Immunotherapy in Advanced NSCLC

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Conquering Thoracic Cancers Worldwide

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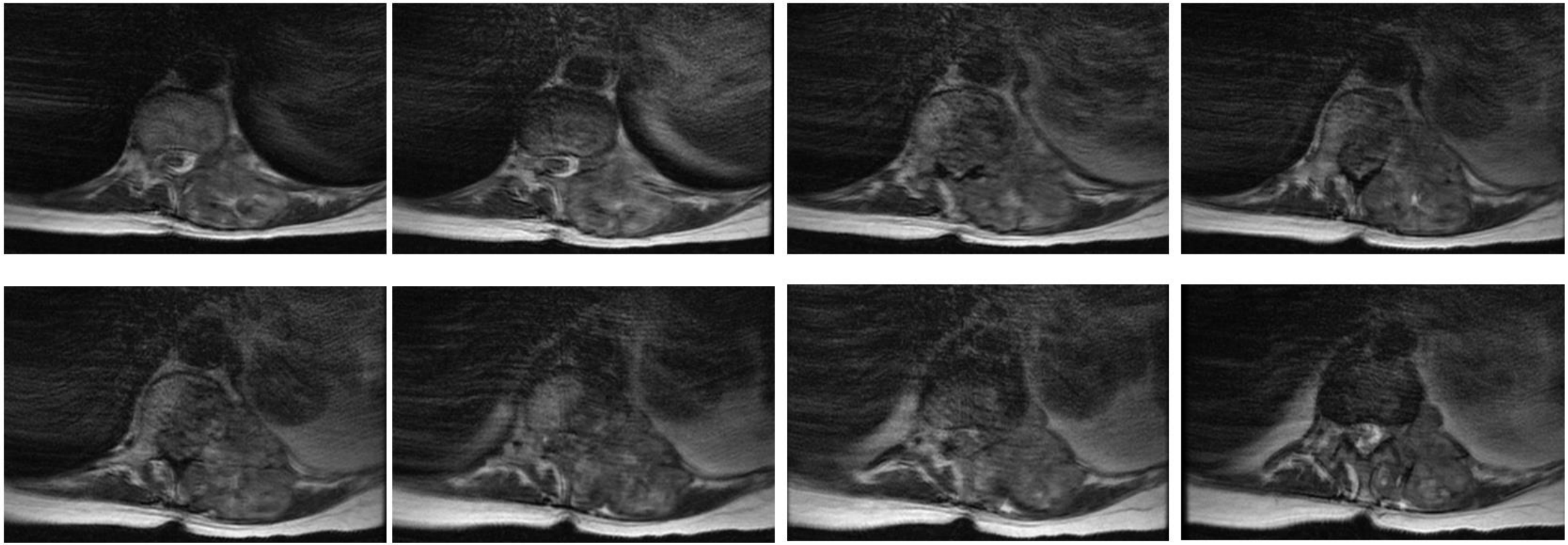
Case Presentation

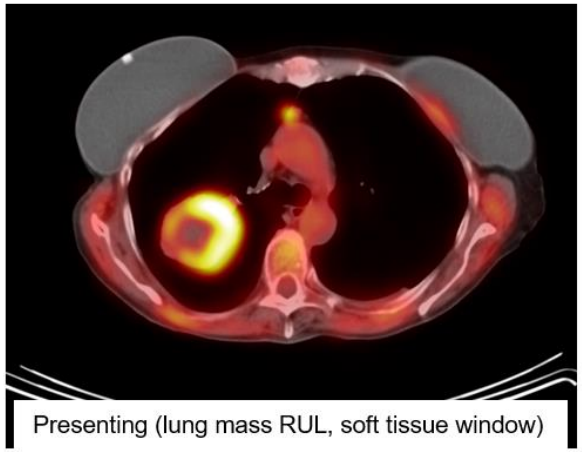
- 62 years old Caucasian female
- Symptoms: severe lower extremities edema and weight loss; back pain 2 months prior
- PMH: breast cancer 20 years ago; ONJ due to zoledronic acid [osteoporosis]
- PSoH: 15 py smoking history
- Biopsy: right lung mass, CK7 + and TTF-1 +; poorly differentiated adenocarcinoma of the lung.
- Staging work up: T3N2M1c (stage IVB); no brain metastasis.
- ECOG PS 1; weight: 86 pounds; normal laboratory parameters.

