Oncology Grand Rounds

New Agents and Strategies in Metastatic Lung Cancer

Thursday, June 11, 2020

5:00 PM – 6:30 PM ET

Faculty

Kelly EH Goodwin, MSN, RN, ANP-BC
Wendi S Lee, MSN, RN, NP-C
Suresh S Ramalingam, MD
Gregory J Riely, MD, PhD

Moderator

Neil Love, MD

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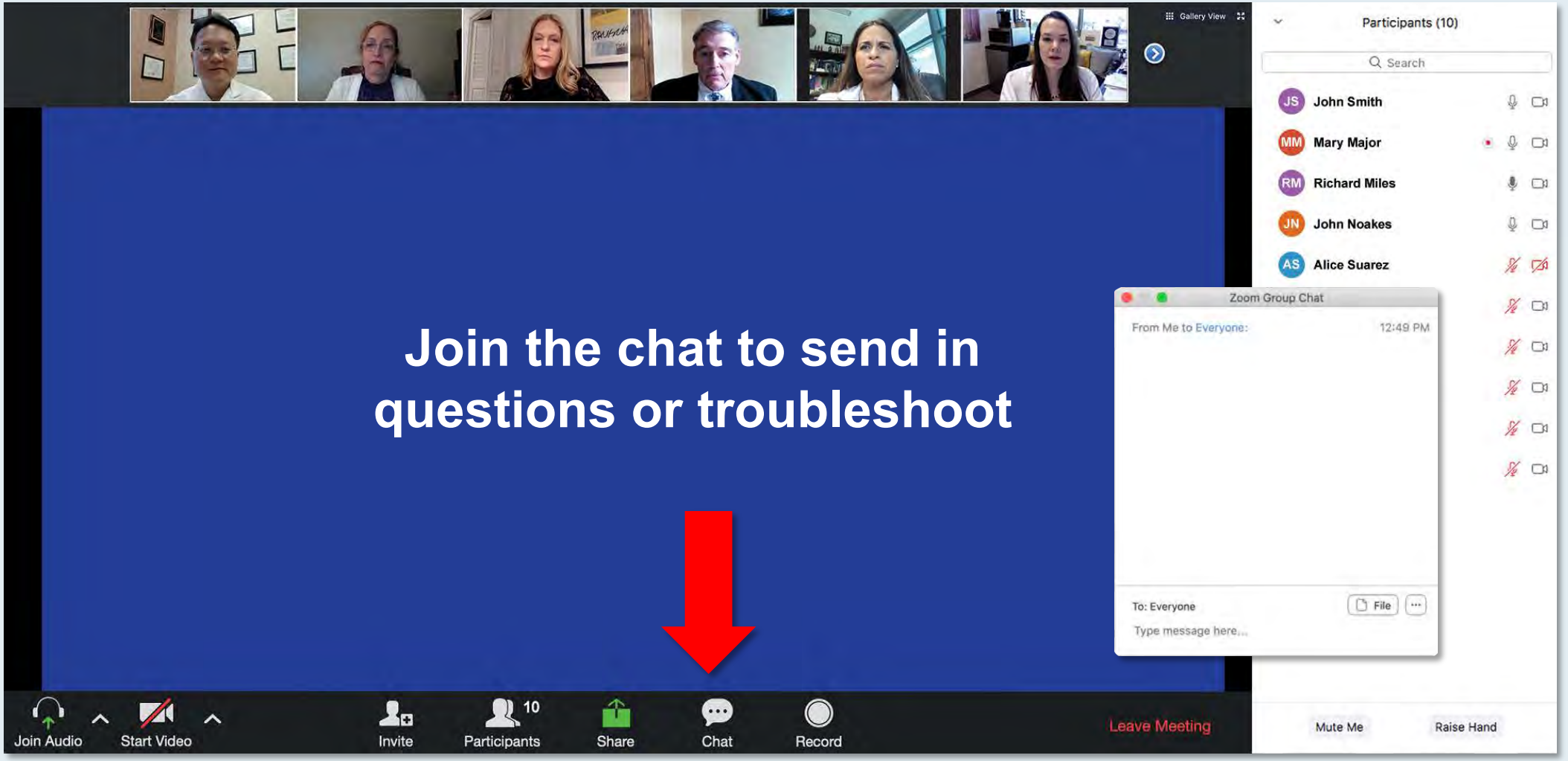

RTP Live Webinar Nursing Series

Monday	Tuesday	Wednesday	Thursday	Friday
25	26 Breast Ca 5:00 PM	27	28 GI Ca 5:00 PM	29
Jun 1	2 Lymphoma 5:00 PM	3	4 CLL 5:00 PM	5
8	9 GYN 5:00 PM	10	11 Metastatic Lung Ca 5:00 PM	12
15	16 Locally Advanced Lung Ca 5:00 PM	17	18 Bladder Ca 5:00 PM	19
22	23 CAR-T 5:00 PM	24	25 PARP 5:00 PM	26
29	30 Prostate Ca 5:00 PM	Jul 1 8 AM	2	3
5	7	8	9	10

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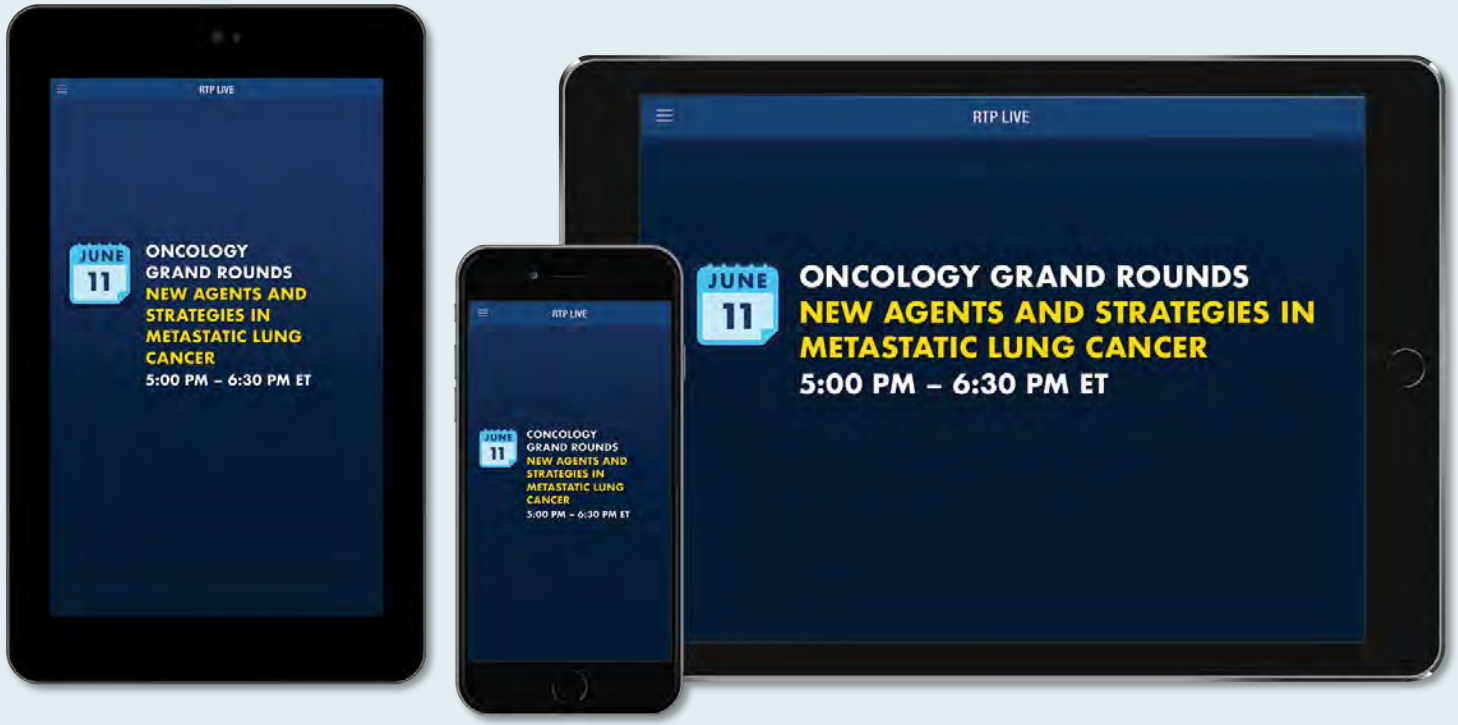

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Oncology Grand Rounds

New Agents and Strategies in Locally Advanced Non-Small Cell Lung Cancer

Tuesday, June 16, 2020

5:00 PM – 6:30 PM ET

Faculty

Benjamin Levy, MD
Stephen V Liu, MD, PhD
Beth Sandy, MSN, CRNP
Elizabeth S Waxman, RN, MSN, ANP-BC

Moderator

Neil Love, MD

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Moderator

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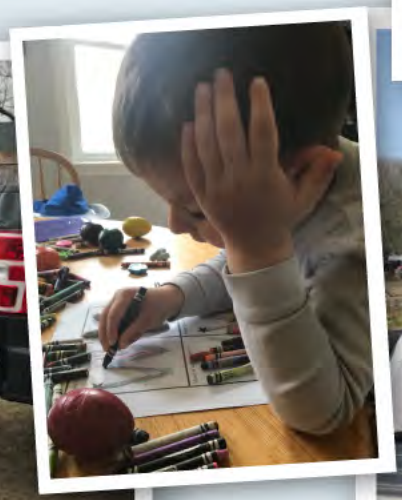
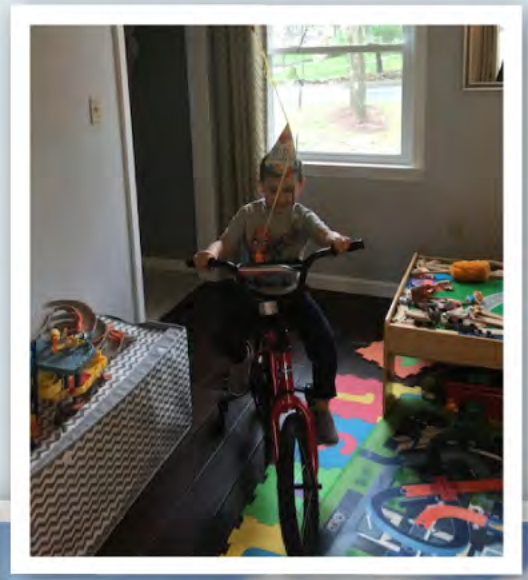
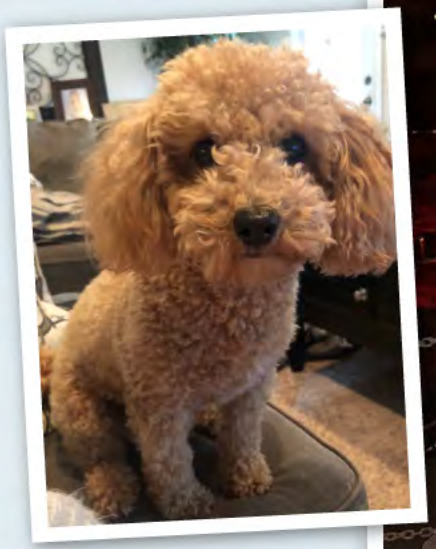
Kelly EH Goodwin, MSN, RN, ANP-BC
Massachusetts General Hospital
Boston, Massachusetts



