ANTICANCER RESEARCH *25*: 1441-1448 (2005)

Temozolomide and Cisplatin in Avdanced Malignant Melanoma

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Abstract. *Background: Temozolomide (TMZ) is an oral alkylating agent; it produces DNA methyl adducts, which are removed by the DNA repair enzyme AGAT. In vitro studies suggest that CDDP may enhance the antitumor activity of TMZ due to the ability of cisplatin (CDDP) to down-regulate AGAT activity. In a previous phase I study, the combination of TMZ and CDDP was tested, and the recommended dose for each drug was defined. On the basis of these results, we designed a phase II study to evaluate the activity and safety profile of the TMZ-CDDP association in patients with advanced melanoma. Patients and Methods: From March 2001 to March 2002, 37 patients with metastatic melanoma, not amenable to surgery, were enrolled in this study. All eligible patients were treated with the combination of CDDP 75 mg/m^2 i.v. d 1, TMZ 200 mg/m^2 p.o. days 1-5 recycled every 4 weeks. Interferon α2b (IFN α2b) was administered at the end of chemotherapy to responsive patients at the dose of 5 M.I.U s.c. 3 times a week for 1 year. Results: A total of 174 courses were administered, with a median number of 4 courses/patient (range 1-10). After chemotherapy, 9 CRs and 9 PRs were observed for an overall response rate of 48.6% (95% C.I., 31.9%-65.6%). One of 5 patients with initial brain metastases showed a complete response to the therapy. Five out of 9 CR patients were still with no evidence of recurrence, ranging from 28+ to 82+ weeks. The median survival time was 48 weeks. The schedule was well tolerated, with the most frequent adverse events reported being nausea and vomiting (59%), alopecia (14%) and fatigue (11%), all well controlled by supportive therapy. Haemotological toxicities were mild to moderate. Side-effects attributable to IFN α2b were also mild and manageable. Conclusion: The combination of TMZ and CDDP seems to be active in untreated patients with advanced melanoma. Absence of recurrence in the majority (5/9; 56%) of CR patients seems to indicate that IFN may act on the duration of the response to chemotherapy. The schedule was well tolerated, with nausea and vomiting as the most frequent adverse events.*

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Key Words: Melanoma, temozolomide, cisplatin, interferon-alpha.

Temozolomide (TMZ), an oral alkylating agent, is a pro-drug of 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC). The advantage of TMZ over dacarbazine (DTIC), which is also a pro-drug of MTIC, is its ability to undergo spontaneous conversion to the highly reactive metabolite MTIC without requiring any metabolic activation. TMZ produces methyl adducts at the O^6 position of guanine *via* the MTIC intermediate (1-6). The methyl adducts produced by TMZ are removed by the alkylguanine alkyltransferase (AGAT) protein, which acts as a DNA repair enzyme (3-6). Depletion of AGAT by the alkyltransferase inhibitors O^6-methylguanine(3) and O^6-benzylguanine (5, 6) potentiates TMZ activity *in vitro* and *in vivo*. Cisplatin (CDDP) also targets DNA, but by different mechanisms. CDDP produces DNA cross-links preferentially at the N^7 positions of guanine and adenine (7). *In vitro* studies suggest that CDDP may enhance the antitumor activity of TMZ by the ability of CDDP to down-regulate AGAT (8). In clinical studies, TMZ showed similar activity, but it is well tolerated and less emetogenic than DTIC (9).

In a phase I study, the safety profile, DLT, MTD, pharmacokinetics and preliminary efficacy of TMZ in combination with CDDP were evaluated (10). The combination of TMZ and CDDP was well tolerated, and the recommended phase II doses were 200 mg/m^2 of TMZ daily

Table I. *Criteria for modification of the dose of TMZ and/or CDDP to the nadir of the previous cycle.*

Nadir	TMZ dose	CDDP dose
ANC >1500/mm^3		
PLT >100,000/mm^3	200	75
ANC <1500/mm^3		
PLT <100,000/mm^3	200	75
ANC <1000/mm^3		
PLT < 50,000/mm^3	150	56
ANC < 500/mm^3		
PLT < 30,000/mm^3	Temozolomide discontinued permanently	CDDP discontinued permanently

on days 1-5 and 75 mg/m^2 of CDDP on day 1 every 4 weeks. The pharmacokinetics of TMZ were not altered by CDDP. On the basis of these results, we designed a phase II study to evaluate the activity and safety profile of the association of TMZ and CDDP in patients with advanced melanoma.

