

Phase III Study of Efavoximal As an Adjunct to Whole-Brain Radiation Therapy for Brain Metastases

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ABSTRACT

Purpose

To determine whether efavoximal, an allosteric modifier of hemoglobin, improves survival in patients with brain metastases when used as an adjunct to whole-brain radiation therapy (WBRT).

Patients and Methods

Patients with brain metastases from solid tumors and a Karnofsky performance score of ≥ 70 were randomly assigned to receive WBRT with supplemental oxygen and either efavoximal at 75 or 100 mg/kg (efavoximal arm) or no efavoximal (control arm). The primary end point was survival.

Results

The study consisted of 515 eligible patients (efavoximal arm, $n = 265$; control arm, $n = 250$). The median survival time (MST) was 5.4 months for the efavoximal arm versus 4.4 months for the control arm (hazard ratio [HR] = 0.87; $P = .16$). For the subgroup of patients with non-small-cell lung cancer (NSCLC) or breast cancer, the MST was 6.0 and 4.4 months, respectively (HR = 0.82; $P = .07$). Cox multiple regression analysis demonstrated a significant reduction in the risk of death for the efavoximal arm in both primary populations. Further analysis indicated that the benefit may be restricted to the subgroup of patients with breast cancer. Response rates (radiographic complete response plus partial response) improved by 7% ($P = .10$) and 13% ($P = .01$) for all patients and for NSCLC and breast cancer patients in the efavoximal arm, respectively. The most common severe adverse event in patients treated with efavoximal was hypoxemia, which was reversible and effectively managed with supplemental oxygen in most patients.

Conclusion

The addition of efavoximal, a noncytotoxic radiation sensitizer, to WBRT may improve response rates and survival in patients with brain metastases, particularly metastases from breast cancer. A confirmatory trial for breast cancer patients has been initiated.

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INTRODUCTION

Brain metastasis is the most common neurologic complication of cancer. It afflicts up to 170,000 individuals annually in the United States alone.^{1,2} Although extracranial systemic disease has a major impact on survival, brain metastases are the cause of death in one third to one half of affected patients.^{2,3} Treatment with corticosteroids can alleviate symptoms in the majority of patients but only for a limited time. Without further treatment, the median survival time (MST) is 1 to 2 months,⁴⁻⁶ emphasizing the need to improve local control and survival.⁷⁻¹⁰ Whole-brain radiation therapy (WBRT) has been the principal treatment, with local control/response rates of 50% to 75%.¹¹⁻¹⁵ Despite the use of WBRT, the prognosis for patients with brain metastases remains poor. Patients generally survive for

only 4.5 months after diagnosis, which has not changed over the last 25 years.^{3,16-18}

Selected patients with good performance status and a single brain metastasis seem to benefit from surgical resection if the lesion is located in a noneloquent area.^{7,19} Furthermore, the use of stereotactic radiosurgery (SRS) provides a less invasive means of achieving a similar outcome to surgery for some patients.²⁰⁻²² The recent publication of the results of Radiation Therapy Oncology Group 9508, a phase III study evaluating WBRT with or without SRS, reported a significant survival benefit in patients with a single brain metastasis who were randomly assigned to the SRS treatment arm.²³ However, no survival advantage was observed with SRS in patients with multiple brain metastases, despite better local control. Because the majority of patients with brain metastases are not ideal candidates for SRS because of their tumor location, disease status, or

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number of lesions, WBRT remains the standard treatment in most patients. One potential approach to improving the benefits of WBRT is to combat hypoxia, a hallmark of brain tumors^{24,25} and a well-recognized cause of radiation resistance.

Hypoxic tumors are more resistant to cell damage caused by ionizing radiation.²⁶ Therefore, tumor hypoxia adversely affects the clinical prognosis of patients receiving radiation therapy.²⁷⁻³⁰ Levels of oxygen have been measured in tumors from patients with various cancers, and the results have confirmed tumor hypoxia in many cancers including brain metastases,^{24,25} breast cancer,³¹ glioblastoma multiforme,²⁴ squamous cell carcinomas of the uterine cervix,³² and head and neck cancer.³³ Several clinical studies have also demonstrated that tumors with a low median partial oxygen pressure (pO₂) have a higher local failure rate after radiation therapy.^{32,33}

Efangroxiral (Efangroxyn, RSR13; Allos Therapeutics Inc, Westminster, CO) is an allosteric modifier of hemoglobin and the first of a new class of pharmaceutical agents. Efangroxiral binds noncovalently in the central water cavity of the hemoglobin tetramer and affects the conformational structure of hemoglobin.^{34,35} This leads to a reduction in hemoglobin oxygen-binding affinity³⁶⁻⁴¹ and thereby facilitates the release of oxygen. By this mechanism, efangroxiral increases whole-blood pO₂ for 50% hemoglobin saturation (p50), resulting in enhanced tumor oxygenation and radiation sensitivity.^{42,43} Unlike other agents that have been used to improve the effectiveness of WBRT, efangroxiral does not need to enter cancer cells to increase radiosensitivity because oxygen readily diffuses across the blood-brain barrier to decrease tumor hypoxia. Theoretically, efangroxiral has the potential to increase the effectiveness of WBRT.

