Pegylated interferon alpha-2b as adjuvant treatment of Stage III malignant melanoma: an evidence-based review

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Introduction: Stage III melanoma, also referred to as regional metastatic melanoma, has five-year survival rates ranging between 40% and 78%. In order to reduce the likelihood of recurrence in this high-risk population, patients undergo resection of primary tumors and all involved nodal basins. Systemic therapy is being pursued in an effort to improve outcome data, but the best strategy has yet to be defined. Interferon alpha-2b remains to date the most promising approach available. Toxicities and intensive intravenous administration, unfortunately, are major concerns. An alternative is the use of interferon in its pegylated subcutaneous form. The aim of this research was to review the evidence for the use of pegylated interferon alpha-2b in Stage III malignant melanoma.

Evidence review: ECOG 1684 was the pivotal trial that first demonstrated a statistically significant benefit in relapse-free and overall survival for adjuvant interferon alpha-2b in high-risk melanoma. Other larger studies, such as ECOG 1690, confirmed a relapse-free survival benefit but did not achieve statistical significance for overall survival. The first study of the pegylated form of interferon alpha-2b in Stage III melanoma, EORTC 18991, is reviewed here. This trial showed a statistically significant improvement in relapse-free survival but not overall survival. Encouraging data of potential equivalent efficacy, easier administration, and fewer Grade 3 and 4 adverse reactions compared with high-dose intravenous interferon raises the question of its potential role in Stage III melanoma in the adjuvant setting.

Keywords: pegylated interferon alpha-2b, melanoma, peg-interferon, adjuvant

Core evidence clinical impact summary for peg-interferon alfa-2b versus observation in Stage III malignant melanoma

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Evidence</th>
<th>Implications</th>
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<tr>
<td><strong>Disease-oriented evidence</strong></td>
<td></td>
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<tr>
<td>Progression-free survival</td>
<td>Hazard ratio 0.82 ( P = 0.01 )</td>
<td>Statistically significant improvement in four-year relapse-free survival in patients on pegylated interferon compared with observation alone (45.6% versus 38.9%)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>Hazard ratio 0.98 ( P = 0.78 )</td>
<td>No statistically significant impact of pegylated interferon alpha compared with observation alone on overall survival (56.8% versus 55.7%)</td>
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<td><strong>Patient-oriented evidence</strong></td>
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<tr>
<td>Safety and tolerability</td>
<td>31% of patients discontinued treatment because of toxicities</td>
<td>Likely compares favorably with high-dose IV interferon</td>
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Introduction

Stage III melanoma, also referred to as regional metastatic melanoma, includes patients with clinical Stage I or II disease who are found to have positive sentinel lymph node involvement, or clinical Stage III disease based on the presence of palpable nodes without evidence of distant metastasis. The 7th edition (2009) of the melanoma staging system according to the American Joint Committee on Cancer specifies that nodal metastases must be looked for with at least one melanoma-associated marker (for example, HMB-45, Melan-A, MART-1) unless diagnostic cellular morphology is present. It also states that even tumor deposits of isolated cells less than 0.1 mm that meet the above criteria of immunologic staining are also scored as N+ and not N0 disease (see Table 1).

This staging system is based on the database analysis of 30,946 patients, of whom 3307 were Stage III. Depending on the extent of nodal involvement (micro- versus macrometastatic nodes, number of nodes involved, or presence of in-transit metastases), this stage is further subcategorized into stages IIIA, IIIB, and IIIC, with five-year survival rates of 78%, 59%, and 40%, respectively (P < 0.0001) (see Figure 1).

In order to improve outcome data and to reduce recurrence risk for Stage III melanoma beyond complete lymph node dissection of all involved nodal basins, several efforts have been attempted, including adjuvant chemotherapy using dacarbazine or nonspecific immune adjuvants, like the Bacillus Calmette-Guerin vaccine and other experimental vaccines. Unfortunately, large randomized trials have failed to support their use in this clinical situation.

Encouraging data do exist for the use of interferon (IFN) alpha (IFNa) and, to date, this remains the only systemic therapy available and approved by the US Food and Drug Administration (FDA), although much discussion about its risks and potential benefits persist. Here we examine first the initial landmark studies that used IFNa in locally advanced melanoma. We then focus the review on the use of IFNa in its pegylated form as an adjuvant treatment of Stage III melanoma.

