Expert Panel:
Processing Treatment Options

EGFR esisters

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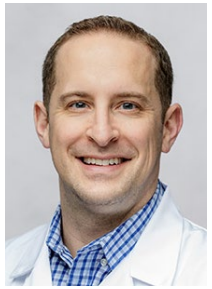

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Session Objectives

1. Explain the treatment options for *EGFR*-positive lung cancer and when each one is typically used.

2. Discuss common challenges and questions about choosing treatments and clinical decision-making.

3. Review treatment considerations in the setting of disease progression and across subsequent lines of therapy.

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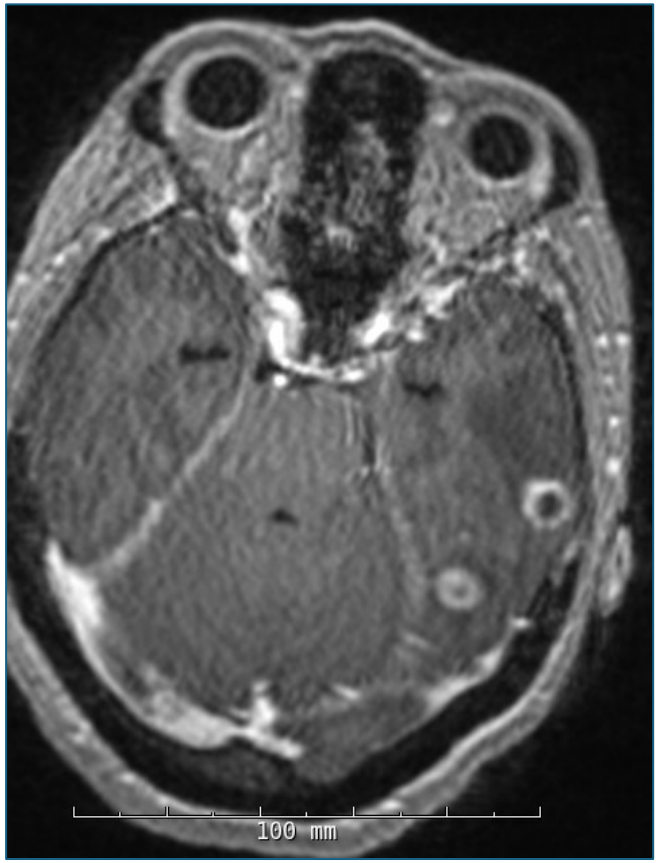
Case Presentation: Oligometastatic *EGFR*m NSCLC

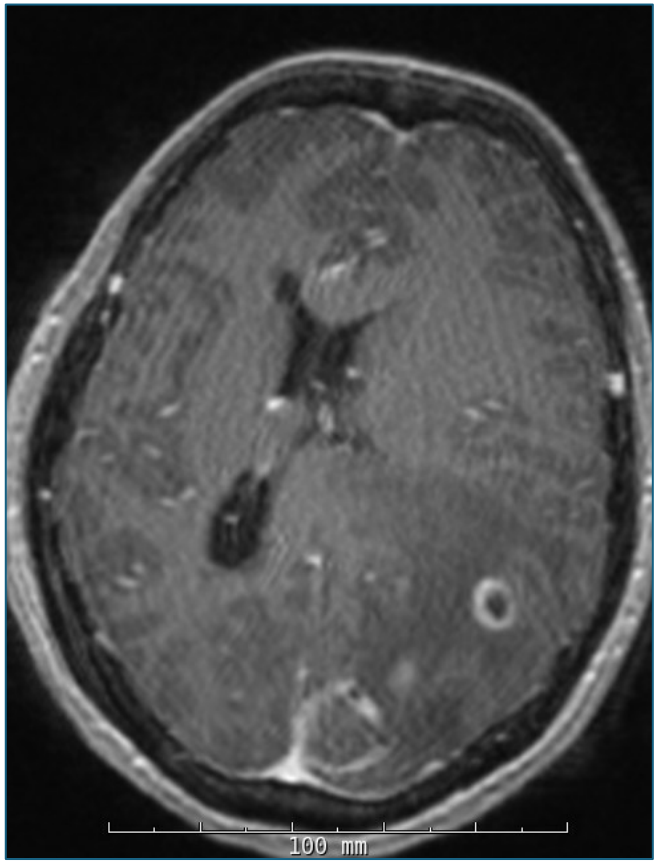
Gaurav Marwaha, MD
Chairperson, Radiation Oncology
Rush University
RUSH MD Anderson Cancer Center
Chicago, IL

Initial Presentation

- 61yo F with 2 weeks of blurry vision, headache, gait instability, nausea/vomiting, found to have large edema in the temporoparietal and occipital lobes
- Patient was admitted to neuro ICU with altered mental status

