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Phase II trial of temozolomide and sorafenib in advanced melanoma patients with or without brain metastases

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Abstract

Purpose—The combination of the oral alkylating agent temozolomide and the oral multi-kinase inhibitor sorafenib was evaluated in advanced melanoma patients.

Patients and Methods—Patients with metastatic melanoma (N=167) were treated on four arms. All patients received sorafenib at 400 mg orally twice daily without interruption. Patients without brain metastases or prior temozolomide were randomized between Arm A: extended dosing of temozolomide (EDT; 75 mg/m² temozolomide daily for 6/8 weeks) and Arm B: standard dosing (SDT; 150 mg/m² temozolomide daily for 5/28 days). Patients previously treated with temozolomide were enrolled on Arm C: EDT. Patients with brain metastases and no prior temozolomide were assigned to Arm D: SDT. The primary endpoint was 6-month progression-free survival (PFS) rate. Secondary endpoints included response rate, toxicity rates, and the rates of *BRAF* or *NRAS* mutations.

Results—The 6-month PFS rate for arms A, B, C, and D were 50%, 40%, 11%, and 23%. The median PFS for patients on arm A, B, C, and D was 5.9, 4.2, 2.2, and 3.5 months, respectively. No significant differences were observed between Arms A and B in 6-month PFS rate, median PFS, or response rates. Treatment was well tolerated in all arms. No significant differences in toxicity were observed between arms A and B except for more grade 3–4 lymphopenia in arm A.

Conclusion—Temozolomide plus sorafenib was well tolerated and demonstrated activity in melanoma patients without prior history of temozolomide. The activity of this combination regimen warrants further investigation.

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Introduction

In the United States an estimated 59,940 new diagnoses of melanoma were made in 2007 (1). Once metastatic disease develops the median survival is less than one year (2). The development of brain metastases in approximately 50% (3,4) of melanoma patients contributes significantly to the rapid morbidity and mortality in patients with metastatic disease. Various combinations of chemotherapy (5–8), or immunotherapy (9–12) have failed to improve survival compared to single agent dacarbazine. (13) Temozolomide is a related oral alkylating agent that has been reported to produce response rates of 4–13% and median PFS of 1.2 months (14,15) in patients with brain metastases, and 1.9 months (16) in patients without brain metastases. Despite this limited activity temozolomide is commonly used for the metastatic melanoma, because of its CNS penetration, tolerability, and ease of delivery. A number of therapies have been safely combined with temozolomide in patients with metastatic melanoma. Preclinical studies have identified tumor angiogenesis as a target in melanoma(17). The combination of temozolomide with the antiangiogenic agent thalidomide yielded encouraging response rates initially(18), but concerns for bleeding, thrombosis and infection, limited further development of this regimen.

By 2002, activating mutations in the serine/threonine kinases *BRAF*, and *NRAS* were identified in 66% (19) and 15% (20) of melanoma cell lines respectively, establishing MAPK signaling as a new therapeutic target in melanoma. Sorafenib, a kinase inhibitor which inhibits BRAF and vascular endothelial growth factor receptors (VEGFR2 and VEGFR3), in addition to other kinases, demonstrated antitumor activity in preclinical investigations.(21) In a single agent phase II trial sorafenib produced no tumor responses and resulted in a median PFS of 2.8 months. (22) A phase II trial combining sorafenib with carboplatin and paclitaxel appeared promising in metastatic melanoma patients (N=105), with a response rate of 27% and median PFS of 8.8 months, but significant toxicity(23).

This clinical trial was designed to assess the safety and preliminary activity of the combination of temozolomide and sorafenib, in patients with metastatic melanoma. This four-arm trial was designed with the following aims: 1) to determine if there was a significant difference in toxicity or efficacy in patients receiving extended versus standard dosing of temozolomide in combination with sorafenib 2) To determine the activity of temozolomide with sorafenib in patients with previous exposure to temozolomide and 3) to determine the safety and activity of temozolomide and sorafenib in patients with brain metastases.

