Systemic Therapy for Melanoma: ASCO Guideline

Seth et al.
Introduction

- Systemic treatment of melanoma has changed rapidly since the introduction of ipilimumab in 2011. In less than 10 years, nine new drugs have been approved for unresectable melanoma, along with four new approvals in the adjuvant setting.
- Newer therapies approved for melanoma include immunotherapy, targeted therapy for mutation-bearing tumors, and injectional therapy for cutaneous or palpable lesions.
- Multiple therapeutic options and longer, more durable survival in this cancer have led to increased clinical activity and cost.
- In addition, the clinical burden associated with the treatment of melanoma has been increasing because of rising incidence in most countries worldwide.
- With both melanoma incidence and treatment cost rising, rational selection of appropriate, evidence-based therapy is essential.
- In light of these changes in available systemic therapy options, a thorough and comprehensive guideline on systemic therapy for melanoma across all stages has been developed by ASCO.
ASCW Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee 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 CPGC

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

This clinical practice guideline addresses four overarching clinical questions:

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

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

3. What systemic therapy options, alone or in combination, have demonstrated clinical benefit in adults with unresectable/metastatic cutaneous melanoma?

4. What systemic therapy options, alone or in combination, have demonstrated clinical benefit in adults with noncutaneous melanoma (stage ≥ II)?

All clinical questions also addressed the subquestion: Are there subpopulations of patients (eg, 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 noncutaneous)

**Target Audience**
Oncologists who treat patients with melanoma
Summary of Recommendations

CLINICAL QUESTION 1
What neoadjuvant systemic therapy options, alone or in combination, have demonstrated clinical benefit in adults with cutaneous melanoma eligible for resection? Are there subpopulations of patients (e.g., clinical features, biomarker status) who benefit more or less from those options?

Recommendation 1
No recommendation can be made for or against the routine use of neoadjuvant therapy for adults with resectable regional or distant metastatic cutaneous melanoma at this time. Patients should be offered or referred for enrollment in clinical trials where possible (Type: No recommendation; Evidence quality: Low; Strength of recommendation: Not applicable).
CLINICAL QUESTION 2
What adjuvant systemic therapy options, alone or in combination, have demonstrated clinical benefit in adults with resected (stage II, III, IV) cutaneous melanoma? Are there subpopulations of patients (eg, clinical features, biomarker status, lymph node dissection v sentinel lymph nodes) who benefit more or less from those options?

Recommendation 2.1
Adjuvant pembrolizumab, nivolumab, or combination dabrafenib and trametinib therapy should not be offered to patients with resected stage II melanoma outside of enrollment in a clinical trial (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate).
Summary of Recommendations

Recommendation 2.2
For patients with resected stage IIIA/B/C/D disease that is BRAF wild type, the following options should be offered (in no particular order): nivolumab × 52 weeks OR pembrolizumab × 52 weeks. Ipilimumab and high-dose interferon are not recommended for routine use in adjuvant therapy. See Table 2 for recommended dosing and scheduling details (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Qualifying Statements
Patients with stage III 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 US Food and Drug Administration (FDA) approved as adjuvant treatment for patients with melanoma with lymph node involvement who have undergone complete disease resection. Patients with stage III 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**
For patients with resected stage IIIA/B/C/D BRAF-mutant (V600E/K*) disease, the following therapy options should be offered (in no particular order): nivolumab × 52 weeks OR pembrolizumab × 52 weeks OR dabrafenib plus trametinib × 52 weeks. See Table 2 for reasonable dosing and scheduling details (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

**Qualifying Statements:** See Other Considerations section in text for discussion of relationship between systemic therapy and resection/completion lymphadenectomy/sentinel lymph node biopsy. Patients with stage III 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 treatment for patients with melanoma with lymph node involvement who have undergone complete resection of their disease. Patients with stage III disease with , 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 dabrafenib plus trametinib in patients with resected stage III/IV melanoma with BRAF mutations other than V600E/K (Type: No recommendation; Evidence quality: Low; Strength of recommendation: Not applicable).

**Recommendation 2.5**

Patients with resected stage IV melanoma should be offered adjuvant nivolumab (Type of recommendation: Evidence based; Evidence quality: High; Strength of recommendation: Strong). Patients with resected stage IV melanoma may be offered pembrolizumab or (in the case of BRAF-mutant disease) dabrafenib plus trametinib (Type of recommendation: Informal consensus; Evidence quality: None; Strength of recommendation: Weak).
Summary of Recommendations

CLINICAL QUESTION 3
What adjuvant systemic therapy options, alone or in combination, have demonstrated clinical benefit in adults with resected (stage II, III, IV) cutaneous melanoma? Are there subpopulations of patients (eg, clinical features, biomarker status, lymph node dissection v sentinel lymph nodes) who benefit more or less from those options?

