Clinical and Biological Efficacy of Recombinant Human Interleukin-21 in Patients with Stage IV Malignant Melanoma without Prior Treatment: A Phase IIa Trial

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Abstract

Purpose: Human interleukin-21 (IL-21) is a class I cytokine that mediates activation of CD8+ T cells, natural killer (NK) cells, and other cell types. We report final clinical and biological results of a phase II study of recombinant human IL-21 (rIL-21) in patients with metastatic melanoma. Experimental Design: Open-label, single-arm, two-stage trial. Eligibility criteria: unresectable metastatic melanoma, measurable disease by Response Evaluation Criteria in Solid Tumors, no prior systemic therapy (adjuvant IFN permitted), adequate major organ function, good performance status, no significant autoimmune disease, and life expectancy at least 4 months. Primary objective: antitumor efficacy (response rate). Secondary objectives: safety, blood biomarkers, and generation of anti-rIL-21 antibodies. rIL-21 (30 µg/kg/dose) was administered by intravenous bolus injection in 8-week cycles (5 dosing days followed by 9 days of rest for 6 weeks and then 2 weeks off treatment). Results: Stage I of the study comprised 14 patients. One confirmed complete response (CR) was observed, and as per protocol, 10 more patients were accrued to stage II (total n = 24: 10 female and 14 male). Best tumor response included one confirmed CR and one confirmed partial response, both with lung metastases. Treatment was overall well tolerated. Biomarker analyses showed increases in serum soluble CD25, frequencies of CD25+ NK and CD8+ T cells, and mRNA for IFN-γ, perforin, and granzyme B in CD8+ Tand NK cells. Conclusions: rIL-21 administered at 30 µg/kg/d in 5-day cycles every second week is biologically active and well tolerated in patients with metastatic melanoma. Confirmed responses, including one CR, were observed.

Melanoma is now one of the most common forms of cancer. In the United States, it is estimated that >62,000 patients will be diagnosed with melanoma in 2008 and >8,400 patients will die from the disease (1). The most recent Australian data indicate 9,722 new cases and 1,200 deaths in 2004.8 The incidence in Australia is double that of the United States (2). Although overall mortality from melanoma is improving in Australia,3 survival for patients with metastatic disease remains poor. The median survival is ~7 months (3), although a small proportion of patients presenting with metastatic disease can have long-term survival (4).

Current approved systemic treatment options for metastatic melanoma include dacarbazine and interleukin-2 (IL-2). Dacarbazine has a response rate of ~10% in phase III trials (5, 6), with a short duration of response. High-dose IL-2 can induce a similar frequency of response; however, a small proportion of these can be durable complete responses (CR; ref. 7). Use of IL-2 either alone or in combination is complicated by its considerable toxicities (8, 9). Recently, immunologic strategies targeting the inhibitory CTLA-4 receptor T cells have led to intriguing clinical responses (10), although these remain relatively infrequent and are variably associated with induction of autoimmune diseases. New therapeutic options are therefore needed for the management of late-stage melanoma.
Interleukin-21 (IL-21) is a pleiotropic cytokine that has key functions in both the innate and adaptive immunity and the regulation of autoimmunity. This article reports our phase Ila study of IL-21 in patients with metastatic melanoma and builds on our phase I experience, showing that IL-21 is safe and well tolerated, induces relevant biological responses, and can lead to antitumor responses including a confirmed complete response. These results suggest that IL-21 may have a role as a single agent in the treatment of patients with melanoma. Preclinical studies showed that IL-21 also has significant activity against various types of cancer in combination with monoclonal antibodies or signaling inhibitors. Clinical trials of such combinations are currently ongoing and may indicate a role for IL-21 in a variety of clinical indications.

IL-21 is a member of the common γ-chain (γc) family of cytokines, which also includes IL-2, IL-4, IL-7, IL-9, and IL-15. The members of this family all share γc as part of a heterodimeric or heterotrimeric receptor, where signaling through γc is responsible for activation of the JAK/STAT signaling pathway (11, 12). IL-21 is primarily produced by activated CD4+ T cells, activated natural killer (NK) T cells, and follicular T helper cells (13–15). The IL-21 receptor is constituted expressed at low levels on all lymphocyte subsets and on dendritic cells, with B cells having the highest constitutive expression.

