Thank you for joining us.
The program will commence momentarily.

Recent Advances in Medical Oncology: Immunotherapy and Other Nontargeted Approaches for Lung Cancer

Wednesday, August 5, 2020

5:00 PM – 6:30 PM ET

Faculty

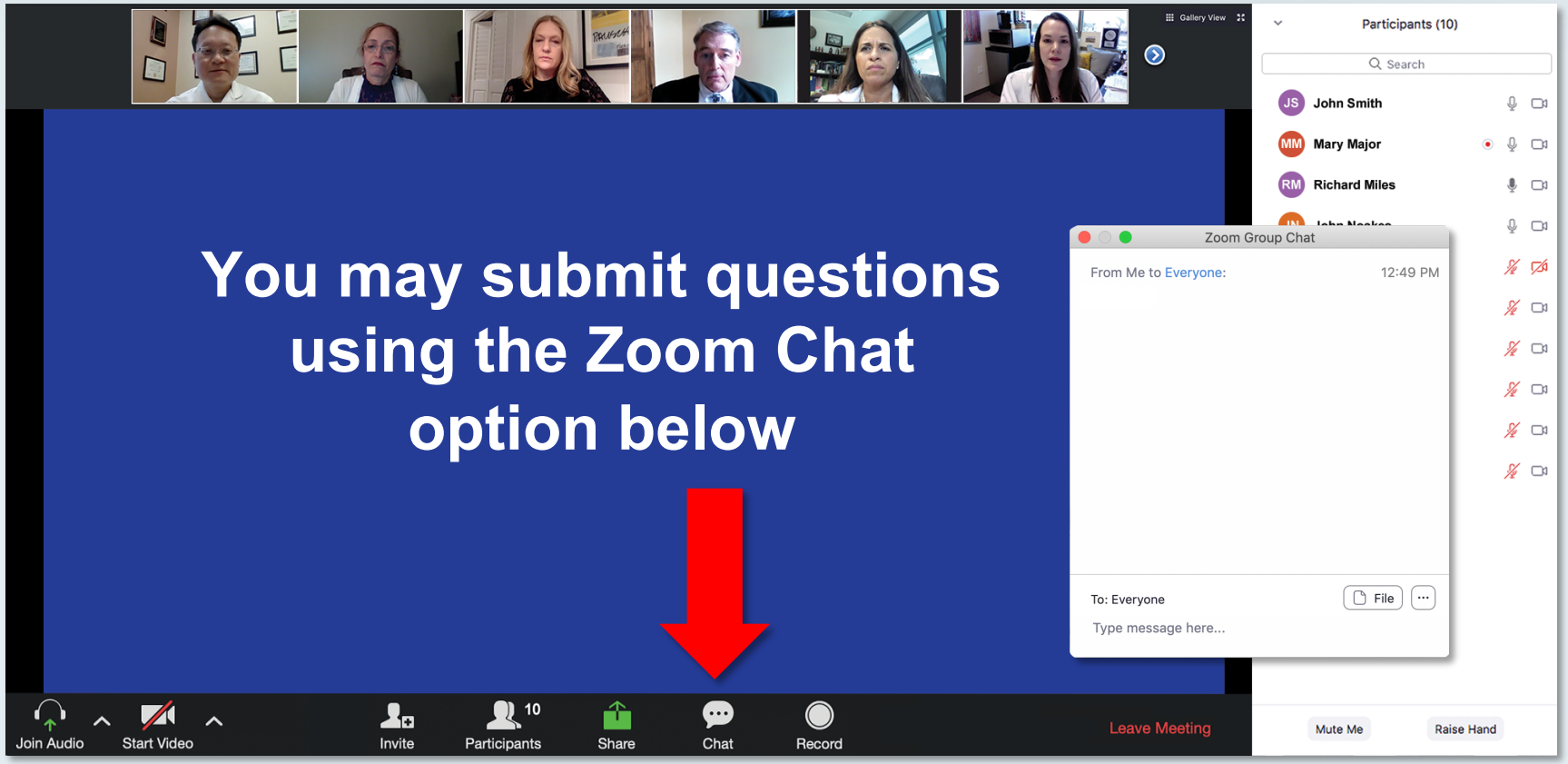
Edward B Garon, MD, MS
Stephen V Liu, MD, PhD
David R Spigel, MD

Moderator

Neil Love, MD

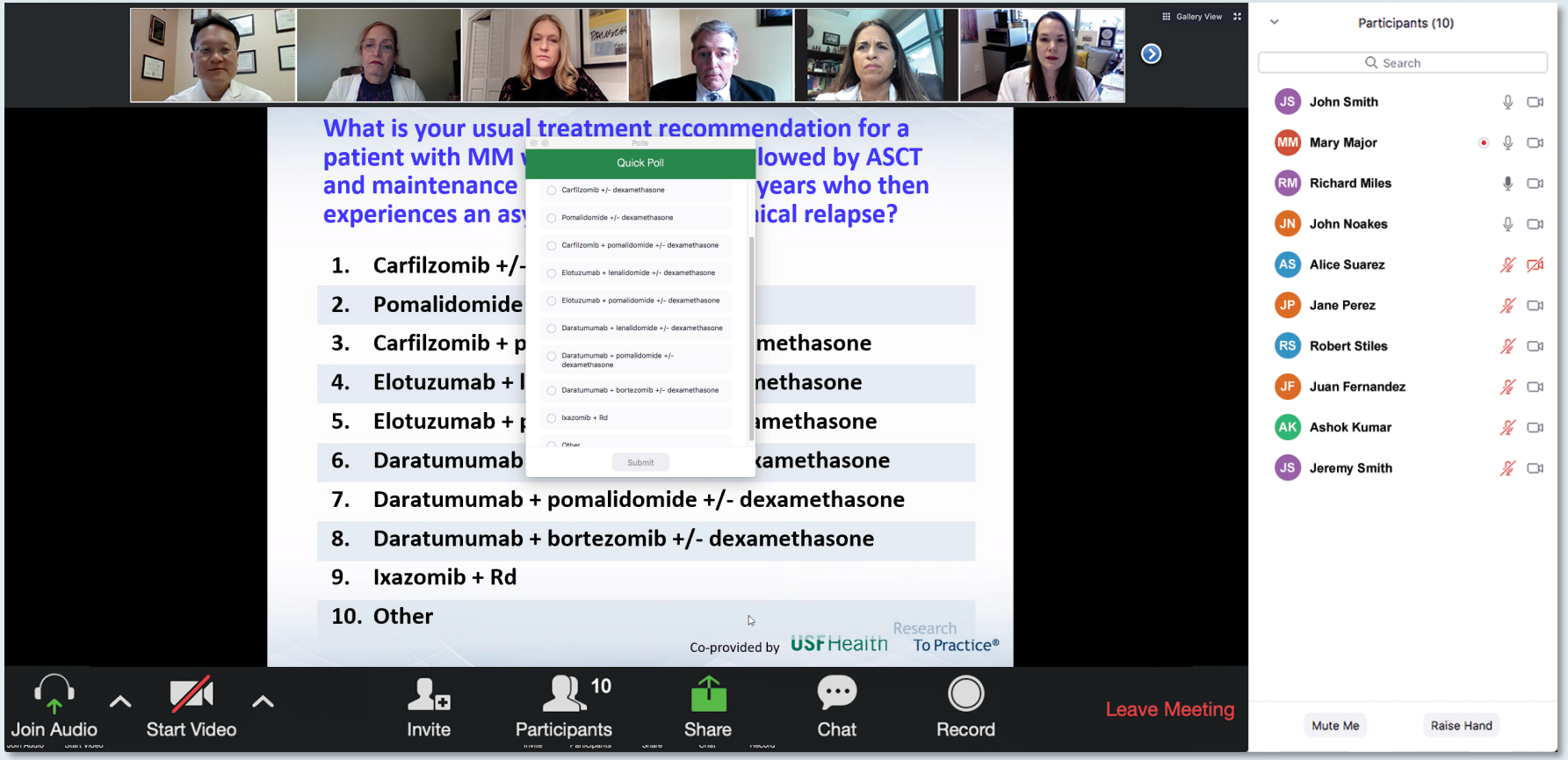
RTP RESEARCH TO PRACTICE

Dr Love and Faculty Encourage You to Ask Questions



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

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.

Commercial Support

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Dr Love — Disclosures

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Dr Garon — Disclosures

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Dr Liu — Disclosures

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Dr Spigel — Disclosures

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Upcoming Live Webinars

Thursday, August 6, 2020
12:00 PM – 1:00 PM ET

Current Questions and Controversies in the Management of Lung Cancer

Faculty
John V Heymach, MD, PhD

Moderator
Neil Love, MD

Friday, August 7, 2020
9:00 AM – 10:00 AM ET

Virtual Molecular Tumor Board: Identification of New and Emerging Genomic Alterations in Metastatic Non-Small Cell Lung Cancer

Faculty
Alexander E Drilon, MD
Andrew McKenzie, PhD
Milan Radovich, PhD

Moderator
Neil Love, MD

Upcoming Live Webinars

Monday, August 10, 2020
5:00 PM – 6:00 PM ET

Recent Advances in Medical Oncology: Hodgkin and Non-Hodgkin Lymphomas

Faculty
Jeremy Abramson, MD
Christopher R Flowers, MD, MS

Moderator
Neil Love, MD

Tuesday, August 11, 2020
5:00 PM – 6:00 PM ET

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

Faculty
Robert Z Orlowski, MD, PhD

Moderator
Neil Love, MD

Upcoming Live Webinars

Wednesday, August 12, 2020
1:00 PM – 2:00 PM ET

Meet The Professors Clinical Investigators Discuss Existing and Emerging Treatment Strategies for Patients with Ovarian, Cervical and Endometrial Cancer

Faculty
Stephanie Lheureux, MD, PhD
Professor Ignace Vergote

Moderator
Neil Love, MD

Wednesday, August 12, 2020
5:00 PM – 6:30 PM ET

Recent Advances in Medical Oncology: Hepatocellular Carcinoma and Pancreatic Cancer

Faculty
Tanios Bekaii-Saab, MD
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP
Alan P Venook, MD

Moderator
Neil Love, MD

Upcoming Live Webinars

Friday, August 14, 2020
9:00 AM – 10:00 AM ET

Virtual Molecular Tumor Board: Recognition and Management of Targetable Tumor Mutations in Less Common Cancer Types

Faculty

Marcia S Brose, MD, PhD
Bryan P Schneider, MD
Milan Radovich, PhD

Moderator

Neil Love, MD

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David R Spigel, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Edward B Garon, MD, MS
Associate Professor
Director, Thoracic Oncology Program
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Jonsson Comprehensive Cancer Center
Los Angeles, California

David R Spigel, MD
Chief Scientific Officer
Program Director, Lung Cancer Research
Sarah Cannon Research Institute
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Stephen V Liu, MD, PhD
Associate Professor of Medicine
Georgetown University Hospital
Washington, DC

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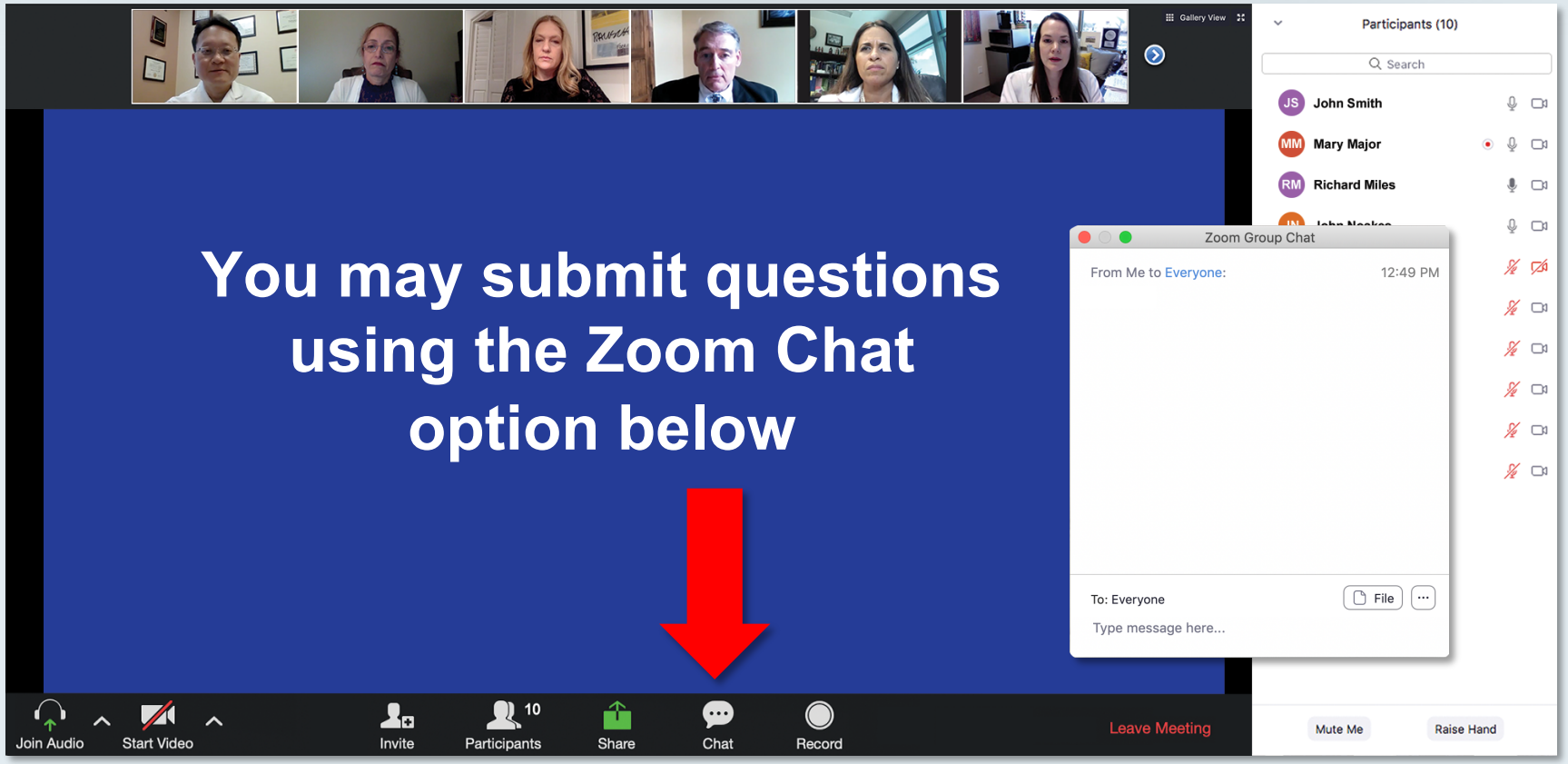

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Neil Love, MD

RTP
RESEARCH
TO PRACTICE

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All sessions moderated by Neil Love, MD and featuring Bryan Schneider, MD and Milan Radovich, PhD of the Indiana University Health Precision Genomics Program

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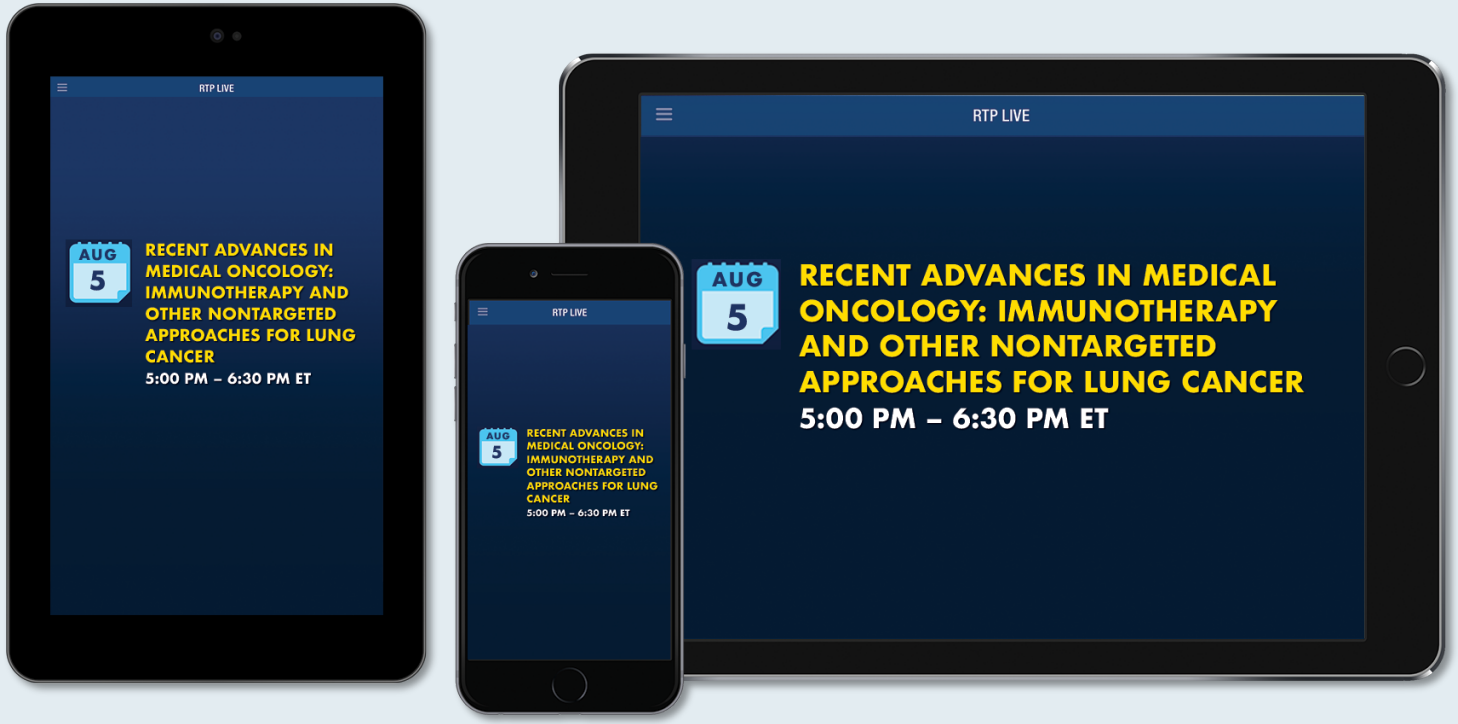

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RTP RESEARCH TO PRACTICE

Consulting Investigators

Matthew Gubens, MD, MS
Associate Professor, Thoracic Medical Oncology
University of California, San Francisco
San Francisco, California

Nasser H Hanna, MD
Professor of Medicine
Tom and Julie Wood Family Foundation
Professor of Lung Cancer Clinical Research
Indiana University
Indianapolis, Indiana

Corey J Langer, MD
Director of Thoracic Oncology
Abramson Cancer Center
Professor of Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Agenda

MODULE 1: Metastatic NSCLC without a Targetable Mutation

MODULE 2: Small Cell Lung Cancer

MODULE 3: Immunotherapy Consolidation After Chemoradiation Therapy

MODULE 1: Metastatic NSCLC without a Targetable Mutation

- **Faculty Cases – Dr Garon**
  - A 52-year-old man with mNSCLC and a KRAS G12V mutation
  - A 91-year-old woman with metastatic squamous cell carcinoma of the lung
- **Key Relevant Data Sets**
- **Questions and Cases from Investigators**

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

Combination Regimens

- Pembrolizumab + platinum and pemetrexed[1]
- Pembrolizumab + carboplatin, paclitaxel or *nab* paclitaxel[2]
- Atezolizumab + carboplatin and paclitaxel and bevacizumab[3]
- Atezolizumab + carboplatin and *nab* paclitaxel[4]
- Nivolumab + ipilimumab[5]
- Nivolumab + ipilimumab and cisplatin[6]
- Nivolumab + ipilimumab and carboplatin[6]

Monotherapy

- Pembrolizumab[7,8]
- Atezolizumab[9]

[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

What first-line treatment would you likely recommend for a 52-year-old man with nonsquamous NSCLC metastatic to the liver and bone with a PD-L1 TPS of 90%?

a. Chemotherapy
b. Chemotherapy + bevacizumab
c. Anti-PD-1/PD-L1 antibody alone
d. Carboplatin/pemetrexed/pembrolizumab
e. Atezolizumab/carboplatin/*nab* paclitaxel
f. Atezolizumab/carboplatin/paclitaxel/bevacizumab
g. Ipilimumab/nivolumab
h. Other

Case Presentation (Dr Garon): A 52-year-old man with mNSCLC and a KRAS G12V mutation

52-year-old man, active, who presented with a mild cough. Chest x-ray showed a mass. PET CT showed a 6-cm lesion in the right lower lobe with multiple involved lymph nodes, 2 liver lesions and several bone lesions. 70 pack-year smoking history. Molecular studies demonstrated a KRAS G12V mutation. PD-L1 was 90% (22C3).

What first-line treatment would you likely recommend for a highly functional 91-year-old woman with metastatic squamous cell cancer of the lung and a PD-L1 TPS of 15%?

a. Chemotherapy
b. Pembrolizumab
c. Atezolizumab
d. Atezolizumab/taxane
e. Atezolizumab/paclitaxel
f. Pembrolizumab/carboplatin/*nab* paclitaxel
g. Pembrolizumab/carboplatin/paclitaxel
h. Ipilimumab/nivolumab
i. Other

Case Presentation (Dr Garon): A 91-year-old woman with metastatic squamous cell carcinoma of the lung

91-year-old woman. Generally good health with 20 pack-year smoking history. Highly functional and living independently, presents with mild dyspnea. Noted on chest x-ray to have a mass in the lungs, which was followed by a CT that showed a 4-cm lung lesion with several lytic bone lesions. Biopsy revealed squamous cell carcinoma. No molecular studies were performed except for PD-L1, which was 15% (22C3). Brain MRI negative. Patient expresses both an interest in active treatment and a focus on quality of life.

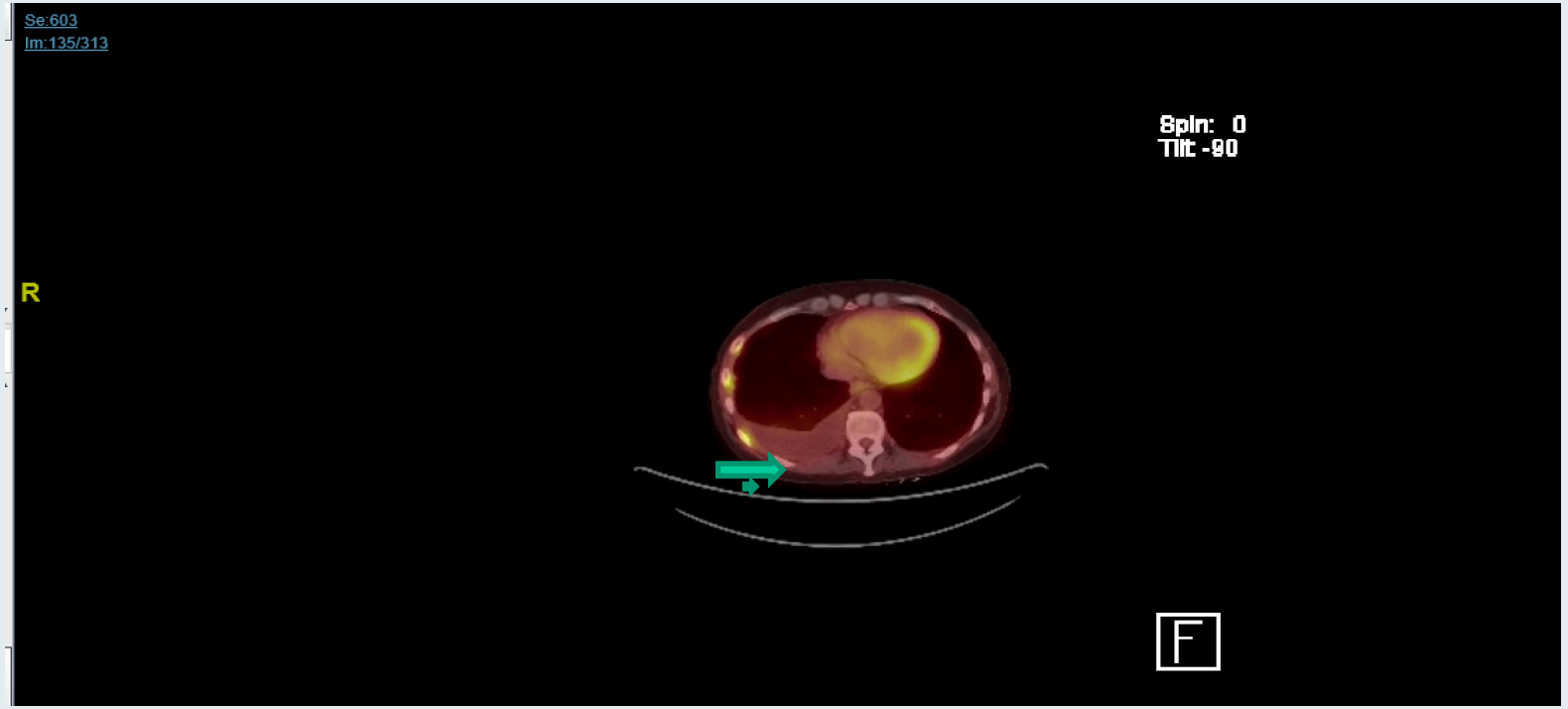
Dr Ibrahim: NSCLC – High TPS with Co-morbidities

47-year-old current smoker with a history of COPD, coronary artery disease and Graves Disease. The Graves was treated with radioactive iodine and the patient is currently on Levothyroxine. She presents with worsening of her chronic cough. Imaging reveals a right lung mass, mediastinal adenopathy and multiple pleura-based nodules. She is frail due to her co-morbid conditions but is also declining quickly. I suggested single agent Pembrolizumab based on the PD-L1 level

Questions:

- Would investigators suggest KEYNOTE-189 instead?
- How does the history of Graves disease factor into this?
- She also does have the KRAS G12C. Would a clinical trial of AMG 510 be the next best option if she does not respond to or has progression on Pembrolizumab?

