SATURDAY, SEPTEMBER 26, 2020

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
Supported by educational grants from Lilly and Merck & Co.

ONQ ONCOLOGY NURSES QUALITY Improvement Series

Immune Checkpoint inhibitors: The Oncology Nurse's Role in the Monitoring and Early Intervention of Immune-related Adverse Events

FACULTY

Arjun V. Balar, MD
Associate Professor of Medicine
Director, Genitourinary Medical Oncology Program
Laura and Isaac Perlmutter Cancer Center
NYU Langone Health
New York, NY

PROGRAM OVERVIEW

This case-based live virtual activity will cover the diagnosis, treatment, and management of patients with cancer who are treated or eligible for treatment with immunotherapy.

TARGET AUDIENCE

This initiative is designed to meet the educational needs of oncology nurses involved in the management of patients with cancer who are treated or eligible for treatment with immunotherapy.

LEARNING OBJECTIVES

Upon completion of the program, attendees should be able to:

- Review the mechanism of action and clinical profiles of available and emerging immunotherapies used alone or in combination across lines of therapy in multiple tumor types
- Describe the side effects and toxicities associated with available immunotherapeutic options for the treatment of patients with various types of cancer and strategies to manage them in clinical practice
- Summarize best practices for the use of biomarker testing in clinical practice to guide treatment making decisions regarding cancer immunotherapies including the potential for response to therapy and the occurrence of irAEs
- Discuss current recommendations and emerging evidence regarding the use of immunotherapies for patients with cancer during the COVID-19 pandemic including the management of irAEs and the utility of telemedicine
- Describe the fundamentals of patient-centered SDM approaches and their utility in optimizing patient care in clinical practice

ACCREDITATION STATEMENT

Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. This CME activity was planned and produced in accordance with the ACCME Essentials.

CREDIT DESIGNATION STATEMENT

Med Learning Group designates this live virtual activity for a maximum of 1.0 *AMA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the live virtual activity.

NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the care of patients with cancer who are treated or eligible for treatment with immunotherapy. **CNE Credits:** 1 ANCC Contact Hour.

CNE ACCREDITATION STATEMENT

Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education for RNs and APNs.

ONCC STATEMENT

The program content has been reviewed by the Oncology Nursing Certification Corporation (ONCC) and is acceptable for recertification points.

DISCLOSURE POLICY STATEMENT

In accordance with the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support, educational programs sponsored by Med Learning Group must demonstrate balance, independence, objectivity, and scientific rigor. All faculty, authors, editors, staff, and planning committee members participating in a MLG-sponsored activity are required to disclose any relevant financial interest or other relationship with the manufacturers of any commercial products and/or providers of commercial services that are discussed in an educational activity.

DISCLOSURE OF CONFLICTS OF INTEREST

Arjun V. Balar, MD, has received consultant fees from Merck, Genentech, AstraZeneca, Pfizer, and Seattle Genetics; and received fees for non-CME/CE services received directly from a commercial interest or its agent from Merck, Genentech, and AstraZeneca.

CME Content Review

The content of this activity was independently peer-reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer-reviewed by a nurse reviewer.
The reviewer of this activity has nothing to disclose.

The staff, planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME/CE activity:
Matthew Frese, General Manager of Med Learning Group has nothing to disclose.
Christina Gallo, SVP, Educational Development of Med Learning Group has nothing to disclose.
Ana Maria Albino, Senior Program Manager of Med Learning Group has nothing to disclose.
Nicole Longo, DO, FACOI, Director of Medical and Scientific Services of Med Learning Group has nothing to disclose.
Lauren Welch, MA, VP of Accreditation and Outcomes of Med Learning Group has nothing to disclose.
Brianna Hanson, Accreditation and Outcomes Coordinator for Med Learning Group, has nothing to disclose.

DISCLOSURE OF UNLABELED USE

Med Learning Group requires that faculty participating in any CME activity disclose to the audience when discussing any unlabeled or investigational use of any commercial product or device not yet approved for use in the United States.

During this lecture, faculty may mention the use of medications for both FDA-approved and non-approved indications.

ONQ ONCOLOGY NURSES QUALITY Improvement Series

METHOD OF PARTICIPATION

There are no fees for participating and receiving CME/CNE credit for this live virtual activity. To receive CME/CNE credit participants must:

1. Read the CME/CNE information and faculty disclosures
2. Participate in the live virtual activity
3. Complete the posttest and online evaluation form

You will receive your certificate as a downloadable file.

DISCLAIMER

Med Learning Group makes every effort to develop CME activities that are science-based. This activity is designed for educational purposes. Participants have a responsibility to use this information to enhance their professional development in an effort to improve patient outcomes. Conclusions drawn by the participants should be derived from careful consideration of all available scientific information. The participant should use his/her clinical judgment, knowledge, experience, and diagnostic decision-making before applying any information, whether provided here or by others, for any professional use.

For CME questions, please contact: Med Learning Group at info@medlearninggroup.com
Contact this CME provider at Med Learning Group for privacy and confidentiality policy statement information at: www.medlearninggroup.com/privacy-policy/

AMERICANS WITH DISABILITIES ACT

Staff will be glad to assist you with any special needs. Please contact Med Learning Group prior to participating info@medlearninggroup.com

This activity is provided by Med Learning Group.

This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).

This activity is implemented in partnership with the Middle Tennesee Chapter.

Supported by an educational grant from Merck & Co., Inc.

ONCOLOGY NURSES QUALITY Improvement Series

Immune Checkpoint inhibitors: The Oncology Nurse's Role in the Monitoring and Early Intervention of Immune-related Adverse Events

I. Overview of Immuno-oncology

a. Immunosurveillance mechanisms by the innate and adaptive immune systems
b. Physiologic function of CTLA-4 and PD-1 as immune checkpoints

II. Available and Emerging Immuno-oncology Therapeutic Options for Advanced Malignancies

a. Mechanisms of action and clinical profiles of available immunotherapies used as monotherapies across lines of treatment in various tumor types
b. Mechanisms of action and clinical profiles of available immunotherapies used as combination therapies across lines of treatment in various tumor types
c. Mechanisms of action and clinical profiles of emerging immunotherapies alone and in combination

III. Immune- and Non-immune-related Biomarkers and Testing Methodologies

a. Prognostic biomarkers across various tumor types
b. Biomarkers predictive of response to treatment across various tumor types
c. Biomarkers predictive of the occurrence of irAEs across various tumor types
d. FDA-approved companion biomarker-based diagnostic tests

IV. Immune-Related Adverse Events Secondary to ICI Therapy

a. Pathophysiologic basis for irAEs across tumor types
b. Rare but serious irAEs: early diagnosis and intervention
c. Surveillance and management of most common irAEs (case-based)
d. Clinical Practice Guidelines (ASCO/NCCN) - how to monitor, classify, and manage irAEs

V. Multidisciplinary Oncology Team – Optimizing Patient Care and Survivorship Through Shared Decision Making

a. Educational strategies for the oncology patient
b. Shared decision making in the care process – use of decision aids
c. Ongoing, routine communication between members of the multidisciplinary health care team throughout treatment
d. Team members and their respective roles/Oncology nurses as integral members of the cancer care team

VI. COVID-19 and Cancer

a. Malignancy as a risk factor for infection
b. Relationship between active or past cancer treatment and infection on outcomes
c. Effect of infection-risk on immunotherapy selection/initiation/continuation
d. Telemedicine as part of routine oncology practice during pandemic

VII. Conclusions

VIII. Questions & Answers

Immune Checkpoint Inhibitors: The Oncology Nurse's Role in the Monitoring and Early Intervention of Immune-Related Adverse Events

Arjun V. Balar, MD
Associate Professor of Medicine
Director, Genitourinary Medical Oncology Program
Laura and Isaac Perlmutter Cancer Center
NYU Langone Health
New York, New York

1

Disclosures

- **Dr. Arjun Balar** discloses that he is a consultant with AstraZeneca/ Medimmune; Genentech, Inc./F. Hoffmann La Roche Ltd.; Merck & Co., Inc., Incyte Inc, Pfizer, and Seattle Genetics.
- During this lecture, faculty may mention the use of medications for both FDA-approved and nonapproved indications.

This activity is supported by an education grant from Merck & Co, Inc.

2

Learning Objectives

- Review the mechanism of action and clinical profiles of available and emerging immunotherapies used alone or in combination across lines of therapy in multiple tumor types
- Describe the side effects and toxicities associated with available immunotherapeutic options for treating patients with various types of cancer and strategies to manage them in clinical practice
- Summarize best practices for the use of biomarker testing in clinical practice to guide treatment-making decisions regarding cancer immunotherapies, including the potential for response to therapy and the occurrence of irAEs

3

Learning Objectives
(continued)

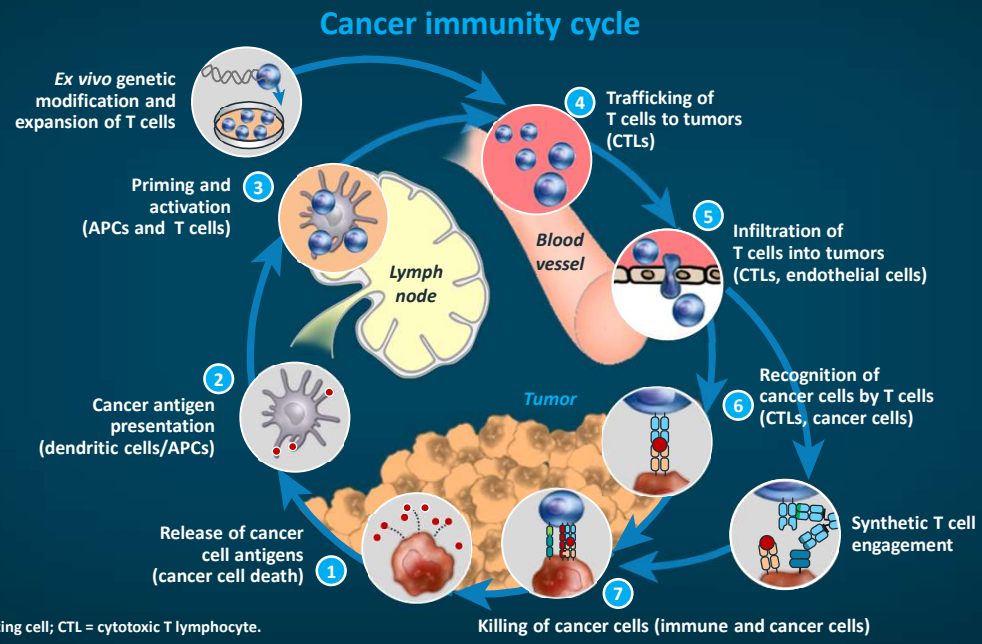
- Discuss current recommendations and emerging evidence regarding using immunotherapies in patients with cancer during the COVID-19 pandemic, including managing irAEs and the utility of telemedicine
- Describe the fundamentals of patient-centered SDM approaches and their utility in optimizing patient care in clinical practice
- Explain the various roles for oncology nurses in managing patients who are treated or eligible for treatment with immunotherapy

