017



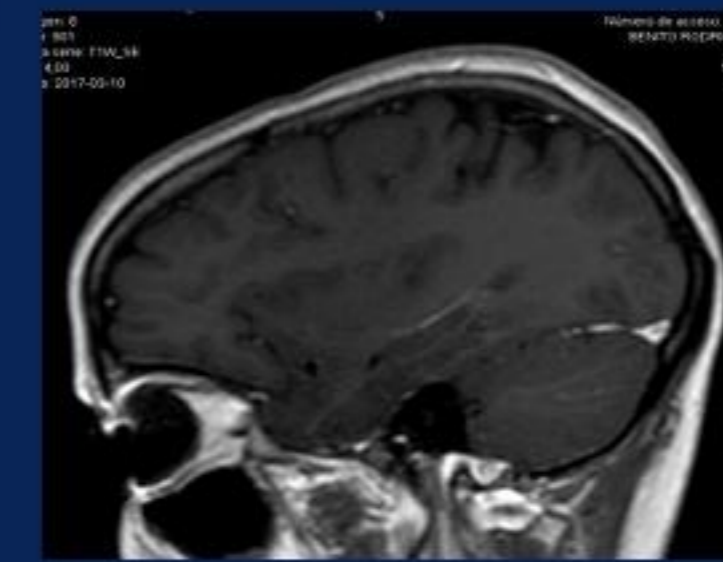
Dec 2017

Case 3 continued

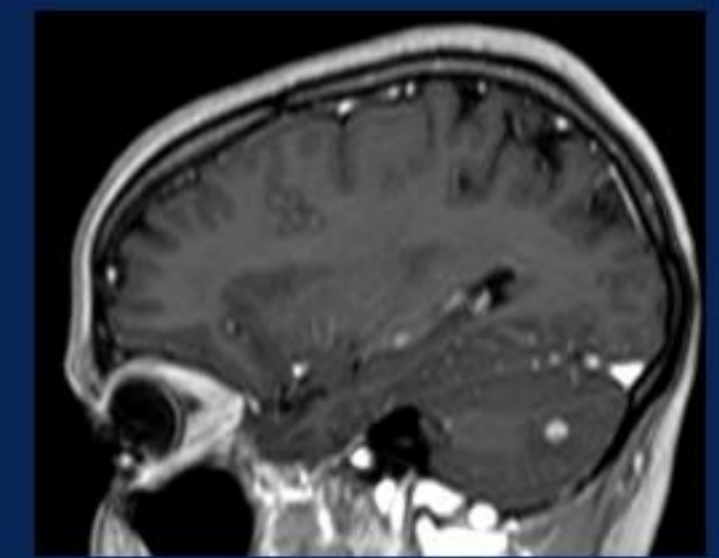
- 22 months later, new exclusive solitary brain metastasis treated with SRS (stereotactic radiosurgery)
- 7 months later (May 2019), Cerebellum lesions and radiological meningeal carcinomatosis. ECOG 0, asymptomatic.
- Lorlatinib (100 mg/ 24) was started
- So far, no progressive disease



