Long-Term Survival in Patients with Metastatic Melanoma Treated with DTIC or Temozolomide

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Disclosures: Christina Kim: None; Christopher W. Lee: None; Laurel Kovacic: None; Amil Shah: None; Richard Klasa: None; Kerry J. Savage: None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors or independent peer reviewers.

ABSTRACT

Background. Patients with metastatic melanoma typically have a poor outcome; however, a small proportion of patients achieve long-term survival (LTS). It is unclear how often LTS is related to sensitivity to chemotherapy.

Methods. All patients with metastatic melanoma treated with either dacarbazine (DTIC) or temozolomide (TMZ) at the British Columbia Cancer Agency (BCCA) from January 1, 1988 to February 1, 2006 were identified through the BCCA pharmacy electronic database, which was then linked to the surveillance and outcomes unit to identify patients with LTS, defined as survival ≥ 18 months following chemotherapy.

Results. In total, 397 patients were treated with either DTIC ($n = 349$) or TMZ ($n = 48$) and 43 patients

(10.8%) were identified with LTS. Two additional patients with LTS were added prior to 1988 for a total of 45 patients. The 5-year overall and progression-free survival rates for patients with LTS were 33% and 16%, respectively. In total, 16% had a complete response (CR) to chemotherapy, which was the only factor identified that correlated with survival in the multivariate analysis. However, most patients with LTS had an incomplete response to chemotherapy.

Conclusions. LTS occurs in select patients who achieve a CR to chemotherapy. However, this occurs in only a minority of patients and, in most cases, the longer survival is likely the result of indolent disease biology or host factors. *The Oncologist* 2010;15:765–771

INTRODUCTION

Patients with metastatic melanoma have a poor prognosis, with a median survival duration of only 6–9 months [1, 2]. Established prognostic factors in metastatic melanoma include the site and number of metastases, the level of lactate dehydrogenase (LDH), and the interval between diagnosis of the primary and the onset of metastatic disease [3–7]. On

one end of the spectrum, patients with nonpulmonary visceral metastases, such as in the liver, and central nervous system (CNS) involvement and/or elevated LDH levels have a median survival time of 3–4 months, whereas those with subcutaneous (s.c.) or cutaneous metastatic disease typically have a median survival time of 12–13 months [6]. Patients with primary ocular or mucosal melanoma also

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have a poorer prognosis than those with primary cutaneous disease [8]. However, there is a small proportion of patients who achieve long-term survival that exceeds these estimates, but it is unknown whether this reflects sensitivity to chemotherapy or immunotherapy, host immune factors, or indolent tumor biology.

Dacarbazine (DTIC) is the only U.S. Food and Drug Administration (FDA) and Health Canada approved cytotoxic drug for the treatment of metastatic melanoma, yet it is unknown whether it improves overall survival (OS). The response rate to DTIC is in the range of 6%–20%, with lower rates reported in randomized trials, and the median duration of response is approximately 6 months [1–2, 9, 10]. Randomized controlled trials have failed to show longer progression-free survival (PFS) or OS times with the use of combination chemotherapy than with single-agent DTIC [9, 11], and the standard of care remains DTIC alone. Previous studies suggest that <5% of patients achieve a complete response (CR) to DTIC (or combinations) and <2% of patients survive >5 years [2, 12]. The majority of prior reports suggest that long-term survival is restricted to patients with favorable clinical features such as nodal, cutaneous, s.c., or pulmonary metastasis [12].

Temozolomide is an imidazotetrazine derivative that was developed as an oral alternative to DTIC [13]. At physiologic pH it converts to MTIC, which is the active metabolite of DTIC. Temozolomide is able to cross the blood–brain barrier and penetrate the CNS. In a randomized, controlled trial comparing temozolomide with DTIC for the treatment of newly diagnosed patients with metastatic melanoma, there was no difference in the median survival time (7.7 months versus 6.4 months) [14], and thus, it is typically used in patients with CNS disease. Currently, there are no data on long-term survival with temozolomide.