Interferon alpha 2b (IFNα2b) as adjuvant therapy of malignant melanoma has been suggested to protect patients from recurrences and, independently from dosage, seems to improve the disease-free survival (11). In this study, we evaluated the activity and safety profile of the association of the TMZ-CDDP treatment with the addition of IFN in advanced patients.

Patients and Methods

Patient selection criteria. Patients with ascertained diagnosis of advanced malignant melanoma entered this study; patients were collected during a one-year period. The disease was in advanced stage or recurrent after surgical primary treatment, and not amenable to further surgery or local therapy. Additional eligibility criteria included age between 18 and 75 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, absence of prior chemotherapy, life expectancy ≥3 months, adequate bone marrow function (ANC ≥1,500/mmc; PTL ≥100,000/mmc; Hb ≥10 g/dl), normal liver and renal function (bilirubin <1.25 x N, creatinine <1.25 x N). Patients with brain metastases, not previously treated with radiotherapy, were eligible; in these cases, no concurrent brain radiotherapy was administered during chemotherapy. Patients may have received previous therapy with biological response modifiers (vaccine-based protocols, IFN) as adjuvant therapy, but not less than 30 days before study entry. Written informed consent was required from each enrolled patient. The study was reviewed and approved by the ethical review board of the National Tumor Institute of Naples, Italy.

Work-up for all patients included physical examination with tumor measurement of palpable or visual lesions, blood cell count with white cell differential and biochemistry, chest radiograph, liver CT and/or ultrasound, bone nuclear scan and brain CT scan.

Treatment plan. The following treatment regimen was used: TMZ was administered orally, in a fasting state, once a day for 5 consecutive days (days 1 through 5) at a dose of 200 mg/m^2; CDDP 75mg/m^2 in 250 ml of saline solution in 30-minute *i.v.* infusion was given on day 1 (4 hours after TMZ), together with a short term hyper-hydration (2 liters of normal saline over 4 hours). Antiemetic prophylaxis with HT3 antagonists was routinely used. Courses were repeated every 4 weeks; in the absence of disease progression or unacceptable toxicity, patients continued to receive treatment with TMZ and CDDP every 28 days for up to 1 year from initial dose (for a total of 16 courses). Interferon alpha 2b (IFNα2b) was administered at the end of chemotherapy (starting 4 weeks after the last course of chemotherapy) to patients with CR, PR or SD at the dose of 5 M.I.U *s.c.* 3 times a week for 1 year.

Criteria for dose adjustment. Complete blood counts were monitored weekly following the first daily dose of each cycle in order to determine the dose of TMZ and CDDP for subsequent cycles.

The criteria listed in Table I were applied for modification of the dose of TMZ and/or CDDP or discontinuation of both TMZ and CDDP (values given apply to the NADIR of the previous cycle). In case of severe diarrhea (WHO grade 3 or 4) or other non-hematological toxicities ≥ grade 3 (except alopecia), therapy was delayed for 1-2 weeks until < grade 2, then restarted with a 25% reduction of cytotoxic drugs. The reduced dose was maintained until the laboratory parameters and/or clinical symptoms returned to grade 1 or better. Thereafter, the full dose was administered. If the laboratory parameters and/or clinical signs failed to return to normal or deteriorated within 4 weeks after reduction of the dose, the patient was withdrawn from the study.

Radiation therapy was permitted only for brain metastases that occurred during IFN treatment (in these cases antiedema drugs, such as dexamethasone, were also used). No other chemotherapy, immunotherapy, hormonal therapy (excluding contraceptives and replacement steroids), radiation therapy, or experimental medications were permitted while the patients were on the study. Any disease progression requiring other forms of specific antitumor therapy was cause for early discontinuation in this study.

Assessment of activity. Response was defined according to the WHO criteria (12) and assessed every 3 courses. Complete response (CR) was defined as the disappearance of all symptoms and signs of all measurable disease, lasting for at least 4 weeks (as assessed by confirmatory CT scans), during which no new lesions appeared. Partial response (PR) was defined as a reduction of >50% in the sum of the products of the perpendicular diameters of all measurable lesions which lasted for at least 4 weeks, during which no new lesions appeared and no existing lesions enlarged. Stable disease (SD) was defined as a less than 50% reduction and less than 25% increase in the sum of the products of the perpendicular diameters of all measurable lesions and the appearance of no new lesions. Progressive disease (PD) was defined as an increase in the product of 2 perpendicular diameters of any measured lesion by more than 25% over the size present at entry on study, or the appearance of new lesions (including brain metastases developed during the study). Patients showing a CR at restaging received, at least, an additional 2 courses as a consolidation of the response (with a maximum of 6 total courses), after which they proceeded with IFNα2b immunotherapy for 1

