Published in final edited form as:
Hematol Oncol Clin North Am. 2009 June ; 23(3): 583–x. doi:10.1016/j.hoc.2009.03.006.

The History and Future of Chemotherapy for Melanoma

Arvin S. Yang, MD, PhD[a] and **Paul B. Chapman, MD**[a,b,*]

[a]Melanoma/Sarcoma Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

[b]Weill Medical College of Cornell University, New York, NY, USA

Abstract

Melanoma is considered a chemotherapy-resistant tumor, but in fact several chemotherapeutic agents show single-agent activity at the level of 10% to 15%, similar to the efficacy of the chemotherapeutic armamentarium used against other tumor types. Several combination chemotherapy regimens have been tested, but no survival benefit has been demonstrated. Few of these trials have been compared with standard dacarbazine (DTIC) in an adequately powered randomized trial, and even the largest of these trials were only powered to detect unrealistically large improvements in overall survival. In this article, the authors review past chemotherapy trials and the current state of chemotherapy for melanoma. Looking to the future, the authors are encouraged by recent observations that the addition of sorafenib to DTIC (or temozolomide) can increase response rates and survival. The authors suggest that this could form the core on which additional active chemotherapeutic drugs could be added with the hope of developing a regimen that improves overall survival. This paradigm of stepwise addition of active chemotherapeutic drugs has been successful in the development of chemotherapy regimens that improve survival in other solid tumor systems. In colon carcinoma, for example, the current regimens were built on fluorouracil (5FU)/leucovorin, which has similar activity to DTIC in melanoma. This could serve as a model for studies on melanoma.

Keywords

Dacarbazine; Temozolomide; Cisplatin; Sorafenib; Combination chemotherapy

SINGLE AGENTS AGAINST MELANOMA

Dacarbazine

DTIC has been considered the standard of care for metastatic melanoma since 1972 and can induce objective responses in some patients. It is a pro-drug that requires conversion in the liver to 5-(3-methyl-1-triazeno)imidazole-4-carboxamide (MTIC), the active compound. The typical DTIC dose is 850 to 1,000 mg/m^2 every 3 weeks.

Among the 8 randomized trials in which DTIC was used as a comparator arm since 1992, more than 1,000 patients have been treated with DTIC with an overall response rate of 13.4% and median survivals ranging from 5.6 months to 11 months (Table 1). Most of the responses were partial although complete responses did occur occasionally. Given the low response rate, it is unrealistic to expect DTIC to have an effect on median survival, but it is

*Corresponding author. Melanoma/Sarcoma Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. chapmanp@mskcc.org (P.B. Chapman)..

likely that there is an effect on survival in the responding patients. In considering the 5 trials in which 1-year survival was reported, the average overall 1-year survival rate was 27% (see Table 1). Thus, any new chemotherapy regimen for melanoma should aim for a response rate greater than 13.4%.

Temozolomide

Temozolomide (TMZ) is administered orally and, like DTIC, is a pro-drug that converts to the active compound, MTIC. Unlike DTIC, TMZ does not require the liver for conversion to MTIC. In a randomized trial comparing TMZ given for 5 days every month with DTIC given once every 3 weeks, there was no difference in response rate or survival.[1]

Despite this, TMZ offers 2 potential advantages over DTIC. TMZ readily crosses the intact blood-brain barrier and can then convert to MTIC raising the possibility that TMZ would have enhanced activity against brain metastases. Unfortunately, the objective response rate of melanoma brain metastases to TMZ is low,[2] although there is some indication that treatment with TMZ is associated with a lower incidence of progression of disease in the brain.[3,4]

Another potential advantage of TMZ is that, as an oral agent, continuous dosing is feasible. An extended-dosing schedule of 75 mg/m^2/day for 42 days followed by 14 days off has been used in several clinical trials. This schedule provides 6 weeks of continuous drug exposure and delivers 50% more drug over 2 months compared with the standard schedule of 5 days every month. However, a phase II trial using extended-dosing TMZ showed only a 12.5% response rate,[5] which is not different from what would be expected with standard-dosing TMZ or with DTIC.

Several investigators have looked into the mechanism of TMZ resistance. One of the methylation targets of TMZ is the O^6 position of guanine, which is repaired by the enzyme methylguanine methyltransferase (MGMT). Loss of MGMT expression, as measured by *MGMT* promoter methylation, has been correlated with an improved response rate to TMZ in glioblastoma[6] and glioma,[7] and with progression-free survival in glioblastoma.[6] However, in melanoma patients, it has not been possible to detect a correlation between response to DTIC or TMZ and loss of MGMT tumor expression.[5,8,9] Efforts to inhibit MGMT have not been successful to date.[10,11] This experience suggests that in melanoma, mechanisms other than MGMT expression are important for TMZ resistance.

Platinum Analogs

Cisplatin—Cisplatin has significant single-agent activity in melanoma ranging from 10% to more than 20%[12-15] with an average of 14.4% (Table 2). There is some suggestion that doses of less than 80 mg/m^2 are associated with lower response rates compared with doses of more than 80 mg/m^2, although this has not been tested in a randomized setting. High doses of cisplatin (≥150 mg/m^2) have generally not been associated with improved response rates.[16]

Carboplatin—Carboplatin has been tested in 3 phase II clinical trials and found to have a response rate similar to cisplatin in melanoma patients (see Table 2). Casper treated 43 patients with 400 mg/m^2 carboplatin every 4 weeks and noted 7 overall responders (16%) with 1 complete response lasting 16 months.[17] Additional phase II testing with the same dosing and schedule demonstrated an 11% overall response rate with 3 out of 27 patients responding with a medium survival of 4.7 months.[18] Similar data were obtained by Evans[19] in a phase II trial, in which 5 out of 26 evaluable (19%) patients responded to 400 mg/m^2 carboplatin every 4 weeks. Currently, carboplatin is administered at a dose calculated to

result in an area-under-the-concentration curve (AUC) of 5 or 6 mg min/mL, although there are no single-agent data testing carboplatin using this dosing method for melanoma. Myelosuppression is the main adverse effect; thrombocytopenia is a dose-limiting toxicity.

