# Immunotherapy: Changing Patient Outcomes in SCLC

***A CME Self-Assessment Program***

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MEDICAL EDUCATION FOR BETTER OUTCOMES

Postgraduate Institute for Medicine

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**Hello, and welcome to *Immunotherapy: Changing Patient Outcomes in SCLC*, a CME Self-Assessment Program.**

**My name is Dr. Leora Horn and I am an Ingram Associate Professor at Vanderbilt University Medical Center.**

**In this activity, I will guide you through the latest evidence on checkpoint inhibitors for the management of ES-SCLC and offer expert insight into effectively and safely incorporating immunotherapy into your practice to improve patient outcomes.**

# Pre-Test

**On a scale from 1-5 (1 being not confident and 5 being completely confident), how confident are you in your ability to _____?**

| | | | | | |
|---|---|---|---|---|---|
| **Incorporate immunotherapy as initial therapy for your patients with Extensive Stage SCLC?** | Not confident | Not very confident | Moderately confident | Somewhat confident | Very confident |
| **Manage immune-related adverse events?** | Not confident | Not very confident | Moderately confident | Somewhat confident | Very confident |

# Pre-Test

## How often do you engage in the following practices to educate your patients about immunotherapy?

| Practice | Always | Sometimes | Never |
|---|---|---|---|
| Offer written material about immunotherapy | | | |
| Direct patients to specific websites | | | |
| Discuss all possible treatment options | | | |
| Describe ~~the~~ side effects of immunotherapy | | | |
| Describe how to monitor for side effects of immunotherapy | | | |

# Pre-Test

## Which of the following are consistent with your current practice for a patient with newly diagnosed ES SCLC?

| | Consistent | Inconsistent |
|---|---|---|
| Recommend chemotherapy alone | | |
| Recommend chemotherapy plus immunotherapy | | |
| Discuss immune-related side effects with patients receiving checkpoint inhibitors | | |
| Reserve immunotherapy for a later line of therapy | | |
| Provide your patients receiving checkpoint inhibitors with pocket cards describing immunotherapy and its side effects | | |
| Offer smoking cessation aids to patients who are still smokers | | |

# Lung Cancer

**2nd**
Most Commonly Diagnosed Cancer

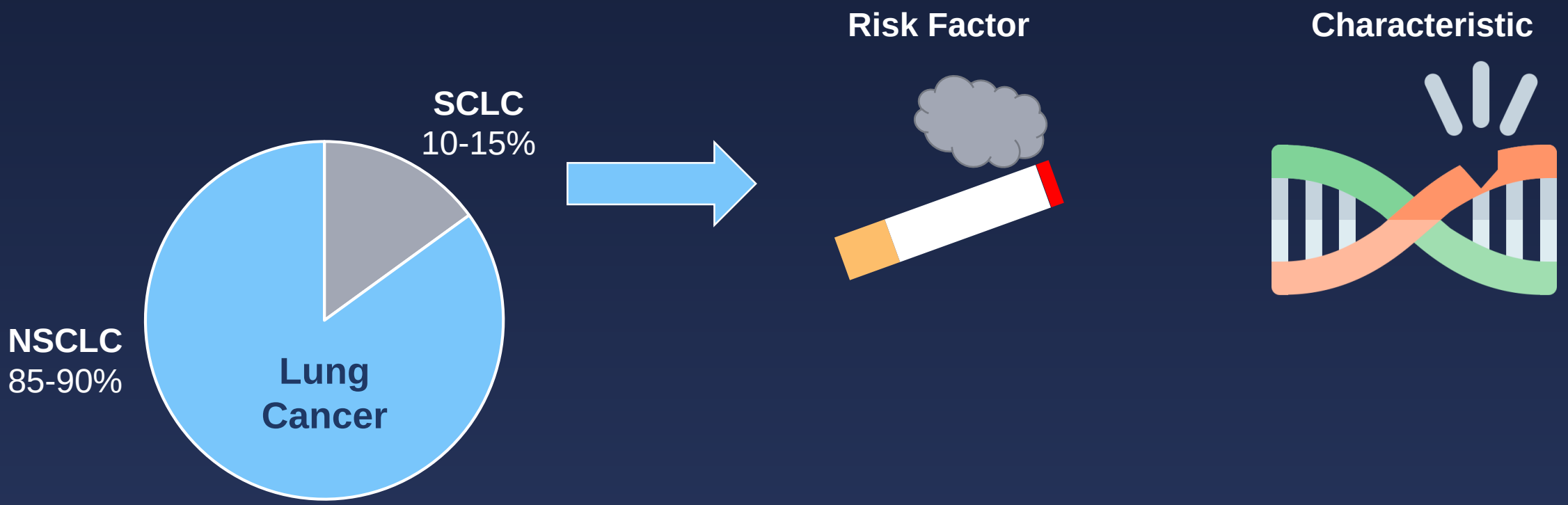
**10 years**
Average OS after first-line therapy

**#1**
Cancer Mortality

**5-10%**
5-Year Survival Rate

van Meerbeeck JP, et al. *Lancet*. 2011;378:1741-1755; Byers LA, et al. *Cancer*. 2015;121:664-672.

# Lung Cancer




van Meerbeeck JP, et al. *Lancet*. 2011;378:1741-1755; Byers LA, et al. *Cancer*. 2015;121:664-672; Icon made by Freepik from www.flaticon.com

# SCLC

- Limited stage (LS) disease is managed by concurrent chemoradiotherapy
- Extensive stage (ES) disease managed with systemic therapy and palliative radiation
- Initial therapy is platinum-based doublet
- FDA approved second line therapy is topotecan
- Immunotherapy is changing the treatment paradigm and improving options

