U.S. Food and Drug Administration Approval: Peginterferon-alfa-2b for the Adjuvant Treatment of Patients with Melanoma

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the setting in which the use of peginterferon-alfa-2b is appropriate for melanoma patients.
2. Define the expectations with regard to survival and side effect profile in patients with melanoma receiving peginterferon-alfa-2b.

CME

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ABSTRACT

On March 29, 2011, the U.S. Food and Drug Administration approved peginterferon alfa-2b (PEG-IFN) (Sylatron[™]; Schering Corporation, Kenilworth, NJ) for the adjuvant treatment of melanoma patients with microscopic or gross nodal involvement following definitive surgical resection including complete lymphadenectomy.

The approval was based on a single, open-label, multicenter trial enrolling 1,256 patients. After surgical resection, patients were randomized (1:1) to either PEG-IFN or observation for 5 years. PEG-IFN, 6 μ g/kg per week, was administered s.c. for eight doses, followed by 3 μ g/kg per week for up to 252 weeks.

Stratification factors included microscopic or gross nodal involvement, number of positive nodes, Breslow

thickness, ulceration, sex, and study center. Patients were assessed for recurrence by the investigators based on physical examination every 3 months for 2 years and every 6 months thereafter.

The relapse-free survival (RFS) interval, the primary efficacy endpoint, was significantly longer in PEG-IFN-treated patients. The median RFS times were 34.8 months and 25.5 months, respectively. There was no statistically significant difference in the overall survival time.

The most common (>60%) grade 1–4 adverse reactions were fatigue, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), pyrexia, headache, anorexia, myalgia, nausea, chills, and injec-

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tion site reactions. The most common serious adverse reactions were fatigue, increased ALT and AST, and pyrexia. Thirty-three percent of patients receiving PEG-IFN discontinued treatment as a result of adverse reac-

tions. Five deaths were reported within 30 days of the last treatment dose, two resulting from cardiovascular disease considered as possibly related to treatment. *The Oncologist* 2012;17:1323–1328

INTRODUCTION

Interferon has a long history in the adjuvant treatment of patients with malignant melanoma. It was first approved in December, 1995 for patients who were rendered disease free by surgery and who were at high risk for recurrence. In the trial that supported the approval, interferon treatment led to a significantly longer overall survival duration, although the survival advantage diminished after a longer follow-up time [1, 2]. Since the first adjuvant interferon trial, 12 additional surgical adjuvant randomized trials have been conducted using various dosing schedules of interferon (interferon- α -2a, interferon- α -2b, interferon γ , peginterferon α -2b [PEG-IFN]) and various comparator regimens [3, 4]. Six of the 12 trials demonstrated a relapse-free survival (RFS) benefit and one showed a survival benefit. A literature-based meta-analysis of 12 interferon trials demonstrated a 17% lower relapse risk than in untreated controls, without a survival advantage [5]. Since the approval of PEG-IFN for melanoma, a meta-analysis of 14 interferon trials reported a modest, but statistically significant, survival advantage in patients with high-risk cutaneous melanoma treated with interferon- α [6].

PEG-IFN is a covalent conjugate of recombinant interferon α -2b with monomethoxy-polyethylene glycol. The biological activity derives from the interferon α -2b moiety. The PEG (polyethylene glycol) protects the molecule from proteolytic breakdown and increases the biological half-life of the interferon protein. Peg-Intron is a longer-acting formulation of Schering-Plough's Intron A, which is a recombinant version of a naturally occurring interferon- α . In contrast to Intron A, which is administered as an i.v. infusion daily for 5 days, weekly for 4 weeks, followed by a s.c. injection three times weekly, Peg-Intron is administered s.c. once a week. [7–9].

On March 29, 2011, the U.S. Food and Drug Administration (FDA) granted approval of PEG-IFN (Sylatron™; Schering Corporation, Kenilworth, NJ) for the adjuvant treatment of patients with American Joint Committee on Cancer (AJCC) stage III melanoma as evidenced by microscopic or gross nodal involvement. In this report, we describe the FDA review process and results that led to this approval.