The purpose of this study was twofold: (a) to determine the overall frequency of long-term survivors in a population-based cohort treated with DTIC or temozolomide with mature follow-up and (B) to determine the proportion of long-term survivors who achieve a sustained CR to chemotherapy.

METHODS

The British Columbia Cancer Agency (BCCA) electronic pharmacy records were searched to identify all patients who received at least one cycle of either DTIC or temozolomide at the BCCA in 1988–2006. Updated information regarding patient status was last obtained in June 2009. Temozolomide is approved for use at the BCCA for patients with metastatic melanoma who have

concurrent brain metastases or for other exceptional reasons that preclude administration of i.v. chemotherapy. The treatment database was linked with the BCCA Surveillance and Outcomes database to identify patients who survived ≥ 18 months from the date of their first treatment with chemotherapy (i.e., “durable” remissions). Several chart records prior to the availability of electronic pharmacy records in 1988 were also manually reviewed to identify other long-term survivors treated with DTIC; however, these cases were excluded from the frequency analysis because of the lack of a systematic approach and recall bias.

All patients had malignant melanoma confirmed by pathology, and had metastatic or unresectable disease. With the exception of one patient who received interleukin (IL)-2 and interferon- α , none of the patients had prior treatment with IL-2, interferon, or alternate chemotherapy in the metastatic setting. A chart review was performed to collect the baseline clinical features of the long-term survivors at the time of treatment with DTIC or temozolomide, including sex, age, performance status, site of primary, site and number of metastases, LDH level, and current patient status. This study was approved by the BCCA Research Ethics Board.

Statistical Analysis

PFS was measured from the date of administration of the first cycle of chemotherapy to the date of documented progression or death. OS was measured from the date of the first cycle of chemotherapy to the date of death from any cause. Given that this was a retrospective study, responses were defined as follows: CR was defined as the complete disappearance of all disease; partial remission or stable disease (PR/SD) was defined as either no response or partial tumor regression with residual disease still present. Progressive disease (PD) was defined as any indication of tumor progression. The Kaplan–Meier method was used for survival estimates, and comparisons were made using the log-rank test [15]. SPSS, versions 11.5 and 14.0 (SPSS, Inc., Chicago, IL), were used for all statistical analyses.

RESULTS

Clinical Features of Long-Term Survivors

On initial screening of the electronic pharmacy database, 413 patients were identified who were treated with DTIC or temozolomide; however, 16 were excluded for privacy reasons because they had not been seen at the BCCA and their clinical records were not available for review (Fig. 1). Of the remaining 397 patients, 349 were treated with DTIC or a DTIC-containing chemotherapy combination

Figure 1. Identification of long-term survivors with metastatic melanoma treated with dacarbazine (DTIC) or temozolomide.

^aNot included in determination of frequency of long-term survivors.

and 48 were treated with temozolomide. In total, there were 39 durable remissions in the DTIC group (11.2%) and four durable remissions (8.3%) in the temozolomide group (total, 10.8%). Two additional patients were identified prior to 1988 for a total of 45 long-term survivors. Of the 41 (91%) long-term survivors who received DTIC, 20 (49%) received DTIC alone, with ($n = 3$) or without ($n = 17$) tamoxifen (Table 1). The majority of the remaining patients received DTIC in combination with cisplatin with or without tamoxifen ($n = 19$). Seven of the latter patients received concurrent treatment with carmustine (BCNU). The final two remaining patients received DTIC in combination with either carboplatin or IL-2. Four patients received temozolomide; the majority of these had CNS metastases and one preferred the oral route of administration. Temozolomide was given in combination with tamoxifen, cisplatin, IL-2, and interferon in one individual.

The presenting clinical characteristics are shown in Table 1. The median time from the diagnosis of melanoma to identification of metastatic disease was 2.6 years (range, 0–21.6 years). The median follow-up of surviving patients was 12 years (range, 4.7–29 years). The median age at the time of diagnosis of metastases was 53 years (range, 22–86 years) and 67% of patients were male. The majority of patients had a good performance status score (0 or 1, 89%), a normal LDH level (76%), and a history of primary cutaneous

melanoma (76%). The most common sites of metastasis were s.c. or cutaneous. However, a moderate proportion had high-risk sites, including the CNS or liver (29%), and 33% had three more sites of metastatic disease (Table 1).

