

Systemic adjuvant therapy for adult patients at high risk for recurrent cutaneous or mucosal melanoma: an Ontario Health (Cancer Care Ontario) clinical practice guideline

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ABSTRACT

Background Previous versions of the guideline from the Program in Evidence-Based Care (PEBC) at Ontario Health (Cancer Care Ontario) recommended that the use of high-dose interferon alfa 2b therapy be discussed and offered to patients with resected cutaneous melanoma with a high risk of recurrence. Subsequently, several clinical trials in patients with resected or metastatic melanoma found that immune checkpoint inhibitors and targeted therapies have a benefit greater than that with interferon. It was therefore considered timely for an update to the guideline about adjuvant systemic therapy in melanoma.

Methods The present guideline was developed by the PEBC and the Melanoma Disease Site Group (DSG). Based on a systematic review from a literature search conducted using MEDLINE, EMBASE, and the Evidence Based Medicine Reviews databases for the period 1996 to 28 May 2019, the Working Group drafted recommendations. The systematic review and recommendations were then circulated to the Melanoma DSG and the PEBC Report Approval Panel for internal review; the revised document underwent external review.

Recommendations For patients with completely resected cutaneous or mucosal melanoma with a high risk of recurrence, the recommended adjuvant therapies are nivolumab, pembrolizumab, or dabrafenib–trametinib for patients with *BRAF* V600E or V600K mutations; nivolumab or pembrolizumab are recommended for patients with *BRAF* wild-type disease. Use of ipilimumab is not recommended. Molecular testing should be conducted to help guide treatment decisions. Interferon alfa, chemotherapy regimens, vaccines, levamisole, bevacizumab, bacillus Calmette–Guérin, and isolated limb perfusion are not recommended for adjuvant treatment of cutaneous melanoma except as part of a clinical trial.

Key Words Melanoma, adjuvant therapy, immune checkpoint inhibitors, targeted therapy, interferon, practice guidelines

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INTRODUCTION

Melanoma is the 8th most common cancer in Canada, and the 15th in mortality¹. Cutaneous melanoma predominates, and most clinical trials have been conducted in patients with cutaneous melanoma. Data used in developing the 8th edition of the American Joint Committee on Cancer (AJCC) cancer staging manual indicate, for cutaneous

melanoma, 5-year melanoma-specific survival rates of 98% for stage I, 90% for stage II, and 77% for stage III disease, with rates as low as 32% for the stage IIID subgroup². Given the poor survival for more advanced but resectable disease, many clinical trials have investigated the use of adjuvant systemic therapy.

Mucosal melanoma is a rare disease: it accounts for approximately 0.03% of all cancers diagnosed³ and 1.4%

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of all melanomas in the United States⁴. The most common sites are the head and neck, the anorectal area, and the vulvovaginal region. Ultraviolet radiation exposure has not been associated with development of mucosal melanoma⁵, and rates are relatively consistent in various populations. Because of lower rates of cutaneous cancer in patients of Hispanic or African background⁴ and in Asian populations^{6,7}, mucosal melanoma constitutes a higher proportion of melanomas in those groups. Characteristics of mucosal melanoma, including causative mutations, differ from those of cutaneous melanoma, and the absolute level of response to treatment can vary. Uveal and other ocular melanomas are outside the scope of the present guideline.

For many years, interferon (IFN) was considered the only effective adjuvant treatment, and previous versions of this guideline recommended that the use of high-dose IFN alfa 2b (HD-IFN- α 2b) therapy be discussed and offered to patients at high risk of recurrence^{8,9}. Several trials found that IFN was associated with a recurrence-free survival (RFS) benefit, but a marginal or absent benefit for overall survival (OS). That small benefit was confirmed in meta-analyses of trials, but was offset by significant adverse effects affecting quality of life. Trials in the metastatic setting found a much greater benefit to be associated with immune checkpoint inhibitors and targeted therapy, and recent trials have confirmed the benefit of some of those agents in the adjuvant setting.

Given the emergence of those new agents, an updated guideline about the adjuvant treatment of melanoma, based on a systematic review of the current evidence, was determined to be required.

