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Chemotherapy in the Management of Advanced Cutaneous Malignant Melanoma

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Abstract

The recent past has witnessed unprecedented clinical progress in the treatment of advanced malignant melanoma through targeting of mutant BRAF in approximately 50 percent of patients and immune check point blockade in all patients. As has been well documented however, responses to targeted therapy are of limited duration and rates of clinical benefit to immunotherapy are modest. Given these factors, palliation of patients with chemotherapy remains an essential aspect of melanoma oncology. Many chemotherapeutics (and combinations with other agents such as immunotherapy) have been evaluated in melanoma however no chemotherapy regimen has been documented to provide an overall survival benefit in a prospective, randomized, well controlled phase III study. Here, we overview the development of the most common chemotherapy regimens for melanoma, discuss the clinical trial evidence supporting and contrasting them and highlight appropriate clinical situations in which they might be employed. Finally, we discuss the future of chemotherapy for melanoma, noting the potential for combinations of chemotherapy with either targeted or immunotherapeutic agents.

Introduction

Major advancements in the treatment of metastatic melanoma have recently been achieved with the approval of the Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) blocking monoclonal antibody ipilimumab and BRAF^{V600E} kinase inhibitor vemurafenib by the United States Food and Drug Administration (FDA). These treatments represent the only approvals of drugs for melanoma other than dacarbazine (1975), Interferon-alpha (1995) and interleukin-2 (1998). These new drugs represent a shift away from treatment with cytotoxic agents. However, chemotherapy continues to be an important tool in the treatment of melanoma. While not having demonstrated an overall survival benefit, chemotherapy has a clear role for palliation of patients with melanoma. Prior to the development of ipilimumab and vemurafenib, the only treatment known to lead to long term remissions in patients with melanoma was high dose IL-2. Unfortunately, this treatment approach is relevant to a select patient population given its toxicity and many of these patients eventually receive chemotherapy as well.

Even in the era of CTLA-4 blockade and targeted therapies, chemotherapy remains an essential treatment option. Many patients are ineligible for treatment with ipilimumab or do not harbor a BRAF^{V600E} mutation. Additionally, even if eligible for treatment, a majority of patients treated with ipilimumab obtain no benefit and all patients treated with small molecule kinase inhibitors eventually relapse from therapy. In this review we focus on the

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available clinical trial evidence underlying the use of chemotherapy in melanoma and highlight the clinical circumstances in which it may be most appropriately employed.

Single Agent Chemotherapy

Alkylating Agents

Dacarbazine and temozolomide—Multiple chemotherapeutics have been evaluated in the treatment of advanced melanoma however only dacarbazine has been approved for use by the FDA. Dacarbazine, and the analog drug temozolomide, are alkylating agents that damage DNA by introducing alkyl groups to guanine bases, eventually cell death via apoptosis and other cell death mechanisms. Upon administration, dacarbazine is hepatically demethylated to 3-methyl-(triazene-1-yl)imidazole-4-carboxamide (MTIC) and subsequently to diazomethane, the active metabolite(1, 2). Dacarbazine has become the “standard of care” benchmark for the treatment of metastatic melanoma. However, the drug has never been shown in a randomized phase III trial to improve overall survival. Generally, dacarbazine is associated with a response rate of approximately 10–20% and a progression-free survival of approximately three to six months(3). The side effect profile of dacarbazine is predominately dictated by nausea, vomiting and bone marrow suppression in the form of leucopenia and anemia. The nausea and vomiting experienced during treatment with TMZ are generally quite manageable with modern anti-emetic regimens. Temozolomide (TMZ), the dacarbazine analog and derivative of triazene, is a prodrug that is converted to MTIC under conditions of physiologic pH within the body(1, 2). In a phase III trial of 305 patients, temozolomide was not found to be significantly more efficacious as compared to dacarbazine in terms of overall survival (OS), 7.7 versus 6.4 months, respectively, and progression-free survival (PFS), 1.9 months versus 1.5 months, respectively(4). A second phase III trial of TMZ versus dacarbazine in 859 patients confirmed this, showing no difference in OS, 9.1 versus 9.4 months or PFS, 2.3 versus 2.2 months, respectively(5).

Both dacarbazine and TMZ cross the blood-brain barrier, making them useful treatments in the setting of brain metastasis. The alkylating activity of TMZ has been extensively evaluated in the context of glioblastoma multiforme (GBM) where it is established that activity is dependent on the methylation status of the O-6-methylguanine-DNA methyltransferase (MGMT) gene promoter. In GBM, methylation of the MGMT promoter dramatically reduces the response rate to TMZ, limiting the clinical utility of the drug(6).

The association of MGMT promoter methylation to clinical benefit has not, to date, been identified in patients with systemically advanced malignant melanoma. Cell line models have indicated that MGMT promoter methylation may be a relevant factor in TMZ sensitivity(7) and the MGMT inhibitor O6-benzylguanine has been shown to reverse the therapeutic resistance to TMZ in a malignant melanoma xenograft model(8). In humans, the role of MGMT promoter methylation was evaluated in a post-hoc analysis of patients with melanoma treated on TMZ clinical trials. Hassell et al(9) showed that the methylation status of the MGMT gene promoter did not correlate with improved survival however promoter methylation did correlate with more severe adverse events, requiring more TMZ dose reductions or discontinuations. Further, attempts have been made to improve the therapeutic efficacy of TMZ with the addition of MGMT inhibitors. A phase I dose expansion and a phase II study of TMZ in combination with the MGMT inhibitor lomeguatrib examined this further however no improvement in response rate or progression-free survival was documented with the combination(10, 11). A follow up pharmacodynamic analysis of tumor specimen from this study revealed that enhancement of TMZ effect was dependent upon the schedule of lomeguatrib administration and that improvement in the therapeutic index of TMZ could be possible(11). This combination has not been taken forward into further clinical development however. Finally, in a phase II study of extended-dose TMZ, no

correlation could be found between response rate and MGMT expression or promoter methylation(12). Given these findings, it is not currently recommended that the MGMT promoter methylation status be evaluated prior to treatment of melanoma patients with TMZ.

