Phase 1B Study of Subcutaneously Administered Interleukin 2 in Combination with 13-cis Retinoic Acid as Maintenance Therapy in Advanced Cancer

Francesco Recchia, Sandro De Filippis, Michele Rosselli, Gaetano Saggio, Alisia Cesta, Luca Fumagalli, and Silvio Rea

ABSTRACT
At present, no therapeutic strategy is available to maintain responses achieved in patients treated with chemotherapy. This Phase 1B study was aimed at identifying the optimal biological dose of chronic maintenance therapy using s.c. interleukin (IL) 2 and oral 13-cis retinoic acid (RA) in patients with either tumor stabilization or response to chemotherapy. IL-2 has no cross-resistance with chemotherapy and improves cancer-related lymphocytopenia, a factor that determines poor prognosis, whereas RA has immunomodulatory properties, potentially synergistic with IL-2. Eighteen patients with advanced solid tumor who achieved a response or stable disease as a result of standard chemotherapy, received RA (0.5 mg/kg) and IL-2 5 days/week for two cycles of 3 weeks/month for up to 1 year. Three doses of IL-2 were used: 9.0, 4.5, and 1.8 × 10^6 IU/day. Monitoring consisted in a weekly blood differential count and a bimonthly assessment of tumor markers, CD4+, CD8+, and natural killer cells. Patients were evaluated for toxicity, response maintenance, time to progression, and survival.

Patients chronically treated with 9 and 4.5 × 10^6 IU of IL-2 developed dose-limiting toxicity grade III or IV, consisting of fever, fatigue, thrombocytopenia, mucositis, and local cutaneous reaction. No grade III or IV toxicity was observed with the 1.8 × 10^6 IU dose, considered as the optimal biological dose. Fifty courses of IL-2 were administered (median, 3 per patient). An increase in total lymphocyte number, CD4/CD8 ratio and natural killer cell count was observed at all of the three dose levels with respect to baseline values. Two patients with a partial response to chemotherapy achieved a complete response after 6 and 7 months, respectively, of IL-2 + RA maintenance therapy. Median time to progression and overall survival were, respectively, 8.1 and 13.7 months (range, 2–48.8+ months). Low-dose IL-2 + RA as maintenance therapy after chemotherapy is, therefore, feasible and well tolerated and improves immunological parameters known to have a prognostic value in cancer.

INTRODUCTION
In recent years, although much progress has been made in the treatment of advanced solid tumors, chemotherapy can cure only a minority of patients. The effectiveness of chemotherapy is limited by the high rate of relapse because of a failure to completely eradicate all residual disease. Even in patients with an apparent complete clinical remission after maximal surgical and/or chemotherapeutic cytoreduction, what is known as “minimal residual disease” often remains (1). Minimal residual disease usually involves resting cells (G0) that may start to divide after appropriate stimuli. Maintenance chemotherapy is ineffective because of the acquired resistance of tumor cells as a result of exposure to cytotoxic drugs, and reinduction chemotherapy usually gives short-lived responses. Patient outcome is also affected by cancer-related immunodeficiency, mainly attributable to impairment of the IL3-2-dependent cell-mediated immune function associated with advanced disease. In fact, lymphocytopenia has been proved to be an important factor determining the poor prognosis of cancer patients, independent from major prognostic factors such as performance status, disease extent, and weight loss (2–4). Cell-mediated immune status (total lymphocyte and CD4+ cell number) is impaired not only during but also after chemotherapy, resulting in a prolonged imbalance of the T-cell subset (5); IL-2 production can be impaired for up to 1 year after chemotherapy treatment (6). After successful cytotoxic treatment, immunological manipulation may restore the impaired immune surveillance by eradicating cell clones resistant to chemotherapy. IL-2, discovered as the T-cell growth factor and defined as “the hormone of the immune response,” has a variety of immunomodulatory properties related to both cell-mediated and humoral immune functions. IL-2 stimulates T-cell proliferation, increases the generation of CTLs, and induces activation of T and B cells. In addition, the proliferation and activation of IL-2 increases the tumoricidal activity of NK cells (7). The mechanism of action of IL-2 depends on the interaction of IL-2 itself with its specific membrane receptor (8).

