Stay Current with FDA-Approved Immunotherapy Treatments

April 6, 2019 | New Orleans
Hyatt Regency New Orleans
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Letter from the President

Dear Colleagues,

Welcome to today’s Advances in Cancer Immunotherapy™ (ACI) program, presented by the Society for Immunotherapy of Cancer (SITC) in collaboration with the American Academy of Emergency Medicine (AAEM), the Association of Community Cancer Centers (ACCC) and the Hematology/Oncology Pharmacy Association (HOPA).

As scientific progress in immunotherapy improves treatment options for many different groups of cancer patients, it is imperative for clinicians to have easy access to high-quality continuing education. With a backdrop of the basics of cancer immunotherapy, this program focuses on treatment and management of adverse events. Through its vast network of experts in tumor immunology and cancer immunotherapy, SITC is pleased to host you for today’s ACI program as you improve your understanding of FDA-approved immunotherapy treatments to further improve patient outcomes.

While you are here today, I encourage you to take advantage of the opportunity to network with your colleagues and other attendees. You will also have this opportunity via a dedicated online community on SITC’s official website, SITC Cancer Immunotherapy CONNECT. For additional services and to remain current with clinical advances in the field, consider joining SITC, the world’s leading member-driven organization specifically dedicated the science and application of cancer immunotherapy. Visit our website (sitcancer.org) or speak to a staff member to learn more about becoming a SITC member.

Today’s presentation materials will be available to all attendees in approximately four weeks. SITC staff will provide instructions via email on how to access these materials. You can also continue your education via free online classes at SITC Cancer Immunotherapy connectED, the society’s online learning portal, at sitcancer.org/connectED.

Finally, I would like to thank our program organizers and faculty for volunteering your time in support of SITC’s mission. We greatly appreciate your willingness to share your knowledge and expertise.

Sincerely,

Mario Sznol, MD
SITC President

This program is organized by the Society for Immunotherapy of Cancer in collaboration with the American Academy of Emergency Medicine, the Association of Community Cancer Centers and the Hematology/Oncology Pharmacy Association.
Program Purpose

Specifically designed by the Society for Immunotherapy of Cancer (SITC) for clinical oncologists, registered nurses, pharmacists, emergency physicians and the entire cancer care team, the Advances in Cancer Immunotherapy™ (ACI) programs are introductory CME-, CNE-, CPE and MOC-certified programs.

SITC partnered with the American Academy of Emergency Medicine, the Association of Community Cancer Centers and the Hematology/Oncology Pharmacy Association to create a comprehensive program providing critical information to incorporate immunotherapy into clinical practice. Each program will present practical information about the necessary hospital operations to offer immunotherapy, strategies to obtain reimbursement, practical barriers to immunotherapy implementation, and guidance for identifying and managing patients who present to the ER with immune-related adverse events.

To foster new relationships and further improve networking opportunities, registered attendees will be automatically enrolled into a private online community via the society’s website, SITC Cancer Immunotherapy CONNECT. Beginning three weeks before the event and for several months post-program, attendees will have an online communal space to connect to other attendees, ask questions of organizers and faculty and share personal experiences of working with patients in their communities. Learn more about SITC CONNECT at www.sitcancer.org/connected.

ACI Webinar Series

Attendees will have an opportunity to connect with experts and stay up-to-date on the latest advances in the immunotherapy field through four educational webinars. These webinars will serve as an ongoing resource as clinical oncologists and other healthcare providers incorporate cancer immunotherapy into practice. The webinars will provide supplemental information to the ACI program, with a focus on updating clinicians about new approvals and recent studies that will impact clinical practice. Each webinar will feature a question and answer session with the webinar faculty experts.

More information regarding the webinars will be provided via email, on the online community forum and at www.sitcancer.org/education/aci/online.

- Thursday, May 23, 2019
  3:00 – 4:00 p.m. CT
  Robert Canter, MD, MAS, FACS – UC Davis Health System
  Robert L. Ferris, MD, PhD – UPMC Hillman Cancer Center

Faculty Presentation Slides

As an added benefit of program attendance, all registered attendees of this Advances in Cancer Immunotherapy™ program will receive FREE access to faculty presentations as permitted by presenters. Approximately four weeks following the meeting, presentations will be available on the SITC website at www.sitcancer.org/education/aci/enduring and in the online community for program attendees. Attendees must be logged into their free CONNECT account on the SITC website to access the presentations. Presentations for those who do not attend the meeting are available at no charge to SITC members 30 days after the program and to non-members on the SITC Resource Library three months after the program. Prior to these dates, access to the materials for non-attendees can be purchased for a small fee. Attendees will receive an email with more information.

Classes

Online education specifically related to this ACI program:

- Introduction to Immunology – Second Edition: Learn about foundational concepts of cancer immunotherapy in this updated, interactive pre-program course intended for ACI attendees.
- Advances in Cancer Immunotherapy™ 2017 Video Series: Twelve modules feature exemplar presentations and videos from ACI programs. Continuing education credits are available for physicians, pharmacists, registered nurses and nurse practitioners.
- Interactive ACI Series: Coming soon! Learn about content presented during the concurrent sessions and refresh your knowledge of plenary session presentations with six interactive modules. Each module provides in-depth coverage of a program presentation and engages learners through interactive case study examples. Continuing education credits will be available for physicians, pharmacists, registered nurses and nurse practitioners.

Please visit SITC’s connectED learning portal for these classes and more at www.sitcancer.org/connected.

Intended Audience

The target audience for this program series is patient care providers and others who wish to learn the basic principles of tumor immunology and cancer immunotherapy, and to improve their ability to integrate cancer immunotherapy into state-of-the-art clinical management for their patients. This intended audience includes clinical oncologists, registered nurses, nurse practitioners, pharmacists, emergency physicians, allied health professionals, other patient care providers and students.

Fee Information

Activity fees are available at: http://www.sitcancer.org/education/aci/registration
Program Details

Educational Objectives

Upon completion of this program, participants will be able to:

• Describe the rationale for common approaches to cancer immunotherapy.
• Identify the appropriate clinical management of common side effects of immunotherapy agents.
• Implement cancer immunotherapy treatments for melanoma, lung, genitourinary, head and neck, and/or hematologic cancers into clinical practice appropriately.
• Identify solutions to overcome operational and financial barriers to integrating immunotherapy into their practice setting.
• Implement appropriate cancer care counsel in the clinical setting.

Joint Accreditation Statement

In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and Society for Immunotherapy of Cancer. Postgraduate Institute for Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Acknowledgment

SITC would like to thank the National Cancer Institute and the National Institutes of Health Medical Arts Branch for their contributions to the creation of the Basic Principles of Cancer Immunotherapy slide presentation and the standardization of cell graphics used throughout the program.

Photo/Video Policy

Photography and videography are prohibited in all SITC general sessions unless prior written approval is received from the SITC office. SITC often employs the services of a professional photographer/videographer at SITC events to capture images and audiovisual (AV) recordings for use in society archival and promotional material. Your attendance at SITC events implies your permission for images and AV recordings captured during these events to be used for purposes of SITC archival materials, promotional materials and publications, and waives your rights for compensation or ownership of these images.

Physician Continuing Medical Education

The Postgraduate Institute for Medicine designates this live activity for a maximum of 3.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Continuing Pharmacy Education

Postgraduate Institute for Medicine designates this continuing education activity for 3.75 contact hour(s) (0.375 CEUs) of the Accreditation Council for Pharmacy Education.

Universal Activity Numbers:
JA4008162-9999-18-204-L01-P; Application; 3.0 hours (S1, S2, S4)
JA4008162-9999-18-205-L04-P; Knowledge; 0.75 hours (S3)

Continuing Nursing Education

The maximum number of hours awarded for this Continuing Nursing Education activity is 3.7 contact hours. Designated for 2.9 contact hours of pharmacotherapy credit for Advance Practice Registered Nurses.

American Board of Internal Medicine’s (ABIM) Maintenance of Certification (MOC)

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 3.75 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.

Claiming Credit

Thank you for attending the Advances in Cancer Immunotherapy™ program! To complete the program evaluation and obtain your continuing education credit, please follow the steps below:

2. Register or login (takes less than one minute to register).
3. Once logged into CME University, follow these steps: Click on the “Find Post-Test/Evaluation by Course” at the top of the page, type “14117” and hit enter.
4. Select the date/location option of “New Orleans, LA on 4/6/19.”
5. Select your profession/the type of credit you are seeking.
6. Complete the online evaluation form.

Upon completion of the online evaluation form, you will receive an immediate certificate to download and/or print for your files. If you have any questions regarding the CME, CNE, CPE or MOC certification for this activity, please contact Postgraduate Institute for Medicine at: inquiries@pimed.com or (303) 799-1930.
Program Planners and Faculty

Organizers

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LSU Health Sciences Center

Eileen T. Mederos, RN
LSU Health Sciences Center

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Louisiana State University Health Sciences Center

Eileen T. Mederos, RN
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American Academy of Emergency Medicine Board of Directors

Eleni Yeatras, RPh, BCOP
Johns Hopkins Sidney Kimmel Cancer Center at Sibley Memorial Hospital

Dan P. Zandberg, MD
UPMC Hillman Cancer Center

Invited Faculty

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St. Luke’s Cancer Center and Temple University

Ambiga Badari, MD
Ochsner Health System

Brian Boulmay, MD
LSU Health Sciences Center

William E. Carson, MD, FACS
The Ohio State University

Tyler Curiel, MD
UT Health San Antonio

Scott E. Delacroix, MD
Louisiana State University Health

Samir N. Khleif, MD
Georgetown University

Eileen T. Mederos, RN
LSU Health Sciences Center

Augusto C. Ochoa, MD
LSU Health Sciences Center

Breanne Peyton-Thomson, PharmD
Ochsner Health System

Connect With Us

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Society for Immunotherapy of Cancer (SITC)
Program Schedule

Saturday, April 6, 2019

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 – 8:00 a.m.</td>
<td>Registration</td>
</tr>
<tr>
<td>8:00 – 8:05 a.m.</td>
<td><strong>Session I: Introduction to Cancer Immunotherapy</strong>&lt;br&gt;<strong>Welcome, Introduction, SITC Resources</strong></td>
</tr>
<tr>
<td>8:05 – 8:30 a.m.</td>
<td><strong>Basic Principles of Cancer Immunotherapy</strong>&lt;br&gt;<em>Augusto C. Ochoa, MD – LSU Health Sciences Center</em></td>
</tr>
<tr>
<td>8:30 – 9:10 a.m.</td>
<td><strong>Session II: Immunotherapy in Practice</strong>&lt;br&gt;<strong>Immunotherapy for the Treatment of Lung Cancer</strong>&lt;br&gt;<em>Samir N. Khleif, MD – Georgetown University</em></td>
</tr>
<tr>
<td>9:10 – 9:50 a.m.</td>
<td><strong>Immunotherapy for the Treatment of Melanoma</strong>&lt;br&gt;<em>William E. Carson, MD, FACS – The Ohio State University</em></td>
</tr>
<tr>
<td>9:50 – 10:00 a.m.</td>
<td>Break</td>
</tr>
<tr>
<td>10:00 – 10:40 a.m.</td>
<td><strong>Immunotherapy for the Treatment of Head and Neck Cancer</strong>&lt;br&gt;<em>Brian Boulmay, MD – LSU Health Sciences Center</em></td>
</tr>
<tr>
<td>10:40 – 11:20 a.m.</td>
<td><strong>Immunotherapy for the Treatment of Genitourinary Malignancies</strong>&lt;br&gt;<em>Scott E. Delacroix, MD – Louisiana State University Health</em></td>
</tr>
<tr>
<td>11:20 – 12:00 p.m.</td>
<td><strong>Immunotherapy for the Treatment of Hematologic Malignancies</strong>&lt;br&gt;<em>Ambuga Badari, MD – Ochsner Health System</em></td>
</tr>
<tr>
<td>12:00 – 12:20 p.m.</td>
<td>Lunch</td>
</tr>
<tr>
<td>12:20 – 12:50 p.m.</td>
<td><strong>Session III: The Future of Cancer Immunotherapy</strong>&lt;br&gt;<strong>What’s Next for Cancer Immunotherapy?</strong>&lt;br&gt;<em>Tyler Curiel, MD – UT Health San Antonio</em></td>
</tr>
<tr>
<td>12:50 – 1:30 p.m.</td>
<td><strong>Session IV: Immunotherapy after Practice</strong>&lt;br&gt;<strong>Practical Barriers in Cancer Immunotherapy Treatment</strong>&lt;br&gt;<em>Sanjiv S. Agarwala, MD – St. Luke’s Cancer Center and Temple University</em></td>
</tr>
<tr>
<td>1:30 – 1:35 p.m.</td>
<td><strong>Closing Remarks</strong></td>
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Disclosure of Conflicts of Interest

Postgraduate Institute for Medicine (PIM) requires instructors, planners, managers, and other individuals who are in a position to control the content of this activity to disclose any real or apparent conflict of interest (COI) they may have as related to the content of this activity. All identified COI are thoroughly vetted and resolved according to PIM policy. PIM is committed to providing its learners with high quality activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

The faculty reported the following financial relationships or relationships they or their spouse/life partner have with commercial interests related to the content of this continuing education activity:

<table>
<thead>
<tr>
<th>Name of Faculty/Moderator</th>
<th>Reported Financial Relationship</th>
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<tbody>
<tr>
<td>Sanjiv S. Agarwala, MD</td>
<td>Consulting Fees: Merck</td>
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<tr>
<td>Ambuga Badari, MD</td>
<td>No relevant financial relationships to disclose</td>
</tr>
<tr>
<td>Brian Boulmay, MD</td>
<td>No relevant financial relationships to disclose</td>
</tr>
<tr>
<td>William E. Carson, MD, FACS</td>
<td>No relevant financial relationships to disclose</td>
</tr>
<tr>
<td>Tyler Curiel, MD</td>
<td>To be announced onsite</td>
</tr>
<tr>
<td>Scott E. Delacroix, MD</td>
<td>No relevant financial relationships to disclose</td>
</tr>
<tr>
<td>Samir N. Khleif, MD</td>
<td>Consulting Fees: Advaxis, AstraZeneca, BioLine, EMD Serono, GSK, IOBiotech, Lycera, McKinsey,</td>
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<td></td>
<td>Northwest, Syndax, UbiVac; Contracted Research: AstraZeneca, IOBiotech, MedImmune, Lycera,</td>
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<tr>
<td></td>
<td>BioLine, Syndax</td>
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<tr>
<td>Eileen T. Mederos, RN</td>
<td>No relevant financial relationships to disclose</td>
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<tr>
<td>Augusto C. Ochoa, MD</td>
<td>No relevant financial relationships to disclose</td>
</tr>
<tr>
<td>Breanne Peyton-Thomas, PharmD</td>
<td>No relevant financial relationships to disclose</td>
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<tr>
<td>Sanjiv S. Agarwala, MD</td>
<td>Consulting Fees: Merck</td>
</tr>
<tr>
<td>Christian M. Capitini, MD</td>
<td>Consulting Fees: Nektar Therapeutics</td>
</tr>
<tr>
<td>Marianne Davies, DNP, AOCNP</td>
<td>Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents:</td>
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<tr>
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<td>Genentech, Merck, BMS, AstraZeneca</td>
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<tr>
<td>Isabella C. Glitza, MD, PhD</td>
<td>Contracted Research: BMS</td>
</tr>
<tr>
<td>Zihai Li, MD, PhD</td>
<td>Contracted Research: BMS</td>
</tr>
<tr>
<td>Brian L. Rini, MD</td>
<td>Consulting Fees: Pfizer, Novartis, BMS; Contracted Research: Merck, Pfizer, BMS</td>
</tr>
<tr>
<td>Thomas R. Tobin, MD, MBA, FAAEM,</td>
<td>No relevant financial relationships to disclose</td>
</tr>
<tr>
<td>FACEP</td>
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<tr>
<td>Eleni Yeatras, RPh, BCOP</td>
<td>No relevant financial relationships to disclose</td>
</tr>
<tr>
<td>Dan P. Zandberg, MD</td>
<td>Contracted Research: BMS, AstraZeneca, Merck, Macrogenics</td>
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</table>
Disclosure Information

The subject matter experts reported the following financial relationships or relationships they or their spouse/life partner have with commercial interests related to the content of this continuing education activity:

<table>
<thead>
<tr>
<th>Name</th>
<th>Financial Relationships</th>
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<tbody>
<tr>
<td>Naval Daver, MD</td>
<td>Consulting Fees: Pfizer, Otsuka, Novartis, BMS, Daiichi-Sankyo, Jazz, Abbvie; Contracted Research: BMS, Pfizer, Incyte, Sunesis, Karyopharm, Daiichi-Sankya, Servier, Genentech, Abbvie, Glycomimetics</td>
</tr>
<tr>
<td>Jessica Geiger, MD</td>
<td>No relevant financial relationships to disclose</td>
</tr>
<tr>
<td>Isabella Glitza, MD, PhD</td>
<td>Contracted Research: BMS</td>
</tr>
<tr>
<td>Lauren Harshman, MD</td>
<td>Consulting Fees: Bayer, Exelixis, Genentech, Dendreon/Valient, Pfizer, Medivation/Astellas, Kew Group, Theragene, Corvus, Merck, Novartis; Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents: Applied Clinical Education, PER, Sanofi; Contracted Research: Bayer, Genentech, Gendreon/Valient, Pfizer, Medivation/Astellas, Merck, BMS, Jannsen, Sotio, Takeda</td>
</tr>
<tr>
<td>Benjamin Levy, MD</td>
<td>Consulting Fees: AstraZeneca, Celgene, Merck, Eli Lilly, Genentech, Takeda</td>
</tr>
<tr>
<td>Charles Lynch</td>
<td>Consulting Fees: Genentech, AbbVie; Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents: Genentech</td>
</tr>
<tr>
<td>Krista Rubin, MS, FNP-BC</td>
<td>Consulting Fees: Merck, EMD Serono</td>
</tr>
<tr>
<td>Thomas R. Tobin, MD, MBA, FAAEM</td>
<td>No relevant financial relationships to disclose</td>
</tr>
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</table>

The Postgraduate Institute for Medicine planners and managers have nothing to disclose.

