Data + Perspectives

Investigators Discuss the Current Applicability and Ongoing Evaluation of Biomarkers of Response to Immune Checkpoint Inhibition

CME Information

TARGET AUDIENCE

This activity is intended for medical oncologists, hematologist-oncologists, hematology-oncology fellows and other healthcare providers involved in the treatment of various solid tumors and hematologic cancers.

OVERVIEW OF ACTIVITY

The past several years have seen an explosion in the emergence of new therapies with the potential to leverage the natural ability of the human body to attack and treat cancer. Known as immune-mediated therapies or cancer immunotherapies, these promising treatments are taking center stage at medical conferences and generating excitement all over the world. Early immune therapies approved by the FDA in the 1990s provided marginal response rates and unfortunately brought with them the possibility of significant toxicities, and investigators have sought to exploit different mechanistic aspects of immunologic functioning to produce greater therapeutic benefit. The newest and perhaps most exciting arena in this endeavor has been the development and assessment of immune-modulating antibodies, or checkpoint immune modulators. These agents are aimed to enhance natural immune responses or overcome tumor-induced immune tolerance rather than block oncogenic tumor growth pathways.

Not surprisingly the introduction of immune checkpoint inhibitors, particularly anti-PD-1/PD-L1 antibodies, has created a multitude of uncertainties, important clinical questions and knowledge gaps awaiting resolution. Foremost among these is the simple question of why certain patients enjoy profound and long-lasting benefits from these agents and others with apparently the same disease experience no clinical effect. This conundrum has impelled scientists to examine the biologic underpinnings of malignant cells, human immune response mechanisms and the cell environment in an effort to discover biomarkers predictive of benefit, or lack thereof, from these agents. While researchers have begun to understand some potential biomarkers, these advances have in no way put the search to rest. Scientists and clinicians are investigating a wide variety of biologic, genomic and immuno¬logic factors across a multitude of diseases and clinical situations. To date none of this work appears to be ready for prime time or immediately actionable in the clinic, but some of this knowledge appears to be quite prescient and its application in clinical trials may represent an optimal treatment approach for appropriate patients. This special CME activity aims to bridge the gap between research and patient care by presenting one-on-one discussions with leading oncology investigators as they review available immunotherapeutic approaches, current understanding of predictive biomarkers and promising ongoing research efforts.

LEARNING OBJECTIVES

- Appraise the rationale for and clinical data with approved anti-PD-1/PD-L1 antibodies in the treatment of various solid tumors and hematologic cancers.
- Describe ongoing research to assist in the identification of biomarkers, tumor characteristics or other clinical features that are indicative of response to immune checkpoint inhibitors in patients with different types of cancer.
- Compare and contrast expert perspectives on the indications for PD-L1 analysis for patients with metastatic non-small cell lung cancer, melanoma and other cancers, and select appropriate individuals for PD-L1 assessment.
- Appreciate the similarities and differences among diagnostic assays and scoring methodologies available to determine PD-L1 status, and use this information to select a validated testing platform for use in practice.
- Describe ongoing research to document the correlation between DNA mismatch repair deficiency or microsatellite instability and response to anti-PD-1 immune checkpoint inhibitors in gastrointestinal and other cancers, and develop related assessment strategies.
- Recognize current investigational efforts to identify other potential biomarkers of response to checkpoint inhibition, and consider how they may be applied in future clinical practice.

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2.75 Medical Knowledge MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

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

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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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Consulting Agreements: 7 Hills Pharma LLC, Actym Therapeutics Inc, Amgen Inc, Array BioPharma Inc, AstraZeneca Pharmaceuticals LP, Benevir Biopharm Inc, Bristol-Myers Squibb Company, Castle Biosciences Incorporated, Checkmate Pharmaceuticals, EMD Serono Inc, Gilead Sciences Inc, Janssen Biotech Inc, Merck, NewLink Genetics, Nimbus Therapeutics, Novartis, Palleon Pharmaceuticals, Syndax Pharmaceuticals Inc, Tempest Therapeutics; **Clinical Trials:** AbbVie Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celldex Therapeutics, Corvus Pharmaceuticals, Delcath Systems Inc, Five Prime Therapeutics Inc, Genentech BioOncology, Immunocore, Incyte Corporation, Intensity Therapeutics, MacroGenics Inc, MedImmune Inc, Merck, Novartis, Pharmacyclics LLC, an AbbVie Company, Tesaro Inc.

