Optimizing the Role of Radiation Oncologists and Other Multidisciplinary Team Members in the Management of Locally Advanced Non-Small Cell Lung Cancer

Tuesday, October 20, 2020
5:00 PM – 6:00 PM ET

Faculty

Walter J Curran Jr, MD
Camille Usher, MS, APRN, NP-C

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Commercial Support

This activity is supported by an educational grant from AstraZeneca Pharmaceuticals LP.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies Corporation, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exelixis Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Genomic Health Inc, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Guardant Health, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Kite, A Gilead Company, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seattle Genetics, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Teva Oncology, Tokai Pharmaceuticals Inc and Verastem Inc.

RTP
RESEARCH
TO PRACTICE

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

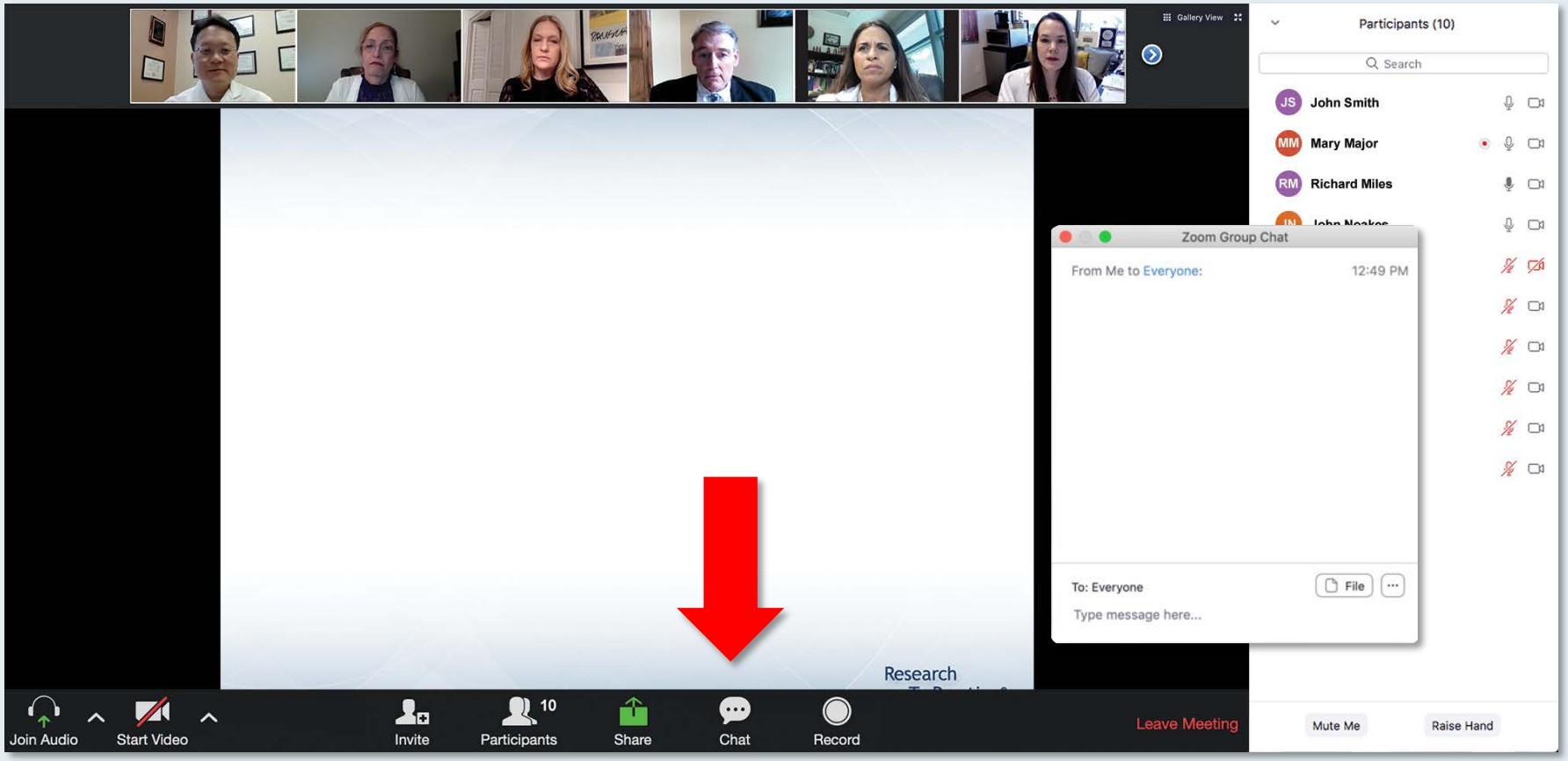
Dr Curran — Disclosures

No financial interests or affiliations to disclose.

Ms Usher — Disclosures

No financial interests or affiliations to disclose.

We Encourage Clinicians in Practice to Submit Questions

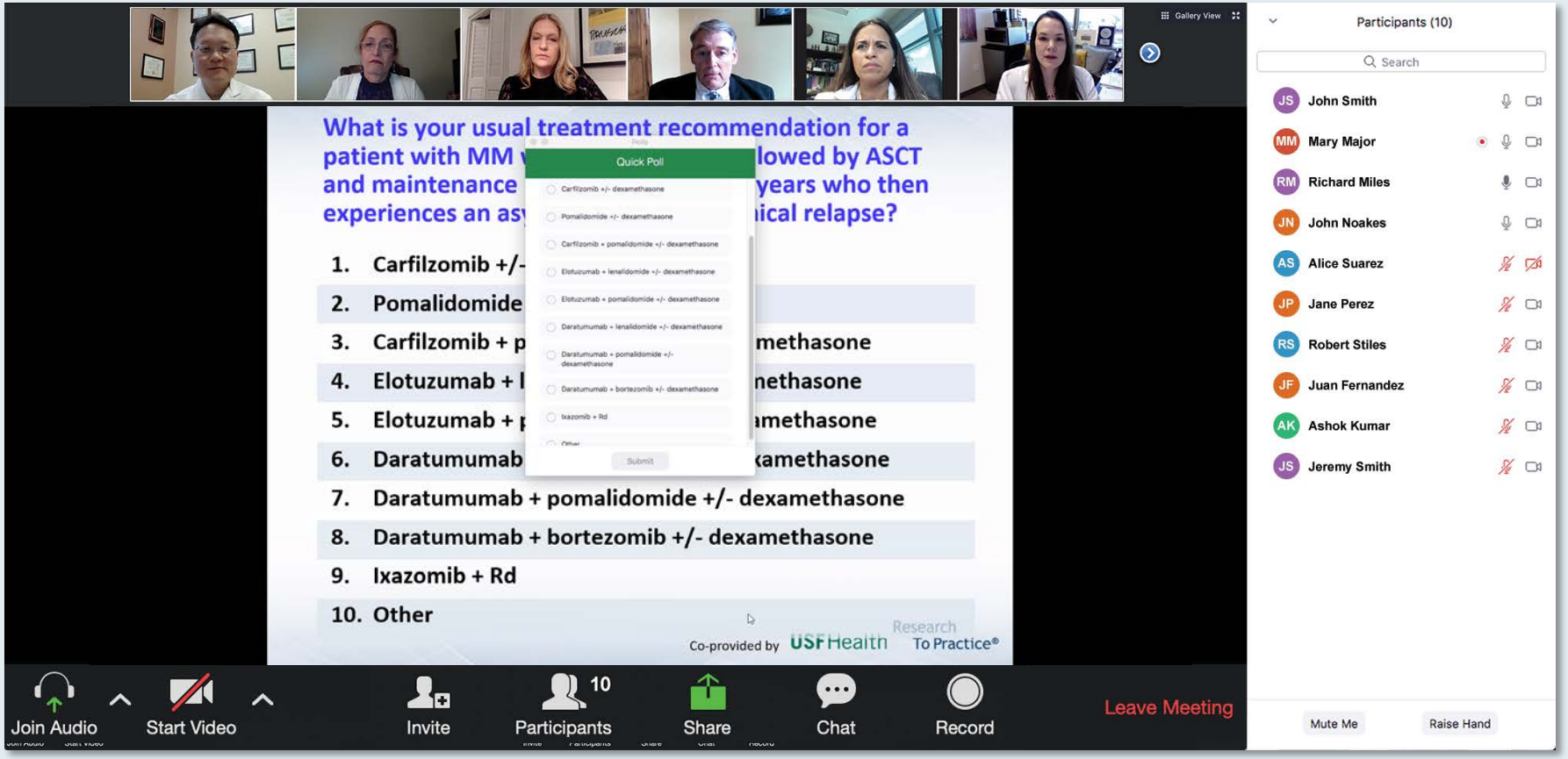


Feel free to submit questions now before the program begins and throughout the program.

RTP RESEARCH TO PRACTICE

Familiarizing Yourself with the Zoom Interface

How to answer poll questions



When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.

RTP RESEARCH TO PRACTICE

Upcoming Webinars

Thursday, October 22, 2020
12:00 PM – 1:00 PM ET

Meet The Professor: Management of Multiple Myeloma

Faculty
Krina K Patel, MD, MSc

Moderator
Neil Love, MD

Saturday, October 24, 2020
8:30 AM – 4:30 PM ET

Current Concepts and Recent Advances in Oncology: A Daylong Clinical Summit Hosted in Partnership with Florida Cancer Specialists

Moderator
Neil Love, MD

Upcoming Webinars

Tuesday, October 27, 2020
1:00 PM – 2:00 PM ET

Meet The Professor: Management of Chronic Lymphocytic Leukemia

Faculty
Brian T Hill, MD, PhD

Moderator
Neil Love, MD

Friday, October 30, 2020
12:30 PM – 1:30 PM ET

Meet The Professor: Immunotherapy and Novel Agents in Gynecologic Cancers

Faculty
Richard T Penson, MD, MRCP

Moderator
Neil Love, MD

Thank you for joining us!

CME and NCPD credit information will be emailed to each participant within 24 hours.

RTP
RESEARCH
TO PRACTICE

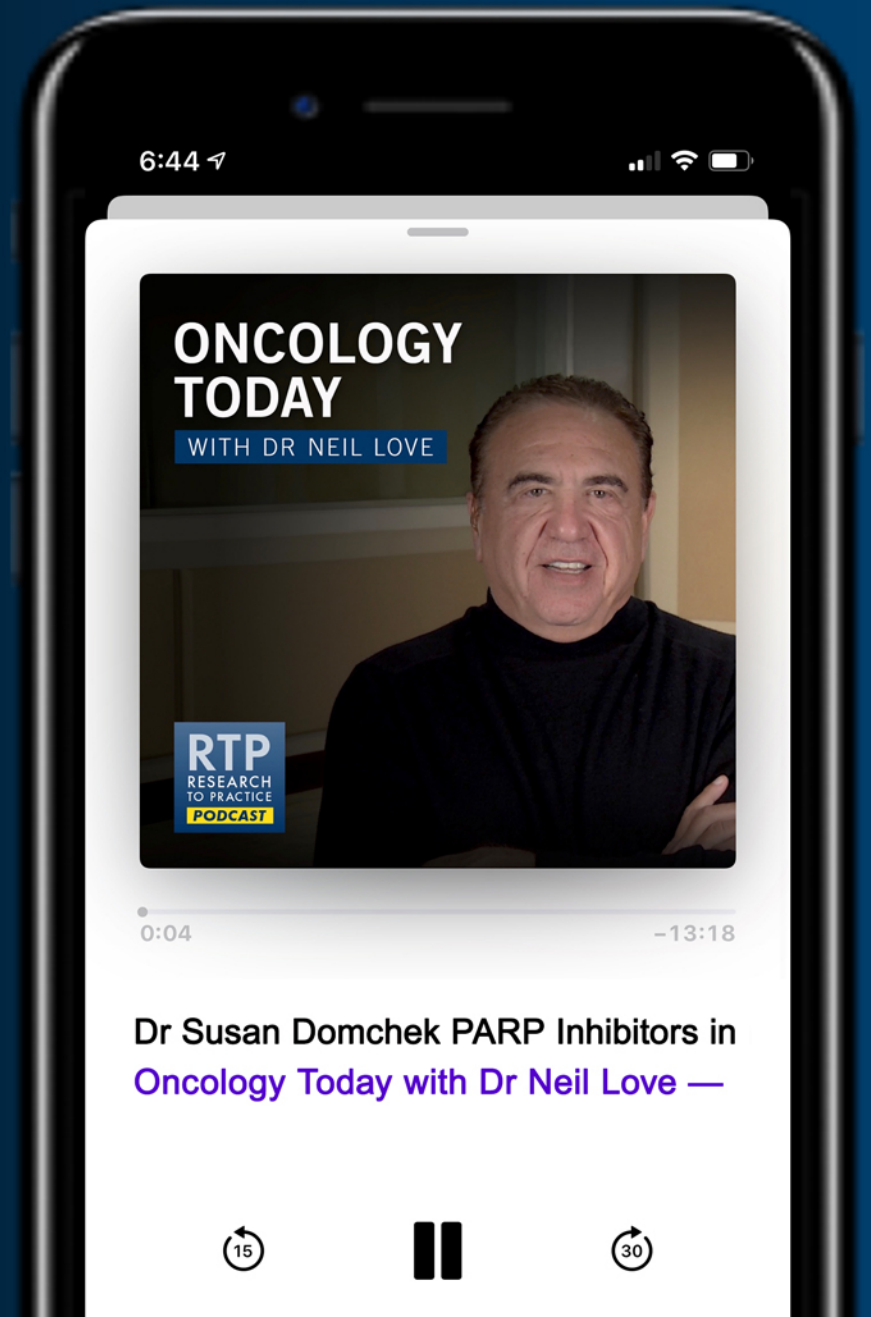
ONCOLOGY TODAY

WITH DR NEIL LOVE

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts



Optimizing the Role of Radiation Oncologists and Other Multidisciplinary Team Members in the Management of Locally Advanced Non-Small Cell Lung Cancer

Tuesday, October 20, 2020
5:00 PM – 6:00 PM ET

Faculty

Walter J Curran Jr, MD
Camille Usher, MS, APRN, NP-C

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

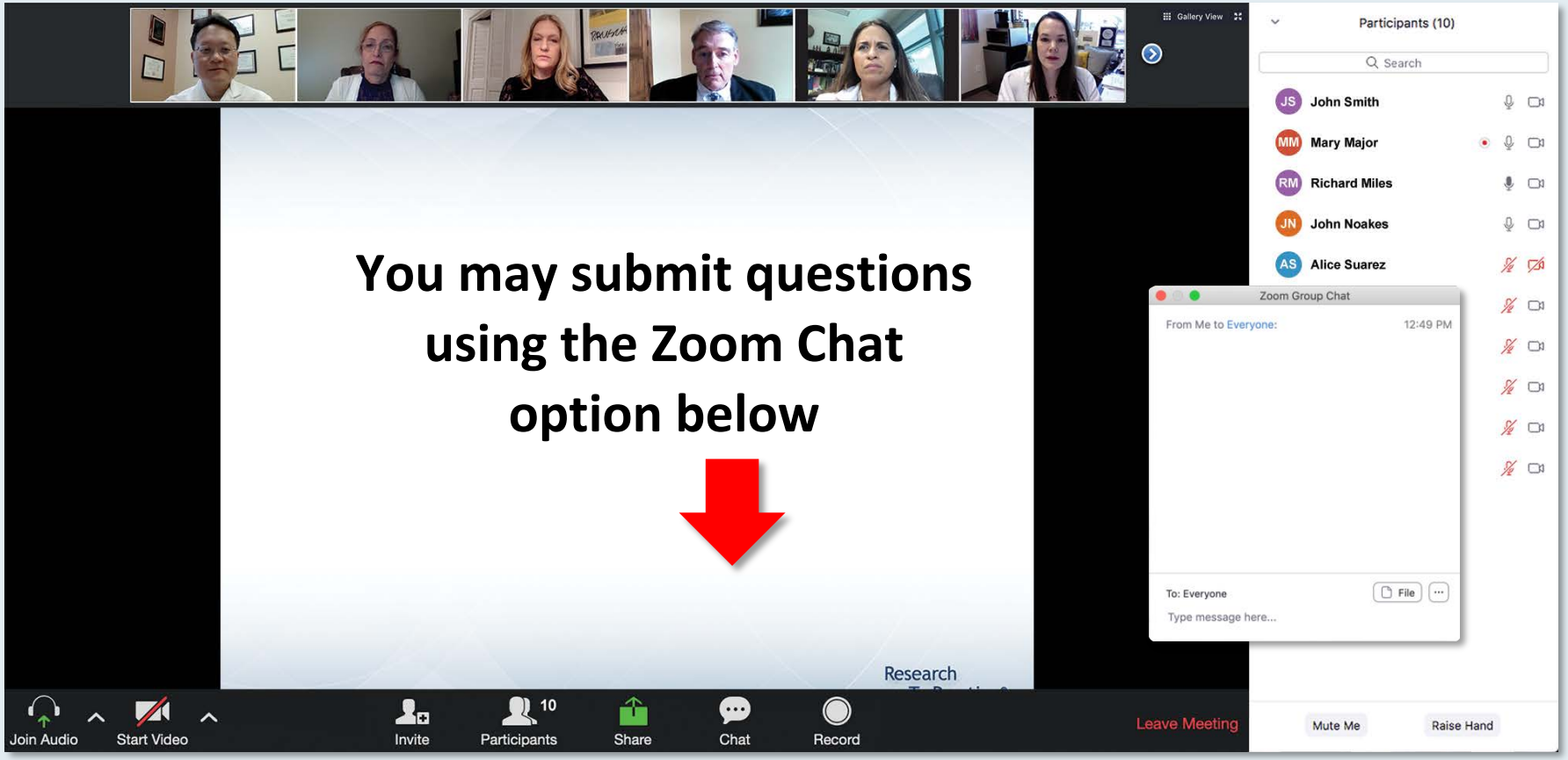
Walter J Curran Jr, MD
Executive Director
Winship Cancer Institute of Emory University
Lawrence W Davis Professor and Chairman
Emory Department of Radiation Oncology
Group Chairman, NRG Oncology
Georgia Research Alliance Eminent Scholar
and Chair in Cancer Research
Atlanta, Georgia

