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ORIGINAL ARTICLE

Serum concentrations of pegylated interferon α-2b in patients with resected stage III melanoma receiving adjuvant pegylated interferon α-2b in a randomized phase III trial (EORTC 18991)

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Abstract
Purpose The EORTC 18991 trial assessed the effect of long-term adjuvant pegylated interferon (Peg-IFN) α-2b administered weekly in patients with lymph node-positive melanoma. Serum concentrations were analyzed to determine exposure to Peg-IFN α-2b.
Methods After surgery, patients were randomized to receive Peg-IFN α-2b or to observation only. The treatment group received 6 μg/kg/week Peg-IFN α-2b subcutaneously for 8 weeks, followed by a maintenance dose of 3 μg/kg/week for up to 5 years. Blood samples were collected between months 3 and 60.
Results A total of 208 Peg-IFN α-2b concentrations from 48 patients were available. Serum trough concentrations increased in a dose-related manner. Mean dose-normalized serum concentrations and intersubject variability over the 5-year study period in patients with melanoma were similar to those observed in patients with chronic hepatitis.
Conclusion Data suggest that the exposure to Peg-IFN α-2b was sustained during long-term adjuvant treatment with Peg-IFN α-2b in patients with melanoma, consistent with the EORTC 18991 trial's conclusion of a significant, sustained, and relapse-free survival benefit.

Keywords Peginterferon alfa-2b · Melanoma · Pharmacokinetics · Cytokines

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Introduction

In the United States, over 60,000 people may be diagnosed with melanoma this year and nearly 8,000 may die due to the disease [1]. Advanced stage IV metastatic melanoma responds poorly to chemotherapy [2]. These patients have poor prognosis, with a median survival time of 6 to 10 months and a 5-year survival rate of <10% [3].

Interferon (IFN) α is a potent cytokine with well-documented antitumor activity against a variety of solid tumors, including melanoma [4]. For over a decade, multiple randomized studies evaluating recombinant IFN α-2b as adjuvant therapy in patients with high-risk melanoma have shown that high-dose IFN α-2b significantly reduces the risk of relapse and death compared with observation [5–7]. However, the high-dose IFN α-2b regimen is associated with significant toxicity, the dosing schedule is cumbersome, and the relatively small magnitude of benefit in terms of overall survival versus the risk profile is controversial [8–10]. Therefore, despite its approval by the US Food and Drug Administration and by regulatory agencies worldwide, the high-dose IFN α-2b regimen has failed to gain widespread acceptance.

Pegylated IFN α (Peg-IFN α) offers potential advantages of increased efficacy, reduced toxicity, and improved

compliance. Peg-IFN α-2b (PEG-Intron; Schering-Plough, Kenilworth, NJ) is a derivative of recombinant IFN α-2b formed by covalently linking a polyethylene glycol (PEG) moiety (average molecular weight of 12 kD) to histidine-34 on IFN α-2b [11]. Pegylation of IFN α-2b does not compromise its biologic activity profile [12], but significantly decreases renal clearance, thereby prolonging its plasma half-life 10 times (from approximately 4–40 h) [13]. As a result, Peg-IFN α-2b can be given as a convenient once-weekly dose, rather than the standard 3 times weekly dose with IFN α-2b, without compromising drug exposure or patient safety [13, 14]. Peg-IFN α-2b has been shown to be both safe and effective in the treatment of chronic hepatitis C infection [15–17]. Preliminary phase I studies have further shown that Peg-IFN α-2b exerts antitumor activity in chronic myelogenous leukemia [18] as well as in solid tumors including renal cell carcinoma and metastatic melanoma [19].

To assess the safety and efficacy of weekly administered Peg-IFN α-2b as a long-term adjuvant to surgical resection of high-risk lesions, a randomized phase III pivotal registration trial (European Organization for Research and Treatment of Cancer [EORTC] 18991) maintained patients with stage III melanoma on Peg-IFN α-2b for up to 5 years [20]. This report describes the exposure in these patients to Peg-IFN α-2b during the study period, based on serum concentrations sparsely sampled in a small subset of the study population.

