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/

Release Date: November 7, 2013

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:

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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.

# Guideline Report History

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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. McCready, 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 ≥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 \((20 \times 10^6 \text{ U/m}^2/\text{d intravenously five days/week for four weeks, then } 10\times10^6 \text{ U/m}^2 \text{ subcutaneously three times weekly for 48 weeks})\) 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 (\(6 \mu\text{g/kg subcutaneously per week for 8 weeks followed by } 3\mu\text{g/kg subcutaneously per week for a duration of 5 years}\)) 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 target 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).

**Subcutaneous 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).
REFERENCES


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.

For this practice guideline, high-risk is defined as patients in the following clinical states who have been rendered disease free by surgery:
- 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 (1).

INTRODUCTION
Melanoma is the most serious form of skin cancer, accounting for only 5% of all skin cancers cases but 80% of skin cancer deaths. The incidence and mortality rates of cutaneous malignant melanoma have risen dramatically over the past several decades, faster than those of any other malignancy. Malignant melanoma continues to increase in incidence in 2008, although mortality is stable in men and decreasing by 0.8% per year in women (2).

Surgical management remains the mainstay of therapy for patients with malignant melanoma; however, despite significant improvements in early detection of melanoma, patients with stage IIB and stage III disease remain at high risk of recurrence after definitive
surgery. The rate of recurrence ranges from 30% to 90% and usually results in death as a consequence of the melanoma (1).

Although interferon alpha is the best studied agent for the adjuvant therapy of resected melanoma, trial results over the past decade have been inconsistent (3-6). Clinical studies evaluating high dose interferon following definitive surgery have generally shown a decrease in cancer recurrence and relapse with no consistent benefit in OS or distant metastases. However, relapse free survival (RFS) and DFS are important endpoints, as patients are willing to accept toxicity for a modest benefit and improvement in quality of life without a benefit in OS (7).

Due to the inconsistencies in trial results, some regard high-dose interferon alpha as standard therapy, while others do not. Moreover, interferon poses a risk to the patient in terms of side effects and imposes greater fiscal burdens in the short term on the cancer care system and on patients or their payers. The Melanoma Disease Site Group (DSG) felt it was important to conduct a systematic review of the efficacy of therapies that have been evaluated in the management of patients who are at high risk for a recurrence of melanoma following the surgical resection of disease that has not extended beyond the regional lymph nodes.

A practice guideline report on systemic adjuvant therapy for patients at high risk for recurrent melanoma was originally completed by the Melanoma DSG in 1998. With the availability of new evidence and the adoption of the new AJCC staging system for cutaneous melanoma (1), the report was rewritten in 2004 and later updated in August 2005. Systematic review and practice guideline manuscripts based on that report have been published in peer-reviewed journals (8,9). The systematic review, as last updated in 2005, can be found in Section 2B of this Evidence-based Series. Due to the availability of additional new evidence, the Melanoma DSG chose to conduct another update of the evidence and recommendations in 2008. A review of the new evidence published since July 2005 is presented here in Section 2A of this report.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario’s Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (10). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC Melanoma DSG and a methodologist.

This systematic review is a convenient and up-to-date source of the best available evidence on systemic adjuvant therapy for patients at high risk of recurrent melanoma published between July 2005 and July 2008. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence, along with the original evidence reviewed in Section 2B, forms the basis of the recommendations developed by the Melanoma DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE (July 2005 to July week 5 2008), EMBASE (week 32 2005 to week 31 2008), and Cochrane Library (2008, Issue 3) databases were systematically updated in OVID using a revised literature search strategy (See Appendix 2). In MEDLINE, the term melanoma:..mp. was combined with treatment-related terms including the MeSH terms.
adjuvant chemotherapy, drug therapy, immunotherapy, immunization, interferons, and the text words adjuvant, vaccin:, immunotherap:, chemotherap:, interferon:, IFN:, and levamisole. These terms were then combined with a search filter designed to identify randomized trials, systematic reviews, and meta-analyses adapted from a strategy developed by the Scottish Intercollegiate Guidelines Network (SIGN), available at www.sign.ac.uk. Modifications were made to the search terms where appropriate for use in EMBASE. The proceedings of the 2006 to 2008 ASCO annual meetings were also searched for abstract reports of relevant studies.

Study Selection Criteria

The study inclusion and exclusion criteria used in the original systematic review (See Section 2B) were adopted for the 2008 update with the following exceptions: Randomized trials without an observation or placebo alone arm were excluded, unless they were trials comparing different interferon doses or schedules. Abstract reports of randomized trials presenting preliminary data only were also excluded.

Synthesizing the Evidence

Results from trials comparing high-dose interferon alpha with observation or another therapy were pooled using the Review Manager software (RevMan 5.0.14) provided by the Cochrane Collaboration (11). Since hazard ratios (HRs), rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes (12), those were extracted directly from the most recently reported trial results where available. The variances of the HR estimates were calculated from the reported confidence intervals (CI) using the methods described by Parmar et al. (12). A random effects model was used for all pooling, as it provides a more conservative estimate of effect (13).

Statistical heterogeneity was calculated using the $\chi^2$ test for heterogeneity and the $I^2$ percentage. A probability level for the $\chi^2$ statistic less than or equal to 10% ($p \leq 0.10$) and/or an $I^2$ greater than 50% were considered indicative of statistical heterogeneity. Results are expressed as HRs with 95% CI. An HR < 1.0 indicates that patients receiving high dose interferon alpha had a lower probability of experiencing an event; conversely, an HR > 1.0 suggests that patients receiving high dose interferon alpha experienced a higher probability of an event.

Methodological Quality Appraisal of Randomized Controlled Trials

Randomized trials identified in the updated literature search that met the inclusion criteria were assessed for key methodological characteristics using information provided in the trial reports. The following elements were assessed: randomization sequence generation, allocation concealment, blinding, analysis details including intention-to-treat analysis, withdrawals, loss to follow-up, funding source, statistical power calculations, length of follow-up and differences in baseline patient characteristics.

RESULTS

Literature Search Results

The literature search update conducted in 2008 identified six trials of interferon (14-19), one trial of a vaccine (20), and two trials of chemotherapy plus interferon (17,21) (Table 1). One of the trials was a three-arm study comparing interferon alone and interferon plus chemotherapy with observation alone (17). In addition, a report presenting quality of life data (22) from a previously-included trial (23) was identified. An individual patient data meta-analysis of adjuvant interferon alpha trials was also obtained and included (24). Of the eleven reports that were included in the update, five have not been fully published and are
available only as meeting abstracts with additional information provided in online presentation slides (16,18-20,24). An abstract report of one of the included trials (25) was excluded due to the availability of a subsequent full publication of the results (15). See Appendix 3 for a flow diagram of the literature search results.

Table 1. Summary of original evidence (Section 2B) and new evidence (Section 2A).

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<tbody>
<tr>
<td># of Studies</td>
<td>Efficacy Results</td>
<td># of Studies</td>
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</table>
| IFNα Versus observation | 9 | Table 6 | 4 | Eggermont, EORTC 18952 (14)  
Eggermont, EORTC 18991 (15)  
McMasters, Sunbelt (16)a  
Garbe, DeCOG (17) | Table 3 |
| Versus other IFNα | 1 | Table 6 | 2 | Gogas, HeCOG (18)a  
Hauschild (19)a | Table 3 |
| Versus other therapy | 1 | Table 6 | - | - | - |
| IFNγ | 2 | Table 6 | 0 | - | - |
| Levamisole | 4 | Table 7 | 0 | - | - |
| Vaccines | 9 | Table 8 | 1 | Eggermont, EORTC 18961 (20)a | Table 3 |
| Chemotherapy | 10 | Table 9 | 0 | - | - |
| Chemotherapy + IFNα | 1 | - | 2 | Stadler (21)  
Garbe (17) | Table 3 |
| Meta-analyses | | | | | |
| IFNα | 2 | - | 1 | Wheatley (24)a | - |

Notes: IFN, interferon; EORTC, European Organisation for Research and Treatment of Cancer; HeCOG, Hellenic Cooperative Oncology Group.
a Abstract report.
b In addition, a quality of life report of a trial included in the original evidence review was identified (22).

Methodological Quality Appraisal of Randomized Trials

Key methodological and quality characteristics were assessed for the eight randomized trials indentified in the updated literature search. Details are reported in Table 2. Five trials reported industry funding (14-17,21). Three trials reported central randomization (14,15,17) but allocation concealment was not described in the remaining five trials. Blinding was not reported in any of the eight trials. Withdrawals were described in the four fully-published trials (14,15,17,21) but not in the four trials available only in abstract form (16,18-20). In the trial by Stadler et al. (21), reasons for withdrawal differed between treatment arms. Statistical power calculations used to determine target sample size were reported in all but one trial (19). Two trials were terminated before reaching the target sample size (16,20). Median follow-up was reported in all but one trial (18) and ranged from 1.8 years (20) to 5.5 years (21). Baseline characteristics were well balanced between treatment arms for all trials with the exception of a gender imbalance in Protocol B of the Sunbelt Melanoma Trial (16).
Table 2. Methodological and quality characteristics of randomized trials identified in 2008 update

<table>
<thead>
<tr>
<th>Trial</th>
<th>Randomization method/Allocation concealment</th>
<th>Blinding</th>
<th>ITT analysis</th>
<th>Withdrawals</th>
<th>Funding source</th>
<th>Planned statistical power</th>
<th>Follow-up</th>
<th>Baseline characteristics</th>
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<tr>
<td>Eggermont 2005 (14)</td>
<td>Central randomization with minimization technique. Stratified by centre, sex, tumour site, stage, # of positive nodes, Breslow thickness.</td>
<td>NR</td>
<td>Yes</td>
<td>Withdrawals reported</td>
<td>NCI Schering-Plough International (education grant)</td>
<td>80% power to detect 10.5% difference in 4-year DMFI with 765 events.</td>
<td>Median 4.65 yrs. 53 pts (3%) lost to follow-up.</td>
<td>Balanced</td>
</tr>
<tr>
<td>Eggermont 2008 EORTC 18991 (15)</td>
<td>Central randomization with minimization technique. Stratified by N1 vs N2, # of nodes, Breslow, ulceration of primary, sex, center.</td>
<td>NR</td>
<td>Yes</td>
<td>Withdrawals reported</td>
<td>Schering Plough Research International</td>
<td>90% power to detect 24% risk reduction (HR 0.76) with 576 DMFS events.</td>
<td>Median 3.8 yrs. 21 pts lost to follow-up in obs arm.</td>
<td>Balanced</td>
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<tr>
<td>McMasters 2008 abstract (16)</td>
<td>Stratified by Breslow thickness and ulceration</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Shering Oncology Biotech</td>
<td>Protocol A: 80% power to detect 15% difference in 4-year survival, with 148 pts per arm (134 assessable), one-sided testing.</td>
<td>Median 5.3 yrs</td>
<td>Gender imbalance in Protocol B</td>
</tr>
<tr>
<td>Garbe 2008 (17)</td>
<td>Central randomization by fax according to permuted block randomization list. No stratification.</td>
<td>NR</td>
<td>Yes</td>
<td>Withdrawals reported</td>
<td>German Cancer Aid, German Cancer Society, Hoffman-LaRoche AG</td>
<td>80% power to detect 15% difference in 4-year survival, with 148 pts per arm (134 assessable), one-sided testing.</td>
<td>Median 3.9 yrs</td>
<td>Balanced</td>
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<tr>
<td><strong>IFN vs another IFN regimen</strong></td>
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<td>Gogas 2007 abstract (18)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>?</td>
<td>NR HeCoG?</td>
<td>804 pts required for 85% power. One-sided significance test at α=0.05. At most 15% higher 3-yr relapse rate in 1 month treatment arm.</td>
<td>Median NR</td>
<td>Balanced</td>
</tr>
<tr>
<td>Hauschild 2008 abstract (19)</td>
<td>NR</td>
<td>NR</td>
<td>840 of 850 pts in ITT analysis</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>Median 4.3 yrs</td>
<td>Balanced</td>
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<td><strong>Chemotherapy plus IFN vs Observation</strong></td>
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<td>Stadler 2006 (21)</td>
<td>Computer generated randomization list. Stratified by staging.</td>
<td>None</td>
<td>Yes</td>
<td>46 withdrawals. Reasons differed between arms.</td>
<td>Viranalive AB</td>
<td>90% power to detect a 20% reduction in relapse rate in each of the randomization strata with 236 pts (10% dropout).</td>
<td>Median 5.5 yrs (prospective) 8.5 yrs after long-term follow-up.</td>
<td>Balanced</td>
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<td>Garbe 2008 (17)</td>
<td>See Garbe 2008 above</td>
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<tr>
<td><strong>Vaccine vs Observation</strong></td>
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<tr>
<td>Eggermont 2008 abstract (20)</td>
<td>Stratified by Breslow thickness, ulceration, staging method, sex, institution</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>NR EORTC?</td>
<td>5 yr DFS 65% vs 74% (HR 0.7) (alpha 5%, power 90%) with 342 events</td>
<td>Median 1.8 yrs</td>
<td>Balanced</td>
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Section 2A: Updated Evidentiary Base
Notes: ITT, intention-to-treat; NR, not reported; NCI, National Cancer Institute; DMFS, distant metastasis-free survival; yrs, years; pts, patients; EORTC, European Organisation for Research and Treatment of Cancer; HeCOG, Hellenic Cooperative Oncology Group; HR, hazard ratio.

a Trial did not reach accrual goal and was therefore underpowered to detect small differences between treatment arms.
b Trial terminated at second interim analysis due to futility.
Outcomes

Interferon Alpha

Randomized Controlled Trials

a) Interferon Alpha versus Observation

Four trials that compared interferon adjuvant therapy with observation alone were identified in the updated literature search (14-17) (Table 3).

The EORTC 18952 was a three-arm trial comparing 13 and 25 months of subcutaneous intermediate dose interferon alpha with observation alone in patients with stage IIb or III resected melanoma (14). No significant difference in OS was detected between either duration of interferon therapy and observation. The EORTC 18991 trial compared long-term subcutaneous pegylated interferon alpha-2b with observation in stage III patients and reported a significant benefit for therapy in RFS (absolute benefit of 6.7% at four years) but no significant benefit in OS (15) after a median therapy duration of 12 months. In a subgroup analysis, the effect of pegylated interferon on RFS and OS appeared to be greater in patients with microscopically positive disease (N1) compared with later stage disease; however, the observed benefits were not statistically significant in univariate or multivariate analyses at the 1% level. The Sunbelt Melanoma Trial incorporated two protocols: one including only patients with a single histologically positive node, and the other including patients with histologically negative- but RT-PCR positive nodes. In an abstract report, no significant benefit for high-dose interferon was detected for OS or DFS; however, the target sample size was not met and the trial was therefore powered to detect only large differences in outcome between treatment arms (16). The DeCOG trial reported by Garbe et al. comparing subcutaneous low-dose interferon alpha-2a with observation reported a significant benefit for interferon in both OS and DFS (17).

Adverse effects were reported for three trials that compared interferon adjuvant therapy with observation alone (14,15,17). In the EORTC 18952 trial, intermediate dose interferon alpha was associated with grade 3/4 influenza-like symptoms in 21% of patients who received 13 months of therapy and 20% of patients who received 25 months of therapy, compared with 3% of patients in the observation arm (14). Severe mood changes were observed in 11-12% of patients who received interferon compared with 4% in the observation arm. Sixteen percent of patients in the 13-month therapy arm and 20% of patients in the 25-month therapy arm stopped or interrupted treatment due to adverse effects. In the EORTC 18991 trial, grade 3/4 adverse effects occurred in 46% of patients who received long-term pegylated interferon compared with 12% in the observation arm (15). These effects were primarily fatigue (16%), liver toxicity (11%) and depression (6%) and did not worsen with increased duration of therapy. Thirty-one percent of patients who started treatment in the pegylated interferon arm stopped treatment due to toxicity. In the DeCOG trial, toxicity was mild for patients who received low dose interferon alpha-2a, with 9% of patients experiencing grade 3/4 adverse effects (17). Treatment was terminated due to adverse effects in 14% of patients.

Two reports comparing adjuvant interferon alpha with observation alone provided quality of life data (17,22). In the DeCOG trial, quality of life data were collected using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 at baseline and six months (17). Patients who received interferon had better scores for physical-, role-, and emotional functioning but a worse fatigue symptoms score compared with the observation arm. A secondary publication of the trial by Hancock et al. (23) which was included in the original evidence review (Section 2B) reported quality of life data (22). The Hancock trial...
compared low-dose interferon alpha-2a with observation alone for patients with resected high-risk melanoma and no significant differences in OS or RFS were detected between treatment arms (23). Quality of life outcomes were also collected using the EORTC QLQ-C30, at baseline and at various time points after randomization. Sixty-two percent of patients in the interferon arm and 56% in the observation arm had valid baseline and follow-up quality of life data available. Patients who underwent observation alone had significantly better scores on four of five functional scales (role-, emotional-, cognitive- and social functioning), a global health status/quality of life scale, and seven of nine symptom scores (fatigue, nausea and vomiting, dyspnoea, appetite loss, constipation, diarrhea, and financial difficulties) (22).

b) Interferon Alpha versus another Interferon Alpha Regimen

Two RCTs were identified that compared different durations of interferon alpha therapy (18,19), both of which are available only in abstract form. No significant differences in OS or DFS between interferon regimens were detected in either trial (Table 3).

The HeCOG trial reported by Gogas et al. was designed to determine if one month of induction high-dose interferon alpha-2b was non-inferior to the conventional one-year interferon regimen (18). The one-month regimen was considered at least as good as the conventional regimen if the 3-year relapse rate was no more than 15% higher in the experimental arm. Using these criteria, the investigators concluded that the regimens were equivalent for relapse rate and not significantly different for OS or grade 3/4 toxicity. The rate of therapy discontinuation was significantly higher in the one-year arm compared with the one-month arm (30% vs 3%; p<0.001), primarily due to disease progression (69%) and toxicity (19%). The results of this trial need to be considered within the context of its high non-inferiority margin, publication status, small size, and lack of detail regarding analysis population for the non-inferiority analysis.

Hauschild et al. reported the results of a DeCOG superiority trial investigating the efficacy of long-term adjuvant low-dose interferon alpha-2a therapy for five years versus a conventional regimen of low-dose interferon alpha-2a for 18 months (19). Only patients with tumour thickness ≥1.5 mm who were lymph-node negative were included in the trial. Treatment discontinuation due to toxicity was 37.9% in the long-term therapy arm compared with 17.8% in the control arm (p<0.001). No significant differences in OS or RFS were observed; therefore, the investigators concluded that the long-term administration of low-dose interferon is not supported.

**Individual Patient Data Meta-analysis**

An individual patient data meta-analysis by Wheatley et al. was identified in the literature search update (24). This meta-analysis is available only in abstract form and insufficient details regarding the analysis and study inclusion are available. Thirteen randomized trials (6067 patients) comparing adjuvant interferon versus no interferon were included, 10 of which provided individual patient data. Published data were used for the three trials that did not provide individual patient data. Results demonstrated a significant OS benefit for interferon (odds ratio [OR] 0.9; CI 0.84 to 0.97; p=0.008). Analysis of only individual patient data indicated an absolute five-year OS benefit of 3% (CI 1% to 5%). No survival difference according to interferon dose or duration of therapy was demonstrated. Event-free survival was also significantly improved in patients who received adjuvant interferon (OR 0.87; CI 0.81 to 0.93; p=0.00006). The authors concluded that adjuvant interferon significantly reduces risk of relapse and improves OS, although the survival benefit is small.
Chemotherapy plus Interferon Alpha

Two trials were identified in the updated literature search that compared adjuvant chemotherapy plus low dose interferon alpha with observation alone (17,21). The trial reported by Stadler et al. (21) included stage II and III patients while the DeCOG trial by Garbe et al. included only stage III patients (17). The DeCOG trial administered interferon alpha and dacarbazine (DTIC) simultaneously while the Stadler trial administered DTIC for two cycles, followed by six months of humanized interferon alpha.

