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

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A. I. Daud, C. Xu, W.-J. Hwu, P. Urbas, S. Andrews, N. E. Papadopoulos, L. C. Floren, A. Yver, R. C. DeConti, V. K. Sondak

Corresponding author: Adil Daud, MD, University of California San Francisco, San Francisco, CA 94143, USA; e-mail: adaud@medicine.ucsf.edu

ONLINE RESOURCE MATERIAL: SUPPLEMENTARY METHODS

Treatment

Treatment continued until the occurrence of distant metastases or unacceptable toxicity. Patients who developed locoregional metastases were not permitted to continue on the pharmacokinetic (PK) portion of the study but could continue treatment after complete surgical excision of the recurrent lesions (as was the case in the European Organisation for Research and Treatment of Cancer [EORTC] 18991 trial).

Protocol-specified guidelines for dose modifications for hematologic toxicities were white blood cells (WBC) $<1 \times 10^9$/L, or absolute neutrophil count (ANC) $<0.5 \times 10^9$/L, or platelets $<50 \times 10^9$/L. In subjects with WBC $<2 \times 10^9$/L or platelet count $<100 \times 10^9$/L, tests were repeated within 1–2 weeks. If cell counts dropped below specified levels, treatment was withheld until they returned to the cutoff level. After recovery, treatment could be restarted one dose level down; if toxicity occurred, a second dose reduction was implemented then a third if required ("off study" during

maintenance). No subsequent dose escalations were permitted after dose reduction for hematologic toxicity.

Safety evaluation

Safety assessments were repeated at weeks 1, 2, 4, 8, and 12 and at 3-month intervals thereafter (post-PK phase) until the conclusion of treatment. Because interferon- and peginterferon-related ocular changes have been reported [1], a baseline ophthalmologic examination was included. An ophthalmologic examination was performed post-baseline if clinically indicated. A 12-lead electrocardiogram was performed at baseline and week 12. Toxicity was assessed according to Common Terminology Criteria for Adverse Events version 3. Disease restaging was performed every 6 months or when signs or symptoms that potentially indicated recurrence were noted.

Throughout the study, the number of subjects reporting each adverse event (AE) and the severity of AEs were recorded. Laboratory values outside the normal range were flagged and abnormalities were reported as AEs. AEs were summarized by number of subjects and % of total study population.

Blood collection and analysis

Samples (5 mL) were collected in additive-free Vacutainer® tubes (Becton, Dickinson and Company, Franklin Lakes, NJ), allowed to clot at room temperature, and centrifuged at 1,500 × *g* for 15 min. The serum was divided between two Corning 2 mL polypropylene cryovials (Corning Incorporated Life Sciences, Lowell, MA), labeled, immediately frozen, and stored at –20°C until assayed.

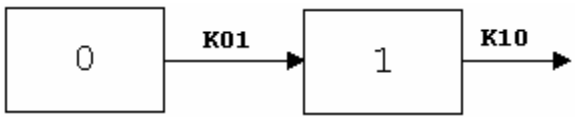
Serum peginterferon α-2b concentrations were determined using a validated electrochemiluminescence immunoassay [2]. The antibodies used in the assay recognize both peginterferon α-2b and free interferon, although the assay was validated using a peginterferon α-2b calibration curve. By convention, the term “peginterferon α-2b” is used here for reporting PK

parameters but refers to both the pegylated and nonpegylated interferon measured by this assay. The calibration curves for peginterferon α-2b were linear over a concentration range of 10–5,000 ng/mL. The assay limit of quantification was 20 pg/mL [2].

Compartmental PK analysis

Concentration data of peginterferon-α2b were used in a compartmental PK analysis. A one-compartment model and a two-compartment model were evaluated. A one-compartment model with first-order absorption and first-order elimination appropriately described the PK profiles for peginterferon-α2b following multiple subcutaneous (SC) dosing (Scheme 1).

Scheme 1 One-compartment with first-order input, first-order output, no lag time



The following primary PK variables were estimated using WinNonlin: apparent volume of distribution (V/F); absorption rate (K01); and elimination rate (K10) (see online resource material – supplementary Table 1).

PD modeling strategy and PK/PD analysis

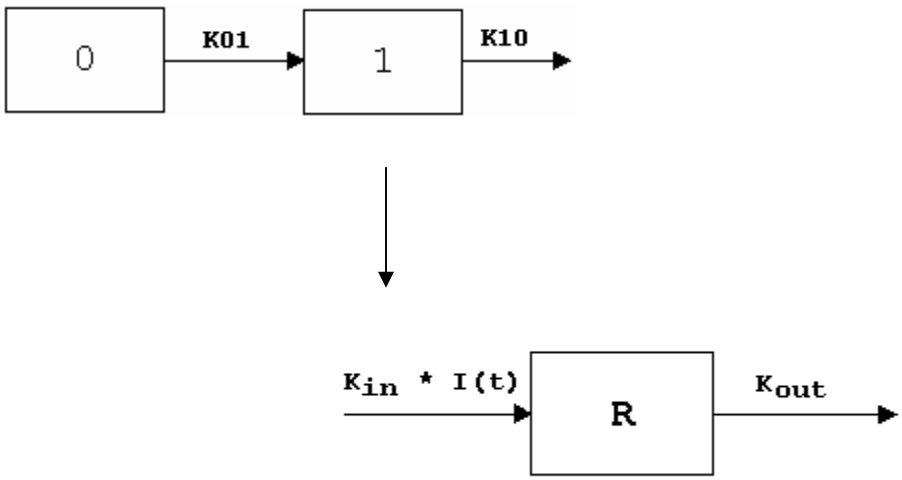
The PK/pharmacodynamic (PK/PD) relationship between peginterferon-α2b area under the concentration-time curve (AUC_{tau}) and ANC changes was assessed in patients with melanoma (n=32) and solid tumors (n=34). Since only two dose levels were specified by the study protocol (excluding dose reductions), we pooled data from a different trial that used a wide dose range in patients with solid tumors with the data from the patients with melanoma in this study to better describe the dose–response relationship. Previously published steady-state exposure values

