Dear Colleague,

The management of squamous cell cancer of the head and neck (SCCHN) has come to include the integrated use of multiple therapeutic techniques, from surgery and radiotherapy to cytotoxic and targeted drugs. Despite our ability to cure patients through the use of these approaches, many patients with both human papilloma virus (HPV)-positive and -negative disease still experience substantial treatment-related toxicity, including late effects of treatment. Keeping this in mind, one important question to answer is: can we develop treatment strategies that are active against SCCHN, while limiting the toxicity burden our patients face?

Encouragingly, much recent evidence has suggested that novel, immunotherapeutic approaches may be one rational approach to treating head and neck cancer in a range of disease and treatment settings, while potentially offering a less toxic management option. Immune checkpoint blockade, which has proven benefits in several solid tumor settings, represents an intriguing area for clinical development in head and neck cancer.

In this two-part CME activity, I review the rationale for clinical testing of immunotherapy, including immune-checkpoint blockade, in head and neck cancer and summarize clinical efficacy evidence on immune checkpoint inhibitors in head and neck cancer. In addition, I’ll discuss research on the question of which patients may benefit the most from the use of novel immunotherapy, and I’ll review several ongoing, important clinical trials testing checkpoint blocking agents in patients with recurrent/metastatic disease. I hope you find this educational activity useful in your daily practice.

Sincerely,

Barbara Ann Burtness, MD
Activity Description and Educational Objectives
In this activity, an expert in the management of head and neck cancers discusses the rationale for and clinical potential of novel immunotherapeutic approaches as disease management.

Upon completion of this activity, participants should be better able to:
• Describe the rationale for clinical testing of immunotherapy, including immune checkpoint blockade, in head and neck cancer
• Summarize clinical efficacy evidence on immune checkpoint inhibitors in head and neck cancer
• Identify immune-related adverse events and potential management strategies associated with the use of novel immunotherapy
• Select patients with recurrent/metastatic head and neck cancer who may be eligible for clinical trials testing novel immunotherapies

Target Audience
This activity has been designed to meet the educational needs of oncologists and other clinicians involved in the management of patients with head and neck cancer.

Requirements for Successful Completion
In order to receive credit, participants must view the activity and complete the post-test and evaluation form. A score of 70% or higher is needed to obtain CME credit. There are no pre-requisites and there is no fee to participate in this activity or to receive CME credit. Statements of Credit are awarded upon successful completion of the post-test and evaluation form.

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Barbara Ann Burtness, MD, has a financial interest/relationship or affiliation in the form of:
Consultant for Amgen; AstraZeneca; Boehringer Ingelheim Pharmaceuticals, Inc.; Merck & Co., Inc.; and VentiRx Pharmaceuticals.
Barbara Burtness, MD, does intend to discuss either non-FDA-approved or investigational use for the following products/devices: durvalumab, pembrolizumab, nivolumab, atezolizumab.

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Historically, locally advanced head and neck cancers have been curable through approaches such as surgery and combined-modality radiation-based treatments. These have been associated with considerable toxicity, and they can often leave patients with late sequelae that are quite troublesome.

In this program, I’ll be reviewing the rationale for testing immunotherapy in head and neck cancer, along with the early evidence that supports the further testing of checkpoint inhibitors in this disease. I’ll also discuss evidence on the search for biomarkers as an aid to selecting patients for immunotherapy, and I’ll profile several important clinical trials that may give us a better sense of the role of checkpoint blockade in head and neck cancer management.

Let’s begin by exploring the rationale for immunotherapy, specifically for immune checkpoint blockade in head and neck cancer. PD-1 is a negative costimulatory receptor which is expressed primarily on T cells. Tumor-infiltrating lymphocytes induce cells in the tumor microenvironment to express PD-L1 and bind to PD-1 receptor to suppress immune surveillance. And we know that prognosis correlates with the presence both of tumor-infiltrating lymphocytes and PD-L1 expression in many cancers, including head and neck cancer.
How, then, does immune checkpoint blockade work in cancer? We believe that this occurs in two phases. The priming phase occurs in the area of the lymph node where the T cell comes into contact with a dendritic cell, and the CTLA-4 pathway potentially downregulates T-cell activity.

Blocking CTLA-4 allows the T cell to remain active. The T cell then migrates into the peripheral tissue and comes into contact with the cancer cell during what we refer to as the effector phase. During this phase, the PD-1 pathway downregulates T-cell activity, allowing cancer cells to evade the immune system. Blocking the PD-1 pathway, either via PD-1 receptor on the T cell or the ligand on the cancer cell, allows the T cell to remain activated.

