# A Phase I and Pharmacokinetic Study of High Dose Tamoxifen and Weekly Cisplatin in Patients with Metastatic Melanoma

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**BACKGROUND.** The authors have previously demonstrated that tamoxifen (TAM) is synergistic with cisplatin (DDP) in patients with metastatic melanoma. In vitro studies have demonstrated that TAM/DDP synergy is dependent on a TAM effect that is currently under investigation. In an attempt to improve the complete response rate of this regimen, the authors initiated a Phase I trial to determine the maximum tolerated dose (MTD) of TAM that could be safely administered with weekly DDP.

**METHODS.** TAM was started on Day 1 at a dose of 80 mg/day and was increased by 40 mg to the MTD in groups of 3 patients. DDP (80 mg/m$^2$) was begun on Day 2 and repeated weekly for a total of 3 weeks. During Week 4, the patients were not treated with DDP but instead evaluated for response. If disease stabilization or regression was documented, the patients received a second 3-week cycle of DDP and were then reevaluated for response. Patients with progressive disease were removed from the study.

**RESULTS.** In 25 consecutive patients, the overall response rate was 20%. No responses were observed in patients treated with TAM at a dose of $<$240 mg/day. Among 13 patients treated at or above this dose, there were 2 complete responses, 3 partial responses, 2 mixed responses, and 6 patients with progressive disease. The overall response rate for patients treated with 240 mg of TAM or higher was 38.5%. Dose-limiting toxicity, which occurred at a TAM dose of 280 mg/day, was primarily hematologic and gastrointestinal in nature. There was one toxic death (due to septic neutropenia) at this dose. There were no episodes of thrombosis.

**CONCLUSIONS.** A TAM dose of 240 mg/day is the recommended Phase II dose. Based on the 38.5% overall response rate at this dose, the authors have initiated a Phase II study. ***Cancer* 1997;79:1037–43.** © *1997 American Cancer Society.*

**KEYWORDS: tamoxifen, cisplatin, melanoma, synergy.**

The authors' previous studies have demonstrated that tamoxifen (TAM) is an important component of a four-drug chemotherapeutic regimen utilized in the treatment of patients with malignant melanoma. This regimen, originally reported by Del Prete et al. and referred to as the Dartmouth regimen, also contains dacarbazine, carmustine, and cisplatin (DDP).[1–3] When TAM is a component of the treatment regimen, the overall response rate has been reported to be approximately 50% by a number of authors in single-institution studies.[1,2,4–11] Two studies have demonstrated a decrease in the overall response rate to 10–20% when TAM is deleted from the regimen, suggesting an important role for TAM.[3,12] In support of this observation, Lattanzi et al. have recently reported an improved survival for those patients treated with the Dartmouth regimen with TAM com-

pared with those treated without TAM.[13] However, it must be noted that these patients were not treated in a prospective randomized fashion. Similarly, Saba et al. have also reported a potential survival advantage associated with the use of this regimen.[14] In this study, patients with metastatic melanoma who were treated with the four-drug combination as originally described enjoyed a survival advantage over patients who refused therapy and were observed for survival ($P < 0.0004$). Again, this study was not a prospective randomized trial and therefore the results must be evaluated with this in mind. Additional clinical trials conducted by the authors have demonstrated that TAM can overcome established clinical resistance to DDP.[6]

In contrast, Rusthoven et al. recently reported the results of a prospective, randomized, placebo-controlled trial in which the response rate of the original Dartmouth regimen was compared with the same regimen without TAM in patients with metastatic melanoma.[15] Treatment with the original regimen resulted in an overall response rate of 30%, compared with an overall response rate of 21% ($P = 0.187$) without TAM. These data do not support the concept of a clinical effect of TAM on the response rate with this regimen.

