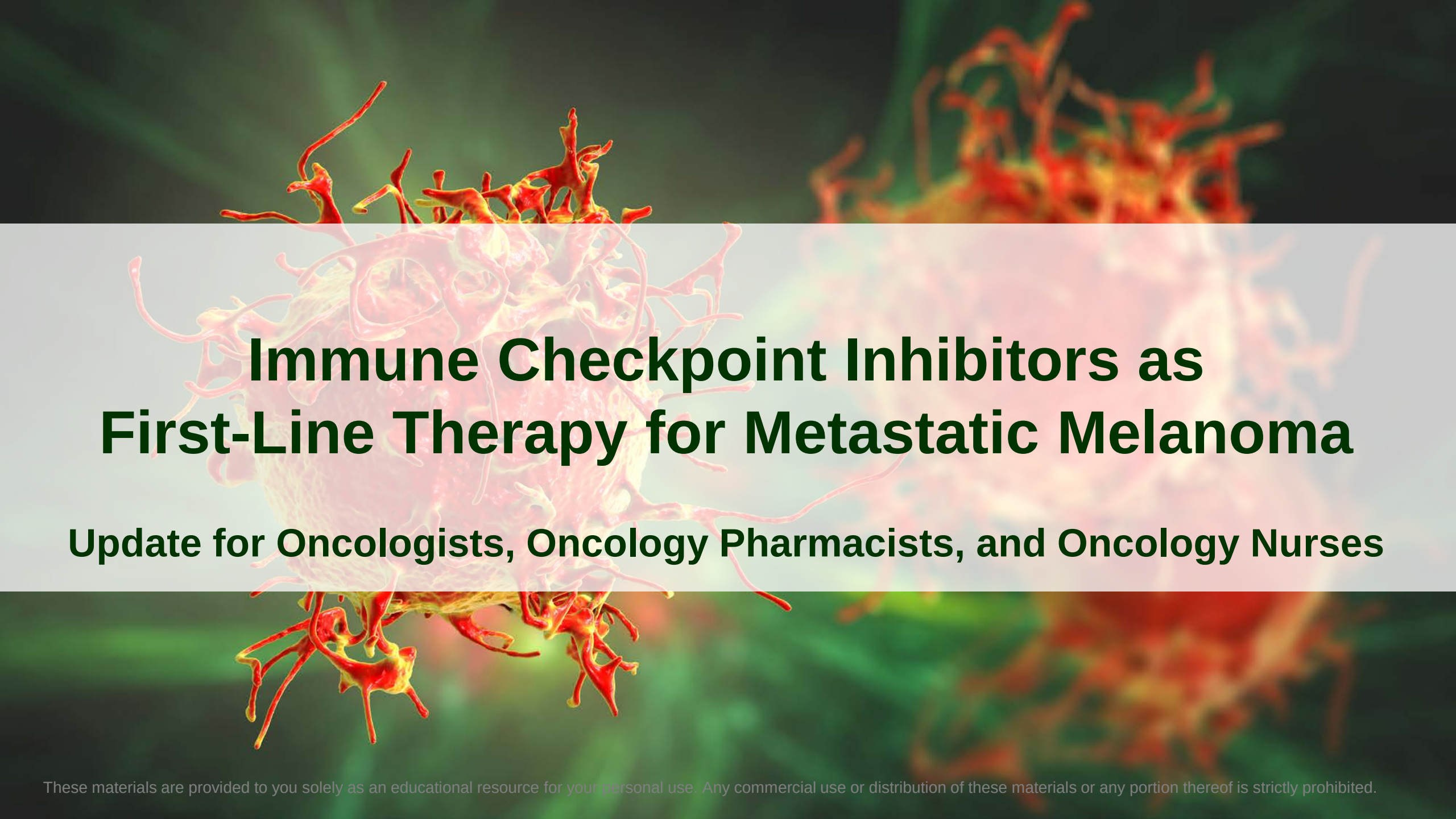
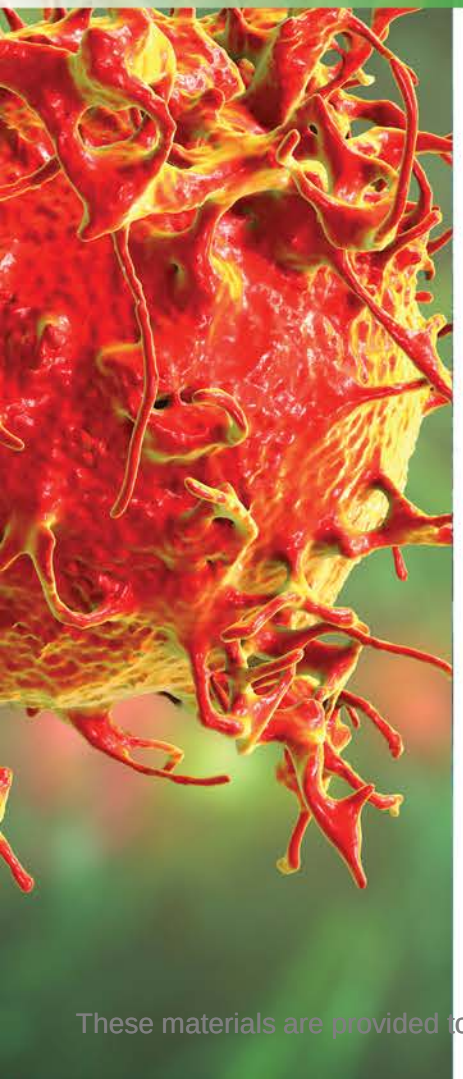


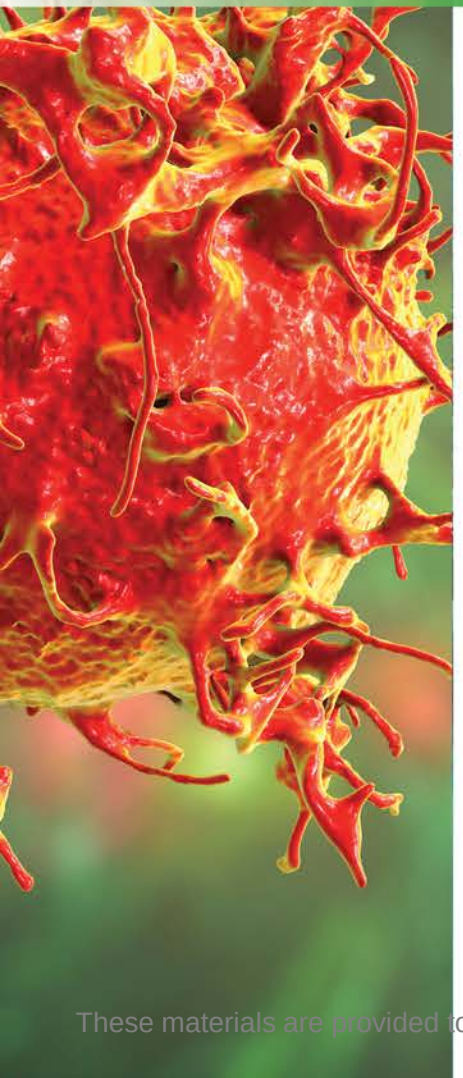
Immune Checkpoint Inhibitors as First-Line Therapy for Metastatic Melanoma

Update for Oncologists, Oncology Pharmacists, and Oncology Nurses



This educational activity is jointly accredited for physicians, nurses, and pharmacists and is supported by an independent educational grant from Bristol Myers Squibb.

Faculty

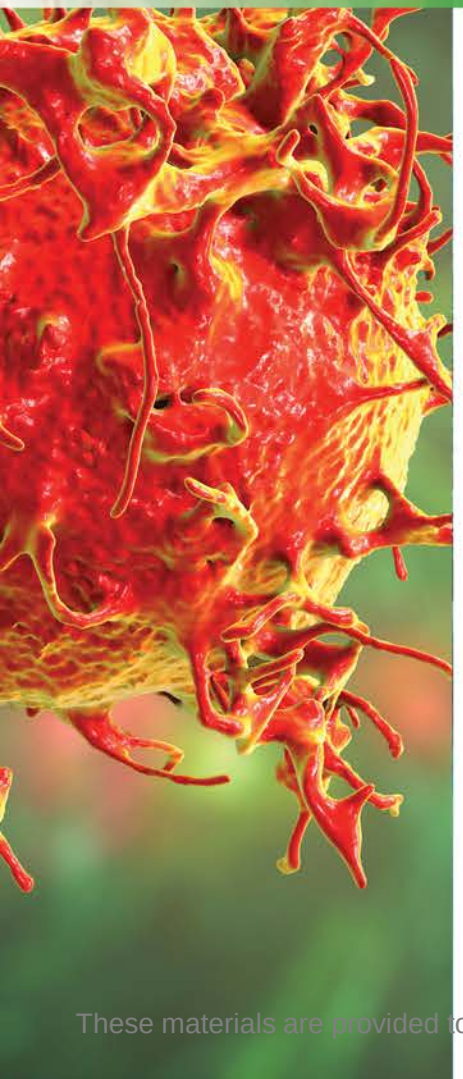


Jaime E. Anderson, PharmD, BCOP, CMQ

Manager, Clinical Pharmacy Services
Clinical Pharmacy Specialist
Melanoma Medical Oncology
Division of Pharmacy
University of Texas MD Anderson Cancer Center
Houston, TX

Dr. Anderson currently serves as manager of clinical pharmacy services and a clinical pharmacy specialist with Melanoma Medical Oncology at the University of Texas MD Anderson Cancer Center in Houston. She received her PharmD from the University of Colorado at Denver and Health Sciences Center School of Pharmacy, completed her Pharmacy Practice Residency (PGY1) at the Cleveland Clinic, and Oncology Pharmacy Practice Residency (PGY2) at MD Anderson. Dr. Anderson is board certified in Oncology Pharmacy and holds a Certificate in Medical Quality (CMQ) from the American Board of Medical Quality.

Faculty

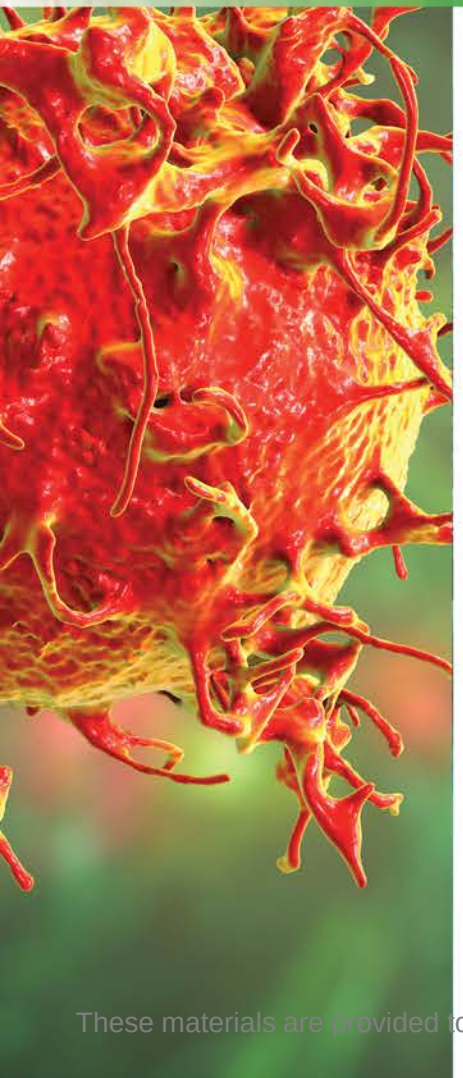


Yana G. Najjar, MD

Assistant Professor of Medicine
Director, Clinical and Translational Research Center
Physician-scientist—Melanoma
Hematology-Oncology, Department of Medicine
UPMC Hillman Cancer Center
Pittsburgh, PA

Dr. Najjar, assistant professor of medicine at the University of Pittsburgh School of Medicine, is a medical oncologist specializing in the treatment of melanoma. Board-certified in internal medicine and medical oncology, she received her MD from the American University of Beirut, completed a post-doctoral fellowship at the NCI, internal medicine residency at the Cleveland Clinic, and hematology/oncology fellowship at UPMC, where she is on the faculty. Dr. Najjar's translational research lab is focused on translational endpoints of novel-novel combinations for the treatment of advanced melanoma. Her research is funded by the Department of Defense, the Melanoma Research Alliance, and the NIH.

Faculty

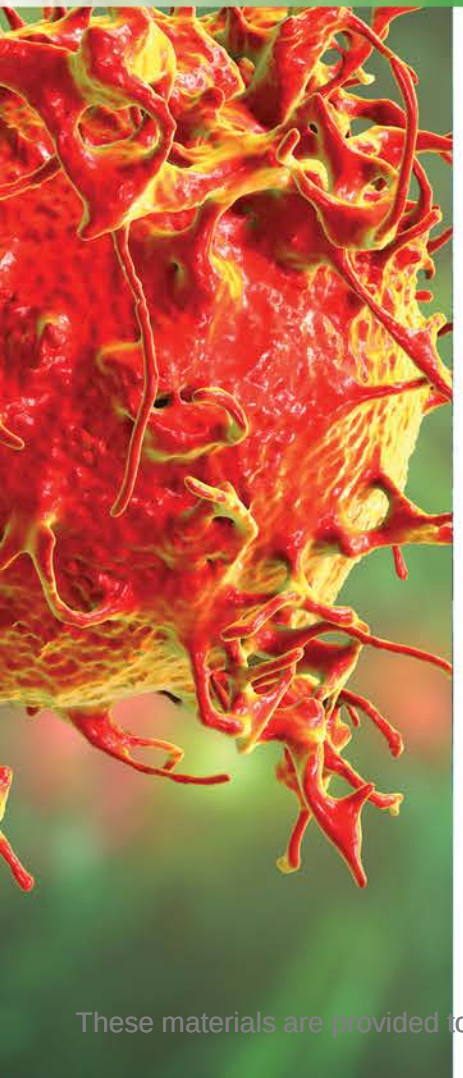


Kathleen M. Madden, RN, MSN, FNP-BC, AOCNP, APHN-BC

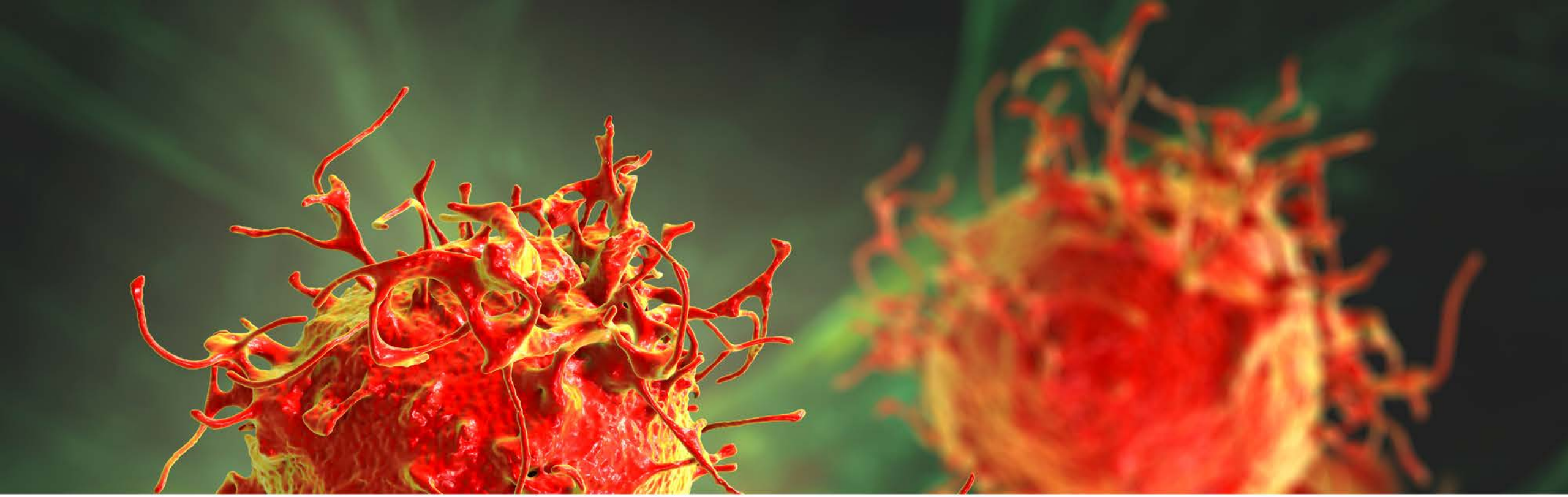
Family Nurse Practitioner, Melanoma/Sarcoma Medical Oncology Group
APN Manager, Melanoma/Cutaneous Oncology & Phase 1 Research
New York University (NYU) Langone Perlmutter Cancer Center
New York, NY

Ms. Madden is a family nurse practitioner in the Melanoma & Cutaneous Medical Oncology Group of the Laura and Isaac Perlmutter Clinical Cancer Center at NYU Langone Medical Center in New York City. Kathy's experience during the past 2 decades at NYU has included working primarily in adult medicine and oncology with a focus on skin cancers with melanoma. She also serves as a sub-investigator for all melanoma and cutaneous research protocols and select phase 1 protocols at the Clinical Cancer Center. Kathy is passionate about integrative healing arts and holds board certifications in Advanced Practice in Oncology and Holistic Nursing.

Learning Objectives

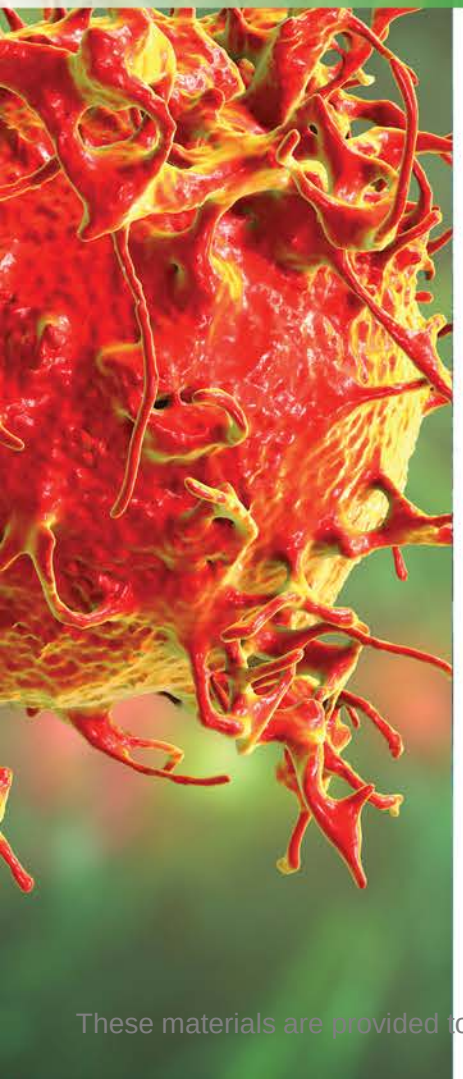


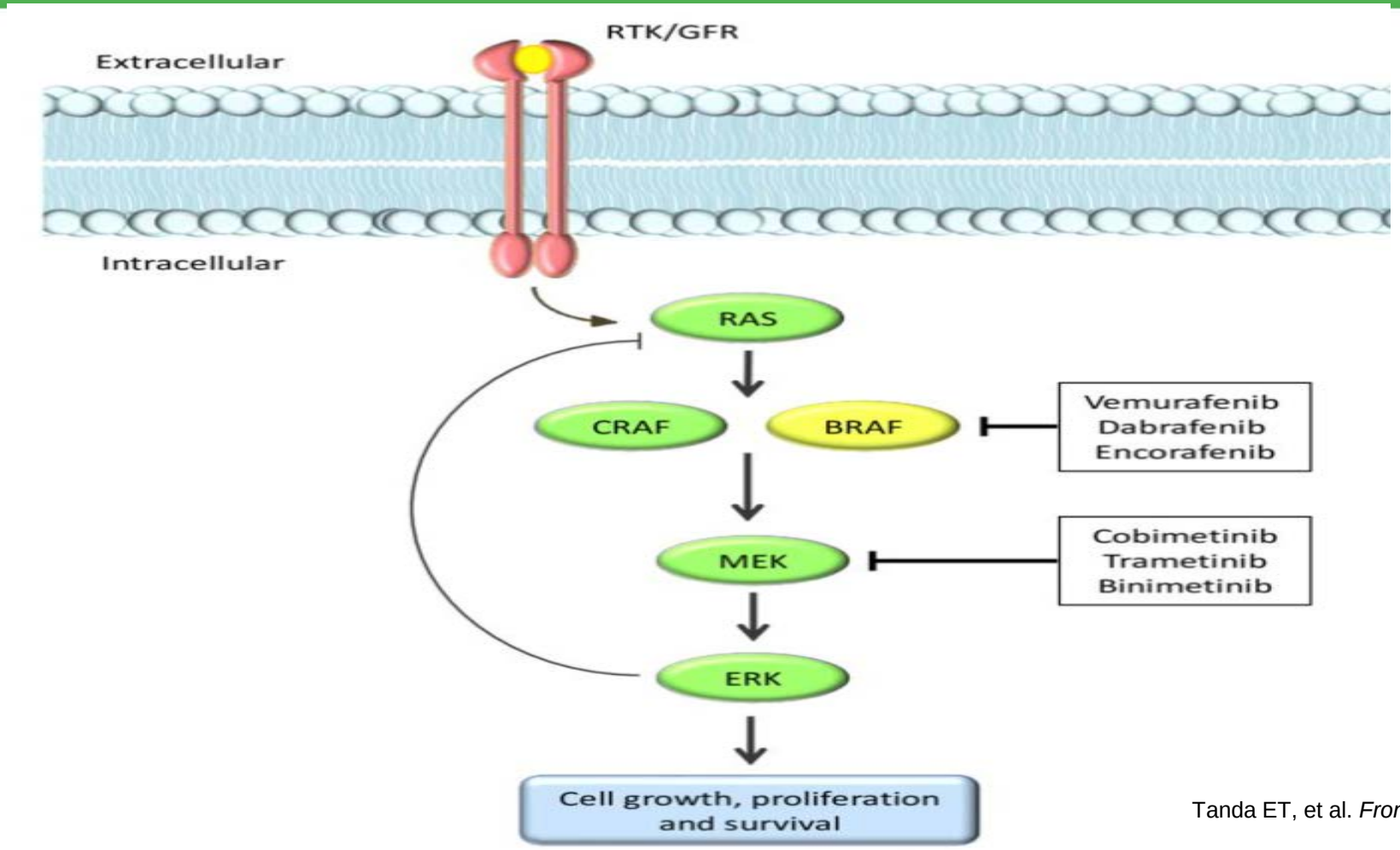
- **Identify** immunotherapy agents and regimens approved and optimal for first-line treatment of metastatic melanoma
- **Indicate** factors that impact selection of first-line agents and regimens
- **Explain** the basis of nonresponse to immunotherapy agents and regimens in use for metastatic melanoma and rational strategies to overcome this nonresponse
- **Formulate** approaches for identifying and mitigating toxicities associated with immunotherapy to optimize treatment outcomes and patient safety



