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

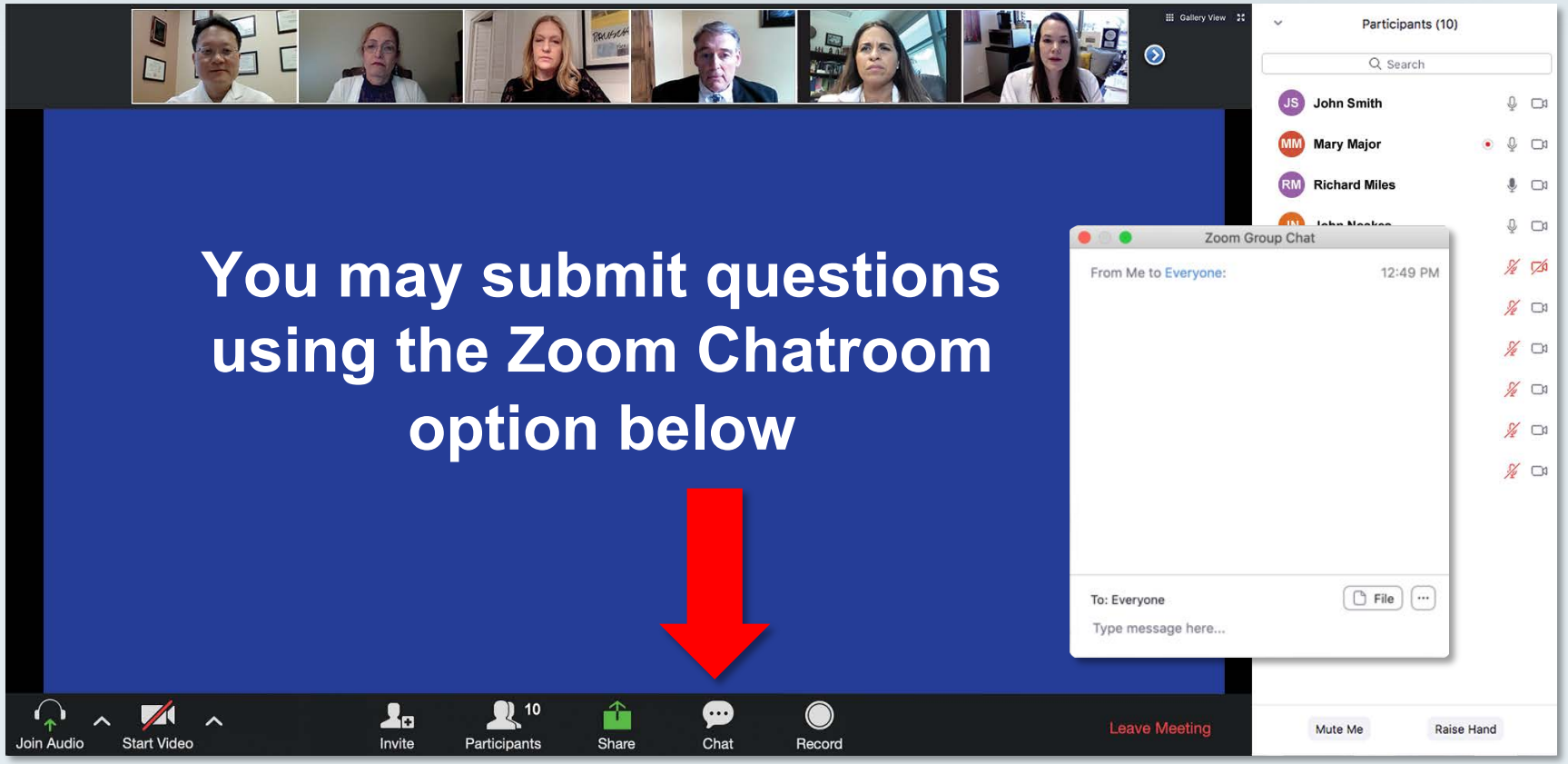
Benjamin Levy, MD
Stephen V Liu, MD, PhD
Beth Sandy, MSN, CRNP
Elizabeth S Waxman, RN, MSN, ANP-BC

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Dr Love and Faculty Encourage You to Ask Questions



Feel free to submit questions **now before** the program commences and **throughout the program.**

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 9 AM	2	3
6	7	8	9	10

About the Enduring Program

- This webinar is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
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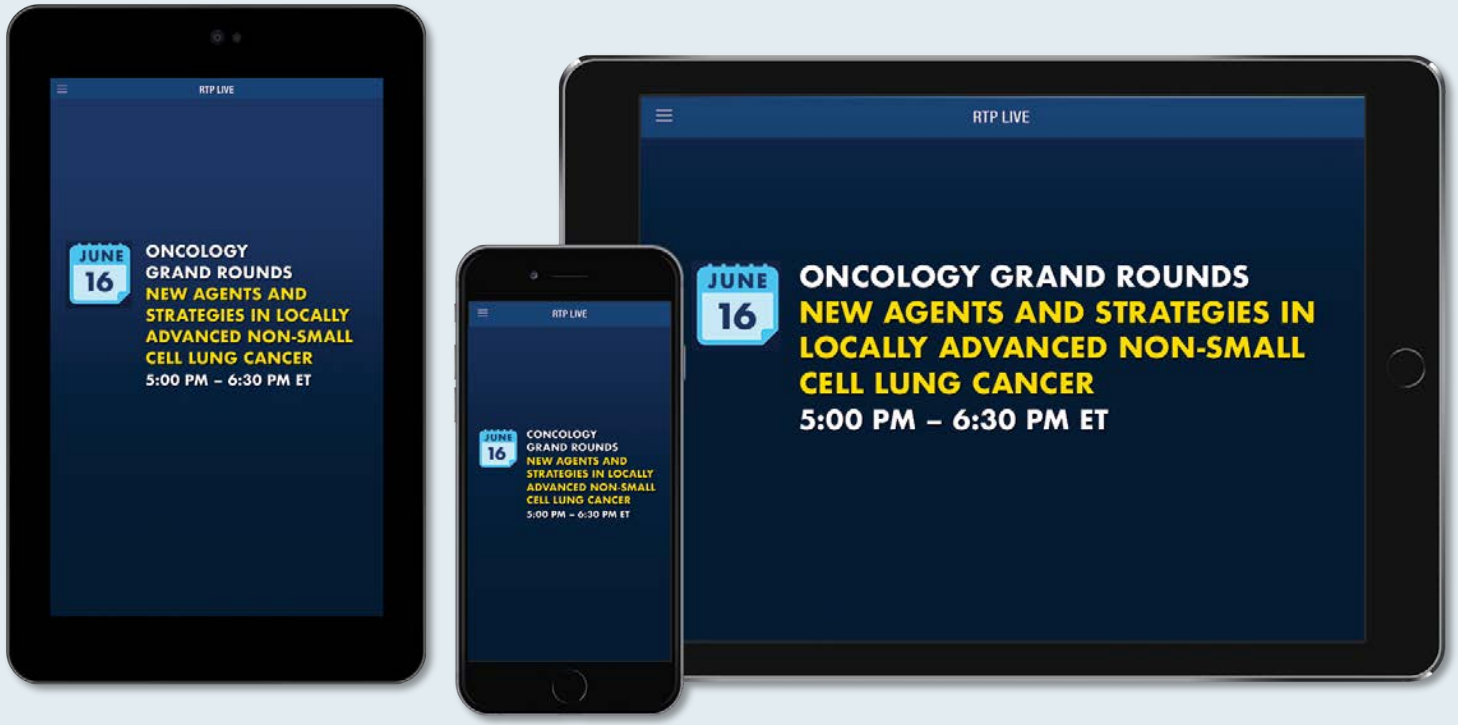

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Oncology Grand Rounds

New Agents and Strategies in Urothelial Bladder Carcinoma

Thursday, June 18, 2020

5:00 PM – 6:30 PM ET

Faculty

Arjun Balar, MD
Anastassia Daskalova, NP
Peter H O'Donnell, MD
Susan K Roethke, CRNP, MSN, ANP-BC, AOCNP

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Oncology Grand Rounds

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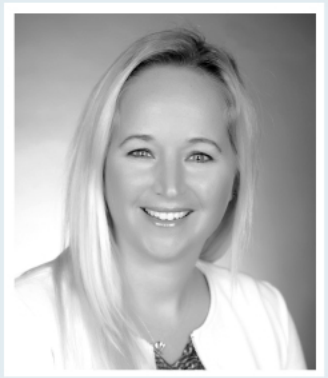
RTP RESEARCH TO PRACTICE


Other Select Ongoing Trials of Immunotherapy for Locally Advanced NSCLC

Benjamin Levy, MD
Johns Hopkins Sidney Kimmel
Cancer Center at Sibley Memorial
Washington, DC

Stephen V Liu, MD, PhD
Georgetown University Hospital
Washington, DC



Beth Sandy, MSN, CRNP
Abramson Cancer Center
University of Pennsylvania
Philadelphia, Pennsylvania

Elizabeth S Waxman, RN, MSN, ANP-BC
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Agenda

Overview: Localized Lung Cancer; Staging; History of Treatment

- Case Presentation: Ms Waxman – 60-year-old woman

Module 1: PACIFIC Trial: Benefits of Postchemoradiation Durvalumab Consolidation

- Case Presentation: Ms Sandy – 71-year-old woman

Module 2: PACIFIC Trial: Side Effects Associated with Chemoradiation Therapy and Durvalumab Consolidation

- Case Presentation: Ms Waxman – 81-year-old woman

Module 3: Management of Immune-Mediated Toxicity

- Case Presentation: Ms Sandy – 68-year-old woman

Module 4: Recent Relevant Data Sets

- ASCO 2020 Plenary: ADAURA study of adjuvant osimertinib for EGFR-mutated NSCLC

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What year was the first checkpoint inhibitor approved for the treatment of lung cancer?

a. 2005

b. 2010

c. 2013

d. 2015

e. 2016

f. 2017

FDA Approves First Immunotherapy Treatment for Lung Cancer

Press Release – March 4, 2015

"The Food and Drug Administration (FDA) approved nivolumab to treat patients with advanced non-small cell lung cancer (NSCLC) that has progressed during or after treatment with platinum-based chemotherapy. Nivolumab, which was initially approved for the treatment of metastatic melanoma, is the first immunotherapy drug to be approved to treat lung cancer. The FDA based the approval on findings from a randomized phase III trial that enrolled 272 patients with advanced NSCLC who were assigned to receive either nivolumab or the chemotherapy drug docetaxel. Participants who received nivolumab had a 41% reduction in the risk of death and lived on average 3.2 months longer than those who received docetaxel. Approximately 30 percent of patients treated with nivolumab were alive 2 years after beginning treatment compared to 13 percent of patients treated with docetaxel.

The FDA also cited safety and efficacy data from a Phase II trial that included 117 participants whose cancer had progressed after they had received a platinum-based chemotherapy and at least one other prior systemic treatment. According to updated results from the trial, 17 participants (14.5 percent) experienced a reduction in tumor size, of whom 59 percent had response durations of 6 months or longer. Median overall survival was 8.2 months and overall survival at 1 year was 40.8 percent."

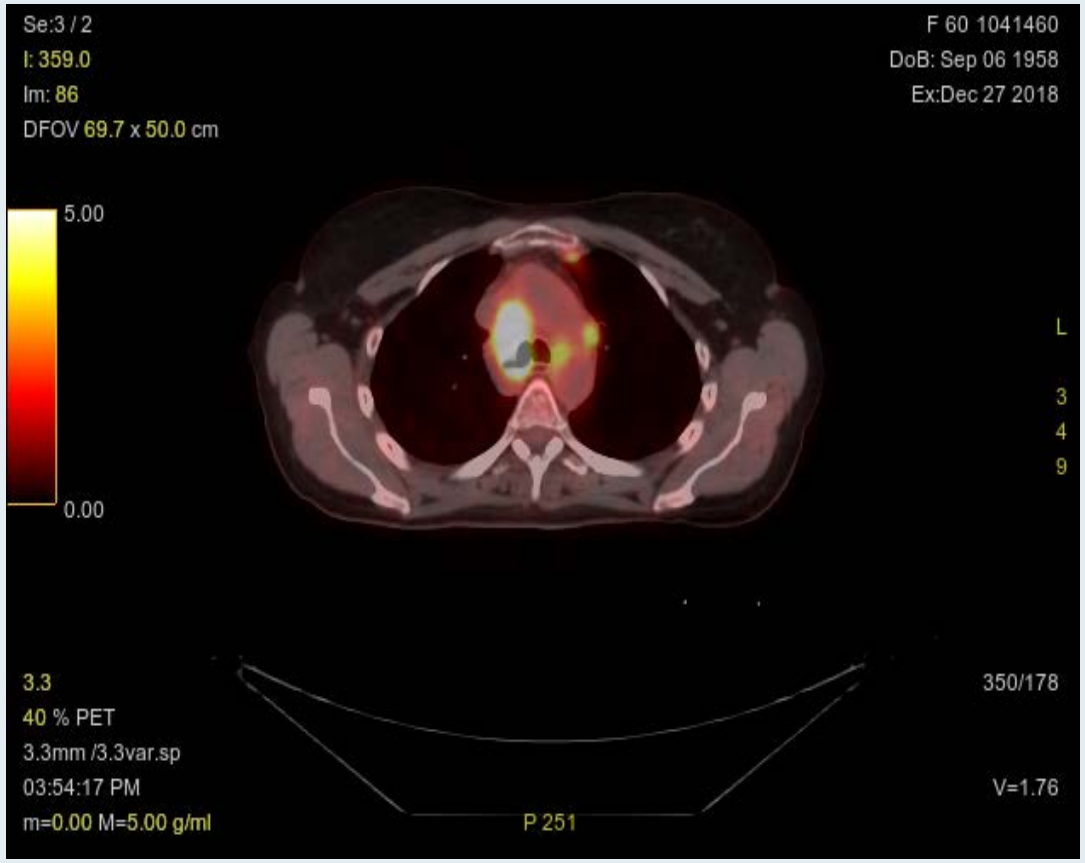
https://www.cancer.gov/news-events/cancer-currents-blog/2015/fda-opdivo

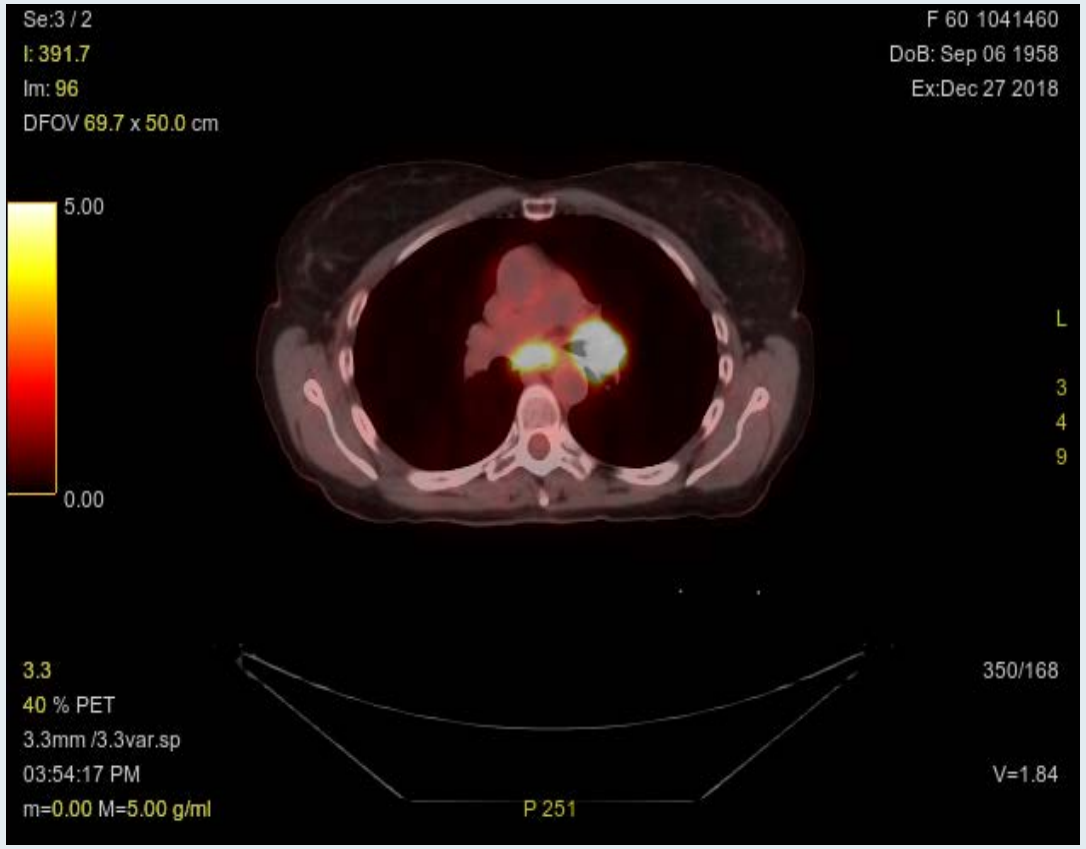
60-year-old woman (from the practice of Ms Waxman)

