



# ADVANCES IN **Cancer** IMMUNOTHERAPY™

A decorative graphic consisting of three concentric circles. The outermost circle is blue, the middle one is green, and the innermost one is yellow. The circles are slightly offset from each other, creating a sense of depth and movement.

## **IMPROVE** Patient Outcomes

Thursday, Jan. 23, 2020 • Charlotte, N.C.  
Omni Charlotte Hotel



Postgraduate Institute  
for Medicine



Society for Immunotherapy of Cancer



CHAMPION OF THE EMERGENCY PHYSICIAN



Association of Community Cancer Centers



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](http://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](http://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.*



Society for Immunotherapy of Cancer





# 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 their communities. Learn more about SITC CONNECT at [www.sitcancer.org/aboutconnect](http://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 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](http://www.sitcancer.org/acionline).

- **Clinical Updates from SITC 2019 Webinar**  
**Tuesday, February 4, 2020**  
2 – 3 p.m. ET  
Sanjiv S. Agarwala, MD – Temple University  
Igor Puzanov, MD, MSCI, FACP – Roswell Park Comprehensive Cancer Center  
Anil Shanker, PhD – Meharry Medical College

- **Clinical Updates from ESMO Congress 2019 Webinar**  
**Friday, February 28, 2020**  
1 – 2 p.m. ET  
Hossein Borghaei, MD – Fox Chase Cancer Center  
Amanda Kirane, MD – UC Davis Comprehensive Cancer Center  
Brian Rini, MD – Vanderbilt University Medical Center

## Faculty Presentation Slides

As an added benefit of program attendance, all registered attendees of this Advances in Cancer Immunotherapy™ program will receive FREE access to faculty presentations as permitted by presenters. Approximately 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](http://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](http://www.sitcancer.org/acionline).



# Program Details

## Intended Audience

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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

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Activity fees are available at: <http://www.sitcancer.org/education/aci/registration>

## Educational Objectives

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*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

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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

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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

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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

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The Postgraduate Institute for Medicine designates this live activity for a maximum of 4.0 *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

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Postgraduate Institute for Medicine designates this continuing education activity for 4.0 contact hour(s) (0.4 CEUs) of the Accreditation Council for Pharmacy Education.

## Universal Activity Numbers:

JA4008162-9999-20-847-L01-P (For 2020 programs)

Type of Activity: Application

## Continuing Nursing Education

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The maximum number of hours awarded for this Continuing Nursing Education activity is 4.0 contact hours. Designated for 1.7 contact hours of pharmacotherapy credit for Advanced Practice Registered Nurses.

*California Board of Registered Nurses*

Provider approved by the California Board of Registered Nursing, Provider Number 13485, for 4.0 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 4.0 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](mailto: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.

**If you are also claiming ABIM MOC credit, please do NOT complete the paper evaluation and follow the instructions under "Claiming MOC Credit".** Complete the paper evaluation if you are only claiming CME credit, and do NOT need ABIM MOC credit.

**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](mailto: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

If you are looking to claim MOC credit, do NOT complete the paper evaluation. To obtain your MOC credits and complete the online program evaluation, 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 "14490" and hit enter.
4. Click on the activity title, "Advances in Cancer Immunotherapy™ (2020)," when it appears.
5. Choose the date/location option of "Charlotte, NC on 1/23/20."
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](mailto:inquiries@pimed.com) or (303) 799-1930.

# Program Planners and Faculty

## Organizers

Asim Amin, MD, PhD  
*Levine Cancer Institute*

Nilanjan Ghosh, MD, PhD  
*Levine Cancer Institute, Atrium Health*

Marina Kanos, MSN, FNP-C, RN  
*Levine Cancer Institute, Atrium Health*

## 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*

Amber Cipriani, PharmD, BCOP, CPP  
*UNC Healthcare*

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*

Brian I. Rini, MD  
*Cleveland Clinic Cancer Center*

Dan P. Zandberg, MD  
*UPMC Hillman Cancer Center*

## Faculty

Asim Amin, MD, PhD  
*Levine Cancer Institute*

Jennifer L. Atlas, MD  
*Levine Cancer Institute*

Earle F. Burgess, MD  
*Levine Cancer Institute, Atrium Health*

Daniel R. Carrizosa, MD, MS  
*Levine Cancer Institute*

Jessica Davis, PharmD, BCOP, CPP  
*Levine Cancer Institute, Atrium Health*

Nilanjan Ghosh, MD, PhD  
*Levine Cancer Institute, Atrium Health*

Hans Hammers, MD, PhD  
*University of Texas Southwestern*

Kathryn F. Mileham, MD, FACP  
*Levine Cancer Institute, Atrium Health*

April K.S. Salama, MD  
*Duke University*

Antoinette Tan, MD, MHS  
*Levine Cancer Institute, Atrium Health*

## Connect With Us



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Society for  
Immunotherapy  
of Cancer (SITC)

# Program Schedule

Thursday, January 23, 2020

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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**  
Asim Amin, MD, PhD – *Levine Cancer Institute*  
4 – 4:05 p.m.      *Transition time*

## Session II: Immunotherapy in Practice

### Concurrent Sessions

4:05 – 4:40 p.m.	<b>Immunotherapy for the Treatment of Skin Cancers</b> April K.S. Salama, MD – <i>Duke University</i>	<b>Immunotherapy for the Treatment of Lung Cancer</b> Kathryn F. Mileham, MD, FACP – <i>Levine Cancer Institute, Atrium Health</i>
4:40 – 4:45 p.m.	<i>Transition time</i>	

### Concurrent Sessions

4:45 – 5:20 p.m.	<b>Immunotherapy for the Treatment of Head and Neck Cancers</b> Daniel R. Carrizosa, MD, MS – <i>Levine Cancer Institute</i>	<b>Immunotherapy for the Treatment of Genitourinary Malignancies</b> Earle F. Burgess, MD – <i>Levine Cancer Institute, Atrium Health</i>
5:20 – 5:25 p.m.	<i>Transition time</i>	

### Concurrent Sessions

5:25 – 6 p.m.	<b>Immunotherapy for the Treatment of Hematologic Malignancies</b> Nilanjan Ghosh, MD, PhD – <i>Levine Cancer Institute, Atrium Health</i>	<b>Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer</b> Antoinette Tan, MD, MHS – <i>Levine Cancer Institute, Atrium Health</i>
6 – 6:30 p.m.	<i>Meal/Break</i>	

## Session III: Immunotherapy Challenges and Beyond

6:30 – 7:10 p.m.      **Toxicity Management**  
Jennifer L. Atlas, MD – *Levine Cancer Institute*  
7:10 – 7:40 p.m.      **Practical Barriers in Cancer Immunotherapy Treatment**  
Jessica Davis, PharmD, BCOP, CPP – *Levine Cancer Institute, Atrium Health*  
7:40 – 8:15 p.m.      **What's next for cancer immunotherapy?**  
Hans Hammers, MD, PhD – *University of Texas Southwestern*  
8:15 – 8:20 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:

<b>Name of Faculty/Moderator</b>	<b>Reported Financial Relationship</b>
Asim Amin, MD, PhD	Consulting Fees: BMS, Exelixis, Merck, BioArray; Fees for Non-CME/CE Services Received Directly from a Commercial Interest <i>or their Agents</i> : BMS, Exelixis, Novartis, Regeneron, Sanofi, BioArray; Contracted Research: BMS, Merck
Jennifer L. Atlas, MD	No relevant financial relationships to disclose
Earle F. Burgess, MD	Consulting Fees: Bayer, Exelixis, Janssen; Contracted Research: Pfizer; Ownership Interest less than 5%: Exelixis, Gilead
Daniel R. Carrizosa, MD, MS	Contracted Research: Merck, Astra-Zeneca, Pfizer, Aeglea Biotherapeutics, Loxo, GlaxoSmithKline
Jessica Davis, PharmD, BCOP, CPP	Consulting Fees: Array BioPharma; Fees for Non-CME/CE Services Received Directly from a Commercial Interest <i>or their Agents</i> : Exelixis
Nilanjan Ghosh, MD, PhD	Consulting Fees: Celgene, TG Therapeutics, Seattle Genetics, Janssen, Gilead and Pharmacyclics; Fees for Non-CME/CE Services Received Directly from a Commercial Interest <i>or their Agents</i> : Celgene, Seattle Genetics, Janssen, Pharmacyclics, AbbVie, Gilead, Astra Zeneca; Contracted Research: Celgene, TG Therapeutics, Genentech, Forty Seven Inc. and Pharmacyclics
Hans Hammers, MD, PhD	Consulting Fees: ARMO, Lilly, Novartis, Pfizer, Merck, BMS, Corvus, Surface Oncology
Marina Kanos, MSN, FNP-C, RN	Consulting Fees: Exelixis
Kathryn F. Mileham, MD, FACP	Consulting Fees: AstraZeneca, Takeda; Fees for Non-CME/CE Services Received Directly from a Commercial Interest <i>or their Agents</i> : Merck; Contracted Research: Celgene
April K.S. Salama, MD	Contracted Research: BMS, Dynavax, Immunocore, Merck; Consulting Fees: Array BioPharma
Antoinette Tan, MD, MHS	Consulting Fees: Celgene, Genentech; Contracted Research: Genentech, Merck

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:

<b>Name of Planner/Manager</b>	<b>Reported Financial Relationship</b>
Sanjiv S. Agarwala, MD	Consulting Fees: Merck, Sharp & Dohme, BMS
Christian M. Capitini, MD	No relevant financial relationships to disclose
Amber Cipriani, PharmD, BCOP, CPP	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 <i>or their Agents</i> : 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 <i>or their Agents</i> : Novartis; Contracted Research: Merck, BMS
Zihai Li, MD, PhD	Contracted Research: BMS

# Disclosure Information

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

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:

<b><i>Name of Subject Matter Expert</i></b>	<b><i>Reported Financial Relationship</i></b>
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 <i>or their Agents</i> : 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 <i>or their Agents</i> : 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 Ingelheim
Laura Wood, MD, FAAEM	Consulting Fees: Eisai; Fees for Non-CME/CE Services Received Directly from a Commercial Interest <i>or their Agents</i> : 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



## **Asim Amin, MD, PhD**

Asim Amin, MD, PhD, received his medical degree from King Edward Medical College. He earned his PhD in Immunology at the University of California Davis and was involved with development of immunotherapy for cancer using monoclonal antibodies. Dr. Amin completed his internal medicine residency at Providence Hospital and fellowship in hematology/oncology at Georgetown University Hospital.

Prior to joining Atrium Health, Dr. Amin served as a Clinical Associate Professor at the Lombardi Cancer Center at Georgetown University where he led research efforts in renal cell carcinoma and melanoma. Dr. Amin is a Clinical Associate Professor of Medicine at the University of North Carolina Chapel Hill. He is a member of the American Society of Clinical Oncology and the Society for Immunotherapy of Cancer.



## **Nilanjan Ghosh, MD, PhD**

Dr. Nilanjan Ghosh is the Chief of the Lymphoma Division and Associate Director of Clinical Trials at the Levine Cancer Institute, as well as a Clinical Associate Professor of Medicine at the University of North Carolina, Chapel Hill. Dr. Ghosh graduated with a bachelor's in medicine and surgery from K. J. Somaiya Medical College, University of Mumbai in India. He then went on to receive his Doctor of Philosophy, Biochemistry & Molecular Biology, College of Medicine and H. Lee Moffitt Cancer Center, University of South Florida. In 2004 Dr. Ghosh began his residency in internal medicine at Albert Einstein College of Medicine at Long Island Jewish Medical Center and in 2010 he completed his medical oncology and hematology fellowship at Johns Hopkins Kimmel Cancer Center in Baltimore.

## **Marina Kanos, MSN, FNP-C, RN**

Marina Kanos, MSN, FNP-C, RN graduated with her BSBA from the University of South Carolina, her BSN from Queens University of Charlotte and her MSN from Duke University. Ms. Kanos is currently a nurse practitioner at Levine Cancer Institute in the department of solid tumor oncology and is specializing in cutaneous oncology and renal cell carcinoma.



# Basic Principles of Cancer Immunotherapy

**Asim Amin, MD, PhD**  
Director of Immunotherapy  
*Levine Cancer Institute*



Asim Amin, MD, PhD, received his medical degree from King Edward Medical College. He earned his PhD in Immunology at the University of California Davis and was involved with development of immunotherapy for cancer using monoclonal antibodies. Dr. Amin completed his internal medicine residency at Providence Hospital and fellowship in hematology/oncology at Georgetown University Hospital.

Prior to joining Atrium Health, Dr. Amin served as a Clinical Associate Professor at the Lombardi Cancer Center at Georgetown University where he led research efforts in renal cell carcinoma and melanoma. Dr. Amin is a Clinical Associate Professor of Medicine at the University of North Carolina Chapel Hill. He is a member of the American Society of Clinical Oncology and the Society for Immunotherapy of Cancer.

# Basic Principles of Cancer Immunotherapy

Asim Amin, MD, PhD – *Levine Cancer Institute*

## Basic Principles of Cancer Immunotherapy

Asim Amin MD, PhD  
Levine Cancer Institute

## Disclosures

- Speaker Bureau/Advisory Board:  
BMS, Merck, Regeneron, BioArray, Exelixis, Novartis
- Contracted Research:  
BMS, Merck
- I will not be discussing non-FDA approved indications during my presentation.

# Basic Principles of Cancer Immunotherapy

Asim Amin, MD, PhD – Levine Cancer Institute

## Principles of Cancer Immunotherapy

- Generation of the anti-tumor immune response
- Immunotherapy approaches
- Immune escape mechanisms
- Overcoming immune suppression
- Biomarkers – predicting response
- Tumor assessment after immunotherapy
- Optimal duration of therapy?

## 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.

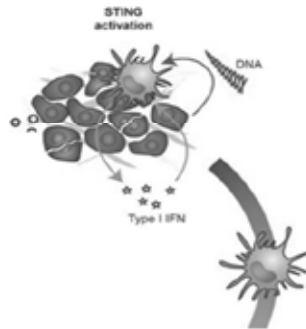
The goal of immunotherapy is to restore the capacity of the immune system to recognize and eliminate cancer.

# Basic Principles of Cancer Immunotherapy

Asim Amin, MD, PhD – Levine Cancer Institute

## Initiation of an anti-tumor immune response

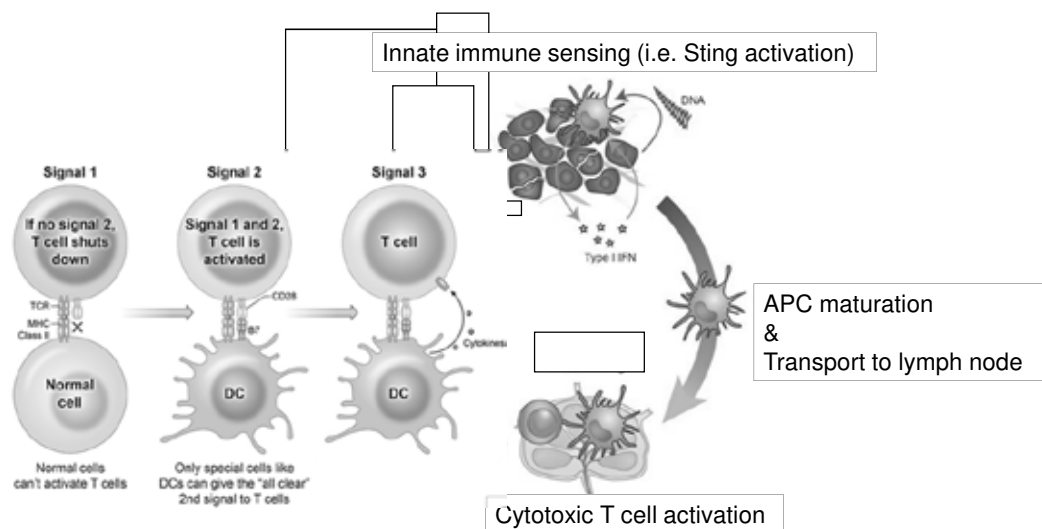
Innate immune sensing (i.e. Sting activation)



APC maturation  
&  
Transport to lymph node

Modified from Corrales et al. Cell Res. 2017

## Initiation of an anti-tumor immune response

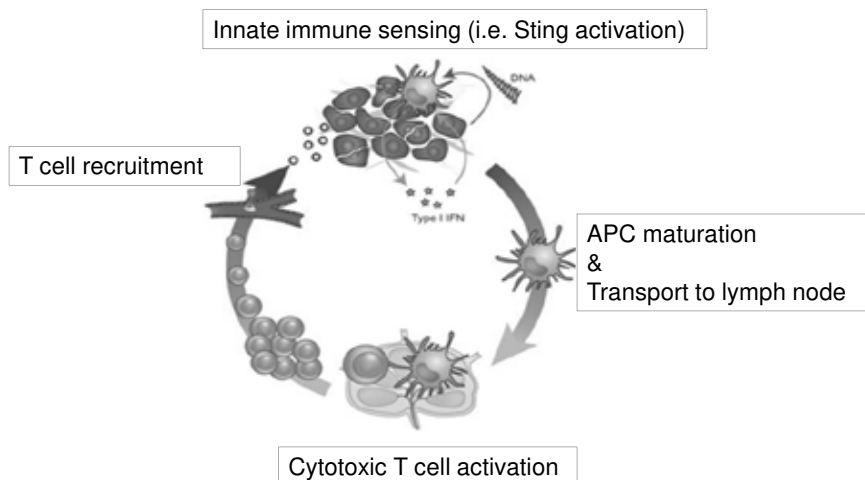


Modified from Corrales et al. Cell Res. 2017

# Basic Principles of Cancer Immunotherapy

Asim Amin, MD, PhD – Levine Cancer Institute

## Initiation of an anti-tumor immune response



Modified from Corrales et al. Cell Res. 2017

## Types of Immunotherapy

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

# Basic Principles of Cancer Immunotherapy

Asim Amin, MD, PhD – Levine Cancer Institute

## The CTLA-4 Checkpoint

### Cytotoxic T-Lymphocyte Associated Protein 4

Up-regulated in response to T cell activation

Limits positive stimulation by competition

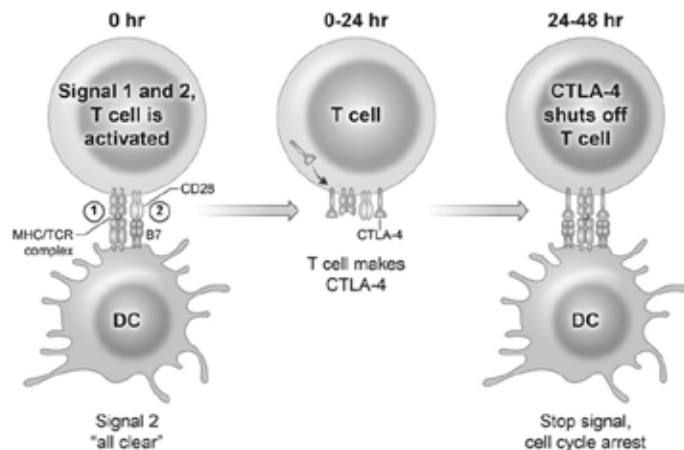


Image courtesy of NCI

## The PD-1/PD-L1 Checkpoint

### Programmed Death 1

Up-regulated in response to T cell activation

Ligands PD-L1 and PD-L2 are up-regulated following inflammation (IFN $\gamma$ )

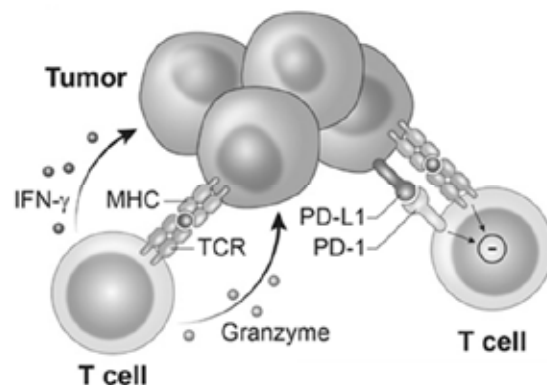
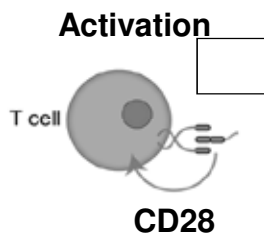


Image courtesy of NCI

# Basic Principles of Cancer Immunotherapy

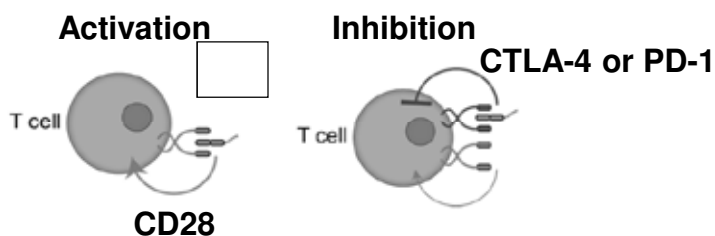
Asim Amin, MD, PhD – Levine Cancer Institute

## 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

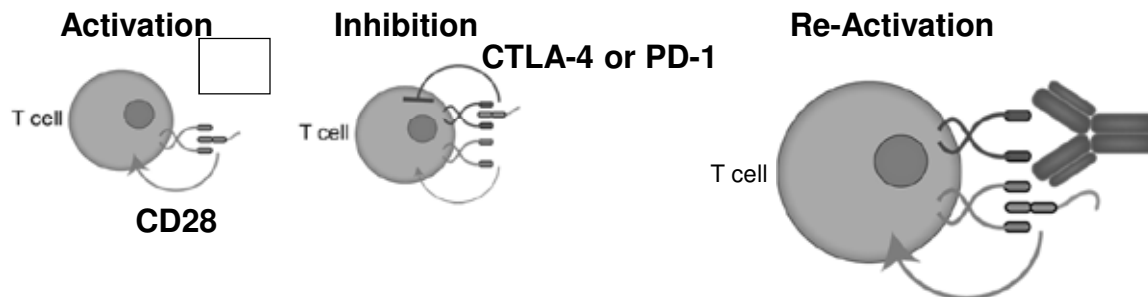


Goal: to reduce immune inhibitory signals and/or enhance stimulatory signals to allow T cells to regain effector functions.

# Basic Principles of Cancer Immunotherapy

Asim Amin, MD, PhD – Levine Cancer Institute

## 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

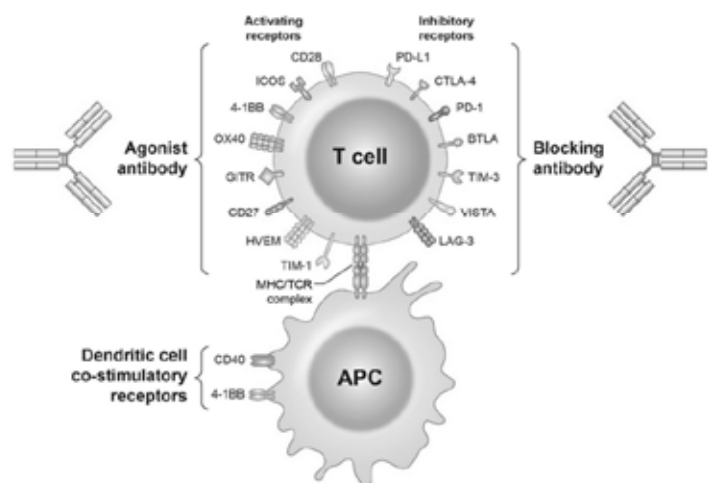


Image courtesy of NCI



# Basic Principles of Cancer Immunotherapy

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## Therapeutic Cancer Vaccines

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

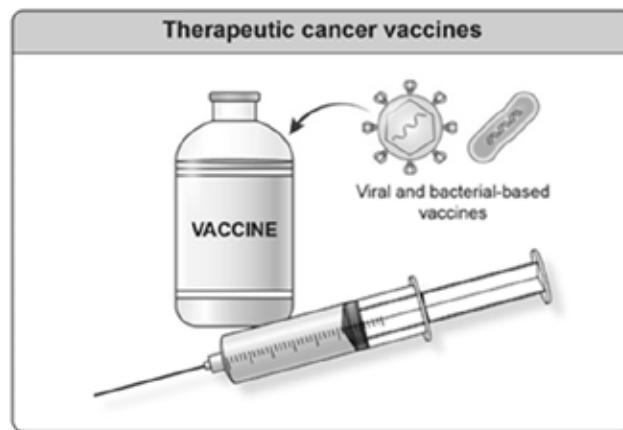


Image courtesy of NCI

## Adoptive Cell Therapy

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

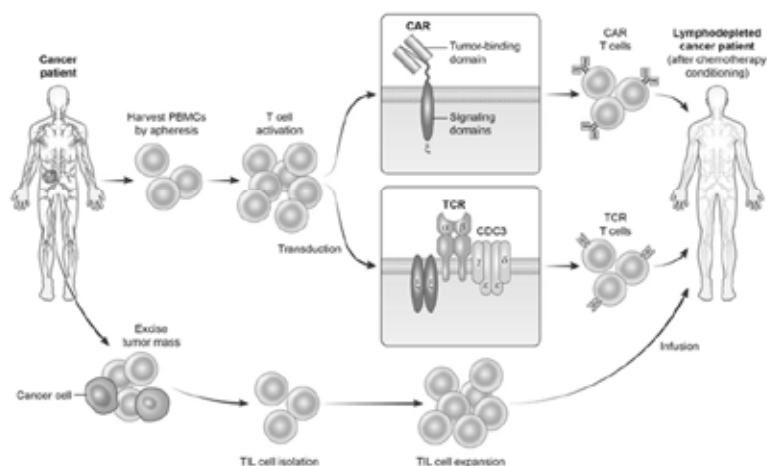


Image courtesy of NCI

# Basic Principles of Cancer Immunotherapy

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## 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

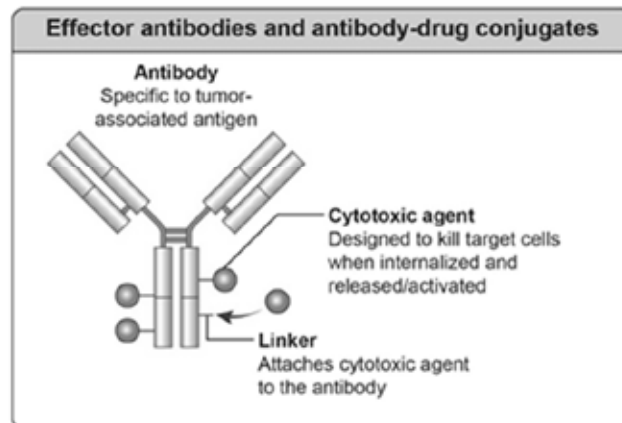
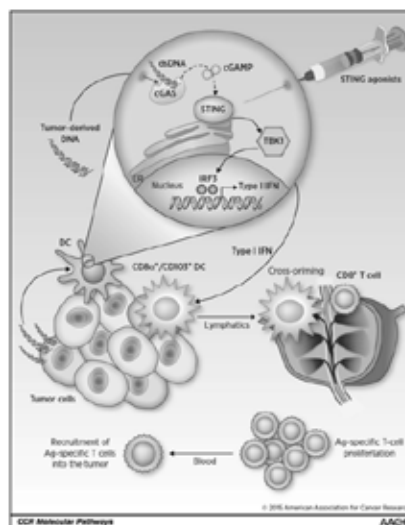


Image courtesy of NCI

## Innate immune activation

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



Corrales, Clin Can Res 2015

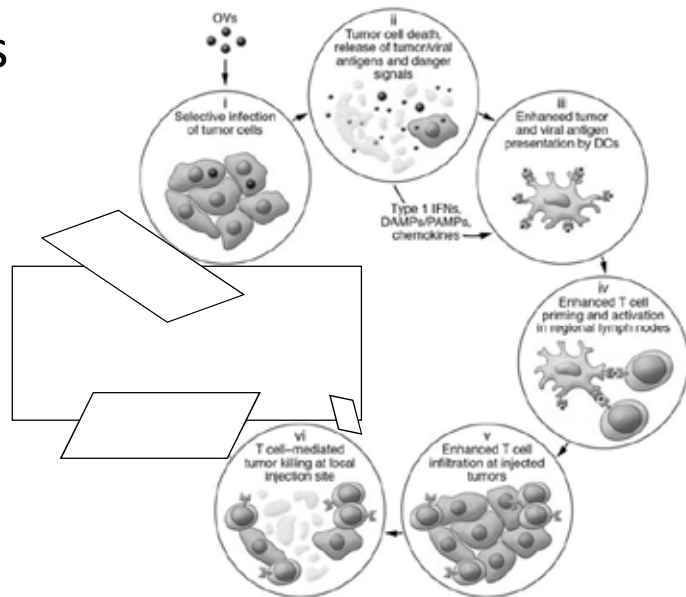
Agents:  
Sting agonists  
TLR agonists  
Immunogenic RNA

# Basic Principles of Cancer Immunotherapy

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## Oncolytic Viruses

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



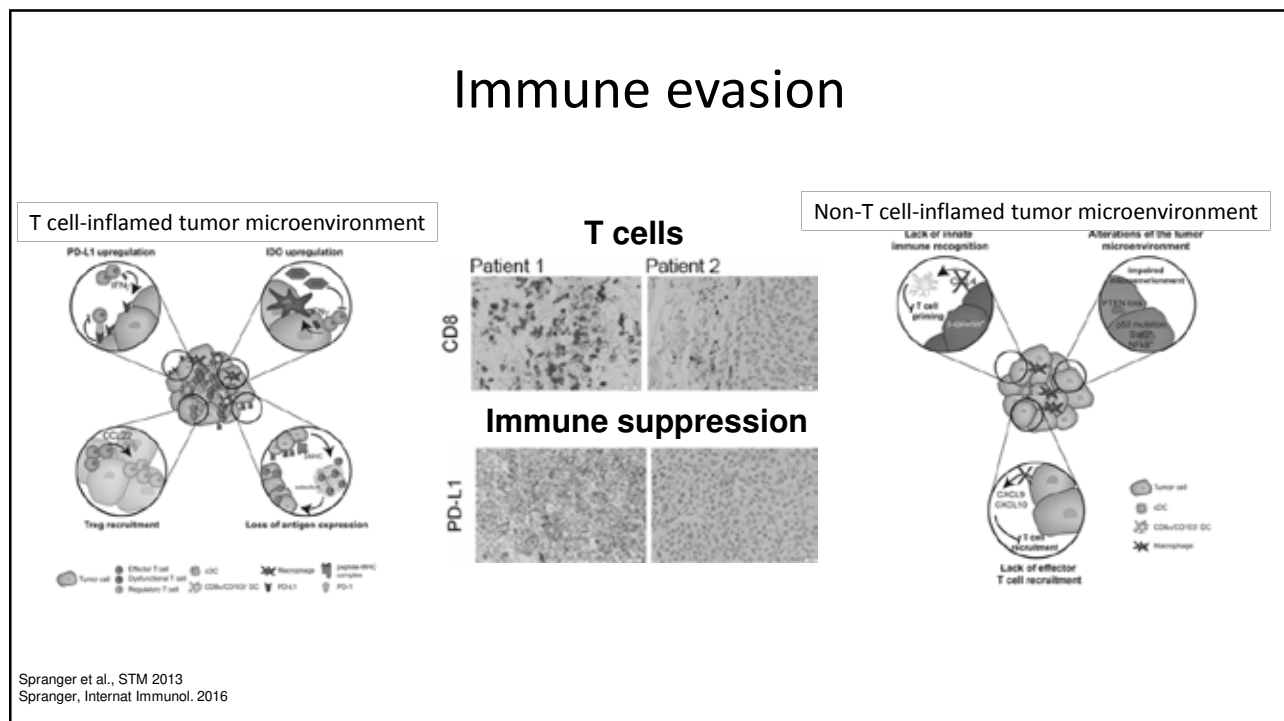
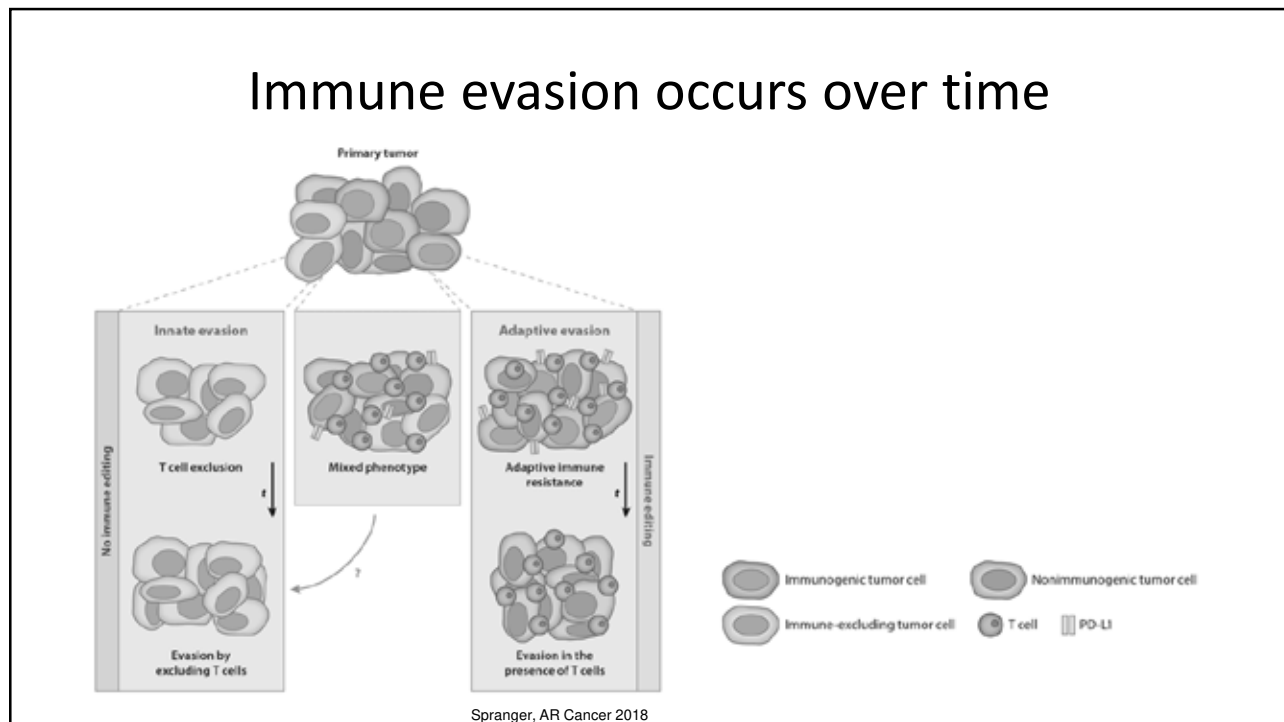
Modified from Bommereddy et al. JCI 2018

## 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.

# Basic Principles of Cancer Immunotherapy

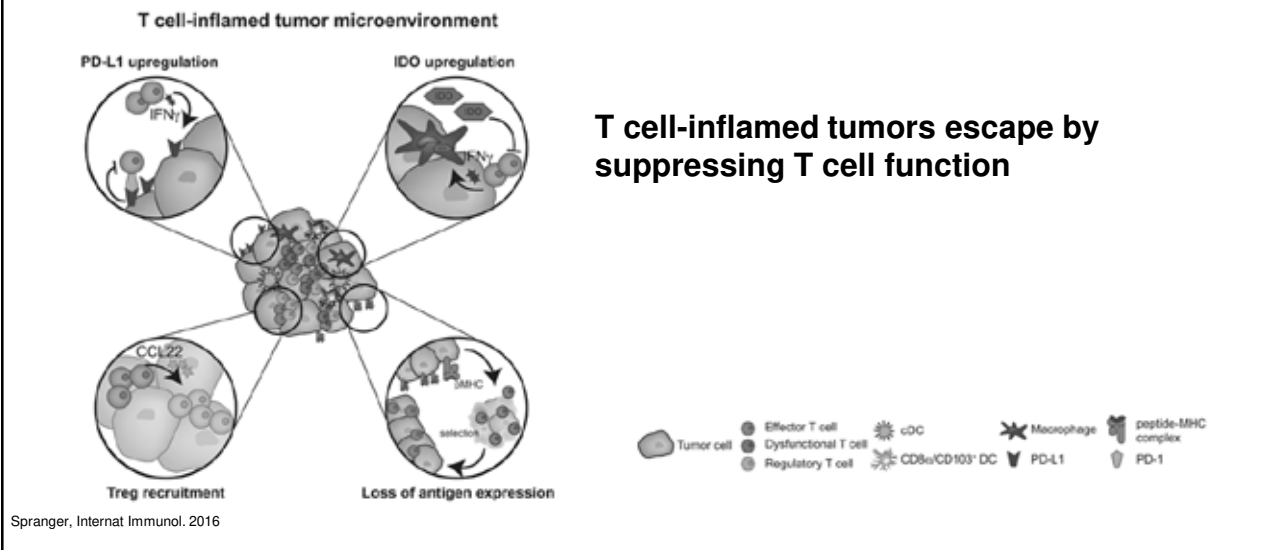
Asim Amin, MD, PhD – Levine Cancer Institute



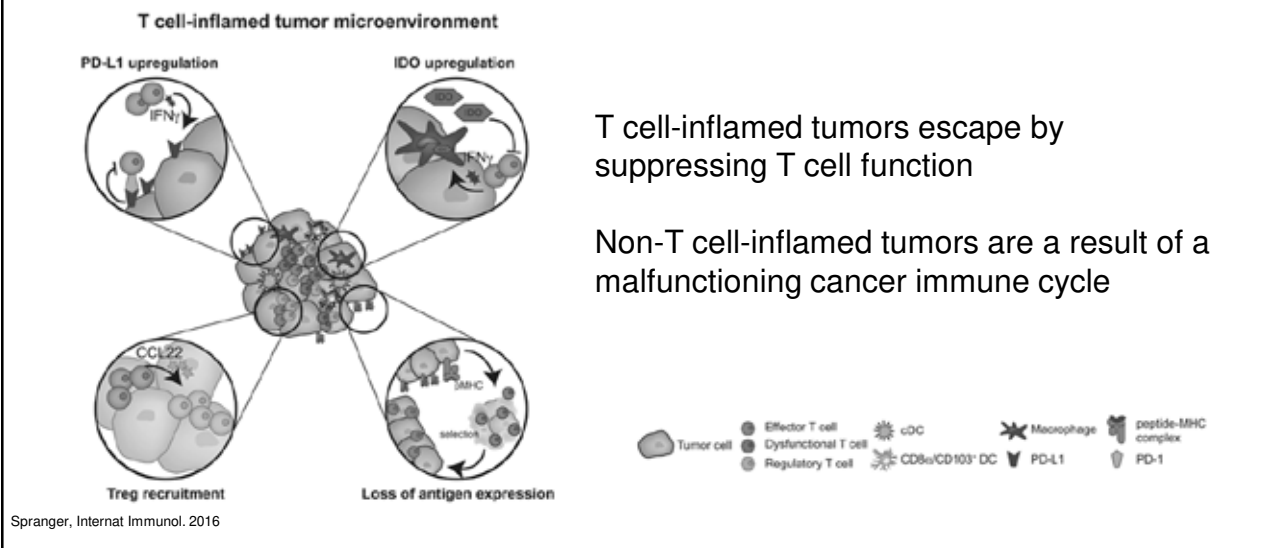
# Basic Principles of Cancer Immunotherapy

Asim Amin, MD, PhD – Levine Cancer Institute

## T cell inflamed tumor microenvironment is immune suppressive



## T cell inflamed tumor microenvironment is immune suppressive

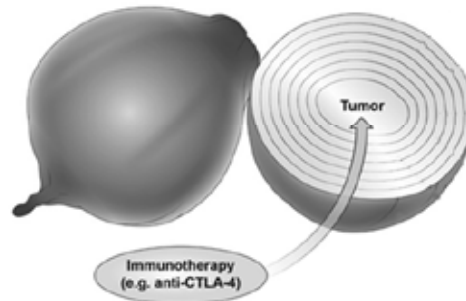


# Basic Principles of Cancer Immunotherapy

Asim Amin, MD, PhD – Levine Cancer Institute

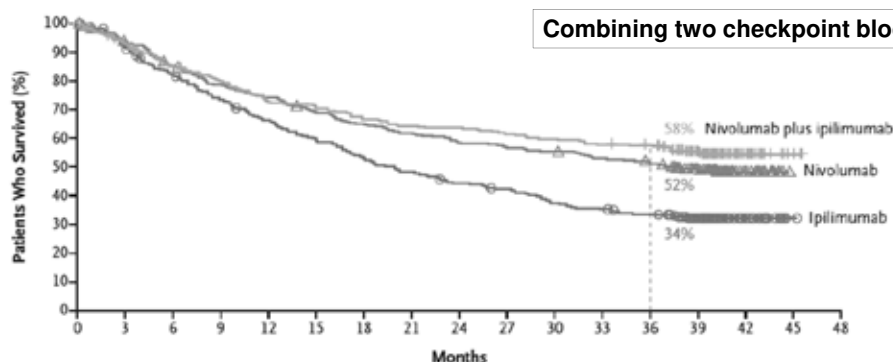
## Multi-layered Immunosuppression

- 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

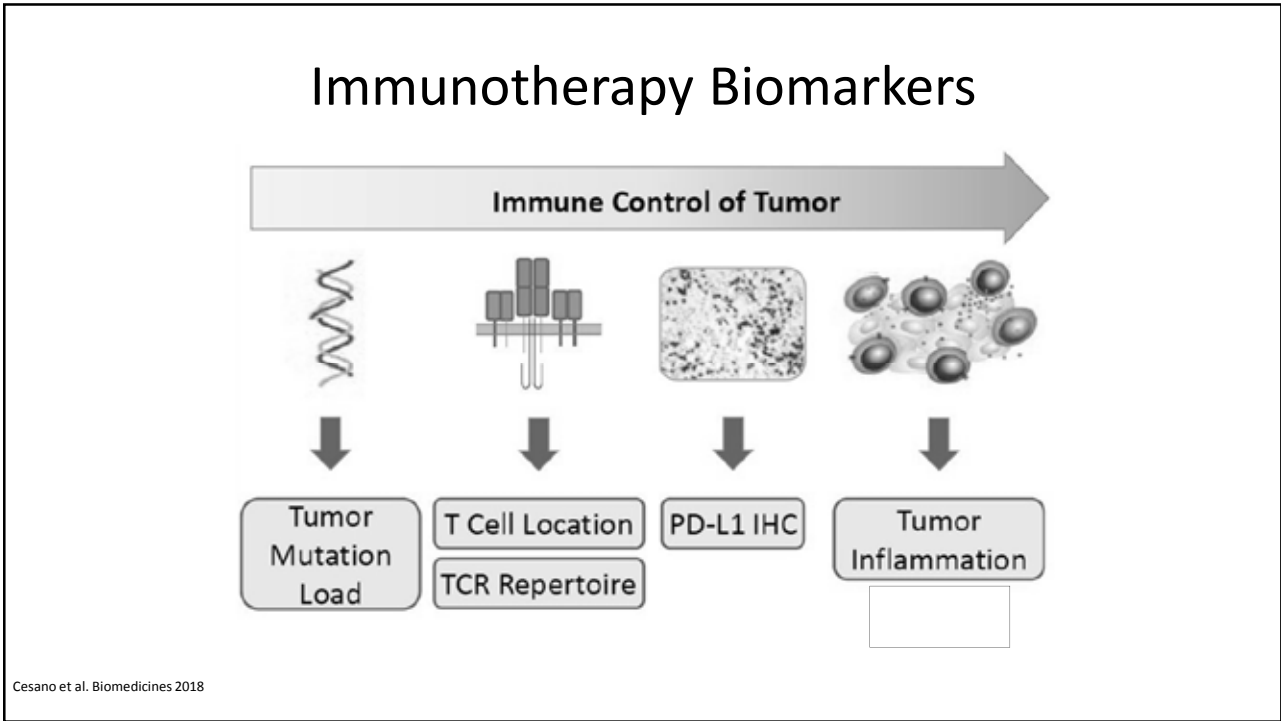
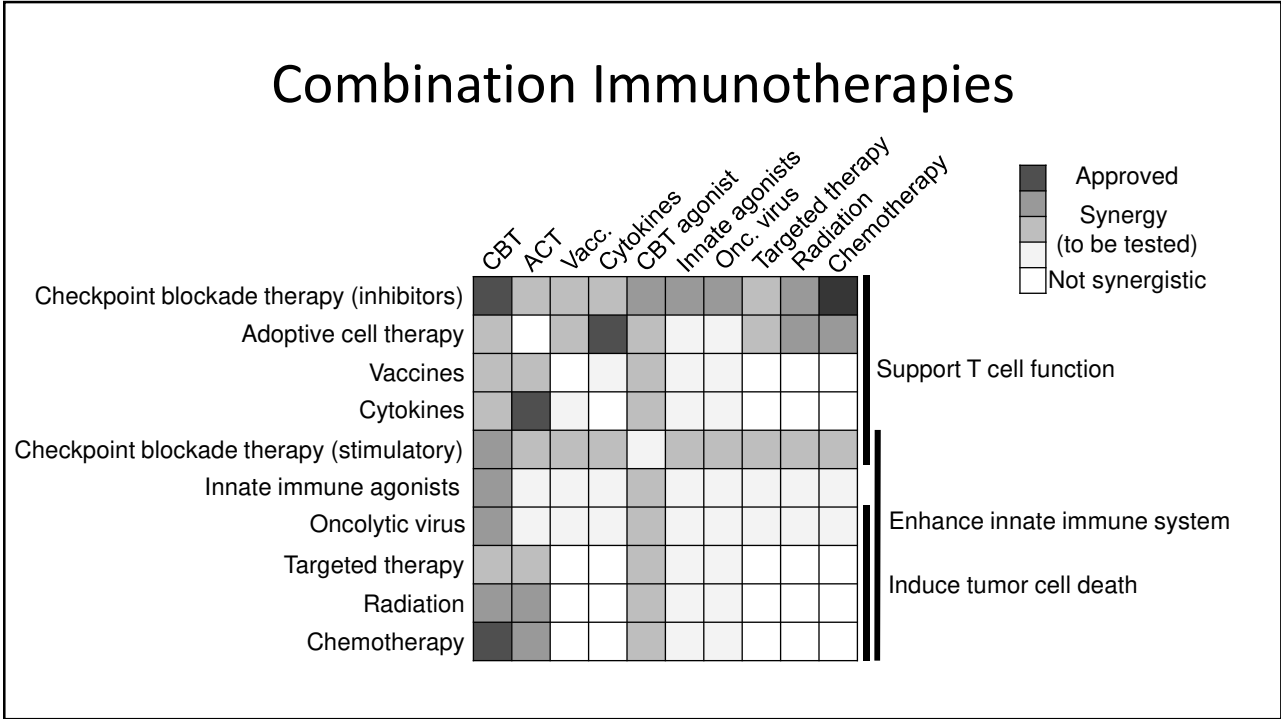
*Dual CTLA-4 and PD-1 inhibition*



Wolchok et al., NEJM 2017

# Basic Principles of Cancer Immunotherapy

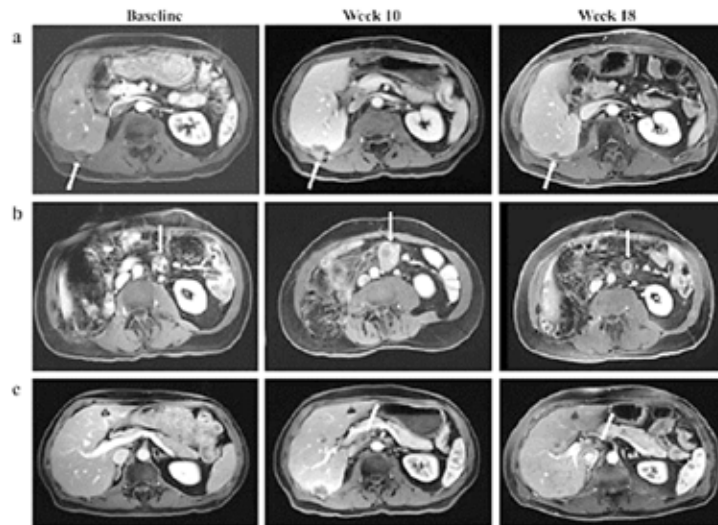
Asim Amin, MD, PhD – Levine Cancer Institute



# Basic Principles of Cancer Immunotherapy

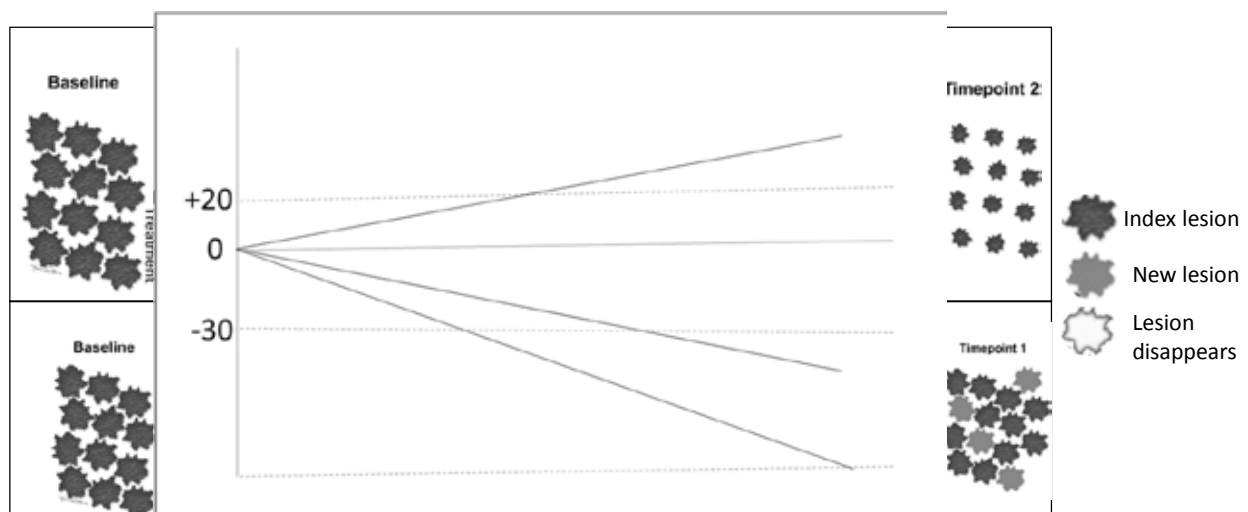
Asim Amin, MD, PhD – Levine Cancer Institute

## Assessment of response



Chae, Oncotarget 2017.

