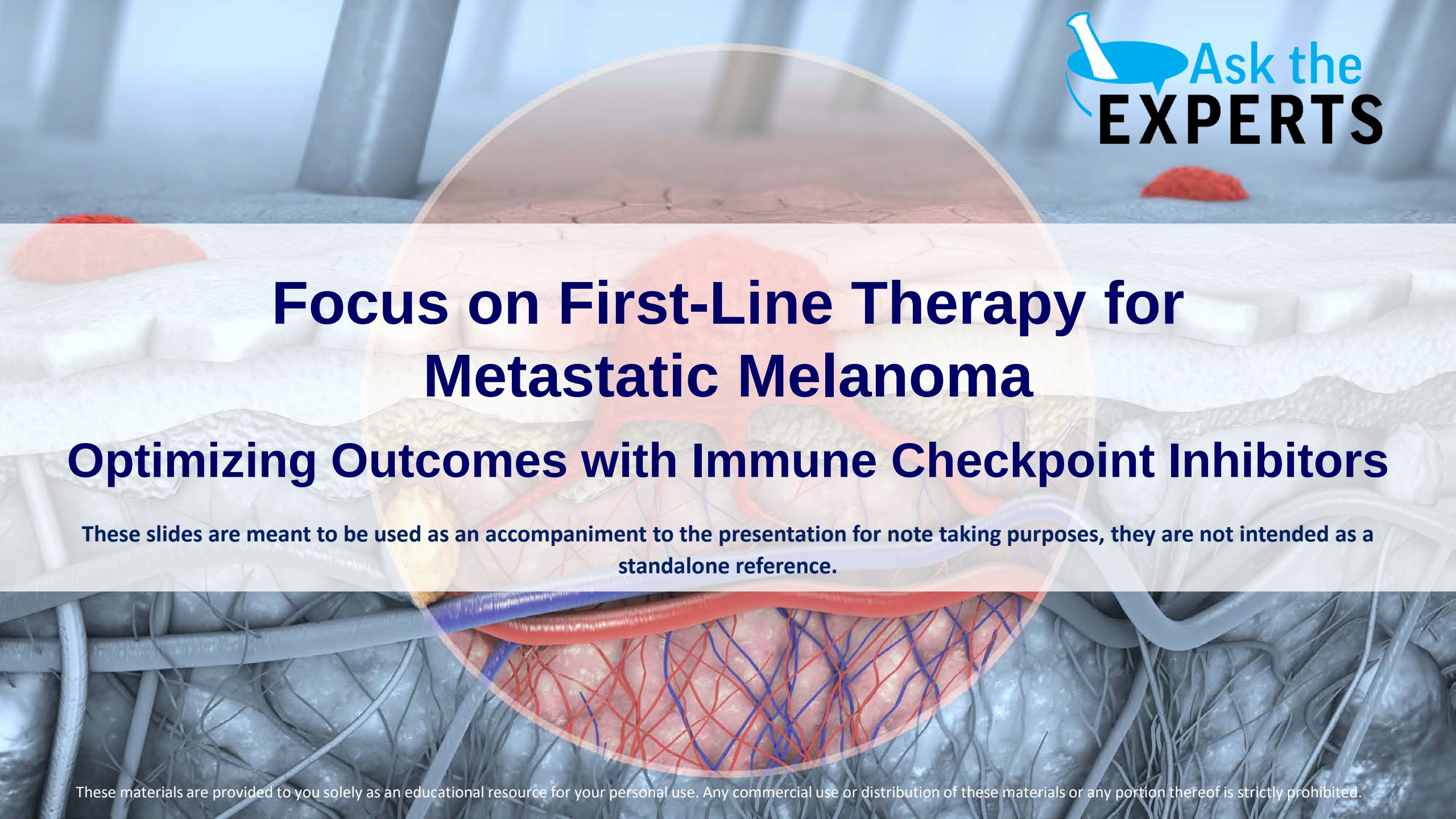
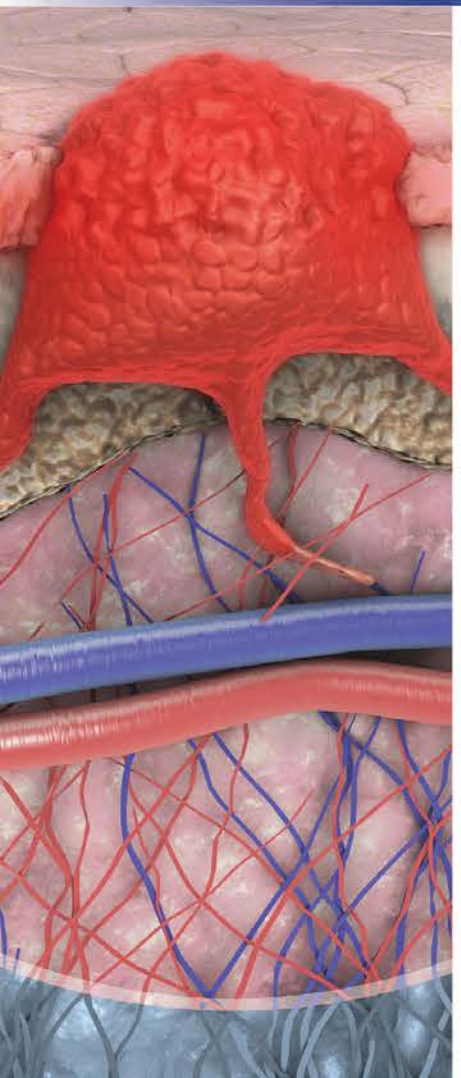


Focus on First-Line Therapy for Metastatic Melanoma

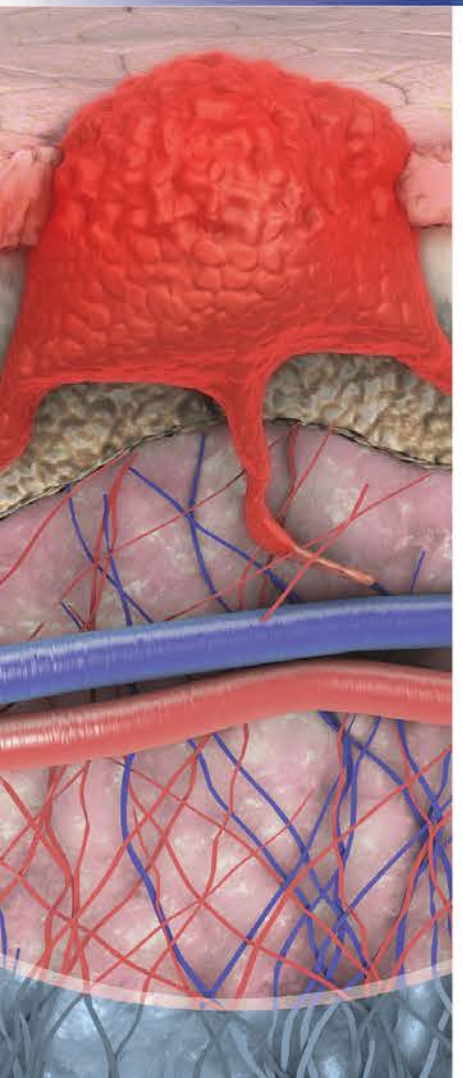
Optimizing Outcomes with Immune Checkpoint Inhibitors

These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.



This educational activity is sponsored by Postgraduate Healthcare Education, LLC and is supported by an educational grant from Bristol Myers Squibb.

Faculty



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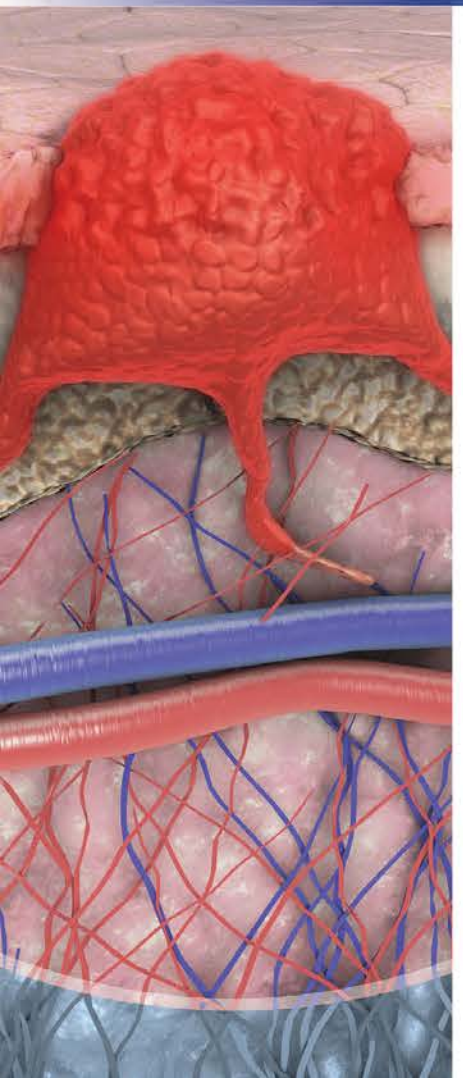
Dr. McPherson is an oncology clinical pharmacist in the ambulatory solid tumor clinics at Huntsman Cancer Institute at University of Utah Health in Salt Lake City, Utah. Dr. McPherson specializes in the treatment of skin cancer using immunotherapy and other targeted therapies. Dr. McPherson's research efforts are published in peer-reviewed journals, including the *Journal of Clinical Oncology*, *Journal for ImmunoTherapy of Cancer*, *JCO Clinical Cancer Informatics*, and *Pharmacotherapy*.

Disclosures



Dr. McPherson has disclosed that he has received grant/research support from Hitachi, LTD.

The clinical reviewer, **Megan May, PharmD, BCOP** has disclosed that she has no relevant affiliations or financial relationships with a commercial interest to disclose.

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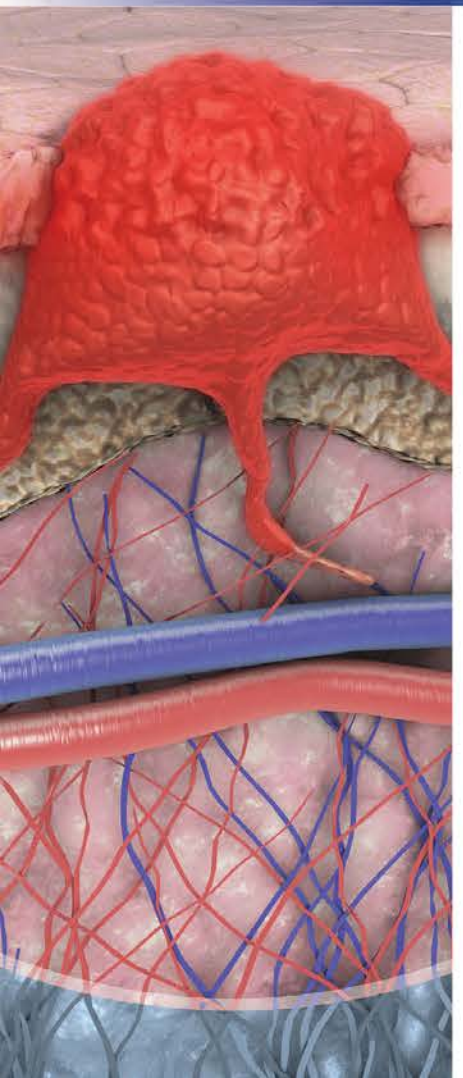