Patients and Methods

Patients

Patients ≥ 18 years, with histologically confirmed metastatic or unresectable melanoma, measurable disease, an ECOG performance status of < 2 , adequate hematologic (White Blood Count [WBC] $\geq 3,000/\text{mm}^3$, absolute neutrophil count [ANC] $\geq 1,500/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$), renal (serum creatinine $\leq 2.0 \times$ upper limit of normal [ULN]), hepatic (bilirubin $\leq 1.5 \times$ ULN AST/ALT $\leq 2.5 \times$ ULN or ≤ 5.0 ULN in the presence of liver metastases), and coagulopathic (INR ≤ 1.5 and PTT $<$ ULN;) function were eligible. There was no limit on the number of prior therapies. Prior sorafenib was allowed. Patients had discontinued prior systemic therapy 4 weeks before entering the study. Prior brain radiotherapy was allowed for patients enrolled on arms C and D. Patients with stable or clinically asymptomatic progressive brain lesions were enrolled on arms C and D. Prior brain radiation therapy was allowed if patients had completed radiation therapy and discontinued steroids prior to enrollment. The study protocol was approved by the institutional review boards at the University of Pennsylvania and Dana Farber/Harvard Cancer Center. All patients provided informed consent before enrollment.

Treatment Plan

The treatment plan is outlined in Table 1. All patients were treated with single-agent sorafenib 400 mg orally twice daily seven days before starting temozolomide and continued without interruption. Patients without brain metastases or prior temozolomide were randomized between: arm A, extended daily dosing (EDT) of temozolomide 75 mg/m² daily for 6/8 weeks (one cycle); or arm B, standard dosing (SDT) of temozolomide 150 mg/m² daily for 5/28 days (one hemi-cycle). Patients with prior temozolomide exposure were assigned to arm C, and received EDT with sorafenib. Patients with brain metastases and no prior temozolomide were assigned to arm D, and received SDT with sorafenib.

Therapy was continued until disease progression or intolerable toxicity. Two dose reductions for sorafenib and one for temozolomide were allowed. For \leq grade 3 toxicities attributable to sorafenib (e.g. hand-foot syndrome, rash, diarrhea) sorafenib was held (<21 days)_until resolution of the toxicity to \leq grade 1 and sorafenib was restarted at the same dose. During dose interruption of sorafenib, patients continued on temozolomide. If the toxicity returned at the same severity, sorafenib was held and restarted at a reduced dose of 200 mg b.i.d. or 200 mg q.d. (second dose reduction). Dose re-escalation of sorafenib was allowed for dose-reduced patients with sorafenib-associated toxicities that resolved to \leq grade 1. For patients that experienced grade 3 granulocytopenia or thrombocytopenia, temozolomide was held (< 28 days)_until resolution of the toxicity to \leq grade 1 toxicity and was restarted a reduced dose: 100 mg/m² (arms B, D) or 50 mg/m² (arms A,C). Prophylactic granulocyte colony stimulating factors were not permitted. All other supportive care measures were permitted.

Assessment of Response and Toxicity

Response assessments consisted of history and physical exam every 4 weeks and CT scans of the chest, abdomen, and pelvis every 8 weeks (one cycle). Responses were investigator-assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Responses were confirmed by followup radiographic evaluation ≥ 4 weeks after the initial response criteria were met. MRI scans of the brain were obtained in follow-up only if clinically indicated. Toxicities were graded using the National Cancer Institute Common Toxicity Criteria Version 3.

Mutations in BRAF and NRAS

Blocks or sections were received from 88 (50%) patients for potential evaluation for mutational status. Tumor cell fraction was enriched and DNA isolated using our previously published techniques(23) DNA was extracted using standard protocols. Screening for mutations by PCR sequencing was done in *BRAF* (exons 11, 15) and *NRAS* (exons 1, 2) as previously reported (24). The PCR products were sequenced using BigDye Terminator v1.1 Cycle on an ABI PRISM 3130x1 Genetic Analyzer (Applied Biosystem). Sequences were analyzed using Mutation Surveyor, DNA Variant Analysis version 3.1 (SoftGenetics LLC). An algorithm for genetic testing was used, in that patients were first screened for mutations in *BRAF* exon 15 and *NRAS* exon 2, and if that was negative, then *BRAF* exon 11 and *NRAS* exon 1 were evaluated.

Statistical Analysis

The primary endpoint was the rate of 6-month progression-free survival (PFS). Secondary endpoints included median PFS, rate of 1-year overall survival (OS), median OS, overall response rate (ORR), toxicity rates, and *BRAF*, and *NRAS* mutational status and PFS. Progression-free survival was defined as the interval of time since receiving first study drug to time of clinical or radiographic progression, or death due to any cause. Patients discontinuing therapy due to toxicity or personal choice, or were actively on trial at the time of analysis were