## Many possible imaging findings



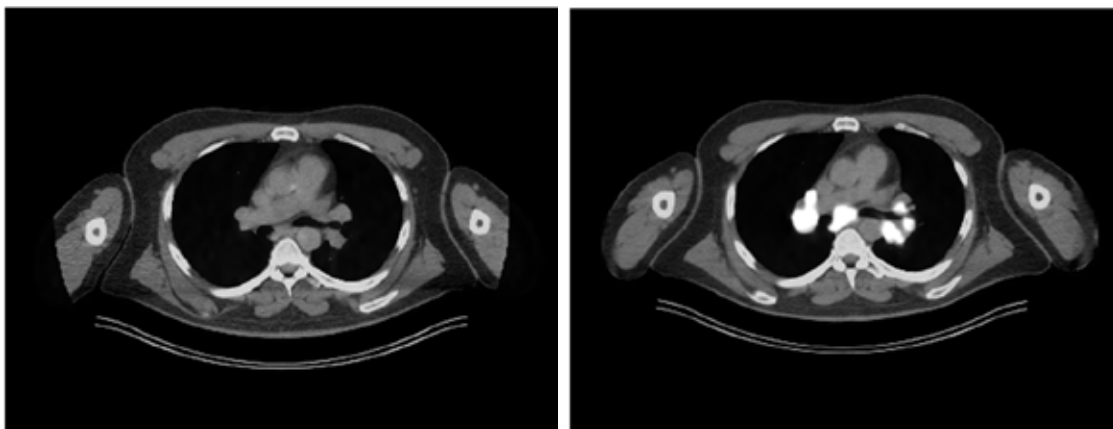
Wang, RadioGraphics 2017.



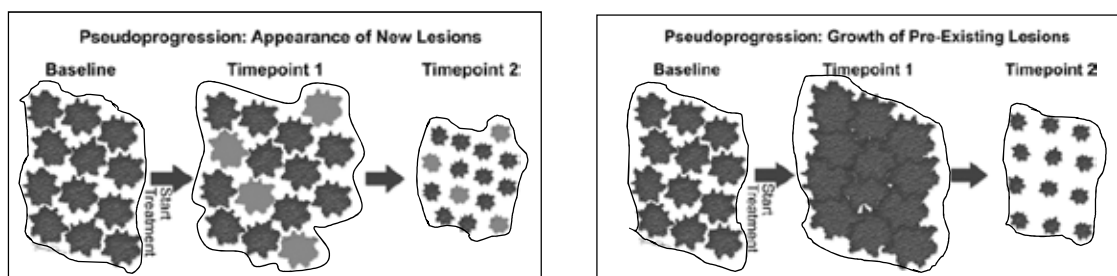
# Basic Principles of Cancer Immunotherapy

Asim Amin, MD, PhD – Levine Cancer Institute

## Imaging Pitfalls after Immunotherapy



## Many possible imaging findings

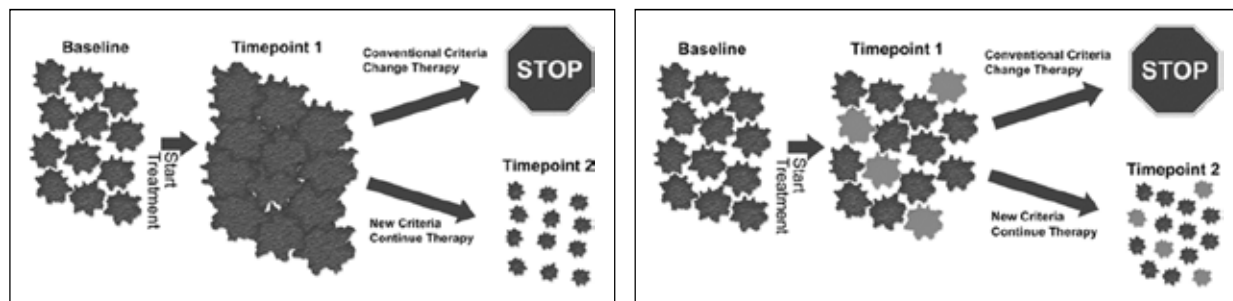


Wang, RadioGraphics 2017.

# Basic Principles of Cancer Immunotherapy

Asim Amin, MD, PhD – Levine Cancer Institute

## 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
<b>Progressive disease</b>	≥20% increase in lesion sum* (absolute size increase ≥5 mm) or 1+ new lesions at any single observation	≥25% increase in tumor burden <sup>†</sup> versus nadir in two consecutive observations ≥4 weeks apart
<b>New measurable lesions<sup>#</sup></b>	Always represent progressive disease	Incorporated into disease burden
<b>New non-measurable lesions</b>	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.

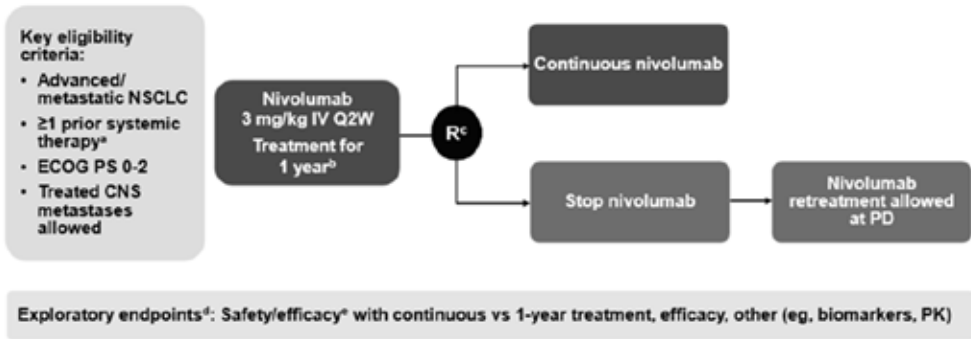
<sup>†</sup>Based on the sum of the products of the two largest perpendicular diameters of all index lesions.

<sup>#</sup>Measurable lesion for RECIST1.1 is ≥10mm at CT; irRC is ≥10x10mm at CT. Smaller lesions are considered non-measurable.

# Basic Principles of Cancer Immunotherapy

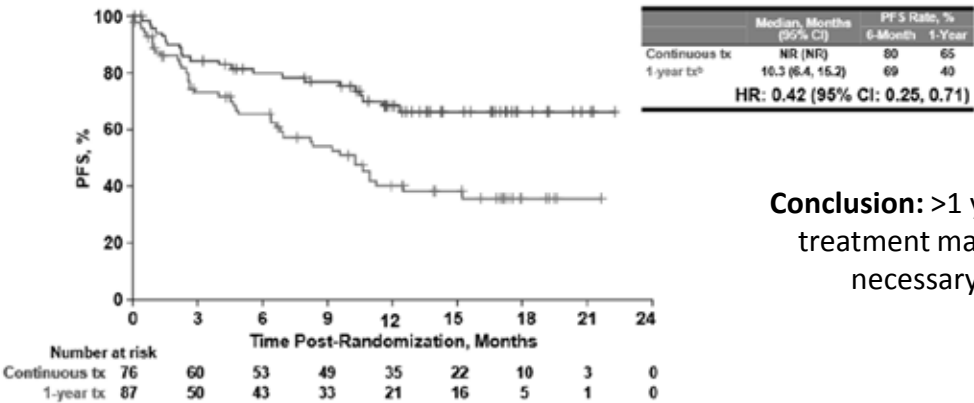
Asim Amin, MD, PhD – Levine Cancer Institute

## When to stop immunotherapy: Checkmate 153



Spigel, Ann Oncol 2017.

## When to stop immunotherapy: Checkmate 153



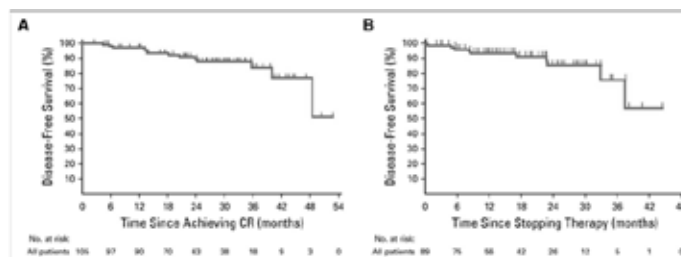
Spigel, Ann Oncol 2017.

## 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%

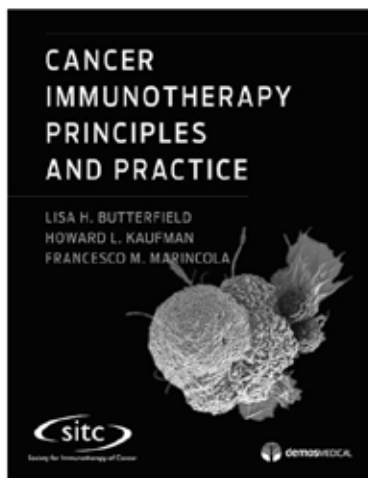


Robert, J Clin Oncol 2018.

## When to stop immunotherapy: clinical measures

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

## Further Resources



# Immunotherapy for the Treatment of Skin Cancers

**April K.S. Salama, MD**  
Associate Professor  
*Duke University*



April K.S. Salama, MD is the Director of the Melanoma Program within the Duke Cancer Institute, and has an interest in investigating novel therapeutics for patients with advanced melanoma and other skin cancers. She established the current melanoma clinical research program at Duke, and has a strong focus on immunotherapy. She has recently completed a pilot study of ipilimumab plus radiation in patients with poor prognosis melanoma, and has also serves as the national co-PI of the dabrafenib/trametinib arm (EAY-131H) of the NCI-MATCH trial. As a clinical researcher with a focus on patients with melanoma, she has expertise with both standard of care and novel immunotherapeutics as well as targeted agents. She leads a collaborative team, with a number of investigator initiated and NCI funded clinical protocols. Recently she has been recognized on a national level for her efforts in clinical trial development and commitment to NCI funded clinical trials as a recipient of the 2017 NCI Cancer Clinical Investigator Team Leadership Award.

# Immunotherapy for the Treatment of Skin Cancers

April K.S. Salama, MD – *Duke University*

## Immunotherapy for the Treatment of Skin Cancers

April K.S. Salama MD  
Associate Professor of Medicine  
Duke University

## Disclosures

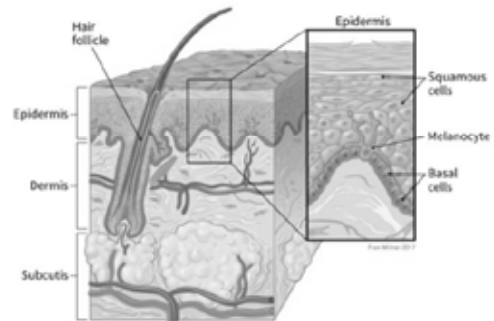
- Consultant: Array
- Research funding (paid to institution): Bristol Myers Squibb, Dynavax, Immunocore, Merck
- I will be discussing non-FDA approved indications during my presentation.

# Immunotherapy for the Treatment of Skin Cancers

April K.S. Salama, MD – Duke University

## 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 <sup>2</sup> IV 5x/wk for 4 wks Maintenance: 10m IU/m <sup>2</sup> 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



# Immunotherapy for the Treatment of Skin Cancers

April K.S. Salama, MD – Duke University

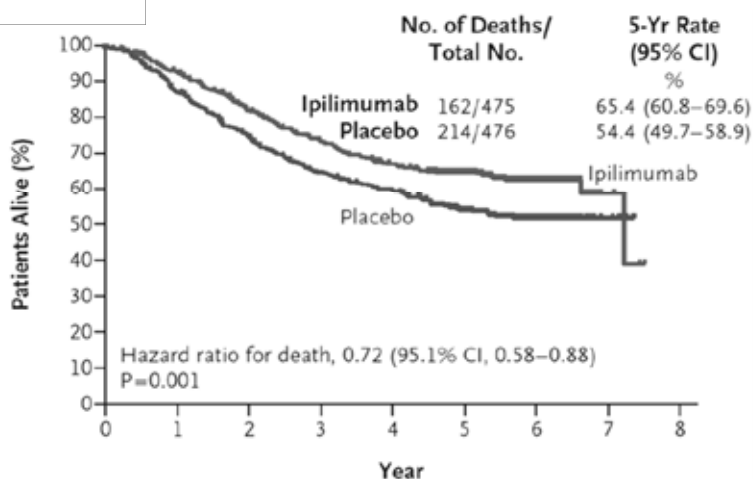
## Approved checkpoint inhibitors in melanoma

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 $\geq$ 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.

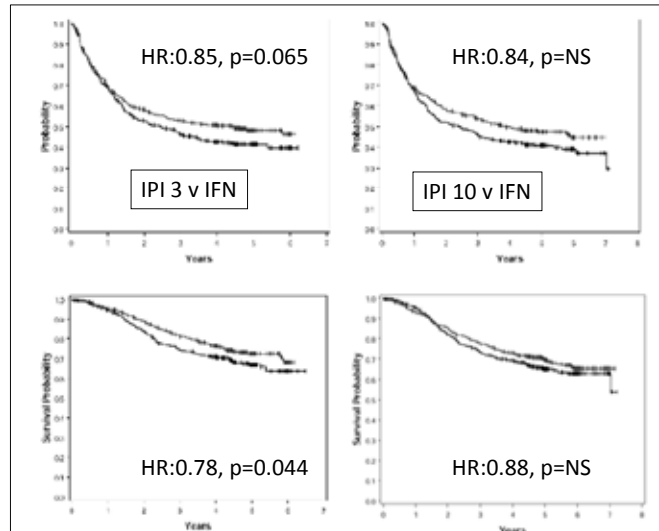
# Immunotherapy for the Treatment of Skin Cancers

April K.S. Salama, MD – Duke University

## 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

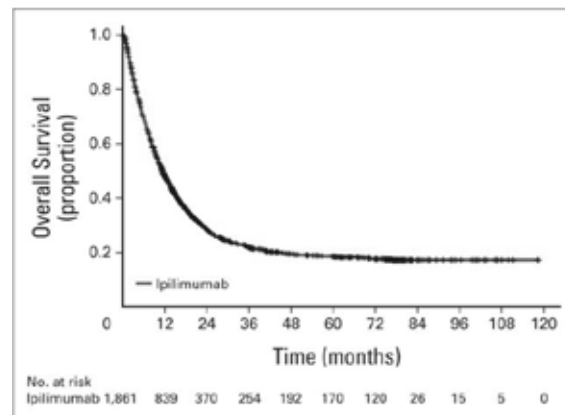
RFS



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.

# Immunotherapy for the Treatment of Skin Cancers

April K.S. Salama, MD – Duke University

## Approved checkpoint inhibitors in melanoma

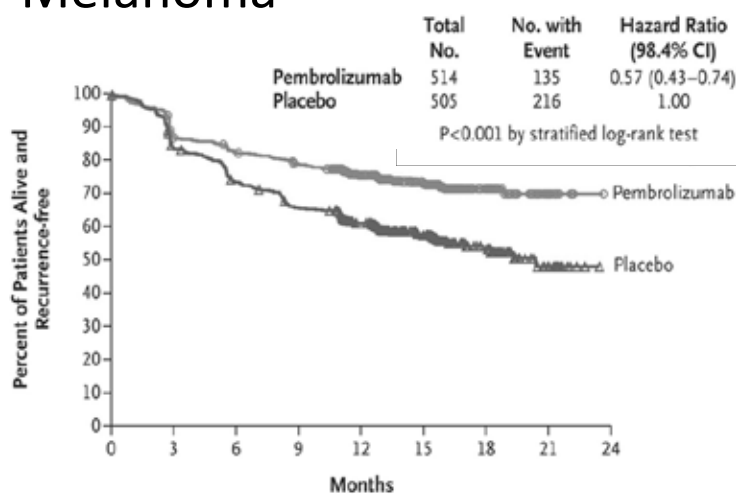
Drug	Approved	Indication	Dose
Pembrolizumab	2014	Advanced/unresectable melanoma with progression after other therapy	200 mg Q3W*
	2015	1 <sup>st</sup> line unresectable/metastatic melanoma	200 mg Q3W*
	2019	Adjuvant therapy of melanoma following complete resection	200 mg Q3W

\*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)



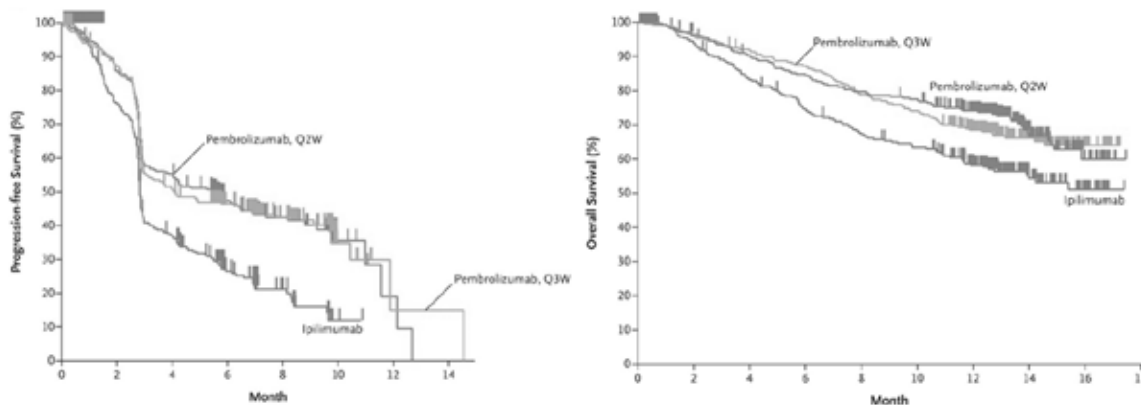
Eggermont, NEJM 2018.

# Immunotherapy for the Treatment of Skin Cancers

April K.S. Salama, MD – Duke University

## 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			

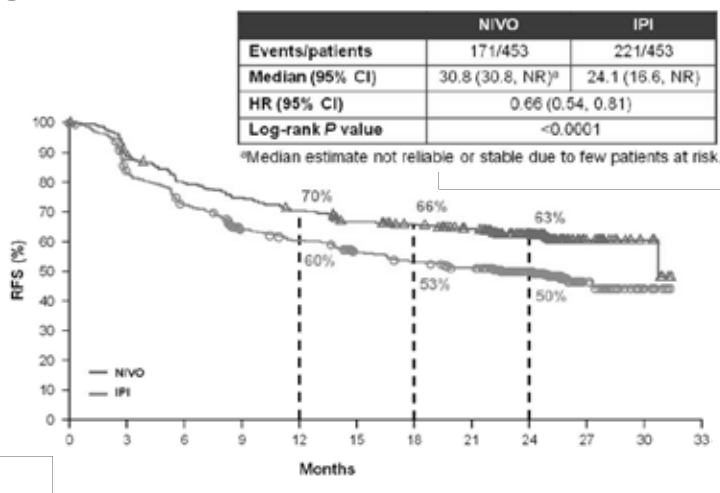
# Immunotherapy for the Treatment of Skin Cancers

April K.S. Salama, MD – Duke University

## Adjuvant Nivolumab vs Ipilimumab in High-Risk Stage III Melanoma

### • CheckMate 238 phase III trial

- NCT02388906
- Ipilimumab 10mg/kg Q3W for four doses, then every 3 months for up to 1 year
- Nivolumab 3mg/kg Q2W for three doses, then every 3 months for up to 1 year



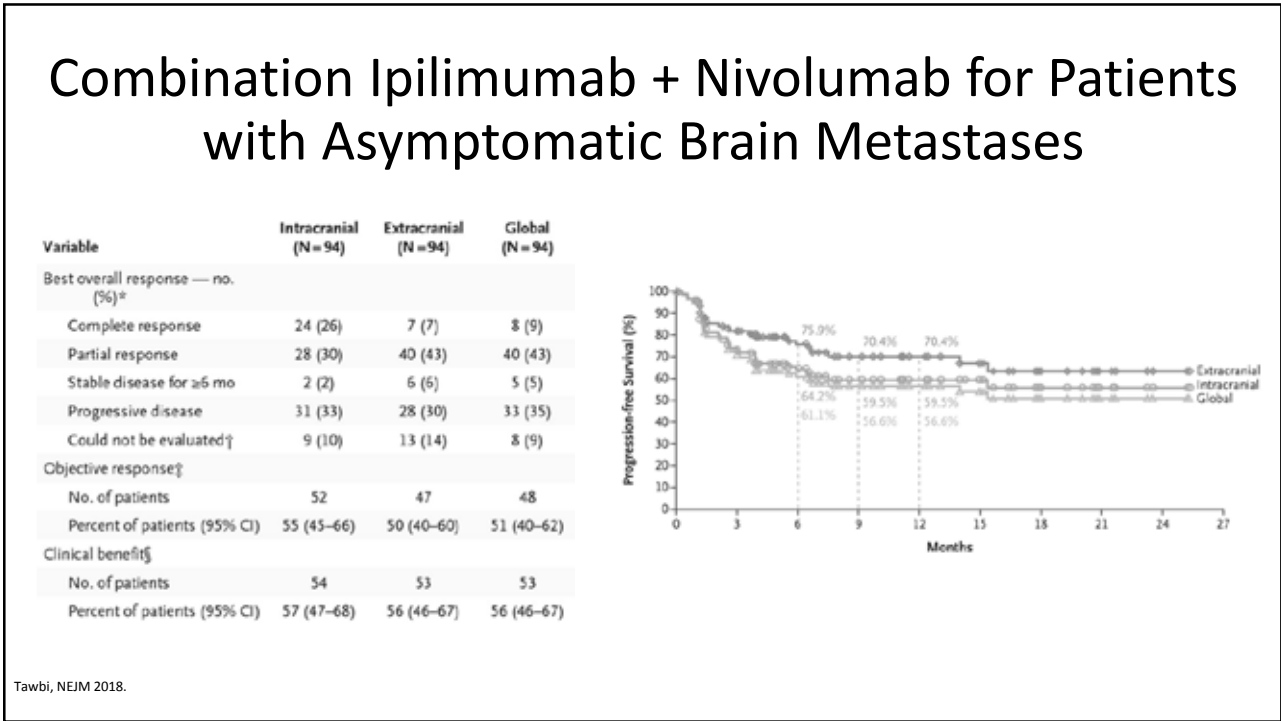
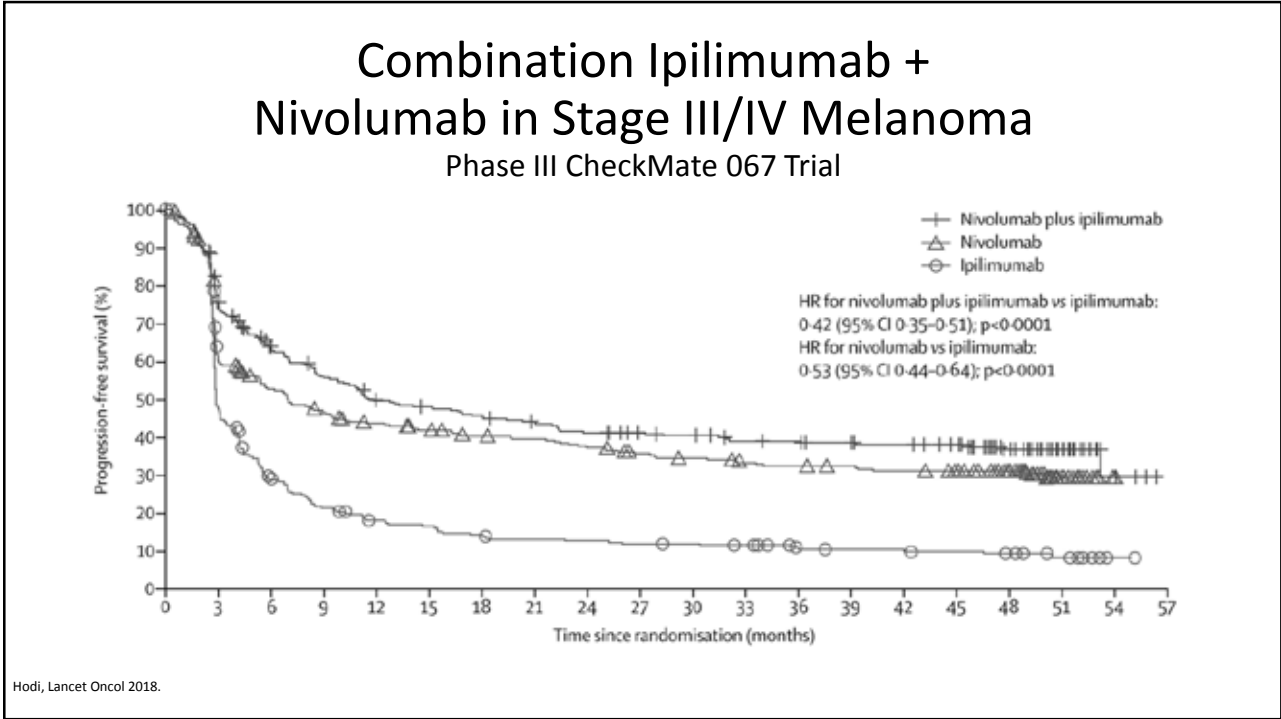
Weber, ASCO 2018.

## 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

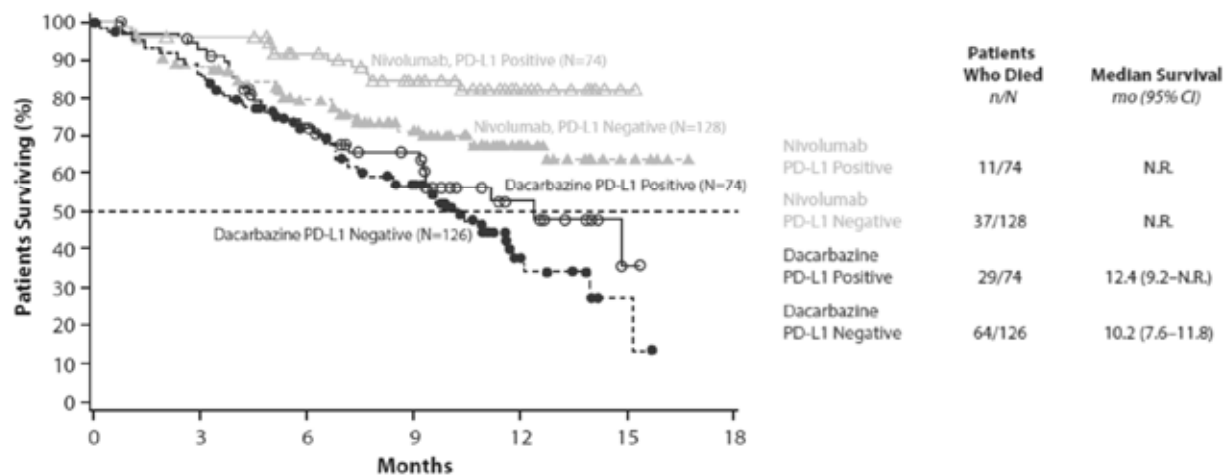
April K.S. Salama, MD – Duke University



# Immunotherapy for the Treatment of Skin Cancers

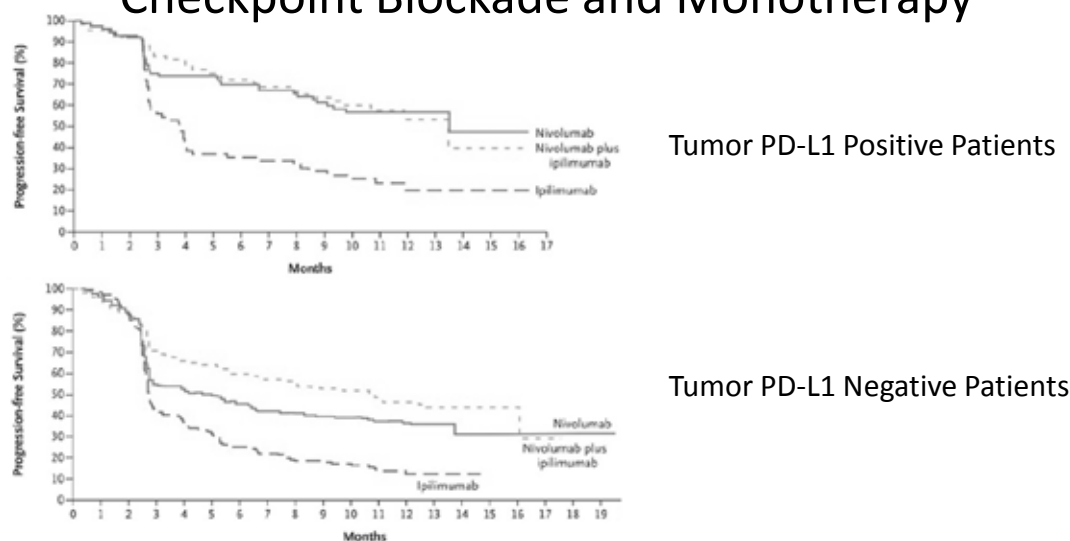
April K.S. Salama, MD – Duke University

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



Robert, NEJM 2015.

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

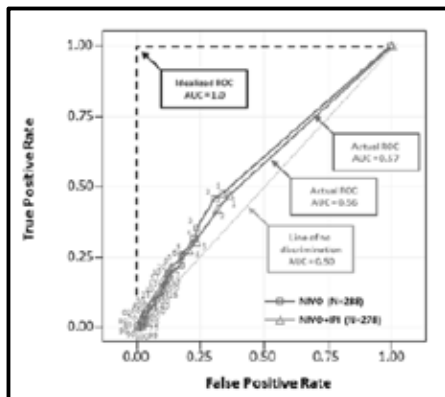


Larkin, NEJM 2015.

# Immunotherapy for the Treatment of Skin Cancers

April K.S. Salama, MD – Duke University

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



Wolchok, NEJM 2017.

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

**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	12	25	NR	20
	Ipi+nivo	11	45	NR	
Huang Nat Med 2019	Pembro	30	19	NR	18
Rozeman Lancet Oncol 2019	Ipi+nivo	86	57	NR	8.3

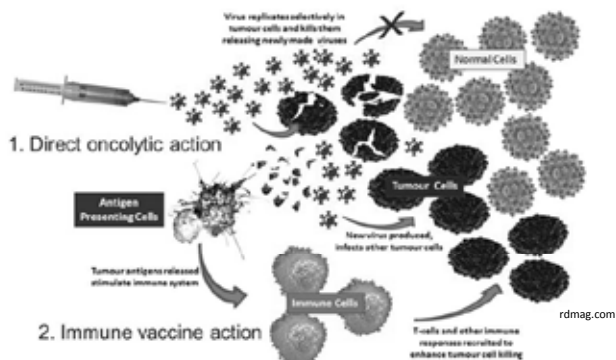
Menzies ASCO Annual Meeting 2019.



# Immunotherapy for the Treatment of Skin Cancers

April K.S. Salama, MD – Duke University

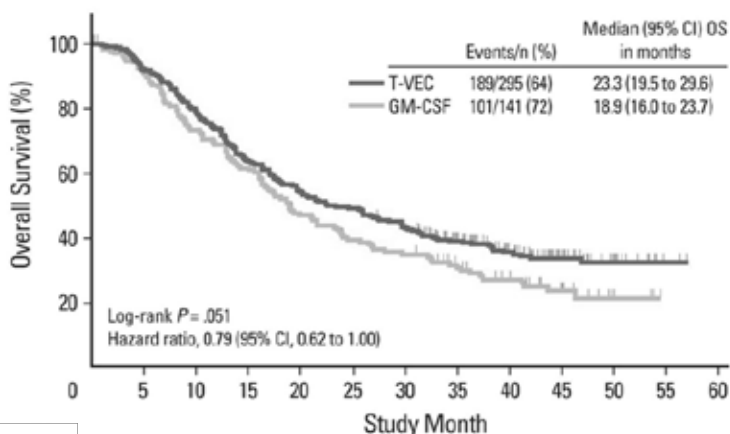
## Approved oncolytic virus in melanoma



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: $\leq 4$ 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.

# Immunotherapy for the Treatment of Skin Cancers

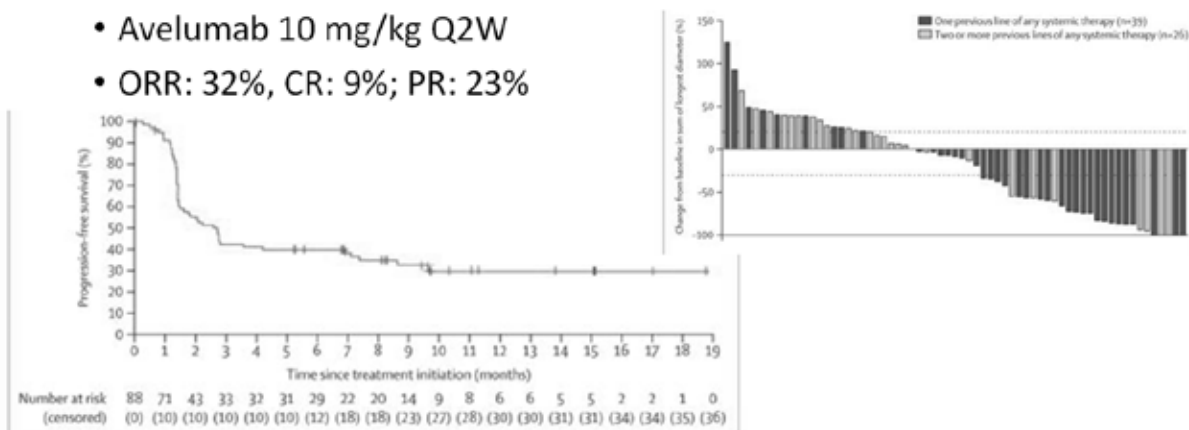
April K.S. Salama, MD – Duke University

## Approved checkpoint inhibitors in other skin cancers

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

## Avelumab in 2<sup>nd</sup>-line metastatic Merkel Cell carcinoma

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



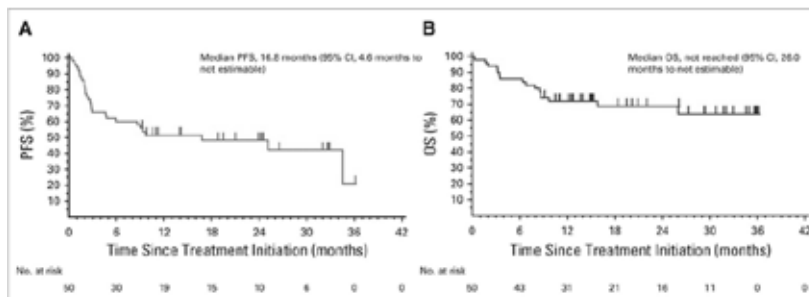
Kaufman, Lancet Oncol 2016.

# Immunotherapy for the Treatment of Skin Cancers

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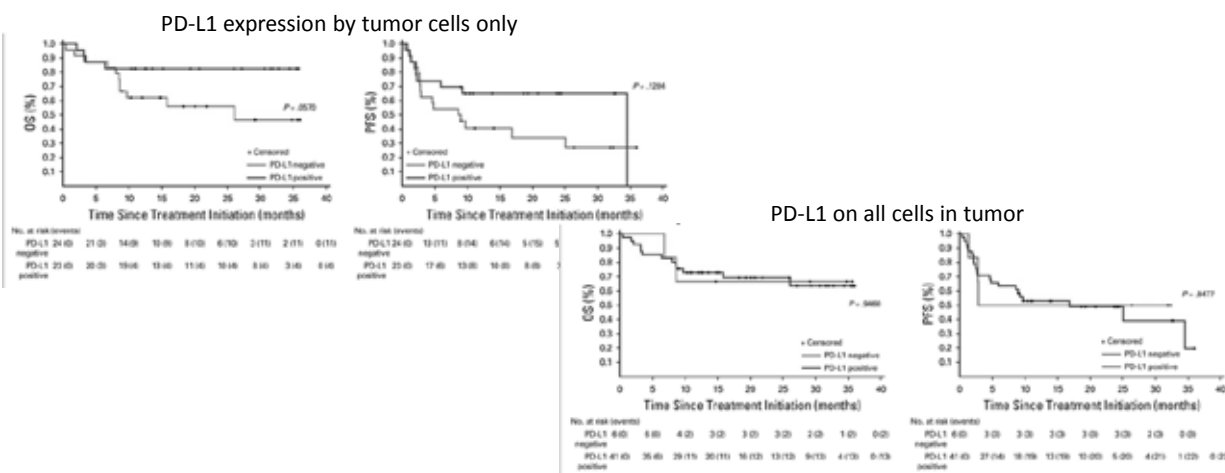
## Pembrolizumab in 1<sup>st</sup>-line advanced Merkel Cell Carcinoma

- 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 1<sup>st</sup>-line advanced Merkel Cell Carcinoma



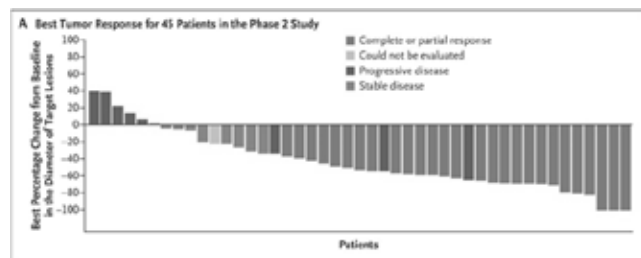
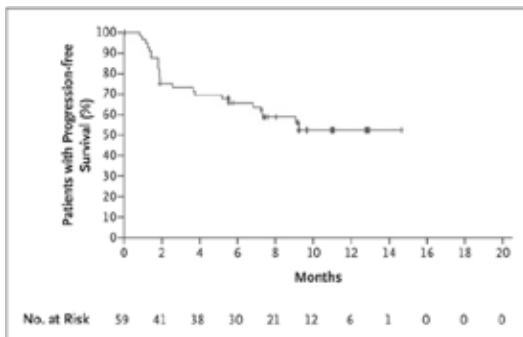
Nghiem, J Clin Oncol 2019.

# Immunotherapy for the Treatment of Skin Cancers

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## Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

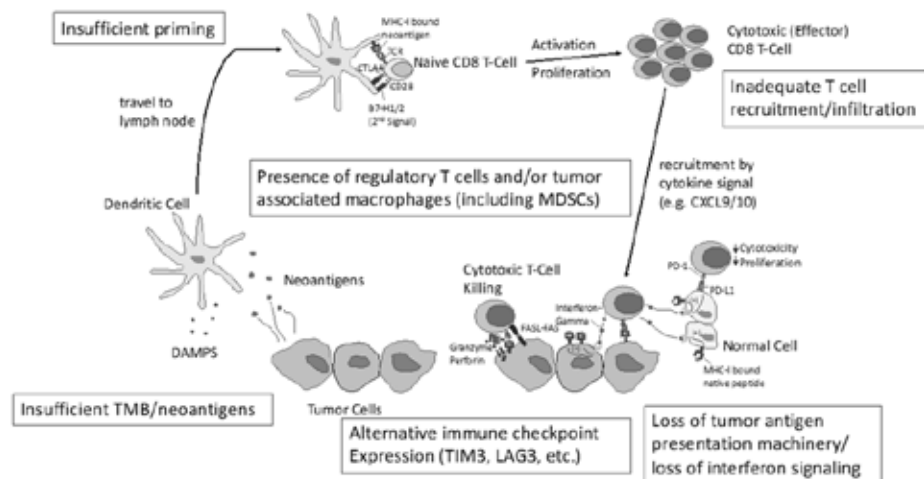
- Cemiplimab 3mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response



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.

