Management of Oligo-PD in Setting of IO in "wild type" mNSCLC

Corey J Langer MD, FACP
Professor of Medicine
Director of Thoracic Oncology
Abramson Cancer Center
University of Pennsylvania
Corey.langer@uphs.upenn.edu
CP: 215-806-6152

CJ Langer: Disclosures

- Consultant – AstraZeneca, Boehringer Ingelheim (BI), Genentech/Roche, Gilead, GSK, Merck, Mirati, Novocure, Pfizer, Regeneron, Sanofi-Aventis, Takeda, Daiichi-Sankyo
- Grant/Research Support – AstraZeneca, Boehringer Ingelheim (BI), Eli Lilly, Inovio, Merck, Oncocyte, Takeda, Trizell, J+J, Amgen, Fujifilm, Navire, Incyte
- Other Financial or Material Support – Amgen, Novartis, OncocyteDX, Incyte

Case*

- 60 year old WM retired police officer with 30 pack year smoking history (quit 2004), CAD (s/p CABG in 2004, several stents most recently 7 years ago, history of MI), iliac artery aneurysm and mesenteric artery dissection
- 09/19, while traveling, pt dev'd a URI, that progressed with increased cough, escalating DOE, ultimately SOB at rest with facial and neck swelling, unable to lay flat; also c/o general malaise, increasing hoarseness and night sweats.
- 11/19 pt presented to his PMD. PE demonstrated diffuse wheezing, facial swelling, engorged neck veins and bilateral SCN with shotty cervical LNs
- PMD ordered a CXR, then CT CAP which showed bulky R sided mediastinal mass, coalescent LAD, cervical LNs, L SCN, bone mets, isolated liver met and RP LN
- Seen by Thoracic Surgery on 11/12/19 and directly admitted for open biopsy of the L SCN, which confirmed poorly differentiated adenoca, TTF-1 (+),
- PD-L1: (+) – 100%
- MRI Brain: 3 mm discrete lesion in L cerebellum

*Cases may have been modified for educational purposes

NGS:

DISEASE ASSOCIATED VARIANTS
GENE PROTEIN CHANGE cDNA CHANGE

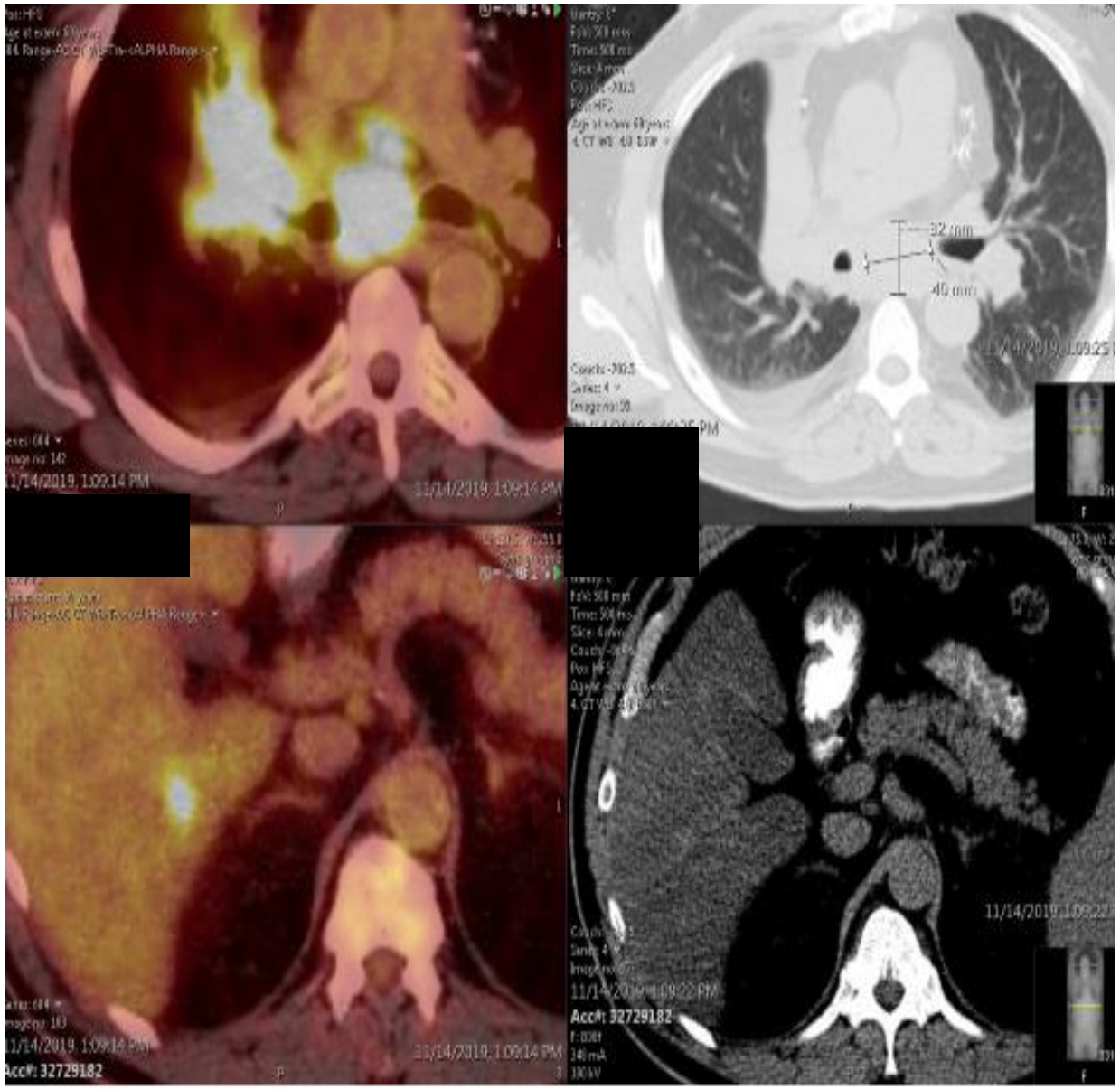
- NF1 p.H2480Qfs*8 c.7440_7443del
- TP53 p.D281Y c.841G>T

VARIANTS OF UNCERTAIN SIGNIFICANCE
GENE PROTEIN CHANGE cDNA CHANGE

- ATRX p.? C.6504+5G>T
- EGFR p.G1209* c.3625G>T
- ESR1 p.A186V c.557C>T
- KDR p.Q441* c.1321C>T
- SMO p.S533R c.1599C>A

TUMOR MUTATIONAL BURDEN

- 5.1 mutations per megabase (u/MB)



Question

Does he have an actionable mutation?

- Yes
- No
- Not sure

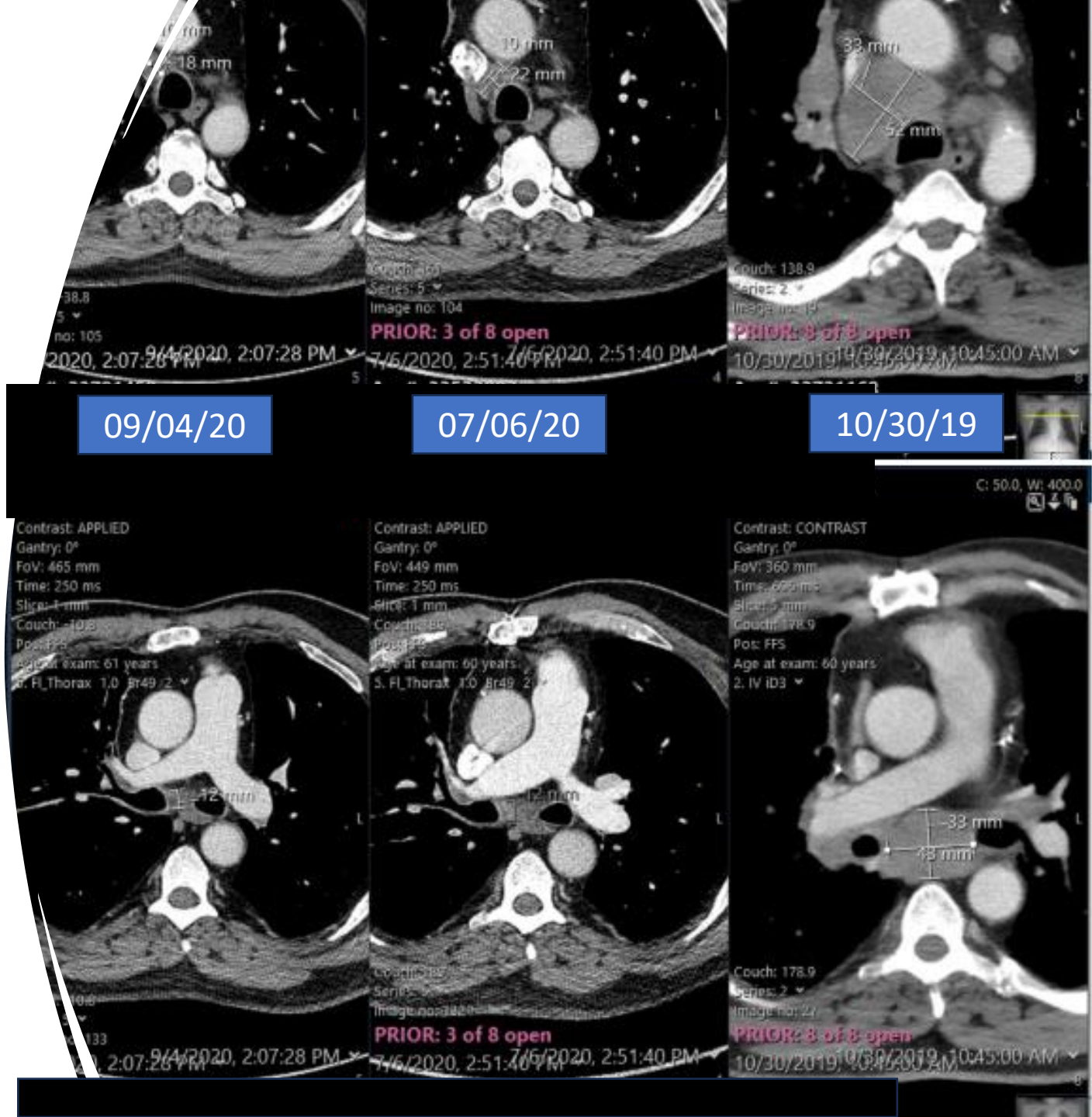
Question

How would you treat this patient?