Multiple schedules of dacarbazine and TMZ(5) have been published however none have been observed to be more efficacious than others. While the side effect profile of the two agents is very similar, the bone marrow suppression of TMZ has a broader spectrum of effect, including lymphopenia beyond the leucopenia and anemia common with dacarbazine. This lymphopenia is generally dose and schedule dependant with higher exposures of TMZ leading to more significant suppression of lymphocyte count(13). Further, within the lymphocyte population, the CD4+ and CD8+ T regulatory cell populations appears to be particularly affected. This superficially might be thought to be a disadvantage in the treatment of melanoma, a disease that has an important immune component. However, multiple retrospective and preclinical analyses have demonstrated an improvement in innate antitumor activity of the immune system after TMZ or similar lymphodepleting treatment(14–18). From a clinical standpoint however, it is important to note that consideration should be given for anti-*Pneumocystis carinii* pneumonia (PCP) prophylaxis (and potentially other opportunistic infections) in patients with melanoma who are being treated with high doses or extended exposures to TMZ.

Despite various attempts to improve the efficacy of TMZ, it remains approximately that of dacarbazine. The major advantage of TMZ is the ease of dosing given the oral formulation of the drug. Despite this advantage, TMZ has not achieved FDA approval for the treatment of metastatic melanoma.

Nitrosoureas—Another class of alkylating agents with documented activity in melanoma are the nitrosoureas. This family of compounds includes fotemustine, carmustine (BCNU), and lomustine (CCNU), among others. While none of these agents has been approved by the FDA for treatment of advanced melanoma, fotemustine has been approved by some European regulators. Nitrosoureas are generally described to have roughly equivalent activity to dacarbazine or TMZ with RR of 10–18%(19–21). The clinical utility of these agents is limited however by the more aggressive and profound side effect profile that treatment with them entails. More specifically, prolonged periods of bone marrow suppression, particularly thrombocytopenia, are often seen after treatments with these agents. Additionally, they are more highly emetogenic and lead to more significant alopecia as opposed to dacarbazine/TMZ.

There may be sub-populations of patients, particularly those with brain metastases, which may benefit from consideration of treatment with nitrosoureas as compared to dacarbazine/TMZ. In a randomized phase III trial of 229 patients treated with fotemustine or dacarbazine, an improved RR, 15% versus 7%, but similar PFS, 1.9 versus 1.8 months, and OS, 1.9 versus 1.8 months, respectively, were observed(21). These results were not statistically different and came with a marked increase in systemic toxicity. Notably however, in patients enrolled without prior brain metastases, the fotemustine arm had a lower risk of metastatic progression to the central nervous system when compared to the dacarbazine arm, 18 versus 23%, respectively. Additionally, the time to the development of brain metastases was significantly increased from 7.2 months for dacarbazine to 22.7 months with fotemustine. The trend toward improved OS and the statistically significant improvement in time to the development of brain metastases were the impetus for the approval of this agent in Europe.

Microtubule Disrupting Agents

Vinca Alkaloids and Taxanes—Beyond alkylating agents, several other classes of cytotoxic chemotherapeutics have been examined in melanoma. Initially there was hope that microtubule toxins would have robust activity as single agents and later in combination with other anti-melanoma treatments. The first class of microtubule directed agents identified were the vinca alkaloids. These agents inhibit the polymerization of tubulin, arresting cells in metaphase and eventually leading to apoptosis. Various members of this class have been evaluated as single agents including vindesine/vinblastine(22, 23), vincristine(24), and vinorelbine(25, 26). Similar to dacarbazine/TMZ, response rates to these agents ranged from approximately 10–20% with PFS on the order of 2–4 months and no improvement in OS. Side effects primarily included neuropathy, gastrointestinal toxicity and bone marrow suppression.

The taxane family of chemotherapies has also been evaluated in melanoma. Whereas vinca alkaloids disrupt microtubules, taxanes stabilize microtubules and interfere with microtubule disassembly. Both paclitaxel and docetaxel were evaluated as single agents(27, 28), with both showing modest activity similar to vinca alkaloids in patients with metastatic melanoma. Other novel taxanes have also been evaluated though results were similar to the classical taxanes above. The fatty acid conjugated docosahexaenoic acid-paclitaxel formulation initially appeared promising(29). However, upon head to head comparison with TMZ in a randomized phase III trial, no statistically significant difference in OS was observed between the two agents(28).

More recently a nanoparticle albumin-bound formulation of paclitaxel (nab-paclitaxel) has been developed. Phase I testing of this agent showed activity in the melanoma patients with both tumor shrinkage and declines in elevated serum LDH values(30). This agent was evaluated in a phase II study of 74 patients with metastatic melanoma(31) showing RRs of 22% and 3% in chemotherapy-naïve and previously treated patients, respectively. Further development of this agent is on-going with a randomized phase III trial of nab-paclitaxel versus dacarbazine, in the upfront setting, actively being accrued (Clinicaltrials.gov identifier: NCT00864253).

Platinums

The development of the DNA-crosslinking family of platinum agents represented a major step forward in the treatment of most advanced epithelial tumors however the translation of these agents to melanoma has been much less impressive. Both cisplatin and carboplatin have shown only modest activity. The described single agent response rates for cisplatin were highly variable ranging from zero to over 50%. However, most trials describing a range of approximately 15–20%(19). Carboplatin has been less extensively tested(32), and its activity compared with other single agents is uncertain. As in other diseases, platinum agents were deemed to have inadequate single agent activity to take forward alone and were examined in combination with other agents. Multiple combination regimens have been described as well as numerous chemoimmunotherapy combinations.