MATERIALS AND METHODS

A single, phase III, open-label, randomized, multicenter trial was submitted, which included 101 participating sites, primarily European. The trial was conducted by The European Organisation for Research and Treatment of Cancer (EORTC) [10].

Study patients had melanoma of any tumor stage with either microscopic or palpable nodal involvement and no distant metastases. They had undergone definitive surgical resection,

including regional lymphadenectomy within 70 days of study entry, and had acceptable hematologic, hepatic, and renal function. Patients with ocular or mucous membrane melanoma were excluded as were patients with in-transit metastasis. Other exclusions were for serious concomitant disease and for prior systemic melanoma therapy.

Randomization was performed using a minimization procedure to balance the following stratification factors: type of nodal involvement (N1, microscopic, nonpalpable node involvement usually discovered by sentinel node biopsy; N2, palpable node involvement), number of positive nodes (one, two to four, five or more, or not assessed), Breslow primary thickness (<1.5 mm, ≥ 1.5 mm to 4 mm, ≥ 4 mm), ulceration of the primary tumor (present, absent, or unknown), gender, and institution.

Patients were randomized 1:1 to the following arms: arm A, in which PEG-IFN was administered at 6 μ g/kg s.c. weekly for eight doses, then at 3 μ g/kg s.c. weekly for up to 5 years or until disease progression, unacceptable toxicity, or death, and arm B, with observation for 5 years beginning at randomization.

Dose modifications for PEG-IFN toxicity were included in the protocol. During the first 8 weeks of treatment, the starting dose of 6 μ g/kg per week could be first decreased to 3 μ g/kg per week, then to 2 μ g/kg per week, and finally to 1 μ g/kg per week. PEG-IFN was permanently discontinued if the patient was unable to tolerate 1 μ g/kg per week. When the PEG-IFN dose was 3 μ g/kg per week, the dose could be decreased to 2 μ g/kg per week and then to 1 μ g/kg per week. PEG-IFN was permanently discontinued if the patient was unable to tolerate 1 μ g/kg per week.

The primary FDA regulatory endpoint was the relapse-free survival (RFS) interval as determined by an independent review committee (IRC) whose members were masked to treatment assignment. The IRC conducted an audit of patient-level data from case report forms (radiology and pathology reports were available upon request) and assigned the following dates for each patient: earliest date of recurrence, last date the patient was free from recurrence, earliest date of distant metastasis, and last date the patient was free from distant metastasis. Secondary endpoints were the distant metastasis-free survival (DMFS) time (the applicant's primary endpoint), the overall survival time, the recurrence-free interval, and quality of life. The RFS time was defined as the time to the earliest of the following events: local-regional relapse, distant metastasis, or death. Investigators were instructed to obtain pathologic evidence of melanoma recurrence unless the recurrence occurred in the brain. The presence of multiple lesions during an imaging examination of the chest or liver was considered as acceptable evidence of distant recurrence.

Tumor assessments during the lower-dose treatment phase

were made by physical examination every 3 months (months 3–24) and then every 6 months (years 2–5). Patients with N1 disease required a chest x-ray and liver ultrasound, and patients with N2 disease required imaging with a chest c-ray or computed tomography (CT) scan of the chest, CT scan of the abdomen, and CT or magnetic resonance imaging scan of the brain at study entry. All patients were to undergo a chest x-ray every 6 months, and additional imaging modalities were performed in accordance with medical practice and physician discretion.

The original analysis plan required a sample size of 879 patients. The final analysis was to be performed after 571 DMFS events, in order to provide 90% power at a two-sided significance level of 0.05 to detect a 10% greater 4-year DMFS rate, assuming that the true DMFS rate at 4 years in the observation arm was 30%. The analysis plan included a proposal for an interim analysis of the DMFS rate after 450 events and used the O'Brien Fleming boundaries for significance determination and adjustment for controlling the type I error rate with a two-sided *p*-value of .05. The study also was planned to have 85% power to detect a 10% absolute difference (35% versus 45%; hazard ratio [HR], 0.76) in the 5-year survival rates after 486 deaths.

