

# 14 Adjuvant systemic therapy of melanoma

Patients with resected AJCC stage IIC, IIB and IIIC disease are at high risk of dying of melanoma (< 50% ten-year survival) and should be considered for adjuvant systemic therapy. Those at intermediate levels of risk (stage IIA, IIB and IIIA) (51–64% ten-year survival) may be considered for clinical trials of adjuvant therapy. The only drug with demonstrated efficacy as adjuvant therapy for high-risk melanoma is interferon-alpha2b. No cytotoxic drug, other biological agent or vaccine has shown superiority over observation. Phase III clinical trials have compared high-dose (20 MU/m<sup>2</sup>), intermediate-dose (5–10 MU), intermediate-dose pegylated interferon, and low-dose (1–3 MU) regimens with observation. Multiple trials have shown that high-dose interferon improves relapse-free survival by approximately 10% at five years, but initially reported benefits in overall survival have disappeared with longer follow-up periods.<sup>1</sup> An individual patient data meta-analysis of ten of 13 observation-controlled trials of various dosing regimens showed a statistically significant benefit of interferon for event-free survival, and an absolute overall survival benefit of 3% (CI 1%–5%) at five years. In this meta-analysis there was no evidence of difference according to dose or duration of therapy. Individual phase III trials of intermediate and low-dose have not shown a clear advantage for interferon over observation.<sup>2</sup>

Long-term pegylated interferon improved four-year relapse-free survival by 7% but had no effect on distant metastasis-free survival or overall survival.<sup>3</sup> High-dose interferon-alpha remains the only FDA-approved systemic adjuvant therapy for melanoma. The toxicity of high-dose interferon-alpha is substantial but reversible, and requires experienced medical oncology management, aggressive supportive measures including the use of prophylactic antidepressants, and careful monitoring and dose-reduction strategies, particularly for hepatotoxicity.<sup>4</sup> Because of the toxicity of high-dose interferon and the uncertain and modest benefits of lower-dosing regimens, clinical trials of new adjuvant therapies are strongly encouraged and observation remains an appropriate comparator in phase III trials.

Evidence summary	Level	Reference
Adjuvant interferon-alpha therapy is the only drug with activity in the adjuvant systemic treatment of melanoma. It improves relapse-free survival by approximately 10% at five years and may have a small impact on overall survival. These benefits must be balanced against considerable, but rapidly reversible, toxicity	I	1, 2

**Recommendations**

	Grade
1. Observation is acceptable management for patients with resected stage I–III melanoma	<b>B</b>
2. These patients be considered for enrolment in clinical trials of adjuvant therapy. Sentinel lymph node biopsy is mandatory staging for the stratification of patients on adjuvant therapy trials. Trials of adjuvant therapy include an observation-only control arm	<b>B</b>
3. Patients with high-risk disease be considered for adjuvant therapy with high-dose interferon-alpha	<b>B</b>
4. Because the toxicity associated with high-dose interferon is considerable, the risks and benefits of therapy in individual patients be carefully reviewed before proceeding	<b>B</b>
5. Patients be treated in an experienced medical oncology facility, monitored closely for toxicity related to treatment with interferon, and dose adjusted based on the degree of toxicity	<b>B</b>

**References**

- 1 Kirkwood JM, Manola J, Ibrahim J, Sondak V, Ernstoff MS, Rao U. A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high-dose interferon for melanoma. *Clin Cancer Res* 2004; 10(5):1670–1677.
- 2 Wheatley K, Ives N, Eggermont AM, Kirkwood JM, Cascinelli N, Markovic S et al. International Malignant Melanoma Collaborative Group Interferon- $\alpha$  as adjuvant therapy for melanoma: an individual patient data meta-analysis of randomised trials. *J Clin Oncol* (meeting abstracts) 2007; (25).
- 3 Eggermont AM, Suci S, Santinami M, Kruit W, Testori A, Marsden J et al. EORTC Melanoma Group EORTC 18991: Long-term adjuvant pegylated interferon-alpha2b (PEG-IFN) compared to observation in resected stage III melanoma, final results of a randomised phase III trial. *J Clin Oncol* (meeting abstracts) 2007; (25).
- 4 Kirkwood JM, Bender C, Agarwala S, Tarhini A, Shipe-Spotloe J, Smelko B et al. Mechanisms and management of toxicities associated with high-dose interferon alfa-2b therapy. *J Clin Oncol* 2002; 20(17):3703–3718.