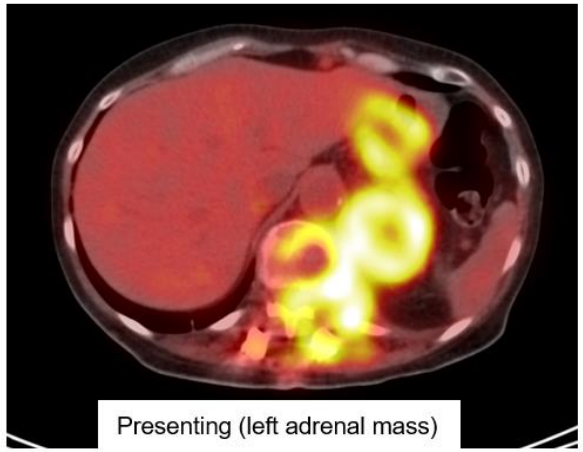
MRI LUMBAR 10/06/2020

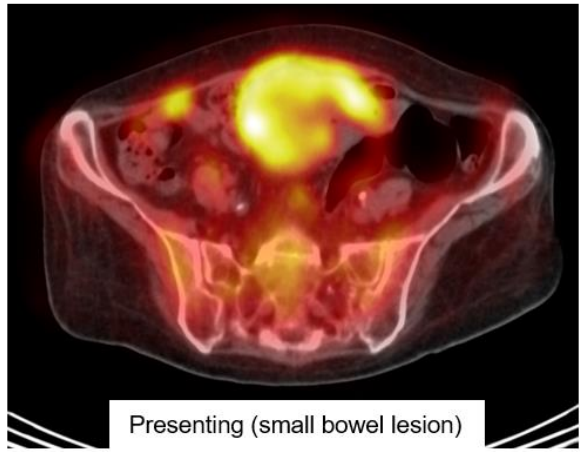


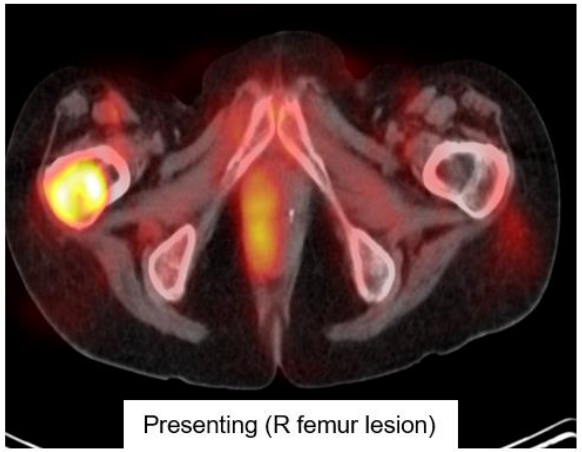
7.8 cm lobulated, heterogeneously T2 hyperintense mass extending from the L-1 vertebral body to the left lamina and transverse process and infiltrating into the adjacent left paraspinal soft tissues and musculature . There is an underlying pathologic fracture and moderate – severe spinal canal stenosis likely represent metastasis.