Received 11/27/00; revised 2/26/01; accepted 2/26/01.

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3 The abbreviations used are: IL, interleukin; OBD, optimal biological dose; NK, natural killer; RA, retinoic acid; ECOG, Eastern Oncology Cooperative Group; TTP, time to progression.
IL-2 measured the immunological response to the different dose-generations for studies on biological response modifiers (21), we stabilization to chemotherapy. To identify the OBD according to advanced solid tumors who had exhibited a response or disease toxicity profile of the two-drug combination in patients with administered p.o., for prolonged periods of time to define the cis-a 5-days/week schedule was very well tolerated (19, 20). The optimal cytokine to restore the cell-mediated immune function damage caused by chemotherapy (14). IL-2 may indeed be the optimal cytokine to restore the cell-mediated immune function in cancer patients after successful chemotherapy, but, nevertheless, IL-2-based maintenance immunotherapy must be easily feasible and well tolerable, even in an outpatient setting. This objective may be achieved in two ways: first by the s.c. administration of IL-2, known to be active with lower toxicity not only in cancer patients (15) but also in HIV-immunodeficient patients (16); and second, the administration of another biological agent in combination with IL-2 to enhance the IL-2 function. Retinoids increase the percentage of peripheral blood lymphoid cells expressing surface markers for T-helper cells and IL-2 receptor (17). Furthermore, retinoids synergize with IL-2 to augment IFN-γ and IL-2 production by human peripheral mononuclear blood cells. In fact, IL-2 that is cultured with 13-cis RA produces a 4- to 90-fold synergistic increase in IFN-γ production, whereas anti-IL-2 antibodies abrogate this effect (18). Finally, retinoids inhibit the proliferation of various cell lines, inducing differentiation and apoptosis. We have reported previously that the chronic administration of a 0.5-mg/kg-dose of 13-cis RA on a 5-days/week schedule was very well tolerated (19, 20).

The above reasons prompted us to carry out a Phase IB study that associated IL-2 administered s.c., with 13-cis RA, administered p.o., for prolonged periods of time to define the toxicity profile of the two-drug combination in patients with advanced solid tumors who had exhibited a response or disease stabilization to chemotherapy. To identify the OBD according to guidelines for studies on biological response modifiers (21), we measured the immunological response to the different dose-

and develops in a paracrine way, through cytokine cascade involving IFN-γ (7). The primary cytotoxic activity of IL-2 may be attributable to the induction of endogenous LAK cell activity and production of tumor inhibitory cytokines (9). In addition, IL-2 inhibits angiogenic activity through the induction of IFN-γ, which in turn induces p-10, an inducible protein with potent antiangiogenic activity (10). High-dose IL-2 has shown efficacy in the treatment of bulky solid tumors, refractory to chemotherapy, with durable response (11); however, the toxicity of high-dose i.v. administration of IL-2 may cause vascular leakage syndrome leading to hypotension, oliguria, respiratory distress, cardiac arrhythmias, and mental status change (11), which makes this approach not feasible as outpatient treatment. Murine studies suggest that IL-2 therapy is more effective in a situation of low tumor burden (12). This setting may be achieved surgically by maximal cytoreduction (13) or by successful chemotherapy, enabling IL-2 to act on cancer cells with sublethal damage caused by chemotherapy (14). IL-2 may indeed be the optimal cytokine to restore the cell-mediated immune function in cancer patients after successful chemotherapy, but, nevertheless, IL-2-based maintenance immunotherapy must be easily feasible and well tolerable, even in an outpatient setting. This objective may be achieved in two ways: first by the s.c. administration of IL-2, known to be active with lower toxicity not only in cancer patients (15) but also in HIV-immunodeficient patients (16); and second, the administration of another biological agent in combination with IL-2 to enhance the IL-2 function. Retinoids increase the percentage of peripheral blood lymphoid cells expressing surface markers for T-helper cells and IL-2 receptor (17). Furthermore, retinoids synergize with IL-2 to augment IFN-γ and IL-2 production by human peripheral mononuclear blood cells. In fact, IL-2 that is cultured with 13-cis RA produces a 4- to 90-fold synergistic increase in IFN-γ production, whereas anti-IL-2 antibodies abrogate this effect (18). Finally, retinoids inhibit the proliferation of various cell lines, inducing differentiation and apoptosis. We have reported previously that the chronic administration of a 0.5-mg/kg-dose of 13-cis RA on a 5-days/week schedule was very well tolerated (19, 20).