The Stadler report presented data from a protocol-planned outcome analysis after the completion of prospective follow-up and a non-protocol long-term follow-up (21). In the planned efficacy analysis, neither RFS nor melanoma-related death were significantly different between treatment arms. A significant benefit for interferon plus DTIC on RFS in an exploratory analysis of high-risk patients (stage IIb and III) triggered the long-term follow-up analysis. In the long-term analysis, a trend towards a benefit for adjuvant therapy on OS was reported (HR 0.71; CI 0.49-1.00; p=0.052) and this difference was statistically significant in the exploratory analysis of high-risk patients (HR 0.58; CI 0.38-0.86; p=0.008). Treatment was generally well-tolerated, with 3.4% of all adverse effects during DTIC treatment and 2.9% of all adverse effects during interferon treatment being grade 3/4.

Results from the three-arm DeCOG trial indicated that the addition of DTIC to adjuvant interferon therapy appeared to reverse the observed beneficial effect of interferon (17). In contrast to the significant benefit in OS and DFS for interferon alone compared with observation, no benefit was reported for interferon plus DTIC compared with observation for either outcome. Adverse effects were mild, with 17% of patients experiencing grade 3/4 effects. Treatment was stopped due to adverse effects in 11% of patients in the DTIC plus interferon arm.

Vaccines

One RCT was identified in the updated literature search that compared adjuvant vaccine therapy with observation alone following resection. The EORTC 18961 trial, reported in abstract form by Eggermont et al., demonstrated that adjuvant ganglioside GM2-KLH21 vaccination in stage II melanoma is not effective and may result in worse outcome than observation alone (20) (Table 3). At the second interim analysis, the stopping criteria were met for the primary outcome of RFS due to futility. After a median follow-up of 1.8 years, results suggest a detrimental effect for vaccination compared with observation in OS (HR 1.57; 99.9% CI 0.68-3.64) and distant metastasis free survival (HR 1.33; 99.9% CI 0.77-2.28). Four percent of patients in the vaccination arm experienced grade 3/4 local toxicity and 2% experienced grade 3/4 fatigue.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Treatment</th>
<th># pts randomized (evaluated)</th>
<th>Dose &amp; schedule</th>
<th>5 year survival (%)</th>
<th>Mortality HR (95% CI)</th>
<th>Disease free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IFN vs Observation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eggermont 2005</td>
<td>IIb: 356 pts</td>
<td>IFNα (13 mos)</td>
<td>553 (553)</td>
<td>10x10⁶ U s.c. 5d/wk, 4 wks, then 10x10⁶ U 3 times/wk, for 1 yr</td>
<td>(4.5 year) 48.3</td>
<td>(versus obs) 0.97 (0.77-1.21) p=0.73</td>
<td>NR</td>
</tr>
<tr>
<td>EORTC 18952</td>
<td>III: N1: 353 pts N2: 679 pts</td>
<td>IFNα (25 mos)</td>
<td>556 (556)</td>
<td>As above but for 2 yrs</td>
<td>53.1</td>
<td>0.85 (0.68-1.07) p=0.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Observation</td>
<td></td>
<td>279 (279)</td>
<td>-</td>
<td></td>
<td>47.7</td>
<td></td>
</tr>
</tbody>
</table>
| Eggermont 2008        | III: all pts | Peg-IFNα2b | 627 | 6μg/kg/wk, s.c. 8 wks, then 3μg/kg/wk for 5 yrs or until distant metastases¹ | (4 year) 56.8 | 0.98 (0.82-1.16) p=0.78 | (RFS) 45.6% vs 38.9%  
Median: 34.8 mos vs 25.6 mos  
HR: 0.82 (0.71-0.96) p=0.01 |                       |
| EORTC 18991           | Observation | 629 | - | | 55.7 |                       |                       |
| McMasters 2008         | Protocol A: Single histologically positive node | IFN | 106 | 20x10⁶ U/m²/d i.v., 4 wks, then 10x10⁶ s.c. 3 times/wk, 48 wks | 72.9 | log-rank p=0.9033 | 5-yr: 73.2% vs 70.2%  
Log-rank p=0.4589 |                       |
| abstract Sunbelt Melanoma Trial | Observation | 112 | - | | 75.4 |                       |                       |
| Protocol B: Histologically negative nodes, RT-PCR positive nodes | CLND + IFN | 184 | 20x10⁶ U/m²/d i.v., 4 wks | 86.8 | log-rank p=0.9505 | 5-yr: 83.7% vs 85.2% vs 83.9%  
Log-rank p=0.2366 |                       |
|                       | CLND | 192 | - | | 85.3 |                       |                       |
|                       | Observation | 180 | - | | 85.5 |                       |                       |
| Garbe 2008           | Protocol A: Single histologically positive node | IFNα2a | 146 | 3x10⁶ U s.c., 3 times/wk, 2 yrs | (4-year) 59.0 | 0.62 (0.42-0.89)⁵-log-rank p=0.0045 | 4-yr: 39.0% vs 27.3%  
HR: 0.69 (0.49-0.96)⁵ Log-rank p=0.018 |                       |
| abstract DeCOG | Observation | 147 | - | | 42.4 |                       |                       |
| **IFN vs another IFN regimen** |       |           |                             |                |                     |                       |                       |
| Gogas 2007           | IIb: 32 pts | IFNα2b (1 mo) | 182 (177) | 15x10⁶ U/m²/d i.v. 5d/wk, 4 wks | NR | Median: 61 mos vs 63 mos  
p=0.444 |                       |
| abstract (18)         | IIc: 73 pts | IFNα2b (1 yr) | 182 (176) | Same as above plus 10x10⁶ U flat dose s.c.3 times/wk, 48 wks | | Median: 32 mos vs 31 mos  
p=0.836 |                       |
<p>|                       | IIl: 39 pts | | | | | |                       |
|                       | IIIb: 104 pts | | | | | |                       |
|                       | IIIc: 67 pts | | | | | |                       |
|                       | Unknown: 38 pts | | | | | |                       |</p>
<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Treatment</th>
<th># pts randomized (evaluated)</th>
<th>Dose &amp; schedule</th>
<th>5 year survival (%)</th>
<th>Mortality HR (95% CI)</th>
<th>Disease free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hauschild 2008 abstract (19)</td>
<td>Thickness ≥1.5 mm Negative lymph nodes, clinically or by SLNB</td>
<td>IFNα2a (18 mos)</td>
<td>427 (421)</td>
<td>3x10⁶ U 3 times/wk s.c., 18 mos</td>
<td>85.9</td>
<td>1.03 (0.71-1.50) p=0.86</td>
<td>(RFS) 75.6% vs 72.6% HR: 1.05 (0.80-1.39) p=0.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IFNα2a (60 mos)</td>
<td>423 (419)</td>
<td>Same as above for 60 mos</td>
<td>84.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Chemotherapy plus IFN vs Observation**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Treatment</th>
<th># pts randomized (evaluated)</th>
<th>Dose &amp; schedule</th>
<th>5 year survival (%)</th>
<th>Mortality HR (95% CI)</th>
<th>Disease free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stadler 2006 (21)</td>
<td>IIa: 90 pts IIb: 20 pts IIia: 31 pts IIib: 105 pts IV: 4 pts wrong diagnosis: 2 pts</td>
<td>DTIC + HuIFN-αLe</td>
<td>128 (128)</td>
<td>DTIC 850 mg/m² d2 of wks 1 and 5. 4 wks after 2nd DTIC injection, HuIFN-αLe 3x10⁶ U 3 times/wk for 6 mos</td>
<td>NR</td>
<td>NR</td>
<td>(RFS) 43.8% vs 50.0% Median: 1002 d vs 461 d Log-rank p=0.068</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observation</td>
<td>124 (124)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

| Garbe 2008b (17) | DeCOG III: all pts | DTIC + IFNα2a | 148 | 3x10⁶ U s.c., 3 times/wk, 2 yrs DTIC 850 mg/m² i.v., d1 every 28d for 6 mos, every 42d for mos 7-12, and every 56d for mos 13-24 | (4-year) | 45.2 | 0.96 (0.67-1.33)c,f Log-rank p=0.75 |
| | | Observation | 147 | | | | 42.4 |

**Vaccine vs Observation**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Treatment</th>
<th># pts randomized (evaluated)</th>
<th>Dose &amp; schedule</th>
<th>5 year survival (%)</th>
<th>Mortality HR (95% CI)</th>
<th>Disease free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eggermont 2008 abstract (20)</td>
<td>Breslow : 1.5-3.0mm: 130 pts 3.0-4.0mm: 234 pts &gt;4.0mm: 306 pts Unknown: 1 pt</td>
<td>Ganglioside GM2-KLH21 vaccine</td>
<td>657 (657)</td>
<td>s.c. vaccine, once weekly, wks 1-4, every 3 mos from 12 wks to 2 yrs, every 6 mos during 3rd yr</td>
<td>(2-year)</td>
<td>89.2</td>
<td>1.57 (0.68-3.64)g p=0.03 (vaccine significantly worse)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observation</td>
<td>657 (657)</td>
<td></td>
<td></td>
<td></td>
<td>92.4</td>
</tr>
</tbody>
</table>

Notes: pts, patients; HR, hazard ratio; CI, confidence interval; IFN, interferon; mos, months; U, units; d, day; wk, week; yr, year; obs, observation; NR, not reported; EORTC, European Organisation for Research and Treatment of Cancer; Peg, pegylated; RFS, relapse-free survival; i.v., intravenous; s.c., subcutaneous; CLND, completion lymph node dissection; DTIC, dacarbazine.

a Trial also includes a IFN plus chemotherapy arm
b Trial also includes a IFN alone arm
c 97.5% confidence interval
d A long-term survival follow-up conducted after protocol completion indicated a mortality HR of 0.71 (95% CI 0.49-1.00; p=0.052) favouring adjuvant therapy
e In the original efficacy analysis, melanoma-related death was not significantly different between treatment arms (log-rank p=0.97)
f Three non-melanoma deaths in each treatment arm were not included as events in the survival analysis. Results remained “practically identical” when these deaths were included as events.
g 99.9% confidence interval
h 98% confidence interval
i Median length of treatment was 12 months

Section 2A: Updated Evidentiary Base
Melanoma DSG Meta-analysis of high-dose interferon trials

In the original systematic review, the Melanoma DSG conducted a meta-analysis of two-year mortality rates from the three ECOG trials of a one-year high-dose interferon alpha regimen, two of which compared adjuvant interferon with observation alone and one of which compared adjuvant interferon with adjuvant ganglioside GM2 vaccine (3-5) (Section 2B). Since HRs are the preferred statistic for pooling time-to-event outcomes rather than number of events at a particular time point (12), the original meta-analysis (Section 2B) was updated using this method (Figure 1). Updated data for the three ECOG trials (26) and abstract data from the Melanoma Sunbelt trial Protocol A (16) were used to estimate HRs.

Overall survival was not significantly different between high-dose interferon and control (HR 0.87; 95% CI 0.75-1.01; p=0.07). A sensitivity analysis without the ECOG 1694 vaccine trial also did not detect a significant difference in mortality between interferon and observation alone (HR 0.93; 95% CI, 0.78-1.12; p=0.45), representing a 2% to 3% absolute risk reduction at five years. No significant heterogeneity was detected between trial results in either analysis.

A meta-analysis of DFS hazard ratios demonstrated a significant benefit for high-dose interferon over control, both in the overall analysis (HR 0.76; 95% CI 0.67-0.87; p<0.0001) and in the sensitivity analysis which excluded the ECOG 1694 vaccine trial (HR 0.77; 95% CI 0.65-0.92; p=0.004), representing a 9% absolute risk reduction at five years (Figure 2).

Figure 1. High dose interferon alpha versus control: Meta-analysis of mortality hazard ratios.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 HDI vs Observation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1684</td>
<td>-0.1972</td>
<td>0.1459</td>
<td>27.4%</td>
<td>0.82 [0.62, 1.09]</td>
<td></td>
</tr>
<tr>
<td>E1690</td>
<td>0.0035</td>
<td>0.1377</td>
<td>30.8%</td>
<td>1.00 [0.77, 1.31]</td>
<td></td>
</tr>
<tr>
<td>Sunbelt Protocol A</td>
<td>0.0677</td>
<td>0.2556</td>
<td>8.9%</td>
<td>1.07 [0.65, 1.77]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>67.1%</td>
<td>0.93 [0.78, 1.12]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 2 (P = 0.51); I² = 0%  Test for overall effect: Z = 0.75 (P = 0.45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 1.1.2 HDI vs vaccine |
|---------------------|------------------|--------|--------|-------------------------------|-------------------------------|
| E1694               | -0.2755          | 0.1331 | 32.9%  | 0.76 [0.58, 0.99]              |                               |
| Subtotal (95% CI)   |                  |        | 32.9%  | 0.76 [0.58, 0.99]              |                               |
| Heterogeneity: Not applicable  Test for overall effect: Z = 2.07 (P = 0.04) |

Total (95% CI) 100.0% 0.87 [0.75, 1.01]  
Heterogeneity: Tau² = 0.00; Chi² = 2.94, df = 3 (P = 0.40); I² = 0%  Test for overall effect: Z = 1.80 (P = 0.07)  Test for subgroup differences: Chi² = 1.60, df = 1 (P = 0.21), I² = 37.5%

Notes: CI, confidence interval; HDI, high dose interferon.
Figure 2. High dose interferon alpha versus control: Meta-analysis of disease-free survival hazard ratios.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.2.1 HDI vs Observation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1684</td>
<td>-0.3238</td>
<td>0.1406</td>
<td>23.4%</td>
<td>0.72 [0.55, 0.95]</td>
<td></td>
</tr>
<tr>
<td>E1690</td>
<td>-0.2152</td>
<td>0.127</td>
<td>28.7%</td>
<td>0.81 [0.63, 1.03]</td>
<td></td>
</tr>
<tr>
<td>Sunbelt Protocol A</td>
<td>-0.1985</td>
<td>0.2732</td>
<td>6.2%</td>
<td>0.82 [0.48, 1.40]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td>58.4%</td>
<td>0.77 [0.65, 0.92]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 3.88, df = 2 (P = 0.38); I² = 0%</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 2.88 (P = 0.004)</td>
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<tr>
<td><strong>1.2.2 HDI vs vaccine</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>E1694</td>
<td>-0.2872</td>
<td>0.1055</td>
<td>41.6%</td>
<td>0.75 [0.61, 0.92]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td>41.6%</td>
<td>0.75 [0.61, 0.92]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 2.72 (P = 0.006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.76 [0.67, 0.87]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 3 (P = 0.93); I² = 0%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.96 (P &lt; 0.0001)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Notes:** CI, confidence interval; HDI, high dose interferon.

**Ongoing Trials**
The National Cancer Institute (NCI) clinical trials database (www.cancer.gov/search/clinical_trials/) was searched on July 16, 2008 for reports of new or ongoing trials that met the inclusion criteria for this review. See Table 4 for a summary table of relevant trials.

**Table 4. Ongoing trials of adjuvant therapy for melanoma.**

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Phase III randomized adjuvant study of high dose interferon alpha-2b therapy in patients with stage II and III melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date last modified</td>
<td>July 12, 2008</td>
</tr>
<tr>
<td>Target enrolment</td>
<td>1,420</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Disease control interval, toxicity</td>
</tr>
<tr>
<td>Sponsorship</td>
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<tr>
<td>Status</td>
<td>Recruiting</td>
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<table>
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<th>Protocol ID</th>
<th>Phase III randomized study of sargramostim (GM-CSF) and peptide vaccination comprised of tyrosinase:368-376, gp100:209-217 antigen, and MART-1:27-35 peptide versus peptide vaccination alone versus GM-CSF alone versus placebo in patients with locally advanced or metastatic melanoma</th>
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<tr>
<td>Target enrolment</td>
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</tr>
<tr>
<td>Primary endpoint</td>
<td>Two-year survival, time to progression</td>
</tr>
<tr>
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<td>ECOG, NCI, SWOG</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing, not recruiting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Phase III study of adjuvant interferon alpha-2b in patients with invasive cutaneous melanoma with early lymph node metastasis detected by intraoperative lymphatic mapping and sentinel lymph node biopsy</th>
</tr>
</thead>
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<tr>
<td>Target enrolment</td>
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</tr>
<tr>
<td>Primary endpoint</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sponsorship</td>
<td>Lurleen Wallace Comprehensive Cancer at University of Alabama-Birmingham, NCI</td>
</tr>
<tr>
<td>Status</td>
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</tr>
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**Section 2A: Updated Evidentiary Base**

<table>
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<tr>
<td>Target enrolment</td>
<td>NR</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>NR</td>
</tr>
<tr>
<td>Sponsorship</td>
<td>DeCOG</td>
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<tr>
<td>Status</td>
<td>Interim analysis presented at ASCO 2002 (#1373)</td>
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**DISCUSSION**

This systematic review addresses a fundamental question from a clinical perspective: 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? In general, the new data published since 2005 comparing adjuvant therapy versus observation alone confirm the conclusions of the original systematic review. The available evidence shows that none of the therapeutic modalities identified confer a significant long-term survival advantage; however, the evidence demonstrates that treatment with interferon-alpha consistently produces a significant improvement in RFS or DFS. Important new evidence identified in the updated literature search includes an RCT demonstrating a DFS benefit for pegylated interferon compared with observation alone (15), and an abstract report of an individual patient data meta-analysis comparing adjuvant interferon versus no interferon (24).

Adjuvant therapy of melanoma with interferon remains controversial. The original guideline recommendation to offer high-dose interferon alpha therapy to high-risk patients was based in part on a meta-analysis of two-year survival rates from the three ECOG trials (Section 2B, Figure 1). The difficulty lies in the inconsistent results for OS in the three ECOG studies (3-5). Although a significant OS benefit was initially observed in the first trial, ECOG 1684, that benefit was no longer apparent with longer follow-up. It has been suggested that the lack of an OS benefit in the second trial, ECOG 1690, was due to the fact that the control group in that trial fared better than the control group in the earlier 1684 trial. One explanation given for that assertion is that a significantly higher proportion of patients in the observation arm received salvage therapy in the ECOG 1690 trial (4). There was also a considerable difference in the stage distribution of patients between the three ECOG trials.

An additional issue in the interpretation of the ECOG high-dose interferon trials is how to incorporate information from the ECOG 1694 trial, given that a no-treatment control arm was not included (5). Data that suggest that the experimental vaccine arm may have resulted in worse outcomes have recently been reported. An abstract report of the EORTC 18961 trial demonstrated that adjuvant ganglioside GM2-KLH21 vaccination was not effective and suggested a detrimental effect for the vaccine arm compared to observation in OS (20). These results call into question the validity of the DFS and OS benefit as well as the pooling of the ECOG 1694 trial results with results from trials comparing interferon with observation alone.

An updated meta-analysis of results from trials comparing a one-year high-dose interferon alpha regimen with control was conducted by the Melanoma DSG to incorporate new evidence, improve methodological rigour, and take into account issues concerning the inclusion of the ECOG 1694 interferon versus vaccine trial. Pooling of mortality hazard ratios from three trials comparing high-dose interferon with observation alone did not demonstrate a significant survival difference between groups (Figure 1). In contrast, an abstract report of an individual patient data meta-analysis comparing any adjuvant interferon therapy with no adjuvant interferon demonstrated a statistically significant benefit for interferon in OS; however, the absolute survival benefit of 3% at five years was very small and limited details regarding methodology and study inclusion are currently available (24).
Despite the lack of a meaningful long-term survival benefit with interferon therapy, there is clear evidence that adjuvant interferon delays recurrence in patients with high-risk melanoma. RFS or DFS represent important outcomes for patients from an emotional, physical and quality-of-life perspective (27). Such outcomes are appropriate endpoints in adjuvant melanoma trials as recurrence of disease will result in mortality in the vast majority of patients. The meta-analysis of DFS HRs conducted by the Melanoma DSG demonstrated a significant benefit for a one-year high-dose interferon alpha regimen over observation alone (HR 0.77; 95% CI 0.65 to 0.92). Similarly, the abstract report of the individual patient data meta-analysis comparing any adjuvant interferon therapy with no adjuvant interferon reported a statistically significant benefit in event-free survival (24). Based on these results, the Melanoma DSG recommends that high-dose interferon be considered and discussed as a reasonable option in appropriate patients, provided that each patient is made aware of the potential benefits and toxicities associated with this therapy.