Multiple Pleural Based Metastatic Lesions



PD-L1

ASK AN EXPERT

Reach out to Foundation Medicines experts
Our Medical Affairs team is available to help you understand the results of this assay

PD-L1 IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS (Dako 22C3 pharmDx™)
Tumor Proportion Score (TPS) (%) 100

Electronically signed by: _____ Date: _____

TPS Companion Diagnostic Indication

Tumor Indication	PD-L1 Expression Level	Intended use
Non-Small Cell Lung Cancer (NSCLC)	TPS ≥1%	PD-L1 IHC 22C3 pharmDx™ is indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA® (pembrolizumab)

NGS

ASK AN EXPERT

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Tumor Mutational Burden (TMB)	Keytruda® (Pembrolizumab)
≥10 Muts/Mb	

For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be performed.

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MS-Stable §
Tumor Mutational Burden 11 Muts/Mb §
CDKN2A loss §
CDKN2B loss §
KRAS G12C
LYN amplification §
MTAP loss §
SMARCA4 G1232S
TP53 R273L

RTP RESEARCH TO PRACTICE

MODULE 1: Metastatic NSCLC without a Targetable Mutation

- **Faculty Cases – Dr Garon**
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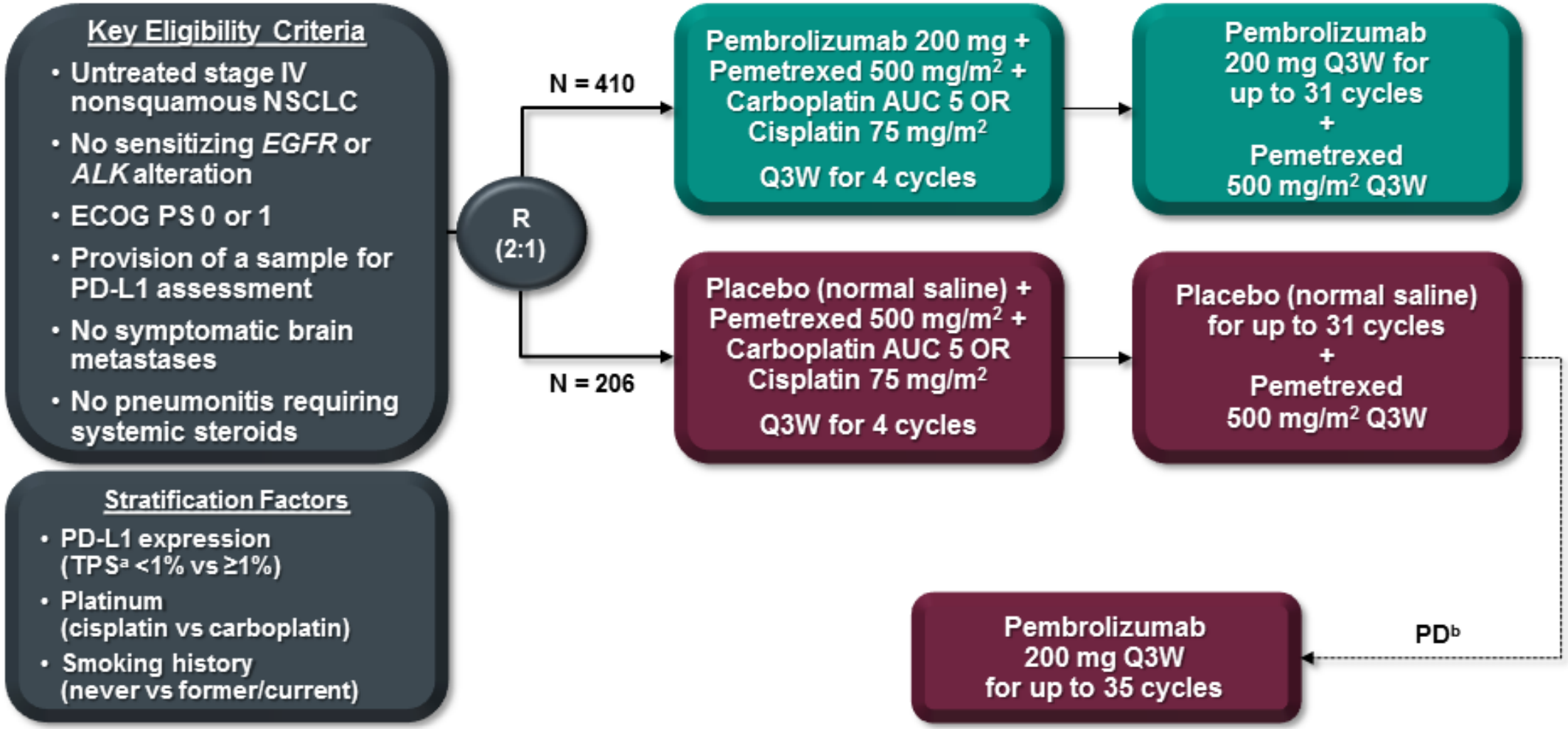
Gandhi KN189
AACR 2018

KEYNOTE-189 Study Design (NCT02578680)

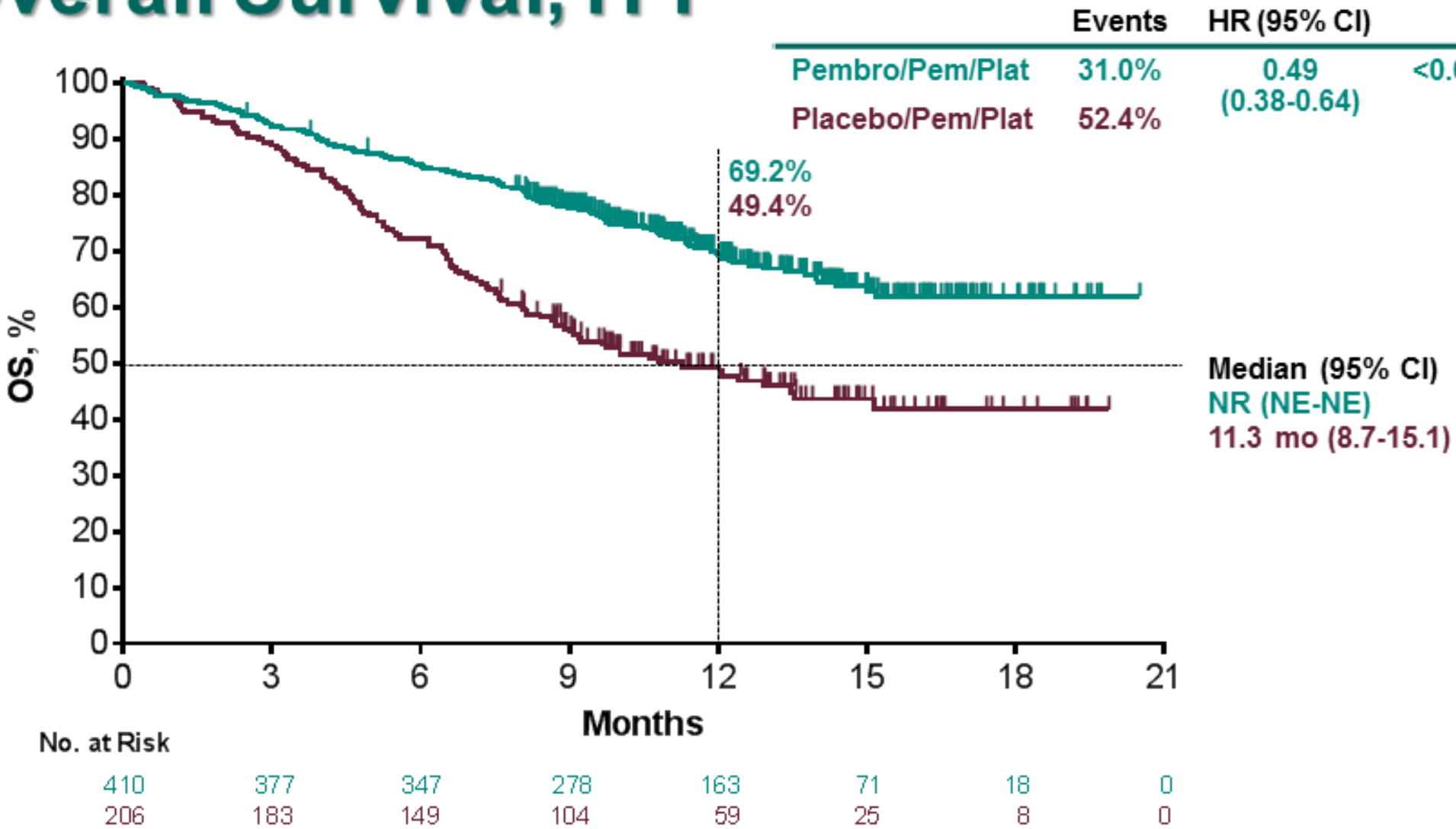


[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

Courtesy of Edward B Garon, MD, MS

Overall Survival, ITT

Gandhi KN189
AACR 2018



Data cutoff date: Nov 8, 2017.

Gandhi et al. AACR 2018;Abstract CT075.

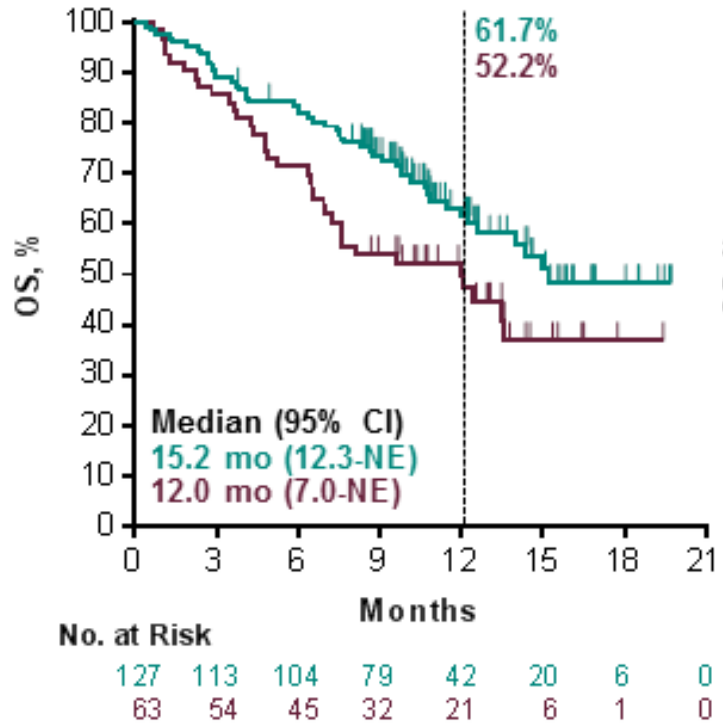
Courtesy of Edward B Garon, MD, MS

Gandhi KN189
AACR 2018

Overall Survival by PD-L1 TPS

TPS <1%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	38.6%	0.59 (0.38-0.92)	0.0095
Placebo/Pem/Plat	55.6%		

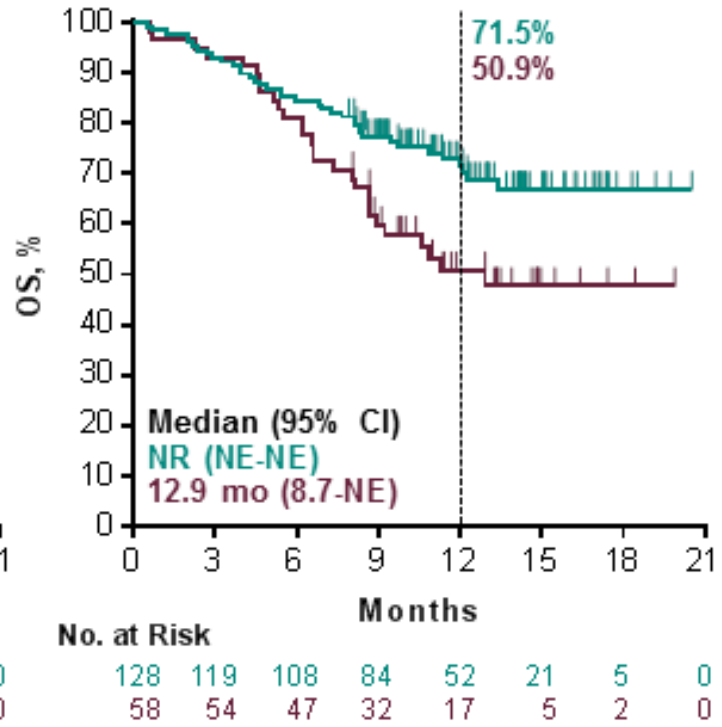


No. at Risk

127	113	104	79	42	20	6	0
63	54	45	32	21	6	1	0

TPS 1-49%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	28.9%	0.55 (0.34-0.90)	0.0081
Placebo/Pem/Plat	48.3%		

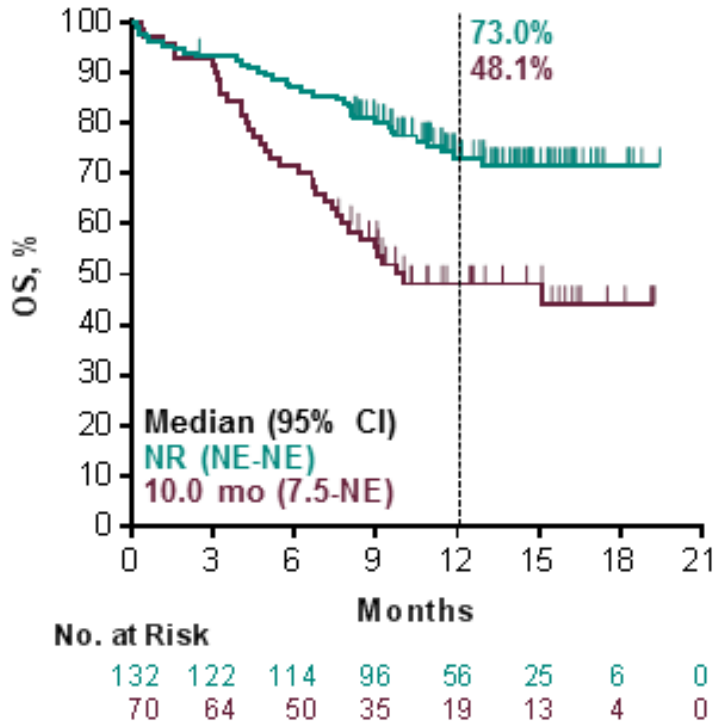


No. at Risk

128	119	108	84	52	21	5	0
58	54	47	32	17	5	2	0

TPS ≥50%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	25.8%	0.42 (0.26-0.68)	0.0001
Placebo/Pem/Plat	51.4%		



No. at Risk

132	122	114	96	56	25	6	0
70	64	50	35	19	13	4	0

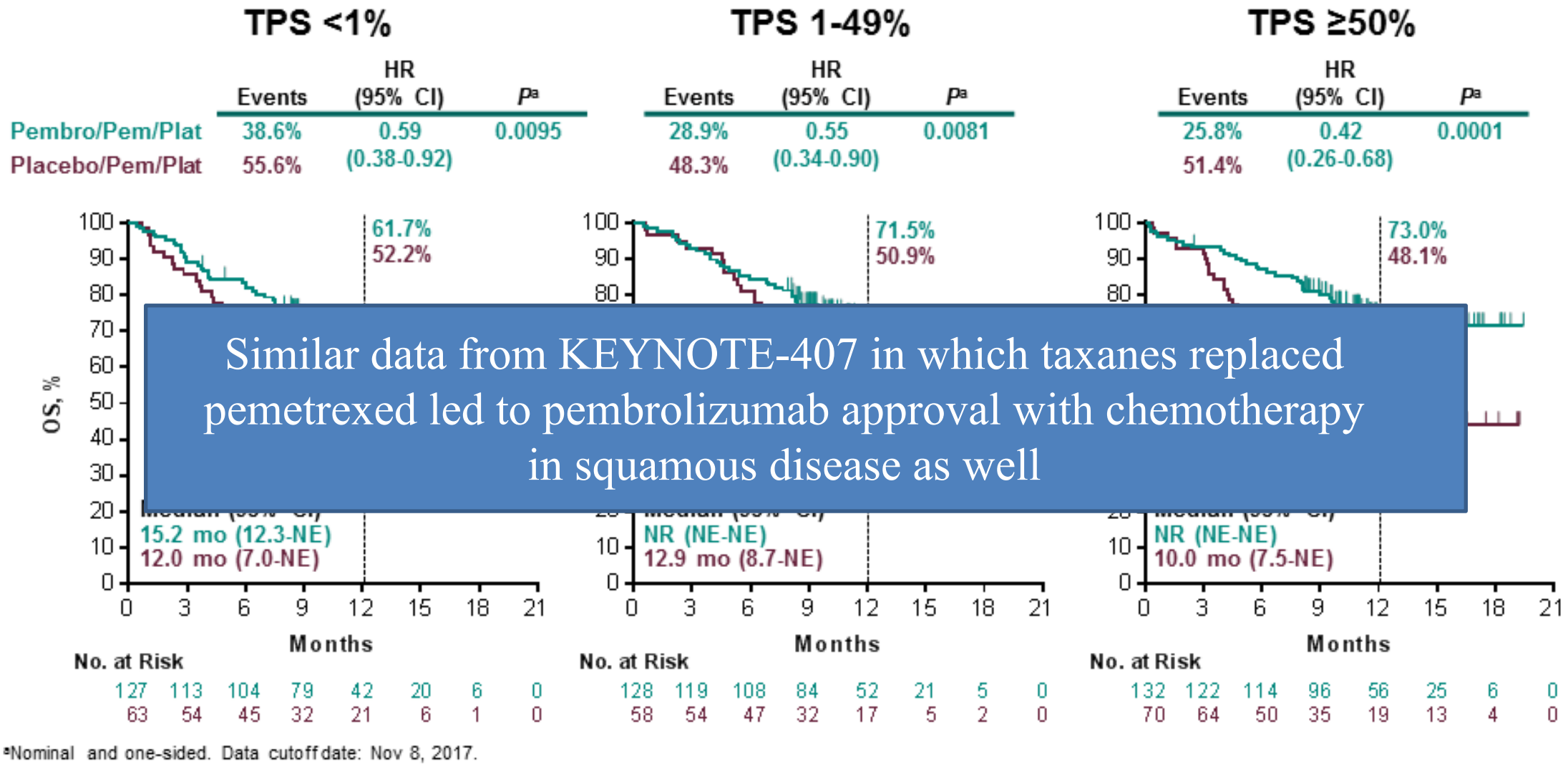
[a]Nominal and one-sided. Data cutoff date: Nov 8, 2017.

Gandhi et al. AACR 2018;Abstract CT075.

Courtesy of Edward B Garon, MD, MS

Gandhi KN189
AACR 2018

Overall Survival by PD-L1 TPS



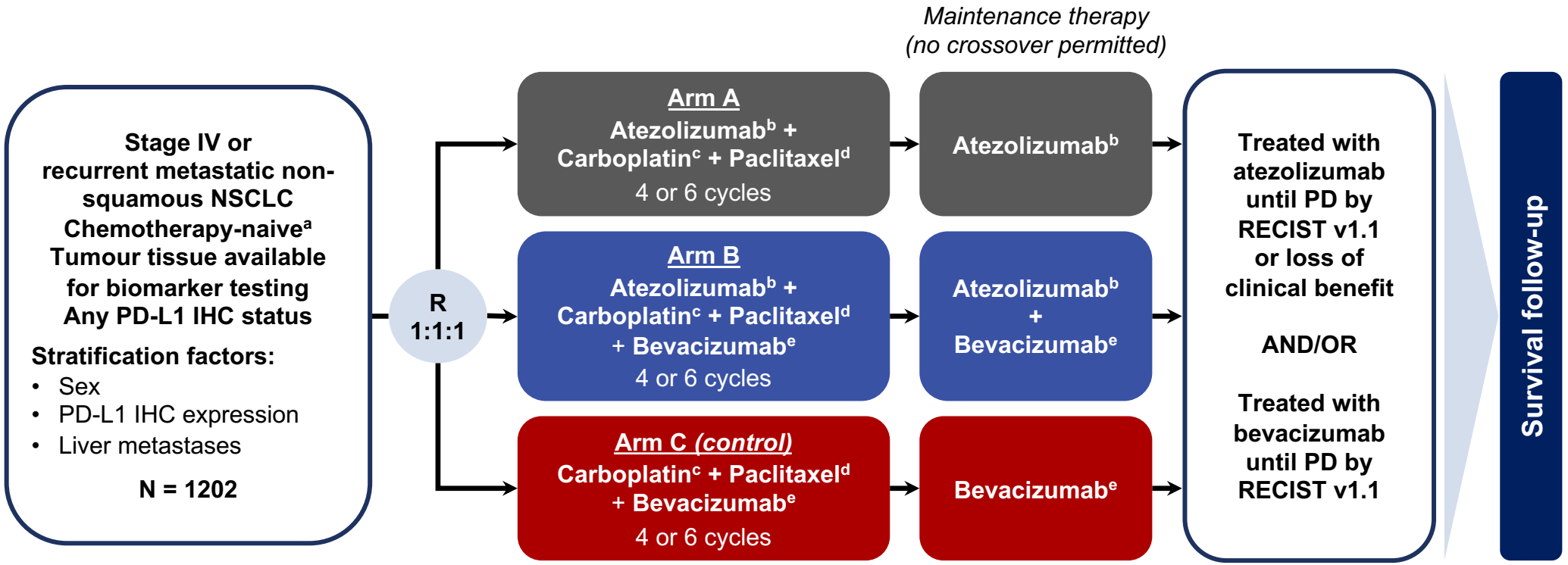
Similar data from KEYNOTE-407 in which taxanes replaced pemetrexed led to pembrolizumab approval with chemotherapy in squamous disease as well

[a]Nominal and one-sided. Data cutoff date: Nov 8, 2017.

Gandhi et al. AACR 2018;Abstract CT075.