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PATIENTS AND METHODS

Patient Selection. Patients with advanced solid tumors exhibiting a complete response to chemotherapy but with a high risk of relapse, or patients with a partial response or disease stabilization, were eligible for the study. Other eligibility criteria included: no age limit, an ECOG performance status of ≤3, a life expectancy of more than 3 months, and clinically or radiographically measurable disease in patients with partial response or stable disease. Required laboratory values included: a leukocyte count of >4 × 10^9/liter, a platelet count of >100 × 10^9/L, normal coagulation parameters, bilirubin concentrations of <30 mmol/liter and creatinine levels of <1.5 mg/dl. Patients with brain metastases and patients subjected to palliative radiation therapy not involving the lesion chosen for measurement of response were included. Patients with malignancies other than curatively treated skin and cervical cancer and patients previously treated with IL-2 and RA were excluded. The local Ethics Committee approved the protocol, and written informed consent was obtained from all of the patients.

Study Design and Treatment Plan. After the initial assessment at 4 weeks after the discontinuation of chemotherapy, patients were entered in the study. The study was designed as a Phase I trial, with the planned dose levels listed in Table 1. The primary objective of the study was to determine the OBD and the toxicity of the combination of self-administered s.c. IL-2 and oral RA. This was accomplished through the evaluation of immunological parameters according to guidelines for biological response modifiers (21). Secondary objectives were the determination of TTP and of survival rates.

Prior to treatment with IL-2 and RA, all of the patients underwent a complete workup to document the extent of the disease, including clinical examination, complete blood cell count, plasma urea, electrolyte, tumor-specific markers, liver function tests, thyroid function tests, electrocardiogram, T4:T8 ratio, NK count, and computed tomographic or magnetic resonance imaging scans of affected regions. X-rays of abnormal areas of bone scan uptake were performed and computed tomographic scanning was used to evaluate hepatic lesions. Before each subsequent course of treatment, all of the patients had another blood cell count and measurement of plasma urea, electrolytes, serum creatinine, GOT, GPT, alkaline phosphatase,
bilirubin, T4:T8 ratio, and NK count. In addition, a blood cell count was repeated weekly with follow-up examinations performed monthly during treatment. Tumor measurements, toxicity, and response assessment were performed every two courses of therapy (4 months), or sooner if the patient appeared to have disease progression.

Outpatient treatment consisted of a fixed dose of 13-cis RA (0.5 mg/kg of body weight) administered p.o. with meals for 5 days/week. This dosage has been used previously by our group for various tumor types (19, 20) showing efficacy with good tolerability and manageable toxicity. IL-2 was administered by s.c. injection daily, at bedtime, 5 days/week for 3 weeks. Sites of injection were rotated daily, using primarily the lower abdomen and the upper and lower extremities. After 1 week of rest, patients started a new 3-week course of therapy. Two months were considered as 1 cycle of therapy. Ancillary therapy included acetaminophen 500 mg p.o. every 6 h. Antidiarrheal and antiemetic medications were prescribed as needed.

The same methodology used for conducting Phase I trials was used but with decreasing instead of increasing dose levels. The dose of IL-2 was decreased from $9 \times 10^6$ IU to $4.5 \times 10^6$ IU and $1.8 \times 10^6$ IU (Table 1). Doses lower than $1.8 \times 10^6$ IU were not investigated because a previous report had suggested that an IL-2 dose of $1 \times 10^6$ IU was not sufficiently active either in increasing lymphocyte count or against tumors (22). At least three patients were enrolled at each dose level before proceeding to the next step, and if a single instance of grade III or IV toxicity occurred in the first cycle of treatment, three additional patients were treated with the same dose level, provided that there was no deterioration of immunological parameters compared with the previous dose level. Patients with grade III or IV toxicity were allowed to continue therapy at a lower dose after the resolution of adverse effects. A delay longer than 1 week in administering the second course of therapy was also considered as dose-limiting toxicity. After the second course of therapy, additional therapeutic cycles were administered for up to 1 year if patients continued to show a partial or complete response or disease stabilization with an improvement in performance status, according to WHO response criteria. After completion of 1 year of treatment, responding patients received IL-2 and RA as maintenance therapy for 5 days/month.

