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Pharmacokinetic/pharmacodynamic analysis of adjuvant pegylated interferon α-2b in patients with resected high-risk melanoma

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Abstract

Purpose High-dose pegylated interferon α-2b (peginterferon α-2b) significantly decreased disease recurrence in patients with resected stage III melanoma in a clinical study. We investigated the pharmacokinetics (PK) and safety of high-dose peginterferon α-2b in patients with high-risk melanoma.

Methods For PK analysis, 32 patients received peginterferon α-2b 6 μg/(kg week) subcutaneously for 8 weeks (induction) then 3 μg/(kg week) for 4 weeks (maintenance). PK profiles were determined at weeks 1, 8, and 12. Exposure–response relationships between peginterferon α-2b and absolute neutrophil count (ANC) and alanine aminotransferase (ALT) level were also studied.

Results Peginterferon α-2b was well-absorbed following SC administration, with a median $T_{\text{max}}$ of 24 h. Mean half-life estimates ranged from 43 to 51 h. The accumulation factor was 1.69 after induction therapy. PK parameters showed moderate interpatient variability. PK profiles were described by a one-compartmental model with first-order absorption and first-order elimination. Toxicity was profiled and was acceptable; observed side effects were similar to those previously described. Dose reduction produced proportional decreases in exposure and predictable effects on ANC in an Imax model; however, a PK/pharmacodynamic (PK/PD) relationship between peginterferon α-2b and ALT could not be established with high precision.

Electronic supplementary material The online version of this article (doi:10.1007/s00280-010-1326-9) contains supplementary material, which is available to authorized users.
**Conclusions** Peginterferon α-2b was well-absorbed and sustained exposure to peginterferon α-2b was achieved with the doses tested. These data confirm and extend previous PK observations of peginterferon α-2b in melanoma and solid tumors. Our PK/PD model of exposure and ANC effect provides useful information for prediction of peginterferon α-2b-related hematologic toxicity.

**Keywords** Peginterferon α-2b · Melanoma · Adjuvant therapy · Pharmacokinetics · Pharmacodynamics

**Introduction**

The conjugation of polyethylene glycol (PEG) to therapeutically useful proteins has been widely employed to reduce clearance and increase systemic exposure while preserving biologic activity [1]. The addition of a 12 kDa mono-methoxypolyethylene glycol (PEG) linker to interferon produces a predominantly mono-polyethylene glycol (PEG) prodrug molecule that retains the activity of the parent interferon and has a prolonged half-life that lends itself to weekly administration [2].

High-dose recombinant (native) interferon α-2b is widely used and is approved by the US Food and Drug Administration as adjuvant therapy in patients with high-risk resected melanoma, based on its effect on disease-free survival (DFS) and overall survival (OS) in the pivotal Eastern Cooperative Oncology Group (ECOG) 1684 trial [3]. Further trials established the effect of interferon α-2b on DFS, although its effects on OS are somewhat controversial, with only modest improvements in OS versus observation [3–7]. High-dose interferon α-2b regimens are associated with high toxicity [8] and a cumbersome, three-times-weekly maintenance dosing schedule. Additionally, several studies have demonstrated that peginterferon α-2b is more effective than nonpegylated interferon in treating hepatitis [9–12] owing to the altered pharmacokinetic (PK) profile and resultant prolonged drug exposure [11–13]. Peginterferon α-2b has also shown promise in the treatment of various solid tumors [2, 13, 14]. Given this information, investigators started studying high-dose peginterferon α-2b for treatment of melanoma in the late 1990s [2, 13, 15].