Methods

Study design

EORTC 18991 was a randomized phase III pivotal registration trial of Peg-IFN α-2b versus observation only, after regional lymph node dissection in patients with American Joint Committee on Cancer stage III [TxN1-2M0] melanoma [21]. This multicenter study was designed, monitored, and sponsored by the Melanoma Group of the EORTC and was funded by Schering-Plough, Kenilworth, NJ, USA. Peg-IFN α-2b was manufactured and supplied by Schering-Plough. A total of 1,256 patients were randomized within 70 days of surgery to Peg-IFN α-2b treatment ($n = 627$), or to observation only ($n = 629$). All patients gave written informed consent, and appropriate local institutional review boards approved the study protocol.

Dose regimen

Patients randomized to the treatment regimen received Peg-IFN α-2b subcutaneously at 6 μg/kg once a week for 8 weeks. This induction period was followed by a subcutaneous maintenance dose of 3 μg/kg Peg-IFN α-2b once weekly for up to 5 years (minus the 8-week induction period) or until the occurrence of distant metastasis. During the induction period a single dose reduction from 6 to 3 μg/kg Peg-IFN α-2b was allowed; during the maintenance period, stepwise dose reductions (3 to 2 to 1 μg/kg/week) were permitted as needed in order to maintain an Eastern Cooperative Oncology Group performance status of 0 or 1.

Blood sampling

Serum samples were collected during routine clinical visits at months 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 16, 17, 18, 24, 30, 36, 42, 48, 54, and 60 from a subset of patients as part of a prognostic factor substudy. These serum samples were obtained for exploratory analysis and were not specifically collected for the determination of serum Peg-IFN α-2b concentration. As no pharmacokinetic assessments were planned in the study protocol, serum samples were only taken from a small proportion of the total study population and were not selected under the control of randomization. Serum samples were not requested from other patients participating in the study. The time at which the blood sample was drawn at each visit relative to the time of the Peg-IFN α-2b dosing was not predetermined. No selection criteria were applied to the patients included in this substudy other than the availability of multiple, sequential samples from individual patients. A number of patients who had dose reductions were selected in order to provide pharmacokinetic data on each of the different doses used by patients in this trial (6, 3, 2, and 1 μg/kg/week).

The date of the previous Peg-IFN α-2b dosing and the date of the blood sample withdrawal were documented and used in the data analysis. Blood samples were collected and serum was separated and frozen at −80°C. Serum samples were assayed for Peg-IFN α-2b at Schering-Plough.

Reasons for exclusion of serum samples from the analysis included missing dosing date, unknown dose information or treatment month, dose of 1.5 μg/kg Peg-IFN α-2b, and concentration data not reported. In addition, the relapse rate in this patient population is very high: relapse or death occurs in about 50% of patients at 2 years, resulting in limited sampling in a high proportion of patients. Side effects may also lead to discontinuation of treatment in around an additional 25% of patients.

Assay method

Serum samples were assayed using an electrochemiluminescent (ECL) immunoassay. In this assay, an antibody sandwich is formed between the Peg-IFN α-2b in the serum and 2 antibodies. The antibodies, both of which bind to Peg-IFN α-2b, are incubated simultaneously with the samples at room

Table 1 Summary of patient demographics and renal function data

Variable	$n = 48$
No. of men/women	23/25
Age (years)[a]	46.2 (20–70)
Weight (kg)[a]	73.4 (46.0–120)
Serum creatinine (mg/dL)[a]	0.85 (0.37–1.19)
Creatinine clearance (mL/h)[a]	107 (54.2–177)

