

## Pegylated Interferon for the Adjuvant Treatment of Melanoma: FDA Approved, but What Is Its Role?

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In 2011, the U.S. Food and Drug Administration (FDA) approved peginterferon-alfa-2b (Sylatron®; Merck/Schering-Plough, Kenilworth, NJ) for the adjuvant treatment of patients with resected node-positive melanoma based on the results of a single, large European Organization for Research and Treatment of Cancer (EORTC) trial showing a statistically significant improvement in the relapse-free survival (RFS) interval without an accompanying overall survival (OS) advantage [1]. The article by Herndon et al. [2] in this issue of *The Oncologist* helps to answer some of the questions that have surrounded this approval and provides important context to physicians counseling melanoma patients. This is particularly important because melanoma oncologists in the U.S. and worldwide had very limited experience using pegylated interferon for the adjuvant therapy of melanoma prior to the FDA approval [3].

Among the questions Herndon et al. [2] address are: Why approve this therapy based only on an RFS improvement? Why approve it for all patients with node-positive melanoma and not a subset, such as those with microscopic nodal involvement detected by sentinel node biopsy? Why approve a 5-year treatment regimen? Regarding the RFS interval, the FDA concluded that “the clinically meaningful prolongation in time without disease . . . , which is evidence of direct clinical benefit given its magnitude” [2], outweighed the risk for toxicity, particularly in view of the lack of alternatives and salvage therapies. Their analysis of the EORTC data also indicated that the RFS benefit was “internally consistent across relevant subsets defined by . . . prognostic variables” [2], an important observation that differs from the conclusion of the EORTC investigators themselves [4]. By contrast, however, post hoc analyses were unable to discern the optimal dose or duration of peginterferon, and so they chose to approve the therapy for all node-positive patients in the dose and schedule used in the EORTC trial. They recognize the significance of

the questions about dose and duration, which they believe is an issue for postmarketing trials to further explore.

Despite the insights Herndon et al. [2] provide, many questions remain about the role of pegylated interferon—or any formulation, dose, and schedule of interferon for that matter—in the adjuvant therapy of patients with melanoma. Thousands of patients have been treated in adjuvant interferon trials evaluating dosing, schedule, toxicity, and quality of life, yet controversies persist regarding the OS benefit and the appropriateness of the RFS time as an endpoint justifying substantial toxicity. More importantly, many have asked whether or not advances in treating metastatic disease (salvage treatment) make adjuvant interferon regimens irrelevant.

We agree with the FDA that the available evidence supporting the RFS benefit with adjuvant interferon and peginterferon is compelling, and note that current and future adjuvant trials (such as two large multicenter trials evaluating ipilimumab compared with either placebo or high-dose interferon-alfa-2b) employ the RFS duration as a primary endpoint, in part because of concerns about the confounding effects of postrelapse therapy on the survival time. But from the patient’s perspective, delaying relapse is potentially more important than ever: we have more effective drugs for treating metastatic melanoma than ever, but their use has not been optimized and improvements are coming at a dramatic rate. Two to 3 years from now, treatments for stage IV melanoma will likely be substantively more effective and probably less toxic than they are now. A few extra months could afford patients access to options that would otherwise not be available in time.

By contrast, evidence supporting a specific interferon dose, duration, or formulation—or identifying subsets of patients most likely to benefit from therapy—is currently uncon-

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vincing. No randomized trial has shown any evidence that extending interferon treatment beyond 12–18 months improves outcomes [5], nor have the roles of 1- or 2-month-long higher-dose i.v. or peginterferon “induction” regimens been specifically shown to be beneficial. The pharmacokinetic properties most important to the salutary effect of interferon therapy or most directly correlated with toxicity remain almost entirely unknown, which is particularly unfortunate because the pharmacokinetic differences between standard and pegylated interferon are now fairly well understood [3, 6]. Specifically, the i.v. induction phase of the FDA-approved high-dose interferon- $\alpha$ -2b regimen results in higher peak plasma levels of interferon than are achievable with any other dose, schedule, or formulation of interferon, but the duration of exposure is short and the overall exposure (area under the dose–duration curve) is similar to that seen over the course of the 2-month induction dose of the peginterferon regimen. Conversely, the peak level is similar for the thrice-weekly s.c. dose of the high-dose interferon- $\alpha$ -2b regimen and the weekly “maintenance” dose of the peginterferon regimen, whereas the peginterferon regimen provides superior exposure to interferon. In the absence of any known toxicities attributable to the continuous presence of interferon over the entire course of therapy (which is very different from the known absence of toxicities attributable to this), these data suggest that peginterferon might be the preferred formulation for maintenance therapy, regardless of what induction regimen is employed. But the possibility that high peak levels may be important for antitumor efficacy in some situations (for instance, in patients with greater amounts of microscopic residual tumor at the start of therapy—presumably those with macroscopic or multi-node-positive disease at surgery), or even all cases, needs to be further explored, as does the possibility that high peak levels contribute heavily to acute toxicity and only marginally to efficacy. More certainty about the importance of these basic pharmacokinetic properties would clearly aid in defining the “optimal”—that is, more efficacious and/or less toxic—approaches.

What about subsets of patients who might benefit most from peginterferon treatment, compared with high-dose interferon or no adjuvant treatment at all? Eggermont et al. [1, 4] found that patients with sentinel node–positive disease and those with ulcerated primaries constituted the groups that fared better with peginterferon than with observation, but the FDA

analysis did not find results in these patient subsets to be statistically significant. Still, when Eggermont et al. [1, 4] analyzed EORTC patients who had both ulcerated primary tumors and sentinel node–positive disease from two trials—one using intermediate-dose interferon and the other using peginterferon—they found an astounding 42% longer OS time (with similar improvements in the distant metastasis-free survival and RFS times) for patients randomized to interferon or peginterferon than with observation [7]. This “subset of a subset” analysis must be considered preliminary and hypothesis generating, but a survival benefit of this magnitude represents a hypothesis that must be tested further. Disappointingly, there are currently no planned trials that directly test this striking observation—only a planned EORTC trial in stage II melanoma patients with ulcerated primaries and negative sentinel nodes, a trial that uses a modified 2-year peginterferon regimen with no induction phase.

The emergence of therapies with a proven OS benefit in patients with unresectable stage IV melanoma, something neither interferon- $\alpha$  nor peginterferon have ever been shown to be capable of, raises the possibility that more effective adjuvant regimens can be developed. An EORTC trial of ipilimumab versus placebo [8] has already been completed and results are eagerly awaited, but the ongoing U.S. Intergroup trial comparing ipilimumab with high-dose interferon more directly tests the question of whether or not ipilimumab should be considered superior to the currently available adjuvant therapy. Adjuvant trials of targeted therapy for patients with mutant *BRAF* melanoma are about to begin, but it is legitimate to question whether or not an adjuvant approach with drugs that seem to inevitably induce resistance will be as successful as approaches based on immunologic agents. For now, although the preferred management of patients with node-positive melanoma remains enrollment in clinical trials, the impact of interferon therapy on the RFS time cannot and should not be ignored. Until and unless something clearly better comes along, adjuvant interferon- $\alpha$  and peginterferon remain relevant to our patients despite the many questions that remain about their optimal use.

#### AUTHOR CONTRIBUTIONS

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**Final approval of manuscript:** Vernon K. Sondak, Ragini Kudchadkar

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See the accompanying article on pages 1323–1328 of this issue.