- 4/2018: Flu-like symptoms resolved, followed by persistent cough
- 12/2018: Admitted to hospital following episode of severe coughing with hemoptysis
  - Work up: Left adenocarcinoma, Stage IIIB (T2b N3 M0), No driver mutation identified
- 2/2019: Completes concurrent platinum/taxane chemotherapy and radiation therapy
  - 3/2019 CT chest: Decrease in the primary tumor in the LLL, improvement in adenopathy
- 3/2019: Maintenance durvalumab
  - After 2 infusions: Cough flares, prescribed Z-pak → improvement but not resolved
  - Durvalumab held x 6 weeks
- 2nd opinion
  - Scans: Residual small lymph nodes and evolving changes related to the previous radiation therapy, but no findings suggestive of drug-related pneumonitis
  - Recommendation: Resume durvalumab

60-year-old woman and nonsmoker (from the practice of Ms Waxman)

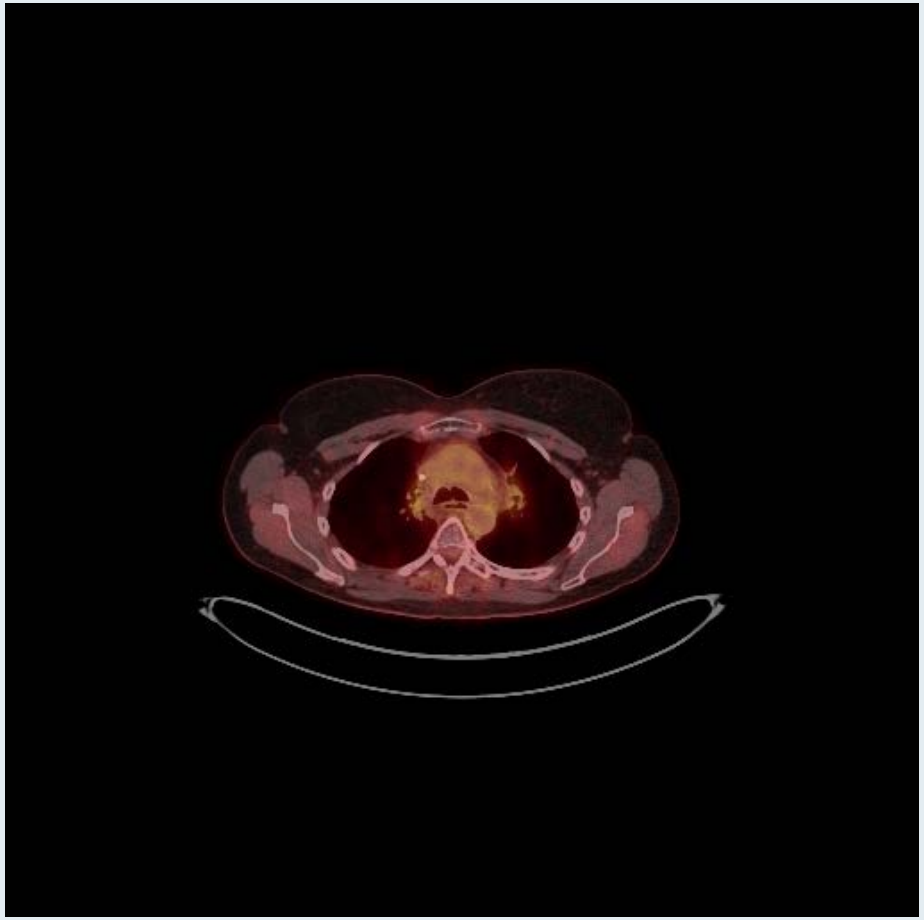
Baseline Images

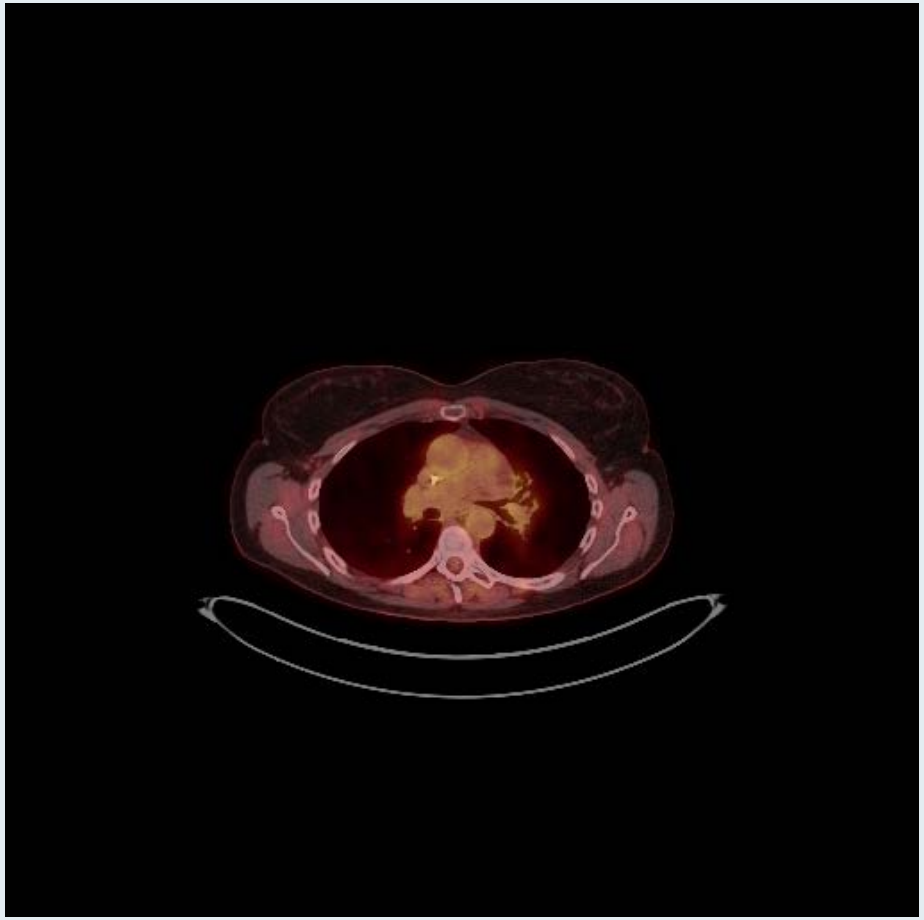




60-year-old woman and nonsmoker (from the practice of Ms Waxman)

After Concurrent Chemo/RT, on Durvalumab

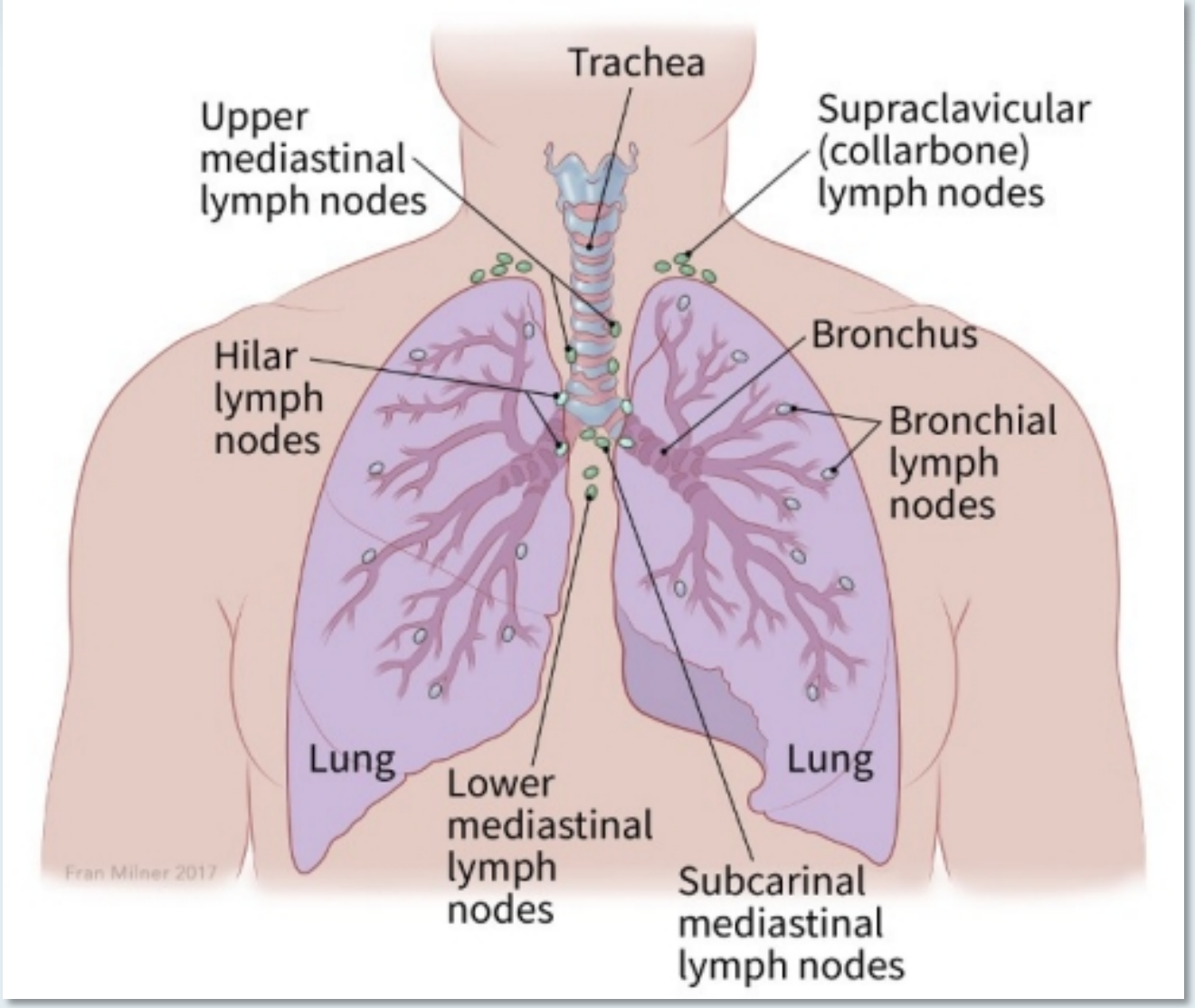




Staging Regional Lymph Nodes in Lung Cancer

NX	Regional lymph nodes cannot be assessed
N0	No regional node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in the contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

Lung Anatomy: Distribution of Lymph Nodes



Lung Cancer Stage Grouping (AJCC 8th Edition)

T/M	Label	N0	N1	N2	N3
T1	T1a ≤1	IA1	IIB	IIIA	IIIB
	T1b >1-2	IA2	IIB	IIIA	IIIB
	T1c >2-3	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Visc Pl*	IB	IIB	IIIA	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB
T3	T3 >5-7	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

Detterbeck FC et al. *Chest* 2017;151(1):193-203.

Stage Distribution at Diagnosis of Patients with Lung Cancer

SEER Analysis: (2004-2010, N = 344,797)

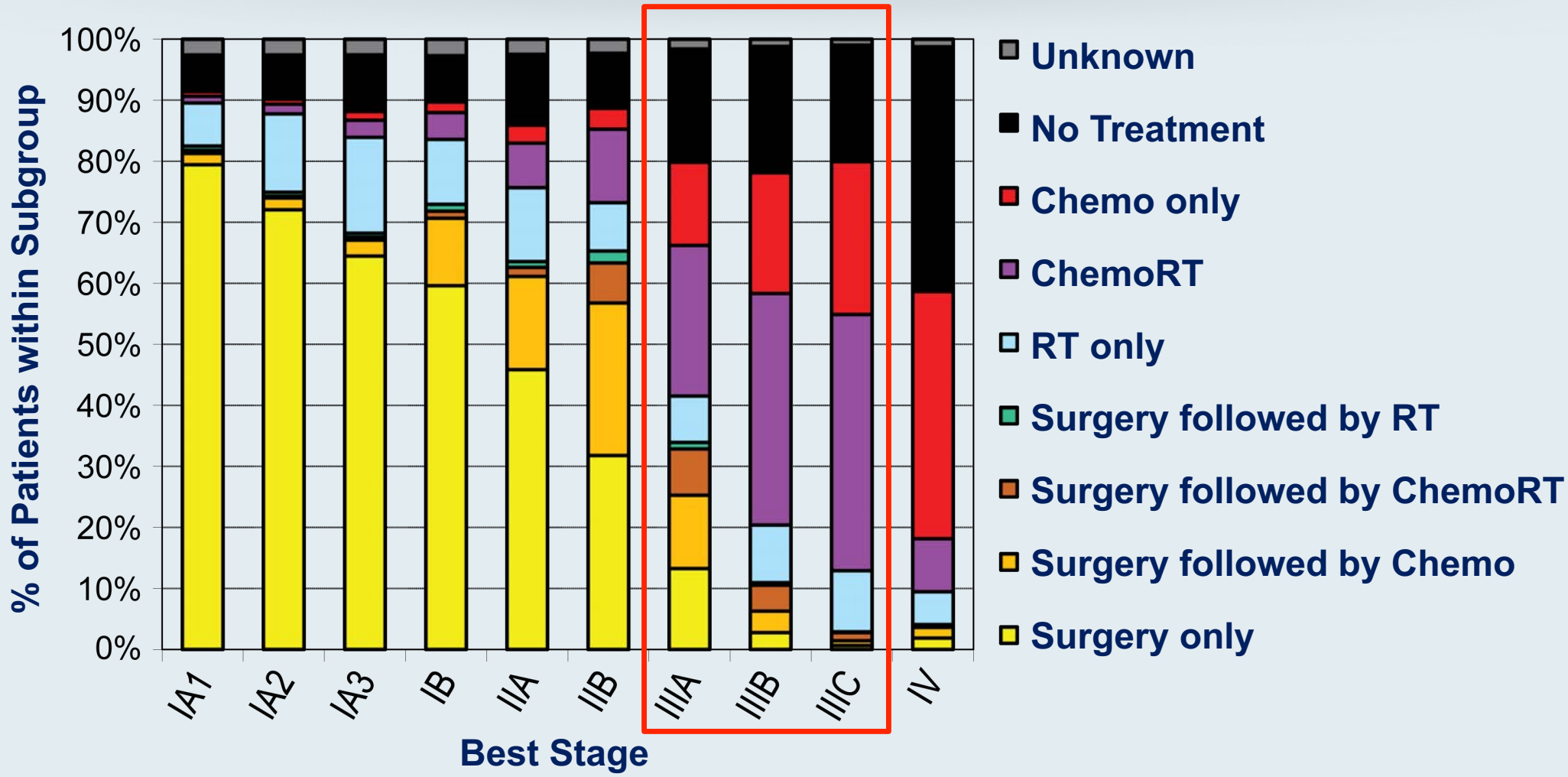
Stage at Diagnosis (AJCC, 7th Edition)	I	II	III	IV	Unknown
% of Patients	18%	7%	19%	49%	5%
Est No. of Patients in USA, 2019	41,067	15,971	43,349	111,794	11,408

Occult disease accounts for approximately 1.5%

Chen VW et al. *Cancer* 2014;120:3781-92. Siegel RL et al. *CA Cancer J Clin*. 2019 Jan;69(1):7-34.

Treatment Received for NSCLC (2000-2012, N = 780,294)

Based on the National Cancer Data Base (NCDB) according to TNM 8th Edition



Chansky K et al. *J Thorac Oncol* 2017;12(7):1109-21.

