

# Dose-dense temozolomide regimen for the treatment of brain metastases from melanoma, breast cancer, or lung cancer not amenable to surgery or radiosurgery: a multicenter phase II study

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**Background:** Brain metastases reduce survival because therapeutic options are limited. This phase II study evaluated the efficacy of single-agent therapy with alternating weekly, dose-dense temozolomide in pretreated patients with brain metastases prospectively stratified by primary tumor type.

**Methods:** Eligible patients had bidimensionally measurable brain metastases from histologically/cytologically confirmed melanoma, breast cancer (BC), or non-small-cell lung cancer (NSCLC). Prior chemotherapy, radiotherapy, and whole-brain radiotherapy (WBRT) were allowed. Patients received temozolomide 150 mg/m<sup>2</sup>/day (days 1–7 and 15–21 every 28- or 35-day cycle).

**Results:** In the intent-to-treat population ( $N = 157$ ; 53 melanoma, 51 BC, and 53 NSCLC), one patient had complete response, nine (6%) had partial responses, and 31 (20%) had stable disease in the brain. Median progression-free survival was 56, 58, and 66 days for melanoma, BC, and NSCLC, respectively. Median overall survival was 100 days for melanoma, 172 days for NSCLC, and not evaluable in the BC group. Thrombocytopenia was the most common adverse event causing dose modification or treatment discontinuation. Grade 4 toxic effects were rare.

**Conclusions:** This alternating weekly, dose-dense temozolomide regimen was well tolerated and clinically active in heavily pretreated patients with brain metastases, particularly in patients with melanoma. Combining temozolomide with WBRT or other agents may improve clinical outcomes.

**Key words:** brain metastases, breast cancer, dose dense, melanoma, NSCLC, temozolomide

## introduction

It is estimated that 8%–10% of patients with advanced cancer will develop symptomatic brain metastases at some point during the course of their disease [1–3]. Brain metastases are particularly frequent in cancers of the lung (40%–50%), breast (15%–25%), and in melanoma (5%–20%) and increasingly are being diagnosed because of advancements in imaging techniques and better control of primary systemic disease resulting in improved survival [3]. Brain metastases are associated with a poor prognosis; without treatment, median survival is 1–2 months [4]. Standard of care for brain metastases is whole-brain radiotherapy (WBRT), stereotactic radiosurgery, or surgery [3]. Median survival achieved with WBRT is 3–4 months [3]. A pioneering study ( $N = 1200$ )

evaluating prognostic factors associated with survival in patients with brain metastases treated with radiation therapy concluded that survival ranged from 7.1 months in patients with Karnofsky performance status (KPS)  $\geq 70$ ,  $< 65$  years old, controlled systemic disease, and brain as the only site of metastases [Recursive Partitioning Analysis (RPA) class I], compared with 4.2 months in patients categorized as RPA class II, to 2.3 months in patients with KPS  $< 70$  with uncontrolled systemic disease (RPA class III) [5, 6]. Numerous trials have explored systemic chemotherapy, including temozolomide, taxane/platinum regimens, vinorelbine/gemcitabine, and topotecan either alone or in combination with WBRT [7–9]. Median overall survival (OS) in these studies ranged from 4.5 to 6.6 months, and most of these patients had brain metastases from lung cancer. Clinical benefit data in patients with brain metastases originating from other malignancies are limited.

Temozolomide is a second-generation, oral alkylating agent with excellent central nervous system (CNS) bioavailability and

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proven activity against primary brain tumors [10–13]. In addition, temozolomide is well tolerated, and hematologic toxicity is usually noncumulative. *O*<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) is a key DNA repair enzyme responsible for tumor resistance to alkylating agents [14, 15]. Based on studies by Tolcher et al. [16] showing that dose-dense regimens of temozolomide (including the alternating weekly regimen) deplete MGMT levels in peripheral blood mononuclear cells, it has been hypothesized that dose-dense temozolomide may deplete MGMT in tumor cells and increase antitumor activity. Accordingly, several clinical trials have evaluated dose-dense temozolomide regimens in patients with primary brain tumors [17, 18].

