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Systemic Therapy for Melanoma
ASCO Guideline

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1 Background & Methodology

Introduction

- Systemic treatment for melanoma has changed rapidly in the last decade, many new drugs have been approved for unresectable melanoma, along with new approvals in the adjuvant setting and increasing research in neoadjuvant therapy; improving overall survival for melanoma substantially.[1]
- Additionally, there is a rising incidence of melanoma in most countries; worldwide, the IARC estimated in 2020 there were 324,635 new diagnoses and 57,043 deaths from melanoma.[2]
- With both melanoma incidence and treatment cost rising, rational evidence-based selection of appropriate therapy is essential.[3]
- ASCO developed a guideline on systemic therapy for melanoma in 2018.[4]
- Since that time, further RCTs have been published addressing newer agents, neoadjuvant therapy, therapy for patients with earlier stage disease, and uveal melanoma.
- Given this large quantity of new data and the importance of this data to practice, ASCO determined that the 2018 guideline should receive a full update.

ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
  - a systematic literature review by ASCO guidelines staff
  - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  - final guideline approval by ASCO EBMC

- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical Questions

This clinical practice guideline addresses four clinical questions:

1. What neoadjuvant systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with cutaneous melanoma eligible for resection?
2. What adjuvant systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with resected (stage II, stage III, stage IV) cutaneous melanoma?
3. What systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with unresectable and/or metastatic cutaneous melanoma?
4. What systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with non-cutaneous melanoma (stage II or greater)?

All clinical questions also addressed the sub-question: Are there subpopulations of patients (i.e. clinical features, biomarker status, specific type of melanoma) who benefit more or less from those options?

Target Population and Audience

Target Population

- Adult patients with melanoma (cutaneous and non-cutaneous).

Target Audience

- Clinicians who treat patients with melanoma.

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2 Summary of Recommendations

Summary of Recommendations

All references to stage in these recommendations refer to stage determined by the 8th edition AJCC criteria unless otherwise noted.

Clinical Question 1

- What neoadjuvant systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with cutaneous melanoma eligible for resection?

Summary of Recommendations

Recommendation 1.1

- Neoadjuvant pembrolizumab (maximum of 3 courses of 200 mg once every 3 weeks) followed by resection and adjuvant pembrolizumab (maximum of 15 courses of 200 mg once every 3 weeks) should be offered to patients with clinical and resectable stage IIIB-IV cutaneous melanoma.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Recommendation 1.2

- Patients with clinical and resectable stage IIIB-IV cutaneous melanoma should be offered or referred for enrollment in clinical trials of neoadjuvant therapy where possible.

Informal consensus	
Evidence Quality	**Strength of Recommendation**
N/A	Strong

Summary of Recommendations

Clinical Question 2

- What adjuvant systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with resected (stage II, stage III, stage IV) cutaneous melanoma?

Recommendation 2.1.1

- Adjuvant pembrolizumab or nivolumab should be offered to patients with resected stage IIB or IIC melanoma. See Table 1 (slide 23) for reasonable doses and schedules.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Qualifying Statement: The recommendation in favor of nivolumab is based at the time of writing on the conference abstract publication of CheckMate 76k[5] and under the assumption that full publication of that data will not contradict the abstract. See the Clinical Interpretation section for further details.

Summary of Recommendations

Recommendation 2.1.2

- Adjuvant therapy should not be offered to patients with resected stage IIA melanoma outside of enrollment in a clinical trial.

Informal consensus	
Evidence Quality	**Strength of Recommendation**
N/A	Strong

Summary of Recommendations

Recommendation 2.2

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

- For patients with resected stage IIIA-D disease that is *BRAF* wild-type, the following adjuvant therapy options should be offered (in no particular order): nivolumab x 52 weeks OR pembrolizumab x 52 weeks. Ipilimumab and high-dose interferon are not recommended for routine use in adjuvant therapy. See the Clinical Interpretation section on shared decision making with patients between these options. See Table 1 (slide 23) for recommended dosing and scheduling details.

Qualifying Statements: Patients with stage IIIA disease with microscopic sentinel nodal metastasis < 1 mm in diameter were not included in the randomized trials that studied efficacy of immune checkpoint inhibitors as adjuvant therapy for melanoma. Both nivolumab and pembrolizumab are FDA approved as adjuvant treatments for patients with melanoma with lymph node involvement who have undergone complete disease resection. Patients with stage IIIA disease with < 1 mm involvement in the sentinel lymph node have a relatively better prognosis and lower risk of relapse. Therefore, treatment should be individualized after discussing risk-benefit quotient with these patients.