The following SITC planners and managers – Mary Dean, JD, CAE; Peter Intile, PhD; Allison Joost; Claire Leischer, MS; Alicia Schuessler, CAE; Elizabeth Siepmann; Julia Schultz, MA; Shelby Stone; Lianne Wiggins; Tara Withington, CAE – have nothing to disclose.

Tara Withington, CAE, Executive Director of SITC, has ownership interest as a partner at Executive Director, Inc.

Disclosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients’ conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer’s product information and comparison with recommendations of other authorities.

Attention Pharmacists: Pharmacists have up to 30 days to complete the evaluation and claim credit for participation so that information can be submitted to CPE Monitor as required.
Basic Principles of Cancer Immunotherapy

Augusto C. Ochoa, MD
Director, Cancer Center
LSU Health Sciences Center
Basic Principles of Cancer Immunotherapy
Augusto C. Ochoa, MD – LSU Health Sciences Center

Audience Response Questions

1. What is a rational explanation for why cancers suppress immune reactivity?
   A. They look like a ‘foreign’ tissue.
   B. They are a ‘self’ tissue and therefore locally disable and evade the immune system.
   C. They overstimulate the immune system.
   D. They are incapable of generating an immune response.

2. What is not a mechanism of cancer immunoediting?
   A. Tumor dormancy and editing.
   B. Extrinsic tumor suppression.
   C. Tumor growth promotion.
   D. Eradication of immune cells.

3. How confident are you in your understanding of the biological mechanisms supporting current cancer immunotherapies?
   A. Not at all confident.
   B. Somewhat confident.
   C. Confident.
   D. Highly confident.

4. How often do you/will you consider immunotherapy for the treatment of patients with cancer?
   A. Never.
   B. Sometimes.
   C. Most of the time.
   D. Always.
Basic Principles of Cancer Immunotherapy
Augusto Ochoa MD
Director, LSU Cancer Center
New Orleans

Disclosures

• No disclosures
• I will not be discussing non-FDA approved indications during my presentation.
The Premise of Cancer Immunotherapy

• Normally, the immune system eliminates mutated and/or damaged cells
• To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of immunotherapy is to restore the capacity of the immune system to recognize and reject cancer.

Why Does the Immune System Fail to Eliminate Cancer?

• Cancer cells grow progressively in immunocompetent hosts without evidence of **T cell exhaustion** or **systemic anergy**
  • **T cell Exhaustion**: CD8+ T cells often become dysfunctional, entering a state known as exhaustion, during certain chronic infections or when they enter a suppressive tumor microenvironment
  • **Systemic Anergy**: A state of immune unresponsiveness. Induced when the T cell's antigen receptor is stimulated, effectively freezing T cell responses pending a "second signal" from the antigen-presenting cell
The 3 E’s of Cancer Immunoediting

R. Schrebier, L Old and M. Smyth
Basic Principles of Cancer Immunotherapy
Augusto C. Ochoa, MD – LSU Health Sciences Center

The 3 E’s of Cancer Immunoediting
Multi-layered Immunosuppression

- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor

Types of Immunotherapy

- T cell checkpoint modulation
- T cell adoptive transfer
- Therapeutic cancer vaccines
- Effector antibodies and antibody-drug conjugates
Basic Principles of Cancer Immunotherapy
Augusto C. Ochoa, MD – LSU Health Sciences Center

T cell Checkpoint Modulation

Antigen-specific T cell Activation
T Cell Checkpoint Modulation

- To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.
- The goal of T cell checkpoint blockade is to make T cell “off-switches” inaccessible to tumor cells, thus restoring tumor-specific immunity.

The CTLA-4 Checkpoint

- **Cytotoxic T-Lymphocyte Associated Protein 4**
- Also known as CD152
- Negative regulator of T cell activation
Anti-CTLA-4 induces regression of transplantable colon carcinoma

Wolchok et al. Lancet Oncol 2010

Ipilimumab (human anti CTLA-4)

- Granted FDA approval for treatment of patients with metastatic melanoma in 2010
The PD-1/PD-L1 Checkpoint

- Promotes T cell tolerization through inhibiting activation signaling
- T cell PD-1 interacts with PD-L1 and PD-L2
- Many cells express PD-L1/PD-L2 and can suppress T cell activation
- Tumors express PD-L1 through two primary mechanisms
  - TIL production of IFN-γ
  - Oncogenic signaling pathways

Anti-PD-1 Slows Tumor Growth in Pre-clinical Models

- PD-1 deletion or inhibition reduced CT26 colon cancer cell growth in BALB/c mice
Therapeutic Cancer Vaccines

- The goal of therapeutic cancer vaccination is to increase the immunogenicity of tumor antigens in order to generate a high frequency of tumor-specific T cells.

Components of a Cancer Vaccine

<table>
<thead>
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<th>Antigen</th>
<th>Adjuvant</th>
<th>Vector</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole tumor</td>
<td>Emulsifiers</td>
<td>Viral vectors</td>
<td>Injection</td>
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<tr>
<td>Protein antigen</td>
<td>Innate agonists</td>
<td>Dendritic cells</td>
<td>Gene gun</td>
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<tr>
<td>Antigenic peptide(s)</td>
<td>Cytokines</td>
<td>Attenuated bacteria</td>
<td>Systemic infusion</td>
</tr>
<tr>
<td>Antibodies</td>
<td></td>
<td></td>
<td>Nasal spray</td>
</tr>
</tbody>
</table>
An intra-nasal HPV E6/E7: α-GalCer vaccine slows growth of TC-1 (m. myeloma) tumors

4-1BB agonist antibody and HPV E6/E7 vaccine synergize in curing TC-1 (m. myeloma) tumors
Intratumoral Injection of Innate Immune Agonists:  
**Direct Vaccination Approach**

- Intratumoral DMXAA (mouse STING agonist) triggers rejection of B16 melanoma

---

Adoptive Cell Transfer

- The goal of adoptive cell transfer is to overwhelm the tumor with a higher frequency of tumor-specific immune cells and/or engineer immune cells to target cancer
Adoptive Cell Therapy Process

CD19 CAR T Cell Therapy for Relapsed B Cell ALL
Effector Antibodies & Antibody-drug Conjugates (ADCs)

- The goal of effector antibodies is to specifically target and kill tumor cells using innate mechanisms which are difficult to evade of suppress and/or through delivery of cytotoxic agents.

Key ADC/Antibody Principles

- **Specificity:** The more tumor specific the target antigen is, the higher the agent can be dosed without limiting toxicity.

- **Internalization:** The target tumor surface protein must internalize to deliver the toxin – it should do so frequently and to a suitable endosomal compartment.

- **Stability:** The toxin must remain inert and tethered to the antibody until it is delivered to its target cell.
Oncolytic Viruses

- The goal of an oncolytic virus is to specifically target and kill tumor cells through viral replication.

Combination Immunotherapies

Graph showing long-term survival with checkpoint blockade.
Combination Immunotherapies

*Dual CTLA-4 and PD-1 inhibition*

Chemotherapy can induce an immune response

---

Chae et al. JITC 2018

---

Chae et al. JITC 2018

---

Chae et al. JITC 2018
Combination Immunotherapies

Radiotherapy can induce an immune response

Immunotherapy Biomarkers

Tumor Mutation Load

T Cell Location

PD-L1 IHC

Tumor Inflammation

Immune Control of Tumor

Cesana et al. Biomed. 2015

Radiotherapy can induce an immune response

Cesano et al. Biomedicines 2018
Further Resources
Immunotherapy for the Treatment of Lung Cancer

Samir N. Khleif, MD
Director, The Loop Immuno-Oncology Lab
Georgetown University
1. Immunotherapy regimens that have demonstrated survival advantages in recent phase III trials in treatment naïve NSCLC patients include all the following EXCEPT:
   A. Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab (vs. Carboplatin/Paclitaxel/Bevacizumab in adenocarcinoma patients).
   B. Single agent pembrolizumab (vs. platinum doublet in PD-L1 expression > 50% NSCLC patients).
   C. Ipilimumab and Nivolumab (vs. platinum doublet in tumor mutational burden, TMB, high NSCLC patients).
   D. Carboplatin/Pemetrexed/Pembrolizumab (vs. Carboplatin/Pemetrexed in adenocarcinoma patients).

2. Which tumor biological feature has been shown to demonstrate lack of response to single agent immunotherapy?
   A. Programmed Death Ligand (PD-L1)
   B. Epidermal Growth Factor Receptor (EGFR) mutation
   C. Tumor Mutational Burden (TMB)
   D. KRAS mutations
Immunotherapy for the Treatment of Lung Cancer

Samir N. Khleif, MD
Director, The Loop Immuno-Oncology Lab
Georgetown University

Disclosures

• Consulting Fees: Advaxis, AstraZeneca, BioLine, EMD Serono, GSK, IOBiotech, Lycera, McKinsey, Northwest, Syndax, UbiVac;

  Contracted Research: AstraZeneca, BioLine, IOBiotech, MedImmune, Lycera, Syndax

• I will not be discussing non-FDA approved indications during my presentation.
Immunotherapy for the Treatment of Lung Cancer

Checkpoint Inhibitors: PD-1 and PD-L1

- PD-1 acts as an “off-switch” for T cells when interacting with PD-L1
- Tumor PD-L1 expression allowing cancer cells to evade immune attack
- Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells

Combination Immune Checkpoint Blockade

- CTLA-4 acts as an “off-switch” for T cells when interacting with B7
- Combination strategies combine both CTLA-4 and PD-1/PD-L1 blockade
FDA-approved Checkpoint Inhibitors in NSCLC

Nivolumab
- PD-1

Pembrolizumab
- PD-1

Atezolizumab
- PD-L1

Durvalumab
- PD-L1

CA209-003: Nivolumab in Heavily-pretreated Advanced NSCLC (NCT00730639)
Phase 1, 5-Year Update

- First report of long-term survival rate in patients with metastatic NSCLC treated with an immune checkpoint inhibitor

- According to the National Cancer Institute’s SEER data, 5-year survival rate for patients with advanced NSCLC is 4.9%

5-Year Survival

<table>
<thead>
<tr>
<th>OS (%)</th>
<th>1 y OS</th>
<th>2 y OS</th>
<th>3 y OS</th>
<th>5 y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (N = 129)</td>
<td>Median OS (95% CI), mo</td>
<td>9.9 (7.8, 12.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Graph]

Advances in Cancer Immunotherapy™ • Saturday, April 6, 2019 • Hyatt Regency New Orleans
Treatment Naïve Regimens: Competing Strategies

- KEYNOTE 024 – Pembrolizumab vs. Chemotherapy in PD-L1 > 50%
- KEYNOTE 042 – Pembrolizumab vs. Chemotherapy in PD-L1 > 1%
- KEYNOTE 189 – Pembrolizumab + Chemotherapy vs. Chemotherapy alone in patients with advanced non-squamous NSCLC
- IMPOWER 150 – Atezolizumab + Chemotherapy (Bev) vs. Chemotherapy (Bev) in patients in advanced non-squamous NSCLC
- KEYNOTE 407 – Pembrolizumab + Chemotherapy vs. Chemotherapy in advanced squamous cell lung cancer
- Checkmate 227 – Ipilimumab + Nivolumab vs. Chemotherapy in advanced NSCLC with high TMB

KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 Positive (>50%) NSCLS Study Design (NCT021427389)

**Key Eligibility Criteria**
- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating EGFR mutation or ALK translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

- Pembrolizumab 200 mg IV Q3W (2 years)
- Platinum-Doublt Chemotherapy (4-6 cycles)
- Pembrolizumab 200 mg Q3W for 2 years

KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 >50% NSCLC

Overall Survival

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 44</td>
<td>NR</td>
<td>0.60</td>
<td>0.005</td>
</tr>
<tr>
<td>Chemo 64</td>
<td>NR</td>
<td>(0.41-0.89)</td>
<td></td>
</tr>
</tbody>
</table>


KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 >1% NSCLC

KEYNOTE-042 Study Design

- Key Eligibility Criteria:
  - Untreated locally advanced or metastatic NSCLC of any histology
  - PD-L1 TPS ≥1%
  - No sensitizing EGFR or ALK alterations
  - ECOG PS 0 or 1
  - No uncontrolled or unstable CNS metastases
  - No history of pneumonitis that required systemic corticosteroids

- stratification factors:
  - Region (east Asia vs. rest of the world)
  - ECOG PS (0 vs 1)
  - Histology (squamous vs non-squamous)
  - PD-L1 TPS <6% vs 1-49%

- Key endpoints:
  - Primary: OS in PD-L1 TPS ≥50%, ≥70%, and ≥1%
  - Secondary: PFS and ORR in TPS ≥50%, ≥70%, and ≥1%; safety in TPS ≥1%

N = 637

Randomized 1:1

Pembrolizumab 100 mg Q3W for up to 35 cycles

Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m² Q3W vs
Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m² Q3W for up to 35 cycles

Lopes et al, ASCO 2018
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 > 1% NSCLC

Overall Survival

Survival benefit seemed to be driven by the TPS > 50% subset with little benefit witnessed in the subset TPS > 1-49%

Lopes et al, ASCO 2018

KEYNOTE-189: Pembrolizumab/Carboplatin/Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC

Key Eligibility Criteria
- Untreated stage IV non-squamous NSCLC
- No sensitizing EGFR or ALK alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No asymptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification Factors
- PD-L1 expression (TPS <1% vs 21%)
- Platinum (carboplatin vs carboplatin)
- Smoking history (never vs former/current)

Ghandi et al, NEJM 2018
KEYNOTE-189: Pembrolizumab/ Carboplatin/ Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC

Ghandi et al, NEJM 2018

PD-L1 < 1%

PD-L1 1 – 49%

PD-L1 ≥ 50%

Ghandi et al, NCI 2018
Immunotherapy for the Treatment of Lung Cancer
Samir N. Khleif, MD – Georgetown University

KEYNOTE-407: Pembrolizumab/chemotherapy vs Chemotherapy for Advanced Squamous-cell NSCLC

**Key Eligibility Criteria**
- Untreated stage IV NSCLC with squamous histology
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

**Stratification Factors**
- PD-L1 expression (TPS <1% vs ≥1%)
- Choice of taxane (paclitaxel vs nab-paclitaxel)
- Geographic region (east Asia vs rest of world)

**R (1:1)**

**Pembrolizumab 200 mg Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk)**

**Placebo (normal saline) Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk)**

**Pembrolizumab 200 mg Q2W for up to 31 cycles**

**Placebo (normal saline) Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk)**

**Optional Crossover**

**Pembrolizumab 200 mg Q3W for up to 35 cycles**

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>54.7% 0.56 (0.45-0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo + Chemo</td>
<td>70.1%</td>
<td></td>
</tr>
</tbody>
</table>

**PFS (RECISTv1.1, BICR)**

**Overall Survival**

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>30.6% 0.64 (0.49-0.85)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Placebo + Chemo</td>
<td>42.7%</td>
<td></td>
</tr>
</tbody>
</table>

Paz-Ares et al, ASCO 2018
IMPOWER 150: Atezolizumab/Carboplatin/Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/Bevacizumab in advanced non-squamous NSCLC

Socinski et al, NEJM 2018

IMPOWER 150: Atezolizumab/Carboplatin/Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/Bevacizumab in advanced non-squamous NSCLC

Socinski et al, NEJM 2018
Tumor Mutational Burden (TMB) may Determine Sensitivity to PD-1 Blockade in NSCLC

- In two independent cohorts, higher nonsynonymous tumor mutational burden (TMB) was associated with improved objective response, durable clinical benefit, and PFS.