Previous studies of systemic chemotherapy for brain metastases have largely enrolled patients with non-small-cell lung cancer (NSCLC) along with small numbers of patients with breast cancer (BC) and melanoma [7, 8, 19–23]. No systematic studies have examined the benefit of temozolomide in patients prospectively stratified by primary malignancy. The present study examined clinical benefit and safety of an alternating weekly (7/14-day), dose-dense temozolomide regimen in patients with brain metastases from melanoma or from breast or lung cancer that were not amenable to surgery or radiosurgery. Patients were prospectively stratified by their primary tumor type.

## methods

### patients

**inclusion criteria.** Patients with a cytologic/histologic diagnosis of NSCLC (first or second line), malignant melanoma (first or second line), or BC and one or more measurable brain metastases  $\geq 1$  cm in diameter were eligible. Eligible patients must have completed previous anticancer therapy at least 4 weeks before study entry. All enrolled patients had an Eastern Cooperative Oncology Group performance status of zero to two and acceptable hematologic (leukocytes  $\geq 3.5 \times 10^9$  cells/l; platelets  $\geq 100 \times 10^9$  cells/l), liver (bilirubin  $\leq 25$   $\mu$ M), and renal (creatinine  $\leq 150$   $\mu$ M; creatinine clearance  $\geq 60$  ml/min) function. After the third and only substantial amendment, inclusion criteria were extended to include irradiated brain metastases. The final and approved protocol and informed consent were reviewed and approved by the local ethics committee. The study was conducted according to the tenets of the Declaration of Helsinki.

**exclusion criteria.** Before the third amendment, patients were excluded if they had received prior WBRT for brain metastases; however, after the third amendment, WBRT for brain metastases was allowed if completed  $\geq 2$  months before study entry. Patients with brain metastases amenable to neurosurgery/radiosurgery were excluded; however, residual or progressive malignant disease after neurosurgery was allowed. Patients with diabetes precluding administration of adequate doses of dexamethasone and patients requiring chronic anticonvulsant therapy were also excluded.

### study design

This was a multicenter, open-label, two-step, phase II trial, and patients were prospectively stratified by primary tumor type. The primary end point was clinical benefit, defined as best radiologic response [including complete response (CR), partial response (PR), or stable disease (SD)] achieved during the study period. Secondary end points included progression-free survival (PFS), neurological progression-free survival (NPFS), OS, and safety.

**assessments.** Baseline measurements of the brain included either magnetic resonance imaging (MRI), with or without gadolinium enhancement, or computed tomography (CT). In cases where a brain lesion diagnosis was not equivocal, a radiolabeled leukocyte brain scan (HexaMethylPropylene Amine Oxime <sup>99</sup>Tc brain single-photon emission computed tomography) was carried out to rule out infectious disease and improve diagnostic accuracy. At baseline, after the first 2 months of treatment, and every 3 months thereafter, clinical and radiologic (CT or MRI) evaluation of brain and other sites of disease was carried out until disease progression. Other baseline measurements included physical examination, hematology, and biochemistry. During study treatment, a CT or an MRI of the brain was carried out every two cycles until disease progression. After the third amendment, a radiologic confirmation of response after 4 weeks was introduced in case of response or SD. Tumor response was evaluated on the basis of World Health Organization response criteria [24]. The best response during study treatment was reported. Response duration was monitored, and responses maintained for at least 4 weeks as evaluated by a sequential CT scan or MRI were recorded. Adverse events (AEs) were graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0.

