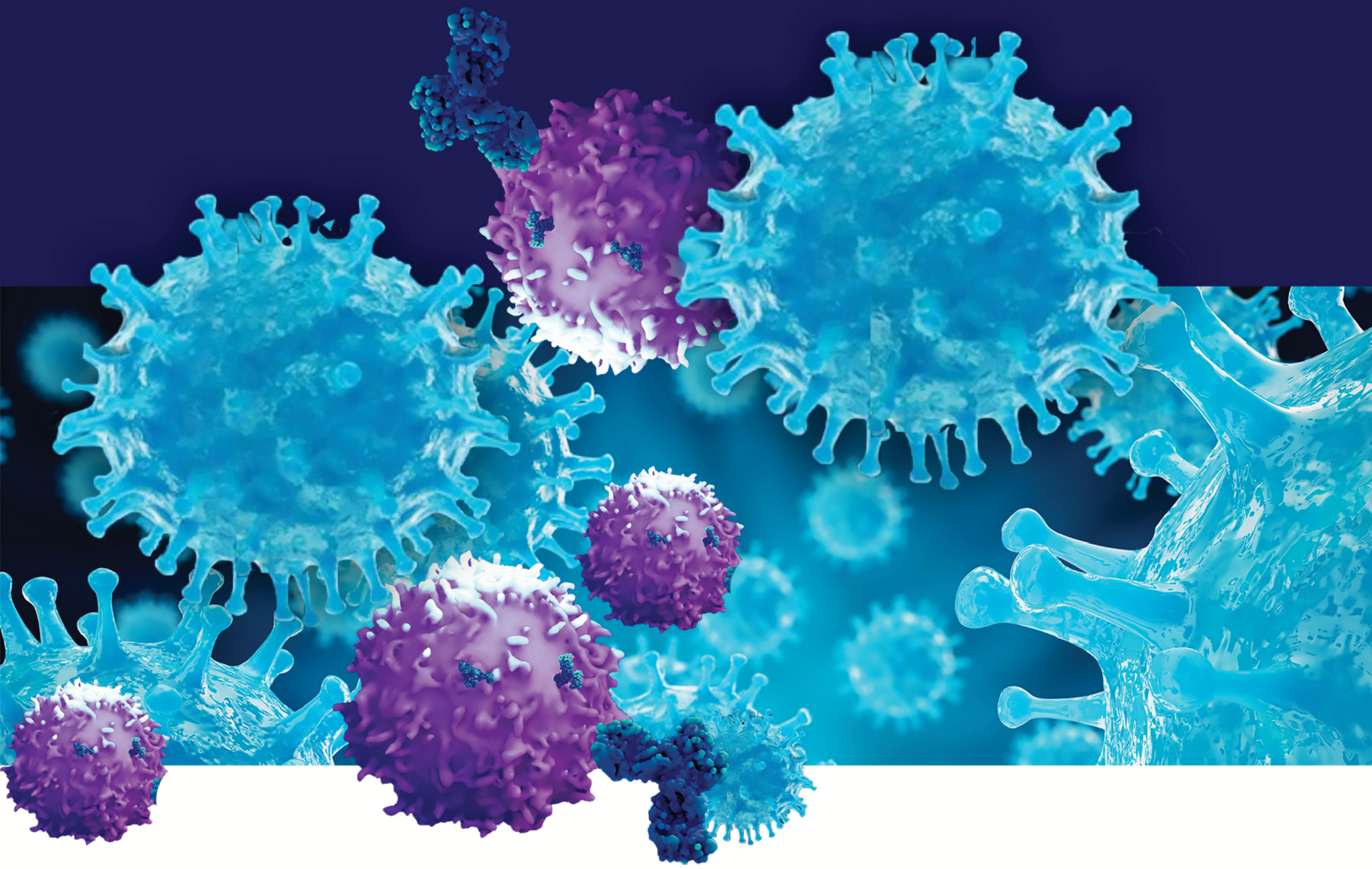
IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence and Management During the **COVID-19 Pandemic:**

IMMUNO-ONCOLOGY IN ADVANCED MELANOMA



MEETING INFO

Thursday, June 17, 2021
12:00 PM – 1:00 PM Eastern

FACULTY

Jeffrey S. Weber, MD, PhD
Deputy Director, Laura and Isaac Perlmutter Cancer Center
Co-Director, Melanoma Research Program
Professor of Medicine, NYU Grossman School of Medicine
New York, NY

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Bristol Myers Squibb.

Program Agenda

I. Introduction of IC-ONC Network - the Goals, Resources and Network Community Building Concept

a. Overview of IC-ONC Collaborative
b. Description of short and long-term goals and available resources that are available to the network community
c. Overview of the current scenario of new cancer immunotherapies for difficult-to-treat cancer malignancies (focus on advanced melanoma, NSCLC, RCC and HCC)
d. Rapidly changing treatment patterns and challenges in clinical practice due to the introduction of novel cancer immunotherapeutics

II. Melanoma Overview

a. Epidemiology
b. Pathogenesis
c. Staging

III. Available and Emerging Immuno-oncology Therapeutic Options for the Treatment of Advanced Melanoma

a. Mechanisms of action and clinical profiles of available immunotherapies used as monotherapies and combination therapies for advanced melanoma.
c. Mechanisms of action and clinical profiles of emerging immunotherapies for advanced melanoma

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

a. Prognostic and predictive biomarkers including BRAFV600-mutations
b. Incorporation of biomarker and genomic testing in the clinical practice setting

V. Immune-Related Adverse Events Secondary to ICI Therapy

a. Types of irAEs associated with immunotherapies for the treatment of advanced melanoma
b. Pathophysiologic basis for irAEs
c. Surveillance and management of most common irAEs (case-based)

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. Immunotherapy and COVID-19 vaccines

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

a. Educational strategies for the oncology patient
    1. Disease state, immuno-oncology medication use – dosing regimen (how and when to take, persistence/adherence, dosing options), potential adverse events and their management, review of treatment plan

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
    1. Emergency physicians as integral members of the cancer care team

VIII. Case Studies and Conclusions

IX. Questions & Answers

IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence and Management During the COVID-19 Pandemic

Track 1: Immuno-oncology in Advanced Melanoma

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 oncologists, oncology pharmacists, oncology nurses and other healthcare professionals and teams 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 MOAs and clinical profiles of available and emerging immunotherapies used alone or in combination across lines of therapy for the treatment of melanoma

• Summarize strategies for monitoring and managing irAEs associated with immunotherapies used alone or in combination across lines of therapy for the treatment of patients with melanoma

• Describe the prognostic and predictive utility of melanoma biomarkers discovered through genomic testing, such as $BRAF^{V600}$-mutations, that can inform patient-specific treatment decision making in the clinical practice setting

• Discuss current recommendations and emerging evidence regarding the use of immunotherapies for patients with melanoma during the COVID-19 pandemic including the management of irAEs and the utility of telemedicine

• Explain patient-centered SDM approaches aimed at optimizing cancer care and survivorship for those with melanoma and the role of emergency care physicians as part of multidisciplinary teams in the diagnosis and management of irAEs associated with immunotherapies used alone or in combination

ACCREDITATION AND DESIGNATION STATEMENTS

Accreditation Statement
Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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 management of patients with cancer who are treated or eligible for treatment with immunotherapy.
Credits: 1.0 ANCC Contact Hour

Accreditation Statement
Ultimate Medical Academy/Complete Conference Management (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 of RNs and APNs.

ABIM Maintenance of Certification:
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 Medical Knowledge MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

CONTINUING PHARMACY EDUCATION CREDIT

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Accreditation Statement
In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Med Learning Group. Amedco LLC 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.

Pharmacists and Pharmacy Technicians
Amedco LLC designates this activity for a maximum of 1.0 knowledge-based CPE contact hour.
NOTE: The only official Statement of Credit is the one you pull from CPE Monitor. You must request your certificate within 30 days of your participation in the activity to meet the deadline for submission to CPE Monitor.

PROGRAM CHAIR

Jeffrey S. Weber, MD, PhD

Deputy Director, Laura and Isaac Perlmutter Cancer Center
Co-Director, Melanoma Research Program
Professor of Medicine, NYU Grossman School of Medicine
New York, NY

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 an MLG-sponsored activity are required to disclose any relevant financial interest or other relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services that are discussed in an educational activity.

DISCLOSURE OF FINANCIAL RELATIONSHIPS

Dr. Weber has intellectual property or is a patent holder on a PD-1 biomarker patent with Biodesix, and a CTLA-4 biomarker patent with Moffitt Cancer Center. He has received consulting fees from BMS, GSK, Merck, Genentech, Amgen, Regeneron, Celldex, Incyte, Astra Zeneca, Pfizer, Protean, Evax. He has ownership interest in Neximmune, Biond, and CytoMx; and has received royalties totaling 900 dollars from a patent held with the Moffitt Cancer Center.

Staff, Planners and Managers

The independent reviewers, 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:

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.

Matthew Frese, General Manager of Med Learning Group has nothing to disclose.
Christina Gallo, SVP, Educational Development for Med Learning Group has nothing to disclose.
Lauren Welch, MA, VP, Outcomes and Accreditation for Med Learning Group has nothing to disclose.
Brianna Hanson, Outcomes and Accreditation Coordinator for Med Learning Group has nothing to disclose.

Debra Gordon, MS, Medical Director for Med Learning Group has nothing to disclose.
Melissa A. Johnson, Senior Program Manager for Med Learning Group has nothing to disclose.
Jessica McMullen, MPH, Program Manager 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 the course of this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications.

METHOD OF PARTICIPATION

There are no fees for participating and receiving CME/CNE credit for the 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 online post-test and evaluation.

You will receive your certificate as a downloadable file.

DISCLAIMER

Med Learning Group makes every effort to develop CME activities that are scientifically based. This activity is designed for educational purposes. Participants have a responsibility to utilize 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 at info@medlearninggroup.com

Provided by Med Learning Group

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

This activity is supported by an educational grant from Bristol Myers Squibb.

WELCOME!

We will start momentarily

Your line is automatically muted upon entry.

Things to Know

- ✓ Please type questions in the Q&A section
- ✓ To receive credit please visit **https://gl13melanomapost.questionpro.com/**
- ✓ Please visit **www.ic-onc.org** for more information and resources
- ✓ To build a complimentary office poster visit **immuneonc.posterprogram.com**
- ✓ ***To request a pair of glasses to view the 3D animations in this presentation, please email jmcmullen@medlearninggroup.com***

1

IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

Combination Treatment Options, Biomarkers, and Immune-Related Adverse Event Occurrence and Management During the COVID-19 Pandemic

Immuno-oncology in Advanced Melanoma

Jeffrey S. Weber, MD, PhD
Deputy Director, Laura and Isaac Perlmutter Cancer Center
Co-Director, Melanoma Research Program
Professor of Medicine, NYU Grossman School of Medicine
New York, NY

2

Disclosures

- Dr. Weber has intellectual property or is a patent holder on a PD-1 biomarker patent with Biodesix and a CTLA-4 biomarker patent with Moffitt Cancer Center. He has received consulting fees from BMS, GSK, Merck, Genentech, Amgen, Regeneron, Celldex Therapeutics, Incyte, Astra Zeneca, Pfizer, Protean, and Evax. He has ownership interest in NexImmune, Biond, and CytomX Therapeutics and has received royalties totaling $900 from a patent held with the Moffitt Cancer Center.
- During the course of this lecture, faculty may mention the use of medications for both FDA-approved and non-approved indications.

This activity is supported by an educational grant from Bristol Myers Squibb.

3

Accreditation

- Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. This CME activity was planned and produced in accordance with the ACCME Essentials.
- Ultimate Medical Academy/Complete Conference Management (CCM) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.
- This educational activity is applicable for CME and CNE credits, in addition to ILNA recertification points. Please complete the necessary electronic evaluation to receive credits and access to the ILNA credits form.

4

Learning Objectives

- Review the mechanisms of action (MOAs) and clinical profiles of available and emerging immunotherapies used alone or in combination across lines of therapy for the treatment of melanoma
- Summarize strategies for monitoring and managing immune-related adverse events (irAEs) associated with immunotherapies used alone or in combination across lines of therapy for the treatment of patients with melanoma
- Describe the prognostic and predictive utility of melanoma biomarkers discovered through genomic testing, such as $BRAF^{V600}$-mutations, that can inform patient-specific treatment decision-making in the clinical practice setting
- Discuss current recommendations and emerging evidence regarding the use of immunotherapies for patients with melanoma during the COVID-19 pandemic, including the management of irAEs and the utility of telemedicine
- Explain patient-centered shared decision-making approaches aimed at optimizing cancer care and survivorship for those with melanoma and the role of emergency care physicians as part of multidisciplinary teams in the diagnosis and management of irAEs associated with immunotherapies used alone or in combination

5

Introduction of the IC-ONC Network

IC-ONC = Immunotherapy Collaborative of Oncology Networked Communities.

