Title
Phase II clinical trial evaluating docetaxel, vinorelbine and GM-CSF in stage IV melanoma.

Permalink
https://escholarship.org/uc/item/0sc8m33c

Journal
Cancer chemotherapy and pharmacology, 68(4)

ISSN
0344-5704

Authors
Eroglu, Zeynep
Kong, Kevin M
Jakowatz, James G
et al

Publication Date
2011-10-01

DOI
10.1007/s00280-011-1703-z

License
https://creativecommons.org/licenses/by/4.0/ 4.0

Peer reviewed
Phase II clinical trial evaluating docetaxel, vinorelbine and GM-CSF in stage IV melanoma

Zeynep Eroglu · Kevin M. Kong · James G. Jakowatz · Wolfram Samlowski · John P. Fruehauf

Received: 6 May 2011 / Accepted: 30 June 2011 / Published online: 19 July 2011 © The Author(s) 2011. This article is published with open access at Springerlink.com

Abstract

Purpose Metastatic melanoma patients have a poor prognosis. No chemotherapy regimen has improved overall survival. More effective treatments are needed. Docetaxel has clinical activity in melanoma and may be more active when combined with vinorelbine. Granulocyte–macrophage colony-stimulating factor (GM-CSF) has shown activity as an adjuvant melanoma therapy. We carried out a phase II study of these agents in patients with stage IV melanoma.

Methods Patients had documented stage IV melanoma and may have had prior immuno or chemotherapy. Previously treated brain metastases were allowed. Docetaxel (40 mg/m² IV) and vinorelbine (30 mg/m² IV) were administered every 14 days, followed by GM-CSF (250 mg/m² SC on days 2 to 12). The primary endpoint of the study was 1-year overall survival (OS). Secondary objectives were median overall survival, response rate (per RECIST criteria), and the toxicity profiles.

Results Fifty-two patients were enrolled; 80% had stage M1c disease. Brain metastases were present in 21%. Fifty-two percent of patients had received prior chemotherapy, including 35% who received prior biochemotherapy. Toxicity was manageable. Grade III/IV toxicities included neutropenia (31%), anemia (14%), febrile neutropenia (11.5%), and thrombocytopenia (9%). DVS chemotherapy demonstrated clinical activity, with a partial response in 15%, and disease stabilization in 37%. Six-month PFS was 37%. Median OS was 11.4 months and 1-year OS rate was 48.1%.

Conclusions The DVS regimen was active in patients with advanced, previously treated melanoma, with manageable toxicity. The favorable 1-year overall survival and median survival rates suggest that further evaluation of the DVS regimen is warranted.

Keywords Melanoma · Phase II · Docetaxel · Vinorelbine · Sargramostim

Introduction

There are an estimated 68,130 new cases of malignant melanoma and 8,700 deaths annually in the United States [1]. Although curable in its early stages, melanoma is the most common fatal form of skin cancer. Patients having metastatic disease have a poor prognosis, with median survival time of less than 9 months and a less than 5% probability of survival beyond 5 years of diagnosis [2]. Currently, dacarbazine and interleukin-2 (IL-2) are the only US Food and Drug Administration–approved agents for the treatment of metastatic melanoma. Response rates after treatment with dacarbazine have been approximately 12%, with no increased survival [3]. Immunotherapy with IL-2
produces responses in approximately 13% of stage IV patients, of which 4% are complete responses, with a subset enjoying durable disease-free survival [4, 5]. Although response rates are significantly increased for combinations of chemotherapy such as cisplatin, vinblastine, and dacarbazine (CVD regimen) with IL-2 and interferon-alpha (biochemotherapy), phase III trials have failed to show a significant overall survival benefit [6–8]. More recently, ipilimumab has been reported to improve survival by approximately 4 months compared to a gp100 melanoma vaccine [9]. However, both biochemotherapy and immunotherapy are associated with increased constitutional, hemodynamic, and myelosuppressive toxicity that can adversely affect quality of life. While recent approaches targeting molecular abnormalities, such as PLX4032, a tyrosine kinase inhibitor of BRAF, have generated enthusiasm, response duration appears to be limited [10, 11].