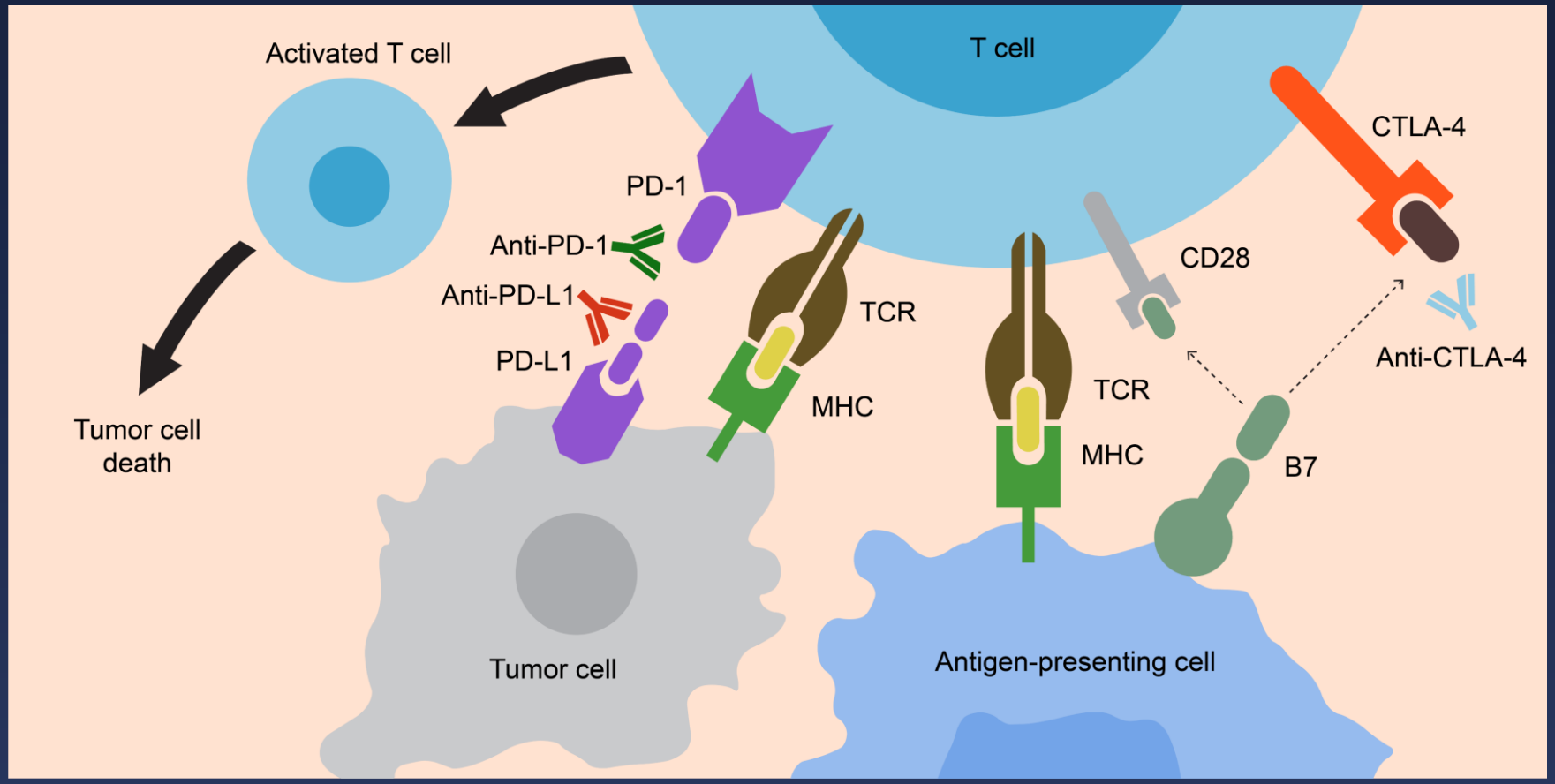
van Meerbeeck JP, et al. *Lancet*. 2011;378:1741-1755; Byers LA, et al. *Cancer*. 2015;121:664-672; NCCN Guidelines for SCLC. Version 1.2019.

# Question 1

**Select the properties of each of the following checkpoint inhibitors.**
*Please choose your selection from each drop-down menu*:

- Atezolizumab
- Durvalumab
- Ipilimumab
- Nivolumab
- Pembrolizumab
- Tremelimumab

# Response: Immunotherapy – Checkpoint Inhibitors




Adapted from Raman R, et al. *Biomed Res Int*. 2015;2015:367354.

# Checkpoint Inhibitors

| Agent | Target | Approval Status |
|---|---|---|
| **Agents approved in Lung Cancer** | | |
| Nivolumab[1] | PD-1 antibody | **SCLC** – after 2 prior therapies including platinum-based therapy<br>NSCLC – patients with progression after platinum-based therapy |
| Pembrolizumab[2] | PD-1 antibody | NSCLC – First-line therapy with pemetrexed/platinum in non-squamous NSCLC; with carboplatin/paclitaxel or nab-paclitaxel for first-line squamous; single agent for NSCLC with high PD-L1 expression; single agent for high PD-L1 after platinum-based therapy |
| Atezolizumab[3] | PD-L1 antibody | **SCLC** – first-line with carboplatin/etoposide for ES-SCLC<br>NSCLC – with bevacizumab/paclitaxel/carboplatin for first-line non-squamous NSCLC; For patients with progression after platinum-based therapy |
| Durvalumab[4] | PD-L1 antibody | NSCLC – unresectable stage III NSCLC following chemoradiotherapy |

1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2019. 2. KEYTRUDA [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2019.
3. TECENTRIQ [package insert]. South San Franciso, CA: Genentech, Inc.; 2019. 4. IMFINZI [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018.

# Checkpoint Inhibitors

| Agent | Target | Approval Status |
|---|---|---|
| **Checkpoint Inhibitors not yet Approved in Lung Cancer** | | |
| Cemiplimab[1] | PD-1 antibody | Approved in other tumor types |
| Avelumab[2] | PD-L1 antibody | Approved in other tumor types |
| Ipilimumab[3] | CTLA-4 antibody | Approved in other tumor types |
| Tremelimumab | CTLA-4 antibody | Phase III |

1. LIBTAYO [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2019. 2. BAVENCIO [package insert]. Rockland, MA: EMD Serono, Inc. 2018.
3. YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2018.

# Question 2

**Which of the following therapies is recommended by current guidelines for a patient newly diagnosed with ES SCLC?**

A. Nivolumab alone
B. Nivolumab plus carboplatin/etoposide
C. Atezolizumab plus carboplatin/etoposide
D. Pembrolizumab plus carboplatin/etoposide
E. Atezolizumab alone

# Question 3

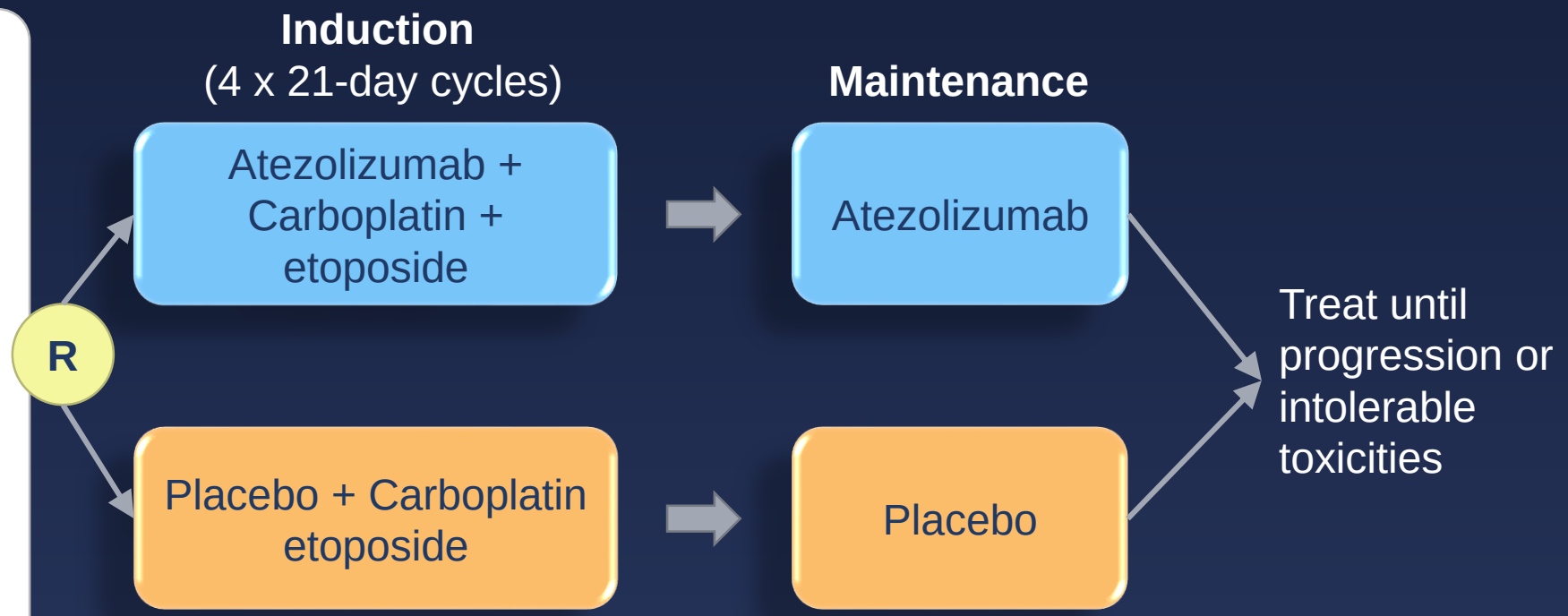
**Which of the following statements accurately summarizes the evidence from the IMpower133 trial of atezolizumab plus chemotherapy versus chemotherapy alone for first-line ES SCLC?**