*Partial or stable response lasting > 6 mo

Rizvi N et al, Science, 2015

CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients

Hellman et al, NEJM, 2018
CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients

Hellman et al, NEJM, 2018
**PD1/PD-L1 Inhibitors Increase Overall Survival in 2L Advanced NSCLC**

**CHECKMATE 017 (nivolumab)**

**CHECKMATE 057 (nivolumab)**

**KEYNOTE 010 (TPS ≥ 1%) (pembrolizumab)**

**OAK (atezolizumab)**

**PD1/PD-L1 Inhibitors Increase Overall Survival in 2L Advanced NSCLC**

**CHECKMATE 017 (nivolumab)**

- **CHECKMATE 057 (nivolumab)**

- **KEYNOTE 010 (TPS ≥ 1%) (pembrolizumab)**

- **OAK (atezolizumab)**

**PACIFIC (NCT02125461): Durvalumab after Chemoradiotherapy in Stage III NSCLC**

- **Patients with locally advanced unresectable NSCLC (Stage III) in a consolidation setting**

- **Absence of progression following at least 2 cycles of platinum-based chemotherapy concomitant with radiation therapy**

- **Durvalumab (n=468)**
  - IV 10 mg/kg Q2W ≤12 months

- **Placebo (n=234)**
  - IV Q2W

**PACIFIC (NCT02125461): Durvalumab after Chemoradiotherapy in Stage III NSCLC**

![Graph showing the probability of progression-free survival for Durvalumab and Placebo over time.](Antonia et al., NEJM 2017)

**Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC**

**Meta-Analysis: CM-057, KN-010, POPLAR**

![Graph showing the hazard ratio of different studies.](CK Lee et al., JTO 2016)
Single-agent Toxicities in 2/3L Randomized Trials

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab OAK</th>
<th>Nivolumab SQ: CM 017 (updated OS; 2L)</th>
<th>Nivolumab NSQ:CM 057 (updated OS; 2/3L)</th>
<th>Pembrolizumab Keynote 010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related Grade 3-5 AEs</td>
<td>15%</td>
<td>8%</td>
<td>11%</td>
<td>13-16%</td>
</tr>
<tr>
<td>Discontinuation due to related AEs</td>
<td>5%</td>
<td>6%</td>
<td>6%</td>
<td>4-5%</td>
</tr>
<tr>
<td>Pneumonitis AEs</td>
<td>1%</td>
<td>5%</td>
<td>3%</td>
<td>4-5%</td>
</tr>
</tbody>
</table>

Rittmeyer, et al., Lancet 2017
Brahmer, et al., NEJM 2015
Borghaei, et al., NEJM 2015
Herbst, et al., Lancet 2015

KEYNOTE-189: Pembrolizumab/Carboplatin/Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC

Ghandi et al, NEJM 2018
KEYNOTE-407: Pembrolizumab/chemotherapy vs Chemotherapy for Advanced Squamous-cell NSCLC

![Graph showing frequency of adverse events for Pembrolizumab/chemotherapy and Placebo/chemotherapy.](image)

Paz-Ares et al, ASCO, 2018

CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients

<table>
<thead>
<tr>
<th>TRAE, %</th>
<th>Nivolumab + ipilimumab (n = 576)</th>
<th>Chemotherapy (n = 570)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td><strong>Any TRAE</strong></td>
<td>75</td>
<td>31</td>
</tr>
<tr>
<td><strong>TRAE leading to discontinuation</strong></td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td><strong>Most frequent TRAEs (≥15%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt;1</td>
<td>0</td>
</tr>
</tbody>
</table>

Hellman et al, NEJM, 2018
**Summary of Frontline Strategies in Advanced NSCLC**

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Drug</th>
<th>PFS (Months)</th>
<th>OS (Months)</th>
<th>PFS HR in PD-L1 neg</th>
<th>Toxicities Grade 3 - 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-024</td>
<td>Pembro</td>
<td>10.3</td>
<td>30</td>
<td>NA</td>
<td>31% vs 53%</td>
</tr>
<tr>
<td>PD-L1 ≥ 50%</td>
<td>Plat/Pem or Gem or Pacli</td>
<td>6</td>
<td>14.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-042</td>
<td>Pembro</td>
<td>5.4</td>
<td>16.7</td>
<td>NA</td>
<td>18% vs 41%</td>
</tr>
<tr>
<td>PD-L1 ≥ 1%</td>
<td>Plat/Pem or Pacli</td>
<td>6.5</td>
<td>12.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMpower150</td>
<td>Atezo + Beva + Carbo/Pacli</td>
<td>8.3</td>
<td>19.2</td>
<td>0.77</td>
<td>60 vs 51%</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>Beva + Carbo/Pacli</td>
<td>6.8</td>
<td>14.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-189</td>
<td>Pembro + Plat/Pem</td>
<td>8.8</td>
<td>NR</td>
<td>0.75</td>
<td>67% vs 66%</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>Plat/Pem</td>
<td>4.9</td>
<td>11.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-407</td>
<td>Pembro + Carbo/Pacli or NabPacli</td>
<td>6.4</td>
<td>15.9</td>
<td>0.68</td>
<td>70% vs 68%</td>
</tr>
<tr>
<td>Squamous</td>
<td>Carbo/Pacli or NabPacli</td>
<td>4.8</td>
<td>11.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CheckMate 227</td>
<td>Nivo + Ipi</td>
<td>7.2</td>
<td>23</td>
<td>0.48</td>
<td>31% vs 36%</td>
</tr>
<tr>
<td>TMB≥10mut/Mb</td>
<td>Plat/Pem or Gem</td>
<td>5.4</td>
<td>16.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Solange Peters, 2018 ASCO Annual Meeting. This is for illustration purposes only and comparing different trials is challenging as populations, indications, and other characteristics vary.*

---

**Case Study: 1**

**Patient Background**
- 58 year-old male, never smoker
- Bilateral lung metastases
- Biopsy shows: Adenocarcinoma
- KRAS mutation and TP53
- PD-L1 is 20% positive (22C3 assay)
- TMB is intermediate 8 mutations/MB

**What do you recommend?**
1. Pembrolizumab
2. Pembrolizumab + carboplatin/pemetrexed
3. Carboplatin/Pemetrexed
4. Atezolizumab + carboplatin/paclitaxel/bevacizumab
Immunotherapy for the Treatment of Melanoma

William E. Carson, MD, FACS
Professor of Surgery, Associate Director of Clinical Research
The Ohio State University
Audience Response Questions

1. When considering treatment with anti-PD1 antibody (pembrolizumab or nivolumab) for melanoma which of the following is NOT correct?
   A. Overall response rate is approximately 40% in first line therapy.
   B. Only patients with tumors that stain positive for PD-L1 by immunohistochemistry respond to treatment.
   C. Randomized phase III trials have established improved overall survival and progression-free survival for patients treated with an anti-PD1 antibody compared with ipilimumab.
   D. BRAF mutation status does not predict potential response to anti-PD1 therapy.

2. When a patient presents with grade 3 or grade 4 diarrhea while on the combination with ipilimumab and nivolumab, which of the following is the correct next step?
   A. Hold ipilimumab but continue with nivolumab, as the CTLA-4 agent is more likely to cause the diarrhea and the liver enzyme elevation.
   B. Hold both the ipilimumab and nivolumab and start infliximab and high dose steroids.
   C. Hold both ipilimumab and nivolumab, and repeat labs weekly until normalized—combination therapy should be resumed at this point.
   D. Hold both the ipilimumab and nivolumab and start high dose corticosteroids.
Immunotherapy for the Treatment of Melanoma

William E. Carson, MD, FACS
Professor of Surgery, Associate Director of Clinical Research
The Ohio State University

Disclosures

• No relevant financial relationships to disclose
• I will not be discussing non-FDA approved indications during my presentation.
FDA-approved Immunotherapies in Melanoma

**Cytokines**

- High-dose Interferon
  - Adjuvant therapy
  - High dose I.V., followed by SQ
  - Treatment for up to one year
- Pegylated Interferon
  - Adjuvant therapy
  - SQ only
  - Longer duration than high dose interferon
- Interleukin-2
  - Stage IV
  - I.V., significant toxicities
  - Long term survival

**Immune Checkpoint Inhibitors**

- Ipilimumab, adjuvant and nonresectable/Stage IV, I.V.- different dosing for adjuvant and nonresectable/Stage IV
- Pembrolizumab, nonresectable/Stage IV, I.V.
- Nivolumab, adjuvant and non resectable/Stage IV, I.V.
- Ipilimumab in combination with nivolumab, Stage IV
FDA-approved Immunotherapies in Melanoma

Oncolytic Viruses

- Talimogene Laharperepvec
- T-VEC
- Non-resectable, intratumoral/intralesional

Adjuvant Ipilimumab in High-Risk Stage III Melanoma

- EORTC 18071 phase III trial
  - NCT00636168
  - Adjuvant ipilimumab vs placebo
  - Ipilimumab 10mg/kg Q3W for four doses, then every 3 months for up to 3 years
Immunotherapy for the Treatment of Melanoma
William E. Carson, MD, FACS – The Ohio State University

Adjuvant Nivolumab vs Ipilimumab in High-Risk Stage III Melanoma

- CheckMate 238 phase III trial
  - NCT02388906
  - Ipilimumab 10mg/kg Q3W for four doses, then every 3 months for up to 1 year
  - Nivolumab 3mg/kg Q2W for four doses, then every 3 months for up to 1 year

<table>
<thead>
<tr>
<th></th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>171/453</td>
<td>221/453</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>30.8 (30.1, NR)</td>
<td>21.3 (16.1, NR)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.66 (0.54, 0.81)</td>
<td>1.05 (0.76, 0.87)</td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

(Miller et al. ASCO 2018)

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>514</td>
<td>505</td>
</tr>
<tr>
<td>No. with Event</td>
<td>135</td>
<td>216</td>
</tr>
<tr>
<td>Hazard Ratio (95.4% CI)</td>
<td>0.57 (0.43–0.74)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

(P<0.001 by stratified log-rank test)

(Eggermont et al. NEJM 2018)
Talimogene laherparepvec (T-VEC) in Stage III/IV Melanoma

- Phase III OPTiM Trial
  - Oncolytic, genetically-engineered herpes virus
  - Intralesional T-VEC
    \(10^6\) pfu/mL, \(10^8\) pfu/mL 3 weeks after initial dose, then Q2W
  - Subcutaneous GM-CSF

Ipilimumab in Stage III/IV Melanoma

- Pooled OS data from 10 phase II/III trials
  - Previously treated (n = 1,257) or treatment-naïve (n = 604)
  - Ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706)
Immunotherapy for the Treatment of Melanoma

William E. Carson, MD, FACS – The Ohio State University

Pembrolizumab in Stage III/IV Melanoma
Phase III KEYNOTE-006 Trial

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma
Phase III CheckMate 067 Trial
Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma
Phase III CheckMate 067 Trial

Hodi et al. Lancet Oncol 2018
Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma
Phase III CheckMate 067 Trial

Tawbi et al. NEJM 2018
Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intracranial (N = 94)</th>
<th>Extracranial (N = 94)</th>
<th>Global (N = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>24 (26)</td>
<td>7 (7)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Partial response</td>
<td>28 (30)</td>
<td>40 (43)</td>
<td>40 (43)</td>
</tr>
<tr>
<td>Stable disease for at least 6 mo</td>
<td>2 (2)</td>
<td>6 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>31 (33)</td>
<td>28 (30)</td>
<td>33 (35)</td>
</tr>
<tr>
<td>Could not be evaluated†</td>
<td>9 (10)</td>
<td>13 (14)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Objective response‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>52</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>Percent of patients (95% CI)</td>
<td>55 (43–66)</td>
<td>50 (40–60)</td>
<td>51 (40–62)</td>
</tr>
<tr>
<td>Clinical benefit§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>54</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>Percent of patients (95% CI)</td>
<td>57 (47–68)</td>
<td>56 (46–67)</td>
<td>56 (46–67)</td>
</tr>
</tbody>
</table>

Tawbi et al. N Engl J Med 2018

HR for nivolumab plus ipilimumab vs ipilimumab:
0.54 (95% CI 0.44–0.67); p = 0.0001
HR for nivolumab vs ipilimumab:
0.65 (95% CI 0.53–0.79); p = 0.0001
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy

Importance of Tumor PD-L1 Status between Combination Checkpoint Blockade and Monotherapy
Adverse Events with Immunotherapies

Emens et al. Eur J Cancer 2017

Emens et al. Eur J Cancer 2017
### Treatment of Immune-Related AEs

<table>
<thead>
<tr>
<th>Grade of immune-related AE (CTCAE/equivalent)</th>
<th>Corticosteroid management</th>
<th>Additional notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Corticosteroids not usually indicated • Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤ grade 1 AE</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2-3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤ grade 1 AE, start 4-6 week steroid taper</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2-3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4-6 week steroid taper • Provide supportive treatment as needed</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2-3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed</td>
<td></td>
</tr>
</tbody>
</table>

Puzanov et al. JITC 2017

### Developmental Immunotherapeutic Strategies for Melanoma

[Diagram showing percent survival over time]
Developmental Immunotherapeutic Strategies for Melanoma
Targeting New Immune Checkpoints

Pilot Study: Radiotherapy (RT) + Intratumoral Immunocytokine (IT-IC) + Ipilimumab + Nivolumab for Advanced Melanoma

A UWCCC Clinical Trial (IND being prepared) with collaboration from Apeiron, NMS and NCI

Goals:

- First in human Phase-1 testing of IT-IC with an IC that can bind to tumor and mediate ADCC
- First in human IT-IC of such an IC immunologically timed after local RT
- First in human testing of this in combination with anti-CTLA4 and/or anti-PD1
- Toxicity/Tolerance/Anti-tumor effects
- Serial biopsies of the same lesions, to look for the changes seen in murine tumors

Protocol Chairs: Mark Albertini, M.D.
Radiation Oncology Co-Chair: Zachary Morris, M.D., Ph.D
Laboratory Co-Chair: Jacqueline A. Hand, Ph.D
Pathology Co-Chair: Erik Ranheim, M.D., Ph.D.
NCI Grant (R35 CA197078-01) PI: Paul M. Sondel, M.D., Ph.D.
Immunotherapy for the Treatment of Melanoma
William E. Carson, MD, FACS – The Ohio State University

Developmental Immunotherapeutic Strategies for Melanoma
Cytokine-based Strategies

Resources

An update on the Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy for the treatment of cutaneous melanoma: version 2.0

https://doi.org/10.1186/s40425-018-0362-6

Open Access

Lee, Margolin Cancers 2011
Rochman et al. Nat Rev Immunol 2009
Case Study 1

- **Background:**
  A 77 year old female has received 9 cycles of nivolumab with overall good tolerance, and only accompanied with a mild grade 1 hepatitis and hypothyroidism, requiring levothyroxine. She has been a lifelong smoker, however has cut down in recent years. During today's visit she appears short of breath and admits to dyspnea, which started fairly rapid, and has worsened over the last few hours. Pulse oximetry at rest shows 88% saturation, however when walking, the saturation drops down to 83%. Physical exam reveals decreased breath sounds with some wheezing, left mildly worse than right. She also is febrile at 101.6.