Initial Presentation

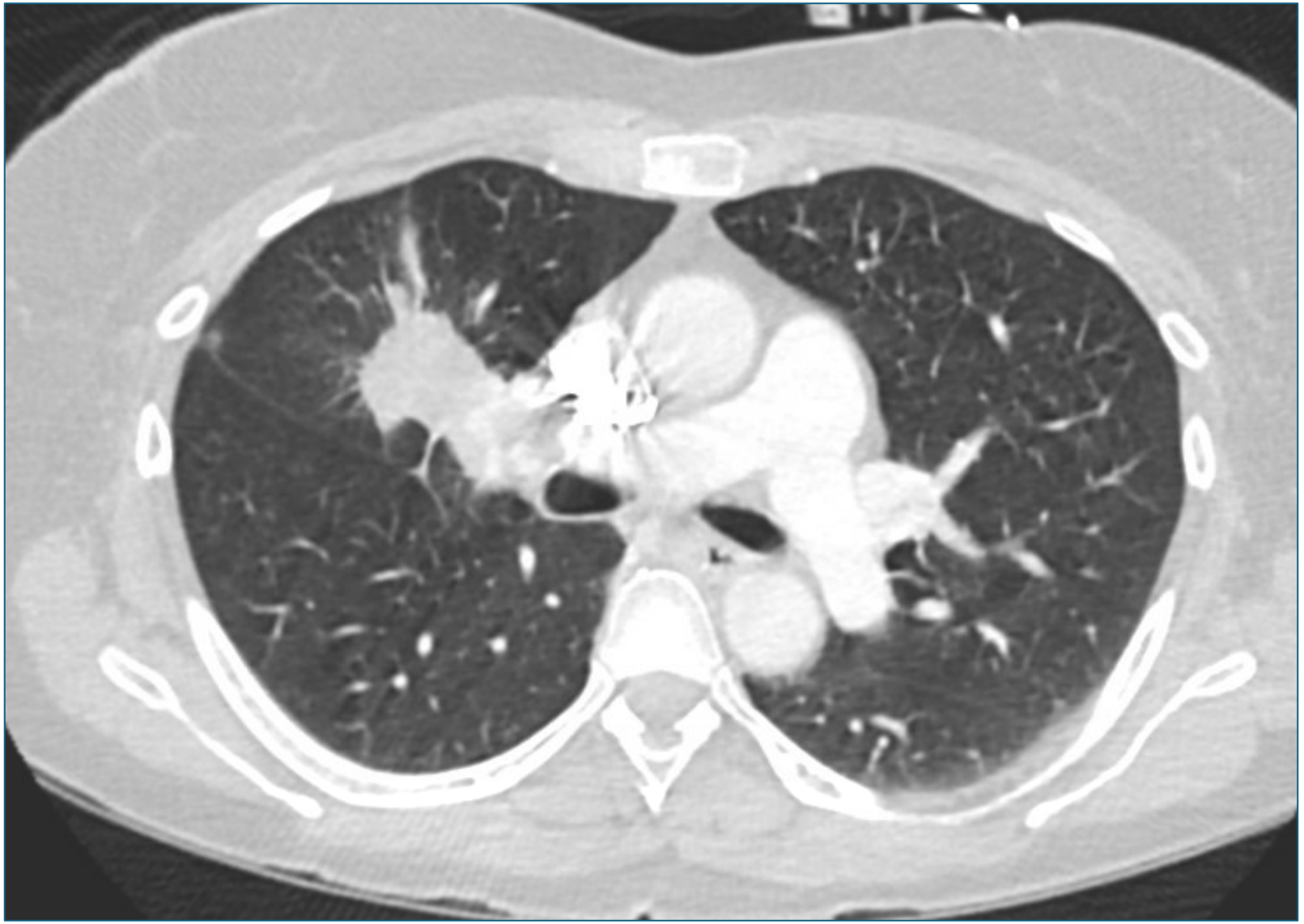




MRI Brain

- Dominant large cystic mass in the left occipital lobe with extensive surrounding edema and mass effect.
- Midline shift to the right measuring 10 mm with mild dilatation of the right lateral ventricle.
- Mild left uncal herniation with distortion of the midbrain. In addition, scattered nodular and ring-enhancing lesions in both cerebellar hemispheres, left temporal and parietal regions.
- Findings most consistent with metastasis.

Images provided courtesy of Dr. Gaurav Marwaha.



CT Chest, Abdomen, Pelvis:

1. Right upper lobe mass, measuring 2.2 x 1.6 cm with possible adjacent necrotic right perihilar lymph node as detailed above, difficult to differentiate from the adjacent mass. Diagnosis of exclusion is primary lung neoplasm. Tissue diagnosis is advised.

2. Several hyperdense rim enhancing masses within the right hepatic lobe concerning for metastatic lesions.

Image provided courtesy of Dr. Gaurav Marwaha.

Biopsy and Staging

Patient underwent L craniotomy and surgical resection of L occipital met:

FINAL DIAGNOSIS
A. Left occipital lesion, Craniotomy and tumor resection: Metastatic adenocarcinoma, consistent with a lung primary

EGFR exon 19del on Tempus

Stage cT1cN0M1c1 (stage IVB)