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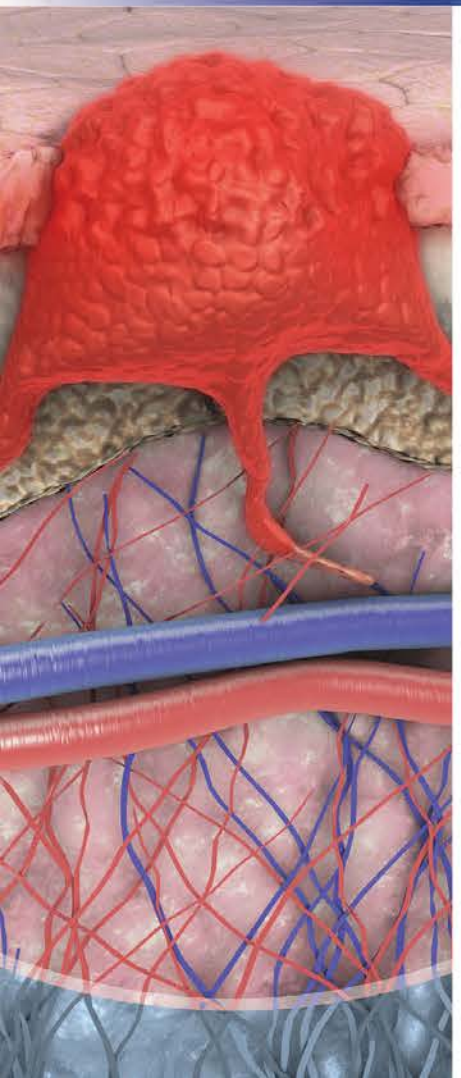
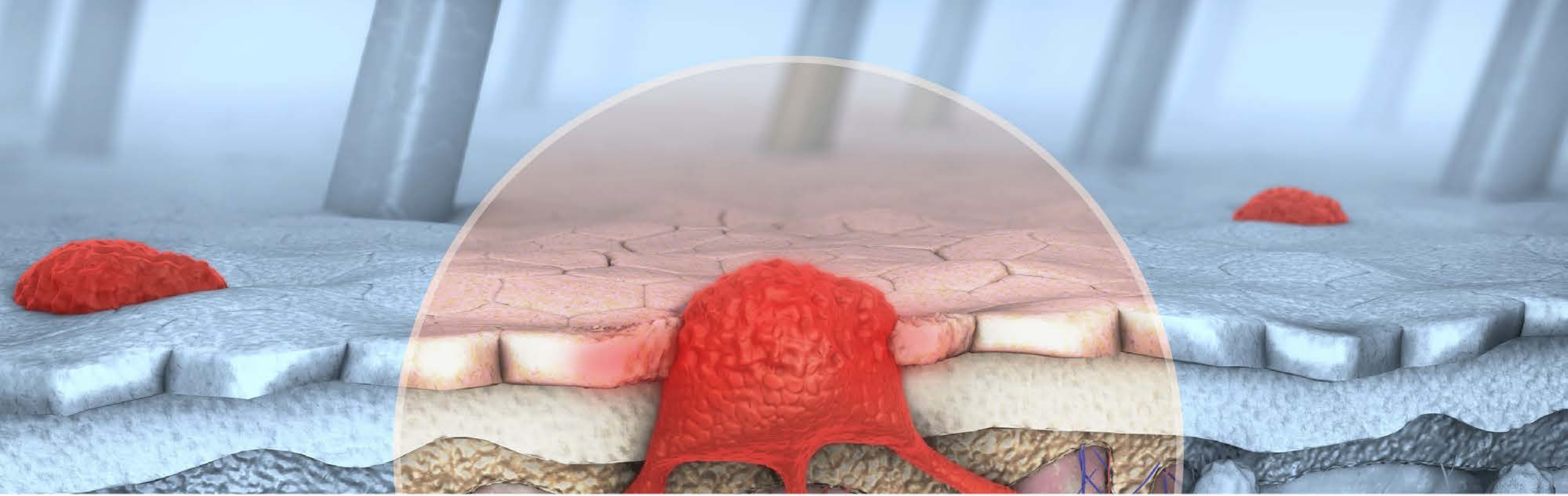
UAN: 0430-0000-23-023-H01-P
Credits: 1.5 hours (0.15 CEUs)
Type of Activity: Application

Learning Objectives



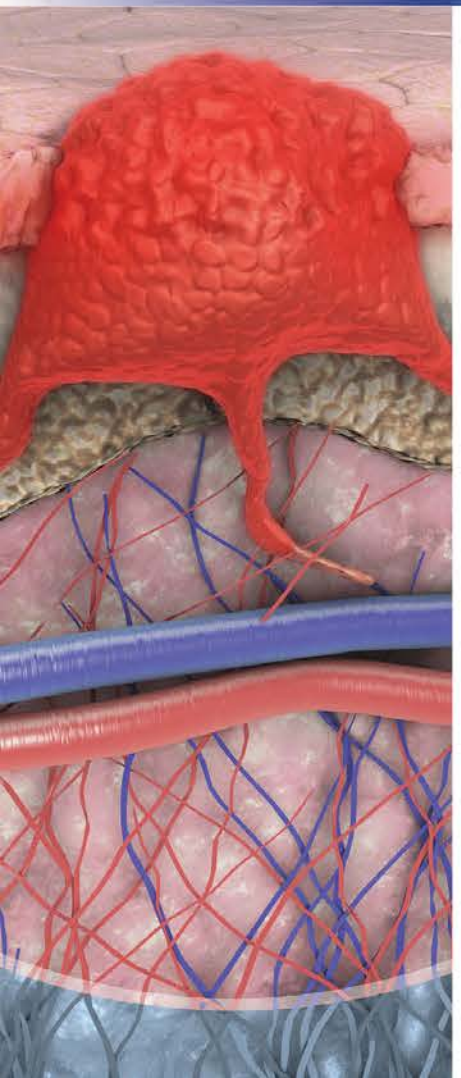
- **Identify** immune checkpoint inhibitor regimens approved for first-line treatment of metastatic melanoma
- **Discuss** factors that impact selection of first-line therapy for metastatic melanoma
- **Formulate** approaches for identifying and mitigating toxicities associated with immune checkpoint inhibitors to optimize treatment outcomes



Metastatic Melanoma

Disease Overview, Pivotal Trials, and Emerging Data

Melanoma: Overview



- **5th most common cancer in United States (US)**
- **1% of skin cancer, majority of deaths**
- **Age-related rise in melanoma rates**
  - **Women >50**: 1% ⬆ per year 2015-2019
  - **Men >50**: Rates stabilized
- **Types vary in frequency and prognosis**
  - **Better prognosis: Cutaneous**
    - Superficial spreading (70%)
  - **Worse prognosis**
    - Nodular (15%), acral (5-10%), mucosal (1% - rare), ocular/uveal (rare)

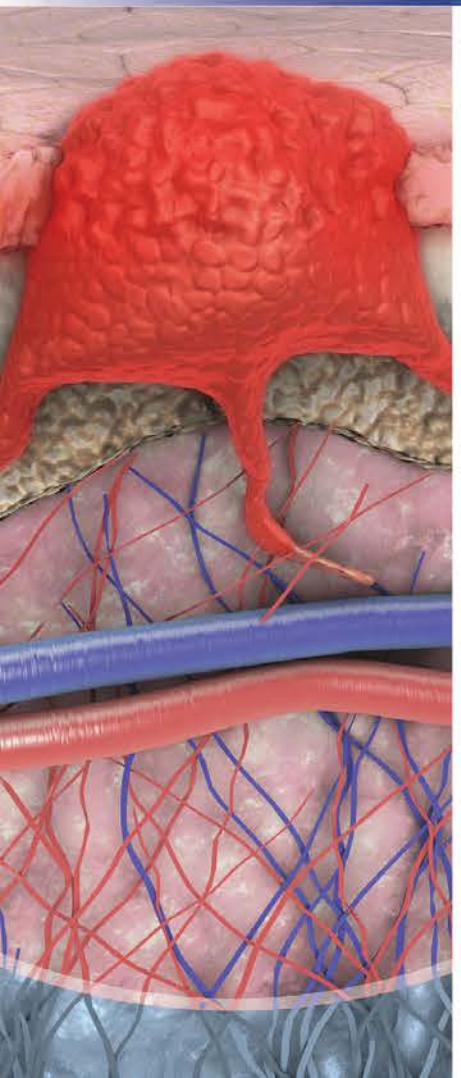
2023:

Estimated new cases: 97,610

Estimated deaths: 7,990
(3-5%↓/yr 2011-2020)

Siegel RL, et al. *CA Cancer J Clin*. 2023;73(1):17-48.; Tsao H, et al. *N Engl J Med*. 2004;351(10):998-1012.; Larkin J, et al. *N Engl J Med*. 2019;381(16):1535-1546.

Melanoma: Risk Factors



- **Male**
- **Age**
  - Age < 50 women, age > 50 men
- **White**
  - Fair skin, light hair/eyes, freckles
- **Dysplastic nevi**
- **Immune suppression / deficiency**
- **1st degree relative**
- **Sunburn/excess sun exposure**
  - > 4 painful burns < 15 y/o or tanning bed use

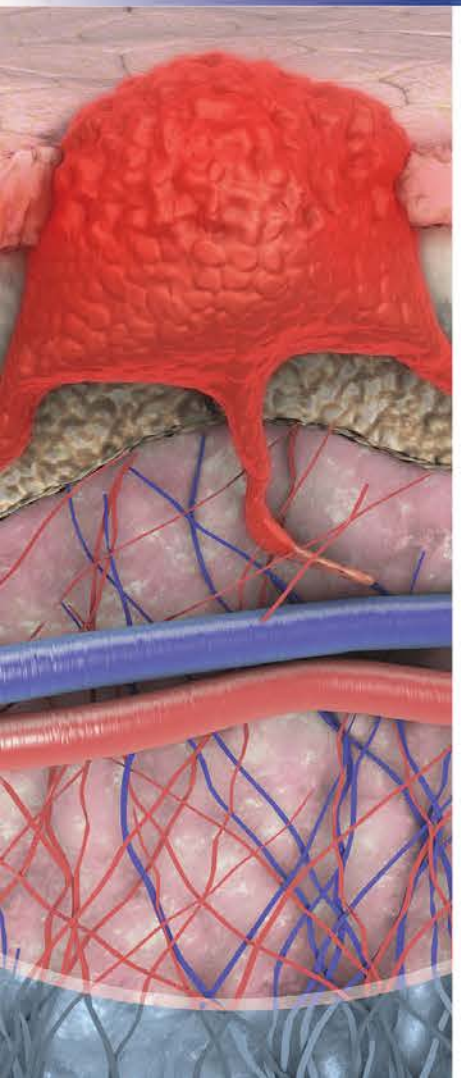
Prevention:

- NO tanning beds
- Avoid sunburn
- Seek shade 10 AM to 4 PM
- Wear protective clothing
- Use SPF ≥ 30 sunscreen (broad-spectrum, mineral-based)
- Examine skin monthly (ABCDE)

ABCDE, asymmetry border color diameter evolving; SPF, sun protection factor

Miller AJ, et al. *N Engl J Med*. 2006 Jul 6;355(1):51-65.; Photo credit: Unsplash.

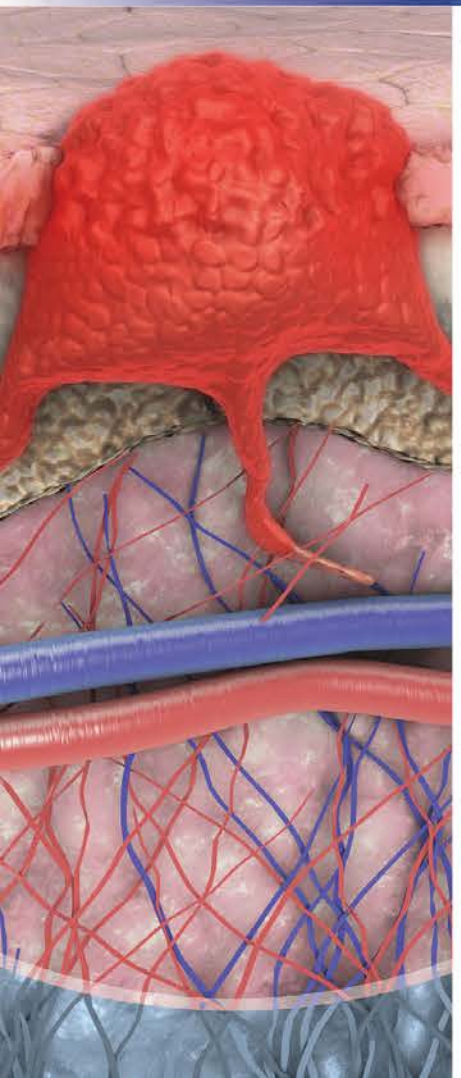
Metastatic Melanoma



- **Historically chemoresistant**
- **5-year relative survival for advanced melanoma**
  - 2004: 15%
  - 2011-2017: 30%
  - Recent landmark clinical trial updates: ≈50%
- **Therapeutic advances have driven survival improvement**
  - **Targeted therapies for *BRAF V600E and V600K* mutations**
    - BRAF + MEK blockade (dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib)
  - **Immune checkpoint inhibition results in durable responses**

Siegel RL, et al. *CA Cancer J Clin*. 2023;73(1):17-48.; Tsao H, et al. *N Engl J Med*. 2004;351(10):998-1012.; Larkin J, et al. *N Engl J Med*. 2019;381(16):1535-1546.

