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Consensus or Controversy?
Clinical Investigators Provide Perspectives on the Current and Future Application of Immune Checkpoint Inhibition in the Management of Metastatic Lung Cancer

Thursday, November 8, 2018
7:00 PM – 8:30 PM
Washington, DC

Moderator

Neil Love, MD

Faculty

Edward B Garon, MD, MS
Giuseppe Giaccone, MD, PhD
Roy S Herbst, MD, PhD
Vali A Papadimitrakopoulou, MD

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Disclosures for Moderator Neil Love, MD

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, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Ariad Pharmaceuticals Inc, Array BioPharma Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech, Genomic Health Inc, Gilead Sciences Inc, Guardant Health, Halozyme Inc, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Kite Pharma Inc, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology, Medivation Inc, a Pfizer Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, 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, Taiho Oncology Inc, Takeda Oncology, Tesaro Inc, Teva Oncology and Tokai Pharmaceuticals Inc.

Faculty Disclosures

Edward B Garon, MD, MS
Contracted Research: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Dynavax, Genentech, Iovance Biotherapeutics, Lilly, Merck, Mirati Therapeutics, Novartis.

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No relevant conflicts of interest to disclose.

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Agenda: Immune Checkpoint Inhibitors in Lung Cancer

Module 1: *Small Cell Lung Cancer*

Module 2: *Nonsquamous Non-Small Cell Lung Cancer (NSCLC)*

Module 3: *Patients with Targetable Tumor Mutations*

Module 4: *Combined PD-1/PD-L1 and CTLA-4 Inhibitors in NSCLC*

Module 5: *Squamous NSCLC*

Module 6: *Immune-Related Adverse Events and Other Clinical Issues*

Module 7: *Patients with Paraneoplastic Syndrome or Autoimmune Disorders*

In preparation for this meeting, we conducted a survey of 8 lung cancer clinical investigators:

 EDWARD B GARON, MD, MS	University of California, Los Angeles
 GIUSEPPE GIACCONE, MD, PHD	Georgetown University
 ROY S HERBST, MD, PHD	Yale Comprehensive Cancer Center
 VALI A PAPADIMITRAKOPOULOU, MD	MD Anderson Cancer Center
 JAMIE CHAFT, MD	Memorial Sloan Kettering Cancer Center
 LEORA HORN, MD, MSC	Vanderbilt University Medical Center
 SURESH S RAMALINGAM, MD	Emory University School of Medicine
 HEATHER WAKELEE, MD	Stanford Cancer Institute

Agenda: Immune Checkpoint Inhibitors in Lung Cancer

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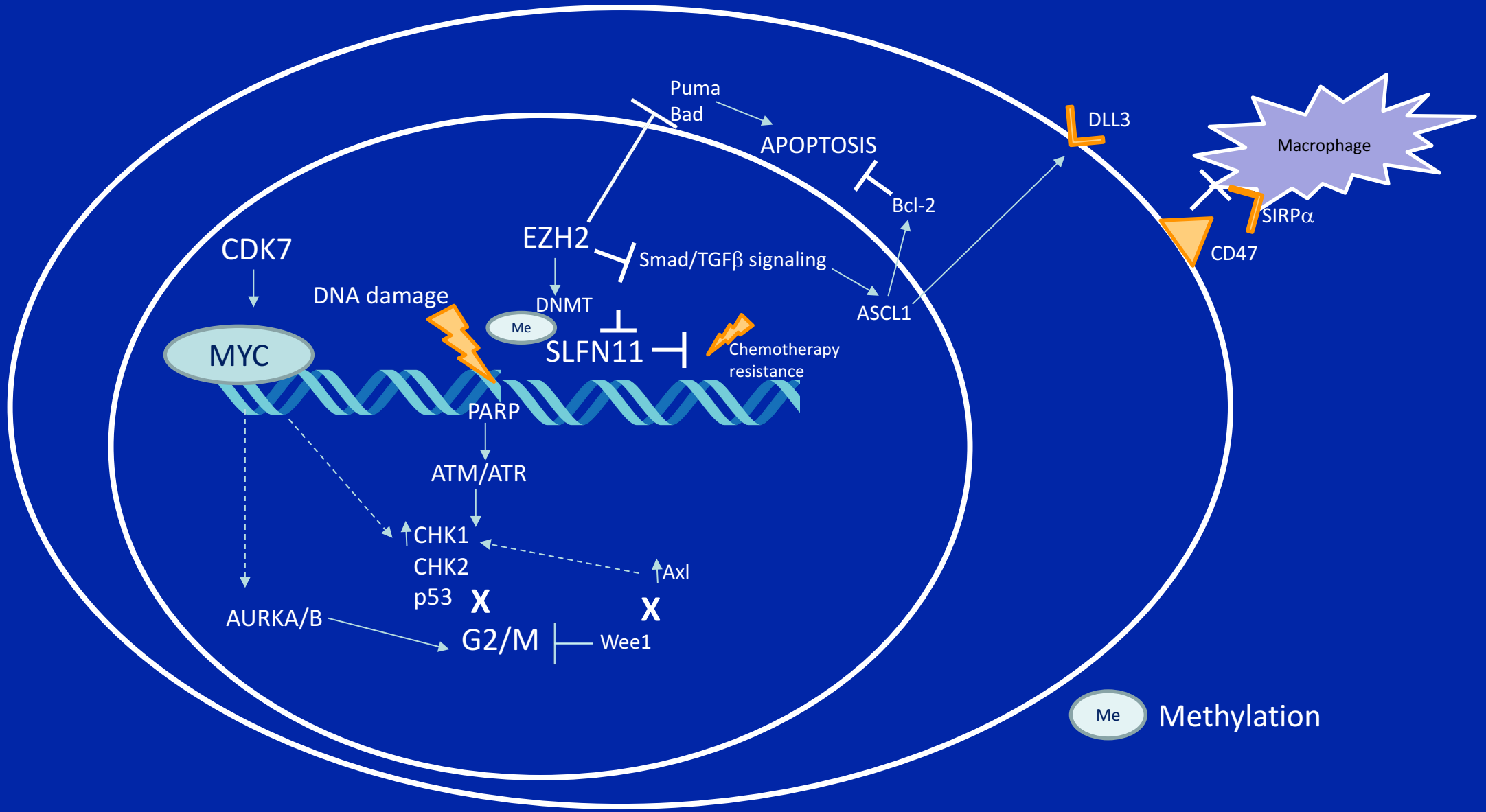
Select Trials of Immune Checkpoint Inhibitor Therapy in SCLC

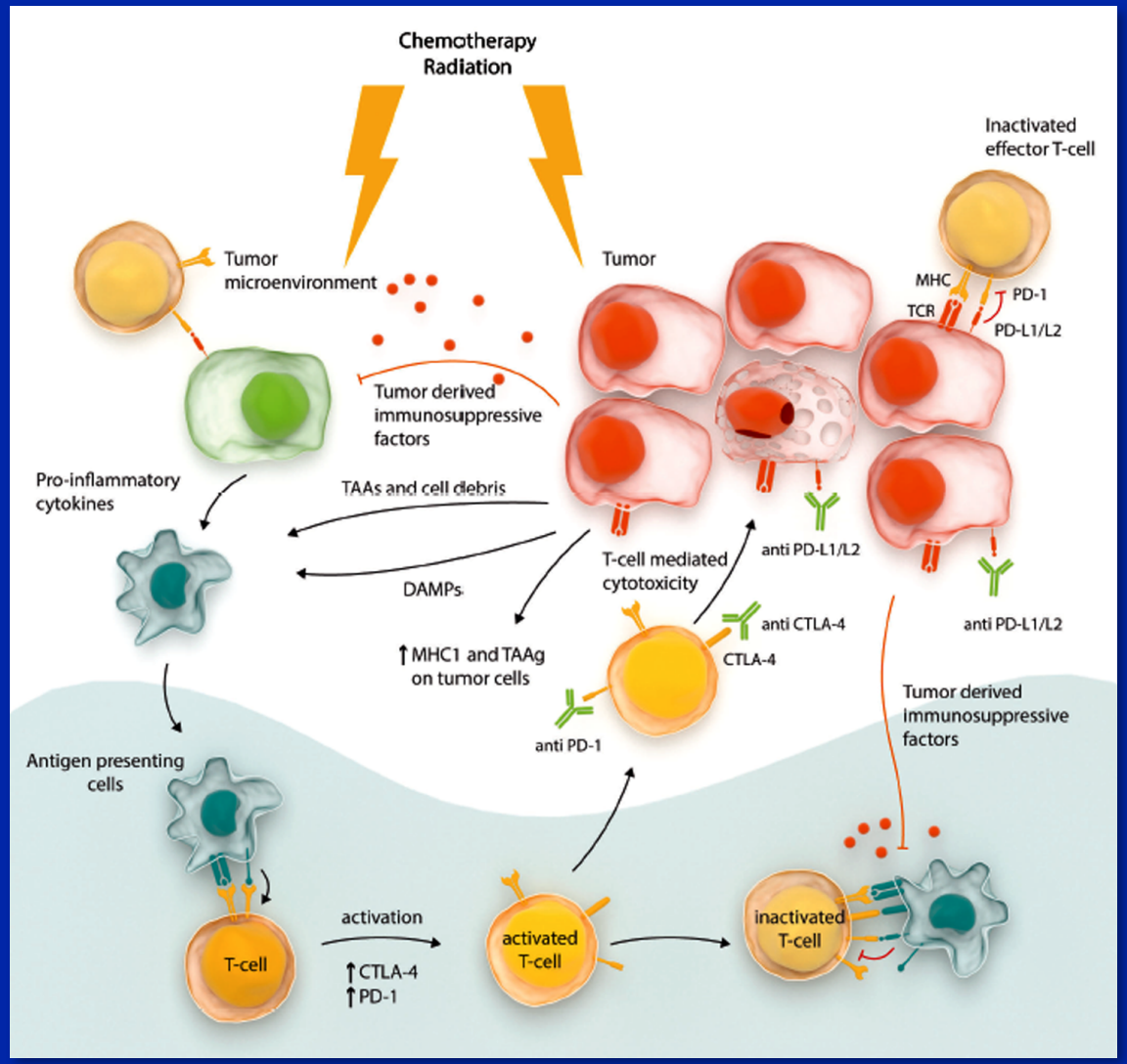
Name	Setting	Randomization	Findings
IMpower133	1L	• Carboplatin/etoposide + atezolizumab • Carboplatin/etoposide + placebo	• OS (HR 0.70, *p* = 0.007) • PFS (HR 0.77, *p* = 0.02)
CheckMate 032	2L+	• Nivolumab (NIVO) • Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (NIVO1/IPI3) • Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (NIVO3/IPI1)	• ORR (10%) • ORR (23%) • ORR (19%)
KEYNOTE-158	2L+	• Pembrolizumab	• ORR (18.7%)
IFTC-1603	2L	• Atezolizumab • Chemotherapy	• ORR (2.3%) • ORR (10%)
CheckMate 331	2L+	• Nivolumab • Chemotherapy	• Did not meet primary endpoint

Critical Pathways in SCLC



Courtesy of Leena Ghandi, MD, PhD - 2018

Rationale for Potential Synergy between Immune Checkpoint Inhibitors and Chemotherapy



- Chemotherapy directly induces pro-inflammatory effects in the tumor microenvironment
- Immune checkpoint inhibitors facilitate T-cell activation and T-cell-mediated antitumor cytotoxicity, overcoming inhibitory effects caused by tumor-derived immunosuppressive factors

Hude I et al. *Haematologica* 2017;102(1):30-42.

NCCN Guidelines Version 1.2019
Small Cell Lung Cancer

PRINCIPLES OF SYSTEMIC THERAPY*

Systemic therapy as primary or adjuvant therapy:

- Limited stage (maximum of 4–6 cycles):
  - Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[1]
  - Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[1]
  - Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[2]
  - Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[3]
  - During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).
  - The use of myeloid growth factors is not recommended during concurrent systemic therapy plus radiotherapy (category 1 for not using GM-CSF).[4]

- Extensive stage (maximum of 4–6 cycles):
  - Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,200 mg (category 1, preferred)[§,5]
  - Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[†,6]
  - Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[†,7]
  - Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[†,8]
  - Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[†,9]
  - Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[†,10]
  - Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[†,11]
  - Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[†,12]

Subsequent systemic therapy:[‡]

- Clinical trial preferred.

- Relapse ≤6 mo, PS 0-2:
  - Topotecan PO or IV[13-15]
  - Irinotecan[16]
  - Paclitaxel[17,18]
  - Docetaxel[19]
  - Temozolomide[20,21]
  - Nivolumab ± ipilimumab[22,23]
  - Pembrolizumab[24]
  - Vinorelbine[25,26]
  - Oral etoposide[27,28]
  - Gemcitabine[29,30]
  - Cyclophosphamide/doxorubicin/vincristine (CAV)[12]
  - Bendamustine (category 2B)[31]

- Relapse >6 mo: original regimen[32,33]

Consider dose reduction or growth factor support for patients with PS 2

UpToDate: Initial Management of Extensive-Stage Small Cell Lung Cancer

Practice Changing UpDate

ONCOLOGY (September 2018)

Immunotherapy for extensive-stage SCLC

- For patients with extensive-stage small cell lung cancer, we recommend the addition of atezolizumab to platinum-based chemotherapy (**Grade 1B**).

Immunotherapy has transformed frontline treatment for non-small cell lung cancer, but its role in small cell lung cancer (SCLC) has been unclear. In a randomized trial of 403 patients with treatment-naïve, extensive-stage SCLC, the addition of the anti-programmed death-ligand 1 (PD-L1) antibody atezolizumab versus placebo to carboplatin and etoposide improved median overall survival (12.3 versus 10.3 months), as well as progression-free survival (5.2 versus 4.3 months) [1]. Rates of toxicity were similar between the two groups. Based on these data, we now recommend the addition atezolizumab to platinum-based chemotherapy for the frontline treatment of extensive-stage SCLC. (See "Extensive-stage small cell lung cancer: Initial management", section on 'Carboplatin plus etoposide, with or without atezolizumab'.)

Kelly K. *UpToDate* 2018.

Regulatory and reimbursement issues aside, what would be your preferred first-line treatment regimen for a patient with extensive-stage small cell lung cancer (SCLC) who is…

	Age 65	Age 80
 EDWARD B GARON, MD, MS	Carboplatin/etoposide + atezolizumab	Carboplatin/etoposide + atezolizumab
 GIUSEPPE GIACCONE, MD, PHD	Carboplatin/etoposide + atezolizumab	Carboplatin/etoposide + atezolizumab
 ROY S HERBST, MD, PHD	Carboplatin/etoposide + atezolizumab	Carboplatin/etoposide + atezolizumab
 VALI A PAPADIMITRAKOPOULOU, MD	Carboplatin/etoposide + atezolizumab	Carboplatin/etoposide + atezolizumab
 JAMIE CHAFT, MD	Carboplatin/etoposide + atezolizumab	Carboplatin/etoposide + atezolizumab
 LEORA HORN, MD, MSC	Carboplatin/etoposide + atezolizumab	Carboplatin/etoposide + atezolizumab
 SURESH S RAMALINGAM, MD	Carboplatin/etoposide + atezolizumab	Carboplatin/etoposide + atezolizumab
 HEATHER WAKELEE, MD	Carboplatin/etoposide + atezolizumab	Carboplatin/etoposide + atezolizumab

IMpower133: A Phase III Trial Evaluating Atezolizumab with Carboplatin and Etoposide in Extensive-Stage SCLC

Eligibility (N = 201)

- Extensive-stage small cell lung cancer
- No prior systemic treatment
- ECOG performance status of 0 or 1
- No active or untreated CNS metastases
- No history of autoimmune disease

R

1:1

Carboplatin + etoposide + atezolizumab for four 21-day cycles → **Maintenance atezolizumab**

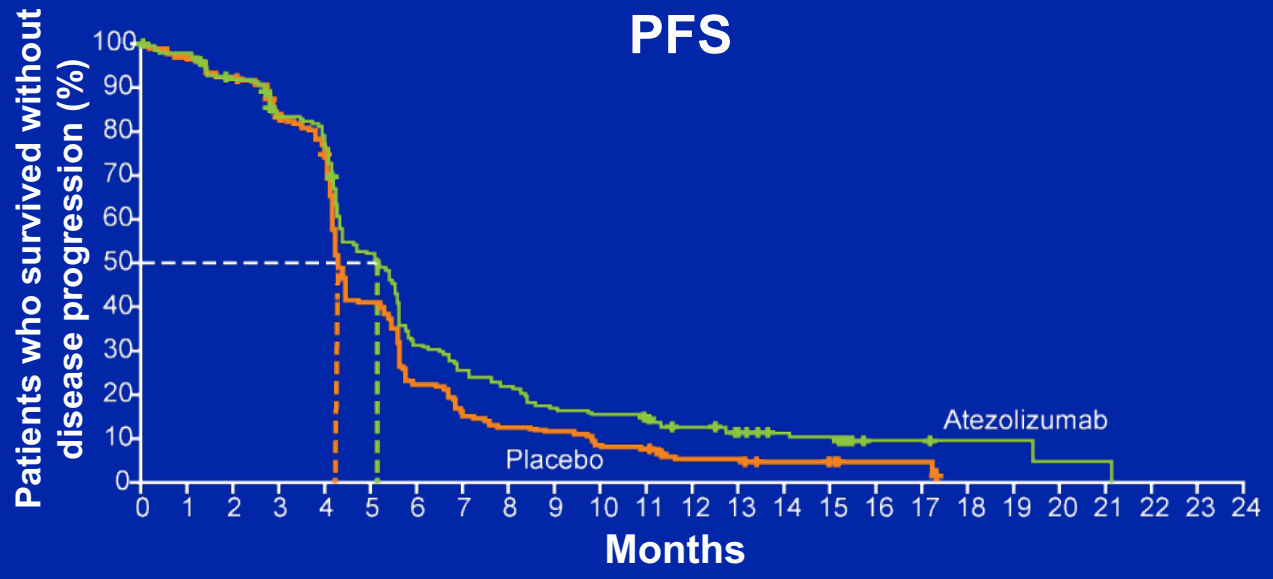
Carboplatin + etoposide + placebo for four 21-day cycles → **Maintenance placebo**

Primary endpoints: Duration of progression-free survival by the investigator using RECIST v1.1 and overall survival

Horn L et al. *N Engl J Med* 2018;[Epub ahead of print].