- **Lab Results:**
  Slightly elevated WBC, hemoglobin 10.8 g/l

What is the most important differential diagnosis for the patient’s symptoms?

A. Pneumonitis - Pneumonitis is a well described side effect of anti-PD1 therapy. The median time at onset is typically after 8 weeks of treatment initiation; however it can occur at any time during treatment.

B. COPD exacerbation – less likely, and can be treated al per guidelines.

C. Pulmonary embolus- cancer patients have a high risk of developing thromboembolic event. While pulmonary embolus is possible, CT scan evaluation of the patient will be able to exclude this, and will show

D. Pneumonia- This is a possible differential diagnosis, and has some overlap with pneumonitis. In both pneumonia and pneumonitis the WBC and temperature can be elevated, however, if pneumonitis is considered, rapid initiation of high dose corticosteroids can be lifesaving.

E. Tumor progression – while tumor progression is certainly possible, it typically does not present with sudden onset shortness of breath.
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E. Tumor progression – while tumor progression is certainly possible, it typically does not present with sudden onset shortness of breath.

Case Study 1 - Conclusion

• Pneumonitis represents a potential life threatening emergency, and clinicians should actively rule out pneumonitis in a patient with new onset shortness of breath while on immunotherapy.
Case Study 2

• Background:
  A 37 year old male is being diagnosed with metastatic melanoma, with sites of disease including his brain (3 small brain metastases), lungs, liver and bones. The mutation analysis performed on a liver biopsy shows that his tumor is no BRAF V600 mutant. He has read extensively about systemic treatment options and is here to discuss his next treatment options.

• Lab Results:
  His hemoglobin is 9.8 g/L, and his LDH is 2 times upper normal institutional limit. All other labs are within normal limit.

Case Study 2

Which regimen could be considered and has shown to most improve outcomes in melanoma patients with CNS metastases?

A. Pembrolizumab – the reported intracranial response rate for 18 melanoma patients with brain metastases was 22% in a phase II trial (Goldberg et al., Lancet Onc 2016)

B. Ipilimumab – While Ipilimumab has shown some efficacy in patients with melanoma brain metastases, both single pembrolizumab and the combination of ipilimumab and nivolumab have led to higher intracranial response rates as well as progression free survival, making Ipilimumab not a first line choice.

C. Ipilimumab and Nivolumab– At a median follow-up of 9.2 months in the CheckMate-204 study (N = 75), the intracranial ORR was 55% and the complete response rate was 21%, with intracranial and extracranial responses largely concordant. Importantly, duration of response was not reached at time of report, suggesting that, similar to extracranial responses, intracranial responses to immunotherapy can be profound and durable.

D. Temozolomide– In the era of immunotherapy, chemotherapy is rarely ever used in the frontline setting. As a single agent, temozolomide only shows a very modest therapeutic effect.

E. Dabrafenib and Trametinib– While the COMBI-MB trial (dabrafenib plus trametinib in patients with MBM and BRAF mutation) reported an intracranial response of 58% in patients without (44/76) and 56% in patients with (9/16) previous local brain therapy (median follow-up, 8.5 and 20.0 months, respectively), the key point is that patient must have a BRAF V600 mutation in order to be eligible for this regimen.
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Case Study 2 - Conclusion

• For immunotherapy, there is now increasing evidence that checkpoint inhibitors may also be effective in patients with melanoma brain metastases with a high rate of durable intracranial responses observed with combination therapy
Immunotherapy for the Treatment of Head and Neck Cancers

Brian Boulmay, MD
Director of Urologic Oncology
LSU Health Sciences Center Health
Audience Response Questions

1. Clinical trial data supports the use of PD-1 antibodies in patients with HNSCC in which scenario?
   A. HNSCC patients with no prior chemotherapy in the recurrent/metastatic setting.
   B. In combination with curative-intent radiotherapy in patients with locoregionally advanced HNSCC.
   C. As adjuvant therapy following curative resection in patients with locoregionally advanced HNSCC.
   D. As neoadjuvant therapy in patients with locoregionally advanced HNSCC who are planned for resection.
   E. HNSCC patients with recurrent/metastatic disease after platinum-based chemotherapy.

2. Which statement is false regarding PD-1 therapy in patients with HNSCC?
   A. Nivolumab increases overall survival in patients with R/M HNSCC compared with single-agent chemotherapy in platinum-refractory disease.
   B. Pembrolizumab has an overall response rate of 40% in patients with R/M HNSCC.
   C. PD-L1 expression is not required for treatment with a PD-1 inhibitor in patients with HNSCC.
   D. Benefit with nivolumab was observed in both patients with HPV-positive and HPV negative tumors.
   E. Pembrolizumab is administered as a fixed dose of 200 mg once every three weeks.
Immunotherapy for the Treatment of Head and Neck Cancer

Brian Boulmay, MD
Associate Professor, LSU Health

Disclosures

• No disclosures
• I will not be discussing non-FDA approved indications during my presentation
Immunotherapy for the Treatment of Head and Neck Cancers

Immuno-Oncology (I-O) developments in treatment of head and neck cancers

- Expression of immunologic markers to guide treatment
- Preventive vaccination against virally mediated cancers
- PD-1 checkpoint inhibitors for the treatment of metastatic disease

Immune Checkpoint Inhibitors (ICI)

PD-1 acts as “off-switch” for T cells, allowing cancer cells to evade immune attack

Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells
FDA-approved Checkpoint Inhibitors for use in Head and Neck Cancers

Pembrolizumab 200 mg IV Q3W
- KEYNOTE – 012/055: Patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (HNSCC) with disease progression on or after platinum-containing chemotherapy
- Accelerated Approval by FDA – August 5, 2016

Nivolumab 240 mg IV Q2W or 480 mg IV Q4W
- CheckMate – 141: Patients with R/M HNSCC with disease progression on or after a platinum-based therapy
- Breakthrough Therapy Designation by FDA – April, 2016
- Approval – November 10, 2016

KEYNOTE-012: Pembrolizumab in R/M HNSCC
Nonrandomized, Phase 1b Trial, Cohorts B, B2

Response assessment: Every 8 weeks until disease progression

Primary end points: ORR (RECIST v1.1, central imaging vendor review), safety
Secondary end points: ORR (investigator), PFS, OS, duration of response (DOR), ORR in HPV+ patients

1Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
2Treatment beyond progression was allowed.
3Initial cohort only.
4Median duration of disease not reached.
Immunotherapy for the Treatment of Head and Neck Cancers
Brian Boulmay, MD – LSU Health Sciences Center Health

KEYNOTE-012

- ORR = 18%
  - CR = 4%
  - PR = 14%
- mOS = 8.0 months
- mPFS = 2.2 months

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab

Phase II Trial, Single Arm

Patients (n=171):
- R/M HNSCC
- Resistant to platinum and cetuximab*
- Measurable disease (RECIST v1.1)
- ECOG PS 0-1

Pembrolizumab
200 mg IV Q3W Fixed dose

Continue until:
- 24 months of treatment
- PD
- Intolerable toxicity
- Investigator/patient decision

Safety and Survival Follow-up

Response assessment: Imaging every 6 to 9 weeks (central radiology review)

Primary end points: ORR (RECIST v1.1) by Response Evaluation Criteria in Solid Tumors and safety

Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

*75% of patients had ≥ 2 prior lines of therapy for metastatic disease
Neither tumor PD-L1 expression or HPV status are sufficiently robust in guiding the use of pembrolizumab at this time.

Bauml J, et al, J Clin Oncol. 2017

CheckMate 141: Nivolumab vs Investigator’s Choice in R/M HNSCC after Platinum Therapy
Phase III Randomized, Safety and Efficacy Trial

Key Eligibility Criteria
- R/M SCCHN of the oral cavity, pharynx, or larynx
- Progression on or within 6 months of last dose of platinum-based therapy
- Irrespective of no. of prior lines of therapy
- Documentation of p16 to determine HPV status (oropharyngeal)
- Regardless of PD-L1 statusa

Stratification factor
- Prior cetuximab treatment

Nivolumab
3 mg/kg IV Q2W

vs.

Investigator’s Choice
- Methotrexate 40 mg/m² IV weekly
- Docetaxel 30 mg/m² IV weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly

Primary endpoint
- OS

Other endpoints
- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02126566.

Ferris & Gillison, NEJM, 2016
**Immunotherapy for the Treatment of Head and Neck Cancers**

Brian Boulmay, MD – LSU Health Sciences Center Health

---

### Checkmate 141

2 year Overall Survival

![Graph showing Checkmate 141 2 year Overall Survival](image)

**Table 1:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI, mo)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 240)</td>
<td>7.7 (5.7-8.8)</td>
<td>0.88</td>
</tr>
<tr>
<td>IC (n = 121)</td>
<td>5.1 (4.0-6.2)</td>
<td>(0.54-0.88)</td>
</tr>
</tbody>
</table>

*Ferris RL. Oral Oncology, 2018*

---

### In Development: KEYNOTE-048

Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

![Diagram illustrating KEYNOTE-048](image)

**Diagram Notes:**

- **Key Eligibility Criteria:**
  - SCC of the oropharynx, oral cavity, hypopharynx, or larynx
  - R/M disease incurable by local therapies
  - ECOG PS 0 or 1
  - Tissue sample for PD-L1 assessment
  - Known p16 status in the oropharynx

- **Stratification Factors:**
  - PD-L1 expression
  - p16 status in oropharynx (positive vs negative)
  - ECOG performance status (0 vs 1)

*Burtness et al. ESMO 2018*
KEYNOTE-048

**PD-L1 CPS ≥ 1%**

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>69%</td>
<td>6.78 (0.64-0.96)</td>
<td>0.00086</td>
</tr>
<tr>
<td>EXTREME</td>
<td>81%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PD-L1 CPS ≥ 20%**

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>62%</td>
<td>0.61 (0.45-0.83)</td>
<td>0.0097</td>
</tr>
<tr>
<td>EXTREME</td>
<td>78%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Burtner et al. ESMO 2018

---

**KEYNOTE-048**

**All Patients**

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab + Chemotherapy</td>
<td>70%</td>
<td>0.77 (0.63-0.93)</td>
<td>0.0034</td>
</tr>
<tr>
<td>EXTREME</td>
<td>80%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)

- 12-month rate: 53.0% (43.9%)
- 24-month rate: 20.0% (18.7%)

Median (95% CI)

- 13.0 months (10.9-14.7)
- 10.7 months (9.3-11.7)

Burtner et al. ESMO 2018
Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

Pseudoprogression

- Early appearance of an increase in tumor burden, followed by tumor regression
- Initially recognized in melanoma trials, incidence up to 10%

Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

Case Report – KEYNOTE-012

- Both KEYNOTE-012 and CheckMate 141 trials showed rare rates of pseudoprogression with pembrolizumab and nivolumab, respectively.
Evaluating Biomarkers in HNSCC

Current FDA approvals of pembrolizumab and nivolumab are NOT contingent upon tumor PD-L1 status

• KEYNOTE - 012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
• KEYNOTE - 040: Phase III pembrolizumab vs. investigator’s choice chemotherapy
  • Did not meet survival endpoints in total population but improved outcomes in patients with PD-L1 expressing tumor
• CheckMate 141: Most benefit was seen in PD-L1-positive tumors

Evaluating Biomarkers in HNSCC

CheckMate 141: 2 Year Update

[Graph showing survival rates for PD-L1 expressers and non-expressers]
**Immune-related Adverse Events**

KEYNOTE-012 and CheckMate 141

### Table 2: Treatment-Related Adverse Events by Grade Severity (all patients as-treated population: N = 1,037)

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Event</th>
<th>Grade 1 or 2 (≤10% of patients)</th>
<th>Grade 3 (any occurrence)</th>
<th>Grade 4 (any occurrence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>79 (7.7%)</td>
<td>11 (1.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (1.4%)</td>
<td>5 (0.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (0.5%)</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13 (1.3%)</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (0.2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>4 (0.4%)</td>
<td>2 (0.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

### CheckMate 141

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>33 (3.2%)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (2.2%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (1.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>18 (1.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>17 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 (1.2%)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10 (1.0%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (0.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Dry eye</td>
<td>7 (0.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5 (0.5%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>4 (0.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Muscular inflammation</td>
<td>3 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1 (0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Immune-related Adverse Events

KEYNOTE-048 – Pembrolizumab monotherapy

**Graph 1:**

- **Incidence %**
  - Hypothyroidism: 30.3%
  - Hypertension: 23.7%
  - Anorexia: 6.7%
  - Grade 3-5: 10.5%
  - Led to death: 0.3%
  - Led to discontinuation: 6.6%

**Graph 2:**

- **Indicators**
  - Pembrolizumab: 30.3%
  - EXTREME: 23.7%
  - Grade 3-5: 10.5%
  - Led to death: 0.3%
  - Led to discontinuation: 6.6%

*Burtness et al. ESMO 2018*
Immune-related Adverse Events

KEYNOTE-048 – Pembrolizumab + Chemotherapy

- Corticosteroids not usually indicated
- If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can tolerate oral medication.
- If 1-day, start methylprednisolone 0.5-1 mg/kg/day if needed.
- If no improvement in 2-3 days, increase corticosteroid dose to 2 mg/kg/day.
- Once improved to ≤ grade 1-2, start 4-6 week steroid taper.
- Continue immunotherapy.

- Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone).
- If progression in 2-3 days, add additional/alternative immune suppressant.
- Once improved to ≤ grade 1, start 4-6 week steroid taper.
- Provide supportive treatment as needed.

- Discontinue immunotherapy.
- Continue intravenous corticosteroids.
- Start proton pump inhibitor for GI prophylaxis.
- Add PCP prophylaxis if more than 1 weeks of immunosuppression expected (≥30 mg prednisone or equivalent/day).