METHODS

Guideline Developers

This guideline was developed by the Systemic Adjuvant Therapy for Adult Patients at High Risk for Recurrent Melanoma Guideline Development Group, which was convened at the request of the Melanoma Disease Site Group (DSG) of Ontario Health (Cancer Care Ontario) [OH(CCO)]. The project was led by a small Working Group that was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology and health research methodology. Other members of the guideline development group served as the Expert Panel and were responsible for review and approval of the draft document. Conflict of interest declarations were collected for all participants and were managed in accordance with the Program in Evidence-Based Care (PEBC) conflict of interest policy. The director of the PEBC waived the requirement that the lead author and 50% of members of the Working Group have no declared interests, with the provision that co-chairs be appointed.

Guideline Development

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle^{10,11}. The process includes a systematic review, interpretation of the evidence, and

drafting of recommendations by the Working Group, internal review by content and methodology experts, and external review by clinicians. The PEBC's guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*. The present publication focuses on the guideline recommendations, with a brief summary of the methods used; the full 5-part document, including the systematic review, can be found on the OH(CCO) Web site¹².

Guideline Objective

This guideline makes recommendations about the use of adjuvant systemic therapy in adult patients with completely resected cutaneous or mucosal melanoma with a high risk of recurrence.

Research Questions

- What systemic therapy should clinicians recommend to adult patients who have been rendered disease-free after resection of cutaneous melanomas (including all sites of metastases, if present) and who are at high risk for subsequent recurrence?
- What systemic therapy should clinicians recommend to adult patients who have been rendered disease-free after the resection of mucosal melanomas?

Target Population

The target population is adult patients with cutaneous or mucosal melanoma with high risk of recurrence who have been rendered disease-free after resection (including resection of all locoregional or distant metastases, if present). Patients with unresected primary disease or metastases fell outside the scope. In determining risk of recurrence, disease with any of the following characteristics was considered high risk:

- Primary melanoma with a tumour thickness greater than 4.0 mm (T4 in AJCC 6th, 7th, or 8th editions)
 - If node-negative, these tumours fall into AJCC stage IIB (no ulceration) or IIC (ulceration).
- Primary melanoma with a tumour thickness greater than 2.0–4.0 mm, with ulceration (T3b, stage IIB if node-negative)
- Primary melanoma with one or more of
 - positive sentinel lymph nodes (micrometastasis);
 - clinically detected positive regional lymph nodes (macrometastasis); or
 - in-transit, satellite, or microsatellite metastases (node-positive and stages IIIA–IIIC in the AJCC 6th or 7th editions, or stages IIIA–IIID in the AJCC 8th edition)
- Distant metastasis (stage IV)
- Recurrence of melanoma that was previously completely resected

It should be noted that AJCC staging categories are for cutaneous melanoma; staging for mucosal melanoma varies depending on the primary site, and the AJCC staging designations might not apply.

Literature Search

The literature search included clinical practice guidelines, systematic reviews, and randomized controlled trials (RCTs). Details for the review, including the research questions, population of interest, interventions and comparators, outcomes, inclusion and exclusion criteria, and databases to search were determined before the literature review and were documented in the project plan. Reviews conducted before 2013 [the search date for version 4 of the PEBC and OH(CCO) guideline] were excluded.

The literature search was conducted in EMBASE, MEDLINE, and the Evidence Based Medicine Reviews database (Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews) for 1996 to 11 June 2018 and was subsequently updated to 28 May 2019. Complete details, including the search strategy and the inclusion and exclusion criteria are reported in the full systematic review¹². The search strategy combined terms for melanoma plus terms for chemotherapy, immunotherapy, vaccines, or systemic therapy (including specific agents), plus terms for clinical practice guidelines, systematic reviews, or RCTs. Abstracts of selected recent conferences and the ClinicalTrials.gov Web site were also reviewed. Web sites of major cancer guideline developers and practice guideline databases were reviewed for recent clinical practice guidelines.

To be included, studies had to be randomized trials of adjuvant systemic therapy in adult patients with melanoma with high risk of recurrence (see the Target Population subsection). Data extraction for the present review was conducted by a health research methodologist (GGF). Because this guideline is an update, some of the data were reproduced from a previous version⁹ and were then verified in a consultation of the primary literature.