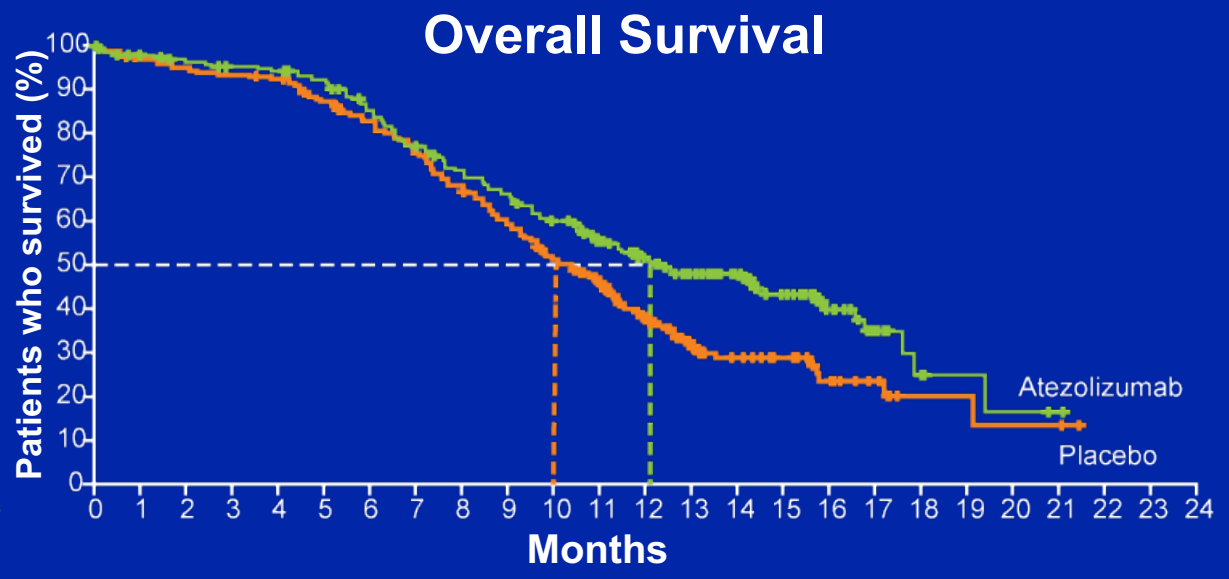
IMpower133: Survival Outcomes with First-Line Atezolizumab and Chemotherapy for Extensive-Stage Small Cell Lung Cancer

PFS



	Median PFS	12-mo PFS	HR	*p*-value
Atezolizumab	5.2 mo	12.6%	0.77	0.02
Placebo	4.3 mo	5.4%		

Overall Survival



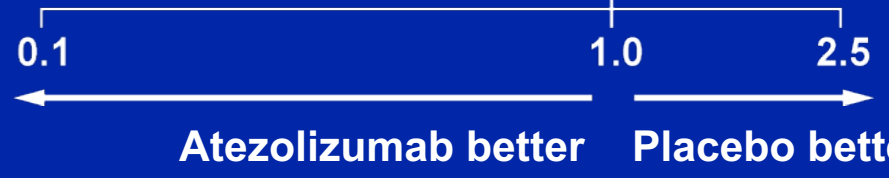
	Median OS	12-mo OS	HR	*p*-value
Atezolizumab	12.3 mo	51.7%	0.70	0.007
Placebo	10.3 mo	38.2%		

- The safety profile of atezolizumab with carboplatin and etoposide was consistent with the previously reported safety profile of the individual agents; no new findings were observed.

Horn L et al. *N Engl J Med* 2018;[Epub ahead of print].

IMpower133: OS According to Baseline Characteristics

Subgroup	No. of patients (%)	Median overall survival (mo)		Hazard ratio for death
		Atezolizumab	Placebo	
Age				
<65 yr	217 (54)	12.1	11.5	0.92
≥65 yr	186 (46)	12.5	9.6	0.53
Brain metastases				
Yes	35 (9)	8.5	9.7	1.07
No	368 (91)	12.6	10.4	0.68
Liver metastases				
Yes	149 (37)	9.3	7.8	0.81
No	254 (63)	16.8	11.2	0.64



Horn L et al. *N Engl J Med* 2018;[Epub ahead of print].

IMpower133: OS and PFS by Tumor Mutational Burden

Subgroup	No. of patients (%)	Median overall survival (mo)		Hazard ratio for death
		Atezolizumab	Placebo	
Tumor mutational burden				
<10 mutations/Mb	139 (34)	11.8	9.2	0.70
≥10 mutations/Mb	212 (53)	14.6	11.2	0.68
<16 mutations/Mb	271 (67)	12.5	9.9	0.71
≥16 mutations/Mb	80 (20)	17.8	11.9	0.63
Intention-to-treat population	403 (100)	12.3	10.3	0.70

Subgroup	No. of patients (%)	Median progression-free survival (mo)		Hazard ratio
		Atezolizumab	Placebo	
Tumor mutational burden				
<10 mutations/Mb	139 (34)	4.3	4.2	0.78
≥10 mutations/Mb	212 (53)	5.5	4.4	0.69
<16 mutations/Mb	271 (67)	5.2	4.3	0.73
≥16 mutations/Mb	80 (20)	5.6	4.3	0.68
Intention-to-treat population	403 (100)	5.2	4.3	0.77

Horn L et al. *N Engl J Med* 2018;[Epub ahead of print]:Appendix

IMpower133: Adverse Events Related to First-Line Atezolizumab and Chemotherapy for Extensive-Stage SCLC

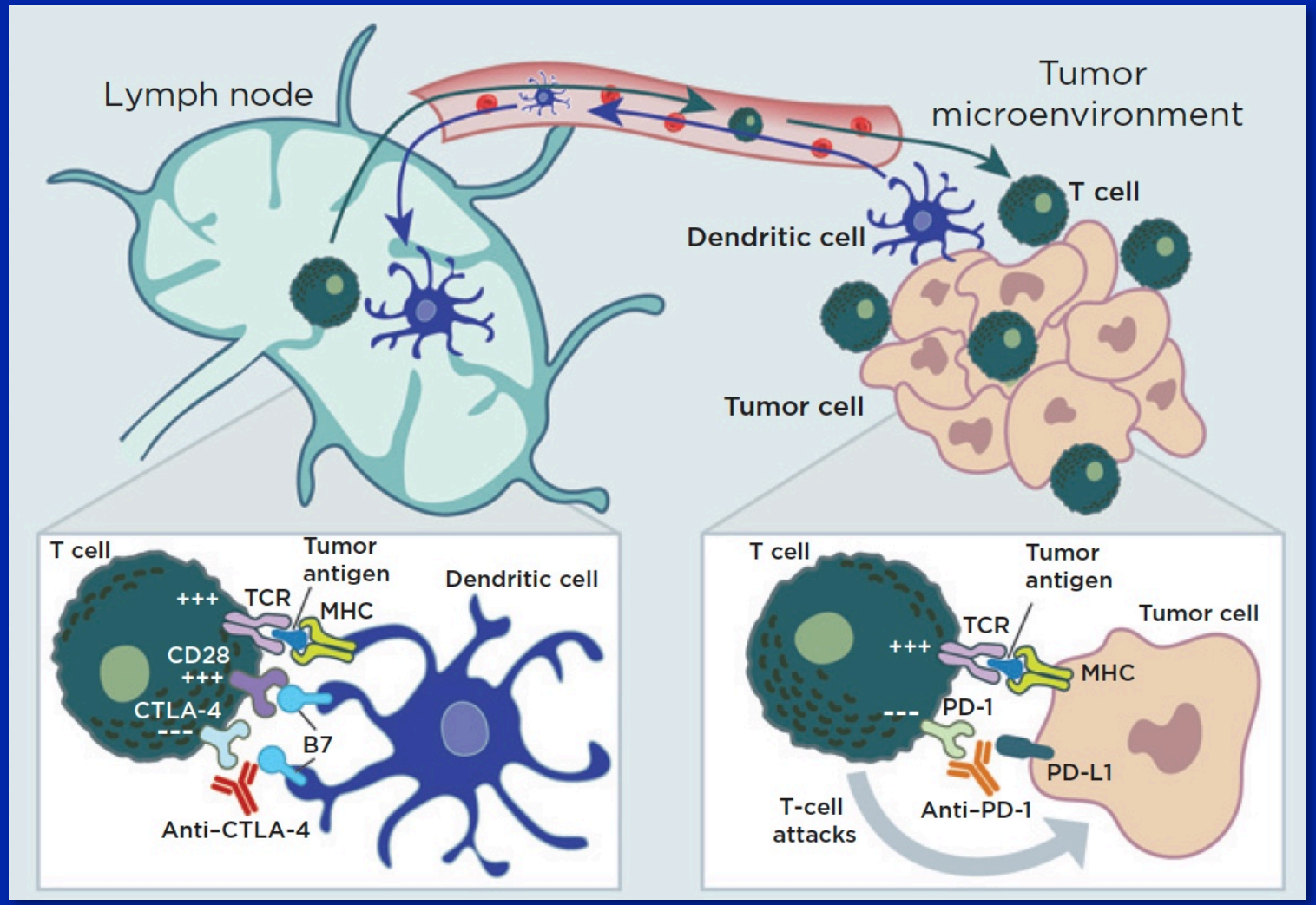
	Atezolizumab (N = 198)		Placebo (N = 196)	
	Grade 3 or 4	Grade 5	Grade 3 or 4	Grade 5
Any adverse event	57%	2%	56%	2%
Neutropenia	23%	1%	25%	0%
Anemia	14%	0%	12%	0%
Thrombocytopenia	10%	0%	8%	0%
Leukopenia	5%	0%	4%	0%
Diarrhea	2%	0%	1%	0%
Febrile neutropenia	3%	0%	6%	0%
Infusion-related reaction	2%	0%	1%	0%

Horn L et al. *N Engl J Med* 2018;[Epub ahead of print].

A patient with metastatic SCLC experiences a response to first-line carboplatin/etoposide but then experiences disease progression after 3 months. What would you recommend if the patient were…

	Age 65	Age 80
 EDWARD B GARON, MD, MS	Nivolumab	Nivolumab
 GIUSEPPE GIACCONE, MD, PHD	Topotecan	Nivolumab
 ROY S HERBST, MD, PHD	Nivolumab/ipilimumab	Nivolumab/ipilimumab
 VALI A PAPADIMITRAKOPOULOU, MD	Nivolumab/ipilimumab	Nivolumab
 JAMIE CHAFT, MD	Nivolumab/ipilimumab	Pembrolizumab
 LEORA HORN, MD, MSC	Nivolumab/ipilimumab	Nivolumab/ipilimumab
 SURESH S RAMALINGAM, MD	Topotecan	Topotecan
 HEATHER WAKELEE, MD	Nivolumab/ipilimumab	Nivolumab

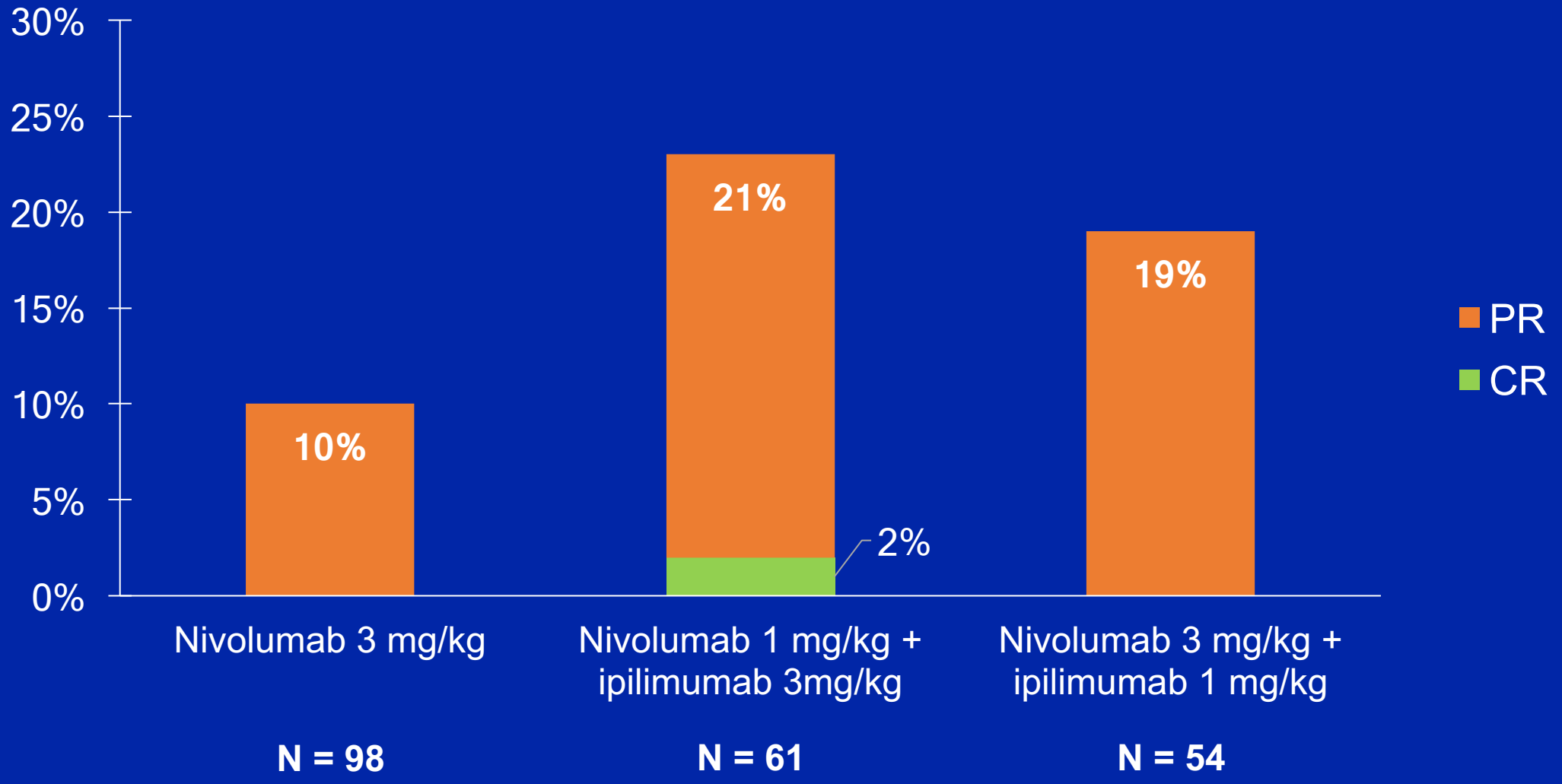
Biologic Rationale for Combining CTLA-4 and PD-1/PD-L1 Inhibitors



- The primary period of activity of anti-CTLA-4 antibodies is during the induction phase of antitumor T-cell immunity within lymphoid tissues.
- PD-1/PD-L1 inhibitors primarily act at the effector phase within the tumor microenvironment.
- The effects of CTLA-4 and PD-1/PD-L1 inhibitors may be additive or synergistic.

Carlino MS, Long GV. *Clin Cancer Res* 2016;22(16):3992-8.

CheckMate 032: Response Rates with Nivolumab Alone and Nivolumab with Ipilimumab in Recurrent SCLC



Antonia SJ et al. *Lancet Oncol* 2016;17(7):883-95.