Immune Checkpoints and Therapeutic Targets

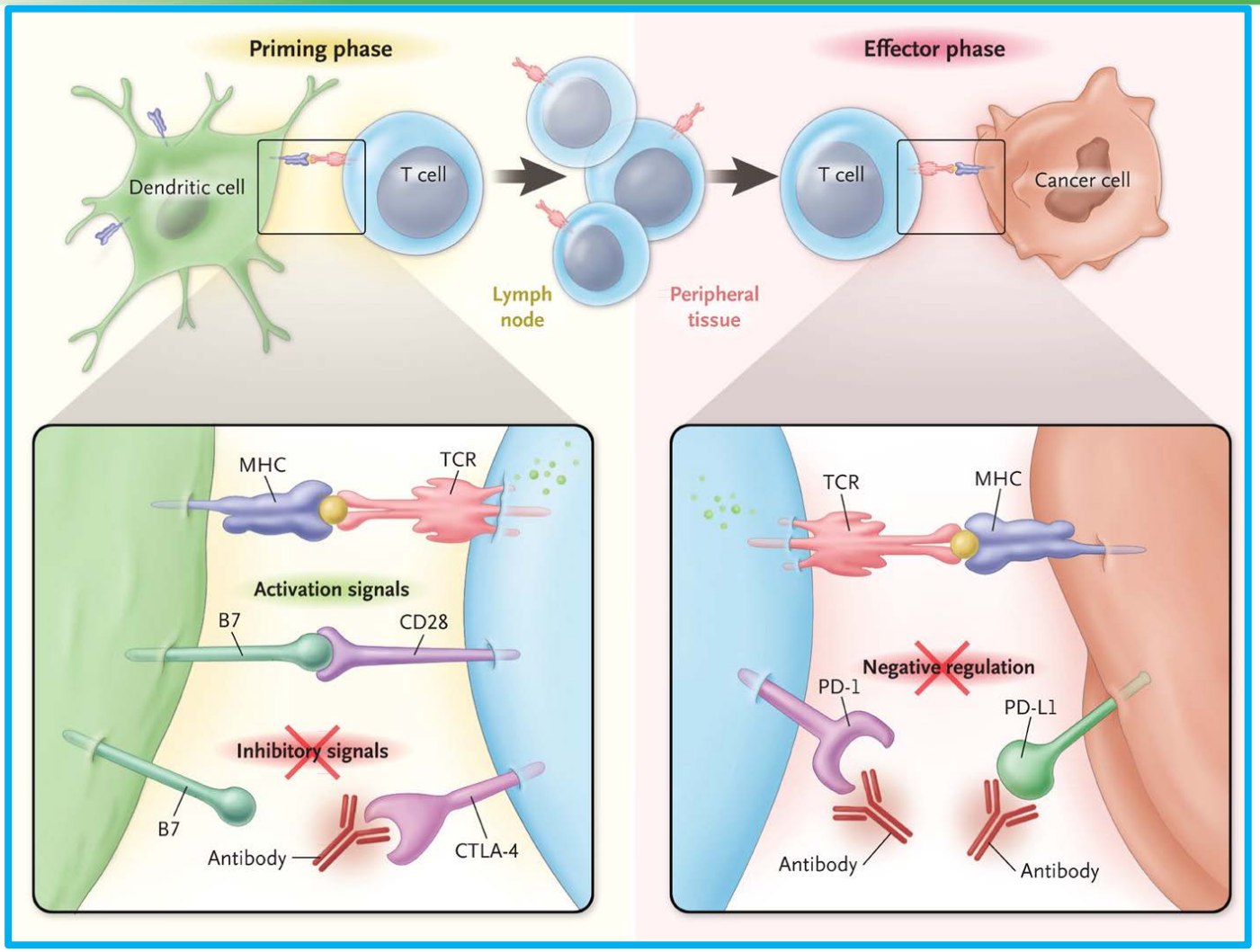
Common Targetable Molecular/Immunologic Alterations in Metastatic Melanoma

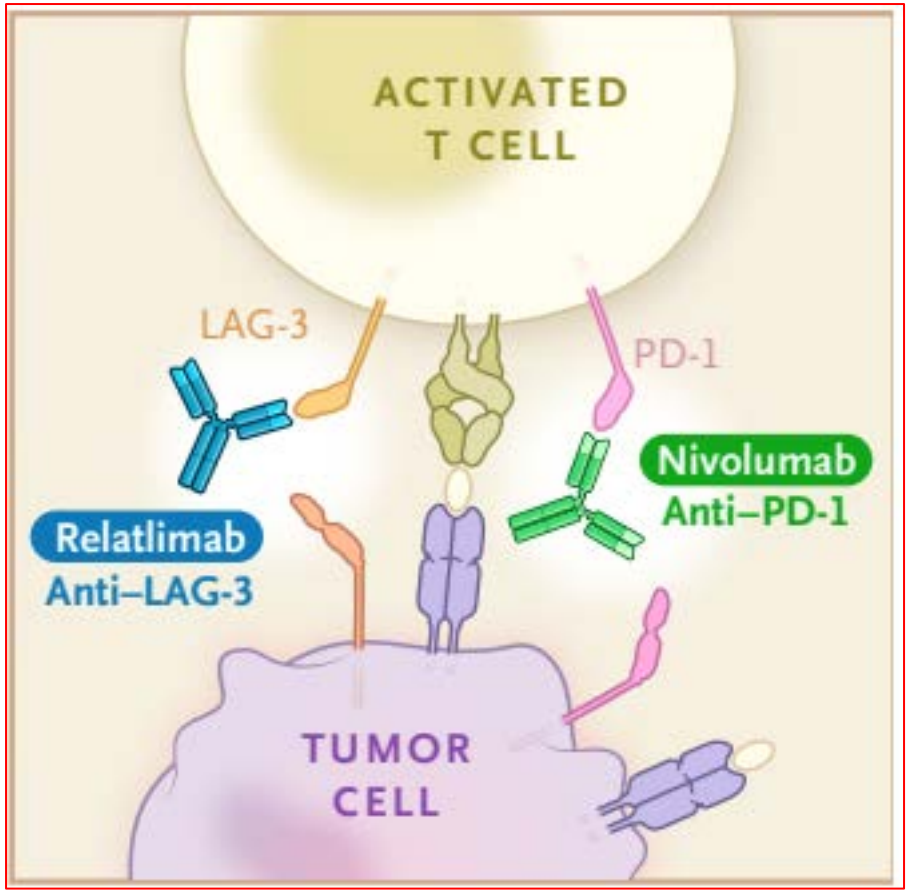




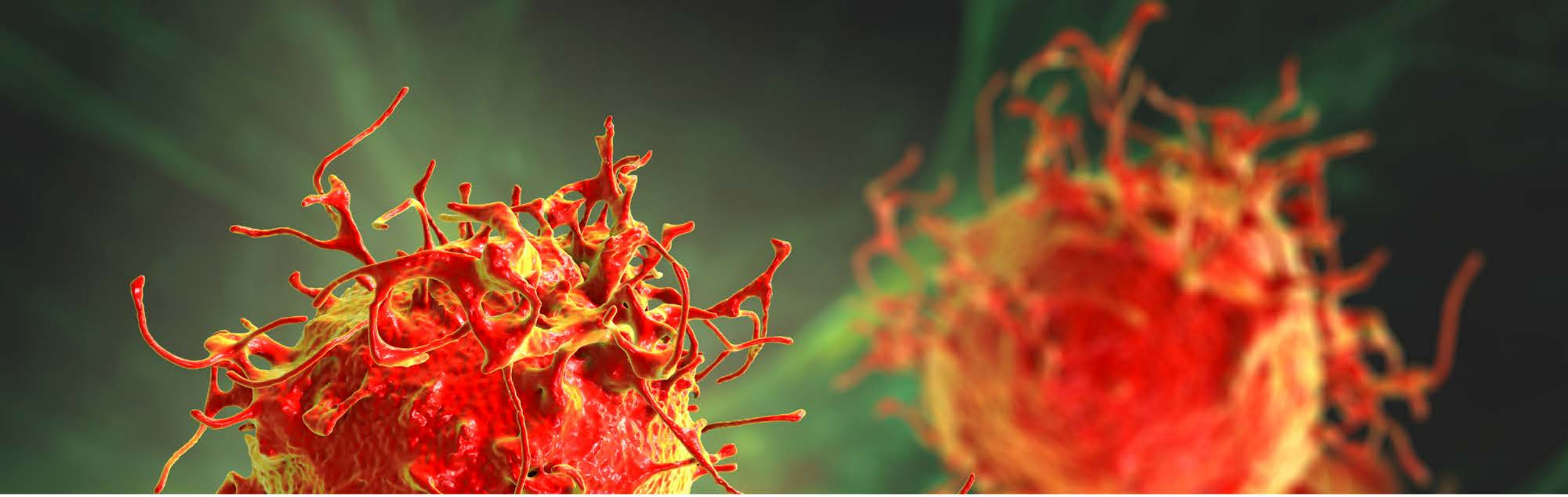
Tanda ET, et al. *Front Mol Biosci*. 2020;7:154.

Inhibitory Receptors With Clinical Targets





Ribas A. *N Engl J Med*. 2012;366(26):2517.
Tawbi HA, et al. *N Engl J Med.* 2022;386(1):24.



Immunotherapy Options for First-Line Treatment

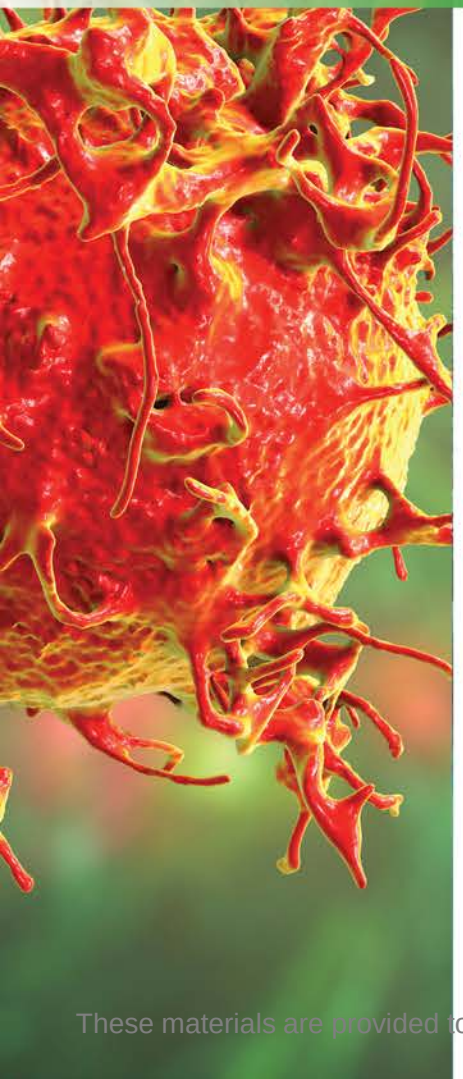
Immune Checkpoint Inhibitors (ICIs)

- Realm of immuno-oncology (IO) agents still evolving
- FDA-approved ICIs for unresectable or metastatic melanoma

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor	
Ipilimumab	3 mg/kg IV over 30 minutes every 21 days x 4 doses
Programmed cell death-1 (PD-1) inhibitors	
Nivolumab	480 mg IV over 30 minutes every 28 days 240 mg IV over 30 minutes every 14 days
Pembrolizumab	200 mg IV over 30 minutes every 21 days 400 mg IV over 30 minutes every 42 days
Programmed cell death-1 ligand (PD-L1) inhibitors	
Atezolizumab (in combination with vemurafenib + cobimetinib)	840 mg IV every 14 days, or 1200 mg IV every 21 days, or 1680 mg IV every 28 days—infused over 30-60 minutes
Lymphocyte-activation gene 3 (LAG-3) inhibitor	
Relatlimab (combo product with nivolumab)	Nivolumab 480 mg/relatlimab 160 mg IV over 30 minutes every 28 days

IBM Micromedex DRUGDEX (electronic version). IBM Watson Health. Accessed September 18, 2022. https://www.micromedexsolutions.com

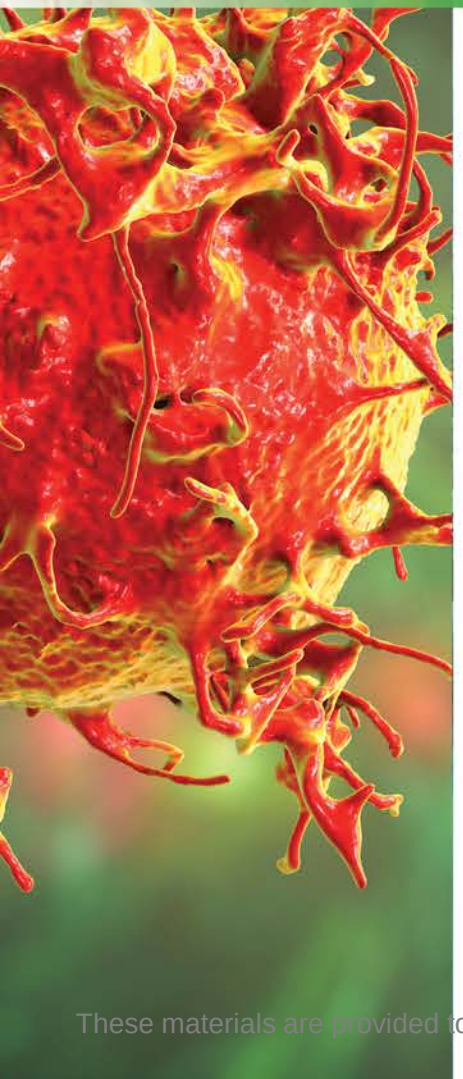
Immune Checkpoint Inhibitors: Monotherapy



- CTLA-4 blocking antibodies
  - Ipilimumab—approved by FDA in 2011
    - Monotherapy no longer recommended as first-line therapy
- PD-1 blocking antibodies as first-line treatment
  - Note: Early monotherapy trials utilized mg/kg dosing, subsequent shift to flat dosing based on population PK modeling
  - **Nivolumab—approved by FDA in 2014**
    - CheckMate-066: 5-year overall survival 39% in BRAF-wild type patients
  - **Pembrolizumab—approved by FDA in 2014**
    - KEYNOTE-001: 5-year overall survival 41%
  - In this setting → Either agent appropriate for monotherapy, both supported by National Comprehensive Cancer Network (NCCN) guidelines as Category 1 recommendation

Robert C, et al. *J Clin Oncol*. 2020;38(33):3937. Hamid O, et al. *Ann of Oncol*. 2019;30(4):582. NCCN Guidelines. Melanoma: Cutaneous. v3.2022.

Immune Checkpoint Inhibitors: Monotherapy



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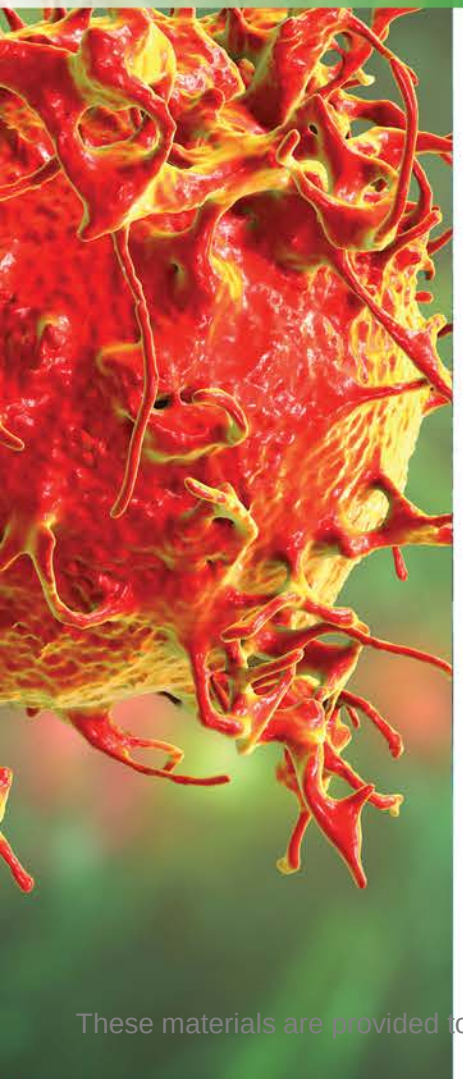
Robert C, et al. *J Clin Oncol*. 2020;38(33):3937. Hamid O, et al. *Ann of Oncol*. 2019;30(4):582. NCCN Guidelines. Melanoma: Cutaneous. v3.2022.

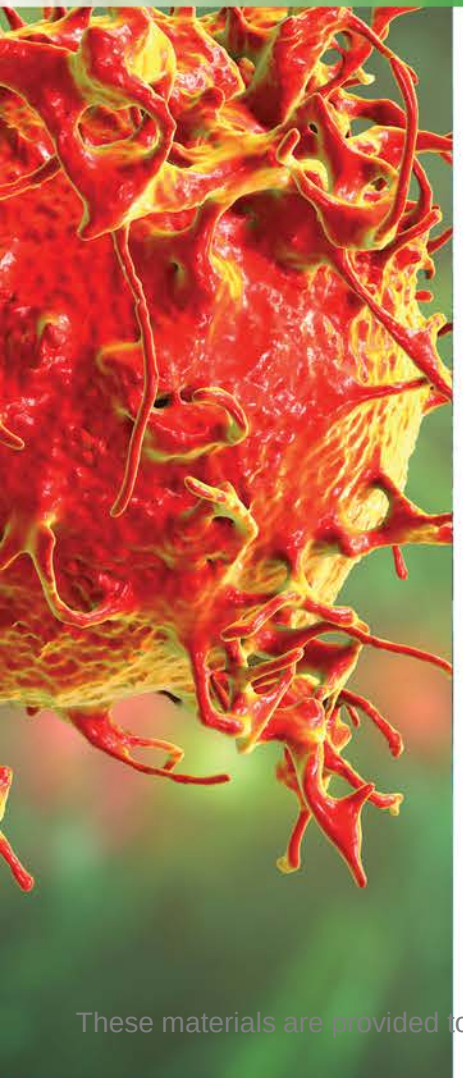
Combination ICIs



- Dual checkpoint blockade with CTLA-4 and PD-1 inhibition
  - Rationale for combination versus monotherapy
    - Increase response rates, survival rates
    - Nonredundant pathways
      - CTLA-4, regulation of T-cell activation in lymph nodes/tissues
      - PD-1, T-cell, and NK-cell activation in peripheral tissues
  - FDA-approved regimen for unresectable and metastatic melanoma
    - Ipilimumab 3 mg/kg + nivolumab 1 mg/kg every 3 weeks for 4 doses (induction)
    - Followed by nivolumab 240 mg IV every 2 weeks **OR** 480 mg IV every 4 weeks (maintenance)
    - “Flipped dose” strategies may be utilized off-label
  - Off-label: Pembrolizumab 2 mg/kg IV + ipilimumab 1 mg/kg IV every 3 weeks for 4 doses, followed by pembrolizumab 2 mg/kg every 3 weeks

Robert C, et al. *J Clin Oncol*. 2020;38(33):3937. Hamid O, et al. *Ann of Oncol*. 2019;30(4):582. NCCN Guidelines. Melanoma: Cutaneous. v3.2022.

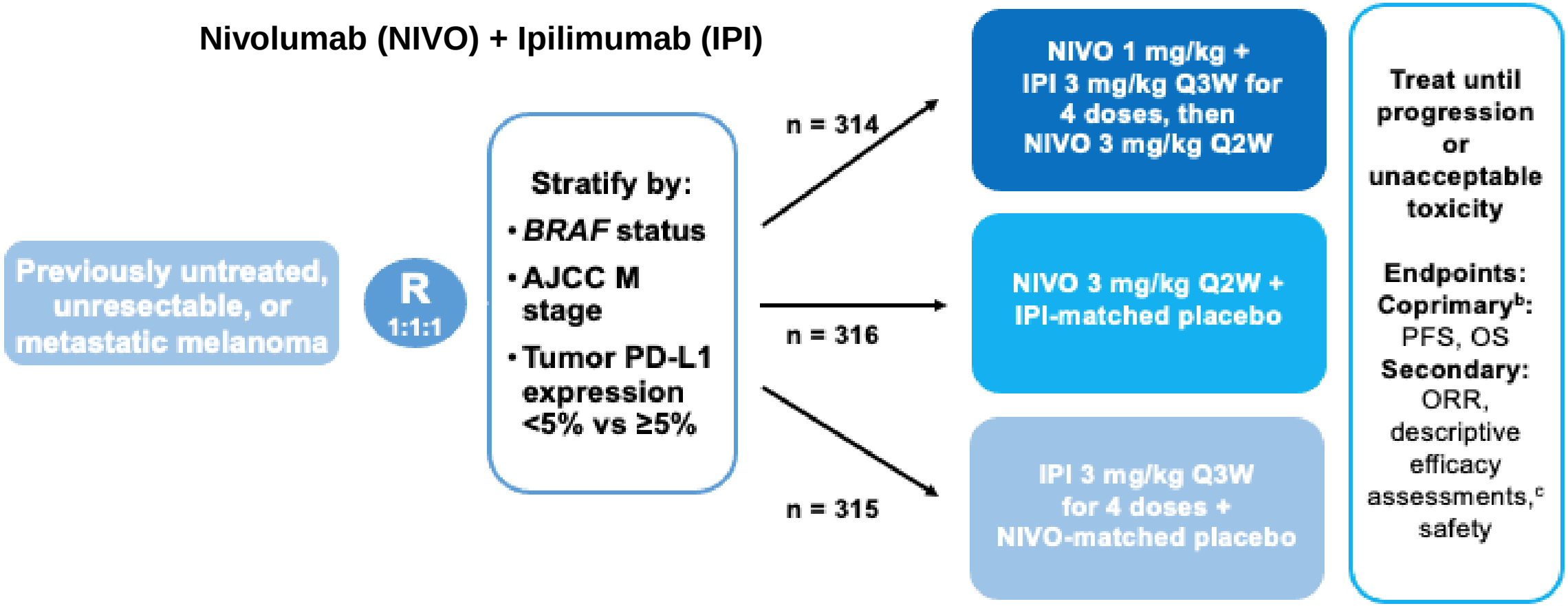
Combination ICIs



- Dual checkpoint blockade of LAG-3 and PD-1
  - Distinct inhibitory immune checkpoints
    - LAG-3 expressed on exhausted CD4+ and CD8+ tumor-infiltrating T cells, and is synergistic with PD-1
  - Nivolumab 480 mg/relatlimab 160 mg
    - FDA approved in 2022
    - This is a fixed dose combination product—Relatlimab is NOT commercially available as a singular entity
    - Single IV infusion reduces preparation time, minimizes risk of errors related to administration, sequencing, flushes, etc.

