

Brain Cancer



Commentary by

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AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

Adding temozolomide to radiation improves survival in patients with glioblastoma

Two-year survival rate is more than twice as high with combination therapy

When compared with radiation therapy alone, radiation combined with temozolomide (Temodar) more than doubled the 2-year overall survival rate of patients with glioblastoma, according to the results of a randomized phase III trial that was presented at the 46th annual meeting of the American Society for Therapeutic Radiology and Oncology.

Surgery plus postoperative radiation therapy remains the mainstay of treatment for glioblastoma, and nitrosourea-based adjuvant chemotherapy only slightly improves survival, said lead author René-Olivier Mirimanoff, MD, a radiation oncologist at the University Hospital, Lausanne, Switzerland. "The alkylating agent temozolomide has excellent bioavailability and brain and cerebrospinal fluid penetration," he noted.

"There is a very important relationship between the DNA repair enzyme methylguanine methyltransferase (MGMT) and temozolomide," stated Dr. Mirimanoff. He then pointed out that in vitro studies have shown synergy between temozolomide and radiation therapy, and a phase II trial testing combined use of these modalities has produced promising survival data.

Patients were eligible for the phase III trial if they had newly diagnosed, histologically proven, and untreated

glioblastoma (WHO grade IV), a WHO performance status of 0 to 2, and adequate organ function; further, subjects needed to be between 18 and 70 years of age. In all, 573 patients were randomly assigned to receive either radiation therapy (60 Gy over 30 days) alone or concurrently with 75 mg/m² of temozolomide orally daily for 7 days/wk over 35–42 days, followed by adjuvant temozolomide (150–200 mg/m² orally) after radiation therapy on days 1–5 every 28 days for up to six cycles.

The two groups were well matched

with respect to age, sex, performance status, surgery, baseline Mini-Mental Status Examination score, and receipt of steroids, Dr. Mirimanoff said. Surgery consisted of biopsy only in 16% of patients, partial resection in 44%, and complete resection in 40%.

Dr. Mirimanoff stated that 93% of patients in both groups received radiation therapy per protocol. In the radiotherapy-temozolomide group, 88% of patients received concomitant temozolomide per protocol.

There is a very important relationship between the DNA repair enzyme [methylguanine methyltransferase] and temozolomide.

— René-Olivier Mirimanoff

Comment

In their randomized phase III study, Mirimanoff et al supported the results of previous trials that investigated the efficacy of temozolomide (Temodar) against newly diagnosed glioblastoma multiforme. Building on a series of studies initially conducted in Britain and later performed in the US, the investigators showed this methylating agent to be active in patients with recurrent or newly diagnosed malignant glioma. Under the auspices of the European Organization for Research and Treatment of Cancer, the team conducted the study to compare surgery and radiation therapy given with and without temozolomide.

In this trial, the researchers administered 75 mg/m² of oral temozolomide on a daily basis throughout the radiotherapy; this was followed by monthly administration of the classic regimen that involved use of 150–200 mg/m²/d of the drug given PO for 5 days every 28 days. As Stupp et al (*J Clin Oncol* 2002;20:1375–1382) noted in an earlier observation, use of temozolomide in patients with newly diagnosed glioblastoma multiforme resulted in an increase in median, 2-year, and disease progression-free survival rates.

An additional observation was the confirmation from earlier work at Duke (Friedman HS et al: *J Clin Oncol* 1998;16:3851–3857) that tumor levels of O6-alkylguanine-DNA alkyltransferase (AGT) are related directly to the efficacy of temozolomide in treating patients with newly diagnosed glioblastoma multiforme. This earlier work demonstrated that tumors with 20% or more of cells staining for AGT were refractory to temozolomide given in a preradiation setting.

Mirimanoff's team, using the surrogate parameter of AGT promoter methylation, has identified a precise relationship between protein and survival. Specifically, patients with methylation of the AGT promoter (and, hence, no AGT) had a far better survival than did those in whom the promoter was unmethylated. This work, therefore, confirmed both the benefit of temozolomide in increasing survival among patients with newly diagnosed glioblastoma multiforme and the relevance of the tumor's AGT status. However, it should be noted that with only 11% of patients remaining free of disease progression at 2 years, this therapy hardly is the gold standard; rather, this research simply confirmed that this drug may be effective in treating these tumors. This drug was approved by the US FDA in 1999 for treatment of patients with refractory anaplastic astrocytoma.