**treatment.** Patients received temozolomide orally, in a fasting state, at a starting dose of 150 mg/m<sup>2</sup> once daily for seven consecutive days repeated every other week [days 1–7 and 15–21 of every 28-day cycle (schedule A)]. The treatment schedule was altered for all patients enrolled after the third amendment to include seven additional days of rest from days 22 to 35, increasing the cycle length to 35 days (schedule B). Treatment was continued until either unacceptable toxicity or disease progression. Dexamethasone was administered daily at a dose of 2–16 mg i.m. or i.v. for the first 2 months; thereafter, an optimal dose of dexamethasone necessary to maintain stable neurological symptoms was administered. In the event of an absolute neutrophil count (ANC)  $< 1500$  cells/ $\mu$ l or a platelet count  $< 100\,000$ / $\mu$ l at any time while on therapy, treatment was delayed until recovery to ANC  $\geq 1500$  cells/ $\mu$ l and platelet count  $\geq 100\,000$ / $\mu$ l. The dose was reduced to 125 mg/m<sup>2</sup>/day if ANC was  $< 500$  cells/ $\mu$ l for 5 days, if ANC was  $< 500$  cells/ $\mu$ l with fever and/or platelet count  $< 25\,000$ / $\mu$ l, or if therapy was delayed by  $\geq 2$  weeks. In the event of NCI-CTCAE grade 3 or 4 non-hematologic toxicity, including gastrointestinal toxicity unresponsive to standard therapy, dosing was delayed until toxicity resolved to baseline or grade 1. Dose reduction to the next lower dose level was also recommended.

**statistical analysis.** Following the Simon optimal two-stage design for phase II studies, the trial was designed to refuse a clinical benefit rate  $\leq 10\%$  (minimal benefit rate required to continue study after completion of first step) and to provide 90% statistical power for assessing therapeutic activity of a clinical benefit rate of 25% with an alpha error  $< 0.05$ . Double data entry was used to eliminate input error. All data were analyzed using SAS 9.1. The statistical analysis was carried out by Quintiles, Milan, Italy. Continuous variables were summarized by descriptive statistics, and categorical variables were summarized using counts of subjects and percentages, with 95% confidence intervals (CIs). PFS and OS were analyzed by the Kaplan–Meier method. Only patients who received at least one dose of study treatment were included in the analysis [modified intent-to-treat population (mITT)].

## results

### patients

During the first step of the trial, 63 patients were enrolled (21 for each tumor type). The clinical benefit (PR plus SD) was

24% (40% for melanoma, 19% for BC, and 24% for NSCLC); therefore, the trial continued to the second step. In total, 162 patients (54 melanoma, 53 BC, and 55 NSCLC) were enrolled across 25 study centers in Italy from December 2000 to October 2005. Eighty-three patients (37 melanoma, 22 breast, and 24 NSCLC) were enrolled from December 2000 to October 2002 and were treated on a 28-day cycle (schedule A). After the third amendment, 79 patients (17 melanoma, 31 breast, and 31 NSCLC) were enrolled and treated on a 35-day cycle (schedule B). Of these, 157 patients received at least one dose of study drug and were included in the mITT analysis. Five patients (one with melanoma, two with BC, and two with NSCLC) were never treated and were not included in the analysis. Baseline characteristics of the mITT population are shown in Table 1. In the mITT population, 98 (62%) patients had received prior chemotherapy for systemic disease and 41 (26%) patients had received prior radiotherapy for the treatment of brain metastases. Overall, 47 (30%) of the patients had received one prior chemotherapy regimen, 19 (12%) had received two prior regimens, and 32 (20%) had received three or more prior regimens. Patients with BC were more heavily pretreated compared with the other cohorts.

The total number of delivered cycles (both schedules) was 356. The primary reason for study withdrawal was disease progression, accounting for 66% of patients on both schedules (Table 2). Overall, 18% of the patients discontinued study treatment because of AEs.

