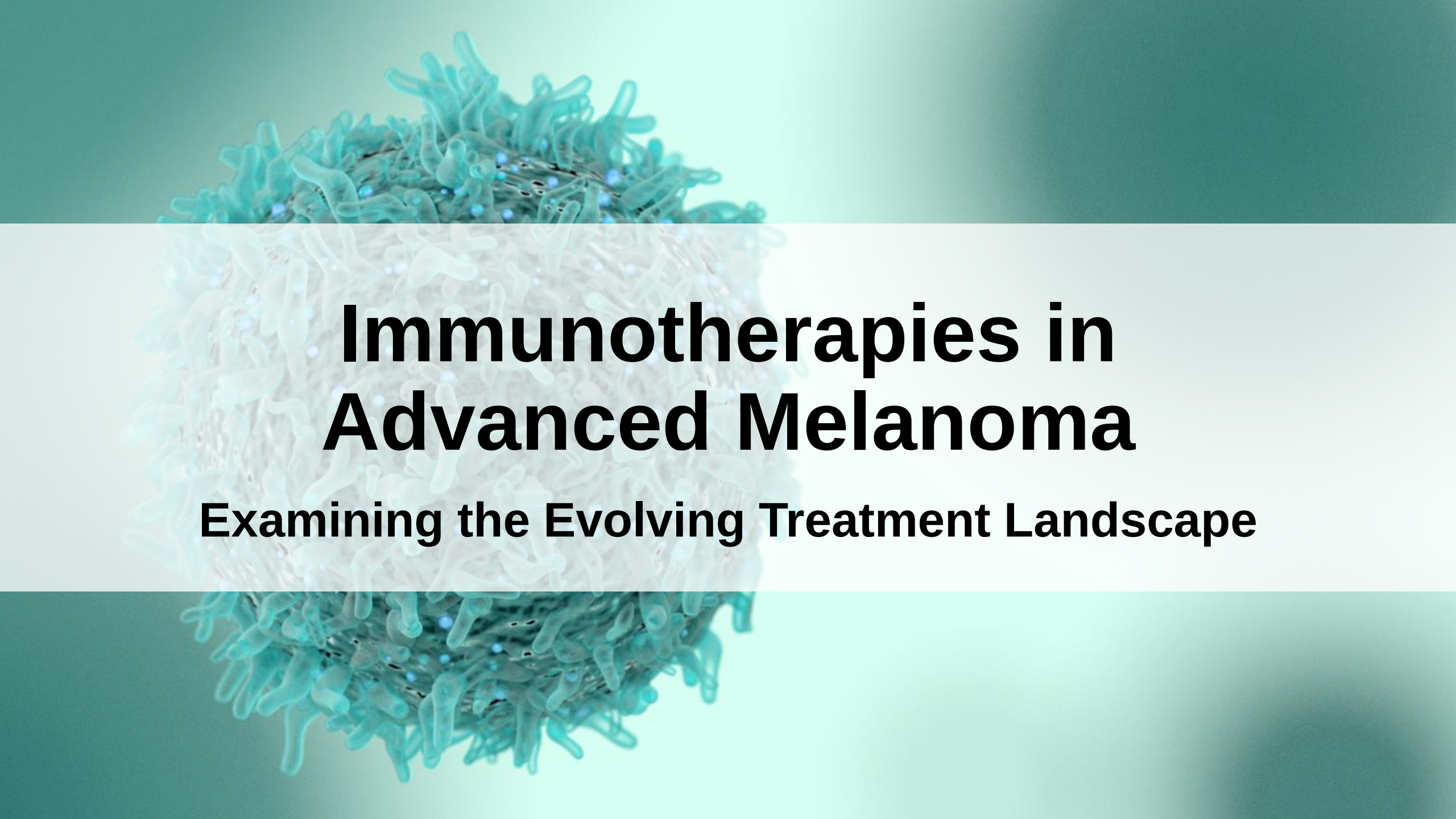
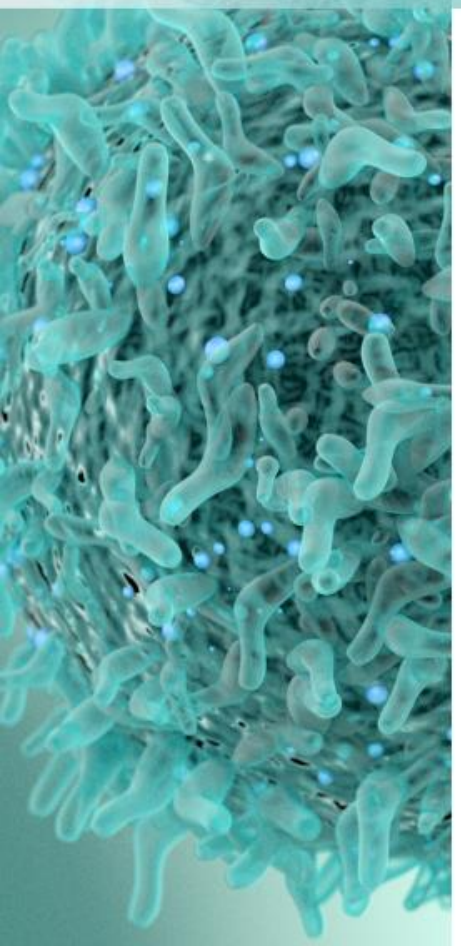


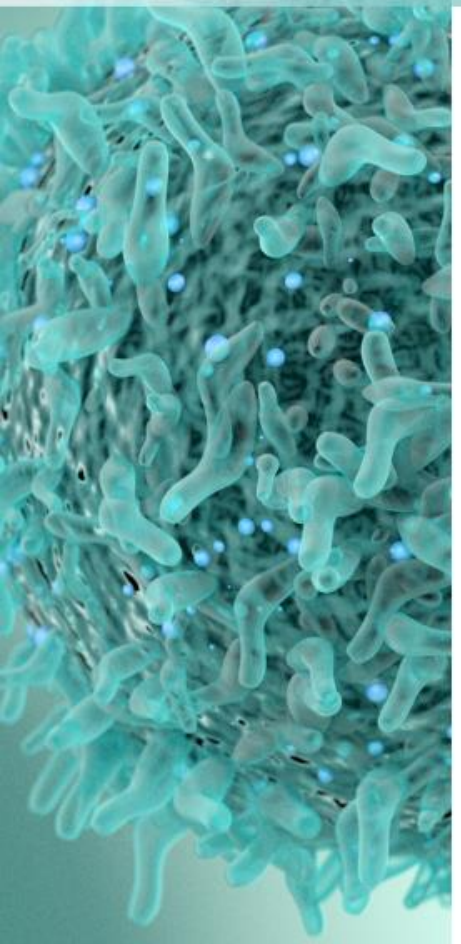
Immunotherapies in Advanced Melanoma

Examining the Evolving Treatment Landscape



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

Faculty

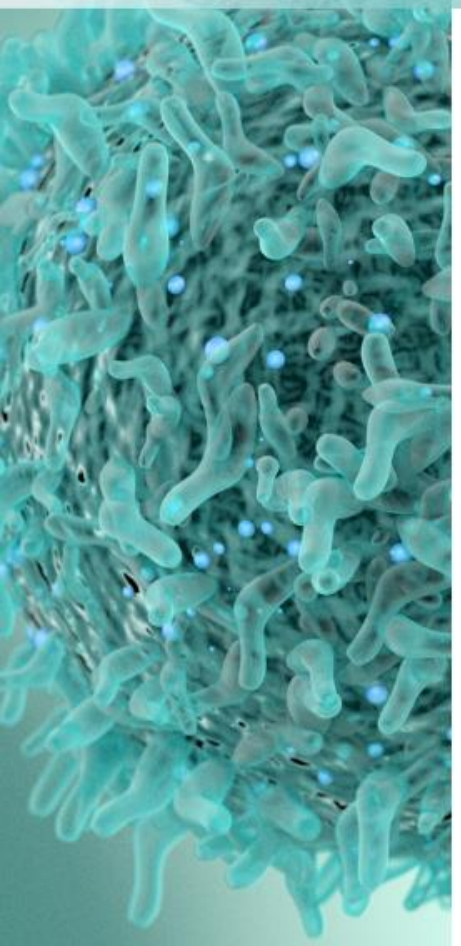


Jaime E. Anderson, PharmD, BCOP, CMQ

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

Dr. Anderson currently serves as a Clinical Pharmacy Specialist in the Melanoma & Sarcoma Medical Oncology departments at the University of Texas MD Anderson Cancer Center in Houston, TX. She received her PharmD from the University of Colorado at Denver and Health Sciences Center School of Pharmacy, completed her PGY1 Pharmacy Practice Residency at the Cleveland Clinic, and PGY2 Oncology Pharmacy Residency at MD Anderson. Dr. Anderson is a Board Certified Oncology Pharmacist and holds a Certificate in Medical Quality from the American Board of Medical Quality.

Disclosures

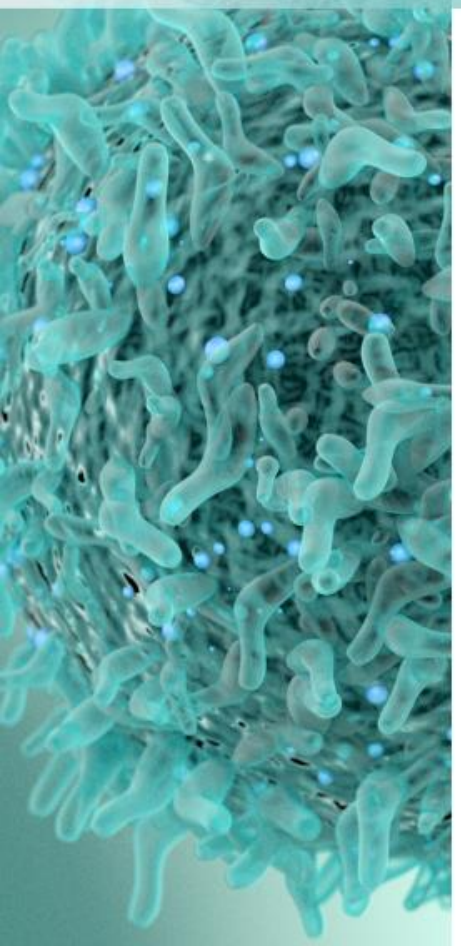


Dr. Anderson has disclosed that she has no actual or potential conflicts of interest in relation to this program.

The clinical reviewer, **Megan May**, **PharmD, BCOP**, has no actual or potential conflicts of interest in relation to this program.

Susanne Batesko, RN, BSN, Robin Soboti, RPh, and Susan R. Grady, MSN, RN-BC, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education (PHE) continuing education activities hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.

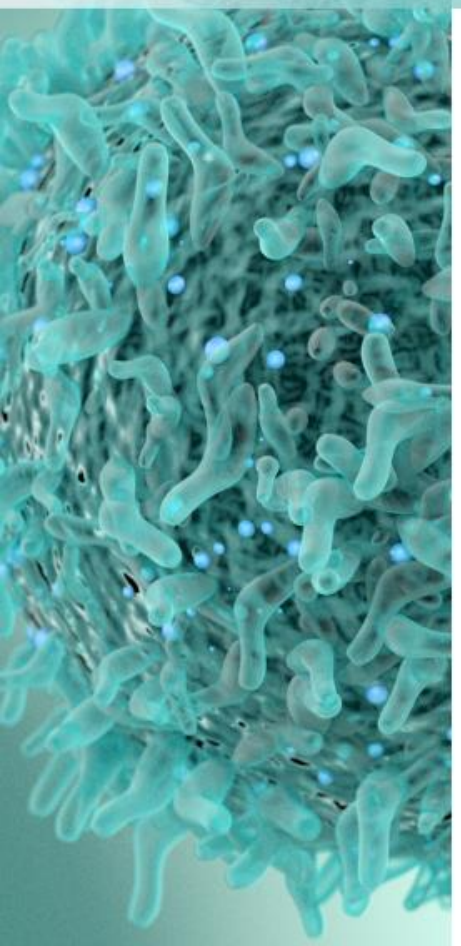
Accreditation



Postgraduate Healthcare Education, LLC is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

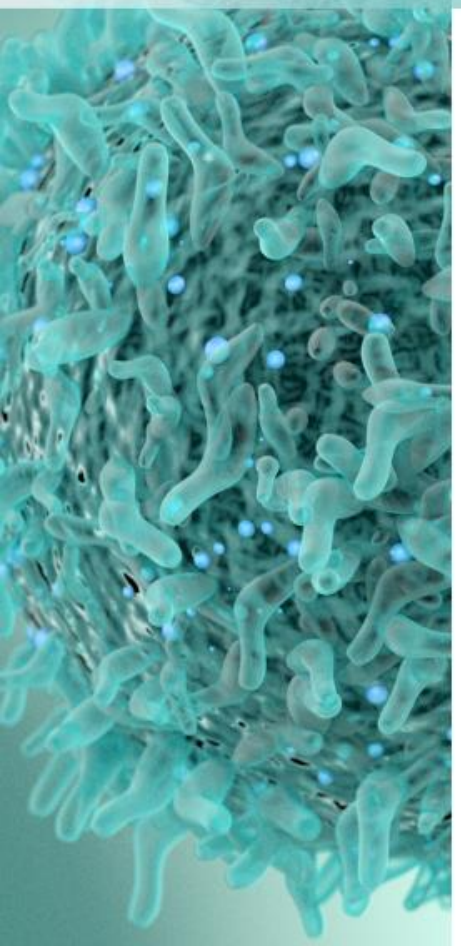
UAN: 0430-0000-20-036-H01-P
Credits: 1.0 hour (0.1 CEU)
Type of Activity: Application

Learning Objectives



- **Assess** the efficacy and safety of current and emerging immunotherapy treatment strategies for advanced melanoma
- **Discuss** the role of immunotherapy in the management of metastatic melanoma to the brain
- **Formulate** strategies to effectively manage unique adverse events when using immunotherapy agents in the treatment of melanoma

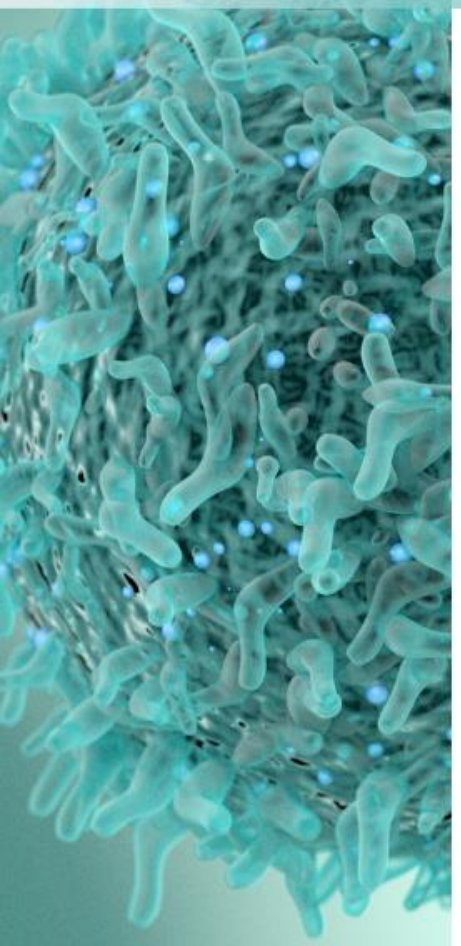
Introduction: Malignant Melanoma



- Malignancy that originates in pigment-producing melanocytes
- The incidence of melanoma continues to increase in men more rapidly than any other malignancy; it is increasing in women second only to lung cancer
- In the U.S., 84% of melanoma patients present initially with localized disease, 9% with regional disease, and 4% with distant metastases
  - 5-year survival rates for early Stage I-II, local melanomas = 50% – 90%
  - 5-year survival rates for Stage III, regional lymph node involvement = 20% – 70%
- Historically, median overall survival (OS) for patients with metastatic melanoma was 8-10 months with approved therapies
  - 5-year survival rate less than 10%

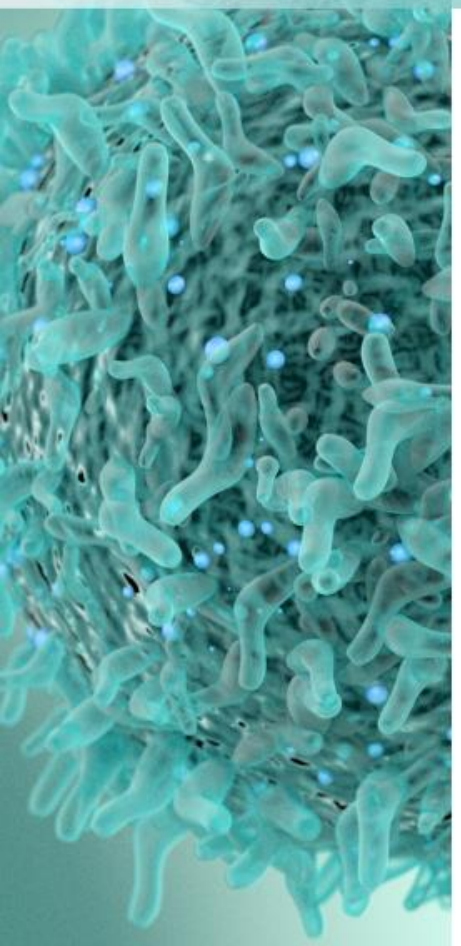
National Comprehensive Cancer Network. NCCN Guidelines: Cutaneous Melanoma. Version 3.2020. Published May 18, 2020. Accessed May 25, 2020. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma_blocks.pdf.