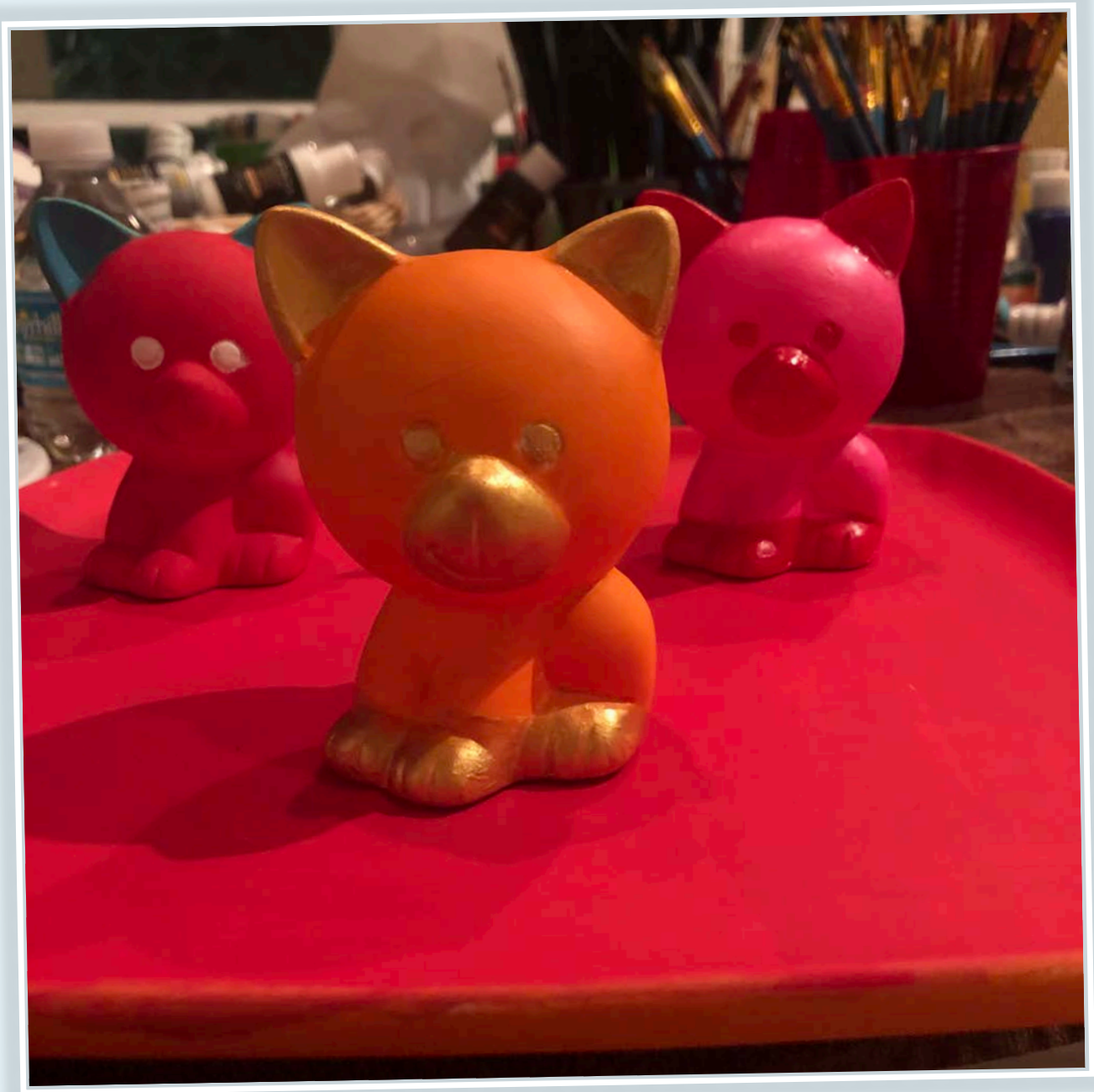


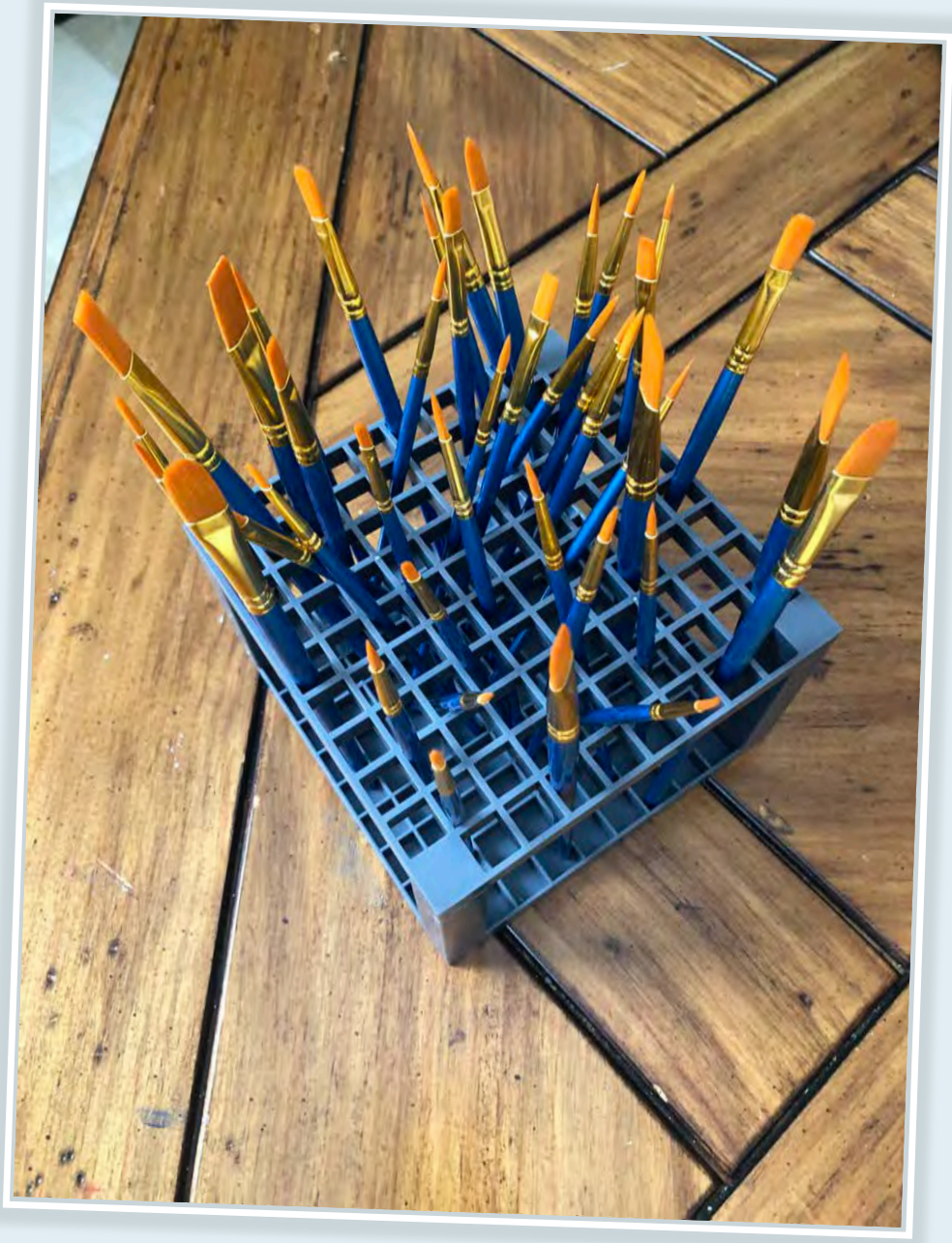
Wendi S Lee, MSN, RN, NP-C
The University of Texas
MD Anderson Cancer Center
Houston, Texas



Suresh S Ramalingam, MD
Emory University School of Medicine
Atlanta, Georgia

Gregory J Riely, MD, PhD
Memorial Sloan Kettering Cancer Center
New York, New York





Agenda

Overview: A Biomarker-Driven Approach to Lung Cancer Treatment

Module 1: Non-Small Cell Lung Cancer (NSCLC) with a Targetable Mutation

- Case Presentation: Ms Goodwin — 63-year-old telecommunications engineer
- Case Presentation: Ms Lee — 74-year-old independently minded Spanish-speaking woman

Module 2: Checkpoint Inhibitors for Metastatic NSCLC without a Targetable Mutation

- Case Presentation: Ms Goodwin — 59-year-old woman on disability with chronic pain and anxiety
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Module 3: Extensive-Stage Small Cell Lung Cancer

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Overview: A Biomarker-driven Approach to Lung Cancer Treatment

Targetable tumor driver mutations in non-small cell lung cancer (NSCLC) generally occur in patients with…

a. Nonsquamous cancer

b. Squamous cancer

c. Both a and b

d. Neither a nor b

e. I don’t know

Which of the following assays are considered standard in the evaluation of newly diagnosed metastatic NSCLC?

a. Multiplex genomic testing/NGS (next-generation sequencing)

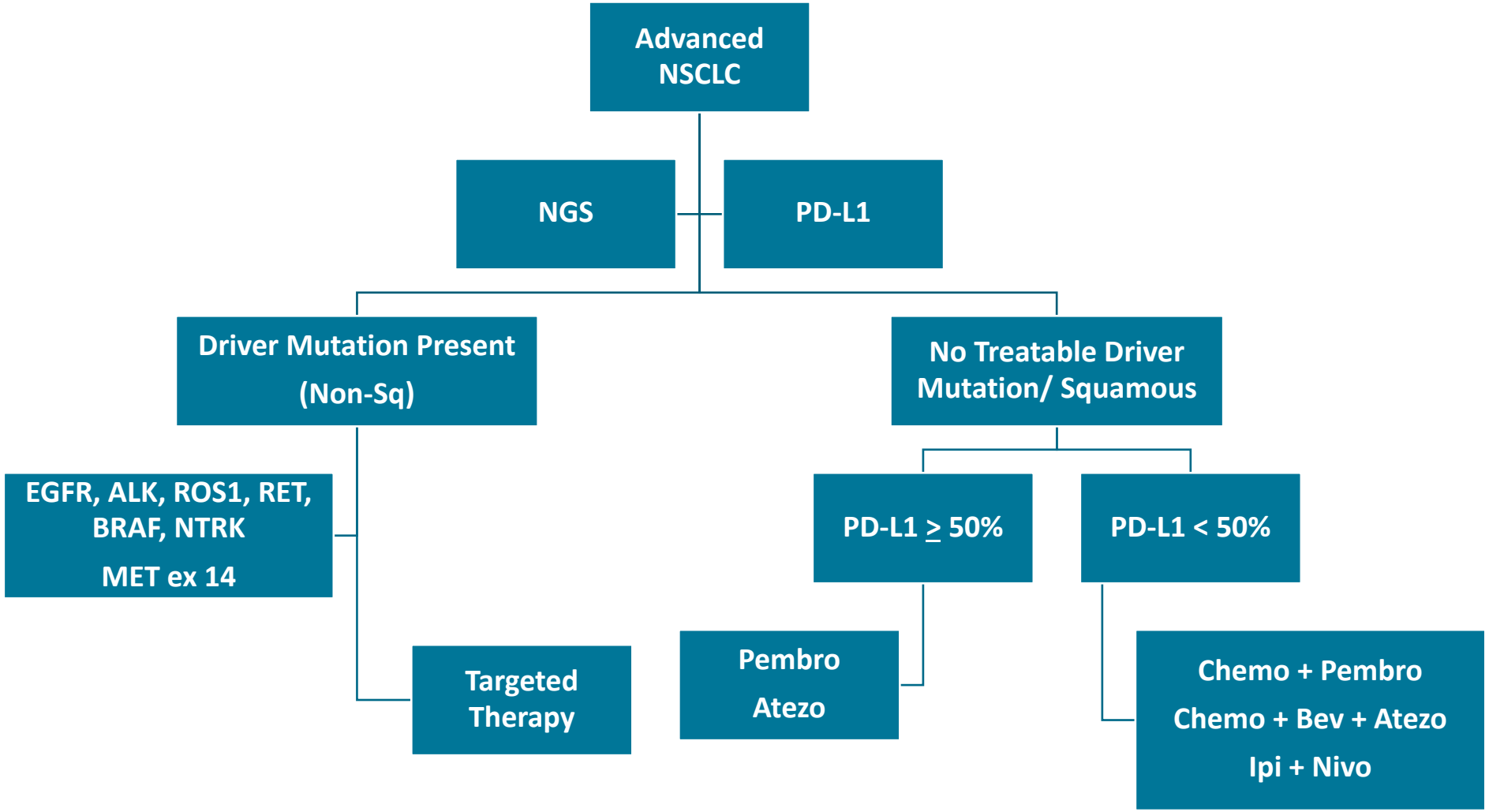
b. PD-L1 assay

c. Both a and b

d. Neither a nor b

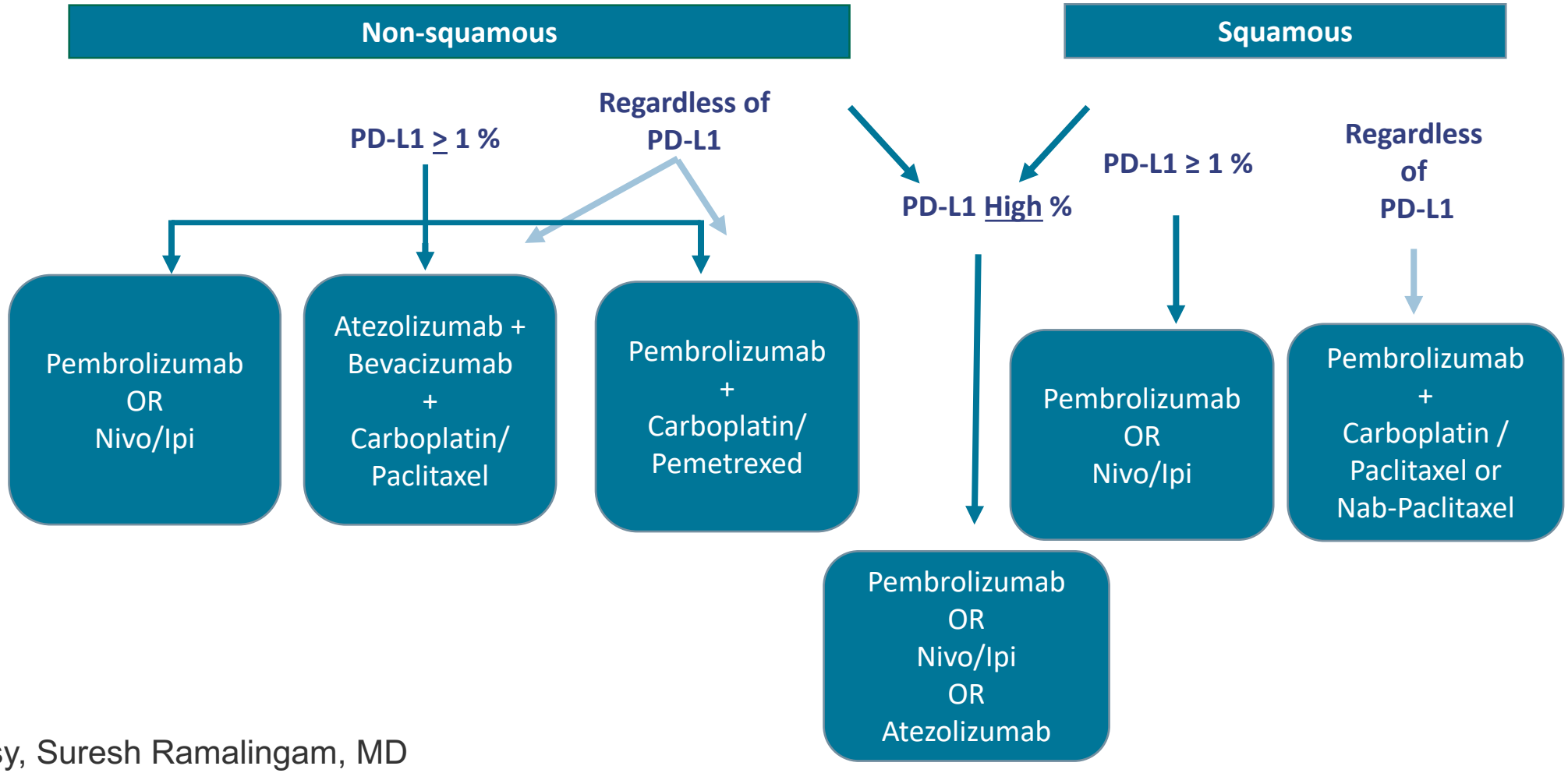
e. I don’t know

Treatment Algorithm for Advanced NSCLC



Courtesy, Suresh Ramalingam, MD

Metastatic NSCLC
First-Line Treatment Schema (No Driver Mutation)



Courtesy, Suresh Ramalingam, MD

Targeted Therapies in 2020

Target	Line of Therapy	
EGFR	1st	Gefitinib, Erlotinib, Afatinib, Dacomitinib, Osimertinib
	2nd	Osimertinib
ALK	1st	Crizotinib, Alectinib, Ceritinib, Brigatinib
	2nd	Alectinib, Ceritinib, Brigatinib, Lorlatinib
	3rd	Lorlatinib
ROS1	Any	Crizotinib, Entrectinib
BRAF	Any	Dabrafenib + Trametinib
NTRK	Any	Larotrectinib, Entrectinib
RET	Any	Selpercatinib
MET ex 14	Any	Capmatinib

Courtesy, Suresh Ramalingam, MD

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Module 1: Non-Small Cell Lung Cancer (NSCLC) with a Targetable Mutation

Compared to erlotinib, osimertinib…

a. Causes less skin toxicity

b. Has greater antitumor efficacy

c. Has a greater antitumor effect in the CNS

d. All of the above

e. Only a and b

f. Only b and c

g. Only a and c

h. I don’t know

In general, what is the most common initial treatment for patients with previously untreated NSCLC with an EGFR tumor mutation and multiple, bilateral asymptomatic brain metastases that would require whole-brain radiation therapy?

a. Whole-brain radiation therapy followed by osimertinib

b. Whole-brain radiation therapy

c. Chemotherapy

d. Osimertinib

e. Erlotinib

f. I don’t know

Patients with metastatic NSCLC and a RET alteration or a MET exon 14 mutation can now receive FDA-approved treatment with a targeted agent.

a. Agree

b. Disagree

c. I don’t know

Targetable Oncogenic Drivers

EGFR sensitizing
- Gefitinib[4]
- Erlotinib[4]
- Afatinib[4]
- Osimertinib[4]
- Necitumumab[4]
- Rociletinib[3]

ALK
- Crizotinib[4]
- Alectinib[4]
- Ceritinib[4]
- Lorlatinib[2]
- Brigatinib[2]

MET
- Crizotinib[2]
- Cabozantinib[2]

