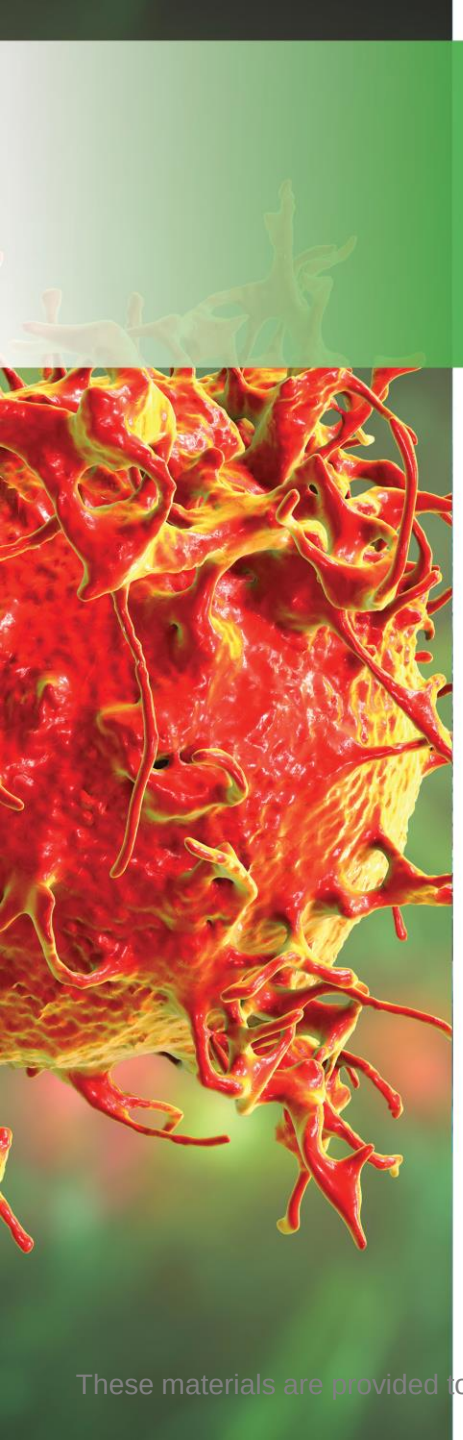
Immune Checkpoint Inhibitors in First-line Therapy for Advanced Melanoma

A Look at the Ever-Changing Treatment Landscape

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.



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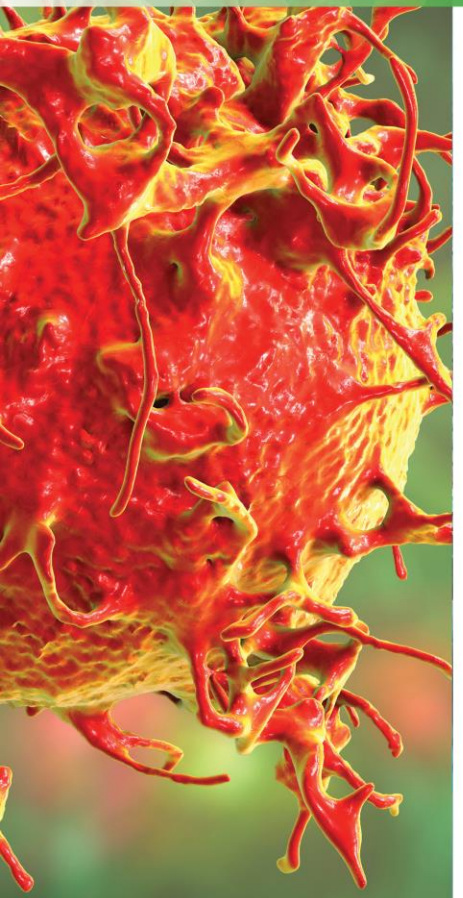
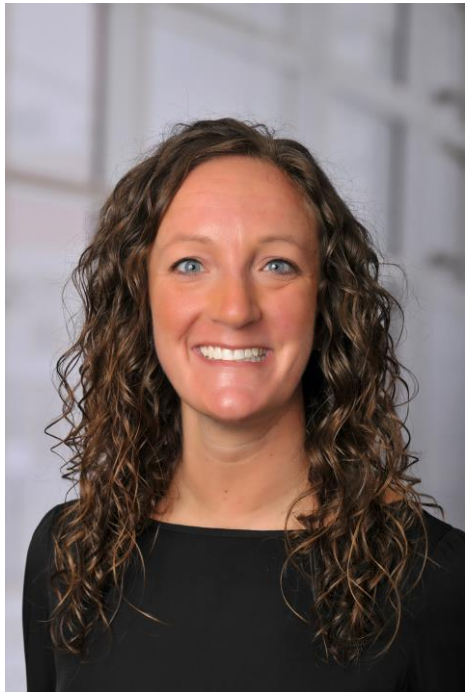
Faculty



Heather L. Armbruster, PharmD, BCOP



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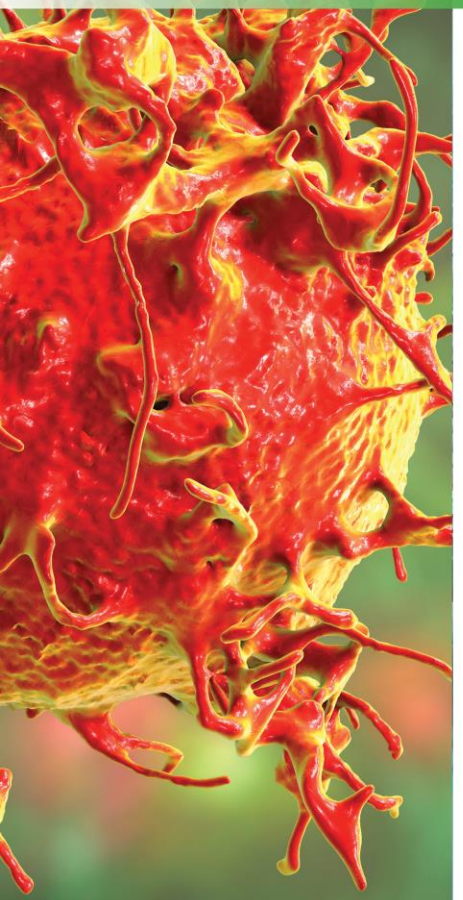
Dr. Armbruster currently practices at The James Cancer Center at The Ohio State University as a specialty practice pharmacist with the melanoma and neuroendocrine teams. She received her PharmD from Ohio Northern University, and completed PGY1 Pharmacy Practice and PGY2 Oncology Specialty residencies at The Johns Hopkins Hospital. After her residency, she remained at Johns Hopkins as their multiple myeloma specialist and helped establish clinical outpatient pharmacy services. She then transitioned to Kaiser Permanente where she worked with general oncologists in Baltimore and Southern Maryland.

Disclosures



Dr. Armbruster has disclosed that she has no relevant affiliations or financial relationships with a commercial interest to disclose.

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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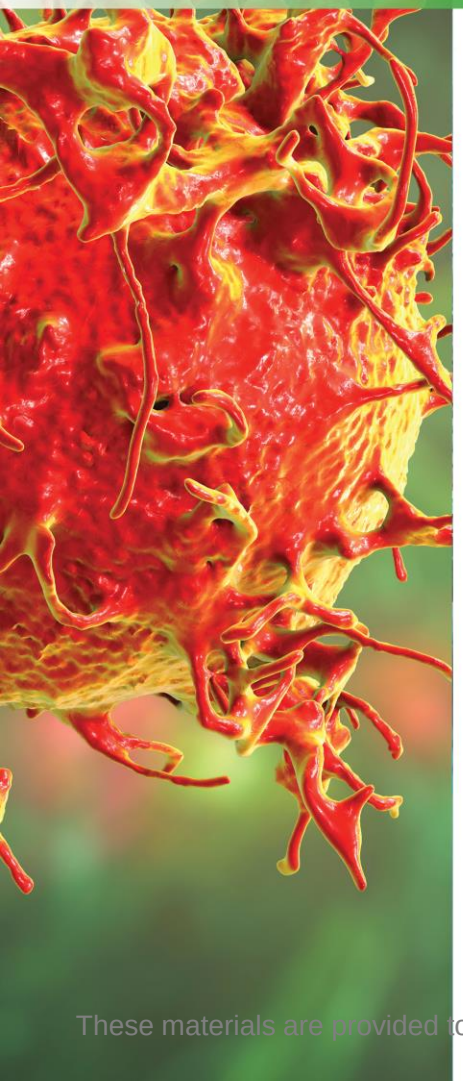

