Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

IMPROVE *Patient Outcomes*

Thursday, Oct. 10, 2019 • Boston

Courtyard Boston Downtown

PIM Postgraduate Institute for Medicine

sitc Society for Immunotherapy of Cancer

AAEM American Academy of Emergency Medicine

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

The 2019-2020 ACI series is jointly provided by Postgraduate Institute for Medicine and 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.

Thank You To Our Supporters

The 2019–2020 Advances in Cancer Immunotherapy™ series is generously supported in part by independent medical education grants from:

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Letter from the President

Dear Colleagues,

Welcome to today's Advances in Cancer Immunotherapy™ (ACI) program, jointly provided by the Society for Immunotherapy of Cancer (SITC) and the Postgraduate Institute for Medicine (PIM), 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 the field of immunotherapy continues to rapidly evolve, it's critical that you and your entire team stay current with the latest FDA-approved immunotherapy treatments. The ACI programs do just that. With a backdrop of the basics of cancer immunotherapy and new topics like common and uncommon toxicities in immunotherapy patients, 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. SITC staff will provide instructions via email on how to access these materials. You can also continue your education via free online courses 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.

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Society for Immunotherapy of Cancer

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CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC
Association of Community Cancer Centers

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Program Details

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 four weeks before the event and for three 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/aboutconnect.

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 free 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 on new developments in the immunotherapy field that 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/acionline.

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 two to four weeks following the meeting, presentation slides and videos 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 90 days 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 on how to access presentations.

Online Courses

Continue your learning with free online education (CME, CNE, CPE and MOC-certified) specifically related to this ACI program:

- *Introduction to Immunology – Third Edition*: This interactive, pre-program online course provides an introduction to the immune system and its role in disease, including cancer. The course teaches basic immunology principles and terminology that are foundational to content covered in the Advances in Cancer Immunotherapy™ program.
- *Mechanisms of Immune-Related Adverse Events – First Edition*: This interactive, pre-program online course covers foundational information on the mechanisms of adverse events associated with cancer immunotherapy. The course content provides a basis for identifying and managing irAEs.
- *Advances in Cancer Immunotherapy™ Online Courses*: Interactive courses are available for the topics presented during today's ACI program and highlight additional online resources. Refresh your knowledge or engage with the content covered during concurrent sessions.

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

Program Details

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

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 immune related adverse events 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.

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.

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.

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.

Physician Continuing Medical Education

The Postgraduate Institute for Medicine designates this live activity for a maximum of 3.5 *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 3.5 contact hour(s) (0.35 CEUs) of the Accreditation Council for Pharmacy Education.

Universal Activity Number:

JA4008162-999-19-895-L01-P
Type of Activity: Application

Continuing Nursing Education

The maximum number of hours awarded for this Continuing Nursing Education activity is 3.5 contact hours. Designated for 1.7 contact hours of pharmcotherapy credit for Advanced Practice Registered Nurses.

California Board of Registered Nurses
Provider approved by the California Board of Registered Nursing, Provider Number 13485, for 3.5 contact hours.

Program Details

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 3.5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Claiming Continuing Education Credit

Participants receive continuing education credits or certificates of attendance by completing the program evaluation form, including the email address used at registration, and submitting it to SITC staff prior to leaving the program. Please watch for an email from CEcertificate@pimed.com with a copy of your certificate approximately four weeks after the program. If you do not receive your certificate within this time frame, please check your spam folder and ensure that your institution accepts email from the above email address.

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.

Upon PIM's receipt of your completed evaluation, you will receive an email from CEcertificate@pimed.com within 3 weeks with a link and directions to complete submitting your credit to the NABP CPE Monitor Service.

Claiming MOC Credit

To complete the program evaluation and obtain your MOC credits, please follow the steps below:

1. Go online to CME University at http://www.cmeuniversity.com.
2. Register or login (takes less than one minute to register). Once logged into CME University, follow these steps:
3. Click on the "Find Post-Test/Evaluation by Course" at the top of the page, type "14668" and hit enter.
4. Click on the activity title, "Advances in Cancer Immunotherapy™ (2019)," when it appears.
5. Choose the date/location option of "Boston, MA on 10/10/19."
6. Select MOC as the type of credit you are seeking.
7. Successfully complete the post-test with a score of 75% or better.
8. 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

Elizabeth Buchbinder, MD
Dana-Farber Cancer Institute

David F. McDermott, MD
Beth Israel Deaconess Medical Center

Virginia Seery, MSN, RN, ANP-BC
Beth Israel Deaconess Medical Center

Program Planning Committee

Sanjiv S. Agarwala, MD
St Luke's Cancer Center and Temple University

Christian M. Capitini, MD
University of Wisconsin Carbone Cancer Center

Marianne Davies, DNP, AOCNP
Yale School of Nursing

Sarah B. Dubbs, MD, FAAEM
University of Maryland School of Medicine

Isabella C. Glitza, MD, PhD
University of Texas MD Anderson Cancer Center

Zihai Li, MD, PhD
MUSC Hollings Cancer Center

Amber Proctor, PharmD
UNC Healthcare

Brian I. Rini, MD
Cleveland Clinic Cancer Center

Dan P. Zandberg, MD
UPMC Hillman Cancer Center

CE Faculty

Joaquim Bellmunt, MD, PhD
Beth Israel Deaconess Medical Center

Elizabeth Buchbinder, MD
Dana-Farber Cancer Institute

Jennifer Espiritu, PharmD, BCOP
Beth Israel Deaconess Medical Center

Glenn J. Hanna, MD
Dana-Farber Cancer Institute

Myrna Nahas, MD
Beth Israel Deaconess Medical Center

Osama E. Rahma, MD
Dana-Farber Cancer Institute

Deepa Rangachari, MD
Beth Israel Deaconess Medical Center

Virginia Seery, MSN, RN, ANP-BC
Beth Israel Deaconess Medical Center

Ryan J. Sullivan, MD
Massachusetts General Hospital

Non-CE Speaker

Howard L. Kaufman, MD, FACS
Replimune Group Inc.

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Program Schedule

Thursday, October 10, 2019

2:30 – 3:30 p.m. **Registration**

Session I: Introduction to Cancer Immunotherapy

3:25 – 3:30 p.m.	**Welcome, Introduction, SITC Resources**
3:30 – 4 p.m.	**Basic Principles of Cancer Immunotherapy** Ryan J. Sullivan, MD – *Massachusetts General Hospital*
4 – 4:05 p.m.	*Transition time*

Session II: Immunotherapy in Practice

	Concurrent Sessions	
4:05 – 4:40 p.m.	**Immunotherapy for the Treatment of Skin Cancers** Elizabeth Buchbinder, MD – *Dana-Farber Cancer Institute*	**Immunotherapy for the Treatment of Lung Cancer** Deepa Rangachari, MD – *Beth Israel Deaconess Medical Center*
4:40 – 4:45 p.m.	*Transition time*	
	Concurrent Sessions	
4:45 – 5:20 p.m.	**Immunotherapy for the Treatment of Head and Neck Cancers** Glenn J. Hanna, MD – Dana-Farber Cancer Institute	**Immunotherapy for the Treatment of Genitourinary Malignancies** Joaquim , MD, PhD – *Beth Israel Deaconess Medical Center*
5:20 – 5:25 p.m.	*Transition time*	
	Concurrent Sessions	
5:25 – 6 p.m.	**Immunotherapy for the Treatment of Hematologic Malignancies** Myrna Nahas, MD – *Beth Israel Deaconess Medical Center*	**Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma** Osama E. Rahma, MD – *Dana-Farber Cancer Institute*
6 – 6:30 p.m.	*Meal/Break*	

Session III: Immunotherapy Challenges and Beyond

6:30 – 7:10 p.m.	**Toxicity Management** Virginia Seery, MSN, RN, ANP-BC – *Beth Israel Deaconess Medical Center*
7:10 – 7:40 p.m.	**Practical Barriers in Cancer Immunotherapy Treatment** Jennifer Espiritu, PharmD, BCOP – *Beth Israel Deaconess Medical Center*
7:40 – 7:55 p.m.	**Break/Conclusion of the CME/CE Program**

Non-CME/CE Program Session

7:55 – 8:30 p.m.	**What's Next for Cancer Immunotherapy?** Howard L. Kaufman, MD – *Replimune Group Inc.*
8:30 – 8:35 p.m.	*Closing Remarks*

Disclosure Information

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:

Name of Faculty/Moderator	*Reported Financial Relationship*
Joaquim Bellmunt, MD, PhD	Royalty: UpToDate; Consulting Fees: MSD, AstraZeneca; Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents: Janssen, MSD; Contracted Research: Takeda, Pfizer
Elizabeth Buchbinder, MD	Consulting Fees: BMS, Novartis, Array, Trieza
Jennifer Espiritu, PharmD, BCOP	No relevant financial relationships to disclose
Glenn J. Hanna, MD	Consulting Fees: Regeneron, Sanofi, BMS, Maverick, Merck; Contracted Research: BMS, Exicure, GSK, Altor BioScience, Kite, Regeneron, Sanofi, Kartos
David F. McDermott, MD	Consulting Fees: BMS, Pfizer, Merck, Novartis, Exelixis, Array BioPharm, Genetech BioOncolgy, Alkermes, Inc., Jounce Therapeutics, X4 Pharma, Peloton Therapeutics, EMD Serono, Eli Lilly and Company; Contracted Research: BMS, Prometheus Laboratories, Merck, Genentech, Pfizer, Exelixis, Novartis, X4 Pharma, Alkermes, Inc., Peloton
Myrna Nahas, MD	No relevant financial relationships to disclose
Osama E. Rahma, MD	Consulting Fees: ImVax, GSK, Maverick, Roche, PRMA, Defined Health, Puretech, Leerink
Deepa Rangachari, MD	Consulting Fees: DynaMed, Advance Medical
Virginia Seery, MSN, RN, ANP-BC	Consulting Fees: Apricity Health, LLC
Ryan J. Sullivan, MD	Consulting Fees: Array Biopharma, Merck, Novartis, Replimune

The ***planners and managers*** 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:

Name of Planner/Manager	*Reported Financial Relationship*
Sanjiv S. Agarwala, MD	Consulting Fees: Merck, Sharp & Dohme, BMS
Christian M. Capitini, MD	No relevant financial relationships to disclose
Marianne Davies, DNP, AOCNP	Consulting Fees: AstraZeneca; Fees for Non-CME/CE Services Received Directly from a Commercial Interest *or their Agents*: Genentech, Merck, BMS, AstraZeneca
Sarah B. Dubbs, MD, FAAEM	No relevant financial relationships to disclose
Isabella C. Glitza, MD, PhD	Consulting Fees: Array, BMS, Novartis; Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents: Novartis; Contracted Research: Merck, BMS
Zihai Li, MD, PhD	Contracted Research: BMS
Amber Proctor, PharmD, BCOP	Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents: Amgen
Brian I. Rini, MD	Consulting Fees: Merck, BMS, Pfizer, Arrowhead, 3DMed; Contracted Research: Merck, BMS, Pfizer, Peloton, AstraZeneca
Dan P. Zandberg, MD	Contracted Research: Merck

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:

Name of Subject Matter Expert	*Reported Financial Relationship*
Pedro Barata, MD	Consulting Fees: Bayer, EMD Serono, BMS, Pfizer
Bhagirathbhai Dholaria, MBBS	Consulting Fees: Celgene
Sarah Dubbs, MD, FAAEM	No relevant financial relationships to disclose
Marc S. Ernstoff, MD	No relevant financial relationships to disclose
Heidi Finnes, PharmD, BCOP	No relevant financial relationships to disclose
Michael Gibson, MD, PhD, FACP	Consulting Fees: Merck, BMS; Fees for Non-CME/CE Services Received Directly from a Commercial Interest *or their Agents*: BMS (non-branded)
Morgan Gwynn, PharmD	No relevant financial relationships to disclose
Thomas Herzog, MD	Consulting Fees: AstraZeneca, Caris, Clovis, Genentech, J & J, Tesaro
Anuradha Krishnamurthy, MD	No relevant financial relationships to disclose
Patrick Ma, MD, MSc	Consulting Fees: AstraZeneca, Apollomics, Inc.; Fees for Non-CME/CE Services Received Directly from a Commercial Interest *or their Agents*: AstraZeneca, Merck, Bayer, BMS
Amy Schippers, PA-C	No relevant financial relationships to disclose
Stefani Spranger, PhD	Consulting Fees: Ribon Therapeutics, Inc., Takeda, Merck, Dragonfly Therapeutics, Inc., Torque, Venus Pharma GmbH, Tango Therapeutics, Replimune; Contracted Research: Takeda, Exilexis
Ryan J. Sullivan, MD	Consulting Fees: Merck, Novartis, Replimune, Rubius; Contracted Research: Merck, Amgen; Clinical Trial Independent Reviewer: Boehringer Ingelhein
Laura Wood, MD, FAAEM	Consulting Fees: Eisai; Fees for Non-CME/CE Services Received Directly from a Commercial Interest *or their Agents*: BMS, Merck, Pfizer, Genentech

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

The following SITC planners and managers – Julie Cabaniss; Mary Dean, JD, CAE; Emily Ehlerding PhD; Allison Joost; Claire Leischer, MS; Alicia Schuessler, CAE; Lianne Wiggins; Tara Withington, CAE – have nothing to disclose.

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.

Program Organizers

Elizabeth Buchbinder, MD

Elizabeth Buchbinder, MD is a clinical oncologist at Dana Farber Cancer Institute specializinging in the treatment of melanoma. She received her training at Tufts Medical School and Beth Israel Deaconess Medical Center in Boston. In addition to treating patients she performs clinical and translational research to help further melanoma treatment. Her primary areas of research are in immunotherapy and novel targeted therapy approaches.

David F. McDermott, MD

David F. McDermott, M.D., is Chief of Medical Oncology at Beth Israel Deaconess Medical Center (BIDMC), Director of the Cutaneous and Immuno-Oncology Programs at BIDMC, co-Director of the BIDMC Cancer Center Immunotherapy Institute, Leader of the Dana Farber/Harvard Cancer Center (DF/HCC) Kidney Cancer Program and co-Principal Investigator of the National Cancer Institute, Specialized Programs of Research Excellence (SPORE) grant, focusing on kidney cancer. Dr. McDermott is Director of the Cytokine Working Group, an innovator in the field of solid tumor immunotherapy and Professor of Medicine at Harvard Medical School.

Dr. McDermott is a nationally and internationally recognized medical oncologist, clinical researcher and expert in three fields of research and clinical management: cancer immunotherapy, melanoma and kidney cancer. Dr. McDermott has particular interest in therapies that enhance the immune response to cancer. His immunotherapy research has focused on developing "targeted" immunotherapies for patients with solid tumors. Dr. McDermott has served on the Program Committee for the American Society of Clinical Oncology, the Medical Advisory Board for the Kidney Cancer Association, the National Cancer Institute Genitourinary Steering Committee and currently serves on the Kidney Cancer Task Force of the National Cancer Institute.

Virginia Seery, MSN, RN, ANP-BC

Ms. Seery is a nurse practitioner at Beth Israel Deaconess Medical Center in Boston, MA taking care of renal cell carcinoma and melanoma patients in the Immuno-oncology program. She has extensive experience with clinical trials and immunotherapy, including managing the inpatient high dose IL-2 service.

Basic Principles of Cancer Immunotherapy

Ryan J. Sullivan, MD
Assistant Professor
Massachusetts General Hospital

Dr. Ryan Sullivan is board certified in Medical Oncology and an Attending Physician in the Division of Hematology/Oncology at Massachusetts General Hospital (MGH). He attended Colby College for undergraduate studies and then matriculated to the University of Connecticut Medical School, graduating in 2001. He first trained in Internal Medicine at Mount Auburn Hospital in Cambridge, MA and then at Beth Israel Deaconess Medical Center (BIDMC) in Hematology/Oncology. At the MGH, he is the Associate Director of the Melanoma Program in the MGH Cancer Center and a member of the Termeer Center for Targeted Therapy. Dr. Sullivan is an active clinical and translational investigator whose main areas of interest are the development of novel molecular targeted and immunotherapeutic combinations for malignant melanoma, the translation of promising preclinical findings into early stage clinical trials, and the development of predictive biomarkers for these investigational as well as standard treatment approaches. In addition, he has an active interest in improving the prediction, through the development of blood-based biomarkers, and management of immune checkpoint inhibitor toxicity.

Basic Principles of Cancer Immunotherapy

Ryan J. Sullivan, MD – *Massachusetts General Hospital*

Audience Response Questions

1. *Which of the following is a hallmark of a productive anti-tumor immune response?*
   - *A. Lack of CD8 T cell infiltration into the tumor*
   - *B. Presence of CD8 T cells within the tumor*
   - *C. Immune suppression within the tumor*
   - *D. High degree of macrophage infiltration*

2. *Immune checkpoint blockade therapy acts primarily on which cell type?*
   - *A. Tumor cells*
   - *B. Tumor stroma*
   - *C. Tumor-reactive T cells*
   - *D. Macrophages*

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?*
   - *E. Never*
   - *F. Sometimes*
   - *G. Most of the time*
   - *H. Always*

Basic Principles of Cancer Immunotherapy

Ryan J. Sullivan, MD
Assistant Professor
Massachusetts General Hospital

Disclosures

- Consulting Fees:
  - Array Biopharma, Merck, Novartis, Replimune
- I will be discussing non-FDA approved indications during my presentation.

Ryan J. Sullivan, MD – *Massachusetts General Hospital*

The Premise of Cancer Immunotherapy

- Normally, the immune system eliminates damaged cells, including precancerous and cancer cells
- To escape, tumors evolve mechanisms to locally disable the immune system.

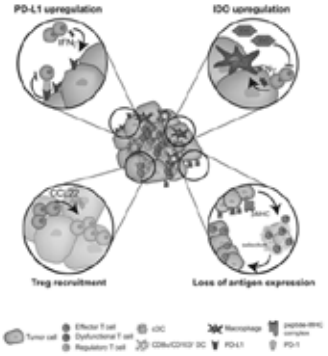
The goal of immunotherapy is to restore the capacity of the immune system to recognize and eliminate cancer.

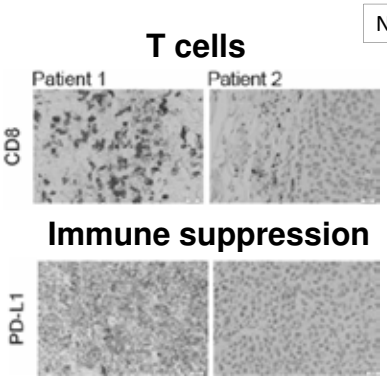
Two major mechanisms of tumor immune escape

- **Render the immune response dysfunctional:** cytotoxic (CD8+) T cells often become dysfunctional or exhausted during chronic stimulation (chronic viral responses or responses against tumors). To enhance T cell dysfunction, the tumor microenvironment upregulates a suite of suppressive molecules.
- **Avoiding an immune response:** A state in which the tumor remains invisible to the immune system. Many features of tumors can result in immune exclusion/avoidance including lack of antigens (T cells don't "see" anything on the tumor) or active immune repellents.

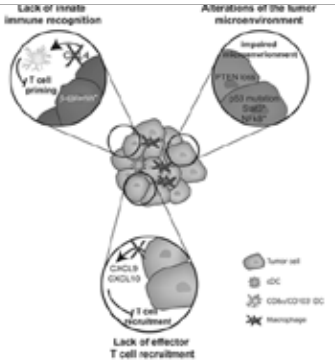
Immune evasion

T cell-inflamed tumor microenvironment



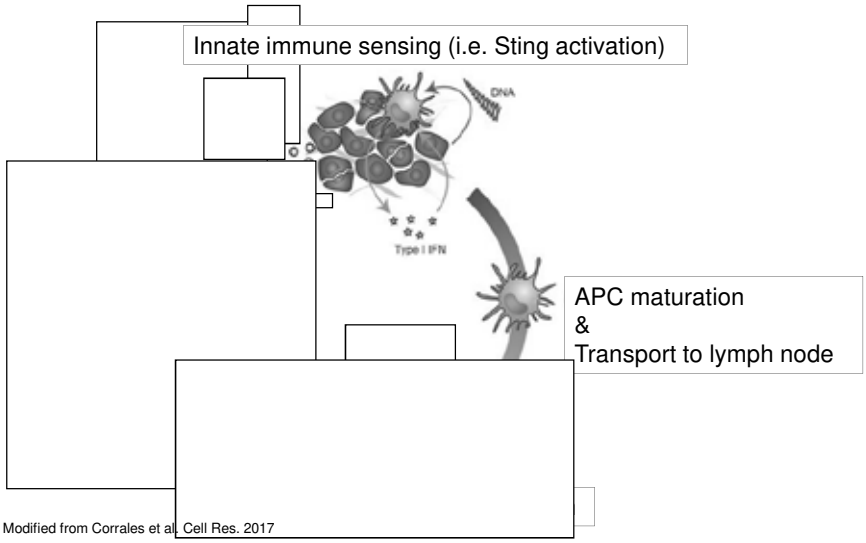


Non-T cell-inflamed tumor microenvironment



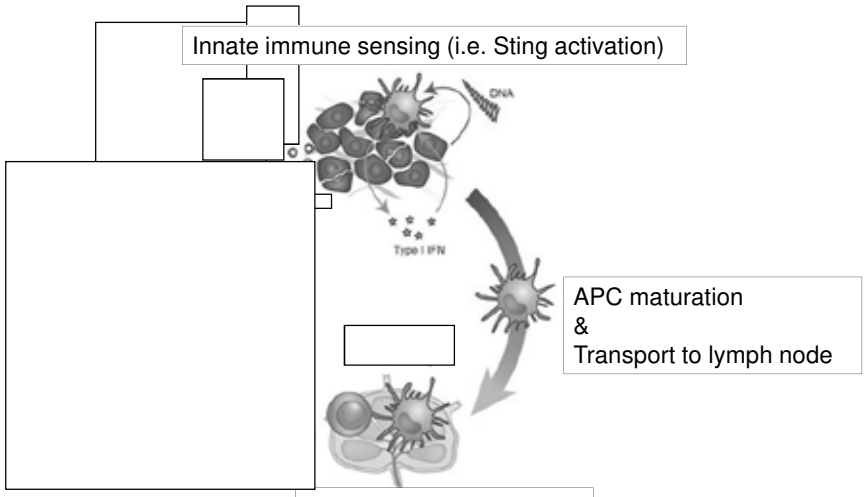
Spranger et al., STM 2013
Spranger, Internat Immunol. 2016

Initiation of an anti-tumor immune response



Modified from Corrales et al. Cell Res. 2017

Initiation of an anti-tumor immune response



Modified from Corrales et al. Cell Res. 2017

Antigen-specific T cell Activation

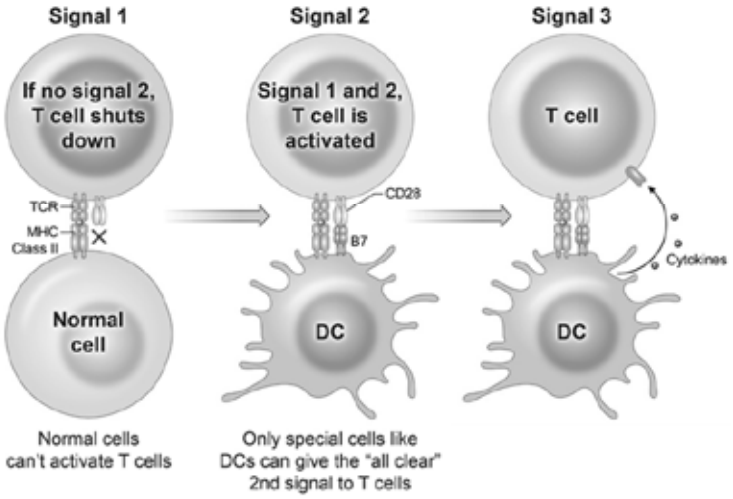
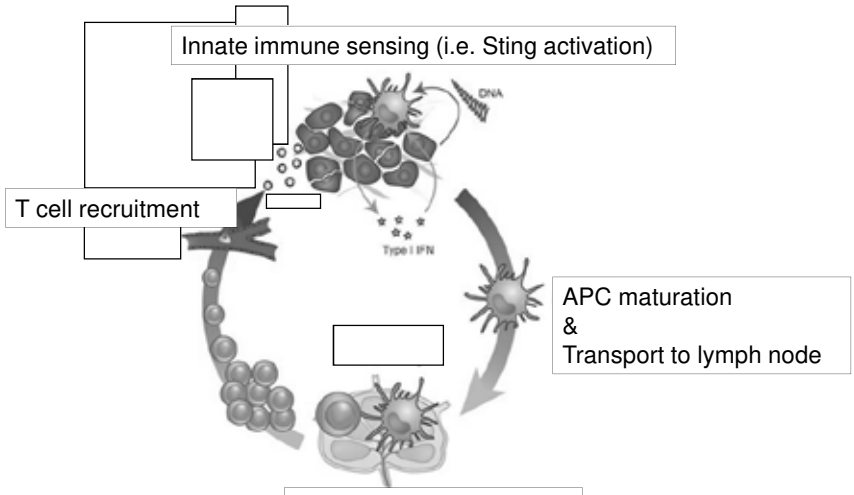


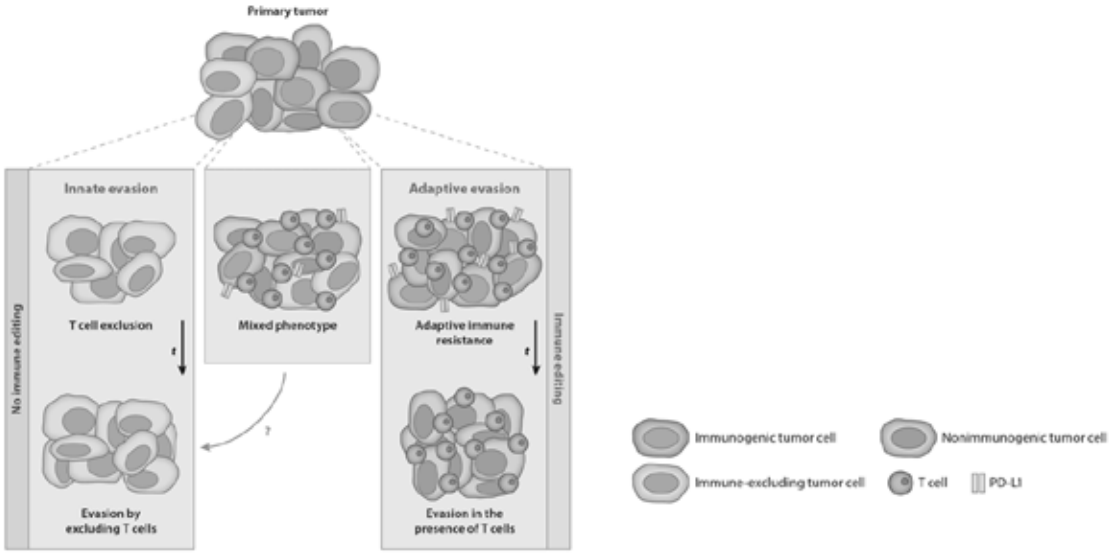
Image courtesy of NCI

Initiation of an anti-tumor immune response



Modified from Corrales et al. Cell Res. 2017

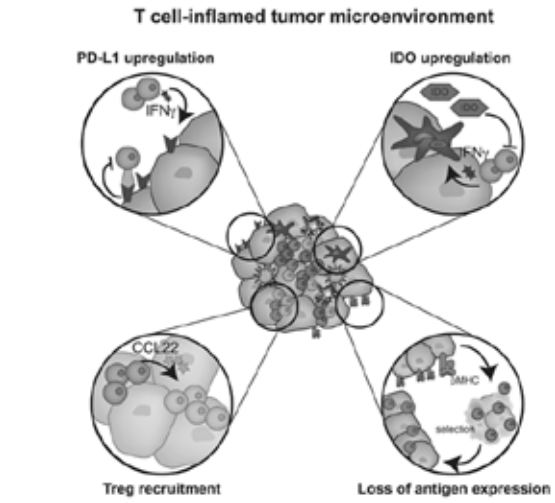
Immune evasion occurs over time



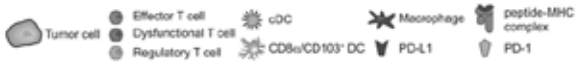
Spranger, AR Cancer 2018

Ryan J. Sullivan, MD – *Massachusetts General Hospital*

T cell inflamed tumor microenvironment is immune suppressive

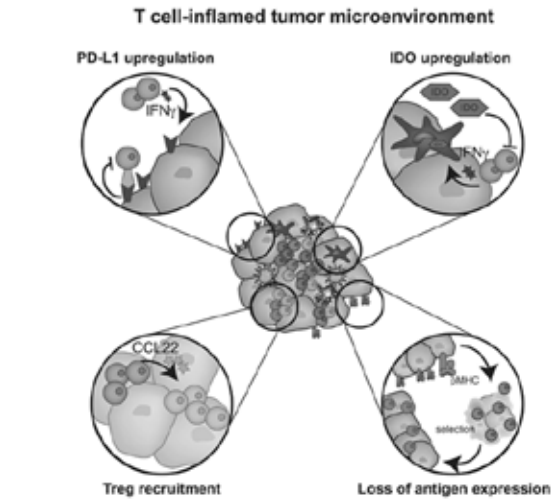


T cell-inflamed tumors escape by suppressing T cell function



Spranger, Internat Immunol. 2016

T cell inflamed tumor microenvironment is immune suppressive



T cell-inflamed tumors escape by suppressing T cell function

Non-T cell-inflamed tumors are a result of a malfunctioning cancer immune cycle

Spranger, Internat Immunol. 2016

Types of Immunotherapy

- Checkpoint blockade immunotherapy
- Cancer vaccines
- Adoptive cell transfer
- Effector antibodies
- Innate immune activation

The CTLA-4 Checkpoint

Cytotoxic **T**-**L**ymphocyte **A**ssociated Protein **4**

Up-regulated in response to T cell activation

Limits positive stimulation by competition

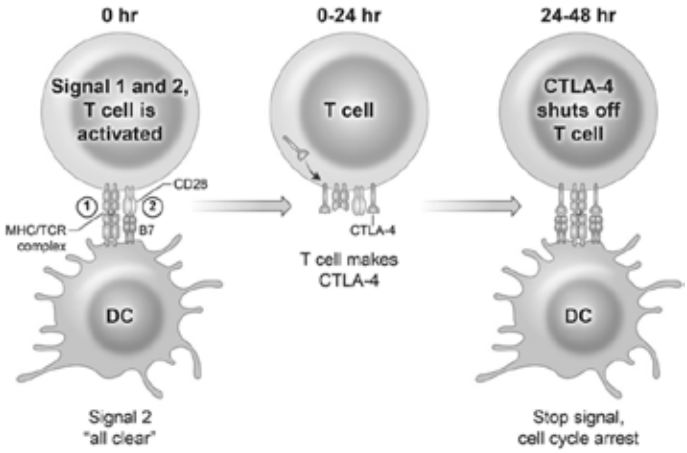


Image courtesy of NCI

The PD-1/PD-L1 Checkpoint

Programmed **D**eath **1**

Up-regulated in response to T cell activation

Ligands PD-L1 and PD-L2 are up-regulated following inflammation (IFNγ)

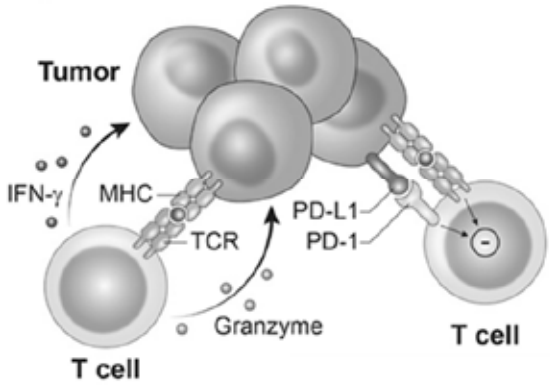
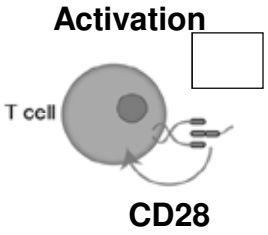


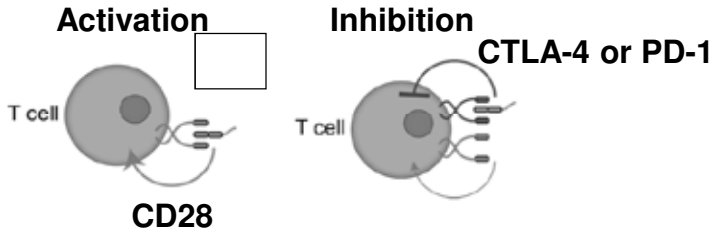
Image courtesy of NCI

Checkpoint blockade therapy unleashes the "brakes" on T cells



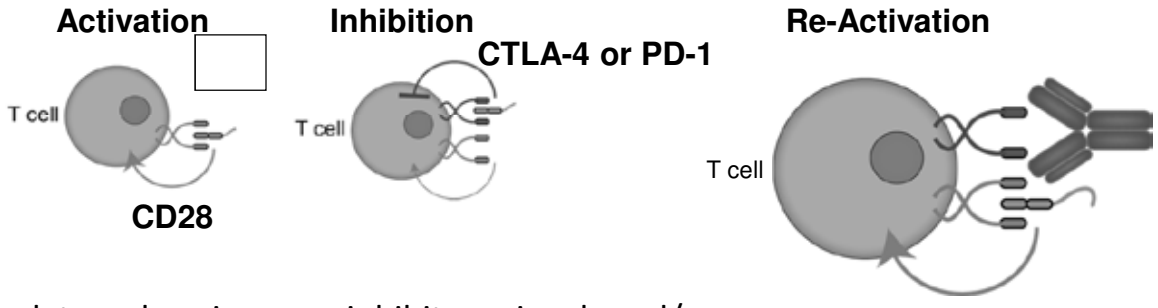
Goal: to reduce immune inhibitory signals and/or enhance stimulatory signals to allow T cells to regain effector functions.

Checkpoint blockade therapy unleashes the "brakes" on T cells



Goal: to reduce immune inhibitory signals and/or enhance stimulatory signals to allow T cells to regain effector functions.

Checkpoint blockade therapy unleashes the "brakes" on T cells



Goal: to reduce immune inhibitory signals and/or enhance stimulatory signals to allow T cells to regain effector functions.

T Cell Checkpoint Modulation

- First generation of checkpoint modulation: blocking inhibitory checkpoints
- Second generation of checkpoint modulation: activating stimulatory checkpoints

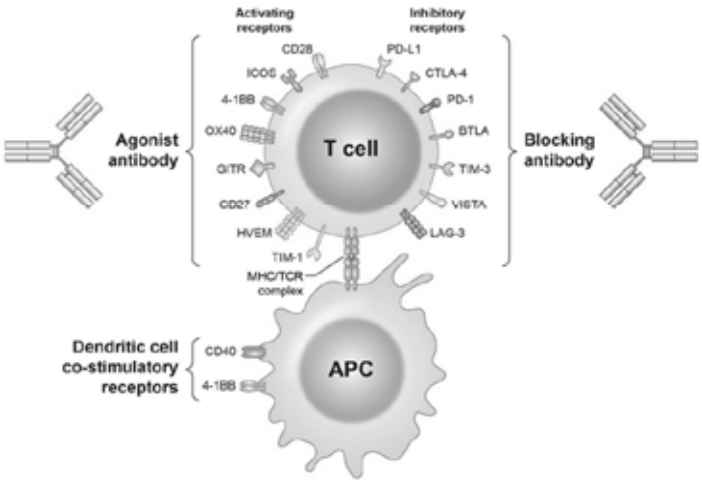


Image courtesy of NCI

Therapeutic Cancer Vaccines

Goal: to increase the immunogenicity of tumor antigens in order to generate a high frequency of tumor-specific T cells.

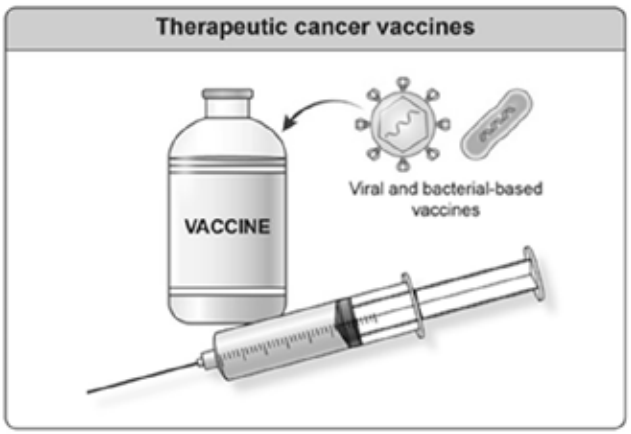


Image courtesy of NCI

Adoptive Cell Therapy

Goal: overwhelm the tumor with a higher frequency of tumor-specific immune cells and/or engineer immune cells to target cancer.

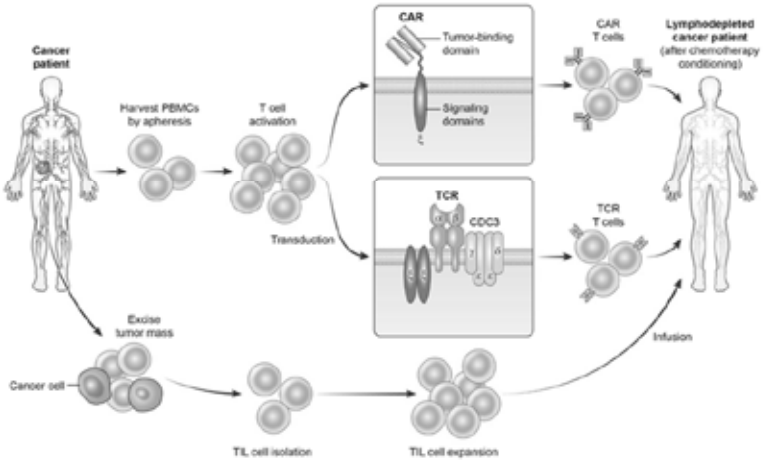


Image courtesy of NCI

Effector Antibodies and Antibody-Drug Conjugates (ADCs)

Goal: specifically target and kill tumor cells using innate mechanisms which are difficult to evade or suppress and/or through delivery of cytotoxic agents

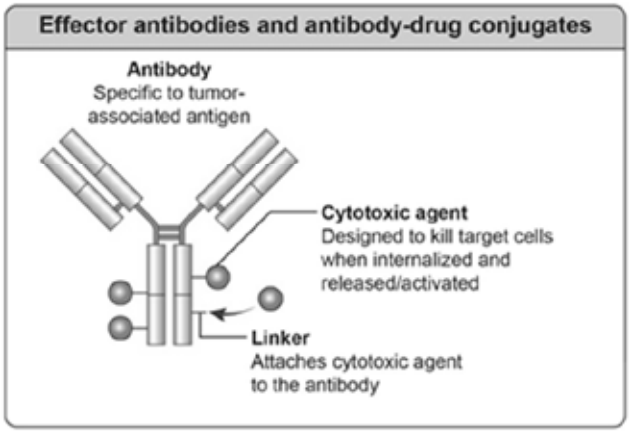
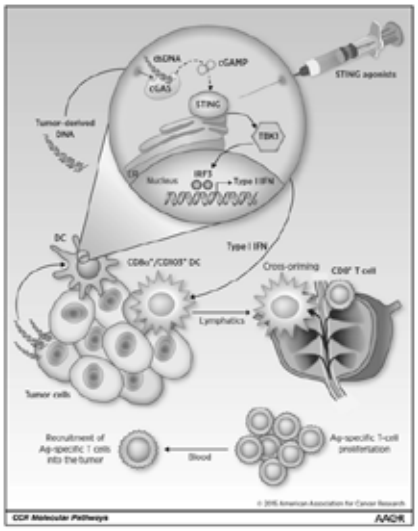


Image courtesy of NCI

Innate immune activation

Goal: enhance innate immune sensing by providing stimulatory agents (frequently into the tumor itself)

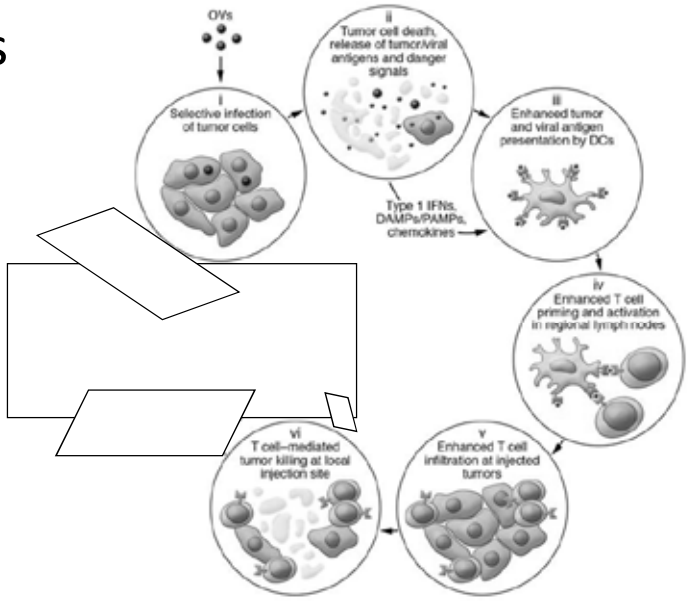


Agents:
Sting agonists
TLR agonists
Immunogenic RNA

Corrales, Clin Can Res 2015

Oncolytic Viruses

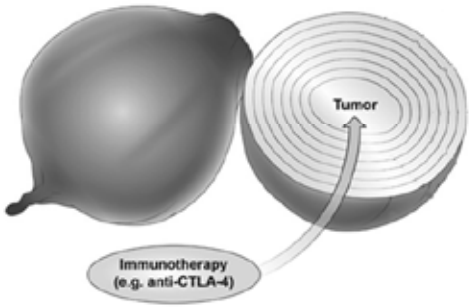
Goal: specifically target and kill tumor cells through viral replication AND release innate immune activators and tumor antigens



Modified from Bommereddy et al. JCI 2018

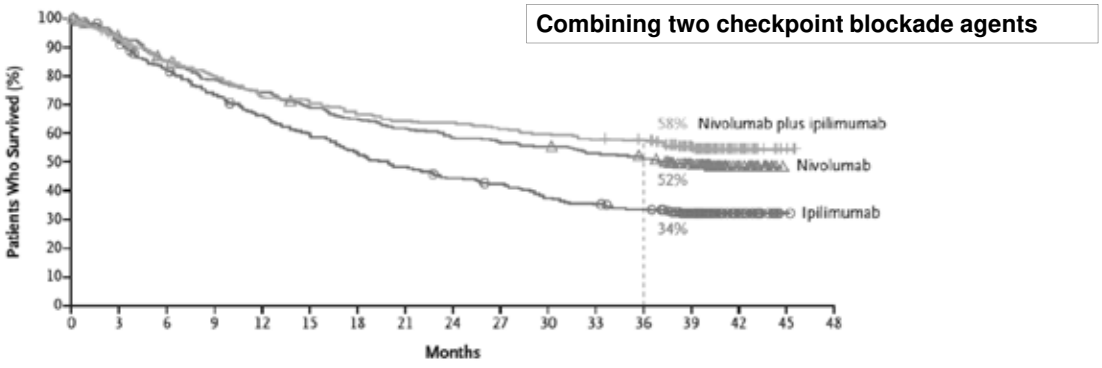
Multi-layered Immunosuppression

- Tumors insulate themselves with dense layers of immune-suppression
- 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
- Combination therapy might be needed to overcome all layers



Combination Immunotherapies

Dual CTLA-4 and PD-1 inhibition

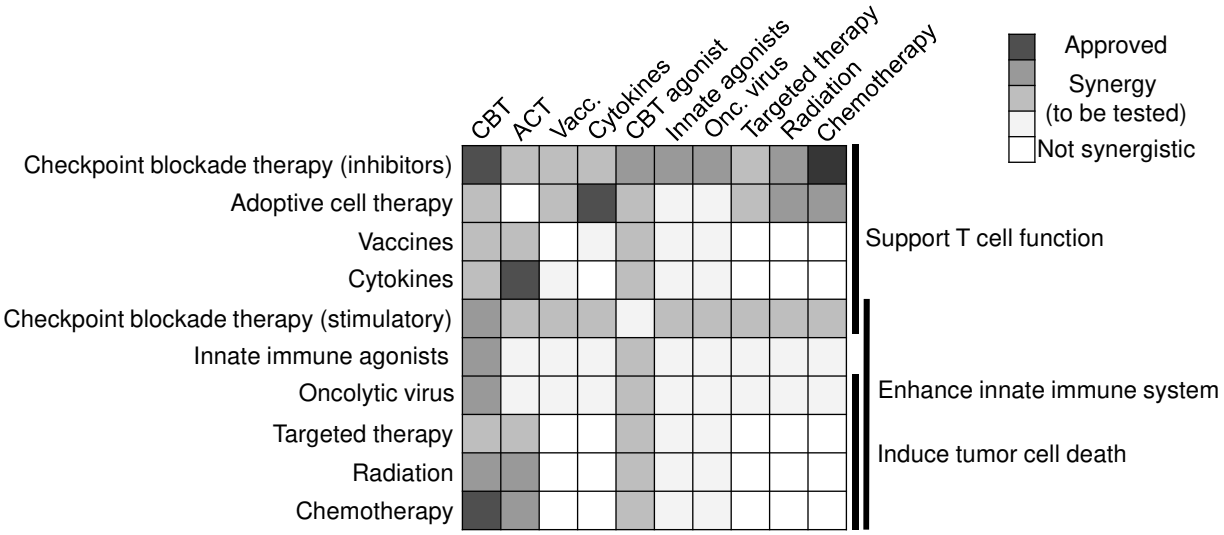


Wolchok et al., NEJM 2017

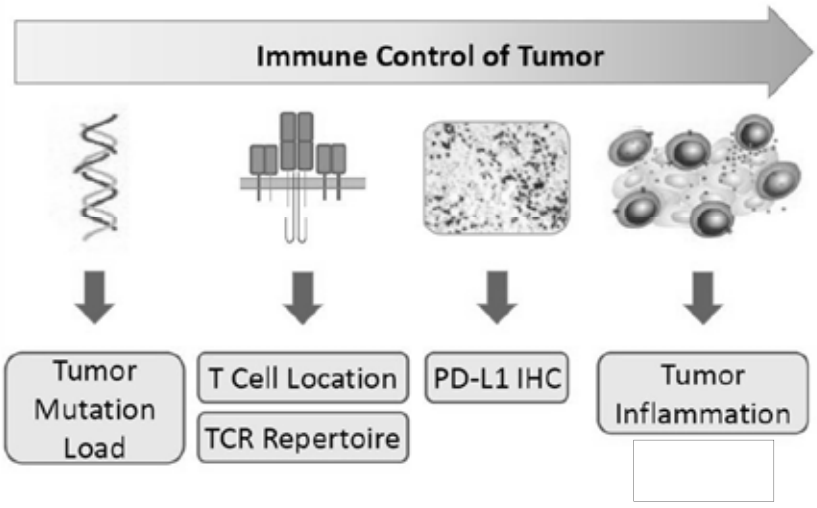
Basic Principles of Cancer Immunotherapy

Ryan J. Sullivan, MD – *Massachusetts General Hospital*

Combination Immunotherapies

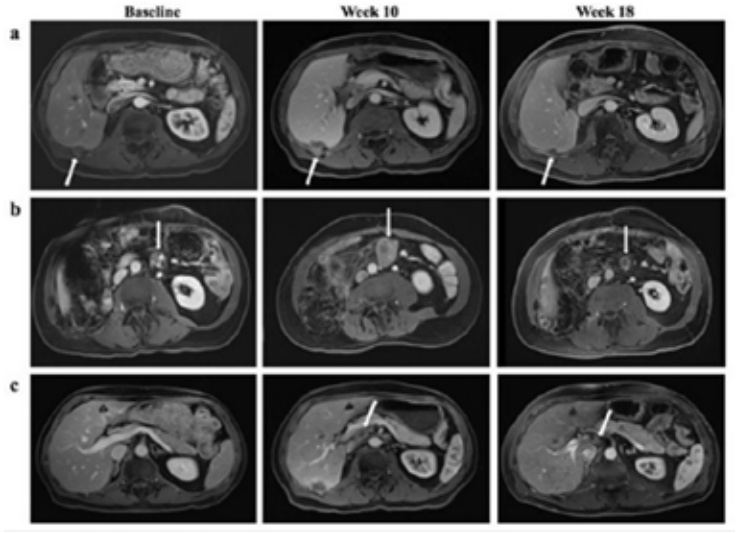


Immunotherapy Biomarkers



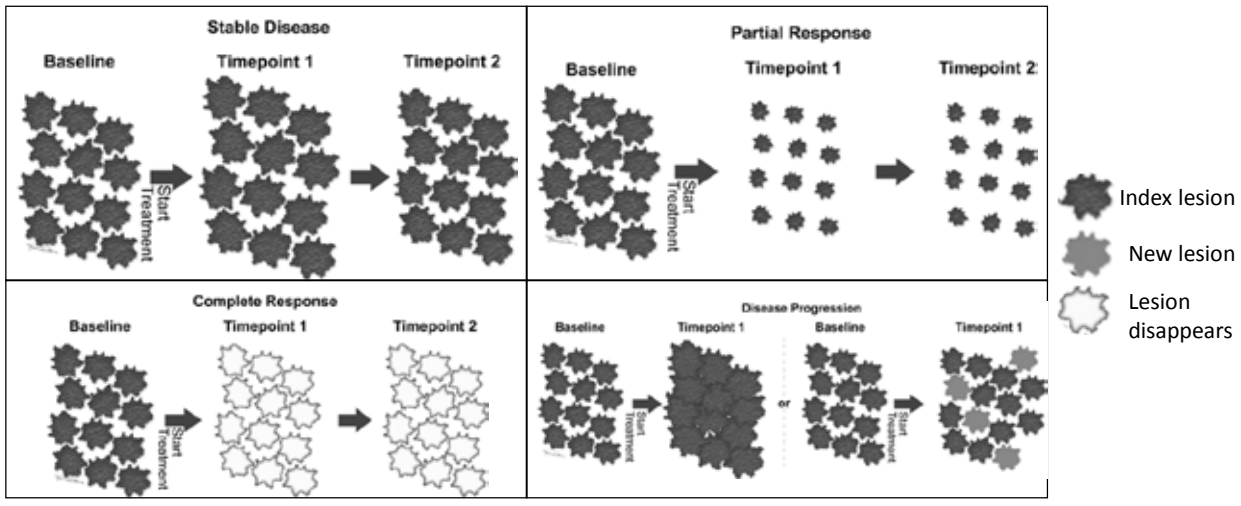
Cesano et al. Biomedicines 2018

Assessment of response



Chae, Oncotarget 2017.