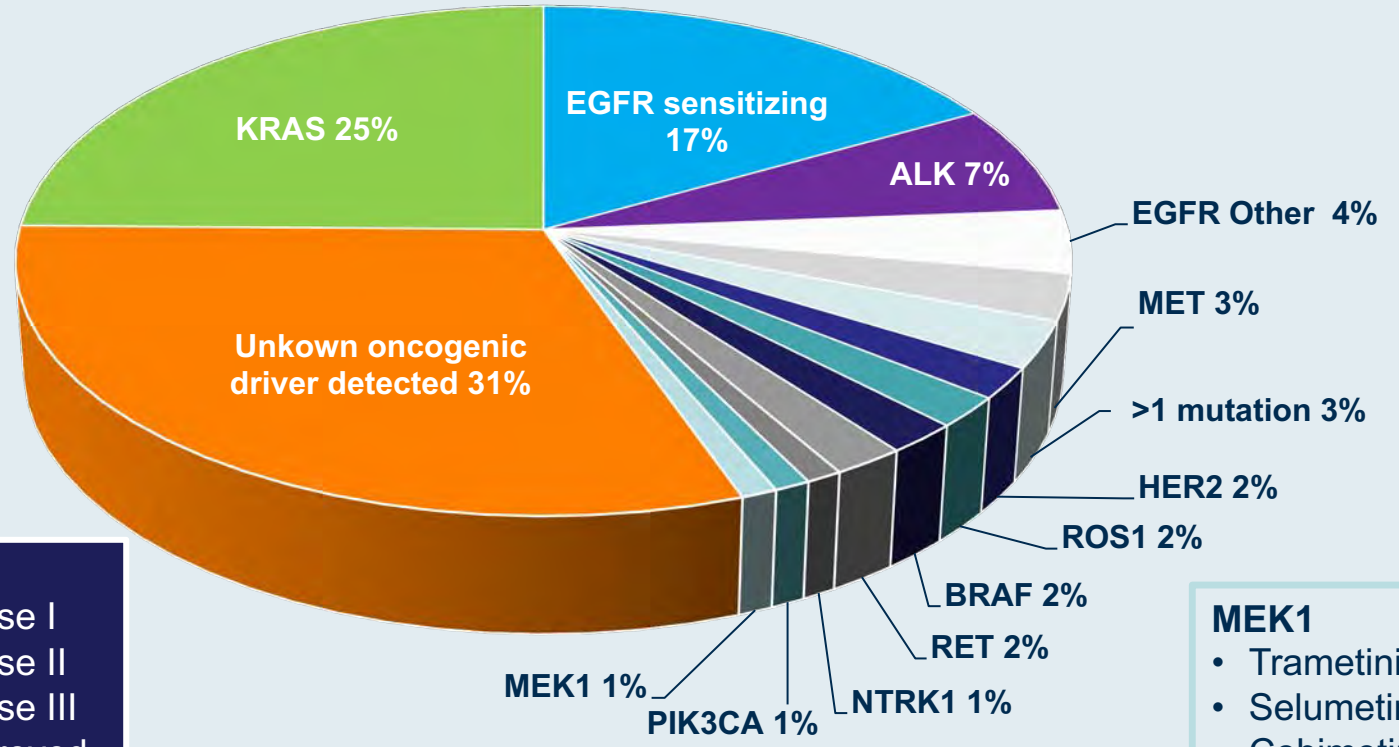
HER2
- Trastuzumab emtansine[2]
- Afatinib[2]
- Dacomitinib[2]

ROS1
- Crizotinib[4]
- Cabozantinib[2]
- Ceritinib[2]
- Lorlatinib[2]
- DS-6051b[1]

BRAF
- Vemurafenib[2]
- Dabrafenib[2]

RET
- Cabozantinib[2]
- Alectinib[2]
- Apatinib[2]
- Vandetanib[2]
- Ponatinib[2]
- Lenvatinib[2]

NTRK1
- Entrectinib[2]
- LOXO-101[2]
- Cabozantinib[2]
- DS-6051b[1]



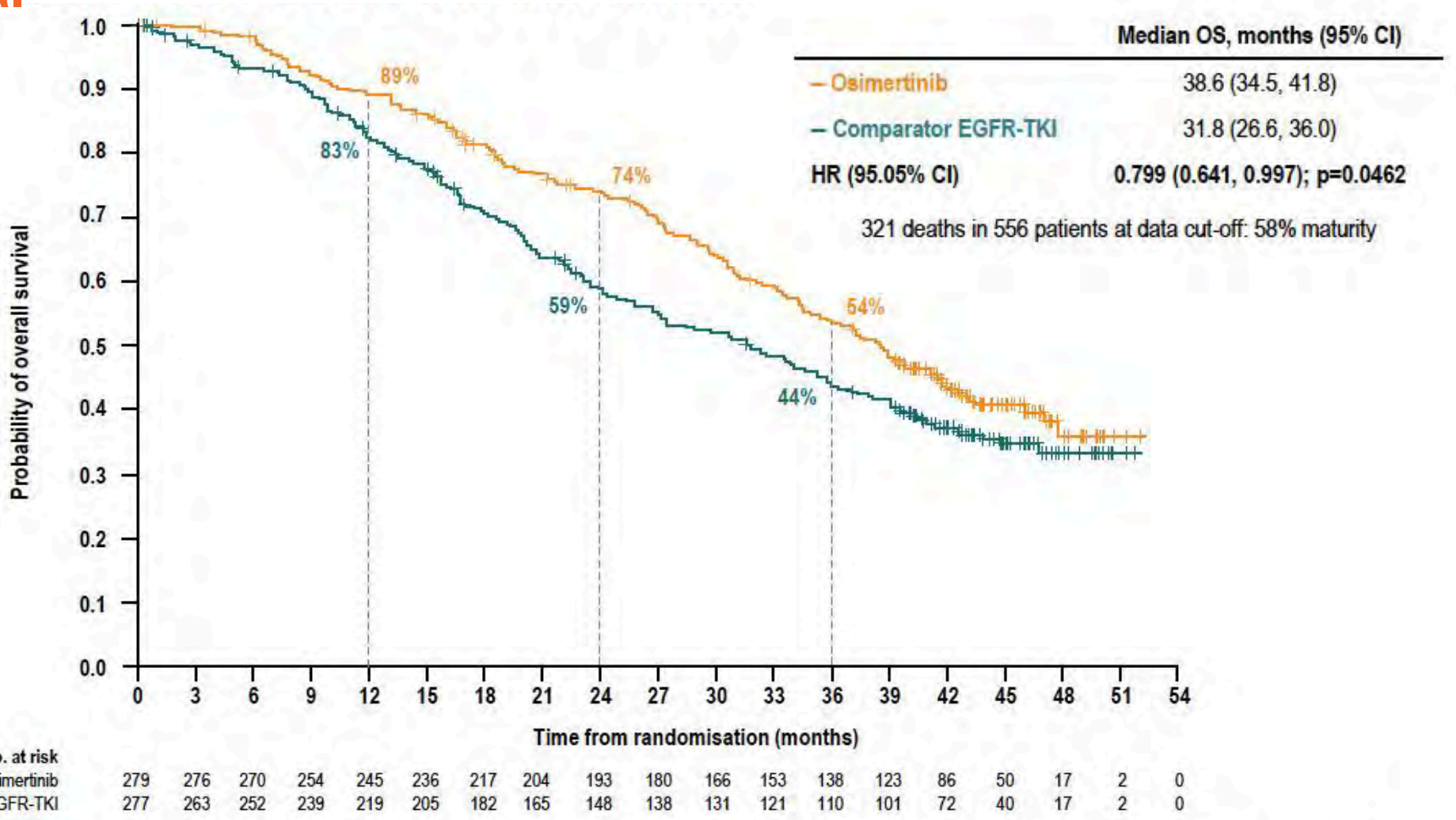
KEY
1 - Phase I
2 - Phase II
3 - Phase III
4 - Approved

MEK1
- Trametinib[2]
- Selumetinib[3]
- Cobimetinib[1]

PIK3CA
- LY3023414[2]
- PQR 309[1]

Presented By Frances Shepherd at 2019 ASCO Annual Meeting.

Osimertinib vs Gefitinib/Erlotinib as first treatment for advanced NSCLC
Overall Survival

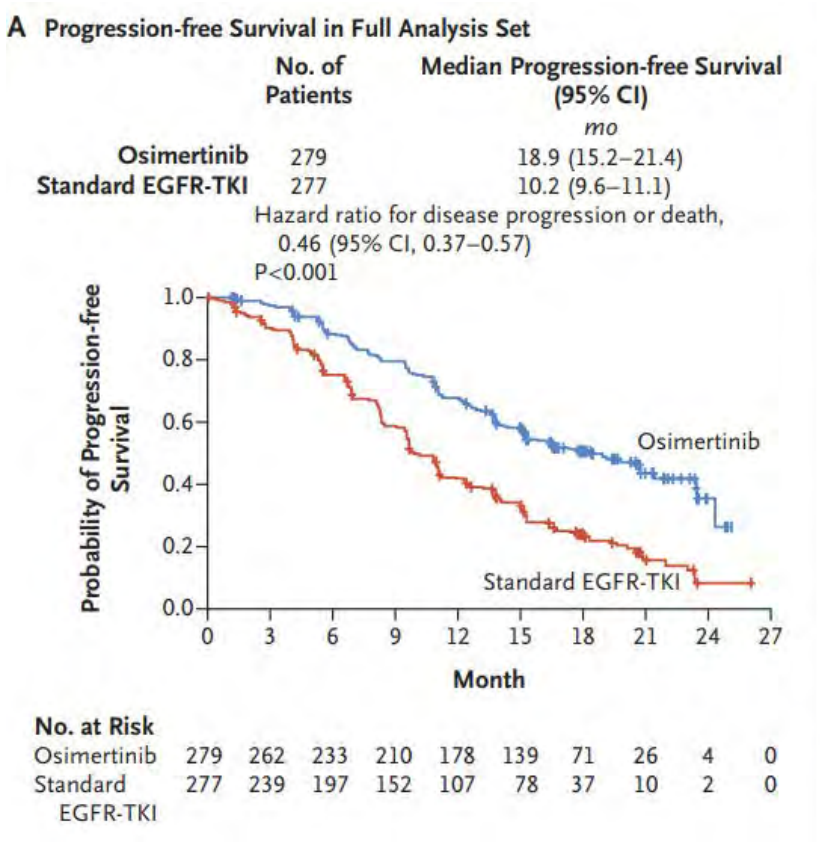


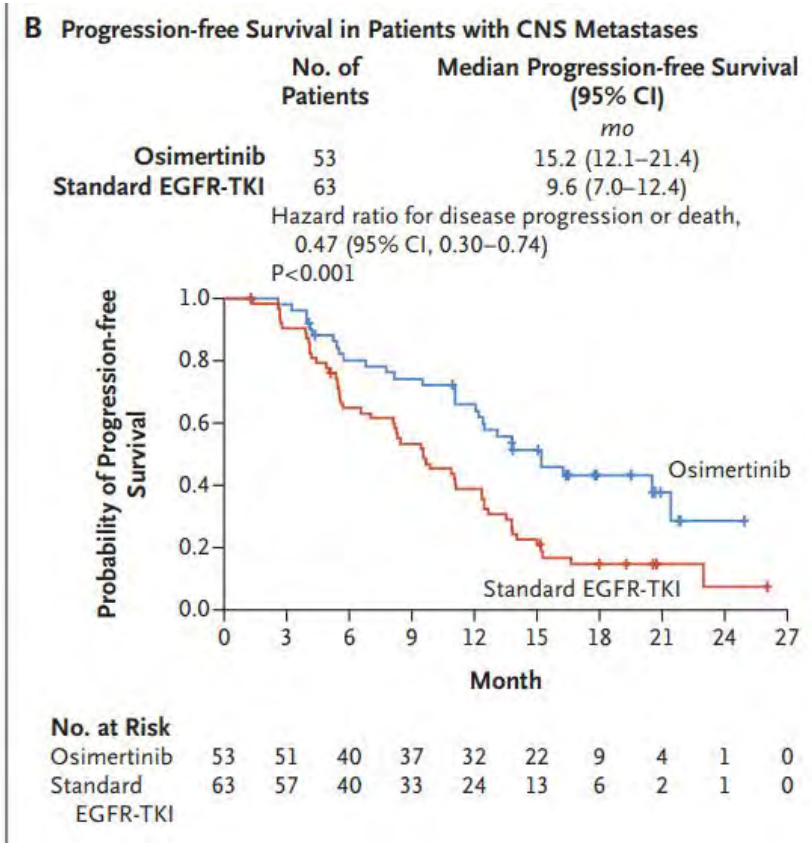
Memorial Sloan Kettering Cancer Center

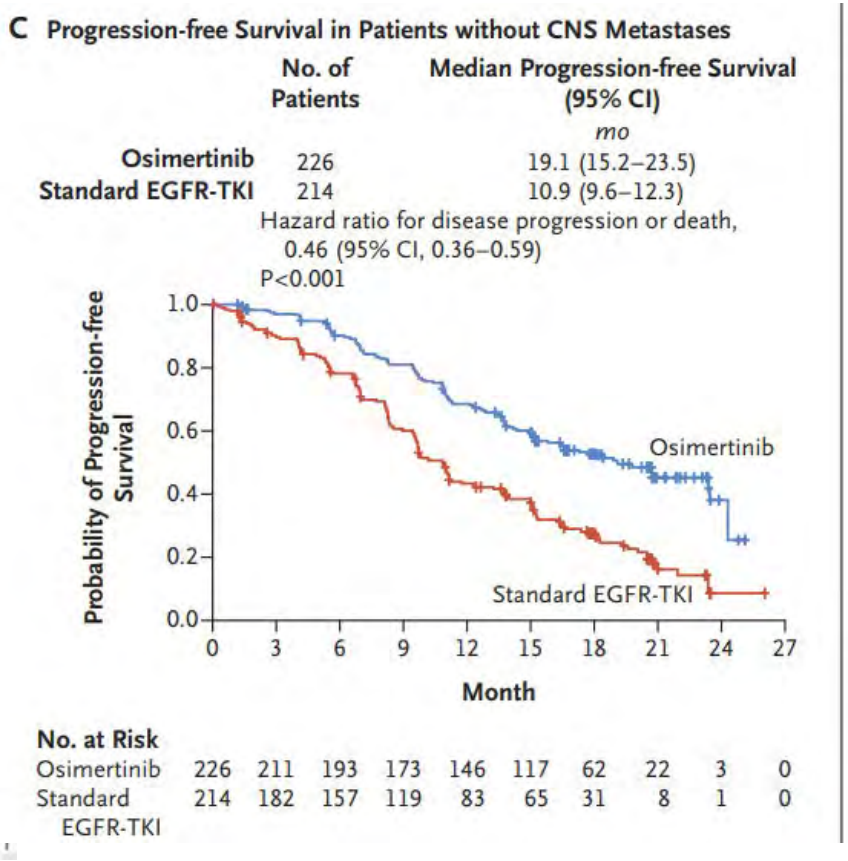
Courtesy of Gregory J Riely, MD, PhD

Ramalingam et al, ESMO 2019

Osimertinib as effective in CNS disease as Systemic disease







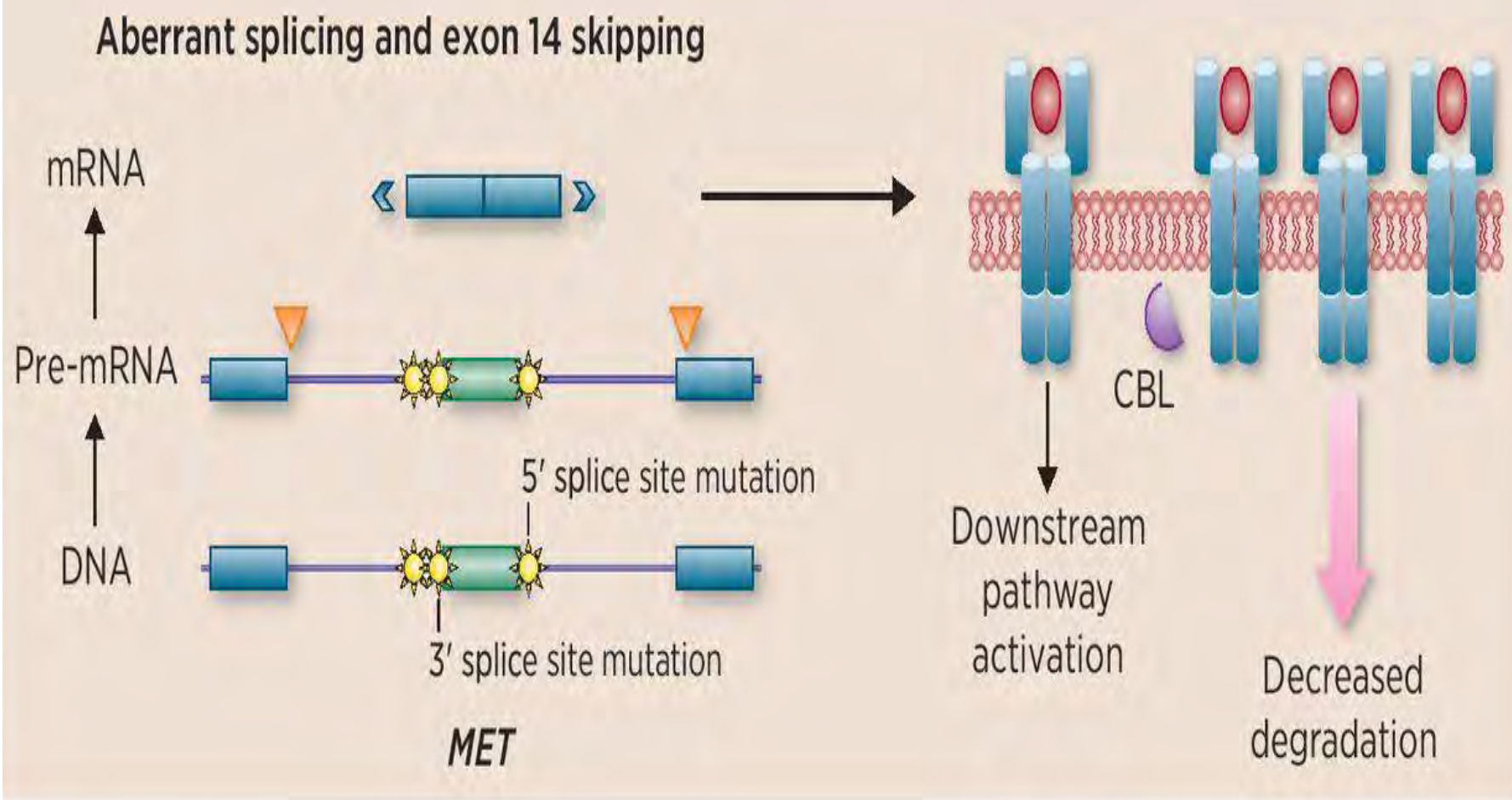
Courtesy of Gregory J Riely, MD, PhD

Soria et al NEJM 2018

Concurrent Osimertinib Plus Gefitinib for First-Line Treatment of EGFR-Mutated Non-Small Cell Lung Cancer (NSCLC)