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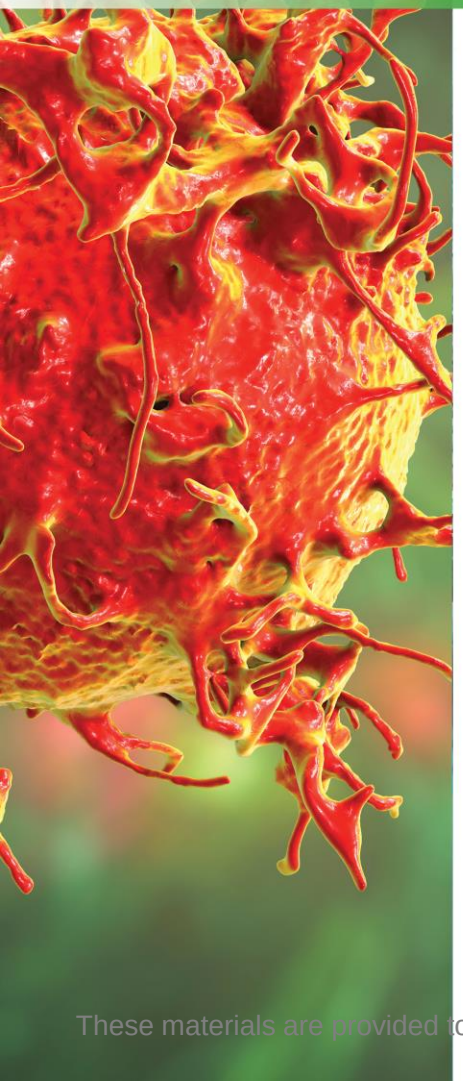
UAN: 0430-0000-21-061-H01-P
Credits: 1.0 hour (0.1 CEU)
Type of Activity: Application

Learning Objectives



- **Describe** the rationale for the use of immune checkpoint inhibitors in the treatment of advanced melanoma in the first-line setting
- **Discuss** clinical evidence supporting the use of these agents, alone and in combination, as first-line therapy
- **Formulate** approaches for individualizing treatment based on drug- and patient-specific factors
- **Identify** strategies for optimally managing adverse events associated with immune checkpoint inhibitor therapy alone or in combination

Background

- Melanocytes
  - Pigment-producing cells in the skin
  - Protect the skin from ultraviolet light
- Risk factors
  - Sun exposure: chronic and intense, intermittent
  - Tanning bed use
  - Phenotypic disposition: fair skin, red hair, blue eyes, atypical moles
  - Immunosuppressant medications
  - Positive family history
  - Genetic mutations (rare)

American Cancer Society. https://www.cancer.org/cancer/melanoma-skin-cancer.html. NCCN Clinical Practice Guidelines. Melanoma: cutaneous. v2.2021.

Subtypes

- Cutaneous
  - Skin: chronic and non-chronic sun damage
  - Acral: soles, palms, subungual sites
- Non-cutaneous
  - Mucosal membranes
  - Uveal tract of the eye
  - Leptomeninges

NCCN Clinical Practice Guidelines. Melanoma: cutaneous. v2.2021.

Epidemiology

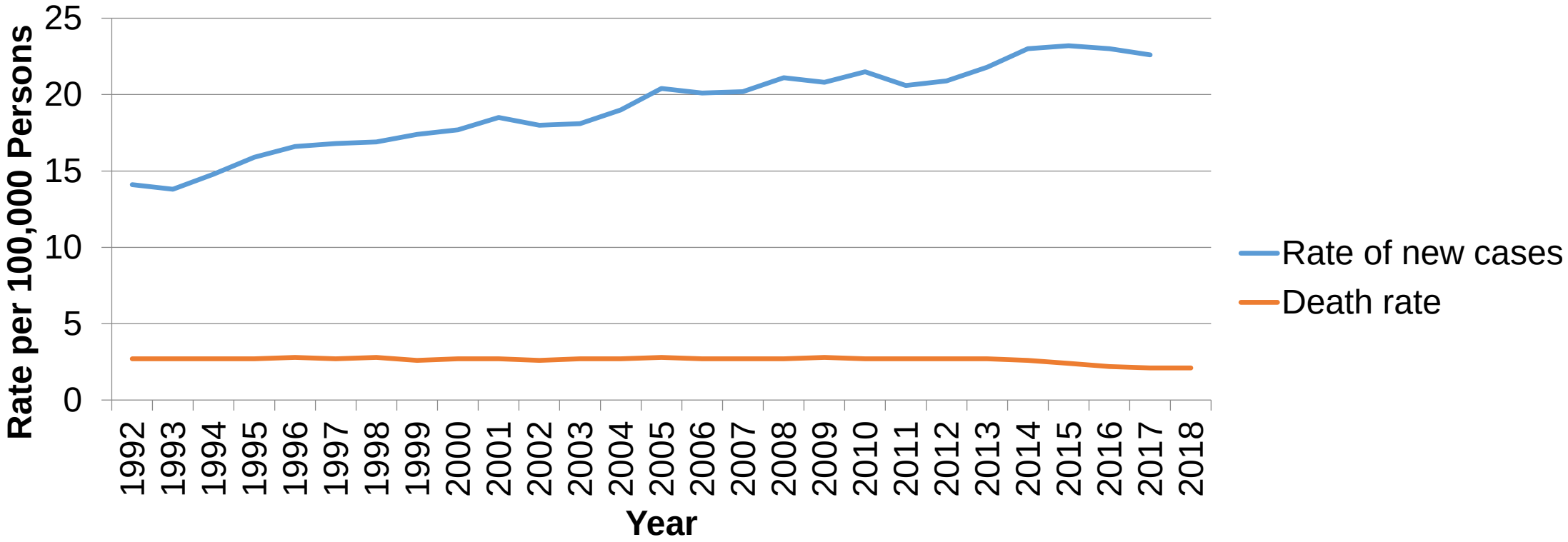
- New diagnoses in 2021: 106,110 (estimated)

Men			Women		
Cancer	**Estimated New Cases**	**Percentage**	**Cancer**	**Estimated New Cases**	**Percentage**
Prostate	248,530	26	Breast	281,550	30
Lung and bronchus	119,100	12	Lung and bronchus	116,660	13
Colon and rectum	79,520	8	Colon and rectum	69,980	8
Urinary bladder	64,280	7	Uterine cancer	66,570	7
Melanoma of the skin	62,260	6	Melanoma of the skin	43,850	5

NCCN Clinical Practice Guidelines. Melanoma: cutaneous. v2.2021. Table recreated from Siegel RL, et al. *CA Cancer J Clin.* 2021;71(1):7-33.

Epidemiology

- Deaths in 2021: 7,180 (estimated)



Graph recreated from National Institutes of Health. https://seer.cancer.gov/statfacts/html/melan.html. Siegel RL, et al. *CA Cancer J Clin*. 2021;71(1):7-33.

Presentation

- Median age at diagnosis: 65 years
- ABCDE rule
  - **A**symmetry: one half does not match the other half
  - **B**order: edges are irregular, ragged, notched, or blurred
  - **C**olor: non-uniform; may include white, pink, red, or blue
  - **D**iameter: larger than 6 mm or ¼ inch
  - **E**volving: changing in size, shape, or color

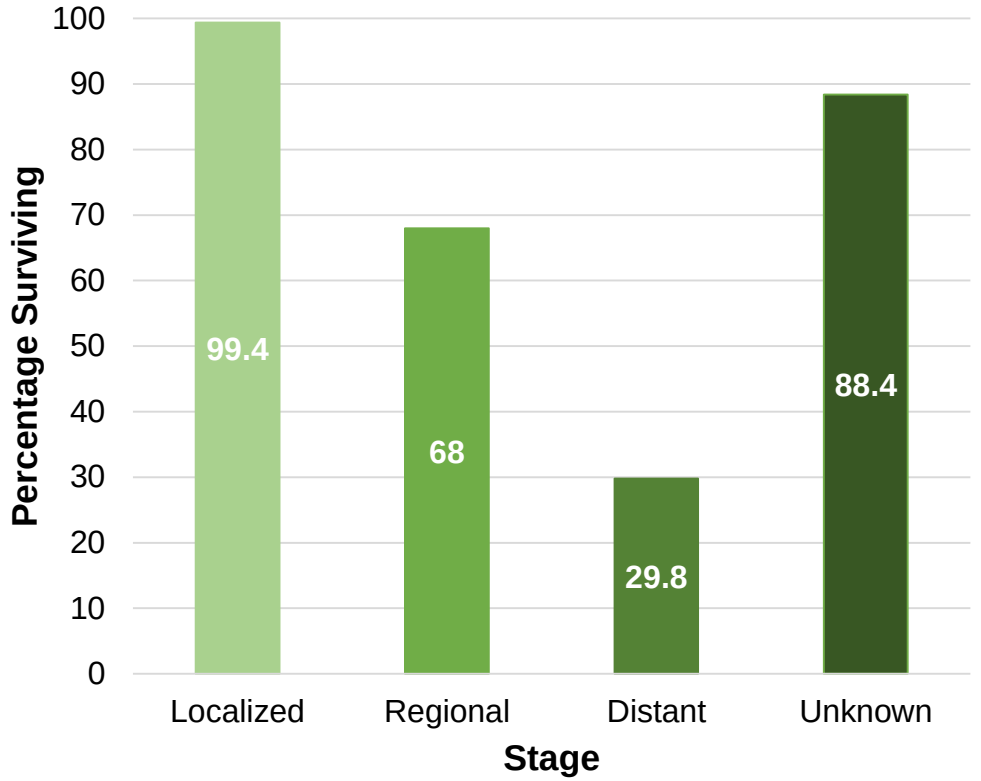
American Cancer Society. https://www.cancer.org/cancer/melanoma-skin-cancer.html. NCCN Clinical Practice Guidelines. Melanoma: cutaneous. v2.2021.