Development of Recommendations

The Working Group drafted recommendations based on the systematic review. Where RCT evidence was limited, recommendations were based on the professional experience of the authors, together with consideration of current practice. Such limitations are clearly indicated in the key evidence and qualifying statements that follow each recommendation.

Internal and External Review Process

Before submission of the draft report for external review, the systematic review and practice guideline were reviewed by the members of the Melanoma DSG and the PEBC Report Approval Panel. The Report Approval Panel consists of the PEBC Scientific Director and two other members with expertise in clinical and methodology issues. The DSG and Report Approval Panel members reviewed the draft systematic review and practice guideline and provided feedback, which was incorporated into the guideline.

Participating as Consultation Group members for the project, 4 cancer patients or survivors reviewed the draft document distributed for internal review and provided feedback on its comprehensibility, appropriateness, and feasibility. The revised draft document was then distributed for external review.

External review included both a targeted peer review that is intended to obtain direct feedback from a small number of content experts, and a professional consultation that is intended to facilitate dissemination of the guideline to Ontario practitioners and to provide opportunity for additional feedback. Results of the feedback can be found in the full guideline report on the OH(CCO) Web site¹².

RESULTS

Search for Guidelines

Only the guidelines by the Cancer Council Australia¹³ and the Society for Immunotherapy of Cancer¹⁴ included recent trials and recommendations about the use of immune checkpoint inhibitors and targeted therapies. The Working Group members decided that those guidelines had several limitations, including a narrower focus, and could not replace development of the present guideline. During the literature update search (May 2019), it was noted that the French Society of Dermatology had a new guideline^{15,16} concerning stage III melanoma (and stage IV, if completely resected), partially replacing their previous guideline on stages I–III disease¹⁷. The 2019 National Comprehensive Cancer Network (NCCN) guideline concerning melanoma represents a significant revision of previous versions and now includes immune checkpoint inhibitors and *BRAF*-targeted therapies^{18,19}. Recommendations in both guidelines are similar to those in the present work. The NCCN guideline includes diagnosis and treatment of stages 0–IV unresectable melanoma, and therefore the section concerning adjuvant systemic therapy is more limited than that in the present work; in contrast, the NCCN guideline has more details on topics such as principles of molecular testing and management of adverse events (AES) associated with targeted therapy.

Search for Systematic Reviews and Primary Literature

The literature search identified 15 systematic reviews and 63 trials (135 publications) that met the inclusion criteria. Most of the trials of IFN compared with observation, and some comparing 2 doses or durations of IFN, were covered in the meta-analysis by the International Melanoma Meta-Analysis Collaborative Group²⁰ that used individual patient data (IPD) for adjuvant IFN- α and in the Cochrane systematic review and meta-analysis by Mocellin *et al.*²¹ for adjuvant IFN- α . Both reviews found small but statistically significant improvements in disease-free survival (DFS) or RFS and in OS. Benefits did not vary with dose, age, sex, site of primary tumour, disease stage (I/II or III/IV), Breslow thickness, or presence of clinically involved nodes. Only patients with ulcerated tumours appeared to receive a benefit. The ongoing European Organisation for Research and Treatment of Cancer (EORTC) 18081 trial (see NCT01502696 at <https://ClinicalTrials.gov/>) being conducted in patients with ulcerated melanoma could potentially confirm that finding. Other IFN trials explored dose, duration, or formulation, but were generally inconclusive. Trials of vaccines and chemotherapy were also negative or inconclusive.

Several recent trials evaluated immune checkpoint inhibitors or targeted therapies and reported greater benefit than had been found in the IFN trials. Immune-related AES

are significant and have to be considered. The EORTC 18071 trial compared ipilimumab with placebo^{22–24}, the Eastern Cooperative Oncology Group E1609 trial compared ipilimumab with IFN^{25,26}, CheckMate 238 compared nivolumab with ipilimumab^{27,28}, and KEYNOTE-054 (EORTC 1325) compared pembrolizumab with placebo²⁹. Conference abstracts have reported an indirect comparison of nivolumab with placebo^{30,31}. Adverse effects were greater with ipilimumab than with nivolumab or pembrolizumab. For BRAF-targeted therapies, vemurafenib is being compared with placebo in the BRIM8 trial³² and combination dabrafenib–trametinib is being compared with placebo in the COMBI-AD trial^{33,34}. Some of the foregoing trials included patients with mucosal melanoma, but the numbers of those patients are too small to reach conclusions specifically for mucosal melanoma. An abstract publication of an ongoing trial suggests that temozolomide–cisplatin might provide some benefit³⁵.