Table II. *Characteristics of patients.*

Characteristics	
Total entered	37
Eligible	37
Males/females	23/14
Age	
median	55
range	28/75
Performance status	
0	31
1	4
2	2
Single metastatic site	15
Multiple metastatic sites	22
Dominant disease sites	
Skin/subcutaneous	4
Lymph nodes	5
Lung	9
Liver	10
CNS	5
Others	4
LDH serum level (normal range, 100-190 U/L)	
median	314
range	109/3730
M Classification AJCC	
M1a	5
M1b	4
M1c	28

year. Patients achieving a PR, or SD continued the treatment until progression of disease.

The main end points of this study were the major response rate, time to progression and overall survival. Each patient remained in the study until disease progression was noted, or either the patient or the investigator thought that it was in the patient's best interest to discontinue. The treatment was stopped for any case of intolerable toxicity.

The duration of a PR was measured from the time of the initial administration of chemotherapy until the time of documented progressive disease. The duration of CR was measured from the time the CR was documented until the date of the first observation of disease progression. Progression-free survival was measured from the administration of the first dose until the first documentation of disease progression. Overall survival was measured from the administration of the first dose until death, or last follow-up.

Progression-free and survival curves were generated with the Kaplan and Meier method (13) according to criteria comparable to the *intention-to-treat analysis* (data for all 37 patients were included into the analysis, whether or not they completed the TMZ-CDDP-IFN planned treatment).

Assessment of toxicity. Toxicity was assessed by physical examination, blood cell count and biochemistry performed at each cycle of therapy. It was scored according to the WHO classification, and the worst toxicity for each patient was registered.

Table III. *Characteristics of complete responder patients.*

Pt	Sex	Age	Sites of disease	Serum LDH	Cycle	Duration (wks)
BR	F	53	Lung, Bone	Normal	3	82+
CL	F	59	Lung, Brain	Elevated	10	47+
AL	M	58	Nodes	Normal	8	40
CL	M	61	Nodes	Normal	3	37+
SM	M	66	Lung	Normal	6	33+
IE	F	60	Skin	Normal	5	30
DD	M	29	Skin, Liver, Lung	Normal	9	28+
TL	M	76	Lung	Normal	5	28
MA	F	62	Lung	Elevated	8	10

Results

Activity. From March 2001 to March 2002, 37 patients with histologically confirmed metastatic melanoma were enrolled. The characteristics of the eligible patients are reported in Table II. Thirty-one patients had an ECOG PS of 0, 4 patients had a PS of 1, and 2 patients had a PS of 2. Fifteen patients had a single metastatic site and 22 patients multiple sites. Dominant sites were: skin or subcutaneous tissues in 4 patients; lymph nodes in 5 patients; lung in 9 patients; liver in 10 patients; CNS in 5 patients; others in 4 patients. Serum lactate dehydrogenase (LDH) levels were elevated in 19 out of 37 patients (51.3%); the median value was 314 U/L (range 109-3,730 U/L; normal range, 100-190 U/L). A total of 174 courses were administered, with a median number of 4 courses/patient (range, 1-10). Nine CRs and 9 PRs were observed for an overall response rate of 48.6% (95% exact confidence interval: 31.9%-65.6%). The characteristics of the complete responder patients are shown in Table III. The remaining patients were classified as SD or PD. One of 5 patients with initial brain metastases obtained a complete response to the therapy. Three out of 37 patients, with negative baseline CT scan, had disease progression with brain localization as failure of therapy. Nevertheless, 3 patients died before the first planned assessment of response because of progressive disease. Overall, 17 (45.9%) patients were classified as PD.

All 18 patients (9 CRs and 9 PRs) presenting an objective response to the TMZ-CDDP therapy as well as the 2 patients with a stable disease after chemotherapy received a treatment with interferon alpha 2b (IFNα2b) at the dose of 5 M.I.U *s.c.* 3 times a week for 1 year, starting 4 weeks after the last course of chemotherapy. No additional response was observed among SD or PR patients during the IFN treatment.