Nitrosoureas

Carmustine (BCNU), lomustine (CCNU), and fotemustine all have single-agent activity in melanoma (see Table 2). BCNU has shown response rates ranging from 10% to 20%.[20-22] Fotemustine, a nitrosourea available in Europe, may be the most active, with response rates over multiple clinical trials averaging 22%.[23-26] In addition, although nitrosoureas are lipid-soluble and cross the blood-brain barrier, only fotemustine was found to have a 25% response rate for cerebral metastasis.[24] In a phase III clinical trial of fotemustine (100 mg/m^2 weekly for 3 weeks) versus DTIC (250 mg/m^2/day for 5 days every 4 weeks), the response rate for fotemustine was 15.2% versus 6.8% for DTIC.[27] The median time to brain metastasis was 22.7 months for fotemustine versus 7.2 months for DTIC. Toxicities associated with nitrosoureas include myelosuppression, which can be prolonged, and gastrointestinal toxicities.

Taxanes

Docetaxel—Preclinical studies indicate that taxanes disturb the cytoskeleton architecture and stabilize microtubules causing mitotic arrest. Docetaxel showed an average response rate of 11.4% in 3 phase II clinical trials (see Table 2). Enzig administered 100 mg/m^2 docetaxel every 3 weeks to chemotherapy naive patients. Two out of 35 (6%) patients responded with 1 complete response. Both these responses lasted longer than 2 years.[28] Using the same dosing and schedule, a second trial was performed at MD Anderson with 5 out of 40 (12.5%) patients responding, with 1 complete response and overall median survival time of 13 months.[29] In a third phase II clinical trial, 38 patients were also treated with 100 mg/m^2 docetaxel every 3 weeks and evaluated after 2 cycles; 5 partial responses were noted in the 30 evaluable patients (17%).[30] In these studies the most common hematological toxicity was neutropenia. Additional toxicities included peripheral neuropathy, fatigue, fluid retention, oral mucositis, and hypersensitivity reactions.

Paclitaxel—Multiple phase I/II trials have been carried out with differing dosing schedules for paclitaxel (see Table 2). In a phase I trial with paclitaxel administered at 200 to 275 mg/m^2 over 24 hours every 3 weeks, there were 4 partial responses noted in the 12 patients enrolled.[31] A phase II trial with paclitaxel administered at 250 mg/m^2 over 24 hours every 3 weeks in 25 patients resulted in 3 partial responses (12%); a further 4 patients had durable objective regression although failing to qualify for partial response.[32] An additional 28 evaluable patients were studied in a second phase II study of paclitaxel administered at 250 mg/m^2 over 24 hours. Four patients (14%) had objective responses with 3 complete responses.[33] Weekly paclitaxel has also been tested in phase II clinical trials but with little success. A phase II study with paclitaxel administered at 80 mg/m^2 over 1 hour weekly for 3 weeks every 4-week cycle had no responses in the 25 patients enrolled.[34] However, 8 patients showed stable disease. A phase II trial performed with paclitaxel administered at 90 mg/m^2 on days 1, 5, and 9 every 3 weeks demonstrated a 15.6% response in 5/32 patients.[35] In general, toxicities associated with paclitaxel included neutropenia, peripheral neuropathy, which can be a dose-limiting toxicity, and fatigue.

Chemotherapy Drugs with Little Activity in Melanoma

Some chemotherapy drugs have been tested and found to have little activity against melanoma. In a phase II study, 30 mg/m^2 of melphalan was given to 17 patients with melanoma with a median of 2 cycles administered without any responses.[36] Phase II studies

with ifosfamide have also been disappointing. Of 12 metastatic melanoma patients, none responded to 3 g/m^2 ifosfamide administered on days 1 and 2 every 3 weeks.[37] Multiple clinical trials concluded that camptothecans have minimal activity in the treatment of metastatic melanoma. Only 3 patients with metastatic melanoma responded out of 72 (4%) cumulative patients treated in 4 phase I/II clinical trials with irinotectan or topotecan single agent or in combination with docetaxel.[38-41] Combining 4 phase II trials with doxorubicin, only 4 out of 90 (4%) patients with metastatic melanoma responded to liposomal doxorubicin.[42-45]

ADDITION OF ANTIANGIOGENIC DRUGS TO DACARBAZINE OR TEMOZOLOMIDE

Because tumors larger than 1 mm must recruit blood vessels to grow, antiangiogenic drugs were anticipated to have single-agent activity, although in melanoma, these agents have shown fairly limited activity so far. However, one thought was to combine these drugs with active chemotherapy agents. Hwu and colleagues tested whether the activity of extended-dosing TMZ could be enhanced by adding 1 of 2 weak antiangiogenic agents: thalidomide or interferon-α2b. Although these drugs have little activity against melanoma as single agents, phase II trials combining either thalidomide or low-dose interferon-α with extended-dose TMZ demonstrated objective response rates of approximately 30%.[46,47] This result, seen in two trials, was twice the response rate observed with extended-dose TMZ alone (see Table 2) and suggested the potential value of the addition of an antiangiogenic drug to TMZ. Subsequent studies with TMZ and thalidomide have reported high rates of thromboembolic events indicating that thalidomide's therapeutic index may be too narrow in melanoma patients.

Sorafenib is a tyrosine kinase inhibitor that has activity against VEGFR and BRAF. Like bevacizumab, thalidomide, and interferon-α, sorafenib has little activity as a single agent in melanoma. However, in a trial of 101 patients with melanoma randomized to DTIC ± sorafenib, the combination of DTIC + sorafenib was associated with a doubling of the response rate, a doubling of the median progression-free survival, and a 50% improvement in progression-free survival at 9 months.[48] With only 101 patients, it is not surprising that this improved response rate and progression-free survival rate were not associated with a detectable improvement in overall survival. Results of trials with TMZ and sorafenib, published only in abstract form to date, show similar results; the addition of sorafenib was associated with a response rate of 26%.[49]

The observations from phase II trials of TMZ combined with thalidomide or interferon-α as well as a randomized trial of DTIC ± sorafenib are consistent with the idea that combining TMZ or DTIC with an antiangiogenic drug can double the objective response rate. With further improvement in the response rate, or with larger trials, an improvement in overall survival should be possible.