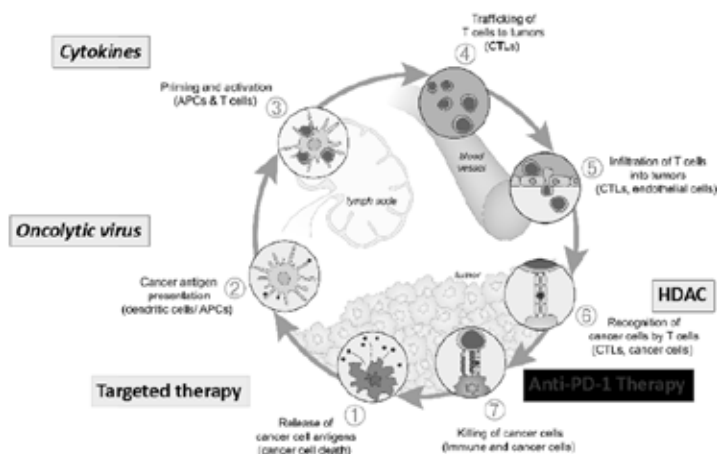
# Immunotherapy for the Treatment of Skin Cancers

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## Developmental Immunotherapeutic Strategies for Melanoma

How do we overcome resistance?

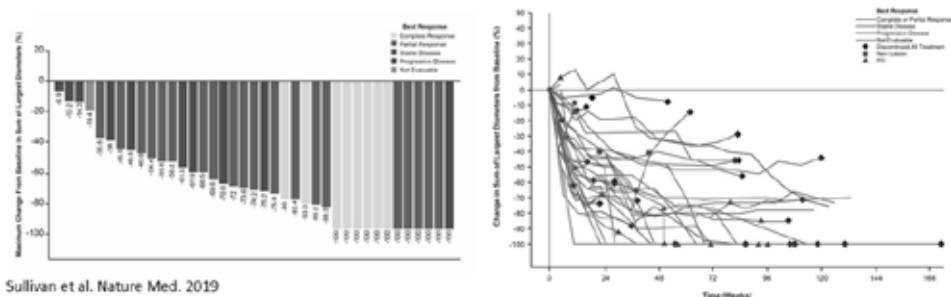
Combination therapy



Modified from Chen and Melman. Immunity 2015.

## In development: Combined IO with BRAF targeted therapy

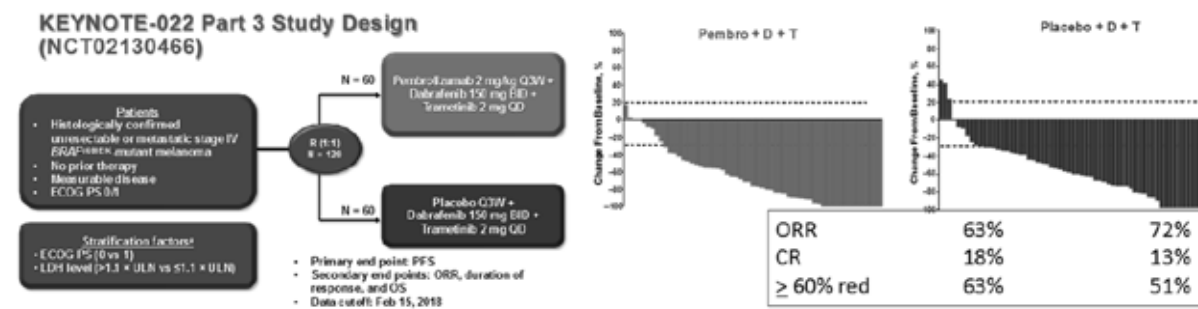
- Cobimetinib + vemurafenib + atezolizumab
- ORR: 71.8%
- Median duration of response: 17.4 mo



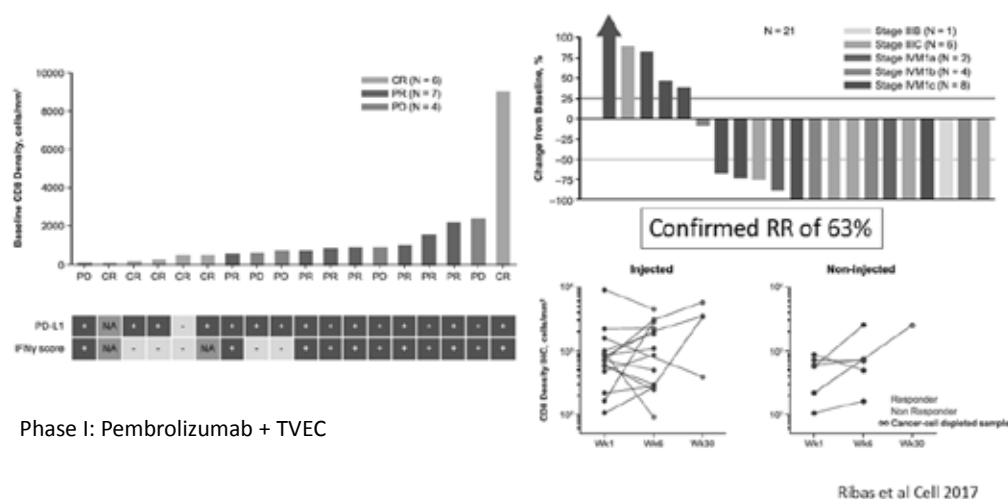
Sullivan et al. Nature Med. 2019

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**In development:** Combined IO with BRAF targeted therapy

Ascieto et al. *Nature Med* 2019,

## In development: Combined IO with Oncolytic Virus



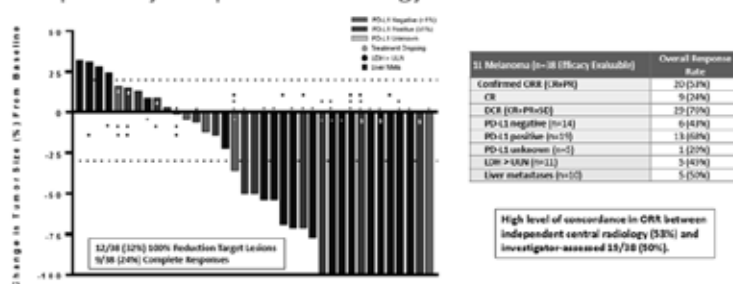
# Immunotherapy for the Treatment of Skin Cancers

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## 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

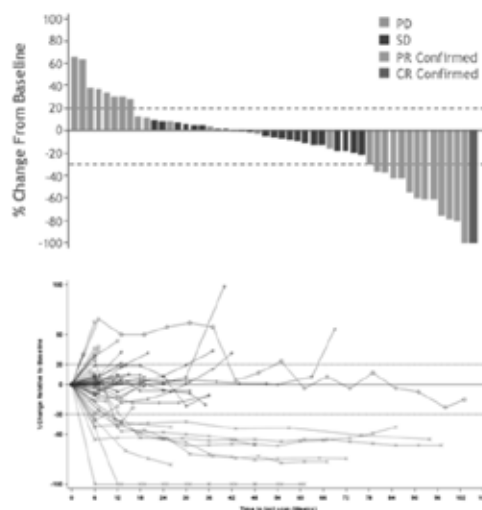
Stage IV IO-Naïve 1L Melanoma Cohort at RP2D Best Overall Response by Independent Radiology



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.

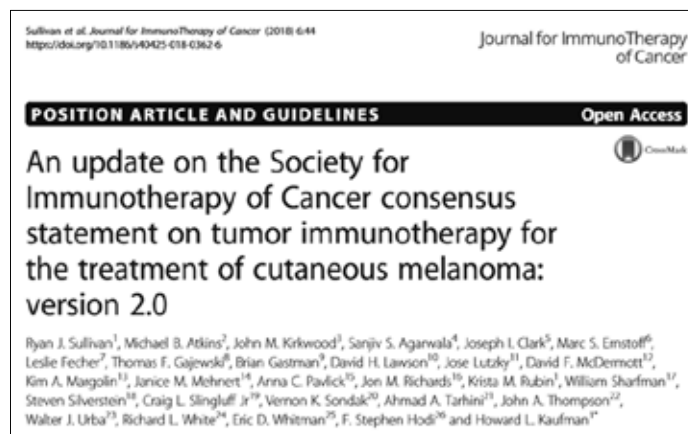
# Immunotherapy for the Treatment of Skin Cancers

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## 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





## Case Studies

### Case Study 1

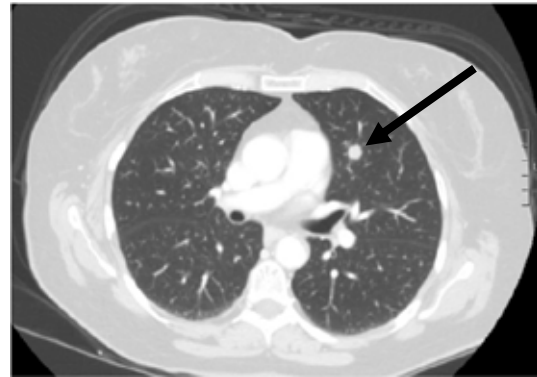
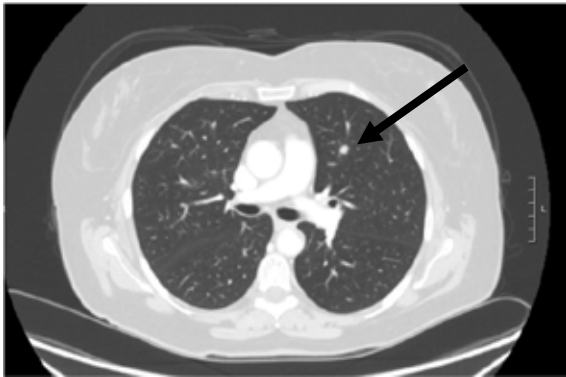
- 69 yo female
- 1970s: melanoma right forearm, with “lymph nodes removed”
- 2014:
  - left back lesion, Clark IV, Breslow 2.5mm, mitotic rate 8, ulceration present, absence of intraepidermal component-metastasis cannot be ruled out
  - WLE and SLNBx of left axilla (2/2 nodes positive; largest nodal metastasis at least 6mm, no extranodal extension)
- Adjuvant pegylated IFN
  - Held after 4 months

# Immunotherapy for the Treatment of Skin Cancers

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## Case Study 1

- 2018



3 months later

## Case Study 1

- Lung biopsy: + for melanoma
- What would you do as next step?
  - A. Surgery
  - B. Anti-PD-1 therapy
  - C. Anti-PD-1/anti-CTLA-4 therapy
  - D. BRAF/MEK inhibitor therapy

## Case Study 1

- Best option would be systemic therapy
  - No OS or prospective data with surgical resection
  - Best front-line therapy for melanoma debated
    - Immunotherapy should include an anti-PD-1 agent
    - Higher rates of toxicity with dual checkpoint
    - BRAF/MEKi therapies: no molecular information on this patient yet; an option for approximately 50% of patients with a BRAF<sup>V600E</sup> mutation; concerns about durability of responses

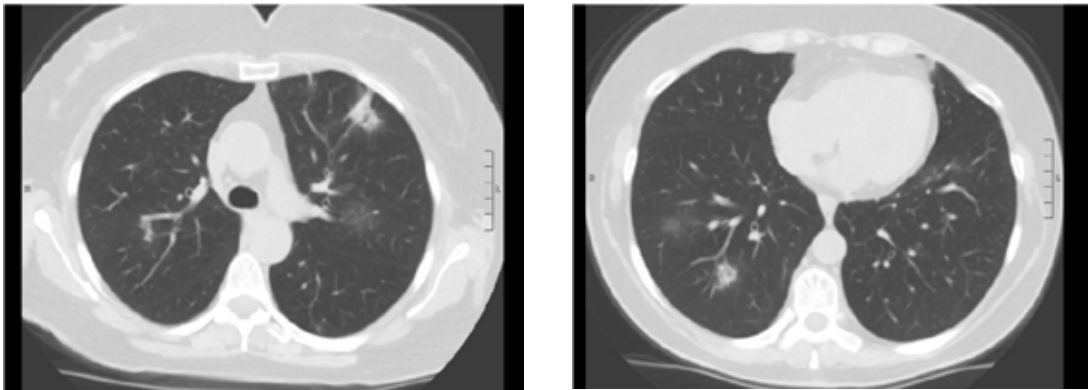
## Case Study 1

- Initiated on nivolumab monotherapy
- 2019:



## Case Study 1

- After approximately 1 year on therapy:



## Case Study 1

- Next steps?
- Options/decisions:
  - Disease progression or immune mediated toxicity
  - Continuation of therapy
  - Diagnostic considerations
    - Biopsy: Alveolar lung tissue with reactive pneumocytes and mild chronic inflammation; **No evidence of malignancy**

# Immunotherapy for the Treatment of Skin Cancers

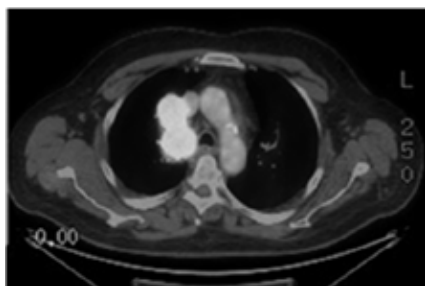
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## Case Study 1

- Additional history:
- Patient reported history of e-cigarette use
- Recent change in e-cigarette liquid: made in a local store
- Current status:
  - Holding further therapy
  - Referral to pulmonology

## Case Study 2

- 70 yo diagnosed with stage III melanoma 2010; received IFN alfa completed in 2011
- 2015: Progressive fatigue, malaise, SOB



# Immunotherapy for the Treatment of Skin Cancers

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## Case Study 2

- Biopsy of lung mass is performed and is positive for metastatic melanoma
- Brain MRI negative
- Molecular studies pending
- Next steps (show of hands):
  - A. Wait for molecular studies before making treatment decision
  - B. Treat with immunotherapy

## Case Study 2

- Treatment of patients with metastatic melanoma and high symptom burden and unknown BRAF status is challenging
- Prolonged time for BRAF results

Agent	High response rate	Quick response	Response durability	Toxicity
Anti-PD-1 monotherapy				
Dual checkpoint inhibition				
BRAF + MEK inhibition				

# Immunotherapy for the Treatment of Skin Cancers

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## Case Study 2

- Patient initiated therapy with ipilimumab/nivolumab
- Presents for C3 with diarrhea
  - Abdominal pain/cramping
  - 8-10 bowel movements a day
- Next steps (show of hands):
  - A. Supportive care with loperamide
  - B. Initiation of prednisone 1mg/kg day
  - C. Infliximab
  - D. Colonoscopy

## Case Study 2

- **Option B is best choice**
  - Steroids are generally indicated as initial management for grade 3 colitis
  - Routine colonoscopy no longer indicated
    - Consider when not improving
    - Prolonged course of steroids
    - Concern for underlying malignancy
  - Infliximab often reserved for steroid refractory cases

# Immunotherapy for the Treatment of Skin Cancers

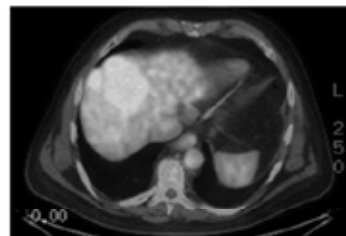
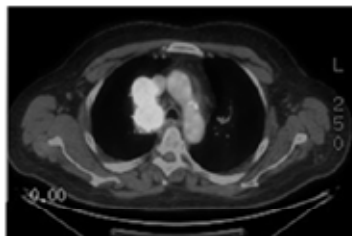
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## Case Study 2

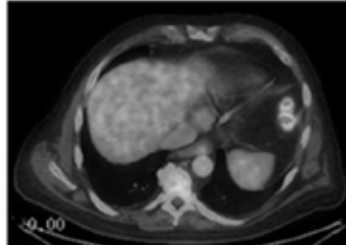
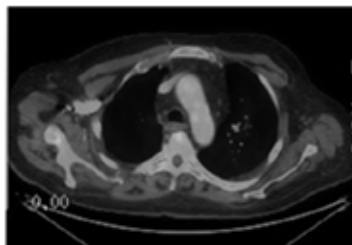
- Patient received high dose steroids
  - Initially improved
  - Difficulty tapering
  - Infliximab X 1 with resolution

## Case Study 2

Pre-treatment



Post-treatment  
(no additional  
therapy)





# Immunotherapy for the Treatment of Skin Cancers

April K.S. Salama, MD – *Duke University*

Thank You

# Immunotherapy for the Treatment of Lung Cancer

**Kathryn F. Mileham, MD, FACP**

Chief, Section of Thoracic Medical Oncology  
*Levine Cancer Institute, Atrium Health*



Kathryn F. Mileham, MD, FACP has been with Atrium Health in Hematology/Oncology for ten years. She is currently the Section Chief for Thoracic Medical Oncology, Chair-Elect of ASCO Cancer Research Committee, and serves on the Lung Cancer Initiative of North Carolina Scientific Advisory Board. Dr. Mileham is an Associate Professor for Atrium Health and was named 2019's Q2 Provider of the Quarter. In addition to being a widely published author and presenter on the topic of thoracic medical oncology, she serves as the principal investigator for both sponsored and investigator-initiated clinical research trials.

# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – *Levine Cancer Institute, Atrium Health*

## Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP

Chief, Section of Thoracic Medical Oncology

Levine Cancer Institute – Atrium Health

## Disclosures

- Takeda (honoraria), AstraZeneca (advisory role), Merck (speakers' bureau), Celgene (research funding)
- I will be discussing non-FDA approved indications during my presentation.

# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

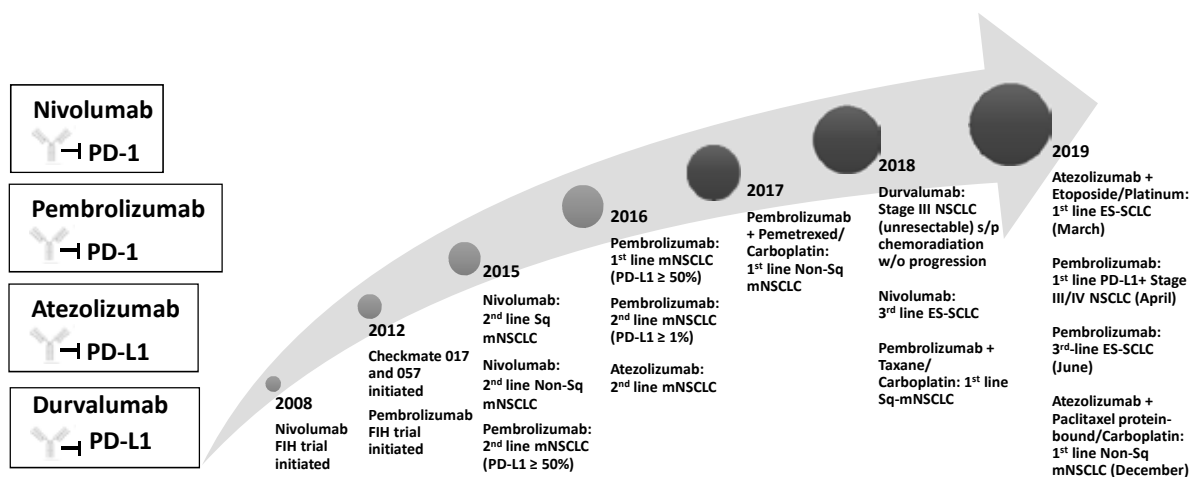
## Lung cancer

- 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

	Male				Female		
		Estimated Deaths				Estimated Deaths	
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



# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## Approved checkpoint inhibitors in NSCLC

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

## Approved checkpoint inhibitors in NSCLC

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

# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## Approved checkpoint inhibitors in NSCLC

Drug	Approved	Indication	Dose
<b>Atezolizumab</b>	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
<b>Atezolizumab + bevacizumab + paclitaxel + carboplatin</b>	2018	1 <sup>st</sup> 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
<b>Durvalumab</b>	2018	Stage III NSCLC, ineligible for surgery and without progression after chemoradiation	10 mg/kg Q2W
<b>Atezolizumab + nab-paclitaxel + carboplatin</b>	2019	1 <sup>st</sup> line metastatic non-squamous NSCLC with no EGFR/ALK mutations	For 4-6 cycles: atezolizumab 1200 mg Q3W + chemotherapy Maintenance: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W

## Treatment Naïve Regimens: Competing Strategies in NSCLC

- **KEYNOTE 024** – Pembrolizumab vs. Chemotherapy in PD-L1  $\geq$  50%
- **KEYNOTE 042** – Pembrolizumab vs. Chemotherapy in PD-L1  $\geq$  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

# Immunotherapy for the Treatment of Lung Cancer

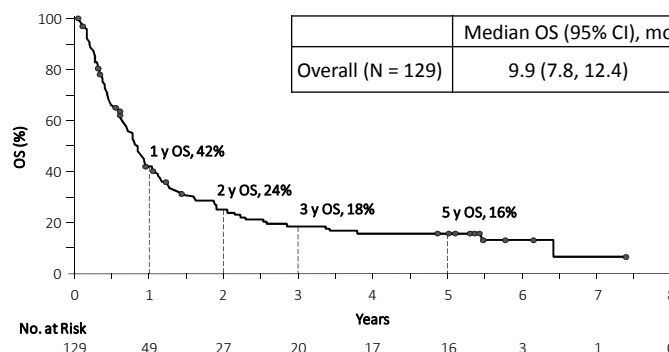
Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## CA209-003: Nivolumab in heavily-pretreated advanced NSCLC (NCT00730639)

### Phase 1, 5-Year Update

#### 5-Year Survival

- 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%



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

## KEYNOTE-001: Pembolizumab in advanced non-small-cell lung cancer

### Phase I, 5-Year Update

#### 101 treatment-naïve mNSCLC

- mOS = 22.3 months (95% CI, 17.1 - 32.3 mos)
- Estimated 5-year OS was 23.2%
- With PD-L1 TPS  $\geq$  50%, 5-year OS = 29.6%

#### 449 previously treated mNSCLC

- mOS = 10.5 months (95% CI, 8.6 - 13.2 mos)
- Estimated 5-year OS = 15.5%
- With PD-L1 TPS  $\geq$  50%, 5-year OS = 25.0%

Compared with analysis at 3 years, only three new-onset treatment-related grade 3 adverse events occurred (hypertension, glucose intolerance, and hypersensitivity reaction, all resolved).

No late-onset grade 4 or 5 treatment-related adverse events occurred.

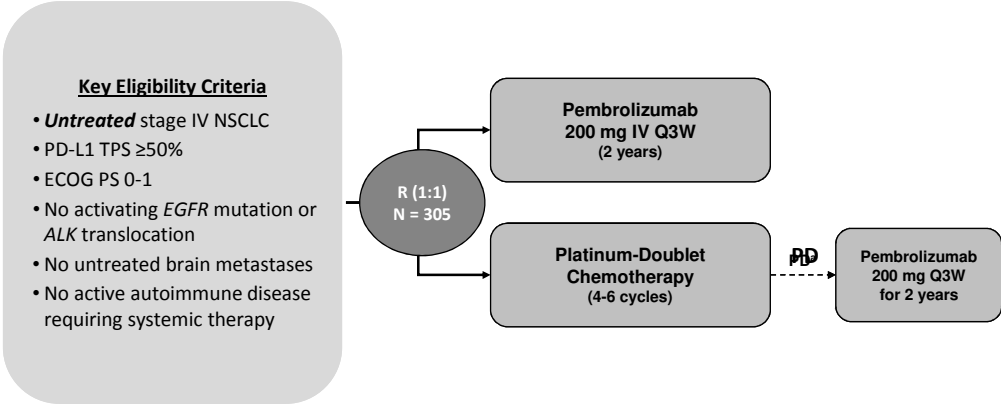
Median follow-up was 60.6 months (range, 51.8 to 77.9 months). At data cutoff—November 5, 2018—450 patients (82%) had died.

Garon et al. ASCO 2019

# Immunotherapy for the Treatment of Lung Cancer

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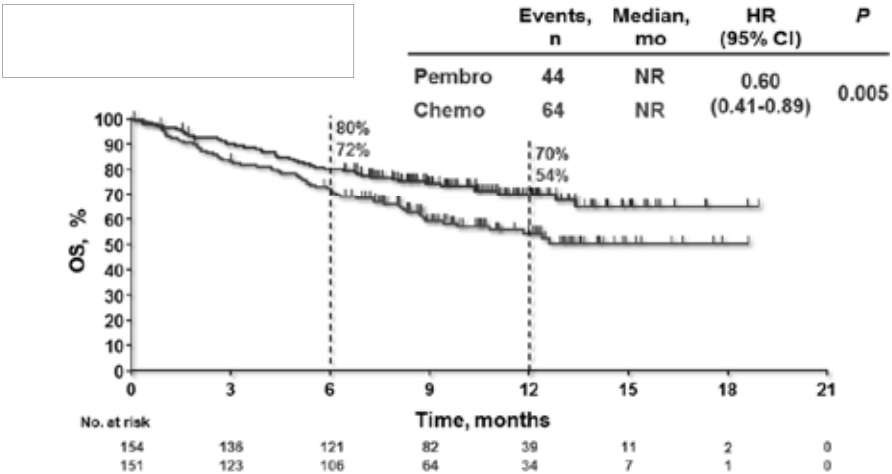
## KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 Positive (≥ 50%) NSCLC Study Design (NCT021427389)



Reck M et al, ESMO 2016, NEJM 2016

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

### Overall Survival



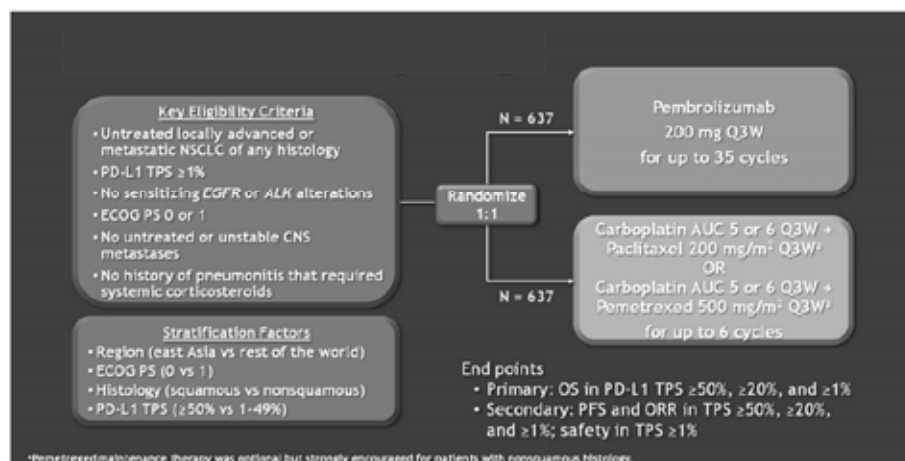
Reck M et al, ESMO 2016, NEJM 2016



# Immunotherapy for the Treatment of Lung Cancer

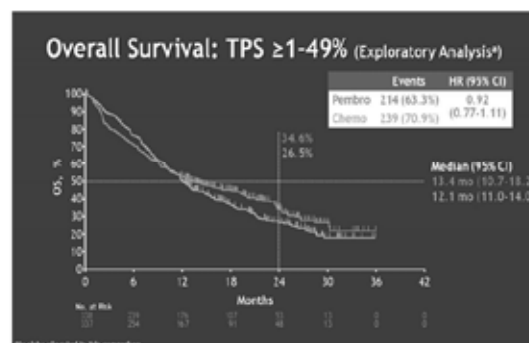
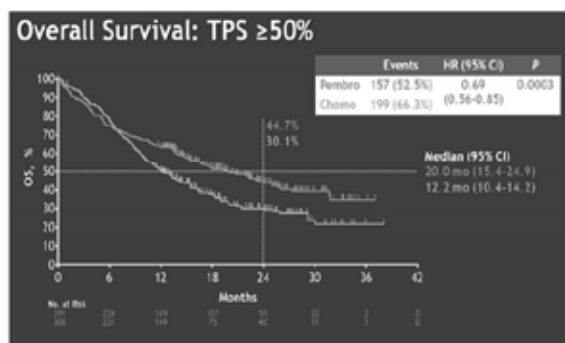
Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 $\geq 1\%$ NSCLC



Lopes et al, ASCO 2018

## KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 $\geq 1\%$ NSCLC Overall Survival



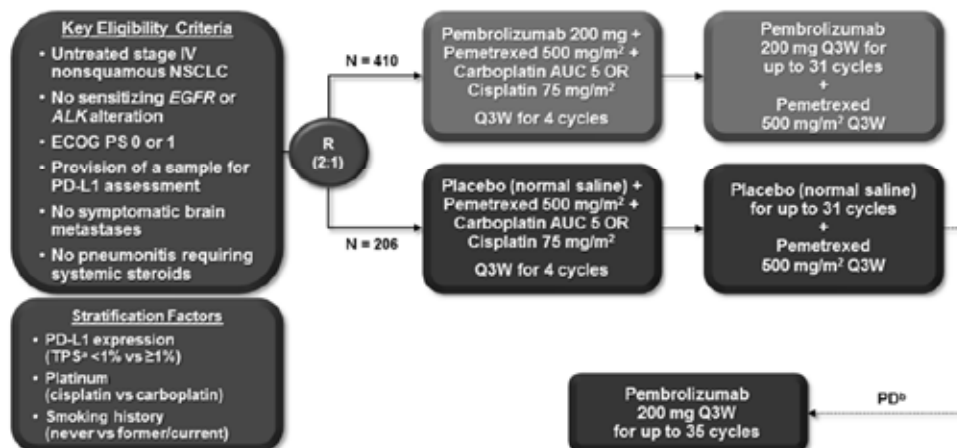
Survival benefit seemed to be driven by the TPS  $\geq 50\%$  subset with little benefit witnessed in the subset TPS = 1 - 49%

Lopes et al, ASCO 2018

# Immunotherapy for the Treatment of Lung Cancer

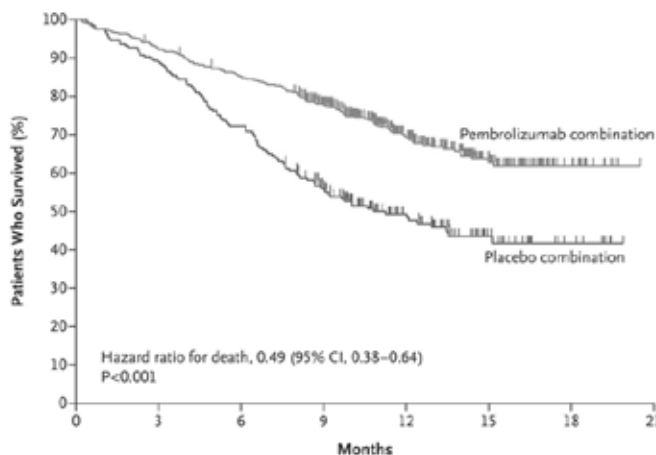
Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## 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

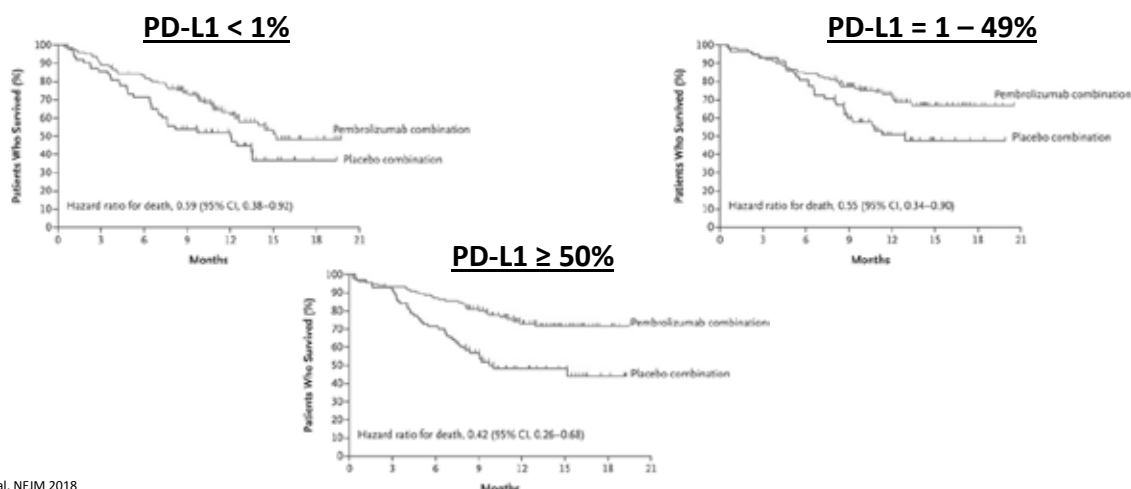


Ghandi et al, NEJM 2018

# Immunotherapy for the Treatment of Lung Cancer

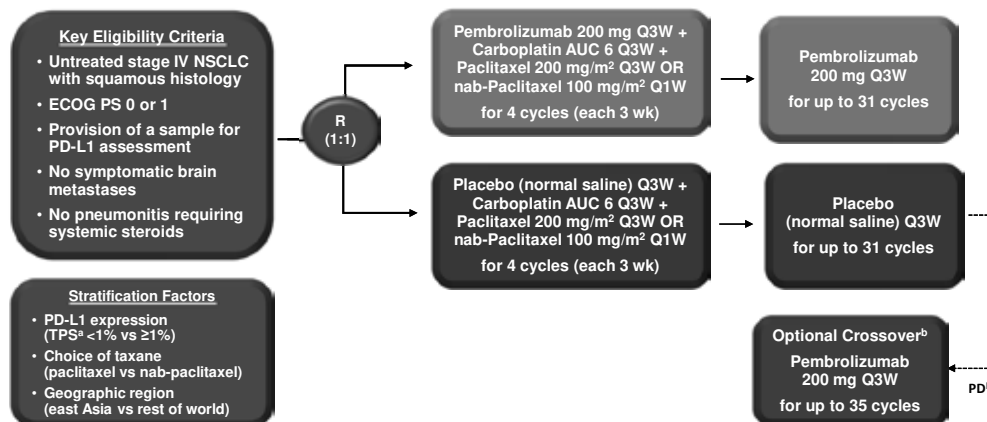
Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

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



Ghandi et al, NEJM 2018

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

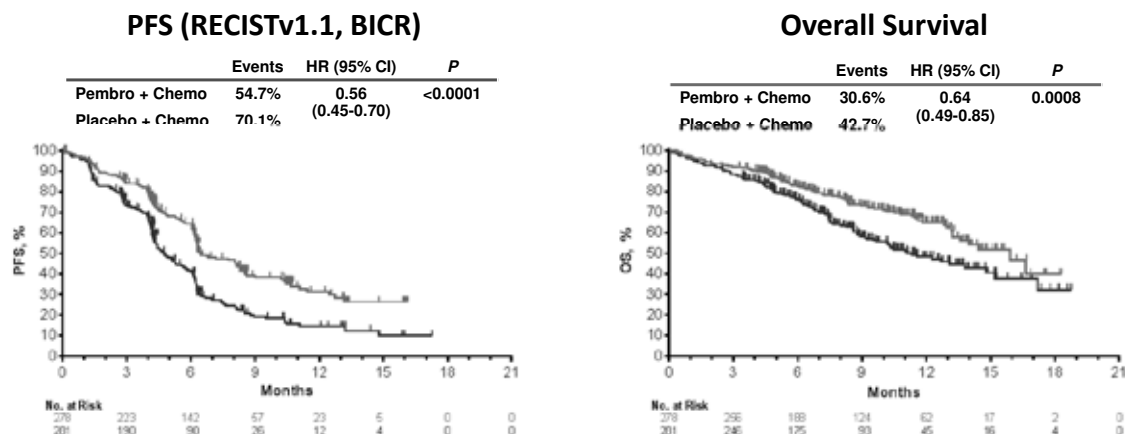


Paz-Ares et al, ASCO 2018

# Immunotherapy for the Treatment of Lung Cancer

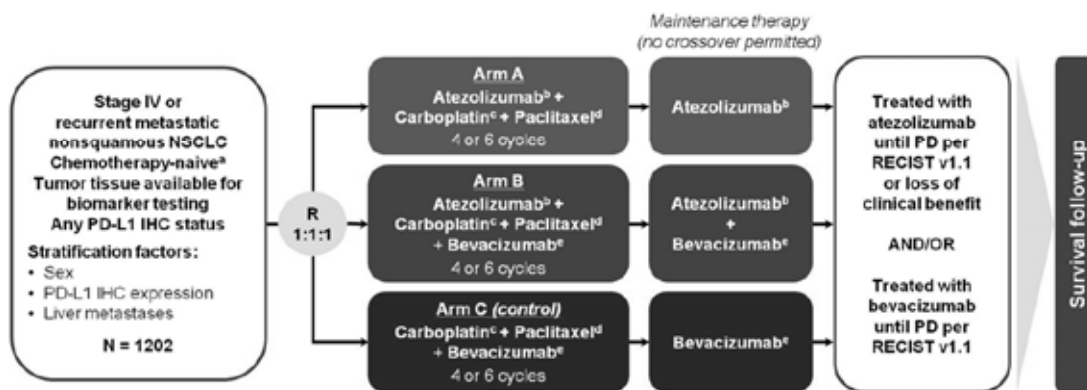
Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

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



Paz-Ares et al, ASCO 2018

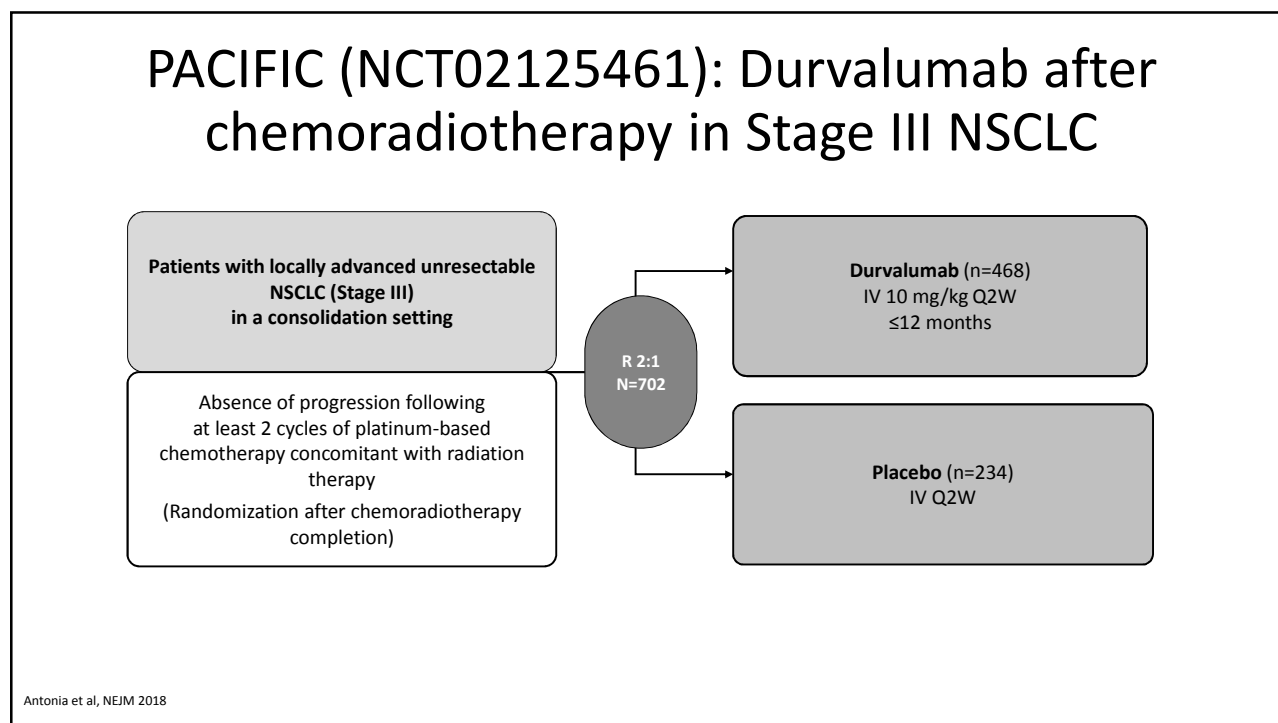
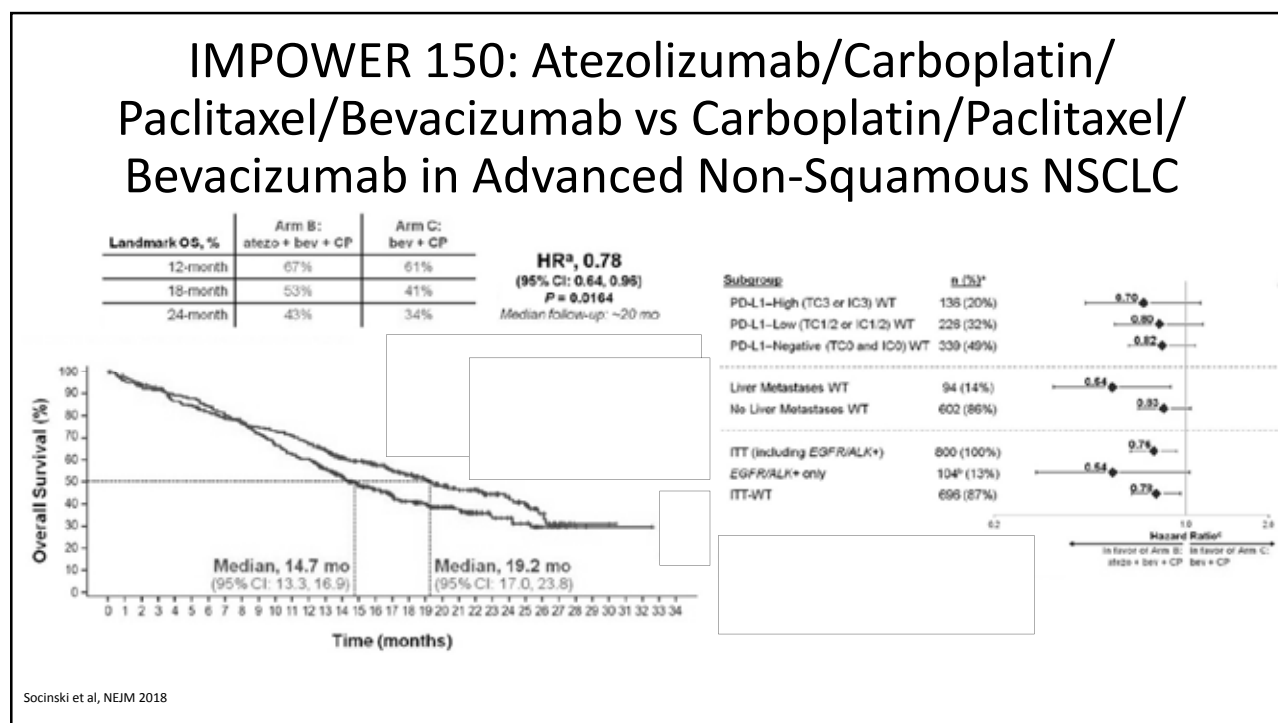
## IMPOWER 150: Atezolizumab/Carboplatin/Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/Bevacizumab in Advanced Non-Squamous NSCLC



Socinski et al, NEJM 2018

# Immunotherapy for the Treatment of Lung Cancer

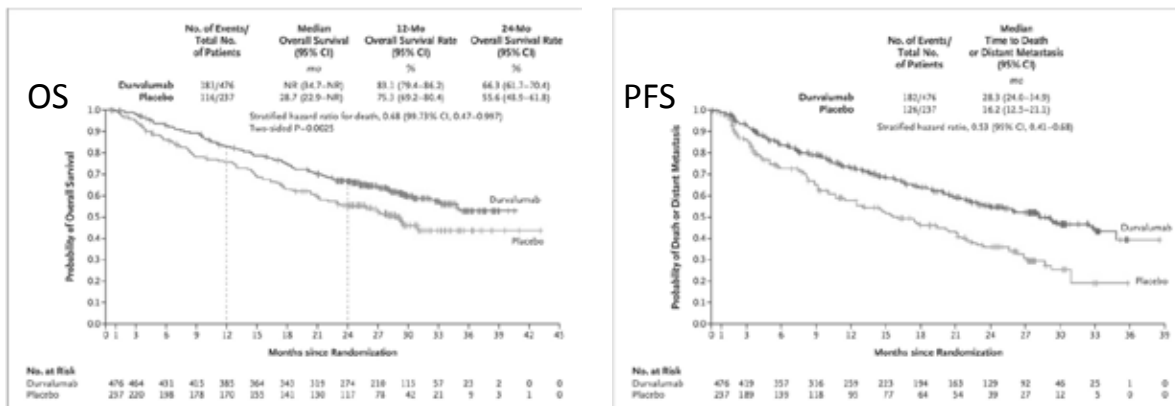
Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health



# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

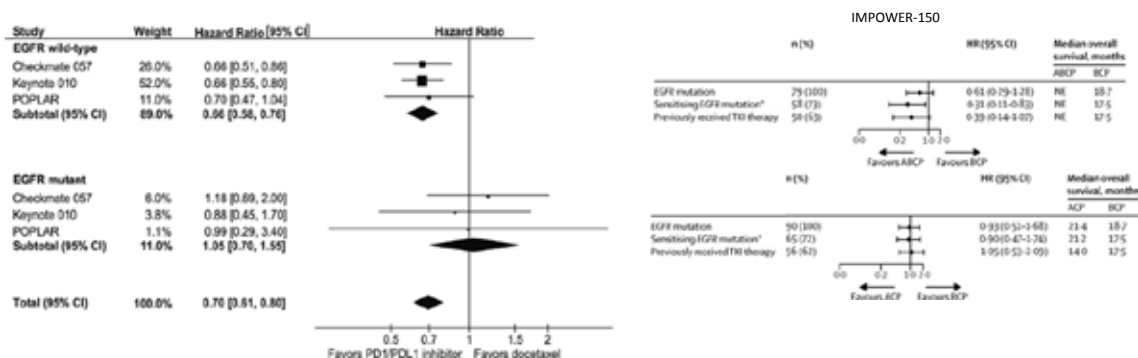
## PACIFIC (NCT02125461): Durvalumab after chemoradiotherapy in Stage III NSCLC



3-year OS update (stratified HR 0.69, 95% CI, 0.55–0.86) = median OS NR with durvalumab vs 29.1 months with placebo.  
12-, 24- and 36-month OS rates were 83.1% versus 74.6%, 66.3% versus 55.3%, and 57.0% versus 43.5%, respectively.