[a] Values are mean (minimum–maximum)

temperature. One antibody, a murine monoclonal antibody (mAb 7N4-1), is labeled with ruthenium trisbipyridine chelate (TAG-NHS ester), whereas the other antibody is a biotinylated sheep polyclonal antibody. The immune complexes formed are captured onto paramagnetic beads that are coated with streptavidin. The beads containing TAG-NHS ester-labeled immune complexes are drawn into an ORIGEN (BioVeris, Gaithersburg, MD) analyzer and placed in close proximity to an electrode via a magnet. The electrode applies a voltage, initiating an ECL reaction between the TAG-NHS ester on the immune complex and tripropylamine (TPA) in the ORIGEN assay buffer. The ECL signal produced is proportional to the concentration of Peg-IFN α-2b in the serum. Samples for this study were quantitatively measured by comparison with a standard curve of Peg-IFN α-2b. Results were calculated and reported in picograms per milliliter (pg/mL). The lower limit of quantitation (LLOQ) of this validated assay was 40 pg/mL. Due to limited sample volume, samples were tested at a minimum 1:2 dilution, making the LLOQ 80 pg/mL.

Data analysis methods

Summary statistics were used to analyze serum concentrations of Peg-IFN α-2b. Serum Peg-IFN α-2b concentrations below the LLOQ were reported as 0 pg/mL.

Results

A total of 208 samples from 48 patients were analyzed. Demographic and renal function data of these patients are summarized in Table 1. The samples collected on the same day as dosing are referred to as day 0 samples. Of the 208 samples, 134 samples were collected during the maintenance phase of treatment on day 0.

Mean serum Peg-IFN α-2b concentrations with summary statistics are shown in Table 2. The mean concentrations of days 1–6 and mean concentrations of day 0 increased in a dose-related manner (Table 2).

The mean concentrations of day 0 over 57 months of maintenance treatment were 298, 778, and 1,069 pg/mL for doses of 1, 2, and 3 μg/kg/week, respectively. The mean concentrations of days 1–6 were higher than the mean concentrations of day 0 (Table 2). This is not unexpected, as a greater number of postdose concentrations were included in the calculation of the mean concentrations from samples collected on days 1–6.

The mean concentrations on day 0 were assumed to approximate the trough concentrations because, although precise blood-draw times were not recorded, these samples were collected approximately 168 h after the weekly dosing. Previous studies (see Table 3) analyzing pharmacokinetics of subcutaneous Peg-IFN α-2b have detected Peg-IFN α-2b at 168 h after dosing and characterized this concentration as trough. A cross-study comparison of mean trough concentrations of Peg-IFN α-2b following once-weekly subcutaneous administration of Peg-IFN α-2b is presented in Table 3. The mean concentration on day 0 at 1 μg/kg/week Peg-IFN α-2b was comparable to the mean trough concentrations in patients with chronic hepatitis treated with Peg-IFN α-2b at 1 μg/kg/week for 24, 36, or 48 weeks (Table 3). At a dose of 2 μg/kg/week, both patient populations also had similar mean trough concentrations. Mean day 0 concentrations of 3 μg/kg/week in the current study were generally higher or similar to the mean week 4 or 5 trough concentrations in the limited sample of patients with chronic myelogenous leukemia or solid tumors (Table 3). In patients with chronic hepatitis following chronic dosing with Peg-IFN α-2b, coefficient of variation values ranged from 101 to 152%, and this range was similar to that in the present study (85 to 110%), demonstrating that both populations exhibited similarly high intersubject variability.

The plots of individual Peg-IFN α-2b concentration versus dose to blood-draw interval following the once-weekly dosing of Peg-IFN α-2b at 1, 2, and 3 μg/kg/week are presented in Fig. 1. Individual concentration of Peg-IFN α-2b on day 0 versus dose is presented in Fig. 2. These plots provide a graphic representation of high intersubject variability and show that this variability was independent of blood-draw interval or dose.

In patients with multiple samples available, plotting individual patient serum levels versus timing of blood sampling (day) at each dose level indicated that serum levels were broadly similar according to day of blood sampling in each patient (data not shown). For example, in individual patients, all samples taken at day 1 indicated similar serum levels of Peg-IFN α-2b. Only one patient had outlying data points occurring on day 0 at the 3 μg/kg dose level.