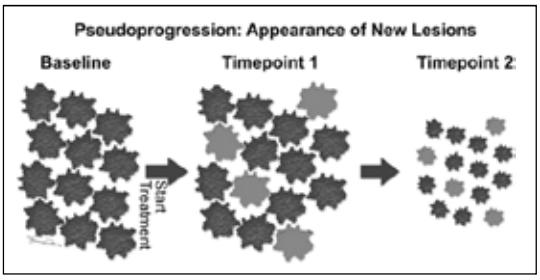
Many possible imaging findings

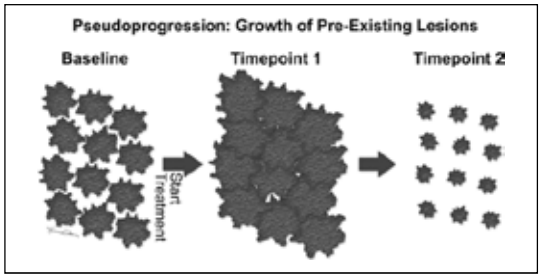


Wang, RadioGraphics 2017.

Ryan J. Sullivan, MD – *Massachusetts General Hospital*

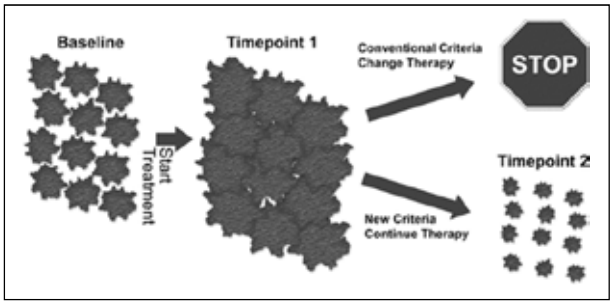
Many possible imaging findings

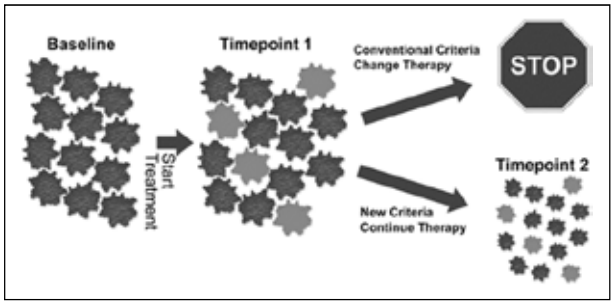




Wang, RadioGraphics 2017.

Assessment of response – unique considerations for immunotherapy





Wang, RadioGraphics 2017.

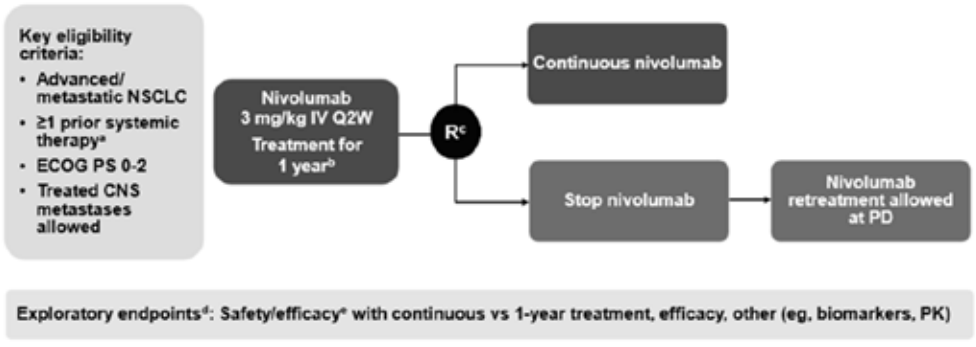
Comparison of disease progression by conventional and immune-related criteria

Treatment Response	RECIST 1.1	irRC
Progressive disease	≥20% increase in lesion sum* (absolute size increase ≥5 mm) or 1+ new lesions at any single observation	≥25% increase in tumor burden[+] versus nadir in two consecutive observations ≥4 weeks apart
New measurable lesions[#]	Always represent progressive disease	Incorporated into disease burden
New non-measurable lesions	Considered equivocal; followed at future examinations to clarify whether it is truly new disease	Does not define progression but precludes complete response

Wang, RadioGraphics 2017.

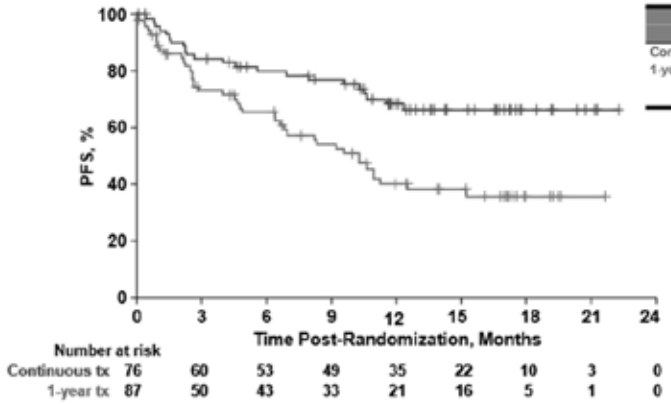
*Sum of lesion diameters: sum of the longest diameter in the plane of measurement for non-nodal target lesions and short-axis diameter for target nodal lesions.
[+]Based on the sum of the products of the two largest perpendicular diameters of all index lesions.
[#]Measurable lesion for RECIST1.1 is ≥10mm at CT; irRC is ≥10x10mm at CT. Smaller lesions are considered non-measurable.

When to stop immunotherapy: Checkmate 153



Spigel, Ann Oncol 2017.

When to stop immunotherapy: Checkmate 153



	Median, Months (95% CI)	PFS Rate, % 6-Month	1-Year
Continuous tx	NR (NR)	80	65
1-year tx[b]	10.3 (6.4, 15.2)	69	40

HR: 0.42 (95% CI: 0.25, 0.71)

Conclusion: >1 year of treatment may be necessary

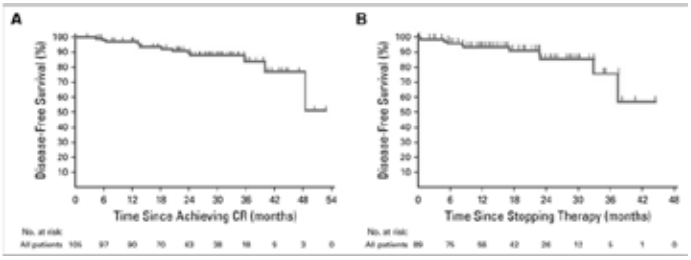
Spigel, Ann Oncol 2017.

When to stop immunotherapy: KEYNOTE-006

- Pembrolizumab 10 mg/kg Q2W or Q3W or ipilimumab 3 mg/kg Q3W for 4 doses
- Could stay on pembrolizumab for up to 2 years
- Of patients who completed 2 y pembro treatment, **86%** did not progress after 20 months follow-up
- More responders with pembrolizumab, but duration of response was similar for pembrolizumab and ipilimumab

When to stop immunotherapy: KEYNOTE-001

- 16% of patients achieved complete response
- Disease-free survival at 24 months after complete response:
  - In all CR patients: 90.9%
  - In patients who discontinued cancer therapy: 89.9%



Robert, J Clin Oncol 2018.

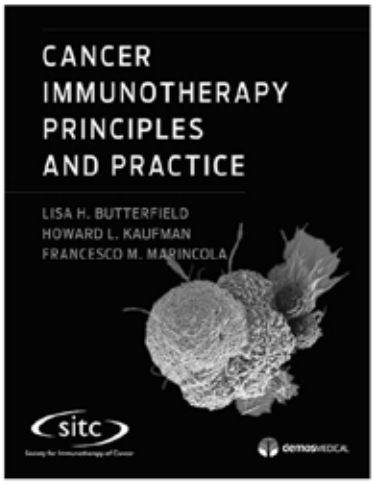
When to stop immunotherapy: clinical measures

- PET-based metabolic response
  - Metabolic response may precede anatomical changes on CT or MRI
- Achievement of CR

Basic Principles of Cancer Immunotherapy

Ryan J. Sullivan, MD – *Massachusetts General Hospital*

Further Resources



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Cancer Immunotherapy

CONNECT

Immunotherapy for the Treatment of Skin Cancers

Elizabeth Buchbinder, MD
Instructor in Medicine
Dana-Farber Cancer Institute

Dr. Elizabeth Buchbinder is a clinical oncologist at Dana Farber Cancer Institute specializing in the treatment of melanoma.She received her training at Tufts Medical School and Beth Israel Deaconess Medical Center in Boston.In addition to treating patients she performs clinical and translational research to help further melanoma treatment.Her primary areas of research are in immunotherapy and novel targeted therapy approaches.

Immunotherapy for the Treatment of Skin Cancers

Elizabeth Buchbinder, MD – *Dana-Farber Cancer Institute*

Audience Response Questions

1. Which of the following statements is true regarding adjuvant therapy for resected, Stage III melanoma?

   A. Adjuvant ipilimumab, either given at the 3 mg/kg or 10 mg/kg dosing level, is associated with improved RFS and OS over interferon and placebo
   B. Adjuvant anti-PD1 therapy is associated with improved RFS compared with ipilimumab and placebo, and is a standard treatment approach for patients with resected Stage III melanoma
   C. The combination of nivolumab plus ipilimumab is associated with improved RFS compared with single agent PD-1 inhibitor therapy in patients with resected Stage III melanoma
   D. There is no difference in tolerability of pembrolizumab, nivolumab, or ipilimumab (at either dose level) given in the adjuvant setting

2. Which statement best reflects the use of PD-L1 expression for patients with unresectable Stage III/Stage IV melanoma?
   A. PD-L1 expression is associated with higher response rates to single-agent anti-PD-1 inhibitor therapy but not dual checkpoint inhibitor therapy (e.g. nivolumab plus ipilimumab)
   B. PD-L1 expression is associated with higher response rates to all therapies including single-agent anti-PD-1 inhibitor therapy, chemotherapy, ipilimumab, and dual checkpoint inhibitor therapy (e.g. nivolumab plus ipilimumab)
   C. PD-L1 expression is associated with higher response rates to both single-agent anti-PD-1 and dual checkpoint inhibitor (e.g. nivolumab plus ipilimumab) therapy, yet is not useful in predicting which patients treated with these therapies will have prolonged survival
   D. PD-L1 expression is not associated with higher response rates to single-agent anti-PD-1 and/or dual checkpoint inhibitor (e.g. nivolumab plus ipilimumab) therapy and thus is not a useful measure to predict treatment response with anti-PD-1 based therapy.

Immunotherapy for the Treatment of Skin Cancers

Elizabeth Buchbinder, MD
Dana-Farber Cancer Institute

Disclosures

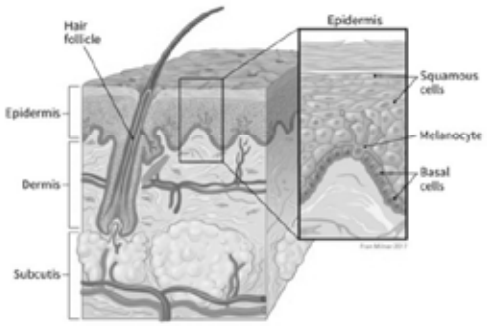
- Consulting Fees: BMS, Novartis, Array, Trieza
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Skin Cancers

Elizabeth Buchbinder, MD – *Dana-Farber Cancer Institute*

Background

- Skin cancer is the most common type of cancer
- Three most common types of skin cancers:
  - Basal cell carcinoma
  - Squamous cell carcinoma
  - Melanoma
- Melanoma was one of the foundational disease states for testing immunotherapies



Cancer.org

Approved cytokines in melanoma

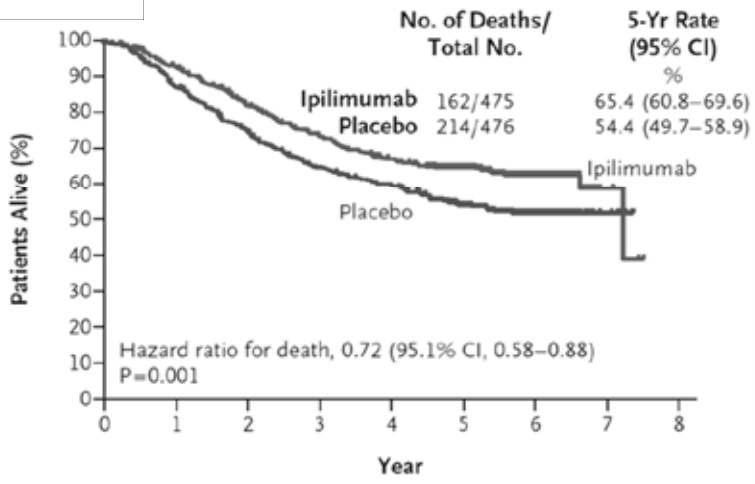
Drug	Indication	Dose
High-dose interferon alfa-2b	Adjuvant – high risk for systemic recurrence	Induction: 20m IU/m^2 IV 5x/wk for 4 wks Maintenance: 10m IU/m^2 s.c. 3x/wk for 48 wks
Interleukin-2 (Aldesleukin)	Stage IV	600k IU/kg/dose Q8hr, up to 14 doses; 9 days of rest; can repeat up to 28 doses per course
Pegylated Interferon alfa-2b (Sylatron)	Adjuvant – microscopic or gross nodal involvement	6 mcg/kg/wk s.c. for 8 doses, then 3 mcg/kg/wk s.c. for up to 5 years

Approved checkpoint inhibitors in melanoma

Drug	Approved	Indication	Dose
Ipilimumab	2011	Unresectable/Metastatic melanoma: newly diagnosed or after progression	3 mg/kg Q3W for 4 doses
	2015	Adjuvant therapy in stage III melanoma after complete resection	10 mg/kg Q3W for 4 doses, then 10 mg/kg Q12W for 3 years
	2017	Unresectable/Metastatic melanoma: newly diagnosed or after progression, all patients ≥ 12 yr	3 mg/kg Q3W for 4 doses

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 12 weeks for up to 3 years



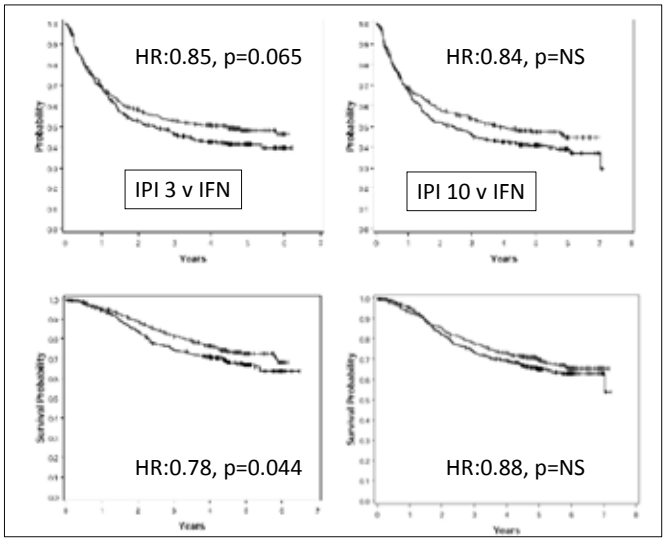
Eggermont, NEJM 2016.

Adjuvant Ipilimumab in High-Risk Stage III Melanoma

- ECOG 1609
  - NCT01274338
  - Adjuvant interferon (IFN) vs ipilimumab 3 mg/kg (IPI 3) vs ipilimumab 10 mg/kg (IPI 10)
  - Ipilimumab Q3W for four doses, then every 12 weeks for up to 3 years
  - IPI 3 "better than IFN", IPI 10 "not better than IFN"
  - IPI3 better tolerated than IPI 10

RFS

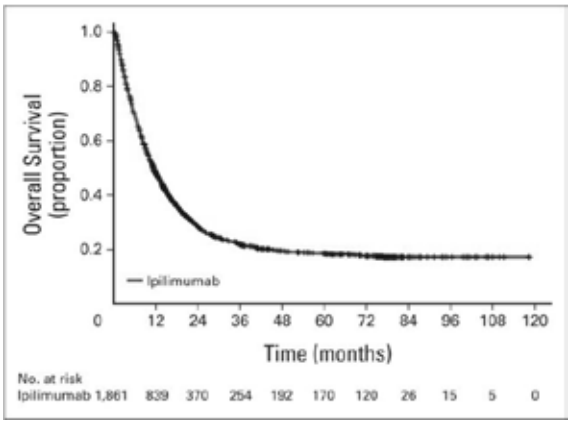
OS



Tarhini, ASCO Annual Meeting 2019.

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)



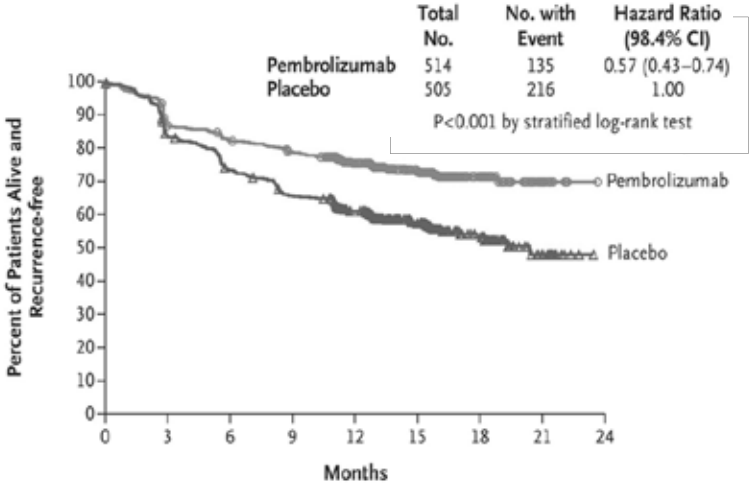
Schadendorf, JCO 2015.

Approved checkpoint inhibitors in melanoma

Drug	Approved	Indication	Dose
Pembrolizumab	2014	Advanced/unresectable melanoma with progression after other therapy	200 mg Q3W*
	2015	1st line unresectable/metastatic melanoma	200 mg Q3W*
	2019	Adjuvant therapy of melanoma following complete resection	200 mg Q3W
*Original approvals were 2 mg/kg Q3W – updated to flat dosing regimen			

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

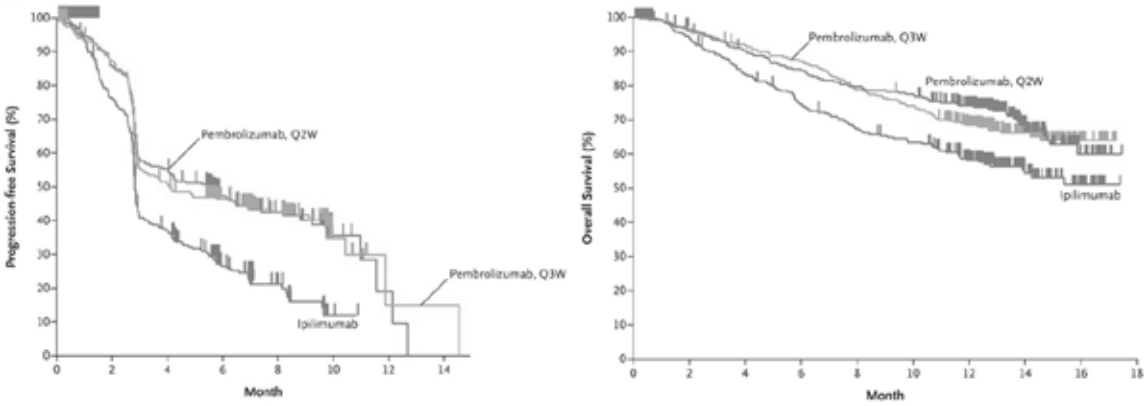
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)



Eggermont, NEJM 2018.

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial



Robert, NEJM 2015.

Approved checkpoint inhibitors in melanoma

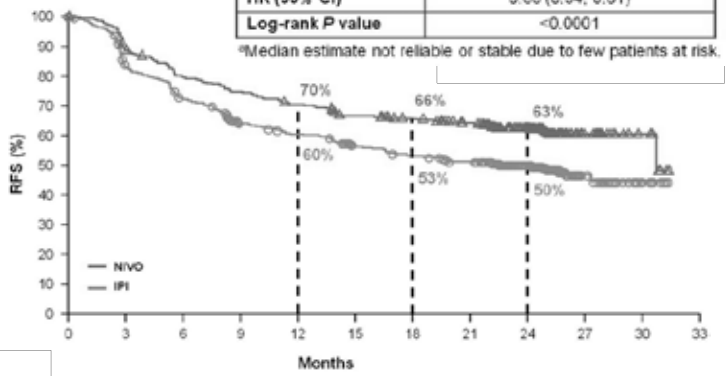
Drug	Approved	Indication	Dose
Nivolumab	2014	Unresectable/metastatic melanoma with progression after other therapy	240 mg Q2W or 480 mg Q4W*
	2017	Adjuvant treatment of melanoma after complete resection	240 mg Q2W or 480 mg Q4W
*Original approval was 3 mg/kg Q2W, updated to flat dosing regimen			

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

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	0.66 (0.54, 0.81)	
Log-rank *P* value	<0.0001	

[a]Median estimate not reliable or stable due to few patients at risk.



Miller, ASCO 2018.

Approved checkpoint inhibitors in melanoma

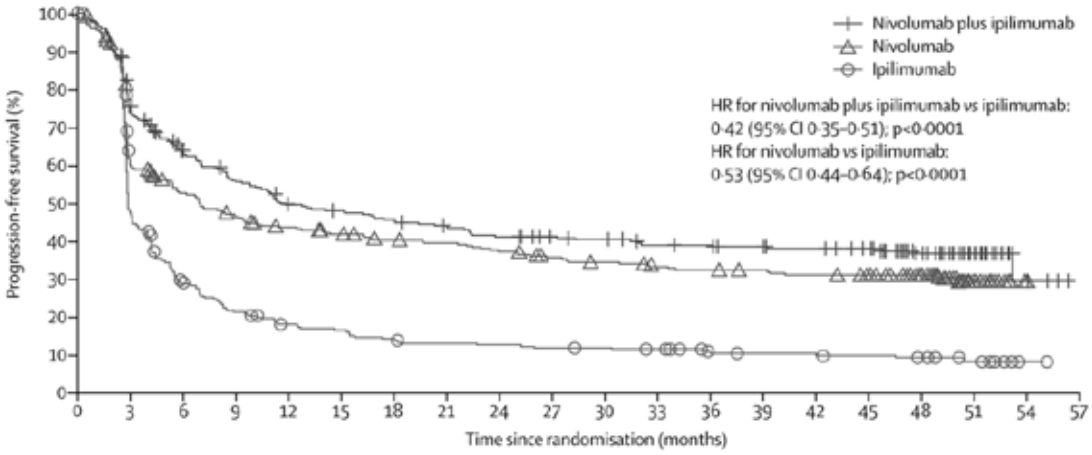
Drug	Approved	Indication	Dose
Nivolumab + Ipilimumab	2015	BRAF V600 WT unresectable/metastatic melanoma	1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W
	2016	BRAF V600 WT or mutant unresectable/metastatic melanoma	1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W

Immunotherapy for the Treatment of Skin Cancers

Elizabeth Buchbinder, MD – *Dana-Farber Cancer Institute*

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

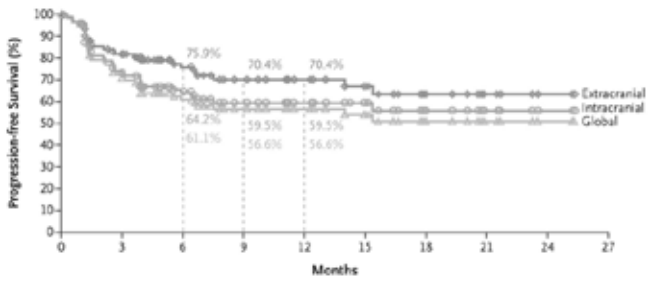
Phase III CheckMate 067 Trial



Hodi, Lancet Oncol 2018.

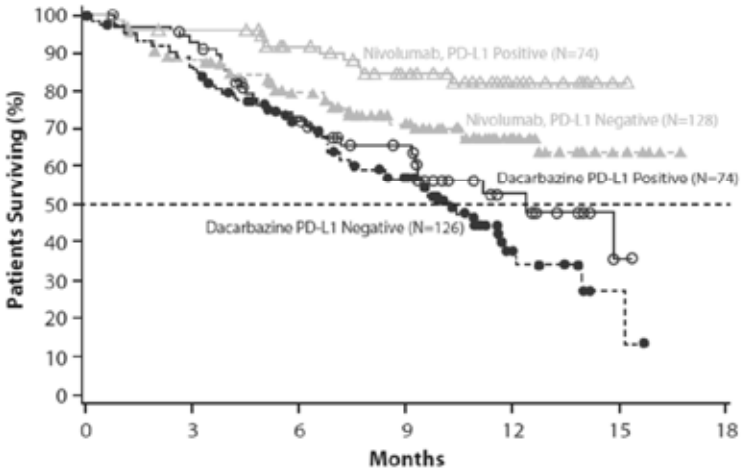
Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)



Tawbi, NEJM 2018.

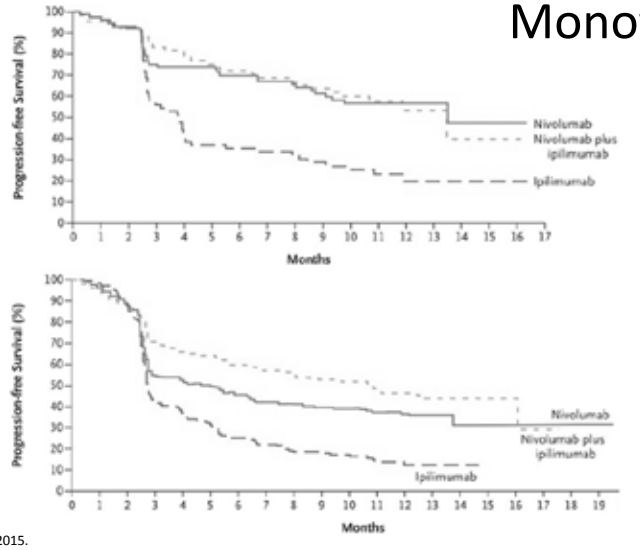
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert, NEJM 2015.

Importance of Tumor PD-L1 Status between Combination Checkpoint Blockade and Monotherapy

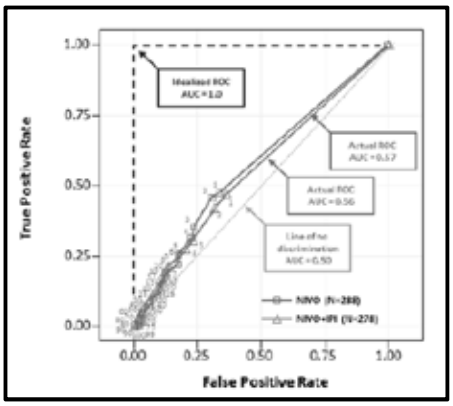


Tumor PD-L1 Positive Patients

Tumor PD-L1 Negative Patients

Larkin, NEJM 2015.

The use of PD-L1 status to predict overall survival is poor with single-agent PD-1 or combined ipi/nivo…



PDL-1 (%)	≥ 1	< 1	≥ 5	< 5	≥ 10	< 10
Ipilimumab	19%	18%	21%	17%	20%	18%
Nivolumab	54%	35%	58%	42%	58%	44%
Ipi/Nivo	65%	54%	72%	56%	85%	55%

…but, PD-L1 status predicts higher response rate with combo at every PD-L1 expression cut-off

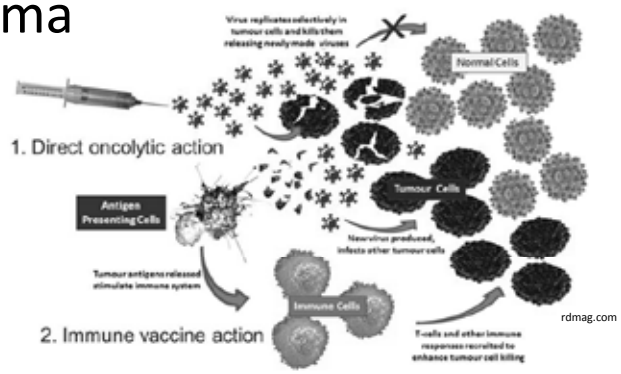
Wolchok, NEJM 2017.

In development: Neoadjuvant immunotherapy in advanced melanoma

Trial	Regimen	N	pCR (%)	med RFS (mo)	med FU (mo)
Amaria Lancet Oncol 2018	*Dab/Tram*	21	58	19.7	18.6
Long Lancet Oncol 2019	*Dab/Tram*	35	49	23.0	27.0
Blank Nat Med 2018	Ipi+nivo	10	33	NR	32
Amaria Nat Med 2018	Nivo Ipi+nivo	12 11	25 45	NR NR	20
Huang Nat Med 2019	Pembro	30	19	NR	18
Rozeman Lancet Oncol 2019	Ipi+nivo	86	57	NR	8.3

Menzies ASCO Annual Meeting 2019.

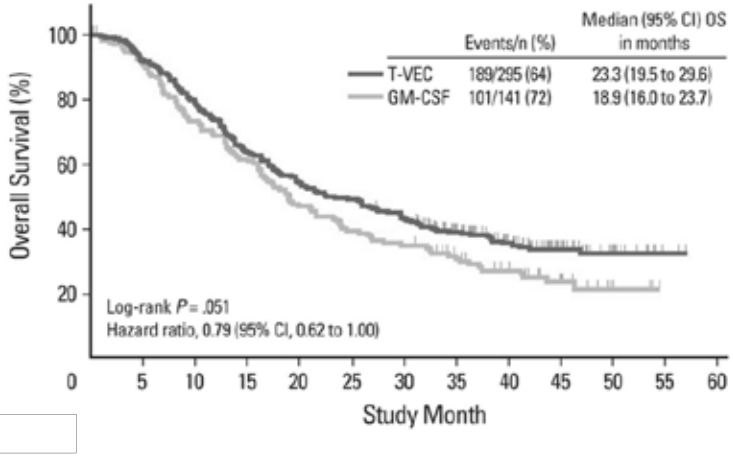
Approved oncolytic virus in melanoma



Drug	Approved	Indication	Dose
Talimogene laherparepvec (T-Vec)	2015	Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in recurrent melanoma after surgery	Intralesional injection: ≤4 mL at 10^6 PFU/mL starting; 10^8 PFU/mL subsequent

Talimogene laherparepvec (T-VEC) in Stage III/IV Melanoma

- Phase III OPTiM Trial
  - Oncolytic, genetically-engineered herpes virus
  - Intralesional T-VEC 106 pfu/mL, 108 pfu/mL 3 weeks after initial dose, then Q2W
  - Subcutaneous GM-CSF



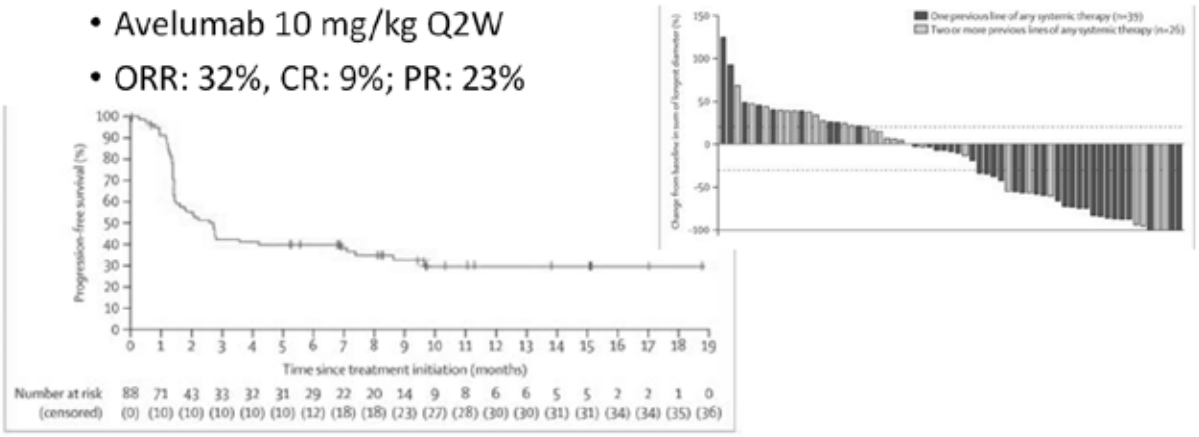
Andtbacka, Kaufman, JCO 2015.

Approved checkpoint inhibitors in other skin cancers

Drug	Approved	Indication	Dose
Avelumab	2017	Patients >12 yr with metastatic **Merkel cell carcinoma**	800 mg Q2W + premedication (first 4 cycles)
Pembrolizumab	2018	Adult/pediatric with recurrent advanced/metastatic **Merkel cell carcinoma**	Adults: 200 mg Q3W Pediatric: 2 mg/kg (up to 200 mg) Q3W
Cemiplimab-rwlc	2018	Metastatic **cutaneous squamous cell carcinoma**, not candidate for curative therapies	350 mg Q3W

Avelumab in 2nd-line metastatic Merkel Cell carcinoma

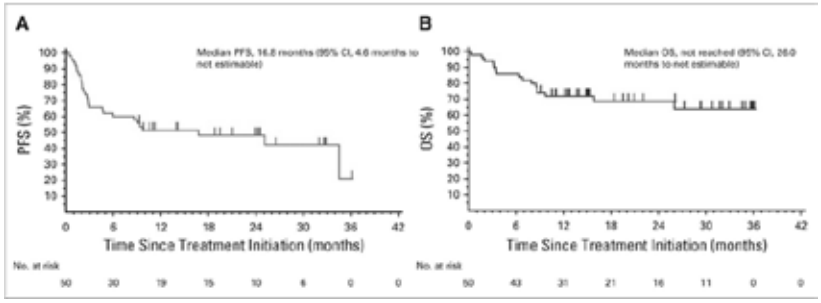
- 1st FDA-approved treatment for this status
- Avelumab 10 mg/kg Q2W
- ORR: 32%, CR: 9%; PR: 23%



Kaufman, Lancet Oncol 2016.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

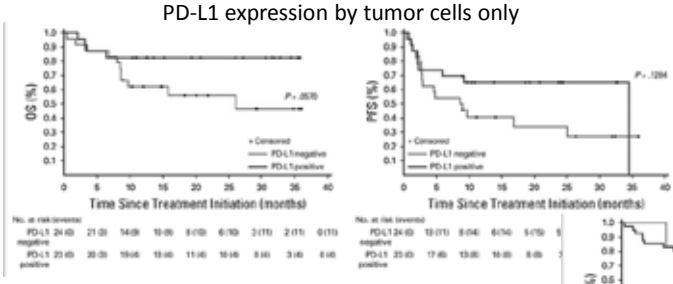
- KEYNOTE-017
- Pembrolizumab 2 mg/kg Q3W up to 2 years
- mPFS: 16.8 months (compared to 90 days for chemo)
- 24-month OS: 68.7%



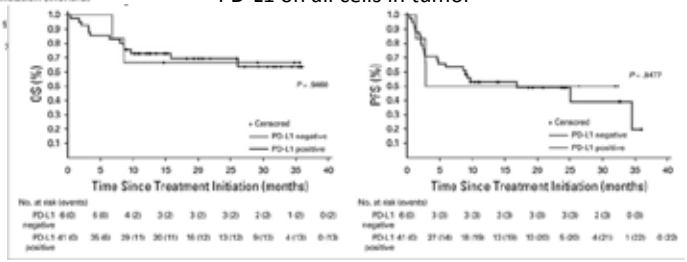
Nghiem, J Clin Oncol 2019.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

PD-L1 expression by tumor cells only



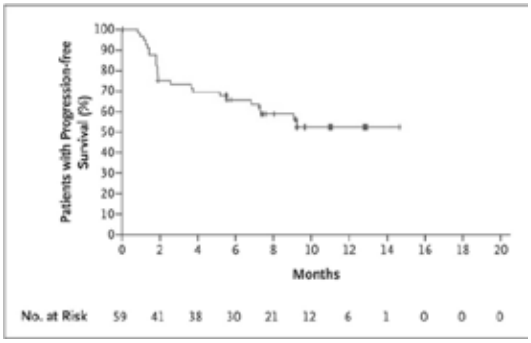
PD-L1 on all cells in tumor

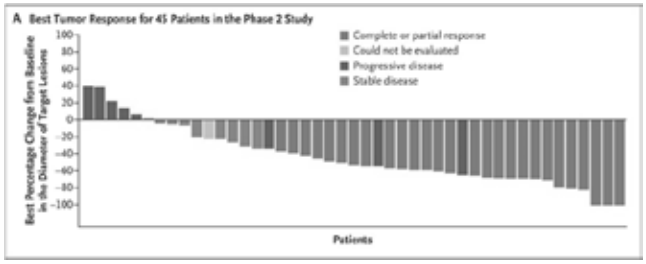


Nghiem, J Clin Oncol 2019.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

- Cemiplimab 3mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response

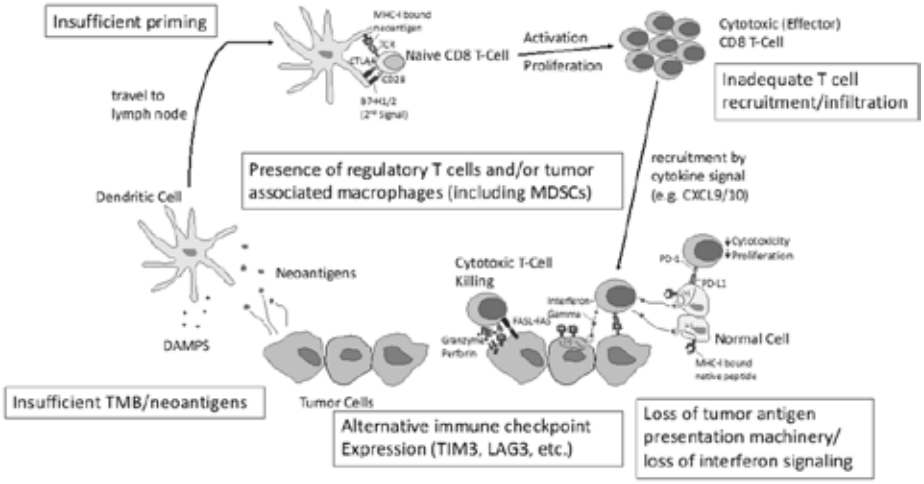




Migden, NEJM 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How does immune checkpoint inhibitor therapy fail?