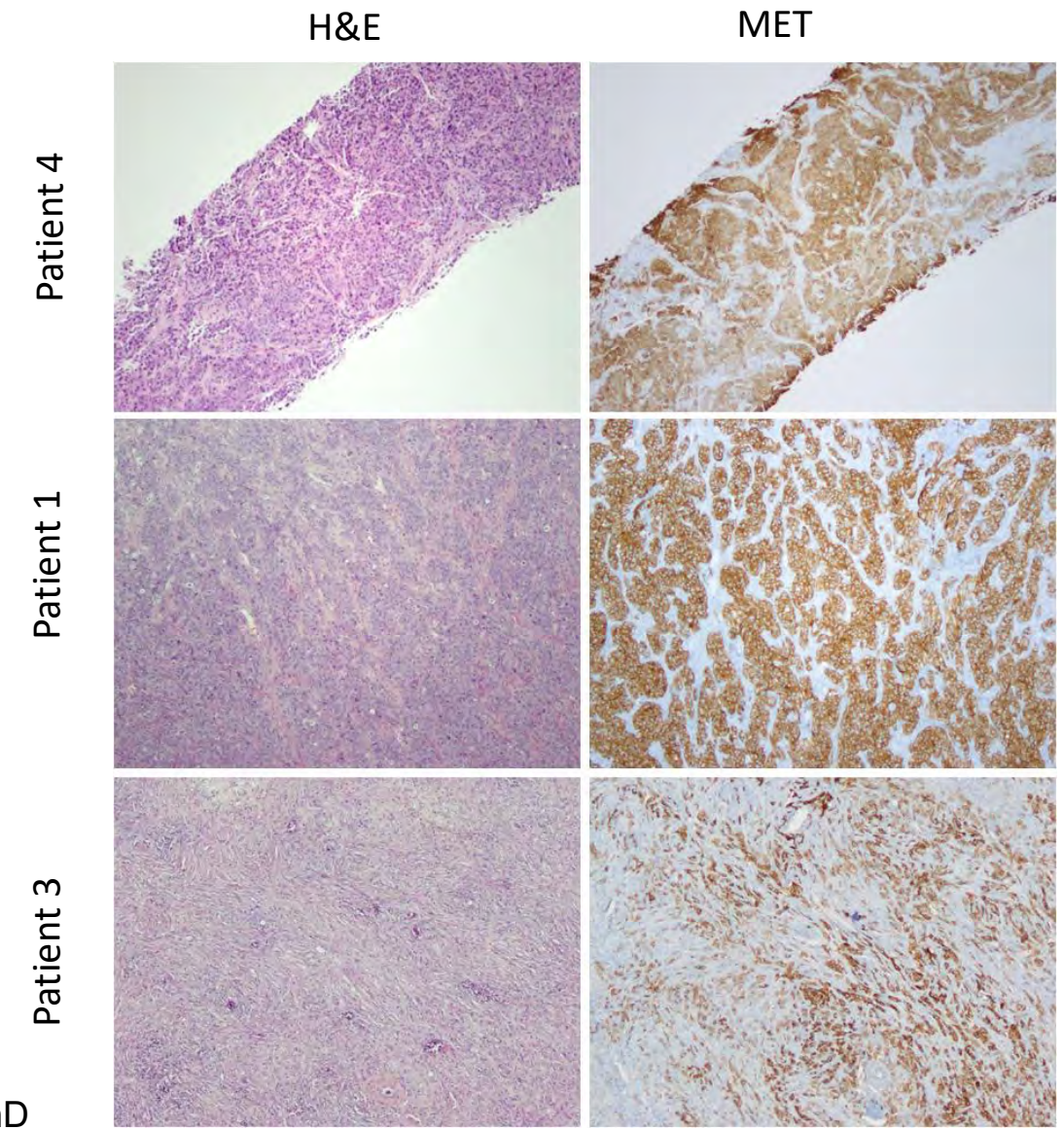
Rotow JK et al.
ASCO 2020;Abstract 9507.

MET Exon 14 Alterations in NSCLC



Courtesy of Gregory J Riely, MD, PhD

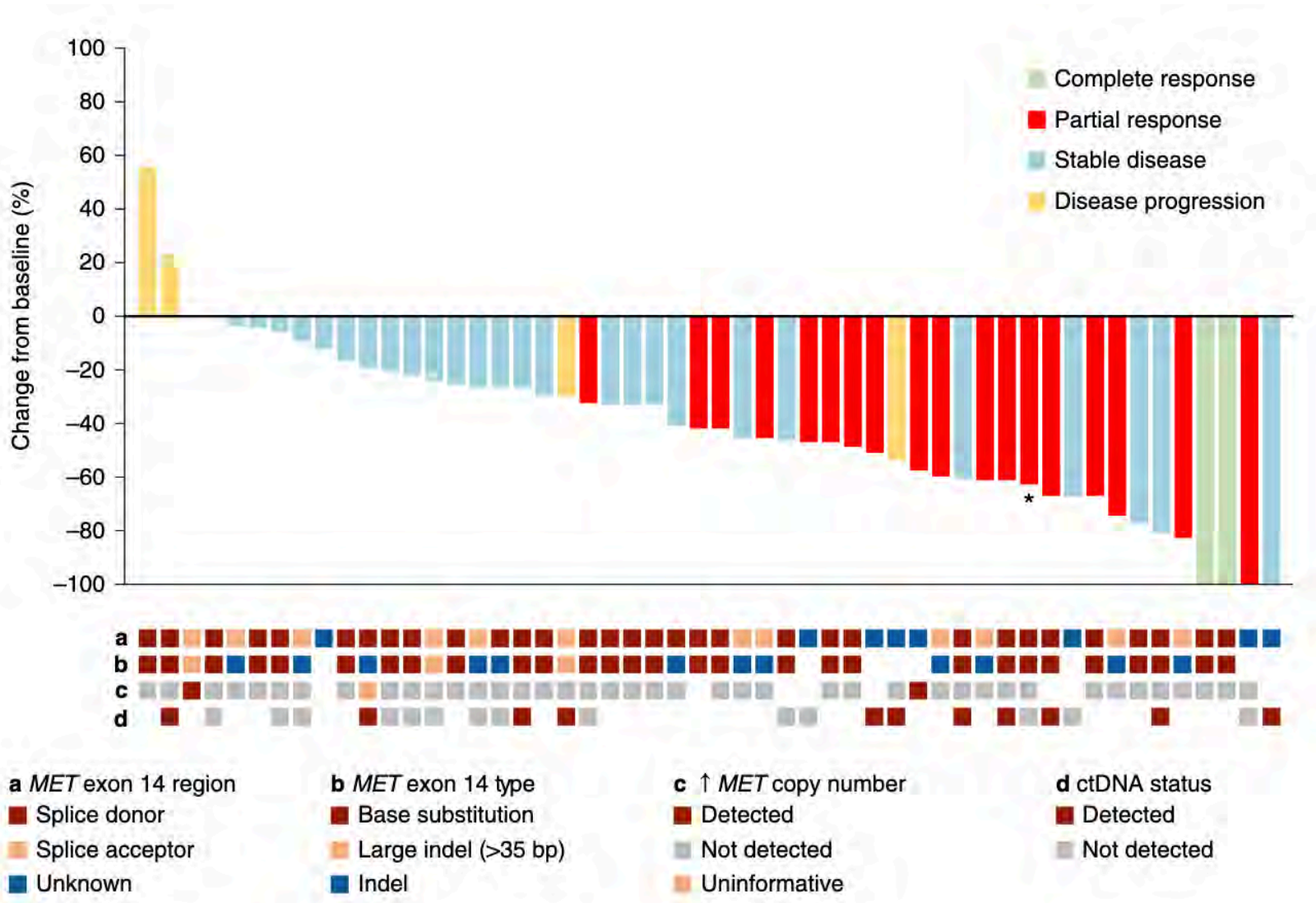
MET exon 14 alterations are associated with high MET expression



Courtesy of Gregory J Riely, MD, PhD

Paik et al, ASCO 2015

Crizotinib in Patients with MET Exon 14 Altered NSCLC



Courtesy of Gregory J Riely, MD, PhD

Drilon et al, Nature Medicine 2020

Capmatinib in MET exon 14

Efficacy Parameters	**Treatment-Naïve N = 28**	**Previously Treated N = 69**
Overall Response Rate[a,b] (95% CI)[c]	68% (48, 84)	41% (29, 53)
Complete Response	4%	0
Partial Response	64%	41%
Duration of Response (DOR)[a]		
Median (months) (95% CI)[d]	12.6 (5.5, 25.3)	9.7 (5.5, 13.0)
Patients with DOR ≥ 12 months	47%	32%

Abbreviations: CI = Confidence Interval

[a] Blinded Independent Review Committee (BIRC) review.

[b] Confirmed response.

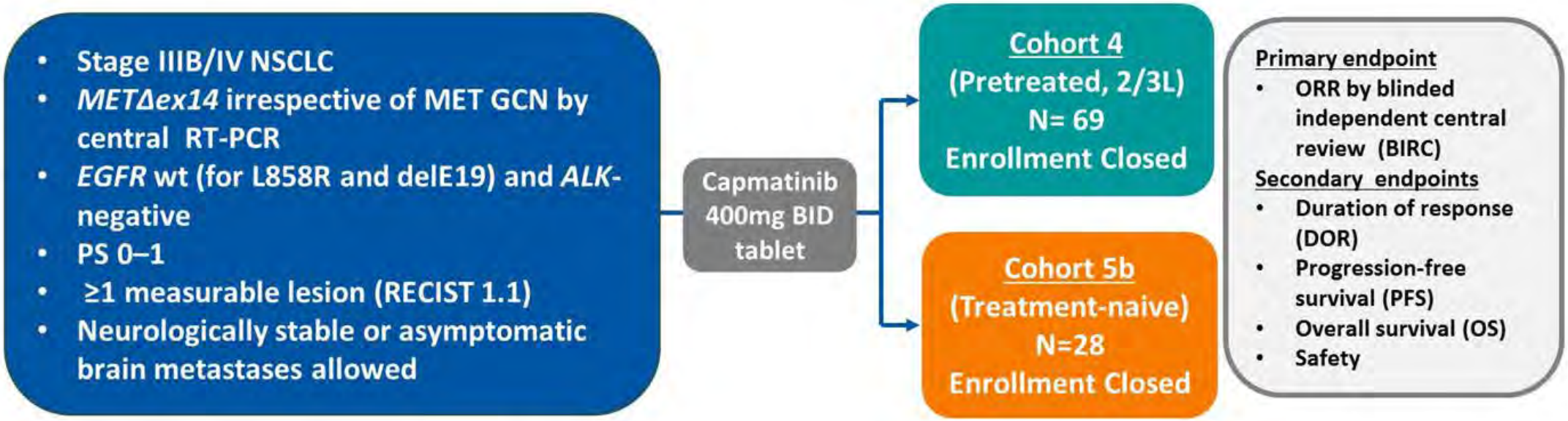
[c] Clopper and Pearson exact binomial 95% CI.

[d] Based on Kaplan-Meier estimate.

Capmatinib prescribing information May 30, 2020

Courtesy of Gregory J Riely, MD, PhD

Phase II GEOMETRY mono-1 trial: Capmatinib in advanced NSCLC with MET exon 14 skipping mutations



Study methodology:

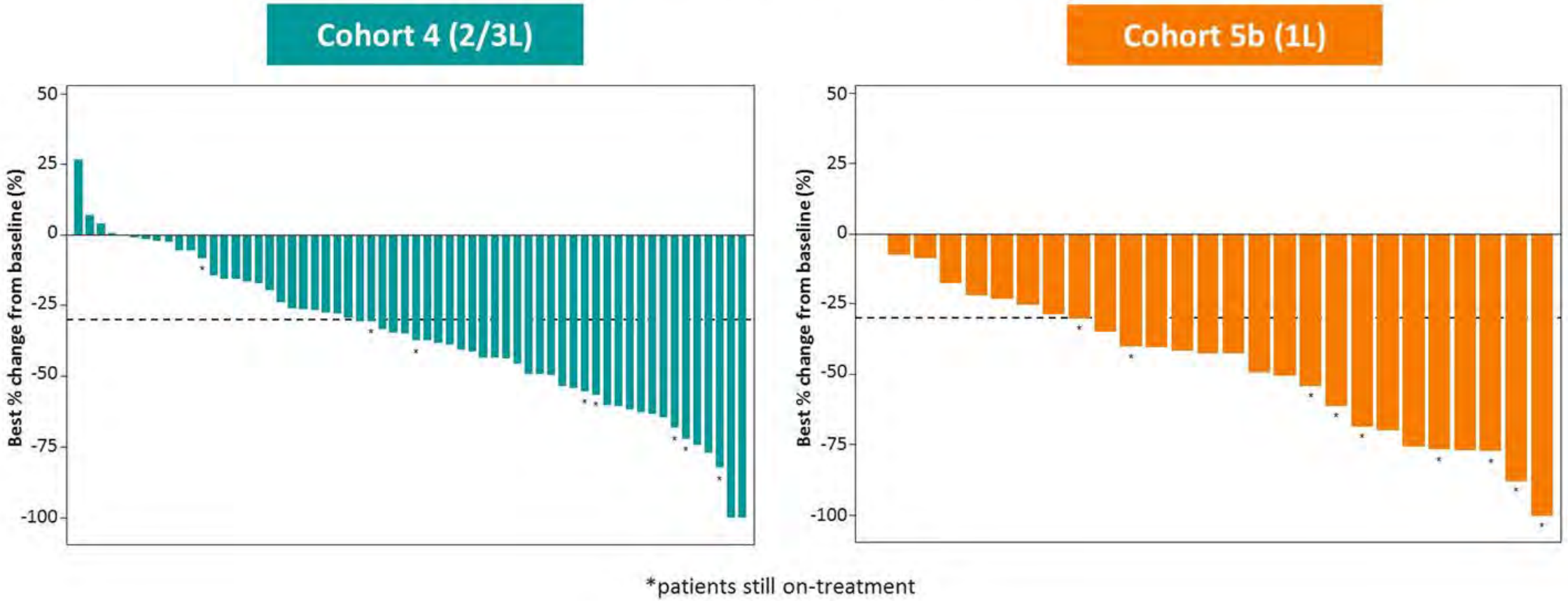
- Cohort 4 and 5b are each analyzed separately and have independent statistical hypothesis
- Primary (ORR) and key secondary (DOR) endpoints based on BIRC including 2 parallel independent radiology reviewers (+ additional one for adjudication)
- Efficacy endpoints based on BIRC and investigator assessment per RECIST 1.1

