Project ID XXXX
Working Title: New Immunotherapies in Cancer Treatment: Understanding the Role of PD-1 and PDL-1 Inhibitors in Lung Cancer Therapeutics
Support Targeted: Merck and Co, Inc., Bristol-Myers Squibb

Summary of Educational Need & Gap Analysis

During the last decade, treatment for non-small cell lung cancer (NSCLC) has become increasingly complex as well as narrowly focused. New treatments target specific genetic mutations within the cancer cells. Gene testing and evaluation of tumor cell pathology is widely used to direct these targeted treatments. The newest of these targeted therapies inhibit programed death receptor-1 (PD-1) and programmed death ligand-1 (PD-L1), thereby promoting normal immune cascade within the tissue.[1-3] By inhibiting these checkpoint receptors on tumor cells, T-cells are able to effectively recognize and target tumor cells causing cell death or stopping further growth.[1] These treatments were recently approved for NSCLC, in addition to other cancer types.[2,3] Several of these new agents were escalated to breakthrough therapy designation with subsequent accelerated FDA approval late in 2015.[2,3] Due to rapid advancements in cancer research and changes to standard treatment, regular practice updates are essential for clinicians as they integrate new research into their daily practice.

Since not all tumor cells exhibit PD-1 or PD-L1 expression, laboratory tests[2,3] have been developed to identify those patients with PD-L1 expressing tumors who will derive the most benefit from these new monoclonal antibody therapies.[4] Much of the published research focuses on new immune modulators in stage 4 cancers in patients previously treated with conventional therapies. With new modalities available to test for PD-L1 expression,[2,3] the possibility of using these therapies earlier in the treatment course and in conjunction with conventional treatments may be a viable option.

Identified Gaps in Practice

Educational Gap No. 1: Clinicians are aware of PD-1 checkpoint immunotherapy in the setting of second-line treatment for NSCLC, but may not routinely activate these agents earlier in therapy course.

> **Current Practice:** PD-1 inhibitors were recently FDA approved for use as second-line treatment in late stage NSCLC, but no specific guidelines are set for use in earlier stages or treatment naïve patients.[2,3,6]
>
> **Best Practice:** Monoclonal antibodies such as PD-1/PD-L1 inhibitors have been evaluated and approved for extending overall survival in late stage NSCLC. Outcomes from new and current trials provide insight into use of these agents earlier in the course of the disease as well as in conjunction with established standard of care treatments.[4,8,10,12-18]

Educational Gap No. 2: Clinicians are not aware of how screening tests for PD-1 and PD-L1 expression in NSCLC will better direct therapy with new PD-1/PD-L1 monoclonal antibody immunotherapy.

Current Practice: Although two PD-1 inhibitors have been FDA approved for treatment of NSCLC, there are no universal guidelines for the use of tumor screening for PD-1/PD-L1 expression prior to initiating therapy.[2,3]

Best Practice: The use of biomarker screening tests for PD-L1 expression on tumor tissue has been evaluated and approved to direct treatment with pembrolizumab in NSCLC. Although a PD-L1 diagnostic test was also developed for use with nivolumab, dosing guidelines do not require use of this test prior to initiating therapy. Outcomes of recent clinical trials have focused on PD-1/PD-L1 expression as a marker for clinical response to these monoclonal antibody therapies. It is important for clinicians to understand the implications of these screening tests in directing treatment choices for individual patients.[2,3,14,15]

Target Audience

This program is designed for oncologists and other clinicians who may participate in treatment of patients with NSCLC.

Program Goal

The goal of this program is to improve the knowledge of oncologists and other clinicians who treat patients with NSCLC in regard to new and rapidly changing pharmaceutical developments in immunotherapy. The program will also offer data to improve understanding of how tissue screening tests can improve treatment by individualizing care for patients.