Courtesy of Edward B Garon, MD, MS

IMpower150 study design



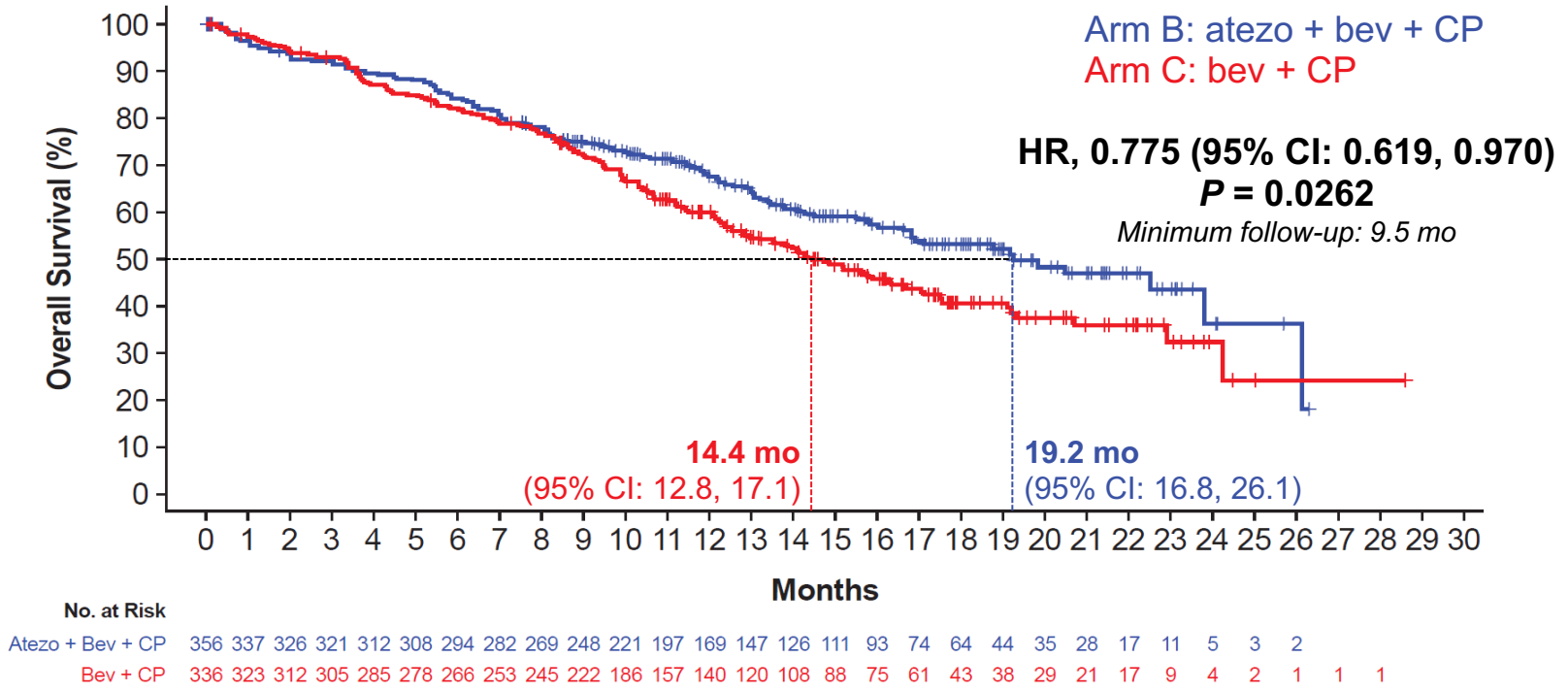
The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. [b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w.
[d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

Courtesy of Edward B Garon, MD, MS

Reck M, et al. IMpower150 PFS analysis.

Preliminary OS in ITT-WT (Arm B vs Arm C)



Data cutoff: September 15, 2017

- Promising preliminary OS benefit for Arm B vs Arm C was observed; next OS interim data are anticipated in 1H 2018

Courtesy of Edward B Garon, MD, MS

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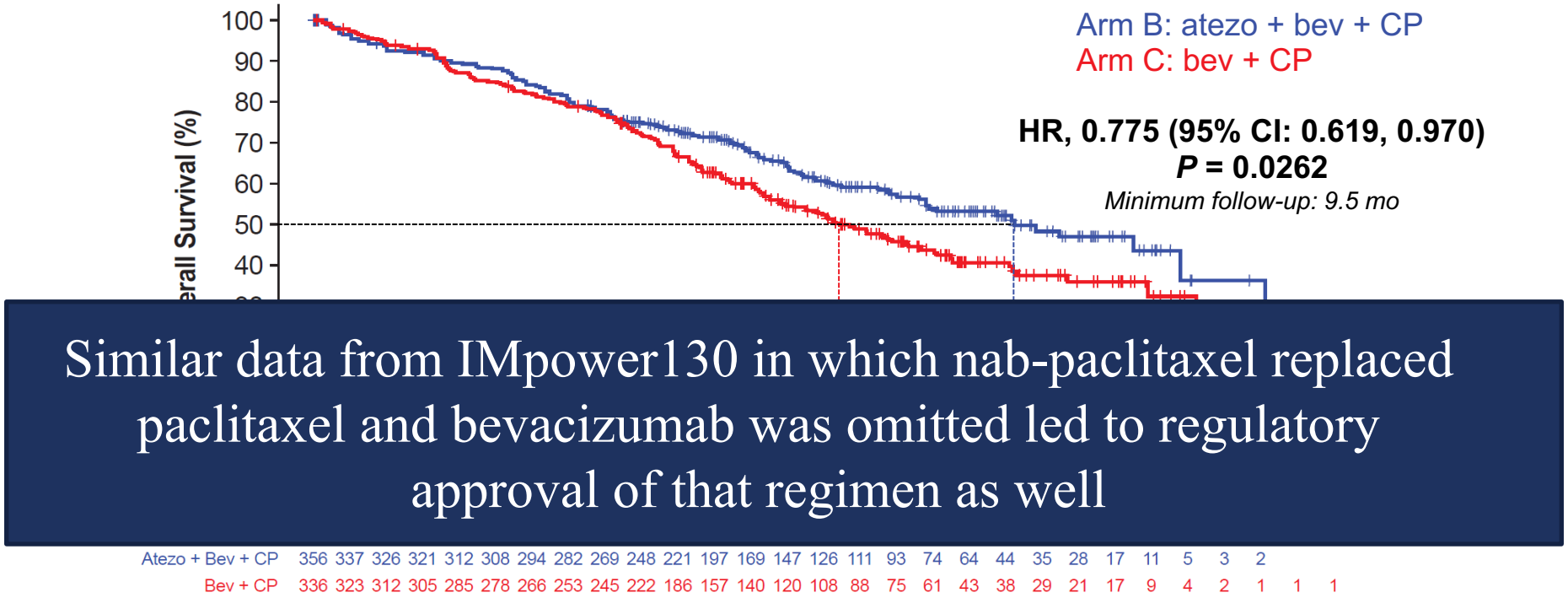

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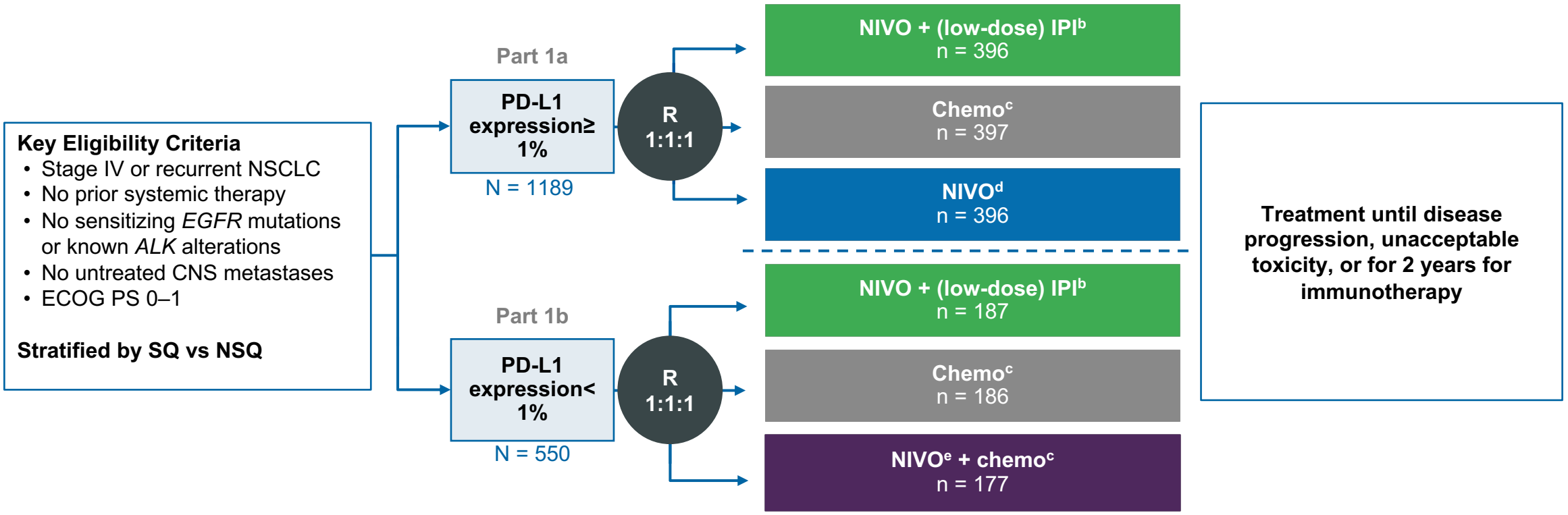
CheckMate 227 Part 1 Study Design[a]



Database lock: July 2, 2019; minimum follow-up for primary endpoint: 29.3 months
[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]TMB primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [g]Alpha allocated was 0.025 overall (0.023 for final analysis)

Peters S. ESMO 2019;Abstract 7128.

Courtesy of Edward B Garon, MD, MS

OS and PFS With NIVO + IPI vs NIVO vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%

Part 1a

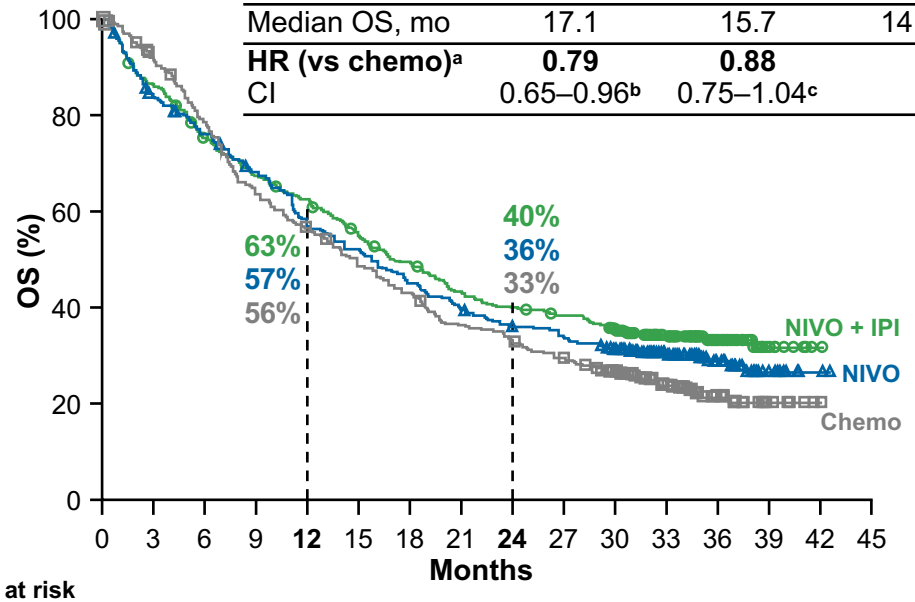
NIVO + IPI

Chemo

NIVO

OS

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS, mo	17.1	15.7	14.9
HR (vs chemo)[a]	**0.79**	**0.88**	
CI	0.65–0.96[b]	0.75–1.04[c]	

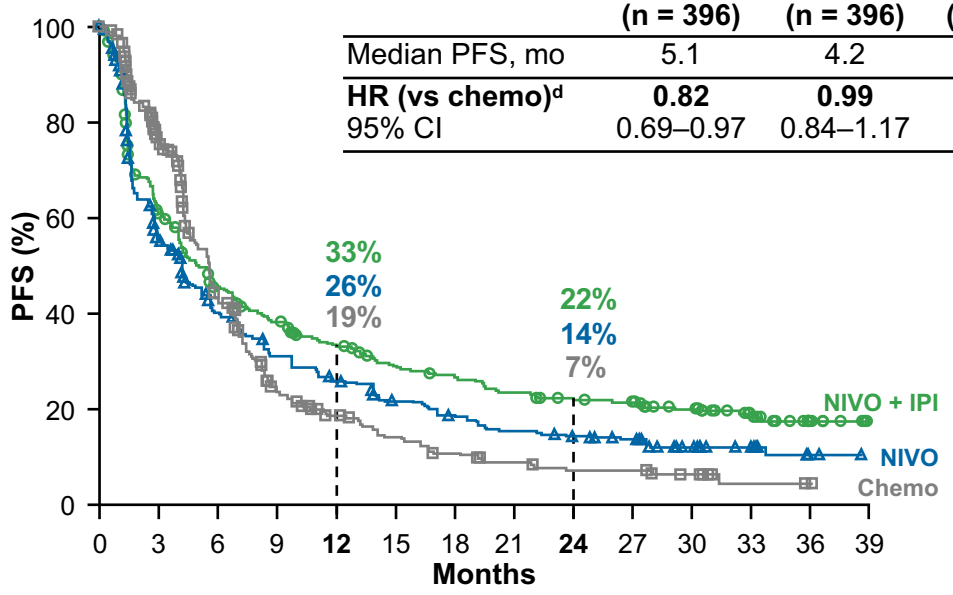


No. at risk

NIVO + IPI	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
NIVO	396	330	299	265	220	201	176	153	139	129	115	70	36	10	2	0
Chemo	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

PFS by BICR

	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median PFS, mo	5.1	4.2	5.6
HR (vs chemo)[d]	**0.82**	**0.99**	
95% CI	0.69–0.97	0.84–1.17	



396	221	158	130	108	91	83	73	65	62	47	31	7	0
396	199	136	104	85	68	56	47	42	37	24	15	3	0
397	253	130	63	44	32	23	17	12	12	8	2	1	0

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (240 mg Q2W). Subsequent systemic therapy was received by 35% of patients in the NIVO + IPI arm, 44% of patients in the NIVO arm, and 54% of patients in the chemo arm; subsequent immunotherapy was received by 6%, 8%, and 43%, respectively.

[a]HR (95% CI) for NIVO + IPI vs NIVO, 0.90 (0.76–1.07); [b]97.72% CI; [c]95% CI; [d]HR (95% CI) for NIVO + IPI vs NIVO, 0.83 (0.71–0.97).

Peters S. ESMO 2019;Abstract 7128.

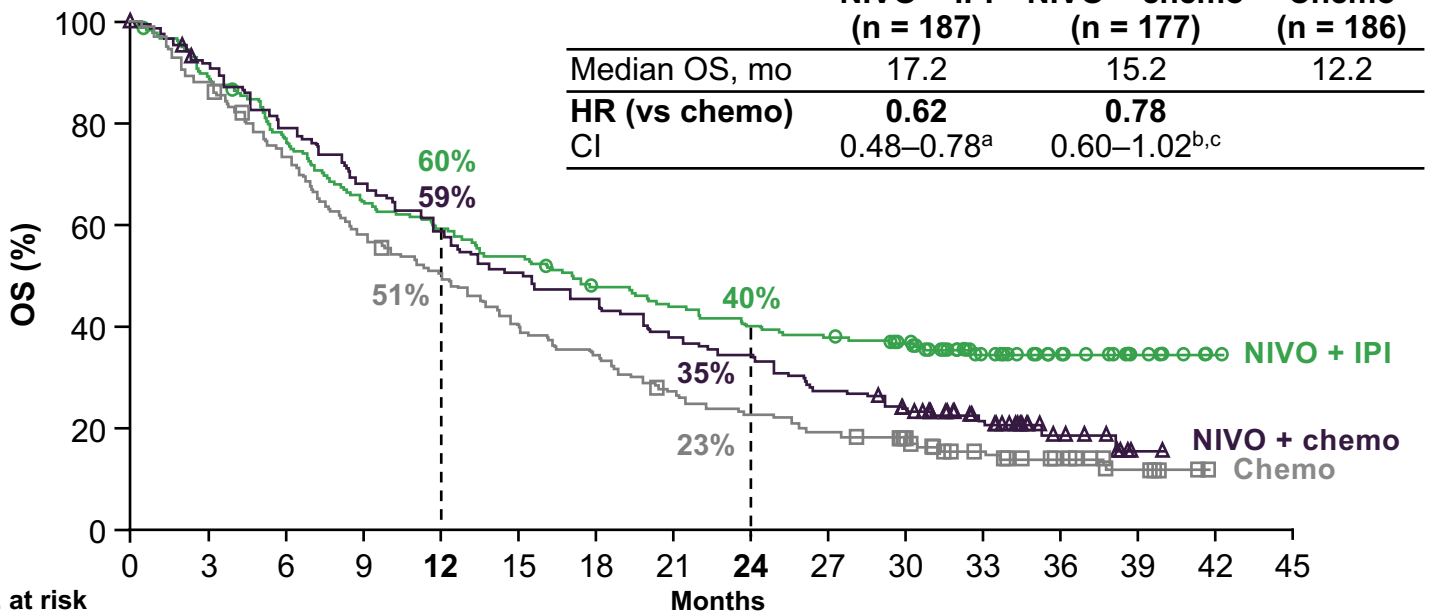
Courtesy of Edward B Garon, MD, MS

OS With NIVO + IPI and NIVO + Chemo vs Chemo in Patients With Tumor PD-L1 Expression < 1%

Part 1b

NIVO + IPI
Chemo
NIVO + chemo

	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS, mo	17.2	15.2	12.2
HR (vs chemo)	**0.62**	**0.78**	
CI	0.48–0.78[a]	0.60–1.02[b,c]	



No. at risk

NIVO + IPI	187	165	142	120	110	100	87	80	73	69	59	34	19	8	2	0
NIVO + chemo	177	159	139	119	102	88	78	67	60	48	40	23	9	1	0	0
Chemo	186	164	135	107	92	74	62	49	41	35	29	19	12	5	0	0

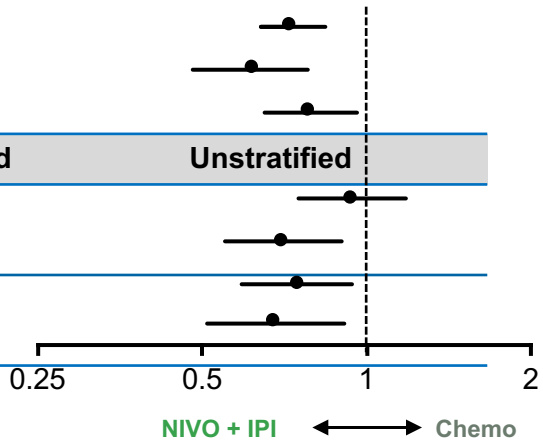
Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm, 41% of patients in the NIVO + chemo arm, and 53% of patients in the chemo arm; subsequent immunotherapy was received by 4%, 4%, and 36%, respectively.
[a]95% CI; [b]97.72% CI; [c]*P* = 0.0352.

Peters S. ESMO 2019;Abstract 7128.

Courtesy of Edward B Garon, MD, MS

OS for NIVO + IPI vs Chemo by Tumor PD-L1 Expression, TMB Status, and Combined Subgroups in All Randomized Patients

		Median OS, months NIVO + IPI n = 583	Chemo n = 583	HR	HR (95% CI)
Randomized groups				**Stratified**	**Stratified**
PD-L1	All randomized (N = 1166)	17.1	13.9	0.73	
	PD-L1 < 1% (n = 373)	17.2	12.2	0.62	
	PD-L1 ≥ 1% (n = 793)	17.1	14.9	0.79[a]	
Additional exploratory subgroups analyses[b,c]				**Unstratified**	**Unstratified**
PD-L1	1–49% (n = 396)	15.1	15.1	0.94	
	≥ 50% (n = 397)	21.2	14.0	0.70	
TMB[d] (mut/Mb)	low, < 10 (n = 380)	16.2	12.6	0.75	
	high, ≥ 10 (n = 299)	23.0	16.4	0.68	



- No consistent correlation was observed between survival outcomes with NIVO + IPI vs chemo and PD-L1 or TMB alone or in combination[1]

[a]Stratified HR (97.72% CI); [b]Patients were not stratified by TMB or PD-L1 ≥ or < 50% – subgroup analyses therefore may be impacted by imbalances and should be interpreted with caution; [c]Not controlled by randomization; [d]Unstratified HR for NIVO + IPI vs chemo in TMB-evaluable (n = 679) and non-evaluable (n = 487) patients was 0.74 (95% CI, 0.61–0.88) and 0.74 (95% CI, 0.60–0.92), respectively.

[1]Hellmann MD, et al. N Engl J Med 2019. doi: www.nejm.org/doi/full/10.1056/NEJMoa1910231. 2019 Sept 28 [Epub ahead of print].

Peters S. ESMO 2019;Abstract 7128.

Courtesy of Edward B Garon, MD, MS

MYSTIC STUDY DESIGN

Phase 3, global, randomised, open-label, multicentre study

- Stage IV NSCLC
- All-comers population (i.e. irrespective of PD-L1 status)
- No sensitising *EGFR* mutation or *ALK* rearrangement
- ECOG PS 0/1
- Immunotherapy- and CT-naïve

N=1118 randomised

1:1:1 R

Stratified by PD-L1 TC (<25% vs ≥25%*) and histology

Durvalumab (n=374)
20 mg/kg q4w until disease progression

Durvalumab + tremelimumab (n=372)
D 20 mg/kg q4w until disease progression +
T 1 mg/kg q4w for up to 4 doses

Platinum-based chemotherapy (n=372)
- Paclitaxel + carboplatin OR
- Gemcitabine + cisplatin/carboplatin (squamous) OR
- Pemetrexed + cisplatin/carboplatin (non-squamous)†

for up to 6 cycles

Primary endpoints (PD-L1 TC ≥25%*):
- PFS‡ (D+T vs CT)
- OS (D vs CT)
- OS (D+T vs CT)

Key secondary endpoints:
- PFS‡ (D vs CT; PD-L1 TC ≥25%*)
- OS (D+T vs CT; PD-L1 TC ≥1%*)
- ORR‡
- DoR
- Safety and tolerability

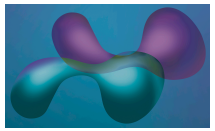
Key exploratory endpoints:
- OS by additional PD-L1 TC cutoffs
- OS by blood TMB

*PD-L1 (SP263) assay using newly acquired or archival (<3 months) tumour biopsy;
†Followed by pemetrexed maintenance therapy if eligible; ‡Blinded independent central review per RECIST v1.1
CT, chemotherapy; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group;
ORR, objective response rate; PFS, progression-free survival; PS, performance status; q4w, every 4 weeks; T, tremelimumab; TMB, tumour mutational burden

ESMO

Rizvi NA et al. ESMO-IO

Courtesy of Edward B Garon, MD, MS



MYST

Poseidon is a similarly designed trial where the two study arms include chemotherapy in addition to the checkpoint inhibitors

- Stage IV NSCLC
- All-comers population (i.e. irrespective of PD-L1 status)
- No sensitising *EGFR* mutation or *ALK* rearrangement
- ECOG PS 0/1
- Immunotherapy- and CT-naïve

N=1118 randomised

1:1:1 R

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Durvalumab (n=374)
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for up to 6 cycles

Primary endpoints (PD-L1 TC ≥25%*):
- PFS‡ (D+T vs CT)
- OS (D vs CT)
- OS (D+T vs CT)

Key secondary endpoints:
- PFS‡ (D vs CT; PD-L1 TC ≥25%*)
- OS (D+T vs CT; PD-L1 TC ≥1%*)
- ORR‡
- DoR
- Safety and tolerability

Key exploratory endpoints:
- OS by additional PD-L1 TC cutoffs
- OS by blood TMB

*PD-L1 (SP263) assay using newly acquired or archival (<3 months) tumour biopsy;
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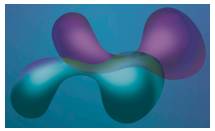
CT, chemotherapy; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group;
ORR, objective response rate; PFS, progression-free survival; PS, performance status; q4w, every 4 weeks; T, tremelimumab; TMB, tumour mutational burden

ESMO

Rizvi NA et al. ESMO-IO

Courtesy of Edward B Garon, MD, MS



CheckMate 9LA study design[a]

Key Eligibility Criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)

N = 719

R 1:1

n = 361

NIVO 360 mg Q3W + **IPI** 1 mg/kg Q6W
+
Chemo[d] Q3W **(2 cycles)**

n = 358

Chemo[d] Q3W **(4 cycles)**
with optional pemetrexed maintenance (NSQ)

Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint
- OS

Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

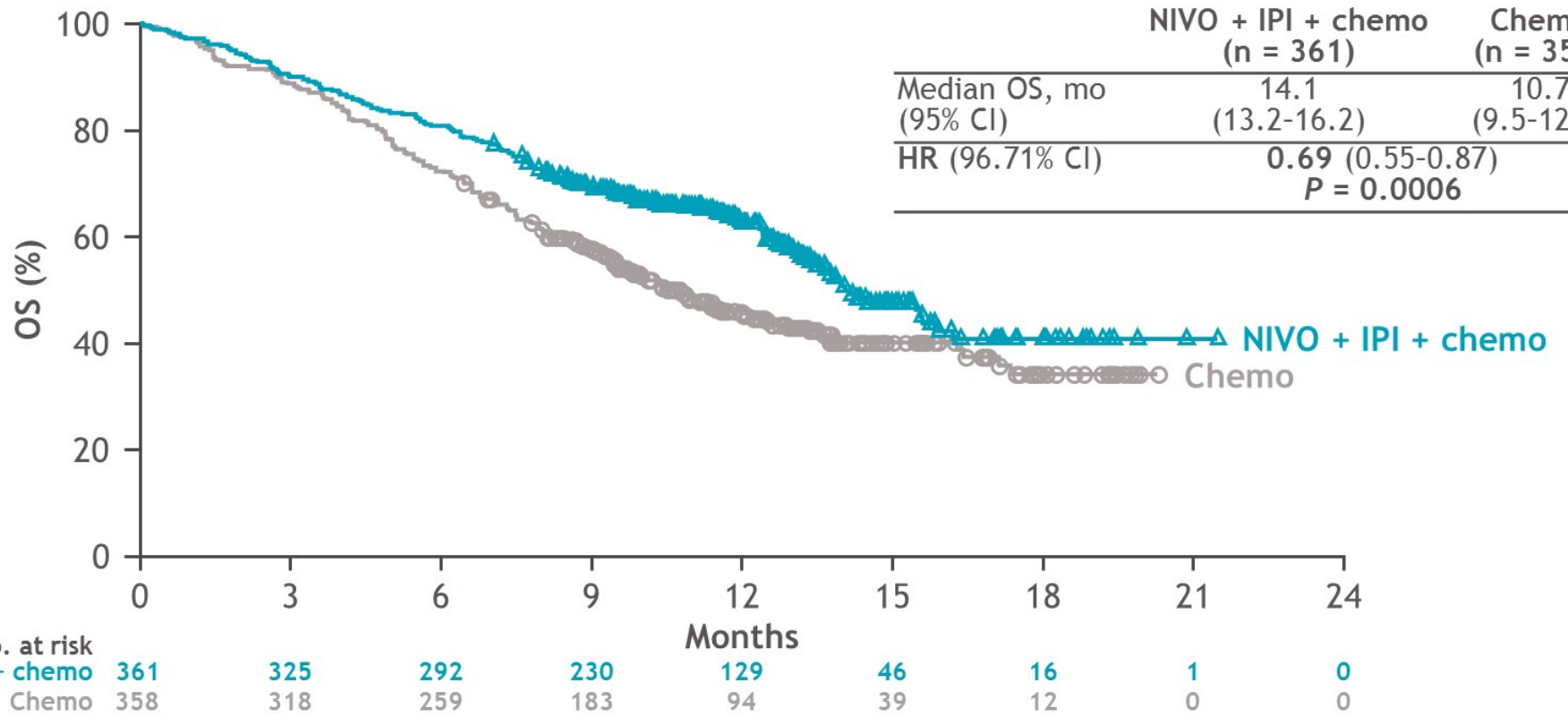
Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.
Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.