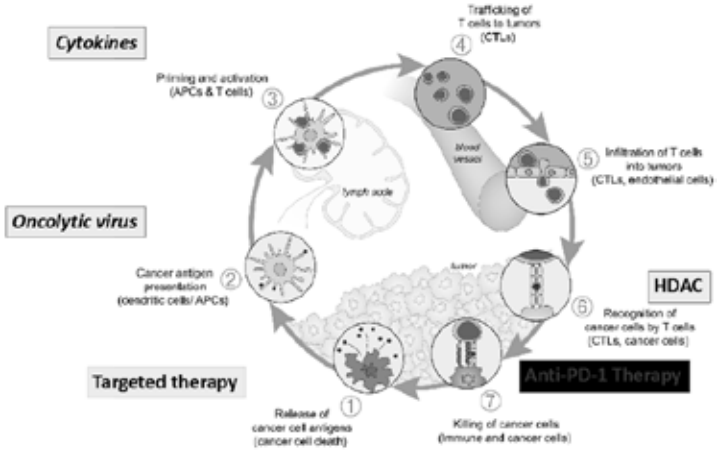


Modified from Liu, Jenkins, Sullivan. Amer J Clin Derm 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How do we overcome resistance?

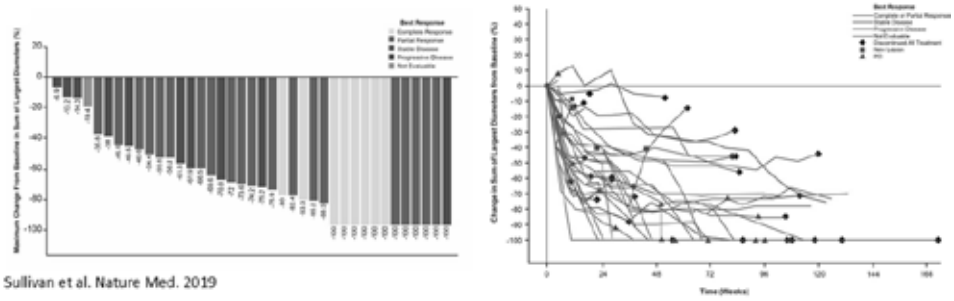
Combination therapy



Modified from Chen and Melman. Immunity 2015.

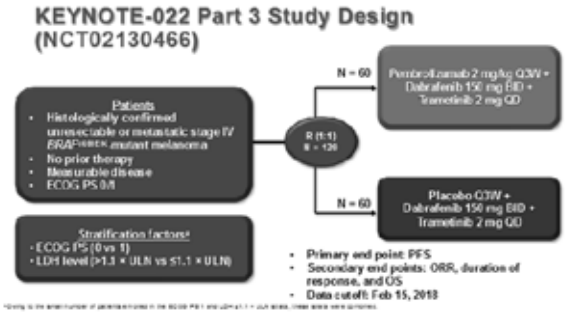
In development: Combined IO with BRAF targeted therapy

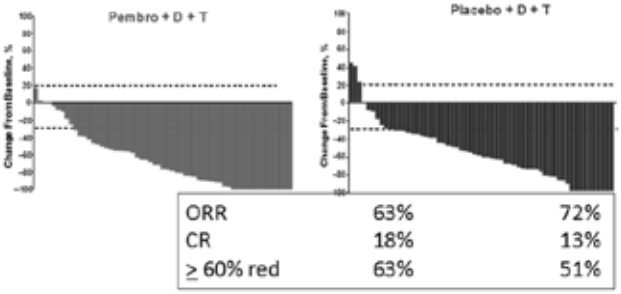
- Cobimetinib + vemurafenib + atezolizumab
- ORR: 71.8%
- Median duration of response: 17.4 mo



Sullivan et al. Nature Med. 2019

In development: Combined IO with BRAF targeted therapy

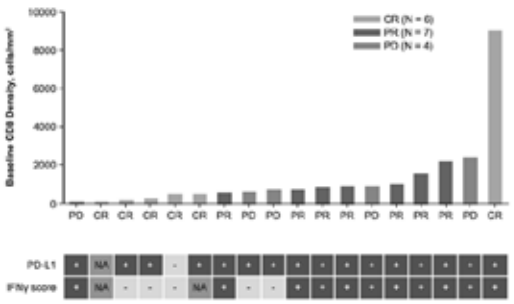




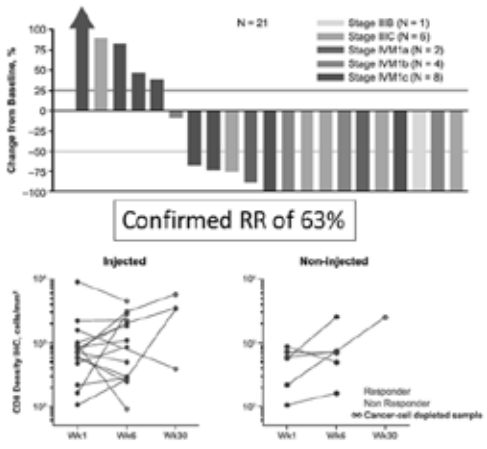
ORR	63%	72%
CR	18%	13%
≥ 60% red	63%	51%

Ascieto et al, *Nature Med* 2019.

In development: Combined IO with Oncolytic Virus



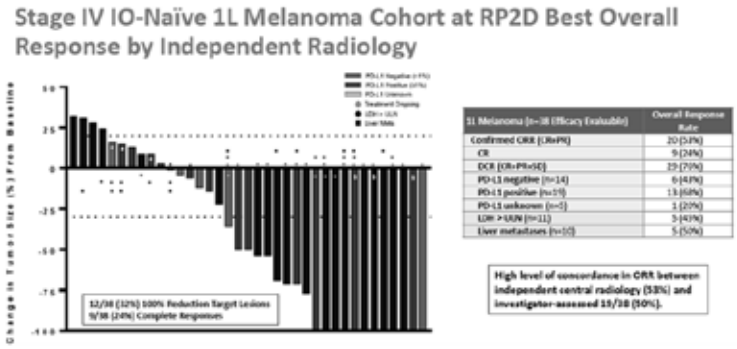
Phase I: Pembrolizumab + TVEC



Ribas et al Cell 2017

In development: Combined IO with IL-2 (NKTR-214)

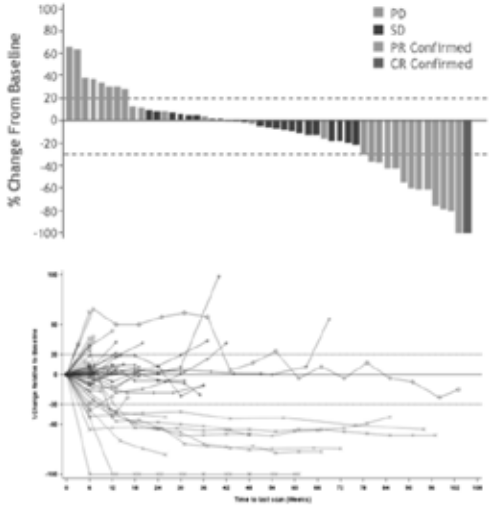
Efficacy (response rate) data from non-randomized cohorts of urothelial bladder cancer, renal cell carcinoma, and melanoma looks promising



Diab et al, ASCO 2018.
Diab et al, SITC 2018.

In development: Combined IO with HDAC inhibitor

- Entinostat + pembrolizumab
- 19% ORR (1 CR, 9 PR)
- Median duration of response: 13 mo
- 9 additional patients with SD for >6 mo



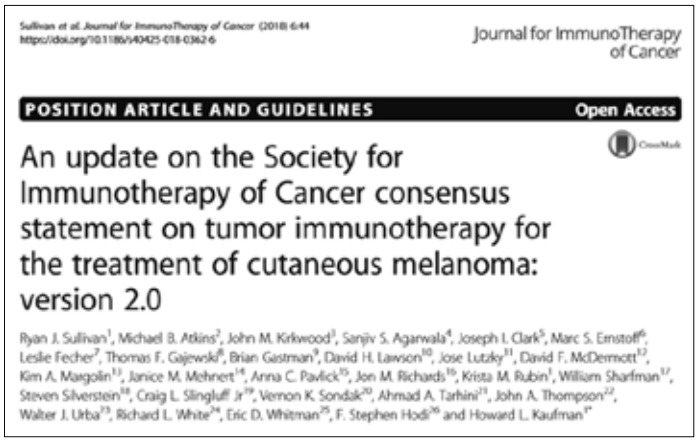
Sullivan et al, AACR 2019.

Conclusions

- Melanoma was one of the foundational disease states for testing immunotherapies
- Avelumab and pembrolizumab are now approved for Merkel cell carcinoma, and cemiplimab is approved for cutaneous squamous cell carcinoma
- Combination immunotherapies may lead to higher response rates and more durable responses

Additional Resources

sitc Society for Immunotherapy of Cancer
Cancer Immunotherapy GUIDELINES


Sullivan et al. Journal for ImmunoTherapy of Cancer (2018) 6:44
https://doi.org/10.1186/s40425-018-0362-6

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

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

Ryan J. Sullivan[1], Michael B. Atkins[2], John M. Kirkwood[3], Sanjiv S. Agarwala[4], Joseph I. Clark[5], Marc S. Ernstoff[6], Leslie Fecher[7], Thomas F. Gajewski[8], Brian Gastman[9], David H. Lawson[10], Jose Lutzky[11], David F. McDermott[12], Kim A. Margolin[13], Janice M. Mehnert[14], Anna C. Pavlick[15], Jon M. Richards[16], Krista M. Rubin[1], William Sharfman[17], Steven Silverstein[18], Craig L. Slingluff Jr[19], Vernon K. Sondak[20], Ahmad A. Tarhini[21], John A. Thompson[22], Walter J. Urba[23], Richard L. White[24], Eric D. Whitman[25], F. Stephen Hodi[26] and Howard L. Kaufman[1*]

Case Studies

Case #1: stage IV

JS, male patient in 60s

- Patient with a history of melanoma 10 years prior, back lesion, <1mm, non-ulcerated, at the time no SLN or adjuvant therapy
- Found to have new pulmonary lesion concerning for primary lung cancer, thoracic surgeon feels this is unresectable
- Biopsy performed and reveals malignant melanoma, BRAF wt

Case #1: stage IV BRAF wt

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - Targeted Rx based on next-generation sequencing
  - Clinical trial

Case #1: stage IV BRAF wt

- Systemic therapy
  - **Nivolumab**
  - **Pembrolizumab**
  - Ipilimumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - Targeted Rx based on next-generation sequencing
  - Clinical trial

Case #2: stage IV

JS, male patient in 60s – SAME PATIENT

- Patient with a history of melanoma 10 years prior, back lesion, <1mm, non-ulcerated, at the time no SLN or adjuvant therapy
- Found to have new pulmonary lesion concerning for primary lung cancer
- Biopsy performed and reveals malignant melanoma, BRAF MUTATED

Case #2: stage IV BRAF mutant

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - BRAF/MEK targeted therapy

Case #2: stage IV BRAF mutant

- Systemic therapy
  - **Nivolumab**
  - **Pembrolizumab**
  - Ipilimumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - BRAF/MEK targeted therapy

Case #3: stage IV

JS, male patient in 60s – SAME PATIENT

- Patient with a history of melanoma 10 years prior, back lesion, <1mm, non-ulcerated, at the time no SLN or adjuvant therapy
- Found to have new pulmonary lesion concerning for primary lung cancer
- Biopsy performed and reveals malignant melanoma, BRAF MUTATED
- Patient having hip pain and found to have right acetabular bony lesion

Case #3: stage IV BRAF mutant

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - BRAF/MEK targeted therapy

  Radiation to hip lesion

Case #3: stage IV BRAF mutant

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - **Nivolumab plus ipilimumab**
  - High-dose IL-2
  - BRAF/MEK targeted therapy

  Radiation to hip lesion

Case #3: What if the patient is found to have a brain metastasis?

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - BRAF/MEK targeted therapy

  Radiation to brain lesion?

Case #3: What if the patient is found to have a brain metastasis?

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - **Nivolumab plus ipilimumab**
  - High-dose IL-2
  - BRAF/MEK targeted therapy

  Radiation to brain lesion?

Immunotherapy for the Treatment of Lung Cancer

Deepa Rangachari, MD
Instructor, Medicine, Harvard Medical School
Beth Israel Deaconess Medical Center

Dr. Deepa Rangachari is an Assistant Professor at Harvard Medical School and thoracic medical oncologist at the Beth Israel Deaconess Medical Center (BIDMC) in Boston, MA. Her area of focus is optimizing the care of patients with advanced lung cancers. She additionally serves as the Associate Director of the BIDMC Hematology/Oncology Fellowship Program.

Immunotherapy for the Treatment of Lung Cancer

Deepa Rangachari, *MD – Beth Israel Deaconess Medical Center*

Audience Response Questions

1. Which of the following has NOT demonstrated benefit as a first-line therapy option for NSCLC patients?
   A. Atezolizumab/bevacizumab/paclitaxel/carboplatin (non-squamous NSCLC, no EGFR/ALK)
   B. Nivolumab + ipilimumab (TMB-high NSCLC)
   C. Pembrolizumab monotherapy (PD-L1 TPS ≥ 1%, no EGFR/ALK)
   D. Pembrolizumab/pemetrexed/carboplatin (non-squamous NSCLC)

2. For a small-cell lung cancer patient who has progressed on platinum and one other therapy, which of the following is NOT an FDA-approved treatment option?
   A. Nivolumab
   B. Pembrolizumab
   C. Atezolizumab/carboplatin/etoposide
   D. Topotecan

Immunotherapy for the Treatment of Lung Cancer

Deepa Rangachari, MD
Instructor, Medicine; Harvard Medical School
Beth Israel Deaconess Medical Center

Disclosures

- Consulting Fees: DynaMed, Advance Medical
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Lung Cancer

Deepa Rangachari, *MD – Beth Israel Deaconess Medical Center*

Lung cancer

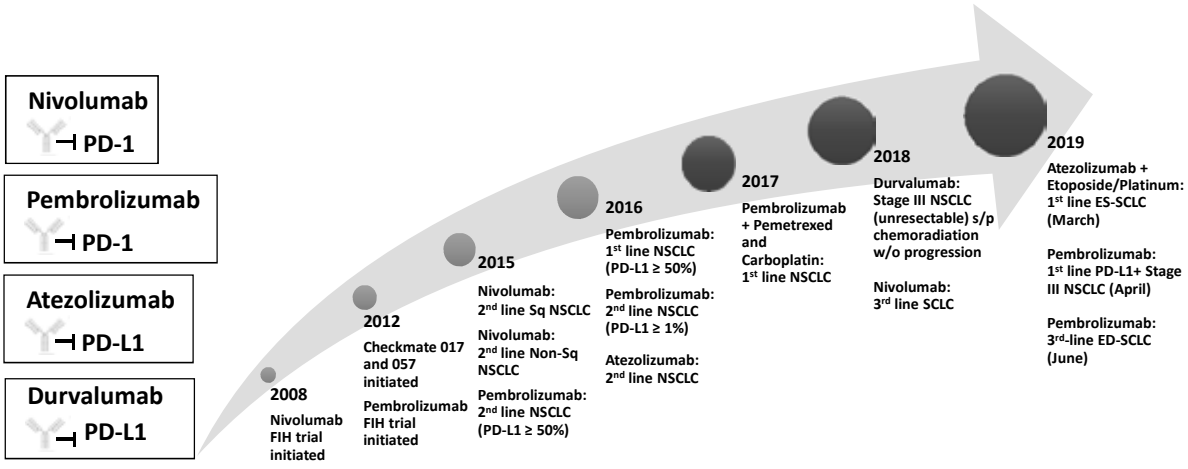
- 80-85% non-small cell lung cancer (NSCLC)
- 10-15% small cell lung cancer (SCLC)
- NSCLC has relatively long and extensive history of immunotherapy use

Estimated Deaths

Male			Female		
Lung & bronchus	76,650	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All sites	**321,670**		**All sites**	**285,210**	

American Cancer Society

FDA-approved checkpoint inhibitors in lung cancer



Approved checkpoint inhibitors in NSCLC

Drug	Approved	Indication	Dose
Nivolumab	2015	Metastatic Squamous NSCLC with progression after chemotherapy (2nd line)	240 mg Q2W or 480 mg Q4W
	2015	Metastatic Non-Squamous NSCLC with progression after chemotherapy (2nd line)	

Approved checkpoint inhibitors in NSCLC

Drug	Approved	Indication	Dose
Pembrolizumab	2015	Metastatic NSCLC with progression after chemotherapy and PD-L1 ≥ 50%	200 mg Q3W
	2016	Metastatic NSCLC with progression after chemotherapy and PD-L1 ≥ 1%	
	2016	1st line metastatic NSCLC with PD-L1 TPS ≥ 50%	
	2019	1st line stage III NSCLC (not candidate for resection or definitive chemoradiation) and Metastatic NSCLC, with PD-L1 TPS ≥ 1% and no EGFR/ALK mutations	
Pembrolizumab + pemetrexed & carboplatin	2017	1st line metastatic Non-Squamous NSCLC	
Pembrolizumab + pemetrexed + platinum	2018	1st line metastatic Non-Squamous NSCLC with no EGFR/ALK mutations	
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel	2018	1st line metastatic Squamous NSCLC	

Approved checkpoint inhibitors in NSCLC

Drug	Approved	Indication	Dose
Atezolizumab	2016	Metastatic NSCLC with progression after Pt-chemotherapy and targeted therapy if EGFR/ALK mutation-positive	840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W
Atezolizumab + bevacizumab + paclitaxel + carboplatin	2018	1st line metastatic non-squamous NSCLC with no EGFR/ALK mutations	For 4-6 cycles: atezolizumab 1200 mg Q3W + chemotherapy + bevacizumab Maintenance: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W
Durvalumab	2018	Stage III NSCLC, ineligible for surgery and without progression after chemoradiation	10 mg/kg Q2W

Treatment Naïve Regimens: Competing Strategies in NSCLC

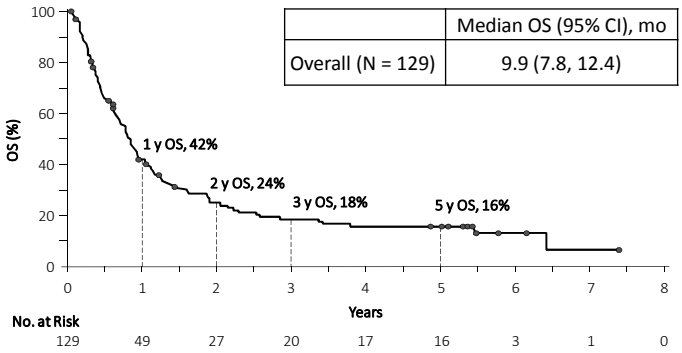
- **KEYNOTE 024** – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 50%
- **KEYNOTE 042** – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 1%
- **KEYNOTE 189** – Pembrolizumab + Chemotherapy vs. Chemotherapy alone in advanced non-squamous NSCLC
- **IMPOWER 150** – Atezolizumab + Chemotherapy (Bev) vs. Chemotherapy (Bev) 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

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



	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

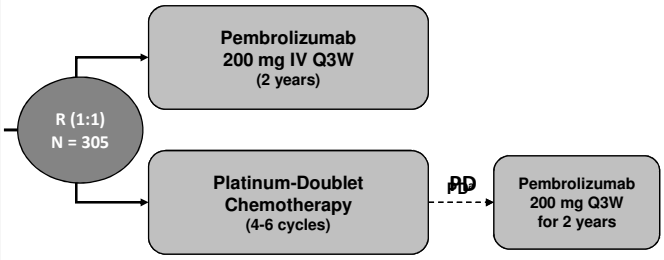
Gettinger et al. JCO 2018
Brahmer et al, AACR 2017
NCI SEER data, Lung and Bronchus Cancer, 2014

KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 Positive (≥ 50%)

NSCLC Study Design (NCT021427389)

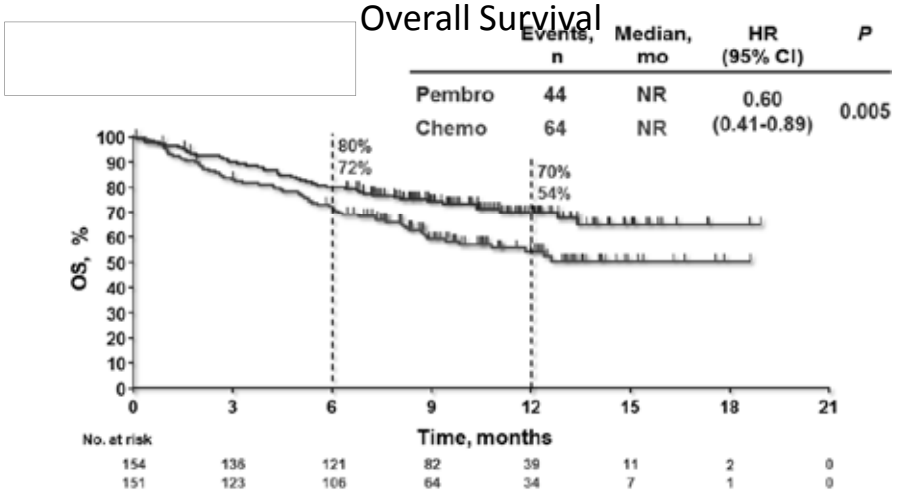
Key Eligibility Criteria

- ***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



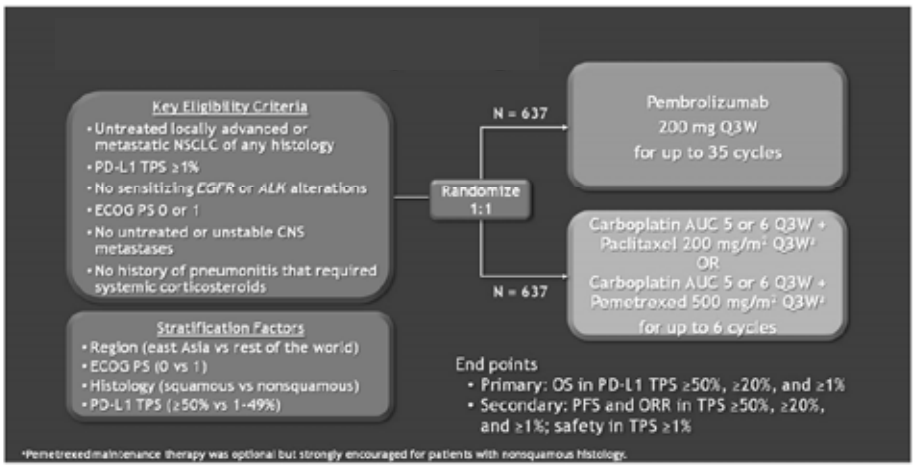
Reck M et al, ESMO 2016, NEJM 2016

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



Reck M et al, ESMO 2016, NEJM 2016

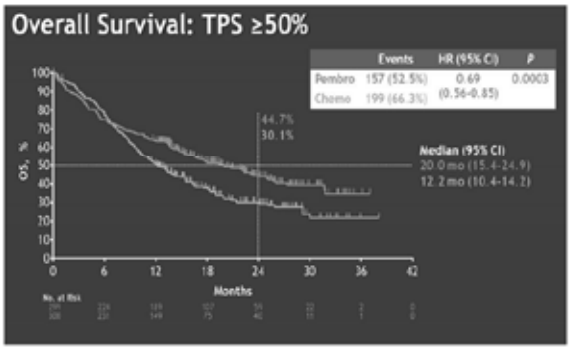
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ **1%** NSCLC

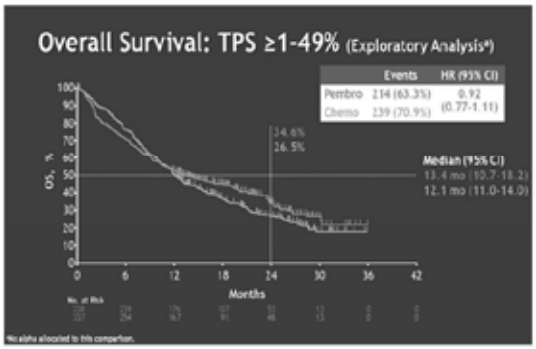


Lopes et al, ASCO 2018

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

Overall Survival

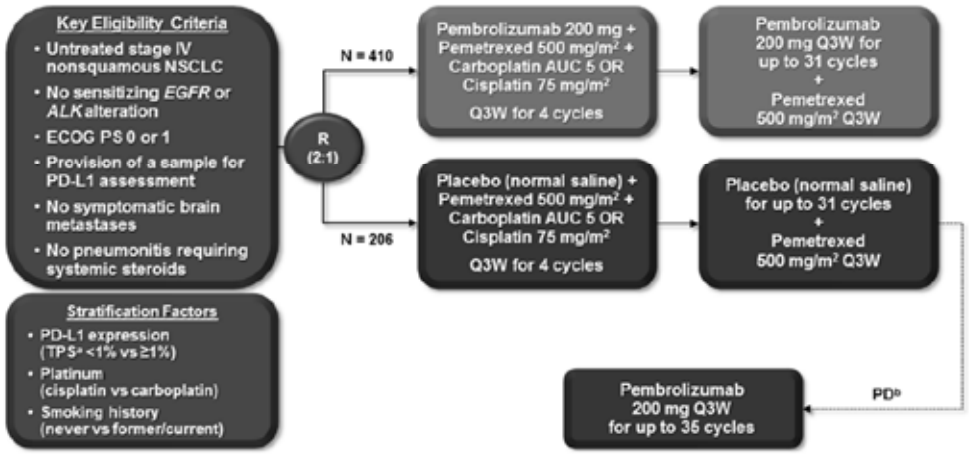




Survival benefit seemed to be driven by the TPS ≥ 50% subset with little benefit witnessed in the subset TPS = 1 - 49%

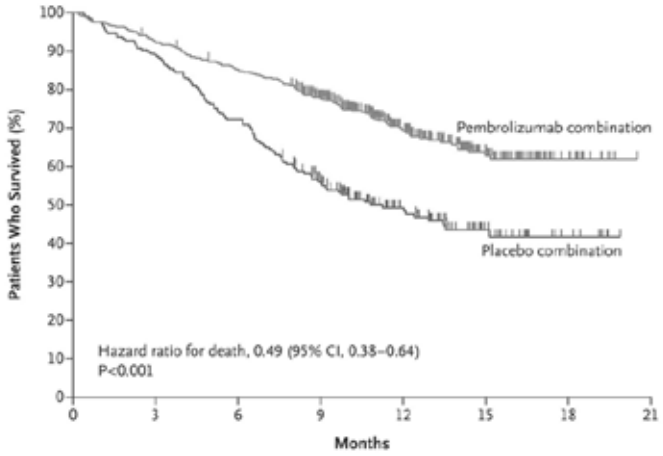
Lopes et al, ASCO 2018

KEYNOTE-189: Pembrolizumab/Platinum/Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC



Ghandi et al, NEJM 2018

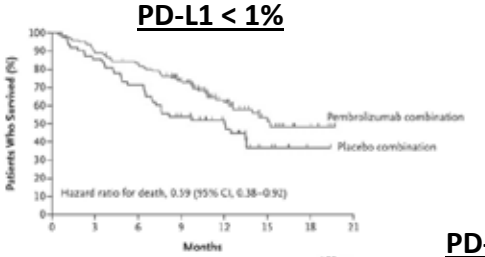
KEYNOTE-189: Pembrolizumab/Platinum/Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC



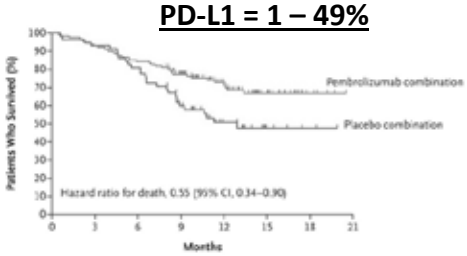
Ghandi et al, NEJM 2018

KEYNOTE-189: Pembrolizumab/Platinum/Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC

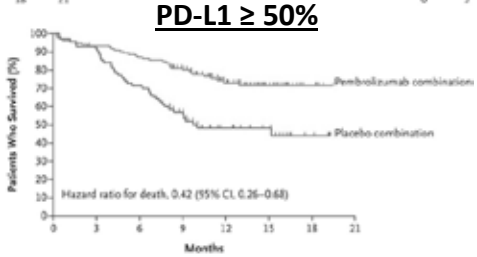
PD-L1 < 1%



PD-L1 = 1 – 49%

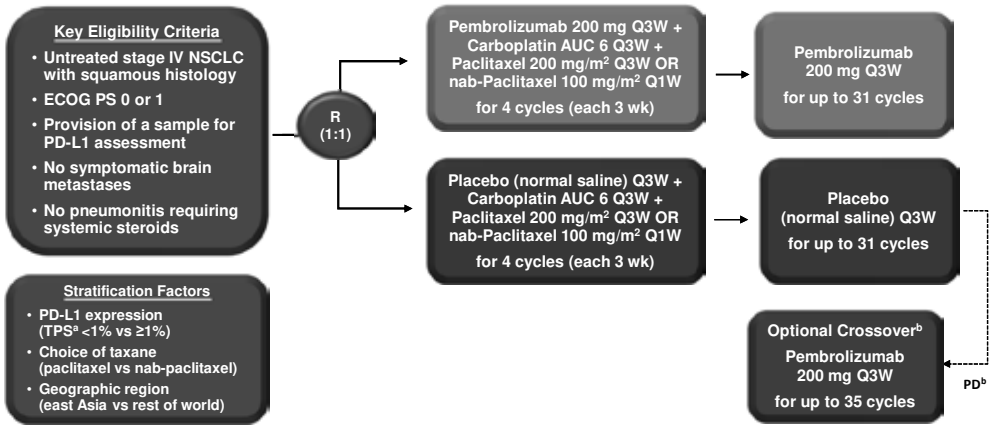


PD-L1 ≥ 50%



Ghandi et al, NEJM 2018

KEYNOTE-407: Pembrolizumab/Chemotherapy vs Chemotherapy Alone for Advanced Squamous-Cell NSCLC

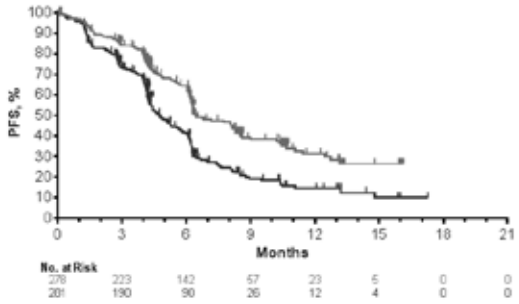


Paz-Ares et al, ASCO 2018

KEYNOTE-407: Pembrolizumab/Chemotherapy vs Chemotherapy Alone for Advanced Squamous-Cell NSCLC

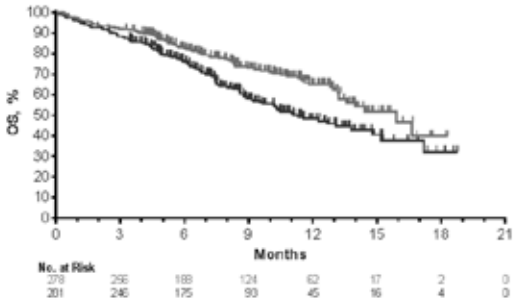
PFS (RECISTv1.1, BICR)

	Events	HR (95% CI)	*P*
Pembro + Chemo	54.7%	0.56 (0.45-0.70)	<0.0001
Placebo + Chemo	70.1%		



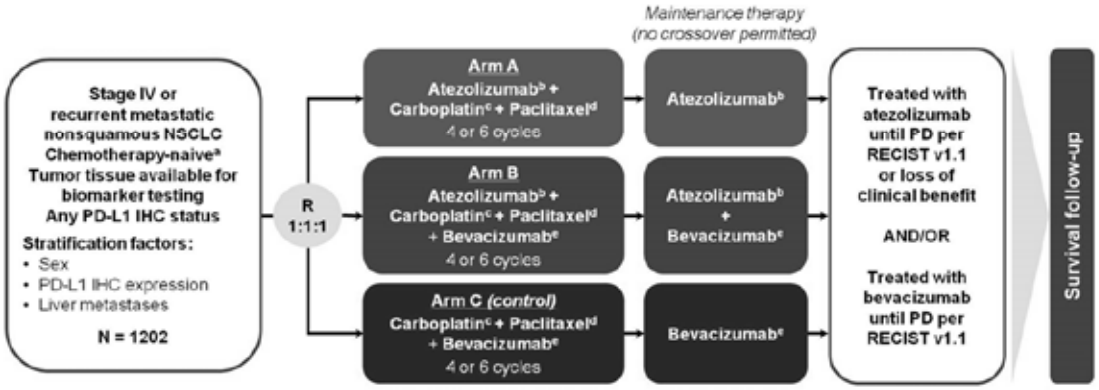
Overall Survival

	Events	HR (95% CI)	*P*
Pembro + Chemo	30.6%	0.64 (0.49-0.85)	0.0008
Placebo + Chemo	42.7%		



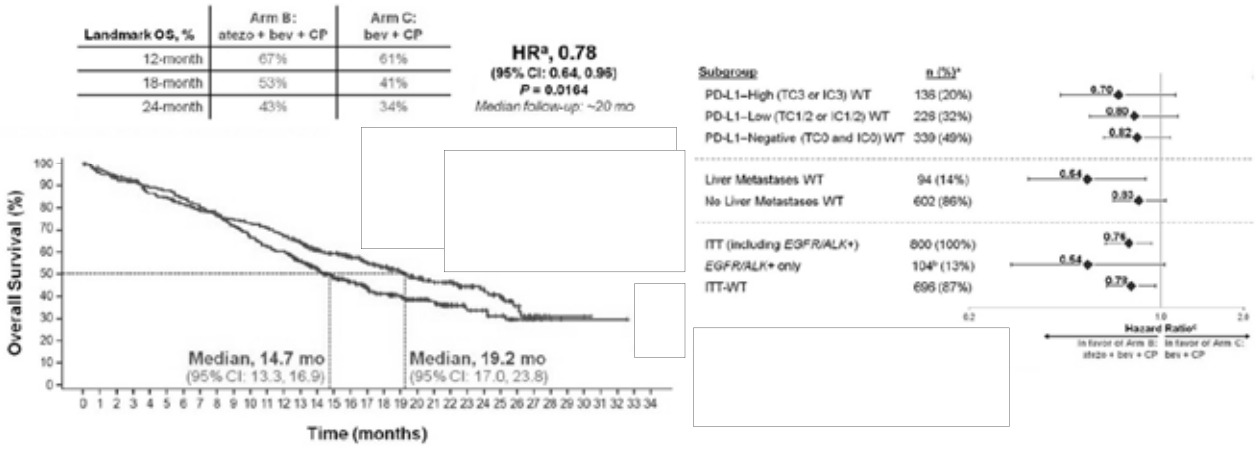
Paz-Ares et al, ASCO 2018

IMPOWER 150: Atezolizumab/Carboplatin/Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/Bevacizumab in Advanced Non-Squamous NSCLC



Socinski et al, NEJM 2018

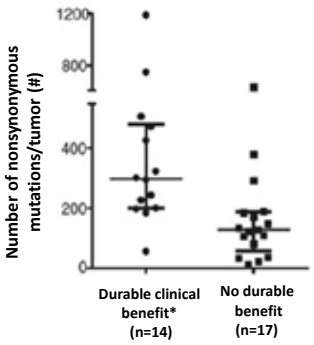
IMPOWER 150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/ Bevacizumab in Advanced Non-Squamous NSCLC

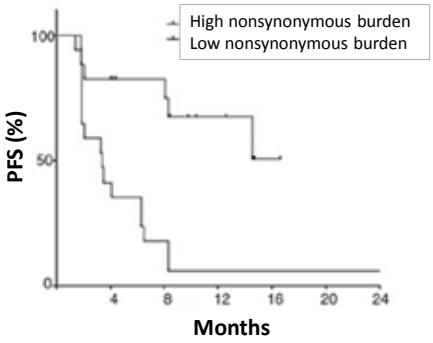


Socinski et al, NEJM 2018

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.

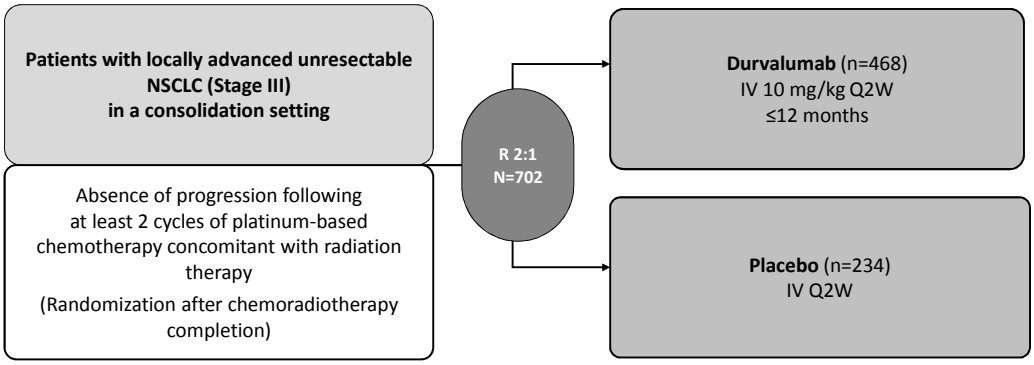




***Partial or stable response lasting > 6 mo**

Rizvi N et al, Science, 2015

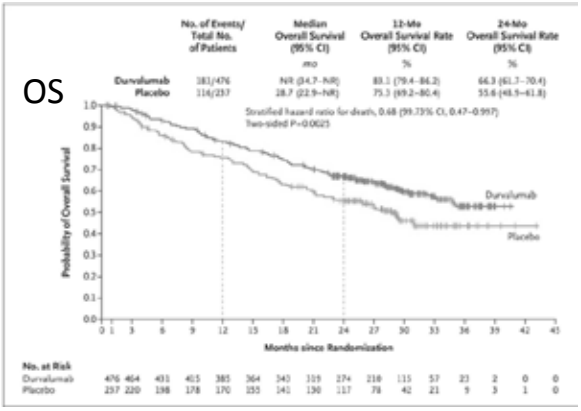
PACIFIC (NCT02125461): Durvalumab after chemoradiotherapy in Stage III NSCLC



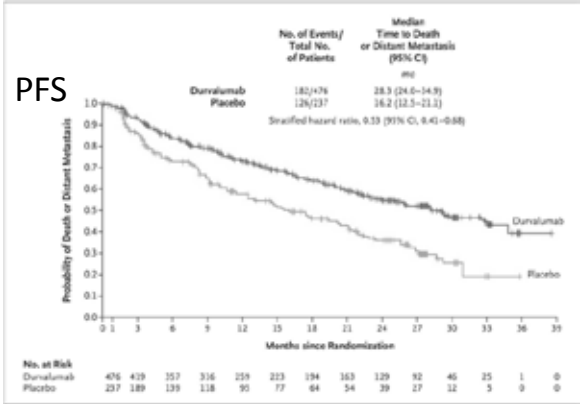
In House Data, AstraZeneca Pharmaceuticals LP. PACIFIC Protocol. 2014.
NIH 2015 NCT02125461, http://clinicaltrials.gov/ct2/show/NCT02125461.
Creelan B, Iannotti NO, Salamat MA, et al. 2016. (PHRR150325-000989)
Ann Oncol. 2015;26 (supplement 1): i24-i28, abstract 95TiP.

PACIFIC (NCT02125461): Durvalumab after chemoradiotherapy in Stage III NSCLC

OS



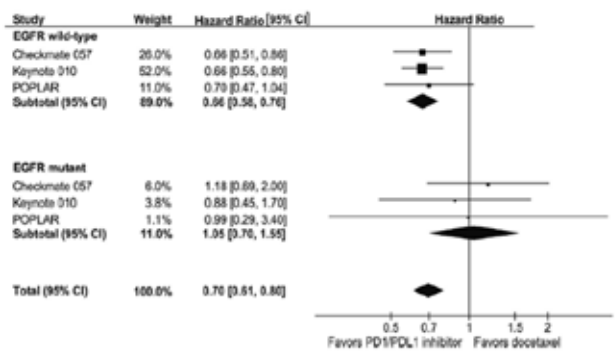
PFS

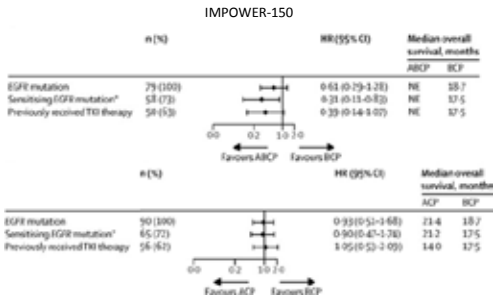


Antonia et al, NEJM 2018

Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

Meta-Analysis: CM-057, KN-010, POPLAR; IMPOWER-150





CK Lee et al., JTO 2016
M Reck et al., Lancet Resp Med 2019

PD-1/PD-L1 Inhibitors Increase *Overall Survival* in 2L Advanced NSCLC

CHECKMATE 017 (nivolumab)

	Median Overall Survival *mo (95% CI)*	1-Yr Overall Survival *% of patients (95% CI)*	No. of Deaths
Nivolumab (N=135)	9.2 (7.3–13.3)	42 (34–50)	86
Docetaxel (N=137)	6.0 (5.1–7.3)	24 (17–31)	113

CHECKMATE 057 (nivolumab)

	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4
HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015		

KEYNOTE 010 (TPS ≥ 1%) (pembrolizumab)

Treatment Arm	Median (95% CI), mo	HR* (95%CI)	P
Pembro 2 mg/kg	14.9 (10.4-NR)	0.54 (0.38-0.77)	0.0002
Pembro 10 mg/kg	17.3 (11.8-NR)	0.50 (0.36-0.70)	<0.0001
Docetaxel	8.2 (6.4-10.7)	–	–

OAK (atezolizumab)

HR, 0.73[a]
(95% CI, 0.62, 0.87)
P = 0.0003
Minimum follow up = 19 months

Brahmer NEJM 2015
Borghaei, NEJM 2015
Herbst Lancet 2016
Rittmeyer Lancet 2017

Small cell lung cancer

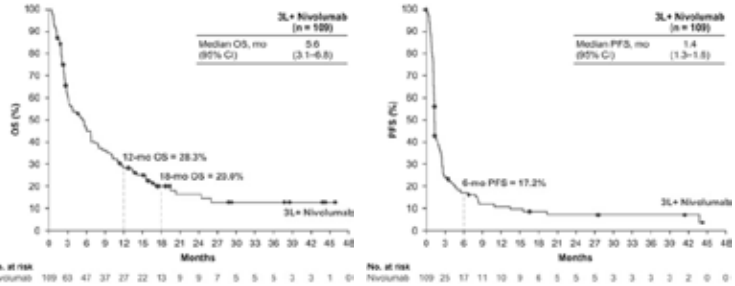
- 10-15% of lung cancers
- Almost exclusively former/current smokers
- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2nd line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

Approved checkpoint inhibitors in SCLC

Drug	Approved	Indication	Dose
Nivolumab	2018	Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy (3rd line)	240 mg Q2W
Atezolizumab + carboplatin + etoposide	2019	1st line extensive stage SCLC	For 4 cycles: atezolizumab 1200 mg + carboplatin + etoposide Q3W Maintenance: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W
Pembrolizumab	2019	Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy (3rd line)	200 mg Q3W

CheckMate-032: Nivolumab in 3rd line SCLC

- Nivolumab in SCLC with progression on platinum chemotherapy and another therapy
- Nivolumab 3 mg/kg Q2W
- @28.3 months:
  - ORR: 11.9%
  - mDOR: 17.9 months

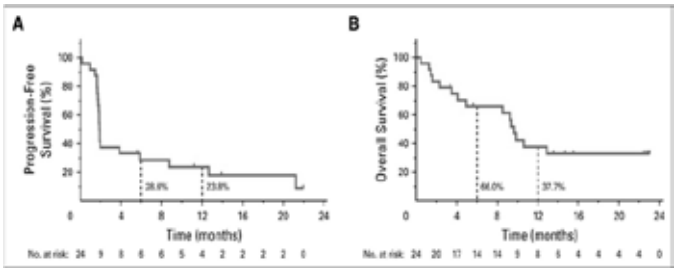


Ready, J Thorac Oncol 2019

Pembrolizumab in 3rd-line SCLC

- KEYNOTE-028: PD-L1+ only (Cohort C1)
- KEYNOTE-158: PD-L1 +/- (Cohort G)
- Combined analysis:
- ORR: 19.3%
  - 2 CR, 14 PR
  - 14/16 responders were PD-L1+
  - 9/16 responders had response ≥18 mo.
- mOS: 7.7 months

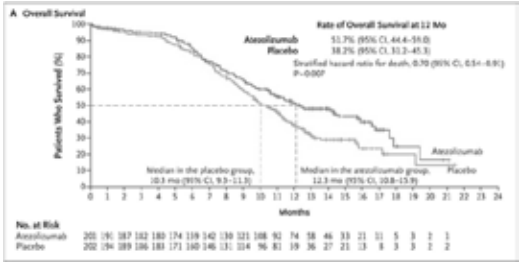
PD-L1+ (KEYNOTE-028)



Ott, J Clin Oncol 2017.