**Table 1.** Patient demographics and baseline characteristics (modified intent-to-treat population)

Characteristic	Melanoma (n = 53)	Breast cancer (n = 51)	NSCLC (n = 53)
Age, years, mean $\pm$ standard deviation	51.1 $\pm$ 11.0	53.9 $\pm$ 11.7	59.1 $\pm$ 7.6
Sex			
Male, n (%)	34 (64)	1 (2)	37 (70)
Body surface area, mean $\pm$ standard deviation	1.8 $\pm$ 0.2	1.7 $\pm$ 0.2	1.7 $\pm$ 0.2
Eastern Cooperative Oncology Group status, n (%)			
0	29 (55)	17 (33)	23 (43)
1	18 (34)	24 (47)	25 (47)
2	6 (11)	10 (20)	5 (10)
Prior therapy for systemic disease, n (%)			
Chemotherapy	21 (40)	41 (80)	36 (68)
Radiotherapy	2 (2)	20 (39)	12 (23)
Whole-brain radiotherapy, n (%)	14 (26)	12 (24)	15 (28)
No. of prior chemotherapy regimens, n (%)			
0	32 (60)	10 (20)	17 (32)
1	13 (24)	13 (25)	21 (40)
2	4 (8)	6 (12)	9 (17)
$\geq$ 3	4 (8)	22 (43)	6 (11)

NSCLC, non-small-cell lung cancer.

## efficacy assessments

The overall objective response rate was 6% (one CR and nine PR), and 31 (20%) patients in the mITT population had SD (Table 3). The disease control rate was 32% (95% CI 20% to 46%) for melanoma (9% PR, 23% SD), 20% (95% CI 10% to 33%) for BC (4% PR, 16% SD), and 26% (95% CI 15% to 40%) for NSCLC (2% CR, 4% PR, 21% SD). However, the majority of responses and SD were transient; only 13 (32%) of the objective responses or SD were confirmed at a 4-week follow-up scan. Response rate and disease control rate were similar regardless of treatment schedule in patients with BC or NSCLC. In patients with melanoma, the response rate was marginally higher in patients treated on schedule A. Disease control rate was also higher in patients who did not receive prior WBRT. Among melanoma patients, the disease control rate was 34% in patients who did not receive prior WBRT compared with 22% in patients who did receive prior WBRT; among BC patients, disease control was achieved only in patients who did not receive prior WBRT (23% versus 0%); and in NSCLC patients, the disease control rate was 29% in patients who did not receive prior WBRT compared with 18% in those who did. Because of the high number of missing data, a formal analysis of neurological symptoms could not be carried out.

Median PFS ranged from 1.9 months in the melanoma group to 2.2 months in the NSCLC group (Figure 1A). Median NPFS was similar and ranged from 2.1 to 2.5 months across all groups and showed no significant difference with modification of the treatment schedule. Median OS ranged from 3.3 months in the melanoma group to 5.7 months in the NSCLC group (Figure 1B). Median OS was not reached in the BC group.

## safety

The most commonly reported AEs were lymphopenia, thrombocytopenia, nausea, vomiting, headache, and asthenia (Table 4). The frequency of all AEs was lower with schedule B. Thrombocytopenia resulted in dose reduction or treatment discontinuation in 30 (19%) patients and occurred at a lower frequency in patients treated on schedule B. Lymphopenia was the most common grade 3 toxicity. Grade 4 hepatic toxicity and grade 4 leukopenia were rare and occurred in  $\leq$ 2% of patients.

**Table 2.** Reason for study withdrawal

	No. of patients (%)		
	Melanoma (n = 53)	Breast cancer (n = 51)	NSCLC (n = 53)
Relapse or progressive disease	38 (72)	33 (65)	33 (62)
Serious adverse events	9 (17)	8 (16)	12 (23)
Investigator's decision	2 (4)	3 (6)	4 (8)
Withdrawal of consent	1 (2)	3 (6)	1 (2)
Other reason	3 (6)	4 (8)	3 (6)

NSCLC, non-small-cell lung cancer.