Interferon alpha

Interferons are pleiotropic cytokines with antiviral, immunomodulatory, and antiangiogenic effects. They inhibit viral replication within host cells, activate immune cells such as macrophages and natural killer cells, and upregulate antigen presentation to lymphocytes. Their use in oncology proliferated early in the 1980s, with some efficacy observed for different malignancies, including hairy cell leukemia, Kaposi’s sarcoma, chronic myelogenous leukemia, and renal cell carcinoma. Single-agent recombinant IFNa was evaluated for metastatic melanoma in Phase I and II trials, with objective response rates of 16%, and about one-third of these being complete. Their use in oncology proliferated early in the 1980s, with some efficacy observed for different malignancies, including hairy cell leukemia, Kaposi’s sarcoma, chronic myelogenous leukemia, and renal cell carcinoma. Single-agent recombinant IFNa was evaluated for metastatic melanoma in Phase I and II trials, with objective response rates of 16%, and about one-third of these being complete.

ECOG 1684

The Eastern Cooperative Oncology Group (ECOG) 1684 trial was a prospective, randomized, controlled trial of high-dose IFNa-2b (HDI) versus observation in high-risk
Table 1 7th Edition (2009) AJCC melanoma staging and classification

<table>
<thead>
<tr>
<th>TNM staging categories</th>
<th>Classification</th>
<th>Thickness (mm)</th>
<th>Ulceration/mitoses</th>
<th>Number of metastatic nodes</th>
<th>Nodal metastatic burden</th>
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<tr>
<td>Tis</td>
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<td>Not applicable</td>
<td>a. Without ulceration and mitosis &lt; 1/mm²</td>
<td>Not applicable</td>
<td>Normal</td>
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<td>T1</td>
<td>≤1</td>
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<td>a. Without ulceration</td>
<td>1</td>
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<tr>
<td>T2</td>
<td>2.01–4</td>
<td>4</td>
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<td>2–3</td>
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<td>T3</td>
<td>4</td>
<td>4</td>
<td>a. Without ulceration</td>
<td>4+</td>
<td>Elevated</td>
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</table>

<table>
<thead>
<tr>
<th>M Site Serum lactate dehydrogenase</th>
<th>M0</th>
<th>No distant metastases</th>
<th>Not applicable</th>
<th>Normal</th>
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</thead>
<tbody>
<tr>
<td>M1a</td>
<td>No distant metastases</td>
<td>Distant skin, subcutaneous or nodal metastases</td>
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<td>Normal</td>
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<tr>
<td>M1b</td>
<td>No distant metastases</td>
<td>Lung metastases</td>
<td>2</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>No distant metastases</td>
<td>All other visceral metastases</td>
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<td>Normal</td>
</tr>
<tr>
<td>M2a</td>
<td>No distant metastases</td>
<td>Any distant metastasis</td>
<td>4</td>
<td>Elevated</td>
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Table 1 (Continued)

Anatomic stage groupings for cutaneous melanoma

<table>
<thead>
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<th>Clinical staging Pathologic staging</th>
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<tr>
<td></td>
</tr>
<tr>
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<tr>
<td>IA</td>
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<td>IA</td>
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<tr>
<td>II</td>
</tr>
<tr>
<td>IA</td>
</tr>
<tr>
<td>III</td>
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(Stage IIB and Stage III) resected melanoma that accrued patients between 1984 and 1990. In total, 287 patients entered the study and 280 were analyzed as the efficacy sample. Patients were randomized by permuted blocks within four categories of clinical and pathologic extent of disease (T4N0M0, any TpN1M0, any TcN1M0, and any TxN1M0 recurrent) to treatment with IFNa 20 MU/m²/day intravenously (IV) five days per week for four weeks, then three times weekly at 10 MU/m²/day subcutaneously (SC) for 48 weeks versus close observation. Treatment was started within 42 days after lymphadenectomy for recurrence and within 56 days after primary surgery and lymphadenectomy for initial presentation. Of note, at that time, even Stage IIB patients underwent complete regional lymph node dissection, which is currently not considered standard practice. However, it is also true that sentinel lymph node sampling was still in the process of becoming standard in this patient population. The primary endpoint was RFS, with the OS endpoint added at a later stage prior to final analysis.