censored from analysis of progression-free survival. For arms A, B, and C a sample size of 38 in each arm provided a power of 0.8 with a two-sided significance level of 0.05 to detect a 25% 6-month PFS rate compared to a null hypothesis of 12% 6-month PFS rate(16). For patients on arm D a sample size of 53 patients provided a power of 0.8 with a two-sided significance level of 0.05 to detect a 6-month PFS of 15% compared to a null hypothesis of 7% 6-month PFS rate(14). Blocked randomization with variable block size was used to randomize patients between arms A and B, stratified by prior sorafenib use. Although not identified as an endpoint in the study protocol, phase II benchmark analysis including the calculation of predicted 6-month PFS rate (Figure 1) and 1-year survival rate (Figure 2) was done according to recommendations of Korn et al.(25) Briefly the predicted 1-year survival rate for each patient was calculated using Table 3 and Appendix table A2(25) and the average predicted OS (π_1) or 6-month PFS rate (π_2) was determined. The treatment was deemed worthy of further study if the null hypothesis of observed OS rate $\leq \pi_1$ or the observed 6-month PFS rate $\leq (\pi_2)$ was rejected with p-value < 0.1 . The 38 subjects enrolled to the arms without brain metastasis or prior temozolomide provided 95% power to detect any toxicity occurring at a rate of at least 8%. Rates of interest were estimated along with 95% confidence intervals. Arms A and B were compared using chi-squared tests for 6-month PFS and response rates and the logrank test for PFS curves. Differences between groups for continuous outcomes and categorical outcomes were assessed by t-tests and Fisher exact tests, using StatXact software. The association between continuous outcomes and categorical outcomes were assessed using Pearson or Spearman correlation coefficients, and chi-square or Fisher exact tests. Kaplan-Meier estimates of progression-free survival and 95% confidence intervals were calculated using Graphpad Prism software.

Results

Patient Accrual and Characteristics

Between June 2005 and May 2008, 180 patients were enrolled. Three patients were ineligible due to decline in performance status from screening to enrollment, and 10 patients were considered inevaluable for response or toxicity because they were removed from study before the first evaluation (one patient) or never received combination therapy (nine patients). A total of 78 patients were randomized between arms A and B. Due to block randomization, 2 additional patients were accrued to arm B in order to meet the target accrual for arm A. Characteristics of patients which are known to be prognostic in Stage IV melanoma patients (age, sex, stage, and LDH) were well balanced (Table 2) in patients randomized between arms A and B. The median number of prior chemotherapy regimens in patients on arms A, B and D was 0 (range: A:0–5, B:0–3, D:0–3). Six patients had prior sorafenib and were not excluded from further analyses. At the time of design there was no evidence that progression on non-temozolomide chemotherapy plus sorafenib regimen predicts inactivity of temozolomide with sorafenib so patients with prior sorafenib or prior sorafenib with non-temozolomide chemotherapy were permitted. A significantly higher percentage of patients on arm C had a baseline ECOG performance status of 1 compared to patients enrolled on arms A, B and D. The average number of prior therapies in patients on arm C was 1.67 ± 1.17 .

Survival and Response

Kaplan-Meier analysis of PFS was conducted (Figure 1A). There was no significant difference in PFS between arms A and B (log-rank test $p=0.692$). The 6-month PFS rate for arms A, B, C, and D were 50%, 40%, 11%, 23% respectively (Table 3). The median PFS for arms A, B, C, and D were 5.9, 4.2, 2.2, and 3.5 months, respectively. Using a recently reported benchmark analysis(25) the predicted 6-month PFS rate was compared to the observed 6-month PFS rate for arms A (16% v. 50%; $p=0.002$), B (17% v. 40%; $p=0.03$), C (15% v. 11%), and D (16% v. 23%; $p=N.S.$).

By September 2008, survival data was available for 157 out of 167 patients with 10 patients lost to follow-up and whose survival duration was censored at the time of last contact. One hundred forty-one deaths had occurred. Kaplan-Meier analysis of OS was conducted for all 4 arms (Figure 1B). The median survival of patients on arms A, B, C, and D were 10.5, 10.5, 5, and 8 months, respectively. Using benchmark analysis (Table 3), the predicted 1-year survival rate was compared to the observed 1-year survival rate for arms A (34% v. 33%; $p = \text{N.S.}$), B (35% v. 48%; $p = \text{N.S.}$), C (18% v. 14%), and D (21% v. 33%; $p = 0.08$).