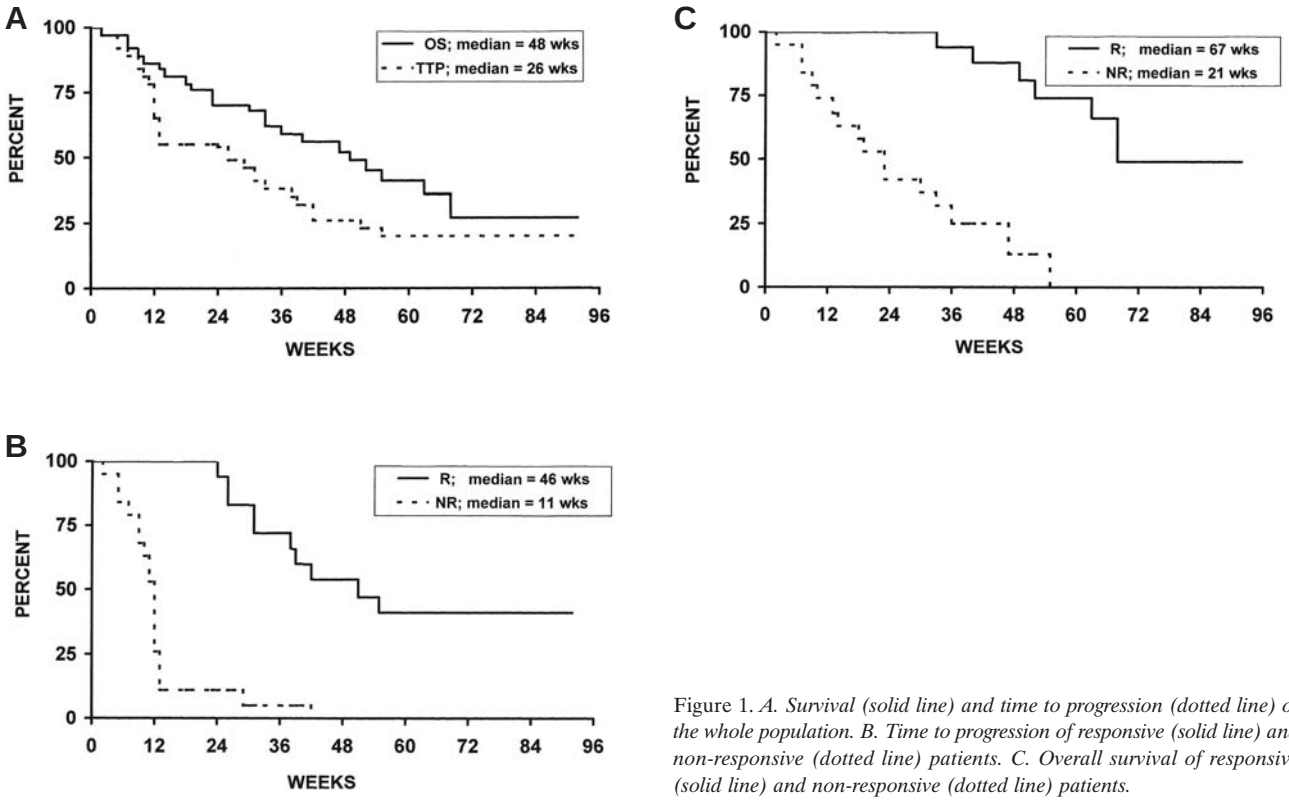

Figure 1. *A. Survival (solid line) and time to progression (dotted line) of the whole population. B. Time to progression of responsive (solid line) and non-responsive (dotted line) patients. C. Overall survival of responsive (solid line) and non-responsive (dotted line) patients.*

After 2 years of median follow-up, 5 out of 9 CR patients were still without evidence of recurrence with a range from 82+ to 28+ weeks. In particular, the patient with a CR of the brain metastases is still alive without disease after 47 weeks. The other CR patients relapsed after 10-40 weeks. The partial responses lasted from 14 to 51+ weeks. The median duration of all responses was 29 weeks. The survival (OS) and time to progression (TTP) curves for the whole series are depicted in Figure 1A. The median survival time was 48 weeks. Figures 1B and 1C indicate the TTP and OS for both responsive (R) and non-responsive (NR) patients.