Metastatic Melanoma: Patient Presentation



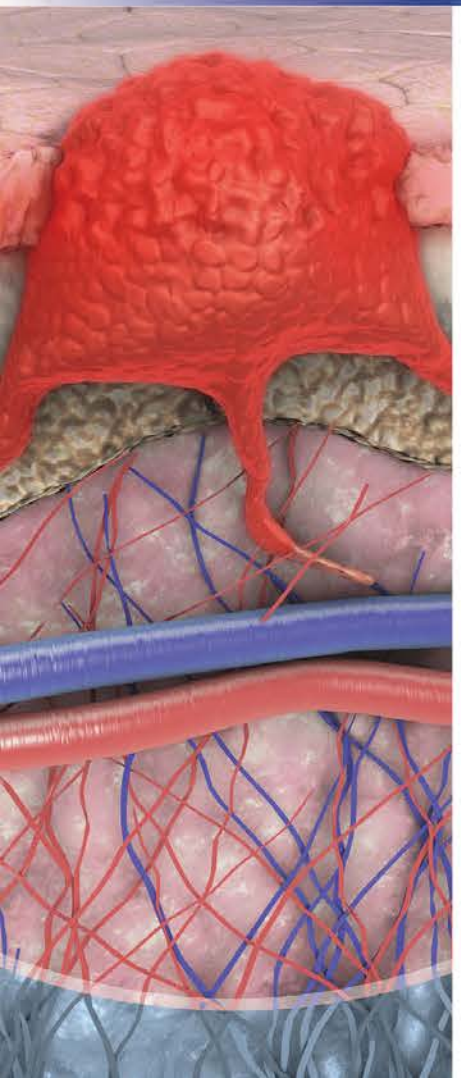
- **Early-stage melanomas are often asymptomatic**
  - Itching, bleeding, crusting of pigmented lesion (ABCDE)
- **Metastatic spread more likely identified by symptoms**
  - Seizures, headaches, vision changes, coughing, hemoptysis, dyspnea, changes in bowel habits, new back pain, systemic symptoms*
- **Elevated LDH surrogate for overall tumor burden**
  - Independent predictor of poor prognosis

* fevers, chills, night sweats, weight loss

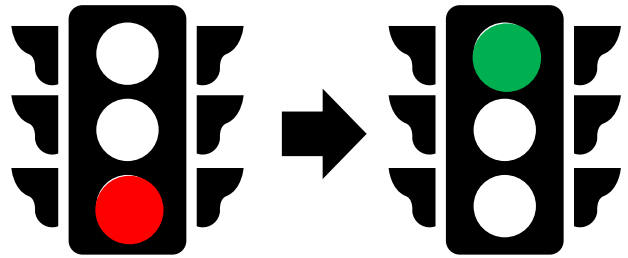
ABCDE, asymmetry border color diameter evolving; LDH, lactate dehydrogenase

Ward WH, et al. Clinical presentation and staging of melanoma. In: Ward WH, Farma JM, editors. Cutaneous Melanoma: Etiology and Therapy [Internet]. Brisbane (AU): Codon Publications; 2017 Dec 21. Chapter 6. Accessed May 3, 2023. https://www.ncbi.nlm.nih.gov/books/NBK481857/doi: 10.15586/codon.cutaneousmelanoma.2017.ch6

Immune Checkpoint Inhibitors (ICIs) for Metastatic Melanoma



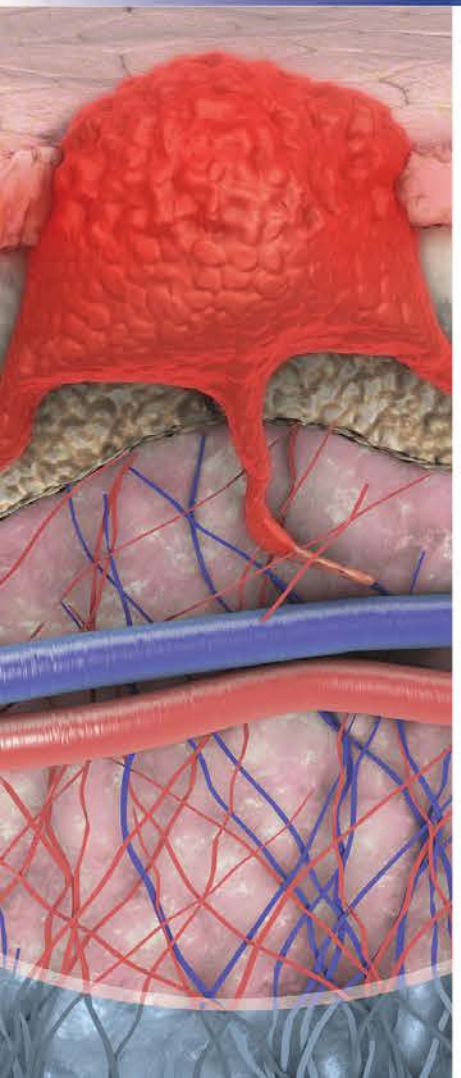
- **Melanoma has high somatic mutation burden**
  - Spontaneous regression fueled research into immune system
- **Immune checkpoints = natural brake systems**
  - CTLA-4 (ipilimumab)
  - PD-1 (nivolumab, pembrolizumab)
  - PD-L1 (atezolizumab)
  - LAG-3 (relatlimab)



- **Inhibition stimulates T-cell activation against cancer**
  - Can also trigger activation against healthy organs

CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; LAG-3, lymphocyte activation gene 3; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1
Robert C. *Nat Commun*. 2020;11(1):3801.; Tawbi HA, et al. *N Engl J Med*. 2022;386(1):24-34.; Ramos-Casals M, et al. *Nat Rev Dis Primer*. 2020;6(1):38.

First-line Treatment Regimens and Pivotal Clinical Trials



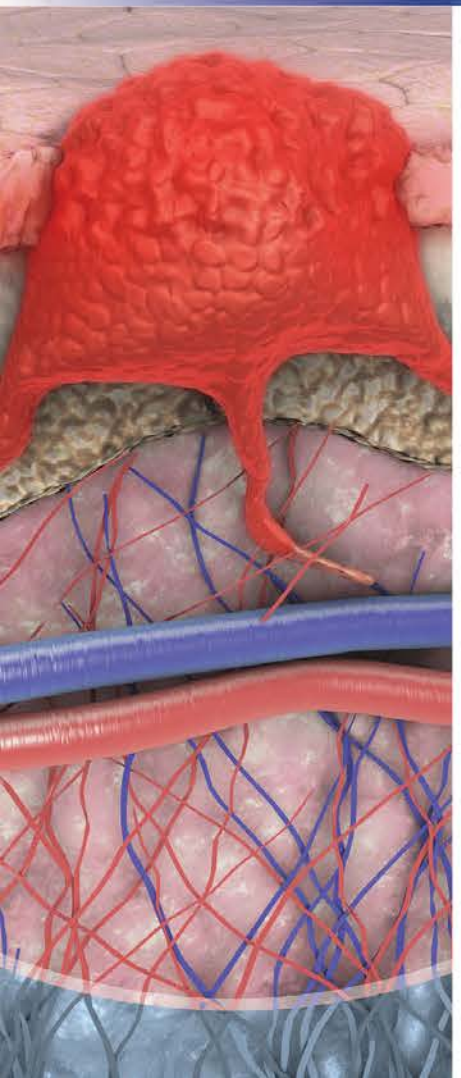
- **Combination PD-1 + CTLA-4 blockade**
  - Nivolumab + ipilimumab (CheckMate 067, CheckMate 204)
- **Combination PD-1 + LAG-3 blockade**
  - Nivolumab + relatlimab (RELATIVITY-047)
- **Anti–PD-1 ICI monotherapy**
  - Pembrolizumab (KEYNOTE-006) or nivolumab (CheckMate 067)
- **Other: BRAF/MEK blockade (Not Preferred)**
  - Dabrafenib + trametinib, encorafenib + binimetinib, vemurafenib + cobimetinib

All NCCN Category 1 Recommendations

UPDATE: Vemurafenib/cobimetinib + atezolizumab removed as first-line therapy option from NCCN Melanoma Guidelines version 2.2023

NCCN, National Comprehensive Cancer Network
Wolchok JD, et al. *N Engl J Med*. 2017;377(14):1345-1356.; Tawbi HA, et al. *Lancet Oncol*. 2021;22(12):1692-1704.; NCCN Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. Version 3.2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492

Pivotal Trial: KEYNOTE-006



- **Phase 3 RCT: untreated metastatic melanoma**
- **Randomized to 1 of 3 trial arms (n = 834)**
  - Pembrolizumab (anti-PD-1 monotherapy) – two different dosing frequencies
  - Ipilimumab (anti-CTLA-4 monotherapy)
- **Pembrolizumab: ↑ OS versus ipilimumab**
- **About half the risk of grade 3/4 AEs vs anti-CTLA-4 monotherapy**

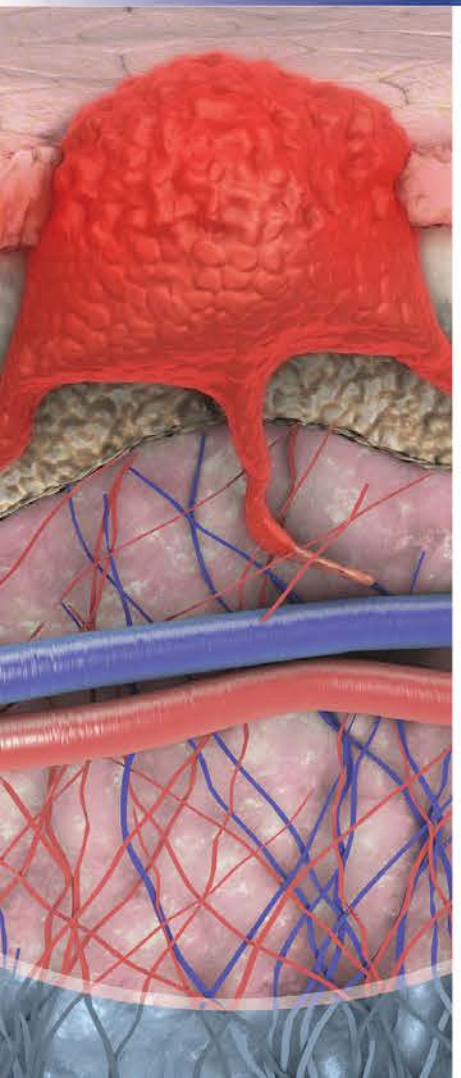
	ipi	pembro
5-year OS (first-line)	33%	42%
5-year ORR	17%	42%
Grade 3/4 AEs	19.9%	10.1-13.3%

Pembrolizumab > Ipilimumab

AEs, adverse effects; ipi, ipilimumab; ORR, overall response rate; OS, overall survival; pembro, pembrolizumab; RCT, randomized controlled trial

Robert C, et al. *N Engl J Med*. 2015;372(26):2521-2532.; Robert C, et al. *Lancet Oncol*. 2019;20(9):1239-1251.

Pivotal Trial: CheckMate 067



- **Phase 3 RCT: untreated metastatic melanoma**
- **Randomized to 1 of 3 trial arms (n = 945)**
  - Nivolumab + ipilimumab (combination PD-1 + CTLA-4 blockade)
  - Nivolumab (anti-PD-1 monotherapy)
  - Ipilimumab (anti-CTLA-4 monotherapy)
- **Nivolumab + ipilimumab: ↑ OS versus both arms**
- **About 3x risk of grade 3/4 AEs over anti-PD-1 monotherapy**

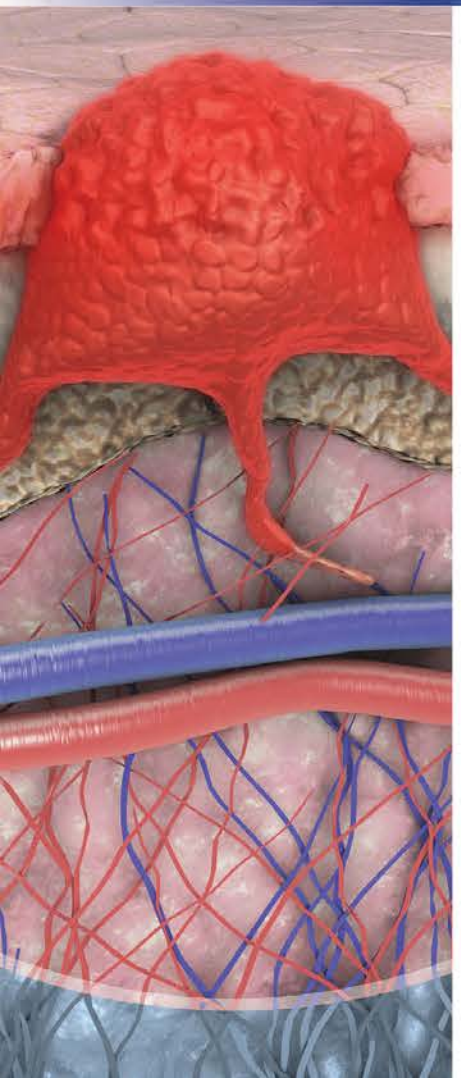
	ipi	nivo	nivo/ipi
5-year OS	26%	44%	52%
7.5-year OS	22%	42%	48%
5-year ORR	19%	45%	58%
Grade 3/4 AEs	28%	23%	59%

Nivolumab + Ipilimumab > Nivolumab > Ipilimumab

nivo, nivolumab

Wolchok JD, et al. *N Engl J Med*. 2017;377(14):1345-1356.; Larkin J, et al. *N Engl J Med*. 2019;381(16):1535-1546.; Wolchok JD, et al. *J Clin Oncol*. 2022;40(2):127-137.; Hodi S, et al. *J Clin Oncol*. 2022;40(no. 16_suppl): 9522-9522.