6

IC-ONC

- This program is part of the Immunotherapy Collaborative of Oncology Networked Communities (IC-ONC), a global information network in which multidisciplinary healthcare providers who are responsible for treating patients with cancer are connected via education.
- **IC-ONC.org** serves as the central location for educational resources and information pertinent to patients with cancer being treated with immunotherapy.
  - It is curated by global, national, and local oncology experts.
  - It provides dates and locations of upcoming live meetings.
  - It provides access to archived and enduring activities.
  - It identifies clinical articles.
  - It is a source of downloadable content and other inter-professional resources from more than 14 collaborative educational partners.
  - It provides access to our open-source immuno-oncology registry: **The Observatory**
- Its objective is to facilitate ongoing communication and collaboration among participating healthcare providers with the aim of providing optimal care for the patient with cancer.
- For more information, please visit **www.ic-onc.org**
- Supported by an educational grant from Bristol Myers Squibb.

IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

7

IC-ONC Observatory

- Through participation in this course, you will become a member of the IC-ONC Observatory
- Your login details will be emailed to you in the coming weeks
- For immediate information, please visit www.ic-onc.org

IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities

8

Pathophysiology of Advanced Melanoma

9

Melanoma Statistics 2021

Melanoma quick stats

- A death from melanoma occurs *every 73 minutes*
- Annual new cases *increased 53%* over last decade
- Average age at diagnosis = 65 years
- Melanoma accounts for *~1% of all skin cancer diagnoses* but comprises a large majority of skin cancer-related deaths

2021 in the US

- 106,110 new cases (62,260 men, 43,850 women)
- 7180 deaths (4600 men, 2580 women)

Lifetime risk of developing melanoma

- Whites: ~2.6% (1 in 38)
- Hispanics: ~0.6% (1 in 167)
- Blacks, Asians/Pacific Islanders: ~0.1% (1 in 1000)

American Cancer Society (ACS). *Cancer Facts & Figures 2021.* ACS. Key statistics for melanoma skin cancer. (www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html). Accessed 3/17/2021.

10

What Is Melanoma?

Melanoma is caused by a constitutive dysregulation in melanocyte growth, resulting in escape from immune surveillance and leading to tumor formation

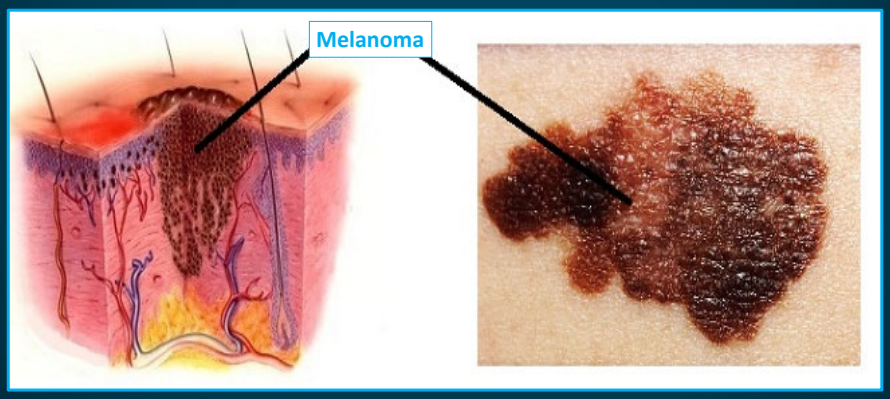
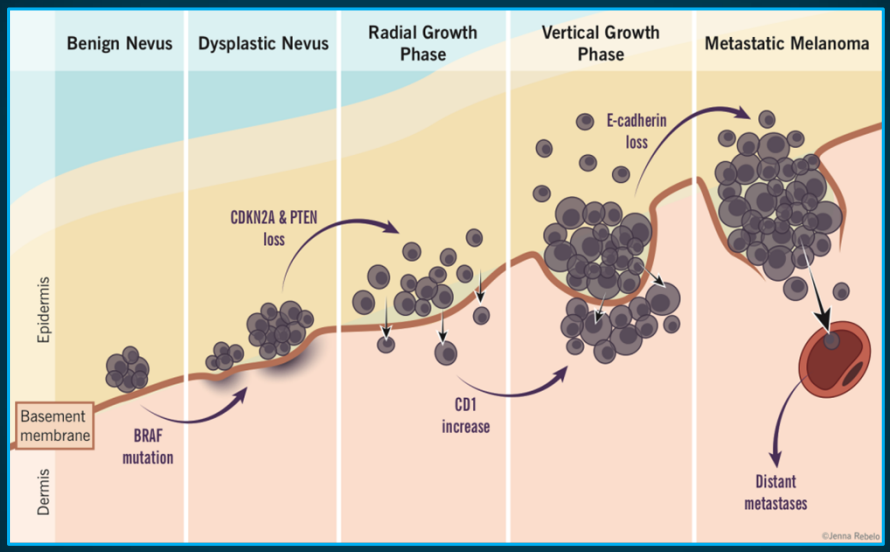


Image courtesy of Dr. Jeffrey Weber.

11

Pathogenesis of Melanoma

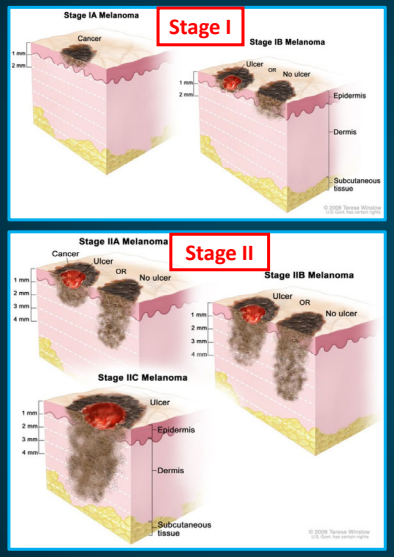


BRAF = B-Raf proto-oncogene; PTEN = phosphatase and tensin homologue; CD = cluster of differentiation.

Seuradge J, Wong E. *McMaster Pathophysiol Rev.* (pathophys.org/melanoma/). Accessed 3/15/2021.

12

Stages of Melanoma—I and II



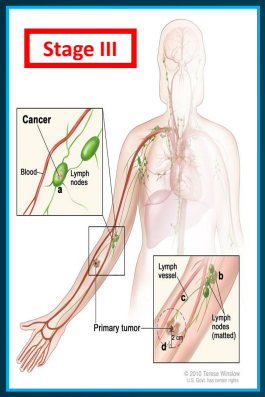
Clinical Staging (cTNM)			
Stage	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b T2a	N0 N0	M0 M0
IIA	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0

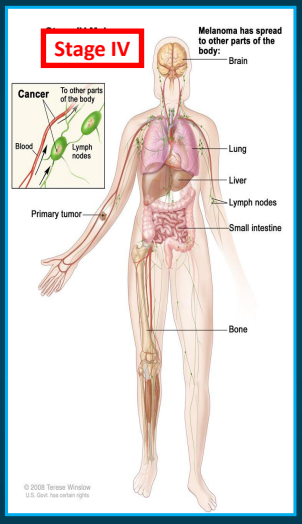
Pathological Staging (pTNM)			
Stage	T	N	M
0	Tis	N0	M0
IA	T1a T1b	N0 N0	M0 M0
IB	T2a	N0	M0
IIA	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0

National Comprehensive Cancer Network (NCCN). Cutaneous melanoma. V2.2021. (Images available at https://visualsonline.cancer.gov/details.cfm?imageid=7277; https://visualsonline.cancer.gov/details.cfm?imageid=7283; https://visualsonline.cancer.gov/details.cfm?imageid=12521; https://visualsonline.cancer.gov/details.cfm?imageid=12528). Accessed 3/15/2021.

13

Stages of Melanoma—III and IV





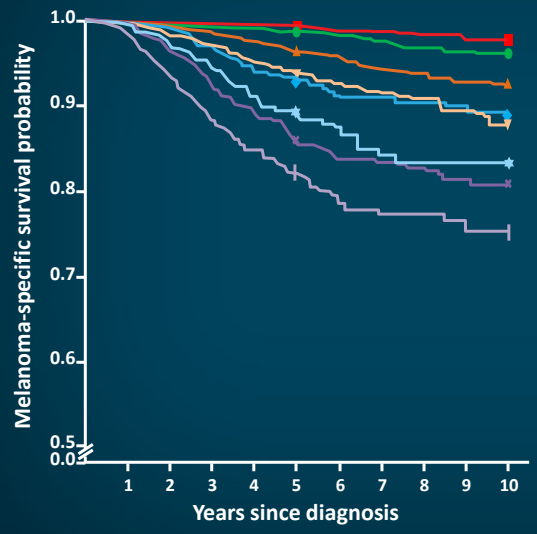
Clinical Staging (cTNM)			
Stage	T	N	M
III	Any T, Tis	≥N1	M0
IV	Any T	Any N	M1

Pathological Staging (pTNM)			
Stage	T	N	M
IIIA	T1a/b, T2a	N1a, N2a	M0
IIIB	T0	N1b, N1c	M0
	T1a/b, T2a	N1b/c, N2b	M0
	T2b, T3a	N1a/b/c, N2a/b	M0
IIIC	T0	N2b/c, N3b/c	M0
	T1a/b, T2a/b, T3a	N2c, N3a/b/c	M0
	T3b, T4a	Any N ≥N1	M0
	T4b	N1a/b/c, N2a/b/c	M0
IIID	T4b	N3a/b/c	M0
IV	Any T, Tis	Any N	M1

NCCN. Cutaneous melanoma. V2.2021. (Image available at https://visualsonline.cancer.gov/details.cfm?imageid=7285). Accessed 3/15/2021.

14

Patient Survival Decreases as Primary Melanoma Stage Increases

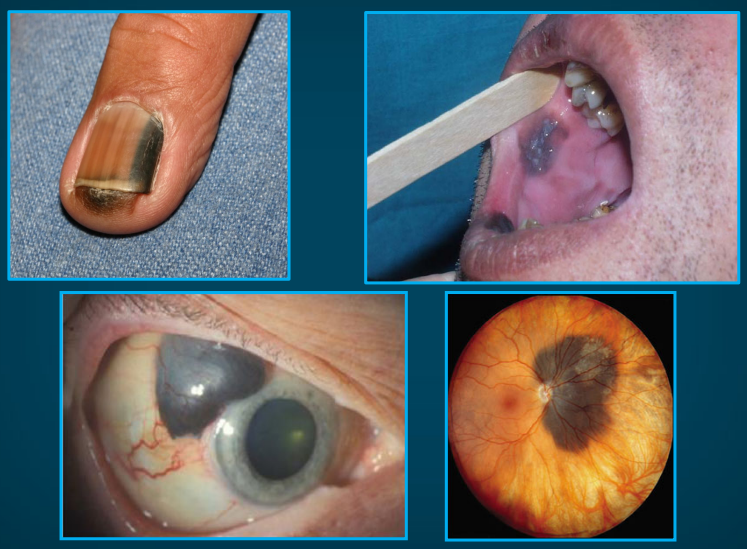


	N	Survival (%)	
		5-year	10-year
T1a	5225	99	98
T1b	2495	99	96
T2a	3254	96	92
T2b	748	93	88
T3a	1590	94	88
T3b	1150	86	81
T4a	538	90	83
T4b	691	82	75

Gershenwald JE, et al. *CA Cancer J Clin*. 2017;67:472-492.