We have recently reviewed the function of IL-21 in cancer and autoimmunity (16, 17). IL-21 stimulates IFN-γ production and enhances the cytolytic activity of NK and CD8+ T cells in synergy with IL-2 and IL-15 (18). IL-21 also has effects on B-cell function (19), CD4+ T cells, (20, 21), and NK T cells (14) and opposes development of regulatory T cells (22–24). Taken together, these data suggest that IL-21 has effects on regulation of autoimmunity. This may be very important in the context of cancer, where “immunoediting” leads to alteration of the antigenic phenotype of the tumor as it evolves (25). If the equilibrium shifts away from immunoreactivity and toward active immunosuppression, then growth of cancers might be enhanced in the resulting permissive immune environment. This provides a rational basis for the clinical development of IL-21 as an anticancer reagent, either alone or in combination.

Recombinant IL-21 (rIL-21) is under clinical development by Novo Nordisk and Zymogenetics. We have previously reported our experience with rIL-21 in a phase I trial of patients with metastatic melanoma (26–28) and another group has recently published the results of a trial in melanoma or renal cell carcinoma (29) using different treatment regimens. These two studies led to the selection of 30 µg/kg as the optimal intravenous dose based on safety and biological activity data. We now report the results of a phase Ila trial in Australian patients with metastatic melanoma.

**Translational Relevance**

Interleukin-21 (IL-21) is a pleiotropic cytokine that has key functions in both the innate and adaptive immunity and the regulation of autoimmunity. This article reports our phase Ila study of IL-21 in patients with metastatic melanoma and builds on our phase I experience, showing that IL-21 is safe and well tolerated, induces relevant biological responses, and can lead to antitumor responses including a confirmed complete response. These results suggest that IL-21 may have a role as a single agent in the treatment of patients with melanoma. Preclinical studies showed that IL-21 also has significant activity against various types of cancer in combination with monoclonal antibodies or signaling inhibitors. Clinical trials of such combinations are currently ongoing and may indicate a role for IL-21 in a variety of clinical indications.

**Materials and Methods**

**rIL-21.** rIL-21 was provided by Novo Nordisk. rIL-21 is expressed in *Escherichia coli* as the NH2-terminal methionylated form. Zymogenetics in Seattle developed processes for production, refolding, and purification of the molecule and analytic methods for assessment of purity and potency. Manufacturing was done in the good manufacturing practice facilities of Avecia. Each vial contained 0.8 ml rIL-21 at a concentration of 10 mg/ml and diluted for administration using sterile saline for injection [0.9% (w/v) sodium chloride].

**Trial design.** The phase Ila component of trial NN028-1614 was an open-label, nonrandomized two-stage design. The primary objective of the trial was to determine the effect of rIL-21 on tumor size in subjects with metastatic melanoma according to Response Evaluation Criteria in Solid Tumors (30). Secondary objectives were to characterize the frequency of adverse events, to confirm the effect of rIL-21 on markers of immunomodulation (biomarkers) in blood, serum, and plasma, to determine if antibodies against rIL-21 were induced during therapy, and to determine progression-free survival. Data on overall survival were collected by investigators under the consent of patients for this study and were included in this publication.

rIL-21 was administered by intravenous bolus injection at a dose of 30 µg/kg, in a dosing regimen of treatment for 5 days followed by 9 days rest ("5+9") for 6 weeks, followed by 2 weeks without dosing, for a treatment cycle length of 8 weeks. An extension cycle of treatment (designated ET-1) was offered to participants if there was no symptomatic tumour progression at the week 8 assessment that required treatment by another modality. A second extension cycle (ET-2) was offered only to participants with objective responses according to Response Evaluation Criteria in Solid Tumors at the week 16 assessment. Participants were followed until progression of disease or death.

Participants were evaluable for tumor response if they had completed the second planned tumor evaluation (week 8). All patients are scheduled for day 5 were evaluable for immunologic endpoints. Participants who completed all evaluations up to and including those scheduled for day 5 were evaluable for immunologic endpoints.