RECOMMENDATIONS

Cutaneous Melanoma

Recommendation 1

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

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

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

Qualifying Statements: Nivolumab, pembrolizumab, and combination dabrafenib–trametinib (for *BRAF* V600E or V600K mutated melanoma) are all appropriate treatments; evidence to suggest which is more effective is currently insufficient. These agents were evaluated in different trials^{27,29,33} and have not been directly compared in the adjuvant setting. For nivolumab and pembrolizumab, treatment-related AEs, which occurred in 85% and 78% of patients respectively, tended to be mild and manageable, with the most common being fatigue, skin reactions (rash, pruritus), diarrhea, nausea, and endocrine disorders. Similar rates of grade 3 or greater treatment-related AEs (14.4% and 14.7%) resulting in treatment discontinuation (9.7% and 13.8%) were reported. Combination dabrafenib–trametinib resulted in a higher rate of serious AEs (36%), including pyrexia, hypertension, and hepatic effects, and a higher rate of discontinuation attributable to AEs (25%). The spectrum of AEs and the contraindications for immunotherapy with nivolumab or pembrolizumab compared with those for dabrafenib–trametinib should be discussed with the patient when adjuvant treatment is being decided.

The foregoing treatments were evaluated in trials requiring patients to have undergone complete regional

lymphadenectomy. The Multicenter Selective Lymphadenectomy Trial–II (MSLT-II)³⁶ and the Dermatologic Cooperative Oncology Group SLT trial^{37,38} found that, in patients with clinically localized cutaneous melanoma (no satellite, in-transit, regional, or distant metastases) and 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 those results, routine immediate completion lymphadenectomy is no longer standard practice for patients with node-positive disease by pathology upon sentinel lymph node biopsy [see guidelines by the PEBC and OH(CCO)³⁹ and the American Society of Clinical Oncology and the Society of Surgical Oncology⁴⁰]. In the absence of complete lymphadenectomy, some patients with positive sentinel lymph nodes assigned as stage IIIA or IIIB might be understaged. The trials and recommendations relating to 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) before adjuvant therapy or adjuvant radiotherapy. In the case of unresectable disease, systemic therapy should be considered upfront.

Patient inclusion in the trials was based on the 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 the stage III substages, stage migration is to be expected. For example, using data from the COMBI-AD trial³⁴, 38% of patients with stage III disease were reclassified into a different subgroup.

Patients with completely resected stage IV disease were included only in the Eastern Cooperative Oncology Group E1609 trial (abstract only, not reported separately)²⁵ and the CheckMate 238 trial (see the Key Evidence subsection)^{27,28}. Data are therefore more limited for that population.

Patients with high-risk stage II disease were not included in the key trials, and some trials excluded all (CheckMate 238) or a portion (KEYNOTE-054, COMBI-AD) of patients with stage IIIA disease. For stage IIIA disease, KEYNOTE-054 excluded N1a melanomas with nodal metastases smaller than 1 mm, and the COMBI-AD trial excluded any nodal metastases smaller than 1 mm. The absolute benefit in patients with stage II or IIIA tumours with nodal disease smaller than 1 mm is unknown. The patient and physician should discuss the benefits and risks (AEs), and such patients should be enrolled onto a clinical trial when possible. Such clinical trials are currently ongoing.

The role of radiotherapy was outside the scope of the literature review; adjuvant radiotherapy is the subject of a separate guideline⁴¹. Patients who received adjuvant radiotherapy were excluded from the trials of immune checkpoint inhibitors and targeted therapy, except for the E1609 trial comparing ipilimumab doses²⁵.

The recommendations from the immunotherapy trials are based on interim results for DFS; most OS results are not yet available, but will be forthcoming. A recent review by Suci *et al.*⁴² supports the view that RFS is a suitable surrogate for OS. Recommendations should be re-evaluated once final results from the relevant studies are reported.

Data concerning targeted therapy for *BRAF* mutations other than V600E or V600K are not available, and therefore adjuvant therapy with nivolumab or pembrolizumab should be considered.