15

Unusual Presentations of Melanoma



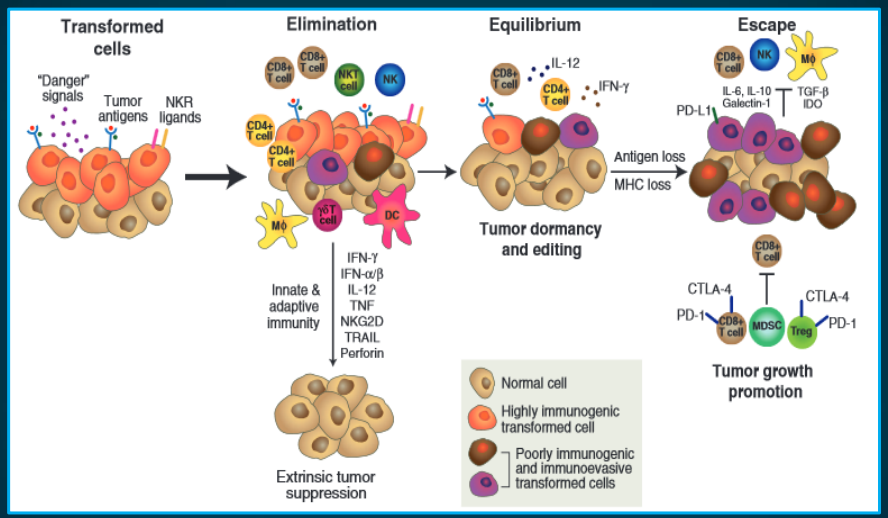
Images courtesy of Dr. Geoffrey Gibney.

16

Mechanisms of Action of Immune Therapy in Advanced Melanoma

17

Avoiding Immune Surveillance

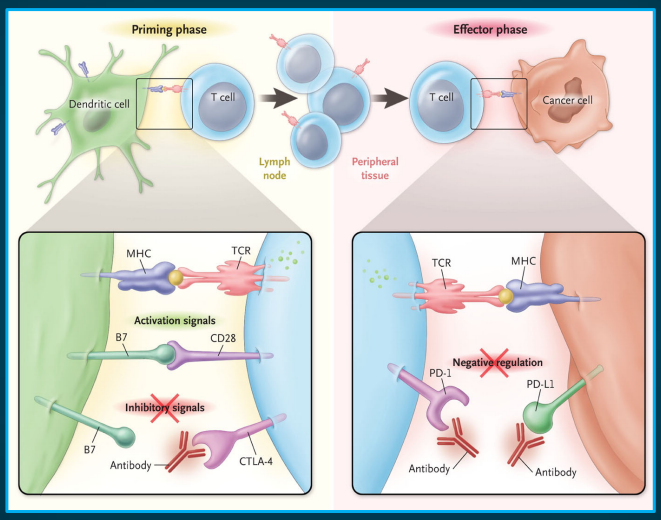


CTLA-4 = cytotoxic T lymphocyte-associated protein 4; MHC = major histocompatibility complex; NK = natural killer; PD-1 = programmed (cell) death 1; PD-L1 = PD ligand 1; TNF = tumor necrosis factor; IFN = interferon; IL = interleukin; MDSC = myeloid-derived suppressor cells; Treg = regulatory T cell.

Modified from Schreiber RD, et al. *Science.* 2011;331:1565-1570.

18

How Does Immune Surveillance Fail?
Checkpoint Blockade: CTLA-4 and PD-1/PD-L1 Inhibitors



TCR = T-cell receptor.

Ribas A. *N Engl J Med*. 2012;366:2517-2519.

19

We will now watch a brief video reviewing immune-suppression mechanisms and the inhibition of immune checkpoints in cancer

20

21

FDA-Approved Immune Checkpoint and Oncolytic Therapies in Melanoma (March 2021)

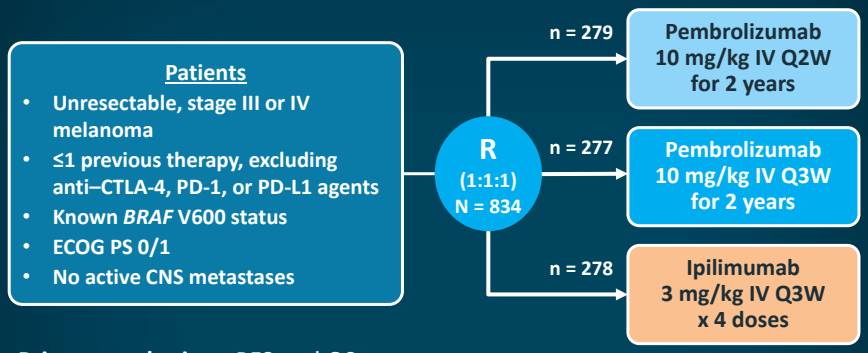
Regimen	Indication	Benefit
Ipilimumab (IPI)[1–3]	• Unresectable advanced melanoma (UAM) • Resected stage III melanoma	• Response rate 11–19% • Risk of death reduced by 28% compared with PBO
Nivolumab[4–6]	• UAM • Resected stage III/IV melanoma	• Response rate 40–44% • Recurrence rate 52% at 4 years; superior to IPI with HR = 0.71
Pembrolizumab[7–9]	• UAM • Resected stage III melanoma	• Response rate 34–42% • RFS = 59% (at 42 mo), superior to PBO HR = 0.59
Nivolumab/IPI[4,10]	UAM	• Response rate 58% • OS = 52% at 5 years
T-VEC[11]	UAM	• Durable response rate 16.3%
Atezolizumab+vemurafenib+cobimetinib[12]	UAM w/*BRAF* mutation	• PFS prolonged by 22% compared with Vem-Cobi

PBO = placebo; HR = hazard ratio; mo = month(s); OS = overall survival; PFS = progression-free survival; RFS = recurrence-free survival.

1. Ipilimumab (Yervoy®) prescribing information (PI), 2020. 2. Eggermont AM, et al. *N Engl J Med.* 2016;375:1845-1855. 3. Hodi FS, et al. *N Engl J Med.* 2010;363:711-723. 4. Nivolumab (Opdivo®) PI, 2021. 5. Weber J, et al. *N Engl J Med.* 2017;377:1824-1835. 6. Robert C, et al. *N Engl J Med.* 2015;372:320-330. 7. Pembrolizumab (Keytruda®) prescribing information (PI) 2021. 8. Long GV, et al. *J Clin Oncol.* 2018;36(suppl): abstract 9503. 9. Eggermont AM, et al. *Ann Oncol.* 2020;31(suppl 4): abstract LBA46. 10. Larkin J. *N Engl J Med.* 2019;381:1535-1546. 11. Andtbacka RH, et al. *J Clin Oncol.* 2015;33:2780-2788. 12. Gutzmer R, et al. *Lancet.* 2020;395:1835-1844.

22

KEYNOTE-006 Study Design (NCT01866319)



- **Primary endpoints:** PFS and OS
- **Secondary endpoints:** ORR, DoR, and safety
- **Stratification factors:** ECOG PS (0 vs 1), line of therapy (first vs second), PD-LI status (positive vs negative)

ECOG = Eastern Cooperative Oncology Group; PS = performance status; CNS = central nervous system; R = randomization; IV = intravenous; Q2W = every 2 weeks; Q3W = every 3 weeks; ORR = objective/overall response rate; DoR = duration of response.

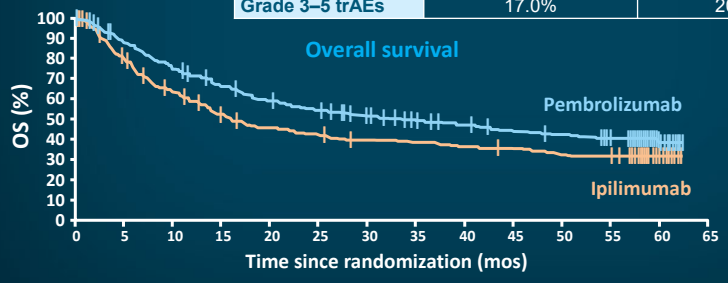
Robert C, et al. *N Engl J Med.* 2015;372:2521-2532.

23

KEYNOTE-006: 5-Year Survival Outcomes

Phase 3 randomized trial of pembrolizumab (n = 556; combined 2 schedules) vs ipilimumab (n = 278) in patients with unresectable stage III or IV melanoma

	Pembrolizumab	Ipilimumab
Median OS (95% CI)	32.7 mos (24.5–41.6)	15.9 mos (13.3–22.0)
	HR = 0.73 (95% CI, 0.61–0.88), *P*= .00049	
5-year OS	38.7%	31.0%
4-year PFS	23.0%	7.3%
Complete response	14.0%	3.0%
Grade 3–5 trAEs	17.0%	20.0%



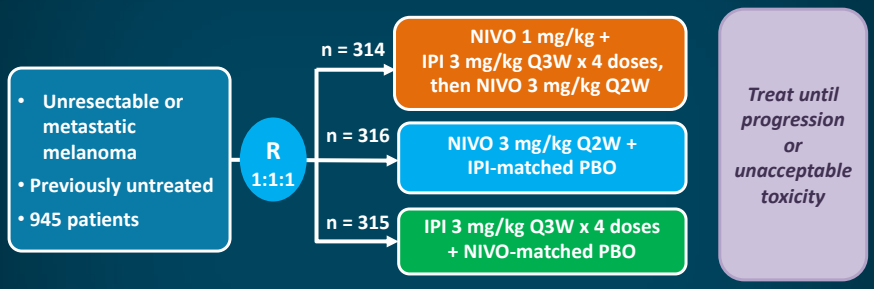
mo(s) = month(s); CI = confidence interval; trAE = treatment-related adverse event.

Robert C, et al. *Lancet Oncol.* 2019;20:1239-1251.

24

CheckMate 067: Study Design

Randomized, double-blind, phase 3 study to compare nivolumab + ipilimumab or nivolumab alone with ipilimumab alone



- **Primary endpoints:** PFS and OS
- **Secondary endpoints:** ORR, descriptive evaluations of OS and PFS and of PD-L1 as predictive biomarker for PFS and OS
- **Stratification factors:** tumor PD-L1 expression, BRAF mutation status, and metastasis stage (AJCC M stage)

AJCC = American Joint Committee on Cancer; NIVO = nivolumab.

Wolchok JD, et al. *N Engl J Med.* 2017;377:1345-1356.

25

CheckMate 067: Overall Response

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Best overall response, n (%)			
Complete response (CR)	61 (19%)	52 (16%)	16 (5%)
Partial response (PR)	122 (39%)	88 (28%)	43 (14%)
Stable disease (SD)	38 (12%)	31 (10%)	69 (22%)
Progressive disease (PD)	74 (24%)	121 (38%)	159 (50%)
Unable to determine	19 (6%)	24 (8%)	28 (9%)
Objective response (CR and PR)			
Patients with response, n (% [95% CI])	183 (58% [53–64])	140 (44% [39–50])	59 (19% [15–24])
OR for comparison with IPI (95% CI), *P*-value	6.46 (4.45–9.38) *P* <.001	3.57 (2.48–5.15) *P* <.001	Reference

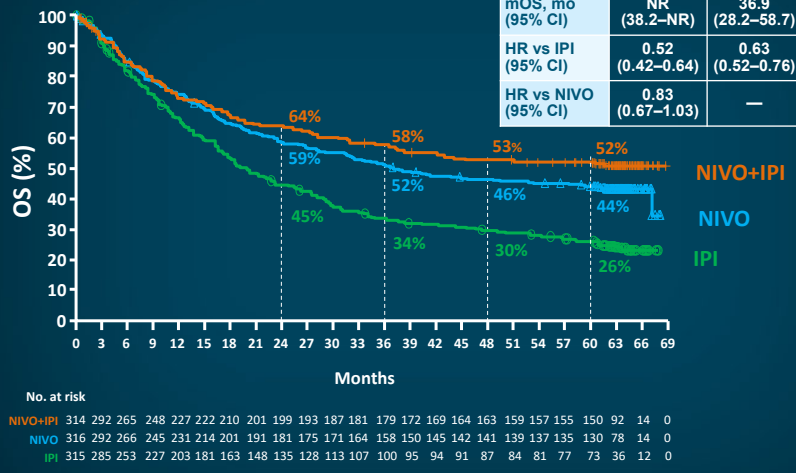
OR = odds ratio.

Wolchok J, et al. *N Engl J Med.* 2017;377:1345-1356.

26

CheckMate 067: OS at 5 Years of Follow-Up

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
mOS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR vs IPI (95% CI)	0.52 (0.42–0.64)	0.63 (0.52–0.76)	—
HR vs NIVO (95% CI)	0.83 (0.67–1.03)	—	—



No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

mOS = median OS; NR = not reached.

Larkin J, et al. *Cancer Res.* 2017;77(13 suppl): abstract CT075. Wolchok JD, et al. *N Engl J Med.* 2017;377:1345–1356. Hodi FS, et al. *Lancet Oncol.* 2018;19:1480-1492. Larkin JM, et al. *N Engl J Med.* 2019;381:1535-1546.