Initial PET CT scan 11/03/2020


Presenting (lung mass RUL, soft tissue window)


Presenting (left adrenal mass)


Presenting (small bowel lesion)

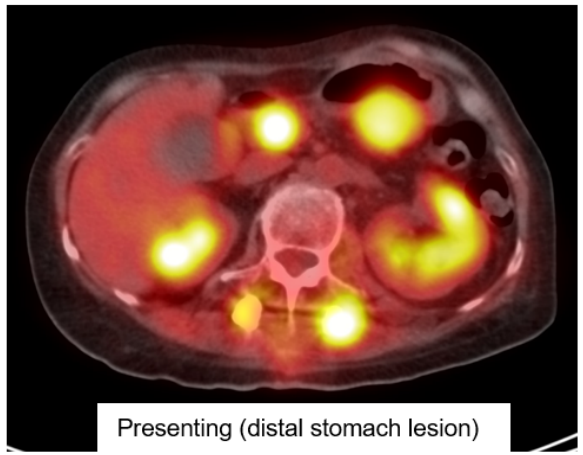

Presenting (R femur lesion)


Presenting (distal stomach lesion)

Large FDG-avid mass in the **right upper lobe** posteriorly adjacent to the minor fissure measuring 5.6 x 5.4 cm with microlobulated margins, demonstrating an SUV max of 11.3. There is a large area of central necrosis within this mass. There is an FDG-avid **anterior mediastinal lymph node** at the anterior aspect of the thoracic aorta measuring 1.0 x 0.7 cm with an SUV max of 5.0. There is an FDG-avid **right hilar lymph node**, difficult to visualize on the non contrast CT, but demonstrating an SUV max of 6.0. There are subtle opacities in the left lower lobe posteriorly adjacent to the costovertebral junction with a bony metastasis discussed below. There is a large mass in the region of the **left adrenal gland** measuring 4.2 x 5.5 cm that is substantially FDG-avid with an SUV max of 11.6. There is a solid mass adjacent to the **lesser curvature of the stomach** measuring 4.3 x 5.4 cm that is substantially FDG-avid with an SUV max of 16.7. This also demonstrates suggestion of central necrosis. There is a target **mesenteric lesion is in the posterior pelvis** measuring 0.9 x 1.2 cm with an SUV max of 10.4. There is an FDG-avid **sclerotic lesion in the right proximal femur** in the superior trochanteric region demonstrating an SUV max of 9.6.

Courtesy of Darryl Eber, MD (Radiology)/Edgardo Santos, MD (Thoracic Oncology)

Initial PET CT scan 11/03/2020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Initial Molecular Profile- Liquid Biopsy 10/29/2020

EGFR Amplification	Necitumumab	Yes	Low (+)
KRAS G13E	Binimetinib	Yes	31.2%
TP53 E198*	None	Yes	20.7%

Variants of Uncertain Significance
NTRK3 T149K (17.2%), *SMO* R726Q (8.5%), *BRCA2* I2521M (6.6%), *DDR2* F588L (5.4%)
The functional consequences and clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Synonymous Alterations
TP53 V197V (20.2%), *NTRK3* I391I (13.3%), *TERT* R416R (0.2%)
This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Additional Biomarkers

Biomarker	Additional Details
Tumor Mutational Burden (TMB)	31.58 mut/MB
MSI-High	NOT DETECTED

Initial Molecular Profile- Tissue Biopsy (spine)

Sent: 10.09.2020
Received: 11.11.2020

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
TMB	**Seq**	**DNA-Tumor**	**High, 21 mut/Mb**	BENEFIT	**pembrolizumab**	**Level 1**
PD-L1 (SP142)	IHC	Protein	Positive | 2+, 90%	BENEFIT	pembrolizumab	Level 3A
				BENEFIT	nivolumab	Level 3B
ERBB2 (Her2/Neu)	IHC	Protein	Negative | 0	LACK OF BENEFIT	pertuzumab, trastuzumab	Level 3B

* Biomarker reporting classification: Level 1 - highest level of clinical evidence and/or biomarker association included on the drug label; Level 2 - strong evidence of clinical significance and is endorsed by standard clinical guidelines; Level 3 - potential clinical significance (3A - evidence exists in patient's tumor type, 3B - evidence exists in another tumor type).

Important Note

TMB-High status should only be used to guide pembrolizumab treatment when no satisfactory alternative treatment options are available.

