The Role of Early Magnetic Resonance Imaging in Predicting Survival on Bevacizumab for Recurrent Glioblastoma: Results From a Prospective Clinical Trial (CABARET)

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BACKGROUND: Bevacizumab has been associated with prolonged progression-free survival for patients with recurrent glioblastoma; however, not all derive a benefit. An early indicator of efficacy or futility may allow early discontinuation for nonresponders. This study prospectively assessed the role of early magnetic resonance imaging (eMRI) and its correlation with subsequent routine magnetic resonance imaging (MRI) results and survival. METHODS: Patients were part of a randomized phase 2 clinical trial (CABARET) comparing bevacizumab with bevacizumab plus carboplatin for recurrent glioblastoma. eMRI was conducted after 4 weeks in the trial (after 2 treatments with bevacizumab [10 mg/kg every 2 weeks]). The results were compared with the results of the subsequent 8-week MRI standard. RESULTS: For 119 of 122 patients, eMRI was available, and 111 had subsequent MRI for comparison. Thirty-six (30%) had an early radiological response, and 17 (14%) had progressive disease. The concordance between eMRI and 8-week MRI was moderate (κ = 0.56), with most providing the same result (n = 79 [71%]). There was strong evidence that progression-free survival and overall survival were predicted by the eMRI response (both P values < .001). The median survival was 8.6 months for an eMRI response, 6.6 months for stable disease, and 3.7 months for progressive disease; the hazard ratio (progressive disease vs stable disease) was 3.4 (95% confidence interval, 1.9-6.0). Landmark analyses showed that eMRI progression was a strong predictor of mortality independent of other potential baseline predictors. CONCLUSIONS: In this study, early progression on MRI appears to be a robust marker of a poor prognosis for patients on bevacizumab. Cancer 2017;000:000-000. © 2017 American Cancer Society.

KEYWORDS: bevacizumab, clinical trial, glioblastoma, magnetic resonance imaging (MRI), prognosis, radiology.

INTRODUCTION
Glioblastoma is an aggressive malignant central nervous system cancer. Management options for recurrent disease, which have been limited, are now changing with the advent of targeted therapies. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), is now a common option for recurrent disease in some countries. VEGF causes peritumoral angiogenesis with an abnormal vascular network, which is hyperpermeable and results in peritumoral edema. VEGF inhibition can result in the rapid normalization of glioma-associated blood vessels, a reduction in vascular permeability, and an improvement in patients’ symptoms.
Whether early radiological changes associated with bevacizumab use truly reflect a disease response remains debated in the literature because, on the whole, improvements in progression-free survival (PFS) have not translated into overall survival (OS) in most de novo and recurrent glioblastoma clinical trials involving bevacizumab.\textsuperscript{2-4} Targeted therapies in cancer medicine are not without significant cost and potentially serious toxicities. Bevacizumab is expensive, is not readily available in some countries because of its cost and/or uncertainty about the benefit of PFS without a corresponding OS benefit, and may be associated with rare but potentially serious toxicities.\textsuperscript{5,6}

It would be ideal if an early indicator of bevacizumab efficacy or futility in an individual patient could help guide management. If such an indicator reliably predicted a response or progression, prolonged and expensive use of the drug, with ongoing exposure to the risk of toxicity, could potentially be avoided for those individuals for whom it is unlikely to result in a durable benefit. In addition, an early switch to an alternative form of therapy might be appropriate, especially because of the increasing availability of clinical trials of other therapies for this patient population.

Our prospective study aimed to determine whether early magnetic resonance imaging (eMRI; ie, after 4 weeks or 2 bevacizumab treatments) was a reliable predictor of prognosis during bevacizumab treatment, with usual-care 8-week magnetic resonance imaging (MRI) used as the reference. We also documented whether changes on eMRI were associated with differential survival outcomes and/or changes in the clinical status or steroid dose. We used scans and data from patients enrolled in the CABARET trial, a randomized phase 2 study comparing bevacizumab monotherapy with bevacizumab plus carboplatin. Examining the role of eMRI was a preplanned exploratory endpoint for this trial.

**MATERIALS AND METHODS**

**Study Population**
The CABARET trial included 122 adult patients with recurrent glioblastoma from 18 Australian sites who had previously received both radiotherapy and temozolomide but no other chemotherapy for glioblastoma. Details of the inclusion and exclusion criteria have been published.\textsuperscript{7} All patients received bevacizumab (10 mg/kg intravenously every 2 weeks); those randomized to doublet therapy also received carboplatin (area under the curve 5 every 4 weeks). Treatment was continued until disease progression or the withdrawal of treatment for other reasons (eg, toxicity). The Response Assessment in Neuro-Oncology (RANO) criteria, including the clinical status and steroid dose, were used for disease assessment for the trial’s primary endpoint: PFS as determined by central radiological review.\textsuperscript{8} There was no evidence of differences in survival outcomes between the 2 randomized treatment arms, so they were combined for this analysis.