The EORTC 18991 trial of pegylated interferon adds consistency to the current body of literature (15). The authors reported the largest adjuvant study ever conducted in stage III melanoma, enrolling 1256 patients. In an intent-to-treat analysis, there was a significant benefit for RFS but not for distant-metastasis free survival or OS; however, the median follow-up is only four years and too short for final conclusions to be made regarding subsets of patients. Pegylated interferon had an acceptable toxicity profile, with the most common side effect being fatigue. Given that there is no intravenous component and all therapy is given subcutaneously, this therapy may provide a more convenient, less toxic alternative to high dose interferon and should be discussed with patients.

Low dose interferon has also been assessed in RCTs. In the original systematic review (Section 2B), six trials compared low-dose interferon versus observation with no clear DFS or OS benefit. The more recent German study by Garbe et al. (17) reported a significant DFS and OS benefit for low-dose subcutaneous interferon compared with observation; however, these results need to be confirmed in additional trials. No RCT has directly compared high dose interferon to low dose interferon. The Wheatley (24) meta-analysis states that there was no evidence of differences according to dose or duration of interferon and that the analysis did not clarify the optimal dose (high, intermediate or low) of interferon. It is unclear from the abstract publication whether there was sufficient power to detect an interaction between the subgroups.

Is one month of high dose interferon sufficient? Two trials have attempted to address this question. The Gogas trial which compared one month versus one year of high dose interferon showed no difference in DFS or OS; however, this was a small study and not sufficient to change practice (18). The Sunbelt Melanoma Trial also used one month of high dose interferon in their RT-PCR positive population and showed no difference in DFS or OS when compared to observation (16). This is a very specific subset of patients and this study did not reach its targeted accrual. While this may provide some reassurance for patients who are unable to complete their therapy, it is insufficient evidence to change practice. The current ongoing ECOG 1697/ME 10 trial which randomizes intermediate risk patients to one month of high dose interferon vs. observation may help answer this question when completed.

Which patients should be considered for treatment with adjuvant high-dose interferon? The ECOG studies examined the role of therapy in patients with AJCC Stage IIB and III melanoma, where patients with Stage IIB disease had no evidence of nodal involvement but had lesions more than 4.0 mm deep and Stage III patients had evidence of regional nodal disease or up to five in-transit lesions. Staging has evolved since the time of those trials. The latest AJCC staging classification (1) is based on an analysis of 17,600 patients (28) and demonstrates the importance of ulceration in the primary lesion. In that system, patients with lesions between 2.0 and 4.0 mm depth of invasion, who have an ulcerated primary
lesion, have the same prognosis as patients with lesions greater than 4.0 mm without ulceration. The high-dose interferon trials provide insufficient information on the benefit of such therapy in those patients. Therefore, a decision to include that group of patients as appropriate candidates for high-dose interferon would have to be made on clinical grounds, as there is no information now or likely in the near future that would enlighten matters. A planned EORTC trial, as well as future results of ECOG 1697/ME 10 trial, will address this question; however, these trials will take many years to complete. This same rationale also needs to be applied to patients with satellitosis, a group underrepresented in the trials mentioned above. A new staging system for melanoma has been proposed that may alter eligibility for clinical trials and may redefine what constitutes high-risk patients.

How should patients with no nodal metastatic disease, as determined through sentinel lymph node biopsy procedures, where the sentinel node is the only node found to harbour metastatic disease, be managed? This question is particularly relevant to patients with intermediate-risk disease (primary melanomas between 1.5 and 4.0 mm deep) who are most commonly subjected to sentinel lymph node procedures. The only trial that has evaluated this group of patients is the Sunbelt Melanoma Trial (16). This trial did not show any benefit in DFS or OS for high dose interferon compared to observation in sentinel lymph node positive patients. It is unfortunate that the trial was underpowered as this is a very relevant group of patients and will represent the bulk of our patients in the future. The ECOG 1697 trial is currently ongoing and may provide some clarification to this subgroup of patients in the future. Until that trial is completed, one cannot state with confidence whether or not adjuvant high-dose interferon would benefit this target population.

CONCLUSIONS

In summary, the results of this review are disappointing as none of the therapeutic modalities examined resulted in meaningful long-term survival advantages in patients with high-risk primary melanomas. However, the data indisputably show a benefit for interferon in DFS and this is an important endpoint for patients as well as a valuable surrogate endpoint. Notwithstanding the results of trials incorporating high-dose interferon alpha, novel therapies should be explored aggressively, and patients should be encouraged to participate in appropriate randomized trials.

CONFLICT OF INTEREST

Members of the Melanoma DSG involved in the development of this updated systematic review and practice guideline were polled for potential conflicts of interest.

ACKNOWLEDGEMENTS

The Melanoma DSG would like to thank Drs. Teresa Petrella, Shailendra Verma, and Ian Quirt and Ms. Karen Spithoff for taking the lead in drafting this systematic review update.

For a complete list of the Melanoma DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/

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For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055    Fax: 905-522-7681
REFERENCES


11. Review Manager (RevMan) [Computer program]. 2008;5.0.


Appendix 1. Staging system for malignant melanoma of the skin.

STAGE GROUPING (AJCC Staging System 1992)

Stage 0  pTis  N0  M0
Stage I   pT1  N0  M0
          pT2  N0  M0
Stage II  pT3  N0  M0
          pT4  N0  M0
Stage III Any pT  N1  M0
               Any pT  N2  M0
Stage IV  Any pT  Any N  M1

TNM STAGING (AJCC Staging System 1992)

Primary Tumour (pT)

pTX Primary tumour cannot be assessed
pT0 No evidence of primary tumour
pTis Melanoma in situ, (atypical melanocytic hyperplasia, severe melanocytic dysplasia), not an invasive lesion (Clark’s Level I)
pT1 Tumour 0.75 mm or less in thickness and invading the papillary dermis (Clark’s Level II)
pT2 Tumour more than 0.75 mm but not more than 1.5 mm in thickness and/or invades to the papillary-reticular dermal interface (Clark’s Level III)
pT3 Tumour more than 1.5 mm but not more than 4 mm in thickness and/or invades the reticular dermis (Clark’s Level IV)
    pT3a Tumour more than 1.5 mm but not more than 3 mm in thickness
    pT3b Tumour more than 3 mm but not more than 4 mm in thickness
pT4 Tumour more than 4 mm in thickness and/or invades the subcutaneous tissue (Clark’s Level V) and/or satellite(s) within 2 cm of the primary tumour
    pT4a Tumour more than 4 mm in thickness and/or invades the subcutaneous tissue
    pT4b Satellite(s) within 2 cm of the primary tumour

Regional Lymph Node (N)

Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis 3 cm or less in greatest dimension in any regional lymph node(s)
N2 Metastasis more than 3 cm in greatest dimension in any regional lymph node(s) and/or in-transit metastasis
    N2a Metastasis more than 3 cm in greatest dimension in any regional lymph nodes
    N2b In-transit metastasis
    N2c Both (N2a and N2b)

Note: In-transit metastasis involves skin or subcutaneous tissue more than 2 cm from the primary tumour not beyond the regional lymph nodes

Distant Metastasis (M)

Mx Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
    M1a Metastasis in skin or subcutaneous tissue or lymph node(s) beyond the regional lymph nodes
    M2a Visceral metastasis

### STAGE GROUPINGS (AJCC Staging System 2001).

<table>
<thead>
<tr>
<th>Clinical Staging*</th>
<th>Pathologic Staging†</th>
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</thead>
<tbody>
<tr>
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<td>N</td>
</tr>
<tr>
<td>0</td>
<td>Tis</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
</tr>
<tr>
<td>II</td>
<td>T2a</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3a</td>
</tr>
<tr>
<td>IIC</td>
<td>T4a</td>
</tr>
<tr>
<td>III†</td>
<td>Any T</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-4a</td>
</tr>
<tr>
<td>IIB</td>
<td>T1-4b</td>
</tr>
<tr>
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<td></td>
<td>Any T</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
</tr>
</tbody>
</table>

* Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

† Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage 1A patients are the exception; they do not require pathologic evaluation of their lymph nodes.

‡ There are no stage III subgroups for clinical staging.

### TNM STAGING (AJCC Staging System 2001).

<table>
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<tr>
<th>T classification</th>
<th>Thickness</th>
<th>Ulceration Status</th>
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<tbody>
<tr>
<td>T1</td>
<td>≤ 1.0 mm</td>
<td>a: without ulceration and level II/III</td>
</tr>
<tr>
<td>T2</td>
<td>1.01 - 2.0 mm</td>
<td>b: with ulceration or level IV/V</td>
</tr>
<tr>
<td>T3</td>
<td>2.01 - 4.0 mm</td>
<td>a: without ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>&gt; 4.0 mm</td>
<td>b: with ulceration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N classification</th>
<th>Number of Metastatic Nodes</th>
<th>Nodal Metastatic Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>1 node</td>
<td>a: micrometastasis*</td>
</tr>
<tr>
<td>N2</td>
<td>2 - 3 nodes</td>
<td>b: micrometastasis†</td>
</tr>
<tr>
<td>N3</td>
<td>4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)</td>
<td>c: in transit met(s)/satellite(s) without metastatic nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M classification</th>
<th>Site</th>
<th>Serum Lactate Dehydrogenase</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastasis</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

* Micrometastases are diagnosed after sentinel or elective lymphadenectomy.
† Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Appendix 2. Literature search strategies.

**MEDLINE**

1. melanoma:.mp.
2. chemotherapy, adjuvant/
3. drug therapy/
4. adjuvant.tw.
5. postoperative.tw.
6. immunotherapy/
7. immunization/
8. exp immunotherapy, active/
9. vaccin:.tw.
10. immunotherap:.tw.
11. chemotherap:.tw.
12. exp interferons/
13. interferon:.tw.
14. IFN:.tw.
15. levamisole.mp.
16. (dacarbazine or lomustine or CCNU or carmustine or BCNU or vincristine).mp.
17. or/2-16
18. 1 and 17
19. Meta-Analysis as topic/
20. meta analy$.tw.
21. metaanaly$.tw.
22. meta analysis.pt. (16185)
23. (systematic adj (review$1 or overview$1)).tw.
24. exp Review Literature as topic/
25. or/19-24
26. cochrane.ab.
27. embase.ab.
28. (psychlit or psyclit).ab.
29. (psychinfo or psycinfo).ab.
30. (cinahl or cinhal).ab.
31. science citation index.ab.
32. bids.ab.
33. cancerlit.ab.
34. or/26-33
35. reference list$.ab.
36. bibliograph$.ab.
37. hand-search$.ab.
38. relevant journals.ab.
39. manual search$.ab.
40. or/35-39
41. selection criteria.ab.
42. data extraction.ab.
43. 41 or 42
44. review.pt.
45. 43 and 44
46. comment.pt.
47. letter.pt.
Section 2A: Updated Evidentiary Base

48 editorial.pt.
49 animal/
50 human/
51 49 not (49 and 50)
52 or/46-48,51
53 25 or 34 or 40 or 45
54 53 not 52
55 Randomized controlled trials as topic/
56 randomized controlled trial.pt.
57 random allocation/
58 Double blind method/
59 Single blind method/
60 clinical trial.pt.
61 exp clinical trials as topic/
62 or/55-61
63 (clinic$ adj trial$1).tw.
64 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
65 Placebos/
66 Placebo$.tw.
67 Randomly allocated.tw.
68 (allocated adj2 random).tw.
69 or/63-68
70 62 or 69
71 Case report.tw.
72 Letter.pt.
73 Historical article.pt.
74 or/71-73
75 70 not 74
76 75 or 54
77 18 and 76
78 (200507: or 200508: or 200509: or 20051: or 2006: or 2007: or 2008:).ed.
79 77 and 78

EMBASE
1 melanoma:.mp.
2 exp adjuvant therapy/
3 drug therapy/
4 adjuvant.tw.
5 postoperative.tw.
6 exp immunotherapy/
7 exp immunization/
8 vaccin:.tw.
9 immunotherap:.tw.
10 chemotherap:.tw.
11 exp interferon/
12 interferon:.tw.
13 IFN:.tw.
14 levamisole.mp.
15 (dacarbazine or lomustine or CCNU or carmustine or BCNU or vincristine).mp.
(meta adj analy$) or metaanalys$.tw.
(systematic adj (review$1 or overview$1)).tw.
or/18-20
cancerlit.ab.
cochrane.ab.
embase.ab.
(psychlit or psyclit).ab.
(psychinfo or psycinfo).ab.
(cinahl or cinhal).ab.
science citation index.ab.
bids.ab.
or/22-29
reference lists.ab.
bibliograph$.ab.
hand-search$.ab.
manual search$.ab.
relevant journals.ab.
or/31-35
data extraction.ab.
selection criteria.ab.
37 or 38
review.pt.
39 and 40
letter.pt.
editorial.pt.
animal/
human/
44 not (44 and 45)
or/42-43,46
21 or 30 or 36 or 41
48 not 47
clinical trial/
randomized controlled trial/
randomization/
single blind procedure/
double blind procedure/
crossover procedure/
placebo/
random$ed controlled trial$.tw.
rct.tw.
random allocation.tw.
randomly allocated.tw.
allocated randomly.tw.
(allocated adj2 random).tw.
single blind$.tw.
double blind$.tw.
((treble or triple) adj blind$).tw.
66  placebo$.tw.
67  Prospective study/
68   or/50-67
69  Case study/
70  case report.tw.
71  abstract report/ or letter/
72   or/69-71
73  68 not 72
74  17 and (49 or 73)
75  (200532: or 200533: or 200534: or 200535: or 200536: or 200537: or 200538: or 200539: 
or 20054: or 20055: or 2006: or 2007: or 2008:).ew.
76  74 and 75

COCHRANE DATABASE OF SYSTEMATIC REVIEWS
1  melanoma:.ti,ab,kw.

COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS
1  melanoma:.hw,ti,ab.
2  adjuvant.tw,hw.
3  1 and 2
Appendix 3. Literature search results flow diagram.

Ovid: MEDLINE, EMBASE, CENTRAL\(^a\) (May 2008 to July 2008)

Results
MEDLINE: 365
EMBASE: 1048
CENTRAL: 219

Retrieved for full text review
MEDLINE: 26
EMBASE: 31\(^b\)
CENTRAL: 9\(^b\)

6 citations met the inclusion criteria.

ASCO: Annual meeting proceedings (2006 to 2008)

Melanoma abstracts
2006: 77
2007: 88
2008: 109

Retrieved for review
2006: 1
2007: 9
2008: 6

5 ASCO abstracts met the inclusion criteria. One additional abstract met the inclusion criteria but was excluded as redundant.

11 citations in total met the inclusion criteria

Notes: CENTRAL, Cochrane Central Register of Controlled Trials; ASCO, American Society of Clinical Trials.

\(^a\) The Cochrane Database of Systematic Reviews was also searched. No relevant citations were identified.

\(^b\) 13 of the 31 EMBASE results and 7 of the 9 CENTRAL results were duplicates of citations identified in the MEDLINE search.
Evidence-based Series #8-1 Version 4: Section 2B

Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Original Evidentiary Base 2005

S. Verma, I. Quirt, D. McCready, K. Bak, M. Charette, N. Iscoe, 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

Updated report Date: August 30, 2005
Original Report Date: June 30, 2004

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.

QUESTION
What systemic therapy should clinicians recommend to patients who have been rendered disease-free following resection of cutaneous melanomas and who are at high risk for subsequent recurrence? Outcomes of interest include overall survival, disease-free survival, adverse effects, and quality of life.

For this practice guideline, high-risk is defined as patients in the following clinical states who have been rendered disease free by surgery:
- primary melanoma with tumour thickness ≥4.0 mm or level V invasion,
- primary melanoma with in-transit metastases,
- primary melanoma with regional lymph node metastases that are clinically apparent or detected at elective lymph-node dissection,
- 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 stage IIB, IIC and III (1).

METHODS
Guideline Development
This practice guideline report was developed by the Program in Evidence-based Care (PEBC) of Cancer Care Ontario, using the methods of the Practice Guidelines Development Cycle (2). Evidence was selected and reviewed by one member of the PEBC’s Melanoma DSG and methodologists.
The practice guideline report is a convenient and up-to-date source of the best available evidence on systemic adjuvant therapy for patients at high risk for recurrent melanoma, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

A practice guideline report on systemic adjuvant therapy for patients at high risk for recurrent melanoma was originally completed in 1998 and published on the Web site. With the publication of further relevant literature on adjuvant therapy and the adoption of a new staging system for cutaneous melanoma, the Melanoma DSG rewrote its 1998 report. This document replaced that 1998 report.

**Literature Search Strategy**

The MEDLINE (1980 through July 2005), CANCERLIT (1983 through 2004), EMBASE (1980 to 2005 week 32), and Cochrane Library (2005, Issue 2) databases were systematically searched. The search terms included the MeSH terms melanoma/th, melanoma/dt, and clinical trial, and the text words random: and adjuvant. A search was also done for published practice guidelines, meta-analyses, and reviews. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the proceedings of the 1996-2005 meetings of the American Society of Clinical Oncology (ASCO) were searched for reports of new or ongoing trials. Articles found by the searches, cited in the relevant papers, or known to members of the Melanoma DSG were retrieved and reviewed.

**Study Selection Criteria**

**Inclusion Criteria**

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

They were randomized controlled trials (RCTs) of systemic therapies for the adjuvant treatment of patients with melanoma. Prior to the literature search, the following four types of treatments were identified as relevant to the guideline question: levamisole, interferon, vaccines, and chemotherapy.

Trials had to include patients at high risk of recurrence, but the study population did not need to be restricted to that group of patients. For this report, high risk is defined by the American Joint Committee on Cancer (AJCC) stages IIB and III (please see Appendix 1 for staging information) and includes primary tumours ≥4.0 mm thick, regional lymph node metastases that are clinically apparent at presentation or are detected at lymph node dissection, and regional lymph node recurrence. All studies were conducted under the previous AJCC staging system. We attempt to define how patients under the new AJCC staging system should be considered, recognizing that the views expressed cannot be based on data but are our view of the information available.

Practice guidelines, meta-analyses, and systematic reviews of adjuvant treatment of malignant melanoma were also eligible for review.

**Exclusion Criteria**

1. Phase I and II studies were not considered for inclusion in this report because of the availability of RCTs.
2. Papers published in a language other than English were not considered.
3. Bacillus Calmette-Guérin (BCG), Corynebacterium parvum, transfer factor, vitamin A, and megestrol acetate have been investigated in the past as adjuvant therapy. However, there
does not appear to be any ongoing interest in these agents. Trials involving these agents have been excluded in this systematic review.

**Synthesizing the Evidence**

Published guidelines for performing a meta-analysis deal with issues related to the comparability among studies of the questions being addressed, the patient populations, the interventions, and the outcomes (3-5). The majority of the trials selected for inclusion in this report addressed a common question, namely: Does the therapy under investigation, when given as adjuvant treatment, improve survival, compared with no treatment? Similar patient groups, albeit with varying risks of recurrence by virtue of entry criteria, participated in the randomized trials. Few trials were restricted to patients at high risk of recurrence (i.e., lesion depth 4.0 mm or greater or completely resected regional nodal metastases). For trials enrolling patients with a range of risks, survival results were not reported separately for the high-risk subgroup. The treatments evaluated fall into the following four distinct groups of interventions: interferons, levamisole, vaccines, and chemotherapy. Dose or schedule varied within each type of treatment. The majority of studies used an observation-only control arm rather than a placebo control, while some compared two active treatments.

