Resident Report

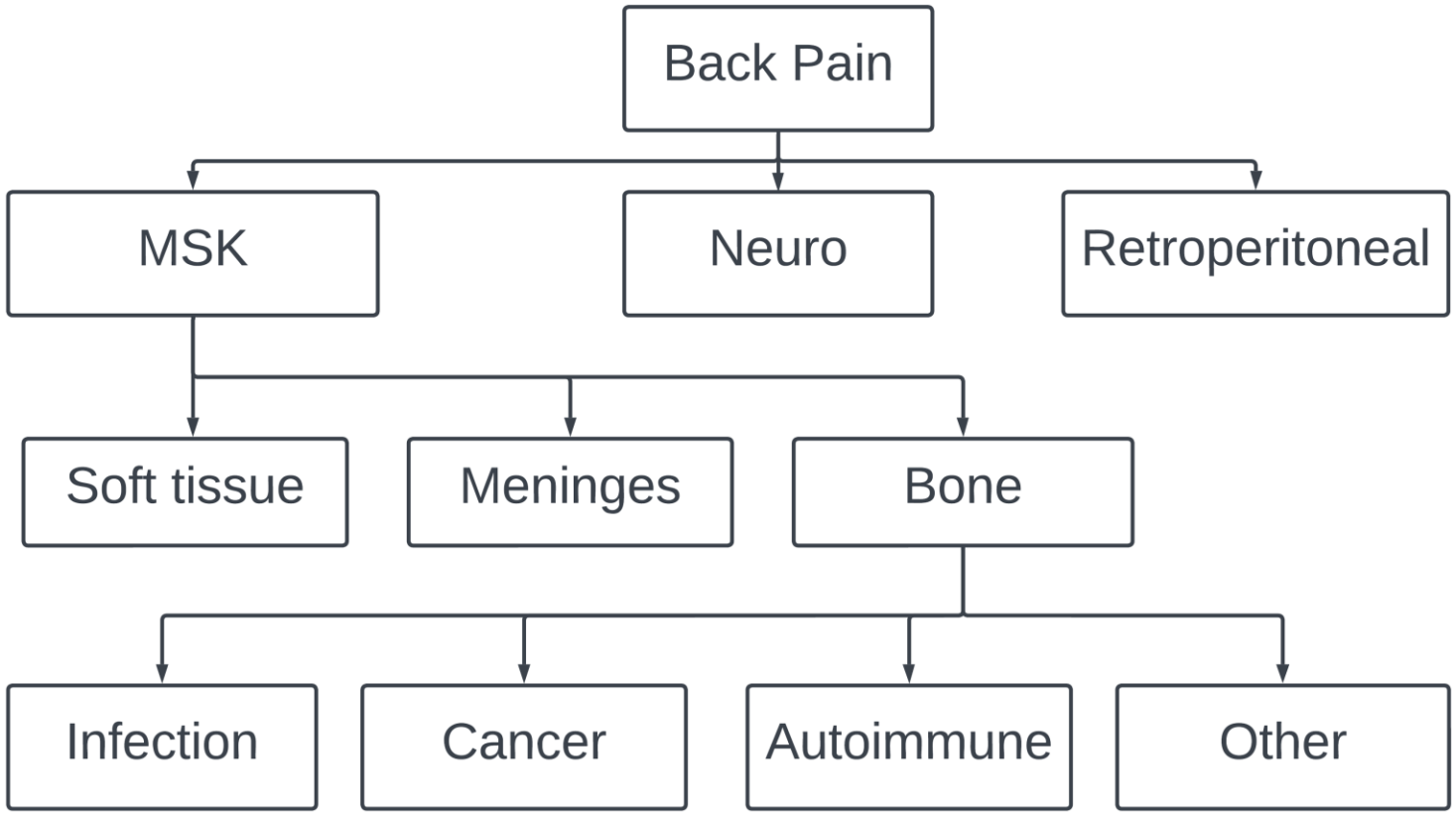
OLIVER CLARK

SUPERVISOR: DR. DIAMOND

Case

Mrs. X is a 46 year-old female with a history of germline PALB2 mutation s/p prophylactic mastectomy in 2020, who presents with a 2 month history of back pain

- Nearly constant pain. Worse with laying flat and sitting/standing up straight. Progressively worsening.
- Taking ibuprofen as needed, is not very effective
- Denies: Shortness of breath, chest pain, abdominal pain, fevers, chills, palpitations



Ddx for back pain

Mnemonic for back pain red flags

- **T**rauma
- **U**nexplained weight loss
- **N**eurological signs (including bowel or bladder dysfunction)
- **A**ge > 50
- **F**ever
- **I**VDU
- **S**teroids for a long time
- **H**istory of cancer

History

Past medical history

Germline PALB2 mutation (Dx 2014)
Fibromyalgia
MDD
Hypertension

Past surgical history

C-section
Prophylactic bilateral mastectomy (2020)

Social Hx:

No tobacco, recreational drugs, occasional alcohol

Medications

Fluoxetine 20 mg Daily PO
Hydrochlorothiazide 25 mg Daily PO
Labetalol 200 mg Daily PO

Allergies: None

Family Hx:

Mother – breast cancer, diagnosed in 40s, BRCA-
MGM with breast cancer in 30s
Maternal aunt with breast cancer in 40s
PGM with breast cancer (unknown age)
PGF with lung cancer (smoker)
She has one 12-year-old son who is healthy

Physical Exam

Vitals: 119/84 , HR 88, T 35.7, 18, 98% on RA

General: Well appearing, NAD

CV: mild tachycardia, otherwise unremarkable

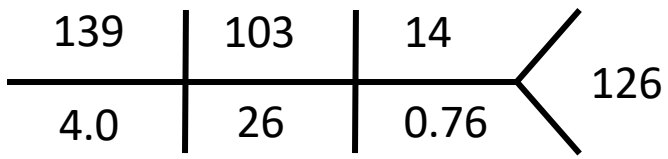
Lungs: CTAB

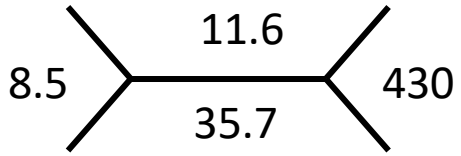
Abdomen: NT, ND

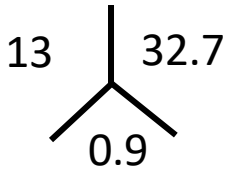
MSK: Tenderness to palpation of spinous process on lower back, otherwise normal curvature and no paraspinal tenderness

Neuro: 5/5 strength in bilateral lower extremities. Normal sensation across lower extremities bilaterally.

