Cancer Therapy: Clinical

ECOG Phase II Trial of Graded-Dose Peginterferon α-2b in Patients with Metastatic Melanoma Overexpressing Basic Fibroblast Growth Factor (E2602)

Ronald S. Go1, Sandra J. Lee3, Donghoon Shin3, Steven M. Callister2, Dean A. Jobe2, Robert M. Conry4, Ahmad A. Tarhini5, and John M. Kirkwood5

Abstract

Purpose: We investigated the use of graded-dose peginterferon α-2b (Peg-IFN) in patients with stage IV melanoma overexpressing basic fibroblast growth factor (FGF-2). The primary objective was suppression of plasma FGF-2 to within reference range (<7.5 pg/mL).

Experimental Design: Plasma FGF-2 was measured at baseline (step 1), and patients with concentrations of 15 pg/mL or more were eligible for study treatment (step 2). Peg-IFN was given weekly at a starting dose of 0.5 μg/kg/wk with increment every 3 weeks based on serial FGF-2 concentrations.

Results: Two hundred seven patients entered step 1; 45 (22%) overexpressed FGF-2 (median = 22 pg/dL). Twenty-nine eligible patients entered step 2 and received treatment. Patients' median age was 64 years (range, 29–84 years). Most had more than two prior therapies. FGF-2 decreased in 28 (97%) patients, with suppression to reference range in 10 (35%). Median time to FGF-2 suppression was 30 days. The best clinical responses were partial response (7%) and stable disease (17%). Median progression-free survival (PFS) and overall survival (OS) were 2.0 and 9.7 months, respectively. Patients who achieved FGF-2 suppression were more likely than those who did not to have a response or stable disease (P = 0.03). VEGF concentrations decreased in 27 patients (93%) during treatment and paralleled those of FGF-2 over time. We found no compensatory increase in VEGF among those with FGF-2 suppression.

Conclusions: Graded-dose Peg-IFN suppresses FGF-2 in patients with metastatic melanoma who overexpress FGF-2. Over one third of patients had complete suppression of plasma FGF-2, which correlated with clinical response to this therapy. Clin Cancer Res; 19(23); 6597–604. ©2013 AACR.

Introduction

Unlike normal melanocytes, melanoma cells express basic fibroblast growth factor (FGF-2) and its receptor (1). Melanocytes transduced to overexpress FGF-2 transform into a phenotype similar to melanoma (1). Antisense targeting of FGF-2 inhibits angiogenesis and induces melanoma regression in nude mice (2). Other angiogenic factors such as VEGF and interleukin-8 (IL-8) are upregulated during the course of melanoma progression and metastasis (3, 4). In patients with melanoma, increased tumor microvascular density and elevated concentrations of circulating angiogenic factors, including FGF-2, VEGF, and IL-8, are potential markers of worse overall prognosis and abbreviated progression-free survival (PFS; refs. 5, 6). Therefore, targeting of angiogenic factors, including FGF-2, VEGF, and IL-8, seems to be rational approaches to therapy.

IFN-α-2b, currently used in adjuvant therapy and for treatment of metastatic disease, is a cytokine with pleiotropic effects (7). Traditionally, when used for its antiproliferative and immunomodulatory effects, high doses (5–20 million units/m², 2–3 times weekly) have been favored. Preclinical studies suggest that lower doses of IFN may have antiangiogenic activity through downregulation of the expression of FGF-2, VEGF, IL-8, and matrix metalloproteinases (8, 9). In vitro, low-dose IFN-α inhibits B16 melanoma cell proliferation by interference with an FGF-2 autocrine growth circuit (10). Animal studies show that regulation of angiogenesis by IFN-α is schedule dependent, and that low-dose daily administration induces the most significant antiangiogenic effects and tumor inhibition (8, 11). Furthermore, early clinical studies in vascular tumors, such as infantile hemangioma, giant cell tumor of the mandible, and renal carcinoma, support the selection and monitoring of IFN therapy in relation to elevated plasma or urine FGF-2.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance
To our knowledge, this is the first study that reports the use of peginterferon α-2b (Peg-IFN) as an antiangiogenic agent in melanoma using an individualized graded-dosing approach based on real-time serial measurements of blood plasma angiogenic factors. We were able to demonstrate that in patients overexpressing basic fibroblast growth factor (FGF-2), suppression of FGF-2 was associated with clinical response or stable disease. Future clinical trials may now rationally consider strategies that exploit the antiangiogenic effects of Peg-IFN in combination with molecularly targeted agents and immunotherapy, as well as chemotherapy.