Presentation

Percentage of Cases by Stage

- Localized (83%)
  - Confined to primary site
- Regional (9%)
  - Spread to regional lymph nodes
- Distant (4%)
  - Cancer has metastasized
- Unknown (5%)
  - Unstaged

5-Year Relative Survival



Graph recreated from National Institutes of Health. https://seer.cancer.gov/statfacts/html/melan.html. Siegel RL, et al. *CA Cancer J Clin*. 2021;71(1):7-33.

Staging and Treatment

Stage	Primary Treatment	Adjuvant Treatment
I	• Wide excision • Consider or offer sentinel lymph node biopsy (SLNB)	• Clinical trial • Observation
II	• Wide excision • Offer SLNB	• Clinical trial • Observation
III Sentinel node positive	• Wide excision • SLNB	• Nivolumab or pembrolizumab • Dabrafenib/trametinib, if *BRAF* V600 mutation • Observation
III Clinical node positive	• Wide excision • Therapeutic lymph node dissection	• Radiation to nodal basin • Nivolumab or pembrolizumab • Dabrafenib/trametinib, if *BRAF* V600 mutation • Observation

NCCN Clinical Practice Guidelines. Melanoma: cutaneous. v2.2021.

Staging and Treatment

Stage	Treatment

III
Clinical satellite/in-transit
	Limited resectable disease
	• Wide excision then adjuvant treatment:
	  • Nivolumab
	  • Pembrolizumab
	  • Dabrafenib/trametinib, if *BRAF* V600 mutation
	• Intralesional talimogene laherparepvec (T-VEC)
	• Systemic therapy as for unresectable/metastatic disease

IV Metastatic	• Nivolumab or pembrolizumab (category 1) • Nivolumab/ipilimumab (category 1) • Combination targeted therapy for *BRAF* V600 mutations (category 1) • Pembrolizumab/low-dose ipilimumab (category 2B) • Atezolizumab/vemurafenib/cobimetinib, if *BRAF* V600 mutation (category 2A) • Pembrolizumab/dabrafenib/trametinib, if *BRAF* V600 mutation (category 2B)

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First-line Regimens for Advanced Melanoma

Preferred Regimens (category 1)

Anti–PD-1 monotherapy
- Nivolumab
- Pembrolizumab

Nivolumab + ipilimumab

Combination targeted therapy[a]
- Vemurafenib + cobimetinib
- Dabrafenib + trametinib
- Encorafenib + binimetinib

[a]If a *BRAF* V600-activating mutation is present.
PD-1, programmed cell death-1.

NCCN Clinical Practice Guidelines. Melanoma: cutaneous. v2.2021.

Category 1 Recommended Regimens

Immune Checkpoint Inhibitor Trials

Trial	Population	Treatment Arms	ORR (%)	Median PFS (months)		Median OS (months)	
CheckMate 066 (N=418)	No prior therapy	Nivolumab Dacarbazine	42 14	5 2	*P* < .001	39 17	*P* < .0001
KEYNOTE-006 (N=834)	Maximum of 1 prior therapy	Pembrolizumab Q2W Pembrolizumab Q3W Ipilimumab	42 17	8 3	*P* < .0001	33 16	*P* = .00049
CheckMate 067 (N=945)	No prior therapy	Nivolumab/ipilimumab Nivolumab Ipilimumab	58 45 19	12 7 3	*P* < .001[a]	72 37 20	*P* < .001[a]

ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks.
[a]*P* value for both nivolumab/ipilimumab and single-agent nivolumab compared with ipilimumab monotherapy. *P* values were not reported for nivolumab/ipilimumab compared with nivolumab monotherapy.

Ascierto PA, et al. *JAMA Oncol*. 2019;5(2):187-194. Robert C, et al. *J Clin Oncol*. 2020;38(33):3937-3946. Robert C, et al. *Lancet*. 2019;20(9):1239-1251.
Wolchok JD, et al. *J Clin Oncol*. 2021;39(suppl 15):9506.

Category 1 Recommended Regimens

Immune Checkpoint Inhibitor Trials

- Nivolumab/ipilimumab compared with anti–PD-1 monotherapy
  - Increased ORR, PFS, and OS
  - Increased adverse events, including treatment discontinuation

CheckMate 067 Adverse Events, n (%)	Nivolumab/Ipilimumab (n=313)	Nivolumab (n=313)	Ipilimumab (n=311)
Grade 3-5, any	215 (69)	136 (44)	173 (56)
Grade 3-5, treatment-related	186 (59)	73 (23)	86 (28)
Leading to discontinuation	96 (31)	25 (8)	42 (14)

- Single-agent ipilimumab is not recommended first-line

Ascierto PA, et al. *JAMA Oncol*. 2019;5(2):187-194. Larkin J, et al. *N Engl J Med*. 2015;373(1):23-34. Larkin J, et al. *N Engl J Med*. 2019;381(16):1535-1546. Robert C, et al. *Lancet*. 2019;20(9):1239-1251.

Immune Checkpoint Inhibitors

- PD-1 inhibitors
  - Nivolumab
  - Pembrolizumab
- Programmed cell death-1 ligand (PD-L1) inhibitor
  - Atezolizumab
- Cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) inhibitor
  - Ipilimumab

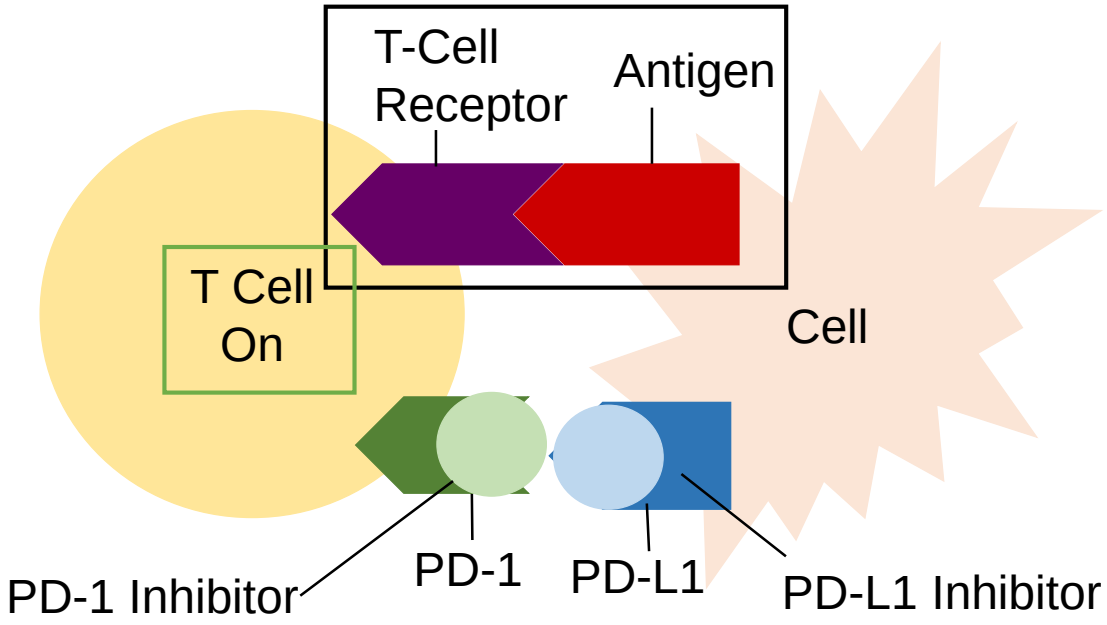
Keytruda [prescribing information]. Merck & Co, Inc; November 2020. Opdivo [prescribing information]. Bristol Myers Squibb Company; January 2021.
Tecentriq [prescribing information]. Genentech, Inc; February 2021. Yervoy [prescribing information]. Bristol Myers Squibb Company; November 2020.