Laboratory studies conducted by the authors have demonstrated that significant cytotoxic synergy exists between TAM and DDP in the human melanoma cell line T-289.[16] It is the authors' hypothesis that this previously unrecognized synergy is the basic mechanism for the improved response rate observed with the Dartmouth regimen. While exploring the mechanism responsible for synergy, the authors determined that it is not related to an effect of TAM on the known mechanisms of DDP resistance. That is, TAM had no effect on the uptake of the DDP analogue $^{3}$H-cis-dichloro(ethylenediammine)platinum(II), the intracellular levels of either metallothionine II or glutathione, or on the formation or repair of DDP-DNA adducts.[16] The authors also found no relationship with estrogen or progesterone receptor status, the levels or activity of calmodulin, or anti-protein kinase C (PKC) activity.[17] Synergy was dependent on a TAM effect because TAM resistance conferred a loss of synergy, whereas DDP resistance could be overcome by increasing the concentration of TAM.

This latter information provided a potential explanation for the results of the clinical trial mentioned earlier evaluating the ability of TAM to overcome established DDP resistance.[6] In DDP-sensitive melanoma cells, TAM/DDP synergy is observed at TAM concentrations of $<0.1$ $\mu$M, whereas in the DDP-resistant cell line 289 $DDP_3$ TAM concentrations of $>1.0$ $\mu$M are required. These data suggest that the dose of TAM used in the clinical trial (20 mg/day) was too low to produce the serum levels ($>1.0$ $\mu$M) required to overcome clinical DDP resistance.[18]

Pooling of the available data in reported clinical trials of the Dartmouth regimen demonstrates that the complete response (CR) rate is in the range of 15–20%.[19] Two additional studies that have used higher doses of TAM in combination with the Dartmouth regimen have reported higher CR rates with no significant change in the overall response rate.[20,21] These clinical data, together with the laboratory data related to TAM concentrations required to overcome in vitro DDP resistance, led the authors to the following conclusions: 1) TAM/DDP synergy is dependent on a tumor cell's innate sensitivity to TAM; 2) Although DDP sensitivity is important, it plays a relatively minor role and can be overcome by increasing the concentration of TAM; and 3) TAM resistance results in complete loss of synergy, regardless of the concentrations of either TAM or DDP employed. Therefore, the authors hypothesized that the clinical use of higher doses of TAM will lead to an improvement in the CR rate without an effect on the overall response rate. To maximize their chances for success, the authors attempted to take advantage of the potential benefit of dose intensity by using weekly DDP.[22]

To further evaluate the clinical importance of TAM/DDP synergy and the importance of the dose of TAM, the authors designed a clinical trial based on the above information. The purpose of this Phase I trial was to identify the dose of TAM that could be safely given to patients in conjunction with DDP, administered at a weekly dose of 80 mg/m$^2$. In addition, the authors sought to determine the pharmacokinetics of both TAM and DDP.

## PATIENTS AND METHODS

### Eligibility Requirements

Patients were required to be 18 years or older and signed written informed consent had to be obtained. They had to have histologically documented metastatic melanoma with measurable or evaluable disease. Adequate renal, liver, and hematologic function was required with an Eastern Cooperative Oncology Group (ECOG) performance status of $\leq 2$. Patients with central nervous system metastases, a history of deep venous thrombosis, or pulmonary embolism were excluded.

### Treatment Plan

TAM was initiated at a dose of 80 mg/day, which was administered 1 day prior to the first dose of DDP and continued daily until response was determined. The daily oral dose of TAM was escalated in increments of 40 mg in groups of 3 patients. Dose escalation did not

occur within the same patient and required three fully evaluable courses at each level in three different patients. The therapeutic plan included the administration of DDP, beginning on Day 2, at a fixed dose of 80 mg/m$^2$/week for 3 weeks. One cycle of therapy was considered to be three weekly doses of DDP. During Week 4, between Cycles 1 and 2, the patient was not treated but underwent restaging studies to evaluate the patient response. Patients who demonstrated either stable disease (SD) or a measurable response were treated with a second 3-week cycle of DDP and then evaluated again for response. Patients who demonstrated progressive disease (PD) at either evaluation were removed from the study and offered other therapy.