Labs and Studies





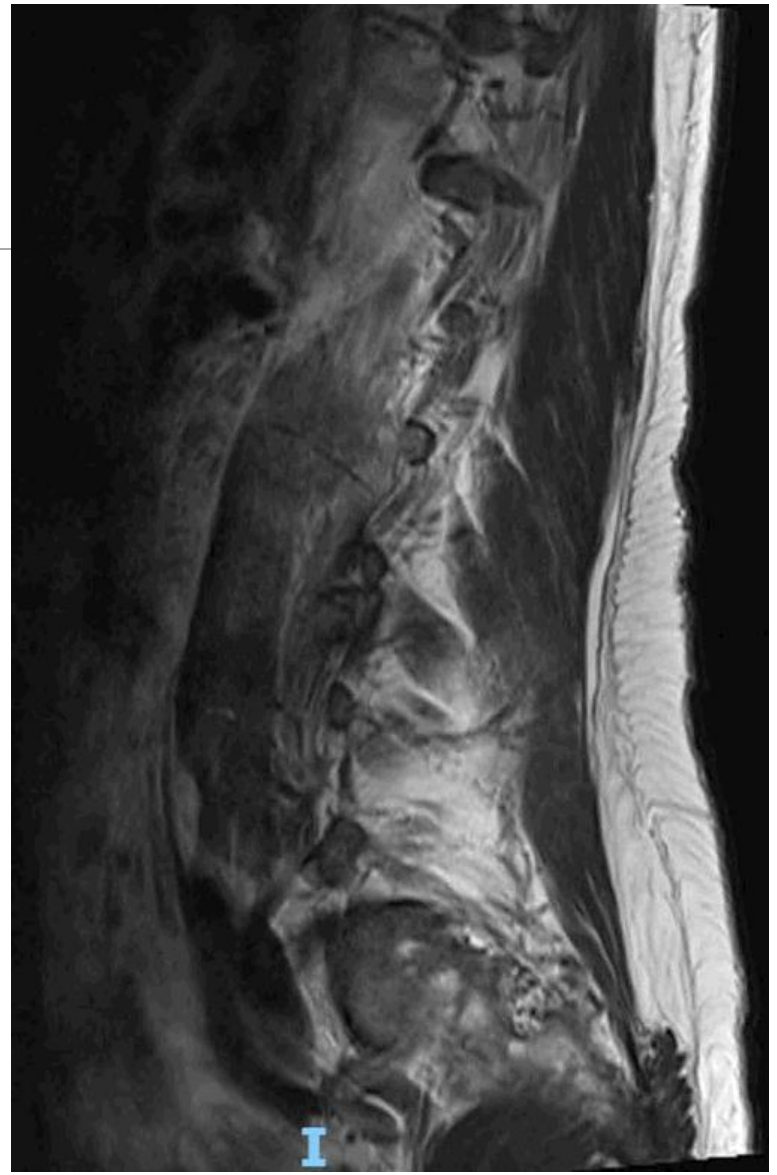


Calcium: 9.2

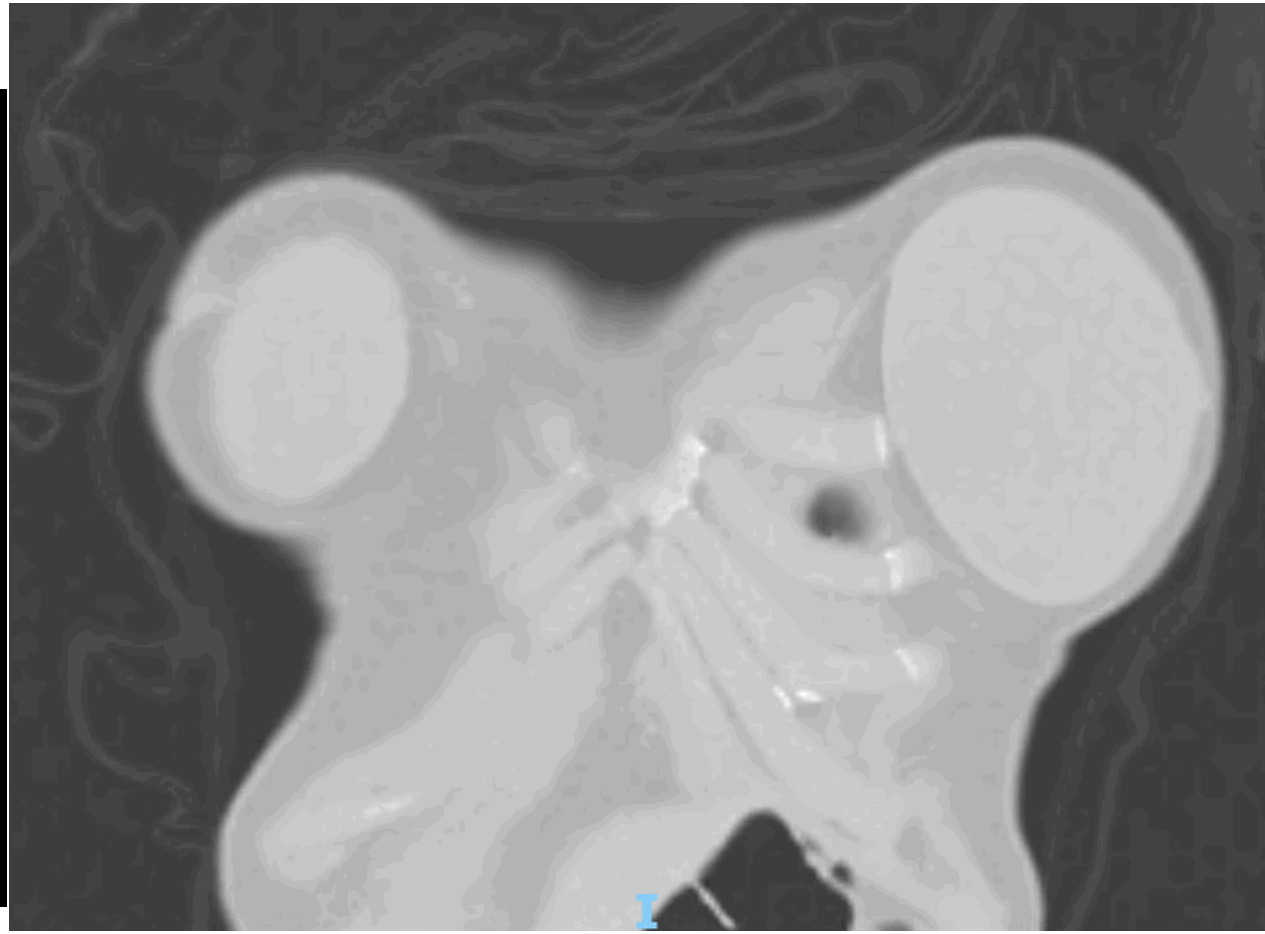
XR Lumbar spine: Hyperlucent lesion at L2 vertebrae with sclerotic margin

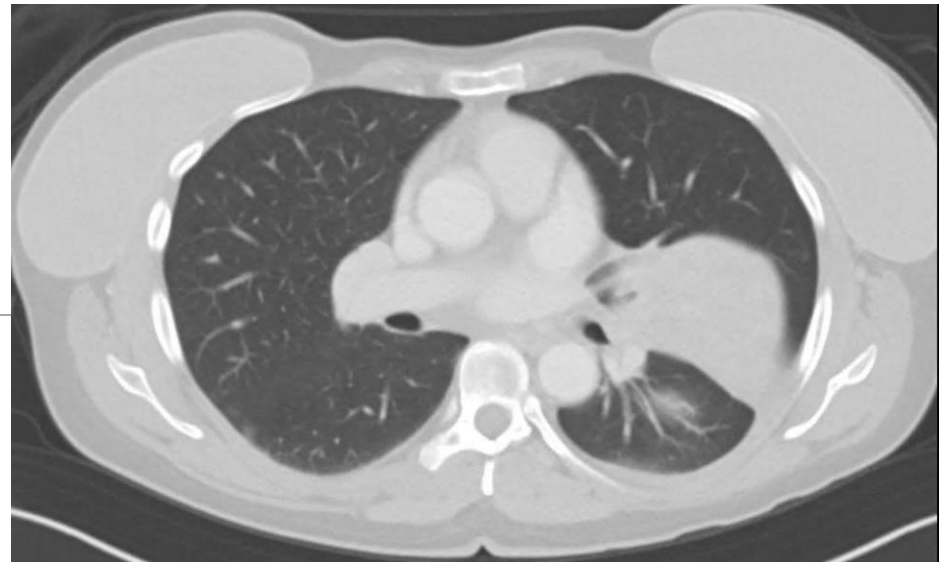
MRI Lumbar Spine

IMPRESSION:
Large enhancing mass within the L2 vertebral body with extension to the left pedicle and left lateral soft tissues, as above. There is significant narrowing of the left L2-3 neural foramen with mass effect on the adjacent left L2 and L3 nerve roots. Additional small marrow replacing lesion in the left sacrum.