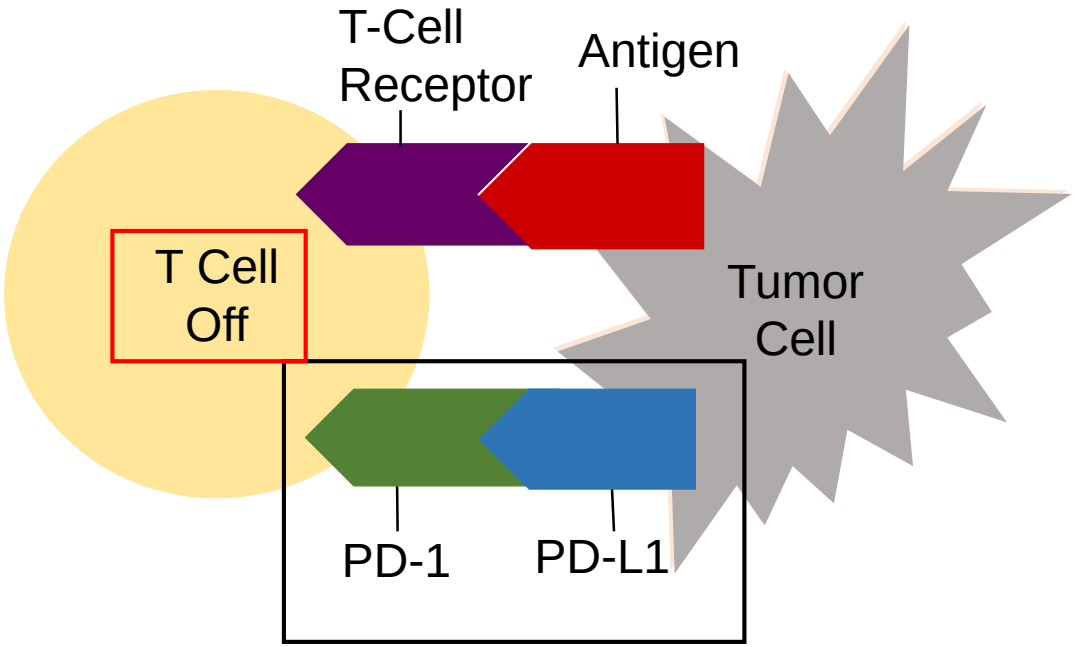
PD-1 and PD-L1 Inhibitors

- Selectively bind PD-1 receptor or PD-L1 to block the binding that occurs between the two
- Disrupts the negative PD-1/PD-L1 receptor signaling
- Prevents T-cell inhibition and stimulates T-cell activation and proliferation

Keytruda [prescribing information]. Merck & Co, Inc; November 2020. Opdivo [prescribing information]. Bristol Myers Squibb Company; January 2021.
Tecentriq [prescribing information]. Genentech, Inc; February 2021.

PD-1 and PD-L1 Inhibitors





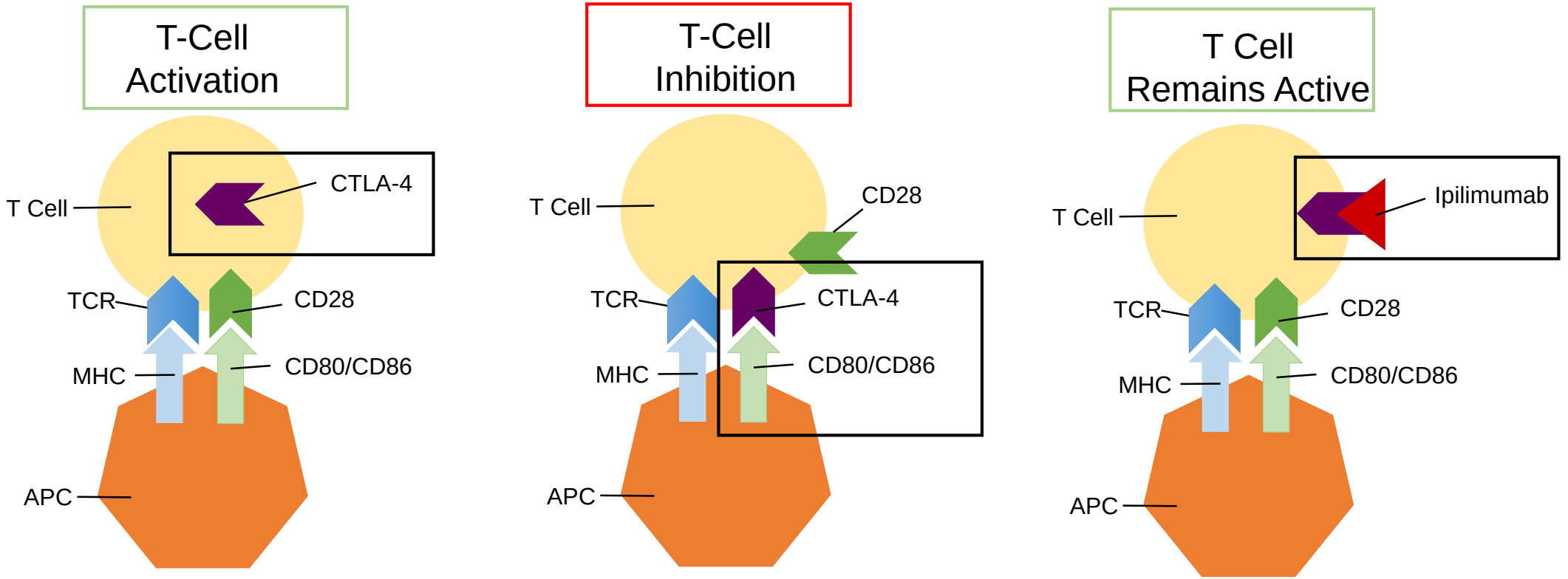
Keytruda [prescribing information]. Merck & Co, Inc; November 2020. Opdivo [prescribing information]. Bristol Myers Squibb Company; January 2021.
Tecentriq [prescribing information]. Genentech, Inc; February 2021.

CTLA-4 Inhibitor

- Selectively blocks CTLA-4, which is a downregulator of T-cell activation pathways
- Allows for enhanced T-cell activation and proliferation

Yervoy [prescribing information]. Bristol Myers Squibb Company; November 2020.

CTLA-4 Inhibitor



APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

Yervoy [prescribing information]. Bristol Myers Squibb Company; November 2020.

Immune Checkpoint Inhibitor Toxicity

- Inflammatory or autoimmune in nature
- Result of uncontrolled activation of immune effector cells affecting normal tissue
- Can occur in any organ of the body

Dermatologic toxicity	Nervous system toxicity
Endocrine	Ocular toxicity
Gastrointestinal	Pulmonary toxicity
Musculoskeletal toxicity	Renal toxicity

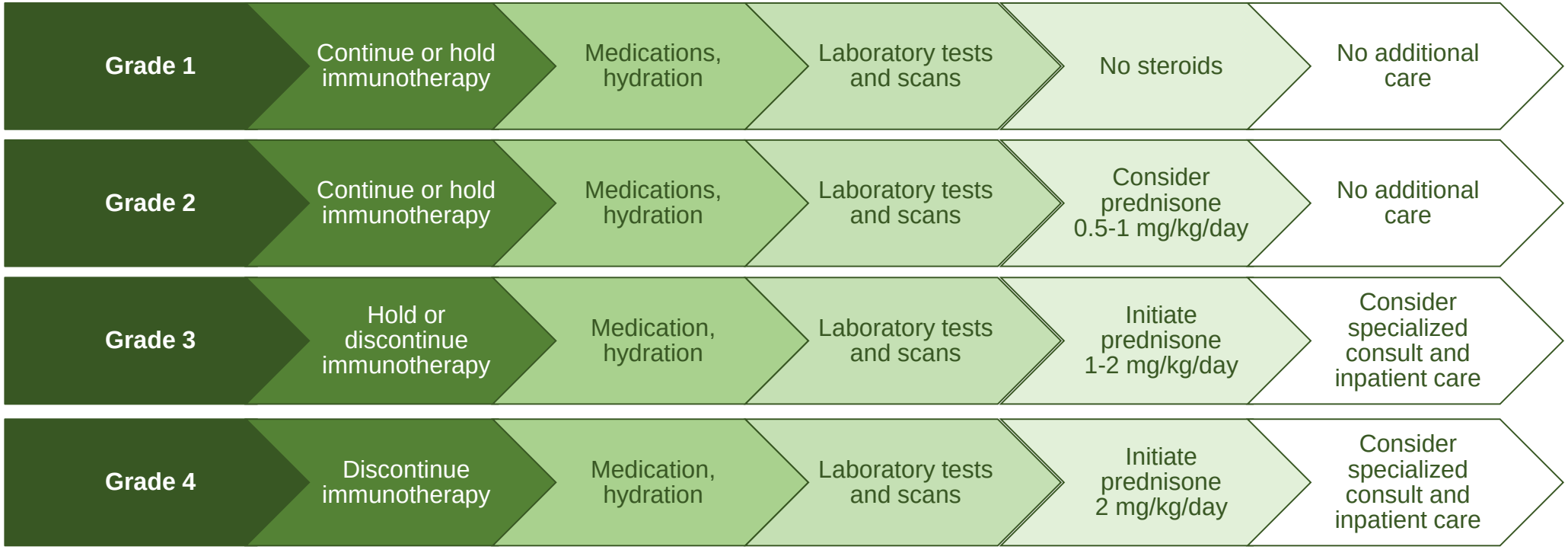
NCCN Clinical Practice Guidelines. Management of immunotherapy-related toxicities. v3.2021.