In June 2002, the protocol was amended based on revised assumptions for the 4-year DMFS-free rate among patients with N1 disease in the observation arm of a second EORTC study, which indicated that the DMFS rate for control patients in the study could approach 40% at 4 years. Thus, based on these revised assumptions, the sample size was increased to 1,200 patients in order to observe the required 576 events to detect a 9.75% greater 4-year DMFS rate (control vs. PEG-IFN, 40% vs, 49.75%) with 90% power.

The analysis plan was also revised following the FDA's meeting with Schering on September 5, 2006. The revised analysis plan stated that the primary efficacy analysis of the RFS rate would be an unadjusted log-rank test to be conducted after 576 DMFS events.

RESULTS

In total, 1,256 patients were registered and randomized at 101 clinical sites from July 18, 2000 to August 15, 2003. The majority of the patients were enrolled from Europe (96%), with the remainder accrued in Australia (3%) and Israel (1%). The countries with the highest accruals were the U.K. (26%) and Italy (18%). Patient demographics for baseline entry variables and tumor characteristics are summarized in Table 1.

Based on 696 RFS events determined by the IRC at the data cutoff date of March 31, 2006, the primary analysis of the RFS probability was performed using the intent-to-treat population, of whom 696 patients experienced RFS events PEG-IFN, 328; observation, 368). The median RFS interval was 34.8 months (95% confidence interval [CI], 26.1–47.4 months) for PEG-IFN and 25.5 months (95% CI, 19.6–30.8 months) for observed patients (Table 2, Fig. 1). In order to maintain a two-sided type I error rate of 0.05, the nominal two-sided significance level for the final analysis of the RFS outcome

was 0.036, based on the number of DMFS events in the interim analysis.

The RFS outcome is a composite endpoint that may be defined by death or relapse. In the PEG-IFN arm there were 328 RFS events (52%), and death was the first RFS event in 1% of patients, distant metastasis was the first event in 30% of patients, and local-regional recurrence was the first event in 22% of patients. Eighty-two percent of patients with local-regional recurrence subsequently developed distant metastasis. In the observation arm, there were 368 RFS events (59%), and death was the first RFS event in 1% of patients, distant metastasis was the first event in 33% of patients, and local-regional recurrence was the first event in 25% of patients. Seventy-three percent of patients with local-regional recurrence subsequently developed distant metastasis.

Sensitivity analyses were performed by the FDA to verify the reliability and robustness of the RFS effect. A "worst-case" scenario analysis of the RFS outcome was conducted to investigate the potential impact of missing data on the RFS event size. In this "worst-case" scenario analysis, RFS dates were re-assigned to the previous office visit date if the event date for patients in the PEG-IFN arm was outside the planned assessment window, and it was reassigned to the next visit date for patients in the observation arm if the event date occurred within 3 months of the previous visit (6 months if after 2 years from randomization). The "worst-case" scenario analysis results using these reassigned dates demonstrated median RFS times of 33.9 months (95% CI, 25.3–47.4 months) for the PEG-IFN group and 28.5 months (95% CI, 20.0–32.9 months) for the observation group and an estimated HR of 0.86 (95% CI, 0.74–0.99), which was consistent with the primary RFS analysis.

There was no significant survival difference between PEG-IFN-treated patients and patients randomized to observation. There were 525 deaths (PEG-IFN, 262; observation, 263). The estimated HR was 0.98 (95% CI, 0.82–1.16; *p*-value = .781).

The safety database was derived from the experiences of 608 patients who received treatment with PEG-IFN from study EORTC 18991 and 628 patients who were observed. Nineteen patients in the intent-to-treat population randomized to the PEG-IFN arm received no treatment and were not included in the review of safety.

There was differential ascertainment for safety information between the two arms. For patients receiving PEG-IFN, adverse event data were collected from the date of randomization until 30 days after the final dose of PEG-IFN. For patients in the observation arm, adverse event data were collected for the total time on study. This leads to a longer duration of follow-up for patients in the observation arm and a possible overestimation of adverse events for these patients.