Key Evidence: The CheckMate 238 trial^{27,28} reported a 2-year RFS of 62.6% for nivolumab (3 mg/kg) and 50.2% for ipilimumab (10 mg/kg) [hazard ratio (HR): 0.66; $p < 0.0001$]. It is the only trial with data for stage IV patients. For that subgroup, the 2-year RFS rates were 58.0% and 44.3% respectively. Fewer AEs were observed with nivolumab: grade 3 or greater AEs occurred in 14.4% and 45.9% of patients, and deaths occurred in 0% and 0.4% ($n = 2$) of the patients.

A combined indirect analysis of patients staged IIIB and IIIC from CheckMate 238 and EORTC 18071 (abstract only³⁰) reported an 18-month RFS of 70.7% for nivolumab, 54.1% for ipilimumab, and 41.8% for placebo. The KEYNOTE-054 trial²⁹ reported an 18-month RFS of 71.4% for pembrolizumab compared with 53.2% for placebo. Grade 3 or greater AEs occurred in 14.7% compared with 3.4% of patients; 1 death occurred in the pembrolizumab arm.

The COMBI-AD trial^{33,34} found that combination dabrafenib–trametinib in patients with *BRAF*V600E or V600K mutations was associated with improved RFS at all time points, the 4-year RFS being 54% compared with 38% (placebo). Benefit was found for all subgroups⁴³. The trial included some stage IIIA patients (those with nodal metastases larger than 1 mm); for that group, the 4-year DFS was 69% compared with 62% (HR: 0.58; 95% CI: 0.32 to 1.06). At 3 years, OS was also better (86% vs. 77%), although not statistically significant because of the interim boundaries set in the protocol.

Vemurafenib is being evaluated in the BRIM8 trial³², which, to date, found a 2-year DFS benefit in patients staged IIC–IIIB (cohort 1), but not IIIC (cohort 2). The study design was such that results for cohort 1 could not be considered significant unless results for cohort 2 found a significant DFS benefit. Interim (immature) OS data found no benefit in patients staged IIIC, but a trend toward benefit ($p = 0.1$) was seen for cohort 1. Because of the study design, the apparently conflicting results according to stage, and the preliminary nature of the data, vemurafenib cannot be recommended at this time.

Interpretation of the Evidence: The trials noted in the key evidence suggest that nivolumab, pembrolizumab, and (for *BRAF*V600E or V600K mutated disease) dabrafenib–trametinib are all effective in reducing recurrence, and current evidence does not suggest that one agent is better than the other. Long-term data and results from other ongoing trials might clarify which, if any, is better overall or for certain subgroups. Although direct evidence is available only for stages IIIB, IIIC, and IV for nivolumab and for a subset of stages IIIA, IIIB, and IIIC for pembrolizumab (using the AJCC 7th edition), it is the opinion of the authors that the overall body of evidence suggests that those agents should offer similar efficacy in patients with a high risk of recurrence regardless of stage III subgroup. Evidence from the meta-static setting suggests that nivolumab and pembrolizumab are equivalent in efficacy and toxicity profile.

Recommendation 2

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

Qualifying Statements: Although ipilimumab might be effective in reducing the risk of melanoma recurrence, it has lesser efficacy and higher rates of serious AEs than are seen with nivolumab, and it is not recommended.

Key Evidence: Although the EORTC 18071 trial^{23,24,44} reported that, compared with placebo, ipilimumab (10 mg/kg) was associated with improved RFS and OS, a high rate of AEs was observed. The rate of grades 3–4 AEs was 54.1% for ipilimumab compared with 26.2% for placebo. Grades 3–4 immune-related AEs were especially prevalent (41.6% vs. 2.7%), with deaths occurring in 5 patients (1.1% vs. 0%). Discontinuation of treatment because of drug-related AEs occurred in 53% of patients.

The CheckMate 238 trial^{27,28} reported a 2-year RFS of 62.6% for nivolumab (3 mg/kg) compared with 50.2% for ipilimumab (10 mg/kg) (HR: 0.66; $p < 0.0001$). Also, fewer AEs occurred with nivolumab: the rate of grade 3 or greater AEs was 14.4% compared with 45.9%, and the rate of deaths was 0% compared with 0.4% (2 patients).