Toxicity. Acute side-effects are summarised in Table IV. No toxic deaths were reported. There was an early death (after one cycle) which was caused by a rapid worsening of the clinical condition due to the disease. The most common toxicities were nausea and vomiting (59%), alopecia (14%) and fatigue (11%) and were well controlled by supportive therapy. Hematological toxicities were mild to moderate. Neutropenia occurred in 49% of patients and was WHO grade 3-4 in 16% of them, with a WBC median value at nadir of 1,700 (range 590-4,800), and ANC of 1,300 (range 360-2,500); 4 (11%) patients required GM-CSF support for neutropenia. Thrombocytopenia affected 24% of patients and was WHO grade 3 in 5% of them, with a PLT median value at nadir of 58,000 (range 27,000-168,000). Anemia occurred in 24% of patients and was WHO grade 3 in 16% of them, with a hemoglobin median value at nadir of 9.4 mg/dl (range 7.6-15.8). No patient required blood transfusion, but 6 patients (16%) were treated with epoietin.

Among patients undergoing the interferon treatment, fever and arthromyalgia were the only adverse events observed (Table IV).

Discussion

In the past, DTIC has been considered as the reference drug for the treatment of patients with advanced malignant melanoma, with a response rate of 20% in monotherapy, and response duration of 4 to 6 months (14). In this study, we evaluated both the activity and safety profile of the TMZ-CDDP combination as an alternative therapeutical approach in such patients.

Phase I trials have confirmed that myelosuppression is the dose-limiting toxicity of TMZ, with a recommended starting dose of 150 mg/m^2/day x 5 escalating to 200 mg/m^2/day x 5, if tolerated, in adults (10). Apart from bone marrow suppression, the drug is well tolerated, with mild nausea and vomiting, easily controlled by antiemetics, being the only other significant side-effects (15).

Table IV. *Acute toxicity.*

	Grade				
WHO toxicity	1-2	3	4	Total *%*	G 3-4 *%*
Neutropenia	12	4	2	18 *49*	6 *16*
Thrombocytopenia	7	2	-	9 *24*	2 *5*
Anemia	3	6	-	9 *24*	6 *16*
Nausea and vomiting	22	-	-	22 *59*	-
Alopecia	5	-	-	5 *14*	-
Fatigue	4	-	-	4 *11*	-
Fever*	22	-	-	22 *59*	-
Arthromyalgia*	22	-	-	22 *59*	-

*toxicities specifically related to the interferon treatment

A phase III trial was then conducted to compare the overall survival of 305 patients with advanced metastatic melanoma treated with either TMZ, 200 mg/m^2 once daily for 5 consecutive days, or DTIC, 250 mg/m^2/day for 5 consecutive days every 3 weeks (9). The median overall survival was 7.9 months among patients receiving TMZ and 5.7 months among those receiving DTIC. This survival difference was significant (p=0.012). The median progression-free survival for patients receiving TMZ was 0.4 times longer than for cases receiving DTIC (1.9 months *vs* 1.5 months).

Activity against melanoma has been detected with several other classes of agents. Among these, CDDP and carboplatin have shown a definite, although modest, activity against melanoma (16, 17). During the past two decades, a number of combination chemotherapy regimens have also been developed using two or more of the active drugs mentioned above. Legha *et al*. previously reported the results of a phase II study of CDDP, vinblastine and DTIC (CVD) administered to patients with distant metastases; they observed an overall response rate of approximately 40% with a 5% CR rate (18).

The safety profile, DLT, MTD, pharmacokinetics and preliminary efficacy of TMZ in combination with CDDP were evaluated in a phase I study (10). In this study, cohorts of 3 patients each received oral TMZ for 5 consecutive days together with CDDP on day 1 (4 hours after temozolomide) at the following TMZ/CDDP dose levels: 100/75, 150/75, 200/75 and 200/100 mg/m^2. The combination of TMZ and CDDP was well tolerated, with two patients developing DLT at the 200/100 mg/m^2 dose level. When 75 mg/m^2 CDDP was combined with standard doses of TMZ, no DLT was observed. Thus, the recommended phase II doses are 200 mg/m^2 TMZ daily on days 1-5 and 75 mg/m^2 CDDP on day 1 every 4 weeks. The pharmacokinetics of TMZ were not altered by the addition of CDDP and this combination was well tolerated.

The rationale for combining TMZ, on a daily schedule for 5 days every 4 weeks, with CDDP on day 1 was partially based on the hypothesis that this combination would have improved the antitumor activity of the single-agent TMZ. Both TMZ and CDDP are DNA-damaging antitumor agents, which may induce cytotoxic effects through different pathways. While TMZ seems to act as a classical alkylating agent (15, 19), CDDP has been demonstrated to also activate nuclear as well as cytoplasmatic signaling pathways involved in regulation of the cell cycle, damage repair and programmed cell death (20).