Questions for Multidisciplinary Team

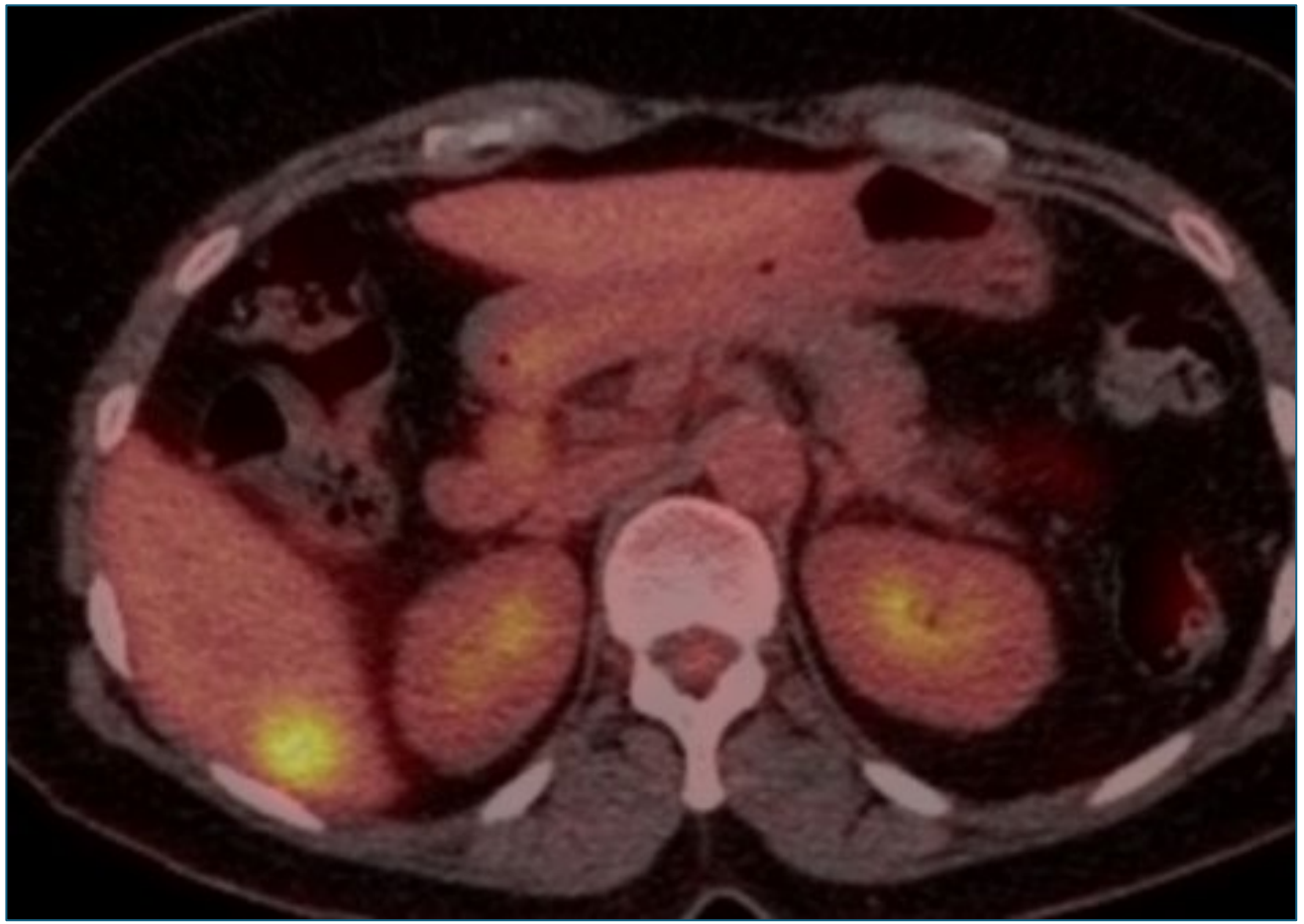
#1) Start with osimertinib or offer cavity and intact brain met SRS?

#2) Consider SBRT to any other sites up front?

SRS, stereotactic radiosurgery; SBRT, stereotactic body radiation therapy

What Actually Happened

- SRS to L Temp met 21 Gy/ 1 fx, L occipital met 21 Gy/ 1 fx and left occipital cavity 27 Gy/ 3 fx.
- Osimertinib started immediately after
- Monitored liver and lung



- ***1 year later***, restaging scans reveal oligoprogression in liver
- No other active sites on PET/CT

Multidisciplinary Team Question #3) Re-biopsy or empirically treat with local therapy? Surgery, ablation, SBRT?

Image provided courtesy of Dr. Gaurav Marwaha.

What Happened – and What Next?

- Liver lesion, biopsies:
  Metastatic pulmonary adenocarcinoma, infiltrating liver parenchyma, with similar molecular profile (*EGFR*m)
- SBRT completed 50 Gy / 5 fx with great response

Multidisciplinary Team Question #4)

6 months later, several more liver and now bone metastases…
Next steps?

What Happened – and What Next?

- Biopsy of liver reveals progressive disease, now with C797S resistance

Multidisciplinary Team Question #5)

What to do next?

What Happened – and What Next?