Approximately 33% of patients receiving PEG-IFN discontinued treatment because of adverse reactions. The most common adverse reactions present at the time of treatment discontinuation were fatigue (27%), depression (17%), anorexia (15%), increased alanine aminotransferase (ALT) (14%), increased aspartate aminotransferase (AST) (14%), myalgia (13%), nausea (13%), headache (13%), and pyrexia (11%).

Characteristic	PEG-IFN (n = 627), n (%)	Observation (n = 629), n (%)	Total (n = 1,256), n (%)
Demographics			
Sex			
Female	262 (42)	263 (42)	525 (42)
Male	365 (58)	366 (58)	731 (58)
Age, yrs			
≥65	64 (10)	80 (13)	144 (11)
Mean (SD)	48.8 (11.9)	48.8 (12.8)	48.8 (12.4)
Median	50.0	50.0	50.0
Performance status score			
0	529 (84)	531 (84)	1060 (84)
1	98 (16)	98 (16)	196 (16)
Tumor characteristics			
Tumor stage			
TxN1	250 (40)	258 (41)	508 (40)
TxN2	375 (60)	368 (59)	743 (59)
Unspecified	2 (<1)	3 (<1)	5 (<1)
n of pathologically positive lymph nodes			
0	2 (<1)	3 (<1)	5 (<1)
1	332 (53)	341 (54)	673 (54)
2–4	216 (34)	207 (33)	423 (34)
≥5	73 (12)	74 (12)	147 (12)
Not evaluable	4 (<1)	4 (<1)	8 (<1)
Presence of a synchronous primary			
No	517 (82)	527 (84)	1044 (83)
Yes	93 (15)	83 (13)	176 (14)
Missing	17 (3)	19 (3)	36 (3)
Site of the primary			
Head	39 (6)	35 (6)	74 (6)
Neck	13 (2)	10 (2)	23 (2)
Trunk	267 (43)	277 (44)	544 (43)
Arm	67 (11)	71 (11)	138 (11)
Leg	201 (32)	197 (31)	398 (32)
Missing/unknown	40 (6)	39 (6)	79 (6)
Breslow thickness of the primary, mm			
<1.5	136 (22)	136 (22)	272 (22)
1.5–3.99	276 (44)	284 (45)	560 (45)
≥4.0	147 (23)	148 (24)	295 (24)
Missing/unknown	68 (11)	61 (10)	129 (10)
Ulceration of the primary			
No	315 (50)	338 (54)	653 (52)
Yes	192 (31)	181 (29)	373 (30)
Missing/unknown	120 (19)	110 (18)	230 (18)
Abbreviations: N, node; PEG-IFN, peginterferon-alfa-2b; SD, standard deviation; T, tumor.			

Table 2. Independent review committee–determined RFS results in the intent-to-treat population

RFS result	PEG-IFN (<i>n</i> = 627)	Observation (<i>n</i> = 629)
<i>n</i> (%) of patients with RFS event	328 (52.3)	368 (58.5)
<i>n</i> (%) of patients without RFS event	299 (47.7)	261 (41.5)
Median duration of RFS (95% CI), mos	34.8 (26.1–47.4)	25.5 (19.6–30.8)
Hazard ratio ^a (95% CI)	0.82 (0.71–0.96)	
Nominal <i>p</i> -value (unadjusted log-rank test)	.011	

Data cutoff date was March 31, 2006.

^aThe hazard ratio was estimated using a Cox proportional hazards regression model with treatment arm as the only covariate. A hazard ratio <1 indicates that treatment with PEG-IFN is associated with a lower risk for recurrence or death than observation.

Abbreviations: CI, confidence interval; PEG-IFN, peginterferon-alfa-2b; RFS, relapse-free survival.

Figure 1. Kaplan–Meier curves of the recurrence-free survival (RFS) probability. The log-rank *p*-value was .011 based on 696 RFS events determined by the independent review committee at the data cutoff date of March 31, 2006.

The incidence of serious adverse reactions was approximately twofold higher (33% vs. 15%) in PEG-IFN–treated patients than in those in the observation arm. Five deaths were reported within 30 days of the last treatment dose, two from cardiovascular disease that were considered possibly related to treatment and three from unrelated causes.