In contrast to a published systematic review by Lens and Dawes (6), we have pooled the results from the three published Eastern Cooperative Oncology Group (ECOG) trials of high-dose interferon alpha therapy (7-9). However, the most recent ECOG trial (1694) had a vaccine as the intervention arm and interferon as the control arm (9). We have pooled the results with and without ECOG 1694 and discuss the advisability of this approach in the Interpretive Summary section. Results were pooled across studies using the Review Manager software provided by the Cochrane Collaboration (Metaview© Update Software) (10). Pooled results are expressed as relative risks (also known as risk ratios) for mortality (with a 95% confidence interval [CI]) such that a relative risk less than 1.0 favours the active treatment group. Data were analyzed using the random effects model (11). All significance tests are two-sided. Ideally, a meta-analysis would be restricted to high-risk patients as defined above. However, most of the studies were not limited to that group of patients. Although attempts were made to derive information for that group from the study reports or to obtain results directly from investigators, limited relevant data were available.

In addition, we have been able to pool mortality data within two of the other groups of therapies (levamisole and chemotherapy). We have not pooled the results from trials of vaccines. The vaccine trials studied a variety of vaccines that differed in the postulated mechanisms by which they were hypothesized to exert their immunomodulatory effects. Therefore, we do not believe that pooling the results from those trials is appropriate.

**RESULTS**

**Literature Search Results**

The following were eligible for inclusion in the systematic review of the evidence on adjuvant therapy: 13 trials of interferon, four trials of levamisole, nine trials of vaccines, and ten trials investigating chemotherapy. Those trials have been summarized in Tables 5 through 9. In addition, one report of a consensus development conference (12), two meta-analyses of interferon alpha therapy, one systematic review of adjuvant interferon alpha therapy, and one trial of chemotherapy plus interferon were reviewed.

**Outcomes**

**Interferon**

Twelve randomized trials investigating adjuvant interferon have been located (Tables 5 and 6). In addition, two meta-analyses of randomized trials of interferon alpha versus
observation have been located and reviewed (13,14). With the exception of the Southwest Oncology Group (SWOG) study of interferon gamma reported by Meyskens et al (15) and the European Organization for the Research and Treatment of Cancer (EORTC) trial (16), all other trials have examined interferon alpha. There are two types of interferon alpha, 2a and 2b, which differ slightly in the carbohydrate components of the compound. Though there is a single report suggesting that one interferon may be less immunogenic than the other (17), it is our contention that there is not enough evidence to suggest the interferons should be viewed differently.

**High-Dose Interferon Alpha**

The results from four RCTs of high-dose interferon alpha have been reported in full (7-9,18), while the results of a fifth trial are available only in abstract form (19) (Table 6). Two trials compared high-dose interferon alpha with observation (7,18), one trial compared high- and low-dose interferon alpha with observation (8), the fourth trial compared a melanoma vaccine with high-dose interferon alpha (9), and the fifth compared high-dose interferon alpha with a melanoma vaccine combined with low-dose interferon alpha (19).

The North Central Cancer Treatment Group (NCCTG) study compared high-dose intramuscular interferon alpha-2a for 12 weeks with observation in 262 patients, including 52 with primary tumours greater than 3.5 mm thick and 169 with regional nodal disease (18). There was no significant difference in survival between the two treatment groups (hazard ratio [HR] = 0.90; p=0.53) at a median follow-up of 6.1 years. In the landmark ECOG 1684 trial, high-dose interferon alpha-2b was compared with observation in patients with lesions 4.0 mm or greater, including resected nodal disease (7). The majority of the 287 patients randomized had either a recurrence of melanoma with lymph node involvement (61%), clinically apparent lymph node involvement at presentation (14%), or clinically unapparent nodal involvement detected through elective lymph node dissection (12%). At a median follow-up of 6.9 years, there was a statistically significant improvement in survival (p=0.0237) in the interferon group, with a reduction in mortality at five years from 63% to 54%. However, an updated analysis (20) published with a median follow-up of 12.6 years showed that the overall survival difference between the two arms was no longer statistically significant (HR=1.22; p=0.18), although relapse-free survival for patients treated with high-dose interferon continued to demonstrate significant clinical benefit (HR=1.38; p=0.02). The precise reasons for the attenuation in overall survival are not clear.

The ECOG 1690 trial was conducted in part to confirm the results of ECOG 1684 and to evaluate the efficacy of a lower, and possibly less toxic, dose of interferon (8). The three-armed study randomized patients to high-dose interferon alpha (the same regimen as ECOG 1684), to low-dose interferon alpha for two years (3X10^6 U/m^2 per day subcutaneously 3 times/week), or to observation. The population eligible for the 1690 trial was identical to that for ECOG 1684 (i.e., completely resected pathologic stage IIB or III primary or recurrent disease). Patients were stratified by stage prior to randomization. Seventy-five percent of trial participants had resected nodal metastases, in contrast with ECOG 1684 where 87% were node-positive. At a median follow-up of 4.3 years, there were no differences in survival detected between either dose of interferon and observation (HR for high-dose interferon versus [vs.] observation, 1.0; 95% CI, 0.75 to 1.33; HR for low-dose interferon vs. observation, 1.04; 95% CI, 0.78 to 1.38). During the time period covered by this preliminary analysis, there were 98 deaths with high-dose interferon, 96 with low-dose interferon, and 93 with observation. Furthermore, an analysis of relapse-free survival by risk group found no difference in treatment effect between node-negative and node-positive patients. Although there was a suggested benefit of high-dose interferon in patients with two or three positive nodes, overall survival by risk group was not reported. A Cox model analysis comparing the
two ECOG trials (1684 and 1690) demonstrated no difference between the overall survival curves for the high-dose intervention groups but, interestingly, a difference in the survival experiences in the observation groups; there was a significantly higher survival rate in the ECOG 1690 observation group compared with ECOG 1684 (HR, 1.64; p=0.0001). Both the preliminary results (21) and the most recent update of the ECOG1690 trial (22), the latter reported at a medium follow-up of 6.6 years, concluded that high-dose interferon versus observation did not result in an overall survival benefit (p=0.18), although the updated analysis demonstrated a trend towards improvement in relapse-free survival (HR=1.24; p=0.09).

A third ECOG-led trial (1694) was closed by the Data Safety Monitoring Committee after an interim analysis revealed a significant benefit for high-dose interferon compared with a melanoma vaccine (9). The population studied was similar to the 1684 and 1690 trials—patients with primary or recurrent melanoma meeting any of the following criteria: 1) tumour >4.0 mm thick, 2) positive lymph nodes found at lymphadenectomy, or 3) clinically apparent positive lymph nodes confirmed by lymphadenectomy; 76% had nodal metastases. Eight hundred eighty participants were randomized to the intervention (GMK vaccine, a ganglioside GM2 vaccine given weekly for one month and then every three months for two years) or to control (high-dose interferon [the dose used in ECOG 1684 and 1690]). In an interim analysis at a median follow-up of 16 months, a statistically significant survival benefit for interferon was detected (HR=1.52; p=0.009, from an analysis of 774 eligible patients). The two-tailed p-value from the intent-to-treat analysis was 0.035. There were 52 deaths in the interferon arm and 81 deaths in the vaccine arm. An analysis of the outcomes by nodal category (0, 1, 2-3, ≥4) indicated that patients with no nodal metastasis (n=202) had the highest benefit in terms of relapse-free survival (HR=2.06; p=0.012) and overall survival (HR=1.88; p-value not reported) with interferon. At a median follow-up period of 2.1 years, high-dose interferon continued to demonstrate superiority to the GM2-KLH vaccine in both overall survival (HR=1.33; p=0.04) and relapse-free survival (HR=1.33; p=0.006) (22). However, although the study has been interpreted as a positive trial favouring high-dose interferon, there is a possibility that the GM2-KLH vaccine might have produced a worse outcome than no treatment. This issue is discussed later, in the Interpretive Summary.

An interim analysis of a trial comparing an allogeneic melanoma vaccine (Melacine) combined with low-dose interferon alpha with high-dose interferon alpha (ECOG 1690 regimen) was recently reported in abstract form (19). The preliminary results have not indicated significant difference in relapse-free survival; median overall survival had not yet been reached at the time of the analysis. It is worth mentioning that we did not include ECOG 2696, a study comparing the combination of high-dose interferon and GM2-KLH/QS21 vaccine to the vaccine alone, as that trial was listed as a Phase II trial, ineligible for our analysis. In a recent pooled analysis of the ECOG and Intergroup trials of high-dose interferon adjuvant therapy, Kirkwood et al (22) demonstrated a median relapse-free survival of 2.3 years (95% CI, 1.9-2.7 years) and a median overall survival of 6.2 years (95% CI, 5.1-8.8 years) for all randomized patients (n=1912). Using updated data from trials E1684 and E1690, a two-sided univariate log-rank comparison of high-dose interferon versus observation performed on 317 patients revealed a significant benefit for high-dose interferon in relapse-free survival (HR=1.30; p=0.006) but not in the overall survival rate (HR=1.08; p=0.42).

We have pooled the results of the three ECOG studies of high-dose interferon (1684, 1690, and 1694). The NCCTG study of high-dose interferon was not included because a different treatment schedule of interferon was investigated. A meta-analysis of two-year death rates abstracted from survival curves in published reports yielded a risk ratio of 0.85 (95% CI, 0.73 to 0.99; p=0.03) (Figure 1) favouring high-dose interferon. No heterogeneity was detected among the results of the studies included (p=0.91). In addition, when the ECOG 1694
study of vaccine versus high-dose interferon was excluded from the meta-analysis, the risk ratio changed to 0.87 (95% CI, 0.71 to 1.07; p=0.18).

Figure 1.
Comparison of high-dose interferon versus control
Outcome: 1/1 Mortality risk ratio at 2 years for interferon versus control

<table>
<thead>
<tr>
<th>Study</th>
<th>Interferon n/N</th>
<th>Control n/N</th>
<th>Weight %</th>
<th>RR (95% CI Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 1684</td>
<td>55/1147</td>
<td>60/140</td>
<td></td>
<td>20.2 0.072,0.61</td>
</tr>
<tr>
<td>ECOG 1690</td>
<td>69/216</td>
<td>60/212</td>
<td></td>
<td>27.7 0.072,0.61</td>
</tr>
<tr>
<td>ECOG 1694</td>
<td>97/1490</td>
<td>119/1440</td>
<td>43.1</td>
<td>0.022,0.51</td>
</tr>
<tr>
<td>Total (E95%CI)</td>
<td>212/402</td>
<td>247/792</td>
<td>160.0</td>
<td>0.053,0.73</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=0.19 df=2 p=0.91
Test for overall effect z=2.13 p=0.03

Quality of life
ECOG 1684 included a retrospective quality-of-life-adjusted survival analysis (Quality-adjusted Time without Symptoms and Toxicity [Q-TWIST]) (20). A model was constructed using the amount of time patients spent with severe symptomatic toxic events, the amount of time without symptoms of relapse, and hypothetical (as opposed to individual patient) utility coefficients. During 84 months of follow-up, patients in the interferon arm spent an average of 5.8 months with at least one incident of grade 3 or 4 toxicity followed by an average of 33.1 months without toxicity before relapse or death. Patients in the control group experienced no severe toxic events and had 30.0 months on average before relapse or death. Because the Q-TWIST scores were not generated by patient assessments of their own health states, any difference in average scores between treatment groups may not be clinically meaningful.

A second Q-TWIST analysis was conducted using data from both the ECOG 1684 and 1690 studies (21). The findings were almost identical for the ECOG study: during 84 months of follow-up, patients receiving interferon spent an average of 31.5 months without toxicity or tumour recurrence and an average of 7.4 months with at least one incident of grade 3 or 4 toxicity. Patients in the control group in that study spent an average of 30.0 months without toxicity or tumour recurrence and experienced no toxicity. During 52 months of follow-up, patients receiving high-dose interferon in the ECOG 1690 study experienced an average of 23.9 months without toxicity or tumour recurrence and 7.5 months with at least one incident of grade 3 or 4 toxicity, compared to 28.7 months and 0.0 months, respectively, for patients in the observation arm. Although those studies suffer from a number of methodological flaws, their results are somewhat reassuring on that, despite its toxicity, high dose interferon is associated with an improvement in quality-of-life-adjusted survival.

Adverse effects
Evidence concerning the risks of high-dose interferon therapy is available from the published reports of the trials described above (7-9,18) and one case report (23). In the trial of high-dose interferon alpha-2a reported by Creagan et al, 44% of patients in the interferon group experienced grade 3 flu-like symptoms and 57% had changes in liver function (i.e. twofold increase in AST levels) (18). Over the course of follow-up (median = 6.1 years), 45% of patients randomized to treatment with interferon for 12 weeks had a worsening in ECOG performance score compared with 16% in the observation group (p<0.0001). Sixty-seven percent of patients in the ECOG 1684 study reported by Kirkwood et al experienced severe
(grade 3 or greater) toxicity, including constitutional and neurologic symptoms, myelosuppression and hepatotoxicity, with 9% of patients having life-threatening toxicities (7). As a consequence, the dose was reduced or the treatment delayed in 35% of patients because of toxicity. The average daily dose delivered in this trial was 18.0 U/m² for the induction phase and 8.1 U/m² for the maintenance phase. Importantly, two patients in the interferon arm died as a result of hepatotoxicity early in the trial. As a consequence, monitoring of liver function became more stringent, and no further deaths have occurred on this regimen in that study or the follow-up study (J. Kirkwood, personal communication).

No treatment-related deaths occurred on high-dose interferon in the ECOG 1690 trial (8). Dose was reduced or treatment delayed for 58% of patients during the induction phase of high-dose interferon therapy and for 59% during maintenance treatment (8). The average daily dose of interferon delivered to the high-dose arm was 18.5 U/m² for the induction phase and 8.2 U/m² for the maintenance phase. A range of serious adverse events, including neurologic and GI symptoms, occurred much more often in the high-dose group than with low-dose interferon. Grade 3 or 4 liver toxicity was reported for 29% of the high-dose interferon patient group, 4% of the low-dose interferon group, and 3% of the observation group. Grade 3 or 4 leukopenia was reported for 14% of the high-dose interferon patient group, 1% of the low-dose interferon group, and none in the observation group.

In the ECOG 1694 trial, the most common grade 3 or 4 toxicities associated with high-dose interferon therapy included fatigue (21% of patients), leukopenia (60%), elevation of liver enzymes (27%), and neurologic symptoms. Ten percent of patients discontinued treatment with interferon because of adverse effects. No treatment-related deaths were reported. The most common grade 3 or 4 adverse effect reported in the vaccine arm was injection-site reactions (2.3% of patients).

A letter to the Lancet described a death, possibly due to rhabdomyolysis secondary to adjuvant interferon therapy, four days into treatment with interferon alpha-2b at a dose of 20X10⁶ U/m², the regimen used in the ECOG 1684 study (23).

**Low-Dose Interferon Alpha**

Five randomized trials comparing low-dose interferon alpha with observation (24-28) and one trial comparing low-dose interferon alpha plus interleukin-2 with observation were located (29) (Table 5 and 6).

A full report of the trial by the French Cooperative Group on Melanoma was published by Grob et al in 1998 (24). That trial included 499 patients with melanoma lesions greater than 1.5 mm in depth without clinical evidence of lymph node metastasis who were randomized to low-dose interferon alpha-2a for 18 months or to no adjuvant treatment. Only 22% of the participants in the trial met the definition for the target population for this practice guideline. There were 59 deaths in the interferon group and 76 in the observation group (HR, 0.72; 95% CI, 0.51 to 1.01). In the interferon group, 52% of patients experienced flu-like symptoms. Ten percent of patients on low-dose interferon reported grade 3 or 4 adverse effects, but there were no treatment-related deaths. The most frequently reported serious adverse effects were asthenia (2% of patients) and depression (1%).

The Austrian Malignant Melanoma Cooperative Group (Pehamberger et al) has completed a trial (25) with the same design and population as the French trial described above (24). The dose of interferon used was the same as the French study (low dose) but the schedule of administration was different. Twenty-seven percent of participants had tumours more than 4.0 mm thick and none had clinical evidence of nodal disease. Seventeen patients in the interferon group and 21 in the control (observation only) group died during the study (Table 6). Overall survival curves were not presented, and the hazard ratio for death was not reported. The Scottish study randomized patients with primary melanomas at least 3.0 mm
thick, or with evidence of regional nodal involvement, to low-dose interferon therapy for six months or to observation (26). Only 95 patients were randomized before the trial was closed. The full report seems to indicate that the trial was closed prematurely due to poor accrual. An initial significant improvement in disease-free survival with interferon was not maintained at longer follow-up. The authors reported an improvement in disease-free and overall survival with interferon but note that the sample size was too small to detect meaningful differences.

Cascinelli et al reported the results of the World Health Organization (WHO) adjuvant melanoma trial comparing low-dose interferon to observation in 444 patients with resected nodal melanoma (27). Though the therapy was well tolerated, they observed no difference in either disease-free or overall survival. Similarly, Hancock et al have reported on a United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR) trial in which 674 patients with completely resected high-risk melanoma were randomized to receive low-dose interferon alpha for two years or no further therapy (28). After a median follow-up period of 3.1 years, no significant differences in overall (p=0.6) or relapse-free survival (p=0.3) were detected between interferon and observation. Finally, Hauschild et al have recently reported the results of a trial of low-dose interferon plus interleukin-2 recently (29). Two hundred and twenty-five patients with melanomas more than 1.5 mm thick and no clinical evidence of nodal metastases were randomized to treatment for 48 weeks with interferon (3x10^6 U subcutaneously) plus interleukin-2 or to observation. After a median observation period of 6.6 years, they had not detected a significant difference in overall survival between treatment and control has been detected (p=0.93).

**Published Meta-analyses and Systematic Reviews of Interferon Alpha (High- and Low-Dose)**

Wheatley et al reported on a literature-based meta-analysis of 12 randomized trials of adjuvant interferon versus observation in melanoma (13). The results indicate that recurrence-free survival was improved with interferon alpha (HR for recurrence, 0.83; 95% CI, 0.77 to 0.90; p=0.000003), corresponding to a 17% reduction in the odds of recurrence. There was no clear benefit for survival (HR for mortality, 0.93; 95% CI, 0.85 to 1.02; p=0.1), corresponding to a 7.3% reduction in the odds of death. It should be noted that the above meta-analysis did not include the ECOG 1694 trial. However, Wheatley et al pooled the vaccine trial with the remaining two ECOG studies and reported no evident survival benefit (HR 0.85; 95% CI, 0.72 to 1.01; p=0.06). Further subgroup analyses were conducted to examine evidence for a dose-response relationship and indicated a significant trend for increasing benefit of interferon with increasing dose in terms of recurrence-free but not overall survival. The authors have stressed the need for more mature data and an individual patient data meta-analysis.

A second literature-based meta-analysis of nine randomized trials of interferon versus observation was published by Pirard et al (14). Similar to the findings of Wheatley, that study detected an improvement in the relapse rate with interferon (odds ratio [OR], 0.74; 95% CI, 0.64 to 0.86), but with no improvement in overall survival.

Lens and Dawes have also recently reported the results of a systematic review of RCTs of interferon but did not include information from ECOG 1694 in their analysis (6). They evaluated the quality of eight published trials of adjuvant interferon, some of which included patients with a lower risk of recurrence than that report, and noted that the quality scores ranged from a low of 22 to a high of 71 out of maximal score of 81. They concluded there was no clear overall survival benefit from interferon and that larger studies were needed to establish the effect of interferon alpha and to identify subgroups of patients who might benefit from adjuvant therapy with interferon. No pooling of trials was undertaken.
Interferon Gamma

Two trials were located that included interferon gamma as an experimental arm (Table 5 & 6) (15,16). The SWOG study was closed early because a planned interim analysis revealed that the control group was faring better than expected in terms of survival (relative risk, 1.31; 95%CI, 0.88 to 1.95; p=0.18) and that the likelihood of finding that interferon gamma would reduce the risk of death by 25% or more was extremely remote (15).