27

CheckMate 067: Safety

	Nivolumab plus ipilimumab group (n=313)			Nivolumab group (n=313)			Ipilimumab group (n=311)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	115 (37%)	151 (48%)	34 (11%)	200 (64%)	54 (17%)	16 (5%)	181 (58%)	74 (24%)	12 (4%)
Diarrhoea	112 (36%)	29 (9%)	1 (<1%)	60 (19%)	9 (3%)	0	87 (28%)	18 (6%)	0
Fatigue	107 (34%)	13 (4%)	0	111 (36%)	3 (1%)	0	86 (28%)	3 (1%)	0
Pruritus	106 (34%)	6 (2%)	0	68 (22%)	1 (<1%)	0	112 (36%)	1 (<1%)	0
Rash	83 (27%)	10 (3%)	0	73 (23%)	1 (<1%)	0	64 (21%)	5 (2%)	0
Nausea	81 (26%)	7 (2%)	0	41 (13%)	0	0	49 (16%)	2 (1%)	0
Pyrexia	58 (19%)	1 (<1%)	1 (<1%)	21 (7%)	0	0	20 (6%)	1 (<1%)	0
Decreased appetite	56 (18%)	4 (1%)	0	35 (11%)	0	0	40 (13%)	1 (<1%)	0
Hypothyroidism	53 (17%)	1 (<1%)	0	32 (10%)	0	0	14 (5%)	0	0
Vomiting	41 (13%)							1 (<1%)	0
Arthralgia	41 (13%)							0	0
Headache	33 (11%)							1 (<1%)	0
Increased aspartate aminotransferase	33 (11%)							2 (1%)	0
Increased alanine aminotransferase	33 (11%)							4 (1%)	1 (<1%)
Dyspnoea	33 (11%)							0	0
Maculopapular rash	32 (10%)							1 (<1%)	0
Hyperthyroidism	32 (10%)	3 (1%)	0	14 (5%)	0 (0%)	0	3 (1%)	0	0
Vitiligo	28 (9%)	0	0	30 (10%)	1 (<1%)	0	16 (5%)	0	0
Hypophysitis	19 (6%)	5 (2%)	0	1 (<1%)	1 (<1%)	0	7 (2%)	5 (2%)	0
Increased amylase	17 (5%)	9 (3%)	0	14 (5%)	7 (2%)	0	11 (4%)	3 (1%)	1 (<1%)
Colitis	14 (5%)	25 (8%)	1 (<1%)	5 (2%)	3 (1%)	0	11 (4%)	23 (7%)	1 (<1%)
Increased lipase	11 (4%)	19 (6%)	15 (5%)	13 (4%)	6 (2%)	10 (3%)	6 (2%)	8 (3%)	4 (1%)
Dehydration	9 (3%)	5 (2%)	0	1 (<1%)	0	0	3 (1%)	2 (1%)	0
Adrenal insufficiency	5 (2%)	5 (2%)	1 (<1%)	2 (1%)	2 (1%)	0	3 (1%)	1 (<1%)	0
Increased transaminases	2 (1%)	9 (3%)	1 (<1%)	1 (<1%)	1 (<1%)	0	3 (1%)	0	0
Hepatotoxicity	2 (1%)	8 (3%)	0	0	1 (<1%)	0	1 (<1%)	0	0
Hepatitis	2 (1%)	5 (2%)	0	0	0	0	0	0	0

Discontinuation due to adverse event:
42% NIVO-IPI
13% NIVO
15% IPI

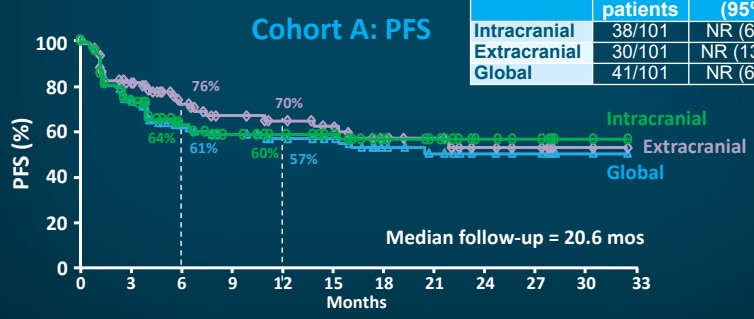
Hodi FS, et al. *Lancet Oncol.* 2018;19:1480-1492. Larkin J, et al. *N Engl J Med.* 2019;381:1535-1546 supplement.

28

NIVO + IPI in Patients with Brain Metastases

- CheckMate 204: Phase 2 trial of NIVO + IPI in 101 patients with metastatic melanoma and at least 1 measurable, nonirradiated brain metastasis (Cohort A)
  - Intracranial clinical benefit rate (CBR) = 58%
- Cohort B included 18 symptomatic patients
  - Intracranial CBR = 22%

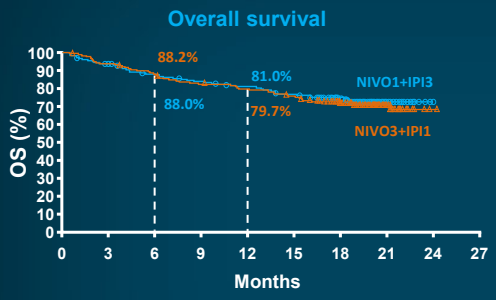
	Events/ patients	Median PFS (95% CI)
Intracranial	38/101	NR (6.5–NR)
Extracranial	30/101	NR (13.9–NR)
Global	41/101	NR (6.5–NR)



Tawbi HA, et al. *N Engl J Med*. 2018;379:722-730. Tawbi HA, et al. *J Clin Oncol*. 2019;37(15 suppl): abstract 9501.

29

CheckMate-511: Evaluation of Less Toxic NIVO + IPI Dosing Regimen



In spite of reversing the doses, there were no clinically meaningful differences between groups for ORR, PFS, or OS

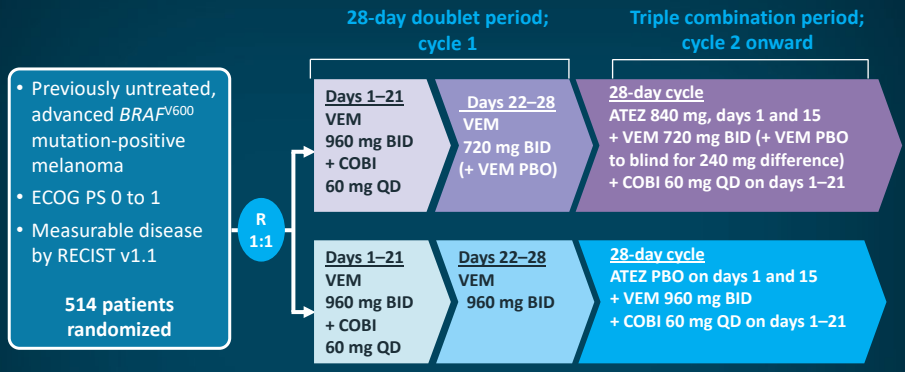
Investigator-Assessed Response		
Response	NIVO3 + IPI1 (n = 180)	NIVO1 + IPI3 (n = 178)
Best overall response, No. (%)		
CR	27 (15.0)	24 (13.5)
PR	55 (30.6)	66 (37.1)
SD	21 (11.7)	21 (11.8)
PD	62 (34.4)	47 (26.4)
Unknown	15 (8.3)	20 (11.2)
ORR (95% CI), %	45.6 (38.1–53.1)	50.6 (43.0–58.1)
P-value	0.35	
Median time to response, mos (range)	2.83 (2.0–17.9)	2.79 (2.3–10.5)
Ongoing responses/ responders, n (%)	63/82 (76.8)	68/90 (75.6)
Median DoR, mos	NR	NR

NIVO1+IPI3 = nivolumab 1 mg/kg + ipilimumab 3 mg/kg; NIVO3+IPI1 = nivolumab 3 mg/kg + ipilimumab 1 mg/kg.

Lebbé C, et al. *J Clin Oncol*. 2019;37:867-875. Lebbé C, et al. ESMO, 2018: abstract 4311 (https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress/Initial-results-from-a-phase-3b-4-study-evaluating-two-dosing-regimens-of-nivolumab-NIVO-in-combination-with-ipilimumab-IPI-in-patients-with-advanced-melanoma-CheckMate-511). Accessed 3/16/2021.

30

IMspire150 Study Design: Front-Line Triplet Therapy



- **Primary endpoint:** Investigator-assessed PFS
- **Key secondary endpoints:** PFS assessed by an IRC, objective response (confirmed by observations at least 4 weeks apart), DoR, and OS
- **Stratification factors:** geographic region and centrally tested LDH level (≤ULN vs >ULN)

VEM = vemurafenib; COBI = cobimetinib; ATEZ = atezolizumab; BID = twice daily; IRC = independent review committee; LDH = lactate dehydrogenase; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; ULN = upper limit of normal.

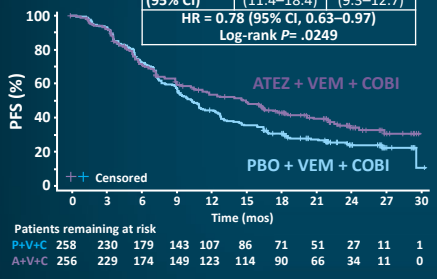
Gutzmer R, et al. *Lancet.* 2020;395:1835-1844. MacArthur GA, et al. American Association for Cancer Research (AACR). 2020: abstract CT012.

31

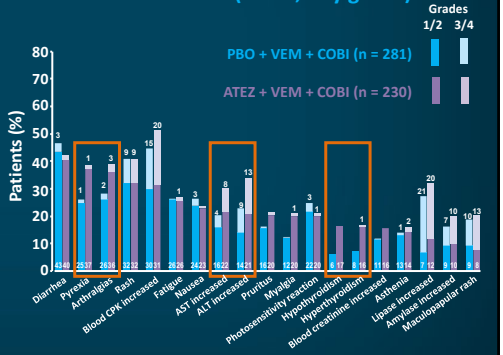
IMSpire150: Atez + Vem + Cobi vs Vem + Cobi in *BRAF*^{V600}-Mutated Melanoma

Primary endpoint: Investigator-Assessed PFS

	ATEZ + VEM + COBI	PBO + VEM + COBI
mPFS, mos (95% CI)	15.1 (11.4–18.4)	10.6 (9.3–12.7)
HR = 0.78 (95% CI, 0.63–0.97) Log-rank *P*= .0249		



Common trAEs (≥15%, any grade)

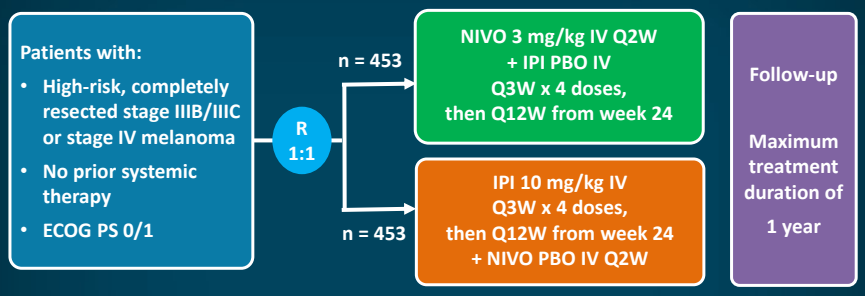


mPFS = median PFS; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase.

Gutzmer R, et al. *Lancet.* 2020;395:1835-1844. McArthur GA, et al. AACR. 2020: abstract CT012.

32

CheckMate 238: Adjuvant Therapy for Resected Stages IIIB/IIIC/IV Melanoma—Study Design



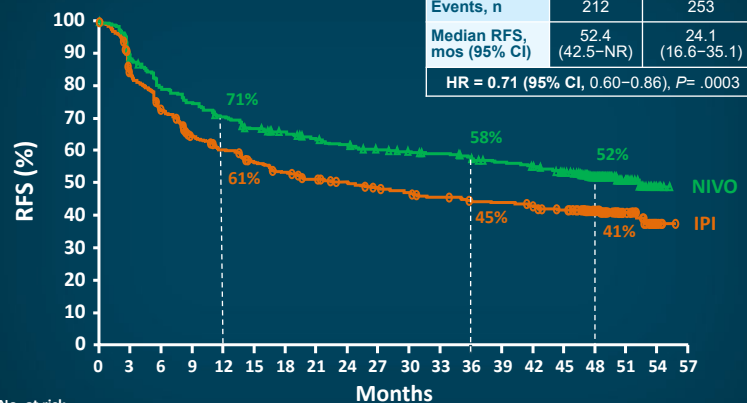
- **Primary endpoint:** RFS
- **Secondary endpoints:** OS, safety, side-effect profiles, RFS according to tumor PD-L1 expression, and health-related quality of life.
- **Stratification factors:** disease stage (IIIB/IIIC vs IV M1a/M1b vs IV M1c) and tumor PD-LI status (negative/intermediate vs positive) based on 5% cutoff
- **Minimum follow-up of 36 months for all patients**

Weber J, et al. *N Engl J Med.* 2017;377:1824-1835. NCT02388906 (CheckMate 238). Weber JS, et al. *Ann Oncol.* 2019;30(suppl 5): abstract 3493.