[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]**NSQ**: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

Presented By Martin Reck at ASCO 2020;Abstract 9501.

Courtesy of Edward B Garon, MD, MS

Primary endpoint: Overall survival[a] at interim analysis



	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	14.1 (13.2-16.2)	10.7 (9.5-12.4)
HR (96.71% CI)	**0.69** (0.55-0.87) ***P* = 0.0006**	

- PFS and ORR were also significantly improved with NIVO + IPI + chemo vs chemo[b]

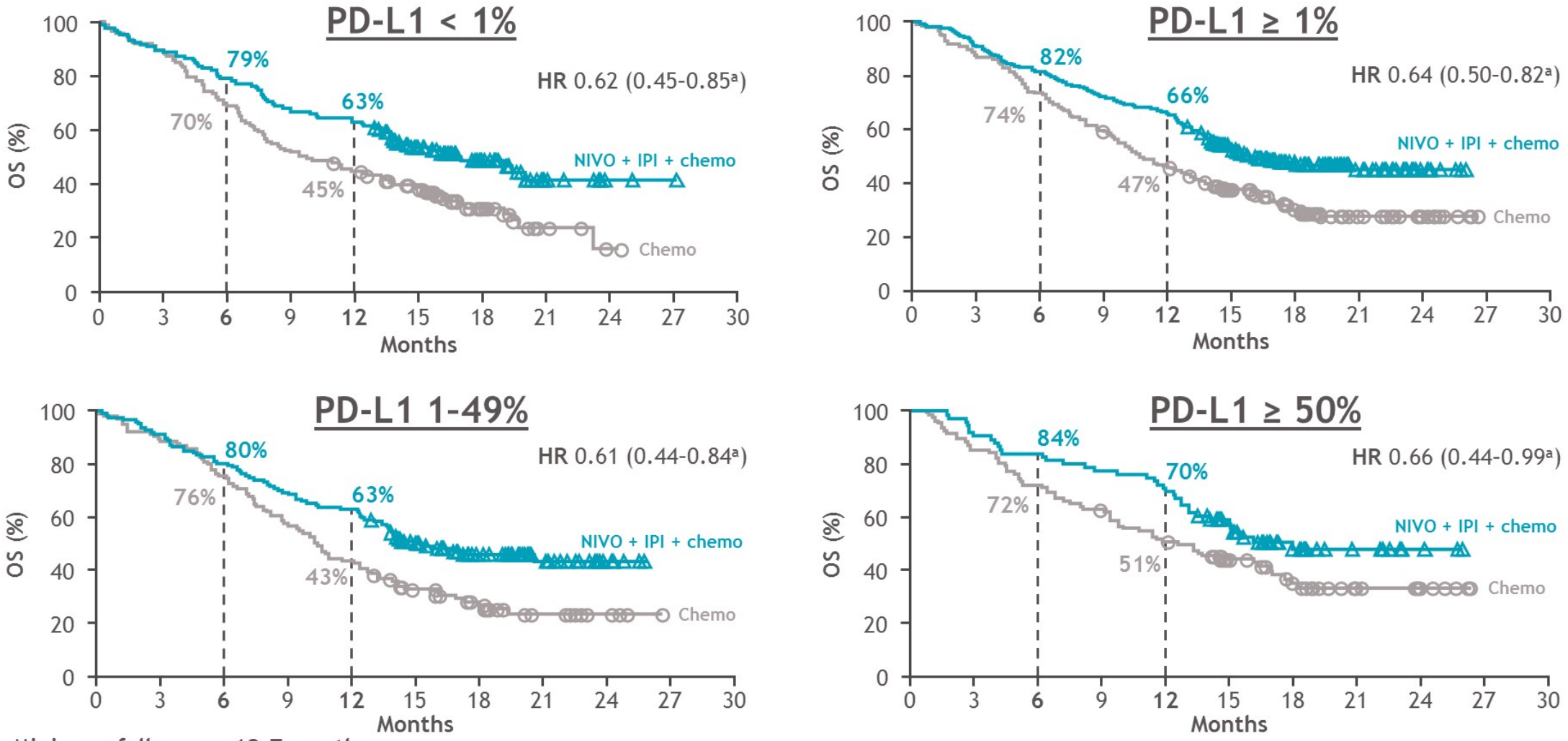
Minimum follow-up: 8.1 months for OS; 6.5 months for PFS / ORR.

[a]Patients remaining in follow-up were censored on the last date they were known to be alive; 57% of patients in the NIVO + IPI + chemo arm and 46% of patients in the chemo arm were censored; [b]Median PFS was 6.8 mo versus 5.0 mo, respectively, HR 0.70 (97.48% CI, 0.57-0.86; *P* = 0.0001), and ORR was 38% versus 25%, respectively, *P* = 0.0003.

Reck M et al. ASCO 2020;Abstract 9501.

Courtesy of Edward B Garon, MD, MS

Overall survival by PD-L1 expression level



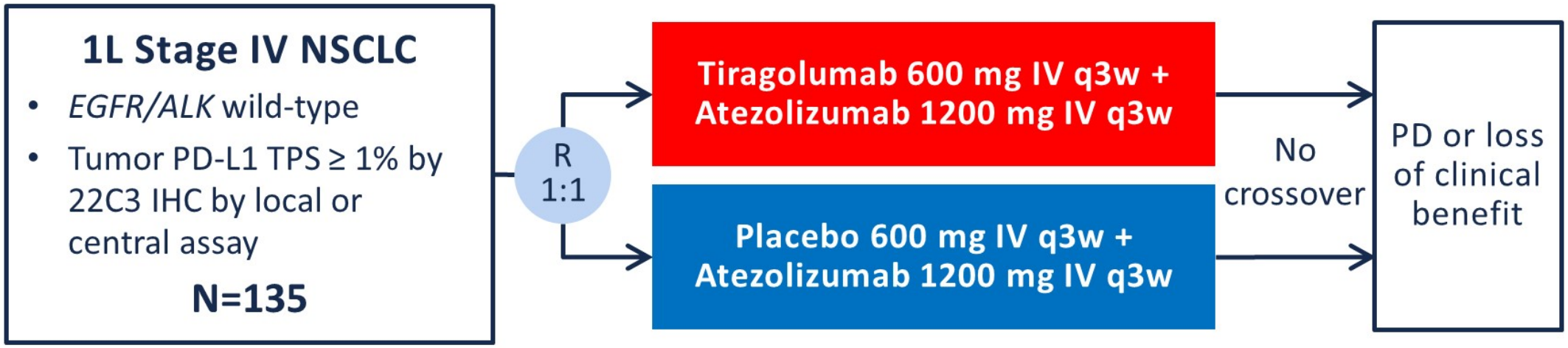
Minimum follow-up: 12.7 months.

[a]95% CI.

Presented By Martin Reck at ASCO 2020;Abstract 9501.

Courtesy of Edward B Garon, MD, MS

CITYSCAPE Study Design



Stratification Factors:

- PD-L1 TPS (1-49% vs ≥ 50%)
- Histology (Non-Squamous vs Squamous)
- Tobacco use (yes vs no)

- **Co-Primary Endpoints: ORR** and **PFS**
- **Key Secondary Endpoints: Safety**, DOR, OS, Patient-reported outcomes (PROs)
- **Exploratory Endpoints:** Efficacy analysis by PD-L1 status

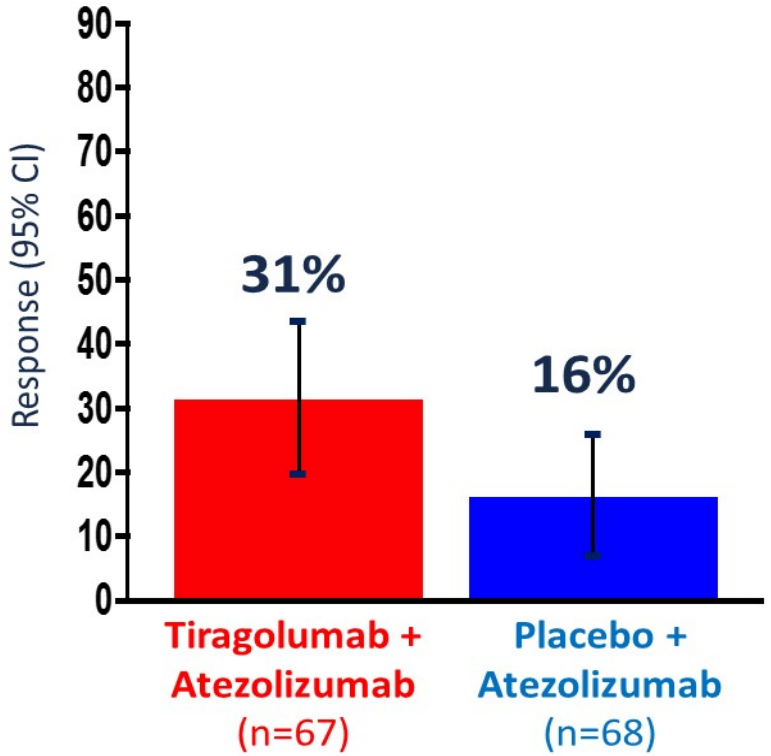
DOR = duration of response; IHC = immunohistochemistry; ORR = confirmed overall response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival ; q3w = every 3 weeks; R = randomized; TPS = tumor proportion score

Rodriguez-Abreu D et al. ASCO 2020;Abstract 9503.

Confirmed Overall Response Rate (ORR) and PFS

ITT: ORR

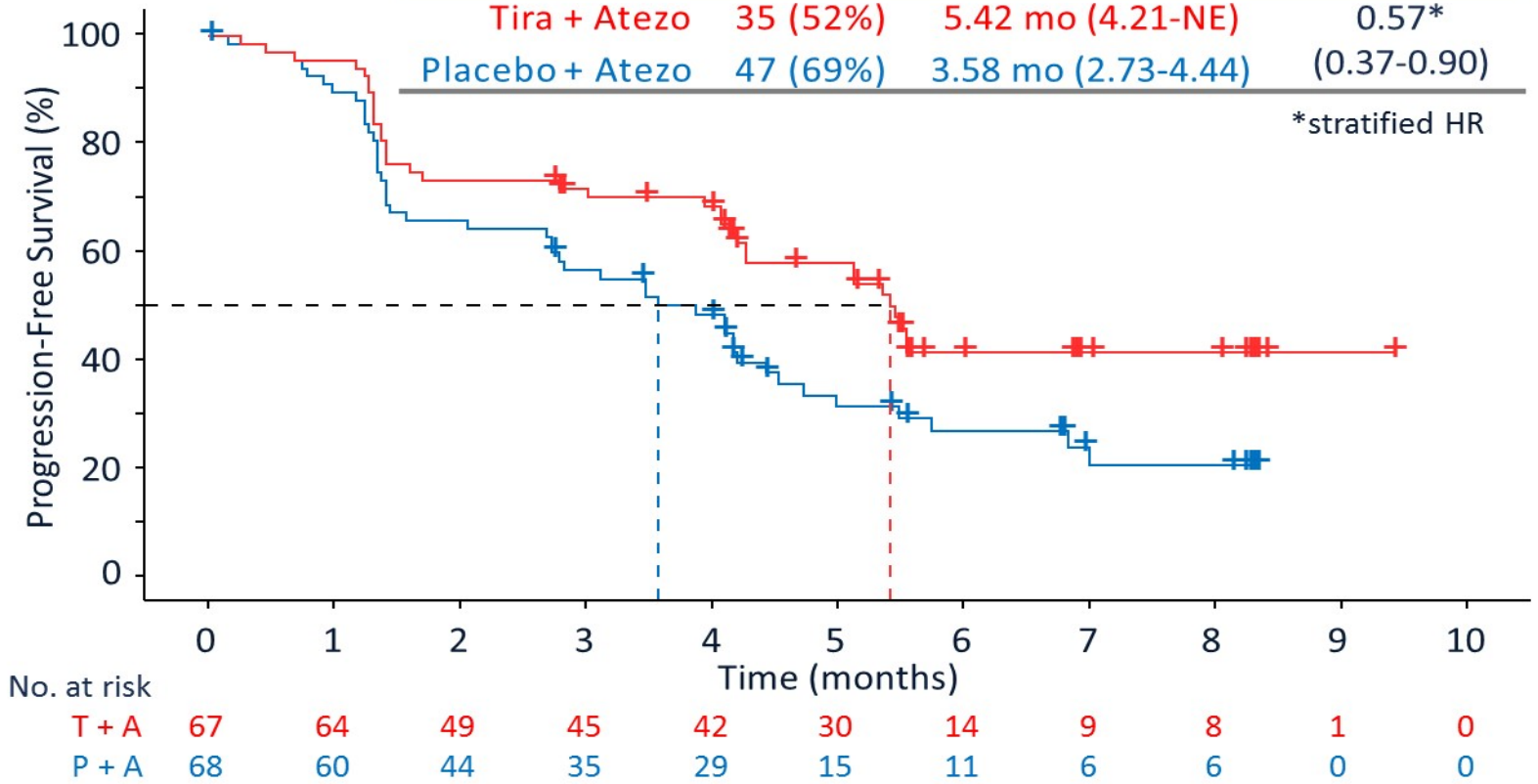
(n=135)



ITT: Investigator-Assessed PFS

	Events	Median (95% CI)	HR (95% CI)
Tira + Atezo	35 (52%)	5.42 mo (4.21-NE)	0.57* (0.37-0.90)
Placebo + Atezo	47 (69%)	3.58 mo (2.73-4.44)	

*stratified HR



ITT= intention-to-treat; NE = non-evaluable, P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab

Primary analysis data cutoff: 30 June 2019

Rodriguez-Abreu D et al. ASCO 2020;Abstract 9503.

Challenging Questions and Cases

Challenging Questions and Cases

Challenging Questions and Cases

MODULE 2: Small Cell Lung Cancer

- **Faculty Cases – Dr Spigel**
  - A 66-year-old man with LS-SCLC
  - A 74-year-old man with LS-SCLC
- **Questions and Cases from Investigators**
- **Key Relevant Data Sets**

A 66-year-old man with extensive-stage SCLC initially responds to carboplatin/etoposide/atezolizumab but develops oligoprogression in the liver 6 months later. Would you recommend local therapy to the liver?

a. Yes
b. Not now, but maybe after other therapy
c. No

Case Presentation (Dr Spigel): A 66-Year-Old Man with LS-SCLC

A 66yo gentleman who presented with LS-SCLC in 2017

Treatment: Carboplatin / Etoposide + RT ending 11/2017 – No PCI

Recurred in 2/2019 in the liver

TMB=7, MSS, PD-L1 unknown

SMARCB1, FAT1, RB1, TP53

Treatment: Carboplatin / Etoposide + Atezolizumab + hepatic ablation

Progression 8/2019 in liver and reginal LAN

Treatment: Protocol-based anti-PD-1 / anti-LAG3 - responding

Have you administered or would you administer at some point ipilimumab/nivolumab to a patient with extensive-stage SCLC that progresses after first-line treatment with combination chemotherapy/immunotherapy?

a. I have
b. I have not but would for the right patient
c. I have not and would not

Case Presentation (Dr Spigel): A 74 Year-Old-Man with LS-SCLC

A 74 yo gentleman who presented with LS-SCLC in 2013

Treatment: Cisplatin/Etoposide + RT ending 9/2013; PCI

Relapsed in the liver 1/2015

TMB / PD-L1 unknown

PARK2, SOX2, TP53, ARID2, FAT1, FOXP1, KEAP1, MDM4

Treatment: Protocol-based Nivolumab/Ipilimumab – stopped 7/2016 d/t rash

In Surveillance – Complete Remission

Case Presentation – Dr Gubens: A 64-year-old man with extensive-stage SCLC

- Prior diagnosis of lymphoma treated with mediastinal RT in the 90s
- Presents with SOB, large hilar node, bilateral lung nodules
- Biopsy: Extensive-stage SCLC, with pleural disease
- Carboplatin / etoposide / atezolizumab, with nice response after 4 cycles
  - Consolidation chest radiation therapy
- Six months later: Pericardial phrenic node, PET positive
- CyberKnife®, with continued maintenance atezolizumab
- Next staging: Extensive disease progression
- Currently, considering second-line treatment options

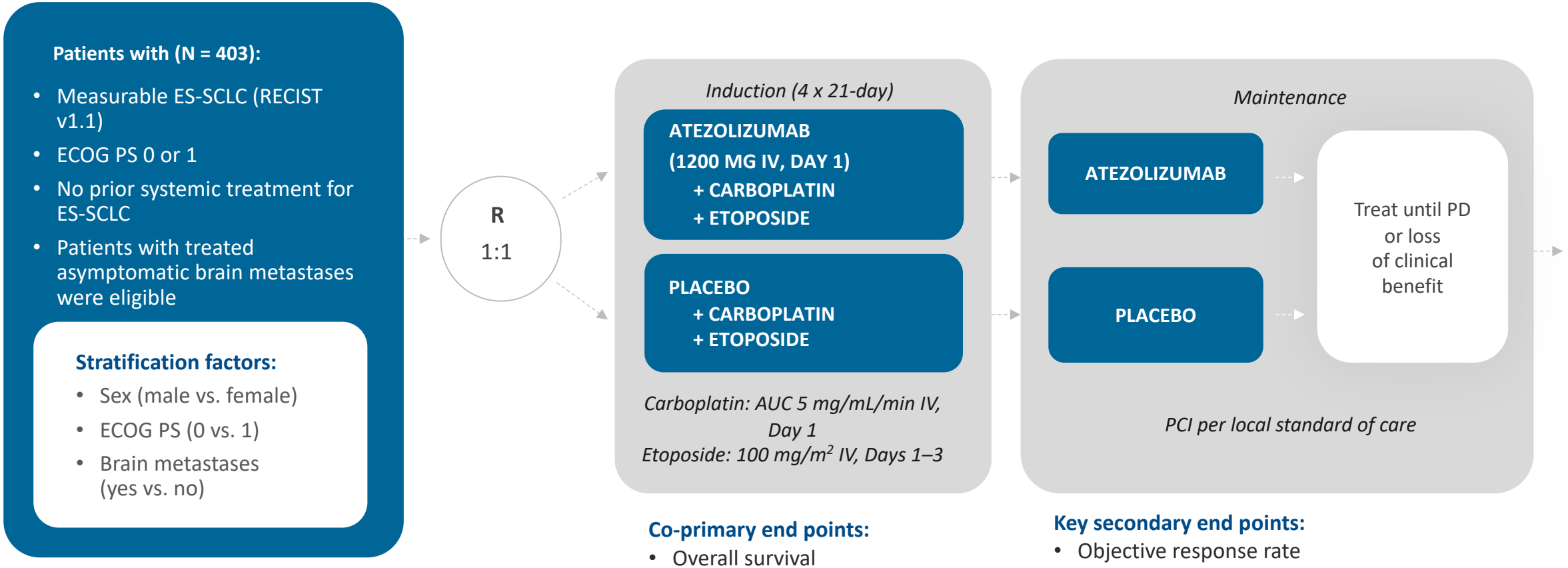
Challenging Questions and Cases

MODULE 2: Small Cell Lung Cancer

- **Faculty Cases – Dr Spigel**
  - A 66-year-old man with LS-SCLC
  - A 74-year-old man with LS-SCLC
- **Questions and Cases from Investigators**
- **Key Relevant Data Sets**

IMpower133

Phase 3, double-blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC

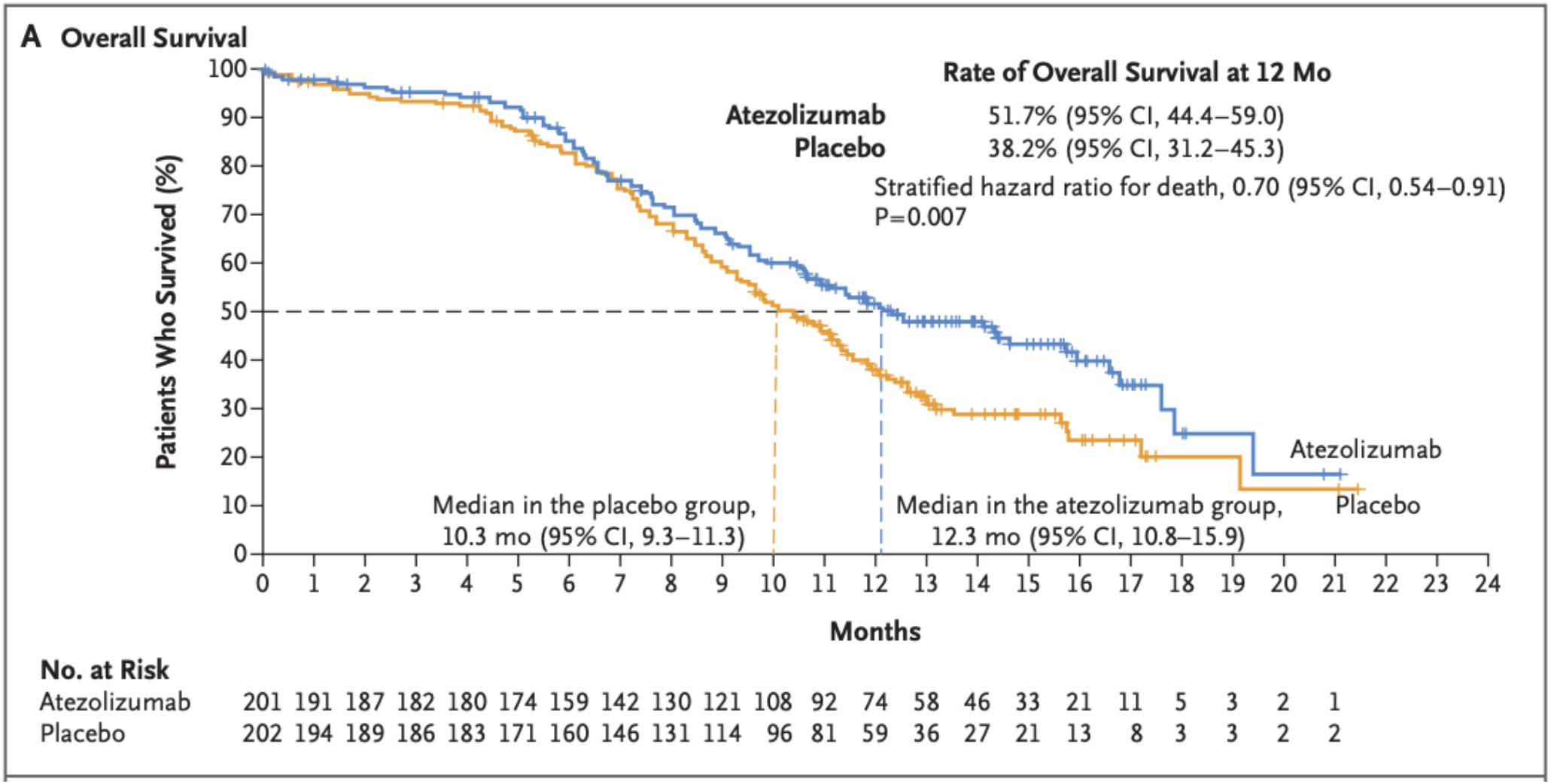


Co-primary end points:
- Overall survival
- Investigator-assessed PFS

Key secondary end points:
- Objective response rate
- Duration of response
- Safety