Exposure associated with Peg-IFN α-2b at doses of 1, 2, and 3 μg/kg/week over 5 years is shown in Fig. 3a and b. The mean concentrations and standard deviations were calculated using every sample from all patients on all days (days 0–7) and plotted on log and linear scales. These data

Table 2 Mean concentration of pegylated interferon (Peg-IFN) α-2b, by timing and weekly subcutaneous dose

Day	Dose (μg/kg)	No. of patients	No. of samples analyzed	Serum concentration of Peg-IFN α-2b (pg/mL)					
				Mean[a]	CV (%)	Min[b]	Max[b]	LS mean	90% CI
0	1	12	29	298	87	15	952	197	112–348
	2	15	43	778	85	165	2,677	590	418–832
	3	27	62	1,069	110	164	5,043	698	518–940
1–6	1	6	26	335	45	175	590	308	213–446
	2	10	14	943	110	194	3,588	606	346–1063
	3	16	34	1,434	84	0[c]	4,450	1,190	845–1677

CV coefficient of variation, *LS* least-squares, *CI* confidence interval

[a] Sample means were taken for patients having multiple samples (each patient counts only once)

[b] Minimum (Min) and maximum (Max) for patient, not sample

[c] Concentration below assay sensitivity (80 pg/mL)

Table 3 Comparison of pegylated interferon (Peg-IFN) α-2b mean trough concentrations, by study and weekly subcutaneous dose

Study	Diagnosis	Dose (μg/kg)	Week	No. of patients	Mean trough concentration (pg/mL)	CV (%)
EORTC 18991	Stage III melanoma	1	12–240	12	298	87
		2	12–240	15	778	85
		3	12–240	27	1,069	110
C97-187[a]	Chronic myelogenous leukemia	3	4	3	529	60
		3	5	3	522	51
C/I97-188[b]	Solid tumors	3	4	3	706	91
		3	5	3	969	89
I95-060 [13], I95-140[c]	Chronic hepatitis	1	24	6	598	152
		2	24	6	940	128
C/I97-010[d]	Chronic hepatitis	1	24	97	248	101
		1	36	87	304	125
		1	48	76	273	142

CV coefficient of variation, *EORTC* European Organization for Research and Treatment of Cancer

[a] Clin Doc 1569532: a phase I study of Peg-IFN alfa-2b (Peg Interferon Alfa-2B, SCH 54031) in subjects with chronic myelogenous leukemia (C97-1 87). Kenilworth, NJ: Schering-Plough Corporation; 2000

[b] Clin Doc 1872327: phase 1 study of Peg-IFN alfa-2b (PEG-Interferon Alfa 2b/PEG-Intron) in subjects with solid tumors (C/I97-188). Kenilworth, NJ: Schering-Plough Corporation; 2001

[c] Clin Doc 98320050: 20-week treatment continuation protocol for subjects with chronic hepatitis C who have completed the polyethylene glycol-interferon alfa-2b (Peg-Intron, SCH 54031) Multiple Rising Dose Study (I95-060). Kenilworth, NJ: Schering-Plough Corporation; 1998

[d] Doc ID 99253050: pharmacokinetic analysis of trough serum Peg-IFN Alfa-2b concentrations and activity in subjects with chronic hepatitis C enrolled in protocol C/I97-010. Kenilworth, NJ: Schering-Plough Corporation; 1999

demonstrate that Peg-IFN α-2b exposure was sustained, and remained consistent in a dose-dependent fashion over the 5 years of treatment.

Discussion

The EORTC 18991 trial was designed to assess the efficacy and safety of weekly subcutaneous Peg-IFN α-2b as adjuvant therapy in resected stage III melanoma. In this post-hoc analysis, we analyzed sparsely sampled serum concentration data from 48 patients. As analysis of serum parameters/pharmacokinetics was not planned in the study protocol blood samples were not obtained from the majority of patients in the study; our substudy sample was limited by the availability of multiple sequential samples for individual patients. Our analysis shows that the serum trough concentrations of Peg-IFN α-2b over the 5-year study period increased in a dose-related manner. The mean serum concentrations of Peg-IFN α-2b and intersubject variability of concentration data in patients with melanoma were similar to those observed in patients with chronic hepatitis from