As current treatment regimens offer limited benefits to patients, more effective and less toxic treatments are needed. In preclinical studies, docetaxel (Taxotere) and vinorelbine (Navelbine) showed significant independent in vitro activity against melanoma specimens. The taxane paclitaxel and the vinca alkaloid derivative vinorelbine have been shown to act synergistically in vitro against melanoma cell lines, with both agents active in the nanomolar range at clinically achievable concentrations [12, 13]. Using an ex vivo adenosine triphosphate (ATP)–based chemosensitivity assay, Neale et al. demonstrated that 43% of vinorelbine-treated and 33% of paclitaxel-treated cutaneous melanomas showed sensitivity in the assay [13]. Furthermore, metronomic docetaxel has also been associated with anti-angiogenesis activity [14].

The safety and clinical activity of the docetaxel and vinorelbine combination have been demonstrated in patients with metastatic non-small cell lung cancer and metastatic breast cancer [15–17]. Retsas et al. evaluated the toxicity and activity of two sequences of paclitaxel combined with vinorelbine in disseminated malignant melanoma in 15 patients [18]. There were no problems with anaphylactic episodes, significant neutropenia, or emesis. The main toxicity noted was alopecia. Three major responses were seen, along with clinically meaningful tumor regressions that did not qualify as major responses in two additional patients. In metastatic melanoma patients, vinorelbine as a single agent has had a favorable toxicity profile, but showed limited clinical efficacy in two trials with 13 and 21 patients [19, 20]. A somewhat better outcome was seen for vinorelbine in combination with tamoxifen, where a 20% response rate was observed in 30 patients [21]. We chose to combine docetaxel (40 mg/m² IV) with vinorelbine (30 mg/m² IV) administered every 2 weeks in a metronomic fashion. We postulated that this schedule would possess both antitumor and anti-angiogenesis activity.

Granulocyte–macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]) may have benefit as an adjuvant therapy in stage III and resected stage IV melanoma. GM-CSF is integral to the functioning of the immune system, and results in activation of macrophages and dendritic cells, which may serve as antigen-presenting cells [22]. In vitro, GM-CSF stimulates peripheral blood monocytes to become cytotoxic to human melanoma cells [23, 24]. Administration of GM-CSF to patients results in an increase in the functional capacity of monocytes, as reflected by increased cytotoxicity [25, 26]. Additionally, GM-CSF, through its action on tumor-infiltrating macrophages, causes the production of angiostatin, an angiogenesis inhibitor [27, 28]. In two separate melanoma models, GM-CSF was found to be the most effective of the cytokines studied for induction of long-term protective immunity [29, 30].

GM-CSF was studied as an adjuvant to surgery in patients with metastatic melanoma in a phase II study by Spitzer and colleagues. The survival rate at 1 year for patients receiving GM-CSF was almost double (89% vs. 45%) that of historically matched controls [31]. GM-CSF was recently evaluated in a phase III cooperative group study as an adjuvant treatment for patients with completely resected stage III–IV melanoma, which demonstrated a significant improvement in disease-free survival, but not in overall survival [32]. We therefore evaluated the activity of the DVS combination (docetaxel, vinorelbine, and GM-CSF [sargramostim]) for the treatment of patients with stage IV melanoma in order to offer a combination of antitumor and anti-angiogenesis effects in tandem with immunostimulation.

Methods

Patients

Adult patients with a diagnosis of biopsy-proven stage IV metastatic melanoma, who had received no more than two prior chemotherapy or biotherapy regimens for metastatic disease, were eligible. Patients with brain metastases were eligible, if metastases were controlled with radiotherapy and asymptomatic. Other eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, absolute neutrophil count (ANC) ≥ 1,500/mm³, platelet count > 100,000/mm³, hemoglobin > 10 g/dl, BUN and serum creatinine < 0.5 × upper limit of laboratory normal (ULN), total and direct bilirubin < 1.5 × ULN, SGOT and SGPT < 3 × ULN, alkaline phosphatase < 3 × ULN, and a life expectancy of at least 12 weeks. Patients were excluded if they had received cancer treatments including radiation within 4 weeks,
surgery within 1 week, pregnant or nursing women had known HIV/AIDS, or an acute infection being treated with IV antibiotics. Institutional review board approval was obtained for the study protocol, and all patients provided written informed consent prior to entering study.