Antonia et al, NEJM 2018  
Gray et al, JTO 2019

## 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

# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## 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=115)	9.2 (7.3–13.3)	42 (34–50)	86
Docetaxel (N=117)	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<sup>a</sup>  
(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 2<sup>nd</sup> line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

# Immunotherapy for the Treatment of Lung Cancer

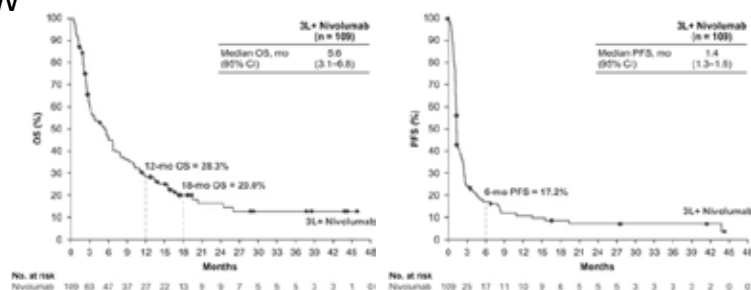
Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## Approved checkpoint inhibitors in SCLC

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

## CheckMate-032: Nivolumab in 3<sup>rd</sup> 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



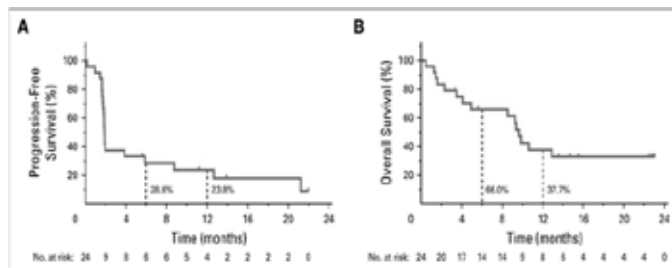
# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## Pembrolizumab in 3<sup>rd</sup>-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  $\geq 18$  mo.
- mOS: 7.7 months

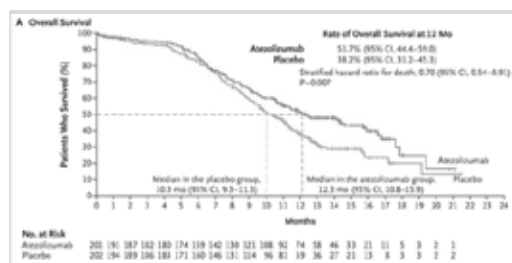
PD-L1+ (KEYNOTE-028)



Ott, J Clin Oncol 2017.

## IMpower133: Atezolizumab + chemo in 1<sup>st</sup>-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.

# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## Conclusions

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

## Resources



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

# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – *Levine Cancer Institute, Atrium Health*

## Case Studies

### Case Study 1

- A 46-year-old female never-smoker presents to medical oncology with a new diagnosis of metastatic adenocarcinoma of the lung based on contrasted CT chest and pleural fluid cytology.
- She has a remote history of Hodgkin lymphoma treated with MOPP-ABVD (and no radiation).
- She initially presented with a right pleural effusion under tension and underwent emergent thoracentesis with the removal of 1700cc of pleural fluid.
- Cytology was positive for malignancy: CK-7 and TTF-1 positive; GATA-3, PAX-8, CDX-2 and CK20 are negative; mucicarmine is negative; napsin and estrogen receptor staining is weak.
- She has recurrent pleuritic pain, shortness of breath, cough, and nausea without emesis. However, her ECOG PS is still zero.

# Immunotherapy for the Treatment of Lung Cancer

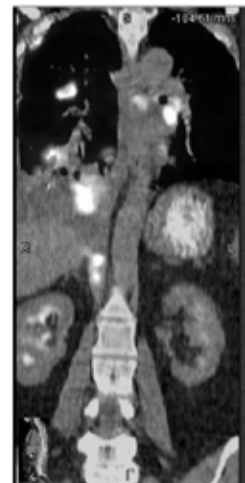
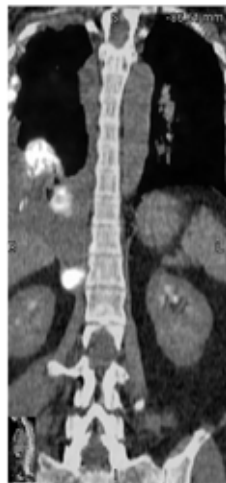
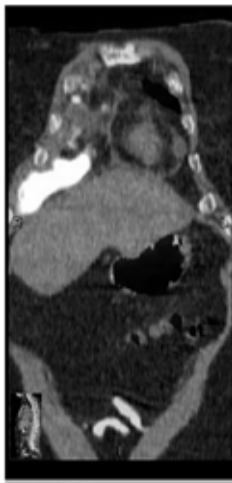
Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## Case Study 1: What additional information do you need?

1. Brain MRI with and without contrast
  1. Standard of care to complete staging
  2. Patient has nausea
2. PET/CT
  1. Standard of care to complete staging
  2. Patient already has known metastatic disease and primary tumor was not identified on contrasted CT with voluminous effusion
3. Molecular studies
  1. Standard of care with metastatic non-squamous non-small cell lung cancer
  2. Recommended with metastatic squamous cell non-small cell lung cancer in never smokers
  3. These should include but are not limited to EGFR, ALK, ROS1, BRAF, PD-L1, +/- NTRK.

## Case Study 1: Additional Information

1. Brain MRI with and without contrast – negative for malignancy
2. PET/CT – as demonstrated
3. Molecular studies
  1. EGFR, ALK, ROS1, BRAF non-mutated on tissue
  2. No driver aberrations on plasma
  3. PD-L1 TPS zero



# Immunotherapy for the Treatment of Lung Cancer

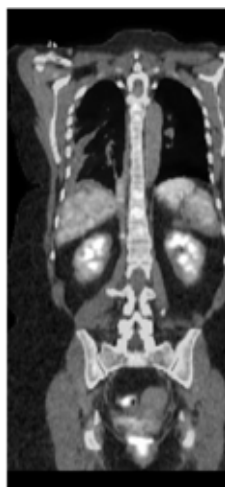
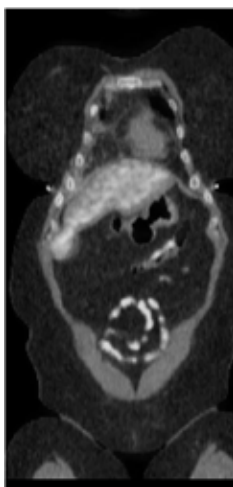
Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## Case Study 1: What is the next step?

- A. Carboplatin-pemetrexed
  - A. Incorrect. This is no longer the standard of care.
- B. Pembrolizumab monotherapy
  - A. Incorrect. The PD-L1 TPS is zero.
- C. Carboplatin-pemetrexed-pembrolizumab
  - A. Correct. Based on KEYNOTE-189, this regimen can improve RR, PFS, OS regardless of PD-L1 TPS when compared with carboplatin-pemetrexed.
- D. Carboplatin-paclitaxel-bevacizumab-atezolizumab
  - A. Correct. Based on IMPOWER-150, this regimen can improve outcome regardless of PD-L1 TPS when compared with carbo-taxol-bevacizumab.
- E. EGFR tyrosine kinase inhibitor
  - A. Incorrect. Just because she is a never smoker does not mean that she will respond to an EGFR TKI. There was no EGFR sensitizing mutation.
- F. Obtain more information prior to starting treatment
  - A. This is no indication for delay treatment in a symptomatic patient with the current information.
  - B. The cell block was sent for broader molecular sequencing and was not revealing.
- G. Pursue clinical trial
  - A. This is always an appropriate option.
  - B. She was excluded due to history of lymphoma.
- H. Provide other supportive interventions
  - A. Consulting palliative medicine, nutrition, social work, navigation, integrative medicine is always an appropriate option.
  - B. She had no indication for palliative radiation. She did have a pleural based catheter placed.

## Case Study 1: Results

- This patient was diagnosed on 3/30/2017.
- The data from IMPOWER150 were not available.
- She was treated with four cycles of pembrolizumab-carboplatin-pemetrexed.
- She then transitioned to pembrolizumab-pemetrexed maintenance.
- She completed 35 cycles of pembrolizumab.
- She continued pemetrexed maintenance.



# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## Case Study 2

- 78-year-old female with a history of hypertension and hyperlipidemia presents with a new diagnosis of extensive stage small cell lung cancer.
- She smoked 2 packs of cigarettes daily for 20 years and quit in 1990.
- She initially presented with unresolving cough and progressive dyspnea.
- CT angiogram of the chest was negative for pulmonary embolus but revealed a right lung mass, adenopathy, post-obstructive consolidation and metastatic findings in the subcutaneous tissue and liver.
- She underwent endobronchial ultrasound with biopsy via bronchoscopy and pathology was consistent with small cell lung cancer (Positive IHC for Synaptophysin, Cytokeratin Cam 5.2, CD56 and TTF-1).

## Case Study 2: What additional information do you need?

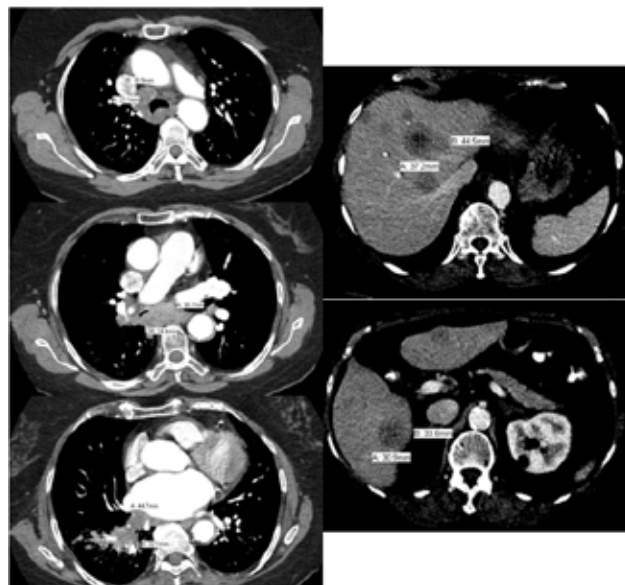
- Brain MRI with and without contrast
  - Standard of care to complete staging
- CT abdomen/pelvis with contrast
  - Standard of care to complete staging
- PET/CT
  - Not required if extensive stage is already established but recommended and if not available, then bone scan may be used to identify metastases
- Labs including sodium
  - SIADH and other paraneoplastic processes are not uncommon in small cell lung cancer
- PD-L1 TPS
  - No indication for PD-L1 TPS or TMB testing in small cell lung cancer
- ECOG PS
  - Good PS (0-2) and poor PS (3-4) due to SCLC should be treated per standard

# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – Levine Cancer Institute, Atrium Health

## Case Study 2: Additional Information

1. Brain MRI with and without contrast – negative for malignancy
2. CT abdomen/pelvis – confirmed extensive metastatic disease in liver; negative for bone involvement
3. PET/CT – not completed
4. Sodium – 141 (normal)
5. ECOG PS – one



## Case Study 2: What is the next step?

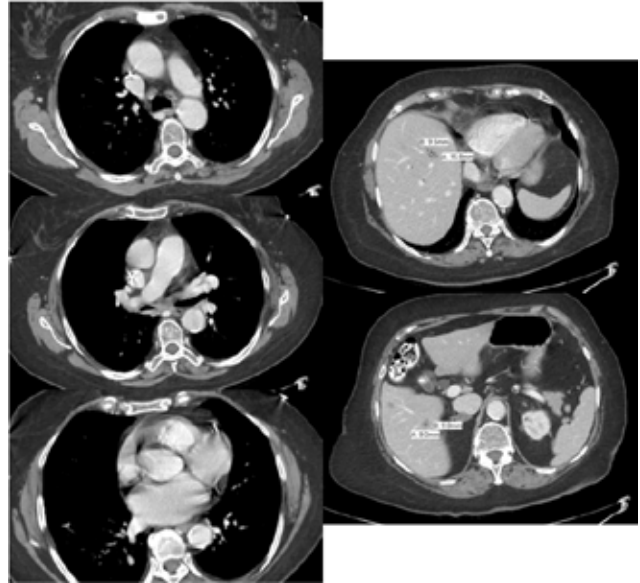
- A. Carboplatin-etoposide
  - A. Incorrect. This is no longer the preferred standard of care, however it remains an appropriate first line treatment option.
- B. Carboplatin-etoposide-atezolizumab
  - A. Correct. Based on IMPOWER133, this regimen can improve PFS, OS regardless of PD-L1 TPS when compared with carboplatin-etoposide.
  - B. However based on cost analyses, potential toxicities, and still challenging outcomes, it has been slow for wide adoption.
- C. Platinum-etoposide-durvalumab
  - A. Although listed in NCCN guidelines based on the CASPIAN trial (Paz-Ares et al, The Lancet 10/4/2019), this regimen does not yet have FDA approval.
- D. Pursue clinical trial
  - A. This is always an appropriate option.
- E. Provide other supportive interventions
  - A. Consulting palliative medicine, nutrition, social work, navigation, integrative medicine is always an appropriate option.
  - B. She had no indication for palliative radiation.

# Immunotherapy for the Treatment of Lung Cancer

Kathryn F. Mileham, MD, FACP – *Levine Cancer Institute, Atrium Health*

## Case Study 2: Results

- This patient received carboplatin-etoposide-attezolizumab.
- After four cycles, she transitioned to atezolizumab maintenance.
- She declined prophylactic cranial irradiation.



Thank you for your attention.



# Immunotherapy for the Treatment of Head and Neck Cancers

**Daniel R. Carrizosa, MD, MS**  
Section Leader: Head and Neck Cancer  
*Levine Cancer Institute*



Daniel R Carrizosa, MD MS Currently serves as the section chief for head and neck oncology at the Levine Cancer Institute part of Atrium Health in Charlotte, NC. He is also an active founding member of the lung cancer section. At Levine, he also serves as the associate program director for the hematology/oncology fellowship and he is the medical director for the outreach and disparities program. He currently serves as an appointed member of the NC Governor's Committee on Cancer Prevention and Control and he is on the executive leadership board for the NC Oncology Association. He was recently a top-5 finalist for Physician of the Year at Atrium Health from a pool of over 3000 physicians. He received his Medical Degree and fellowship training at the University of North Carolina at Chapel Hill and received his Bachelor of Science in Engineering and his Master of Science from Duke University.

## Immunotherapy for the Treatment of Head and Neck Cancer

Daniel R Carrizosa, MD MS

Chief, Section of Head and Neck Medical Oncology

Levine Cancer Institute – Atrium Health

## Disclosures

- Contracted Research: Aeglea Biotherapeutics, Astra-Zeneca, GlaxoSmithKline, Loxo, Merck, Pfizer
- I will be discussing non-FDA approved indications during my presentation.

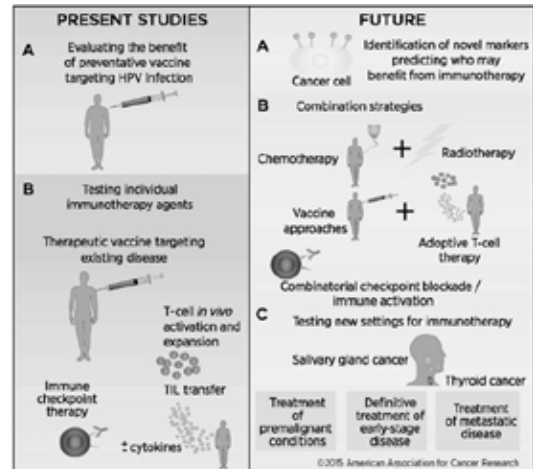
# Immunotherapy for the Treatment of Head and Neck Cancers

Daniel R. Carrizosa, MD, MS – Levine Cancer Institute

## 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

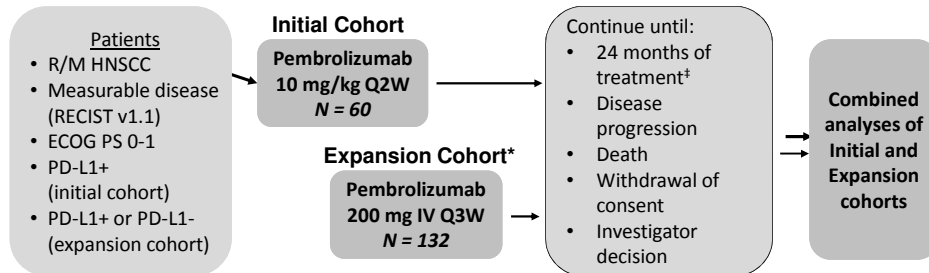
Drug	Approved	Indication	Dose
Pembrolizumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	200 mg Q3W
Nivolumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	240 mg Q2W or 480 mg Q4W
Cemiplimab-rwlc	2018	Metastatic cutaneous squamous cell carcinoma, not candidate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

# Immunotherapy for the Treatment of Head and Neck Cancers

Daniel R. Carrizosa, MD, MS – Levine Cancer Institute

## KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts<sup>†</sup> 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<sup>§</sup>

<sup>†</sup>Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.

<sup>‡</sup>Treatment beyond progression was allowed.

<sup>§</sup>Initial cohort only.

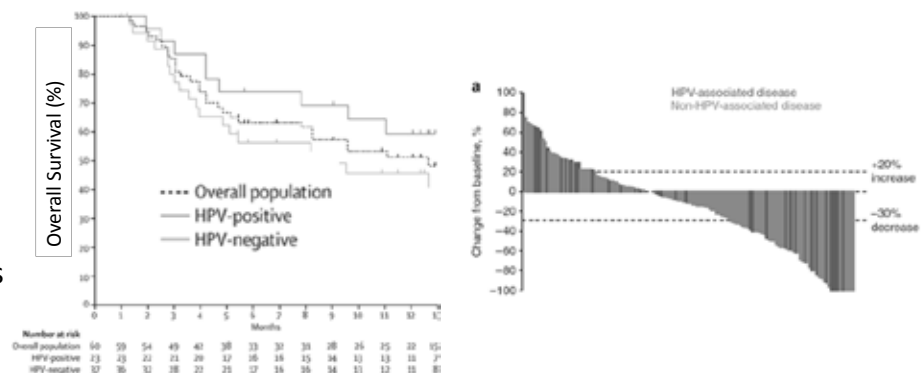
\*Median duration of disease not reached.

Seiwert, ASCO 2017.

## KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts<sup>†</sup> B, B2

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

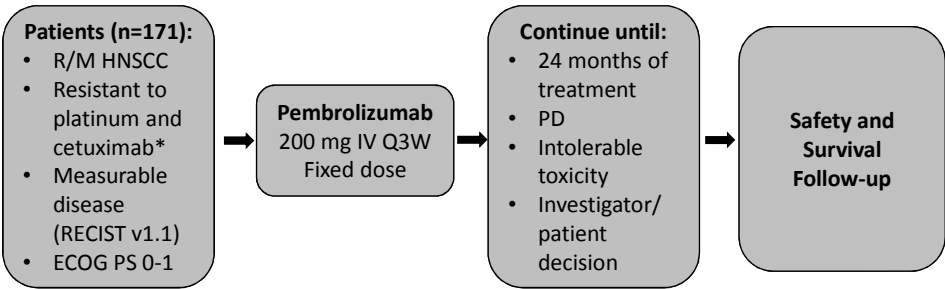


Seiwert, ASCO 2017.  
Mehra, Br J Can 2018.

# Immunotherapy for the Treatment of Head and Neck Cancers

Daniel R. Carrizosa, MD, MS – Levine Cancer Institute

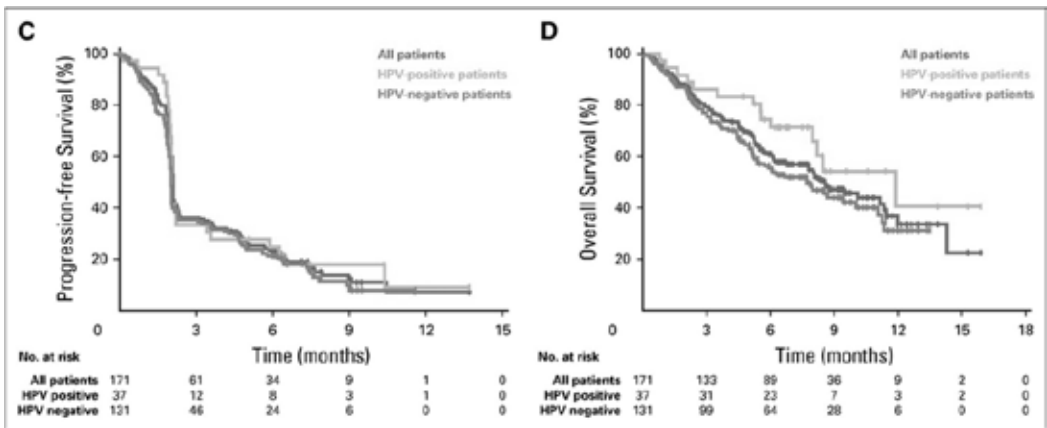
## KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab Phase II Trial, Single Arm



**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

Baumli, J Clin Oncol 2017.

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



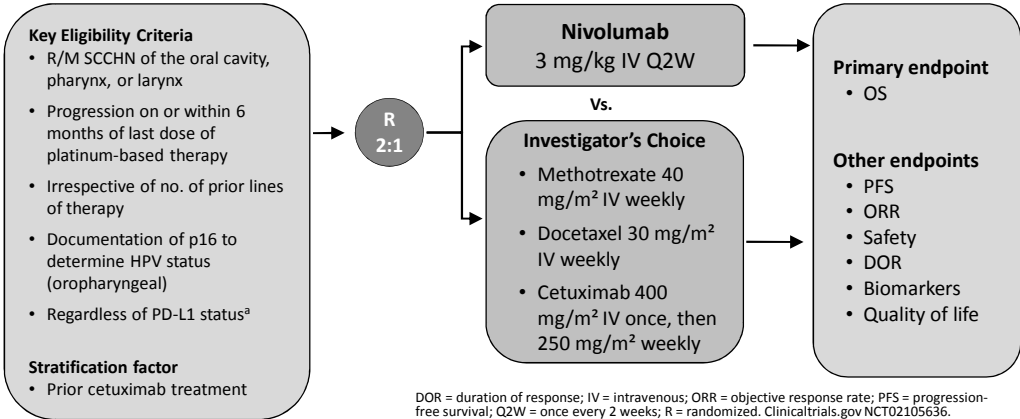
Baumli, J Clin Oncol 2017.

# Immunotherapy for the Treatment of Head and Neck Cancers

Daniel R. Carrizosa, MD, MS – Levine Cancer Institute

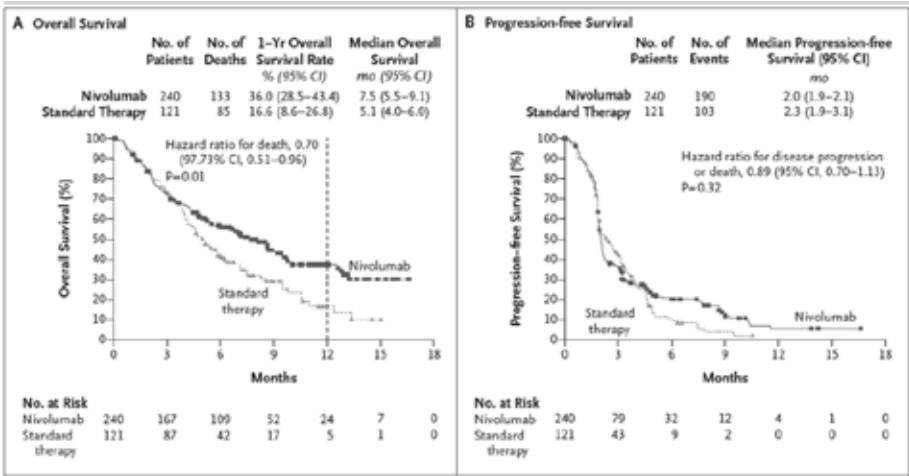
## CheckMate 141: Nivolumab vs Investigator’s Choice in R/M HNSCC after Platinum Therapy

Phase III Randomized, Safety and Efficacy Trial



Ferris & Gillison, NEJM 2016.

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



Ferris & Gillison, NEJM 2016.

# Immunotherapy for the Treatment of Head and Neck Cancers

Daniel R. Carrizosa, MD, MS – Levine Cancer Institute

## 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
- $\geq 1$  assessable lesion



**Cemiplimab**  
3 mg/kg IV Q2W



### Primary endpoint

- Response rate

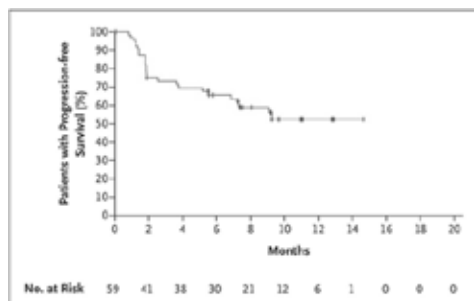
### Other endpoints

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

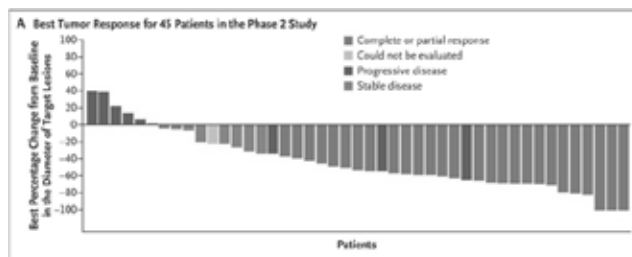
Migden, NEJM 2018.

## 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



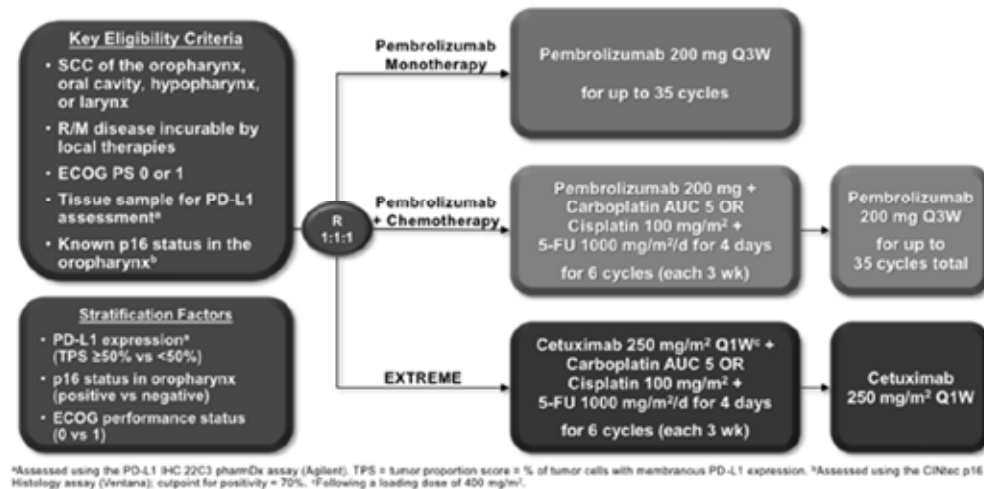
Migden, NEJM 2018.



# Immunotherapy for the Treatment of Head and Neck Cancers

Daniel R. Carrizosa, MD, MS – Levine Cancer Institute

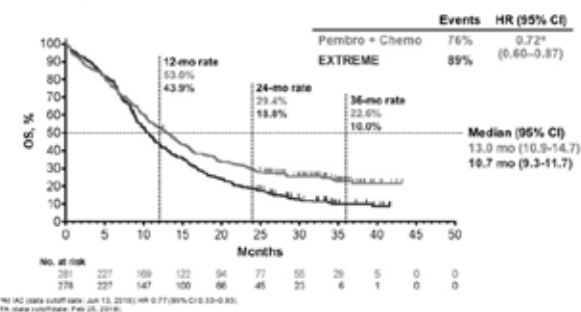
## KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC



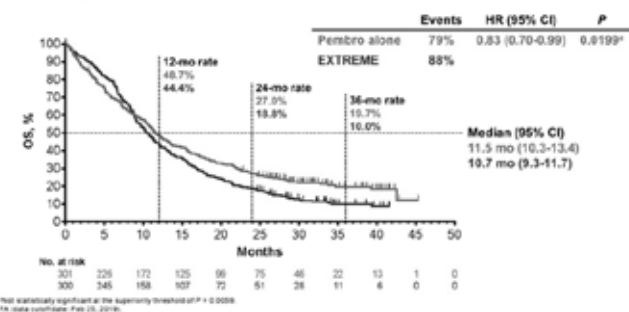
Rischin, ASCO 2019.

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

OS, P+C vs E, Total Population



OS, P vs E, Total Population



Rischin, ASCO 2019.



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

### Summary of Overall Survival

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

<sup>a</sup>Superiority demonstrated. <sup>b</sup>No inferiority demonstrated (boundary of 1.2). <sup>c</sup>No statistical testing performed. <sup>d</sup>Superiority not demonstrated.  
1. Burtness B et al. Ann Oncol 2018;29(suppl 8):LSA03\_P08.

Rischin, ASCO 2019.

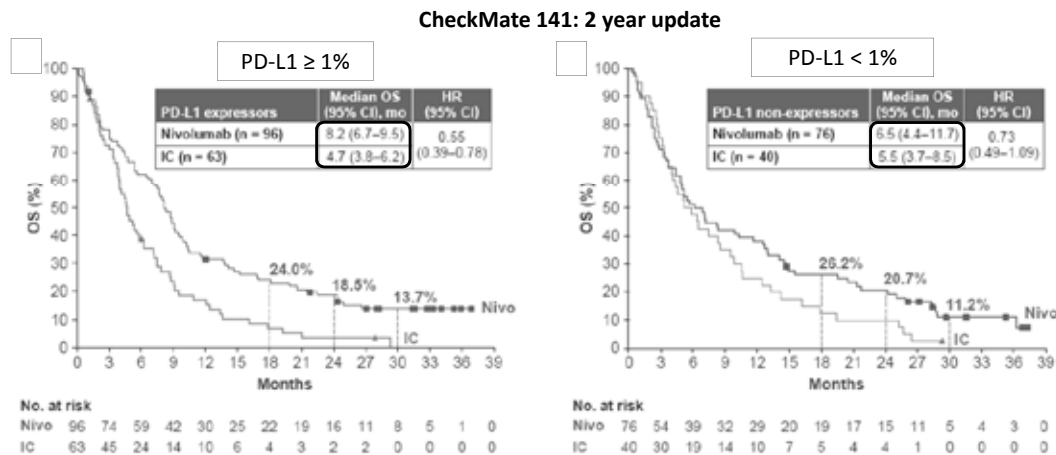
## Evaluating Biomarkers in HNSCC

- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1<sup>st</sup> 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

# Immunotherapy for the Treatment of Head and Neck Cancers

Daniel R. Carrizosa, MD, MS – Levine Cancer Institute

## Evaluating Biomarkers in HNSCC



Ferris, Oral Oncol 2018.

## In development: T-VEC + pembrolizumab KEYNOTE-137

- T-Vec 10<sup>6</sup> PFU/mL intratumoral injection followed by 10<sup>8</sup> 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.

# Immunotherapy for the Treatment of Head and Neck Cancers

Daniel R. Carrizosa, MD, MS – Levine Cancer Institute

## Resources



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

## Case Studies

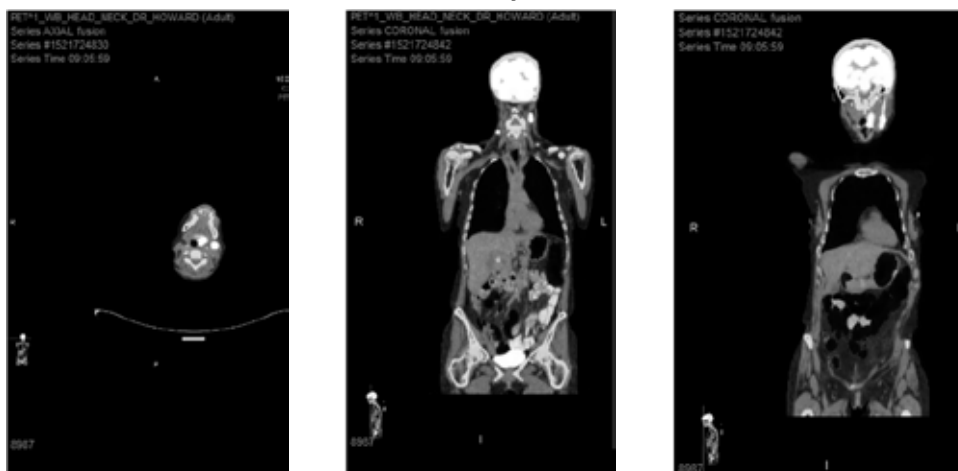
# Immunotherapy for the Treatment of Head and Neck Cancers

Daniel R. Carrizosa, MD, MS – Levine Cancer Institute

## Case Study 1

- 50 yo female presents to office after being referred by ENT
  - 3 months of progressive dysphagia/odynophagia
  - Left tonsillar mass on flexible fiberoptic visualization
  - FNA of left cervical lymph node
    - Squamous cell carcinoma – P40 positive
    - P16 negative
  - PET scan shows no evidence of disease outside the head and neck
  - PMHx: Only Tobacco and ETOH Abuse
  - SHx: 80 oz beer daily but quit at cancer diagnosis (no DTs); current smoker with 10 pack year history (1 pack every 3 days)
  - Exam: benign except for mild submental lymphedema, no palpable lymphadenopathy or visible oropharyngeal mass

## Case Study 1



## Case Study 1

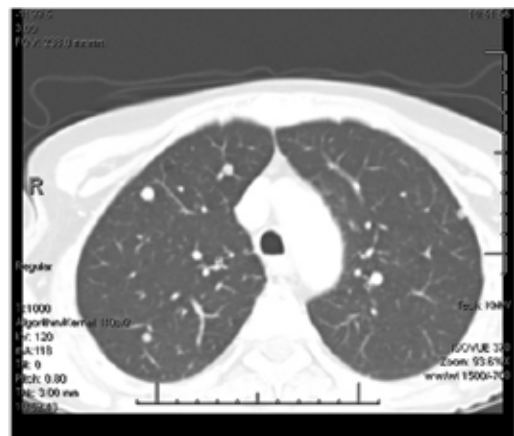
- What would be your expected treatment plan?
  - Referral for TransOral Robotic Surgery
    - Incorrect: Though on NCCN as an option, patient has high risk of Extranodal extension and would likely need trimodality therapy that will have greater risk of morbidity
  - Induction chemotherapy
    - Incorrect: Category 3 on NCCN as there is no survival benefit and no indication per LCI guidelines (bulky cervical lymphadenopathy, inability to start radiation in a timely manner)
  - Concurrent chemoradiation with Cisplatin
    - Correct: Personal preference of Bolus Cisplatin (100mg/m<sup>2</sup> q3wks \* 3) as she is a young patient with no hearing or renal issues but weekly cisplatin (40mg/m<sup>2</sup>) is also an option
  - Clinical Trial
    - Correct: always on option but patient was not interested in research

## Case Study 1

- Treated with Bolus Cisplatin (100mg/m<sup>2</sup>) with concurrent radiation
  - Received all three cycles with no delay or dose reduction
  - No renal dysfunction or clinical hearing loss or tinnitus
- PET Scan 3 months following completion of radiation
  - Complete Response (CR) with no residual tonsillar mass or lymphadenopathy

Daniel R. Carrizosa, MD, MS – *Levine Cancer Institute*

- Coming in for 6 month follow-up
- Has been “not feeling well like when I was diagnosed with cancer”
- Lost 8 lbs without intent
- No clinical lymphadenopathy and no lesion on direct visualization of the tonsil
- CT Scan of neck ordered:



## Case Study 1



## Case Study 1

- What would you do now?
  - Biopsy to document recurrence and check PD-L1
    - Correct: PD-L1 would guide treatment therapy and prove recurrence in smoker
  - Empirically treat with Extreme Regimen (Platinum/Cetuximab/5-FU)
    - Incorrect: Keynote 048 would favor either pembrolizumab (CPS $\geq$ 1) or chemoimmunotherapy (platinum/5-FU/pembrolizumab for any or unknown CPS)
  - Treat with Pembrolizumab
    - Correct if PD-L1 (CPS)  $\geq$  1; Incorrect if CPS of 0
  - Treat with Platinum/5-FU/Pembrolizumab
    - Correct: Option available without knowing CPS or if patient needs immediate response or if there is a concern that they are progressing rapidly

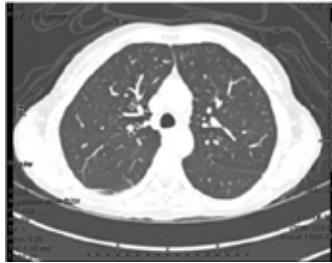


# Immunotherapy for the Treatment of Head and Neck Cancers

Daniel R. Carrizosa, MD, MS – Levine Cancer Institute

## Case Study 1

- Patient underwent biopsy:
  - CT-guided core showed squamous cell carcinoma c/w known disease
  - CPS 25%
- Started on Pembrolizumab alone w/ CR after 3 doses



## Case Study 2

- 77 yo female with a past medical history of Diabetes Mellitus, hypertension and R MCA CVA and recurrent TIAs presents in follow-up
  - Patient treated 6 years prior for squamous cell carcinoma of the Right Upper lobe and NED
    - Resected (T2aN0M0) with lobectomy
    - Adjuvant chemotherapy (carboplatin/paclitaxel \* 4)
  - Diagnosed with Right Squamous Cell Carinoma of the Pinna/Conchal Bowl 1 year ago and s/p MOHS surgery
    - Margins negative
  - Presents with enlarging mass in Right Neck
- MEDS: Clopidogrel, ASA, Insulin, Carvedilol, Losartan, Ezetimibe, Tramadol
- PMHx: DM, HTN, R MCA CVA (mild left-sided deficits), recurrent TIAs, MI (s/p drug eluting stent), GERD, hypercholesterolemia, COPD

## Case Study 2

- PE
  - Right ear with scarring and no lesion
  - Right Neck: 2 firm, mildly tender, immobile 2cm lesions inferior to right mastoid
  - Chest CTA
  - CV: irregularly irregular

## Case Study 2

- What would you do now?
  - CT Scan of the Neck/PET Scan
    - Correct: low-density enhancing lesion inferior to right ear lobe between tail of parotid and mastoid (2.3\*1.4cm), 2 Level 2A necrotic lymph nodes (1.8\*1.6cm and 1.4\*1cm), small lymph nodes in superior mediastinum with low density concerning for mets.
    - Correct: Above lesions are all FDG avid, No hilar lymphadenopathy, no other FDG-avid lesions.
  - Biopsy Lesion or cervical lymph node
    - Correct: Right FNA with malignant cells, poorly-differentiated c/w squamous cell carcinoma.
  - Refer to Surgery
    - Correct: Patient is not a surgical candidate due to comorbidities
  - Refer to Hospice as no treatment available for metastatic cutaneous squamous cell carcinoma
    - Incorrect: If patient is not a surgical candidate, could consider radiation or systemic therapy

# Immunotherapy for the Treatment of Head and Neck Cancers

Daniel R. Carrizosa, MD, MS – *Levine Cancer Institute*

## Case Study 2

- Patient not a surgical candidate due to comorbidities and could not come off of Plavix
- Patient saw radiation oncology and refused radiation (family member had bad experience)
- No history of autoimmune disease
- ECOG 1

## Case Study 2

- What would you do now?
  - Refer to Hospice as patient refused radiation
    - Incorrect: see below
  - Extreme Chemotherapy (carboplatin/cetuximab/5-FU)
    - Incorrect: No data in cutaneous squamous cell carcinoma of the head and neck
  - Cemiplimab-rwlc
    - Correct: Patient has no contraindication to PD-L1 blockade, higher response rates than chemotherapy or biologics
  - Cetuximab
    - Incorrect: As patient is a candidate for immunotherapy, would favor immunotherapy and this could be considered if ineligible for immune checkpoint inhibition or clinical trials.
  - Refer for Clinical Trial
    - Always correct

## Case Study 2

- Patient started Cemiplimab and had partial response after 3 cycles.
  - Pain had resolved and she was feeling well/hopeful
- Unfortunately, she then had a large hemorrhagic stroke leading to functional decline and death within a few weeks.

# Immunotherapy for the Treatment of Genitourinary Cancers

**Earle F. Burgess, MD**  
Medical Oncology  
*Levine Cancer Institute, Atrium Health*



Dr Earle Burgess earned his medical degree from the Medical College of Georgia. He completed his internship and residency in internal medicine at Vanderbilt University Medical Center in Nashville, Tennessee, and his fellowship in hematology/oncology at the same institution. Dr Burgess currently practices at the Levine Cancer Institute within Atrium Health in Charlotte, North Carolina, where he is an associate professor of medicine and leads the genitourinary oncology section. His research interests are focused on clinical and translational research with an emphasis in biomarker discovery and novel therapeutics in urothelial and prostatic malignancies.

## Immunotherapy for the Treatment of Genitourinary Malignancies

Earle F Burgess, MD  
Chief, Genitourinary Oncology Section  
Levine Cancer Institute  
Atrium Health

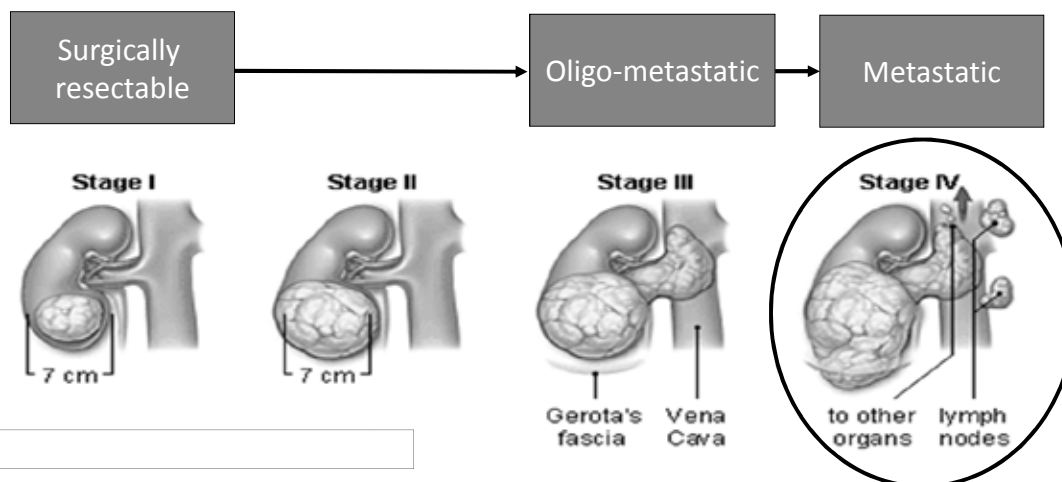
## Disclosures

- Consulting: Bayer, Exelixis, Janssen
- Research Funding: Pfizer
- Ownership Interest: Exelixis, Gilead
- I will be discussing non-FDA approved indications during my presentation.