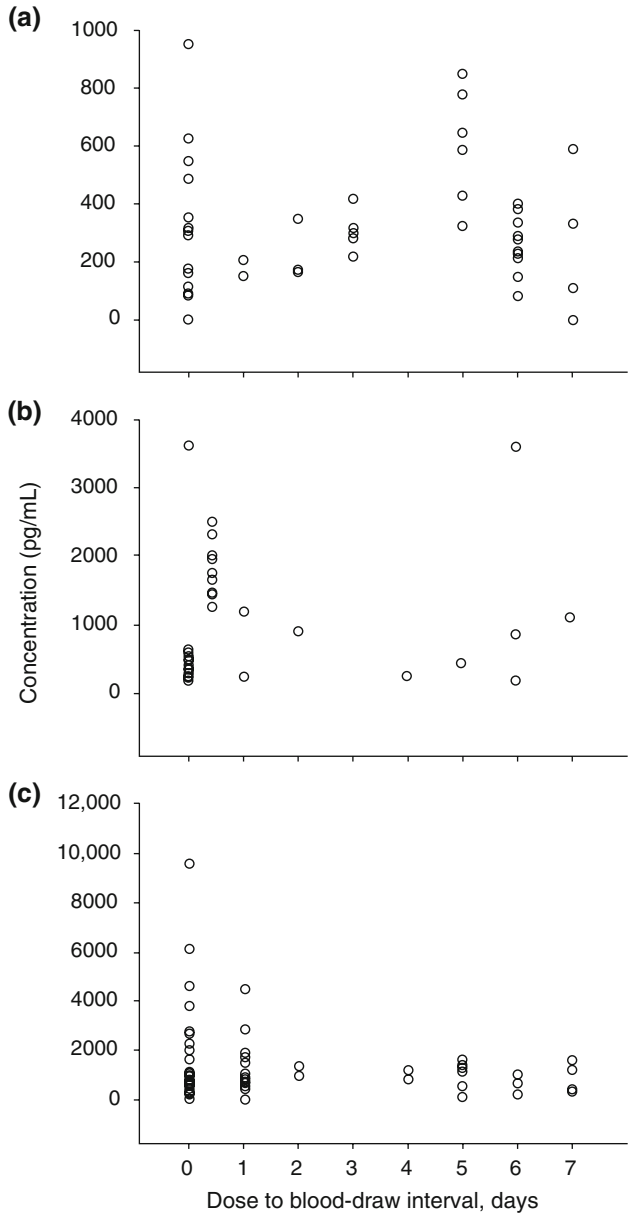

Fig. 1 Individual concentration of pegylated interferon (Peg-IFN) α-2b versus dose to blood-draw interval following weekly subcutaneous administration of Peg-IFN α-2b, at doses of 1 (**a**), 2 (**b**), and 3 μg/kg (**c**)

week 24 to week 48, suggesting no major difference in dose-normalized exposure between these populations. Notably outlying data points were observed for individual patient data on days 5 and 6 in the 1 μg/kg and 2 μg/kg dose groups (Fig. 1); however, this intersubject variability is consistent with studies in patients with chronic hepatitis.

Pharmacokinetics of subcutaneously administered Peg-IFN α-2b has been evaluated in healthy volunteers [22], and in patients with chronic hepatitis [13, 23], chronic myelogenous leukemia [18, 24], and solid tumors [14]. After single doses, peak concentration and area under time versus concentration curve of Peg-IFN α-2b increased in a

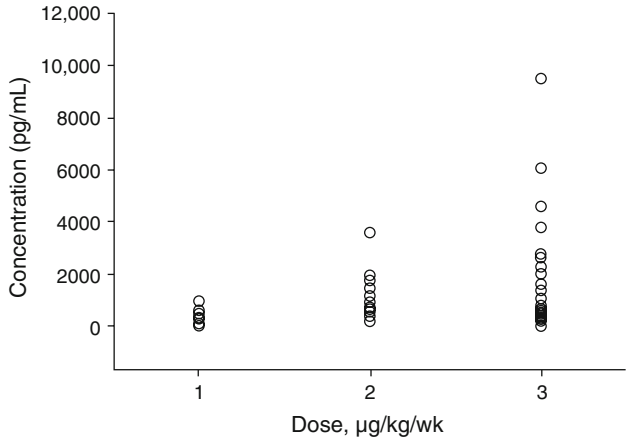

Fig. 2 Individual concentration of pegylated interferon (Peg-IFN) α-2b on day 0 versus dose, following weekly subcutaneous administration of Peg-IFN α-2b