Burtness et al. ESMO 2018

Putana Journal for Immunotherapy of Cancer 2017
### Developmental Immunotherapies for HNSCC

- Durvalumab, atezolizumab, avelumab, CK-301 (anti-PD-L1)
- Cemiplimab (anti-PD-1)
- Ipilimumab, tremelimumab (anti-CTLA-4)
- Varlilumab (anti-CD27)
- PF-04518600, tavolimab (anti-OX40)

---

**Developmental Immunotherapies for HNSCC**

Cemiplimab (REGN2810) for treatment of patients with cutaneous squamous cell carcinoma (cSCC)

FDA approved – 09/28/2018

- Patients with metastatic cSCC
- Patients with locally advanced cSCC who are not candidates for radiation or surgery

- ORR 46% in 82 patients in study
- Responses durable, median DOR not reached

---

**Cemiplimab (REGN2810)**

- ORR 46% in 82 patients in study
- Responses durable, median DOR not reached
Developmental Immunotherapies for HNSCC

**MASTERKEY 232/KEYNOTE-137**
- Taliomogene laherparepvec (T-Vec)
  - Genetically engineered herpes virus
- T-Vec 10⁶ PFU/mL intratumoral injection followed by 10⁸ PFU/mL Q3W
- Pembrolizumab 200 mg IV Q3W
- Eligibility:
  - R/M HNSCC not suitable for curative therapy
  - Progressed after platinum treatment
  - At least 1 injectable cutaneous, subcutaneous, or nodal tumor ≥ 10 mm in longest diameter

Conclusions

1. Chemotherapy offers short survival with many side effects
2. PD-1 antibodies nivolumab and pembrolizumab are approved in *platinum-refractory* recurrent / metastatic HNSCC.
3. Most patients have fewer side effects with anti-PD1 therapy versus chemotherapy
4. Clinical trials are underway to improve immunotherapy response rates and testing immunotherapy in other settings
Patient Case Study 1

Patient Background Information:

• 78 yo M with a history of CAD, HTN, HLD
• Presents with painful left sided neck mass
• Lost 30 lbs. due to anorexia

November 2014

• PET CT
  • Large L sided cervical mass
  • Periepiglottic tumor with no airway compromise
  • Multiple cervical osseous metastases
• Palliative hypofractionated XRT initiated
Patient Case Study 1
January 2015

- Cervical disease decreased – pain improved
  - Carboplatin/paclitaxel 1st line
- PET CT revealed new osseous and axillary mets
  - Started on cetuximab 2nd line

Patient Case Study 1
June 2015

- Progression in cervical nodes
  - Re-irradiation not an option
- Enrolled in KEYNOTE-055
  - Started on pembrolizumab
Patient Case Study 1
October 2015

- Patient experienced near CR
- Response lasted 1 year
- No side effects of note

Patient Case 2

- pT4pN2cM0 squamous cell carcinoma of the larynx in 2017
- Laryngectomy
- Adjuvant chemoradiotherapy
Patient Case 2

- Patient started on nivolumab, as per Checkmate-141
- No subjective adverse events
- Developed hypothyroidism
  - Unclear association with nivolumab
  - Possibly secondary to prior radiotherapy
Patient Case 2

- CT Thorax after three months:

- CT thorax after ten months:
Immunotherapy for the Treatment of Genitourinary Cancers

Scott E. Delacroix, MD
Director of Urologic Oncology
Louisiana State University Health
Audience Response Questions

1. Examples of immunotherapy treatments for renal cell carcinoma include all of the following except:
   A. High-dose interleukin-2
   B. Nivolumab
   C. Sunitinib

2. A 65-year-old male presents with a cough and bilateral lung nodules of ≤ 1.5 cm in diameter, consistent with clear cell RCC. Complete staging reveals a left-sided renal mass and no other metastases. Laparoscopic nephrectomy confirms histology. After a good response to one year’s treatment with sunitinib, reimaging shows lung involvement with no bone or liver metastases. The patient remains asymptomatic. What is the best treatment option?
   A. Sorafenib
   B. Everolimus
   C. Nivolumab
   D. Cabozantinib
   E. Interferon-alpha
Immunotherapy for the Treatment of Genitourinary Malignancies

Scott E. Delacroix, MD
Director of Urologic Oncology
Louisiana State University Health

Disclosures

• No relevant financial relationships to disclose
• I will not be discussing non-FDA approved indications during my presentation
Immunotherapy for the Treatment of Genitourinary Cancers

Scott E. Delacroix, MD – Louisiana State University Health

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**Immunotherapy for Metastatic Kidney Cancer (Renal Cell Carcinoma; RCC)**

- **Surgically resectable** → **Oligo-metastatic** → **Metastatic**

---

**History of Immunotherapy in mRCC**

- Vaccines
- IFN-α and IL-2 based regimens
- Targeted Therapies
- Nivolumab
- Bevacizumab + IFN-α
- Ipilimumab + Nivolumab
- PD-1 blockade
- Anti-CTLA-4
- Vaccines Agonists

---

*Images and diagrams from reemakeup.blogspot.com*
FDA-approved Immunotherapies for mRCC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved</th>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td>1992</td>
<td>Metastatic RCC</td>
<td>600,000 International Units/kg (0.037 mg/kg) IV q8hr</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td></td>
<td></td>
<td>Infused over 15 minutes for a maximum 14 doses, THEN 9 days of rest, followed by a maximum of 14 more doses (1 course)*</td>
</tr>
<tr>
<td>Interferon-a (with bevacizumab)</td>
<td>2009</td>
<td>Clear cell RCC***</td>
<td>9 MIU s.c. three times a week</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>2015</td>
<td>Clear cell RCC, Refractory to prior VEGF</td>
<td>3mg/kg 240mg IV q 2 week or 480mg IV q 4 wks</td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>2018</td>
<td>Clear cell RCC, treatment naïve</td>
<td>3mg/kg nivo plus 1mg/kg ipi q3 wks x 4 doses then nivo maintenance at flat dosing</td>
</tr>
</tbody>
</table>

*Retreatment: Evaluate after 4 weeks, advisable only if tumor shrinkage and no retreatment contraindications (see package insert for details)

High Dose IL-2 in mRCC

- 20 year analysis of 259 patients
- ORR = 20%
  - 9% CR (n = 23)
  - 12% PR (n = 30)
- Median duration of response = 15.5 months
- Median OS = 19 months
**Second-Line Nivolumab in mRCC**

- CheckMate 025 Phase III trial
- Nivolumab = anti-PD-1 antibody
- Metastatic, clear-cell disease
- One or two previous antiangiogenic treatments
- Nivolumab (3 mg/kg IV Q2W) vs everolimus (10 mg daily)

**PD-L1 subgroups**

**PD-L1 ≥ 1%**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Median Overall Survival (95% CI)</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>94</td>
<td>21.8 (6.5–28.1)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>87</td>
<td>18.8 (11.9–19.9)</td>
</tr>
</tbody>
</table>

**PD-L1 < 1%**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Median Overall Survival (95% CI)</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>276</td>
<td>27.4 (21.4–NE)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>299</td>
<td>23.2 (11.7–26.2)</td>
</tr>
</tbody>
</table>
First-line Nivolumab + Ipilimumab in mRCC

**Patients**
- Treatment-naive advanced or metastatic clear-cell RCC
- Measurable disease
- KPS ≥70%
- Tumor tissue available for PD-L1 testing

**Randomize 1:1**

**Stratified by**
- IMDC prognostic score (0 vs 1–2 vs 3–6)
- Region (US vs Canada/Europe vs Rest of World)

**Treatment**

**Arm A**
- 3 mg/kg nivolumab IV + 1 mg/kg ipilimumab IV Q3W for four doses, then 3 mg/kg nivolumab IV Q2W

**Arm B**
- 50 mg sunitinib orally once daily for 4 weeks (6-week cycles)

**Treatment until progression or unacceptable toxicity**

**Nivolumab** = anti-PD-1 antibody  
**Ipilimumab** = anti-CTLA-4 antibody

---

First-line Nivolumab + Ipilimumab in mRCC

**No. of Patients**
- Nivolumab + Ipilimumab: 425
- Sunitinib: 422

**Median (95% CI)**
- NR (28.2–NE)
- 26.0 (22.1–NE)

**Hazard ratio for death**
- 0.43 (95% CI, 0.44–0.89)
- P < 0.001

**Overall Survival**

- Nivolumab + Ipilimumab vs Sunitinib
  - 12-Mo Overall Survival (95% CI)
    - Nivolumab + Ipilimumab: 80 (76–84)
    - Sunitinib: 72 (67–76)
  - 18-Mo Overall Survival (95% CI)
    - Nivolumab + Ipilimumab: 75 (70–78)
    - Sunitinib: 60 (55–65)
First-line Nivolumab + Ipilimumab in mRCC
PD-L1 Subgroups

In Development: First-line Atezolizumab + Bevacizumab in PD-L1+ mRCC
**In Development: First-line Checkpoint Inhibitors + Axitinib in mRCC**

**JAVELIN Renal 101**

- **KEYNOTE-426**
- Pembrolizumab + axitinib in mRCC
- Positive for OS and PFS (10/18/2018)

**In Development: First-line Pembrolizumab in mRCC**

**KEYNOTE - 427**

<table>
<thead>
<tr>
<th></th>
<th>N = 110</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>38 (29 – 48)</td>
</tr>
<tr>
<td>Confirmed BOR, n (%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>3 (3)</td>
</tr>
<tr>
<td>PR</td>
<td>39 (35)</td>
</tr>
<tr>
<td>SD</td>
<td>35 (32)</td>
</tr>
<tr>
<td>PD</td>
<td>31 (28)</td>
</tr>
<tr>
<td>No assessment</td>
<td>2 (2)</td>
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</tbody>
</table>
Immunotherapy for Metastatic Bladder Cancer
(Urothelial Carcinoma; UC)

Approved Checkpoint Inhibitors for mUC

**Cisplatin Refractory**

<table>
<thead>
<tr>
<th>Drug/Trial name</th>
<th>Phase</th>
<th>No. of patients</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
<th>Duration of response</th>
<th>Grade 3/4 AE (treatment related deaths)</th>
<th>Maximal duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CISPLATIN REFRACTORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>II</td>
<td>310</td>
<td>16%</td>
<td>7.1 mo</td>
<td>22.1 mo</td>
<td>18% (0 deaths)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>(Mvigor210 cohort 2)</td>
<td></td>
<td></td>
<td>(6% CR)</td>
<td>(1 yr 23%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>III</td>
<td>631</td>
<td>13%</td>
<td>NR</td>
<td>8.6 mo</td>
<td>21.7 mo</td>
<td>20%</td>
<td>NR</td>
</tr>
<tr>
<td>(Mvigor211)</td>
<td></td>
<td></td>
<td>(5% CR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>III</td>
<td>542</td>
<td>21%</td>
<td>7.1 mo</td>
<td>10.3 mo</td>
<td>NR</td>
<td>14% (4 deaths)</td>
<td>2 years</td>
</tr>
<tr>
<td>KEYNOTE-045</td>
<td></td>
<td></td>
<td>(1% CR)</td>
<td>(1 yr 33%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>II</td>
<td>265</td>
<td>19.6%</td>
<td>2 mo</td>
<td>8.7 mo</td>
<td>NR</td>
<td>16% (3 deaths)</td>
<td>2 years</td>
</tr>
<tr>
<td>(CheckMate275)</td>
<td></td>
<td></td>
<td>(6% CR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avelumab</td>
<td>Ib</td>
<td>242</td>
<td>17%</td>
<td>6.6 weeks</td>
<td>6.5 mo</td>
<td>NR</td>
<td>10% (1 death)</td>
<td>NR</td>
</tr>
<tr>
<td>JAVELIN</td>
<td></td>
<td></td>
<td>(6% CR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durvalumab</td>
<td>I/I</td>
<td>191</td>
<td>17.8%</td>
<td>1.5 mo</td>
<td>18.2 mo</td>
<td>NR</td>
<td>7% (2 deaths)</td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(6% CR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Anti-PD-L1 Antibodies**
1) Atezolizumab
2) Avelumab
3) Durvalumab

**Anti-PD-1 Antibodies**
1) Nivolumab
2) Pembrolizumab

**In development: Combinations**
1) IO + IO
2) IO + Chemotherapy
Approved Checkpoint Inhibitors for mUC

**Cisplatin Ineligible**

<table>
<thead>
<tr>
<th>CISPLATIN INELIGIBLE</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab IMVigor210 cohort 1</td>
<td>II</td>
<td>119</td>
<td>23% (5% CR)</td>
<td>2.7 mo</td>
<td>15.9 mo, 5yr NR</td>
</tr>
<tr>
<td>Pembrolizumab KEYNOTE-052</td>
<td>II</td>
<td>370</td>
<td>29% (7% CR)</td>
<td>6mo 30%</td>
<td>6mo 67%</td>
</tr>
</tbody>
</table>

**Anti-PD-L1 Antibodies**
1) Atezolizumab
   - PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area

**Anti-PD-1 Antibodies**
1) Pembrolizumab
   - PD-L1 CPS ≥ 10

**In development: Combinations**
1) IO + IO
2) IO + Chemotherapy

---

**Tumor Mutational Burden (TMB) May Signal Responses with PD-1 Blockade**

Atezolizumab in mUC

---

Rosenberg et al. Lancet 2016

Ghatalia et al. Ther Adv Med Oncol 2018
The Spectrum of Prostate Cancer

- Organ Confined, Low Risk
- Organ Confined, Risk of Metastases
- Metastatic Disease
- Castration Resistant Prostate Cancer (CRPC)

Risk of Cancer
Rising PSA, No Metastases
Rising PSA, No/minimal Metastases

Sipuleucel-T in mCRPC

- First anticancer therapeutic vaccine

Drake et al. Curr Opin Urol 2010
Kantoff et al. NEJM 2010

Kantoff et al. NCM 2010

Drake et al. Curr Opin Urol 2010
Limited efficacy of Checkpoint Inhibitors in mCRPC

No FDA-approved CIs for mCRPC

- Pembrolizumab is approved for all Microsatellite Instability-High (MSI-H) solid tumors
- MSI-H incidence is low in PC
  - Localized PC ~2%
  - Autopsy series of mCRPC ~12%
- MSI testing may offer pembrolizumab as an option

Future Combinations in mCRPC to Engage Immune System

- Hormonal therapy
- Radiation
- Radium-223
- PARP inhibitors
- Chemotherapy
- New targets
Immunotherapy for the Treatment of Genitourinary Cancers
Scott E. Delacroix, MD – Louisiana State University Health

irAEs with Immune Checkpoint Inhibitors in GU Cancers
Meta-analysis of 8 studies

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Incidence, any grade (GU only trials) (%)</th>
<th>Incidence, grades 3–5 (GU only trials) (%)</th>
<th>Incidence any grade (non-GU clinical trials) (%)</th>
<th>Incidence, grades 3–5 (non-GU clinical trials) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroid/thyroiditis</td>
<td>0.8–9</td>
<td>0–0.6</td>
<td>3.9–12</td>
<td>0–0.1</td>
</tr>
<tr>
<td>Diabetes/DKA</td>
<td>0–1.5</td>
<td>0–0.7</td>
<td>0.8–0.8</td>
<td>0.4–0.7</td>
</tr>
<tr>
<td>LFT changes/hepatitis</td>
<td>1.5–5.4</td>
<td>1–3.8</td>
<td>0.3–3.4</td>
<td>0.3–2.7</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2–4.4</td>
<td>0–2</td>
<td>1.8–3.5</td>
<td>0.25–1.9</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>NR</td>
<td>NR</td>
<td>0.2–0.8</td>
<td>0.0–0.2</td>
</tr>
<tr>
<td>Colitis/diarrhea</td>
<td>1–10</td>
<td>1–10</td>
<td>2.4–4.1</td>
<td>1.0–2.5</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0–0.5</td>
<td>0–0.2</td>
<td>0.2–0.9</td>
<td>0.2–0.4</td>
</tr>
<tr>
<td>Renal Dysfunction/nephritis</td>
<td>0.3–1.6</td>
<td>0–1.6</td>
<td>0.3–4.9</td>
<td>0.0–0.5</td>
</tr>
<tr>
<td>Myositis</td>
<td>0.8–5</td>
<td>0–0.8</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

- Similar incidence overall

Maughan et al. Front Oncol 2017

Immune-related Adverse Events

<table>
<thead>
<tr>
<th>Grade of immune-related AE</th>
<th>Corticosteroid management</th>
<th>Additional notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cotricosteroids not usually indicated</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>If indicated, start oral prednisone 0.5–1 mg/kg/day if patient can tolerate medication</td>
<td>Start protein pump inhibitors for GI prophylaxis</td>
</tr>
<tr>
<td></td>
<td>If IV required, start methylprednisolone 0.5–1 mg/kg/day IV</td>
<td>Continue immunotherapy on emergence of Grade 1 and off corticosteroids</td>
</tr>
<tr>
<td></td>
<td>If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day</td>
<td>Add FCP prophylaxis if more than 3 weeks of immunesuppression expected (≥30 mg prednisone or equivalent/day)</td>
</tr>
<tr>
<td></td>
<td>Once improved to Grade 1 AE, start 4–6 week taper taper</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Start prednisone 1–2 mg/kg/day (or equivalent dose of methylprednisolone)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If no improvement in 2–3 days, add additional alternative immune suppressant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Once improved to Grade 1, start 4–6 week taper taper</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Provide supportive treatment as needed</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Start prednisone 1–1 mg/kg/day (or equivalent dose of methylprednisolone)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If no improvement in 2–3 days, add additional alternative immune suppressant, eg, infliximab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Provide supportive care as needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discontinue immunotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continue intravenous corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Add protein pump inhibitors for GI prophylaxis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Add FCP prophylaxis if more than 3 weeks of immunesuppression expected (≥30 mg prednisone or equivalent/day)</td>
<td></td>
</tr>
</tbody>
</table>

Puzanov Journal for ImmunoTherapy of Cancer 2017
Additional Resources

Case Study 1: Metastatic Kidney Cancer
You are seeing a 65 year old woman with kidney cancer that was resected 3 years ago but has now recurred in the lungs and liver. She was initially treated with sunitinib but progressed after 9 months. What would immunotherapy option is most proven to treat her disease in the post VEGF targeted therapy setting?