Recommendation 3.1
For patients with BRAF wild-type unresectable/metastatic cutaneous melanoma, the following treatment options should be offered (in no particular order): ipilimumab plus nivolumab followed by nivolumab OR nivolumab OR pembrolizumab. See Table 3 for recommended dosing and scheduling details. (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong)

Qualifying Statements: In the relevant randomized trials, nivolumab could be continued beyond 2 years,4 while pembrolizumab was limited to 2 years. It is possible that shorter courses of therapy, as short as 1 year, may be reasonable. However, no high-quality data in the melanoma setting address what the duration of therapy should be. For longer dosing cycles (eg, up to 6 weeks between doses, as has been approved in Europe for pembrolizumab), appropriate monitoring for disease progression is still necessary.
Summary of Recommendations

Recommendation 3.2
For patients with BRAF-mutant (V600) unresectable/metastatic cutaneous melanoma, the following treatment options should be offered (in no particular order): ipilimumab plus nivolumab followed by nivolumab OR nivolumab OR pembrolizumab OR dabrafenib plus trametinib OR encorafenib plus binimetinib OR vemurafenib plus cobimetinib. See Table 3 for recommended dosing and scheduling details (Type: Evidence based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Qualifying Statements
Switching between BRAF/MEK inhibitor combinations may be reasonable if patients experience toxicity, as each combination can present somewhat different toxicity profiles. In the clinical context of BRAF/MEK inhibitor failure, no data exist regarding the efficacy of switching to a different BRAF/MEK combination. For longer dosing cycles for anti–programmed death 1 (PD1) regimens (eg, up to 6 weeks between doses, as has been approved in Europe for pembrolizumab), appropriate monitoring for disease progression is still necessary.
Summary of Recommendations

**Recommendation 3.3**
After progression on anti-PD1 therapy, patients with unresectable/metastatic *BRAF* wild-type cutaneous melanoma may be offered ipilimumab or ipilimumab-containing regimens. Talimogene laherparepvec (T-VEC) therapy may be offered to patients with injectable lesions (Type: Informal consensus; Evidence quality: Informal consensus; Strength of recommendation: Weak).

**Recommendation 3.4**
After progression on first-line anti-PD1 therapy, patients with *BRAF*-mutant (V600) unresectable/ metastatic cutaneous melanoma may be offered in combination BRAF/MEK inhibitor therapy, as described in Recommendation 3.2. Similarly, those who have progressed after combination BRAF/MEK inhibitor therapy may be offered anti-PD1 therapy. In either case, ipilimumab or ipilimumab-containing regimens may be offered instead (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak).
Summary of Recommendations

Recommendation 3.5
For patients with injectable (cutaneous/subcutaneous/nodal) unresectable lesions who are not eligible or do not desire the recommended systemic therapies, T-VEC may be offered as primary therapy (Type: Evidence based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Weak)
Summary of Recommendations

CLINICAL QUESTION 4
What systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with **noncutaneous melanoma (stage ≥ II)**? Are there subpopulations of patients (eg, clinical features, biomarker status, specific type of melanoma) who benefit more or less from those options?

**Recommendation 4.1**
No recommendation for or against any specific systemic therapy for patients with **uveal** melanoma may be made at this time. Patients should be offered or referred for enrollment in clinical trials where possible (Type: No recommendation; Evidence quality: Low; Strength of recommendation: Not applicable).
Summary of Recommendations

**Recommendation 4.2**
In the absence of additional data, the consensus of the Expert Panel is that patients with unresectable/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. (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak).

**Recommendation 4.3**
No recommendation for or against any specific systemic therapy for patients with any other form of noncutaneous melanoma may be made at this time. Patients should be offered or referred for enrollment in clinical trials where possible. (Type: No recommendation; Evidence quality: No evidence; Strength of recommendation: Not applicable).
Health Disparities

- Patients with cancer who are members of racial/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\(^5,6\)

- Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline

- In the specific case of melanoma, there is evidence that the incidence rate of melanoma is lower in those with dark-pigmented skin versus light-pigmented skin.\(^7\)

- However, there is also evidence that African Americans are often diagnosed with melanoma at a later stage and experience increased mortality.\(^8\)
Patient and Clinician Communication

- With all cancers, clinician expertise when informing patients about their disease, their diagnosis, and their treatments and when offering and recruiting patients regarding clinical trials, is vital.

- Adverse effect management is a crucial element of patient and clinician communication. The adverse effects of the recommended immunotherapies and targeted therapies will vary by patient and by agent. Clinicians should recognize that even grade 1 adverse events, if chronic, can substantially affect quality of life (eg, diarrhea).
  - ASCO has developed a guideline on immune-related events in immune checkpoint therapy, as has ESMO.\(^9\)
  - ASCO has also published a guideline on the screening, assessment, and management of fatigue.\(^10\)

- Patients’ access to information on and opportunities to enroll in clinical trials may vary substantially depending on the setting where they receive care. Clinicians should work to inform themselves of relevant clinical trials.
Cost Considerations

- Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs.\textsuperscript{12}

- Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.\textsuperscript{13,14}

- For the specific case of systemic therapy for melanoma, a nonsystematic review was conducted to identify relevant cost-effectiveness analyses.

- Four cost-effectiveness analyses were identified regarding therapy for patients with advanced melanoma; their reported results are summarized in the guideline text.

- More generally, it is expected that the costs associated with the therapies recommended in this guideline will differ substantially
Discussion

- Melanoma therapy has undergone a revolution. With the discovery of multiple effective immunotherapies and targeted therapies, melanoma’s lethal history has been altered.

- In this guideline, the Expert Panel attempts to use the most accurate, up-to-date data to guide the recommendations as an aid to all oncologists who care for patients with melanoma.

- Clinical trials for melanoma have produced an abundance of clinical data, but several trials that are ongoing, unpublished, and/or published only in abstract form will provide new information for the treatment of melanoma.

- One issue that has complicated this guideline is the relatively recent change in AJCC staging criteria from the seventh to the eighth edition. In this guideline, we have attempted to use eighth edition staging where possible, particularly in the recommendations. In any case where staging refers to the seventh edition (as in a majority of randomized trials cited as evidence), the Expert Panel attempts to note this fact.
Additional Resources

More information, including a Data Supplement, slide sets, 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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