Introduction: Advanced Melanoma



- The availability of effective treatments for unresectable or metastatic melanoma – *or advanced melanoma* – has remained a significant challenge for decades
  - Cytotoxic therapies may have 10%-20% response rates but are short-lived
  - Use of recombinant biological response modifiers limited to individuals with good performance status
- Need for development of effective therapies targeting the advanced melanoma patient population to improve progression-free survival (PFS) and OS
  - Evolving target for standard of care
  - Expanding effective therapies to earlier settings in high-risk patients

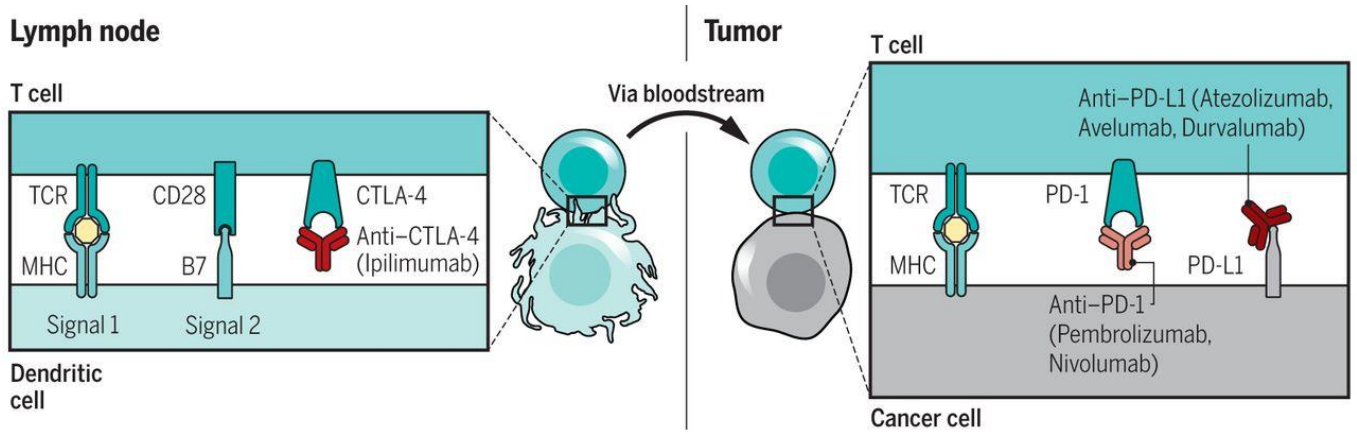
Immunotherapy Approaches for Melanoma



- The importance of the immune system in melanoma is known but not well understood
  - Malignancy associated with spontaneous regression
- Early therapies for melanoma included high-dose interleukin-2 and interferon α-2b-based regimens
- Novel development of checkpoint inhibitor (CPI) monoclonal antibodies targeting:
  - Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)
  - Programmed cell death 1 (PD-1) receptor
  - Programmed cell death ligand 1 (PD-L1)

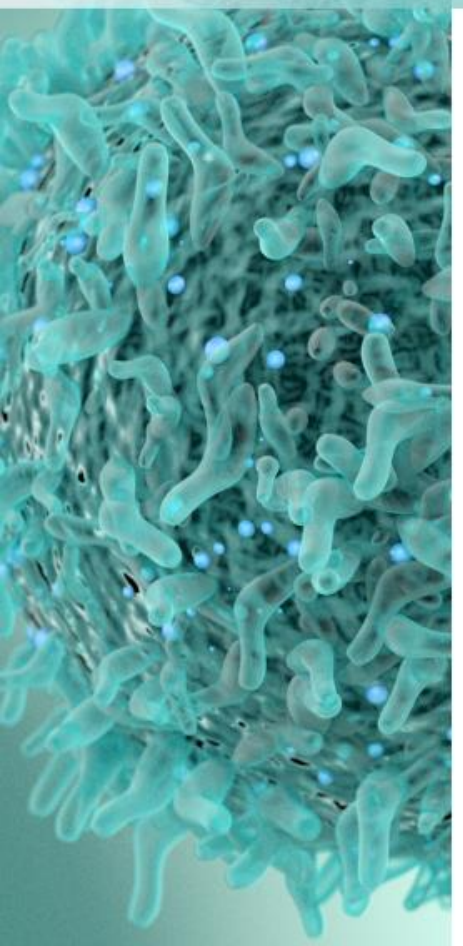
Checkpoint Inhibitors: CTLA-4

- Immune checkpoint pathways regulate the activation of T cells to prevent autoimmunity processes in the body
  - T cell activation requires more than 1 stimulatory signal
  - Tumor cells can exploit this process to evade recognition of the immune system
- CTLA-4 can stop potentially autoreactive T cells at the initial stage of naïve T cell activation in lymph nodes
  - Functions during priming phase of T cell activation



Buchbinder EI, et al. *Am J Clin Oncol.* 2016;39(1):98-106.; Ribas A, et al. *Science*. 2018;359(6382):1350-5.

Checkpoint Inhibitors: CTLA-4



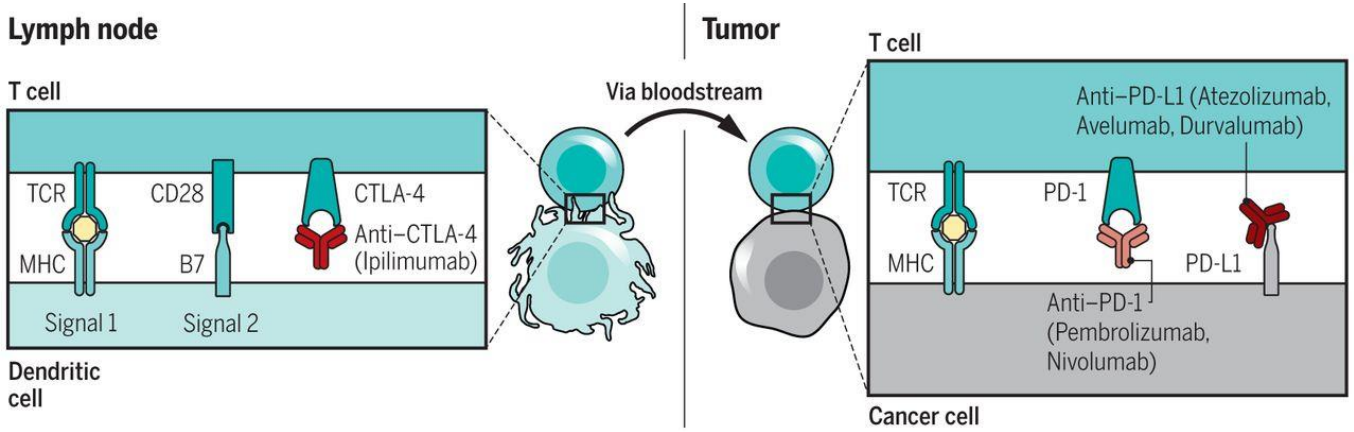
- Inhibiting the action of CTLA-4 allows the binding of CD28 and B7, leading to proliferation and differentiation of T cells
- Ipilimumab is currently the only FDA-approved CTLA-4 inhibitor
  - Unresectable or metastatic melanoma: 3 mg/kg IV over 90 minutes every 3 weeks for 4 doses
    - Can be administered as a 30-minute infusion, followed by a 1-hour observation period (for the first cycle)
  - Adjuvant following completion of regional lymph node dissection: 10 mg/kg IV over 90 minutes every 3 weeks for 4 doses, then every 12 weeks for up to 3 years

Momtaz P, et al. *J Clin Oncol.* 2015;33(30):3454-8.;
YERVOY (ipilimumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.

FDA, United States Food and Drug Administration.

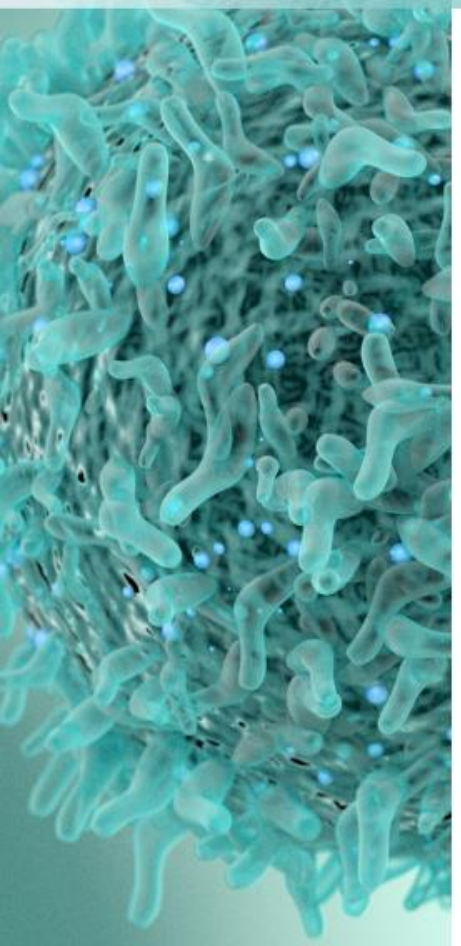
Checkpoint Inhibitors: PD-1

- PD-1 is also a member of the B7/CD28 family of costimulatory receptors
  - Binds to ligands PD-L1 and PD-L2
- Regulates previously activated T cells at the later stages of an immune response in peripheral tissues
  - Functions during effector phase of T cell activity



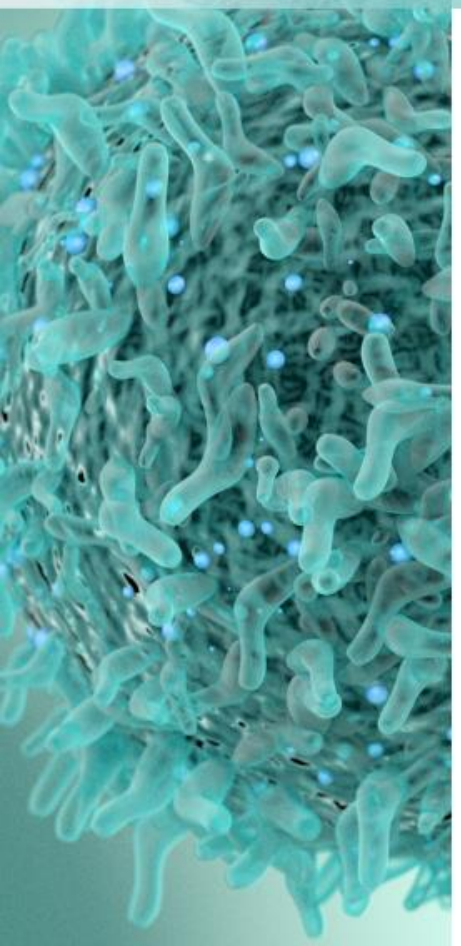
Buchbinder EI, et al. *Am J Clin Oncol.* 2016;39(1):98-106.; Ribas A, et al. *Science*. 2018;359(6382):1350-5.

Checkpoint Inhibitors: PD-1



- Inhibiting PD-1 from binding to PD-L1 allows activated T cells to further proliferate and restore antitumor immune responses
- FDA-approved PD-1 inhibitors for the treatment of unresectable or metastatic melanoma or in the adjuvant setting following complete resection of regional lymph nodes:
  - **Nivolumab 240 mg IV every 2 weeks, 480 mg IV every 4 weeks**
  - **Pembrolizumab 200 mg IV every 3 weeks, 400 mg IV every 6 weeks**
  - Both are administered as 30-minute infusions
  - For adjuvant therapy, duration is up to 12 months

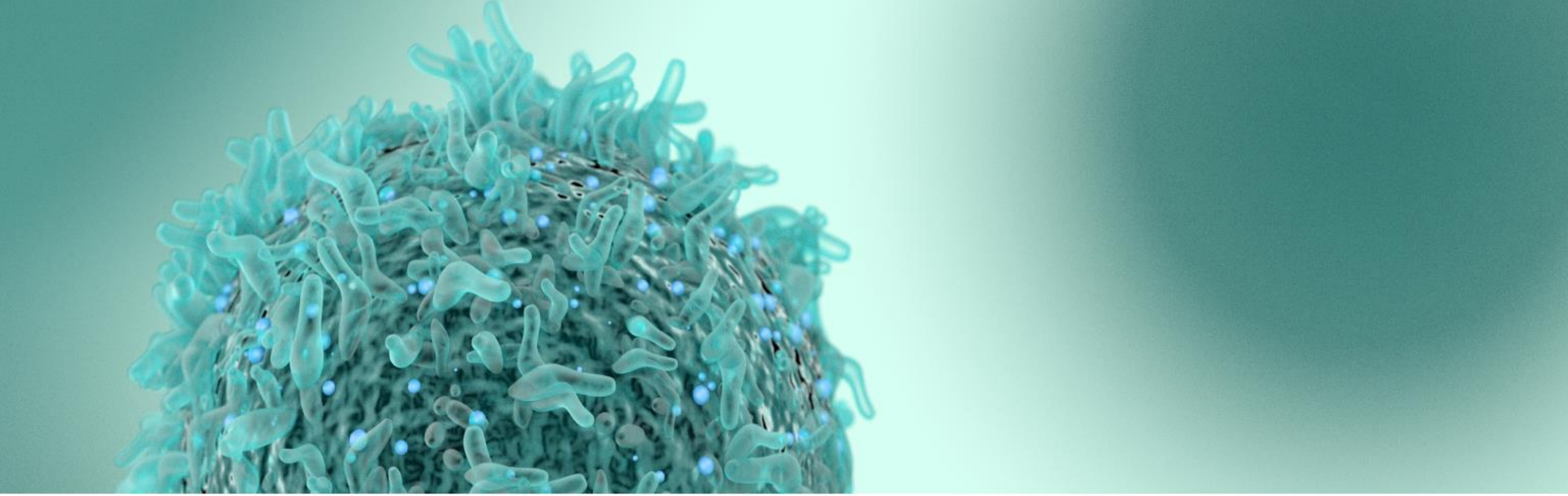
KEYTRUDA (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co, Inc.; 2020.;
OPDIVO (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.



Immunotherapy Approaches: Dual Checkpoint Blockade - CTLA-4 + PD-1 inhibition

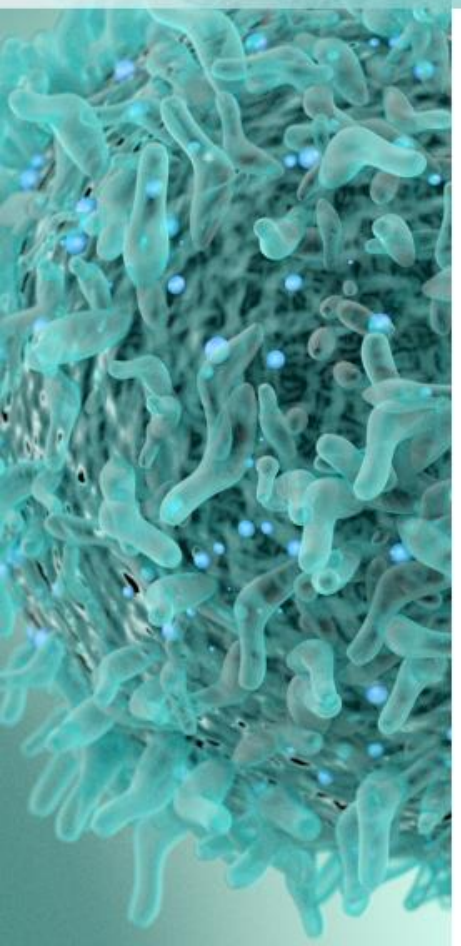
- Non-redundant effects on the immune pathway due to differences in timing of T cell activation and location of activity
- Inhibiting CTLA-4 can induce a proliferative signal found in a subset of memory T cells
- Inhibiting PD-1 is associated with changes in genes believed to be involved with cell death and natural killer (NK) cell function
- The use of CTLA-4 and PD-1 inhibitors can also produce different effects on circulating cytokines

Buchbinder EI, et al. *Am J Clin Oncol.* 2016;39(1):98-106.; Ribas A, et al. *Science*. 2018;359(6382):1350-5.