Cancer-Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
KRAS	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 2 | p.G13E**
TP53	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 6 | p.E198***
MSI	Seq	DNA-Tumor	Stable
Mismatch Repair Status	IHC	Protein	Proficient
NTRK1/2/3	Seq	RNA-Tumor	Fusion Not Detected
ALK	Seq	DNA-Tumor	Mutation Not Detected
		RNA-Tumor	Fusion Not Detected

Biomarker	Method	Analyte	Result
AR	IHC	Protein	Negative | 0
	Seq	RNA-Tumor	Variant Transcript Not Detected
ATM	Seq	DNA-Tumor	Mutation Not Detected
BRAF	Seq	DNA-Tumor	Mutation Not Detected
BRCA1	Seq	DNA-Tumor	Mutation Not Detected
BRCA2	Seq	DNA-Tumor	Variant of Uncertain Significance Exon 15 | p.I2521M
CDH1	Seq	DNA-Tumor	Mutation Not Detected

- **Question # 1:** How would you treat this patient?

Summary: 62 yo; ECOG PS: 1; stage IVB
K-RAS G13E; TP53; TMB high (tissue and liquid); PD-L1 90%

Monotherapy Checkpoint Inhibitor?

Platinum-based doublet plus checkpoint inhibitor?

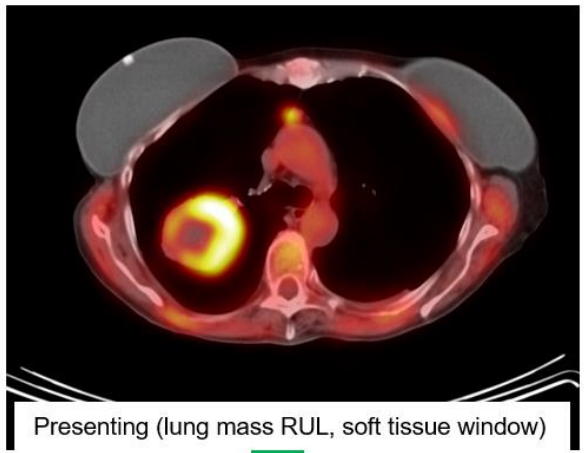
Platinum-based doublet plus dual checkpoint inhibition?

- She started single agent pembrolizumab with good clinical response, improving her performance status, gaining weight, and became pain free. Patient continued her physical therapy.

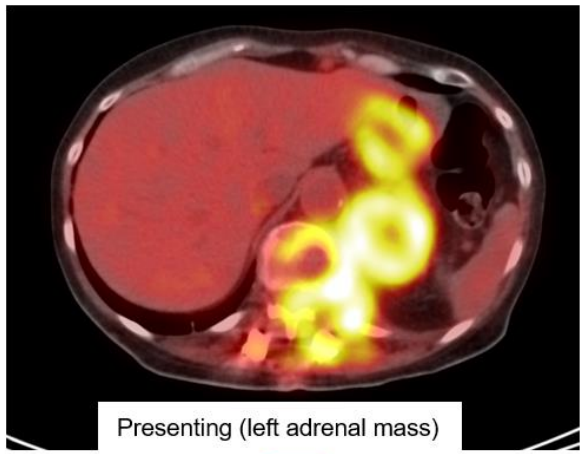
- See radiological response at 4 months after treatment started:

Follow up PET CT scan 04/30/2021 (below)

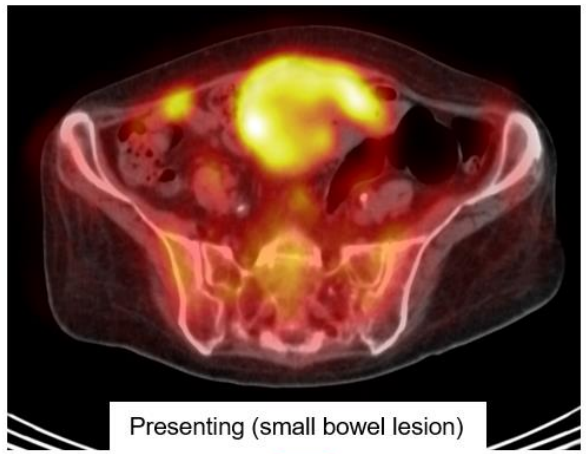
Courtesy of Darryl Eber, MD (Radiology)/Edgardo Santos, MD (Thoracic Oncology)