Combination Chemotherapy

Given the modest response rates observed with single agent chemotherapy, there has been historical interest in the development of combination chemotherapy regimens. Similar rational has led to the development of more effective strategies in many other solid tumors however this has not been widely efficacious in malignant melanoma. Initial development of combination chemotherapy regimens suggested that the response rates, and possibly survival, could be improved with the addition of further agents to dacarbazine or TMZ(33–

38). Multiple regimens were developed notably including BOLD (bleomycin, vincristine, lomustine, dacarbazine), CVD (cisplatin, vinblastine, dacarbazine) and the Dartmouth regimen (dacarbazine, cisplatin, carmustine, tamoxifen).

Overtime, it is now clear that the currently understood combination chemotherapy regimens are not superior to single agent treatment with dacarbazine or TMZ. In a seminal multi-center, randomized phase III trial, the Dartmouth regimen was compared with single agent dacarbazine showing no statistically significant survival advantage of the combination therapy(39). Although the response rate with the Dartmouth regimen showed a trend toward significance for dacarbazine alone, the overall survival of the patients treated on the study was similar. As would be expected, toxicity with the combination was markedly increased with the combination regimen. Therefore, at this time treatment with multi-agent chemotherapy would not be considered a standard of care.

With the development of newer cytotoxic chemotherapeutics, such as nab-paclitaxel, the question of combination therapy is again arising however. In a phase II study of nab-paclitaxel in combination with carboplatin, a RR of 25.6% was documented in chemotherapy naïve patients as well as a RR of 8.8% in patients previously treated with chemotherapy(40). As expected, toxicity was increased with the use of doublet chemotherapy with bone marrow suppression, neuropathy, fatigue, nausea and vomiting being reported.

Chemotherapy in Combinations

Chemoimmunotherapy

Immunological agents have been of interest in the treatment of melanoma with sub-populations of patients deriving significant benefits from interferon alpha (INF- α), interleukin-2 (IL-2) and more recently ipilimumab. While review of the primary role of immunology in melanoma is outside the scope of this review (please see the review by Mukherji and colleagues within this *Clinics in Dermatology* series), the role of immunotherapy in combination with chemotherapy has been previously investigated and is of relevance.

The two agents most commonly combined with chemotherapy were INF- α and IL-2. These agents were combined with various chemotherapy cocktails in numerous different treatment schedules however results were less impressive than hoped. While often showing improved response rates, in the range of 27–64%, more than 10 chemoimmunotherapy regimens have been compared with chemotherapy without demonstrating an improvement in overall survival as compared to dacarbazine alone(41–49).

Additionally, when added to chemotherapy, and especially combination chemotherapy, immunotherapy adds increased toxicity making the improvement in response rate difficult to justify. Various attempts have been made to circumvent this issue without success. Some have argued that the reduction in dose of immunologics, IL-2 specifically, that is required for tolerability with chemotherapy renders them inactive. As this hypothesis is proposed, there is an important dose dependency to the treatment efficacy of high dose IL-2. Upon combination with chemotherapy, it is not possible to reach this critical dose threshold and therefore the treatment advantage of IL-2 in selected patients is lost(50). Some data does exist to support this logic given that responses to high dose IL-2 have been documented in patients who have failed to response to prior chemoimmunotherapy regimens(51).

The dose-dependency of IL-2 is supported by the results of a phase II study, in which high dose bolus IL-2 was given to patients who had progressed on or after treatment with an IL-2

chemoimmunotherapy regimen(51). Complete responses to treatment with high dose IL-2 were observed in 4 of 26 patients (15%), all of whom had failed to respond to the original IL-2 containing chemoimmunotherapy regimen. Finally, a meta-analysis of 18 trials comparing chemotherapy alone to chemoimmunotherapy demonstrated that while improving response rates, chemoimmunotherapy delivered no improvement in overall survival(49). Given this, the use of chemoimmunotherapy is not recommended outside of the clinical trial setting.

The possibility for additive or synergistic benefit of chemotherapy with immunotherapeutics does continue to exist however. The recently published phase III trial of ipilimumab and dacarbazine demonstrated an advantage to the combination as compared to single agent dacarbazine(52). Few would recommend administration of this combination given the overall survival benefit of ipilimumab alone(53). However, this study does demonstrate the feasibility of combining chemotherapy with CTLA-4 blockade. Additionally, the side effect profile of the combination regimen was somewhat different from that seen with ipilimumab alone. While the immune related adverse events associated with ipilimumab are notable for colitis, amongst others, the combination regimen delivered more hepatic toxicity, again suggesting an immunomodulatory role for dacarbazine. Beyond combination with ipilimumab, TMZ and dacarbazine are also being evaluated with a number of other novel immunotherapeutics(54, 55), though the clinical utility of these combinations is currently uncertain.

Chemotherapy Combined with Targeted Therapy

As the underlying molecular mechanisms of melanoma and cancer more generally have become elucidated, there has been a shift away from cytotoxic agents in drug development. In cases where oncogenic driver lesions can be identified, targeted therapies have led to impressive responses (i.e. - BRAF^{V600E} melanoma)(56). Commonly however, the development of newer targeted therapeutics has allowed for the disruption of molecular pathways that are important for neoplastic growth but not sufficient in and of themselves to lead to tumor regressions. In these situations the possibility exists for the development of combination treatment regimens, potentially with chemotherapy, that would be more efficacious than any single agent alone.

Inhibitors of angiogenesis are an obvious example where combination with chemotherapy could be of clinical utility. Phase II studies have been reported with the combination of the anti-vascular endothelial growth factor A (VEGF-A) monoclonal antibody bevacizumab with chemotherapeutics including carboplatin and paclitaxel(57), dacarbazine with INF- α (58), fotemustine(59) and nab-paclitaxel(60). To date, reported efficacy has shown a slight improvement compared with chemotherapy alone. Notably, the multi-targeted (including anti-VEGF receptor and wild-type BRAF) tyrosine kinase inhibitor sorafenib was combined with carboplatin and paclitaxel without notable efficacy(61). Given the highly vascular character of malignant melanoma however, angiogenesis will likely continue to be an area of clinical interest in the future.

