Phase II Trial of Temozolomide and Sorafenib in Advanced Melanoma Patients with or without Brain Metastases


Abstract

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

Experimental Design: Patients with metastatic melanoma \( (n = 167) \) were treated on four arms. All patients received sorafenib at 400 mg p.o. twice daily without interruption. Patients without brain metastases or prior temozolomide were randomized between arm A: extended dosing of temozolomide (75 mg/m² temozolomide daily for 6 of every 8 weeks) and arm B: standard dosing (150 mg/m² temozolomide daily for 5 of every 28 days). Patients previously treated with temozolomide were enrolled on arm C: extended dosing of temozolomide. Patients with brain metastases and no prior temozolomide were assigned to arm D: standard dosing. The primary end point was 6-month progression-free survival (PFS) rate. Secondary end points included response rate, toxicity rates, and the rates of \( \text{BRAF} \) or \( \text{NRAS} \) mutations.

Results: The 6-month PFS rate for arms A, B, C, and D were 50%, 40%, 11%, and 23%, 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.

Conclusion: Temozolomide plus sorafenib was well tolerated and showed activity in melanoma patients without prior history of temozolomide. The activity of this combination regimen warrants further investigation. (Clin Cancer Res 2009;15(24):7711–8)

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 1 year (2). The development of brain metastases in ∼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 with single agent dacarbazine (13). Temozolomide is a related oral alkylating agent that has been reported to produce response rates of 4% to 13% and median progression-free survival (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 central nervous system (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 \( \text{BRAF} \) and \( \text{NRAS} \) were identified in 66% (19) and 15% (20) of melanoma cell lines, respectively, establishing mitogen-activated protein kinase signaling as a new therapeutic target in melanoma. Sorafenib, a kinase inhibitor that inhibits \( \text{BRAF} \) and vascular endothelial growth factor receptors (VEGFR2 and VEGFR3), in addition to other kinases, showed antitumor activity in preclinical
Translational Relevance

This four-arm phase II trial characterizes the safety and activity of combining the Raf/vascular endothelial growth factor receptor inhibitor sorafenib with temozolomide in patients with metastatic melanoma. Preclinical evidence indicates that activating BRAF mutations and angiogenesis are important molecular targets in melanoma. The results suggest that this regimen is active in melanoma patients including patients with brain metastases, who have a poor prognosis. The identification of an active treatment regimen for melanoma patients with brain metastases is an unmet need in oncology practice. This article 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 multi-kinase inhibitors such as sorafenib with chemotherapy for metastatic melanoma.

Patients and Methods

Patients. Patients ages ≥18 y, with histologically confirmed metastatic or unresectable melanoma, measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, adequate hematologic (WBC > 3,000/mm³; absolute neutrophil count, >1,500/mm³; platelets of >100,000/mm³), renal (serum creatinine of ≤2.0 x upper limit of normal (ULN)), hepatic (bilirubin ≤ 1.5 x ULN aspartate aminotransferase/alanine aminotransferase ≤ 2.5 x ULN or ≤ 5.0 ULN in the presence of liver metastases), and coagulopathic (international normalized ratio < 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 wk before entering the study. Prior brain radiation therapy was allowed if patients had completed radiation therapy and discontinued steroids before 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 p.o. twice daily 7 d 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 of every 8 wk (one cycle); or arm B, standard dosing (SDT) of temozolomide 150 mg/m² daily for 5 of every 28 d (one hemicycle). 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 ≥ grade 3 toxicities attributable to sorafenib (e.g., hand-foot syndrome, rash, diarrhea), sorafenib was held (<21 d) until resolution of the toxicity ≥ 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 twice daily (b.i.d.) or 200 mg daily (q.d.) (second dose reduction). Dose re-escalation of sorafenib was allowed for dose-reduced patients with sorafenib-associated toxicities that resolved to ≥ grade 1. For patients that experienced ≥ grade 3 granulocytopenia or thrombocytopenia, temozolomide was held (<28 d) until resolution of the toxicity ≥ grade 1 toxicity and was restarted at a reduced dose: 100 mg/m² (arms B and D) or 50 mg/m² (arms A and 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 wk and computed tomography scans of the chest, abdomen, and pelvis every 8 wk (one cycle). Responses were investigator assessed using the Response Evaluation Criteria in Solid Tumors guidelines. Responses were confirmed by followup radiographic evaluation ≥4 wk after the initial response criteria were met. Magnetic resonance imaging 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 3130 × 1 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 end point was the rate of 6-mo PFS. Secondary end points included median PFS, rate of 1-y overall survival (OS), median OS, overall response rate (ORR), toxicity rates, and BRAF and NRAS mutational status and PFS. PFS 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 PFS. 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-mo PFS rate compared with a null hypothesis of 12% 6-mo 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-mo PFS of 15% compared with a null hypothesis of 7% 6-mo 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
end point in the study protocol, phase II benchmark analysis including the calculation of predicted 6-mo PFS rate (Fig. 1) and 1-y survival rate (Fig. 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 (π₁) or 6-mo PFS rate (π₂) was determined. The treatment was deemed worthy of further study if the null hypothesis of observed OS rate ≤ π₁ or the observed 6-mo PFS rate ≤ π₂ was rejected with a P value of <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 (95% CI). Arms A and B were compared using χ² tests for 6-mo PFS and response rates and the log-rank 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 χ² or Fisher exact tests. Kaplan-Meier estimates of PFS and 95% CIs 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 invaluable 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, two additional patients were accrued to arm B 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 lactate dehydrogenase), 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 nontemozolomide chemotherapy plus sorafenib regimen predicts inactivity of temozolomide with sorafenib, so patients with prior sorafenib or prior sorafenib with nontemozolomide chemotherapy were permitted. A significantly higher percentage of patients on arm C had a baseline ECOG performance status of 1 compared with 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 (Fig. 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%, and 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 with the observed 6-month PFS rate for arms A (16% versus 50% \( P = 0.002 \)), B (17% versus 40% \( P = 0.03 \)), C (15% versus 11%), and D (16% versus 23% \( P = \) not significant [NS]).

