

Transcript Details

This is a transcript of an educational program accessible on the ReachMD network. Details about the program and additional media formats for the program are accessible by visiting: <https://reachmd.com/programs/cme/immunotherapy-changing-patient-outcomes-in-sclc/10710/>

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Immunotherapy: Changing Patient Outcomes in SCLC

Dr. Leora Horn:

Hello and welcome to Immunotherapy: Changing Patient Outcomes in Small Cell Lung Cancer, 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 extensive stage small cell lung cancer and offer expert insight into effectively and safely incorporating immunotherapy into your practice to improve patient outcomes.

Lung cancer is the second most common cancer diagnosed and the number one cause of cancer-related mortality in the United States. With the incidence of cigarette consumption declining, the incidence of small cell lung cancer has also decreased. However, 10 to 15% of all new lung cancer diagnoses in the U.S. each year are attributed to small cell lung cancer. While we have identified multiple driver mutations in non-small cell lung cancer, the absence of driver mutations in small cell lung cancer has limited our progress. What we do know is that p53 and RB are universally lost in patients with small cell lung cancer. We also know that patients with small cell lung cancer have tumors with a high mutation burden based on data from the TCGA.

Small cell lung cancer is broken down into two stages. Limited stage disease is equivalent to stage I-III, while extensive stage disease is equivalent to stage IV. Limited stage disease is managed with concurrent chemoradiation therapy while extensive stage disease is managed with systemic therapy and radiation is used primarily to palliate symptoms. Initial therapy is platinum-based doublet therapy and second line therapy is topotecan. Immunotherapy is changing the treatment paradigm and improving options for patients with this disease.

Question 1

The immune checkpoint inhibitors that are currently approved target either CTLA4 or the PD-1/PD-L1 axis. PD-1 is expressed in T-cells while PD-L1 is expressed on tumor cells, and antibodies either bind to PD-1 or PD-L1 and block this interaction. Agents that are approved target either PD-1 or PD-L1. PD-1 is expressed in T-cells while PD-L1 is expressed on the tumor cell. Binding with PD-1 to PD-L1 is normally a negative interaction that down regulates the immune system. Agents that block the PD-1 and PD-L1 axis allow activation of an immune response. The other agents approved in this area are the CTLA-4 inhibitors that target the T-cell, increasing activation of T-cells and trafficking of the T-cells into the tumor microenvironment.

Nivolumab and pembrolizumab are both approved in non-small cell lung cancer and are anti-PD-1 antibodies. Nivolumab is also approved as a third line therapy in patients with small cell lung cancer. Atezolizumab and durvalumab are also approved in patients with non-small cell lung cancer and they are anti-PD-L1 antibodies. Atezolizumab was recently FDA approved in combination with platinum-based chemotherapy for patients with small cell lung cancer.

Ipilimumab is currently the only anti-CTLA-4 inhibitor approved for patients with melanoma and is being investigated in other tumor types. Other agents that are currently under investigation include avelumab in patients with non-small cell lung cancer, although it is approved in other tumor types and tremelimumab, another CTLA-4 inhibitor that is currently in phase 3 in patients with both small cell and non-small cell lung cancer.

Question 2

The correct answer is Atezolizumab plus carboplatin and Etoposide.

Question 3

The correct answer is Atezolizumab plus chemotherapy improved both overall survival and progression free survival.

IMpower133 was a global phase III trial that compared carboplatin and etoposide with or without atezolizumab in patients with newly diagnosed extensive stage small cell lung cancer. An important consideration in this trial is that patients have to have an ECOG performance status of 0 or 1 and patients with asymptomatic brain metastases were eligible only after those brain metastases were radiated. After four cycles of induction therapy with chemotherapy with or without atezolizumab patients continued on maintenance therapy until disease progression or intolerable toxicities. The co-primary endpoints were progression free survival and overall survival.