Camille Usher, MS, APRN, NP-C
Associate Lead Nurse Practitioner
Radiation Oncology
Winship Cancer Institute of Emory University
Atlanta, Georgia

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

RTP
RESEARCH
TO PRACTICE

We Encourage Clinicians in Practice to Submit Questions

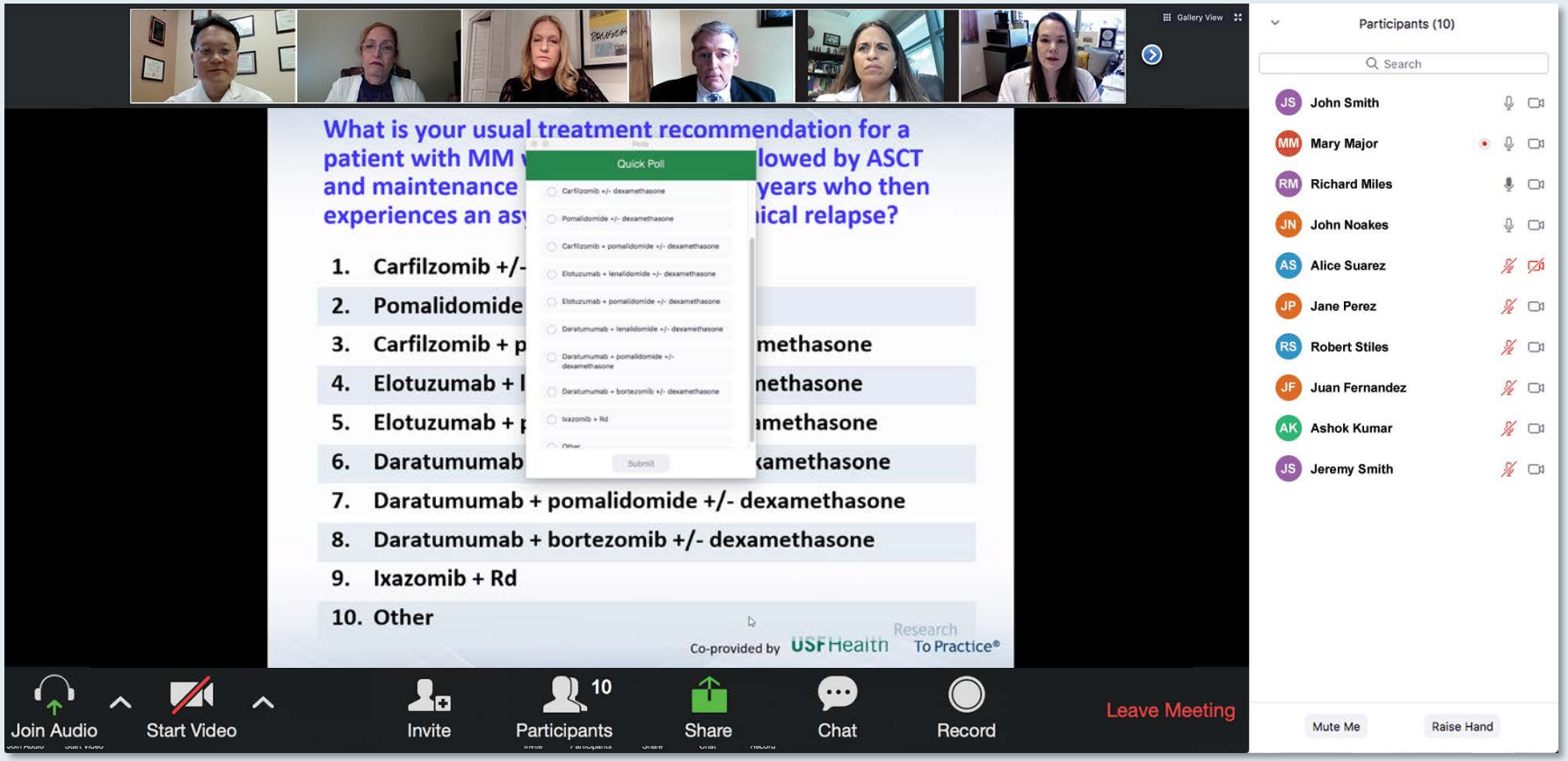


Feel free to submit questions now before the program begins and throughout the program.

RTP RESEARCH TO PRACTICE

Familiarizing Yourself with the Zoom Interface

How to answer poll questions



When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.

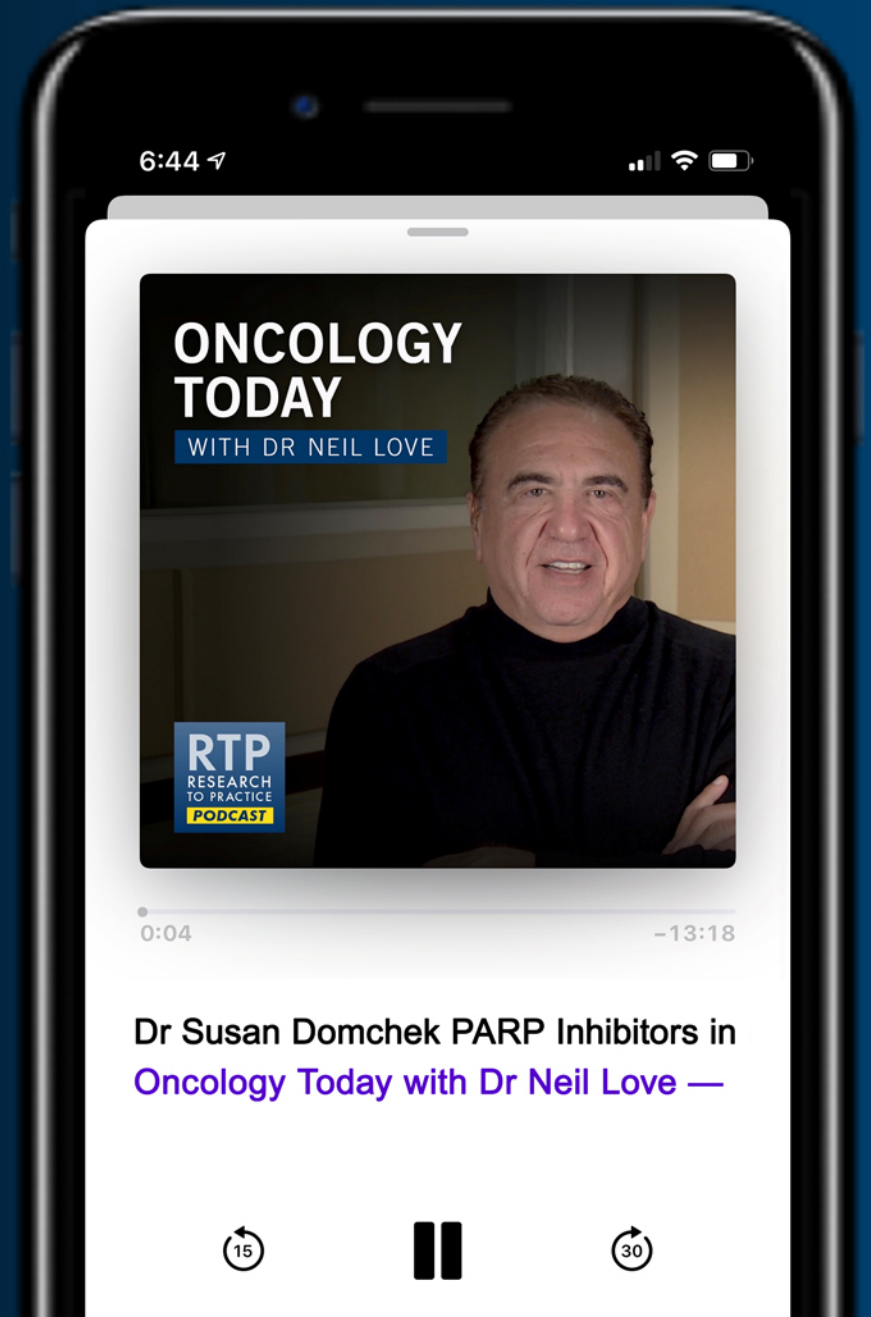
ONCOLOGY TODAY

WITH DR NEIL LOVE

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts



Meet The Professor
Management of Multiple Myeloma

Thursday, October 22, 2020
12:00 PM – 1:00 PM ET

Faculty

Krina K Patel, MD, MSc

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Current Concepts and Recent Advances in Oncology

A Daylong Clinical Summit Hosted in Partnership with Florida Cancer Specialists

Saturday, October 24, 2020
8:30 AM – 4:30 PM ET

Faculty

Arjun Balar, MD
Johanna Bendell, MD
Axel Grothey, MD
Brad S Kahl, MD
Shaji K Kumar, MD
Kathleen Moore, MD
Loretta Nastoupil, MD
William K Oh, MD
David M O'Malley, MD
Robert Z Orlowski, MD, PhD
Gregory J Riely, MD, PhD
Hope S Rugo, MD
David R Spigel, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

RTP
RESEARCH TO PRACTICE

Saturday, October 24, 2020 — 8:30 AM – 4:30 PM ET

8:30 AM Lung Cancer: Gregory Riely, David Spigel

9:30 AM Multiple Myeloma: Shaji Kumar, Robert Orlowski

10:45 AM CLL/Lymphomas: Brad Kahl, Loretta Nastoupil

11:45 AM Gastrointestinal Cancers: Johanna Bendell, Axel Grothey

1:15 PM Genitourinary Cancers: Arjun Balar, William Oh

2:15 PM Gynecologic Cancers: Kathleen Moore, David O'Malley

3:30 PM Breast Cancer: Hope Rugo, Sara Tolaney

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Management of Chronic Lymphocytic Leukemia

Tuesday, October 27, 2020
1:00 PM – 2:00 PM ET

Faculty

Brian T Hill, MD, PhD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor
Immunotherapy and Novel Agents in Gynecologic Cancers

Friday, October 30, 2020
12:30 PM – 1:30 PM ET

Faculty

Richard T Penson, MD, MRCP

Moderator

Neil Love, MD

RTP
RESEARCH TO PRACTICE

Optimizing the Role of Radiation Oncologists and Other Multidisciplinary Team Members in the Management of Locally Advanced Non-Small Cell Lung Cancer

Tuesday, October 20, 2020
5:00 PM – 6:00 PM ET

Faculty

Walter J Curran Jr, MD
Camille Usher, MS, APRN, NP-C

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Agenda

MODULE 1: Overview of Locally Advanced Unresectable Lung Cancer

- Staging, history of treatment, rationale for checkpoint inhibition
- Ms Usher: A 64-year-old woman with Stage IIIA T1bN2 adenocarcinoma of the lung
- Dr Curran: A 54-year-old man with Stage IIIA T2N2M0 squamous cell carcinoma

MODULE 2: Immune Checkpoint Inhibition in the Management of Locally Advanced NSCLC

- PACIFIC trial: Durvalumab consolidation after successful completion of chemoradiation therapy
- KEYNOTE-799 trial: Pembrolizumab in combination with chemotherapy followed by consolidation pembrolizumab
- Dr Curran: A 45-year-old woman and never smoker with Stage III NSCLC and an EGFR mutation
- Impact of radiation therapy on the immune system

MODULE 3: Management of Side Effects Associated with Chemoradiation Therapy and Durvalumab

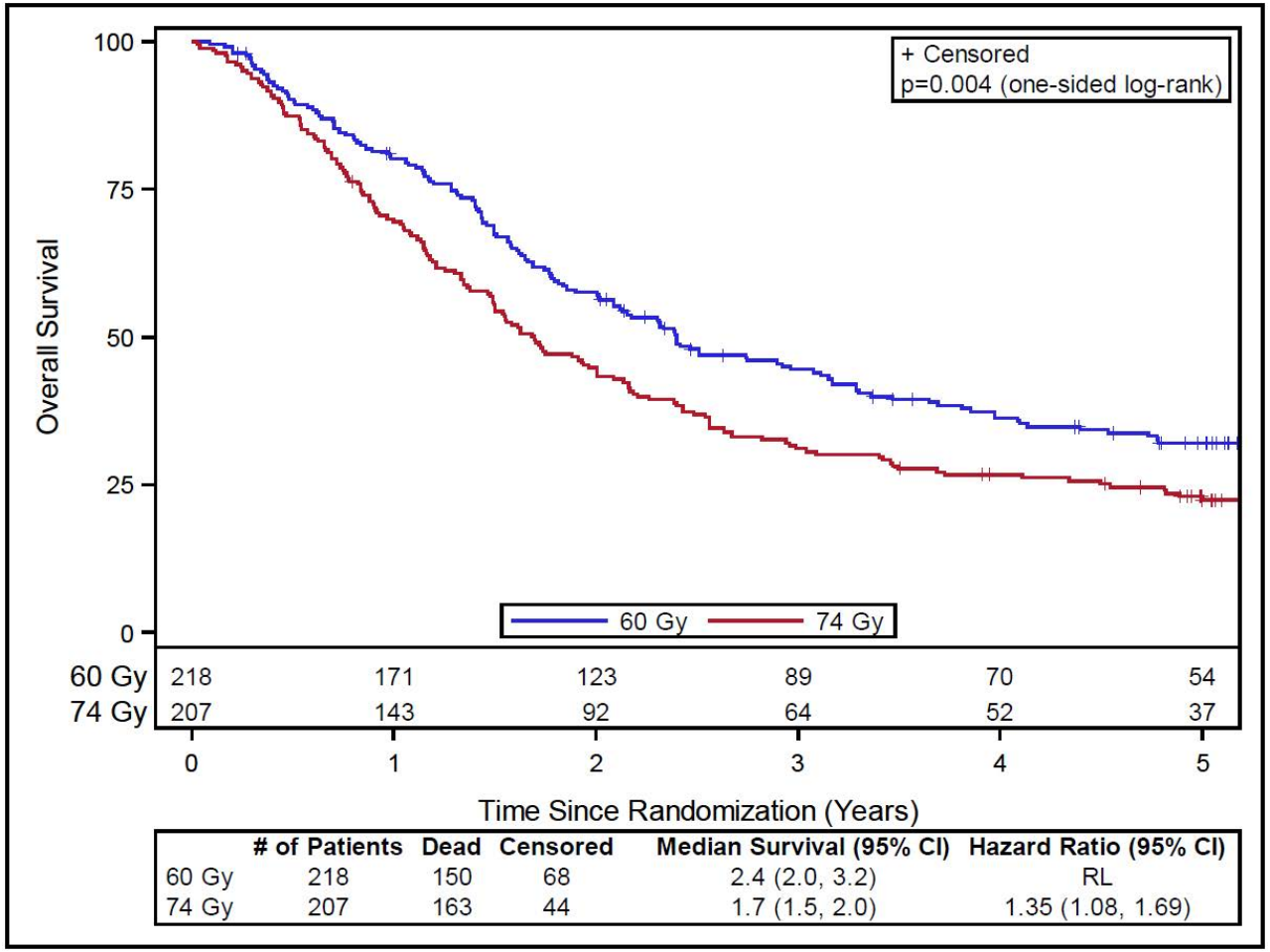
- Ms Usher: A 75-year-old man who developed pneumonitis after chemoradiation therapy
- Ms Usher: A 73-year-old man who developed postchemoradiation esophagitis
- Dr Curran: A 61-year-old man with locally advanced NSCLC and a recent myocardial infarction
- Ms Usher: A 76-year-old woman and smoker with a history of breast cancer

Patients who receive higher doses of radiation therapy with chemotherapy for locally advanced NSCLC…