**eMRI and Protocol**
In addition to standard MRI at the baseline and every 8 weeks, each participant also underwent eMRI at approximately 4 weeks as part of a prospectively designed exploratory endpoint to determine the role of eMRI in disease assessment. The results from eMRI were compared with the baseline MRI results, but they were not used in determining the overall disease response or progression and were not acted upon by treating sites with the exception of any potential safety concerns (eg, central nervous system hemorrhage). Both the eMRI results and the 8-week MRI results for this substudy were based on the trial’s central radiology review, which was not conducted in real time and did not take eMRI into consideration when it was determining the disease response on subsequent MRI. An individual trial participant’s series of scans was reviewed and reported by the same central radiologist. eMRI, as an exploratory substudy, was reviewed by the central radiologists only after the trial’s primary endpoint (a PFS date based on standard-timing imaging or the cessation of treatment for any other reason) had been established for that patient. Radiologists were blinded to the study treatment, steroid dosing, and clinical and neurological findings, and these were not included in this substudy comparison, which compares only radiographic findings without the clinical/steroid dosing component of the RANO criteria.

Each site was asked to conduct MRI in accordance with the acquisition protocol provided for the trial to ensure that, whenever possible, the quality of MRI was standardized. The scan series included precontrast and postcontrast T1-weighted imaging (volumetric acquisition) and T2/fluid-attenuated inversion recovery (FLAIR) sequences (maximum slice thickness of 5 mm with no interslice gap).

**Data Analysis and Statistical Methods**
Radiological findings from eMRI were compared with the findings of 8-week MRI, the first standard scan on the trial, to determine the level of correlation between the two. This comparison did not include the clinical status or steroid dosing, as described in the RANO criteria, but rather was based on T1 and T2/FLAIR changes alone. A $\kappa$ statistic was calculated to determine the concordance between results from eMRI and results from 8-week MRI.
A preplanned exploratory objective of the trial was to correlate the eMRI response at 4 weeks with PFS and OS. PFS and OS dates were calculated from the date of eMRI, and they were described with the Kaplan-Meier method and compared with proportional hazards regression models. In additional landmark analyses,9 OS was modeled from eMRI as a function of baseline risk factors (including the age, Eastern Cooperative Oncology Group performance status, number of relapses, and extent of initial surgery) and eMRI findings (progression or no progression).

When eMRI showed progression, the type of radiological progression (a T1 contrast-enhancing measurable lesion, a nonmeasurable lesion, a T2/FLAIR increase, or a new lesion) was documented, and OS for patients with contrast-enhancing (T1C+) progression versus T2/FLAIR progression was calculated.

Using a chi-square test, we also compared the clinical status (improved, stable, or deteriorated) and steroid dose (none, reduced, stable, or increased), as formally documented by sites at the week 4 visit (both components of the RANO criteria), for patients with a response, stable disease, or progressive disease at the time of eMRI.

As part of the CABARET trial, an experimental grading scale for T2/FLAIR changes was developed by the neuroradiologists who participated in the central radiology review and was applied at the time of the central review (modified RANO criteria).7 This classified T2/FLAIR changes into 5 categories (Supporting Table 1 [see online supporting information]). As an exploratory approach for determining the potential utility of this grading system, PFS and OS were calculated for patients categorized by the amount/grade of the T2/FLAIR change on eMRI. We also compared patients with T1C+ progression versus T2/FLAIR progression at week 4.

RESULTS
In total, 122 patients were randomized, and 120 underwent at least 1 treatment. Data for eMRI were available for 119 of these patients: 2 patients who withdrew consent after randomization but before treatment and 1 who did not undergo eMRI were excluded. One hundred eleven of the 119 patients underwent both 4-week MRI and 8-week MRI; the remainder had no MRI after week 4 because of the cessation of treatment for clinical progression, for toxicities, or by choice.

Concordance
The concordance between eMRI and 8-week MRI results for the 111 patients is shown in Table 1. The κ statistic indicated moderate concordance (κ = 0.56). For 71% (n = 79), eMRI and 8-week MRI resulted in the same disease status finding. The disease status on eMRI was the same or better than the status on 8-week MRI for 99 patients (89%), and this is relevant to the decision to cease futile treatment. For 16 of the 17 patients with progressive disease at week 4, radiological progression or death occurred a median of 27.5 days later (range, 0-61 days). The 1 remaining patient was recorded to have a decreased tumor volume but also a new lesion, which resulted in the attribution of progressive disease on eMRI, and then subsequently had a partial response at 8 weeks with a continued decrease in the tumor volume and no new lesion documented at this time point. No subsequent MRI was conducted for this patient, who had treatment 3 days after the 8-week MRI but no subsequent therapy, chose to leave the trial 6 weeks after the 8-week scan, and died 1 week later.