**Patient population.** Eligible patients had historically confirmed surgically incurable metastatic malignant cutaneous melanoma. Other inclusion criteria: age ≥18 years, measurable disease by Response Evaluation Criteria in Solid Tumors, Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy at least 4 months, adequate bone marrow function (WBC ≥2.5 × 10^9/L, absolute neutrophil count ≥1.5 × 10^9/L, platelet count ≥100 × 10^9/L, hemoglobin ≥100 g/L, lymphocytes ≥0.8 × 10^9/L, no sign of hemolytic anemia), bilirubin ≤1.25 times upper limit of normal, aspartate aminotransferase/serum glutamic oxaloacetic transaminase ≤2.5 times upper limit of normal (unless attributable to liver metastases in which case ≤5 times upper limit of normal), lactate dehydrogenase ≤2 times upper limit of normal, calculated creatinine clearance ≥60 ml/min, body mass index ≥15 kg/m², and use of effective contraception. Key exclusion criteria: completely resected metastatic disease, ocular or mucosal melanoma, acute or active infection requiring systemic treatment, hepatitis B or C or HIV positive, autoimmune disease (vittigo and treated pernicious anemia were permitted), uncontrolled brain metastases or edema, prior chemotherapy or biological anticancer drugs (prior adjuvant IFN-α was permitted if completed at least 6 months before study entry), radiotherapy or major surgery within 4 weeks before study entry, concurrent systemic corticosteroids (topical or inhalational corticosteroids were permitted), significant cardiovascular disease or other severe systemic disease, other prior malignancy (except basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, or any curatively treated nonhematologic malignancy with no evidence of recurrence for at least 3 years), and pregnancy or breast-feeding. Minor surgery for isolated metastases was permitted at the discretion of the principal investigator and such patients were not necessarily removed from the trial.

All participants exposed to rIL-21 were evaluable for safety. Participants who completed all evaluations up to and including those scheduled for day 5 were evaluable for immunologic endpoints. Participants were evaluable for tumor response if they had completed the second planned tumor evaluation (week 8). All patients are accounted for in the final analysis.

All hematology, biochemistry, and urinalysis laboratory testing and immunoglobulin isotype testing was done by Mayne Health Dorevitch Pathology. The Cancer Trials Australia Laboratory performed some of the biomarker assays. Cell markers of NK-, T-, and B-cell subsets and monocytes were analyzed by flow cytometry at Westmead Millennium Cancer Therapy: Clinical Research.
Table 1. Participant demographics

<table>
<thead>
<tr>
<th>Sex, n (%)</th>
<th>N = 24</th>
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<tbody>
<tr>
<td>Male</td>
<td>14 (58.3)</td>
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<tr>
<td>Female</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td>Age (y), median (range)</td>
<td>54.5 (25.0-67.0)</td>
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<td>ECOG performance status, n (%)</td>
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<tr>
<td>0</td>
<td>19 (79.2)</td>
</tr>
<tr>
<td>1</td>
<td>5 (20.8)</td>
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<tr>
<td>AJCC stage, n (%)</td>
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<tr>
<td>M1a</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>M1b</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>M1c</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Baseline lactate dehydrogenase, n (%)</td>
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<tr>
<td>Normal</td>
<td>22 (91.7)</td>
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<tr>
<td>High</td>
<td>2 (8.3)</td>
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<tr>
<td>Duration of stage IV disease (y)</td>
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<tr>
<td>Median (range)</td>
<td>0.2 (0.0-4.6)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.9 (1.3)</td>
</tr>
</tbody>
</table>