COMBINATION CHEMOTHERAPY REGIMENS

Because there are several chemotherapy drugs that have single-agent activity in melanoma (discussed earlier), there is rationale for combining drugs into combination regimens. Many of the combination regimens tested in melanoma have combined DTIC with immunologic agents (eg, interferon, interleukin-2), hormones (eg, tamoxifen), or novel biologic agents such as bcl-2 antisense each of which individually have shown little single-agent activity. In this section, some of the common combinations of cytotoxic chemotherapeutic regimens used in melanoma are discussed and the few phase III randomized trials that have been published are highlighted.

Dacarbazine/Carmustine/Cisplatin/Tamoxifen (Dartmouth Regimen)

This regimen was first described in 1984 and a 55% response rate was observed in 20 melanoma patients.[50] A subsequent series of single institution studies confirmed high response rates of 40% to 50%.[51-54] Some reports suggested that the addition of tamoxifen was important for the high response rate even though tamoxifen has no single-agent activity in melanoma; other reports did not agree.[55] A multi-institutional, phase III randomized trial compared the Dartmouth regimen directly to single-agent DTIC in 240 patients with metastatic melanoma.[56] The response rate was 18.5% in the combination chemotherapy cohort compared with 10.2% in the DTIC cohort. Although this difference was not statistically significant ($P = .09$), there was a statistically significant increase in response rate associated with the combination regimen among the cohort of patients with M1a or M1b disease. There was no significant difference in survival in this trial powered to detect a 50% improvement in median overall survival.

Subsequently, a smaller randomized trial was reported that compared this combination to DTIC/interferon-α.[57] This trial showed a higher response rate in the experimental and control arms (26.4% versus 17.3%) but the difference was not statistically significant. The trial also failed to show a statistically significant improvement in overall or 1-year survival.

Cisplatin/Vinblastine/Dacarbazine

Cisplatin/vinblastine/dacarbazine (CVD), a combination chemotherapy regimen developed at the MD Anderson Cancer Center, consists of 3-week cycles of cisplatin 20 mg/m^2/day × 4; vinblastine 2 mg/m^2/day × 4, and DTIC 800 mg/m^2 on day 1. In a single institution phase II trial with 50 evaluable patients, a response rate of 40% was achieved with an estimated 1-year survival of 50%.[58] In a randomized trial against biochemotherapy in which CVD was the control arm, the same investigators reported that CVD showed an objective response rate of 27% and an estimated 1-year survival of approximately 40%.[59] This single institution experience shows that the regimen is associated with a response rate 2 to 3 times higher than with DTIC and a 1-year survival rate twice as high as DTIC. Of course, it is difficult to control for patient selection bias and there has been no peer-reviewed published study comparing the CVD regimen to DTIC.

Carboplatin/Paclitaxel

Preclinical studies support synergistic actions between cisplatin and paclitaxel,[60] and this combination has shown some clinical activity in melanoma in chemotherapy-naive patients. A combination of carboplatin at an AUC of 7.5 and paclitaxel at 175 mg/m^2 over 3 hours was administered to 17 patients in a phase II trial.[61] There was a 20% response rate with 3 partial responders in the 15 evaluable patients, with a median survival of 9 months. Grade III or IV hematological toxicities occurred in 11/15 (73%) of those treated during the clinical study. A larger phase II study for second line therapy revealed few responses.[62] In this randomized trial, paclitaxel monotherapy was administered at 100 mg/m^2 weekly for 6 weeks then 2 weeks off, versus paclitaxel 80 mg/m^2 and carboplatin 200 mg/m^2 weekly for 6 weeks and 2 weeks off. Forty patients were enrolled and overall response rates were less than 10% for both arms. More recently, albumin-bound paclitaxel has also been tested with carboplatin in a phase I trial with 3 out of 10 treated patients obtaining a partial response.[63]

Recently, sorafenib has been tested in combination with carboplatin and paclitaxel. A phase I trial with 38 patients (24 with melanoma, most having progressed after prior therapy) received sorafenib either 100, 200, or 400 mg twice daily on days 2 to 19 of a 21-day cycle with carboplatin at AUC 6 and paclitaxel at 225 mg/m^2 administered on day 1.[64] The overall response was 10 out of 24 treated patients with 1 complete response. These encouraging response rates prompted 2 phase III trials of carboplatin and paclitaxel with or without

sorafenib. The first trial treated 270 patients who had previously progressed on systemic chemotherapy with paclitaxel at 225 mg/m^2 and carboplatin at AUC 6 once every 3 weeks with or without sorafenib at 400 mg twice daily on days 2 to 19. There was no difference in progression-free survival, which was the primary endpoint, or in response rate.[65] The control group (no sorafenib) showed a response rate of 11% with a median progression-free survival of 17.4 weeks; the median overall survival was 42 weeks. The cohort receiving sorafenib had essentially identical outcomes. That the addition of sorafenib to carboplatin/paclitaxel did not improve response rate contrasts with the original observations in the phase I trial[64] and with the observations of McDermott who showed that sorafenib doubled the response rate to DTIC.[48] This difference may be explained by the different chemotherapy regimens or by the fact that the DTIC/sorafenib patients were chemotherapy-naive. A second, larger phase III cooperative group trial randomizing previously untreated melanoma patients to carboplatin and paclitaxel with or without sorafenib has finished accrual and is awaiting the results of overall survival as the primary endpoint.

Myeloablative Chemotherapy Regimens with Autologous Bone Marrow Rescue

The concept of combination chemotherapy has been pushed to the extreme by several investigators who explored the use of myeloablative chemotherapy using alkylating agents at potentially lethal doses followed by autologous bone marrow rescue.[66-77] Among 263 evaluable patients with metastatic melanoma in 12 studies, there was an overall response rate of 52% with individual trials showing response rates ranging from 22% to 61% (Fig. 1). There were 33 reported complete responders (12.5% complete response rate) but the duration of the complete response was generally short. Few complete responders maintained a complete response longer 12 months.[67,69] This experience confirms that alkylating agents can induce responses in up to half of melanoma patients if the doses are sufficiently high. However, complete responses remain infrequent and are generally short-lived.

Phase III Trials of Combination Chemotherapy in Melanoma

Although many phase III trials have been published comparing combination therapy with DTIC, this article focuses only on the trials comparing combination chemotherapy with DTIC. Of the combination chemotherapy regimens tested in melanoma over the past 30 years, there are only three published randomized trials comparing with DTIC that have accrued at least 50 patients in each cohort. As noted earlier, the Dartmouth regimen was compared with DTIC and showed an increased objective response rate but no overall survival benefit.[56] The trial was sufficiently powered to detect a 50% improvement in survival.

