Immunotherapy: Changing Patient Outcomes in SCLC

A CME Self-Assessment Program

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

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<td><strong>Incorporate immunotherapy as initial therapy for your patients with Extensive Stage SCLC?</strong></td>
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<td><strong>Manage immune-related adverse events?</strong></td>
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How often do you engage in the following practices to educate your patients about immunotherapy?

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<tr>
<td>Discuss all possible treatment options</td>
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<td></td>
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<tr>
<td>Describe the side effects of immunotherapy</td>
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<tr>
<td>Describe how to monitor for side effects of immunotherapy</td>
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Which of the following are consistent with your current practice for a patient with newly diagnosed ES SCLC?

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<thead>
<tr>
<th></th>
<th>Consistent</th>
<th>Inconsistent</th>
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<tr>
<td>Recommend chemotherapy alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommend chemotherapy plus immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discuss immune-related side effects with patients receiving checkpoint inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reserve immunotherapy for a later line of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide your patients receiving checkpoint inhibitors with pocket cards describing immunotherapy and its side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offer smoking cessation aids to patients who are still smokers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lung Cancer

2nd Most Commonly Diagnosed Cancer

10 years Average OS after first-line therapy

#1 Cancer Mortality

5-10% 5-Year Survival Rate

Lung Cancer

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

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

# Checkpoint Inhibitors

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<tr>
<th>Agent</th>
<th>Target</th>
<th>Approval Status</th>
</tr>
</thead>
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<tr>
<td><strong>Agents approved in Lung Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab¹</td>
<td>PD-1 antibody</td>
<td>SCLC – after 2 prior therapies including platinum-based therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC – patients with progression after platinum-based therapy</td>
</tr>
<tr>
<td>Pembrolizumab²</td>
<td>PD-1 antibody</td>
<td>NSCLC – First-line therapy with pemetrexed/platinum in non-squamous NSCLC; with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>carboplatin/paclitaxel or nab-paclitaxel for first-line squamous; single agent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for NSCLC with high PD-L1 expression; single agent for high PD-L1 after</td>
</tr>
<tr>
<td></td>
<td></td>
<td>platinum-based therapy</td>
</tr>
<tr>
<td>Atezolizumab³</td>
<td>PD-L1 antibody</td>
<td>SCLC – first-line with carboplatin/etoposide for ES-SCLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC – with bevacizumab/paclitaxel/carboplatin for first-line non-squamous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCLC; For patients with progression after platinum-based therapy</td>
</tr>
<tr>
<td>Durvalumab⁴</td>
<td>PD-L1 antibody</td>
<td>NSCLC – unresectable stage III NSCLC following chemoradiotherapy</td>
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## Checkpoint Inhibitors

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<tr>
<td>Cemiplimab&lt;sup&gt;1&lt;/sup&gt;</td>
<td>PD-1 antibody</td>
<td>Approved in other tumor types</td>
</tr>
<tr>
<td>Avelumab&lt;sup&gt;2&lt;/sup&gt;</td>
<td>PD-L1 antibody</td>
<td>Approved in other tumor types</td>
</tr>
<tr>
<td>Ipilimumab&lt;sup&gt;3&lt;/sup&gt;</td>
<td>CTLA-4 antibody</td>
<td>Approved in other tumor types</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>CTLA-4 antibody</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

Checkpoint Inhibitors not yet Approved in Lung Cancer

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
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