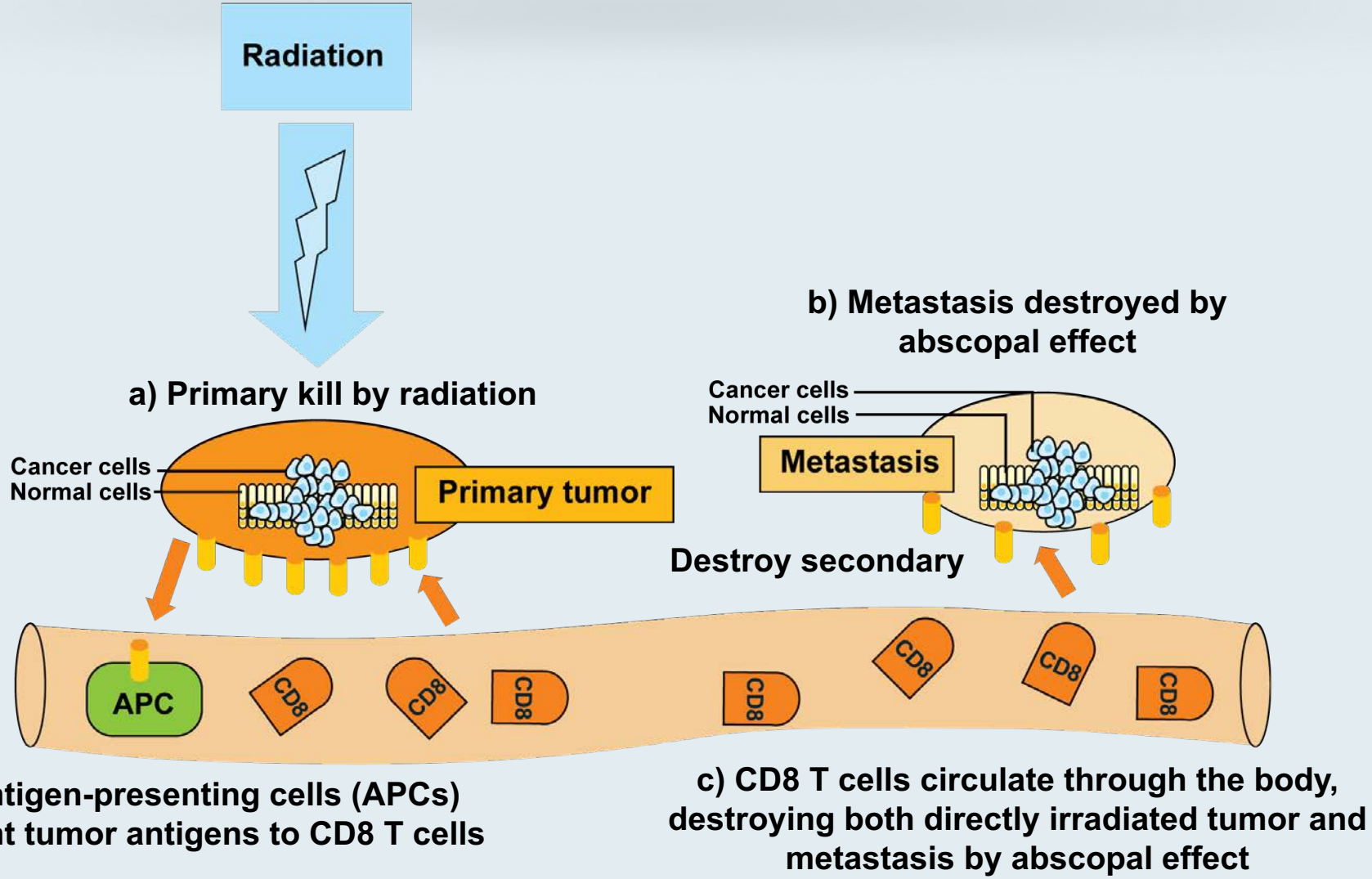
Selected Negative Trials after concurrent chemotherapy + radiation

TRIAL	DESIGN	MEDIAN OS	HR	P VALUE
CALGB 39801[1]	Induction chemo ➡ CRT vs. cCRT	14 vs 12	N/R	0.3
LUN 01-24[2]	cCRT ➡ docetaxel vs cCRT	23.2 vs 21.2	N/R	0.883
SWOG S0023[3]	cCRT ➡ docetaxel ➡ placebo vs cCRT ➡ docetaxel ➡ gefitinib	35 vs 23	0.63	.0013
RTOG 0617[4]	cCRT ➡ chemo vs cCRT + cetuximab ➡ chemo	24 vs 25	1.07	0.29
START[5]	Sequential or cCRT ➡ placebo vs Sequential or cCRT ➡ tecemotide	25.6 vs 22.3	0.88	.123

1. Vokes et al J Clin Oncol 2007
2. Hanna et al J Clin Oncol 2008
3. Kelly et al J Clin Oncol 2008
4. Bradley et al Lancet Oncol 2015
5. Butts et al Lancet Oncol 2014

Courtesy of Benjamin Levy, MD

Proposed Mechanism for the Abscopal Effect



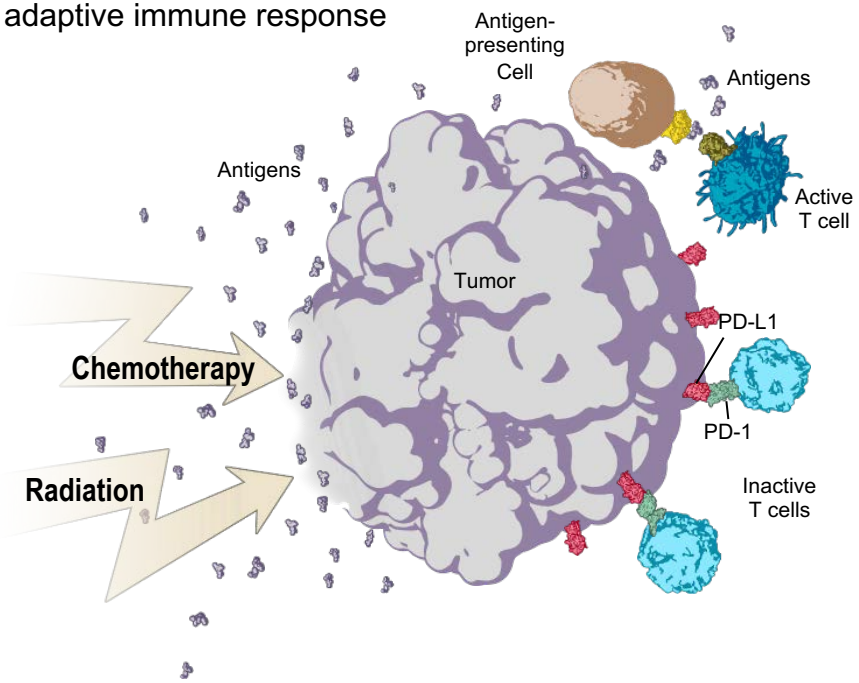
Wani SQ et al. *Cureus* 2019;11(2):e4100.

Rationale of checkpoint inhibitors after chemoradiation[1–6]

CHEMORADIATION

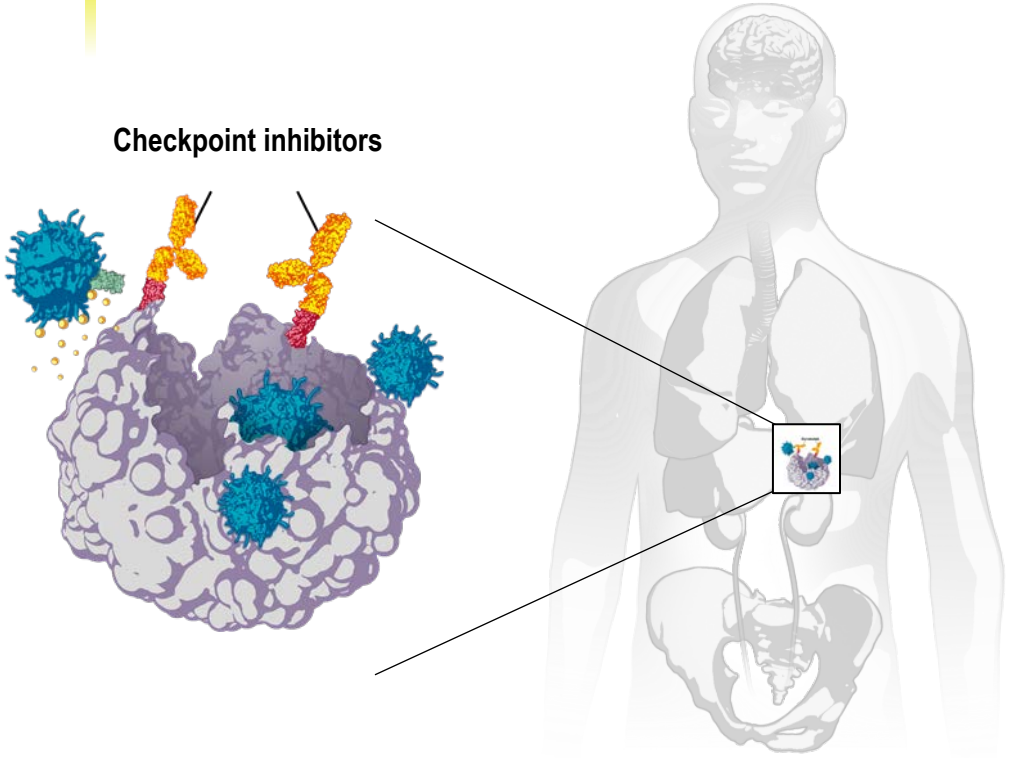
Chemoradiation induces tumor antigen release and an adaptive immune response

PD-L1 overexpression leads to immune cell evasion



CHECKPOINT INHIBITOR

PD-1/PD-L1 inhibitors reverse immune suppression and lead to a systemic antitumor response



Courtesy of Benjamin Levy, MD

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When was the last time that you encountered a patient with lung cancer who continued to smoke after their diagnosis?

a. Within the last week

b. 1 week to 4 weeks ago

c. 1 month to 6 months ago

d. 6 months to 12 months ago

e. More than 1 year ago

f. Never

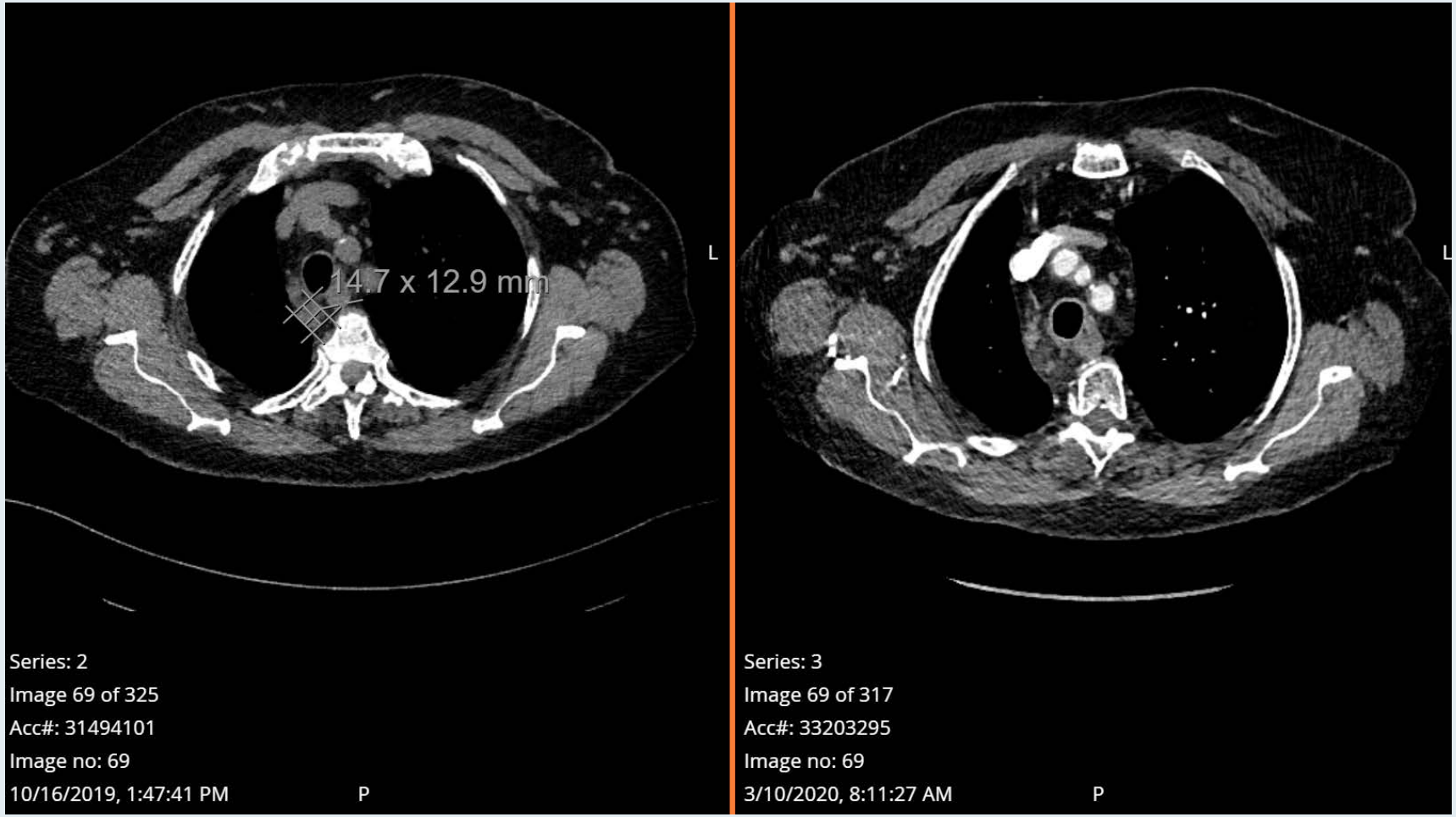
71-year-old woman (from the practice of Ms Sandy)

- 8/2018: Stage IB NSCLC → Resected 2.3-cm RLL
  - PMH of PVD, COPD and HTN
- 10/2019: Recurrence, with hilar adenopathy
- 12/2019 Bronchoscopy: Poorly differentiated carcinoma
- 12/2019 - 2/2020: Concurrent weekly paclitaxel/carboplatin x 8
  - Moderate esophagitis, no weight loss
  - SOB worsened on chemo/radiation
  - CINV significant after week 1, added IV aprepitant
  - HTN (compliance issues), increased amlodipine to 10mg
- Patient stopped smoking; previously 2 packs per day
- 3/2020 CT chest: Stable disease → S/P maintenance durvalumab x 2 → 4/22/20 monthly durvalumab due to COVID-19

71-year-old woman (from the practice of Ms Sandy)

Recurrence on 10/2019 CT chest with hilar lymphadenopathy

CT chest 3/10/2020 stable disease



PACIFIC: Study Design

Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study[1]

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history

Durvalumab 10 mg/kg q2w for up to 12 months N=476

Placebo 10 mg/kg q2w for up to 12 months N=237

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

Key secondary endpoints

- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

*Using the Ventana SP263 immunohistochemistry assay

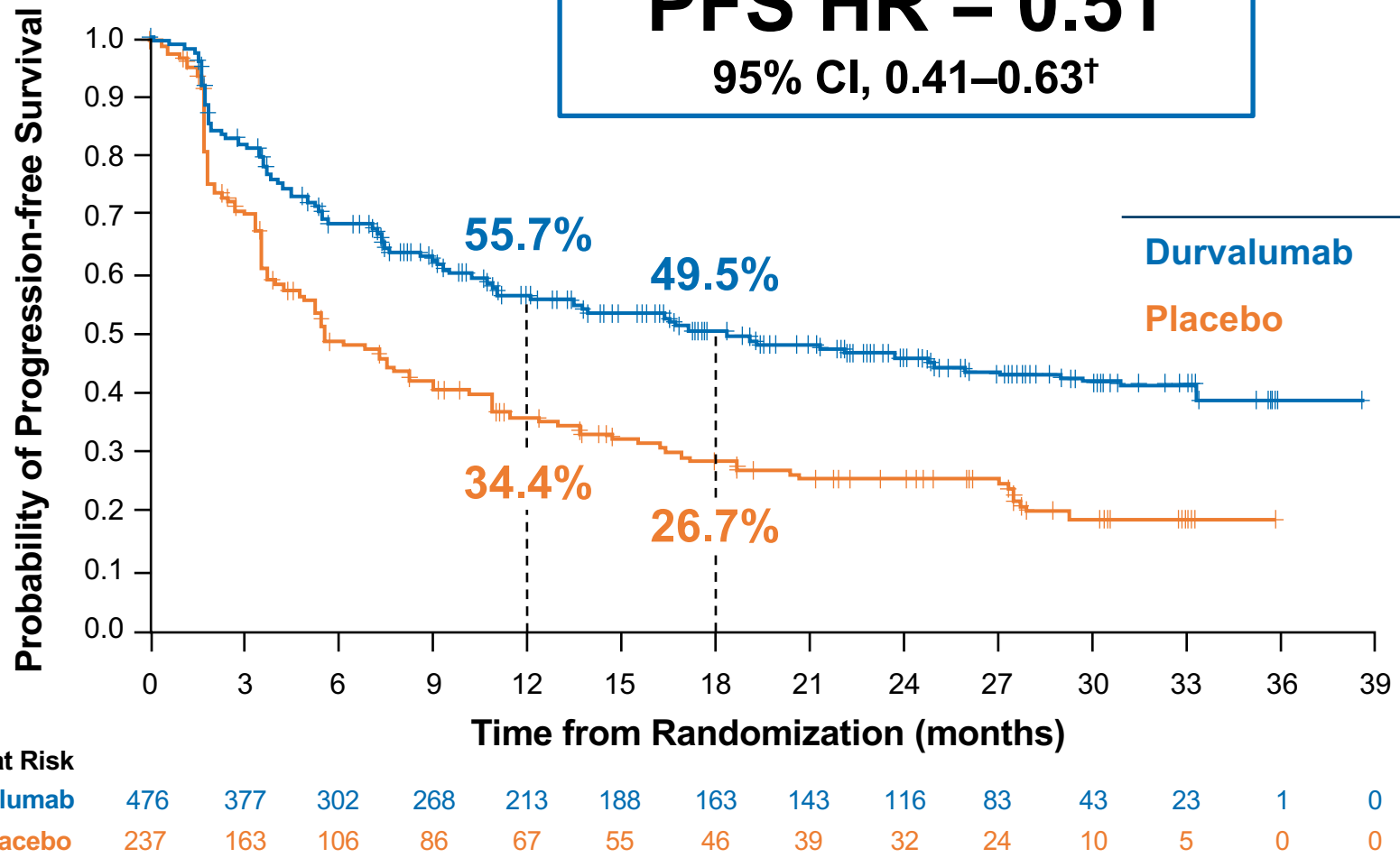
†Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression. BICR, blinded independent central review; cCRT, concurrent CRT; PFS2, time to second progression; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis. ClinicalTrials.gov number: NCT02125461

1. Antonia SJ, et al. N Engl J Med 2017;377:1919–29.

Courtesy of Benjamin Levy, MD

Updated Progression-free Survival by BICR* (ITT)

PFS HR = 0.51
95% CI, 0.41–0.63†



	No. of events / No. of patients (%)	Median PFS (95% CI) months
Durvalumab	243/476 (51.1)	17.2 (13.1–23.9)
Placebo	173/237 (73.0)	5.6 (4.6–7.7)