One hundred and thirty-seven patients were randomized to the observation arm and 143 to the IFNa arm, with a similar distribution of patient characteristics and known prognostic factors between the groups. Of note, the majority of patients (63.5% in the observation arm and 60.8% in the IFNa arm) belonged to the TxN1M0 recurrent group.

After a median follow-up of 6.9 (range 0.6–9.6) years, median RFS was 1.72 years in the IFNa group (95% confidence interval [CI] 1.07–2.88) versus 0.98 years in the observation group (95% CI 0.50–1.65) with a one-sided P value of 0.0023. RFS at five years was 37% in the treatment arm versus 26% in the observation arm.

Overall median survival time was 3.82 years (95% CI 2.34–7.08) for the IFNa group and 2.78 years (95% CI 1.83–4.03) for the observation group, again with a significant one-sided P value of 0.0237. OS at five years was 46% in the treatment arm versus 37% in the observation arm.

There was a suggestion that the greatest benefit was obtained by the microscopic node-positive group, although the study was not powered to determine this, with only 34 patients enrolled in this specific category. Hazard plots suggested that the greatest benefits were achieved early within the first year of treatment.
These results prompted the approval of IFNa as adjuvant therapy for high-risk melanoma by the FDA in 1995.

Toxicities were common, requiring dose delays or reductions in at least 37% of patients during the IV intensive phase and in 36% during the subsequent SC phase. Most treatment withdrawals secondary to toxicity happened within the first four months of treatment.

ECOG 1690

This Intergroup trial was designed to confirm the results of ECOG 1684 and to compare HDI and low-dose interferon (LDI) versus observation in a prospective fashion. Again, patients were randomized by permuted blocks to treatment with HDI for one year (20 MU/m²/day IV five days/week for four weeks then 10 MU/m²/day SC three times a week for 48 weeks), LDI for two years (3 MU/m²/day SC three times a week), or observation. Eligibility criteria were the same as those described in ECOG 1684, although patients with normal regional lymph nodes (T4cN0M0) were not required to undergo staging lymph node dissection.

Strict dose modifications for toxicities were enforced, without attempts at dose re-escalation. Primary endpoints were RFS for the HDI versus LDI groups, and LDI versus observation groups.

With a predefined target accrual of 625 patients, the study enrolled 642 patients between 1991 and 1995, with 608 being analyzed. Baseline characteristics across treatment groups were comparable. As in ECOG 1684, the majority of patients (50.8%) belonged to the recurrent disease in regional lymph nodes after wide excision of primary melanoma (TxN1M0 recurrent) group.

After a median follow-up of 4.3 years, five-year RFS was 44%, 40%, and 35% in the HDI, LDI, and observation groups, respectively. There was a significant RFS benefit in the HDI group compared with observation (hazard ratio [HR] = 1.28, \( P = 0.025 \)) but not so with LDI (HR LDI/observation = 1.19, \( P = 0.17 \)). Five-year OS was 52%, 53%, and 55% in the HDI, LDI, and observation groups, respectively, with no statistically significant benefit seen.
Comparison of ECOG 1690 and ECOG 1684 revealed interesting findings. For patients randomized to the observation arms, those enrolled in ECOG 1690 enjoyed better OS than their ECOG 1684 counterparts (median OS 6.0 years in ECOG 1690 versus 2.8 years in ECOG 1684 observation arms). There was also an improvement in RFS in both the observation and treatment arms. The reasons behind these findings are not entirely clear. However, the authors concluded that, because IFN had received FDA approval at the time of this study, postrelapse IFN-containing salvage therapy for patients in the observation arm was the main confounding factor.

Toxicities described were similar to those in the ECOG 1684 study, with dose delays or reductions in 58% of patients in the HDI IV phase and in 59% of patients in the SC maintenance phase. No toxic deaths were reported.