Response to Chemotherapy and Outcome of Long-Term Survivors

Response was assessable in 44 patients. In one patient, response assessment was not possible because of a lack of measurable disease following splenectomy. In total, seven patients (16%) had a CR to chemotherapy. Of note, one patient included in this group had residual abnormalities in the liver that remained stable over a 5-year time period and were felt by the radiologist to represent “burnt out” disease. Thirty patients (67%) had PR/SD and the remainder had PD (Table 1). In total, 39 patients ultimately progressed and 34 received additional therapy, most commonly second-line chemotherapy ($n = 8$), retreatment with DTIC, temozolomide, or a combination with either of these agents ($n = 9$), or tamoxifen alone ($n = 5$). Four patients received immunotherapy second line: chemoimmunotherapy ($n = 2$) (cisplatin and interferon- α ; temozolomide, cisplatin, BCNU, tamoxifen, IL-2); IL-1 β ($n = 1$); interferon- α ($n = 2$). Three patients received intralesional gene therapy and one patient received melacine vaccine. In the third-line setting, four patients received immunotherapy (interferon- α , $n = 2$; IL-1 β , $n = 1$; IL-2, $n = 1$).

Table 1. Baseline characteristics of patients treated with DTIC or temozolomide chemotherapy

Characteristic	DTIC or temozolomide, n (%) (n = 45)
Median age, yrs	53 (22–86)
Sex	
Male	30 (67)
Female	15 (33)
Primary site	
Skin	34 (76)
Mucosal	2 (4.4)
Ocular	3 (6.7)
Primary unknown	6 (13)
Site of metastasis	
CNS	4 (9)
Liver	9 (20)
Lung	20 (44)
Subcutaneous/cutaneous	22 (49)
Other (gastrointestinal, adrenal, spleen, bone, muscle, nasopharynx)	13 (29)
n of metastatic sites	
1	15 (33)
2	15 (33)
≥3	15 (33)
Concurrent chemotherapy	
DTIC alone ^a	20 (45)
DTIC combination ^b	21 (47)
Temozolomide alone	3 (6.7)
Temozolomide combination ^c	1 (2.2)
Performance status score ^d	
0	24 (53)
1	16 (36)
2–3	4 (8.9)
LDH	
Normal	34 (76)
Elevated	10 (22)
Unavailable	1 (2.2)
Median time from diagnosis to metastasis, mos	31 (0–259)
Metastasectomy prior to chemotherapy	
Yes	8 (18)
Pulmonary metastasectomy	3 (6.7)
Nonpulmonary visceral metastasectomy	5 (11)
No	37 (82)

(continued)

Table 1. (Continued)

Characteristic	DTIC or temozolomide, n (%) (n = 45)
Metastasectomy following chemotherapy	
Yes	10 (22)
Cutaneous or subcutaneous metastasectomy	4 (8.9)
Pulmonary metastasectomy	1 (2.2)
Nonpulmonary visceral metastasectomy	4 (8.9)
No	35 (78)
Mean n of chemotherapy cycles	6.5 (1–19)
Initial response ^e	
Complete remission	7 (16)
Partial remission/stable disease	30 (67)
Disease progression	7 (16)
Median progression-free survival time, mos	9 (0–347)
Median overall survival time, mos	29 (18–347)
Median follow-up of survivors, mos	140 (56–346)

^aIncludes three patients who received additional treatment with tamoxifen.
^bCombinations include: DTIC and cisplatin with or without tamoxifen (n = 11); DTIC, cisplatin, and carmustine (BCNU) with or without tamoxifen (n = 7); DTIC, cisplatin, interleukin-2, interferon- α , and tamoxifen (n = 1); DTIC and interleukin-2 (n = 1); DTIC and carboplatin (n = 1).
^cCombination was temozolomide, tamoxifen, cisplatin, interleukin-2, and interferon.
^dPerformance status not available for one patient.
^eNo measurable disease to follow in one patient who had a splenectomy for metastases to the spleen.
Abbreviations: CNS, central nervous system; DTIC, dacarbazine; LDH, lactate dehydrogenase.