Study design

The DVS regimen consisted of docetaxel 40 mg/m² IV over 1 h, vinorelbine 30 mg/m² IV over 6 to 10 min on day 1, every 14 days, and GM-CSF, 250 mg/m² SC on days 2 to 12. Patients received a cycle of this regimen every 2 weeks.

Clinical assessments

Prior to treatment, patients underwent complete history and physical examinations, baseline computed tomographic (CT) scans of chest, abdomen, pelvis, MRI of brain or CT head with contrast, and laboratory tests including complete blood count and differential, metabolic panel and liver function panel. Every 2 weeks patients had history and physical, toxicity assessment, and repeated laboratory testing done.

Tumor response was assessed with Response Evaluation Criteria in Solid Tumors (RECIST) every two cycles (every 8 weeks) [33]. All sites of disease at baseline were documented. CT scans of the chest, abdomen, and pelvis were performed every 8 weeks. Complete response (CR) was defined as the disappearance of all lesions; partial response (PR) was defined as at least a 30% decrease in sum of longest diameter from baseline with no new lesions or progression of nontarget lesions; and progressive disease (PD) was defined as a 20% increase in sum of longest diameter from the smallest measurement since the start of treatment, unequivocal progression in nontarget lesions, or the appearance of any new lesion. Patients not progressing for a minimum of 8 weeks as confirmed by CT imaging were considered to have stable disease (SD).

Toxicity was graded according to National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0. Safety was assessed through adverse event monitoring, physical examinations, vital signs, and clinical laboratory tests, including full hematology and chemistry panels done before each dosing. Chemotherapy doses were reduced by 20 percent in cases of persistent hematologic toxic effects or grade 3 or 4 non-hematologic toxic effects. Patients who discontinued study treatment were followed every 3 months, or until death, to collect data on overall survival.

Statistical analysis

The primary outcome was 1-year overall survival, with secondary endpoints of 1-year overall survival, median overall survival, tumor response rate, and safety. Overall survival and progression-free survival endpoints were assessed using the Kaplan–Meier product limit method. A 95% confidence interval for the median survival time and median progression-free survival time was calculated using the Brookmeer and Crowley method [34].

A 2008 meta-analysis by Korn et al. examined phase II cooperative group trials in metastatic melanoma to determine overall survival benchmarks for single-arm phase II trials [35]. The study included predicted 1-year overall survival rates for patients determined from a logistic regression model based on gender, performance status, presence of visceral disease, and whether the trial included brain metastases patients. For each patient on the trial, the authors recommend obtaining his or her predicted 1-year overall survival rate from provided tables, and determining the average of the predicted values for the patient cohort (i.e., the historical control rate). After the trial is complete, the proportion of patients alive at 1 year is obtained and compared to the calculated historical control rate. They suggested that the treatment may be worthy of further study if a comparison of the two rates gives a $P$-value $<0.10$.

Results

Patients

Fifty-two patients were enrolled in the trial and began treatment. Patient characteristics are summarized in Table 1. Patients with distant metastases are subclassified according to the site(s) of disease involvement and the serum lactic dehydrogenase (LDH) level [36]. Patients with M1a disease only have distant skin, subcutaneous, or lymph node metastases with normal LDH levels and have the best prognosis. M1b disease indicates lung metastases with normal LDH. Patients with M1c disease have other visceral metastases, or metastases with an elevated LDH, and have the worst prognosis. Approximately eighty percent of the patients in this trial had M1c disease. Lung, soft tissue, and lymph nodes were the most common sites of metastatic disease; 21.2% of patients also had brain metastases. Two-thirds of patients had received prior biological or chemotherapy; 51.9% had chemotherapy and 34.6% had prior IL-2 or interferon treatment. Fifty percent of patients had prior treatment after diagnosis with stage IV melanoma.
Overall response

There were no complete responses, and 8 partial responses, for an objective response rate of 15.4%. Table 2 shows best overall response per RECIST criteria. All patients were included in the response rate calculation, including nine patients with no post-baseline CT scan who were counted as non-responders (of the nine, only one died prior to CT scan). Clinical benefit rate (CR + PR + SD) was 52%. One patient is still currently on study.