4

Overview of Immuno-oncology

5

Antitumor Immunity Is a Dynamic Process

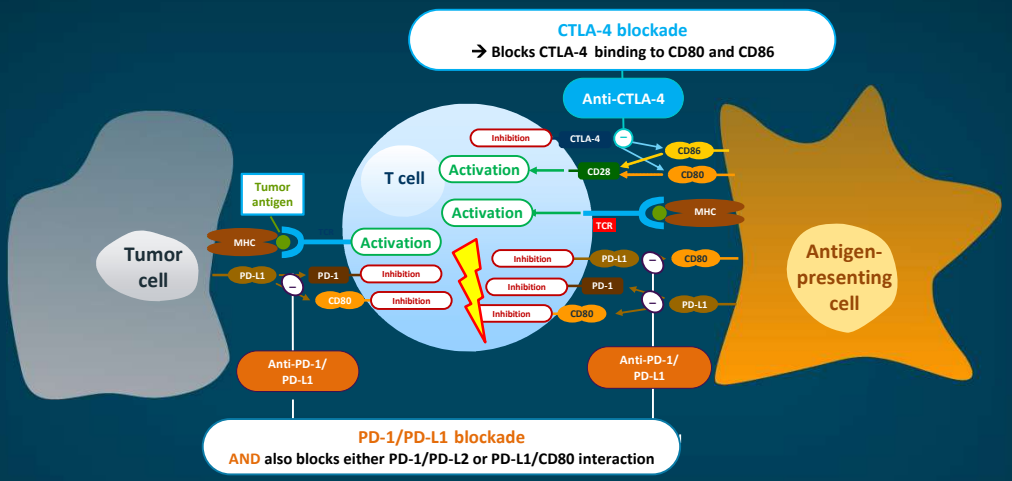


APC = antigen-presenting cell; CTL = cytotoxic T lymphocyte.

Hegde PS, Chen DS. *Immunity*. 2020;52:17-35.

6

Immune Checkpoints: CTLA-4, PD-1, and PD-L1

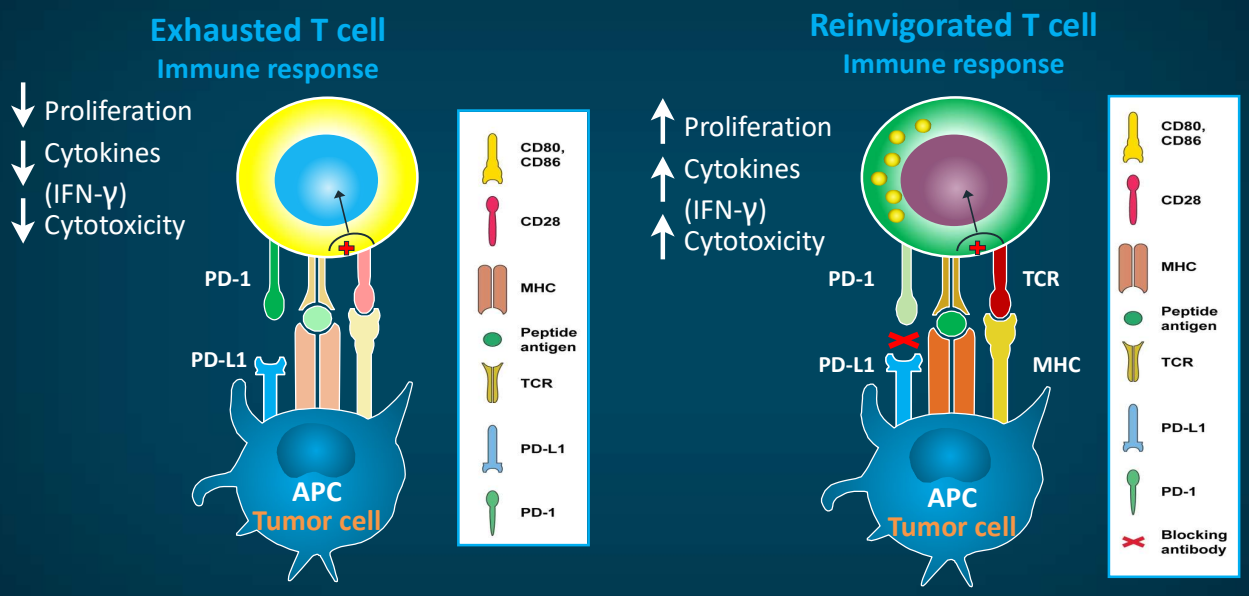


CTLA = cytotoxic T lymphocyte antigen; PD-1 = programmed (cell) death 1; PD-L1 = PD ligand 1; CD = cluster of differentiation; MHC = major histocompatibility complex; TCR = T cell receptor.

Adapted from Singh PP, et al. *Gastroenterol Rep* (Oxf). 2015;3:289-297. Adapted from Chen DS, et al. *Clin Cancer Res*. 2012;18:6580-6587.

7

Immune Checkpoint Inhibitors: MoA



MoA = mechanism of action; IFN-γ = interferon-gamma.

Adapted from Dyck L, Mills KHG. *Eur J Immunol*. 2017;47:765-779.

8

The Cancer Immunology Balancing Act

Immune surveillance
Immune system recognizes malignant cells

Immune escape

- **Antigen presentation:** *antigen loss (immune-editing), HLA* ↓
- **Immune checkpoints:** ***PD-1, PD-L1, CTLA-4, TIM3***
- **Cytokines:** *TGF-β, IL-4, IL-6*
- **Immunosuppressive ME:** *IDO*
- **Cellular immune escape:** *T-regs, M2 macrophages, MDSCs*
- **T-cell anergy**

HLA = human leukocyte antigen; TIM3 = T-cell immunoglobulin and mucin-domain containing-3; TGF-β = transforming growth factor beta; ME = microenvironment; IL = interleukin; IDO = indoleamine-2, 3-dioxygenase; T-reg = regulatory T cell; MDSC = myeloid-derived suppressor cell.

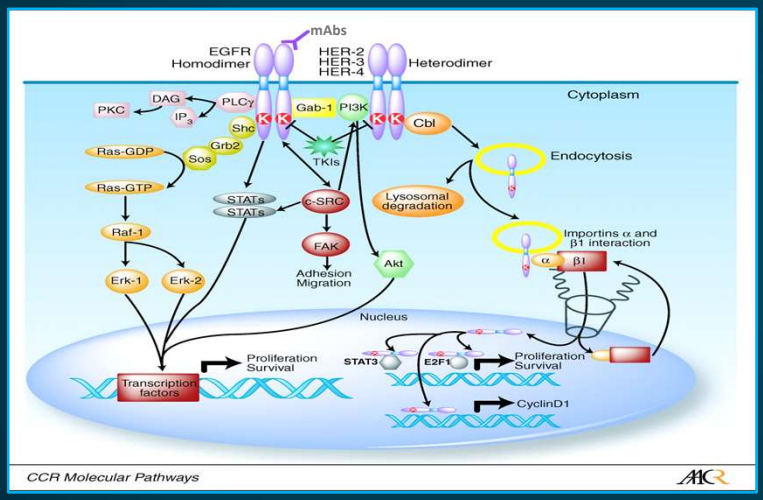
Monjazeb AM, et al. *Front Oncol*. 2013;3:197. Davies M. *Cancer Manag Res*. 2014;6:63-75.

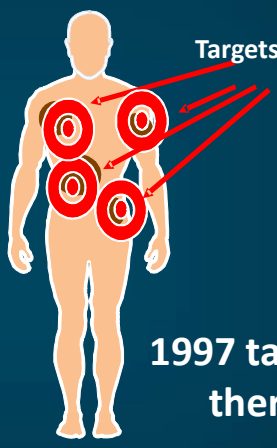
9

Cancer Therapy Through the Ages

Targeted Therapy

Signaling pathways and inhibitors of EGFR





Targets the tumor

1997 targeted therapy

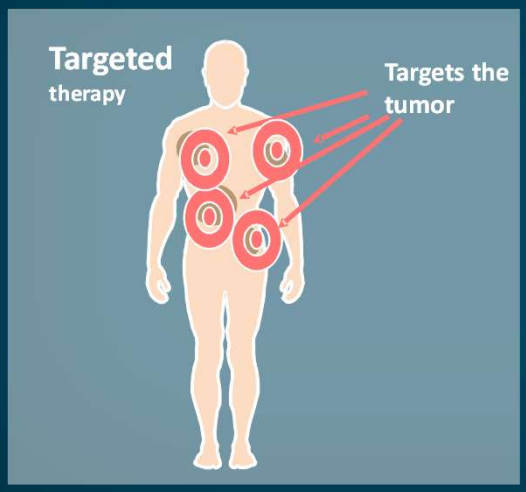
EGFR = epidermal growth factor receptor; mAb = monoclonal antibody; HER = human epidermal growth receptor; DAG = 1,2-diacylglycerol; IP_3 = inositol 1,3,5-triphosphate; PLCγ = phospholipase Cγ; Erk = extracellular signal-regulated kinase; FAK = focal adhesion kinase; PKC = protein kinase C.

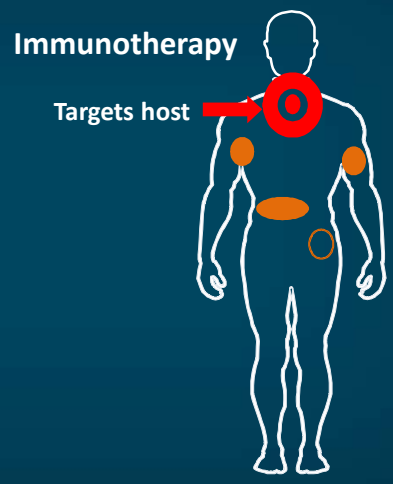
Scaltriti M, Baselga J. *Clin Cancer Res*. 2006;12:5268-5272. Røsland GV, Engelsen AS. *Basic Clin Pharmaccol Toxicol*. 2015;116:9-18.