Proposed Learning Objectives

Upon completion of this educational program, participants should be able to:

Learning objectives		Quality measures (IOM Priorities)
Explain the tumor expression of PD-1 and PD-L1 and how this affects cancer progression		• Early intervention and evidence-based practices to promote progression-free survival
Identify how immunotherapy fits into current cancer treatment		• Safety aspects of treatment • Quality of care and best practices to promote progression-free survival
Summarize recent clinical trials and FDA approvals of PD-1 inhibitors		• Safety aspects of care delivery • Evidence-based treatment practices to promote progression-free survival
Discuss the rationale for adding PD-1/PD-L1 checkpoint inhibitors into the cancer treatment regimen prior to advanced disease		• Safety aspects of care delivery • Evidence-based treatment, early intervention, and screening
Discuss the role of laboratory testing for PD-1/PD-L1 tumor expression prior to initiating treatment with PD-1 inhibitors		• Safety aspects of care delivery • Evidence-based treatment practices to promote progression-free survival

Proposed Agenda/Content Outline

Virtual Grand Rounds (one 30-minute activity with audio/slides):

The Role of PD-1/PD-L1 Checkpoint Inhibitor Immunotherapy in the Clinical Treatment of Patients With Advanced NSCLC

Introduction (5 min)

The faculty will review information relevant to the CME/CE and will present participants with important knowledge points. Follow-up questions at the end of the section will evaluate competence based on completed content. After completion of a posttest, answers will be correlated with expert responses to reinforce the learning objectives.

The Role of PD-1 Checkpoint Inhibitor Immunotherapy in the Clinical Treatment of Patients With Advanced NSCLC.

A 30-minute activity (audio/slides) will cover the following topics:

- Current standard of care treatments for advanced/metastatic NSCLC.
  - Role of new immunotherapy treatments
- PD-1 immunotherapeutics approved for NSCLC.
  - nivolumab (Opdivo); pembrolizumab (Keytruda)
- Role of rapidly progressing clinical trials with some pushing into "breakthrough therapy" status and accelerated approval
  - Use of PD-1/PD-L1 inhibitors in early stage/resectable disease
  - Use of PD-1/PD-L1 inhibitors in conjunction with current standard of care treatments.

This section will review the current standard of care for NSCLC in advanced stages and outline the role of PD-1/PD-L1 inhibitors in treatment of NSCLC. It will also define the use of PD-1 inhibitors in current clinical practice and expand on integration of PD-1/PD-L1 inhibitors into the standard of care for NSCLC patients in all stages of disease through clinical trial data.

Virtual Grand Rounds (one 30-minute activity with audio/slides):

The Role of PD-L1 Expression Screening in Directing NSCLC Treatment With Currently Approved PD-1 inhibitors.

Introduction (5 min)

The faculty will review relevant information pertinent to the CME/CE and will present participants with important knowledge points. Follow-up questions at the end of the section will evaluate competence based on completed content. After completion of a posttest, answers will be correlated with expert responses to reinforce the learning objectives.

The Role of PD-L1 Tumor Expression Screening in Directing NSCLC Treatment With Currently Approved PD-1 Inhibitors.

A 30-minute activity (audio/slides) will cover the following topics:

- Current standards for initiation of immunotherapy in NSCLC treatment (NCCN guidelines).
- Variation in screening requirements/options based on FDA approved PD-1 inhibitors.
    - nivolumab; pembrolizumab
- Rapidly progressing clinical trials and how this will affect future treatment with PD-1/PD-L1 inhibitors in relation to pre-treatment screening.

This section will review the current standards for initiation of treatment with PD-1/PD-L1 inhibitors in advanced NSCLC and outline the differences between approved PD-1 inhibitors in relation to pre-treatment screening for PD-L1 expression. There will also be discussion of recent clinical trials resulting in approval of new PD-1 inhibitors for use in NSCLC and ongoing trials working to expanded use of PD-1/PD-L1 inhibitors in NSCLC.

