ECOG Phase II trial of graded-dose peginterferon α-2b in patients with metastatic melanoma over-expressing basic fibroblast growth factor (E2602)

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Running Title: Peg-interferon α-2b suppresses FGF-2 in melanoma patients

Keywords: pegylated interferon, metastatic melanoma, angiogenesis, basic fibroblast growth factor, phase II clinical trial

This study was conducted by the Eastern Cooperative Oncology Group (Robert L. Comis, MD, Chair) and supported in part by the Public Health Service Grants CA23318, CA66636, CA21115, CA39229 and from the National Cancer Institute, National Institutes of Health, and the Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute. Additional funding was provided by Gundersen Medical Foundation and Gundersen Health System.
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**Potential Conflicts of Interest:**

The authors (Go, Lee, Shin, Callister, Jobe, Conry, Tarhini, and Kirkwood) have no potential conflicts of interest to disclose.

Word count: 3,218

Tables: 2

Figures: 3

Supplementary Table: 1
To our knowledge, this is the first study to report the use of peginterferon α-2b (Peg-IFN) as an anti-angiogenic 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 over-expressing 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 anti-angiogenic effects of Peg-IFN in combination with molecularly targeted agents and immunotherapy, as well as chemotherapy.
ABSTRACT

Purpose: We investigated 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 normal range (≤7.5 pg/mL).

Experimental Design: Plasma FGF-2 was measured at baseline (Step 1), and patients with concentrations ≥15 pg/mL were eligible for study treatment (Step 2). Peg-IFN was given weekly at 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 >2 prior therapies. FGF-2 decreased in 28 (97%) patients, with suppression to normal 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). Vascular endothelial growth factor (VEGF) concentrations decreased in 27 patients (93%) during treatment and paralleled those of FGF-2 over time. We found no compensatory rise 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 a third of patients had complete suppression of plasma FGF-2, which correlated with clinical response to this therapy.
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 vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8) are up-regulated during the course of melanoma progression and metastasis (3, 4). In melanoma patients, 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) (5, 6). Therefore, targeting of angiogenic factors including FGF-2, VEGF and IL-8 appear to be rational approaches to therapy.

Interferon 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 anti-proliferative and immunomodulatory effects, high doses (5-20 million units/m², 2-3 times weekly) have been favored. Pre-clinical studies suggest that lower doses of interferon may have anti-angiogenic activity through down-regulation of the expression of FGF-2, VEGF, IL-8, and matrix metalloproteinases (8, 9). In vitro, low-dose interferon-α inhibits B16 melanoma cell proliferation by interference with an FGF-2 autocrine growth circuit (10). Animal studies show that regulation of angiogenesis by interferon-α is schedule-dependent, and that low-dose daily administration induces the most significant anti-angiogenic 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 concentrations (12-14). Recently, a longer-acting
formulation of interferon, 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 based on 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 anti-angiogenic 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 normal 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 0-2. They might have been previously untreated or could have received up to 3 prior systemic therapies for metastatic disease. Previous treatment with interferon 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 pre-registration. 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 Figure 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 normal range (≤7.5 pg/mL) was confirmed by 2 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/week administered subcutaneously. After 3 weeks, the same dose was given if the plasma FGF-2 concentration had declined by ≥30% or if it had been suppressed to within normal range. Peg-IFN dose was increased every 3 weeks if plasma FGF-2 concentration had decreased by <30% and remained above normal range. The 6 Peg-IFN doses designated in this study were 1 (0.5 µg/kg/week), 2 (1.0 µg/kg/week), 3 (2.0 µg/kg/week), 4 (3.0 µg/kg/week), 5 (4.0 µg/kg/week), and 6 (5.0 µg/kg/week). Induction treatment was continued until plasma FGF-2 concentration was suppressed for 2 consecutive determinations or until a maximum dose of 5.0 µg/kg/week 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 based on 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 non-anemia/non-febrile 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, while 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 (Minneapolis, MN). 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 × normal range) as a criterion for FGF-2 overexpression. To account for inter-assay 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 (SMC and DAJ) at the Gundersen Microbiology Research Laboratory.

**Statistical Analysis**

The primary endpoint of this trial was the suppression of plasma FGF-2 concentration ($\leq 7.5$ 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. Based on the sample size of 30 eligible patients, our 1-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 2-sided type I error of .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 there would be 6 responders and 24 non-responders 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 non-progressive disease and those with progressive disease were at least 1.2. A 1-sided type I error of 0.05 was used.
As an exploratory evaluation, we evaluated a $2 \times 2$ table of objective tumor responses as non-progressive/progressive and FGF-2/VEGF as high/low. For FGF-2, the cut-off 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 concentration between the groups were at least 60% (e.g., 80% vs. 20%), then there would be at least 80% power. A 1-sided type I error of .05 was used. A similar analysis was carried out for the VEGF concentration using the median value as the cut-off 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. Landmark analysis method was 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 3 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 PET scan was obtained) and 2 for outdated baseline FGF-2 measurements (more than 4 weeks prior to step 2 registration). Although FGF response could not be evaluated in these 3 cases, results of 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 normal range (51.7%). Patients had a median of 2 prior systemic therapies (range, 0-3), and 8 (27.5%) had been treated with interferon previously.

**Treatment**

All of the 29 eligible patients received Peg-IFN according to study protocol. Of these, 9 went on to receive maintenance therapy. The median numbers of induction and maintenance cycles were 3 (range, 1-6 cycles) and 4 (range, 1-9 cycles), respectively. The reasons for termination of treatment were progressive disease (86.2%), treatment toxicities (6.9%), death from disease (3.4%), and symptomatic deterioration without objective disease progression (3.4%).