As with interferon alfa-2b, the most serious adverse reactions were severe depression, cardiac adverse events, and retinopathy or other visual changes. The most common severe or life-threatening (National Cancer Institute grade 3–4) adverse reactions were fatigue (16%), depression (7%), increased ALT (11%), increased AST (11%), pyrexia (4%), increased γ -glutamyltransferase (4%), myalgia (4%), and headache (4%) in the PEG-IFN–treated group, compared with $\leq 1\%$ in the observation group for these reactions.

Depression occurred in 59% of PEG-IFN–treated patients and 24% of patients in the observation group. Depression was severe or life threatening in 7% of PEG-IFN–treated pa-

tients, compared with <1% of patients in the observation arm. Cardiac adverse reactions, including myocardial infarction, bundle-branch block, ventricular tachycardia, and supraventricular arrhythmia, occurred in 4% of PEG-IFN–treated patients, compared with 2% of patients in the observation group.

DISCUSSION

The approval of PEG-IFN for the adjuvant treatment of patients with AJCC stage III melanoma with microscopic or gross nodal involvement was based on a sustained and clinically meaningful longer RFS time (median, 34.8 months for patients randomized to receive PEG-IFN compared with 25.5 months for those receiving no additional therapy). The result is internally consistent across relevant subgroups defined by baseline demographics and prognostic variables. Additional evidence supporting the validity of the observed PEG-IFN treatment effect on the RFS time is provided by the extensive

prior experience with the predecessor drug, interferon alfa-2b, which has been demonstrated to have a similar effect on RFS outcomes [1–6].

Although the toxicities associated with PEG-IFN treatment are considerable and have a negative impact on global health related-quality of life [11], they are often reversible with treatment interruption or discontinuation. As such, they can be outweighed in a risk:benefit assessment by a robust benefit outcome.

The FDA has stated that the RFS time is direct evidence of clinical benefit when the adjuvant treatment has minimal toxicity [12], as in the case of hormonal agents for the adjuvant treatment of breast cancer. However, the FDA recently approved three drugs for the adjuvant treatment of solid tumors, either alone (imatinib) [13] or in combination with cytotoxic chemotherapy (oxaliplatin, trastuzumab) [14, 15]. In those instances, evidence of a disease-free survival benefit alone was sufficient to support regular approval, despite the demonstration of a greater risk for severe toxicities involving the neurologic, cardiac, gastrointestinal, and vascular (edema) systems. Similarly, in 2002, the FDA Oncologic Drugs Advisory Committee agreed that approval of interferon alfa-2b for the adjuvant treatment of melanoma was appropriate even though subsequent studies did not provide evidence of an effect on the overall survival time. The toxicity profile of PEG-IFN is similar to, if not more favorable than, that observed for the interferon alfa-2b regimen indicated for the adjuvant treatment of melanoma.

The ideal dose of PEG-IFN as well as the ideal duration of PEG-IFN therapy are unknown at this time. Describing a recommended dose, when many patients were unable to tolerate therapy as planned, was problematic. The FDA conducted multiple exploratory analyses to investigate relationships between the extent of therapy and outcomes. All these analyses

were limited by their retrospective approach and are more consistent with “responder” analyses in which the optimal treatment duration is based on who lives longest prior to recurrence. In this setting, patients who relapse early do not contribute to the analysis of appropriate dosing at later time points. In the absence of better information, product labeling both describes the planned treatment and provides information characterizing the dropout rate for toxicity and average treatment durations. This issue will be addressed as a postmarketing requirement.

Given the clinically meaningful prolongation in time without disease observed in study EORTC 18991, which is evidence of direct clinical benefit given its magnitude, the scarcity of alternative, noninterferon-based adjuvant treatments, and the absence of curative salvage treatments for patients with recurrent melanoma, the risks for toxicity during treatment with PEG-IFN do not outweigh the benefit of the 18% lower risk for disease recurrence.

AUTHOR CONTRIBUTIONS

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See the accompanying commentary on pages 1223–1224 of this issue.