The recently reported European Organisation for Research and Treatment of Cancer (EORTC) 18991 phase III trial studied the efficacy of peginterferon α-2b in high-risk melanoma. Improvement in recurrence-free survival (RFS) was seen in patients with node-positive melanoma treated for up to 5 years with high-dose peginterferon α-2b compared with observation alone [15]. Therefore, high-dose peginterferon α-2b [6 μg/(kg week) for 8 weeks followed by 3 μg/(kg week) for up to 5 years] could become a new option for the adjuvant treatment of stage III patients with high-risk melanoma. The dose used in the EORTC 18991 trial was substantially higher than that generally used for the treatment of hepatitis C [1.5 μg/(kg week)]; 6 μg/(kg week) subcutaneous (SC) dosing is expected to provide an exposure (area under the curve; AUC) similar to high-dose native interferon α-2b 180 MIU/week intravaneously, which is the weekly dose a patient with a body surface area of 1.8 m² would receive in the first 4 weeks of standard high-dose adjuvant therapy for melanoma [20 MIU/(m² day) five times weekly] [13]. A recent publication reported limited PK data from a small subset of patients (7%) receiving peginterferon α-2b during the maintenance phase in the 18991 study [16]. The results indicated sustained exposure to peginterferon α-2b during long-term adjuvant treatment, with dose-related changes in serum trough concentrations. Mean serum concentrations were similar to those observed in patients with hepatitis C; high inter-subject variability was observed, consistent with hepatitis C studies. However, PK analysis was not planned in the 18991 study protocol and was assessed using serum samples obtained during routine clinical visits 1–6 months apart for exploratory analysis of prognostic factors; therefore multiple sequential samples were not available for all patients, and blood sampling was not always well-timed relative to administration of the weekly drug dose. These factors have important implications for the trough level estimates in the 18991 PK analysis.

To provide data on the actual exposure and PK parameter estimates for patients treated with this high-dose schedule of peginterferon α-2b, we conducted a prospective, single-arm, open-label trial in resected, high-risk, stages II and III melanoma. Given that absolute neutrophil count (ANC) reduction and alanine aminotransferase (ALT) elevations are two of the most common and significant dose-limiting organ toxicities with interferon treatment, and possibly peginterferon α-2b [17], we explored PK/pharmacodynamic (PK/PD) models of ANC and ALT changes following peginterferon α-2b SC administration and attempted to model the expected effect of dose modification on bone marrow suppression and hepatic toxicity.

**Methods**

**Trial design**

This prospective, open-label, single-arm, phase II PK trial was conducted at four sites worldwide. The primary goal was to determine the PK profile of peginterferon α-2b when administered at the EORTC 18991 trial dose and schedule in patients with high-risk melanoma. The secondary objective was to assess the safety of this regimen. Additionally, exploratory modeling of the PD relationship between peginterferon α-2b exposure and ANC and ALT was carried out.
The trial was approved by the local institutional review boards and registered at http://www.clinicaltrials.gov (NCT00457418). The trial opened in February 2007 and completed accrual in September 2007.

Patients

Eligible patients were ≥18 years old and had histologically documented American Joint Committee on Cancer stage IIB, IIC, IIIA, IIIB, or IIIC melanoma, an ECOG performance status of 0 or 1, and adequate bone marrow, renal, and hepatic function. Full lymphadenectomy had to be performed within 90 days prior to starting therapy. Patients with a history of treatment with any interferon, chemotherapy, or immunotherapy, and those with melanoma that could not be completely surgically resected were excluded, as were those with preexisting autoimmune disease or psychiatric conditions. This study was conducted in accordance with Good Clinical Practice guidelines and signed informed consent was obtained prior to treatment initiation.

Treatment

Patients received peginterferon α-2b 6 µg/kg SC once weekly during an 8-week induction period, followed by a maintenance dosage of 3 µg/kg SC once weekly for the remainder of the treatment period for a maximum of 5 years. The first 12 weeks constituted the PK phase (8 weeks of induction and 4 weeks of maintenance); the remainder was the post-PK phase. Dose modification guidelines were provided to manage toxicities, allowing patients to continue treatment while maintaining an ECOG performance status score of 0 or 1, per the EORTC 18991 trial [15]. Treatment was withheld if hematologic toxicity occurred: white blood cells <1 × 10^9/L; ANC ≤0.5 × 10^9/L; platelets <50 × 10^9/L. After recovery, treatment could be restarted one dose level down; subsequent dose escalations were not permitted after dose reduction for hematologic toxicity (see online resource material—supplementary methods).

Safety evaluation

The cutoff date for safety data presented here was May 2008. Baseline evaluations included history, physical examination, complete blood count with differential, lipid profiles, and renal, hepatic, and thyroid function assessments (see online resource material—supplementary methods).