Data cut off: April 15, 2019; median duration of follow-up for DOR: 9.7 months in Cohort 4 and 9.6 months in Cohort 5b
Additional data on *MET* mutated patients will be generated in Cohort 6 (2L; N~30) and Cohort 7 (1L; N~27)

Wolf et al, ASCO 2019

Courtesy of Gregory J Riely, MD, PhD

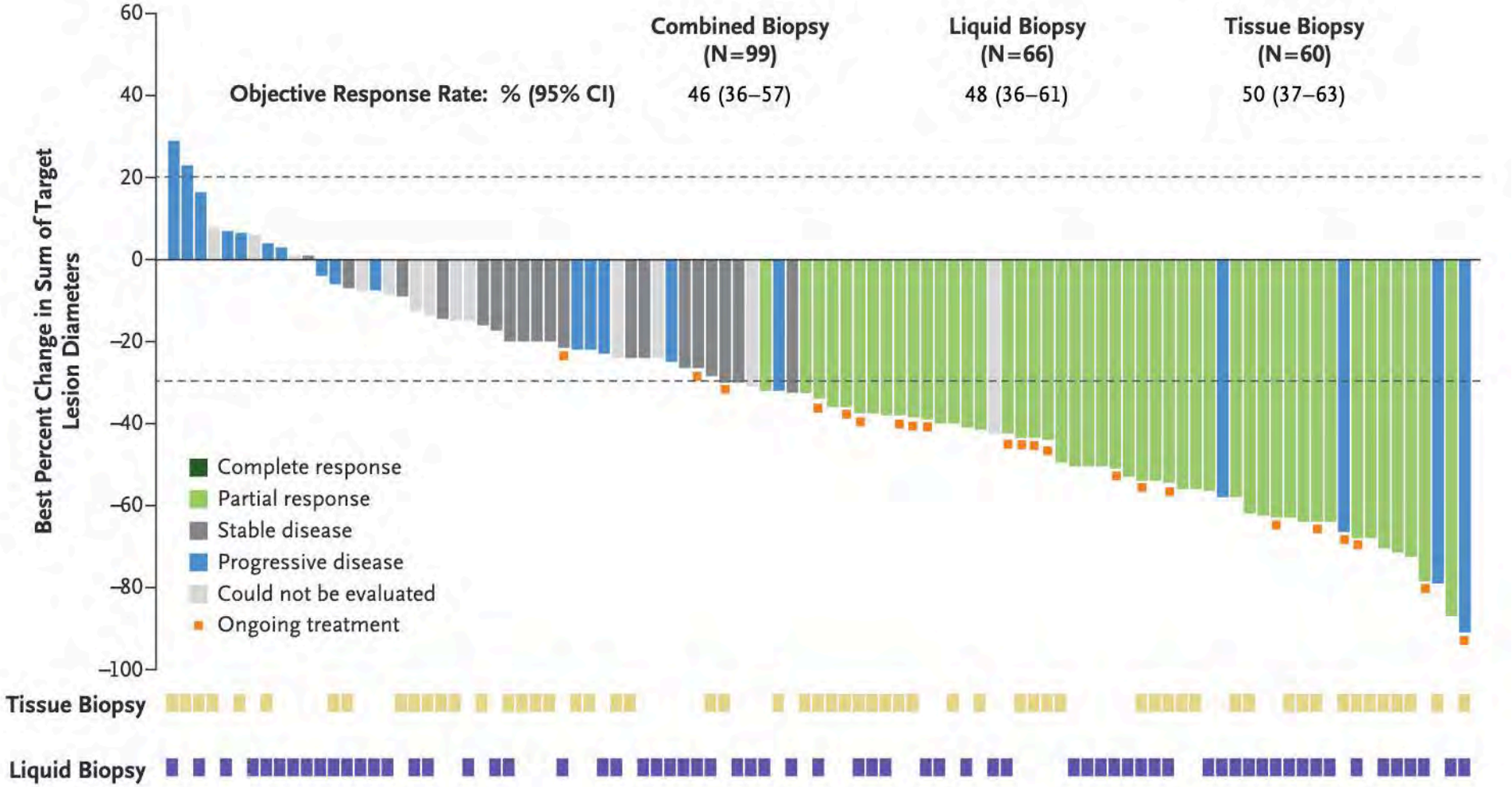
GEOMETRY mono-1: Capmatinib in MET exon 14-mutated NSCLC



Wolf et al, ASCO 2019

Courtesy of Gregory J Riely, MD, PhD

Phase II VISION Trial: Tepotinib in NSCLC with MET exon 14 skipping mutations



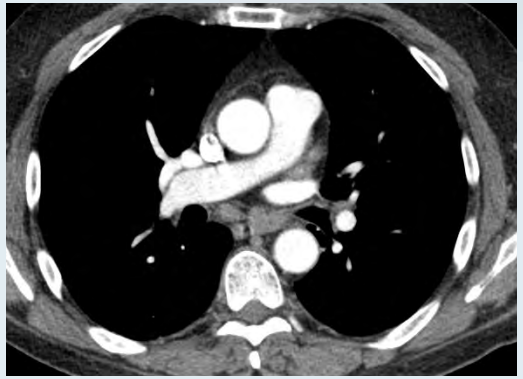
Courtesy of Gregory J Riely, MD, PhD

Paik et al, NEJM 2020

63-year-old single man (former smoker, daily marijuana, ETOH) with a PMH of anxiety, HTN (from the practice of Ms Goodwin)

- 6-7/2018: Vision loss, flashing lights, “purple halo”
  - Lung, liver, bone, choroidal and multiple small brain metastases
  - Liver biopsy: Poorly differentiated adenoarcinoma c/w lung primary, EGFR exon 19 del
- 8/2018 – 12/2019: Osimertinib 80mg QD → Fatigue, mild DOE while exercising, b/l hip pain
- 1/2020 Restaging CTs: Worsening bony mets, increase in abdominal LAN → palliative RT
  - Liquid biopsy: EGFR exon 19 del, TP53, MET amplification
- 2/2020 CT Head: New 9-mm L precentral gyrus met → SRS and continue osimertinib
- 3/2020: Periaortic LN biopsy: EGFR 19 del, no MET amplification
- Worsening constitutional complaints, pain: Plans for chemo + osimertinib c/b COVID19
- 4/25/2020: Admitted new BLE DVTs, RLE cellulitis, low platelets → Osimertinib held
- 5/20/2020: Scheduled to initiate carboplatin/pemetrexed +/- osimertinib

63-year-old man (from the practice of Ms Goodwin)

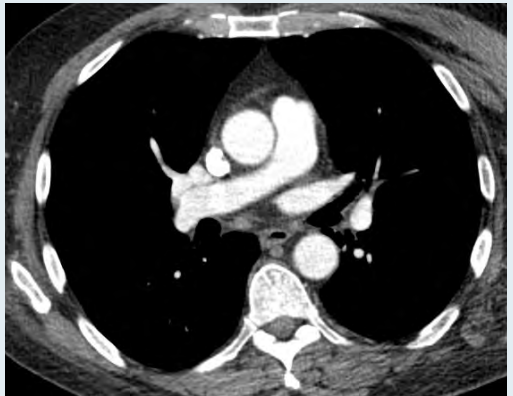


6/19/2018 (Diagnosis)

- Osteolytic lesions in the thoracic vertebrae, LEFT glenoid, and LEFT inferior scapula, with associated nondisplaced pathologic T1 spinous process fracture, c/w metastasis
- Mediastinal and hilar lymphadenopathy c/w metastasis
- Spiculated LLL nodule c/w metastasis
- Other smaller indeterminate pulmonary nodules in the RIGHT lung

9/27/2018 (S/P Months After Initiating Osimertinib)

- Slight interval decrease in size of the LLL nodule and subcarinal lymph nodes
- Multiple lytic osseous lesions, some which appear slightly increased from prior examination and represent treatment response



1/17/2020 (Disease Progression)

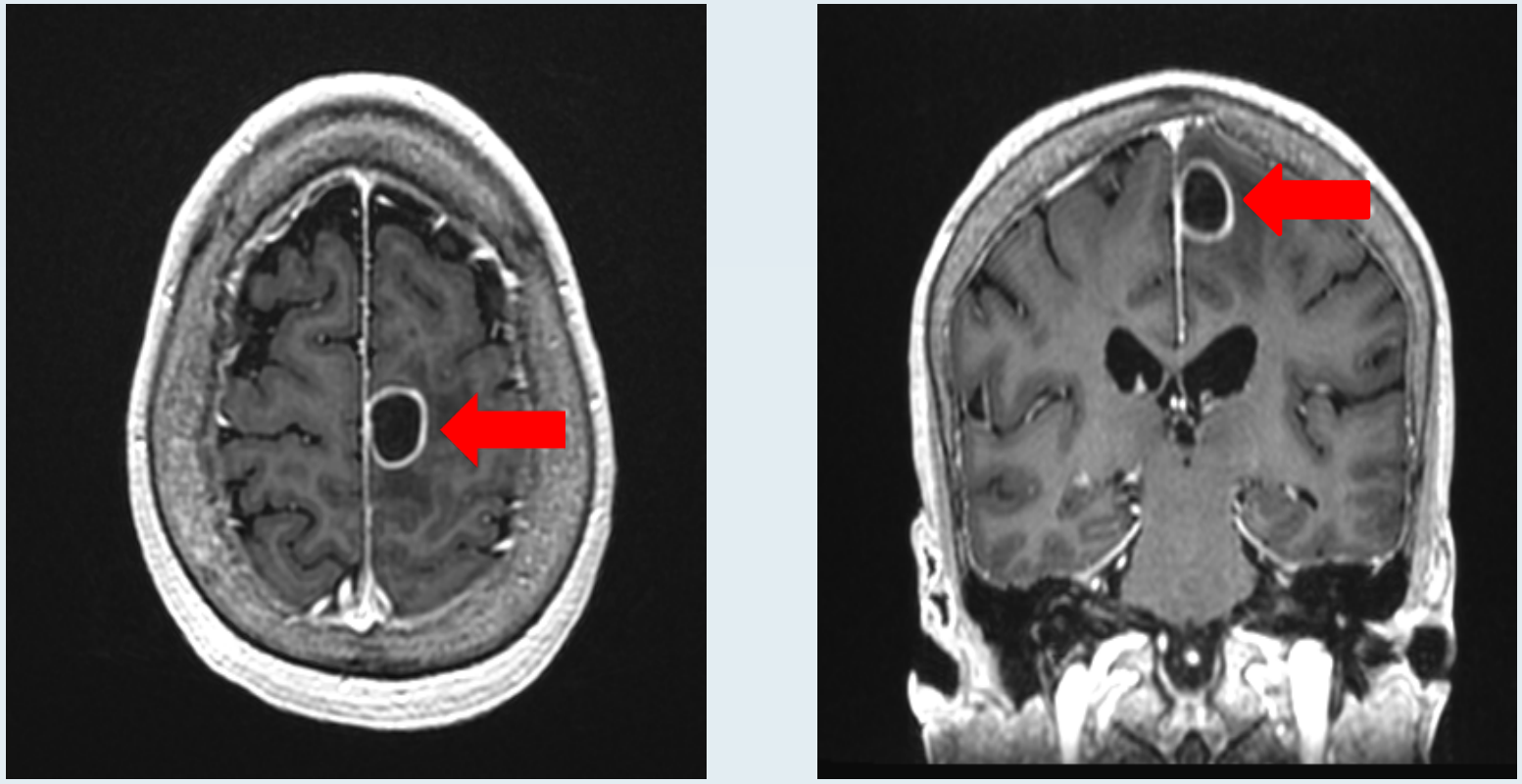
- Increase in lytic component of osseous metastases within the left scapula and right T5 transverse process, c/w progressive osseous metastases
- New indeterminate 2mm RML nodule

74-year-old independently minded woman whose primary language is Spanish (from the practice of Ms Lee)

- 1/2016: Adenocarcinoma of lung, with EGFR exon 19 deletion
- Attempted surgery but intraoperatively was found to have pleural disease
- Carboplatin/paclitaxel plus bevacizumab x 4 → maintenance bevacizumab → PD 9/2016
- 10/2016 – 9/2017: Erlotinib, with good response, discontinued due to toxicity
- 11/2017– 4/2018: Mild PD
- 5/2018: MD Anderson, *initiates osimertinib*, but lost to follow up
- 8/2018: Admitted to outside hospital with right leg weakness, dizziness; brain mets
  - Confirmed that pt never started osimertinib due to toxicity concerns
- 9/2018: Gamma Knife® radiosurgery to the left frontal lobe and *initiates osimertinib*
  - 12/2018 PET/CT: Significant improvement to brain mass
- *Re-starts osimertinib* with continued response until 12/2019
  - Pt reveals she discontinued osimertinib in 9/2018 due to mucositis and skin toxicity
- 3/2020 PET/CT: Decreased size and activity of the LLL mass

74-year-old woman (from the practice of Ms Lee)

MRI of the Brain (8/2018)



A new 1.9 cm ring-enhancing lesion in the left superior frontal gyrus

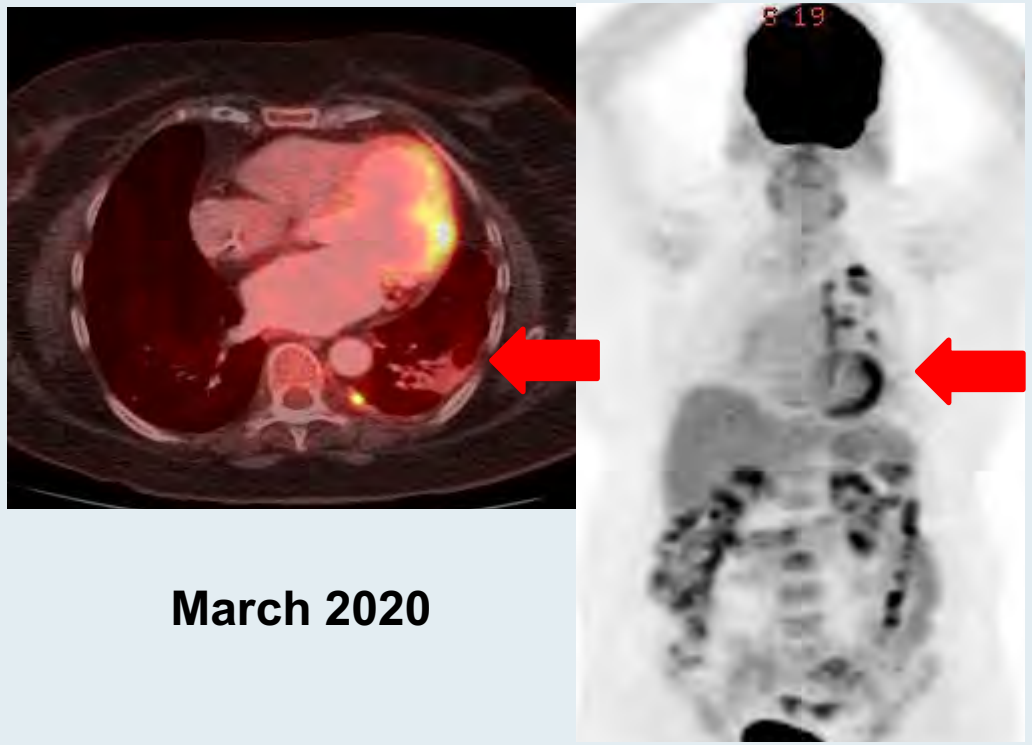
74-year-old woman (from the practice of Ms Lee)