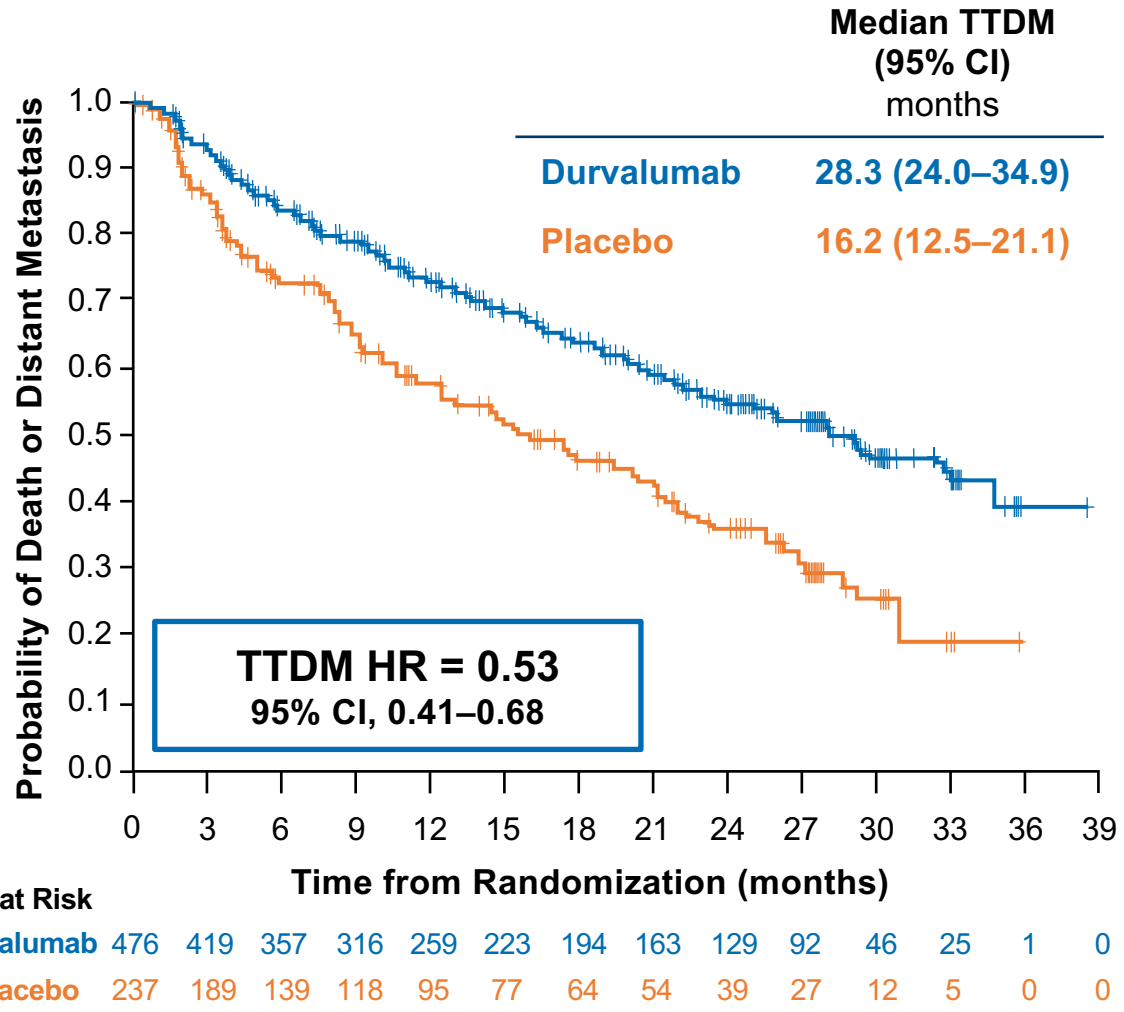
No. at Risk														
Durvalumab	476	377	302	268	213	188	163	143	116	83	43	23	1	0
Placebo	237	163	106	86	67	55	46	39	32	24	10	5	0	0

Antonia SJ et al. *N Engl J Med* 2018;379(24):2342-50.

Courtesy of Benjamin Levy, MD

*Median duration of follow-up was 25.2 months (range 0.2–43.1)
†No formal statistical comparison was made because the study had achieved significance for PFS at the first planned IA (data cutoff of Feb 13, 2017)

Updated Time to Death or Distant Metastasis (TTDM) by BICR* (ITT)



Antonia SJ et al. *N Engl J Med* 2018;379(24):2342-50.

Updated Incidence of New Lesions by BICR* (ITT)

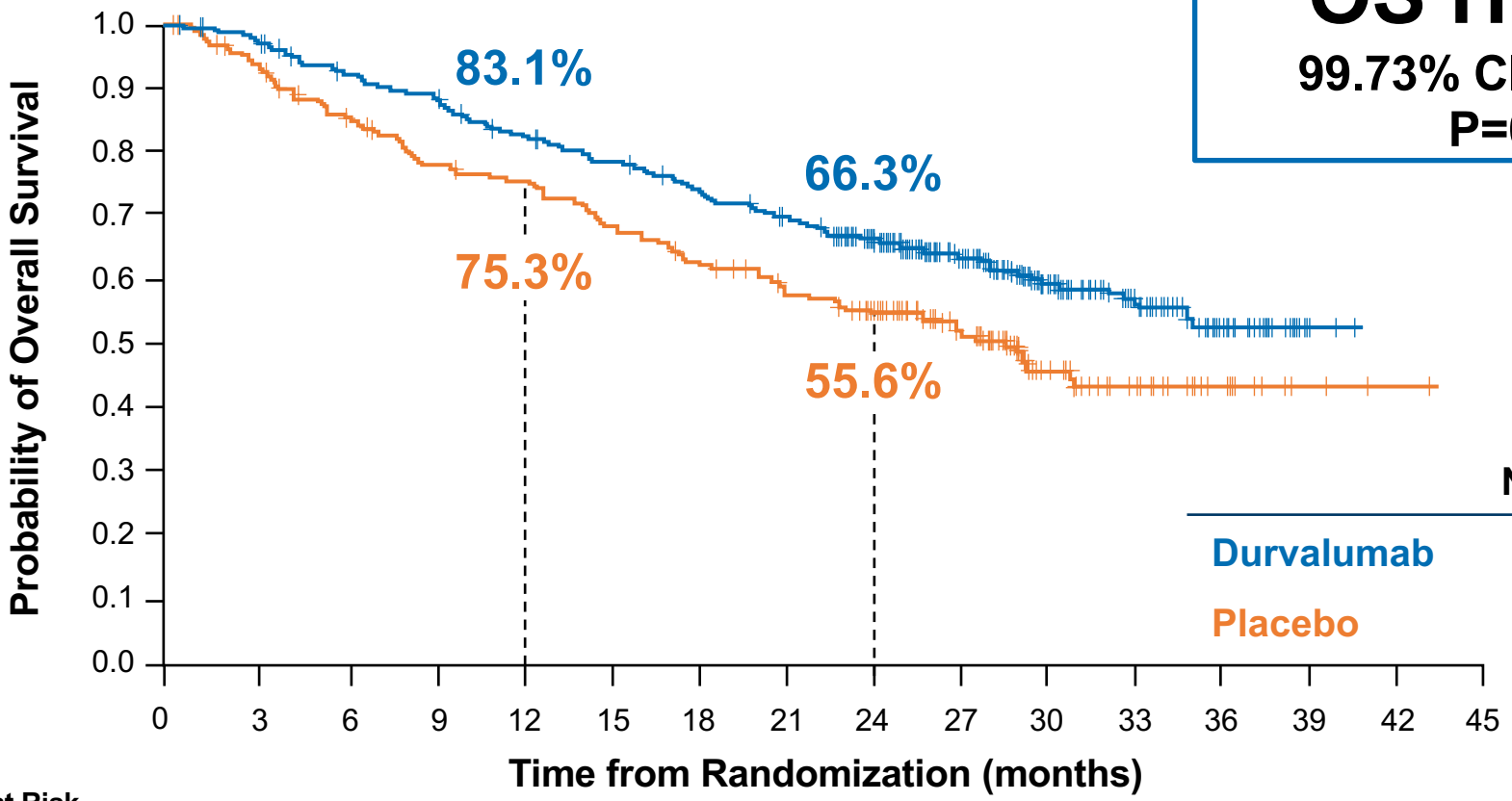
New Lesion Site†	Durvalumab (N=476)	Placebo (N=237)
Patients with any new lesion, n (%)	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal	3 (0.6)	5 (2.1)
Other	10 (2.1)	5 (2.1)

Courtesy of Benjamin Levy, MD

*Median duration of follow-up was 25.2 months (range 0.2–43.1)

†A patient may have had more than one new lesion site

Overall Survival* (ITT)



OS HR = 0.68
99.73% CI, 0.469–0.997†
P=0.00251

	No. of events / No. of patients (%)	Median OS (95% CI) months
Durvalumab	183/476 (38.4)	NR (34.7–NR)
Placebo	116/237 (48.9)	28.7 (22.9–NR)

No. at Risk																
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Antonia SJ et al. *N Engl J Med* 2018;379(24):2342-50.

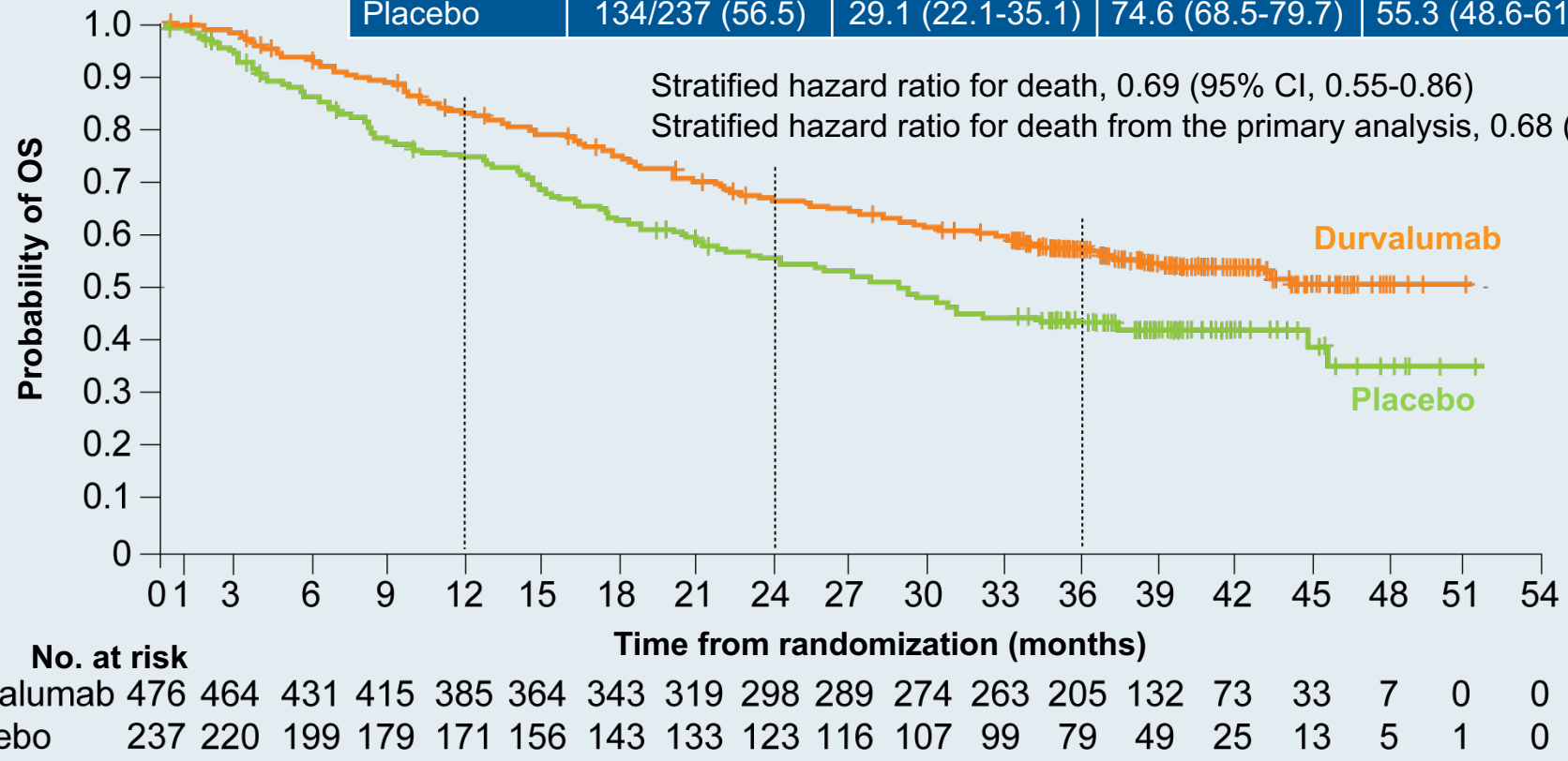
Courtesy of Benjamin Levy, MD

*Median duration of follow-up for OS was 25.2 months (range 0.2–43.1)
†Adjusted for interim analysis

NR, not reached

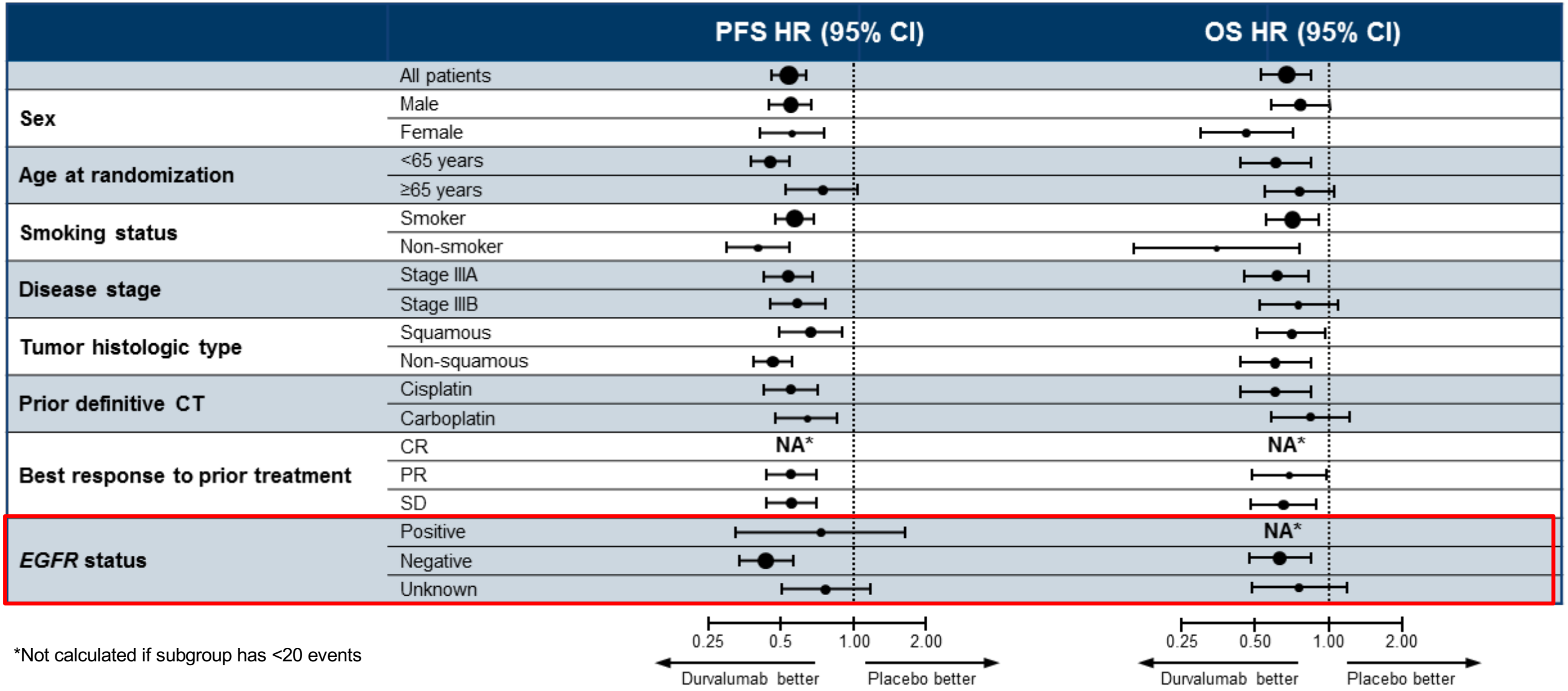
PACIFIC: 3-Year Overall Survival Analysis in the Intention-to-Treat Population

	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
Durvalumab	210/476 (44.1)	NR (38.4-NR)	83.1 (79.4-86.2)	66.3 (61.8-70.4)	57.0 (52.3-61.4)
Placebo	134/237 (56.5)	29.1 (22.1-35.1)	74.6 (68.5-79.7)	55.3 (48.6-61.4)	43.5 (37.0-49.9)



Gray JE et al. *J Thorac Oncol* 2020;15(2):288-93.