Blood collection and analysis

Blood samples for PK analysis were collected predose and at 24, 48, 96, and 168 h postdose during weeks 1, 8, and 12. In addition, a predose sample was drawn at weeks 11 and 12 to determine trough levels (see online resource material—supplementary methods).

Noncompartmental PK analysis

PK parameters for individual serum peginterferon α-2b concentration–time data were estimated using noncompartmental (NCA) methods (WinNonlin software, version 4, Pharsight, Mountain View, CA). Samples with concentrations below the limit of quantitation of the bioanalytical assay were assigned a concentration of 0 pg/mL. The following parameters were calculated from the concentration–time data using this NCA: area under the curve during the dosing interval (AUCint), maximal serum concentration (Cmax), average concentration within dosing interval (Cavg), minimum (trough) serum concentration (Cmin), observed time to achieve maximal serum concentration (Tmax), mean apparent clearance (CL/F), terminal half-life (t1/2), and accumulation factor (R) [18]. For weeks 1–8 (induction) R was defined as the ratio of the AUC0–168h for week 8 divided by the AUC0–168h for week 1. At week 1, the single dose CL/F was calculated using dose/AUC∞. At weeks 8 and 12, CL/F was calculated as dose/AUC0–168h. CL/F was not determined for those patients whose elimination t1/2 could not be accurately determined at week 1.

Compartmental PK analysis

A one-compartment model and a two-compartment model were evaluated using WinNonlin software. A one-compartment model with first-order absorption and first-order elimination (no lag time) appropriately described the PK profiles for peginterferon α-2b following multiple SC dosing (see online resource material—supplementary methods and supplementary Table 1). Individual serum concentrations at weeks 1, 8, and 12 and trough concentration at weeks 10 and 11 were used to obtain the individual fitted PK parameters (data not shown). Once the parameter values were determined, the predicted serum concentration–time profiles were generated and compared with actual data obtained to assess the usefulness of the PK model. The initial PK parameter estimates were based on either the relevant literature or the initial value calculated by the WinNonlin software.

PD modeling strategy and PK/PD analysis

Blood samples were collected at baseline and approximately every week subsequently to determine ANC and ALT levels. PK/PD models were developed in order to characterize the time course of ANC or ALT response after SC administration of peginterferon α-2b, using WinNonlin.
software. For both ANC and ALT, model selection was driven by the available PK and PD data and was based on:
(1) graphical goodness-of-fit analysis, (2) estimated uncertainty in parameter estimates as reported by %CV, (3) Akaike information criteria (AIC), and (4) plausibility of parameter estimates. Initial parameter estimates were based on the relevant literature or initial values provided by the WinNonlin software and their plausibility ascertained. Since only two dose levels were specified by this study protocol (excluding dose reductions), we pooled data from all 32 patients in our study with those of a different trial [2], which used a wide dose range in patients with solid tumors, to better describe the dose–response relationship. Previously published steady-state exposure values (AUC\textsubscript{tau} at week 4) from 34 patients with solid tumors treated with doses ranging from 0.75 to 7.5 μg/(kg week) (3–12 patients in each dose group) [2] were used, along with the corresponding ANC data from the same patients [unpublished data, provided by Schering-Plough (now Merck & Co.)]. In this previously published study, blood samples were collected predose (hour 0) and at 24, 48, 72, and 168 h postdose during weeks 1 and 4. Six of the 34 patients with solid tumors were melanoma patients.

**Effects of peginterferon α-2b exposure on ANC**

The exposure–response relationship between steady-state exposure to peginterferon α-2b (AUC\textsubscript{tau}) and changes in ANC from baseline was assessed at week 8 [dose 6 μg/(kg week)] and week 12 [3 μg/(kg week)]. The inhibitory Imax model was used to describe the exposure–response relationship of ANC change as % of baseline and peginterferon α-2b AUC\textsubscript{tau} (see online resource material—supplementary methods and supplementary Table 1).

Based on serum concentrations and ANC data obtained from patients in this study, a fully integrated PK/PD model was used to describe the effect of peginterferon α-2b on ANC over time. The PK component was a one-compartment model with first-order absorption and first-order elimination. The PD component of the model is an indirect inhibition response model driven by the PK profiles [19, 20].