Still, some pressing questions remain. First, since an 11% progression-free survival at 2 years is hardly anything to cheer about, how do we get better results with the drug? Second, what do we do with patients whose tumors are AGT-positive at diagnosis? The results of recent and future research may offer answers for some patients diagnosed with AGT-positive tumors.

— Henry S. Friedman, MD

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The 2-year survival was improved from 10% to 26%, and this was highly statistically significant.

— René-Olivier Mirimanoff

Patients were given a median of three chemotherapy cycles after radiotherapy; only 47% of the subjects received the full six cycles, and “progressive disease” most often was listed as the reason for discontinuation of treatment.

Many patients received additional therapy after disease progression, including surgery (23%) and some type of chemotherapy (65%). Dr. Mirimanoff said that 60% of the patients in the radiation therapy-alone arm were given temozolomide once they had progressed, and 25% of those in the study group that had received both temozolomide and radiation therapy were given additional temozolomide once they had progressed.

The actuarial median overall survival time was significantly longer in the radiotherapy-temozolomide group than in the radiotherapy-alone group (14.6 vs 12.1 months, respectively), Dr. Mirimanoff stated, adding, “But, more importantly, the 2-year survival was improved from 10% to 26%, and this was

highly statistically significant.”

To assess risk-specific survival, patients were stratified by a recursive partitioning analysis (RPA) classification, ranging from class III (those with the most favorable features) to class V (those with the most adverse features). The actuarial 2-year rate of overall survival was significantly higher with radiotherapy-temozolomide than with radiation therapy alone among patients in class III (31% vs 14%) and class IV (25% vs 9%). In contrast, combination therapy did not confer a significant survival benefit among patients in class V (15% vs 8%), although there were few patients in this subgroup.

According to Dr. Mirimanoff, the most provocative findings came from an analysis suggesting that MGMT methylation (silencing) status also influenced outcomes. Overall, 45% of 207 patients tested had methylation of the repair enzyme, and, among this

subset, the 2-year survival rate with radiotherapy-temozolomide was double that seen among patients who received radiation therapy alone (46% vs 23%, respectively). Patients who did not have methylation of MGMT had poorer survival in general, regardless of whether they received radiotherapy-temozolomide or radiation therapy alone (14% vs 2%), he said.

Future studies might include integration of such treatments as farnesyl transferase inhibitors and antiangiogenesis agents.

Mirimanoff R, Mason W, Kortmann R, et al. Radiotherapy (RT) and concomitant and adjuvant temozolomide (TMZ) versus radiotherapy alone for newly diagnosed glioblastoma (GBM): overall results and recursive partitioning analysis (RPA) of a phase III randomized trial of the EORTC Brain Tumor and Radiotherapy Groups and the NCIC Clinical Trial Group. Paper presented at the 46th Annual Meeting of the American Society for Therapeutic Radiology and Oncology; October 3–6, 2004; Atlanta, Georgia. Abstract 55.

SOCIETY FOR NEURO-ONCOLOGY

Promising results in overcoming temozolomide resistance

Researchers combine temozolomide and O6-BG to treat malignant glioma

Eleven patients have remained stable, and five patients have shown a near complete response for at least 6 to 23 cycles.

— Jennifer Quinn

At the Society for Neuro-Oncology’s ninth annual meeting, researchers from The Brain Tumor Center at Duke University Medical Center reported promising initial findings from an ongoing phase II trial that combined temozolomide (Temozar) therapy with O6-benzylguanine (O6-BG) to restore temozolomide sensitivity in drug-resistant malignant glioma patients.

Jennifer Quinn, MD, noted that the major mechanism of resistance to alkyl-nitrosourea therapy involves the DNA repair protein O6-alkylguanine-DNA alkyltransferase (AGT), which removes

chloroethylation or methylation damage from the O6-position of guanine. As an AGT substrate, O6-BG inhibits AGT by “suicide inactivation.”

The team completed a phase I trial of temozolomide plus O6-BG that defined the maximum tolerated dose of temozolomide as 472 mg/m² orally (PO) when the drug was given as a single dose every 28 days. Dr. Quinn noted that in January 2003, the team began testing temozolomide plus O6-BG in a phase II trial in an attempt to restore temozolomide sensitivity among drug-resistant malignant glioma patients and

to find out more about the possible toxicity of this drug combination.