(AUC_{tau} at week 4) from patients with solid tumors treated with doses ranging from 0.75 to 7.5 μg/kg/week (total 34 participants; 3–12 patients in each dose group [2-4], were used, along with the corresponding ANC data from the same patients (unpublished data, provided by Schering-Plough). Six of the 34 patients with solid tumors were melanoma patients.

The inhibitory Imax model can be described using the following equation: $E = E0 - I_{max} \cdot C/(IC_{50} + C)$, with baseline effect E0 = 100% when no drug is present. The maximum drug inhibitory effect corresponds to I_{max}. The AUC_{tau} at 50% of I_{max} is IC_{50}. Imax model parameters are shown in the online resource material supplementary Table 1.

The fully integrated PK/PD model for ANC is shown in Scheme 2. The PK profiles for SC dosing can be described by a one-compartment model (absorption and first-order elimination).

Scheme 2 Integrated PK/PD model for absolute neutrophil count



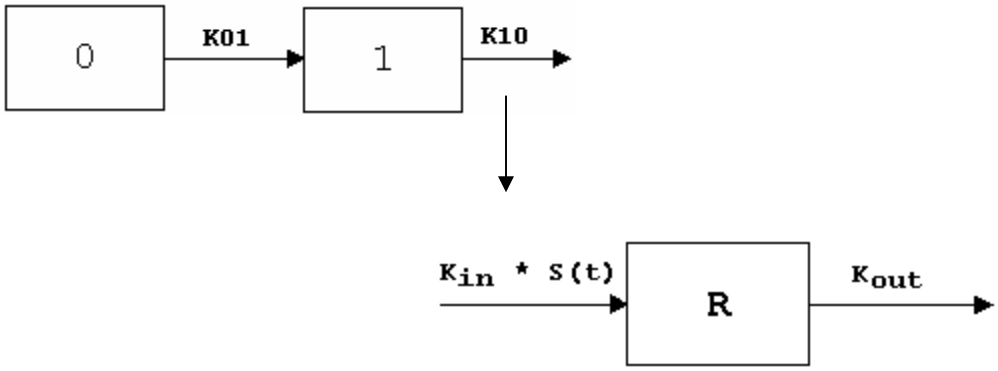
The PD component of the model is an indirect inhibition response model [5,6] driven by the PK profiles. The measure of ANC response, R, was transferred as percentage changes from baseline. Decreases in ANC following multiple SC doses of peginterferon α-2b may be due to the impact of peginterferon α-2b on the input or production rate (K_{in}) rather than output (loss or elimination) rate (K_{out}).

The K_{in} parameter represents the zero-order constant for production of response and K_{out} defines the first-order rate constant for loss of the response. IC_{50} is the peginterferon α-2b concentration that produces 50% if maximum inhibition is achieved at the effect site (supplementary Table 1).

The one-compartment PK model linked with an indirect response PD model appeared to reasonably capture the time course of the ANC. Supplementary Figures 1a and 1b show that the observed and predicted median ANC (percentage of baseline) were matched. It is clear from the plot that data points are distributed equally around the unity line; no obvious bias was observed (Figure 1b). Figure 1c shows the weighted residual vs the predicted concentration plot and Figure 1d shows the weighted residual vs the time plot, indicating no obvious trend. These diagnostic plots indicated that the model adequately described the data.

Another important PD surrogate of high-dose interferon effect is elevation in levels of the transaminases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Blood samples for ALT and AST were collected at baseline and approximately weekly following SC administration of peginterferon-α2b. Dose reductions are commonly employed for grade 3 or greater elevations in AST/ALT in patients undergoing high-dose interferon treatment. The fully integrated PK/PD model for ALT is shown in Scheme 3.

Scheme 3 Integrated PK/PD model for alanine aminotransferase count



The PD component of the model is an indirect stimulatory response model. The measure of response R, ALT level, was transferred as percentage changes from baseline. S_{max} is the maximum effect by peginterferon α-2b, SC_{50} is peginterferon α-2b concentration producing 50% of maximum stimulation achieved at the effect site and γ is the Hill coefficient (supplementary Table 1).

There was a poor fit between actual ALT levels and the PK/PD model, particularly with individual patient datasets, which were highly variable. The variability of estimated parameters was as high as 70% to 80% for K_{in}, K_{out}, and S_{max}. There was no clear trend in the rate of increase, and ALT levels did not reduce when the dose was reduced but instead increased further for some patients. The Hill coefficient was high (13.5) and beyond the plausibility of the parameter estimate. The high Hill coefficient indicates large changes in ALT levels with very small dose/concentration changes in the middle of the dose range.

SUPPLEMENTARY METHODS REFERENCES

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