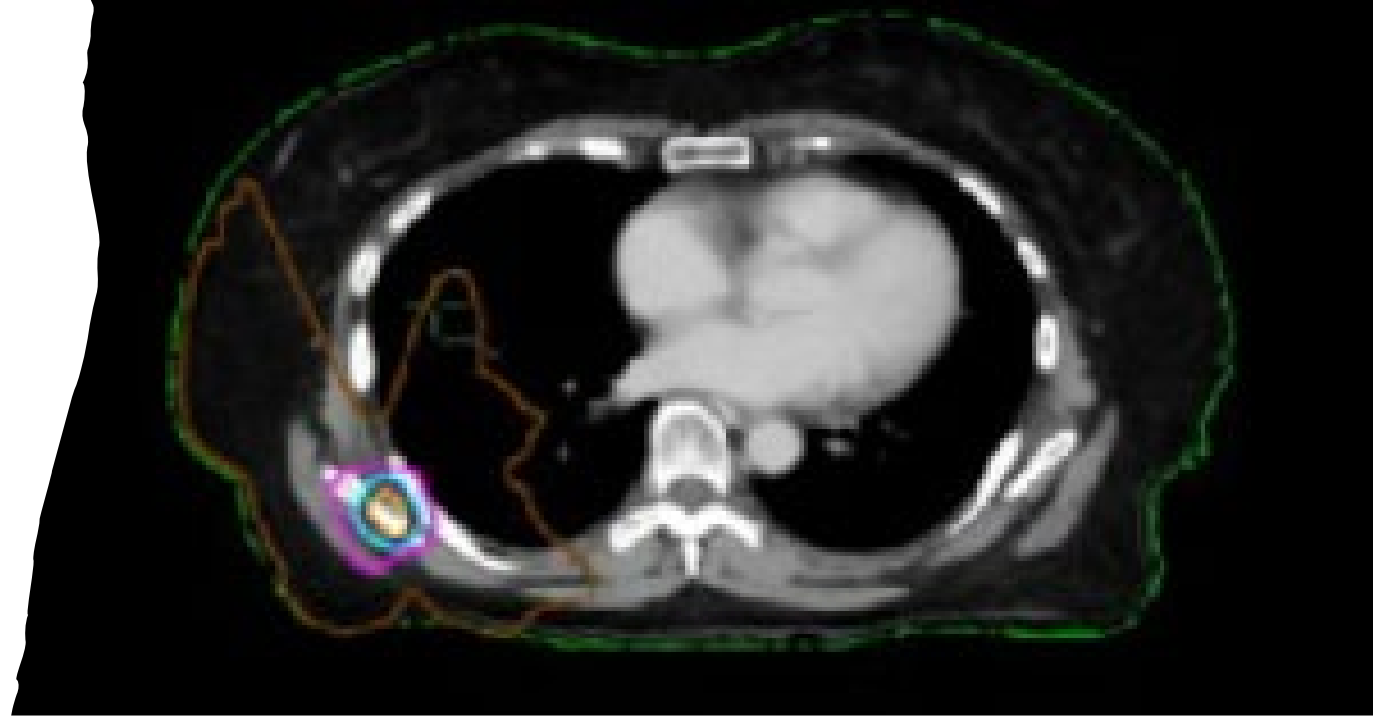
- Patient started on a clinical trial (BDTX) with initial good response
- Patient progressed again in same areas, started on CARBOplatin/PEMEtrexed/amivantamab -> Dato-DXD + osimertinib
- **2 years later**, now with oligoprogression in liver and R scapula

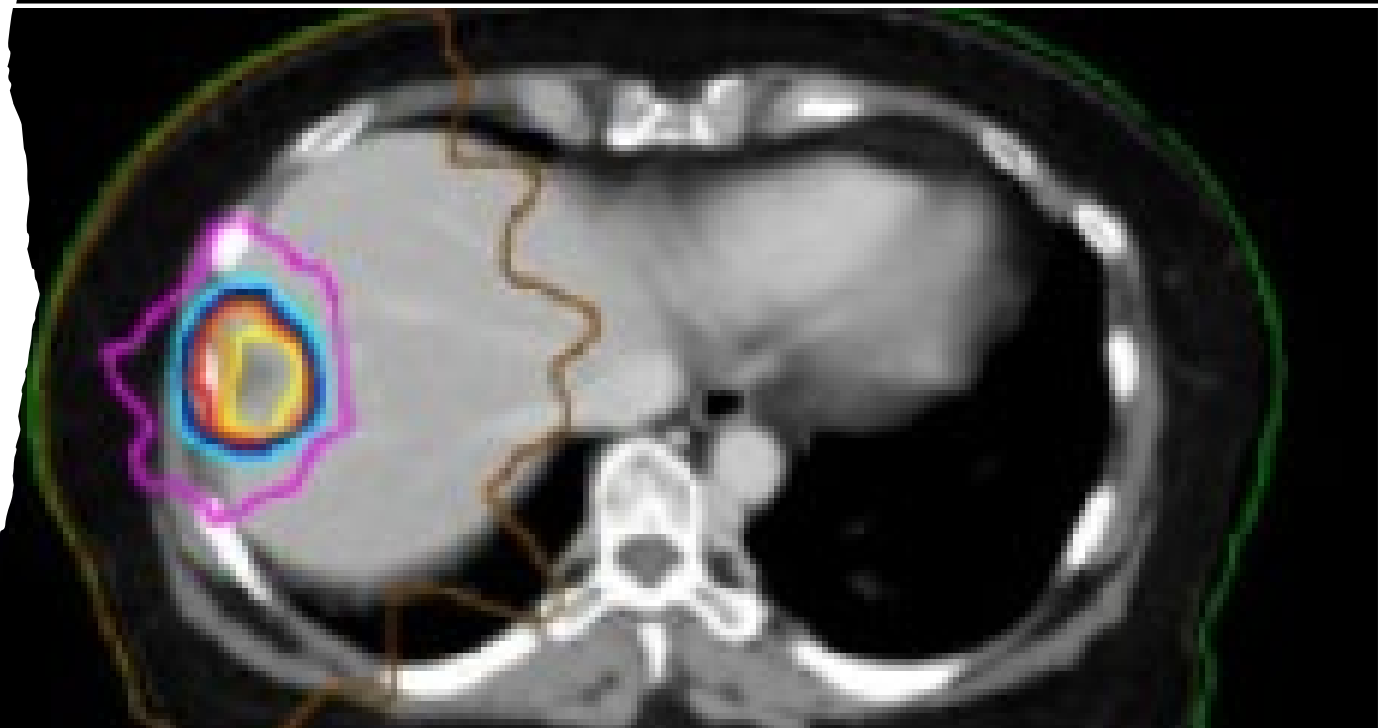
- Multidisciplinary Team Question #6)

Change in systemic therapy or local ablation?

Current Status

- SBRT 50 Gy in 5fx to liver and 40Gy in 5fx to right scapula
- Doing well!
- Now 5 years from initial diagnosis





Images provided courtesy of Dr. Gaurav Marwaha.

