Food and Drug Administration Drug Approval Summary: Temozolomide Plus Radiation Therapy for the Treatment of Newly Diagnosed Glioblastoma Multiforme

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Abstract On March 15, 2005, the U.S. Food and Drug Administration approved temozolomide (Temodar capsules, Schering-Plough Research Institute) for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment. Five hundred seventy-three glioblastoma multiforme patients were randomized to receive either temozolomide + radiotherapy (n = 287) or radiotherapy alone (n = 286). Patients in the temozolomide + radiotherapy arm received concomitant temozolomide (75 mg/m^2) once daily for the duration of radiation therapy (42-49 days). This was followed, 4 weeks later, by six cycles of temozolomide, 150 or 200 mg/m^2 daily for 5 days, every 4 weeks. Patients in the control arm received radiotherapy only. In both arms, radiotherapy was delivered as 60 Gy/30 fractions to the tumor site with a 2 to 3 cm margin. *Pneumocystis carinii* pneumonia prophylaxis was required during temozolomide + radiotherapy treatment and was continued until recovery of lymphocytopenia (Common Toxicity Criteria grade <1). At disease progression, temozolomide salvage treatment was given to 161 of 282 patients (57%) in the radiotherapy alone arm, and to 62 of 277 patients (22%) in the temozolomide + radiotherapy arm. Patients receiving concomitant and maintenance temozolomide + radiotherapy had significantly improved overall survival. The hazard ratio was 0.63 (95% confidence interval, 0.52-0.75; log-rank, P < 0.0001). Median survival was 14.6 months (temozolomide + radiotherapy) versus 12.1 months (radiotherapy alone). Adverse events during temozolomide treatment included thrombocytopenia, nausea, vomiting, anorexia, constipation, alopecia, headache, fatigue, and convulsions.

Temozolomide is an orally administered cytotoxic agent of the imidazotetrazine class that is chemically related to dacarbazine. Unlike dacarbazine, which requires hepatic metabolism for activation, temozolomide is spontaneously hydrolyzed at physiologic pH to the active species 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide and to temozolomide acid metabolite. 5-(3-Methyltriazen-1-yl)imidazole-4-carboxamide is further hydrolyzed to 5-amino-imidazole-4-carboxamide, which is a known intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species (1, 2). Cytochrome *P*450 enzymes play only a minor role in the metabolism of temozolomide and 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide. About 39% of the administered temozolomide total radioactive dose is recovered over 7 days: 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is unchanged temozolomide (65.6%), 5-amino-imidazole-4-carboxamide (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%).

Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%. Temozolomide has good blood-brain barrier permeability achieving cerebrospinal fluid concentrations that are 20% to 40% of plasma levels (3–5).

Temozolomide previously received accelerated approval by the U.S. Food and Drug Administration in January 1999 for the treatment of anaplastic astrocytoma patients who were refractory to both nitrosourea and procarbazine (6). Approval was based on a 22% response rate (12 of 54 patients). The complete response rate, in this group of patients, was 9% (5 of 54 patients). The median duration of all responses was 50 weeks (range, 16-114 weeks). The median duration of complete response was 64 weeks (range, 52-114 weeks). Median progression-free survival was 4.4 months and median overall survival was 15.9 months. Approval was based on the observed response rate. At the time of approval, no results

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were available from randomized controlled trials in refractory anaplastic astrocytoma that show clinical benefit such as improvement in disease-related symptoms or prolonged survival.

Accelerated approval requires that studies be expeditiously done that show clinical benefit. The study described herein, by demonstrating survival benefit for temozolomide + radiotherapy compared with radiotherapy alone, is sufficient to convert the anaplastic astrocytoma indication to full approval.

Patients and Methods

One randomized open-label, multicenter trial conducted by the European Organization for the Research and Treatment of Cancer, in cooperation with the National Cancer Institute of Canada, the Swiss Group for Clinical Cancer Research (SAKK), and the Trans-Tasman Radiation Oncology Group, was submitted (7). No U.S. patients were enrolled. Submissions to the Food and Drug Administration that contain only foreign data are acceptable under provisions of the Code of Federal Regulations (8).