How Checkpoint Blockade Works in Cancer

<table>
<thead>
<tr>
<th>Agent Molecule/Target</th>
<th>Current Status</th>
</tr>
</thead>
</table>
| Nivolumab | Fully human IgG4; PD-1 |• Phase 3 trial completed  
• Ongoing first line |
| Pembrolizumab | Humanized IgG4; PD-1 |• Phase 1b data reported  
• Phase 3 trials ongoing |
| Durvalumab (MEDI4736) | Engineered human IgG1; PD-L1 |• Phase 3 trials ongoing |
| Atezolizumab (MPDL3280A) | Engineered human IgG1; PD-L1 |• Early phase multtumor studies (including SCCHN) |

These observations have led to the development of several PD-1–targeting therapies, known as the immune checkpoint inhibitors. And these have been tested in a number of different cancers. The most extensive clinical experience with these agents has been in lung cancer, renal cell cancer, and melanoma. Many PD-1–targeting agents have, however, been tested in head and neck cancer, and we now have several agents in late-phase trials. I’d like to go through this table with you now.

First, we see nivolumab. This is a fully human IgG4 which targets PD-1. The first phase 3 trial of this has been completed, and there’s an ongoing phase 3 trial for first-line patients. Pembrolizumab is a humanized IgG4 antibody, which, again, targets PD-1. And this is an agent for which we have extensive data from a phase 1b expansion trial, and phase 3 trials are currently ongoing.

Durvalumab, which you may remember as MEDI4736, is an engineered human IgG1. This targets the ligand PD-L1, and phase 3 trials are ongoing.

And the drug that was previously known as MPDL3280A, now known as atezolizumab, is an engineered human IgG1 which targets PD-L1. And this agent is in early-phase trials in a number of different solid tumors, including squamous cell cancer of the head and neck.

KEYNOTE-012 Trial Design

<table>
<thead>
<tr>
<th>Patients</th>
<th>Pembrolizumab 200 mg Q3W</th>
</tr>
</thead>
</table>
|• Recurrent or metastatic SCCHN, regardless of PD-L1 or HPV status  
• Have measurable disease based on RECIST 1.1  
• ECOG performance status of 0 or 1 |
|• Treatment for 24 months  
• Documented disease progression  
• Intolerable toxicity |

Response assessment: every 8 weeks

Primary endpoints: ORR per modified RECIST 1.1 by investigator review; safety
Secondary endpoint: PFS, OS, duration of response

ECOG: Eastern Cooperative Oncology Group; HPV: human papilloma virus; ORR: overall response rate; RECIST: Response Evaluation Criteria In Solid Tumors.

To date, we’ve seen the most clinical data on checkpoint blockade in head and neck cancer from early studies of the IgG4 humanized antibody against PD-1, pembrolizumab. The schema that you see here is from the KEYNOTE-012 trial, which was a phase 1b expansion trial that looked at pembrolizumab in a number of different solid tumors.

Initially, patients had to have some evidence of PD-L1 expression in their tumors or in tumor stroma for enrollment, but eventually during expansion, they also looked at patients who were PD-L1-negative. Patients had to have recurrent or metastatic squamous cell cancer of the head and neck. They had to have measurable...
disease. They had to have good performance status. By and large, these were heavily pretreated patients, although there was a small number of patients who had declined first-line therapy.

Patients were treated with pembrolizumab 200 mg every 3 weeks, and treatment could continue for 24 months, unless patients had intolerable toxicity or documented disease progression. There were a small number of patients who had documented disease progression but appeared to have clinical benefit who were allowed to stay on trial for an additional cycle to see if there was evidence for a late response.

WE NOW HAVE UPATED RESULTS FROM AN EXPANSION COHORT WITH 117 PATIENTS, SHOWING THAT AN OVERALL RESPONSE RATE WAS SEEN OF 25% IN ALL PATIENTS. AND YOU CAN SEE THAT THIS WAS FAIRLY COMPARABLE AT 20% FOR THE HPV-POSITIVE PATIENTS AND 27% IN THE HPV-NEGATIVE PATIENTS. THERE WAS ONE PATIENT WHO HAD A CLINICAL COMPLETE RESPONSE, AND THIS WAS A PATIENT WHO HAD HPV-POSITIVE DISEASE.

Looking at tumor shrinkage in this waterfall plot, we can see that 56% of patients experienced a decrease in target lesions, and that this was seen both for HPV-positive and for HPV-negative patients.

We now have updated results from an expansion cohort with 117 patients, showing that an overall response rate was seen of 25% in all patients. And you can see that this was fairly comparable at 20% for the HPV-positive patients and 27% in the HPV-negative patients. There was one patient who had a clinical complete response, and this was a patient who had HPV-positive disease.