33

Checkmate-238: 48-month RFS in all patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	212	253
Median RFS, mos (95% CI)	52.4 (42.5–NR)	24.1 (16.6–35.1)
HR = 0.71 (95% CI, 0.60–0.86), *P*= .0003		



No. at risk

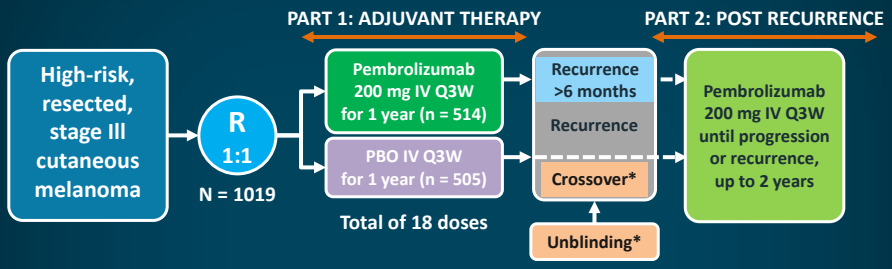
NIVO 3 mg/kg	453	395	354	332	311	293	283	271	262	250	245	240	233	224	218	206	147	37	11	0
IPI 10 mg/kg	453	366	316	273	253	234	220	208	201	191	185	177	171	168	163	154	113	32	10	0

Ascierto PA, et al. *Lancet Oncol.* 2020;21:1465-1477. Weber JS, et al. *Ann Oncol.* 2019;30(suppl 5): abstract 3493.

34

EORTC 1325/KEYNOTE-054: Study Design

Pembrolizumab vs PBO in resected stage IIIA/B/C melanoma



*Unblinding/crossover: anti-PD-1 for all or just as good if only for those at time of recurrence?

- **Primary endpoints:** RFS in overall population and in patients with PD-L1-positive tumors
- **Secondary endpoints:** DMFS, OS, safety, health-related quality of life
- **Stratification factors:** AJCC-7 stage (IIIA [>1 mm metastasis] vs IIIB vs IIIC 1–3 positive lymph nodes vs IIIC >4 positive lymph nodes) and region (17 regions, each with 1–3 countries)

DMFS = distant-metastasis-free survival.

Eggermont AM, et al. *N Engl J Med.* 2018;378:1789-1801. Eggermont AM, et al. *J Clin Oncol.* 2020;38(15 suppl): abstract 10000..

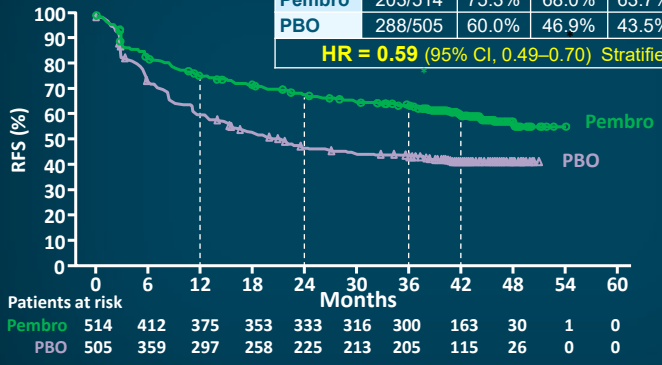
35

Keynote-054 Updated RFS Analysis

- Cut-off date (3-Apr-2020); median duration of follow-up: 3.5 years; 491 RFS events[1]

	Events/n	1 Year	2 Years	3 Years	3.5 Years (95% CI)
Pembro	203/514	75.3%	68.0%	63.7%	59.8% (55.3–64.1)
PBO	288/505	60.0%	46.9%	43.5%	41.4% (37.0–45.8)

HR = 0.59 (95% CI, 0.49–0.70) Stratified logrank *P* <.001



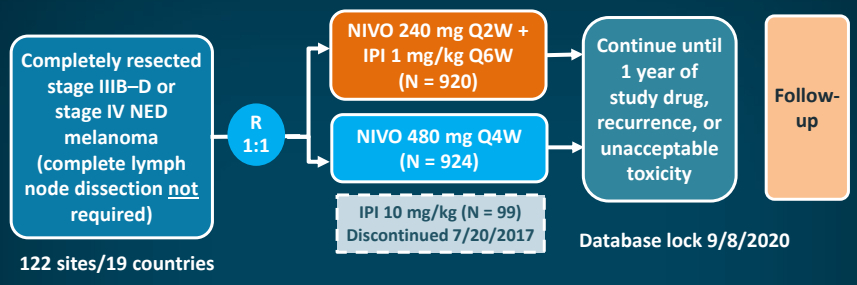
- Occurrence of an irAE was significantly associated with longer RFS in pembrolizumab arm (HR = 0.61, 95% CI 0.39–0.95, *P*= .03)[2]

Pembro = pembrolizumab; irAE = immune-related adverse event.

Eggermont AM, et al. *Ann Oncol.* 2020;31(suppl 4): abstract LBA46. Eggermont AM, et al *JAMA Oncol.* 2020;6:519-527.

36

CheckMate 915 study design



- **Primary endpoints:** RFS (ITT population) and PD-L1 <1%
- **Secondary endpoints:** OS, association between RD-L1 and RFS, outcomes on next-line therapies
- **Stratified** by tumor PD-L1 expression (<1% vs 1% to <5% vs ≥5%) and AJCC-8 stage (IIIB vs IIIC–D vs IV)
- Minimum follow-up of approximately 24 months (median 28 months)

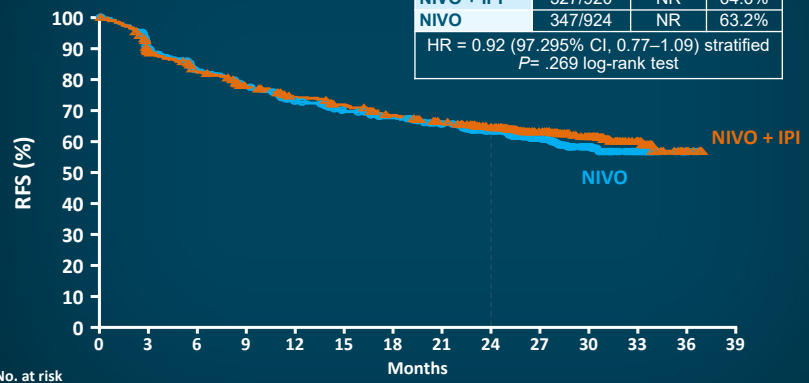
AJCC = American Joint Committee on Cancer; NED = no evidence of disease; ITT = intention to treat.

Long G, et al. *AACR.* 2021: abstract CT004.

37

Checkmate-915 Dual Primary Endpoint: RFS in ITT Population

	Events/N	Median RFS	24-mo RFS
NIVO + IPI	327/920	NR	64.6%
NIVO	347/924	NR	63.2%
HR = 0.92 (97.295% CI, 0.77–1.09) stratified *P*= .269 log-rank test			

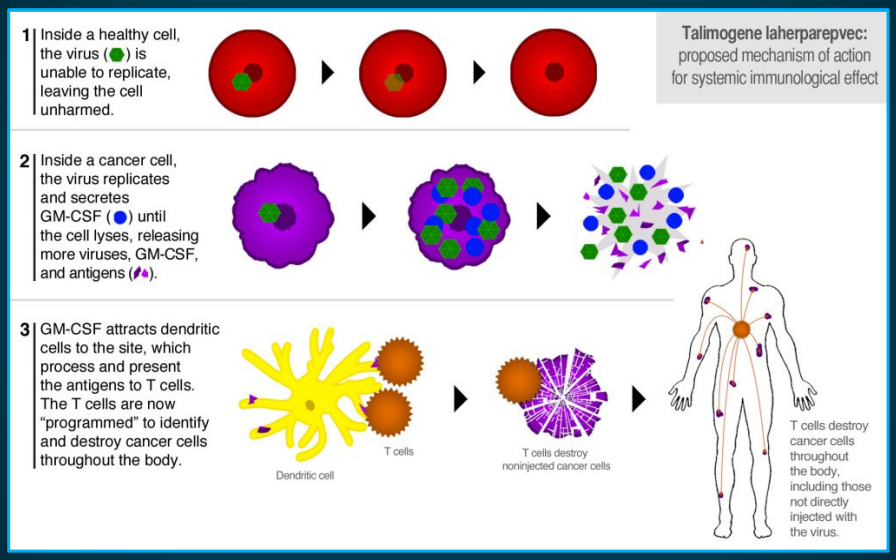


No. at risk													
NIVO + IPI	920	783	720	669	630	605	572	547	505	371	193	74	9	0
NIVO	924	793	721	669	615	578	554	525	476	362	181	69	5	0

Long G, et al. *AACR.* 2021: abstract CT004.

38

Talimogene Laherparepvec (T-VEC)



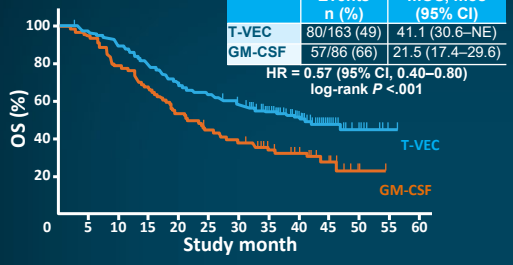
GM-CSF = granulocyte macrophage colony-stimulating factor.

Courtesy of Dr. Jeffrey Weber.

39

Talimogene Laherparepvec (T-VEC) Phase 3 Study

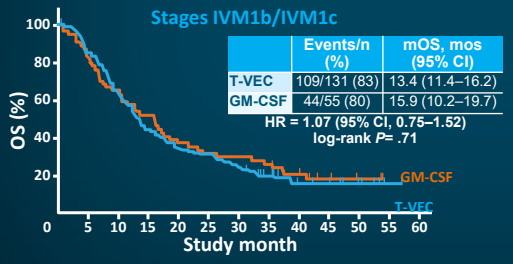
Stages IIIB/IIIC/IVM1a



	Events n (%)	mOS, mos (95% CI)
T-VEC	80/163 (49)	41.1 (30.6–NE)
GM-CSF	57/86 (66)	21.5 (17.4–29.6)

HR = 0.57 (95% CI, 0.40–0.80)
log-rank *P* <.001

Stages IVM1b/IVM1c



	Events/n (%)	mOS, mos (95% CI)
T-VEC	109/131 (83)	13.4 (11.4–16.2)
GM-CSF	44/55 (80)	15.9 (10.2–19.7)

HR = 1.07 (95% CI, 0.75–1.52)
log-rank *P*= .71

NE = not evaluable.

Andtbacka RH, et al. *J Clin Oncol*. 2015;33:2780-2788.