A. Atezolizumab plus chemotherapy improved OS but not PFS
B. Atezolizumab plus chemotherapy improved both OS and PFS
C. The addition of atezolizumab to chemotherapy did not improve OS or PFS
D. Atezolizumab plus chemotherapy improved PFS but not OS
E. The addition of atezolizumab resulted in an unacceptable level of toxicity

# IMpower133 Phase III Trial of First-Line Atezolizumab Plus Chemotherapy

**Eligibility**

- ES-SCLC, with measurable disease
- No prior systemic therapy
- ECOG PS 0,1
- Pts with asymptomatic brains mets were eligible

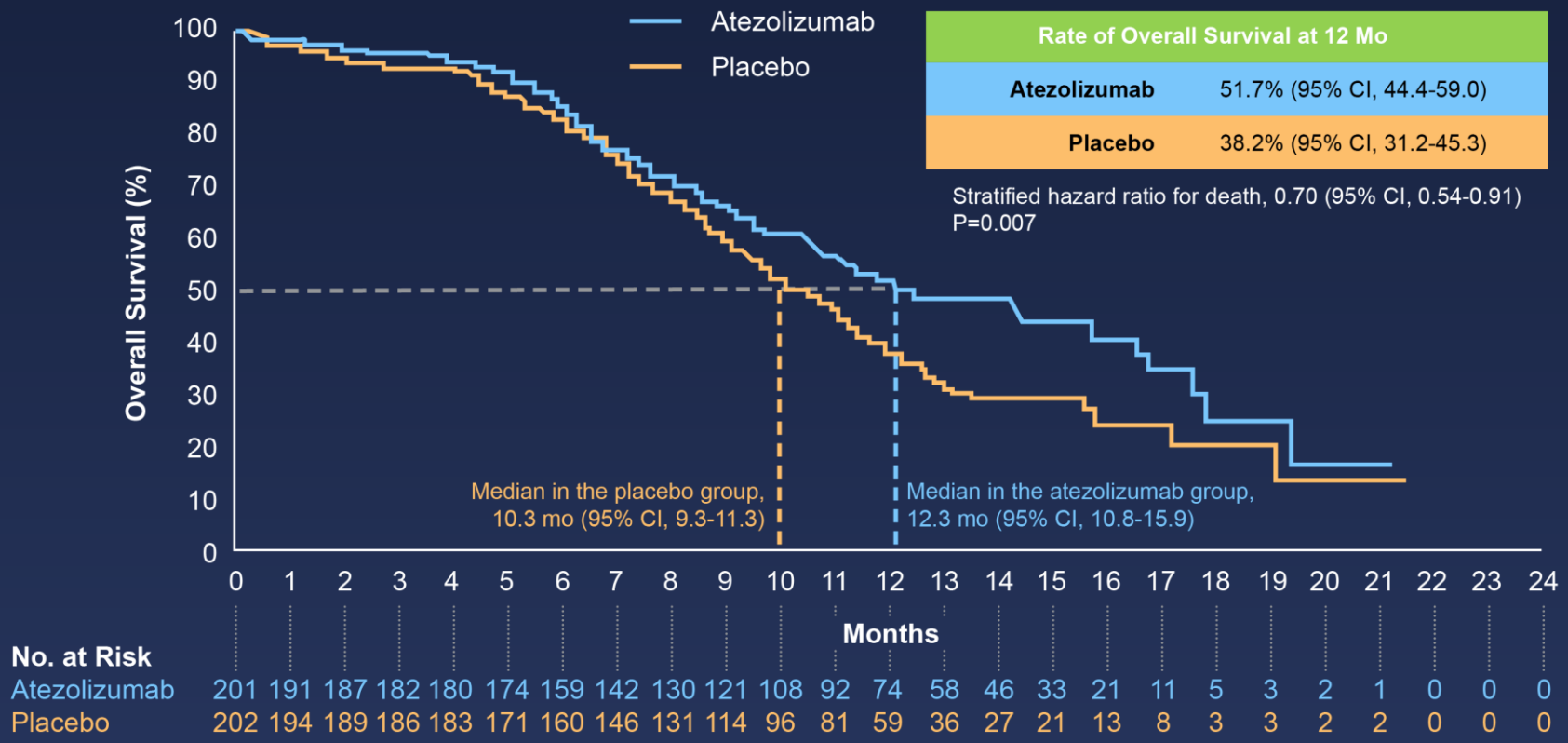



**Co-primary Endpoints**

- Overall survival
- Investigator-assessed PFS

Horn L, et al. *N Engl J Med*. 2018;379:2220-2229.