Summary of Recommendations

Recommendation 2.3

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

- For patients with resected stage IIIA-D disease that is *BRAF* mutant (V600E/K*), the following adjuvant therapy options should be offered (in no particular order): nivolumab x 52 weeks OR pembrolizumab x 52 weeks OR dabrafenib plus trametinib x 52 weeks. See the Clinical Interpretation section on shared decision making with patients between these options. See Table 2 (slide 24) for reasonable dosing and scheduling details.

Qualifying Statements: Patients with stage IIIA disease with microscopic sentinel nodal metastasis <1 mm diameter were not included in the randomized trials that studied efficacy of immune checkpoint inhibitors and BRAF-targeted agents as adjuvant therapy for melanoma. Nivolumab, pembrolizumab, and dabrafenib plus trametinib are FDA approved as adjuvant treatments for patients with melanoma with lymph node involvement who have undergone complete resection of their disease. Patients with stage IIIA disease with less than 1 mm involvement in the sentinel lymph node usually have a good prognosis and low risk of relapse. Therefore, treatment should be individualized after discussing risk-benefit quotient with these patients.

Summary of Recommendations

Recommendation 2.4

- No recommendation can be made for or against adjuvant BRAF/MEK inhibitor therapy in patients with resected stage III/IV melanoma with *BRAF* mutations other than V600E/K.

No recommendation	
Evidence Quality	**Strength of Recommendation**
N/A	N/A

Recommendation 2.5.1

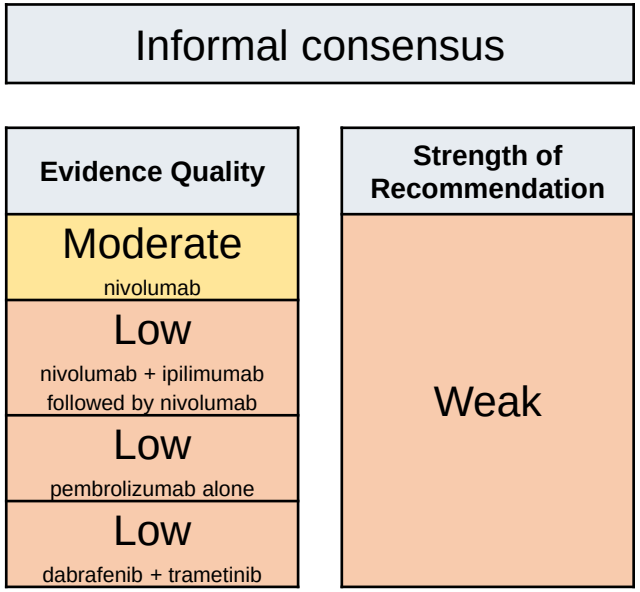
- Patients with resected stage IV melanoma should be offered adjuvant therapy.

Informal consensus	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Recommendation 2.5.2

- Reasonable options for therapy are: nivolumab alone nivolumab plus ipilimumab followed by nivolumab, pembrolizumab alone, and dabrafenib plus trametinib (in patients with *BRAF* V600E/K disease). See the Clinical Interpretation section (in the guideline manuscript) on shared decision making with patients between these options.



Summary of Recommendations

Clinical Question 3

- What systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with unresectable and/or metastatic cutaneous melanoma?

Recommendation 3.1

- For patients with *BRAF* wild-type, unresectable and/or metastatic cutaneous melanoma, the following treatment options should be offered (in no particular order): nivolumab plus ipilimumab followed by nivolumab OR nivolumab plus relatlimab OR nivolumab OR pembrolizumab. See Table 2 (slide 24) for recommended dosing and scheduling details. See the Clinical Interpretation section (in the guideline manuscript) on shared decision making with patients between these options.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Recommendations

Recommendation 3.2.2

- Combination therapy with nivolumab plus ipilimumab is preferred as first-line therapy over BRAF/MEK inhibitor combination therapy. See the Clinical Interpretation section (in the guideline manuscript) on shared decision making with patients between these options.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High dabrafenib + trametinib	Strong
Low other BRAF/MEK inhibitors	

Recommendation 3.3

- After progression on anti-PD-1-based therapy, patients with unresectable and/or metastatic *BRAF* wild-type cutaneous melanoma may be offered ipilimumab or ipilimumab containing regimens. Patients should be offered or referred for enrollment in clinical trials where possible.