Like angiogenesis, the marked resistance to apoptosis exhibited by melanoma(62) seemed to be an area of therapeutic potential in melanoma. This led to the development of the anti-sense oligonucleotide to Bcl-2, oblimersen. Oblimersen was evaluated in combination with dacarbazine in melanoma with mixed results(63). Overall the combination did not improve the overall survival of an all-comer melanoma population. In subset analysis however, it did appear that patients with melanoma who had normal LDH levels obtained significant benefit(64). Given the lack of generalizability of the agent however, this treatment combination regimen was not taken forward.

Other molecular combinations with chemotherapy have been described pre-clinically and are rational treatment strategies to begin to test in clinical trials. The combination of TMZ with the poly(ADP-ribose) polymer (PARP) inhibitor ABT-888 has been described to have activity in melanoma xenografts that are insensitive to TMZ alone(65). This suggests that some melanomas are deficient in DNA mismatch repair allowing treatment with the PARP inhibitor to prime cells for apoptosis after treatment with chemotherapy. In a phase I study of the PARP inhibitor AZD2281 in combination with dacarbazine, two responses were seen in melanoma patients during the dose escalation however a cohort expansion of chemotherapy naïve melanoma patients revealed no further responders. Inhibitors of various growth pathways, such as AKT(66)and the mammalian target of rapamycin (mTOR)(67) have also been described to be synergistic with chemotherapy in preclinical melanoma studies. The utility of these and other combinations has yet to be evaluated clinically.

Another area of targeted therapy that is of interest in combination with chemotherapy includes molecules influencing the “stemness” of melanoma. The importance of embryological pathways, such as Notch and Hedgehog, in melanoma are increasingly being recognized(68–70) and it has been shown pre-clinically that inhibition of these pathways can have a retardant effect on the growth of melanoma cells(71, 72). Synergy has also been reported between Notch inhibition and chemotherapy(73) and this has led to an on-going National Cancer Institute supported study to examine the benefit of this combination in advanced melanoma (ClinicalTrials.gov Identifier:NCT01196416).

Adjuvant and Neoadjuvant Chemotherapy

Given the lack of an overall survival benefit from chemotherapy in the metastatic setting, it now seems intuitive that there would not be a standard role for chemotherapy in the adjuvant or neoadjuvant setting. This realization has not been generally understood until relatively recently however. Many chemotherapies(74), chemotherapy combination(75, 76) and chemoimmunotherapies(77, 78) have been leveraged in adjuvant clinical trials without success. Most recently TMZ was evaluated in a neoadjuvant phase II study. Clinical results were similar to those seen in the metastatic setting in terms of response rate (18.8%). However, this did not appear to add to the overall survival of the treated patients. A positive element of the study however was the demonstration of feasibility in administering neoadjuvant TMZ and obtaining adequate pre- and post-treatment tissue for genetic testing(79). This trial highlights the only potential clinically acceptable use of neoadjuvant or adjuvant chemotherapy in melanoma, that being an attempt to convert an unresectable patient to resectable after a robust response. This would obviously be a highly select group of patients where clinical judgment would be important. Other than this however, the use of chemotherapy in the neoadjuvant or adjuvant situations is not indicated.

Clinical Decision Making and Future Directions in Chemotherapy for Melanoma

With the development of vemurafenib and ipilimumab, the first line treatment of melanoma is now associated with an overall survival benefit for the first time. Clearly, in patients who harbor BRAF^{V600E} mutations or who are candidates for ipilimumab, these agents should be used preferentially to chemotherapy. Additionally, in highly selected patients, IL-2 continues to be a treatment option associated with long term benefit. Many patients unfortunately do not fit these criteria in the first line setting and most will not fit them in the second line. As such, chemotherapy continues to be an important tool in the armamentarium of the melanoma oncologist. As recommended by the National Comprehensive Cancer Network (NCCN) guidelines, patients who are fit should be offered participation in a clinical trial where possible. When this is not possible, the data indicate that treatment with

single agent chemotherapy (dacarbazine or TMZ) is the evidence based recommendation, given no improvement in overall survival from combination chemotherapy or chemoimmunotherapy. There are developments on the clinical horizon that may alter this therapeutic landscape in the relatively near future. Nab-paclitaxel is an interesting agent that may become a new first line chemotherapeutic treatment option when combined with carboplatin or bevacizumab. These combinations may also eventually come into the general clinical setting as salvage regimens. Novel agents and combinations of chemotherapy with other targeted therapies and immunotherapies, such as anti-PD-1, -PD-L1, -GITR etc., may also someday become relevant in the non-trial setting. While these approaches are scientifically exciting and have extraordinary potential, they highlight need for continued research into the mechanisms of melanoma and underscore the role that chemotherapy does and will continue to play in the treatment of malignant melanoma for the foreseeable future.