By September 2008, survival data was available for 157 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 four arms (Fig. 1B). The median survival

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### Table 1. Four-arm trial design

<table>
<thead>
<tr>
<th>Arm</th>
<th>Brain metastases</th>
<th>Prior temozolomide</th>
<th>Randomized</th>
<th>Temozolomide dosing</th>
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</thead>
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<tr>
<td>A</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Extended*</td>
</tr>
<tr>
<td>B</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Standard†</td>
</tr>
<tr>
<td>C</td>
<td>Allowed</td>
<td>Required</td>
<td>No</td>
<td>Extended</td>
</tr>
<tr>
<td>D</td>
<td>Required</td>
<td>No</td>
<td>No</td>
<td>Standard</td>
</tr>
</tbody>
</table>

*Extended dosing: temozolomide 75 mg/m² p.o. q.d. for 6 of every 8 wk.
†Standard dosing: temozolomide 150 mg/m² p.o. q.d. for 5 of every 28 d.
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 with the observed 1-year survival for arms A (34% versus 33%; \( P = \text{NS} \)), B (35% versus 48%; \( P = \text{NS} \)), C (18% versus 14%), and D (21% versus 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 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 a 48% stable disease (best response) rate was observed from temozolomide and sorafenib. CNS tumors were not included as target lesions because the majority of patients were treated with prior radiation therapy. Of the six patients with prior sorafenib, four had stable disease and two had progressive disease. The 15% to 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 Response Evaluation Criteria in Solid Tumors criteria was 11 months.

Safety. The only significant difference in grade 3 to 4 toxicities (Table 5) in patients randomized between arms A and B was lymphopenia (53% versus 15%, \( P < 0.05 \)). Grade 3 to 4 lymphopenia as also observed in 32% of patients on arm C who had significantly less exposure to extended dosing of temozolomide compared with 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 toxicities were fatigue, hand/foot skin reaction, rash, hypertension, and diarrhea. A high proportion of patients experienced chronic grade 1 to 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 of 167 patients (37%) evaluable for response (Table 6). BRAF V600E and V600K mutations were identified in 26 of 62 (42%) patients. NRAS mutations (G13D, G13R, Q61R, Q61K, or Q61L) were identified in 8 of 62 (13%) patients. The remaining patients, 28 of 62 (45%), had no detectable mutations at either locus (WT/WT). Kaplan-Meier analysis of PFS (Fig. 2) did not identify a significant difference between patients with mutant BRAF/WT NRAS versus WT BRAF/WT NRAS (hazard ratio, 1.0; 95% CI, 0.56-1.8; \( P > 0.05 \)) or WT BRAF/Mutant NRAS versus WT BRAF/WT NRAS (hazard ratio, 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 end point (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. Although 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 with reported PFS in patients with or without brain metastases receiving temozolomide.