Phase I studies in healthy volunteers and oncology patients confirmed the feasibility and safety of administering doses of efangroxiral at 75 or 100 mg/kg, either of which was sufficient to reach the desired pharmacodynamic end point (to increase whole-blood p50 by approximately 10 mmHg) and establish a strong correlation between efangroxiral concentration in RBCs and p50 shift.^{44,45} A phase II study demonstrated that survival significantly improved in patients with brain metastases from solid tumors who were treated with 75 or 100 mg/kg of efangroxiral within 30 minutes before standard WBRT versus a case-matched historical control group of recursive partitioning analysis (RPA) class II patients in the Radiation Therapy Oncology Group Brain Metastases Database.⁴⁶

These encouraging results led us to perform the current phase III study, RT-009, which is also called the Radiation Enhancing Allosteric Compound for Hypoxic Brain Metastases (REACH) study. In this study, we tested the hypothesis that adding efangroxiral to WBRT plus supplemental oxygen would improve survival better than WBRT with supplemental oxygen alone.

PATIENTS AND METHODS

Eligibility Criteria

Enrollment was open to RPA class I or II patients with brain metastases originating from solid tumors, excluding small-cell lung cancer, germ cell tumors, and lymphomas. Additional eligibility criteria included no prior treatment for brain metastases (other than resection with measurable lesion remaining), age \geq 18 years, and adequate hematologic, hepatic, and renal function as defined by hemoglobin \geq 10 g/dL, WBC count \geq 2,000 cells/ μ L, platelet count \geq 75,000 cells/ μ L, creatinine \leq 2.0 mg/dL, bilirubin \leq 2.0 mg/dL, and transaminases $3\times$ the upper limit of normal. Patients were required to have no other concurrent active malignancy, no planned therapy for brain metastases through the 1-month post-WBRT follow-up visit, and standard pulse oximetry (SpO₂) measurement (resting and exercise) \geq 90%. Women could not be breastfeeding or pregnant, and females of childbearing potential and all nonsterile males were required to use contraception. Patients were excluded if they had prior exposure to efangroxiral, had received chemotherapy within 7 days, or had used investigational agents within 28 days before WBRT. Informed consent was obtained from all patients. Human experimentation guidelines of the appropriate regulatory authorities and the guidelines of the investigators' institutions were followed in the conduct of clinical research.

Random Assignment

Patients were randomly assigned 1:1 to receive standard WBRT plus supplemental oxygen and either efangroxiral (efangroxiral arm) or no efangroxiral (control arm) using permuted blocks within strata that were defined by RPA class and primary site.⁴⁷ In total, there were four strata, as follows: (1) RPA class I; (2) RPA class II non-small-cell lung cancer (NSCLC); (3) RPA class II breast cancer; and (4) RPA class II other cancer sites.

Treatment

All patients received a standard 2-week course of WBRT (3 Gy/fraction for 10 days) plus supplemental oxygen (4 L/min via nasal cannula). Oxygen was administered beginning 35 minutes before, during, and for at least 15 minutes after daily WBRT. Supplemental oxygen was administered to both arms to ensure that any treatment effect between treatment arms was attributable to efangroxiral. For the efangroxiral arm, administration began on the first day of WBRT and continued every day (Monday through Friday) of the

Table 1. Severity Grading for Hypoxemia (sponsor defined per protocol)

Grade				
0	1	2	3	4
Nonexistent	Supplemental oxygen required > 3 hours but < 4 hours after end of efangroxiral infusion	SpO ₂ < 90% while breathing supplemental oxygen at 4 L/min; supplemental oxygen required \geq 4 hours after end of efangroxiral infusion; increase in supplemental oxygen > 4 L/min during the efangroxiral infusion and/or during the 4-hour recovery period	Symptomatic hypoxemia defined as decreased SpO ₂ with headache, dizziness, dyspnea, or hypotension; preinfusion SpO ₂ < 90% attributed to efangroxiral; decreased SpO ₂ requiring hospitalization; NOTE: if the patient refuses hospitalization and is discharged home on supplemental oxygen, a grade 3 classification would still be appropriate	Decreased SpO ₂ requiring continuous positive airway pressure and/or mechanical ventilation

Abbreviation: SpO₂, standard pulse oximetry.