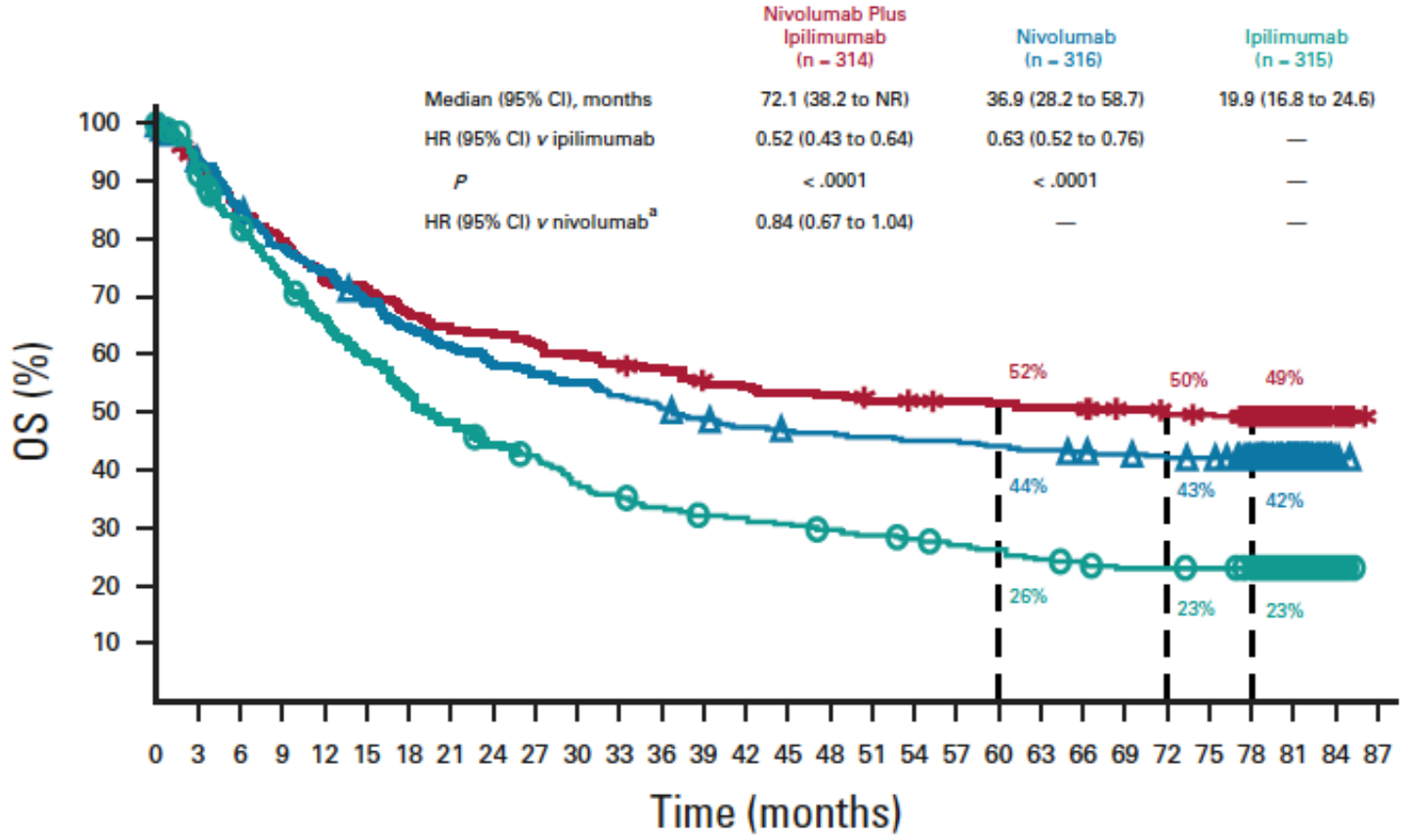
Tawbi HA, et al. *N Engl J Med.* 2022;386(1):24. Maruhashi T, et al. *J Immunother Cancer*. 2020;8(2):e001014.

CheckMate 067:
A Randomized, Double-Blind, Phase 3 Study



Wolchok J, et al. American Society of Clinical Oncology (ASCO) Annual Meeting 2021. Abstract 9506.

CheckMate 067:
6.5-y Update on Overall Survival

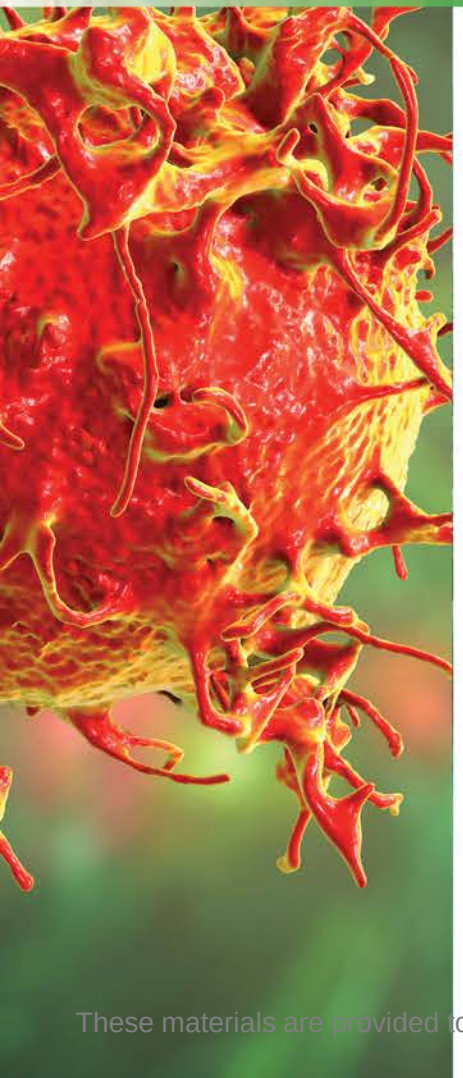


No. at risk:

Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	138	66	10	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	117	59	3	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	61	32	7	0

Wolchok J, et al. *J Clin Oncol*. 2022;40(2):127.

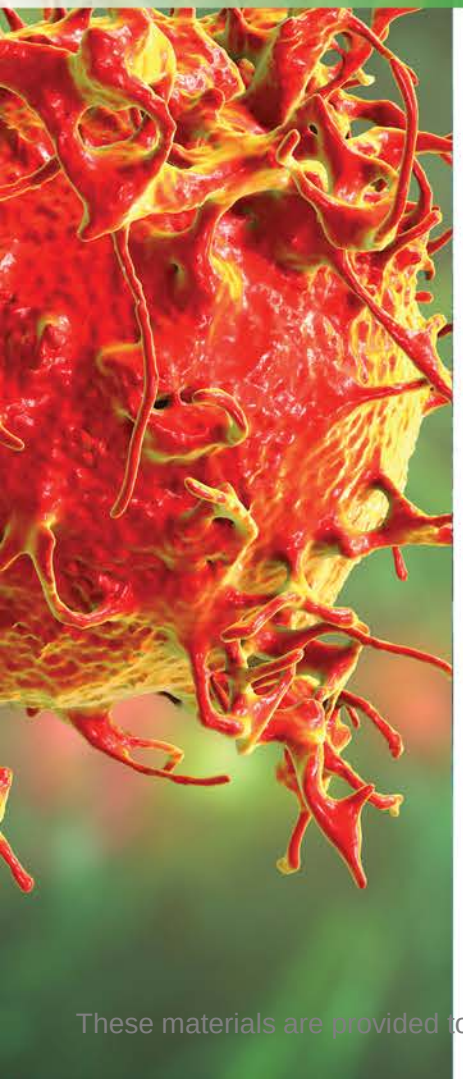
CheckMate 067: Combination IO Associated With Significant Toxicity



	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%)	7 (2%)	0	21 (7%)	1 (<1%)	0	23 (7%)	1 (<1%)	0
Arthralgia	41 (13%)	2 (1%)	0	31 (10%)	1 (<1%)	0	22 (7%)	0	0
Headache	33 (11%)	2 (1%)	0	24 (8%)	0	0	25 (8%)	1 (<1%)	0
Increased aspartate aminotransferase	33 (11%)	18 (6%)	1 (<1%)	11 (4%)	3 (1%)	0	10 (3%)	2 (1%)	0
Increased alanine aminotransferase	33 (11%)	25 (8%)	2 (1%)	9 (3%)	3 (1%)	1 (<1%)	7 (2%)	4 (1%)	1 (<1%)
Dyspnoea	33 (11%)	3 (1%)	0	18 (6%)	1 (<1%)	0	12 (4%)	0	0
Maculopapular rash	32 (10%)	6 (2%)	0	14 (5%)	2 (1%)	0	37 (12%)	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

Wolchok J, et al. *J Clin Oncol*. 2022;40(2):127.

CheckMate 067: Combination IO Associated With Significant Toxicity



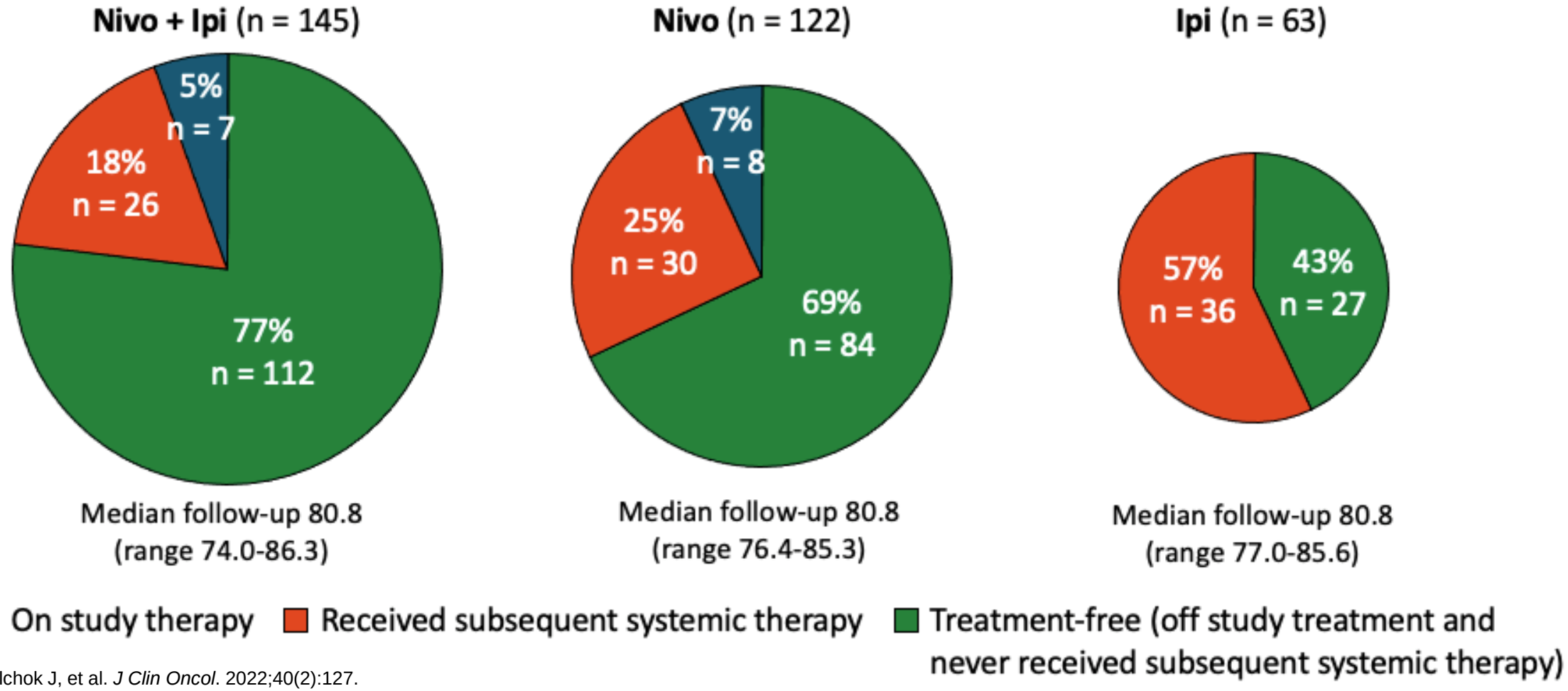
	Nivolumab plus ipilimumab group (n=313)			Nivolumab group (n=313)			Ipilimumab group (n=311)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	115 (37%)	151 (48%)	34 (11%)	200 (64%)	54 (17%)	16 (5%)	181 (58%)	74 (24%)	12 (4%)
Diarrhoea	112							%)	0
Fatigue	107							)	0
Pruritus	106							%)	0
Rash	83							)	0
Nausea	81							)	0
Pyrexia	58							%)	0
Decreased appetite	56							%)	0
Hypothyroidism	53								0
Vomiting	41							%)	0
Arthralgia	41								0
Headache	33							%)	0
Increased aspartate aminotransferase	33							)	0
Increased alanine aminotransferase	33							)	1 (<1%)
Dyspnoea	33								0
Maculopapular rash	32							%)	0
Hyperthyroidism	32								0
Vitiligo	28								0
Hypophysitis	19							)	0
Increased amylase	17							)	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

Grade 3-4 toxicity:
59% with IPI/NIVO
22% NIVO
28% IPI

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

Wolchok J, et al. *J Clin Oncol*. 2022;40(2):127.

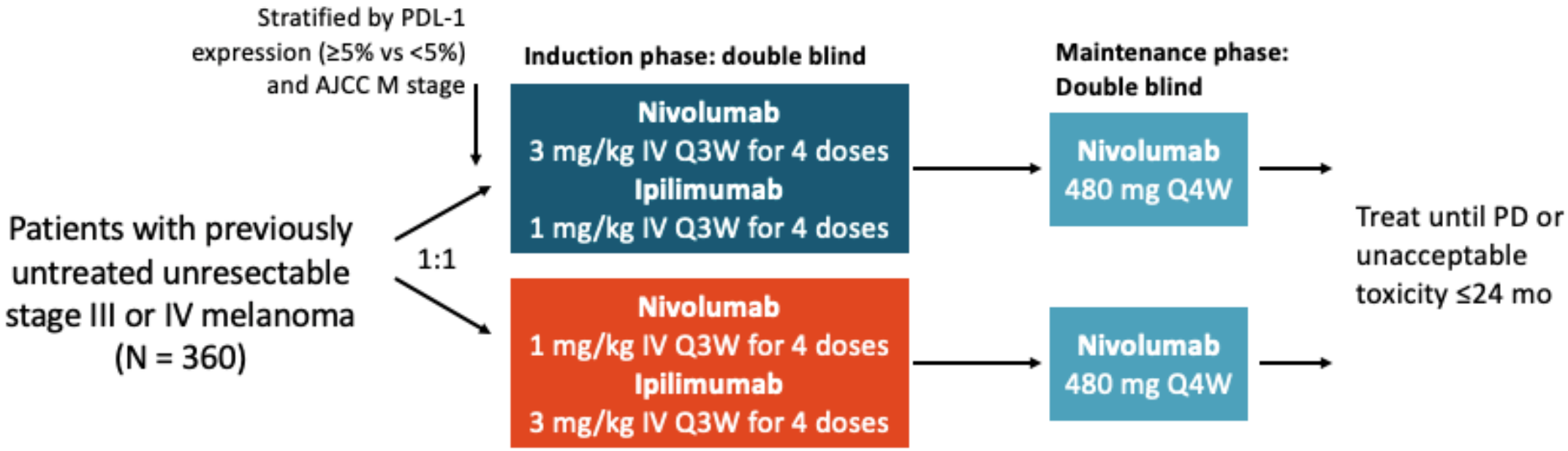
CheckMate 067: Patients Alive and Treatment-Free (6.5-y Follow-up)



Wolchok J, et al. *J Clin Oncol*. 2022;40(2):127.

CheckMate 511 Study Design Dose: Adjustment to Mitigate Toxicity

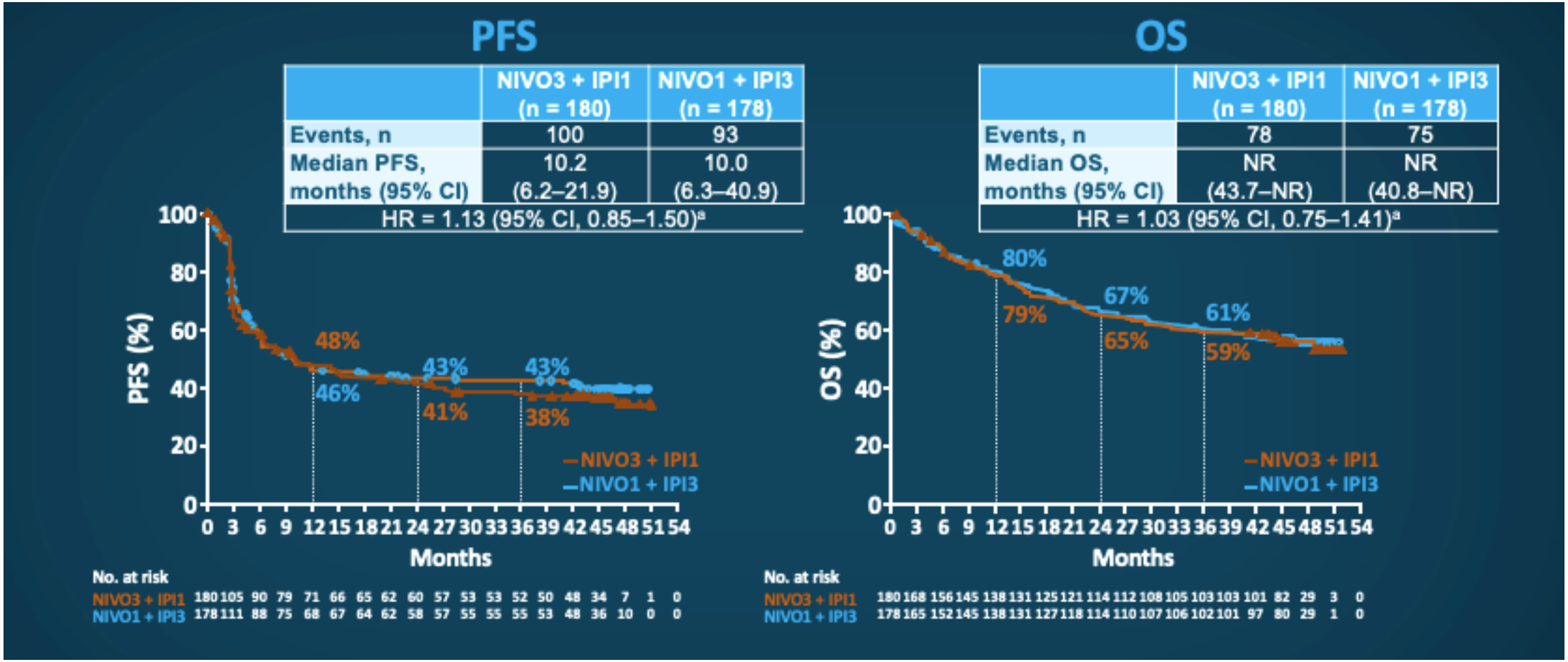
- Randomized, double-blind, phase 3b/4 trail



- Primary endpoint: Incidence of grade 3-5 treatment-related adverse events (TRAEs)
- Secondary endpoints: ORR (investigator-assessed by RECIST v1.1), PFS, OS

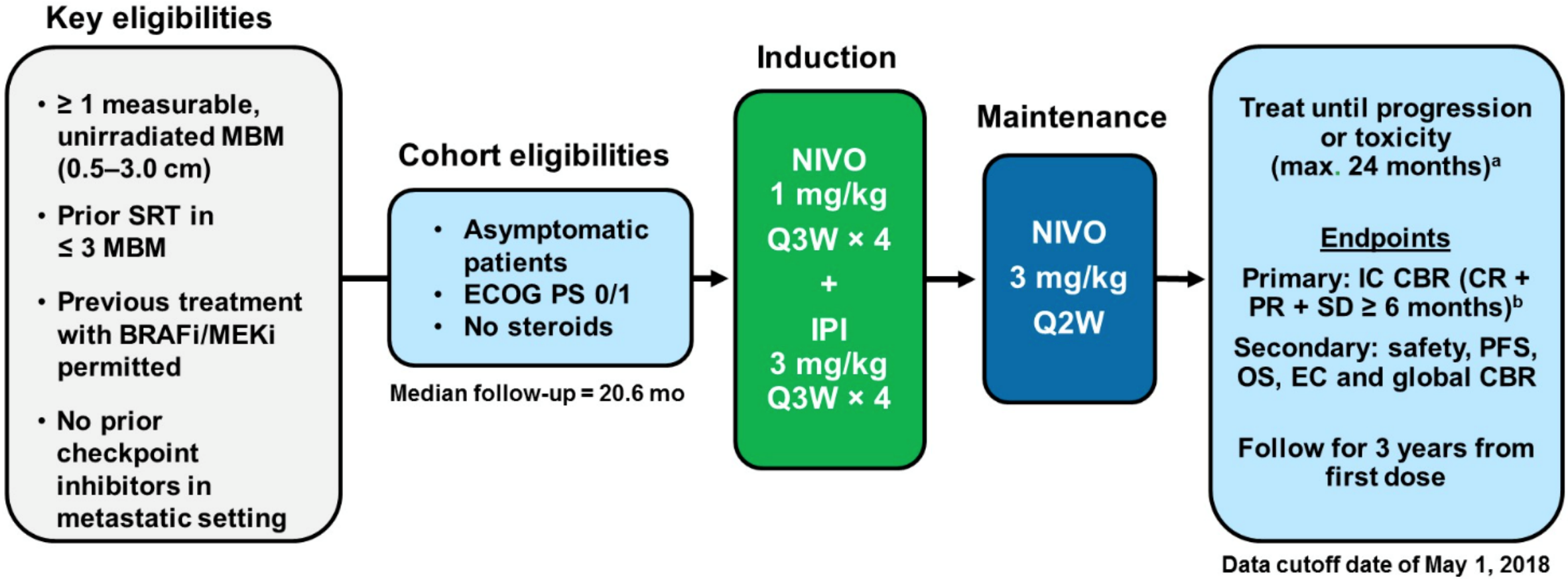
Lebbé C, et al. ASCO 2021. Abstr 9516.

CheckMate 511: Survival Outcomes



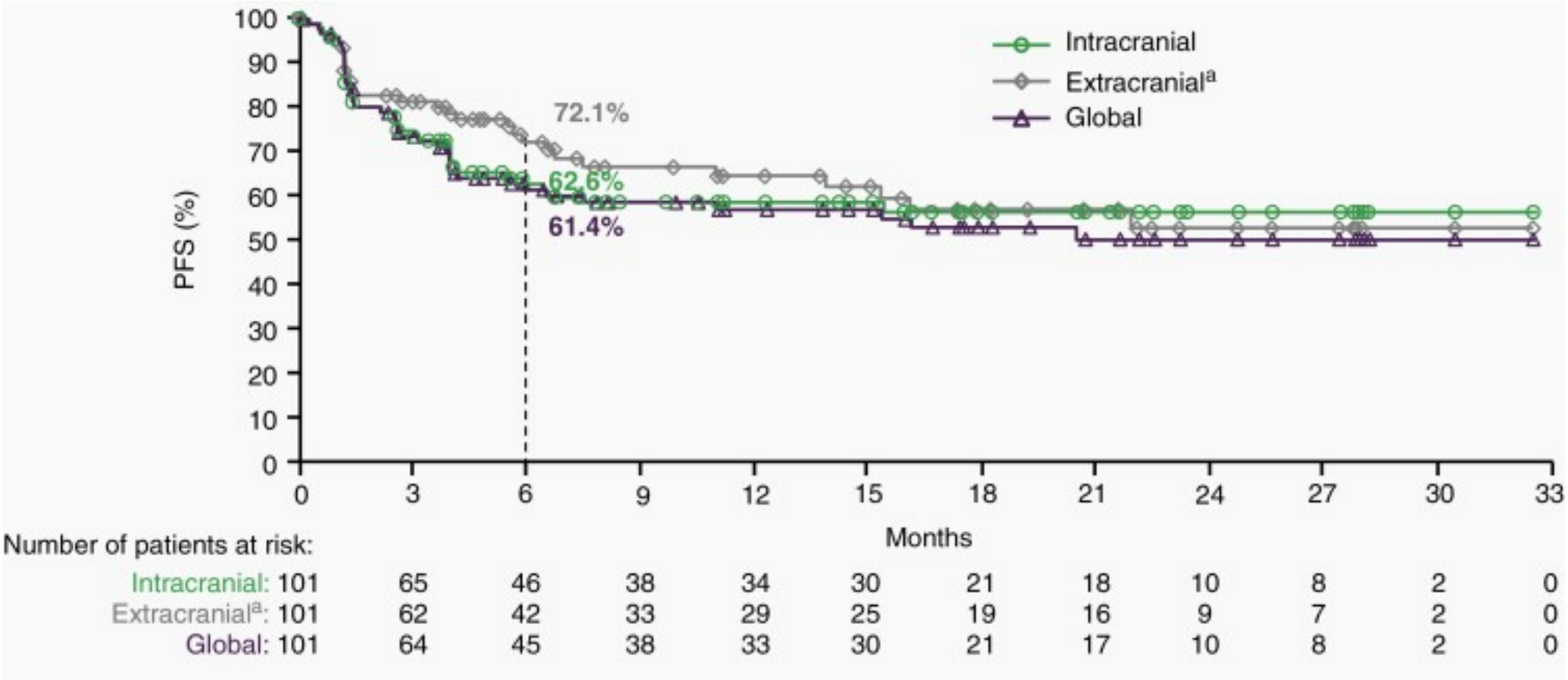
Lebbé C, et al. ASCO 2021. Abstr 9516.