A combined indirect analysis of the foregoing two trials (abstract only³⁰) reported an 18-month RFS of 70.7% for nivolumab, 54.1% for ipilimumab, and 41.8% for placebo.

The E1609 trial^{25,26} (abstracts only) compared ipilimumab at 3 mg/kg and at 10 mg/kg with HD-IFN- α 2b. Preliminary results suggested equal efficacy for ipilimumab at 3 mg/kg and 10 mg/kg (3-year RFS: 56% vs. 54%). Results at approximately 4.5 years after accrual of the last patient have been reported. The OS was significantly better for 3 mg/kg ipilimumab compared with HD-IFN- α 2b (HR: 0.78; 95.6% CI: 0.61 to 1.00; $p = 0.044$), and a trend toward a benefit in RFS was observed (HR: 0.85; 99.4% CI: 0.66 to 1.09; $p = 0.065$). A trend toward a benefit was also observed for 10 mg/kg ipilimumab compared with HD-IFN- α 2b in OS (HR: 0.88; 95.6% CI: 0.69 to 1.12) and RFS (HR: 0.84; 99.4% CI: 0.65 to 1.09). Grade 3 or greater AEs (mostly immune-related) were experienced by 37% of patients receiving 3 mg/kg ipilimumab, in 58% of those receiving 10 mg/kg ipilimumab, and in 79% of those receiving HD-IFN- α 2b, leading to treatment discontinuation in 35%, 54%, and 20% of patients. Grade 5 AEs possibly related to treatment occurred in 3, 8, and 2 patients (0.6% vs. 1.6% vs. 0.3%).

Interpretation of the Evidence: Because the trials found nivolumab to be more effective than ipilimumab and to be associated with fewer AEs, use of ipilimumab is not supported. That conclusion might have to be re-evaluated when the final trial results, including OS, are reported, together with results from the ongoing CheckMate 915 and SWOG 1404 trials.

Recommendation 3

Use of IFN- α for adjuvant treatment of cutaneous melanoma is no longer recommended outside of a clinical trial.

Qualifying Statements: The EORTC 18081 trial (see NCT01502696 at <https://ClinicalTrials.gov/>) comparing pegylated IFN- α 2b for 2 years with observation in ulcerated stage II melanoma had an estimated completion date in April 2019. That trial might confirm the results of the International Melanoma Meta-Analysis Collaborative Group IPD meta-analysis²⁰, which suggested that IFN- α is of benefit in ulcerated melanoma.

Interferon might have a limited role in high-risk patients not eligible for other treatments.

Key Evidence: The Cochrane meta-analysis²¹ included 18 RCTs involving 10,499 patients and compared HD-IFN- α with observation or any other treatment in patients with regional lymph node metastasis (and undergoing radical lymph node dissection) or with a tumour thickness greater than 1 mm. Adjuvant HD-IFN- α was associated with an improved DFS (HR: 0.83; 95% CI: 0.78 to 0.87; $p < 0.00001$) and OS (HR: 0.91; 95% CI: 0.85 to 0.97; $p = 0.003$), representing an absolute improvement of about 6% in 5-year DFS and 3% in OS.

The International Melanoma Meta-Analysis Collaborative Group²⁰ conducted an IPD meta-analysis comparing IFN- α with no IFN- α (observation only) in high-risk melanoma. It included fifteen IFN- α trials involving 7744 patients. Individual patient data were available from eleven of those trials (5861 patients), and summary data from the remaining trials were used. Administration of IFN- α was associated with a significant improvement in event-free survival [EFS (HR: 0.86; 95% CI: 0.81 to 0.91; $p < 0.00001$)] and OS (HR: 0.90; 95% CI: 0.85 to 0.97; $p = 0.003$). For trials providing IPD, the 5-year OS was 49.1% with IFN- α compared with 46.1% without; the 10-year OS was 39.9% compared with 37.1%; the 5-year EFS was 37.8% compared with 34.3%; and the 10-year EFS was 31.2% compared with 28.5%. Although statistically significant, the absolute differences are small.