Checkpoint Inhibitors as Adjuvant Therapy After Resection

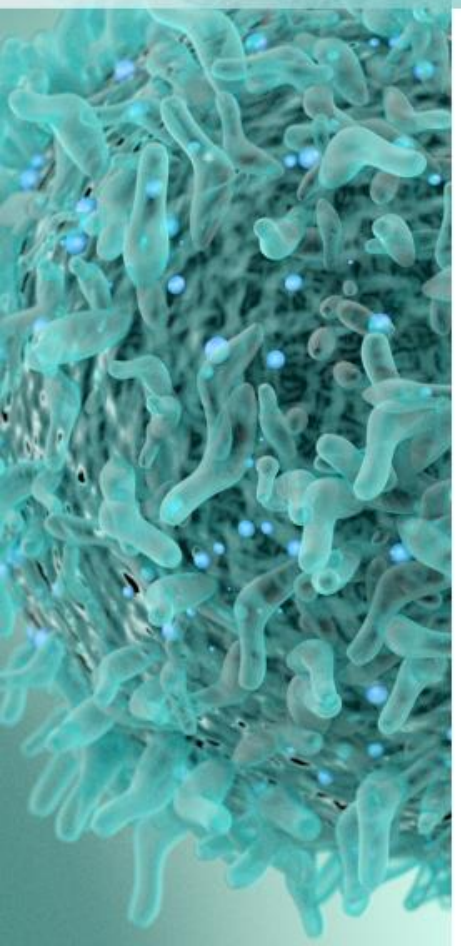
Updates to Staging with Regional Disease



- American Joint Committee on Cancer (AJCC) for melanoma staging
  - AJCC, 7th edition (2009), implemented in 2010
  - AJCC, 8th edition (2018), implemented in 2019
- Utilizes the **T**(thickness), **N**(nodal), **M**(metastasis) staging
  - Tumor thickness now taken into account for Stage III patients with AJCC-8
  - Evaluation of lymph node disease:
    - Microscopic (AJCC-7) → clinically occult (AJCC-8)
    - Macroscopic (AJCC-7)→ clinically evident (AJCC-8)
    - AJCC-7 had Stage III patients designated as Stage IIIA, IIIB, or IIIC based on:
      - Number of metastatic lymph nodes,
      - Whether it was micro- or macrometastasis, or
      - If in-transit metastasis was present
    - AJCC-8 has added a Stage IIID, representing patients who are T4b, N3a-c

Gershenwald JE, et al. *Ann Surg Oncol.* 2018;25(8):2105-10.

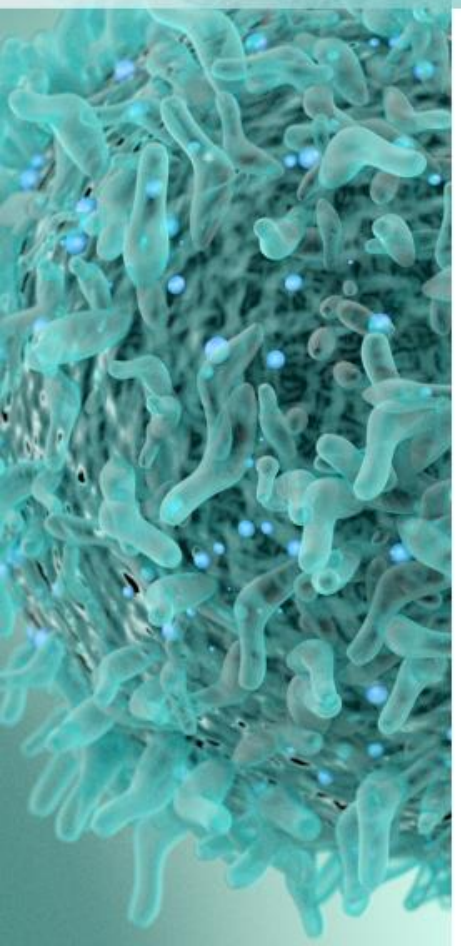
Adjuvant Immunotherapy for Melanoma



- Significant progress has been made in this treatment setting over the last several years
- For decades, systemic adjuvant therapy options were limited to interferon α-2b
  - High rates of toxicity and dose reductions or discontinuation
- Immunotherapy
  - Ipilimumab 10 mg/kg dose gained FDA indication in 2015
  - Nivolumab gained FDA indication in December 2017
  - Pembrolizumab gained FDA indication in February 2019

KEYTRUDA (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co, Inc.; 2020.;
OPDIVO (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.;
YERVOY (ipilimumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.

Adjuvant Ipilimumab – EORTC 18071

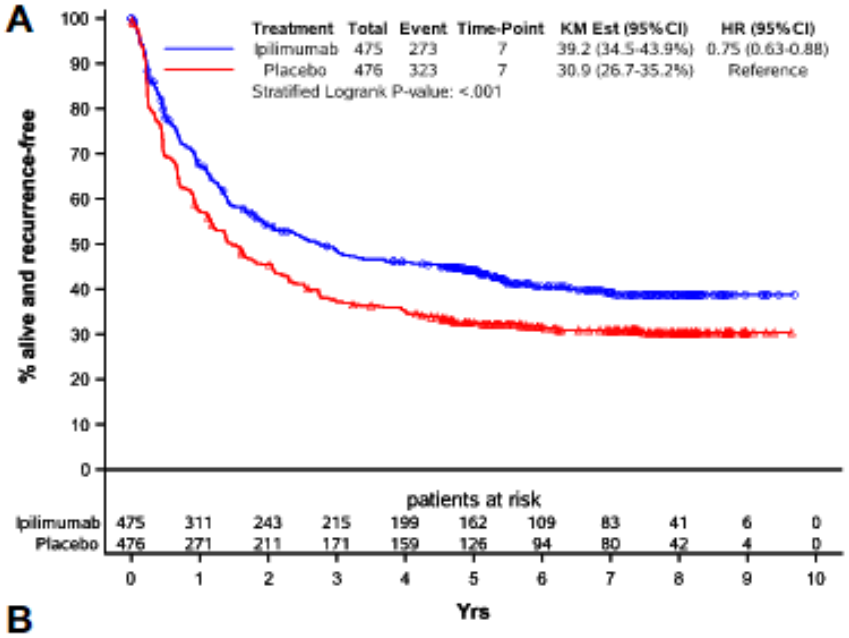


- Patients ≥ 18 years of age with cutaneous melanoma, metastatic to regional lymph nodes, AJCC-7 Stage IIIA, IIIB, or IIIC (no in-transit disease)
  - Complete regional lymph node dissection required within 12 weeks
- Randomized, double-blinded phase 3 trial
  - 1:1 placebo or ipilimumab 10 mg/kg IV every 3 weeks for 4 doses, then every 3 months for up to 3 years, or until progression or unacceptable toxicity
- **Primary endpoint:** Recurrence-free survival (RFS)
- **Secondary endpoints**: OS, safety

Eggermont AMM, et al. *Eur J Cancer*. 2019;119:1-10.; Eggermont AM, et al. *Lancet Oncol*. 2015;16(5):522-30.

Adjuvant Ipilimumab – EORTC 18071

- Updated data analysis of 951 randomized patients with long-term median follow-up
  - 6.6 years in the ipilimumab group
  - 7.1 years in the placebo group
- 7-year RFS rate
  - 39.2% with ipilimumab
    (95% CI: 34.5 – 43.9)
  - 30.2% with placebo
    (95% CI: 26.7 – 35.2)
- Benefit seen across all subgroups



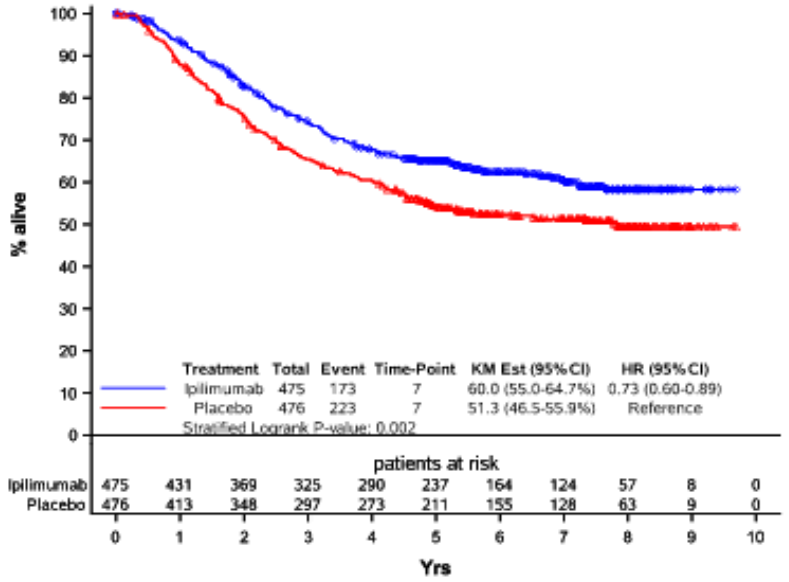
Eggermont AMM, et al. *Eur J Cancer*. 2019;119:1-10.

CI, confidence interval.

Adjuvant Ipilimumab – EORTC 18071

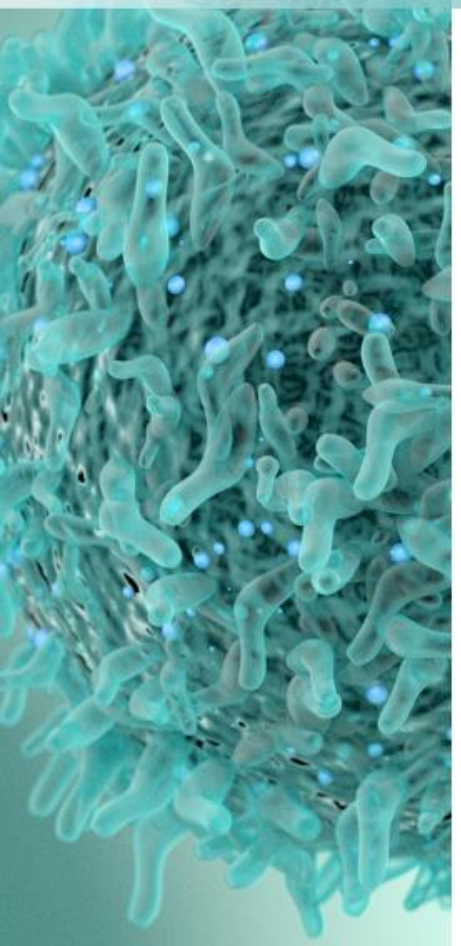
	Ipilimumab (N = 471)	Placebo (N = 474)
Any grade adverse event (AE)	465 (99%)	432 (91%)
Grade 3-4 AE	254 (54%)	118 (25%)
Discontinued treatment due to AE	245 (52%)	20 (4%)

- 7-year OS rate
  - 60% with ipilimumab (95% CI: 55 – 64.7)
  - 51.3% with placebo (95% CI: 46.5 – 55.9)
- Benefit seen across all subgroups



Eggermont AMM, et al. *Eur J Cancer*. 2019;119:1-10.; Eggermont AM, et al. *Lancet Oncol*. 2015;16(5):522-30.

Adjuvant Nivolumab – Checkmate 238



- Patients ≥ 15 years of age with AJCC-7 Stage IIIB, IIIC, or IV melanoma
  - Complete regional lymph node dissection or resection of metastatic disease required within 12 weeks
  - Resected brain metastases also eligible
- Randomized, double-blinded phase 3 trial
  - 1:1 to receive either nivolumab 3 mg/kg IV every 2 weeks or ipilimumab 10 mg/kg IV every 3 weeks for 4 doses and then every 12 weeks
  - Treatment administered up to 1 year or until recurrence or unacceptable toxicity

Weber J, et al. *N Engl J Med.* 2017;377(19):1824-35.

Adjuvant Nivolumab – Checkmate 238

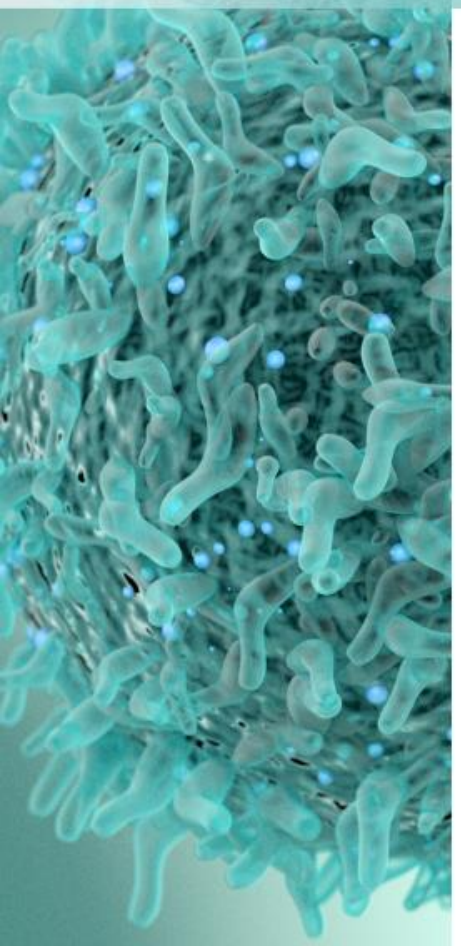
- 906 patients were randomized: 453 patients per arm
- **Primary endpoint**: RFS
  - 36-month follow-up
    - Nivolumab – 58% RFS rate (188/453 patients)
    - Ipilimumab – 45% RFS rate (239/453 patients)
    - Nivolumab demonstrated superior RFS versus ipilimumab (HR, 0.68; P < 0.0001)
- **Secondary endpoints**: OS, safety

	Nivolumab (N = 452)	Ipilimumab (N = 453)
Treatment-related AE, any grade	385 (85.2%)	434 (95.8%)
Treatment-related AE, grade 3-4	65 (14.4%)	208 (45.9%)
Treatment-related AE leading to discontinuation, any grade	35 (7.7%)	189 (41.7%)

Weber J, et al. *Ann Oncol*. 2019;30(suppl_5):v533-63.; Weber J, et al. *N Engl J Med*. 2017;377(19):1824-35.

HR, hazard ratio.

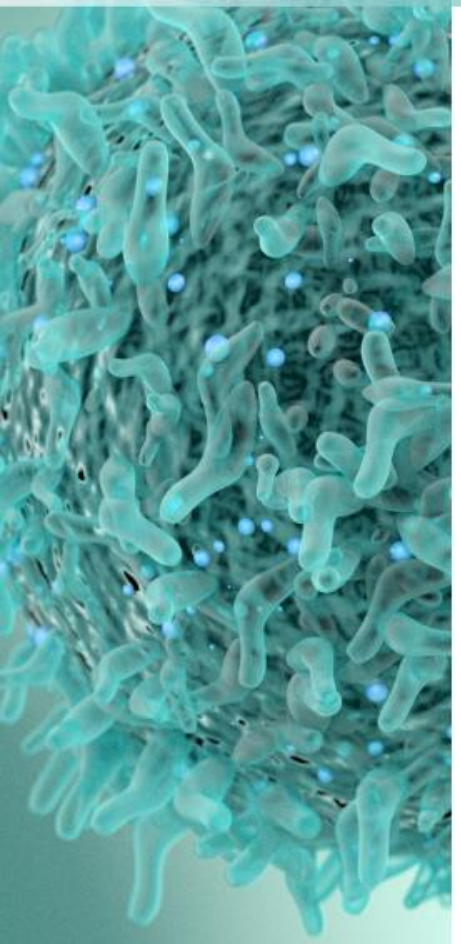
Adjuvant Pembrolizumab – KEYNOTE-054



- Patients ≥ 18 years of age with cutaneous melanoma, metastatic to regional lymph nodes, AJCC-7 Stage IIIA, IIIB, or IIIC (no in-transit disease)
  - Complete regional lymph node dissection required within 13 weeks
- Randomized, double-blinded phase 3 trial
  - 1:1 to either placebo or pembrolizumab 200 mg IV every 3 weeks for a total of 18 doses (approximately 1 year) or until recurrence or unacceptable toxicity
  - Part 2 of this study did allow crossover to receive pembrolizumab with documented recurrence

Eggermont AMM, et al. *N Engl J Med*. 2018;378(19):1789-801.