2-week WBRT course for a total of 10 doses. Efavoxir was administered intravenously via a central venous access device over 30 minutes; the infusion was completed no more than 30 minutes before WBRT. The intended daily dose of efavoxir was 75 or 100 mg/kg. The control arm received the same treatment without administration of efavoxir; no placebo was administered. An amendment to the original study protocol revised the dosing guidelines, making the initial efavoxir dose dependent on sex and body weight. If the SpO₂ while breathing room air at screening (at rest and during exercise) and on WBRT day 1 was $\geq 93\%$, efavoxir was administered as follows: males with a body weight of ≤ 95 kg and females weighing ≤ 70 kg were initially administered 100 mg/kg of efavoxir; and males with a body weight of more than 95 kg and females weighing more than 70 kg were administered 75 mg/kg of efavoxir. If the SpO₂ while breathing room air on WBRT day 1 was less than 93%, efavoxir was omitted that day. Dosing modifications were permitted based on SpO₂ and anticipated adverse events (AEs) that were temporally related to the administration of efavoxir. Dose reductions to 50 mg/kg were permitted through protocol exemptions on a case-by-case basis.

Efficacy Assessments

The primary efficacy end point was overall survival, which was measured from the time of random assignment until death or January 31, 2003, whichever occurred first. Response rate, which was defined as best response (complete plus partial response) after WBRT, was evaluated as a secondary end point. Radiographic assessments were performed by either magnetic resonance imaging or computed tomography (consistent testing was required throughout) at baseline, 1 month after WBRT, 3 months after WBRT, and every 3 months thereafter until progression or death. Neuroradiologists who were blinded to all other study data independently reviewed all scans. Response evaluations of up to three indicator lesions (target lesions) were made relative to the baseline scan. A complete response was defined as complete resolution of all target lesions, and a partial response was defined as at least a 50% reduction in the sum of the bidimensional products of all indicator lesions. Progressive disease was defined as an increase in the bidimensional product of greater than 25% in at least one target lesion or the progression of any treated lesion that was not enumerated as a target lesion. The appearance of new lesions did not constitute disease progression. All other evaluations were reported as stable disease. Other secondary efficacy end points evaluated were radiologic and clinical progression, cause of death, and quality of life.

Safety Assessments

All patients who received at least one dose of study treatment, defined as efavoxir and/or WBRT, comprised the safety analysis population. An AE was considered treatment emergent if the AE increased in severity over the baseline severity grade and if the onset date was after the first administration of study treatment but no more than 7 days after the last dose of study treatment. All treatment-emergent AEs, with the exception of hypoxemia, were evaluated and assigned a grade using the National Cancer Institute Common Toxicity Criteria version 2.0.⁴⁸ The relationship of the event to efavoxir was assessed by the investigator. Because all patients were to receive supplemental oxygen (considered grade 3 by the National Cancer Institute Common Toxicity Criteria), a sponsor-defined grading scale was designed for the AE of hypoxemia (Table 1).

Statistical Considerations

The primary survival analysis was performed using a two-sided log-rank test (unadjusted for covariates) on two coprimary populations (all eligible patients and the eligible patients with NSCLC and breast cancer). The study design had 85% power to detect a difference in survival assuming a true 35% MST increase in the treatment arm from 4.57 to 6.17 months. The design parameters also resulted in 75% power, assuming the same treatment effect, in the slightly smaller population of all eligible patients with NSCLC/breast cancer. For survival analysis, January 31, 2003, was stipulated as the cutoff date for follow-up because it allowed for the prespecified number of events (at least 402 deaths overall and 308 deaths in the NSCLC/breast cancer populations) and permitted at least 6 months of follow-up on each patient. The covariate and treatment effects were estimated using the hazard ratio (HR) with a 95% CI and two types of Cox regression models (single regression, where only one covariate was entered into the model, and multiple regression, which included

Table 2. Distribution of Prognostic Factors by Treatment Group (all eligible patients)

Covariate	% of Patients	
	Control (n = 250)	Efavoxir (n = 265)
Primary site		
NSCLC	58	55
Breast	20	22
Other	22	23
Age, years		
< 65	73	72
≥ 65	27	28
Baseline KPS		
100	16	13
90	37	46
80	31	23
70	16	17
Sex		
Female	56	56
Male	44	44
Control of primary cancer		
Controlled	24	26
Uncontrolled	76	74
RPA class		
I	10	11
II	90	89
No. of sites of extracranial metastases		
0	36	31
1 to 2	46	48
≥ 3	18	22
Presence of liver metastases		
Yes	16	20
No	84	80
No. of brain metastases		
1	20	17
2 to 3	32	30
> 3	47	52
Sum of bidimensional products of lesions		
< 250 mm ²	25	26
250-1,000 mm ²	46	50
> 1,000 mm ²	28	23
Primary disease duration		
≥ 1 month	68	67
< 1 month	32	33
Prior brain tumor resection		
Yes	10	8
No	90	92
Baseline hemoglobin		
< 12 g/dL	16	17
≥ 12 g/dL	84	83
Site location		
United States	47	50
Canada	32	29
ROW	21	21
Altitude at treatment site		
< 2,000 feet	86	87
$\geq 2,000$ feet	14	13
Body weight*		
High weight	26	25
Low weight	74	75