10

Cancer Therapy Through the Ages

New Concept—Immunotherapy





1997 targeted therapy

Scaltriti M, Baselga J. Clin Cancer Res. 2006;12:5268-5272. Røsland GV, Engelsen AS. *Basic Clin Pharmaccol Toxicol.* 2015;116:9-18.

11

Unmet Need for Immunotherapy Biomarkers: Background

- Clinical successes in cancer immunotherapy and across multiple tumor types highlight critical need for biomarkers[1]
- Predictive—who is most likely to benefit from the therapies?
- Prognostic—factors that predict outcomes irrespective of treatment
- Mechanism of action of biomarkers—how therapy functions in order to inform decision making

Evaluating the performance of a predictive biomarker[1,2]
A trial designed ***to assess the clinical validity*** of a predictive biomarker must **predefine** its clinically meaningful performance metrics.
Guidelines for informative reporting of studies on ***prognostic*** as well as ***diagnostic*** markers exist; apply them to cancer immunotherapy.
Choice of specific performance metric and benchmark performance level that must be attained is ***dependent on intended clinical use*** (ie, determine predictive vs prognostic value of a biomarker).
Clinical utility vs clinical validity*:* there must be evidence suggesting that the use of the test is likely to lead to clinically meaningful benefit to the patient beyond current standards of care.

1. Butterfield LH. *Semin Cancer Biol.* 2018;52:12-15. 2. Dobbin KK, et al. *J Immunother Cancer.* 2016;4:77.

12

Current Immune Biomarker Status

Current

- PD-L1[1]
- MSI-H/dMMR[2,3]
- TMB[4]

Under investigation

- Neoantigens[5,6]
- PD-L2[8]
- Inflammatory gene signatures[7]
- Tregs[12]
- Host factors[14]
- TILs[9,10]
- MDSCs[11]
- LAG-3[13]
- IDO1[15]

TMB = tumor mutational burden; TILs = tumor-infiltrating lymphocytes; LAG-3 = lymphocyte activation gene-3.

1. Hirsch FR, et al. *J Thorac Oncol*. 2017;12:208-222. 2. Vilar E, Gruber SB. *Nat Rev Clin Oncol*. 2010;7:153-162. 3. Hause RJ, et al. *Nat Med*. 2016;22:1342-1350. 4. Astor L. *Targeted Oncol*. 2020. (www.targetedonc.com/view/fda-approves-pembrolizumab-for-tmb-high-solid-tumors). Accessed 6/17/2020. 5. Efremova M, et al. *Front Immunol*. 2017;8:1679. 6. Rooney MS, et al. *Cell*. 2015;160:48-61. 7. Yuan J, et al. *J Immunother Cancer*. 2016;4:3. 8. Zhao SG, et al. *J Natl Cancer Inst*. 2019;111:301-310. 9. Ma W, et al. *J Hematol Oncol*. 2016;9:47. 10. Galon J, et al. *Science*. 2006;313:1960-1964. 11. Okla K, et al. *Crit Rev Clin Lab Sci*. 2018;55:376-407. 12. Santegoets SJ, et al. *Cancer Immunol Immunother*. 2015;64:1271-1286. 13. Du W, et al. *Discov Med*. 2018;25:277-290. 14. Chen DS, Mellman I. *Nature*. 2017;541:321-330. 15. Gibney GT, et al. *Lancet Oncol*. 2016;17:e542-e551.

13

Current FDA-Approved PD-1 Inhibitors*

Agent	Target	Approved Indications	
Cemiplimab[1]	PD-1	Cutaneous squamous cell carcinoma (2nd line)	
Nivolumab[2]	PD-1	• Bladder cancer (advanced/metastatic, 2nd line) • Head and neck (recurrent/metastatic, 2nd line) • Hepatocellular carcinoma (2nd line) • Hodgkin lymphoma (relapsed/progressed after SCT or 4th line)	• Melanoma (metastatic and adjuvant) • MSI-H/dMMR CRC (2nd line) • NSCLC (metastatic, 2nd line) • RCC (advanced, 1st and 2nd line) • SCLC (metastatic, 2nd line)
Pembrolizumab[3]	PD-1	• Bladder cancer (1st and 2nd line metastatic, and HR BCG unresponsive CIS) • Cervical cancer (2nd line) • Cutaneous squamous cell carcinoma (recurrent or metastatic, not curable by surgery or radiation) • Endometrial carcinoma (advanced, not MSI-H or dMMR, 2nd line) • Esophageal cancer (recurrent locally advanced or metastatic, 2nd line) • Gastric cancer (3rd line) • Head and neck (1st and 2nd line) • Hepatocellular carcinoma (2nd line)	• Hodgkin lymphoma (4th line) • Melanoma (all metastatic and adjuvant) • Merkel cell carcinoma (recurrent locally advanced or metastatic) • MSI-H or dMMR tumors (1st and 2nd line) • NSCLC (1st and 2nd line) • Primary mediastinal large B-cell lymphoma (3rd line) • RCC (advanced,1st line) • SCLC (metastatic, 3rd line) • TMB-H tumors (2nd line)

SCT = stem cell transplant; MSI-H = microsatellite instability-high; dMMR = mismatch repair deficiency; CRC = colorectal cancer; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SCLC = small cell lung cancer; HR = high risk; BCG = Bacillus Calmette-Guerin; CIS = carcinoma in situ.

**See prescribing information for complete detailing of approved indications*

1.Cemiplimab (Libtayo®) prescribing information (PI), 2019 (www.regeneron.com/sites/default/files/Libtayo_FPI.pdf). 2. Nivolumab (Opdivo®) PI, 2020 (https://packageinserts.bms.com/pi/pi_opdivo.pdf). 3.Pembrolizumab (Keytruda®) PI, 2020 (www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf).

14

Current FDA-Approved PD-L1 and CTLA-4 Inhibitors*

Agent	Target	Approved Indications
Atezolizumab[1]	PD-L1	• Bladder cancer (1st and 2nd line) • ES-SCLC (1st line) • NSCLC (1st and 2nd line) • TNBC (PD-L1+ unresectable, locally advanced [LA] or metastatic)
Avelumab[2]	PD-L1	• Bladder cancer (LA/metastatic, 2nd line) • Merkel cell carcinoma (metastatic) • RCC (advanced,1st line)
Durvalumab[3]	PD-L1	• Bladder cancer (LA/metastatic, 2nd line) • ES-SCLC (1st line) • NSCLC (unresectable, stage III, without disease progression following platinum-based chemo-XRT)

Agent	Target	Approved Indications
Ipilimumab[4]	CTLA-4	• Melanoma (unresectable or metastatic, adjuvant resected) • HCC (2nd line) • RCC (untreated advanced, 1st line) • MSI-H or dMMR CRC (2nd line) • NSCLC (metastatic, 1st line)

It is very important to become familiar with these agents since the number and breadth of cancer indications are rapidly changing

**See prescribing information for complete detailing of approved indications*

ES-SCLC = extensive-stage small cell lung cancer; TNBC = triple negative breast cancer; XRT = radiation therapy; HCC = hepatocellular carcinoma.

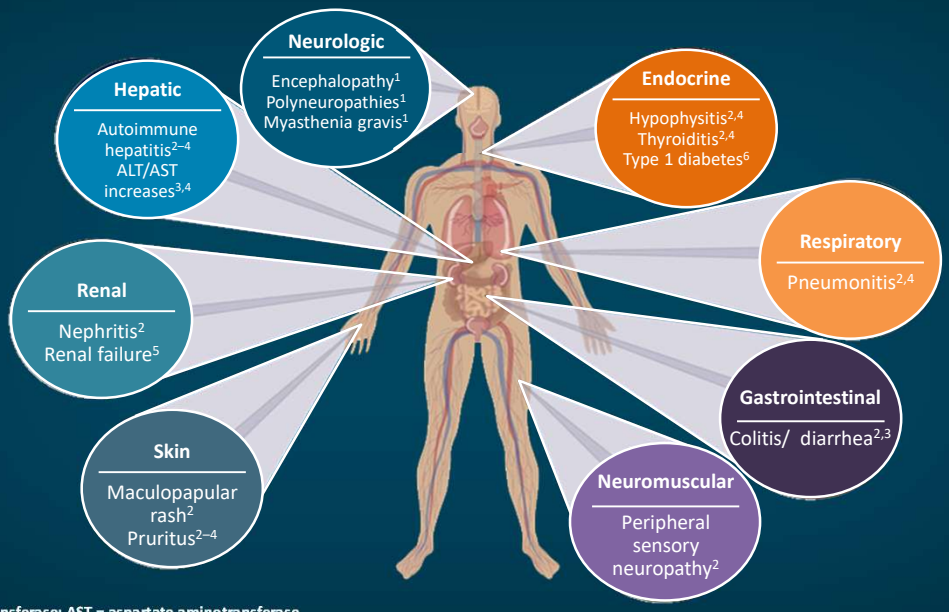
1. Atezolizumab (Tecentriq®) PI, 2019 (www.gene.com/download/pdf/tecentriq_prescribing.pdf). 2. Avelumab (Bevencio®) PI, 2019 (www.emdserono.com/content/dam/web/ corporate/non-images/country-specifics/us/pi/bavencio-pi.pdf). 3. Durvalumab (Imfinzi®) PI, 2020 (www.azpicentral.com/imfinzi/imfinzi.pdf). 4. Ipilimumab (Yervoy®) PI, 2020 (http://packageinserts.bms.com/pi/pi_yervoy.pdf).

15

Immune-Related Adverse Events (irAEs)

16

Virtually Any Organ Can Be Subject to Autoimmunity

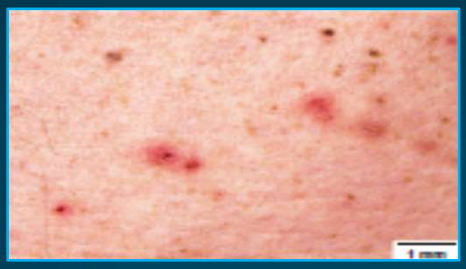


ALT = alanine aminotransferase; AST = aspartate aminotransferase.