Toxicity

Toxicity observations were based on all treated patients. All patients reported at least one treatment-related adverse event. The majority of observed adverse events were mild or moderate (grades 1 or 2) in severity. Most common grade 1 or 2 events were alopecia, anemia, and fatigue (Table 3). The most common grade 3 or 4 toxicity was neutropenia, which occurred in 16 patients, followed by anemia in 8 patients. Only one patient had to be removed from the study secondary to prolonged neutropenia; four other patients requested to be taken off study secondary to intolerance of side effects. There were no treatment-related deaths.

Progression-free survival

Figure 1 shows the Kaplan–Meier plot of progression-free survival. Median progression-free survival was calculated at 134 days (4.8 months), with a 95% confidence interval of 91 to 214 days. Patients who were still alive and had not yet progressed were censored. For these patients, date of their last clinical assessment by investigator without progression was entered as date of censoring. One patient who died prior to first CT scan assessment was counted as having progressed. Four patients had central nervous system (CNS) progression. One had intracerebral hemorrhage.
and was taken off study; the second had systemic metastases as well and was taken off study; the third complained of fatigue and asked to be taken off study. However, the fourth patient with new brain metastases, who had no progression of systemic metastases, was continued on the trial, as this regimen is not considered active against CNS metastases. 6-month progression-free survival rate was 37%.

**Overall survival**

Median overall survival was calculated at 320 days (11.4 months), with 95% confidence interval of 190 to 390 days. Figure 2 shows the Kaplan–Meier product limit estimation plot of overall survival. Twenty-five of 52 patients were alive after 1 year, resulting in a 1-year overall survival rate of 48.1%. Based on the method for determining predicted survival rates recommended by Korn et al., a historical 1-year overall survival rate of 24.3% was obtained for our patient cohort. A comparison of the two survival rates gives a \( P \)-value of 0.012, indicating that this regimen merits further study. The difference between the historical and observed 1-year survival rate was 23.8%, with a 95% confidence interval of 4–41%.

At the end of the observation period in October 2010, eleven patients (21.2%) were still alive and were censored on the Kaplan–Meier curve (shown as tick marks). Nine patients were alive 2 years after starting treatment, and two patients were alive after 6 years.

**Discussion**

Anemia and neutropenia were the most frequent grade 3 or 4 adverse events related to the DVS regimen. This was expected, given the known toxicities of docetaxel. This was also not surprising considering that two-thirds of patients had received prior treatment with biological or chemotherapy agents, with many having recently completed other melanoma regimens, which may have contributed to the myelosuppresion seen in some of the patients. One patient had to be taken off study for prolonged neutropenia; however, there were no other unexpected adverse events or treatment-related deaths. The toxicity of the DVS regimen thus appears superior compared to CVD-biochemotherapy or high-dose IL-2.

For the trial reported here, patients treated with the DVS regimen had a median progression-free survival of 4.8 months. The objective response rate of 15.4% is similar to that seen with other chemotherapy regimens used to treat melanoma. However, therapy with DVS led to median overall survival of 11.4 months, and a 1-year overall survival of 48.1%. This rate was approximately twofold higher than the 24.3% predicted survival rates calculated according to the methods described by Korn et al. and was statistically significant \( (P < 0.012) \), indicating that this regimen merits further study. While this regimen did not result in a high response rate, it led to prolonged survival for both previously treated and untreated patients with advanced melanoma. This outcome may be related to immune modulation by GM-CSF in combination with antiangiogenic and antitumor effects mediated by metronomic docetaxel (14, 31–32). The 1-year survival seen for this patient cohort compares favorably with dacarbazine, temozolomide, IL-2, and CVD-biochemotherapy treatments. While the DVS regimen appears to be active in prolonging survival for both previously treated and untreated patients with advanced melanoma, subset analysis was not performed due to the small sample size of treatment naïve cases (33%).

It should be noted as a caveat that the Korn data were derived from multi-institutional trials performed over many decades, rather than a short-term one-institution study. There are potential selection biases implicit in our trial and current prognostic variables that are not factored into the Korn model, which may have affected patient survival.
Nevertheless, the Korn analysis provides a useful benchmark for consideration. Based on our observed efficacy and toxicity profiles, the docetaxel, vinorelbine, and GM-CSF regimen is of interest for further study in randomized phase III trial.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