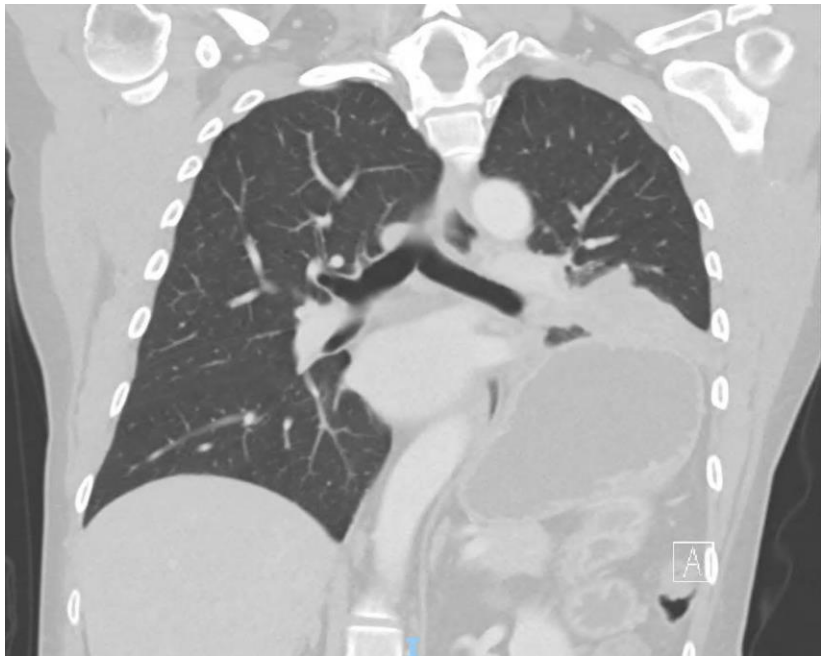


CT Chest

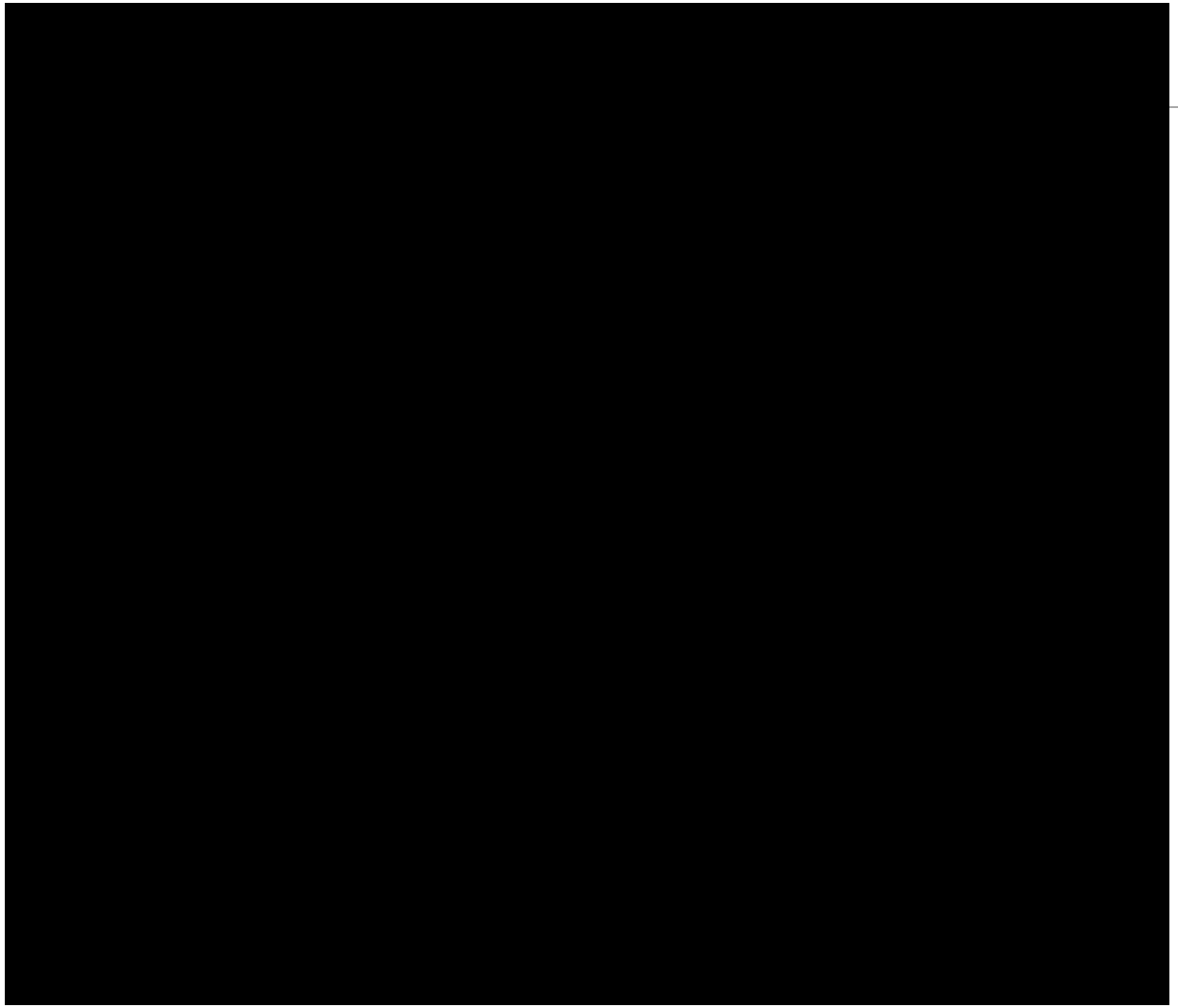


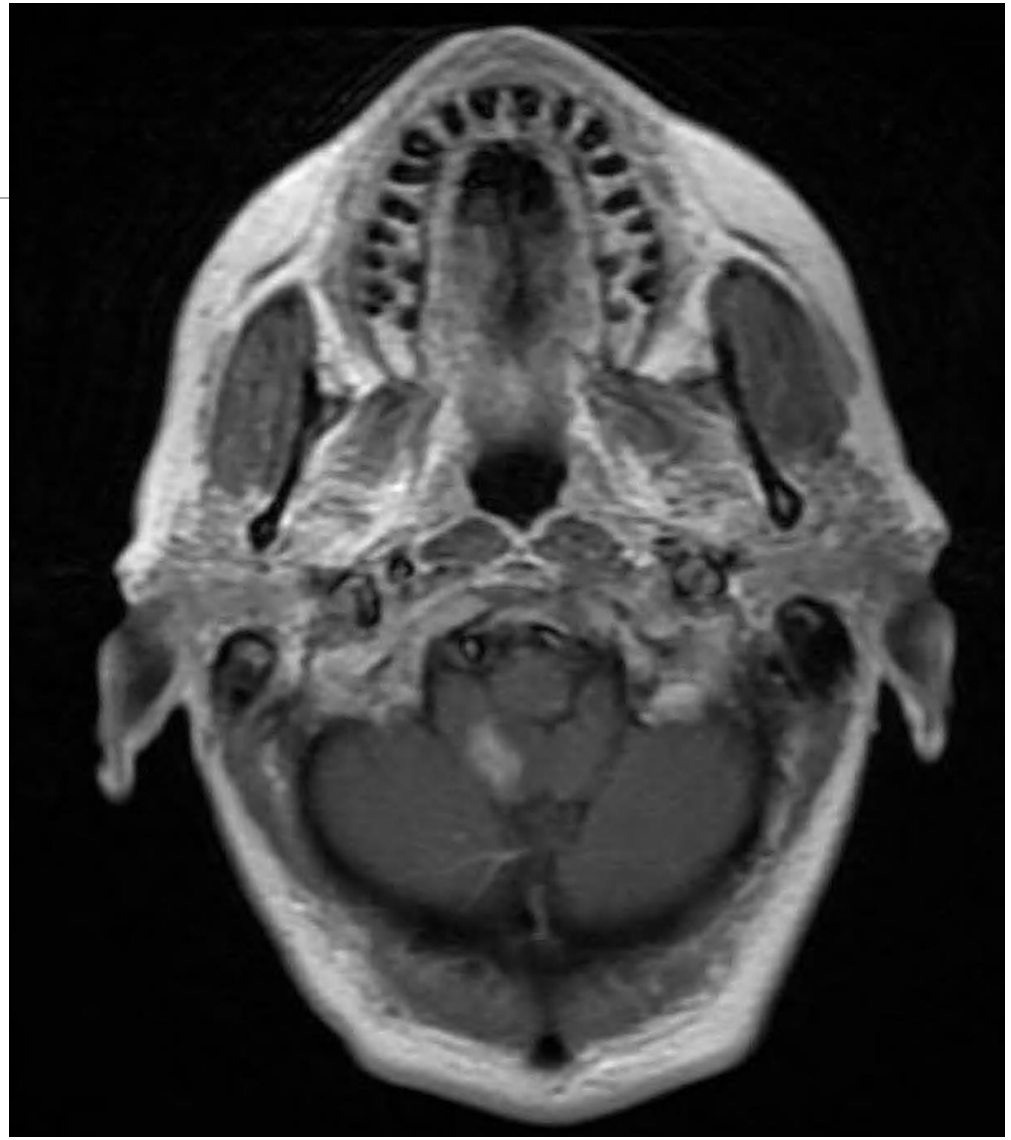


CT c/a/p:
IMPRESSION:
1. Large heterogeneous left upper lobe/left hilar lung mass with adjacent left hilar lymphadenopathy. This results in occlusion of one of the left upper lobe segmental bronchi branches.