- Single agent pembrolizumab
- Pembrolizumab, in combination with pemetrexed and carboplatin
- Enrollment on Insigna trial comparing 1 vs 2
- POSEIDON: Pemetrexed/carboplatin/durvalumab/tremelimumab
- Other

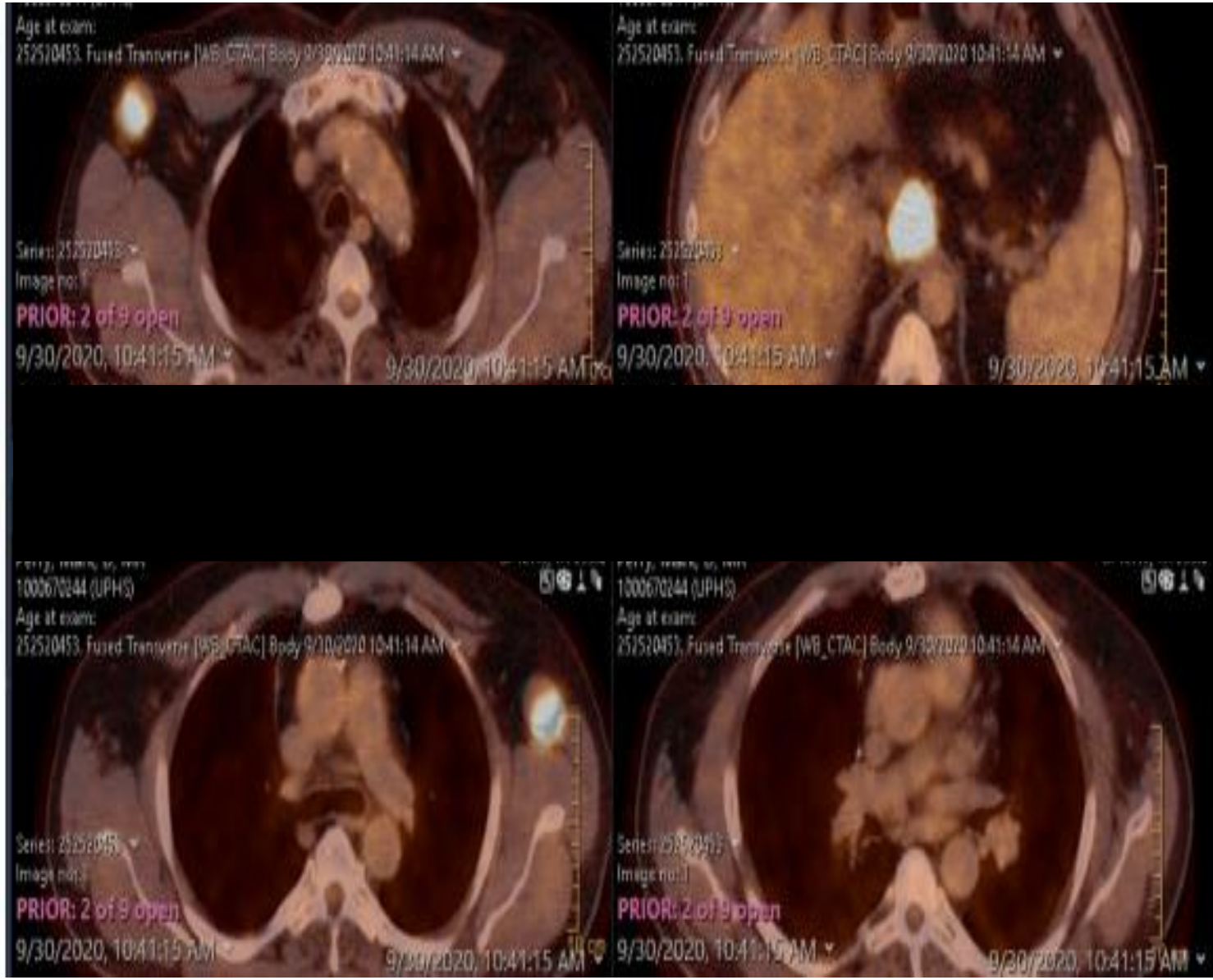
Tx-Course

- Started single agent pembro 12/19 with marked improvement in Sx. SVC Sx, hoarseness, and DOE subsided within 3 wks by 2nd cycle and night sweats by 3rd cycle. “Doc, I feel the best I’ve felt in 4 mos”
- CT shows dramatic improvement in mediastinal LAD and resolution of hepatic mets
- Bones increasingly sclerotic
- F/U Brain MRI proves (-)
- Did well until 09/20 when, after 14 cycles, he developed bilateral axillary LAD.
- CT CAP confirmed these findings, as well as large Gastro-hepatic ligament LN; other sites of tumor continued to regress
- Axillary Bx (+) pd adenoca



Abnormal FDG uptake associated with multiple lymph nodes, suspicious for viable neoplasm, as follows:

- Left intraparotid lymph node, 10 x 9 mm (CT image 27) with max SUV 3.8 (PET image 230).
- Right level 2A lymph node, 15 x 11 mm (CT image 34) with max SUV 4.4 (PET image 222).
- Right axillary lymph node, 26 x 23 mm (CT image 65) with max SUV 12.8 (PET image 190).
- Left axillary lymph node, 27 x 24 mm (CT image 74) with max SUV 14.1 (PET image 180).
- Gastrohepatic lymph node, 39 x 33 mm (CT image 117) with max SUV 12.8 (PET image 141).



Question

Does this qualify as Oligo-PD?

- Yes
- No
- Not sure

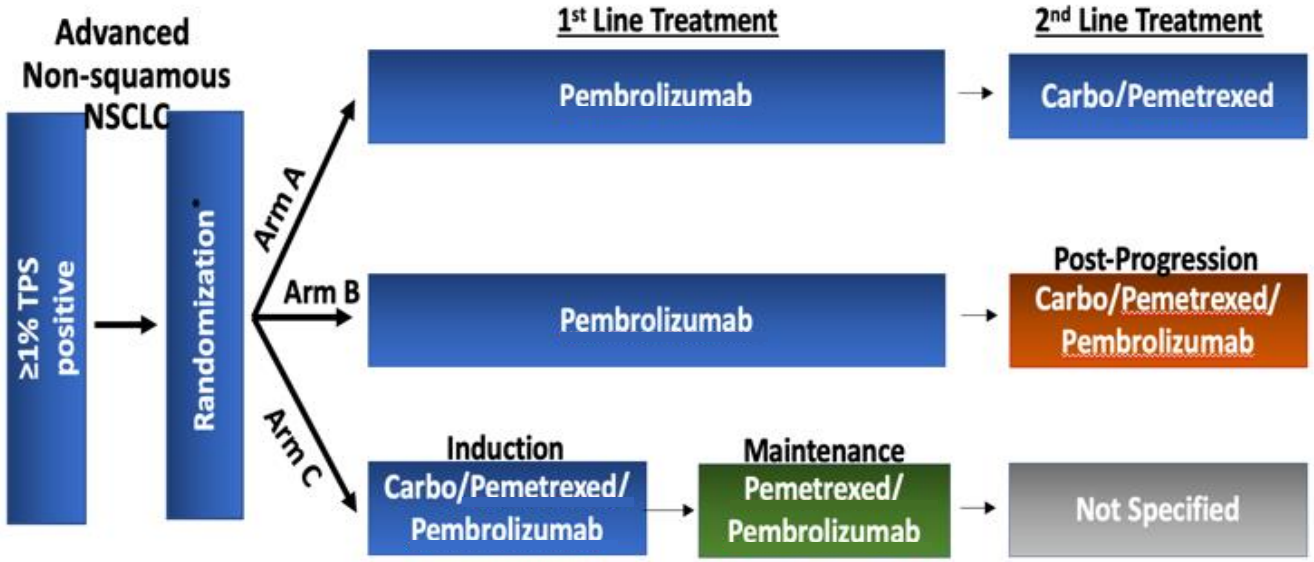
Question

With isolated PD as noted in the axilla and RPLN, what's the next step?