The benefit with IFN did not vary with the dose [no significant trend in effect for the high- (20 MU/m²), intermediate- (5–10 MU/m²), low- (3 MU/m²), or very-low-dose (1 MU/m²) regimens] or duration of treatment (≤ 6 , 12–18, or ≥ 24 months). Results suggest that low-, intermediate-, and high-dose IFN- α regimens are associated with similar benefit; data for very-low-dose IFN (EORTC 18871 and DBG 80-1 trials) are unclear. For OS, the effect is weaker and statistically significant only for the low-dose group (HR: 0.86; 95% CI: 0.77 to 0.96; $p = 0.007$).

The meta-analysis also did not find a differential IFN benefit by age, sex, site of primary tumour, disease stage (I/II vs. III/IV), Breslow thickness, or presence of clinical nodes. For patients with ulcerated tumours, EFS was improved (5-year EFS: 32.9% vs. 26.9%; 10-year EFS: 27.3% vs. 20.4%; HR: 0.79; 99% CI: 0.66 to 0.94; $p = 0.0006$), as was OS (5-year OS: 46.0% vs. 38.1%; 10-year OS: 38.5% vs. 28.0%; HR: 0.77; 99% CI: 0.64 to 0.92; $p = 0.0002$). The EFS and OS benefits were approximately 6% and 8% at 5 years, and slightly higher at 10 years. No significant benefit was observed in patients with non-ulcerated tumours.

Adverse effects of HD-IFN- α and their management—based primarily on the E1684, E1690, and 1694 trials—have been reviewed by others^{45,46}. Dose reduction or delay was

required in 28%–44% of patients during the induction phase and in 36%–52% during the maintenance phase in those trials. Treatment was discontinued because of AEs in 10%–26% of patients. Most patients experienced acute flu-like symptoms (fever, chills, headache, myalgia, nausea, and vomiting) with grade 3 or greater AEs in 4%–18% of patients. Fatigue, which has been reported in 70%–100% of patients (18% grade 3 or greater), and neuropsychiatric symptoms increase in severity over time. Other AEs are anorexia, cardiotoxicity, hepatotoxicity, autoimmunity, ocular toxicity, and altered laboratory findings. Although generally manageable with careful monitoring, supportive care, and dose modifications, those AEs often have a profound negative effect on quality of life and can be life-threatening.

Interpretation of the Evidence: The meta-analyses indicate that IFN- α is associated with a small but statistically significant improvement in OS and DFS. For most patients, the AEs are judged to outweigh the possible small benefit. The IPD meta-analysis suggests that the IFN- α benefit applies only to ulcerated tumours, a finding that must be confirmed in a trial designed to test efficacy specifically in ulcerated melanoma. The benefits of nivolumab, pembrolizumab, and (for *BRAF*-mutant melanoma) dabrafenib-trametinib exceed those of IFN- α , and therefore IFN- α is not recommended.

Recommendation 4

Chemotherapy regimens, vaccines, levamisole, bevacizumab, bacillus Calmette–Guérin, and isolated limb perfusion are not recommended for the adjuvant treatment of cutaneous melanoma, except as part of a clinical trial.

Key Evidence: Most completed trials found no survival benefit. A few trials suggested a possible benefit for some of the agents, but they were either too small or were discontinued early because of more promising results with IFN- α and are therefore inconclusive. Some trials are ongoing.

Mucosal Melanoma

Recommendation 5

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: Mutation characterization is required before targeted agents are considered. Compared with cutaneous melanoma, mucosal melanoma has a different origin and spectrum of mutations. *BRAF* mutations are less common than they are 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* mutation⁴⁷; however, no trials of the adjuvant use of *KIT* inhibitors were found.

The trials forming the key evidence for cutaneous melanoma (see recommendations 1 and 2) excluded mucosal

melanoma, with the exception of the CheckMate 238 trial, which included 29 patients (3.2% of the total). That small number is insufficient to allow for any conclusions to be drawn specifically for that subgroup.

There might be a role for chemotherapy, but evidence is not sufficient to make a recommendation at this time. Adjuvant treatment of mucosal melanoma with HD-IFN- α 2b compared with temozolomide–cisplatin was studied in a phase II trial⁴⁸ in patients with stages II and III mucosal melanoma and in a subsequent phase III trial^{942qin} patients with stages I–II mucosal melanoma, reported only in abstract form³⁵. The phase II study found that temozolomide–cisplatin resulted in a better OS and DFS than did HD-IFN- α 2b or placebo. A follow-up phase III study confirmed the benefit of temozolomide–cisplatin compared with HD-IFN- α 2b. The available evidence is limited because of a lack of full publication and inconsistency with studies in metastatic melanoma⁴⁹.