Pivotal Trial: RELATIVITY-047



- **Phase 3 RCT: untreated metastatic melanoma**
- **Randomized to 1 of 2 trial arms (n = 714)**
  - Nivolumab + relatlimab (combination PD-1 + LAG-3 blockade)
  - Nivolumab (anti–PD-1 monotherapy)
- **Nivolumab + relatlimab: ↑ PFS versus nivolumab alone**
  - **OS:** improvement not yet significant; long-term outcomes not yet known
- **About 2x risk of grade 3/4 AEs as nivolumab**

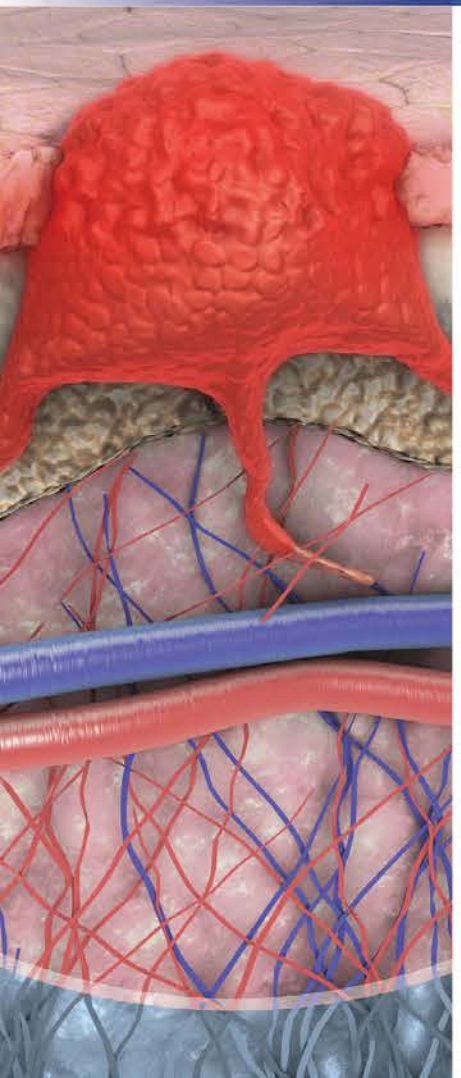
	nivo	nivo/rela
Median PFS (months)*	4.6	10.1
ORR	32.6%	43.1%
Grade 3/4 AEs	9.7%	18.9%
Myocarditis	*0.6%*	*1.7%*
Adrenal insufficiency	*0.8%*	*4.2%*

Nivolumab + Relatlimab > Nivolumab

* P = 0.006; PFS, progression-free survival; rela, relatlimab

Tawbi HA, et al. *N Engl J Med*. 2022;386(1):24-34.

Pivotal Trial: CheckMate 204

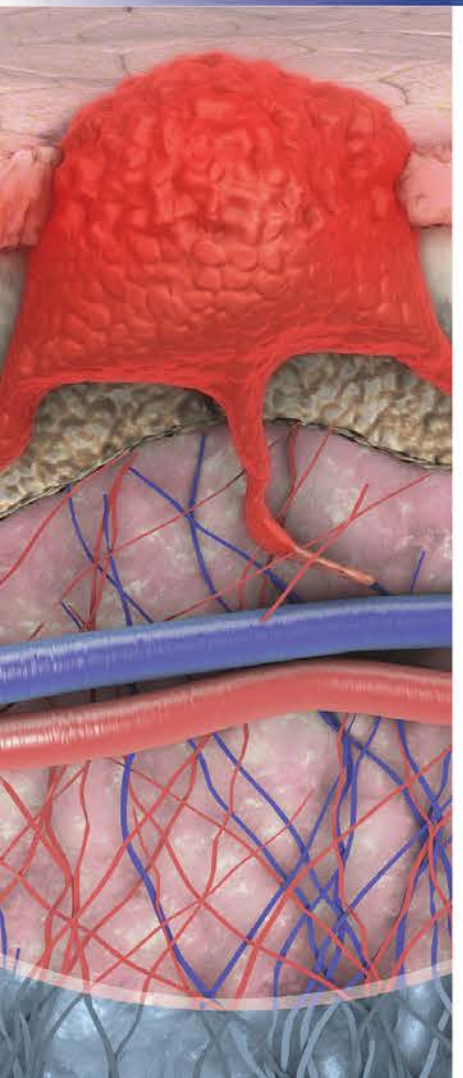


- **Phase 2 trial: melanoma with untreated brain metastases**
- **Open-label, two arm study (n = 165)**
  - **Arm A**: Asymptomatic brain metastases; **Arm B**: Symptomatic brain metastases
  - Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 4 doses → Nivolumab 3 mg/kg every 2 weeks for up to 2 years
    - Low-dose dexamethasone permitted for Arm B
- **Nivolumab + ipilimumab similar outcomes for asymptomatic brain metastases to patients without brain metastases**
  - **3-year OS:** 71.9% (Arm A), 36.6% (Arm B)
  - **3-year ORR:** 53.5% (Arm A), 16.7% (Arm B)
- **Symptomatic disease challenging, but still may benefit**

Asymptomatic > Symptomatic disease

Tawbi HA, et al. *Lancet Oncol*. 2021;22(12):1692-1704.

Future Directions and Emerging Data

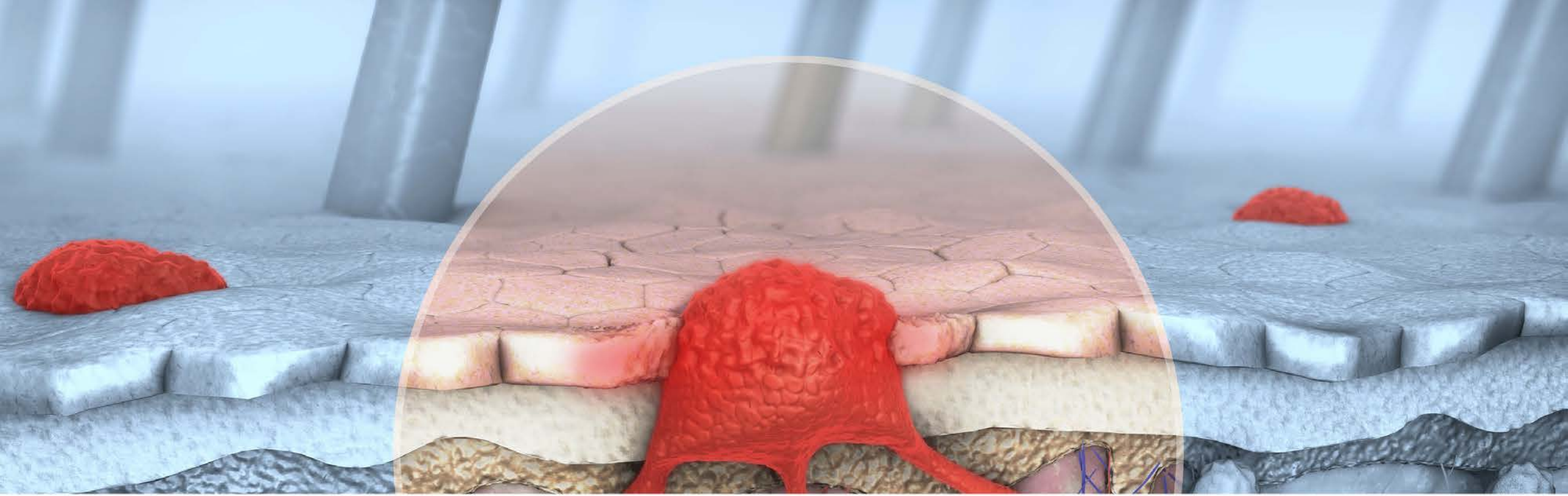


- **Long-term outcomes for nivolumab + relatlimab**
- **Neoadjuvant pembrolizumab for resected stage III/IV**
  - FDA may approve to reduce relapse after surgery
- **PD-1 refractory metastatic melanoma**
  - **Pembrolizumab + lenvatinib** (phase 2 LEAP-004)
  - **TIL therapy** (phase 3 trial with mostly PD-1 refractory patients)
  - **BNT111** (phase 2 mRNA-based melanoma vaccine)

FDA, US Food and Drug Administration; mRNA, messenger ribonucleic acid; TIL, tumor-infiltrating lymphocytes

Melanoma Research Alliance. Melanoma clinical trials to watch: March 2023. Accessed May 3, 2023. https://www.curemelanoma.org/blog/article/melanoma-clinical-trials-to-watch-march-2023; NCCN Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. Version 3.2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492

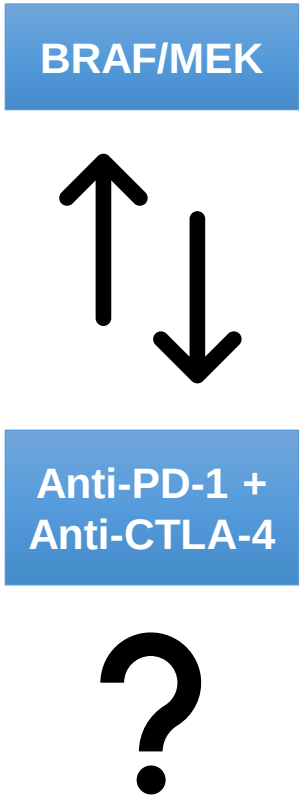
Questions & Answers



Individualizing First-line Therapy

Factors to Consider for the Optimal Treatment of Each Patient with Metastatic Melanoma

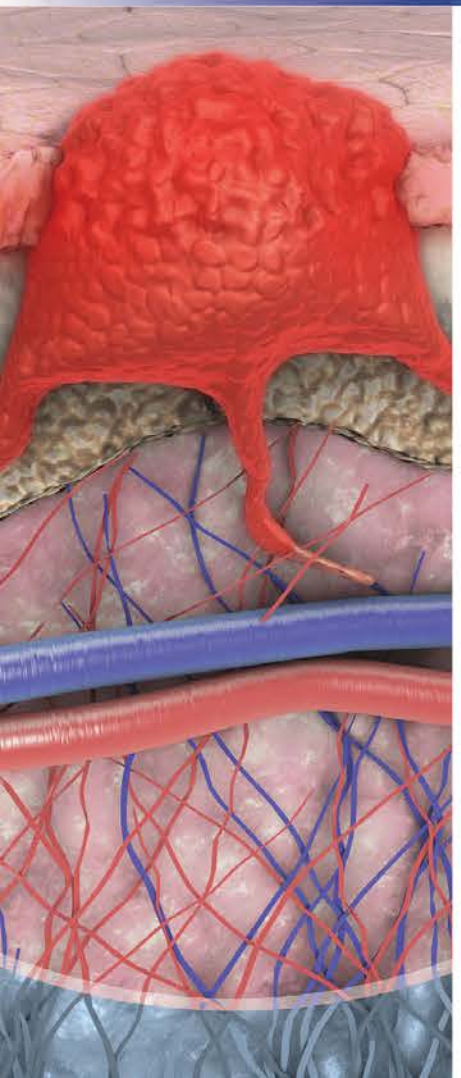
Recent Data on First-line ICI Therapies: DREAMseq Trial



- **Phase 3 RCT: untreated *BRAFV600*+ metastatic melanoma**
- **Randomized to 1 of 2 sequence arms:**
  - **Arm A**: nivolumab + ipilimumab → dabrafenib + trametinib
  - **Arm B**: dabrafenib + trametinib → nivolumab + ipilimumab
- **Upfront nivolumab + ipilimumab: superior OS at 10 months**
  - **2-year OS:** 72% versus 52% (*P* = .0095) → study halted accrual early
- **Paradigm shift**
  - Half of patients with *BRAF*-mutant melanoma previously received BRAF/MEK blockade first line

Atkins MB, et al. *J Clin Oncol*. 2023;41(2):186-197.