**Table 3.** Brain tumor response by tumor type and treatment schedule

	Schedule A, n (%) [CI]			Schedule B, n (%) [CI]			Overall, n (%) [CI]			Total, n (%) N = 157
	Melanoma (n = 36)	BC (n = 22)	NSCLC (n = 23)	Melanoma (n = 17)	BC (n = 29)	NSCLC (n = 30)	Melanoma (n = 53)	BC (n = 51)	NSCLC (n = 53)	
CR	0	0	0	0	0	1 (3)	0	0	1 (2)	1 (<1)
PR	4 (11)	1 (5)	1 (4)	1 (6)	1 (3)	1 (3)	5 (9)	2 (4)	2 (4)	9 (6)
SD	9 (25)	5 (23)	5 (22)	3 (18)	3 (10)	6 (20)	12 (23)	8 (16)	11 (21)	31 (20)
Disease control (CR + PR + SD)	13 (36) [21–54]	6 (27) [11–50]	6 (26) [10–48]	4 (24) [7–50]	4 (14) [4–32]	8 (27) [12–46]	17 (32) [20–46]	10 (20) [10–33]	14 (26) [15–40]	41 (26)
PD	23 (64) [46–79]	16 (73) [50–89]	17 (74) [52–90]	13 (77) [50–93]	25 (86) [68–96]	22 (73) [54–88]	36 (68) [54–80]	41 (80) [67–90]	39 (74) [60–85]	116 (74)

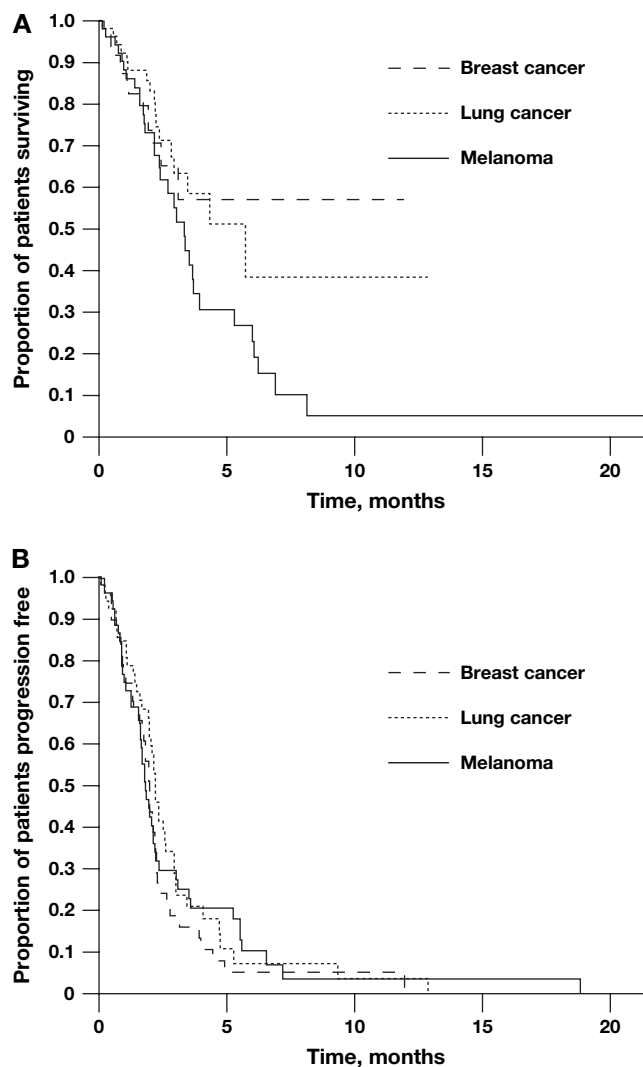
CI, confidence interval; BC, breast cancer; NSCLC, non-small-cell lung cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

**discussion**

This study represents the first large, multicenter study of a dose-dense temozolomide regimen in patients with brain metastases, in which patients were prospectively stratified by primary tumor type. Although this study, designed in 2000, has certain limitations because data were not collected on control of systemic disease at baseline, and patients were not stratified by RPA class, the results are no less important. The rationale for the treatment regimen was based on several considerations. First, temozolomide effectively crosses the blood–brain barrier and has demonstrated good clinical activity against primary brain tumors [11–13]. Second, dose-dense temozolomide regimens may overcome resistance to alkylating agents.