Kleeberg et al have reported the results of a randomized trial comparing low-dose interferon alpha (10X10^6 U subcutaneously for 12 months), interferon gamma (0.2 mg subcutaneously for 12 months), or observation (EORTC 18871) (23). At some centres, a fourth treatment arm was included to investigate Iscador M®. A total of 830 patients were included. After a median follow-up of 8.2 years, no significant improvements in disease-free survival or overall survival were detected for interferon alpha, interferon gamma, or Iscador M®. At some centers, a fourth treatment arm was included to investigate *Viscum album praeparatum mali* (Iscador M®). A total of 830 patients were included. After a median follow-up of 8.3 years, no significant improvements in disease-free survival or overall survival were detected for any of the treatment arms.

Table 5. RCTs of interferon as adjuvant treatment in high-risk melanoma: patient and trial characteristics.

<table>
<thead>
<tr>
<th>Author, year (Reference)</th>
<th># pts. rand. (# eval.)</th>
<th>Stage (# of pts.)</th>
<th>Treatment arm</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose interferon alpha</td>
<td></td>
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<tr>
<td>Creagan, 1995 (18) (NCCTG)</td>
<td>264 (262)</td>
<td>Node-negative, thickness &gt;1.69 mm (102) Regional nodal disease (160)</td>
<td>IFN α2a Observation</td>
<td>20X10^6 U/m2 im 3x/wk for 12 wks</td>
</tr>
<tr>
<td>Kirkwood, 1996 (7) (ECOG 1684)</td>
<td>287 (280)</td>
<td>Stage IIIB: (thickness &gt;4 mm) (31) III (regional nodal disease): -not clinically apparent (34) -clinically apparent (41) -recurrence (174)</td>
<td>IFN α2b Observation</td>
<td>20X10^6 U/m2 iv 5 d/wk for 4 wks; 10X10^6 U/m2 sc 3x/wk for 48 wks</td>
</tr>
<tr>
<td>Kirkwood, 2000 (8) (ECOG 1690)</td>
<td>642 (608)</td>
<td>Stage IIIB (thickness &gt;4mm) (163) III (regional nodal disease): -not clinically apparent (68) -clinically apparent (83) -recurrence (326)</td>
<td>High-dose IFN α2b Low-dose IFN α2b Observation</td>
<td>(as in ECOG 1684) Emulsiolipid 1mL sc d1,8,15,22, then q12wks</td>
</tr>
<tr>
<td>Kirkwood, 2001 (9) (ECOG 1694)</td>
<td>880 (774)</td>
<td>Node-negative (202) Micrometastases (315) Macrometastases (306) Ulceration: No (416)</td>
<td>High-dose IFN α2b GMK vaccine</td>
<td>(as in ECOG 1684) 1mL sc d1,8,15,22, then q12wks</td>
</tr>
<tr>
<td>Author, year (Reference)</td>
<td># pts. rand. (# eval.)</td>
<td>Stage (# of pts.)</td>
<td>Treatment arm</td>
<td>Dose</td>
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<tr>
<td>--------------------------</td>
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<tr>
<td>Mitchell, 2003 (19) [abstract]</td>
<td>600 (455)</td>
<td>Resected stage III melanoma</td>
<td>High-dose IFN α2b</td>
<td>(as in ECOG 1690) 5X106 U/m2 3x/wk for 2 yrs + allogeneic melanoma vaccine (Melacine) for 2 yrs</td>
</tr>
<tr>
<td>Grob, 1998 (24) (France)</td>
<td>499 (489)</td>
<td>Thickness &gt; 1.5 mm, No clinically detectable nodal metastases</td>
<td>IFN α2a Observation</td>
<td>3X106 U sc 3X/wk for 18 mos.</td>
</tr>
<tr>
<td>Pehamberger, 1998 (25) (Austria)</td>
<td>311 (311)</td>
<td>Thickness ≥ 1.5 mm, No clinically detectable nodal metastases</td>
<td>IFN α2a Observation</td>
<td>3X106 U sc daily for 3 wks, then 3X/wk for 1 yr.</td>
</tr>
<tr>
<td>Cameron, 2000 (26) (Scotland)</td>
<td>96 (94)</td>
<td>Thickness ≥ 3 mm or regional lymph node metastases.</td>
<td>IFN α2b Observation</td>
<td>3X106 U sc 3X/wk for 6 mos.</td>
</tr>
<tr>
<td>Cascinelli, 2001 (27) (WHO)</td>
<td>444 (426)</td>
<td>Node-negative (12) Nodal metastases (432) Ulceration: No (163) Yes (159) Not assessed (112)</td>
<td>IFN α2a Observation</td>
<td>3X106 U sc 3x/wk for 3 yrs.</td>
</tr>
<tr>
<td>Hancock, 2004 (28) (UKCCCR)</td>
<td>674 (674)</td>
<td>Localized (130) Locally metastatic (74) Regionally metastatic at diagnosis (85) Regionally metastatic at recurrence (385)</td>
<td>IFN α2a Observation</td>
<td>3X106 U 3x/wk for 2 yrs.</td>
</tr>
<tr>
<td>Hauschild, 2003 (29)</td>
<td>225 (223)</td>
<td>Thickness &gt; 1.5 mm without lymph node metastases.</td>
<td>IFN α2b plus IL-2 Observation</td>
<td>IFN 3X106 U/m2 sc daily for 1 wk, then 3x/wk for 4 wks IL-2 9X106 IU/m2 sc d8-11 (both cycles repeated q6wks. x 8)</td>
</tr>
<tr>
<td>Interferon gamma</td>
<td></td>
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</tr>
<tr>
<td>Meyskens, 1995 (15) (SWOG)</td>
<td>284 (202)</td>
<td>Thickness ≥ 1.5 mm (74) Regional nodal metastases (128)</td>
<td>IFN γ Observation</td>
<td>0.2 mg/d sc for 1 yr</td>
</tr>
<tr>
<td>Kleeberg, 2004 (16) (EORTC)</td>
<td>830 (830)</td>
<td>Stage IIb (340) Stage III (490)</td>
<td>IFN α2b IFN γ Iscador-M® Observation</td>
<td>1X106 U sc qod 0.2 mg/d sc qod sc 3x/wk</td>
</tr>
</tbody>
</table>

NOTES: CI = confidence interval; d = day; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; eval. = number of patients evaluated; HR = hazard ratio; IL-2
 interleukin-2; im = intramuscularly; IFN = interferon; iv = intravenously; mos. = months; NCCTG = North Central Cancer Treatment Group; NR = not reported; obs = observation; q = every; qod = every other day; rand. = number of patients randomized; ref. = reference number; sc = subcutaneously; SWOG = Southwest Oncology Group; UKCCCR = United Kingdom Coordinating Committee on Cancer Research; vs. = versus; WHO = World Health Organization; wk(s) = week(s); yr(s) = year(s).
* abstracted from survival curves.
Table 6. RCTs of interferon as adjuvant treatment in high-risk melanoma: outcomes.

<table>
<thead>
<tr>
<th>Author, year (Reference)/ Treatment arm</th>
<th># pts rand. (# eval.)</th>
<th>Median follow-up (yrs)</th>
<th>Survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 yrs</td>
</tr>
<tr>
<td>Creagan, 1995 (18) (NCCTG) IFN-α2a Observation</td>
<td>264 (262)</td>
<td>6.1</td>
<td>73*</td>
</tr>
<tr>
<td>Kirkwood, 1996 (7) (ECOG 1684) IFN-α2b Observation</td>
<td>287 (280)</td>
<td>6.9</td>
<td>63*</td>
</tr>
<tr>
<td>Kirkwood, 2000 (8) (ECOG 1690) HDI-α2b LDI-α2b Observation</td>
<td>642 (608)</td>
<td>4.3</td>
<td>72*</td>
</tr>
<tr>
<td>Kirkwood, 2001 (9) (ECOG 1694) HDI-α2b GMK vaccine</td>
<td>880 (774)</td>
<td>1.3</td>
<td>78*</td>
</tr>
<tr>
<td>Mitchell, 2003 (19) [abstract] HDI-α2b LDI-α2b + allogeneic melanoma vaccine</td>
<td>600 (455)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Grob, 1998 (24) (France) IFN-α2a Observation</td>
<td>499 (489)</td>
<td>5.0</td>
<td>92*</td>
</tr>
<tr>
<td>Pehamberger, (25)1998 (Austria) IFN-α2a Observation</td>
<td>311 (311)</td>
<td>3.4 (mean)</td>
<td>NR</td>
</tr>
<tr>
<td>Cameron, 2000 (26) (Scotland) IFN-α2b Observation</td>
<td>96 (94)</td>
<td>6.5</td>
<td>60*</td>
</tr>
<tr>
<td>Cascinelli, 2001 (27) (WHO) IFN-α2a Observation</td>
<td>444 (426)</td>
<td>7.3</td>
<td>60*</td>
</tr>
<tr>
<td>Hancock, 2004 (28) (UKCCCR) IFN-α2a Observation</td>
<td>674 (674)</td>
<td>3.1</td>
<td>64*</td>
</tr>
<tr>
<td>Author, year (Reference)/ Treatment arm</td>
<td># pts rand. (# eval.)</td>
<td>Median follow-up (yrs)</td>
<td>Survival rate (%)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Hauschild, 2003 (29) IFN-α2b plus IL-2</td>
<td>225 (223)</td>
<td>6.6</td>
<td>95* 92* 78* 79*</td>
</tr>
<tr>
<td>IFN-γ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meyskens, 1995 (15) (SWOG) IFN-γ Observation</td>
<td>285 (202)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Kleeberg, 2004 (16) (EORTC) IFN-α2b</td>
<td>830 (830)</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>IFN-γ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iscador-M® Observation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTES: ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; eval. = number of patients evaluated; HDI = high dose interferon; IFN = interferon; IL-2 = interleukin-2; LDI = low dose interferon; NCCTG = North Central Cancer Treatment Group; NR = not reported; rand. = number of patients randomized; SWOG = Southwest Oncology Group; UKCCCR = United Kingdom Coordinating Committee on Cancer Research; WHO = World Health Organization; yr(s) = year(s).

* Data were abstracted from survival curves.
† p=0.023.
‡ Survival calculated using the mortality rate (death related to melanoma): 17 patients died in IFN group (n=154) vs. 21 patients in the Observation group (n=157).

Levamisole

Levamisole is an anti-helminthic with disputed immunostimulatory properties in vitro. On the basis of that activity, levamisole has been investigated as adjuvant therapy in a number of cancers. Apart from results as adjuvant therapy in colon cancer when combined with a cytotoxic agent, the trials in other cancers have been negative.

There are four randomized controlled trials of levamisole in melanoma (Table 7), of which three are placebo-controlled (30-33). The (NCIC) study (34) enrolled a heterogeneous group of patients with 50% being at high risk of recurrence (personal communication, B. Zee). The total dose of levamisole used in this level I study was 800 mg over a two-week period for an 80 kg individual. Three smaller trials evaluated total doses of 450 mg (31,31), 600 mg (32), and 600 to 1000 mg (33) over a two-week period. Whether those differences in dose are substantive is difficult to know in the absence of any data that demonstrate a dose-response relationship for levamisole with any measure of activity.

Survival data from those four trials are summarized in Table 7. Although the initial report by Spitler et al (31) described a survival trend in favour of levamisole compared with placebo in the subgroup of patients without lymph node disease (p=0.07, two-sided), there was no survival difference between treatments for the total study population. That lack of benefit was confirmed by a subsequent report of long-term follow-up (30). Loutfi et al (32) and Lejeune et al (33) concluded that there was no meaningful impact on survival with levamisole compared with placebo. The only study in which levamisole had an impact, albeit a marginal one, was the study from the NCIC (34) in which there was a statistically significant difference in the survival rate in favour of levamisole when the five-year point estimates of
overall survival were assessed (78% for levamisole versus 62% for control, p=0.027, 2-sided). However, when the whole survival experience was compared between the groups, the difference in survival was not significant (p=0.08, two-sided). That difference represented a risk reduction in mortality of 29% and was observed in all risk groups, including the group to which this systematic review is directed.

Without an intermediate marker of activity for levamisole, it is impossible to categorically state whether or not there are substantive differences in the regimens used in those four trials. This systematic review is directed at a specific segment of the population involved in those trials. While a meta-analysis restricted to data from the high-risk subgroup might help to reconcile the seemingly disparate findings, survival results are not reported separately for that patient subgroup, and data for individual cases are generally not available. However, it is our belief that the regimens evaluated are unlikely to be substantially different in their clinical activity and that the impact of levamisole does not differ across risk groups. A meta-analysis of five-year death rates (Figure 2), abstracted from survival curves in published reports, yields a risk ratio of 0.94 (95% CI, 0.75 to 1.20; p=0.6). No heterogeneity was found among the results from these studies (p=0.19).

After the review of the available information with respect to levamisole, we have concluded that, if levamisole has an impact on the clinical course of malignant melanoma when given in the adjuvant setting, that effect is marginal.

**Adverse effects**

Morbidity from levamisole is generally mild, although it was severe enough to result in discontinuation of therapy in 41% of patients in the NCIC study (34), 44% in the Loutfi et al study (compared with 16% in the placebo group) (32), and 17% in the Lejeune et al study (compared with no patients in the placebo group) (33). Data on toxicity was reported for two of the placebo-controlled trials (32,33). In the study by Loutfi et al, 22% of patients on levamisole reported a flu-like syndrome (compared with 3% on placebo), 14% reported nausea and vomiting (compared with 8% on placebo), and 14% reported musculoskeletal symptoms (compared with no patients on placebo) (32). The most commonly reported adverse events in the Lejeune et al study were nausea and vomiting (27% with levamisole versus 10% with placebo), weakness (27% versus 14%), and anorexia (22% versus 8%) (33). Hematologic abnormalities were noted for 7% of patients on levamisole and none of the placebo group in the Loutfi et al study (32), and for 16% and 5%, respectively, of those groups in the Lejeune et al study (33). No treatment-related mortality has been observed in the four levamisole studies summarized here.
Table 7. Randomized controlled trials of levamisole as adjuvant treatment in high-risk melanoma.

<table>
<thead>
<tr>
<th>Author, year (Reference)</th>
<th>Stage (number of patients)</th>
<th># rand (# eval)</th>
<th>Treatment groups</th>
<th>Median follow-up (years)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spitler, 1980, 1991 (30,31)</td>
<td>Primary, local recurrence or in transit metastasis - thickness: ≤0.75 mm (6) 0.76-1.24 mm (21) 1.25-3.99 mm (55) ≥4.0 mm (24) Lymph node disease (90) Metastasis beyond regional lymph node drainage (4)</td>
<td>203 (200)</td>
<td>Levamisole 150 mg for 3 d q2wks for 2 yrs. Placebo</td>
<td>10.5</td>
<td>2 yrs 79%* 78%* 5 yrs 62%* 64%* 10 yrs 52%* 47%*</td>
</tr>
<tr>
<td>Loutfi, 1987 (32)</td>
<td>Node-negative, Clark level III, IV &amp; V - thickness: ≤0.75 mm (16) 0.76-1.49 mm (25) 1.50-3.99 mm (34) ≥4.0 mm (7) not assessed (55)</td>
<td>156 (137)</td>
<td>Levamisole 150 mg 2x/wk for 3 yrs. Placebo</td>
<td>5.0</td>
<td>2 yrs 92%* 93%* 5 yrs 74%* 80%*</td>
</tr>
<tr>
<td>Lejeune, 1988 (33) (EORTC)†</td>
<td>Node-negative, Clark level III, IV &amp; V - thickness: ≤1.5mm (27) 1.5-3.0 mm (77) &gt;3.0 mm (60) unknown (110)</td>
<td>325 (274)</td>
<td>Levamisole 150-250 mg 2x/wk for 2 yrs. Placebo</td>
<td>4.6</td>
<td>2 yrs 85%* 85%* 5 yrs 56%* 56%*</td>
</tr>
<tr>
<td>Quirt, 1991 (34) (NCIC-CTG)‡</td>
<td>Thickness: 0.76-1.5 mm (152) 1.51-4.0 mm (183) &gt;4.0 mm (57) unknown (2) Satellitosis, in-transit or node-positive (149)</td>
<td>577 (543)</td>
<td>Levamisole 2.5 mg/kg 2x/wk for 3 yrs. Observation</td>
<td>8.5</td>
<td>2 yrs 78%* 80%* 5 yrs 74% (p=0.027 vs. control at 5 yrs) 62%</td>
</tr>
</tbody>
</table>

NOTES: d = day(s); EORTC = European Organization for Research and Treatment of Cancer; eval. = number of patients evaluated; NCIC-CTG = National Cancer Institute of Canada Clinical Trials Group; q = every; rand. = number of patients randomized; ref. = reference number; vs. = versus; wk(s) = week(s); yrs = years.

* abstracted from survival curves.
† This trial also included a dacarbazine arm - see Table 9 for details.
‡ This trial also included BCG and levamisole plus BCG arms.
Vaccines

Nine randomized trials of vaccines are summarized in Table 8, one of a viral oncolysate (35), one of a ganglioside (36), one of a polyvalent vaccine (37), one of vaccinia melanoma cell lysate (38), and five of whole-cell vaccines (39-43). Six RCTs compared vaccine with observation, while three trials were double-blind (35-37). Seven of the nine trials were confined to patients with nodal involvement, and the majority of patients in one of the other trials were node positive (41). None of the reported trials have shown a statistically significant improvement in overall survival for patients treated with vaccines, an observation confirmed in a recent update of the SWOG 9035 trial (44). However, in that study, the subset analysis of patients who were positive for human leukemic antigen (HLA)-A2 and/or HLA-C3 demonstrated a significant five-year overall survival benefit of 93% for vaccine patients compared with 74% for patients in the observation group (p=0.009). This clearly hypothesis-generating observation cannot be used to direct clinical decisions. For obvious reasons attesting to heterogeneity of the studies and vaccines employed, we have elected not to pool those data in our analysis.

Table 8. Randomized controlled trials of vaccine as adjuvant treatment in high-risk melanoma.