Biomarkers. Serum levels of sCD25 were assessed by IL-2R IMMULITE 2000 Assay (Siemens Medical Solutions Diagnostics) according to the manufacturer’s instructions. Quantitative real-time reverse transcription-PCR was done as described previously (27). Briefly, total RNA was extracted from isolated CD8+ and CD56+ cells as well as peripheral blood mononuclear cell suspensions. Quantitative real-time reverse transcription-PCR was done in duplicates using TaqMan PCR core reagents and the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems). Primers and FAM-labeled probes for granzyme B, perforin-1, IFN-γ, and 18S rRNA were ordered as Assays-on-Demand (Applied Biosystems). Data were analyzed using ABI Prism SDS 2.2 software (Applied Biosystems), and expression levels were normalized to 18S rRNA levels. For immunophenotyping of leukocyte subsets, whole blood was collected in 6 mL ACD vacutainer tubes. All samples were shipped at ambient temperature and analyzed within 24 h of receipt. The following antibodies from BD Biosciences were used: CD3 (clone SK7), CD4 (clone SK3), CD8 (clone SK1), CD14 (clone MoP9), CD16 (clone NKP15), CD25 (clone 2A3), CD45 (clone 2D1), CD56 (clone NCAM16.2), and CD64 (clone 10.1). Samples were analyzed on a FACSCalibur flow cytometer using CellQuest acquisition software (version 3.3; BD Biosciences). Acquired data were analyzed with WinList flow cytometry data analysis software (version 3.0; Verity Software House).

Immunogenicity. Antibodies against rIL-21 were measured at day 52 by ELISA as described previously (26).

Statistical analysis. The sample size was chosen according to Gehan’s rule. Fourteen participants were planned to be enrolled in the first stage of the study. With a true response rate of 30%, there was a 99% probability of observing at least one responder in this initial population. With a true response rate of 20% or 10%, there was correspondingly 96% and 77% probability for obtaining one responder. Further participants were planned to be enrolled in the second stage up to a maximum of 40. The number of additional participants was chosen to be sufficient to obtain a SE of 8% for the estimate of response rate determined by the preliminary estimate in stage I. Data for secondary endpoints are presented descriptively.

Results

Patients

Patient characteristics are presented in Table 1. One confirmed CR was observed in the initial cohort of 14 patients, and as per protocol, the study population was expanded to a total of 24 patients (14 male and 10 female). Most patients had M1c disease, although only 2 patients had elevation of serum lactate dehydrogenase above normal. Fourteen participants received ET-1; of these, 1 patient subsequently withdrew consent, 1 withdrew due to an adverse event (hypersensitivity), and 2 withdrew due to progressive disease. Only 1 participant continued and completed ET-2. Minor protocol deviations occurred, including exemptions to eligibility criteria, delayed timing of drug administration, and dose and assessment scheduling issues. None were judged to have any effect on the results of the trial.

Tumor response

The overall response rate according to Response Evaluation Criteria in Solid Tumors was 8.3% (95% confidence intervals, 2.7-27%). The median time to progression was <8 weeks. Responses according to Response Evaluation Criteria in Solid Tumors for individual participants are shown in Fig. 1. Nine participants were progression-free and alive at week 8 and 3 of the 24 participants were progression-free and alive at week 16. One confirmed CR and one confirmed partial response were observed. Both patients had lung metastases. The patient with CR by week 8 had progressive disease 11 weeks later. The patient with partial response had stable disease at week 8 but partial response at week 16; the duration of response in this patient was 56 days. Another patient had CR in target lesions and stable disease in nontarget lesions but progressed in the brain. Median overall survival was 9.2 months (Fig. 2), with a median duration of follow-up of 8.7 months.

Safety and toxicity

Adverse events are described in Table 2. Overall, rIL-21 was administered intravenously at daily doses of 30 µg/kg in the
adverse event reported as hypersensitivity reaction. Another participant ceased rIL-21 treatment due to drug-induced hepatitis evaluated to be probably related to rIL-21. The most common changes in laboratory values with severity reported and grade 4 clinical adverse events were not reported. Grade 3 severity as the worst grade clinical adverse event appeared to be related to rIL-21 treatment, as values returned to or approached baseline levels in patients, no evidence of hemolysis was observed. Changes in vital signs and minor increases in pulse and body temperature were observed during rIL-21 dosing periods. Changes in laboratory values returned to or approached baseline levels in patients, no evidence of hemolysis was observed. Changes in laboratory values returned to or approached baseline levels in the 9-day nondosing periods.