This study met its primary endpoint with a significant improvement in overall survival with patients treated with atezolizumab and chemotherapy compared to placebo. With the median overall survival of 10.3 months in patients in the placebo group compared to 12.3 months for patients receiving atezolizumab. A 12-month overall survival, when we looked at the landmark analysis, was also improved for patients receiving atezolizumab with a 12-month overall survival of 52% compared to 38% for patients on placebo.

There was also an improvement in progression free survival for patients treated with chemotherapy and atezolizumab with a median progression free survival of 5.2 months for patients receiving atezolizumab and chemotherapy compared to 4.3 months for patients receiving placebo.

We recently had data from CheckMate-451. This was a slightly different study design for patients who were treated with four to six cycles of induction chemotherapy with platinum and etoposide and those patients who had a response to therapy or stable disease were randomized to either nivolumab alone, nivolumab and ipilimumab or placebo. Unfortunately, this study did not meet its primary endpoints. There was no significant improvement for patients treated with nivolumab or nivolumab and ipilimumab compared to placebo with a median overall survival of 10.4 months, 9.2 months and 9.6 months, respectively.

There are two ongoing phase III studies in the first line setting. The KEYNOTE-604 study is a very similar design to the IMpower133 study looking at pembrolizumab and platinum-based chemotherapy compared to platinum-based chemotherapy and placebo in patients with extensive stage disease. The CASPIAN study is looking at platinum and etoposide with or without durvalumab or durvalumab and tremelimumab in patients with extensive stage disease. We are anticipating data from these studies to read out in the next year.

Question 4

The correct answer is phase II evidence demonstrated that both nivolumab and pembrolizumab have efficacy in the third line setting.

The data from the nivolumab comes from the CheckMate-032 study. This was a large phase I study that looked at nivolumab with or without ipilimumab in patients who had progressed on platinum-based chemotherapy. This study demonstrated a response rate of 12% for patients treated with nivolumab alone compared to 21% for patients treated with nivolumab and ipilimumab. The overall survival for patients treated with nivolumab alone was 4.1 months compared to 7.8 months for patients treated with nivolumab and ipilimumab. There has also been some interesting data looking at tumor mutation burden and how that predicts response to second and third line nivolumab or nivolumab and ipilimumab in patients with small cell lung cancer suggesting patients with high tumor mutation burden have a benefit with nivolumab and ipilimumab.

The CheckMate-331 study looked at nivolumab compared to chemotherapy with either topotecan or amrubicin in patients who had progressed on first line chemotherapy. Unfortunately, this study also failed to meet its primary endpoint with no significant improvement in overall survival for patients treated with nivolumab compared to chemotherapy where the median overall survival was 7.5 months for nivolumab and 8.4 months for patients treated with chemotherapy. An interesting subset analysis did show that patients with platinum-resistant or refractory disease appeared to have some benefit with nivolumab compared to chemotherapy; however, overall, this was a negative study.

The other data that we have in this setting is a combined analysis of the KEYNOTE-028 and 158 studies. These are studies looking at single agent pembrolizumab as a second line therapy or beyond in patients with extensive stage small cell lung cancer. An updated analysis that included 131 patients noted an almost 20% response rate for patients treated with pembrolizumab. Progression free survival was not impressive at two months, but the median overall survival was 7.7 months for patients enrolled in these trials. There are ongoing studies, as mentioned before, looking at pembrolizumab in combination with chemotherapy in the first line setting in patients with extensive stage small cell lung cancer.

Question 5

The correct answer is rash and hypothyroidism.

Immune-related adverse events can commonly occur in patients treated with checkpoint inhibitors. However, the majority of adverse events are grade 1-2. It is important to remember that these drugs can really affect any organ including endocrinopathies, pneumonitis, GI toxicities, eye toxicities, skin toxicities, CNS toxicities, bone and joint toxicities as well as blood toxicities.

In the IMpower133 study, we did not see a significant increase in grade 3-4 adverse events for patients treated with carboplatin, etoposide, and atezolizumab compared to patients treated with chemotherapy alone. Importantly, in this study we also did not see an increased incident of perineoplastic syndromes in patients treated with combination chemotherapy and a checkpoint inhibitor as we know perineoplastic syndrome can be common in patients with small cell lung cancer.