**Pooled analysis of Intergroup trials**

The data from ECOG 1684 and ECOG 1690 were updated to April 2001 and reported in a pooled analysis. The main goals were to identify prognostic factors and to assess treatment effects with longer follow-up.

For ECOG 1684, median follow-up was extended from 6.9 to 12.6 years. There was still a statistical significant RFS benefit for HDI over observation (HR = 1.38, \( P = 0.02 \)), with no statistically significant improvement in OS (HR = 1.22, \( P = 0.18 \)) (Figure 2).

For ECOG 1690, median follow-up was extended from 4.3 to 6.6 years. The RFS benefit of HDI over observation trended towards statistical significance without reaching it (HR 1.24, \( P = 0.09 \)), and still without OS benefit (Figure 3).

Pooling data from both studies in order to compare HDI versus observation, a total of 713 patients were available for...
analysis with a median follow-up of 7.2 years. Findings from ECOG 1690 were confirmed, with HDI having an advantage in terms of RFS (HR = 1.3, P = 0.006) but without a significant OS benefit (HR = 1.08, P = 0.42) (Figure 4).

**Additional data analysis**

Wheatley et al presented an individual patient data meta-analysis of all available randomized trials evaluating the role of adjuvant IFN in high-risk melanoma at the 2007 American Society of Clinical Oncology meeting. Event-free survival (EFS) and OS were assessed, and odds ratios (OR) and CIs calculated for patients who received IFN at various doses versus no IFN. In total, 6067 patients were included. In this individual patient data review of IFN studies, there was a statistically significant benefit of IFN for EFS, with an OR of 0.87, CI 0.81–0.93, and P value of 0.00006. It also demonstrated an OS survival benefit for IFN, with an OR of 0.9, CI 0.84–0.97, and P value of 0.008. In other words, the absolute benefit for OS provided by IFN was statistically significant at 3% with a CI of 1%–5% at five years.

The most recent meta-analysis examining the effects of IFNα versus observation or any regimen other than IFNα in high-risk melanoma was presented by Mocellin et al. Fourteen randomized, controlled trials and a total of 8122 patients were
included, with 4362 (53.7%) patients randomly assigned to the IFNa arm. The meta-analysis showed statistically significant benefit for patients who underwent IFNa treatment (HR for disease recurrence 0.82, 95% CI 0.77–0.87, \( P < 0.001 \)). There was also a statistically significant improved OS for patients undergoing IFNa treatment (HR for death 0.89, 95% CI 0.83–0.96, \( P = 0.002 \)). Subgroup analysis did not identify any statistically significant relationship between DFS or OS according to IFNa regimen or type, TNM disease stage, or study design.

**Peg-interferon in melanoma**

Pegylation involves the conjugation of a protein with polyethylene glycol (PEG). Following SC injection of such pegylated protein, rate of absorption is reduced, renal and cellular clearance is reduced, and the immunogenicity of such protein is also reduced.\(^{10}\) There are currently two forms of pegylated IFN, mainly being used for the treatment of chronic viral hepatitis. Of those, pegylated interferon alpha-2b (pegIFNa-2b, PEG-Intron®, Schering Corporation, Kenilworth, NJ) has been the only one studied in melanoma.

The pharmacokinetic profile of pegIFNa-2b has been previously described in chronic hepatitis C patients and later confirmed in Phase I and II trials in oncology.\(^{10}\) Its long serum half-life of approximately 40 hours (compared with four hours for regular IFNα-2b) supports once-weekly administration. The maximum tolerated dose is 6 \( \mu \)g/kg/week. The safety and side effect profile is similar between pegylated and nonpegylated forms.\(^{10,11}\)

**EORTC 18991**

The European Organization for Research and Treatment of Cancer (EORTC) 18991 was a large Phase III, randomized, controlled trial, the aim of which was to assess the effect of long-term administration of pegIFNa-2b in patients with resected Stage III melanoma.\(^{12}\) Ninety-nine centers in 17 (mostly European) countries participated in this trial, which included systemic treatment-naïve, nonocular, nonmucosal Stage III melanoma (TxN1-2M0). Patients were randomized in a one-to-one ratio to treatment with pegIFNa-2b for five years versus observation alone. The treatment arm consisted of an induction phase of pegIFNa-2b given as 6 \( \mu \)g/kg SC a week for eight weeks, followed by a maintenance phase of pegIFNa-2b given as 3 \( \mu \)g/kg SC per week for five years. Dose adjustments were prespecified according to toxicities and to maintain an ECOG performance status of 0–1. The primary endpoint was RFS and secondary endpoints were distant metastasis-free survival, OS, and safety.