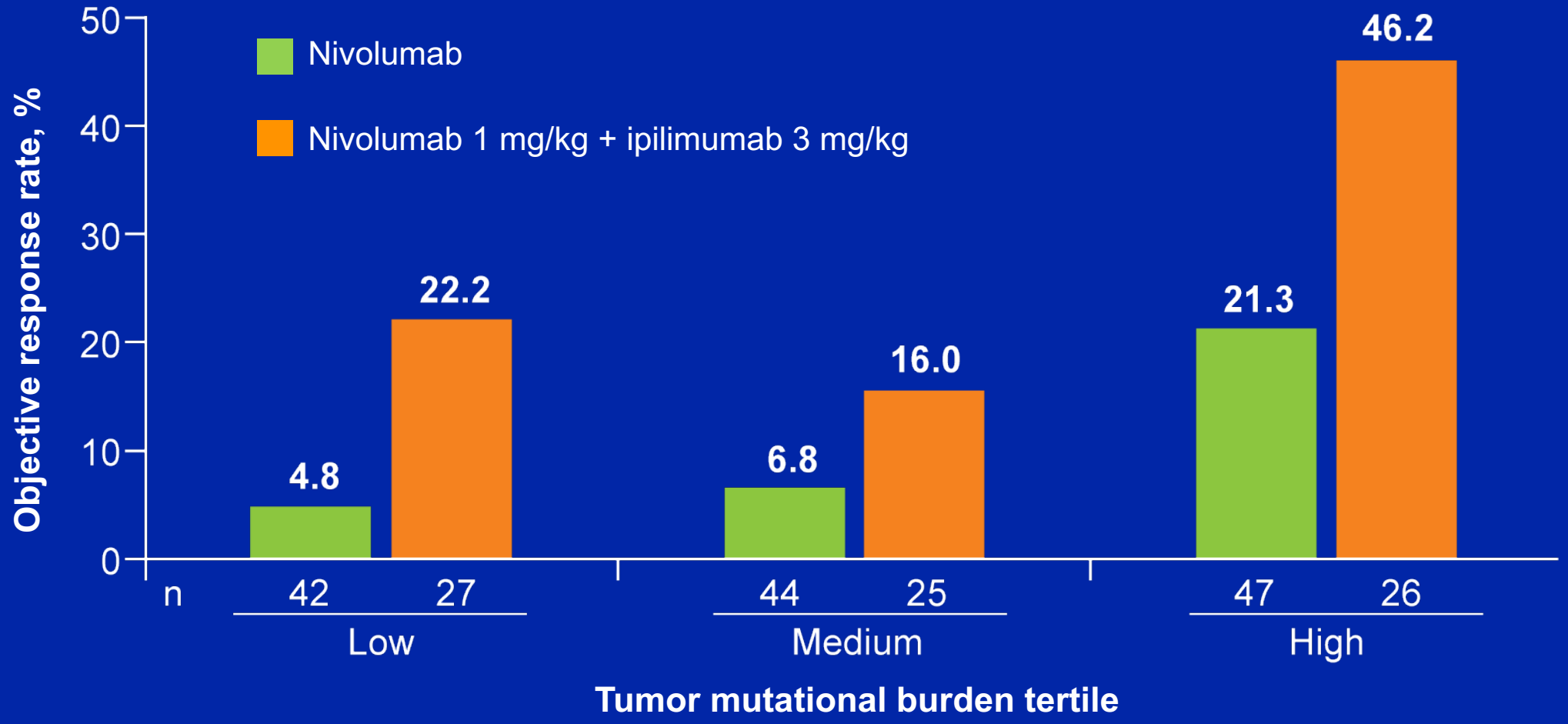
CheckMate 032: Safety Findings for Nivolumab Alone and Nivolumab with Ipilimumab in Recurrent SCLC

Grade 3 or 4	Nivolumab 3 mg/kg	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg
Treatment-related AEs	13%	30%	19%
Pneumonitis	1%	2%	2%
Diarrhea	0%	5%	2%
Increased lipase	0%	9%	0%
Cardiomyopathy	0%	2%	0%
Renal failure	0%	2%	0%

- Two patients who received nivolumab 1 mg/kg and ipilimumab 3 mg/kg died from treatment-related adverse events (myasthenia gravis and worsening of renal failure), and one patient who received nivolumab 3 mg/kg and ipilimumab 1 mg/kg died from treatment-related pneumonitis.

Antonia SJ et al. *Lancet Oncol* 2016;17(7):883-95.

CheckMate 032: Tumor Mutational Burden (TMB) and Efficacy of Nivolumab Alone and in Combination with Ipilimumab



Hellmann MD et al. *Cancer Cell* 2018;33(5):853-61.

FDA Grants Nivolumab Accelerated Approval for Third-Line Treatment of Metastatic Small Cell Lung Cancer

Press Release – August 16, 2018

"On August 16, 2018, the Food and Drug Administration granted accelerated approval to nivolumab for patients with metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy.

Approval was based on demonstration of a durable overall response rate (ORR) in a subgroup of patients from CheckMate-032 (NCT01928394), a multicenter, open-label trial in patients with metastatic solid tumors. This subgroup comprised 109 patients with metastatic SCLC, with disease progression after platinum-based therapy and at least one other prior line of therapy, regardless of tumor PD-L1 status.

The recommended dose and schedule of nivolumab for this indication is 240 mg every 2 weeks over 30 minutes."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm617370.htm

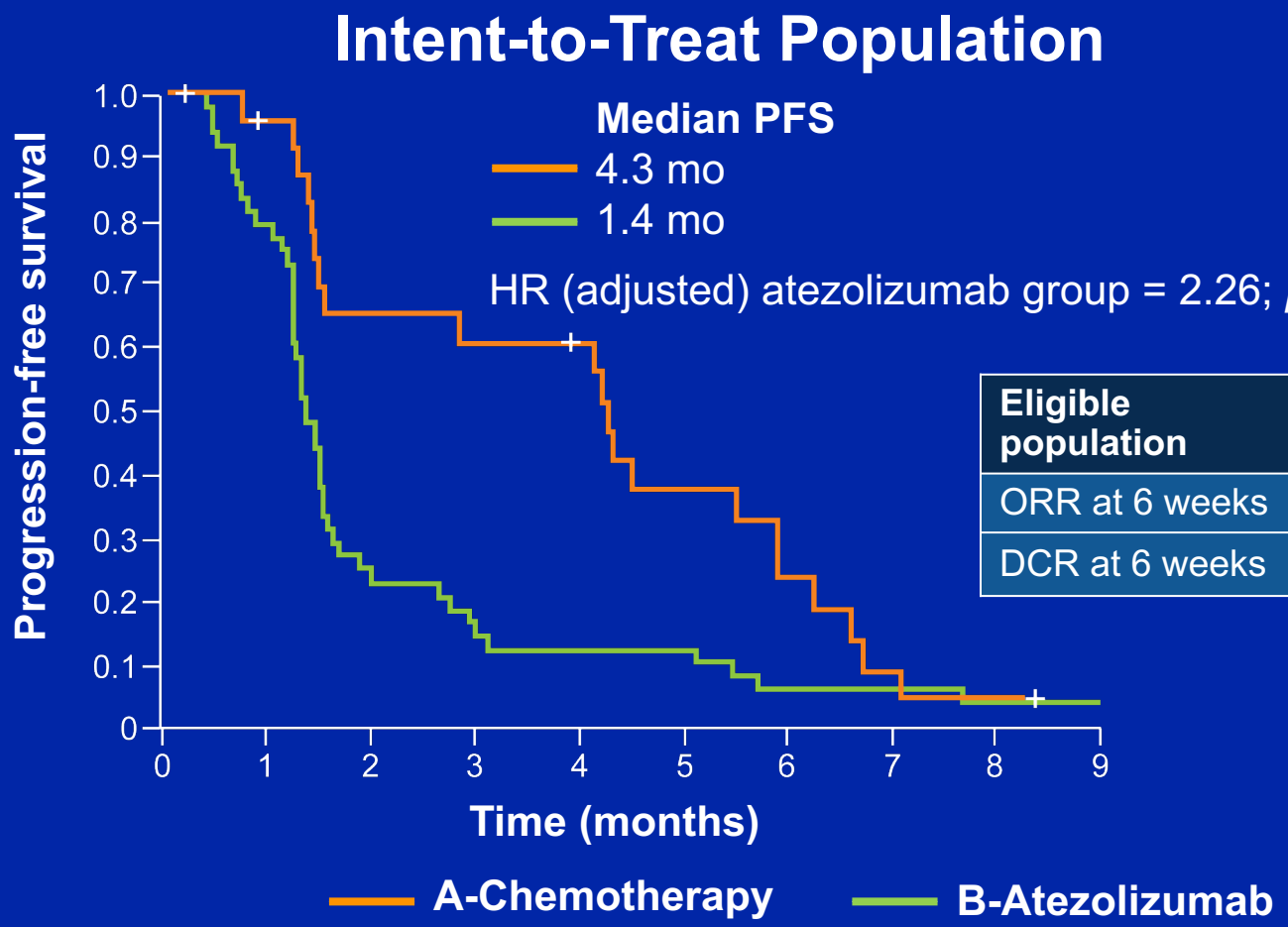
KEYNOTE-158: A Phase II Study of Pembrolizumab in Advanced SCLC After Failure of, Progression on or Intolerance to Standard Therapy

First Response and Duration of Response

	Overall (N = 107)	PD-L1 positive (n = 42)	PD-L1 negative (n = 50)
ORR	19%	36%	6%
Best overall response			
Complete response	3%	5%	2%
Partial response	16%	31%	4%
Disease control	30%	43%	20%

Chung HC et al. *Proc ASCO* 2018;Abstract 8506.

IFCT-1603: Response Rate and PFS in the Phase II Study of Second-Line Atezolizumab or Chemotherapy for SCLC



Eligible population	Chemotherapy (n = 20)	Atezolizumab (n = 43)	Total (n = 64)
ORR at 6 weeks	10%	2.3%	4.8%
DCR at 6 weeks	65%	20.9%	34.9%

- IFCT-1603 trial did not show any efficacy or safety signals for single drug atezolizumab used as treatment in relapsed SCLC.

Pujol J et al. *Proc ESMO* 2018;Abstract 1664O.

CheckMate 331 Study Does Not Meet Primary Endpoint of Overall Survival with Nivolumab in Relapsed SCLC

Press Release – October 12, 2018

The Phase III CheckMate 331 study evaluating nivolumab versus the current standard of care, topotecan or amrubicin (where approved), in patients with SCLC who experienced relapse after platinum-based chemotherapy did not meet its primary endpoint of overall survival.

The safety profile of nivolumab in this trial was consistent with that observed in previously reported monotherapy studies involving patients with SCLC.

https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-announces-phase-3-checkmate-331-study-doe

Select Ongoing Phase III Trials of Immune Checkpoint Inhibitor Therapy in SCLC

Clinical trial	Setting	Patients enrolled	Randomization	Primary estimated completion
CASPIAN (NCT03043872)	1L; Extensive stage	984	• Carboplatin or cisplatin + etoposide (EP) • Durvalumab + tremelimumab + EP • Durvalumab + EP	March 2019
KEYNOTE-604 (NCT03066778)	1L; Extensive stage	453	• Placebo + etoposide/platinum • Pembrolizumab + etoposide/platinum	January 2019
CheckMate 451 (NCT02538666)	Maintenance; Extensive stage	1,327	• Placebo • Nivolumab • Nivolumab and ipilimumab	October 2018

www.clinicaltrials.gov; Accessed November 2018.

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Brahmer *et al. Journal for ImmunoTherapy of Cancer* (2018) 6:75
https://doi.org/10.1186/s40425-018-0382-2

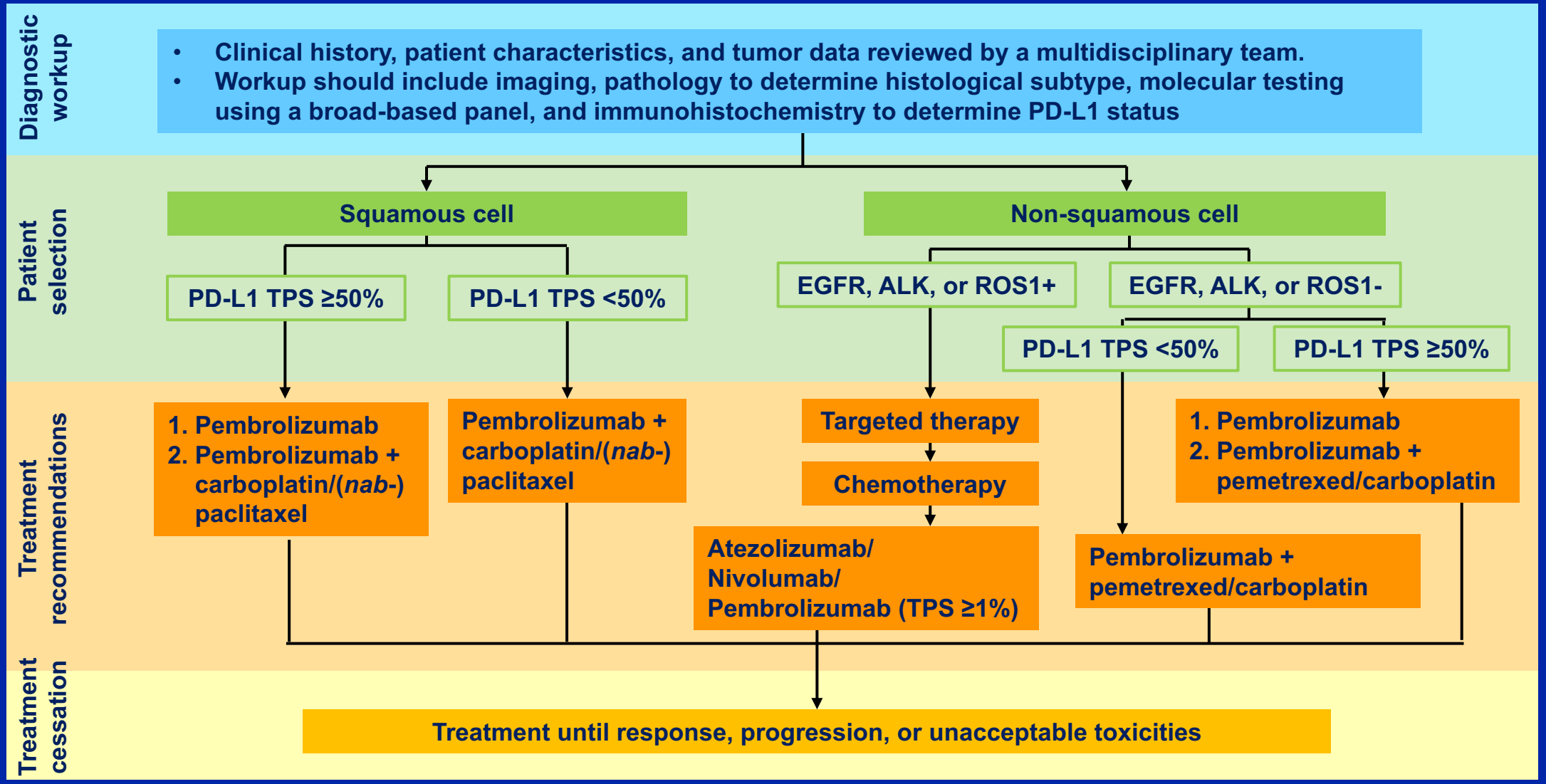
Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES **Open Access**

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC)

Julie R. Brahmer[1], Ramaswamy Govindan[2], Robert A. Anders[3], Scott J. Antonia[4], Sarah Sagorsky[5], Marianne J. Davies[6], Steven M. Dubinett[7], Andrea Ferris[8], Leena Gandhi[9], Edward B. Garon[10], Matthew D. Hellmann[11], Fred R. Hirsch[12], Shakuntala Malik[13], Joel W. Neal[14], Vassiliki A. Papadimitrakopoulou[15], David L. Rimm[16], Lawrence H. Schwartz[17], Boris Sepesi[18], Beow Yong Yeap[19], Naiyer A. Rizvi[20] and Roy S. Herbst[21*]

SITC Consensus Statement: Advanced or Metastatic NSCLC Treatment Algorithm



Brahmer JR et al. *J Immunother Cancer* 2018;6(1):75.

Select Trials of Immune Checkpoint Inhibitor Therapy in Nonsquamous NSCLC

Name	Setting	Eligibility criteria	Randomization	Findings
KEYNOTE-042	1L	PD-L1 TPS ≥1%	• Pembrolizumab • Platinum-based chemo	• TPS ≥50% OS (HR 0.69) • TPS ≥20% OS (HR 0.77) • TPS ≥1% OS (HR 0.81)
KEYNOTE-189	1L	—	• Pembrolizumab + pemetrexed/platinum • Placebo + pemetrexed/platinum	• OS (HR 0.49, p < 0.001) • PFS (HR 0.52, p < 0.001)
IMpower132	1L	—	• Atezolizumab + pemetrexed + carboplatin or cisplatin • Placebo + pemetrexed + carboplatin or cisplatin	• PFS (HR 0.60, *p* < 0.0001) • Interim OS (HR 0.81, *p* = 0.0797)
IMpower130	1L	—	• Atezolizumab + *nab* paclitaxel + carboplatin • Placebo + *nab* paclitaxel + carboplatin	• PFS (HR 0.64, *p* < 0.0001) • OS (HR 0.79, *p* = 0.033)
IMpower150	1L	—	• Atezolizumab + carboplatin/paclitaxel (ACP) • Bevacizumab + carboplatin/paclitaxel (BCP) • Atezolizumab + BCP (ABCP)	WT (ABCP vs BCP) • PFS (HR 0.62, *p* < 0.001) Teff-high WT (ABCP vs BCP) • PFS (HR 0.51, *p* < 0.001)

Reimbursement and regulatory issues aside, which first-line treatment regimen would you recommend for a patient with metastatic nonsquamous lung cancer and no identified targetable mutations with a PD-L1 TPS of 10% who is…

	Age 65	Age 80
 EDWARD B GARON, MD, MS	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 GIUSEPPE GIACCONE, MD, PHD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 ROY S HERBST, MD, PHD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 VALI A PAPADIMITRAKOPOULOU, MD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 JAMIE CHAFT, MD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 LEORA HORN, MD, MSC	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 SURESH S RAMALINGAM, MD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 HEATHER WAKELEE, MD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab

Reimbursement and regulatory issues aside, which first-line treatment regimen would you recommend for a patient with metastatic nonsquamous lung cancer and no identified targetable mutations with a PD-L1 TPS of 60% who is…

	Age 65	Age 80
 EDWARD B GARON, MD, MS	Pembrolizumab	Pembrolizumab
 GIUSEPPE GIACCONE, MD, PHD	Pembrolizumab	Pembrolizumab
 ROY S HERBST, MD, PHD	Carbo/pem/pembro	Pembrolizumab
 VALI A PAPADIMITRAKOPOULOU, MD	Pembrolizumab	Pembrolizumab
 JAMIE CHAFT, MD	Pembrolizumab	Pembrolizumab
 LEORA HORN, MD, MSC	Pembrolizumab	Pembrolizumab
 SURESH S RAMALINGAM, MD	Pembrolizumab	Pembrolizumab
 HEATHER WAKELEE, MD	Pembrolizumab	Pembrolizumab

A patient presents with metastatic nonsquamous lung cancer with no identified targetable mutations and moderate respiratory distress secondary to extensive tumor in the lung. What would be your most likely treatment recommendation if the patient had a PD-L1 TPS of…

	60%	90%
 EDWARD B GARON, MD, MS	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 GIUSEPPE GIACCONE, MD, PHD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 ROY S HERBST, MD, PHD	Pembrolizumab	Pembrolizumab
 VALI A PAPADIMITRAKOPOULOU, MD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 JAMIE CHAFT, MD	Atezolizumab/carboplatin/paclitaxel ± bevacizumab	Pembrolizumab
 LEORA HORN, MD, MSC	Carboplatin/pemetrexed/pembrolizumab	Pembrolizumab
 SURESH S RAMALINGAM, MD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 HEATHER WAKELEE, MD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab

KEYNOTE-042: Phase III Results of First-Line Pembrolizumab in Advanced/Metastatic NSCLC (TPS ≥1%)

Primary analysis: Median OS in PD-L1 TPS ≥50%, ≥20% and ≥1%			
Patient subgroup	**Pembrolizumab**	**Chemotherapy***	**HR (*p*-value)**
TPS ≥50% (n = 299; 300)	20.0 mo	12.2 mo	0.69 (0.0003)
TPS ≥20% (n = 413; 405)	17.7 mo	13.0 mo	0.77 (0.0020)
TPS ≥1% (n = 637; 637)	16.7 mo	12.1 mo	0.81 (0.0018)
TPS ≥1%-49% (n = 338; 337)[a]	13.4 mo	12.1 mo	0.92 (NR)

* Carboplatin/paclitaxel or carboplatin/pemetrexed up to 6 cycles; [a] Exploratory analysis

- Duration of response was longer in patients who received pembrolizumab than in those who received chemotherapy, at all PD-L1 levels examined.
- At the time of this analysis, no significant PFS benefit was observed with pembrolizumab compared to chemotherapy.