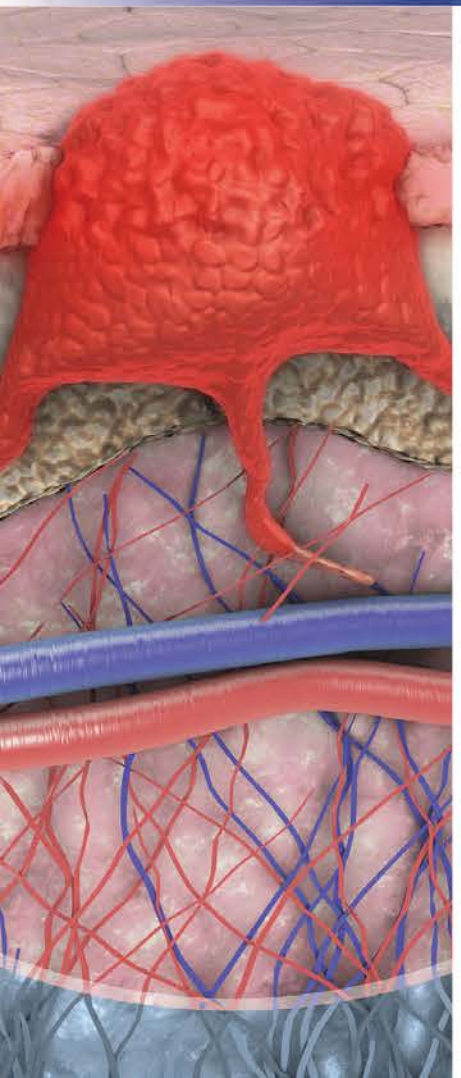
Individualizing First-Line Therapy for Metastatic Melanoma



- **Must consider how pivotal data relate to patient-specific factors for most evidence-based decision**
- **Summarizing key facts**
  - **CheckMate-067:** long-term OS with PD-1 + CTLA-4 > PD-1 blockade alone (48% vs. 42% at 7.5 years), with ↑ grade 3/4 irAEs (23% versus 59%)
    - CheckMate 204: Consistent benefit with asymptomatic untreated brain metastases
  - **DREAMseq:** 2-yr OS with PD-1 + CTLA-4 blockade > BRAF/MEK blockade in the first-line setting (72% versus 52%); when possible, use ICI therapy first
  - **RELATIVITY-047:** short-term data on PD-1 + LAG-3 blockade (nivolumab + relatlimab) points to ↑ efficacy with 2x toxicity; need long-term results
  - ICI therapy delayed onset of action compared to BRAF/MEK blockade

Switzer B, et al. *JCO Oncol Pract*. 2022;18(5):335-351.; Atkins MB, et al. *J Clin Oncol*. 2023;41(2):186-197.; Tawbi HA, et al. *N Engl J Med*. 2022;386(1):24-34.; NCCN Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. Version 2.2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492

Patient-Specific Factors: Disease Burden + Clinical Status

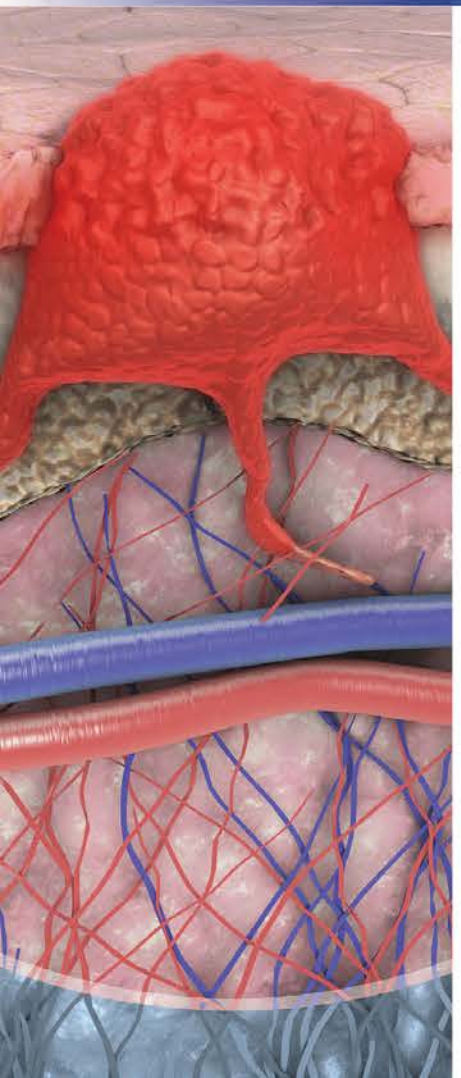


- **Oligometastatic stage IV disease**
  - Surgery, SRS, or intralesional T-VEC may be appropriate
  - If NED → adjuvant anti-PD-1 (**Approved; NCCN Category 1**) with nivolumab or pembrolizumab for one year
- **High tumor burden/rapid progression/unstable**
  - May consider BRAF/MEK blockade first
- **Poor clinical status without need for rapid response**
  - Concern about reserves in case of immune-related toxicity
  - Consider anti-PD-1 monotherapy instead of combination ICI

NED, no evidence of disease; SRS, stereotactic radiosurgery; T-VEC, talimogene laherparepvec.

Switzer B, et al. *JCO Oncol Pract*. 2022;18(5):335-351.; NCCN Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. Version 2.2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492

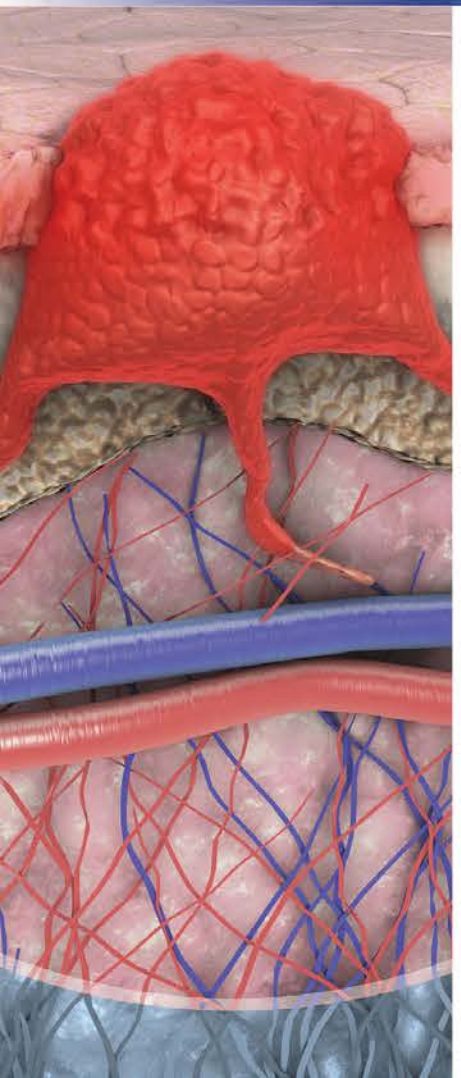
Patient-Specific Factors: Melanoma Untreated Brain Metastases



- Multidisciplinary discussion with neurosurgery, radiation oncology, and medical oncology recommended
- Combination anti-PD-1 + anti-CTLA-4 therapy with nivolumab + ipilimumab preferred (CheckMate 204)
- **Symptomatic or asymptomatic?**
  - **Symptomatic/high-risk scenario**: consider resection/SRS to stabilize, then combination nivolumab + ipilimumab
  - **Asymptomatic**: nivolumab + ipilimumab, may still consider SRS or other local

Switzer B, et al. *JCO Oncol Pract*. 2022;18(5):335-351.; NCCN Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. Version 2.2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492

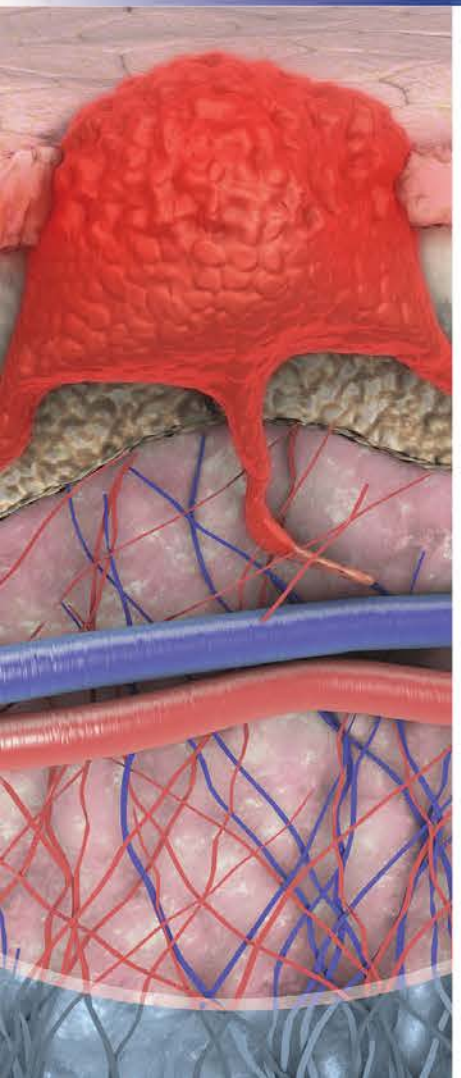
Patient-Specific Factors: Past Treatment



- **Metastatic melanoma may develop following prior diagnosis with earlier stage disease**
- **Anti-PD-1 ICI used in the adjuvant setting**
  - Nivolumab: Stage III or IV resected melanoma
  - Pembrolizumab: Stage IIB, IIC, III/IV resected melanoma
- **At time of disease progression may consider:**
  - Clinical trial
  - Repeating anti-PD-1 ICI, depending on time to recurrence
  - Combination PD-1 + CTLA-4 blockade
  - Combination PD-1 + LAG-3 blockade

Switzer B, et al. *JCO Oncol Pract*. 2022;18(5):335-351.; NCCN Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. Version 2.2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492

Other Special Circumstances and Contraindications

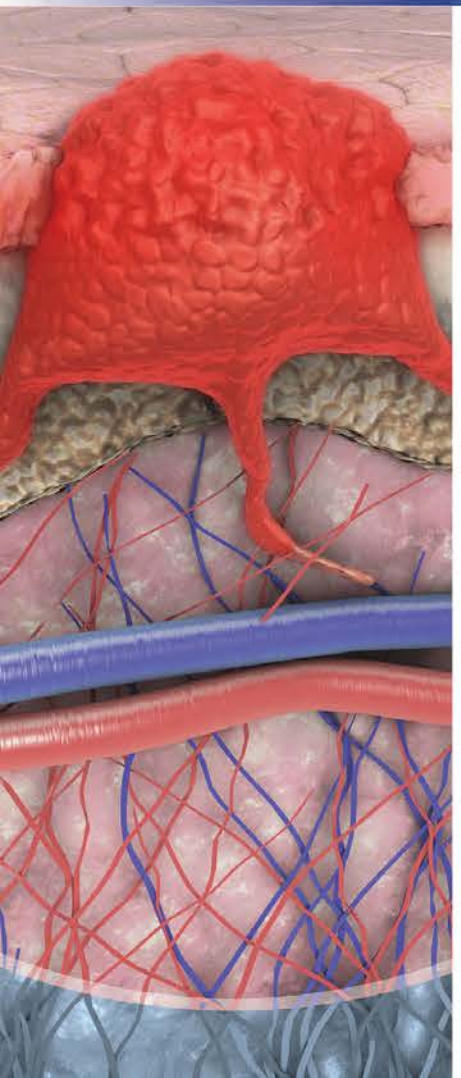


- **Concurrent autoimmune disease**
  - High risk of flare
  - Overall risk varies by disease state (e.g., IBD higher risk than RA)
- **Organ transplantation**
  - General contraindication as may result in organ rejection
  - May be possible but must exhaust other options
- **Pregnancy**
  - PD-1 and CTLA-4 involved in fetal tolerability
  - ICI may result in fetal harm

IBD, inflammatory bowel disease; RA, rheumatoid arthritis

Haanen J, et al. *Ann Oncol*. 2020;31(6):724-744.; Portuguese AJ, et al. *J Natl Compr Canc N*etw. 2022;20(4):406-416.e11.; Andrikopoulou A, et al. *ESMO Open*. 2021;6(5):100262.; NCCN Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. Version 2.2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492