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EDITOR — **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, Adaptive Biotechnologies, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Ariad Pharmaceuticals Inc, Array BioPharma Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Baxalta Inc, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, CTI BioPharma Corp, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Halozyme Inc, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Kite Pharma Inc, Lexicon Pharmaceuticals Inc, Lilly, Medivation Inc, a Pfizer Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, NanoString Technologies, Natera Inc, Novartis, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seattle Genetics, Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro Inc, Teva Oncology and Tokai Pharmaceuticals Inc.

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This activity is supported by an educational grant from Merck.

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

Release date: June 2018

Expiration date: June 2019

Select Publications

Antonia S et al. **Impact of tumor mutation burden on the efficacy of nivolumab or nivolumab + ipilimumab in small cell lung cancer: An exploratory analysis of CheckMate 032.** *Proc IASLC* 2017;**Abstract OA 07.03a**.

Antonia SJ et al. **Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): A multicentre, open-label, phase 1/2 trial.** *Lancet Oncol* 2016;17(7):883-95.

Azad N et al. **Nivolumab in mismatch-repair deficient (MMR-d) cancers: NCI-MATCH Trial (Molecular Analysis for Therapy Choice) arm Z1D preliminary results.** *Proc ASCO-SITC* 2017;**Abstract O37**.

Borghaei H et al. **Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer.** *N Engl J Med* 2015;373(17):1627-39.

Brahmer J et al. **Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer.** *N Engl J Med* 2015;373(2):123-35.

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.

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Dudley JC et al. **Microsatellite instability as a biomarker for PD-1 blockade.** *Clin Cancer Res* 2016;22(4):813-20.

Eroglu Z et al. **High response rate to PD-1 blockade in desmoplastic melanomas.** *Nature* 2018;553(7688):347-50.

Gajewski TF et al. **Molecular profiling to identify relevant immune resistance mechanisms in the tumor microenvironment.** *Curr Opin Immunol* 2011;23(2):286-92.

Gandara DR et al. **Blood-based biomarkers for cancer immunotherapy: Tumor mutational burden in blood (bTMB) is associated with improved atezolizumab (atezo) efficacy in 2L+ NSCLC (POPLAR and OAK).** *Proc ESMO* 2017;**Abstract 1295O**.

Goodman A et al. **Analysis of over 100,000 patients with cancer for CD274 (PD-L1) amplification: Implications for treatment with immune checkpoint blockade.** *Proc ASCO-SITC* 2018;**Abstract 47**.

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.

Le DT et al. **Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade.** *Science* 2017;357(6349):409-13.

Llosa NJ et al. **The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints.** *Cancer Discov* 2015;5(1):43-51.

Luke JJ, Ott PA. **PD-1 pathway inhibitors: The next generation of immunotherapy for advanced melanoma.** *Oncotarget* 2015;6(6):3479-92.

McGranahan N et al; TRACERx Consortium. **Allele-specific HLA loss and immune escape in lung cancer evolution.** *Cell* 2017;171(6):1259-71.e11.

McGranahan N et al. **Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade.** *Science* 2016;351(6280):1463-9.

Mittal D et al. **New insights into cancer immunoediting and its three component phases — elimination, equilibrium and escape.** *Curr Opin Immunol* 2014;27:16-25.

Reck M et al. **Primary PFS and safety analyses of a randomized phase III study of carboplatin + paclitaxel +/– bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150).** *Proc ESMO* 2017;**Abstract LBA1_PR**.

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.

Seiwert TY et al. **Inflamed-phenotype gene expression signatures to predict benefit from the anti-PD-1 antibody pembrolizumab in PD-L1+ head and neck cancer patients.** *Proc ASCO* 2015;**Abstract 6017**.

Spranger S et al. **Density of immunogenic antigens does not explain the presence or absence of the T-cell-inflamed tumor microenvironment in melanoma.** *Proc Natl Acad Sci USA* 2016;113(48):E7759-68.

Topalian SL et al. **Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy.** *Nat Rev Cancer* 2016;16(5):275-87.