Drug Names

vemurafenib	Zelboraf
ipilimumab	Yervoy
temozolomide	Temodar
docetaxel	Taxotere
nab-paclitaxel	Abraxane
interleukin-2	Proleukin
interferon-alpha	Intron A
bevacizumab	Avastin
sorafenib	Nexavar

References

1. Bajetta E, Del Vecchio M, Bernard-Marty C, Vitali M, Buzzoni R, Rixe O, et al. Metastatic melanoma: chemotherapy. *Seminars in oncology*. 2002; 29(5):427–45. Epub 2002/10/31. [PubMed: 12407508]
2. Li Y, McClay EF. Systemic chemotherapy for the treatment of metastatic melanoma. *Seminars in oncology*. 2002; 29(5):413–26. Epub 2002/10/31. [PubMed: 12407507]
3. Crosby T, Fish R, Coles B, Mason MD. Systemic treatments for metastatic cutaneous melanoma. *Cochrane Database Syst Rev*. 2000; (2):CD001215. Epub 2000/05/05. [PubMed: 10796759]
4. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2000; 18(1):158–66. Epub 2000/01/07. [PubMed: 10623706]
5. Patel PM, Suci S, Mortier L, Kruit WH, Robert C, Schadendorf D, et al. Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV melanoma: final results of a randomised phase III study (EORTC 18032). *Eur J Cancer*. 2011; 47(10):1476–83. Epub 2011/05/24. [PubMed: 21600759]
6. Hegi ME, Diserens A-C, Gorlia T, Hamou M-F, de Tribolet N, Weller M, et al. MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma. *New England Journal of Medicine*. 2005; 352(10):997–1003. [PubMed: 15758010]
7. Boeckmann L, Nickel AC, Kuschal C, Schaefer A, Thoms KM, Schon MP, et al. Temozolomide chemoresistance heterogeneity in melanoma with different treatment regimens: DNA damage accumulation contribution. *Melanoma research*. 2011; 21(3):206–16. Epub 2011/04/05. [PubMed: 21460749]

8. Wedge SR, Porteous JK, Newlands ES. Effect of single and multiple administration of an O6-benzylguanine/temozolomide combination: an evaluation in a human melanoma xenograft model. *Cancer chemotherapy and pharmacology*. 1997; 40(3):266–72. Epub 1997/01/01. [PubMed: 9219512]
9. Hassel JC, Sucker A, Edler L, Kurzen H, Moll I, Stresemann C, et al. MGMT gene promoter methylation correlates with tolerance of temozolomide treatment in melanoma but not with clinical outcome. *British journal of cancer*. 2010; 103(6):820–6. Epub 2010/08/26. [PubMed: 20736948]
10. Ranson M, Middleton MR, Bridgewater J, Lee SM, Dawson M, Jowle D, et al. Lomeguatrib, a potent inhibitor of O6-alkylguanine-DNA-alkyltransferase: phase I safety, pharmacodynamic, and pharmacokinetic trial and evaluation in combination with temozolomide in patients with advanced solid tumors. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2006; 12(5):1577–84. Epub 2006/03/15. [PubMed: 16533784]
11. Ranson M, Hersey P, Thompson D, Beith J, McArthur GA, Haydon A, et al. Randomized trial of the combination of lomeguatrib and temozolomide compared with temozolomide alone in chemotherapy naive patients with metastatic cutaneous melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007; 25(18):2540–5. Epub 2007/06/20. [PubMed: 17577032]
12. Rietschel P, Wolchok JD, Krown S, Gerst S, Jungbluth AA, Busam K, et al. Phase II study of extended-dose temozolomide in patients with melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008; 26(14):2299–304. Epub 2008/05/10. [PubMed: 18467721]
13. Neyns B, Tosoni A, Hwu WJ, Reardon DA. Dose-dense temozolomide regimens: antitumor activity, toxicity, and immunomodulatory effects. *Cancer*. 2010; 116(12):2868–77. Epub 2010/06/22. [PubMed: 20564393]
14. Ghiringhelli F, Menard C, Puig PE, Ladoire S, Roux S, Martin F, et al. Metronomic cyclophosphamide regimen selectively depletes CD4+ CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients. *Cancer immunology, immunotherapy : CII*. 2007; 56(5):641–8. Epub 2006/09/09.
15. Banissi C, Ghiringhelli F, Chen L, Carpentier AF. Treg depletion with a low-dose metronomic temozolomide regimen in a rat glioma model. *Cancer immunology, immunotherapy : CII*. 2009; 58(10):1627–34. Epub 2009/02/18.
16. Su YB, Sohn S, Krown SE, Livingston PO, Wolchok JD, Quinn C, et al. Selective CD4+ lymphopenia in melanoma patients treated with temozolomide: a toxicity with therapeutic implications. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004; 22(4):610–6. Epub 2004/01/17. [PubMed: 14726505]
17. Antony PA, Piccirillo CA, Akpınarlı A, Finkelstein SE, Speiss PJ, Surman DR, et al. CD8+ T cell immunity against a tumor/self-antigen is augmented by CD4+ T helper cells and hindered by naturally occurring T regulatory cells. *J Immunol*. 2005; 174(5):2591–601. Epub 2005/02/25. [PubMed: 15728465]
18. Gattinoni L, Finkelstein SE, Klebanoff CA, Antony PA, Palmer DC, Spiess PJ, et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8+ T cells. *The Journal of experimental medicine*. 2005; 202(7):907–12. Epub 2005/10/06. [PubMed: 16203864]
19. Atkins M. The role of cytotoxic chemotherapeutic agents either alone or in combination with biological response modifiers. In: Kirkwood J., editor. *Molecular Diagnosis, Prevention & Therapy of Melanoma*. New York: Marcel Dekker; 1997. p. 219
20. Houghton, A.; Legha, S.; Bajorin, D. Chemotherapy for metastatic melanoma. In: Balch, C.; Houghton, A.; Milton, editors. *Cutaneous Melanoma*. Hagerstown, Maryland: Lippincott Williams & Wilkins; 1992. p. 498
21. Avril MF, Aamdal S, Grob JJ, Hauschild A, Mohr P, Bonerandi JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004; 22(6): 1118–25. Epub 2004/03/17. [PubMed: 15020614]
22. Quagliana JM, Stephens RL, Baker LH, Costanzi JJ. Vindesine in patients with metastatic malignant melanoma: a Southwest Oncology Group study. *Journal of clinical oncology : official*