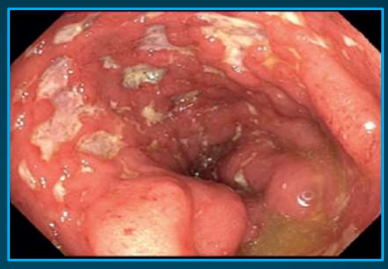
1. Hottinger AF. *Curr Opin Neurol*. 2016;29:806-812. 2. Teply BA, Lipson EJ. *Oncology (Williston Park)*. 2014;28(suppl 3):30-38. 3. Hodi FS, et al. *N Engl J Med*. 2010;363:711-723. 4. Topalian SL, et al. *N Engl J Med*. 2012;366:2443-2454. 5. Forde PM, et al. *Anticancer Res*. 2012;32:4607-4608. 6. Mellati M, et al. *Diabetes Care*. 2015;38:e137-e138.

17

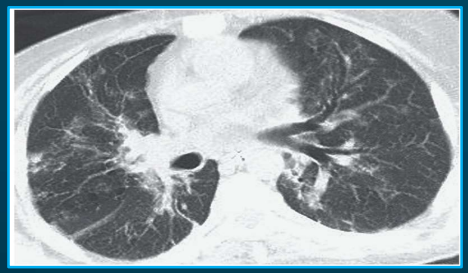
Spectrum of Immune-Related Adverse Events



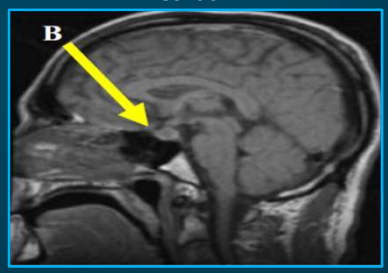
Rash[1]



Colitis[2]



Pneumonitis[3]



Hypophysitis[4]

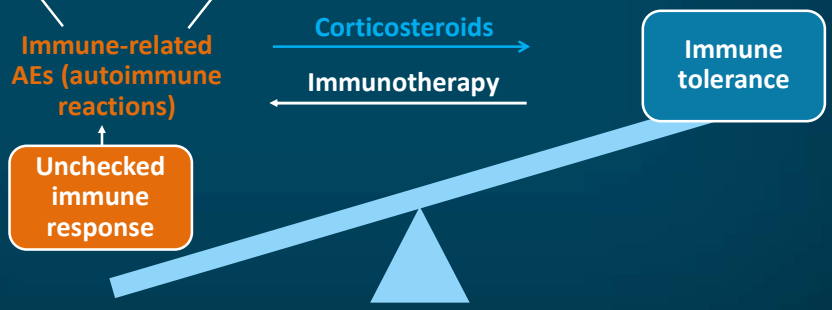
1. Koelzer VH, et al. *J Immunother Cancer*. 2016;4:47. 2. Geukes Foppen MH, et al. *ESMO Open*. 2018;3:e000278. 3. Nishino M, et al. *N Engl J Med*. 2015;373:288-290. 4. Blansfield JA, et al. *J Immunother*. 2005;28:593-598.

18

Toxicities With Immune Checkpoint Inhibitors (ICIs)

Organ-specific events[1,2]
- Skin
- Gastrointestinal
- Liver
- Pulmonary
- Endocrine system
- Musculoskeletal
- Renal
- Hematologic
- Cardiovascular
- Neurologic
- Ocular

General events[2]
- Fatigue
- Pyrexia, chills
- Infusion reactions



AE = adverse event.

1. Brahmer JR, et al. *J Clin Oncol.* 2018;36:1714-1768. 2. Naidoo J, et al. *Ann Oncol*. 2015;26:2375-2391.

19

The Truth About irAEs

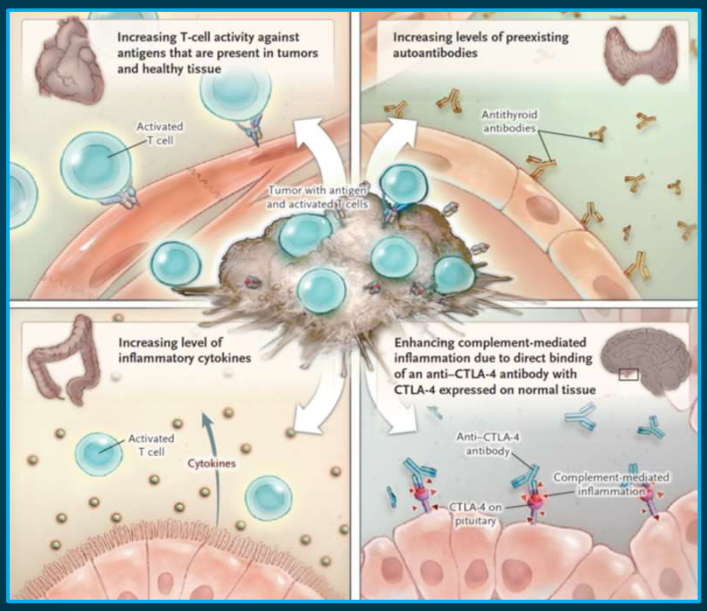
- What is the *mechanism*?
- *When* do they occur?
- *Who* can develop irAEs?
- Do they correlate with efficacy?
- Does immunosuppression reduce the efficacy of anticancer agents?
- What are the risks of immunosuppression (glucocorticoids, other agents)?
- Restarting immune checkpoint blockade when irAEs resolve; balancing risks and benefits

irAE = immune-related adverse event.

Postow MA, et al. *N Engl J Med.* 2018;378:158-168.

20

Possible Mechanisms for irAEs

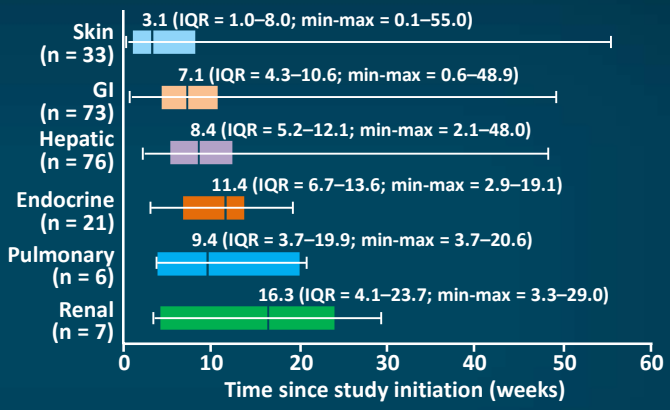


Postow MA, et al. *N Engl J Med*. 2018;378:158-168.

21

Time of Onset of irAEs With ICIs

Time to onset of grade 3/4 treatment-related AEs



- IrAEs can emerge **weeks to months** after therapy
- A patient's history of treatment with ICI agents may be relevant in the emergency setting

GI = gastrointestinal; IQR = interquartile range.

Sznol M, et al. *J Clin Oncol*. 2017;35:3815-3822. Postow MA, et al. *N Engl J Med*. 2018;378:158-168. Weber JS, et al. *J Clin Oncol*. 2012;30:2691-2697. Pallin DJ, et al. Acad Emerg Med. 2018;25:819-827.

22

Severity of irAEs

- **Severity (G1–4) determines management.**[1,2]
  - Grades for the most part follow the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0[3]
- Recommendations on management are based on consensus opinion[1,2,4]
- Patients with **grade 3 and 4 irAEs can present in ED**[1]
- Deaths from irAEs are very rare, but deaths due to myocarditis, pneumonitis, colitis, and neurologic events have been documented[2,4]

G = grade; ED = emergency department.

1. Brahmer JR, et al. *J Clin Oncol.* 2018;36:1714-1768. 2. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95. 3. NCI: CTCAE 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf). Accessed 10/2018. 4. Postow MA, et al. *N Engl J Med.* 2018;378:158-168.

23

General Approach to Immune-Mediated Symptoms

irAE is always included in differential and is often diagnosed by exclusion

Rule out other etiologies (eg, infection, other drugs, neoplasm, metabolic causes)

Can affect any organ system

Early recognition, evaluation, and treatment are critical for patient safety

Puzanov I, et al. *J Immunother Cancer*. 2017;5:95. Brahmer JR, et al. *J Clin Oncol.* 2018;36:1714-1768.

24

irAEs—Grading and Management Principles

Severity—CTCAE grade	Ambulatory vs inpatient care	Corticosteroids	Other immunosuppressive drugs	Immunotherapy
1 ***Mild***	Ambulatory	Not recommended	Not recommended	Continue with close monitoring *(exception neurologic/some hematologic toxicities)*
2 ***Moderate***	Ambulatory	Topical steroids *or* Systemic steroids oral (low-dose) 0.5–1 mg/kg/day	Not recommended	Suspend temporarily* until symptoms and/or lab values revert to grade 1 levels or lower
3 ***Severe***	Hospitalization	**Systemic steroids (high-dose)** Oral *or* intravenous (IV) 1–2 mg/kg/day x 3 days, then reduce to 1 mg/kg/day; long taper (≥1 month)	To be considered for unresolved symptoms after 3–5 days of steroids Organ specialist referral advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4 ***Very severe***	Hospitalization; *consider intensive care unit (ICU)*	**Systemic steroids (high dose)** IV methylprednisolone 1–2 mg/kg/day x 3 days, then reduce to 1 mg/kg/day; long taper (≥1 month)	To be considered for unresolved symptoms after 3–5 days of steroids Organ specialist referral advised	Discontinue ***permanently***
5 ***Death***				

Some dysimmune toxicities may follow a specific management; this must be discussed with the organ specialist.
***In the case of skin or endocrine disorders, immunotherapy can be maintained.**

Champiat S, et al. *Ann Oncol*. 2016;27:559-574. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768.

25

Organ Distribution of Immune-Related Toxicities

- Activating the immune system can kill cancer cells but ***may also cause inflammation*** *against normal cells.* This can be seen in any organ and can occur weeks to months (or longer) after treatment
- **Combination therapy** (usually blockade of CTLA-4 and PD-1) has greater rates of significant toxicity than single-agent immune-checkpoint therapy

Most common	Less common
• **Skin** • **Colon** } ***Most common*** *(average 2–3 months after therapy)* • **Thyroid, adrenal, or pituitary glands** • **Liver** • **Lungs** • **Gastrointestinal**	• **Blood or bone marrow** *(hemolytic anemia/ thrombocytopenia)* • **Cardiovascular** *(myocarditis, vasculitis)* • **Joints or muscles** • **Neurological** *(neuropathy, myelitis, myasthenia)* • **Ocular** *(blepharitis, conjunctivitis, iritis, scleritis, uveitis)* • **Pancreatic** *(pancreatitis, diabetes)* • **Renal** *(nephritis)*

Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. Postow MA, et al. *N Engl J Med*. 2018;378:158-168.