The combination of temozolomide and sorafenib yielded one complete response in a patient on Arm B (Table 4). All other responses were partial. There was no significant difference in overall response rate (ORR) between arms A (24%, [95% CI 11–40%]) and B (15%, [95% CI 6–30%]). Patients with prior temozolomide had no responses. In patients with brain metastases (arm D), a 15% ORR in peripheral tumors and 48% SD (best response) rate was observed from temozolomide and sorafenib. CNS tumors were not included as target lesions since the majority of patients were treated with prior radiation therapy. Of the 6 patients with prior sorafenib 4 had SD and 2 had PD. The 15–24% response rate observed in patients without prior temozolomide treatment is similar to previous reported response rates for single agent temozolomide. Nevertheless, responses were durable; the median PFS from time of enrollment for patients with tumor response by RECIST criteria was 11 months.

Safety

The only significant difference in grade 3–4 toxicities (Table 5) in patients randomized between arms A and B was lymphopenia (53% v. 15%, $p < 0.05$). Grade 3–4 lymphopenia was also observed in 32% of patients on arm C who had significantly less exposure to extended dosing of temozolomide compared to patients enrolled on arm A. Despite this high rate of lymphopenia there were no documented opportunistic infections, and no prophylactic antibiotics were given.

Other common (>10%) grade 3–4 toxicities were fatigue, hand/foot skin reaction, rash, hypertension, and diarrhea. A high proportion of patients experienced chronic grade 1–2 toxicity, with the most common being nausea, vomiting, anorexia, and weight loss. One patient had significant delay in wound healing at the site of previous radiation. Three patients had deep venous thrombosis and one patient had arterial thrombosis. There were no episodes of symptomatic hemorrhage into an existing CNS lesion.

BRAF and NRAS mutational analysis

Eighteen of 88 (20%) tumor blocks obtained could not be used for DNA extraction for one of several reasons: volume of tumor was too small, admixture of stroma and tumor did not allow us to obtain over 70% tumor, and no tumor was present in the blocks provided. Genotyping results for both BRAF exons 11, 15 and NRAS exons 1, 2 from high-quality DNA was available from tumor blocks for 62/167 patients (37%) evaluable for response (Table 6). BRAF V600E and V600K mutations were identified in 26/62 (42%) patients. NRAS mutations (G13D, G13R, Q61R, Q61K, or Q61L) were identified in 8/62 (13%) patients. The remaining patients, 28/62 (45%) had no detectable mutations at either locus (WT/WT). Kaplan-Meier analysis of PFS (Figure 2) did not identify a significant difference between patients with *mutant BRAF* /WT NRAS versus WT BRAF /WT NRAS (HR=1.0, 95% CI 0.56–1.8; $p > 0.05$) or WT BRAF /Mutant NRAS versus WT BRAF /WT NRAS (HR 2.6, 95% CI 0.86–7.7; $p > 0.05$).

Discussion

This study evaluated the activity and safety of combining temozolomide and sorafenib in patients with Stage IV melanoma. The primary endpoint (rate of 6 month PFS) was significantly different from the null hypothesis in patients without prior temozolomide, indicating that

temozolomide and sorafenib is an active regimen in metastatic melanoma. While response rates were not significantly different than those observed with other temozolomide-based regimens, a high rate of stable disease contributed to prolongation of PFS compared to reported PFS in patients with or without brain metastases receiving temozolomide. *BRAF* or *NRAS* mutational status of the patient's tumor was not predictive of outcome. The safety profile of this completely oral regimen appears to be excellent. While profound and persistent lymphopenia was observed, there were no opportunistic infections (26). Most grade 3–4 toxicities were reversible with brief drug holidays. Chronic administration of this combination did result in a high percentage of burdensome grade 1–2 toxicities including fatigue, nausea, anorexia, diarrhea, weight loss and rash.

One of the goals of this study was to determine if extended versus standard dosing of temozolomide was more active or safe in combination with sorafenib. There was no significant difference in efficacy outcomes between extended versus standard dosing of temozolomide in combination with sorafenib. There was a trend towards increased response rate and 6-month PFS with extended dosing of temozolomide and sorafenib compared to standard dosing of temozolomide with sorafenib, without a significant increase in toxicity. While the sample size for each arm was sufficient to compare the rates of 6 month PFS of each schedule with historical benchmarks (see below), the sample size may not have been adequate to completely rule out a significant difference in activity between the two temozolomide dosing schedule. It should also be noted that there are other schedules of temozolomide which were not tested in combination with sorafenib. Some consider standard dosing schedule for temozolomide as 200 mg/m² p.o. q.d. for 5 /28 days instead of 150 mg/m² that was used in this study. Recently a dose intense bi-weekly schedule of temozolomide 150 mg/m² po for 7 out of every 14 days was compared with DTIC in a randomized phase III trial for patients with stage IV melanoma (27). While this regimen provides the most temozolomide exposure of any temozolomide dosing schedule commonly used, there was no difference in overall survival in this phase III trial and increased toxicity in patients treated with dose intense temozolomide compared to patients treated with standard temozolomide in a randomized phase III trial versus DTIC was observed. These results suggest that exploring additional schedules of temozolomide in combination with sorafenib is not warranted.