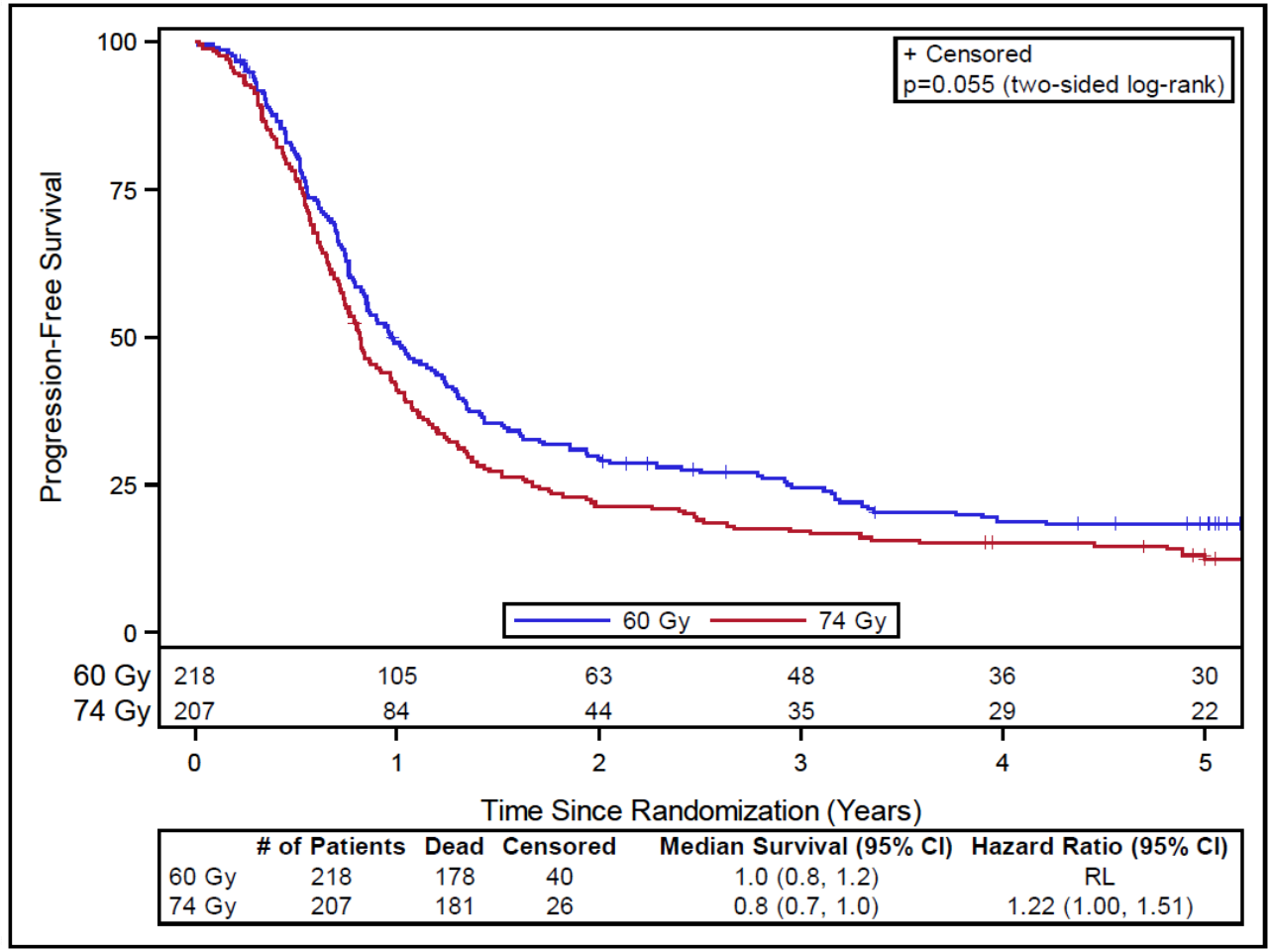
a. Have fewer recurrences
b. Have more recurrences
c. Do not exhibit a significant difference in disease course
d. I don’t know

RTP
RESEARCH
TO PRACTICE

RTOG 0617 Overall and Progression-free Survival by RT Dose



	# of Patients	Dead	Censored	Median Survival (95% CI)	Hazard Ratio (95% CI)
60 Gy	218	150	68	2.4 (2.0, 3.2)	RL
74 Gy	207	163	44	1.7 (1.5, 2.0)	1.35 (1.08, 1.69)



	# of Patients	Dead	Censored	Median Survival (95% CI)	Hazard Ratio (95% CI)
60 Gy	218	178	40	1.0 (0.8, 1.2)	RL
74 Gy	207	181	26	0.8 (0.7, 1.0)	1.22 (1.00, 1.51)

1. Bradley JD, et al. *Int J Radiat Oncol Biol Phys.* 2017;99:S105.

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

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

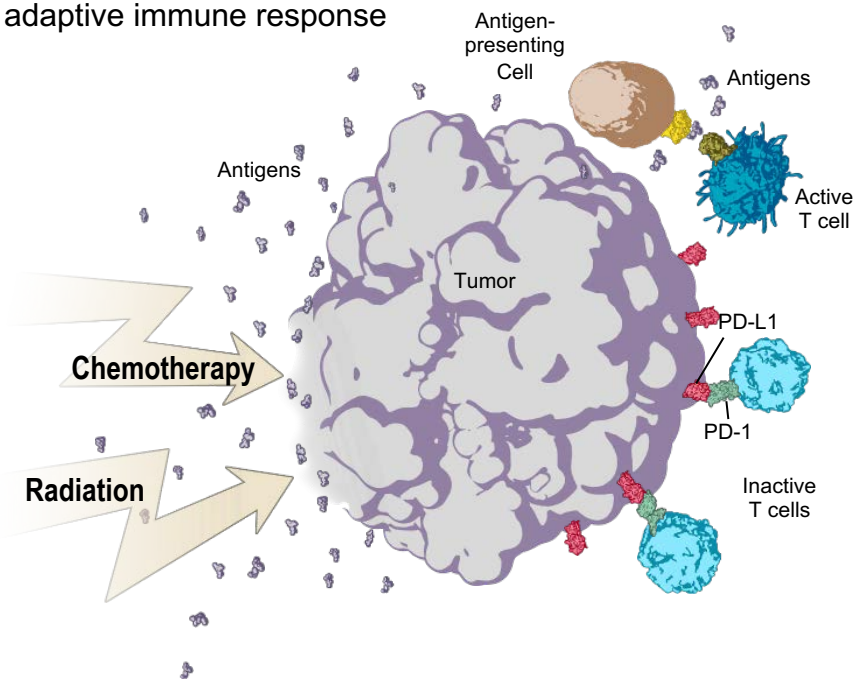
Courtesy of Benjamin Levy, MD

Rationale of checkpoint inhibitors after chemoradiation

CHEMORADIATION

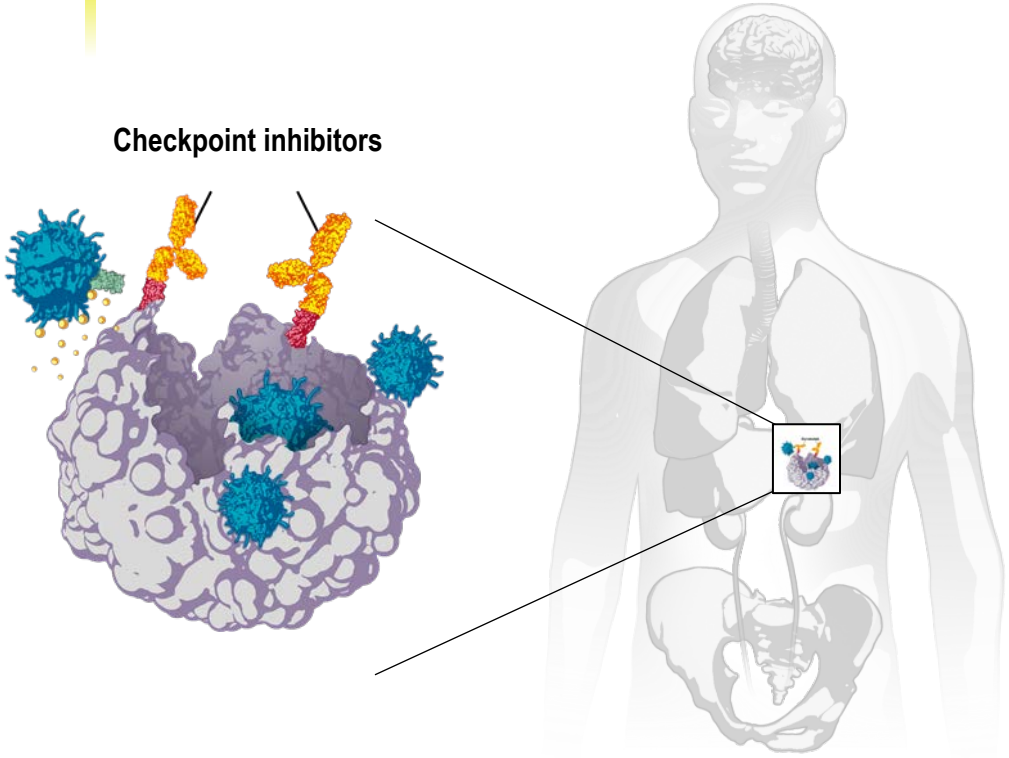
Chemoradiation induces tumor antigen release and an adaptive immune response

PD-L1 overexpression leads to immune cell evasion



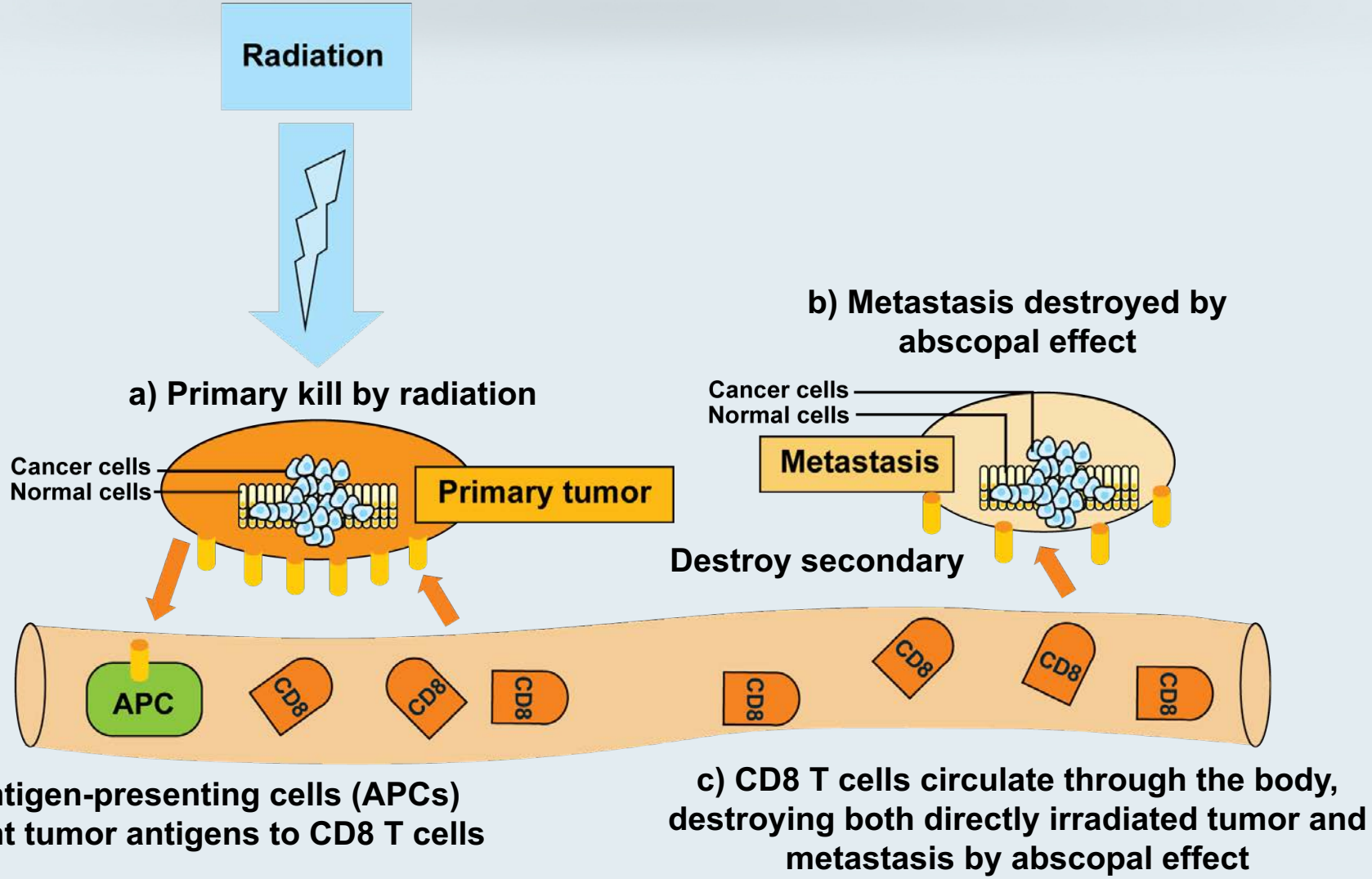
CHECKPOINT INHIBITOR

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



Courtesy of Benjamin Levy, MD

Proposed Mechanism for the Abscopal Effect



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

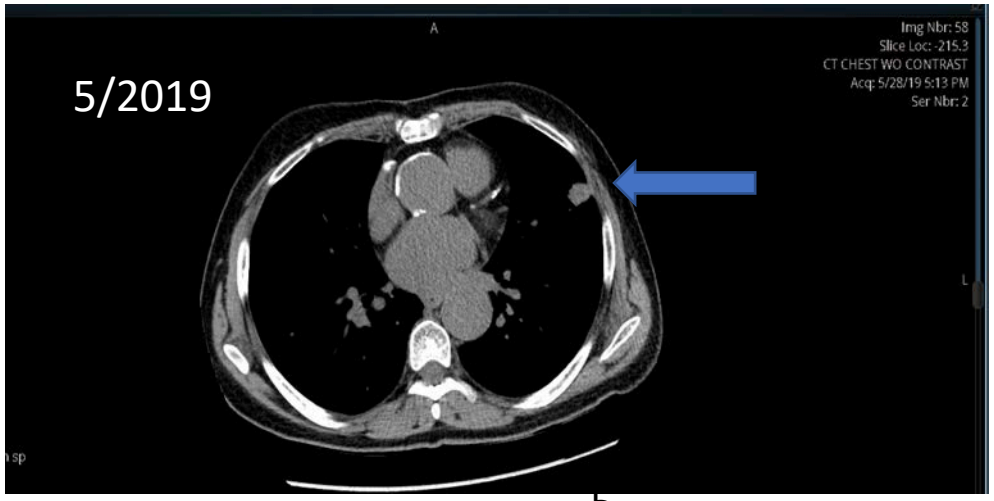
Case Presentation – Ms Usher: A 64-year-old woman with T1bN2 Stage IIIA adenocarcinoma of the lung

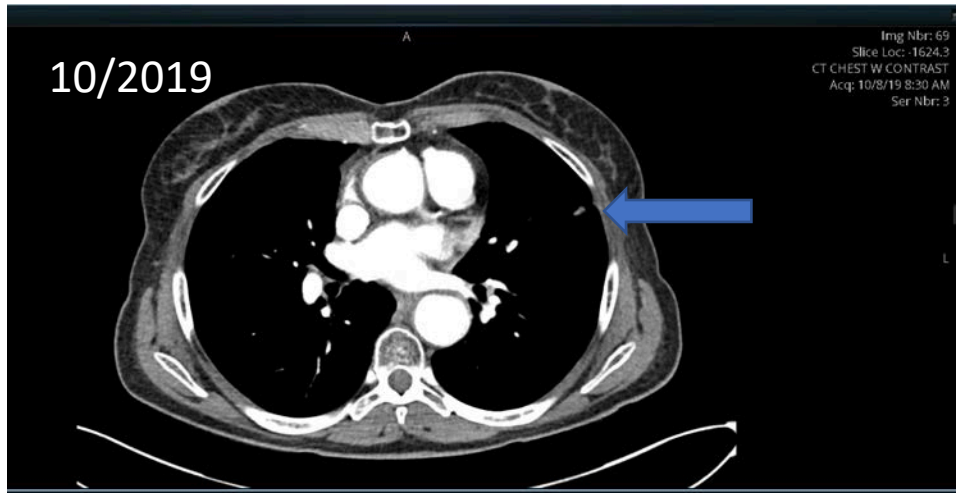
- T1bN2 Stage IIIA PD-L1 TPS 90% poorly differentiated carcinoma of the left upper lobe.
- 3/2019 presented to her primary care doctor with a persistent dry cough for 5-6 days.
- 5/28/19 CT-chest showed spiculated lesion in the left upper lobe abutting the adjacent pleural with mediastinal adenopathy worrisome for primary lung cancer.
- 6/6/19 PET-CT avid left upper lobe pulmonary nodule. Multiple large prevascular nodal masses (level 5 and 3) on the left. However, the largest lesion has an extremely high SUV value.
- 7/9/19 CT-guided biopsies of the left lung mass showed poorly differentiated carcinoma EGFR/ALK/ROS-1 neg, PD-L1 TPS 90%. Biopsy of left paramediastinal mass also confirmed poorly differentiated carcinoma. MRI Brain on 7/16/19 did not show evidence of metastatic disease.
- She is s/p chemoradiation to 60 Gy over 30 fractions with weekly carbo/paclitaxel, completed on 10/1/19. She is currently on 1 year consolidation durvalumab, planned to complete Fall 2020.
- 15/30 fractions in, patient c/o night time cough and burning with swallowing. Started on Magic Mouthwash