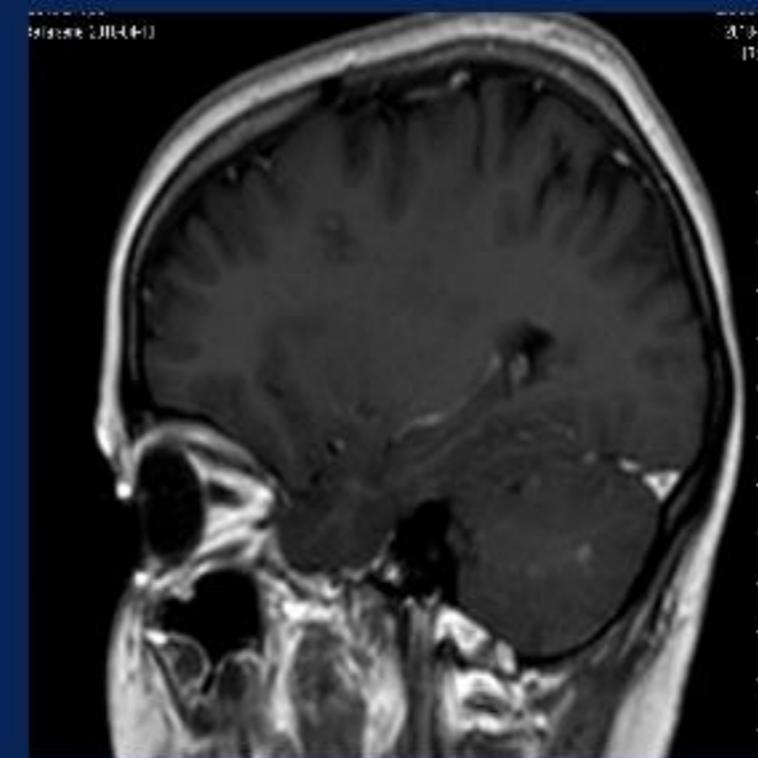
April 2017: Alectinib



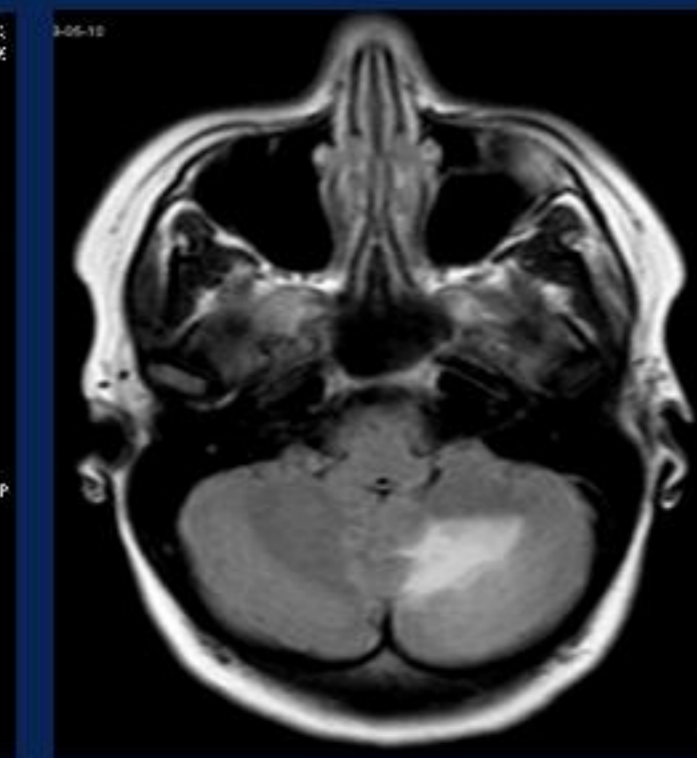
June 2017



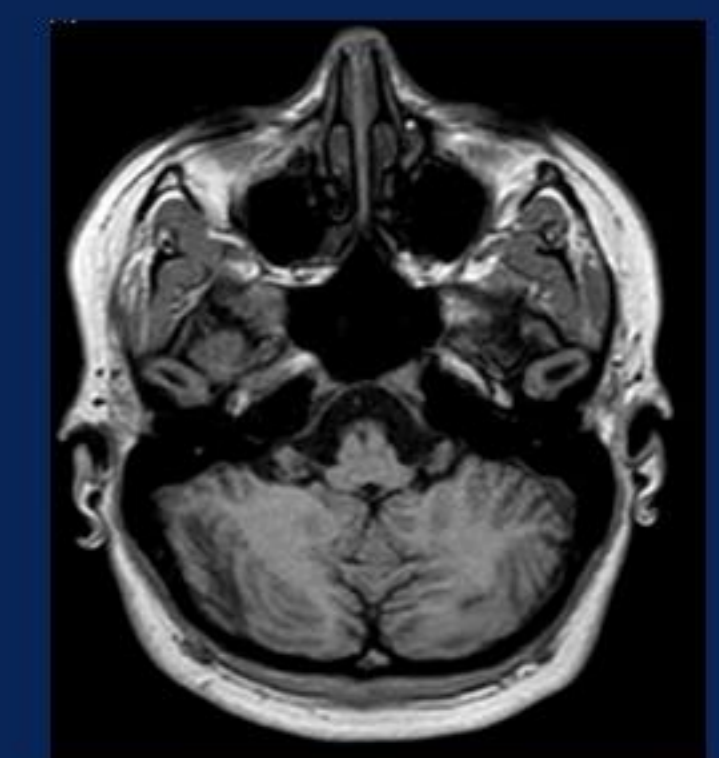
Oct 2018 SRS + Alectinib



Feb 2019



May 2019: Lorlatinib



Feb 2021

Take Home Message

- Patients with advanced NSCLC ALK + tumors have long-term survival but cure is not an option yet.
- CNS is a recurrent site of progression in ALK+ tumors and its inaccessibility for sampling remains a challenge.
- The spectrum of coverage of ALK mutations is different for each ALKi but we don't have drugs approved based on mechanisms of resistance.
- Treatment success is more than survival: short and long-term risk of toxicities, potential interactions, and even pill burden has to be taken into consideration when deciding on a therapeutic strategy.

Case 4

- 61 year-old female presented with cough. CXR was performed showing lung nodules.
- CT chest showed innumerable diffuse bilateral pulmonary nodules, enlarged bilateral mediastinal and hilar lymphadenopathy and a liver lesion measuring 1.1 cm.
- PET/CT with bone metastases
- Brain MRI with multiple small brain metastases. No CNS symptoms



Case 4 continued

- IR-guided biopsy of a left lung nodule revealed **moderately differentiated lung adenocarcinoma** (Positive for CK7, TTF-1, Napsin-A). PD-L1 (Dako 22C3) TPS = 0%
- **EGFR exon 19 del.**
- Patient was started on Osimertinib. Radiation to the brain deferred. She had an excellent response in all sites of the disease including the brain and resolution of respiratory symptoms.