With a median follow-up in surviving patients of 140 months (range, 56–346 months), the median PFS time was 9 months (range, 0–347 months) and the 5-year PFS rate was 16%, with a clear plateau after 5 years suggesting cures in a minority of patients (Fig. 2A). The median OS time was 29 months (range, 18–347 months) and the 5-year OS rate was 33% (Fig. 2B). There was no difference in terms of PFS ($p = .972$) or OS ($p = .126$) in patients who received DTIC alone ($n = 20$) compared with those who received DTIC in combination ($n = 21$) (results not shown).

Twenty patients (DTIC, $n = 19$; temozolomide, $n = 1$) survived ≥ 3 years after receiving chemotherapy (range, 3.02–28.9 years), one of whom had CNS involvement at diagnosis. Of note, none of these patients received IL-2 for

Figure 2. Long-term survival in patients with metastatic melanoma treated with DTIC or temozolomide: (A) Progression-free survival; (B) Overall survival.

relapsed disease. Excluding the two patients identified by recall, this represented 4.5% of our original cohort of 397 patients. Of these patients, seven (35%) attained a CR to chemotherapy, 12 (60%) had PR/SD, and one patient, who eventually died of metastatic melanoma almost 5 years following chemotherapy, had PD. Six patients remain in continuous remission, five of whom had a CR to initial chemotherapy, including three with hepatic metastases at diagnosis. The remaining patient had a best response of SD to initial chemotherapy; however, over the subsequent years, cutaneous and s.c. metastases slowly spontaneously regressed, and residual nodules were negative for disease involvement.

The 5-year PFS rate was superior in patients who achieved a CR to DTIC or temozolomide chemotherapy

Figure 3. Survival according to response to chemotherapy: (A) Progression-free survival; (B) Overall survival.

Abbreviations: CR, complete remission; PD, progressive disease; PR/SD, partial remission/stable disease.

(CR, 69%; PR/SD, 3%; PD, 0%; $p < .0001$) (Fig. 3A). Similarly, the 5-year OS rate was more favorable in this subset (CR, 80%; PR/SD, 21%; PD, 0%; $p < .00001$) (Fig. 3B). On univariate analysis, only attainment of a CR was predictive of PFS ($p < .00001$) and OS ($p = .0018$) (Table 2).

DISCUSSION

A minority of patients with metastatic melanoma have prolonged survival that far exceeds conventional expectations. It is unclear whether the dominant driving force in these long-term survivors is the host immune response against the melanoma, inherent indolent disease biology, or response to therapy. Overall, in our highly select group of patients who survived ≥ 1.5 years, only 16% had a CR as their best response to initial chemotherapy. In those patients who sur-

Table 2. Factors associated with progression-free survival (PFS) or overall survival (OS)

Factor	PFS <i>p</i> -value	OS <i>p</i> -value
Performance status >1	.638	.925
Male sex	.676	.265
Age >55 yrs	.584	.440
Elevated lactate dehydrogenase	.091	.538
Nonpulmonary visceral metastases	.156	.778
Noncutaneous primary	.331	.857
Combination chemotherapy	.980	.141
Complete response	<.00001	.0018

vived >3 years, a greater proportion had a CR (35%), and attainment of a CR was the only factor identified that correlated with survival in the whole cohort of long-term survivors. Given the absence of relapses after 5 years (Fig. 2A), it appears that there is a small group of patients with highly chemosensitive disease who are cured with chemotherapy, similar to what has been reported with immunotherapy with IL-2 [16]. Spontaneous remission has been reported to occur in metastatic melanoma patients; however, frequency estimates are approximately <1% and thus, this would not account for the number of long-term survivors seen in this study [17, 18].

