ASCO® Guidelines

Systemic Therapy for Melanoma: ASCO Guideline Update				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
What neoadjuvant systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with cutaneous melanoma eligible for resection? Are there subpopulations of patients (i.e. clinical features, biomarker status) who benefit more or less from those options?	**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.	EB	M	S
	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.	IC	N/A	S
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? Are there subpopulations of patients (i.e. clinical features, biomarker status, lymph node dissection vs. sentinel lymph nodes) who benefit more or less from those options?	**2.1.1.** Adjuvant pembrolizumab or nivolumab should be offered to patients with resected stage IIB or IIC melanoma. See Table 1 (in the guideline manuscript) for reasonable doses and schedules.	EB	M	S
	Qualifying Statement: The recommendation in favor of nivolumab is based at the time of writing on the conference abstract publication of CheckMate 76k and under the assumption that full publication of that data will not contradict the abstract. See the Clinical Interpretation section for further details.			
	2.1.2. Adjuvant therapy should not be offered to patients with resected stage IIA melanoma outside of enrollment in a clinical trial.	IC	N/A	S
	2.2. 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 (in the guideline manuscript) for recommended dosing and scheduling details.	EB	H	S

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	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 US 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.			
	2.3. 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 (in the guideline manuscript) for reasonable dosing and scheduling details.	EB	H	S
	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.			
	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.	N/A	N/A	N/A
	2.5.1. Patients with resected stage IV melanoma should be offered adjuvant therapy.	IC	M	S

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	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.	IC	M nivolumab L nivolumab + ipilimumab followed by nivolumab L pembrolizumab alone L dabrafenib + trametinib	W
What systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with unresectable and/or metastatic cutaneous melanoma? Are there subpopulations of patients (i.e. clinical features, biomarker status, presence of brain metastases) who benefit more or less from those options?	**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 (in the guideline manuscript) for recommended dosing and scheduling details. See the Clinical Interpretation section (in the guideline manuscript) on shared decision making with patients between these options.	EB	H	S
	3.2.1. For patients with *BRAF* mutant (V600) unresectable and/or metastatic cutaneous melanoma, one of the following treatment options should be offered as first-line therapy: nivolumab plus ipilimumab followed by nivolumab OR nivolumab plus relatlimab OR nivolumab OR pembrolizumab OR dabrafenib plus trametinib OR encorafenib plus binimetinib OR vemurafenib plus cobimetinib. See Table 2 (in the guideline manuscript) for recommended dosing and scheduling details. See the Clinical Interpretation section (in the guideline manuscript) on shared decision making with patients between these options.	EB	H	S

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	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.	EB	H dabrafenib + trametinib L other BRAF/MEK inhibitors	S
	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.	IC	L	W
	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.	IC	L	W
	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.	EB	L	W
What systemic therapy options, alone or in combination, have demonstrated clinical benefits in adults with non-cutaneous melanoma (stage II or greater)? Are there subpopulations of patients (i.e. clinical features, biomarker	**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).	EB	M	S
	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.	N/A	VL	N/A

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status, specific type of melanoma) who benefit more or less from those options?	**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.	IC	VL	W
	4.3. 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.	N/A	N/A	N/A

NOTE: All references to stage in these recommendations refer to stage determined by the 8th edition AJCC criteria unless otherwise noted.
Abbreviations. AJCC. American Joint Committee on Cancer; EB, evidence based; FDA, US Food and Drug Administration; H, high; IC, informal consensus; L, low; M, moderate; PD-1, programmed cell death protein 1; N/A, not applicable; S, strong; T-Vec, talimogene laherparepvec; US, United States; VL, very low; W, weak