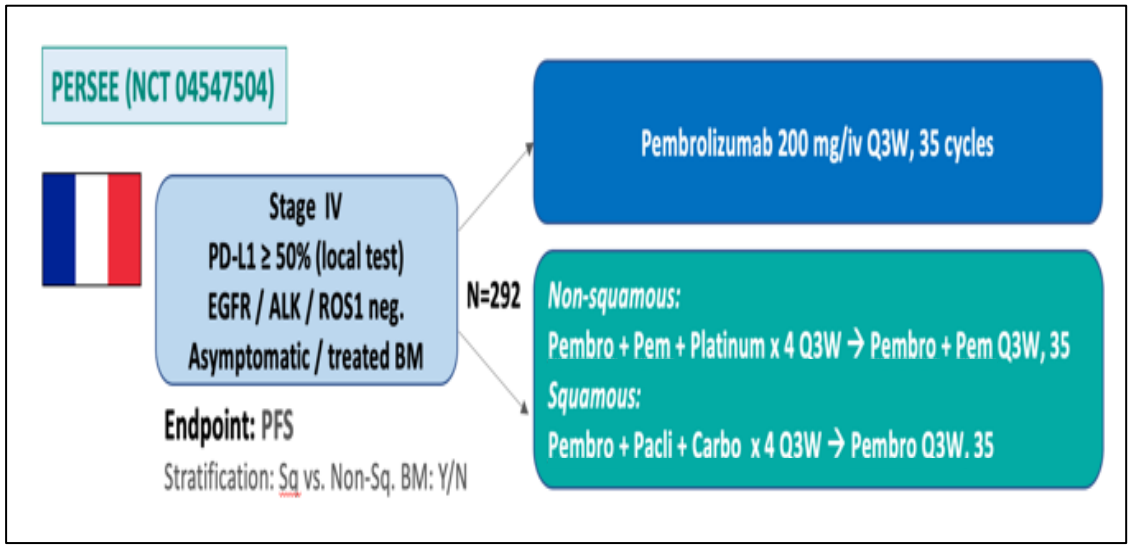
- Addition of pemetrexed/carboplatin to pembrolizumab
- Switch from pembrolizumab to pem/carbo
- Local XRT to axilla and G-H lig LN, with continuation of single agent pembrolizumab
- 1 and 3 combined

Ongoing Trials

INSIGNA
H. Borghaei/A. Chiang



PERSEE
GFPC 01-2020
R. Descourt / C. Decroisette



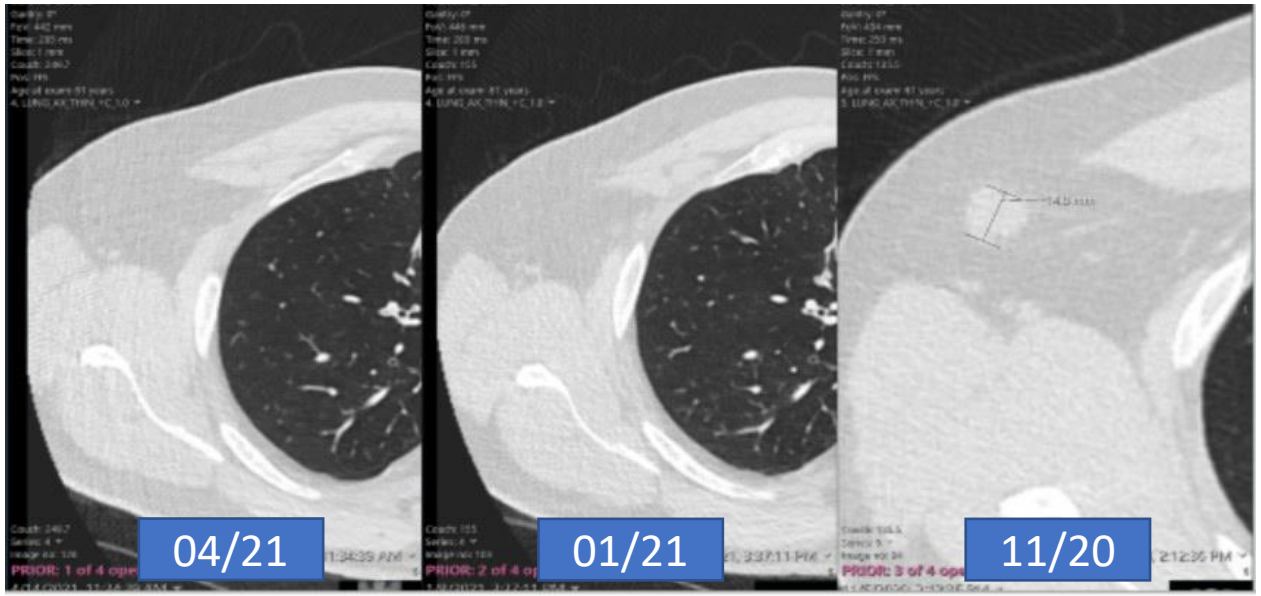
Primary Endpoint: OS
Integrated Biomarker Objective:

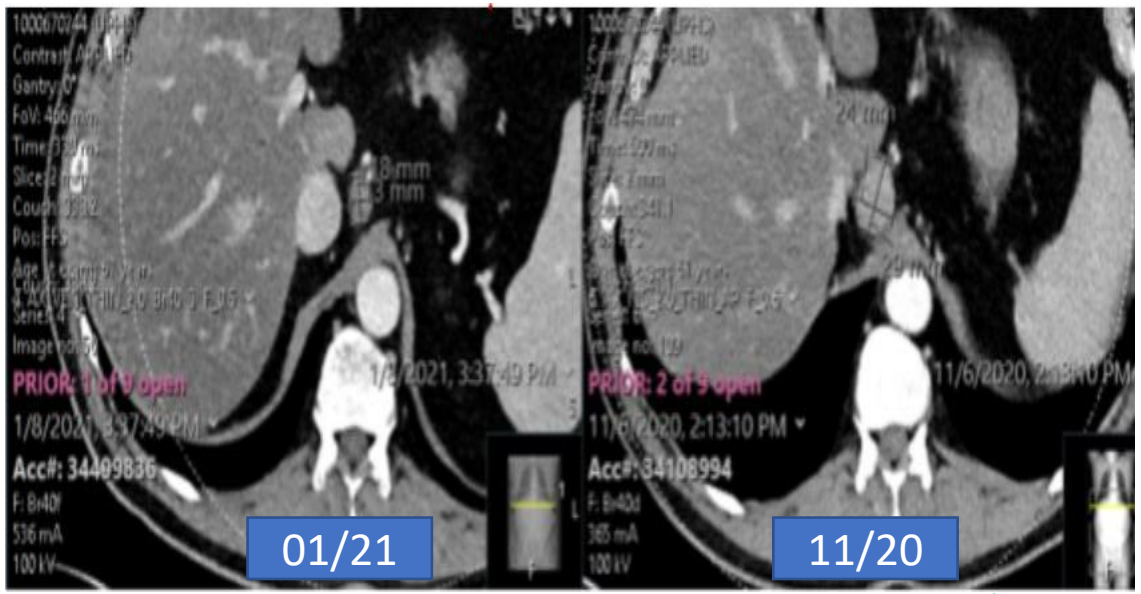
- To establish a ***predictive signature*** for clinical benefit (OS), to treatment with chemo combined with pembrolizumab versus pembrolizumab alone in patients with PD-L1 expressing tumors (>=1%, 1-49%, >=50%).
- To establish a ***prognostic signature*** associated with better outcome (OS) to 1st line treatment with pembrolizumab alone in patients with PD-L1 expressing tumors (>=1%, 1-49%, >=50% TPS).

NCT03793179; NCT04547504

Tx-Course (cont'd)

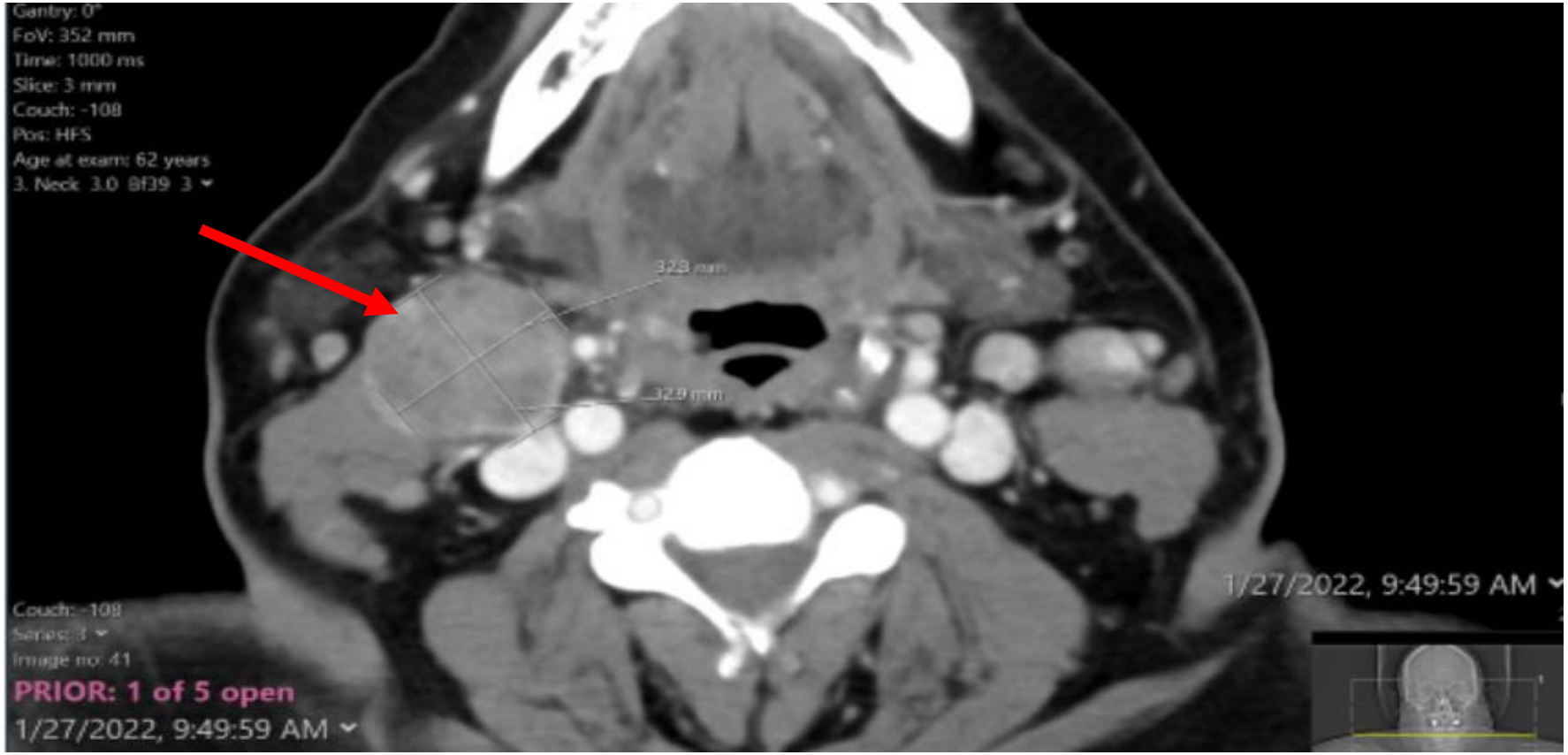
- Focal PD in both axilla and upper RP LN, near CR all other sites
- Treatment Site: Bilateral Axilla and Abdomen
  - INI_Axilla_L 5000 cGy, 25/25 fx, 200 cGy/fx (11/13/2020)
  - INI_Axilla_R 5000 cGy, 25/25 fx, 200 cGy/fx (11/13/2020)
  - INI_GH 5000 cGy, 25/25 fx, 200 cGy/fx (11/13/2020)
- Did well with near complete resolution of nodal PD, received additional 2 cycles during XRT

