INTERACTIVE TUMOR PANEL

Clinical Investigators Discuss Available Research Shaping the Current and Future Role of Immune Checkpoint Inhibitors in the Management of Lung Cancer

CME Information

TARGET AUDIENCE

This activity is intended for medical oncologists, hematologists, surgeons, radiation oncologists, oncology nurses and other healthcare professionals involved in basic, translational and clinical cancer research or treatment.

OVERVIEW OF ACTIVITY

The past several years have seen an explosion in the emergence of new therapies that leverage the natural ability of the human body to attack and treat cancer. Known as cancer immunotherapies, these treatments are generating excitement all over the world as they have reshaped the management of lung cancer in previously unimagined ways. That being said, a number of controversies and questions remain with regard to the current application of these agents in clinical practice.

These video proceedings from a CME symposium held during the 2018 AACR Annual Meeting feature discussions with leading lung cancer researchers regarding actual patient cases and related clinical research findings. By providing information on important developments, this activity will assist medical oncologists and other healthcare professionals to address existing management uncertainties and determine the current and future roles of immune checkpoint inhibitors in this disease.

LEARNING OBJECTIVES

- Analyze the biologic basis for the development of immune checkpoint inhibitors designed to boost an individual's immune response to combat cancer.

- Appreciate available Phase III data documenting the benefit of sequential anti-PD-L1 therapy after the completion of chemoradiation therapy for Stage III non-small cell lung cancer (NSCLC), and consider the role of durvalumab for appropriate patients.

- Recognize available and emerging research information validating the utility of diagnostic assays designed to measure PD-L1 status, assess which testing platforms should be used and appropriately employ the results to individualize first- and later-line therapy for patients with metastatic NSCLC based on their potential response (or lack thereof) to an immune checkpoint inhibitor.

- Compare and contrast the mechanisms of action, efficacy and safety/toxicity of approved and investigational anti-PD-1/PD-L1 antibodies for the treatment of NSCLC to determine the current and/or potential utility of these agents in clinical practice.

- Review published research documenting the safety and efficacy of anti-PD-1 antibodies used as monotherapy or in combination with chemotherapy for patients with newly diagnosed metastatic NSCLC.

- Describe the biologic rationale for and current clinical role of anti-PD-1/PD-L1 antibodies alone or in combination with other therapeutic approaches for small cell lung cancer (SCLC).

- Describe ongoing research to assist in the identification of additional biomarkers, tumor characteristics or other clinical features that are indicative of response to immune checkpoint inhibitors in patients with lung cancer.

- Recall the design of ongoing clinical trials evaluating anti-PD-1/PD-L1 antibodies in combination with other immunotherapeutic and systemic therapies for NSCLC and SCLC, and counsel appropriate patients about availability and participation.

ACCREDITATION STATEMENT

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Please note, this program has been specifically designed for the following ABIM specialty: **medical oncology**.

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CONTENT VALIDATION AND DISCLOSURES

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FACULTY — The following faculty (and their spouses/partners) reported relevant conflicts of interest, which have been resolved through a conflict of interest resolution process:

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MODERATOR — **Dr Love** is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Ariad

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 11 or later, Firefox 56 or later,
Chrome 61 or later, Safari 11 or later, Opera 48 or later
Adobe Flash Player 27 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

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Neil Love, MD

Routy B et al. **Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors.** *Science* 2018;359(6371):91-7.

Zitvogel L et al. **Cancer and the gut microbiota: An unexpected link.** *Sci Transl Med* 2015;7(271):271ps1.

Leena Gandhi, MD, PhD

Ahn MA et al. **Risk of pneumonitis in patients with advanced NSCLC treated with pembrolizumab in KEYNOTE-001.** *Proc ESMO Asia* 2015;**Abstract 459P**.

Antonia SJ et al; PACIFIC Investigators. **Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer.** *N Engl J Med* 2017;377(20):1919-29.

Goldstraw P et al; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions. **The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer.** *J Thorac Oncol* 2016;11:39-51.

Rusch V et al; Members of the IASLC Staging Committee. **The IASLC lung cancer staging project: A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer.** *J Thorac Oncol* 2009;4(5):568-77.

Taunk NK et al. **Immunotherapy and radiation therapy for operable early stage and locally advanced non-small cell lung cancer.** *Transl Lung Cancer Res* 2017;6(2):178-85.

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Apetoh L et al. **Combining immunotherapy and anticancer agents: The right path to achieve cancer cure?** *Ann Oncol* 2015;26(9):1813-23.

Borghaei H et al. **Updated results from KEYNOTE-021 cohort G: A randomized, phase 2 study of pemetrexed and carboplatin (PC) with or without pembrolizumab (pembro) as first-line therapy for advanced nonsquamous NSCLC.** *Proc ESMO* 2017;**Abstract LBA49**.

Chen DS, Mellman I. **Oncology meets immunology: The cancer-immunity cycle.** *Immunity* 2013;39(1):1-10.

Facciabene A et al. **Tumour hypoxia promotes tolerance and angiogenesis via CCL28 and T(reg) cells.** *Nature* 2011;475(7355):226-30.

Ferrara N et al. **Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer.** *Nat Rev Drug Discov* 2004;3(5):391-400.

Gabrilovich DI, Nagaraj S. **Myeloid-derived suppressor cells as regulators of the immune system.** *Nat Rev Immunol* 2009;9(3):162-74.

Gabrilovich DI et al. **Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells.** *Nat Med* 1996;2(10):1096-103.

Grabosch S et al. **PD-L1 biology in response to chemotherapy in vitro and in vivo in ovarian cancer.** *J Immunother Cancer* 2015;3(Suppl 2):302.