Patients with newly diagnosed glioblastoma multiforme were randomized to either radiotherapy alone or radiotherapy + temozolomide. Radiotherapy was delivered as 60 Gy/30 fractions to the tumor or resection site with a 2 to 3 cm margin to both treatment groups. For the temozolomide + radiotherapy treatment group, temozolomide 75 mg/m^2 per mouth per day was administered for the duration of radiotherapy (42-49 days). Four weeks after the completion of radiotherapy, maintenance temozolomide [150 mg/m^2 orally daily for 5 days during cycle 1 (28 days) and 200 mg/m^2 orally daily for 5 days every 28 days for cycles 2-6] was to be administered, if tolerable.

Antiemetic prophylaxis with a 5-HT3 antagonist was required during the maintenance phase. Corticosteroids were administered at the discretion of the treating physician. At the time of tumor progression, further treatments, including temozolomide, were administered at the discretion of the treating physician. *Pneumocystis carinii* prophylaxis was mandatory during radiotherapy in all subjects receiving concomitant therapy and was continued until recovery of lymphocytopenia (Common Toxicity Criteria grade ≤1).

The primary study objective was overall survival. Secondary objectives included toxicity profile, progression-free survival, and quality of life as measured by the European Organization for the Research and Treatment of Cancer quality of life questionnaires QLQ-C30 and the lung cancer module QLQ-LC13. Analyses were generally conducted on the intent-to-treat population.

The main eligibility criteria included newly diagnosed glioblastoma multiforme (WHO grade 4); any type of prior surgery (complete or partial resection, or biopsy only); no prior chemotherapy or radiotherapy; WHO performance status ≤2 and age ≥18 to ≤70 years. Central neuropathology review was done for 485 subjects (85% of the enrolled 573 subjects) to confirm the local histology findings.

Subjects were stratified by study center, age (<50 versus ≥50 years), WHO performance status (0-1 versus 2), and extent of the resection at surgery (biopsy only versus complete/incomplete resection).

Disease progression criteria included radiologic progression (increase of contrast uptake on magnetic resonance imaging or computer tomography of >25% as measured by two perpendicular diameters compared with the smallest measurements ever recorded for the same lesion by the same technique), and clinical progression based on deterioration of performance status and/or of neurologic function, or an increase in corticosteroid dosage by 50%. Measurements to determine objective tumor response were not done.

Table 1. Demographics and performance status

	Radiotherapy only (*n* = 286)	Radiotherapy + temozolomide (*n* = 287)
Sex (%)		
Female	109 (38)	103 (36)
Male	175 (61)	185 (64)
Missing	1 (<1)	0
Age (y)		
Median	56.0	55.0
Range	23-70	18-70
Age (%)		
18-<50 y	81 (28)	90 (31)
50-<65 y	163 (57)	156 (54)
65 y or older	41 (14)	42 (15)
Histology (%)		
Central pathology review		
Eligible	228 (80)	222 (77)
Glioblastoma multiforme	200 (70)	188 (65)
Glioblastoma multiforme (giant cell)	2 (1)	4 (1)
Glioblastoma multiforme (with oligodendroma component)	25 (9)	27 (9)
Glioblastoma multiforme (gliosarcoma)	1 (<1)	3 (1)
Ineligible	11 (4)	13 (5)
No central pathology review	46 (16)	53 (18)
Type of surgery (%)		
Brain biopsy only	46 (16)	47 (17)
Brain debulking (partial resection)	126 (44)	125 (43)
Brain debulking (total resection)	113 (40)	116 (40)
Weeks from surgery to randomization		
Subjects with biopsy only (%)	46 (16)	47 (16)
Median (wk)	4.0	3.4
Range (wk)	1.9-6.0	1.1-5.9
Subjects with debulking (%)	239 (84)	241 (84)
Median (wk)	4.1	4.3
Range (wk)	0.0-6.1	1.0-6.0
WHO performance status (%)		
0	112 (39)	116 (40)
1	139 (49)	136 (47)
2	34 (12)	36 (13)
Mini-mental status evaluation (%)	273 (96)	278 (97)
Median score	29.0	29.0
Number of subjects per range (%)		
0-11	4 (1)	4 (1)
12-28	121 (42)	125 (43)
29-30	148 (52)	149 (52)
Missing	12 (4)	10 (3)
Corticosteroids at randomization (%)	214 (75)	194 (67)