Abbreviations: RPA, recursive partitioning analysis; NSCLC, non-small-cell lung cancer; ROW, rest of world; KPS, Karnofsky performance score.

*High weight: males > 95 kg, females > 70 kg; low weight: males ≤ 95 kg, females ≤ 70 kg.

Table 3. Univariable and Multivariable Proportional Hazards Regression Analyses (all eligible patients)

Factor	Univariable			Multivariable*†		
	HR	95% CI	P	HR	95% CI	P
Treatment group						
Efaproxiral	0.87	0.71 to 1.05	.16	0.74	0.61 to 0.90	.003
Control	1.00	—		1.00	—	
KPS						
70	2.65	1.87 to 3.77	< .0001	2.47	1.69 to 3.61	< .0001
80	1.36	0.99 to 1.90		1.29	0.90 to 1.84	
90	1.19	0.87 to 1.61		1.04	0.75 to 1.45	
100	1.00	—		1.00	—	
No. of extracranial metastatic sites						
> 2	2.02	1.54 to 2.64	< .0001	2.04	1.43 to 2.92	.0005
1-2	1.34	1.07 to 1.67		1.38	1.07 to 1.79	
0	1.00	—		1.00	—	
Prior brain tumor resection						
Yes	0.55	0.38 to 0.80	.002	0.50	0.33 to 0.75	.0009
No	1.00	—		1.00	—	
Primary site						
NSCLC	0.78	0.62 to 0.98	.005	0.85	0.65 to 1.11	.01
Breast	0.62	0.46 to 0.83		0.59	0.42 to 0.84	
Other	1.00	—		1.00	—	
Age, years						
≥ 65	1.45	1.18 to 1.80	.0005	1.48	1.17 to 1.88	.001
< 65	1.00	—		1.00	—	
Sex						
Male	1.47	1.21 to 1.78	.0001	1.60	1.26 to 2.02	.0001
Female	1.00	—		1.00	—	
No. of brain lesions						
> 3	1.25	0.96 to 1.62	.01	1.19	0.90 to 1.58	.008
2-3	0.90	0.68 to 1.21		0.81	0.60 to 1.10	
1	1.00	—		1.00	—	
Baseline Hgb						
≥ 12 g/dL	0.76	0.59 to 0.98	.03	0.78	0.59 to 1.02	.07
< 12 g/dL	1.00	—		1.00	—	

Abbreviations: HR, hazard ratio; KPS, Karnofsky performance score; NSCLC, non-small-cell lung cancer; Hgb, hemoglobin.

*Six patients were excluded from the regression analyses because of missing baseline scan information (n = 5) and missing weight (n = 1).

†All covariates not listed have a $P > .2$ from the multivariable model.

16 baseline categoric covariates, in addition to the treatment arm). These covariates and their distribution are listed in Table 2. Categoric covariates were analyzed using indicator variables for each level of the covariate. HRs for these nominal covariates compare the given level of the covariate with the reference level, which is indicated by 1.00 in Table 3. The Kaplan-Meier method⁴⁹ was used to estimate survival over time, censoring patients who remained alive as of January 31, 2003. Statistical significance was assessed using the Wald test statistic for two-level covariates and the likelihood ratio test for covariates with three or more levels. No approximation to the likelihood in the event of tied failure times was used. Tests of the proportional hazards assumption were made based on an inspection of the deviance residual plots as well as kernel smoothing plots of the hazard functions. Two-tailed $P < .05$ denoted statistical significance. SAS version 8.2 (SAS Institute, Cary, NC) was used for all data analyses.