<table>
<thead>
<tr>
<th>Author, year (Reference)</th>
<th>Stage, number of patients</th>
<th># rand. (# eval.)</th>
<th>Treatment groups</th>
<th>Median follow-up (years)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vaccine</td>
</tr>
<tr>
<td>McIlmurray, 1977 (39)</td>
<td>Lymph node metastases</td>
<td>15 (15)</td>
<td>Autologous irradiated tumour cells plus BCG Observation</td>
<td>Followed for at least 2 years.</td>
<td>1 yr 50%</td>
</tr>
<tr>
<td></td>
<td># positive nodes:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;4 (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aranha, 1979 (40)</td>
<td>Palpable “clinically involved” regional nodes.</td>
<td>31 (31)</td>
<td>VCN treated autochthonous tumour cells plus BCG Observation</td>
<td>1.3</td>
<td>1 yr 84%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher, 1981 (41) (NCI)†</td>
<td>Node-negative, Clark level IV with thickness &gt;2.25 mm or level V with local recurrence (30)</td>
<td>181 (166)</td>
<td>Neuraminidase-treated allogeneic cells plus BCG Observation</td>
<td>2.4</td>
<td>2 yrs 65%*</td>
</tr>
<tr>
<td></td>
<td>Lymph node metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td># positive nodes:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-2 (71)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;2 (65)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morton, 1982‡ (42)</td>
<td>Lymph node metastases</td>
<td>149 (140)</td>
<td>Allogeneic melanoma cells plus BCG Observation</td>
<td>4.2 (mean)</td>
<td>2 yrs 59%*</td>
</tr>
<tr>
<td></td>
<td>-clinically positive (102)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-clinically negative (38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, year (Reference)</td>
<td>Stage, number of patients</td>
<td># rand. (# eval.)</td>
<td>Treatment groups</td>
<td>Median follow-up (years)</td>
<td>Survival</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>-------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Livingston, 1994 (36)</td>
<td>Lymph node metastases # positive nodes: 1 (51) 2-4 (46) &gt;4 (25)</td>
<td>123 (122)</td>
<td>GM2/BCG vaccine BCG alone (double-blind)</td>
<td>5.25</td>
<td>2 yrs 50%* 4 yrs 48%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control 33%* 29%*</td>
</tr>
<tr>
<td>Wallack, 1998 (35)</td>
<td>Lymph node metastases # positive nodes: 1 (107) 2-3 (74) 4-5 (18) &gt;5 (18)</td>
<td>250 (217)</td>
<td>Vaccinia melanoma oncolysate Placebo: live vaccinia virus</td>
<td>3.9</td>
<td>2 yrs 70% 3 yrs 60% 5 yrs 49%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control 66% 56% 48%</td>
</tr>
<tr>
<td>Bystryn, 2001 (37)</td>
<td>Lymph nodes clinically palpable at presentation or ≥ 2 histologically positive nodes.</td>
<td>38 (38)</td>
<td>Polyclonal, shed antigen, melanoma vaccine Placebo vaccine (human albumin)</td>
<td>2.5</td>
<td>1 yr 83% 2 yrs 67% 3 yrs 53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control 77% 61% 33%</td>
</tr>
<tr>
<td>Hersey, 2002 (38)</td>
<td>Stage IIB (161) Stage III 1 positive lymph node (319) ≥ 2 (220)</td>
<td>700 (673)</td>
<td>Vaccinia melanoma cell lysates Observation</td>
<td>20</td>
<td>5 yrs 60% 10 yrs 53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Observation 55% 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ITT analysis; HR, 0.83; 95% CI, 0.67-1.04; p=0.11</td>
</tr>
<tr>
<td>Sondak, 2002 (43) (SWOG)</td>
<td>Node-negative, Clark’s level IV or thickness 1.5 - 4.0 mm.</td>
<td>689 (600)</td>
<td>Allogeneic melanoma vaccine Observation</td>
<td>5.6</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control NR</td>
</tr>
</tbody>
</table>

NOTES: BCG = Bacillus Calmette-Guérin; CI = confidence interval; eval. = number of patients evaluated; HR = hazard ratio; ITT = intent-to-treat; NCI = National Cancer Institute; NR = not reported; q = every; rand. = number of patients randomized; ref. = reference number; SWOG = Southwest Oncology Group; VCN = Vibrio cholerae neuroaminidase; yr(s) = year(s).

* abstracted from survival curves.
† This trial also included BCG and methyl-CCNU arms - see Table 9 for details.
‡ This trial also included a BCG arm.

Chemotherapy
Ten trials of chemotherapy are summarized in Table 9 (33,41,45-52). None of the trials were limited to high-risk patients. Two trials compared dacarbazine with observation (45,46), one compared dacarbazine with placebo (33), and five trials evaluated dacarbazine in combination with other agents (including immunomodulatory agents such as BCG) that are not commonly used at present, against observation alone (47-51). There was also a trial of methyl lomustine (methyl-CCNU) versus control (41) and a trial of carmustine (BCNU) combined with actinomycin-D and vincristine versus control (52).

In the largest study of chemotherapy (46), 47% of patients treated with dacarbazine were alive after three years compared with 42% of control (p=0.64). Only the study by
Hansson et al (49) reported a statistically significant survival benefit for patients who received chemotherapy as adjuvant treatment \( (p<0.025) \). That was the smallest of the chemotherapy trials, with only 26 patients randomized to three treatment groups. Data from the two active-treatment arms (dacarbazine alone and dacarbazine in combination with CCNU and vincristine) were combined and compared with results for nine patients in the control group, but that trial is far too small to permit any conclusions.

Three-year mortality rates, from the text or from survival curves in the published reports from seven studies, were pooled and are presented in Figure 3. Three studies were not included in the meta-analysis because the number of deaths at three years could not be ascertained (45,51) or because no survival data were reported (47). The mortality risk ratio from the pooled analysis \( (0.94; 95\% \text{ CI}, 0.84 \text{ to } 1.06; \ p=0.3) \) does not demonstrate any difference between chemotherapy and control. No heterogeneity was found among the results from these studies \( (p=0.52) \).

Because response rates to chemotherapy in advanced disease have been unsatisfactory, there is no current interest in pursuing chemotherapy alone in the adjuvant setting.

Chemotherapy plus Interferon
A single trial of three cycles of a single dose of dacarbazine followed by interferon alpha-2a \( (9\times10^6 \text{ U daily for three weeks}) \) compared with observation in 26 patients with melanoma lesions between 1.50 and 5.00 mm in depth was closed early (53). At a median follow-up of 4.5 years, there had been two deaths in the control group and eight in the adjuvant therapy group.

### Figure 3.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Chemotherapy</th>
<th>Control</th>
<th>RR (random) 95% CI</th>
<th>Weight</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher</td>
<td>29/46</td>
<td>20/43</td>
<td>9.35</td>
<td>0.36</td>
<td>1.08</td>
</tr>
<tr>
<td>Veronesi</td>
<td>126/242</td>
<td>124/213</td>
<td>5.27</td>
<td>0.27</td>
<td>0.91</td>
</tr>
<tr>
<td>Persico</td>
<td>1/17</td>
<td>2/3</td>
<td>2.61</td>
<td>0.27</td>
<td>1.29</td>
</tr>
<tr>
<td>Kaaks et al.</td>
<td>10/25</td>
<td>9/23</td>
<td>7.43</td>
<td>0.27</td>
<td>1.21</td>
</tr>
<tr>
<td>Lentz et al.</td>
<td>31/96</td>
<td>30/118</td>
<td>6.72</td>
<td>0.27</td>
<td>0.72</td>
</tr>
<tr>
<td>Qin et al.</td>
<td>16/49</td>
<td>25/47</td>
<td>24.66</td>
<td>0.27</td>
<td>0.72</td>
</tr>
<tr>
<td>Kaniovskis et al.</td>
<td>51/88</td>
<td>56/88</td>
<td>24.66</td>
<td>0.27</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Total (95\% CI) 560 544
Total events: 262 (Chemotherapy), 265 (Control)
Test for heterogeneity: Q(6) = 6.22, df = 6 (p = 0.52), I^2 = 0%
Test for overall effect: Z = 1.64 (p = 0.33)
Table 9. Randomized controlled trials of chemotherapy as adjuvant treatment in high-risk melanoma.

<table>
<thead>
<tr>
<th>Author, year (Reference)</th>
<th>Stage, number of patients</th>
<th># rand. (# eval.)</th>
<th>Treatment groups</th>
<th>Median follow-up (years)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-agent dacarbazine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lejeune, 1988 (33) (EORTC)†</td>
<td>Node-negative, Clark level III, IV &amp; V - thickness: ≤1.5mm (27) 1.5-3.0 mm (77) &gt;3.0 mm (60) unknown (110)</td>
<td>325 (274)</td>
<td>Dacarbazine 250 mg/m2, for 5d q28d for 6 cycles Placebo</td>
<td>4.0</td>
<td>3 yrs 4 yrs 68%* 61%* 74%* 69%*</td>
</tr>
<tr>
<td>Hill, 1981 (45) (COG)</td>
<td>Localized primary or solitary recurrent melanoma (64) Lymph node metastases (157) Metastasis to distant site (47)</td>
<td>174 (165)</td>
<td>Dacarbazine 4 courses of 4.5 mg/kg/d for 10d over 1 yr Observation</td>
<td>2.5</td>
<td>At last follow-up 43% 55%</td>
</tr>
<tr>
<td>Veronesi, 1982† (46)</td>
<td>Node-negative, Clark level III, IV &amp; V (98) Lymph node metastases # involved regional nodes: 1 (290) 2-3 (200) ≥4 (134) unknown (39)</td>
<td>931 (761)</td>
<td>Dacarbazine 24 cycles of 200 mg/m2 for 5d Observation</td>
<td>3.4 (mean)</td>
<td>3 yrs 47% 42%</td>
</tr>
<tr>
<td><strong>Dacarbazine in combination with other agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacquillat, 1982 (47)</td>
<td>Primary malignant melanoma - Clark’s level III, IV or V.</td>
<td>117 (117)</td>
<td>Dacarbazine 80 mg/m2 x5d (twice before surgery) Vinblastine 60 mg/m2 Thiopeta 60 mg/m2 Rucromycin 60 µg/m2 Methotrexate 30 mg/m2 Procarbazine 30 mg/2/d x7d</td>
<td>NR</td>
<td>NR NR NR</td>
</tr>
<tr>
<td>Quirt, 1983 (48)</td>
<td>Node-negative, Clark level III, IV &amp; V (57) In-transit or lymph node metastases (37)</td>
<td>94 (94)</td>
<td>Dacarbazine 2 injections of 850 mg/m2 4 wks apart plus BCG Observation</td>
<td>6.4</td>
<td>3 yrs 61% 47%</td>
</tr>
<tr>
<td>Author, year (Reference)</td>
<td>Stage, number of patients</td>
<td># rand. (# eval.)</td>
<td>Treatment groups</td>
<td>Median follow-up (years)</td>
<td>Survival</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------------</td>
<td>------------------</td>
<td>------------------</td>
<td>--------------------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Hansson, 1985 (49)</strong></td>
<td>Clinical stage I (thickness &gt;2.25 mm) or Clark level IV or V (18) Regional lymph node metastases (8)</td>
<td>26 (26)</td>
<td>Dacarbazine 250 mg/m2 for 5d q4wks for 1 yr or Dacarbazine, CCNU &amp; vincristine Observation</td>
<td>3.7</td>
<td>3 yrs 95%* 79%* 4 yrs 94% 52%</td>
</tr>
<tr>
<td><strong>Karakousis, 1987 (50)</strong></td>
<td>Node-negative, Clark level II, III, IV &amp; V (50) Metastases to regional lymph nodes (7) Regional lymphatic recurrence (25)</td>
<td>82 (82)</td>
<td>Dacarbazine 200 mg/m2 for 5d q4wks for 1 yr plus Estracyt 15 mg/kg daily for 1 yr Observation</td>
<td>6.1</td>
<td>3 yrs 59%* 68%* 4 yrs 55%* 68%* 6 yrs 55%* 56%*</td>
</tr>
<tr>
<td><strong>Fisher, 1981 (41) (NCI)§</strong></td>
<td>Node-negative, Clark level IV with thickness &gt;2.25 m or level V or with local recurrence (30) Lymph node metastases # positive nodes: 1-2 (71) &gt;2 (65)</td>
<td>181 (166)</td>
<td>Methyl-CCNU 200 mg/m2 q6 wks for 18 mos Observation</td>
<td>2.4</td>
<td>2 yrs 68%* 70%* 3 yrs 51%* 54%*</td>
</tr>
<tr>
<td><strong>Karakousis, 1993 (52)</strong></td>
<td>In-transit metastases 12 Regional node metastases 107 In-transit &amp; regional 20 Distant metastases 34</td>
<td>173 (173)</td>
<td>BCNU 80 mg/m2 iv q4wks plus actinomycin-D 10 µg/kg plus vincristine 1.0 mg/m2 iv q2wks Observation</td>
<td>4.7</td>
<td>5 yrs 30% 25% (p=0.59)</td>
</tr>
</tbody>
</table>

**NOTES:** BCG = Bacille Calmette-Guérin; COG = Central Oncology Group; d = days; EORTC = European Organization for Research and Treatment of Cancer; eval. = number of patients evaluated; mos = months; NCI = National Cancer Institute; NR = not reported; q = every; rand. = number of patients randomized; ref. = reference number; SWOG = Southwest Oncology Group; wk(s) = week(s); yr(s) = year(s).  
* abstracted from survival curves.  
† This trial also included a levamisole arm - see Table 7 for details.  
‡ This trial also included BCG and dacarbazine plus BCG arms.  
§ This trial also included BCG and vaccine arms - see Table 8 for details.

**CONFLICT OF INTEREST**  
Melanoma DSG members were asked to disclose potential conflict of interest information; no conflicts were declared.
JOURNAL REFERENCES

- Practice Guideline publication:

- Systematic Review publication:
  This material has been published as “Verma S, Quirt I, McCready D, Bak K, Charrette 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” © 2006 American Cancer Society; Publisher: Wiley-Liss, Inc. DOI: 10.1002/cncr.21760

ACKNOWLEDGEMENTS

The Melanoma DSG would like to thank Shailendra Verma, Ian Quirt, David McCready, Kate Bak, Manya Charette, and Neill Iscoe for taking the lead in drafting this systematic review.

For a complete list of the Melanoma DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/
REFERENCES


Evidence-based Series #8-1 Version 4: Section 3

Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma: Guideline Development and External Review - Methods and Results

Current Report Date: June 22, 2009
T. Petrella, S. Verma, K. Spithoff, I. Quirt, D. McCready, and the Melanoma Disease Site Group

Original Report Date: June 30, 2004
S. Verma, I. Quirt, D. McCready, K. Bak, M. Charette, N. Iscoe, 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

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.

THE PROGRAM IN EVIDENCE-BASED CARE
The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-based Series:
Each Evidence-based Series is comprised of three sections.

- Section 1: Guideline Recommendations. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its
interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- **Section 2: Evidentiary Base.** Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.

- **Section 3: EBS Development Methods and External Review Process.** Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

**DEVELOPMENT OF THE ORIGINAL EVIDENCE-BASED SERIES - VERSION 2 (AUGUST 30, 2005)**

The original evidence-based series was developed by the Melanoma DSG of CCO's PEBC. The series was a convenient source of the best available evidence on systemic adjuvant therapy for patients at high risk for recurrent melanoma, developed through systematic review, evidence synthesis, and input from practitioners in Ontario. The first guideline on this topic was completed by the Melanoma DSG in 1998. Due to the availability of new evidence and the adoption of a new AJCC staging system, a re-written guideline was completed in 2004 and later updated in 2005. A summary of the development and review process of that guideline document follows.

**Disease Site Group Consensus Process**

The members of the Melanoma DSG reviewed the rewritten document at a meeting held in September 2002. The group unanimously agreed that interferon has activity in the adjuvant setting. However, one member of the DSG objected to the word “offered” in the Key Recommendation, pointing out that the issue of adjuvant interferon is controversial and that the use of the word “offered” precludes further clinical trials being undertaken. This member suggested alternate wording for the recommendation: “We recommend that interferon therapy be discussed with the high risk patient. It may be used as adjuvant treatment, provided that each patient has been made aware of the controversies, relative risks, benefits, and costs of this therapy and wishes to proceed.” The group noted this objection but decided to let the Key Recommendation stand as currently written, to be reviewed by practitioners in Ontario.

Another issue raised at the meeting of the Melanoma DSG concerned the new AJCC staging system, which highlights the presence of ulceration as an important prognostic factor. Under the new staging system, patients with lesions between 2.0 and 4.0 mm with ulceration have the same prognosis as patients with lesions greater than 4.0 mm without ulceration. None of the trials included in this document were conducted under the new staging system. However, the group felt that new trials based on the new staging criteria were unlikely to be undertaken. For this reason, the Target Population has been amended to include patients with shallower, ulcerated lesions. The DSG plans to seek input from Ontario practitioners about the appropriateness of including these new patients when this document is circulated for practitioner feedback.

**External Review by Ontario Clinicians**

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the Melanoma DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

<table>
<thead>
<tr>
<th>BOX 1: DRAFT RECOMMENDATIONS (approved for external review November 2002)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Population</strong></td>
</tr>
<tr>
<td>These recommendations apply to adult patients with high-risk malignant melanoma</td>
</tr>
</tbody>
</table>
who are rendered disease-free following resection.

**Recommendation**
We recommend that interferon therapy be discussed and offered to the high-risk group defined above. 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.

**Qualifying Statements**
Patients and practitioners should be aware that there have been four randomized trials of high-dose interferon alpha in patients at high risk for recurrent melanoma. The evidence from the randomized trials is conflicting. The ECOG 1684 trial detected a significant improvement in overall survival after prolonged follow-up, but a subsequent large randomized trial (ECOG 1690) failed to find any survival benefit for interferon compared with observation. Results from a third trial (ECOG 1694) that compared high-dose interferon with a melanoma vaccine demonstrated a significant survival benefit for interferon. A fourth trial of high-dose interferon over a shorter treatment time failed to detect any benefit.

**Methods**
Practitioner feedback was obtained through a mailed survey of 91 practitioners in Ontario (50 general surgeons, 20 plastic surgeons, 17 medical oncologists, and three dermatologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on November 11, 2002. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Melanoma DSG reviewed the results of the survey.

**Results**
Forty-three responses were received out of the 91 surveys sent (47% response rate). Responses included returned completed surveys as well as phone, fax, and e-mail responses. Of the practitioners who responded, 30 indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 10.
Table 10. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a clinical practice guideline, as</td>
<td></td>
</tr>
<tr>
<td>stated in the “Choice of Topic” section of the report, is clear.</td>
<td>30 (100) 0 0</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>29 (97) 1 (3) 0</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>28 (97) 1 (3) 0</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted</td>
<td>26 (90) 2 (7) 1 (3)</td>
</tr>
<tr>
<td>according to my understanding of the data.</td>
<td></td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>30 (100) 0 0</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>26 (87) 1 (3) 3 (10)</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>24 (83) 3 (10) 2 (7)</td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely</td>
<td>Very likely or likely Unsere Not at all likely or unlikely</td>
</tr>
<tr>
<td>would you be to make use of it in your own practice?</td>
<td>27 (90) 2 (7) 1 (3)</td>
</tr>
</tbody>
</table>

**Summary of Written Comments**

Fifteen respondents (50%) provided written comments. The main points contained in the written comments were:

A number of questions were received from practitioners requesting clarification of the role of sentinel lymph node biopsy in the management of patients who would meet the target population of this guideline.

One practitioner commented that more should have been mentioned about patients who should be excluded from the target population due to age and/or comorbidities.

One practitioner commented that it is unclear whether patients with micrometastases only via the sentinel node would be included in the population.

One practitioner commented that the evidence for both interferon and levamisole indicated that both agents appeared to have similar results in melanoma patients.

**Modifications/Action**

The role of sentinel lymph node biopsy in the management of malignant melanoma is the subject of a separate practice guideline being developed by the Melanoma DSG. A reference to this guideline has been included under “Related Guidelines.”

An additional “Qualifying Statement” has been added to address this comment. Microscopic disease was not discussed specifically in the guideline. A discussion of this issue has been added to the “Interpretive Summary.” The results of the Sunbelt trial will be important in providing evidence for this group and other patients, and the target population may need to be modified once the results of the trial become available.

The levamisole studies would now likely be considered underpowered. No additional changes were made to the guideline to address this comment.

**Practice Guidelines Coordinating Committee Approval Process**

The practice guideline report was circulated to members of the PGCC for review and approval. Seven of the 12 members of the PGCC returned ballots. Four PGCC members approved the practice guideline report as written, two members approved the report with suggestions for consideration by the Melanoma DSG and one member approved the report conditional on the Melanoma DSG addressing specific concerns. The main suggestion of the PGCC member was that the DSG outline the dose and schedule of high-dose interferon being recommended.

**Modifications/Actions**
The DSG amended the recommendation to include details on the dose and schedule of high-dose interferon. The regimen endorsed by the DSG is the same regimen used in the three ECOG studies of high-dose adjuvant interferon. Other minor changes were made to the report in response to the suggestions for consideration.

Peer Review Feedback
The practice guideline was submitted to Current Oncology and was accepted for publication without any changes. The systematic review was submitted for publication in Cancer and four peer reviewers provided extensive feedback on the document. The main suggestions included:
Authors failed to take into account the updated results of trials by Kirkwood et al., Sosman et al. and Sondak et al.
One reviewer pointed out that the E1694 trial does not contain BCG in the vaccine.
Addressing the conclusions of the two Q-TWiST analyses as well as commenting on Wheatley’s et al. secondary meta-analysis would be helpful.
One reviewer suggested including the results of the ECOG 2696 trial.
A statement explaining why this systematic review was important despite the lack of new data should be added to the Introduction.
A set of guideline and recommendations as to who should receive HDI and in what clinical scenarios needs to be added to the document.