Patients with prior exposure to temozolomide (arm C) had a 0% response rate and short PFS. Few patients on arms A (11%), B (10%), and D (22%) had received prior chemotherapy for metastatic melanoma. The 23% 6 month progression free survival rate, median PFS of 3.5 months and overall survival of 8 months for patients on arm D are superior to any previous single agent temozolomide trial in this patient population. Increasing use of stereotactic radiosurgery alone or in combination with whole brain radiation therapy could have contributed independently to prolonged CNS-progression free survival and overall survival in patients on arm D. While concurrent steroid use was not permitted upon entry to the trial for safety concerns, once treatment was deemed well tolerated in individual patients, steroids for treatment of brain edema was frequently employed for symptomatic brain edema in patients on arm D.

The addition of sorafenib failed to improve the response rate or progression-free survival compared to carboplatin/paclitaxel alone among patients who previously received dacarbazine or temozolomide (28). The efficacy of carboplatin/paclitaxel with sorafenib versus carboplatin/paclitaxel/placebo in the first-line setting in patients with metastatic melanoma was tested in a randomized phase III (ECOG 2603). Recently, this study was stopped early after an interim analysis found that further study conduct was futile with regard to achieving the primary endpoint of significantly improved overall survival.

While randomized trials have determined that sorafenib does not improve progression-free or overall survival for melanoma when it is added to carboplatin and paclitaxel there is evidence that sorafenib may augment the efficacy of other chemotherapy backbones. A randomized phase II trial (N=101) found no overall survival benefit, but a significant difference in time to progression between treatment with dacarbazine with sorafenib compared to dacarbazine and placebo in patients with chemotherapy-naïve metastatic melanoma (29). Dacarbazine and sorafenib yielded a 24% ORR which is identical to the ORR for Arm A in this trial. Patients treated with dacarbazine and sorafenib had a 41% 6-month PFS rate, and the similar population of patients on Arms A and B in this trial collectively had a 44% 6-month PFS rate. These results suggest that the type of chemotherapy that is paired with sorafenib may be a key determinant of efficacy.

Recently, Korn et al. reported a meta-analysis that established benchmarks to assess the activity of phase II regimens for metastatic melanoma. Benchmark analysis found a significant difference between observed and predicted 6-month PFS rate for patients without prior temozolomide or brain metastases (arms A and B), but not for patients with brain metastases without prior temozolomide (arm D). In contrast, observed rates of 1-year survival were significantly different from predicted rates only in patients with brain metastases and no prior temozolomide (arm D). These results underscore some of the prevailing controversies that accompany the interpretation of phase II trials in metastatic melanoma. Based on benchmark analysis, it is reasonable to recommend a randomized phase III trial of temozolomide and sorafenib in patients without brain metastases, since the discrepancy between the 6-month PFS and the 1-year survival results points out that the large variance in the estimates for median overall survival suggests that a larger sample size is necessary to detect a survival advantage compared to historical benchmarks. Unlike the method to calculate the predicted 1-year survival rate, the calculation of predicted PFS rate does not take into account the inclusion of patients with brain metastases. Most trials including patients with brain metastases do not report 6-month PFS and therefore the true benchmark rates of 6-month PFS for this patient population may not be captured by the methodology of Korn et al. Based on these results it is reasonable to propose a randomized phase III trial of temozolomide and sorafenib versus temozolomide in patients with brain metastases.