The High Cost of ICI Therapy



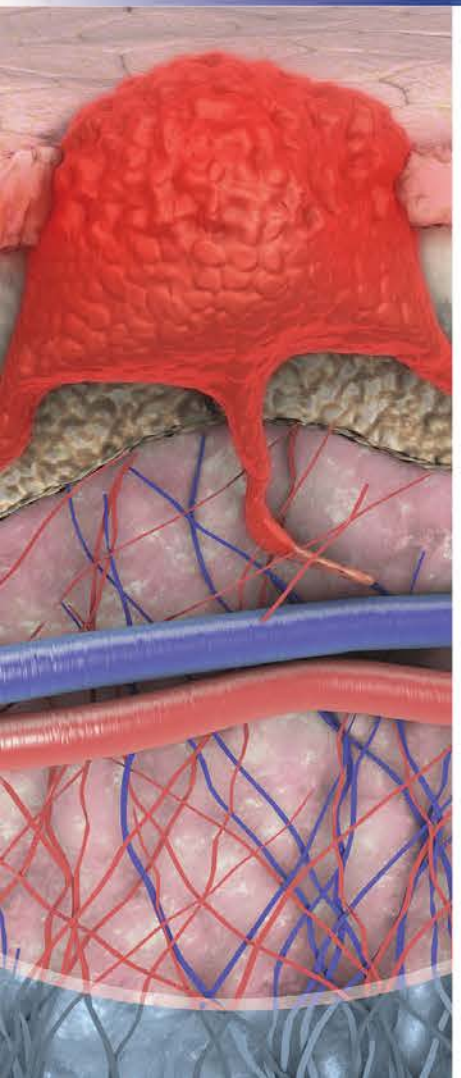
- **ICIs are expensive:** about $1 million/patient (pembrolizumab)
- **Cost-effectiveness analysis in melanoma**
  - Willingness-to-pay threshold $100,000/QALY
  - Nivolumab and pembrolizumab are both cost-effective
  - Nivolumab + ipilimumab is cost-effective using long-term 5-year OS data
- **Medicare coverage applies if one is true:**
  1. FDA approved indication
  2. Minimum NCCN category 2A recommendation
- **Patient assistance + copay assistance**
  - Copay assistance available for non-Medicare patients

Responsible for 20% without supplemental plan; may need grant assistance (e.g., PAN Foundation)

PAN, Patient Access Network; QALY, quality-adjusted life-year

Andrews A. Am Health Drug Benefits. 2015;8(Spec Issue):9. Verma V, et al. J Immunother Cancer. 2018;6(1):128. Baker T, et al. Pharmacoecon Open. 2022;6(5):697-710. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. Version 2.2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492

Drug and Food Interactions with ICI Therapy

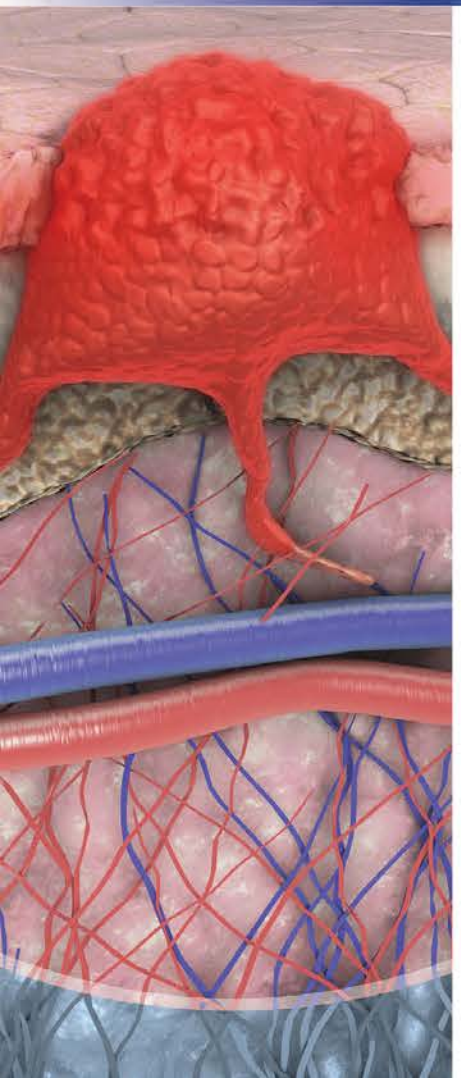


- **Drug interactions → concern for reduced efficacy**
  - Cannabis
  - Acetaminophen
  - Others (e.g., antibiotics, proton pump inhibitors, metformin, opioids)
- **High-fiber diet with no use of OTC probiotics → improved efficacy**
  - Longest PFS from ICI therapy in patients with melanoma

OTC, over-the-counter.

Bar-Sela G, et al. *Cancers (Basel).* 2020;12(9):2447.; Bessede A, et al. *Ann Oncol*. 2022;33(9):909-915.; Spencer CN, et al. *Science*. 2021;374(6575):1632-1640.

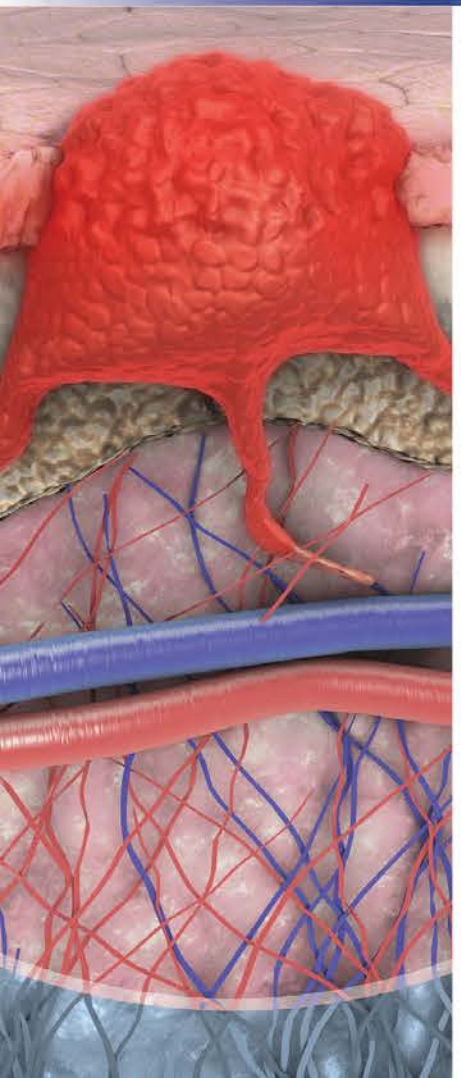
Treating Rare, Aggressive Melanoma Subtypes



- **Clinical trial preferred whenever possible**
- **Uveal melanoma**
  - Tebentafusp (only FDA-approved therapy for uveal subtype)
  - Nivolumab + ipilimumab
- **Mucosal melanoma**
  - **<u>No FDA approved therapies specifically for mucosal subtype</u>**
  - Nivolumab + ipilimumab most effective (pooled analysis)
  - KIT mutation: KIT inhibitor (e.g., imatinib, dasatinib, nilotinib, ripretinib; off-label)

Nathan P, et al. *N Engl J Med*. 2021;385(13):1196-1206.; Pelster MS, et al. *J Clin Oncol*. 2021;39(6):599-607.; D'Angelo SP, et al. *J Clin Oncol*. 2017;35(2):226-235.; NCCN Clinical Practice Guidelines in Oncology. Melanoma: uveal. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf

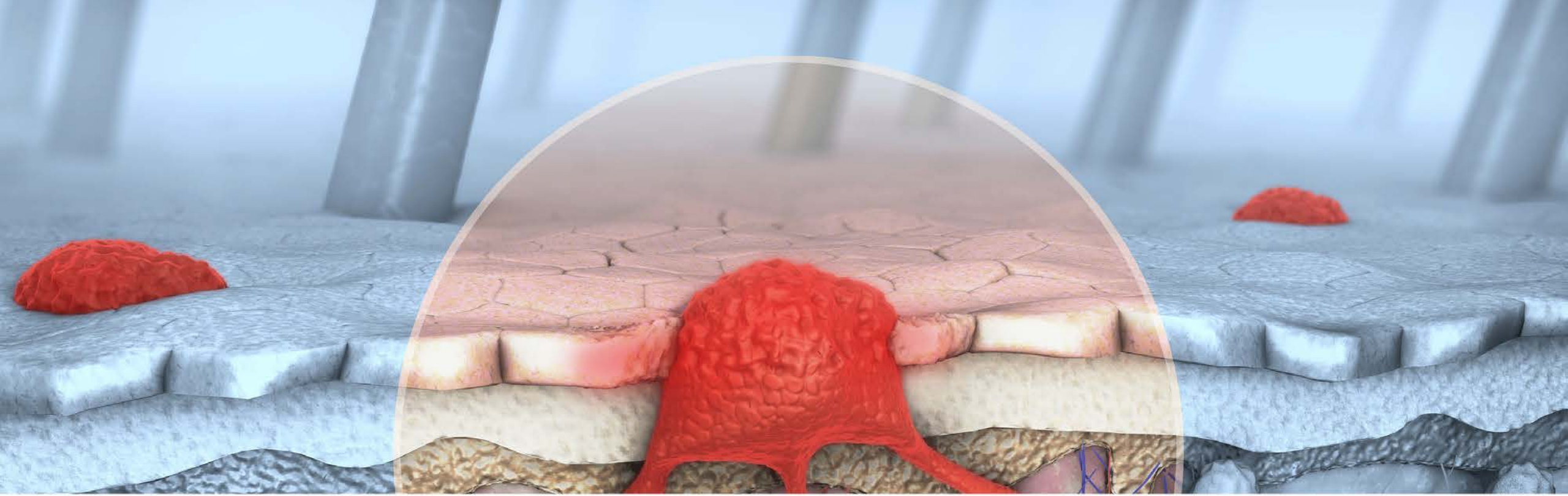
Key Takeaways for Individualizing First-Line Therapy



- **If eligible for clinical trial, consider enrollment**
- **If limited disease, consider resection or stereotactic radiosurgery**
- **Consider combination ICI for all patients when possible**
  - Most benefit: high tumor burden, brain metastasis, visceral disease
- **Clinical/toxicity concerns?**
  - Consider anti–PD-1 ICI monotherapy
- **Need rapid response?**
  - If *BRAFV600*+, consider BRAF/MEK combination therapy

Switzer B, et al. *JCO Oncol Pract*. 2022;18(5):335-351.; NCCN Clinical Practice Guidelines in Oncology. Melanoma: cutaneous. Version 3.2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492

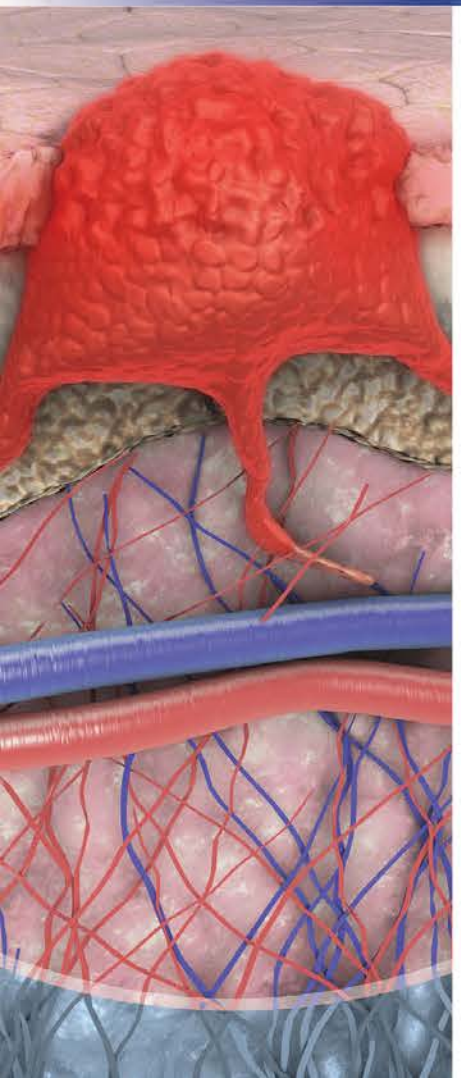
Questions & Answers



Immune-Related Toxicity

Optimizing the Identification and Timely Treatment of Immune-Related Adverse Events