IMpower133: Atezolizumab + chemo in 1st-line SCLC

- Induction phase: four 21-day cycles of carboplatin and etoposide + atezolizumab (1200 mg once per cycle) or placebo
- Maintenance phase: either atezolizumab or placebo
- @13.9 mo:
  - mOS = 12.3 vs 10.3 mo
  - mPFS = 5.2 vs 4.3 mo



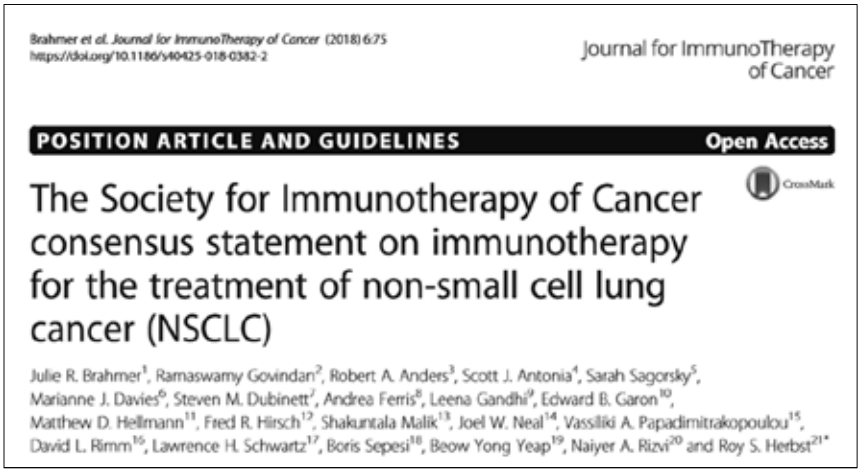
Horn, NEJM 2018.

Conclusions

- NSCLC has been a proving ground for checkpoint inhibitors
- Moving from 2nd/3rd line options to the front line
- Clear-cut biomarkers still lacking

Resources

sitc Society for Immunotherapy of Cancer
Cancer Immunotherapy GUIDELINES



Brahmer et al. Journal for ImmunoTherapy of Cancer (2018) 6:75
https://doi.org/10.1186/s40425-018-0382-2

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC)

Julie R. Brahmer[1], Ramaswamy Govindan[2], Robert A. Anders[3], Scott J. Antonia[4], Sarah Sagorsky[5], Marianne J. Davies[6], Steven M. Dubinett[7], Andrea Ferris[8], Leena Gandhi[9], Edward B. Garon[10], Matthew D. Hellmann[11], Fred R. Hirsch[12], Shakuntala Malik[13], Joel W. Neal[14], Vassiliki A. Papadimitrakopoulou[15], David L. Rimm[16], Lawrence H. Schwartz[17], Boris Sepesi[18], Beow Yong Yeap[19], Naiyer A. Rizvi[20] and Roy S. Herbst[21*]

Case Studies

Case Study 1

Your patient is a 59 y/o gentleman with a 45 pack/year tobacco history presents with R-sided weakness and falls and ultimately diagnosed with adenocarcinoma of the lung with metastases to the brain and bone.

Following palliative brain radiotherapy for the symptomatic brain metastases, he presents to your clinic for systemic therapy counseling and planning.

Aside from tobacco use and HTN, he has no other medical problems. ECOG PS is 1.

Comprehensive tumor molecular profiling performed on a nodal aspirate shows the following: microsatellite- stable, tumor mutation burden (TMB)- 50 muts/mb, PD-L1 22C3 tumor proportion score (TPS) 50%, and KRAS G12C mutation amongst many others.

Case Study 1

Which of the following is advised as an evidence-based palliative systemic therapy regimen in this patient's case?

A. Carboplatin/Pemetrexed
B. Carboplatin/Pemetrexed/Pembrolizumab
C. Pembrolizumab
D. B and C
E. All of the above

Case Study 1

Answer:

A. Carboplatin/Pemetrexed
B. Carboplatin/Pemetrexed/Pembrolizumab
C. Pembrolizumab
D. B and C
E. All of the above

Case Study 1

Discussion:

Notable aspects of this patient's case include the following:

59 y/o gentleman with a 45 pack/year tobacco history presents with adenocarcinoma of the lung with metastases to the brain and bone.

He has no other medical problems. ECOG PS is 1.

Comprehensive tumor molecular profiling shows: microsatellite- stable, tumor mutation burden (TMB)- 50 muts/mb, PD-L1 TPS 50%, and KRAS G12C mutation.

On the basis of the landmark KEYNOTE trials, either **Pembrolizumab** alone (**KEYNOTE-024**) OR combination chemoimmunotherapy with **Carboplatin/Pemetrexed/Pembrolizuma**b (**KEYNOTE-189**) is a reasonable FDA-approved regimen for this patient due to **high tumor PD-L1 (TPS ≥50%) and absence of other actionable genomic alterations**.

Given high likelihood of brisk response with less toxicity associated with single agent Pembrolizumab vs. combination chemoimmunotherapy, **Pembrolizumab alone** is generally favored in this setting (high tumor PD-L1)– though whether upfront combination therapy might be superior in this setting remains uncertain.

Case Study 2

Six months into the treatment course, the patient develops a grade 3 colitis from Pembrolizumab. He is admitted and treated with high dose IV steroids and remains on a slow outpatient PO steroid taper.

Most recent CT torso and MRI brain performed just prior to hospitalization shows overall partial response to therapy since initiation of Pembrolizumab 6 months ago; there are no new sites of disease/evidence of disease progression.

Case Study 2

What do you advise next for your patient?

A. Resume Pembrolizumab IV every 3 weeks.
B. Administer Pembrolizumab at extended intervals of IV every 6 weeks.
C. Switch to Carboplatin/Pemetrexed.
D. Transition to active surveillance for now.

Case Study 2

Answer:

A. Resume Pembrolizumab IV every 3 weeks.
B. Administer Pembrolizumab at extended intervals of IV every 6 weeks.
C. Switch to Carboplatin/Pemetrexed.
D. Transition to active surveillance for now.

Deepa Rangachari, MD – *Beth Israel Deaconess Medical Center*

Case Study 2

Discussion:

The patient has had a known, significant immune-related adverse event (colitis, grade 3).

Suspension of Pembrolizumab and treatment with high dose steroids, followed by steroid taper over a minimum of 4-6 weeks is advised.

Re-challenge with Pembrolizumab might be considered in future following detailed discussion of risks, benefits, and alternatives with the patient.

Immune-related adverse events may be accompanied by continued durable disease control even in the absence of continued regular administration of the immune checkpoint inhibitor.

Active surveillance is a safe and viable strategy if the overall disease burden is stable.

Immunotherapy for the Treatment of Head and Neck Cancers

Glenn J. Hanna, MD
Medical Oncologist, Head and Neck Cancers
Dana-Farber Cancer Institute

Dr. Glen Hanna completed his residency training in internal medicine at Beth Israel Deaconess Medical Center and fellowship training in hematology and medical oncology at th e Dana-Farber Cancer Institute in 2016. Prior to this, he earned his medical degree from Georgetown University School of Medicine in 2010, where he graduated summa cum laude, a member Alpha Omega Alpha Honor Society and the Kober Medalist for academic excellence. Dr. Hanna also graduated summa cum laude from the University of Florida. He joined the faculty of the Center for Head and Neck Oncology in 2017. Dr. Hanna's clinical and translational research efforts are focused on both molecular and immunologic biomarker discovery to foster precision medicine approaches to treat head and neck cancers and improve patient outcomes. He maintains foundation and industry support to explore immuno-oncology approaches to treat head and neck cancers and high-risk oral precancerous lesions using novel combination immune checkpoint blockade, intra-tumoral injectables, and immune effector cell (IEC) therapies.

Immunotherapy for the Treatment of Head and Neck Cancers

Glenn J. Hanna, MD – *Dana-Farber Cancer Institute*

Audience Response Questions

1. What is the most common clinical target for checkpoint inhibition therapy for the treatment of head and neck cancers?
   A. TIGIT
   B. Programmed Death Protein 1
   C. Tumor infiltrating lymphocytes
   D. Tumor associated macrophages

2. Which immune checkpoint inhibitor is approved for treatment of advanced cutaneous squamous cell carcinoma?
   A. Durvalumab
   B. Pempbrolizumab
   C. Nivolumab
   D. Cemiplimab

Immunotherapy for the Treatment of Head and Neck Cancer

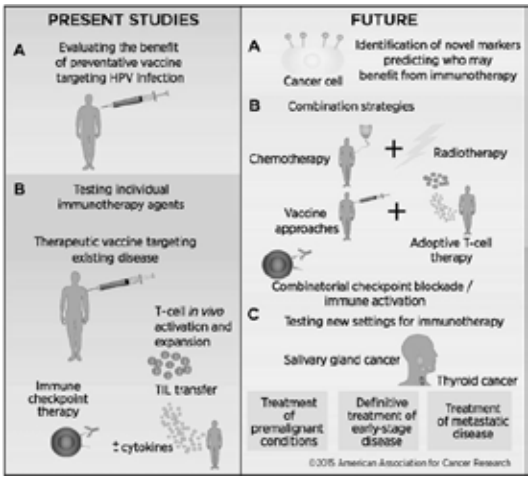
Glenn J. Hanna, MD
Dana-Farber Cancer Institute

Disclosures

- Consulting Fees:
  - Regeneron, Sanofi, BMS, Maverick, Merck
- Contracted Research:
  - BMS, Exicure, GSK, Altor BioScience, Kite, Regeneron, Sanofi, Kartos
- I will 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
  - Therapeutic vaccines for established cancers
  - CAR-T and cell-mediated therapies
  - Combinations with immunotherapies



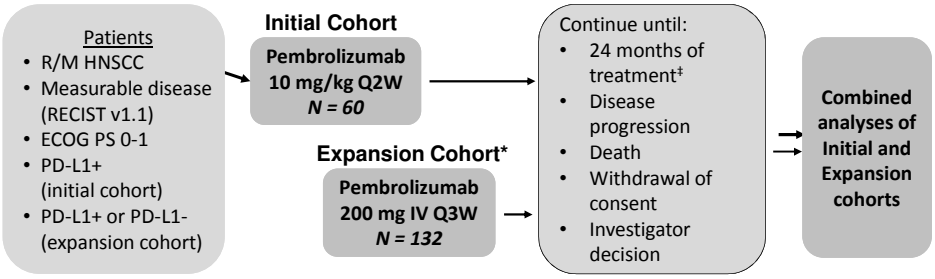
Schoenfeld, Cancer Immunol Res, 2015

Approved checkpoint inhibitors in Head and Neck Cancers

Drug	Approved	Indication	Dose
Pembrolizumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	200 mg Q3W
Nivolumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	240 mg Q2W or 480 mg Q4W
Cemiplimab-rwlc	2018	Metastatic cutaneous squamous cell carcinoma, not candidate for curative therapies (any site)	350 mg Q3W
Pembrolizumab + platinum + fluorouracil	2019	Recurrent/metastatic HNSCC 1st line – all patients	200 mg Q3W
Pembrolizumab	2019	Recurrent/metastatic HNSCC 1st line – PD-L1 CPS ≥ 1	200 mg Q3W
Pembrolizumab	2019	Recurrent locally advanced/metastatic squamous cell carcinoma of esophagus (PD-L1 CPS ≥ 10)	200 mg Q3W

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 §

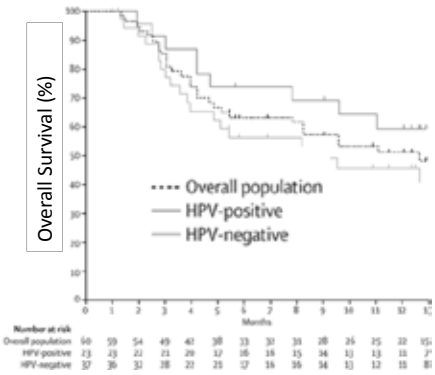
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*Median duration of disease not reached.

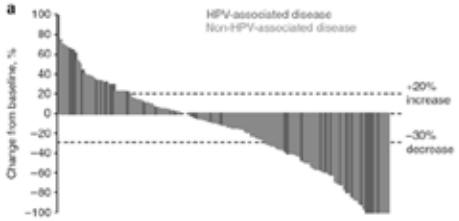
Seiwert, ASCO 2017.

KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts† B, B2

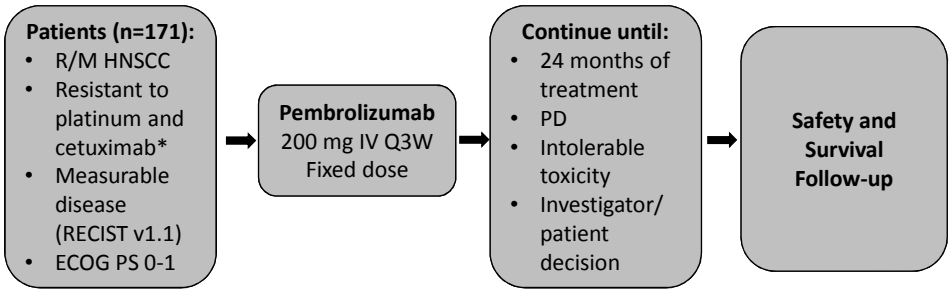
- ORR = 18%
  - CR = 4%
  - PR = 14%
- mOS = 8.0 months
- mPFS = 2.1 months





Seiwert, ASCO 2017.
Mehra, Br J Can 2018.

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab
Phase II Trial, Single Arm



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

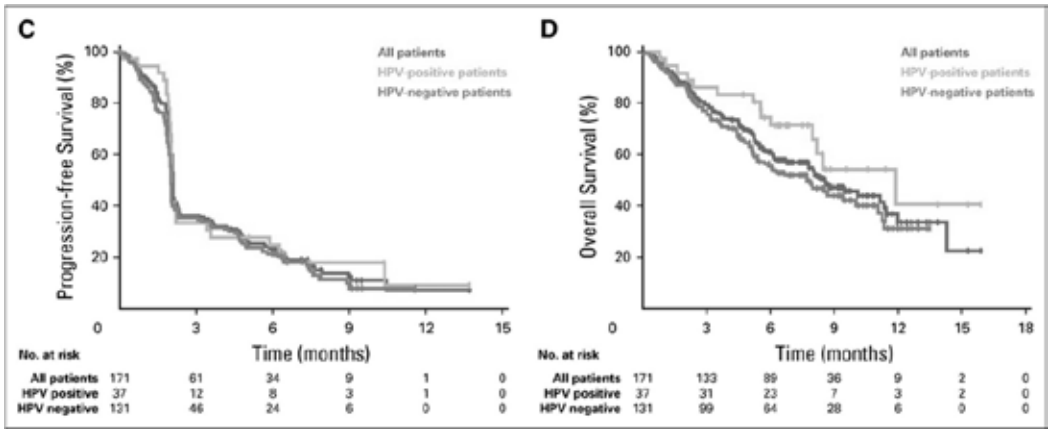
Primary end points: ORR (RECIST v1.1) by Response Evaluation Criteria in Solid Tumors and safety

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

Bauml, J Clin Oncol 2017.

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab
Phase II Trial, Single Arm



Bauml, 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 status[a]

Stratification factor
- Prior cetuximab treatment

R 2:1

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

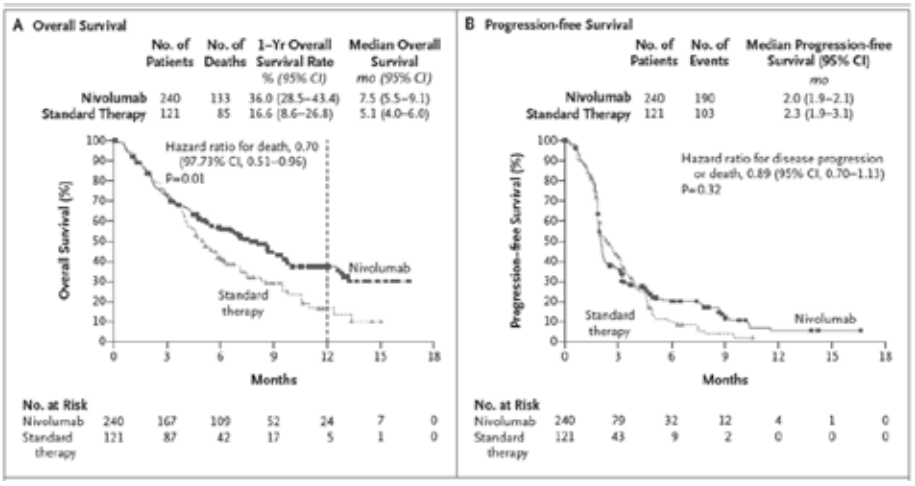
Other endpoints
- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

[a]Tissue required for testing

Ferris & Gillison, NEJM 2016.

Checkmate 141: Nivolumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy



Ferris & Gillison, NEJM 2016.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

Key Eligibility Criteria
- Advanced cutaneous squamous-cell carcinoma (any site)
- Not eligible for surgery
- ECOG 0-1
- ≥1 assessable lesion

→ **Cemiplimab**
3 mg/kg IV Q2W →

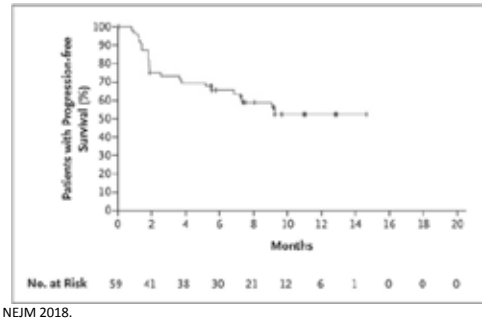
Primary endpoint
- Response rate

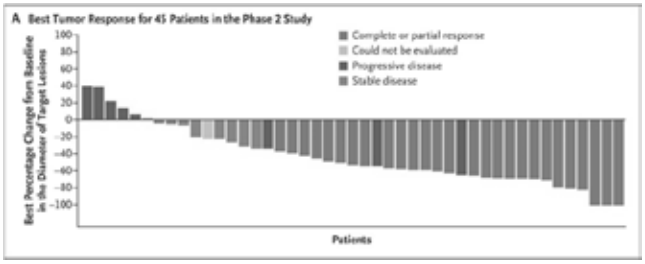
Other endpoints
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

Migden, NEJM 2018.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

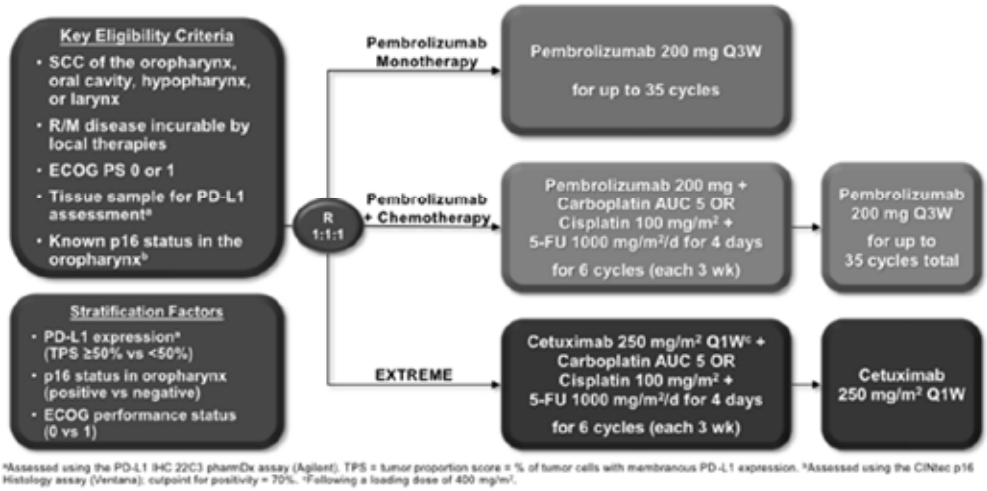
- Cemiplimab 3 mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response





Migden, NEJM 2018.

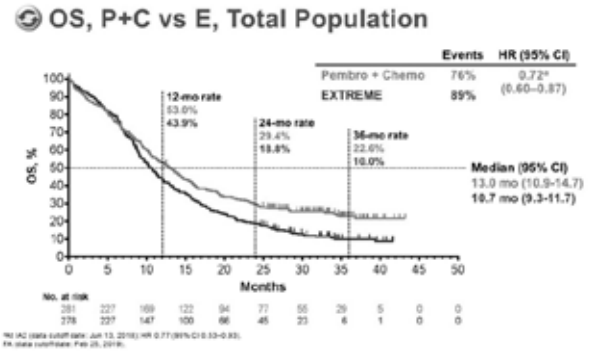
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

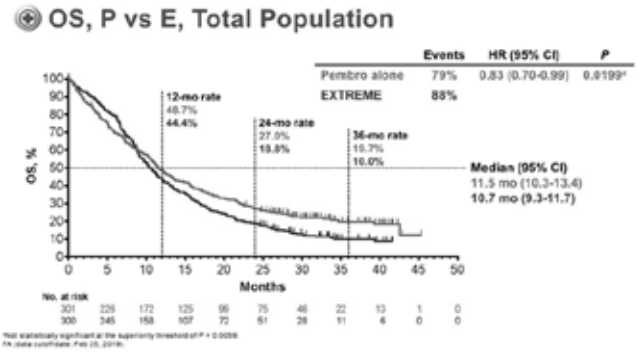


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Rischin, ASCO 2019.

KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC





Rischin, ASCO 2019.

KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

Summary of Overall Survival

Population	IA2[1] HR (95% CI)	FA HR (95% CI)
Pembrolizumab monotherapy **vs EXTREME**		
PD-L1 CPS ≥20	0.61 (0.45–0.83); *P* = 0.0007[a]	0.58 (0.44–0.78)[c]
PD-L1 CPS ≥1	0.78 (0.64–0.96); *P* = 0.0086[a]	0.74 (0.61–0.90)[c]
Total	0.85 (0.71–1.03)[b]	0.83 (0.70–0.99); *P* = 0.0199[d]
Pembrolizumab + chemotherapy **vs EXTREME**		
PD-L1 CPS ≥20	—	0.60 (0.45–0.82); *P* = 0.0004[a]
PD-L1 CPS ≥1	—	0.65 (0.53–0.80); *P* < 0.0001[a]
Total	0.77 (0.63–0.93); *P* = 0.0034[a,b]	0.72 (0.60–0.87)[c]

[a]Superiority demonstrated. [b]Noninferiority demonstrated (boundary of 1.2). [c]No statistical testing performed. [d]Superiority not demonstrated.
1. Burtness B et al. *Ann Oncol* 2018;29(suppl 8):LBA8_PR.

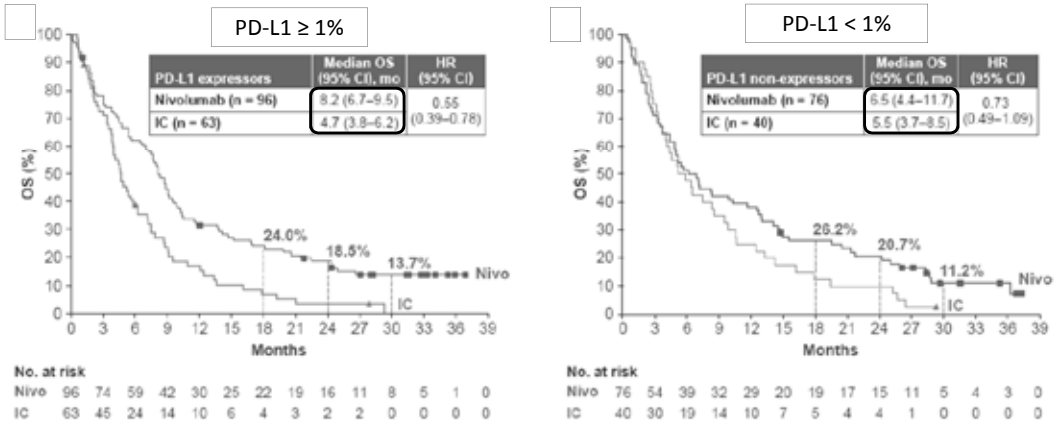
Rischin, ASCO 2019.

Evaluating Biomarkers in HNSCC

- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS ≥ 1 (KEYNOTE-048)
- All other approvals not dependent on PD-L1 expression
  - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - Checkmate 141: Most benefit seen in PD-L1 positive tumors
  - KEYNOTE-040: pembrolizumab vs investigator's choice chemotherapy – did not meet survival endpoints in total population but improved outcomes in PD-L1-expressors

Evaluating Biomarkers in HNSCC

CheckMate 141: 2 year update



Ferris, Oral Oncol 2018.

In development:
T-VEC + pembrolizumab

KEYNOTE-137

- T-Vec 10^6 PFU/mL intratumoral injection followed by 10^8 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
- ORR: 16.7%

Harrington, ASCO 2018.

In development: Checkpoint inhibitors + radiotherapy

- NCT03247712: neoadjuvant nivolumab + SBRT
  - Decreased tumor size prior to surgery; high pathologic CR rate
- KEYNOTE-412: pembrolizumab + chemoradiation
  - Safety confirmed
- REACH: avelumab + cetuximab + radiation
  - Safety confirmed

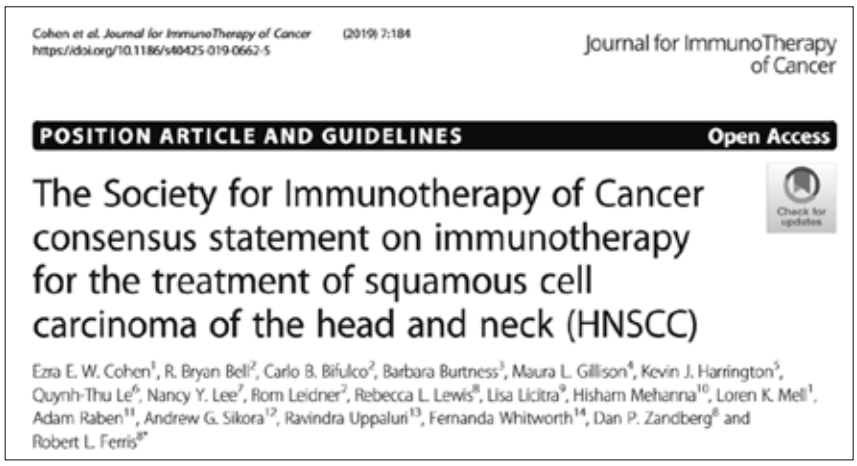
Leidner, AACR 2019.
Siu, AACR 2018.
Tao, ASCO 2018.

Conclusions

- Cytotoxic chemotherapy achieves limited survival with unfavorable side effects.
- Checkpoint inhibitors that target the PD-1 axis, nivolumab and pembrolizumab, are approved in platinum-refractory/exposed recurrent/metastatic HNSCC.
- Nivolumab and pembrolizumab are in general better tolerated than cytotoxic chemotherapy.
- Ongoing areas of research include: combinations of immunotherapy with radiation and/or other drugs, development of predictive biomarkers and approaches to overcoming resistance.

Resources

sitc Society for Immunotherapy of Cancer
Cancer Immunotherapy GUIDELINES



Cohen et al. Journal for ImmunoTherapy of Cancer (2019) 7:184
https://doi.org/10.1186/s40425-019-0662-5

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC)

Ezra E. W. Cohen[1], R. Bryan Bell[2], Carlo B. Bifulco[2], Barbara Burtness[3], Maura L. Gillison[4], Kevin J. Harrington[5], Quynh-Thu Le[6], Nancy Y. Lee[7], Rom Leidner[7], Rebecca L. Lewis[8], Lisa Licitra[9], Hisham Mehanna[10], Loren K. Mell[1], Adam Raben[11], Andrew G. Sikora[12], Ravindra Uppaluri[13], Fernanda Whitworth[14], Dan P. Zandberg[8] and Robert L. Ferris[8*]

Case Studies

Case 1

55M (former smoker) diagnosed in December 2017 with locoregionally advanced, HPV+ SCC arising from the right tonsil

Staging: cT3N2M0 (**stage II**, AJCC 2017 8th ed)

He received definitive concurrent chemoradiation with bolus cisplatin (35/35 fractions to 70 Gy involving the oropharynx and bilateral necks, 3-cycles cisplatin 100 mg/m^2)

Completed all therapy March 2018

Case 1

55M (former smoker) diagnosed in December 2017 with locoregionally advanced, HPV+ SCC arising from the right tonsil

Staging: cT3N2M0 (**stage II**, AJCC 2017 8th ed)

He received definitive concurrent chemoradiation with bolus cisplatin

Completed all therapy March 2018

Clinical evidence of chest wall soft tissue nodule with biopsy-proven HPV+ **metastatic recurrence in August 2019**

NPL shows local recurrence in the right larynx and scans clarify mediastinal adenopathy

Case 1

55M (former smoker) with R/M HPV+ SCC arising from the right tonsil. Completed cisplatin-RT in March 2018, with local and distant recurrence in August 2019

NPL shows local recurrence in the right larynx with no stridor but evolving dysphagia and dry cough

Therapeutic options?

Case 1

55M (former smoker) with R/M HPV+ SCC arising from the right tonsil. Completed cisplatin-RT in March 2018, with local and distant recurrence in August 2019

NPL shows local recurrence in the right larynx with no stridor but evolving dysphagia and dry cough

Therapeutic options:

- Clinical trial protocol
- First-line chemoimmunotherapy (platinum + 5-FU + pembrolizumab) or pembrolizumab alone (CPS PD-L1 testing)
- Platinum-based chemotherapy with cetuximab?

Case 1

55M (former smoker) with R/M HPV+ SCC arising from the right tonsil. Completed cisplatin-RT in March 2018, with local and distant recurrence in August 2019

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Therapeutic options:

- Clinical trial protocol
- **First-line chemoimmunotherapy (platinum + 5-FU + pembrolizumab) or pembrolizumab alone (CPS PD-L1 testing)**
- Platinum-based chemotherapy with cetuximab?

Case 2

55M (never smoker) initially diagnosed with HPV+ SCC of the left base of tongue with ipsilateral level II/III cervical adenopathy in October 2016

Staging: cT4N1M0 (**stage III**, AJCC 2017 8th ed)

Treatment: definitive concurrent chemoradiation with weekly cisplatin ending February 2017

Case 2

55M (never smoker) initially diagnosed with HPV+ SCC of the left base of tongue with ipsilateral level II/III cervical adenopathy in October 2016

Staging: cT4N1M0 (stage III, AJCC 2017 8th ed)

Treatment: definitive concurrent chemoradiation with weekly cisplatin ending February 2017

Restaging: PET-CT in June 2017 shows local residual disease and new lung metastases

Case 2

55M (never smoker) with platinum-refractory, locoregionally persistent and now metastatic HPV+ SCC of the left base of tongue with pulmonary involvement

Restaging: PET-CT in June 2017 shows local residual disease and new lung metastases

Case 2

55M (never smoker) with platinum-refractory, locoregionally persistent and now metastatic HPV+ SCC of the left base of tongue with pulmonary involvement

Restaging: PET-CT in June 2017 shows local residual disease and new lung metastases

Started nivolumab (3 mg/kg IV D1, 15) q28d **in July 2017**

Interval scan: in September 2017 his lung lesions had resolved and his local disease showed regression (partial response)

Case 2

55M (never smoker) with platinum-refractory, locoregionally persistent and now metastatic HPV+ SCC of the left base of tongue with pulmonary involvement

Started nivolumab (3 mg/kg IV D1, 15) q28d in July 2017

Interval scan: in September 2017 his lung lesions had resolved and his local disease showed regression (partial response)

In **January 2018** he has new left neck pain and a PET-CT is obtained

Glenn J. Hanna, MD – *Dana-Farber Cancer Institute*

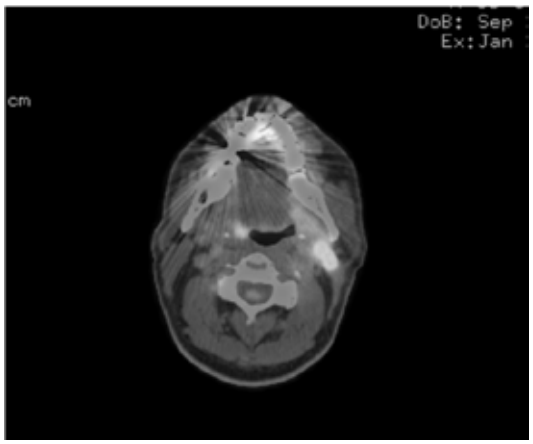
Case 2

What would be your best next step?

A. US-guided left neck biopsy

B. Discontinue PD-1 blockade and start second line chemotherapy or clinical trials

C. Consider palliative radiation



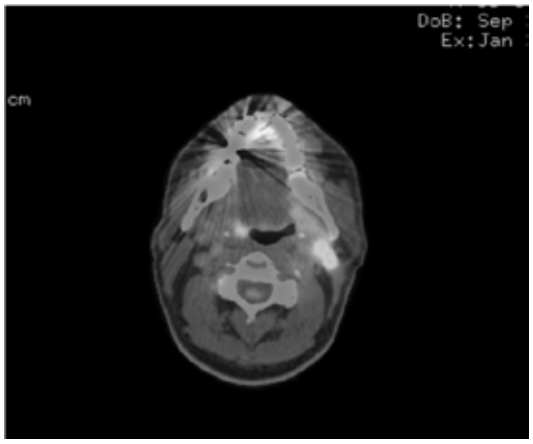
Case 2

What would be your best next step?

A. US-guided left neck biopsy

B. Discontinue PD-1 blockade and start second line chemotherapy or clinical trials

C. Consider palliative radiation
- Localized disease with slow progression
- Clear clinical benefit from PD-1i at distant site
- Would continue PD-1 blockade during or after SBRT or IMRT



Case 2

55M (never smoker) with platinum-refractory, locoregionally persistent and now metastatic HPV+ SCC of the left base of tongue with pulmonary involvement

Started nivolumab (3 mg/kg IV D1, 15) q28d in July 2017 with PR

In January 2018 imaging shows focal regional node progression and he receives SBRT

He has continued on nivolumab with no further disease progression

Case 3

83M (never smoker) initially diagnosed with SCC of the left ventrolateral oral tongue

Staging: cT3N0M0 (stage III, AJCC 2017 8th ed)

Treatment: he declined surgery and radiation but had oral pain symptoms and elective for palliative therapies; started on pembrolizumab in **January 2019**

Case 3

83M (never smoker) initially diagnosed with SCC of the left ventrolateral oral tongue

Staging: cT3N0M0 (stage III, AJCC 2017 8th ed)

Treatment: he declined surgery and radiation but had oral pain symptoms and elective for palliative therapies; started on pembrolizumab in **January 2019**

Develops a clinical response after one dose but then has two episodes of PD-1 induced colitis requiring steroid tapers

Pembrolizumab discontinued in **May 2019**

Case 3

83M (never smoker) initially diagnosed with SCC of the left ventrolateral oral tongue

Staging: cT3N0M0 (stage III, AJCC 2017 8th ed)

Treated with pembrolizumab in January to **May 2019**. Develops a clinical response after one dose but then has two episodes of PD-1 induced colitis requiring steroid tapers

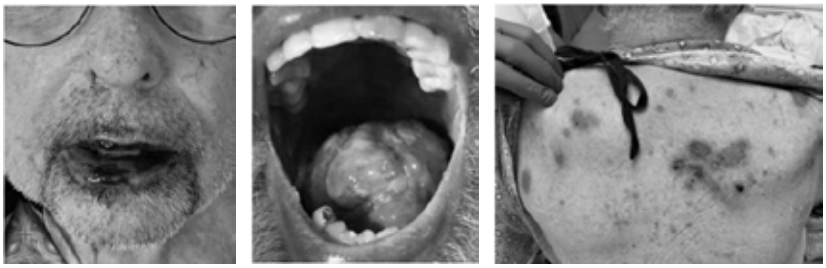
Event: in **August 2019** calls with mucositis, oral pain with difficulty swallowing, skin rash…

Case 3

83M (never smoker) initially diagnosed with SCC of the left ventrolateral oral tongue

Treated with pembrolizumab in January to **May 2019**. Develops a clinical response after one dose but then has two episodes of PD-1 induced colitis requiring steroid tapers

Event: in **August 2019** calls with mucositis, oral pain with difficulty swallowing, skin rash…



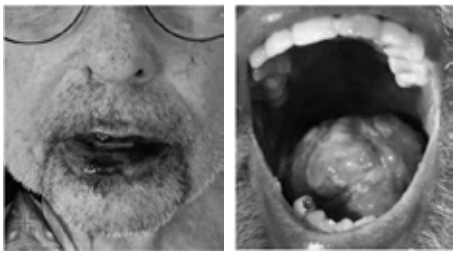
Case 3

Pembrolizumab or **PD-1 induced SJS-like reaction or erythema multiforme**

Treatment:

- Urgent dermatologic consultation with biopsy

  negative for immunofluorescence studies (IgA, IgG, IgM, C3, fibrinogen)
- High-dose IV corticosteroids
- Topical immunosuppression to skin and lips
- Oral rinses for pain control; nutritional support
- Permanent PD-1 inhibitor discontinuation



Immunotherapy for the Treatment of Genitourinary Cancers

Joaquim Bellmunt, MD, PhD
Director Bladder Cancer Program, Genitourinary Oncology
Beth Israel Deaconess Medical Center

Prof. Joaquim Bellmunt is an associate professor at Harvard Medical School in Boston, MA, USA, and Director of the Bladder Cancer Program at the Beth Israel Deaconess Medical Center, also in Boston, MA.

As a genitourinary medical oncologist, Prof. Bellmunt has acted as principle investigator on numerous clinical trials in his specialized field; his research efforts have primarily focused on the use of immunotherapy in the treatment of genitourinary malignancies, with a growing interest in the value of implementing prospective patient data into clinical trials to improve our understanding of the underlying genetic and biological mechanisms of response and resistance.

Prof. Bellmunt is a founding member and past-president of *Grupo Español de Tumores Genitourinarios*, and has served on the Scientific Committee at the American Society of Clinical Oncology-Genitourinary Symposium.

He has published extensively in his field (with more than 400 peer-reviewed publications and more than 100 book or congress contributions to his name), and, as an active member of numerous national and international oncology associations, has been instrumental in developing treatment guidelines for the European Association of Urology, the European Society of Medical Oncology, *Sociedad Española de Oncología Médica*, and the US Society for Immunotherapy of Cancer.

Immunotherapy for the Treatment of Genitourinary Cancers

Joaquim Bellmunt, MD, PhD – *Beth Israel Deaconess Medical Center*

Audience Response Questions

1. Which of the following is NOT a currently approved immunotherapy treatment for renal cell carcinoma?
   A. Nivolumab
   B. Ipilimumab
   C. High-dose interleukin-2
   D. Durvalumab

2. Treatment with an immune checkpoint inhibitor (i.e. pembrolizumab) can be recommended to which of the following patients:
   A. Metastatic castrate-sensitive prostate cancer
   B. Metastatic castrate-resistant prostate cancer resistant to abiraterone acetate and enzalutamide
   C. Metastatic castrate-resistant prostate cancer with microsatellite instability
   D. Combination with PARP inhibitor such as olaparib for patients with advanced prostate cancer and BRCA2 positive tumor

Immunotherapy for the Treatment of Genitourinary Malignancies

Joaquim Bellmunt, MD, PhD
Director, Bladder Cancer Program, Genitourinary Oncology
Beth Israel Deaconess Medical Center

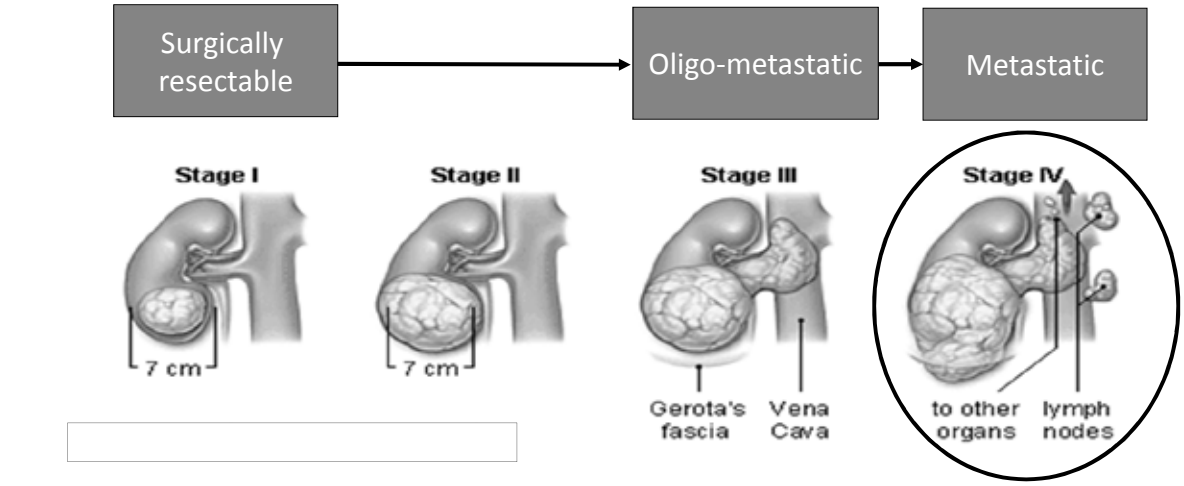
Disclosures

- Royalty:
  - UpToDate
- Consulting Fees:
  - MSD, AstraZeneca
- Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents:
  - Janssen, MSD
- Contracted Research:
  - Takeda, Pfizer
- I will be discussing non-FDA approved indications during my presentation.