A second randomized trial was a 3-armed trial in which patients were treated with either DTIC/Bacillus Calmette-Guerin (BCG) (N = 130), or DTIC/bleomycin/hydroxyurea/BCG (N = 161), or the combination without BCG (N = 95).[78] Patients receiving combination chemotherapy had a 29% response rate compared with an 18% response rate in the DTIC cohort, which was a statistically significant difference; BCG had no detectable effects on response. With this number of patients, the trial was sufficiently powered to detect a median survival difference of approximately 50%. Perhaps not surprisingly, there was no overall survival difference observed although responders showed significantly improved survival over nonresponders.

A third trial compared DTIC with DTIC + vindesine.[79] In that trial, 9/51 (18%) patients treated with DTIC responded compared with 15/59 (25%) of patients treated with the combination. The difference was not statistically significant nor was the difference in median survival, although again, responders showed significantly improved median survival over nonresponders (11.7 versus. 3.4 months; $P < .0001$).

These 3 randomized trials showed that combination chemotherapy induced objective responses more frequently than DTIC although the response rates were still less than 30%. Neither of the 2 trials that looked at overall survival was able to detect a benefit in median overall survival, but neither was powered to detect a difference of less than 50%. It seems unlikely that chemotherapy regimens with objective response rates this low would be associated with a 50% improvement in median overall survival. It is possible that these regimens can improve median overall survival by a smaller margin, but much larger studies would have been needed to detect this.

ADJUVANT CHEMOTHERAPY FOR MELANOMA

The role of adjuvant chemotherapy in melanoma has been recently reviewed.[80] In other tumor types in which adjuvant chemotherapy has been shown to improve median overall survival, the magnitude of improvement ranged from 4% to 35%. Thus, adjuvant trials in melanoma should be powered to detect small improvements in overall survival. To detect even a 30% improvement in survival with 80% power, a 2-arm adjuvant trial would need more than 500 patients. In addition, active adjuvant chemotherapy regimens generally have activity in the metastatic setting of at least 20%. Thus, the guiding principles for developing adjuvant chemotherapy in melanoma should be a regimen associated with at least a 20% response rate.

Given the requirements of a treatment regimen with at least a 20% response rate and a clinical trial design with at least 500 patients, there has not yet been a realistic test of adjuvant chemotherapy in melanoma patients. The trial that comes closest to an adequate test was reported by Veronesi and colleagues[81] published 25 years ago. In this 4-arm study, 761 patients were randomized to DTIC, BCG, DTIC 1 BCG, or observation after complete surgical resection. There was no survival difference at 3 years. Even this trial does not meet the requirements of adequate statistical power or of an adequately active treatment regimen. Although this is the largest adjuvant chemotherapy trial on melanoma, it only had the power to detect a benefit of at least 50% improvement in survival – clearly outside what has ever been seen in other tumor types. As noted earlier, the response rate of DTIC in the metastatic setting is less than 20%.

Other adjuvant chemotherapy trials have been reported but these were so under-powered as to be uninformative. Adjuvant chemotherapy trials in melanoma should not be carried out unless they use a regimen with at least a 20% response rate in the metastatic setting and are adequately powered to be able to detect improvements in overall survival as small as 30%.

THE FUTURE

DTIC (or TMZ) remains the standard chemotherapy treatment of metastatic melanoma although it is not known if there is a small overall survival benefit associated with treatment. Combination chemotherapy regimens can induce objective responses in a higher proportion of patients than DTIC alone although the 2 largest randomized trials did not detect an overall survival benefit compared with DTIC. Because these trials were powered only to detect a large difference in survival (>50%), it remains possible that combination chemotherapy can improve survival by a smaller margin. However, larger studies with at least 400 patients per cohort would be needed to detect these small benefits. One option to develop combination chemotherapy regimens that improve overall survival would be to conduct randomized trials using active combinations with a sufficient number of patients to detect a realistic improvement in survival. Studies of this size have been difficult to conduct on melanoma. Indeed, the largest randomized trial ever conducted on melanoma had a total of 771 patients.[82] Therefore, although current combination chemotherapy regimens might be

associated with a small improvement in overall survival, it seems unlikely that the melanoma community will be able to conduct a trial large enough to test this hypothesis.

Another option would be to develop a combination treatment with a higher response rate that would be expected to improve overall survival to a level more easily detected. The experience with metastatic colon cancer may be useful. Since the 1960s, 5FU had been the standard therapy, which, like DTIC, induced responses in less than 15% of patients but was not believed to improve overall survival. The addition of leucovorin, a drug with no single-agent activity itself, almost doubled the objective response rate but it still was not clear if this improved overall survival. This may be analogous to the recent observations that addition of sorafenib to DTIC or to TMZ can double the response rate in metastatic melanoma but may not affect overall survival. Building on 5FU/leucovorin, the colon cancer community added chemotherapy drugs that had 10% single-agent activity: oxaliplatin or irinotecan. This further increased the response rate to the point that a benefit in overall survival could be demonstrated. However, to detect these improvements, the randomized trials had 695 and 795 patients, respectively. In the melanoma field, we might build on the results with DTIC/sorafenib by adding either cisplatin or carboplatin. This stepwise approach could lead us to a combination chemotherapy regimen that improves overall survival but larger randomized trials than in the past must be run to detect important improvements in overall survival.

A third option is to focus on responders. Most investigators have observed that patients who respond to therapy live longer. Many have rejected these observations arguing that this observation could be explained by selection bias and that patients who tolerate and respond to therapy are more likely to live longer anyway. However, survival improvement among responders has been reported in several randomized chemotherapy trials[78,79,83] in which this bias would not exist. There are long-term survivors among responders, which is not seen in untreated patients.

This cohort of responding patients should be studied to understand why they respond to treatment. There are currently many genetic tools that allow us to genotype tumors (or patients) before therapy and then see which genetic changes correlate with response to treatment. This approach is being used with so-called “targeted therapy” agents and is beginning to be used for chemotherapy in other tumor types. Instead of considering the small proportion of melanoma patients who respond to treatment as statistical aberrations, they should be viewed as consistent but low frequency events worthy of study that could give us clues leading to improved therapy.