Patients who exhibited evidence of disease progression were removed from the study and treated with “salvage” chemotherapy, and they were included in the analysis according to an intent-to-treat principle.

**Response and Toxicity Evaluation.** Tumor measurements were taken by physical examination and measurable disease was documented prior to initiation of therapy. Standard response criteria were used (23). Student- $t$ test was used for statistical analysis. TTP was defined as the length of time from the date of the first course of immunotherapy to any relapse, to the appearance of a second primary cancer, or to the date of death, whichever occurred first. TTP and overall survival were estimated by means of the Kaplan and Meier product-limit method (24). The analysis of data was performed on January 31, 2001.

### RESULTS

**Patient Characteristics.** Eighteen patients were entered into the study from January 1997 to April 1998. All of the patients had metastatic disease and could be evaluated for response and toxicity. Eleven patients had undergone radical-intent surgery, 5 patients had undergone a palliative surgical procedure, whereas 2 patients had only a biopsy of their disease. All of the patients had previously received a total of 180 courses of chemotherapy with a median of 10 courses per patient and 12 courses of high-dose chemotherapy with peripheral blood progenitor cell transplantation. Ten patients had received radiotherapy. Seven patients had previously received at least one form of endocrine therapy. ECOG performance status was 0–1 in 13 patients, 2 in 4 patients, and 3 in 1 patient. In total, the 18 patients received 50 courses of IL-2 + RA therapy with a mean number of courses administered per patient of 3 (range, 1–6).

Median patient age was 50 years (range, 29–76 years). Patient characteristics are listed in Table 2.

**Toxicity.** Standard WHO criteria for assessing toxicity were used (23). No treatment-related death was observed. Of the 18 patients entered in the study (Tables 1 and 3), a total of 6 patients were entered at the level-1 dose. Two patients developed grade III fever and grade III cutaneous toxicity with a swelling of cutaneous injection sites, and a third patient developed grade III thrombocytopenia. At the level-2 dose, one patient, who had been previously treated with radiotherapy, developed grade IV mucositis and was treated with total parenteral nutrition for 8 days, whereas four patients had grade III

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**Table 2** Characteristics of patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
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</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>29–76</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>7</td>
<td>39</td>
</tr>
<tr>
<td>Females</td>
<td>11</td>
<td>61</td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
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<tr>
<td>0–1</td>
<td>13</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>6</td>
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<tr>
<td>Site of primary disease</td>
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<tr>
<td>Stomach</td>
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<tr>
<td>Breast</td>
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<tr>
<td>Ovary</td>
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<td>6</td>
</tr>
<tr>
<td>Lung</td>
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<td>11</td>
</tr>
<tr>
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<td>6</td>
</tr>
<tr>
<td>Lymphoma</td>
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<td>6</td>
</tr>
<tr>
<td>Other</td>
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<td>33</td>
</tr>
<tr>
<td>Stage of disease</td>
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<td></td>
</tr>
<tr>
<td>IV</td>
<td>18</td>
<td>100</td>
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<tr>
<td>Metastatic sites$^a$</td>
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<tr>
<td>Liver</td>
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<td>28</td>
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<tr>
<td>Lung</td>
<td>6</td>
<td>33</td>
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<tr>
<td>Abdomen</td>
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<td>22</td>
</tr>
<tr>
<td>Bone</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Nodes</td>
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<td>22</td>
</tr>
<tr>
<td>Brain</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

$^a$ Five patients had two metastatic sites and one patient had three metastatic sites.
fever, with severe swelling of the injection sites. No patient who was entered at level 3 had any grade III or IV toxicity; therefore, for additional Phase II studies, the OBDs of IL-2 and RA were established as 1.8×10^6 IU and 0.5 mg/kg of body weight, respectively. The response maintenance rate was 78.6% (95% confidence interval, 49.2–95.3%).