CheckMate 204: Ipilimumab/Nivolumab for Patients With Melanoma Brain Metastases (MBM)



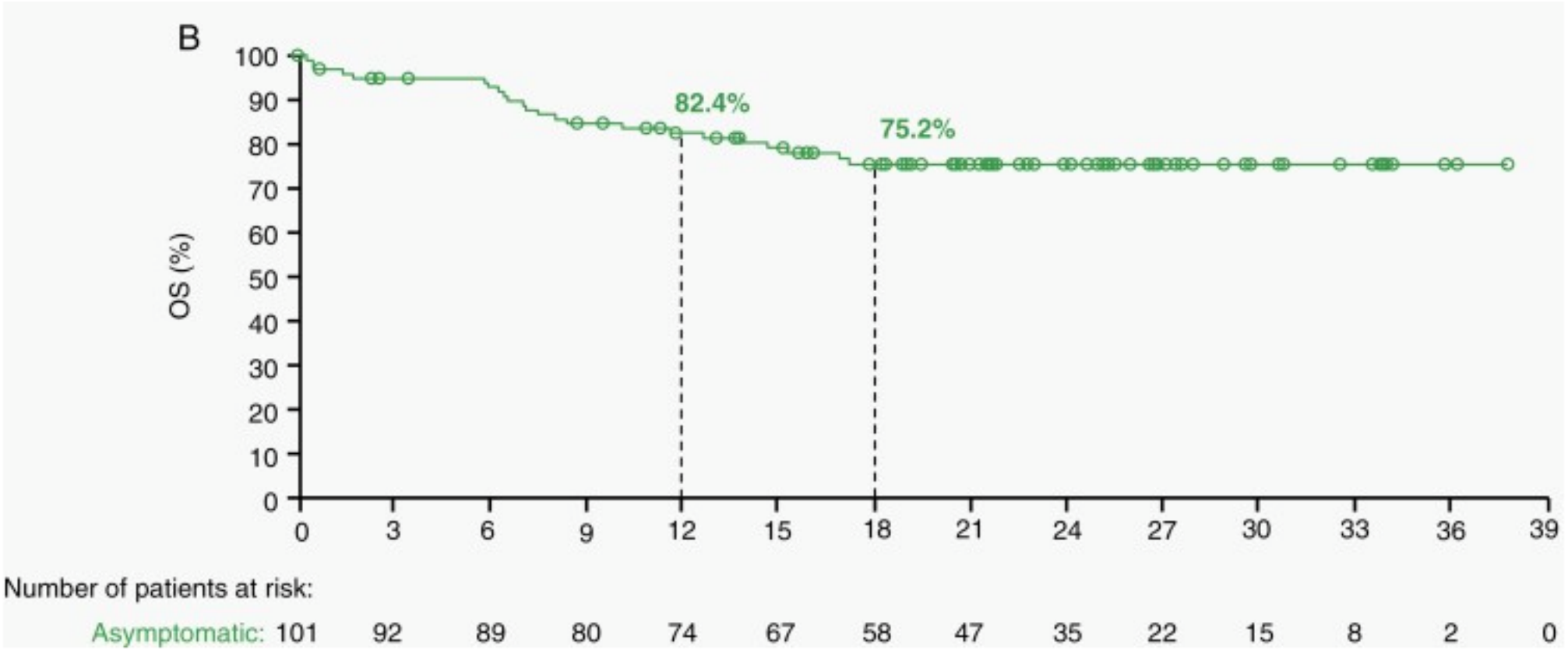
Tawbi HA, et al. ASCO 2019. Abstr 9501.

CheckMate 204:
PFS in Asymptomatic Patients



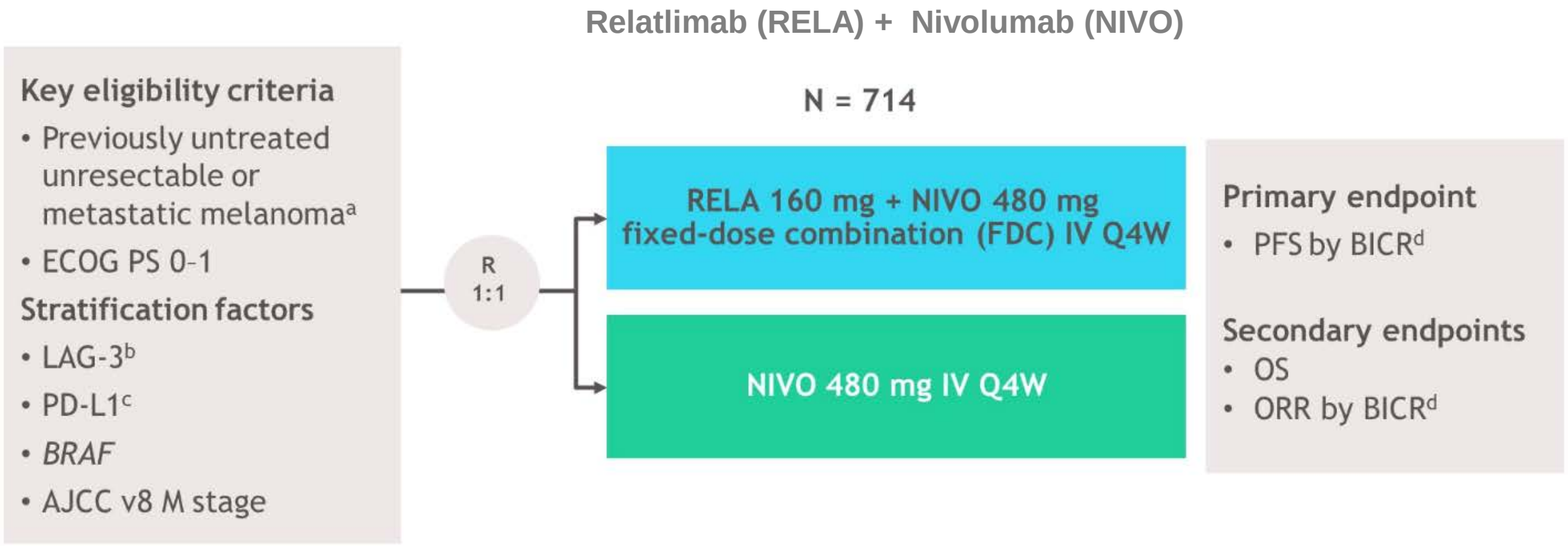
Tawbi HA, et al. *Neuro Oncol*. 2021;23(11):1961.

CheckMate 204: OS in Asymptomatic Patients



Tawbi HA, et al. *Neuro Oncol*. 2021;23(11):1961.

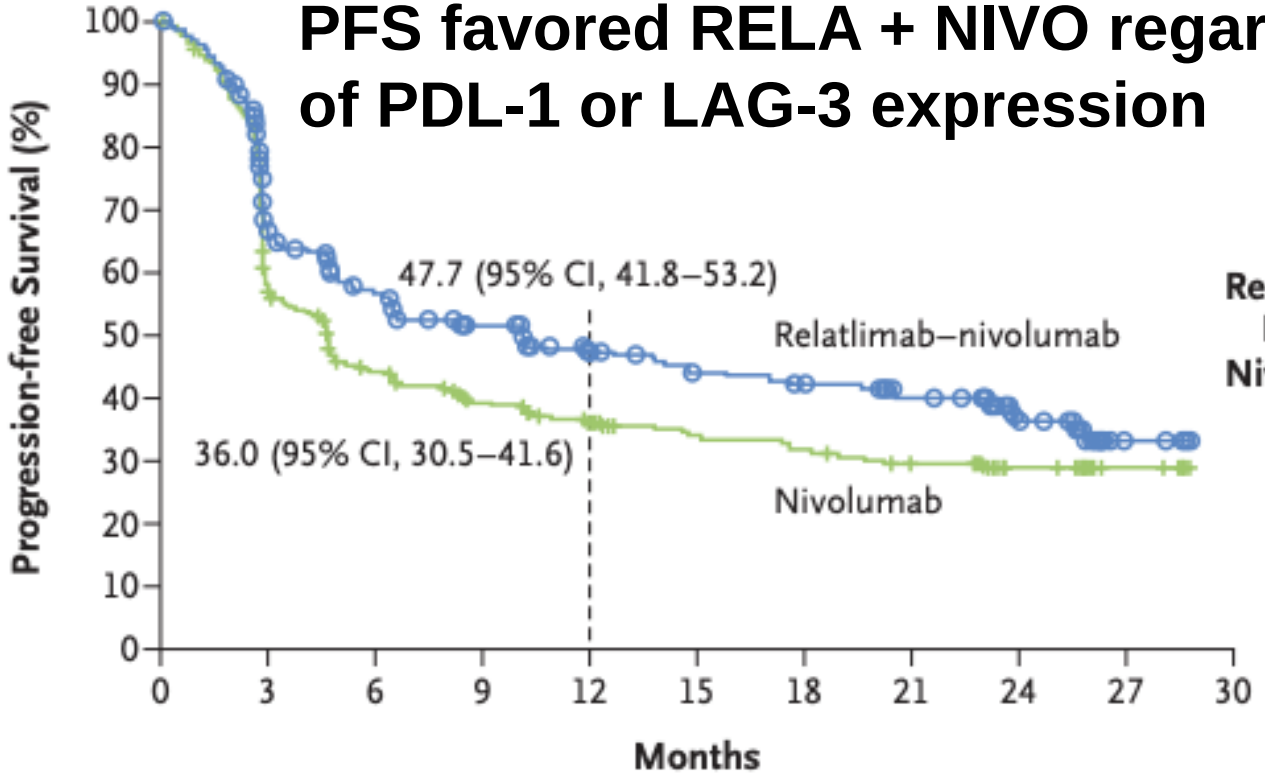
RELATIVITY-047: A Randomized, Double-Blind, Phase 2/3 Study



Lipson EJ, et al. ASCO 2021. Abstr 9503.

RELATIVITY-047: PFS

PFS favored RELA + NIVO regardless of PDL-1 or LAG-3 expression



	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Relatlimab–Nivolumab	355	10.12 (6.37–15.74)
Nivolumab	359	4.63 (3.38–5.62)

Hazard ratio for progression or death, 0.75 (95% CI, 0.62–0.92)
P=0.006

No. at Risk											
Relatlimab–nivolumab	355	201	163	132	99	81	75	67	30	6	0
Nivolumab	359	174	124	94	72	61	57	49	27	6	0

Tawbi HA, et al. *N Engl J Med.* 2022;386(1):24.

RELATIVITY-047: Toxicity

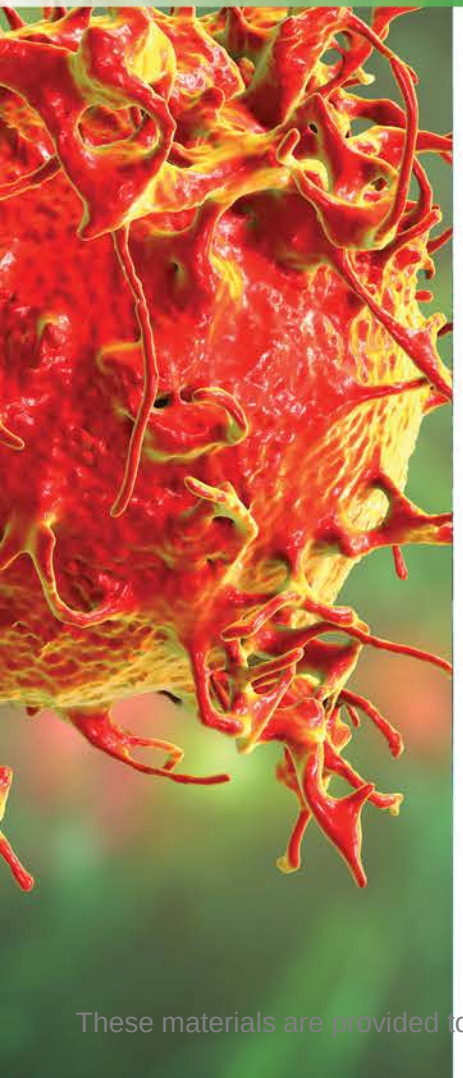
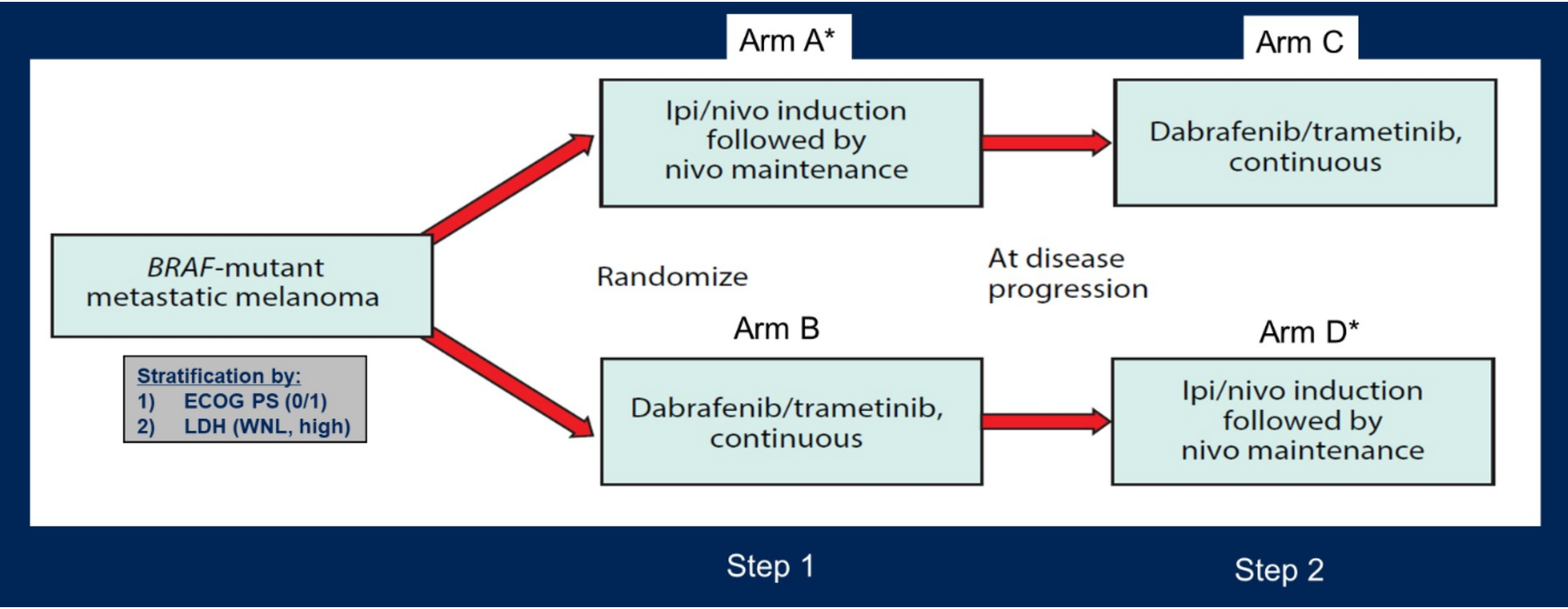


Table 2. Summary of Adverse Events.

Adverse Event	Relatlimab–Nivolumab (N=355)		Nivolumab (N=359)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
	number of events (percent)			
Any adverse event	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
Treatment-related adverse event	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Led to discontinuation of treatment	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
Treatment-related adverse event in ≥10% of patients in the relatlimab–nivolumab group				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0
Immune-mediated adverse event*				
Hypothyroidism or thyroiditis	64 (18.0)	0	50 (13.9)	0
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Diarrhea or colitis	24 (6.8)	4 (1.1)	11 (3.1)	5 (1.4)
Hyperthyroidism	22 (6.2)	0	24 (6.7)	0
Hepatitis	20 (5.6)	14 (3.9)	9 (2.5)	4 (1.1)
Adrenal insufficiency	15 (4.2)	5 (1.4)	3 (0.8)	0
Pneumonitis	13 (3.7)	2 (0.6)	6 (1.7)	2 (0.6)
Hypophysitis	9 (2.5)	1 (0.3)	3 (0.8)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	4 (1.1)	0	4 (1.1)	0

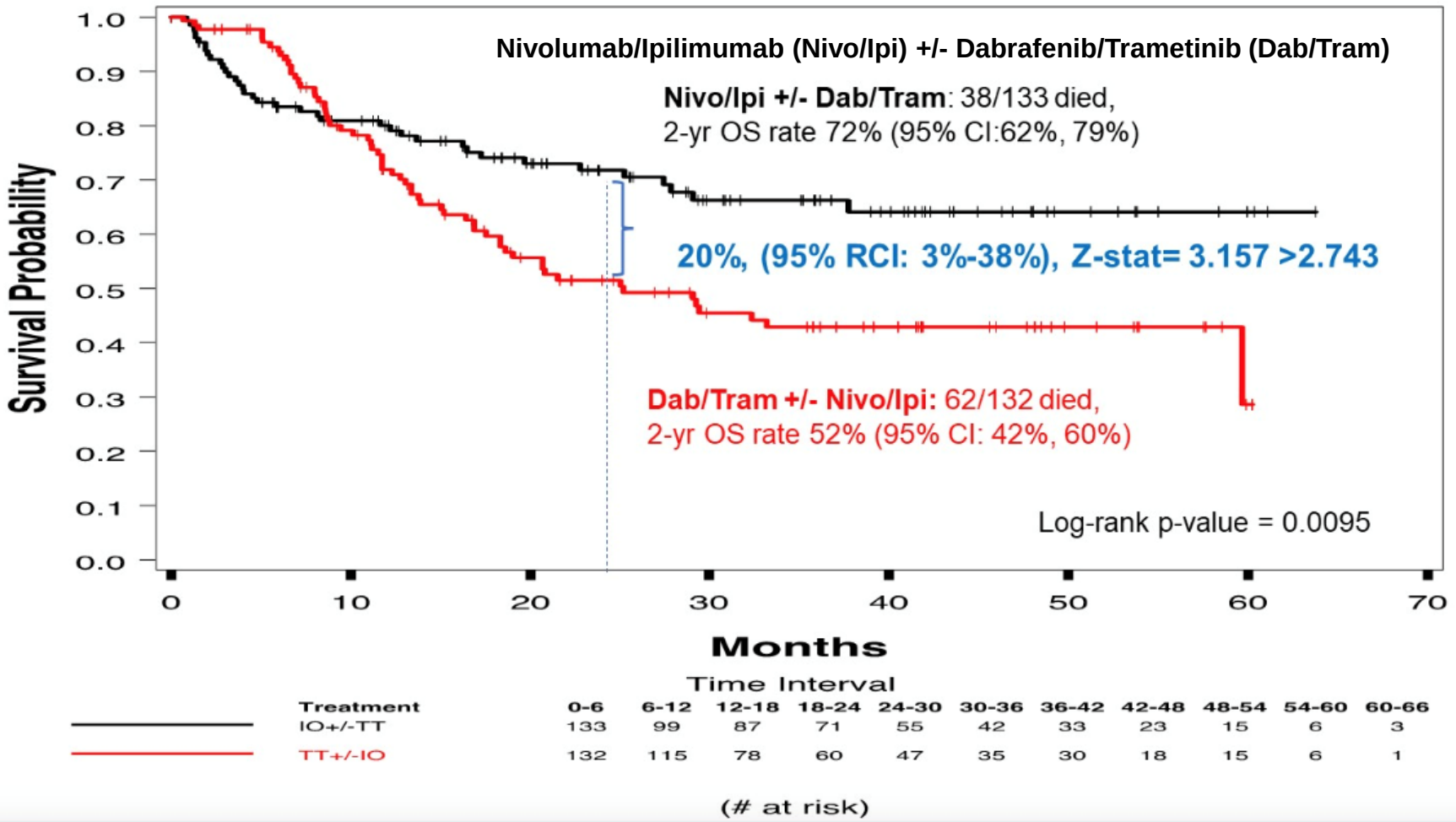
Tawbi HA, et al. *N Engl J Med.* 2022;386(1):24.

DREAMseq: Optimal Sequence in Patients With BRAF V600E/K Metastatic Melanoma



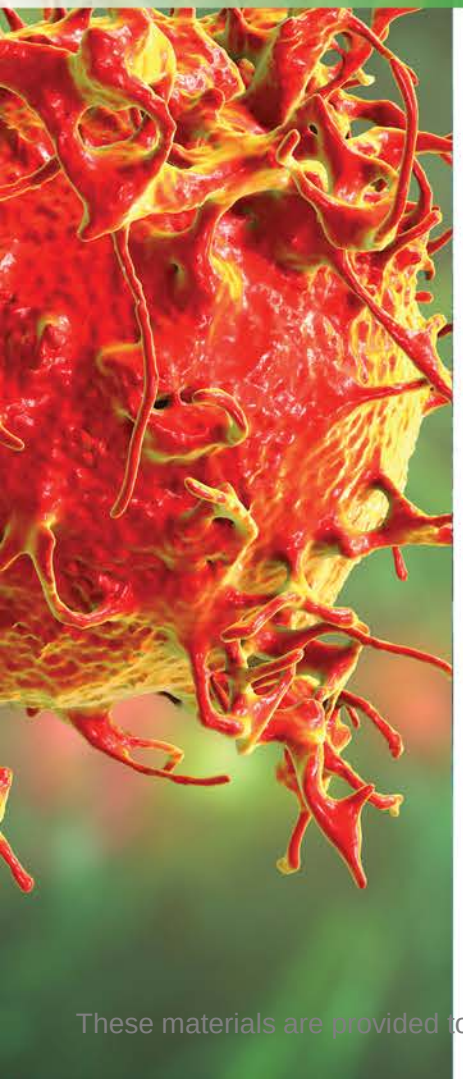
Atkins MB, et al. ASCO 2021. Abstr 356154.

DREAMseq: Overall Survival



Atkins MB, et al. ASCO 2021. Plenary series. Abstr 356154.

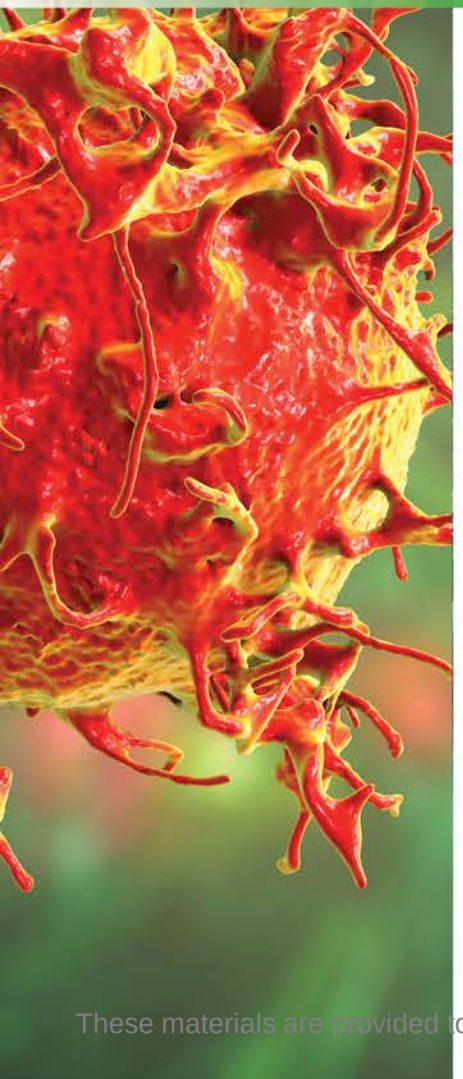
Combining Targeted Therapy With ICIs



- Use of BRAF + MEK inhibitors in patients with BRAF-mutant unresectable or metastatic melanoma generally associated with high response rates, limited duration of response
- Use of ICI generally associated with durable responses, but lower objective response rates
- Rationale for triplet therapy (BRAFi + MEKi + ICI)
  - Distinct mechanisms of action
  - Enhanced immunogenicity of the tumor microenvironment
  - Anticipated higher objective response rates, higher frequency of durable responses?