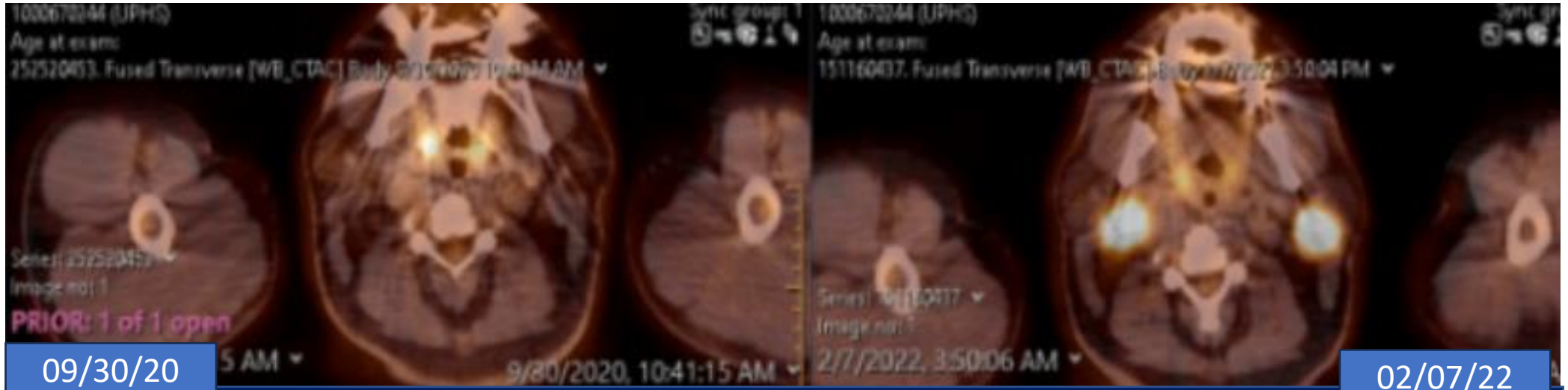




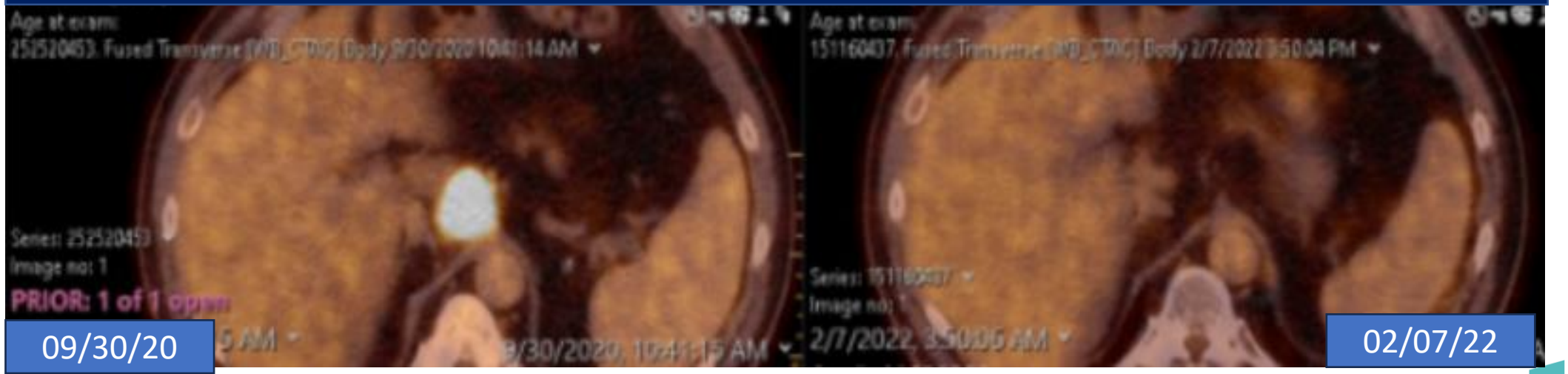
Tx-Course (cont'd)

- Continued pembro single agent for another 21 cycles till 03/22 when he developed bilateral upper cervical LNs with bulky disease in R submandibular region.
- Biopsy again showed adenocarcinoma, NGS unchanged





Clear PD in upper cervical LNs, with interval resolution of G-H lig LN: 09/20 vs 02/22



Question

With isolated PD noted this time in the cervical LNs, what's the next step?

- Addition of pemetrexed/carboplatin to pembrolizumab
- Switch from pembrolizumab to pem/carbo
- Local XRT to cervical LNs and R submandibular region, with continuation of single agent pembrolizumab
- 1 and 3 combined

Question

As of 01/24, pt has now received > 4 years of pembrolizumab.

What would you do at this point?

- Stop pembrolizumab
- Continue at 3-4 wk intervals
- Continue at 6 wk intervals
- Consult Dr. Gandara and Dr. Wakelee

Backup Slides

OLIGO-METASTASES

- Definitely Tx'd Metachronous or Synchronous Mets
  - Oligo-remnant tumor, undergoing Systemic Tx
    - Oligo-PD in setting of Systemic Tx

What are the implications?

Local therapy such as surgery, radiation, or other ablative procedures can be added to systemic therapy to extend longevity

Evaluation of Pembrolizumab Post Local Ablative Therapy in Oligometastatic Disease

Primary endpoint:
- PFS

Secondary endpoints:
- OS, safety/tolerability

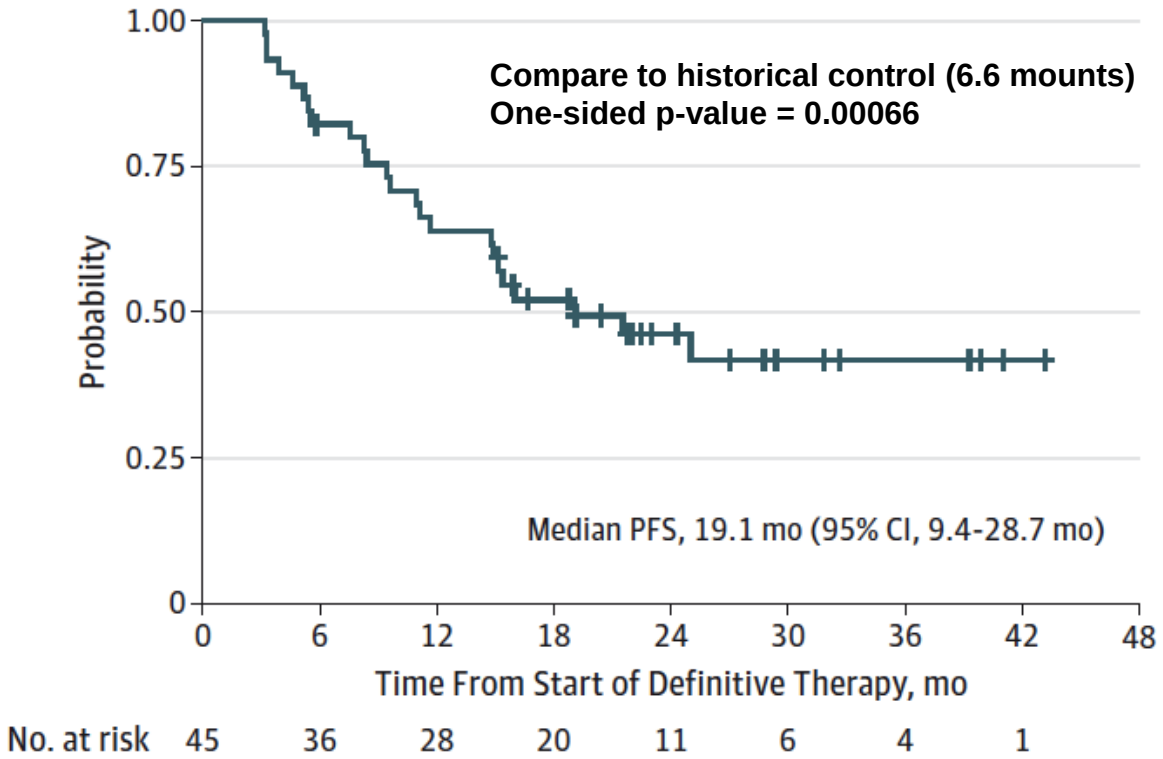
- Patients are followed for an additional 12 months after enrollment has ended
- 80% power to detect increase in median PFS from 6.6 months vs 10 months
- Assuming exponential survival and one-sided 5% significance level

*Any form of LAT was acceptable, including surgery, chemoradiotherapy, stereotactic radiotherapy, and/or interventional ablation.