# Immunotherapy for the Treatment of Genitourinary Cancers

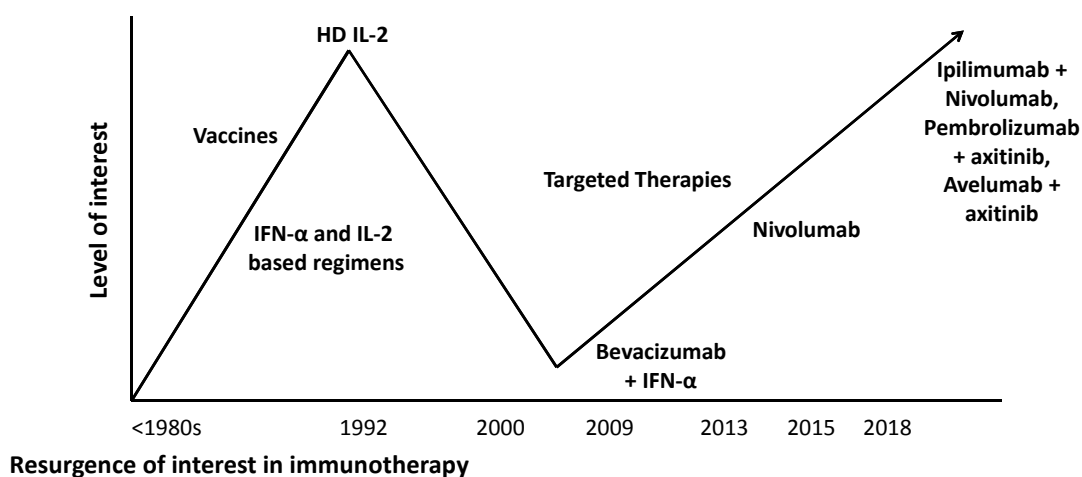
Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

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



reemakeup.blogspot.com

## History of Immunotherapy in mRCC



# Immunotherapy for the Treatment of Genitourinary Cancers

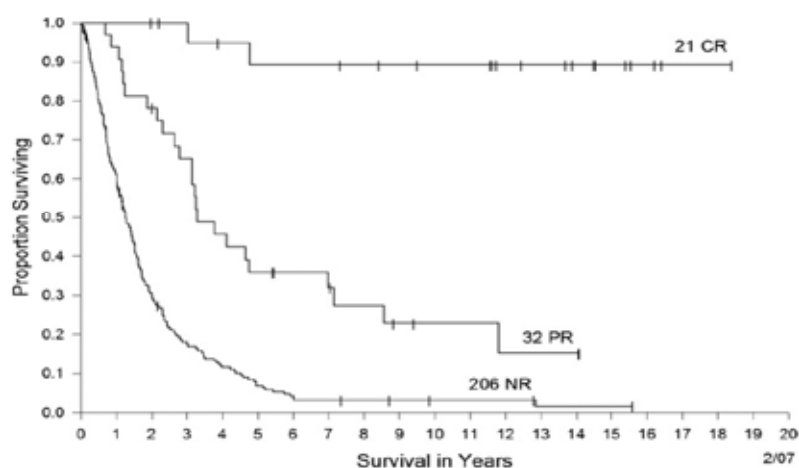
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## FDA-approved Immunotherapies for mRCC

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- $\alpha$ + 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

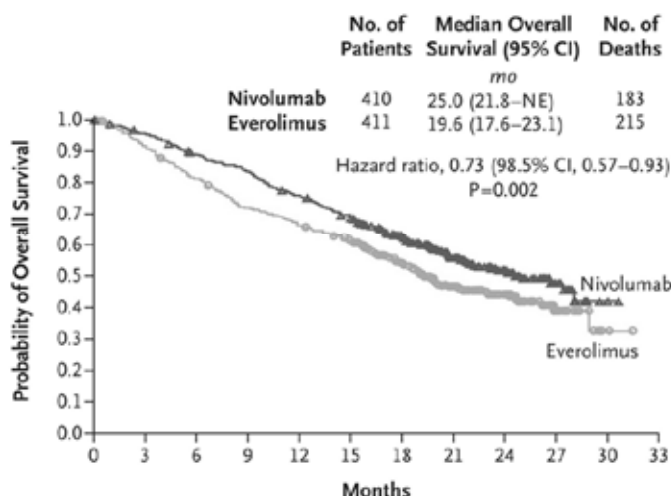


# Immunotherapy for the Treatment of Genitourinary Cancers

Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## Second-Line Nivolumab in mRCC

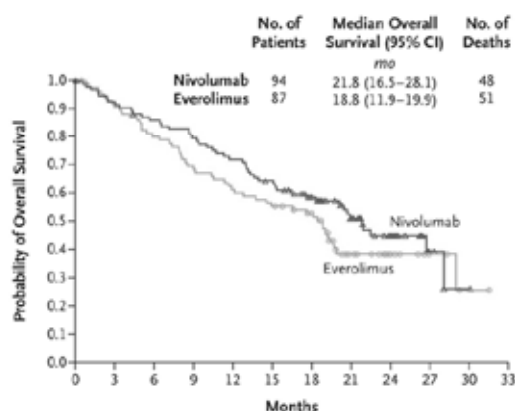
- CheckMate 025 Phase III trial
- Metastatic, clear-cell disease
- One or two previous antiangiogenic treatments
- Nivolumab (3 mg/kg IV Q2W) vs everolimus (10 mg daily)



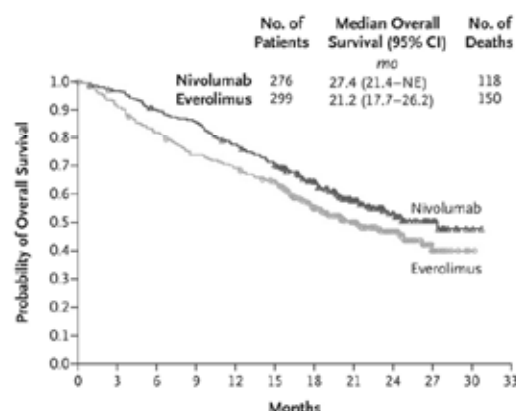
Motzer et al. NEJM 2015

## Second-Line Nivolumab in mRCC PD-L1 subgroups

### PD-L1 $\geq 1\%$



### PD-L1 < 1%

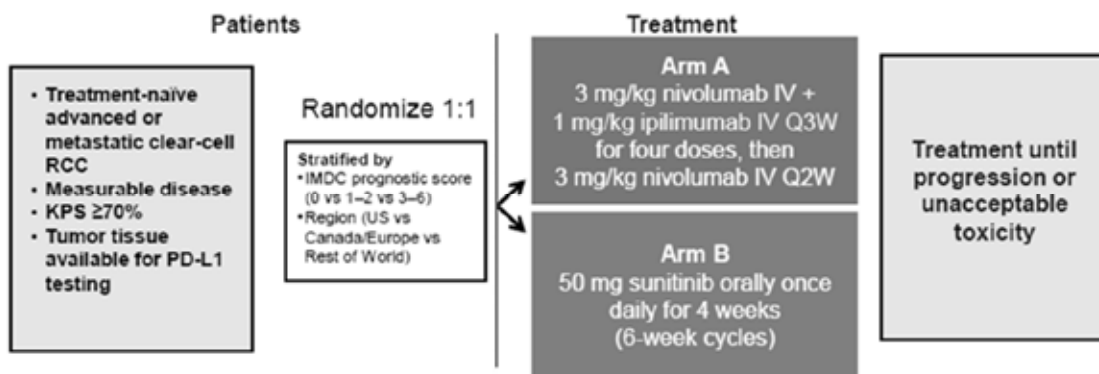


Motzer et al. NEJM 2015

# Immunotherapy for the Treatment of Genitourinary Cancers

Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## First-line Nivolumab + Ipilimumab in mRCC



Nivolumab = anti-PD-1 antibody

Ipilimumab = anti-CTLA-4 antibody

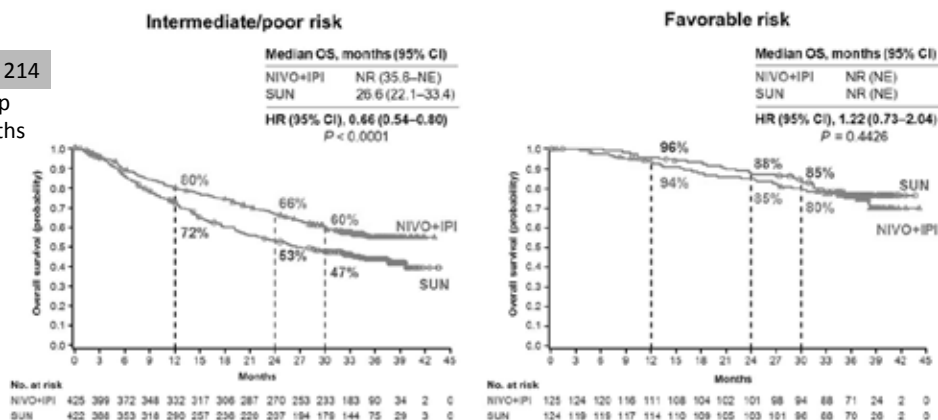
IMDC = International Metastatic RCC Database Consortium

Escudier et al. ESMO 2017

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

CheckMate 214

Follow-up  
= 30 months



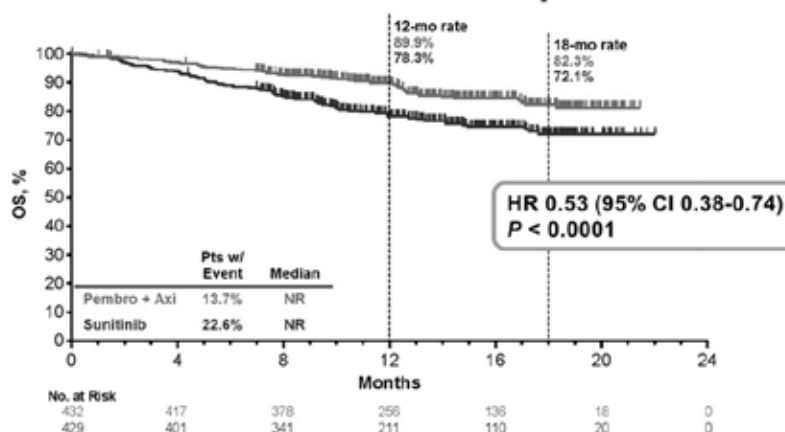
Tannir et al. ASCO GU 2019

# Immunotherapy for the Treatment of Genitourinary Cancers

Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

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

### KEYNOTE-426: OS in the ITT Population

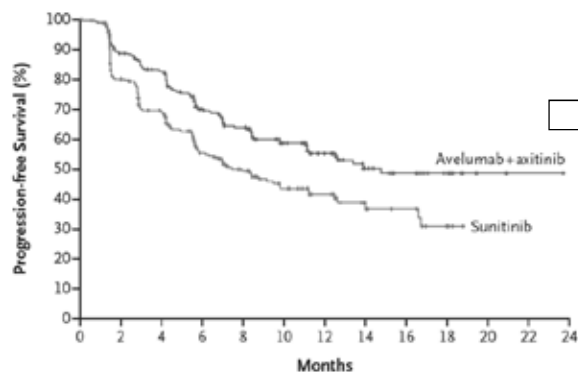


Rini, ASCO 2019

## 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



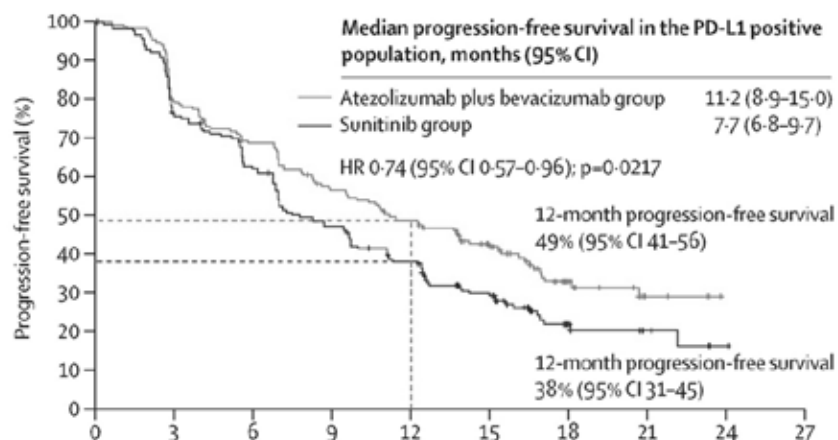
Motzer, NEJM 2019.

# Immunotherapy for the Treatment of Genitourinary Cancers

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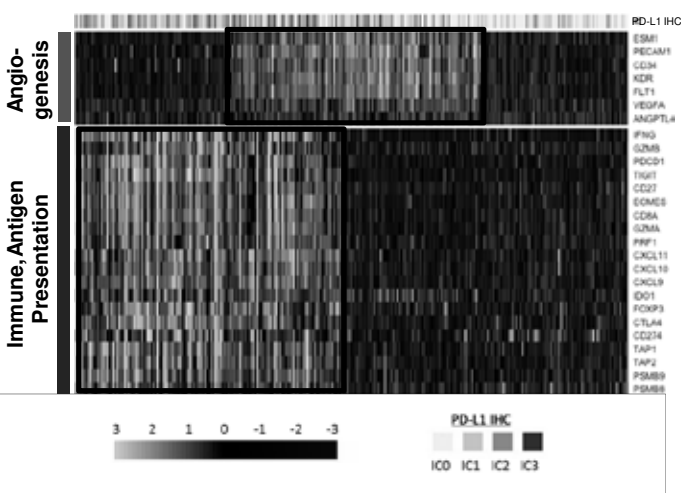
## In Development: First-line atezolizumab + bevacizumab in PD-L1+ mRCC

Immotion151



Rini, The Lancet 2019.

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



Identification of gene signatures based on association with clinical outcome

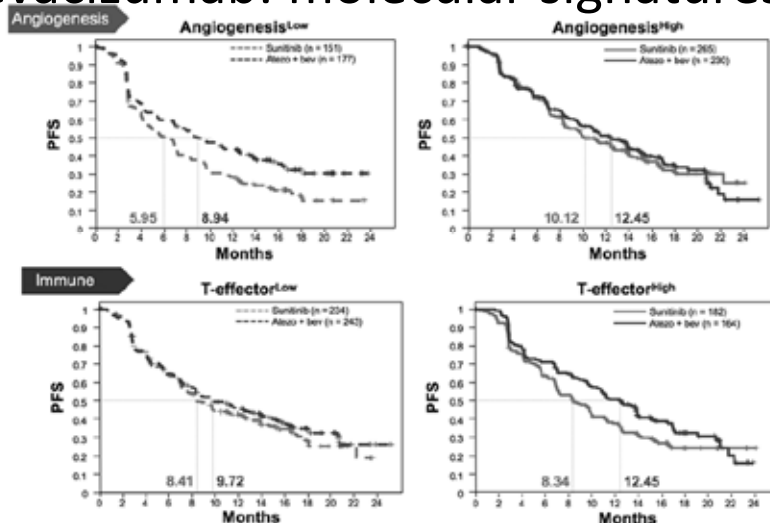
- T<sub>eff</sub>: CD8a, IFNG, PRF1, EOMES, CD274
- Angio: VEGFA, KDR, ESM1, PECAM1, CD34, ANGPTL4

Rini et al, ESMO 2018

# Immunotherapy for the Treatment of Genitourinary Cancers

Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## 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.

# Immunotherapy for the Treatment of Genitourinary Cancers

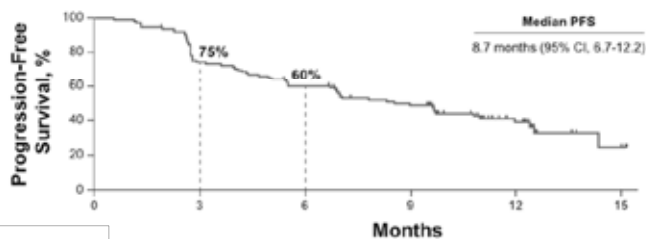
Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## 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



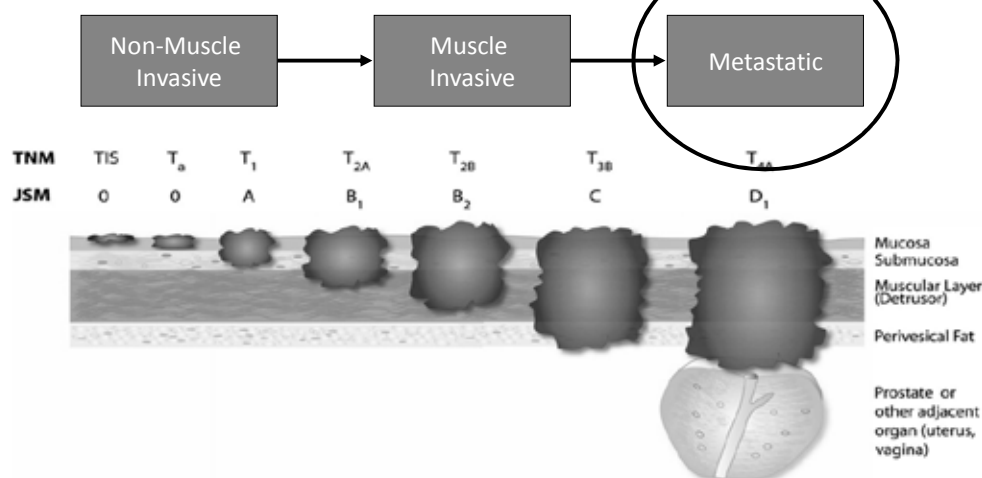
	N = 110
Confirmed ORR, % (95% CI)	36.4
CR, %	3 (3)
PR, %	37 (34)
DCR, %	57 (47-67)
DOR, median (range), mo	Not Reported
DOR ≥ 6 mo (responders), %	77

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

# Immunotherapy for the Treatment of Genitourinary Cancers

Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## 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

# Immunotherapy for the Treatment of Genitourinary Cancers

Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## Approved checkpoint inhibitors for mUC – *cisplatin ineligible*

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

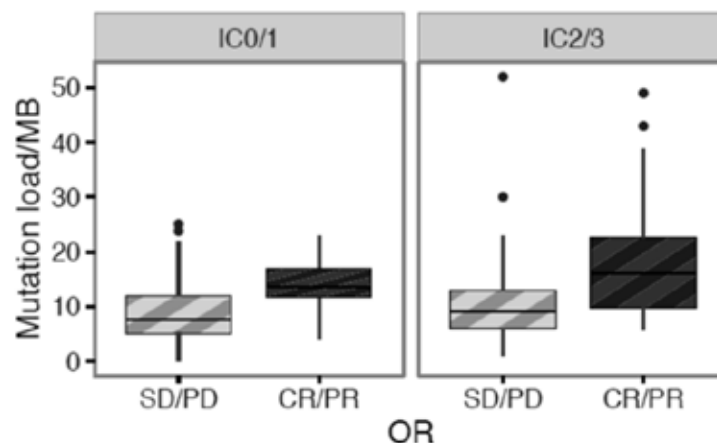
June 2018

### FDA limits the use of Atezolizumab and Pembrolizumab for some urothelial cancer patients

- Locally advanced or metastatic urothelial carcinoma and ineligible for cisplatin-based chemo and tumor PD-L1 (CPS  $\geq 10$ , pembro; IC  $\geq 5\%$  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

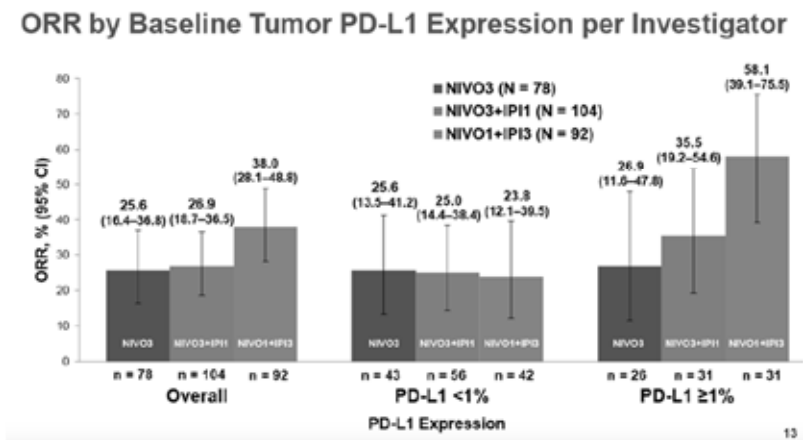
Atezolizumab in mUC



Rosenberg et al. Lancet 2016

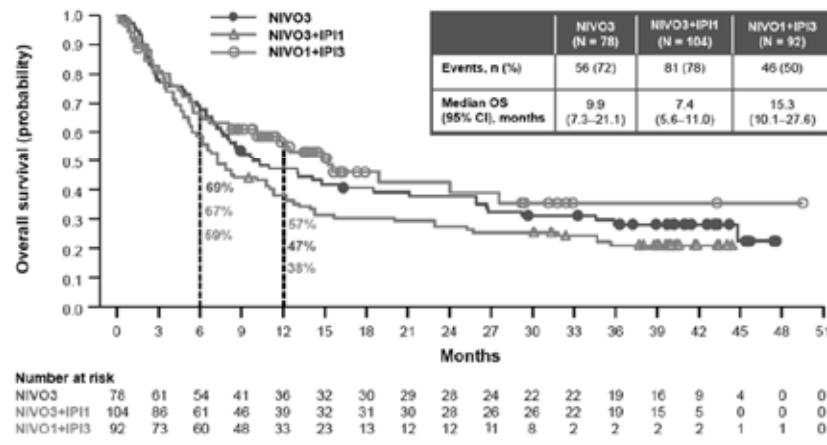


In development: Ipilimumab + Nivolumab  
CheckMate 032



Rosenberg, ESMO 2018

In development: Ipilimumab + Nivolumab  
CheckMate 032



Rosenberg, ESMO 2018

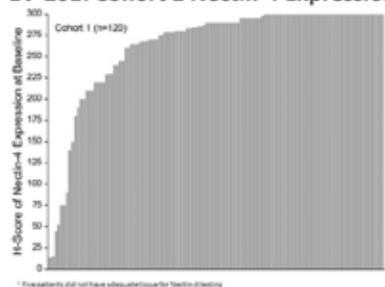
# Immunotherapy for the Treatment of Genitourinary Cancers

Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## Approved antibody-drug conjugate for mUC

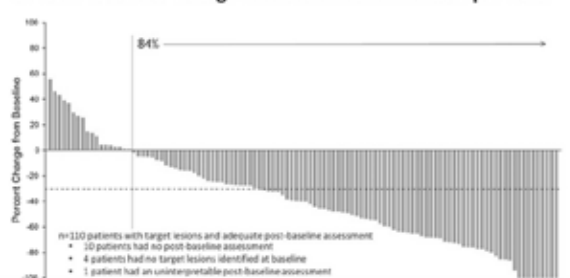
Drug	Approved	Indication	Dose
Enfortumab vedotin	December 2019	Locally advanced/metastatic UC with previous $\alpha$ PD-1/PD-L1 and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

EV-201: Cohort 1 Nectin-4 Expression

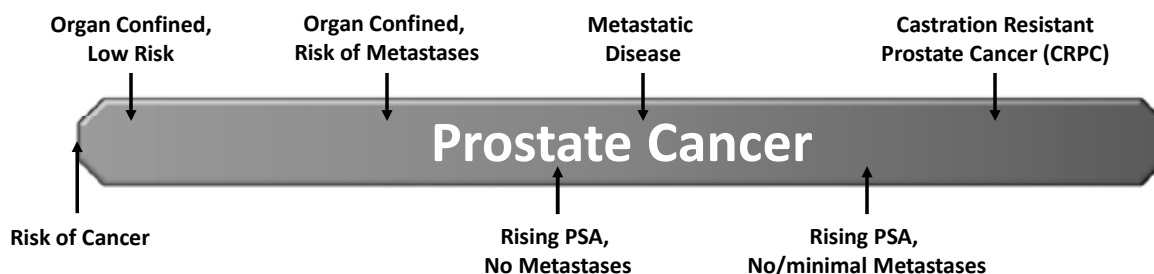


Petrylak, ASCO 2019.

EV-201: Cohort 1 Change in Tumor Measurements per BICR



## The Spectrum of Prostate Cancer

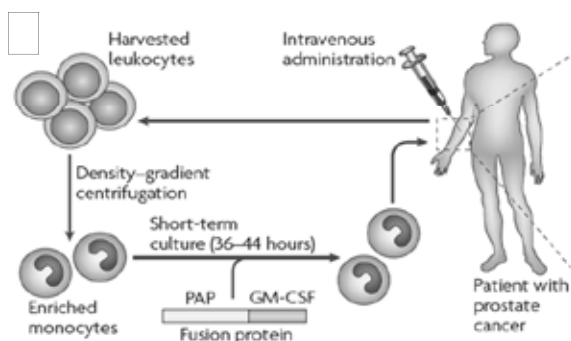


# Immunotherapy for the Treatment of Genitourinary Cancers

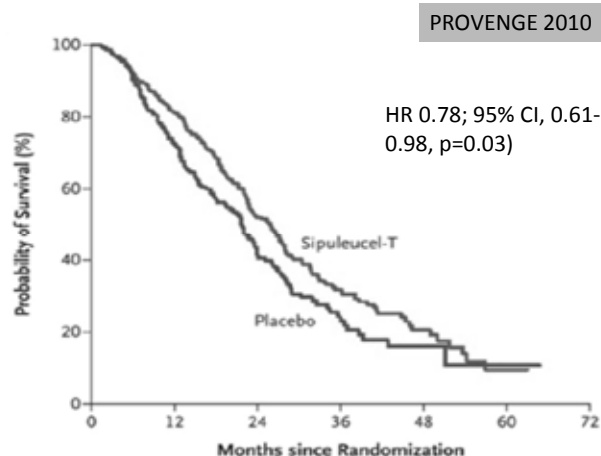
Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## Sipuleucel-T in mCRPC

First anti-cancer therapeutic vaccine



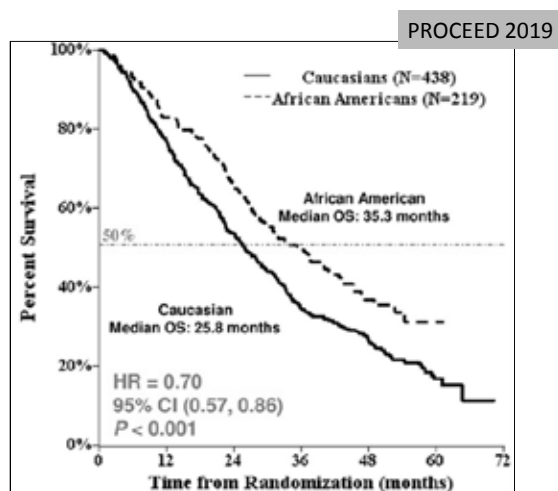
Drake et al. Curr Opin Urol 2010  
Kantoff et al. NEJM 2010



## 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)

Sartor et al. ASCO 2019



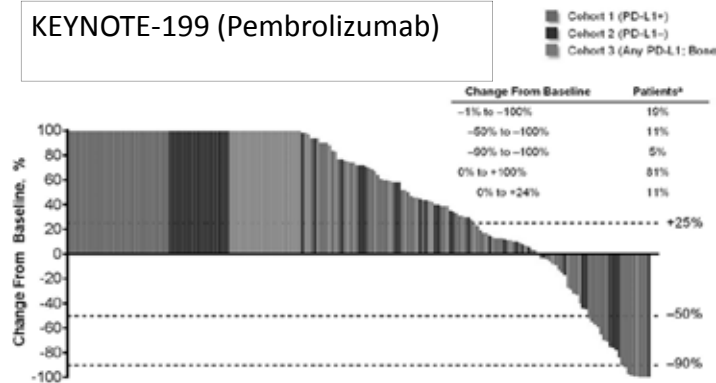
# Immunotherapy for the Treatment of Genitourinary Cancers

Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## Limited efficacy of Checkpoint Inhibitors in mCRPC

No FDA-approved CIs for mCRPC

### KEYNOTE-199 (Pembrolizumab)



DeBono et al. ASCO 2018

- 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

## 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

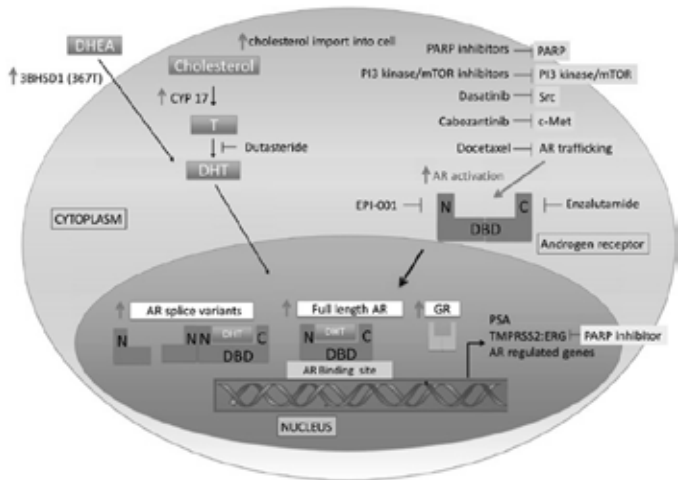
Sharma, GU Cancer Symp 2019.

# Immunotherapy for the Treatment of Genitourinary Cancers

Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## 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

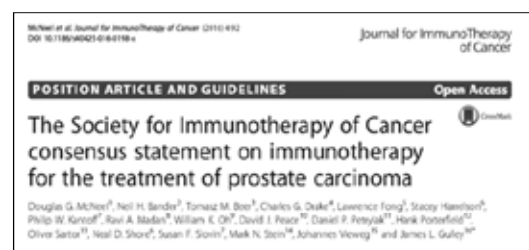
# Immunotherapy for the Treatment of Genitourinary Cancers

Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## 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

## Additional Resources



## Case Studies

### Case Study 1

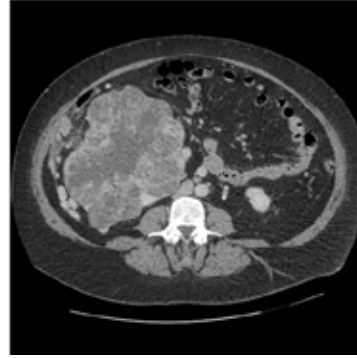
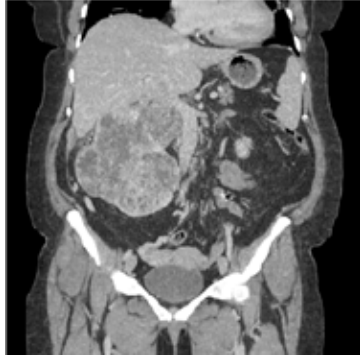
55 yo female presented with 3 week history of progressive, severe right flank pain.

- CT urogram: 17cm right renal mass, soft tissue peritoneal nodules, possible right adnexal mass.
- CT chest: multiple sub-centimeter pulmonary nodules.
- MRI Abd: right renal vein occlusion, mass invades right adrenal gland and right/caudate hepatic lobes
- Hb 10.4 g/dL; otherwise, CBC, CMP within normal limits. ECOG PS 1.

# Immunotherapy for the Treatment of Genitourinary Cancers

Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## Case Study 1



- CT guided biopsy of:
  - Peritoneal nodule: metastatic carcinoma consistent with renal primary; IHC: PAX-8, cam5.2, CK AE1/AE3 +, ER -
  - Right renal mass: renal cell carcinoma, clear cell type, PAX-8 + by IHC

## Case Study 1

Diagnosis: Metastatic renal cell clear cell carcinoma, IMDC intermediate risk

- What is preferred initial therapeutic intervention?
  - A. Cytoreductive nephrectomy
  - B. Cabozantinib
  - C. Axitinib + pembrolizumab
  - D. Ipilimumab + nivolumab



## Case Study 1

- What is preferred initial therapeutic intervention?

A. Cytoreductive nephrectomy

B. Cabozantinib

→ C. Axitinib + pembrolizumab

D. Ipilimumab + nivolumab

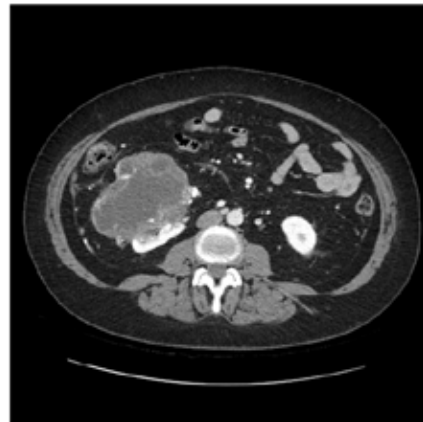
A. Unresectable, no data with modern IO regimens

B. Less robust trial data

D. May have lower response rate, higher serious irAE rate

## Case Study 1

After 6 months of therapy, significant partial response noted, including resolution of peritoneal and pulmonary metastatic sites.



## Case Study 1

- What is the next step in her care?
  - A. Cytoreductive nephrectomy
  - B. Continue axitinib + pembrolizumab
  - C. Discontinue axitinib and continue pembrolizumab
  - D. Switch to ipilimumab + nivolumab

## Case Study 1

- Underwent attempted cytoreductive nephrectomy, which was aborted due to intra-operative finding of multiple, persistent peritoneal nodules.
- 4 peritoneal nodules were biopsied, final path:  
DENSE SCLEROTIC TISSUE WITH SCATTERED CHRONIC INFLAMMATION, NO MALIGNANCY IDENTIFIED.
- Continues on axitinib + pembrolizumab at this time.

## Case Study 2

64 yo male originally presented with gross hematuria. Diagnostic evaluation identified urothelial carcinoma of the right ureter, s/p right nephroU. Developed pulmonary recurrence 1 year later.

- Previously received: gemcitabine + carboplatin, weekly paclitaxel followed by progression.
- Tissue NGS analysis did not identify an actionable molecular aberration.
- Minimal dyspnea on exertion, fatigue. ECOG PS 1. Desires aggressive therapy.

## Case Study 2

Diagnosis: Platinum refractory metastatic urothelial carcinoma of the bladder

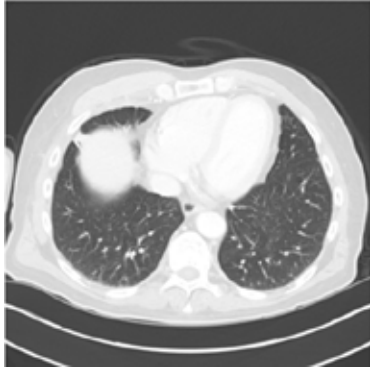
- What is preferred next therapeutic intervention?
    - A. Pembrolizumab
    - B. Best supportive care
    - C. Clinical trial enrollment with ipilimumab + nivolumab
    - D. Enfortumab vedotin
- A. Appropriate  
B. Appropriate but pt declines  
D. Accelerated approval for post-chemo and post-IO pts

# Immunotherapy for the Treatment of Genitourinary Cancers

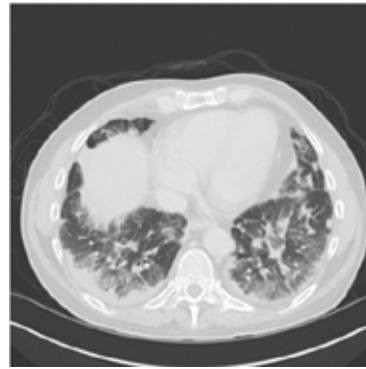
Earle F. Burgess, MD – Levine Cancer Institute, Atrium Health

## Case Study 2

Received 2 doses of ipilimumab + nivolumab and presented with cough and shortness of breath.



Pre-treatment



Current

## Case Study 2

- What is the next step in his care?
  - A. Continue ipi/nivo, add prednisone 10mg daily
  - B. Hold ipi/nivo, begin empiric azithromycin
  - C. Hold ipi/nivo, begin high dose corticosteroids
  - D. Transition to best supportive care

## Case Study 2

- Admitted to ICU, received high dose corticosteroids followed by prolonged taper.
- Subsequently developed steroid refractory colitis, requiring single dose of infliximab, followed by full recovery.
- Withdrawn from clinical trial for irAE. Post-recovery imaging demonstrated a radiographic complete response.
- No additional systemic therapy in over 4 years.

## Thank you!

Earle Burgess, MD

[earle.burgess@atriumhealth.org](mailto:earle.burgess@atriumhealth.org)

# Immunotherapy for the Treatment of Hematologic Malignancies

**Nilanjan Ghosh, MD, PhD**  
Chief, Lymphoma Division  
*Levine Cancer Institute, Atrium Health*



Dr. Nilanjan Ghosh is the Chief of the Lymphoma Division and Associate Director of Clinical Trials at the Levine Cancer Institute, as well as a Clinical Associate Professor of Medicine at the University of North Carolina, Chapel Hill. Dr. Ghosh graduated with a bachelor's in medicine and surgery from K. J. Somaiya Medical College, University of Mumbai in India. He then went on to receive his Doctor of Philosophy, Biochemistry & Molecular Biology, College of Medicine and H. Lee Moffitt Cancer Center, University of South Florida. In 2004 Dr. Ghosh began his residency in internal medicine at Albert Einstein College of Medicine at Long Island Jewish Medical Center and in 2010 he completed his medical oncology and hematology fellowship at Johns Hopkins Kimmel Cancer Center in Baltimore.

# Immunotherapy for the Treatment of Hematologic Malignancies

Nilanjan Ghosh, MD, PhD – *Levine Cancer Institute, Atrium Health*

## Immunotherapy for the Treatment of Hematologic Malignancies

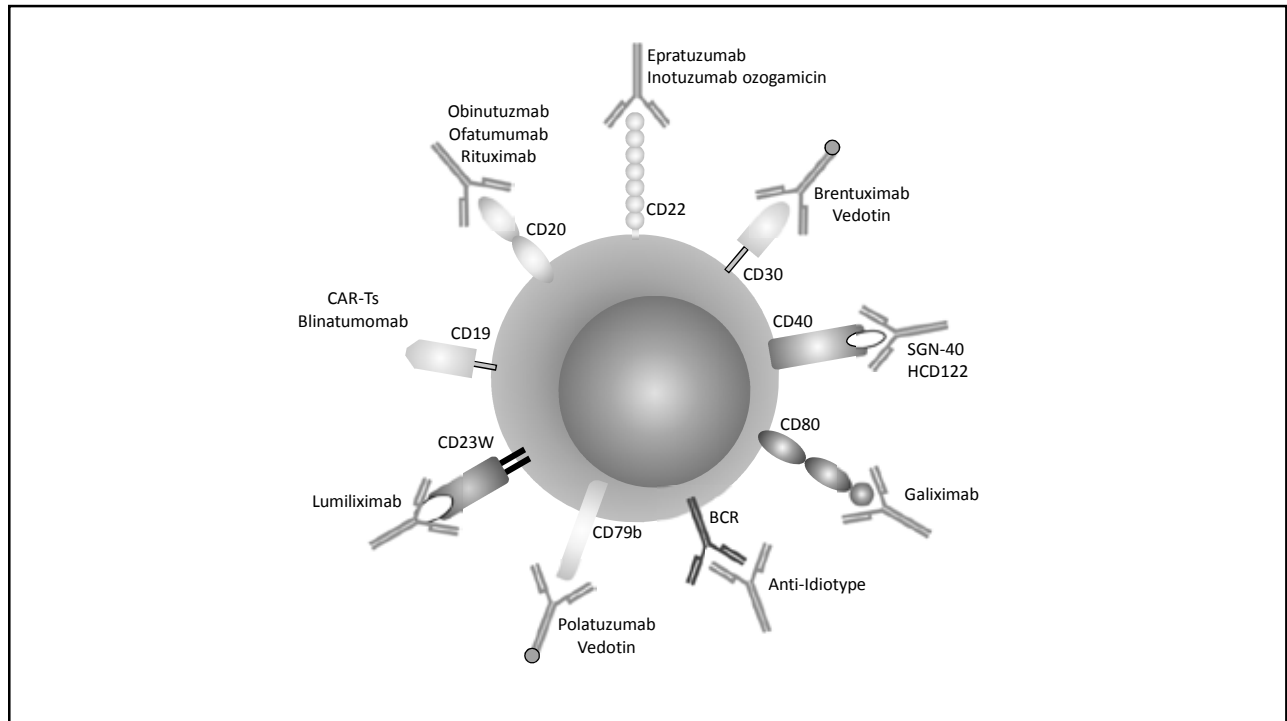
Nilanjan Ghosh, MD, PhD  
Chief, Lymphoma Division  
Levine Cancer Institute, Atrium Health

## Disclosures

- **Research support:**
  - Celgene, Genentech, Forty Seven Inc, TG Therapeutics, Pharmacyclics
- **Speakers bureau:**
  - Celgene, Seattle Genetics, Janssen, Pharmacyclics, AbbVie, Gilead, and Astra Zeneca
- **Consulting:**
  - Celgene, TG Therapeutics, Seattle Genetics, Janssen, Gilead, and Pharmacyclics
- I will be discussing non-FDA approved indications during my presentation.

# Immunotherapy for the Treatment of Hematologic Malignancies

Nilanjan Ghosh, MD, PhD – *Levine Cancer Institute, Atrium Health*



## Checkpoint inhibitors



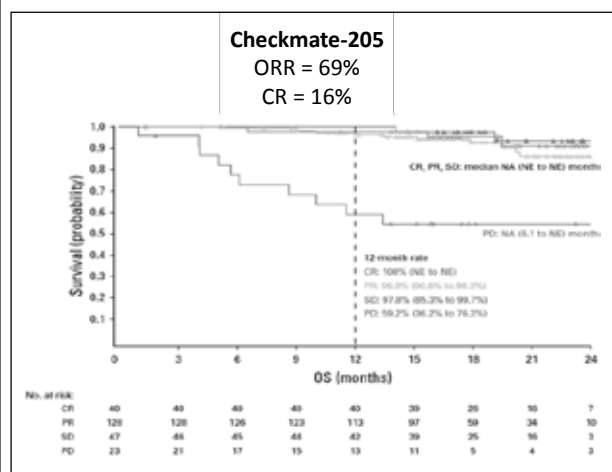
# Immunotherapy for the Treatment of Hematologic Malignancies

Nilanjan Ghosh, MD, PhD – Levine Cancer Institute, Atrium Health

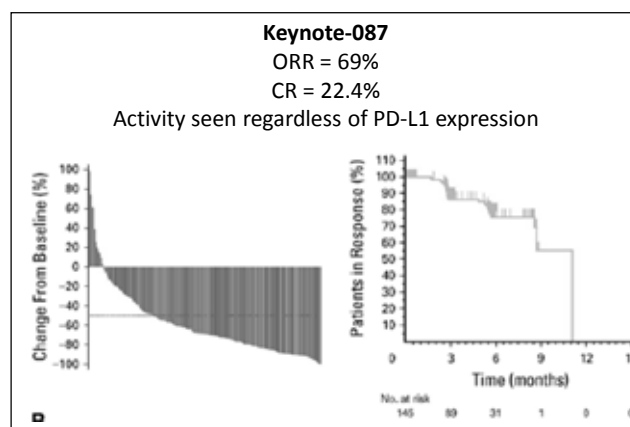
## FDA-approved Checkpoint inhibitors: Lymphoma

Drug	Approved	Indication	Dose
Nivolumab	2016	Classical Hodgkin lymphoma, relapsed after HSCT and brentuximab vedotin or $\geq 3$ 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



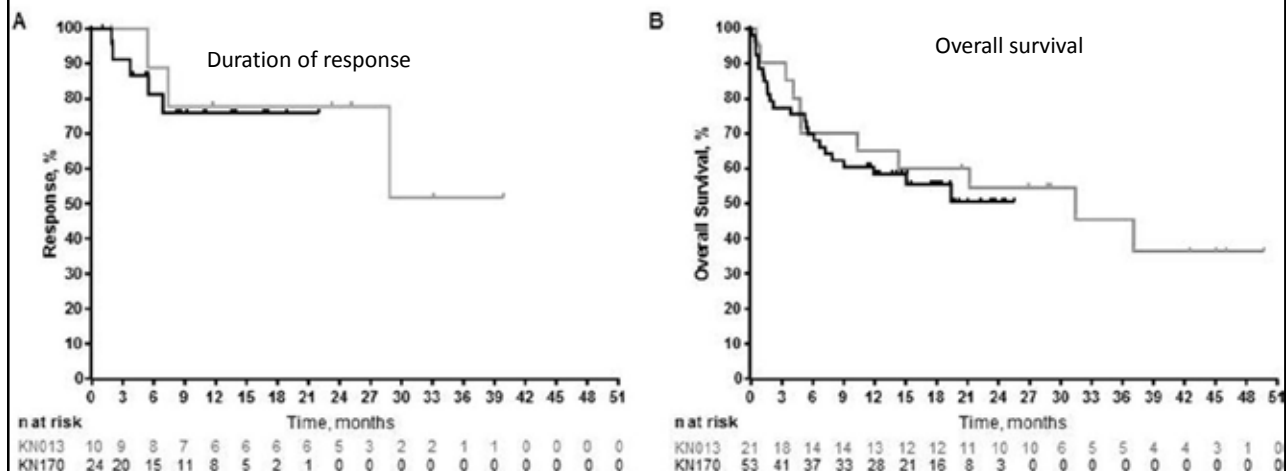
Armand, J Clin Oncol 2018.  
Chen, J Clin Oncol 2017.