Modifications/Actions
A literature search was conducted in order to update the document and add the results of the missing trials.
Discussion regarding BCG has been removed form the document.
The conclusions of the two Q-TWiST analyses as well as Wheatley’s et al. secondary meta-analysis were addressed in the document.
The group decided not to include the results of the ECOG 2696 trial since it was a phase II study.
A statement addressing the value of the document had been added to the introduction.
The target population is identified in the document however additional information on patient selection has been added to the discussion section.

Box 2 summarizes the final clinical recommendations as included in the August 30, 2005 updated guideline document.

<table>
<thead>
<tr>
<th>BOX 2:</th>
<th>RECOMMENDATIONS (August 30, 2005 guideline document)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Population</strong></td>
<td>These recommendations apply to adult patients with high-risk malignant melanoma who are rendered disease-free following resection.</td>
</tr>
<tr>
<td><strong>Recommendation</strong></td>
<td>We recommend that high-dose interferon alpha therapy (20 X10^6 U/m^2/d intravenously five days/week for four weeks, then 10 X 10^6 U/m^2 subcutaneously three times weekly for 48 weeks) be discussed and offered to the high-risk group as defined in the guideline question. 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.</td>
</tr>
<tr>
<td><strong>Qualifying Statements</strong></td>
<td>Patients and practitioners should be aware that there have been four randomized trials of high-dose interferon alpha in patients at high risk for recurrent melanoma. The evidence from the randomized trials is conflicting. The Eastern Cooperative Oncology Group (ECOG) 1684 trial detected a significant improvement in overall survival, but a subsequent large randomized trial (ECOG 1690) failed to find any survival benefit for...</td>
</tr>
</tbody>
</table>
interferon compared with observation. Results from a third trial (ECOG 1694) that compared high-dose interferon with a melanoma vaccine demonstrated a significant survival benefit for interferon. A fourth trial of high-dose interferon over a shorter treatment time failed to detect any benefit.

Practitioners should be aware that elderly patients (age 65 and older) were underrepresented in the high-dose interferon trials. Given the toxicities of interferon, particularly in the presence of other significant comorbidities, caution is advised.

The role of adjuvant interferon in patients with micrometastases as determined solely through sentinel lymph node dissection has not been defined and is the subject of ongoing trials. However, until such data is available, it is reasonable to discuss the benefits and risks of interferon therapy with such patients, particularly in those with more than one microscopically involved lymph node at the time of dissection, who would not be eligible for the ongoing randomized controlled trial.

DEVELOPMENT OF THE CURRENT EVIDENCE-BASED SERIES - VERSION 3.2009
Development and Internal Review
An updated EBS was initiated by the Melanoma DSG of the CCO PEBC in 2008 and completed in 2009. The series is a convenient and up-to-date source of the best available evidence on systemic adjuvant therapy for patients at high risk for recurrent melanoma developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. The original systematic review up to July 2005 has been retained in Section 2B of the new series while new evidence from July 2005 to July 2008 is presented in Section 2A. The updated Guideline Recommendations as contained in Section 1 of the current series are based on the totality of the evidence included in Sections 2A and 2B.

Disease Site Group Consensus Process
The members of the Melanoma DSG reviewed the new evidence contained in Section 2A at a meeting held in November 2008. The DSG agreed that there is no strong evidence supporting a significant overall survival benefit with the addition of adjuvant interferon for patients at high risk of recurrent melanoma; however, a significant benefit in disease-free or relapse-free survival has been demonstrated. A discussion was held regarding the appropriateness of a recommendation based on a disease-free survival benefit in the absence of a survival benefit. The consensus of the group was that disease-free survival is a clinically important outcome and a recommendation to discuss and offer adjuvant interferon therapy is warranted, provided that the patient understands the potential risks and benefits. One DSG member strongly disagreed with the recommendation to offer adjuvant interferon therapy in the absence of a clear survival benefit. The DSG agreed that the first recommendation should encourage the enrolment of patients in randomized trials.

A discussion was held regarding the recommendation supporting the use of adjuvant pegylated interferon as a reasonable alternative to high-dose interferon. In the absence of a trial comparing pegylated interferon with high-dose interferon, the DSG agreed that one regimen could not be recommended over the other. The DSG recommended that a Qualifying Statement be added to indicate that selection of patients for either therapy should be at the discretion of the physician based on patient preferences, tolerability and other factors affecting therapy.

Report Approval Panel
Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Report Approval Panel included:
- The authors should more explicitly describe how the new data align with or contradict the old data.
• The authors state that there are reasons to believe that disease-free survival (DFS) predicts for overall survival (OS) yet the majority of the data do not support this. If such a relation does exist, the strength of the predictive properties appears to be relatively weak. Citations of evidence should be provided to support the suggestion that when improvements in DFS have not been associated with OS improvement, the reason may be contamination resulting from treatment crossover.

• Citations of evidence should be provided to support that the symptomatic nature of a patient’s life would be improved by superior DFS.

• The authors should report the results of the meta-analysis results as magnitude of benefit in terms of absolute differences in time to event as opposed to only reporting hazard ratios.

• The authors should more explicitly discuss data to support the recommendation of high-dose interferon as compared with low dose treatment. The dose comparison in the Wheatley meta-analysis should be discussed and the authors should confirm their agreement or present their disagreement.

• The authors recommend that patients should participate in randomized trials. The background supporting that randomized trials, as opposed to developmental trials, are the current priority has not been presented.

• In the study selection criteria, the authors should clarify whether a comparison of interferon with a new agent would be ineligible.

• The authors have included blinding as a quality variable. Given the nature of interferon, there is a high risk of pseudo-blinding. The authors should reconsider or clarify the need to account for this variable.

• Comments about the significant limitations of the Gogas et al. non-inferiority trial should be added to Section 1 and the Results in Section 2A. The authors appear to reject the conclusions of the trial but this is not clearly evident until the Discussion in Section 2.

Modifications/Actions

The following modifications and responses were made to address key issues raised by the Report Approval Panel:

• Several sentences were added to the Discussion in Section 2A to more explicitly outline how the new data align with the data in the original systematic review in Section 2B.

• The authors have not claimed that lack of association between DFS and OS improvement may be due to contamination resulting from treatment crossover. Although the presence of such contamination was identified as a possible explanation for better than expected outcome in the control arm of the ECOG 1690 trial, there are no data to determine whether contamination from treatment crossover was an issue in other trials.

• A reference to a study of melanoma patient utilities demonstrating that the DFS outcome is an important clinical endpoint that is highly valued by patients was added (3).

• Estimates of absolute risk reductions were calculated from the pooled hazard ratios and reported in the text of Sections 1 and 2A.

• A paragraph was added to the Discussion section in Section 2A on the evidence for low dose interferon.

• The recommendation was modified to state that patients should participate in clinical trials, rather than randomized trials specifically.

• The study selection criteria were retained as written, as trials comparing interferon with a new adjuvant agent would be excluded.

• Blinding was retained as a methodological quality characteristic in Table 2. Although the authors recognize that blinding of patients would be difficult in the context of interferon therapy, blinding of health care providers, outcome assessors, and data analysts is still achievable and should be reported.
● Additional comments on the limitations of the non-inferiority trial by Gogas et al. were added to the text of Section 1 and Section 2A.

**External Review by Ontario Clinicians**

The PEBC external review process includes a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners. Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and review and approval of the report by the PEBC Report Approval Panel, the Melanoma DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 3 summarizes the draft recommendations developed by the Melanoma DSG.

**BOX 3:**

**DRAFT RECOMMENDATIONS** (approved for external review April 17, 2009)

- 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 x10^6 U/m^2/d intravenously five days/week for four weeks, then 10X10^6 U/m^2 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.

**DRAFT 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.

Methods
Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Medical oncologists, surgeons, and dermatologists in the PEBC database who are involved in the treatment of melanoma in Ontario were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on May 19, 2009. The consultation period ended on June 19, 2009. The Melanoma DSG reviewed the results of the survey.

Results
One response was received. Results of the feedback survey are reported in Table 11.

Table 11. Responses to four items on the professional consultation survey.

<table>
<thead>
<tr>
<th>Question</th>
<th>Lowest Quality (1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>Highest Quality (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rate the overall quality of the guideline report.</td>
<td></td>
<td></td>
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<td></td>
<td>Strongly Disagree (1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>Strongly Agree (5)</td>
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<tr>
<td>2. I would make use of this guideline in my professional decisions.</td>
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<td></td>
<td>Access to medical oncology specialists in the community and access to staging modalities (i.e. PET scans)</td>
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<td>3. I would recommend this guideline for use in practice.</td>
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<tr>
<td>4. What are the barriers or enablers to the implementation of this guideline report?</td>
<td>Access to medical oncology specialists in the community and access to staging modalities (i.e. PET scans)</td>
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</table>

Conclusion
This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Melanoma DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

RELATED PRINT AND ELECTRONIC PUBLICATIONS

Funding
The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055     Fax: 905-522-7681
REFERENCES


OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2009. In October 2013, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Gastrointestinal Cancer Disease Site Group endorsed the recommendations found in Section 1 (Clinical Practice Guideline) in November 2013.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

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?

Literature Search and New Evidence

The new search from July 2008 to October 2013 yielded 12 RCTs, two meta-analysis evaluating the management of patients with stage II or III melanoma. One ongoing study was identified from clinicaltrials.gov. Brief results of these searches are shown in the Document Review Tool.
Impact on Guidelines and Its Recommendations
The new data supports existing recommendations. Hence, the Melanoma Disease Site Group ENDORSED the 2009 recommendations on the use of systemic therapy for the management of patients at risk of recurring melanoma.

Document Review Tool

<table>
<thead>
<tr>
<th>Number and title of document under review</th>
<th>8-1: Systematic Adjuvant therapy for Patient a High Risk for Recurrent melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Report Date</td>
<td>June 22, 2009</td>
</tr>
<tr>
<td>Clinical Expert</td>
<td>Dr. Teresa Petrella</td>
</tr>
<tr>
<td>Research Coordinator</td>
<td>Judy A. Brown</td>
</tr>
<tr>
<td>Date Assessed</td>
<td>October 31, 2013</td>
</tr>
<tr>
<td>Approval Date and Review Outcome (once completed)</td>
<td>November 4, 2013 (ENDORSED)</td>
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</tbody>
</table>

**Original 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?

**Target Population:**
Patients at high risk of recurrence (stages IIB and III)

**Study Section Criteria:**

**Inclusion Criteria:**
- Randomized controlled trials (RCTs) of systemic therapies for the adjuvant treatment of patients with melanoma. Prior to the literature search, the following four types of treatments were identified as relevant to the guideline question: levamisole, interferon, vaccines, and chemotherapy.
- Trials had to include patients at high risk of recurrence, but the study population did not need to be restricted to that group of patients. For this report, high risk is defined by the American Joint Committee on Cancer (AJCC) stages IIB and III (please see Appendix 1 for staging information) and includes primary tumours ≥4.0 mm thick, regional lymph node metastases that are clinically apparent at presentation or are detected at lymph node dissection, and regional lymph node recurrence. All studies were conducted under the previous AJCC staging system. We attempt to define how patients under the new AJCC staging system should be considered, recognizing that the views expressed cannot be based on data but are our view of the information available.
- Practice guidelines, meta-analyses, and systematic reviews of adjuvant treatment of malignant melanoma were also eligible for review.

**Exclusion Criteria:**
- Phase I and II studies were not considered for inclusion in this report because of the availability of RCTs.
- Papers published in a language other than English were not considered.
- Bacillus Calmette-Guérin (BCG), *Corynebacterium parvum*, transfer factor, vitamin A, and megestrol acetate have been investigated in the past as adjuvant therapy. However, there does not appear to be any ongoing interest in these agents. Trials involving these agents have been excluded in this systematic review.
- Randomized trials without an observation or placebo-alone arm were excluded, unless they were trials comparing different interferon doses or schedules.
- Abstract reports of randomized trials presenting preliminary data only were also excluded.

**Search Details:**
August 2008 to September 2013 (Medline Aug wk 1 and Embase wk 30)
**Brief Summary/Discussion of New Evidence:**

There were 2,080 articles identified from Medline and Embase, along with 30 conference abstracts from ASCO and 20 trials from clinicaltrials.gov up for consideration.

*Twelve RCTs* examined systemic adjuvant therapies for patients at high risk for recurrent melanoma from August 2008 to the present. Two compared interferon (IFN) to observation alone, four compared IFN to other IFN regimens and one compared two regimens of IFN to an observational group. Three RCTs evaluated IFN and chemotherapy and one looked at vaccination and observation groups (see 1-5 below for brief overview of RCTs). *Two Meta-analyses* (see 6 below for meta-analysis) were found, both examining INF and observational groups. One study pooled data from two large RCTs. There was one ongoing study identified from clinicaltrials.gov (see 7 below).

1. **IFN vs. Observation (2 RCTs)**

Since the last update (July 2008), two RCTs examining INF vs. observation were found. One study examining HDI induction, with 4 weeks therapy, found no improvement in RFS or OS over observation for patients with intermediate and high-risk melanoma (1). A positive marginally significant impact on RFS for PEG-IFN—2b compared to observation, after a median follow-up of 6.8 years, was found in the EORTC 18991 trial (2). However, the finding was slightly diminished from the previous results seen at a median 3.8 years follow-up. No significant increases in DMFS or OS were found in the study, but quality of life was greatly diminished (3).

<table>
<thead>
<tr>
<th>Trial/Reference</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>Intergroup trial E 1697</td>
<td>HDI (n=581): postoperative adjuvant interferon (IFN) alfa2b 20 MU/m2/day for 5 days/week X 4 weeks vs. observation (n=596)</td>
<td>Pts with intermediate and high-risk melanoma defined as T3</td>
<td>DFS (median): 6.8 years (95% CI 5.1, 9.0; n=425). vs. 7.3 years (95% CI 5.3, 9.8; n=413)</td>
<td>Adjuvant HDI induction with only 4 weeks therapy neither improved RFS nor OS over observation for pts with intermediate and high-risk melanoma.</td>
</tr>
<tr>
<td>Agarwala et al., 2011 (1) (ASCO 8505)</td>
<td>PEG-IFN-alpha2b (n=627) (pegIFN-2b 6g/kg/week for 8 weeks then 3g/kg/week for up to 5 years) vs. observation (n=629)</td>
<td>AJCC stage III (TxN1-2M0) follow-up (median): 7.6 yrs</td>
<td>DMFS: HR=0.87 (95% CI: 0.82–0.92), p=0.006 PEG-IFN—2b discontinued for toxicity in 37% of patients.</td>
<td>Adjuvant PEG-IFN—2b leads to a significant and sustained improvement in RFS. There is an expected negative effect on QoL.</td>
</tr>
<tr>
<td>EORTC 18991</td>
<td>PEG-IFN-alpha2b (n=629) (pegIFN-2b 6g/kg/week for 8 weeks then</td>
<td>AJCC stage III (TxN1-2M0) QoL: PEG-IFN-alpha2b treatment arm compared with the observation group decreased global HRQOL at an expected negative effect on</td>
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<tr>
<td>Eggermont et al., 2012 (2)</td>
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</table>
2. IFN vs. other IFN regimens (4 RCTs – 1 pooled analysis)
Six RCTs compared IFN with other IFN regimens. The IMI study found a shorter HDI regimen to be just as effective as conventional HDI, with no more toxicity (5). A pooled analysis of the two studies cited above (IMI and DECOG) confirmed no significant difference for RFS or OS for a shorter regime of HDI as compared to conventional HDI (9). Likewise, the EADO study showed no advantage of a prolonged IFN regime (Peg-IFN – 36 months) over conventional 18-month low-dose IFN (10). The Hellenic cooperative Oncology Group found no significant difference between 4-week INF_a_2b regimen compared to the same regimen followed by a 48 week SC maintenance therapy (11). Finally, in a sub-population of Asian individuals with acral melanoma, there was a trend towards longer RFS in the 1-year IFN arm than that in the 4-week arm, although the difference was not statistically significant (12).

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td><strong>Italian Melanoma Intergroup (IMI) Trial</strong></td>
<td>HDI Arm (n=172): INFNa2b 20 MU/m2iv 5 d/wk for 4 wks every other month vs. HDI Arm (n=158): standard high dose regimen of a 4 week iv course followed by 10 MU/m2IFNa2b sc 3 times/wk for 11 months</td>
<td>Following lymphadenectomy, stage III (AJCC2002) patients</td>
<td>OS (median): 88.7 vs. 82.6 mos OS (5 yrs): 60.1% (95%CI: 53.66.5%) vs. 52.7% (95%CI: 44.9-59.8%); p=NS DFS (median): 47.9 vs 35.6 mos; p=NS RFS (5 yrs): 45.8% (95%CI: 37.4-53.7%) vs. 44.3% (95%CI: 35.7-52.6%); p=NS TX: similar in both groups, except for leucopenia higher in HDI group (23% vs 12%; p=0.0331)</td>
<td>Data show that a shorter but more intensive HDI regimen is more feasible and not more toxic than conventional HDI.</td>
</tr>
<tr>
<td><strong>EADO</strong></td>
<td>Arm A (n=443): PegIFN_a_2b flat dose 100 g/week SC for 36 months Arm B (n=453): FN_a_2b 3 MIU SC TIW for 18 months</td>
<td>≥1.5mm without clinically detectable regional node or distant metastases (AJCC stage IB–IIIB) Follow-up: 4.7 yrs</td>
<td>DFS: 66.2% vs 64.8%, p=0.43; HR= 0.91 (95% CI: 0.73–1.15) DMFS: 71.3% vs 72.6%, p=0.86; HR= 1.02 (95% CI: 0.80–1.32) OS: 77.0% vs 78.4%, p=0.55; HR= 1.09 (95% CI: 0.82–1.45) TX[GR3&amp;4]: 44.6% vs. 26.6% in first 18 mos</td>
<td>This trial did not show superiority for adjuvant Peg-IFN over conventional low-dose IFN in melanoma patients without clinically detectable nodes.</td>
</tr>
<tr>
<td><strong>UPDATE</strong></td>
<td>Arm A (n=421): 3 MU IFNa/a2a three times a week subcutaneously for either 18 months vs. Arm B (n=419): patients with resected cutaneous melanoma of at least 1.5 mm tumor thickness Follow-up</td>
<td>RFS: 75.6% vs. 72.6%, P = .72; HR= 1.05 (95% CI: 0.80-1.39) DMFS: 81.9% vs 79.7%, P = .56; HR=1.10 (95% CI: 0.80-1.52) OS: 85.9% v 84.9%; P = .86;</td>
<td>A prolongation of conventional LDI therapy from 18 to 60 months showed no clinical benefit in patients with intermediate and high-risk primary melanoma.</td>
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</table>
the above for 60 months | (median) 4.3 yrs | HR=1.03 (95% CI: 0.71-1.50) | DM: 44% vs. 47%; p=0.46  
DMFS: HR=1.0; p=0.39  
OS: HR=1.0; p=0.85  
Termination of treatment due to adverse events or QoL related reasons: 26.0% vs. 14.8%; p<0.001 | The final analysis of pulsed adjuvant HDI treatment showed no significant DMFS or OS differences in comparison to conventional HDI. There is a clearly favorable safety and QoL profile of the pulsed regimen.

**DeCOG**
Mohr et al., 2012 (14) (ASCO 8505)

| Arm A (n=NR): HDI regimen vs. Arm B (n=NR): 3 courses of IFNa2b 20 MU/m² iv on 5 days a week for 4 weeks repeated every 4 months | 627 patients with stage III (AJCC 2002) resected intransit or lymph node metastasis from cutaneous malignant melanoma  
Follow-up (median): 55.4 vs. 55.3 mos | DM: 44% vs. 47%; p=0.46  
DMFS: HR=1.0; p=0.39  
OS: HR=1.0; p=0.85  
Termination of treatment due to adverse events or QoL related reasons: 26.0% vs. 14.8%; p<0.001 | The final analysis of pulsed adjuvant HDI treatment showed no significant DMFS or OS differences in comparison to conventional HDI. There is a clearly favorable safety and QoL profile of the pulsed regimen.

