



**Evidence-based Series 8-1 Version 4 - IN REVIEW**

A Quality Initiative of the  
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

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

*Members of the Melanoma Disease Site Group*

An assessment conducted in November 2016 placed Evidence-based Series (EBS) 8-1 Version 4 IN REVIEW. This means that it is undergoing review for currency and relevance. The Melanoma Disease Site Group has determined that it is still appropriate for this document to continue to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document.

[\(PEBC Assessment & Review Protocol\)](#)

The reviewed EBS report consists of:

Section 1: Clinical Practice Guideline (ENDORSED)

Section 2A: Updated Evidentiary Base 2009

Section 2b: Original Evidentiary Base 2005

Section 3: EBS Development Methods and External Review Process

Section 4: Document Review Summary and Tool

and is available on the CCO Web site (<http://www.cancercare.on.ca>) PEBC Melanoma DSG page at: <https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/melanoma-ebs/>

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Verma S, Quirt I, McCready D, Bak K, Charette M, Iscoe N; on behalf of the Melanoma Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Systematic review of systemic adjuvant therapy for patients at high risk for recurrent melanoma. Cancer. 2006;106(7):1431-42.

Verma S, Quirt I, McCready D, Charette M, Iscoe N; Melanoma Disease Site Group. Systemic adjuvant therapy for patients at high risk for recurrent melanoma. Curr Oncol. 2005;12(2):31-6.

IN REVIEW

## Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original June 2004	1980 through July 2005	Full Report	Web publication	NA
Version 2 June 2005	1980 through July 2005	Full Report	Web publication	NA
Version 3 June 2009	July 2005 to July 2008	Full Report	Web publication	NA
Current Version 4 Nov 2013	July 2008 to October 2013	New data found in section 4: <a href="#">Document Review Summary and Tool</a>	Updated Web publication	2009 recommendations is <a href="#">ENDORSED</a>

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## Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Updated Guideline Recommendations 2009

*T. Petrella, S. Verma, K. Spithoff, I. Quirt, D. McCreedy,  
and the Melanoma Disease Site Group*

A Quality Initiative of the  
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)  
Developed by the Melanoma Disease Site Group

Report Date: June 22, 2009

These guideline recommendations have been **ENDORSED**, which means that the recommendations are still current and relevant for decision making. Please see [Section 4: Document Review Summary and Tool](#) for a summary of updated evidence published between 2008 and 2013, and for details on how this Clinical Practice Guideline was **ENDORSED**.

Original Report Date: June 30, 2004  
Current Report Date: June 22, 2009

### INTENDED USERS

These guidelines are intended for use by clinicians and health care providers involved in the management and referral of patients with resected melanoma at high risk for recurrence.

### QUESTION

What systemic therapy should clinicians recommend to patients who have been rendered disease-free following the resection of cutaneous melanomas and who are at high risk for subsequent recurrence?

Outcomes of interest include overall survival (OS), disease-free survival (DFS), adverse effects, and quality of life.

### TARGET POPULATION

These recommendations apply to adult patients with high-risk malignant melanoma who are rendered disease-free following resection. For this practice guideline, high risk is defined as patients in the following clinical states:

- primary melanoma with tumour thickness  $\geq 4.0$  mm,
- primary melanoma with in-transit metastases,
- positive sentinel lymph nodes,
- primary melanoma with regional lymph node metastases that are clinically apparent,
- regional lymph node recurrence,
- involved nodes were excised but there was no known primary melanoma.

- The target population also includes those patients who would now be classified as American Joint Committee on Cancer (AJCC) stage IIB, IIC and III. (See Section 2A, Appendix 1).

## RECOMMENDATIONS

- Patients with high-risk melanoma should be encouraged to participate in appropriate clinical trials exploring novel therapeutics, given that at most a small OS benefit exists with currently available therapies.
- The Melanoma Disease Site Group recommends that high dose interferon alpha 2b therapy ( $20 \times 10^6$  U/m<sup>2</sup>/d intravenously five days/week for four weeks, then  $10 \times 10^6$  U/m<sup>2</sup> subcutaneously three times weekly for 48 weeks) be discussed and offered to the high-risk group defined above to increase DFS. It may be used as adjuvant treatment, provided that each patient has been made aware of the relative risks, benefits, and costs of this therapy and wishes to proceed.
- The Melanoma Disease Site Group recommends that pegylated interferon (6µg/kg subcutaneously per week for 8 weeks followed by 3µg/kg subcutaneously per week for a duration of 5 years) be considered as a reasonable alternative to high dose interferon in high-risk melanoma patients. It may be used as adjuvant treatment, provided that each patient has been made aware of the relative risks, benefits, and costs of this therapy and wishes to proceed.
- At this time, there is insufficient evidence to recommend one month of high dose interferon alone.