Treatment-arm comparisons of response rate in the brain, cause of death, and quality of life (assessed by the Spitzer Questionnaire and Karnofsky performance score [KPS]) were made using the χ^2 test. All end points were analyzed using a denominator of the entire eligible patient population (or eligible NSCLC/breast cancer population). Cause of death was assessed as neurologic (progressive disease in the brain and no extracranial progression), non-neurologic (no progressive disease in the brain), or indistinguishable (progressive disease in the brain and extracranial progression). If cause of death was missing, it was assumed to be neurologic progression. For the quality

of life analyses, the percentage of patients in each arm with a stable or improving score (compared with baseline) was determined for each visit (1, 3, and 6 months after WBRT). This percentage was then used in a Cochran-Mantel-Haenszel test to obtain a composite P value over time. Time to radiographic or clinical tumor progression was reported by cumulative incidence estimates, and Gray's test⁵⁰ was used for treatment-arm comparisons. An additional, nonprespecified analysis was performed on progression-free survival (PFS), where death or radiographic progression in the brain constituted an event. This allowed for a conservative comparison of PFS between the treatment arms using the log-rank statistic. Clinical progression in the brain was based on at least one of the following occurring after WBRT day 10: an increase from baseline by 1 in neurologic function status score, a decrease from baseline by 3 in the Mini Mental State Examination score, or the use of subsequent therapy for brain metastases.

RESULTS

Patient Characteristics and Disposition

There were 538 patients from 82 clinical research sites and 12 countries randomly assigned to this study. As assessed by independent review of prerandom assignment information, 23 patients

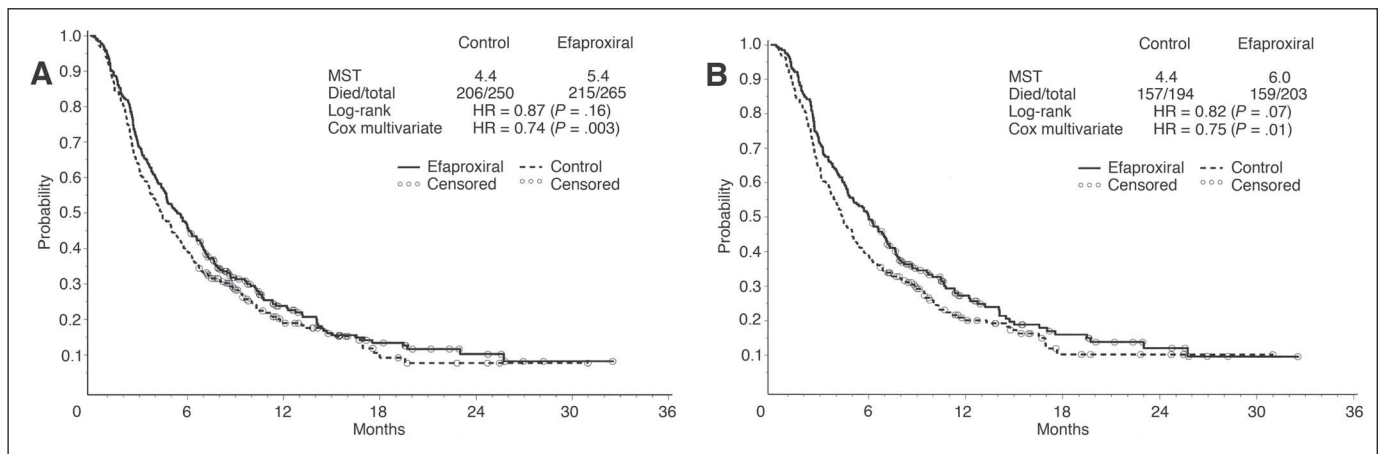


Fig 1. (A) Kaplan-Meier survival curve (all eligible patients). (B) Kaplan-Meier survival curve (eligible non-small-cell lung cancer and breast cancer patients). MST, median survival time; HR, hazard ratio.

(efaproxiral arm, $n = 6$; control arm, $n = 17$) were deemed to be in violation of major eligibility criteria; therefore, 515 patients were included in the efficacy analyses for all eligible patients, of whom 397 had NSCLC or breast cancer. Table 2 demonstrates that the treatment arms were generally well balanced for the efficacy population.

Five hundred twenty-nine patients received at least one dose of study treatment, making up the safety analysis population; of those patients, 266 patients (50%) were in the efaproxiral arm. Ninety-five percent of patients in the efaproxiral arm and 97% of patients in the control arm received all 10 doses of intended WBRT. Eighty-two percent (218 of 266 patients) of the patients in the efaproxiral arm received at least seven doses of efaproxiral, and the mean daily dose of efaproxiral was 83.6 mg/kg. No patients were lost to follow-up in the survival analysis of January 31, 2003.