# IMpower133: Overall Survival

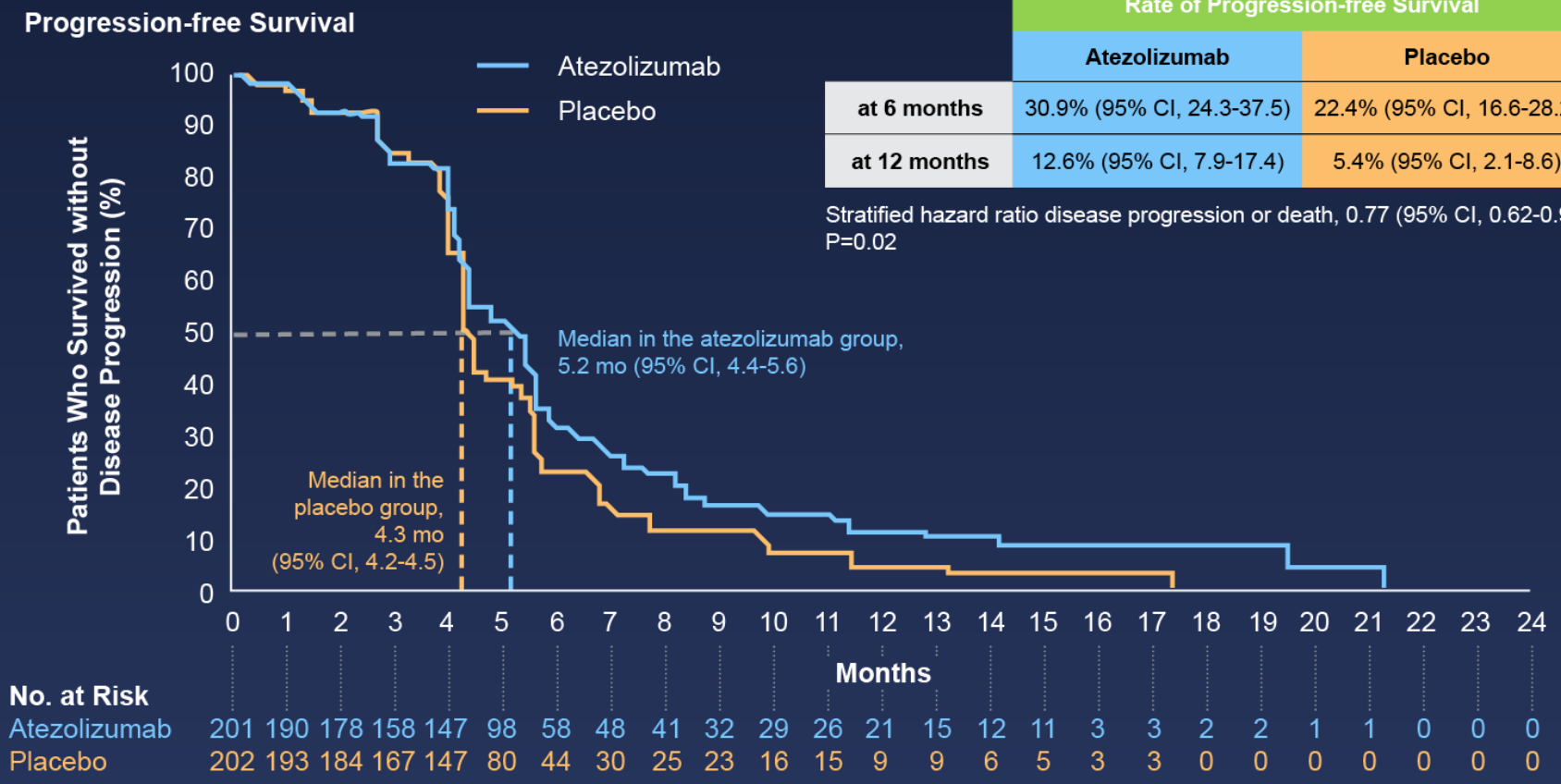



| Rate of Overall Survival at 12 Mo | |
|---|---|
| **Atezolizumab** | 51.7% (95% CI, 44.4-59.0) |
| **Placebo** | 38.2% (95% CI, 31.2-45.3) |

Stratified hazard ratio for death, 0.70 (95% CI, 0.54-0.91)
P=0.007

Horn L, et al. *N Engl J Med*. 2018;379:2220-2229.

# IMpower133: Progression-Free Survival




| | Rate of Progression-free Survival | |
|---|---|---|
| | Atezolizumab | Placebo |
| at 6 months | 30.9% (95% CI, 24.3-37.5) | 22.4% (95% CI, 16.6-28.2) |
| at 12 months | 12.6% (95% CI, 7.9-17.4) | 5.4% (95% CI, 2.1-8.6) |

Stratified hazard ratio disease progression or death, 0.77 (95% CI, 0.62-0.96)
P=0.02

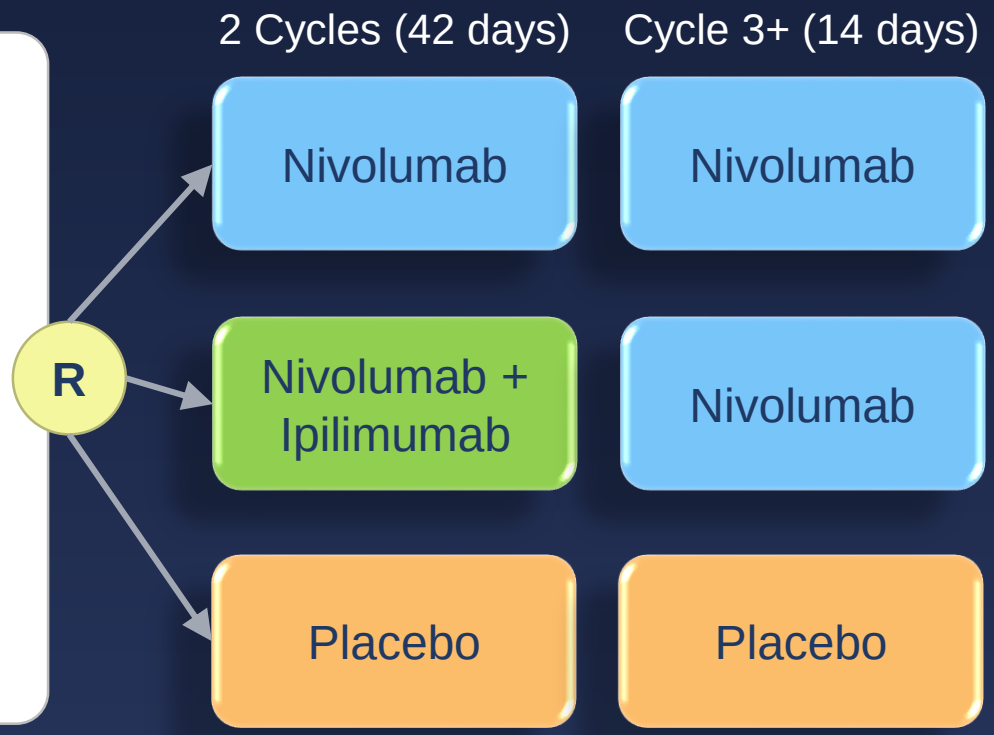
Horn L, et al. *N Engl J Med*. 2018;379:2220-2229.