Host Response and Tumor Response. All of the patients were evaluated on an intent-to-treat basis. No further dose de-escalation was carried out below 1.8×10^6 IU, because lower doses of IL-2 have been shown to be not active (22). Baseline values of lymphocytes, T4:T8 ratio, and NK number were not different at the three dose levels (Table 4). There was a progressive increase in lymphocyte and NK number and in the T4:T8 ratio during the course of immunotherapy with respect to the baseline mean number at all of the three dose levels (Figs. 1, 2, and 3). If the immunological data are taken separately for each dose level, the long-term (after the third cycle) increase of the number of lymphocytes reached statistical significance at the third dose level only (Fig. 4); however, this was probably attributable to the small number of patients evaluated at each dose level. In fact, all of the patients initially treated at level 1 and 2 who developed grade III or IV toxicity after the first course of immunotherapy, were treated with the lower dose level of IL-2.

After a minimum of 8 weeks of maintenance biotherapy, the 18 patients were reassessed for response. The original categories of response to chemotherapy were as follows: complete response in 2 patients, partial response in 2 patients, stable disease in 14 patients. After IL-2 + RA maintenance therapy, the responses were as follows: complete response in 4 patients, stable disease in 11 patients, and progressive disease in 3 patients (Table 5). After a median follow-up time of 25 months, 4 patients (22.2%) were alive with 3 of them (16.6%) disease-free. The median TTP was 8.1 months (range, 2–48.8). The median survival rate was 13.7 months (range, 2.2–48.8), and the 1- and 2-year survival rates were 62 and 28%, respectively (Fig. 5). Two patients, exhibiting a partial response to chemotherapy, were converted to a complete response after IL-2 + RA therapy. The first patient, with breast cancer metastatic to bones, after induction with anthracycline-based chemotherapy, received high-dose chemotherapy with PBPC transplantation (Table 6). After high-dose chemotherapy, the bone lesions were still symptomatic and serum markers were elevated. Tumor markers, bone scan, and magnetic resonance image of the spine normalized after 5 months of IL-2 + RA therapy (second level). The second patient, with brain metastases from a carcinoma of unknown origin, had a partial response to chemotherapy. This patient refused brain radiotherapy. Disappearance of brain metastases was accomplished after 5 months of IL-2 + RA therapy (Table 6; third level).
DISCUSSION

Cancer therapy using “biologics,” which are usually derivatives of normal regulatory factors, circumvents the induction of a host response. The use of these drugs, however, requires a complete redesign of clinical trials because the maximum tolerated dose may not always represent the most active dose; in fact, depending on the therapeutic purpose, different dosages, or regimens, or administration routes can be more optimal. Small quantities of biologicals can interact with specific receptors of different affinities, sometimes with a preference for a specific body compartment, e.g., the lymphatic compartment for IL-2 and lymphocytes (25). Endocrine and paracrine loops may further modulate the signal by amplifying or by down-modulating responses (26). The concept of OBD has, therefore, been described previously (21). A practical example is represented by IL-2, which, when administered in a high-dose bolus, produces durable objective responses in advanced cancer (11), whereas if administered s.c. in HIV-immunodeficient patients, it restores the cell-mediated immune function and increases the effectiveness of antiretroviral treatment, experienced an improvement of all of the immunological parameters and the conversion of a partial response to a complete response (35).

On the basis of the fact that advanced cancer is associated with chronic immunodeficiency involving the IL-2-dependent immune function, the aim of the present study was to determine an immunologically active dose of IL-2 that would be compatible with good quality of life for prolonged periods of time and likely to be clinically effective. For this reason, we designed a chronic, intermittent maintenance immunotherapy schedule. The first two doses of IL-2 in the experiment (9.0 and 4.5 $\times 10^6$ IU) were too toxic and would absolutely prevent normal activities of everyday life, whereas the third dose (1.8 $\times 10^6$ IU daily) was well tolerated. Doses lower than 1.8 $\times 10^6$ IU were not explored, because a previous report (22) suggested that an IL-2 dose of 1.0 $\times 10^6$ IU daily was well tolerated. Doses lower than 1.8 $\times 10^6$ IU were not explored, because a previous report (22) suggested that an IL-2 dose of 1.0 $\times 10^6$ IU daily neither achieved a major clinical objective response nor displayed any detectable immunological activity; on the contrary, a decrease in peripheral lymphocyte count was observed in 19 patients affected by renal cell carcinoma (22). On the basis of these findings, the IL-2 dose of 1.8 $\times 10^6$ IU was identified as the reference dose for the Phase II study.