**Effects of peginterferon α-2b exposure on ALT**

Again, a fully integrated PK/PD model was used to describe the effect of peginterferon α-2b on the time course of ALT change. The PK and PD components for the model were as described for ANC above.

Statistical analyses

The protocol-defined target sample size was 12 subjects; assuming an inter-subject coefficient of variation of 40%, this was deemed sufficient to define the PK parameters such that the 90% CI would be within 24% of the mean. Therefore, between 20 and 30 subjects were to be enrolled to ensure that 12 subjects would receive the full scheduled dose of peginterferon α-2b for 12 weeks. Summary statistics are provided for PK parameters by dose and week with the mean and %CV for the serum concentration data at each sampling time. Steady state was assessed using log-transformed C\textsubscript{min} for weeks 10, 11, and 12 using an ANOVA model extracting effects due to week and patient. Ratio estimates and corresponding 90% CI were provided for each week versus the average of the subsequent weeks. ANC and ALT data were summarized by week.

**Results**

**Patient characteristics and treatment exposure**

Thirty-two patients participated in this trial. Baseline patient demographics are summarized in Table 1. Dose intensity was calculated by dividing the total dose received in each phase by the corresponding time period for each individual subject. Median dose intensity was 5.8 μg/(kg week) during the induction phase (weeks 1–8), 3.0 μg/(kg week) during the PK maintenance phase (weeks 9–12), and 2.9 μg/(kg week) during the post-PK phase. Most patients (84%) received 7–8 weeks of induction therapy. The median duration of treatment was 8.0 weeks (range 5.0–8.4) for induction and 4.0 weeks (range 1.0–4.1) for the PK maintenance phase.

A total of 30 patients participated in the post-PK phase (two patients did not enter follow-up), of whom 15 (50%) discontinued therapy: 5 (17%) each due to adverse events (AEs), disease progression, and patient preference. By July 2008 (last database lock), 15 (50%) patients remained on treatment at a median of 13 months after beginning therapy.

**Safety**

Safety analyses were performed on all 32 patients. The observed side effects of peginterferon α-2b were similar to those previously described [2, 13, 15]. All patients reported ≥1 treatment-emergent AEs (TEAEs) of any grade; 22 (69%) reported grade 3 or 4 TEAEs. TEAEs reported in ≥10% of patients are presented in Table 2. The most commonly occurring AEs included fatigue, fever, chills, headache, anorexia, and nausea. Decreases in ANC (all grades) were observed in seven (22%) patients; decreases of grades 3 and 4 were observed in three (9%) patients.

Serious AEs were reported in six (19%) patients: lower limb and wrist fracture (one patient); drug hypersensitivity,
bronchitis, and dehydration (one patient); urticaria (one patient); cholecystitis (one patient); and atrial fibrillation (two patients). All serious AEs were grade 3 with the exception of one grade 2 atrial fibrillation.

AEs leading to dose modification were reported in 17 (53%) patients and included fatigue and increased ALT level (four patients (13%) each). Decreases in ANC (all grades) led to dose reduction in two (6%) patients. AEs leading to treatment discontinuation were reported in seven (22%) patients and included lower leg fracture, atrial fibrillation, fatigue, supraventricular tachycardia, blurred vision, staphylococcal infection, and hypertriglyceridemia (one patient each). No treatment-related deaths were reported.

Pharmacokinetics

Of the 32 patients enrolled on the study, five (16%) patients discontinued treatment during the initial 12 weeks (PK phase): two (6%) due to AEs, one (3%) due to disease progression, and two (6%) due to noncompliance with protocol. Another seven (22%) had missed/reduced doses, or missed one or more specified PK sampling points, during the PK phase. Data from the remaining 20 patients who received full doses and provided all blood samples in the PK phase were used for the primary PK analyses, as per the protocol (a minimum of 12 patients was required). Data from all 32 patients were pooled with data from patients with advanced solid tumors (n = 34) [2] to help construct the PK/PD model.
Arithmetic means and coefficients of variation (%CV) of the estimated PK parameters at weeks 1, 8, and 12 from the noncompartmental PK analysis (n = 20) are summarized in Table 3. Peginterferon α-2b was well-absorbed following SC administration, with a median $T_{\text{max}}$ of 24 h. Dose-related decreases in $C_{\text{max}}$, $C_{\text{avg}}$, $C_{\text{min}}$, and $AUC_{\tau}$ were observed following a dose decrease from 6 to 3 μg/ (kg week). After 8 weeks of dosing at 6 μg/(kg week) in the induction phase, the accumulation factor ($R$) was 1.69.