**Table 2. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm A</th>
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<th>Arm C</th>
<th>Arm D</th>
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<td>40</td>
<td>38</td>
<td>53</td>
<td>167</td>
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<td>58</td>
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<td>Sex, %</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>58</td>
<td>75</td>
<td>74</td>
<td>66</td>
<td>69</td>
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<td>26</td>
<td>34</td>
<td>31</td>
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<tr>
<td>AJCC stage, %</td>
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<td>8</td>
<td>18</td>
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<td>M1c</td>
<td>90</td>
<td>77</td>
<td>97</td>
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<td>92</td>
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<td>ECOG PS, %</td>
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<td>PS 0</td>
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<td>50*</td>
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<tr>
<td>Prior chemotherapy, %</td>
<td>11</td>
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<td>100</td>
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<td>LDH, %</td>
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<td>61</td>
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<td>36</td>
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<td>ULN &lt; LDH &lt; 2 x ULN</td>
<td>23</td>
<td>23</td>
<td>42</td>
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<td>&gt;2 x ULN</td>
<td>16</td>
<td>19</td>
<td>22</td>
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Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Group; LDH, lactate dehydrogenase; PS, performance status; ULN, upper limit of normal.

* \( P < 0.05 \) compared with arms A, B, and D.
BRAF or NRAS mutational status of the patient’s tumor was not predictive of outcome. The safety profile of this completely oral regimen seems to be excellent. Although profound and persistent lymphopenia was observed, there were no opportunistic infections (26). Most grade 3 to 4 toxicities were reversible with brief drug holidays. Chronic administration of this combination did result in a high percentage of burdensome grade 1 to 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 toward increased response rate and 6-month PFS with extended dosing of temozolomide and sorafenib compared with standard dosing of temozolomide with sorafenib, without a significant increase in toxicity. Although 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 that were not tested in combination with sorafenib. Some consider SDT schedule for temozolomide as 200 mg/m² p.o. q.d. for 5 of every 28 days instead of 150 mg/m² that was used in this study. Recently a dose intense biweekly schedule of temozolomide 150 mg/m² po for 7 of every 14 d was compared with dacarbazine in a randomized phase III trial for patients with stage IV melanoma (27). Although this regimen provides the most temozolomide exposure of any temozolomide dosing schedule commonly used, there was no difference in OS in this phase III trial and increased toxicity in patients treated with dose intense temozolomide compared with patients treated with standard temozolomide in a randomized phase III trial versus dacarbazine 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 PFS rate, median PFS of 3.5 months, and OS 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 PFS and OS in patients on arm D. Although 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 used for symptomatic brain edema in patients on arm D.

### Table 3. Benchmark analysis of PFS and OS

<table>
<thead>
<tr>
<th>Arm</th>
<th>A</th>
<th>B</th>
<th>P</th>
<th>C</th>
<th>D</th>
<th>P</th>
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<tr>
<td>Median PFS, mo</td>
<td>5.9</td>
<td>4.2</td>
<td>2.2</td>
<td>3.5</td>
<td>16</td>
<td>6</td>
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<tr>
<td>Predicted 6-mo PFS rate*, %</td>
<td>16</td>
<td>0.002</td>
<td>17</td>
<td>0.03</td>
<td>15</td>
<td>0.03</td>
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<tr>
<td>95% CI</td>
<td>33-66</td>
<td>25-57</td>
<td>11</td>
<td>14-26</td>
<td>16</td>
<td>14-26</td>
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<tr>
<td>Predicted 1-y OS rate*, %</td>
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<td>5</td>
<td>10.5</td>
<td>5</td>
<td>8</td>
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<tr>
<td>95% CI</td>
<td>34</td>
<td>35</td>
<td>18</td>
<td>33</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td>No. of patients evaluated</td>
<td>34</td>
<td>35</td>
<td>48</td>
<td>14</td>
<td>NS</td>
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*Calculated from Korn et al., 2008.