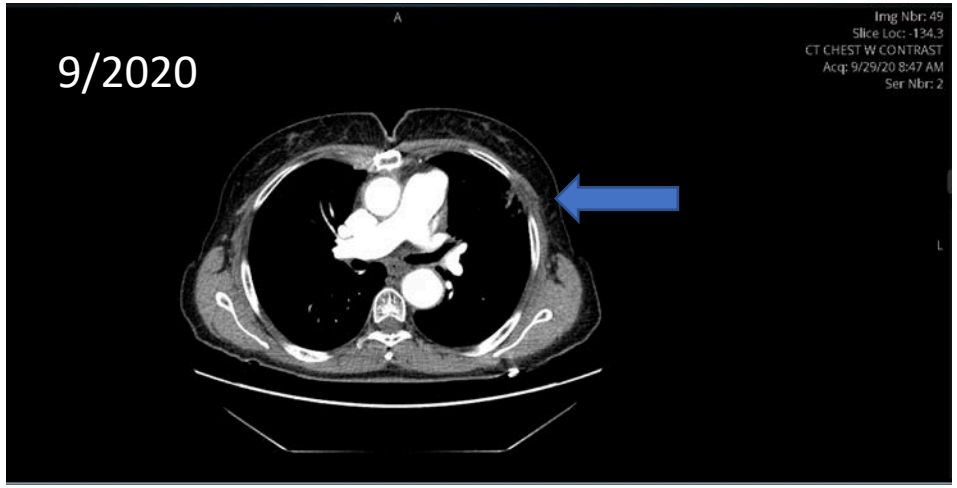
Case Presentation – Ms Usher: A 64-year-old woman with T1bN2 Stage IIIA adenocarcinoma of the lung (cont)

- 1/7/20 report ongoing cough. Took cheratussin on average every other day. Also noted occasional mild rash to the chest since starting durvalumab in 10/19.
- CT Chest New patchy consolidative and groundglass opacities in L lung
- 5/2020 rash is persistent after 5th cycle of durvalumab, treated with topical steroid
- 6/2/20 CT chest improvement in the nodular and groundglass opacities in LUL and lower lobes
- 9/29/20 streaky groundglass in the LUL likely indicative of post radiation change. Emphysema
- Currently doing well. Rash resolved. Cough is less frequent and intense

Case Presentation – Ms Usher: A 64-year-old woman with T1bN2 Stage IIIA adenocarcinoma of the lung (cont)





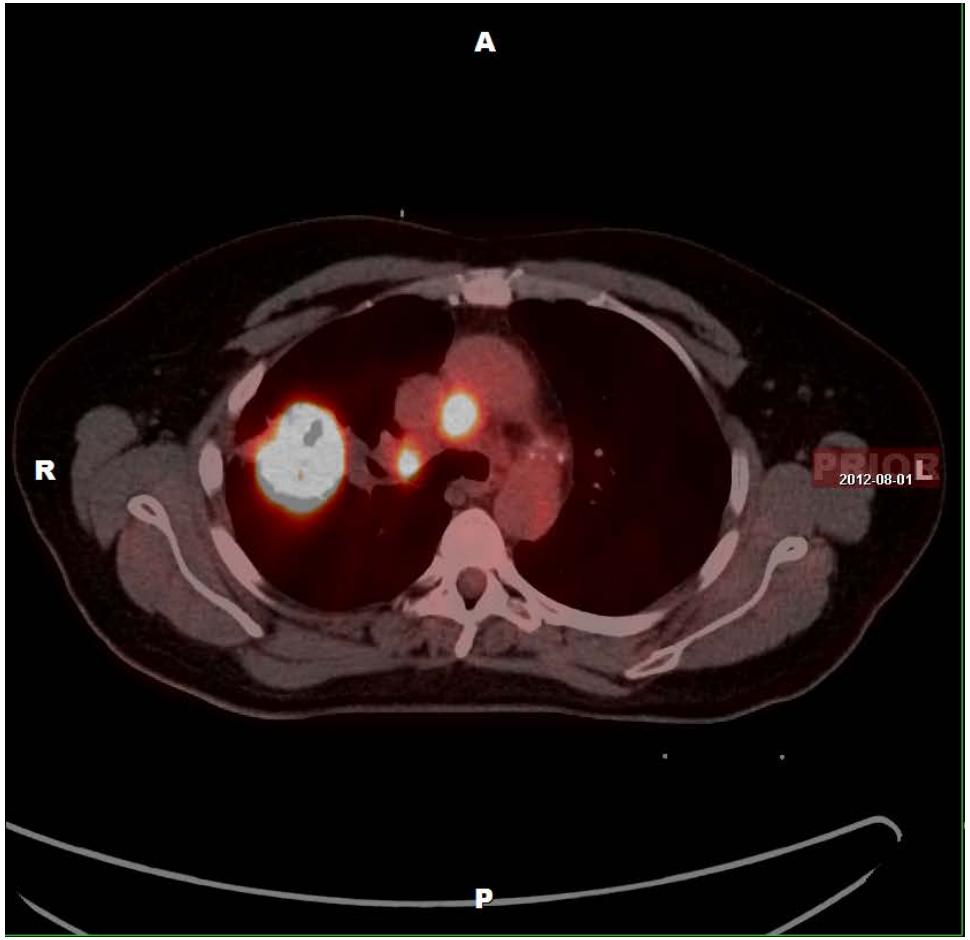


Case Presentation – Dr Curran: A 54-year-old man with Stage IIIA T2N2M0 squamous cell carcinoma of the lung

- 54 yo Male with 25 pack year tobacco history presenting with cough and R lung mass on Chest X Ray.

- PET/CT Scan
  - PET avid 5 cm right lung mass
  - PET avid right hilar and pretracheal LN
- EBUB Biopsy: Squamous Cell Cancer
- No Extrathoracic Disease on Staging

- Clinical Stage: T2N2M0 Stage IIIA

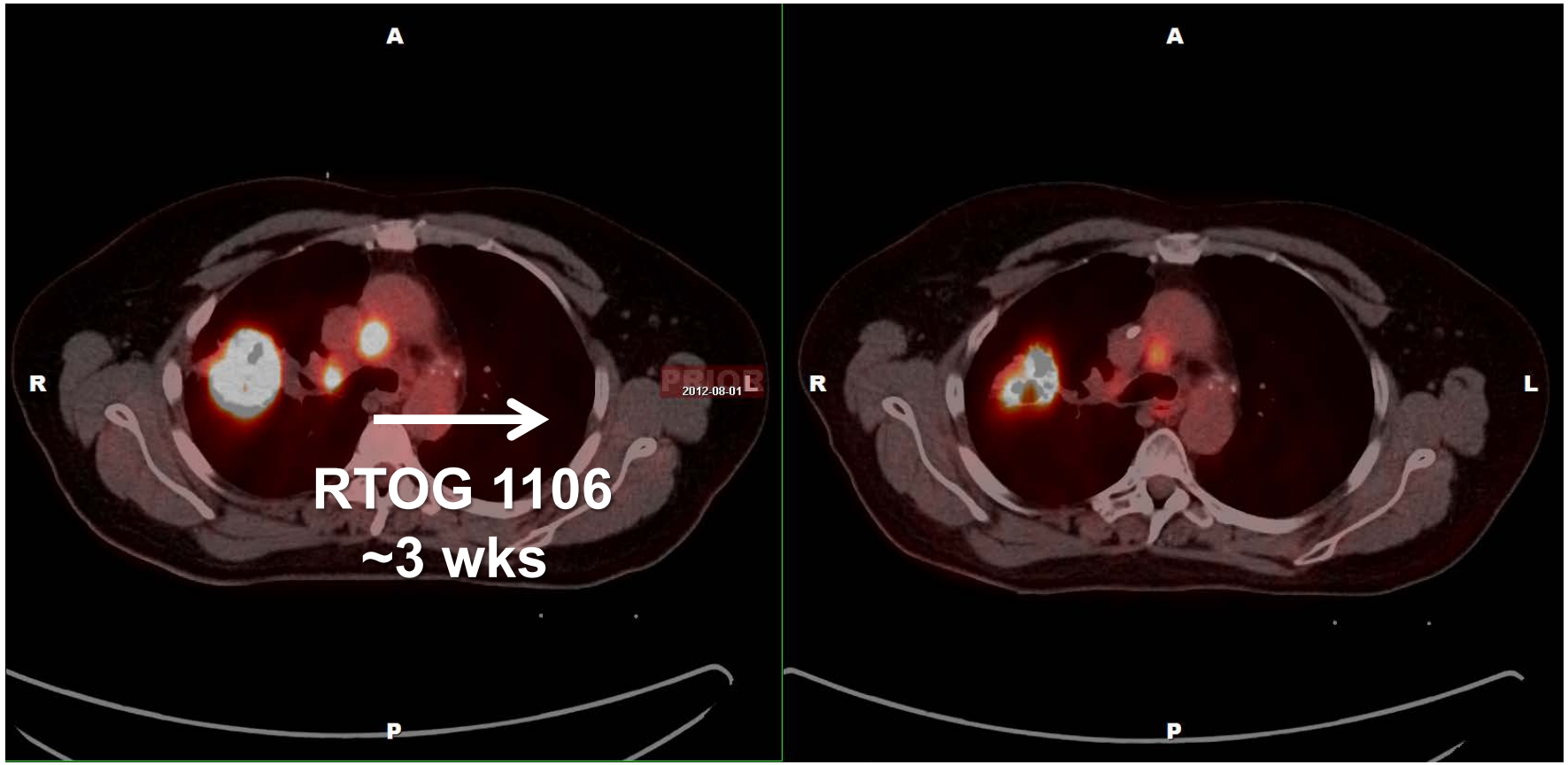


Case Presentation – Dr Curran: A 54-year-old man with Stage IIIA T2N2M0 squamous cell carcinoma of the lung (cont)

- Pt's disease considered unresectable for cure
- Plan: 60 Gy RT/wkly carbo/paclitaxel followed by durvalumab
- Mid treatment PET/CT obtained
- >50% response
- Should plan be changed?

Initial PET/CT

Mid-Tx PET/CT



Case Presentation – Dr Curran: A 54-year-old man with Stage IIIA T2N2M0 squamous cell carcinoma of the lung (cont)

- Should Mid-Course PET Response Alter Treatment Plan?
- Concept of Adaptive Therapy
- Results of NRG Oncology/RTOG Trial to Be Presented at ASTRO 2020
- Will Settle Issue of Adaptive RT Dose Intensification

- Patient Completed 60 Gy RT and Carbo/Paclitaxel
- Excellent Response after Chemo-RT
- Tolerated Durva and Under Active Surveillance

Agenda

MODULE 1: Overview of Locally Advanced Unresectable Lung Cancer

- Staging, history of treatment, rationale for checkpoint inhibition
- Ms Usher: A 64-year-old woman with Stage IIIA T1bN2 adenocarcinoma of the lung
- Dr Curran: A 54-year-old man with Stage IIIA T2N2M0 squamous cell carcinoma

MODULE 2: Immune Checkpoint Inhibition in the Management of Locally Advanced NSCLC

- PACIFIC trial: Durvalumab consolidation after successful completion of chemoradiation therapy
- KEYNOTE-799 trial: Pembrolizumab in combination with chemotherapy followed by consolidation pembrolizumab
- Dr Curran: A 45-year-old woman and never smoker with Stage III NSCLC and an EGFR mutation
- Impact of radiation therapy on the immune system

MODULE 3: Management of Side Effects Associated with Chemoradiation Therapy and Durvalumab

- Ms Usher: A 75-year-old man who developed pneumonitis after chemoradiation therapy
- Ms Usher: A 73-year-old man who developed postchemoradiation esophagitis
- Dr Curran: A 61-year-old man with locally advanced NSCLC and a recent myocardial infarction
- Ms Usher: A 76-year-old woman and smoker with a history of breast cancer

In general, should durvalumab be recommended as consolidation treatment for a patient with locally advanced NSCLC who underwent surgical excision and chemoradiation therapy as initial treatment?

a. Yes

b. No

c. I don’t know

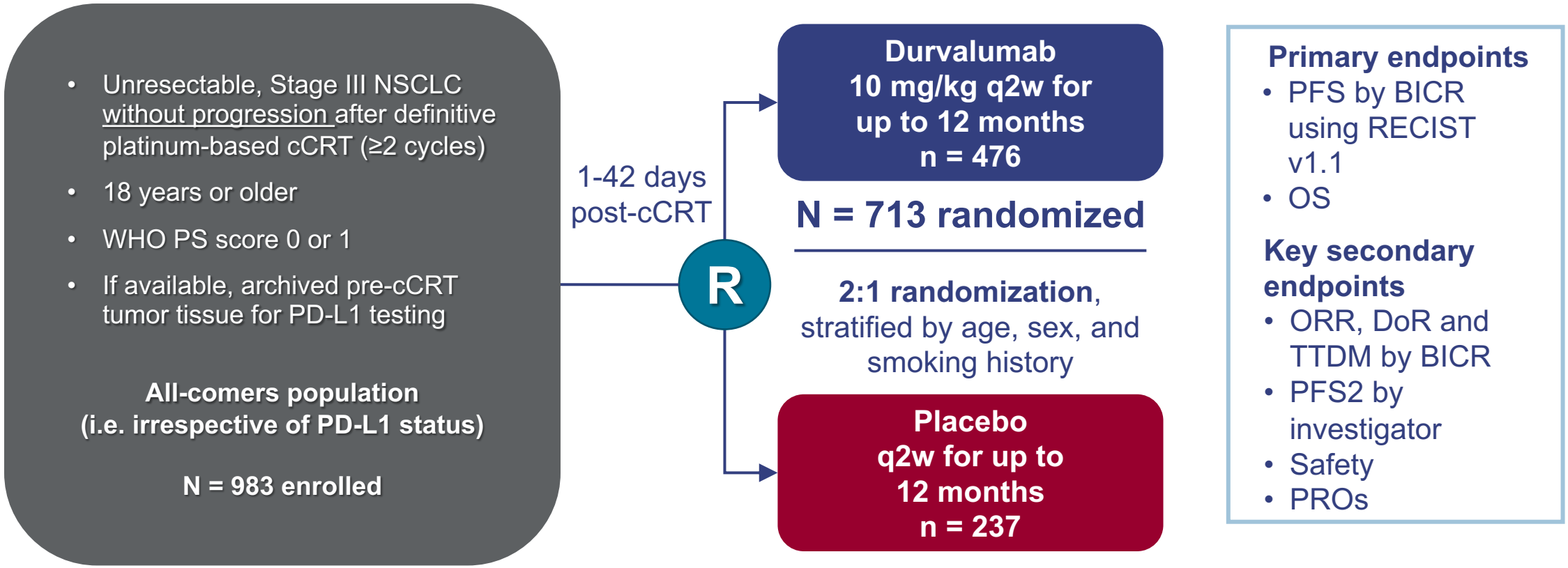
In general, should durvalumab be recommended as consolidation treatment for an older, frail patient who is unable to tolerate chemotherapy and receives only radiation therapy for unresectable Stage IIIB NSCLC?

a. Yes

b. No

c. I don’t know

PACIFIC: Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study[1,2]



- Data cutoff (March 22, 2018) for the planned OS IA occurred after 299 events (61% of the target 491 events)
- OS sample size assumption: ≥85% power to detect an HR of 0.73 with 491 events, using a 2.5% 2-sided significance level