concentrations (12–14). Recently, a longer-acting formulation of IFN, peginterferon α-2b (Peg-IFN), was approved by the U.S. Food and Drug Administration for the adjuvant treatment of patients with melanoma at a dose of 6 μg/kg (induction for 8 weeks), then 3 μg/kg (maintenance up to 5 years) injected subcutaneously once a week on the basis of a phase III trial (15, 16).

In this phase II trial, we investigated the use of a low-dose regimen of Peg-IFN as an antiangiogenic agent in patients with metastatic melanoma and elevated plasma concentration of FGF-2. The primary objective of the study was to determine whether circulating FGF-2 concentration can be suppressed to within reference range with Peg-IFN. The secondary objectives were to determine the efficacy and safety profile of Peg-IFN, as well as the association between changes in angiogenic factors (FGF-2 and VEGF) and anti-tumor activity.

Patients and Methods
Patient selection
To be eligible, patients must have been at least 18 years of age, had stage IV melanoma from any primary site, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. They might have been previously untreated or could have received up to 3 prior systemic therapies for metastatic disease. Previous treatment with IFN was allowed. Exclusion criteria included active second cancer, history of myocardial infarction within the prior 6 months, history of severe depression, and current pregnancy. Patients with central nervous system (CNS) involvement were allowed, provided that CNS-directed therapy was given and the CNS disease had been clinically stable for at least 3 months. All patients were required to have a baseline measurement of plasma FGF-2 at study for preregistration. Those who overexpressed FGF-2 (≥15 pg/mL) were allowed to go on to register and receive study treatment within 3 working days of registration.

Study design
The treatment schema is shown in Fig. 1. The induction phase corresponded to the period from the beginning of Peg-IFN therapy until the documented suppression of plasma FGF-2 concentration to within reference range (<7.5 pg/mL) was confirmed by two consecutive determinations at least 3 weeks apart. Plasma FGF-2 concentrations were measured and Peg-IFN dose adjusted every 3 weeks. The starting dose of Peg-IFN was 0.5 μg/kg/wk administered subcutaneously. After 3 weeks, the same dose was given if the plasma FGF-2 concentration had declined by 30% or more, or if it had been suppressed to within reference range. Peg-IFN dose was increased every 3 weeks if plasma FGF-2 concentration had decreased by less than 30% and remained above reference range. The six Peg-IFN doses designated in this study were 1 (0.5 μg/kg/wk), 2 (1.0 μg/kg/wk), 3 (2.0 μg/kg/wk), 4 (3.0 μg/kg/wk), 5 (4.0 μg/kg/wk), and 6 (5.0 μg/kg/wk). Induction treatment was continued until plasma FGF-2 concentration was suppressed for two consecutive determinations or until a maximum dose of 5.0 μg/kg/wk was reached. If there was no disease progression, the patient would then enter the maintenance phase, receiving the same dose of Peg-IFN at the end of induction phase to complete another 12 months of therapy. Subsequent Peg-IFN doses were adjusted on the basis of plasma FGF-2 concentrations measured serially every 6 weeks.

All toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0). Dose modifications were required only for grades 3 and 4 nonanemia/nonfebrile toxicities. When grade 3 or 4 toxicities occurred, Peg-IFN was held until toxicity returned to grade ≤1. Treatment was then restarted at the next lower dose level. If the toxicity occurred during the induction phase, the retreatment automatically placed the patient into the maintenance phase. Protocol treatment was discontinued if the toxicity did not return to grade ≤1 within 3 weeks or any time there was evidence of clinical disease progression. FGF-2 concentrations were not used to determine clinical response or disease progression.