The following definitions were used:

*Complete response (CR):* the complete regression of all target lesion(s) for at least 4 weeks.

*Partial response (PR):* a decrease in the mean greatest dimension of the target lesion(s) by ≥50% lasting at least 4 weeks.

*Stable disease (SD):* less than 25% decrease or increase in the size of the target lesion(s) for at least 8 weeks without the appearance of new lesions.

*Mixed response (MR):* measurable regression of tumor with either SD or PD in other areas.

*Progressive disease (PD):* a progressive increase in the size of target lesion(s) of ≥25% or the appearance of any new lesions.

*Toxic dose (TD):* the occurrence of Grade 4 hematologic toxicity or Grade 3 nonhematologic toxicity in two of six patients treated at the same dose level.

*Maximum tolerated dose (MTD):* the dose level immediately below the TD.

Dose escalation was performed with the following rules. If 1 Grade 4 hematologic toxicity or Grade 3 nonhematologic toxicity was encountered in the first three patients, three additional patients were to be entered at the same dose. If a second patient (two of six) also experienced a Grade 4 hematologic or Grade 3 nonhematologic toxicity, escalation was then terminated. If no additional patients experienced Grade 4 hematologic or Grade 3 nonhematologic toxicity, escalation was then resumed. The National Cancer Institute's ''common toxicity'' grading system was used to assess and grade toxicity.

## Pharmacokinetic Studies

### *Cisplatin*

On the first day of DDP administration, DDP concentration samples were drawn just prior to and 2, 4, 6, 8, 12, 18, and 24 hours after the infusion. Plasma samples were spun through Centrifree micropartition cones (Amicon, Beverly, MA) eliminating >99.9% of the serum proteins. The ultrafiltrate was collected and stored (−70 °C) until processing. Samples were analyzed for platinum content using a Perkin-Elmer 5100 PC Atomic Absorption Spectrophotometer (Oak Brook, IL) at a wavelength of 265.9 nanometers. Peak area data were used to compare samples with a standard curve for the determination of plasma DDP concentrations.

The terminal disposition rate constant, half-life ($t_{1/2}$), apparent volume of distribution at steady state ($Vd_{ss}$), and total body clearance ($CL_T$) were determined in 5 patients treated at or above a dose of TAM of 240 mg/day. The terminal disposition rate and the $t_{1/2}$ were determined from the best-fit line of the natural logarithms of the concentration in serum versus time for those points after the distribution phase, by least squares regression. The slope of the line is the terminal disposition rate and $t_{1/2}$ equals 0.693/terminal disposition rate. The area under the serum concentration-versus-time curve (AUC) and area under the first moment curve (AUMC) were calculated from each patient's data utilizing the linear trapezoidal rule. The $Vd_{ss}$ and $CL_T$ were determined by noncompartmental analysis. $Vd_{ss}$ equals [dose × $AUMC_{0-\infty}$/$(AUC_{0-\infty})^2$] and $CL_T$ equals dose/$AUC_{0-\infty}$.

### *Tamoxifen high performance liquid chromatography assay*

TAM samples were drawn just prior to and 24 hours after the first dose of TAM and then at weekly intervals for the first cycle of therapy. The tamoxifen assay utilized a mobile phase comprised of 7% double distilled water and 0.18% triethylamine in methanol (i.e., add water and triethylamine and a sufficient quantity to volume with methanol). There was no pH adjustment. Samples for analysis were injected onto an Alltech (Deerfield, IL) Versapack C18 column at ambient temperature (~25 °C), eluted at a flow rate of 1.2 mL/minute, and detected by ultraviolet light (UV) absorption at 277 nm. Retention time for TAM was 6.9 minutes. Intrarun and interrun coefficients of variation were <10%.