KEYNOTE-012: Pembrolizumab Efficacy (Response)

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Total (N = 117)</th>
<th>HPV+ (n = 34)</th>
<th>HPV− (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>0 (%)</td>
<td>0 (%)</td>
<td>22 (27.2)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (0.9)</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>28 (23.9)</td>
<td>6 (17.6)</td>
<td>22 (27.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>29 (24.8)</td>
<td>9 (26.5)</td>
<td>19 (23.5)</td>
</tr>
</tbody>
</table>


Looking at tumor shrinkage in this waterfall plot, we can see that 56% of patients experienced a decrease in target lesions, and that this was seen both for HPV-positive and for HPV-negative patients.

KEYNOTE-012: Treatment Exposure and Response Duration

CR: complete response; PD: progressive disease; PR: partial response.

Looking at treatment exposure and response duration, responses typically occurred between week 8 and 16 after therapy initiation. The median duration of response has not yet been reached in these data. Forty patients remained on treatment at the time of the presentation at ASCO in 2015, and 86% of responding patients remained in response.

A Visual Representation of Response to PD-1 Therapy in HNC

HNC: head and neck cancer.

Before moving on to safety findings from the study, I’d like to briefly show an illustration of how these responses can manifest in the clinic. These are taken from a patient who received pembrolizumab on the KEYNOTE-012 trial. As you can see, the patient had measurable disease in the lungs.
If you look at the images from cycle 4, found in the middle two panels, you can see that there was a 28% reduction in the size of these target lesions, and by the time the patient got to cycle 8, they had reduced in size by more than 50%.

We also learned from this study that pembrolizumab appeared to be well tolerated. Overall adverse events included fatigue, decreased appetite, hypothyroidism, rash, and pruritus. And you'll note that these toxicities are reminiscent of the clinical experience in melanoma and in lung cancer.

In sum, pembrolizumab was demonstrated to be active in head and neck cancer, with more than half of patients experiencing reductions in target lesions. The activity was similar in patients with HPV-associated and HPV-negative disease, and this drug has now moved into phase 3 testing.

Other checkpoint inhibitors have also been studied in head and neck cancer, including durvalumab, which you may remember as MEDI4736. This is a human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity. This agent was tested in an ongoing phase 1/2, multicenter, open-label study in multiple solid tumors that included squamous cell cancer of the head and neck. And the dose that was tested was 10 mg/kg on an every-2-week basis for 1 year.

**KEYNOTE-012: Pembrolizumab Safety and Summary**

- Overall adverse events included:
  - Fatigue (17.2%)
  - Decreased appetite (7.3%)
  - Hypothyroidism (7.3%)
  - Rash (7.3%)
  - Pruritus (6.8%)
- Similar to IRAEs noted with checkpoint inhibitors in other tumor settings

- Pembrolizumab active in HNC, with more than half of patients experiencing reductions in target lesions
- Similar activity in HPV+ and HPV- disease

*Please see the Practice Aid in this program for a summary of how to manage immune-related adverse events associated with checkpoint inhibitors in the solid tumor setting.

**Durvalumab: Initial Findings in SCCHN**

- Human IgG1 mAb
- Blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity
- Tested in an ongoing phase 1/2, multicenter, open-label study in multiple solid tumor types, including SCCHN at a dose of 10 mg/kg Q2W for 1 year

**Durvalumab in SCCHN: Efficacy Summary**

<table>
<thead>
<tr>
<th>Tumor Response Overall and by PD-L1 Status</th>
<th>Durvalumab 10 mg/kg</th>
<th>PD-L1+ (n = 22)</th>
<th>PD-L1- (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST response (ORR), n/N (%), 95% CI</td>
<td>7/82 (11)</td>
<td>4/22 (18)</td>
<td>3/37 (9)</td>
</tr>
<tr>
<td>DCR 24 weeks, n/N (%), 95% CI</td>
<td>9/62 (15)</td>
<td>4/22 (18)</td>
<td>4/37 (11)</td>
</tr>
<tr>
<td>Range of ongoing duration of response, weeks</td>
<td>16.1+ to 55.4+</td>
<td>41.1+ to 53.1+</td>
<td>16.1+ to 55.4+</td>
</tr>
<tr>
<td>Ongoing responders, n/N (%)</td>
<td>5/7 (71)</td>
<td>2/4 (50)</td>
<td>3/3 (100)</td>
</tr>
</tbody>
</table>

* DCR (defined as CR + PR + SD ≥ 24 weeks) and ORR (confirmed CR and PR) are based on RECIST v1.1. Duration of response for the 2 patients no longer responding per RECIST were 8.4 and 56.3 weeks; PD-L1 status was determined via the PD-L1 (SP263) IHC assay.