Study evaluations
Clinical examinations and basic laboratory tests were performed before treatment, every 3 weeks during induction, and every 6 weeks during the maintenance phase. Computed tomography (CT) scans of the chest, abdomen, and pelvis were performed every 9 and 12 weeks during induction and maintenance phases, respectively. Responses were assessed using RECIST (Response Evaluation Criteria in Solid Tumors) v.1 guidelines (17).

Correlative studies
Patients were required to submit a paired sample of plasma and urine at the time of study registration and serially every 3 to 6 weeks during treatment. Plasma FGF-2 was measured in real time, whereas plasma VEGF and urine FGF-2 and VEGF were batched and measured later because the latter values were not used to determine Peg-IFN dosing. For both FGF-2 and VEGF assays, we used ELISA kits manufactured by R&D Systems. The 95th percentile value of serum FGF-2 in healthy individuals set by the assay
manufacturer is 7.5 pg/mL. In our experience, the mean value of FGF-2 in healthy individuals (n = 10) was 0.9 pg/mL (range, 0–5.2 pg/mL). We, therefore, arbitrarily used a value of ≥15 pg/mL (2 x reference range) as a criterion for FGF-2 overexpression. To account for interassay variability, aliquoted plasma samples used in the previous assay were paired with the more current sample and assayed simultaneously. All angiogenic factor assays were performed centrally (S.M. Callister and D.A. Jobe) at the Gundersen Microbiology Research Laboratory.

Statistical analysis

The primary endpoint of this trial was the suppression of plasma FGF-2 concentration (≤7.5 pg/mL for 2 consecutive determinations at least 3 weeks apart) with Peg-IFN. It was of interest to test the null hypothesis of 10% FGF-2 suppression rate versus the alternative hypothesis of 30% suppression. On the basis of the sample size of 30 eligible patients, our one-sample binomial test had an 84% power to detect this 20% difference in the proportion of respondents who exhibited suppression of FGF-2 concentrations. This was based on a two-sided type I error of 0.05.

The secondary objectives included evaluating overall survival (OS), PFS, and objective tumor responses. For the objective tumor responses, the associations with the FGF-2/VEGF concentrations in the plasma and urine were assessed. Longitudinally collected FGF-2 and VEGF data were summarized descriptively for each case. The lowest concentrations of FGF-2 and VEGF during the induction phase of treatment were correlated with the objective tumor responses. Objective tumor response was dichotomized into those with or without disease progression under protocol therapy [complete response (CR) + partial response (PR) + stable disease vs. progressive disease]. The Wilcoxon rank-sum test was used for these comparisons. The expected tumor response rate was 20%, so we assumed that there would be 6 responders and 24 nonresponders among the 30 eligible cases. With this sample size, the power would be at least 80% if the standardized difference of FGF-2 concentrations between those who had nonprogressive disease and those with progressive disease were at least 1.2. A one-sided type I error of 0.05 was used.

As an exploratory evaluation, we evaluated a 2 x 2 table of objective tumor responses as nonprogressive/progressive and FGF-2/VEGF as high/low. For FGF-2, the cutoff value of 7.5 pg/mL was used to define "high" and "low" groups. For the dichotomized comparisons, proportions of cases with low FGF-2 were compared between those with and without progressive disease. Fisher exact tests were used to compare the proportions. If the difference in the proportions of cases achieving suppression of FGF-2 concentrations between the groups was at least 60% (e.g., 80% vs. 20%), then there would be at least 80% power. A one-sided type I error of 0.05 was used. A similar analysis was carried out for the VEGF concentration using the median value as the cutoff value. Given the exploratory nature of these tests, no adjustments were made for multiple comparisons.

The distributions of OS and PFS were estimated using the Kaplan–Meier method. The landmark analysis method was used for these comparisons.
used to compare the survival curves between those who showed plasma FGF-2 suppression and those who did not using log-rank test (18). We chose 63 days after registration as the landmark time point to allow at least three treatment cycles for response (at least 2 treatment cycles were needed to determine FGF-2 suppression). The survival time in the landmark time was defined as time to event (death or progressive disease) or censoring from the landmark time point. Patients who experienced an event of interest (death in OS and progressive disease for PFS) before the landmark time were excluded from the analysis.