Progression-free and Overall Survival by Subgroup (ITT)



*Not calculated if subgroup has <20 events

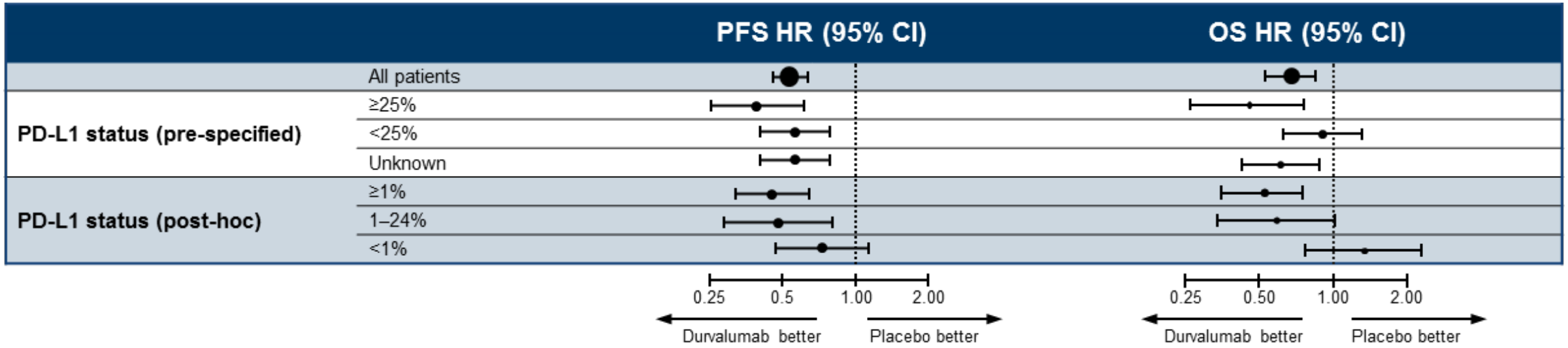
Antonia SJ et al. *N Engl J Med* 2018;379(24):2342-50.

Courtesy of Benjamin Levy, MD

Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of March 22, 2018

NA, not available

PACIFIC Trial: Subgroup Analysis by PD-L1 Status



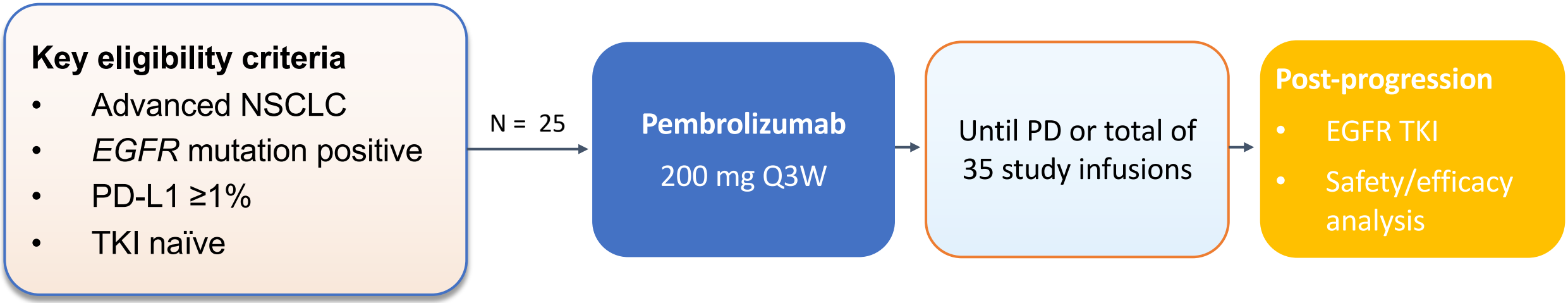
- Important facts regarding PD-L1 status:
  - PD-L1 testing was not required
  - 37% of patients with unknown PD-L1 status
  - PD-L1 status was obtained pre-CRT (getting a sample post-CRT medically not feasible)
  - PD-L1 expression-level cutoff of 1% was part of an unplanned post-hoc analysis requested by a health authority

Antonia SJ et al. *N Engl J Med* 2018;379(24):2342-50.

Courtesy of Benjamin Levy, MD

Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of March 22, 2018

Immunotherapy in *EGFR*-Positive Patients[1]



- **Primary objective:** ORR of pembrolizumab prior to TKI
- **Secondary objectives:** safety, PFS, OS of pembrolizumab; safety and efficacy of subsequent EGFR TKI therapy

Planned enrollment: 25 patients

Closed (October 2017): 11 patients (8 with PD-L1 >50%) enrolled

→ **RR: 0%**

1. Lisberg AE et al. *J Clin Oncol*. 2018;36(suppl 15):9014.

Courtesy of Benjamin Levy, MD

Studies of Immune Checkpoint Inhibition in Unresectable and/or Locally Advanced NSCLC

Study	Phase (N)	Study population	Treatment
Hoosier CRN LUN 14-179 (NCT02343952)	II (N = 92)	• Unresectable Stage III NSCLC	• CRT → Pembrolizumab
Rutgers Cancer Institute (NCT02621398)	I (N = 23)	• Unresectable Stage II or Stage IIIA/IIIB NSCLC	• CRT + Pembrolizumab at start of CRT, 2 weeks before end of CRT or 2-4 weeks after CRT
PACIFIC-2 (NCT03519971)	III (N = 300)	• Unresectable Stage III NSCLC	• CRT + Durvalumab → Durvalumab until PD • CRT + Placebo → Placebo until PD

CRT = chemoradiation therapy

Durm G et al. ASCO 2018;Abstract 8500; Jabbour SK et al. ASCO 2019;Abstract 8511; www.clinicaltrials.gov

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- Case Presentation: Ms Sandy – 68-year-old woman

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A 75-year-old patient with metastatic non-small cell lung cancer and a PD-L1 level of 60% is being started on pembrolizumab. How often should treatment be administered?

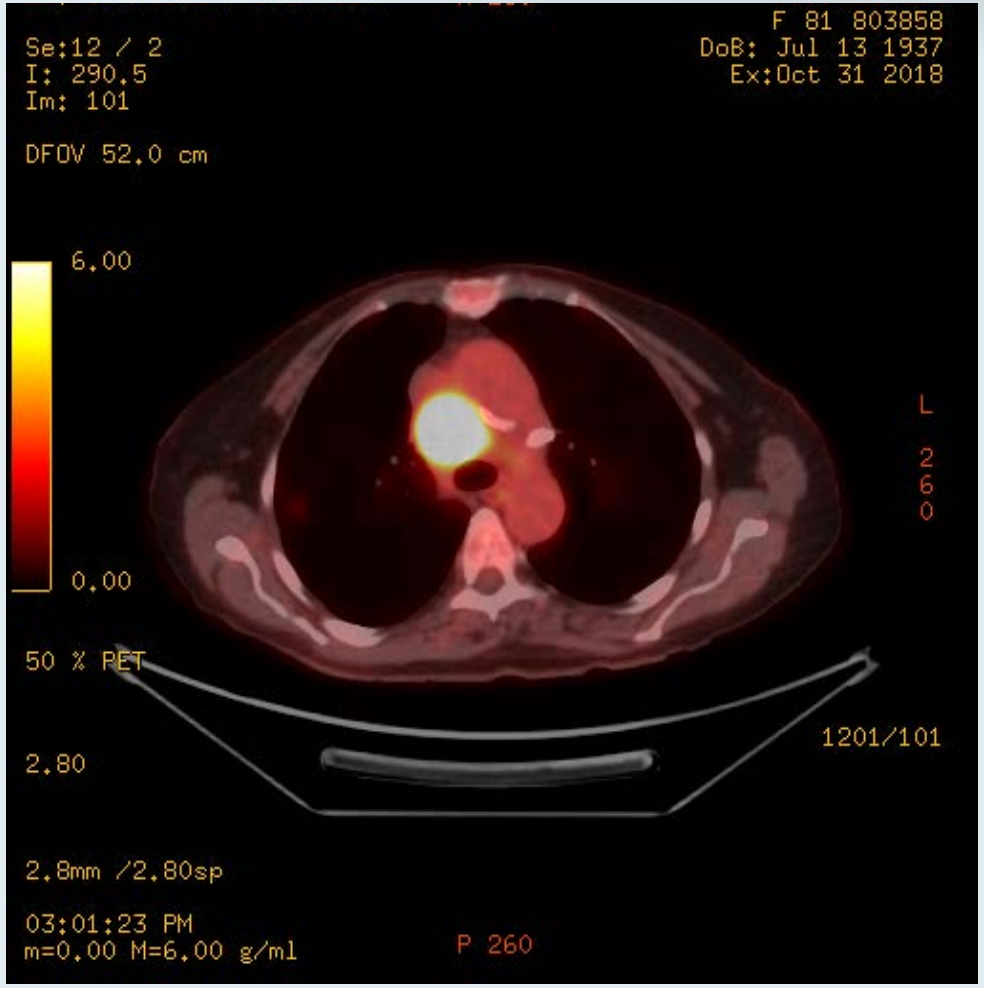
a. Every 3 weeks

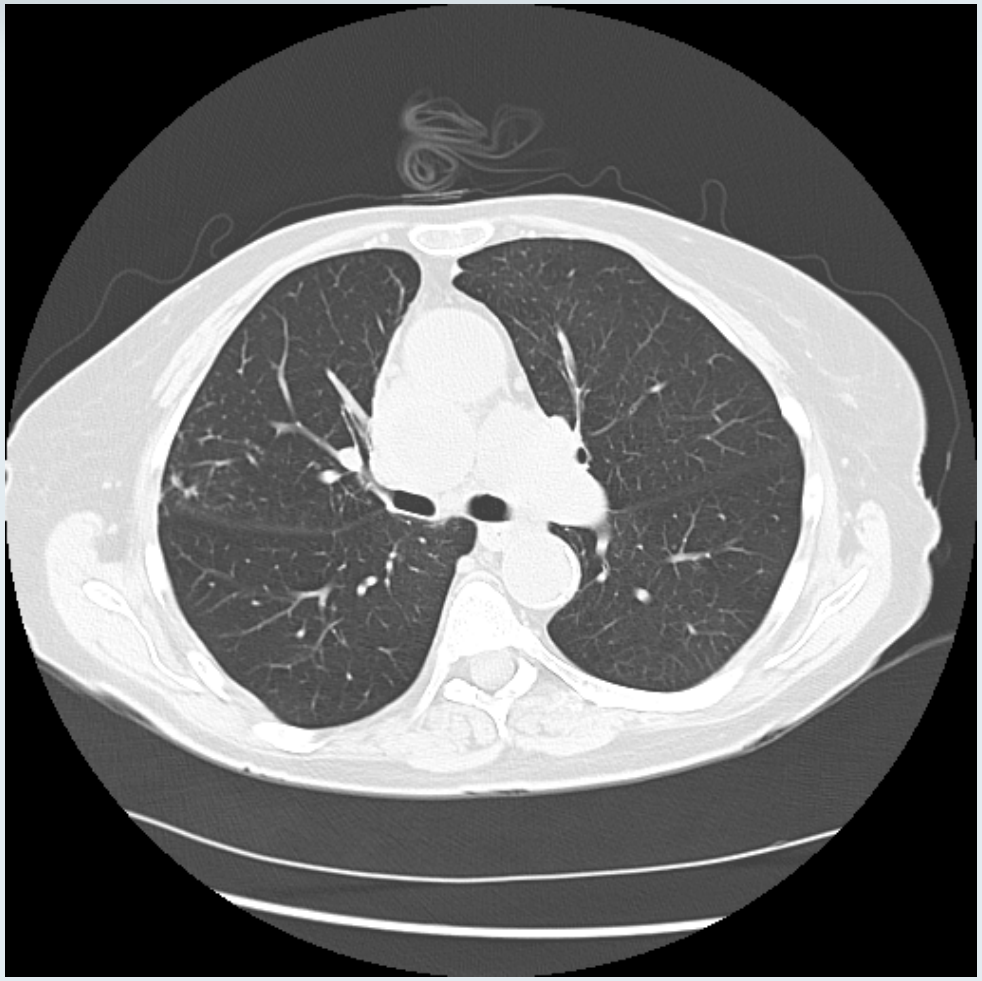
b. Every 6 weeks

81-year-old woman (from the practice of Ms Waxman)

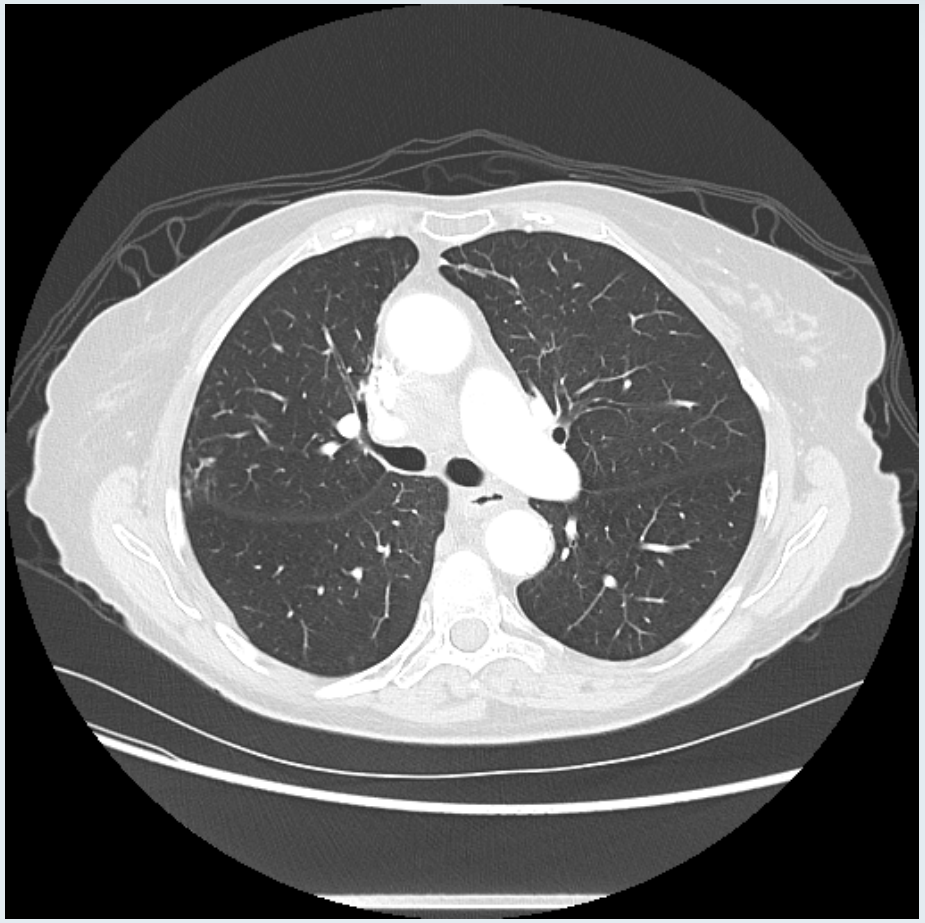
- 10-11/2018: Presents with weakness, SOB, and weight loss
  - Work up: T1a N2 adenocarcinoma of the lung, no driver mutations identified
- 12/2018 – 1/2019: Concurrent weekly carboplatin/paclitaxel and radiation therapy
- 2/2019 – 1/2020: Maintenance durvalumab
  - 1/2020 PET/CT: Multiple new bilateral pulmonary nodules, suspicious for metastatic disease
  - Durvalumab held
  - Biopsy of left lung nodule: Lung parenchyma with features of organizing pneumonia, no evidence of malignancy

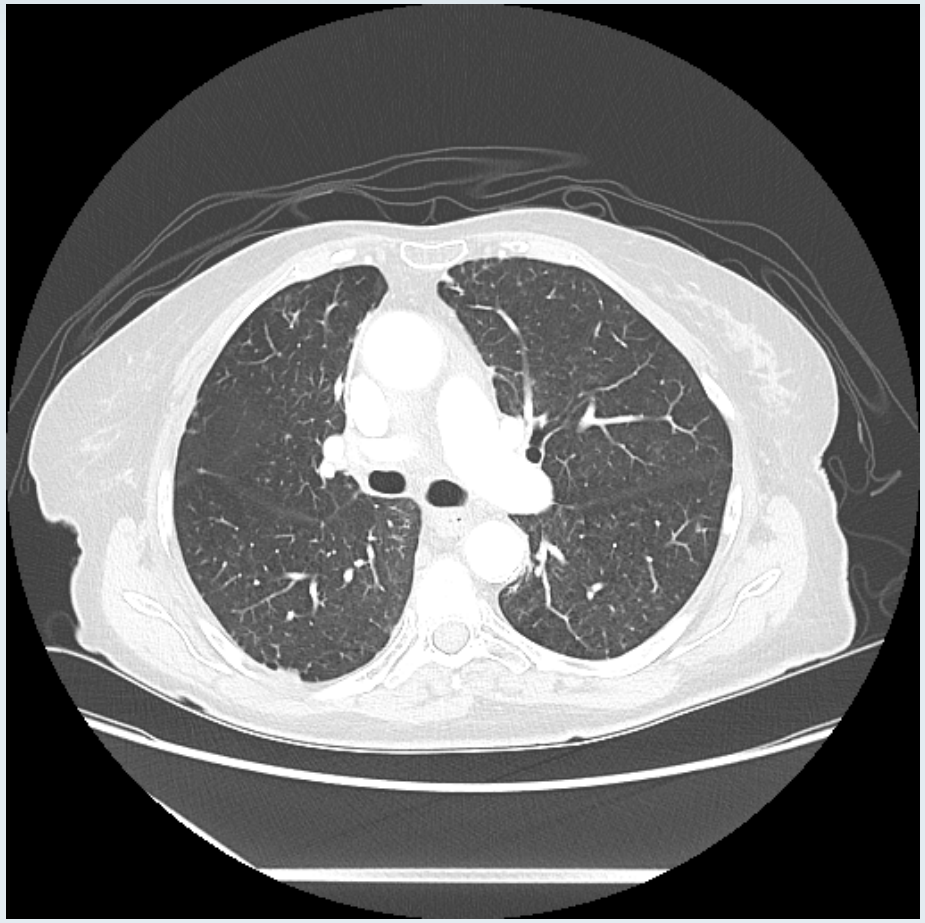
81-year-old woman (from the practice of Ms Waxman)
Baseline Findings