MRI brain – T2 FLAIR

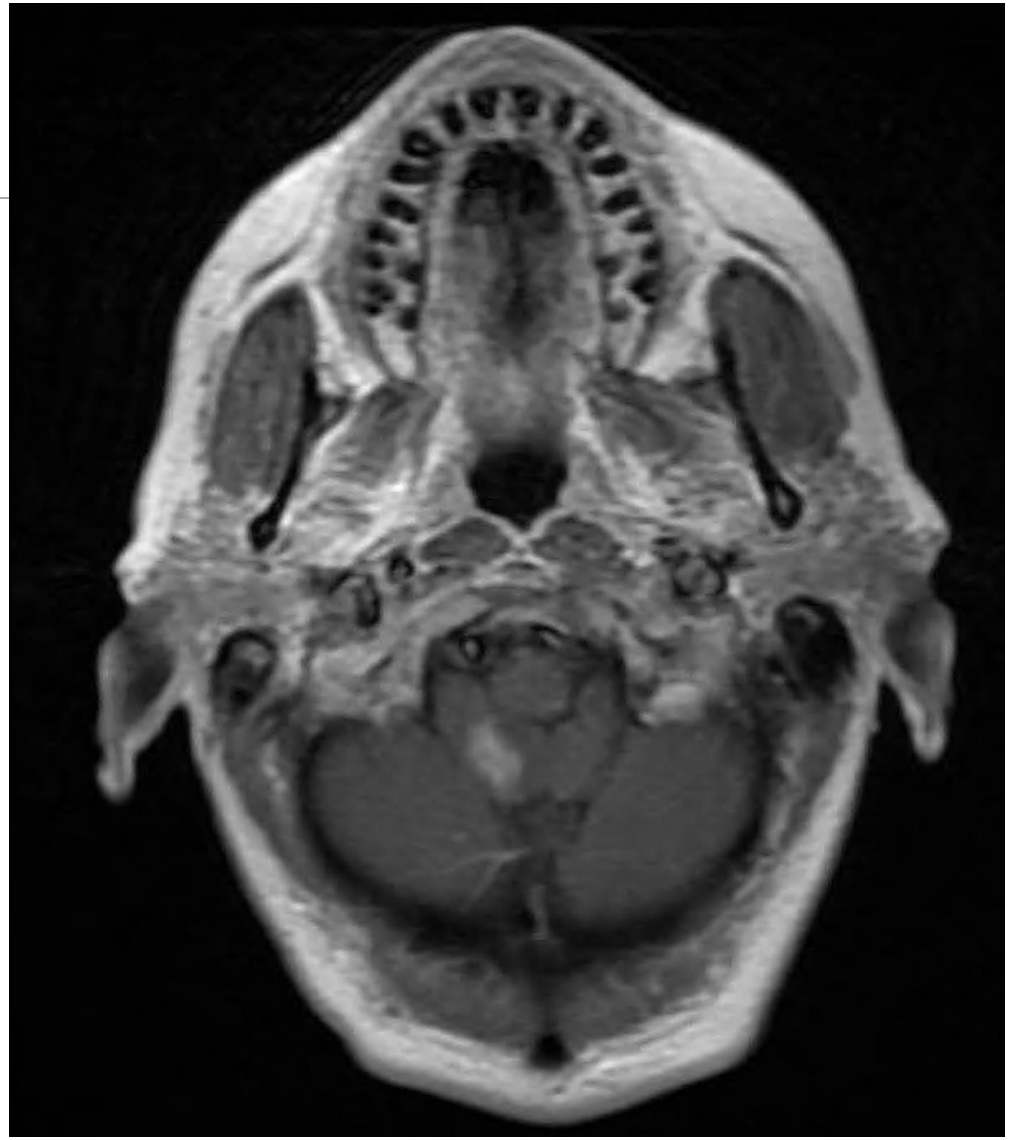




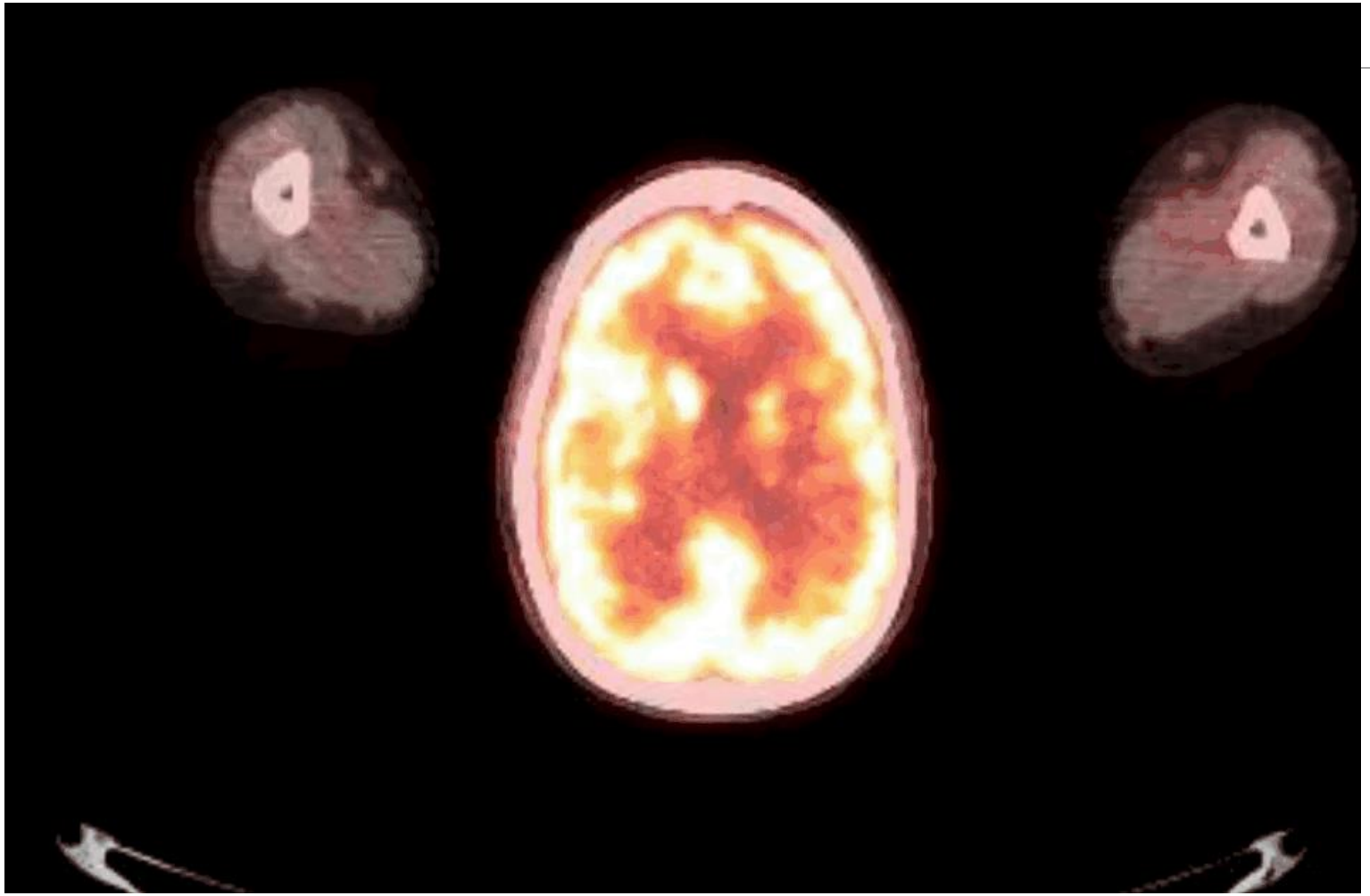
MRI brain

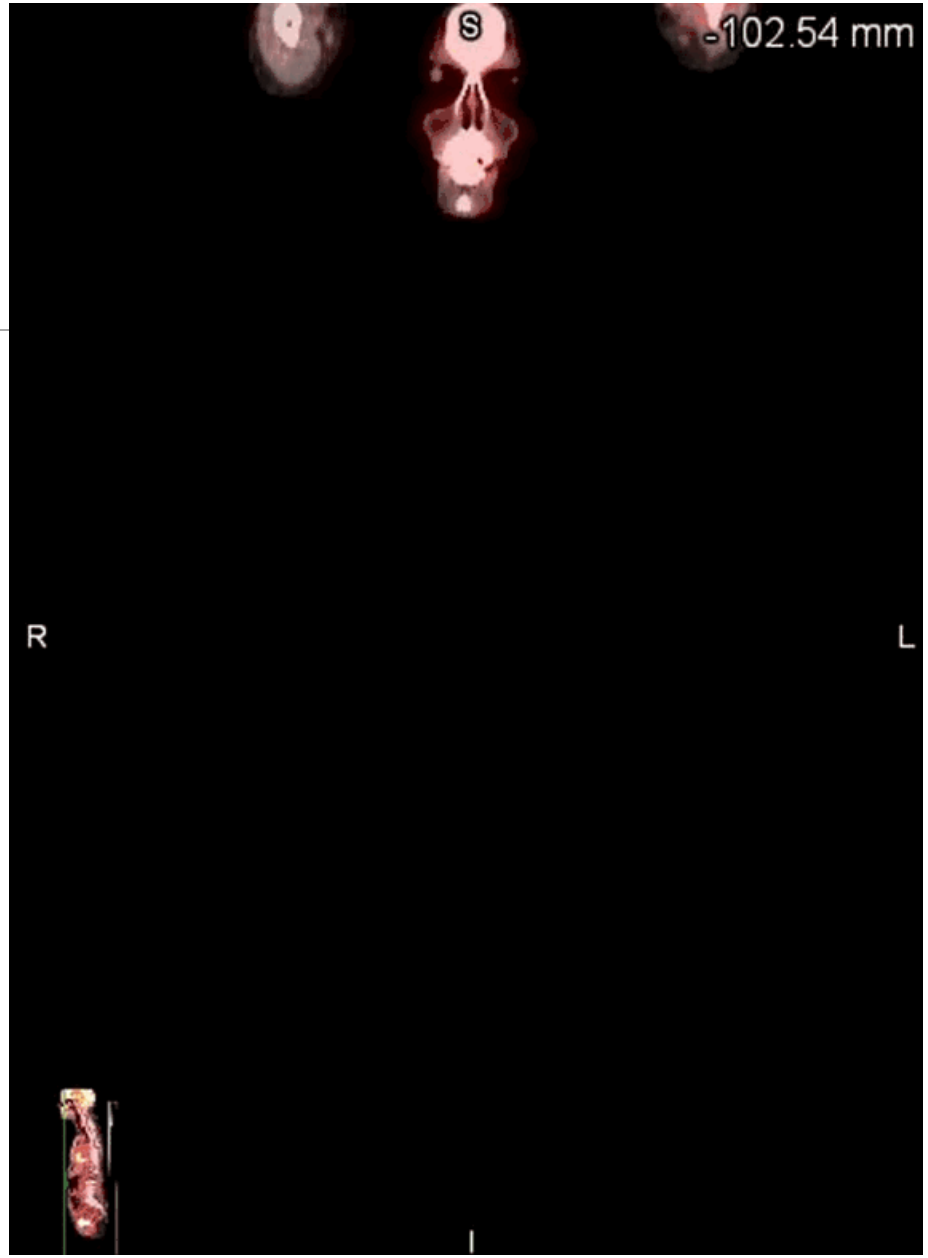
MRI brain:
IMPRESSION:

1. Single enhancing mass identified in the right cerebellar tonsil as detailed above. Given the patient's clinical history, this is consistent with a brain metastasis. This causes mild mass effect upon the medulla oblongata. No additional lesions are present.



FDG PET – Mid Thigh-Skull Base





FDG PET – Mid Thigh-Skull Base

Lesion 1: FDG avid primary left lung cancer, SUV max = 10, approximate anatomic dimensions 69 x 51 mm. Medially, there appears to be direct hilar invasion, appearing contiguous with hypermetabolic tumor, fusion image 103, SUV max = 6.9.

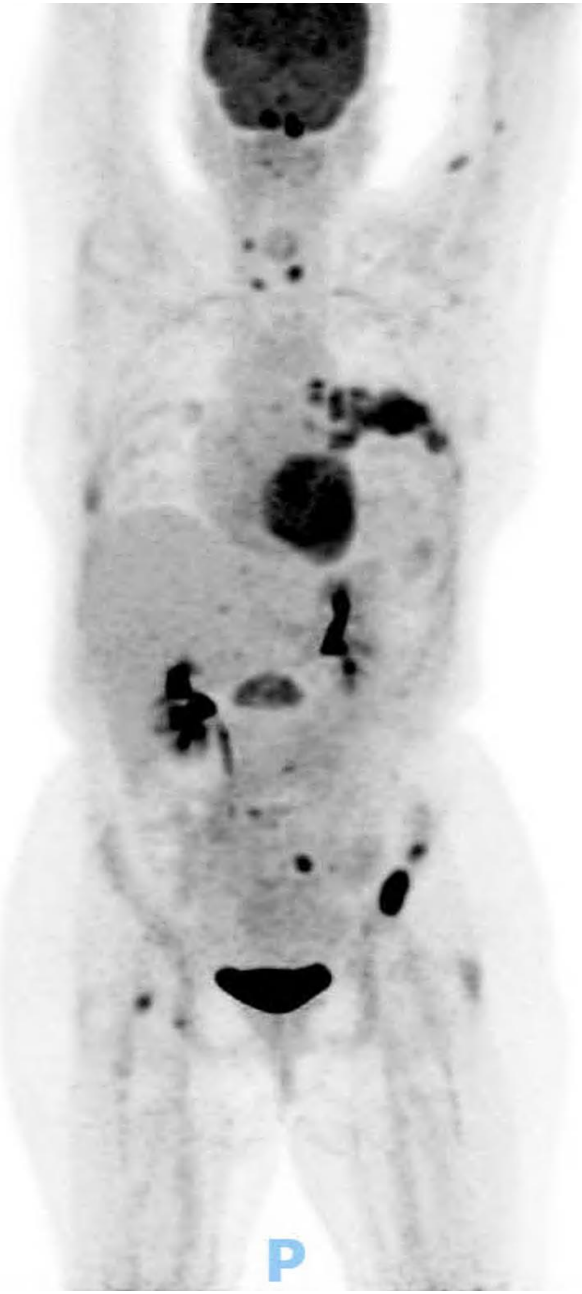
Lesion 2: Metastatic mediastinal lymph node includes prevascular node, SUV max 6.7, fusion image 96, anatomic disease measures approximately 22 x 13 mm. Additional aorticopulmonary window lymph node metastasis, fusion image 91, SUV max = 7.2, anatomic correlate is difficult to visualize.