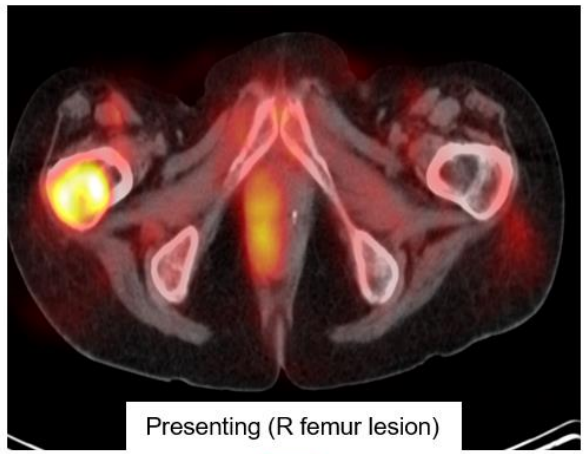
Presenting (lung mass RUL, soft tissue window)



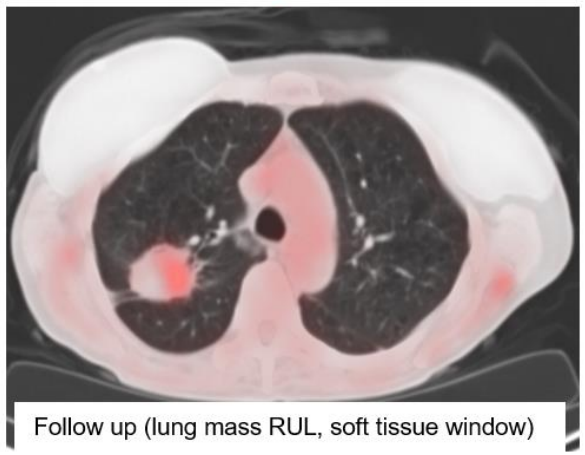
Presenting (left adrenal mass)



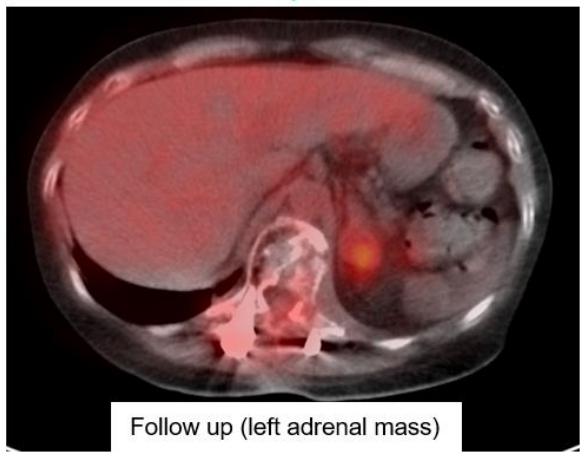
Presenting (small bowel lesion)



Presenting (R femur lesion)



Follow up (lung mass RUL, soft tissue window)



Follow up (left adrenal mass)

Follow up (small bowel lesion)

Follow up (R femur lesion)

Follow up PET CT scan 04/30/2021

PET CT 11.03.2020

Presenting (distal stomach lesion)

Follow up (distal stomach lesion)

The FDG-avid pulmonary mass in the posterior segment of the right upper lobe adjacent to the minor fissure is again noted with spiculated margins, measuring 3.9 x 3.1 cm with associated FDG uptake demonstrating an SUV max of 3.9 (previously measured 4.7 x 4.3 cm with an SUV max of 4.1). Interval resolution of the left pleural effusion. No new suspicious FDG-avid pulmonary nodule, pulmonary mass or consolidation. The left adrenal mass is again noted measuring 2.1 x 2.1 cm. The mass-like area adjacent to the lesser curvature of the stomach is again noted measuring 2.4 x 2.8 cm with only mild FDG uptake with an SUV max of 2.2 (previously measured 2.9 x 3.7 cm with an SUV max of 3.0). No suspicious FDG-avid osseous lesions are seen within the vertebral bodies. No other suspicious FDG-avid osseous lesions are noted in the rest of the body. **IMPRESSION: Overall, there is interval response to therapy. No new FDG-avid tumor is noted in the rest of the body**.