Case Presentation: LCT for Stage IV *EGFR*m NSCLC

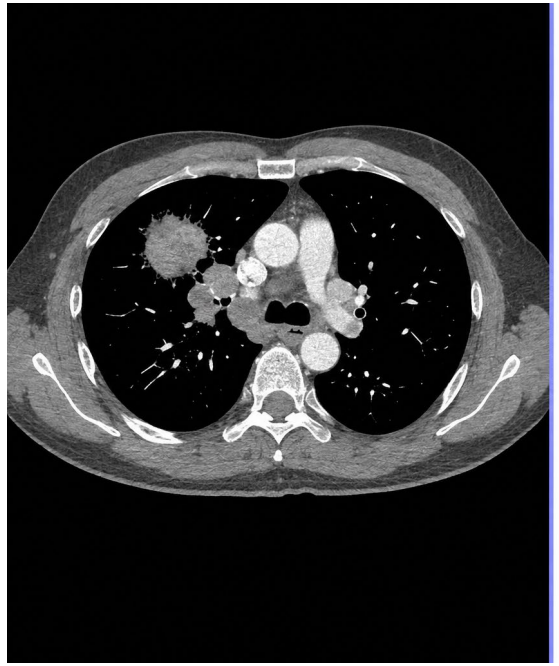
Mara Antonoff, MD, FACS
Program Director of Education, Thoracic, and Cardiovascular Surgery
University of Texas MD Anderson Cancer Center
Houston, TX

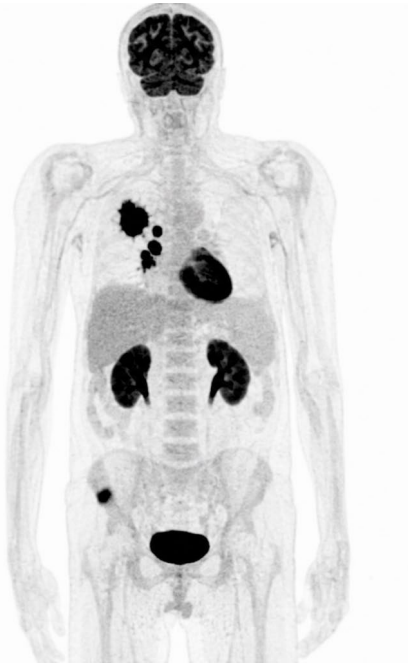
Initial Presentation

- 41-yo woman in previously excellent health
- Works as dental hygienist, lives with spouse and 3 children, enjoys cycling and Pilates
- Developed persistent cough after respiratory infection went through household, had multiple rounds of antibiotics without resolution
- Starting having right-sided chest discomfort intermittently, as well

Diagnosis

- Imaging revealed 4.6 cm right upper lobe mass
- Enlarged right hilar and mediastinal lymph nodes
- 3 sub-centimeter brain metastases
- Solitary lesion in the R iliac bone
- No neurologic symptoms or bone pain





Biopsy: Lung adenocarcinoma with an EGFR exon 19 deletion

Images provided courtesy of Dr. Mara Antonoff.

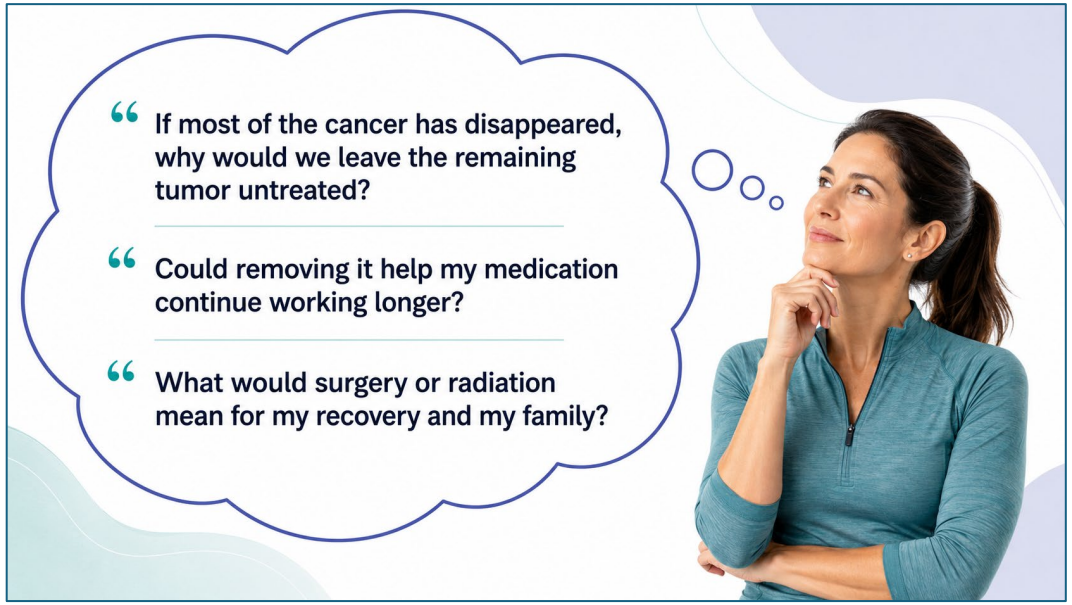
Response to Systemic Therapy

- Osimertinib + carboplatin-pemetrexed x 4 cycles →maintenance osi
- Brain metastases resolve without radiation
- Iliac lesion becomes sclerotic and metabolically inactive
- Primary tumor decreases from 4.6 cm → 2.1 cm
- 1 right hilar lymph node remains enlarged and mildly PET-avid
- No new disease after 4.5 months of treatment
- Remains active, working, cycling, and caring for her children

Excellent systemic response

Should local therapy be considered based on her disease burden at diagnosis or the disease that remains now?