Other limited series have also reported long-term survivors following a variety of chemotherapy agents used in metastatic melanoma [2, 4, 12, 19]. However, many of these studies combined patients who received chemotherapy with those who underwent metastasectomy. The latter group clearly includes those who are potentially cured with surgery, typically individuals with solitary pulmonary, s.c., or cutaneous metastases [20–24]. However, there is very little information regarding long-term survival, and possibly cure, following conventional chemotherapy with DTIC, particularly in a population-based cohort, and there is no information on the frequency of long-term survival following the use of temozolomide. Hill and colleagues [2] reported on the CR rate in a collection of phase III studies involving 580 patients treated with DTIC or DTIC combinations and found that 26 patients (4.4%) achieved a CR, with a 6-year survival rate of 31%, which is comparable with the results of our study. Further, durable CRs were seen in patients with visceral metastases, including in the liver. Interestingly, in both studies, there is a notable predominance of males in this more favorable population.

It is currently unknown what factors predict chemosensitivity in metastatic melanoma. The active metabolite in

DTIC and temozolomide is MTIC, and resistance to these drugs correlates with elevated O6-methylguanine-DNA methyltransferase (MGMT), which removes the alkyl group from the O6 position of the guanine, a critical site of DNA alkylation. High levels of MGMT result in chemoresistance by blunting the therapeutic effect of alkylating type chemotherapy agents. In glioblastoma multiforme, methylation of the *MGMT* promoter results in epigenetic silencing of the gene and has been associated with benefit from temozolomide [25]. Recent studies using melanoma-derived cell lines demonstrated a significant correlation between temozolomide sensitivity and MGMT expression, but not promoter methylation of the *MGMT* gene; however, this has not been studied in primary tumors. Thus, evaluation of tumor MGMT levels may be useful in selecting patients sensitive to either temozolomide or DTIC.

High-dose IL-2 is FDA approved in the U.S. for use in metastatic melanoma based on phase II trials, which showed an overall response rate of 16% and a 6% CR rate [26–30]. This regimen has never been compared directly with DTIC, although it has been reported that IL-2 responses appear to be more durable than what is expected with standard chemotherapy with DTIC or combinations. However, the frequency of CRs and the proportion of these that are durable are very similar to what was observed in our study with chemotherapy. It is highly likely that different molecular, biological, or host factors exist that predict tumor response to either chemotherapy or immunotherapy, and delineating these factors would be critical in selecting patients for these therapies. Further, the predictive factors of response likely differ in patients treated with chemotherapy or immunotherapy.

Long-term survival did not occur exclusively in patients who achieved an initial CR in response to chemotherapy. In fact, 30 of the 45 long-term survivors had an initial response of either a PR or SD. Eight of those patients survived >5 years despite the fact that four of them developed PD <1 year following the initiation of chemotherapy. Further, many of the patients who achieved long-term survival had high-risk features at diagnosis. Given that achieving a CR to chemotherapy was the only factor identified that correlated with outcome suggests that there are likely other biologic or immunologic factors determining outcome in those patients who achieve an incomplete response or with disease progression. In those cases, established clinical prognostic factors do not accurately reflect the underlying biological heterogeneity.

In summary, long-term survival occurs in a subset of patients with metastatic melanoma. A minority of patients can achieve a CR as a result of treatment with chemotherapy and, given the observed durability in some cases, are poten-

tially cured. Predicting which patients will respond is vital in selecting who would benefit most from chemotherapy. Finally, the largest proportion of long-term survivors with metastatic melanoma have a suboptimal response to treatment, but clearly indolent disease biology. Identification of these individuals would aid in prognostication and possible selection for more immunologically directed therapies.