A. Interferon-alfa
B. Thalidomide
C. Nivolumab
D. Atezolizumab
Immunotherapy for the Treatment of Hematologic Malignancies

Ambuga Badari, MD
Hematology and Medical Oncology
Ochsner Health System
Audience Response Questions

1. Blinatumomab, a bi-specific T-cell engager (BiTE), is effective and FDA approved for the following condition:
   A. Acute lymphoblastic leukemia
   B. Myeloma
   C. Follicular non-Hodgkin lymphoma
   D. Diffuse large B-cell lymphoma

2. The major toxicity associated with antigen-specific CD19 CAR-T cell therapy for acute lymphoblastic leukemia is:
   A. Hepatotoxicity
   B. Vitiligo
   C. Thrombocytopenia
   D. Cytokine release syndrome
Immunotherapy for the Treatment of Hematologic Malignancies

Ambuga Badari, MD – Ochsner Health System

Disclosures

- No relevant financial relationships to disclose
- I will not be discussing non-FDA approved indications during my presentation.
Monoclonal Antibodies Targeting B Cell Lymphomas

FDA-approved Checkpoint Inhibitors for Lymphomas

- **Nivolumab** (anti-PD-1)
  
  **CheckMate 205/039:**
  
  Patients with cHL that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin

- **Pembrolizumab** (anti-PD-1)
  
  **KEYNOTE-087:**
  - Adult and pediatric patients with refractory cHL, or,
  - patients whose disease has relapsed after three or more lines of therapy

  **KEYNOTE-170:**
  - Adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or,
  - those who have relapsed after 2 or more prior lines of therapy
Patient Selection Criteria for Checkpoint Inhibitor Therapies

- Expression of the ligand for checkpoint inhibition
  - e.g. PD-L1 expression or MSI status for anti-PD-1 therapy (in solid tumors)
- Relapse or progression after previous therapies
  - Nivolumab: After prior HSCT and brentuximab therapy
  - Pembrolizumab: Relapse after three prior treatments, PMBCL
- Presence of co-morbidities
  - e.g. Presence of active autoimmune disease which could be worsened

Nivolumab in Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N=23)</th>
<th>Failure of Both Stem-Cell Transplantation and Brentuximab (N=13)</th>
<th>No Stem-Cell Transplantation and Failure of Brentuximab (N=3)</th>
<th>No Brentuximab Treatment (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>4 (17)</td>
<td>1 (7)</td>
<td>0</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Partial response</td>
<td>16 (69)</td>
<td>11 (85)</td>
<td>3 (100)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (13)</td>
<td>2 (15)</td>
<td>0</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Objective response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>20</td>
<td>13</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Percent of patients (95% CI)</td>
<td>87 (66–97)</td>
<td>87 (66–98)</td>
<td>100 (99–100)</td>
<td>80 (78–99)</td>
</tr>
<tr>
<td>Progression-free survival at 24 wks</td>
<td>86 (62–95)</td>
<td>85 (62–98)</td>
<td>NC</td>
<td>80 (10–97)</td>
</tr>
<tr>
<td>Overall survival — wks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Range at data cutoff</td>
<td>21–75</td>
<td>21–75</td>
<td>32–55</td>
<td>30–50</td>
</tr>
</tbody>
</table>
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Nivolumab in Hodgkin Lymphoma

Ansell et al. NEJM 2015

Pembrolizumab in Hodgkin Lymphoma

Zinzani et al. Hematological Oncology 2017
Immunotherapy for the Treatment of Hematologic Malignancies

Ambuga Badari, MD – Ochsner Health System

Pembrolizumab in Primary Mediastinal Large B cell Lymphoma


B Cell Malignancies are CD19+

Chimeric Antigen Receptor (CAR) T cell Therapy

- Engineering patient T cells to target and eliminate cells presenting specific antigens

FDA-approved CAR T Cell Therapies for Lymphoma

- Axicabtagene ciloleucel
  - ZUMA-1: Adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma, high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma

- Tisagenlecleucel
  - JULIET: adult patients with relapsed/refractory large B cell lymphoma—including diffuse large B cell lymphoma (DLBCL), high-grade B cell lymphoma and DLBCL arising from follicular lymphoma—after 2 or more lines of systemic therapy.
Patient Selection Criteria for CAR T Therapies

- Expressions of the desired antigen for CAR T therapy
  - e.g. CD19
- Disease burden
  - CAR T trials: <30% to minimize the risk of cytokine release syndrome
- Presence of co-morbidities
  - e.g. Presence of active autoimmune diseases which could be worsened

Axicabtagene ciloleucel in B Cell Lymphoma
Overall Survival

Duration of Response
Schuster et al. NEJM 2017

Axicabtagene ciloleucel in B Cell Lymphoma
Overall Survival

Neelapu et al. NEJM 2017
**Patient Selection Criteria for CAR T Therapies**

- Expression of the desired antigen for CAR T therapy (e.g., CD19)
- Disease burden
- CAR T trials: <30% to minimize the risk of cytokine release syndrome
- Presence of co-morbidities (e.g., Presence of active autoimmune diseases which could be worsened)

**Axicabtagene ciloleucel in B Cell Lymphoma**

**Duration of Response**

![Graph showing duration of response with median survival times for complete, objective, and partial responses.](image)

**Axicabtagene ciloleucel in B Cell Lymphoma**

**Overall Survival**

![Graph showing overall survival rates for diffuse large B-cell lymphoma and follicular lymphoma.](image)

**Tisagenlecleucel in B Cell Lymphoma**

**Duration of Response**

![Graph showing response rates and median survival times.](image)

**Tisagenlecleucel in B Cell Lymphoma**

**Overall Survival**

![Graph showing overall survival rates for diffuse large B-cell lymphoma and follicular lymphoma.](image)
Immunotherapy for the Treatment of Hematologic Malignancies
Ambuga Badari, MD – Ochsner Health System

**Tisagenlecleucel in B Cell Lymphoma**
**Duration of Response**

- Diffuse Large B-Cell Lymphoma, Response Duration
  - Median, not reached; 86% had response at median follow-up of 28.6 mo

- Follicular Lymphoma, Response Duration
  - Median, not reached; 39% had response at median follow-up of 38.6 mo

**FDA-approved CAR T Cell Therapies for Acute Leukemia**

- **Tisagenlecleucel**
  - ELIANA: patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

- **ELIANA**
  - Patients with relapsed/refractory B cell precursor ALL

**BiTE (Blinatumomab) Therapy**

- Combines anti-CD19 F(ab) with anti-CD3 F(ab)
- Lacks the Fc region
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- FDA approval: Patients with relapsed/refractory B cell precursor ALL

**Blinatumomab for B-ALL**

- Kantarjian et al. NEJM 2017
BiTE (Blinatumumab) Therapy

- Combines anti-CD19 F(ab) with anti-CD3 F(ab)
- Lacks the Fc region
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- FDA approval: Patients with relapsed/refractory B cell precursor ALL

Blinatumomab for B-ALL

![Graph showing median overall survival comparison between Blinatumomab and Chemotherapy. Median survival is 7.7 months for Blinatumomab (95% CI 5.6-9.6) and 4.0 months for Chemotherapy (95% CI 2.9-5.3) with a hazard ratio of 0.71 (95% CI 0.55-0.93) and a p-value of 0.01.](image)
Immunotherapies for Multiple Myeloma

- No approved checkpoint inhibitors
  - KEYNOTE-183/185/023: Halted or discontinued due to risk/benefit profile
- Vaccine-based approaches
  - Non-antigen Specific
    - Attenuated measles
    - Whole cell – FM-CSF
    - Dendritic – tumor fusions
  - Antigen Specific
    - Idiotype: RNA < DNA, protein
    - Pulsed dendritic cells
    - Tumor-specific peptides

In Development: BCMA+ CAR T Therapy for Myeloma

- bb2121
  - B cell maturation antigen (BCMA)
  - Phase I CRB-401 study
  - Previously treated patients with relapsed/refractory multiple myeloma
Immunotherapies for Multiple Myeloma

- No approved checkpoint inhibitors
- KEYNOTE-183/185/023: Halted or discontinued due to risk/benefit profile
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- Phase I CRB-401 study
- Previously treated patients with relapsed/refractory multiple myeloma

Raje et al. ASCO 2018

Cytokine Release Syndrome (CRS)

- Hypotension
- Fever, constitutional symptoms
- Increased vascular permeability
- Tachycardia
- Inflammatory cytokine release
- IL-6, TNF, IFN-γ
- Cytokine storm

CRS Management

- Tocilizumab
  - Monoclonal antibody that blocks IL-6 signaling

- Tocilizumab + corticosteroids
- Extensive co-morbidities or older age?
- Vigilant supportive care
  - Assess for infection
  - Treat fever and neutropenia if present, monitor fluid balance, antibiotics, analgesics as needed

- Tocilizumab
  - Day after T Cell Infusion

- IL-6
- IFN-γ
- CRP
- CRP, IL-6, and CRP levels peak at 4 days

June et al. Science 2018

Lee et al. Blood 2018

Advances in Cancer Immunotherapy™ • Saturday, April 6, 2019 • Hyatt Regency New Orleans
Case Study 1

- 63y/o woman diagnosed with acute mixed phenotypic Ph+ (p210) leukemia
- She had good performance status, with multiple siblings, and 1 sister was 10/10 match
- Initial plan was for allogeneic stem cell transplant in first CR
- Initial induction treatment was with Hyper CVAD
- She received Hyper CVAD cycles 1A, 1B, 2A with IT chemotherapy and Dasatinib
- There was no CNS involvement
- Bone marrow biopsy after 3 cycles demonstrated complete morphologic response.
### Case Study 1

- She was on maintenance Dasatinib
- Developed cardio-respiratory complications, Dasatinib was held
- She was off of ALL treatments for about 5 months
- No evidence of relapse in peripheral blood
- Refused follow up bone marrow biopsy

---

### Case Study 1

- 5 months later, she presented with increasing WBC counts
- Repeat bone marrow biopsy demonstrated **relapsed disease**, morphologically similar to initial diagnosis and was Ph +
- She was treated with Hyper CVAD again and completed 3 cycles again
- She however, refused TKI due to complications previously
- CNS involvement was still absent
Case Study 1

- She eventually presented with increasing WBC count, of > 100k
- A repeat bone marrow biopsy again demonstrated relapsed acute bi-phenotypic leukemia, Ph +
- Blasts were mostly positive for lymphoid lineage markers, with very scant myeloid markers
- No CNS disease
- She received 1 cycle Blinatumomab
- No CRS
- However, continued to have persistently high WBC count after C1
- Treatment changed to Clofarabine

Case Study 2

- 62y/o male presented with several weeks back pain, weight loss
- Imaging showed pathologic rib fractures, retro peritoneal adenopathy
- Bone biopsy revealed grade 2 / admixed with grade 3a follicular lymphoma
- Initially treated with Rituximab-Bendamustine, with no response after 3 cycles
- Treatment changed to Ofatumumab – CHOP
- Minimal response by PET after 3 cycles
- PS = ECOG 1
Case Study 2

What is the next course of action?

1. Continue the current treatment
2. Biopsy and change treatment to EPOCH if transformed to DLBCL
3. Biopsy and change treatment to ICE if transformed to DLBCL
4. Autologous stem cell transplantation
5. Clinical trial
6. CAR-T

Case Study 2

• Biopsy of mass showed CD 20+ large cell lymphoma
• Treatment changed to R-ICE
• Repeat imaging after 2 cycles shows mixed response, with areas of decreased PET avidity and areas of increased avidity
• His performance status has declined slightly but still ECOG 1
Case Study 2

**What is the next course of action?**

1. Continue the current treatment and re-image after 2 more cycles
2. Autologous stem cell transplantation
3. Allogeneic stem cell transplantation
4. Clinical trial
5. CAR-T therapy
What’s Next for Cancer Immunotherapy?

Tyler Curiel, MD  
Professor of Medicine  
UT Health San Antonio

*Slides not available at time of printing. Enclosed separately.*
Practical Barriers in Cancer Immunotherapy Treatment

Sanjiv S. Agarwala, MD
Chairman of Medical Oncology
St. Luke’s Cancer Center and Temple University
Audience Response Questions

1. When developing a reimbursement strategy for Immunotherapy agents, which of the following would be a key element for success?
   A. Limiting IO agent use to those agents with Medicare National Coverage Determination.
   B. Identify a point person from your reimbursement of financial staff to focus on nuances of various patient assistance programs.
   C. Limit the use of IO agents that are used in combination therapy.
   D. Streamline the process by submitting only claims you believe will be reimbursed, thus saving time on the employee work load.

2. When considering off-label use for IO agents, which of the following is true?
   A. Commercial payers are easier to negotiate with than Medicare.
   B. Developing a standardized process is critical.
   C. The patient needs to be informed of the risk for non-coverage and consent to proceeding.
   D. A and B
   E. B and C

3. A 52 year old male presented to the clinic with metastatic melanoma. He has been treated in another facility with a combination of ipilimumab and nivolumab from which he had a PR which lasted 9 months. He now has disease progression and has been referred to you for re-treatment with immunotherapy because “it has worked before”. You are considering putting him on pembrolizumab monotherapy.
   Which of the following is true?
   A. There is no evidence that this approach will work, and it is not going to be reimbursed.
   B. The evidence is limited and there is possibility of denial and a peer to peer review of the case may be necessary.
   C. There is level one evidence for this approach, reimbursement is certain.
   D. There is a higher likelihood of the combination being reimbursed and you should advise the patient to take the combination instead.
Practical Barriers in Cancer Immunotherapy Treatment
Sanjiv S. Agarwala, MD
Professor & Chief
St. Luke’s Cancer Center, Temple University

Disclosures

• Consulting Fees: Merck
• I will not be discussing non-FDA approved indications during my presentation.
IO Pipeline and Research

- Current products on the market are the “tip of the iceberg” when looking at manufacturers’ Immuno-Oncology (I-O) pipelines
- During the next one to five years, we can expect a new IO product or indication every few months
- Not only new products, but a myriad of new combinations and regimens
- Take advantage of pipeline reports published by various organizations

Strategies for New Information

- Immuno-Oncology Champion
  - Identify an “Immuno-Oncology Champion” from among your providers to be the “I-O point person” responsible for all product questions and staff education (can be physician, advance practice nurse of pharmacists)
- Education group
  - Identify a core group within your practice to manage patient education, including the review of existing patient materials and/or the development of new materials specific to I-O agents and management of their adverse effects
- Staff education
  - Proactively update staff on new information and consider use of manufacturer-provided resources including on-site training/education
Emergency Response

- Develop protocols
  - Use your “I-O Champion” to take the lead in developing/revising any treatment protocols that may be impacted by the addition of new I-O therapies in your practice

- Patient education
  - Educate all patients on an I-O therapy to clearly identify themselves as such; make sure that these patients can be quickly identified as being on an I-O therapy in their medical record

- Staff education
  - Ensure staff understand and can identify the most common adverse events associated with I-O products, and know when these events could be potentially be life-threatening and/or require immediate clinical attention

Manage Reimbursement/Finances

- New to market I-O agents may not yet have specific J-Code
  - Ensure process is in place for appropriate management/billing until J-Code is assigned or in the case of Hospital Outpatient Prospective Payment Services a C-Code (Temporary = C9399)

- Identify a point person from within your financial or reimbursement staff to focus on I-O agents and understand the nuances of the various patient support programs
  - Manufacturer benefits verification programs, replacement programs, co-pay support programs, co-pay foundations, and patient assistance programs

- Ensure your practice has sufficient Patient Advocacy
  - Most practices have found that Financial Counselors/Medication Assistance Coordinators pay for themselves many times over; if you are not sure if you have enough, it’s a good time to conduct an analysis.
Develop Approval Process

- High dollar medication approval process
  - Full benefits investigation, utilize pharma services if offered and allowed per hospital/institution policy
  - Prioritize staff resources to enroll every viable patient into a support program, regardless of on or off-label
- Robust off-label policy and procedure
  - All off-label requests require predetermination
  - Patients are made aware of risks and benefits, including financial risk
  - Patients are required to sign an ABN or NONC
  - Peer review process for appeal if needed
Medicare