Results

Between September 2003 and June 2011, 207 patients registered into step 1 and were screened for plasma FGF-2 concentrations. Of these, 45 (21.7%) patients overexpressed plasma FGF-2, with a median concentration of 22.0 pg/dL (range, 15.0–216.0 pg/dL). Within the latter group, 32 patients enrolled into step 2 and received treatment (Fig. 1). Three patients who received treatment were subsequently excluded from further analysis, 1 for the lack of a baseline CT scan (only a positron emission tomography scan was obtained) and 2 for outdated baseline FGF-2 measurements (more than 4 weeks before step 2 registration). Although FGF response could not be evaluated in these 3 cases, results of the analysis including these patients for all other efficacy endpoints are similar to those excluding them.

Patient characteristics

The clinical features of the 29 eligible patients are summarized in Table 1. The median age was 64 years (range, 29–84 years), and most patients were men (69%) with cutaneous primary (72.4%) who had lactate dehydrogenase (LDH) concentrations within reference range (51.7%). Patients had a median of 2 prior systemic therapies (range, 0–3) and 8 (27.5%) had been treated with IFN previously.

Table 1. Clinical features of patients on study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>20 (69.0)</td>
</tr>
<tr>
<td>Women</td>
<td>9 (31.0)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>29 (100.0)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>1</td>
<td>16 (55.2)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>21 (72.4)</td>
</tr>
<tr>
<td>Mucosa</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Eye</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>M classification</td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>M1b</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>M1c</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>15 (51.7)</td>
</tr>
<tr>
<td>Elevated</td>
<td>10 (34.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (13.8)</td>
</tr>
</tbody>
</table>

Efficacy

Plasma FGF-2 concentration was suppressed for two consecutive measurements at least 3 weeks apart in 10 patients—an FGF-2 suppression rate of 34.5% [95% confidence interval (CI), 17.9%–54.3%; \( P < 0.001 \) compared with a null hypothesis of 10% response rate]. The median time to FGF-2 suppression was 29.5 days (range, 14–116 days). The median duration of response was 21 days (range, 21–384 days). The objective tumor response rates were as follows: CR (0%), PR (6.9%), stable disease (17.2%), and progression (75.9%). The nonprogression rate was 24.1% (95% CI, 10.3%–43.5%). The median PFS was 2 months (range, 0.6–13.7 months; 95% CI, 1.8–2.3), and the median OS was 9.7 months (range, 1.7–45.4 months; 95% CI, 4.4–12.5).

The landmark analysis of OS was performed 63 days after registration to compare the OS between those who achieved FGF-2 suppression and those who did not. Three patients were excluded because they died before the landmark time. The median survivals for the suppressed and nonsuppressed groups were 7.8 months (95% CI, 0.1–10.4) and 7.7 months (95% CI, 3.1–14.4), respectively (Fig. 2; \( P = 0.31 \)). Patients who achieved FGF-2 suppression were more likely than those who did not to have a response or stable disease (50% vs. 10.5%; \( P = 0.03 \); Fig. 3A).

Adverse events

All 32 patients were included in the adverse event analysis, the results of which are summarized in Table 2. Thirteen (40.6%) patients experienced at least one major (grade \( \geq 3 \)) adverse event, with the most common being fatigue (21.9%), followed by nausea (9.4%), neutropenia (6.3%), and infection without neutropenia (6.3%). One patient died while on therapy associated with progressive disease.

Correlative studies

Plasma FGF-2 concentration was suppressed to within reference range in only 10 patients (34.5%), but it decreased in nearly all patients (28 of 29; 97%) during Peg-IFN therapy (Fig. 3A). Plasma VEGF concentrations decreased...
concurrently in 27 patients (93%; Fig. 3A). No compensatory increase in plasma VEGF concentration was observed among those who had plasma FGF-2 suppressed. Serial values of plasma FGF-2 and VEGF concentrations over time are shown in Fig. 3B and C, respectively. The pretreatment values of plasma FGF-2 and VEGF for patients relative to their tumor response are depicted in Fig. 3D. As a group, the mean posttreatment values were lower than the pretreatment values for both FGF-2 (6.7 vs. 29.5 pg/mL; \( P = 0.005 \)) and VEGF (37.9 vs. 127.5 pg/mL; \( P = 0.059 \)). Patients who achieved an objective response or stable disease had similar FGF-2 at baseline (mean, 21.1 vs. 32.2 pg/mL; \( P = 0.49 \)) but perhaps higher VEGF (261.6 vs. 84.9 pg/mL; \( P = 0.08 \)) concentrations compared with those who did not. Additional data on angiogenic factor concentrations in the plasma and urine are shown in the Supplementary Table S1.