26

Dermatologic irAEs

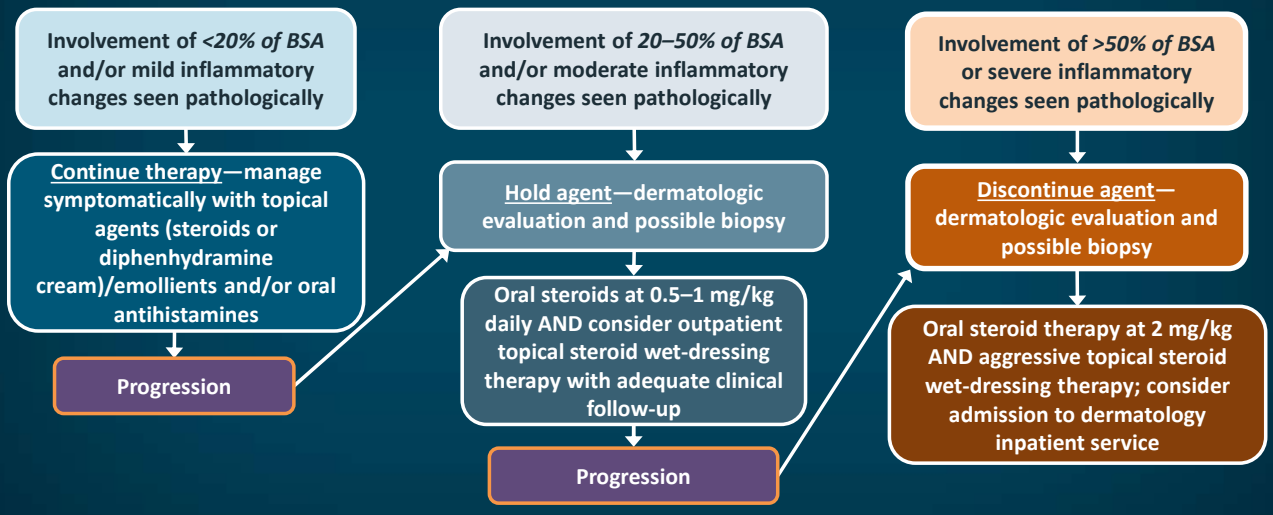
- **Rash/pruritus**—*most commonly reported AE*[1]
  - ~34–59% with monotherapy and ~53–72% with combination therapy1,2
  - Pruritus can also occur in the absence of rash[3]
- **Presentation is highly variable.**[3,4]
  - ***Pruritus***, rash, dermatitis, erythema, toxic epidermal necrolysis, palmoplantar erythrodysesthesia, bullous pemphigoid, photosensitivity, vitiligo
- Stevens-Johnson syndrome and bullous dermatoses require prompt dermatology evaluation and high-dose steroids[5]

1. Sibaud V. *Am J Clin Dermatol.* 2018;19:345-361. 2. Nivolumab (Opdivo®) PI, 2019 (https://packageinserts.bms.com/pi/pi_opdivo.pdf). 3. Friedman CF, et al. *JAMA Oncol.* 2016;2:1346-1353. 4. Brahmer JR, et al. *J Clin Oncol.* 2018;36:1714-1768. 5. Johnson DB, et al. *JAMA.* 2018;320:1702-1703. 6. Images courtesy of Dr. David Ettinger. 7. Pathria M, et al. *Int J Case Rep Imag.* 2016;7:300-302 (www.ijcasereportsandimages.com/archive/2016/005-2016-ijcri/CR-10639-05-2016-pathria/ijcri-1063905201639-pathria.pdf).

27

Management of Rash/Pruritus: Algorithm

Dermatologic irAEs (rash and/or pruritus) from checkpoint-inhibitor therapy



BSA = body surface area.

Kottschade L, et al. *Melanoma Res.* 2016;26:469-480.

28

Pneumonitis

Presentation[1]	Differential diagnosis	Diagnosis considerations
• Progressive cough • Dyspnea on exertion • Pleuritic chest pain • Fever (uncommon) Clinical presentation and imaging findings can be *subtle*	• Pneumonia[1] • Changes associated with lung-cancer burden[1] Chest X-ray: good for initial work up, can miss subtle findings *Computed tomography (CT) of chest should be considered* Failure to make the diagnosis and start corticosteroids can result in disease progression	• Occurs in ~1 in 20 patients treated with ICI monotherapy (<5%) and is somewhat higher with combination therapy[1,2] • Less common with CTLA-4 antibodies[1–3] — PD-1 inhibitors > PD-L1 inhibitors (in theory)[4] • High index of suspicion in patients without obvious signs of other infection • **Potentially fatal—early diagnosis and intervention are critical[1,2]**

1. Chuzi S, et al. *Cancer Manag Res*. 2017;9:207-213. 2. Haanen JBAG, et al. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142. 3.Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. 4. Khunger M, et al. *Chest*. 2017;152:271-281. Kalisz KR, et al. *Radiographics*. 2019;39:1923-1937.

29

Pneumonitis: General Management Principles

Grade (NCI CTCAE v4)	Management	Follow-up
Grade 1 *Radiographic changes only*	• Consider delay of I-O therapy • Monitor for symptoms every 2–3 days • Consider pulmonary and ID consults	Reimage at least every 3 weeks IF WORSENS: • Treat as grade 2 or 3–4
Grade 2 *Mild to moderate new symptoms*	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	Reimage every 1–3 days IF IMPROVES: • On symptom return to near baseline, taper steroids over ≥ 1 mo, then resume I-O therapy per protocol and consider prophylactic abx IF NOT IMPROVING AFTER 2 WEEKS or WORSENING: • Treat as grade 3–4
Grade 3–4 *Severe new symptoms; new/worsening hypoxia; life-threatening*	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2–4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic abx for opportunistic infections • Consider bronchoscopy, lung biopsy	IF IMPROVES TO BASELINE: • Taper steroids over at least 6 weeks IF NOT IMPROVING AFTER 48 HOURS or WORSENING: • Provide additional immunosuppression (eg, infliximab or mycophenolate mofetil*)

Patients on IV steroids may be switched to equivalent dose of oral corticosteriods (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to equivalent dose of oral corticosteroids.

ID = infectious disease; abx = antibiotics; I-O = immunooncology.

Adapted from Weber JS, et al. *Oncologist*. 2016;21:1230-1240.

*Agents not currently FDA-approved for irAEs

30

Gastrointestinal (GI) irAEs

Presentation	Differential diagnosis	Diagnosis considerations
• Diarrhea[1,2] • Colitis[1,2] (abdominal pain, fever, rectal bleeding, peritoneal signs) Onset occurs after an average of 3 infusions[3] Most commonly seen with[3–6]: – Ipilimumab (30–40%) – Combination therapy Less common with[3,6]: – PD-1/PD-L1 inhibitors – Anti-PD-1 monotherapy (≤19%)	• *Clostridium difficile* colitis[6,7] • Other forms of viral and bacterial gastroenteritis[7] • Ischemic colitis[7] There is *significant similarity* between colitis as an **immunotherapy-associated irAE** and **inflammatory bowel disease** (eg, clinical presentations, radiologic findings)[1]	• Alternative etiologies (eg, infection, effects of medications) should be ruled out[3] • <1% with fatal bowel perforation[4] – In large ipilimumab study, 31% of patients reported GI disorders (eg, diarrhea and colitis)[8] • **Immune-related colitis is potentially fatal—early diagnosis and intervention are critical**[3,8]

1. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. 2. Haanen JBAG, et al. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142. 3. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95. 4. Gupta A, et al. *Aliment Pharmacol Ther*. 2015;42:406-417. 5. Ipilimumab (Yervoy®) PI, 2019 (https://packageinserts.bms.com/pi/pi_yervoy.pdf). 6. Hryniewicki AT, et al. *J Emerg Med*. 2018;55:489-502. 7. Pallin DJ, et al. Acad *Emerg Med*. 2018;25:819-827. 8. Weber JS, et al. *Cancer*. 2013;119:1675-1682.

31

GI Toxicity: Management Principles

General Points

- Management of diarrhea/colitis
  - Important to **consider bioavailability** of **oral corticosteroids** in patients with moderate to severe symptoms
  - Very reasonable to initiate IV steroids and transition to oral on symptom improvement; should occur within 48 hours

Management

- Hospitalization, possible ICU monitoring
- Low threshold for starting steroids (initiated in parallel to diagnostic testing)
- Consult gastroenterology for ≥ grade 2
- Consider treatment with antitumor necrosis factor (TNF) agent (infliximab*) for moderate, severe, or refractory colitis
- Beware of **rebound diarrhea**
- Long taper (≥1month) after improvement of symptoms to grade 0 or 1

*Not currently FDA approved for irAEs

Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. Haanen JBAG, et al. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142. Hryniewicki AT, et al. *J Emerg Med*. 2018;55:489-502. Roberts K, et al. *Asia Pac J Clin Oncol*. 2017;13:277-288. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95. Weber JS, et al. *Oncologist*. 2016;21:1230-1240. Linardou H, Gogas H. *Ann Transl Med*. 2016;4:272. National Comprehensive Cancer Network (NCCN) practice guidelines. Management of immunotherapy-related toxicities. V1.2020 (www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf).

32

Infliximab*

- Anti-TNFα chimeric mAb → binds circulating TNFα[1]
- Indications include ankylosing spondylitis, Crohn's disease, psoriasis/psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis[1]
- Highly effective for irAEs not responsive to corticosteroids within 48–72 hours[2]
- Dosing
  - Standard (rheumatologic conditions): 5 mg/kg at 0, 2, and 6 weeks; every 8 weeks for maintenance[1]
  - For irAEs: 5 mg/kg IV x 1 or 2 doses often sufficient to control symptoms[2]
- Trials and guidelines addressing use of infliximab and other biologics to reduce or obviate need for chronic or high-dose steroids[3,4]
  - NCT02763761: phase 2 study of infliximab and low-dose prednisone (withdrawn due to lack of accrual)

*Not currently FDA-approved for irAEs

1. Infliximab (Remicade®) PI, 2018 (www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf). 2. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. 3. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95. 4. ClinicalTrials.gov. NCT02763761 (https://clinicaltrials.gov/ct2/show/NCT02763761). Accessed 4/29/2020.