Lopes G et al. *Proc ASCO* 2018;Abstract LBA4.

FDA Grants Regular Approval for Pembrolizumab in Combination with Chemotherapy for First-Line Treatment of Metastatic Nonsquamous NSCLC

Press Release – August 20, 2018

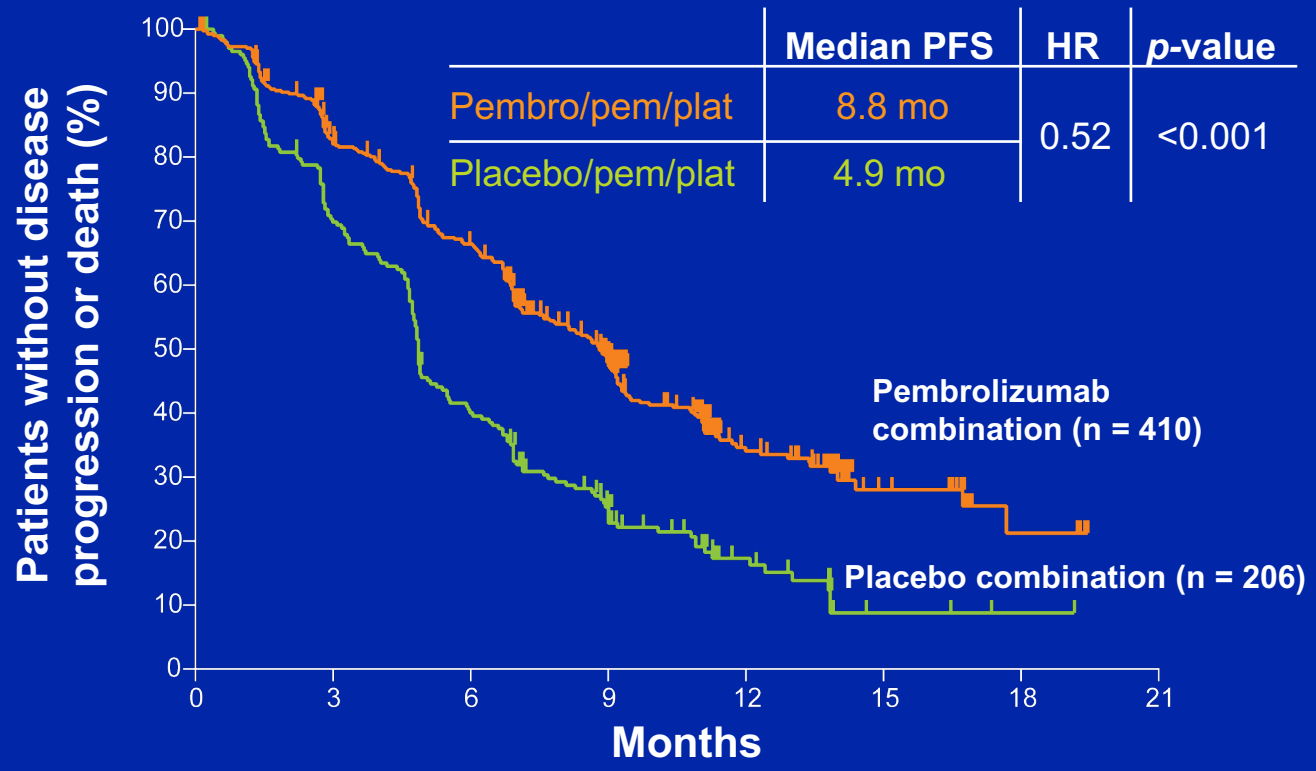
"On August 20, 2018, the Food and Drug Administration approved pembrolizumab in combination with pemetrexed and platinum as first-line treatment of patients with metastatic, non-squamous non-small cell lung cancer (NSqNSCLC), with no EGFR or ALK genomic tumor aberrations.

Today's approval represents fulfillment of a postmarketing commitment demonstrating the clinical benefit of this product. This action is based on the results of KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active controlled study enrolling 616 patients receiving first-line treatment for metastatic NSqNSCLC."

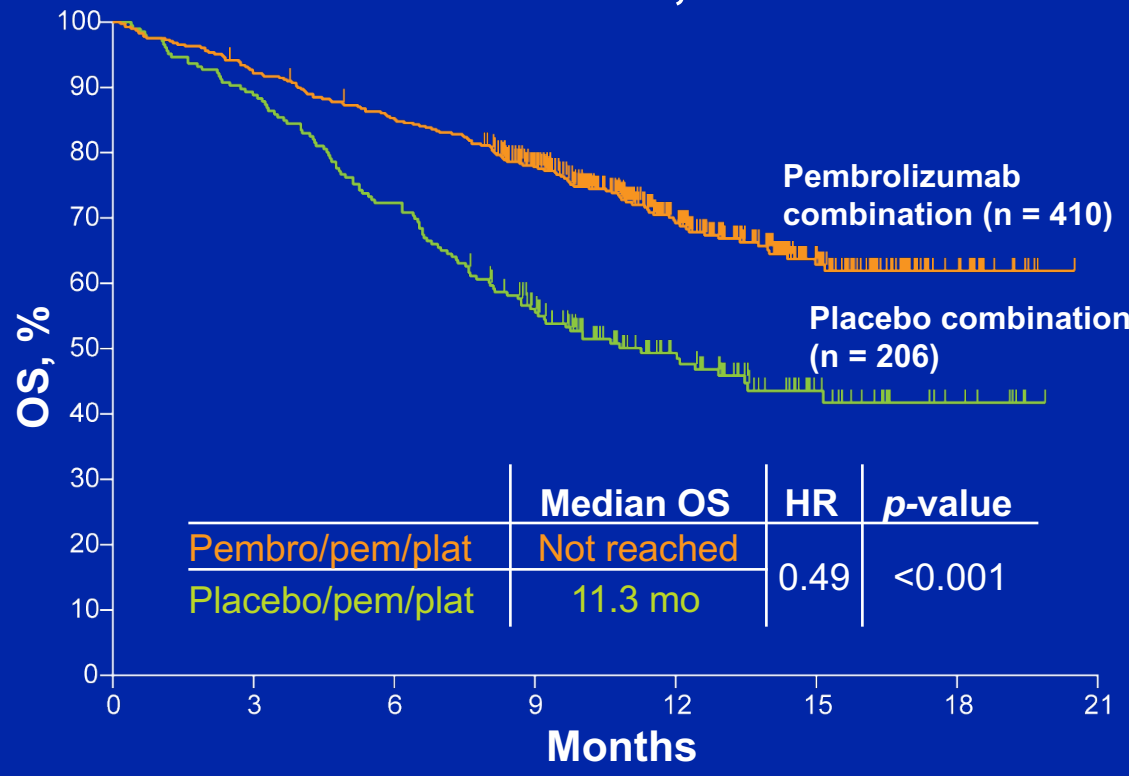
https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm617471.htm

KEYNOTE-189: PFS and OS Results (Primary Endpoint Analyses)

Progression-Free Survival, ITT



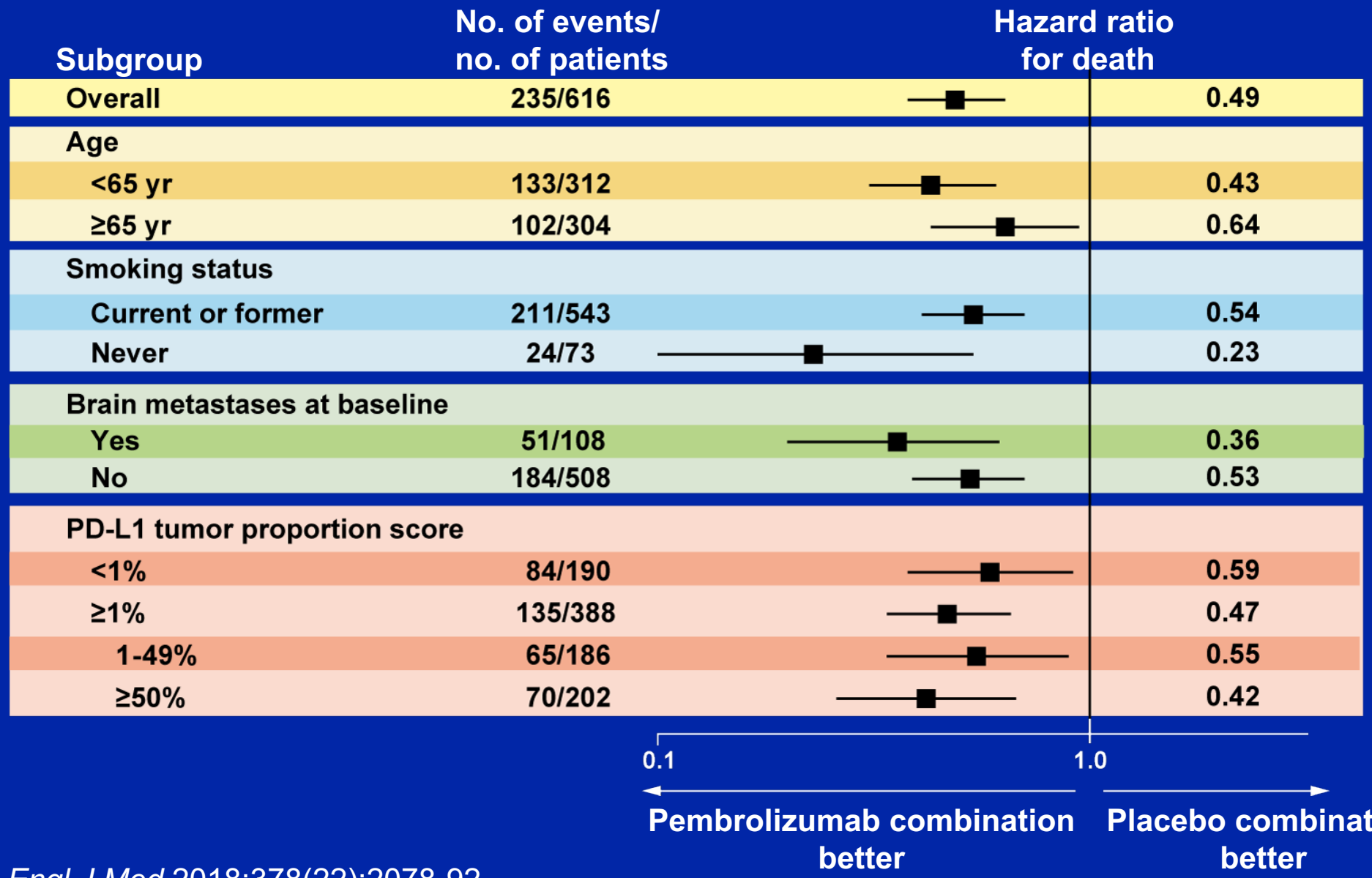
Overall Survival, ITT



- Response rate (pembro combination vs placebo combination): 47.6% versus 18.9% ($p < 0.001$)

Gandhi L et al. *N Engl J Med* 2018;378(22):2078-92.

KEYNOTE-189: OS According to Baseline Characteristics



Gandhi L et al. *N Engl J Med* 2018;378(22):2078-92.

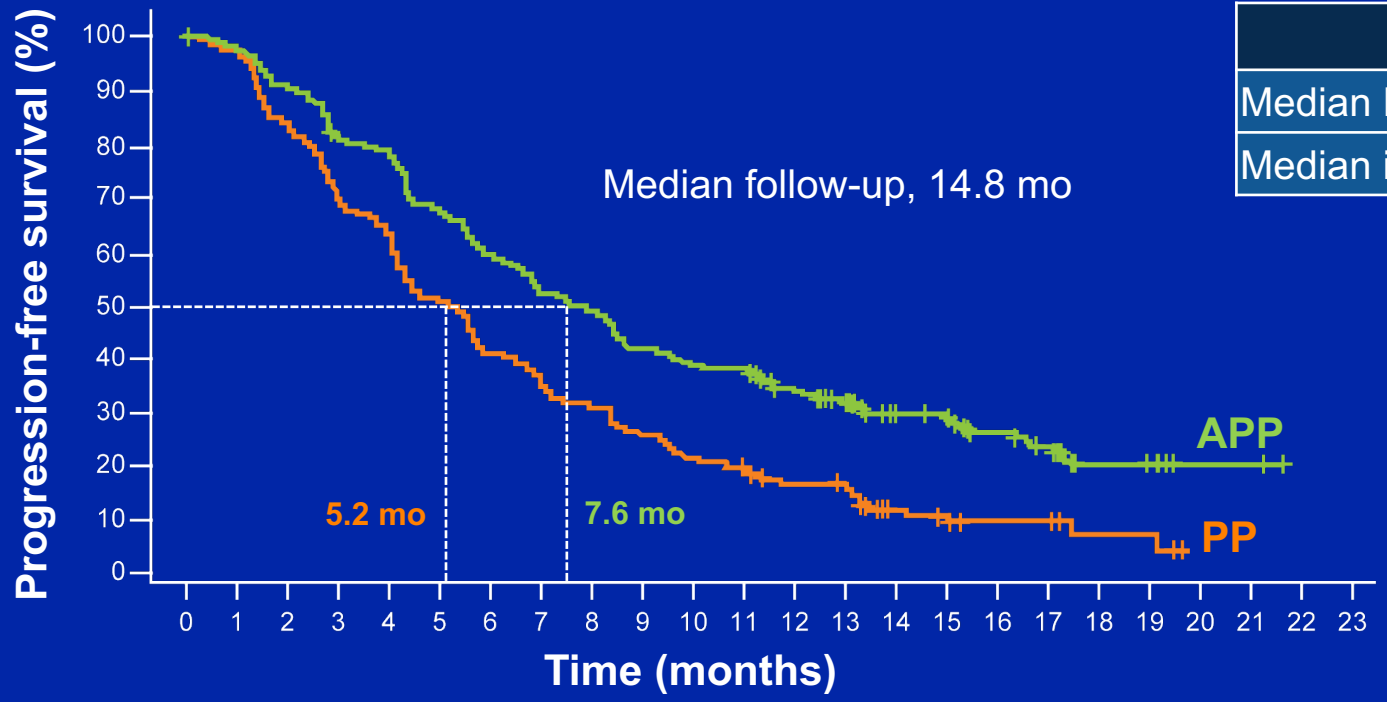
KEYNOTE-189: Adverse Events (AEs) for Pembrolizumab with Chemotherapy in mNSCLC

Grade 3-5 AEs	Pembrolizumab combination (N = 405)	Placebo combination (N = 202)
Any AE	67.2%	65.8%
Anemia	16.3%	15.3%
Neutropenia	15.8%	11.9%
Rash	1.7%	1.5%
Thrombocytopenia	7.9%	6.9%
Pneumonitis	2.7%	2.0%

- Safety profiles of the pembrolizumab combination did not increase the frequency of AEs commonly associated with the chemotherapy regimen alone.
- The incidence of most immune-mediated adverse events was not higher with pembrolizumab combination therapy than that previously observed with pembrolizumab monotherapy.

Gandhi L et al. *N Engl J Med* 2018;378(22):2078-92.