Adjuvant Pembrolizumab – KEYNOTE-054



- 1014 patients were randomized
- **Primary endpoint:** RFS (both intention-to-treat, subgroup of PD-L1- positive tumor patients)

	Pembrolizumab (N = 514)	Placebo (N = 505)
Intention-to-treat - At 12 months - At 18 months	 75.4% (95% CI, 71.3 – 78.9) 71.4% (95% CI, 66.8 – 75.4)	 61% (95% CI, 56.5 – 65.1) 53.2% (95% CI, 47.9 – 58.2)
PD-L1-positive tumor* - At 12 months	*428 patients* 77.1% (95% CI, 72.7 – 80.9)	*425 patients* 62.6% (95% CI, 57.7 – 67)

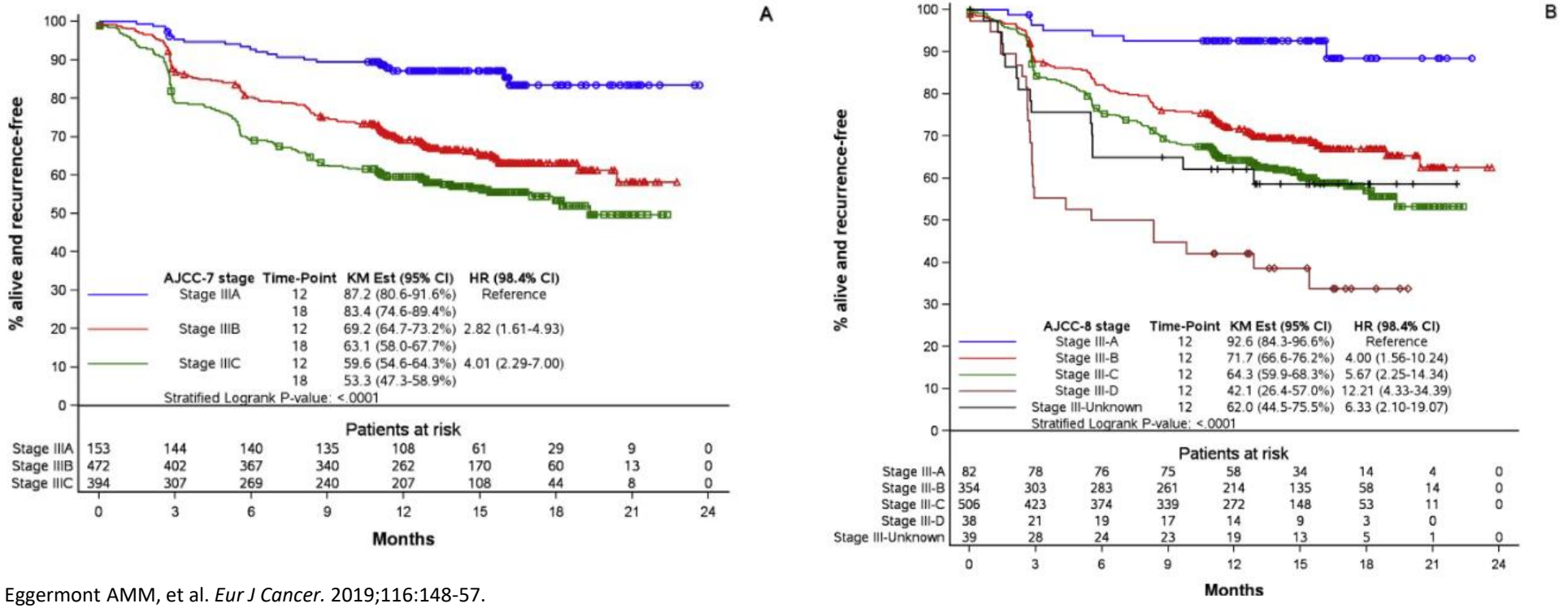
*Melanoma score ≥ 2 (i.e., staining on > 1% of cells)

- **Secondary endpoint:** Safety measures, OS
  - Pembrolizumab had 77.8% any grade treatment-related AE and 14.7% grade 3-4 treatment-related AE

Eggermont AMM, et al. *N Engl J Med*. 2018;378(19):1789-801.

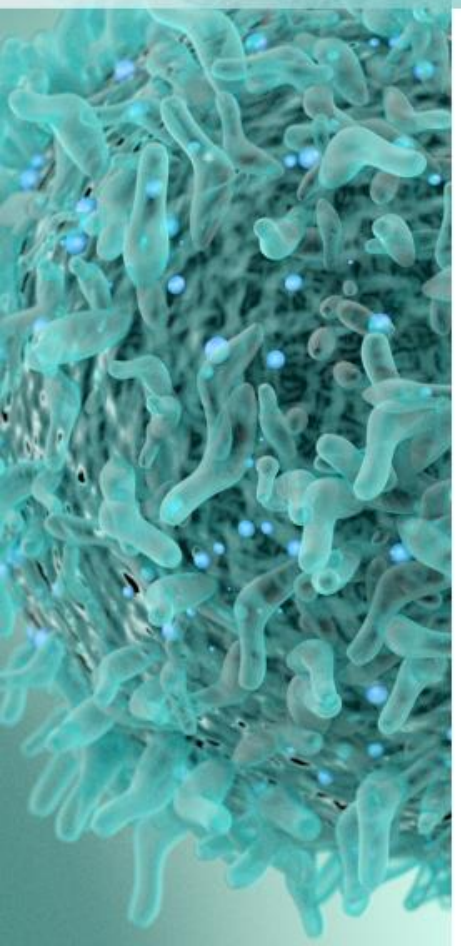
Adjuvant Pembrolizumab – KEYNOTE-054

- AJCC-8 classification of melanoma was based on data gathered when CPI were not used as adjuvant therapy
- Predictive importance of AJCC-7 and AJCC-8 on RFS



Eggermont AMM, et al. *Eur J Cancer.* 2019;116:148-57.

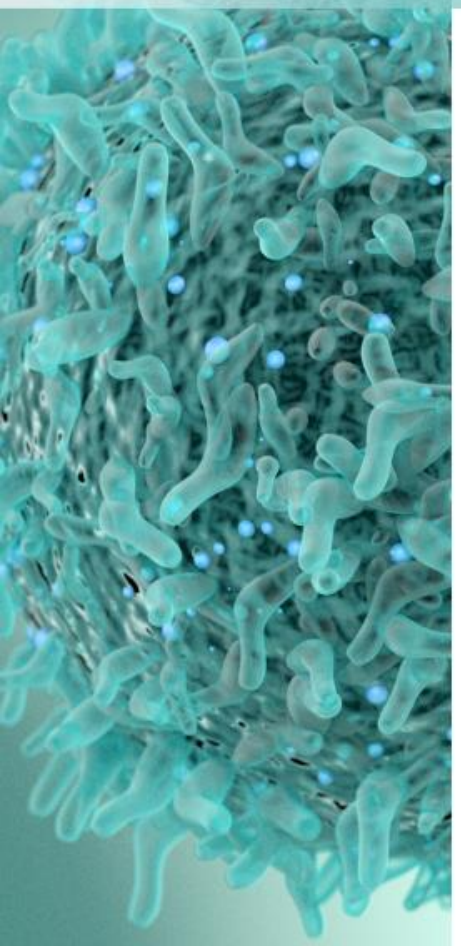
Adjuvant Ipilimumab + Nivolumab – IMMUNED



- Patients 18-80 years of age with Stage IV melanoma, rendered no evidence of disease (NED) with surgical resection or radiation
- Randomized 1:1:1, double-blinded phase 2 trial, placebo-controlled
  1) Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks for up to 1 year
  2) Nivolumab 3 mg/kg IV every 2 weeks for up to 1 year
  3) Double-matched placebo
- **Primary endpoint**: RFS
- **Secondary endpoints**: OS, time to recurrence (TTR)

Zimmer L, et al. *Lancet*. 2020;395(10236):1558-68.

Adjuvant Ipilimumab + Nivolumab – IMMUNED



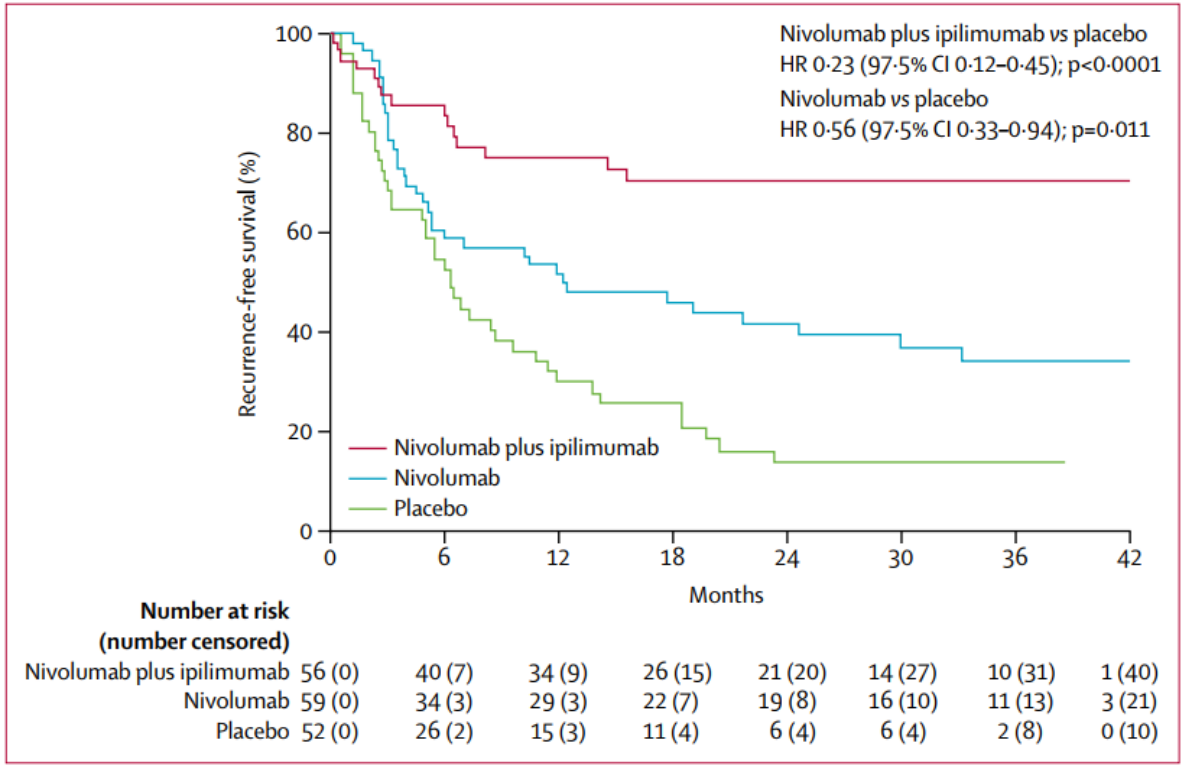
- Median follow-up of 28.4 months

	Ipilimumab + nivolumab (N = 55)	Nivolumab (N = 56)	Placebo (N = 51)
Median time on treatment, weeks	6.5	21.9	24.5
Completed 1 year of treatment	11 (20%)	21 (38%)	10 (20%)
Treatment-related AE • Grade 3-4	53 (96%) 39 (71%)	47 (84%) 15 (27%)	28 (55%) 3 (6%)
Treatment-related AE leading to discontinuation • Grade 3-4	34 (62%) 29 (53%)	7 (13%) 5 (9%)	1 (2%) 0

Zimmer L, et al. *Lancet*. 2020;395(10236):1558-68.

Adjuvant Ipilimumab + Nivolumab – IMMUNED

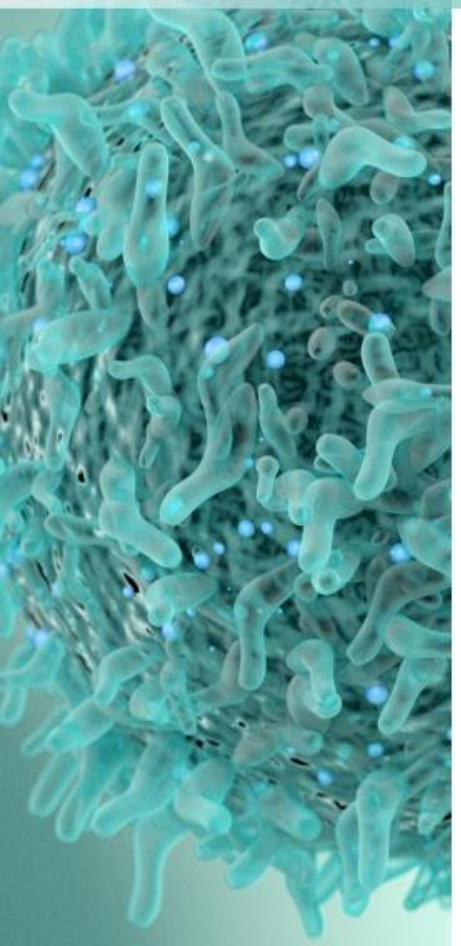
- **Primary endpoint**: RFS
  - Nivolumab + ipilimumab
    - Median not reached
  - Nivolumab
    - Median 12.4 months
  - Placebo
    - Median 6.4 months
- **Secondary endpoint**: TTR
  - Nivolumab + ipilimumab
    - Median not reached
  - Nivolumab
    - Median 17.7 months
  - Placebo
    - Median 6.4 months



- OS will be assessed once the last patient off therapy is followed up for 2 years

Zimmer L, et al. *Lancet*. 2020;395(10236):1558-68.

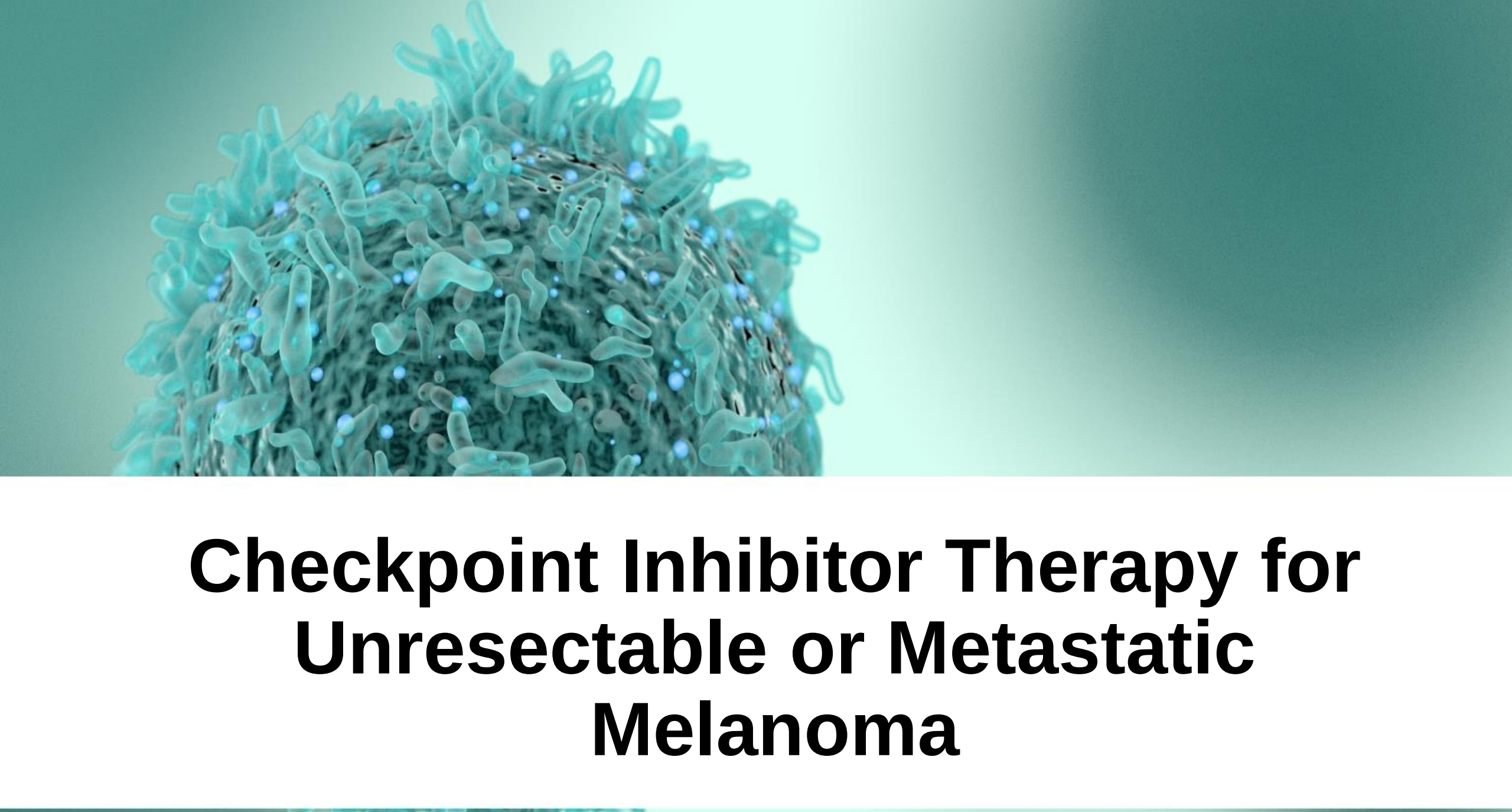
Summary – Adjuvant Immunotherapy



- Nivolumab – Resected Stage III and Stage IV melanoma
  - NCCN Category 1 for Stage IIIB, IIIC (AJCC-7), Stage IV
- Pembrolizumab – Resected Stage III melanoma
  - NCCN Category 1 for Stage IIIA, IIIB, IIIC (AJCC-7)
- Ipilimumab only recommended if patient has prior exposure to anti-PD-1 therapy
- Future data watch
  - Will combination ipilimumab + nivolumab gain an FDA-approved indication for adjuvant treatment of resected Stage IV?
  - Pembrolizumab for high-risk Stage IIB/IIC (KEYNOTE-716)
  - Nivolumab for high-risk Stage IIA vs. IIB vs. IIC (NivoMela)

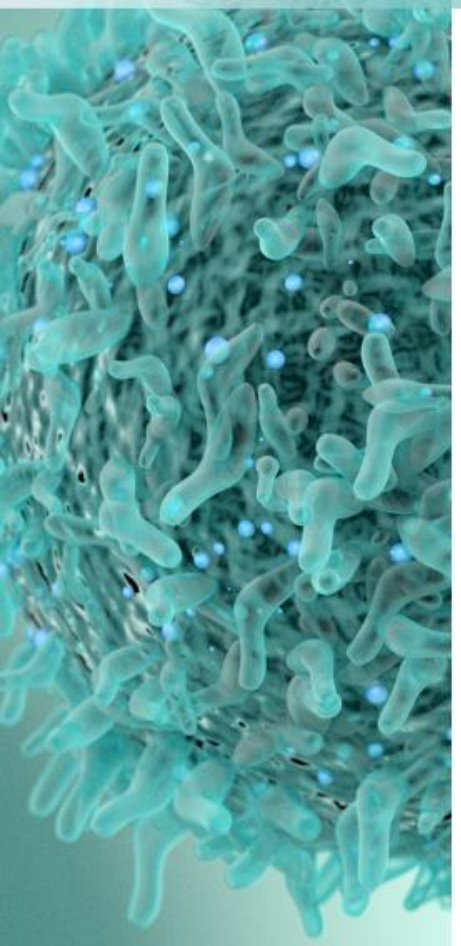
National Comprehensive Cancer Network. NCCN Guidelines: Cutaneous Melanoma. Version 3.2020. Published May 18, 2020. Accessed May 25, 2020.https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma_blocks.pdf.