Highlights Podcast CME activity (30 minute audio podcast aired on xxxxx)
PD-1/PDL-1 Inhibitor Immunotherapy in Treatment of NSCLC: Current and Future Practice
Combined topics of PD-1/PD-L1 treatment (VGR activity 1) and PD-1/PD-L1 expression screening (VGR activity 2).

Clinical pearl Email series (total of 3)
Reinforcement of learning (sent to participants after completion of the program)

Combined downloadable slides/speaker notes for Activities 1 and 2
Provides additional resources for learners to reinforce the content presented.

Suggested Faculty

Julie R. Brahmer, MD, MSc -Associate Professor of Oncology, Director of the Thoracic Oncology Program, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Baltimore, Maryland

Heather Wakelee, MD - Associate Professor of Medicine, Department of Medicine, Division of Oncology, Stanford University, Palo Alto, California

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Appendix A: Literature Review Supporting the Educational Need

NSCLC has a complex oncologic pathway presenting in several subtypes and is the greatest cause of cancer-related mortality in the United States and the world.[1,5] NSCLC affects both smokers and nonsmokers and is frequently diagnosed in late stages leading to a low 5-year survival rate of just 5%.[1,5] The National Comprehensive Cancer Network (NCCN) Guidelines Version 4.2016 treatment algorithm introduces checkpoint immunotherapy as second-line therapy in metastatic NSCLC, but suggest the possibility of earlier initiation.[6]

New research in immune checkpoint pathways indicate that some cancer cells overexpress PD-L1 causing PD-1 binding, downregulation of T-cell immunity and subsequent cancer cell

immune evasion.[1-3,7] By blocking this cascade, PD-1 inhibitors, nivolumab and pembrolizumab, allow normal immune activation and response to the malignant cells in some patients.[7-9]

In recent clinical studies, PD-1 inhibitors have shown response in up to one quarter of enrolled NSCLC patients. Specifically, an overall response rate of 22.5% (95% CI: 17.6% to 28.2%) was seen with PD-1 inhibitors used in NSCLC patients.[10] Despite this encouraging data, further research is imperative to identify those patients who may benefit from this highly specific immunotherapy treatment prior to initiation of therapy.[10]

Through a series of clinical trials termed Checkmate and Keynote, nivolumab and pembrolizumab, respectively, were evaluated and eventually approved for second-line treatment in NSCLC patients.[11,12] Active clinical trials are currently investigating nivolumab, pembrolizumab, and other PD-1/PD-L1 checkpoint inhibitors in the setting of first-line treatment, monotherapy, combination treatment with standard chemotherapy agents, treatment in resected tumors, and combination treatment with other immunotherapeutics.[11-13] PD-1 and PD-L1 expression has been strongly associated with KRAS and EGFR mutations, respectively, indicating the possibility of expanded treatment options in patients with these specific tumor cell mutations for which effective targeted drug therapies have already been identified.[11,13,14]

In one study evaluating the effectiveness of PD-1 inhibitors, a response rate of 36% was reported in patients with positive PD-L1 expression. This same study found no response in patients with negative PD-L1 expression.[15,16] Another study reported that although PD-L1 expression was an indicator of overall response to PD-1 immunotherapy, this expression was heterogeneous within a single patient.[15] This finding prompts further research into biomarker expression aimed at effectively identifying appropriate treatment candidates.[15] Pembrolizumab treatment is accompanied by a companion biomarker diagnostic test, PD-L1 IHC 22C3 pharmDx test, to identify patients who are more likely to benefit from the treatment.[3,11,12] There is also a diagnostic test for PD-L1 available to accompany nivolumab, PD-L1 IHC 28-8 pharmDx test, but treatment does not require prior testing.[2] Further tests are in development stages, but varying protocols and scoring systems create difficulty in standardizing the tests for broad use in oncology populations.[17] New data derived from PD-L1 humanized antibodies indicates the possibility of nuclear and optical imaging agents as additional biomarker testing options for patients receiving checkpoint immunotherapy.[18]

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