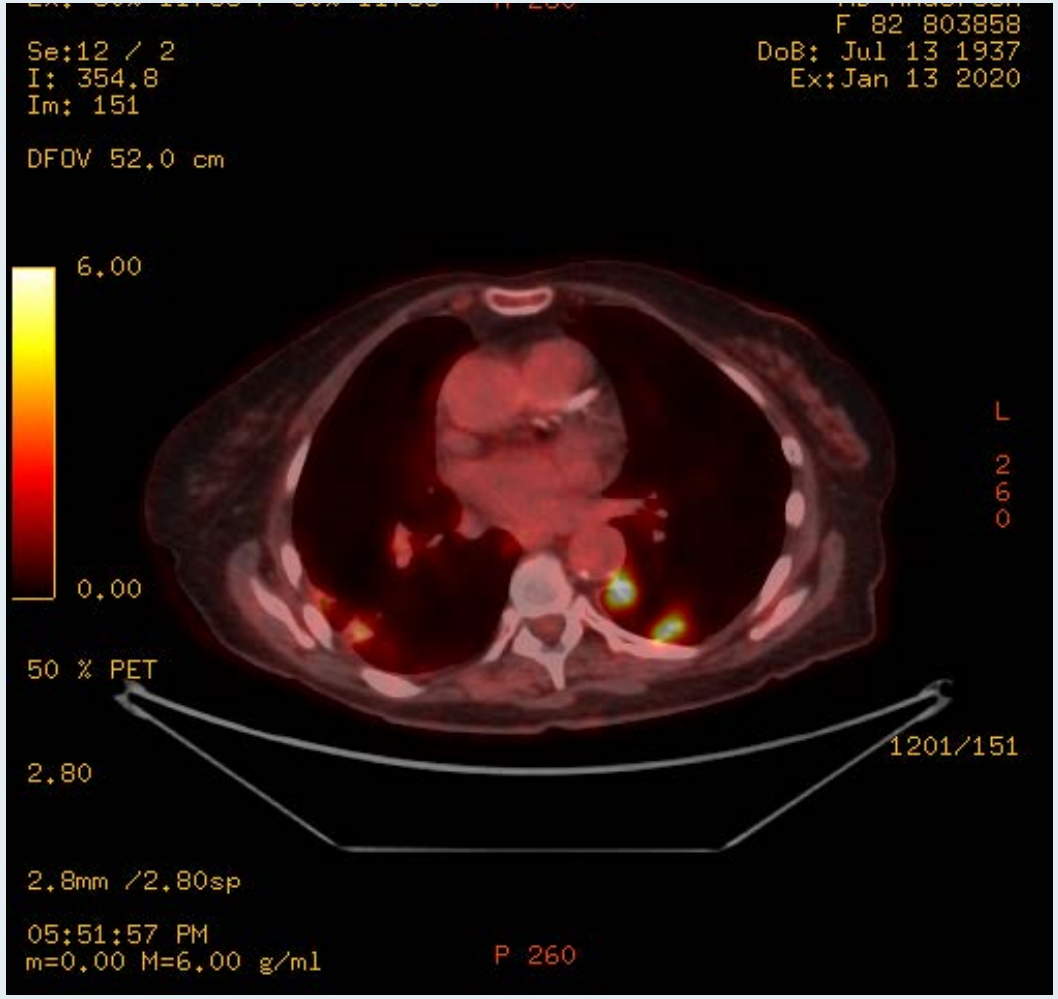
81-year-old woman (from the practice of Ms Waxman)
Response to Treatment



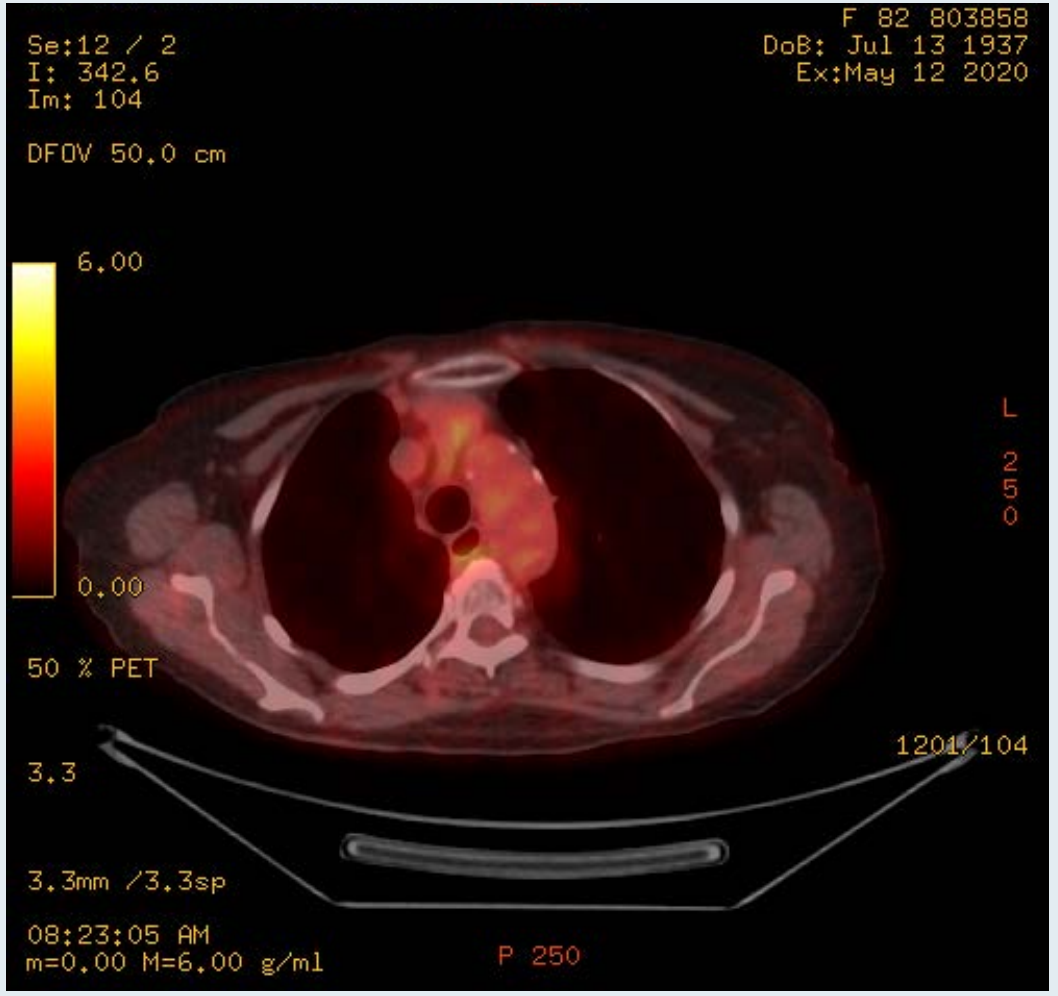


81-year-old woman (from the practice of Ms Waxman)

Suspicious Findings



Newest Scan



PACIFIC: Overall Toxicity

- PACIFIC (12 months durvalumab consolidation)
  - Grade 3-4 AEs seen in 30.5% (vs. 26.1% with placebo)
  - Immune toxicity in 24.4% (vs. 8.1% with placebo)
  - Discontinuation due to AE was 15.4% (vs. 9.8% with placebo)

Common AEs (any cause, any grade)

	Durvalumab	Placebo
Cough	35.2%	25.2%
Fatigue	24.0%	20.5%
Dyspnea	22.3%	23.9%
Diarrhea	18.5%	19.7%

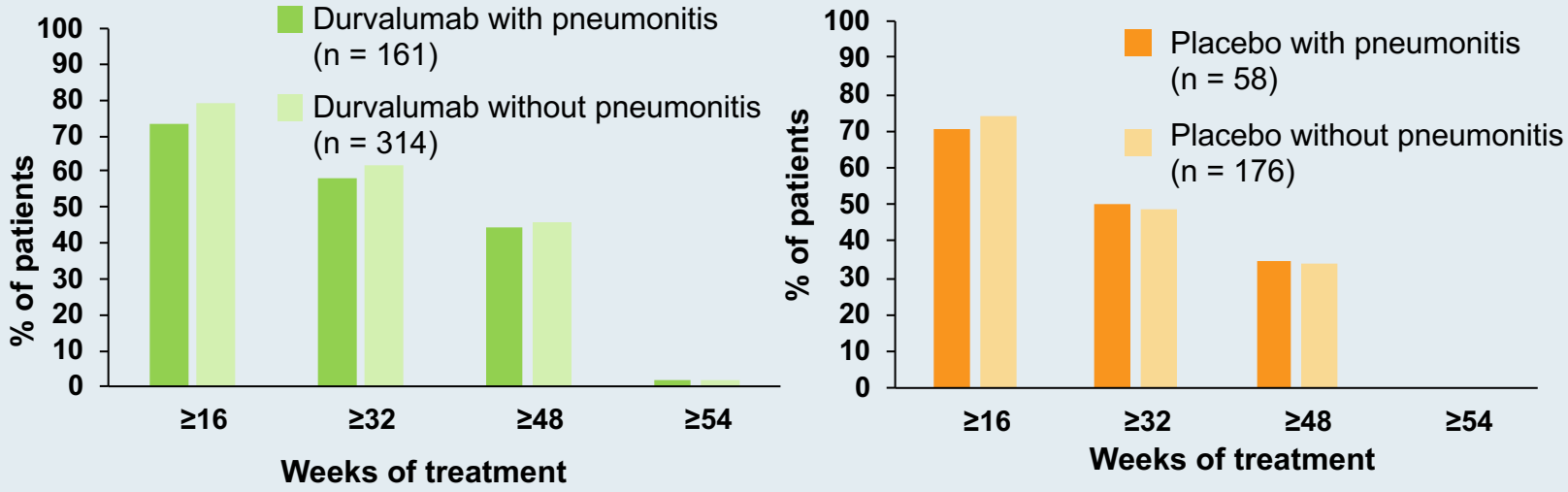
Antonia, NEJM 2018
Naidoo, ASCO 2020

Courtesy of Stephen V Liu, MD, PhD

PACIFIC: Incidence and Time to Onset of Pneumonitis, and Treatment Exposure

Pneumonitis	Durvalumab (N = 475)	Placebo (N = 234)
Any grade pneumonitis or radiation pneumonitis	96.8%	94.9%
Grade 3/4 pneumonitis or radiation pneumonitis	29.9%	26.1%
Median time to onset from 1st dose	55.0 days	55.0 days
Median time to onset from radiotherapy	73.0 days	76.5 days
Median duration	64.0 days	57.0 days

- Overall treatment exposure was similar for patients with or without pneumonitis



Vansteenkiste JF et al. *Proc IASLC/WCLC* 2018;Abstract MA05.02.

Multi-institutional Study of Pneumonitis After Durvalumab and Chemoradiotherapy: Impact on Survival Outcomes

- N = 36 patients with NSCLC (89% Stage III) treated according to PACIFIC paradigm
- Grade ≥2 pneumonitis
  - 3-months: 26%
  - 6-months: 29%
- Median time to development of pneumonitis after completion of RT: 71 days (range: 29-270)
- The development of pneumonitis did not impact survival outcomes

	Pneumonitis	No pneumonitis	*p*-value
PFS at 9 months	70%	66%	0.94
OS at 9 months	100%	83.3%	0.32

Sita T et al. IASLC North America 2019;Abstract OA03.03.

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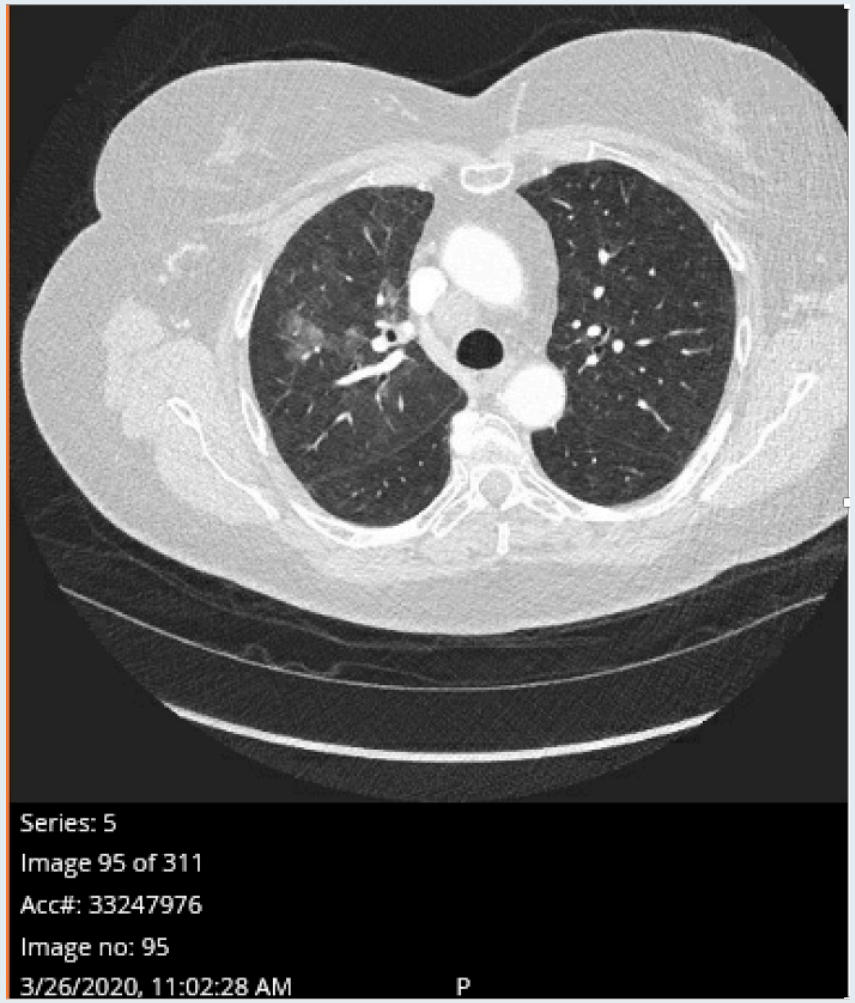
68-year-old woman (from the practice of Ms Sandy)

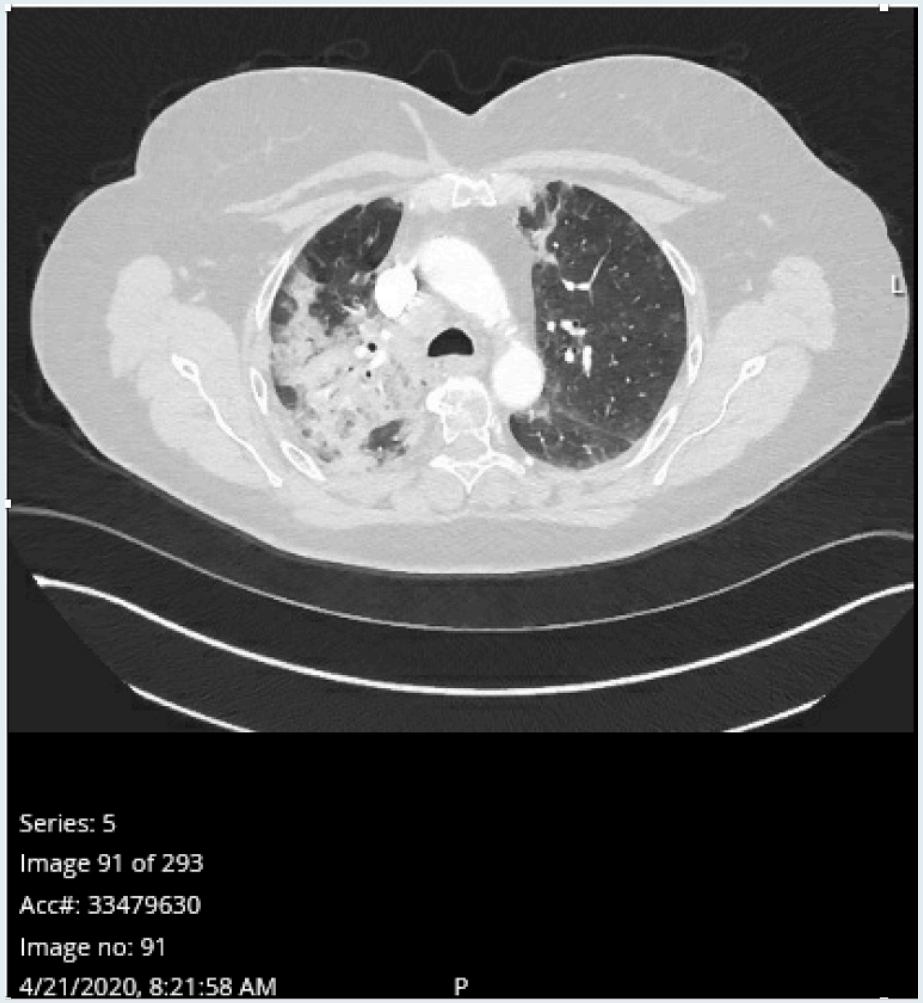
- Screening CT → PET/Bronch/EBUS: RUL mass, LN levels 4R and 11R: Adenocarcinoma
  - PMH of anxiety, PAC c BL iliac arterial stents
- Concurrent paclitaxel/carboplatin weekly x 6 with daily RT x 7
  - Tolerated quite well, moderate esophagitis on last week of chemo/rads
  - Post chemo/rads scan: No disease progression
- Late 3/2020: Initiates maintenance durvalumab
- 4/10/2020: SOB, progressively worsened
- 4/21/2020 CT chest: Pneumonitis, attributed to RT due to timing, appearance
  - Held durvalumab, Prednisone 60mg (tapered off 5/13)
  - COVID-19 testing: Negative
- 5/15/2020 CT chest: Pneumonitis now more consistent with radiation fibrosis than GGO's
- 5/18/2020 telehealth visit: Doing well, still coughing
  - Due to substantial radiation changes, waiting 2 more weeks before resuming durvalumab