## RESULTS

A total of 25 consecutive patients were enrolled on this study with the following characteristics (Table 1). There were 16 males and 9 females with a median age of 53 years (range, 23–72 years). All patients had an

**TABLE 1**
**Patient Characteristics**

| | |
|---|---|
| Gender | |
| Male | 16 |
| Female | 9 |
| Age (yrs) | |
| Median | 53 |
| Range | 23–72 |
| Pretreatment tumor location | |
| Lymph nodes | |
| Retroperitoneal | 6 |
| Other | 2 |
| Liver | 9 |
| Lung | 6 |
| Subcutaneous | 3 |
| Spleen | 3 |
| Bone | 1 |
| Ascites | 1 |

**TABLE 2**
**Toxicity**

| Week | 4 | | 8 | |
|---|---|---|---|---|
| Renal (average ↑ Cr) | 0.14 | | 0.45 | |
| | Grade 3 | Grade 4 | Grade 3 | Grade 4 |
| ANC | 1 | 1 | 0 | 1 |
| Hgb/Hct | 0 | 0 | 0 | 0 |
| Platelets | 1 | 1 | 0 | 0 |
| Periph. neuro. | 0 | 0 | 1 | 0 |
| Ototoxicity | 0 | 0 | 0 | 0 |
| Nausea/vomiting | 2 | 1 | 2 | 0 |

↑Cr: serum creatinine elevation; ANC: absolute neutrophil count; Hgb/Hct: hemoglobin/hematocrit; Periph. neuro: peripheral neuropathy.

ECOG performance status of 1 or better except for 2 young males who had a performance status of 2 and were previously untreated. All patients completed at least one cycle of therapy and were eligible for response and toxicity determinations.

Three patients were entered at dose levels of 80, 120, 160, 200, and 240 mg/day. When 2 patients receiving the 280 mg/day dose experienced unacceptable toxicity, an additional 7 patients were entered at the 240 mg/day dose to more clearly define this dose as the MTD.

## Response

In the 25 treated patients, 5 measurable responses (2 CR and 3 PR) were observed for an overall response rate of 20% (95% confidence interval [CI], 6.83–40.70). In addition, two patients exhibited a mixed response. No response was observed in patients who were treated with a TAM dose $<$ 240 mg/day. Four patients responded at the 240 mg/day dose and 1 patient at the 280 mg/day level. In the 13 patients treated at or above this dose of TAM, 2 CRs (15.4%) and 3 PRs (23.1%) were observed for an overall response rate of 38.5% (95% CI, 13.86–68.42). The overall response rate in females was 44%, compared with 6% in males. The two patients who exhibited MRs were also male. Similar to the authors' experience with the Dartmouth regimen, response was observed in patients with both soft tissue and visceral metastases. One of the patients who experienced a CR had disease limited to her liver. The 2 patients with CRs survived 9 and 13+ months, respectively. One of the 2 CR patients failed with new disease documented in the thyroid gland and skin 9 months after entering CR. This patient was retreated with this regimen and was again in CR (6+ months) at last follow-up. Measurable response was evident in all patients who responded at the first 4-week evaluation. Both CR patients had an unmeasurable residual abnormality present on a computed tomography scan performed 3 weeks after Cycle 2. Both patients were observed without further treatment due to the indeterminate nature of the abnormalities. In each case, complete clearing of all residual abnormalities was observed.