- journal of the American Society of Clinical Oncology. 1984; 2(4):316–9. Epub 1984/04/01. [PubMed: 6707719]
23. Nelimark RA, Peterson BA, Vosika GJ, Conroy JA. Vindesine for metastatic malignant melanoma. A phase II trial. American journal of clinical oncology. 1983; 6(5):561–4. Epub 1983/10/01. [PubMed: 6613921]
 24. Bedikian AY, Papadopoulos NE, Kim KB, Vardeleon A, Smith T, Lu B, et al. A pilot study with vincristine sulfate liposome infusion in patients with metastatic melanoma. Melanoma research. 2008; 18(6):400–4. Epub 2008/11/18. [PubMed: 19011511]
 25. Whitehead RP, Moon J, McCachren SS, Hersh EM, Samlowski WE, Beck JT, et al. A Phase II trial of vinorelbine tartrate in patients with disseminated malignant melanoma and one prior systemic therapy: a Southwest Oncology Group study. Cancer. 2004; 100(8):1699–704. Epub 2004/04/10. [PubMed: 15073859]
 26. Jimeno A, Hitt R, Quintela-Fandino M, Cortes-Funes H. Phase II trial of vinorelbine tartrate in patients with treatment-naïve metastatic melanoma. Anti-cancer drugs. 2005; 16(1):53–7. Epub 2004/12/23. [PubMed: 15613904]
 27. Einzig AI, Hochster H, Wiernik PH, Trump DL, Dutcher JP, Garowski E, et al. A phase II study of taxol in patients with malignant melanoma. Investigational new drugs. 1991; 9(1):59–64. Epub 1991/02/01. [PubMed: 1673965]
 28. Aamdal S, Wolff I, Kaplan S, Paridaens R, Kerger J, Schachter J, et al. Docetaxel (Taxotere) in advanced malignant melanoma: a phase II study of the EORTC Early Clinical Trials Group. Eur J Cancer. 1994; 30A(8):1061–4. Epub 1994/01/01. [PubMed: 7654429]
 29. Homsí J, Bedikian AY, Kim KB, Papadopoulos NE, Hwu WJ, Mahoney SL, et al. Phase 2 open-label study of weekly docosahexaenoic acid-paclitaxel in cutaneous and mucosal metastatic melanoma patients. Melanoma research. 2009; 19(4):238–42. Epub 2009/06/13. [PubMed: 19521262]
 30. Ibrahim NK, Desai N, Legha S, Soon-Shiong P, Theriault RL, Rivera E, et al. Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. Clinical cancer research : an official journal of the American Association for Cancer Research. 2002; 8(5):1038–44. Epub 2002/05/15. [PubMed: 12006516]
 31. Hersh EM, O'Day SJ, Ribas A, Samlowski WE, Gordon MS, Shechter DE, et al. A phase 2 clinical trial of nab-paclitaxel in previously treated and chemotherapy-naïve patients with metastatic melanoma. Cancer. 2010; 116(1):155–63. Epub 2009/10/31. [PubMed: 19877111]
 32. Evans LM, Casper ES, Rosenbluth R. Phase II trial of carboplatin in advanced malignant melanoma. Cancer treatment reports. 1987; 71(2):171–2. Epub 1987/02/01. [PubMed: 3542209]
 33. Legha SS, Ring S, Papadopoulos N, Plager C, Chawla S, Benjamin R. A prospective evaluation of a triple-drug regimen containing cisplatin, vinblastine, and dacarbazine (CVD) for metastatic melanoma. Cancer. 1989; 64(10):2024–9. Epub 1989/11/15. [PubMed: 2804890]
 34. McClay EF, Mastrangelo MJ, Berd D, Bellet RE. Effective combination chemo/hormonal therapy for malignant melanoma: experience with three consecutive trials. International journal of cancer Journal international du cancer. 1992; 50(4):553–6. Epub 1992/02/20. [PubMed: 1537621]
 35. Margolin KA, Liu PY, Flaherty LE, Sosman JA, Walker MJ, Smith JW 3rd, et al. Phase II study of carmustine, dacarbazine, cisplatin, and tamoxifen in advanced melanoma: a Southwest Oncology Group study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1998; 16(2):664–9. Epub 1998/02/20. [PubMed: 9469356]
 36. Rusthoven JJ, Quirt IC, Iscoe NA, McCulloch PB, James KW, Lohmann RC, et al. Randomized, double-blind, placebo-controlled trial comparing the response rates of carmustine, dacarbazine, and cisplatin with and without tamoxifen in patients with metastatic melanoma. National Cancer Institute of Canada Clinical Trials Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1996; 14(7):2083–90. Epub 1996/07/01. [PubMed: 8683240]
 37. Creagan ET, Suman VJ, Dalton RJ, Pitot HC, Long HJ, Veeder MH, et al. Phase III clinical trial of the combination of cisplatin, dacarbazine, and carmustine with or without tamoxifen in patients with advanced malignant melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1999; 17(6):1884–90. Epub 1999/11/24. [PubMed: 10561229]