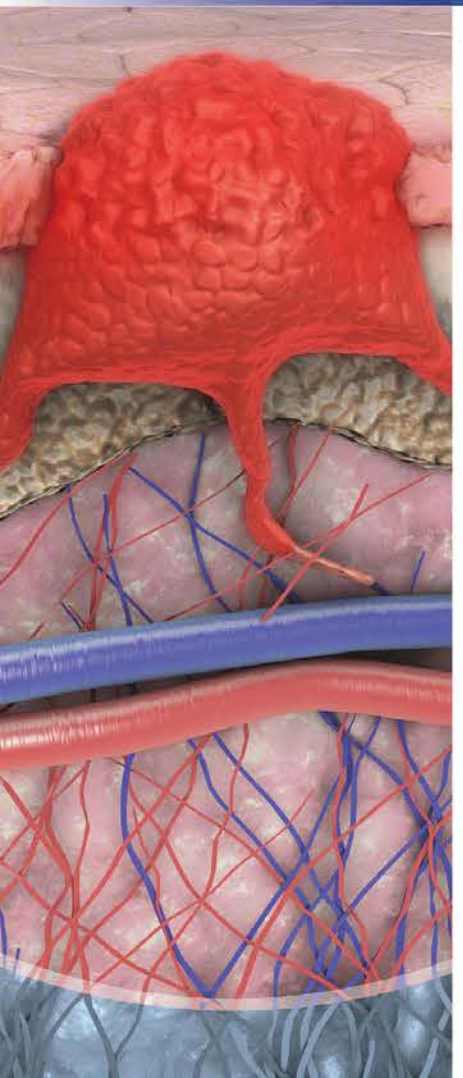
Immune-Related Adverse Events (irAEs)



- **Immune attack of self-antigen from T-cell overactivation**
  - Differ from toxicities related to traditional chemotherapy
- **Can impact <u>any</u> organ, similar to autoimmune disease (“-itis”)**
- **Highly unpredictable timeline**
  - Necessitates vigilance from patient, caregivers, and other clinicians
- **Grade 3/4 toxicity profiles of ICI regimens**
  - PD-1 ICI alone (nivolumab or pembrolizumab): 10% to 15%; Long-term: 23%
  - PD-1 + LAG-3 ICIs (nivolumab + relatlimab): 18.9%
  - PD-1 + CTLA-4 ICIs (nivolumab + ipilimumab): 55%; Long-term: 59%

Ramos-Casals M, et al. *Nat Rev Dis Primer*. 2020;6(1):38.; Wolchok JD, et al. *J Clin Oncol*. 2022;40(2):127-137.; Tawbi HA, et al. *N Engl J Med*. 2022;386(1):24-34.; NCCN Clinical Practice Guidelines in Oncology. Management of immunotherapy-related toxicities. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Types of irAEs

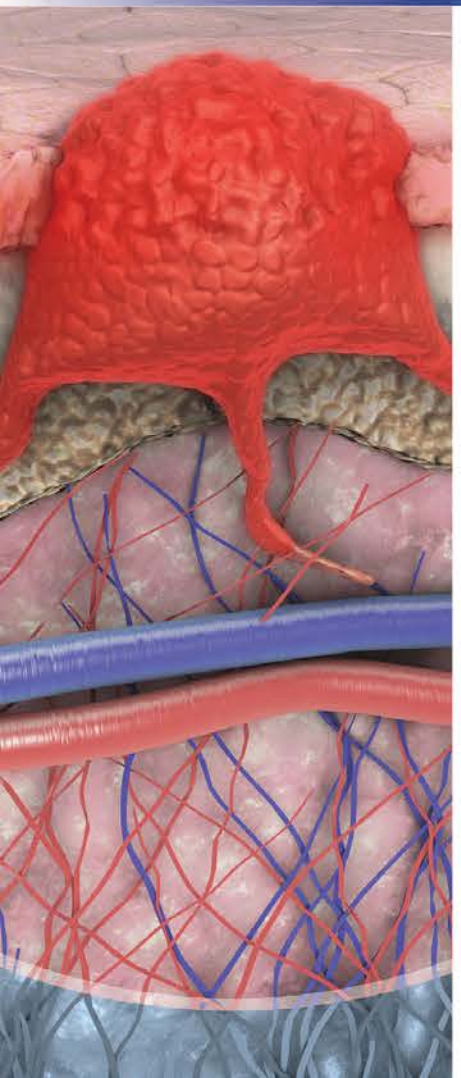


Dermatologic	Rheumatologic	Nervous System
Maculopapular rash	Arthritis	Myasthenia gravis
Pruritis	Myositis	Guillain-Barré syndrome
Blistering disorder	Polymyalgia rheumatica	Peripheral neuropathy
Mucositis	Sicca syndrome	Aseptic meningitis
Endocrine	**Ocular**	Encephalitis
Thyroiditis	Uveitis	Transverse myelitis
Hypophysitis	Episcleritis	**Cardiovascular**
T1D	Scleritis	Myocarditis
Gastrointestinal	**Pulmonary**	**Hematologic**
Colitis	Pneumonitis	Hemolytic anemia
Hepatitis	**Renal**	ITP
Pancreatitis	Nephritis	

ITP, immune thrombocytopenia; T1D, type 1 diabetes.

Brahmer JR, et al. *J Immunother Cancer*. 2021;9(6):e002435.; NCCN Clinical Practice Guidelines in Oncology. Management of immunotherapy-related toxicities. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Core Principles of irAE Management

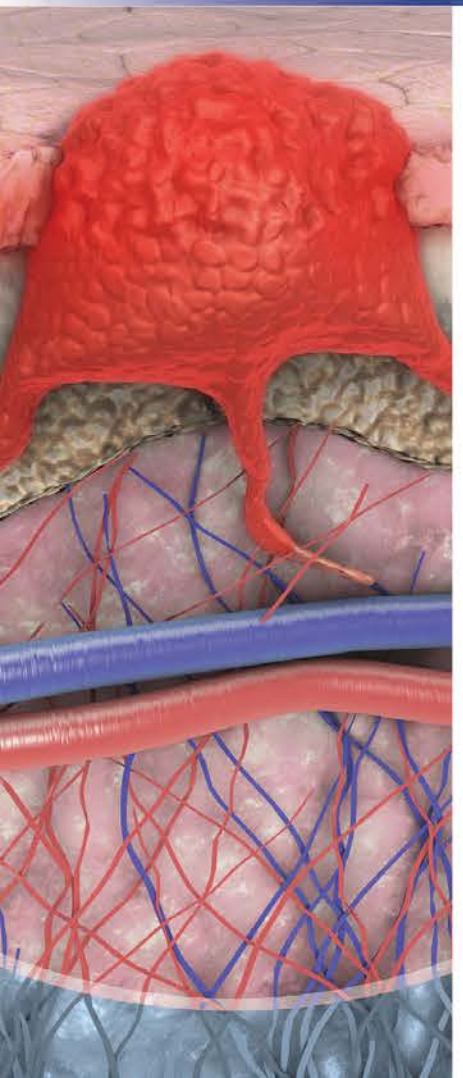


- **Workup is challenging, so must consider all possibilities**
  - Results of workup should not delay empiric treatment for severe irAE
  - Cover all potential differential diagnoses until ruled out
- **Consider treating irAEs before transition to more severe AEs**
  - Grade 3 or 4 irAEs often require inpatient care
- **High-dose corticosteroids are mainstay of therapy**
  - Oral prednisone/methylprednisolone IV 0.5-2 mg/kg/day (based on grade)
  - Slow taper over 4-6 weeks lowers risk of irAE recurrence
- **Often requires collaboration with subspecialty experts**
- **Secondary immunosuppressants may be needed if refractory**

IV, intravenous

Ramos-Casals M, et al. *Nat Rev Dis Primer*. 2020;6(1):38.; NCCN Clinical Practice Guidelines in Oncology. Management of immunotherapy-related toxicities. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

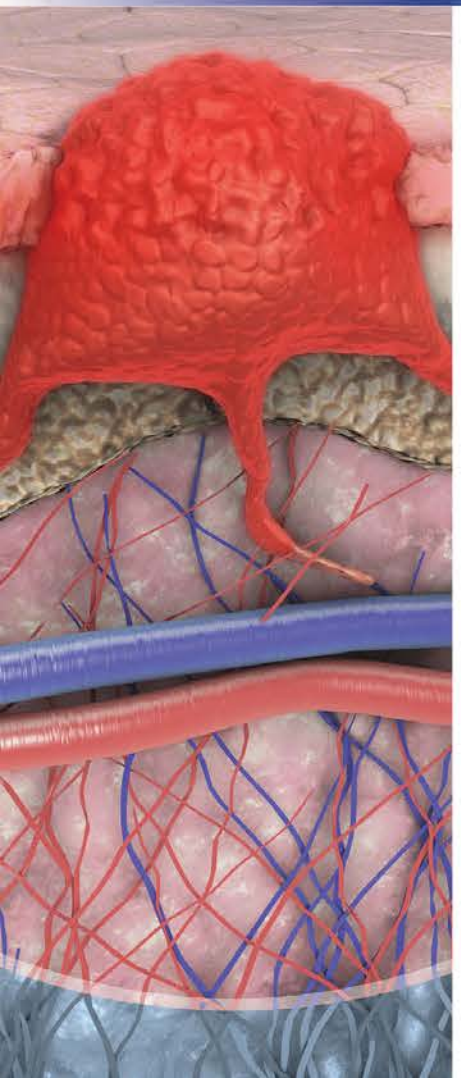
Steroid Tapers



- **Important to taper to avoid long-term steroid AEs**
- **An art, not a science: start once irAE grade 1 or less**
  - Steps every 5-7 days common
  - Hepatitis, pneumonitis, arthritis: ≥ 6-8 week tapers common
  - Pneumonitis, arthritis: may require chronic treatment
- **Pharmacists play a key role in ensuring adherence**
  - Steroid taper care plans are complex and change over time
  - Supportive care needs are easily missed
- **Patient education and monitoring plans are vital**
  - Success depends on clear communication for ongoing recovery

Ramos-Casals M, et al. *Nat Rev Dis Primer*. 2020;6(1):38.; Medina P, et al. *J Pharm Pract*. 2020;33(3):338-349.; NCCN Clinical Practice Guidelines in Oncology. Management of immunotherapy-related toxicities. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Supportive Care Concerns with Immunosuppression for irAEs

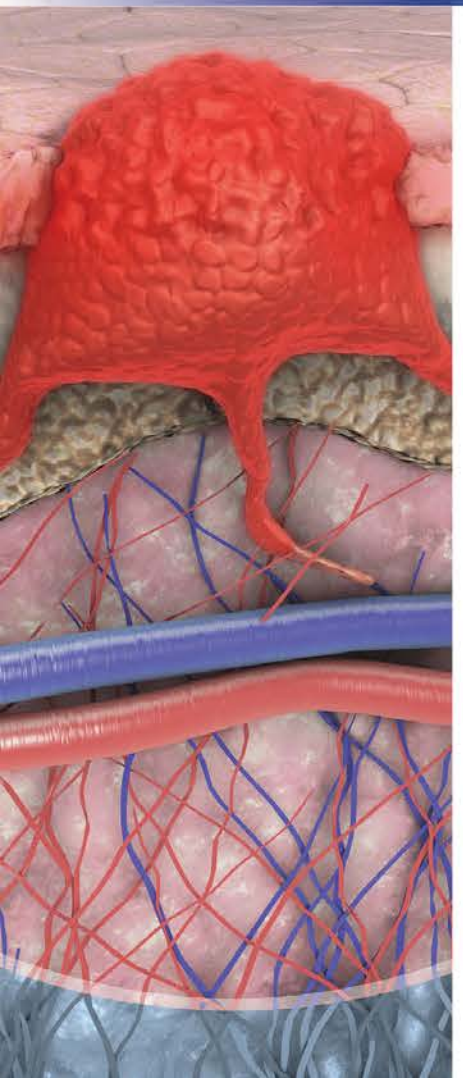


- **Use symptomatic treatments with extreme caution**
  - Risk of masking life-threatening irAE
  - Example: loperamide for grade 1 diarrhea
- **PJP prophylaxis:** prednisone ≥ 20 mg for ≥ 4 weeks
- **GI prophylaxis:** NSAID use/anticoagulation; GI discomfort
- **Sleep aid:** baseline insomnia; may need after starting steroid (e.g., trazodone)
- **Hyperglycemia prophylaxis: history of type 2 diabetes**
  - Sliding scale insulin may be necessary
- **Bone prophylaxis**: calcium + vitamin D with extended steroids

GI: gastrointestinal; NSAID: nonsteroidal anti-inflammatory drug; PJP: *Pneumocystis jirovecii* pneumonia.