The results of the present study demonstrated that this regimen has activity in patients with brain metastases from all three tumor types, particularly melanoma. In addition, antitumor activity appeared to be greater in patients who had not received prior irradiation for brain metastases and in patients who were less heavily pretreated with chemotherapy for systemic disease. Patients with BC had the lowest disease control rate but were also more heavily pretreated than patients with melanoma or NSCLC. The main limitation of this regimen was that patients progressed quickly, and both PFS and OS were relatively short. In addition, the regimen caused dose-limiting thrombocytopenia in a subset of patients, which is consistent with data reported in other studies with this regimen [18, 25]. This is not surprising given that the majority of patients had received prior chemotherapy for systemic disease. This prompted lengthening of the cycle to allow a longer recovery period; the amended treatment cycle reduced the frequency of all AEs without compromising the survival benefit.

The limited activity and transient nature of the tumor responses observed across tumor types in this study has been documented in other trials of systemic chemotherapy for the treatment of brain metastases (Table 5) [7, 8, 19, 20, 25–28]. There do not appear to be substantial differences in the median OS achieved with different temozolomide schedules and other experimental systemic chemotherapy regimens. However, because of the relatively small numbers of patients in some studies and variable prior treatment history, it is difficult to compare results across studies. None the less, the survival data



**Figure 1.** Kaplan–Meier estimates of progression-free (A) and overall survival (B) by tumor type.

from the present study are similar to those reported in other trials of systemic chemotherapy.

In patients with BC, a variety of regimens have been investigated for the treatment of brain metastases including

topotecan, temozolomide, cisplatin, and vinorelbine plus mitoxantrone [8, 22, 28–30]. Trials of single-agent topotecan in patients with metastatic BC demonstrated very modest clinical activity, and further trials using this agent were not recommended [31]. Single-agent temozolomide using the standard 5-day regimen did not produce any objective responses in patients with brain metastases from BC [27]. In the present study, although the disease control rate was lowest in the BC group, two patients achieved a PR. Overall, the results of the present study indicate that single-agent temozolomide is active, but it is probably not the optimal strategy for treating brain metastases, particularly for BC.

More favorable outcomes have been achieved when temozolomide was combined with radiotherapy, and there is evidence to indicate that temozolomide may have a radiosensitizing effect [32, 33]. Studies combining temozolomide with WBRT reported response rates ranging from 55% to 96% with median survival ranging from 15 to 36 weeks [34]. In a phase II trial of temozolomide (75 mg/m<sup>2</sup>/day) administered concurrently with WBRT for 4 weeks followed by six cycles of 200 mg/m<sup>2</sup>/day × 5 days every 28-day cycle in patients with brain metastases from breast and lung cancer, Antonadou et al. [35] reported a median survival of 36 weeks. More recently, a phase II trial of temozolomide plus WBRT followed by temozolomide maintenance (standard 5-day schedule) reported a median OS of 52 weeks in patients with

brain metastases from NSCLC and other solid tumors, including BC [30]. Similarly, Addeo et al. [36] demonstrated that concomitant WBRT and temozolomide plus the standard 5-day maintenance temozolomide schedule was well tolerated and produced an encouraging objective response rate (45%) and a significant improvement in quality of life. The ongoing SWS-SAKK-70/03 and RTOG-0320 randomized trials are investigating WBRT with or without dose-dense temozolomide in patients with brain metastases from NSCLC. It is hoped that these studies will provide further clarification of the benefit of combining WBRT with a dose-dense temozolomide regimen.

Combinations of WBRT with chemotherapy have also been reported to yield high response rates in patients with brain metastases from BC; however, this often fails to translate into improved survival. In one study, WBRT plus topotecan resulted in a 72% objective response rate, but median OS was only 17 weeks [22]. Similar results were obtained in a recent phase III trial of WBRT with or without efaproxiral in patients with brain metastases from breast or lung cancer; median OS in the efaproxiral plus WBRT arm was 23 and 18 weeks for breast and lung cancer patients, respectively [37].