Now What?



Possible Strategies:

- Continue osimertinib alone
- Radiation to the residual lung and nodal disease
- Pulmonary resection with lymph node assessment

- ***What additional info is needed before recommending LCT?***
- ***How should surgery and radiation be considered?***
- ***Should the previous brain and bone sites also receive local treatment?***

Considerations & Take-Aways

- 41 years old
- EGFR exon 19 deletion
- Initial brain and bone metastases
- Excellent response to osimertinib
- Residual resectable lung/nodal disease
- No progression at 4.5 months

What matters most when deciding whether local therapy offers meaningful value to this patient?

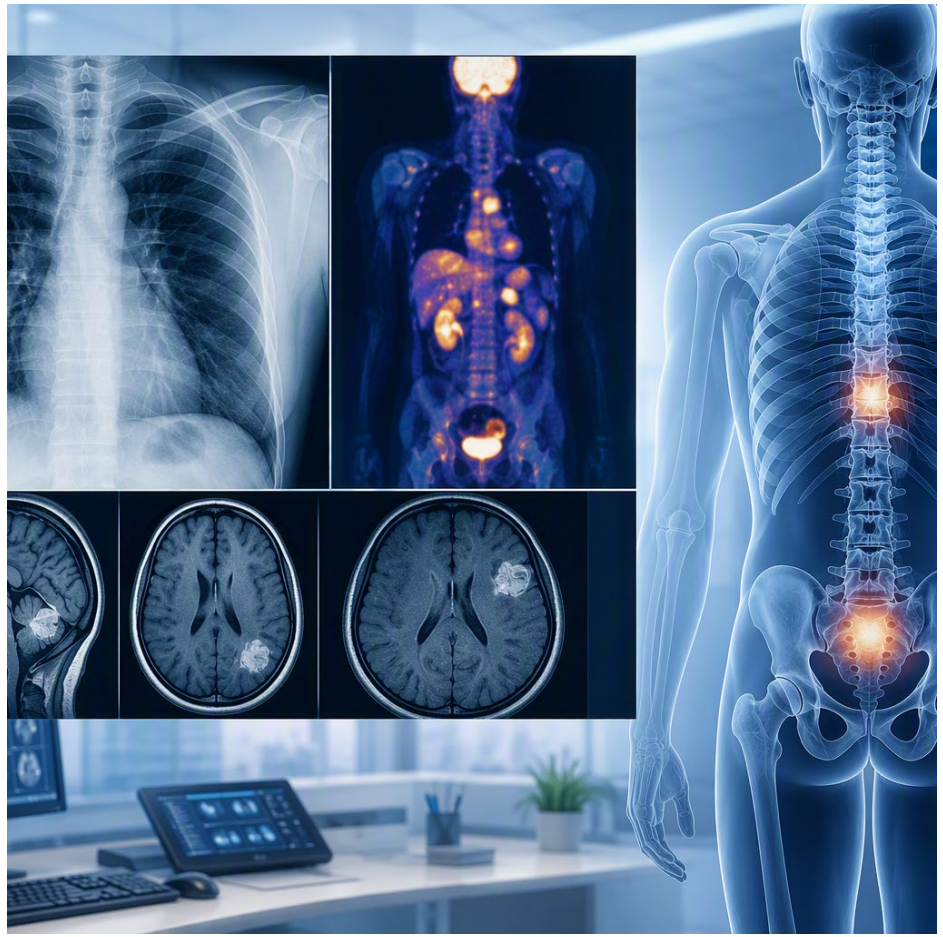
Case Presentation: 72-yo with Hip Pain and Progressive Dyspnea

Christine Lovly, MD, PhD, FASCO

Chief, Division of Thoracic Medical Oncology

City of Hope Comprehensive Cancer Center

Duarte, CA



Illustrative multimodality imaging + metastatic distribution

Presentation **Clinical context**

- 72-year-old gentleman
- Vascular surgeon; semi-professional diver
- Presenting symptoms: hip pain + progressive shortness of breath

Initial CXR **Left-sided pleural effusion**

Staging PET **Thoracic + extrathoracic disease**

Possible primary site

2.3 cm left upper lobe nodule
Mediastinal lymphadenopathy

Extrathoracic sites

Right adrenal nodule
Left femur + left sacrum
Extensive spinal metastases

Brain MRI **Small high right frontal lesion**

<1 cm intraparenchymal lesion in the high right frontal lobe

Liquid Biopsy Result

ctDNA Next-Generation Sequencing Report

Illustrative report for case discussion

MOLECULAR PATHOLOGY REPORT

Specimen: Peripheral blood plasma ctDNA

PATIENT	DISEASE CONTEXT	ASSAY TYPE	RESULT STATUS
72-year-old gentleman	Metastatic NSCLC	Plasma ctDNA NGS	Positive / Variant detected

KEY DETECTED ALTERATION

EGFR D770_N771insSVD / D770_N771>ASVDN

VAF 5%

Gene	Variant	Variant class	VAF	Interpretation
EGFR	**D770_N771insSVD / D770_N771>ASVDN**	Exon 20 insertion	5%	Actionable driver alteration detected

