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Systemic Adjuvant Therapy for Adult Patients at High Risk for Recurrent Melanoma

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A targeted update of the Guideline was conducted in November 2023. As a result of this update, a new recommendation (Recommendation1B) has been added. The PEBC has a formal and standardized process to ensure the currency of each document
PEBC Assessment & Review Protocol

Guideline 8-1 Version 6 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1161

Section 1: Guideline Recommendations
Section 2: Recommendations and Key Evidence
Section 3: Guideline Methods Overview
Section 4: Systematic Review
Section 5: Internal and External Review

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PUBLICATIONS RELATED TO THIS REPORT

Petrella TM, Fletcher GG, Knight G, McWhirter E, Rajagopal S, Song X, Baetz TD. Systemic adjuvant therapy for adult patients at high risk for recurrent cutaneous or mucosal melanoma: An Ontario Health (Cancer Care Ontario) clinical practice guideline. Curr Oncol. 2020;27(1):e43-e52. https://doi.org/10.3747/co.27.5933

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Petrella T, Verma S, Spithoff K, Quirt I, McCready D; Melanoma Disease Site Group. Adjuvant interferon therapy for patients at high risk for recurrent melanoma: An updated systematic review and practice guideline. Clin Oncol (R Coll Radiol). 2012 Aug;24(6):413-23.

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Guideline Document History*

GUIDELINE VERSION	SYSTEMATIC REVIEW Search Dates	SYSTEMATIC REVIEW Data	PUBLICATIONS	NOTES and KEY CHANGES
Version 4 November 7, 2013	July 2008- September 2013	New data appended in Section 4	CCO website	New data appended in Section 4; 2009 recommendations endorsed
Version 4 December 8, 2017	2013 to October 2017	New data replace previous Section 4	CCO website	Section 4 of 2013 version has been relabelled Appendix 1. Recommendations require updating in a new version
Version 5 August 14, 2019	1996- June 2018 trials; 2013-2018 reviews or guidelines	Guideline rewritten	CCO website	Systematic reviews merged, recommendations rewritten
Update of version 5 June 2023	NA	2 Trials added to Section 1 and Section 2 **Only**	Updated web publication on CCO/OH website	Recommendation 1 was updated with evidence from 2 RCTs. For details see **Appendix 10**

*For full Guideline History since the original publication of May 27, 1998, please see Appendix 9

Systemic Adjuvant Therapy for Adult Patients at High Risk for Recurrent Melanoma

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To make recommendations regarding the use of adjuvant systemic therapy in adult patients with completely resected cutaneous or mucosal melanoma with a high risk of recurrence.

TARGET POPULATION

Adult patients with cutaneous or mucosal melanoma with high risk of recurrence who are rendered disease-free following resection (including resection of all locoregional or distant metastases, if present). Patients with unresected primary disease or metastases fall outside the scope of this document.

INTENDED USERS

Medical oncologists, surgical oncologists, and other health care providers involved in the management and referral of patients with resected melanoma at high risk for recurrence.

RECOMMENDATIONS

A. Cutaneous Melanoma

Recommendation 1a

1a.1 Nivolumab or pembrolizumab is recommended as adjuvant therapy for patients with completely resected cutaneous melanoma without *BRAF* V600E or V600K mutations with high risk of recurrence (stage IIIA [>1 mm nodal metastasis] to IIID, IV).

1a.2 Nivolumab, pembrolizumab, or dabrafenib plus trametinib is recommended as adjuvant therapy for patients with completely resected cutaneous melanoma with *BRAF* V600E or V600K mutations and high risk of recurrence (stage IIIA [>1 mm nodal metastasis] to IIID, IV).

1a.3 Molecular testing of high-risk melanoma patients to characterize mutations should be conducted to help guide appropriate treatment decisions.