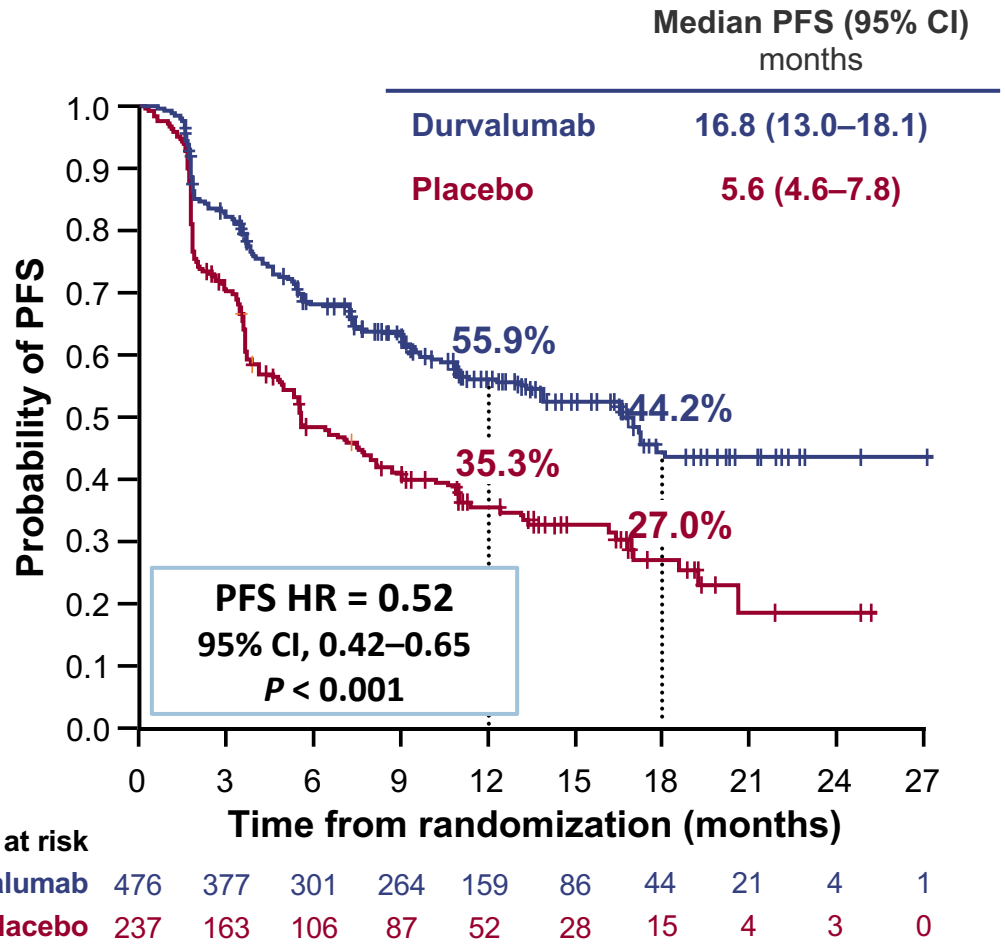
ClinicalTrials.gov number: NCT02125461

1. Antonia SJ, et al. *N Engl J Med.* 2017;377:1919-1929.
2. Antonia SJ, et al. *N Engl J Med.* 2018;379:2342-2350.

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

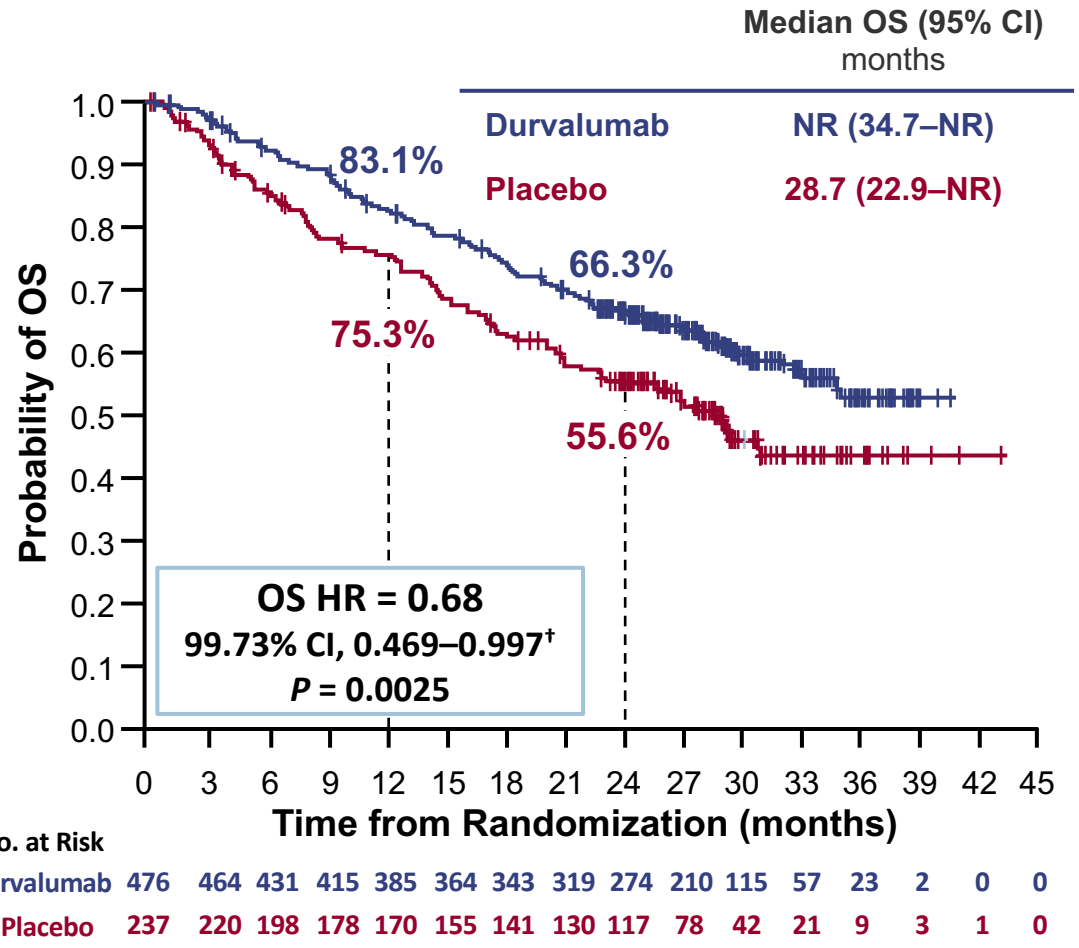
PACIFIC: Primary Endpoints (ITT)[1,2]

PFS (BICR)[1]



No. at risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

OS[2]*



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

*Median duration of follow-up was 25.2 months (range 0.2–43.1); †Adjusted for interim analysis; NR, not reached. Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of Mar 22, 2018.

1. Antonia SJ, et al. *N Engl J Med.* 2017;377:1919-1929.
2. Antonia SJ, et al. *N Engl J Med.* 2018;379:2342-2350.

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

PFS and OS by Pre-specified Subgroup (ITT)[1,2]

		PFS (BICR)			OS		
		HR (95% CI)	No. of events / no. of patients (%) Durvalumab	Placebo	HR (95% CI)	No. of events / no. of patients (%) Durvalumab	Placebo
	All patients		214/476 (45.0)	157/237 (66.2)		183/476 (38.4)	116/237 (48.9)
Sex	Male		155/234 (46.4)	111/166 (66.9)		141/334 (42.2)	80/166 (48.2)
	Female		59/142 (41.5)	46/71 (64.8)		42/142 (29.6)	36/71 (50.7)
Age at randomization	<65 years		108/261 (41.4)	91/130 (70.0)		89/261 (34.1)	58/130 (44.6)
	≥65 years		106/215 (49.3)	66/107 (61.7)		94/215 (43.7)	58/107 (54.2)
Smoking status	Smoker		197/433 (45.5)	140/216 (64.8)		169/433 (39.0)	103/216 (47.7)
	Non-smoker		17/43 (39.5)	17/21 (81.0)		14/43 (32.6)	13/21 (61.9)
Disease stage	Stage IIIA		108/252 (42.9)	82/125 (65.6)		101/252 (40.1)	70/125 (56.0)
	Stage IIIB		104/212 (49.1)	72/107 (67.3)		79/212 (37.3)	44/107 (41.1)
Tumor histologic type	Squamous		117/224 (52.2)	66/102 (64.7)		103/224 (46.0)	56/102 (54.9)
	Non-squamous		97/252 (38.5)	91/135 (67.4)		80/252 (31.7)	60/135 (44.4)
Prior definitive CT	Cisplatin		115/266 (43.2)	97/129 (67.4)		94/266 (35.3)	64/129 (49.6)
	Carboplatin		91/199 (45.7)	65/102 (63.7)		84/199 (42.2)	47/102 (46.1)
Best response to prior treatment	CR	NA*	2/9 (22.2)	4/7 (57.1)	NA*	2/9 (22.2)	3/7 (42.9)
	PR		99/232 (42.7)	72/111 (64.9		83/237 (35.0)	50/112 (44.6)
	SD		108/222 (48.6)	77/114 (67.5)		93/223 (41.7)	61/115 (53.0)
***EGFR* status**	Positive		17/29 (58.6)	11/14 (78.6)	NA*	10/29 (34.5)	6/14 (42.9)
	Negative		131/315 (41.6)	112/165 (67.9)		117/317 (36.9)	80/165 (48.5)
	Unknown		66/132 (50.0)	34/58 (58.6)		56/130 (43.1)	30/58 (51.7)
PD-L1 status	≥25%		48/115 (41.7)	31/44 (70.5		37/115 (32.2)	23/44 (52.3)
	<25%		85/187 (45.5)	68/105 (64.8)		74/187 (39.6)	41/105 (39.0)
	Unknown		81/174 (46.6)	58/88 (65.9)		72/174 (41.4)	52/88 (59.1)

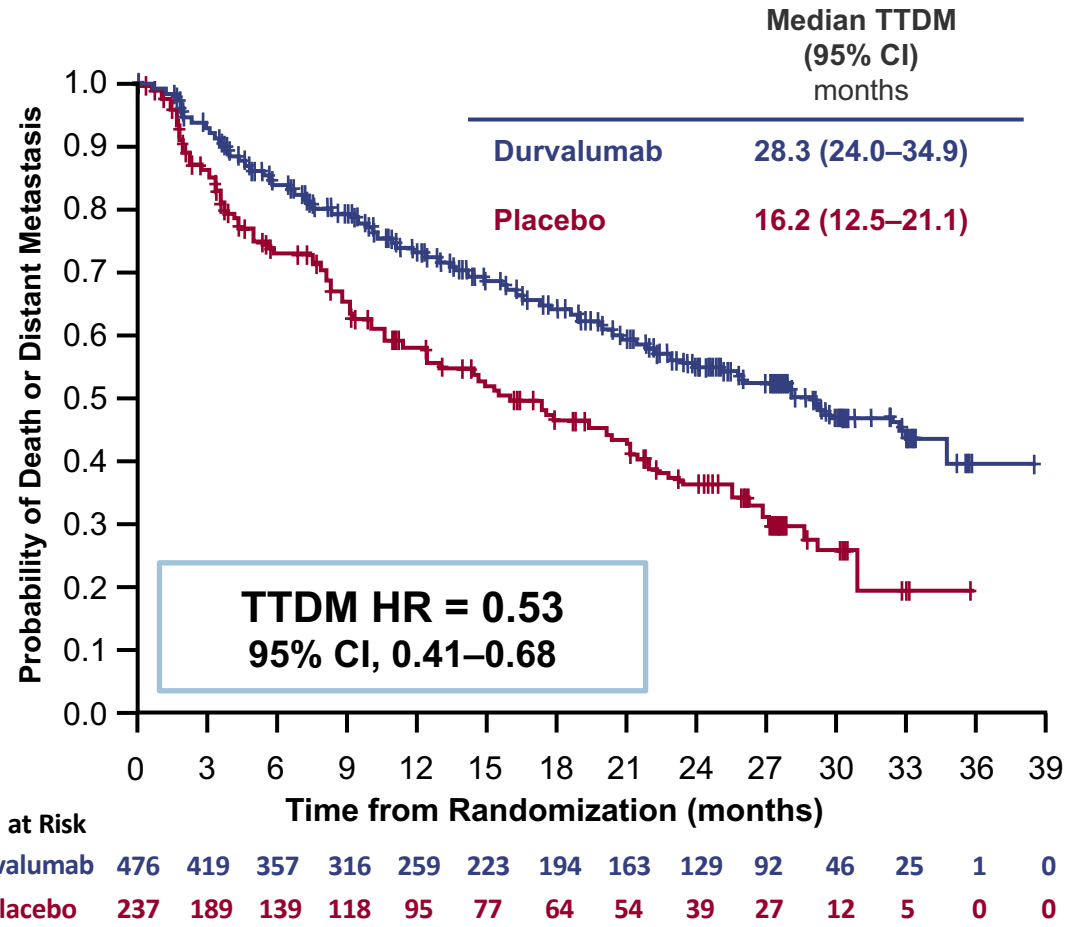
*Not calculated if subgroup has <20 events; NA, not available.
Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of Mar 22, 2018.

1. Antonia SJ, et al. *N Engl J Med.* 2017;377:1919-1929.
2. Antonia SJ, et al. *N Engl J Med.* 2018;379:2342-2350.

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

Updates: ITT Population by BICR[1]

Time to Death or Distant Metastasis (TTDM)



Incidence of New Lesions

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)

*A patient may have had more than one new lesion site;
†Monitoring for post-baseline CNS metastases was not specified in the protocol; brain scans were obtained at the investigator's discretion upon suspicion of new lesions.

1. Antonia SJ, et al. *N Engl J Med.* 2018;379:2342-2350.

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

Good PS, Stage III NSCLC Patients: Is Adjuvant Durvalumab a Standard?

- Yes!!
- Many ongoing trials were closed or modified
- What is next?
  - Induction IO therapy?
  - Doublet IO therapy?
  - Concurrent and adjuvant IO therapy?
  - Induction and adjuvant IO?
  - Concurrent and adjuvant IO therapy with RT and less or no chemo?

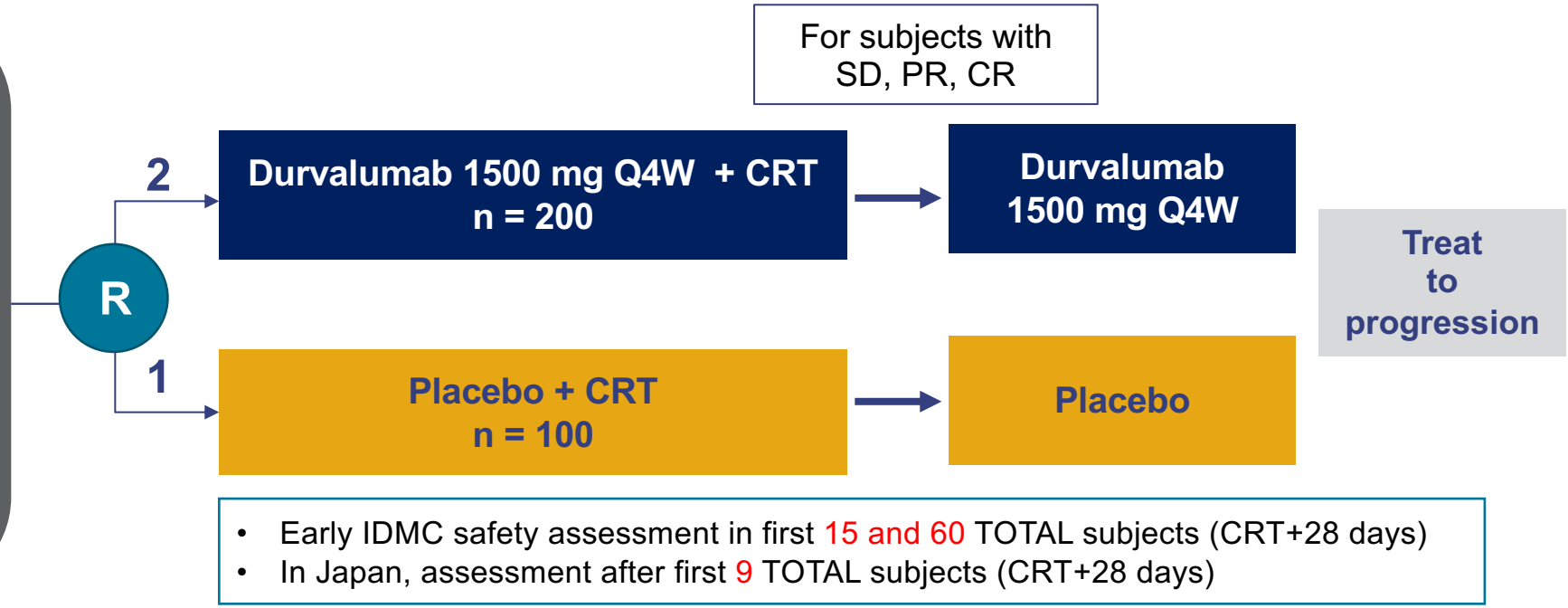
Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

PACIFIC 2: A Phase III Study of Durvalumab Given Concurrently With Platinum-based Chemo-RT for Patients With Stage III NSCLC

Study Population

- Patients with unresectable, Stage III NSCLC
- All-comers (PD-L1 expression-agnostic)
- ECOG PS 0-1

Randomized N = 300 patients



- Early IDMC safety assessment in first 15 and 60 TOTAL subjects (CRT+28 days)
- In Japan, assessment after first 9 TOTAL subjects (CRT+28 days)

Stratification
- Age (<65 yr, ≥65 yr)
- Stage (IIIA vs IIIB/C)

- **Primary Endpoints: ORR, PFS**
- **Key Secondary Endpoints:** OS, OS24

1. https://clinicaltrials.gov/ct2/show/NCT03519971

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

Supporting Safety Data for Pacific 2
CLOVER: A Phase I Study of Durvalumab + Chemo-RT

- Phase I durvalumab + chemo-RT for patients with multiple tumor types
- Locally advanced NSCLC cohort (similar to PACIFIC 2)
  - 14 patients treated
  - 8 have completed course of CRT
  - 1 DLT (Gr 4 transaminitis that resolved)
  - 1 death due to AE not related to IP (acute coronary syndrome w/ previous cardiac history)
- Recruitment completed