In total, 1256 patients were randomized and analyzed based on intention-to-treat population. Both treatment and observation groups had comparable baseline characteristics. Median age was 50 years, 43% of patients had N1 disease and 57% of patients had N2 disease. Compliance in the induction phase of the treatment arm was good (range of treatment 7.3–8.0 weeks) and median duration for the maintenance phase was 12 (3.8–33.4) months.

After a median follow-up of 3.8 years, there was a significantly improved four-year RFS for pegIFNa-2b compared with observation alone (45.6% versus 38.9%, HR = 0.82, \( P = 0.01 \)). No statistical significance was reached for the four-year distant metastasis-free survival (48.2% for pegIFNa-2b versus 45.4% for observation, HR = 0.88, \( P = 0.11 \)) and for four-year OS rates (56.8% for pegIFNa-2b and 55.7% for observation groups, HR = 0.98, \( P = 0.78 \)).

Kaplan-Meier curves indicated that the treatment benefit began early and remained throughout the study. Patient subgroup analysis suggested that earlier disease (N1) and fewer numbers of lymph nodes involved showed more benefit from pegIFNa-2b treatment effect compared with more advanced disease (Figure 5).

The findings from this EORTC 18991 trial confirmed what has been seen with the use of standard IFNAs, namely, a modest, statistically significant improvement in RFS, without such an effect for OS.

One hundred and ninety-one (31%) of the 608 patients who received allotted intervention in the pegIFNa-2b group discontinued treatment because of toxicities. The most common toxicities that prompted discontinuation of treatment (without necessarily being Grade 3 or 4 toxicities) were fatigue (25%), followed by depression (16%), anorexia (15%), elevated liver function tests (13%), myalgias (13%), headaches (12%), nausea (12%), and fever (11%). Although stepwise dose reductions were carried out in order to maintain an ECOG performance status of 0–1, specific data about the number or percentage of patients who actually required such dose reductions was not specified.

When compared with the toxicity profiles of HDI in the prior ECOG 1684 and ECOG 1690 trials, the incidence of Grade 3 and 4 adverse events with pegIFNa-2b was less than with HDI. For example, Grade 3 and 4 fatigue was reported in 16% of patients on pegIFNa-2b compared with 24% of patients on HDI. Grade 3 and 4 myalgias affected 5% of patients on pegIFNa-2b, compared with 17% of patients on HDI.

**Quality of life impact**

While the toxicities described with the use of pegIFNa-2b in the EORTC 18991 study are similar to and in fact, compare favorably with, those of nonpegylated IFN trials, the impact...
of quality of life with pegIFNa-2b versus observation alone was formally addressed as a secondary endpoint during the EORTC 18991 study and published separately.\textsuperscript{13} The EORTC Quality of Life Questionnaire C30 (EORTC QLQ-C30) used for this evaluation is a validated tool that is commonly used in international oncology trials.\textsuperscript{14} An additional nonvalidated IFNa-specific symptom checklist was also included. All randomly assigned patients in both treatment and placebo arms were included. Times of assessment were at baseline, three months, 12 months, and yearly thereafter. The results of the study revealed a negative impact on global health-related quality of life for patients on the pegIFNa-2b arm compared with placebo. Loss of social functioning, appetite loss, fatigue, and symptoms specific to pegIFNa-2b therapy were more pronounced in the treatment group. Other measurements showed a similar trend, losing statistical significance after the initial three-month evaluation.