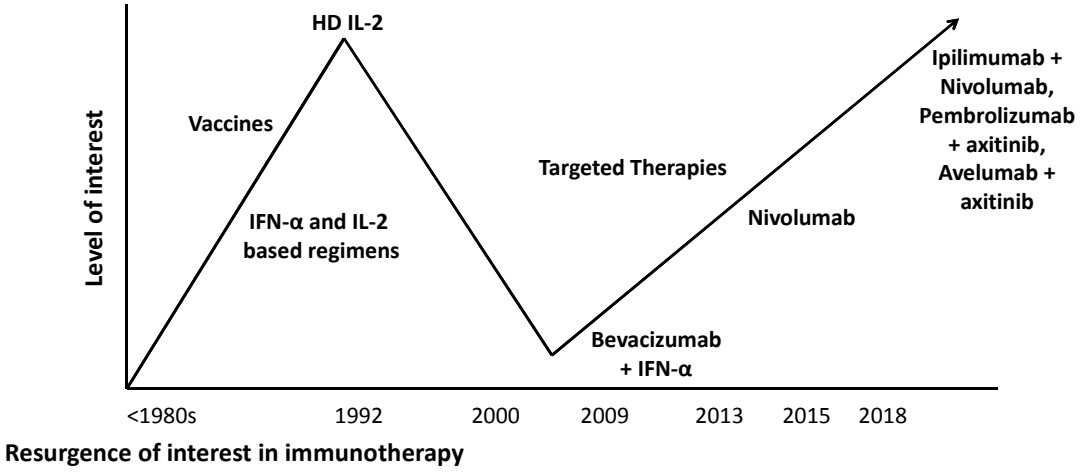
Immunotherapy for the Treatment of Genitourinary Cancers

Joaquim Bellmunt, MD, PhD – *Beth Israel Deaconess Medical Center*

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



History of Immunotherapy in mRCC



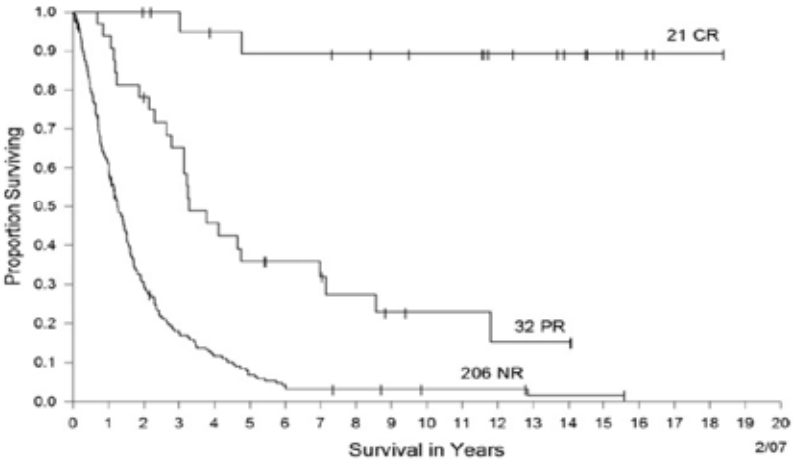
Joaquim Bellmunt, MD, PhD – *Beth Israel Deaconess Medical Center*

FDA-approved Immunotherapies for mRCC

Drug	Approved	Indication	Dose
High dose Interleukin-2	1992	Metastatic RCC	600,000 International Units/kg (0.037 mg/kg) IV q8hr infused over 15 minutes for a maximum 14 doses, THEN 9 days of rest, followed by a maximum of 14 more doses (1 course)
Interferon-a + bevacizumab	2009	Clear cell RCC	IFN 9 MIU s.c. three times a week + bev 10 mg/kg Q2W
Nivolumab	2015	Clear cell RCC refractory to prior VEGF targeted therapy	3mg/kg or 240mg IV Q2W or 480mg IV Q4W
Nivolumab +ipilimumab	2018	Clear cell RCC, treatment naïve	3mg/kg nivo plus 1mg/kg ipi Q3W x 4 doses then nivo maintenance at flat dosing
Pembrolizumab + axitinib	2019	Advanced RCC, Treatment naïve	200 mg pembro Q3W + 5 mg axitinib twice daily
Avelumab + axitinib	2019	Advanced RCC, Treatment naïve	800 mg avelumab Q2W + 5 mg axitinib twice daily

High Dose IL-2 in mRCC

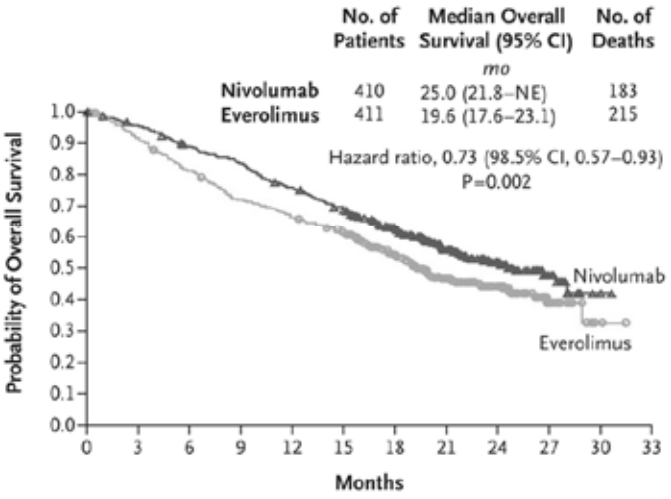
- 20 year analysis of 259 patients
- ORR = 20%
  - 9% CR (n = 23)
  - 12% PR (n = 30)
- Median duration of response = 15.5 months
- Median OS = 19 months



Klapper et al. Cancer 2008

Second-Line Nivolumab in mRCC

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

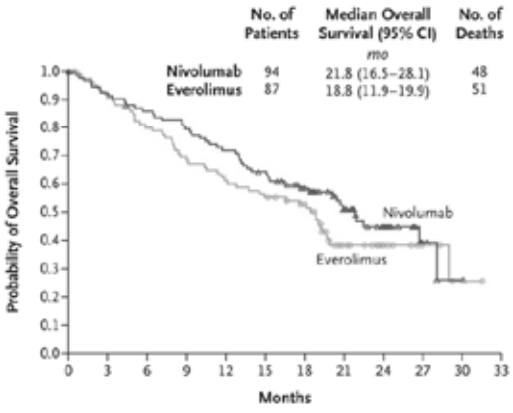


Motzer et al. NEJM 2015

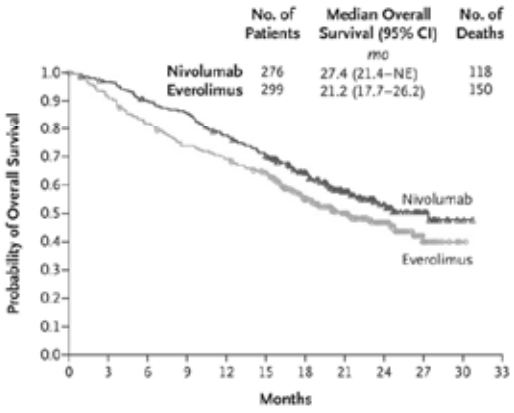
Second-Line Nivolumab in mRCC

PD-L1 subgroups

PD-L1 ≥ 1%

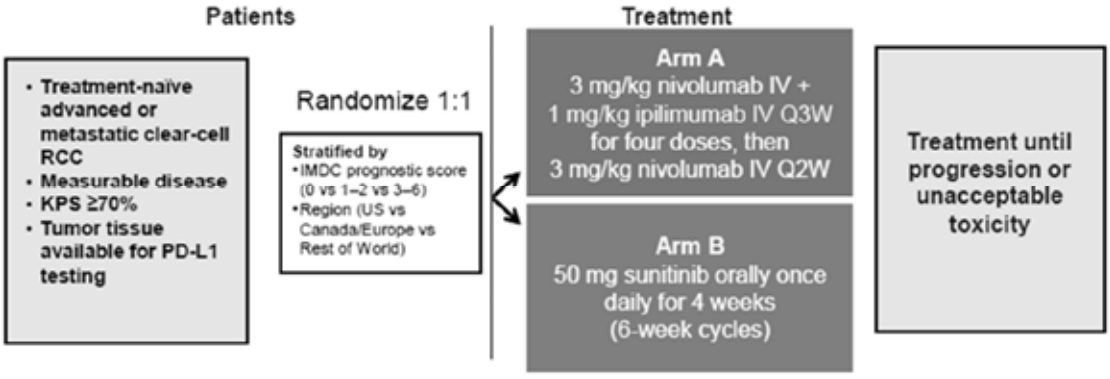


PD-L1 < 1%



Motzer et al. NEJM 2015

First-line Nivolumab + Ipilimumab in mRCC

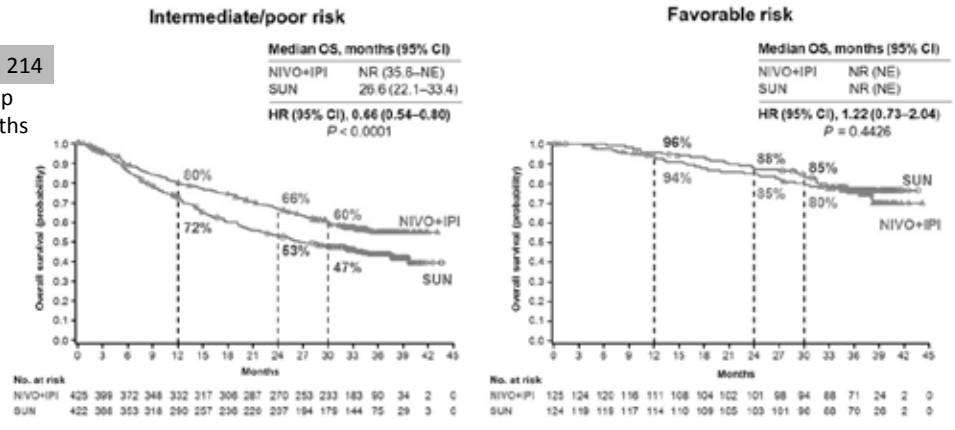


Nivolumab = anti-PD-1 antibody Ipilimumab = anti-CTLA-4 antibody
IMDC = International Metastatic RCC Database Consortium

Escudier et al. ESMO 2017

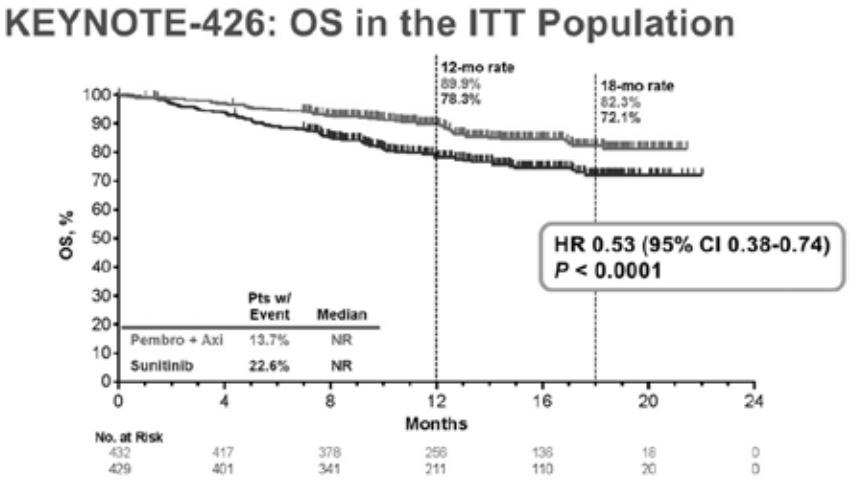
First-line Nivolumab + Ipilimumab in mRCC by IMDC Risk: overall survival

CheckMate 214
Follow-up
= 30 months



Tannir et al. ASCO GU 2019

First-line Pembrolizumab + axitinib in advanced RCC: overall survival

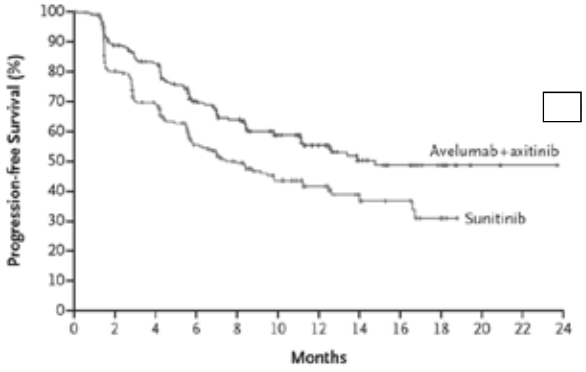


Rini, ASCO 2019

First-line avelumab + axitinib in mRCC: progression-free survival

- Primary Endpoint: PFS and OS in PD-L1+
- Median PFS – 13.8 mo vs 7.2 mo (HR 0.61; 95% CI, 0.47–0.79)
- ORR: 61.9% vs 29.7
- OS data: immature

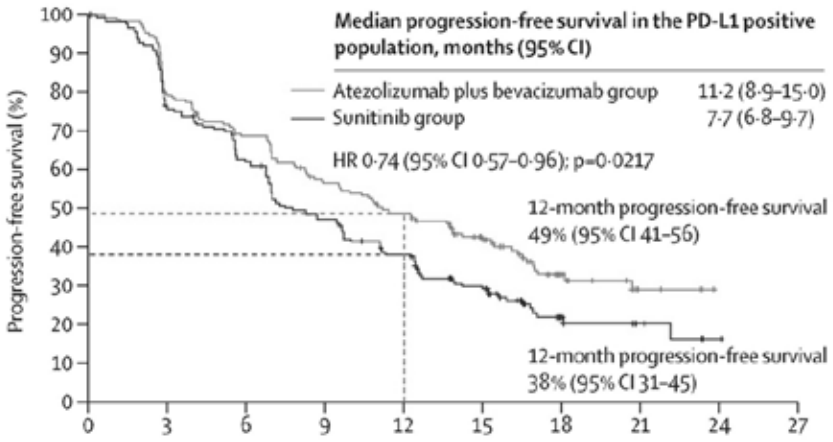
JAVELIN 101 : PFS in the PD-L1+ Population



Motzer, NEJM 2019.

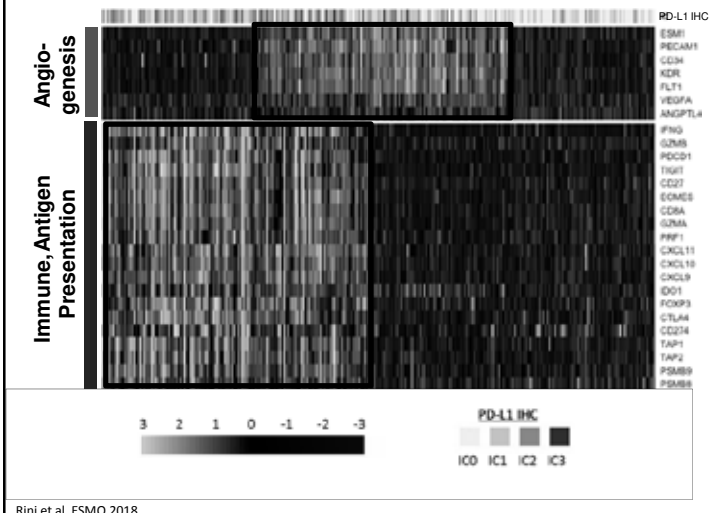
In Development: First-line atezolizumab + bevacizumab in PD-L1+ mRCC

Immotion151



Rini, The Lancet 2019.

In Development: First-line atezolizumab + bevacizumab: molecular signatures

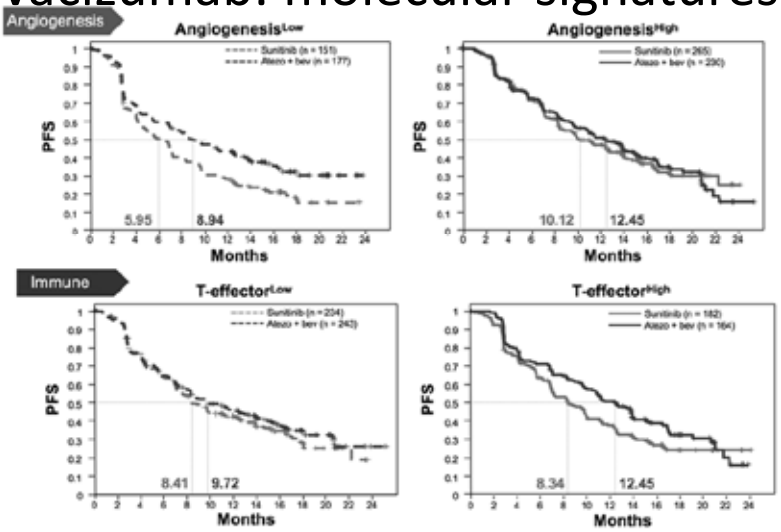


Identification of gene signatures based on association with clinical outcome

- T_{eff}: *CD8a*, *IFNG*, *PRF1*, *EOMES*, *CD274*
- Angio: *VEGFA*, *KDR*, *ESM1*, *PECAM1*, *CD34*, *ANGPTL4*

Rini et al, ESMO 2018

In Development: First-line atezolizumab + bevacizumab: molecular signatures



Rini et al, ESMO 2018

Front-line phase 3 trials with immunotherapy agents (efficacy summary)

	CheckMate 214	KEYNOTE-426	JAVELIN 101	IMmotion151
Intervention	Ipilimumab + Nivolumab	Pembrolizumab + Axitinib	Avelumab + Axitinib	Atezolizumab + Bevacizumab
Comparator	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Primary Endpoint	OS, PFS, ORR in int/poor risk	OS, PFS	PFS, OS in PD-L1+	PFS in PD-L1+; OS
mOS, months	NR vs 37.9 (30 mo min followup)	NR vs NR (median 12.8 mo followup)	Not reported	33.6 vs 34.9 (median 24 mo followup)
PFS, months	9.7 vs 9.7	15.1 vs 11.1	13.8 vs 7.2	11.2 vs 7.7
ORR (ITT), %	41% vs 34%	59.3% vs 35.7%	51.4% vs 25.7%	37% vs 33%
CR rate (ITT)	10.5% vs 1.8%	5.8% vs 1.9%	3.4% vs 1.8%	5% vs 2%

IIT: Intent-to-Treat; PFS: progression-free survival; ORR: overall response rate; OS: overall survival

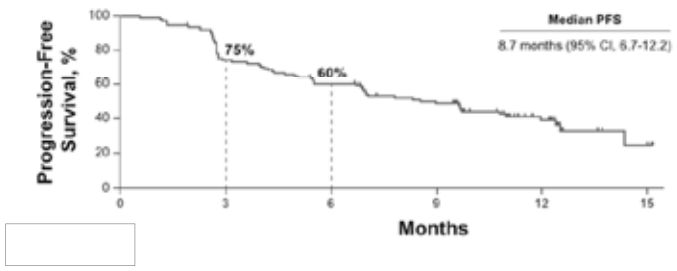
Tannir, ASCO GU 2019.
Rini, NEJM 2019.
Motzer, NEJM 2019.
Rini, Lancet 2019.

Ongoing front-line phase 3 trials with immunotherapy agents for front-line ccRCC

Trial number	Trial Name	Treatment Arm	Comparator Arm	Population Size	Primary End Point
NCT03141177	CheckMate 9ER	Cabozantinib + Nivolumab	Sunitinib	630	PFS
NCT02811861	CLEAR	Lenvatinib + Pembrolizumab or Everolimus	Sunitinib	1050	PFS
NCT03729245	CA045002	NKTR-214 + Nivolumab	Sunitinib	600	ORR, OS
NCT03937219	COSMIC-313	Cabozantinib + Ipilimumab + Nivolumab	Sunitinib	676	PFS

PFS: progression-free survival; ORR: overall response rate; OS: overall survival

In Development: First-line pembrolizumab monotherapy in mRCC KEYNOTE - 427

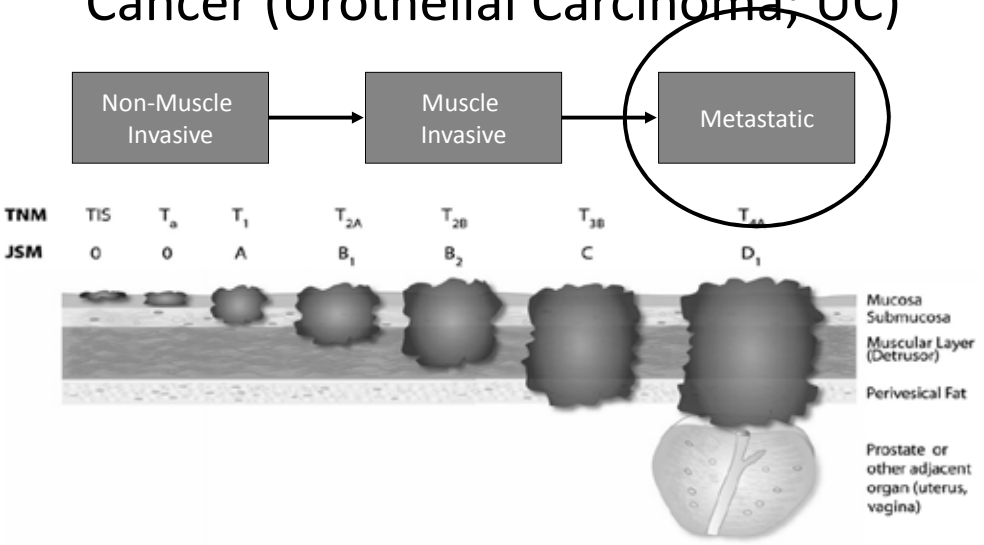


	N = 110
Confirmed ORR, % (95% CI)	36.4
CR, %	3 (3)
PR, %	37 (34)
DCR, %	57 (47-67)
DOR, median (range), mo	Not Reported
DOR ≥ 6 mo (responders), %	77

Donskov et al. ESMO 2018
Tykodi et al, ASCO 2019

Joaquim Bellmunt, MD, PhD – *Beth Israel Deaconess Medical Center*

Immunotherapy for Metastatic Bladder Cancer (Urothelial Carcinoma; UC)



Approved checkpoint inhibitors for mUC – *cisplatin refractory*

Drug	Approved	Indication	Dose
Atezolizumab	2016 (2018)	Advanced/metastatic UC	1200 mg Q3W
Avelumab	2017	Advanced/metastatic UC	10 mg/kg Q2W
Durvalumab	2017	Advanced/metastatic UC	10 mg/kg Q2W
Nivolumab	2017	Advanced/metastatic UC	240 mg Q2W or 480 mg Q4W
Pembrolizumab	2017 (2018)	Advanced/metastatic UC	200 mg Q3W

Approved checkpoint inhibitors for mUC – *cisplatin ineligible*

Drug	Approved	Indication	Dose
Atezolizumab	2017 (2018)	Advanced/metastatic UC (PD-L1 ≥5%)	1200 mg Q3W
Pembrolizumab	2017 (2018)	Advanced/metastatic UC (PD-L1 CPS ≥10)	200 mg Q3W

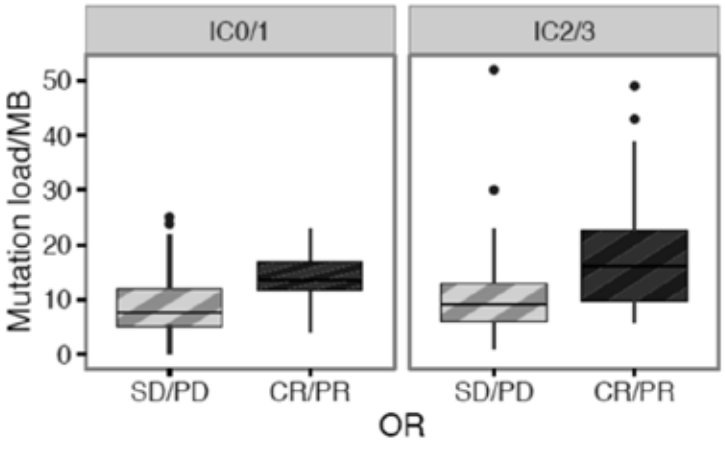
June 2018

FDA limits the use of Tecentriq and Keytruda for some urothelial cancer patients

- Locally advanced or metastatic urothelial carcinoma and ineligible for cisplatin-based chemo and tumor PD-L1 (CPS ≥ 10, pembro; IC ≥ 5% tumor area, atezo)
- Patients ineligible for any platinum-containing chemotherapy regardless of PD-L1 status

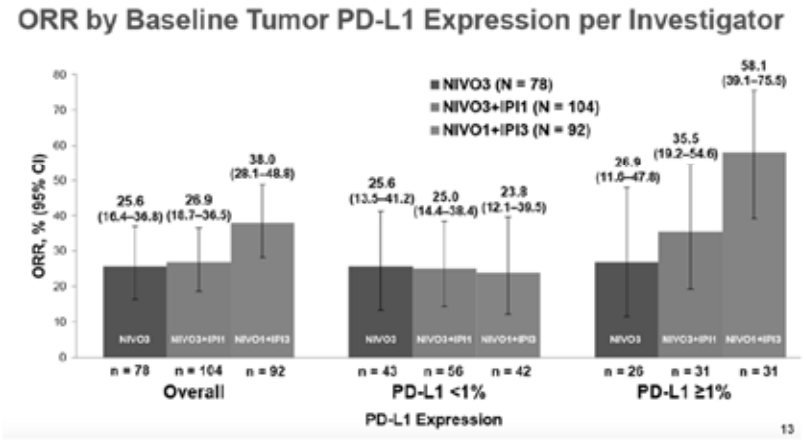
Tumor Mutational Burden (TMB) May Signal Responses with PD-1 Blockade

Atezolizumab in mUC



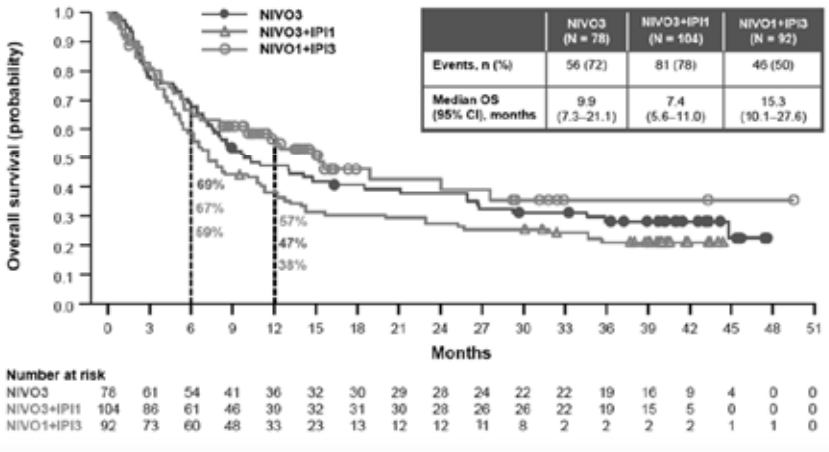
Rosenberg et al. Lancet 2016

In development: Ipilimumab + Nivolumab CheckMate 032



Rosenberg, ESMO 2018

In development: Ipilimumab + Nivolumab CheckMate 032

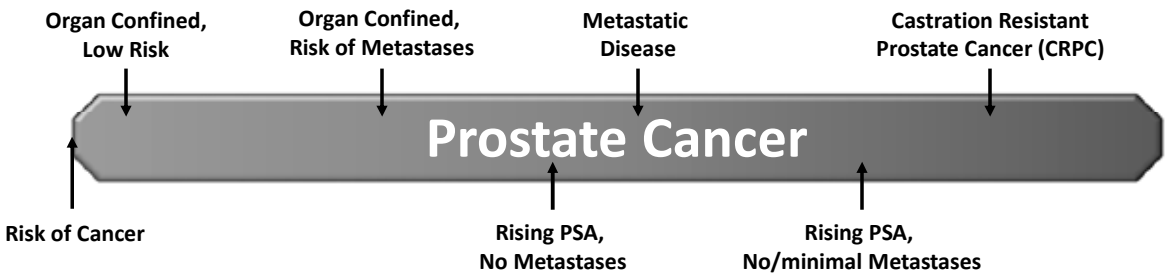


	NIVO3 (N = 78)	NIVO3+IPI1 (N = 104)	NIVO1+IPI3 (N = 92)
Events, n (%)	56 (72)	81 (78)	46 (50)
Median OS (95% CI), months	9.9 (7.3–21.1)	7.4 (5.6–11.0)	15.3 (10.1–27.6)

Rosenberg, ESMO 2018

Joaquim Bellmunt, MD, PhD – *Beth Israel Deaconess Medical Center*

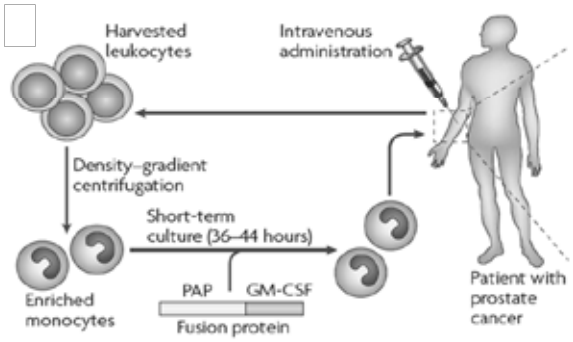
The Spectrum of Prostate Cancer

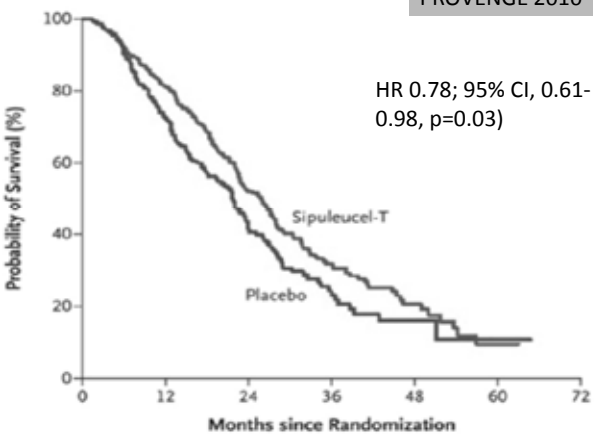


Sipuleucel-T in mCRPC

PROVENGE 2010

First anti-cancer therapeutic vaccine





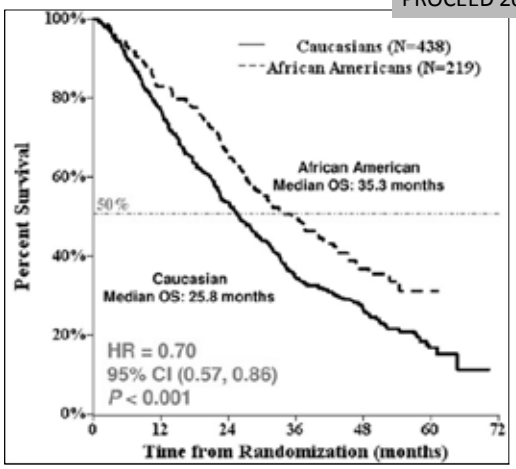
HR 0.78; 95% CI, 0.61-0.98, p=0.03)

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

Sipuleucel-T in mCRPC

- Post-hoc analysis of Phase 3 trial PROCEED (N = 1902 mCRPC patients)
- African-Americans (AA) = 438; Caucasians (CAU) = 219
- Median OS = 35.2 (AA) vs 29.9 mo (CAU); HR 0.81, 95% CI 0.68–0.97; p = 0.03.
- AA race was independently associated with prolonged OS on multivariate analysis (HR 0.60, 95% CI 0.48–0.74; p < 0.001)

PROCEED 2019

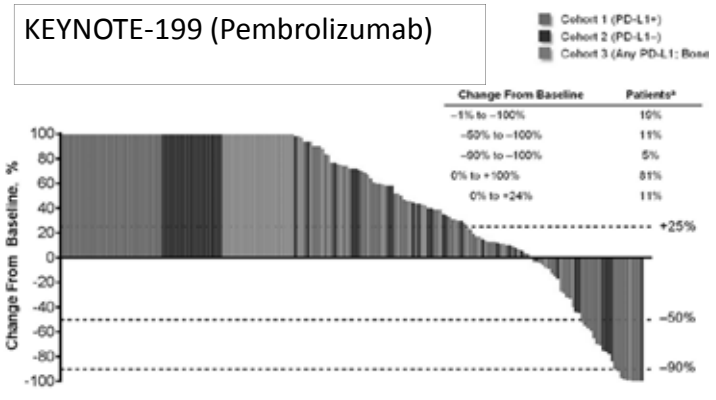


Sartor et al. ASCO 2019

Limited efficacy of Checkpoint Inhibitors in mCRPC

No FDA-approved CIs for mCRPC

KEYNOTE-199 (Pembrolizumab)



- 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

DeBono et al. ASCO 2018

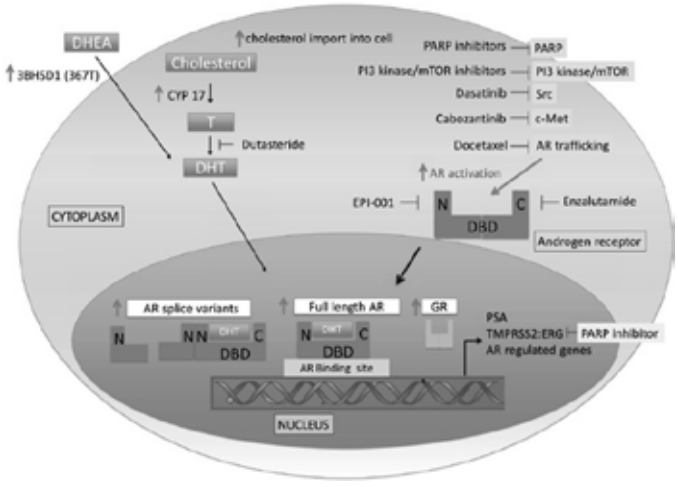
In development: nivolumab + ipilimumab in mCRPC

- Checkmate 650
- Nivo 1 mg/kg + Ipi 3 mg/kg Q3W for 4 doses, then Nivo 480 mg Q4W
- Progressed after 2nd-gen hormonal: 26% response @ 11.9 mo, 2 CR
- Progressed after chemo+hormonal: 10% response @ 13.5 mo, 2 CR
- Higher ORR in:
  - PD-L1 > 1%
  - DNA damage repair deficient
  - homologous recombination deficiency
  - high tumor mutational burden

Sharma, GU Cancer Symp 2019.

Future Combinations in mCRPC to Engage Immune System

- Hormonal therapy
- Radiation
- Radium-223
- PARP inhibitors
- Chemotherapy
- New targets



Stein et al. Asian J Andrology 2014

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

Similar incidence overall

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

Maughan et al. Front Oncol 2017

Conclusions

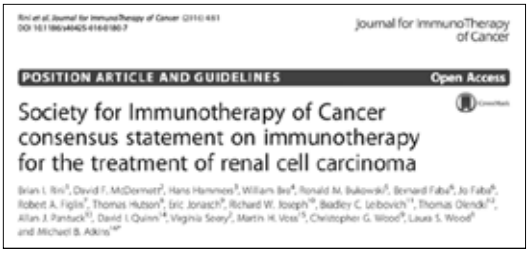
- The role of immunotherapy in GU malignancies is increasing
- In RCC, many front-line checkpoint inhibitor options are approved
- Multiple checkpoint inhibitors approved for advanced/metastatic urothelial carcinoma
- Low immune engagement in prostate cancer has limited the application of immunotherapy in this disease

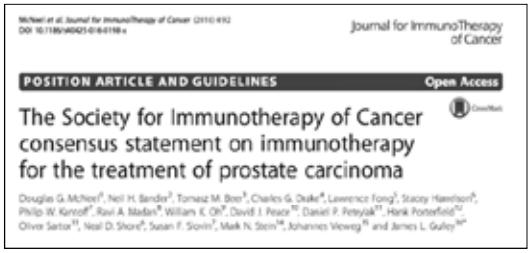
Immunotherapy for the Treatment of Genitourinary Cancers

Joaquim Bellmunt, MD, PhD – *Beth Israel Deaconess Medical Center*

Additional Resources

sitc Society for Immunotherapy of Cancer
Cancer Immunotherapy GUIDELINES





Immunotherapy for the Treatment of Hematologic Malignancies

Myrna R. Nahas, MD
Instructor of Medicine
Beth Israel Deaconess Medical Center

Dr. Myrna Nahas is a translational immuno-oncologist specializing in hematologic malignancies. She focuses on translating novel pre-clinical immunotherapies into early phase clinical trials to combat hematologic malignancies, while maintaining patient care to make the statement, 'bedside-to bench-to bedside,' come to fruition. Dr. Nahas completed a post-doctoral fellowship in the Avigan lab in which she examined novel immunotherapeutic strategies to target hematologic malignancies. Combining In-vitro and in-vivo molecular, cell biology, and immunotherapy techniques murine, she studied the impact of hypomethylating agents (HMAs) and a personalized dendritic cell (DC)/AML fusion vaccine on the immunogenicity of leukemia cells and the associated tumor microenvironment. Dr. Nahas demonstrated that HMA + fusion vaccination results in enhanced immunologic responses as well as increased survival in mice. Given her interest in designing scientific immunologic correlates, she assessed the impact of a CTLA-4 agonist molecule in patients with graft-versus-host disease through analysis of correlative and clinical data. At the Dana-Farber Harvard Cancer Center, Dr. Nahas is leading an investigator-initiated phase II clinical trial in relapsed multiple myeloma (MM) to investigate the effects of combining checkpoint blockade and a personalized dendritic cell/multiple myeloma fusion vaccine based on pre-clinical data. This study will unravel how the combination of checkpoint inhibitors and a novel dendritic-based fusion vaccine modifies the immune microenvironment allowing us to uncover novel predictive biomarkers to identify responders from non-responders to immune therapy in MM. Dr. Nahas is currently an attending physician at BIDMC caring for patients in both outpatient and inpatient clinical settings.

Immunotherapy for the Treatment of Hematologic Malignancies

Myrna R. Nahas, MD – *Beth Israel Deaconess Medical Center*

Audience Response Questions

1. FDA-approved CAR T therapies for the treatment of B-cell lymphoma or leukemia target which antigen?
   A. CD20
   B. CD22
   C. PD-1
   D. CD19

2. Immune checkpoint inhibitor treatments or bispecific T-cell engager treatments have been FDA-approved for all of the following indications EXCEPT:
   A. Multiple myeloma
   B. Relapsed/refractory classical Hodgkin lymphoma
   C. Relapsed/refractory primary mediastinal large B-cell lymphoma
   D. B-cell precursor acute lymphoblastic leukemia

Immunotherapy for the Treatment of Hematologic Malignancies

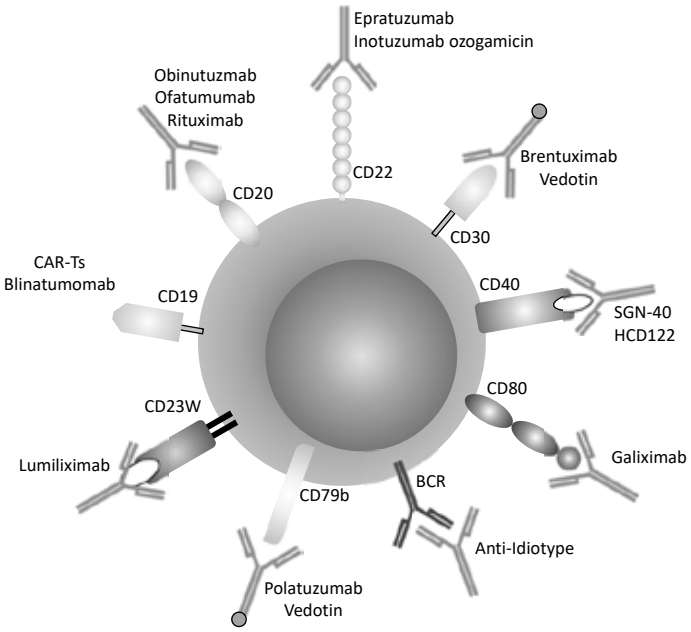
Myrna Nahas, MD
Instructor of Medicine
Beth Israel Deaconess Medical Center

Disclosures

- No relevant financial relationships to disclose
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Hematologic Malignancies

Myrna R. Nahas, MD – *Beth Israel Deaconess Medical Center*



Checkpoint inhibitors

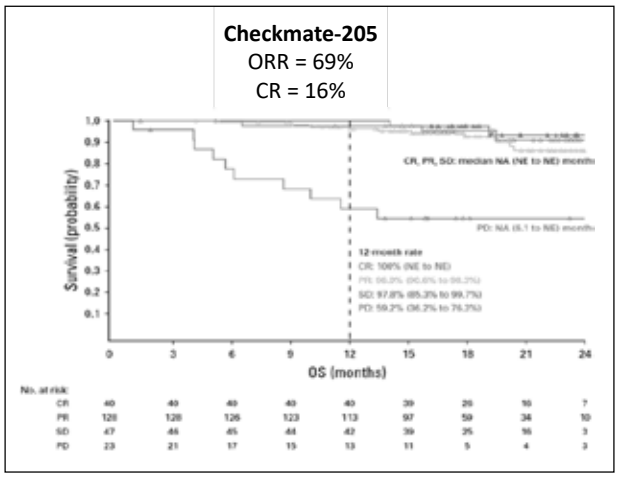
Myrna R. Nahas, MD – *Beth Israel Deaconess Medical Center*

FDA-approved Checkpoint inhibitors: Lymphoma

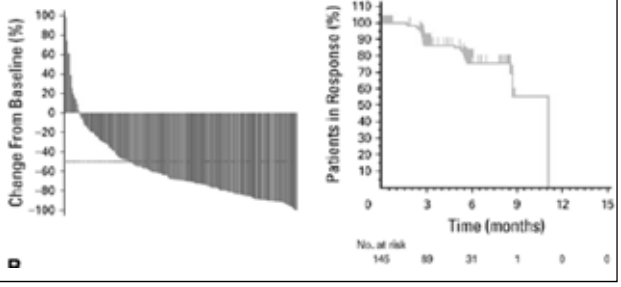
Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg q2w or 480 mg q4w
Pembrolizumab	2017	Adult/pediatric refractory classical Hodgkin lymphoma or relapsed after 3 previous therapies	200 mg q3w adults 2 mg/kg (up to 200 mg) q3w (pediatric)
Pembrolizumab	2018	Adult/pediatric refractory primary mediastinal large B-cell lymphoma or relapsed after 2 previous therapies	200 mg q3W adults 2 mg/kg (up to 200 mg) q3w (pediatric)

Checkpoint inhibitors: Hodgkin Lymphoma

Checkmate-205
ORR = 69%
CR = 16%



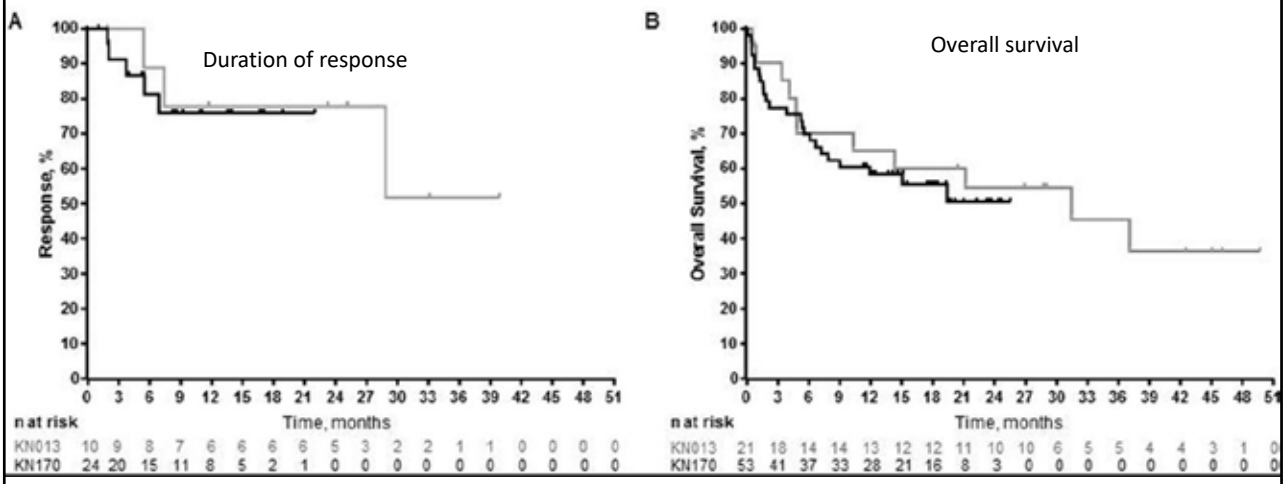
Keynote-087
ORR = 69%
CR = 22.4%
Activity seen regardless of PD-L1 expression



Armand, J Clin Oncol 2018.
Chen, J Clin Oncol 2017.

Myrna R. Nahas, MD – *Beth Israel Deaconess Medical Center*

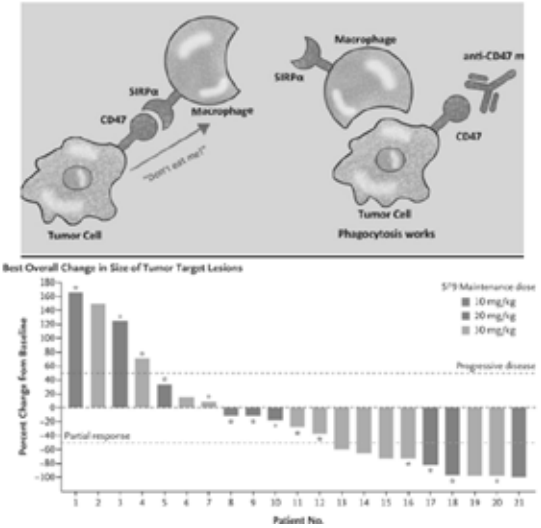
Pembrolizumab in Primary Mediastinal Large B cell Lymphoma



Armand, Blood 2018.

In development: Macrophage checkpoint: CD47

- Phase 1b: Hu5F9-G4 + rituximab in rituximab refractory disease
- DLBCL – ORR = 40%, CR = 33%
- Follicular lymphoma – ORR = 71%, CR = 43%

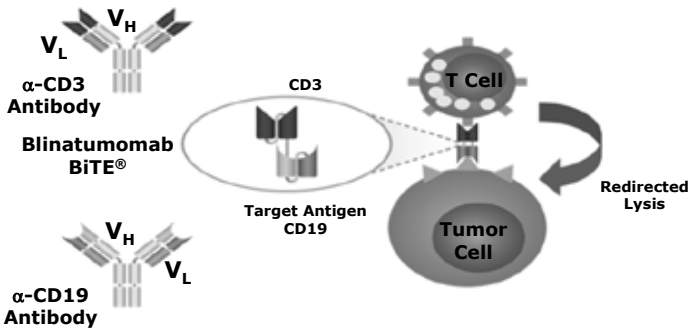


Advani, NEJM 2018.