AEs with T-VEC

AEs in 292 patients	Any Grade No. (%)	Grade 3/4 No. (%)
Fatigue	147 (50.3)	5 (1.7)
Chills	142 (48.6)	0 (0)
Pyrexia	125 (42.8)	0 (0)
Nausea	104 (35.6)	1 (0.3)
Influenza-like illness	89 (30.5)	2 (0.7)
Injection-site pain	81 (27.7)	3 (1.0)
Vomiting	62 (21.2)	5 (1.7)
Diarrhea	55 (18.8)	1 (0.3)
Headache	55 (18.8)	2 (0.7)
Myalgia	51 (17.5)	1 (0.3)
Arthralgia	50 (17.1)	2 (0.7)
Pain in extremity	48 (16.4)	4 (1.4)
Pain	47 (16.1)	2 (0.7)
Peripheral edema	35 (12.0)	2 (0.7)
Constipation	34 (11.6)	0 (0)
Cough	31 (10.6)	0 (0)
Decreased appetite	30 (10.3)	0 (0)
Pruritis	28 (9.6)	0 (0)
Cellulitis	17 (5.8)	6 (2.1)
Injection-site erythema	15 (5.1)	0 (0)
Dyspnea	13 (4.5)	3 (1.0)
Injection-site pruritis	5 (1.7)	0 (0)

40

Unique Features of Immunotherapy

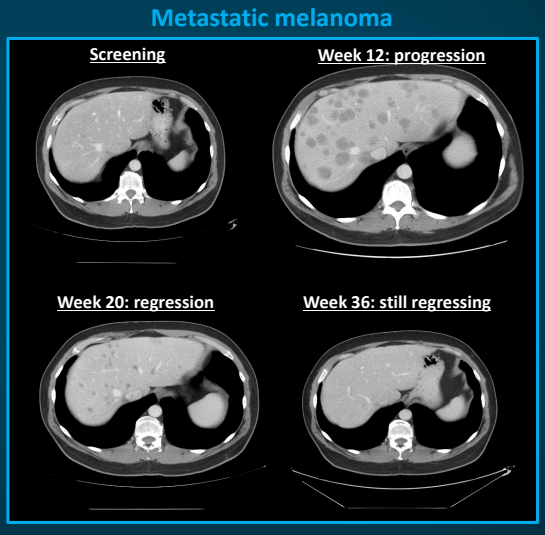
- Tumor-response kinetics
  - Responses can differ from those associated with chemotherapy and targeted therapy, which has led to the development of immune-related response criteria (irRC)
  - There can be slow regression, progression followed by regression, or even new lesions that arise, followed by regression of all existing disease
- Immune-related adverse events (irAEs)
  - Adverse events also differ from those seen with targeted and chemotherapy and usually are due to autoinflammatory side effects or irAEs

Wolchok JD, et al. *Clin Cancer Res*. 2009;15:7412-7420. Weber JS, et al. *J Clin Oncol*. 2015;33:2092-2099.

41

CTLA-4 Blockade: Progression Followed by Regression

Paradoxical kinetics of response to ipilimumab



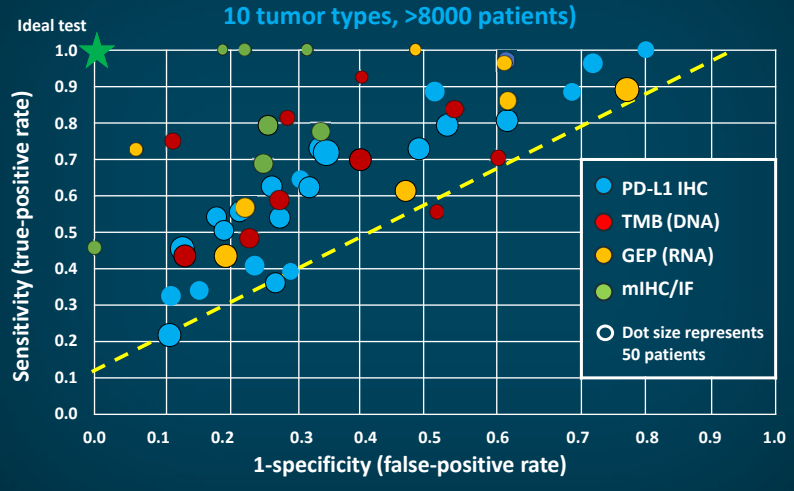
Saenger YM, Wolchok JD. *Cancer Immun*. 2008;8:1.

42

Biomarkers to Guide Immunotherapy in Patients with Melanoma

43

Meta-analysis: Extracted Sensitivity and Specificity for 45 Studies



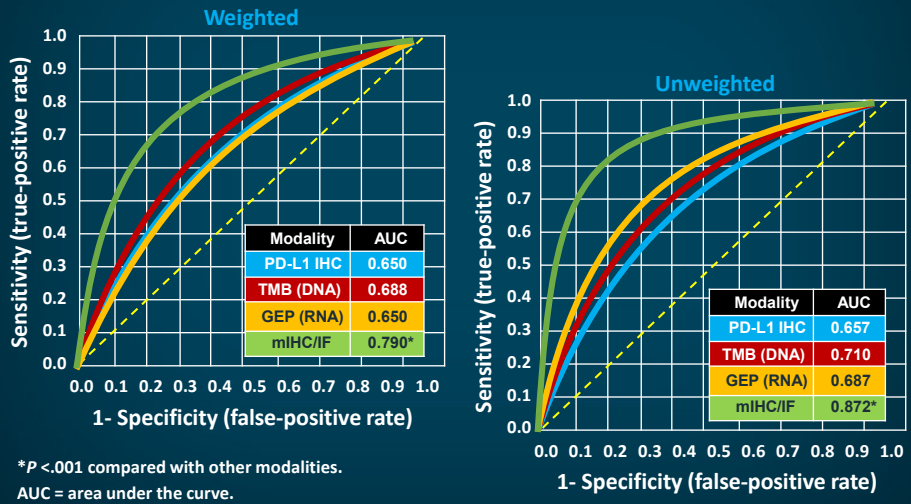
IHC = immunohistochemistry; TMB = tumor mutational burden; GEP = gene expression profiling; DNA = deoxyribonucleic acid; RNA = ribonucleic acid; IF = immunofluorescence; mIHC/IF = multiplex IHC/IF.

Lu S, et al. *JAMA Oncol.* 2019;5:1195-1204.

44

Receiver Operating Characteristics (ROC) Curves Estimate Biomarker Predictive Value

You want it above 0.9!

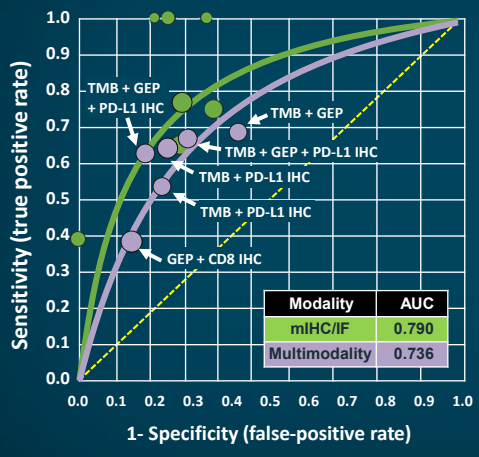


*P <.001 compared with other modalities.
AUC = area under the curve.

Lu S, et al. *JAMA Oncol.* 2019;5:1195-1204.

45

Multimodality: Combining Multiple Biomarkers to Predict Response Still Has a Low ROC!



- The mIHC/IF studies included in this meta-analysis test an average of 2–3 markers
- Emerging technologies claim ability to test 10–50 markers

Lu S, et al. *JAMA Oncol.* 2019;5:1195-1204.

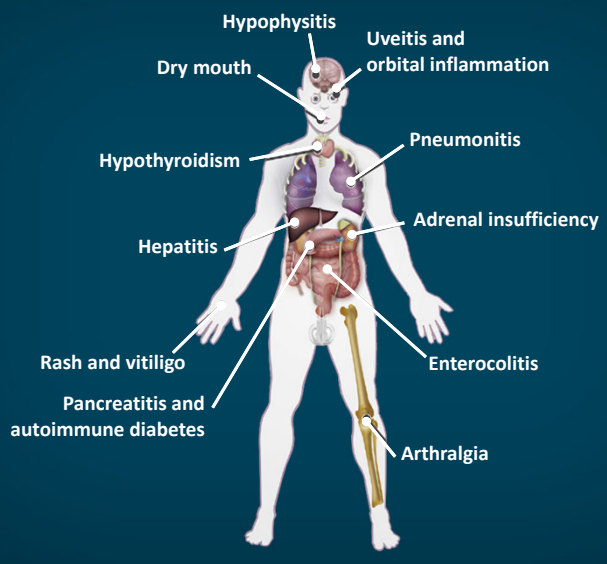
46

Managing Immune-Related Adverse Events (irAEs)

Optimizing Patient Outcomes

47

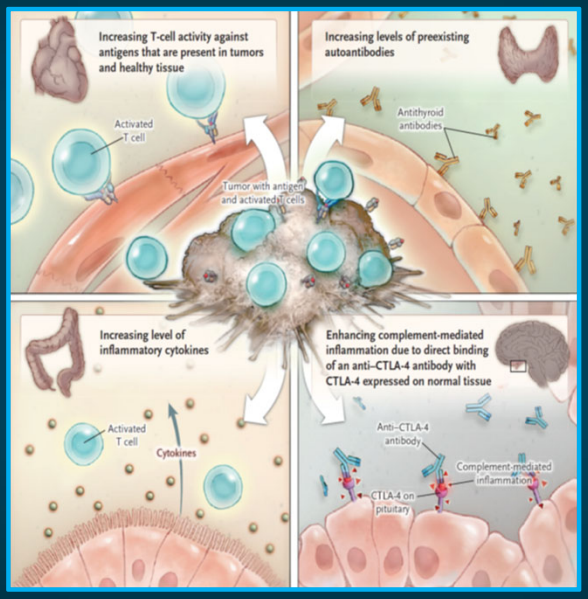
irAEs: Clinical Spectrum



Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.

48

Possible Mechanisms for irAEs



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

49

Immune-Checkpoint Inhibitors: Considerations

- ICIs *block, augment, and amplify* T-cell activity, enhancing tumor recognition and immune-mediated tumor destruction
- Collaterally, this amplification can impact on normal healthy tissue, thereby creating inflammatory "autoimmune-like" effects (ie, an "-itis" or "-opathy")
- Any new symptoms should be considered as possibly being related to ICI treatment
- Rule out other possible etiologies for symptoms
- Toxicity grading should guide management
  - Use CTCAE to be familiar with specific irAE grading
- irAEs typically are mild to moderate and often respond to immunosuppressant therapy
- **Early identification, reporting, and intervention** can impact outcomes of irAEs, adherence to medication scheduling, and quality of life

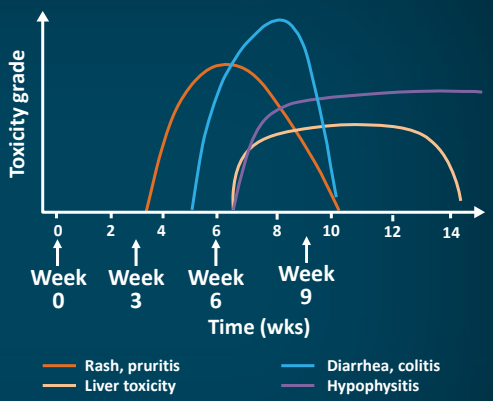
ICI = immune-checkpoint inhibitor; CTCAE = Common Terminology Criteria for Adverse Events.

Champiat S, et al. *Ann Oncol*. 2016;27:559-574. Madden KM, Hoffner B. *Clin J Oncol Nurs*. 2017;21(4 suppl):30-41.

50

Pattern of Onset of irAEs: Kinetics

- Onset is typically 6–12 weeks after start of therapy
  - Can occur at any time point, ie, days, weeks, or months after starting therapy
  - May wax and wane for up to 2 years
- May impact 1 or more organ systems
- Intensity can range from mild to severe
- Dosing, frequency, and the combination of drugs/therapies can influence toxicity



wk = week(s).

Modified from Weber JS, et al. *J Clin Oncol.* 2012;30:2691-2697.

51

Incidence of Most Common irAEs

	Ipilimumab	PD-1 Inhibitors	Ipilimumab + Nivolumab
Any body system	27%	16%	56%
Colitis	12%	3%	15%
Skin	3%	2%	6%
Endocrinopathy **Hypopituitarism** **Hypothyroidism**	 3% <1%	 <1% 1%	 Not reported 1%
Liver	2%	3%	20%

Most common cause of death from irAEs is colonic perforation

NR = not reported.

Corrie P. *Prescriber.* 2016;27(7):23-28.

52

We will now watch a brief video exploring irAEs

53

54

Management of irAEs
Based on CTCAE Severity Grade

Severity CTCAE Grade	Patient Care Setting	Steroids	Other Immunosuppressive Drugs	Immunotherapy and Subsequent Approach
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Not recommended up front Topical steroids or systemic steroids oral 0.5–1 mg/kg/d for persistent grade 2	Not recommended	Suspend* temporarily
3	Hospitalization	Systemic steroids oral or IV 1–2 mg/kg/d for ≥3 d then taper over 4–6 wk	Consider for patients with lack of improvement after 2–3 d of steroid course Organ specialist advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization; consider intensive care unit	Systemic steroids IV methylprednisolone 1–2 mg/kg/d and switch to oral prednisone for ≥3 d with taper over 4–6 wk	Consider for patients with lack of improvement after 2–3 d of steroid course Organ specialist advised	Discontinue permanently

***Outside of skin or endocrine disorders, where immunotherapy can be maintained.**

d = day(s).