# Immunotherapy for the Treatment of Hematologic Malignancies

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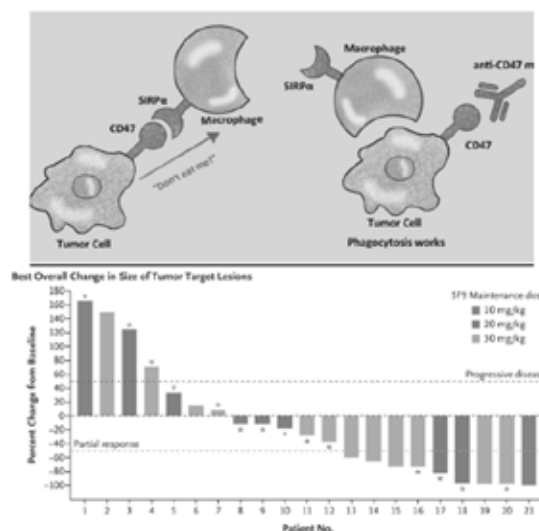
## Pembrolizumab in Primary Mediastinal Large B cell Lymphoma



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%

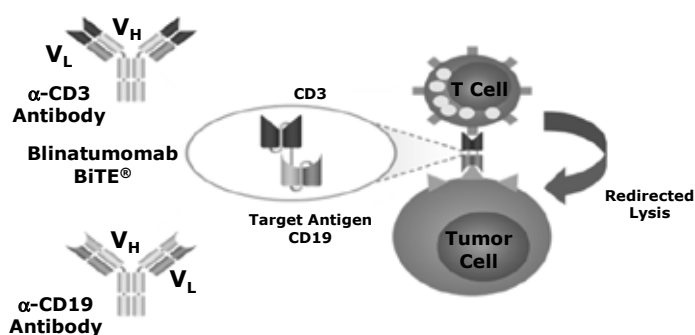


Advani, NEJM 2018.

## Bi-specific T-cell engagers (BiTEs)

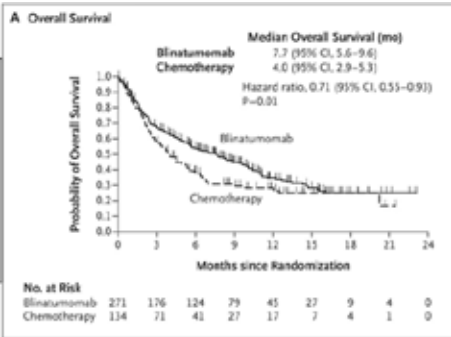
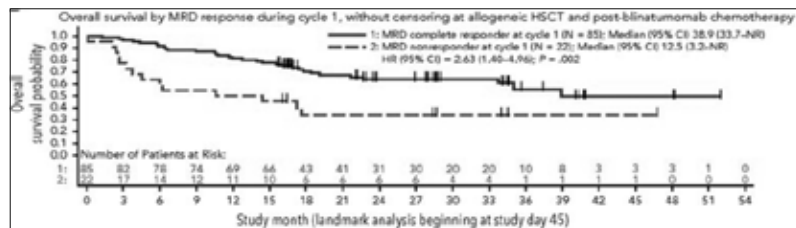
### BiTE (Blinatumomab) Therapy

- 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  $\geq 0.1\%$



Bargou et al. Science 2008

## Blinatumomab: B-ALL



Gökbuget, Blood 2018.  
Kantarjian, NEJM 2017.

## Antibody-drug conjugates (ADC)

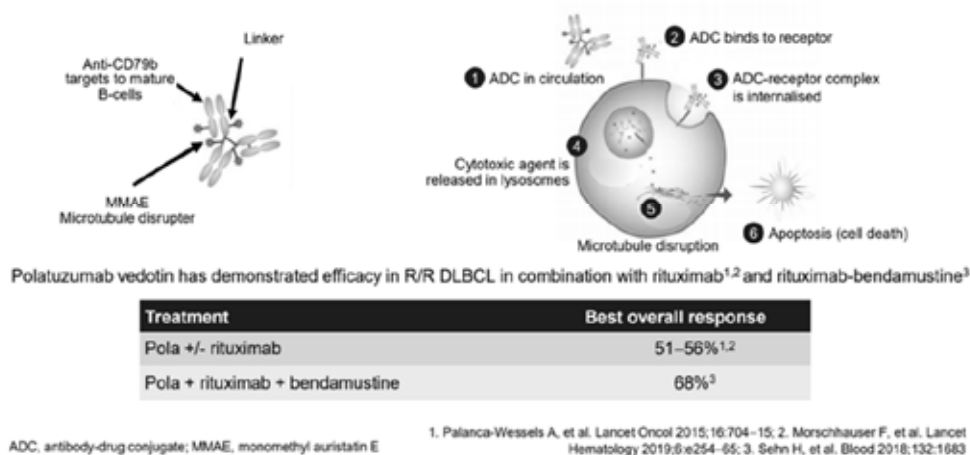
# Immunotherapy for the Treatment of Hematologic Malignancies

Nilanjan Ghosh, MD, PhD – Levine Cancer Institute, Atrium Health

## FDA-Approved Antibody-Drug Conjugates

Drug	Target antigen	Year of approval	Indication
Brentuximab vedotin	CD30	2011	<ul style="list-style-type: none"> <li>Classical Hodgkin lymphoma, relapsed after HSCT or <math>\geq 2</math> previous therapies</li> <li>Anaplastic large cell lymphoma <math>\geq 1</math> previous therapies</li> </ul>
		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 $\geq 2$ previous therapies

## Polatuzumab vedotin: DLBCL



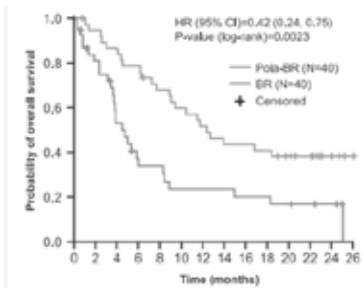
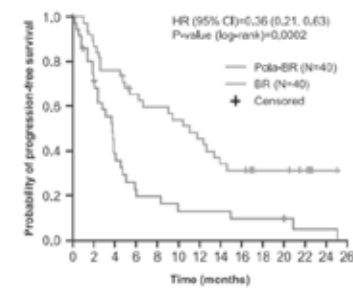
Slide credit: Tilly et al. ICML 2019

# Immunotherapy for the Treatment of Hematologic Malignancies

Nilanjan Ghosh, MD, PhD – Levine Cancer Institute, Atrium Health

## Polatuzumab vedotin: DLBCL

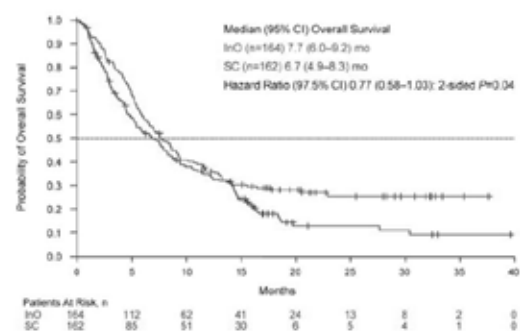
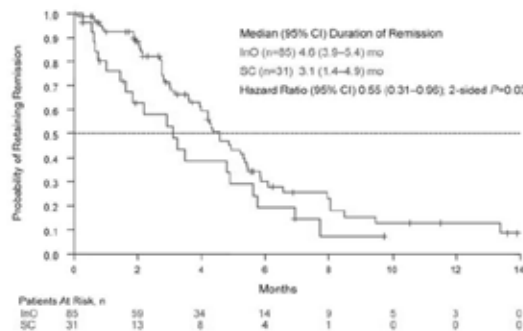
- Randomized phase 2 study
- Pola-BR vs. BR in R/R DLBCL
- Higher CR = 40% vs. 18% (p: 0.03)
- Median PFS = 7.6 m (HR=0.34, p<0.01)
- Median OS = 12.4 m (HR=0.42, p<0.01)
- Ongoing phase 3 (POLARIX)
- Frontline DLBCL- R-CHOP vs R-CHP+Pola



Sehn, Blood 2018.

## Inotuzumab ozogamicin for ALL

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

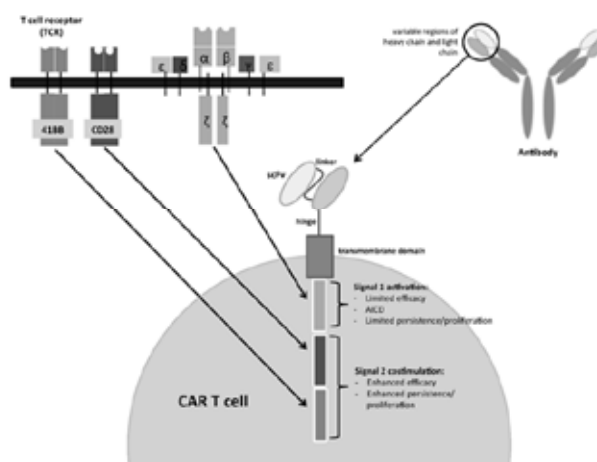


Kantarjian, NEJM 2016.

## 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

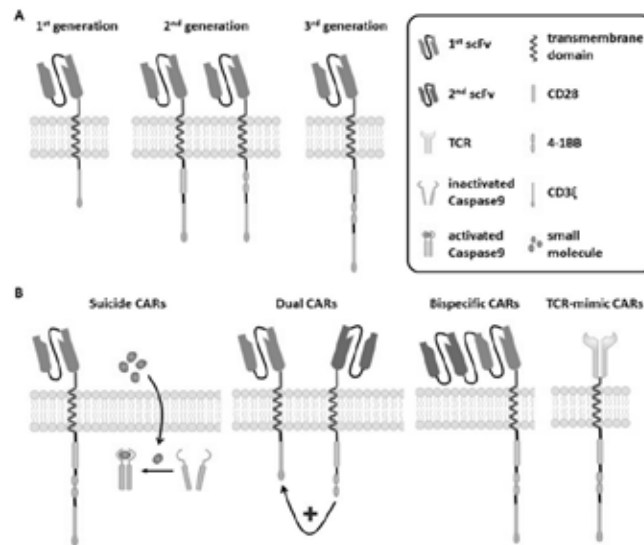


Klampasta, Cancers 2017.

# Immunotherapy for the Treatment of Hematologic Malignancies

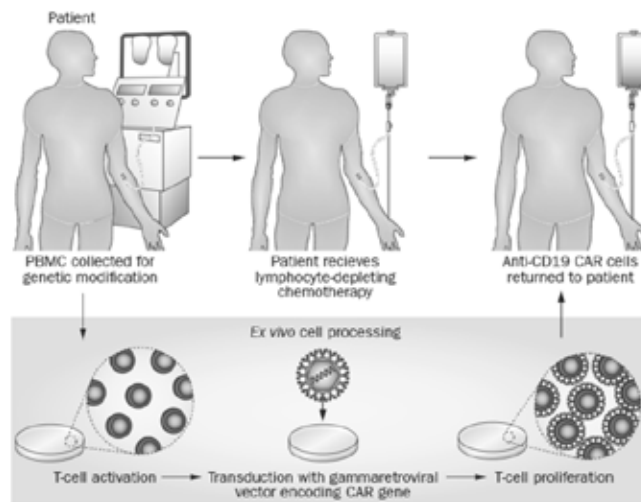
Nilanjan Ghosh, MD, PhD – Levine Cancer Institute, Atrium Health

## Evolution of CAR Constructs



Hofman, J Clin Med 2019.

## CAR T manufacturing and administration



Kochenderfer, Nat Rev Clin Oncol 2013.



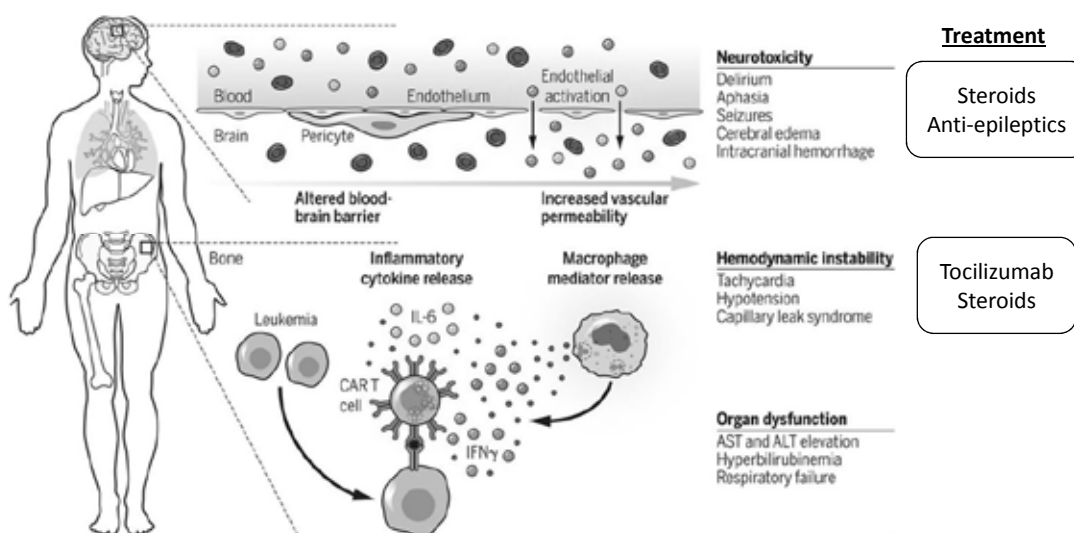
# Immunotherapy for the Treatment of Hematologic Malignancies

Nilanjan Ghosh, MD, PhD – Levine Cancer Institute, Atrium Health

## 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

# Immunotherapy for the Treatment of Hematologic Malignancies

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## 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 <sup>6</sup> CAR-positive, viable T-cells per kg bodyweight (up to 2x10 <sup>8</sup> )
Tisagenlecleucel	2017	Patients ≤25 yr with refractory B-cell acute lymphoblastic leukemia or in 2+ relapse	0.2-0.5x10 <sup>6</sup> CAR-positive, viable T-cells per kg if under 50 kg 0.1-2.5x10 <sup>8</sup> 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 <sup>8</sup> CAR-positive, viable T-cells

## Eligibility considerations for CAR

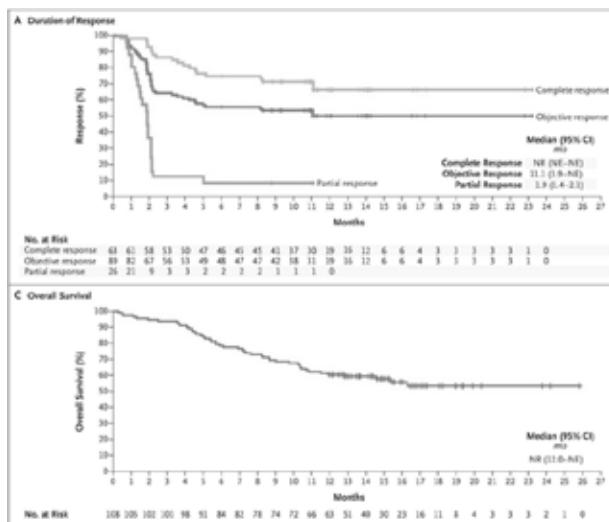
- Disease
  - Relative stability during CAR T manufacturing (~2-6 weeks)
  - Bridging therapy (chemo, RT, steroids, lenalidomide, ibrutinib)
  - CNS control
- Patient
  - Adequate cell counts
  - DVT, bleeding, infection, neuro disorders
  - Functional status: at screen vs. day of CAR T infusion
- Other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

# Immunotherapy for the Treatment of Hematologic Malignancies

Nilanjan Ghosh, MD, PhD – Levine Cancer Institute, Atrium Health

## CD19 CAR in DLBCL- ZUMA1 (Axi-cel)

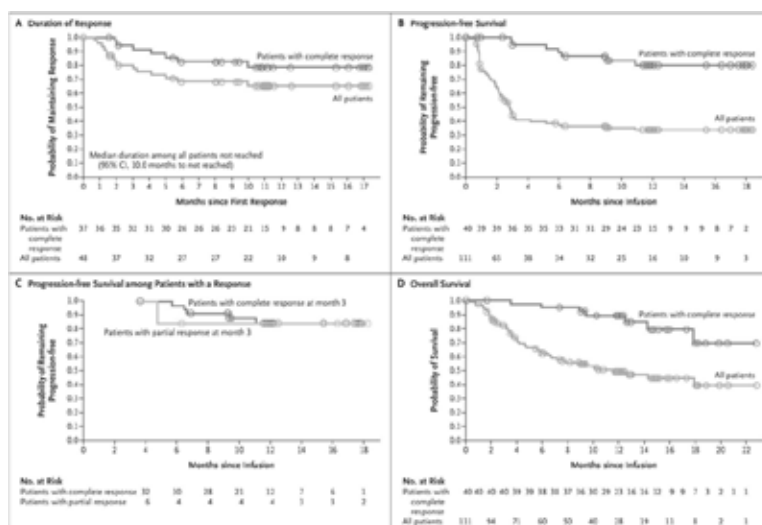
- CD19/CD28 $\zeta$
- ORR = 82%
- CR = 54%
- 1.5-yr estimated OS = 52%
- CRS grade  $\geq 3$  = 13%
- Neurotox grade  $\geq 3$  = 28%



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  $\geq 3$  = 18%
- Neurotox grade  $\geq 3$  = 11%



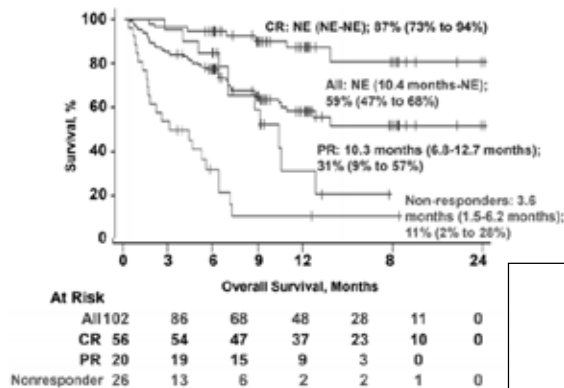
Schuster, NEJM 2019.

# Immunotherapy for the Treatment of Hematologic Malignancies

Nilanjan Ghosh, MD, PhD – Levine Cancer Institute, Atrium Health

## 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  $\geq 3$  = 1%
- Neurotox grade  $\geq 3$  = 13%

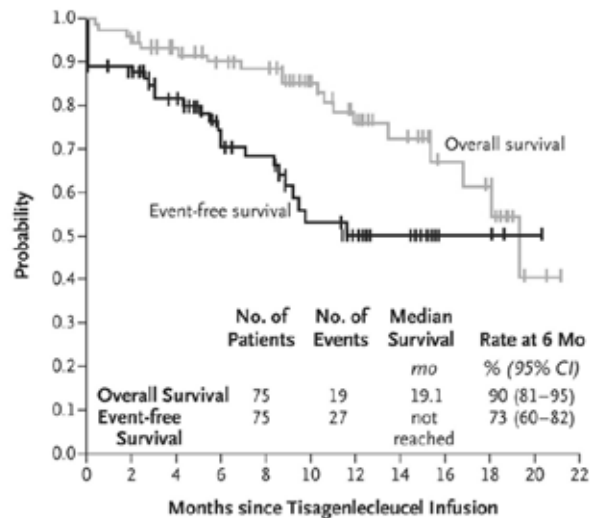


Abramson et al. ASCO Abstract 7505 June 3, 2018

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  $\geq 3$  = 47%
- Neurotox grade  $\geq 3$  = 13%

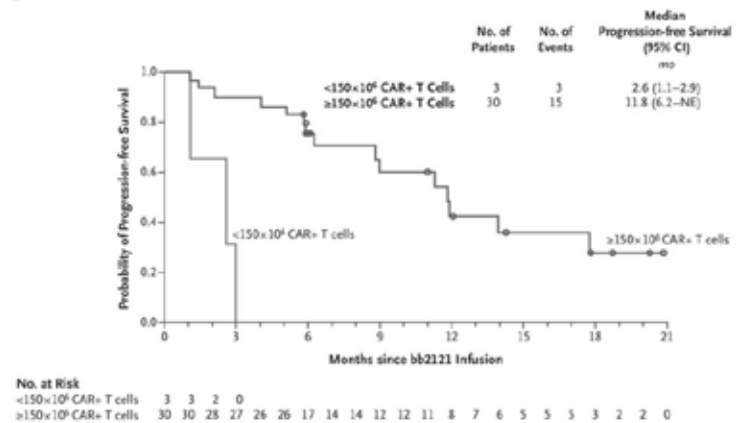


Maude et al. NEJM 2018

## 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.

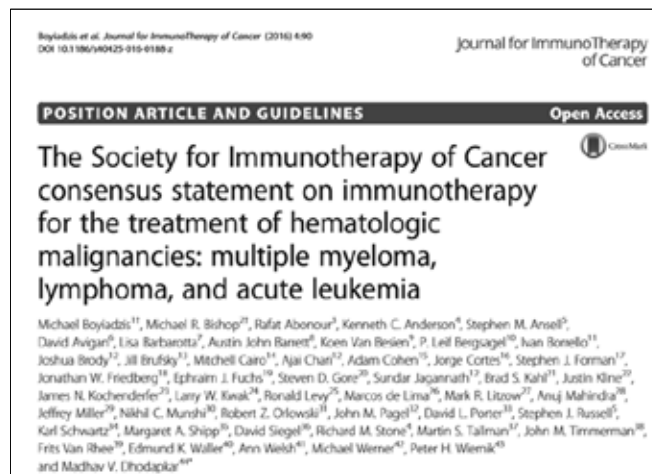
## Conclusions

- 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

# Immunotherapy for the Treatment of Hematologic Malignancies

Nilanjan Ghosh, MD, PhD – Levine Cancer Institute, Atrium Health

## Additional Resources



# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

**Antoinette Tan, MD, MHS**  
Chief of Breast Medical Oncology  
*Levine Cancer Institute, Atrium Health*



Antoinette R. Tan, MD, MHS, is the Chief of Breast Medical Oncology and Co-Director of the Phase I Program at Levine Cancer Institute, Atrium Health. She is Chief of Medical Oncology at Levine Cancer Institute-Pineville. She is a Clinical Professor in the Department of Medicine at the University of North Carolina. She is also a Full Professor of Medicine at Levine Cancer Institute, Atrium Health.

She graduated from Rutgers University in 1993 with a bachelor's degree in Biological Sciences. She received her medical degree from Rutgers-Robert Wood Johnson Medical School in 1996 through an accelerated BA/MD program.

After completing her internship and residency in internal medicine at North Shore University Hospital–New York University School of Medicine and Memorial Sloan-Kettering Cancer Center, she completed an oncology fellowship at the National Cancer Institute. Dr. Tan also obtained formal training in clinical research during her fellowship and was awarded a Master of Health Sciences degree from Duke University School of Medicine. Prior to joining Levine Cancer Institute, Dr. Tan was an Associate Professor of Medicine at Rutgers Cancer Institute of New Jersey. In 2010, she was appointed to be Director of Phase I and Investigational Therapeutics at Rutgers Cancer Institute of New Jersey.

Her research interests focus on targeted treatments for triple-negative breast cancer and drug development. She has extensive experience in the conduct of early phase clinical trials and breast cancer studies. Dr. Tan has served on the American Society of Clinical Oncology Education Program, as Chair and as a Breast Cancer Track Leader. In 2012, she was awarded the NCI Cancer Clinical Investigator Team Leadership Award.

# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – Levine Cancer Institute, Atrium Health

## Immunotherapy for the Treatment of Breast Cancer

Antoinette Tan, MD

Chief of Breast Medical Oncology

Levine Cancer Institute, Atrium Health

## Disclosures

- Consulting Fees: Celgene, Genentech
- Contracted Research: Genentech, Merck
- I will be discussing non-FDA approved indications during my presentation.



# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – Levine Cancer Institute, Atrium Health

## Why Immunotherapy for Breast Cancer?

- Higher expression of PD-L1 in TNBC than in HR+ breast cancers
  - In one study up to 26% of primary TNBCs expressed PD-L1 on cancer cell surface
- The presence of TILs suggest an immune response to tumor-associated antigens, and a higher level of TILs is reported in TNBCs and may have prognostic significance
- TNBC is characterized by genomic instability and high rates of genetic mutations, which implicate production of more neoantigens and increased immunogenicity
- The tumor mutational load is higher in TNBC compared with other subtypes

Mittendorf EA, et al. Cancer Immunol Res 2014;2:361-370  
 Tung N, et al. NPJ Breast Cancer 2016;2:16002  
 Loi S, et al. Ann Oncol 2014;25:1544-1550  
 Adams S, et al. J Clin Oncol 2014;32:2959-2966  
 Budczies J, et al. J Pathol Clin Res 2015;1:225-238  
 Banerji S, et al. Nature 2012;486:405-409

## Modest Response Rate with Checkpoint Inhibitor Monotherapy

Agent	Subtype	N	ORR	ORR (PD-L1+)*
<b>Pembrolizumab</b>				
•Single agent (Keynote-012)	TNBC	32	18.5%	18.5%
•Single agent (Keynote-028)	ER+	25	12.0%	12.0%
•Single agent (Keynote-086-A)	TNBC	170	4.7%	4.8%
•Single agent (Keynote-086-B)	TNBC	84	23.0%	23.0%
•Plus trastuzumab (PANACEA)	HER2+	58		15.0%
<b>Atezolizumab</b>				
•Single agent	TNBC	115	10.0%	13.0%
<b>Avelumab</b>				
•Single agent (Javelin)	All	168	4.8%	33.3%
	ER+/HER2-	72	2.8%	NR
	HER2+	38	3.8%	NR
	TNBC	58	8.6%	44.4%

Nanda et al, JCO 2016; Rugo et al, CCR 2018; Dirix et al, BCRT 2017;  
 Loi et al, SABCS 2017; Emens et al, JAMA Onc 2018; Adams et al, Ann Onc 2018

\*Studies used different antibodies and cutoffs for PD-L1 positivity

# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – Levine Cancer Institute, Atrium Health

## KEYNOTE-012: Long-Term Follow-Up

- Median PFS: 1.9 mo
- 12-month PFS: 15%
- 5 responders in original analysis (1 CR, 4 PR)
- 3 patients had long-lasting responses (> 6 mo)
  - Patient 1: D/C pembrolizumab 11 mo after achieving CR; remained in CR with no additional treatment
  - Patient 2: D/C pembrolizumab after 2 y; maintained response for 22.7 mo
  - Patient 3: D/C pembrolizumab after 2 y; developed PD after 7.7 mo and restarted treatment

Nanda R, et al. SABCs 2016. Abstract P6-10-03.

## Outline

- FDA approval of atezolizumab and nab-paclitaxel based on IMpassion130 for metastatic triple-negative breast cancer
- Areas of promising investigation for triple-negative breast cancer
  - Neoadjuvant chemotherapy and immunotherapy
  - Adjuvant immunotherapy in patients without a pathologic complete response (pCR) to neoadjuvant chemotherapy
- Using checkpoint inhibitors in other subtypes of breast cancer
- Other immunotherapy-based combinations in the metastatic setting

# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – Levine Cancer Institute, Atrium Health

## IMpassion130: updated OS from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + *nab*-paclitaxel in previously untreated locally advanced or metastatic triple-negative breast cancer

Peter Schmid,<sup>1</sup> Sylvia Adams,<sup>2</sup> Hope S. Rugo,<sup>3</sup> Andreas Schneeweiss,<sup>4</sup> Carlos H. Barrios,<sup>5</sup> Hiroji Iwata,<sup>6</sup> Véronique Diéras,<sup>7</sup> Volkmar Henschel,<sup>8</sup> Luciana Molinero,<sup>9</sup> Stephen Y. Chui,<sup>9</sup> Amreen Husain,<sup>8</sup> Eric P. Winer,<sup>10</sup> Sherene Loi,<sup>11</sup> Leisha A. Emens<sup>12</sup>

<sup>1</sup>Barts Cancer Institute, Queen Mary University of London, London, UK; <sup>2</sup>New York University Langone Medical Center, New York, NY; <sup>3</sup>University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; <sup>4</sup>University Hospital and German Cancer Research Center Heidelberg, Heidelberg, Germany; <sup>5</sup>Centro de Pesquisa Clínica, HSL, PUCRS, Porto Alegre, Brazil; <sup>6</sup>Aichi Cancer Center Hospital, Nagoya, Japan; <sup>7</sup>Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; <sup>8</sup>F. Hoffmann-La Roche Ltd, Basel, Switzerland; <sup>9</sup>Genentech, Inc, South San Francisco, CA; <sup>10</sup>Dana-Farber Cancer Institute, Boston, MA; <sup>11</sup>Peter MacCallum Cancer Centre, Melbourne, Australia; <sup>12</sup>University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA

Dr Peter Schmid

## Rationale of IMpassion130 Trial

- Atezolizumab selectively targets PD-L1 to prevent interaction with PD-1
- Chemotherapy may enhance tumor-antigen-release and anti-tumor responses to checkpoint inhibition

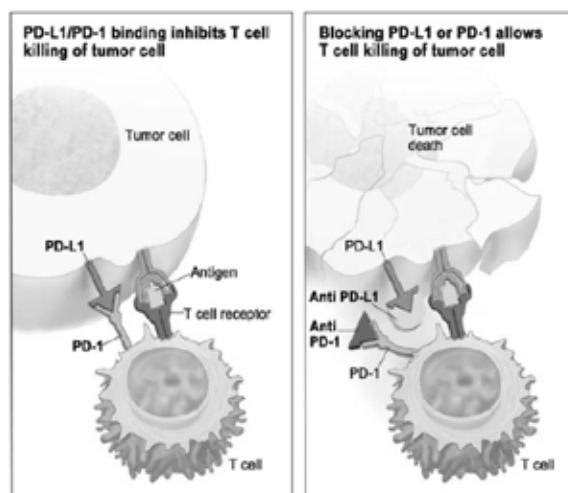


Image courtesy of the NIH.

# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – Levine Cancer Institute, Atrium Health

## IMpassion130 Study Design

**Patients with metastatic or inoperable, locally advanced TNBC without prior therapy for advanced TNBC<sup>a</sup>**

### Stratification factors:

- Prior (curative setting) taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 IC status (positive [ $\geq 1\%$ ] vs negative [ $< 1\%$ ])<sup>c</sup>

1:1

**Atezolizumab**  
840 mg IV q2w  
+ **nab-paclitaxel**  
100 mg/m<sup>2</sup> IV on d1, d8, d15<sup>b</sup>

Double blind; no crossover permitted

**Placebo**  
q2w IV  
+ **nab-paclitaxel**  
100 mg/m<sup>2</sup> IV on d1, d8, d15<sup>b</sup>

Treatment until PD per RECIST 1.1 or intolerable toxicity

Survival follow-up

- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS<sup>d</sup>
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

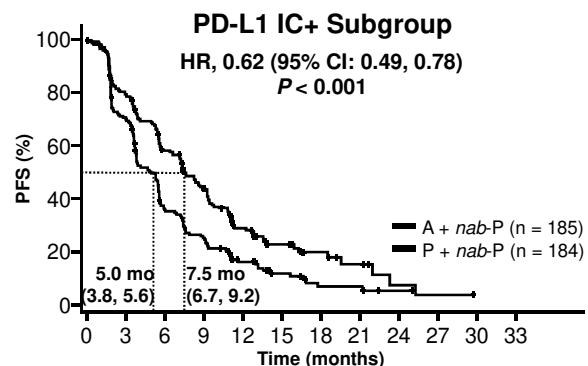
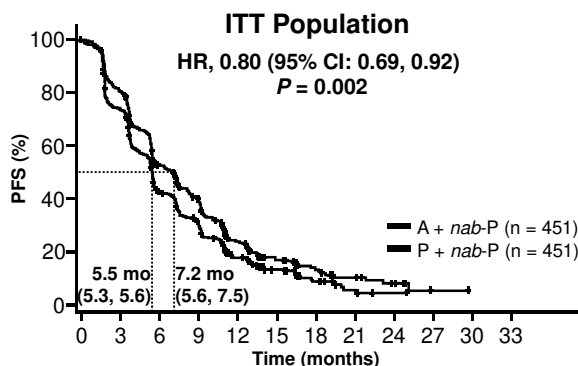
<sup>a</sup> Prior chemotherapy in the curative setting allowed if treatment-free interval  $\geq 12$  months. <sup>b</sup> 28-day cycle. <sup>c</sup> Centrally evaluated per VENTANA SP142 IHC assay. <sup>d</sup> Efficacy endpoints assessed by investigators per RECIST 1.1. NCT02425891.

Dr Peter Schmid

IMpassion130: Updated OS  
<http://bit.ly/2Q7ZiR8>

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## Primary PFS Analysis in the ITT and PD-L1 IC+ Subgroup



- PFS benefit driven by PD-L1 IC+ patients, as a treatment effect was not observed in PD-L1 IC- patients<sup>1</sup>
- Based on these data,<sup>2</sup> atezolizumab + nab-paclitaxel received accelerated approval by the FDA<sup>3</sup> and is recommended for patients with PD-L1 IC+ mTNBC in the NCCN<sup>4</sup> and AGO<sup>5</sup> guidelines

Data cutoff: April 17, 2018. Median follow-up (ITT): 12.9 months.

1. Emens SABCs 2018. 2. Schmid *New Engl J Med*. 2018. 3. Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2019.

4. NCCN Clinical Practice Guidelines. Breast Cancer. V1.2019. 5. AGO Guidelines Breast Version 2019.1.

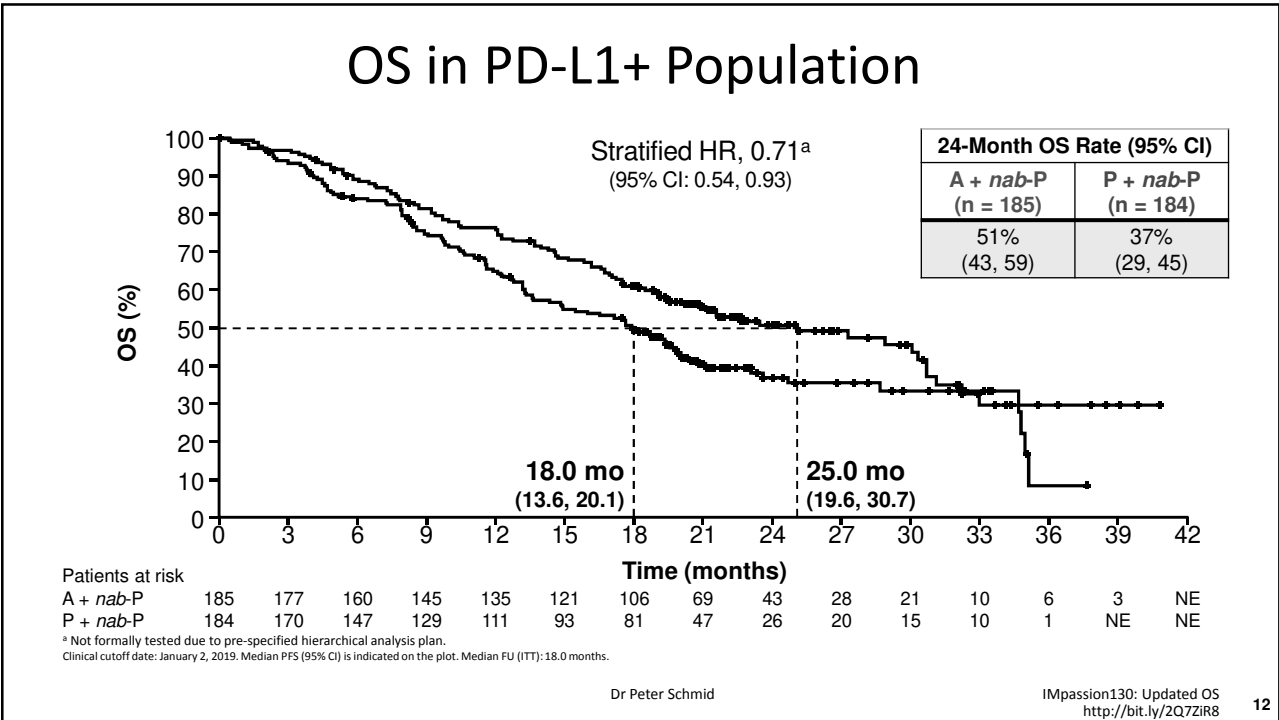
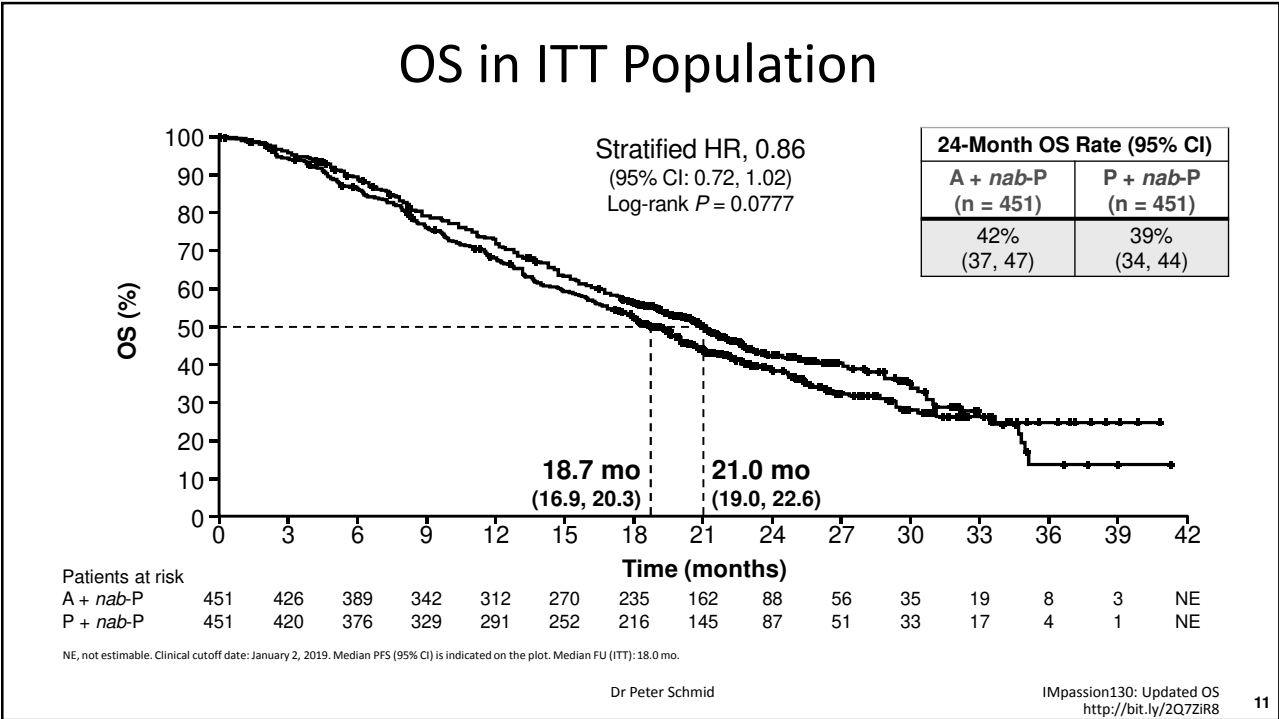
Dr Peter Schmid

IMpassion130: Updated OS  
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# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

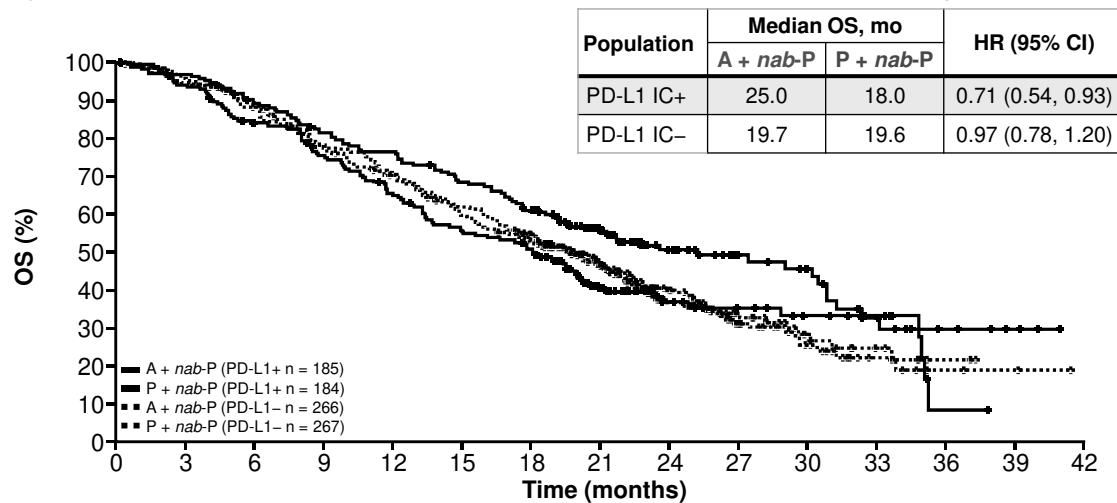
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# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – Levine Cancer Institute, Atrium Health

## Comparison of OS in PD-L1+ and PD-L1– Populations



Clinical cutoff date: January 2, 2019.

Dr Peter Schmid

IMpassion130: Updated OS  
<http://bit.ly/2Q7ZiR8>

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## Conclusions

- IMpassion130 is the first and only Phase III study to show the clinically meaningful benefit of first-line immunotherapy in mTNBC
- PD-L1 IC status predicts clinical benefit with atezolizumab + nab-paclitaxel
- Although not formally testable due to the pre-specified statistical analysis plan, a median OS improvement from 18 to 25 months was observed in the PD-L1+ population (HR, 0.71)
- Atezolizumab + nab-paclitaxel was well tolerated, with no cumulative toxicities and no new- or late-onset safety signals
- Atezolizumab + nab-paclitaxel sets a new benchmark as the first therapy to cross the 2-year landmark OS benefit in first-line therapy for PD-L1+ mTNBC
- Atezolizumab + nab-paclitaxel is approved by the FDA<sup>1</sup> and recommended for the treatment of patients with PD-L1 IC+ mTNBC in the NCCN<sup>2</sup> and AGO<sup>3</sup> guidelines

1. Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2019. 2. NCCN Clinical Practice Guidelines. Breast Cancer. V1.2019. 3. AGO Guidelines Breast Version 2019.1.