Immune Checkpoint Inhibitor Toxicity

- Most occur during first 14 weeks of treatment
  1. Skin rash or pruritus
  2. Colitis
  3. Liver toxicity
  4. Endocrinopathy
- Endocrinopathy can occur at any point during treatment
- Incidence and timing varies slightly based on regimen

Martins F, et al. *Nat Rev Clin Oncol.* 2019;16(9):563-580.

Immune Checkpoint Inhibitor Toxicity



****This is a general overview. Guidelines should be used for toxicity management.****

NCCN Clinical Practice Guidelines. Management of immunotherapy-related toxicities. v3.2021.

Immune Checkpoint Inhibitor Toxicity

Start high-dose steroids based on the specific toxicity and grade of toxicity

If steroid refractory after 2-3 days, add an additional immunosuppressant agent: infliximab, mycophenolate, etc.

Once symptoms improve to grade 1 or better, taper steroids over 4-6 weeks

NCCN Clinical Practice Guidelines. Management of immunotherapy-related toxicities. v3.2021.

Immune Checkpoint Inhibitor Toxicity

If treated with an ipilimumab-containing regimen, can consider re-challenging with anti–PD-1 monotherapy

Resume treatment when steroids are at a dose ≤ prednisone 10 mg/day or less and symptoms are improved to grade 1+

If re-challenged and toxicity recurs, permanently discontinue immunotherapy

NCCN Clinical Practice Guidelines. Management of immunotherapy-related toxicities. v3.2021.

Immune Checkpoint Inhibitor Dosing

	Nivolumab	Pembrolizumab	Nivolumab + Ipilimumab
Dose	240 mg/480 mg	200 mg/400 mg	1 mg/kg + 3 mg/kg
Frequency	Q2W/Q4W	Q3W/Q6W	Q3W
Route	IV	IV	IV
Duration	Until progression, intolerance, or maximum clinical benefit		Maximum of 4 cycles, then continue on single-agent nivolumab

IV, intravenous; Q4W, every 4 weeks; Q6W, every 6 weeks.

Keytruda [prescribing information]. Merck & Co, Inc; November 2020. NCCN Clinical Practice Guidelines. Melanoma: cutaneous. v2.2021.
Opdivo [prescribing information]. Bristol Myers Squibb Company; January 2021. Yervoy [prescribing information]. Bristol Myers Squibb Company; November 2020.

Immune Checkpoint Inhibitor Dosing

Alternative Nivolumab/Ipilimumab Dosing

Trial	Population	Treatment Arms		ORR (%)	Median PFS (months)		Median OS (months)	
CheckMate 511 (N=358)	No prior therapy	NIVO3 + IPI1 NIVO1 + IPI3	47 53	OR=0.8 0	10 10	HR=1.13	NR NR	HR=1.03

HR, hazard ratio; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; NR, not reached; OR, odds ratio.

Adverse Events	NIVO3 + IPI1 (n=180)	NIVO1 + IPI3 (n=178)
Grade 3 to 5, treatment-related	34%	48%
Leading to treatment discontinuation	26%	39%

- New 3-year survival data

Lebbe C, et al. *J Clin Oncol.* 2021;39(suppl 15):9516.

First-line Regimens for Advanced Melanoma

Preferred Regimens (category 1)

Anti–PD-1 monotherapy
- Nivolumab
- Pembrolizumab

Nivolumab + ipilimumab

Combination targeted therapy[a]
- Vemurafenib + cobimetinib
- Dabrafenib + trametinib
- Encorafenib + binimetinib

[a]If a *BRAF* V600-activating mutation is present.

NCCN Clinical Practice Guidelines. Melanoma: cutaneous. v2.2021.

Category 1 Recommended Regimens

Targeted Therapy Trials

Trial	Population	Treatment Arms	ORR (%)	Median PFS (months)		Median OS (months)	
COMBI-v (N=704)	No prior therapy *BRAF* V600	Dabrafenib/trametinib Vemurafenib	64 51	11 7	*P* < .001	NR 17	---
COMBI-d (N=947)	No prior therapy *BRAF* V600E/K	Dabrafenib/trametinib Dabrafenib/placebo	69 53	11 9	*P* < .0004	25 19	*P* = .0107
coBRIM (N=495)	No prior therapy *BRAF* V600	Vemurafenib/cobimetinib Vemurafenib/placebo	70 50	13 7	---	23 17	---
COLUMBUS (N=768)	Maximum of 1 prior therapy[a] *BRAF* V600E/K	Encorafenib/binimetinib Encorafenib Vemurafenib	64 52 41	15 10 7	*P* < .0001[b] *P* = .0038[b]	34 24 17	*P* < .0001[b] *P* = .0033[b]

[a]First-line therapy had to be with an immune checkpoint inhibitor. [b]Compared with single-agent vemurafenib.

Ascieto P, et al. *Eur J Cancer.* 2020;126:33-44. Dummer R, et al. *Lancet Oncol.* 2018;19(10):1315-1327. Long GV, et al. *Lancet*. 2015;386(9992):444-451.
McArthur GA, et al. Presented at Society for Melanoma Research; Salt Lake City, Utah; 2019. Robert C, et al. *N Engl J Med.* 2015;372(1):30-39.

Targeted Therapy: MAP Kinase Inhibitors

- BRAF inhibitors
  - Selectively inhibit some mutated forms of protein kinase BRAF, resulting in cell death
  - Vemurafenib, dabrafenib, encorafenib
- MEK inhibitors
  - Selectively inhibit mitogen-activated extracellular kinase (MEK) 1 and 2, a downstream effector of *BRAF*, activation and kinase activity
  - Cobimetinib, trametinib, binimetinib

Braftovi [prescribing information]. Array BioPharma Inc; April 2020. Cotellic [prescribing information]. Genentech USA, Inc; January 2018. Mekinist [prescribing information]. Novartis; June 2020. Mektovi [prescribing information]. Array BioPharma Inc; October 2020. Tafinlar [prescribing information]. Novartis; April 2020. Zelboraf [prescribing information]. Genentech USA, Inc; May 2020.

Targeted Therapy: MAP Kinase Inhibitors

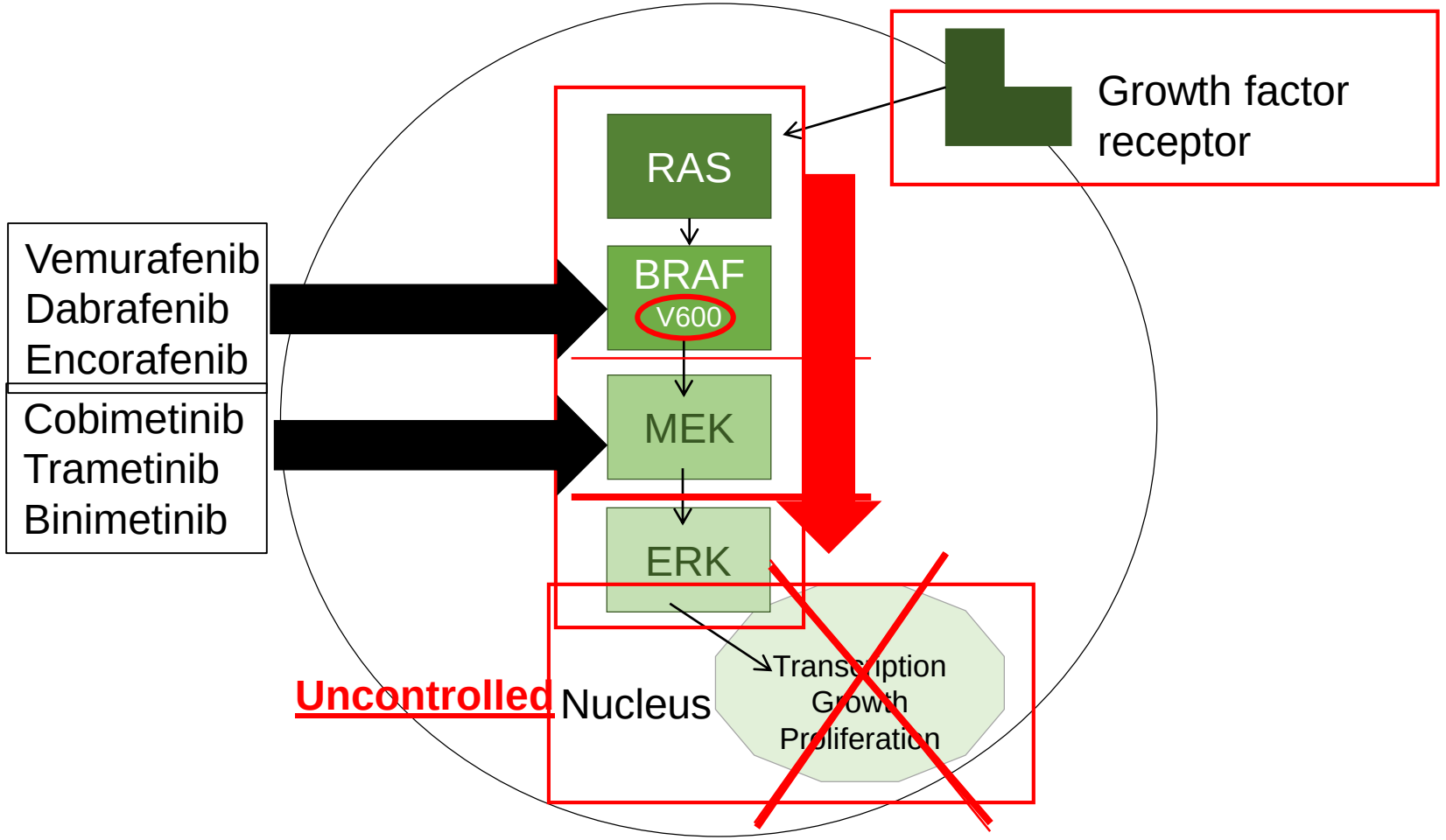


Image recreated from Personalized Medicine in Oncology.
http://www.personalizedmedonc.com/article/dabrafenib-plus-trametinib-two-kinase-inhibitors-used-in-combination-to-target-different-parts-of-the-mapk-pathway.