Table 2. Salvage therapy

Therapy	Number of subjects who entered follow-up phase (%)	
	Radiotherapy only (n = 282)	Radiotherapy + temozolomide (n = 277)
Any therapy	195 (69.1)	146 (52.7)
Temozolomide	161 (57.1)	62 (22.4)
Lomustine	40 (14.2)	44 (15.9)
Procarbazine	24 (8.5)	21 (7.6)
Vincristine	23 (8.2)	22 (7.9)
Carmustine	18 (6.4)	23 (8.3)
Other cancer drug therapies	98 (34.8)	113 (40.8)
Surgery	13 (4.6)	21 (7.6)

For safety evaluations, an adverse event was defined as any untoward medical occurrence or experience in a subject that occurs following randomization regardless of causal relationship.

Results

A total of 573 subjects were randomized to temozolomide + radiotherapy (n = 287) or radiotherapy alone (n = 286) over a 19-month period by 85 participating institutions in Europe, Canada, and Australia. No individual study center contributed more than 31 subjects.

The radiotherapy only and radiotherapy + temozolomide treatment arms were well matched with regard to baseline demographic characteristics, performance status, and mental status (Table 1).

Progression-free survival. Concomitant and maintenance temozolomide + radiotherapy compared with radiotherapy only significantly improved progression-free survival (log-rank, $P < 0.0001$). Median progression-free survival was 6.9 months (temozolomide + radiotherapy) versus 5.0 months (radiotherapy alone).

Salvage therapy. Two hundred eighty-two subjects in the radiotherapy only arm and 277 subjects in the radiotherapy + temozolomide arm entered the follow-up phase. More subjects in the radiotherapy only arm versus the radiotherapy + temozolomide arm received salvage therapy after disease progression: 195 subjects (69%) in the radiotherapy arm and 146 subjects (53%) in the radiotherapy + temozolomide arm. The most common salvage therapies are summarized in Table 2.

Survival. Survival results are summarized in Fig. 1. Survival results were mature because, at database lock, 480 of the 573 (84%) subjects on study had died and the median follow-up in surviving patients was at least 26 months for both treatment arms. Median survival was 14.6 and a 12.1 months for radiotherapy + temozolomide and radiotherapy patients, respectively.

Quality of life. Data collected for the health-related quality of life analysis were not submitted with the current application.

Safety. Approximately 90% of subjects in each treatment arm received the intended radiotherapy dose. During the concomitant phase, ~80% of subjects in the radiotherapy + temozolomide arm received the intended temozolomide dose intensity. During the maintenance phase, the protocol-specified dose was delivered on schedule for the majority of subjects in the radiotherapy + temozolomide arm.

During the initial 6 to 7 weeks of protocol treatment, adverse events including thrombocytopenia, nausea, vomiting, anorexia, and constipation were more frequent in the temozolomide + radiotherapy arm than in the radiotherapy alone arm. The incidence of other adverse events was comparable in the two arms. The most common adverse