Both TMZ (19, 21-23) and CDDP (24) are active against melanoma, a tumor type with limited therapeutic options for advanced disease. In addition, TMZ and CDDP have non-overlapping DLTs, implying that the tolerable doses of TMZ and CDDP in combination are similar to the tolerable doses of the single agents. Also, TMZ is only minimally renally excreted (2, 21, 22), suggesting that, even in the presence of CDDP-induced nephropathy, CDDP does not alter the pharmacokinetic profile of TMZ.

Our data, revealing a 49% overall response rate, suggest a good activity for the combination of TMZ and CDDP. When we compared our results with those from a previous study based on CDDP-DTIC-fotemustine and showing similar prognostic characteristics (25), we found a higher response rate for the combination TMZ-CDDP (49% *vs* 38%), with 24% *vs* 17% CR rates. Surprisingly, a relatively low SD rate (only 2 patients; 5%) was observed in our series. No explanation of such a phenomenon (presence of either responsive or progressive disease) has been inferred.

Furthermore, these responses had a longer duration; in fact, 5 out of 9 CR patients are still alive without evidence of disease from 28 to 82 weeks. Although preliminary (mainly due to the small number of treated cases), the present data strongly suggest that this schedule may represent an active regimen for patients with advanced melanoma and may justify adequately powered trials in order to better define the efficacy of such a combination.

TMZ demonstrated activity in patients with brain metastases (26), since it crosses the blood-brain barrier and achieves effective concentrations in the CNS (27, 28). An

objective response rate of 96% was reported in a study of concurrent TMZ and radiotherapy in patients with brain metastases from different malignancies (not including melanoma) (29). In our study, 1 of 5 patients with brain metastases achieved a response lasting 47 weeks and 3 patients had a progression in the CNS. Given the small number of patients, it is difficult to draw conclusions and hazardous to speculate on or interpret these observations.

Regarding the toxicity, the proposed schedule was mainly characterized by nausea and vomiting, that required treatment with serotonin antagonists; however, no patient required a reduction or delay of oral administration of TMZ. Hematological toxicities were mild and few patients needed G-CSF support; few blood transfusions and no platelet transfusion were needed.

Although comparisons with the TMZ-CDDP regimen of this study are simply indicative, a lower response rate (14%) and a lower median survival (6.8 months) have been reported for the classical DTIC-CDDP regimen, which also showed significant renal and hematopoietic toxicities (30).

As mentioned above, some durable CRs were reported, with no evidence of recurrence in 5 out of 9 CR patients after a follow-up time ranging from 28 to 82 weeks. IFN might have contributed to prolonging the median duration of responses, further confirming the positive effect of IFN on the maintenance of the clinical response, as also observed by our group (31) and other authors (32). Although not conclusive, O'Day *et al*. have recently demonstrated that maintenance biotherapy in patients achieving PR or SD with induction concurrent biochemotherapy did improve PFS and OS compared with historical controls (33). Despite the high frequency of adverse events previously described (34), IFN was administered at low dose without interfering with the management of our patients, nor affecting the dose intensity, nor worsening the acute side-effects of the cytotoxic treatment. The low intermittent dosage of rIFNalpha2b used in our regimen, and the concomitant administration of paracetamol, prevented the peculiar flu-like symptoms in most patients and rendered them acceptable in the others.

In conclusion, this phase II study demonstrated that the combination of TMZ and CDDP seems to present activity higher than expected from each single agent. Therefore, a reasonably good rationale is here demonstrated to justify a large multicenter phase III study (*i.e.*, TMZ-CDDP combination versus DTIC-based regimens) in patients with advanced melanoma.

Acknowledgements

The temozolomide utilized in this study was kindly furnished by Schering Plough, Italy.

A special thanks to the *Melanoma Cooperative Group of Naples*: Aprea P., Ascierto P.A., Botti G., Caracò C., Castello G., Celentano E., Comella G., Daponte A., Lombardi M.L., Mozzillo N., Parasole R., Picone A. and Tatangelo F., National Tumor Institute "G. Pascale", Naples, Italy; Satriano R.A., Ruocco V., 2nd University of Naples, Italy; Palmieri G., Division of Cancer Genetics, ICB-CNR, Alghero (SS), Italy. The authors would like to thank Dr. A. Criscuolo for data management and Mrs J.Bryce for her technical assistance.

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Received November 30, 2004
Accepted February 4, 2005