Thus far, 56 patients have been treated; they were divided into two independent groups based on histology. Thirty-two patients have glioblastoma multiforme, whereas 24 have anaplastic astrocytoma or anaplastic oligodendroglioma. Patients were given 120 mg/m² of O6-BG via intravenous (IV) infusion over 1 hour and followed immediately by 30 mg/m²/d given via a 48-hour IV infusion. The patients were given 475 mg/m² of

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This study, in which this reviewer is a participant, attempts to utilize the O6-alkylguanine-DNA alkyltransferase (AGT)-depleting agent O6-benzylguanine (O6-BG) to restore sensitivity to malignant glioma that became resistant to temozolomide (Temozar). To believe that only AGT produces resistance to this methylating agent is an oversimplification—methylator resistance is produced by DNA mismatch repair deficiency. Nevertheless, an AGT depletor may restore sensitivity to methylating agents that are resistant by virtue of AGT.

In the report, updated now by Quinn and others, 5 of 24 patients with anaplastic astrocytoma or anaplastic oligodendroglioma and just 1 of 32 patients with glioblastoma multiforme responded to temozolomide therapy. These data suggested that 15%–20% of patients with anaplastic astrocytoma that is resistant to temozolomide may have sensitivity restored through the use of O6-BG. A trial building on these results for registration with the US FDA is being planned.

Unfortunately, the results for temozolomide in treating glioblastoma multiforme patients are far less impressive and reflect mechanisms of resistance other than AGT or a suboptimal schedule. For example, in the original phase I trial of temozolomide, whereas no one responded to the 1-day schedule, some patients responded to the 5-day schedule. Thus, a phase I study to evaluate use of a 5-day temozolomide/5-day O6-BG regimen in this patient population now is being designed.

— Henry S. Friedman, MD

temozolomide PO within 60 minutes of the end of the 1-hour O6-BG infusion; temozolomide dosing was repeated on day 1 of a 28-day cycle.

The group is using radiographic response criteria to evaluate activity via T1-weighted, enhanced magnetic resonance imaging. She noted that 38 patients have shown progressive disease after the first or second cycle, and 11 have remained stable over at least 6 to 23 cycles. Interestingly, five patients who have shown a near complete response have either an anaplastic astro-

cytoma or an anaplastic oligodendroglioma. Two patients are not evaluable for response.

Dr. Quinn added that drug-related toxicities have been limited to hematologic events, including 25 episodes of grade 4 neutropenia, 7 episodes of grade 4 thrombocytopenia, 2 episodes of grade 3 thrombocytopenia, 1 episode of grade 3 febrile neutropenia, and 1 episode of grade 3/4 anemia.

“This therapy does look potentially viable,” she said. “All of these patients

already had failed [temozolomide], and those having responses are having enduring responses.” The most exciting results have been seen among patients with anaplastic astrocytoma or anaplastic oligodendroglioma, as they have had enduring responses.

Quinn J. Phase II trial of temozolomide (Temodar) plus O6-benzylguanine (O6-BG) in the treatment of patients with Temodar-resistant malignant glioma. Paper presented at the 9th Annual Meeting of the Society for Neuro-Oncology; November 18–21, 2004; Toronto, Canada. Abstract TA-45.



Patients with anaplastic astrocytoma or anaplastic oligodendroglioma have had enduring responses.

— Jennifer Quinn

SOCIETY FOR NEURO-ONCOLOGY

‘Encouraging news’: Vaccine increases survival in phase I brain cancer trial

Immunotherapy targets antigen found in 47% of malignant gliomas

A phase I study initiated 2 years ago by researchers at the Brain Tumor Center at Duke Comprehensive Cancer Center used a therapeutic vaccine against malignant glioma and demonstrated a doubling of time to disease progression and an increase in patient survival when compared with historic controls.

In a presentation of results at the Society for Neuro-Oncology’s ninth annual meeting Gary Archer, PhD, stated, “Brain tumors are an absolutely devastating disease; the survival time you can expect from the initial diagnosis is 12–18 months at best. With this study, we’re seeing some positive stories—certainly more than we’d originally hoped.”

The use of immunotherapy to treat malignant gliomas requires generation of a strong immune response in the brain, which traditionally has been considered to be an immunologically privileged site protected from the rest of systemic circulation. Even more important, the immune response must be specific to the tumor and must not initiate a response that would be worse, such as a devastating encephalomyelitis, in normal brain tissue.