The arithmetic means of observed peginterferon α-2b concentrations over time are shown in Fig. 1. Although the dose level changed from 6 to 3 μg/(kg week) at week 9 (maintenance phase), mean trough levels remained similar at weeks 10, 11, and 12. Mean predose (trough) serum concentrations (%CV) of peginterferon α-2b at week 8/AUC$_{\tau}$ peginterferon α-2b at week 1

$C_{\text{avg}}$, average concentration within dosing interval; $C_{\text{max}}$, maximum serum concentration; $C_{\text{min}}$, minimum serum concentration; CL/F, apparent clearance; %CV, coefficient of variation expressed as a percentage; NA, not available; R, accumulation factor; $t_{1/2}$, terminal half-life; $T_{\text{max}}$, observed time to achieve $C_{\text{max}}$

$^{a}$Median (range)

$^{b}$Accumulation factor $R = AUC_{\tau}$ peginterferon α-2b at week 8/AUC$_{\tau}$ peginterferon α-2b at week 1

$^{c} n = 14$; CL/F cannot be reported for some patients because $t_{1/2}$ cannot be determined accurately

$^{d} n = 19$; no concentration data were available for one patient at week 12

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**Noncompartmental analysis**

The PK profile of peginterferon α-2b following once-weekly subcutaneous dosing in patients who completed 12 weeks of protocol-specific therapy without dose modification and who had complete pharmacokinetic samples for weeks 1, 8, and 12 (n = 20). Experimentally observed values (open circles) as well as the curve-fitted line using a one-compartment pharmacokinetic model are included.
first-order elimination. The one-compartmental model-predicted concentration–time profile is shown in Fig. 1. After the peak is reached, serum levels follow a monoexponential decay. The observed and model-predicted concentrations correlate well, as demonstrated in Fig. 1. The model describes the concentration–time profiles for the induction treatment of 6 μg/(kg week) from weeks 1–8 as well as the initial portion of the maintenance phase at 3 μg/(kg week) (serum trough levels at weeks 9–11 and a full profile at week 12). The consistent fit of this model across two dose levels suggests linear kinetics of peginterferon α-2b through this dose range. Based on this model-predicted concentration–time profile, steady state was reached at week 4 following 6 μg/(kg week) SC dosing, and there was no apparent additional accumulation during the initial maintenance phase at 3 μg/(kg week) (weeks 9–12; Fig. 1). Therefore, this PK model provides a reasonable estimate of exposure to peginterferon α-2b for use in the integrated PK/PD model.

PK/PD modeling

PK/PD models were developed in order to characterize the association between exposure and ANC or ALT response after SC administration of peginterferon α-2b and to provide a model of the effect of dose reduction on these parameters.

Effects of peginterferon α-2b on ANC

Using pooled data from our patients with high-risk melanoma (n = 32) along with those from patients with advanced solid tumors (n = 34) [2], a nonlinear PK/PD relationship is seen between AUCtau and change in ANC from baseline (Fig. 2). With increasing exposure to peginterferon α-2b, the ANC decreased relatively rapidly when AUCtau <200,000 pg h/mL, but the relationship between AUCtau and change in ANC from baseline appeared to reach the maximum effect at exposure (AUCtau) 400,000 pg h/mL, with <10% decline of ANC between 200,000 and 600,000 pg h/mL.

The median ANC change (% baseline) over time after weekly SC administration of peginterferon α-2b demonstrated a rapid onset of effect within 1 week then a plateau between weeks 2 and 8; when the dose changed to 3 μg/ (kg week), a slow return towards baseline level followed (Fig. 3a). The low number of patients at week 6 (n = 4) and the interpatient variability account for the wide error bars at this time point. Particularly, one patient had an ANC increase of 38% from baseline due to ANC rebound following treatment cessation at weeks 4 and 5 [at week 6 ANC was measured before dosing was resumed at 6 μg/(kg week)].