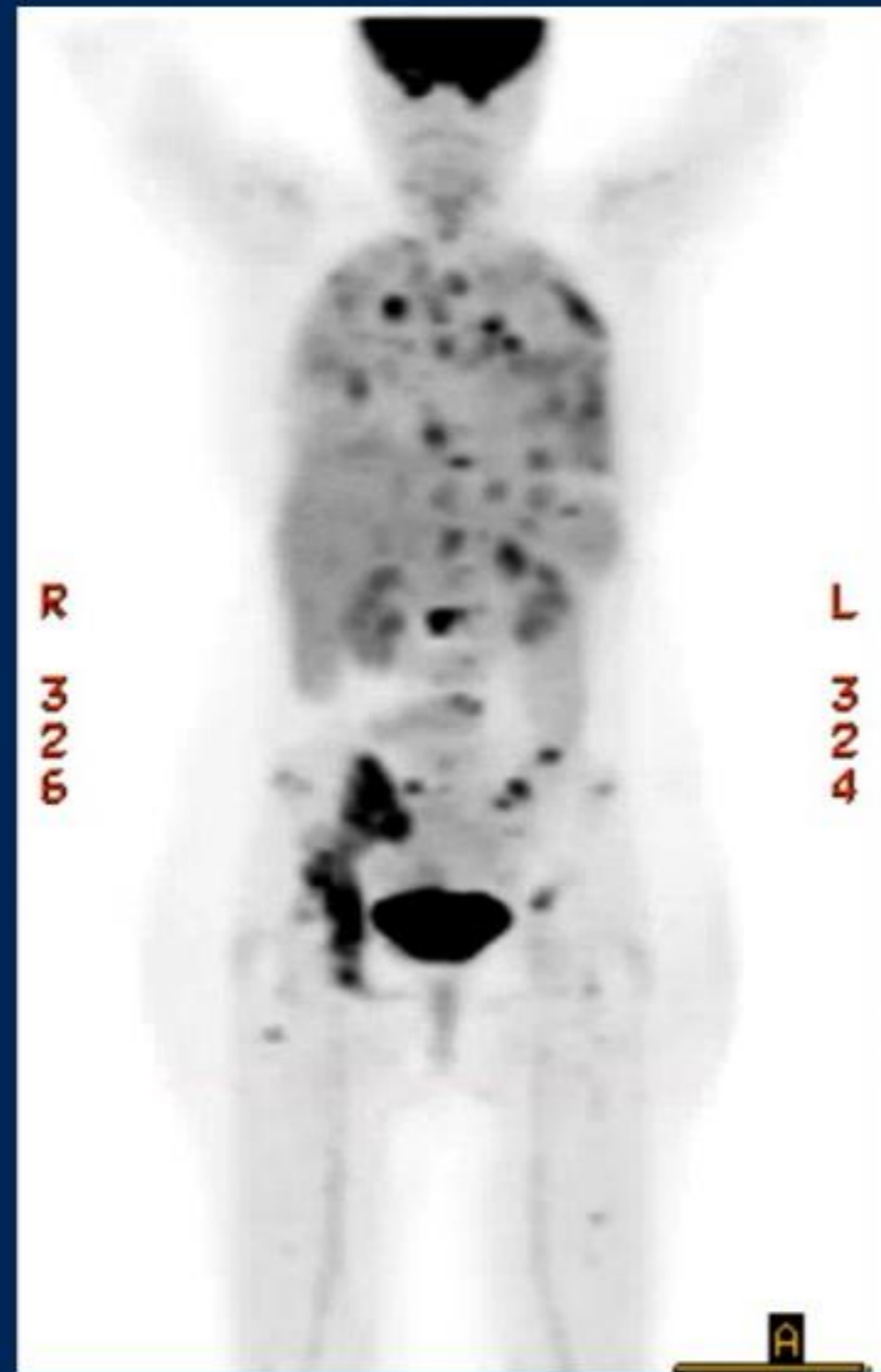
Baseline



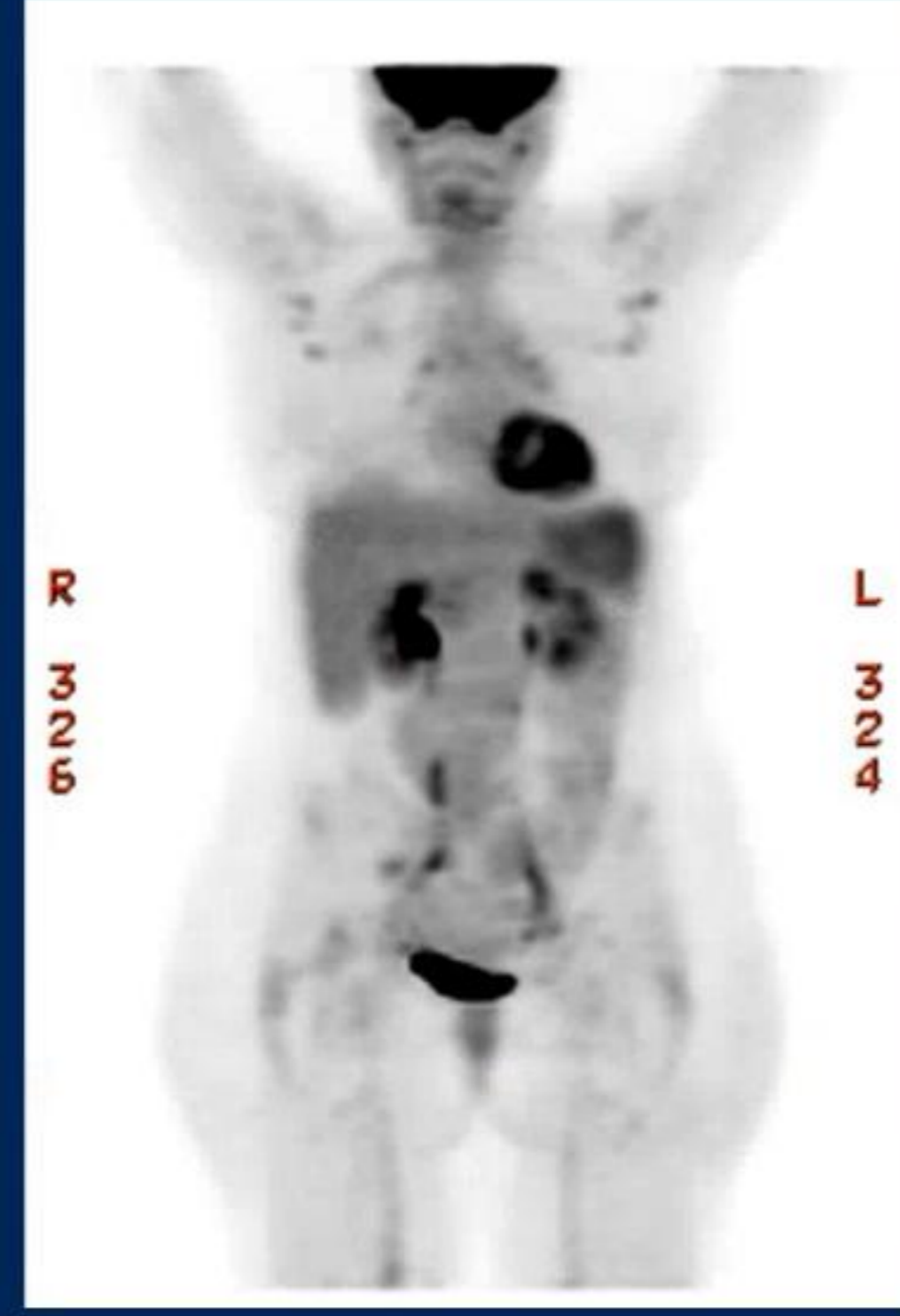
2 months on therapy

Case 4 continued

- 9 month later new bone pain
- PET/CT with PET positive bone metastasis, new lung nodule and hilar adenopathy