- Most Medicare Administrative Contractors (MAC) have at least one I-O agent Local Coverage Determination (LCD)
- Some MAC have separate LCD for all agents
  - CGS published atezolizumab LCD within the first six weeks of release of the agent
- No successful reimbursement outside the FDA label indications
- No National Coverage Determinations (NCD) to date

Off-Label Medication Process:

**Medicare Pre-Treatment**

1. Off-label medication use is considered
2. Risk/benefit conversation (including payment risk) occurs with patient
3. Patient wishes to proceed with off-label medication use → No
4. Patient wishes to proceed with off-label medication use → Yes

**Key**
- Clinical Team
- Reimbursement Specialist
- Medication Assistance Coordinator

Alternate treatment options are considered
Practical Barriers in Cancer Immunotherapy Treatment
Sanjiv S. Agarwala, MD – St. Luke’s Cancer Center and Temple University

**Off-Label Medication Process:**

**Medicare Pre-Treatment**

- Off-Label Treatment is scheduled
- Alternate treatment options are considered

---

**Medicare Pre-Treatment**

1. Off-Label Treatment is scheduled
2. Alternate treatment options are considered
3. Requires evidence of off-label medication use
   - Sufficient evidence
     - Notifies Medication Assistance
   - Insufficient evidence
     - RPh enters off-label medication use into off-label data base
4. RPh escalates off-label request to disease-specific leader, division director, and pharmacy director
   - Approved
   - Not approved
   - Key: Clinical Team, Reimbursement Specialist, Medication Assistance Coordinator

---

**Off-Label Medication Process:**

- Explores manufacturer assistance/replacement options
- Notifies provider of likelihood of Medicare payment based on evidence, as well as availability of manufacturer assistance/replacement options
- Updates patient and readdresses risks/benefits
- Yes
- Patient wishes to proceed with off-label medication use
- No
- Obtains patient signature on ABN
- Key: Clinical Team, Reimbursement Specialist, Medication Assistance Coordinator
Practical Barriers in Cancer Immunotherapy Treatment
Sanjiv S. Agarwala, MD – St. Luke’s Cancer Center and Temple University

**Off-Label Medication Process:**

*Medicare Post-Treatment*

- Patient receives off-label therapy
- Claim is submitted to Medicare
- Payer’s decision is received
- Appeals denial (5 levels allowed)
- Approved
- Not approved
- Approved
- Not approved
- Arranges payment for Medicare allowed amount

**Key**

- Clinical Team
- Reimbursement Specialist
- Medication Assistance Coordinator
- Chief Financial Officer
- Managed Care
- Financial Counseling

**Commercial Payers**

- Policies primarily based upon published scientific evidence
- Clinical policy guidelines and pathways
  - Vendor Pathways examples: Well Point, New Century Health, AIM
  - Clinical policies examples: Anthem, Aetna, UHC, Cigna, Humana
- Often the clinical policies require medication eligibility restrictions beyond the label and additional criteria to be met in order to assure reimbursement
  - Example: Anthem clinical policy for nivolumab includes patient’s current ECOG score 0-2 be met
Commercial Payers

- Use of maximum dosages regardless of weight
  - Maximum allowable units per day and per date span for specialty drugs
- Use of National Drug Code (NDC) units versus CPT/Healthcare Common Procedure Coding System (HCPCS) units creates confusion and concern for underpayment
  - J code represents the amount of drug per billing unit
    - 1 J code per medication
    - J code established by CMS
  - NDC represents the manufacturer and size of the vial
    - 1 NDC code for each vial size for each manufacturer
    - NDC code established by FDA and manufacturer
  - Monitor closely for errors in underpayment

Commercial Payers

- Disproportionate approvals of total billing units versus doses for a specific period of time
  - Example: Authorization for 90mg pembrolizumab for 6 infusions but date range is for nine months- *Make sure that the dates and authorizations match*
- Always pursue authorization/pre-determination for IO’s, regardless of whether the therapy is on or off-label
  - Retrospective denials often occur, particularly for off-label uses, even when there was a pre-determination in acceptance of the use
Commercial Payers

- Billing for waste with immuno-oncology agents
  - Proper usage of the JW modifier
    - JW modifier will indicate the amount of waste volume represented
    - I-O agents that are single-use vials or single-use package for unused portion are eligible
    - Multi-dose vials are not eligible (and currently not available)
  - Not all payers will pay for waste or only pay for part
  - Some payers do not allow rounding of doses and do not pay for waste (a lose/lose situation for providers)
  - Proper documentation necessary in the medical record for discarded waste
    - Mandated wastage rationale for any JW lines on Medicare claims on January 1, 2017

Off-Label Medication Process:

**Commercial Payers**

1. Off-label medication use is considered
2. Risk/benefit conversation (including payment risk) occurs with patient
3. Patient wishes to proceed with off-label medication use
4. **Key**
   - Clinical Team
   - Reimbursement Specialist
   - Managed Care
   - Medication Assistance Coordinator
   - Financial Counseling
   - Chief Financial Officer
5. Alternate treatment options are considered
Off-Label Medication Process:

**Commercial Payers**

1. **Off-Label Treatment is scheduled**
2. **Alternate treatment options are considered**
3. **RPh enters off-label medication use into off-label data base**
4. **Submits pre-determination request to payer**
   - **Payer’s decision is received**
      - **Approved**
      - **Not approved**

**Key**
- Clinical Team
- Reimbursement Specialist
- Medication Assistance Coordinator
- Chief Financial Officer
- Managed Care
- Financial Counseling

Or...

1. **Submits appeal to payer and notifies Medication Assistance**
2. **Payer’s decision is received**
   - **Approved**
   - **Not approved**

**Additional Notes**
- Commercial Payers
- Off-Label Treatment is scheduled
- Alternate treatment options are considered
- RPh enters off-label medication use into off-label data base
- Submits pre-determination request to payer
- Payer’s decision is received
- Approved
- Not approved

**Key**
- Clinical Team
- Reimbursement Specialist
- Medication Assistance Coordinator
- Chief Financial Officer
- Managed Care
- Financial Counseling

**Payer’s decision is received**
- Approved
- Not approved

**Sufficient evidence**
- Reviews evidence for off-label medication use
- Insufficient evidence
Practical Barriers in Cancer Immunotherapy Treatment
Sanjiv S. Agarwala, MD – St. Luke’s Cancer Center and Temple University

Off-Label Medication Process: Commercial Payers

- Off-Label Treatment is scheduled
- Reviews evidence for off-label medication use
  - Sufficient evidence
  - Insufficient evidence
- Alternate treatment options are considered
- RPh escalates off-label request to disease-specific leader, division director, and pharmacy director

Off-Label Treatment is scheduled
- Patient wishes to proceed with off-label medication use
  - Yes
  - No
- Notifies Managed Care
- Consults with payer to determine if contract allows billing patient if off-label medication is not covered due to being not medically necessary or experimental/investigational
- Payer’s response is received
  - Approved
  - Not approved
  - Not approved
Off-Label Medication Process:
*Commercial Payers*

- Off-Label Treatment is scheduled
- Alternate treatment options are considered
- Off-Label Treatment is scheduled

**Off-Label Medication Process:**

**Commercial Payers**

- Off-Label Treatment is scheduled
- Alternate treatment options are considered

**Key**

- Clinical Team
- Reimbursement Specialist
- Medication Assistance Coordinator
- Chief Financial Officer
- Managed Care
- Financial Counseling

**Off-Label Medication Process:**

- Off-Label Treatment is scheduled
- Alternate treatment options are considered

**Key**

- Clinical Team
- Reimbursement Specialist
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- Chief Financial Officer
- Managed Care
- Financial Counseling
Denials – Common Reasons

- Lack of pre-certification or authorization
- Medical necessity
- Experimental and investigational
- Requires additional information
- Non-covered service/medication on the plan benefit
- Out of network provider
- Timely filing of claims
- Multiple diagnoses coding for disease states and metastases- payer does not apply correct codes to medications
- Error in number of units billed to payer
- Insurance duplicity or delay

General Rules for Denials

- Discover the root cause of the denial
  - Review payer specific policy, LCD, NCD
  - Determine if pre-certification or prior authorization was completed
  - Review documentation
    - Reimbursement is linked to the quality of the bill
    - Coders obtain information from medical record but sometimes required information is missing
- Look for denial trends with payers
  - Drugs, diagnosis, charge threshold
- Exceeds total units allowable
Handling Denials

- Work with Finance to develop a method for routing denials to appropriate personnel
  - Leverage IT to create work queue and notification process
- Consider appropriateness of resources
  - Workload (average number of denials/appeals)
  - Strict appeal timelines of many payers
- Consider training/experience of personnel
  - Ideally a nurse or pharmacist with oncology experience
  - Ability to learn and understand financial systems and processes
  - Ability to navigate electronic medical record

Handling Denials

- Request medical peer to peer interaction
  - Offer additional information and rationale to discuss with clinical reviewers who made initial determination
- Monitor for trends
  - Increased denials for repetitive reasons may require payer, billing or provider education
- Hold payer accountable
  - Regardless of the size of the organization
    - Example: Payer not recognizing authorization because it came from a third party administrator and denying claims for reason of “lack of pre-certification”
Handling Denials

- Challenge outdated payer policies
  - Develop reconsideration packet (for both commercial payer and Medicare) with evidence to support addition of covered diagnoses and/or regimens excluded from payer policies

Future Considerations

- Payer ability to keep up with accelerating evidence based new indications (e.g., new lines of therapy, new tumor types)
- Increasing utilization of anti-PD1s in combination with a host of agents (e.g., chemo, targeted, immunotherapeutic)
- Potential for coverage policies to be biomarker driven (e.g., PDL1 overexpression)
- Financial implications of agents becoming first line
Practical Barriers in Cancer Immunotherapy Treatment
Sanjiv S. Agarwala, MD – St. Luke’s Cancer Center and Temple University

Off-Label Medication Process: Medicare Post-Treatment

- Patient receives off-label therapy
- Claim is submitted to Medicare
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- Payer’s decision is received
- Not approved
- Approved
- Arranges payment for Medicare-allowed amount

Clinical Team
Reimbursement Specialist
Medication Assistance Coordinator
Managed Care Chief Financial Officer
Financial Counseling
Practical Barriers in Cancer Immunotherapy Treatment
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Off-Label Medication Process: Commercial Payers

Off-label medication use is considered

Risk/benefit conversation (including payment risk) occurs with patient

Patient wishes to proceed with off-label medication use

RPh enters off-label medication use into off-label database

Payer’s decision is received

Approved

Not approved

If insufficient evidence, RPh escalates off-label request to disease-specific leader, division director, and pharmacy director

Payer will not consider pre-determination request

Submits pre-determination request to payer

Payment risk is assessed with patient

Patient wishes to proceed with off-label medication use

Submits appeals to payer and notifies Medication Assistance Coordinator

Payer’s decision is received

Approved

Not approved

Sufficient evidence

Notifies provider and Medication Assistance Coordinator

Reviews evidence for off-label medication use

Not approved

Explores manufacturer assistance/replacement options

Approved

Notifies patient and readdresses risks/benefits

Not approved

Reimbursement Specialist

Managed Care

Chief Financial Officer

Financial Counseling

Medication Assistance Coordinator

Reimbursement Specialist

Clinical Team

Off-label treatment is scheduled

Off-label treatment is scheduled
Practical Barriers in Cancer Immunotherapy Treatment
Sanjiv S. Agarwala, MD – St. Luke’s Cancer Center and Temple University

Alternative treatment options are discussed

Off-Label Medication Process: Commercial Payers (continued)

Patient wishes to proceed with off-label medication use

Financial Counseling

Reimbursement Specialist

Managed Care

Chief Financial Officer

Financial Counseling

Clinic Team

Clinical Team

Medication Assistance Coordinator

Notifies Managed Care

Yes

Patient wishes to proceed with off-label medication use

Consults with payer to determine if contract allows billing patient if off-label medication is not covered due to being not medically necessary or experimental/investigational

Chief Financial Officer

Financial Counseling

Determines appropriate amount for patient to deposit toward treatment costs prior to receiving off-label medication

Notifies provider of deposit amount

Communicates deposit amount to patient and addresses risks/benefits

Payer’s response is received

Not approved

Obtains patient signature on notice of non-coverage and notifies Financial Counseling

Off-label treatment is scheduled

Patient wishes to proceed with off-label medication use

Yes

Consults with payer to determine if contract allows billing patient if off-label medication is not covered due to being not medically necessary or experimental/investigational

Chief Financial Officer

Obtains patient signature on notice of non-coverage and notifies Financial Counseling

Arranges payment for deposit
Take-Home Points

From Basic Principles to Clinical Applications of Cancer Immunotherapy and Overcoming Barriers to Incorporating Immunotherapy into Community Practice

Clinical Applications of Cancer Immunotherapy

MELANOMA
- Many immunotherapies for melanoma have been granted FDA approval and should be considered significant elements of the standard of care
  - Immunotherapies are FDA-approved as both adjuvant and systemic treatments
  - Immunotherapeutic FDA approvals vary across disease stages
  - Patient disease stage and characteristics will dictate appropriate therapeutic selection
  - Anti-PD-1 agents nivolumab and pembrolizumab, as well as anti-CTLA-4 ipilimumab, have been FDA approved for treatment of melanoma patients in specific settings
  - Combination ipilimumab/nivolumab is also approved for stage IV patients

LUNG CANCER
- Patient disease characteristics are imperative for selecting appropriate immunotherapies for treatment of patients with lung cancer
  - Pembrolizumab as a single-agent or in combination with chemotherapy should be considered significant elements of the standard of care for first-line treatment of patients with advanced NSCLC
  - Nivolumab, pembrolizumab, and atezolizumab have similar benefits and toxicity profiles as second-line treatments

GENITOURINARY CANCERS
Immunotherapies are approved and active across GU malignancies
- Sipuleucel-T offers a survival advantage compared to placebo in asymptomatic or minimally symptomatic metastatic castrate-resistant prostate carcinoma
- Nivolumab is approved for platinum-resistant metastatic bladder cancer and induce durable response in approximately 20 percent of patients
- Anti-PD-L1 atezolizumab and pembrolizumab are effective in patients with PD-L1-positive bladder carcinoma
- Anti-PD-L1 agents avelumab and durvalumab are approved for locally advanced or metastatic bladder cancer whose disease has progressed during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy
- First-line combination nivolumab + ipilimumab should be considered an element of standard of care for IMDC intermediate/poor risk advanced renal cell carcinoma patients
- Single-agent nivolumab is approved for previously treated patients with metastatic RCC

HEMATOLOGIC MALIGNANCIES
- Nivolumab and pembrolizumab are approved for the treatment of patients with Hodgkin lymphoma
- CAR T therapies axicabtagene ciloleucel and tisagenlecleucel are approved for the treatment of patients with relapsed DLBCL
- Blinatumomab is approved for Philadelphia-chromosome positive ALL patients, as well as patients who have MRD+ ALL who have not progressed after previous therapy
- Tisagenlecleucel is approved for the treatment of patients (≤ 25 years of age) with relapsed B-ALL
- Gemtuzumab ozogamicin is approved for patients with AML
- Immunotherapies – including CAR T therapies – are in development for treatment of patients with multiple myeloma

HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)
- PD-1 antibodies nivolumab and pembrolizumab are approved in second-line recurrent/metastatic HNSCC in the oral cavity, oropharynx, larynx, and hypopharynx
Take-Home Points

Overcoming Barriers to Incorporating Immunotherapy into Practice

HOSPITAL OPERATIONS AND REIMBURSEMENT

- As immunotherapies are increasingly utilized, hospitals must invest in the staffing infrastructure to ensure benefits evaluations are completed, predeterminations are submitted, and denials are appealed.
- Emergency response protocols for immunotherapies should be readily in place, and staff education should be provided on unique immune-related adverse events.
- Reimbursement teams should be well-versed in Medicare local and national coverage determinations, as well as commercial payer clinical guidelines and pathways.