IMpower132: Efficacy and Safety Results of First-Line Atezolizumab and Platinum/Pemetrexed in Metastatic Nonsquamous NSCLC



	APP	PP	HR	*p*-value
Median PFS	7.6 mo	5.2 mo	0.596	<0.0001
Median interim OS	18.1 mo	13.6 mo	0.813	0.0797

	APP	PP
ORR	47%	32%
CR	2%	1%
PR	45%	32%
Median DoR, mo	10.1	7.2
Ongoing response, %	42%	30%

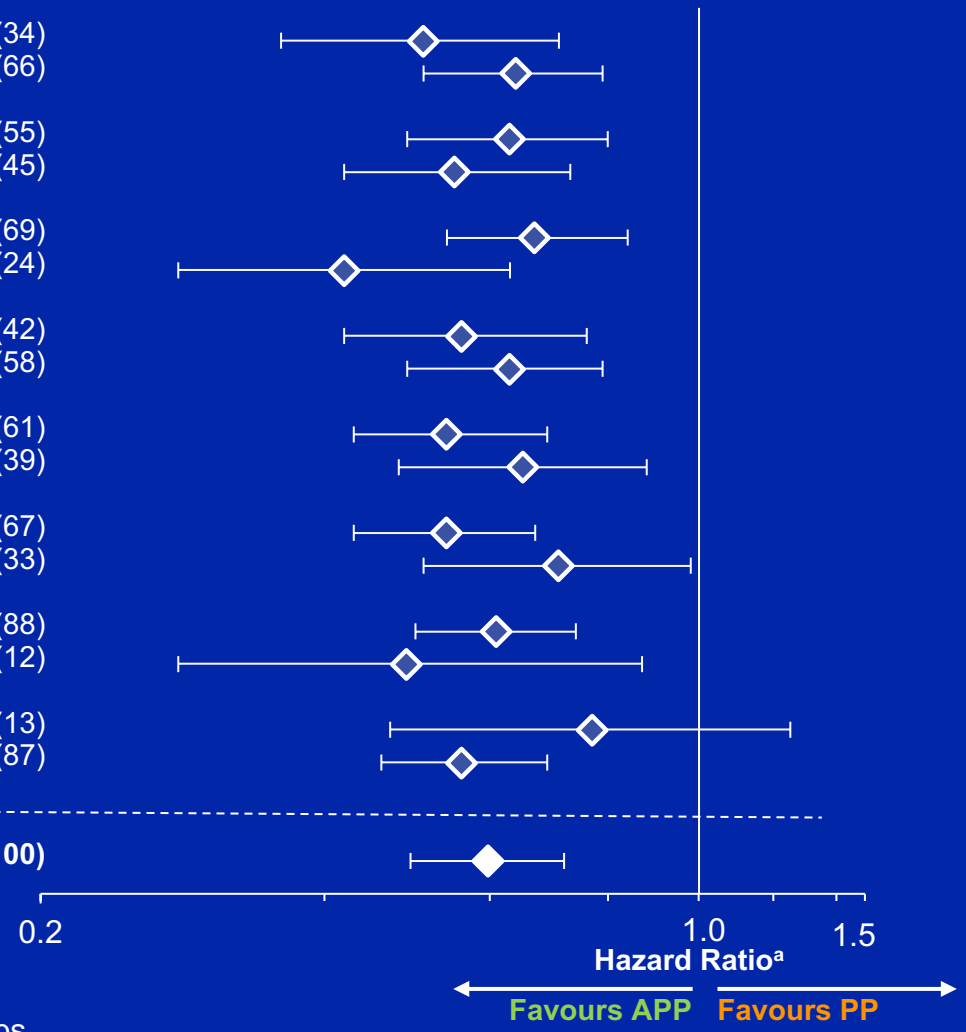
APP = atezolizumab + PP; PP = pemetrexed + cisplatin or carboplatin

- No new safety signals were identified with the APP combination; the safety profile is consistent with known safety risks of the individual therapies.

Papadimitrakopoulou VA et al. *Proc WCLC* 2018;Abstract OA05.07.

IMpower132: PFS in Key Patient Subgroups

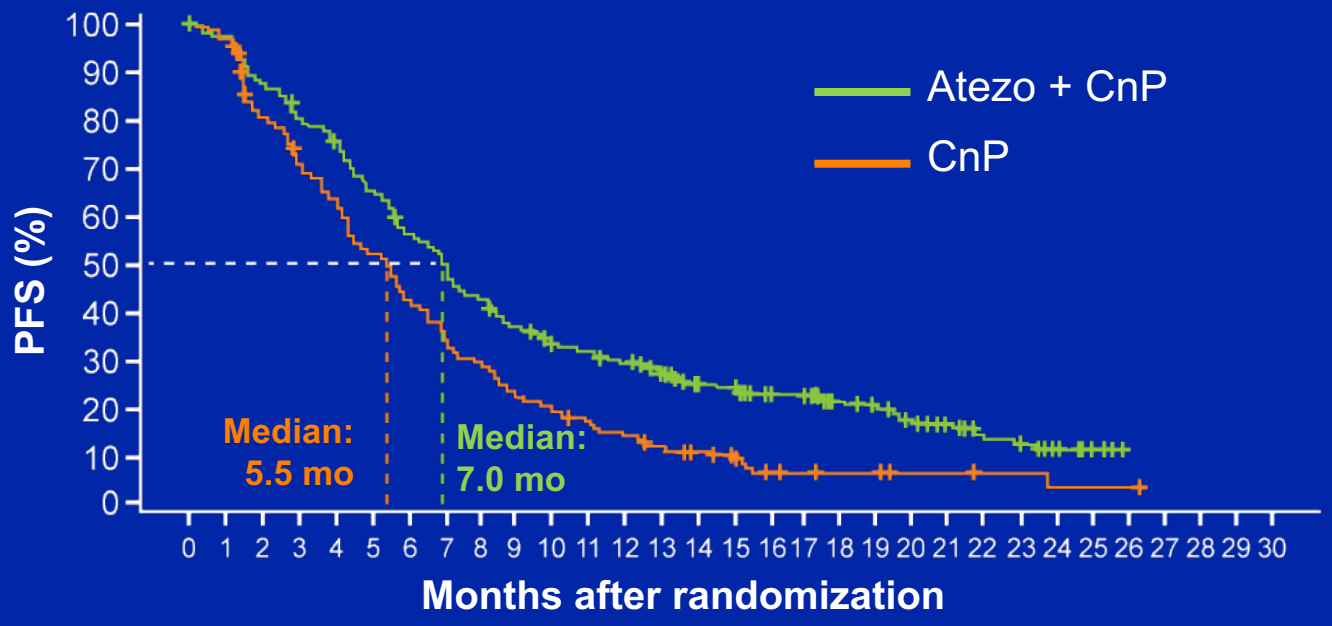
Subgroup	n (%)	HR (95% CI)[a]	Median PFS, mo	
			APP	PP
Female	194 (34)	0.51	8.3	5.3
Male	384 (66)	0.64	7.5	4.9
< 65 y	320 (55)	0.63	6.9	4.4
≥ 65 y	258 (45)	0.55	8.4	5.6
White[b]	396 (69)	0.67	6.9	4.9
Asian	136 (24)	0.42	10.2	5.3
ECOG PS 0[b]	240 (42)	0.56	8.6	5.8
ECOG PS 1	336 (58)	0.63	6.8	4.4
Received carboplatin	352 (61)	0.54	8.1	5.5
Received cisplatin	226 (39)	0.65	7.1	4.4
Intended 4 cycles	387 (67)	0.54	7.8	4.5
Intended 6 cycles	191 (33)	0.71	7.6	5.6
Current or former smoker	511 (88)	0.61	7.5	5.1
Never smoker	67 (12)	0.4	8.6	5.5
Liver metastases	73 (13)	0.77	4.4	4.0
No liver metastases	505 (87)	0.56	8.4	5.5
ITT population	**578 (100)**	**0. 60**	**7.6**	**5.2**

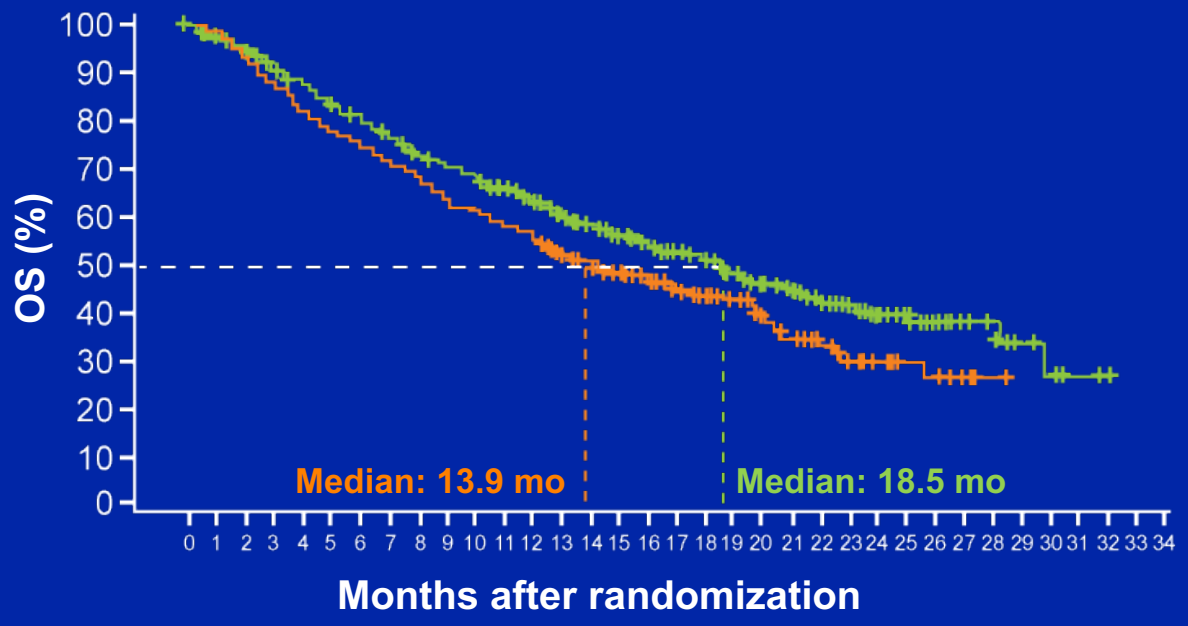


[a] Stratified HR for ITT; unstratified for all other subgroups.
[b] Patients with other/unknown race (n = 46) and unknown baseline ECOG PS (n = 2) not included.
Data cutoff: May 22, 2018.

Papadimitrakopoulou VA et al. *Proc WCLC* 2018;Abstract OA05.07.

IMpower130: PFS and OS with Carboplatin/*Nab* Paclitaxel (CnP) with or without Atezo in the ITT-WT Population





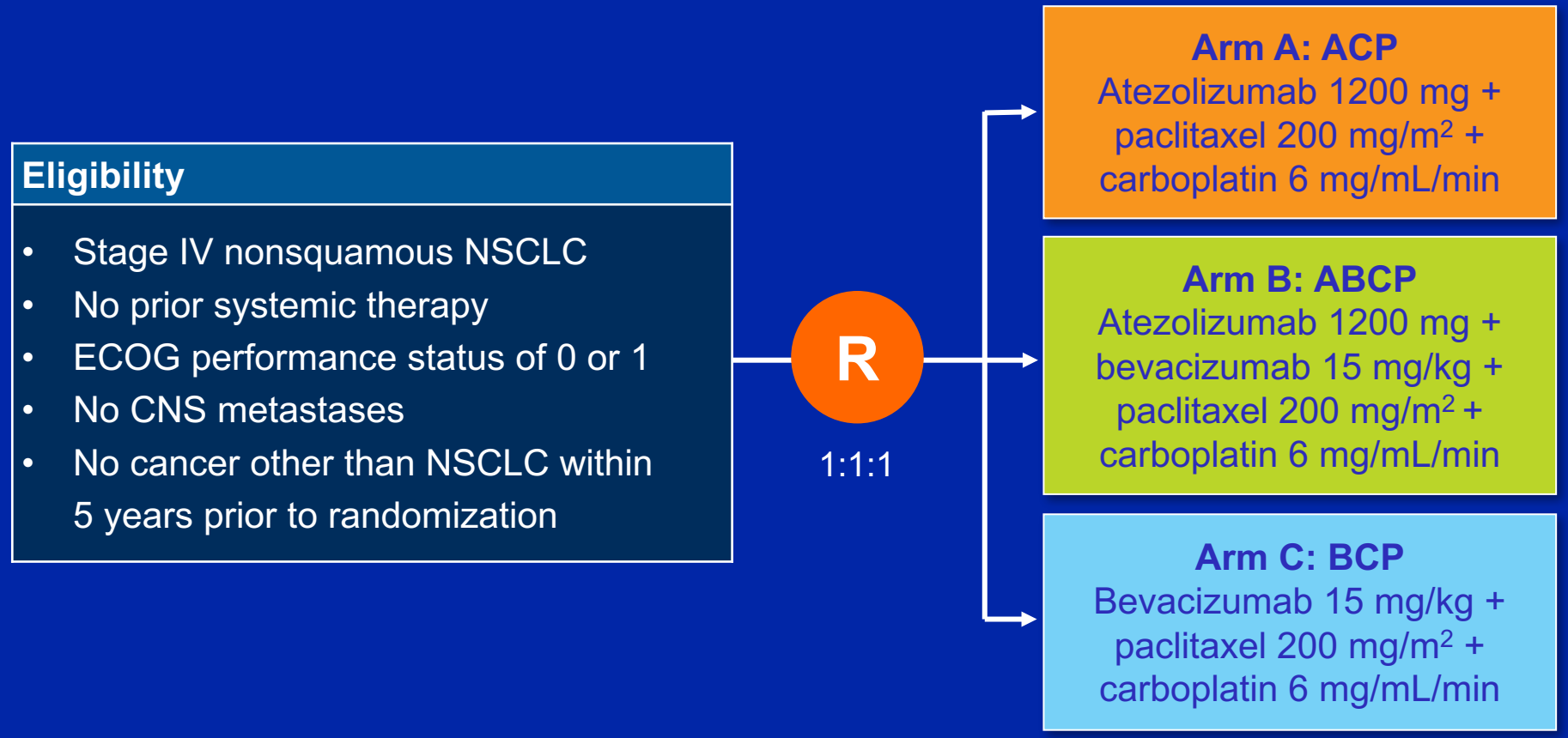
PFS (ITT-WT)	6-month	1-year	HR	*p*-value
Atezo + CnP	56.1%	29.1%	0.64	$p < 0.0001$
CnP	42.5%	14.1%		

OS (ITT-WT)	1-year	2-year	HR	*p*-value
Atezo + CnP	63.1%	39.6%	0.79	$p = 0.033$
CnP	55.5%	30.0%		

- Outcomes for patients with EGFR or ALK genomic alterations suggest treatment benefit was mostly driven by the ITT-WT population.
- Atezo with chemotherapy had a safety profile consistent with the AEs associated with single-agent therapy; no new safety signals were identified.

Cappuzzo F et al. *Proc ESMO* 2018;Abstract LBA53.

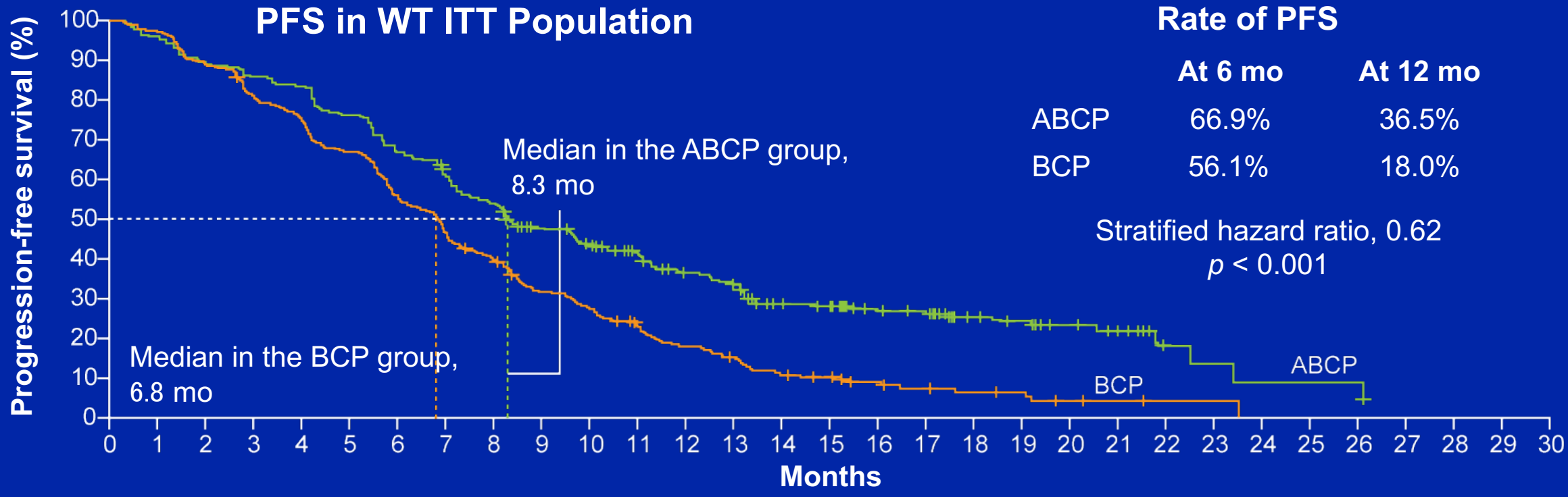
IMpower150: A Phase III Trial of Atezolizumab with Bevacizumab and Chemotherapy in mNSCLC



Coprimary endpoints: PFS based on investigator assessment (per RECIST 1.1) and overall survival

Socinski MA et al. *N Engl J Med* 2018;378(24):2288-301.