1. https://clinicaltrials.gov/ct2/show/NCT03509012

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

ECOG/ACRIN 5181
Randomized Phase III Trial of Durvalumab Concurrent & Consolidative Therapy or Consolidative Therapy Alone for Patients with Unresectable Stage III NSCLC

- Activated for Enrollment in April 2020
- Scheduled to Enroll 660 Patients

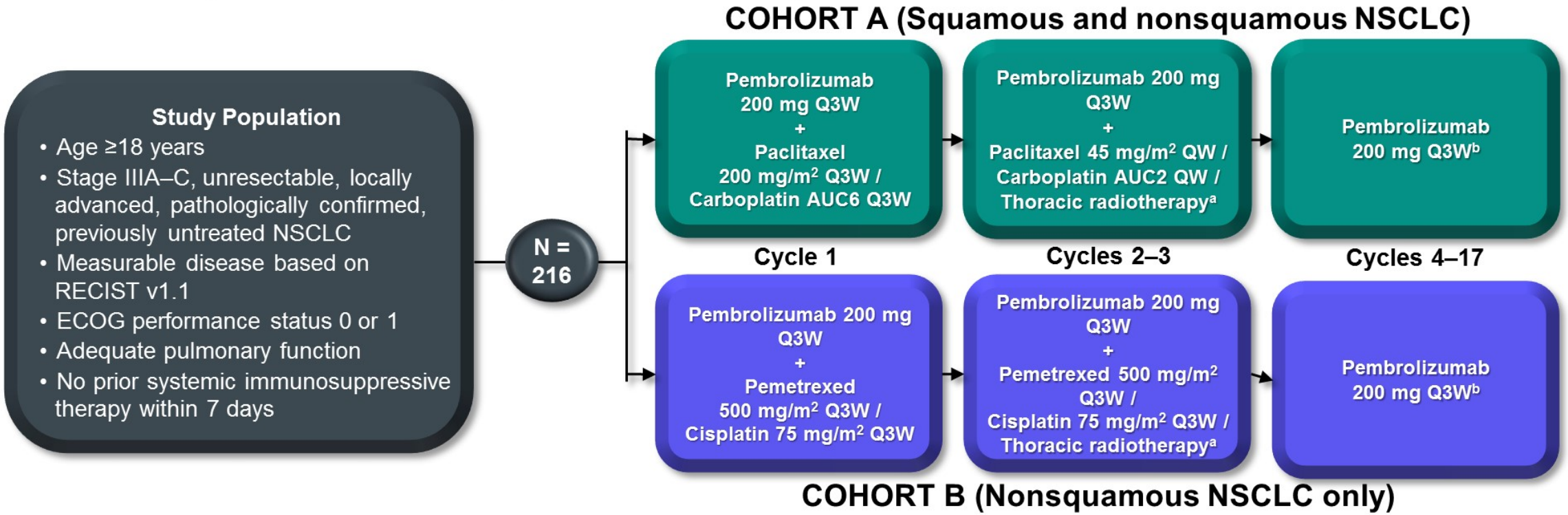
Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

Ongoing Phase II KEYNOTE-799 Trial Design

Study Design
- Nonrandomized, open-label study
- Choice of chemotherapy per investigator
- Nonsquamous NSCLC patients eligible for cohort A or B
- Squamous NSCLC patients eligible for cohort A only
- Cohort A fully accrued at data cutoff; cohort B is still accruing

Primary Objectives
- ORR per RECIST version 1.1 by BICR
- Percentage of patients who develop grade ≥3 pneumonitis

Secondary Objectives
- PFS, OS, safety



[a]60 Gy in 30 daily 2-Gy fractions.
[b]Treatment will continue until cycle 17 is completed or until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, or study withdrawal. Pembrolizumab therapy will be discontinued permanently in patients who develop grade ≥3 or recurrent grade 2 pneumonitis.

Jabbour SK et al. ASCO 2020;Abstract 9008.

KEYNOTE-799: Baseline Characteristics

All Treated Patients

	Cohort A (N = 112)	Cohort B (N = 73)
Age, median (range), y	66.0 (46–90)	64.0 (35–78)
Men, n (%)	76 (67.9)	40 (54.8)
ECOG PS 1, n (%)	61 (54.5)	34 (46.6)
Squamous, n (%)	73 (65.2)	0
Nonsquamous, n (%)	39 (34.8)	73 (100)
Former/current smoker, n (%)	106 (94.6)	70 (95.9)
PD-L1 TPS ≥1%	66 (58.9)	30 (41.1)

TPS, tumor proportion score.
Data cutoff date: January 3, 2020.

Jabbour SK et al. ASCO 2020;Abstract 9008.

KEYNOTE-799: ORR and Duration of Response

Pts with ≥15 wks follow-up	Cohort A (N = 112)	Cohort B (N = 53)
ORR, n (%) [90% CI]	75 (67.0) [58.9–74.3]	30 (56.6) [44.4–68.2]
CR	3 (2.7)	2 (3.8)
PR	72 (64.3)	28 (52.8)
SD, n (%)	23 (20.5)	18 (34.0)
PD, n (%)	1 (0.9)	0
Not evaluable, n (%)	3 (2.7)	0
No assessment, n (%)	10 (8.9)	5 (9.4)
Duration of response, median (range),[a] mo	NR (1.6+ to 10.5+)	NR (1.7+ to 10.5+)
Response duration ≥6 mo,[a] n (%)	30 (91.1)	9 (100)
6-mo PFS rate,[a] %	81.4	85.2
6-mo OS rate,[a] %	87.2	94.8

[a]Kaplan-Meier estimate. "+" indicates there is no progressive disease by the time of last disease assessment.
Data cutoff date: January 3, 2020.

Jabbour SK et al. ASCO 2020;Abstract 9008.

KEYNOTE-799: Incidence of Grade ≥3 Pneumonitis (Safety)

	Cohort A (N = 112)	Cohort B (N = 73)
Grade ≥3 pneumonitis (all cause),[a] n (%) [90% CI]	**9 (8.0) [4.3–13.6]**	**4 (5.5) [1.9–12.1]**
Treatment-related adverse events	105 (93.8)	64 (87.7)
Grades 3–5	72 (64.3)	30 (41.1)
Led to death	4[a] (3.6)	0
Led to discontinuation of any treatment component	32 (28.6)	9 (12.3)
Immune-mediated adverse events and infusion reactions	53 (47.3)	20 (27.4)
Grades 3–5	17 (15.2)	6 (8.2)
Led to death	4 (3.6)	0

[a]Four (3.6%) patients in cohort A and none in cohort B had treatment-related grade 5 pneumonitis.
Data cutoff date: January 3, 2020.

Jabbour SK et al. ASCO 2020;Abstract 9008.

KEYNOTE-799: Conclusions

- Pembrolizumab plus CCRT shows promising antitumor activity in patients with unresectable, locally advanced stage III NSCLC
  - ORR in both cohorts exceeded 50%
  - Estimated response duration was ≥6 months for most patients with a response

- Incidence of adverse events among patients who received pembrolizumab plus CCRT was consistent with the established toxicity profiles of CCRT for stage III NSCLC[1] and pembrolizumab monotherapy[2]
  - Incidence of grade ≥3 pneumonitis was 8.0% in cohort A and 5.5% in cohort B
  - Observed rates of grade ≥3 pneumonitis were within the expected range for immunotherapy combined with CCRT[3]

1. Yoon SM, *World J Clin Oncol* 2017;8:1-20. 2. Mok T, et al. *Lancet* 2019;393:1819-1830. 3. Peters S, et al. *Lung Cancer* 2019;133:83-87.

New Non I-O Options for Stage III NSCLC

- New Chemotherapy Regimens?
- More Targeted Therapies?
- Better Radiation Delivery?
- Better Integration with I-O Approaches?

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

Should osimertinib be incorporated into the treatment of unresectable adenocarcinoma of the lung in a patient with an EGFR tumor mutation?

a. Yes

b. No

c. I don’t know

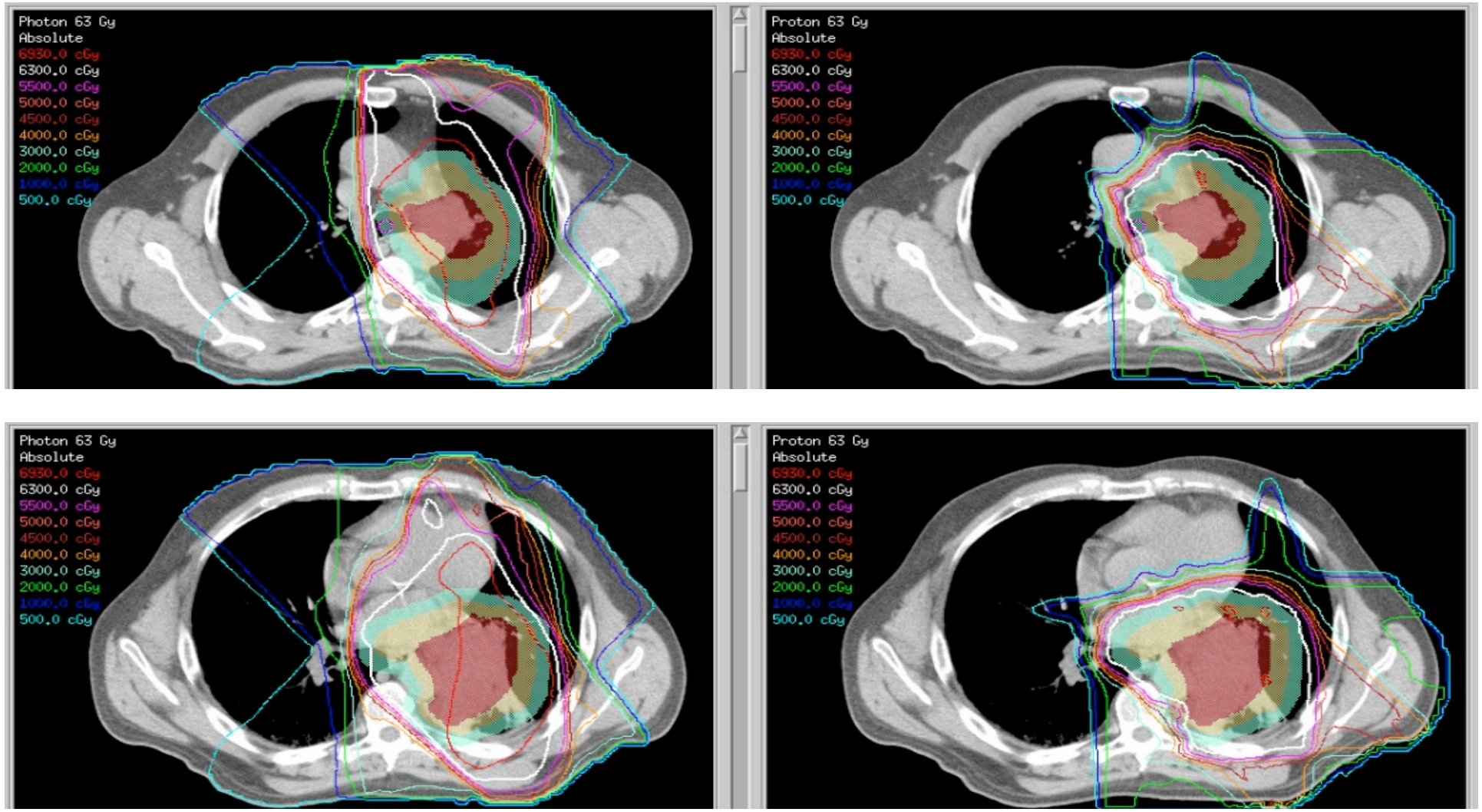
Case Presentation – Dr Curran: A 45-year-old woman and never smoker with Stage III NSCLC and an EGFR mutation

- 45 yo never smoker female presenting with fever and cough
- COVID-19 nasopharyngeal test negative
- CT chest demonstrated bulky left lower lung mass and left sided mediastinal adenopathy
- EBUS biopsy: adenocarcinoma, with EGFR mutation
- Pt recommended for concurrent chemo-RT and adjuvant durvalumab
- Because of bulky disease, patient is considered for proton therapy

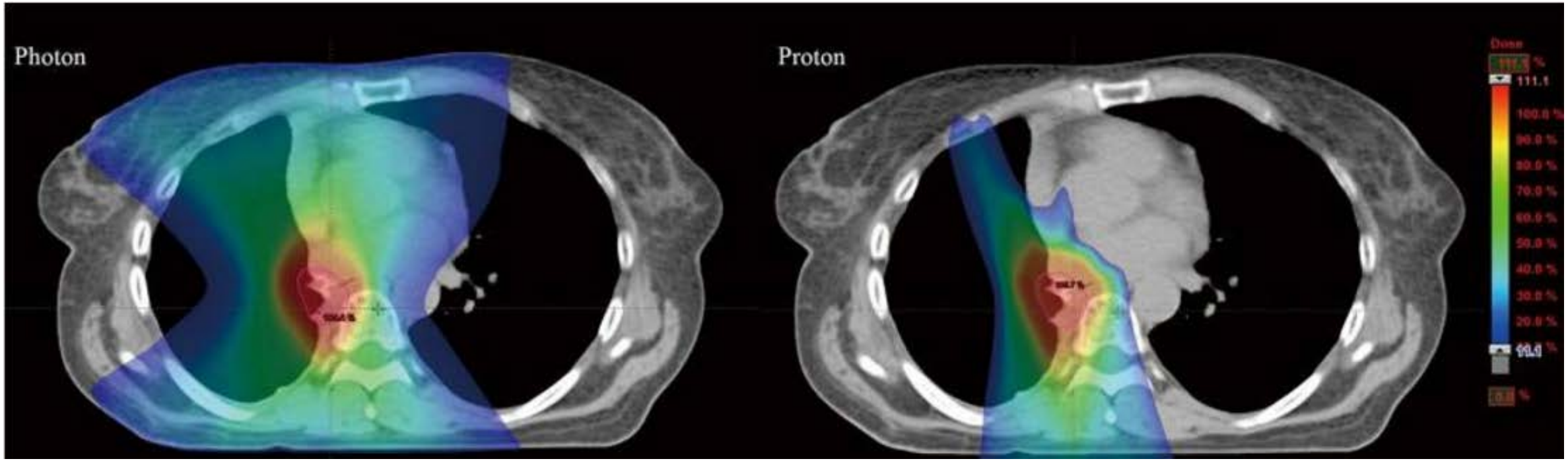
Case Presentation – Dr Curran: A 45-year-old woman and never smoker with Stage III NSCLC and an EGFR mutation (cont)

Photon 3-DCRT

Proton



Difference between IMRT & Proton Beam RT



Images from Diwanji TP, et al. *Transl Lung Cancer Res*. 2017;6(2):131-147.

Case Presentation – Dr Curran: A 45-year-old woman and never smoker with Stage III NSCLC and an EGFR mutation (cont)

- Patient received concurrent Proton Therapy and chemotherapy
- Well tolerated and scheduled to start durvalumab soon
- What is the role of EGFR targeted agents?

What is the effect of radiation therapy on immune function?

a. No effect
b. Suppression of antitumor immunity
c. Enhancement of antitumor immunity
d. Data are not available to answer this question
e. I don’t know

Radiation as Immunosuppressant What is the Data?

- Decline in blood counts with large field RT well known
- Blood count depression with pelvic RT vs prostate only RT
- Lymphocyte count sufficient?
- Concept of RT dose to circulating immune cells?