33

NCCN and Additional Immunosuppression

Diarrhea
Colitis

G2
- Hold immunotherapy
- Prednisone/methylprednisolone (1-2 mg/kg/day)
- No response in 2-3 days—continue steroids, *consider* adding infliximab or vedolizumab within 2 weeks

G3/4
- *G3*: Discontinue anti-CTLA-4; consider resuming anti-PD(L)1 after toxicity resolution
- *G4*: Permanently discontinue IO agent causing toxicity
- Consider inpatient care
- Methylprednisolone IV (1-2 mg/kg/day)
- No response in 2 days, continue steroids, *strongly consider* adding infliximab or vedolizumab†, within 2 weeks

Initiation of anti-TNFα therapy (ie infliximab) within ~72 hours after 2-3 days of steroid non-responsiveness may be indicated for *severe irAEs* (in consultation with medical specialist)

**Moderate (G2) and severe (G3/4) symptoms require infectious stool assessment. †Consider vedolizumab for infliximab-refractory or infliximab-contraindicated cases.*

NCCN Guidelines. Management of Immunotherapy-Related Toxicities. Version 1.2020 – December 16, 2019.

*Infliximab and vedolizumab not currently FDA-approved for irAEs

34

Other Biologics*

- Anecdotal or case reports of use
- Adalimumab[1]
  - Anti-TNFα recombinant monoclonal antibody
- Etanercept[2]
  - Recombinant TNF receptor linked to IgG1 Fc portion
- Tocilizumab[3,4]
  - Anti-IL-6 receptor monoclonal antibody

*Not currently FDA-approved for irAEs

IgG = immunoglobulin G; Fc = fragment crystallizable (region).

1. Adalimumab (Humira®) PI, 2020 (www.rxabbvie.com/pdf/humira.pdf). 2. Etanercept (Enbrel®) PI, 2020 (www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/enbrel/enbrel_pi.pdf). 3. Tocilizumab (Actemra®) PI, 2019 (www.gene.com/download/pdf/actemra_prescribing.pdf). 4. Stroud CR, et al. *J Oncol Pharm Pract*. 2019;25:551-557.

35

Hepatic Toxicity

Presentation	Differential diagnosis	Diagnosis considerations[4,5]
Ranges from asymptomatic increased liver function (ALT, AST, bilirubin) → fulminant hepatitis[1,2] Median time to onset is highly variable: 4 to 25 weeks[3]	Alternative etiologies should be ruled out[1,2]: • Viral • Other medications • Malignancy	• 10% with anti-CTLA-4 mAb • <5% with anti-PD-1/PD-L1 mAb • Grade 3+ events: 1–2% • Increased toxicity with combinations (eg, vemurafenib)

1. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. 2. Haanen JBAG, et al. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142. 3. Zhang X, et al. *Drug Des Devel Ther*. 2016;10:3153-3161. 4. Naidoo J, et al. *Ann Oncol*. 2015;26:2375-2391. 5. Vemurafenib (Zelboraf®) PI, 2017 (www.gene.com/download/pdf/zelboraf_prescribing.pdf).

36

Hepatic Toxicity: Management Principles

General Points

- For severe cases, use high-dose IV steroids; permanently discontinue drug
- For patients with persistently elevated LFTs or who are refractory to steroids, consider:
  - Hepatobiliary consult
  - Mycophenolate* (500–1000 mg BID)
- Minimize alcohol intake
- **No infliximab (FDA warnings and precautions)**

Management

- **Grade 2**: hold drug and initiate systemic corticosteroids (1 mg/kg prednisone or equivalent)
  - *AST or ALT* **>3 x and ≤5.0 x** ULN ± *total bilirubin* **≤3.0** x ULN
  - Monitor 1–2 times weekly until resolution to <grade 2 (or baseline)
  - For patients continuing to trend up, start steroids at 0.5 mg/kg prednisone
- **Grade ≥3**
  - *AST or ALT* **>5.0 x** ULN ± *total bilirubin* **>3.0** x ULN
  - Discontinue therapy (for most patients)
  - As above
  - Start steroids at 1–2 mg/kg prednisone

*Not currently FDA-approved for irAEs

LFT = liver-function test; BID = twice daily; ULN = upper limit of normal.

Suzman DL, et al. *Liver Int*. 2018;38:976-987. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. Haanen JBAG, et al. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142. Zhang X, et al. *Drug Des Devel Ther*. 2016;10:3153-3161. Naidoo J, et al. *Ann Oncol*. 2015;26:2375-2391. Infliximab (Remicade®) PI, 2018 (www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf).

37

Endocrinopathies

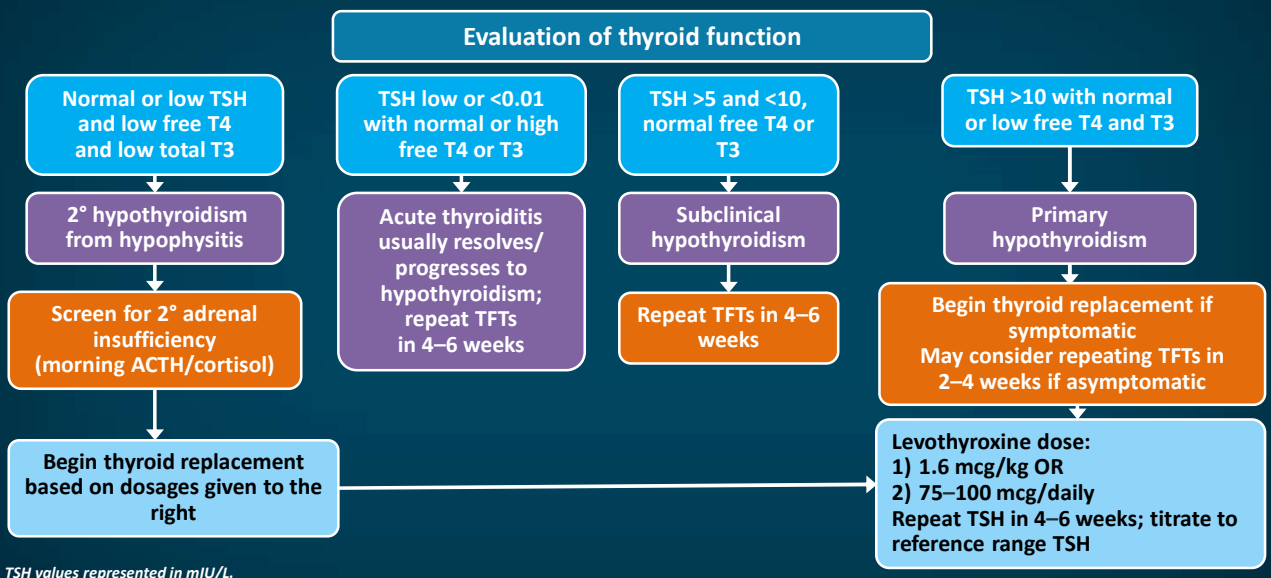
Thyroid: *Hyper → hypothyroidism*
Adrenal: *Adrenal insufficiency*
Pituitary: *Hypophysitis → hypopituitarism*
Pancreas: *Type 1 diabetes mellitus*

- Generally of G1–2; rarely high-grade (hypothyroidism, hypophysitis)
- Management
  - **Toxicity is generally irreversible**; therefore, management is hormone replacement
    - Symptomatic hyperthyroidism: methimazole
  - ***Adrenal insufficiency***: start methylprednisolone (or equivalent) immediately; substitute with hydrocortisone once prednisone reaches 10 mg/day
  - ***Grades 3–4***: hold anti-PD-1 treatment and add glucocorticoid ± hormone replacement; continue anti-PD-1 therapy if improvement to grade 2 or lower
  - **Diabetes:** Hold therapy and refer to endocrinology
    - May rechallenge once blood glucose is controlled
    - Corticosteroids **not known to be effective** in autoimmune diabetes

Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. Haanen JBAG, et al. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142. Chang J, et al. *BMJ Case Rep*. 2019;12:e228135. Roberts K, et al. *Asia Pac J Clin Oncol*. 2017;13:277-288. Godwin JL et al. *J Immunother Cancer*. 2017;5:40.

38

Thyroiditis: Most Common Endocrinopathy



TSH values represented in mIU/L.

TSH = thyroid-stimulating hormone; TFT = thyroid-function test; ACTH = adrenocorticotropic hormone.

Adapted from Kottschade L, et al. *Melanoma Res*. 2016;26:469-480.

39

Pancreatitis

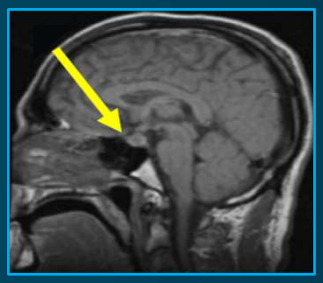
Presentation[1]	Asymptomatic Management[1]	Symptomatic Management
Often presents with: • Vague abdominal pain *and/or:* • Extreme fatigue • Nausea • Vomiting	(Ie, mildly impaired fasting glucose, elevated amylase and lipase only) Monitor symptoms closely; can continue therapy	**Pancreatitis** • Hold therapy and start steroids (0.5–1 mg/kg) • Treat based on symptoms; labs are not reliable • May rechallenge when <grade 2[2,3] • Steroid therapy may not prevent short- and long-term adverse outcomes or improve overall survival[4] **General** • Taper steroids based on symptoms, not labs[2,3] • Hospitalization in severe cases, with higher dose steroids (1–2 mg/kg)[2]

1. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. 2. Roberts K, et al. *Asia Pac J Clin Oncol*. 2017;13:277-288. 3. Grover S, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:13-19. 4. Abu-Sbeih H, et al. *J Immunother Cancer*. 2019;7:31. National Comprehensive Cancer Network (NCCN) practice guidelines. Management of immunotherapy-related toxicities. V1.2020 (www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf). Accessed 6/1/2020.