NCCN, National Comprehensive Cancer Network.



Checkpoint Inhibitor Therapy for Unresectable or Metastatic Melanoma

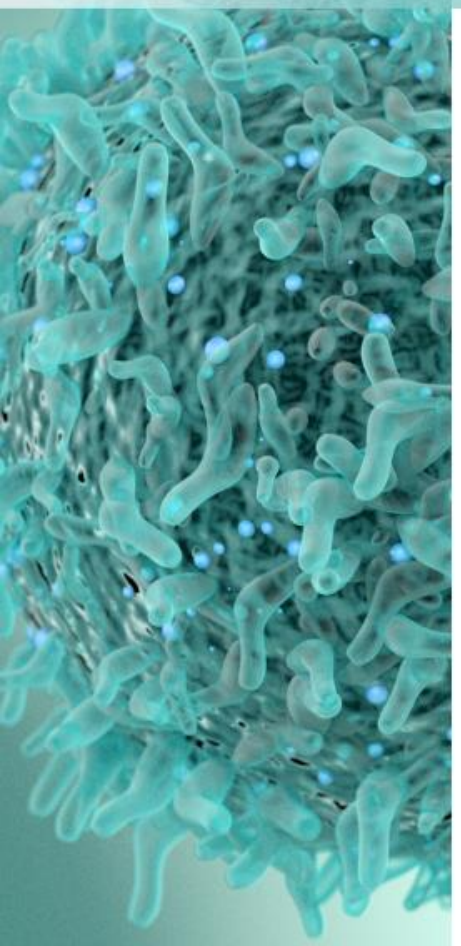
Unresectable or Metastatic Melanoma



- Over the last decade, there have been significant improvements in PFS and OS of advanced melanoma patients
- First-line systemic therapy, NCCN Category 1:
  - PD-1 inhibitor monotherapy (nivolumab or pembrolizumab)
  - Dual checkpoint inhibition (ipilimumab 3 mg/kg + nivolumab 1 mg/kg)
  - BRAF + MEK inhibitors if *BRAF* mutation present
- Second-line systemic therapy, preferred regimens:
  - Select therapy with differing mechanism of activity
  - PD-1 inhibitor monotherapy (nivolumab or pembrolizumab)
  - Dual checkpoint inhibition (ipilimumab 3 mg/kg + nivolumab 1 mg/kg)
  - BRAF + MEK inhibitors if *BRAF* mutation present
  - Other therapies → ipilimumab monotherapy, cytotoxic agents

National Comprehensive Cancer Network. NCCN Guidelines: Cutaneous Melanoma. Version 3.2020. Published May 18, 2020. Accessed May 25, 2020. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma_blocks.pdf.

Advanced Melanoma - Pembrolizumab



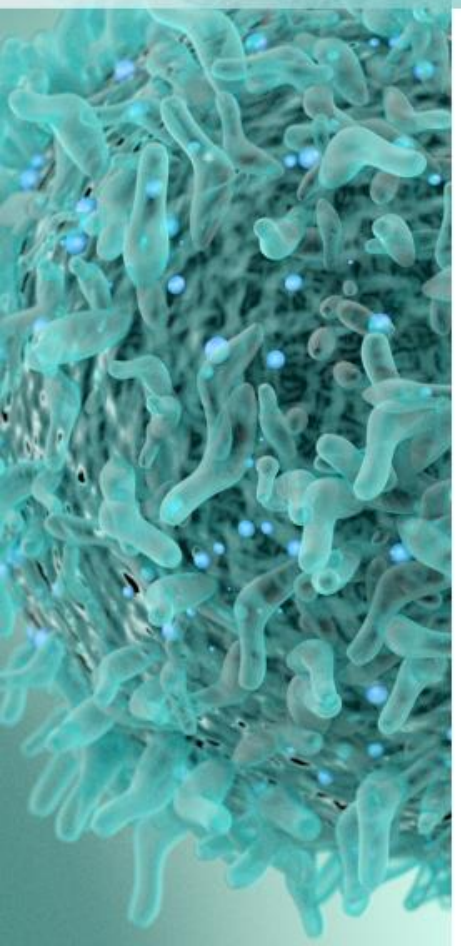
- Pembrolizumab was the first PD-1 inhibitor to gain FDA approval for advanced melanoma in September 2014

	Response rates	PFS, 2 years	OS, 2 years
KEYNOTE-002 (2 mg/kg, 10 mg/kg) vs. chemotherapy	22% – 28% 4%	16% – 22% 0.6%	36% – 38% (95% CI, 31.1 – 45.2) 30% (95% CI, 23 – 36.7)
	Response rates	**PFS, 48 months**	**OS, 5 years**
KEYNOTE-006 (10 mg/kg) vs. ipilimumab 3 mg/kg x 4 doses	42% 17%	23% 7.3%	38.7% (95% CI, 34.2 – 43.1) 31% (95% CI, 25.3 – 36.9)

- Pembrolizumab was compared to current “standards” at the time, ipilimumab or investigator’s choice chemotherapy
- Demonstrated benefit for PFS and OS
- Pembrolizumab should be considered as first-line therapy for unresectable or metastatic melanoma

Hamid O, et al. *Eur J Cancer.* 2017;86:37-45.; Robert C, et al. *Lancet Oncol*. 2019;20(9):1239-51.

Advanced Melanoma - Nivolumab



- Nivolumab approved by the FDA for advanced melanoma in December 2014

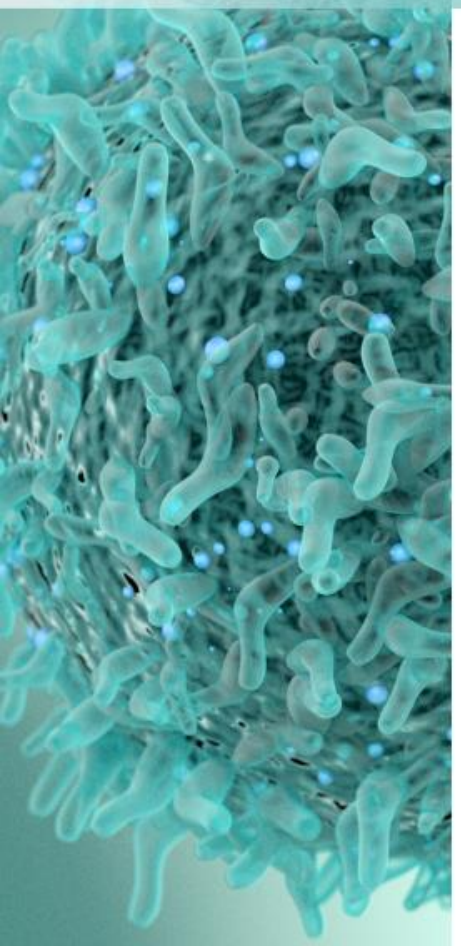
	Response rates	Median PFS, months	Median OS, months
CheckMate-037 (3 mg/kg) vs. chemotherapy	27% 10%	3.1 3.7	15.7 14.4
CheckMate-066 (3 mg/kg)* vs. dacarbazine	43% 14%	5.1 2.2	37.5 (P < 0.001) 11.2

*Treatment-naïve

- CheckMate-066 demonstrated improved response rate, PFS, and OS compared with chemotherapy
- Nivolumab should be considered as first-line therapy for unresectable or metastatic melanoma

Ascierto PA, et al. *JAMA Oncol*. 2019;5(2):187-94.; Larkin J, et al. *J Clin Oncol.* 2018;36(4):383-90.

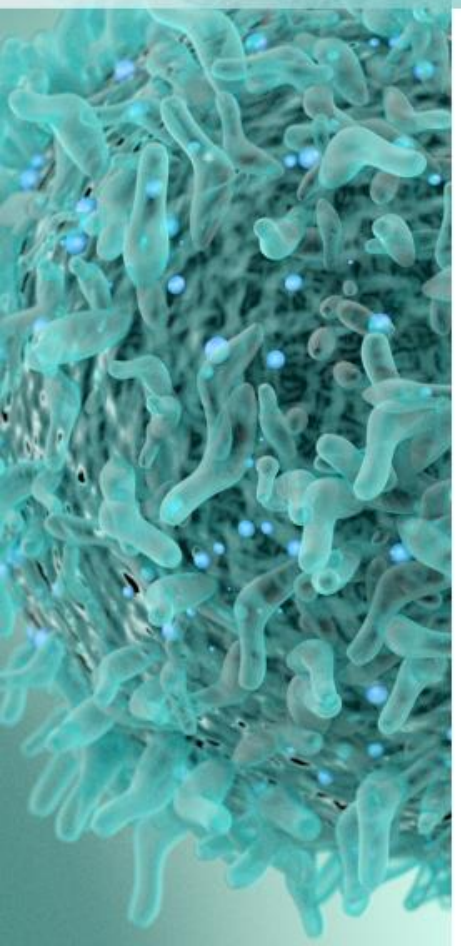
Advanced Melanoma – CheckMate 067



- Treatment-naïve adult patients with unresectable Stage III or metastatic Stage IV melanoma
- Randomized 1:1:1, double-blinded, placebo-controlled (matched) phase 3 trial with 3 arms
  1) Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV every 3 weeks for 4 doses, then nivolumab 3 mg/kg every 2 weeks
  2) Nivolumab 3 mg/kg every 2 weeks
  3) Ipilimumab 3 mg/kg every 3 weeks for 4 doses
- **Primary endpoints:** PFS and OS, compared between ipilimumab and either nivolumab-containing arm

Larkin JV, et al. *N Engl J Med*. 2019; 381(16):1535-46.

Advanced Melanoma – CheckMate 067



- 945 patients randomized, 5-year follow-up

	Ipilimumab + nivolumab (N = 314)	Nivolumab (N = 316)	Ipilimumab (N = 315)
Median OS, months	Not reached	36.9 (95% CI, 28.2 – 58.7)	19.9 (95% CI, 16.8 – 24.6)
OS at 5 years, %	52	44	26
Median PFS, months	11.5 (95% CI, 8.7 – 19.3)	6.9 (95% CI, 5.1 – 10.2)	2.9 (95% CI, 2.8 – 3.2)
PFS at 5 years, %	36	29	8
Best overall response, n - Complete response - Partial response - Stable disease	 69 (22%) 114 (36%) 38 (12%)	 60 (19%) 81 (26%) 30 (9%)	 18 (6%) 42 (13%) 69 (22%)
Objective response, n	183 (58%)	140 (45%)	59 (19%)
Median duration of response, months	Not reached	Not reached	14.4

Larkin JV, et al. *N Engl J Med*. 2019;381(16):1535-46.

Metastatic Melanoma – CheckMate 067

- Selected adverse events

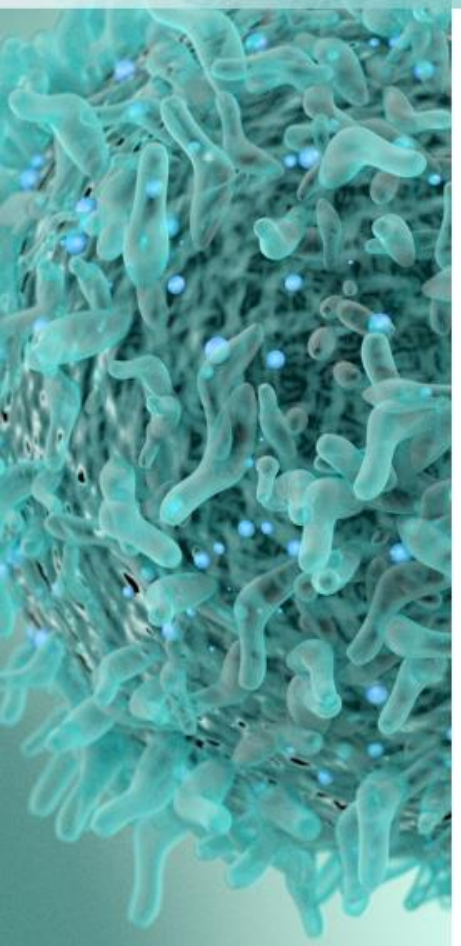
	Ipilimumab + nivolumab (N = 314)		Nivolumab (N = 316)		Ipilimumab (N = 315)	
	All grades	**Grade 3-4**	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Any treatment-related AE	300 (96%)	184 (59%)	270 (86%)	67 (21%)	268 (86%)	26 (28%)
Discontinuation related to treatment AE	123 (39%)	95 (30%)	37 (12%)	24 (8%)	49 (16%)	43 (14%)
Fatigue	119 (38%)	13 (4%)	114 (36%)	3 (1%)	89 (29%)	3 (1%)
Rash	93 (30%)	10 (3%)	72 (23%)	1 (< 1%)	68 (22%)	5 (2%)
Diarrhea	142 (45%)	29 (9%)	67 (21%)	9 (3%)	105 (34%)	18 (6%)
Increased AST	51 (16%)	19 (6%)	14 (4%)	3 (1%)	12 (4%)	2 (1%)
Increased ALT	60 (19%)	27 (9%)	13 (4%)	4 (1%)	12 (4%)	5 (2%)

- 5-year safety follow-up similar to previous reported analyses

Larkin JV, et al. *N Engl J Med*. 2019;381(16):1535-46.;
Wolchok JD, et al. *N Engl J Med.* 2017;377(14):1345-56.

ALT, alanine transaminase;
AST, aspartate transaminase.

Advanced Melanoma – CheckMate 511



- Patients ≥ 18 years of age with unresectable Stage III or metastatic Stage IV melanoma
- Randomized 1:1, double-blinded, phase 3b/4
- Part 1: 2 arms
  1) Nivolumab 3 mg/kg + ipilimumab 1 mg/kg IV every 3 weeks for 4 doses
  2) Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV every 3 weeks for 4 doses
- Part 2: Open label, maintenance nivolumab 480 mg IV every 4 weeks until progression or unacceptable toxicity
  - Started 6 weeks after the last combination dose
- **Primary endpoint:** Rate of treatment-related grade 3-5 AEs
- **Secondary endpoints:** Overall response rate (ORR), PFS, OS

Lebbe C, et al. *J Clin Oncol.* 2019;37(11):867-75.

Advanced Melanoma – CheckMate 511

- 360 patients randomized, with median follow-up of 18 months

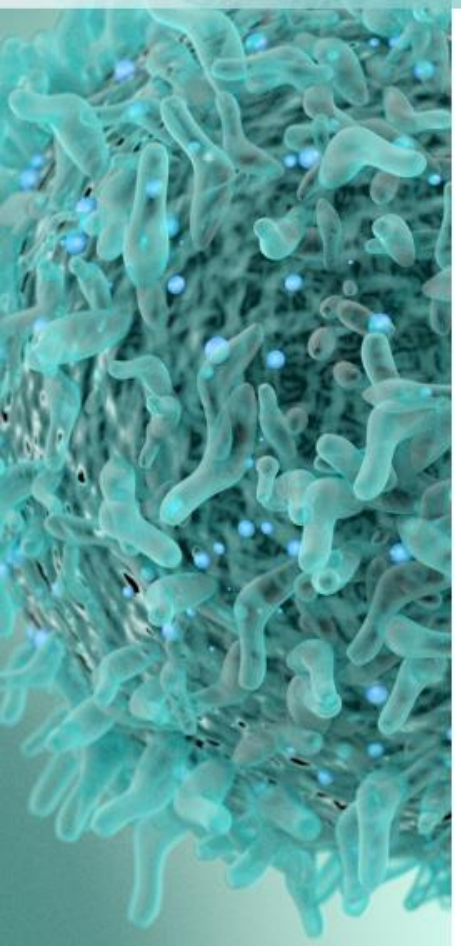
	Nivo 3 + Ipi 1 (N = 180)	Nivo 1 + Ipi 3 (N = 178)
Treatment-related grade 3-5 AE	33.9% (27 – 41.3)*	48.3% (40.8 – 55.9)
	Difference of 14.4% (95% CI, 4.3 – 24.5) P = 0.006	
Discontinuation due to treatment-related AE	43 (23.9%)	59 (33.1%)
Diarrhea, grade 3-4	5 (2.8%)	11 (6.2%)
ALT increased, grade 3-4	3 (1.7%)	8 (4.5%)
AST increased, grade 3-4	1 (0.6%)	5 (2.8%)
ORR	45.5% (38.1 – 53.1)	50.6% (43 – 58.1)
12-month PFS	47.2%	46.4%
12-month OS	79.7%	81%

*1 grade 5 event, due to autoimmune myocarditis, rhabdomyolysis

- Off-label dose for advanced melanoma: Nivolumab 3 mg/kg + ipilimumab 1 mg/kg IV every 3 weeks for 4 doses, followed 6 weeks later with nivolumab 480 mg every 4 weeks

Lebbe C, et al. *J Clin Oncol.* 2019;37(11):867-75.; Micromedex. IBM Watson Health, Greenwood Village, Colorado, USA. https://www.micromedexsolutions.com. Accessed April 28, 2020.