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

NRG RTOG 0617 – Effective (RT) Dose to Circulating Immune Cells, 2019

- NRG-RTOG 0617: Poorer survival with high dose RT for Stage III NSCLC
- **Was this due to RT toxicity to the immune system?**

- **Effective dose to circulating immune cells (EDIC) modelled based on RT dosimetry factors applied to 453 eligible Stage III NSCLC pts enrolled on RTOG 0617**

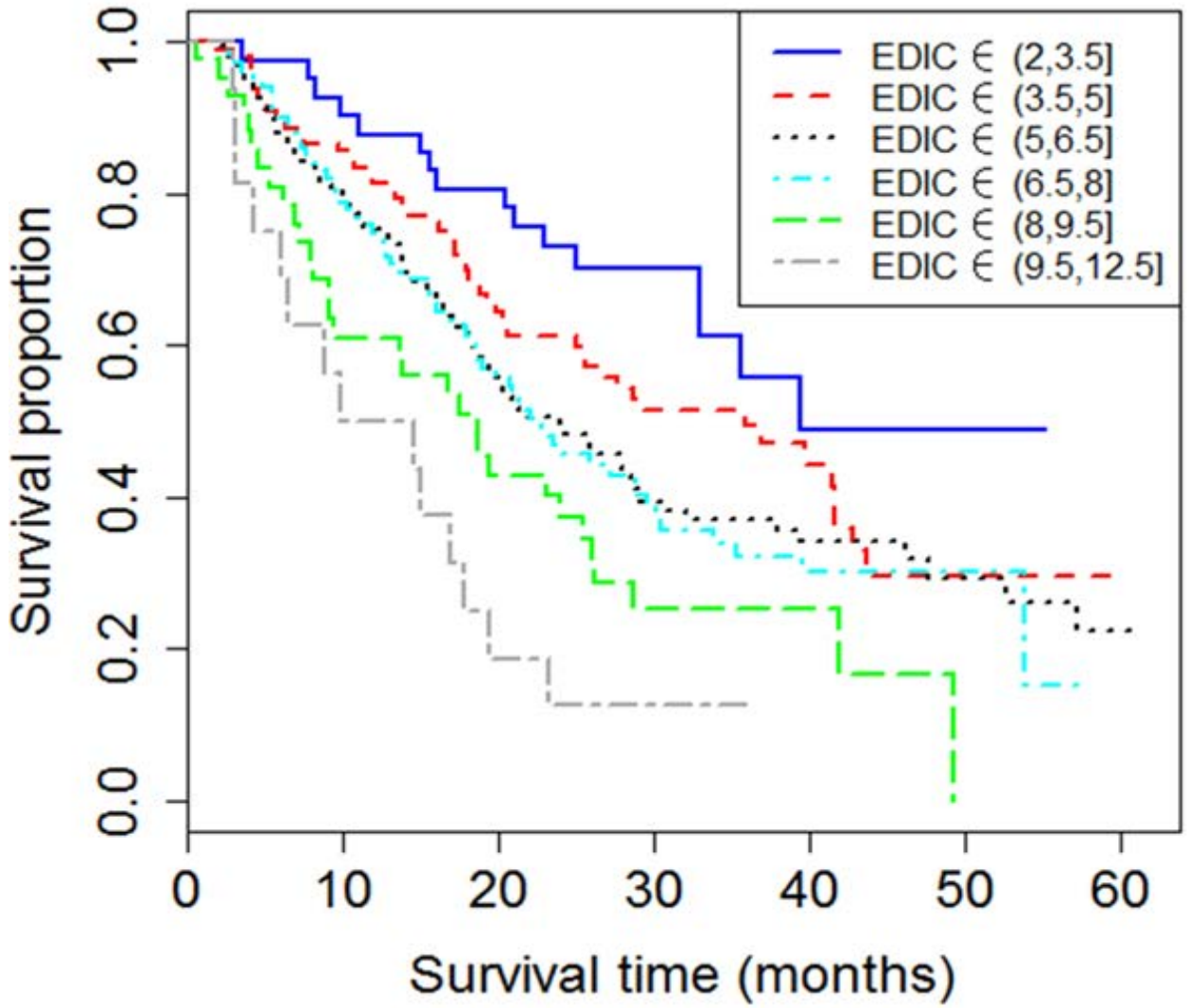
- **EDIC ranged from 2.05 to 12.20 Gy (median 5.94 Gy)**

- **EDIC SIGNIFICANTLY and INVERSELY associated with survival and local PFS after adjusting for other factors**

Jin et al.

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

Survival in NRG/RTOG 0617 Trial Correlation with Immune System RT Dose



Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

Agenda

MODULE 1: Overview of Locally Advanced Unresectable Lung Cancer

- Staging, history of treatment, rationale for checkpoint inhibition
- Ms Usher: A 64-year-old woman with Stage IIIA T1bN2 adenocarcinoma of the lung
- Dr Curran: A 54-year-old man with Stage IIIA T2N2M0 squamous cell carcinoma

MODULE 2: Immune Checkpoint Inhibition in the Management of Locally Advanced NSCLC

- PACIFIC trial: Durvalumab consolidation after successful completion of chemoradiation therapy
- KEYNOTE-799 trial: Pembrolizumab in combination with chemotherapy followed by consolidation pembrolizumab
- Dr Curran: A 45-year-old woman and never smoker with Stage III NSCLC and an EGFR mutation
- Impact of radiation therapy on the immune system

MODULE 3: Management of Side Effects Associated with Chemoradiation Therapy and Durvalumab

- Ms Usher: A 75-year-old man who developed pneumonitis after chemoradiation therapy
- Ms Usher: A 73-year-old man who developed postchemoradiation esophagitis
- Dr Curran: A 61-year-old man with locally advanced NSCLC and a recent myocardial infarction
- Ms Usher: A 76-year-old woman and smoker with a history of breast cancer

RTP
RESEARCH
TO PRACTICE

Case Presentation – Ms Usher: A 75-year-old man who developed pneumonitis after chemoradiation therapy

- 75 yo M with right apical NSCLC, cT4N2M0.
- PMH: Hepatitis C, hypertension, left hip arthroplasty and left temple melanoma excised in 2010.
- His PET/CT had shown a 6.6 cm right apical tumor with right hilar and mediastinal LAD and scattered hypermetabolic RLL nodules without distant metastatic disease.
- 3/18/20: Bronchoscopy with EBUS and biopsy, results NSCLC
- He completed concurrent chemoradiation (60 Gy) with carboplatin and paclitaxel (4 of 6 cycles) on 5/18/20.

Courtesy of Camille Usher, MS, APRN, NP-C

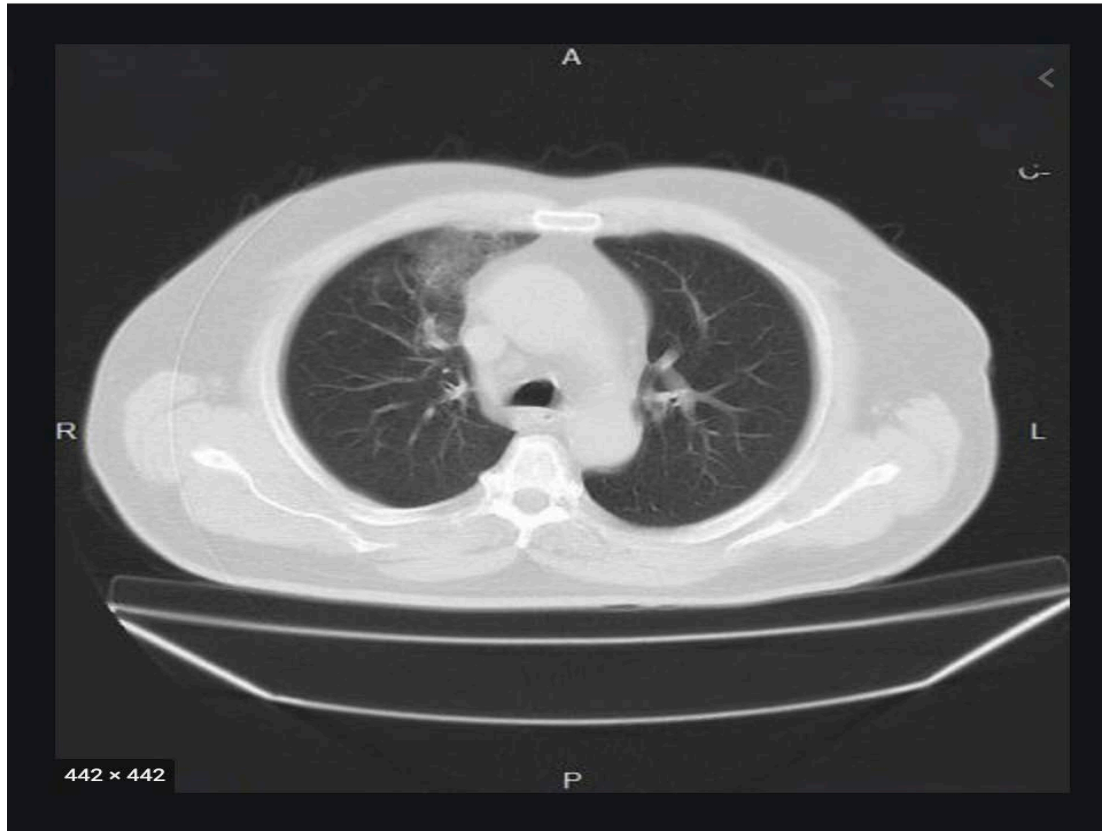
Case Presentation – Ms Usher: A 75-year-old man who developed pneumonitis after chemoradiation therapy (cont)

- Shortly after treatment on 5/24/20, the patient developed 2-3 days of fever, fatigue, SOB, and a cough.
  - CXR on admission showed hazy opacities in the right lung. He was started on empiric antibiotics. CT Chest had showed bilateral patch GGOs R>L with decrease in size of RUL mass. On 5/29/20, he underwent BAL and TBBx. This was notable for a lymphocytic infiltrate and negative cultures. He was then started on pred 1 mg/kg daily. He was discharged on 6/5/20 with the following taper 40 mg of pred, to be decreased by 10 mg per day every 10 days.
- Saw patient in clinic on 8/2020, remains short of breath with walking short distances, desaturating to the mid-high 80s. He uses oxygen at home and at night.
- He continued prednisone 20 mg daily with PPI. PPI for prophylaxis against steroid-induced gastritis.
- Pt will RTC clinic in November with PET-CT. Hopefully, can begin steroid taper at that time

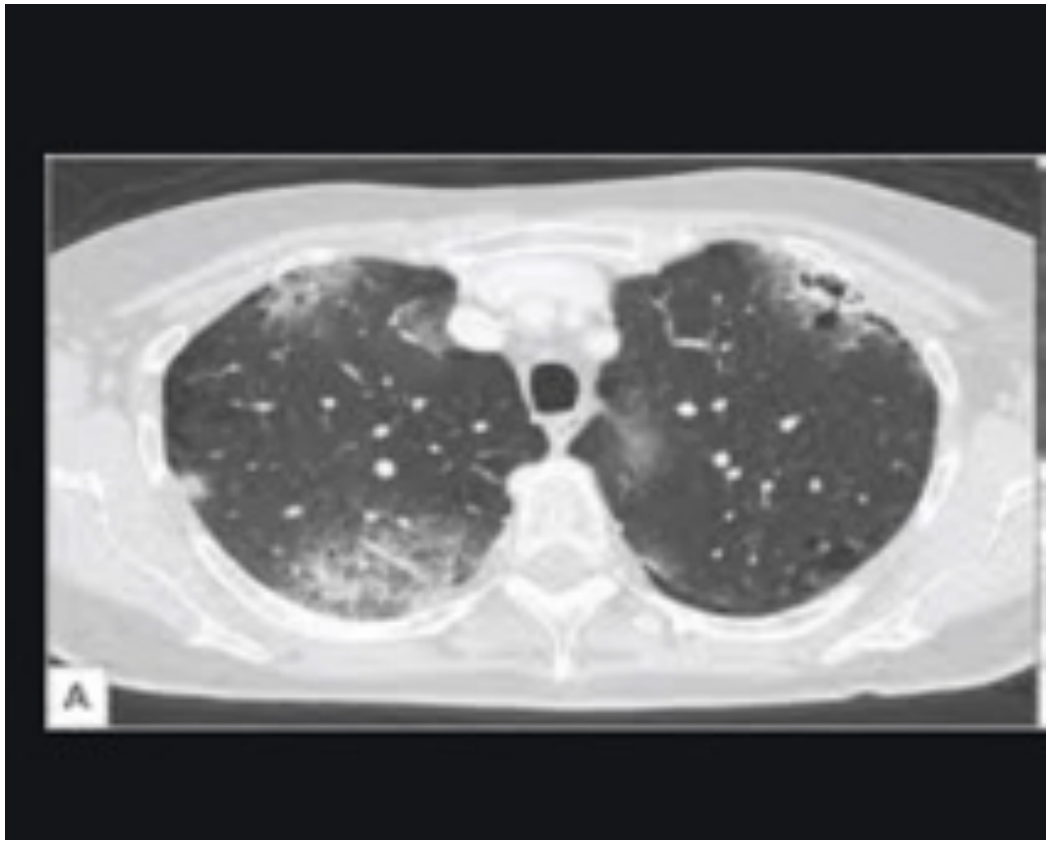
Courtesy of Camille Usher, MS, APRN, NP-C

Pneumonitis

Radiation induced



Drug induced



Courtesy of Camille Usher, MS, APRN, NP-C

Management

- Diagnosis of exclusion
- Unresponsive to antibiotic therapy
- Management depends on severity of the pneumonitis
- Early recognition is important
- Consider “drug holiday”
- Systemic corticosteroid therapy should be promptly initiated
  - Treat with prednisone - standard dosing is 1 mg/kg/day for high grade pneumonitis. Can also use solumedrol dose pack for low grade pneumonitis
- Ground glass opacities may be observed in drug or radiation induced lung disease

Courtesy of Camille Usher, MS, APRN, NP-C

Education

- Potential side effects: sore throat (mediastinum in the field), cough, dyspnea, fatigue, chest pain/pressure, possible skin irritation on the back
- Hydrate (64 oz/day)
- Light exercise for 30 minutes/day to combat fatigue
- High protein diet
- Magic Mouthwash prior to meals. Swish and swallow
- Smoking Cessation
- Signs, symptoms, and onset of Radiation pneumonitis

Courtesy of Camille Usher, MS, APRN, NP-C

Nursing Considerations

- Foster a good working relationship with Med Onc team
- Meet patient at some point between initial consult and completion of treatment to establish rapport
- Health maintenance
- Involve dietician, pulmonology, supportive oncology early, smoking cessation clinic early
- Symptoms typically present ~10-15 fractions (2-3 weeks) into treatment
- Familiarize yourself with natural history of radiation pneumonitis and radiation fibrosis, particularly when looking at imaging and managing symptoms

Courtesy of Camille Usher, MS, APRN, NP-C

Case Presentation – Ms Usher: A 73-year-old man who developed postchemoradiation esophagitis

3/2020: Developed a cough and fever for several weeks. Pt was treated with antibiotics following a chest x-ray by his PCP. Of note, patient smoked heavily in the remote past. Quit about 40 years ago. Had smoked for approximately 10-15 years, about 1 pack per day. The patient works as a consultant to small businesses. Follow-up chest x-ray showed a persistent abnormality in his left upper lobe

4/2020: Work up revealed adenocarcinoma of the lung (T2 N3 M0 stage IIIB non-small cell lung cancer) by lung biopsy. PET-CT hilar and mediastinal nodal involvement, including contralateral paratracheal involvement

5/13/ to 6/17/2020: Underwent concurrent chemoradiation with carboplatin and paclitaxel

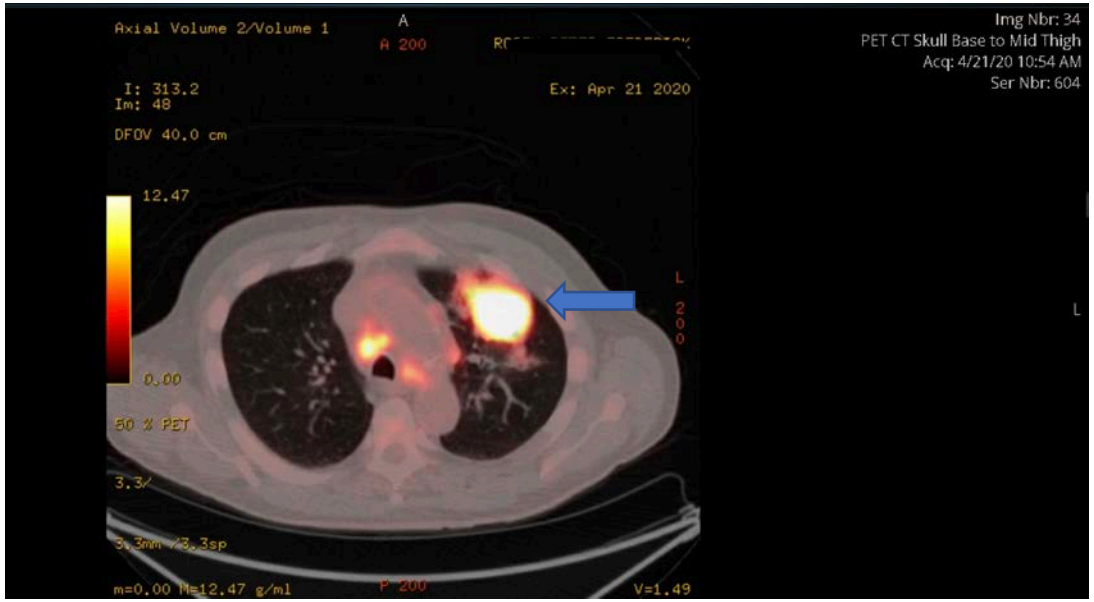
5/26/20: At 11/30 fractions patient developed burning sensation in his esophagus with swallowing, along with intermittent cough and fatigue

Case Presentation – Ms Usher: A 73-year-old man who developed postchemoradiation esophagitis (cont)