68-year-old woman (from the practice of Ms Sandy)

3/26/2020 CT chest: 1-month post-RT scan, pre-durvalumab

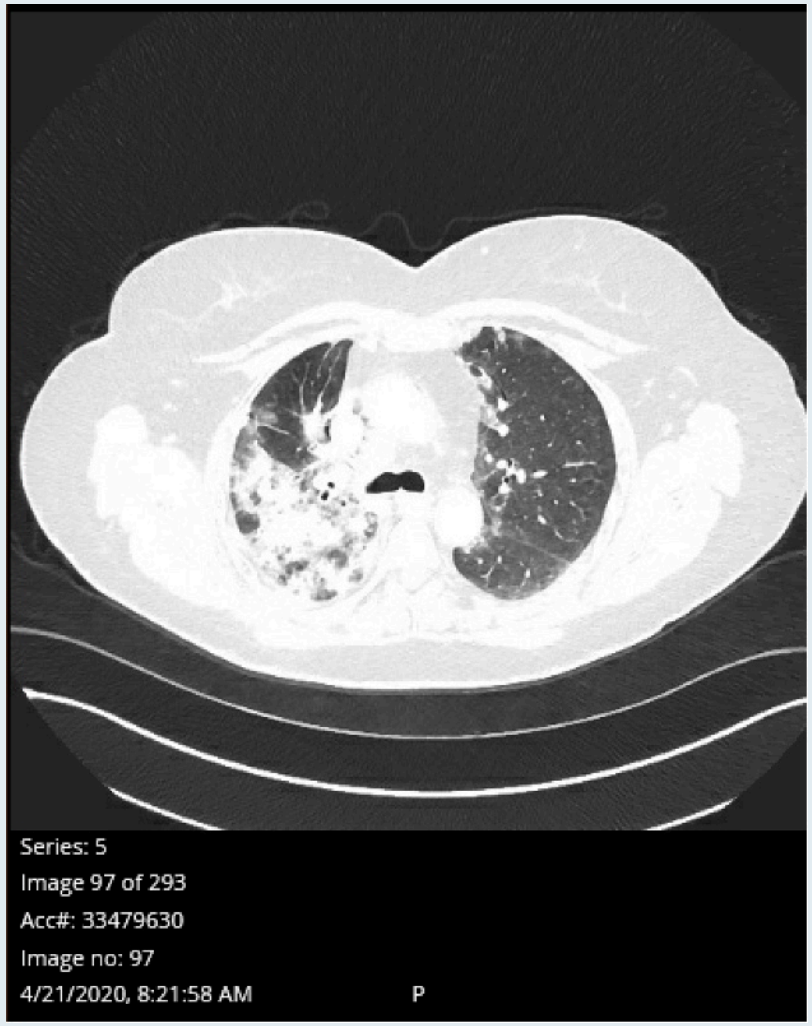


4/21/2020 CT chest: Pneumonitis

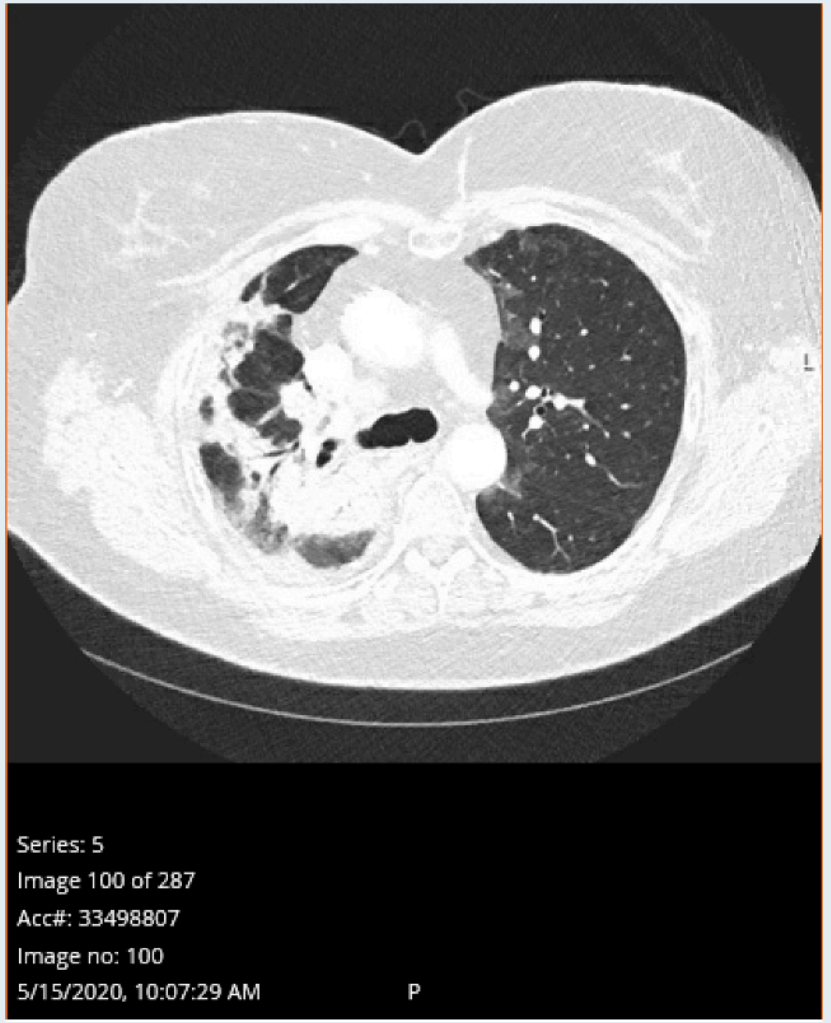


68-year-old woman (from the practice of Ms Sandy)

4/21/2020 CT chest



5/15/2020 CT chest



At the Jersey Shore with her husband on their boat

Immune Mediated Toxicity

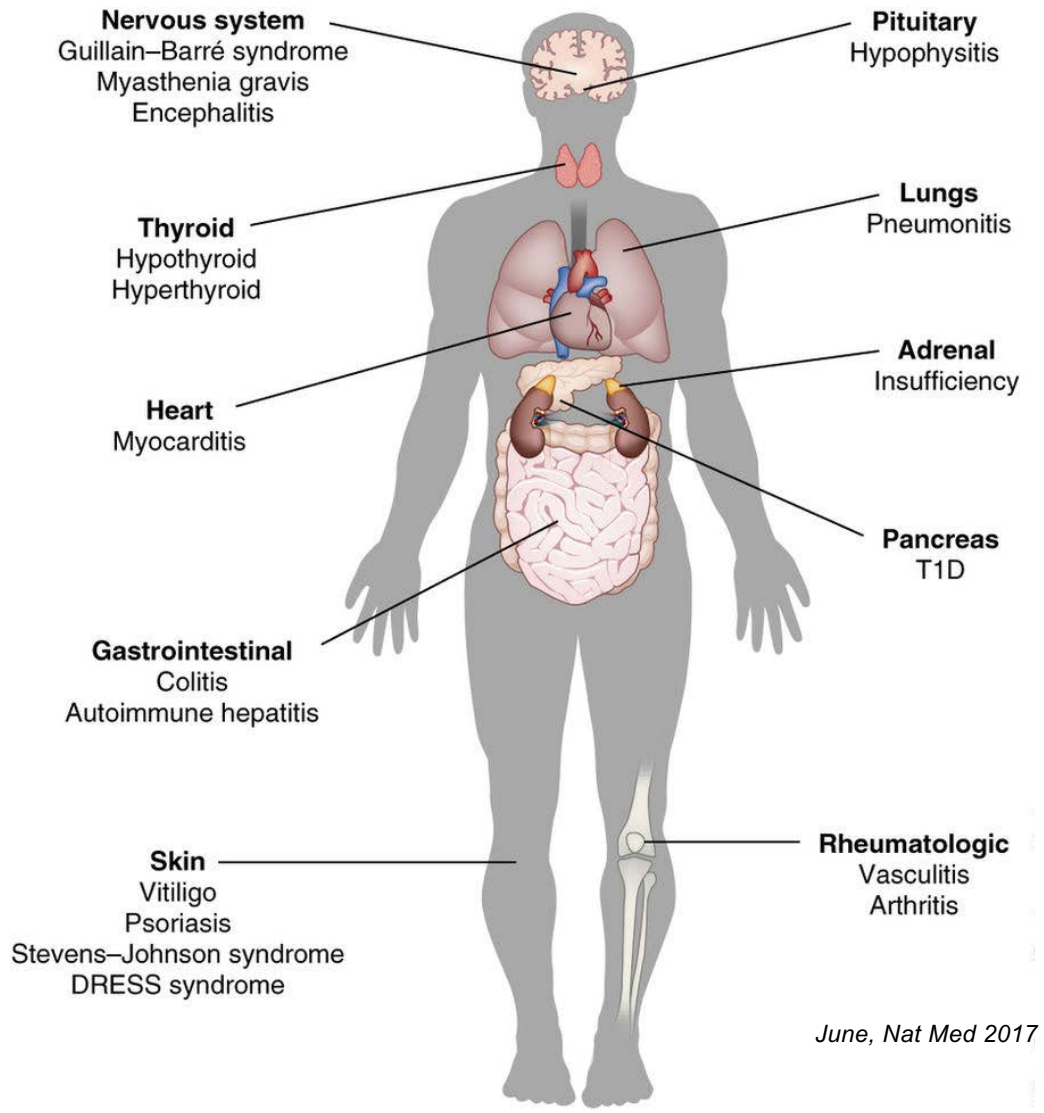
- Use of checkpoint inhibitors (including durvalumab)
  - Restore the ability of a patient's T-cells to attack tumors
  - Generate an immune-mediated anti-tumor response
  - The same checkpoints also prevent auto-immunity
  - Inhibiting those checkpoints can lead to autoimmune toxicity

June, Nat Med 2017

Courtesy of Stephen V Liu, MD, PhD

Immune Mediated Toxicity

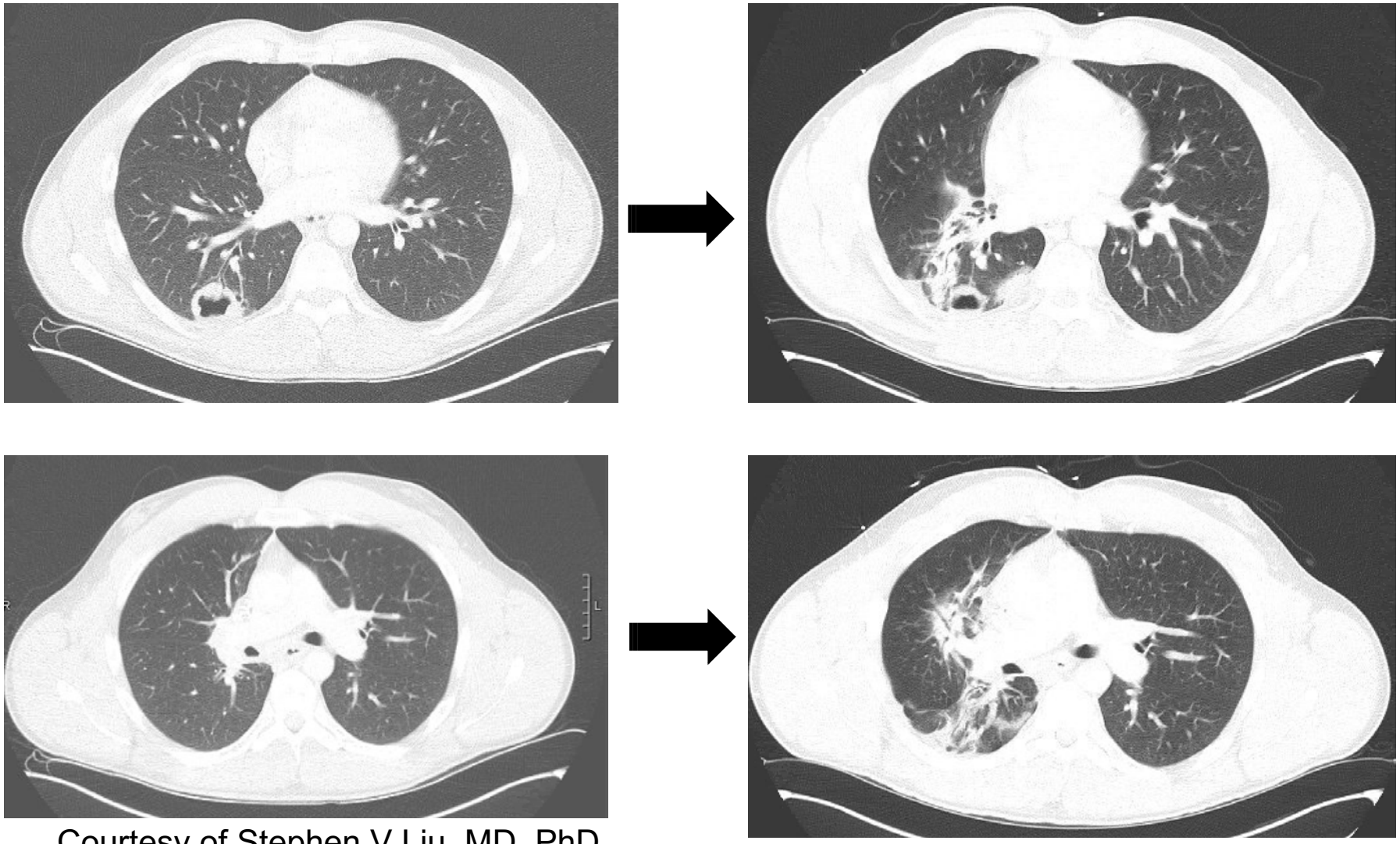
- Any organ/system can be affected
  - Special concern in stage III NSCLC for the lungs
  - Radiation alone can cause pneumonitis
  - Generally low grade, if any
  - Potential for serious toxicity
  - Early recognition is the key to avoiding poor outcomes



June, Nat Med 2017

Courtesy of Stephen V Liu, MD, PhD

Pneumonitis



Courtesy of Stephen V Liu, MD, PhD

Images from Stephen Liu, MD

Georgetown | Lombardi

Pneumonitis

- Pneumonitis differential
  - Radiation pneumonitis (consider radiation fields)
  - Immune mediated pneumonitis (consider timing)
  - Pneumonia or infection (consider other symptoms)
- If non-infectious, initial management of radiation pneumonitis and immune mediated pneumonitis is similar (steroid therapy)

Courtesy of Stephen V Liu, MD, PhD

Pneumonitis Management

- Symptoms must be monitored closely
  - Engage entire medical team and caregivers
  - New dyspnea/cough, new hypoxia warrant workup
    - Low threshold to hold therapy for evaluation
- Management guided by grade of pneumonitis
  - Grade 1: asymptomatic, no intervention needed
  - Grade 2: symptomatic, intervention required
  - Grade 3: severe symptoms, limiting ADLs, oxygen indicated
  - Grade 4: life threatening

Brahmer, JCO 2018

Courtesy of Stephen V Liu, MD, PhD

Pneumonitis Management

- Grade 2 symptomatic pneumonitis
  - Hold immunotherapy
  - Radiographic imaging
  - Steroids: prednisone 1-2 mg/kg/d, taper over 4-6 weeks
  - Consider antibiotics
  - Monitor every 3 days, should improve in 2-3 days

Brahmer, JCO 2018

Courtesy of Stephen V Liu, MD, PhD

Pneumonitis Management

- Grade 3 severe pneumonitis
  - Inpatient management
  - Permanently discontinue therapy
  - CT scan
  - Start IV steroids (methylprednisolone 1-2 mg/kg/d)
    - Escalate immunosuppression if not improving within 48h
  - Pulmonary and ID consultations

Brahmer, JCO 2018

Courtesy of Stephen V Liu, MD, PhD

Other Immune Mediated Adverse Events

- Non-pneumonitis immune mediated events with durvalumab
  - 56.3% occur within 3 months; 83.1% within 6 months
  - Thyroid disorders (seen in 11.4% of patients)
  - Rash/dermatitis (seen in 1.9%)
  - Diarrhea/colitis (seen in 1.1%)

	Thyroid	Rash	Diarrhea
Time to Onset	85 days	37 days	61 days
Duration	63.5 days	117 days	74 days
Time to Resolution	56 days	104 days	47.5 days

Naidoo, ASCO 2020

Courtesy of Stephen V Liu, MD, PhD

Immune Mediated Adverse Events

- Hormone replacement if indicated
- For severe immune related side effects, treatment is immune suppression (steroids)
  - Early and aggressive intervention important for severe cases
  - When steroids tapered off, side effects may return
    - Long courses of steroids may be needed
    - Potential risk of infection and other complications of steroid use
  - Lowering the dose or changing schedule is not effective