**Mao et al., 2011 (12)**

See also: Si et al., 2011 (15) (ASCO 8544)

| Arm A (n=77): 4-week (15 x 10⁶U/m²d1-5/w x 4w) vs. Arm B (n=70): 1-year adjuvant HDIFN (15 x 10⁶U/m²d1-5/w x 4w+9 x 10⁶Utiw x 48w) | Patients with resected high-risk (stage IIb-IIIC) Acral Melanoma  
Follow-up (median): 36.1 mos | DFS (median): 17.9 vs. 22.5 months (P = .72).  
RFS (2yr) 43.9% (95% CI: 32.1-57.7% vs 44.4% (95% CI:32.7–55.9%)  
RFS (3yr) 37.4% (95% CI: 26.6–48.2%) vs. 35.6% (95% CI: 23.8–47.4%)  
RFS (median patients with more nodal metastases (n ≥ 3): 7.6 vs. 12.0 mos; P=0.02  
RFS (median patients with stage IIIb-IIIc AM or with ≥ 3 nodal metastases) 7.6 vs. 12.0 mos; P=0.02 | The induction dose of 15 x 10⁶U/m² and the maintenance dose of 9 x 10⁶U were tolerable, which may be the optional dose intensity for adjuvant IFN-2b therapy in Chinese high risk AM population. No statistical significance was detected in RFS between the 4-week and 1-year regimen while a 1-year regimen may show clinical benefits in patients with stage IIIb-IIIc AM or with ≥ 3 nodal metastases.

**Hellenic Cooperative Oncology Group**
Pectasides et al., 2009 (11)

**UPDATE**

| Arm A (n=177): FN alpha-2b 15 x 10⁶U/m² IV x 5/7 days weekly x 4 weeks vs. Arm B (n=176): same regimen followed by IFN-alpha-2b 10 x 10⁶U (flat dose) administered subcutaneously three times a week for 48 weeks | Patients with stage IIb, IIC, and III melanoma, within 56 days of curative surgery  
Follow-up: 5 yrs | DFS (median): 24.1 mos vs. 27.9 mos (P = .9)  
DFS: HR= 0.94 (95% CI:0.72–1.23), p = 0.65  
OS (median): 64.4 mos versus 65.3 mos (P = .49)  
TX (Gr1&2): NS  
TX (Gr3&4): NS  
Rates of any grade of hepatotoxicity, nausea/vomiting, alopecia, and psychiatric disorders are higher in group B | There were no significant differences in OS and RFS between the regimens of 1 month and 1 year of treatment.

**DeCOG MM-ADJ-5 and the Italian Melanoma Intergroup (IMI)**
Weichenthal et al., 2013 (9)(ASCO e20028)

| intermittent IV HDI (iHDI) regimens vs. standard HDI | DeCOG trial contributed data on 627 MM pts. with stage III (AJCC 2002) resected intransit or lymph node metastasis. From the Italian IMI trial 330 pts. with stage III | RFS: HR=1.11 (95% CI 0.93-1.33)  
OS: HR=1.04 (95% CI 0.84-1.29) | The pooled analysis of the two pulsed adjuvant HDI treatments showed no significant differences for RFS or OS as compared to conventional HDI.
regional lymph node metastasis excluding intransit metastasis were evaluable.

3. IFN vs. other IFN regimen vs. observation (1 RCT)
The Nordic IFN trial found that, compared to observation, intermediate adjuvant therapy did not significant improving overall survival among patients with cutaneous melanoma (16), with a decreased quality of life almost equal to that of high dose interferon alpha-2b (17).

<table>
<thead>
<tr>
<th>Trial/Reference</th>
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<th>Population/Follow-up</th>
<th>Outcomes/Results</th>
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</tr>
</thead>
<tbody>
<tr>
<td>NORDIC IFN trial</td>
<td>Group A (n=284): observation only vs. Group B (n=285): 4 weeks of induction followed by 12 months of maintenance therapy vs. Group C (n=286): 1 month of induction and 24 months of maintenance</td>
<td>Patient inclusion criteria were: histologically verified resected cutaneous melanoma, AJCC stage IIB–IIC (T4N0M0), or stage III (TxN1–3M0); age 18 years or older</td>
<td>OS (med): 56·1 (IQR 22·3 to &gt;120·0) vs. 72·1 (25·8 - &gt;120) vs. 64·3 mos (24·7 - &gt;120) p=0·60</td>
<td>Adjuvant therapy with intermediate-dose interferon alfa-2b did not significantly improve overall survival. Interferon alfa-2b with 1-year maintenance therapy significantly improved RFS, but we recorded no significant effect for 2-year maintenance therapy.</td>
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<td>Brandberg et al., 2012 (17)</td>
<td>See also, Hansson et al., 2011b (QoFL) (18) (ASCO 8547)</td>
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<td>QoFL: While patients in Arm A improved or remained at baseline levels; patients in Arms B and C reported decreased functioning and quality of life, and an increase in side-effects during their treatment.</td>
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<tr>
<td>NORDIC IFN trial</td>
<td>Group A (n=284): observation only vs. Group B (n=285): 4 weeks of induction followed by 12 months of maintenance therapy vs. Group C (n=286): 1 month of induction and 24 months of maintenance</td>
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<tr>
<td>Hansson et al., 2011a (16)</td>
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<td>Follow-up (median): 72.1 mos.</td>
<td>OS (GrpB&amp;C vs. obs) HR=0·91 (95% CI 0·74–1·10) p=0·642</td>
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<td>OS (Grp B vs. obs) HR=0·91 (0·72–1·14) p=0·652</td>
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<td>OS (Grp C vs. obs) HR=0·91 (0·72–1·15) p=0·858</td>
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<td>RFS (med): 23·2 (IQR 5·6 to &lt;120) vs. 37·8 (10·8 - &gt;120) vs. 28·6 mos (8·6 - &gt;120) p=0·034</td>
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<td>RFS: (GrpB&amp;C vs. obs): HR=0·80 (0·67–0·96) p=0·030</td>
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<td>RFS: (Grp B vs. obs): HR=0·77 (0·63–0·96) p=0·034</td>
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<td>RFS: (Grp C vs. obs): HR=0·83 (0·68–1·03) p=0·178</td>
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<td>TX: NS</td>
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</table>
4. IFN vs. Chemotherapy (3 RCTs)

Three RCTs examined IFN and chemotherapy. An intergroup study showed an improvement in RFS with a short course of BCT compared to HDI, in patients with high risk melanoma (19). No differences in OS and grade IV toxicity were found in this study. Kim et al, (20) also found BCT to be more effective than IFN for patients who had undergone lymphadenectomy for melanoma metastatic to regional lymph nodes. Finally, Lian et al, (21) confirmed the effectiveness and safety of temozolomide-based chemotherapy and HDI compared to observation in patients with resected mucosal melanoma.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>SWOG S0008 (CALGB, COG, ECOG, and SWOG) Flaherty et al., 2012 (19) (ASCO 8504)</td>
<td>HDI (n=NR): vs. BCT HDI (n=NR): dacarbazine 800 mg/m2 day 1, cisplatin 20 mg/m2/ days 1-4, vinblastine 1.2 mg/m2 days 1-4, IL-2 9 MU/m2/day continuous IV days 1-4, IFN 5 MU/m2/day SC days 1-4, 8, 10, 12, and G-CSF</td>
<td>402 patients who were high risk (Stage III A-N2a thru Stage III C N3)</td>
<td>RFS (median 6yrs): HR 0.77 (90% CI: 0.62 - 0.96) p = 0.02 RFS: 1.9 yrs (90% CI: 1.4 - 2.5) vs. 4yrs (90% CI:1.9 - 5.9) RFS (5 yrs): 47% vs. 39% OS (median): HR 1.0 [90% CI: 0.78 - 1.27] with median OS not yet reached for BCT v 8.4 yrs (90% CI: 4.5 - 9.3); p = 0.49 OS(5yrs): 56% in both arms TX(GR3): 57% vs. 36% TX(GR4): 7% vs. 40%</td>
<td>In HRM pts, BCT provides a statistically significant improvement in RFS compared to HDI, but no discernible difference in OS and more grade IV toxicity. BCT represents a shorter, alternative treatment for pts with HRM, and a potential control arm and basis for future combinations in the adjuvant setting.</td>
</tr>
<tr>
<td>Kim et al., 2009 (20)</td>
<td>biochemotherapy (n=71) VS. IFN further randomized to either high-dose IFN (HDII) (n=34) or intermediate-dose IFN (IDI) (n=33)</td>
<td>Patients who had undergone lymphadenectomy for melanoma metastatic to regional lymph nodes</td>
<td>RFS (median): p=0.86 OS (median): p=0.45 utility analysis was performed because of slow accrual.</td>
<td>Biochemotherapy is not more effective than IFN as adjuvant therapy for melanoma. These findings support early termination of this trial.</td>
</tr>
<tr>
<td>Lian et. Al., 2013 (21) See also: Lian et. Al., 2012 (22) (ASCO 8506)</td>
<td>Group A (n=63): HDI alone vs. Group B (n=63): 15 x 10(6) U/m(2)/d IFN-alpha2b, + 9 x 10(6) U IFN-alpha2b vs. Group C (n=63): temozolomide (200 mg/m(2)/d) plus cisplatin (75 mg/m(2))</td>
<td>Patients with mucosal melanoma in stage II/III after surgery</td>
<td>OS (median): 21.2 (95% CI, 15.8–26.6 months), 40.4 (95% CI, 32.5–48.3 months), and 48.7 mos (95% CI, 41.8–55.6 months) (P &lt; 0.001) RFS (median): 5.4 (95% CI, 4.2–6.6 months), 9.4 (95% CI, 7.9–10.9 months), and 20.8 mos (95% CI, 17.9–23.7 months) (P &lt; 0.01) TX: mild to moderate all grops</td>
<td>Both temozolomide-based chemotherapy and HDI are effective and safe as adjuvant therapies for resected mucosal melanoma as compared with observation alone. However, HDI tends to be less effective than temozolomide-based chemotherapy for patients with resected mucosal melanoma in respect to RFS. The temozolomide plus cisplatin regimen might be a better choice for patients with resected mucosal melanoma.</td>
</tr>
</tbody>
</table>

5. Vaccination vs. observation (1 RCT)

Section 4: Document Review Summary and Review Tool
The EORTC 18961 study found ganglioside GM2-KLH/QS-21 vaccination versus observation to be ineffective and potentially detrimental in stage II melanoma patients (23).

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>EORTC 18961</td>
<td>Ganglioside GM&lt;sup&gt;2&lt;/sup&gt;-KLH/QS-21 vaccination vs. observation</td>
<td>Stage II melanoma</td>
<td>RFS (4yr): 69.4% vs. 68.2%; HR=1.03 (95% CI:0.84-1.25) p=0.81 DMFS (4yr): 78.8% vs. 76.1%; HR=1.11 (95% CI:0.88-1.40) p=0.36 OS (4yr): 83.6% vs. 81.5%; HR=1.16 (95% CI:0.90-1.51) p=0.25</td>
<td>Adjuvant GM&lt;sup&gt;2&lt;/sup&gt;-KLH/QS-21 vaccination is ineffective and could even be detrimental in stage II melanoma patients. For the primary endpoint, RFS, the criteria for stopping for futility were met and for DMFS and OS, there was a trend favoring OBS. Thus, the EORTC IDMC recommended that GM2-KLH/QS-21 vaccine be stopped in the patients still receiving treatment. Patients continued to be followed for the trial's endpoints.</td>
</tr>
</tbody>
</table>

**UPDATE**

**DFS** Disease-free (or recurrence-free Survival); **DM** Distant Metastasis; **DMFS** Distant Metastasis Free Survival; **OM** Overall mortality; **OS** Overall Survival; **QoL** Quality of Life; **RFS** Recurrence Free Survival; **TX** late toxicity

6. Meta-Analysis

Petralla et al., (24) identified seven studies examining adjuvant interferon therapy and found no significant long-term overall benefit among high-risk resected melanoma patients. However, benefit in DFS for high-dose interferon or pegylated interferon treatments were found. Mocellin et al., (25) also found an improvement for adjuvant interferon alpha for the treatment of people with high-risk (AJCC TNM stage II-III) cutaneous melanoma in terms of disease-free survival. However, the study found effectiveness for overall survival, though to a lesser extent than DFS.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>RCT Population</th>
<th>Outcome/Results</th>
<th>Authors' conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patrella et al., 2012 (24)</td>
<td>adjuvant high-dose interferon vs. observation</td>
<td>Adult patients with high-risk malignant melanoma who are rendered disease free after resection 7 studies</td>
<td>HDI vs. observation OS (2 studies): HR= 0.93 (95% CI: 0.78-1.12) P= 0.45 DFS (2 studies): HR= 0.77 (95% CI: 0.65-0.92) P= 0.004 HDI vs. vaccine OS (1 study): HR= 0.76 (95% CI: 0.58-0.99) P= 0.04 DFS (1 study): HR= 0.75 (95% CI: 0.61-0.92) P= 0.006</td>
<td>Our updated literature review indicates that adjuvant interferon therapy does not confer a significant long-term overall survival benefit in patients with high-risk resected primary melanoma; however, a significant DFS benefit for high-dose interferon or pegylated interferon treatment has been shown.</td>
</tr>
</tbody>
</table>
Patients with high-risk skin melanoma, that is, people with regional lymph node metastasis (American Joint Committee on Cancer (AJCC) TNM (tumour, lymph node, metastasis) stage III) undergoing radical lymph node dissection, or people without nodal disease but with primary tumour thickness greater than 1 mm (AJCC TNM stage II).

18 RCTs (10,499 patients – 1995 to 2011)

DFS (17 trials): HR = 0.83 (95% CI: 0.78-0.870) p=0.00001

OS (15 trials): HR = 0.91 (95% CI:0.85-0.97) p = 0.003

The results of subgroup analysis failed to answer the question of whether some treatment features (i.e. dosage, duration) might have an impact on interferon efficacy or whether some participant subgroups

The results of this meta-analysis support the therapeutic efficacy of adjuvant interferon alpha for the treatment of people with high-risk (AJCC TNM stage II-III) cutaneous melanoma in terms of both disease-free survival and, though to a lower extent, overall survival. Interferon is also valid as a reference treatment in RCTs investigating new therapeutic agents for the adjuvant treatment of this participant population.

### 7. Ongoing Trials

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Official title</th>
<th>Status</th>
<th>Protocol ID</th>
<th>Completion date</th>
<th>Last updated</th>
</tr>
</thead>
</table>

Clinical Expert Interest Declaration: There was no conflict of interest declared.

Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?  **No**

2. On initial review, a. Does the newly identified evidence  **a) Yes**

   b.  **b) Yes**
support the existing recommendations?

b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?

3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary: No

4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year? No

Review Outcome: ENDORSED

DSG/GDG Approval Date: November 4, 2013

DSG/GDG Commentary:

New References Identified


Search Strategy:

MEDLINE
1 melanoma:.mp.
2 chemotherapy, adjuvant/
3 drug therapy/
4 adjuvant.tw.
5 postoperative.tw.
6 immunotherapy/
7 immunization/
8 exp immunotherapy, active/
9 vaccin:.tw.
10 immunotherap:.tw.
11 chemotherap:.tw.
12 exp interferons/
13 interferon:.tw.
14 IFN:.tw.
15 levamisole.mp.
16 (dacarbazine or lomustine or CCNU or carmustine or BCNU or vincristine).mp.
17 or/2-16
18 1 and 17
19 Meta-Analysis as topic/
20 meta analy$.tw.
21 metaanaly$.tw.
22 meta analysis.pt. (16185)
23 (systematic adj (review$1 or overview$1)).tw.
24 exp Review Literature as topic/
25 or/19-24
26 cochrane.ab.
27 embase.ab.
28 (psychlit or psyclit).ab.
29 (psychinfo or psycinfo).ab.
30 (cinahl or cinhal).ab.
31 science citation index.ab.
32 bids.ab.
33 cancerlit.ab.
34 or/26-33
35 reference list$.ab.
36 bibliograph$.ab.
37 hand-search$.ab.
38 relevant journals.ab.
39 manual search$.ab.
40 or/35-39
41 selection criteria.ab.
42 data extraction.ab.
43 41 or 42
44 review.pt.
45 43 and 44
46 comment.pt.
47 letter.pt.
48 editorial.pt.
49 animal/
50 human/
51 49 not (49 and 50)
52 or/46-48,51
53 25 or 34 or 40 or 45
54 53 not 52
55 Randomized controlled trials as topic/
56 randomized controlled trial.pt.
57 random allocation/
58 Double blind method/
59 Single blind method/
60 clinical trial.pt.
61 exp clinical trials as topic/
62 or/55-61
63 (clinic$ adj trial$1).tw.
64 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
65 Placebos/
66 Placebo$.tw.
67 Randomly allocated.tw.
68 (allocated adj2 random).tw.
69 or/63-68
70 62 or 69
71 Case report.tw.
72 Letter.pt.
73 Historical article.pt.
74 or/71-73
75 70 not 74
76 75 or 54
77 18 and 76
78 (200507: or 200508: or 200509: or 2006: or 2007: or 2008:).ed.
79 77 and 78

EMBASE
1 melanoma:.mp.
2 exp adjuvant therapy/
3 drug therapy/
4 adjuvant.tw.
5 postoperative.tw.
6 exp immunotherapy/
7 exp immunization/
8 vaccin:.tw.
9 immunotherap:.tw.
10 chemotherap:.tw.
11 exp interferon/
12 interferon:.tw.
13 IFN:.tw.
14 levamisole.mp.
15 (dacarbazine or lomustine or CCNU or carmustine or BCNU or vincristine).mp.
16 or/2-15
17 1 and 16
18 exp Meta Analysis/
19 ((meta adj analy$) or metaanalys$).tw.
20 (systematic adj (review$1 or overview$1)).tw.
21 or/18-20
22 cancerlit.ab.
23 cochrane.ab.
24 embase.ab.
25 (psychlit or psyclit).ab.
26 (psychinfo or psycinfo).ab.
27 (cinahl or cinhal).ab.
28 science citation index.ab.
29 bids.ab.
30 or/22-29
31 reference lists.ab.
32 bibliographic.ab.
33 hand-search.ab.
34 manual search.ab.
35 relevant journals.ab.
36 or/31-35
37 data extraction.ab.
38 selection criteria.ab.
39 37 or 38
40 review.pt.
41 39 and 40
42 letter.pt.
43 editorial.pt.
44 animal/
45 human/
46 44 not (44 and 45)
47 or/42-43,46
48 21 or 30 or 36 or 41
49 48 not 47
50 clinical trial/
51 randomized controlled trial/
52 randomization/
53 single blind procedure/
54 double blind procedure/
55 crossover procedure/
56 placebo/
57 randomized controlled trial$.tw.
58 rct.tw.
59 random allocation.tw.
60 randomly allocated.tw.
61 allocated randomly.tw.
62 (allocated adj2 random).tw.
63 single blind$.tw.
64 double blind$.tw.
65 ((treble or triple) adj blind$).tw.
66 placebo$.tw.
67 Prospective study/
68 or/50-67
69 Case study/
70 case report.tw.
71 abstract report/ or letter/
72 or/69-71
73 68 not 72
74 17 and (49 or 73)
75 (200532: or 200533: or 200534: or 200535: or 200536: or 200537: or 200538: or 200539: or 20054:
or 20055: or 2006: or 2007: or 2008:).ew.
76 74 and 75
COCHRANE DATABASE OF SYSTEMATIC REVIEWS
1 melanoma:.ti,ab,kw.

COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS
1 melanoma:.hw,ti,ab.
2 adjuvant.tw,hw.
3 1 and 2
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