Interpretive comment

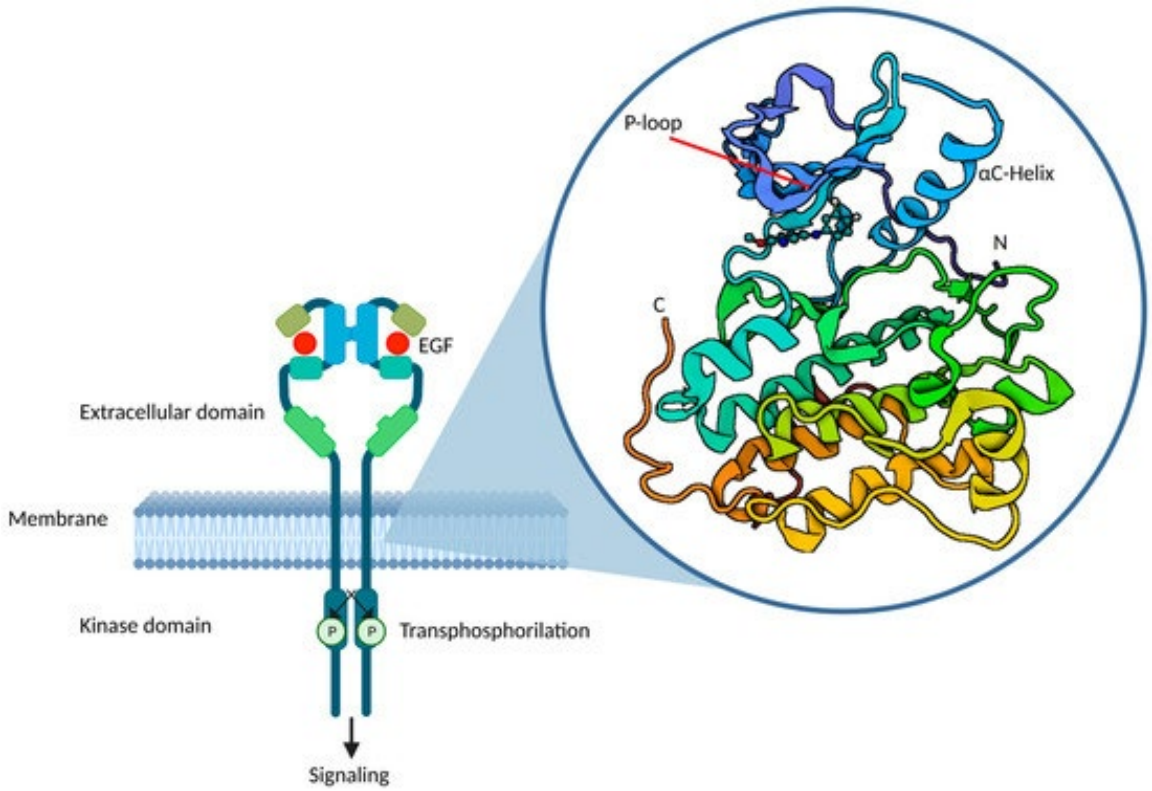
EGFR exon 20 insertion detected in plasma ctDNA at 5% VAF. Correlate with tissue pathology and complete staging.

Report note

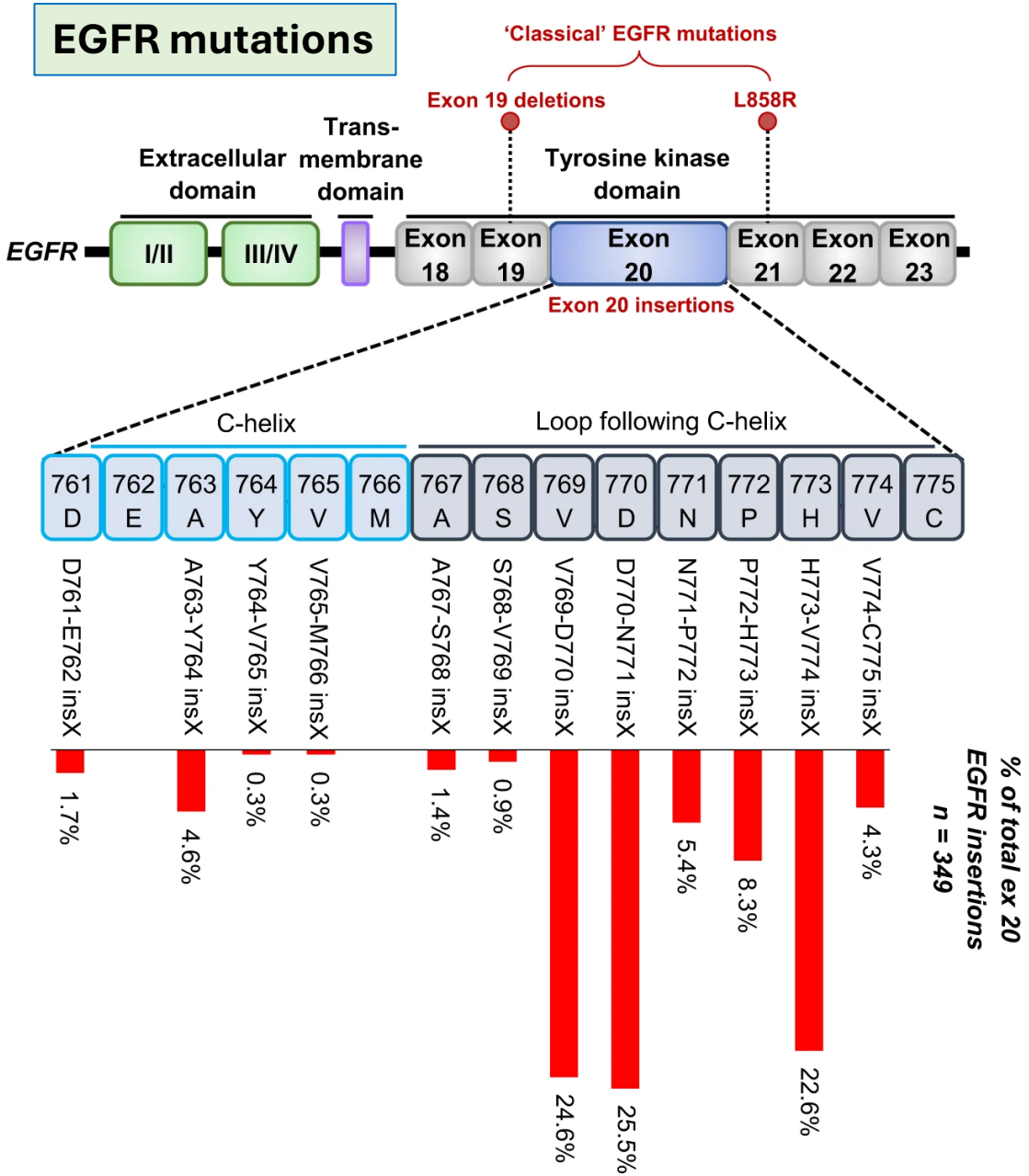
This slide is formatted as a teaching mock report and should not be used as an actual clinical laboratory report.