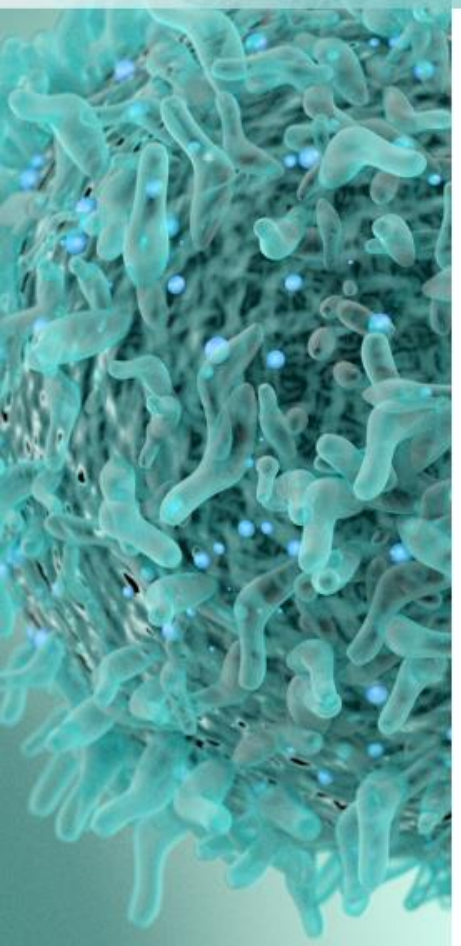
Melanoma Brain Metastases



- Poor prognosis, median OS approximately 4-5 months
- Traditionally, prospective trials using immunotherapy have excluded melanoma patients with untreated brain metastases
  - Contraindication for high-dose interleukin-2 therapy
  - Possible use of corticosteroids to manage symptoms related to intracranial swelling
- Management of brain metastases can present a challenge to overall treatment planning, varying with the extent of intracranial and extracranial disease burden
  - **Symptomatic** – Prioritize brain-directed therapy (i.e., surgery if resectable or radiation modalities using stereotactic radiosurgery or whole brain radiotherapy)
    - Patient may require supraphysiologic doses of dexamethasone for symptom control
  - **Asymptomatic** – Still proceed with radiation prior to or in conjunction with systemic therapy?

National Comprehensive Cancer Network. NCCN Guidelines: Cutaneous Melanoma. Version 3.2020. Published May 18, 2020. Accessed May 25, 2020. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma_blocks.pdf.

Brain Metastases – CheckMate 204



- Adult patients with malignant melanoma with ≥ 1 measurable brain metastasis (0.5-3 cm) not previously irradiated
  - No neurologic symptoms or not requiring corticosteroids
- Open label, phase 2 trial
  - Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV every 3 weeks for 4 doses followed by 3 mg/kg IV every 2 weeks until progression or unacceptable toxicity
  - If severe AE occurred during induction (combination), could transition to maintenance nivolumab once toxicity resolved
- **Primary endpoint:** Rate of intracranial clinical benefit
  - Stable disease for > 6 months after starting treatment, complete response, or partial response
- **Secondary endpoints:** Rates of extracranial and global clinical benefit, ORR (complete response + partial response)

Tawbi HA, et al. *N Engl J Med.* 2018;379(8):722-30.

Brain Metastases – CheckMate 204

- 94 patients assessed, median follow-up of 20.6 months for primary endpoint only

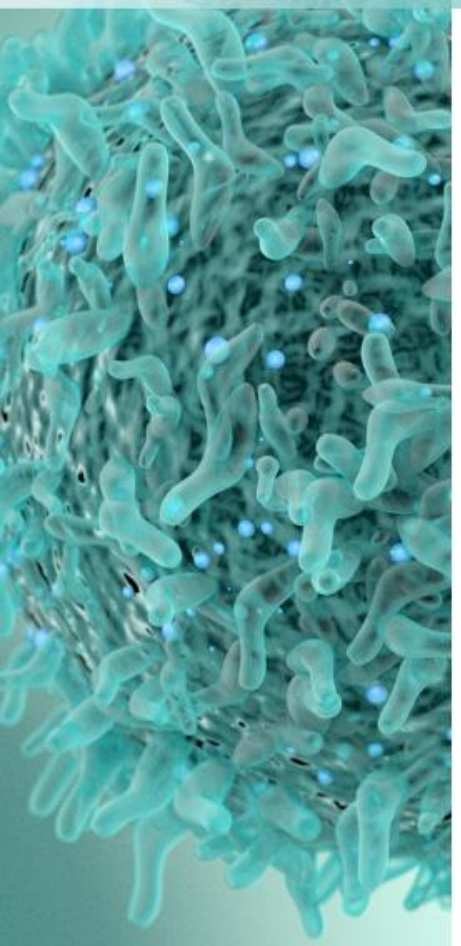
	Intracranial	Extracranial*	Global*
Clinical benefit rate	58.4% (95% CI, 48.2 – 68.1)	56% (95% CI, 46 – 67)	56% (95% CI, 46 – 67)
ORR	55% (95% CI, 45 – 66)	50% (95% CI, 40 – 60)	51% (95% CI, 40 – 62)

*Data from prior analysis of 14 months median follow-up

- 33 patients (35%) received all 4 induction cycles and 55 patients (59%) received maintenance nivolumab
- Of patients who had an intracranial objective response (partial or complete), 90% were ongoing at the time of analysis

Tawbi HA, et al. *N Engl J Med.* 2018;379(8):722-30.

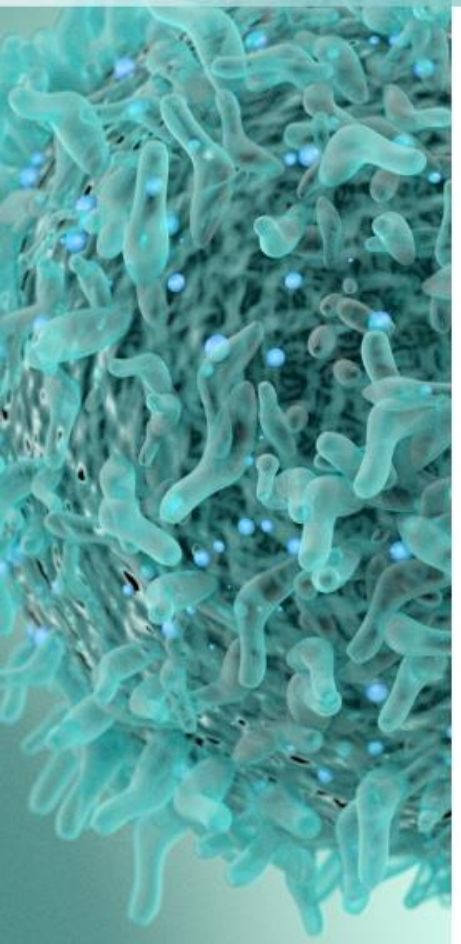
Brain Metastases – CheckMate 204



- A later amendment added a second arm of 20 symptomatic patients with brain metastases
  - Neurologic symptoms, could be receiving corticosteroids
- 18 patients treated, median follow-up of 5.2 months
  - 2 patients (11%) received all 4 induction cycles
- Results
  - Intracranial clinical benefit rate = 22.2% (95% CI, 6.4 – 47.6)
  - Intracranial objective response rate = 16.7%
- Further investigation warranted for this patient population

Tawbi HA, et al. *J Clin Oncol*. 2019;37(15_suppl):9501.;
Tawbi HA, et al. *N Engl J Med*. 2018;379(8):722-30.

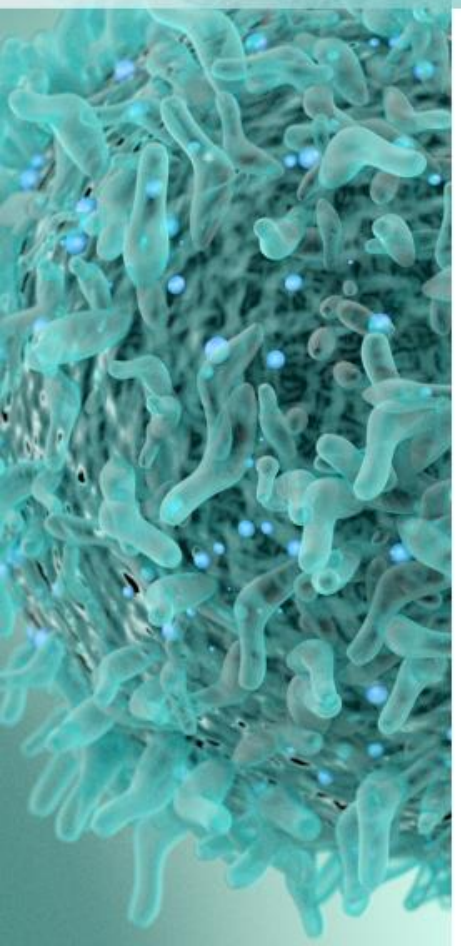
Anti-PD1 Brain Collaboration (ABC) Trial



- Patients ≥ 18 years of age with malignant melanoma metastatic to the brain, naïve to CPI therapy
- Randomized, open-label, phase 2 trial with 3 cohorts
  - **Cohort A:** Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV every 3 weeks for 4 doses, then nivolumab 3 mg/kg every 2 weeks
  - **Cohort B:** Nivolumab 3 mg/kg IV every 2 weeks
  - **Cohort C:** Nivolumab 3 mg/kg IV every 2 weeks
    - Only cohort to include patients who failed local therapy, were neurologically symptomatic, had leptomeningeal disease (LMD), or combination thereof
- **Primary endpoint:** Best intracranial response (ICR) at ≥ 12 weeks (% of patients with complete or partial ICR)
- **Secondary endpoints:** Intracranial PFS, OS

Long GV, et al. *Ann Oncol*. 2019;30(suppl_5):v533-63.;
Long GV, et al. *Lancet Oncol.* 2018;19(5):672-81.

Anti-PD1 Brain Collaboration (ABC) Trial



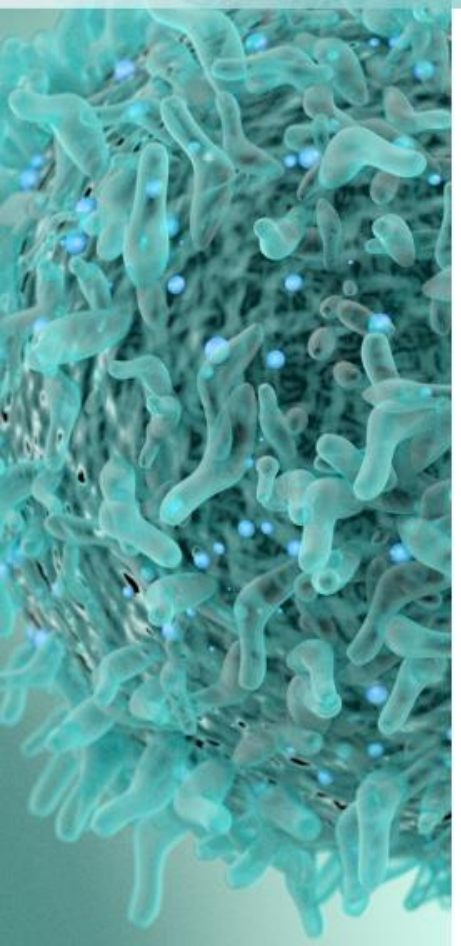
- 76 patients, median follow-up of 34 months

	Cohort A (N = 35)	Cohort B (N = 25)	Cohort C (N = 16)
ICR	51%	20%	6%
- Complete ICR	26%	16%	0%
Intracranial PFS, 24 months	49%	15%	6%
OS, 24 months	63%	51%	19%

- Upfront nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV given every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks demonstrates durable ICRs

Long GV, et al. *Ann Oncol*. 2019;30(suppl_5):v533-63.;
Long GV, et al. *Lancet Oncol.* 2018;19(5):672-81.

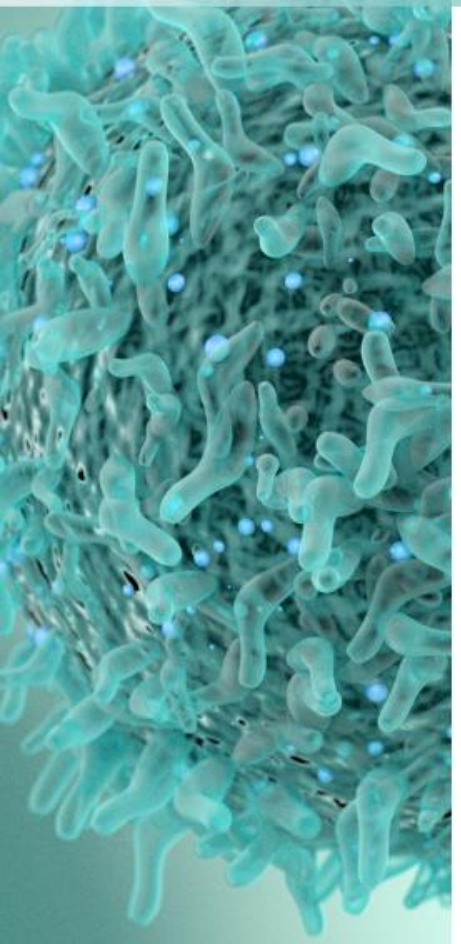
Checkpoint Inhibitors – Subpopulations



- CheckMate and KEYNOTE families of trials have various subgroup analyses reviewing efficacy
- Patients with *BRAF* mutations
  - Efficacy of PD-1 monotherapy or dual CPI present regardless of *BRAF* mutation status
- Presence of tumor PD-L1 expression
  - Different PD-L1 expression thresholds across studies
  - Response rates and survival measures tend to improve with increasing PD-L1 expression, but durable responses seen in patients with little to no expression
  - For advanced melanoma, expression of PD-L1 should not be used to exclude patients from receiving PD-1 therapy

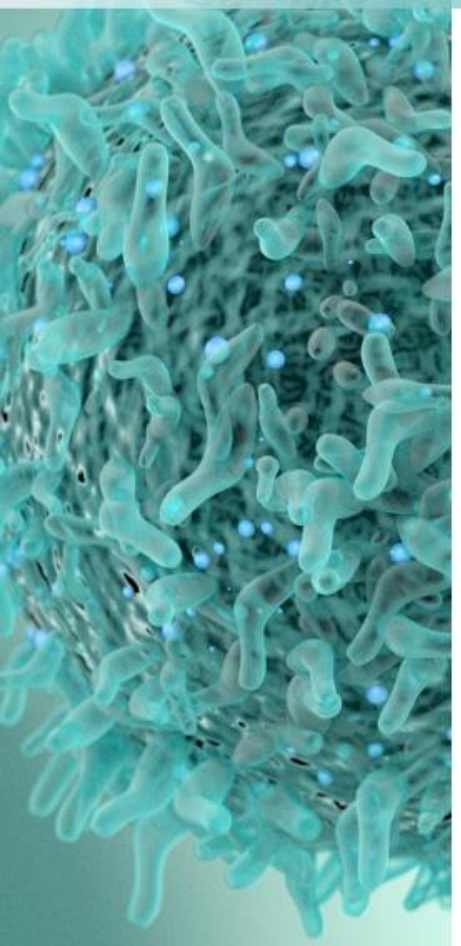
National Comprehensive Cancer Network. NCCN Guidelines: Cutaneous Melanoma. Version 3.2020. Published May 18, 2020. Accessed May 25, 2020. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma_blocks.pdf.

Summary – Advanced Melanoma Immunotherapy



- Use of PD-1 inhibitors as either monotherapy or in dual checkpoint inhibition (nivolumab + ipilimumab) has shown improvement of PFS and OS in advanced melanoma patients
  - Is combination therapy better than monotherapy for OS?
- Generally, either pembrolizumab or nivolumab as monotherapy have similar value with respect to efficacy
- Both nivolumab (monotherapy) and pembrolizumab are now administered as flat doses
  - Pharmacokinetic models based on weight, exposure, toxicity from pooled patient populations, and mixed tumor types

National Comprehensive Cancer Network. NCCN Guidelines: Cutaneous Melanoma. Version 3.2020. Published May 18, 2020. Accessed May 25, 2020. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma_blocks.pdf.