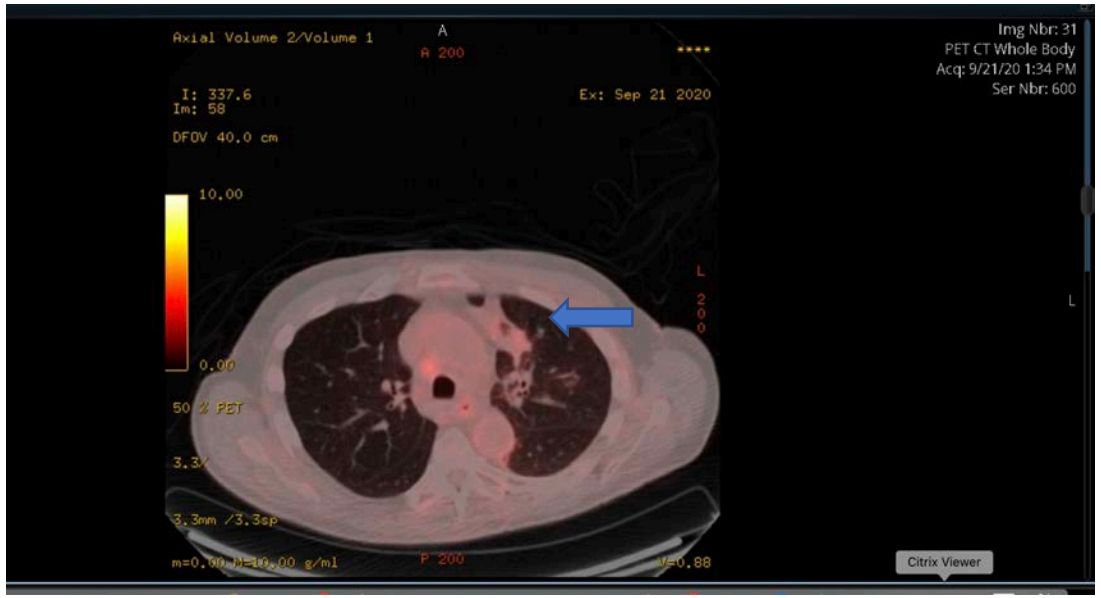
- One month post chemoRT, treatment related symptoms (fatigue and esophagitis) resolved and he was back to golfing. Cough persisted but lessened and he used guaifenesin less.
- 7/17/20 CT Chest shows primary tumor has decreased in size, reflective of positive treatment response. Increased mediastinal lymphadenopathy noted, but likely inflammatory etiology given he just completed his radiation treatment very recently
- 7/22/20 C1D1 Durvalumab maintenance
- 9/22/20 completed Cycle 3 of Durvalumab
- 10/7/2020 immunoprofile TTF1/NAPSIN positive AE1/3 positive
- Currently, patient is doing well. Cough resolved

Case Presentation – Ms Usher: A 73-year-old man who developed postchemoradiation esophagitis (cont)

Pre chemoXRT



3 months post chemoXRT



Side effect management during treatment

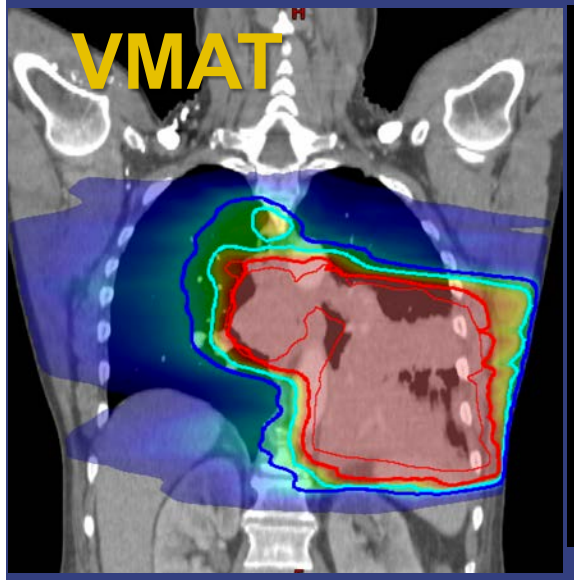
- Cough
  - Cough drops or dextromethorphan
  - Guaifenesin 10 mg-100 mg/5 ml PO Q6hr prn
  - Benzonatate (honorable mention, typically ineffective)

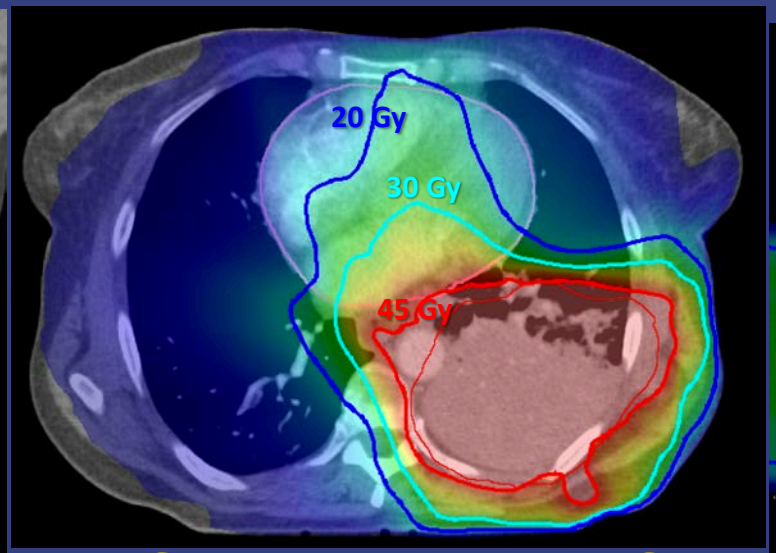
- Esophagitis
  - Famotidine 20 mg Daily or pantoprazole 40 mg consider titrating up to BID if needed
  - Magic Mouthwash potentially helps with cough (particularly in this patient)
  - Supplement with BOOST®/Ensure®. Encourage high protein diet
  - Involve Clinical Dietician
  - Avoid coffee, extreme food temps, spicy or acidic foods, dry hard textured foods

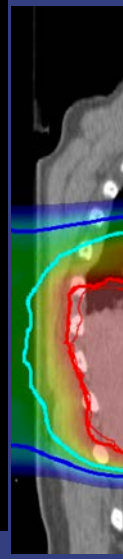
Case Presentation – Dr Curran: A 61-year-old man with locally advanced NSCLC found secondary to acute myocardial infarction

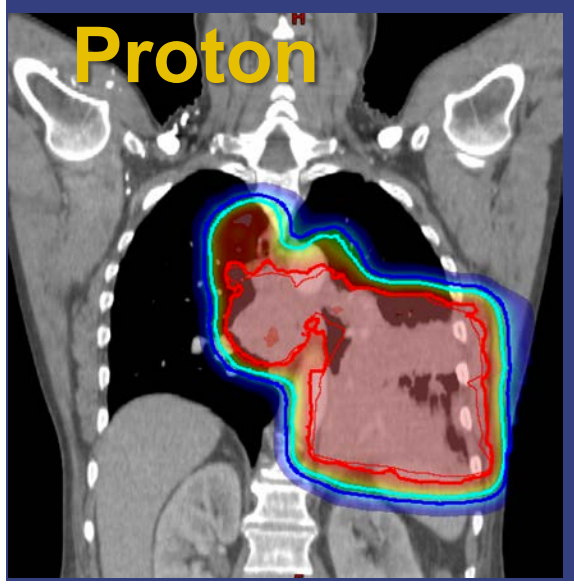
- 61 yo male admitted to coronary care unit with acute MI
- Also found to have bulky left lung mass which on biopsy = Squamous Cell Ca
- Coronary recovery leaves patient with low ejection fraction but ambulatory
- Lung cancer staging: T3N2M0, medically/anatomically unresectable

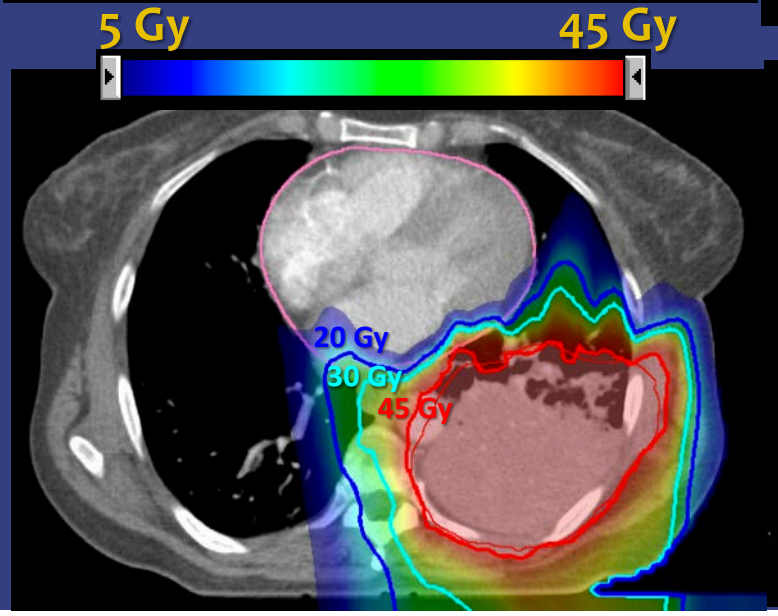
- Following oncology consults, advised to consider proton therapy to reduce RT dose to heart and to consider reduced # of weekly chemo treatments

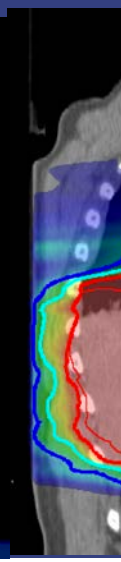

VMAT

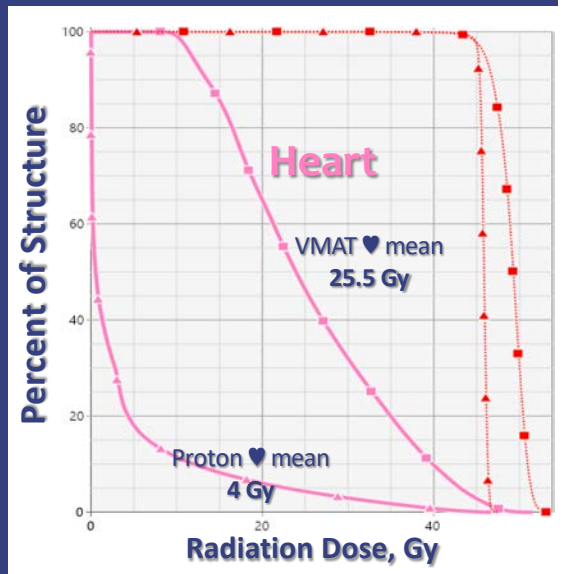

20 Gy
30 Gy
45 Gy

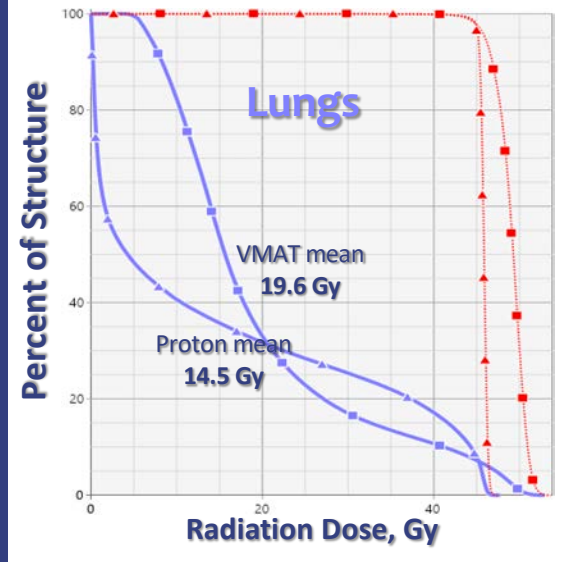

Heart


Proton


5 Gy
45 Gy
20 Gy
30 Gy
45 Gy


Heart


Heart
VMAT ♥ mean
25.5 Gy
Proton ♥ mean
4 Gy
Percent of Structure
Radiation Dose, Gy


Lungs
VMAT mean
19.6 Gy
Proton mean
14.5 Gy
Percent of Structure
Radiation Dose, Gy

Case Presentation – Dr Curran: A 61-year-old man with locally advanced NSCLC found secondary to acute myocardial infarction (cont)

- Patient started on proton therapy with concurrent chemo, with greatly reduced RT dose to heart versus non-proton therapy
- Currently on week 3 doing well on cardiac rehab as well

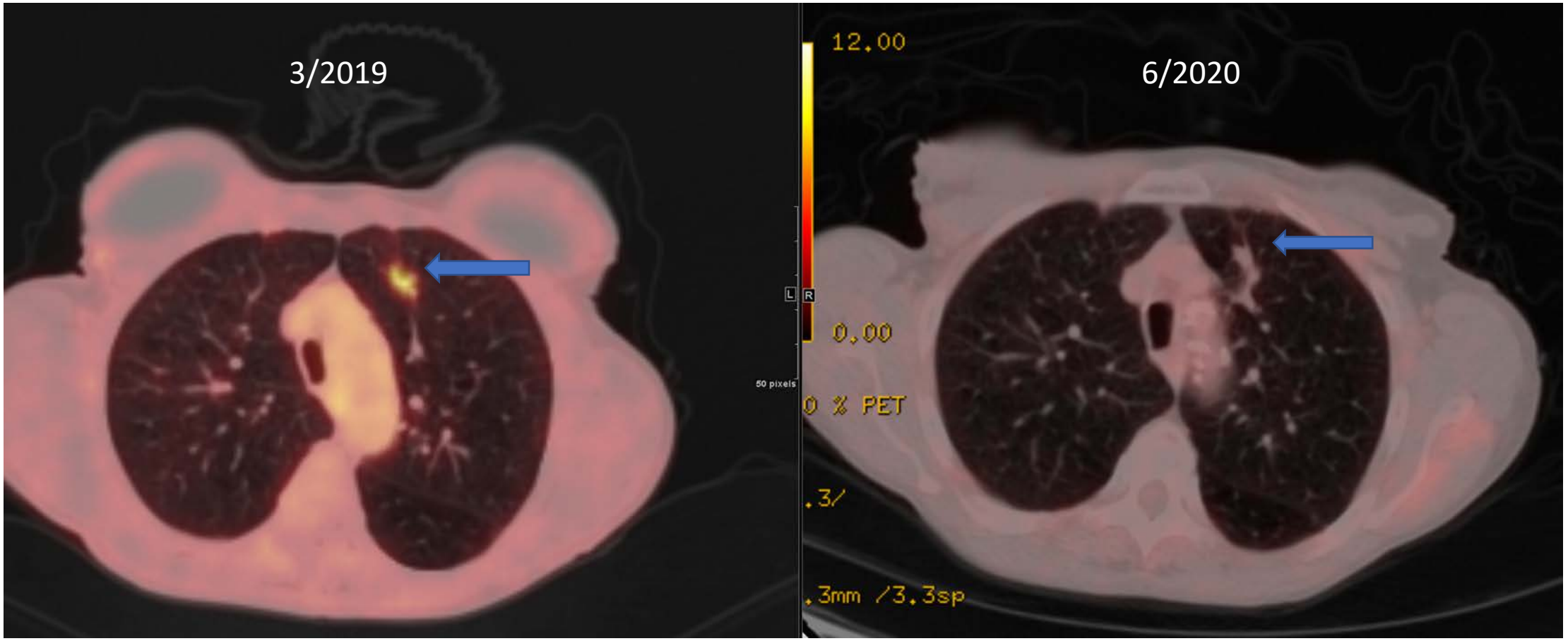
Case Presentation – Ms Usher: A 76-year-old woman and smoker with a history of breast cancer

- Initially dx in 12/2013 with Stage III NSCLC s/p radiation to 44 Gy EBRT and SBRT boost with weekly carboplatin and paclitaxel from 01/06/2014 through 02/03/2014
- PMH of 60 pack year smoker, Asthma, Stage II Breast CA s/p mastectomy and adjuvant chemo and endocrine therapy (no radiation), Scoliosis, Osteopenia, H. Pylori
- She developed a second primary T1 lesion in the left upper lobe in 2019 biopsy showing adeno then treated by SBRT, 18 Gy x 3 fractions completed 4/26/20
- Most recently found to have new lingular and left lower lobe lesions treated with SBRT 50 Gy x 5 fractions, completed 7/21/20
- Continues to smoke but decreased from 1 ppd to 6 cigarettes/day

Case Presentation – Ms Usher: A 76-year-old woman and smoker with a history of breast cancer and Stage III NSCLC (cont)

- Dyspnea has progressively worsened over the years
- Started seeing Pulmonology in 10/2014
- PFTs steadily worsening
- Compliant with fluticasone and salmeterol 500/50 and uses albuterol rescue inhaler 3-4x/day. Continues to smoke ~6 cigarettes/day. Currently using supplemental O2 at night and with exertion
- Surveillance CT Chest every 4-6 months
- Continue to reinforce smoking cessation

Case Presentation – Ms Usher: A 76-year-old woman and smoker with a history of breast cancer and Stage III NSCLC (cont)



Meet The Professor
Management of Multiple Myeloma

Thursday, October 22, 2020
12:00 PM – 1:00 PM ET

Faculty

Krina K Patel, MD, MSc

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

CME and NCPD credit information will be emailed to each participant within 24 hours.

RTP
RESEARCH
TO PRACTICE