**Induction**
(4 x 21-day cycles)
- Atezolizumab + Carboplatin + etoposide
- Placebo + Carboplatin etoposide

**Maintenance**
- Atezolizumab
- Placebo

**Co-primary Endpoints**
- Overall survival
- Investigator-assessed PFS

IMpower133: Overall Survival

IMpower133: Progression-Free Survival

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

Primary Endpoint
- Overall survival

Secondary Endpoints
- PFS, tumor mutation burden

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

N = 810

Overall Survival, months

Nivolumab

Nivolumab + Ipilimumab

Placebo

2 Cycles (42 days)
Cycle 3+ (14 days)

15
13
11
9
7
5
3
1
-1

10.4
9.2
9.6

Nivolumab
Nivo/Ipi
Placebo

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

**KEYNOTE-604**
- **Pembrolizumab + Etoposide + Platinum**
- **Placebo + Etoposide + Platinum**
- Treat until PD

**Primary Endpoints**
- PFS
- OS

**CASPIAN**
- **Durvalumab + Etoposide + Platinum**
- **Durvalumab + Tremelimumab + Etoposide + Platinum**
- **Placebo + Etoposide + Platinum**
- **Placebo + Etoposide + Platinum (2 cycles)**

**Primary Endpoint**
- OS

4 cycles

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

Nivolumab (3mg/kg) n = 147
- Treat until progression or unacceptable toxicity

Nivolumab (1mg/kg) + Ipilimumab (3mg/kg) n = 95

R 3:2

Treat until progression or unacceptable toxicity

OS
- Nivolumab 4.1 months
- Nivolumab+Ipilimumab 7.8 months

ORR, %
- Nivolumab 12
- Nivo/Ipi 21

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*

**Primary Endpoint**
- Overall survival

**Secondary Endpoints**
- PFS, ORR

---

**Treat until progression or unacceptable toxicity**

**Failed to meet its primary endpoint**

**Comparison Table**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, mo (95% CI)</td>
<td>7.5 (5.7-9.2)</td>
<td>8.4 (7.0-10.0)</td>
</tr>
<tr>
<td>PFS, mo (95% CI)</td>
<td>1.4 (1.4-1.5)</td>
<td>3.8 (3.0-4.2)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>14</td>
<td>16</td>
</tr>
</tbody>
</table>

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

# IMpower133 – Grade 3 or Greater irAE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Atezolizumab (n = 198)</th>
<th>Placebo (n = 196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>23.2%</td>
<td>24.5%</td>
</tr>
<tr>
<td>Anemia</td>
<td>14.1%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Decreased neutrophil count</td>
<td>14.1%</td>
<td>16.8%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10.1%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>
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

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

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

Question 7

Which of the following irAEs is not usually reversible?

A. Diarrhea
B. Pneumonitis
C. Hepatitis
D. Hypothyroidism
# Management of Endocrinopathies: Key Points

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

Recommendation:
- Nivolumab ± ipilimumab
- Pembrolizumab
- Chemotherapy

Palliative management

Subsequent systemic therapy or palliative management

ECOG PS 0-2

Response
Continue until progression or unacceptable toxicity

ECOG PS 3-4

No response or unacceptable toxicity
Consider subsequent systemic therapy or palliative management

ECOG PS 0-2

Relapsed or primary progressive ES-SCLC

ECOG PS 3-4

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

**ES-SCLC**

- Without localized symptomatic sites or brain mets
  - ECOG PS 0-2 or ECOG PS 3-4 (due to ES-SCLC)
  - Combination systemic therapy

- With localized symptomatic sites
  - SVC syndrome
    - Lobar obstruction
    - Bone mets
  - Systemic therapy ± RT

- With brain mets
  - Asymptomatic
    - Systemic therapy before or after WBRT
  - Symptomatic
    - WBRT before systemic therapy

**Category 1 Recommendation:** Carboplatin/etoposide plus atezolizumab

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

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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This sweepstakes is managed by RMEI Medical Education, LLC (RMEI), a full-service medical education company. The winner will be selected via automated random drawing on a monthly basis from among all eligible entries and notified through the contact information provided. In accordance with our privacy policy, we do not share your information with any third parties. By entering the sweepstakes, you grant RMEI permission to use your email address to reach you for notification and prize fulfillment. Only individuals who complete the evaluation forms and provide contact information will be eligible to win. Open to those who have a US postal address and who are 18 years or older. Only one prize per person and per household will be awarded. The prize will be a $100 Amazon gift card.
**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 __________?

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| **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?

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