Courtesy of David R Spigel, MD

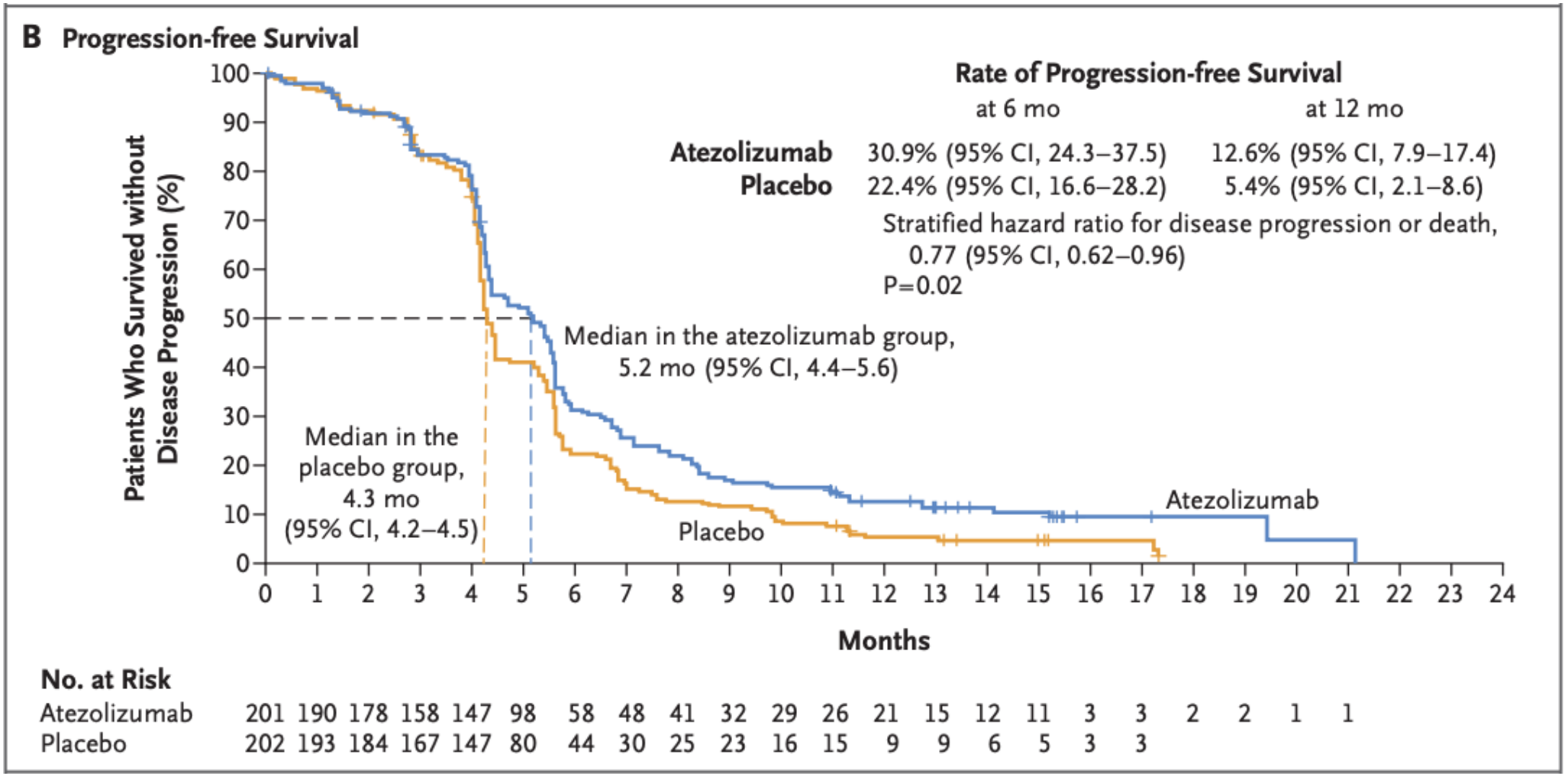
IMpower133



Horn, NEJM 2018

Courtesy of David R Spigel, MD

IMpower133



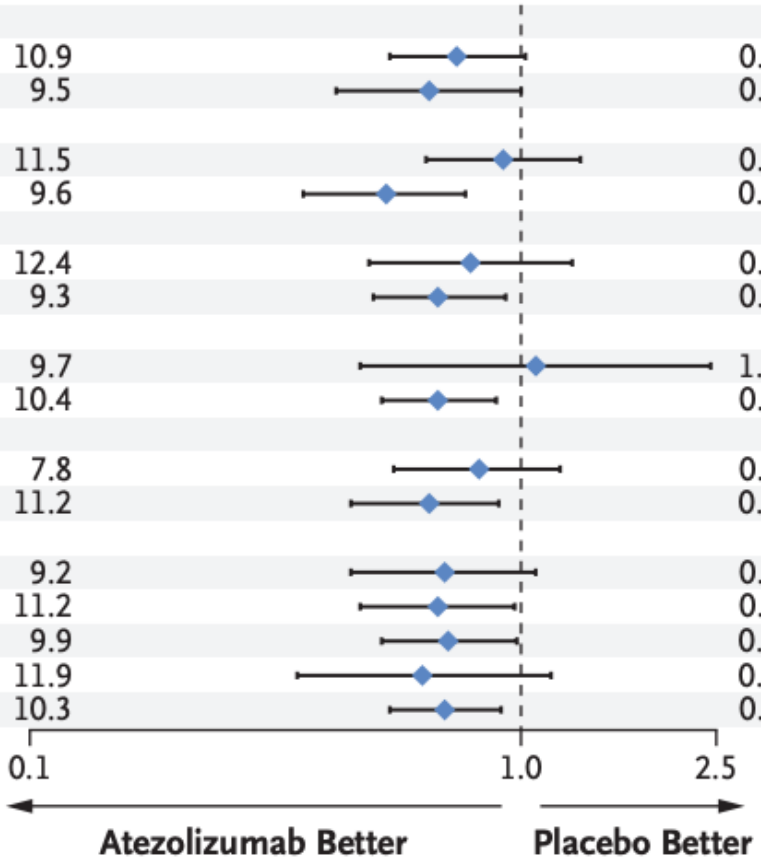
Horn, NEJM 2018

Courtesy of David R Spigel, MD

IMpower133

C Overall Survival According to Baseline Characteristics

Subgroup	No. of Patients (%)	Median Overall Survival (mo)		Hazard Ratio for Death (95% CI)
		Atezolizumab	Placebo	
Sex				
Male	261 (65)	12.3	10.9	0.74 (0.54–1.02)
Female	142 (35)	12.5	9.5	0.65 (0.42–1.00)
Age				
<65 yr	217 (54)	12.1	11.5	0.92 (0.64–1.32)
≥65 yr	186 (46)	12.5	9.6	0.53 (0.36–0.77)
ECOG score				
0	140 (35)	16.6	12.4	0.79 (0.49–1.27)
1	263 (65)	11.4	9.3	0.68 (0.50–0.93)
Brain metastases				
Yes	35 (9)	8.5	9.7	1.07 (0.47–2.43)
No	368 (91)	12.6	10.4	0.68 (0.52–0.89)
Liver metastases				
Yes	149 (37)	9.3	7.8	0.81 (0.55–1.20)
No	254 (63)	16.8	11.2	0.64 (0.45–0.90)
Tumor mutational burden				
<10 mutations/Mb	139 (34)	11.8	9.2	0.70 (0.45–1.07)
≥10 mutations/Mb	212 (53)	14.6	11.2	0.68 (0.47–0.97)
<16 mutations/Mb	271 (67)	12.5	9.9	0.71 (0.52–0.98)
≥16 mutations/Mb	80 (20)	17.8	11.9	0.63 (0.35–1.15)
Intention-to-treat population	403 (100)	12.3	10.3	0.70 (0.54–0.91)



Horn. NEJM 2018

Courtesy of David R Spigel, MD

IMpower133

Patients - no. (%)	Atezolizumab (n = 198)	Placebo (n = 196)
PATIENTS WITH ≥1 AE Grade 3-4 AEs Grade 5 AEs	198 (100) 133 (67.2) 4 (2.0)	189 (96.4) 125 (63.8) 11 (5.6)
TREATMENT-RELATED AES Treatment-related Grade 3-4 AEs Treatment-related Grade 5 AEs	188 (94.9) 112 (56.6) 3 (1.5)	181 (92.3) 110 (56.1) 3 (1.5)
IMMUNE-MEDIATED AES, %	39.9	24.5
SERIOUS AES Treatment-related serious AEs	74 (37.4) 45 (22.7)	68 (34.7) 37 (18.9)
AEs leading to withdrawal from any treatment	22 (11.1)	6 (3.1)
AEs leading to withdrawal from carboplatin	5 (2.5)	1 (0.5)
AEs leading to withdrawal from etoposide	8 (4.0)	2 (1.0)

Horn, NEJM 2018

Courtesy of David R Spigel, MD

CASPIAN

Phase 3, randomized, open-label multicenter trial

- Treatment-naïve ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥12 weeks
- Measurable disease per RECIST v1.1

N=805

R
1:1:1

Stratified by planned platinum agent (carboplatin vs cisplatin)

DURVALUMAB + EP
Durvalumab 1500 mg + EP q3w for up to 4 cycles

DURVALUMAB
1500 mg q4w until disease progression

EP
q3w for up to 6 cycles†

OPTIONAL PCI

DURVALUMAB + TREMELIMUMAB + EP*
Durvalumab 1500 mg + tremelimumab 75 mg + EP q3w for up to 4 cycles

DURVALUMAB +
1500 mg q4w until disease progression

Primary end point:

- Overall survival
- Investigator-assessed PFS

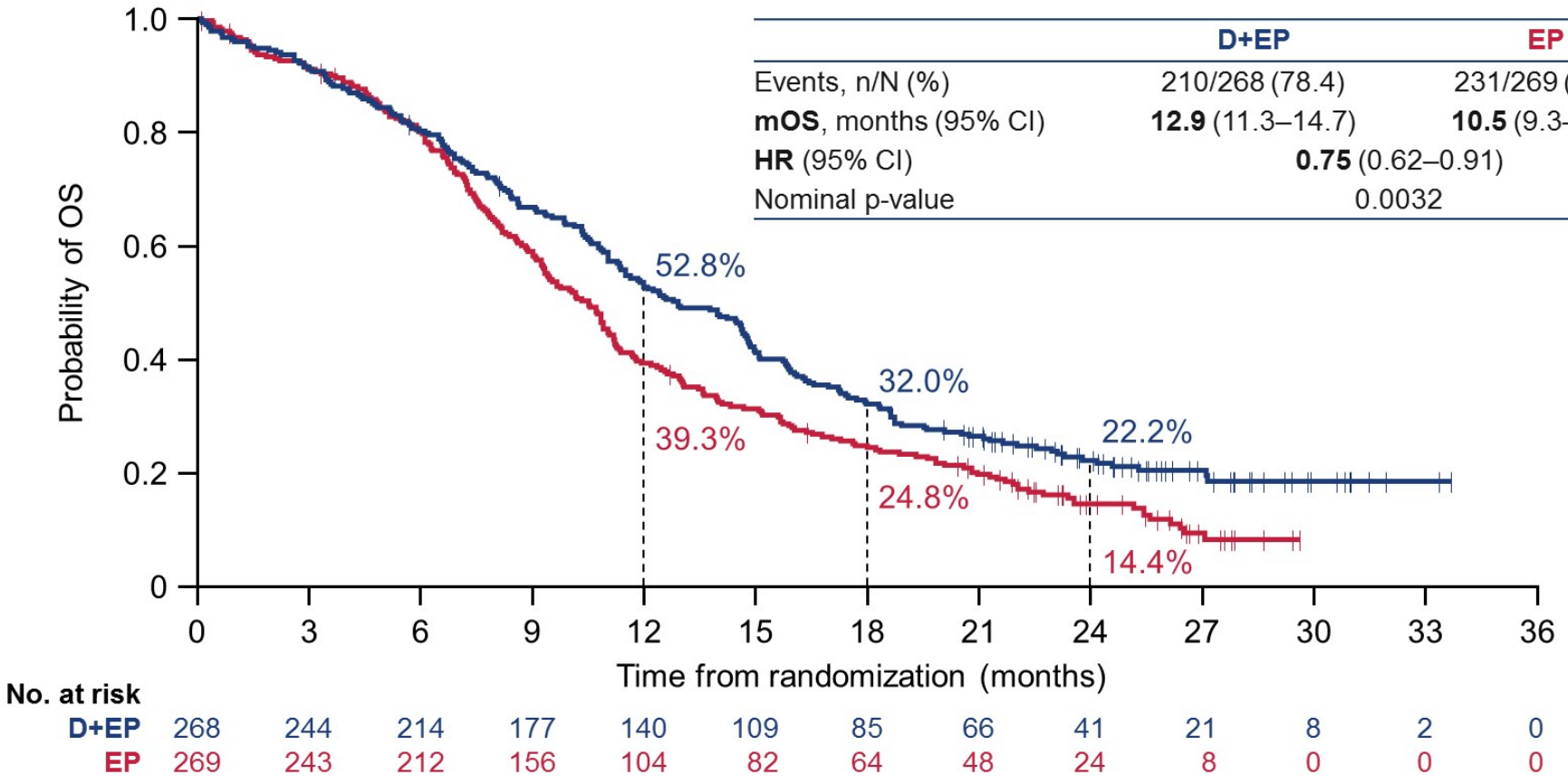
Secondary end points:

- Objective response rate
- Duration of response
- Safety

Courtesy of David R Spigel, MD

CASPIAN

Updated Overall Survival: D+EP vs EP



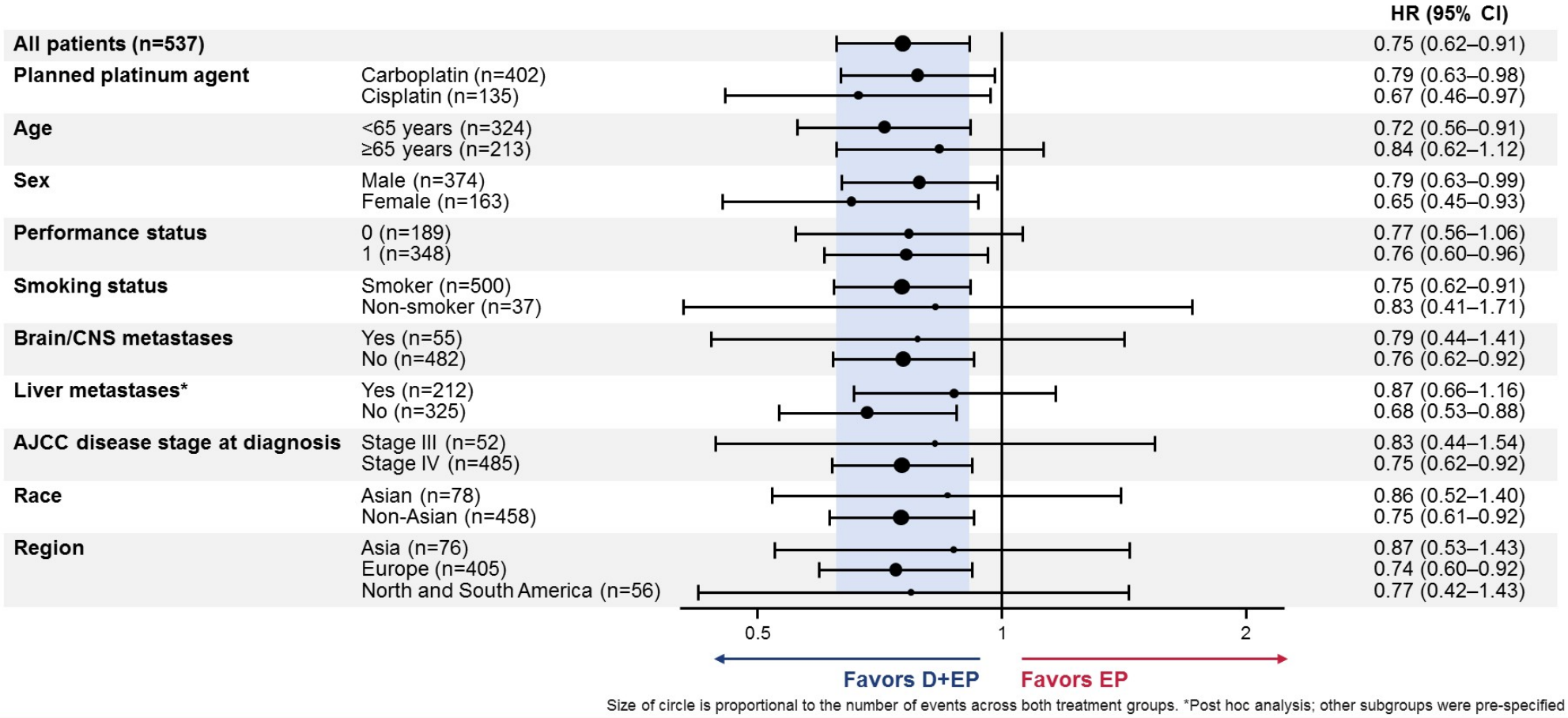
	D+EP	EP
Events, n/N (%)	210/268 (78.4)	231/269 (85.9)
mOS, months (95% CI)	**12.9** (11.3–14.7)	**10.5** (9.3–11.2)
HR (95% CI)	**0.75** (0.62–0.91)	
Nominal p-value	0.0032	

Presented By Luis Paz-Ares at ASCO 2020

Courtesy of David R Spigel, MD

CASPIAN

Overall Survival: D+EP vs EP Subgroup Analysis



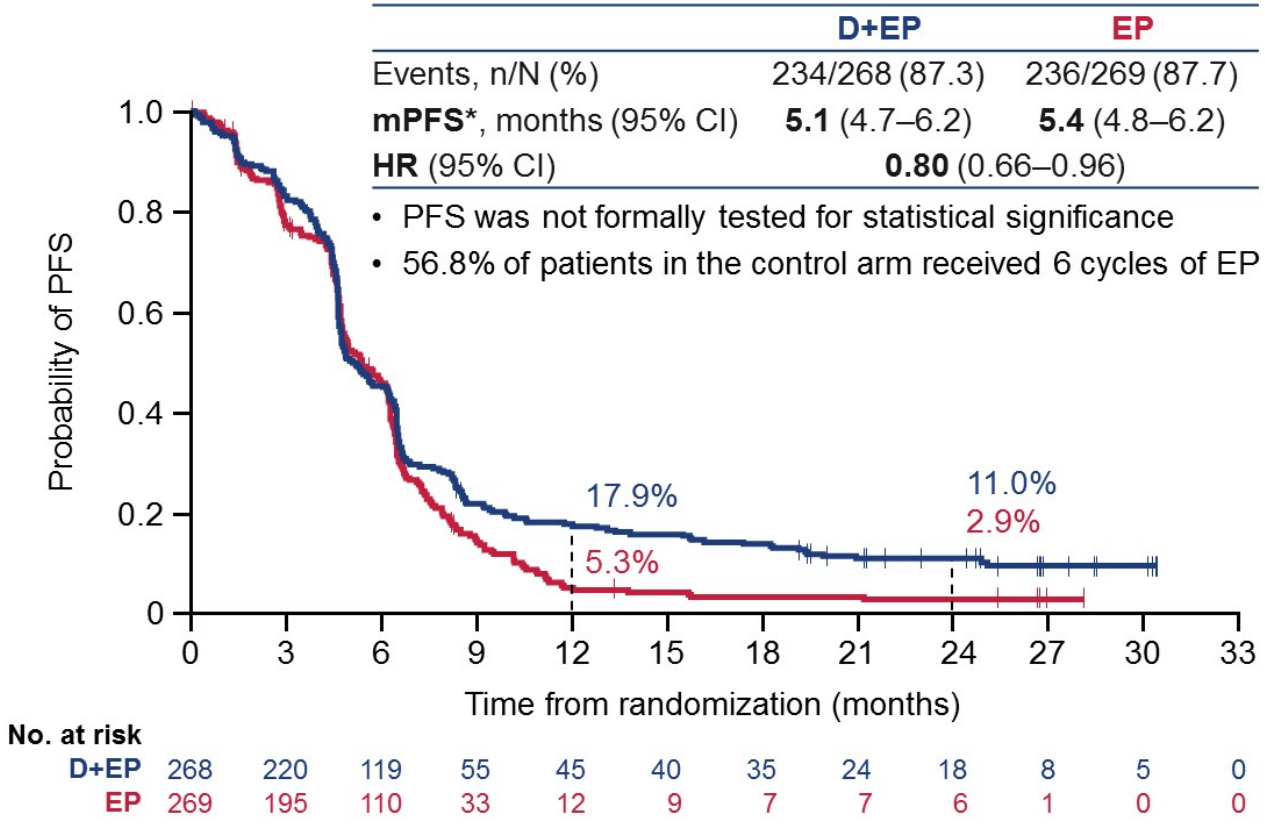
Size of circle is proportional to the number of events across both treatment groups. *Post hoc analysis; other subgroups were pre-specified

Presented By Luis Paz-Ares at ASCO 2020

Courtesy of David R Spigel, MD

CASPIAN

Updated Progression-free Survival: D+EP vs EP

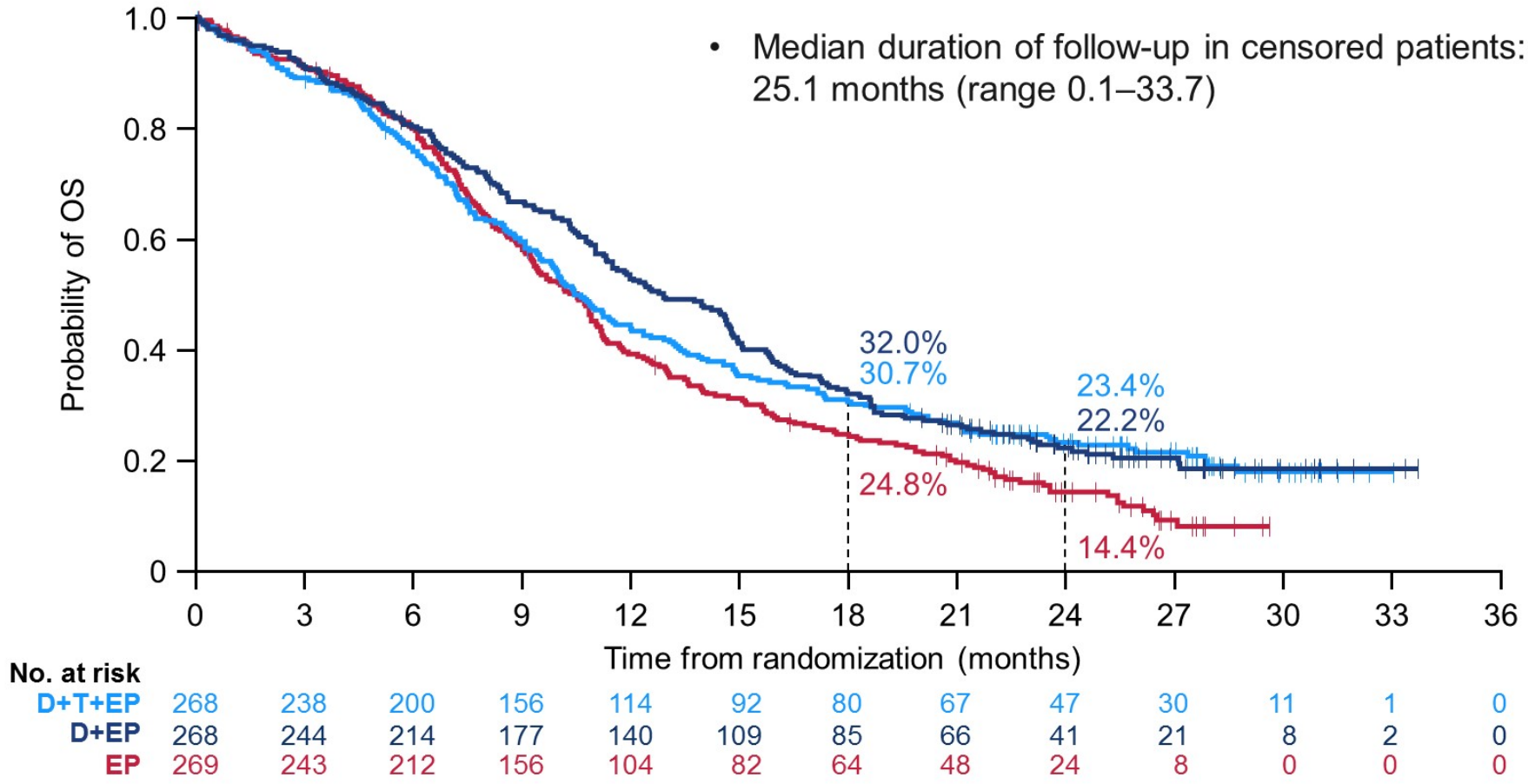


Landmark PFS, %	D+EP (n=268)	EP (n=269)
6 months	45.4	45.8
12 months	17.9	5.3
18 months	13.9	3.4
24 months	11.0	2.9