Survival

The survival analysis was performed with a median potential follow-up of 15.2 months (range, 6.1 to 35.3 months). An inspection of the deviance residual plots as well as kernel smoothing plots of the hazard functions did not indicate departure from the proportional hazards assumptions. For the coprimary populations, Kaplan-Meier plots presenting the number of deaths and estimating survival over time are provided in Figures 1A and 1B. For all eligible patients, the MST was 4.4 months for the control arm and 5.4 months for the efaproxiral arm ($HR = 0.87$; $P = .16$). For the NSCLC/breast cancer population, the MST was 4.4 months for the control arm and 6.0

months for the efaproxiral arm ($HR = 0.82$; $P = .07$). The estimates for the treatment effect in these two coprimary populations were similar in a 12-month follow-up analysis, with slightly lower P values ($P = .13$ and $P = .05$ for all eligible patients and NSCLC/breast cancer patients, respectively). In an exploratory analysis by primary tumor type, the largest efaproxiral treatment effect was observed in the 107 patients with metastases from breast cancer ($HR = 0.51$; $P = .003$, unadjusted log-rank test). There did not seem to be a treatment benefit in the 290 patients with NSCLC ($HR = 0.97$; $P = .83$, unadjusted log-rank test) or in the group of 118 patients with other tumor types ($HR = 1.12$; $P = .58$, unadjusted log-rank test).

To account for confounding factors and bias of the treatment effect estimate that may result from omission of strong covariates^{51,52} (attenuation) in this heterogeneous population, a Cox regression analysis was performed with 16 covariates, in addition to treatment arm (Table 2). These prognostic factors were based on the literature,^{3,53} the conduct of the study, and the mechanism of action of the drug. The regression results for all eligible patients demonstrated a 26% reduction in the risk of death for patients in the efaproxiral arm ($HR = 0.74$; 95% CI, 0.64 to 0.90; $P = .003$). KPS, number of extracranial metastatic sites, and sex had the highest statistical significance in the multiple regression model. Eight covariates, including treatment arm, were statistically significant predictors of survival in the multiple regression model. HR estimates from both the univariable and multivariable models are listed in Table 3. Covariates with a $P > .2$ are not

Table 4. Follow-Up Radiographic Scans

Follow-Up Period	All Eligible Patients				Eligible NSCLC/Breast Cancer Patients			
	Control (n = 250)		Efaproxiral (n = 265)		Control (n = 194)		Efaproxiral (n = 203)	
	No. of Scans	No. Alive	No. of Scans	No. Alive	No. of Scans	No. Alive	No. of Scans	No. Alive
1 month	190	234	209	252	153	181	166	197
3 months	100	158	136	182	81	125	109	145
6 months	53	99	82	123	40	76	71	102

Abbreviation: NSCLC, non-small-cell lung cancer.

Progression*	Control (%)	Efaproxiral (%)	P
Radiographic progression			
All eligible patients	18	21	.53
Eligible NSCLC/breast cancer patients	15	15	.78
Clinical progression			
All eligible patients	51	49	.49
Eligible NSCLC/breast cancer patients	50	48	.58

Abbreviation: NSCLC, non-small-cell lung cancer.
*Progression at 1 year after random assignment.

listed. In the NSCLC/breast cancer population, the Cox multiple regression model yielded a 25% reduction in the risk of death (HR = 0.75; 95% CI, 0.60 to 0.94; P = .01) in patients treated in the efaproxiral arm.

Response Rate and Other Secondary End Points

The point estimates of response rate (complete plus partial response) were 38% (96 of 250 patients) for the control arm and 46% (121 of 265 patients) for the efaproxiral arm (P = .10). Twice the number of patients had a complete response in the efaproxiral arm (n = 28) compared with the control arm (n = 14). Evaluation of the NSCLC/breast cancer population established a 13% increase in the response rate in the efaproxiral arm (54%) versus the control arm (41%; P = .01). Table 4 demonstrates that the number of eligible patients with follow-up scans decreased rapidly over time as a result of short survival.

Other secondary efficacy end points included time to radiologic and clinical progression in the brain, cause of death, and quality of life. Table 5 shows that there was not a significant difference in the cumulative incidence at 1 year after random assignment of radiographic or clinical progression in the brain between the treatment groups for the eligible population or for the NSCLC/breast cancer population. Figures 2A and 2B display the Kaplan-Meier plots of PFS for all eligible patients (P = .21) and the NSCLC/breast cancer population (P = .06).

Of the 206 deaths in the control arm, 30 (15%) were a result of neurologic progression, 124 (60%) were a result of non-neurologic progression, and 52 (25%) were indistinguishable. Of the 215 deaths in the efaproxiral arm, 37 (17%) were a result of neurologic progression, 126 (59%) were a result of non-neurologic progression, and 52 (24%) were indistinguishable. The proportion of deaths caused by neurologic progression was not significantly different between the arms (P = .46). Similar results were observed for the NSCLC/breast cancer population.

The numbers and percentages of patients with stable or improving quality of life, as assessed by the Spitzer Questionnaire and KPS at 1, 3, and 6 months after WBRT, are listed in Table 6. A larger percentage of patients in the efaproxiral arm had stable or improving quality-of-life scores over the course of the follow-up visits.