This vaccine is based on a peptide technology licensed to Alteris Therapeutics, Inc., which targets the deletion mutation of the epidermal growth factor receptor (EGFR) known as EGFRvIII. This tumor-specific antigen, which is found in about 47% of malignant gliomas, stimulates cancer growth as it enhances tumor cell survival, proliferation, invasion, and growth of new tumor vessels. The in-frame EGFRvIII deletion combines distant parts of the molecule and pro-

duces a novel glycine at the fusion junction. “The peptide used in the vaccine is designed to recruit immune system defenses targeting EGFRvIII to stop or slow the growth of cancer cells,” said Dr. Archer.

The phase I trial involved patients with newly diagnosed malignant gliomas to determine the safety of using a vaccination containing mature dendritic cells that were loaded with a peptide spanning the fusion junction (PEPvIII) and that were conjugated to a keyhole limpet hemocyanin (KLH). A total of 20 patients enrolled in the study; 16 patients completed the vaccination sequence, which consisted of three injections of PEPvIII–KLH-loaded, mature dendritic cells. The injections were given 2 weeks apart

and began 2 weeks after completion of postresection radiotherapy.

None of the patients showed a hypersensitivity reaction to KLH or PEPvIII before vaccination. Post vaccination, however, all 16 patients reacted to KLH, and 10 of 16 reacted to PEPvIII. All of the patients tested also had significant increases in antigen-specific T-cell proliferation in vitro after vaccination. No humoral responses to PEPvIII were identified. Two patients showed residual disease following surgery and radiation therapy; one had a nearly complete response, and the other had no disease progression over 653 days. Of the 17 patients who had no radiographically evident disease, 4 of 15 had not progressed, and the median overall time to disease progression was 288 days.

The median survival time for pa-

The peptide used in the vaccine is designed to recruit immune system defenses targeting EGFRvIII to stop or slow the growth of cancer cells.

— Gary Archer

Comment

Chemotherapy has been the traditional therapeutic strategy used to treat brain tumors following surgery and radiotherapy. Results to date have been modest, as can be seen by studies reviewed in this volume. Still, researchers, physicians, and patients have reason for a small degree of optimism in the treatment of these difficult neoplasms—and some hope relies on ways to harness the human body’s own immune system to fight cancer.

Many investigators are researching the role of vaccines as therapy for brain cancer. Archer and others selected the mutant epidermal growth factor receptor known as EGFRvIII as a target, as they sought to slow, or even stop, the growth of neoplastic cells. In this vein, researchers involved in a current clinical trial are treating patients with dendritic cells; this study is using a peptide spanning the fusion junction of EGFRvIII. Thus far, no toxicity using this method has been observed, and results suggest that autologous mature dendritic cells are safe for use in this patient population.

Preliminary data suggest that an immune response eventually may be detected, although it still is too early to make this assumption. Similarly, to say that there will be a clinical benefit from use of this method is preliminary at present. Nevertheless, strategies such as these should be pursued to complement the work being conducted with chemotherapy and small-molecule inhibitors.

— Henry S. Friedman, MD

The vaccines were well tolerated and these early data are showing good evidence of efficacy in malignant glioma.

— Gary Archer

tients with glioblastoma multiforme was 596 days. This compared favorably with the 417 days reported in recent trials of polifeprosan 20 with carmustine implant (Gliadel; *Westphal M et al: Neuro-Oncology 2003;5:79–88*), the 480 days for radiation therapy and concurrent temozolomide (Te-

modar; *Stupp R et al: J Clin Oncol 2002;20:1375–1382*), or the 556 days for radiolabeled antitenascin monoclonal antibodies (*Reardon DA et al: J Clin Oncol 2002;20:1389–1397*).

“The vaccines were well tolerated, and these early data are showing good evidence of efficacy in malignant gli-

oma,” Dr. Archer concluded, adding, “and it’s encouraging news.”

Archer GE, Bigner D, Friedman A, et al. Dendritic cell vaccine for intracranial tumors I (DC VICTORI Trial). Paper presented at the 9th Annual Meeting of the Society for Neuro-Oncology; November 18–21, 2004; Toronto, Canada. Abstract IM-02.

SOCIETY FOR NEURO-ONCOLOGY

Cancer stem cell hypothesis offers new brain cancer target

Not every cancer cell is created equal; some are more potent than others in initiating a new tumor

Studies at The Hospital for Sick Children at The University of Toronto suggest that cancerous stem cells in brain cancer may drive the growth of tumors and initiate new tumors.