Informal consensus	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Summary of Recommendations

Recommendation 3.4

- After progression on 1st line anti-PD-1-based therapy, patients with *BRAF* mutant (V600) unresectable and/or metastatic cutaneous melanoma may be offered combination BRAF/MEK inhibitor therapy as described in Recommendation 3.2.1. Similarly, those who have progressed after combination BRAF/MEK inhibitor therapy may be offered anti-PD-1-based therapy as described in Recommendation 3.2.1.

Informal consenus	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Recommendation 3.5

- For patients with injectable (cutaneous or subcutaneous or nodal) unresectable lesions who are not eligible or do not desire the recommended systemic therapies, T-VEC may be offered as primary therapy.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Summary of Recommendations

Clinical Question 4

- What systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with non-cutaneous melanoma (stage II or greater)?

Recommendation 4.1.1

- HLA-A*02:01-positive patients with metastatic uveal melanoma should be offered tebentafusp (20 µg once on day 1, 30 µg once on day 8, and 68 µg once weekly after that until progression).

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Recommendations

Recommendation 4.1.2

- For all patients with uveal melanoma other than those addressed by Recommendation 4.1.1, no recommendation for or against any specific systemic therapy may be made at this time. Patients should be offered or referred for enrollment in clinical trials where possible.

No recommendation

Evidence Quality	Strength of Recommendation
Very low	N/A

Recommendation 4.2

- In the absence of further data, the consensus of the Expert Panel is that patients with unresectable and/or metastatic mucosal melanoma may be offered therapy as described in Recommendations 3.1 through 3.5. Patients should be offered or referred for enrollment in clinical trials where possible.

Informal consensus

Evidence Quality	Strength of Recommendation
Very low	Weak

Summary of Recommendations

Recommendation 4.3

No recommendation	
Evidence Quality	**Strength of Recommendation**
N/A	N/A

- No recommendation for or against any specific systemic therapy for patients with any other form of non-cutaneous melanoma may be made at this time. Patients should be offered or referred for enrollment in clinical trials where possible.

Table 1. Reasonable Dose and Schedule Details for Recommended Regimens – Neoadjuvant and Adjuvant Therapy

Regimen (Recommendation #)	Dosing Schedules (Source)[a]
Neoadjuvant plus adjuvant pembrolizumab (1.1)	Pre-resection: pembrolizumab, maximum of 3 courses of 200 mg iv once every 3 weeks Post-resection: pembrolizumab, maximum of 15 courses of 200 mg iv once every 3 weeks (SWOG S1801[6])
Pembrolizumab x 52 weeks (2.1.1, 2.2, 2.3, 2.5.2)	Pembrolizumab 200 mg iv once every 3 weeks for 52 weeks (EORTC 1325[7])
Nivolumab x 52 weeks (2.1.1, 2.2, 2.3, 2.5.2)	Nivolumab 240 mg iv once every 2 weeks or once 480 mg iv once every 4 weeks for 52 weeks (CheckMate 238[8] and US FDA label)
Dabrafenib plus trametinib x 52 weeks (2.3, 2.5.2)	Dabrafenib 150 mg orally twice daily plus trametinib 2 mg orally once daily for 52 weeks (COMBI-AD[9])
Nivolumab plus ipilimumab followed by nivolumab (2.5.2)	Nivolumab 1 mg/kg iv plus ipilimumab 3 mg/kg iv once every 3 weeks for four doses, followed by nivolumab 3mg/kg once every 2 weeks for 1 year or until disease recurrence, whichever comes first (IMMUNED trial[10])

NOTE: These were doses and schedules considered reasonable at the time of publication of this guideline. Additional doses and schedules may have been approved at the time of reading.
[a] A particular regimen may have been used in many trials, only one source is provided.

Table 2. Reasonable Dose and Schedule Details for Recommended Regimens – Unresectable and/or Metastatic Disease