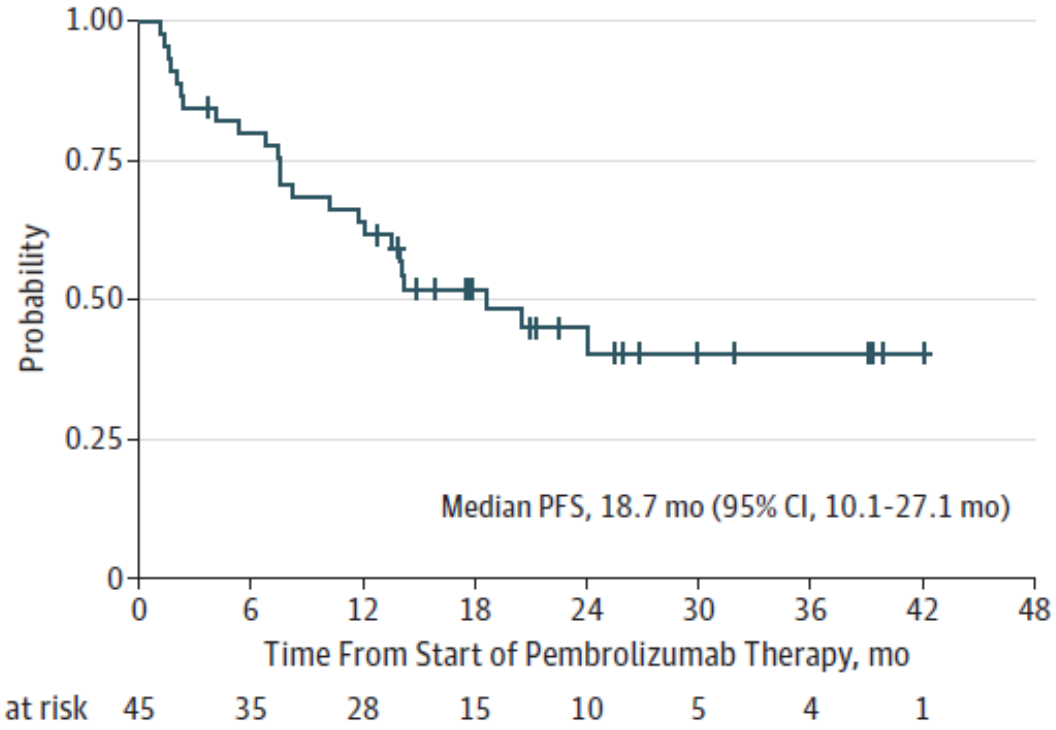
Bauml et al JAMA Oncol. 2019;5(9):1283-1290

PFS after LAT in NSCLC Pts with Oligo-metastases

Progression-Free Survival From Start of LAT



Progression-Free Survival From Start of Pembrolizumab Therapy



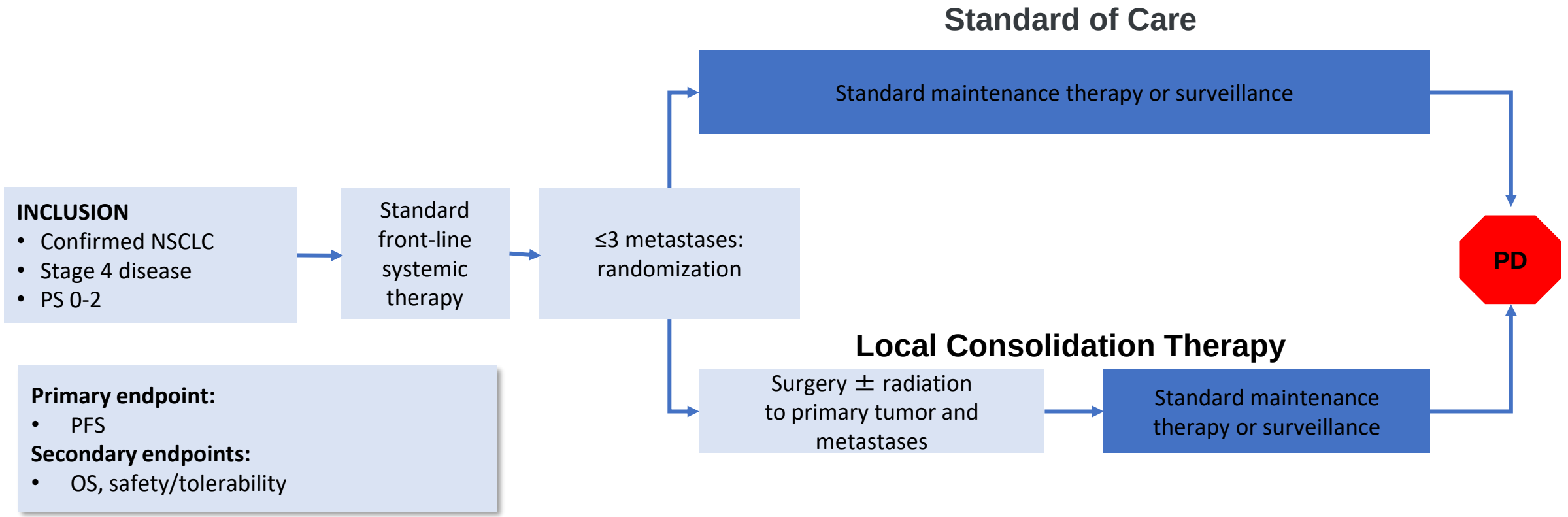
- Of the 45 patients who received pembrolizumab, 28 completed 8 cycles, and 18 completed 16 cycles
- 5 yr update: 62% remain alive

Bauml et al JAMA Oncol. 2019;5(9):1283-1290

Isolated Progression in IO-Treated Pts

- Paucity of Data
- Tendency to extrapolate from our experience with oligo-remnant tumor (Gomez et al) and with isolated PD in EGFR and ALK Pts receiving TKIs
- Differentiating Pharmacokinetc Failure (e.g failure to cross the BBB or affect the CNS) vs Systemic Resistance
  - Radiate CNS PD if extra-cranial disease is “under control”
  - Potential abscopal effect of XRT outside the CNS, especially if there are a limited # of growing mets