At the Society for Neuro-Oncology’s ninth annual meeting, Peter Dirks, MD, PhD, recounted, “A number of years ago, I started thinking that brain cancer might be organized like the stem cell system.... So we decided to try to find a cancerous stem cell to determine if that cell would have the unique ability to drive the growth of a tumor and initiate new tumors. We basically found that the same principles applied.”

Dr. Dirks and his colleagues prospectively isolated a CD133-positive cell subpopulation from human brain tumors that exhibited stem cell properties in vitro. The brain tumor stem cell (BTSC) represented a fraction of the total cells within the tumor; these stem cells were isolated from low- and high-grade tumors from both children and adults. The researchers reported that their observations supported the theory that these cells were indeed BTSCs—they generated clusters of clonally derived cells

resembling neurospheres, underwent self-renewal and proliferation, and differentiated to reorganize into the phenotype of the tumor from which they were extracted.

In defining a class of BTSCs that can be isolated prospectively from a wide range of brain tumors, these data supported the application of the principles of leukemogenesis to solid tumors—only a small subset of cancer stem cells is enriched for clonogenic capacity, and these cells alone can propagate a tumor.

The researchers then sought to verify this principle in vivo. The team accomplished CD133-positive cell isolation and in vivo engraftment on cells that were cultured for only a brief time or not at all, reported Dr. Dirks.

“We found that only the CD133-positive brain tumor fraction contains cells that are capable of tumor initiation in non-obese diabetic, severe combined immunodeficient (NOD-SCID) mouse forebrains,” he said. “Injection of as few as 100 CD133-positive cells produced a tumor that could be serially transplanted and was a phenocopy of the patient’s original tumor, whereas the injection of

100–1,000 times more CD133-negative cells engrafted but never formed a tumor. Not every cell in brain cancer is growing and dividing. Only the CD133-positive cells were able to grow tumors. This gives us a new target we weren’t looking for before.”

Since most cancer treatments target rapidly proliferating cells, Dr. Dirks said, these data show that it may be time to focus on more quiescent cells. “Not every cancer cell is created equal,” he noted. “Some are more potent in initiating new tumor formation, and those cells are generally minority populations.”

Dr. Dirks added, “We need to start to figure out what are the genes and molecular signaling pathways that make these stem cells grow and renew themselves,” he added. “If we can figure out what makes them tick, we can look at better ways to address therapies for cancer treatment that focus on these key brain tumor initiating stem cells.”

Singh SK, Hawkins C, Clarke ID, et al. Adult human glioma growth is exclusively maintained in vitro and in vivo by CD133+ cancer stem cells. Paper presented at the 9th Annual Meeting of the Society for Neuro-Oncology; November 18–21, 2004; Toronto, Canada. Abstract MOD-09.

Not every cell in brain cancer is growing and dividing. Only the CD133+ cells were able to grow tumors. This gives us a new target we weren’t looking for before.

— Peter Dirks

CHEMOTHERAPY FOUNDATION SYMPOSIUM

Radiation sensitizer shows promise in breast cancer patients with brain metastases

‘Encouraging’ near doubling of median survival prompts additional investigation

Efaproxiral (RSR-13) is the first noncytotoxic radiation sensitizer that appears to provide a survival benefit in cancer patients with brain metastases, investigator John Suh, MD, said at the 22nd Chemotherapy Foundation Symposium. According to a subgroup analysis of the recent RT-

009 phase III trial, efaproxiral administration improved median survival from 4.5 months to about 9 months in patients with brain metastases from breast cancer who underwent whole brain radiation therapy (WBRT) and supplemental oxygen treatment. “The near doubling of median survival is very

encouraging,” said Dr. Suh, director of the Cleveland Clinic Gamma Knife Center, Cleveland, Ohio.

Efaproxiral also is being studied in other types of cancer, including cervical and locally advanced non-small cell lung cancer (NSCLC), to explore its thera-

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Part of the reason why these [breast cancer] patients did better is that they were able to get a greater peak concentration of this drug.

— John Suh

The near doubling of median survival is very encouraging.