BASELINE



2 MONTHS



9 MONTHS

Agree/Disagree:

**Would you perform a biopsy of a
progressive lesion**

Case 4 continued

- ctDNA no alterations
- Tissue NGS
 - EGFR Exon 19 L747_S752 del/ins Q
 - EGFR C797S
 - NTRK amplification

Multiple Choice Question: What would you do next?

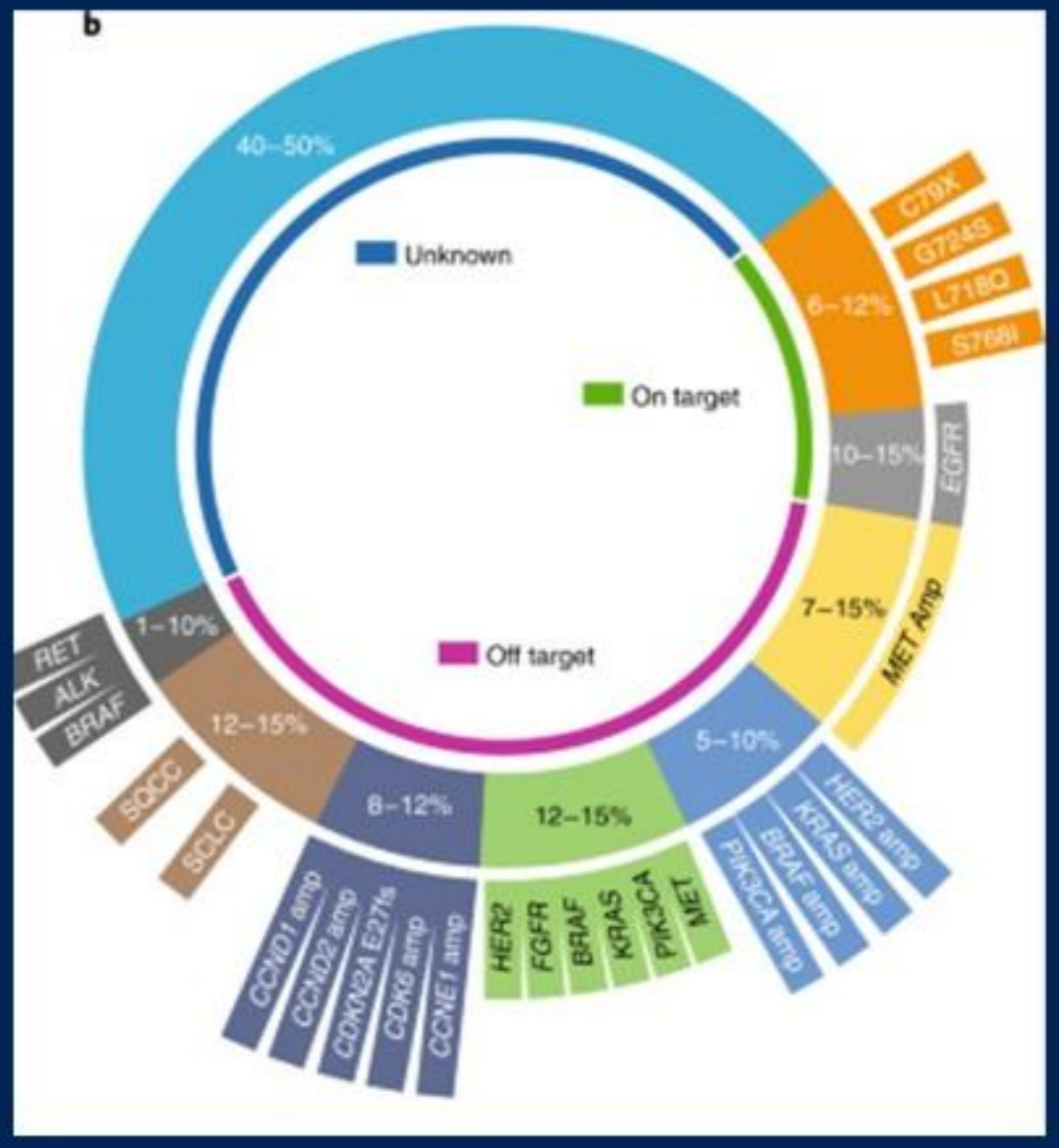
- A. Switch to platinum doublet +/- immunotherapy
- B. Switch to platinum doublet and continue on osimertinib
- C. Switch to erlotinib
- D. Add erlotinib to osimertinib