BRAF/MEK Inhibitor Toxicity

- BRAF inhibitors
  - Arthralgia
  - Cutaneous squamous cell carcinoma *(lower risk when given with a MEK inhibitor)*
  - QTc prolongation
- MEK inhibitors
  - Cardiomyopathy
  - Ocular toxicity
- Combinations
  - Nausea/vomiting/diarrhea
  - Fatigue

BRAF/MEK Combination	Unique Toxicity Profile
Vemurafenib Cobimetinib	Photosensitivity Skin reaction
Dabrafenib Trametinib	Pyrexia Hyperglycemia
Encorafenib Binimetinib	Fatigue Gastrointestinal toxicity

Braftovi [prescribing information]. Array BioPharma Inc; April 2020. Cotellic [prescribing information]. Genentech USA, Inc; January 2018. Mekinist [prescribing information]. Novartis; June 2020. Mektovi [prescribing information]. Array BioPharma Inc; October 2020. Tafinlar [prescribing information]. Novartis; April 2020. Zelboraf [prescribing information]. Genentech USA, Inc; May 2020.

First-line Regimens for Advanced Melanoma

Preferred Regimens (category 1)
Anti–PD-1 monotherapy • Nivolumab • Pembrolizumab
Nivolumab + ipilimumab
Combination targeted therapy[a] • Vemurafenib + cobimetinib • Dabrafenib + trametinib • Encorafenib + binimetinib

[a]If a *BRAF* V600-activating mutation is present.

NCCN Clinical Practice Guidelines. Melanoma: cutaneous. v2.2021.

First-line Regimens for Advanced Melanoma

Preferred Regimens (category 1)	Other Recommended Regimens
Anti–PD-1 monotherapy • Nivolumab • Pembrolizumab	Pembrolizumab + low-dose ipilimumab (category 2B)
Nivolumab + ipilimumab	Vemurafenib + cobimetinib + atezolizumab[a] (category 2A)
Combination targeted therapy[a] • Vemurafenib + cobimetinib • Dabrafenib + trametinib • Encorafenib + binimetinib	Dabrafenib + trametinib + pembrolizumab[a] (category 2B)

[a]If a *BRAF* V600-activating mutation is present.

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Other Recommended Regimens for Advanced Melanoma

Alternative Combination Immune Checkpoint Inhibitor Trial

Trial	Population	Treatment Arms	ORR (%)	Median PFS (months)		Median OS (months)	
KEYNOTE-029 (N=153)	Advanced melanoma	Pembrolizumab/ipilimumab	62	NR	---	NR	---

Adverse Events	Pembrolizumab + Ipilimumab 1 mg/kg
Grade 3 to 5, treatment-related	47%
Treatment discontinuation	36%

- Limited to phase 1b data

Carlino MS, et al. *Clin Cancer Res.* 2020;26(19):5086-5091.

Alternative Combination Immune Checkpoint Inhibitor Dosing

	Pembrolizumab + Ipilimumab
Dose	200 mg + 1 mg/kg
Frequency	Q3W
Route	IV
Duration	Maximum of 4 cycles, then continue on single-agent pembrolizumab

Carlino MS, et al. *Clin Cancer Res.* 2020;26(19):5086-5091.

Other Recommended Regimens for Advanced Melanoma

3-Drug Trials

Trial	Population	Treatment Arms	ORR (%)	Median PFS (months)		Median OS (months)	
IMspire150 (N=514)	No prior therapy *BRAF* V600	Atezolizumab/vem/cobi Placebo/vem/cobi	66 65	15 11	*P* = .025	---	---
KEYNOTE-022 (N=120)	No prior therapy *BRAF* V600E/K	Pembrolizumab/D/T Placebo/D/T	63 72	17 11	---	NR 26	---

cobi, cobimetinib; D, dabrafenib; T, trametinib; vem, vemurafenib.

- Improved PFS and duration of response
- OS data are immature

Ferrucci PF, et al. *J Immunother Cancer.* 2020;8(2):e001806. Gutzmer R, et al. *Lancet.* 2020;395(10240):1835-1844.

Other Recommended Regimens for Advanced Melanoma

3-Drug Trials

Adverse Events, n (%)	Atezolizumab/Vem/Cobi (n=230)	Placebo/Vem/Cobi (n=281)
Grade 3 to 5, treatment-related	182 (79)	205 (73)
Leading to treatment discontinuation	29 (13)	44 (16)
	Pembrolizumab/D/T (n=60)	**Placebo/D/T (n=68)**
Grade 3 to 5, treatment-related	35 (58)	15 (25)
Leading to treatment discontinuation	28 (47)	12 (20)

- Higher toxicity with the 3-drug regimens

Ferrucci PF, et al. *J Immunother Cancer.* 2020;8(2):e001806. Gutzmer R, et al. *Lancet.* 2020;395(10240):1835-1844.

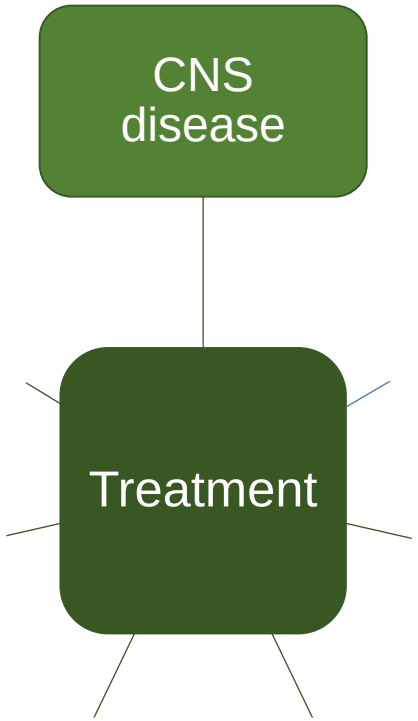
3-Drug Regimen Dosing

	Atezolizumab/Vem/Cobi	Pembrolizumab/D/T
Immune checkpoint inhibitor	C2+: Atezolizumab 840 mg Q2W	Pembrolizumab 200 mg Q3W
BRAF inhibitor	C1D1-21: Vemurafenib 960 mg BID C1D22+: Vemurafenib 720 mg BID	Dabrafenib 150 mg BID
MEK inhibitor	Cobimetinib 60 mg daily Days 1-21/28 for all cycles	Trametinib 2 mg daily
Duration	Until progression or intolerance	Until progression or intolerance

BID, twice daily; C, cycle; D, day.

Ferrucci PF, et al. *J Immunother Cancer.* 2020;8(2):e001806. Gutzmer R, et al. *Lancet.* 2020;395(10240):1835-1844.

Treatment Considerations

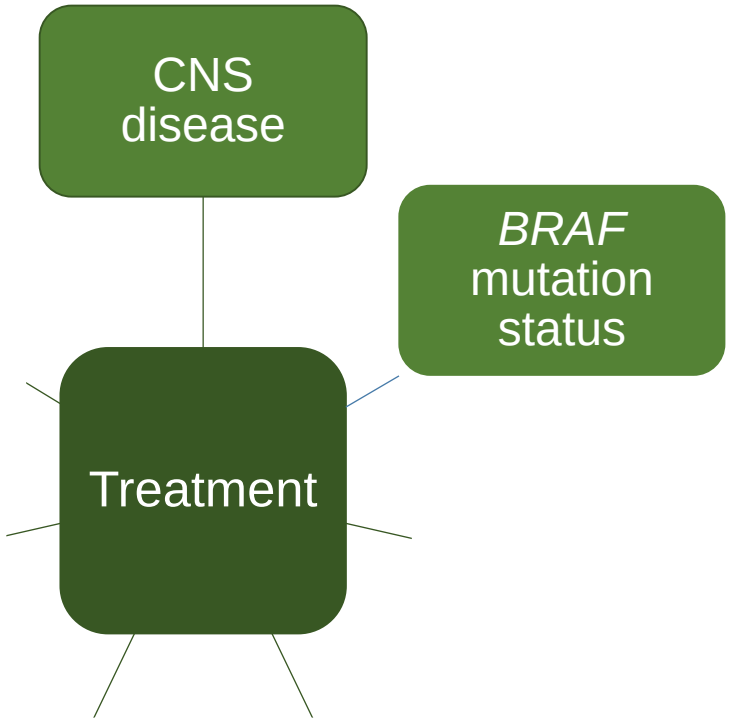


Recommended Regimens Studied in Patients With Brain Metastases

- Dabrafenib/trametinib
- Nivolumab
- Nivolumab/ipilimumab (preferred)
- Pembrolizumab

NCCN Clinical Practice Guidelines. Melanoma: cutaneous. v2.2021.