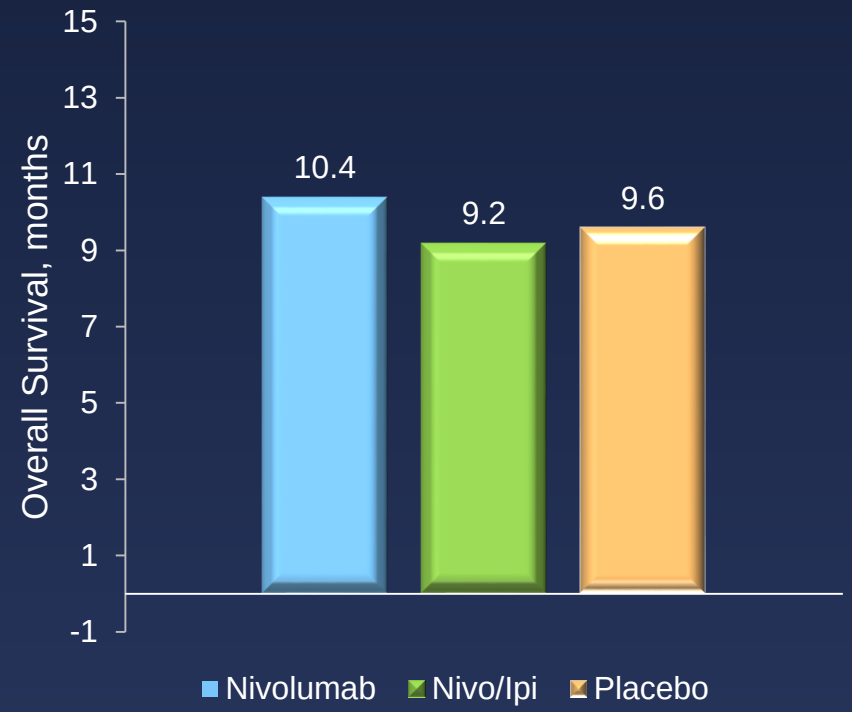
# CheckMate-451 Phase III Trial of Nivolumab With and Without Ipilimumab as Maintenance

**Eligibility**

- ED-SCLC
- Response or stable disease after first-line platinum-based CT
- ECOG PS 0,1

N = 810




**Primary Endpoint**

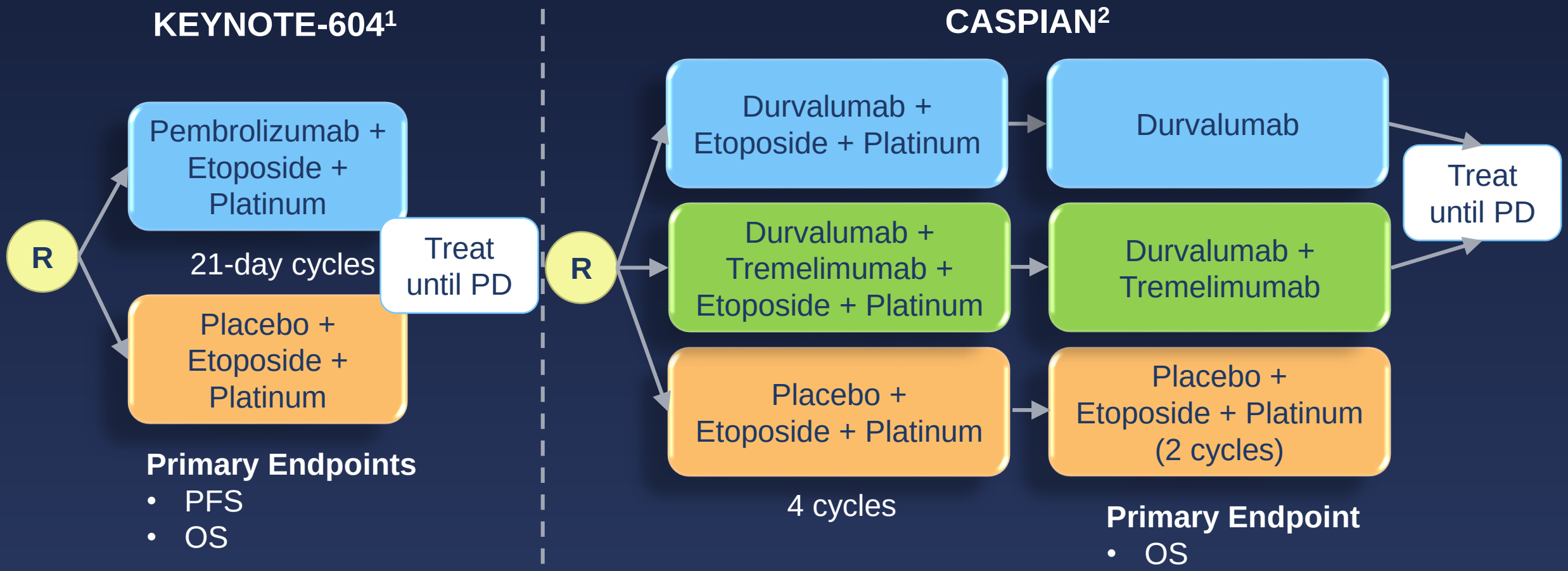
- Overall survival

**Secondary Endpoints**

- PFS, tumor mutation burden

Ready N, et al. *J Clin Oncol*. 2016;34:TPS8579; Owonikoko T, et al. ELCC 2019. Abstract LBA1_PR.

# Other First-Line Phase III Trials KEYNOTE-604 and CASPIAN




1. Rudin C, et al. *J Thorac Oncol*. 2017;12:S2400. 2. Paz-Ares LG, et al. *J Clin Oncol*. 2017;35:TPS8586.

# Question 4

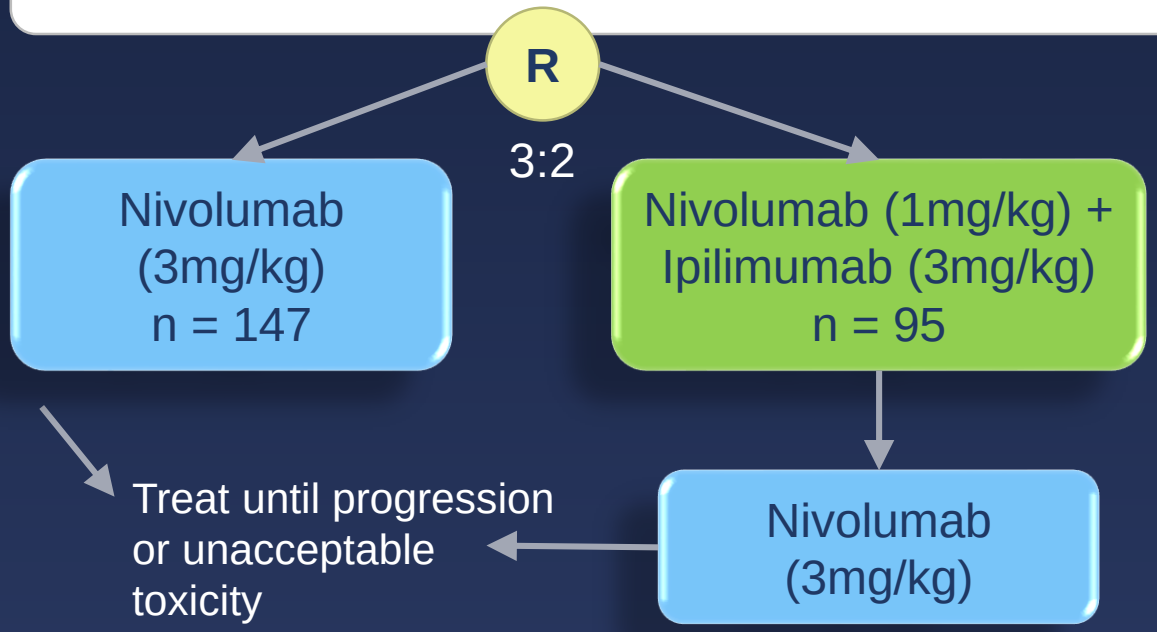
**Which of the following statements accurately summarizes the evidence on checkpoint inhibitors in later lines of therapy?**