Abbreviations: ctDNA, circulating tumor DNA; NGS, next-generation sequencing; VAF, variant allele frequency.

Normal (‘Wild Type”) EGFR structure

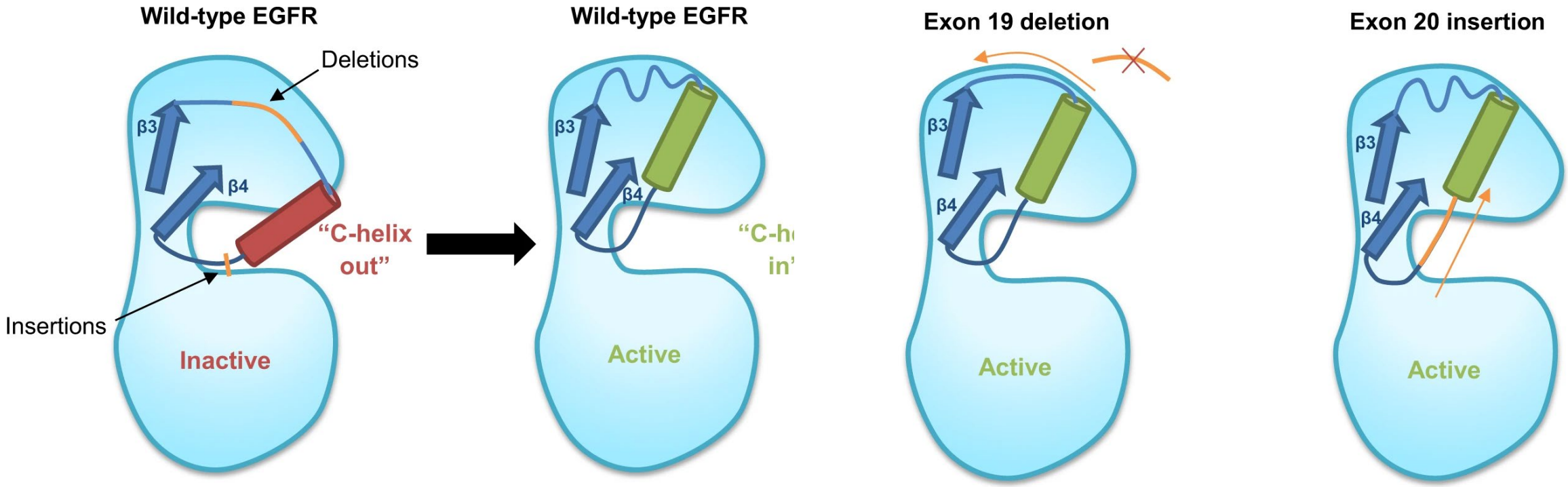


EGFR mutations



Pretelli G nt. J. Mol. Sci. 2023, 24(10), 8878; https://doi.org/10.3390/ijms24108878
Vyse, S., Huang, P.H. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Sig Transduct Target Ther 4, 5 (2019).

How EGFR mutations work!



Vyse, S., Huang, P.H. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Sig Transduct Target Ther 4, 5 (2019).

Treatment Options: Stage IV *EGFR* Exon 20 Insertion NSCLC

Frontline Systemic Therapy

- Platinum/pemetrexed
- Amivantamab + carboplatin/pemetrexed (preferred biomarker-directed option when appropriate)
- Consider clinical trial enrollment

CNS & Local Therapy

- SRS for limited brain metastases
- Radiation for painful bone lesions
- Orthopedic evaluation for weight-bearing femoral metastasis
- Bone-modifying agent

Molecular Testing

- Confirm EGFR exon 20 insertion
- Broad NGS
- PD-L1 testing
- Assess co-mutations

Subsequent-Line Options

- Sunvozertinib
- Amivantamab-based therapy if not previously received
- Clinical trials of next-generation exon 20 inhibitors
- Cytotoxic chemotherapy options
- Individualized management based on prior exposure

Teaching Points

- EGFR exon 20 insertions are biologically distinct from classic EGFR mutations (EGFR exon 19 deletion and EGFR L858R)
- Limited activity of standard EGFR TKIs
- Early multidisciplinary management is essential due to CNS and skeletal disease burden

Please Send in Your Questions!

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