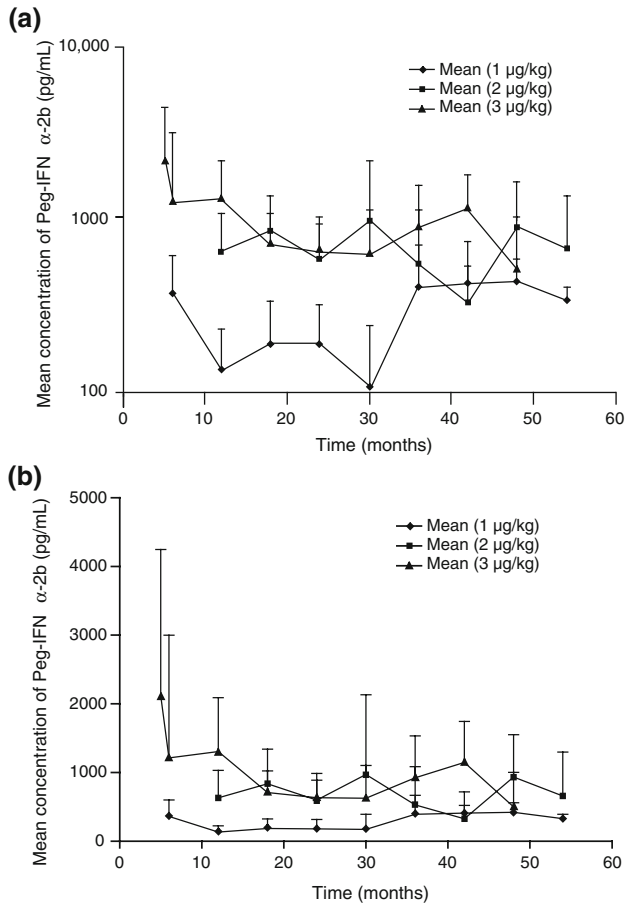

Fig. 3 Exposure associated with pegylated interferon (Peg-IFN) α-2b dosing of 1, 2, and 3 μg/kg/week over 5 years using (**a**) a log scale and (**b**) a linear scale for the *y* axis. Error bars indicate standard deviations of the mean. Mean concentrations and standard deviations were calculated using every sample from all patients on all days (days 0–7); data were included only when the number of serum samples per data points was ≥3

dose-related manner over a dose range of 0.25 to 9 μg/kg/week, and plasma concentrations at peak levels were maintained for 48 to 72 h, with Peg-IFN α-2b still being detectable at 168 h (7 days) after dosing. Following multiple dosing (weekly administration for 4 weeks), the exposure increased, with an accumulation factor of approximately 1.5 irrespective of disease or dose. In patients with chronic hepatitis, mean serum trough concentrations (concentrations at 168 h postdose) after weekly dosing at 1 μg/kg for 24, 36, or 48 weeks were similar (Table 3), indicating that the exposure to IFN α-2b reached a steady state within 24 weeks. The dose-related increases in trough concentrations and the observed similarity between melanoma and chronic hepatitis populations in terms of trough concentrations are reminiscent of normal pharmacokinetic behavior of Peg-IFN α-2b during long-term dosing and suggest that Peg-IFN α-2b exposure was sustained at levels comparable to those seen in hepatitis patients from 24 to 48 weeks.