Discussion

This phase II ECOG–American College of Radiology Imaging Network (ACRIN) trial studied the antiangiogenic and antitumor effects of Peg-IFN in patients with metastatic melanoma who were selected according to overexpression of FGF-2 in their plasma. We report several pertinent findings of this study. Approximately one fifth of the patients

Figure 2. Comparison of OS among those who did and did not achieve suppression of plasma FGF-2.

Figure 3. Plasma angiogenic factor concentrations during Peg-IFN therapy. A, best percentage change of angiogenic factor concentrations from baseline relative to tumor response. The orange doughnut-shaped symbol highlights the patients who had suppression of plasma FGF-2. Patients without a visible change in their angiogenic factor had 0% change, consistently undetectable plasma concentrations, or had progressive disease soon after treatment and declined further angiogenic factor measurement. B and C, serial angiogenic factor concentrations over time. D, baseline angiogenic factor concentrations for each patient relative to tumor response. The green, yellow, and orange diamonds represent patients who had partial response, stable disease, and progressive disease, respectively.
with metastatic melanoma overexpressed FGF-2. Using a graded-dosing Peg-IFN regimen based on real-time serial FGF-2 plasma concentrations, we have documented clinical antitumor activity and the suppression not only of FGF-2 but also of VEGF. Suppression of plasma FGF-2 was found to be associated with the clinical outcome of antitumor response or stable disease. This study did not document longer survival in association with the modulation of FGF-2 in the patients enrolled in this trial, but the number of patients studied did not reach the threshold recommended by Korn and colleagues (19). An increase in plasma VEGF was not observed as a compensatory mechanism when FGF-2 pathway is targeted in metastatic melanoma. Alternatively, this could be due to concomitant Peg-IFN, whose receptors are in development in melanoma and other cancers (32). A recent phase I/II trial of dovitinib, a small-molecule inhibitor of FGF receptors as well as other class III receptor tyrosine kinases, showed an acceptable safety profile but limited clinical activity (26% stable disease; ref. 33). In our study, the antitumor response rate was low (7% partial response and 7% stable disease) but comparable with the results of another trial using fixed-dose Peg-IFN in conjunction with bevacizumab and endostatin (28–31).

In contrast, our study has shown that in the majority (>90%) of patients with metastatic melanoma treated, plasma FGF-2 and VEGF concentrations were reduced by Peg-IFN. Antitumor response and stable disease were more likely among those whose FGF-2 concentrations were suppressed to within reference range than among those whose were not. Several factors, including patient selection and Peg-IFN dosing regimen, may potentially explain the discrepancies between these findings. Unlike previous studies, only patients who overexpressed FGF-2, the presumptive antiangiogenic target of Peg-IFN, were included in our study. Because fewer than a quarter of patients overexpress FGF-2, an antiangiogenic signal may be easily overlooked if the study population is not enriched with the putative biologic target. Our Peg-IFN dosing regimen was novel in that we adjusted the dose based on real-time measurement of plasma FGF-2 concentration to maximize biologic response and minimize toxicity. Preclinical studies suggest that the regulation of angiogenesis by IFN is dose and schedule dependent, with low dose and constant tumor exposure being the most effective (8, 11). Moreover, the optimal biologic dose of Peg-IFN may vary from patient to patient. Therefore, an individualized approach may be more effective.