40

Other Endocrinopathies

- Hypophysitis[1]
  - Clinically presents with fatigue, abrupt-onset headache, possible visual changes, possible nausea and vomiting, behavior changes
  - Low or undetectable ACTH and morning cortisol levels
  - Enlarged pituitary on MRI (7/8 patients, 88%)
- Panhypopituitarism[1]
- Adrenal insufficiency[2,3]
  - Primary—rare
  - Secondary—almost universal after hypophysitis



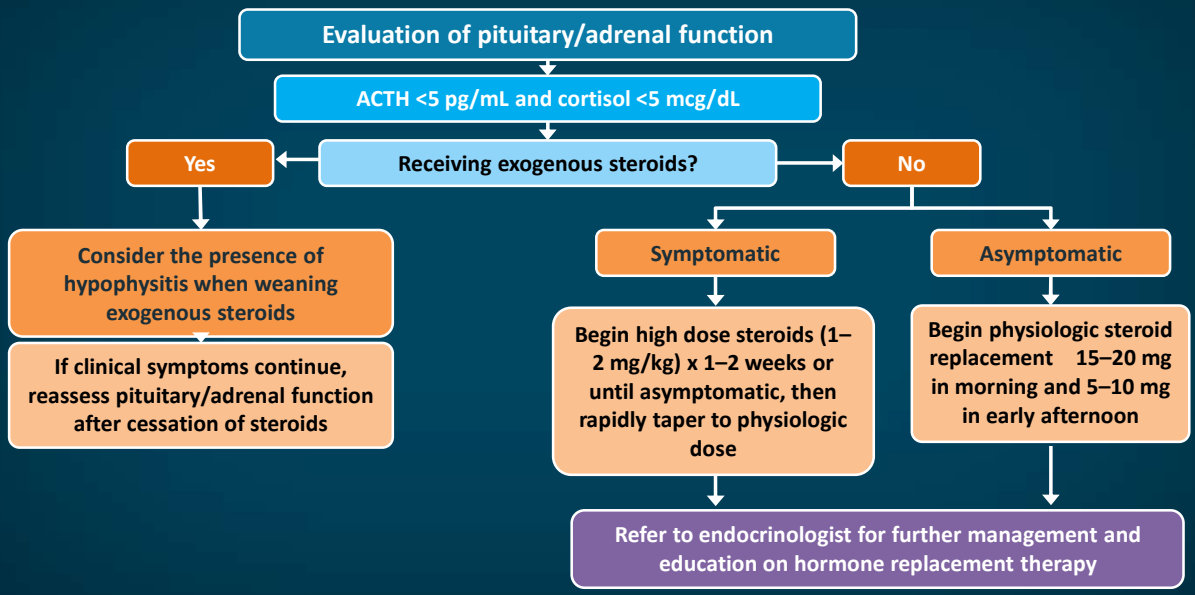
Autoimmune hypophysitis induced by CTLA-4 blockade

MRI = magnetic resonance imaging.

1. Blansfield JA, et al. *J Immunother.* 2005;28:593-598. 2. Roberts K, et al. *Asia Pac J Clin Oncol.* 2017;13:277-288. 3. Brahmer JR, et al. *J Clin Oncol.* 2018;36:1714-1768. Image from Blansfield et al.

41

Pituitary/Adrenal Toxicity



Adapted from Kottschade L, et al. *Melanoma Res.* 2016;26:469-480.

42

Primary Adrenal Insufficiency/Adrenal Crisis

- Severe symptoms, unable to perform activities of daily life (ADLs)
- Medically significant or life-threatening consequences
- Volume depletion, electrolyte abnormalities, and low or undetectable morning cortisol and high ACTH

- **Hospitalize with fluid replacement, correct electrolytes, and treat with high-dose steroids** (1–2 mg/kg)
- Condition typically does not resolve, and patients require lifelong physiologic glucocorticoid replacement
- Patients need to be instructed in stress-dose steroids and sick-day dosing
- Patients experiencing symptomatic improvement to grades 0–1 and are stable on hormonal replacement therapy can be rechallenged with immunotherapy

Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. Pallin DJ, et al. Acad *Emerg Med*. 2018;25:819-827. Bornstein SR, et al. *J Clin Endocrinol Metab*. 2016;101:364-389. O'Kane GM, et al. *Oncologist*. 2017;22:70-80. Peiró I, et al. *Endocrine Abstracts*. 2018;56: abstract GP184.

43

Neuromuscular Disorders

- Several cases of Guillain-Barre-type syndrome and myasthenia gravis have been reported[1,2]
- Severe motor/sensory neuropathy[1,2]
- Overall incidence = 2–4%; G3/G4 = <1%[3,4]
- Consult with neurology (MRI of spine, lumbar puncture, serum antiganglioside antibody tests)[1,2]

1. Spain L, et al. *Ann Oncol*. 2017;28:377-385. 2. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. 3. Dalakas MC. *Ther Adv Neurol Disord*. 2018;11:1756286418799864. 4. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95.

44

Uveitis/Iritis

- **Mild**
  - "Dry eyes"
  - Manage symptomatically
  - Can continue therapy
- **Moderate-symptomatic** (ie, pain, visual changes)
  - Hold therapy
  - Refer to ophthalmology
  - Topical steroids
  - Can rechallenge with improvement in symptoms
- **Severe**
  - As above
  - May need systemic steroids in addition if topical not working in 2–3 days
  - Discontinue therapy
  - Ophthalmologic consultation advised, ***either in ED or following day***

Brahmer JR, et al. *J Clin Oncol.* 2018;36:1714-1768. Pallin DJ, et al. *Acad Emerg Med.* 2018;25:819-827. Puzanov I, et al. *J Immunother Cancer.* 2017;5:95.

45

Rheumatologic Toxicities

General Points	Rheumatologic Conditions	Considerations
• Poorly recognized from RCTs • Lack of standardized reporting (arthralgia, arthritis, joint pain, joint effusion-aggregate >20%) • CTCAE grading possibly underestimates severity (significant disability or impaired self-care ADLs to reach Grade 3) • No mention for monitoring or management in labels or patient information	• Inflammatory arthritis —~5% in retrospective cohort of anti-PD-1-treated patients • Sicca syndrome • Polymyalgia rheumatica/giant cell arteritis • Myositis (dermatomyositis, polymyositis) • Single-organ vasculitis • Psoriasis • Scleroderma, others	• Arthralgia is frequently induced by PD-1 antibodies. • Mainly affects large joints • Mild symptoms may be manageable with NSAIDS ± low-dose steroids • Consult rheumatology

RCT = randomized controlled trial; NSAID = nonsteroidal anti-inflammatory drug.

Cappelli LC, et al. *Ann Rheum Dis.* 2017;76:43-50. Buder-Bakhaya K, et al. *Cancer Immunol Immunother.* 2018;67:175-182. Puzanov I, et al. *J Immunother Cancer.* 2017;5:95.

46

Cardiac Toxicity

Presentation	Differential diagnosis	Diagnosis considerations
Possible signs and symptoms: • Chest pain • Arrhythmias – Complete heart block • Palpitations • Peripheral edema • Progressive or acute dyspnea • Pleural effusions • Fatigue Myocarditis occurs *early,* with **median time of 1–2 months;** most cases occur within 3 months of starting ICI therapy	Alternative etiologies should be ruled out: • Viral • Other medications • Pneumonitis • Ischemia	• Pharmacovigilance studies report rates of: – 0.27% with combination therapy (anti-PD-1 and anti-CTLA4) – 0.06% in anti-PD-1 monotherapy • Can occur after single dose • Check troponin, CK, BNP, if any concern • Consult cardiology • Obtain ECG, ECHO; may consider cardiac MRI

CK = creatine kinase; BNP = brain natriuretic peptide; ECG = electrocardiogram; ECHO = echocardiogram.

Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. Ganatra S, Neilan TG. *Oncologist*. 2018;23:879-886. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95. NCCN practice guidelines. Management of immunotherapy-related toxicities. V1.2020 (www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf).

47

Cardiac Toxicity: Management Principles

General Points

- Hospitalization is required for close monitoring (telemetry/cardiac critical care). Cardiology consult +/– cardiac catheterization indicated, depending on risk factors
- **High risk** for development of **conduction abnormalities,** including complete heart block

Management

- **Any Grade**: permanently discontinue drug and initiate systemic corticosteroids
- Treatment recommendations are based on *anecdotal evidence* and life-threatening nature of cardiovascular events
  - Hold therapy
  - Initiate high-dose steroids
  - If no improvement, can consider initiation of mycophenolate, infliximab, or antithymocyte globulin*

*Not currently FDA-approved for irAEs

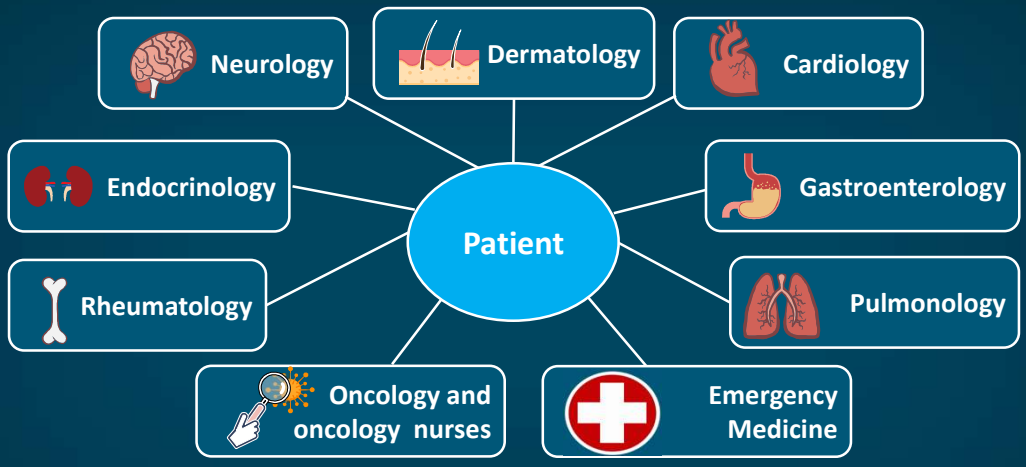
Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. Ganatra S, Neilan TG. *Oncologist*. 2018;23:879-886. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95.

48

Multidisciplinary Approaches to irAEs

49

Multidisciplinary Approach to irAEs



- Focus on safety
- Ask the patient and relatives about cancer history and use of immunotherapies
- Diagnose by exclusion of other causes
- Consult with other specialties
- Recognize rare, life-threatening cases and act promptly

50

Emergency Care Considerations

Challenges and Preconceptions

- Toxicities from ICIs can ***mimic*** other diseases
- AEs can emerge months after treatment and ***may continue to evolve*** after presentation
- AEs can involve a single organ system or affect multiple systems simultaneously
- Cancer/chemotherapy can lead to the assumption of immunosuppression, whereas **with ICIs,** the immune system is **hyperactive**
- Differential may be unclear if steroids were already initiated

Approaches and Interventions

- Modify **history-taking** to:
  - Include inquiries regarding ICIs within past 1 year
  - Ask patients and/or caregivers about ICI status
  - Ask for a "wallet card" that details any ICI therapy
  - Increase awareness that ICI history can be relevant with vague symptoms or specific conditions
- Standardize nursing assessment flow charts to include irAE assessment
- **Communicate with oncology**
- Increase team awareness
  - Higher-grade toxicity usually requires more urgent intervention

Pallin DJ, et al. *Acad Emerg Med.* 2018;25:819-827. Daniels GA, et al. *Emerg Med J.* 2019;36:369-377.