The observed and predicted changes in median ALT with time are shown in Fig. 3b. The ALT profile demonstrates a delayed onset with a peak and trough pattern, with ALT levels gradually increasing over time and reaching a maximum between weeks 5 and 8 in the range of 2.5–3× baseline level. When the dose changed to 3 μg/(kg week) (week 9), ALT levels gradually decreased to approximately 2× baseline values between weeks 10 and 12.

As shown in Fig. 3b, the indirect stimulatory response model could describe the average trend of ALT change.
following SC administration of peginterferon α-2b, but the fit was not as good as the ANC model. The individual ALT levels were highly variable; a notably large standard error was observed at week 4. Therefore, this model should be treated with caution. Further details are provided in the online resource material (supplementary methods and supplementary Table 1). Similar results were observed when PK/PD modeling was carried out using data only from patients who received full doses and provided all blood samples in the PK phase.

Discussion

Peginterferon α-2b is assuming a role in melanoma therapy based on the recent pivotal EORTC 18991 trial showing its efficacy in resected stage III melanoma [15]. The dose used in the EORTC 18991 trial, 6 μg/(kg week) for 8 weeks followed by 3 μg/(kg week) for up to 5 years, is much higher than that used for hepatitis C [1.5 μg/(kg week)]. Prior to the current study being initiated, there were only limited data on systemic exposure to high-dose peginterferon α-2b, and no data were available for melanoma patients receiving adjuvant therapy.

We show that peginterferon α-2b was well-absorbed following SC administration. Some accumulation occurred following 8 weeks of treatment at 6 μg/(kg week). The AUC_{τ} for the 6 μg/(kg week) dose in this study was comparable with that observed in a small phase I/II trial [2] in patients with advanced solid tumors, although the AUC_{τ} for 3 μg/(kg week) was lower in our study [2]. As expected, the CL/F of peginterferon α-2b was greatly reduced compared with the clearance of native interferon α-2b (231 mL/h kg) [23]. Therefore, peginterferon α-2b has an approximately 10-fold longer $t_{1/2}$ as compared with native interferon α-2b (43–51 vs. 4 h, respectively). The CL/F and $t_{1/2}$ in patients with melanoma were similar to those reported in patients with hepatitis C (22 mL/h kg and 27–39 h, respectively). The $C_{max}$ observed here was 3,980–5,070 pg/mL at the 6 μg/(kg week) dose and 2,620 pg/mL at the 3 μg/(kg week) dose (measured at 24 h). In a hepatitis C study, $C_{max}$ varied between 15 and 44 h postdose [23]. Hence, the $C_{avg}$ observed in the current study for the 3 μg/(kg week) dose (1,400 pg/mL) was comparable to the mean serum concentration observed in the limited PK analysis of the 18991 study (1,434 pg/mL). There is a difference in mean trough estimate at the 3 μg/(kg week) dose level between the 18991 PK study (1,069 pg/mL) and the present study (626 pg/mL). This may be because the timing of sampling to assess trough levels in the 18991 PK study was not as rigorous as in our study, and the 18991 analysis may have included post-dose samples, potentially leading to an overestimation of mean trough concentration [16]. In addition, PK sampling took place over a much longer time period for the 18991 PK analysis compared with the present study (up to 5 years vs. 12 weeks, respectively).

The comparison of pegylated and native interferon α-2b doses used in clinical trials is complicated by the differing measurement methods and units, schedules, and the specific activities. Data in patients with hepatitis C show that 0.25 μg/(kg week) peginterferon α-2b results in a similar anti-viral effect as 9 MIU/week (3 MIU three times weekly) native interferon α-2b. Extrapolating from this
data, 6.0 µg/(kg week) may achieve exposure comparable with that of interferon α-2b at 20 MIU/m²/day intravenous infusion five times weekly (180 MIU/week). The observed AUCₙₐᵣᵢ in patients with melanoma confirmed the extrapolation. We observed that SC dosing of 6 µg/(kg week) for 8 weeks followed by 3 µg/(kg week) was well tolerated with toxicity similar to that observed in the EORTC 18991 trial; based on our experience with high-dose native interferon α-2b in patients with melanoma, it appeared to us that our patients had lower incidence of fever and chills, but more skin rashes and hypertriglyceridemia. The data suggest that high-dose peginterferon α-2b has a better overall tolerability profile compared with high-dose native interferon α-2b. In phase I/II studies, peginterferon α-2b has also been shown to be well tolerated and clinically active in chronic myelogenous leukemia and renal cell cancer [13].