IMpower150: PFS Results of First-Line Atezolizumab with Bevacizumab and Chemotherapy in Metastatic Nonsquamous NSCLC



Rate of PFS

	At 6 mo	At 12 mo
ABCP	66.9%	36.5%
BCP	56.1%	18.0%

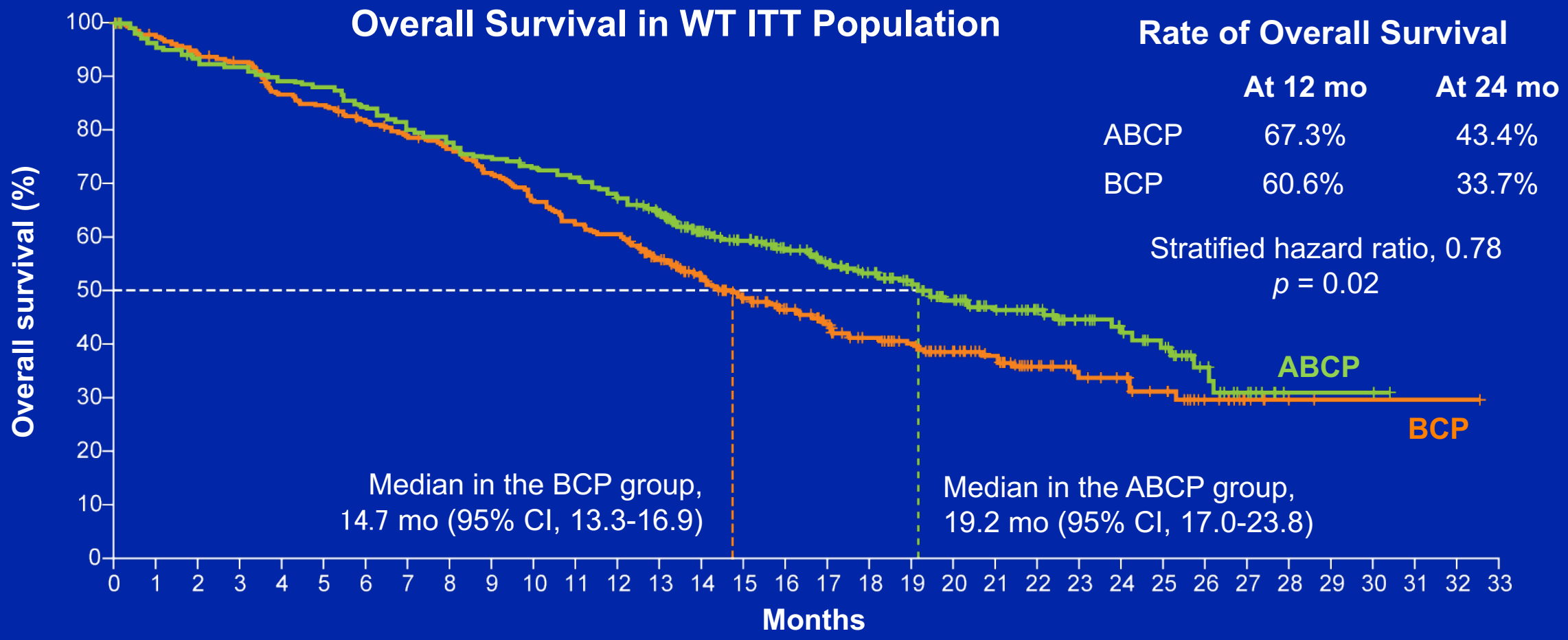
Stratified hazard ratio, 0.62
$p < 0.001$

WT = wild type; ABCP = atezolizumab + BCP; BCP = bevacizumab/carboplatin/paclitaxel

- Median PFS was significantly longer in the ABCP vs BCP group in the effector T-cell (Teff)-high WT population:
  - 11.3 mo vs 6.8 mo (HR 0.51, $p < 0.001$).
- PFS was also higher in the ABCP arm for the entire ITT population, patients with low or negative PD-L1 expression and patients with low Teff gene signatures.

Socinski MA et al. *N Engl J Med* 2018;378(24):2288-301.

IMpower150: Interim Analysis of Overall Survival



Rate of Overall Survival

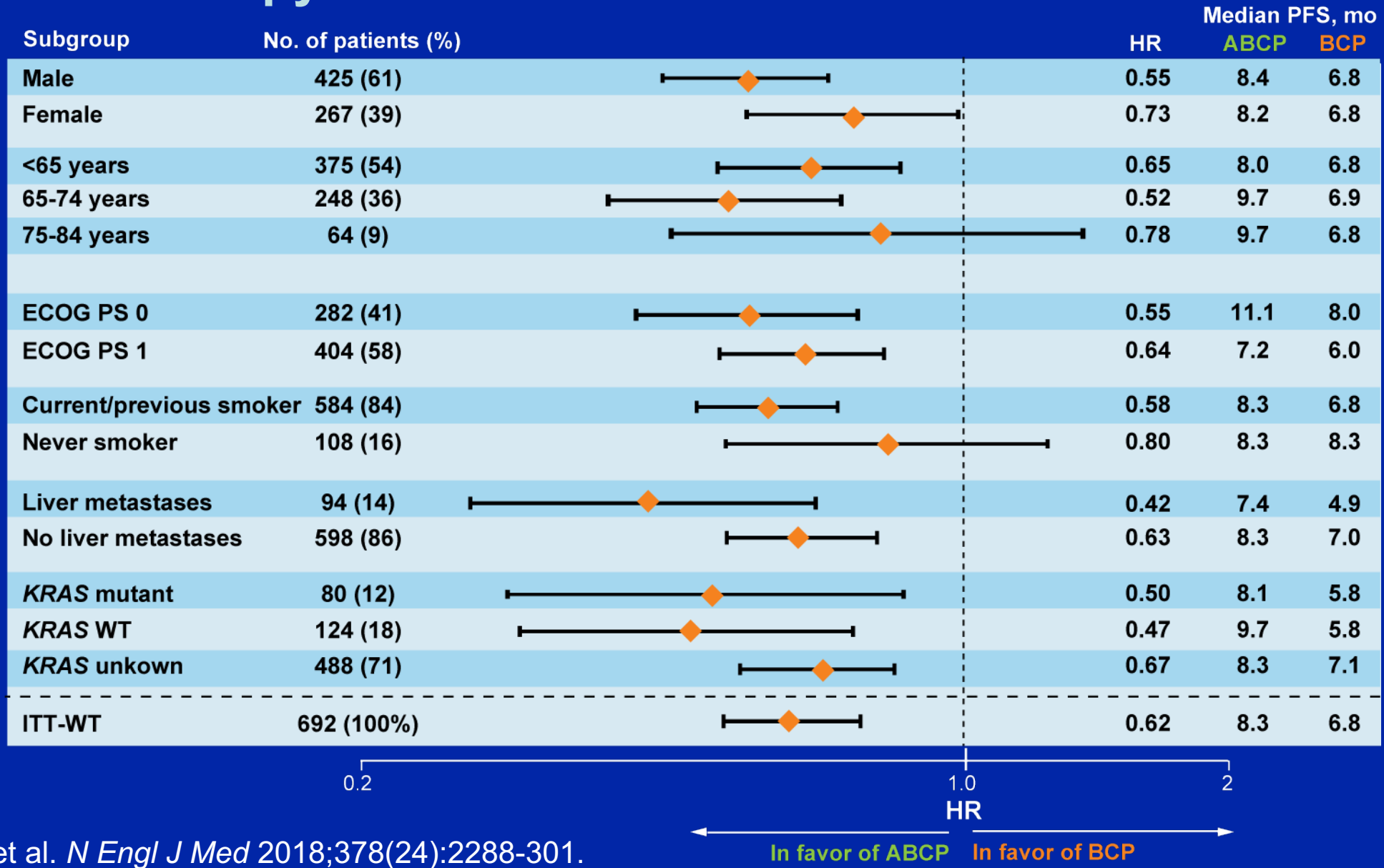
	At 12 mo	At 24 mo
ABCP	67.3%	43.4%
BCP	60.6%	33.7%

Stratified hazard ratio, 0.78
$p = 0.02$

WT = wild type; ABCP = atezolizumab + BCP; BCP = bevacizumab/carboplatin/paclitaxel

Socinski MA et al. *N Engl J Med* 2018;378(24):2288-301.

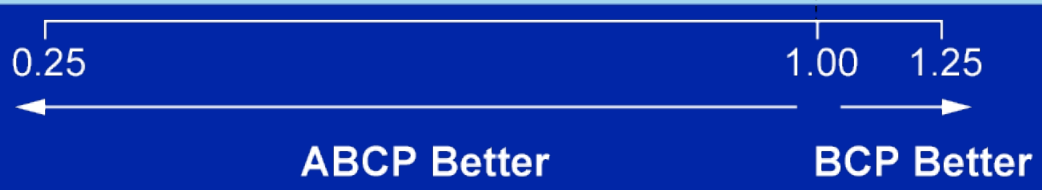
IMpower150: Efficacy of First-Line Atezolizumab with Bevacizumab and Chemotherapy in mNSCLC with Liver Metastases



Socinski MA et al. *N Engl J Med* 2018;378(24):2288-301.

IMpower150: Efficacy of First-Line Atezolizumab with Bevacizumab and Chemotherapy in mNSCLC with Activating Mutations

Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio
		ABCP	BCP	
ITT population	800 (100)	8.3	6.8	0.61
Patients with EGFR or ALK genetic alterations	108 (14)	9.7	6.1	0.59
WT population	692 (87)	8.3	6.8	0.62



- The addition of atezolizumab to bevacizumab and chemotherapy as first-line treatment resulted in a significant improvement in PFS and OS, regardless of PD-L1 expression and EGFR or ALK genetic alteration status.
- Safety profile of ABCP was consistent with previously reported safety risks of the individual medicines.

Socinski MA et al. *N Engl J Med* 2018;378(24):2288-301.

Select Ongoing Phase III Trials of Immune Checkpoint Inhibitors Alone and Combined with Chemotherapy

Clinical trial	Setting	Patients enrolled	Randomization	Estimated primary completion
JAVELIN Lung 100 (NCT02576574)	1L	1,224	• Avelumab • Platinum-based chemotherapy	October 2019
NCT03003962	1L	650	• Durvalumab • Platinum-based chemotherapy	September 2019
KEYNOTE-033 (NCT02864394)	2L+	740	• Pembrolizumab • Docetaxel	September 2019
NCT03117049	1L; Nonsquamous	530	• Nivolumab + chemotherapy + bevacizumab • Placebo + chemotherapy + bevacizumab	April 2020
CheckMate 9LA (NCT03215706)	1L	700	• Nivolumab + ipilimumab + chemotherapy • Chemotherapy	August 2019

www.clinicaltrials.gov; Accessed November 2018.

Agenda: Immune Checkpoint Inhibitors in Lung Cancer

Module 1: *Small Cell Lung Cancer*

Module 2: *Nonsquamous Non-Small Cell Lung Cancer (NSCLC)*

Module 3: *Patients with Targetable Tumor Mutations*

Module 4: *Combined PD-1/PD-L1 and CTLA-4 Inhibitors in NSCLC*

Module 5: *Squamous NSCLC*

Module 6: *Immune-Related Adverse Events and Other Clinical Issues*

Module 7: *Patients with Paraneoplastic Syndrome or Autoimmune Disorders*

In general, when do you believe checkpoint inhibitors should be introduced into the treatment algorithm for a patient who is presenting with metastatic non-small cell lung cancer (NSCLC) with a PD-L1 TPS of 60% and one of the following targetable gene mutations?

	EGFR	ALK rearrangement	ROS1 rearrangement
 EDWARD B GARON, MD, MS	After targeted tx	After targeted tx	After targeted tx
 GIUSEPPE GIACCONE, MD, PHD	After targeted tx and 1 line of chemo	After targeted tx and 1 line of chemo	After targeted tx and 1 line of chemo
 ROY S HERBST, MD, PHD	After targeted tx	After targeted tx and 1 line of chemo	After targeted tx and 1 line of chemo
 VALI A PAPADIMITRAKOPOULOU, MD	After targeted tx	After targeted tx and 1 line of chemo	After targeted tx and 1 line of chemo
 JAMIE CHAFT, MD	After targeted tx	After targeted tx	After targeted tx
 LEORA HORN, MD, MSC	After targeted tx and 2 lines of chemo	After targeted tx and 2 lines of chemo	After targeted tx and 2 lines of chemo
 SURESH S RAMALINGAM, MD	After targeted tx and 1 line of chemo	After targeted tx and 1 line of chemo	After targeted tx and 1 line of chemo
 HEATHER WAKELEE, MD	After targeted tx and 1 line of chemo	After targeted tx and 2 lines of chemo	After targeted tx and 2 lines of chemo

In general, when do you believe checkpoint inhibitors should be introduced into the treatment algorithm for a patient who is presenting with metastatic non-small cell lung cancer (NSCLC) with a PD-L1 TPS of 60% and one of the following targetable gene mutations?

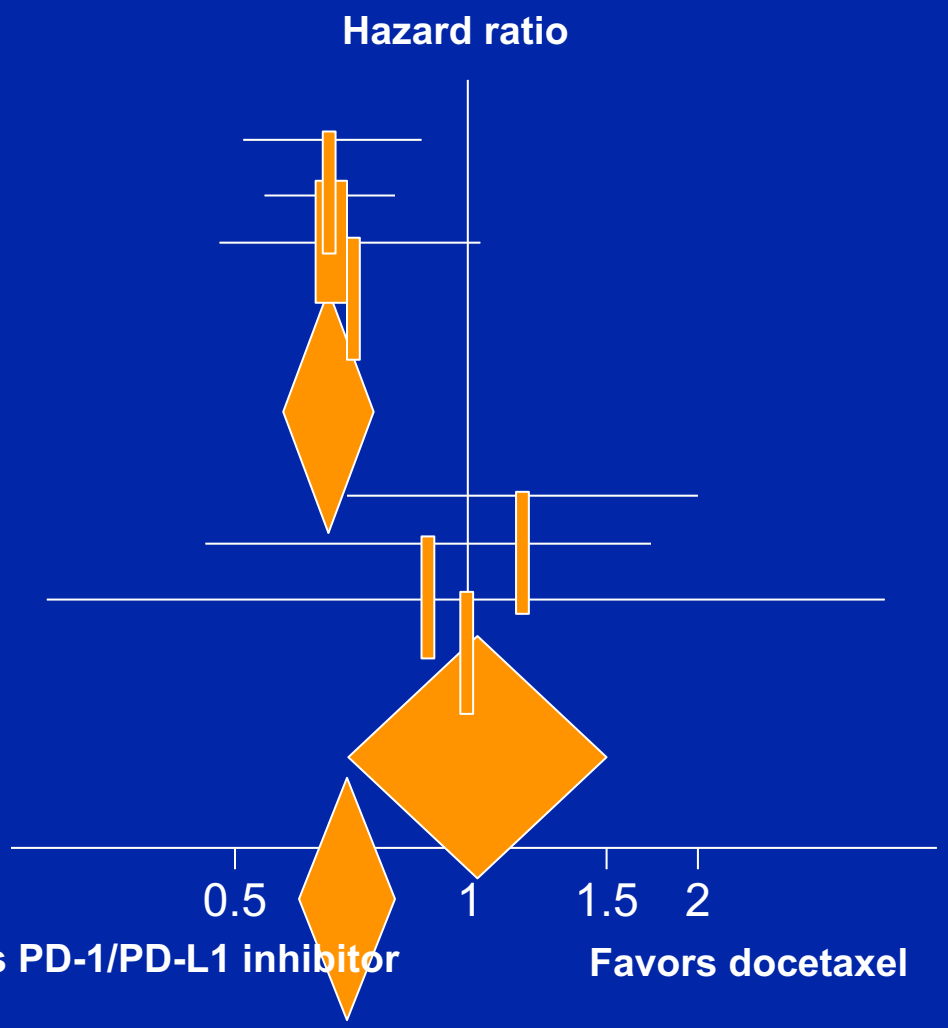
	BRAF V600E	HER2
 EDWARD B GARON, MD, MS	First line w/ chemo	First line w/ chemo
 GIUSEPPE GIACCONE, MD, PHD	After targeted tx but before chemo	After targeted tx
 ROY S HERBST, MD, PHD	After targeted tx but before chemo	First line w/ chemo
 VALI A PAPADIMITRAKOPOULOU, MD	After targeted tx but before chemo	First line w/ chemo
 JAMIE CHAFT, MD	First line as monotherapy	First line as monotherapy
 LEORA HORN, MD, MSC	After targeted tx but before chemo	After clinical trial with targeted therapy
 SURESH S RAMALINGAM, MD	After targeted tx but before chemo	First line as monotherapy
 HEATHER WAKELEE, MD	First line as monotherapy	After targeted tx and 1 line of chemo

In general, when do you believe checkpoint inhibitors should be introduced into the treatment algorithm for a patient who is presenting with metastatic non-small cell lung cancer (NSCLC) with a PD-L1 TPS of 60% and one of the following targetable gene mutations?

	RET rearrangement	MET exon 14
 EDWARD B GARON, MD, MS	First line w/ chemo	First line w/ chemo
 GIUSEPPE GIACCONE, MD, PHD	After targeted tx	After targeted tx and 1 line of chemo
 ROY S HERBST, MD, PHD	After targeted therapy	After targeted tx but before chemo
 VALI A PAPADIMITRAKOPOULOU, MD	After targeted tx and 1 line of chemo	After targeted tx and 1 line of chemo
 JAMIE CHAFT, MD	First line w/ chemo	After targeted tx but before chemo
 LEORA HORN, MD, MSC	After targeted tx	After targeted tx and 2 lines of chemo
 SURESH S RAMALINGAM, MD	First line as monotherapy	First line as monotherapy
 HEATHER WAKELEE, MD	After targeted tx and 1 line of chemo	After targeted tx and 1 line of chemo

Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC — A Meta-Analysis

Study	Weight	Hazard ratio
EGFR wild-type		
CheckMate 057	26.0%	0.66
KEYNOTE-010	52.0%	0.66
POPLAR	11.0%	0.70
Subtotal	**89.0%**	**0.66**
EGFR mutant		
CheckMate 057	6.0%	1.18
KEYNOTE-010	3.8%	0.88
POPLAR	1.1%	0.99
Subtotal	**11.0%**	**1.05**
Total	**100.0%**	**0.70**



Lee CK et al. *J Thorac Oncol* 2017;12(2):403-7.

ImmunoTarget: Efficacy of Immune Checkpoint Inhibitor (ICI) Monotherapy in Patients with NSCLC with Activating Molecular Alterations

Mutation	N	RR	PFS (mo)	OS (mo)	Impact (+) or no impact (x) on PFS of			
					PD-L1	Smoking	No. of prior tx lines	Subtype
Total	551	19%	2.8	13.3				
KRAS	271	26%	3.2	13.5	+	x	x	x
EGFR	125	12%	2.1	10	+	x	x	x
BRAF	43	24%	3.1	13.6	x	+	x	NA
MET	36	16%	3.4	18.4	NA	x	NA	x
HER2	29	7%	2.5	20.3	NA	+	x	NA
ALK	23	0	2.5	17	x	x	x	NA
RET	16	6%	2.1	21.3				
ROS1	7	17%	—	—				

- Response to ICI monotherapy is consistent with ICI registration trials but inferior to that observed with targeted therapies, thus should be considered only after exhaustion of targeted therapy.

Mazieres J et al. *Proc ASCO* 2018;Abstract 9010.