The baseline immunological status of our patients seemed sufficiently compensated, with the total number of lymphocytes and CD4:CD8 ratio within minimum normal values. Considering that all of the patients had undergone chemotherapy and had had a tumor response, this finding was in accordance with the results of a preliminary study in which the lymphocyte count in non-small cell lung carcinoma patients responding to standard chemotherapy showed a tendency to increase, compared with previous counts, whereas in patients with progressive disease, a
significant decrease of these circulating immune cells was observed (36).

Patients who were treated with IL-2 + RA had a significant benefit in all of the immunological parameters evaluated. The improvement of the immune function increased with the amount of biotherapy administered at all of the dose-levels. These results suggest that the repeated long-term s.c. administration of IL-2, can achieve long-term significant restoration of the immune function at a wide range of dosages (1.8–9 × 10^6 IU/day), although with substantially different, dose-dependent toxicity profiles.

Previous retrospective studies demonstrated that the significant improvement of immunological parameters, mainly CD4 count (37) and total lymphocyte count (38, 39), is related to prolonged survival in patients treated with IL-2 s.c. In addition, 2 patients in our study obtained a clear benefit on tumor outcome from biotherapy, improving their response from partial to complete response. The reduction in tumor size paralleled the improvement of all of the immunological parameters and may suggest that the presence of a valid host immune defense function is necessary to achieve a complete tumor response, whatever the setting, complete response being the best indicator of successful tumor treatment by any cytotoxic chemotherapy agent (40).

The intermittent administration of RA in association with IL-2 was well tolerated, as described previously. On the basis of preclinical information, we assumed that RA might improve IL-2 activity, e.g., through modulation of surface IL-2-specific receptors. The primary aim of this study was to investigate the tolerability of this association, and, therefore, the net immunological effect of the administration of IL-2 + RA is not described. At present, we are conducting a randomized Phase II study in which patients are treated with IL-2 maintenance therapy after chemotherapy and are randomized to receive RA or not, to discriminate the net immunological effect that is possibly induced by RA.

We conclude that the association of s.c. IL-2 at a dose of 1.8 × 10^6 IU/day with oral RA at a dose of 0.5 mg/kg in an intermittent schedule, repeated for a long-term period, is feasible, has low toxicity, and results in the improvement of biomarkers for patient outcome, such as long-term CD4 count, and of markers for tumor outcome, such as the conversion of partial response to complete response.

Further prospective studies will be necessary to verify whether IL-2-based maintenance immunotherapy can increase the effectiveness of standard chemotherapy on overall survival and to confirm whether any biomarker, such as CD4 count changes during or after immunotherapy, may predict overall survival.

### Table 6 Patients with partial response (PR) converted to complete response (CR) after IL-2-RA therapy

<table>
<thead>
<tr>
<th>Initials/Age</th>
<th>Disease</th>
<th>Site of metastases</th>
<th>Previous chemotherapy courses</th>
<th>Response to chemotherapy</th>
<th>Cycles of IL-2/RA</th>
<th>Response to immunotherapy</th>
<th>Time to progression (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 B.R./52</td>
<td>Breast cancer</td>
<td>Bones</td>
<td>12+hdct³</td>
<td>PR</td>
<td>6 maintenance</td>
<td>CR</td>
<td>48.8+</td>
</tr>
<tr>
<td>2 S.A./55</td>
<td>C.U.P.³</td>
<td>Brain</td>
<td>9</td>
<td>PR</td>
<td>6 maintenance</td>
<td>CR</td>
<td>33.7+</td>
</tr>
</tbody>
</table>

³ hdct: high-dose chemotherapy with peripheral progenitor cells transplantation; C.U.P.: carcinoma of unknown primary.

### REFERENCES