Schmitt AM, et al. *Expert Rev Anticancer Ther*. 2022;22(1):17.

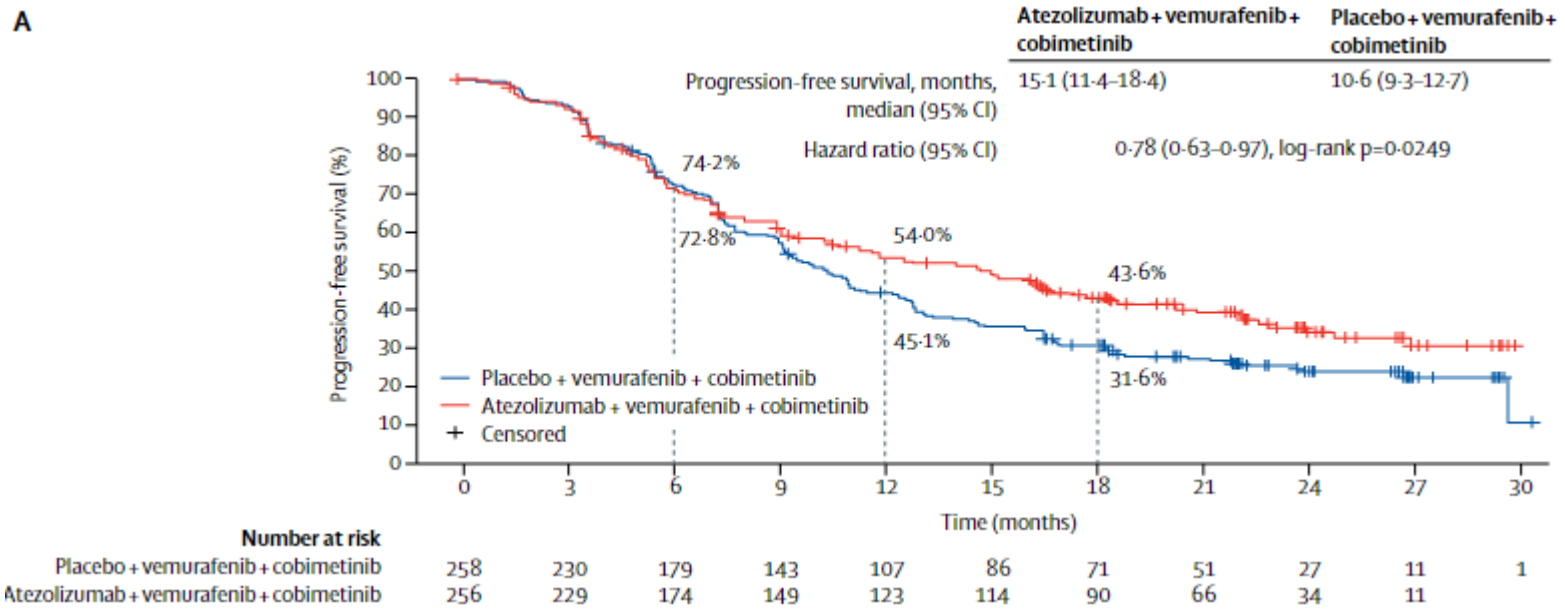
Combining Targeted Therapy With ICIs



- Only 1 regimen of triplet therapy approved by the FDA for unresectable or metastatic melanoma (July 2020)
  - Other combinations have shown similar progression-free survival (PFS) but are *not* FDA approved
- IMspire-150/TRILOGY trial
  - **Run-in period:** Vemurafenib 960 mg orally BID (days 1-21) then 720 mg BID (days 22-28) + cobimetinib 60 mg daily (days 1-21)
  - **Followed by:** Atezolizumab 840 mg IV every 14 days + vemurafenib 720 mg orally BID + cobimetinib 60 mg daily for 21 days on/7 days off
- **Note**: Atezolizumab is *not* indicated for use as monotherapy in advanced melanoma—Vemurafenib + cobimetinib *is* indicated for use in advanced melanoma, even without atezolizumab

Schmitt AM, et al. *Expert Rev Anticancer Ther*. 2022;22(1):17. Gutzmer R, et al. *Lancet*. 2020;395(10240):1835. NCCN Guidelines. Melanoma: Cutaneous. v3.2022.

Atezolizumab + Vemurafenib + Cobimetinib



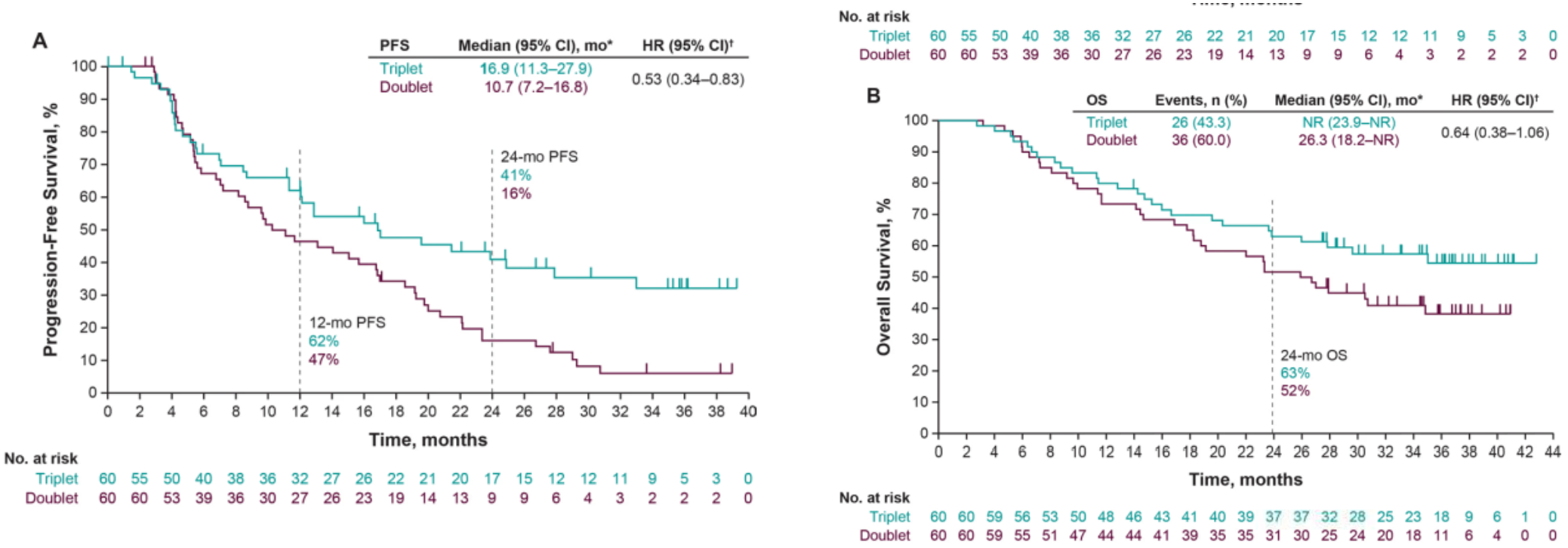
Toxicity Profile

- Grade 3-4 adverse effects
  - 79% in triplet group
  - 73% with placebo/doublet
- Hepatic failure and fulminant hepatitis reported in triplet group, deemed treatment related
- Treatment discontinuation due to adverse effects
  - 13% in triplet arm
  - 16% in placebo/doublet arm

Schmitt AM, et al. *Expert Rev Anticancer Ther*. 2022;22(1):17. Gutzmer R, et al. *Lancet*. 2020;395(10240):1835. NCCN Guidelines. Melanoma: Cutaneous. v3.2022.

KEYNOTE-022:
Combining Targeted Therapy With ICIs

Pembrolizumab 200 mg IV q21 days + dabrafenib 150 mg orally BID + trametinib 2 mg orally once daily



Ferrucci PF, et al. *J Immunother Cancer*. 2020;8(2):e001806. NCCN Guidelines. Melanoma: Cutaneous. v3.2022.

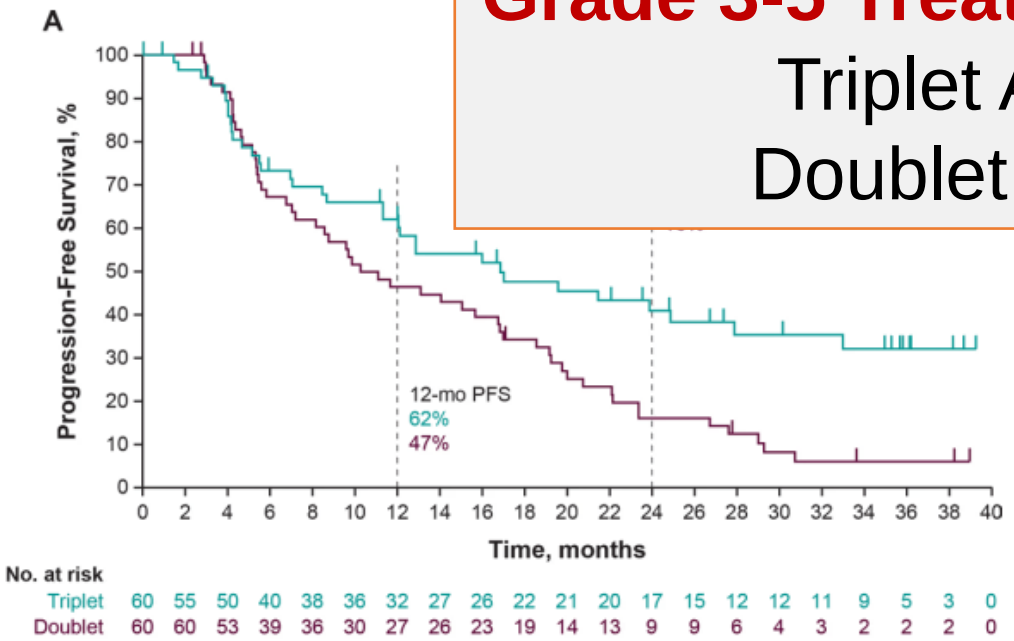
KEYNOTE-022:
Combining Targeted Therapy With ICIs

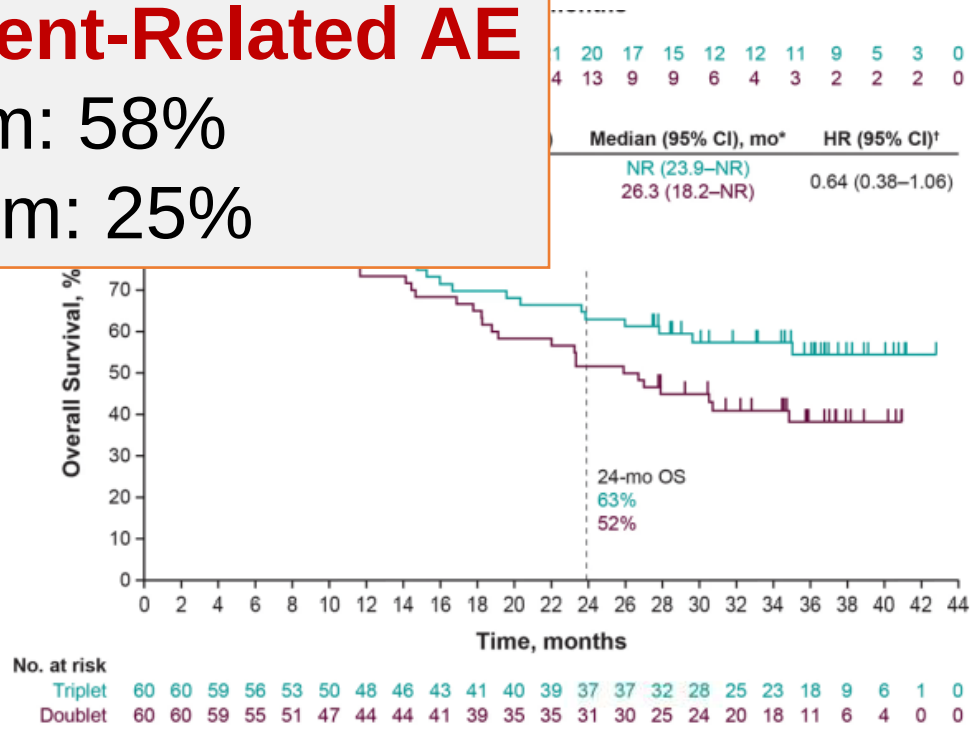
Pembrolizumab 200 mg IV q21 days + dabrafenib 150 mg orally BID + trametinib 2 mg orally once daily

Grade 3-5 Treatment-Related AE

Triplet Arm: 58%

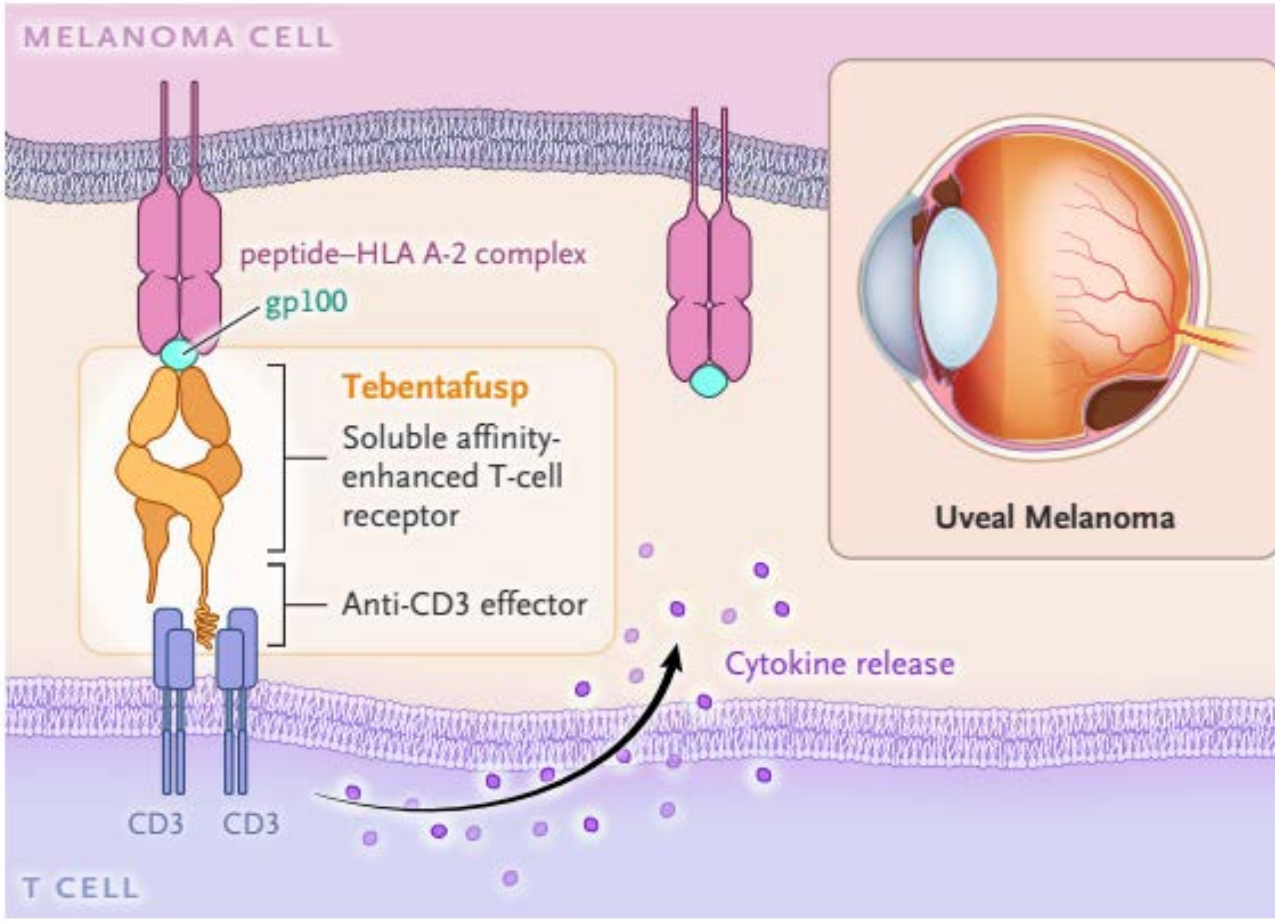
Doublet Arm: 25%

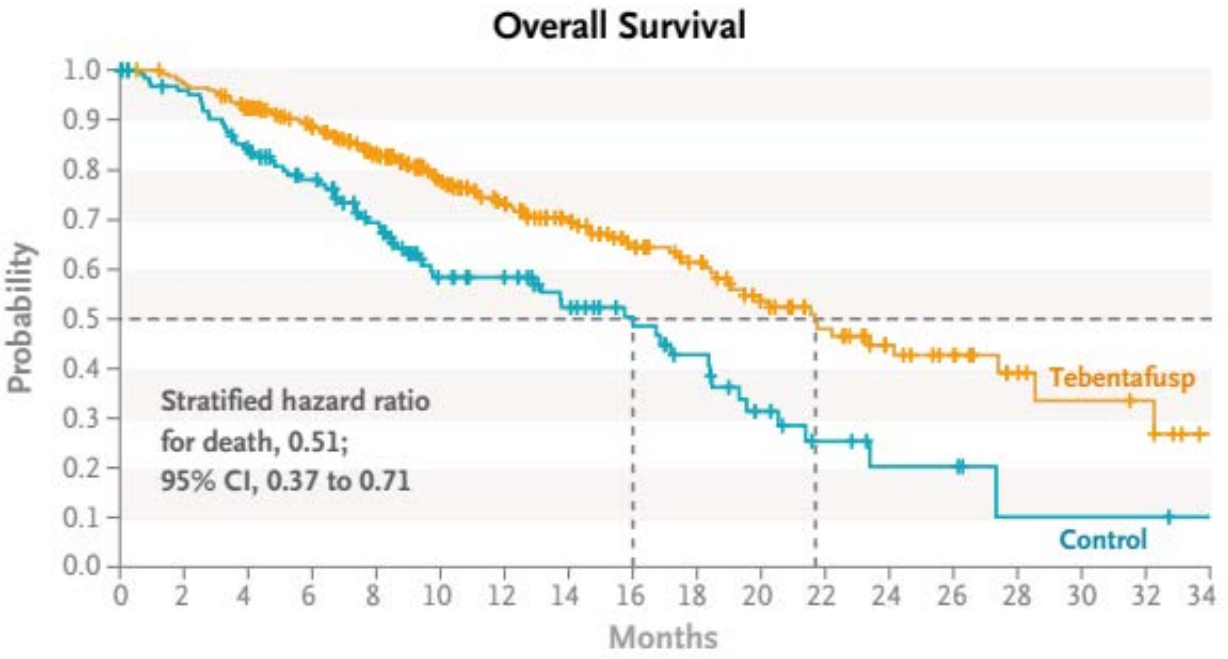




Ferrucci PF, et al. *J Immunother Cancer*. 2020;8(2):e001806. NCCN Guidelines. Melanoma: Cutaneous. v3.2022.

Bispecifics: A New Paradigm
Tebentafusp for Uveal Melanoma

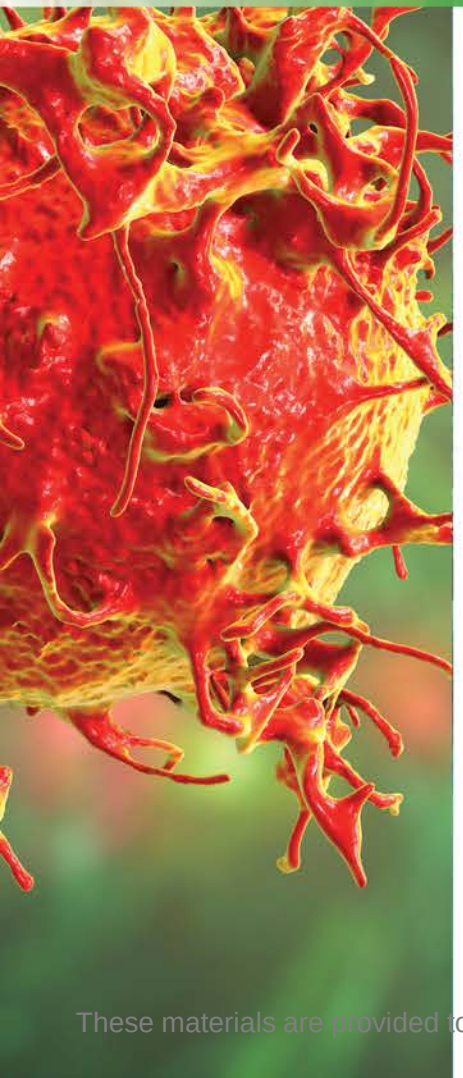




1-Year Survival		
Tebentafusp Group	73%	95% CI, 66 to 79
Control Group	59%	95% CI, 48 to 67

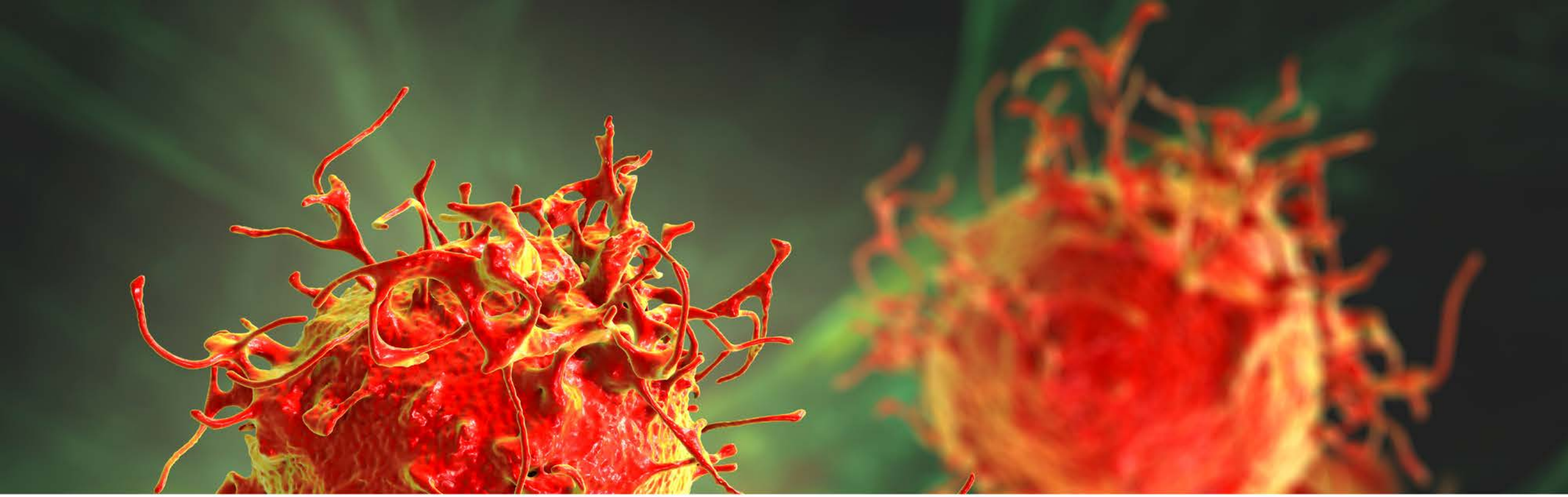
Nathan P, et al. *N Engl Med*. 2021;385(13):1196.