Lesion 3: Large destructive lesion of the left aspect of L2, SUV max 6.1, with osseous destruction and epidural tumoral extension, fusion image 162. Lateral left psoas muscular infiltrative disease, with approximate anatomic dimensions measuring 52 x 38 mm, demonstrated on recent MRI 3/22/2022. Left hemivertebral body endplate destructive changes, appears marginally progressed comparing to previous MR, better detailed on 4/15/2022.

Lesion 4: Left skull base metastasis with lytic destructive lesion, extending into the left occipital condyle, SUV max = 12.

Lesion 5: Largest pelvic metastasis, approximates the anterior left iliac wing, SUV max 17.

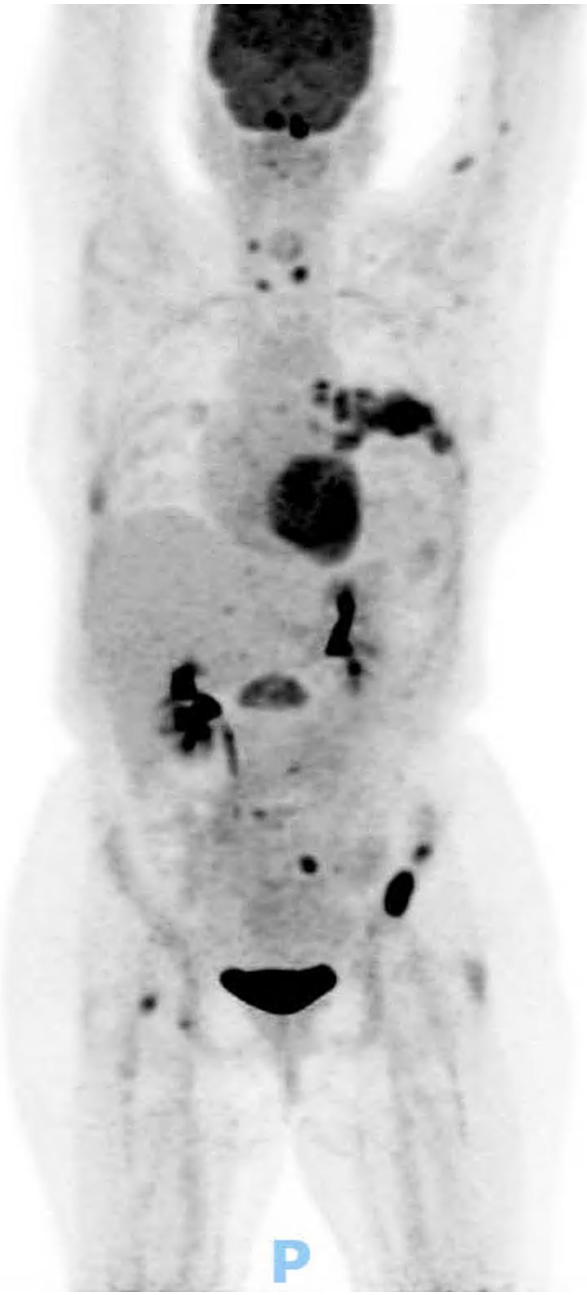
Lesion 6: Asymmetric FDG avidity localizing to the right adrenal gland, SUV max = 3.3, fusion image 142. Trace nodular density 6 x 8 mm.



FDG PET – Mid Thigh-Skull Base

IMPRESSION:

Stage IV lung cancer with multifocal metastatic bone disease, mediastinal metastasis, and likely right adrenal/left retroperitoneal nodal focus.



L2 mass biopsy

1. L2 mass biopsy:

-METASTATIC ADENOCARCINOMA

-See comment

2. L2 mass biopsy:

-METASTATIC ADENOCARCINOMA

Electronically signed by I-Tien Yeh, MD on 4/1/2022 at 8:32 AM

Comment

Immunostains show tumor to be positive for CK7. There is focal weak positivity on CDX2 and MUC4 stained slides. All other stains, including GATA3, PAX8, ER, CK20, TTF1 and CD10 are negative. The findings are not specific for a primary site, but could include upper GI/pancreatobiliary sites. Clinical correlation recommended.

L2 mass biopsy

DIAGNOSIS:

Soft tissue, L2 mass, biopsy (S22-03788, parts 1 & 2, 3/29/2022):
- Involved by moderately to poorly differentiated adenocarcinoma. See note.
- Mesothelin staining is focally positive (2+ intensity, in 10% of tumor cells).
- PD-L1 staining is negative.

NOTE:

The patient's reported history of non-small cell lung carcinoma (prior specimen not available for review) is noted. The current specimen shows moderate to poorly formed glands involving soft tissue and fragments of bone in a background of blood. Per submitted surgical pathology report, immunohistochemical stains performed at the outside institution (not available for review) showed that the tumor cells stained positive for CK7 with focal weak staining for CDX2 and MUC4 and showed negative staining for GATA3, PAX-8, ER, CK20, TTF-1 and CD10. These findings are most consistent with a metastatic lung primary although a gastrointestinal primary cannot be entirely excluded.

Next generation sequencing (NGS)

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
PD-L1 (22c3)	IHC	Protein	Positive, TPS: 50%	BENEFIT	cemiplimab, pembrolizumab	Level 1
PD-L1 (28-8)	IHC	Protein	Positive | 1+, 10%	BENEFIT	nivolumab/ipilimumab combination	Level 1
ALK	Seq	RNA-Tumor	Fusion Not Detected	[illegible]	alectinib, brigatinib, ceritinib, crizotinib, lorlatinib	Level 2
BRAF	Seq	DNA-Tumor	Mutation Not Detected	[illegible]	dabrafenib and trametinib combination therapy, vemurafenib	Level 2
EGFR	Seq	DNA-Tumor	Mutation Not Detected	[illegible]	erlotinib, gefitinib	Level 2
KRAS	Seq	DNA-Tumor	Pathogenic Variant Exon 2 | p.G12V			
RET	Seq	RNA-Tumor	Fusion Not Detected	[illegible]	pralsetinib, selpercatinib	Level 2
ROS1	Seq	RNA-Tumor	Fusion Not Detected	[illegible]	ceritinib, crizotinib, entrectinib, lorlatinib	Level 2
MET	CNA-Seq	DNA-Tumor	Amplification Not Detected	[illegible]	crizotinib	Level 3
	Seq	RNA-Tumor	Variant Transcript Not Detected			

NGS

Genomic Signatures

Biomarker	Method	Analyte	Result
Microsatellite Instability (MSI)	Seq	DNA-Tumor	Stable
Tumor Mutational Burden (TMB)	Seq	DNA-Tumor	Result: Low 5 Low 10 High
Genomic Loss of Heterozygosity (LOH)	Seq	DNA-Tumor	Low - 8% of tested genomic segments exhibited LOH (assay threshold is ≥ 16%)

Genes Tested with Pathogenic or Likely Pathogenic Alterations

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
KRAS	Seq	DNA-Tumor	Pathogenic Variant	p.G12V	2	c.35G>T	32
PALB2	Seq	DNA-Tumor	Pathogenic Variant	p.W1038*	10	c.3113G>A	59

Unclassified alterations for DNA and RNA sequencing can be found in the MI Portal.
Formal nucleotide nomenclature and gene reference sequences can be found in the Appendix of this report

Genes Tested with Variants of Uncertain Significance

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
ATM	Seq	DNA-Tumor	Variant of Uncertain Significance	p.L439P	10	c.1316T>C	50
NTRK3	Seq	DNA-Tumor	Variant of Uncertain Significance	p.A636E	17	c.1907C>A	30
PALB2	Seq	DNA-Tumor	Variant of Uncertain Significance	p.D997N	9	c.2989G>A	14
STK11	Seq	DNA-Tumor	Variant of Uncertain Significance	c.734+5G>A	5	c.734+5G>A	37