Gomez et al., 2016 Impact of Local Consolidative on Patient Outcome

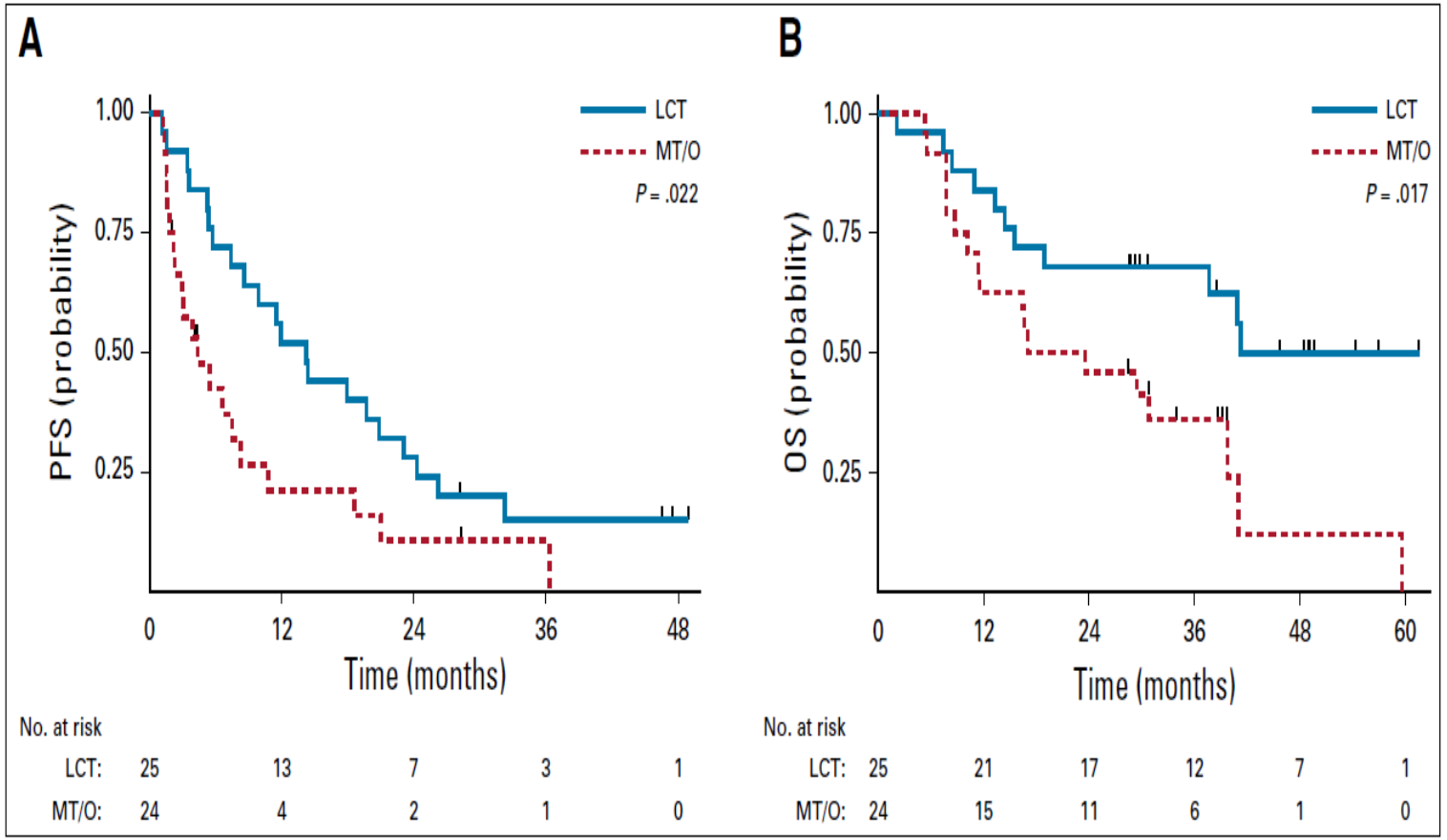


Patients were followed for AEs and progression every 6 weeks (± 2 weeks) after randomization for the first year and at the physician's discretion thereafter
Maintenance therapy: pemetrexed and bevacizumab (for non-squamous NSCLC), erlotinib, crizotinib (for patients with ALK rearrangement), and observation

Gomez DR, et al. Lancet Oncology. 2016 17(12):1672–1682.

Gomez, et al 2019: Updated Results, Including Overall Survival

- With an updated median follow-up time of **38.8 months**, PFS benefit was durable (14.2 months) with LCT compared with MT/O 14.2 vs 4.4 [p=0.022])
- OS benefit in the LCT arm (41.2 vs 17.0 months [p=.017])
- No additional grade ≥3 toxicities were observed
- Survival after progression was longer in the LCT group (37.6 vs 9.4 [p=0.034])



(A) Progression-free survival (PFS) and (B) overall survival (OS) in patients given local consolidative therapy (LCT) or maintenance therapy or observation (MT/O) for oligometastatic non-small-cell lung cancer

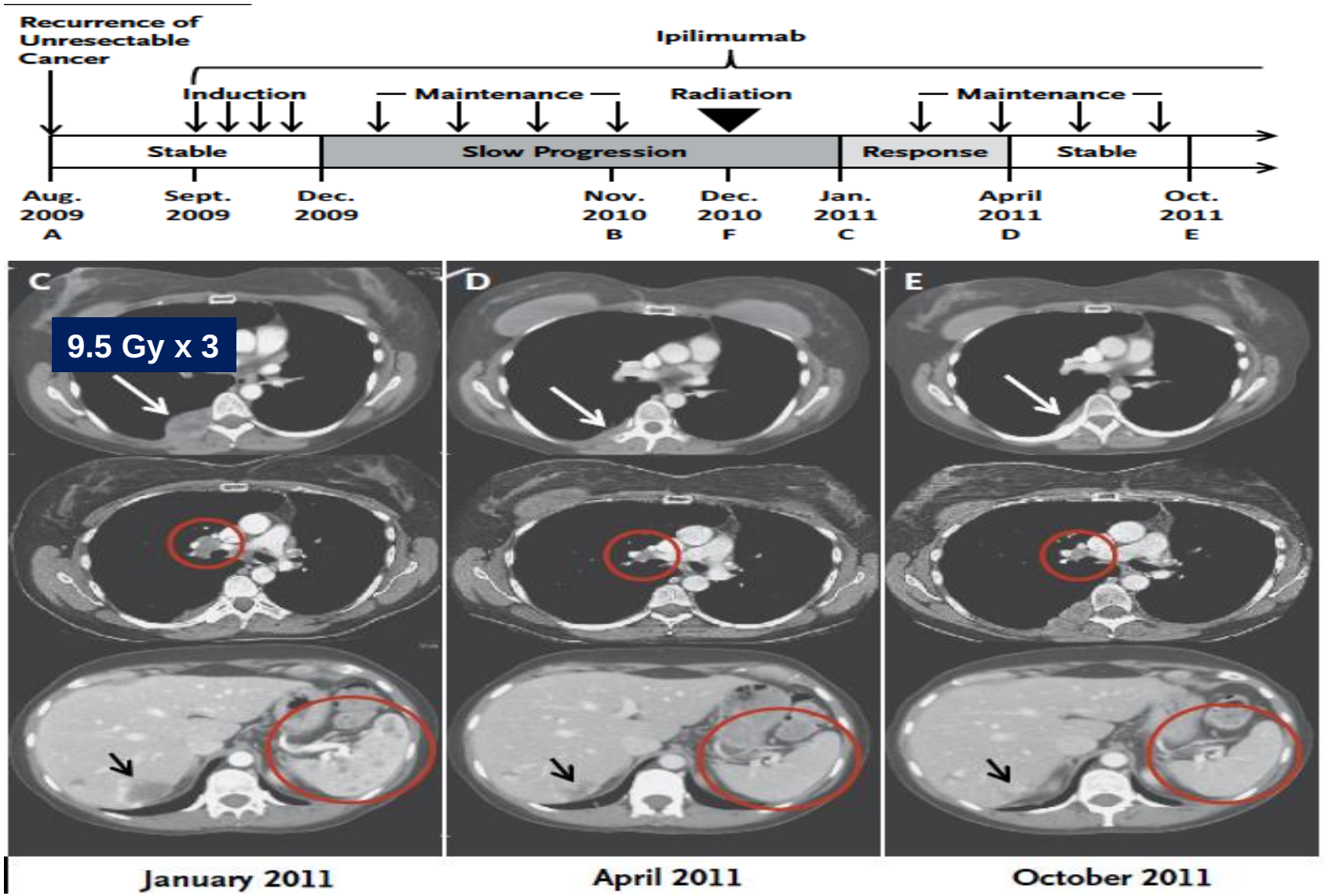
Gomez et al J Thorac Oncol. 2019;37(18):1558-1565

Is there an Abscopal Effect in Patients with Isolated or More Generalized PD?

Melanoma Data

NSCLC Data

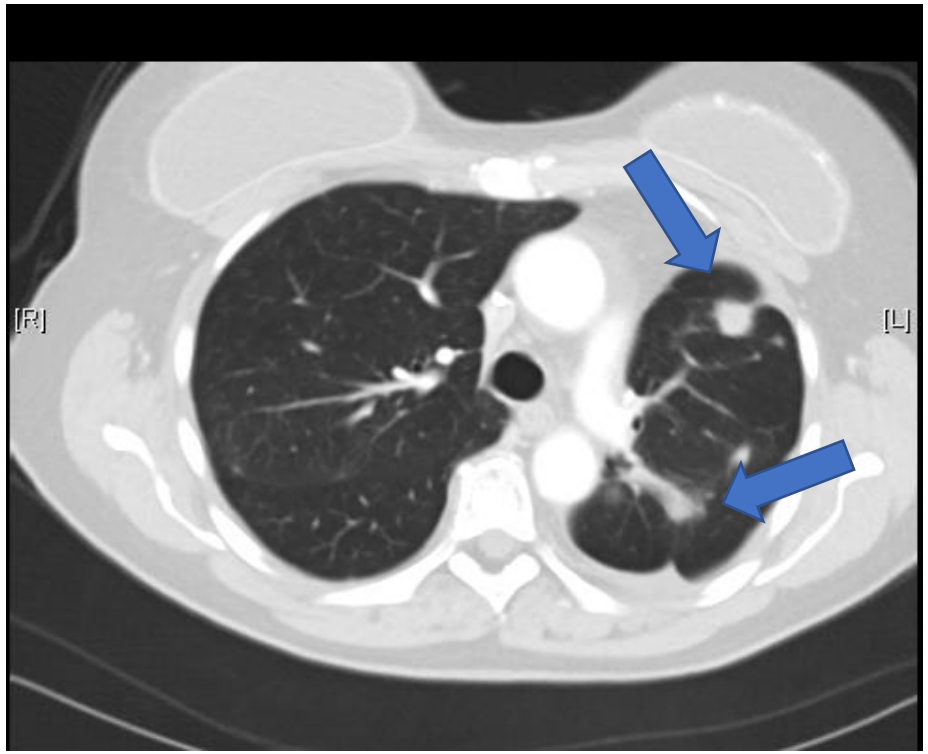
Abscopal Effect in a Patient with Melanoma