38. Bafaloukos D, Gogas H, Georgoulas V, Briassoulis E, Fountzilas G, Samantas E, et al. Temozolomide in combination with docetaxel in patients with advanced melanoma: a phase II study of the Hellenic Cooperative Oncology Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2002; 20(2):420–5. Epub 2002/01/12. [PubMed: 11786569]
39. Chapman PB, Einhorn LH, Meyers ML, Saxman S, Destro AN, Panageas KS, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1999; 17(9):2745–51. Epub 1999/11/24. [PubMed: 10561349]
40. Kottschade LA, Suman VJ, Amatruda T 3rd, McWilliams RR, Mattar BI, Nikcevich DA, et al. A phase II trial of nab-paclitaxel (ABI-007) and carboplatin in patients with unresectable stage IV melanoma : a North Central Cancer Treatment Group Study, N057E(1). *Cancer*. 2011; 117(8): 1704–10. Epub 2011/04/08. [PubMed: 21472717]
41. Vuoristo MS, Hahka-Kemppinen M, Parvinen LM, Pyrhonen S, Seppa H, Korpela M, et al. Randomized trial of dacarbazine versus bleomycin, vincristine, lomustine and dacarbazine (BOLD) chemotherapy combined with natural or recombinant interferon-alpha in patients with advanced melanoma. *Melanoma research*. 2005; 15(4):291–6. Epub 2005/07/22. [PubMed: 16034308]
42. Legha SS, Ring S, Bedikian A, Plager C, Eton O, Buzaid AC, et al. Treatment of metastatic melanoma with combined chemotherapy containing cisplatin, vinblastine and dacarbazine (CVD) and biotherapy using interleukin-2 and interferon-alpha. *Ann Oncol*. 1996; 7(8):827–35. Epub 1996/10/01. [PubMed: 8922197]
43. Legha SS, Ring S, Eton O, Bedikian A, Buzaid AC, Plager C, et al. Development of a biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2 for patients with metastatic melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1998; 16(5):1752–9. Epub 1998/05/20. [PubMed: 9586888]
44. Eton O, Legha SS, Bedikian AY, Lee JJ, Buzaid AC, Hodges C, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2002; 20(8): 2045–52. Epub 2002/04/17. [PubMed: 11956264]
45. Atkins MB, Hsu J, Lee S, Cohen GI, Flaherty LE, Sosman JA, et al. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008; 26(35): 5748–54. Epub 2008/11/13. [PubMed: 19001327]
46. Bajetta E, Del Vecchio M, Nova P, Fusi A, Daponte A, Sertoli MR, et al. Multicenter phase III randomized trial of polychemotherapy (CVD regimen) versus the same chemotherapy (CT) plus subcutaneous interleukin-2 and interferon-alpha2b in metastatic melanoma. *Ann Oncol*. 2006; 17(4):571–7. Epub 2006/02/14. [PubMed: 16469753]
47. Keilholz U, Punt CJ, Gore M, Kruit W, Patel P, Lienard D, et al. Dacarbazine, cisplatin, and interferon-alfa-2b with or without interleukin-2 in metastatic melanoma: a randomized phase III trial (18951) of the European Organisation for Research and Treatment of Cancer Melanoma Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2005; 23(27):6747–55. Epub 2005/09/20. [PubMed: 16170182]
48. Ridolfi R, Chiarion-Sileni V, Guida M, Romanini A, Labianca R, Freschi A, et al. Cisplatin, dacarbazine with or without subcutaneous interleukin-2, and interferon alpha-2b in advanced melanoma outpatients: results from an Italian multicenter phase III randomized clinical trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2002; 20(6):1600–7. Epub 2002/03/16. [PubMed: 11896110]
49. Ives NJ, Stowe RL, Lorigan P, Wheatley K. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007; 25(34):5426–34. Epub 2007/12/01. [PubMed: 18048825]

50. McDermott DF, Atkins MB. More support for the judicious use of high-dose interleukin-2 in patients with advanced melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007; 25(25):3791–3. Epub 2007/09/01. [PubMed: 17761967]
51. Tarhini AA, Kirkwood JM, Gooding WE, Cai C, Agarwala SS. Durable complete responses with high-dose bolus interleukin-2 in patients with metastatic melanoma who have experienced progression after biochemotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007; 25(25):3802–7. Epub 2007/09/01. [PubMed: 17761969]
52. Robert C, Thomas L, Bondarenko I, O'Day S, M DJ, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *The New England journal of medicine*. 2011; 364(26):2517–26. Epub 2011/06/07. [PubMed: 21639810]
53. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *The New England journal of medicine*. 2010; 363(8):711–23. Epub 2010/06/08. [PubMed: 20525992]
54. Eigentler TK, Weide B, de Braud F, Spitaleri G, Romanini A, Pflugfelder A, et al. A dose-escalation and signal-generating study of the immunocytokine L19-IL2 in combination with dacarbazine for the therapy of patients with metastatic melanoma. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2011Epub 2011/10/27.
55. O'Day S, Pavlick A, Loquai C, Lawson D, Gutzmer R, Richards J, et al. A randomised, phase II study of intetumumab, an anti- α v-integrin mAb, alone and with dacarbazine in stage IV melanoma. *British journal of cancer*. 2011; 105(3):346–52. Epub 2011/07/14. [PubMed: 21750555]
56. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *The New England journal of medicine*. 2011; 364(26):2507–16. Epub 2011/06/07. [PubMed: 21639808]
57. Perez DG, Suman VJ, Fitch TR, Amatruda T 3rd, Morton RF, Jilani SZ, et al. Phase 2 trial of carboplatin, weekly paclitaxel, and biweekly bevacizumab in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group study, N047A. *Cancer*. 2009; 115(1):119–27. Epub 2008/12/18. [PubMed: 19090009]
58. Vihinen PP, Hernberg M, Vuoristo MS, Tyynela K, Laukka M, Lundin J, et al. A phase II trial of bevacizumab with dacarbazine and daily low-dose interferon- α 2a as first line treatment in metastatic melanoma. *Melanoma research*. 2010; 20(4):318–25. Epub 2010/04/09. [PubMed: 20375744]
59. Del Vecchio M, Mortarini R, Canova S, Di Guardo L, Pimpinelli N, Sertoli MR, et al. Bevacizumab plus fotemustine as first-line treatment in metastatic melanoma patients: clinical activity and modulation of angiogenesis and lymphangiogenesis factors. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2010; 16(23):5862–72. Epub 2010/10/30. [PubMed: 21030496]
60. Boasberg P, Cruickshank S, Hamid O, O'Day S, Weber R, Spitler L. Nab-paclitaxel and bevacizumab as first-line therapy in patients with unresectable stage III and IV melanoma. *J Clin Oncol*. 2009; 27:15s. (suppl; abstr 9061).
61. Hauschild A, Agarwala SS, Trefzer U, Hogg D, Robert C, Hersey P, 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009; 27(17):2823–30. Epub 2009/04/08. [PubMed: 19349552]
62. Soengas MS, Lowe SW. Apoptosis and melanoma chemoresistance. *Oncogene*. 2003; 22(20):3138–51. Epub 2003/06/06. [PubMed: 12789290]
63. Bedikian AY, Millward M, Pehamberger H, Conry R, Gore M, Trefzer U, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006; 24(29):4738–45. Epub 2006/09/13. [PubMed: 16966688]
64. Agarwala SS, Keilholz U, Gilles E, Bedikian AY, Wu J, Kay R, et al. LDH correlation with survival in advanced melanoma from two large, randomised trials (Oblimersen GM301 and EORTC 18951). *Eur J Cancer*. 2009; 45(10):1807–14. Epub 2009/05/08. [PubMed: 19419855]