Dr Peter Schmid

IMpassion130: Updated OS  
<http://bit.ly/2Q7ZiR8>

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# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – Levine Cancer Institute, Atrium Health

## IMPassion 130: Summary and Implications

- **FDA accelerated approval for atezolizumab and nab-paclitaxel in PD-L1+ metastatic TNBC on 3/8/19**
  - Continued approval may be contingent upon verification of clinical benefit in confirmatory trials
- **PD-L1+ (PD-L1 stained tumor-infiltrating immune cells [IC]) as “determined by an FDA-approved test”**
  - Ventana PD-L1 (SP142) assay approved as a companion diagnostic for selecting TNBC patients
- **If PD-L1  $\geq$  1%, consider atezolizumab and *nab*-paclitaxel if**
  - No previous treatment in the metastatic setting **i.e. first-line**
  - Previous curative chemotherapy completed  $\geq$  12 months
  - Counsel modest PFS benefit, undefined OS benefit

## Phase III Clinical Trials with Immunotherapy for Breast Cancer

Study of Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy for Previously Untreated Metastatic TNBC	NCT02819518 KEYNOTE-355	Metastatic with no prior systemic therapy for metastatic disease	Not recruiting	858	Experimental: 1) nab-paclitaxel + pembrolizumab 2) paclitaxel + pembrolizumab 3) gemcitabine + carboplatin + pembrolizumab Comparator: 1) nab-paclitaxel + placebo 2) paclitaxel + placebo 3) gemcitabine + carboplatin + placebo
A Study of Atezolizumab and Paclitaxel vs Placebo and Paclitaxel in Participants with Previously Untreated Metastatic TNBC	NCT03125902 IMpassion131	Metastatic with no prior systemic therapy for metastatic disease	Not recruiting	540	Experimental: paclitaxel + atezolizumab Comparator: paclitaxel + placebo
A Study of the Efficacy and Safety of Atezolizumab plus Chemotherapy for Patients with Early Relapsing Recurrent TNBC	NCT03371017 IMpassion132	Metastatic; disease progression within 12 months from last treatment of curative intent	Recruiting	350	Experimental: gemcitabine + carboplatin + atezolizumab OR capecitabine + atezolizumab Comparator: gemcitabine + carboplatin + placebo OR capecitabine + placebo

# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – Levine Cancer Institute, Atrium Health

## Neoadjuvant Setting

San Antonio Breast Cancer Symposium®, December 10-14, 2019

Schmid KN522 SABCS 2019

## Background

- Patients with TNBC who achieve pathological complete response (pCR) after neoadjuvant chemotherapy have sustained clinical benefit<sup>1,2</sup>
- Taxane- and anthracycline-based neoadjuvant regimens produce pCR rates of ~40%<sup>3</sup>; addition of platinum increases pCR rates to ~50-55%<sup>4-7</sup>
- Meta-analysis of individual patient data showed a strong association of pCR after neoadjuvant chemotherapy with improved long-term EFS (HR 0.24) and OS (HR 0.16) benefit<sup>8</sup>
- Neoadjuvant pembrolizumab + chemotherapy showed manageable safety and antitumor activity in early TNBC<sup>9,10</sup>

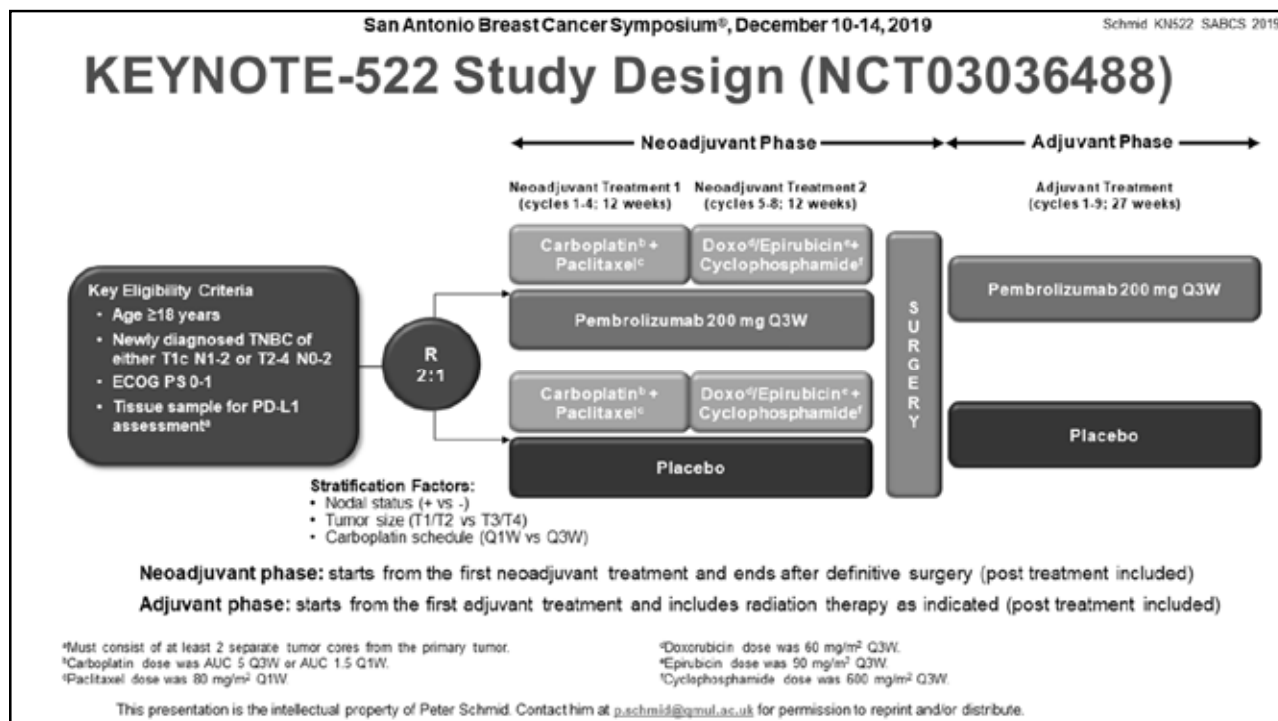
1. Cortazar P et al. *Lancet* 2014;384:164-72. 2. Huang M et al. Poster. ESMO Breast Cancer; May 2-4, 2019; Berlin, Germany. 3. Loibl S et al. *Ann Oncol* 2019;30:1279-88. 4. von Minckwitz G et al. *Lancet Oncol* 2014;15:747-56. 5. Sikov VM et al. *J Clin Oncol* 2015;33:13-21. 6. Petrelli F et al. *Breast Cancer Res Treat* 2014;14:223-32. 7. Loibl S et al. *Lancet Oncol* 2016;19:497-505. 8. Spring LM et al. *Cancer Research* 2019;79:Abstract GS2-03. 9. Schmid P et al. *J Clin Oncol* 2017;35(15S):Abstract 556. 10. Nanda R et al. *J Clin Oncol* 2017;35(15S):Abstract 506.

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# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – Levine Cancer Institute, Atrium Health



San Antonio Breast Cancer Symposium®, December 10-14, 2019 Schmid KN522 SABCS 2019

## Baseline Characteristics, ITT Population

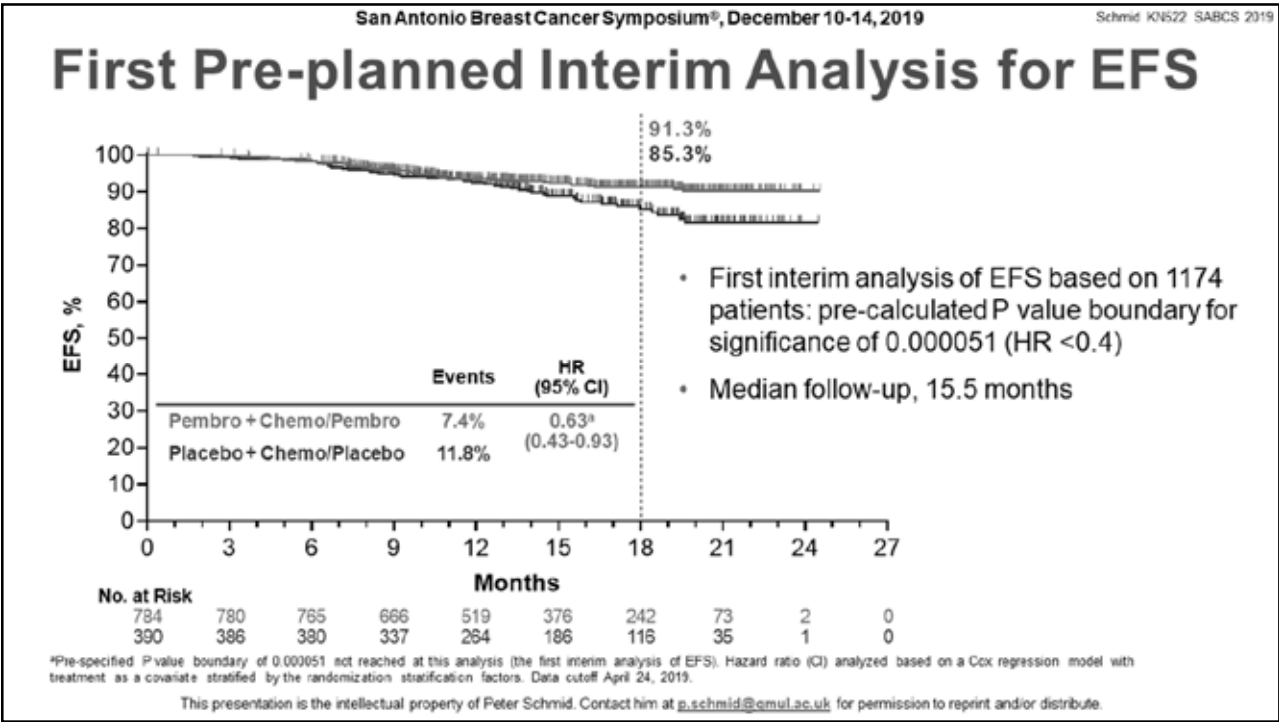
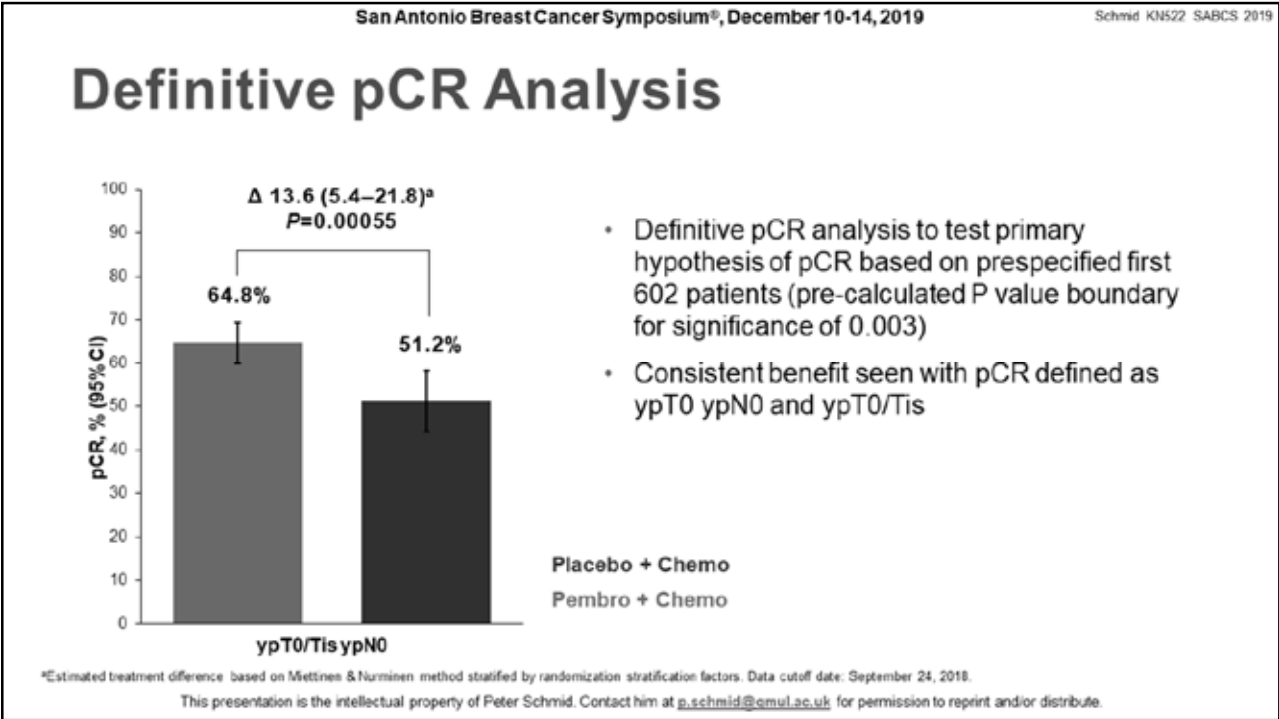
Characteristic, n (%)	All Subjects, N = 602	
	Pembro + Chemo N = 401	Placebo + Chemo N = 201
Age, median (range), yrs	49 (22-80)	48 (24-79)
ECOG PS 1	73 (18.2)	28 (13.9)
PD-L1-positive <sup>a</sup>	334 (83.3)	164 (81.6)
Carboplatin schedule		
Q1W	167 (41.6)	83 (41.3)
Q3W	234 (58.4)	118 (58.7)
Tumor size		
T1/T2	296 (73.8)	148 (73.6)
T3/T4	105 (26.2)	53 (26.4)
Nodal involvement		
Positive	208 (51.9)	104 (51.7)
Negative	193 (48.1)	97 (48.3)

<sup>a</sup>PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1-positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1-positive = CPS ≥1. Data cutoff date: September 24, 2018.

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# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

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# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – Levine Cancer Institute, Atrium Health

## KEYNOTE-522: Conclusions

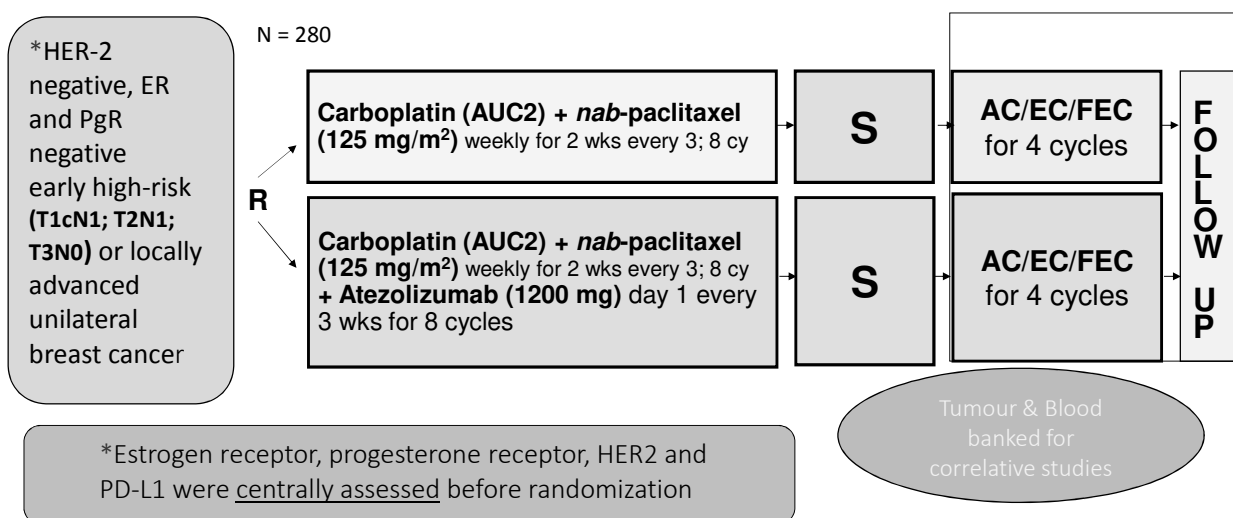
- In patients with early-stage TNBC, neoadjuvant pembrolizumab + chemotherapy associated with a larger pCR benefit vs chemo alone
  - Particularly for patients with stage III or node-positive disease
  - Benefit seen in patients who received less than planned full chemotherapy
  - Similar benefit observed regardless of PD-L1 expression level
- Neoadjuvant pembrolizumab added to chemotherapy associated with higher rate of lower residual cancer burden
- Rate of immune-mediated adverse events in study consistent with that reported previously and no new safety signal observed
- Additional follow-up needed to confirm EFS benefit and long-term safety profile

Schmid. SABCs 2019. Abstr GS3-03.

Slide credit: [clinicaloptions.com](http://clinicaloptions.com)

San Antonio Breast Cancer Symposium®, December 10-14, 2019

## Design of the NeoTRIP trial



# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – Levine Cancer Institute, Atrium Health

San Antonio Breast Cancer Symposium®, December 10-14, 2019

## NeoTrip ITT Analysis: pCR rate

ITT population		
	With atezo (138)	No atezo (142)
% pCR rate	43.5	40.8
95% CI	35.1-52.2	32.7-49.4
Difference: atezo vs no atezo (95% CI)	2.63 (14.0-8.8)	
*Odds ratio (95% CI)	1.11 (0.69-1.79)	
*p-value	0.66	

\*Cochran-Mantel-Haenszel test, controlling for PD-L1 expression and disease stage and quantified by OR and rate difference

San Antonio Breast Cancer Symposium®, December 10-14, 2019

## NeoTrip Conclusions

- The addition of atezolizumab to *nab*-paclitaxel and carboplatin did not significantly increase the rate of pCR in women with TNBC
- In multivariate analysis the presence of PD-L1 expression was the most significant factor influencing rate of pCR (OR 2.08)
- Treatment-related adverse events were similar with either regimen except for a significantly higher overall incidence of SAEs and liver transaminases abnormalities with atezolizumab.
- Continuous follow up for the primary endpoint of EFS and other efficacy endpoints is ongoing, and molecular studies are under way

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# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

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## Toxicities with Adding Checkpoint Inhibitor to Neoadjuvant Chemotherapy in Breast Cancer

San Antonio Breast Cancer Symposium\*, December 10-14, 2019

### Any immune-mediated adverse events

AE	KN 522		NeoTRIP	
	Pembro	No Pembro	Atezo	No Atezo
Thyroid abnormalities	21.7%	8.5%	8.0%	1.4%
Skin reaction	5.5%	1.0%	0%	0%
Adrenal insufficiency + Hypophysitis	4.5%	0.3%	0%	0%
Pneumonitis	1.9%	1.5%	0%	0%
Hepatitis	1.4%	0.5%	0.7%	0%
Colitis	1.8%	1.0%	1.5%	0%

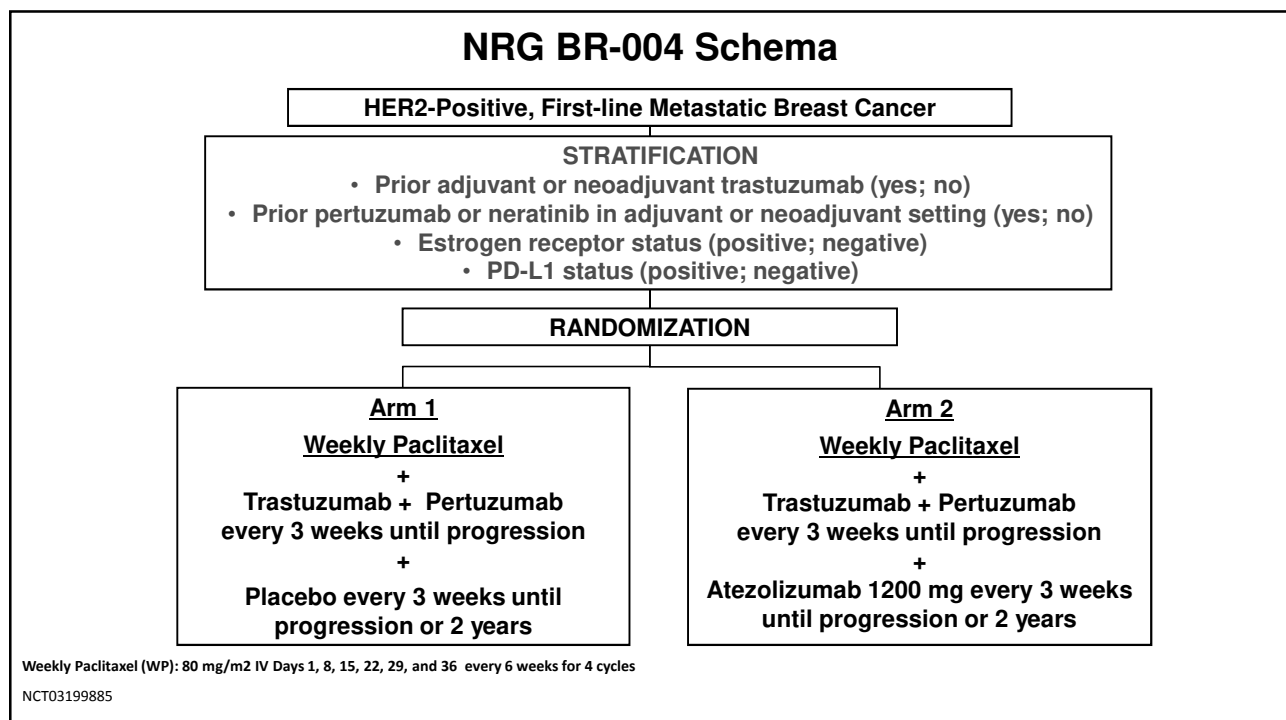
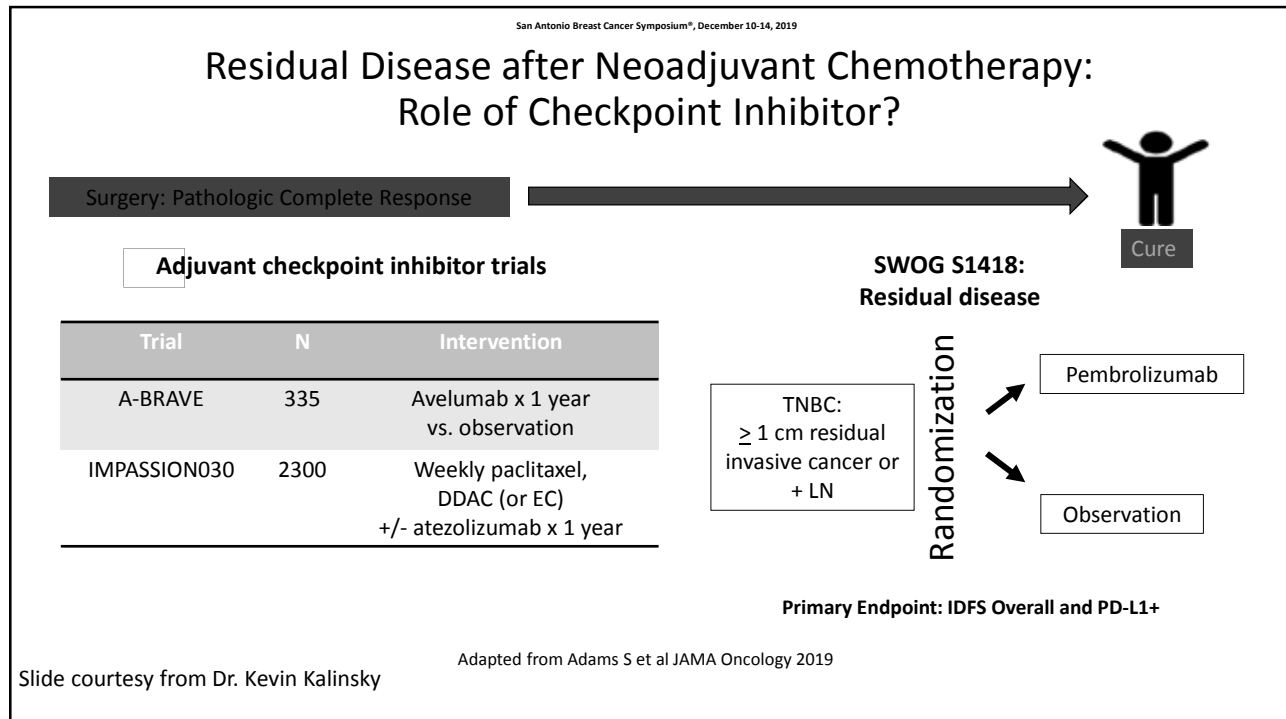
Schmid P et al SABCS 2019; Gianni L et al SABCS 2019; Nanda R et al ASCO meeting 2017  
Slide courtesy from Dr. Kevin Kalinsky

## Post-Neoadjuvant Immunotherapy

- Given that patients with residual disease after neoadjuvant chemotherapy for TNBC have a very poor prognosis, there are a number of clinical trials attempting to optimize therapy for this extremely high-risk population
- Immunotherapy may be a good opportunity for a subset of these patients

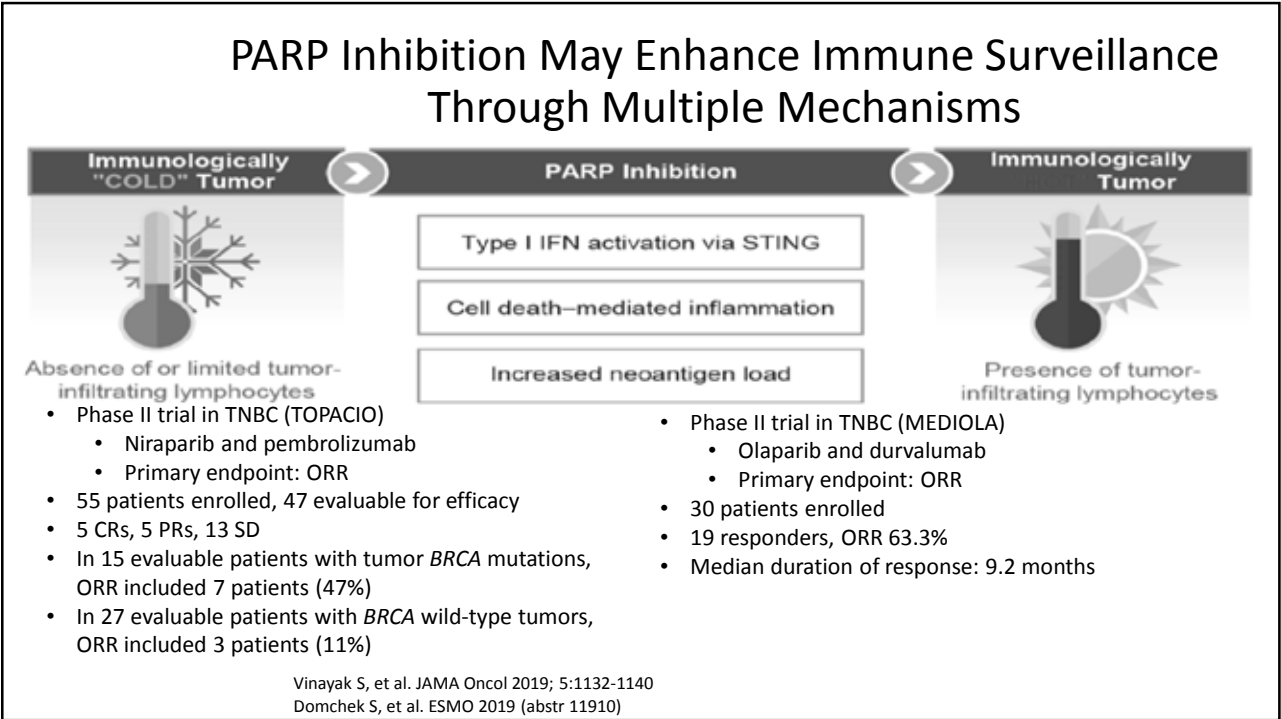
# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

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## Case Studies

# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

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## Case Study 1

A 46-year-old premenopausal female presents with a palpable mass in the right breast.

On mammogram, there is a 4 cm mass in the right breast and a 1.5 cm mass in the right axilla.

Ultrasonography-guided core needle biopsy of the breast mass reveals a poorly differentiated, estrogen receptor-negative, progesterone receptor-negative, *HER2*-negative invasive ductal cancer. Biopsy of the right axillary node is also positive.

She undergoes genetic testing and does not have germline BRCA 1/2 mutation.

She undergoes neoadjuvant doxorubicin and cyclophosphamide followed by paclitaxel and carboplatin followed by lumpectomy and sentinel lymph node biopsy. Nodes are clear but she has residual 2 cm of breast tumor.

She undergoes radiation therapy and 6 cycles of adjuvant capecitabine.

## Case Study 1

Fifteen months after completing chemotherapy, she presents with abdominal pain.

CT scan CAP reveals numerous liver lesions.

Do you:

- A. Start gemcitabine and carboplatin
- B. Biopsy the liver lesion and then start gemcitabine and carboplatin
- C. Biopsy the liver lesion and then start nab-paclitaxel and atezolizumab
- D. Biopsy the liver lesion, send sample for PD-L1 testing, and if positive, start nab-paclitaxel and atezolizumab



# Immunotherapy for the Treatment of Additional Solid Tumors: Breast Cancer

Antoinette Tan, MD, MHS – *Levine Cancer Institute, Atrium Health*

## Case Study 2

A 31 year old female presents with de novo metastatic breast cancer. She presents with a palpable left breast mass measuring 4.5 cm and left axillary adenopathy. Both the breast mass and left axillary node undergo biopsy and consistent with a ER0%, PR0%, and HER2-negative (IHC0) breast cancer. Staging studies performed. A CT scan shows numerous pulmonary nodules. She is asymptomatic.

What would you do next?

- A. Start nab-paclitaxel and atezolizumab immediately
- B. Biopsy the lung nodule to confirm is TNBC and refer to genetic counselor for BRCA testing.
- C. Biopsy the lung nodule, send it for PD-L1 testing, and refer to genetic counselor for BRCA testing.

## Case Study 2

You find out that her lung nodule is consistent with triple-negative breast cancer. It is PD-L1 positive immune cells. Her genetic test comes back as having a pathogenic mutation in BRCA1.

What would you do next?

- A. Start nab-paclitaxel and atezolizumab.
- B. Start PARP inhibitor.
- C. Start gemcitabine and carboplatin.
- D. Start PARP inhibitor and a checkpoint inhibitor.

# Toxicity Management

**Jennifer L. Atlas, MD**  
Medical Oncology  
*Levine Cancer Institute*

## Toxicity Management

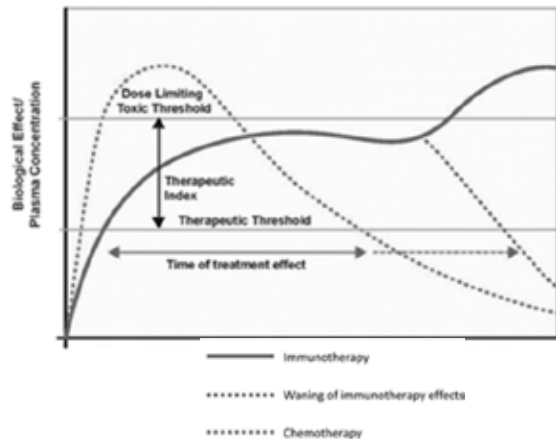
Jennifer Atlas, MD  
Levine Cancer Institute  
Atrium Health

## Disclosures

- I have no disclosures.
- I will be discussing non-FDA approved indications during my presentation.

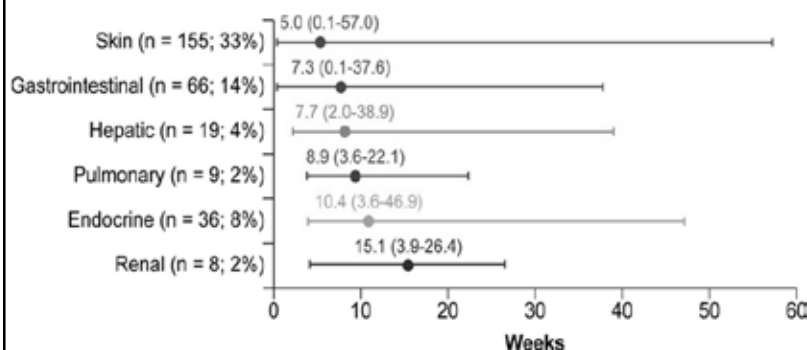
## Immune-related adverse events (irAEs)

- 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, JTO 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, JTO 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  $\leq$  75% (**Grade 3+:**  $\leq$  43%)
- PD-1/PD-L1 inhibitors: toxicities less dose-dependent
  - Any grade toxicity  $\leq$  30% (**Grade 3+:**  $\leq$  20%)
- Life-threatening irAEs are rare but treatment-related deaths reported in up to 2% of clinical trial patients

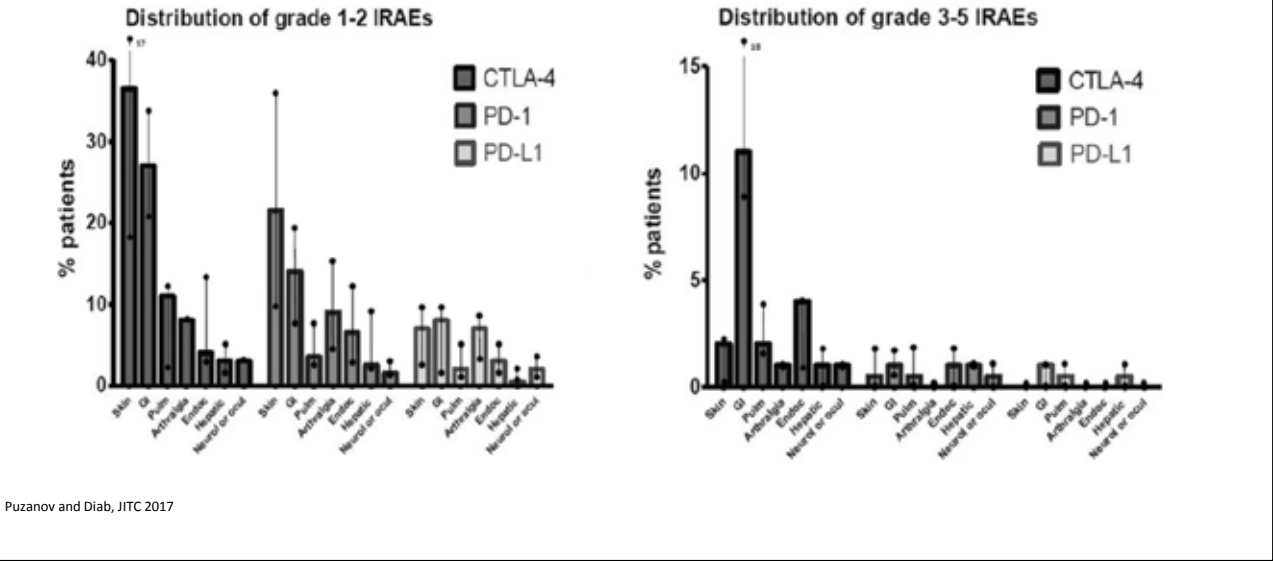
Puzanov and Diab, JTO 2017.  
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

## Incidence of specific irAEs by ICI

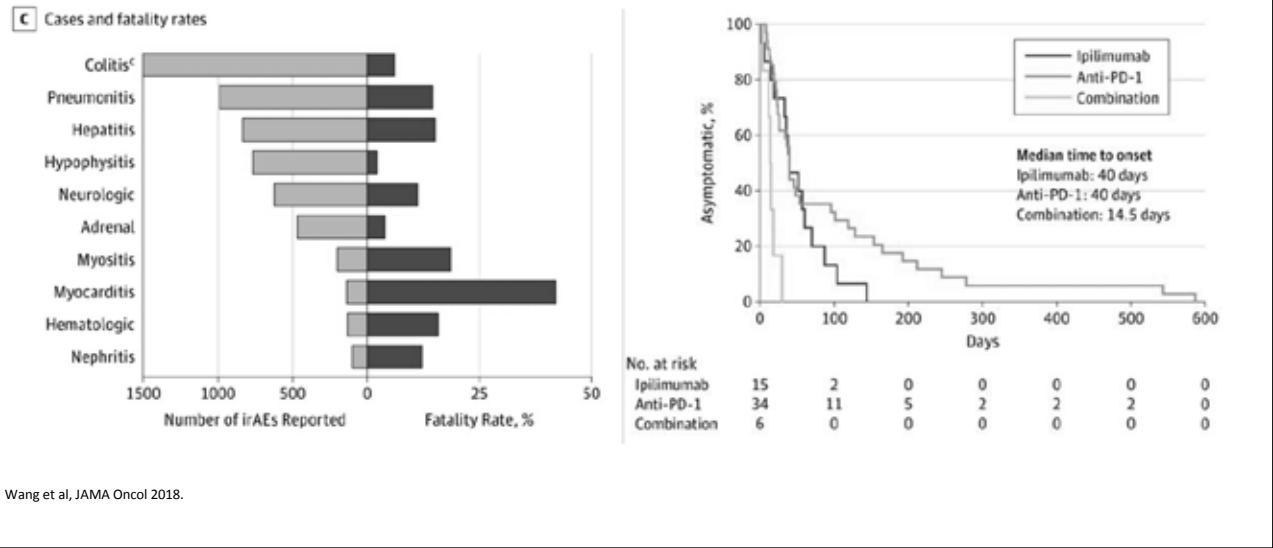
Drug	Dermatitis	Colitis	Hepatitis	Endocrinopathies	Pneumonitis
	All grades [%] (grade 3-4)				
Ipilimumab	14.5 (12)	10 (7)	5 (2)	10 (3)	<1
Ipilimumab/Nivolumab	30 (3)	26 (16)	13 (6)	35 (4)	6 (2.2)
Nivolumab	28 (1.5)	2.9 (0.7)	1.8 (0.7)	12 (0)	3.1 (1.1)
Pembrolizumab	20 (0.5)	1.7 (1.1)	0.7 (0.4)	12.5 (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, JTO 2017

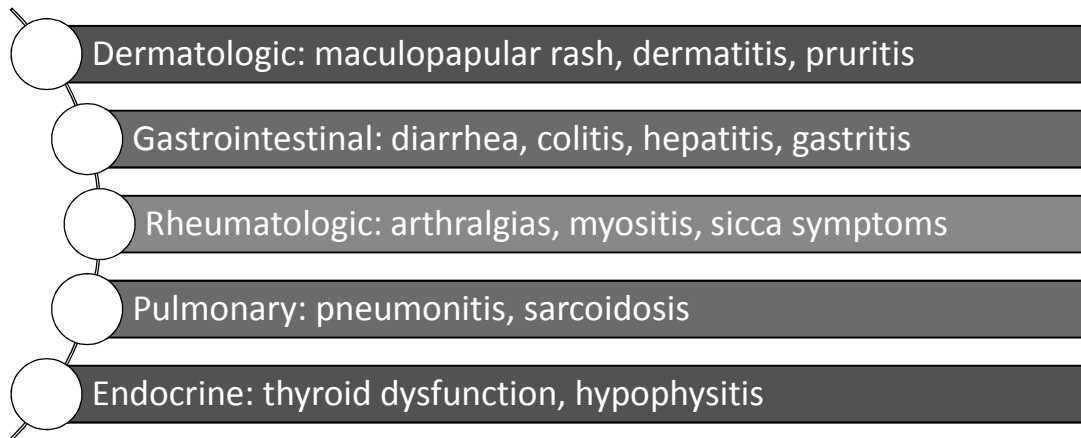
Severity of irAEs by ICI



Fatal Events with ICIs

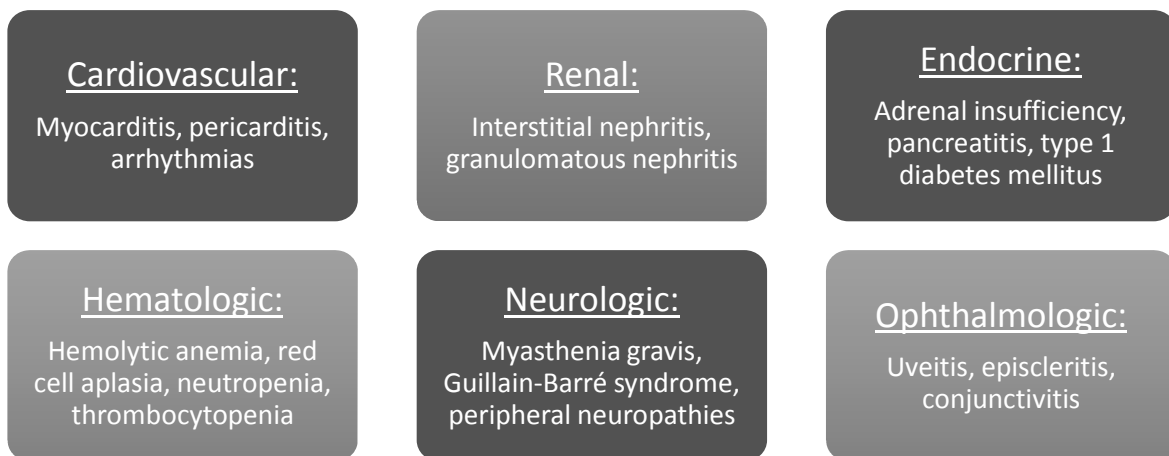


## Common irAEs with ICI



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

## Uncommon irAEs with ICI



Puzanov and Diab, JTO 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<sub>2</sub> 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, JTC 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, JTC 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
- 1<sup>st</sup> 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	<ul style="list-style-type: none"><li>• Start <b>prednisone 0.5-1 mg/kg/day</b> (or equivalent dose of IV methylprednisolone)</li><li>• If no improvement in 2-3 days, <b>increase dose</b> to 2 mg/kg/day</li><li>• Once improved to ≤grade 1, start <b>4-6 week steroid taper</b></li></ul>	<ul style="list-style-type: none"><li>• <b>Hold immunotherapy</b> during corticosteroid use</li><li>• <b>Continue immunotherapy</b> once resolved to ≤grade 1 and off corticosteroids</li><li>• Start proton pump inhibitor for GI prophylaxis</li></ul>

Pazanov & Diab, JITC 2017.

## General corticosteroid management

Grade of irAE	Corticosteroid Management	Additional Notes
3	<ul style="list-style-type: none"> <li>Start <b>prednisone 1-2 mg/kg/day</b> (or equivalent dose of IV methylprednisolone)</li> <li>If no improvement in 2–3 days, <b>ADD additional</b> immunosuppressant</li> <li>Once improved to ≤ grade 1, start <b>4–6-week steroid taper</b></li> </ul>	<ul style="list-style-type: none"> <li><b>Hold immunotherapy</b>; if symptoms do not improve in 4–6 weeks, <b>discontinue immunotherapy</b></li> <li>Start proton pump inhibitor for GI prophylaxis</li> <li>Add PJP prophylaxis if more than 3 weeks of immunosuppression expected (&gt;30 mg prednisone or equivalent/day)</li> </ul>
4		<ul style="list-style-type: none"> <li><b>Discontinue immunotherapy</b></li> <li>Start proton pump inhibitor for GI prophylaxis</li> <li>Add PJP prophylaxis if more than 3 weeks of immunosuppression expected (&gt;30 mg prednisone or equivalent/day)</li> </ul>

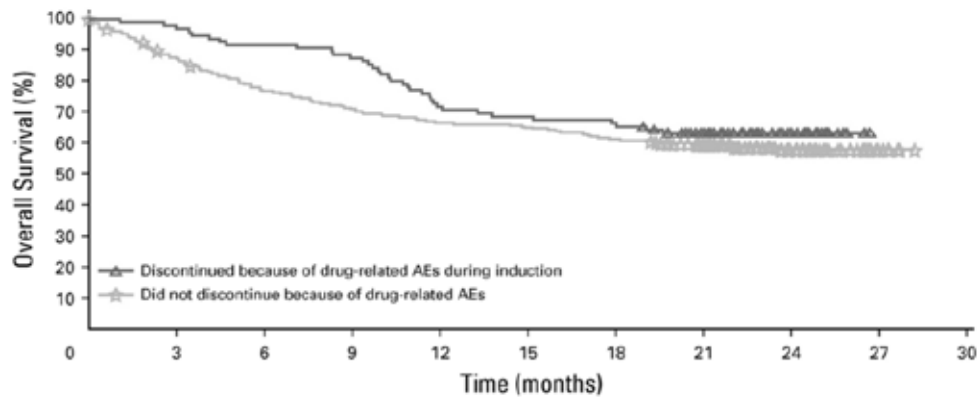
Pazanov & Diab, JITC 2017.

## Additional immunosuppressives

- **Infliximab: anti-TNF- $\alpha$  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; 2<sup>nd</sup> dose may be administered after 2 weeks
- **Vedolizumab:  $\alpha 4\beta 7$  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. JTC. 2018 Dec 5;6(1):142.  
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

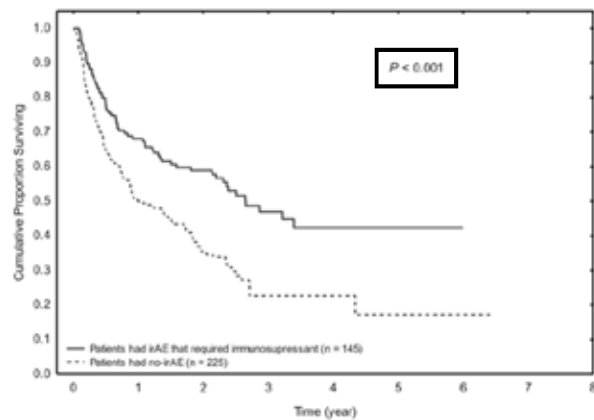
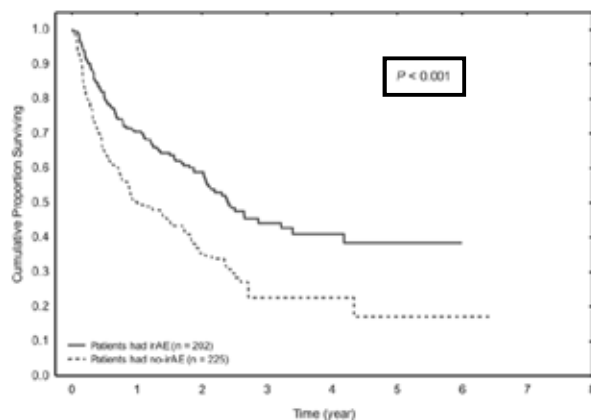
## Effect of irAEs on patient outcomes



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.

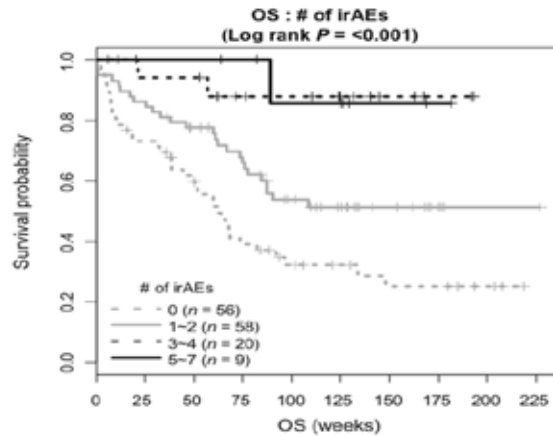
## Autoimmunity as prognostic marker?



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

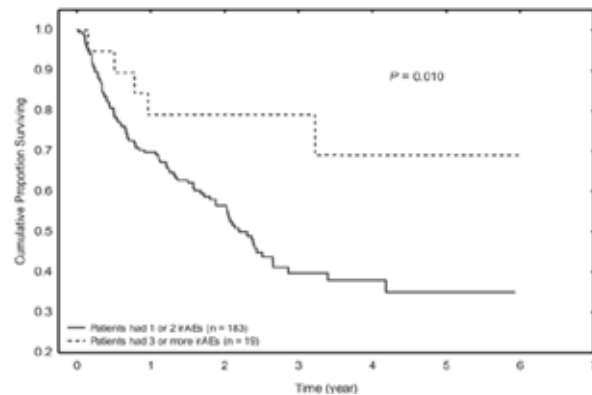
Abu-Sbeih, J Immunoth Prec Oncol 2018.