Tebentafusp



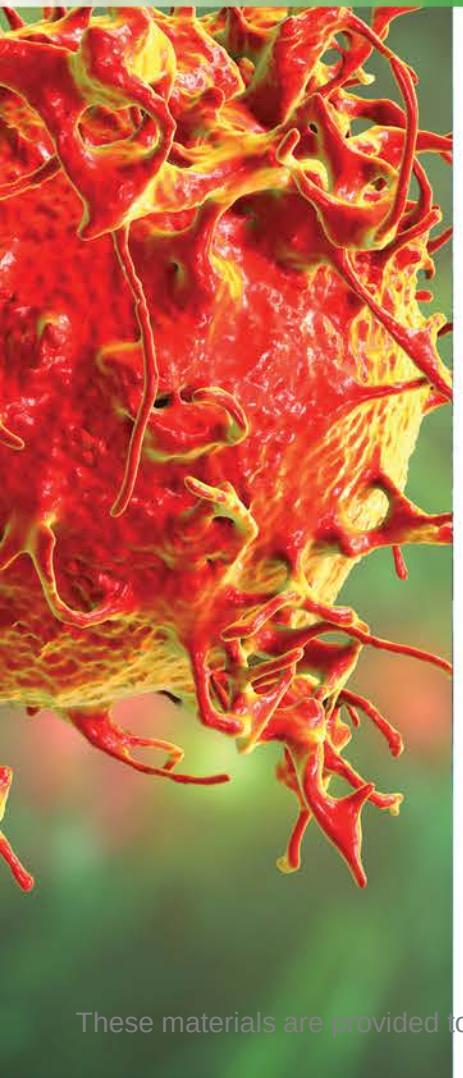
- First FDA-approved therapy for metastatic uveal melanoma
  - Can ONLY be utilized in patients who are HLA-A*02:01-positive
- Weekly IV therapy, intrapatient dose escalation
  - Day 1 = 20 micrograms (mcg) IV
  - Day 8 = 30 mcg IV
  - Weekly thereafter = 68 mcg IV
- Risk of cytokine release syndrome (CRS) highest while receiving the first 3 weekly doses (admit for observation with first 3 doses), though overall severity of CRS grade 1-2
  - Monitor for 16 hours after infusion for the first 3 doses
  - Escalate dose the following week if tolerating therapy
  - Starting with Week 4 dose, if no prior grade 2 or higher hypotension occurs, can administer in outpatient setting with observation period 30 minutes after infusion

Nathan P, et al. *N Engl Med*. 2021;385(13):1196.



Individualizing First-Line Treatment

Melanoma Brain Metastasis (MBM)



- **Approximately 50% to 60% of stage IV melanoma patients develop MBM**
  - Third most common metastatic brain tumor type in adults, following lung and breast cancer
- Historically poor life expectancy, survival rates between ~4-6 months
- Clinical trials and emergence of new therapies providing much needed hope to this patient population
- **Risk factors for developing MBM:**
  - Primary tumor on the head, neck, trunk, or abdomen
  - Primary tumor was ulcerated, deep, or invasive
  - Elevated lactate dehydrogenase (LDH) at time of diagnosis of unresectable stage III or stage IV
  - Presence of *NRAS* or *BRAF* mutation
  - Metastases to visceral organs

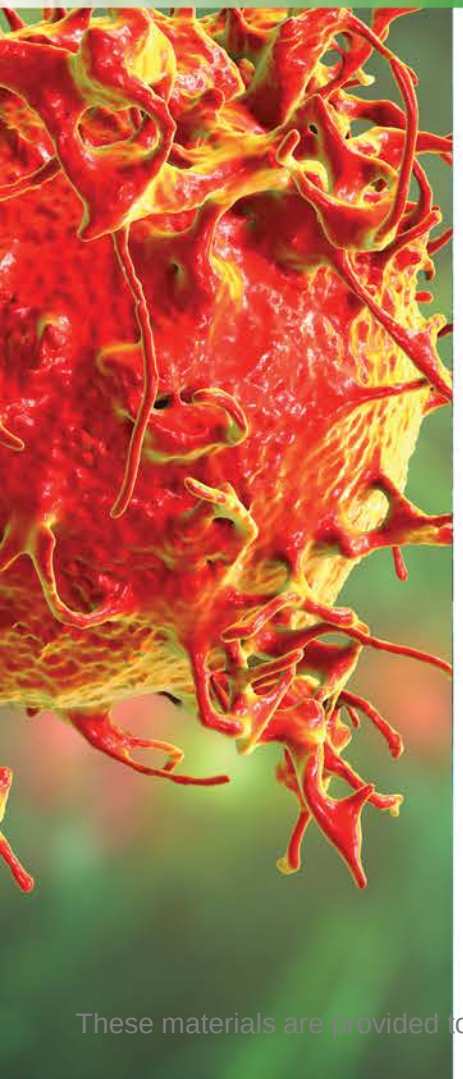
Zakrzewski J, et al. *Cancer.* 2011;117(8):1711.
Bedikian AY, et al. *Am J Clin Oncol*. 2011;34(6):603.

Patient-Specific Factors Associated With Better Outcomes for MBM

Characteristics of both the patient and the cancer will affect the patient's prognosis, such factors include:
Younger age: <60 years old
Fewer vs more brain metastases: <3 lesions
No extracranial disease (presence of disease outside the cranium)
Normal LDH
High performance status: ECOG 0-1 (Eastern Cooperative Oncology Group)

Brain metastases. AIM at Melanoma Foundation. Accessed July 4, 2022, https://www.aimatmelanoma.org/stages-of-melanoma/brain-metastases/
Kuske, M., et.al. Am J Clin Dermatol (2018) 19:529–541

First-Line Systemic Therapy Approaches for Patients With MBM



- A thorough evaluation of patient and disease characteristics, including comorbidities and tumor mutational status, is the best guide in selecting a first-line immunotherapy option
- Patients who seem to benefit the most from combination immunotherapy ipilimumab + nivolumab
  - Treatment naïve
  - Tendencies toward aggressive disease features, such as:
    - Elevated LDH levels
    - Asymptomatic brain metastases
    - Liver metastases
    - Mucosal primary tumor

Dalmasso C, et al. *Cancers*. 2021;13(17):4493.
Brain metastases. AIM at Melanoma Foundation. Accessed July 4, 2022, https://www.aimatmelanoma.org/stages-of-melanoma/brain-metastases/

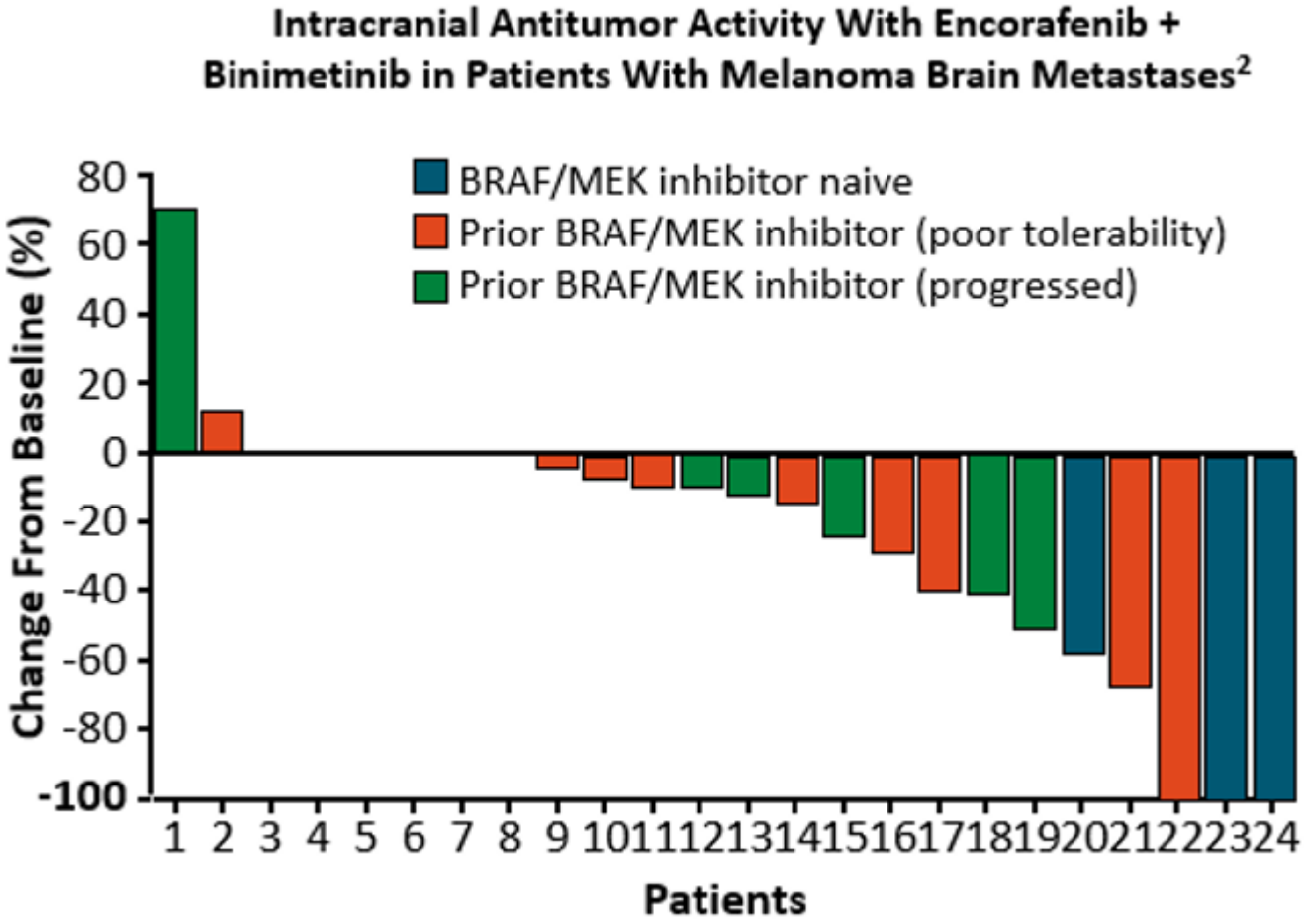
Summary of Immunotherapy Trials for MBM

Trial for MBM	Immunotherapy Agents	Overall Survival
Checkmate 204	Ipilimumab (IPI) 3 mg/kg + Nivolumab (NIV) 1 mg/kg x 4 cycles followed by maintenance NIV 480 mg IV q4w	72% (3 year) Tawbi. *Lancet Oncol*. 2021;22(12):1692
ABC trial	NIV 3 mg/kg q2w *versus* NIV 1 mg/kg + IPI 3 mg/kg q3w followed by NIV 3 mg/kg q2w	51% (5 year) Long. ASCO 2021. Abstr 9508
NIBIT-M2	Fotemustine (FOTE), IPI + FOTE, *or* IPI + NIV	41% (4 year) Di Giacomo. *Clin Cancer Res*. 2021;27(17):473
DREAMseq (EA6134)	IPI 3 mg/kg + NIV 1 mg/kg ≥ progression of disease (pod) Dabrafenib (DAB) + Trametinib (TRAM) DAB 150 mg bid + TRAM 2 mg ≥ pod IPI + NIV	72% (2 year) 52% (2 year) Atkins. ASCO 2021 Abstr 356154
TRICOTEL Phase 2 BRAF V600 w/CNS metastases	**BRAF WT-Cohort 1:** Atezolizumab (ATEZ) 840 mg days 1,15 + Cobimetinib (COB) 60 mg days 1-21 ***BRAF Mutant-Cohort 2:** Vemurafenib (VMF) 720 mg bid + COB 60 mg days 1-21 + ATEZ 840 mg days 1,15 cycle 2	**Cohort 2:** 44% (intracranial response) Dummer. ASCO 2022. Abstr 9515
S2000 (EA6192) Phase 2 BRAF V600 w/CNS metastases	Encorafenib+ Binimetninb + Nivolumab *versus* Nivolumab + Ipilimumab	Primary endpoint is PFS, not reached; study currently enrolling

Di Giacomo AM. *Lancet Oncol*. 2022;23(2):e53. Gogas H, et al. *Ann Oncol*. 2021;32(3):384.

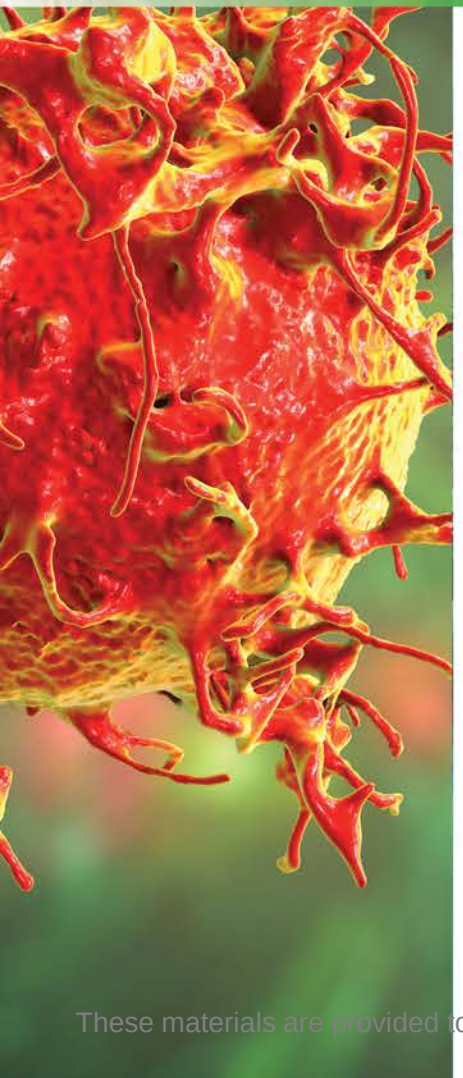
BRAF Inhibitor + MEK Inhibitor
Clinical Pearls: Brain Metastases

- Dabrafenib + trametinib[1] and encorafenib + binimetinib[2] have demonstrated antitumor activity against intracranial *BRAF*-mutant melanoma
- Because median duration of response is typically limited (~6 mo), radiation therapy (RT) often is added to treatment regimen
- Concurrent use of *BRAF/MEK*-targeted agents and RT can increase risk of dermatitis, so medications are often held for a few days before/after and during RT[3]



1. Davies MA, et al. *Lancet Oncol.* 2017;18(7):863. 2. Holbrook K, et al. *Cancer.* 2000;126(3):523. 3. Anker CJ, et al. *Int J Radiat Oncol Biol Phys.* 2016;95(2):632.

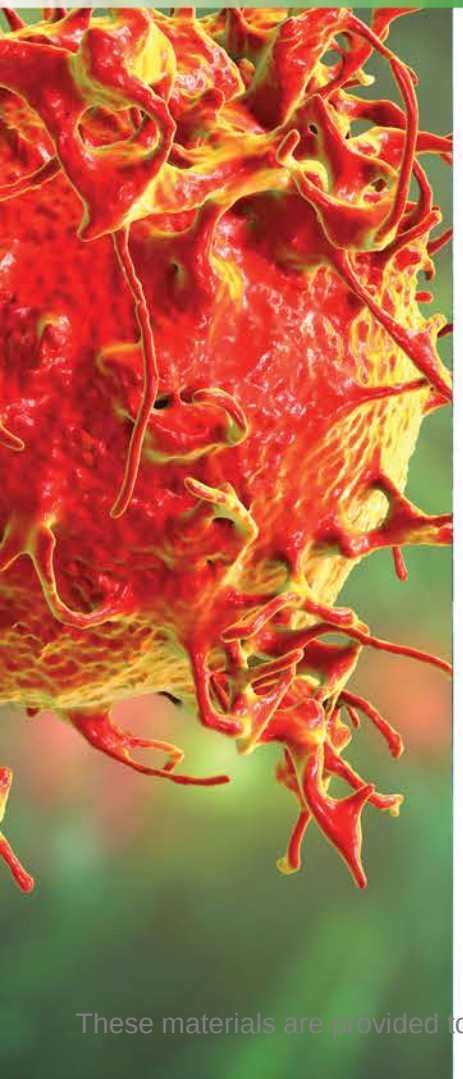
Leptomeningeal Disease (LMD)



- LMD is notable in various tumor types, potentially due to patients living longer with both extracranial and intracranial parenchymal metastatic disease related to advances in systemic therapy and improved imaging
- Autopsy reports suggest actual frequency of cancer patients with neurologic symptoms (~18% had evidence of LMD)
- LMD can be local or disseminated through the entire central nervous system (CNS), and may result in rapid neurologic disability and death
- Untreated LMD—survival can be as short at 4-6 weeks
- Even with current treatment options, prognosis remains poor, and therefore, LMD presents some of the greatest challenges in neuro-oncology

Ferguson SD, et. al. *Front Oncol*. 2022;11:800053.

Leptomeningeal Disease: Immunotherapy and Intrathecal Therapy



- Phase 2 trial with ipilimumab + nivolumab
  - Median OS was 2.9 months, 33% had grade 3 or 4 toxicity, 78% required steroids for symptom control
- Intrathecal (IT) nivolumab + systemic nivolumab—Phase 1/2b trial (NCT03025256) is ongoing
  - IT nivolumab generally well tolerated with no grade 3/4 toxicities observed
  - Addition of IV nivolumab did not increase expected toxicity from systemic anti-PD-1 administration
  - Median OS 4.9 mo; OS 3 mo (63%), 6 mo (42%), 12 mo (30%)

Ferguson SD, et. al. *Front Oncol*. 2022;11:800053. John I, et al. ASCO 2021. Abstr 9519.

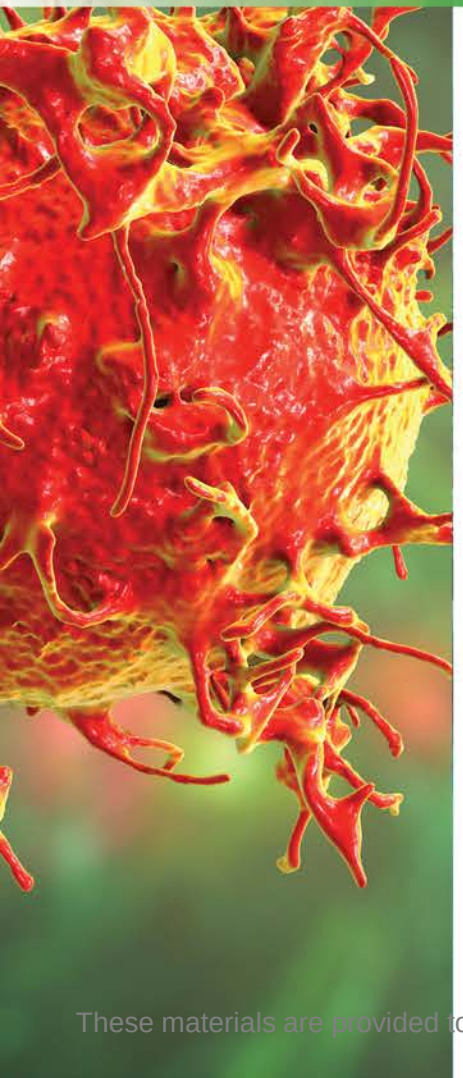
Targetable & Predictable Biomarkers and Therapeutic Approaches for MBM

Biomarker	Discordance Level	Targeted Therapies	Intracranial Response Rate	Extracranial Response Rate	Intracranial PFS
BRAF mutation	0%	Dabrafenib + trametinib	44-58%	44-75%	Not given (NG)
		Vemurafenib + cobimetinib	18%	33%	4
PD-L1 expression	9-89%*	Ipilimumab	16%	14%	1.5
		Pembrolizumab	22%	22%	4-10
		Ipilimumab + nivolumab	50%	55%	Not reached (NR)

*Discordance rate from primary to distant metastasis (no specific data about brain metastasis available).

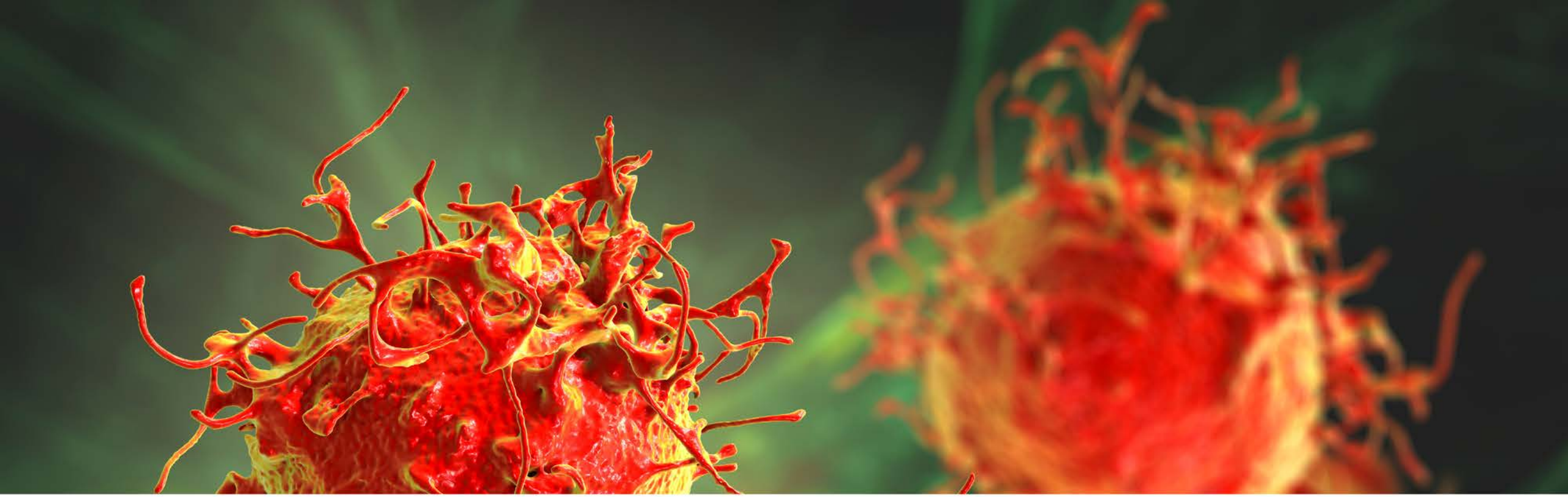
Steindl A, et al. *NeuroOncol Adv*. 2021;3(suppl 5):v35.