65. Palma JP, Wang YC, Rodriguez LE, Montgomery D, Ellis PA, Bukofzer G, et al. ABT-888 confers broad in vivo activity in combination with temozolomide in diverse tumors. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2009; 15(23): 7277–90. Epub 2009/11/26. [PubMed: 19934293]
66. Sinnberg T, Lasithiotakis K, Niessner H, Schitteck B, Flaherty KT, Kulms D, et al. Inhibition of PI3K-AKT-mTOR signaling sensitizes melanoma cells to cisplatin and temozolomide. *The Journal of investigative dermatology*. 2009; 129(6):1500–15. Epub 2008/12/17. [PubMed: 19078992]
67. Thallinger C, Werzowa J, Poepl W, Kovar FM, Pratscher B, Valent P, et al. Comparison of a treatment strategy combining CCI-779 plus DTIC versus DTIC monotherapy in human melanoma in SCID mice. *The Journal of investigative dermatology*. 2007; 127(10):2411–7. Epub 2007/05/18. [PubMed: 17508024]
68. Pinnix CC, Lee JT, Liu ZJ, McDaid R, Balint K, Beverly LJ, et al. Active Notch1 confers a transformed phenotype to primary human melanocytes. *Cancer research*. 2009; 69(13):5312–20. Epub 2009/06/25. [PubMed: 19549918]
69. Panelos J, Massi D. Emerging role of Notch signaling in epidermal differentiation and skin cancer. *Cancer biology & therapy*. 2009; 8(21):1986–93. Epub 2009/09/29. [PubMed: 19783903]
70. Li C, Chi S, Xie J. Hedgehog signaling in skin cancers. *Cellular signalling*. 2011; 23(8):1235–43. Epub 2011/03/15. [PubMed: 21397013]
71. Zhang JP, Qin HY, Wang L, Liang L, Zhao XC, Cai WX, et al. Overexpression of Notch ligand Dll1 in B16 melanoma cells leads to reduced tumor growth due to attenuated vascularization. *Cancer letters*. 2011; 309(2):220–7. Epub 2011/07/15. [PubMed: 21752535]
72. Huynh C, Polisenio L, Segura MF, Medicherla R, Haimovic A, Menendez S, et al. The novel gamma secretase inhibitor RO4929097 reduces the tumor initiating potential of melanoma. *PloS one*. 2011; 6(9):e25264. Epub 2011/10/08. [PubMed: 21980408]
73. Meng RD, Shelton CC, Li YM, Qin LX, Notterman D, Paty PB, et al. gamma-Secretase inhibitors abrogate oxaliplatin-induced activation of the Notch-1 signaling pathway in colon cancer cells resulting in enhanced chemosensitivity. *Cancer research*. 2009; 69(2):573–82. Epub 2009/01/17. [PubMed: 19147571]
74. Eigentler TK, Radny P, Hauschild A, Gutzmer R, Linse R, Pfohler C, et al. Adjuvant treatment with vindesine in comparison to observation alone in patients with metastasized melanoma after complete metastasectomy: a randomized multicenter trial of the German Dermatologic Cooperative Oncology Group. *Melanoma research*. 2008; 18(5):353–8. Epub 2008/09/11. [PubMed: 18781134]
75. Kudriavtsev DV, Kudriavtseva GT, Mardynskii Iu S. Adjuvant chemotherapy as a component of complex treatment for skin melanoma. *Voprosy onkologii*. 2008; 54(2):170–7. Epub 2008/06/05. [PubMed: 18522165]
76. Saba HI, Cruse CW, Wells KE, Klein CJ, Reintgen DS. Adjuvant chemotherapy in malignant melanoma using dacarbazine, carmustine, cisplatin, and tamoxifen: a University of South Florida and H. Lee Moffitt Melanoma Center Study. *Annals of plastic surgery*. 1992; 28(1):60–4. Epub 1992/01/01. [PubMed: 1642408]
77. Lewis KD, Robinson WA, McCarter M, Pearlman N, O'Day SJ, Anderson C, et al. Phase II multicenter study of neoadjuvant biochemotherapy for patients with stage III malignant melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006; 24(19):3157–63. Epub 2006/07/01. [PubMed: 16809738]
78. Buzaid AC, Colome M, Bedikian A, Eton O, Legha SS, Papadopoulos N, et al. Phase II study of neoadjuvant concurrent biochemotherapy in melanoma patients with local-regional metastases. *Melanoma research*. 1998; 8(6):549–56. Epub 1999/01/26. [PubMed: 9918417]
79. Shah GD, Socci ND, Gold JS, Wolchok JD, Carvajal RD, Panageas KS, et al. Phase II trial of neoadjuvant temozolomide in resectable melanoma patients. *Ann Oncol*. 2010; 21(8):1718–22. Epub 2010/01/19. [PubMed: 20080829]