A total of 13 serious adverse events were reported in 8 participants. Of those, 8 serious adverse events in 4 participants were evaluated as probably or definitely related to rIL-21 treatment. These included hypersensitivity, pyrexia, sinus tachycardia, myalgia, arthralgia, chills, and hepatitis. For the majority of the participants, the rIL-21 dose was unchanged. One participant had his rIL-21 dose reduced to 1.0 g/kg due to drug-induced hepatitis evaluated to be probably related to rIL-21. Another participant ceased rIL-21 treatment due to an adverse event reported as hypersensitivity reaction.

**Biomarker Analyses**

Biomarker analyses included flow cytometry of mononuclear cell subpopulations, lymphocyte effector molecules (IFN-γ, perforin, and granzyme B mRNA measurements), serum soluble IL-2 receptor (sCD25) levels, and serum immunoglobulins. Results of these analyses are described below. Alterations in biomarkers did not correlate with clinical benefit.

**Lymphocyte subpopulations.** The frequency of CD8+ T and NK cells expressing CD25 increased significantly by 24 h after rIL-21 administration, whereas, in the CD4+ T-cell population, no increase in the percentage of CD25+ cells was observed, indicating differential rIL-21-mediated effects on CD4+ versus CD8+ T cells (Fig. 3A). Notably, the frequency of CD4+CD25 bright cells did not increase (Supplementary Fig. S1). Consistent with these findings, the early activation marker CD69 and the lymph node homing molecules CD62L and CCR7 were up-regulated on CD8+ T and NK cells but remained relatively stable on CD4+ T cells (Fig. 3B-D; ref. 27).

Despite these differences in activation markers, simultaneous significant reduction in absolute numbers of peripheral blood NK, CD8+ T, and CD4+ T cells were observed on dosing day 4 of two separate dosing periods (Fig. 4A). For B cells, a similar trend was seen. In contrast to the observed decline in peripheral blood lymphocyte subsets, the absolute number of monocytes increased on dosing day 4 of two separate dosing periods (Fig. 4B). All monocytes express CD64 and a proportion of monocytes express CD16, the two receptors mediating antibody-mediated cellular cytotoxicity. Both the proportion of the monocytes expressing CD16 (FcγRIII) and the cell surface level of CD64 (FcγRI) significantly increased during dosing (Fig. 4B).

**Effectors molecules.** In line with activation of CD8+ T and NK cells, significant induction above baselines values were

![Table 2. Adverse events and laboratory abnormalities in >20% of patients](image-url)
recorded for mRNA expression of the key effector molecules IFN-γ, perforin, and granzyme B on day 5 of dosing (Fig. 4C and D).

sCD25. In accordance with previous clinical trials with rIL-21 (26, 29), significant increases in serum levels of sCD25 were observed during dosing periods, representing immunoactivation as a pharmacodynamic signature of the "5+9" dosing regimen (Supplementary Fig. S3).

Serum immunoglobulins. Minor changes in serum immunoglobulins were observed with rIL-21 administration; however, immunoglobulin levels remained within normal ranges during the course of the study for most patients (Supplementary Fig. S2).

Immunogenicity
Anti-rIL-21 antibodies were detected in one patient.

Discussion
This phase IIa clinical trial confirmed that rIL-21 administered at a dose of 30 μg/kg/dose in the "5+9" regimen is well tolerated in patients with unresectable metastatic melanoma. The primary objective of the study was to show clinical efficacy as determined by response rate. One confirmed CR and one confirmed partial response were observed. A further patient had CR of target lesions and stable disease in nontarget lesions but progressed. The overall response rate for the study was 8.3%. Although low, this confirms previous observations of antitumor activity of rIL-21 and suggests that this cytokine can mediate such effects as a single agent. Its antitumor efficacy in terms of response rate is comparable with standard therapies such as dacarbazine or high-dose IL-2 and newer therapies such as anti-CTLA-4 monoclonal antibodies (10), although at present only scant data are available on duration of response. Notably, the patient with confirmed CR in our original phase I study (26) continues in CR 32 months after it was initially documented.