REFERENCES

1. 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; 18:158–66. [PubMed: 10623706]
2. Margolin K, Atkins B, Thompson A, et al. Temozolomide and whole brain irradiation in melanoma metastatic to the brain: a phase II trial of the Cytokine Working Group. J Cancer Res Clin Oncol. 2002; 128:214–8. [PubMed: 11935312]
3. Atkins MB, Gollob JA, Sosman JA, et al. A phase II pilot trial of concurrent biochemotherapy with cisplatin, vinblastine, temozolomide, interleukin 2, and IFN-alpha 2B in patients with metastatic melanoma. Clin Cancer Res. 2002; 8:3075–81. [PubMed: 12374674]
4. Paul MJ, Summers Y, Calvert AH, et al. Effect of temozolomide on central nervous system relapse in patients with advanced melanoma. Melanoma Res. 2002; 12:175–8. [PubMed: 11930115]
5. Rietschel P, Wolchok JD, Krown S, et al. Phase II study of extended-dose temozolomide in patients with melanoma. J Clin Oncol. 2008; 26:2299–304. [PubMed: 18467721]

6. Hegi ME, Diserens A-C, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005; 352:997–1003. 10.1056/NEJMoa043331. [PubMed: 15758010]
7. Paz MF, Yaya-Tur R, Rojas-Marcos I, et al. CpG island hypermethylation of the DNA repair enzyme methyltransferase predicts response to temozolomide in primary gliomas. Clin Cancer Res. 2004; 10:4933–8. [PubMed: 15297393]
8. Ma S, Egyhazi S, Ueno T, et al. O6-methylguanine-DNA-methyltransferase expression and gene polymorphisms in relation to chemotherapeutic response in metastatic melanoma. Br J Cancer. 2003; 89:1517–23. [PubMed: 14562026]
9. Middleton MR, Lunn JM, Morris C, et al. O6-methylguanine-DNA methyltransferase in pretreatment tumour biopsies as a predictor of response to temozolomide in melanoma. Br J Cancer. 1998; 78:1199–202. [PubMed: 9820180]
10. Ranson M, Hersey P, Thompson D, et al. Randomized trial of the combination of lomeguatrib and temozolomide compared with temozolomide alone in chemotherapy naive patients with metastatic cutaneous melanoma. J Clin Oncol. 2007; 25:2540–5. 10.1200/JCO.2007.10.8217. [PubMed: 17577032]
11. Gajewski TF, Sosman J, Gerson SL, et al. Phase II trial of the O6-alkylguanine DNA alkyltransferase inhibitor O6-benzylguanine and 1,3-bis(2-chloroethyl)-1-_nitrosourea in advanced melanoma. Clin Cancer Res. 2005; 11:7861–5. [PubMed: 16278409]
12. Al-Sarraf M, Fletcher W, Oishi N, et al. Cisplatin hydration with and without mannitol diuresis in refractory disseminated malignant melanoma: a Southwest Oncology Group study. Cancer Treat Rep. 1982; 66:31–5. [PubMed: 6796269]
13. Goodnight JE Jr, Moseley HS, Eilber FR, et al. cis-Dichlorodiammineplatinum(II) alone and combined with DTIC for treatment of disseminated malignant melanoma. Cancer Treat Rep. 1979; 63:2005–7. [PubMed: 393385]
14. Schilcher RB, Wessels M, Niederle N, et al. Phase II evaluation of fractionated low and single high dose cisplatin in various tumors. J Cancer Res Clin Oncol. 1984; 107:57–60. [PubMed: 6538200]
15. Chary KK, Higby DJ, Henderson ES, et al. Phase I study of high-dose cis-dichlorodiammineplatinum(II) with forced diuresis. Cancer Treat Rep. 1977; 61:367–70. [PubMed: 266972]
16. Steffens T, Bajorin D, Chapman P, et al. A phase II trial of high dose cisplatin and dacarbazine. Cancer. 1991; 68:1230–7. [PubMed: 1873774]
17. Casper ES, Bajorin D. Phase II trial of carboplatin in patients with advanced melanoma. Invest New Drugs. 1990; 8:187–90. [PubMed: 1696568]
18. Chang A, Hunt M, Parkinson DR, et al. Phase II trial of carboplatin in patients with metastatic malignant melanoma. A report from the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1993; 16:152–5. [PubMed: 8452109]
19. Evans LM, Casper ES, Rosenbluth R. Phase II trial of carboplatin in advanced malignant melanoma. Cancer Treat Rep. 1987; 71:171–2. [PubMed: 3542209]
20. Ramirez G, Wilson W, Grage T, et al. Phase II evaluation of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU; NSC-409962) in patients with solid tumors. Cancer Chemother Rep. 1972; 56:787–90. [PubMed: 4574056]
21. De Vita VT, Carbone PP, Owens AH Jr, et al. Clinical trials with 1,3-bis(2-chloroethyl)-1-nitrosourea, NSC-409962. Cancer Res. 1965; 25:1876–81. [PubMed: 5858571]
22. Luce JK. Chemotherapy of malignant melanoma. Cancer. 1972; 30:1604–15. [PubMed: 4565819]
23. Calabresi F, Aapro M, Becquart D, et al. Short report: multicenter phase II trial of the single agent fotemustine in patients with advanced malignant melanoma. Ann Oncol. 1991; 2:377–8. [PubMed: 1954183]
24. Jacquillat C, Khayat D, Banzet P, et al. Final report of the French multicenter phase II study of the nitrosourea fotemustine in 153 evaluable patients with disseminated malignant melanoma including patients with cerebral metastases. Cancer. 1990; 66:1873–8. [PubMed: 2224783]
25. Kleeberg UR, Engel E, Israels P, et al. Palliative therapy of melanoma patients with fotemustine. Inverse relationship between tumour load and treatment effectiveness. A multicentre phase II trial of the EORTC-Melanoma Cooperative Group (MCG). Melanoma Res. 1995; 5:195–200. [PubMed: 7543785]

