

# Adjuvant therapy with high-dose interferon $\alpha 2b$ in patients with high-risk stage IIB/III melanoma

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In 2007, a predictably curative therapy for metastatic melanoma has yet to be identified, but we have begun to understand the immunosuppressive impact of melanoma upon the human host, and how melanoma evades the immune response through the induction of tumor tolerance.<sup>1</sup> Interferon  $\alpha 2b$  (IFN- $\alpha 2b$ ) at high dosage is critical to the reversal of signaling defects in the T cells of patients with melanoma<sup>2</sup> and to the effective polarization of dendritic cells. These immunoregulatory effects have been uniquely achieved with levels of IFN $\alpha$  that are only attainable *in vivo* using the high-dose regimen of IFN- $\alpha 2b$  (HDI) that was originally explored in the trial conducted by the Eastern Cooperative Oncology Group, known as E1684.<sup>3</sup>

Pathologic evaluation of primary melanoma microstage and the presence of regional draining 'sentinel' nodes reliably predict risks of relapse and mortality. For patients with stage IIB melanoma (classified as cutaneous disease with >4 mm Breslow depth or >2 mm Breslow depth if ulcerated) relapse and mortality risks exceed 35%. For the more advanced disease stage III (regional lymph node involvement), the risk of relapse and death progressively increases with increasing lymph node involvement. Risk of recurrence or death also depends on whether lymph nodes are involved microscopically (stage IIIA) or grossly (stage IIIB), with the risk of disease recurrence ranging from 35% to more than 70%. In 1984, we began trials of HDI for patients with operable but high-risk melanoma (stage IIB and III) in whom microscopic residual melanoma posed an unacceptable risk. We had observed durable long-term remissions in patients with advanced inoperable disease treated with HDI, and noted that the efficacy of this agent seemed greater, the smaller the disease burden. Both of these observations suggested that HDI might cure microscopic residual disease, where no therapy can reliably achieve this goal.

Three studies conducted by the US national cooperative group have evaluated the benefit of HDI as an adjuvant therapy for high-risk melanoma.

All three trials demonstrated significant and durable reductions in the frequency of relapse in patients receiving HDI compared with observation or vaccination, while the first and third trials demonstrated significantly improved survival in the HDI group than in the observation group (E1684) or in the group treated with the vaccine GMK (E1694). In the E1684 trial, the median relapse-free survival (RFS) of patients in the HDI arm was 1.72 years compared with 0.98 years for those in the observation only arm ( $P_1 = 0.0023$ ). Median overall survival (OS) was also higher in the HDI arm than the observation only arm (3.82 vs 2.78 years;  $P_1 = 0.0237$ ).<sup>4</sup> E1694 was closed early, on the basis of an analysis that demonstrated that patients who did not receive HDI had significantly increased risks of mortality and relapse.<sup>5</sup> The results of E1690 were inconsistent with E1684 and E1694, in that OS benefit did not correspond with RFS benefit, as was seen in the E1684 and E1694 trials. E1690 began before, but was completed after FDA approval of HDI for high-risk melanoma. Not surprisingly, patients who were assigned to observation in this trial, where no nodal staging by either elective or sentinel lymph-node surgery was required, systematically received treatment with HDI when they later developed lymph-node relapse without other evidence of disease. This asymmetrical crossover to HDI may explain why this trial showed RFS benefits of HDI, but not OS benefits as had been observed in the prior (E1684) and subsequent (E1694) US Cooperative Group trials.

The analysis of pooled data from each of the foregoing US national cooperative group studies has been updated to a median follow-up of 12.6 years for E1684, 6.6 years for E1690 and 4 years for E1694. For the E1684 trial, a significant clinical benefit of HDI versus observation is evident with respect to RFS (hazard ratio (HR) 1.38;  $P_2 = 0.02$ ). For all patients entering E1684 regional lymphadenectomy was mandatory, so in this trial, RFS is tantamount to 'distant disease-free survival', an end point that has been the focus of the European Organisation for Research

and Treatment of Cancer as a surrogate for OS. Improvement of OS with HDI over observation remains, with diminished magnitude, at this most recent update (HR 1.22;  $P_2 = 0.18$ ). The smaller OS benefit of HDI observed with late re-analysis of this study does not detract from the meaning of the mature observation published at a median follow-up of 6.9 years—considerably longer than for many other recent trial reports. Since the differences in RFS for the HDI group remain stable out to more than 15 years, the reduction in OS benefit over time raises interesting questions regarding competing causes of mortality; the diminishing benefit may be attributable to deaths from vascular or other events among the treatment cohort, who are now well into their eighth decade of life (current median age >70 years).<sup>6</sup> In E1694, at a median follow-up of 2.1 years, HDI continued to demonstrate superiority to GMK in terms of both RFS (HR 1.33;  $P_2 = 0.006$ ) and OS (HR 1.32;  $P_2 = 0.04$ ).

The cost-benefit analyses we performed following the initial approval of HDI have shown that this regimen compares favorably with accepted standards of cost per year of life gained.<sup>7,8</sup> Toxicity for the HDI regimen has been shown to be easily addressed by experienced medical oncologists—and demonstrates that this regimen can be administered through to completion at one year in 90% of patients who do not relapse.<sup>5</sup>

Finally, a recent meta-analysis of individual patient data from all the available randomized trials evaluating adjuvant IFN therapy was unable to clarify the optimum dosage (high, intermediate or low) of IFN, but did demonstrate a statistically significant benefit for IFN in terms of both RFS and OS.<sup>9</sup> Following several large and rigorous trials of the US co-operative groups conducted over the past 25 years, data from a variety of quarters now support our initial empiric findings, as shown in Supplementary Table 1 online. Patients who are candidates for HDI but do not receive this treatment stand to lose universally agreed upon long-term RFS benefits, amounting to reductions of 24–38% in relapse rate, and 22–32% in mortality analyzed on the basis of hazard ratios for treatment with IFN versus observation, or IFN versus GMK vaccination.<sup>6</sup>

In summary, among all the trials of adjuvant therapy for intermediate or high risk melanoma reported to date from the co-operative groups across the world, no therapy has ever achieved the durable RFS and independently significant OS

benefits that have been observed with HDI. Recent understanding of the molecular impact of HDI upon STAT1 and STAT3 signaling derangements in melanoma, and the identification of factors such as serum cytokine profile and autoimmune response induction may predict therapeutic benefit of the HDI regimen<sup>3,10–13</sup> and suggest our emerging ability to more precisely select appropriate patients for improved therapeutic outcome.

**Supplementary information** in the form of a Table is available on the *Nature Clinical Practice Oncology* website.

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#### Competing interests

JM Kirkwood declared associations with the following companies: Roche and Schering-Plough. See the article online for full details of the relationships. The other authors declared no competing interests.