Treatment Considerations



Mutational Testing

- *BRAF* status
  - High-risk stage III
  - Stage IV
  - Disease recurrence
- PD-L1 status does not guide clinical decision-making

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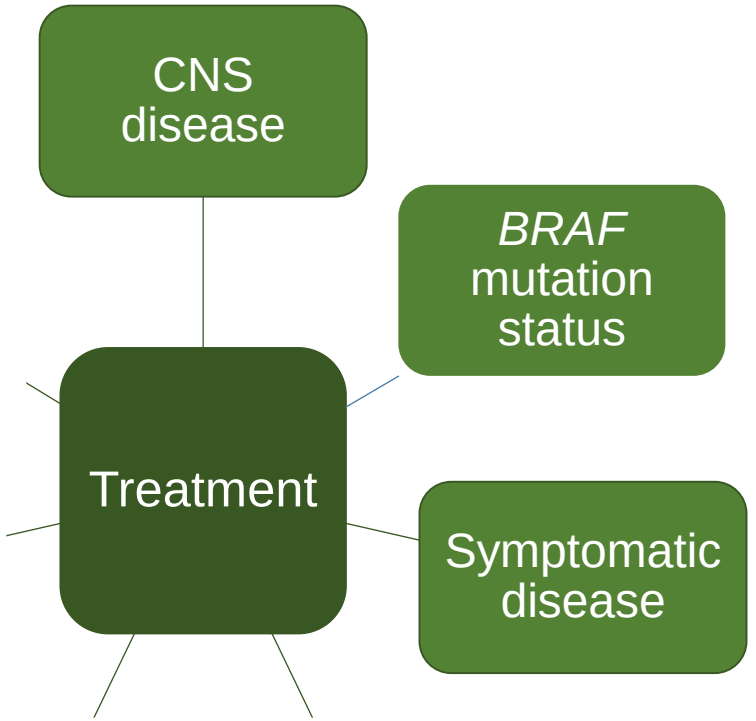
Treatment Considerations



Symptomatic Disease

- Targeted therapy preferred, if *BRAF* V600-acitvating mutation is present
- Targeted therapy has a shorter time to response compared with immune checkpoint inhibitors

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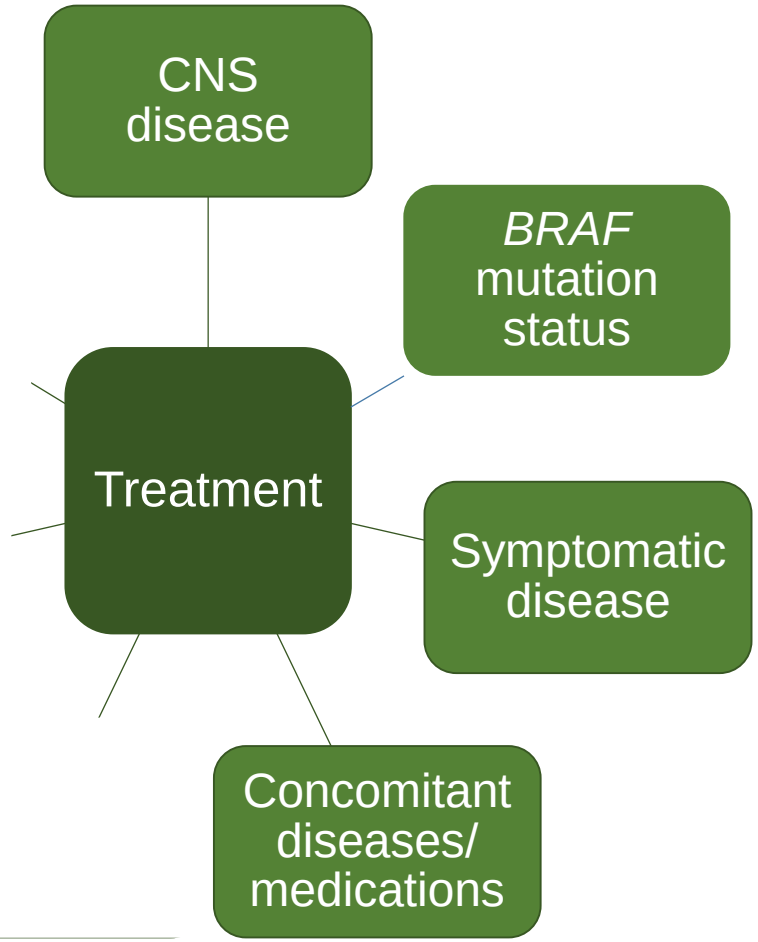
Treatment Considerations



Immune Checkpoint Inhibitors May Be Preferred

- Prolonged QTc interval
- Heart failure
- Drug-drug interactions

Targeted Therapy May Be Preferred

- Autoimmune disease
- Immunosuppressant agents
- Transplant recipients

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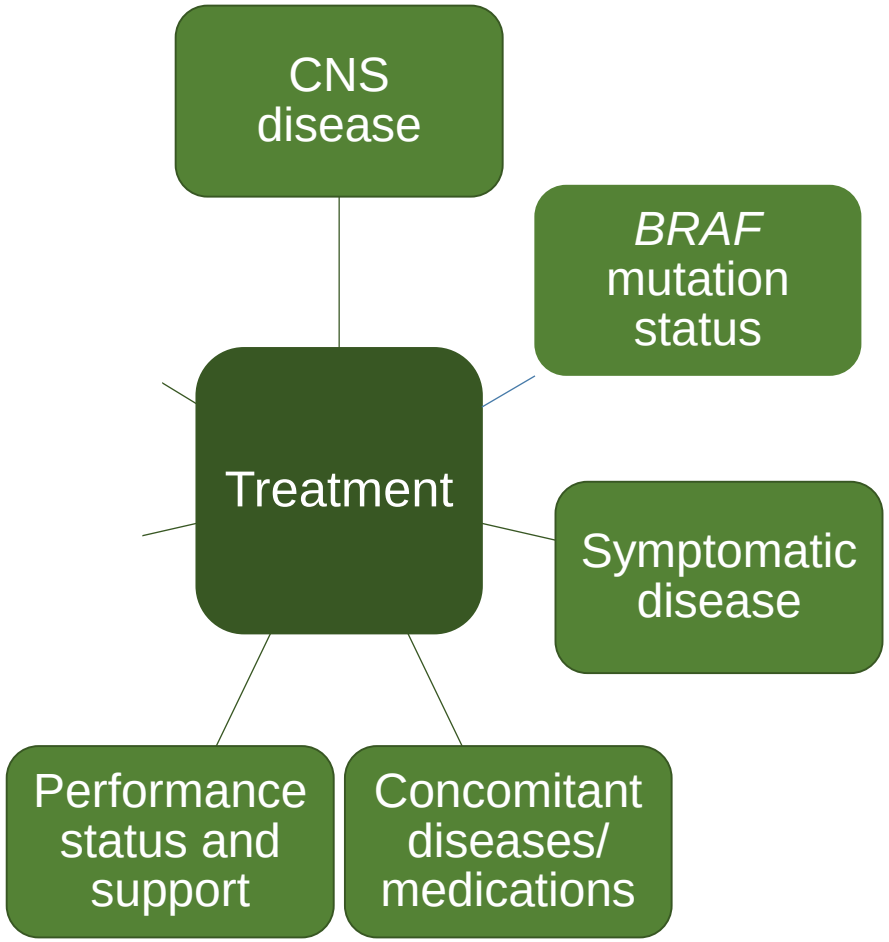
Treatment Considerations

Performance Status and Support

- Three-drug and combination immune checkpoint inhibitor regimens are more toxic than single-agent anti–PD-1 regimens
- Compared with targeted therapy regimens, there is less toxicity with immune checkpoint inhibitors. However, toxicity with immune checkpoint inhibitors can be permanent
- Some patients have more support than others at home