Qualifying Statements for Recommendation 1

- Nivolumab, pembrolizumab, or the combination dabrafenib plus trametinib (for *BRAF* V600E/K mutated melanoma) are all appropriate treatments; there is currently insufficient evidence to suggest which of these is more effective. These agents were

evaluated in different trials [1-3] (see Table 4-4) and have not been directly compared in the adjuvant setting. For nivolumab and pembrolizumab, treatment-related adverse events (AEs) tended to be mild and manageable, and occurred in 85% and 78% of patients, respectively, with the most common being fatigue, skin reactions (rash, pruritus), diarrhea, nausea, and endocrine disorders. Rates of grade 3+ treatment-related AEs (14.4% and 14.7%) resulting in treatment discontinuation (9.7% vs. 13.8%) were similar. The combination dabrafenib plus trametinib resulted in a higher rate of serious AEs (36%), including pyrexia, hypertension, and hepatic effects, and higher rate of discontinuation due to AEs (25%). The spectrum of adverse effects and contraindications for immunotherapy with nivolumab or pembrolizumab compared with that for dabrafenib plus trametinib should be discussed with the patient when deciding on adjuvant treatment.

- These treatments were evaluated in trials requiring patients to have complete regional lymphadenectomy. The Multicenter Selective Lymphadenectomy Trial-II (MSLT-II) [4] and the Dermatologic Cooperative Oncology Group (DeCOG)-SLT trial [5,6] found that in patients with clinically localized cutaneous melanoma (no satellite, in-transit, regional, or distant metastases) with positive sentinel lymph nodes, immediate completion lymph node dissection compared with nodal observation with ultrasonography and completion lymphadenectomy only upon recurrence did not improve melanoma-specific survival but led to higher morbidity (lymphedema). Based on these results, routine immediate completion lymphadenectomy is no longer standard practice for patients with pathologically node-positive disease by sentinel lymph node biopsy (see guidelines by the Program in Evidence-Based Care/Cancer Care Ontario [7] and the American Society of Clinical Oncology/Society of Surgical Oncology [8]). In the absence of complete lymphadectomy, some patients with positive sentinel lymph nodes assigned as stage IIIA or IIIB may be understaged. These trials and recommendations regarding axillary resection do not apply to patients with clinically positive lymph nodes (by palpation or radiologic investigation), and the standard of care is dissection of lymph nodes in that area (axillary, groin, or head and neck) prior to adjuvant therapy or adjuvant radiotherapy. In the case of unresectable disease, up-front systemic therapy should be considered.
- Patient inclusion in these trials was based on the American Joint Committee on Cancer (AJCC) 7th edition, which subdivides stage III into IIIA, IIIB, and IIIC groups. The AJCC 8th edition now in effect has an additional IIID category; with revised criteria for stage III substages there will be stage migration. For example, using data from the COMBI-AD trial [9], 38% of stage III patients were reclassified to a different subgroup.
- Stage IV patients with completely resected disease were only included in the Eastern Cooperative Oncology Group (ECOG) E1609 trial (abstract only, not reported separately) [10] and the CheckMate 238 trial (see key evidence) [1,11]. Data are therefore more limited for this population.
- The role of radiotherapy was outside the scope of the literature review; adjuvant radiotherapy is the subject of a separate guideline [12]. Patients who received adjuvant radiotherapy were excluded from the trials of immune checkpoint inhibitors and targeted therapy, except for the E1609 trial comparing ipilimumab doses [10].
- The recommendations from the immunotherapy trials are based on interim results for disease-free survival (DFS); most overall survival (OS) results are not yet available but are forthcoming. A recent review by Suciu et al. [13] supports the view that recurrence-

free survival is a suitable surrogate for OS. Recommendations should be reevaluated once final results for the relevant studies are reported.

- Data on targeted therapy for *BRAF* mutations other than V600E/K are not available, and therefore adjuvant therapy with nivolumab or pembrolizumab should be considered.