Presented By Luis Paz-Ares at ASCO 2020

CASPIAN

Overall Survival: All Arms



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Courtesy of David R Spigel, MD

CASPIAN

Safety Summary

	D+T+EP (n=266)	D+EP (n=265)	EP (n=266)
Any-grade all-cause AEs, n (%)	264 (99.2)	260 (98.1)	258 (97.0)
Grade 3/4 AEs	187 (70.3)	165 (62.3)	167 (62.8)
Serious AEs	121 (45.5)	85 (32.1)	97 (36.5)
AEs leading to treatment discontinuation	57 (21.4)	27 (10.2)	25 (9.4)
Immune-mediated AEs	96 (36.1)	53 (20.0)	7 (2.6)
AEs leading to death	27 (10.2)	13 (4.9)	15 (5.6)
Treatment-related AEs leading to death	12 (4.5)	6 (2.3)	2 (0.8)

Presented By Luis Paz-Ares at ASCO 2020

Courtesy of David R Spigel, MD

Standard Of Care: First-Line Treatment of ES-SCLC

2 FDA-Approved / NCCN Listed Regimens

- Platinum-Etoposide + Immunotherapy

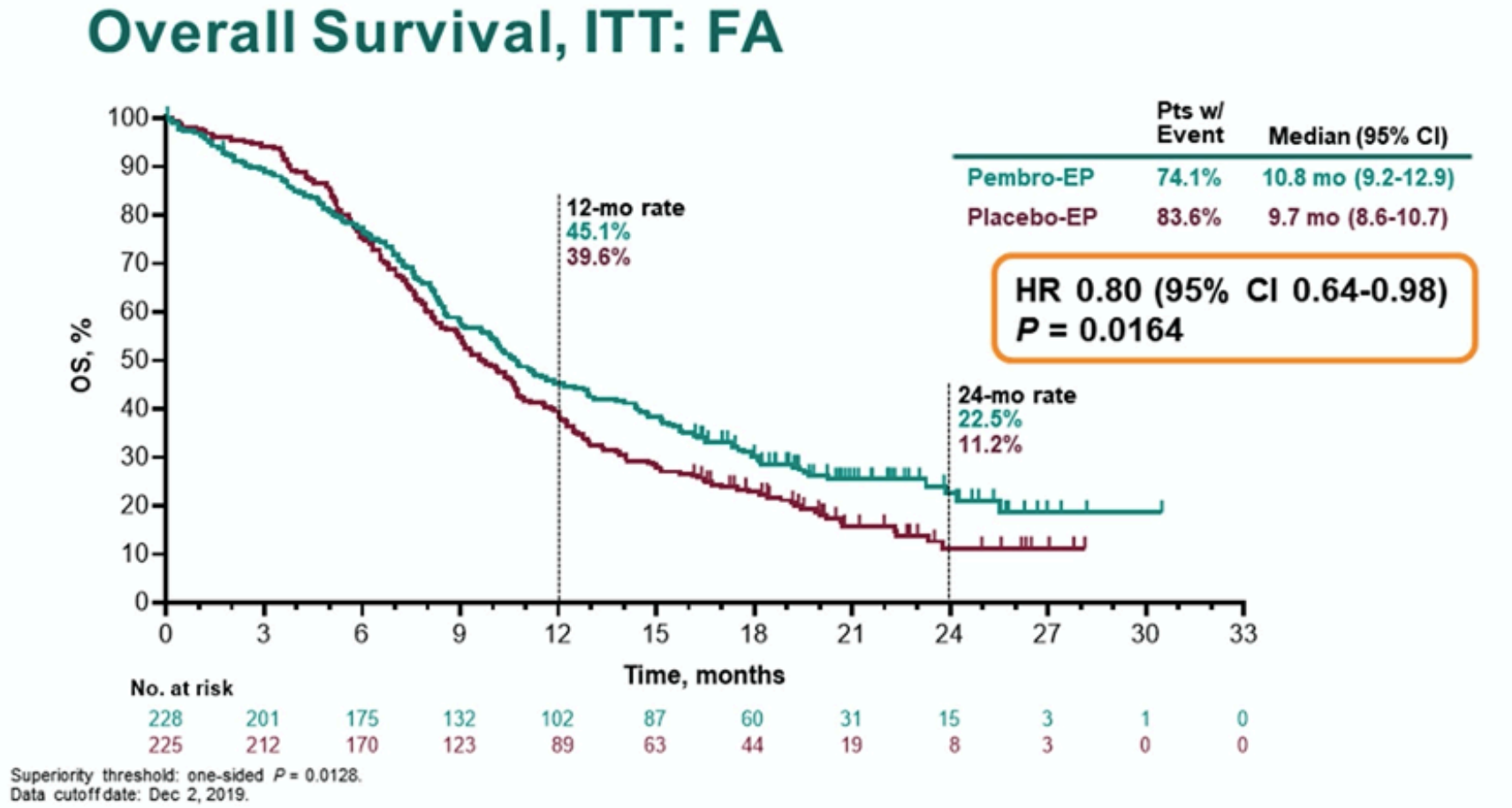
  IMpower133

  CASPIAN

- Use in practice will depend on experience and pathways

Courtesy of David R Spigel, MD

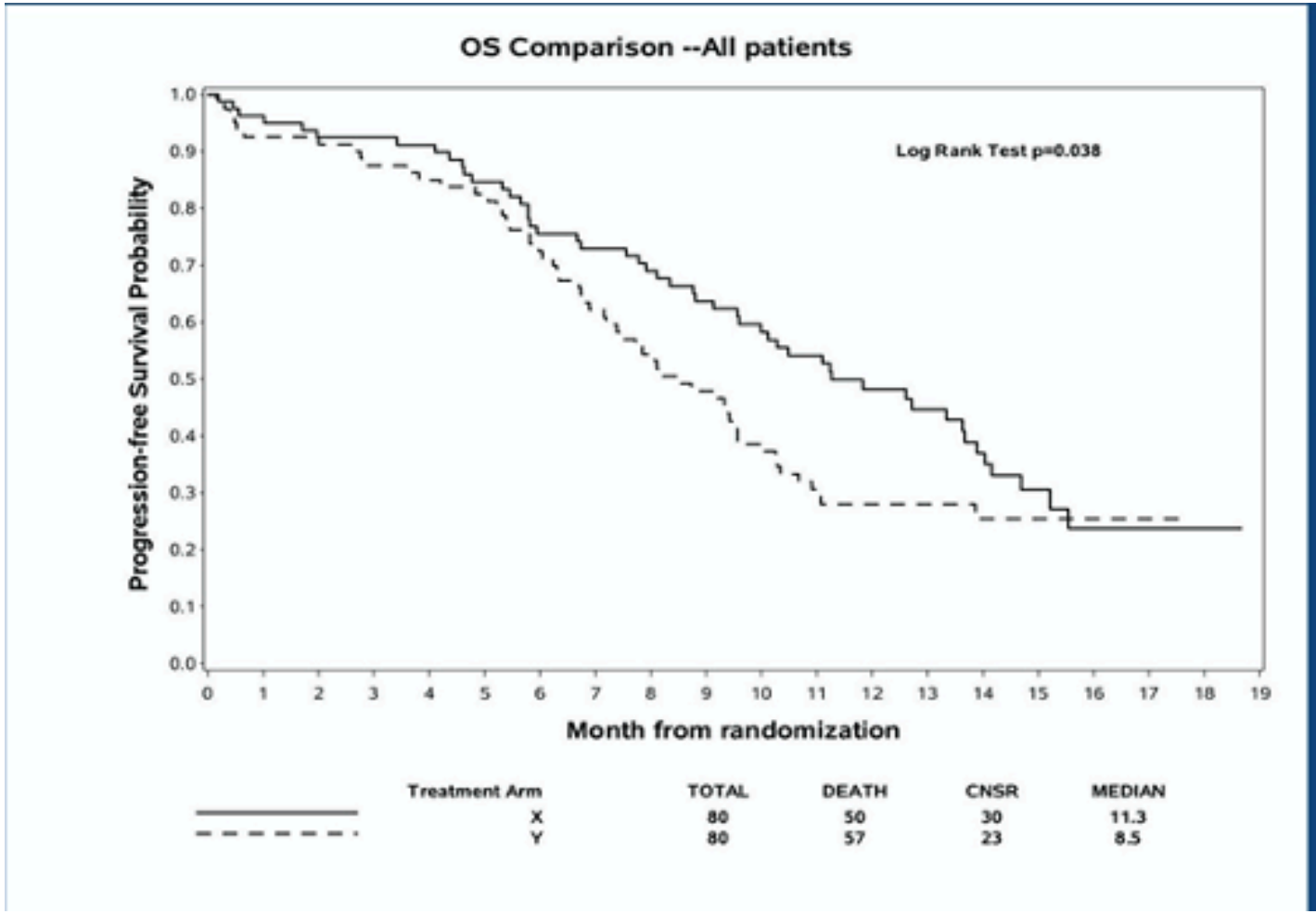
KEYNOTE-604: Phase III Platinum-Etoposide +/- Pembrolizumab in First-Line ES-SCLC



Presented By Rudin at ASCO 2020

Courtesy of David R Spigel, MD

ECOG-ACRIN EA5161: Phase II Platinum-Etoposide +/- Nivolumab in First-Line ES-SCLC (Overall Survival)



	Nivolumab + CE	CE
mOS, months	11.3	8.5
HR (95% CI)	0.67 (0.46-0.98)	
p=0.038		

X=Nivolumab + CE; Y=CE

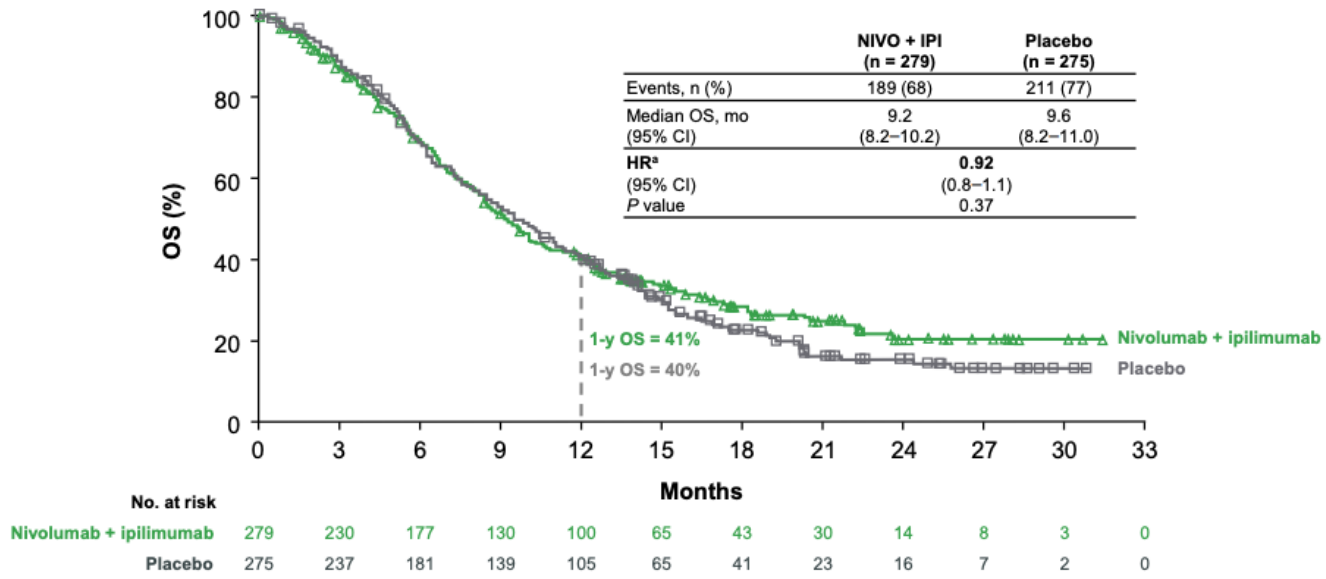
CE = Platinum/Etoposide

Presented By Leal at ASCO 2020

Courtesy of David R Spigel, MD

CheckMate-451: Maintenance Nivolumab, Nivolumab/Ipilimumab, Placebo in First-Line ES-SCLC

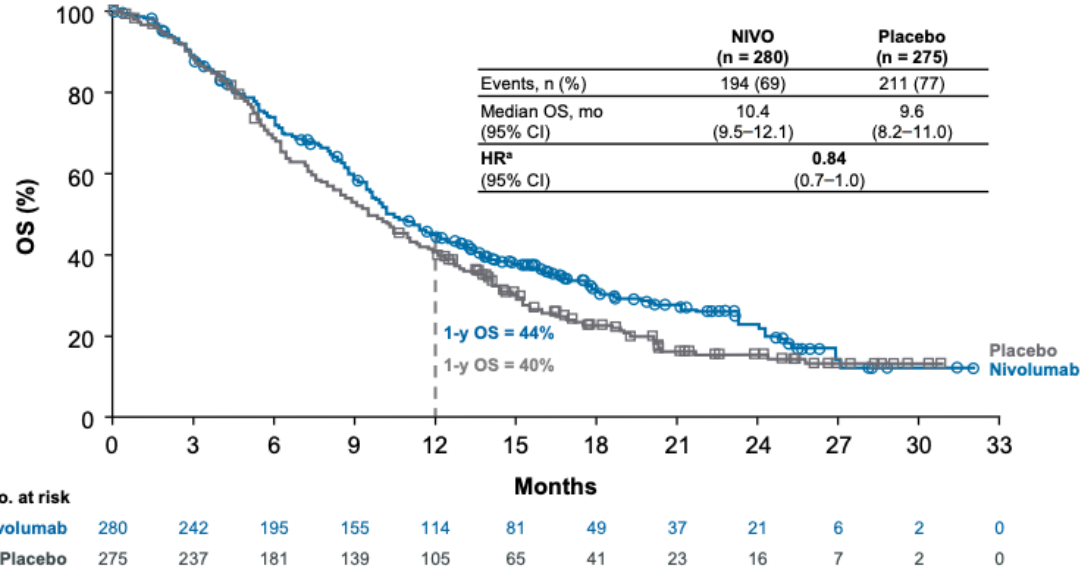
OS for Nivolumab Plus Ipilimumab Versus Placebo (Primary Endpoint)



	NIVO + IPI (n = 279)	Placebo (n = 275)
Events, n (%)	189 (68)	211 (77)
Median OS, mo (95% CI)	9.2 (8.2–10.2)	9.6 (8.2–11.0)
HR[a] (95% CI)	0.92 (0.8–1.1)	
P value	0.37	

No. at risk												
Nivolumab + ipilimumab	279	230	177	130	100	65	43	30	14	8	3	0
Placebo	275	237	181	139	105	65	41	23	16	7	2	0

OS for Nivolumab Versus Placebo



	NIVO (n = 280)	Placebo (n = 275)
Events, n (%)	194 (69)	211 (77)
Median OS, mo (95% CI)	10.4 (9.5–12.1)	9.6 (8.2–11.0)
HR[a] (95% CI)	0.84 (0.7–1.0)	

No. at risk												
Nivolumab	280	242	195	155	114	81	49	37	21	6	2	0
Placebo	275	237	181	139	105	65	41	23	16	7	2	0

Presented By Owonikoko at ASCO 2020

Courtesy of David R Spigel, MD

Accelerated Approval of Lurbinectedin for Metastatic SCLC

Press Release – June 15, 2020

"On June 15, 2020, the Food and Drug Administration granted accelerated approval to lurbinectedin for adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

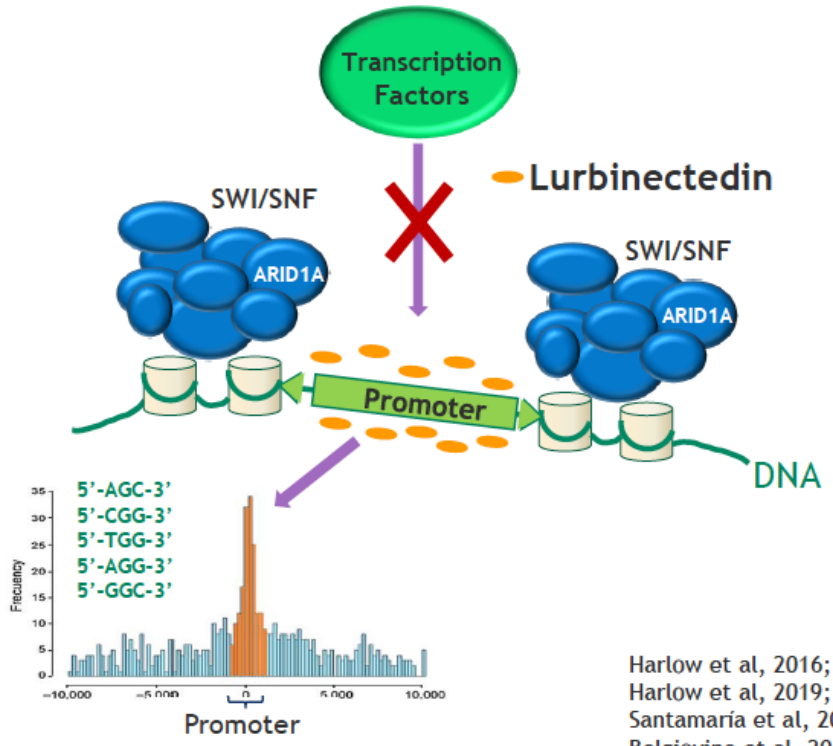
Efficacy was demonstrated in the PM1183-B-005-14 trial (Study B-005; NCT02454972), a multicenter open-label, multi-cohort study enrolling 105 patients with metastatic SCLC who had disease progression on or after platinum-based chemotherapy. Patients received lurbinectedin 3.2 mg/m^2 by intravenous infusion every 21 days until disease progression or unacceptable toxicity.

The recommended lurbinectedin dose is 3.2 mg/m^2 every 21 days."

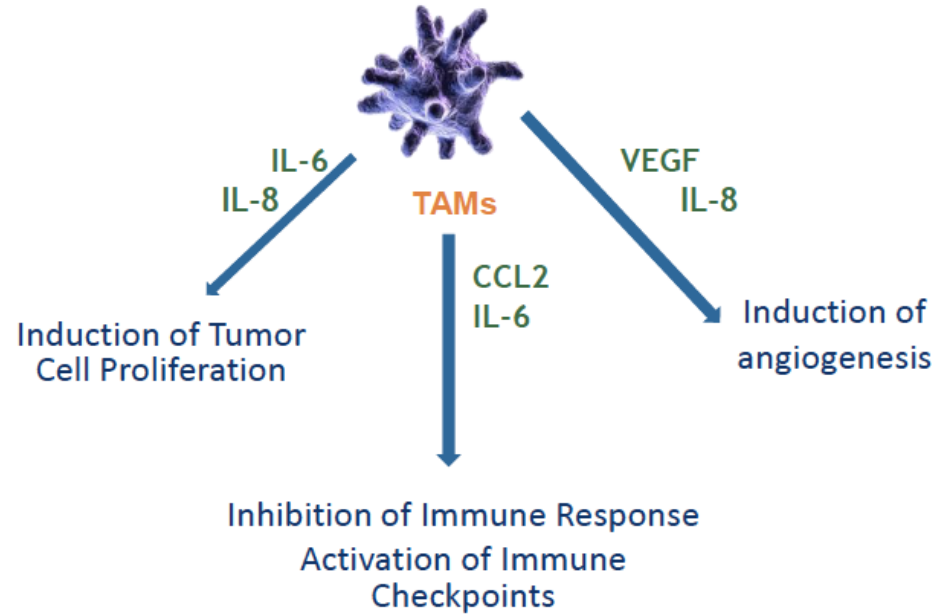
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-lurbinectedin-metastatic-small-cell-lung-cancer.