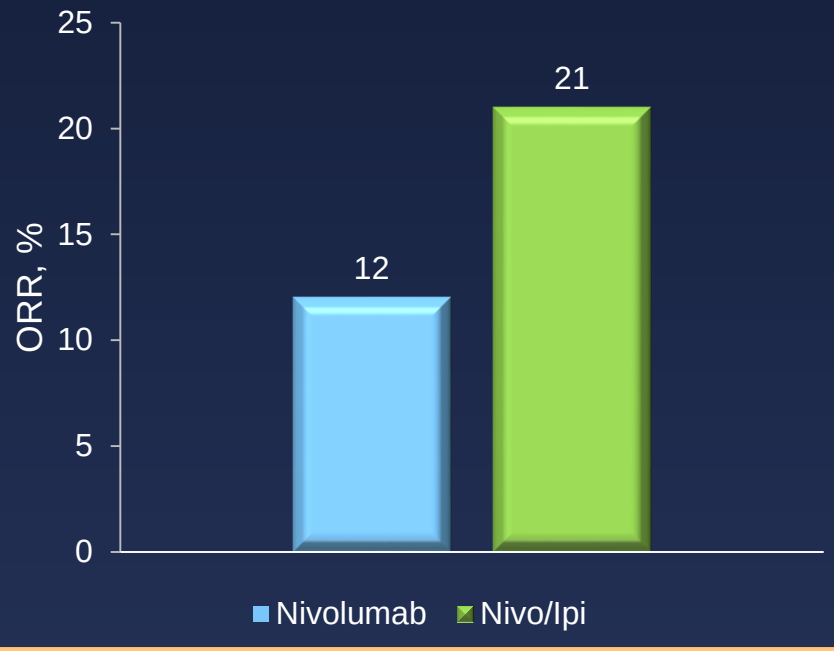
A. Phase 2 evidence demonstrated that both nivolumab and pembrolizumab have efficacy in the third-line setting
B. Pembrolizumab plus chemotherapy improved OS as second-line therapy in a phase 3 trial
C. Maintenance nivolumab plus ipilimumab significantly improved OS in a phase 3 trial
D. Phase 2 evidence demonstrated that nivolumab, pembrolizumab, and atezolizumab each have efficacy in the third-line setting
E. Maintenance pembrolizumab significantly improved OS vs placebo

# CheckMate-032 Phase II Nivolumab

**Eligibility**

- LD- or ED-SCLC
- Recurrence or progression after ≥ 1 platinum-based CT
- ECOG PS 0,1




**OS**

| Nivolumab | Nivolumab+Ipilimumab |
|---|---|
| 4.1 months | 7.8 months |

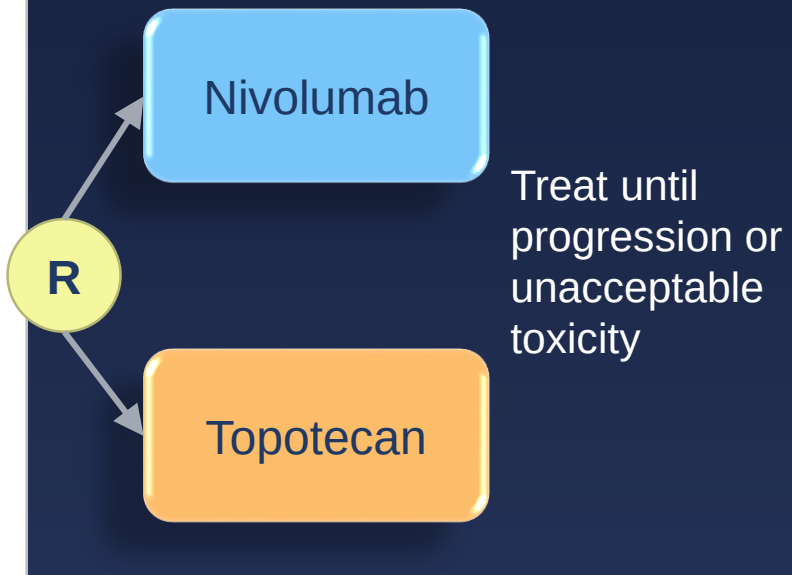
Antonia SJ, et al. *Lancet Oncol*. 2016;17:883-895; Hellmann MD, et al. *J Clin Oncol*. 2017;35:8503-8503.

# CheckMate-331 Phase III Trial of Second-Line Nivolumab

**Eligibility**

- LD- or ED-SCLC
- Recurrence or progression after first-line platinum-based CT
- ECOG PS 0,1

*N* = 480




Treat until progression or unacceptable toxicity

| | Nivolumab | Chemotherapy |
|---|---|---|
| OS, mo (95% CI) | 7.5 (5.7-9.2) | 8.4 (7.0-10.0) |
| PFS, mo (95% CI) | 1.4 (1.4-1.5) | 3.8 (3.0-4.2) |
| ORR, % | 14 | 16 |

*Failed to meet its primary endpoint*

**Primary Endpoint**
- Overall survival

**Secondary Endpoints**
- PFS, ORR

Horn L, et al. *J Clin Oncol*. 2016;34:TPS8578-TPS8578; Reck M, et al. *Ann. Oncol*. 2018;29(suppl 10). Asbstract LBA5.

# Combined Analysis – KEYNOTE-028 and KEYNOTE-158

- 2 or more prior therapies
- *N* = 131
- Median follow-up of 7.7 months

| | |
|---|---|
| **ORR** | **19.3%** (95% CI 11.4%-29.4%) |
| **PFS** | **2 months** (95% CI 1.9-3.4) |
| **OS** | **7.7 months** (95% CI 5.2-10.1) |

12-month PFS rate = **7%**

12-month OS rate = **34%**

24-month PFS = **13%**

24-month OS = **21%**

Chung HC et al. AACR Annual Meeting, 2019 Abstract CT073.