Immune Checkpoint Inhibitor with Targeted Therapy for Advanced NSCLC with EGFR or ALK Mutations

Study	N	Genetic alteration	Treatment	Setting	ORR	Median DoR
Gettinger et al Phase I	20	EGFR mutation	Nivolumab + erlotinib	TKI naïve or treated	3 (15%)	13.8 mo 17.6 mo 38.2 mo
Kim et al Phase Ib	21	ALK+	Atezolizumab + alectinib	TKI naïve	18 (86%)	20.3 mo
Shaw et al Phase Ib/II	28	ALK+	Avelumab + lorlatinib	Any no. prior regimens, including 0	13 (46%)	7.4 mo
Ahn et al Phase Ib*	34	EGFR	Durvalumab + osimertinib	TKI treated TKI naïve	9/23 (39%) 7/10 (70%)	NR

* The Phase III CAURAL study was temporarily suspended in 2015 due to concerns about the durvalumab and osimertinib combination increasing the likelihood of interstitial lung disease-like events on the TATTON study.

Gettinger S et al. *J Thorac Oncol* 2018;13(9):1363-72; Kim DW et al. *Proc ASCO* 2018;Abstract 9009; Shaw AT et al. *Proc ASCO* 2018;Abstract 9008; Ahn M et al. *Proc ESMO* 2016;Abstract 136O.

Select Ongoing Phase III Trials of ICI Therapy in Metastatic Nonsquamous NSCLC with Targetable Mutations

Clinical trial	Setting	Patients enrolled	Randomization	Estimated primary completion
KEYNOTE-789 (NCT03515837)	2L+; EGFR mutation	480	• Pembrolizumab + pemetrexed/platinum • Placebo + pemetrexed/platinum	May 2023
CheckMate722 (NCT02864251)	2L+; EGFR mutation without exon 20 T790M mutation	465	• Nivolumab + platinum doublet • Nivolumab + ipilimumab • Platinum doublet	September 2019

www.clinicaltrials.gov; Accessed November 2018.

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Module 7: *Patients with Paraneoplastic Syndrome or Autoimmune Disorders*

Select Trials of Nivolumab/Ipilimumab in NSCLC

Name	Setting	Eligibility criteria	Randomization	Findings
CheckMate 227	1L	Squamous or nonsquamous	• Nivolumab + ipilimumab • Nivolumab • Chemotherapy	PFS (HR 0.58, $p < 0.001$)
CheckMate 568	1L	Squamous or nonsquamous	• Nivolumab + ipilimumab	• ORR (27%) • TMB <5 ORR (4%) • TMB <10 ORR (10%) • TMB ≥10 ORR (44%) • TMB ≥15 ORR (39%)

Reimbursement and regulatory issues aside, which first-line treatment regimen would you recommend for a 65-year-old patient with metastatic nonsquamous lung cancer and no identified targetable mutations with a…

	PD-L1 TPS 0%	PD-L1 TPS 0%, TMB 15 mut/Mb
 EDWARD B GARON, MD, MS	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 GIUSEPPE GIACCONE, MD, PHD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 ROY S HERBST, MD, PHD	Carboplatin/pemetrexed/bevacizumab	Carboplatin/pemetrexed/pembrolizumab
 VALI A PAPADIMITRAKOPOULOU, MD	Carboplatin/pemetrexed/pembrolizumab	Nivolumab/ipilimumab
 JAMIE CHAFT, MD	Carboplatin/pemetrexed/bevacizumab	Nivolumab/ipilimumab
 LEORA HORN, MD, MSC	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 SURESH S RAMALINGAM, MD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 HEATHER WAKELEE, MD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab

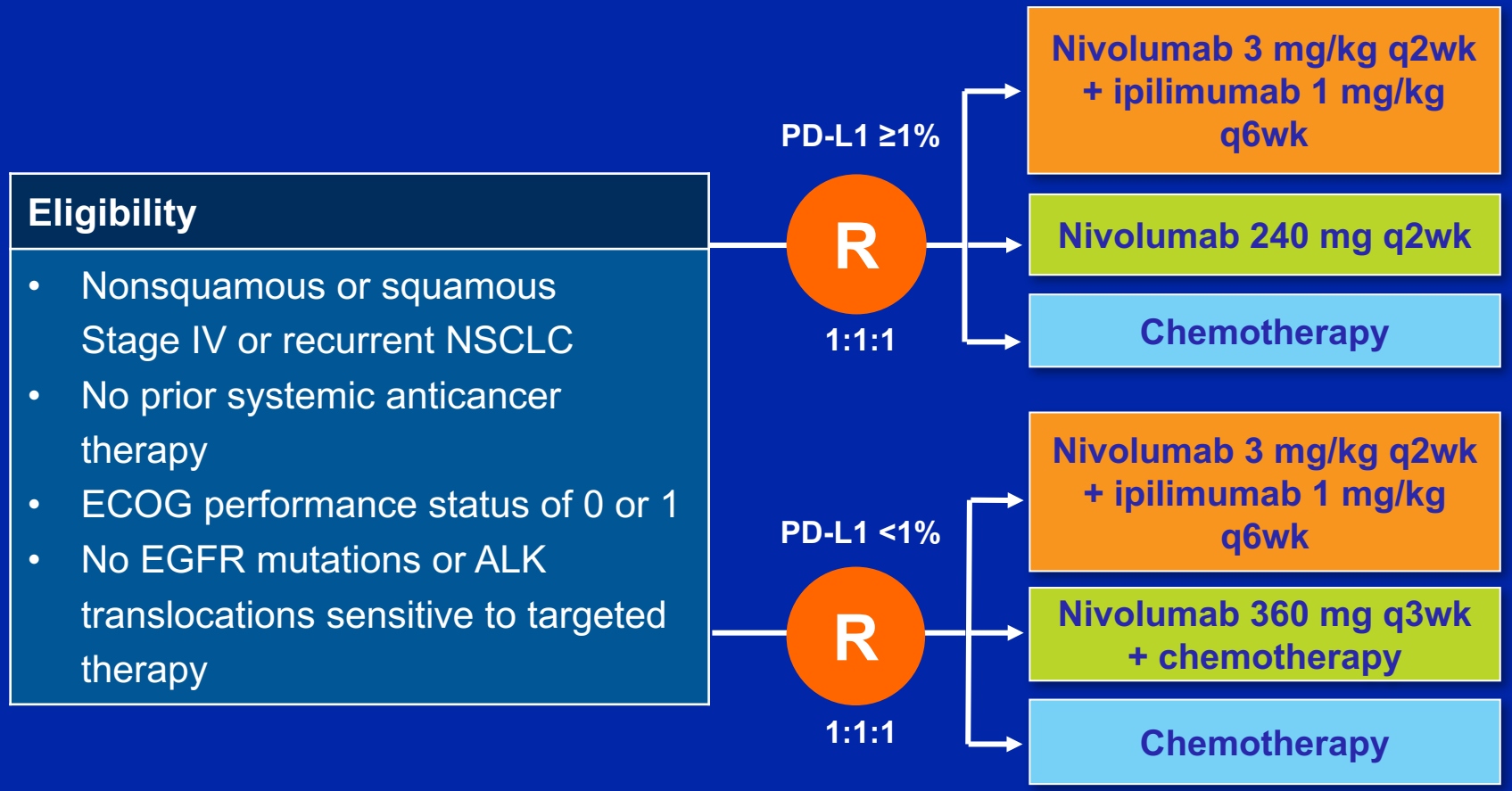
Reimbursement and regulatory issues aside, which first-line treatment regimen would you recommend for an 80-year-old patient with metastatic nonsquamous lung cancer and no identified targetable mutations with a…

	PD-L1 TPS 0%	PD-L1 TPS 0%, TMB 15 mut/Mb
 EDWARD B GARON, MD, MS	Carboplatin/pemetrexed/pembrolizumab	Nivolumab
 GIUSEPPE GIACCONE, MD, PHD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 ROY S HERBST, MD, PHD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 VALI A PAPADIMITRAKOPOULOU, MD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab
 JAMIE CHAFT, MD	Carboplatin/pemetrexed	Carboplatin/pemetrexed/pembrolizumab
 LEORA HORN, MD, MSC	Carboplatin/pemetrexed/pembrolizumab	Nivolumab/ipilimumab
 SURESH S RAMALINGAM, MD	Carboplatin/pemetrexed	Carboplatin/pemetrexed
 HEATHER WAKELEE, MD	Carboplatin/pemetrexed/pembrolizumab	Carboplatin/pemetrexed/pembrolizumab

Do you believe current data support the use of tumor mutation burden as a factor in clinical decision-making for patients with lung cancer?

 EDWARD B GARON, MD, MS	Yes
 GIUSEPPE GIACCONE, MD, PHD	Yes
 ROY S HERBST, MD, PHD	No
 VALI A PAPADIMITRAKOPOULOU, MD	Yes
 JAMIE CHAFT, MD	Yes
 LEORA HORN, MD, MSC	No
 SURESH S RAMALINGAM, MD	No
 HEATHER WAKELEE, MD	No

CheckMate 227: Nivolumab and Ipilimumab in NSCLC with a High Tumor Mutational Burden

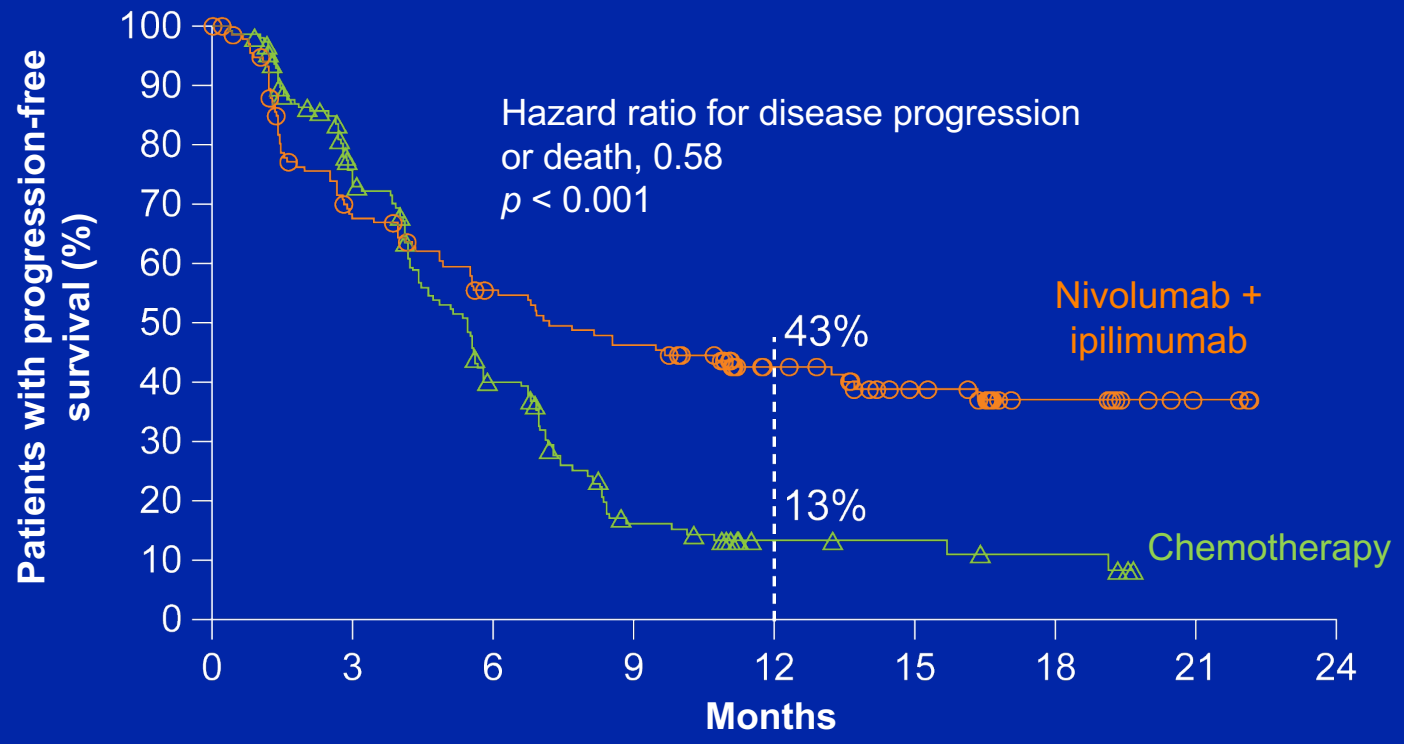


Coprimary endpoints: OS in PD-L1-selected populations and PFS in tumor mutational burden-selected populations

Borghaei H et al. *Proc ASCO* 2018;Abstract 9001.

CheckMate 227: First-Line Nivolumab with Ipilimumab in Metastatic NSCLC

Coprimary endpoint for nivolumab + ipilimumab versus chemotherapy arms: PFS in high tumor mutational burden (TMB) population (≥10 mut/Mb)[1]



	Nivolumab + ipilimumab (n = 139)	Chemotherapy (n = 160)
Median PFS	7.2 mo	5.5 mo
HR (*p*-value)	0.58 (<0.001)	

Secondary endpoint for nivolumab + chemotherapy (n = 177) versus chemotherapy arms (n = 186): PFS in patients with <1% PD-L1 TPS[2]

- Median PFS: 5.6 mo vs 4.7 mo (HR 0.74)
- PFS benefit was enhanced in patients with high TMB

[1] Hellmann MD et al. *N Engl J Med* 2018;378(22):2093-104.
[2] Borghaei H et al. *Proc ASCO* 2018;Abstract 9001.

CheckMate 227: Treatment-Related Adverse Events in mNSCLC

Adverse events (Grade 3 or 4)	Nivolumab and ipilimumab (N = 576)	Nivolumab (N = 391)	Chemotherapy (N = 570)
Any Grade 3 or 4	31%	19%	36%
Any serious event	18%	8%	11%
Leading to discontinuation of treatment	12%	7%	5%
Rash	2%	1%	0%
Diarrhea	2%	1%	1%
Anemia	2%	1%	11%
Neutropenia	0%	0%	10%

Hellmann MD et al. *N Engl J Med* 2018;378(22):2093-104.

Tumor Mutational Burden (TMB) as a Biomarker for Clinical Benefit from Dual Immune Checkpoint Blockade with Nivolumab (Nivo) + Ipilimumab (Ipi) in First-Line (1L) Non-Small Cell Lung Cancer (NSCLC): Identification of TMB Cutoff from CheckMate 568

Ramalingam SS et al.

Proc AACR 2018;Abstract CT078.

CheckMate 568: Identification of TMB Cutoff to Select Patients for First-Line Nivolumab with Ipilimumab in Metastatic NSCLC

- In CheckMate 568, 288 patients with chemotherapy-naïve Stage IV NSCLC received nivo 3 mg/kg q2wk + ipi 1 mg/kg q6wk for up to 2 years.
- An appropriate TMB cutoff associated with enhanced efficacy was determined with receiver operating characteristic (ROC) curves.

Patient group	ORR
Overall	27%
TMB <5 mut/Mb	4%
TMB <10 mut/Mb	10%
TMB ≥10 mut/Mb	44%
TMB ≥15 mut/Mb	39%

← Chosen as cutoff to define population for coprimary efficacy endpoint in CheckMate 227

Ramalingam SS et al. *Proc AACR* 2018;Abstract CT078.

Select Ongoing Phase III Trials of Combined PD-1/PD-L1 and CTLA-4 Inhibitors in NSCLC

Clinical trial	Setting	Patients enrolled	Randomization	Estimated primary completion
MYSTIC (NCT02453282)	1L	1,118	• Durvalumab • Durvalumab + tremelimumab • Standard chemotherapy	December 2018
POSEIDON (NCT03164616)	1L	1,000	• Durvalumab + tremelimumab + chemotherapy • Durvalumab + chemotherapy	September 2019
NCT03515629	1L	585	• Pembrolizumab • REGN2810 (anti-PD-1) + ipilimumab • REGN2810 + ipilimumab + chemotherapy	March 2023
KEYNOTE-598 (NCT03302234)	1L	548	• Pembrolizumab + ipilimumab • Pembrolizumab + placebo	February 2023
eNERGY (NCT03351361)	1L	242	• Nivolumab + ipilimumab • Chemotherapy	June 2021
NCT03409614	1L	690	• REGN2810 (anti-PD-1) + chemotherapy • REGN2810 + ipilimumab + chemotherapy • Chemotherapy	July 2022
CheckMate 9LA (NCT03215706)	1L; squamous and nonsquamous	700	• Nivolumab + ipilimumab + chemotherapy • Chemotherapy	August 2019

www.clinicaltrials.gov; Accessed November 2018.