In this analysis, differences in exposure between the 2 and 3 μg/kg doses were observed in months 0–12 but were less pronounced later in the study (Fig. 3). More subjects received 3 μg/kg/week at the beginning of the maintenance phase compared with later on in the maintenance phase (for example, at month 48); therefore the month 0–12 data are representative of the exposure at 3 μg/kg in the intent-to-treat population. In months 0–12, patients who had dose reductions (and may have had higher exposure) could still contribute to the mean concentration data, resulting in differences between 2 and 3 μg/kg during this period. Subjects who could tolerate the 3 μg/kg dose throughout the study and contributed to the 3 μg/kg dose data at month 48 may have relatively low exposure. In addition, the mean concentrations plotted included all samples (unbalanced trough and post-dose samples) and this may have contributed to the minimal differences in exposure for the 2 μg/kg and 3 μg/kg doses later in the study. Furthermore, the number of samples during the late stage of maintenance phase (months 24–54) was small ($n < 10$).

The sustained exposure to IFN α-2b over a 5-year study period is consistent with the primary conclusion of the EORTC 18991 trial that long-term treatment with Peg-IFN α-2b produced a robust, sustained clinical benefit in terms of disease-free survival with no novel toxicities [20].This conclusion is consistent with evidence from clinical studies in various diseases that both the magnitude of exposure to IFN α-2b and the duration of exposure are important for therapeutic efficacy. Clinical trials in melanoma patients have suggested that the high-dose IFN α-2b regimen was more effective than low- or intermediate-dose IFN α-2b in prolonging relapse-free survival and that a robust efficacy required prolonged dosing [6, 8, 9]. The EORTC 18952 trial [25] evaluated the low dose (5 million units) 3 times weekly for 25 months and the intermediate dose (10 million units) 3 times weekly for 13 months in high-risk melanoma patients. The low-dose regimen appeared to be more effective than the intermediate dose regimen, suggesting that the efficacy of IFN α-2b in melanoma may be more dependent on duration of treatment than on dose [25]. In patients with chronic myelogenous leukemia receiving IFN α-2b, cytogenetic remission tended to be dose-dependent and required a sustained tumor exposure to IFN α-2b [26–28]. It has been shown that Peg-IFN α-2b produced antileukemic activity in patients with chronic myelogenous leukemia who were either resistant or intolerant to IFN α-2b therapy, indicating that improved efficacy requires sustained exposures at elevated levels [18]. In well-controlled studies, chronic hepatitis patients treated with Peg-IFN at doses of 1.0 or 1.5 μg/kg experienced higher sustained viral response rates than those treated with nonpegylated IFN at the standard dose of 3 MIU three times weekly [15, 16].

Serum concentration data from the current study have a number of limitations. The data analysis was conducted retrospectively. Blood sampling schemes were not specified in the protocol, and serum samples were collected as part of a prognostic factor substudy associated with the EORTC 18991 trial. Patients who participated in the substudy were not selected under the control of randomization. Of 627 patients randomized to receive Peg-IFN α-2b, 48 patients had blood samples collected and included in the data analysis, which is 7% of the population assigned to Peg-IFN α-2b. Furthermore, as only the date of the previous Peg-IFN α-2b dose and the date of the blood sample draw were documented, the exact elapsed time from previous dose is unknown, and it is possible that the day 0 serum concentrations may have included postdose sample data. Thus, the mean values of the trough concentrations may have been overestimated. In this study, interpatient variability on day 0 data is quite high, with some outlying data points, indicating the possibility that at least some of the 'trough' samples were actually obtained after the next dose was administered rather than before.

In addition, sample storage stability has been established in the ECL immunoassay method at −80°C for 34 months. However, samples in this study were stored for up to 60 months. Thus, some or all samples analyzed may be affected by this limitation in established stability.

In summary, weekly subcutaneous administration of Peg-IFN α-2b in patients with high-risk melanoma for up to 5 years did not appear to have any adverse effects on patients' exposure to Peg-IFN α-2b, as suggested by the similarity of trough concentration data from the present trial to those from earlier phase I clinical studies in chronic hepatitis, chronic myelogenous leukemia, or solid tumors. The robust, sustained relapse-free survival observed in the EORTC 18991 trial is consistent with the sustained exposure to Peg-IFN α-2b revealed by the present analysis.

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