Advancement of Precision Medicine in MBM

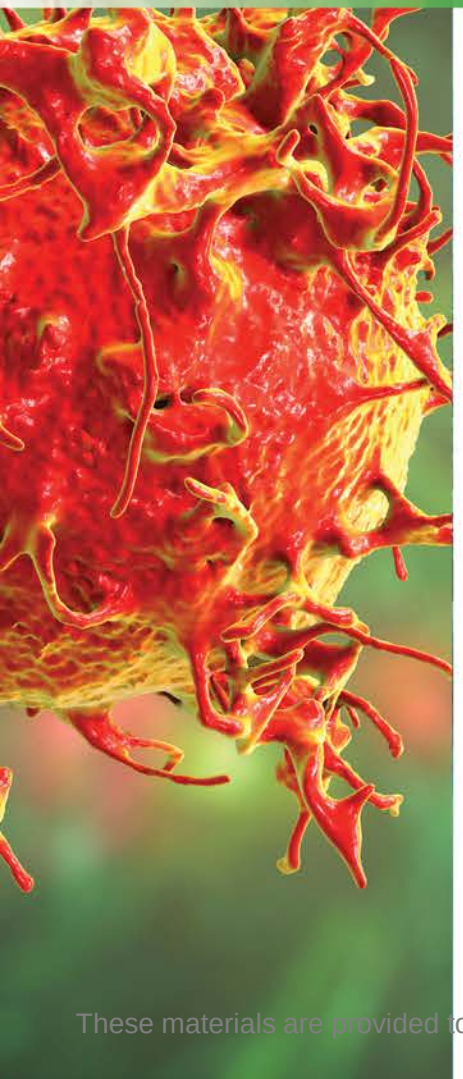


- The best survival rates have been seen with upfront combination therapies
  - Stereotactic radiosurgery (SRS)/CNS–directed therapy + immunotherapy followed by dual targeted therapy after disease progression on immuno-oncology (I/O) therapy
- BRAF V600 mutations have clinically significant response rates for advanced melanoma with both intra- and extracranial disease
  - Recent studies appeal for molecular testing for biomarkers of MBM
  - Tissue availability still presents a clinical obstacle
- Newly approved and emerging new therapies
  - Although promising, need additional research re: efficacy with MBM (relatlimab + nivolumab, encorafenib + binimetinib)

Steindl A, et al. *NeuroOncol Adv*. 2021;3(suppl 5):v35.
Becco P, et al. *Cancers (Basel).* 2020;12(6):1640.



Immune-Related Adverse Events: Prevention and Management



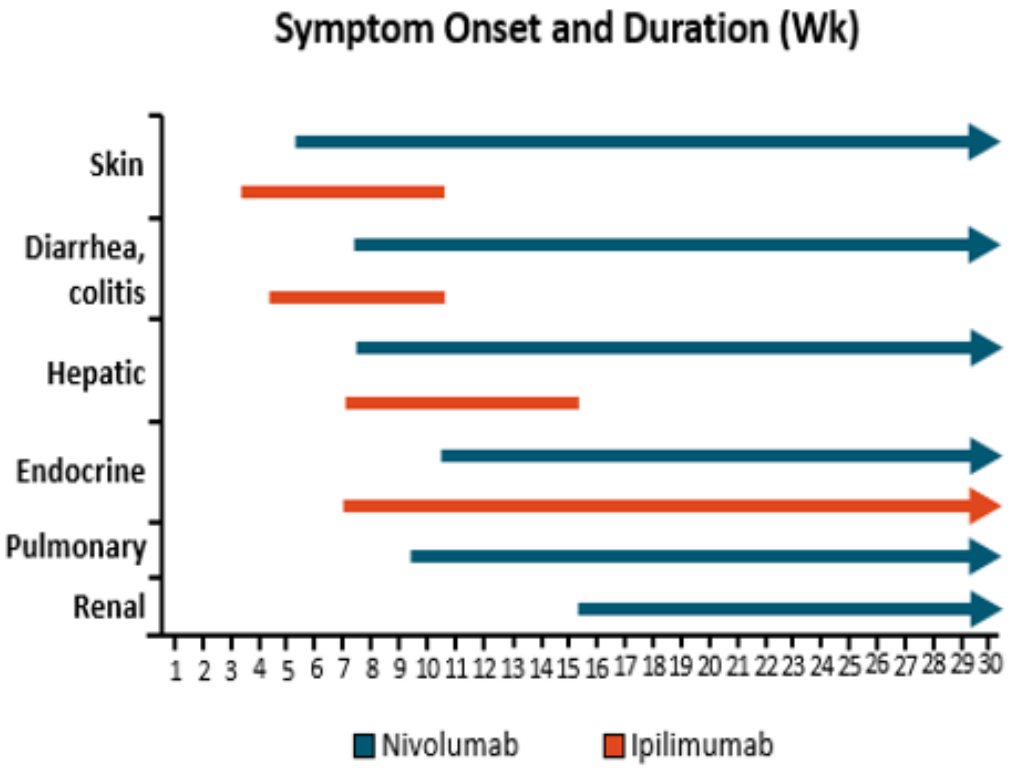
Setting Expectations:
Monitoring & Management of ICI Therapy

ANY organ system can be impacted by immune checkpoint inhibitor (ICI) therapies

- T-cell activation can aggravate normal healthy tissue, creating inflammatory effects
- Some immune-related adverse events (irAEs) can be predictable and manageable, especially if identified and treated early
- Unreported and unmanaged irAEs could have potentially life-threatening consequences
- Education at the start of therapy and ongoing at every time point of contact is essential

Woods, L., et.al. Immune Checkpoint Inhibitors, Side Effects, Immunotherapy, Patient Education. CJON 2019, 23(3), 271-280.

irAE Kinetics: Onset, Duration, & Severity



Onset

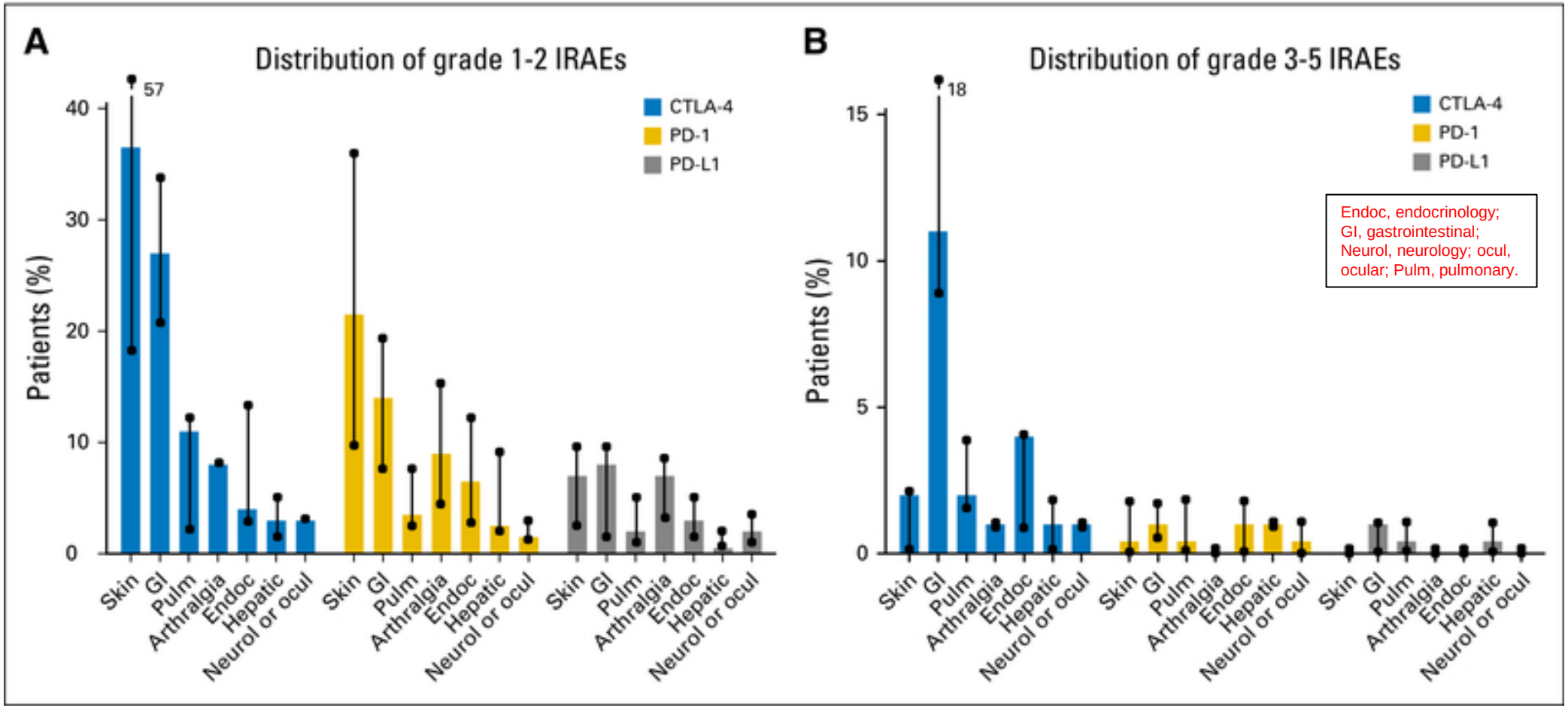
- Median onset is 5-12 wk after initiation of ICI therapy
  - Within days of first dose
  - After month of treatment
  - After discontinuation of therapy

Severity

- Incidence/severity higher with combination ICI therapies especially those with anti–CTLA-4 agents
  - High-grade AE with 1 ICI class does not negate safe administration with another ICI class

Madden KM, et al. *Clin J Oncol Nurs*. 2017;21(4 suppl):30. Davies M, et al. *Immunotargets Ther.* 2017;6:51. Puzanov I, et al. *J Immunother Cancer*. 2017;5(1):95. Martins F, et al. *Nat Rev Clin Oncol*. 2019;16(9):563.

Distribution of irAEs Based on Grade With CTLA-4 & PD-1



Distribution of (A) grade 1-2 and (B) grade 3-5 irAEs for all tumor types in the main clinical trials with anti–CTLA-4, PD-1, or anti–PD-L1 antibodies as single therapies. The values quoted are the median (range) irAE rates for the set of clinical trials as a whole.

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

General Principles for Managing Immunotherapy irAEs

- Educate patients about potential toxicities and to contact treating team immediately
  - Advise patient to inform their other health care professionals that they are receiving immunotherapy
- Beginning of each cycle: Assess labs, physical exam, and review of potential irAEs
- Thyroid tests every cycle for first 3 months, then every 2-3 cycles (may be done with every treatment)
- Maintain low threshold for steroids or immunosuppression if irAE is persistent, impacting QOL or evolving

Grade	Management
1 (mild)	• Symptomatic management • Continue therapy • Immunosuppression not needed
2 (mild to moderate)	• Symptomatic management • Consider discontinuing until resolution to grade 1 • Consider immunosuppression if intolerable or persistent • Involve consultants as needed
3 or 4 (severe)	• Discontinue therapy • Start immunosuppression • Refer/involve consultants • At resolution, gradually taper off immunosuppression

Educate patients to recognize potential toxicities and to contact the treating office providers if / when they occur

ASCO guideline update: Schneider BJ, et al. *J Clin Oncol*. 2021;39(36):4073.

Dermatologic irAEs

Onset of adverse event

- ~Day 1 to 25 months; posttreatment

Grade 1 (mild) CTCAE Guidelines

- Covers <10% of body surface area (BSA)

Grade 2 (moderate)

- 10-30% of BSA

Grade 3-4 (severe/life threatening)

- Covers >30% of BSA
- Life-threatening consequences—potentially

Kottschade L, et al. *Melanoma Res.* 2016;26(5):469. Davies M. *Cancer Manag Res*. 2014;6:63-75. NCCN Guidelines. Management of Immune Checkpoint Inhibitor-Related Toxicities. v1.2022. Common Terminology Criteria for Adverse Events (CTCAE Version 5.0. November 27, 2017.

Evaluation & Management of Dermatologic irAEs

Signs/Symptoms	Evaluation	Management
Rash, pruritus, hair/skin depigmentation, oral ulcerations **SEVERE:** skin peeling, blisters	Rule out other causes: • Cellulitis, contact dermatitis, sun exposure/burn If symptoms persist >1-2 weeks or recur: • Consider dermatology consultation/possible skin biopsy	• Mild-to-moderate dermatitis manage symptomatically with: – Topical steroids, anti-itch creams (Sarna, oral antihistamines) • Persistent rash >1 week or if interferes with activities of daily living: – Start moderate-potency steroid cream (triamcinolone 0.1%) – Or moderate dose of steroids at 0.5 mg/kg/day prednisone – Itching antihistamines (H1, H2) – Hydroxyzine, gabapentinoid for itching *If serious desquamation, discontinue treatment and use higher-dose steroids 1-2 mg/kg and admit to hospital.*

NCCN Guidelines. Immune Checkpoint Inhibitor-Related Toxicities . v1.2022. Kottschade L, et al.. *Melanoma Res*. 2016;26(5):469-480. Schneider BJ, et al. *J Clin Oncol*. 2021;39(36):4073. Davies M. *Cancer Manag Res.* 2014;6:63-75.

Gastrointestinal irAEs

Onset of adverse event: diarrhea (liquid stool) and colitis

- 3 days to 10 weeks; after several months
- Combo therapy = earlier onset

Grade 1 (mild)

- <4 stools/day over baseline; asymptomatic

Grade 2 (moderate)

- 4-6 stools/day over baseline; IV fluids indicated <24 h;
- **Colitis**: With abdominal pain, blood in stool; no interference with activities of daily living (ADLs)

Grade 3 (severe)

- ≥7 stools/day over baseline; IV fluids 24 h; interferes with ADLs
- **Colitis**: Severe abdominal pain, peritoneal signs

Grade 4 (potentially life-threatening)

Life-threatening; perforation if left untreated

NCCN Guidelines. Management of Immune Checkpoint Inhibitor-Related Toxicities. v1.2022.
CTCAE. Version 5.0. November 27, 2017.

Assessment & Management of GI irAEs

Symptoms/Signs	Evaluation	Management
Increased gas, bloating, cramps, decrease in appetite, change in quality or frequency of stools, blood in stool, pain	• Change in bowel frequency vs baseline • Assess quality and characteristic of stool • Assess for liquid diarrhea +/– abdominal pain, mucus or blood in stool • Stool cultures (r/o infection) • Stool WBCs (r/o inflammation) • r/o pancreatitis—draw amylase and lipase **SEVERE** symptoms: • Abdominal ultrasound or CT scan (r/o colitis/perforation) • Endoscopy/colonoscopy (+biopsy) • Gastroenterology consult	• **Grade 1:** Continue treatment, supportive care • **Grade 2:** Withhold treatment until grade 1; discontinue if recurrent; if lasting >5 days, initiate steroids (methylprednisolone 0.5-1.0 mg/kg/day or oral equivalent) + supportive care • **Grade 3:** Withhold treatment until grade 1; supportive measures + steroids 1-2 mg/kg/day • **Grade 4:** Permanent discontinuation • IV steroids 2 mg/kg, slow taper over ~1 month, followed by oral steroid taper • Supportive care includes: – Hydration – Dietary modifications (low fiber/low residue) – Anti-emetics – Anti-diarrheal (loperamide; diphenoxylate/atropine) – Antispasmodics (dicyclomine hydrochloride) – Bulking agents (cholestyramine) **Non-responsive to steroid therapy (refractory)** • Infliximab 5 mg/kg (IV) q2 weeks apart

r/o, rule out; WBCs, white blood cells.

Kottschade L, et al. *Melanoma Res*. 2016;26(5):469-480. Davies M. *Cancer Manag Res.* 2014;6:63-75. Fecher, LA, Agarwala SS, Hodi FS, Weber JS. Ipilimumab and its toxicities: a multi-disciplinary approach. *Oncologist.* 2013;18(16):733-743. NCCN Guidelines. Management of Immune Checkpoint Inhibitor-Related Toxicities. v1.2022. Schneider BJ, et al. *J Clin Oncol*. 2021;39(36):4073.

Less Common irAEs: Presenting Signs & Symptoms

Less Common immune-related adverse event	Typical Presentation
Pneumonitis	Dyspnea, dry cough, fever, chest pain
Renal	Elevated serum creatinine, azotemia, inability to maintain acid-base or electrolyte balance, urine output change, edema
Ocular	Vision changes, photophobia, tenderness/pain, eyelid swelling, proptosis, red/purple discoloration, eye redness
Neurologic	Progressive or fluctuating muscle weakness, usually proximal to distal; absent/reduced deep tendon reflexes; sensory-motor deficit; headache, photophobia, neck stiffness with nausea/vomiting; confusion, altered behavior, seizures, short-term memory loss, depressed level of consciousness; focal weakness; speech abnormality
Cardiovascular	Generalized malaise and fatigue, dyspnea, edema, chest pain, decreased ejection fraction on echocardiogram
Musculoskeletal	Joint pain, swelling; inflammatory symptoms; stiffness after inactivity; myalgias; myositis

Spiers L, et al. *Rheumatology (Oxford)*. 2019;58(suppl 7):vii7. ; Schneider BJ, et al. *J Clin Oncol*. 2021;39(36):4073.; Brumbaugh AD, et al. *Cardiol Rev*. 2019;27(2):97.

Pulmonary irAEs

Onset of symptoms

- 2 days through duration of treatment

Grade 1 (mild)

- Radiographic changes only

Grade 2 (moderate)

- Mild-to-moderate symptoms, limiting ADLs
- Worsens from baseline

Grade 3-4 (severe/potentially life-threatening)

- Severe symptoms
- New/worsening hypoxia, oxygen support—a necessity
- Life-threatening

NCCN Guidelines Immune Checkpoint Inhibitor-Related Toxicities . v1.2022 . CTCAE. Version 5.0. November 27, 2017.
Kottschade L, et al. *Melanoma Res.* 2016;26(5):469. Schneider BJ, et al. *J Clin Oncol*. 2021;39(36):4073.
Davies M. *Cancer Manag Res*. 2014;6:63

Assessment & Management of Pulmonary irAEs

Symptoms/Signs	Evaluation	Management
• Dyspnea, cough, wheezing; hypoxia • Chest pain • Radiographic changes	• Oxygen saturation at rest and with ambulation • **Grade 1:** Monitor every 2-3 days • **Grade 2-4:** Daily monitoring • Pulmonary and infectious disease consult • CT scan • Bronchoscopy with biopsy	• **Grade 1:** Consider withholding treatment • **Grade 2:** Withhold treatment; steroid 1-2 mg/kg/day prednisone equivalent – Baseline supportive O2 may need adjusting • **Grade 3-4:** 2-4 mg/kg/day prednisone equivalent – Oxygen support – Albuterol nebulizer – IV/oral steroid – Slow steroid taper ~1 month • Antimicrobial prophylaxis

Kottschade L, et al.. *Melanoma Res*. 2016;26(5):469-480. Davies M. *Cancer Manag Res.* 2014;6:63-75. Schneider BJ, et al. *J Clin Oncol*. 2021;39(36):4073.

Hepatic irAEs

Onset of adverse event

- 9 days to months

Grade 1 (mild)

- AST/ALT >ULN to 3x ULN and/or total bilirubin >ULN to 1.5x ULN

Grade 2 (moderate)

- AST/ALT >3x-5x ULN and/or total bilirubin >1.5x-3x ULN

Grade 3-4 (severe/potentially life-threatening)

- Grade 3: AST/ALT >5x-20x ULN, total bilirubin >10x ULN
- Grade 4: AST/ALT >5x-20x ULN and/or total bilirubin >3x ULN

Kottschade L, et al. *Melanoma Res.* 2016;26(5):469. Davies M. *Cancer Manag Res*. 2014;6:63. CTCAE. Version 5.0. November 27, 2017. Management of Immune Checkpoint Inhibitor-Related Toxicities

Assessment & Management of Hepatic irAEs

Symptoms/Signs	Evaluation	Management
Nausea, anorexia, vague abdominal discomfort, right upper quadrant (RUQ) pain, dehydration, jaundice, bleeding, bruising, dark urine	• Liver enzymes (AST, ALT, ALK, total and direct bilirubin) every 3 days • r/o infectious hepatitis • Liver ultrasound • GI/hepatology consult	Hold hepatic toxic drugs • **Grade 1:** Continue treatment • **Grade 2:** Withhold treatment; start 0.5-1 mg/kg/day prednisone equivalent – Return to grade 1; resume treatment • **Grade 3-4:** Permanently discontinue treatment – 1-2 mg/kg/day prednisone – IV/oral steroid – Mycophenolate mofetil 500-1000 mg bid – Taper both immunosuppressives slowly

NCCN Guidelines. Management of Immune Checkpoint Inhibitor-Related Toxicities. v1.2022.
Kottschade L, et al. *Melanoma Res.* 2016;26(5):469. Davies M. *Cancer Manag Res*. 2014;6:63. Schneider BJ, et al. *J Clin Oncol*. 2021;39(36):4073.

Assessment & Management of Endocrine irAEs

Condition	Symptoms/Signs (Onset: 4-20+ weeks)	Evaluation	Treatment
Hyperthyroidism	Palpitations, weight loss, nervousness, irritability, diarrhea, feeling hot	Thyroid-stimulating hormone (TSH), triiodothyronine, thyroxin	Symptomatic treatment: Beta-blockers
Hypothyroidism	Weight gain, fatigue, dry skin, constipation, feeling cold	Thyroid panel (TSH, T4, T3)	Levothyroxine repletion 1.6 mg/kg/day Adjust dose to maintain free T4 in mid-range
Hypophysitis	Visual disturbances, fatigue, headaches, weakness, confusion, hallucinations, memory loss, labile mood, insomnia, anorexia	**Hormone levels:** ACTH, FSH, LH, prolactin, ADH, oxytocin, testosterone; r/o sepsis **Endocrinology consult;** MRI of brain (thin cuts) w/focus on pituitary gland, r/o brain metastases Risk for progression to adrenal insufficiency/crisis	Stress dose IV steroids with mineralocorticoid if adrenal crisis Hormone replacement (hydrocortisone)
Adrenalitis	Fatigue, malaise, hypotension, vague GI symptoms, weight loss, hypoglycemia, fainting Adrenal insufficiency Adrenal crisis	Morning cortisol, ACTH, cosyntropin stimulation test (CST); aldosterone AM cortisol <3 mcg/dL: adrenal insufficiency Primary: Low cortisol, **high** ACTH (primary adrenal) Secondary: Low cortisol, **low** ACTH (pituitary disease) Endocrinology consult	May require lifetime replacement—hydrocortisone Stress dosing requirements Dexamethasone (not measured in cortisol assays) Isotonic saline for sodium repletion

NCCN Guidelines. Management of Immune Checkpoint Inhibitor-Related Toxicities. v1.2022. Schneider B, et al. *J Clin Oncol*. 2021;30(36):4073. Fecher LA, et al. *Oncologist.* 2013;18(6):733. Corsello SM, et al. *J Clin Endocrinol Metab*. 2013;98(4):1361. Kottschade L, et al. *Melanoma Res.* 2016;26(5):469.

Steroid Therapy Considerations

Take medication and taper as directed

- Rapid taper may result in rebound flare of symptoms

Use an H2 blocker or a proton pump inhibitor daily

Management of severe irAEs

- Taper slowly over ~4 weeks (rapid taper may cause rebound flare)
- Consider reducing prednisone by 10 mg every 3-5 days

Prolonged use

- Consider anti-infective prophylaxis for *Pneumocystis jirovec*i pneumonia (PJP), viral and fungal infections
- Trimethoprim/sulfamethoxazole M/W/F (or suitable alternative if sulfa allergy) +/- fluconazole +/- famciclovir or acyclovir/valacyclovir
- Monitor blood sugars

NCCN Guidelines. Management of Immune Checkpoint Inhibitor-Related Toxicities. v1.2022.

