## SYSTEMIC THERAPY FOR MELANOMA: ASCO GUIDELINE

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| **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 (eg, clinical features, biomarker status) who benefit more or less from those options? | 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 |
| **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 vs sentinel lymph) | 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.  
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: Informal consensus  
Evidence quality: Low  
Strength of recommendation: Moderate |

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| nodes) who benefit more or less from those options? | **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. | Type: Evidence based, benefits outweigh harms  
Evidence quality: High  
Strength of recommendation: Strong |
| 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 | **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. | |
| 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 |
| 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 |
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<td>What systemic therapy options, alone or in combination, have demonstrated clinical benefit in adults with unresectable/metastatic cutaneous melanoma? Are there subpopulations of patients (eg, clinical features, biomarker status, presence of brain metastases) who benefit more or less from those options?</td>
<td>For patients with <em>BRAF</em> 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. Qualifying Statements: In the relevant randomized trials, nivolumab could be continued beyond 2 years, 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.</td>
<td>Type: Evidence based, benefits outweigh harms  Evidence quality: High  Strength of recommendation: Strong</td>
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<td>For patients with <em>BRAF</em>-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. 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.</td>
<td></td>
<td>Type: Evidence based, benefits outweigh harms  Evidence quality: High  Strength of recommendation: Strong</td>
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<td>After progression on anti-PD1 therapy, patients with unresectable/metastatic <em>BRAF</em> 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.</td>
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<td>Type: Informal consensus  Evidence quality: No evidence  Strength of recommendation: Weak</td>
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| 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                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                     |
| 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                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                     |
| 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? | 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                                                                                                                                                                                                                                         |
| 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                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                     |
| 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                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                     |