26. Schallreuter KU, Wenzel E, Brassow FW, et al. Positive phase II study in the treatment of advanced malignant melanoma with fotemustine. Cancer Chemother Pharmacol. 1991; 29:85–7. [PubMed: 1742855]
27. Avril MF, Aamdal S, Grob JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol. 2004; 22:1118–25. [PubMed: 15020614]
28. Einzig AI, Schuchter LM, Recio A, et al. Phase II trial of docetaxel (Taxotere) in patients with metastatic melanoma previously untreated with cytotoxic chemotherapy. Med Oncol. 1996; 13:111–7. [PubMed: 9013474]
29. Bedikian AY, Weiss GR, Legha SS, et al. Phase II trial of docetaxel in patients with advanced cutaneous malignant melanoma previously untreated with chemotherapy. J Clin Oncol. 1995; 13:2895–9. [PubMed: 8523052]
30. Aamdal S, Wolff I, Kaplan S, et al. Docetaxel (Taxotere) in advanced malignant melanoma: a phase II study of the EORTC Early Clinical Trials Group. Eur J Cancer. 1994; 30A:1061–4. [PubMed: 7654429]
31. Wiernik PH, Schwartz EL, Einzig A, et al. Phase I trial of taxol given as a 24-hour infusion every 21 days: responses observed in metastatic melanoma. J Clin Oncol. 1987; 5:1232–9. [PubMed: 2887641]
32. Legha SS, Ring S, Papadopoulos N, et al. A phase II trial of taxol in metastatic melanoma. Cancer. 1990; 65:2478–81. [PubMed: 1970948]
33. Einzig AI, Hochster H, Wiernik PH, et al. A phase II study of taxol in patients with malignant melanoma. Invest New Drugs. 1991; 9:59–64. [PubMed: 1673965]
34. Walker L, Schalch H, King DM, et al. Phase II trial of weekly paclitaxel in patients with advanced melanoma. Melanoma Res. 2005; 15:453–9. [PubMed: 16179874]
35. Bedikian AY, Plager C, Papadopoulos N, et al. Phase II evaluation of paclitaxel by short intravenous infusion in metastatic melanoma. Melanoma Res. 2004; 14:63–6. [PubMed: 15091196]
36. Hochster H, Strawderman MH, Harris JE, et al. Conventional dose melphalan is inactive in metastatic melanoma: results of an Eastern Cooperative Oncology Group Study (E1687). Anticancer Drugs. 1999; 10:245–8. [PubMed: 10211556]
37. Negretti E, Ferrari L, Bonfante V, et al. Phase II study with ifosfamide in advanced malignant melanoma. Tumori. 1988; 74:163–5. [PubMed: 3368970]
38. Dumez H, Awada A, Piccart M, et al. A phase I dose-finding clinical pharmacokinetic study of an oral formulation of irinotecan (CPT-11) administered for 5 days every 3 weeks in patients with advanced solid tumours. Ann Oncol. 2006; 17:1158–65. [PubMed: 16600980]
39. Tas F, Camlica H, Kurul S, et al. Combination chemotherapy with docetaxel and irinotecan in metastatic malignant melanoma. Clin Oncol (R Coll Radiol). 2003; 15:132–5. [PubMed: 12801051]
40. Janik JE, Miller LL, Korn EL, et al. A prospective randomized phase II trial of GM-CSF priming to prevent topotecan-induced neutropenia in chemotherapy-naivepatients with malignant melanoma or renal cell carcinoma. Blood. 2001; 97:1942–6. [PubMed: 11264156]
41. Kraut EH, Walker MJ, Staubus A, et al. Phase II trial of topotecan in malignant melanoma. Cancer Invest. 1997; 15:318–20. [PubMed: 9246152]
42. Vorobiof DA, Rapoport BL, Mahomed R, et al. Phase II study of pegylated liposomal doxorubicin in patients with metastatic malignant melanoma failing standard chemotherapy treatment. Melanoma Res. 2003; 13:201–3. [PubMed: 12690306]
43. Smylie MG, Wong R, Mihalcioiu C, et al. A phase II, open label, monotherapy study of liposomal doxorubicin in patients with metastatic malignant melanoma. Invest New Drugs. 2007; 25:155–9. [PubMed: 16957835]
44. Fink W, Zimpfer-Rechner C, Thoelke A, et al. Clinical phase II study of pegylated liposomal doxorubicin as second-line treatment in disseminated melanoma. Onkologie. 2004; 27:540–4. [PubMed: 15591712]
45. Ellerhorst JA, Bedikian A, Ring S, et al. Phase II trial of doxil for patients with metastatic melanoma refractory to frontline therapy. Oncol Rep. 1999; 6:1097–9. [PubMed: 10425308]