**Results from this study in the squamous cell cancer of head and neck population were recently reported from 62 patients. This early study, encouraging and durable antitumor activity was noted, including in heavily pretreated patients. There was some indication that PD-L1 expression correlated with response rate,**
so you can see from this table that the response rate in the PD-L1-expressing cancers was 18%, compared to 8% for the PD-L1 non-expressing cancers.

Dr. Burtness: In the KEYNOTE-012 study, evaluation of PD-L1 expression is ongoing, but the data that we've seen to date from this cohort suggests that PD-L1 expression correlates with benefit from pembrolizumab. Other evidence from the same trial suggested that a signature of interferon-gamma response genes may also be potentially useful as a biomarker for pembrolizumab activity in head and neck cancer.
Is There a Future for Immunotherapy in Head and Neck Cancer?

PD-L1 Expression as a Marker in SCCHN

**PD-L1 Prevalence Determined With a Genentech/Roche Anti-PD-L1 IHC Assay**

<table>
<thead>
<tr>
<th>Indication</th>
<th>PD-L1+ (IC), %</th>
<th>PD-L1+ (TC), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>184</td>
<td>26</td>
</tr>
<tr>
<td>RCC</td>
<td>88</td>
<td>10</td>
</tr>
<tr>
<td>Melanoma</td>
<td>56</td>
<td>5</td>
</tr>
<tr>
<td>SCCHN</td>
<td>101</td>
<td>19</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>141</td>
<td>5</td>
</tr>
<tr>
<td>CRC</td>
<td>77</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>83</td>
<td>4</td>
</tr>
</tbody>
</table>


In addition, Herbst and colleagues recently evaluated biomarkers to predict the activity of PD-L1 inhibition using atezolizumab in a variety of solid tumors. As you can see here, when they stained for PD-L1, they found that it could be expressed either on tumor cells or on tumor-infiltrating lymphocytes, and the degree of expression was variable. You see here examples of no staining, 1+ staining, 2+ staining, and 3+ staining.

You can see that the patients who had the highest degree of PD-L1 expression were those who had the longest duration of disease control.

In summary, this evidence suggests that atezolizumab is most effective in patients in whom preexisting immunity is suppressed by PD-L1, and that this immunity can be reinvigorated on antibody treatment.

PD-L1 Expression as a Marker in SCCHN (Cont’d)

<table>
<thead>
<tr>
<th>IHC 0 (n = 60)</th>
<th>Median CI</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.14</td>
<td>5.57 to 17.57</td>
<td>4.14 to 73.14+</td>
</tr>
<tr>
<td>IHC 1 (n = 34)</td>
<td>17.14</td>
<td>6.00 to 43.29</td>
</tr>
<tr>
<td>IHC 2 (n = 23)</td>
<td>18.14</td>
<td>6.00 to 48.14</td>
</tr>
<tr>
<td>IHC 3 (n = 33)</td>
<td>37.28</td>
<td>18.29 to 59.00</td>
</tr>
<tr>
<td>Unknown (n = 25)</td>
<td>19.71</td>
<td>6.29 to NE</td>
</tr>
</tbody>
</table>


How can we integrate immune checkpoint inhibitors with the standard approaches to treating head and neck cancer? Standard treatments like chemoradiation can lead to cell death either in a way that’s immunogenic or tolerogenic. Phenotypic changes in surviving cells may be immunomodulatory. This has been described in several tumor types, and preclinical models support combination therapy.

The known immunomodulatory effect of radiation also supports combination approaches with checkpoint inhibitors. Trials are currently underway looking at the combination of either ipilimumab, which targets CTLA-4, or pembrolizumab, which targets PD-1, together with radiation.

**Priming for Immunotherapy and Future Combinations**

- Standard treatments may lead to tolerogenic or immunogenic cell death
  - Cetuximab, CRT
- Phenotypic changes in surviving cells may be immunomodulatory
  - Described in several tumor types; preclinical models support combination therapy
- Known immunomodulatory effect of radiation also supports combination approaches with checkpoint inhibitors
  - Ipilimumab (CTLA-4)
  - Pembrolizumab (PD-1)

CRT: chemoradiotherapy; CTLA: cytotoxic T-lymphocyte-associated protein; HNC: head and neck carcinoma.
Is There a Future for Immunotherapy in Head and Neck Cancer?