Mechanistically, sorafenib is a small molecule multi-kinase inhibitor. Although sorafenib is a potent BRAF inhibitor in vitro, it is not clear that this is the case in patients at clinically achievable doses sorafenib. The *BRAF* V600E mutation rate (41%) in these patients was at the low end of the range observed in previous reports. While initial studies conducted in melanoma cell lines described the *BRAF* mutation rate at 60–70% (30), this genotyping effort identified a lower rate in one of the larger (n=62) prospectively conducted studies of an unselected population of human melanoma. There was no significant association between *BRAF* mutational status and response rate or PFS in patients treated with temozolomide and sorafenib. Previous studies with sorafenib (22,23) did not identify a significant association between *BRAF* mutational status and outcome. Based on the cumulative data available, *BRAF* mutation status can not be recommended as a selection criteria for future clinical trials involving sorafenib and chemotherapy for advanced melanoma. BRAF and NRAS mutational status could be a predictive maker in clinical trials of more specific BRAF inhibitors, and this approach is currently being investigated(31). These results raise the possibility that the activity observed when sorafenib is combined with chemotherapy may be related to inhibition of angiogenesis. This hypothesis is further supported by analysis of pretreatment tumors tissue from patients on a phase I/II clinical trial of sorafenib, carboplatin and paclitaxel(23), which found a significant correlation between high VEGFR2 expression and response rate(32).

The current results indicate that temozolomide and sorafenib may be an active regimen in temozolomide-naïve metastatic melanoma patients without and with brain metastases.

Especially since there is no well-defined treatment algorithm for the treatment of patients without targetable oncogenic mutations, and patients with mutated tumors who have progressed on selective kinase inhibitors, these results deserve further investigation. The major limitation of this phase II study is the lack of a control group. The negative results of two prior randomized trials testing the efficacy of sorafenib, carboplatin and paclitaxel highlights the need to conduct large randomized controlled trials to determine the true efficacy of sorafenib and temozolomide.

Statement of Translational Relevance

This four arm phase II trial characterizes the safety and activity of combining the Raf / VEGFR inhibitor sorafenib with temozolomide, in patients with metastatic melanoma. Preclinical evidence indicates activating BRAF mutations and angiogenesis are important molecular targets in melanoma. The results suggest this regimen is active in melanoma patients including patients with brain metastases, who have a poor prognosis. The identification of an active treatment regimens for melanoma patients with brain metastases is an unmet need in oncology practice. This manuscript reports the BRAF and NRAS genotyping of one of the largest prospectively collected unselected population of human melanoma tumors and determines that there is no correlation between mutation status and outcome in patients treated with sorafenib and temozolomide. The results of this study will guide the design of future clinical trials combining multikinase inhibitors such as sorafenib with chemotherapy for metastatic melanoma.

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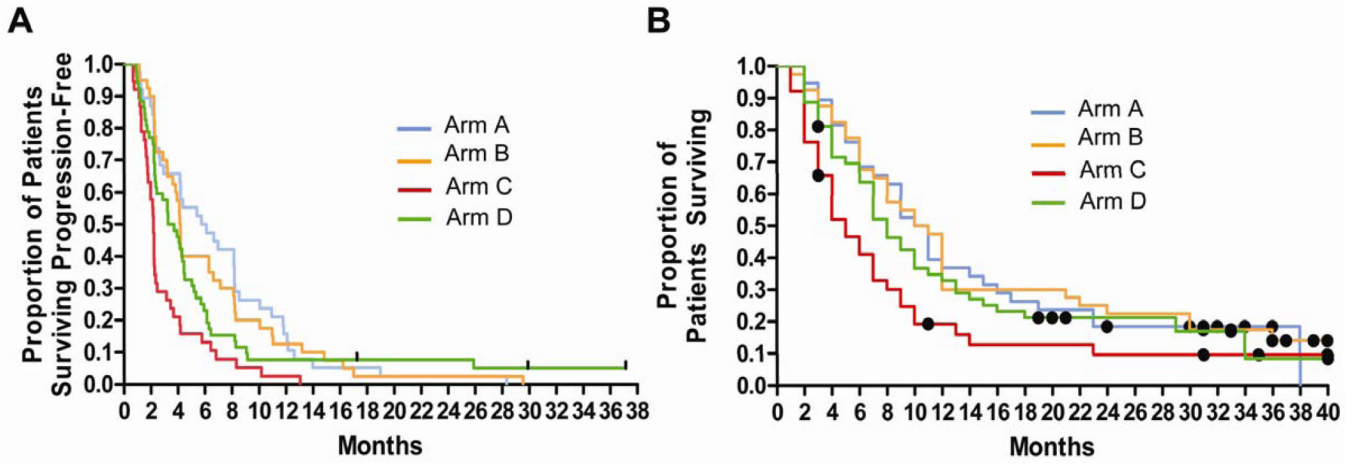


Fig 1. Progression-free survival (PFS) and overall survival (OS) in melanoma patients treated with temozolomide and sorafenib. (A–B): Kaplan-Meier curves for (A) PFS and (B) OS; Arm A (Blue): patients without brain metastases or prior temozolomide, treated with extended dosing temozolomide (EDT) Arm B (orange); patients without brain metastases or prior temozolomide treated with standard dosing temozolomide (STD), Arm C (red) Patients with prior temozolomide, EDT Arm D (green) patients with brain metastases, without prior temozolomide, STD: Dots: censored patients.