Regimen (Recommendation #)	Dosing Schedules (Source)
Nivolumab plus ipilimumab followed by nivolumab until disease progression (3.1, 3.2.1)	• Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg iv once every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg iv once every 2 weeks (CheckMate 067[11]) • Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg iv once every 3 weeks for 4 doses, followed by nivolumab 240 mg iv once every 2 weeks or 480 mg every 4 weeks (US FDA prescribing information)
Nivolumab plus relatlimab (3.1, 3.2.1)	• Relatlimab 160 mg and nivolumab 480 mg iv once every 4 weeks until progression (RELATIVITY-047[12])
Nivolumab (3.1, 3.2.1)	• Nivolumab 3 mg/kg iv once every 2 weeks (CheckMate 067[11]) • Nivolumab 240 mg iv once every 2 weeks (US FDA approved) • Nivolumab 480 mg iv once every 4 weeks (US FDA approved)
Pembrolizumab (3.1, 3.2.1)	• Pembrolizumab 10 mg/kg iv once every 2 weeks or once every 3 weeks (KEYNOTE 006[13]) • Pembrolizumab 2 mg/kg iv once every 3 weeks (KEYNOTE 002[14]) • Pembrolizumab 200 mg iv once every 3 weeks (US FDA approved) • Pembrolizumab 400 mg iv once every 6 weeks (EU EMA approved [based on Lala et al 2018[15]])
Vemurafenib plus cobimetinib (3.2.1)	Vemurafenib 960 mg orally twice daily without pause plus cobimetinib 60 mg orally once daily in a cycle of 21 days with 7 days off (CoBRIM[16])
Dabrafenib plus trametinib (3.2.1)	Dabrafenib 150 mg orally twice daily plus trametinib 2 mg orally once daily (COMBI-v[17])
Encorafenib plus binimetinib (3.2.1)	Encorafenib 450 mg orally once daily plus binimetinib 45 mg orally twice daily (COLUMBUS[18])

NOTE: These were doses and schedules considered reasonable at the time of publication of this guideline. Additional doses and schedules may have been approved at the time of reading.

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3 Discussion

Discussion

- **Ongoing Research:** There are several ongoing trials that are scheduled to be completed by 2025 investigating options recommended in this guideline and that would help clarify the recommendations.
- **Anti-PD-1 Therapy Potential Equivalence:** The issue of the potential equivalence, or lack thereof, of the two relevant anti-PD-1 therapies nivolumab and pembrolizumab was a source of difficulty for the Expert Panel
- **BRAF/MEK Inhibitor Potential Equivalence:** The same issues arise, although not to the same level of importance, with the three BRAF/MEK inhibitor combinations.
- **Changes in Staging Criteria:** One issue that has complicated the 2020 guideline and this full update is that many of the relevant trials were conducted prior to the switch between the 7th and the 8th edition AJCC staging criteria.[19]

Patient and Clinician Communication

- With all cancers, clinician expertise when informing patients about their disease, diagnosis, treatments, and when offering and recruiting patients into clinical trials is vital.
- Side effect management is crucial. The side effects of the recommended immunotherapies and targeted therapies vary. Clinicians should recognize that even grade 1 adverse events, if chronic, can substantially affect quality of life. Long-term management of durable side effects should be a part of patient-clinician communications.
- ASCO has a guideline on managing immune-related adverse events from immune checkpoint therapy,[20] as has the ESMO.[21] ASCO also has a guideline on the screening, assessment, and management of fatigue.[22]
- Patients' access to information on and opportunities to enroll in clinical trials may vary substantially. Clinicians should work to inform themselves of relevant clinical trials.
- Clinicians may also encourage patients to seek out patient support organizations. ASCO's Cancer.Net online resource provides information on such organizations in the US.

Health Disparities

- Although ASCO guidelines provide recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care.
- Patients with cancer who are members of racial and/or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[23,24]
- Awareness of these disparities in access to care should be considered in the context of this guideline, and healthcare providers should strive to deliver the highest level of cancer care to these vulnerable populations.
- In the specific case of melanoma, there is evidence that the incidence rate of cutaneous melanoma is lower in those with dark-pigmented skin versus light-pigmented skin.[25]
- However, there is also evidence that African Americans are often diagnosed with melanoma at non-cutaneous sites including mucosal and acral—and that trials addressing these subtypes will afford a chance to address this. Disease also often is discovered at a later stage and therefore may incur increased morbidity and mortality.[26]

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/melanoma-guidelines

- Patient information is available at www.cancer.net

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Abbreviations

- AJCC, American Joint Committee on Cancer
- ASCO, American Society of Clinical Oncology
- EBMC, Evidence Based Medicine Committee
- EMA, European Medicines Agency
- EORTC, European Organisation for Research and Treatment of Cancer
- ESMO, European Society for Medical Oncology
- EU, European Union
- FDA, US Food and Drug Administration
- IARC, International Agency for Research on Cancer
- iv, intravenously
- N/A, not applicable
- PD-1, programmed cell death protein 1
- RCT, randomized controlled trial
- SWOG, Southwest Oncology Group
- T-VEC, talimogene laherparepvec
- US, United States

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