May 2018

December 2018

74-year-old woman (from the practice of Ms Lee)

December 2019



March 2020

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Module 2: Checkpoint Inhibitors for Metastatic NSCLC without a Targetable Mutation

The benefit of a single-agent checkpoint inhibitor is more than twice that of chemotherapy as first-line treatment for patients with metastatic NSCLC and a high PD-L1 level (>50%).

a. Agree

b. Disagree

c. I don’t know

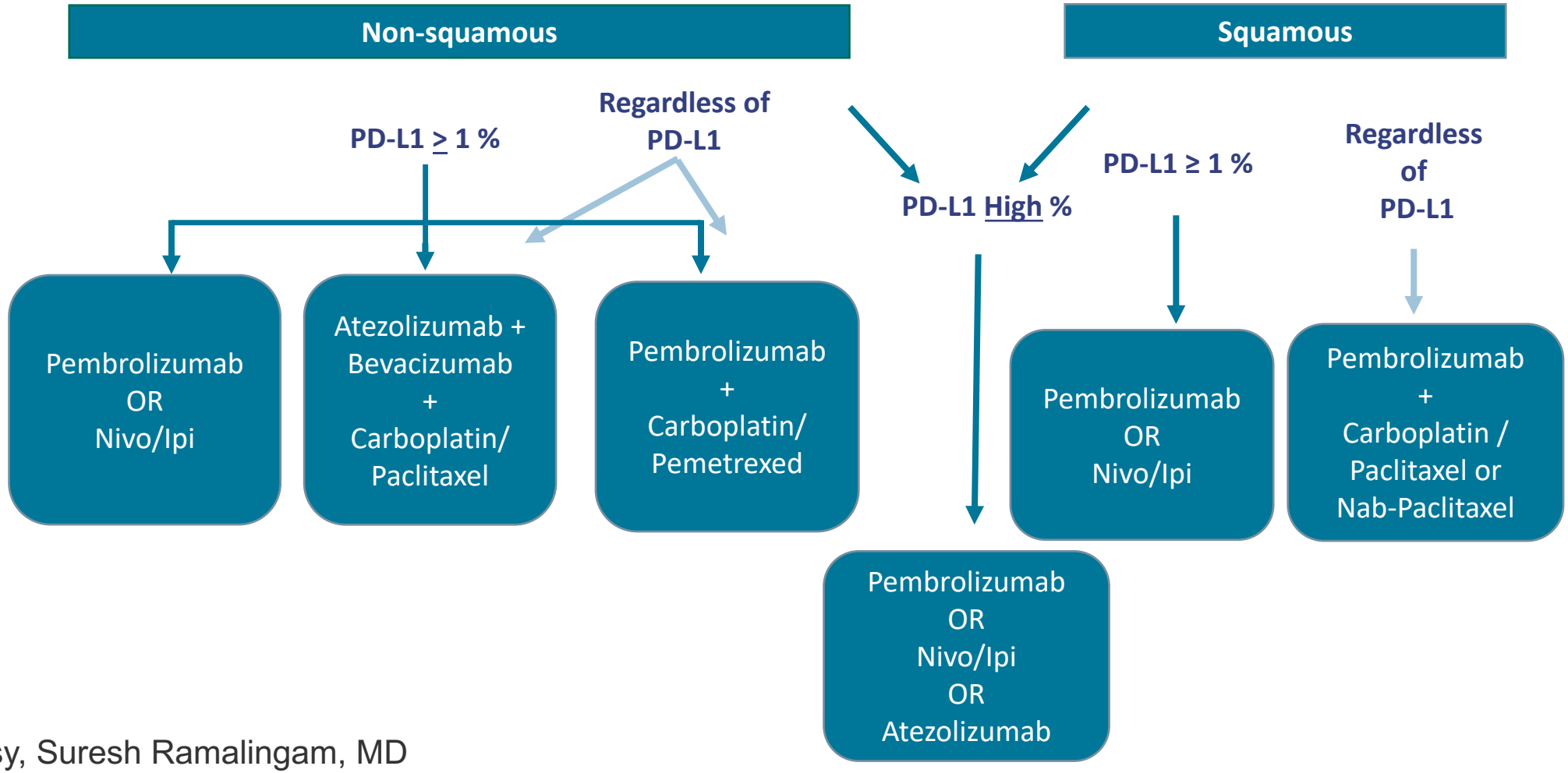
Checkpoint inhibitors are generally included as part of first-line treatment for patients with metastatic NSCLC and a PD-L1 level <1%.

a. Agree

b. Disagree

c. I don’t know

Metastatic NSCLC
First-Line Treatment Schema (No Driver Mutation)



Courtesy, Suresh Ramalingam, MD

First-Line Treatment in Select Clinical Situations for Patients with Metastatic NSCLC without a Targetable Mutation

Clinical situation	Treatment questions
High PD-L1 level (>50%)	Adding chemotherapy to a checkpoint inhibitor? Nivolumab/ipilimumab?
Negative PD-L1 level (<1%)	Chemotherapy plus checkpoint inhibitor? Chemotherapy plus nivolumab/ipilimumab?

Nivolumab + Ipilimumab versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: Three-Year Update from CheckMate 227 Part 1

Ramalingam SS et al.
ASCO 2020;Abstract 9500.

Nivolumab (NIVO) + Ipilimumab (IPI) + 2 Cycles of Platinum-Doublet Chemotherapy (Chemo) vs 4 Cycles Chemo as First-Line (1L) Treatment (tx) for Stage IV/Recurrent Non-Small Cell Lung Cancer (NSCLC): CheckMate 9LA

Reck M et al.
ASCO 2020;Abstract 9501.

FDA-Approved Immunotherapy Options for the First-Line Treatment of Metastatic NSCLC

Combination regimen	FDA approval	Pivotal study	Histologic type	HR (OS)
Pembrolizumab + Platinum and pemetrexed[1]	8/20/18	KEYNOTE-189	Nonsquamous	0.49
Pembrolizumab + Carboplatin, paclitaxel or *nab* paclitaxel[2]	10/30/18	KEYNOTE-407	Squamous	0.64
Atezolizumab + Carboplatin and paclitaxel and bevacizumab[3]	12/6/18	IMpower150	Nonsquamous	0.78
Atezolizumab + Carboplatin and *nab* paclitaxel[4]	12/3/19	IMpower130	Nonsquamous	0.79
Nivolumab + Ipilimumab[5]	5/15/20	CheckMate-227	PD-L1 TPS≥1, EGFR and/or ALK *wt*	0.62
Nivolumab + Ipilimumab and chemotherapy[6]	5/26/20	CheckMate-9LA	EGFR and/or ALK *wt*	0.69
Monotherapy	**FDA approval**	**Pivotal study**	**Histologic type**	**HR (OS)**
Pembrolizumab[7,8]	4/11/19 10/24/16	KEYNOTE-042 KEYNOTE-024	PD-L1 TPS≥1%	0.63
Atezolizumab[9]	5/18/20	IMpower110	PD-L1 TPS≥50, EGFR and/or ALK *wt*	0.59

[1] Gandhi L et al. *NEJM* 2018;378(22):2078-92. [2] Paz-Ares L et al. *NEJM* 2018;379(21):2040-51.
[3] Socinski MA et al. *NEJM* 2018;378(24):2288-301. [4] West H et al. *Lancet Oncol* 2019;20(7):924-37.
[5] Hellmann MD et al. *N Engl J Med* 2019;381(21):2020-31. [6] Reck M et al. ASCO 2020;Abstract 9501.
[7] Mok TSK et al. *Lancet* 2019;393(10183):1819-30. [8] Reck M et al. *J Clin Oncol* 2019;37(7):537-46.
[9] Spigel DR et al. ESMO 2019;Abstract LBA78

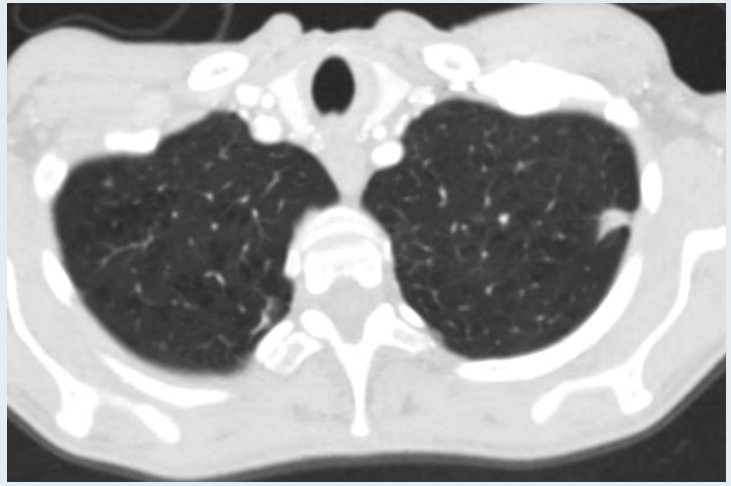
56-year-old woman and current smoker who is disabled s/p CABG c/b chronic pain with a PMH of emphysema, GERD, anxiety (from the practice of Ms Goodwin)

- 10/2018: Developed cough → CXR: LUL nodular opacity, CT Chest: 1.3-cm spiculated nodule
- 12/2018: LUL VATS wedge resection d/t severe emphysema
  - Poorly differentiated adenoCA (T1Nx)
- 6/2019 surveillance CT: Chest NED
- 10/2019: Admitted with dry cough, wheeze, worsening DOE, hypoxia (SpO2 84%)
  - Improved with antibiotics, steroids, nebulizers
- 12/10/2019: Worsening/persistent pain → Diffuse metastatic disease, incl hepatic and renal mets
- 12/28/2019: Increasing symptom burden (pain, hypoxia) → Repeat scan: Rapid progression
  - PD-L1: 100%
- Declines chemo + immunotherapy due to QOL concerns (DNR/DNI)
- 12/31/2019: Pembrolizumab
  - Tolerating well
  - Nice response to therapy with improved energy, pain, respiratory symptoms

56-year-old woman (from the practice of Ms Goodwin)

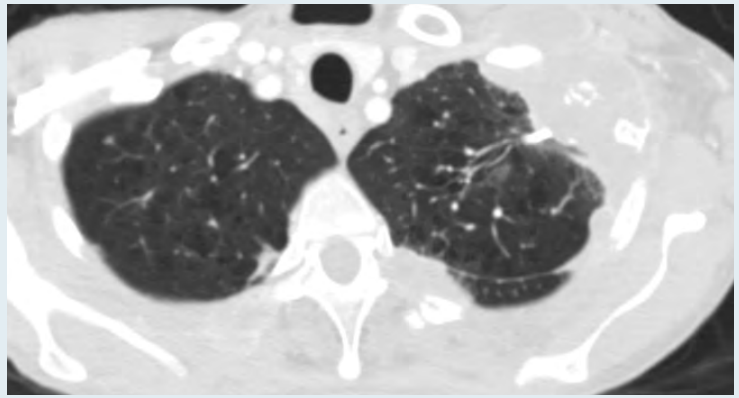
October 2018

Early stage lung CA



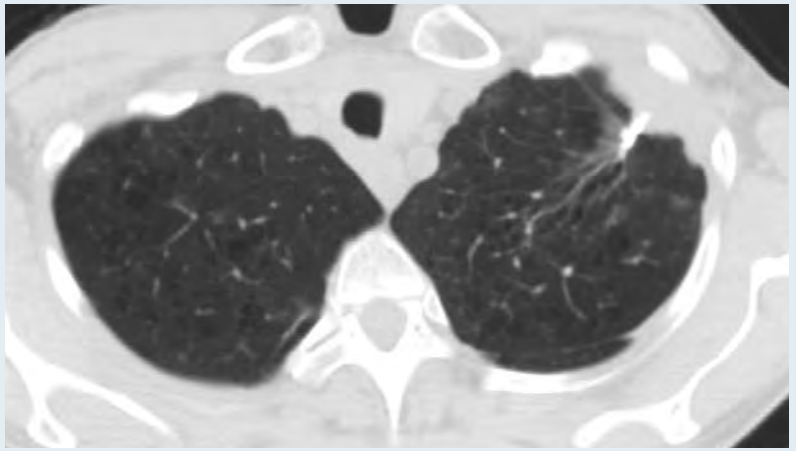
December 2019

Metastatic recurrence



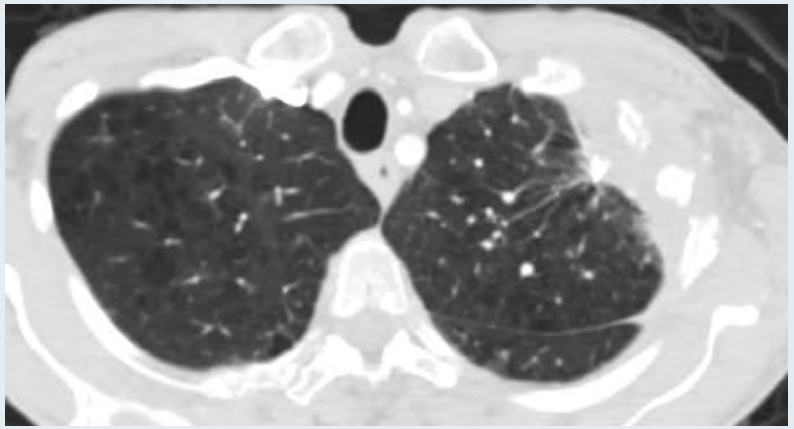
June 2019

NED



February 2020

Restaging s/p 2 cycles of pembrolizumab



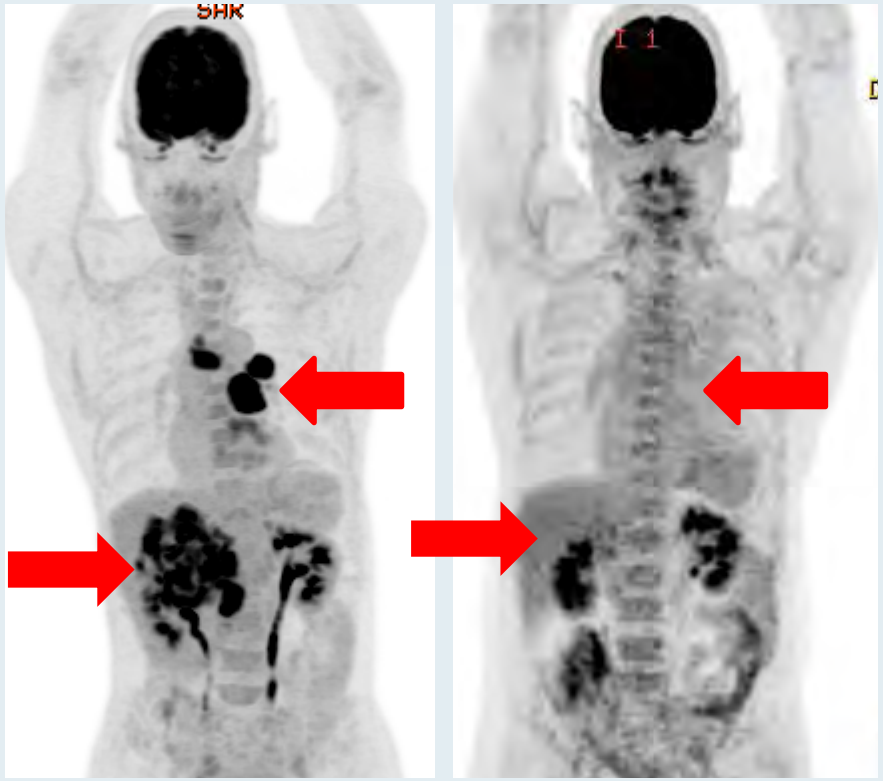
56-year-old woman (from the practice of Ms Goodwin)