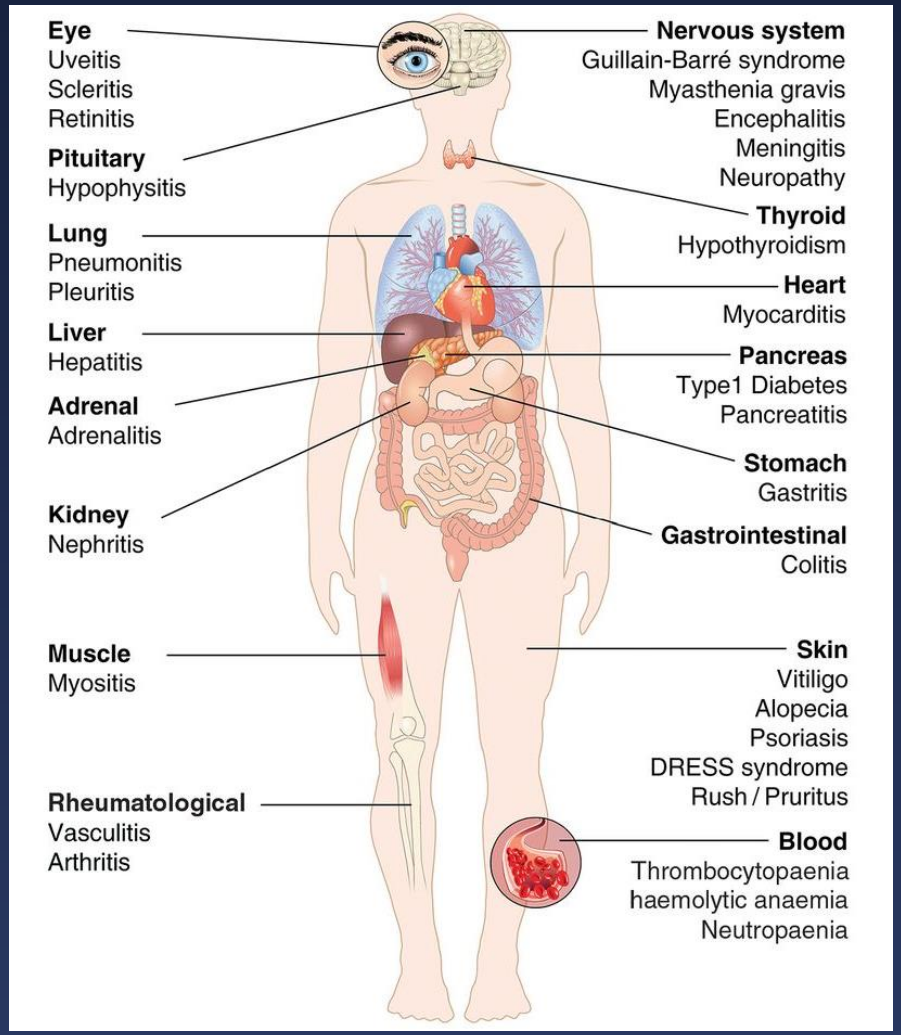
# Question 5

**Which of the following are common irAE associated with checkpoint inhibitors?**

A. Rash and hypothyroidism
B. Cold sensitivity
C. Neutropenia and alopecia
D. Hypertension

# Immune-Related Adverse Events

**Any organ**
**Any time**




***Most common:***

- Rash
- Endocrinopathies
- Gastrointestinal
- Hepatitis

Varricchi G, et al. *ESMO Open*. 2017;2:e000247.

# IMpower133 – Grade 3 or Greater irAE

| | Atezolizumab n = 198 | Placebo n = 196 |
|---|---|---|
| Neutropenia | 23.2% | 24.5% |
| Anemia | 14.1% | 12.2% |
| Decreased neutrophil count | 14.1% | 16.8% |
| Thrombocytopenia | 10.1% | 7.7% |

# Question 6

**Which of the following reflects current guideline recommendations for the management of a grade 2 rash in a patient receiving a checkpoint inhibitor?**

A. Continue immunotherapy, monitor, and prescribe low-dose steroids
B. Withhold immunotherapy, consider low-dose steroid therapy
C. Reduce the dose of immunotherapy, monitor, and prescribe low-dose steroids
D. Discontinue immunotherapy and prescribe high-dose steroids

# Guideline Recommendations for Managing irAEs

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Immunotherapy** | Continue | Withhold<br>Resume when ≤grade 1 | Withhold<br>Consider resuming when ≤grade 1 | Discontinue permanently |
| **Additional Management** | Monitor closely | Low dose prednisone should be considered | Prednisone 1-2 mg/kg/d<br>or<br>Methylprednisone IV 1-2 mg/kg/d | Manage as for grade 3 – consider hospitalization<br>Infliximab if not resolved in 2-3 days |

Steroids should always be tapered over at least 4-6 weeks

Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768.

# Question 7

**Which of the following irAEs is not usually reversible?**

A. Diarrhea
B. Pneumonitis
C. Hepatitis
D. Hypothyroidism

# Management of Endocrinopathies: Key Points[1]

| | |
|---|---|
| **Basics** | • 10% of patients receiving immunotherapy[2]<br>• More common with PD-1/PD-L1 inhibitors<br>• Frequently irreversible |
| **Diagnosis** | • Distinguish primary from secondary causes |
| **Management** | • Hold immunotherapy<br>• Supplement with hormones, monitor levels<br>• Endocrinology consult<br>• Steroids not usually needed for hypo- or hyperthyroidism<br>• Resume immunotherapy once resolved to baseline |

1. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. 2. Barroso-Sousa R, et al. *JAMA Oncology*. 2018;4:173-182.

# Patient Case 1

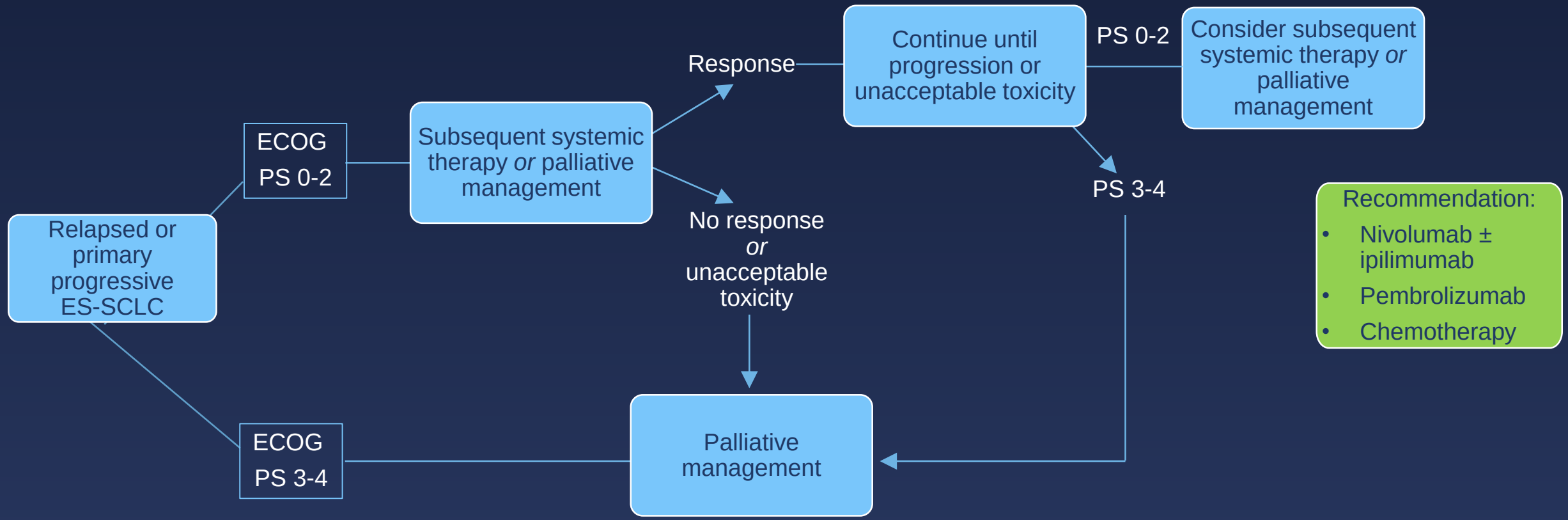
- 70-year old male patient diagnosed with SCLC 2 years prior
- Managed with 4 cycles of carboplatin + etoposide and concurrent radiotherapy and achieves a partial response
- At 18-month follow-up, the patient has recurrent disease
- Receives 4 cycles of carboplatin + etoposide
- At follow-up 6 months later, the patient has recurrent disease and imaging also indicates bone metastases

# Question 8

**Based upon current evidence and clinical guidelines, which of the following therapies would you now recommend for this patient?**

A. Atezolizumab
B. Nivolumab or pembrolizumab
C. Docetaxel
D. Best supportive care alone

# Guideline Recommended Therapy for Relapsed or Progressive ES-SCLC




NCCN Guidelines for SCLC. Version 1.2019.