Immune-Related Adverse Event (irAE) Management

MECHANISMS

- The major function of CTLA-4 and the PD-1/PD-L1 immune checkpoints is to prevent occurrence of autoimmune diseases.
- Disruption of this crucial function with anti-CTLA-4 or anti-PD-1/PD-L1 immunotherapeutic agents can lead to development of irAEs in some individuals.

GENERAL CONSIDERATIONS

- Adverse events caused by immunotherapies have distinct, underlying causation that differs compared to chemo/radiotherapies.
- Quickly determine whether a patient is receiving immunotherapy before any treatment.
- Emphasize to patients to report symptom(s) early.
- Always consider/have high-suspicion of irAEs in patients on immunotherapy, which can present with vague symptoms.
- Most irAEs occur within the first few months of therapy, but can present late and potentially after discontinuation.
- Combination anti-PD-1/CTLA-4 immunotherapy significantly increases grade 3-4 AE incidence.
- Treatment of irAEs requires a multidisciplinary team, since many patients have irAEs for more than one organ system; consult early with organ-specific consultants.

NURSING PERSPECTIVE

- Nurses have a crucial role in empowering and educating patients and their families about potential immune-related AEs.
- Nurses must understand and communicate that every patient is unique and that the grade and kind of toxicities will vary among patients.
- It is imperative to implement a multidisciplinary approach with doctors, advanced practitioners, nurses, and pharmacists when treating cancer patients with immunotherapy.
- Using the CTCA guidelines for prompt identification, treatment, and close monitoring of immune-mediated AEs can improve patient outcomes, improve QOL, and decrease prolonged hospitalizations.

IDENTIFICATION OF irAEs IN THE EMERGENCY DEPARTMENT

- When taking patient history for patients with cancer, inquire in more detail about their treatment; they may not report they are on immunotherapy.
- Emergency physicians who encounter apparent irAEs in the emergency department should contact the hematology-oncology team as soon as possible.
Glossary of Terms

Abscopal effect – Occurs when localized treatment of a tumor results in a shrinking of the targeted tumor as well as the tumors outside the scope of the localized treatment.

Adaptive immunity – One of the two arms of the immune system, also referred to as acquired immunity. The cells and molecules that comprise the adaptive immune system (e.g., T cells, B cells, and antibodies) are characterized by the ability to generate immunological memory.

Antibody – A protein secreted by B cells upon activation by a specific antigen. Antibodies function to bind and neutralize threats due to an exquisite specificity for the antigen that triggered their production. Prior to B cell activation, antibodies are present on the cell surface and referred to as B cell receptors (BCR).

Antigen – Any substance that elicits an immune response, especially the production of antibodies (antibody-generating). Antigens can include pathogens (infectious disease), allergens (atopy), autoantigens (autoimmunity), and neoantigens (malignancy).

Antigen-presenting cells (APC) – A group of specialized immune cells including dendritic cells, macrophages, and B cells that sample antigens from the blood and tissues for display to T and B cells.

B cells – Adaptive immune cells that can function as APC or contribute to humoral immunity by secreting antibodies specific for a particular antigen. B cells recognize antigens via direct binding with their B cell receptor (BCR).

Biomarker – A measurable characteristic indicative of normal or pathological biological processes, or response to pharmacological intervention. Biomarkers may come from bodily fluids or tissues and can include gene signatures, protein expression patterns, or constellations of cell subsets, etc.

Bullous pemphigoid – Very rare autoimmune skin condition that results in the formation of blisters known as bullae. Could potentially be a lethal condition.

Cancer vaccine – A class of immunotherapeutic designed to induce an adaptive immune response (and subsequent immunological memory) against cancer. These drugs typically contain a “danger” signal as well as parts of the tumor cells so that the immune system perceives it as a threat. Preventive vaccines prevent the development of cancer and therapeutic vaccines treat existing cancer.

Central tolerance – Removal or suppression of self-reactive T cells and B cells, in the thymus and bone marrow, respectively.

CHAI – CTLA-4 haploinsufficiency with autoimmune infiltration, is due to heterozygous loss of function mutations in CTLA-4, leading to development of lymphocytic infiltrations in multiple tissues and accompanied with organ dysfunction.

Co-stimulation – An activating signal given by an APC to a T cell as the second signal required for successful T cell activation, also called Signal 2.

Combination therapy – Therapeutic approaches that combine more than one method of treatment. Also called multimodality therapy.

CTLA-4 – An immune checkpoint receptor found on the surface of T cells that can shut down an immune response upon engagement with its binding partner (B7-1 or B7-2). Some cancers have evolved the ability to signal through this immune checkpoint, which halts the antitumor response.

Cytokines – Proteins secreted by immune cells to communicate with other cells, like sending a “liquid email”. Interferons, interleukins, and chemokines are examples of different types of cytokines.

Dendritic cell (DC) – Due to their prominent role in processing and presenting antigens to T and B cells, these innate immune cells are often referred to as “professional” antigen presenting cells.

Downregulation – A reduction in the quantity of a cellular component (cell surface receptors, cytokine secretion, etc.) in response to a variable.

DRESS – Drug reaction (or rash) with eosinophilia and systemic symptoms. Could potentially be a lethal condition.
Glossary of Terms

Hypophysitis – Inflammation of the pituitary gland resulting in severe fatigue, headaches and other endocrinopathies.

Immune checkpoints – Inhibitory pathways hardwired into the immune system to help maintain self-tolerance and limit the duration and extent of an inflammatory response as a means of minimizing collateral tissue damage. Engagement of an immune checkpoint results in the functional de-activation of certain cellular responses and can be thought of as “applying the brakes”.

Immune checkpoint inhibitors – Drugs that block signaling through specific immune checkpoint pathways and allow the immune system to “take the brakes off” so that immune cells can resume their effector functions.

Immune-mediated colitis – Diffuse inflammation of the bowel which could lead to severe dehydration and bowel perforation.

Immune-mediated myocarditis – Immune-mediated inflammation of the myocardium.

Immune-mediated myositis – Immune-mediated swelling of the muscles as well as muscle weakness and pain.

Immune-mediated pancreatitis – Immune-mediated diffuse inflammation of the pancreas and/or elevation of amylase/lipase.

Immune-mediated pneumonitis – Diffuse inflammation of the lung tissue.

Immunologic tolerance – The ability of the immune system (B and T cells) to mount a response to a specific antigen, which could be either a self-antigen or a foreign one.

Immunological memory – A unique feature of the adaptive immune system that refers to its ability to “remember” previous antigen encounters by establishing a pool of long-lived cells specific for any given threat. In this way, the immune system is able to respond swiftly to subsequent challenges with the same antigen.

Immunosuppression – A condition in which the immune system is rendered incapable of adequately protecting the body against infection and disease.

Immune-related adverse events (irAE) – A particular type of side effects that can arise as a result of immunotherapy. Tipping the balance of the immune system in favor of activation to eliminate malignant cells can also lead to inappropriate immune responses against normal healthy tissues (autoimmunity), including dermatitis, colitis, and hepatitis.

Innate immunity – One of the two arms of the immune system. The cells and molecules that comprise the innate immune system (e.g., macrophages, dendritic cells, and TLR) function by recognizing features of pathogens or cellular damage that are common to multiple sources, such as an aspect of a cell wall that is present in several species of bacteria.

IPEX – Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, which is an inherited disease characterized by multiple autoimmune diseases due to absence of regulatory T cells (Treg).

LATAIE – LRBA deficiency with autoantibodies, regulatory T (Treg) cell defects, autoimmune infiltration, and enteropathy, is a hereditary disease that is characterized by lower CTLA-4 expression on regulatory T cells leading to lymphocytic infiltration of many tissues, including the GI tract.

Leukocyte – A term used to encompass all white blood cells, including innate and adaptive immune cells.

Ligand – The binding partner of a receptor that can be thought of like a handshake. Once a ligand has bound its receptor, a signal can be transduced to regulate cellular functions.

Lymphocyte – A term that refers specifically to T cells, B cells, and NK cells.

Major histocompatibility complex (MHC) – Cell surface proteins that function as antigen presentation scaffolding, much like a horse rider (antigen) in a saddle (MHC). The immune receptors on T cells cannot “see” antigen unless presented in the context of the right MHC molecule and this interaction is called Signal 1.

Monoclonal antibodies (mAbs) – Antibodies generated in a laboratory by identical immune cells that are all clones of a unique parent cell. As such, mAbs bind with high specificity to the same part of an antigen and this minimal off-target binding makes them attractive therapeutic agents.
Glossary of Terms

**Natural killer (NK) cells** – A type of cytotoxic lymphocyte of the innate immune system that provides protection against tumor formation as well as virally-infected cells.

**Neoantigen** – A newly formed antigen that has not been previously recognized by the immune system. In the context of cancer, neoantigens are the product of tumor-specific mutated genes.

**Oncoytic virus** – A class of immunotherapeutics in which a virus is engineered to preferentially infect and kill cancer cells, as well as induce systemic antitumor immunity.

**PD-1** – An immune checkpoint receptor found on the surface of T cells that can shut down an immune response upon engagement with its binding partner (PD-L1). Some cancers have evolved the ability to signal through this immune checkpoint, which halts the antitumor response.

**Peripheral Tolerance** – Multiple immunological mechanisms, including regulatory T cells that suppress self-reactive T and B cells to prevent autoimmunity. These mechanisms rely on CTLA-4 and PD-1/PD-L1 pathways.

**Pruritus** – Dermatological sensation that causes one to want to scratch.

**Receptors** – Cell surface proteins that can send signals to other cells upon engagement with their binding partner (ligand), much like a handshake. Such signaling helps mediate immune responses.

**Regulatory T cells (Treg)** – Also called “suppressor T cells”, this subpopulation of T cells modulates immune responses and maintains tolerance to self, thereby preventing autoimmunity. Treg are often induced and recruited to the tumor microenvironment, which contributes to a poor antitumor response.

**T cells** – Adaptive immune cells that play a central role in cell-mediated immunity. There are two main types of conventional T cells: CD4+ T cells and CD8+ T cells. CD4+ T cells are also called “helper” T cells (Th cells) because they help induce B cells to secrete antibodies and assist in the activation of CD8+ T cells. CD8+ T cells are the major contributors to antitumor immunity and are often referred to as “cytotoxic T lymphocytes” (CTL) due to their ability to directly kill the cells they target. T cells recognize specific antigens via binding of the T cell receptor (TCR) to antigen presented on MHC molecules by APC (Signal 1).

**Toll-like receptors (TLR)** – Also called “pattern recognition receptors”, these innate immune molecules recognize evolutionarily conserved danger signals derived from pathogens or cellular damage and can be thought of as an early alarm system in the activation of an immune response.

**Tumor microenvironment (TME)** – The area in and around a tumor, including surrounding blood vessels, structural cells like fibroblasts, immune cells, and signaling molecules. The tumor interacts with and influences this environment to help promote angiogenesis, tumor growth, and suppression of the immune system.

**Upregulation** – An increase in the quantity of a cellular component (cell surface receptors, cytokine secretion, etc.) in response to a variable.

**Vitiligo** – Hypopigmentation of the skin.
Additional Resources

Cancer Immunotherapy Guidelines
SITC is proud to offer Cancer Immunotherapy Guidelines—a series of manuscripts designed to help medical professionals determine when and how best to use immunotherapy to treat their patients. Each guideline is developed using a systematic process providing unbiased and relevant expert consensus recommendations. SITC also employs an online update procedure to more quickly address newly published information with implications for the published guidelines. SITC currently provides Cancer Immunotherapy Guideline manuscripts, as well as select easy-to-access Pocket Guides, for the following disease states:
- Bladder carcinoma*
- Prostate carcinoma*
- Renal cell carcinoma*
- Cutaneous melanoma*
- Non-small cell lung cancer*
- Hematologic malignancies
*Pocket Guide available
SITC is consistently working to provide new additions to the Cancer Immunotherapy Guidelines series. Manuscripts and Pocket Guides for the following diseases are currently under development and expected to publish in the near future:
- Head and neck carcinoma (New in 2019)
- Acute leukemia (New in 2019)
- Lymphoma (New in 2019)
- Renal cell carcinoma (Update in 2019)
- Multiple myeloma (New in 2020)
- Immune checkpoint inhibitor and cytokine-related adverse events (New in 2020)
- Immune effector cell-related adverse events (New in 2020)
Additionally, SITC is excited to introduce a new webinar series based on SITC’s Cancer Immunotherapy Guidelines. Guideline authors will lead each disease-specific webinar to discuss the rationale behind the consensus recommendations, as well as provide an opportunity for attendees to ask direct questions to experts in the field. Cancer Immunotherapy Guideline webinars take place soon after publication of each new manuscript. Webinar materials are currently available for the following guidelines:
- Melanoma
- Non-small cell lung cancer
For more information about SITC’s Cancer Immunotherapy Guidelines series and for free access to all materials, please visit our website at https://www.sitcancer.org/research/cancer-immunotherapy-guidelines.

Cancer Immunotherapy Principles and Practice Textbook
‘Cancer Immunotherapy Principles and Practice’ is the authoritative textbook on cancer immunobiology and the mechanisms that contribute to harnessing the immune system to combat malignant disease. This comprehensive reference work—edited by current SITC president Lisa H. Butterfield, PhD, and past SITC Presidents Howard L. Kaufman, MD, FACS, and Francesco M. Marincola, MD—covers every major topic that has shaped immunotherapy development and propelled it to the forefront of cancer treatment innovation.
For more information on content and how to order, please visit https://www.sitcancer.org/research/cancer-immunotherapy-principles-practice.

Toxicity Management Materials
To help healthcare professionals better understand and manage unique immune-related adverse events associated with immune checkpoint inhibitors, SITC experts developed and published “Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group,” in SITC’s open-access journal, The Journal for ImmunoTherapy of Cancer. This manuscript provides expert consensus recommendations on pre-treatment screening, toxicity characteristics, and specialist referrals, among other critical pieces of information.
For free manuscript access, please visit https://jitc.biomedcentral.com.
In addition, the newly available “SITC’s Guide to Managing Immunotherapy Toxicity,” is a practical reference guide to the management of immune-related toxicities designed for healthcare practitioners in both hospital and community clinic settings.
For more information on content and how to order, please visit https://www.springerpub.com/sitc-s-guide-to-managing-immunotherapy-toxicity-9780826172143.html.
The American Academy of Emergency Medicine (AAEM) is the specialty society of emergency medicine

For over 25 years, AAEM has been a leader in protecting board certification in emergency medicine and confronting the harmful influence of the corporate practice of medicine.

We support fair and equitable practice environments that allow emergency physicians to deliver the highest quality of patient care.

We provide advocacy and education for our over 8,000 members.

Learn more about AAEM’s mission at
Access Global Patient Reported Data

The key to discovery lies within the patient.

Join this collaboration of researchers, clinicians and patients in eradicating lung cancer.

Actively enrolling for Immunotherapy PRO Study.

Obtain your professional account at lungcancerregistry.org

LUNG CANCER REGISTRY
Continue Learning With SITC

Stay current with best clinical practices for cancer immunotherapy following today’s Advances in Cancer Immunotherapy™ (ACI) program.

ACI Webinar Series
Log in to the free ACI webinars to learn about new treatment approvals and emerging scientific data relating to clinical applications of cancer immunotherapy. Hosted by experts in the field, the webinars provide an opportunity to continue your learning from this ACI program and interact with faculty during a dedicated question-and-answer session.

• Thursday, May 23, 2019
  3:00 – 4:00 p.m. CT
  Robert Canter, MD, MAS, FACS – UC Davis Health System
  Robert L. Ferris, MD, PhD – UPMC Hillman Cancer Center

Interactive Online ACI Classes
Participate in these short, interactive online classes to deepen your understanding of what you learned at today’s ACI program in cancer immunotherapy. Learn about specific disease states and practical barriers to implementation while engaging with case study examples. Each class will take approximately 30 minutes to complete and is also eligible for CME, CNE or CPE credits.

ACI Video Series
View recordings of select ACI programs, including concurrent sessions on specific disease states you may not have attended today, and earn additional CE credit.

SITC Cancer Immunotherapy Guidelines Webinars
Ask questions as leading experts discuss the most recent immunotherapy treatment standards for specific disease states – stemming from SITC’s Cancer Immunotherapy Guidelines.

Visit sitcancer.org/ACIonline to learn more about these educational opportunities.