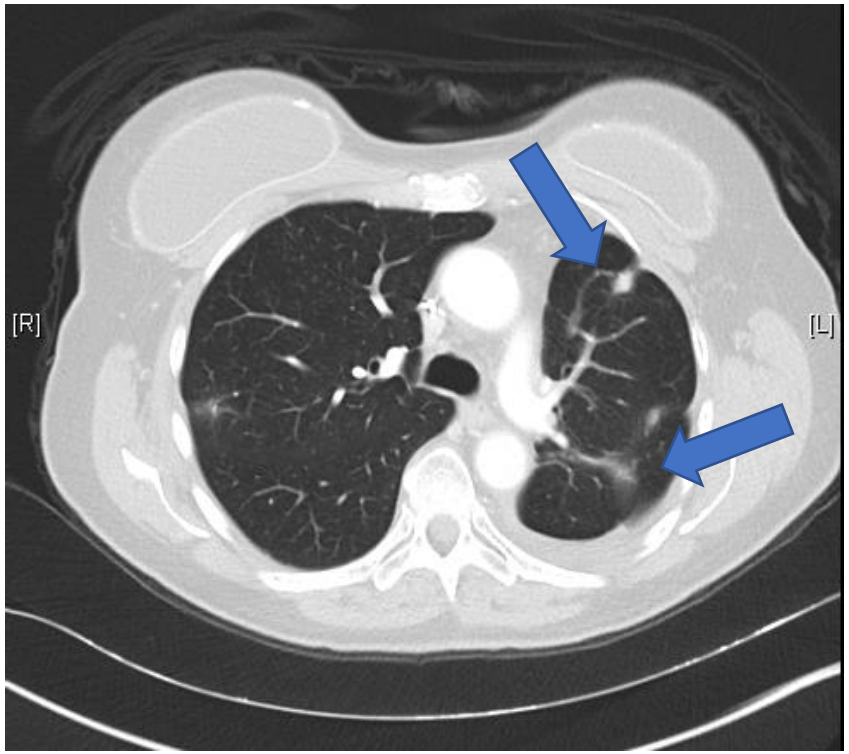
Postow *et al*. *NEJM* 2012

Abscopal Effect in NSCLC

63 year old WF s/p XRT to LLL on Pembro



10/01/14



11/24/14

PD-1-RADVAX:

A stratified phase I trial of pembrolizumab (PD-1 mAb) with hypofractionated radiotherapy in patients with advanced and metastatic cancers

Trial Design

- Phase I cohort study of a fixed dose of Pembrolizumab in combination with 2 distinct regimens of hypofractionated RT.
- There will be 5 groups of patient diagnoses:

Stratum 1

- Metastatic melanoma patients w/ PD while on PD-1 or PD-L1 therapy
- Metastatic NSCLC patients with PD while on PD-1 or PD-L1 therapy

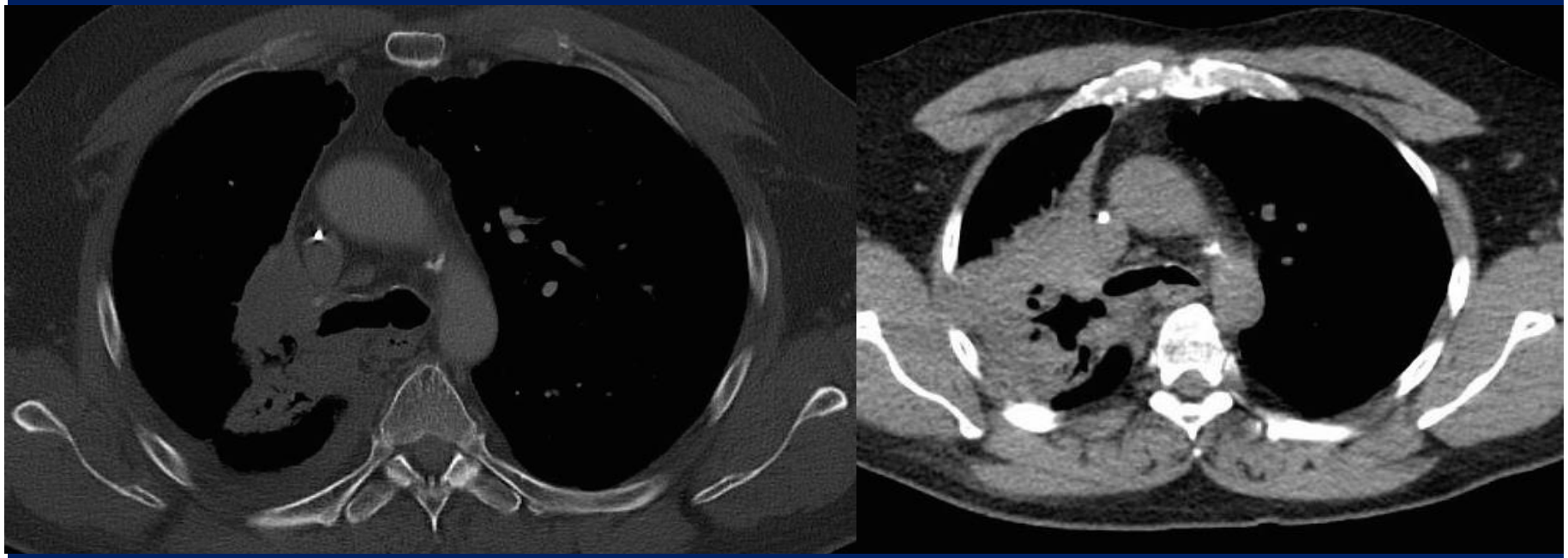
Stratum 2

- Metastatic & locally advanced pancreatic Ca patients
- Metastatic breast Ca patients
- Other metastatic sites

PI: Amit Maity

Stratum 1: Patient 15

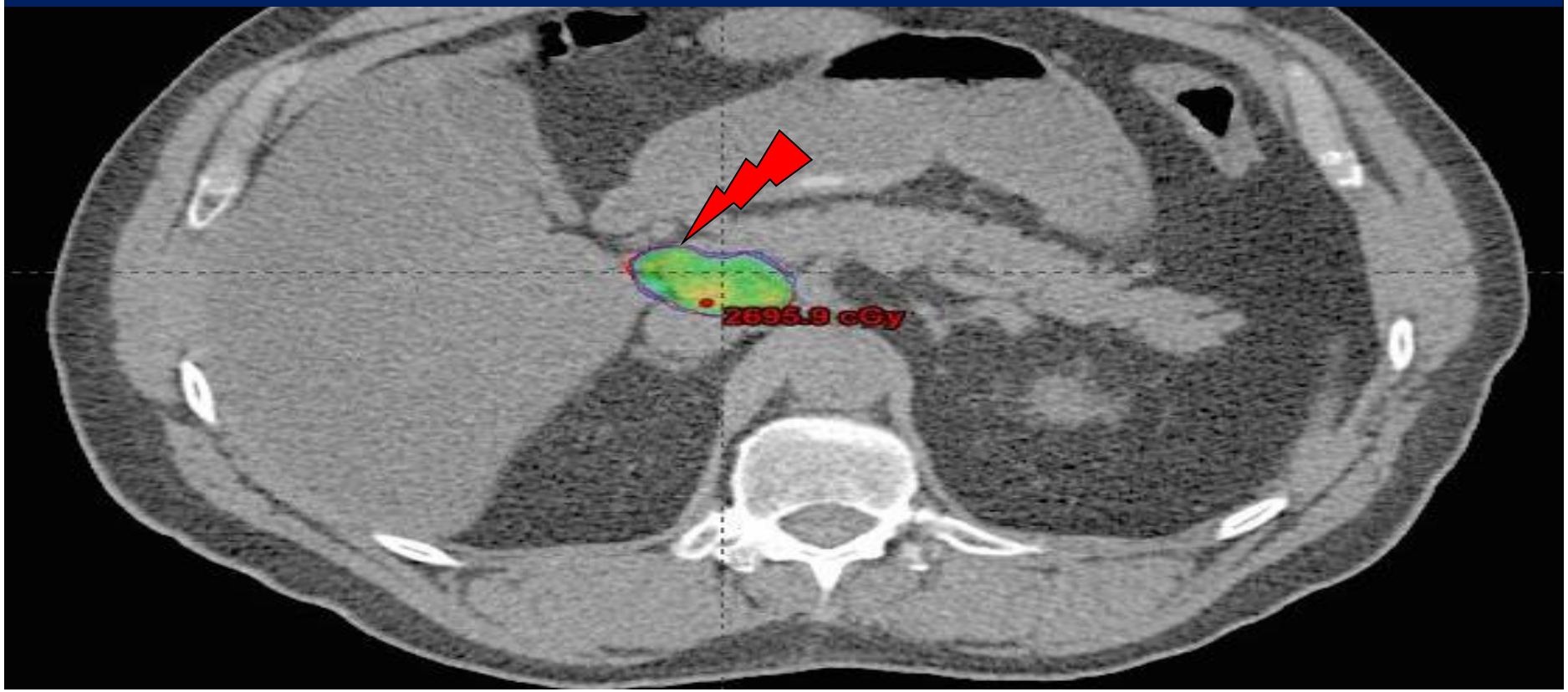
- 9/2013: Dx w/metastatic NSCLC (R hilar mass with bone mets)
  - Carbo/paclitaxel x 6 cycles
  - palliative RT to R lung mass (37.5 Gy)
- 9/2014 – 5/2015: nivolumab