— John Suh

peutic potential. Dr. Suh described the agent as a synthetic allosteric modifier of hemoglobin that effectively “emulates and amplifies” physiological tissue oxygenation. The molecule binds non-covalently in the hemoglobin tetramer, affecting the structure of hemoglobin and reducing its oxygen-binding affinity. This action facilitates oxygen release from hemoglobin, increasing both whole blood p50, which is the partial pressure of oxygen (pO₂) at which 50% hemoglobin is saturated, and tissue pO₂.

Treatment of brain metastases has been a primary area of focus for efaproxiral development. The gold standard for treatment of brain metastases has been WBRT, which has produced median survival rates of about 4.5 months in randomized trials. “There is a great need to improve on these results,” Dr. Suh said.

Accordingly, investigators undertook a phase II study of efaproxiral, enrolling 69 patients with breast cancer, NSCLC, and other types of cancer. When compared with a historic control of RPA class II patients (n = 1,070), a median survival of 6.4 months found among patients given efaproxiral (n = 57) was significantly higher than the 4.1 months observed for the control group (P = 0.0174). Those results led to the launch of the phase III trial (RT-009), in which a total of 515 eligible patients were randomized to receive WBRT plus supplemental oxygen alone or with efaproxiral; the primary end point was survival. Overall, there was no significant improvement in survival gained by adding efaproxiral to WBRT plus supplemental oxygen. Only a small numerical difference was seen, with a median overall survival of 5.4 months for the experimental arm and of 4.4 months for controls (P = 0.16).

However, the difference in survival approached significance when results from only the subset of 397 patients with breast cancer or NSCLC were ex-

amined. Median survival was 6 months for those in the efaproxiral group and 4.4 months for members of the control group (P = 0.07). The greatest effect was seen in the subset of 107 eligible patients with breast cancer, in which median overall survival was 9.0 months for the efaproxiral group and only 4.5 months for controls (hazard ratio = 0.51, P = 0.003). “Part of the reason why these (breast cancer) patients did better is that they were able to get a greater pharmacokinetic concentration of this drug as measured by [red blood cell] concentration,” Dr. Suh stated.

These findings led to the confirmatory phase III trial known as ENRICH (RT-016), which will seek to enroll 360 women with brain metastases from breast cancer at leading medical centers worldwide. Two interim analyses are planned at one-third and two-thirds the required number of events. The study is expected to complete enrollment by the third quarter of 2006.

Suh J. Clinical trial results of RSR 13 (efaproxiral) in therapy of brain metastases. Paper presented at the 22nd Chemotherapy Foundation Symposium; November 9–13, 2004; New York, NY. Abstract 72.

Comment

The treatment of patients with brain metastases remains challenging, particularly in light of the difficulties of treating intracranial disease and the diverse spectrum of malignancies that metastasize to the brain. Among the strategies used over the past 20 years to treat patients with these tumors has been radiosensitization—the deployment of agents designed to enhance the antitumor activity of radiation without increasing neurotoxicity. Unfortunately, no radiosensitizer has enhanced the activity of radiotherapy effectively in this setting.

Efaproxiral is an allosteric hemoglobin modifier that decreases hemoglobin’s affinity for oxygen. This effect, also known as a right shift of the curve relating blood oxygen concentration to hemoglobin oxygen saturation, effectively produces oxygen unloading at the tissue level. This effect is important, because oxygen is the most efficient radiosensitizer yet identified.

The results of a recent phase III trial that evaluated the effect of efaproxiral in treating brain metastases suggested that the drug, when combined with whole-brain radiotherapy and supplemental oxygen, increased the median survival of metastatic breast cancer patients from 4.5 to 9 months.

The US Food and Drug Administration Oncologic Drugs Advisory Committee (ODAC) reviewed these data and noted that patients with metastatic breast cancer who were treated with efaproxiral represented a subgroup analysis of the overall trial. While acknowledging the activity of this agent, ODAC considered the potential bias introduced by subgroup analysis and recommended that a trial limited to breast cancer patients be performed. This confirmatory phase II trial, known as the Enhancing Whole Brain Radiation Therapy in Patients with Breast Cancer and Hypoxic Brain Metastases (ENRICH; RT-016) trial, will include 360 women with brain metastases from breast cancer; this research currently is being conducted at 35 US centers.

A trial also will be conducted in Europe and South America. If investigators confirm the results of the RT-009 trial, they will demonstrate unequivocally for the first time that noncytotoxic radiation sensitization benefits cancer patients with brain metastases.

— Henry S. Friedman, MD