46. Hwu WJ, Krown SE, Menell JH, et al. Phase II study of temozolomide plus thalidomide for the treatment of metastatic melanoma. J Clin Oncol. 2003; 21:3351–6. [PubMed: 12947072]
47. Hwu WJ, Panageas KS, Menell JH, et al. Phase II study of temozolomide plus pegylated interferon-alpha-2b for metastatic melanoma. Cancer. 2006; 106:2445–51. [PubMed: 16639739]
48. McDermott DF, Sosman JA, Gonzalez R, et al. Double-blind randomized phase II study of the combination of sorafenib and dacarbazine in patients with advanced melanoma: a report from the 11715 Study Group. J Clin Oncol. 2008; 26:2178–85. [PubMed: 18445842]
49. Amaravadi R, Schuchter LM, McDermott DF, et al. Updated results of a randomized phase II study comparing two schedules of temozolomide in combination with sorafenib in patients with advanced melanoma. Proc Am Soc Clin Oncol. 2007; 25:8527.
50. Del Prete SA, Maurer LH, O'Donnell J, et al. Combination chemotherapy with cisplatin, carmustine, dacarbazine, and tamoxifen in metastatic melanoma. Cancer Treat Rep. 1984; 68:1403–5. [PubMed: 6541973]
51. McClay EF, Mastrangelo MJ, Berd D, et al. Effective combination chemo/hormonal therapy for malignant melanoma: experience with three consecutive trials. Int J Cancer. 1992; 50:553–6. [PubMed: 1537621]
52. Saba HI, Cruse CW, Wells KE, et al. Treatment of stage IV malignant melanoma with dacarbazine, carmustine, cisplatin, and tamoxifen regimens: a University of South Florida and H. Lee Moffitt Melanoma Center Study. Ann Plast Surg. 1992; 28:65–9. [PubMed: 1642409]
53. Richards JM, Gilewski TA, Ramming K, et al. Effective chemotherapy for melanoma after treatment with interleukin-2. Cancer. 1992; 69:427–9. [PubMed: 1728371]
54. Lattanzi SC, Tosteson T, Chertoff J, et al. Dacarbazine, cisplatin and carmustine, with or without tamoxifen, for metastatic melanoma: 5-year follow-up. Melanoma Res. 1995; 5:365–9. [PubMed: 8541728]
55. Rusthoven JJ, Quirt IC, Iscoe NA, et al. National Cancer Institute of Canada Clinical Trials Group. Randomized, double-blind, placebo-controlled trial comparing the response rates of carmustine, dacarbazine, and cisplatin with and without tamoxifen in patients with metastatic melanoma. J Clin Oncol. 1996; 14:2083–90. [PubMed: 8683240]
56. 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; 17:2745–51. [PubMed: 10561349]
57. Middleton MR, Lorigan P, Owen J, et al. A randomized phase III study comparing dacarbazine, BCNU, cisplatin and tamoxifen with dacarbazine and interferon in advanced melanoma. Br J Cancer. 2000; 82:1158–62. [PubMed: 10735499]
58. Legha SS, Ring S, Papadopoulos N, et al. A prospective evaluation of a triple-drug regimen containing cisplatin, vinblastine, and dacarbazine (CVD) for metastatic melanoma. Cancer. 1989; 64:2024–9. [PubMed: 2804890]
59. Eton O, Legha SS, Bedikian AY, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. J Clin Oncol. 2002; 20:2045–52. [PubMed: 11956264]
60. Jekunen AP, Christen RD, Shalinsky DR, et al. Synergistic interaction between cisplatin and taxol in human ovarian carcinoma cells in vitro. Br J Cancer. 1994; 69:299–306. [PubMed: 7905279]
61. Hodi FS, Soiffer RJ, Clark J, et al. Phase II study of paclitaxel and carboplatin for malignant melanoma. Am J Clin Oncol. 2002; 25:283–6. [PubMed: 12040289]
62. Zimpfer-Rechner C, Hofmann U, Figl R, et al. Randomized phase II study of weekly paclitaxel versus paclitaxel and carboplatin as second-line therapy in disseminated melanoma: a multicentre trial of the Dermatologic Co-operative Oncology Group (DeCOG). Melanoma Res. 2003; 13:531–6. [PubMed: 14512795]
63. Stinchcombe TE, Socinski MA, Walko CM, et al. Phase I and pharmacokinetic trial of carboplatin and albumin-bound paclitaxel, ABI-007 (Abraxane) on three treatment schedules in patients with solid tumors. Cancer Chemother Pharmacol. 2007; 60:759–66. [PubMed: 17285317]
64. Flaherty KT, Schiller J, Schuchter LM, et al. A phase I trial of the oral, multikinase inhibitor sorafenib in combination with carboplatin and paclitaxel. Clin Cancer Res. 2008; 14:4836–42. [PubMed: 18676756]

65. Hauschild A, Agarwala SS, Trefzer U, et al. Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. J Clin Oncol. in press.
66. McElwain TJ, Hedley DW, Gordon MY, et al. High dose melphalan and non-cry-opreserved autologous bone marrow treatment of malignant melanoma and neuroblastoma. Exp Hematol. 1979; 7(Suppl 5):360–71. [PubMed: 400698]
67. Thomas MR, Robinson WA, Glode LM, et al. Treatment of advanced malignant melanoma with high-dose chemotherapy and autologous bone marrow transplantation. Preliminary results-Phase I study. Am J Clin Oncol. 1982; 5:611–22. [PubMed: 6762087]
68. Cornbleet MA, McElwain TJ, Kumar PJ, et al. Treatment of advanced malignant melanoma with high-dose melphalan and autologous bone marrow transplantation. Br J Cancer. 1983; 48:329–34. [PubMed: 6351883]
69. Lazarus HM, Herzig RH, Wolff SN, et al. Treatment of metastatic malignant melanoma with intensive melphalan and autologous bone marrow transplantation. Cancer Treat Rep. 1985; 69:473–7. [PubMed: 3891085]
70. Wolff SN, Herzig RH, Fay JW, et al. High-dose thiotepa with autologous bone marrow transplantation for metastatic malignant melanoma: results of phase I and II studies of the North American Bone Marrow Transplantation Group. J Clin Oncol. 1989; 7:245–9. [PubMed: 2492594]
71. Shea TC, Antman KH, Eder JP, et al. Malignant melanoma. Treatment with high-dose combination alkylating agent chemotherapy and autologous bone marrow support. Arch Dermatol. 1988; 124:878–84. [PubMed: 3288124]
72. Peters WP, Eder JP, Henner WD, et al. High-dose combination alkylating agents with autologous bone marrow support: a Phase 1 trial. J Clin Oncol. 1986; 4:646–54. [PubMed: 3517240]
73. Tchekmedyian NS, Tait N, Van Echo D, et al. High-dose chemotherapy without autologous bone marrow transplantation in melanoma. J Clin Oncol. 1986; 4:1811–8. [PubMed: 3537218]
74. Slease RB, Benear JB, Selby GB, et al. High-dose combination alkylating agent therapy with autologous bone marrow rescue for refractory solid tumors. J Clin Oncol. 1988; 6:1314–20. [PubMed: 3045266]
75. Antman K, Eder JP, Elias A, et al. High-dose combination alkylating agent preparative regimen with autologous bone marrow support: the Dana-Farber Cancer Institute/Beth Israel Hospital experience. Cancer Treat Rep. 1987; 71:119–25. [PubMed: 3542208]
76. Thatcher D, Lind M, Morgenstern G, et al. High-dose, double alkylating agent chemotherapy with DTIC, melphalan, or ifosfamide and marrow rescue for metastatic malignant melanoma. Cancer. 1989; 63:1296–302. [PubMed: 2646005]
77. Corringham R, Gilmore M, Prentice H, et al. High-dose melphalan with autologous bone marrow transplant treatment of poor prognosis tumors. Cancer. 1983; 52:1783–7. [PubMed: 6354413]
78. Costanzi JJ, Al-Sarraf M, Groope C, et al. Combination chemotherapy plus BCG in the treatment of disseminated malignant melanoma: A Southwest Oncology Group study. Med Pediatr Oncol. 1982; 10:251–8. [PubMed: 7045615]
79. Ringborg U, Rudenstam CM, Hansson J, et al. Dacarbazine versus dacarbazine-vindesine in disseminated malignant melanoma: a randomized phase II study. Med Oncol Tumor Pharmacother. 1989; 6:285–9. [PubMed: 2693850]
80. Shah GD, Chapman PB. Adjuvant therapy of melanoma. Cancer J. 2007; 13:217–22. [PubMed: 17620773]
81. Veronesi U, Adamus J, Aubert C, et al. A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. N Engl J Med. 1982; 307:913–6. [PubMed: 7050717]
82. Bedikian AY, Millward M, Pehamberger H, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. J Clin Oncol. 2006; 24:4738–45. [PubMed: 16966688]
83. Costanza ME, Nathanson L, Schoenfeld D, et al. Results with methyl-CCNU and DTIC in metastatic melanoma. Cancer. 1977; 40:1010–5. [PubMed: 332319]
84. Cocconi G, Bella M, Calabresi F, et al. Treatment of metastatic malignant melanoma with dacarbazine plus tamoxifen. N Engl J Med. 1992; 327:516–23. [PubMed: 1635566]