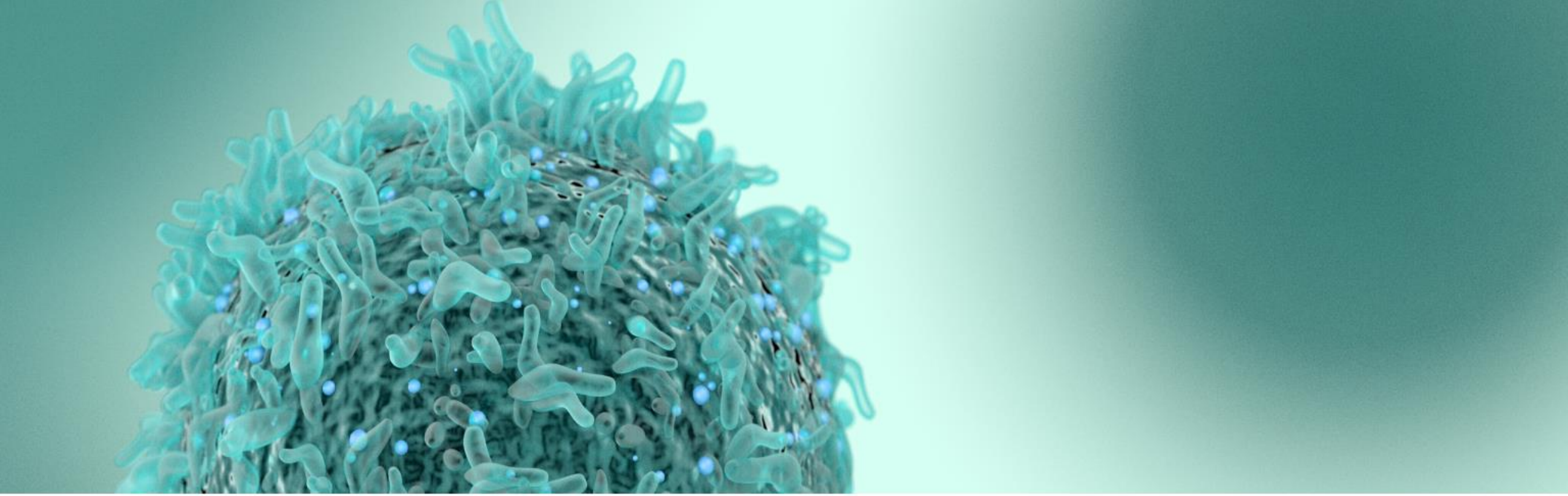


Advanced Melanoma Immunotherapy – What's Next?

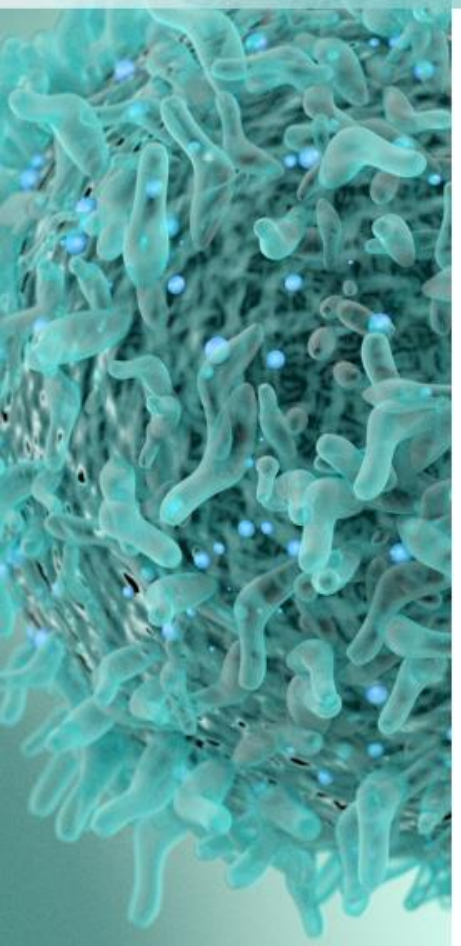
- Formally evaluating use of PD-1 or PD-L1 inhibitors in combination with or sequenced with targeted therapy (BRAF + MEK inhibitors) in patients with *BRAF* V600 mutations
- **IMspire 150**: Randomized, phase 3 trial
  - Atezolizumab 840 mg IV on days 1 and 15 of 28-day cycle + cobimetinib 60 mg orally daily on days 1-21 of 28-day cycle + vemurafenib 960 mg orally BID x 28 days, then 720 mg daily
  - Vemurafenib 960 mg orally BID (continuous) + cobimetinib 60 mg daily on days 1-21 of a 28-day cycle
- **KEYNOTE-022:** Randomized, double-blinded, 5-part phase 1/2 trial
  - Pembrolizumab 2 mg/kg IV every 3 weeks + dabrafenib + trametinib, compared to only dabrafenib + trametinib
- **DREAMseq** (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): Open-label, phase 3 trial
  - Ipilimumab + nivolumab followed by crossover to dabrafenib + trametinib at disease progression, compared to reverse sequence

McArthur GA, et al. 2020 AACR Virtual Annual Meeting; Abstract CT012.; Clinicaltrials.gov identifier: NCT02224781; Clinicaltrials.gov identifier: NCT02130466.

BID, twice daily.



Management of Checkpoint Inhibitor Immune-Mediated Toxicities



Immune-Mediated Toxicities

- Infusion-related reactions (IRRs)
  - Infrequent – up to 5% incidence with combination nivolumab + ipilimumab
  - Fever, chills/rigors, urticaria, flushing, hypotension, angioedema
- **Mild** → Hold infusion until symptoms resolve, then resume as tolerated
- **Moderate** → Hold infusion, treat symptoms, resume at half-rate slower
  - Administer steroids as a last resort
- **Severe** → Treat per institutional hypersensitivity guidelines
  - Permanently discontinue CPI therapy

Consider pre-medication with subsequent cycles:

acetaminophen, diphenhydramine, famotidine

Do NOT routinely pre-medicate with corticosteroids!

National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. V 1.2020. Published December 16, 2019. Accessed April 28, 2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

Immune-Mediated Toxicities

Immune-mediated AE	Mild	Moderate	Severe
Dermatologic	***< 10% BSA ± symptoms***	***10%-30% BSA ± symptoms***	***> 30% BSA ± symptoms***
Maculopapular rash, pruritis, bullous dermatitis, SJS/TEN	Topical emollients Oral antihistamine Topical moderate-potency steroids	Topical moderate- to high-potency steroids Consider prednisone 0.5-1 mg/kg/day Pruritis: gabapentin, pregabalin	Hold or discontinue immunotherapy Topical high-potency steroids Prednisone/methylprednisolone 0.5-2 mg/kg/day **Adjunct options**
Colitis	***< 4 bowel movements/day above baseline***	***4-6 bowel movements/day above baseline, colitis symptoms***	***> 6 bowel movements/day above baseline***
Watery diarrhea, cramping, abdominal pain, nocturnal bowel movements	Consider holding immunotherapy Stool sampling for infectious source Consider loperamide if infectious cause ruled out, hydration	Consider holding immunotherapy Consider CT of abdomen/pelvis, endoscopy Prednisone/methylprednisolone 1-2 mg/kg/day **Adjunct options**	Grade 3: Discontinue if ipilimumab, may resume anti-PD-1 when resolved Grade 4: Discontinue immunotherapy IV methylprednisolone 1-2 mg/kg/day **Adjunct options**
Hepatitis	***Transaminases < 3x ULN***	***Transaminases 3-5x ULN***	***Grade 3: Transaminases 5-20x ULN*** ***Grade 4: Transaminases > 20x ULN*** ***Grade > 1 transaminitis with bilirubin > 1.5x ULN***
Transaminitis without elevated bilirubin	Rule out viral etiology, disease-related hepatic dysfunction Limit or discontinue drug- or dietary-induced sources	Hold immunotherapy Consider prednisone 0.5-1 mg/kg/day	Discontinue immunotherapy Prednisone/methylprednisolone 1-2 mg/kg/day **Adjunct options**
Pneumonitis	***Asymptomatic, < 25% parenchymal involvement or confined to one lobe***	***New or worsening shortness of breath, cough, chest pain, hypoxia, fever***	***> 50% parenchymal involvement or all lung lobes, requiring oxygen, limiting self-care ADLs***
Focal or diffuse inflammation (ground-glass opacities) of lung parenchyma ± dry cough	Consider holding immunotherapy Assess for infectious sources (viral, bacterial) Consider CT of chest	Hold immunotherapy Consider bronchoscopy with bronchoalveolar lavage Prednisone/methylprednisolone 1-2 mg/kg/day	Discontinue immunotherapy Prednisone/methylprednisolone 1-2 mg/kg/day **Adjunct options**

National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. V 1.2020. Published December 16, 2019. Accessed April 28, 2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

ADLs, activities of daily living; BSA, body surface area; CT, computed tomography; IV, intravenously; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; ULN, upper limit of normal.

Immune-Mediated Toxicities

Immune-mediated AE	Moderate	Severe
Nephritis	***Creatinine 2-3x baseline***	***Grade 3: Creatinine > 3x baseline, > 4 mg/dL*** ***Grade 4: Creatinine > 6x baseline, dialysis***
Elevated serum creatinine, urine output change, azotemia Limit nephrotoxic medications	Hold immunotherapy Prednisone 0.5-1 mg/kg/day, increase to 1-2 mg/kg/day if persistent > 1 week	Discontinue immunotherapy Prednisone/methylprednisolone 1-2 mg/kg/day Infliximab or mycophenolate mofetil
Myasthenia gravis	***Symptoms interfering with some ADLs, mild generalized weakness***	***Dysphagia, respiratory muscle weakness, inability to ambulate, rapidly progressive symptoms***
Progressive muscle weakness, visual changes (ptosis, double vision), facial muscle weakness *May occur with myositis and myocarditis, overlapping symptoms with GBS*	Discontinue immunotherapy Pyridostigmine 30 mg TID and titrate as tolerated Consider prednisone 20 mg daily, titrate up by 5 mg every 3-5 days to 1 mg/kg/day (do not exceed 100 mg/day)	Discontinue immunotherapy Methylprednisolone 1-2 mg/kg/day Plasmapheresis or IVIG Rituximab if refractory to plasmapheresis or IVIG
Guillain-Barre syndrome (GBS)	***Symptoms interfering with ADLs***	***Dysphagia, respiratory muscle weakness, inability to ambulate, rapidly progressive symptoms***
Progressive, typically symmetrical muscle weakness with absent/reduced deep tendon reflexes Dysregulation of autonomic nerves may be present	Discontinue immunotherapy Methylprednisolone 1 gram IV daily x 5 days (then 4 week taper) with IVIG or plasmapheresis Gabapentin, pregabalin, or duloxetine for neuropathic pain	
Myocarditis	***Grade 3: Cardiac markers > ULN, arrhythmia, echocardiogram findings without hypotension*** ***Grade 4: Cardiac markers > 3x ULN, arrhythmia, hemodynamic instability***	
May occur with myositis and myasthenia gravis Often nonspecific symptoms	Discontinue immunotherapy Consider pulse methylprednisolone 1 gram IV daily x 3-5 days, taper over 6+ weeks If no improvement in 24 hours, consider infliximab, IVIG, mycophenolate mofetil, or anti-thymocyte globulin	
Encephalitis		
Confusion, altered mental status, headaches, seizures, aphasia, memory or cognition impairment	Discontinue immunotherapy Trial of methylprednisolone 1-2 mg/kg/day Could consider pulse methylprednisolone 1 gram IV daily x 3-5 days with IVIG or plasmapheresis	

National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. V 1.2020. Published December 16, 2019. Accessed April 28, 2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

IVIG, intravenous immune globulin; TID, three times daily.

Corticosteroid Tapers/Adjunctive Therapies

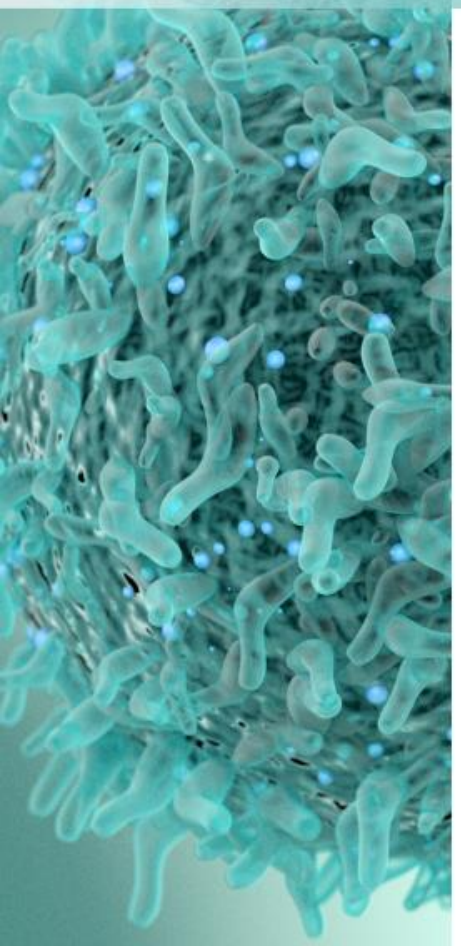
Adjunctive therapy considerations	Immune-mediated toxicity
Infliximab	Steroid-refractory moderate/severe colitis, allow to taper corticosteroids over 4 weeks or less Steroid-refractory severe pneumonitis Nephritis if grade 2 severity for > 1 week on steroids Myocarditis, severe myositis Inflammatory arthritis
Vedolizumab	Infliximab-refractory colitis only
Mycophenolate mofetil	Steroid-refractory hepatitis (500 mg – 1 g BID) Steroid-refractory pneumonitis (1 – 1.5 g BID) Myocarditis, severe myositis (500 mg – 1 g BID) Nephritis if grade 2 severity for > 1 week on steroids (500 mg – 1 g BID)
Intravenous immune globulin (IVIG)	Severe bullous dermatitis Steroid-refractory severe pneumonitis GBS, transverse myelitis Myasthenia gravis, severe myositis, myocarditis Encephalitis
Rituximab	Severe bullous dermatitis Myasthenia gravis refractory to plasmapheresis or IVIG Severe encephalitis, refractory to plasmapheresis or IVIG after 7-14 days
Omalizumab	Refractory and severe pruritis

Typical corticosteroid taper:

- Dermatologic
  - At least 4 weeks
- Gastrointestinal/colitis:
  - At least 4-6 weeks
- Hepatitis
  - At least 4-6 weeks
- Pneumonitis
  - At least 6 weeks
- Nephritis
  - 4-6 weeks
- Myocarditis
  - At least 6 weeks

National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. V 1.2020. Published December 16, 2019. Accessed April 28, 2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

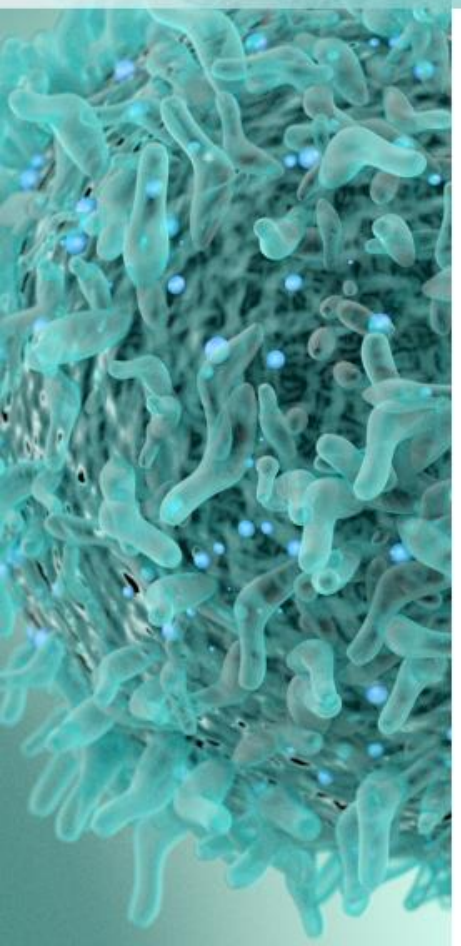
Immune-Mediated Toxicities – Endocrine/Pancreatic



- New-onset hyperglycemia
  - Fasting glucose > 200 mg/dL or random glucose > 250 mg/dL
  - History of controlled/uncontrolled type II diabetes mellitus?
  - Consider new-onset type I diabetes mellitus, assess for diabetic ketoacidosis (DKA)
    - Hold immunotherapy if workup positive for DKA
- Asymptomatic elevations in amylase/lipase
  - Limit drug- or dietary-induced sources, consider CT of abdomen if persistent
- Acute pancreatitis – radiologic findings on CT, clinical presentation, amylase/lipase > 3x ULN
  - Hold (moderate) or discontinue (severe) immunotherapy
  - Prednisone/methylprednisolone 0.5 – 2 mg/kg/day

National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. V 1.2020. Published December 16, 2019. Accessed April 28, 2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

Immune-Mediated Toxicities - Endocrine

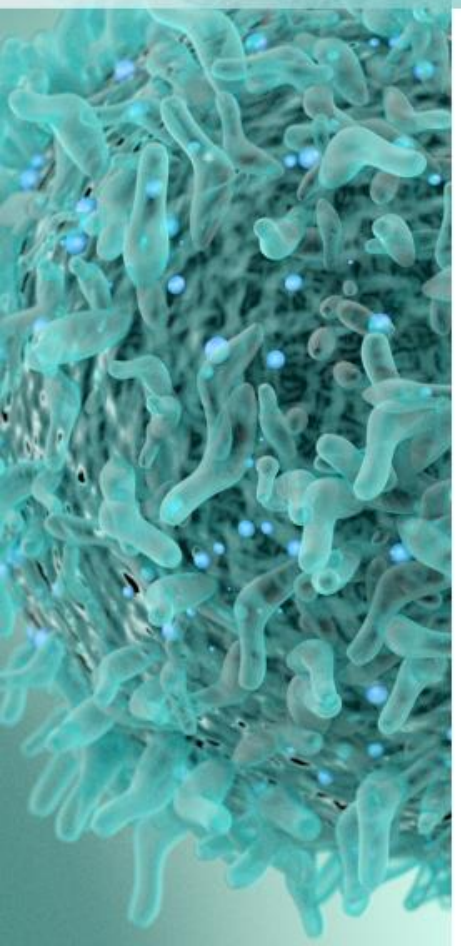


- Clinical, primary hypothyroidism
  - **TSH > 10 µU/mL:** Start oral levothyroxine ~1.6 mcg/kg/day (or 75-100 mcg daily, 50-75 mcg daily if elderly)
  - Monitor TSH every 4-6 weeks, adjust dose to reference range
- Asymptomatic hypothyroidism
  - TSH > 10 µU/mL, normal free T4: may consider oral levothyroxine
- Thyrotoxicosis
  - Suppressed TSH < 0.01 µU/mL, normal or high free T4
  - If tachycardic, may use β-blockers as needed until symptoms resolve
  - Generally evolves to hypothyroidism

National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. V 1.2020. Published December 16, 2019. Accessed April 28, 2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

TSH, thyroid-stimulating hormone.