References

1. Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics, 2010. Cancer J Clin 59:225–249
2. Markovitch S, Erickson L, Rao R (2007) Malignant melanoma in the 21st century, Part 2: staging, prognosis, and treatment. Mayo Clin Proc 82:490–513
3. Middleton MR, Grob JJ, Aaronson N, Fierbeck G, Aaronson N, Fierbeck G, Tilgen W, Seiter S, Gore M, Aamal S, Cebon J, Coates A, Dreno B, Henz M, Schadendorf D, Kapp A, Weiss J, Fraass U, Statkevich P, Muller M, Thatcher N (2000) Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 18:158–166
4. Atkins MB, Lotze MT, Butcher JP, Fisher RI, Weiss G, Margolin K, Abrams J, Sznol M, Parkinson D, Hawkins M, Paradise C, Kunkel L, Rosenberg SA (1999) High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 17:2105–2116
5. Smith FO, Downey SG, Klapper JA, Yang JC, Sherry RM, Royal RE, Kammula US, Hughes MS, Restifo NP, Levy CL, White DE, Steinberg SM, Rosenberg SA (2008) Treatment of metastatic melanoma using interleukin-2 alone or in conjunction with vaccines. Clin Cancer Res 14:5610–5618
6. Atkins MB, Hsu J, Lee S, Cohen GI, Flaherty LE, Sosman JA, Sondak VK, Kirkwood JM (2008) 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. J Clin Oncol 26:5748–5754
7. Eton O, Legha SS, Bediakian AY, Lee JJ, Buzaid AC, Hodges C, Ring SE, Papadopoulos NE, Plager C, East MJ, Zhan F, Benjamins RN (2002) Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. J Clin Oncol 20:2045–2052
8. Ives NJ, Stowe RL, Lorigan P, Wheatley K (2007) Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2, 621 patients. J Clin Oncol 25:5426–5434
9. Hodi FS, O’Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebèe C, Peschel C, Quirt I, Clark JJ, Wolchok JD, Weiser J, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711–723
10. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, O’Dwyer PJ, Lee RJ, Grippo JF, Nolop K, Chapman PB (2010) Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 363:809–819
11. Nazarian R, Shi H, Wang Q, Kong X, Koya RC, Lee H, Chen Z, Lee MK, Attar N, Szegar H, Chodon T, Nelson SF, McArthur G, Sosman JA, Ribas A, Lo RS (2010) Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. Nature 468:973–977
12. Photiou A, Shah P, Leong LK, Moss J, Retsas S (1997) In vitro synergy of paclitaxel (Taxol) and vinorelbine (Navelbine) against human melanoma cell lines. Eur J Cancer 33:463–470
13. Neale MH, Myatt NE, Houry GG, Weaver P, Lamont A, Hungerford JL, Kurbacher CM, Hall P, Corrie PG, Cree IA (2001) Comparison of the ex vivo chemosensitivity of uveal and cutaneous melanoma. Melanoma Res 11:601–609
14. Wu H, Xin Y, Zhao J, Sun D, Li W, Hu Y, Wang S (2011) Metronomic docetaxel chemotherapy inhibits angiogenesis and tumor growth in a gastric cancer model. Cancer Chemother Pharmacol Feb 3. [Epub ahead of print]
15. Sanchez JM, Balana C, Font A, Sanchez JJ, Manzano JL, Guilhot M, Margeli M, Richardet M, Rosell R (2002) Phase II non-randomized study of three different sequences of docetaxel and vinorelbine in patients with advanced non-small cell lung cancer. Lung Cancer 38:309–315
16. Rodriguez J, Calvo E, Cortes J, Santisteban M, Perez-Calvo J, Martinez-Monge R, Brugarolas A, Fernandez-Hidalgo O (2002) Docetaxel plus vinorelbine as salvage chemotherapy in advanced breast cancer: a phase II study. Breast Cancer Res Treat 76:47–57
17. Gomez-Bernal A, Cruz JJ, Garcia-Palomo A, Arizcun A, Pujol E, Diaz P, Martin G, Fonseca E, Sanchez P, Rodriguez C, del Barco E, Lopez Y (2003) Biweekly docetaxel and vinorelbine in anthracycline-resistant metastatic breast cancer: a multicenter phase II study. Am J Clin Oncol 26:127–131
18. Retsas S, Mohith A, Mackenzie H (1996) Taxol and vinorelbine: a new active combination for disseminated malignant melanoma. Anticancer Drugs 7:161–165