51

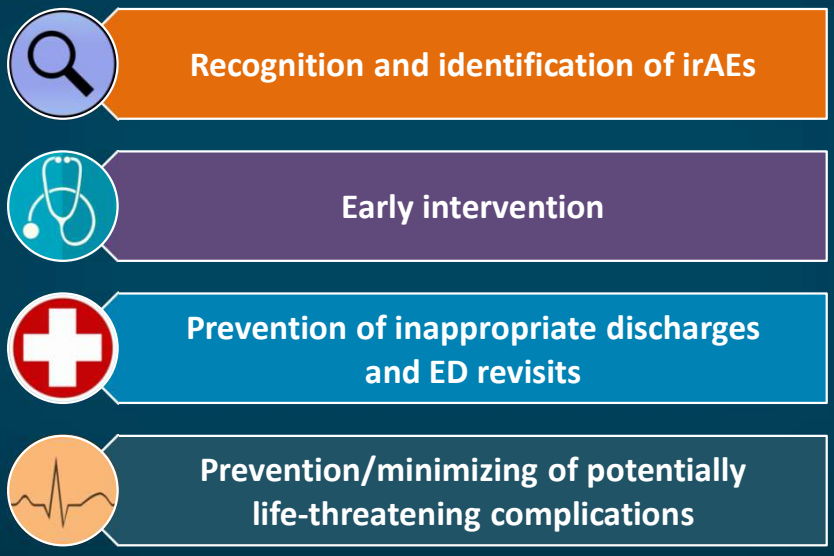
Navigating Immunotherapy During COVID-19

- irAEs and symptoms related to COVID-19 *can be similar*, which can present challenges to assessment and care during cancer treatment
- **Potential mitigation strategies**:
  - Streamline COVID-19 testing for shorter turn-around time and should be performed immediately before treatment and considered periodically during treatment.
  - Minimizing highly myelosuppressive agents
  - Expanding use of personal protective equipment (PPE)
  - Using oral therapy options when appropriate (can eliminate need for in-person treatment visits)
  - Splitting of health care teams to encourage geographic separation and minimize risk for cross contamination
  - Telemedicine and working with local oncology teams to minimize medical travel and points of contact with health care system

Alhalabi O, Subbiah V. *Trends Cancer.* 2020;6:533-535.

52

Critical Points in Approach to Management of Immune Checkpoint-Inhibitor Toxicities



Hryniewicki AT, et al. *J Emerg Med.* 2018;55:489-502.

53

Shared Decision-Making (SDM)

- Provides a **patient-centered approach** to decision-making when multiple options may be medically reasonable (including no intervention)
- Uses **decision aids (DAs)** that present organized, evidence-based, and unbiased information to *assist in communicating* with each patient
- Engages the **patient's *values, goals, concerns, expertise*** (of living with the condition), ***and preferences*** (including treatment burdens)
- Involves "**choice-awareness,**" which enhances execution of the SDM process
- Benefits include enhanced patient satisfaction, heightened patient therapeutic adherence, and enriched provider/patient relationships

SHARE workshop tool 1 (www.ahrq.gov/sites/default/files/wysiwyg/professionals/education/curriculum-tools/shareddecisionmaking/tools/tool-1/share-tool1.pdf). Kunneman M, et al. *Mayo Clin Proc Innov Qual Outcomes*. 2018;2:60-68.

54

5 Essential Steps of SDM: SHARE Approach

1. **S**eek your patient's participation
2. **H**elp your patient explore and compare treatment options
3. **A**ssess your patient's values and preferences
4. **R**each a decision with your patient
5. **E**valuate your patient's decision

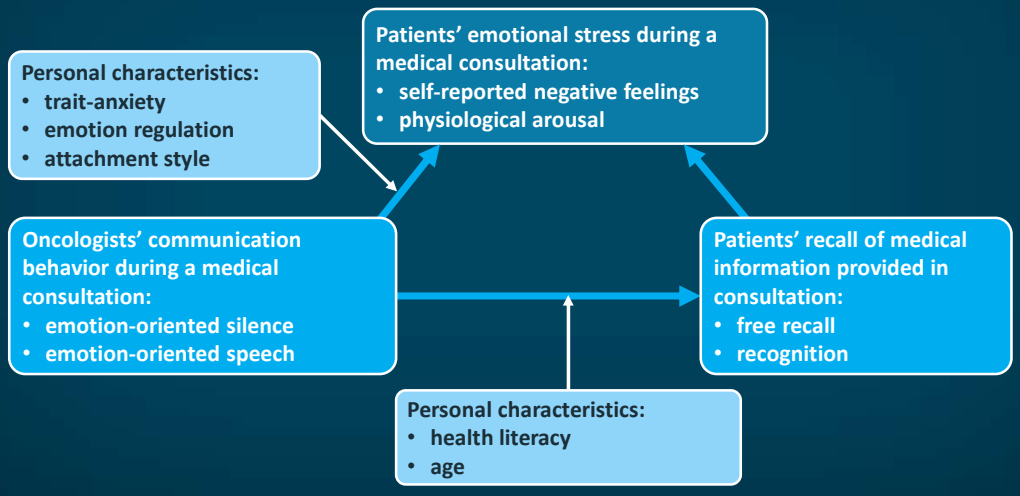
It's all about Communication!

AHRQ. Share approach factsheet (www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf).

55

Barriers to Communication

It has been suggested that approximately 20–60% of medical information provided to patients is immediately forgotten.



Mendendorp NM, et al. *Patient Educ Couns.*2017;100:1338-1344. Adapted from Visser LNC, et al. *Patient Educ Couns.* 2019;102:43-52.

56

Strategies for Effective Communication

Evidence-Based Recommendations on Handling Information

- Ask patients what types of information and level of detail they wish to have
- Offer information about quality-of-life issues as well as anticancer therapy
- Use the number of patient concerns as a marker for distress and poor adjustment
- Recognize that patient misunderstandings about clinical trials are common.
- In transitions to hospice care, avoid using phrases such as "*there is nothing more that can be done*"

Evidence-Based Recommendations on Dealing With Patient Emotions

- Do not assume that patients will request help for emotional issues
- Consider the patient-physician encounter as providing both cognitive data about patient understanding and emotional data about patient feelings
- Explicitly solicit emotional data from patients about their mood in order to detect distress

Back A. *Oncology (Williston Park)*. 2006;20:67-74.

57

Case Study 1

- A 68-year-old man with metastatic urothelial bladder cancer is initially treated with 6 cycles of platinum-based chemotherapy, achieving a partial response. After 6 months, his cancer progresses and he is treated with an anti PD-1 antibody. After 3 cycles of treatment, he achieves a response and continues treatment until 9 months later, when he develops disease progression and subsequently discontinues immunotherapy. He has tolerated treatment well, developing only mild rash, successfully treated with topical corticosteroids.
- Although he has discontinued immunotherapy, which continued assessment approach is most appropriate for this patient?

a) Monitoring for irAEs should continue for 30 days following treatment discontinuation

b) Monitoring for irAEs should continue for up to 4-5 months following treatment discontinuation

c) Monitoring for irAEs should continue for up to a year after treatment discontinuation

d) Monitoring for irAEs after treatment discontinuation is not necessary

58

Case Study 2

A 72 year old woman with stage 3 non-small cell lung cancer initially is treated with definitive chemoradiation. Approximately 18 months later she develops metastases to the adrenal gland and liver and is receiving platinum-based chemotherapy in combination with an anti-PD-1 antibody. After 3 cycles of treatment, the patient presents with worsening shortness of breath on exertion and a dry, nonproductive cough. She denies any fevers or chills or recent sick contacts, and her influenza vaccination is up to date. At rest, she is breathing comfortably and is fully conversant.

What is the most appropriate next step in management?

a) Hold chemoimmunotherapy treatment and emergently initiate corticosteroids for immune-related pneumonitis

b) Hold chemoimmunotherapy treatment, obtain a CT Chest and consider additional workup for immune-related pneumonitis

c) Continue chemoimmunotherapy treatment and refer the patient to a pulmonary specialist for further workup and management

d) Hold chemoimmunotherapy and begin oral antibiotics for bacterial pneumonia

59

Conclusions—irAEs

- Immune checkpoints inhibitors are firmly established as treatment standards in a range of cancers; irAEs are increasingly important
- High index of clinical suspicion and differential diagnosis is fundamental
- **Rates of irAEs** are **highest with combination therapy**
  - Anti-CTLA-4 drives a significant portion of autoimmunity
- No reliable means to predict who will develop irAEs and when
  - Can occur up to 4-5 months after treatment discontinuation
- *Early diagnosis and aggressive systemic corticosteroids* are **key to preventing life-threatening consequences**, as well as **affording opportunities for retreatment** due to diagnosis and intervention at lower irAE grades
- New ASCO/NCCN guidelines have been released on management of irAEs

ASCO = American Society of Clinical Oncology.

60

Conclusions—irAEs
(continued)

- Endocrinopathies are **generally irreversible** and are managed with hormone replacement
- Immunotherapy rechallenge is reasonable; HCP must **balance** between ***nature/severity of toxicity*** and ***response/potential for clinical benefit*** to continued treatment, with the caveat that treatment cannot be restarted while remaining on high-dose steroids
- Biologics (TNFα antagonists) are highly effective in managing irAEs refractory to high-dose steroids or steroid-taper refractory
- Beware of rebound symptoms (eg, gastrointestinal-related, rash), with thoughtful consideration for length of steroid taper
- Importance of a multidisciplinary team approach to irAEs
  - Organ-specific specialists are key members of the team

61

Thank you!

Questions and Answers

62


Build your own complimentary poster for the office!
Supplement your Course Learning. It's fast and easy.
We'll ship it to you directly free of charge
For more information and additional resources please visit
ONQ.POSTERPROGRAM.COM
ONQ
ONCOLOGY
NURSES
QUALITY
Improvement Series

63