Immune-Mediated Toxicities - Endocrine



- Hypophysitis → Headache, dizziness, fevers, severe fatigue
  - Check labs: Morning cortisol, ACTH, FSH, LH, TSH, free T4, testosterone (men), estrogen (women)
  - MRI brain with pituitary cuts
  - If severe, acute symptoms, consider prednisone/methylprednisolone 1-2 mg/kg, with 1- to 2-week rapid taper once symptoms improved
  - Hold immunotherapy until acute symptoms resolved
  - Hormone supplementation as indicated per labs (e.g., testosterone)
    - Physiologic replacement: oral hydrocortisone 15-20 mg in AM and 10 mg in PM
    - Central hypothyroidism (low TSH, low free T4): levothyroxine ~1.6 mcg/kg

Hormone supplementation may be indefinite, life-long therapy

National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. V 1.2020. Published December 16, 2019. Accessed April 28, 2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

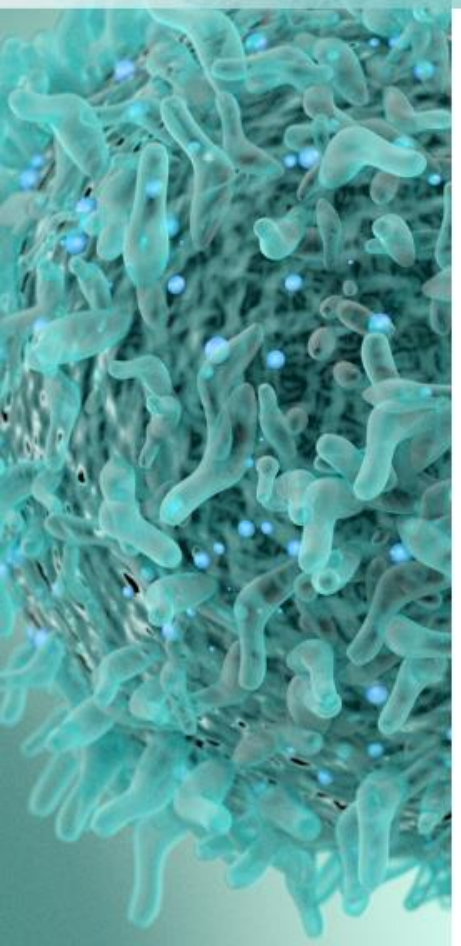
Routine Monitoring for Immune-Mediated Toxicities

- **Laboratory analysis:**
  - Liver function tests prior to and periodically during treatment
  - Thyroid function tests prior to and periodically during treatment
  - Ipilimumab – *baseline, every cycle*
    - Liver function, clinical chemistries, thyroid function, ACTH
  - NCCN recommendations:
    - CBC with differential, comprehensive metabolic panel prior to every cycle or at least every 4 weeks
    - Thyroid function tests every 4-6 weeks during immunotherapy
- **Clinical exam and patient history at each visit to assess for:**
  - Routine vital signs, including pulse oximetry
  - Dermatologic conditions
  - Pneumonitis
  - Colitis, gastritis, pancreatitis
  - Hypophysitis, adrenal insufficiency
  - Neurologic conditions
  - Ocular conditions

KEYTRUDA (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co, Inc.; 2020.; OPDIVO (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.; National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. V 1.2020. Published December 16, 2019. Accessed April 28, 2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.; YERVOY (ipilimumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2020.

CBC, complete blood count.

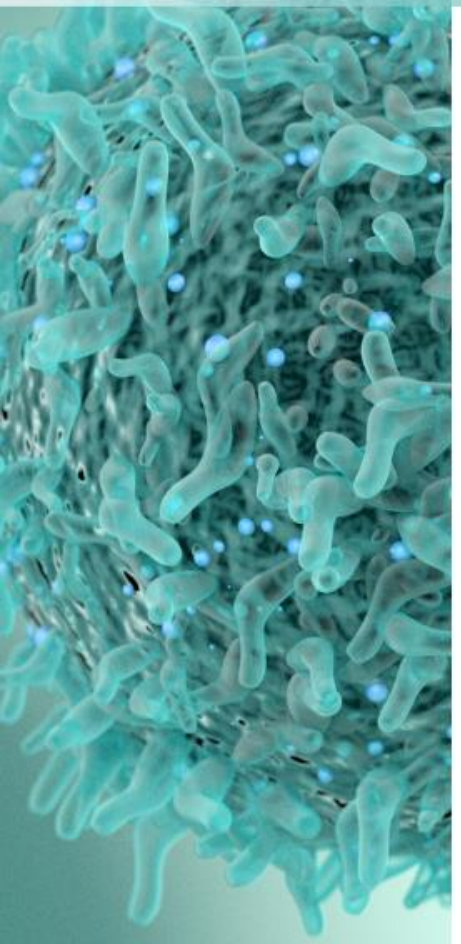
Supportive Care with Corticosteroids



- Considerations for patients on corticosteroids
  - Monitor for signs/symptoms of hyperglycemia
  - Minimize insomnia by timing doses for early morning and/or mid-afternoon (e.g., 2-4 PM)
- Prophylaxis on corticosteroid therapy
  - H2 blockers or proton pump inhibitors may be used to minimize gastritis
    - Continue until steroid taper completed
  - Pneumocystis jiroveci pneumonia (PJP): prophylaxis recommended if prednisone equivalent ≥ 20 mg/day for 4 weeks or more
  - Antifungal or antiviral (e.g., herpes simplex, herpes zoster) prophylaxis recommended
  - Vitamin D and calcium supplementation may be appropriate if on long-term corticosteroids

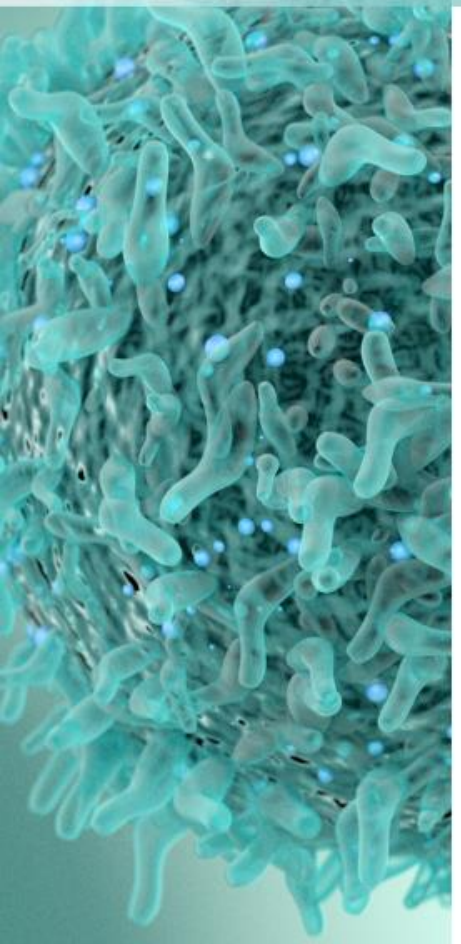
National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. V 1.2020. Published December 16, 2019. Accessed April 28, 2020. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

Patient Education with Immunotherapy

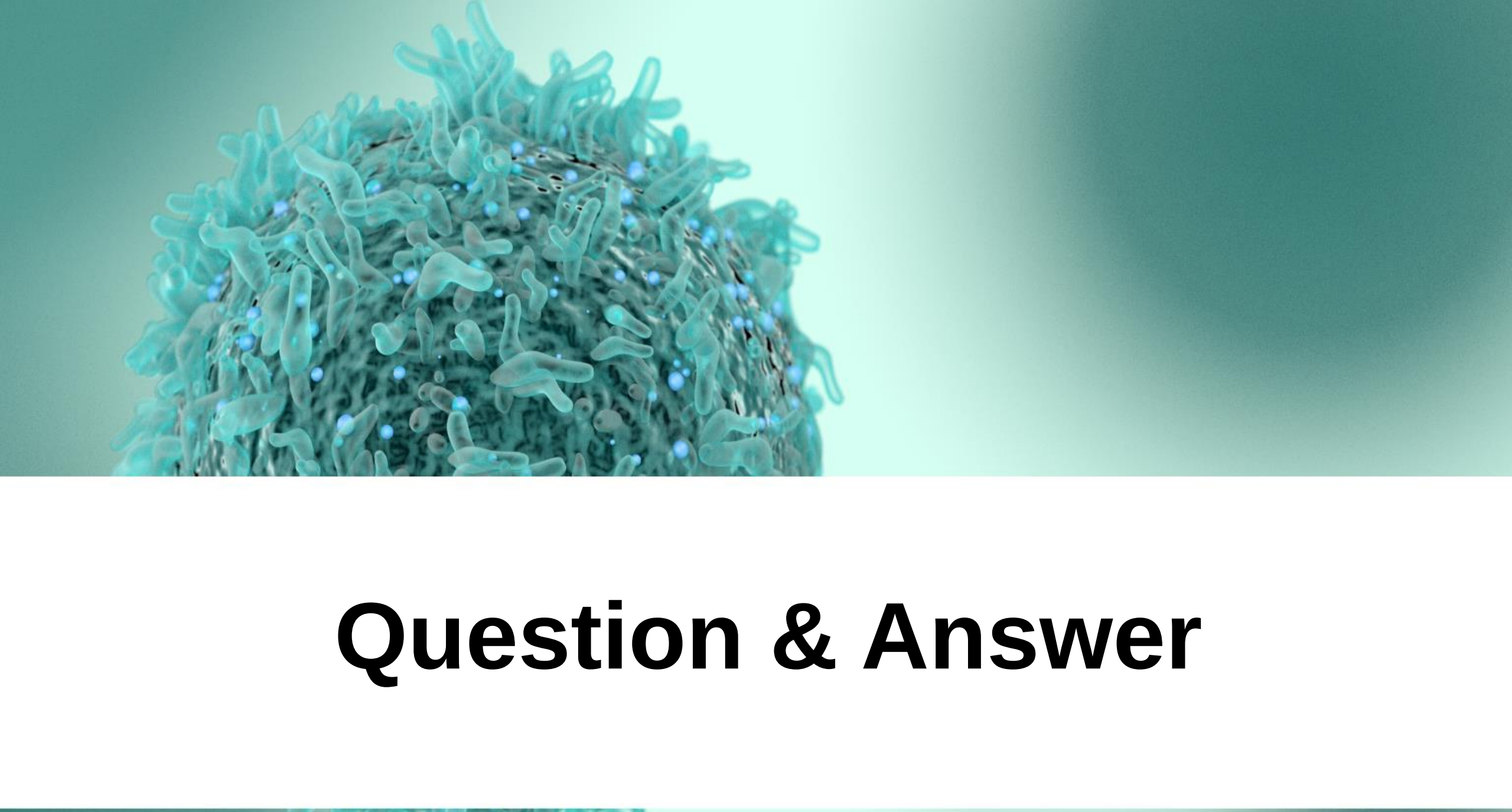


- Utilize patient education tools developed by the applicable manufacturer
  - Kits, wallet cards with physician contact information, symptom diaries
  - Many resources available online
- Early intervention for immune-mediated AEs is critical
  - Report new symptoms or any worsening of previous symptoms provider is aware of
  - Some toxicities have potential to escalate quickly
- Patients with adrenal insufficiency who require physiologic replacement of hydrocortisone
  - Importance of stress dosing on “sick days”, discuss when to come to the emergency room
  - Obtain medical alert bracelet
- Encourage patients to inform other involved providers they are receiving immunotherapy for melanoma
  - Notify oncologist before taking steroids prescribed by another provider
  - Report any new medications or over-the-counter products

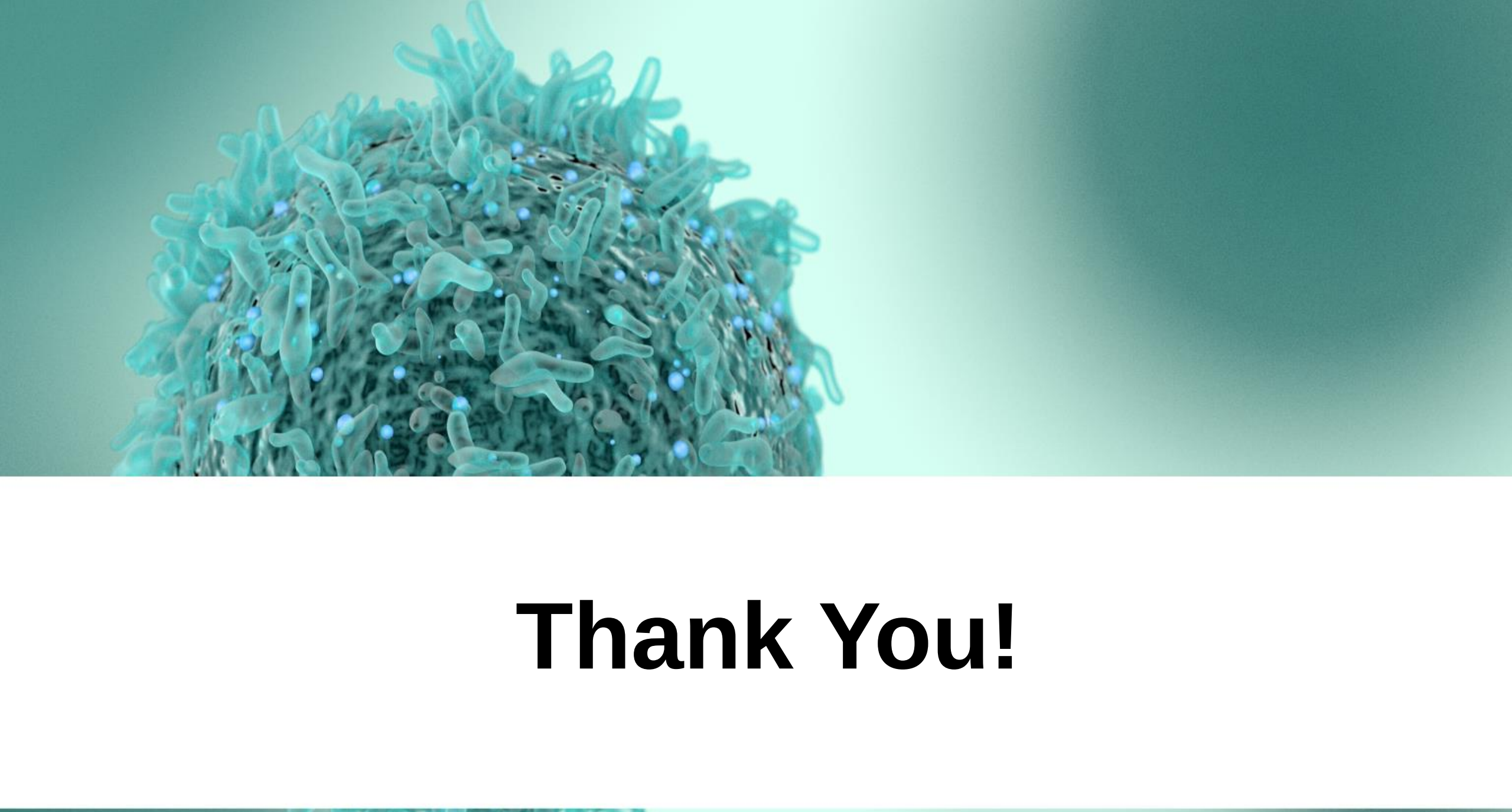
Summary – Immunotherapy in Melanoma



- The discovery of novel targets within the immune pathway has unlocked a new paradigm for more effective treatment of advanced melanoma
  - Advances in treating patients with earlier stage melanoma and special populations with an unmet need
- CPI regimens have unique potential to elicit immune-mediated AEs
  - Corticosteroids are the mainstay of management, but adjunctive therapies add a new dimension
- Pharmacists have important roles to play in educating both patients and providers



Question & Answer



Thank You!