Lurbinectedin

CANCER IS FREQUENTLY A TRANSCRIPTIONAL DISEASE CAUSED BY DEREGULATED ONCOGENIC TRANSCRIPTION FACTORS



BY INHIBITING ACTIVE TRANSCRIPTION IN TUMOR ASSOCIATED MACROPHAGES (TAMS), LURBINECTEDIN DOWNREGULATES IL-6, IL-8, CCL2 AND VEGF



Harlow et al, 2016; Cancer Res 72: 6657-68
Harlow et al, 2019; Clin Cancer Res doi: 10.1158/1078-0432.CCR-18-3511
Santamaría et al, 2016. Mol Cancer Ther 15:2399-412
Belgiovine et al, 2017 Br J Cancer 117:628-38

Paz Ares, ASCO 2019

Courtesy of David R Spigel, MD

Lurbinectedin: Phase II Basket Trial

PRIMARY OBJECTIVE : ORR by RECIST V.1.1

(confirmed responses)

SCLC patients

PS 0-2

One prior chemotherapy line

Prior immunotherapy was allowed

Active CNS mets excluded

➢ **Lurbinectedin 3.2 mg/m², 1h iv, q3wk**

≥ 2 responses in first 15 patients*

Enroll up to 100 patients

* 5 confirmed responses observed in the first 15 treated patients

Statistical assumptions for SCLC cohort

Null hypothesis :
≤15% get a response
($p \leq 0.15$)

Alternative hypothesis:
≥30% get a response
($p \geq 0.30$)

Statistical power 95%

≥ 23% of confirmed responses needed to reject the null hypothesis

Data cut-off: January 15th 2019

Paz Ares, ASCO 2019

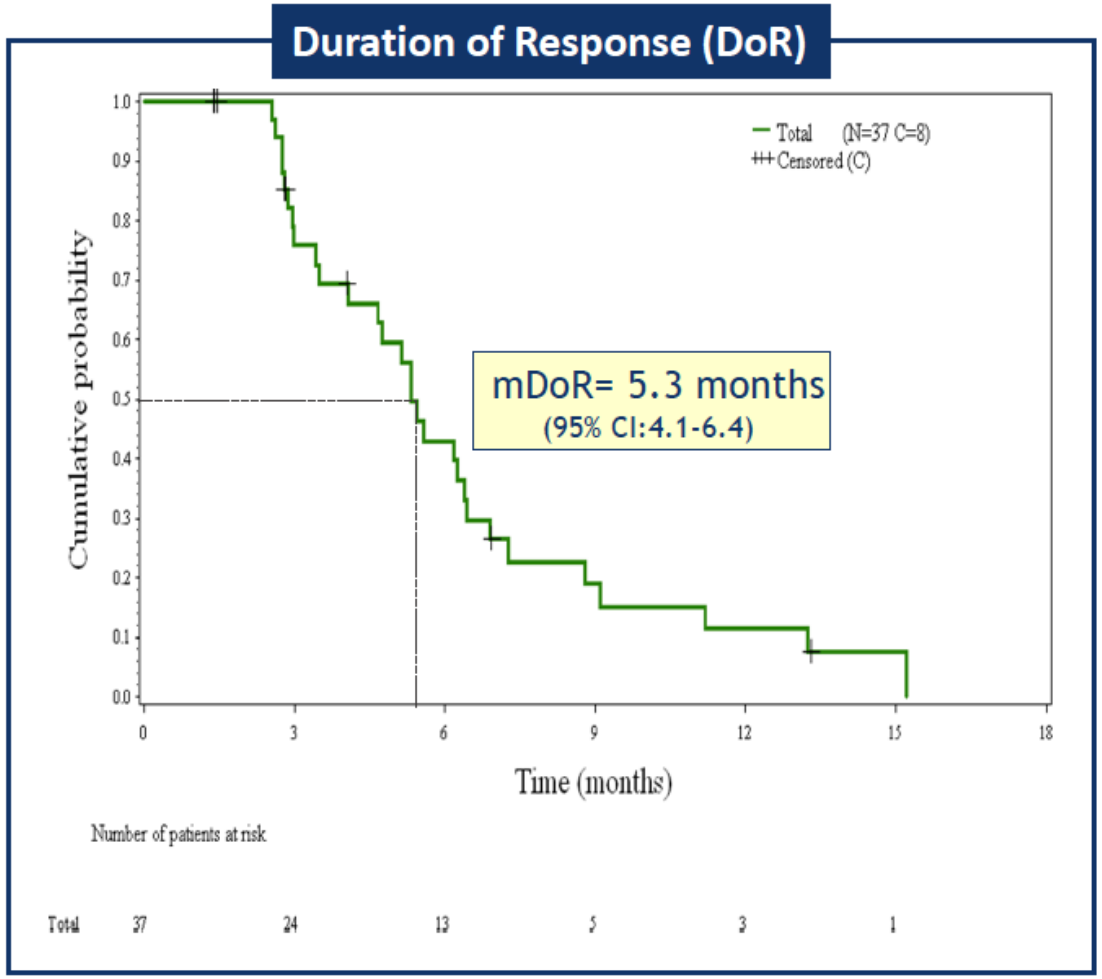
Courtesy of David R Spigel, MD

Lurbinectedin: Phase II Basket Trial ORR

	Overall (n=105)
ORR, % (95% CI)	**35.2 (26.2-45.2)**
Best response	n (%)
- PR (confirmed)	37 (35.2) #
- SD	35 (33.3)
- PD	28 (26.7)
- NE* (non- evaluable)	5 (4.8)
Disease Control Rate,% (95% CI)	68.6 (58.8-77.3)

5 of 8 patients who failed prior immunotherapy had confirmed response

* Treatment discontinuation without any tumor assessment performed



Paz Ares, ASCO 2019

Courtesy of David R Spigel, MD

Lurbinectedin: Phase II Basket Trial Safety

n=105		Gr 1-2 n (%)	Gr 3-4 n (%)
Hematological AEs *	Neutropenia	6 (5.7)	24 (22.9)
	Anemia	2 (1.9)	7 (6.7)
	Thrombocytopenia	2 (1.9)	5 (4.8)
Non-Hematological AEs	Febrile neutropenia	.	5 (4.8)
	Fatigue	54 (51.4)	7 (6.7)
	Nausea	34 (32.4)	.
	Decreased appetite	22 (21.0)	.
	Vomiting	19 (18.1)	.
	Diarrhea	13 (12.4)	1 (1.0)
	Constipation	10 (9.5)	.
	Pneumonia	.	2 (1.9)
	Alanine aminotransferase increased *	.	2 (1.9)
	Skin ulcer	.	1 (1.0)

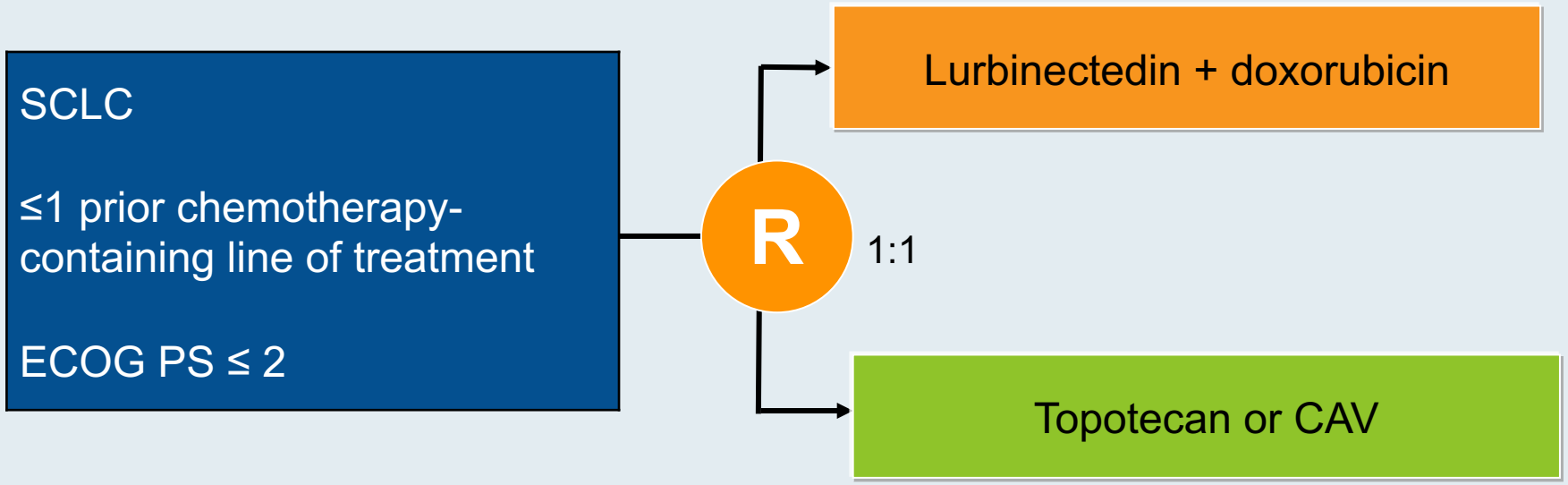
* Lab abnormalities associated with a specific treatment, were considered a SAE, or were reasons for dose reduction or treatment delay

Paz Ares, ASCO 2019

Courtesy of David R Spigel, MD

ATLANTIS: A Phase III Trial of Lurbinectedin/Doxorubicin versus Chemotherapy for SCLC

Trial Identifier: NCT03269669 (Closed)



Primary endpoint: Overall survival

www.clinicaltrials.gov; Accessed July 2020.

Novel Agents and Strategies in SCLC

- LS-SCLC: Durvalumab
- First-Line ES-SCLC: Tiragolumab (Anti-TIGIT)
  Venetoclax
- Relapsed SCLC: Liposomal Irinotecan
  SC-011 (ADC)
  AMG 757 (Anti-DLL3/CD3 Bispecific Ab)

Paz Ares, ASCO 2019

Courtesy of David R Spigel, MD

MODULE 3: Immunotherapy Consolidation After Chemoradiation Therapy

- **Faculty Cases – Dr Liu**
  - A 71-year-old man with locally advanced NSCLC
  - A 39-year-old man with locally advanced NSCLC
- **Questions and Cases from Investigators**
- **Key Relevant Data Sets**

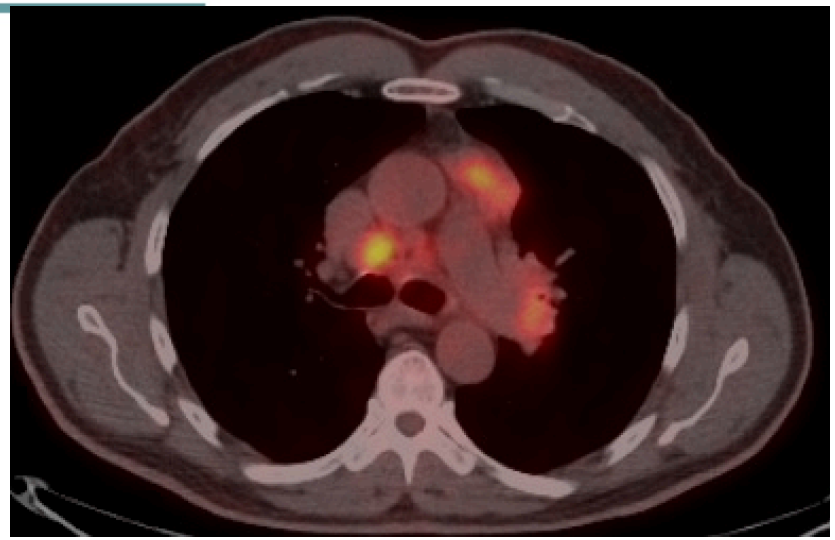
What would you most likely recommend as consolidation treatment for a patient with locally advanced NSCLC who has completed chemoradiation therapy and is found to have an EGFR activating mutation?

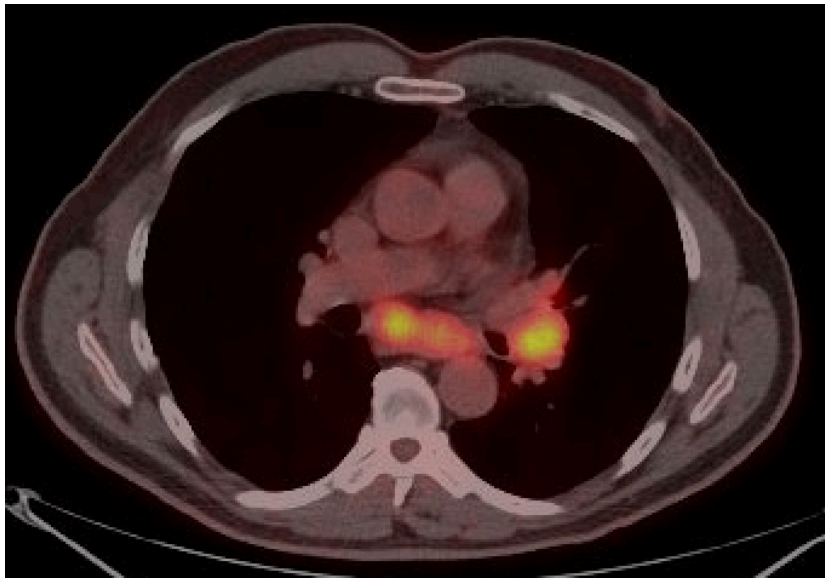
a. Durvalumab
b. Osimertinib
c. Durvalumab + osimertinib
d. Durvalumab followed by osimertinib
e. Other

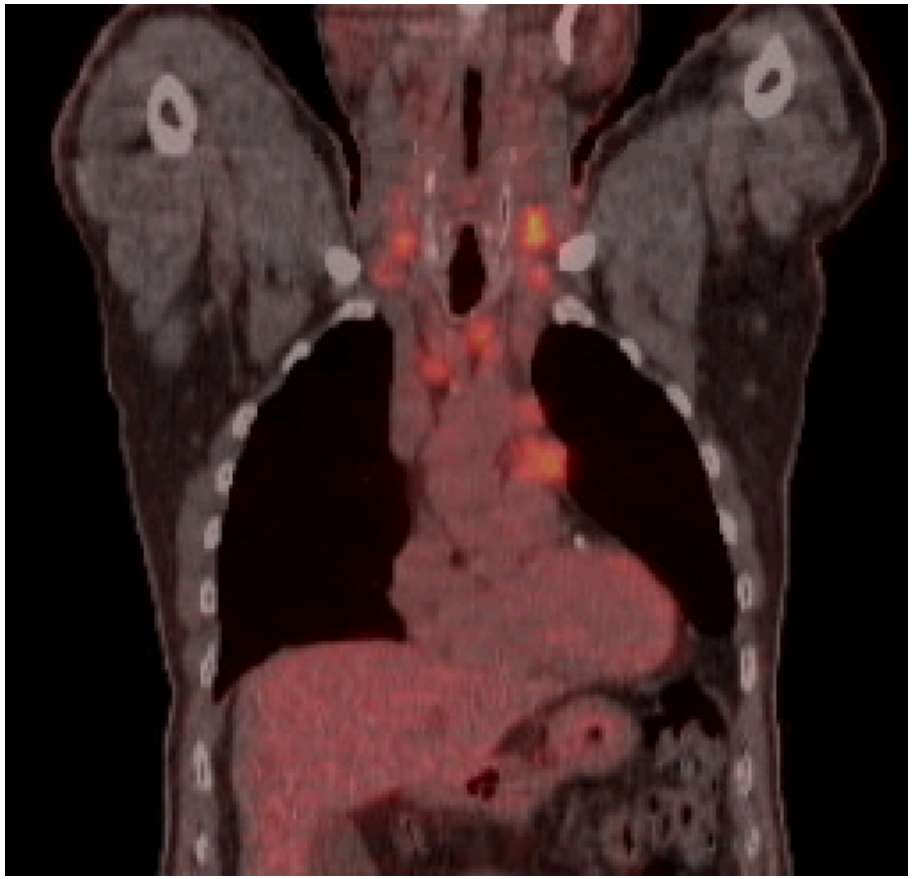
Case Presentation (Dr Liu): 71-Year-Old Man with Locally Advanced NSCLC

- 71 year old male presented with a lower neck mass
  - Ultrasound guided biopsy done July 2019
  - Pathology showed a TTF1+ NSCLC, PD-L1 30%
    - Insufficient tissue for EGFR/ALK/NGS
  - PET/CT showed a left suprahilar lung mass with enlarged, hypermetabolic nodes in the bilateral supraclavicular, bilateral paratracheal, anterior mediastinal, subcarinal and AP window stations
  - MRI brain with no metastases

Case Presentation (Dr Liu): 71-Year-Old Man with Locally Advanced NSCLC (cont)







Case Presentation (Dr Liu): 71-Year-Old Man with Locally Advanced NSCLC (cont)

- 71 year old male with T2N3M0 lung adenocarcinoma
  - Concurrent chemoradiation (60 Gy)
  - Weekly carboplatin + paclitaxel
  - Course complicated by severe esophagitis
  - Recovered and CT showed good response to therapy
- Discussed consolidation durvalumab
- Original FNA showed lung adenocarcinoma, TTF1+
  - PD-L1 30% but insufficient for EGFR/ALK/NGS
  - ctDNA showed EGFR L858R

Case Presentation (Dr Liu): 71-Year-Old Man with Locally Advanced NSCLC (cont)

- Should we offer durvalumab to EGFR+ post CRT?
- Durvalumab improves PFS and OS
  - Less benefit in EGFR+ NSCLC
    - That subset was small, not a primary endpoint
- Durvalumab may complicate efforts to give osimertinib at the time of relapse
  - Will withholding durvalumab make relapse more likely?
    - Unfortunately, most patients are still not cured

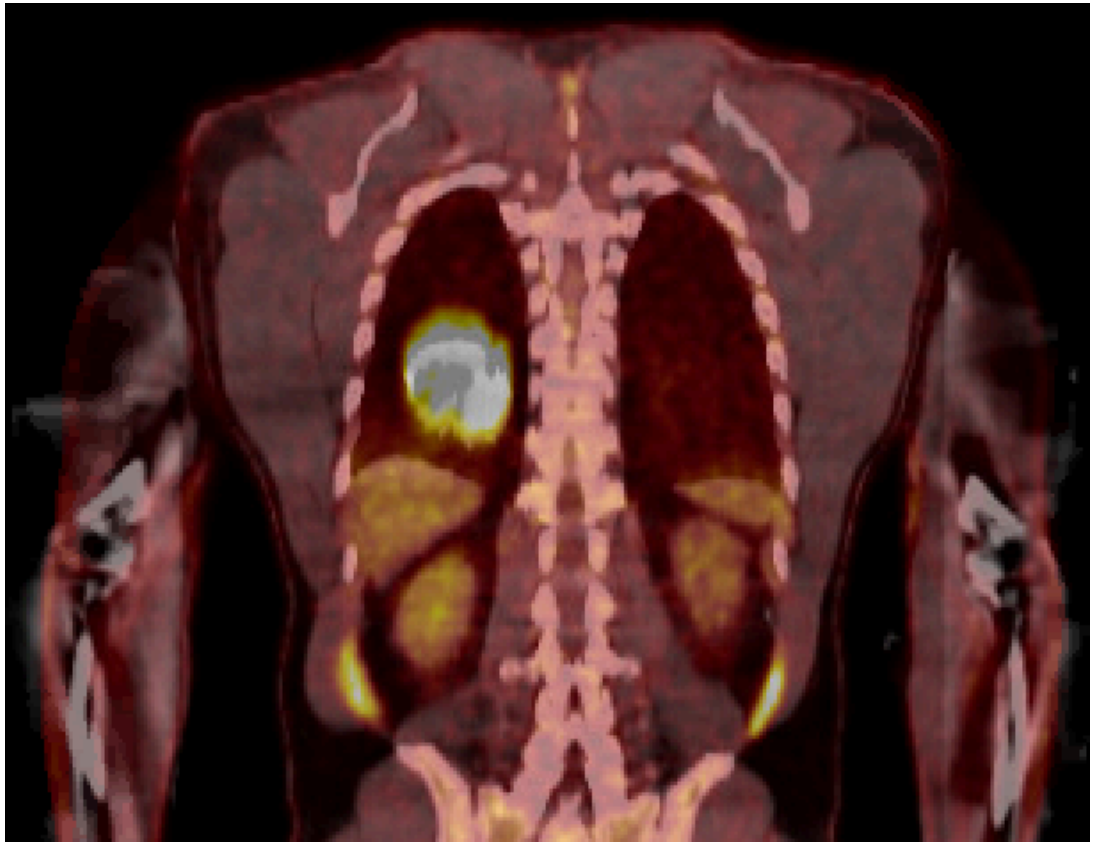
Case Presentation (Dr Liu): 71-Year-Old Man with Locally Advanced NSCLC (cont)

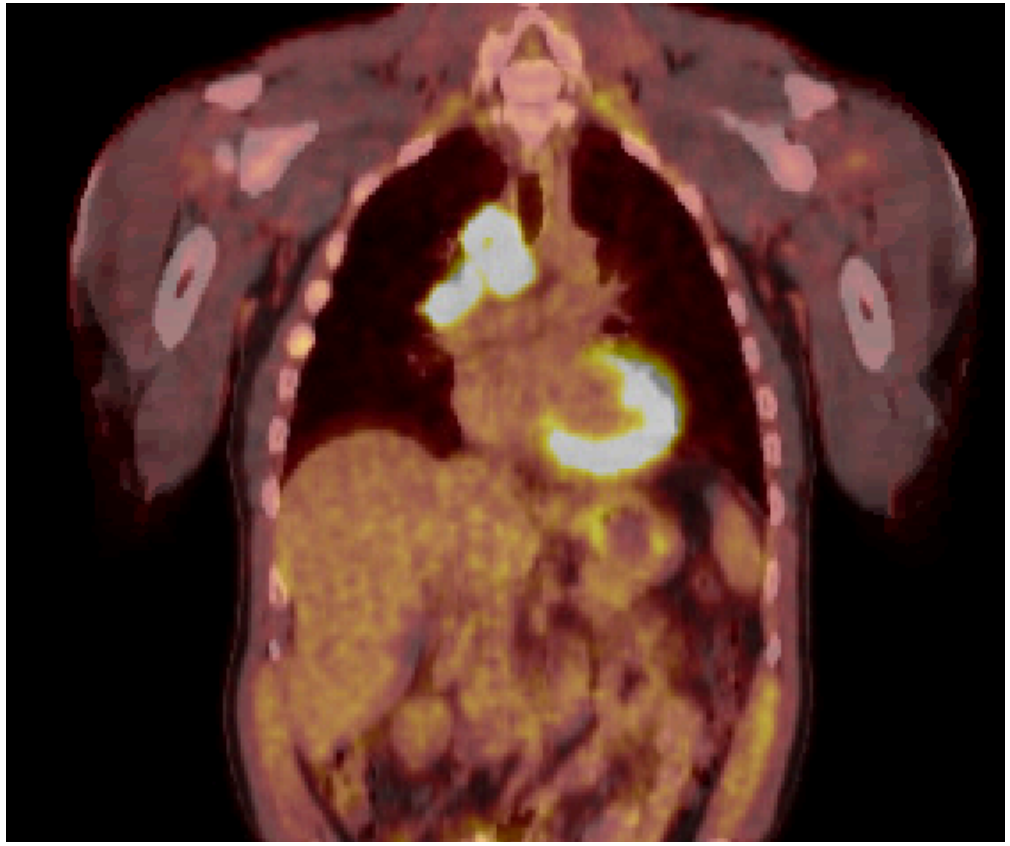
- 71 year old male with T2N3M0 lung adenocarcinoma
  - Concurrent chemoradiation (60 Gy)
  - Weekly carboplatin + paclitaxel
  - Began durvalumab consolidation January 2020
  - CT in April showed no disease

Case Presentation (Dr Liu): 39-Year-Old Man with Locally Advanced NSCLC

- 39 year old male with dyspnea, hypoxic in ER
  - PET/CT showed large right lung mass with enlarged mediastinal adenopathy
  - MRI brain with no metastases
  - Bronchoscopy showed endobronchial tumor, obstruction of RUL, pathology showed poorly differentiated NSCLC
  - PD-L1 0%, mutations in TP53 and PIK3CA
  - T4N2M0 unresectable NSCLC

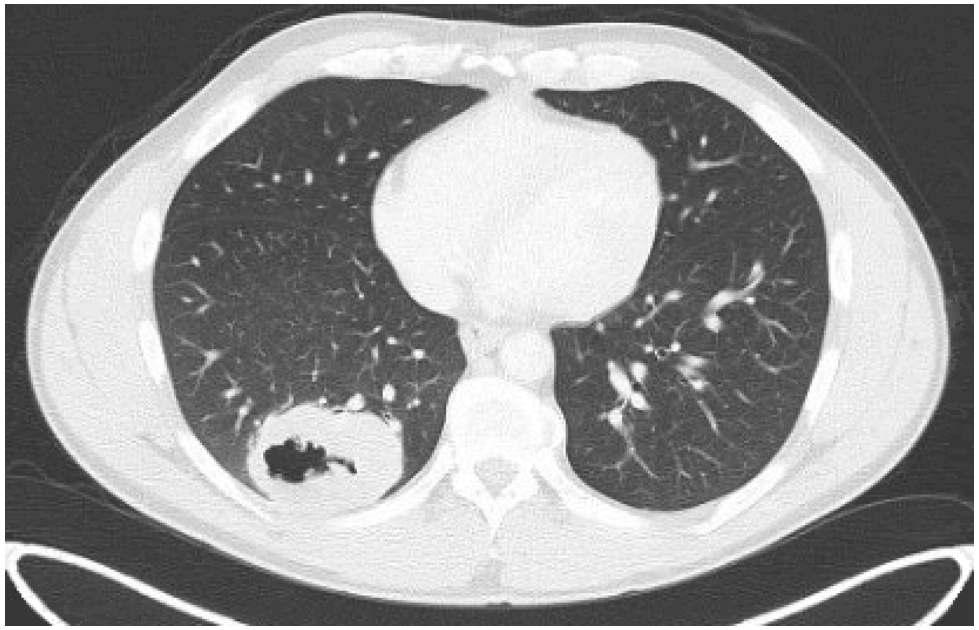
Case Presentation (Dr Liu): 39-Year-Old Man with Locally Advanced NSCLC (cont)

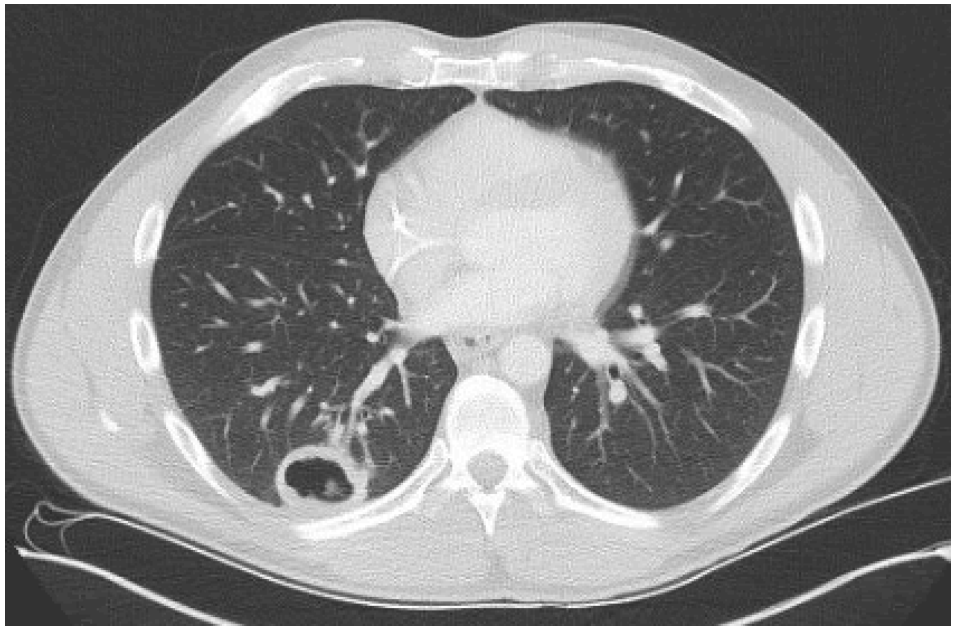




Case Presentation (Dr Liu): 39-Year-Old Man with Locally Advanced NSCLC (cont)