Michot JM, et al. *Eur J Cancer*. 2016;54:139-148. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768.

55

Additional Management Considerations

	Symptom management
Steroid Refractory	***No response or worsening symptoms on steroids*** • Additional immunosuppressant treatment may be needed – Infliximab 5 mg/kg—may repeat Q4W (GI/colitis) – Mycophenolate mofetil 1 g twice daily (hepatic) – Cyclosporine or intravenous immunoglobulin (IVIG) (neurologic) – Methotrexate • **Do not discontinue steroids**; continue and taper when symptoms respond • Collaborate with specialists
Supportive Measures	• High-dose or prolonged use >4 wk ± additional suppressant therapy – Consider prophylaxis with antimicrobial/antifungal/antiviral to prevent opportunistic infections (PCP, shingles, candida) – Collaborate with specialists for long-term/permanent organ dysfunction

GI = gastrointestinal; PCP = pneumocystis pneumonia.

Weber JS, et al. *J Clin Oncol*. 2015;33:2092-2099. Gangadhar TC, Vonderheide RH. *Nat Rev Clin Oncol*. 2014;11:91-99. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. Madden KM, Hoffner B. *Clin J Oncol Nurs*. 2017;21(4 suppl):30-41.

56

irAEs: System-Based Management and Long-Term Considerations

Type of irAE	Management
Endocrine	• Hypothyroidism: treat with thyroid hormone, usually long-term • Hyperthyroidism: in symptomatic patients, treat with beta blockers (propranolol or atenolol) • Hypophysitis: hormone replacement therapy; consider steroids for headaches or other neurological problems • Adrenal Insufficiency precautions
GI	• Colitis: diet adjustment, systemic administration of steroids, treatment with infliximab if steroid refractory • Wean steroids over ~4 weeks
Dermatologic	• Topical antihistamines/steroids, OTC medications, behavior modification (ie, heat) • Initiate corticosteroids (oral or IV depending on severity) to be weaned over several weeks
Neurologic	• Consider high-dose steroids (1–2 mg/kg or equivalent) • Plasmapheresis or IVIG may be required for myasthenia gravis or GBS • Neuroleptics for neuropathy management as needed
Musculoskeletal/ Arthritis	• Consider workup for rheumatoid arthritis—needs referral • If negative, continue supportive care • Consider 0.5 mg–1.0 mg/kg prednisone or equivalent

GBS = Guillain-Barré syndrome; OTC = over the counter.

Slide courtesy of Dr. Jeffrey Weber.

57

irAEs: System-Based Management and Long-Term Considerations (continued)

IrAE	Management
Hepatic	• Consider high-dose (HD) steroids (1–2 mg/kg or equivalent) • Monitor LFTs—return to grade 1 • R/O viral hepatitis • Mycophenolate if steroid refractory; avoid infliximab
Pulmonary	• Consider HD steroids (1–2 mg/kg or equivalent) • Supportive O_2 • CXR, CT, rule out COVID-19
Renal	• Consider HD steroids (1–2 mg/kg or equivalent) • Monitor output, UA, BUN/creatinine
Ocular	• Consider HD steroids (1–2 mg/kg or equivalent) • Ophthalmologic steroid drops, ophthalmologic referral
Cardiac	• Consider HD steroids (1–2 mg/kg or equivalent) • Cardiology consult, Echo, EKG, troponin, CPK levels

LFT = liver-function test; EKG = electrocardiogram; R/O = rule out; CXR = chest x-ray; CT = computed tomography (scan); UA = urinalysis; BUN = blood urea nitrogen; Echo = echocardiogram.

Slide courtesy of Dr. Jeffrey Weber.

58

Relevant Resources

Guidelines for Management of Immunotherapy Toxicities	
ESMO 2017	www.esmo.org/Guidelines/Supportive-and-Palliative-Care/ Management-of-Toxicities-from-Immunotherapy
SITC 2017	Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. See Puzanov I, et al, *J Immunother Cancer*. 2017;5:95.
ASCO 2018	Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. See Brahmer JR, et al, *J Clin Oncol*. 2018;36:1714-1768.
NCCN 2021	NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities, version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

ESMO = European Society for Medical Oncology; SITC = Society for Immunotherapy of Cancer; ASCO = American Society of Clinical Oncology.

59

COVID-19 and Cancer

60

Treatment of Advanced Melanoma in Era of COVID-19

Key Questions and Considerations

1. Are patients with melanoma at increased risk for infection and/or complications from COVID-19?
2. Does immunotherapy increase the risk for more severe disease or death from COVID-19?
3. What are the current recommendations for use of immunotherapy in patients with melanoma to mitigate risks related to COVID-19?
4. What are some additional considerations for COVID-19 risk mitigation in the care of melanoma patients?
   - Risk-mitigation measures
   - Role of telemedicine
   - Impact on practice patterns

61

Cancer and COVID-19 Risk

Literature review including >10 studies focused on COVID-19 in cancer patients[1]

Key findings/conclusions

- Data suggest an **increased risk of acquiring SARS-CoV-2 infection** compared with general population[1]
  - Individuals with cancer comprised a larger proportion of COVID-19 patients in both the United States (6%)[2] and China (1%)[3]
- Compared with COVID-19 patients without cancer, those with cancer appeared to have an **increased risk for severe outcomes, including intubation and death,** after adjusting for other COVID-19 risk factors[1]
- Overall case fatality rates among cancer patients range from 11% to 28%, with disproportionately higher rates in some subgroups[1]:
  - Lung cancer (18% to 55%)
  - Hematologic malignancy (33% to 41%)

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1. Fung M, Babik JM. *Clin Infect Dis*. 2020; Jun 27:Epub ahead of print. 2. Miyashita H, et al. *Ann Oncol*. 2020;31:1088-1089. 3. Liang W, et al. *Lancet Oncol.* 2020;21:335-337.

62

Theoretical Concerns About ICI Use During COVID-19 Outbreak

Effects on cellular immunity or immune-related neutropenia may impair immune response to virus[1]

- Hematologic irAEs are uncommon
- Limited data on viral infections or reactivations as a complication to ICIs
  - However, few cases of infections secondary to irAE treatment have been reported

Possible negative interference of ICI in pathogenesis of COVID-19[2,3]

- Synergistic immune hyperactivation (ie, treatment-induced cytokine-release syndrome plus infection-related cytokine storm)

Potential overlap between coronavirus-related interstitial pneumonia and pulmonary toxicity from anti-PD-1/PD-L1 agents[2,3]

1. Kattan J, et al. *Immunotherapy.* 2020;12:351-354. 2. Bersanelli M. *Immunotherapy*. 2020;12:269-273. 3. Rossi E, et al. *J Immunother Cancer*. 2020;8:e000952.

63

Risk of COVID-Related Mortality in Larger Cohorts of Patients Receiving Cancer Therapy

800 patients in prospective observational UK Coronavirus Cancer Monitoring Project, who were diagnosed 3/18 to 4/26/2020[1]

- After adjusting for age, gender, and comorbidities, chemotherapy in past 4 weeks had no significant effect on mortality from COVID-19 disease, compared with cancer patients who had not received recent chemotherapy
- No significant effect on mortality for patients with cancer receiving immunotherapy (6%), hormonal therapy (8%), targeted therapy (9%), radiotherapy (10%) within 4 weeks of COVID-19 diagnosis

Observational study of 890 patients at 19 centers in UK, Italy, Spain, and Germany, who were recruited 2/26 to 4/1 (censored 5/11/2020)[2]

- Active treatment with chemotherapy (23.1%), targeted therapy (10.4%), and immunotherapy (6.3%) at time of COVID-19 diagnosis did not worsen mortality

1. Lee LY, et al. *Lancet.* 2020;395:1919-1926. 2. Pinato DJ, et al. *Cancer Discov.* 2020;10:1465-1474.

64

Guidance Regarding ICI Treatment During COVID-19

ASCO

- Consider less frequent dosing intervals
- Where possible, COVID-19 testing prior to therapy with these agents is reasonable
- Special precautions/considerations
  - Some agents are associated with a risk of inflammatory reactions and complications (eg, pneumonitis)
  - Immunosuppression for serious irAEs may not be advisable

"The potential harms and benefits of therapy should be carefully considered for each patient"

NCCN

- In all stages/settings, consider lowest-frequency dosing schedule of available regimens
- For stage IV disease, single-agent anti-PD-1 is recommended over combination ipilimumab/ nivolumab due to:
  - More substantial inflammation/possible exacerbation of COVID-19
  - Need for steroids/other immunosuppressants that may adversely affect SARS-CoV-2–infected individuals
  - Increased resource utilization for visits related to toxicities/monitoring

"Decisions…should be individualized, with preference for agents with the lowest toxicity profile"

ASCO (www.asco.org/asco-coronavirus-resources/care-individuals-cancer-during-covid-19/cancer-treatment-supportive-care). NCCN (www.nccn.org/covid-19/pdf/Melanoma.pdf). Accessed 3/3/2021.

65

ASCO Guidance Regarding Initiating/Resuming Anticancer Therapy After COVID-19 Infection

After "symptoms of COVID-19 have resolved and there is some certainty the virus is no longer present (eg, a negative SARS-Cov-2 test), unless the cancer is rapidly progressing and the risk:benefit assessment favors proceeding with cancer treatment"

"…once transmission-based precautions are no longer necessary would be reasonable"

- Recommended strategy for determining duration of transmission-based precautions depends on whether patient is considered immunocompromised
- Conditions causing a high degree of immunocompromise:
  - Receipt of chemotherapy for cancer
  - Untreated HIV infection with CD4 T lymphocyte count <200/mm^3
  - Combined primary immunodeficiency disorder
  - Receipt of the equivalent of prednisone >20 mg/day for more than 14 days

HIV = human immunodeficiency virus.

ASCO (www.asco.org/asco-coronavirus-resources/care-individuals-cancer-during-covid-19/cancer-treatment-supportive-care. Centers for Disease Control and Prevention (CDC) (www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html). Accessed 3/3/2021.

66

ASCO Guidance Regarding COVID-19 Vaccines in Cancer Patients*

- The Pfizer and Moderna vaccines were shown to be safe and effective for the general population and there was no evidence that they would not be safe for most cancer patients, although it should be noted that patients receiving immunosuppressive and cytotoxic treatments were excluded from participation in the vaccine trials to date so there is little to no data on the safety and efficacy of the Pfizer and Moderna vaccines in cancer patients.
- At this time, patients with cancer may be offered vaccination against COVID-19 as long as components of that vaccine are not contraindicated.

*Statement issued prior to authorization of the Johnson & Johnson vaccine on 2/27/2021.

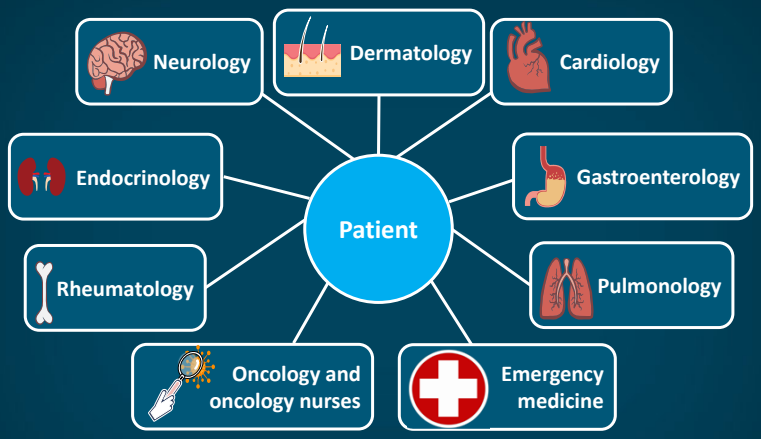
ASCO. COVID-19 vaccine and patients with cancer (www.asco.org/asco-coronavirusresources/covid-19-patient-care-information/covid-19-vaccine-patients-cancer). Accessed 3/3/2021

67

Multidisciplinary Approaches to irAEs

68

Multidisciplinary Approach to irAEs



- Focus on safety
- Ask 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

69

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.

70

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

- Recognition and identification of irAEs
- Early intervention
- Prevention of inappropriate discharges and ED revisits
- Prevention/minimizing of potentially life-threatening complications

ED = emergency department.