Agenda: Immune Checkpoint Inhibitors in Lung Cancer

Module 1: *Small Cell Lung Cancer*

Module 2: *Nonsquamous Non-Small Cell Lung Cancer (NSCLC)*

Module 3: *Patients with Targetable Tumor Mutations*

Module 4: *Combined PD-1/PD-L1 and CTLA-4 Inhibitors in NSCLC*

Module 5: *Squamous NSCLC*

Module 6: *Immune-Related Adverse Events and Other Clinical Issues*

Module 7: *Patients with Paraneoplastic Syndrome or Autoimmune Disorders*

Select Trials Combining Chemotherapy and Checkpoint Inhibitors in Squamous NSCLC

Name	Setting	Randomization	Findings
KEYNOTE-407	1L	• Pembrolizumab + carboplatin + paclitaxel or *nab* paclitaxel • Placebo + carboplatin + paclitaxel or *nab* paclitaxel	• PFS (HR 0.56, $p < 0.001$) • OS (HR 0.64, $p < 0.001$)
IMpower131	1L	• Atezolizumab + carboplatin + paclitaxel • Atezolizumab + carboplatin + *nab* paclitaxel • Carboplatin + *nab* paclitaxel	Atezo + CnP vs CnP • PFS (HR 0.71, $p = 0.0001$) • Interim OS (HR 0.96, $p = 0.6931$)

CnP = carboplatin/*nab* paclitaxel

Reimbursement and regulatory issues aside, what first-line treatment regimen would you recommend for a patient with metastatic squamous cell lung cancer and a PD-L1 TPS of 10% who is…

	Age 65	Age 80
 EDWARD B GARON, MD, MS	Pembrolizumab/carboplatin/paclitaxel	Pembrolizumab/carboplatin/paclitaxel
 GIUSEPPE GIACCONE, MD, PHD	Pembrolizumab/carboplatin/ *nab* paclitaxel	Pembrolizumab/carboplatin/ *nab* paclitaxel
 ROY S HERBST, MD, PHD	Pembrolizumab/carboplatin/paclitaxel	Pembrolizumab/carboplatin/paclitaxel
 VALI A PAPADIMITRAKOPOULOU, MD	Pembrolizumab/carboplatin/paclitaxel	Pembrolizumab/carboplatin/ *nab* paclitaxel
 JAMIE CHAFT, MD	Pembrolizumab/carboplatin/ *nab* paclitaxel	Pembrolizumab/carboplatin/ *nab* paclitaxel
 LEORA HORN, MD, MSC	Pembrolizumab/carboplatin/paclitaxel	Pembrolizumab/carboplatin/paclitaxel
 SURESH S RAMALINGAM, MD	Pembrolizumab/carboplatin/paclitaxel	Pembrolizumab/carboplatin/ *nab* paclitaxel
 HEATHER WAKELEE, MD	Pembrolizumab/carboplatin/paclitaxel	Pembrolizumab/carboplatin/ *nab* paclitaxel

Reimbursement and regulatory issues aside, what first-line treatment regimen would you recommend for a patient with metastatic squamous cell lung cancer and a PD-L1 TPS of 60% who is…

	Age 65	Age 80
 EDWARD B GARON, MD, MS	Pembrolizumab	Pembrolizumab
 GIUSEPPE GIACCONE, MD, PHD	Pembrolizumab	Pembrolizumab
 ROY S HERBST, MD, PHD	Pembrolizumab	Pembrolizumab
 VALI A PAPADIMITRAKOPOULOU, MD	Pembrolizumab	Pembrolizumab
 JAMIE CHAFT, MD	Pembrolizumab	Pembrolizumab
 LEORA HORN, MD, MSC	Pembrolizumab	Pembrolizumab
 SURESH S RAMALINGAM, MD	Pembrolizumab	Pembrolizumab
 HEATHER WAKELEE, MD	Pembrolizumab	Pembrolizumab

A patient presents with metastatic squamous lung cancer with no identified targetable mutations and moderate respiratory distress secondary to extensive tumor in the lung. What would be your most likely treatment recommendation if the patient had a PD-L1 TPS of…

	60%	90%
 EDWARD B GARON, MD, MS	Pembrolizumab/carboplatin/paclitaxel	Pembrolizumab/carboplatin/paclitaxel
 GIUSEPPE GIACCONE, MD, PHD	Pembrolizumab/carboplatin/ *nab* paclitaxel	Pembrolizumab/carboplatin/ *nab* paclitaxel
 ROY S HERBST, MD, PHD	Pembrolizumab	Pembrolizumab
 VALI A PAPADIMITRAKOPOULOU, MD	Pembrolizumab/carboplatin/ *nab* paclitaxel	Pembrolizumab/carboplatin/ *nab* paclitaxel
 JAMIE CHAFT, MD	Pembrolizumab/carboplatin/ *nab* paclitaxel	Pembrolizumab/carboplatin/ *nab* paclitaxel
 LEORA HORN, MD, MSC	Pembrolizumab/carboplatin/ *nab* paclitaxel	Pembrolizumab
 SURESH S RAMALINGAM, MD	Pembrolizumab/carboplatin/paclitaxel	Pembrolizumab/carboplatin/paclitaxel
 HEATHER WAKELEE, MD	Pembrolizumab/carboplatin/ *nab* paclitaxel	Pembrolizumab/carboplatin/ *nab* paclitaxel

KEYNOTE-407: A Phase III Trial of First-Line Pembrolizumab with Chemotherapy for Advanced Squamous NSCLC

Eligibility (N = 559)

- Stage IV squamous NSCLC
- No prior systemic therapy
- Life expectancy of at least 3 months
- ECOG performance status of 0 or 1
- Adequate organ function
- No major surgery within 3 weeks before first dose
- No radiation therapy >30 Gy within 6 months of first dose

R

1:1

Carboplatin + paclitaxel or *nab* paclitaxel (first 4 cycles) + pembrolizumab 200 mg (up to 35 cycles)

Carboplatin + paclitaxel or *nab* paclitaxel (first 4 cycles) + saline placebo (up to 35 cycles)

Coprimary endpoints: PFS and OS

www.clinicaltrials.gov. NCT02775435; Paz-Ares L et al. *N Engl J Med* 2018;[Epub ahead of print].

KEYNOTE-407: Second Interim Analysis of First-Line Pembrolizumab with Chemotherapy in Advanced Squamous NSCLC

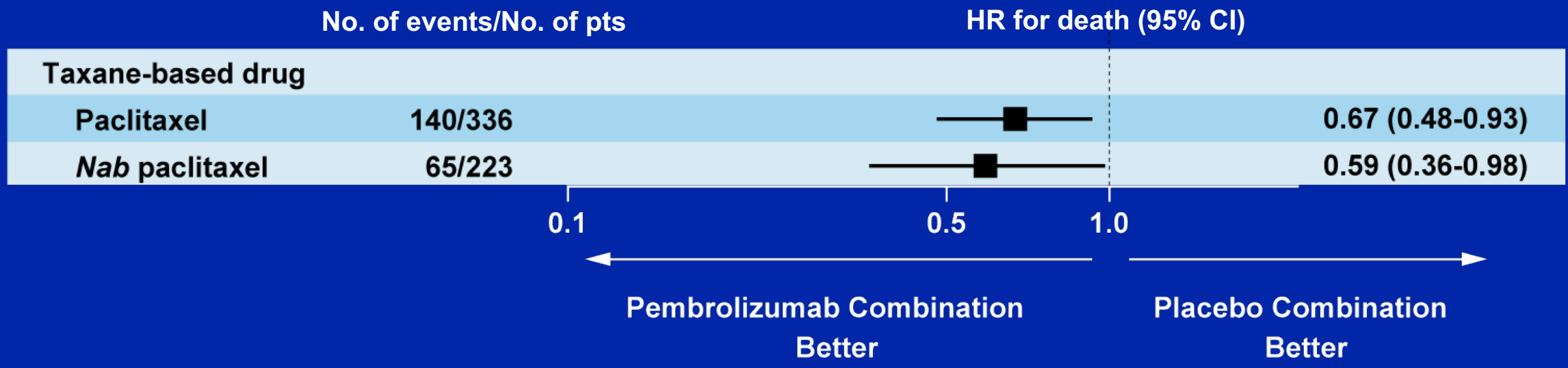
Coprimary endpoints: PFS and OS in ITT	Pembrolizumab + chemotherapy* (n = 278)	Placebo + chemotherapy* (n = 281)	HR (*p*-value)
Median PFS	6.4 mo	4.8 mo	0.56 (<0.001)
Median OS	15.9 mo	11.3 mo	0.64 (<0.001)

* Chemotherapy = carboplatin with paclitaxel or *nab* paclitaxel

- PFS and OS benefit with pembrolizumab with chemotherapy was observed irrespective of PD-L1 TPS.
- ORR and DoR were greater with pembrolizumab with chemotherapy than with chemotherapy alone.
- Observed toxicities were consistent with the known safety profiles of the individual agents, and no new safety signals were identified:
  - Grade 3-5 immune-mediated AEs (pembrolizumab vs placebo arms): 10.8% vs 3.2%
  - 2 deaths occurred due to pneumonitis (1 on each treatment arm)

Paz-Ares L et al. *N Engl J Med* 2018;[Epub ahead of print].

KEYNOTE-407: Impact of Choice of Taxane on Outcomes



- The treatment effect was similar between the patients who received paclitaxel and those who received *nab* paclitaxel.

Paz-Ares L et al. *N Engl J Med* 2018;[Epub ahead of print].

FDA Approves Pembrolizumab in Combination with Chemotherapy for First-Line Treatment of Metastatic Squamous NSCLC

Press Release – October 30, 2018

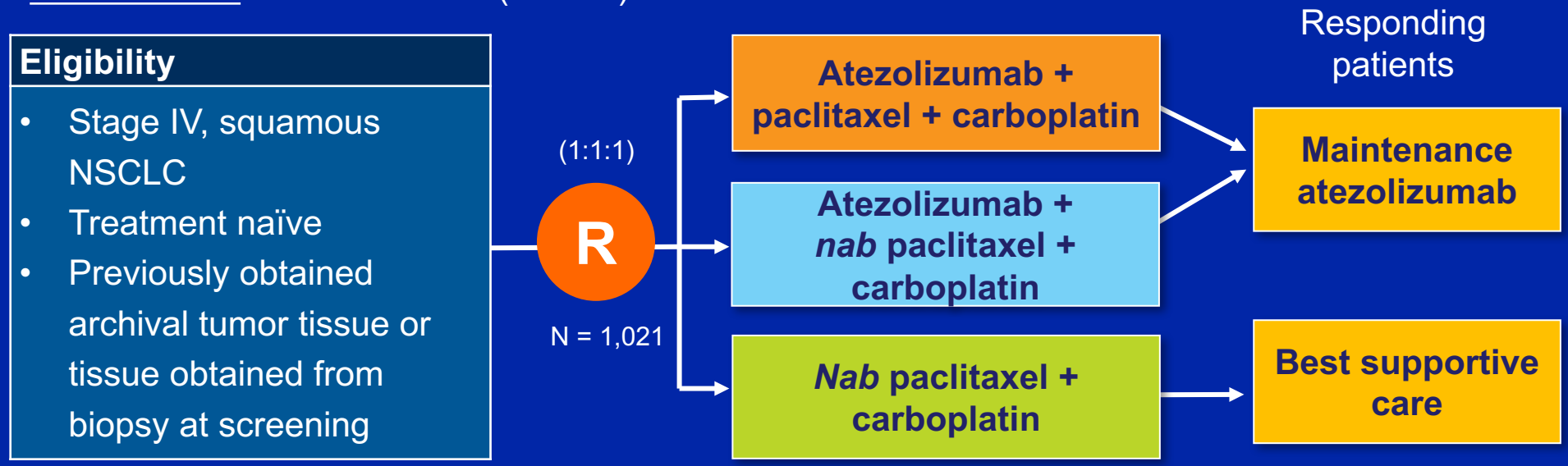
"On October 30, 2018, the Food and Drug Administration approved pembrolizumab in combination with carboplatin and either paclitaxel or *nab*-paclitaxel as first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC).

Approval was based on KEYNOTE-407 (NCT02775435), a randomized, multi-center, double-blind, placebo-controlled trial in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients were randomized (1:1) to pembrolizumab 200 mg or placebo in combination with carboplatin, and investigator's choice of either paclitaxel every 3 weeks or *nab*-paclitaxel weekly on a 3-week cycle for 4 cycles followed by pembrolizumab or placebo. Patients continued pembrolizumab or placebo until disease progression, unacceptable toxicity, or a maximum of 24 months."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm624659.htm

IMpower131: A Phase III Trial of First-Line Atezolizumab with Chemotherapy Compared to Chemotherapy Alone for Squamous Cell NSCLC

Trial Identifier: NCT02367794 (Closed)



Coprimary Endpoints: PFS and OS in ITT population

www.clinicaltrials.gov. Accessed May 2018; Jotte RM et al. *Proc ASCO* 2018;Abstract LBA9000.

IMpower131: First-Line Atezolizumab with Chemotherapy in Advanced Squamous NSCLC

Coprimary endpoints: PFS and OS in ITT	Atezolizumab + CnP (n = 343)	CnP (n = 340)	HR (*p*-value)
Median PFS	6.3 mo	5.6 mo	0.71 (0.0001)
Median OS (first interim analysis)	14.0 mo	13.9 mo	0.96 (0.6931)
PFS and OS in PD-L1 high	**(n = 53)**	**(n = 48)**	**HR**
Median PFS	10.1 mo	5.5 mo	0.44
Median OS	23.6 mo	14.1 mo	0.56

- PFS benefit with atezolizumab and *nab* paclitaxel/carboplatin (CnP) versus CnP alone was observed across all PD-L1-expressing subgroups; next interim OS analysis anticipated later in 2018.
- Atezolizumab with CnP had a manageable safety profile consistent with the known risks of the individual therapies.

Jotte RM et al. *Proc ASCO* 2018;Abstract LBA9000.

Agenda: Immune Checkpoint Inhibitors in Lung Cancer

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The risk of Grade 3/4 toxicities with checkpoint inhibitors is…

 EDWARD B GARON, MD, MS	About the same in patients older than 75 and those younger than 65
 GIUSEPPE GIACCONE, MD, PHD	About the same in patients older than 75 and those younger than 65
 ROY S HERBST, MD, PHD	About the same in patients older than 75 and those younger than 65
 VALI A PAPADIMITRAKOPOULOU, MD	About the same in patients older than 75 and those younger than 65
 JAMIE CHAFT, MD	About the same in patients older than 75 and those younger than 65
 LEORA HORN, MD, MSC	About the same in patients older than 75 and those younger than 65
 SURESH S RAMALINGAM, MD	About the same in patients older than 75 and those younger than 65
 HEATHER WAKELEE, MD	Greater in patients older than 75 than in patients younger than 65

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

J Oncol Pract 2018;14(4):247-9.

ASCO Guideline: Management of IRAEs in Patients Receiving Immune Checkpoint Inhibitor Therapy

Toxicity grade	General recommendations
Grade 1	• Continue with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities.
Grade 2	• Therapy may be suspended and resumed when symptoms revert to grade 1 or less. • Corticosteroids may be administered.
Grade 3	• Suspension of therapy and the initiation of high-dose corticosteroids. • Corticosteroids should be tapered over the course of at least 4 to 6 weeks. • Some refractory cases may require infliximab or other immunosuppressive therapy.
Grade 4	• Permanent discontinuation is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement.

Brahmer JR et al. *J Clin Oncol* 2018;36(17):1714-68.

Are anti-PD-1/PD-L1 antibodies effective in patients with brain metastases? Have you observed any meaningful clinical responses to anti-PD-1/PD-L1 antibodies in a patient with brain metastases?

	Effective in brain mets?	Meaningful responses?
 EDWARD B GARON, MD, MS	Yes, but less effective than with systemic metastases	Yes
 GIUSEPPE GIACCONE, MD, PHD	Yes, but less effective than with systemic metastases	No
 ROY S HERBST, MD, PHD	Yes, about as effective as with systemic metastases	Yes
 VALI A PAPADIMITRAKOPOULOU, MD	Yes, about as effective as with systemic metastases	No
 JAMIE CHAFT, MD	Yes, about as effective as with systemic metastases	Yes
 LEORA HORN, MD, MSC	Yes, about as effective as with systemic metastases	Yes
 SURESH S RAMALINGAM, MD	Yes, but less effective than with systemic metastases	No
 HEATHER WAKELEE, MD	Yes, about as effective as with systemic metastases	Yes

For a patient with metastatic NSCLC who experiences a clinical response to an anti-PD-1/PD-L1 antibody at first evaluation and is tolerating it well, how long would you continue treatment?

	Complete response	Partial response
 EDWARD B GARON, MD, MS	Indefinitely or until disease progression/toxicity	Indefinitely or until disease progression/toxicity
 GIUSEPPE GIACCONE, MD, PHD	Indefinitely or until disease progression/toxicity	Indefinitely or until disease progression/toxicity
 ROY S HERBST, MD, PHD	Indefinitely or until disease progression/toxicity	Indefinitely or until disease progression/toxicity
 VALI A PAPADIMITRAKOPOULOU, MD	Indefinitely or until disease progression/toxicity	Indefinitely or until disease progression/toxicity
 JAMIE CHAFT, MD	1 Year	2 Years
 LEORA HORN, MD, MSC	2 Years	2 Years
 SURESH S RAMALINGAM, MD	2 Years	2 Years
 HEATHER WAKELEE, MD	2 Years	2 Years

Based on your own clinical experience and the available data, do you believe hyperprogression is an actual clinical phenomenon?

 EDWARD B GARON, MD, MS	No
 GIUSEPPE GIACCONE, MD, PHD	Yes
 ROY S HERBST, MD, PHD	No
 VALI A PAPADIMITRAKOPOULOU, MD	No
 JAMIE CHAFT, MD	No
 LEORA HORN, MD, MSC	Yes
 SURESH S RAMALINGAM, MD	Yes
 HEATHER WAKELEE, MD	Yes

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Regulatory and reimbursement issues aside, what would be your preferred first-line treatment regimen for a 65-year-old patient with extensive-stage SCLC and…

	Neurologic paraneoplastic syndrome	Symptomatic SIADH
 EDWARD B GARON, MD, MS	Carboplatin/etoposide	Carboplatin/etoposide + atezolizumab
 GIUSEPPE GIACCONE, MD, PHD	Carboplatin/etoposide	Carboplatin/etoposide + atezolizumab
 ROY S HERBST, MD, PHD	Carboplatin/etoposide + atezolizumab	Carboplatin/etoposide
 VALI A PAPADIMITRAKOPOULOU, MD	Carboplatin/etoposide	Carboplatin/etoposide + atezolizumab
 JAMIE CHAFT, MD	Cisplatin/etoposide	Carboplatin/etoposide
 LEORA HORN, MD, MSC	Carboplatin/etoposide	Carboplatin/etoposide + atezolizumab
 SURESH S RAMALINGAM, MD	Carboplatin/etoposide	Carboplatin/etoposide + atezolizumab
 HEATHER WAKELEE, MD	Carboplatin/etoposide	Carboplatin/etoposide

SIADH = syndrome of inappropriate antidiuretic hormone secretion