Bi-specific T-cell engagers (BiTEs)

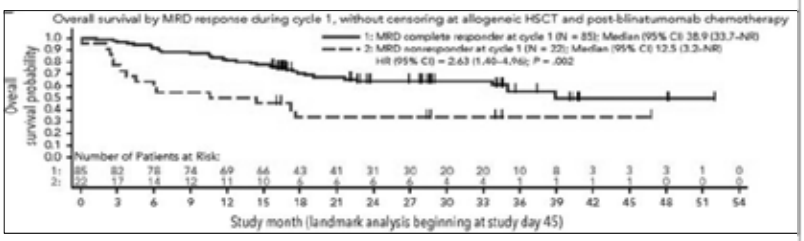
BiTE (Blinatumomab) Therapy

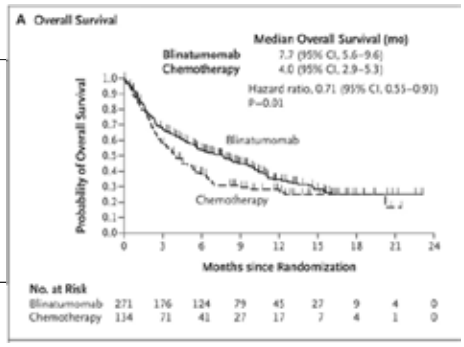
- Facilitates T cell engagement with CD19+ tumor cells (Similar to CD19 CAR T)
- Approval:
- Adult/pediatric R/R B-cell precursor acute lymphoblastic leukemia
- Adult/pediatric B-cell precursor acute lymphoblastic leukemia in 1st or 2nd complete remission, MRD ≥ 0.1%



Bargou et al. Science 2008

Blinatumomab: B-ALL





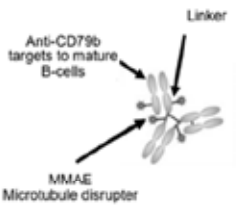
Gökbuget, Blood 2018.
Kantarjian, NEJM 2017.

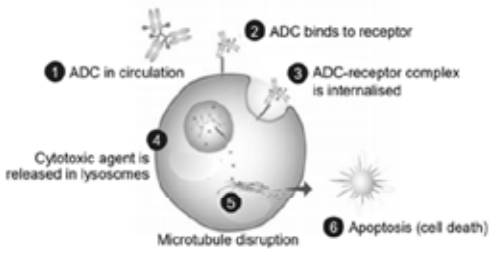
Antibody-drug conjugates (ADC)

FDA-Approved Antibody-Drug Conjugates

Drug	Target antigen	Year of approval	Indication
Brentuximab vedotin	CD30	2011	• Classical Hodgkin lymphoma, relapsed after HSCT or ≥2 previous therapies • Anaplastic large cell lymphoma ≥ 1 previous therapies
		2018	cHL - first line with combination chemo
Inotuzumab ozogamicin	CD22	2017	Relapsed/refractory/MRD+ B-cell ALL
Polatuzumab vedotin (w/ bendamustine & rituximab)	CD79b	2019	DLBCL ≥ 2 previous therapies

Polatuzumab vedotin: DLBCL





Polatuzumab vedotin has demonstrated efficacy in R/R DLBCL in combination with rituximab[1,2] and rituximab-bendamustine[3]

Treatment	Best overall response
Pola +/- rituximab	51–56%[1,2]
Pola + rituximab + bendamustine	68%[3]

ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E

1. Palanca-Wessels A, et al. Lancet Oncol 2015;16:704–15; 2. Morschhauser F, et al. Lancet Hematology 2019;6:e254–65; 3. Sehn H, et al. Blood 2018;132:1683

Slide credit: Tilly et al. ICML 2019

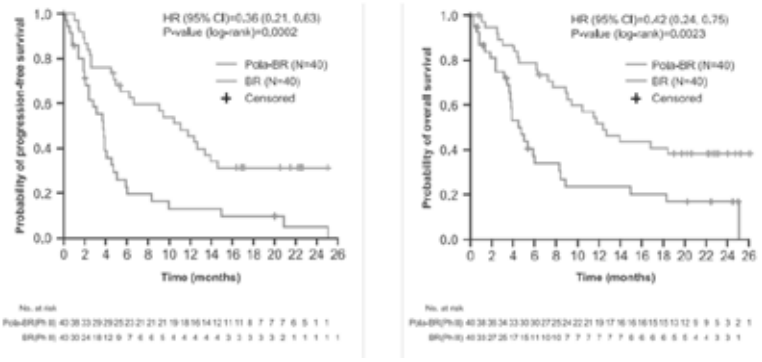
Myrna R. Nahas, MD – *Beth Israel Deaconess Medical Center*

Polatuzumab vedotin: DLBCL

- Randomized phase 2 study
- Pola-BR vs. BR in R/R DLBCL

- Higher CR = 40% vs. 18% (p: 0.03)
- Median PFS = 7.6 m (HR=0.34, p<0.01)
- Median OS = 12.4 m (HR=0.42, p<0.01)

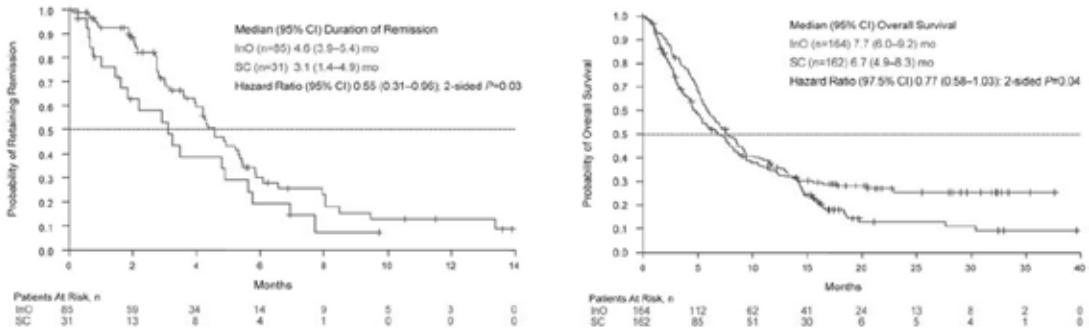
- Ongoing phase 3 (POLARIX)
- Frontline DLBCL- R-CHOP vs R-CHP+Pola



Sehn, Blood 2018.

Inotuzumab ozogamicin for ALL

- Anti-CD22 antibody conjugated to calicheamicin
- Higher response, MRD-negativity, PFS, and OS than standard-of-care

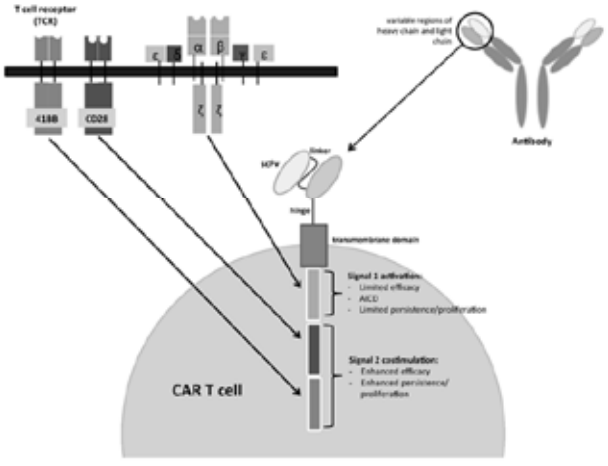


Kantarjian, NEJM 2016.

Chimeric Antigen Receptor Therapy (CAR T)

Chimeric antigen receptors

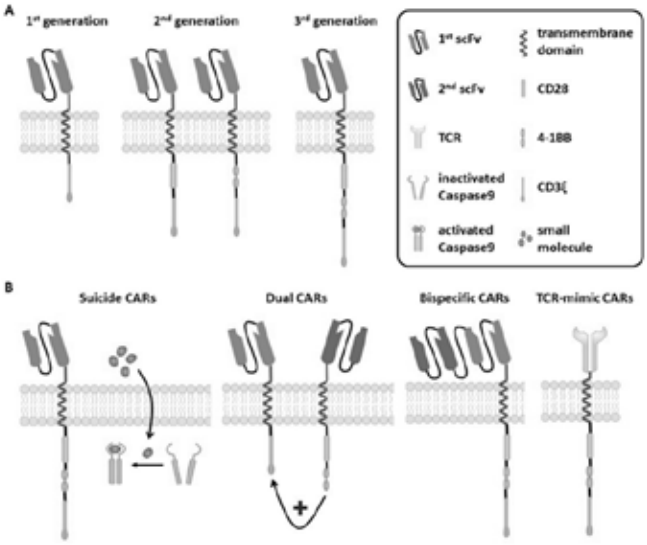
- Specific and potent: B - specific, T - toxic
- Overcome immune tolerance
- Targets surface molecules in native conformation
- Independent of antigen presenting cell and MHC complex



Klampasta, Cancers 2017.

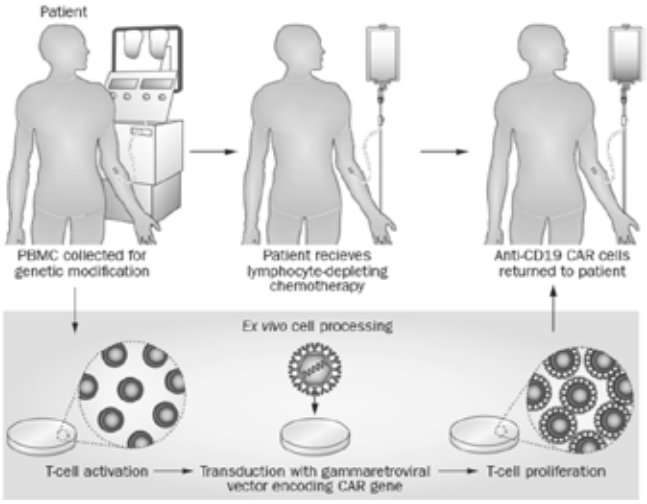
Myrna R. Nahas, MD – *Beth Israel Deaconess Medical Center*

Evolution of CAR Constructs



Hofman, J Clin Med 2019.

CAR T manufacturing and administration

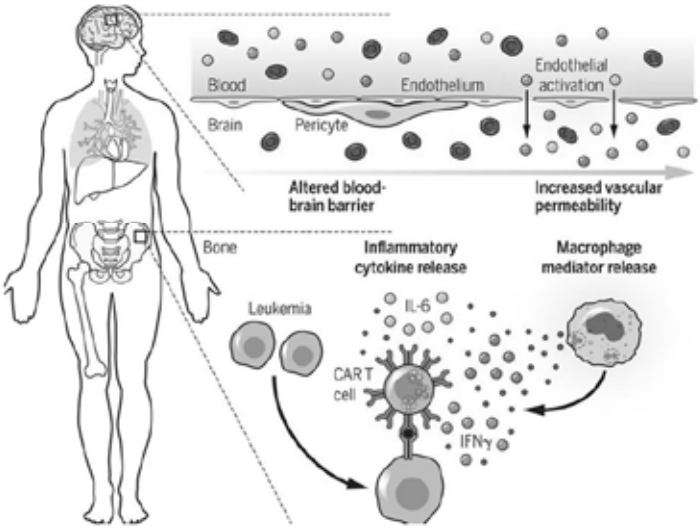


Kochenderfer, Nat Rev Clin Oncol 2013.

CAR T Side Effects

- Cytokine Release Syndrome (CRS)
- Neurotoxicity
- B Cell aplasia
- Macrophage Activation Syndrome (MAS)/HLH

CAR T Side Effects



June et al. Science 2018

FDA-Approved CAR T cell therapies

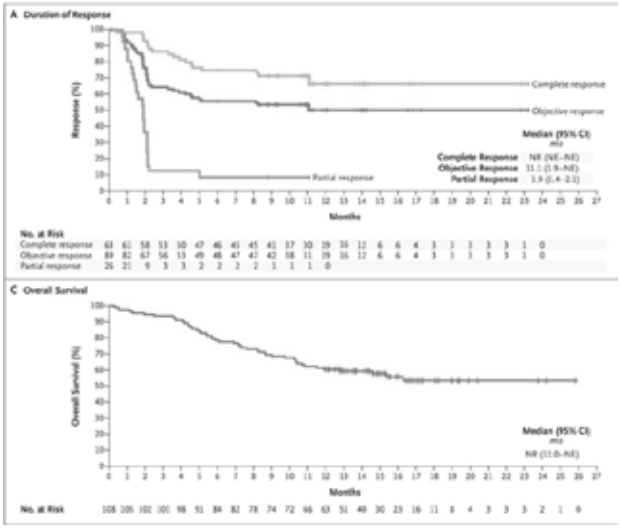
DRUG	APPROVED	INDICATION	DOSE
Axicabtagene ciloleucel	2017	Adults with r/r large B-cell lymphoma. Including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T-cells per kg bodyweight (up to 2x10^8)
Tisagenlecleucel	2017	Patients ≤25 yr with refractory B-cell acute lymphoblastic leukemia or in 2+ relapse	0.2-0.5x10^6 CAR-positive, viable T-cells per kg if under 50 kg 0.1-2.5x10^8 CAR-positive, viable T-cells if over 50 kg
Tisagenlecleucel	2018	Adults with r/r large B-cell lymphoma after 2+ therapies Including DLBCL, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma	0.6-6.0 x 10^8 CAR-positive, viable T-cells

Eligibility considerations for CAR

- Disease
  - Relative stability during CAR T manufacturing (~2-6 weeks)
  - Bridging therapy (chemo, RT, steroids, lenalidomide, ibrutinib)
  - CNS control
- Patient
  - Adequate cell counts
  - DVT, bleeding, infection, neuro disorders
  - Functional status: at screen vs. day of CAR T infusion
- Other
  - Social support, reimbursement

CD19 CAR in DLBCL- ZUMA1 (Axi-cel)

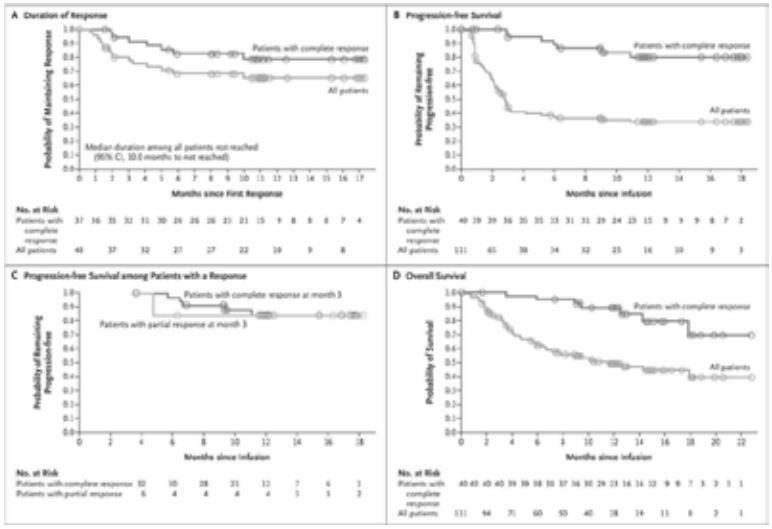
- CD19/CD28ʒ
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade ≥3 = 13%
- Neurotox grade ≥3 = 28%



Neelapu, NEJM 2017.

CD19 CAR in DLBCL - JULIET (Tisa-cel)

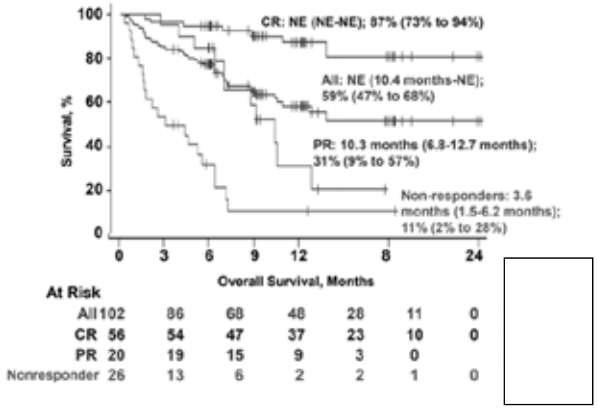
- CD19/4-1-BB
- ORR = 52%
- CR = 40%
- 1-yr estimated OS = 49%
- CRS grade ≥3 = 18%
- Neurotox grade ≥3 = 11%



Schuster, NEJM 2019.

CD19 CAR in DLBCL - TRANSCEND (Liso-Cel)

- CD19/4-1-BB, CD4:CD8 = 1:1
- ORR = 75%
- CR = 55%
- 1-yr estimated OS = 59%
- CRS grade ≥3 = 1%
- Neurotox grade ≥3 = 13%

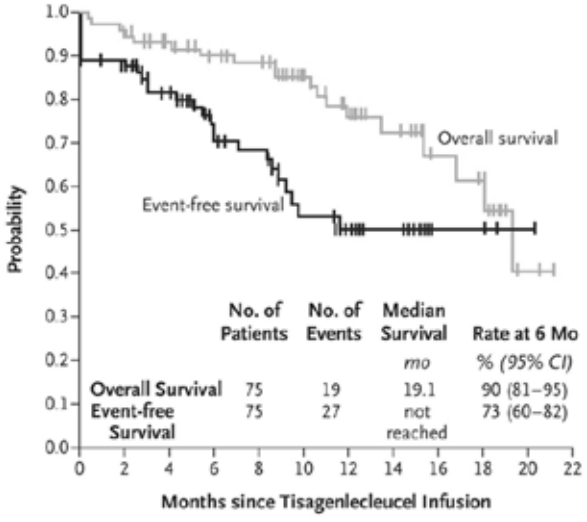


Abramson et al. ASCO Abstract 7505 June 3, 2018

Abramson JS, et al. HemaSphere. 2018;2(S1): Abstract S800.

CD19 CAR in B-ALL: ELIANA (Tisa-cel)

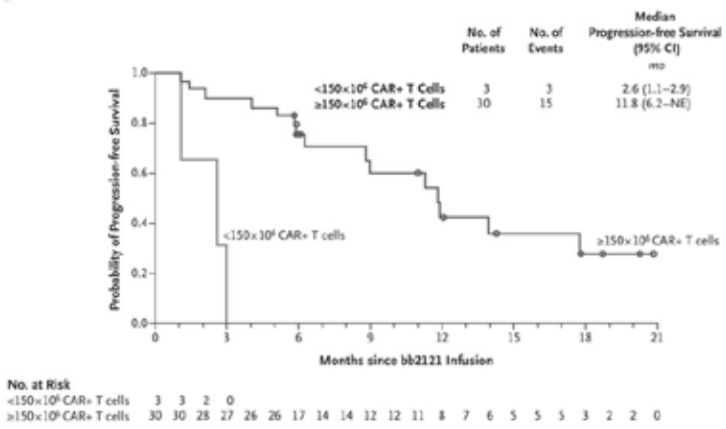
- CD19/4-1-BB
- ORR = 81%
- CR = 60%, CRi = 21%
- CRS grade ≥3 = 47%
- Neurotox grade ≥3 = 13%



Maude et al. NEJM 2018

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
  - ORR: 85%, CR: 45%



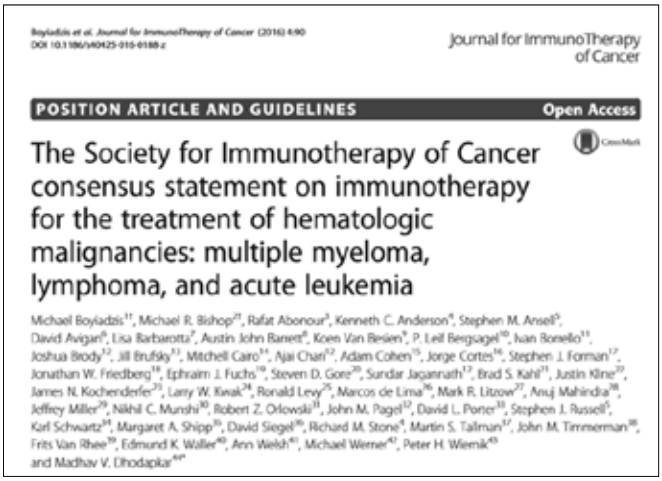
Raje, NEJM 2019.

Conclusions

- Many immunotherapy options for hematological malignancies
- Checkpoint inhibitors for Hodgkin lymphoma and PMBCL – high response rate, excellent tolerance, durable responses if CR
- Blinatumomab and inotuzumab for ALL – effective salvage, deeper remissions
- Polatuzumab vedotin for DLBCL – effective salvage, potential to become frontline
- CAR T therapy – ever-increasing indications; patient selection and toxicity management still concerns

Additional Resources

sitc Society for Immunotherapy of Cancer
Cancer Immunotherapy GUIDELINES



Boyiadzis et al. Journal for ImmunoTherapy of Cancer (2016) 4:90
DOI 10.1186/s40425-016-0188-z

journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of hematologic malignancies: multiple myeloma, lymphoma, and acute leukemia

Michael Boyiadzis[1†], Michael R. Bishop[2†], Rafat Abonour[3], Kenneth C. Anderson[4], Stephen M. Ansell[5], David Avigan[6], Lisa Barbarotta[7], Austin John Barrett[8], Koen Van Besien[9], P. Leif Bergsagel[10], Ivan Borello[11], Joshua Brody[12], Jill Brufsky[13], Mitchell Cairo[14], Ajai Chari[12], Adam Cohen[15], Jorge Cortes[16], Stephen J. Forman[17], Jonathan W. Friedberg[18], Ephraim J. Fuchs[19], Steven D. Gore[20], Sundar Jagannath[12], Brad S. Kahl[21], Justin Kline[22], James N. Kochenderfer[23], Larry W. Kwak[24], Ronald Levy[25], Marcos de Lima[26], Mark R. Litzow[27], Anuj Mahindra[28], Jeffrey Miller[29], Nikhil C. Munshi[30], Robert Z. Orlowski[31], John M. Pagel[32], David L. Porter[33], Stephen J. Russell[5], Karl Schwartz[34], Margaret A. Shipp[35], David Siegel[36], Richard M. Stone[4], Martin S. Tallman[37], John M. Timmerman[38], Frits Van Rhee[39], Edmund K. Waller[40], Ann Welsh[41], Michael Werner[42], Peter H. Wiernik[43] and Madhav V. Dhodapkar[44*]

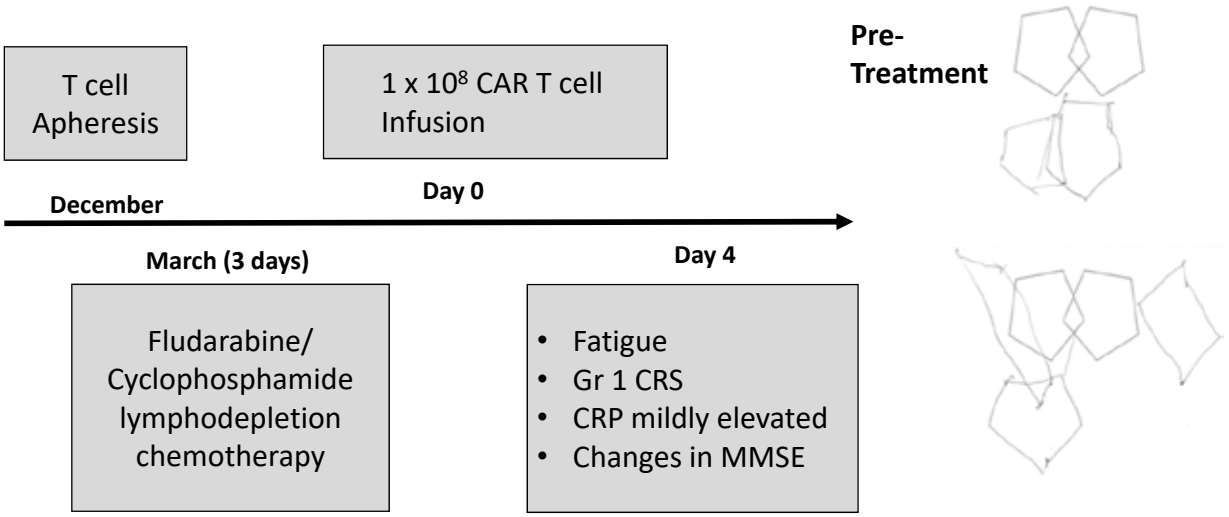
Case Studies

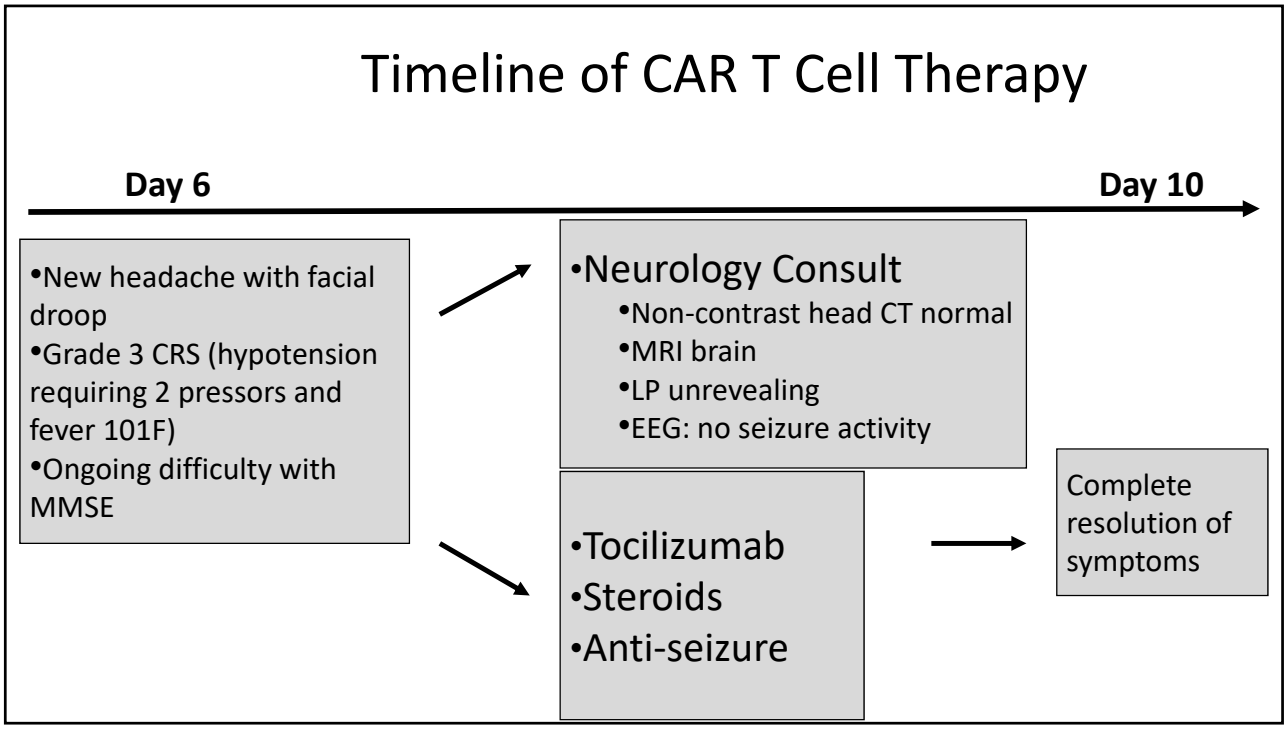
Case Study 1

- 72 year-old active, healthy female (ECOG 0) with no significant PMH diagnosed with bulky ABC subtype, p53 deleted *aggressive* DLBCL

- <u>TREATMENT SUMMARY:</u>
  - 6 cycles DA-EPOCH-R (Feb - Jun 2016)→ Complete Response (CR)
  - Relapse 3 months later
  - 3 cycles Rituximab, Gemcitabine, and Cisplatin→ Progressive Disease (PD)
  - Enrolled on CAR T cell clinical trial

Timeline of CAR T Cell Therapy





Neurotoxicity

- 133 patients (ALL, NHL, CLL) treated with CD-19 CAR T cell with 4-1BB costimulatory domain
- 53 of 133 (40%) with neurotoxicity
- 48 of these 53 (91%) also had CRS
- The 5 without CRS had only grade 1 neurotoxicity
- All patients with grade 3 or higher neurotoxicity had an antecedent fever
- **Median 4.5 days (range 2-17 days) after CRS**
- Median time from onset of neurotoxicity to highest grade 1 day (range 0-19)
- Median duration of reversible neurotoxicity was 5 days (range 1-70 days)

Gust et al. Cancer Discovery. 2017

Neurotoxicity CTCAE grade		Grade 0[a]	Grade 1–2[a]	Grade 3–5[a]	Total	Univariate[b]	Multivariable[c]
Overall, n (%)		80 (60)	25 (19)	28 (21)	133 (100)		
Age, n (%)	<40 years	11 (41)	10 (37)	6 (22)	27	0.094	
	40–60 years	42 (66)	8 (13)	14 (22)	64		
	>60 years	27 (64)	7 (17)	8 (19)	42		
Sex, n (%)	Male	59 (63)	17 (18)	17 (18)	93	0.4	
	Female	21 (53)	8 (20)	11 (28)	40		
Diagnosis, n (%)	ALL	22 (47)	11 (23)	14 (30)	47	0.084	
	CLL	16 (67)	2 (8)	6 (25)	24		
	NHL	42 (68)	12 (19)	8 (13)	62		
Race, n (%)	White	62 (56)	22 (20)	26 (24)	110	0.17[d]	
	Not white	18 (78)	3 (13)	2 (9)	23		
Prior therapies	Median (range)	4 (1–11)	4 (1–10)	4 (1–11)	4 (1–11)	0.5	
Transplant history, n (%)	Auto	17 (68)	5 (20)	3 (12)	25	0.5	
	Allo	14 (50)	8 (29)	6 (21)	28		
Karnofsky score[e], n (%)	60–70	7 (50)	3 (21)	4 (29)	14	0.5	
	80–90	65 (61)	18 (17)	23 (22)	106		
	100	8 (62)	4 (31)	1 (8)	13		
Preexisting neurologic comorbidities, n (%)	Any	26 (45)	16 (28)	16 (28)	58	0.0059[d]	0.0023[d]
	PN[f]	14 (47)	7 (23)	9 (30)	30	0.2	
	CNS involvement	6 (43)	5 (36)	3 (21)	14	0.2	
	Headache disorder	6 (43)	5 (36)	3 (21)	14	0.2	
	Other	5 (50)	2 (20)	3 (30)	10	0.7	
	ICH[g]	4 (67)	1 (17)	1 (17)	6	1	
	Seizures	2 (33)	2 (33)	2 (33)	6	0.3	
	Cog impairment[h]	1 (25)	2 (50)	1 (25)	4	0.1	
	MTX CNS toxicity[i]	1 (50)	1 (50)	0	2	0.4	
Marrow disease, %	Median (range)	0.6 (0–97)	0.4 (0–93)	25.8 (0–97)	1.3 (0–97)	0.072	0.0165
Total CD19[+] cells in marrow, %	Median (range)	5.3 (0–99)	12.4 (0–93)	29.1 (0–97)	8.8 (0–99)	0.062	
CD8[+] central memory enriched CAR-T cells[k], n (%)	Selected	48 (67)	11 (15)	13 (18)	72 (54)	0.242	
Lymphodepletion regimen[l], n (%)	Cy/Flu	58 (56)	23 (22)	23 (22)	104	0.11	0.0259
	Non-Cy/Flu	22 (76)	2 (7)	5 (17)	29		
CAR-T cell dose, n (%)	2×10^6 cells/kg	20 (57)	10 (29)	5 (14)	35	<0.0001	0.0089
	2×10^6 cells/kg	55 (64)	15 (17)	16 (19)	86		
	2×10^7 cells/kg	5 (42)	0	7 (58)	12		
Cytokine release syndrome, n (%)	None (G 0)	35 (88)	5 (13)	0	40	<0.0001	n/a
	Mild (G 1–2)	44 (57)	19 (25)	14 (18)	77		
	Severe (G 3–5)	1 (6)	1 (6)	14 (88)	16		

Neelapu et al. Nature Review. 2016

Case Study 2

- 30 year-old male with no PMH diagnosed with Stage IV Hodgkin lymphoma
- *TREATMENT HISTORY:*
  - 6 cycles of ABVD → CR
  - Relapsed → ASCT
  - Relapsed → Anti-PD-1 blockade

Myrna R. Nahas, MD – *Beth Israel Deaconess Medical Center*

Patient Develops New Symptoms

- Headache
- Fatigue
- Dizziness with standing

What is the differential?

A. ?
B. ?
C. ?
D. ?

What is the differential?

A. Progressive disease with CNS involvement
B. Hypophysitis
C. Adrenal insufficiency alone
D. Dehydration

What are your next steps?

What are your next steps?

- Vitals: Orthostatic hypotension
- Physical exam: Pale
  - ADMIT PATIENT

Work-Up Shows…

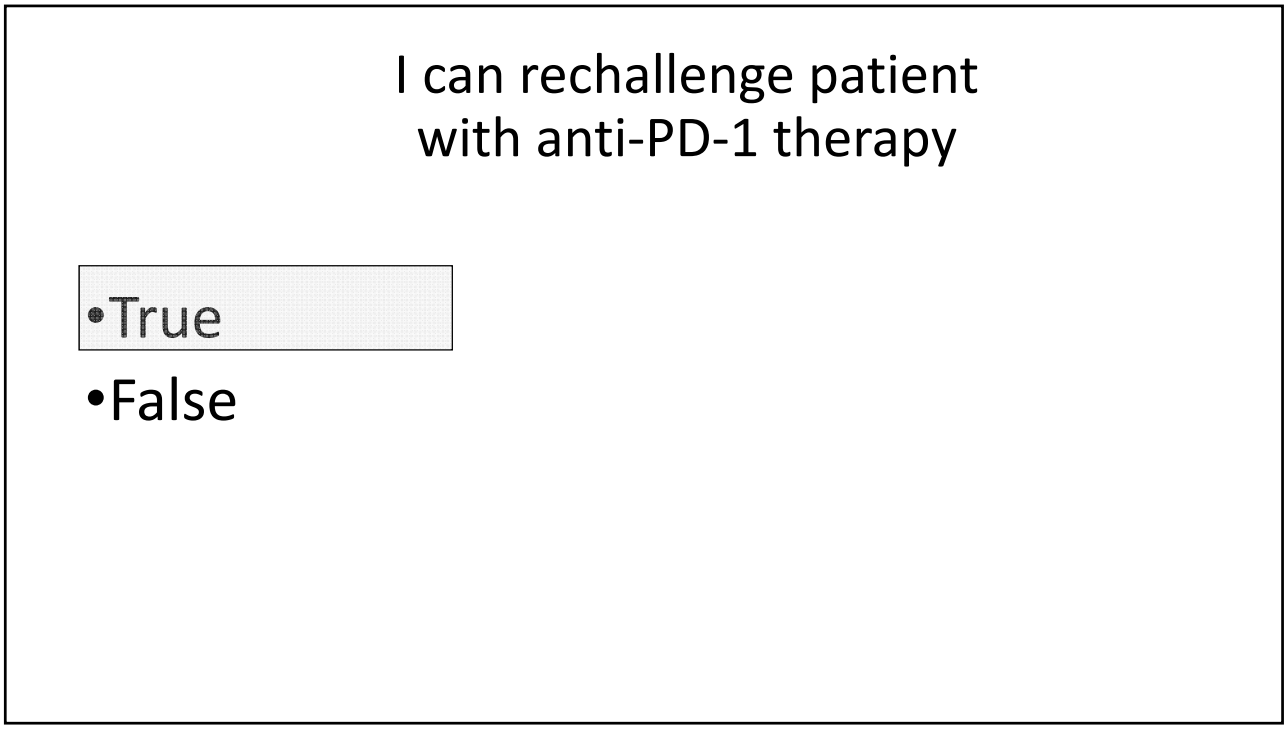
- Low TSH
- Low ACTH
- Low LH
- Brain MRI: a swollen pituitary gland is seen
- Now what should you do?

Management

- STOP immunotherapy
- Endocrine consult:
  - High-dose glucocorticoids, levothyroxine, and sex hormone replacement
- Almost all patients experienced resolution of acute symptoms within a few days

I can rechallenge patient with anti-PD-1 therapy

- True
- False


I can rechallenge patient with anti-PD-1 therapy
•True
•False

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

Osama E. Rahma, MD
Medical Oncologist
Dana-Farber Cancer Institute

Dr. Rahma received his medical degree from University of Damascus in 1998. He completed his residency in Internal Medicine at East Carolina University followed by Geriatrics Fellowship at University of Hawaii. Dr. Rahma joined the National Cancer Institute (NCI) as an Immunotherapy Research Fellow in the Vaccine Branch in 2009 and completed a Fellowship in Medical Oncology in 2013 specializing in Cancer Immunotherapy and Gastrointestinal (GI) Oncology. While at NCI, his efforts led to the development of many clinical studies investigating immunotherapy in GI malignancies. Prior to joining Dana-Farber Cancer Institute, Dr. Rahma was the leader of the Hepatobiliary and Pancreatic Cancer Program at University of Virginia where he led translational research efforts as the Principal Investigator of many clinical trials.

Dr. Rahma joined the Center for Immuno-Oncology at Dana-Farber to be part of national and international efforts to advance the field of Cancer Immunotherapy. He is currently the chair of two investigator-initiated clinical trials using a novel combination of immune checkpoint inhibitor (anti-PD-1) and neoadjuvant chemoradiation in pancreatic and rectal cancer. Dr. Rahma is also the Harvard Cancer Center site Principal Investigator for many sponsored trials using the combination of novel immunotherapeutic agents. Dr. Rahma is leading the Immune Toxicity Work Group at Dana-Farber, a program that is devoted to understand factors that may predict immune related toxicities.

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

Osama E. Rahma, MD – Dana-Farber Cancer Institute

Audience Response Questions

1. Which of the following treatments are currently approved by the FDA for treatment of advanced HCC?
   A. Atezolizumab
   B. Pembrolizumab
   C. Durvalumab
   D. Avelumab

2. Which of the following is NOT an ongoing immunotherapies strategy for treating HCC?
   A. Checkpoint inhibitor blockade
   B. Blocking inhibitory cytokines: TGF- β, LAG-3, Tim-3
   C. Bispecific T cell engagers
   D. Adoptive cell transfer

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

Osama E. Rahma, MD – Dana-Farber Cancer Institute

Immunotherapy for the Treatment of Hepatocellular Carcinoma

Osama Rahma, MD
Assistant Professor of Medicine, Harvard Medical School
Center for Immuno-Oncology, Gastrointestinal Cancer
Dana-Farber Cancer Institute

Disclosures

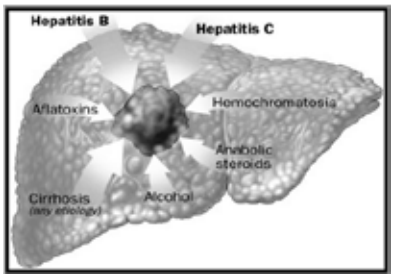
- Consulting Fees: Puretech, Imvax, GSK, Maverick, Roche, Leerink, PRMA, Defined Health
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

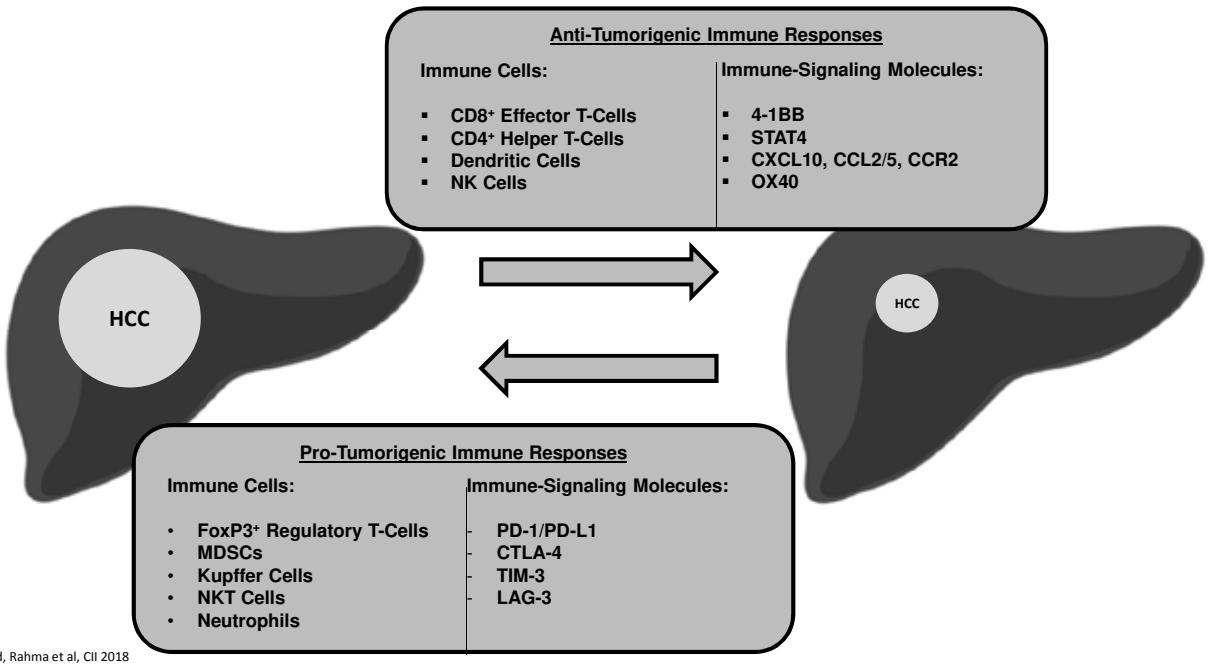
Osama E. Rahma, MD – Dana-Farber Cancer Institute

Background

- HCC is the most common type of primary liver cancer
- Often associated with cirrhosis (HBV or HCV, alcohol abuse)
- 3rd leading cause of cancer death worldwide
- Treatment options:
  - Curative: orthotopic liver transplantation, surgical resection
  - Chemoembolization, radiofrequency ablation, microwave ablation, radiation, chemotherapy, targeted therapy
- Many patients are ineligible for surgery/transplant – there's a need for systemic therapies in HCC



Johns Hopkins Kimmel Cancer Center



Obeid, Rahma et al, CII 2018

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

Osama E. Rahma, MD – Dana-Farber Cancer Institute

Liver Immunobiology

- The liver is exposed to a **flood of pathogenic and non-pathogenic antigens** and hence has developed an inherent **immune tolerogenicity**
- **Cirrhosis results in an active inflammatory process** in the liver which ultimately results in cancer
- **HCV and HBV infections** also result in immune mediated inflammation which promotes cancer development

Liver Immunobiology

- However, the immune response is made dysfunctional by
  - Expression of a greater proportion of **T-regulatory/cytotoxic T cells**
  - **Hypofunctional NK cells**
  - **Expansion of MDSCs**
  - secretion of **immunoregulatory cytokines**
  - **Expression of inhibitory ligands** that suppress immune activation and
  - **Downregulation of stimulatory ligands** that activate the immune system.

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

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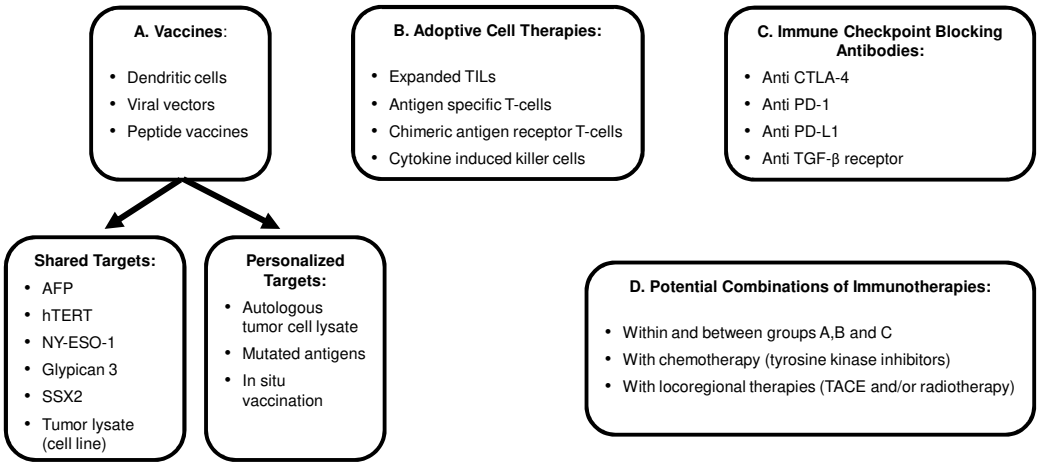
Immunotherapeutic Strategies in HCC



Obeid, Rahma et al, CII 2018

Approved checkpoint inhibitors for HCC

Drug	Approved	Indication	Dose
Nivolumab	2017	HCC with previous sorafenib	240 mg Q2W or 480 mg Q4W
Pembrolizumab	2018	HCC with previous sorafenib	200 mg Q3W

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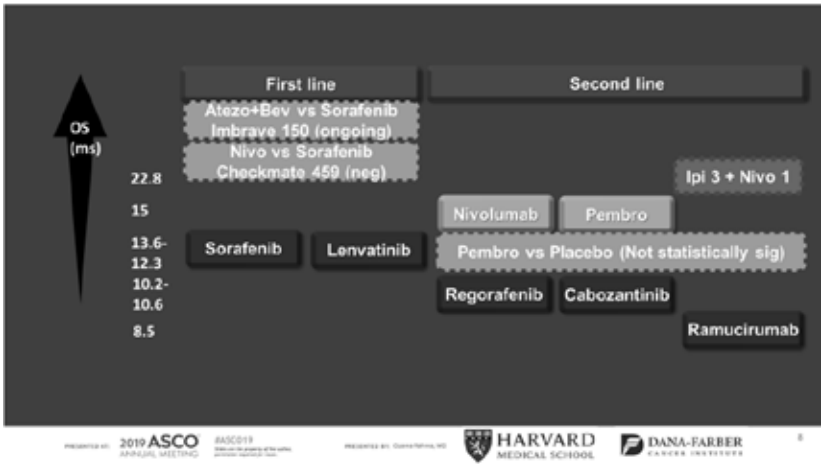
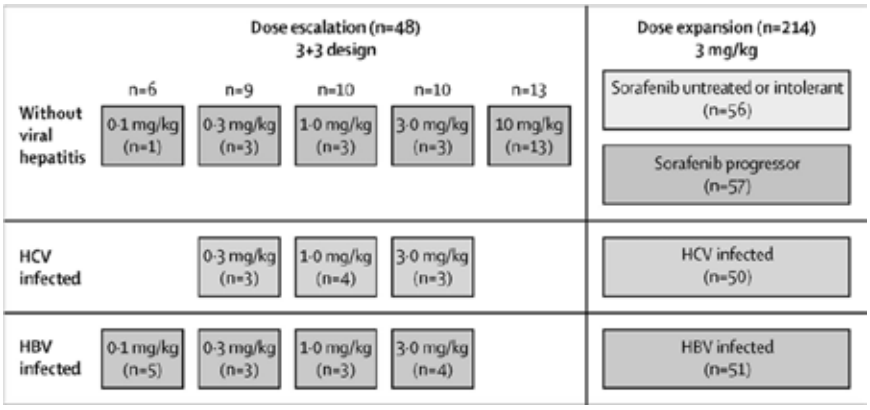
Current Treatment Paradigm in HCC



CheckMate 040

- Phase I/II open label study
- Child-Pugh A or B7, advanced HCC
- Previous sorafenib allowed
- Safety/tolerability for escalation; ORR for expansion



El-Khoueiry, The Lancet 2017.