Brahmer JR, et al. *J Immunother Cancer*. 2021;9(6):e002435.; Schneider BJ, et al. *J Clin Oncol*. 2021;39(36):4073-4126.; NCCN Clinical Practice Guidelines in Oncology. Management of immunotherapy-related toxicities. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

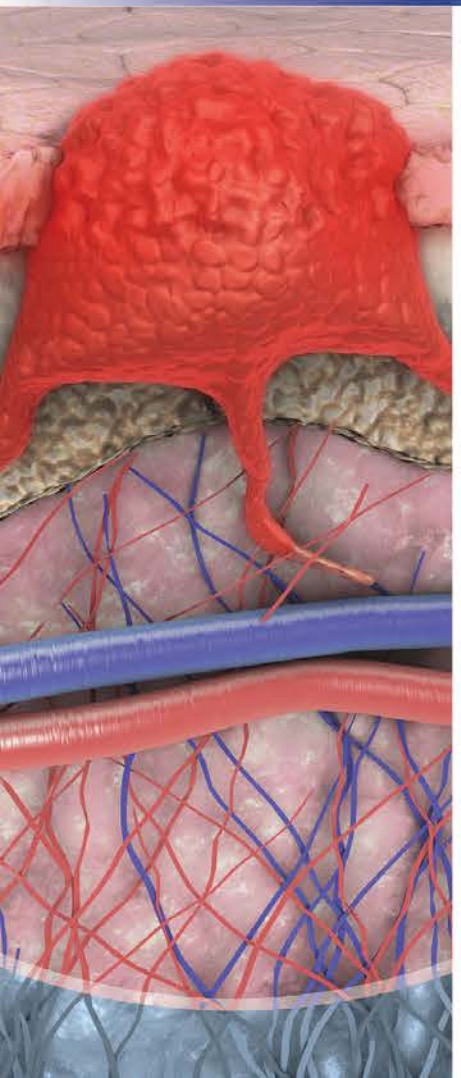
Common irAE Management Pearls



- **Generally reversible; focus on early identification/treatment**
- **Rash/pruritus**
  - Over-the-counter/topical corticosteroids until irAE reaches grade ≥ 3
- **Colitis**
  - Can be life-threatening; treat at grade 2 (≥ 4-6 stools in 24 hours)
- **Hepatitis**
  - Transaminase ↑ alone common
  - Steroid taper often extended (6-8 weeks)
- **Pneumonitis**
  - Most common cause of mortality among all irAEs
  - Very challenging to diagnose
  - Chronic treatment sometimes required

Brahmer JR, et al. *J Immunother Cancer*. 2021;9(6):e002435.; Schneider BJ, et al. *J Clin Oncol*. 2021;39(36):4073-4126.; NCCN Clinical Practice Guidelines in Oncology. Management of immunotherapy-related toxicities. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Endocrine irAE Management Pearls

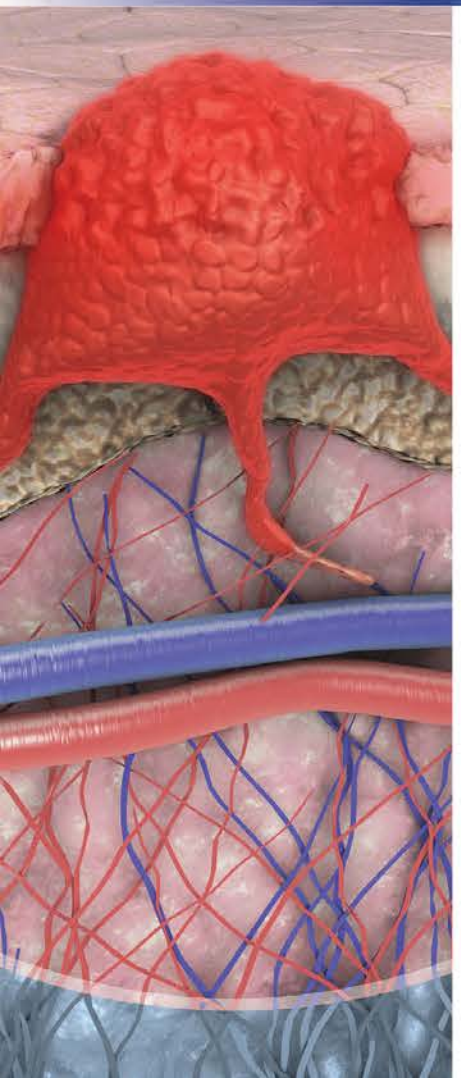


- **Usually permanent; focus on lifelong hormone replacement**
- **Severe fatigue on ICI therapy → 8 AM endocrine workup for:**
  - **Thyroiditis:** asymptomatic hyperthyroidism → (burnout) → primary hypothyroidism
    - Levothyroxine 1.2-1.6 µg/kg/day, use IBW, reduce dose in special populations
  - **Hypophysitis:** secondary adrenal insufficiency → hydrocortisone AM and PM doses
    - May need to replace for secondary thyroid/gonadal deficiencies
  - **Type 1 diabetes mellitus:** majority present in DKA
    - No cases of reversal → basal + bolus insulin

AM, morning; DKA, diabetic ketoacidosis; IBW, ideal body weight; PM, evening

Barroso-Sousa R, et al. *JAMA Oncol*. 2018;4(2):173-182.; Faje AT, et al. *Cancer*. 2018;124(18):3706-3714.; NCCN Clinical Practice Guidelines in Oncology. Management of immunotherapy-related toxicities. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

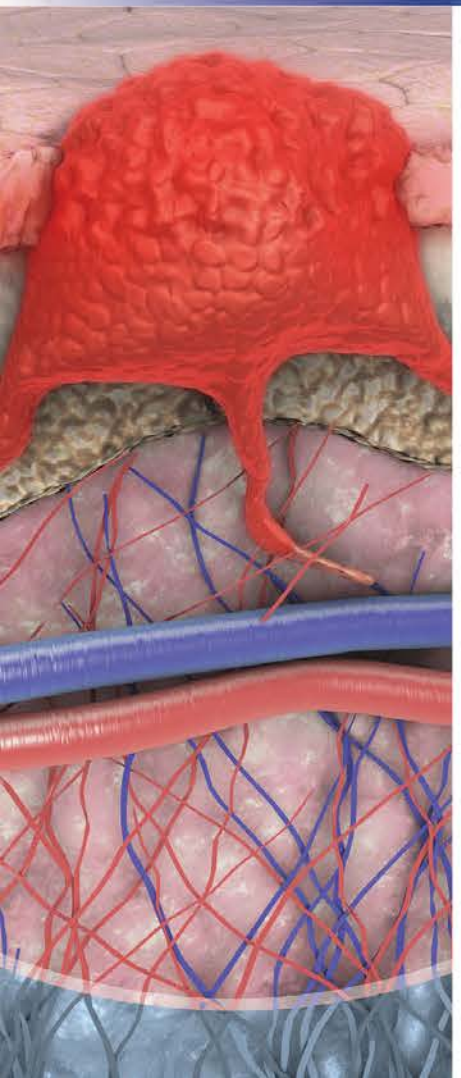
Notable Rare irAE Pearls



- **Myocarditis (3M's: + myositis / myasthenia gravis)**
  - Non-specific signs/symptoms within weeks of single dose of ICI therapy
  - Emergency; 25% to 50%+ mortality
- **Oral toxicities**
  - *Sicca syndrome*: severe dry mouth; dental concerns
  - *Mucositis*: chemotherapy is not the only culprit
  - Grading based on dietary impact
  - Requires topical/oral corticosteroids (both) and salivary intervention (sicca only)
- **Many other potential rare irAEs**
  - Most important to not exclude possibility when on ICI therapy

Naqash AR, et al. *J Clin Oncol*. 2022;40(29):3439-3452.; NCCN Clinical Practice Guidelines in Oncology. Management of immunotherapy-related toxicities. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

The Pharmacist's Role: Strategies to Optimize irAE Outcomes



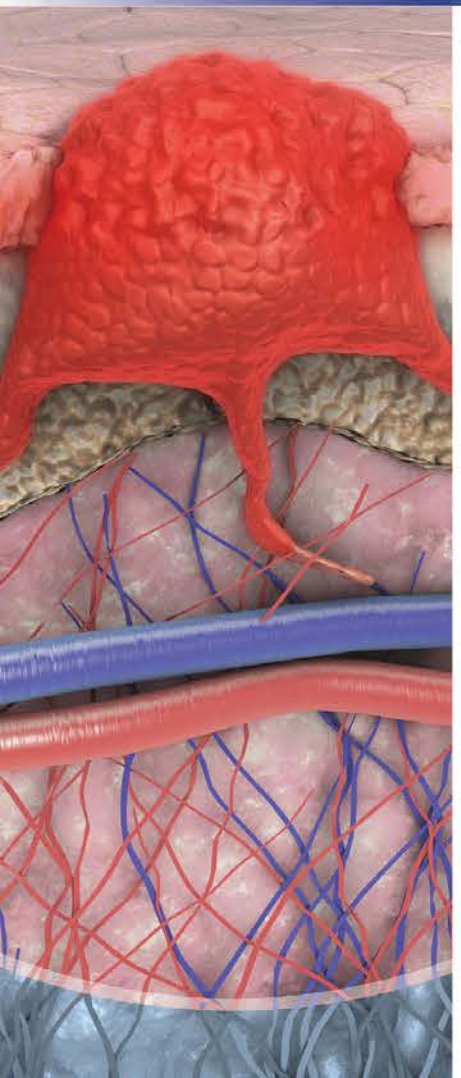
- **Prevent:** know spectrum, identify at-risk populations, and educate
  - Patients must recognize symptoms and report irAEs promptly
- **Anticipate:** get baseline, ensure monitoring, and give wallet card
- **Identify:** prompt patient reporting; consider irAE in differential
- **Treat:** hold ICI and/or treat as appropriate, refer, and use prophylaxis
- **Monitor:** design plan, escalate if needed, and address steroid AEs

Pharmacists across various care settings can play a vital part in 1 or more of these roles

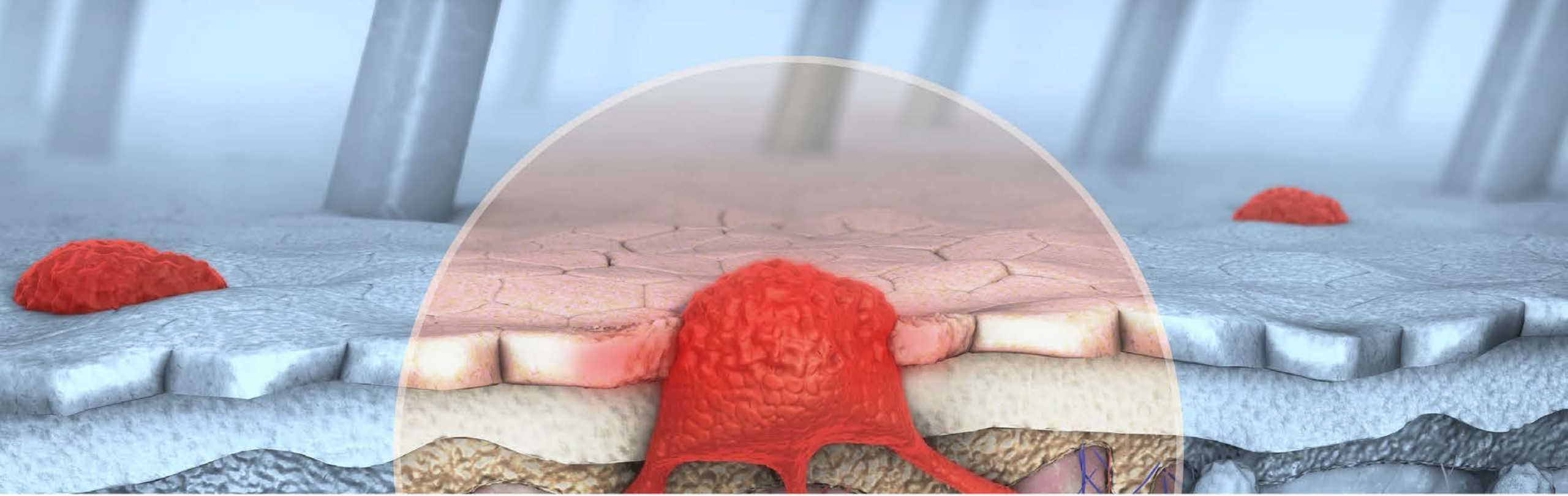
Champiat S, et al. *Ann Oncol*. 2016;27(4):559-574.; Medina P, et al. *J Pharm Pract*. 2020;33(3):338-349.

Questions & Answers

Conclusions



- **ICI-containing therapies have reshaped the first-line treatment landscape for metastatic melanoma**
  - Emerging data point to long-term survival in about 50% of patients
- **Providers must use patient-specific factors to individualize evidence-based decisions for first-line therapy**
  - Combination PD-1 + CTLA-4 blockade has best efficacy but high toxicity
  - Consider tumor burden, clinical status, brain metastases, past treatment, contraindications, potential high-risk comorbidities, and drug interactions
- **irAEs are challenging to manage, and require extensive interprofessional care coordination for success**
  - Pharmacists in many care settings can play a role in effectively identifying and managing irAEs



Thank you!