Question 6

The correct answer is withhold immunotherapy, consider low-dose steroid therapy, and resume immunotherapy if toxicity results to grade 1 or below.

There are multiple guidelines available to help physicians in managing immune-related adverse events. For patients with grade 1 adverse events, it is okay to continue therapy and monitor closely. While patients with grade 2 adverse events, therapy should be held and they can resume therapy once the toxicity is less than or equal to grade 1. For the majority of grade 3 and 4 adverse events, treatment should be discontinued permanently and patients should be treated with steroids 1-2 mg/kg and an appropriate subspecialist may need to be consulted to help in managing the toxicity. The steroids should be tapered over a four to six-week period.

Question 7

The correct answer is hypothyroidism.

For patients with endocrinopathies, even if they are grade 3 and 4, it is reasonable to continue to treat patients with their checkpoint inhibitor while placing them on the appropriate supplements. It is important to remember that endocrinopathies are quite common in patients receiving checkpoint inhibitor therapy, occurring in approximately 10% of patients. They commonly occur with both PD-1 and PD-L1 inhibitors and they are frequently irreversible which is different from patients who experience toxicities such as colitis or pneumonitis which are often reversible when treated with steroids. It is important to see these patients in collaboration with an endocrinologist and help distinguish primary from secondary causes.

A 70-year-old, Caucasian male smoker was diagnosed with small cell lung cancer two years prior. He was initially treated with four cycles of carboplatin and etoposide with concurrent radiation therapy and had a partial response to therapy. After 18 months, he had recurrent disease and was treated once again with carboplatin and etoposide as he had chemo-sensitive disease. Following his fourth cycle of therapy, imaging noted progressive disease with new bone metastases.

Question 8

The correct answer is nivolumab or pembrolizumab.

The current guidelines for patients with extensive stage small cell lung cancer who had progressed on platinum-based chemotherapy and are candidates for subsequent therapy include either nivolumab or nivolumab/ipilimumab or single-agent pembrolizumab. Chemotherapy is also a potential option for these patients. Remembering that at this time, nivolumab is the only FDA approved therapy for patients in the third line setting.

A 64-year-old man presents with dyspnea and chest pain. He has a 30-pack year smoking history and no other comorbidities. He also notes a 30-pound unintentional weight loss. A CT scan shows a 5 cm right hilar mass and mediastinal adenopathy. A PET scan notes increased uptake in his hilar mass, the mediastinal adenopathy as well as multiple liver lesions. A biopsy of the liver lesions is positive for small cell lung cancer.

Question 9

The correct answer is atezolizumab plus platinum-based chemotherapy followed by maintenance atezolizumab.

Current guidelines for patients with newly diagnosed extensive stage small cell lung cancer depend on the patient's presenting symptoms. Patients with localized symptomatic sites. The current guidelines for patients with newly diagnosed extensive stage small cell lung cancer depend on the extent of disease and presenting symptoms. Patients without localized symptomatic sites of brain metastases should be considered for combination systemic therapy with atezolizumab. Patients with localized symptomatic sites can be considered for chemotherapy and radiation therapy. Patients with brain mets at diagnosis, if they are asymptomatic, they can be considered for systemic therapy and carboplatin, etoposide, and atezolizumab is an option, although these patients were not included in the IMpower133 study. In patients with symptomatic brain metastases, they may require whole brain radiation therapy prior to starting on systemic therapy with carboplatin, etoposide and atezolizumab.

Question 10

The best answer is review the side effects of chemotherapy alone versus combination chemotherapy with immunotherapy, noting that

the combination therapy improves progression free survival and overall survival.

When working with patients, we want to work on shared decision-making. It is important for the physician and the care team to work together to understand the patient's preferences to provide the patients with different options of therapy and help them come to a decision on therapy that they can feel is in their best interest.

Thank you for participating in this self-assessment program. Please do not forget to complete the program evaluation to receive CME credit.