Additional Management Considerations

Steroid Therapy	Potential Management Considerations
Steroid Refractory	**No response or worsening symptoms on steroids** • Additional immunosuppressant treatment may be needed - Infliximab 5 mg/kg—may repeat every 4 weeks (GI/enterocolitis) - Mycophenolate mofetil 1 g bid (hepatic) - Cyclosporine or IV immunoglobulin, rituximab (neuro) - Methotrexate, tocilizumab (rheum or derm) • DO NOT discontinue steroids; continue and taper when symptoms respond • Collaborate with organ specialists
Supportive Measures	**High dose or prolonged use >4 weeks +/- additional suppressant therapy** • Consider prophylaxis with antimicrobial/antifungal/antiviral to prevent opportunistic infections (Pneumocystis jiroveci pneumonia, shingles, Candida) • Collaborate with specialists for long-term/permanent organ dysfunction

Schneider B, et al. *J Clin Oncol*. 2021;30(36):4073 .NCCN Guidelines. Management of Immune Checkpoint Inhibitor-Related Toxicities. v1.2022.
Brahmer, J. et al. 2018 Jun 10;36(17):1714-1768. .

FDA-Approved BRAF + MEK Inhibitor Regimens: Most Common Toxicities

All Grade/ Grade ≥3 Adverse Events, %	COMBI-D[1] Dabrafenib Trametinib	COMBI-V[2] Dabrafenib Trametinib	co-BRIM[3] Vemurafenib Cobimetinib	COLUMBUS[4] Encorafenib Binimetinib
Pyrexia	63/5	53/4	26/2	20/4
Photosensitivity	--	4/0	28/2	4/0.5
Nausea	40/1	35/< 1	40/1	44/2
Arthralgia	28/1	24/1	32/2	29/1
Increased Alanine aminotransferase	15/4	--	23/11	13/6[5]
Hyperkeratosis	6/0	4/0	10/0	15/0.5
Hand–foot syndrome	6/<1	4/0	--	17/0
Cutaneous Squamous cell	3/3	1/1	2/2	4/0
Decreased ejection fraction	4/1	8/4	8/1	8/2

1. Long GV, et al. *N Engl J Med*. 2017;377(19):1813. 2. Robert C, et al. *N Engl J Med*. 2015;372(1):30. 3. Larkin. *N Engl J Med*. 2014;371(20):1867.
4. Ascierto PA, et al. *Eur J Cancer*. 2020;126:33

BRAF Inhibitor Adverse Event Management

Dermatologic

Skin exam at baseline and every 2 mo while receiving therapy
Cutaneous squamous cell ca is the most common

- Does not require dose reduction

Photosensitivity

- No sun exposure; use protection (avoidance, sunscreen, hat, sun protective clothing)

Ocular

Ask about visual symptoms at each clinic visit

Steroid eye drops for uveitis

Referral for ophthalmology evaluation

Cardiac

ECG at baseline

- Monthly for 3 mo, then every 3 mo

Hold for QTc >500 ms or ≥60 ms above baseline (grade 3)

Restart at a reduced dose if QTc decreases to grade 2

Hepatic

Monthly liver function tests

- Hold for grade 3 liver function test and reduce dose when grade ≤2

General

Nausea

- Use antiemetics

Pyrexia

- Use ibuprofen, acetaminophen, steroids

Arthralgia/myalgia

- Use nonsteroidal anti-inflammatory or opioids

Kottchade, L., Reed, ML. Clinical Journal of Oncology Nursing . 2017, Vol. 21 Issue 4, p87-96.; Czupryn,M. Cisneros, J. CJON 2017, 21(4), 11-29.

MEK Inhibitor Adverse Event Management

Ocular	Dermatologic	Hepatic	Heme	Cardiac	GI
Permanently discontinue therapy for patients with retinal vein occlusion Perform ophthalmologic exams any time a patient reports visual disturbances Reduce dose for toxicities that resolve or improve	Dermatologic exam prior to starting therapy and every 2 mo until 6 mo after discontinuation of therapy For grade 3 or 4 skin toxicity, hold drug for up to 3 wk; reduce dose if symptoms improve	Monitor liver function tests at baseline and at least monthly while receiving therapy Reduce dose for toxicity	Monitor complete blood cell count Discontinue for any hemorrhagic event	Assess LVEF prior to initiation of therapy 1 mo after starting therapy and then at 2- to 3-mo intervals during therapy Withhold treatment for up to 4 wk if absolute LVEF value decreases by 10% from pretreatment values and is less than the lower limit of normal	Diarrhea can be managed with antidiarrheal medications

Kottchade, L., Reed, ML. Clinical Journal of Oncology Nursing . 2017, Vol. 21 Issue 4, p87-96. Czupryn,M. Cisneros, J. CJON 2017, 21(4), 11-29.

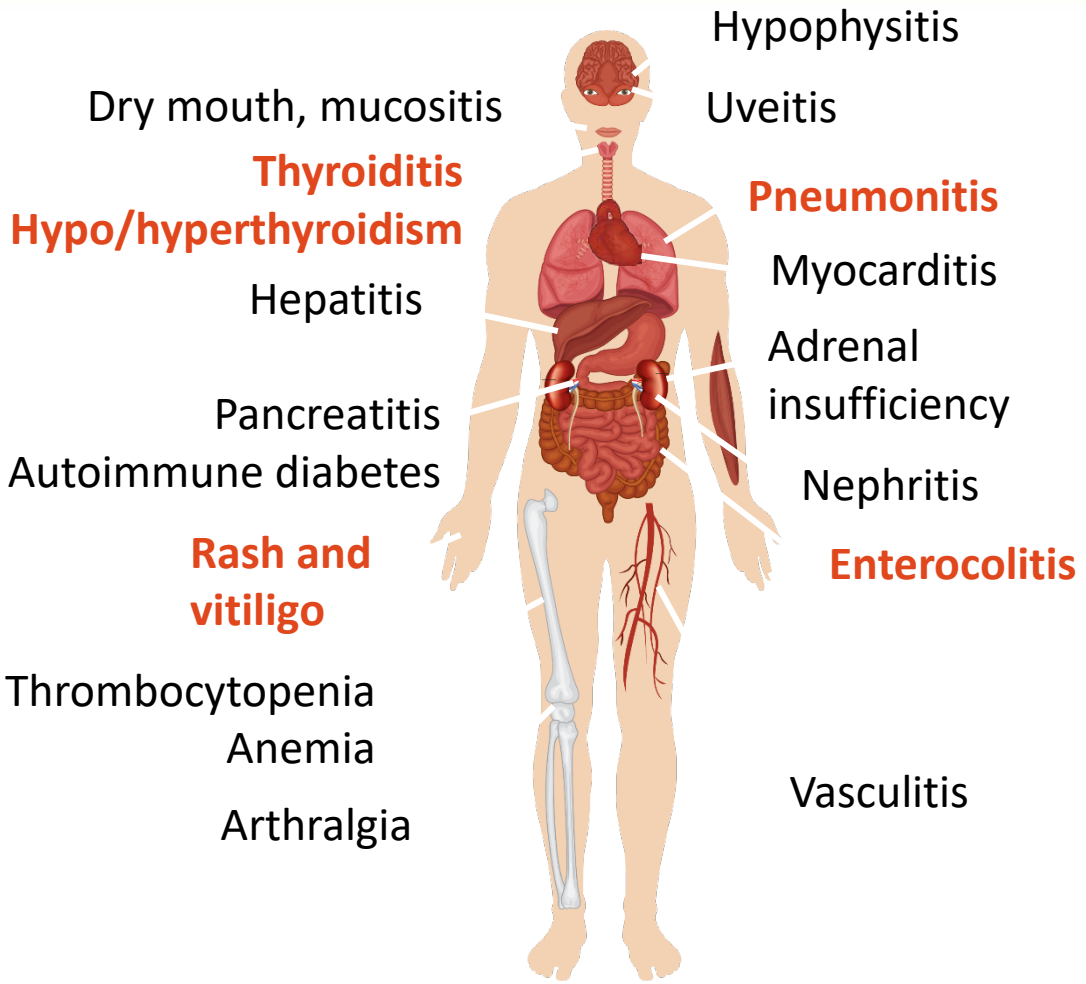
Patient Prep & Management on Checkpoint Inhibitors

- Thorough physical assessment and evaluation of adverse effects (baseline and at each office visit or point of contact)
- Assess patient's health literacy. Provide resources that meet patient's learning needs. Direct patients to reliable digital, print, video, or audio resources as needed
- Due to the unique kinetics, ICI education is reliant on the patients understanding and skill to interpret a change and report those changes **<u>at the onset</u>**
- Symptom check list for patient reference
- Discuss patient treatment, personal goals, and expectations
- Discuss potential reproductive issues and initiate referrals as appropriate

Woods, L., et.al. CJON 2019, 23(3), 271-280

Patient Education: Immunotherapy

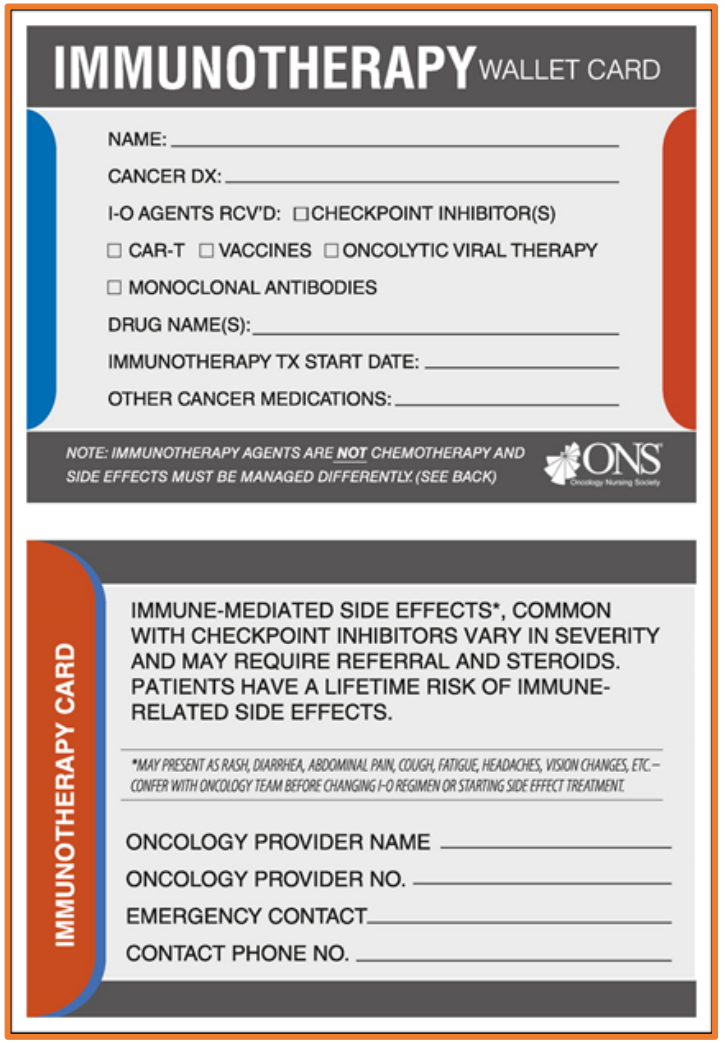
- **Immunotherapy (immune checkpoints):** stimulation of immune system to “see” tumors and attack; inflammation can occur head to toe; response tends to take longer
- Adverse events: Fatigue, rash, itching, nausea, diarrhea, lab abnormalities; any part of the body can be impacted
- Adverse events can occur with first infusion or months & up to 2 years after cessation of therapy; patients should report adverse events even after therapy is stopped.



Darnell EP, et al. *Curr Oncol Rep*. 2020;22(4):39. Michot JM, et al. *Eur J Cancer*. 2016;54:139.

Patient Education: General

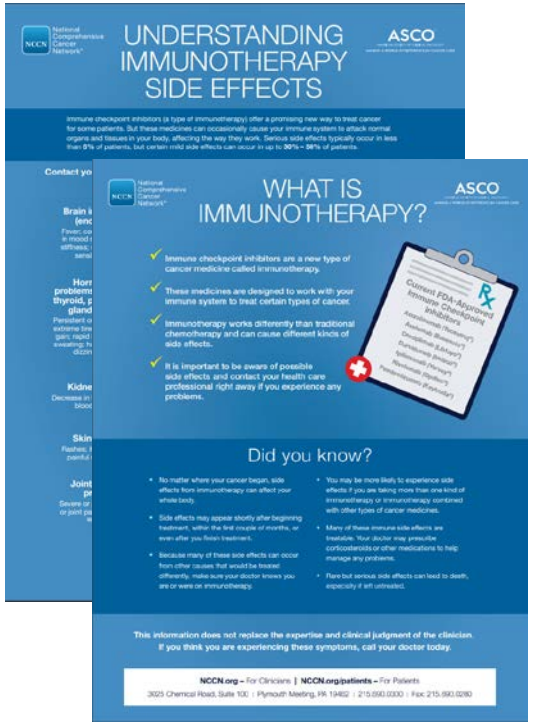
- Educational sessions
  - Review specific mechanisms of selected treatment
  - Pretreatment and at each office visit/encounter
  - Provide & explain wallet cards and education sheets
- Assess patients' ability to communicate symptoms
  - Language barrier
  - Access to phone/computer
- Provide a calendar or treatment schedule
  - Follow-up visits
  - Important time points
- Encourage patients to keep a treatment diary
- Provide culturally competent education

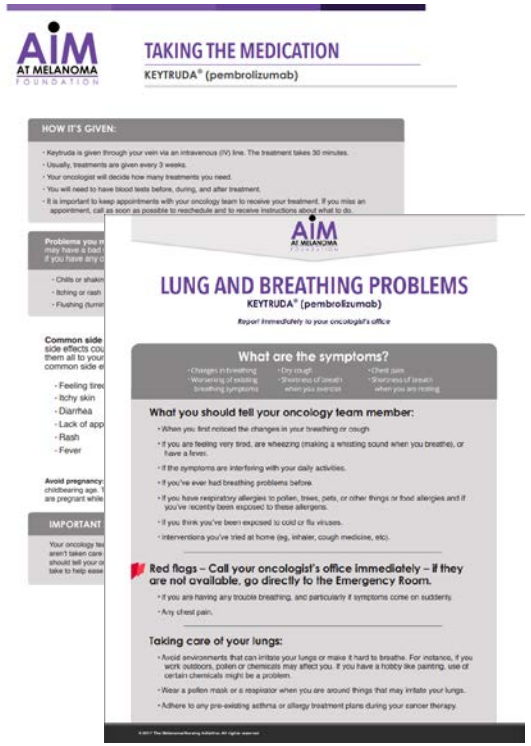


Woods, L., et.al. CJON 2019, 23(3), 271-280. Oncology Nursing Society. www.ONS.org

Patient Resources

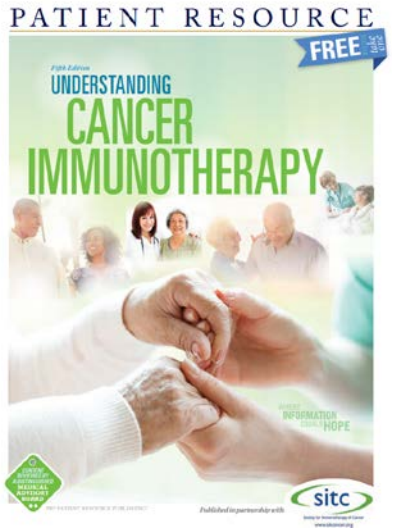
ASCO:
www.cancer.net/about-us/asco-answers-patient-education-materials



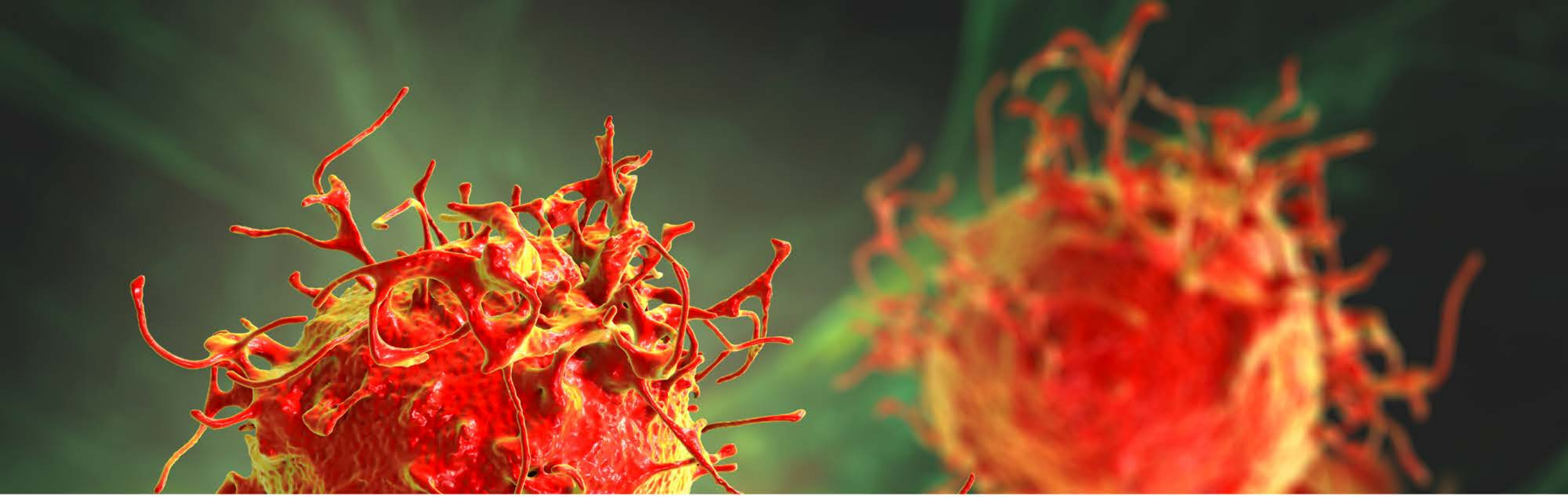


aimwithimmunotherapy.org/patient-action-plans/

American Cancer Society:
www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/what-is-immunotherapy.html

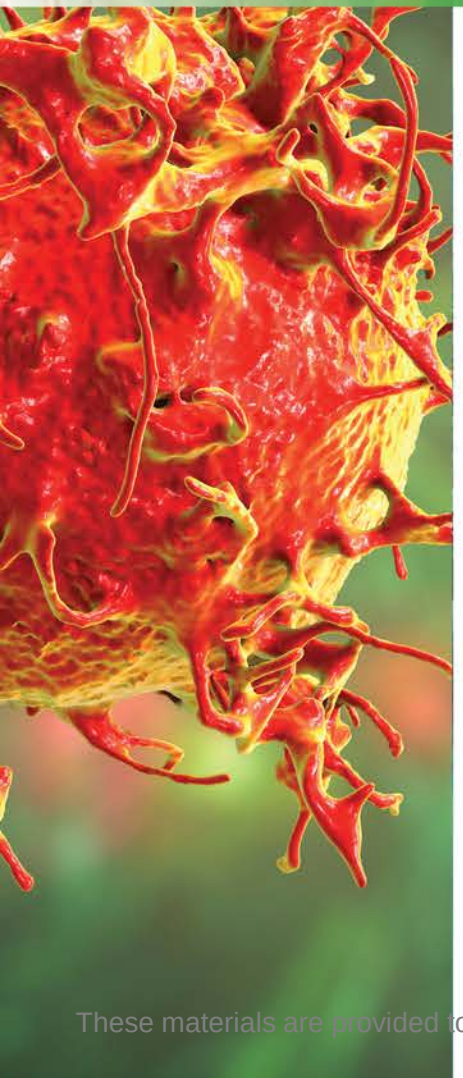


sitcancer.org/connectedold/p/patient



Faculty and Case Discussion

Patient Case: Flori



- Flori is a healthy, active 41-year-old woman of middle eastern descent. She is married, a homemaker, and fulltime mom to 3 children attending primary school
- 12/2020: Flori developed the worst headache of her life, accompanied by nausea and vomiting, followed by ataxia and weakness
- She was rushed to her local ER. CT imaging scan revealed several scattered tumors including a 2.5 cm hemorrhagic lesion in her cerebellum, which was resected during her admission. Several margins were positive, and she was referred for a radiosurgery consult
- Gamma knife (GK) radiosurgery was performed to surgical bed and 5 other smaller tumors
- **Confirmatory diagnosis of metastatic melanoma, V600E mutated tumor**
- Further workup did not reveal any extracranial disease. Flori has unknown primary stage IV metastatic disease to the CNS
- Consulted with Medical Oncology

Patient Case: Flori (Q1)

Based on Flori's recent surgical resection and diagnosis of metastatic melanoma to CNS, BRAF V600E+ mutation, she continues to have migraine headaches, dizziness and weakness in her left lower extremity, She has not received any relief since having GK 2 weeks prior. Performance status ECOG 1, LDH 324 U/L.

Given Flori's current symptoms, performance status, and LDH—what treatment option would you recommend next, if any?

A. No further treatment because the surgery and GK radiation are effective enough therapy
B. Chemotherapy, as this is a mainstay in the care of oncology patients and has the most historic data compared to newer therapies
C. Start olaparib for her BRCA+ mutation
D. Nivolumab 1 mg/kg + ipilimumab 3 mg/kg induction IV every 3 weeks x 4 infusions, followed by maintenance nivolumab 480 mg

Patient Case: Flori (Q2)

Flori tolerated nivolumab 1 mg/kg + ipilimumab 3 mg/kg induction x 4 cycles and 5 cycles of maintenance nivolumab 480 mg every 4 weeks. She then developed grade 2 GI toxicity with symptoms of nausea, anorexia, abdominal cramping, and semisoft-to-liquid diarrhea (8x per day). Steroids did not suppress the diarrhea, which increased to 12x per day. Infliximab was administered x 2 to control the GI symptoms. New imaging reveals 2 new brain metastases.

Given the immunotherapy data, which therapy would you recommend for Flori?

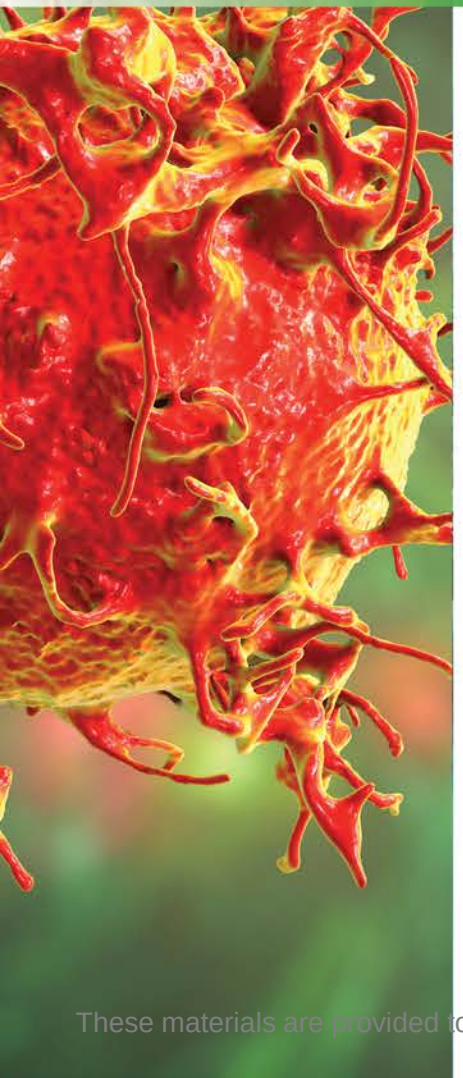
A. Nivolumab 240 mg IV monotherapy every 2 weeks

B. Refer for SRS and consider targeted *BRAF/MEK* oral therapy

C. Pembrolizumab 600 mg IV monotherapy every 6 weeks

D. Temozolomide 150 mg/m^2 oral daily + relatlimab 160 mg IV every 3 weeks

Faculty Discussion



- Considerations for next-line or salvage therapies in patients?
- Considerations for uveal or mucosal advanced melanomas?