Clinical strategies to control brain metastases must also consider the biologic characteristics of the tumor and control of extracranial disease. In fact, the long-term survival (>20 months) achieved in patients with brain metastases from HER2-positive BC who were treated with trastuzumab-based

**Table 4.** Common adverse events (all grades)

	Schedule A, n (%)			Schedule B, n (%)			All histologies, n (%) (N = 157)
	Melanoma (n = 36)	BC (n = 22)	NSCLC (n = 23)	Melanoma (n = 17)	BC (n = 29)	NSCLC (n = 30)	
Lymphopenia	15 (42)	7 (32)	10 (44)	1 (6)	6 (21)	6 (20)	45 (29)
Thrombocytopenia	12 (33)	6 (27)	15 (65)	1 (6)	6 (21)	6 (20)	46 (29)
Nausea	12 (33)	5 (23)	5 (22)	1 (6)	3 (10)	2 (7)	28 (18)
Vomiting	12 (33)	6 (27)	3 (13)	2 (12)	4 (14)	4 (13)	31 (20)
Headache	7 (19)	6 (27)	3 (13)	3 (18)	3 (10)	4 (13)	26 (17)
Asthenia	7 (19)	6 (27)	7 (30)	2 (12)	1 (3)	7 (23)	30 (19)

BC, breast cancer; NSCLC, non-small-cell lung cancer.

**Table 5.** Summary of efficacy of systemic therapy in patients with brain metastases

Study	Primary tumor type	Treatment	N	Disease control rate <sup>a</sup> (%)	OS (months)
Agarwala et al. [26]	Melanoma	TMZ, 5 days	151	32	3.8
DeCOG/ADO [25]	Melanoma	TMZ, alternating weekly	45	15	4.3
Bernardo et al. [19]	NSCLC	Vinorelbine + GEM + carboplatin	20	70	8.3
Cortes et al. [20]	NSCLC	PAC + cisplatin	25	38 <sup>b</sup>	5.3
Trudeau et al. [27]	Breast	TMZ, alternating weekly	19	16	Not reported
Christodoulou et al. [28]	Mixed	TMZ, 5 days + cisplatin	32	47	5.5
Abrey et al. [7]	Mixed	TMZ, 5 days	34	50	6.6
Christodoulou et al. [8]	Mixed	TMZ, 5 days	24	21	4.5
Present study	Melanoma	TMZ, alternating weekly	53	32	3.3
	NSCLC		53	26	5.7
	Breast		51	20	Not reached

OS, overall survival; TMZ, temozolomide; NSCLC, non-small-cell lung cancer; GEM, gemcitabine; PAC, paclitaxel.

<sup>a</sup>Disease control rate = complete response + partial response + stable disease.

<sup>b</sup>Intracranial response rate.

therapy may be attributed to better control of extracranial disease [38, 39]. Several studies have also shown that small-molecule tyrosine kinase inhibitors (e.g. lapatinib, gefitinib, and erlotinib), which have systemic activity in tumors with specific molecular phenotypes, are a viable option for treating brain metastases [40–42]. Lapatinib has demonstrated activity against brain metastases from HER2-positive BC, whereas gefitinib and erlotinib were particularly effective in patients with brain metastases from primary lung tumors harboring epidermal growth factor receptor amplifications or mutations [40, 42]. Combining temozolomide with other therapeutic agents that have demonstrated activity against systemic metastatic disease could potentially enhance the clinical benefit in pretreated patients with brain metastases.

In summary, this alternating weekly (7/14-day), dose-dense temozolomide regimen is well tolerated and has antitumor activity in patients with brain metastases from melanoma, BC, and NSCLC and compares favorably with other temozolomide-dosing schedules, particularly in patients with melanoma; however, single-agent temozolomide is probably not the optimal therapeutic strategy, especially in patients with NSCLC or BC. The combination of temozolomide with WBRT or other agents with CNS and systemic antitumor activity may improve clinical outcome of patients with brain metastases. Larger studies of dose-dense temozolomide plus concomitant WBRT are ongoing.

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