The relatively low frequency and duration of responses can be attributed to multiple tumor escape mechanisms, including down-regulation of antigen expression, elaboration of immunosuppressive factors, or induction of active immunosuppression (31). In contrast to the rIL-21-specific activation of NK and CD8+ T cells, IL-2 activates both NK cells and CD8+ and CD4+ T-cell subsets, including regulatory T cells (32, 33). This unique feature of the biology of IL-21 may be of benefit in combination with drugs such as sunitinib, which has recently been proposed to have immunomodulatory effects similar to IL-21 with respect to effects on regulatory T cells and IFN-γ production of T cells (34). This points to the notion of IL-21 as a cytokine with a unique mechanism of action that at least in part may explain why clinical and biological activity is obtainable at doses associated with minimal or easily manageable toxicity.

sCD25 has been shown in previous trials to be a robust pharmacodynamic biomarker of rIL-21-mediated systemic immunoactivation (26, 29). This study has confirmed significant induction of serum sCD25 levels 24 h after rIL-21 dosing and onwards in a pattern that clearly reflects an underlying signature of the dosing regimen. Both NK and T cells increase cell surface expression of CD25 on activation (35). The frequency of CD25+ NK and CD8+ T cells increased significantly at 24 h after dosing suggestive of activation of these cells, whereas no change was
observed in frequency of the CD25+ population of CD4+ T cells. Notably and in line with previous findings, the frequency of CD4+CD25bright cells did not increase (36).

We confirmed other biological effects such as reduction in lymphocyte subsets possibly due to increased lymphocyte homing to lymph nodes and/or tumor (27, 37) or endothelial adhesion (29). In support of the latter, expression of the IL-21 receptor α-chain has recently been shown in primary human endothelial cells (38).

Activation of both NK and CD8+ T cells by rIL-21 was shown by up-regulation of mRNA for the key effector molecules IFN-γ, granzyme B, and perforin. This suggests that these two subsets are the main producers of serum sCD25 and further supports that rIL-21 has differential effects on CD8+ T and NK cells versus CD4+ T cells.

We have also observed increases in blood monocytes and in expression of CD16 and CD64, key mediators of antibody-mediated cellular cytotoxicity. No apparent differences in biomarker responses were observed between clinical responders and nonresponders (data not shown). With regards to safety variables, an increased level of serum IL-10 has been reported previously in patients experiencing dose-limiting toxicities, suggestive of a mechanism for counterbalancing the rIL-21-mediated immunostimulation (39).

IL-21 has a range of activities likely to potentiate antitumor immunoresponses (16). Animal studies have shown that IL-21 enhances antibody-mediated cellular cytotoxicity (40–42). Preliminary human data in patients with B-cell lymphoproliferative malignancies, using rIL-21 with rituximab (an anti-CD20 monoclonal antibody), have shown 2 CR, 5 partial responses, and 1 stable disease of a total of 21 participants (43, 44). Other combinations are also being tested (16). Our data provide a further rationale for combination of rIL-21 with monoclonal antibodies. Such combination strategies are currently under investigation in non-Hodgkin’s lymphoma (ClinicalTrials.gov identifier: NCT00347971) and colorectal cancer (Eudract 2006-004231-30).

Future studies will evaluate potential for further antitumor activity at higher doses of rIL-21 in melanoma and different therapeutic combinations in other indications. A particular area of interest is the combination of rIL-21 and tyrosine kinase signaling inhibitors (45, 46), where preclinical data suggest greater efficacy than with either agent alone (47, 48). Exploratory trials assessing the combinations of rIL-21 and sunitinib or sorafenib are currently ongoing in renal cell carcinoma (European Clinical Trials database 2006-005751-16 and ClinicalTrials.gov identifier: NCT00389285). Preliminary reports indicated that, in the study involving rIL-21 plus...
sorafenib in renal cell carcinoma, 16 of 18 patients experienced tumor shrinkage, with three confirmed partial responses. This study is ongoing having accrued 33 patients and is awaiting data on progression-free survival from the phase II component. Our data show that rIL-21 has modest but real clinical activity in melanoma as a single agent. The biological rationale for combining rIL-21 with other treatment modalities is strong. The results of current and future studies are awaited with interest.

Acknowledgments

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Disclosure of Potential Conflicts of Interest

R.F. Kefford, consultant, Novo Nordisk. The other authors disclosed no potential conflicts of interest.

References


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