- 39 year old male with T4N2M0 NSCLC
  - Cisplatin + etoposide with concurrent radiation May 2019
  - CT scan after chemoradiation showed no progression

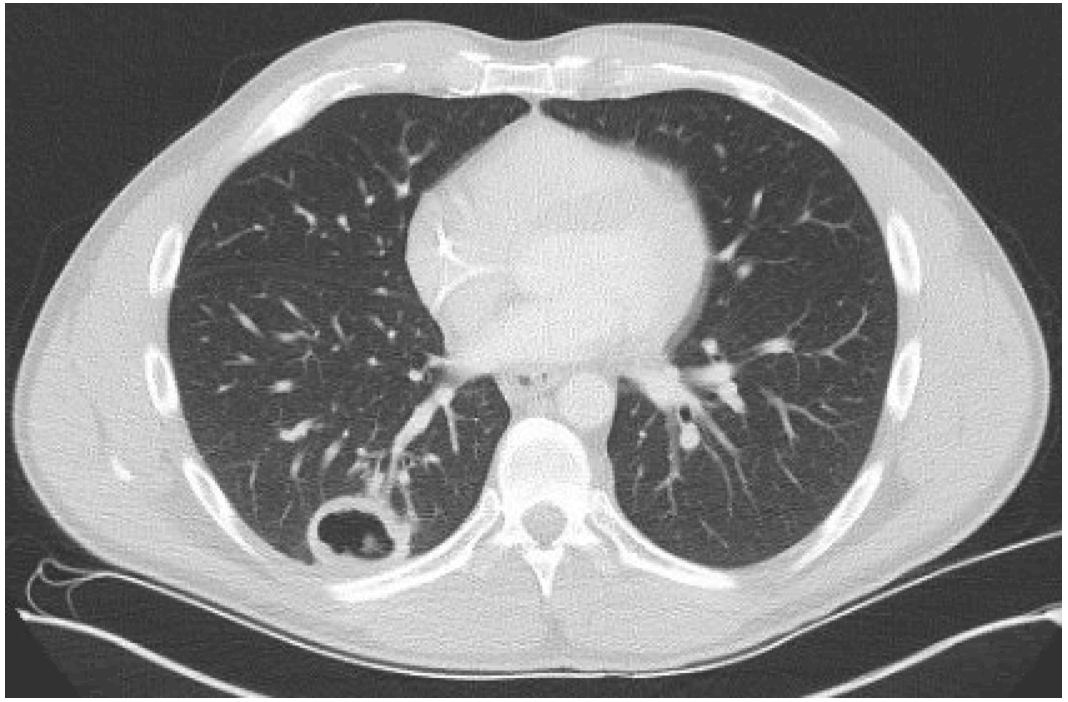


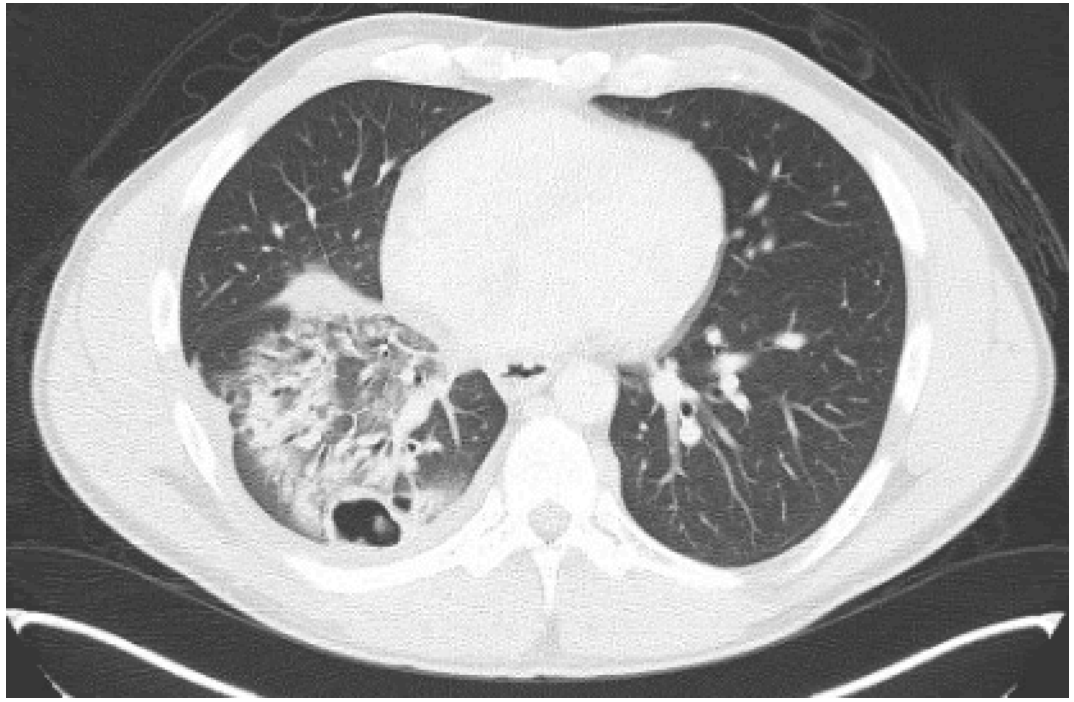


Case Presentation (Dr Liu): 39-Year-Old Man with Locally Advanced NSCLC (cont)

- 39 year old male with T4N2M0 NSCLC
  - Cisplatin + etoposide with concurrent radiation May 2019
  - Consolidation durvalumab began July 2019
  - Received 6th dose of durvalumab and became more dyspneic before dose #7 in September 2019
  - CT performed showed improvement in adenopathy but diffuse right sided opacities

Case Presentation (Dr Liu): 39-Year-Old Man with Locally Advanced NSCLC (cont)





Case Presentation (Dr Liu): 39-Year-Old Man with Locally Advanced NSCLC (cont)

- 39 year old male with T4N2M0 NSCLC
  - Cisplatin + etoposide with concurrent radiation May 2019
  - Consolidation durvalumab began July 2019
  - Received 6th dose of durvalumab and became more dyspneic before dose #7 in September 2019
  - Hypoxic in ER, CT performed showed improvement in adenopathy but diffuse right sided opacities
  - Improved with steroids (10-week course)
  - Surveillance CT January 2020 showed recurrence in mediastinum and LUL (biopsy confirmed)

Challenging Questions and Cases

Challenging Questions and Cases

Challenging Questions and Cases

MODULE 3: Immunotherapy Consolidation After Chemoradiation Therapy

- **Faculty Cases – Dr Liu**
  - A 71-year-old man with locally advanced NSCLC
  - A 39-year-old man with locally advanced NSCLC
- **Questions and Cases from Investigators**
- **Key Relevant Data Sets**

PACIFIC Trial

- Patients with unresectable, Stage III NSCLC without disease progression following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Archived tumor tissue obtained before cCRT (if available) provided for PD-L1 testing*

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

N=983 screened

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

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 by BICR
- DoR by BICR
- TTDM by BICR
- PFS2 per investigator
- Safety and tolerability
- PROs

Antonia, WCLC 2018

Courtesy of Stephen V Liu, MD, PhD

PACIFIC

- Select inclusion criteria
  - Unresectable stage III NSCLC
  - Received at least 2 cycles of platinum-based chemotherapy
  - Radiation at least to a dose of 60 Gy
  - Have not progressed after chemoradiation
  - No PD-L1 requirement, no EGFR/ALK exclusion
  - ECOG PS 0-1
  - Intact organ function

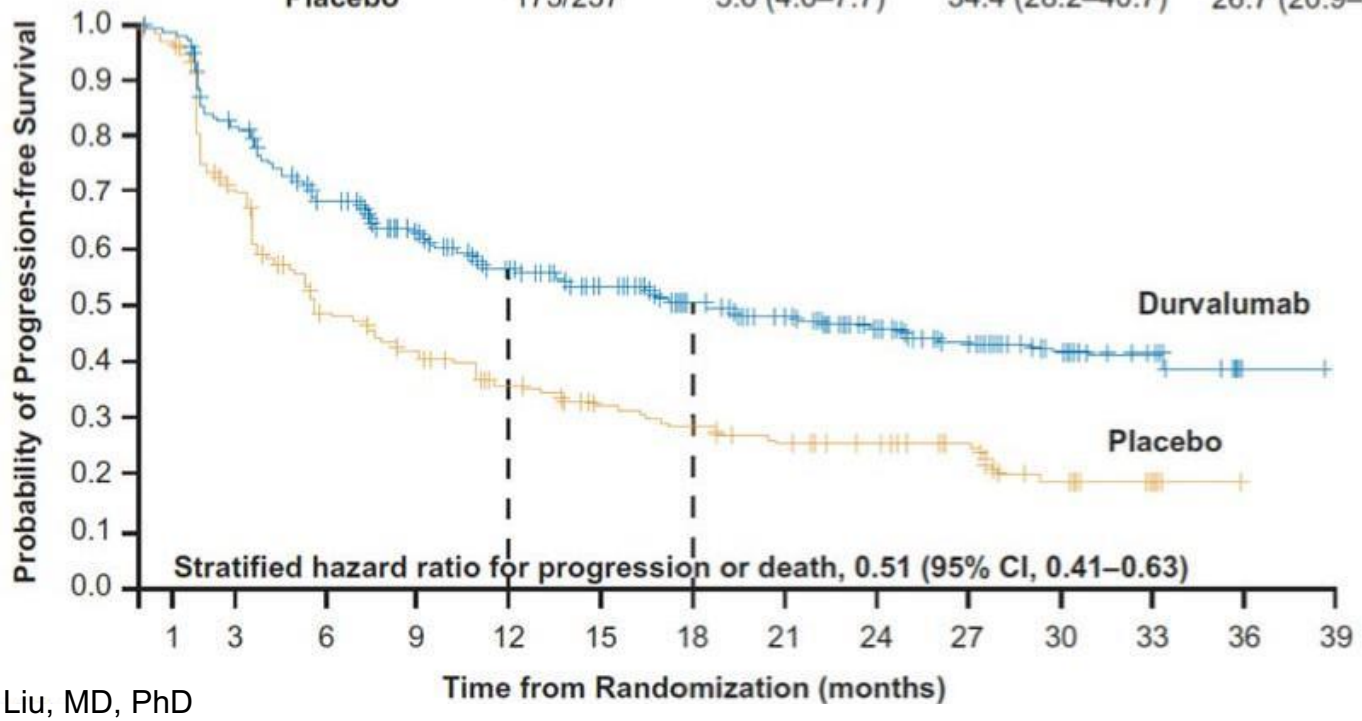
Antonia, NEJM 2017

Courtesy of Stephen V Liu, MD, PhD

PACIFIC

- Significant improvement in PFS

	No. of Events/ Total No. of Patients	Median PFS (95% CI)	12-mo PFS (95% CI)	18-mo PFS (95% CI)
		mo	%	%
Durvalumab	243/476	17.2 (13.1–23.9)	55.7 (50.9–60.2)	49.5 (44.6–54.2)
Placebo	173/237	5.6 (4.6–7.7)	34.4 (28.2–40.7)	26.7 (20.9–32.9)



Antonia, NEJM 2018

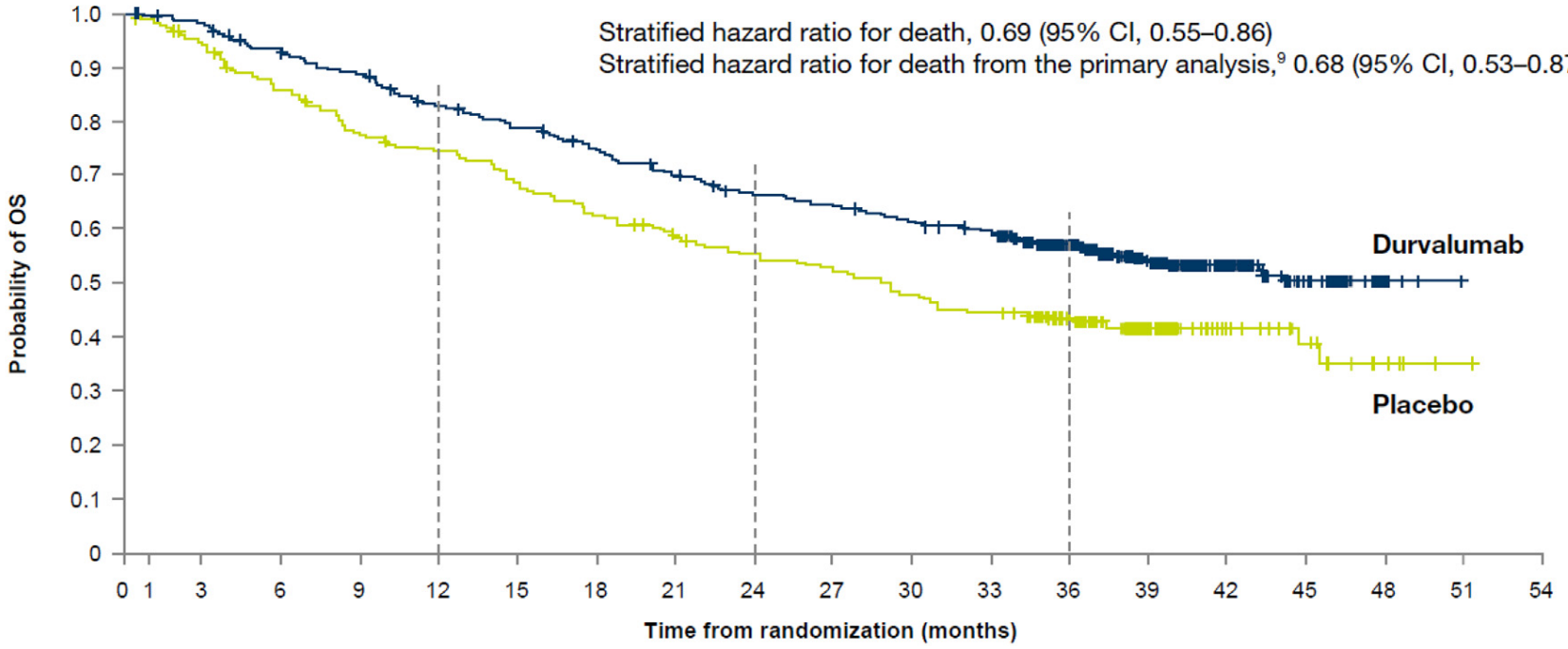
Courtesy of Stephen V Liu, MD, PhD

Georgetown | Lombardi

PACIFIC

- Significant improvement in OS

	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)



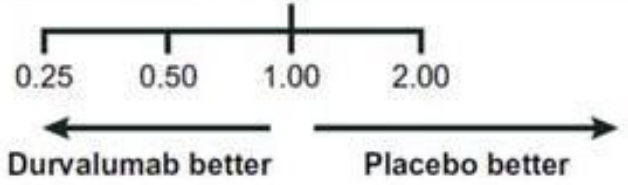
Gray, JTO 2020

Courtesy of Stephen V Liu, MD, PhD

PACIFIC Subsets

- PD-L1 and outcomes
  - PD-L1 negative subset with trend towards less benefit
  - Note 59% were unknown and all results were pre-CRT

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Death (95% CI)
	no. of events / no. of patients (%)		
All patients	183/476 (38.4)	116/237 (48.9)	0.68 (0.53–0.87)†
PD-L1 status			
≥1%	70/212 (33.0)	45/91 (49.5)	0.53 (0.36–0.77)
≥25%*	37/115 (32.2)	23/44 (52.3)	0.46 (0.27–0.78)
1–24%	33/97 (34.0)	22/47 (46.8)	0.60 (0.35–1.03)
<1%	41/90 (45.6)	19/58 (32.8)	1.36 (0.79–2.34)
Unknown	72/174 (41.4)	52/88 (59.1)	0.62 (0.43–0.89)

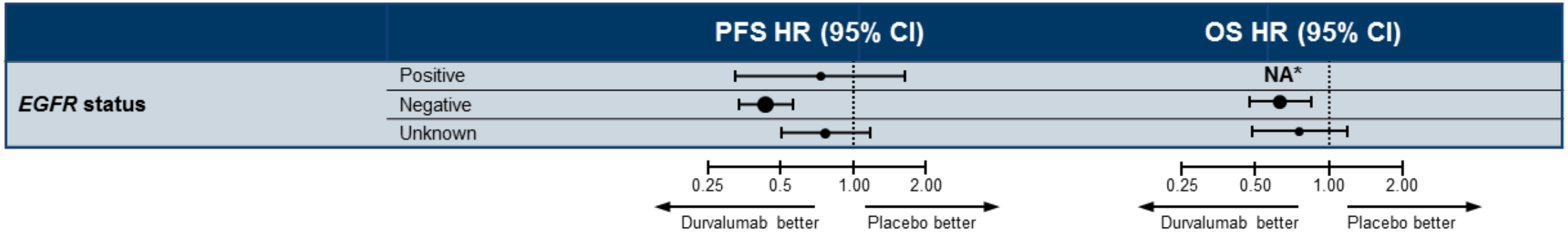


Antonia, NEJM 2018

Courtesy of Stephen V Liu, MD, PhD

PACIFIC Subsets

- EGFR and outcomes
  - EGFR mutant PFS less impressive
  - 43 patients with EGFR mutations included (188 unknown)



  - Concern regarding use of EGFR TKI after durvalumab
  - Ongoing Phase III LAURA trial (NCT03521154)
    - Osimertinib (vs placebo) after chemoradiation

Antonia, WCLC 2018

Courtesy of Stephen V Liu, MD, PhD

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

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Courtesy of Stephen V Liu, MD, PhD

Pneumonitis in PACIFIC

- Occurs relatively frequently with chemoradiation but a higher incidence observed with durvalumab

Pneumonitis

	Durvalumab	Placebo
Any Grade	33.9%	24.8%
Grade 3-4	3.4%	2.6%
Grade 5	1.1%	1.7%
Time to Onset	55 days	55 days

Vansteenkiste, WCLC 2018

Courtesy of Stephen V Liu, MD, PhD

Real-World Rates of Pneumonitis After Consolidation Durvalumab

Real-World Survey of Pneumonitis/Radiation Pneumonitis in LA-NSCLC After Approval of Durvalumab: HOPE-005/CRIMSON Retrospective Cohort Study

- >80% developed pneumonitis
- More than half of them were asymptomatic, but 5% needed HOT and 1.5% developed fatal pneumonitis
- V20 was an independent risk factor for symptomatic pneumonitis (Grade ≥2)
- With careful consideration, durvalumab-rechallenge could be an option after corticosteroid therapy for pneumonitis

Incidence of Pneumonitis in US Veterans with NSCLC Receiving Durvalumab After Chemoradiation Therapy

- In this real-world cohort, clinical significant pneumonitis was:
  - More frequent compared to clinical trial reports
    - Asymptomatic infiltrates on imaging: 39.8%
    - Clinically significant pneumonitis: 21.1%
      - Grade 2 (7.3%), Grade 3 (11.4%), Grade 4 (1.6%), Grade 5 (0.8%)
  - Not associated with increased risk of death

Saito et al. ASCO 2020; Abstract 9039. Thomas T et al. ASCO 2020; Abstract 9034.

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-Related Events

- Non-pneumonitis immune-related 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

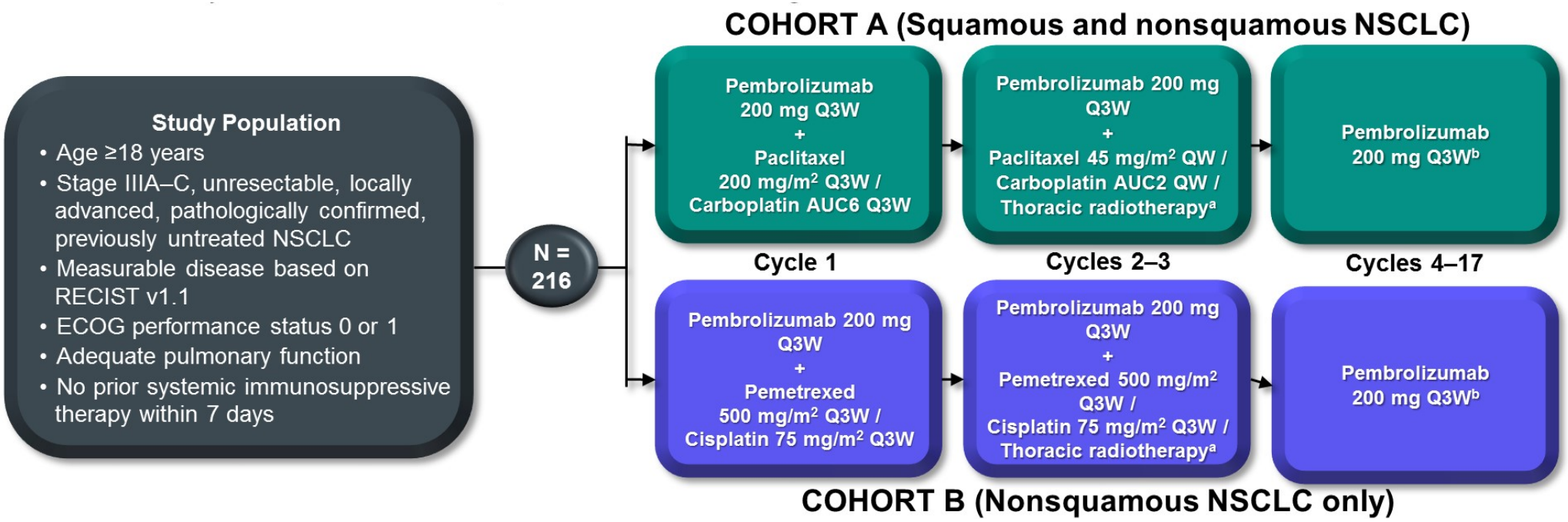
Emerging Strategies

- Locally advanced, unresectable NSCLC
  - Different immune checkpoint inhibitors
  - Targeted therapy (LAURA trial)
  - Different timing
- PACIFIC 2 (NCT03519971)
  - Durvalumab given with concurrent chemoradiation
- KEYNOTE-799 (NCT03631784)
  - Pembrolizumab-based chemoradiation

Courtesy of Stephen V Liu, MD, PhD

Phase II KEYNOTE-799 Trial

- Non-randomized, open-label study



Jabbour, ASCO 2020

Courtesy of Stephen V Liu, MD, PhD

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KEYNOTE-799

	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

Jabbour, ASCO 2020

Courtesy of Stephen V Liu, MD, PhD

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KEYNOTE-799

	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

Jabbour, ASCO 2020

Courtesy of Stephen V Liu, MD, PhD

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Emerging Strategies

- Locally advanced, unresectable NSCLC
  - Different checkpoint inhibitors
  - Targeted therapy (LAURA trial)
  - Different timing
- Resectable NSCLC
  - Adjuvant immunotherapy
  - Neoadjuvant immunotherapy
  - Neoadjuvant chemoimmunotherapy

Courtesy of Stephen V Liu, MD, PhD

Challenging Questions and Cases

Ongoing Phase III Studies of Neoadjuvant Chemo-Immunotherapy in NSCLC

Study Identifier (N)	Eligibility	Randomization	Estimated Primary Completion
KEYNOTE-671 (N = 786)	Stage II-IIIB	• Pembro + Platinum doublet or pemetrexed → *S* → Pembro • Placebo + Platinum doublet or pemetrexed → *S* → Placebo	Jan 2024
CheckMate 816 (N = 350)	Stage IB-IIIA	• Platinum doublet → *S* • Platinum doublet + Nivolumab → *S* • Nivolumab + Ipilimumab → *S*	May 2023
IMpower030 (N = 450)	Stage II-IIIA, Select IIIB	• Atezo + Platinum-based chemo → *S* → Atezo • Platinum-based chemo → *S* → BSC	Nov 2024
NCT04025879 (N = 452)	Stage IIA-IIIB	• Platinum doublet + Nivolumab → *S* → Nivolumab • Platinum doublet + Placebo → *S* → Nivolumab	May 2023

S, surgery

Clinicaltrials.gov, Accessed August 5, 2020

Current Questions and Controversies in the Management of Lung Cancer

A Meet The Professor Series

Thursday, August 6, 2020
12:00 PM – 1:00 PM ET

Faculty

John V Heymach, MD, PhD

Moderator

Neil Love, MD

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