Case 4 continued.

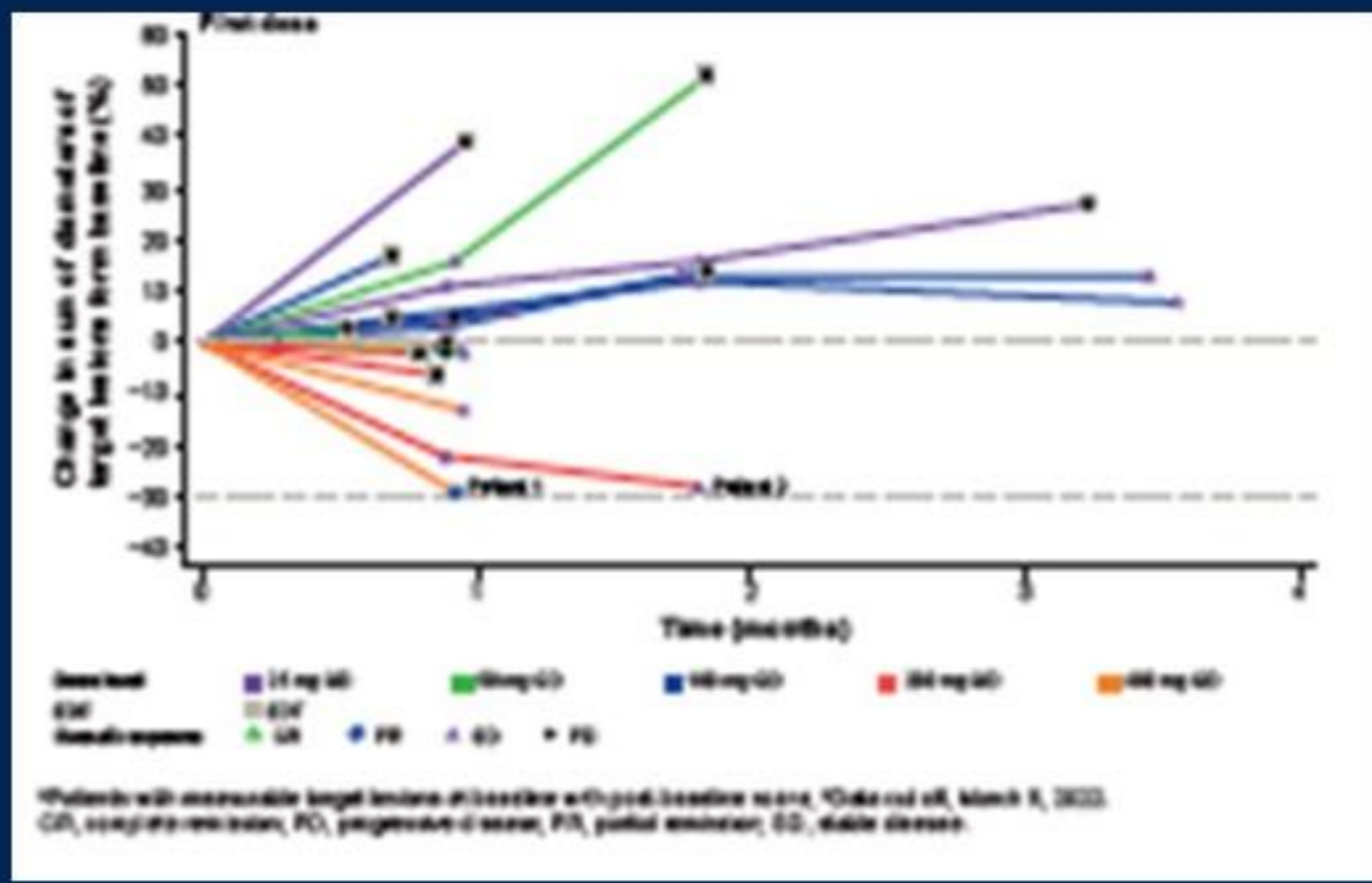
- Patient was continued on osimertinib and erlotinib was added.
- Imaging 2 month after therapy showed progression both in CNS and further systemic progression.
- Patient was switched to chemotherapy