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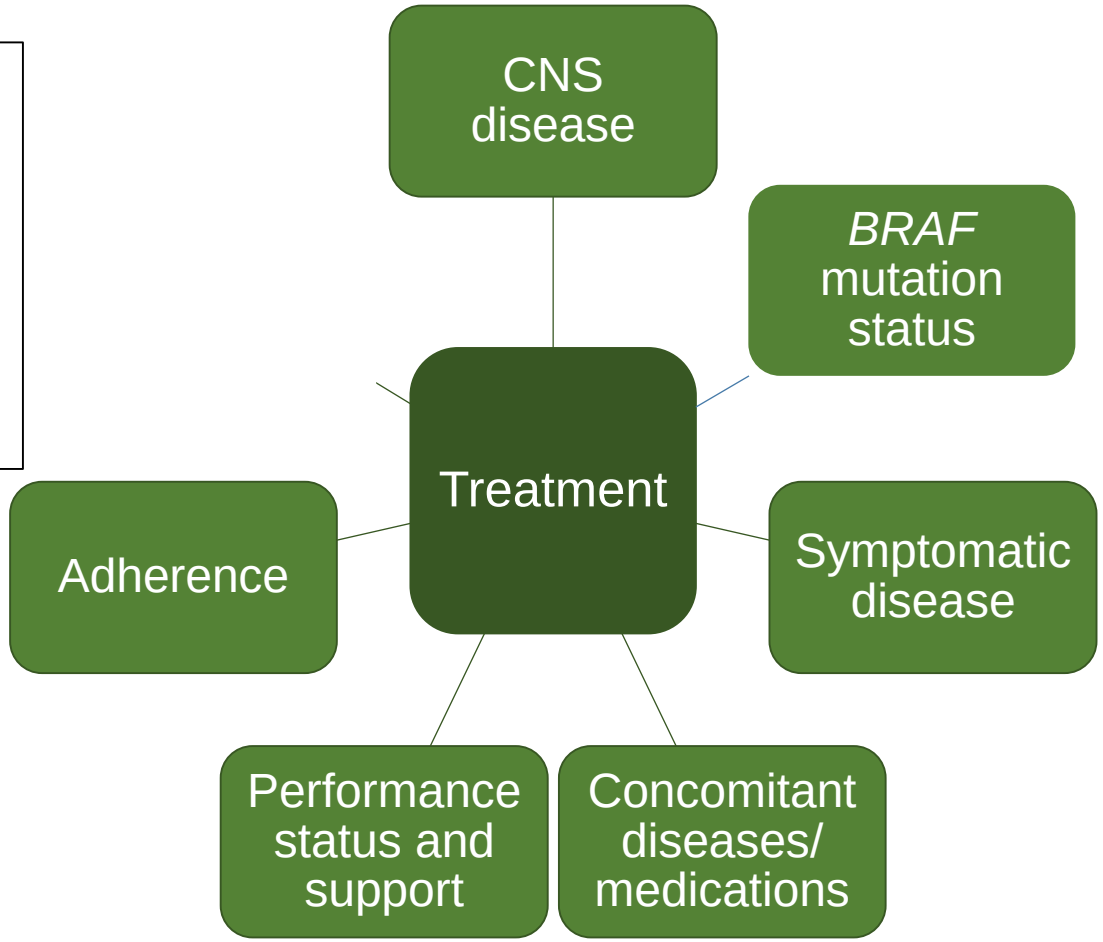
Treatment Considerations

Adherence

- Can the patient take the regimen appropriately at home?
- Is the patient able to travel to clinic for regular infusions?



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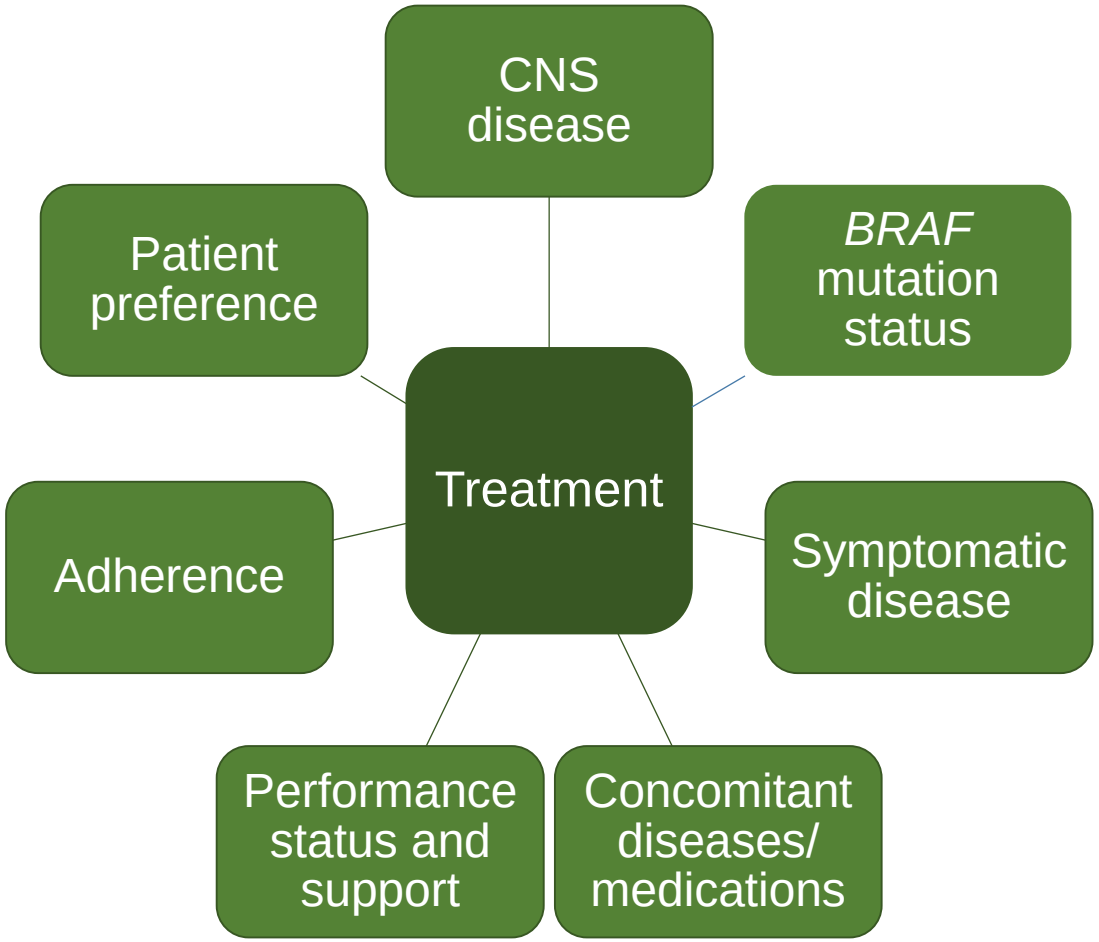
Treatment Considerations



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Other Immune Checkpoint Inhibitor Regimens for Advanced Melanoma

- Single-agent ipilimumab
  - Regimen: 3 mg/kg Q3W x 4 doses
  - Second-line option for patients who have received or are not candidates for the other preferred regimens
- Ipilimumab + intralesional T-VEC
  - Second-line option (category 2B)
  - Useful in certain circumstances

Trial	Population	Treatment Arms	ORR (%)		Median PFS (months)
Phase 2 (N=198)	No prior therapy or 1 or 2 prior lines of therapy	T-VEC/ipilimumab Ipilimumab	39 18	*P* = .002	8.2 6.4

Chesney J, et al. *J Clin Oncol.* 2018;36(17):1658-1667. NCCN Clinical Practice Guidelines. Melanoma: cutaneous. v2.2021.

Other Immune Checkpoint Inhibitor Trials for Advanced Melanoma

Trial	Population	Treatment Arms	Median PFS (months)	Grade 3/4 Adverse Events
Relativity-047 (N=714)	Previously untreated advanced melanoma	Relatlimab/nivolumab Nivolumab	10.1 4.6	19% 10%

- Lymphocyte-activation gene 3 (LAG-3) inhibits T-cell activity and is upregulated in melanoma
- Relatlimab is a human IgG4 LAG-3–blocking antibody
- Relatlimab 160 mg + nivolumab 480 mg IV Q4W

Ig, immunoglobulin.

Lipson EJ, et al. *J Clin Oncol*. 2021;39(suppl 15):9503.

Ongoing Immune Checkpoint Inhibitor Trials

Adjuvant Therapy

- Single-agent pembrolizumab in high-risk, stage II disease

Metastatic Disease

- Pembrolizumab + lenvatinib
- Fianlimab + cemiplimab

Neoadjuvant Therapy

- Single-agent anti–PD-1 regimens and nivolumab + ipilimumab in clinically palpable stage III disease

Amaria RN, et al. *Lancet Oncol.* 2019;20(7):e378-e389. Arance AM, et al. *J Clin Oncol.* 2021;39(suppl 15):9504. Fernandez AMA, et al. *Ann Oncol*. 2020;31(suppl 4):S1142-S1215. Hamid O, et al. *J Clin Oncol.* 2021;39(suppl 15):9515. Kato Y et al. *PLoS One.* 2019;14(2):e0212513. Luke JJ, et al. *Future Oncol*. 2020;16:4429-4438.

Role of the Pharmacist

Education

- Dosing
- Administration
- Adverse events
- Procurement
- Safe handling
- Storage
- Contact information

Monitoring

- Adherence
- Laboratory tests
- Tests
- Adverse events

Management

- Supportive care
- Steroids
- Holding/dose-reducing/stopping therapy

Question & Answer

Thank you!