Patients with recurrent or metastatic head and neck carcinoma (N = 360)

- Primary endpoint: OS
- Study no longer recruiting patients

Nivolumab 3 mg/kg IV every 2 weeks until disease progression

Cetuximab, methotrexate, or docetaxel

Checkmate141: Phase 3 Study of Nivolumab in Recurrent/Metastatic SCCHN

KEYNOTE-040: Phase 3 Study of Pembrolizumab in First-Line Recurrent/Metastatic SCCHN

Patients with recurrent or metastatic SCCHN (estimated N = 780)

- Primary endpoint: PFS
- Study is ongoing and recruiting participants

Pembrolizumab 200 mg, IV day 1, each week in 3-week cycles up to 24 months

Pembrolizumab + platinum + 5-FU

Cetuximab + platinum + 5-FU

Pembrolizumab

5-FU: fluorouracil.

Before we conclude today, let’s review a few important phase 3 trials that will hopefully give us some new information on the role of novel immunotherapy in head and neck cancer. The first trial I’d like to discuss is the phase 3 Checkmate141 study, which tested the PD-1 antibody nivolumab compared with investigator’s choice of standard care in patients with recurrent or metastatic head and neck cancer that was previously treated with cisplatin.

You see the schema here. The primary endpoint of the trial was overall survival. And patients were randomized either to nivolumab 3 mg/kg IV every 2 weeks until disease progression, or to the investigator’s choice of cetuximab, methotrexate, or docetaxel. This trial has completed recruitment, and we’re looking forward to learning the results.

The next trial is KEYNOTE-040, a phase 3 study of pembrolizumab versus standard treatment, such as methotrexate, docetaxel, or cetuximab, for patients with previously treated platinum-refractory recurrent or metastatic head and neck cancer.

Patients are randomly assigned to receive either pembrolizumab or investigator’s choice of standard treatment in order to determine if pembrolizumab can extend progression-free survival compared with the comparator regimens. And this trial is currently accruing.

Durvalumab is also being evaluated in a phase 3 trial, either as monotherapy or in combination with a CTLA-4–targeting agent, or...
the patients are going to be compared to those receiving standard therapy for recurrent metastatic squamous cell cancer.

### Ongoing Studies of Checkpoint Inhibitors in Nasopharyngeal Cancer

<table>
<thead>
<tr>
<th>Study Status</th>
<th>Treatment</th>
<th>Population</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>Nivolumab</td>
<td>Patients with recurrent/metastatic nasopharyngeal cancer</td>
<td>Response (RECIST 1.1)</td>
</tr>
<tr>
<td>Currently recruiting patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized Phase 2</td>
<td>Pembrolizumab vs standard of care</td>
<td>Patients with recurrent/metastatic nasopharyngeal cancer</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>(KEYNOTE-122)</td>
<td>(capecitabine, gemcitabine, or docetaxel)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not yet recruiting</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical trials testing immune checkpoint inhibitors in other SCCHN settings, including as adjuvant therapy (in resectable disease) and in locally advanced disease, are planned or being developed; updates on these protocols may be viewed at [clinicaltrials.gov](https://clinicaltrials.gov).

In addition to these large phase 3 trials, we also have other ongoing trials that will test the use of checkpoint inhibitors in recurrent or metastatic nasopharyngeal cancer. There’s a phase 2 trial currently recruiting patients that looks at nivolumab with a primary endpoint of response, and there’s a randomized phase 2 trial planned with pembrolizumab in comparison with a standard of care consisting of capecitabine, gemcitabine, or docetaxel in patients with recurrent metastatic nasopharynx cancer that’s previously treated. That trial has endpoints of progression-free survival and overall survival.

**Conclusions**

- Checkpoint inhibitors targeting either PD-1 or PD-L1 appear to be active in both HPV-associated and HPV-negative HNC
  - Awaiting the results of phase 3 trials to determine where these agents will play a role in patient management

- These important trials may also help us to validate biomarkers, such as PD-L1 expression, to select patients for these new treatments

- It will also be important to determine whether conventional therapies, such as chemotherapy, cetuximab, and radiation, may prime tumors for immune checkpoint inhibitors

HPV: human papilloma virus.

In conclusion, checkpoint inhibitors targeting either PD-1 or PD-L1 appear to be active in both human papilloma virus–associated and HPV-negative head and neck cancer, and we await the results of phase 3 trials to determine where these agents will play a role in patient management.

These important trials may also help us to validate biomarkers, such as PD-L1 expression, to select patients for these new treatments. It will also be important to determine whether conventional therapies, such as chemotherapy, cetuximab, and radiation, may prime tumors for immune checkpoint inhibitors.

Thank you very much for joining me today, and I hope this discussion has been useful to your practice.
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Is There a Future for Immunotherapy in Head and Neck Cancer?

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