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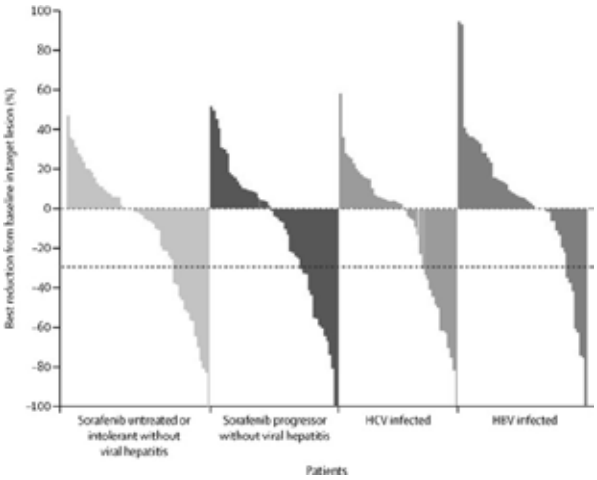
CheckMate 040

- ORR: 20%, 3 CR, 39 PR
- @ 6 mo: OS = 83%, PFS = 37%
- @ 9 mo: OS = 74%, PFS = 28%
- No difference if previously treated with sorafenib
- No difference in AEs if HBV/HCV(+)
- Gr 3/4 TrAE: elevation of AST/ALT, elevation of bilirubin, and hepatitis



El-Khoueiry, The Lancet 2017.

KEYNOTE-224

- Phase 2 non-randomized trial
- Previously treated with sorafenib
- Child-Pugh class A
- Pembrolizumab IV 200 mg Q3W
- Primary endpoint: objective response
- 104 patients enrolled and treated

Zhu, Lancet Oncol 2018.

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

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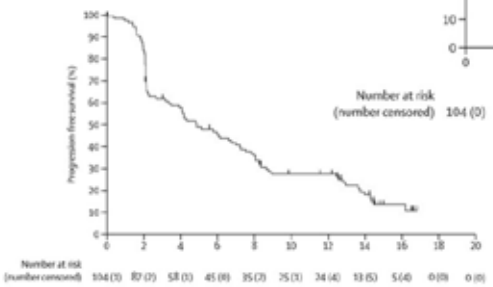
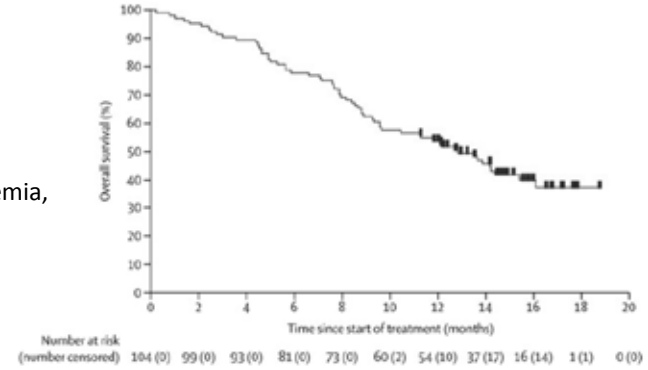
KEYNOTE-224

- ORR: 17%, 1 CR, 17 PR
- mPFS: 4.9 months
- mOS: 12.9 months
- G 3/4 treatment-related adverse events: Increased ALT, AST, fatigue, hyperbilirubinemia, ulcerative esophagitis, and hepatitis





Zhu, Lancet Oncol 2018.

KEYNOTE-240

- Ph III, randomized
- Advanced HCC with previous systemic therapy, radiographic progression on/intolerance to sorafenib
- Child Pugh A
- Pembrolizumab 200 mg IV Q3W vs placebo
- 413 patients randomized 2:1
- Primary endpoints were OS and PFS

Finn, ASCO 2019

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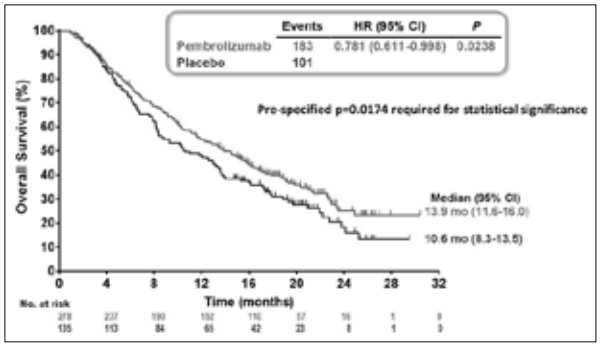
KEYNOTE-240

- Results: primary endpoints did not meet statistical significance.
  - OS: HR = 0.78, p = 0.0238
  - PFS: HR = 0.78, p = 0.0209
  - ORR 16.9% (95% CI 12.7-21.8) vs 2.2% (95% CI 0.5-6.4%), p = 0.00001



Finn, ASCO 2019

In development: Atezolizumab + bevacizumab

- Phase Ib; First line
  - Resulted in breakthrough therapy designation
- Atezolizumab 1200 mg + bevacizumab 15mg/kg Q3W
- Partial responses in 62% of patients: *Combination has synergistic clinical activity*
- Regardless of viral infection, region, metastasis
- mPFS, DOR, and OS not reached at 10.3 months
- Gr 3/4 TRAE in 35% of patients – hypertension, autoimmune encephalitis, mental status change and intra-abdominal hemorrhage

Stein, ASCO 2018

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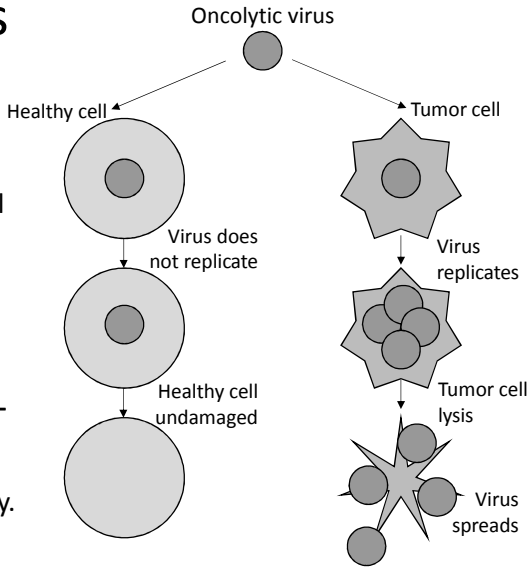
Vaccine Therapies

- Increase specific immune responses to tumor antigens
- Peptide vaccines: another option but no trials that have shown any success yet.
- Dendritic cells:
  - NCT01974661; Phase 1 Trial With the **Cell-Based Immune Primer Ilixadencel, Alone, and Combined With Sorafenib**, in Advanced Hepatocellular Carcinoma

Oncolytic Viruses

- Viruses that preferentially replicate in cancer cells
  - NCT0055437; Randomized dose-finding clinical trial of **oncolytic immunotherapeutic vaccinia JX-594** in liver cancer. Nat Med. 2013 Mar;19(3):329-36.
  - A phase 3 randomized, open-label study comparing the **oncolytic immunotherapy Pexa-Vec followed by sorafenib (SOR) vs SOR** in patients with advanced hepatocellular carcinoma (HCC) without prior systemic therapy. J Clin Oncol 2016; 34: TPS4146



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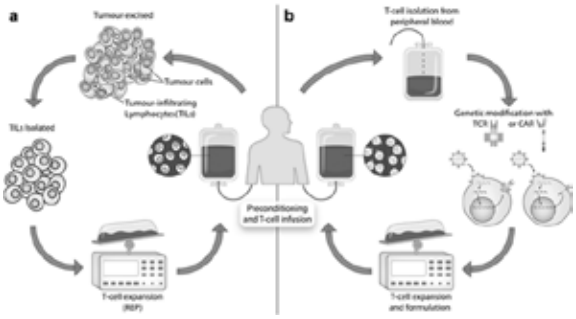
Adoptive Cell Transfer

- Passive administration of autologous lymphocytes following *ex vivo* cultivation
- Cell subsets that have been studied in HCC include NK cells, cytokine-induced killer (CIK) cells or TILs, and chimeric antigen receptor T cells (CAR-T cells).
  - NCT03563170; Molecularly Informed Integrated Immunotherapy Combining **Innate High-affinity Natural Killer (haNK) Cell Therapy w/ Adenoviral & Yeast-based Vaccines** to Induce T-cell Responses in Subjects w/ Advanced, Unresectable & Untransplantable HCC



Met *et al*, Principles of adoptive T cell therapy in cancer.

Conclusions

- Since many patients are ineligible for surgical resection/transplant, there is a great need for systemic therapies in HCC
- Currently both pembrolizumab and nivolumab are considered standard of care as a second line post-sorafenib
- Many ongoing trials with combinations of immunotherapies or targeted therapies (anti-angiogenesis) in HCC

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

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Case Studies

Case Study 1

Mr. AB is a 65 yo male with h/o liver cirrhosis who was found to have 2 liver lesions during routine US. Further workup including chest/abd and pelvic ctscan revealed a lung lesion with a biopsy consistent with metastatic HCC. The patient has a Child Pugh of A. He presented to your office to explore treatment options.

1. The next treatment option for this patient is:

   A. Start Nivolumab 240mg every 2 weeks.

   B. Start Sorafenib 400mg daily.

   C. Strat combination of Sorafenib and nivolumab.

   D. Strat combination of atezolizumab and bevacizumab.

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Case Study 1

Mr. AB is a 65 yo male with h/o liver cirrhosis who was found to have 2 liver lesions during routine US. Further workup including chest/abd and pelvic ctscan revealed a lung lesion with a biopsy consistent with metastatic HCC. The patient has a Child Pugh of A. He presented to your office to explore treatment options.

1. The next treatment option for this patient is:

   A. Start Nivolumab 240mg every 2 weeks. Nivolumab has not shown better activity compared to sorafenib in the first line setting.

   B. Start Sorafenib 400mg daily. Sorafenib remains the first line option in HCC.

   C. Strat combination of Sorafenib and nivolumab. This combination has not been tested in clinical trials.

   D. Strat combination of atezolizumab and bevacizumab. The preliminary result of Phase IB of this combination is promising, however, the phase III of the combination vs sorafenib will not be released until 2022.

Case Study 1

- The patient was started on sorafenib 400 mg daily which he tolerated well beside developing rash and intermittent diarrhea. However, his 9-months restaging scan showed increase size and number of liver lesions consistent with progression of disease.

- Your next step is:

   A. Strat nivolumab 240mg every 2 weeks.

   B. Start pembrolizumab 200mg every 3 weeks.

   C. A or B.

   A. Refer the patient to clinical trial.

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

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Case Study 1

- The patient was started on sorafenib 400 mg daily which he tolerated well beside developing rash and intermittent diarrhea. However, his 9 months restaging scan showed increase size and number of liver lesions consistent with progression of disease.
- Your next step is:

A. Strat nivolumab 240mg every 2 weeks.

B. Start pembrolizumab 200mg every 3 weeks.

C. A or B. Both nivolumab and pembrolizumab have similar activity and are considered second line options in HCC.

D. Refer the patient to clinical trial. This is a possibility, however, this could be offered when patient progresses on nivolumab

Case Study 1

- The patient was started on nivolumab and had stable disease so far for the past 6 months.

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

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Case Study 2

Mr. NL is a 55 yo male with h/o liver cirrhosis due to hepatitis C and large HCC liver mass with multiple satellite lesions which was not amendable to surgical resection or liver transplant. He recently developed a progression of disease while on sorafenib. He is Child Pugh A. His AST is 60, ALT 75 and ALP 100. Hepatitis C viral load is 10,000.

The next treatment option for this patient is:

A. Refer the patient to GI to start treatment for hepatitis C before considering treatment with nivolumab.

B. Start TKIs (levatinib or cabozantinib) since PD-1 inhibitors are contraindicated due to hepatitis C.

A. Start TKIs (levatinib or cabozantinib) since PD-1 inhibitors are contraindicated due to elevated LFTs.

B. Start nivolumab 240mg every 2 weeks.

Case Study 2

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The next treatment option for this patient is:

A. Refer the patient to GI to start treatment for hepatitis C before considering treatment with nivolumab. Nivolumab could be started safely in patients with hepatitis C based on Checkmate-240.

B. Start TKIs (levatinib or cabozantinib) since PD-1 inhibitors are contraindicated due to hepatitis C. Nivolumab could be started safely in patients with hepatitis C based on Checkmate-240.

A. Start TKIs (levatinib or cabozantinib) since PD-1 inhibitors are contraindicated due to elevated LFTs. Nivolumab could be started safely in patients with elevated LFTs.

B. Start nivolumab 240mg every 2 weeks. Nivolumab is considered second line in HCC.

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

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Case Study 2

- The patient was started on nivolumab 240mg every 2 weeks. He returned for a follow up 8 weeks after starting nivolumab. His LFTs were as follow: AST 500, ALT 750 and ALP 110.
- Your next step is:
  - A. Hold nivolumab.
  - B. Obtain restaging scan.
  - C. Continue Nivolumab and obtain restaging scan as planned before the next cycle.
  - D. A and B

Case Study 2

- The patient was started on nivolumab 240mg every 2 weeks. He returned for a follow up 8 weeks after starting nivolumab. His LFTs were as follow: AST 500, ALT 750 and ALP 110.
- Your next step is:
  - A. Hold nivolumab. Immune hepatitis is a know adverse event of nivolumab. Therefore treatment should be held.
  - B. Obtain restaging scan. Increased LFTs could be due to progression of disease which should be ruled out.
  - C. Continue Nivolumab and obtain restaging scan as planned before the next cycle. Both immune hepatitis and progression of disease should be ruled out as above.
  - (D.) A and B

Immunotherapy for the Treatment of Additional Solid Tumors: Hepatocellular Carcinoma

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Case Study 2

The patient underwent a restaging scan and was found to have progression of disease. He eventually deteriorated and was placed on hospice.

Toxicity Management

Virginia Seery, MSN, RN, ANP-BC
Nurse Practitioner
Beth Israel Deaconess Medical Center

Ms. Seery is a nurse practitioner at Beth Israel Deaconess Medical Center in Boston, MA taking care of renal cell carcinoma and melanoma patients in the Immuno-oncology program. She has extensive experience with clinical trials and immunotherapy, including managing the inpatient high dose IL-2 service.

Toxicity Management

Virginia Seery, MSN, RN, ANP-BC – *Beth Israel Deaconess Medical Center*

Audience Response Questions

1. Which of the following is NOT a common immune-related adverse event observed after immune checkpoint blockade treatment?
   A. Dermatitis
   B. Cytokine release syndrome
   C. Colitis
   D. Endocrinopathy

2. A higher incidence of cytokine release syndrome has been observed in CAR T therapy patients with all of the following risk factors EXCEPT:
   A. High CAR T cell dose
   B. Higher lymphodepletion intensity
   C. Higher disease burden
   D. Higher target expression by cancer cells

Toxicity Management

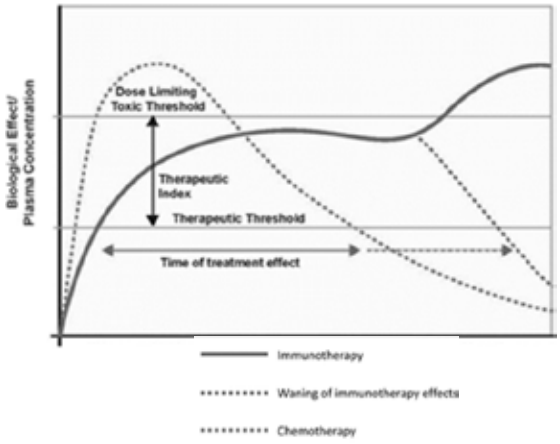
Virginia Seery, MSN, RN, ANP-BC
Nurse Practitioner
Beth Israel Deaconess Medical Center

Disclosures

- Consulting Fees:
  - Apricity Health, LLC
- I will be discussing non-FDA approved indications during my presentation.

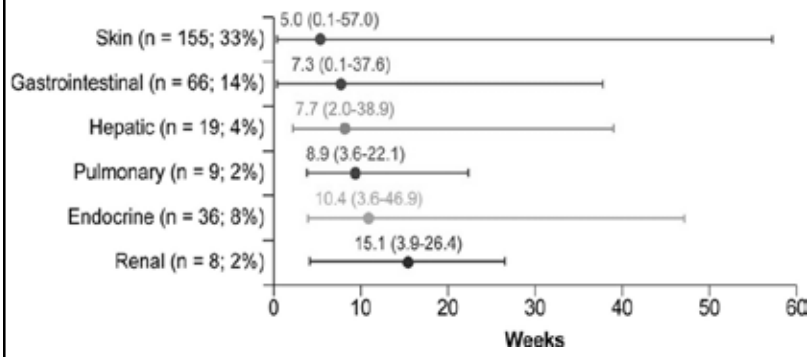
Immune-related adverse events (irAEs)

- Immune checkpoint inhibitor (ICI) toxicities often have delayed onset and prolonged duration relative to chemotherapy toxicity
- Toxicities result from non-specific activation of the immune system and can mimic a number of other medical conditions



Puzanov and Diab, JITC 2017

Onset of irAEs



- Can be days to months after therapy initiation
- May occur even after treatment is discontinued
- Important to identify patients who are currently **OR** previously on ICI treatment!

Pallin, Acad Emerg Med 2018
Puzanov and Diab, JITC 2017

Incidence of irAEs

- Overall incidence of all-grade irAEs with single-agent ICI reported as 15-90% in studies
- Anti-CTLA-4 inhibitor (ipilimumab): dose-dependent toxicities
  - Any grade toxicity ≤ 75% (**Grade 3+: ≤ 43%**)
- PD-1/PD-L1 inhibitors: toxicities less dose-dependent
  - Any grade toxicity ≤ 30% (**Grade 3+: ≤ 20%**)
- Life-threatening irAEs are rare but treatment-related deaths reported in up to 2% of clinical trial patients

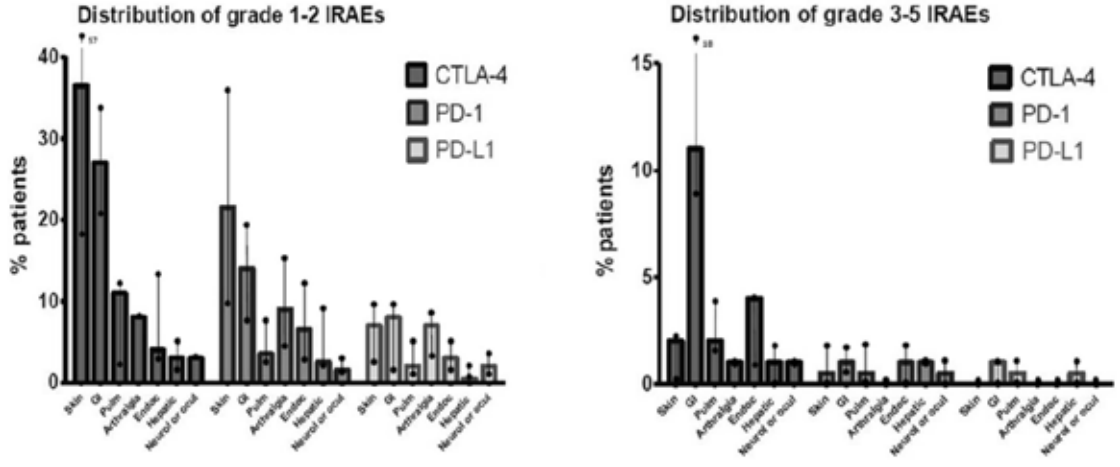
Puzanov and Diab, JITC 2017.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

Incidence of specific irAEs by ICI

Drug	Dermatitis	Colitis	Hepatitis	Endocrinopathies	Pneumonitis
	All grades (grade 3-4)				
Ipilimumab	14.5 (12)	10 (7)	5 (2)	10 (3)	<1
Ipilimumab/Nivolumab	30 (3)	26 (16)	13 (6)	35 (4)	6 (2.2)
Nivolumab	28 (1.5)	2.9 (0.7)	1.8 (0.7)	12 (0)	3.1 (1.1)
Pembrolizumab	20 (0.5)	1.7 (1.1)	0.7 (0.4)	12.5 (0.3)	3.4 (1.3)
Atezolizumab	17 (0.8)	1 (<1)	1.3 (<1)	5.9 (<1)	2.6 (<1)
Avelumab	15 (0.4)	1.5 (0.4)	0.9 (0.7)	6.5 (0.3)	1.2 (0.5)
Durvalumab	11 (1)	1.3 (0.3)	1.1 (0.6)	16.2 (0.1)	2.3 (0.5)

Puzanov and Diab, JITC 2017

Severity of irAEs by ICI



Puzanov and Diab, JITC 2017

Common irAEs with ICI's

- Dermatologic: maculopapular rash, dermatitis, pruritis
- Gastrointestinal: diarrhea, colitis, hepatitis, gastritis
- Rheumatologic: arthralgias, myositis, sicca symptoms
- Pulmonary: pneumonitis, sarcoidosis
- Endocrine: thyroid dysfunction, hypophysitis

Puzanov and Diab, JITC 2017.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

Uncommon irAEs with ICI's

Cardiovascular:
Myocarditis, pericarditis, arrhythmias

Renal:
Interstitial nephritis, granulomatous nephritis

Endocrine:
Adrenal insufficiency, pancreatitis, type 1 diabetes mellitus

Hematologic:
Hemolytic anemia, red cell aplasia, neutropenia, thrombocytopenia

Neurologic:
Myasthenia gravis, Guillain-Barré syndrome, peripheral neuropathies

Ophthalmologic:
Uveitis, episcleritis, conjunctivitis

Puzanov and Diab, JITC 2017.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

Pre-treatment screening

- Patient History
  - Autoimmune, infectious, endocrine, organ-specific diseases
  - Baseline bowel habits
- Dermatologic
  - Full skin and mucosal exam
- Pulmonary
  - Baseline O_2 saturation
- Cardiovascular
  - ECG
  - Troponin I or T
- Blood tests
  - CBC with diff
  - CMP
  - TSH and free T4
  - HbA1c
  - Total CK
  - Fasting lipid profile
  - Infectious disease screen:
    - Hepatitis serologies
    - CMV antibody
    - HIV antibody and antigen (p24)
    - TB testing (T-spot, quantiferon gold)

Pazanov & Diab, JITC 2017.

Additional screening for high-risk patients

- Endocrine tests
  - 8 am cortisol and ACTH
- Cardiac tests
  - Brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT pro-BNP)
- Pulmonary tests
  - PFTs
  - 6MWT

Pazanov & Diab, JITC 2017.

Approach to Treatment

- Treatment approach is guided by grading of specific toxicity
- Resources for grading:
  - SITC Toxicity Management Working Group
  - Common Terminology Criteria for Adverse Events
  - National Comprehensive Cancer Network
- 1st line for **MOST** irAE's is systemic high-dose corticosteroids
  - Endocrine toxicities managed with hormone replacement
  - Some grade 1-2 irAEs may respond to topical steroids (dermatologic, ophthalmologic)
- OTC drugs may not be appropriate for managing symptoms
  - i.e. loperamide for colitis may result in bowel perforation

General corticosteroid management

Grade of irAE	Corticosteroid Management	Additional Notes
1	Usually not indicated	Continue immunotherapy
2	• Start **prednisone 0.5-1 mg/kg/day** (or equivalent dose of IV methylprednisolone) • If no improvement in 2-3 days, **increase dose** to 2 mg/kg/day • Once improved to ≤grade 1, start **4-6 week steroid taper**	• **Hold immunotherapy** during corticosteroid use • **Continue immunotherapy** once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis

Pazanov & Diab, JITC 2017.

General corticosteroid management

Grade of irAE	Corticosteroid Management	Additional Notes
3	• Start **prednisone 1-2 mg/kg/day** (or equivalent dose of IV methylprednisolone) • If no improvement in 2–3 days, **ADD additional** immunosuppressant • Once improved to ≤ grade 1, start **4–6-week steroid taper**	• **Hold immunotherapy**; if symptoms do not improve in 4–6 weeks, **discontinue immunotherapy** • Start proton pump inhibitor for GI prophylaxis • Add PJP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4		• **Discontinue immunotherapy** • Start proton pump inhibitor for GI prophylaxis • Add PJP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

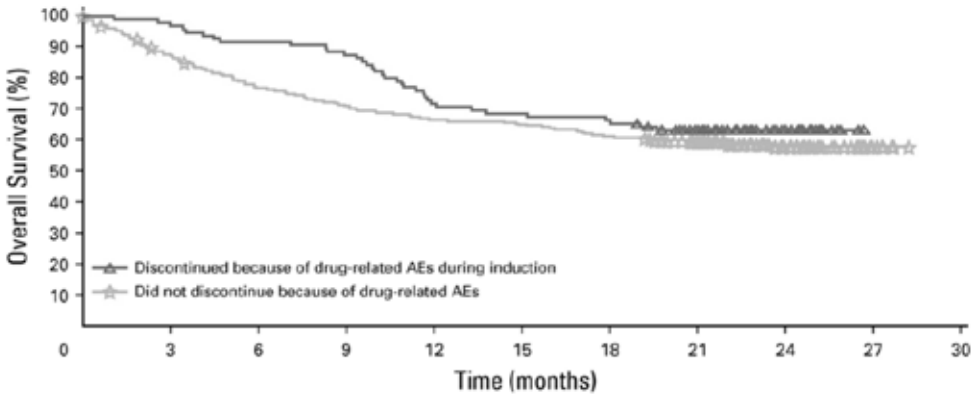
Pazanov & Diab, JITC 2017.

Additional immunosuppressives

- Infliximab: anti-TNF-α mAb
  - Hepatotoxic so should NOT be used for immune-mediated hepatitis
  - Risk for hepatitis B and tuberculosis activation; obtain hepatitis serologies and TB testing prior to initiation
  - Dose: 5 mg/kg; 2nd dose may be administered after 2 weeks
- Vedolizumab: α4β7 integrin mAb
  - **Selective GI immunosuppression** → inhibits migration of T cells across endothelium into inflamed GI tissues
  - Dose: 300 mg; repeat dose at 2 and 6 weeks
- Others: mycophenolate, IVIG, tacrolimus

Abu-Sbeih H. JITC. 2018 Dec 5;6(1):142.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

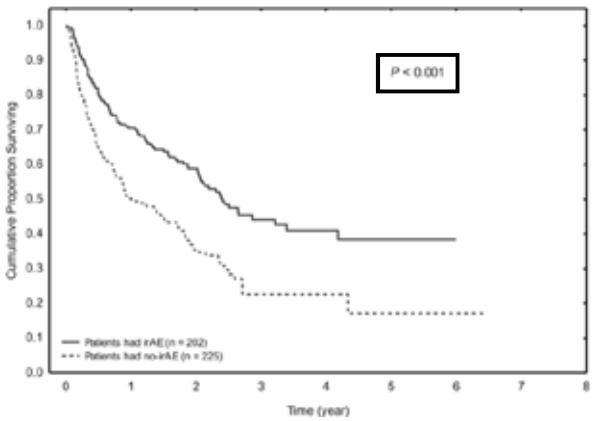
Effect of irAEs on patient outcomes

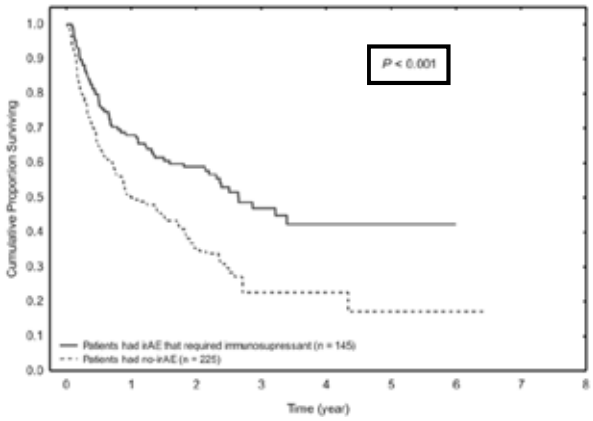


No significant difference in survival in melanoma patients who discontinued ipilimumab + nivolumab due to irAEs versus those who did not discontinue treatment

Schadendorf D. J Clin Oncol 2017 Dec; 35(35):3807-3814.

Autoimmunity as prognostic marker?

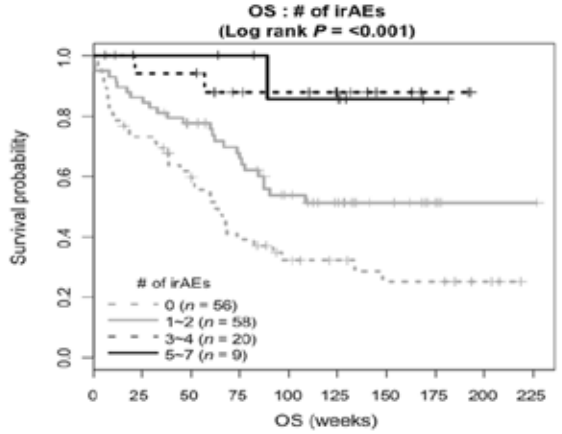




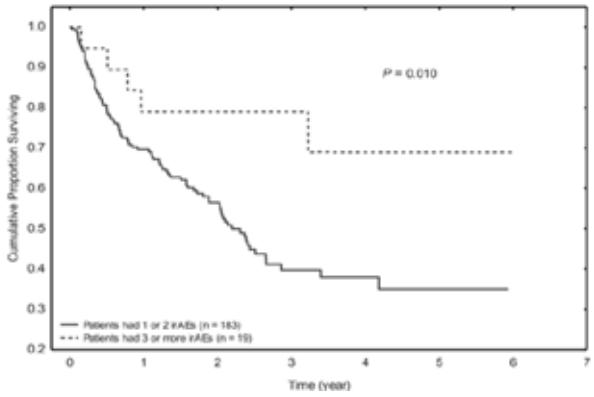
Based on **retrospective** data, patients who experience irAEs (regardless of needing treatment) may have better outcomes compared to patients who do not experience irAEs

Abu-Sbeih, J Immunoth Prec Oncol 2018.

Number of irAEs on patient outcomes



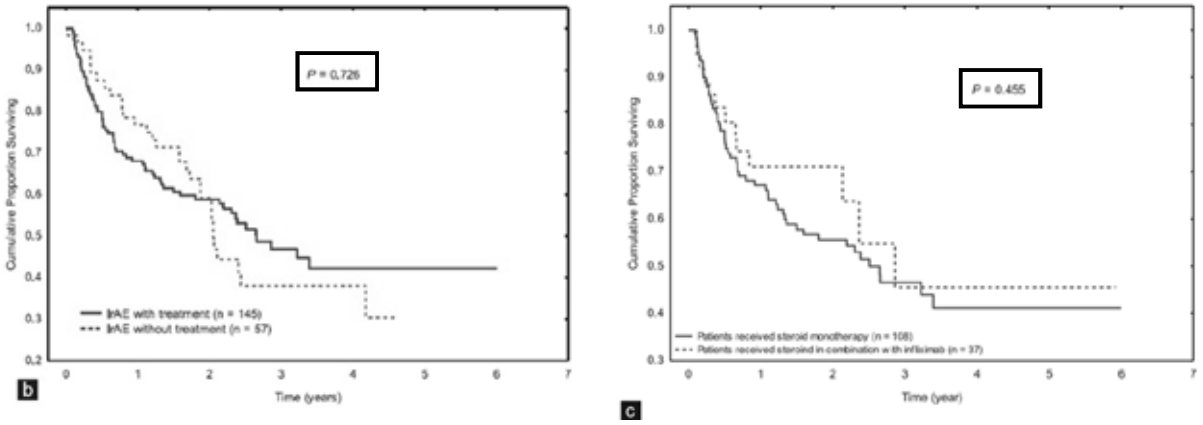
Nivolumab in metastatic melanoma: greater OS in patients with 3+ irAEs versus ≤ 1 irAE



Patients receiving ICI's for various malignancies: greater OS in those with 3+ irAEs versus ≤ 2 irAEs

Freeman-Keller, Clin Can Res 2016.
Abu-Sbeih, J Immunoth Prec Oncol 2018.

Impact of toxicity management on patient outcomes

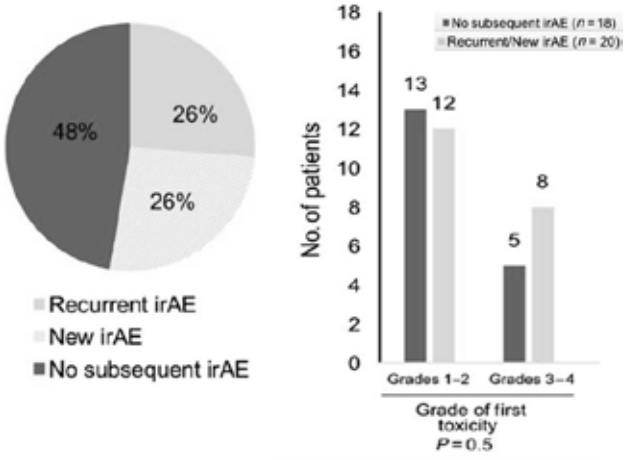


While still under debate, the administration of immunosuppressive treatments NOR the type of immunosuppressant used for irAE management does not seem to impact cancer control

Abu-Sbeih, J Immunoth Prec Oncol 2018.

Rechallenging with ICI after irAEs

- Patients should not be rechallenged until irAE resolved to grade ≤1
- Re-challenge with anti-PD-1/L1 after anti-CTLA-4 ± anti-PD-1 likely safe
- Caution in re-challenging with same ICI in patients who previously had grade 3-4 irAEs



Santini FC. Cancer Immunol Res 2018.

Patients with autoimmune disorders

- Ipilimumab in melanoma patients
  - 29% experienced flare of pre-existing disorder; 29% experienced new irAEs
  - 56% experienced no flare OR additional irAEs
- PD-1 in melanoma patients
  - 38% experienced flare; 29% experienced new irAEs
  - Lower response rates in patients who remained on immunosuppressive treatment (15% vs 44%)
- Efficacy appears similar for patients with autoimmune disorders compared to those without

Kahler KC. Cancer Immunol Immunother. 2018.

ICI use in SOT or SCT

- Patients who relapse after allogeneic SCT:
  - Ipilimumab: 32% response (10 mg/kg); 14% GVHD; 21% irAEs
  - Anti-PD-1: 77% response; 26% died due to new-onset GVHD
- Solid organ data is limited; most is in renal SOT patients
  - One retrospective study (n=39) reported graft loss in 81% and death in 46%
  - Also reported rapid time to rejection with median onset of 21 days
- PD-1 pathway appears to be more critical in allograft immune tolerance compared to CTLA-4 pathway

Davids MS. NEJM 2016.
Haverkos BM. Blood 2017.
Abdel-Wahab. JITC 2019.

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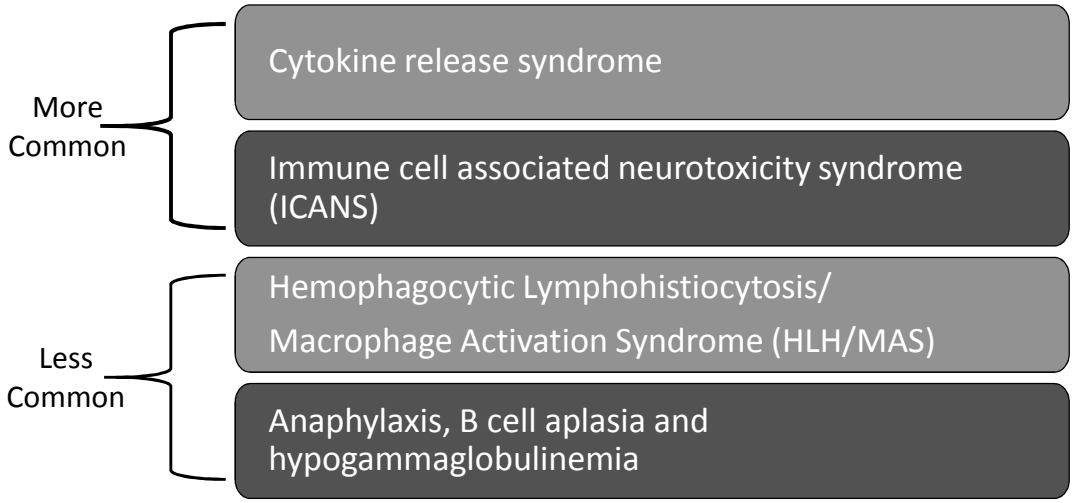
CAR T-cell related toxicities



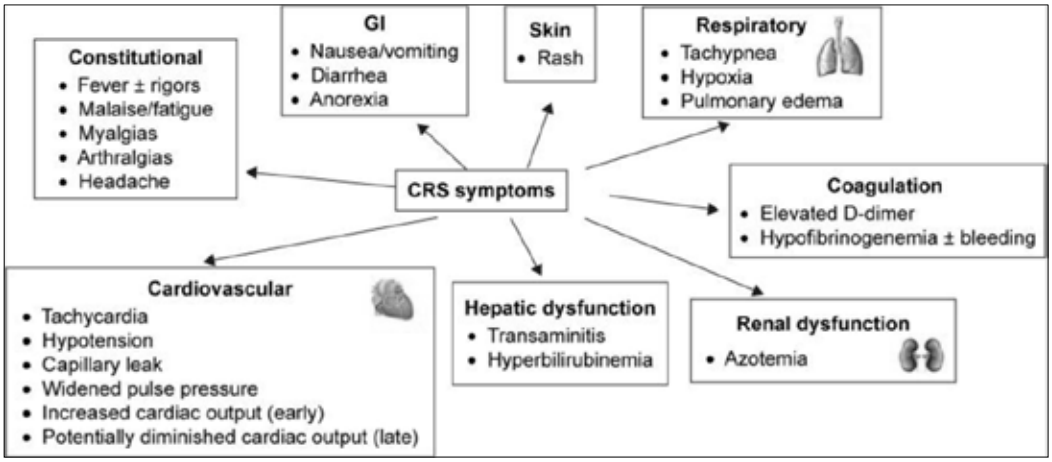
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

CRS and Neurotoxicity

- Should not be viewed as two unrelated adverse events
  - Overlapping toxicities from excessive immune activation
  - May occur together or exclusive of one another
  - However, they do have distinct timing and responses to treatment
- Risk factors for both include:
  - High disease burden
  - Higher infused CAR-T cell dose
  - High intensity lymphodepletion regimen
  - Pre-existing endothelial activation
  - Severe thrombocytopenia

Santomasso BD. Cancer Discov 2018.
Wang Z. Biomark Res. 2018.

Cytokine release syndrome



Riegler LL. Ther Clin Risk Manag 2019.

Cytokine release syndrome

- Occurs in ~70% of patients; severe = 12-47%
  - Median onset 2-3 days after infusion, typical duration 7-8 days
- Multiple grading systems exist (MSKCC, CarTox, ASTCT)
  - Hypotension and hypoxia are main drivers of CRS severity
- Tocilizumab approved for CRS treatment (blocks IL-6R)
  - Dose for patients >30 kg: 8 mg/kg (up to 800 mg/dose)
  - May be repeated every 8 hours up to 4 doses
- Consider adding dexamethasone 10 mg q6h for grade 3-4 CRS and/or refractory to tocilizumab

Lee DW. BBMT 2019.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

Neurotoxicity

- Also called CAR-T Related Encephalopathy Syndrome (CRES) or iIEC-associated neurologic syndrome (ICANS)
- Occurs in 20-64% of patients, ≥ grade 3 in 11-42%
  - Onset 4-5 days after infusion, typical duration 5-12 days
- Common symptoms include encephalopathy, headache, delirium, anxiety, tremor, aphasia
  - Severe neurotoxicity: seizures, cerebral edema, hemi/paraparesis
- Diagnosis usually based on clinical symptoms
  - MRI/CT often negative although ~30% will have abnormal MRI (poorer outcome)
- Also has multiple grading systems which guide treatment
  - Usually includes early use of high-dose steroids (dexamethasone 10 mg IV q6h)

Wang Z. Biomark Res. 2018.
Hunter BD. J Natl Cancer Inst. 2019.

HLH/MAS

- Inflammatory syndrome caused by hyperactivation of macrophages and lymphocytes
- Rare; frequency reported to be as low as ~1%
- Should be managed with anti-IL-6 and corticosteroid therapy
- If no improvement after 48 hours, consider adding etoposide for additional immunosuppression
  - Dose: 75-100 mg/m^2
  - May be repeated after 4-7 days

Box 5 | Diagnostic criteria for CAR-T-cell-related HLH/MAS

A patient might have HLH/MAS if he/she had a peak serum ferritin level of >10,000 ng/ml during the cytokine-release syndrome phase of CAR-T-cell therapy (typically the first 5 days after cell infusion) and subsequently developed any two of the following:

- Grade ≥3 increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels*
- Grade ≥3 oliguria or increase in serum creatinine levels*
- Grade ≥3 pulmonary oedema*
- Presence of haemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry

Titov A. Cell Death Dis. 2018.
Neelapu SS. Nat Rev Clin Oncol. 2018.

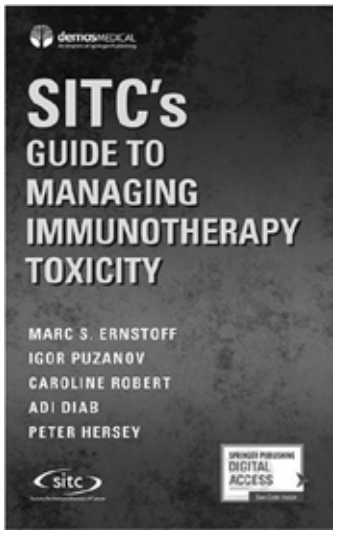
The importance of patient education

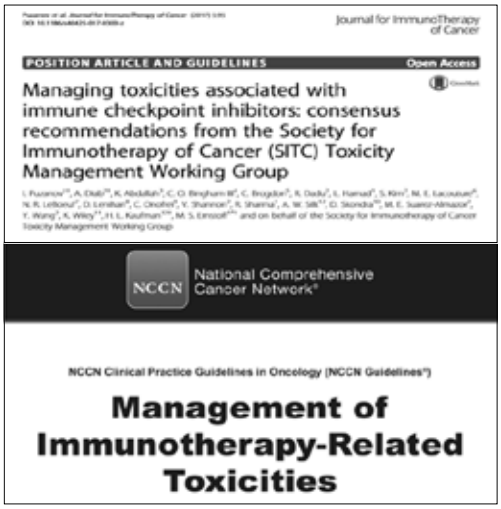
- Many immune-related adverse events can present in similar ways to other disease states, but the treatment of them is very different.
- Patients may not go back to their oncologist for treatment of irAEs and need to identify themselves as immunotherapy recipients
  - Emergency room & general practitioners need to understand the proper identification and management of irAEs
- Reassure patients that irAEs will likely resolve over time (except endocrinopathies)

Education along the healthcare continuum

- Patients may not go back to their original clinic for adverse event management
- Emergency departments and primary care physicians need to recognize and know how to manage irAEs
- For example, the most common irAE in emergency departments is diarrhea – recognize immune-related symptoms versus other causes

Additional Resources





Case Study 1

- Mr. L is a 71 y.o. male with Stage IV melanoma with widely metastatic disease, including CNS metastases
- Received 2 doses of combination ipilimumab and nivolumab
- Presented with abdominal pain of unclear etiology; CT scan shows clear disease regression. Ipi/nivo held
- 10 days later, he developed recurrent abdominal pain, nausea, vomiting and loose stools

Case Study 1

- What would be your plan?