AEs

The majority of treatment-emergent AEs were grade 1 (mild) to grade 2 (moderate) in severity in both treatment arms. Table 7 lists the most commonly reported (≥ 3%) grade 3 or 4 treatment-emergent AEs for patients treated with efaproxiral. The most commonly reported grade 3 AE in efaproxiral-treated patients was hypoxemia, which was reported in 11% of patients (29 of 266 patients); however, no grade 4 hypoxemia was reported. Hypoxemia was also the most commonly reported AE related to study drug (data not shown); most patients (73%) experiencing hypoxemia (any grade) as an AE were asymptomatic, and the only treatment required was supplemental oxygen. Overall, grade 4 AEs were reported at comparable frequencies in the two treatment arms (28 of 263 patients in the control arm, 11%; and 33 of 266 patients in the efaproxiral arm, 12%). With few exceptions, all AEs were treatable; the majority of AEs were resolved by the 1-month follow-up period.

DISCUSSION

This phase III, randomized, clinical trial represents one of the largest studies ever conducted in patients with brain metastases. The results of this study suggest that efaproxiral, a noncytotoxic radiation sensitizer,

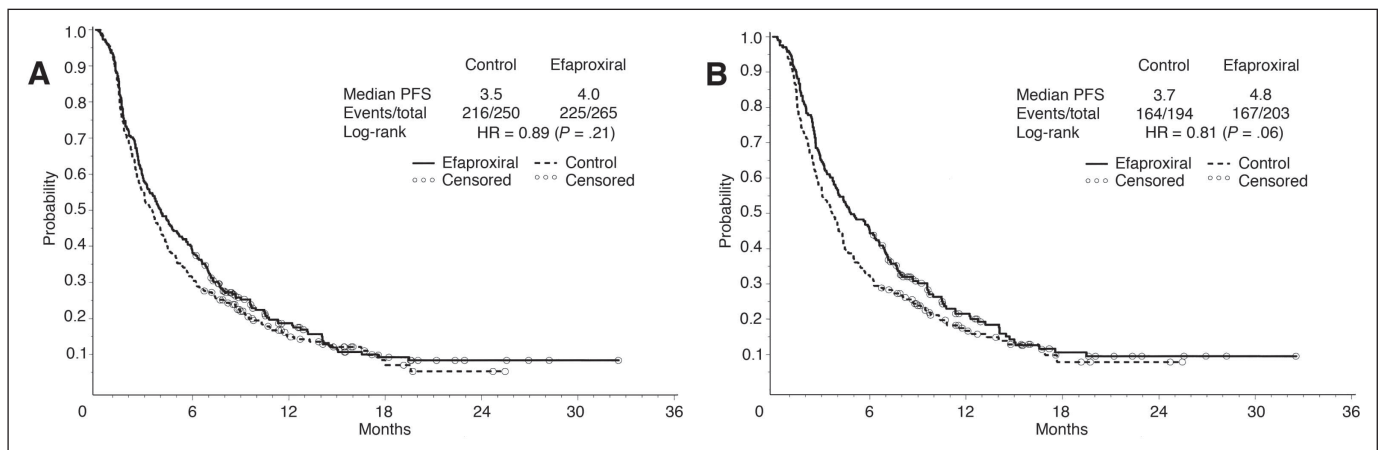


Fig 2. (A) Kaplan-Meier radiographic progression-free survival (PFS) curve (all eligible patients). (B) Kaplan-Meier radiographic PFS curve (eligible non-small-cell lung cancer and breast cancer patients). HR, hazard ratio.

Table 6. Proportion of Patients With Stable or Improving Quality of Life by Visit and Treatment Arm*

Patients	Spitzer Questionnaire								KPS							
	1 Month		3 Months		6 Months		Odds Ratio	P	1 Month		3 Months		6 Months		Odds Ratio	P
	No.	%	No.	%	No.	%			No.	%	No.	%	No.	%		
All eligible																
Control, n = 250	92	37	51	20	38	15	1.21	.12	90	36	46	18	36	14	1.38	.008
Efaproxiral, n = 265	114	43	62	23	43	16			117	44	63	24	48	18		
Eligible NSCLC/breast cancer																
Control, n = 194	75	39	42	22	32	16	1.28	.05	72	37	37	19	31	16	1.48	.003
Efaproxiral, n = 203	97	48	54	27	40	20			95	47	55	27	42	21		

Abbreviations: KPS, Karnofsky performance status; NSCLC, non-small-cell lung cancer.