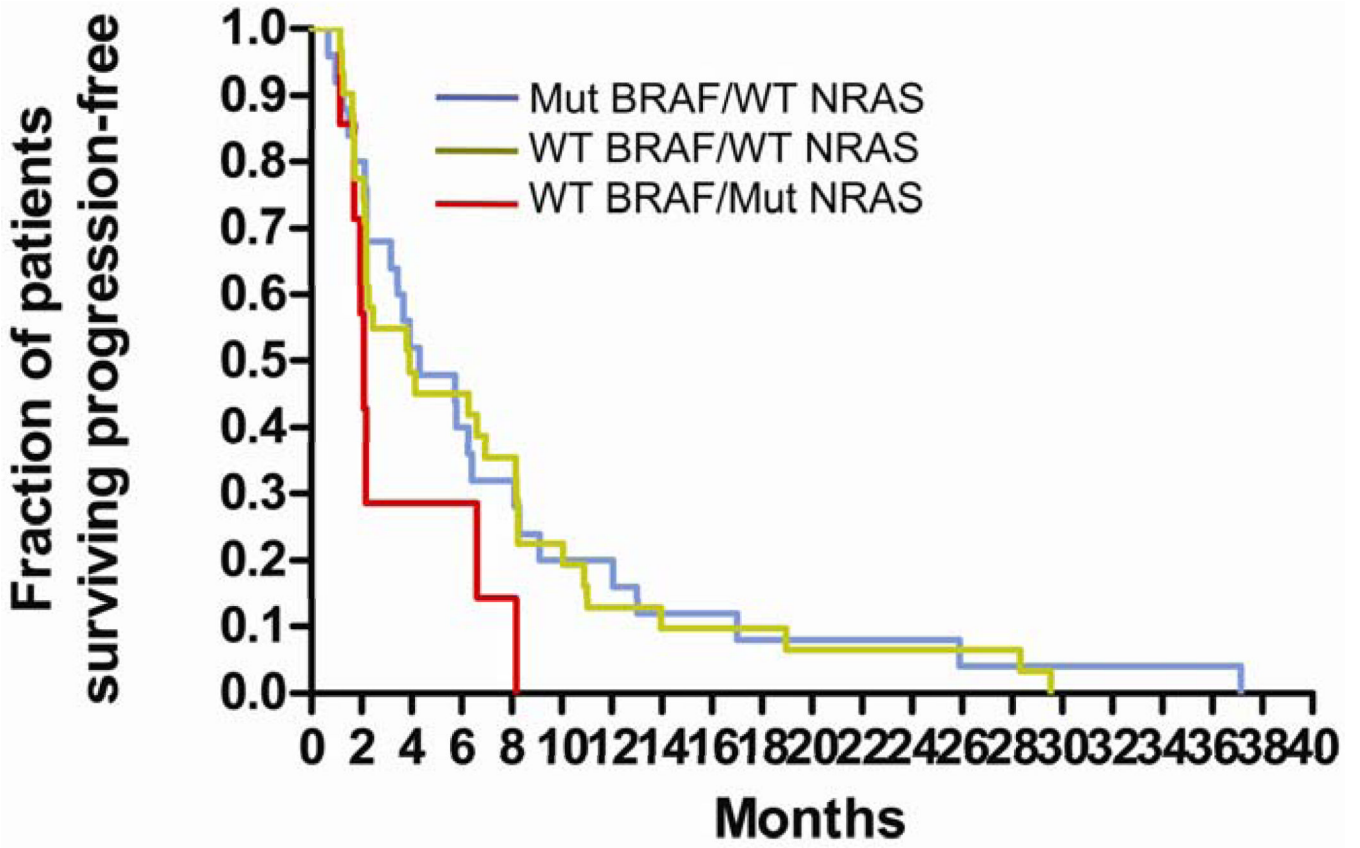


Fig 2. Kaplan-Meier curves for progression-free survival (PFS) for patients with tumor genotypes wild-type BRAF/mutant NRAS (WT/MuNRAS; red), mutant BRAF/wild-type NRAS (MuBRAF/WT; blue), wild-type BRAF/wild-type NRAS (WT/WT; green)