AUTHOR CONTRIBUTIONS

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REFERENCES

- Gogas HJ, Kirkwood JM, Sondak VK. Chemotherapy for metastatic melanoma: Time for a change? *Cancer* 2007;109:455–464.
- Hill GJ 2nd, Kremenz ET, Hill HZ. Dimethyl triazeno imidazole carboxamide and combination therapy for melanoma. IV. Late results after complete response to chemotherapy (Central Oncology Group protocols 7130, 7131, and 7131A). *Cancer* 1984;53:1299–1305.
- Bedikian AY, Johnson MM, Warneke CL et al. Prognostic factors that determine the long-term survival of patients with unresectable metastatic melanoma. *Cancer Invest* 2008;26:624–633.
- Brand CU, Ellwanger U, Stroebe W et al. Prolonged survival of 2 years or longer for patients with disseminated melanoma. An analysis of related prognostic factors. *Cancer* 1997;79:2345–2353.
- Balch CM, Soong SJ, Murad TM et al. A multifactorial analysis of melanoma. IV. Prognostic factors in 200 melanoma patients with distant metastases (stage III). *J Clin Oncol* 1983;1:126–134.
- Barth A, Wanek LA, Morton DL. Prognostic factors in 1,521 melanoma patients with distant metastases. *J Am Coll Surg* 1995;181:193–201.
- Balch CM, Soong SJ, Gershenwald JE et al. Prognostic factors analysis of 17,600 melanoma patients: Validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol* 2001;19:3622–3634.
- Hussein MR. Extracutaneous malignant melanomas. *Cancer Invest* 2008;26:516–534.
- Lui P, Cashin R, Machado M et al. Treatments for metastatic melanoma: Synthesis of evidence from randomized trials. *Cancer Treat Rev* 2007;33:665–680.
- Serrone L, Zeuli M, Sega FM et al. Dacarbazine-based chemotherapy for metastatic melanoma: Thirty-year experience overview. *J Exp Clin Cancer Res* 2000;19:21–34.
- Chapman PB, Einhorn LH, Meyers ML et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol* 1999;17:2745–2751.
- Ahmann DL, Creagan ET, Hahn RG et al. Complete responses and long-term survivals after systemic chemotherapy for patients with advanced malignant melanoma. *Cancer* 1989;63:224–227.
- Newlands ES, Stevens MF, Wedge SR et al. Temozolomide: A review of its discovery, chemical properties, pre-clinical development and clinical trials. *Cancer Treat Rev* 1997;23:35–61.
- Middleton MR, Grob JJ, Aaronson N et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000;18:158–166.
- Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
- Legha SS, Ring S, Eton O et al. Development of a biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2 for patients with metastatic melanoma. *J Clin Oncol* 1998;16:1752–1759.
- Kalialis LV, Drzewiecki KT, Mohammadi M et al. Spontaneous regression of metastases from malignant melanoma: A case report. *Melanoma Res* 2008;18:279–283.
- Papac RJ. Spontaneous regression of cancer. *Cancer Treat Rev* 1996;22:395–423.
- Coates AS, Segelov E. Long term response to chemotherapy in patients with visceral metastatic melanoma. *Ann Oncol* 1994;5:249–251.
- Essner R. Surgical treatment of malignant melanoma. *Surg Clin North Am* 2003;83:109–156.
- Feun LG, Gutterman J, Burgess MA et al. The natural history of resectable metastatic melanoma (stage IVA melanoma). *Cancer* 1982;50:1656–1663.
- Overett TK, Shiu MH. Surgical treatment of distant metastatic melanoma. Indications and results. *Cancer* 1985;56:1222–1230.
- Wong JH, Skinner KA, Kim KA et al. The role of surgery in the treatment of nonregionally recurrent melanoma. *Surgery* 1993;113:389–394.
- Ollila DW, Caudle AS. Surgical management of distant metastases. *Surg Oncol Clin N Am* 2006;15:385–398.
- Hegi ME, Diserens AC, Gorlia T et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005;352:997–1003.
- Atkins MB, O'Boyle KR, Sosman JA et al. Multiinstitutional phase II trial of intensive combination chemoimmunotherapy for metastatic melanoma. *J Clin Oncol* 1994;12:1553–1560.
- Flaherty LE, Robinson W, Redman BG et al. A phase II study of dacarbazine and cisplatin in combination with outpatient administered interleukin-2 in metastatic malignant melanoma. *Cancer* 1993;71:3520–3525.
- Petrella T, Quirt I, Verma S et al. Single-agent interleukin-2 in the treatment of metastatic melanoma. *Curr Oncol* 2007;14:21–26.
- Petrella T, Quirt I, Verma S et al. Single-agent interleukin-2 in the treatment of metastatic melanoma: A systematic review. *Cancer Treat Rev* 2007;33:484–496.
- Atkins MB, Lotze MT, Dutcher JP et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 1999;17:2105–2116.