## Toxicity

The dose intensity of this program was such that the patient received what would normally be considered 3 months of DDP within a 2-week time frame. Despite this, significant toxicity was uncommon at the lower doses of TAM (Table 2). At the 4-week evaluation, only 2 patients exhibited significant toxicity, both at the 280 mg/day dose, which proved to be the TD. Both of these patients experienced both Grade 4 neutropenia and thrombocytopenia. The first patient was a 61-year-old female who developed nausea, vomiting, and anorexia during treatment with a profound decrease in her performance status. She was asymptomatic prior to the start of therapy and subsequently became bedridden and unable to eat. Despite experiencing a $>$50% reduction in her liver metastasis, she declined further therapy. Her anorexia was such that she required parental nutrition for several weeks after her removal from the study. In addition, she developed Grade 3 neutropenia and thrombocytopenia. The second patient was a 67-year-old male who developed profound neutropenia, thrombocytopenia, an elevation in serum creatinine (2.1 mg/dL), and septicemia resulting in death. This patient was also treated at the TD dose for TAM and was the second patient to develop dose-limiting toxicity at that dose.

This treatment was well tolerated from a renal standpoint. At Week 4 (1 complete cycle), the average

**TABLE 3**
**Cisplatin Pharmacokinetics**

| Patient no. | (Dose) | $AUC_{0-24}$ | $t_{1/2}$ alpha | $t_{1/2}$ terminal | $CL_T$ | $VD_{SS}$ |
|---|---|---|---|---|---|---|
| 1 | (240 mg/day) | 13,573 | 0.4 | 26.73 | 4.8 | 69.6 |
| 2 | (240 mg/day) | 11,949 | 0.41 | 24.4 | 5.4 | 79 |
| Mean: 240 ± 95% CI | | 12,761 ± 1730 | 0.405 ± 0.01 | 25.6 ± 2.5 | 5.1 ± 0.6 | 74.3 ± 5.4 |
| 3 | (280 mg/day) | 13,678 | 0.62 | 48.7 | 3.9 | 137.4 |
| 4 | (280 mg/day) | 9596 | 0.55 | 66.2 | 4.1 | 206.2 |
| 5 | (280 mg/day) | 9849 | 0.51 | 46.3 | 4.8 | 190 |
| Mean: 280 ± 95% CI | | 11,041 ± 2812 | 0.56 ± 0.06 | 53.7 ± 13.4 | 4.3 ± 0.54 | 177.9 ± 1.4 |
| Total (n = 5 patients) mean ± 95% CI | | 11,729 ± 1865 μg/L*hr | 0.5 ± 0.084 hrs | 42.5 ± 16.0 hrs | 4.6 ± 0.54 L/hr/$m^2$ | 136.4 ± 59.2 L/$m^2$ |

AUC: area under the curve; $t_{1/2}$: terminal disposition rate half-life; CL: total body clearance; $VD_{SS}$: apparent volume of distribution at steady state; CI: confidence interval.

rise in serum creatinine was 0.14 mg/dL. Only 1 patient developed an abnormal serum creatinine of 1.6 mg/dL (normal for the study was 1.5 mg/dl). During the second cycle 4 patients developed abnormal elevations in serum creatinine at levels of 1.6, 1.8, 2.4, and 2.6 mg/dL at TAM doses of 240 and 280 mg/day. Seven patients received 2 complete cycles of therapy with an average rise in serum creatinine of 0.45 mg/dL. Elevation of the serum creatinine was not observed at TAM doses < 240 mg/day. Similarly, neurologic toxicity was minimal. One patient developed Grade 2 peripheral neuropathy approximately 4 weeks after completing Cycle 2.

As described earlier, 1 patient developed severe neutropenia and thrombocytopenia resulting in a septic death at the 280 mg/day dose of TAM. This developed 1 week after the completion of Cycle 1. In addition, at this same dose a second patient developed Grade 3 neutropenia and thrombpcytopenia. At the 240 mg/day dose, 1 of 10 patients developed Grade 4 neutropenia (second cycle) and an additional patient was observed with Grade 2 thrombocytopenia. A decline in the hemoglobin of 1–3 g/dL was common by Week 4, with an additional decline of 1–3 g/dL after Week 8. Aside from a decrease in hemoglobin, no significant hematologic toxicity was observed in patients treated at a dose of <240 mg/day.