19. Jimeno A, Hitt R, Quintela-Fandino M (2005) Phase II trial of vinorelbine tartrate in patients with treatment-naive metastatic melanoma. Anticancer Drugs 16:53–57
20. Whitehead RP, Moon J, McCachren SS, Hersh EM, Samlowski WE, Beck JT, Tchekmedyan NS, Sondak VK (2004) A Phase II trial of vinorelbine tartrate in patients with disseminated malignant melanoma and one prior systemic therapy: a southwest oncology group study. Cancer 100:1699–1704
21. Feng LG, Savraj N, Hurley J, Marin M, Lai S (2000) A clinical trial of intravenous vinorelbine tartrate plus tamoxifen in the treatment of patients with advanced malignant melanoma. Cancer 88:584–588
22. Filder JJ, Kleinnerman ES (1984) Lymphokine-activated human blood monocytes destroy tumor cells but not normal cells under cocultivation conditions. J Clin Oncol 2:937–943
23. Grabstein KH, Urdal DL, Tushinski RJ, Mochizuki DY, Price VL, Cantrell MA, Gillis S, Conlon PJ (1986) Induction of macrophage tumoricidal activity by granulocyte-macrophage colony-stimulating factor. Science 232:506–508
24. Thomassen MJ, Barna BP, Rankin D, Wiedermann HP, Ahmad M (1989) Differential effect of recombinant granulocyte macrophage colony-stimulating factor on human monocytes and alveolar macrophages. Cancer Res 49:4086–4089
25. Wing EJ, Magee DM, Whiteside TL, Kaplan SS, Shadduck RK (1989) Recombinant human granulocyte macrophage colony-stimulating factor enhances monocyte cytotoxicity and secretion of tumor necrosis factor alpha and interferon in cancer patients. Blood 73:643–646
26. Chachoua A, Oratz R, Hoogmoed R, Caron D, Peace D, Liebes L, Blum RH, Vilcek J (1994) Monocyte activation following
systemic administration of granulocyte-macrophage colony-stimulating factor. J Immunother 15:217–224
27. Kumar R, Dong Z, Fidler IJ (1996) Differential regulation of metalloelastase activity in murine peritoneal macrophages by granulocyte-macrophage colony-stimulating factor and macrophage colony-stimulating factor. J Immunol 157:5104–5111
28. Dong Z, Kumar R, Yang X, Fidler IJ (1997) Macrophage-derived metalloelastase is responsible for the generation of angiostatin in Lewis lung carcinoma. Cell 88:801–810
29. Dranoff G, Jaffee E, Lazenby A, Golombek P, Levitsky H, Brose K, Jackson V, Hamada H, Pardoll D, Mulligan RC (1993) Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. Proc Natl Acad Sci USA 90:3539–3543
30. Armstrong CA, Botella R, Galloway TH, Murray N, Kramp JM, Song IS, Ansel JC (1996) Antitumor effects of granulocyte-macrophage colony-stimulating factor production by melanoma cells. Cancer Res 56:2191–2198
31. Spitler LE, Grossbard ML, Ernstoff MS, Silver G, Jacobs M, Hayes FA, Soong SJ (2000) Adjuvant therapy of stage III and IV melanoma using granulocyte-macrophage colony stimulating factor. J Clin Oncol 18:1614–1621
32. Lawson DH, Lee SJ, Tarhini AA, Margolin KA, Ernstoff MS, Kirkwood JM (2010) E4697: phase III cooperative group study of yeast-derived granulocyte macrophage colony-stimulating factor (GM-CSF) versus placebo as adjuvant treatment of patients with completely resected stage III–IV melanoma. J Clin Oncol 28:15s, (suppl; abstr 8504)
33. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 45:228–247
34. Brookmeyer R, Crowley J (1982) A confidence interval for the median survival time. Biometrics 38:29–41
35. Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, Moon J, Sondak VK, Atkins MB, Eisenhauer EA, Parulekar W, Markovic SN, Saxman S, Kirkwood JM (2008) Meta-analysis of phase ii cooperative group trials in metastatic stage IV melanoma to determine progression free and overall survival benchmarks for future phase II trials. J Clin Oncol 26:527–534
36. (2010) Melanoma of the Skin. In: AJCC Cancer Staging Manual. Springer, New York, p 325