NSCLC Initial Evaluation

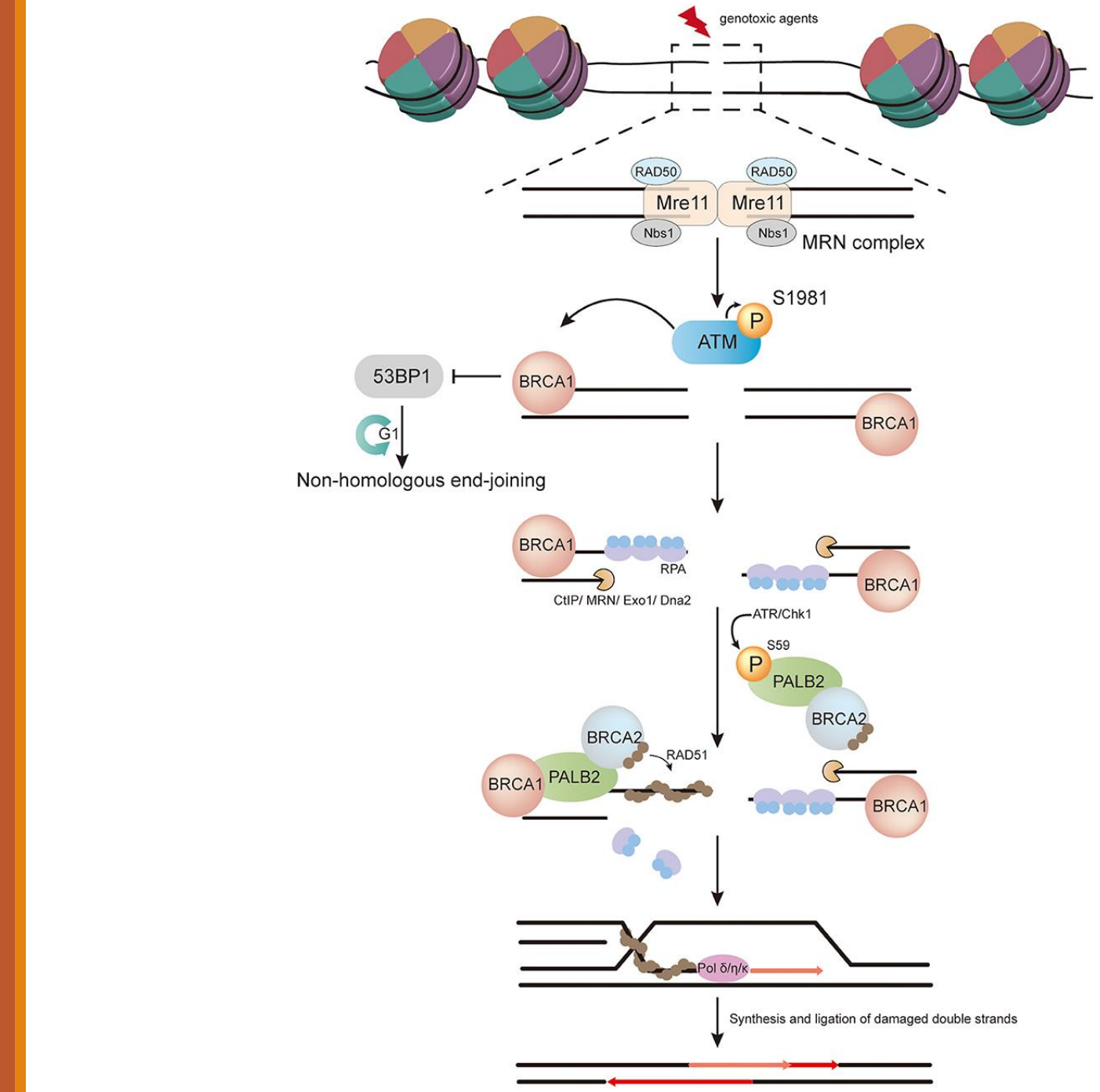
- H&P including performance status
- Smoking cessation counseling if relevant (use 5A's framework)
- CBC, BMP
- CT Chest, Abdomen, Pelvis
- MRI Brain
- Biomarker testing

For patients with Stage IV:

- FDG PET/CT scan
- Pathological confirmation of metastatic lesion, if possible
- ctDNA (Guardant or FoundationOne)
- Integrate palliative care

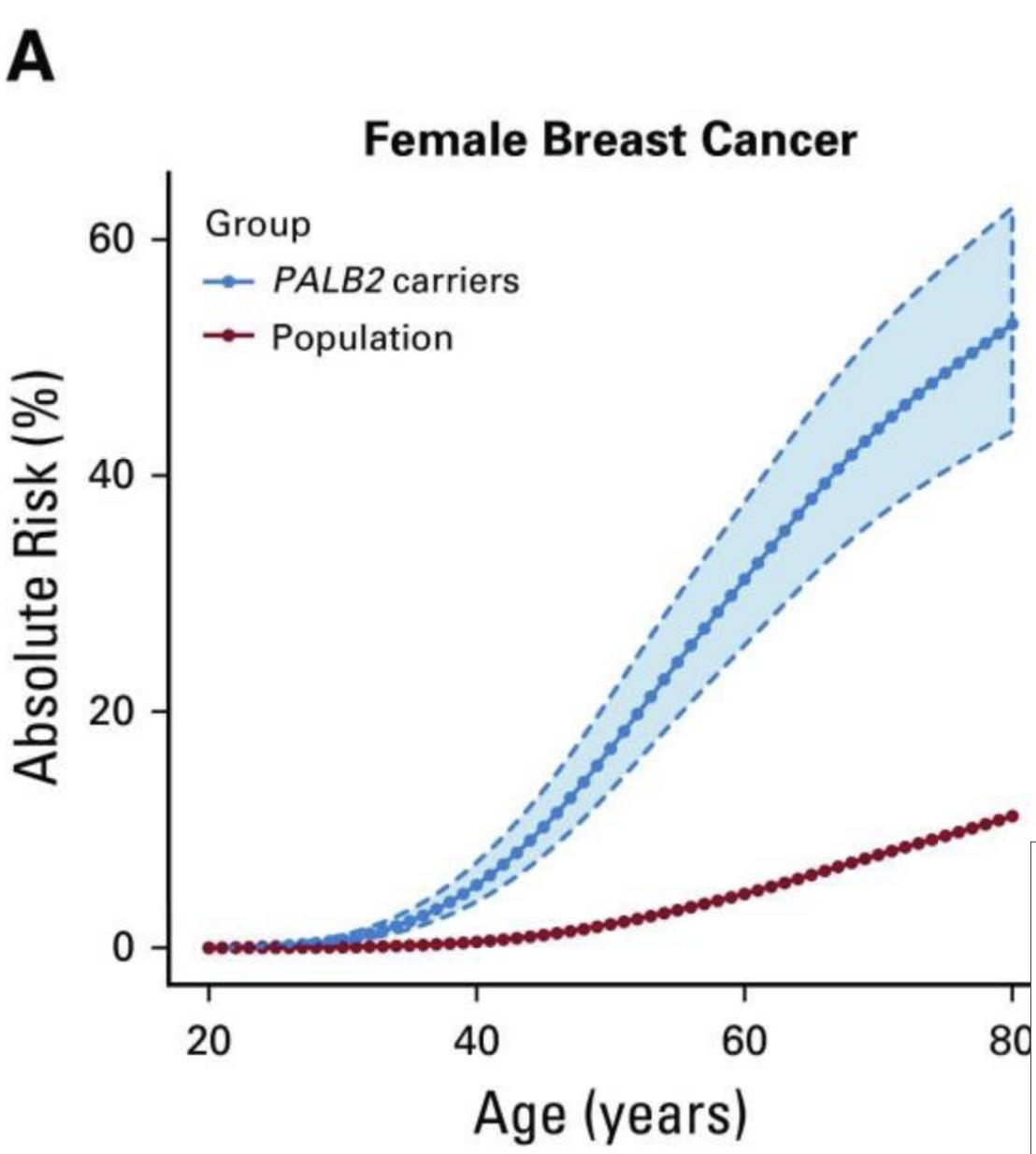
PALB2 Mutation

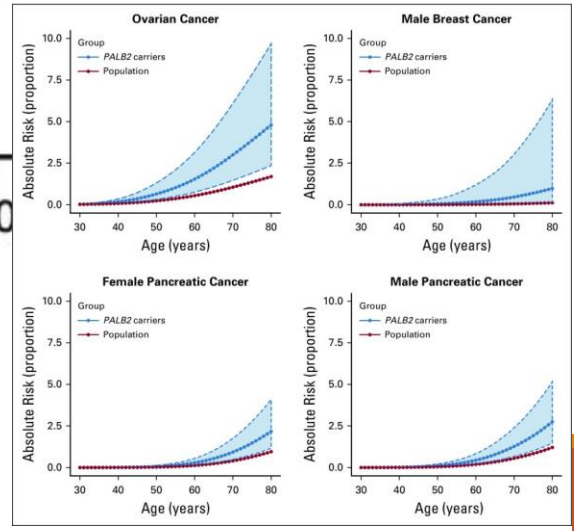
- **P**artner **a**nd **L**ocalizer of **B**RCA**2**
- Tumor suppressor protein/gene
- Binds, colocalizes with BRCA2 in the nucleus
- Assists in formation of the BRCA1-PALB2-BRCA2 complex
- Allows RAD51 binding to ssDNA, which allows further homologous recombination



PALB2 Mutation

- Homozygous PALB2 mutation leads to Fanconi Anemia Subtype D1
- Heterozygous PALB2 mutation leads to increased risk for
  - Breast (Male and female)
    - 50: 13-21%
    - 80: 44-63%
  - Ovarian
  - Pancreas
  - (Lung?)
  - In one study 4.7 in 1,000 breast cancer cases





Patient summary

- In summary, Mrs. X is a 46 year-old female with a history of germline PALB2 mutation s/p prophylactic mastectomy who presents with back pain, found to have Stage IV non-small cell lung cancer (PD-L1 50%, KRAS G12V, PALB2 mutations) with metastasis to bone and brain.