Roth, JCO 1992

Courtesy of Stephen V Liu, MD, PhD

Monitoring with Immunotherapy

- History and physical
  - New symptoms, new findings, vital signs
- Regular blood tests when receiving immunotherapy
  - CBC, BMP, LFTs, TSH
- Symptom directed evaluation as needed
  - Cortisol, troponin, CPK, gonadotropins
- Direct and open communication with the team
  - Not just during treatment visits
- *<u>Anything</u> notable and new needs to be reported!*

Courtesy of Stephen V Liu, MD, PhD

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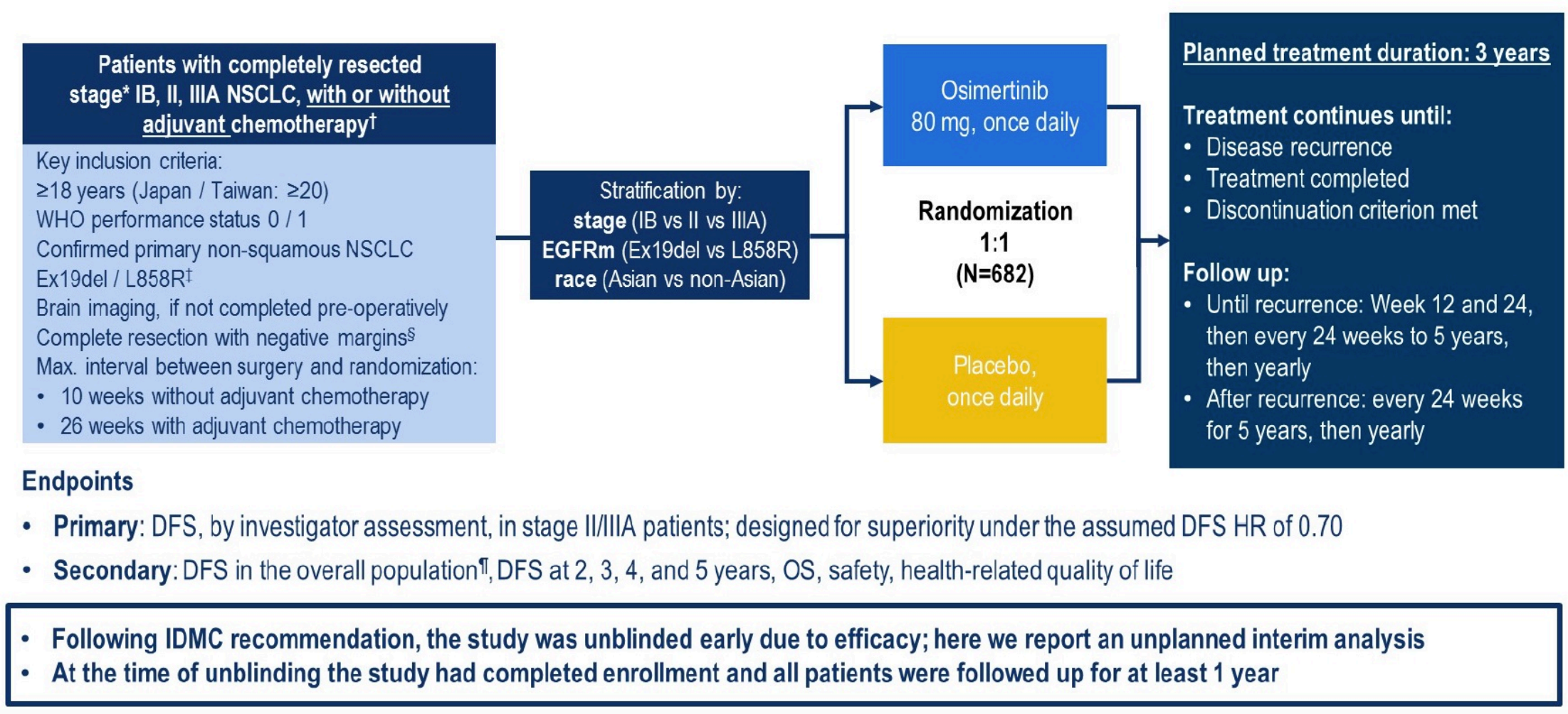
Osimertinib as Adjuvant Therapy in Patients (pts) with Stage IB–IIIA EGFR Mutation Positive (EGFRm) NSCLC After Complete Tumor Resection: ADAURA

Herbst RS et al.
ASCO 2020;Abstract LBA5.

Discussion of LBA5

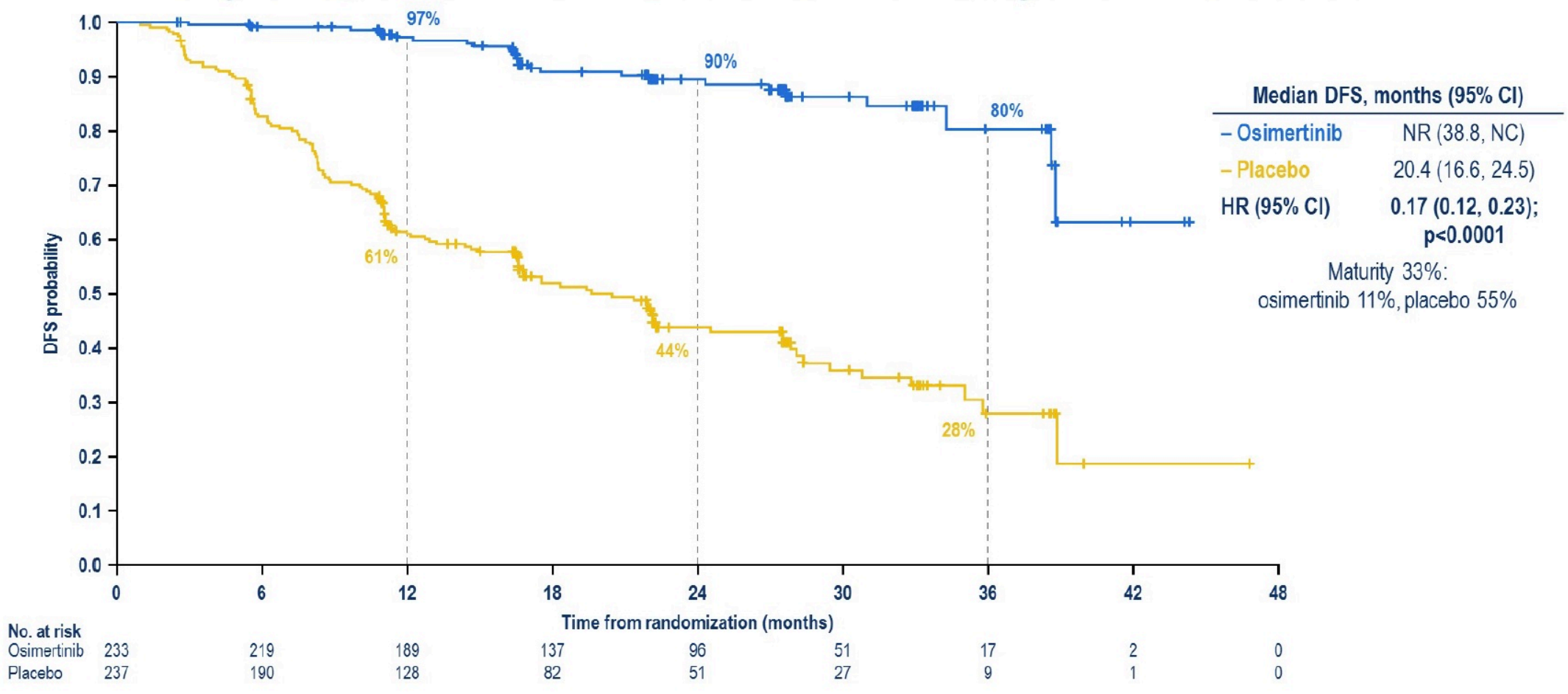
Discussant: David R Spigel, MD, FASCO | Sarah Cannon Research Institute

ADAURA Phase III Trial Schema



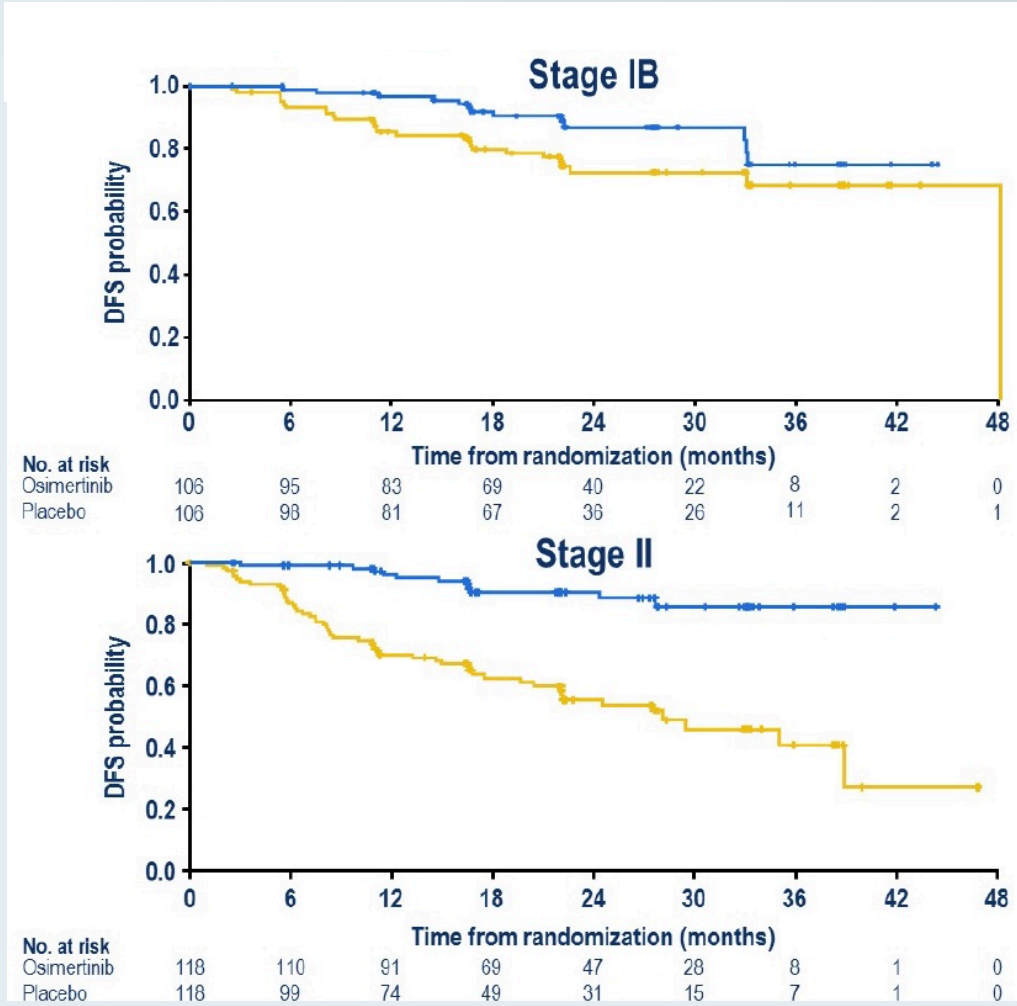
Herbst RS et al. ASCO 2020;Abstract LBA5.

ADAURA Primary Endpoint: Inv-Assessed DFS (Stage II/IIIA)

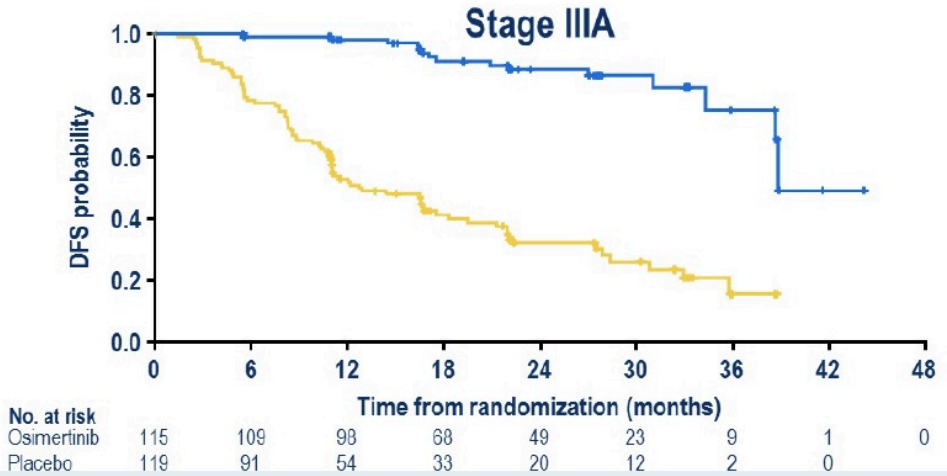


Herbst RS et al. ASCO 2020;Abstract LBA5.

ADAURA: DFS by Stage

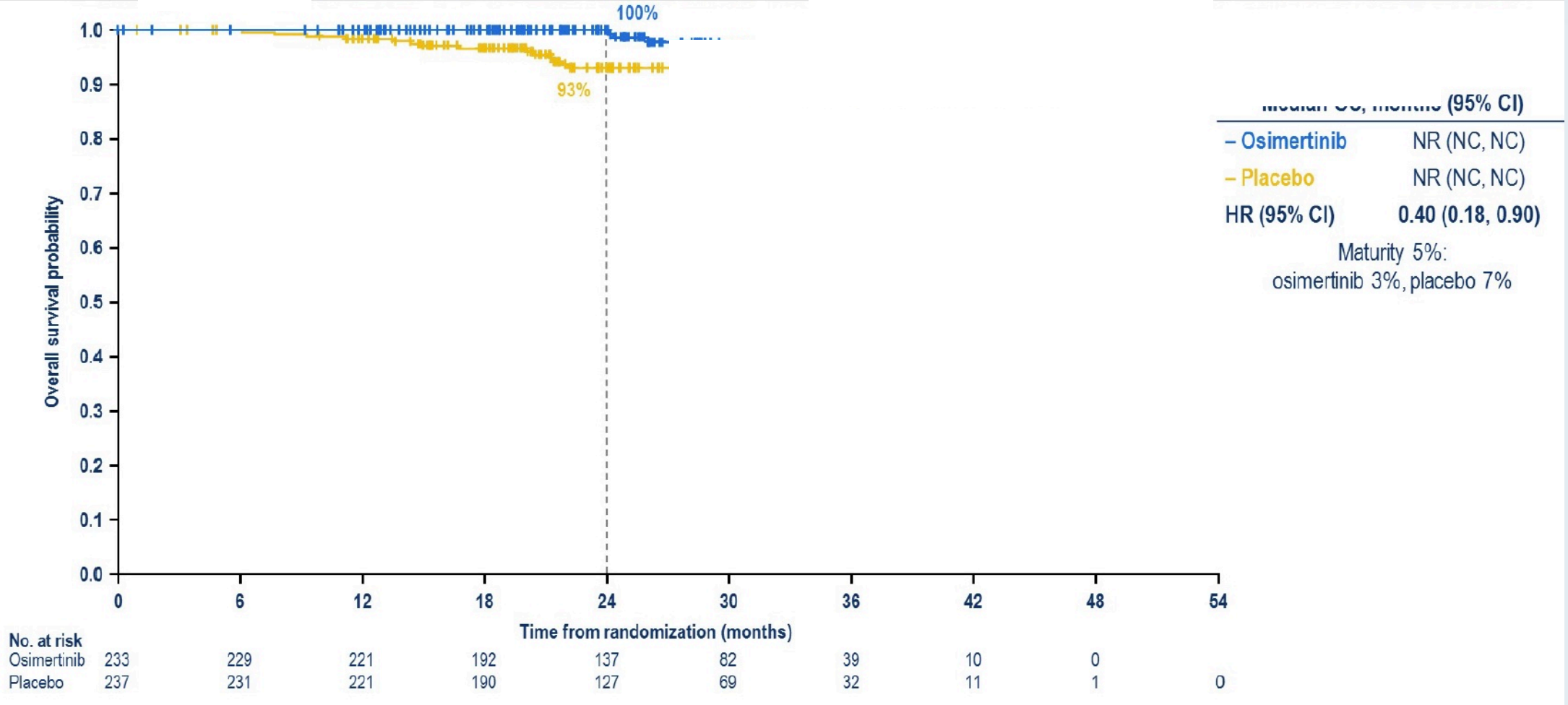


	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	**0.50 (0.25, 0.96)**	**0.17 (0.08, 0.31)**	**0.12 (0.07, 0.20)**



Herbst RS et al. ASCO 2020;Abstract LBA5.

ADAURA: Early Snapshot of OS (Stage II/IIIA)



Herbst RS et al. ASCO 2020;Abstract LBA5.

ADAURA: Safety Summary

AE, any cause*, n (%)	Osimertinib (n=336)	Placebo (n=343)
Any AE	327 (97)	306 (89)
Any AE Grade ≥3	68 (20)	48 (14)
Any AE leading to death	0	1 (<1)
Any serious AE	54 (16)	44 (13)
Any AE leading to discontinuation	38 (11)	15 (4)
Any AE leading to dose reduction	25 (7)	2 (1)
AE, possibly causally related†, n (%)		
Any AE	303 (90)	190 (55)
Any AE Grade ≥3	32 (10)	9 (3)
Any AE leading to death	0	0
Any serious AE	9 (3)	2 (1)

Herbst RS et al. ASCO 2020;Abstract LBA5.

Thank you for joining us!

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