## QUALIFYING STATEMENTS

- The intent of adjuvant therapy is to eliminate micrometastatic disease that is residual following curative resection with the goal of delaying or preventing recurrence. DFS is an appropriate endpoint in melanoma as it is expected that recurrence of disease would lead to mortality in the majority of cases. It is a meaningful endpoint in adjuvant melanoma trials as postponing when disease recurs or prolonging the disease free period has substantial effects on quality of life.
- There is currently no trial that compares Interferon alpha 2b to pegylated interferon and it is likely that no such trial will be conducted in the future. Selection of patients for either therapy should be at the discretion of the treating physician based on the individual patient, tolerability or other circumstances that may affect therapy.
- AJCC stage IIB, IIC and III melanoma includes patients with high-risk features such as ulceration and in-transit metastases and therefore it is reasonable to apply current recommendations to these high-risk patients.
- With emerging new technologies and new diagnostics, staging is an evolving field. A new staging system for melanoma has been proposed and will be revised in 2009 that may alter eligibility and may redefine what constitutes high-risk melanoma.
- Practitioners should be aware that elderly patients (age 65 and older) were under represented in the high-dose interferon trials. Given the toxicities of interferon, particularly in the presence of other significant comorbidities, caution is advised.

**KEY EVIDENCE*****Interferon***

- An abstract report of an individual patient data meta-analysis of 13 randomized trials (6067 patients) comparing adjuvant interferon versus no interferon showed a statistically significant overall effect favouring interferon for both event-free survival and OS, although the absolute effect on 5-year OS was very small at 3% (1).

***High-dose interferon versus control***

- Five randomized trials have compared high-dose interferon alpha versus control in patients at high risk for recurrent melanoma and the results are conflicting.
  - The Eastern Cooperative Oncology Group (ECOG) 1684 trial detected a significant improvement in OS (2).
  - A subsequent large randomized trial (ECOG 1690) failed to find an OS benefit for interferon compared with observation (3).
  - Results from a third trial (ECOG 1694) that compared high-dose interferon with a melanoma vaccine demonstrated a significant OS benefit for interferon (4). Recent results from the EORTC 18961 trial which compared post-operative adjuvant ganglioside GM2-KLH21 vaccine to observation in stage II patients showed a detrimental effect for the vaccine arm (5). This has implications in the interpretation of the ECOG 1694 results (4) and the magnitude of the DFS and OS benefit.
  - A fourth trial of high-dose interferon over a shorter treatment time failed to detect any benefit (6).
  - The Sunbelt Melanoma trial failed to detect an OS or DFS benefit for interferon; however, this trial did not reach targeted enrolment and was therefore underpowered to detect clinically significant differences between arms (7).
- A meta-analysis conducted by the Melanoma Disease Site Group of three trials comparing a one-year high-dose interferon regimen with observation alone demonstrated no significant difference in OS (HR 0.93; 95% CI, 0.78-1.12; p=0.51; 2-3% absolute risk reduction at five years) but a significant benefit for interferon in DFS (HR 0.77; 95% CI 0.65-0.92; p=0.004; 9% absolute risk reduction at five years).

***Sub-cutaneous interferon versus observation***

- One large trial, EORTC 18991, compared long-term pegylated interferon alpha-2b with observation in stage III patients and reported a significant benefit for therapy in relapse-free survival (RFS) (absolute benefit of 6.7%, HR 0.82, p=0.01) but no significant benefit in OS (8).
- Two trials compared various doses of subcutaneous interferon with observation alone.
  - The EORTC 18952 was a three-arm trial comparing 13 and 25 months of intermediate dose interferon alpha with observation alone in patients with stage IIb or III resected melanoma. No significant difference in OS was detected between either duration of interferon therapy and observation (9).
  - The DeCOG trial comparing low-dose interferon alpha-2a with observation reported a significant benefit for interferon in both OS (HR 0.62; 97.5% CI 0.42-0.89) and DFS (HR 0.69; 97.5% CI 0.49-0.96) (10).

***Duration of interferon therapy***

- Two abstract trial reports compared different durations of interferon alpha therapy.
  - One trial reported that a one-month high-dose regimen resulted in non-inferior (no more than 15% higher) relapse rate compared with a conventional one-year intermediate-dose regimen and there was no significant difference in OS or grade 3/4 toxicity (11). These results should be considered in the context of its high non-inferiority margin, small size, and lack of detail regarding the analysis population for the non-inferiority analysis.
  - A superiority trial comparing a five-year- versus an 18 month low-dose interferon regimen reported no significant difference in OS or RFS between arms (12).

### *Interferon plus chemotherapy*

- One trial comparing two cycles of dacarbazine (DTIC) followed by six months of humanized interferon alpha with observation alone reported no significant difference in RFS or melanoma-related death between arms in the pre-planned analysis; however, a non-protocol long-term follow-up demonstrated a trend towards benefit for adjuvant therapy in OS (HR 0.71; 95% CI, 0.49-1.00; p=0.052) that was significant in an exploratory analysis of high-risk patients (HR 0.58; 95% CI, 0.38-0.86; p=0.008) (13).
- A trial comparing concurrent interferon alpha and DTIC with observation alone reported no benefit for adjuvant therapy in OS or DFS (10).

### *Vaccines*

- Data from randomized controlled trials do not suggest an improvement in OS with vaccines for patients with resected high-risk melanoma (10 trials).
- An abstract report of the EORTC 18961 trial demonstrated significantly worse OS for patients who received ganglioside GM2-KLH21 vaccine compared with patients in the observation alone arm (HR 1.57; p=0.03) (5).

### *Chemotherapy*

- Data from randomized controlled trials do not suggest an improvement in OS with adjuvant chemotherapy alone for patients with resected high-risk melanoma (10 trials).

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