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

71

Shared Decision-Making (SDM)

- Provides a **patient-centered approach** to decision-making when multiple options may be medically reasonable (including no intervention)
- Utilizes **decision aids (DAs)** that present organized, evidence-based, and unbiased information to *assist with in communication* 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.

72

5 Essential Steps of SDM: SHARE Approach

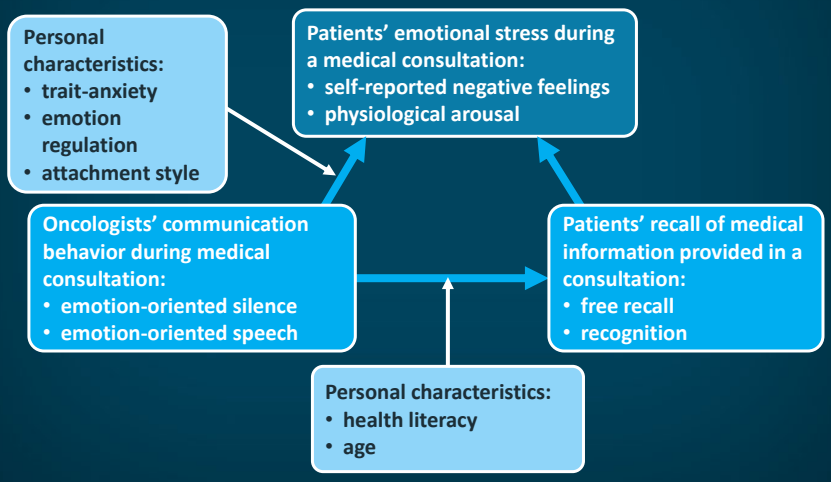
It's all about communication!

AHRQ. Share approach factsheet (www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf). Accessed 3/18/2021.

73

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.

74

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.

75

Case Studies

76

Case Scenario 1

- A 70-year-old male with metastatic melanoma to liver, lungs, and skin received 3 doses of ipilimumab and nivolumab and tolerated the therapy well except for a mild rash that was felt to be grade 1
- After cycle 2, he noticed regression of several of the skin lesions, and his baseline-high LDH normalized
- A week after cycle 3, he experienced abdominal cramps and developed diarrhea 1–2 X daily (grade 1) 2 days later
- The patient had no other complaints except poor appetite

77

Case Scenario 1 (continued)

- The diarrhea persisted at grade 1–2 over the next 2–3 days, so he was brought in for evaluation
- At the clinic visit, he reported intermittent nausea and vomiting; more upper abdominal cramping occurring for 4–5 days; moderately severe, transient, intermittent low-grade fever to 100.5° F; and fatigue
- Lab results showed mild hypokalemia, normal BUN/creatinine, normal LFTs, but previously normal albumin was now 3.2 g/dL
- A blood culture was drawn, but there was no evidence of infection on exam; CXR was obtained, which was unremarkable, as was a KUB film

KUB = kidney, ureter, and bladder.

78

Case Scenario 1
What Would You Do Next?

A. Give oral methylprednisolone (Medrol® dosepak) and send home for follow-up by phone the next day

B. Send home; administer loperamide HCl (Imodium®) and anti-nausea medications and observe to see if diarrhea increases to grade 3

C. Start prednisone 60 mg PO daily for a week and taper over a week

D. Admit for CT of abdomen/pelvis with contrast and IV hydration, and start methylprednisolone 2 mg/kg IV, followed by taper over 30 days within 1–2 days after symptoms resolve

PO = by mouth (orally).

79

Case Scenario 1
What Would You Do Next?

A. Give oral methylprednisolone (Medrol® dosepack) and send home for follow-up by phone the next day

B. Send home; administer loperamide HCl (Imodium®) and anti-nausea medications and observe to see if diarrhea increases to grade 3

C. Start prednisone 60 mg PO daily for a week and taper over a week

D. Admit for CT of abdomen/pelvis with contrast and IV hydration, and start methylprednisolone 2 mg/kg IV, followed by taper over 30 days within 1– days after symptoms resolve

PO = by mouth (orally); CT = computed tomography (scan).

80

Case Scenario 2

- A 55-year-old woman presents with metastatic melanoma from an unknown primary, including multiple 1–2 cm lung metastases and two small asymptomatic vertebral lesions
- Results from an MRI of her brain show a small 0.5 cm lesion in the right frontal lobe with minimal surrounding vasogenic edema
- Mutation analysis of tumor demonstrates an *NRAS* mutation, *BRAF* wild-type
- She has a distant history of Crohn's disease but has not been on steroids for 6 months; she has had no flares in years and no diarrhea in 5 years

MRI = magnetic resonance imaging.

81

Case Scenario 2 (continued)

- The referring physician sent her tissue for assessment of tumor PD-L1 expression using a new commercial assay that found positive expression in >10% of the tumor cells
- Labs were essentially within normal limits, with a normal LDH
- The patient is started on pembrolizumab single-agent therapy after SRS is given to the brain metastasis
- At week 12, there is a partial response, and the patient continues therapy
- At week 18, her grade 2 diarrhea is managed with loperamide HCl (Imodium®) and sulfasalazine, resulting in her diarrhea averaging 1–2 x daily

SRS = stereotactic radiosurgery.

82

Case Scenario 2

Which of the Following Would You Now Offer as Treatment?

A. Carboplatin + paclitaxel

B. Continue pembrolizumab

C. Stop pembrolizumab and start nivolumab

D. Switch to ipilimumab + nivolumab

E. Trametinib in combination with an anti-PD-1 agent

F. Encorafenib and binimetinib

83

Case Scenario 2

Which of the Following Would You Now Offer as Treatment?

A. Carboplatin + paclitaxel

B. Continue pembrolizumab

C. Stop pembrolizumab and start nivolumab

D. Switch to ipilimumab + nivolumab

E. Trametinib in combination with an anti-PD-1 agent

F. Encorafenib and binimetinib

84

Key Takeaways

- Immunotherapies can produce durable responses in patients with advanced melanoma
- Long-term survival is now around 50% in patients with advanced melanoma who are treated with combination immunotherapy
- Antitumor immune responses can be unconventional and may be delayed
- Adverse events are often highly manageable, especially if reported and addressed at the onset
- Grading symptoms → guides management

85

Immuno-oncology in Advanced Melanoma

Project ECHO®

Med Learning Group
New York

86

Electronic Evaluation Form

- Before we move to Q&A, I want to remind you to fill out your evaluation form electronically by following the directions on the following slide.
- Once you complete the evaluation form, your certificate of credit will be provided as a PDF that you can save for your records.
- You will also have the opportunity to download a PDF of the program slides.
- Even if you do not need credit, we appreciate you completing the evaluation form.

87

IC-ONC Immunotherapy Collaborative of Oncology Networked Communities

Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence and Management During the **COVID-19 Pandemic:**
IMMUNO-ONCOLOGY IN ADVANCED MELANOMA

Receive your Certificate of Credit

Let us know how you liked the program

Please follow instructions below to obtain your certificate

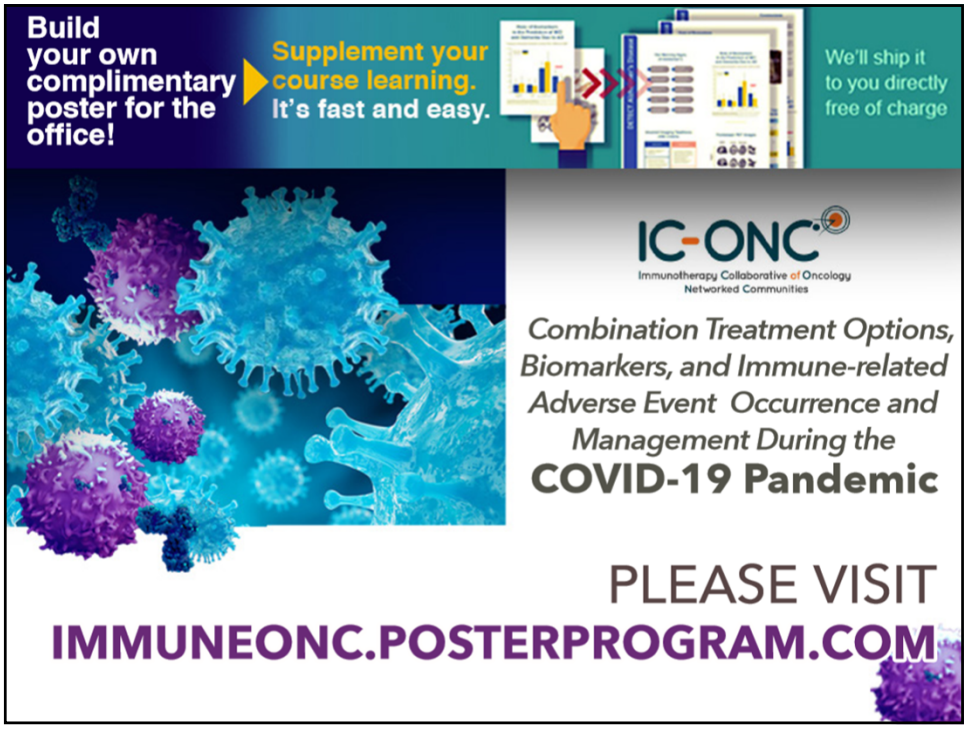
Step 1: Go to **https://gl13melanomapost.questionpro.com/**

Step 2: Complete contact information

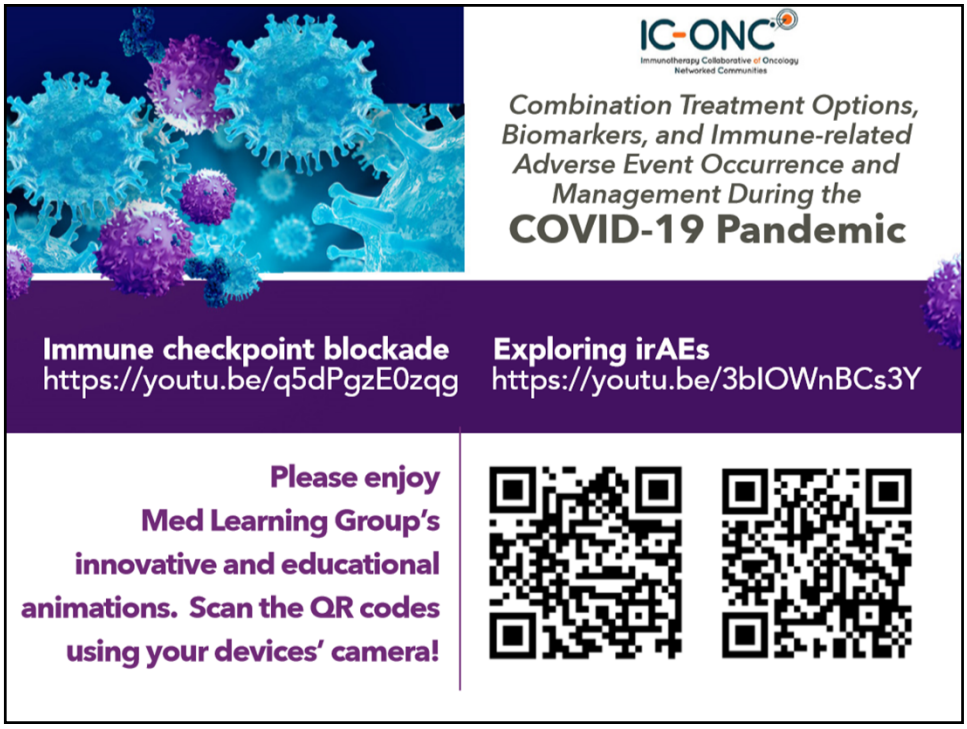
Step 3: Complete your post-survey and evaluation

Step 4: Print your certificate and download the program book

88


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
IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities
Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence and Management During the
COVID-19 Pandemic
PLEASE VISIT
IMMUNEONC.POSTERPROGRAM.COM

89


IC-ONC
Immunotherapy Collaborative of Oncology Networked Communities
Combination Treatment Options, Biomarkers, and Immune-related Adverse Event Occurrence and Management During the
COVID-19 Pandemic
Immune checkpoint blockade
https://youtu.be/q5dPgzE0zqg
Exploring irAEs
https://youtu.be/3bIOWnBCs3Y
Please enjoy Med Learning Group's innovative and educational animations. Scan the QR codes using your devices' camera!

90

Thank you!

Questions and Answers

91