Living her best life with cancer

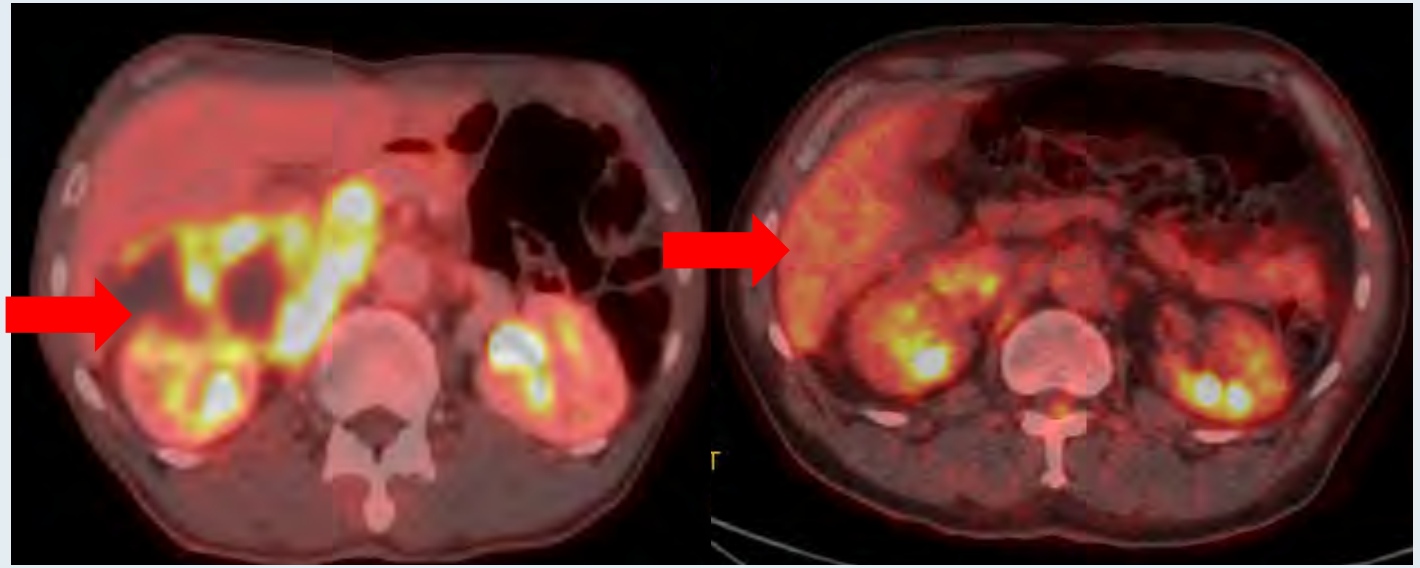
58-year-old spiritual man on disability who lost insurance coverage (from the practice of Ms Lee)

- 6/2019: Presents with chronic abdominal pain → CT abdomen/pelvis: Large right retroperitoneal mass
  - Biopsy: Consistent with adenocarcinoma of the lung (CK7, CEA, and TTF-1 positive)
    - Molecular alterations: BRAF G466V, KRAS K117N, and TP53 E271K
    - PD-L1: 1%
- 8/2019: MD Anderson PET/CT: LUL primary 3.5-cm, 5.6-cm left mediastinal mass, bilateral paratracheal adenopathy
  - MRI brain: Negative
- Carboplatin/pemetrexed/pembrolizumab x 4
  - 10/2019 restaging CT after 3 cycles: Decrease in all areas of disease
- Currently, on cycle 14 of maintenance pemetrexed/pembrolizumab
  - Tolerating treatment well, with no noticeable side effects
- 4/2020 restaging PET/CT: Continued response, no evidence of progression or new disease

58-year-old man (from the practice of Ms Lee)



August 2019 April 2020



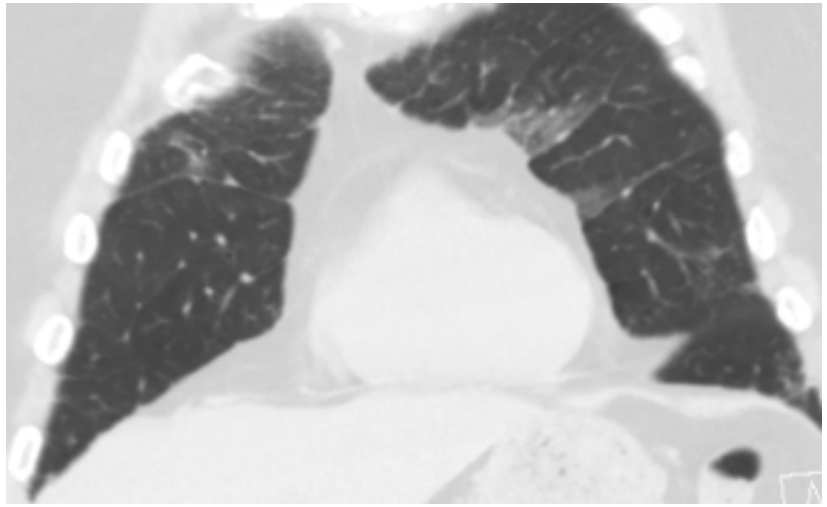
August 2019 April 2020

58-year-old man (from the practice of Ms Lee)

- Hanging out with his buddies
- He is the tallest of the three
- He had a College Scholarship to play basketball, but broke his ankle during his last season in high school

IO-Related Pneumonitis

Mild (Gr 1)	Moderate (Gr 2)	Severe (Gr 3-4)
• Consider holding immunotherapy • Reassess in 1-2 weeks • Pulse oximetry (resting and with ambulation) • Consider CT chest w/ or w/o contrast • Repeat CT in 4 weeks or as clinically indicated for worsening symptoms	• Hold immunotherapy • Consult pulmonary specialist • Must r/o infection (nasal swab, sputum, blood culture, urine culture) • Bronchoscopy • CT chest • Empiric abx if infection not r/o • Prednisone/methylprednisolone 1-2 mg/kg/day – monitor every 3-7 days	• Permanently d/c immunotherapy • Inpatient care • Infectious workup • Bronchoscopy • Methylprednisolone 1-2 mg/kg/day – assess response w/in 48 hours and plan to taper over 6 weeks • If not improvement after 48 hours THEN



Consider adding:

- Infliximab 5mg/kg/IV, 2nd dose may be repeated 14 days at discretion of tx provider
- IVIG
- Mycophenolate mofetil 1-1.5g BID then taper in consultation w/pulmonary service

Courtesy, Suresh Ramalingam, MD

Agenda

Overview: A Biomarker-Driven Approach to Lung Cancer Treatment

Module 1: Non-Small Cell Lung Cancer (NSCLC) with a Targetable Mutation

- Case Presentation: Ms Goodwin — 63-year-old telecommunications engineer
- Case Presentation: Ms Lee — 74-year-old independently minded Spanish-speaking woman

Module 2: Checkpoint Inhibitors for Metastatic NSCLC without a Targetable Mutation

- Case Presentation: Ms Goodwin — 59-year-old woman on disability with chronic pain and anxiety
- Case Presentation: Ms Lee — 58-year-old spiritual man on disability who lost insurance coverage

Module 3: Extensive-Stage Small Cell Lung Cancer

- Case Presentation: Ms Goodwin — 68-year-old widow and teacher’s aide
- Case Presentation: Ms Lee — 78-year-old grandfather from Oklahoma

Module 3: Extensive-Stage Small Cell Lung Cancer

The combination of chemotherapy and a checkpoint inhibitor has become the standard first-line treatment for extensive-stage small cell lung cancer.

a. Agree

b. Disagree

c. I don’t know

Overview of Small Cell Lung Cancer

Cell of origin

- Neuroendocrine

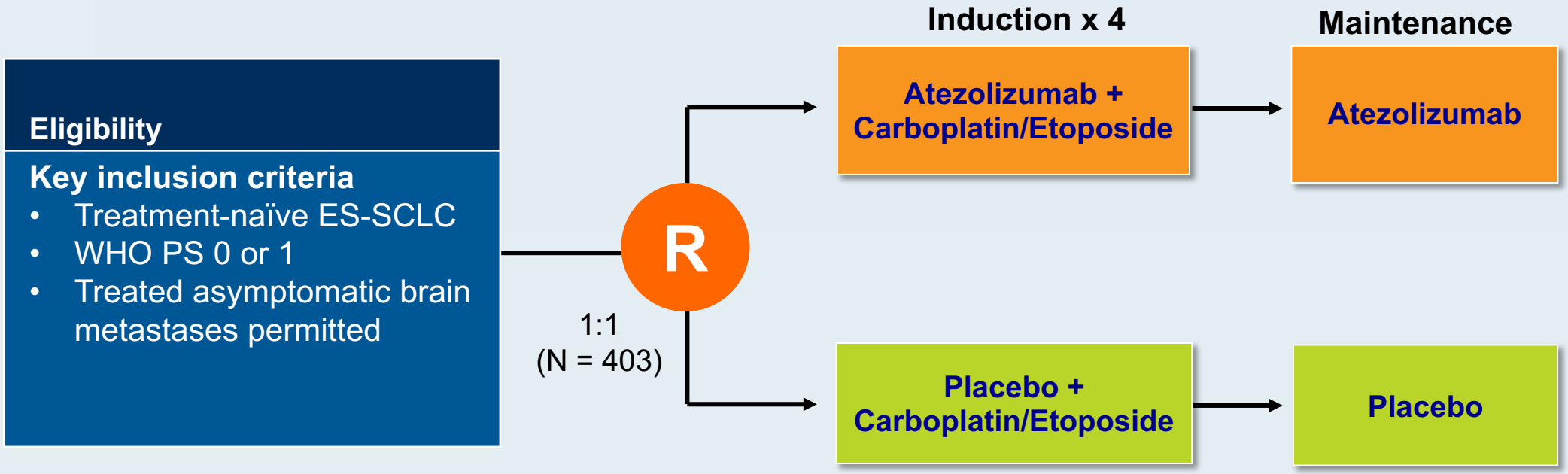
Initial presentation

- Smoking history/comorbidities
- Hilar and mediastinal nodes/symptomatic
- Brain metastases, high growth rate
- Superior vena cava (SVC) syndrome

Clinical issues

- Chemoresponsive/now with CIs
- Paraneoplastic syndromes (SIADH, neurologic)

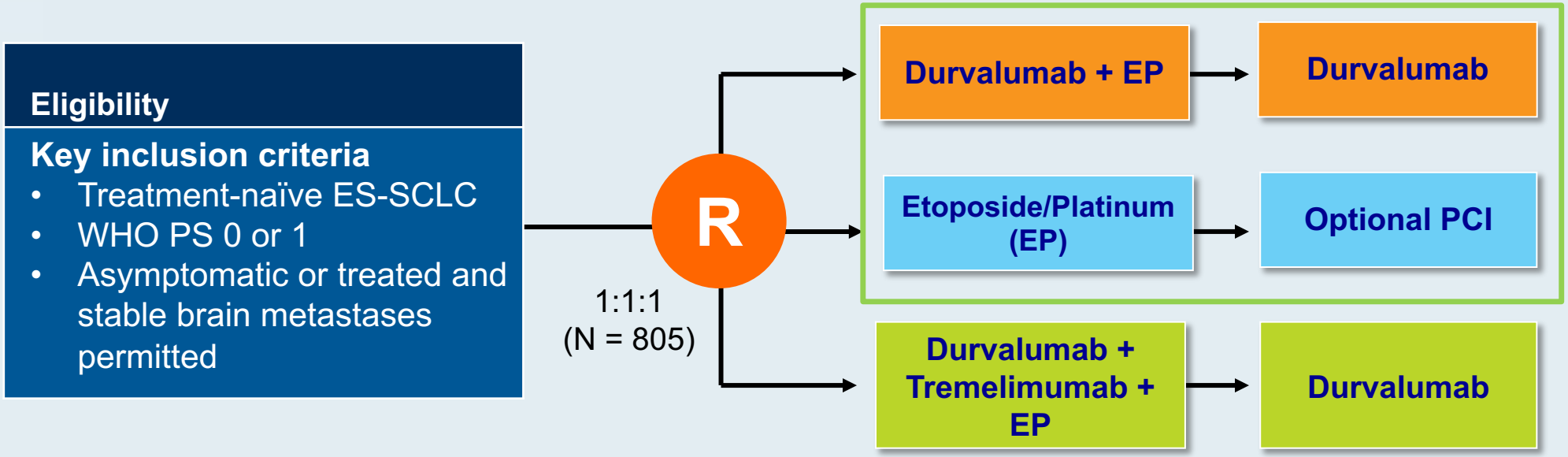
IMpower133 Phase III Study Design



Coprimary endpoints: Overall survival and investigator-assessed PFS
Key secondary endpoints: Objective response rate, duration of response, safety

Liu SV et al. ESMO 2018;Abstract PL02.07.

CASPIAN Phase III Study Design



The durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

Primary endpoint: Overall survival
Key secondary endpoints: PFS, ORR, safety and tolerability, PROs

Paz-Ares L et al. ESMO 2019;Abstract LBA89.

FDA-Approved First-Line Chemoimmunotherapy Regimens in ES-SCLC

	IMpower133[1]			
	Carbo/etoposide + atezolizumab (n = 201)	Carbo/etoposide + placebo (n = 202)	HR	*p*-value
Median PFS	5.2 mo	4.3 mo	0.77	0.02
Median OS	12.3 mo	10.3 mo	0.70	0.007

	CASPIAN[2]			
	Platinum/etoposide + durvalumab (n = 268)	Platinum/etoposide + placebo (n = 269)	HR	*p*-value
Median PFS	5.1 mo	5.4 mo	0.80	Not tested
Median OS	12.9 mo	10.5 mo	0.75	0.0032

[1] Horn L et al. *N Engl J Med* 2018;379(23):2220-9. [2] Paz-Ares LG et al. ASCO 2020;Abstract 9002.