Stage IV NSCLC Treatment

PD-L1 ≥1%–49% First-line Therapy

ADENOCARCINOMA, LARGE CELL, NSCLC NOS
Preferred
- **(Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[48,49]**

PD-L1 ≥50% First-line Therapy

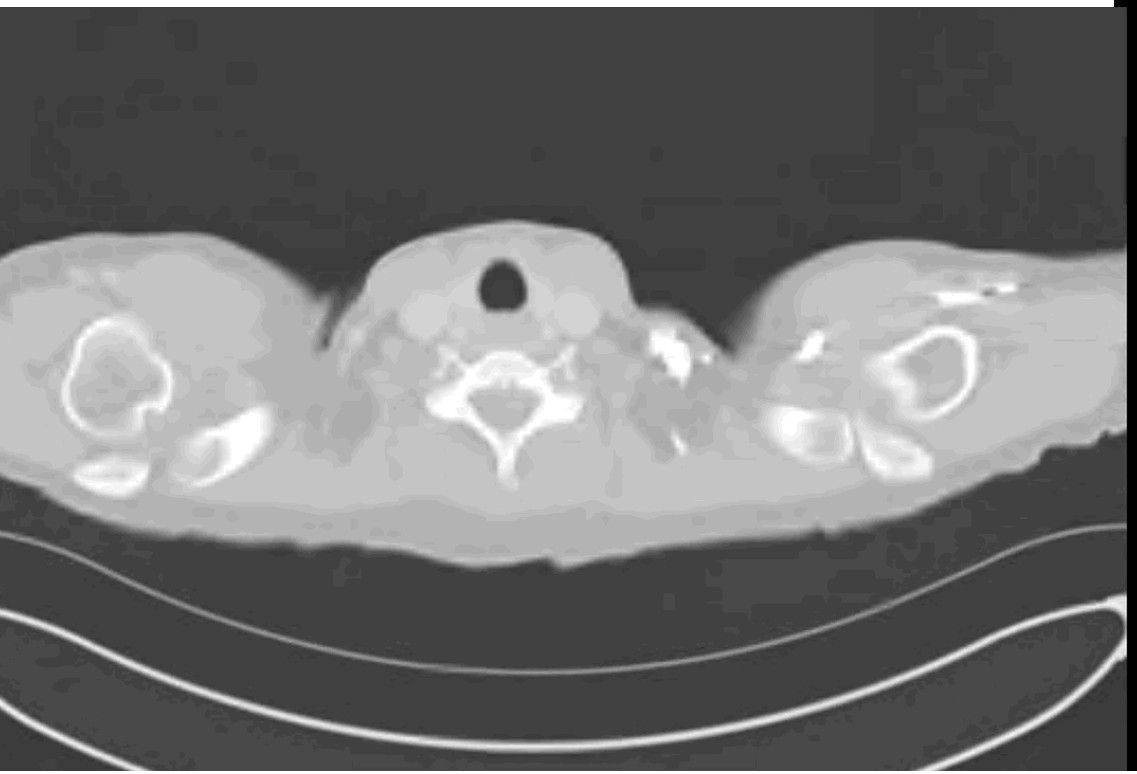
ADENOCARCINOMA, LARGE CELL, NSCLC NOS
Preferred
- **Pembrolizumab (category 1)[46,47]**
- **(Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[48,49]**
- **Atezolizumab (category 1)[50]**
- **Cemiplimab-rwlc (category 1)[51]**

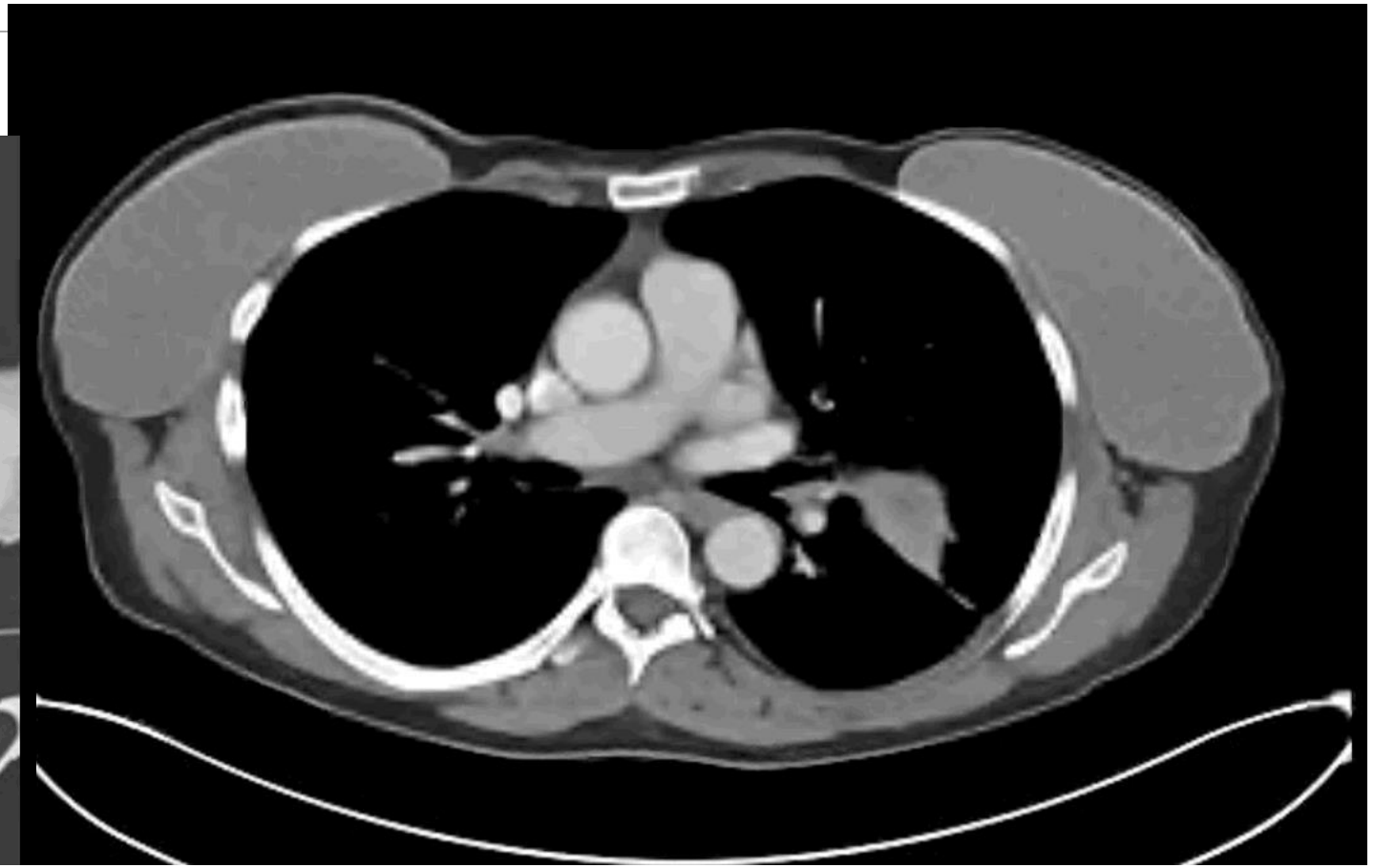
TESTING RESULTS[ll,mm]
EGFR **exon 19 deletion or exon 21 L858R mutation positive**
EGFR **S768I, L861Q, and/or G719X mutation positive**
EGFR **exon 20 insertion mutation positive**
KRAS **G12C mutation positive**
ALK **rearrangement positive**
ROS1 **rearrangement positive**
BRAF **V600E mutation positive**
NTRK1/2/3 **gene fusion positive**
METex14 **skipping mutation positive**
RET **rearrangement positive**
ERBB2 (HER2) **mutation positive**
PD-L1 ≥1% and negative for actionable molecular biomarkers above
PD-L1 <1% and negative for actionable molecular biomarkers above

Clinical course

- Month 1: Palliative radiation to brain and left elbow lesion
- Months 1-8: Carboplatin, pemetrexed, pembrolizumab
- Months 8-14: Maintenance pemetrexed and pembrolizumab
- Month 13: Palliative radiation to sacrum
- Month 14: Palliative radiation to intracranial lesions
- Month 14: Abdominal pain, receives interval staging CT scans