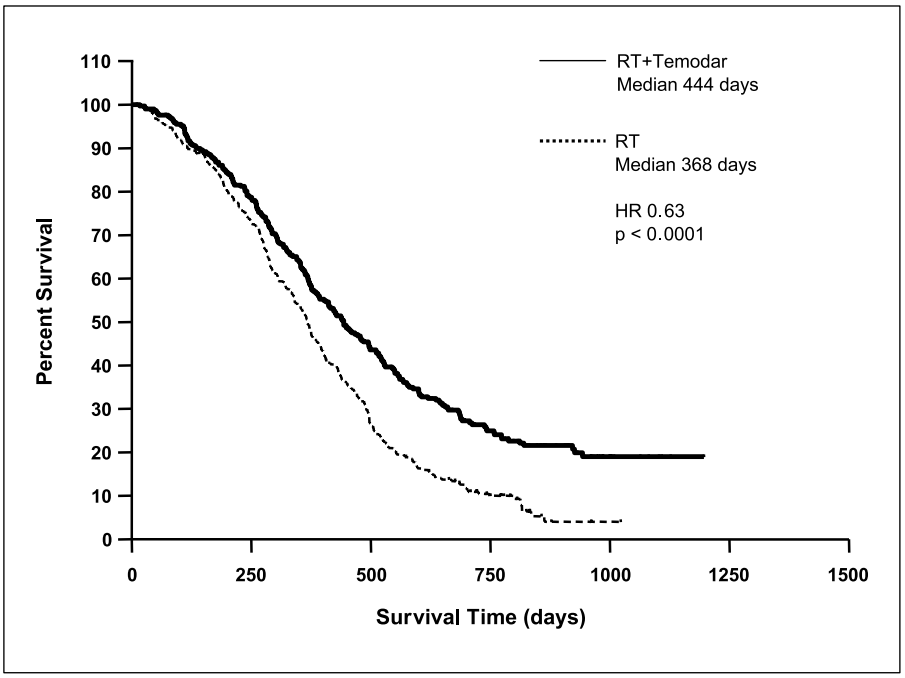

Fig. 1. Kaplan-Meier estimates of survival probability for the study patients treated with either temozolomide + radiotherapy (*TMZ + RT*; n = 287) or radiotherapy alone (*RT*; n = 286). The hazard ratio is presented as TMZ + RT / RT.

events across the cumulative temozolomide experience were alopecia, nausea, vomiting, anorexia, headache, and constipation (Table 3). When laboratory abnormalities and adverse events were combined, grade 3 or grade 4 platelet abnormalities, including thrombocytopenic events, were observed in 14% of the patients treated with temozolomide, and grade 3 or grade 4 neutrophil abnormalities, including neutropenic events, were observed in 8% of patients).

A total of 32 subjects died during treatment or within 30 days after the end of treatment: 13 (5%) subjects in the radiotherapy arm (treatment period of 6 weeks) and 19 (7%) subjects in the temozolomide + radiotherapy arm (treatment period of

Table 3. Number of patients with adverse events (%)*

	Concomitant phase radiotherapy alone (n = 285)		Concomitant phase radiotherapy + temozolomide (n = 288)†		Maintenance phase temozolomide (n = 224)	
	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3
Subjects reporting any adverse event	258 (91)	74 (26)	266 (92)	80 (28)	206 (92)	82 (37)
Body as a whole—general disorders						
Anorexia	25 (9)	1 (<1)	56 (19)	2 (1)	61 (27)	3 (1)
Dizziness	10 (4)	0	12 (4)	2 (1)	12 (5)	0
Fatigue	139 (49)	15 (5)	156 (54)	19 (7)	137 (61)	20 (9)
Headache	49 (17)	11 (4)	56 (19)	5 (2)	51 (23)	9 (4)
Weakness	9 (3)	3 (1)	10 (3)	5 (2)	16 (7)	4 (2)
Central and peripheral nervous system disorders						
Confusion	12 (4)	6 (2)	11 (4)	4 (1)	12 (5)	4 (2)
Convulsions	20 (7)	9 (3)	17 (6)	10 (3)	25 (11)	7 (3)
Memory impairment	12 (4)	1 (<1)	8 (3)	1 (<1)	16 (7)	2 (1)
Disorders of the eye						
Vision blurred	25 (9)	4 (1)	26 (9)	2 (1)	17 (8)	0
Disorders of the immune system						
Allergic reaction	7 (2)	1 (<1)	13 (5)	0	6 (3)	0
Gastrointestinal system disorders						
Abdominal pain	2 (1)	0	7 (2)	1 (<1)	11 (5)	1 (<1)
Constipation	18 (6)	0	53 (18)	3 (1)	49 (22)	0
Diarrhea	9 (3)	0	18 (6)	0	23 (10)	2 (1)
Nausea	45 (16)	1 (<1)	105 (36)	2 (1)	110 (49)	3 (1)
Stomatitis	14 (5)	1 (<1)	19 (7)	0	20 (9)	3 (1)
Vomiting	16 (6)	1 (<1)	57 (20)	1 (<1)	66 (29)	4 (2)
Injury and poisoning						
Radiation injury NOS	11 (4)	1 (<1)	20 (7)	0	5 (2)	0
Musculoskeletal system disorders						
Arthralgia	2 (1)	0	7 (2)	1 (<1)	14 (6)	0
Platelet, bleeding and clotting disorders						
Thrombocytopenia	3 (1)	0	11 (4)	8 (3)	19 (8)	8 (4)
Psychiatric disorders						
Insomnia	9 (3)	1 (<1)	14 (5)	0	9 (4)	0
Respiratory system disorders						
Coughing	3 (1)	0	15 (5)	2 (1)	19 (8)	1 (<1)
Dyspnea	9 (3)	4 (1)	11 (4)	5 (2)	12 (5)	1 (<1)
Skin and s.c. tissue disorders						
Alopecia	179 (63)	0	199 (69)	0	124 (55)	0
Dry skin	6 (2)	0	7 (2)	0	11 (5)	1 (<1)
Erythema	15 (5)	0	14 (5)	0	2 (1)	0
Pruritus	4 (1)	0	11 (4)	0	11 (5)	0
Rash	42 (15)	0	56 (19)	3 (1)	29 (13)	3 (1)
Special senses other, disorders						
Taste perversion	6 (2)	0	18 (6)	0	11 (5)	0