Goel S et al. **Normalization of the vasculature for treatment of cancer and other diseases.** *Physiol Rev* 2011;91(3):1071-121.

Hodi FS et al. **Bevacizumab plus ipilimumab in patients with metastatic melanoma.** *Cancer Immunol Res* 2014;2(7):632-42.

Langer CJ et al; KEYNOTE-021 Investigators. **Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: A randomised, phase 2 cohort of the open-label KEYNOTE-021 study.** *Lancet Oncol* 2016;17(11):1497-508.

Motz GT et al. **Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors.** *Nat Med* 2014;20(6):607-15.

Oyama T et al. **Vascular endothelial growth factor affects dendritic cell maturation through the inhibition of nuclear factor-κB activation in hemopoietic progenitor cells.** *J Immunol* 1998;160(3):1224-32.

Peng J et al. **Chemotherapy induces programmed cell death-ligand 1 overexpression via the nuclear factor-κB to foster an immunosuppressive tumor microenvironment in ovarian cancer.** *Cancer Res* 2015;75(23):5034-45.

Roland CL et al. **Cytokine levels correlate with immune cell infiltration after anti-VEGF therapy in preclinical mouse models of breast cancer.** *PLoS One* 2009;4(11):e7669.

Select Publications

Voron T et al. **VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors.** *J Exp Med* 2015;212(2):139-48.

Wallin JJ et al. **Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma.** *Nat Commun* 2016;7:12624.

Zhang P et al. **Upregulation of programmed cell death ligand 1 promotes resistance response in non-small-cell lung cancer patients treated with neo-adjuvant chemotherapy.** *Cancer Sci* 2016;107(11):1563-71.

Matthew D Hellmann, MD

Carbone DP et al; CheckMate 026 Investigators. **First-line nivolumab in stage IV or recurrent non-small-cell lung cancer.** *N Engl J Med* 2017;376(25):2415-26.

Hellmann MD et al. **Genomic features of response to combination immunotherapy in patients with advanced non-small-cell lung cancer.** *Cancer Cell* 2018;[Epub ahead of print].

Jordan EJ et al. **Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies.** *Cancer Discov* 2017;7(6):596-609.

Kowanetz M et al. **Tumor mutation load assessed by FoundationOne (FM1) is associated with improved efficacy of atezolizumab (atezo) in patients with advanced NSCLC.** *Proc ESMO* 2016;Abstract 77P.

Reck M et al; KEYNOTE-024 Investigators. **Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer.** *N Engl J Med* 2016;375(19):1823-33.

Rimm D et al. **A prospective, multi-institutional assessment of four assays for PD-L1 expression in NSCLC by immunohistochemistry: Topic: Pathology.** *Proc IASLC* 2016;Abstract ORAL01.01.

Rizvi H et al. **Molecular determinants of response to anti-programmed cell death (PD)-1 and anti-programmed death-ligand 1 (PD-L1) blockade in patients with non-small-cell lung cancer profiled with targeted next-generation sequencing.** *J Clin Oncol* 2018;36(7):633-41.

Rizvi NA et al. **Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer.** *Science* 2015;348(6230):124-8.

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Ahn M-J et al. **Osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: Results from the TATTON phase Ib trial.** *Proc ELCC* 2016;Abstract 136O.

Akbay EA et al. **Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors.** *Science* 2013;3(12):1355-63.

Antonioli L et al. **Anti-CD73 in cancer immunotherapy: Awakening new opportunities.** *Trends Cancer* 2016;2(2):95-109.

Chen N et al. **Upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: Implication for optional immune targeted therapy for NSCLC patients with EGFR mutation.** *J Thorac Oncol* 2015;10:910-23.

Cho JH et al. **Retrospective molecular epidemiology study of PD-L1 expression in patients with EGFR-mutant non-small cell lung cancer.** *Cancer Res Treat* 2018;50(1):95-102.

Gainor J et al. **EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: A retrospective analysis.** *Clin Cancer Res* 2016;22(18):4585-93.

Gibbons DL et al. **Efficacy, safety and tolerability of MEDI4736 (durvalumab [D]), a human IgG1 anti-programmed cell death-ligand-1 (PD-L1) antibody, combined with gefitinib (G): A phase I expansion in TKI-naïve patients (pts) with EGFR mutant NSCLC.** *Proc ELCC* 2016;Abstract 57O.

Hellmann M et al. **Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): Results of an open-label, phase 1, multicohort study.** *Lancet Oncol* 2017;18(1):31-41.

Moya-Horno I et al. **Combination of immunotherapy with targeted therapies in advanced non-small cell lung cancer (NSCLC).** *Ther Adv Med Oncol* 2018;10:1-12.

Rizvi NA et al. **Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC.** *Proc ASCO* 2014;Abstract 8022.

Streicher K et al. **Increased CD73 and reduced IFNG signature expression in relation to response rates to anti-PD-1(L1) therapies in EGFR-mutant NSCLC.** *Proc ASCO* 2017;Abstract 11505.

Select Publications

Hossein Borghaei, DO, MS

Chaft JE et al. **Neoadjuvant nivolumab in early-stage, resectable non-small cell lung cancers.** *Proc ASCO* 2017;Abstract 8508.

Gangadhar TC et al. **Efficacy and safety of epacadostat plus pembrolizumab treatment of NSCLC: Preliminary phase I/II results of ECHO-202/KEYNOTE-037.** *Proc ASCO* 2017;Abstract 9014.

Herbst RS et al. **Interim safety and clinical activity in patients with advanced NSCLC from a multi-cohort phase 1 study of ramucirumab (R) plus pembrolizumab (P).** *Proc ESMO* 2016;Abstract LBA38.

Mellman I et al. **Cancer immunotherapy comes of age.** *Nature* 2011;480(7378):480-9.