**Efficacy**

Plasma FGF-2 concentration was suppressed for 2 consecutive measurements at least 3 weeks apart in 10 patients—an FGF-2 suppression rate of 34.5% (95% CI: 17.9%-54.3%; \( P < \)
0.001 compared with 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 non-progression rate was 24.1% (95% CI: 10.3%-43.5%). The median PFS was 2 months (range, 0.6-13.7 months; 95% confidence interval [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).

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 non-suppressed groups were 7.8 months (95% CI: 0.1-10.4) and 7.7 months (95% CI: 3.1-14.4), respectively (Figure 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 1 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 normal 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 Figures 3B and 3C, respectively. The pre-treatment values of plasma FGF-2 and VEGF for patients relative to their tumor response are depicted in Figure 3D. As a group, the mean post-treatment values were lower than the pre-treatment values for both FGF-2 (6.7 pg/mL vs. 29.5 pg/mL; \( P = 0.005 \)) and VEGF (37.9 pg/mL 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 pg/mL vs. 32.2 pg/mL; \( P = 0.49 \)) but perhaps higher VEGF (261.6 pg/mL 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-ACRIN trial studied the anti-angiogenic and anti-tumor 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 a fifth of the patients 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 et al. (19). A rise in plasma VEGF was not observed as a compensatory mechanism when FGF-2 was suppressed by Peg-IFN.
To our knowledge, this is the first study to report the use of Peg-IFN as an anti-angiogenic agent in a graded-dosing approach based on real-time serial measurements of blood plasma angiogenic factors. Previous phase II trials in melanoma have evaluated varied but fixed dosages of Peg-IFN ranging from approximately 0.5-6.0 µg/kg/week as a single agent or in combination with other drugs (dacarbazine, interleukin-2, sorafenib, thalidomide, temozolamide). Response rates ranged from 0% to 29%, with higher rates of responses in trials where chemotherapy agents were included (20-27). Only 1 of these studies measured pre- and post-treatment serum angiogenic factor concentrations, without finding any association with antitumor responses or altered survival outcome. In addition, FGF-2 and VEGF concentrations were not found to change significantly from baseline (26). Similar findings of dissociation between presence of clinical antitumor response and lack of angiogenic response were noted in several phase II trials using daily or intermittent regimens of recombinant non-pegylated interferon 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 normal 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 anti-angiogenic target of Peg-IFN, were included in our study. Because fewer than a quarter of patients overexpress FGF-2, an anti-angiogenic 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 in order to maximize biologic response and minimize toxicity. Pre-clinical 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. Pre-clinical and clinical studies suggest that up-regulation 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 rise in VEGF. This suggests that up-regulation 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) (33). In our study, the anti-tumor response rate was low (7% partial response and 7% stable disease) but comparable to 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 of this, a synergistic drug interaction was observed when combining FGF receptor inhibitors (SU5402, PD166866) with the multi-kinase/BRAF
inhibitor sorafenib or the V600E mutant-specific BRAF inhibitor vemurafenib in a pre-clinical 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 anti-tumor 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 anti-angiogenic effects of Peg-IFN in combination with molecularly targeted agents and immunotherapy, as well as chemotherapy.
REFERENCES


Figure Legends

Figure 1. E2602 study schema. Abbreviations: FGF-2, basic fibroblast growth factor; VEGF, vascular endothelial growth factor.

Figure 2. Comparison of overall survival among those who did and did not achieve suppression of plasma basic fibroblast growth factor (FGF-2).

Figure 3. Plasma angiogenic factor concentrations during Peg-IFN therapy. (A) Best % 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-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. Abbreviations: FGF-2, basic fibroblast growth factor; VEGF, vascular endothelial growth factor.
**Table 1. Clinical features of patients on study**

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Abbreviation: ECOG, Eastern Cooperative Oncology Group.
Table 2. Adverse events in patients

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<th>Toxicity</th>
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<th>Grade ≥3, n (%)</th>
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<td>Dizziness</td>
<td>6 (18.8)</td>
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<tr>
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<tr>
<td>Chills</td>
<td>7 (21.9)</td>
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<tr>
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<td>Laboratory - ALT</td>
<td>10 (31.3)</td>
<td>1 (3.1)</td>
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<tr>
<td>Nausea</td>
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Stage IV cutaneous or ocular or unknown primary

N = 32

PRE REGISTER

Plasma FGF-2 ≥15 pg/mL

Yes

PEGINTERFERON α-2b
0.5 µg/kg/wk
Plasma FGF-2 concentration q 3 wks
Dose escalate q 3wks per protocol up to a maximum dose of 5.0 µg/kg/wk

Induction

No

Disease progression

Discontinue protocol therapy

Maintenance

Plasma FGF-2 concentration ≤7.5 pg/mL

Yes

Plasma B-FGF concentration q 6 wks
Adjust dose accordingly
Maximum dose of 5.0 µg/kg/wk

Peginterferon α-2b × 12 mos

No

Correlative studies: plasma and urine FGF-2 and VEGF
ECOG Phase II trial of graded-dose peginterferon α-2b in patients with metastatic melanoma over-expressing basic fibroblast growth factor (E2602)

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Clin Cancer Res  Published OnlineFirst October 11, 2013.

Updated version  Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-13-1414

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