Immune-Related Adverse Events (irAEs) in Front-Line Chemoimmunotherapy Studies in SCLC

IMpower133

Reck et al. ESMO 2019

Patients, n (%)	Atezo + CP/ET (n = 198)	Placebo + CP/ET (n = 196)
Patients with ≥ 1 AE	198 (100)	189 (96.4)
Grade 3–4 AEs	134 (67.7)	124 (63.3)
Treatment-related AEs	188 (94.9)	181 (92.3)
Serious AEs	77 (38.9)	69 (35.2)
Immune-related AEs	82 (41.4)	48 (24.5)
Treated with steroids or hormone replacement therapy[a]	40 (20.2)	11 (5.6)
AEs leading to withdrawal from any treatment[b]	24 (12.1)	6 (3.1)
AEs leading to withdrawal from atezolizumab/placebo	23 (11.6)	5 (2.6)
AEs leading to withdrawal from carboplatin	5 (2.5)	1 (0.5)
AEs leading to withdrawal from etoposide	8 (4.0)	2 (1.0)
Treatment-related Grade 5 AEs	3 (1.5)	3 (1.5)

- Median duration of treatment with atezolizumab was 4.7 months (range: 0 to 29)
- Median number of doses received:
  - Atezolizumab: 7 (range: 1 to 39)
  - Chemotherapy: 4 for carboplatin; 12 doses etoposide (for both arms)

[a] An event consistent with an immune-mediated mechanism of action requiring treatment with systemic corticosteroids or hormone replacement therapy.
[b] Incidence of treatment-related AEs and AEs leading to withdrawal from any treatment are for any treatment component.
CCOD 24 January 2019

IMpower133 Updated OS Analysis: presented by Dr Martin Reck http://bit.ly/2Z32WhW

CASPIAN

Paz Ares et al. WCLC 2019

	Durvalumab + EP (n=265)	EP (n=266)
Any-grade all-cause AEs, n (%)	260 (98.1)	258 (97.0)
Grade 3/4 AEs	163 (61.5)	166 (62.4)
Serious AEs	82 (30.9)	96 (36.1)
AEs leading to treatment discontinuation*	25 (9.4)	25 (9.4)
Immune-mediated AEs†	52 (19.6)	7 (2.6)
AEs leading to death	13 (4.9)	15 (5.6)
Treatment-related AEs leading to death‡	5 (1.9)	2 (0.8)

*Includes patients who permanently discontinued at least one study drug
†An event that is associated with drug exposure and consistent with an immune-mediated mechanism of action, where there is no clear alternate aetiology and the event required treatment with systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy; majority of immune-mediated AEs were low grade and thyroid related
‡AEs assessed by the investigator as possibly related to any study treatment. Causes of death were cardiac arrest, dehydration, hepatotoxicity, pancytopenia, and sepsis (one patient each) in the durvalumab + EP arm; pancytopenia and thrombocytopenia/haemorrhage (one patient each) in the EP arm

AE, adverse event

IMpower133: **16.9%** higher incidence of irAEs in atezolizumab arm vs control arm

CASPIAN: **17.0%** higher incidence of irAEs in durvalumab arm vs control arm

Courtesy of Anna Farago, MD, PhD

68-year-old widow and former smoker with PMH of anxiety, Afib, HTN (from the practice of Ms Goodwin)

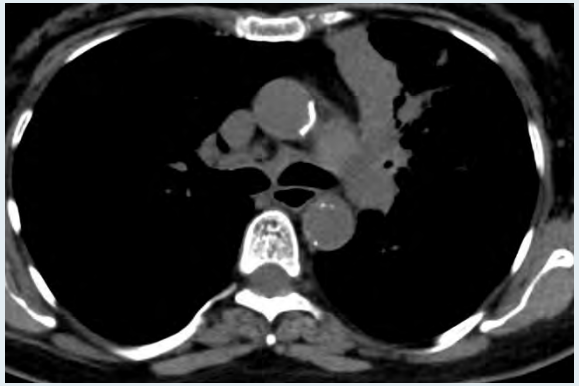
- 4/10/2019 CT Chest for persistent cough: 8 x 9-cm mass, diffuse osseous, multiple liver lesions
- 4/13/2019 Presents to local ED for dyspnea, pain; leaves AMA; Presents to MGH ED requesting admission
  - MRI Brain: Negative; MRI Spine: c/f LMD; Liver biopsy: SCLC
- 4/19/2019: Carbo/etoposide + atezolizumab x 4 → 7-week treatment holiday/vacation → maintenance atezolizumab
  - Tolerated well symptomatically, with cytopenias requiring GCSF, PRBCs, dose reduction
- 1/2020 Restaging CT Chest: Infectious/inflammatory changes vs early progression?
- 3/6/2020: Progression in lungs, liver, bones; MRI Brain: Numerous new brain mets
- 3/26/2020: Completes WBRT → Presents urgently 2 days later with MS changes
- 4/7/2020: Admitted MGH: Stable disease; Infectious work up: negative; Delirium due to steroids, memantine?
  - Transferred to psychiatry, with declining clinical status
- 4/17/2020: Discharged home, declines home hospice initially but enrolled 5/11

68-year-old widow (from the practice of Ms Goodwin)

April 2019 – large LUL mass

June 2019 - response

January 2020 - Increased nodular opacity with linear bands corresponding to treated LUL CA. There are also subtle tree-in-bud nodules and bronchial wall thickening. Possibilities include infection and recurrent CA. Interval decrease in the L apical nodule c/w inflammatory process.



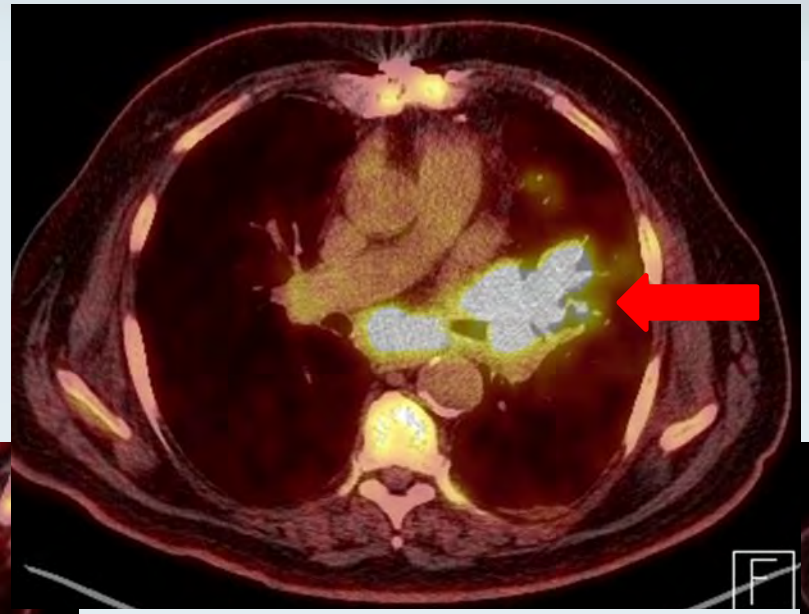
March 2020 - Significant increase in mass-like consolidation within the LLL c/f disease recurrence. Increasing surrounding atelectasis and tree-in-bud which may be infectious/inflammatory. Enlarging paratracheal and subcarinal lymphadenopathy which may be reactive or disease related.

78-year-old man and prior smoker with a PMH of atrial fibrillation requiring anticoagulation (from the practice of Ms Lee)

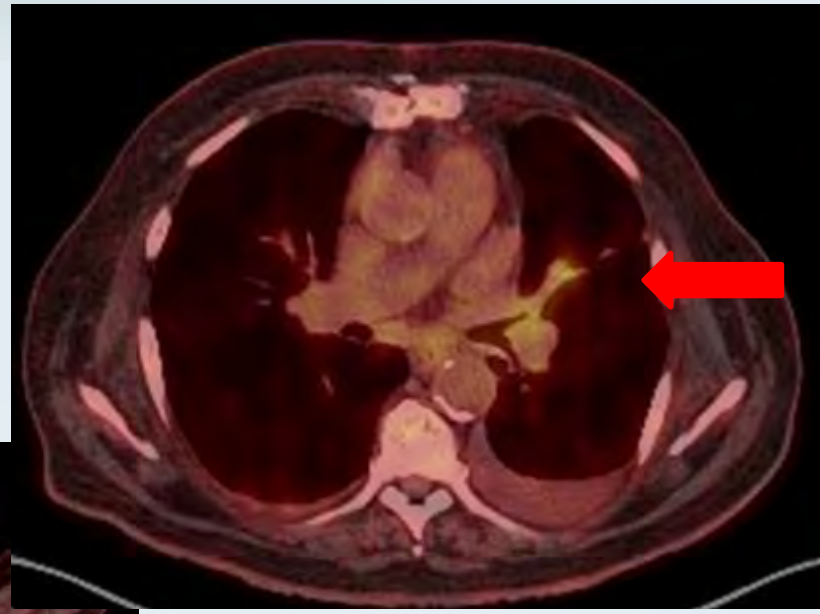
- Late 2019: Presents with cough, shortness of breath (antibiotics)
- 1/2020 CT chest: Left hilar mass
- 2/2020 Bronchoscopy with biopsy: small cell carcinoma
  - PET/CT: 5.8-cm left hilar mass, extensive mediastinal adenopathy, left paratracheal mass (2.2 cm), subcarinal adenopathy and contralateral paratracheal, hilar and cervical adenopathy
  - CT of the head: Negative
  - Pancytopenia: Platelets as low as 61,000, Hgb: 9, and WBC: 2.9
  - Possible liver cirrhosis
- 3/2020: Carboplatin, etoposide and atezolizumab
  - Improvement on imaging after cycle 2
- 5/20/2020: S/P cycle 4 and planning for consolidated radiotherapy and continue atezolizumab maintenance therapy every 3 weeks

78-year-old man (from the practice of Ms Lee)

Initial PET in February 2020 prior to treatment



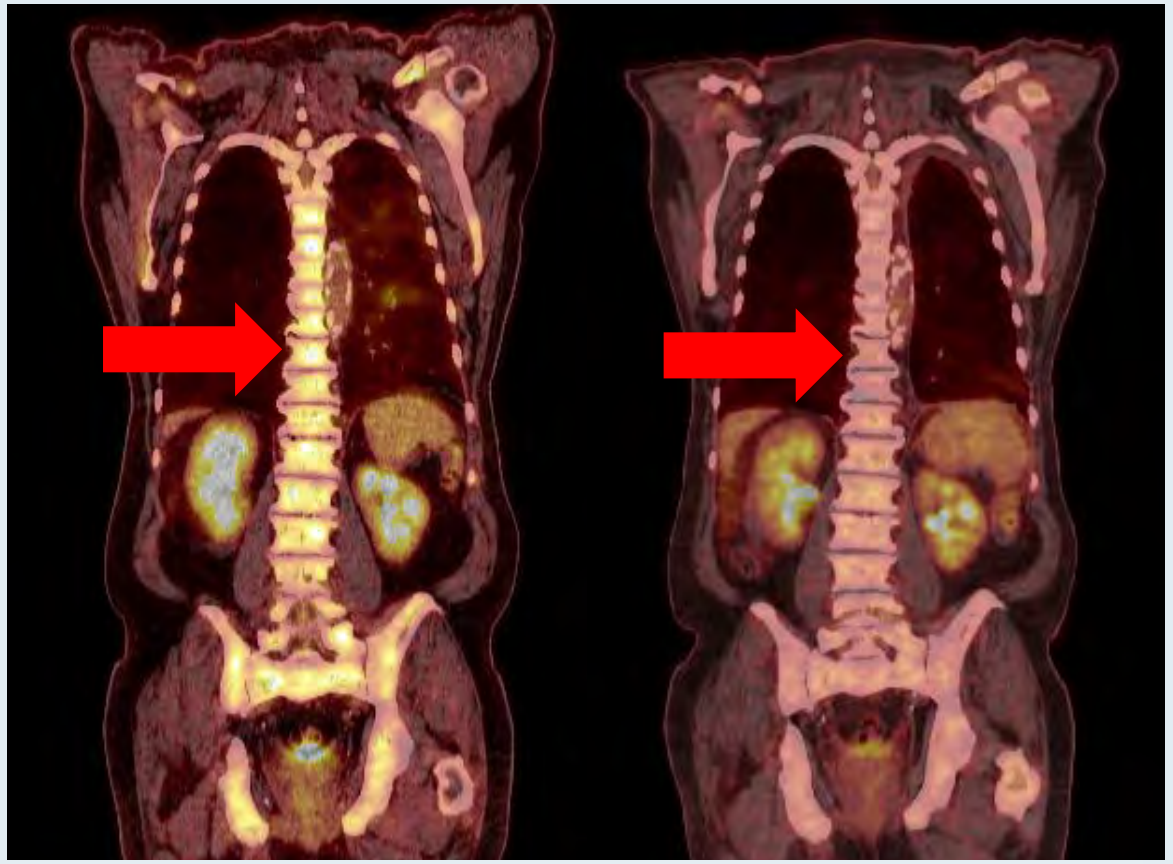
Restaging PET in April 2020 after 2 cycles of chemo/IO



78-year-old man (from the practice of Ms Lee)

- At diagnosis he had pancytopenia with platelets as low as 61,000, hemoglobin of 9, and White count 2.9.
- BMA revealed diffuse infiltration of the medullary space by metastatic carcinoma.
- Other complicating factors: evidence of possible liver cirrhosis on imaging (hepatitis serologies negative/biopsy deferred), and history of a-fib requiring anticoagulation
- Hematology recs for low dose anticoagulation based on weekly platelet counts

Bone Marrow Infiltration on Initial PET and Improvement on Restaging PET



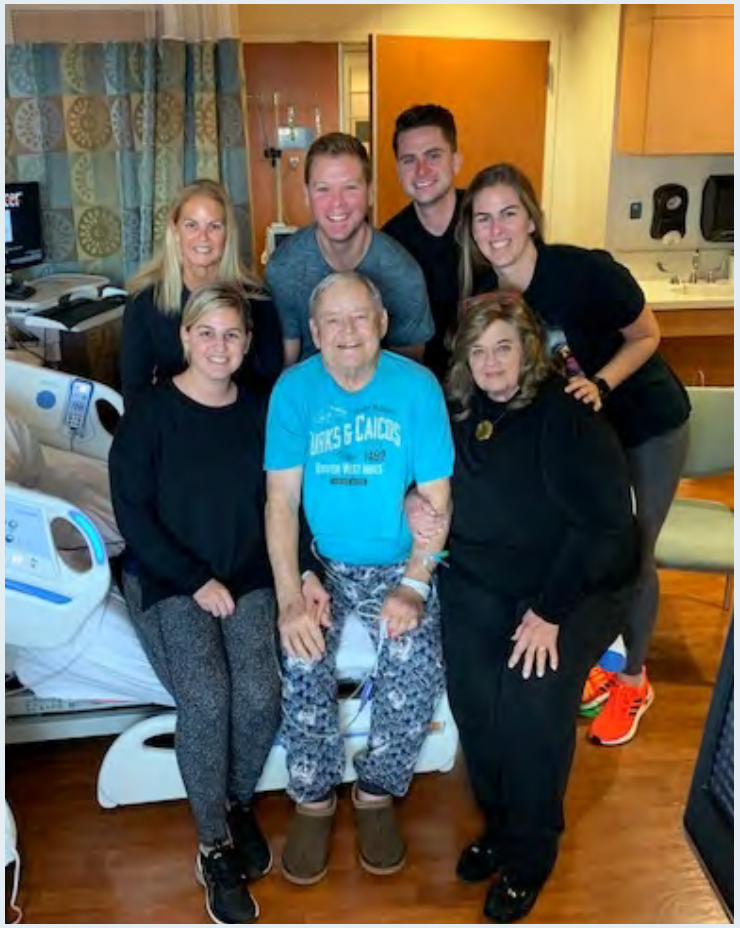
78-year-old man (from the practice of Ms Lee)

- Depends on his family for support
- They are very close and his wife, daughter, daughter-in-law and three granddaughters “keep him in line,” and “he does whatever they tell him to do”
- Relocated to Houston temporarily for treatment
- Family Rotate Trips to Houston to stay with him
- Spends time playing cards and walking around the courtyard at his apt
- When at home in Oklahoma, he sits on his deck and watches golfers on the course
- He can’t wait to get back to playing golf

78-year-old man (from the practice of Ms Lee)

The Life of the Party!

78-year-old man (from the practice of Ms Lee)



With Family in the Hospital

After Starting Therapy

Just Last Week in Clinic

Thank you for joining us!

CNE (NCPD) credit information will be emailed to each participant tomorrow morning.