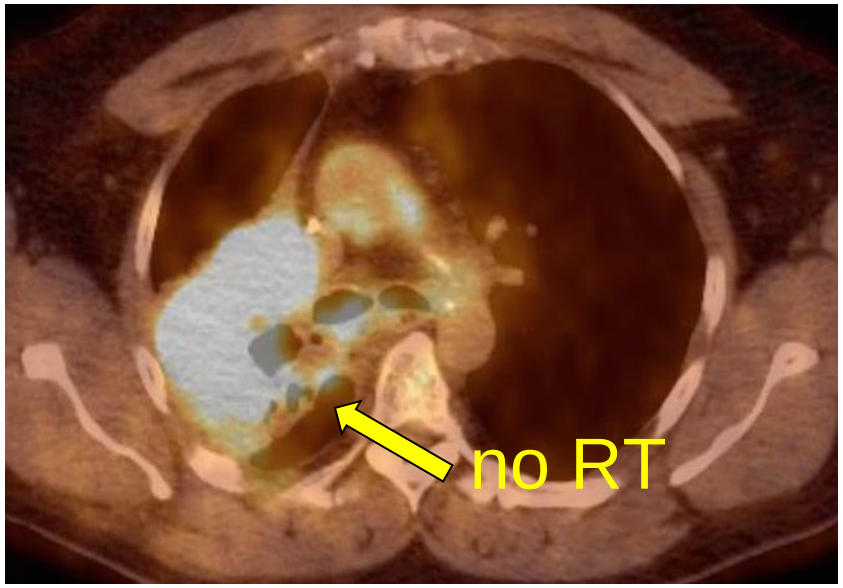


1/2015

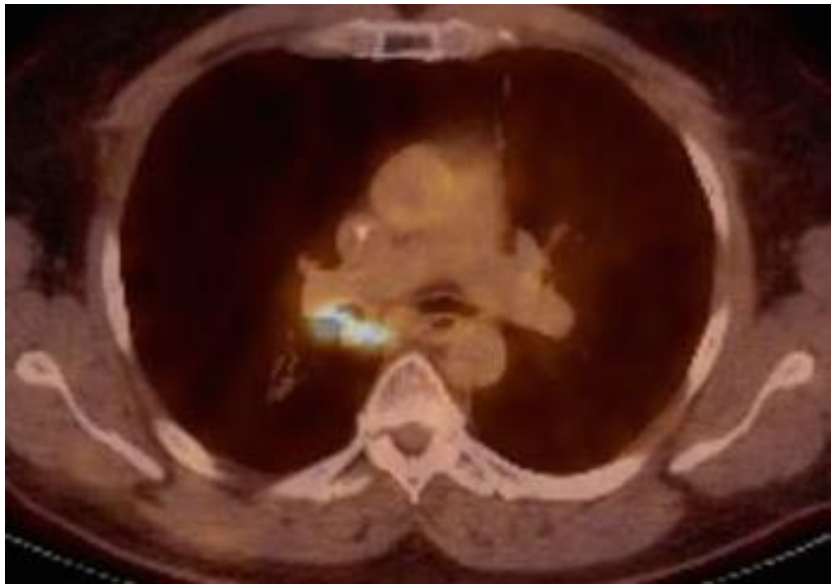
5/2015: PD

- 5/2015: Taken off nivolumab and enrolled on RADVAX study
- Started on pembrolizumab and given 8 Gy x 3 to paraaortic mass (6/2015)
- Continued on pembro for 6+ cycles

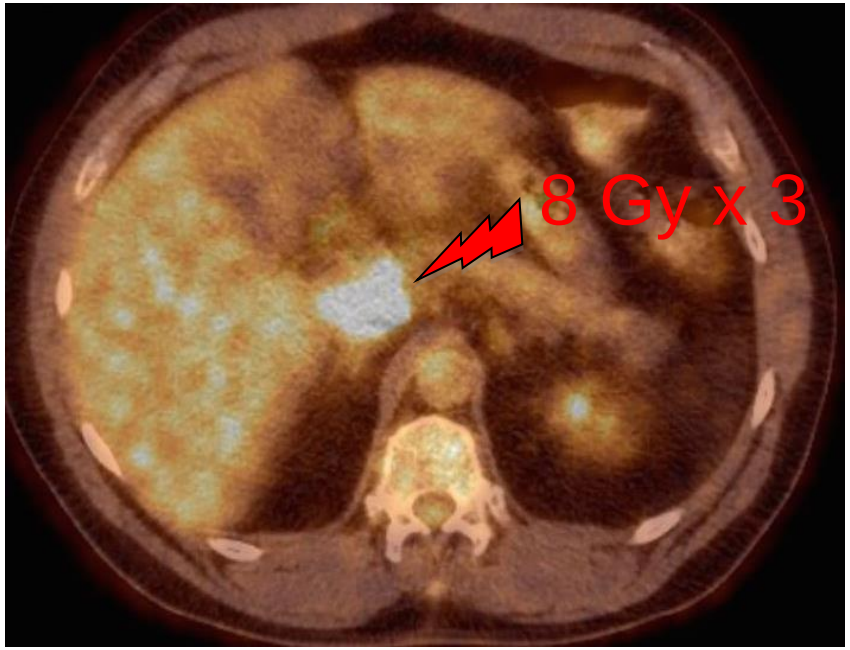


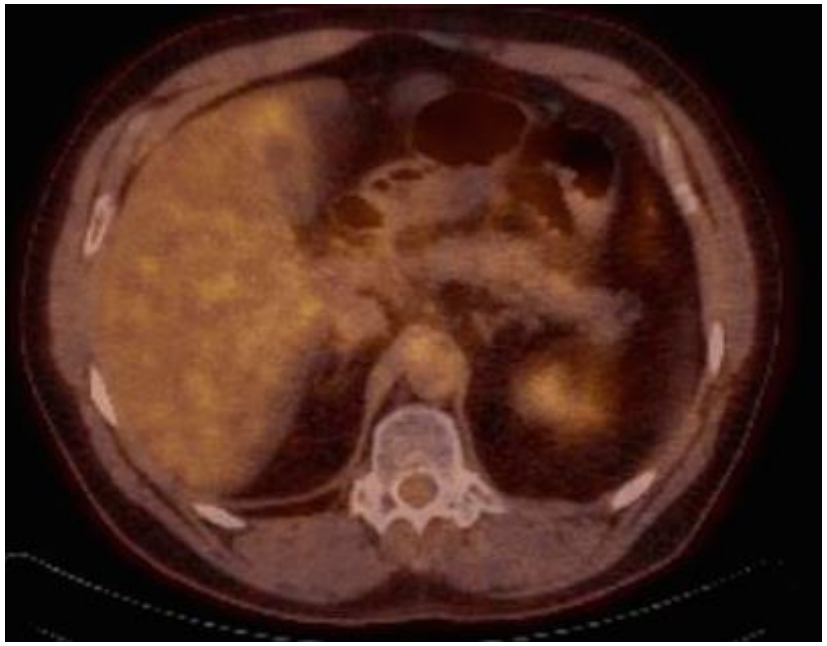


5/2015 (pre-RADVAX)



12/2015





Oligoprogression Setting

- Does the addition of local Tx help patients with oligoprogression?
- Factors to consider
  - How many new or enlarging lesions are there?
  - How large are the potential targets?
  - Where are they located?
    - Radiation therapy (I.e. lung, brain, adrenal, bone, etc)
    - Surgery (example of a single brain metastasis in non-eloquent area)
    - Local ablative therapy like thermal or cryoablation (i.e. liver, away from big blood vessels
  - Is there a safe and effective next-in-line drug therapy?
  - Continue drug therapy or change it? Give it during RT or not?
  - Always a risk-to-benefit estimate. Don't want to make the treatment worse than the disease!
  - Typically requires a multidisciplinary discussion between oncology specialists about a strategy for each patient

Trials testing ablative therapy in oligometastatic NSCLC

- Local therapy is helpful
  - Gomez et al. *
  - Iyengar et al. *
  - Palma et al. *
  - Siva et al. *
  - Tsai et al. #
- Local therapy is not helpful
  - Schoenfeld et al.*

Pending trial:
NRG LU002 - Iyengar

***Synchronous and metachronous**
#Oligoprogression

Tsai at al. JCO 2022 – CURB Trial
Oligoprogression setting

Randomized Phase II trial at Memorial Sloan Kettering comparing:

- Systemic therapy alone (doctor's choice of drugs or whether to switch drugs)
- Systemic therapy plus local therapy (i.e. radiation therapy)

- Eligible patients had 5 or fewer sites of metastatic cancer (including brain)
- Primary endpoint was progression-free survival

<u>Results:</u>

- Trial stopped early due to more failures in the systemic therapy only arm
- Trial showed benefit in progression-free survival for patients given systemic + local therapy
- No overall survival benefit to local therapy

Recommendations for local ablation

	Patient selection	Toxicity risk	Timing
Best candidates	Good performance status Low burden of disease (one oligometastasis) Multiple systemic therapy options	Small lesions Treatment unlikely to cause toxicity (eg, small resection or tumor far from critical structures)	Metachronous oligometastases Responding to systemic therapy
Less favorable	Borderline performance status (eg, ECOG 2) Moderate burden of disease (two to five oligometastases)	Larger lesions Moderate risk of toxicity or impact on organ function	Synchronous oligometastases Overlapping toxicities (eg, immunotherapy and thoracic radiotherapy)
Unfavorable	Poor performance status High burden of disease (> 5 metastases)	Very large lesions High risk of toxicity Comorbidities precluding radiotherapy or surgery	No response to systemic therapy Rapid disease progression

FIG 2. Management aid for selecting suitable patients for local ablation. ECOG, Eastern Cooperative Oncology Group.

Kasper K et al. JCO February 2022


Penn Medicine
Abramson Cancer Center