We developed PK/PD models and performed simulations in order to visualize the effect of peginterferon α-2b exposure on ANC and ALT levels, as these are clinically relevant interferon toxicities. We modeled the relationship between peginterferon α-2b AUCₙₐᵣᵢ and the observed reduction in ANC using data from our study as well as data from a prior study in patients with advanced solid tumors [2]. This analysis shows a steep dose response followed by a plateau around AUC 400,000 pg h/mL. The PK/PD model predicts that the ANC nadir is reached approximately 2 weeks after treatment initiation. The trough peginterferon α-2b concentration (Cₘᵟᵢₙ) closely mirrors the ANC nadir (Fig. 3a). A similar relationship between peginterferon α-2b dose and ANC changes after 4 weeks of dosing was reported in patients with hepatitis C [23]. Future studies with more intensive PD and PK sampling will assist in confirming that the wave-like fluctuation in ANC levels shown in Fig. 3a occur in clinical practice, as predicted by the PK/PD model.

Since clinicians may be interested in peginterferon α-2b dose reductions for excessive neutropenia, we also simulated the effect of dose reduction on the ANC. If peginterferon α-2b dose is reduced from 6 µg/(kg week) to 0, the ANC trends upward rapidly. While stepwise dose reductions (3–2–1 µg/kg) were prescribed in the EORTC 18991 trial, the Imax model used here suggests that treatment should be interrupted and resumed at a much lower dose (50 or 33% of starting dose) upon resolution of neutropenia, if grade 3 or 4 neutropenia is observed. Clearly, future trials should examine this clinically relevant issue.

Progressive transaminase elevations (reversible upon discontinuation of the drug) are a major factor in the ability of patients with melanoma to tolerate the full prescribed dose of peginterferon α-2b; ALT elevation is an important PD surrogate of high-dose interferon effect on the liver [3–5, 15]. Although the number of patients with grade 3 ALT elevations in the current study is low (four patients; 13%), the frequency is consistent with the EORTC 18991 trial data (10% grade 3 liver function test AEs) [15]. There were no grade 4 ALT elevations in our study. We explored this relationship using a fully integrated PK/PD model. Our model predictions for ALT did not appear to fit our observed data as well as for ANC, so further evaluation of this aspect of peginterferon administration is also clearly warranted.

In this study, the PK profile of high-dose peginterferon α-2b in patients with resected high-risk melanoma is described. The tolerability and safety of this dose and schedule appears to be broadly similar to that seen in previous studies. The PK/PD model of the effects of peginterferon α-2b exposure on ANC provides a useful framework. In contrast to high-dose interferon α-2b, hematologic and/or hepatic toxicity was less common and primarily grade 1 or 2 in severity with peginterferon α-2b 6 µg/(kg week) (induction) and 3 µg/(kg week) (maintenance). Based on the safety profile and PK data, combined with greater dosing convenience, peginterferon α-2b may potentially improve compliance and efficacy of adjuvant therapy for patients with high-risk melanoma.

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Conflict of interest statement A.I.D. has received research funding or funding for equipment or drugs from Schering-Plough (now Schering Corp., a Division of Merck & Co.). C.X. is a full-time employee of Merck & Co. W.J.H. has received research funding and drugs from, and is consultant to, Schering-Plough (now Schering Corp., a Division of Merck & Co.). V.K.S. is a paid consultant to and on the speakers’ bureau of Schering-Plough (now Schering Corp., a Division of Merck & Co.), P.U., S.A., N.E.P., L.C.F., and R.D.C. declared no conflicts of interest.

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