Take home message

- On target and off target resistance to Osimertinib has been reported
- C797S mutation inhibits covalent binding of osimertinib to EGFR protein
- 1st generation inhibitors (erlotinib and gefitinib) are not affected due to different binding site
- Novel 4th generation EGFR inhibitors (EAI045, BLU 945, BLU 701) are currently in development.



Passaro et al Nature Cancer 2021



- EGFR ex19del, T790M and C797S
- L858R, T790M and C797S

Shum et al AACR 2022

TARGETED THERAPY

original reports

Clinical Benefit of Comprehensive Genomic Profiling for Advanced Cancers in India

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abstract

PURPOSE Comprehensive genomic profiling (CGP) assay is increasingly used in low-middle-income countries to detect clinically relevant genomic alterations despite its clinical benefits not being well known. Here, we describe the proportion of patients with advanced cancer in India who received targeted therapy for an actionable genetic alteration identified on CGP assays.

METHODS This was a multicenter, retrospective cohort study in adult patients with advanced nonhematologic malignancies who underwent a CGP test. If patients received a targeted therapy for ≥ 6 months, they were considered to have obtained a clinical benefit from the medication, whereas those continuing for ≥ 12 months were considered to have attained an exceptional response. Descriptive statistics were used to describe the proportion of patients with subsequent targeted therapy.

RESULTS During 2019-2020, 12 medical oncologists provided CGP reports for 297 patients; 221 met the inclusion criteria. Patients received a median of two lines (range: 0-5) of prior systemic therapy. On the basis of the CGP assay, 21 patients (10%) received targeted therapy. Among them, 33% was for human epidermal growth factor receptor 2 (HER2) amplification (nonbreast cancer) and 19% for HER2 or epidermal growth factor receptor exon 20 insertion mutation (lung cancer). After excluding patients with HER2 or epidermal growth factor receptor exon 20 insertions, 8% of 217 patients received targeted therapy. In the overall cohort of 221 patients, clinical benefit was seen in nine patients (4%), of whom two were exceptional responders (1%).

CONCLUSION We observed that in a low-middle-income country setting, 10% of patients received targeted therapy on the basis of CGP assay. Only 4% of patients who underwent CGP testing obtained a clinical benefit.