*Percentages and statistical tests are based on a denominator of all randomly assigned and eligible patients.

may improve response rates to WBRT and survival in patients with brain metastases, particularly metastases from breast cancer.

There are two main issues that result from the analysis of this trial. First, the results of the primary analysis did not demonstrate a convincing survival advantage for patients in the efaproxiral arm overall (HR = 0.87; 95% CI, 0.71 to 1.05), but the multivariable analysis did indicate a treatment benefit (HR = 0.74; 95% CI, 0.61 to 0.90). One plausible reason for the difference in the results is that the prognostic factors were not balanced by treatment group; however, an inspection of the distribution of prognostic factors in Table 2 does not seem to indicate this. It is possible that the individual effects of minor imbalances are small but, when considered together, have a cumulatively larger impact. An additional possibility is more technical in nature because the treatment effect estimate in the unadjusted analysis could be biased as a result of attenuation. As described by Akazawa et al⁵² and Fleming and Lin,⁵¹ omission of strong covariates from the estimation of the treatment effect in clinical trials biases the treatment effect estimate towards the null hypothesis, effectively reducing the power for detecting a difference as a result of the intervention.

The second issue is in regards to the different treatment benefits observed by primary site. This may be related to different levels of hypoxia within different primary tumors or could simply be a random result of performing subset analyses. A confirmatory trial has been initiated in patients with brain metastases from breast cancer that should resolve this question.

Before commencing the study, it was hypothesized that an improvement in response would result in survival benefit; therefore, the

response rate (best response) was analyzed as a secondary efficacy end point. The clearest evidence supporting the therapeutic advantage of efaproxiral administration is derived from the 7% response rate improvement of the efaproxiral arm compared with the control arm. A statistically significant improvement (13% increase; $P = .01$) in the response rate was observed in the population of patients with brain metastases from NSCLC/breast cancer. The study did not show a decrease in neurologic death with the addition of efaproxiral, but this is not surprising given the difficulty in determining cause of death, the subjectivity involved in determination of causation, and extracranial disease involvement.

Although there was no observed difference between treatment arms in time to progression (both radiologic and clinical) in the brain, it is recognized that establishing differences in these end points is problematic when study patients have anticipated short survival times and infrequent end point evaluations. To have adequate power for evaluating this end point in future trials, it would be beneficial to perform scans at more frequent intervals. An alternative method may be to evaluate progression at a fixed time point after treatment, for example, at the 3-month follow-up visit. Either way, the high percentage of patients succumbing to systemic disease progression makes demonstrating an improvement in progression (or survival, for that matter) complicated.

Most AEs experienced by patients in this study were mild to moderate in severity, and the majority of AEs were reversible, resolving by the 1-month follow-up visit. A low frequency of grade 3 to 4 AEs was reported, with hypoxemia being the most commonly reported severe AE that was also efaproxiral related. Events of hypoxemia were not unexpected because it is a direct effect of the pharmacology of the drug (decreased oxygen-hemoglobin affinity and decreased oxygen uptake in the lungs). Significantly, no grade 4 events of hypoxemia were reported, and all events of hypoxemia were effectively managed with supplemental oxygen.

Although surgery and SRS have proven beneficial for some patients with brain metastases, the majority of patients are not ideal candidates for either option based on tumor location, number of intracranial lesions, and extent of extracranial disease. Efaproxiral in combination with WBRT presents a potential treatment option for these patients. Despite the disadvantage of a central intravenous administration, efaproxiral enhances the diffusion of oxygen across the blood-brain barrier and maintains the ability to

Table 7. Most Commonly* Reported Grade 3 or 4 Treatment-Emergent Adverse Events Regardless of Causality

Adverse Event†	Control (n = 263)		Efaproxiral (n = 266)	
	No. of Patients	%	No. of Patients	%
Hypoxemia	3	1	29	11
Headache	9	3	16	6
Vomiting	6	2	12	5
Nausea	4	2	9	3
Constipation	5	2	8	3

*Three percent or more of efaproxiral arm.

†Excludes disease progression.

treat multiple lesions independent of tumor location. It is also well tolerated. Furthermore, it should be feasible to combine efaproxiral with SRS.

In conclusion, efaproxiral is the first noncytotoxic radiation sensitizer that demonstrates a potential survival advantage as an adjunct to WBRT; however, the conclusion may be restricted to patients with primary breast cancer. Efaproxiral is generally safe

when administered to heavily pretreated cancer patients as an adjunct to WBRT. The main AE was primarily reversible hypoxemia. On the basis of the study results, a confirmatory trial of WBRT with or without efaproxiral (the Enhancing Whole Brain Radiation in Patients With Breast Cancer and Hypoxic Brain Metastases [ENRICH] trial) has been initiated in patients with brain metastases from breast cancer.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

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