Not surprisingly, this regimen resulted in moderate amounts of nausea and vomiting that appeared to be dependent on the TAM dose. Patients treated with a TAM dose of <240 mg/daily generally experienced Grade 1 nausea and vomiting. Patients treated at or above this dose exhibited more consistent and significant Grade 3/4 nausea and vomiting. In two cases, significant vomiting abated although the nausea/anorexia persisted.

### Pharmacokinetics

DDP pharmacokinetics were available for 5 patients: 2 at 240 mg/day and 3 at 280 mg/day (Table 3). As

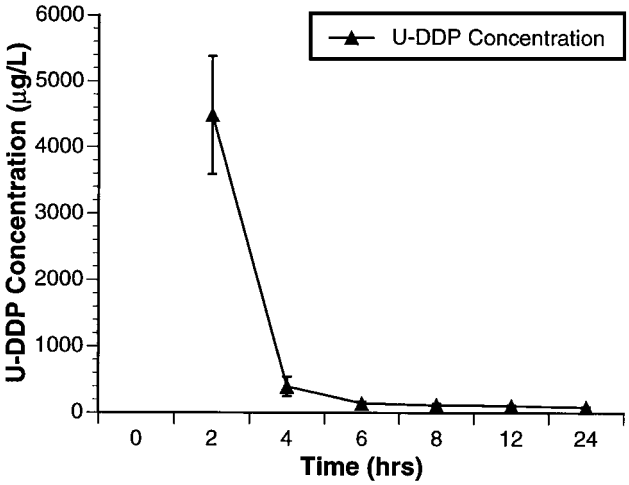


**FIGURE 1.** The time course of the concentration of cisplatin found in the plasma ultrafiltrate of patients at the specified time points is presented. Samples were spun through Centrifree micropartition cones (Amicon), which eliminate >99% of serum proteins. The ultrafiltrate was analyzed using a Perkin Elmer 5100 PC Atomic Absorption Spectrophotometer at a wavelength of 265.9 nanometers.

seen in Figure 1 the peak concentrations for ultrafiltered DDP (U-DDP) occurred, as expected, at the conclusion of the 2-hour infusion. From that point, there was a rapid decline in U-DDP concentration for up to 4 hours, with a slow final elimination. The $AUC_{(0-24)}$ was 11,729 ± 1865 μg/L*hour (mean ± 95% CI), with an alpha $t_{1/2}$ of 0.5 ± 0.08 hours and a clearance ($CL_T$) of 4.6 ± 0.54 L/hour/$m^2$. The terminal $t_{1/2}$ and $Vd_{ss}$ were 42.4 ± 16.0 hours and 136.4 ± 59.2 L/$m^2$, respectively.

TAM pharmacokinetic analysis, available for 6 patients, was complicated by the authors' inability to obtain standards for the N-desmethyl and 4OH TAM metabolites, despite contacting a variety of sources. Thus, the analyses performed are for the parent com-

pound only. Although it would be interesting to evaluate the metabolites, it is important to point out that the in vitro observation of synergy is with the parent compound, TAM citrate. Three patients each were treated at the 240 and 280 mg/day doses. There was no significant difference in the two dose levels. At 24 hours after the first dose, the mean plasma concentration of TAM was 0.36 ± 0.17 (mean ± 95% CI) $\mu$M whereas steady state concentrations at 7 and 14 days after initiation of therapy increased to 1.13 ± 0.47 $\mu$M and 1.75 ± 0.30 $\mu$M, respectively.

## DISCUSSION

In the current study, the authors evaluated the MTD of TAM that can be given in combination with weekly DDP based on the rationale described earlier. They have demonstrated that it is possible to give TAM at a dose of 240 mg/day in this setting. The dose-limiting toxicity proved to be hematologic in nature; however, problems with nausea, vomiting, and anorexia were not trivial. Although the number of patients was insufficient to determine statistical significance, there was a trend toward worsening gastrointestinal (GI) toxicity based on a TAM dose $\geq$ 240 mg/day. In the first patient, who was treated at what later proved to be the TD for TAM, the GI side effects were severe enough to persuade her to forgo further therapy, despite significant shrinkage of her liver metastasis. In other patients, nausea and/or anorexia proved to be more of a problem than actual vomiting.