NOTE: Grade 5 (fatal) adverse events are included in the grade ≥3 column.
Abbreviation: NOS, not otherwise specified.
*Incidence of ≥5%.
†One patient who was randomized to radiotherapy only arm received radiotherapy + temozolomide.

6 weeks in the concomitant phase and up to 6 months in the maintenance phase). For 8 subjects in the radiotherapy arm and 11 subjects in the temozolomide + radiotherapy arm, the cause of death was disease progression. In six subjects in the temozolomide + radiotherapy arm, death was caused by, or temporally associated with, serious adverse events considered at least possibly related to temozolomide. In those six patients, the cause of death was pneumonia (with unknown WBC count) in three patients, aspiration pneumonia in one patient, respiratory insufficiency in one patient, and decreased consciousness, possibly due to an interaction of temozolomide and radiation therapy, in one patient. In the five patients on the radiotherapy alone arm who died during the above time period and whose deaths were not attributed to disease progression, two died of a pulmonary embolus, two died of pneumonia, and one died of unknown cause.

Discussion

Treatment with temozolomide administered concomitantly with brain radiotherapy and then as maintenance chemotherapy produced a significant survival benefit compared with radiation therapy alone in patients with newly diagnosed glioblastoma multiforme (hazard ratio, 0.63; 95% confidence interval, 0.52-0.75; log-rank, $P < 0.0001$). Median survival was 14.6 months (temozolomide + radiotherapy) versus 12.1 months (radiotherapy alone). This result likely represents an important treatment advance. Temozolomide has an acceptable adverse event profile and was safely administered, on a daily schedule, concomitantly with radiation therapy and subsequently as maintenance therapy. Whereas two previous meta-analyses of high grade glioma trials (glioblastoma multiforme and anaplastic astrocytoma) comparing radiation therapy plus chemotherapy to radiation therapy alone have suggested a modest survival benefit for combined radiation therapy plus chemotherapy arm (hazard ratio, 0.85; 95% confidence interval, 0.78-0.91, $P < 0.0001$ in the more recent analysis; refs. 9, 10), the individual trials included in the meta-analyses failed to show a significant survival benefit.

Supportive evidence indicating benefit for combined temozolomide plus radiation therapy in glioma treatment comes from one phase 3 study and two phase 2 studies. All studies enrolled newly diagnosed glioblastoma multiforme patients. The phase 3 study randomized 110 patients to either temozolomide + radiotherapy or radiotherapy alone. The temozolomide and radiotherapy doses and schedule were identical to those of the present report. The temozolomide + radiotherapy patients also received six cycles of maintenance temozolomide (150 mg/m^2 on days 1 to 5, and days 15 to 19 every 28 days).

Overall survival was significantly increased in the temozolomide + radiotherapy group ($P < 0.001$). Median survival was not reported but 1-year survival was 55% versus 16% and 2-year survival was 15% versus 0% (11).

One phase 2 study enrolled 64 patients. The concomitant temozolomide + radiotherapy and the maintenance temozolomide doses and schedule were identical to the present report. Median survival was 16 months and the 1-year and 2-year survivals were 58% and 31%, respectively (12).

The second phase 2 study enrolled 21 patients. The concomitant temozolomide + radiotherapy and the maintenance temozolomide doses and schedule were identical to the present report. Median survival was 15.7 months and the 1-year survival was 58% (13).

In summary, newly diagnosed glioblastoma multiforme patients receiving concomitant temozolomide + radiotherapy followed by maintenance temozolomide had significantly improved overall survival compared with patients receiving radiation therapy alone. Therapy was generally well tolerated. This trial represents an important stepping stone along the path of improved glioblastoma therapy.

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