A. Admit the patient for supportive care and further GI workup

B. Hydrate the patient and send him home with VNA and antiemetics/antidiarrheals with clinic visit in 3 days

C. Set up a GI consult and start steroids

D. Administer a 3rd dose of ipilimumab/nivolumab after IV hydration and antiemetics

Case Study 1

- He was admitted and underwent CT showing small bowel enteritis
- Began IV solumedrol
- Had EGD c/w enteritis clinically with biopsy confirmation
- GI symptoms and pain improved; he was DC'ed to home with IV solumedrol
- Transitioned to oral prednisone 100 mg (2 mg/kg) one week later with continued improvement
- Prednisone tapered to 80 mg daily after one week
- Reported recurrent diarrhea with urgency and incontinence

Case Study 1

- What would be your next management step?
  - A. Set up an infliximab infusion, continue antidiarrheals
  - B. Admit the patient, restart IV fluids, resume IV steroids, obtain GI consult for infliximab
  - C. Continue the steroid taper and BRAT diet while giving antidiarrheals
  - D. Set up outpatient IV fluids, IV steroids and GI consult

Case Study 1

- He was admitted for IV hydration and IV solumedrol with improvement
- GI consult done with recommendation for infliximab
- DC'ed to home with PICC line in place
- Received one dose of infliximab as outpatient 6 days later
- Transitioned to oral steroids 2 weeks later
- Slow taper of oral prednisone which he tolerated well
- Serial torso CT's show stable regressed melanoma, including brain

Case Study 2

- Ms. S. is a 76 y.o. female with Stage IIIC melanoma of the RLE
- She started pembrolizumab when her disease was deemed unresectable
- Increased SQ nodules noted along RLE c/w disease progression after 5 cycles of pembro
- TVEC (modified herpes virus given by intra-tumoral injection) added
- PET shows FDG avid lung nodules – biopsy done c/w sarcoid felt r/t immunotherapy
- Evidence of disease regression on RLE with decreased size of nodules and no new sites of disease
- 13 months into pembro, noted to have grade 2 transaminitis (ALT 121, AST 92)
- What would be your approach?

Case Study 2

- A. Continue immunotherapy and ask her to call with new GI symptoms
- B. Hold pembrolizumab and refer to hepatology
- C. Assess for symptoms of hepatitis, review meds for hepatotoxins, ask about ETOH use, hold pembrolizumab
- D. Continue immunotherapy and have labs repeated in one week

Virginia Seery, MSN, RN, ANP-BC – *Beth Israel Deaconess Medical Center*

Case Study 2

- Assess for symptoms of hepatitis – she had no N/V, anorexia, RUQ pain
- Look for other hepatotoxic agents – atorvastatin held, acetaminophen and alcohol reduced
- Pembrolizumab held
- TVEC continued
- Returned 3 weeks later – transaminases down to grade 1
- Pembro restarted
- 3 weeks later, transaminases back to grade 2 (ALT 150, AST 113, Tbili 0.4)
- What would your approach be here?

Case Study 2

- A. Continue pembrolizumab and watch LFT's closely
- B. Hold pembrolizumab and watch LFT's closely
- C. Continue pembrolizumab, refer to hepatology
- D. Permanently discontinue pembrolizumab

Case Study 2

- Pembro held
- Repeat labs showed grade 3 LFT's (ALT 208, AST 170, Tbili 0.6)
- Remains asymptomatic
- Management?
  - A. Continue pembrolizumab, hold hepatotoxins and avoid ETOH, hepatology consult
  - B. Hold pembrolizumab and check LFT's weekly
  - C. Hold pembrolizumab and obtain hepatology consult
  - D. Continue pembrolizumab and check LFT's weekly

Case Study 2

- Pembro held
- Hepatitis screen checked and negative
- Urgent hepatology consult
- LFT's worsening (ALT 357, AST 329, Tbili 0.7)
- Autoimmune markers sent (IgG, IgM, ANA, ASMA, AMA) – ANA positive
- Liver MRI shows fibrosis
- Liver biopsy done showing plasma cell predominant hepatitis and significant necrosis c/w moderate to severe autoimmune hepatitis
- Remains asymptomatic

Virginia Seery, MSN, RN, ANP-BC – *Beth Israel Deaconess Medical Center*

Case Study 2

- How would you manage this patient?
  - A. Begin prednisone 1-2 mg/kg/day, monitor LFT's every 2 days, close hepatology follow up, consider permanent discontinuation of pembro
  - B. Begin prednisone 0.5 mg/kg/day to start, monitor LFT's every 3 days, close hepatology follow up, consider permanent discontinuation of pembro
  - C. Admit to the hospital, begin IV methylprednisolone, daily LFT's, inpatient hepatology consult
  - D. Begin prednisone 0.5 mg/kg/day, monitor LFT's weekly, restart pembro when LFT's return to grade 1

Case Study 2

- Placed on prednisone 1.5 mg/kg daily
- PPI and PCP prophylaxis started
- LFT's returned to grade 1 within 3 days of starting steroids
- LFT's returned to normal within 3 weeks
- Slow steroid taper over 3-4 months
- Statin restarted
- PET scan shows no evidence of disease and pembro remains on hold

Practical Barriers in Cancer Immunotherapy Treatment

Jennifer Espiritu, PharmD, BCOP
Clinical Pharmacy Specialist, Hematology/Oncology
Beth Israel Deaconess Medical Center

Practical Barriers in Cancer Immunotherapy Treatment

Jennifer Espiritu, PharmD, BCOP – *Beth Israel Deaconess Medical Center*

Audience Response Questions

1. Which of the following is TRUE regarding off-label use of a drug:
   A. You can prescribe any drug without prior authorization
   B. Generally there is a strict process that one must go through to get an off-label drug approved
   C. Medicare does not require prior authorization so off-label use is simpler
   D. All of the above

2. Biosimilars are:
   A. Approved in every disease setting
   B. Reimbursed at the same rate as the reference product
   C. Used at every institution
   D. Highly similar to the reference product, but are not identical

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

Jennifer Espiritu, PharmD, BCOP
Clinical Pharmacy Specialist
Beth Israel Deaconess Medical Center

Disclosures

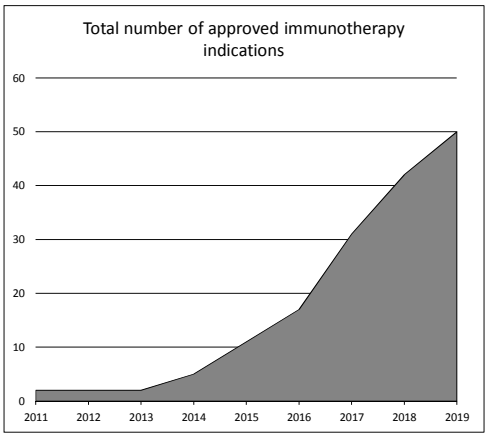
- I have no conflicts to disclose
- I will be discussing non-FDA approved indications during my presentation.

Practical Barriers in Cancer Immunotherapy Treatment

Jennifer Espiritu, PharmD, BCOP – *Beth Israel Deaconess Medical Center*

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 few 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



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 practitioner or pharmacist)
- 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 (or attend programs like this!)

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Manage Reimbursement/Finances

- New-to-market I-O agents may not yet have specific J-Code
  - Ensure a 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

Practical Barriers in Cancer Immunotherapy Treatment

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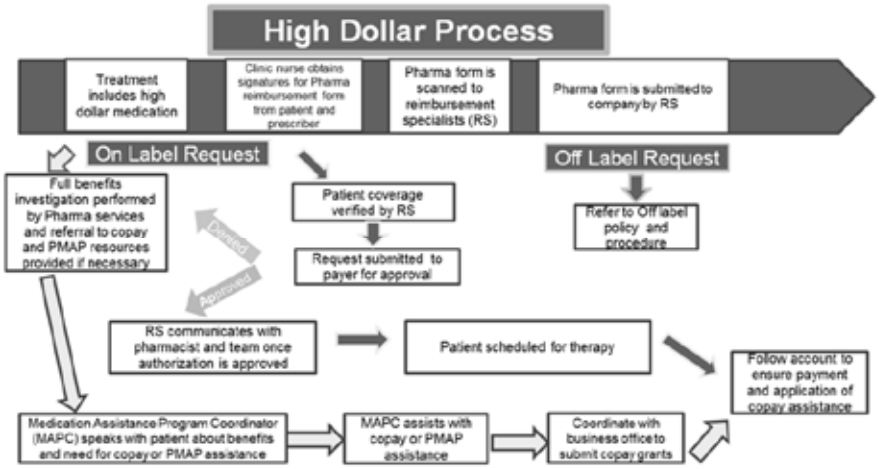

Medicare

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

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Off-label medication process: *Medicare pre-treatment*

1. Before off-label use is considered, a **risk/benefit conversation** (medical, financial risks) needs to occur with the patient
2. If patient and treating physician wish to proceed, pharmacist and reimbursement specialist work together to gather **sufficient evidence** for off-label use
3. Medication assistance coordinator, reimbursement specialist, and clinical team **determine payment options**
   - Manufacturer assistance/replacement options
   - Medicare payment
4. Patient and the team decide **whether to proceed** with off-label use

Off-label medication process

5. After the patient receives off-label therapy, the **claim is submitted** to Medicare
6. If the claim is not immediately approved, up to **5 levels of appeals** are allowed
7. If claim is ultimately denied, financial counselors arrange for **payment** of the Medicare allowed amount

Practical Barriers in Cancer Immunotherapy Treatment

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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

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Commercial Payers

- Disproportionate approvals of total billing units versus doses for a specific period of time
  - Example: Authorization for 90 mg 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 institutions)
  - Proper documentation necessary in the medical record for discarded waste
    - Mandated wastage rationale for any JW lines on Medicare claims on January 1, 2017

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Off-label medication process: *Commercial payers*

1. Before off-label use is considered, a **risk/benefit conversation** (medical, financial risks) needs to occur with the patient.
2. Pharmacist and reimbursement specialist work together to submit **pre-determination request** to payer.
3. If denied, an **appeal** can be filed.
4. If still denied, if there is sufficient evidence for off-label use, reimbursement specialist and medication assistance coordinator **explore payment options.**

Off-label medication process: *Commercial payers*

5. Patient and team decide **whether to proceed** with off-label use
6. Managed care, reimbursement specialist, and CFO determine the appropriate amount for the **patient to deposit** toward the treatment
7. Patient submits deposit and **off-label treatment is given**

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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, local coverage determinations, national coverage determinations (LCDs & NCDs)
  - 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

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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, pharmacist, or pharmacy technician 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”

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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

Practical barriers beyond payment

- IO-related medical emergencies
- Biosimilars
- CAR T treatments

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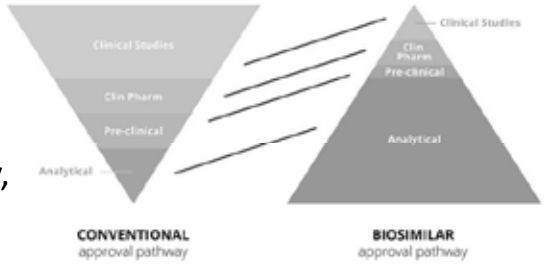
IO Management Strategies

- 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

Biosimilars

- FDA requires biosimilars to be highly similar, but not identical, to reference product
- Has to demonstrate no clinically meaningful differences in efficacy, safety, and potency
- Primarily tested through non-clinical pathways – examining structural and functional nature of the product



Isaacs *et al*, Consid Med 2017.

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Biosimilars approved by the FDA

Cancer-related Biosimilar	Reference Product	Approval Date
Zarxio (filgrastim-sndz)	Neupogen (filgrastim)	March 2015
Mvasi (bevacizumab-awwb)	Avastin (bevacizumab)	September 2017
Ogivri (trastuzumab-dkst)	Herceptin (trastuzumab)	December 2017
Fulphilia (pegfilgrastim-jmdb)	Neulasta (pegfilgrastim)	June 2018
Nivestym (filgrastim-aafi)	Neupogen (filgrastim)	July 2018
Truxima (rituximab-abbs)	Rituxan (rituximab)	November 2018
Herzuma (trastuzumab-pkrb)	Herceptin (trastuzumab)	December 2018
Ontruzant (trastuzumab-qyyp)	Herceptin (trastuzumab)	March 2019
Kanjinti (trastuzumab-anns)	Herceptin (trastuzumab)	June 2019

Biosimilar	Reference Product	Approval Date
Inflectra (infliximab-dyyb)	Remicade (infliximab)	April 2016
Erelzi (etanercept-szzs)	Enbrel (etanercept)	August 2016
Amjevita (adalimumab-atto)	Humira (adalimumab)	September 2016
Renflexis (infliximab-abda)	Remicade (infliximab)	May 2017
Cyltezo (adalimumab-adbm)	Humira (adalimumab)	August 2017
Ixifi (infliximab-qbtx)	Remicade (infliximab)	December 2017
Retacrit (epoetin alfa-epbx)	Procrit (epoetin alfa)	May 2018
Hyrimoz (adalimumab-adaz)	Humira (adalimumab)	October 2018
Udenyca (pegfilgrastim-cbqv)	Neulasta (pegfilgrastim)	November 2018
Eticovo (etanercept-ykro)	Enbrel (etanercept)	April 2019

Biosimilars – practical considerations

- Healthcare providers, pharmacists, and patients are critical for biosimilar acceptance and usage
- Substitution policies vary by state – “interchangeable products” can be substituted without prescriber input
- Incentives to prescribe biosimilars from Medicare

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Unique considerations for CAR T therapies

- Large up-front cost instead of smaller costs over time
- Potential side effects can lead to large costs as well
- Medicare coverage:
  - National coverage determination in August 2019
  - Will be covered by Medicare if administered in health care facilities that follow FDA REMS (risk evaluation and mitigation strategies)
  - May be covered for off-label indications

BIDMC Local Practices

Immuno-Oncology Champions
- BIDMC Immunotherapy Institute
- Immuno-Oncology Toxicity Clinic

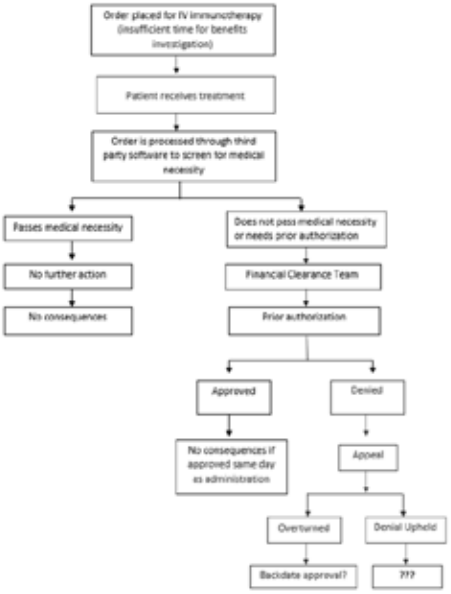
Financial clearance process
- Third party vendor
- IT programming
- Financial clearance team
- Clinicians (MDs, NPs, nurses, pharmacists)

Practical Barriers in Cancer Immunotherapy Treatment

Jennifer Espiritu, PharmD, BCOP – *Beth Israel Deaconess Medical Center*

BIDMC Local Practices

BIDMC Local Practices



Jennifer Espiritu, PharmD, BCOP – *Beth Israel Deaconess Medical Center*

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 checkpoint inhibitors in combination with a host of agents (e.g., chemo, targeted, immunotherapeutic)
- Potential for coverage policies to be biomarker driven (e.g., PD-L1 overexpression)
- Financial implications of agents becoming first line
- Emergence of biosimilars and CAR T treatments

Practical Barriers in Cancer Immunotherapy Treatment

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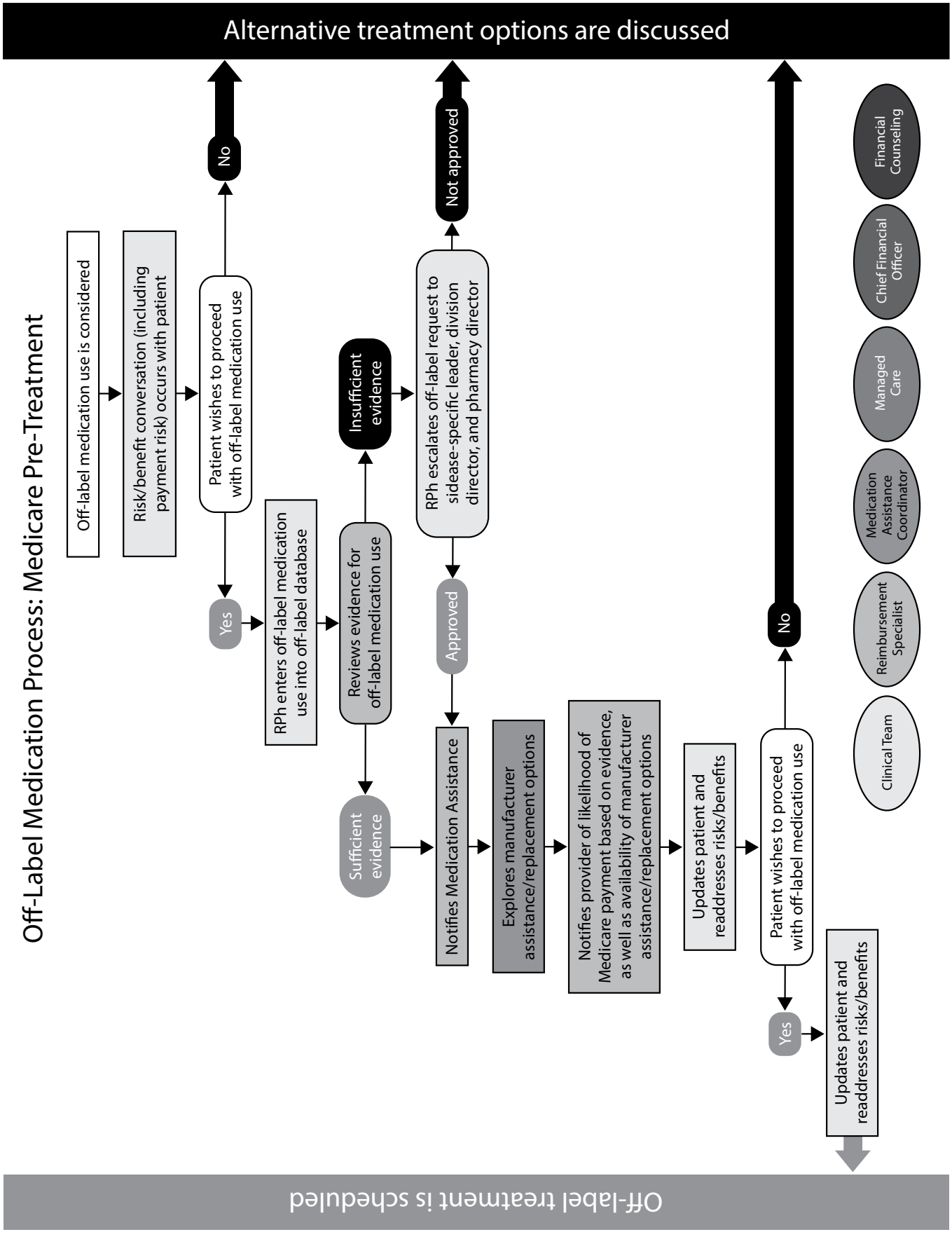

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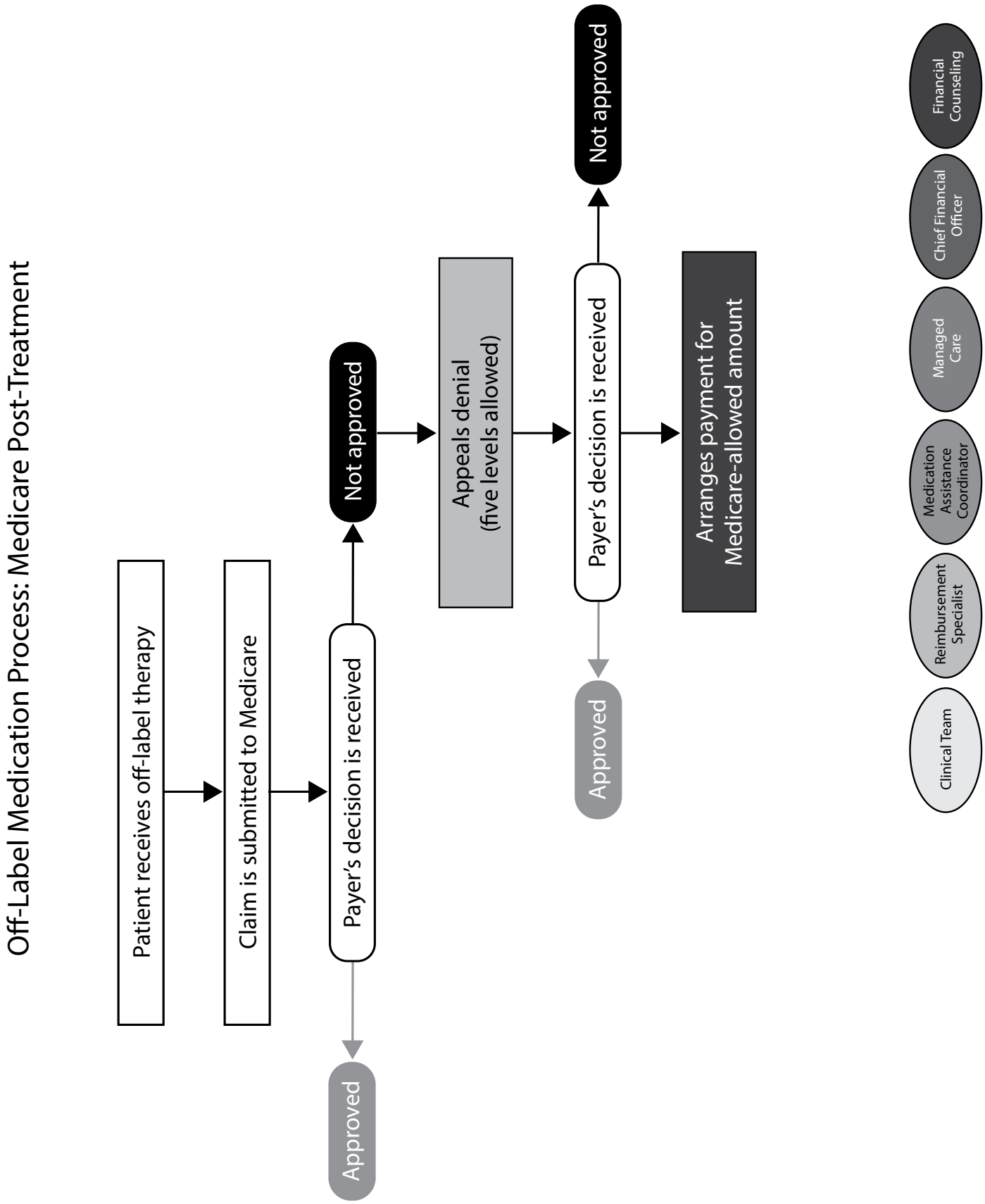

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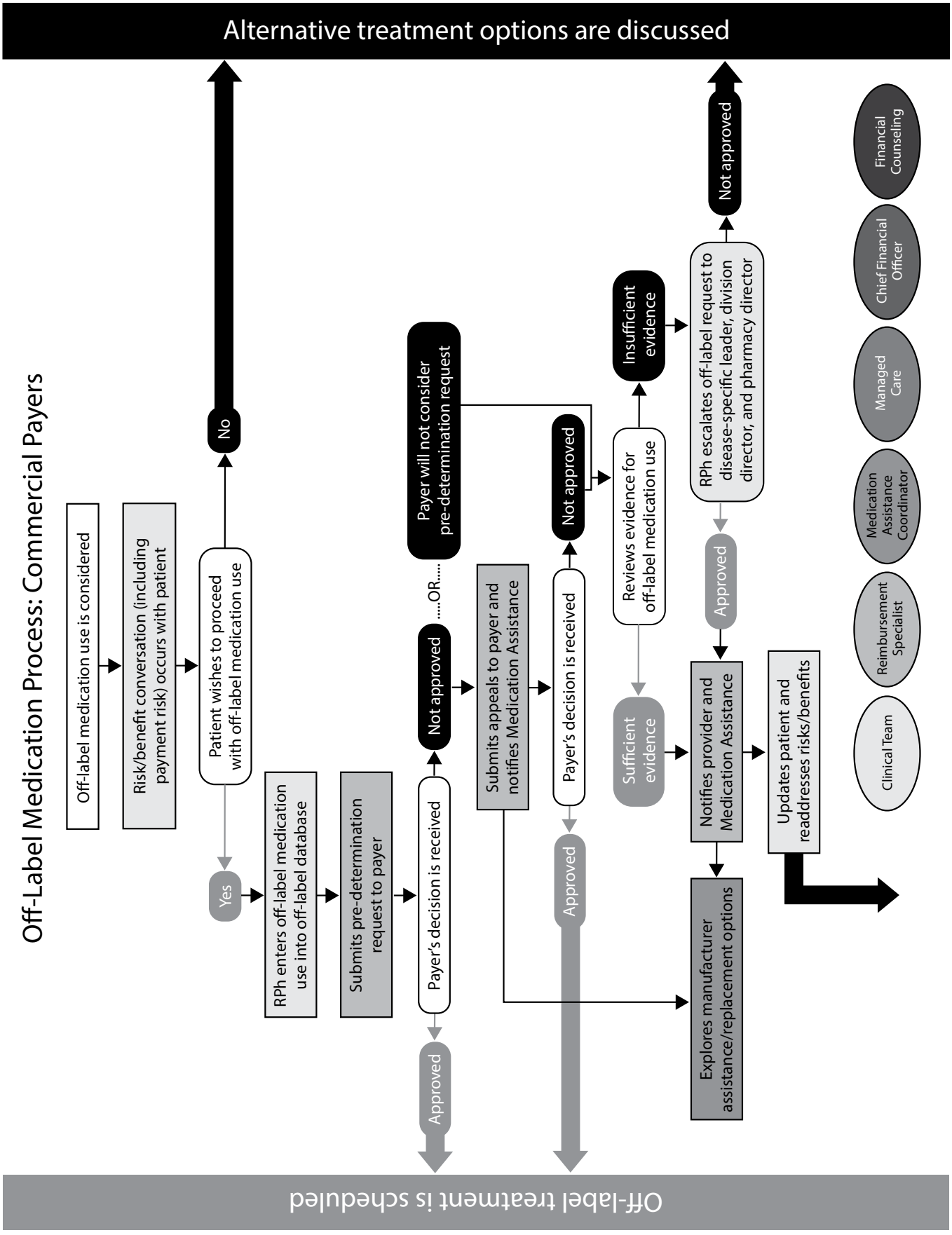

Practical Barriers in Cancer Immunotherapy Treatment

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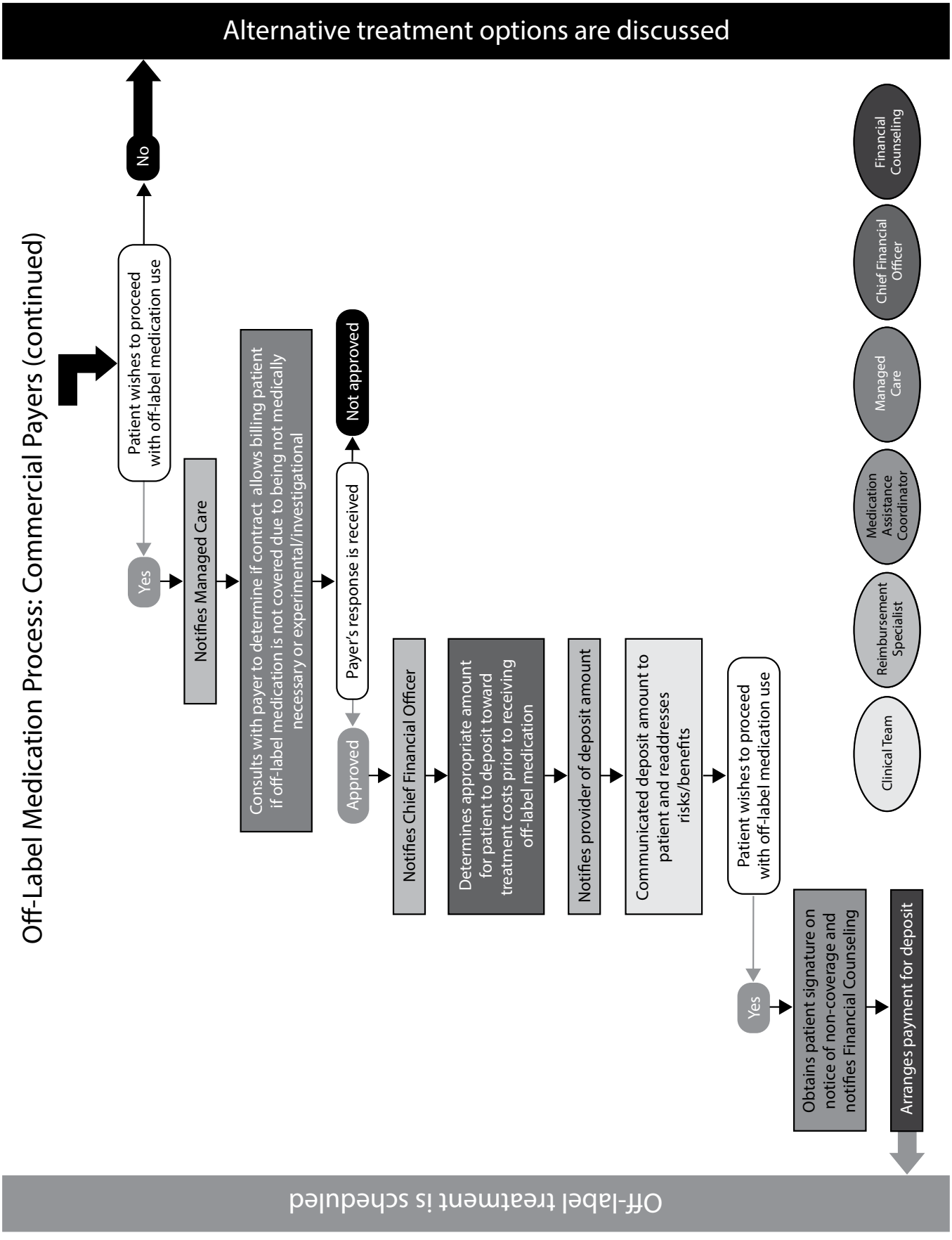


Non-CE Speaker

What's Next for Cancer Immunotherapy?

Howard L. Kaufman, MD, FACS
Chief Medical Officer
Replimune Group Inc.

(slides to be provided separately)

Dr. Howard L. Kaufman has been a leading authority on tumor immunotherapy for the treatment of melanoma. He led the first successful phase III trial of an oncolytic herpes virus in patients with melanoma resulting in the first FDA approval of an oncolytic virus. He also completed a clinical trial demonstrating therapeutic responses of a new PD-L1-directed monoclonal antibody in patients with Merkel cell carcinoma. Dr. Kaufman has maintained a funded laboratory in tumor immunology for nearly 20 years. He was born in Chicago, Illinois and received his MD degree from Loyola University, completed a residency in General Surgery at Boston University and fellowship training in Tumor Immunology and Surgical Oncology at the National Cancer Institute. He has previously held appointments as Chief, Division of Surgical Oncology and Associate Director, Herbert Irving Comprehensive Cancer Center, Columbia University and Director, Rush University Cancer Center. Dr. Kaufman has published over 500 peer-reviewed scientific papers, books, review articles and abstracts. He is a member of numerous professional societies and served as President of the Society for Immunotherapy of Cancer. He received the Daland Prize, MRF Humanitarian Award and UIC Distinguished Alumnus Award. He has served on the Board of Directors for several professional organizations, including the Melanoma Research Foundation, Melanoma Research Alliance, Commission on Cancer, American Cancer Society-Eastern Division and the University of Illinois Chicago College of Liberal Arts and Sciences. In 2017, he became the Chief Medical Officer at Replimune, Inc. focusing on oncolytic immunotherapy and also has an academic appointment at Massachusetts General Hospital.

Take-Home Points

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

Clinical Applications of Cancer Immunotherapy

SKIN CANCERS

- Many immunotherapies for skin cancer have been granted FDA approval and should be considered significant elements of the standard of care
- 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
- Avelumab (anti-PD-L1) and pembrolizumab are approved for some Merkel cell carcinoma patients.
- Patient disease state and characteristics will dictate appropriate therapeutic selection.

LUNG CANCER

- Patient disease stage and 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 options for 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
- Atezolizumab combined with chemotherapy is approved for 1st line treatment of small cell lung cancer, while nivolumab and pembrolizumab therapies can be used in later treatment lines.

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, avelumab, and durvalumabare approved for platinum-resistant metastatic bladder cancer
- Atezolizumab (anti-PD-L1) and pembrolizumab are effective in patients with PD-L1-positive bladder carcinoma, whether platinum-resistant or ineligible
- First-line combination nivolumab + ipilimumab, pembrolizumab + axitinib, and avelumab + axitinib should be considered options for 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, and pembrolizumab is also approved for PMBCL
- CAR T therapies axicabtagene ciloleucel and tisagenlecleucel are approved for the treatment of patients with relapsed DLBCL, and Tisagenlecleucel is also approved for the treatment of patients (≤ 25 years of age) with relapsed B-ALL
- Blinatumomab is approved for Philadelphia-chromosome positive ALL patients, as well as patients who have MRD+ ALL who have not progressed after previous therapy
- Several antibody-drug conjugates are approved for patients with hematologic malignancies
- 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
- Pembrolizumab monotherapy (PD-L1 CPS ≥ 1) and pembrolizumab + chemotherapy (all patients) are options for first-line treatment of recurrent/metastatic HNSCC
- Cemiplimab is approved for metastatic cutaneous squamous cell carcinoma originating at any site
- Combination treatments are being explored in HNSCC

BREAST AND GYNECOLOGIC CANCERS

- Immunotherapy treatments are beginning to play a role in breast and gynecological cancers
- Atezolizumab + paclitaxel is approved for advanced/metastatic triple-negative breast cancer with PD-L1 ≥ 1%
- Pembrolizumab monotherapy is approved for recurrent/metastatic cervical cancer after progression on previous therapy with PD-L1 CPS ≥ 1

Take-Home Points

HEPATOCELLULAR CARCINOMA

- Hepatocellular carcinoma patients with previous sorafenib treatment are eligible for monotherapy with either nivolumab or pembrolizumab
- Breakthrough therapy designation has been granted to atezolizumab + bevacizumab in first-line advanced/metastatic HCC

MSI-HIGH/dMMR CANCERS

- In the first tissue-agnostic approval, pembrolizumab is approved for adult/pediatric patients with MSI-H or dMMR solid tumors after progression on other treatment
- Specifically in MSI-H/dMMR colorectal cancer, nivolumab monotherapy or combination ipilimumab + nivolumab are approved for patients after progression on chemotherapy
- Other tissue-agnostic biomarkers are being explored, including the microbiome, POLE mutation, and mutational signatures beyond TMB

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, pre-determinations 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
- Emergence of new treatment options including biosimilars and adoptive cellular therapies may warrant new clinical infrastructure considerations

Part B — Immune-Related Adverse Event (irAE) Management

MECHANISMS

- The major function of the CTLA-4 and PD-1/PD-L1 immune checkpoints is to prevent occurrence of autoimmune reactions
- 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
- Adverse events caused by immunotherapies have distinct, underlying causation that is different than chemo/radiotherapies

GENERAL CONSIDERATIONS

- Adoptive cellular therapies come with the possibility of severe side effects including cytokine release syndrome and neurotoxicity
- 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 (T reg) 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.

Glossary of Terms

- 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.
- 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.
- Oncolytic 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.

SITC Resources

Cancer Immunotherapy Guidelines

The Society for Immunotherapy of Cancer (SITC) Cancer Immunotherapy Guidelines are a collection of consensus-based clinical recommendations developed to provide guidance on the use of immunotherapy to treat specific types of cancer and associated toxicities. These guidelines are an essential resource for the oncology healthcare community regarding patient selection, use of biomarkers, treatment scheduling, combination therapies, toxicity management, and clinical endpoints for U.S. Food and Drug Administration (FDA)-approved immunotherapies.

SITC Cancer Immunotherapy Guidelines are currently available for the following disease states:

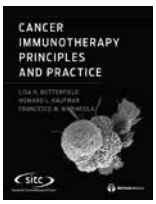
- Bladder Carcinoma
- Cutaneous Melanoma
- Head and Neck Cancers
- Hematologic Malignancies
- Non-small Cell Lung Cancer
- Prostate Cancer
- Renal Cell Carcinoma

New guidelines are in development for the following disease states and topics: Acute Leukemia, Immune Checkpoint Inhibitor & Cytokine-related Adverse Events, Immune Effector Cell-related Adverse Events, Lymphoma, and Multiple Myeloma.

As a companion piece, easy-to-access Pocket Guides are available which contain key guideline points, treatment recommendations, and algorithms. SITC also offers free live webinars based on the Cancer Immunotherapy Guidelines that take place soon after the publication of each new manuscript. Following the live webinar, materials are archived on the SITC website and available on-demand free of charge.

Visit sitcancer.org/guidelines to learn more.

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 covers every major topic that has shaped immunotherapy development and propelled it to the forefront of cancer treatment innovation. A second edition is currently under development.

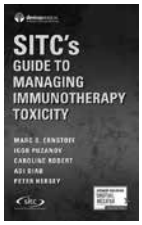
For more information on the textbook, please visit: www.sitcancer.org/CIPPtextbook

SITC Toxicity Management Consensus Recommendations

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, along with other critical information.

For free, open-access to the manuscript, please visit: https://jitc.biomedcentral.com.

SITC's Guide to Managing Immunotherapy Toxicity



In March 2019, SITC published "SITC's Guide to Managing Immunotherapy Toxicity," a handbook designed to provide clinical oncologists, emergency physicians, hospitalists, and other medical practitioners further insight into specific immune-related toxicities and their management. Part I of the handbook offers overviews of immune checkpoint inhibitors in the clinic and approved immunotherapeutic combinations. It also covers mechanisms of action, indications, and toxicities exhibited in patients combating early, advanced, and metastatic stages of cancer. Part II is organized by the impact of toxicities on major organ sites. Beginning with general principles of immune-related toxicity management, subsequent chapters focus on a number of specific toxicities. Each chapter offers guidance on toxicity assessment and treatment, along with how to support the patient through acute and chronic effects. This handbook also contains a discussion on special patient population management, fatigue management, and cost effectiveness.

For more information on the handbook, please visit: https://www.sitcancer.org/toxicitybook.

Notes

Notes

Notes

American Academy of Emergency Medicine

CHAMPION OF THE EMERGENCY PHYSICIAN

Today's emergency physician has a lot to navigate.
That's why AAEM is in your corner providing advocacy and education.

A Strong Voice

Your concerns reach the ears of our leaders in Washington. AAEM actively works to ensure the needs of EPs are being addressed on the national and state levels. We offer support & legal assistance to members whose rights are threatened. The strength of the Academy is in your corner.

Effective Advocacy

For over 20 years we have been committed to your personal and professional well being. Our primary concern is supporting you: your practice rights, your autonomy, your relationship with your patients. That's the AAEM difference.

Why I Joined

Hear from fellow EPs why they chose to become a member and how AAEM is addressing APP independent practice.

Top Tier Education

In addition to the Annual Scientific Assembly, AAEM offers educational opportunities online and in-person at our Oral Board Review, Written Board Review, and ED Management Solutions courses, as well as other regional courses and meetings.

Meaningful Connections

AAEM is over 8,000 members strong and growing. We offer multiple ways for you to get involved with the topics that matter most to you through engaging committees & projects plus multiple ways to network with fellow members in the U.S. and around the globe.

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ASSOCIATION OF COMMUNITY CANCER CENTERS

IMMUNO-ONCOLOGY INSTITUTE

As immunotherapy for cancer continues to evolve, ACCC adapts to meet the changing needs of the oncology community.

The ACCC Immuno-Oncology Institute is the only initiative dedicated to educating multidisciplinary teams to go beyond a clinical understanding of IO and tackle real-world implementation issues.

With the care of patients on immunotherapies now extending beyond the cancer team, the ACCC Immuno-Oncology Institute is at the forefront of developing critical education to empower healthcare professionals across care delivery settings.

Access resources at the intersection of science, business, operations, and policy to support all facets of immunotherapy integration at

accc-cancer.org/immunotherapy

The **Association of Community Cancer Centers (ACCC)** is the leading education and advocacy organization for the multidisciplinary cancer team. ACCC is a powerful network of 24,000 cancer care professionals from 2,100 hospitals and practices nationwide. ACCC is recognized as the premier provider of resources for the entire oncology care team. For more information, visit accc-cancer.org or call 301.984.9496. Follow us on Facebook, Twitter, and LinkedIn, and read our blog, ACCCBuzz.

The **ACCC Immuno-Oncology Institute** is the leader in optimizing the delivery of cancer immunotherapies for patients by providing clinical education, advocacy, research, and practice management solutions for cancer care teams across all healthcare settings.

Association of Community Cancer Centers

The ACCC Immuno-Oncology Institute is supported by Bristol-Myers Squibb (charitable donation) and Merck & Co, Inc. (educational grant).

Society for Immunotherapy of Cancer

Do your patients still have questions about cancer immunotherapy?

Whether your patients are battling cancer or you are helping dedicated caregivers, information is critical to a successful treatment plan

The Society for Immunotherapy of Cancer's (SITC) free online patient course, *Understanding Cancer Immunotherapy* provides resources and basic education about cancer and immunotherapy for patients and caregivers. The course's interactive modules offer easy-to-understand information about immunotherapy as a cancer treatment option by covering the following areas:

- Treatment options and care providers
- Education on cancer and the immune system
- Types of cancer immunotherapy treatments
- The importance of reporting side effects
- Links to other helpful patient and caregiver resources

To access this self-guided course for your patients, please visit **sitcancer.org/PatientCourse**

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SITC Cancer Immunotherapy connectED

The Society for Immunotherapy of Cancer's (SITC) free go-to source for cancer immunotherapy education

SITC connectED is for clinicians

- Access more than 75 educational activities including online classes, videos and webinars from world-renowned leaders in the field of cancer immunotherapy
- Earn CME, CNE or CPE credits through online activities about treatments for lung cancer, melanoma, genitourinary and gastrointestinal cancers, head and neck cancers and hematologic malignancies

SITC connectED is for researchers

- Review more than 14 years of enduring materials from past SITC meetings and articles from the *Journal for ImmunoTherapy of Cancer* (JITC)
- Monitor the global progress of cancer immunotherapy research

SITC connectED is for patients

- Access the *Patient Resource Guides* and companion online activities
- Learn the basics of immunotherapy for the treatment of a variety of cancers
- Participate in free online classes and webinars

sitcancer.org/connectED

Society for Immunotherapy of Cancer

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sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

2019-2020 *Advances in Cancer Immunotherapy™ Online Education Series*

Continue learning after today's program

As a component of SITC's regional, ACI programs, SITC is pleased to offer free online, CME-, CPE-, CNE- and MOC-certified programs via the society's online learning portal, SITC Cancer Immunotherapy connectED. Included in these programs are:

Advances in Cancer Immunotherapy™ Webinars

Free ACI webinars to learn about new treatment approvals and emerging scientific data relating to clinical applications of cancer immunotherapy

Online Advances in Cancer Immunotherapy™ Courses

These free, accredited, interactive online courses deepen your understanding of cancer immunotherapy and provide updates on FDA approvals in several diseases states and the latest guidelines on how to treat immune-related adverse events. Disease states and topics from today's program, including presentations from concurrent sessions, are offered as online courses

SITC Cancer Immunotherapy Guidelines Webinars

Ask questions as leading experts discuss the most recent immunotherapy treatment standards for specific disease states. sitcancer.org/guidelines

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PIM Postgraduate Institute for Medicine

sitc Society for Immunotherapy of Cancer

AAEM American Academy of Emergency Medicine

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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