85. Thomson DB, Adena M, McLeod GR, et al. Interferon-alpha 2a does not improve response or survival when combined with dacarbazine in metastatic malignant melanoma: results of a multi-institutional Australian randomized trial. Melanoma Res. 1993; 3:133–8. [PubMed: 8518552]

86. Bajetta E, Di Leo A, Zampino MG, et al. Multicenter randomized trial of dacarbazine alone or in combination with two different doses and schedules of interferon alfa-2a in the treatment of advanced melanoma. J Clin Oncol. 1994; 12:806–11. [PubMed: 8151323]

87. Falkson CI, Ibrahim J, Kirkwood JM, et al. Phase III trial of dacarbazine versus dacarbazine with interferon alpha-2b versus dacarbazine with tamoxifen versus dacarbazine with interferon alpha-2b and tamoxifen in patients with metastatic malignant melanoma: an Eastern Cooperative Oncology Group study. J Clin Oncol. 1998; 16:1743–51. [PubMed: 9586887]

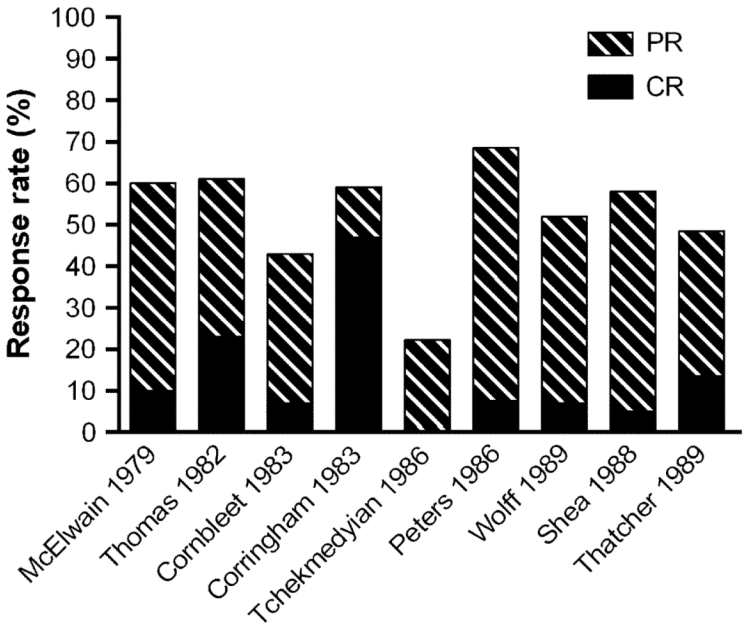

Fig. 1.
Response rates of trials using myeloablative chemotherapy followed by autologous bone marrow rescue.

Table 1

Efficacy of DTIC in randomized trials since 1992 in which DTIC was the control arm

Trial	Number in DTIC Arm	Number of DTIC Responders	Response Rate to DTIC(%)	Median Overall Survival (mo)	1 y Overall Survival (%)
Cocconi et al[84]	52	12	23	6.7	30
Thomson et al[85]	83	14	17		
Avril et al[27]	117	8	7	5.6	
Chapman et al[56]	116	12	10	6.3	27
Bajetta etal[86]	82	16	20	11	
Falkson et al[87]	69	22	32	10	20
Middleton et al[1]	149	28	19	6.4	22
Bedikian et al[82]	385	29	8	7.8	30
Total	1055	141	13.4[a]		27 (average)

[a]The total DTIC responders/total treated.

Table 2
Efficacy of other single-agent chemotherapy drugs in melanoma

Agent	No. of Evaluable Melanoma Patients	No. of Responders	Response Rate(%)
Temozolomide	(205)	(27)	(13.2)
Middleton[1]	156	21	13.5
Rietschel[5]	49	6	12.5
Cisplatin	(104)	(15)	(14.4)
Chary[15]	11	3	27
Goodnight[13]	10	1	10
Schilcher[14]	16	4	25
Al-Sarraf[12]	67	7	10
Carboplatin	(96)	(15)	(15.6)
Casper[17]	43	7	16
Chang[18]	27	3	11
Evans[19]	26	5	19
Fotemustine	(314)	(69)	(22)
Calabresi[23]	30	6	20
Jacquillat (brain)[24]	153	37	24.1
Schallreuter[26]	19	9	47.3
Avril[27]	112	17	15.2
BCNU	(119)	(22)	(18.5)
Ramirez[20]	99	19	19
De Vita[21]	20	3	15
Paclitaxel	(122)	(16)	(13.1)
Weirnik[31]	12	4	33
Legha[32]	25	3	12
Einzig[33]	28	4	14
Walker[34]	25	0	0
Bedikian[35]	32	5	15.6
Docetaxel	(105)	(12)	(11.4)
Einzig[28]	35	2	5.7
Bedikian[29]	40	5	12.5
Aamdal[30]	30	5	16.7

Numbers in parentheses are the totals from the trials listed. Response rates in parentheses are the percent total responders among the total number treated.