Courtesy of Darryl Eber, MD (Radiology)/Edgardo Santos, MD (Thoracic Oncology)

Clinical Course:

- By March 2022 (16 months from therapy initiation), the patient underwent small bowel resection; pathology revealed: positive for malignancy, favor metastatic poorly differentiated carcinoma.

- Ten months after SBRT to left adrenal gland, nodule double in size as well as in activity. The patient underwent thru left adrenalectomy (October 2022; 2 years after initial therapy). Pathology revealed: metastatic poorly differentiated carcinoma; the morphology seen was similar to the morphology seen in prior specimens diagnosed as "poorly differentiated carcinoma" from the left paraspinal region, small intestine and biopsy of RUL mass.

Clinical Course:

- Patient asked medical oncologist for how long she needs to continue therapy.

Question # 2: What would you do?

a. Stop IO now, after two years of therapy? Watch for progression.

b. Would you continue IO for two more years?

c. Indefinite treatment

d. Would you add chemotherapy to IO now? and continue Pem/Pem?

Follow up.

- The patient continued on pembrolizumab alone.

- After a discussion with the patient, MRD test was ordered using Signatera (tumor-informed test from adrenal metastasis resected in October 2022). Signatera has been checked in August 2023, November 2023 and February 2024. All of them have been negative.

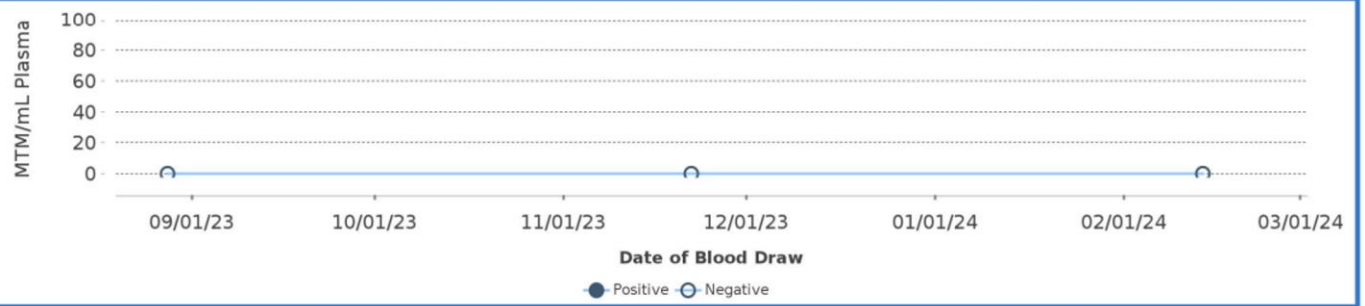
FINAL RESULTS SUMMARY

Signatera Negative ⊖

MTM/mL:
Not Detected

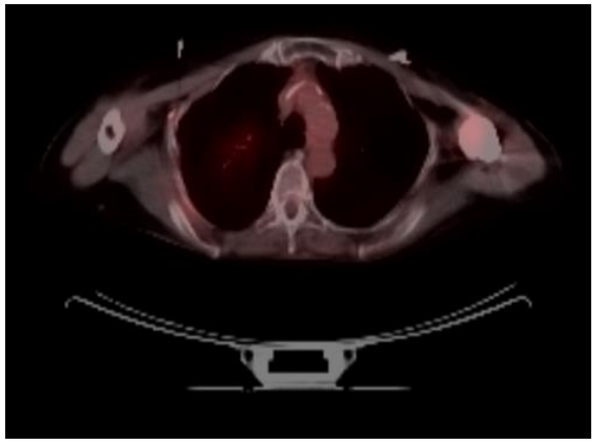
Mean tumor molecules per mL is calculated based on the mean of ctDNA molecules detected per mL of the patient's plasma. *See Limitations section below.*