### Table 4. Response rates

<table>
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<th>Arms</th>
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<th>A + B</th>
<th>C</th>
<th>D</th>
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<tr>
<td>Temozolomide dosing</td>
<td>Extended</td>
<td>Standard</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Brain metastases</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<tr>
<td>ORR*, %</td>
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<td>15</td>
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<tr>
<td>95% CI</td>
<td>(11-40)</td>
<td>(6-30)</td>
<td>(11-30)</td>
<td>(7-29)</td>
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<td>Stable disease rate, %</td>
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<td>58</td>
<td>50</td>
<td>26</td>
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<tr>
<td>95% CI</td>
<td>(26-59)</td>
<td>(41-73)</td>
<td>(39-62)</td>
<td>(33-62)</td>
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<td>Progressive disease rate, %</td>
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<td>27</td>
<td>31</td>
<td>26</td>
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<tr>
<td>Total evaluate (no.)</td>
<td>38</td>
<td>40</td>
<td>79</td>
<td>38</td>
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*ORR: There was one complete response in arm A. All other responses were partial responses.
The addition of sorafenib failed to improve the response rate or PFS compared with 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 end point of significantly improved OS.

Although randomized trials have determined that sorafenib does not improve PFS or OS 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 OS benefit, but a significant difference in time to progression between treatment with dacarbazine with sorafenib compared with dacarbazine and placebo in patients with chemotherapy-naive 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. (25) 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.

Table 5. Toxicity

<table>
<thead>
<tr>
<th>Toxicity, %</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
<th>Arm D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr 1-2</td>
<td>Gr 3-4</td>
<td>Gr 1-2</td>
<td>Gr 3-4</td>
</tr>
<tr>
<td>Hematological Toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>34</td>
<td>—</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>55</td>
<td>16</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>79</td>
<td>53*</td>
<td>68</td>
<td>15*</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>34</td>
<td>—</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>37</td>
<td>5</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Nonhematologic Toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>18</td>
<td>—</td>
<td>13</td>
<td>—</td>
</tr>
<tr>
<td>Alopecia</td>
<td>61</td>
<td>—</td>
<td>40</td>
<td>—</td>
</tr>
<tr>
<td>Anorexia</td>
<td>66</td>
<td>3</td>
<td>55</td>
<td>—</td>
</tr>
<tr>
<td>Constipation</td>
<td>55</td>
<td>—</td>
<td>38</td>
<td>—</td>
</tr>
<tr>
<td>Dehydration</td>
<td>11</td>
<td>—</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>61</td>
<td>11</td>
<td>48</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>79</td>
<td>16</td>
<td>73</td>
<td>13</td>
</tr>
<tr>
<td>Hand/foot syndrome</td>
<td>71</td>
<td>26</td>
<td>73</td>
<td>13</td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
<td>—</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>16</td>
<td>—</td>
<td>18</td>
<td>—</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29</td>
<td>3</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Myalgia</td>
<td>34</td>
<td>3</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>71</td>
<td>11</td>
<td>75</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>87</td>
<td>13</td>
<td>85</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>47</td>
<td>3</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32</td>
<td>8</td>
<td>35</td>
<td>—</td>
</tr>
<tr>
<td>Weight loss</td>
<td>63</td>
<td>16</td>
<td>55</td>
<td>5</td>
</tr>
</tbody>
</table>

*P < 0.05.

Table 6. BRAF, NRAS mutations, and PFS

<table>
<thead>
<tr>
<th>Mu BRAF/WT</th>
<th>WT/WT</th>
<th>WT/Mu NRAS</th>
<th>Total no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, no. sequenced (%)</td>
<td>26 (42)</td>
<td>28 (4g)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Arm A, no. (%)</td>
<td>3 (19)</td>
<td>10 (63)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Arm B no. (%)</td>
<td>4 (25)</td>
<td>10 (63)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Arm C no. (%)</td>
<td>11 (61)</td>
<td>2 (11)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Arm D no. (%)</td>
<td>8 (53)</td>
<td>6 (40)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>4.3</td>
<td>3.9</td>
<td>2.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.0 (0.56-1.8)</td>
<td>2.6 (0.86-7.7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Mu BRAF, mutant BRAF includes BRAF V600E and V600K mutations; WT, wild-type; Mu NRAS includes WMSG13D, G13R, Q61R, Q61K, and Q61L mutations; HR, hazard ratio.
(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, because the discrepancy between the 6-month PFS and the 1-year survival results points out that the large variance in the estimates for median OS suggests that a larger sample size is necessary to detect a survival advantage compared with 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. (25). 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 multikinase inhibitor. Although sorafenib is a potent BRAF inhibitor \textit{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. Although initial studies conducted in melanoma cell lines described the BRAF mutation rate at 60\% to 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 cannot 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 because 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.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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### References

Clinical Cancer Research

Phase II Trial of Temozolomide and Sorafenib in Advanced Melanoma Patients with or without Brain Metastases


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