CT Chest, Abdomen, Pelvis



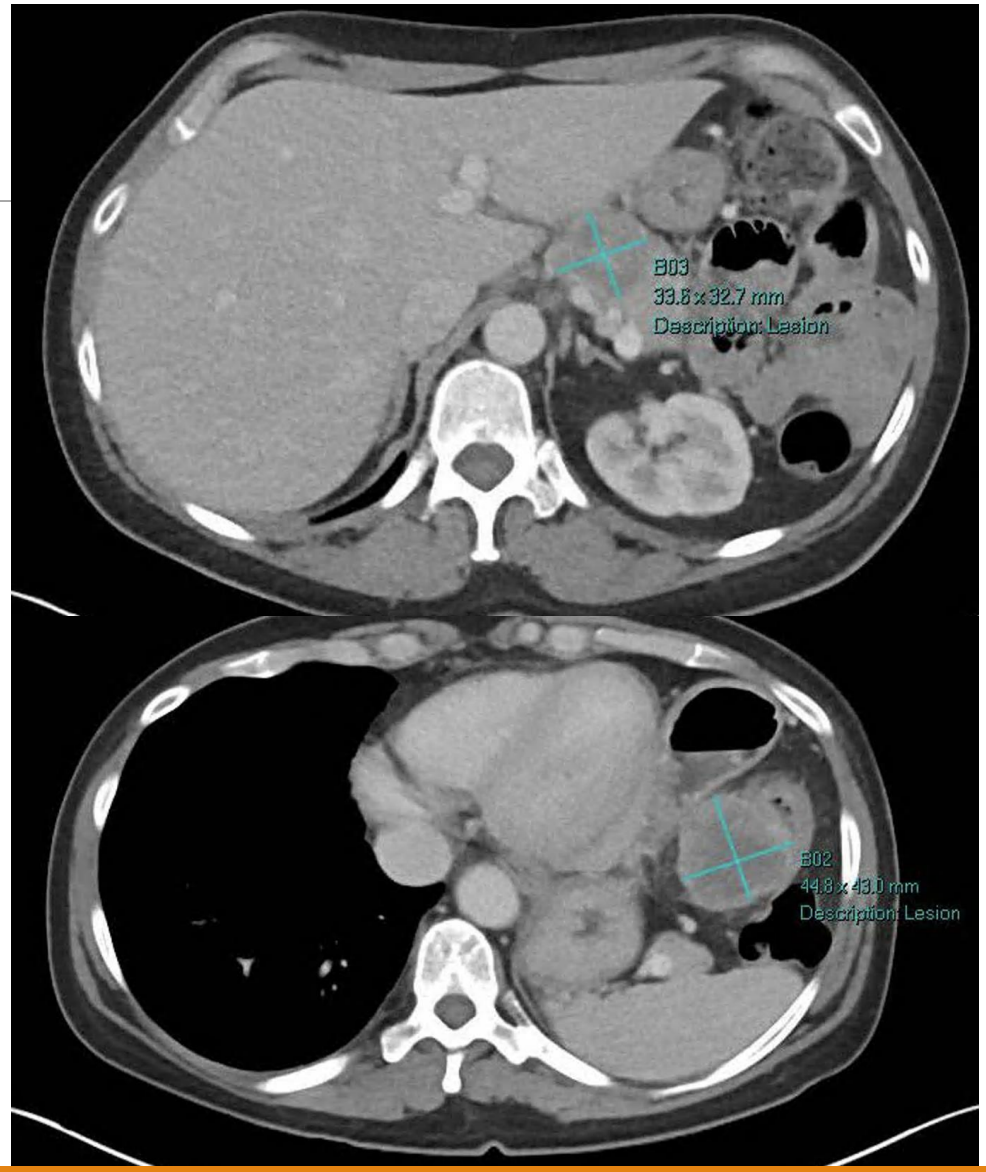


CT Chest, Abdomen, Pelvis

Abdomen, pelvis: Heterogeneous, approximate (4.5 cm x 4.3 cm) (series 2, image 46) mass adjacent to splenic flexure and (3.4 cm x 3.3 cm) (series 2, image 58) mass in or near pancreas body moderately increasing. Upper liver hypodense focus (5.0 HU) (series 2, image 50) unchanged, compatible with cyst or myelolipoma. Elongate radiodensity extending into inferior vena cava (series 2, image 74) unchanged, compatible with foreign matter. Upper lumbar vertebra with associated retrolisthesis unchanged. Vascular calcification. Minimal intra-abdominal fat. No evidence of splenomegaly, hydronephrosis, bulky mesenteric adenopathy, gross ascites, bowel obstruction, or new or enlarging liver or bone gross untoward mass.

IMPRESSION:

Increasing upper abdomen masses compatible with neoplasm.



Pancreatic mass biopsy

MICROSCOPIC DESCRIPTION:
Atypical glandular cells with altered nuclear to cytoplasmic ratios, irregular nuclear membranes, visible to prominent nucleoli, and moderate amounts of focally vacuolated cytoplasm present singly, in crowded groups and gland-like arrangements
Fibroconnective tissue focally present with associated chronic inflammation

Immunohistochemical studies show that the atypical cells stain positive with antibodies to Cytokeratin 7, CEA, MUC4 and CDX-2 (focal), and stain negative with Cytokeratin 20.

According to the outside report, but not submitted for review, the atypical cells stain negative for Napsin A and TTF-1.

DIAGNOSIS:
Positive for malignant cells
Adenocarcinoma
See comment

COMMENT:
Although this may represent a metastasis from the patient's reported history of a MUC4 positive primary non small cell lung carcinoma, which was not available for review, a primary pancreaticobiliary adenocarcinoma or a metastasis from another gastrointestinal site cannot be entirely excluded. The cytomorphologic and immunohistochemical features are similar to those present in the patient's prior soft tissue, L2, biopsy (NIH surgical pathology SS-22-5397). Clinicopathologic and radiologic correlation are recommended.

Patient summary

- In summary, Mrs. X is a 46 year-old female with a history of germline PALB2 mutation s/p prophylactic mastectomy who presents with back pain, found to have Stage IV non-small cell lung cancer (PD-L1 50%, KRAS G12V, PALB2 mutations) s/p combination chemotherapy and immunotherapy, and palliative radiation to brain, elbow, and sacral lesions, now with new pancreatic mass of adenocarcinoma origin.
- What do you think this is?

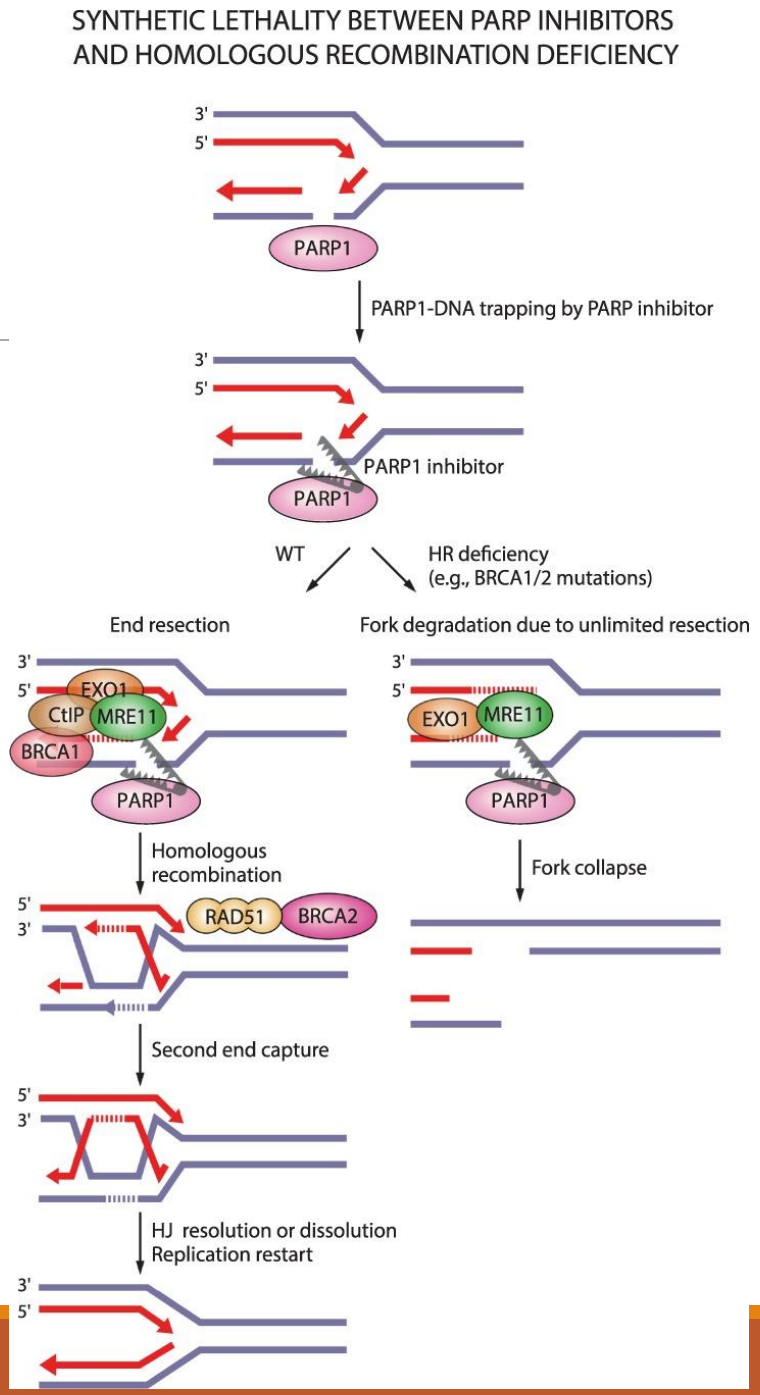
Comparing biopsies

- What do you think this is?
- Can compare immunostaining
- Can compare NGS

	L2 mass	Pancreatic mass
CK7	+	+
CDX2	+	+
MUC4	+	+
GATA3	-	
PAX8	-	
ER	-	
CK20	-	
TTF1	-	-
CD10	-	
PDL1	-	
Mesothelin	+	
CEA		+
Napsin-A		-

Olaparib

- Olaparib is a PARP (**P**oly[**A**DP-**R**ibose] **P**olymerase) inhibitor
- PARP1 and PARP2 are involved in Base Excision Repair
- PARP1 normally detects and binds to sites of DNA strand damage
  - For double strand breaks, it causes Poly(ADP-ribosyl)ation and recruits MRE11 for double strand break repair
- PARP1 inhibition + PALB2 deficiency leads to synthetic lethality in these cells



Genetic counselling: who to refer

- Individuals with any blood relative with a known P/LP variant in a cancer susceptibility gene
- A P/LP variant identified on tumor genomic testing that has implications if found in germline
- Patients with strong personal or family history of
  - Breast cancer
  - Ovarian cancer
  - Pancreatic cancer
  - Prostate cancer
  - Colorectal cancer
- Li-Fraumeni syndrome or Cowden syndrome or Lynch syndrome testing criteria

Summary

- Back pain has broad Ddx, red flags can be remembered by TUNA FISH
- Stage IV NSCLC involves any form of metastasis (M_1)
- Complete initial diagnostic testing for Stage IV NSCLC involves tissue biopsy, MRI brain, NGS, and can include ctDNA testing or FDG PET
- PALB2 mutations mimic BRCA2, and lead to increased risk of breast, ovarian, pancreatic cancer, and maybe lung cancer
- Patients with strong family history of cancer, patients with known mutations, and relatives of concern should be referred for genetic counselling

Bibliography

Wu S, Zhou J, Zhang K, Chen H, Luo M, Lu Y, Sun Y, Chen Y. Molecular Mechanisms of PALB2 Function and Its Role in Breast Cancer Management. Front Oncol. 2020 Feb 28;10:301. doi: 10.3389/fonc.2020.00301. PMID: 32185139; PMCID: PMC7059202.

Yang X, Leslie G et al. Cancer Risks Associated With Germline *PALB2* Pathogenic Variants: An International Study of 524 Families. J Clin Oncol. 2020 Mar 1;38(7):674-685. doi: 10.1200/JCO.19.01907. Epub 2019 Dec 16. PMID: 31841383; PMCID: PMC7049229.

Zhou J et al.. Spectrum of PALB2 germline mutations and characteristics of PALB2-related breast cancer: Screening of 16,501 unselected patients with breast cancer and 5890 controls by next-generation sequencing. Cancer. 2020 Jul 15;126(14):3202-3208. doi: 10.1002/cncr.32905. Epub 2020 Apr 27. PMID: 32339256; PMCID: PMC7384117.

Chen A. PARP inhibitors: its role in treatment of cancer. Chin J Cancer. 2011 Jul;30(7):463-71. doi: 10.5732/cjc.011.10111. PMID: 21718592; PMCID: PMC4013421.

NCCN guidelines for:

Non-small cell lung cancer

Genetic/Familial High-Risk Assessment