Table 1

Four-arm Trial Design

Arm	Brain Metastases	Prior Temozolomide	Randomized	Temozolomide Dosing
A	No	No	Yes	Extended*
B	No	No	Yes	Standard**
C	Allowed	Required	No	Extended
D	Required	No	No	Standard

* Extended Dosing: Temozolomide 75 mg/m² po qd for 6 out of every 8 weeks

** Standard Dosing: Temozolomide 150 mg/m² po qd for 5 out of every 28 weeks

Table 2

Patient Characteristics

Characteristic	Arm				Total
	A	B	C	D	
Number of patients	38	40	38	53	167
Age, years					
Median	62	61	61	58	61
Range	(26-83)	(44-84)	(35-78)	(37-83)	(26-84)
Sex, %					
Male	58	75	74	66	69
Female	42	25	26	34	31
AJCC Stage, %					
M1a	2	5	0	0	2
M1b	8	18	3	0	6
M1c	90	77	97	100	92
EEOG PS, %					
PS 0	71	90	50	72	75
PS 1	29	10	50*	28	25
No. prior therapies, median	0	0	1	0	0
Prior chemotherapy, %	11	10	100	19	37
LDH, %					
<ULN	61	58	36	47	51
ULN < LDH < 2XULN	23	23	42	36	31
>2XULN	16	19	22	17	18

* p < 0.05 compared to Arms A, B, D. Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Group; PS Performance Status; ULN, Upper Limit of Normal

Table 3
Benchmark Analysis of Progression Free survival (PES) and Overall Survival (OS)

Arm	A	B	C	D	P
Median PFS, months	5.9	4.2	2.2	3.5	
Predicted 6-month PFS rate*, %	16	17	15	16	NS
6-month PFS rate, %	50	40	11	23	NS
95%	33-66	25-57	4-26	14-40	
Median OS months	10.5	10.5	5	8	
Predicted 1 yr OS rate*, %	34	35	18	21	NS
Observed 1 year OS rate, %	34	48	14	33	<0.1
95%CI	21-47	30-60	6-30	22-47	
Number of patients evaluated	35	38	35	51	

* Calculated from Korm et al.25

Table 5

Toxicity

Toxicity, %	Arm A		Arm B		Arm C		Arm D	
	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4
Hematological Toxicity								
Anemia	34	-	45	5	24	-	30	-
Leukopenia	55	16	30	5	21	8	25	9
Lymphopenia	79	53*	68	15*	74	32	64	13
Neutropenia	34	-	15	3	5	5	9	9
Thrombocytopenia	37	5	23	3	24	3	32	-
Non-Hematological Toxicity								
Abdominal pain	18	-	13	-	5	3	11	-
Alopecia	61	-	40	-	13	-	30	-
Anorexia	66	3	55	-	47	5	53	15
Constipation	55	-	38	-	24	5	30	2
Dehydration	11	-	8	3	5	-	13	6
Diarrhea	61	11	48	3	18	3	55	6
Fatigue	79	16	73	13	58	5	74	6
Hand/foot syndrome	71	26	73	13	45	11	64	8
Headache	18	-	15	8	11	-	4	-
Hoarseness	16	-	18	-	16	-	17	2
Hypertension	29	3	13	13	16	5	26	2
Myalgia	34	3	25	3	26	-	23	2
Nausea	71	11	75	3	55	5	58	13
Rash	87	13	85	3	50	8	62	11
Stomatitis	47	3	38	0	39	3	47	4
Vomiting	32	8	35	-	42	3	47	9
Weight loss	63	16	55	5	37	5	55	6

* P<0.05

Table 6*BRAF*, *NRAS* mutations and PFS

	<i>Mu BRAF/WT</i>	<i>WT/WT</i>	<i>Wt/Mu NRAS</i>	Total No.
Total No Sequenced (%)	26(42)	28(45)	8(13)	62
Arm A, No. (%)	3(19)	10(63)	3(18)	16
Arm B, No. (%)	4(25)	10(63)	2(12)	16
Arm C, No. (%)	11(61)	2(11)	5(28)	15
Arm D, No. (%)	8(53)	6(40)	1(7)	15
Median PFS, mo	4.3	3.9	2.1	
HR [95% CI]	1.0 [0.56-1.8]		2.6 [0.86-7.7]	

Abbreviations: *Mu BRAS* Mutant BRAF includes *BRAF* V600K mutations; *WT* Wild-Type; *Mu NRAS* includes *NRAS* G13D, G13R, Q61R, Q61K, Q61L mutations; PFS, Progression-free survival.