Similar quality of life evaluations have been studied with different regimens involving nonpegylated IFN. HDI and pegIFNa-2b have not been compared head to head for quality of life impact. However, there is a suggestion that pegIFNa-2b compares favorably. Mohr et al from the German Dermatologic Cooperative Oncology Group, presented preliminary data of the health-related quality of life assessment in a group of patients receiving HDI using the same EORTC QLQ-C30 scale at the 2007 meeting of the American Society of Clinical Oncology.\textsuperscript{15} The global quality of life score decreased 41\% after the initial four weeks of IV HDI, and then an average of 22\% during the SC treatment phase.\textsuperscript{15} With the caveat of this being an indirect comparison of separate studies, it is interesting to note that the global quality of life score in patients receiving pegIFNa-2b decreased 16\% at three months and 15\% at two years,\textsuperscript{14} comparing favorably with HDI. No data for the one-month evaluation were available.

**Economic impact**

Cost-effectiveness studies that have looked into adjuvant IFNa in melanoma have applied different models to extrapolate clinical results using the data of the different studies available. Such analysis has been carried out for the US, Canada, UK, and Spain.\textsuperscript{16–18} In general, the cost-effectiveness ratios postulated range between US$20,000 and US$50,000 per life year gained. There seems to be a larger cost-effective margin for younger patients in more advanced stages of disease. The controversy arises mostly around the data that these calculations are based on. Cost-effectiveness is favorable when there is an OS advantage, something that has only been seen in the ECOG 1684 trial described and not so in the others as reviewed here. The question arises as to whether these cost-effectiveness assessments represent a gross overestimate if no survival advantage is proven? Moreover, the negative impact in health-related quality of life experienced by patients on IFNAs makes it highly unlikely that the intervention is favorable in terms of cost per quality-adjusted life year (QALY). This is illustrated in the most recent analysis performed by Cormier et al.

![Figure 5](https://www.dovepress.com/)

**Figure 5** Kaplan-Meier curves of (A) recurrence-free survival, (B) distant metastasis-free survival, and (C) overall survival for patients treated in EORTC 18991. Reprinted from The Lancet, Vol 372, Eggermont AMM, Suciu S, Santinami M, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected Stage III Melanoma: Final Results of EORTC 18991, a randomized phase III trial. 117–126. © 2008, with permission from Elsevier.
who quote a cost-effectiveness ranging from US$76,000 to US$169,000 per QALY (depending on disease stage), crossing the historic threshold of US$100,000 per QALY as the cost-effective limit.16

There are no studies available addressing these same questions for pegIFNa-2b in the adjuvant setting for high-risk resected melanoma. Perhaps a preliminary assumption might be that this is unlikely to be favorable, given that the EORTC 18991 study did not show an OS benefit with treatment, and the health-related quality of life impact associated with treatment was clearly detrimental. On the other hand, and quite importantly, the ease of administration and improved tolerability of pegIFNa-2b compared with regular IFNa provides an additional layer to be examined and considered within this complex problem.

Future trials and unanswered questions

There are two additional trials looking into the use of pegIFNa-2b in high-risk melanoma that have completed patient enrollment and are looking into improvements in DFS. One of them, initiated by the European Association of Dermatologic Oncology, recruited 890 patients and randomized them to pegIFNa-2b 100 µg weekly for 36 months versus IFNa 3 MU three times a week for 18 months. The second one, initiated by the German Dermatologic Cooperative Oncology Group, has recruited 880 patients and randomized them to pegIFNa-2b 180 µg weekly for 24 months or IFNa 3 MU three times a week for 24 months. Outcome data for both studies are not available at this time.19

While there certainly are patients who benefit from treatment with pegIFNa-2b, we have yet to recognize those who will and thus spare those who will not the significant drug toxicities. Markers to identify such individuals are not yet available, and this remains an ongoing effort in research. In the meantime, the current evidence behind pegIFNa-2b is not enough to satisfy our pursuit for more effective treatment options in melanoma. However, should interferon be considered as “standard of care” (and it is relatively routinely given in the community), then the question arises as to whether pegIFNa-2b should also be approved, given the equivalent efficacy, easier administration, and possibly less toxicity.

Multiple trials have looked into IFN with its variations in route of administration, dosage, length of treatment, and formulations. While all of these remain important and necessary questions for the advancement of treating such a challenging disease, it also highlights the lack of more compelling treatment options, with a clear survival advantage, that patients who suffer from this terrible illness so desperately need.

Disclosure

The authors report no conflicts of interest in this work.

References