Significant hematologic toxicity was observed at the highest dose of TAM. At the TD, this unfortunately resulted in a single toxic death due to neutropenic sepsis. Thrombocytopenia also proved to be a common problem at the higher doses; however, clinical bleeding was not observed. No episodes of either deep venous thrombosis or pulmonary embolism were observed.

Clinical response appeared to be associated with TAM dose and female gender. As noted earlier, tumor shrinkage was not observed in patients treated below 240 mg/day of TAM with the exception of 1 patient who exhibited a MR. At or above this dose of TAM, the overall response rate was 38.5%. The determination of whether or not there is a true relationship between female gender and clinical response will require the results of the ongoing Phase II study because 7 of the 9 women who were entered onto the trial were entered at the highest doses of TAM. Thus, it is unclear if the higher response rate observed in women was related to gender or the fact that they entered the trial at the higher dose levels of TAM.

It is important to note that the evaluation of TAM pharmacokinetics demonstrated that the dose of 240 mg/day of TAM produced plasma levels required for synergy in DDP-resistant tumors. As mentioned earlier, in vitro studies predicted that plasma concentrations of TAM of $\geq$1 $\mu$M would be required to overcome de novo DDP resistance. This study demonstrated that steady state plasma levels of tamoxifen, at both 7 and 14 days, exceeded this value.

DDP pharmacokinetic analysis revealed that TAM had no effect on either the $AUC_{(0-24)}$ or the alpha $t_{1/2}$ when compared with previously published values.[23,24] In contrast, the $CL_T$, terminal $t_{1/2}$, and $Vd_{ss}$ were affected. The $CL_T$ was reduced in all patients, resulting in an increase in the $Vd_{ss}$ and a subsequent increase in the terminal $t_{1/2}$. The increase in the $VD_{ss}$ may have been the result in an increase in the tissue DDP as a result of a previously unrecognized effect of TAM. This would effectively decrease the clearance and increase the terminal half-life. To the authors' knowledge, this is the first study to demonstrate such an effect.

The reason for the reduced DDP clearance is not immediately apparent. It is possible that high plasma levels of TAM may alter the protein or tissue binding of DDP. This would result in a reduction in the clearance of DDP and an increase in the $Vd_{ss}$, resulting in a prolongation of the terminal $t_{1/2}$. One could speculate that the reduced clearance resulted in an increase in the uptake of DDP into tissues, including tumor cells. This would be at least a partial explanation for the apparent effect of the TAM dose-response relationship suggested by the results of this trial. This is supported by the observation that the neutropenia and thrombocytopenia encountered in this trial were related to the TAM dose. As stated earlier, there was no neutropenia or thrombocytopenia observed at the lower doses of TAM despite the use of weekly DDP. Only at a dose of TAM of >240 mg/day was hematologic toxicity observed. A similar increase in hematologic toxicity was also observed in two previous studies that employed a high dose of TAM as part of the Dartmouth regimen.[21,25] However, in vitro studies conducted by the authors would argue against this conclusion; the authors previously demonstrated that increasing the concentration of TAM had no effect on the intracellular uptake of the DDP analogue [$^3$H]-DEP.[16]

The impact of TAM/DDP synergy on the clinical response of patients with metastatic melanoma remains controversial. The current study supports the concept of a dose-response relationship for TAM; however, further studies will be required for confirmation. The authors are currently conducting a Phase II study of this combination in patients with metastatic melanoma, using a TAM dose of 240 mg/day. The forthcoming results of this trial will help to further

define the role of TAM/DDP synergy in the clinical response of patients with this disease.

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