## Number of irAEs on patient outcomes



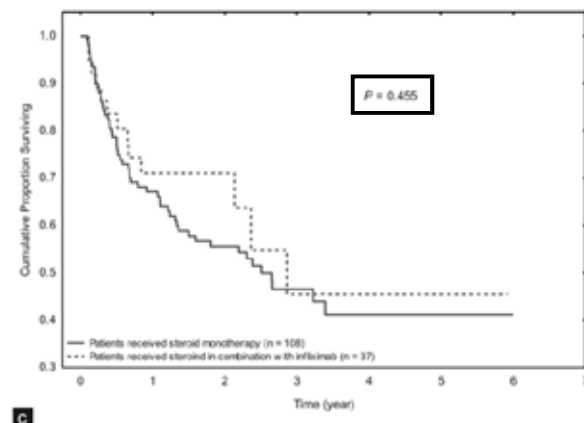
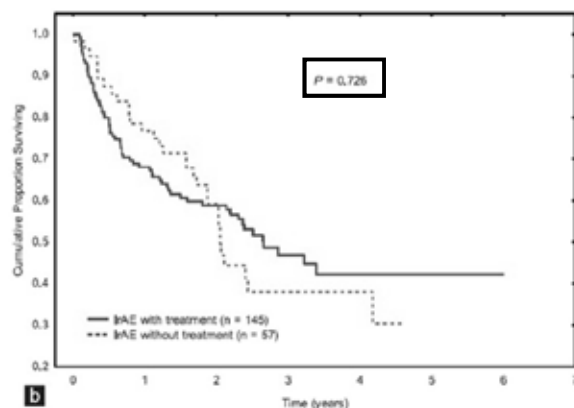
Nivolumab in metastatic melanoma: greater OS in patients with 3+ irAEs versus  $\leq 1$  irAE

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



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

## Impact of toxicity management on patient outcomes

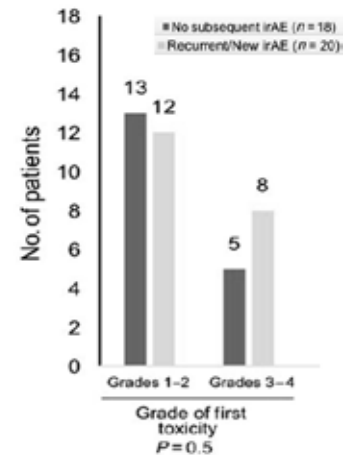
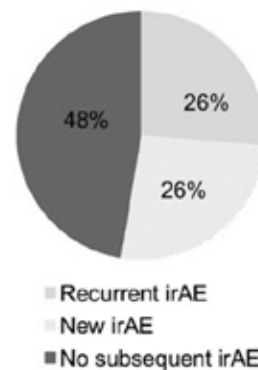


While still under debate, the administration of immunosuppressive treatments NOR the type of immunosuppressant used for irAE management does not seem to impact cancer control

Abu-Sbeih, J Immunoth Prec Oncol 2018.

## Rechallenging with ICI after irAEs

- Patients should not be rechallenged until irAE resolved to grade  $\leq 1$
- Re-challenge with anti-PD-1/L1 after anti-CTLA-4  $\pm$  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

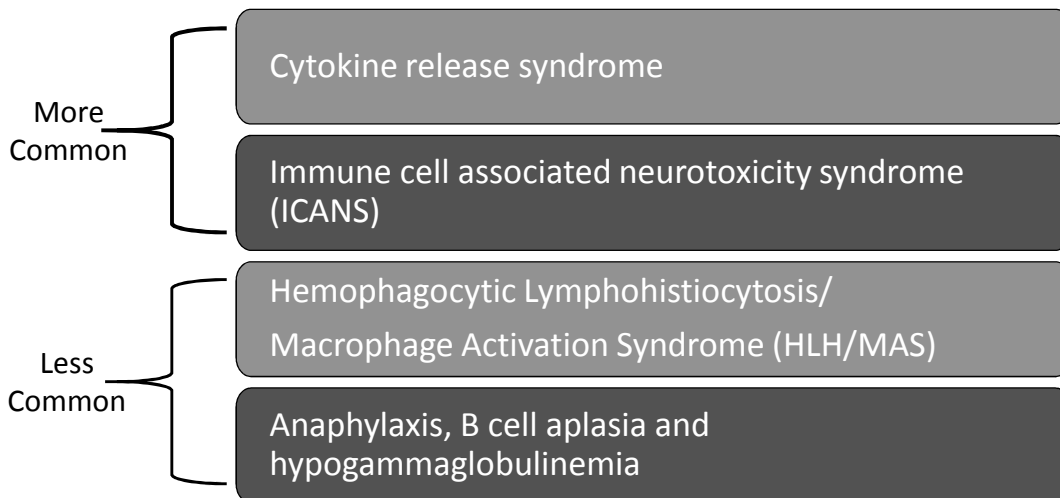
Kahler KC. Cancer Immunol Immunother. 2018.

## 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. JTC 2019.

## CAR T-cell related toxicities



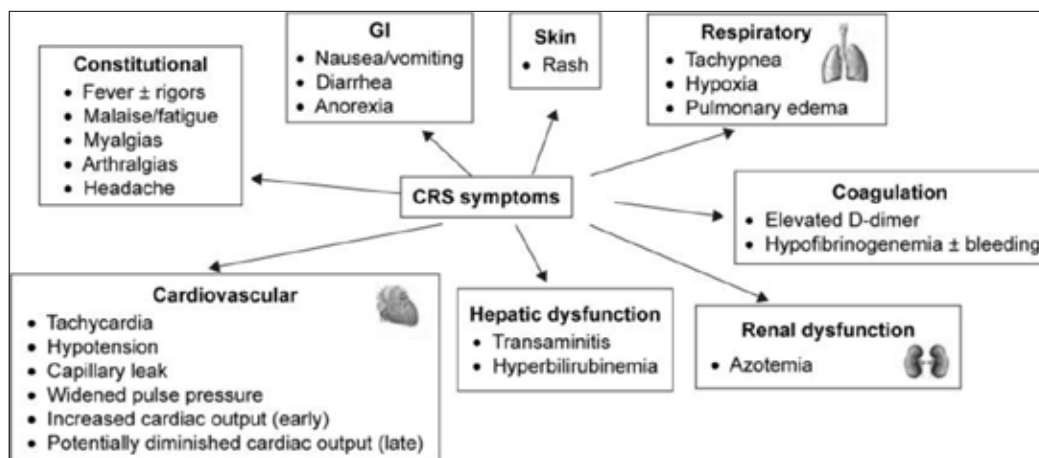
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

## 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<sup>2</sup>
  - 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.

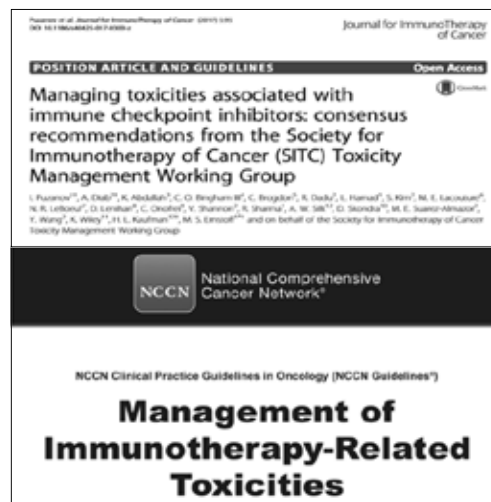
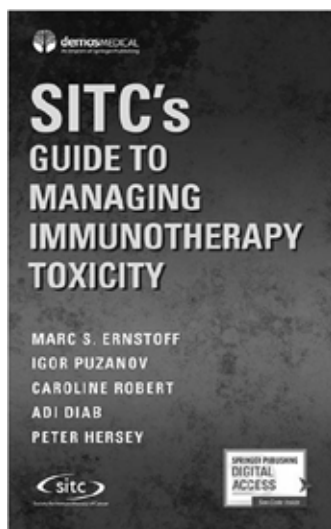
## The importance of patient education

- 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 – Brief Summary

- 60-year-old man with stage IV malignant melanoma
- 12/18/2015: Underwent wide local excision and sentinel lymph node mapping. The surgical specimen showed no residual melanoma from the left shoulder area. Zero out of 3 sentinel lymph nodes that mapped to the left axilla showed any evidence of involvement. He was staged as T1b N0 melanoma.
- 01/09/2018: Presented with abdominal pain. He was evaluated at the local Emergency Department where a CT scan of the abdomen and pelvis showed a right-sided mesenteric mass that measured 4.2 x 2.8 x 3.1 cm. Two small hypodense lesions were noted in the liver.
- 01/11/2018: PET CT scan showed a left axillary nodule with increased metabolic activity. Lobular mass noted in the anterior mesentery of the mid abdomen with increased uptake consistent with a metastatic deposit.
- 02/01/2018: Underwent a biopsy of the mesenteric mass that confirmed metastatic malignant melanoma.
- 02/10/2018: MRI of the brain was obtained that showed no evidence of CNS metastasis.
- 02/21/2018: Initiated treatment with combination immunotherapy ipilimumab plus nivolumab.
- 03/02/2018: Presented to clinic with grade 1 diarrhea. Initiated on bland diet and monitoring of symptoms.
- 03/08/2018: Presented with escalation of his diarrhea to grade 3.

## Case Study 1



## Case Study 1

- What is the preferred diagnostic test for immunotherapy induced colitis?
  - A. Stool studies
  - B. Flexible sigmoidoscopy with biopsy
  - C. Colonoscopy
  - D. CT abdomen and pelvis with contrast

## Case Study 1

- Empirically initiated on high dose steroids intravenously.
- 03/09/2018: Underwent a flexible sigmoidoscopy with pathology consistent with autoimmune colitis.
- 03/10/2018: Received infliximab for ongoing colitis symptoms.
- 03/12/2018: Initiated on steroid taper with prednisone 80mg orally once daily, to be decreased by 10mg every 5 days.
- 03/28/2018: Presented to clinic with complaints of continued episodes of small volume diarrhea of 10 bowel movements in the past 24 hours.
- 04/02/2018 – 04/23/2018: Patient admitted for ongoing diarrhea. He underwent endoscopy on 2 occasions that demonstrated colitis. He was treated with high-dose steroids and 2 doses of infliximab. He was treated with 1 dose of vedolizumab without resolution of symptoms.
- CT of the abdomen and pelvis obtained on 4/18/2018 showed clear evidence of pancolitis.
- 05/02/2018: Underwent total colectomy. Pathology demonstrated moderate to severe active chronic pancolitis.
- 08/20/2018: Patient underwent repeat flexible sigmoidoscopy. Endoscopically the mucosa appeared more like divergent colitis, but biopsies demonstrated severely active chronic colitis with non-healing necrotizing granulomas.

## Case Study 1

- 09/06/2018 – 02/13/2019: Received treatment with vedolizumab under the care of GI.
- Now on active surveillance.

## Case Study 1

- What biologic agent is the preferred choice for steroid refractory autoimmune colitis?
  - A. Tocilizumab
  - B. Infliximab
  - C. Vedolizumab
  - D. Mycophenolate

## Case Study 2 – Brief Summary

- 75 year old woman with Stage IV malignant melanoma.
- 2005: Patient was treated for a right upper extremity malignant melanoma with wide local excision and sentinel lymph node biopsy with re-excision of the primary malignant melanoma margins.
- July 2018: Established care with a new primary care physician after recently moving to North Carolina. She reported a persistent cough with clear mucus production and underwent a chest x-ray with a lingular infiltrate for which she was started on a Z-Pak.
- 08/20/2018: She underwent a repeat chest x-ray with persistent opacity.
- 09/10/2018: CT chest - Lingular bronchi appear obstructed. Postoperative consolidation within the lingula is present. Subcarinal and left hilar adenopathy are present. Small fusiform right pleural lesion is present, possibly unrelated. A small sclerotic lesion of the T3 vertebral body may be a bone island. Subcarinal node measures 3.1 x 3.3 cm. Left hilar node measures 1.9 x 2.7 cm. Right posterior pleural lesion, 0.6 x 1.8 cm. Possible lingular endobronchial neoplasm with left hilar and subcarinal nodal metastases. Nonspecific small fusiform right pleural effusion, possibly unrelated.

## Case Study 2

- 09/20/2018: Patient underwent EBUS with FNA biopsy of the left upper lobe which revealed necrotic cellular debris. Lymph node biopsy of region 7 revealed positive for malignant cells consistent with malignant melanoma.
- 09/24/2018: PET/CT - there is a hypermetabolic thick bandlike consolidation extending from the left hilum into the lingula. This lesion measures 28 x 62 mm with a max SUV of 12.3. This appears to represent a combination of central lung and perihilar obstructive atelectasis and inflammation. In addition there is a large hypermetabolic subcarinal mass measuring 30 x 33 mm with a max SUV of 49.1. Mild uptake in the region of the porta hepatis appears to represent misregistered bowel activity. There is a focal uptake involving the spinous process of L2 to vertebral body which appears sclerotic on CT with a max SUV of 3.6. This lesion is nonspecific and could represent metastatic disease though benign processes could also account for these findings.
- 09/28/2018: Initial medical oncology consultation for her diagnosis of stage IV malignant melanoma. We discussed potential systemic therapy with combination immunotherapy with ipilimumab 3 mg/kg IV and Nivolumab 1 mg/kg IV every 3 weeks for 4 doses followed by maintenance Nivolumab versus single agent anti-PD1 antibody therapy. BRAF mutation not detected.

## Case Study 2

- She received 2 infusions of Ipilimumab and nivolumab.
- 11/15/2019: She was experiencing severe fatigue, right eye ptosis, and dyspnea with exertion and at rest over the last 2 days. She reported weakness and was present in a wheelchair. Her extraocular movements are intact. She denies any fevers, headaches, dysphasia, facial nerve deficits, or dysphagia. She did have mild to moderate arthralgias and myalgias. She did have dyspnea with exertion and at rest with a persistent dry cough. She reported a decreased appetite.

## Case Study 2

- What diagnostic test is most commonly abnormal with checkpoint inhibitor induced myocarditis?
  - A. EKG
  - B. Echocardiogram
  - C. BNP
  - D. Troponin

## Case Study 2

- What is the best way to monitor a patient with myasthenia gravis for respiratory failure?
  - A. NIF
  - B. Single breath count
  - C. O2 saturation
  - D. A and B

## Case Study 2

- Patient had MRI brain which was negative for evidence of metastatic disease.
- She had laboratory testing which revealed a decreased TSH of 0.12 and an elevated free T4 of 2.84 consistent with thyroiditis.
- She was diagnosed with immunotherapy induced myasthenia gravis for which she ultimately required plasmapheresis, treatment with pyridostigmine, high-dose steroids and IVIG. She did require intubation. Antibody testing confirmed myasthenia gravis. EMG was completed.
- Patient was diagnosed with myocarditis and went into sustained ventricular tachycardia requiring cardioversion on 3 occasions. She underwent a TTE which revealed a left ventricular ejection fraction of 50% with right ventricle moderately dilated with moderate pulmonary hypertension noted.
- In light of her multiple toxicities and declining functional status, patient and family chose to proceed with comfort care and enrollment in hospice.



# Practical Barriers in Cancer Immunotherapy Treatment

**Jessica Davis, PharmD, BCOP, CPP**

Clinical Pharmacist Coordinator  
*Levine Cancer Institute, Atrium Health*



Jessica Davis, PharmD, BCOP, CPP received her Doctor of Pharmacy degree from the South Carolina College of Pharmacy – Medical University of South Carolina in 2014. She completed a PGY1 Pharmacy Practice Residency at Boston Medical Center and a PGY2 Oncology Pharmacy Residency at the University of North Carolina Medical Center. She became a Board Certified Oncology Pharmacist (BCOP) in 2017. Dr. Davis is currently a clinical pharmacist coordinator at Levine Cancer Institute – Atrium Health in Charlotte, NC. She is a member of the HOPA Time to Talk Immuno-Oncology Task Force and is actively involved in professional pharmacy organizations such as HOPA and NCOP.

# Practical Barriers in Cancer Immunotherapy Treatment

Jessica Davis, PharmD, BCOP, CPP – *Levine Cancer Institute, Atrium Health*

## Practical Barriers in Cancer Immunotherapy Treatment

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Clinical Pharmacist Coordinator, Levine Cancer Institute

## Disclosures

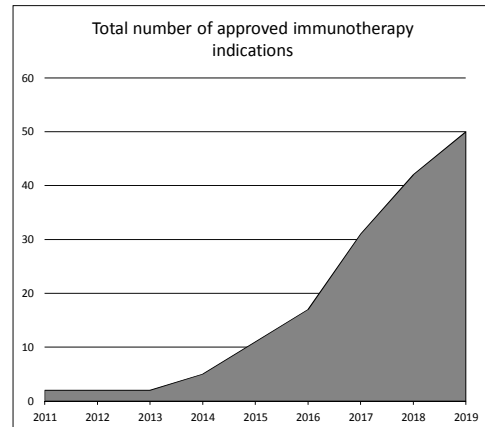
- I have the following disclosures:
  - Speakers Bureau for Exelixis, Inc
  - Advisory board for Array BioPharma
- I will be discussing non-FDA approved indications during my presentation.

# Practical Barriers in Cancer Immunotherapy Treatment

Jessica Davis, PharmD, BCOP, CPP – Levine Cancer Institute, Atrium Health

## 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!)

# Practical Barriers in Cancer Immunotherapy Treatment

Jessica Davis, PharmD, BCOP, CPP – *Levine Cancer Institute, Atrium Health*

## Financial Considerations

Processes for High Dollar Medications

Medicare

Commercial Payers

Denials

## Manage Reimbursement/Finances

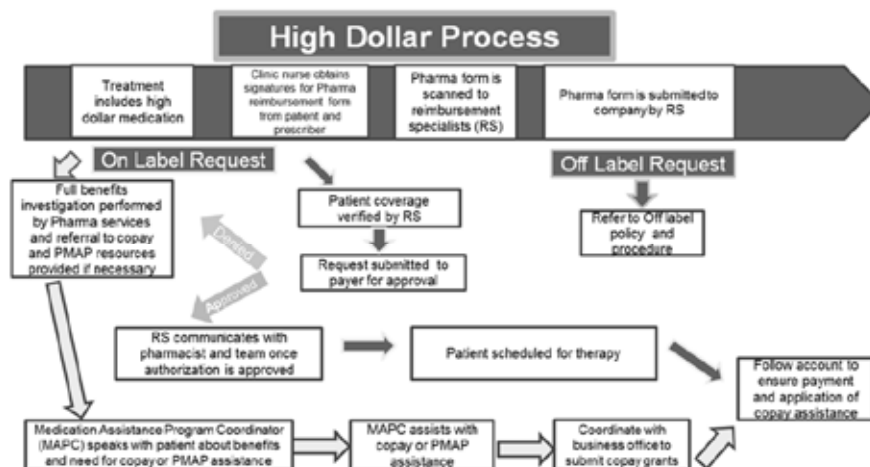
- **New-to-market I-O agents may not yet have specific J-Code**
  - Ensure a process is in place for appropriate management/billing until J-Code is assigned or, in the case of Hospital Outpatient Prospective Payment Services, a C-Code (Temporary = C9399)
- **Identify a point person from within your financial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

# Practical Barriers in Cancer Immunotherapy Treatment

Jessica Davis, PharmD, BCOP, CPP – Levine Cancer Institute, Atrium Health

## 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

Jessica Davis, PharmD, BCOP, CPP – Levine Cancer Institute, Atrium Health

## Medicare

- Most Medicare Administrative Contractors (MAC) have at least one I-O agent for 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

## 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

## 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

# Practical Barriers in Cancer Immunotherapy Treatment

Jessica Davis, PharmD, BCOP, CPP – Levine Cancer Institute, Atrium Health

## Commercial Payers

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

## Commercial Payers

- Disproportionate approvals of total billing units versus doses for a specific period of time
  - Example: Authorization for 200 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



# Practical Barriers in Cancer Immunotherapy Treatment

Jessica Davis, PharmD, BCOP, CPP – Levine Cancer Institute, Atrium Health

## 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

## 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**

## 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

# Practical Barriers in Cancer Immunotherapy Treatment

Jessica Davis, PharmD, BCOP, CPP – Levine Cancer Institute, Atrium Health

## 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

## 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

# Practical Barriers in Cancer Immunotherapy Treatment

Jessica Davis, PharmD, BCOP, CPP – *Levine Cancer Institute, Atrium Health*

## Handling Denials

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

## Handling Denials

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

# Practical Barriers in Cancer Immunotherapy Treatment

Jessica Davis, PharmD, BCOP, CPP – Levine Cancer Institute, Atrium Health

## Practical Barriers Beyond Payment

IO-Related Medical Emergencies

Biosimilars

CAR T Treatments

## Management Strategies for IO-Related Medical Emergencies

### Develop protocols

- Develop/revise any treatment protocols that may be impacted by the addition of new I-O therapies and/or I-O-related medical emergencies in your practice
- Develop policies/procedures to ensure appropriate and timely delivery of treatments for I-O medical emergencies and financial reimbursement thereafter

### Patient education

- Educate all patients on an I-O therapy to clearly identify themselves as such and to recognize adverse events
- Ensure that these patients can be quickly identified as being on I-O therapy in their medical record

### Staff education

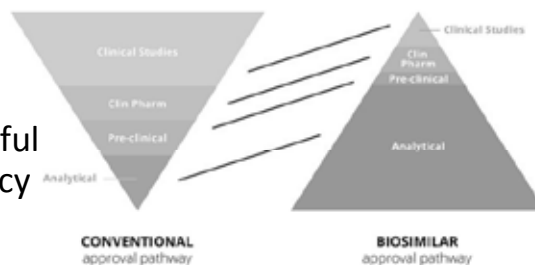
- Ensure staff understand and can identify the most common adverse events associated with I-O products, and know when these events could be potentially be life-threatening and/or require immediate clinical attention
- Educate staff on policies/procedures regarding treatment of and financial reimbursement for medical emergencies

# Practical Barriers in Cancer Immunotherapy Treatment

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## Biosimilars

- FDA requires biosimilars to be highly similar, but not identical, to reference product
- Must 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.

## 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-szsz)	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

# Practical Barriers in Cancer Immunotherapy Treatment

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## 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
  - Vary by institutional policies (e.g. Pharmacy and Therapeutics committee may approve products to be interchanged by pharmacist without prescriber approval)
- Incentives to prescribe biosimilars from Medicare
- Formulary product (reference or biosimilar) varies by insurance company
  - Product (reference or biosimilar) preferred by insurance company may change with limited or no notice



## 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

# Practical Barriers in Cancer Immunotherapy Treatment

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## Local Practices

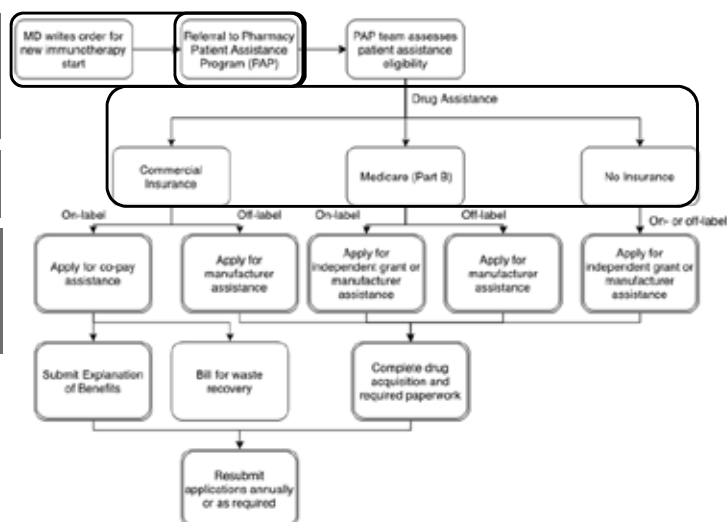
Pharmacy Patient Assistance Program

## Levine Cancer Institute

All patients (new starts) are referred to PAP team through electronic medical record

PAP team comprised of pharmacy technicians

PAP team assists with drug assistance and waste recovery for all intravenous therapy





# Practical Barriers in Cancer Immunotherapy Treatment

Jessica Davis, PharmD, BCOP, CPP – Levine Cancer Institute, Atrium Health

## Levine Cancer Institute

### On-label processes

Commercial insurance:  
patients may qualify for co-pay assistance

Commercial insurance:  
-submit EOB  
-bill for waste recovery



Medicare (or other government insurance):  
-will not qualify for co-pay assistance through manufacturer  
-may qualify for independent grants or free drug through manufacturer based on income  
-per institutional policy, not allowed to pursue assistance for on-label indications for Medicare patients

## Levine Cancer Institute

### Off-label processes

Commercial insurance: will need denial from insurance prior to obtaining free drug from manufacturer

Medicare (or other government insurance):  
-denial from insurance is difficult to obtain prior to drug administration as Medicare does not require prior authorizations  
-may need to obtain drug coverage through manufacturer retroactively; need to confirm with manufacturer



No insurance:  
-will need to apply for manufacturer assistance or independent grants for all drugs regardless of indication  
-typically approved with limited barriers unless very income (above manufacturer or grant income limits)

All patients receiving assistance:  
-coordinate drug acquisition for patients receiving free drug to ensure drug availability prior to scheduled infusion time  
-ensure appropriate billing and paperwork is completed  
-resubmit application annually

# Practical Barriers in Cancer Immunotherapy Treatment

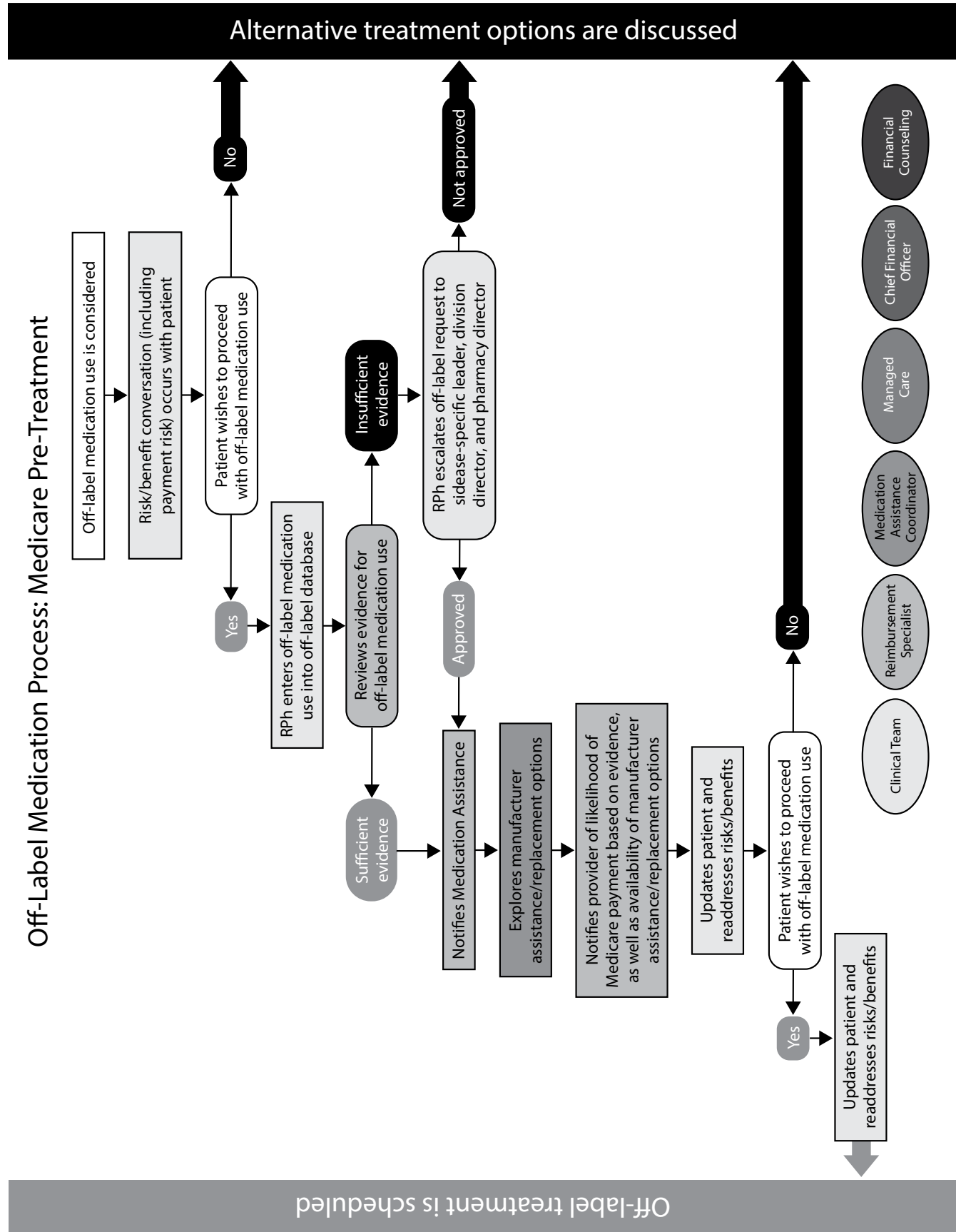
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## Future Considerations

- 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 other 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

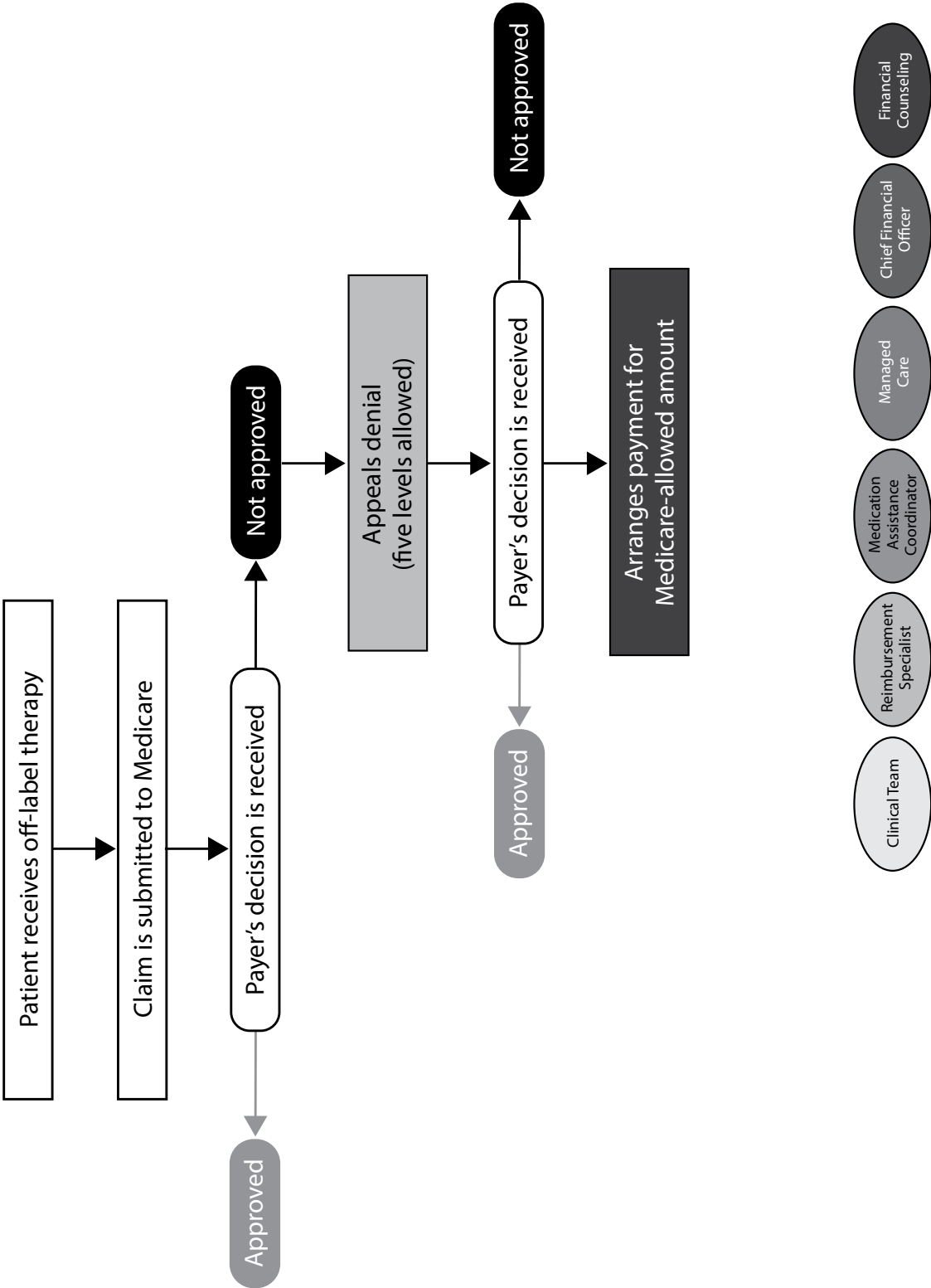
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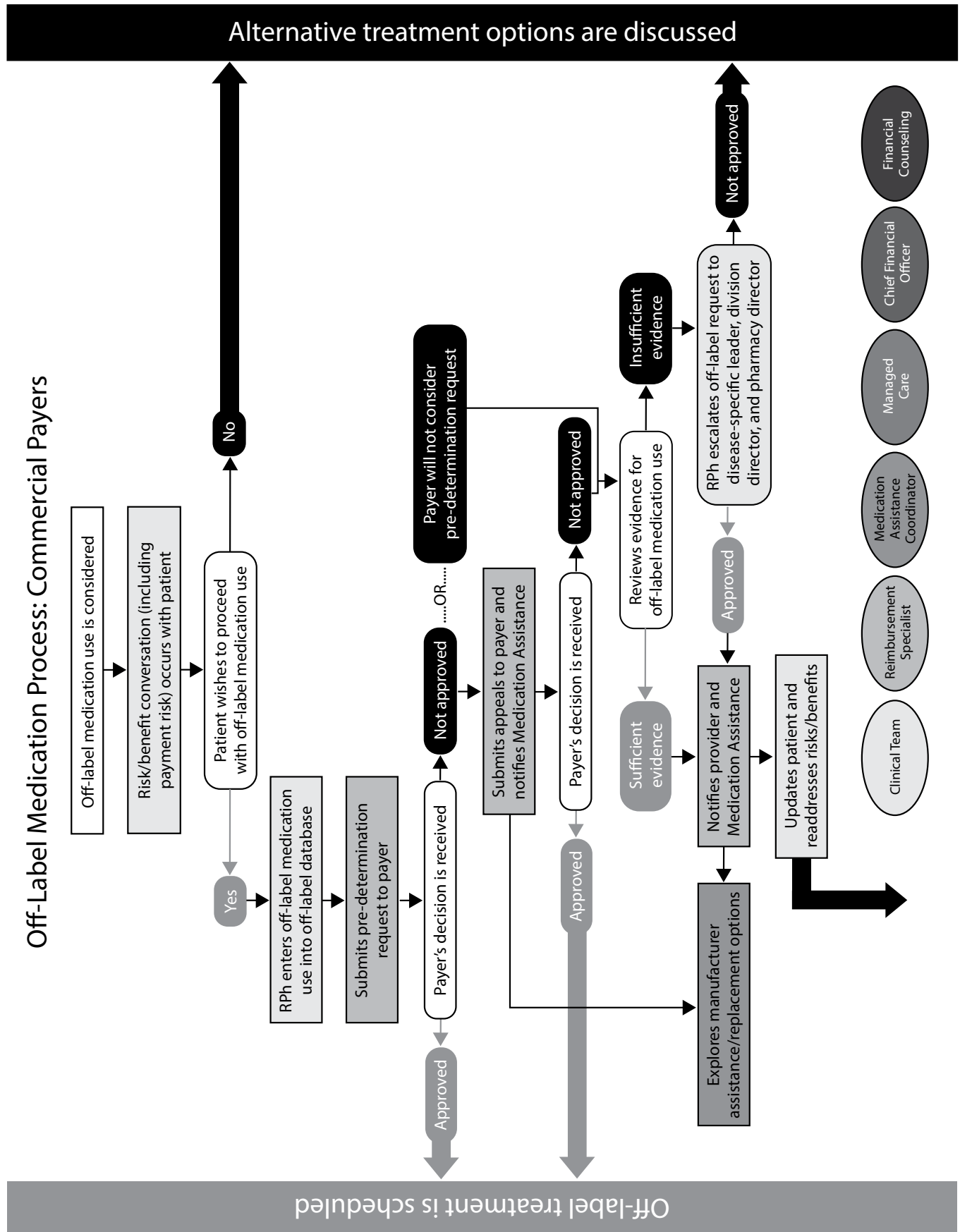
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Off-Label Medication Process: Medicare Post-Treatment



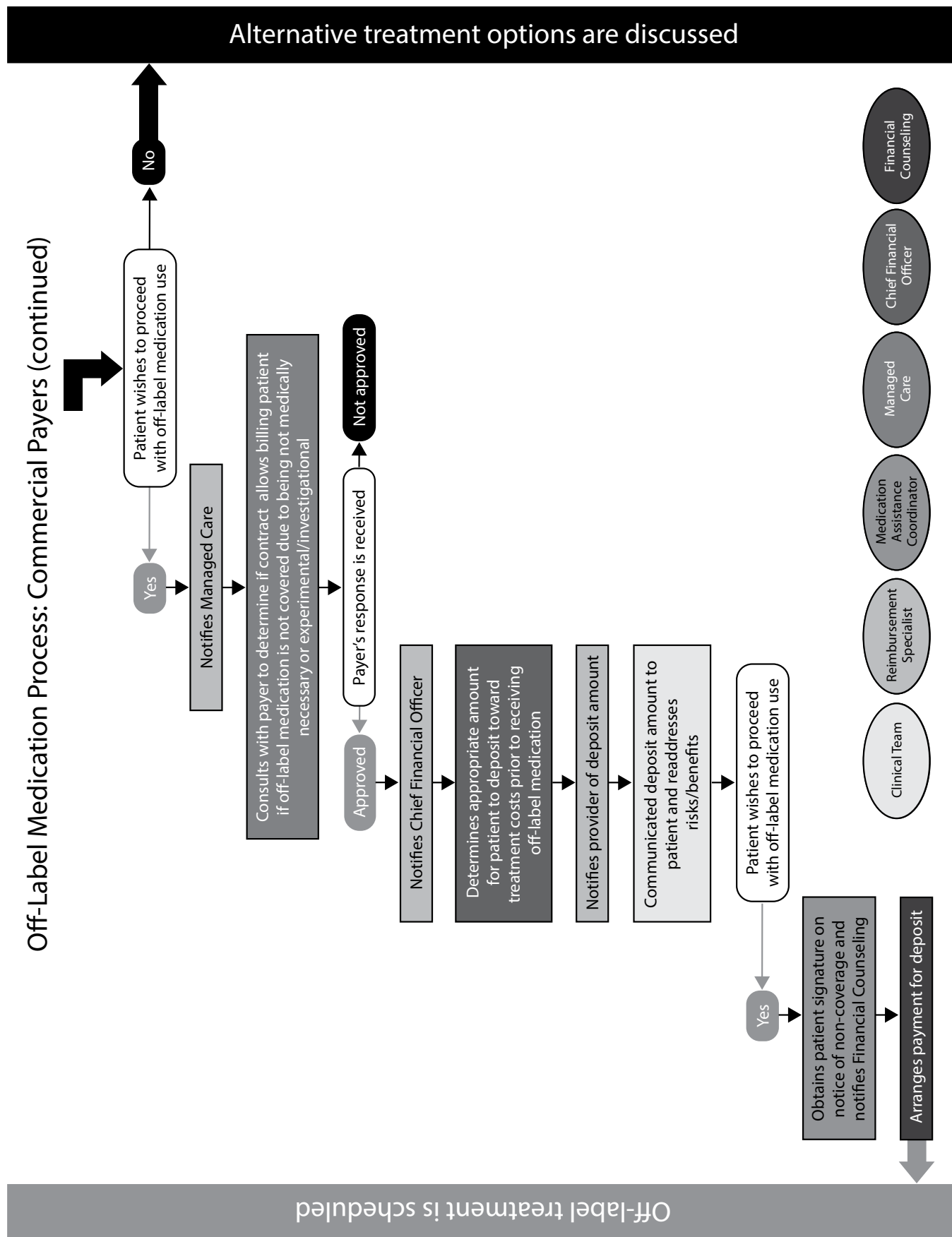
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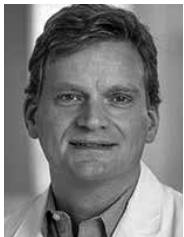


# What's Next for Cancer Immunotherapy?

**Hans Hammers, MD, PhD**

Associate Professor

*University of Texas Southwestern*



Dr. Hammers received his M.D. and Ph.D. degrees from the University of Lubeck in Germany. He completed a fellowship in Hematology and Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital in Baltimore, MD. He was an Assistant Professor at Johns Hopkins, when he was recruited to join the leadership of the KCP. In June of 2016, Dr. Hammers joined the faculty at UT Southwestern, where he is Associate Professor in the Department of Internal Medicine and Co-Leader of Clinical Research of the KCP. His research interest is in immunotherapies for kidney cancer. Dr. Hammers is the inaugural recipient of the Eugene P. Frenkel Scholar Award.

*Slides not available at time of printing.*

# 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

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### 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 durvalumab are 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 ( $\leq 25$  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  $\geq 1$ ) 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  $\geq 1\%$
- Pembrolizumab monotherapy is approved for recurrent/metastatic cervical cancer after progression on previous therapy with PD-L1 CPS  $\geq 1$



# 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

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### 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 expert clinical recommendations that provide guidance on the use of immunotherapy to treat specific types of cancer and the management of associated toxicities. These guidelines are an essential resource for the oncology healthcare community, with topics including 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:

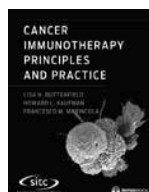
- Bladder Carcinoma
- Cutaneous Melanoma
- Head and Neck Cancers
- Hematologic Malignancies
- Non-small Cell Lung Cancer
- Prostate Cancer
- Renal Cell Carcinoma

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

As companions to the published guidelines, quick-reference Pocket Guides are available, which contain key 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 webinars, materials are archived on the SITC website and available on-demand free of charge.

Visit [sitcancer.org/guidelines](https://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 in development.

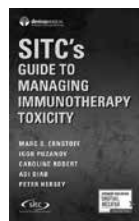
For more information on the textbook, please visit: <https://www.sitcancer.org/CIPPTextbook>.

## SITC Toxicity Management Consensus Recommendations

To help healthcare professionals better understand and manage the 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. The manuscript provides expert consensus recommendations on pre-treatment screening, toxicity characteristics of different agents and events that require specialist referral, along with other critical information.

## 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 both general principles of immune-related toxicity management and specific recommendations for commonly reported adverse events. Part I of the

handbook offers overviews of immune checkpoint inhibitors in the clinic and approved immunotherapeutic combinations. Also covered are mechanisms of action for approved agents and the most common toxicities exhibited in patients treated with checkpoint inhibitors during early, advanced, and metastatic stages of cancer. Part II is organized by major organ site. Each chapter offers guidance on assessment and treatment of adverse events, along with recommendations for patient support during acute and chronic toxicity. The handbook also contains a discussion on management of special patient populations, fatigue and financial considerations.

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

## Journal for ImmunoTherapy of Cancer



*Journal for ImmunoTherapy of Cancer (JITC)*

is the open access, peer reviewed, online journal of SITC. The journal publishes articles on all aspects of tumor immunology and cancer immunotherapy and, in doing so, aims to enrich communication and advance scientific understanding among the many stakeholders in this rapidly evolving field. Topics of interest range widely across the basic science-translational-clinical spectrum and include tumor-host interactions, the tumor microenvironment, animal models, predictive and prognostic immune biomarkers, novel pharmaceutical and cellular therapies, vaccines, combination immune-based therapies, and immune-related toxicity.

JITC publishes high quality original research articles, literature reviews, position papers and practice guidelines, case reports, and commentaries. Together, these articles make JITC the leading forum for research in tumor immunology and cancer immunotherapy.

To read the journal, please visit <https://jitc.bmj.com/>.

## Notes

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# 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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[www.aaem.org/whyaem](http://www.aaem.org/whyaem)

CHAMPION OF THE EMERGENCY PHYSICIAN

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](http://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](http://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.

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



Association of Community Cancer Centers



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](http://sitcancer.org/PatientCourse)

SITC-0619-150

## SITC Cancer Immunotherapy connectED

### SITC connectED is for clinicians

- Receive free access to CME-, CNE-, CPE- and MOC-certified courses
- Learn basic principles of cancer immunotherapy
- Remain current with the latest clinical applications for cancer immunotherapy
- Improve your understanding of immune-related adverse event management

### SITC connectED is for researchers

- Stay up-to-date with current science and advances in the cancer immunotherapy field
- Access more than 15 years of SITC meeting content and *Journal for ImmunoTherapy of Cancer* (JITC) articles

### SITC connectED is for patients

- Access patient resources on clinical trials, financial assistance, support groups and much more
- Learn how immunotherapy treats specific cancer types

Online education and resources  
from SITC, the world's leading  
cancer immunotherapy organization



Society for Immunotherapy of Cancer

[sitcancer.org/connectED](http://sitcancer.org/connectED)

SITC-0619-150



# 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 disease 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](http://sitcancer.org/guidelines)

Visit [sitcancer.org/acionline](http://sitcancer.org/acionline) today to register for these ACI online programs