Multiple lines of evidence support the existence of cross-talk between FGF and VEGF pathways in melanoma progression. Preclinical and clinical studies suggest that upregulation of the FGF pathway may serve as a mechanism of resistance to anti-VEGF therapy and potentially vice versa (32). It is notable that among the patients with complete suppression of FGF-2, we did not observe any compensatory increase in VEGF. This suggests that upregulation of the VEGF pathway may not be a primary escape mechanism when the FGF-2 pathway is targeted in metastatic melanoma. Alternatively, this could be due to concomitant Peg-IFN suppression of VEGF production.

Early-phase clinical trials targeting the FGF ligands and their receptors are in development in melanoma and other cancers (32). A recent phase I/II trial of dovitinib, a small-molecule inhibitor of FGF receptors as well as other class III receptor tyrosine kinases, showed an acceptable safety profile but limited clinical activity (26% stable disease; ref. 33). In our study, the antitumor response rate was low (7% partial response and 7% stable disease) but comparable with the results of another trial using fixed-dose Peg-IFN as a single agent (20). This suggests that FGF or FGF receptor targeting alone may not be sufficient for therapy of metastatic advanced melanoma and that combinations with other targeted agents or chemotherapy may be required to achieve more meaningful results. In support

<table>
<thead>
<tr>
<th>Table 2. Adverse events in patients</th>
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<tr>
<td><strong>Toxicity</strong></td>
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<tr>
<td>Cardiovascular</td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>Hypertension</td>
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<td>Constitutional</td>
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<td>Chills</td>
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<td>Fatigue</td>
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<td>Gastrointestinal</td>
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<td>Constipation</td>
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<td>Laboratory—ALT—ALT</td>
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<td>Nausea</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Other</td>
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<tr>
<td>Hematologic</td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Neutropenia</td>
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<tr>
<td>Infectious disease</td>
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<tr>
<td>Infection without neutropenia</td>
</tr>
<tr>
<td>Musculoskeletal</td>
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<tr>
<td>Myalgia</td>
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<td>Neurologic</td>
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<td>Confusion</td>
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<td>Depression</td>
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<td>Tremor</td>
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<tr>
<td>Pain</td>
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<tr>
<td>All other</td>
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<td>Total</td>
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of this, a synergistic drug interaction was observed when combining FGF receptor inhibitors (SU5402, PD166866) with the multitkinae/BRAF inhibitor sorafenib or the V600E mutant-specific BRAF inhibitor vemurafenib in a preclinical model targeting melanoma overexpressing FGF-2, FGF-5, and FGF-18. In contrast, the addition of the same FGF receptor inhibitors to dacarbazine showed only modestly increased activity (34).

In conclusion, we have shown that graded dosages of Peg-IFN titrated against plasma FGF-2 exhibit antitumor activity that correlates with suppression of FGF-2 concentrations in patients with refractory metastatic melanoma selected for elevated baseline FGF-2 concentrations. Titration of Peg-IFN based on an individual patient's serial plasma FGF-2 concentrations is feasible and provides a route to optimize dosing of Peg-IFN in melanoma. Future clinical trials may now rationally consider strategies that exploit the angiogenic effects of Peg-IFN in combination with molecularly targeted agents and immunotherapy, as well as chemotherapy.

Disclosure of Potential Conflicts of Interest
A.A. Tarhini is consultant/advisor board member and received commercial research grant from Merck. J.M. Kirkwood received commercial research grant from Prometheus and is consultant/advisor board member of GlaxoSmithKline, Merck, Vical, Bristol–Myers Squibb, and Celgene. No potential conflicts of interest were disclosed by the other authors.

References

Disclaimer
The contents of this study are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

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Development of methodology: R.S. Go, J.M. Kirkwood
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.S. Go, S.M. Callister, D.A. Jobe, R.M. Conry, A.A. Tarhini, J.M. Kirkwood
Analysis and interpretation of data (e.g., statistical analysis, bioinformatics, computational analysis): R.S. Go, S.J. Lee, D. Shin, S.M. Callister, D.A. Jobe, J.M. Kirkwood
Writing, review, and/or revision of the manuscript: R.S. Go, S.J. Lee, A.A. Tarhini, J.M. Kirkwood
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R.S. Go
Study supervision: R.S. Go, J.M. Kirkwood

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