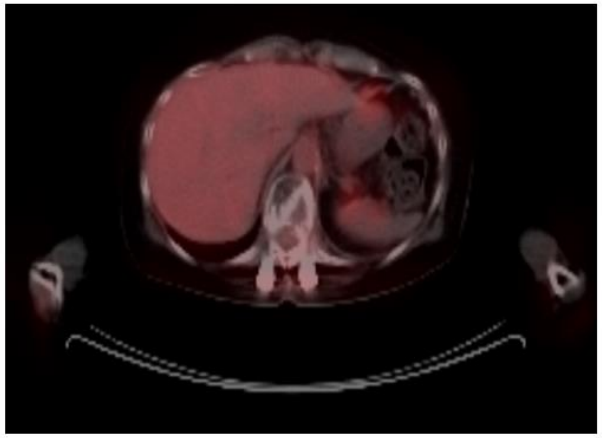
Historical Results

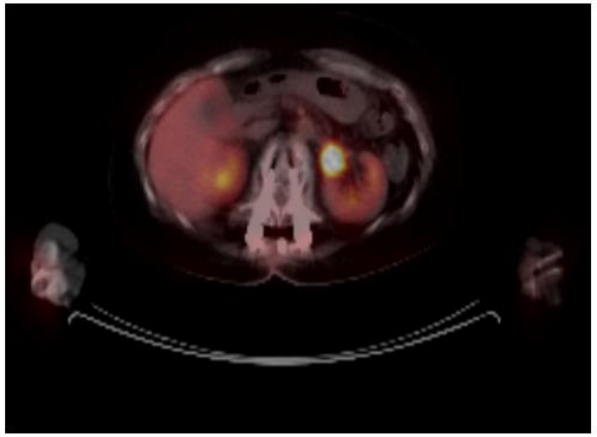


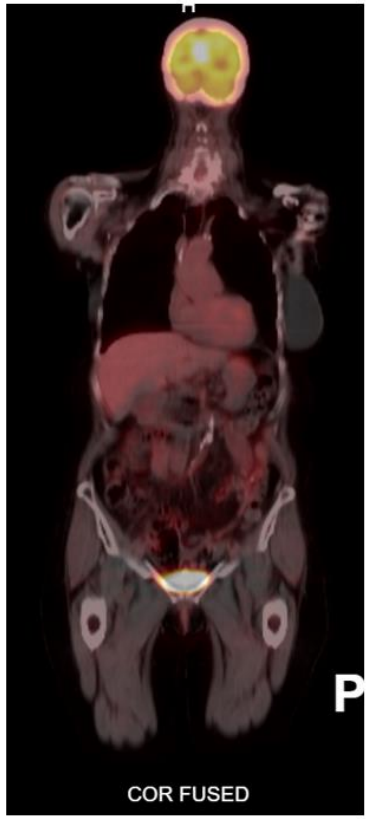
Date	Reported MTM/mL
Feb 14, 2024	0.00
Nov 22, 2023	0.00
Aug 28, 2023	0.00

PET CT scan 02/02/2024









PET/CT impression: Continued interval response to therapy. Stability in the patient's treated lesion in the right lung. No new FDG-avid pulmonary nodule, pulmonary mass or consolidation. No new FDG-avid tumor in the body. Stability in the minimal FDG uptake in the sacrum. This is also likely treated and stable. No new FDG-avid osseous lesion. Fat- and bowel-containing ventral abdominal wall hernia without any inflammation. Stable non obstructing renal calculi.

- **Final plan** discussed with the patient and two thoracic oncologists: if the patient persists Signatera negative plus NED by PET CT scan, therapy will be discontinued on November 2024 (2 years after last intervention; patient has remained thus far with stable disease).