Recommendation 1b (new evidence in 2023)

1b. ***New Recommendation for Stage IIB and IIC: Nivolumab or pembrolizumab is recommended as adjuvant therapy for patients with completely resected, node-negative cutaneous melanoma with and without BRAF V600E or V600K mutations with high risk of recurrence (Stage IIB and IIC).***

Qualifying Statements for Recommendation 1b

- The recommendations from the immunotherapy trials are based on interim results for recurrence-free survival (RFS) and/or distant metastases-free survival (DMFS); most overall survival (OS) results are not yet available but are forthcoming
- There is currently no data for targeted therapy for BRAF mutated Stage IIB, IIC melanoma. These patients should be offered immunotherapy.

Recommendation 2

2.1 Ipilimumab is not recommended as adjuvant therapy for patients with completely resected cutaneous melanoma with high risk of recurrence.

Qualifying Statements for Recommendation 2

- While ipilimumab may be effective in reducing the risk of melanoma recurrence, this agent has lower efficacy and higher rates of serious adverse effects than nivolumab and is not recommended.

Recommendation 3

3.1 Use of interferon alpha (IFN-α) for adjuvant treatment of cutaneous melanoma outside of a clinical trial is no longer recommended.

Qualifying Statements for Recommendation 3

- The EORTC 18081 trial (NCT01502696) comparing pegylated IFN-α2b for two years to observation in ulcerated stage II melanoma has an estimated completion of April 2019. This trial may confirm results of the individual patient meta-analysis by the International Melanoma Meta-Analysis Collaborative Group [14], which suggested IFN-α is of benefit in ulcerated melanoma.
- IFN may have a limited role in high-risk patients not eligible for other treatments.

Recommendation 4

4.1 Chemotherapy regimens, vaccines, levamisole, bevacizumab, Bacillus Calmette-Guerin, and isolated limb perfusion are not recommended for adjuvant treatment of cutaneous melanoma except as part of a clinical trial.

B. Mucosal Melanoma

Recommendation 5

5.1 Immune checkpoint inhibitors (nivolumab or pembrolizumab) or targeted therapy (in patients with identified mutations) are recommended for adjuvant therapy of mucosal melanoma with high risk of recurrence.

Qualifying Statements for Recommendation 5

- Mutation characterization is required prior to consideration of targeted agents. Mucosal melanoma has a different origin and spectrum of mutations than cutaneous melanoma. *BRAF* mutations are less common than in cutaneous melanoma, and therefore inhibitors are of little value in unselected patients. *KIT* mutations are more prevalent in mucosal melanoma, and inhibitors such as imatinib appear to be of value in advanced melanoma with *KIT* mutations [15]; however, no trials on adjuvant use of KIT inhibitors were found.
- The trials forming the key evidence for cutaneous melanoma (see Recommendations 1-2) excluded mucosal melanoma, with the exception of the CheckMate 238 trial, which included 29 patients (3.2% of total). This small number is insufficient to allow any conclusions specifically for this subgroup.
- There may be a role for chemotherapy, but evidence is not sufficient at this time to make a recommendation. Adjuvant treatment of mucosal melanoma with high-dose IFN-α2b compared with temozolomide plus cisplatin was studied in a phase II trial [16] of patients with stage II/III mucosal melanoma and a subsequent phase III trial in stage I-III mucosal melanoma that has been reported only in abstract form [17]. The phase II study found temozolomide plus cisplatin to result in better OS and DFS than IFN-α2b or placebo. A follow-up phase III study confirmed benefit of temozolomide plus cisplatin compared with IFN-α2b. The available evidence is limited due to lack of full publication and inconsistency with studies in metastatic melanoma [18]

FURTHER QUALIFYING STATEMENTS

The recommended adjuvant therapies have potential for adverse effects (see above key evidence and qualifying statements). While usually manageable and reversible, they may be severe. It was outside the scope of the accompanying systematic review to deal with the management of these adverse effects. The user may refer to other guidelines such as those by the Multinational Association of Supportive Care in Cancer [19], ECOG [20], the American Society of Clinical Oncology/National Comprehensive Cancer Network [21,22], Cancer Care Ontario [23] and others [24,25].

There are several ongoing trials, and the above recommendations may need to be revisited upon their completion.