Key Evidence: Targeted agents and immune checkpoint inhibitors have not been evaluated specifically as adjuvant therapy in mucosal melanoma. Key evidence is considered to be the trials supporting their use in cutaneous melanoma^{27–30,33,34} (see the earlier recommendations) and the data from trials in advanced or metastatic melanoma in which those agents were shown to be effective. D'Angelo *et al.*⁵⁰ conducted a pooled analysis of nivolumab alone or combined with ipilimumab in unresectable stage III or IV mucosal melanoma, finding that nivolumab–ipilimumab had greater efficacy than either nivolumab monotherapy or ipilimumab monotherapy (objective response rate: 37.1% vs. 23.3% vs. 8.3%), but with a much greater rate of grades 3–4 AEs (40% vs. 8% vs. not stated). Compared with ipilimumab alone, PFS was better with nivolumab–ipilimumab (HR: 0.35; 95% CI: 0.19 to 0.64) and with nivolumab alone (HR: 0.62; 95% CI: 0.39 to 0.98). A *post hoc* analysis of patients with advanced mucosal melanoma in the KEYNOTE-001, -002, and -006 trials reported that pembrolizumab provided a durable tumour response⁵¹.

Interpretation of the Evidence: Recommendations for the use of immune checkpoint inhibitors in mucosal melanoma are based on extrapolation of results from cutaneous melanoma (see recommendations 1 and 2) and from trials in nonresectable mucosal melanoma.

For targeted therapy, the authors believe that cutaneous and mucosal melanoma with the same mutations would benefit from the same targeted therapies. Adjuvant therapy with dabrafenib–trametinib can therefore be considered in mucosal melanoma in which BRAFV600E or V600K is the primary mutation.

Further Qualifying Statements: The recommended adjuvant therapies have potential for AEs (see the earlier Key Evidence and Qualifying Statements subsections). Although usually manageable and reversible, those AEs can be severe. It was outside the scope of the accompanying systematic review to deal with management of those AEs. The reader can refer to other guidelines such as those from the Multinational Association of Supportive Care in Cancer⁵², the Eastern Cooperative Oncology Group⁵³, the

American Society of Clinical Oncology and the NCCN^{54,55}, OH(CCO)⁵⁶, and others^{57,58}.

Several trials are ongoing, and the foregoing recommendations might have to be revisited upon completion of those trials.

Implementation Considerations

Most trials of the adjuvant use of immune checkpoint inhibitors and targeted agents in melanoma are ongoing, with promising preliminary results. As a result, indications and approvals are changing rapidly. Nivolumab, pembrolizumab, and combination dabrafenib–trametinib were approved by Health Canada in early 2019 for adjuvant use in melanoma. At the time of the present review, immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab) and targeted therapies were being evaluated for approval and funding in Ontario. Funding might be interim pending final results of the trials mentioned in the various Key Evidence subsections of this review. Doses for administration of immune checkpoint inhibitors and targeted therapies have not been standardized and should conform with the approved indications.

REVIEW AND UPDATE

The currency of each PEBC document is ensured by periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. That process is described in the *PEBC Document Assessment and Review Protocol*.

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The complete version of this guideline and accompanying systematic review can be found at the OH(CCO) Web site: <https://www.cancercaresontario.ca/en/guidelines-advice/types-of-cancer/1161>.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: TMP reports grants from Roche, Novartis, Merck, and personal fees from Novartis, Merck, Bristol–Myers Squibb, and EMD Serono, outside the submitted work. GGF reports grants to the PEBC at McMaster University from OH(CCO) or the MOH during the conduct of the literature review and guideline development. GK reports personal fees from Bristol–Myers Squibb, Merck, Roche, and Sanofi, outside the submitted work. EM reports serving on advisory boards for Novartis, Merck, Bristol–Myers Squibb, and Roche, outside the submitted work, and work as a local principal investigator on the COMBI-AD, COMI-A Plus, and MEC.5 trials. XS

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