# Patient Case 2

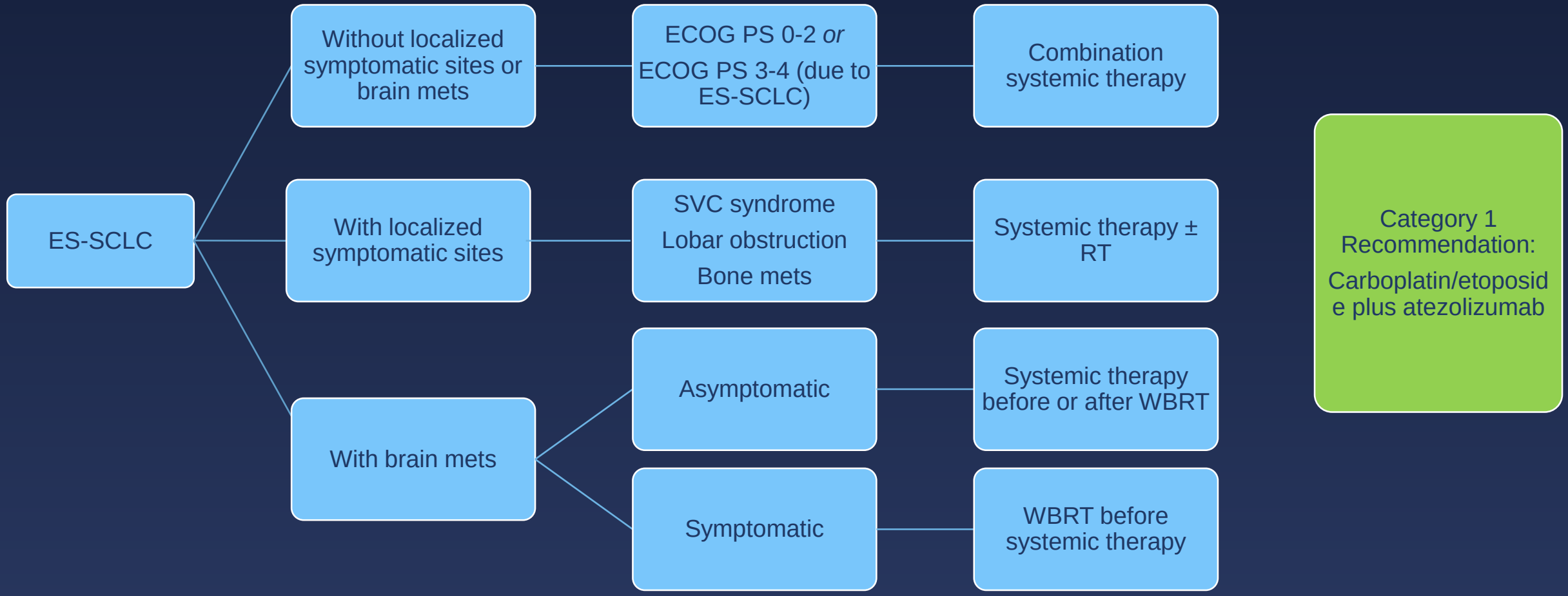
- A 64-year old man presents with shortness of breath and chest pains
- He has a 30-pack year smoking history
- He also notes unintentional weight loss
- A CT scan indicates a 5 cm right hilar mass and mediastinal adenopathy
- FDG PET scan indicates uptake in the right hilar mass, hypermetabolic mediastinal lymph nodes, and multiple liver lesions
- A liver lesion biopsy is positive for SCLC

# Question 9

**Based upon current evidence and clinical guidelines, which of the following therapies would you recommend for this patient?**

A. Cisplatin or carboplatin plus etoposide
B. Atezolizumab plus platinum-based chemotherapy followed by maintenance atezolizumab
C. Platinum-based chemotherapy followed by maintenance nivolumab plus ipilimumab
D. Cisplatin, etoposide, and radiotherapy

# Current Guidelines for Newly Diagnosed ES-SCLC




NCCN Guidelines for SCLC. Version 1.2019.

# Question 10

**You and your patient are discussing atezolizumab plus chemotherapy as initial therapy. Your patient expresses concern about how combining chemotherapy and immunotherapy will affect the number of side effects. Which of the following is the best way to address this with your patient?**

A. Tell your patient that the combination approach is more effective and the side effects are a small price to pay

B. Review the side effects of chemotherapy alone versus combination chemotherapy/immunotherapy, noting that the combination improves survival

C. Provide your patient with written material to read at home and ask them to come back with any questions

D. Because the patient has voiced concerns about combination therapy, tell them that chemotherapy alone would be their best choice

# Shared Decision Making – Three Talk Model


**1**
Work **together**

**2**
Discuss **alternatives**

**3**
Preference-based **decisions**

Elwyn G, et al. *BMJ*. 2017;359:j4891.

# Your Feedback is Important!

## COMPLETE THE EVALUATION FORM AND YOU WILL BE ENTERED INTO A DRAWING FOR A $100* AMAZON GIFT CARD!

*The expense for this gift card is solely funded by RMEI Medical Education, LLC. No supporter funding was used for the expense of this gift card.

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# Post-Test

**Now that you have participated in this education, on a scale from 1-5 (1 being not confident and 5 being completely confident), how confident are you in your ability to _____?**

| | | | | | |
|---|---|---|---|---|---|
| **Incorporate immunotherapy as initial therapy for your patients with Extensive Stage SCLC?** | Not confident | Not very confident | Moderately confident | Somewhat confident | Very confident |
| **Manage immune-related adverse events?** | Not confident | Not very confident | Moderately confident | Somewhat confident | Very confident |

# Post-Test

**Following your participation in this education, how often do you intend to engage in the following practices to educate your patients about immunotherapy?**

| Practice | Always | Sometimes | Never |
|---|---|---|---|
| Offer written material about immunotherapy | | | |
| Direct patients to specific websites | | | |
| Discuss all possible treatment options | | | |
| Describe side effects of immunotherapy | | | |
| Describe how to monitor for side effects of immunotherapy | | | |