PFS and OS
There was strong evidence of differences in PFS and OS according to the eMRI status (Table 2). Patients with progressive disease on eMRI had shorter survival than patients with either stable disease or a response. Figure 1 shows the OS for all 3 groups. The hazard ratio, if disease progression was seen on eMRI, with respect to stable disease was 3.35 (95% confidence interval, 1.88-5.95).
Proportional hazards regression models were fitted to the time from eMRI to death from any cause to assess whether the eMRI result had any prognostic value beyond baseline risk factors (Table 3). For both univariate and multivariate models, patient age and progression on eMRI were the only predictors for which there was evidence of an association with OS. Of these, eMRI progression was the strongest predictor of mortality, and it was independent of other potential predictors (multivariate model hazard ratio, 3.85; 95% confidence interval, 2.2-6.9; \(< .001\)).

### Clinical Status and Steroid Dose

The clinical status, determined and formally documented by the site at the week 4 visit, was compared for patients with an eMRI response, stable disease, and progressive disease. Most patients (\(n = 88\) [74%]) had a stable clinical status at this time, and there was no association between the eMRI result and the clinical status \((P = .30)\). At week 4, 65 patients (55%) had a stable steroid dosage or were not receiving steroids at the baseline and week 4; 45 (38%) were on a decreased dosage or had ceased steroids after the baseline. Only 9 patients (8%) had increased their steroid dosage. There was no association between eMRI results and steroid use \((P = .89)\).

### T2/FLAIR Changes

OS was shorter for patients with any increase in T2/FLAIR signal abnormality on eMRI \((n = 5)\) versus any decrease \((n = 49)\); however, statistical inference is limited by the small sample size. Table 4 shows a comparison of OS based on T2/FLAIR grading, and Figure 2 shows Kaplan-Meier curves comparing T2/FLAIR decrease, stability, and increase. When the T2/FLAIR signal change

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**TABLE 2.** Progression-Free Survival and Overall Survival Based on the 4-Week MRI Response and Calculated From the Date of 4-Week MRI \((n = 105)\)

<table>
<thead>
<tr>
<th>Week 4 MRI Result</th>
<th>No.</th>
<th>Survival, Median (95% CI), mo</th>
<th>HR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete or partial response(^a)</td>
<td>33</td>
<td>2.8 (2.6-4.6)</td>
<td>0.99 (0.63-1.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stable disease</td>
<td>56</td>
<td>2.7 (2.5-2.8)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16</td>
<td>0.9 (0.7-1.0)</td>
<td>8.39 (4.21-17)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete or partial response(^a)</td>
<td>36</td>
<td>8.6 (6.1-10.0)</td>
<td>0.81 (0.54-1.22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stable disease</td>
<td>66</td>
<td>6.6 (4.6-7.4)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>17</td>
<td>3.7 (2.2-4.7)</td>
<td>3.35 (1.89-5.95)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging.

Fourteen patients whose disease had progressed, as measured by clinical deterioration at the week 4 visit, were excluded. Only 1 of these 14 patients had radiological progressive disease at this time point.

\(^a\)Reported on this scan only and not necessarily confirmed on subsequent imaging.

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**TABLE 3.** Univariate and Multivariate Proportional Hazards Regression Models Assessing the Prognostic Value of eMRI Beyond Baseline Risk Factors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Value</th>
<th>HR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td>2 vs 0 or 1</td>
<td>1.26 (0.84-1.88)</td>
<td>.27</td>
</tr>
<tr>
<td>Initial glioblastoma surgery</td>
<td>Resection vs biopsy or debulking</td>
<td>0.98 (0.67-1.42)</td>
<td>.89</td>
</tr>
<tr>
<td>Age</td>
<td>(\geq 65) vs (&lt; 65) y</td>
<td>1.56 (1.00-2.44)</td>
<td>.06</td>
</tr>
<tr>
<td>Relapse</td>
<td>1 vs (&gt;2) or unknown</td>
<td>1.14 (0.77-1.68)</td>
<td>.50</td>
</tr>
<tr>
<td>eMRI Progression</td>
<td>vs not</td>
<td>3.61 (2.06-6.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Multivariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td>2 vs 0 or 1</td>
<td>1.32 (0.88-1.99)</td>
<td>.18</td>
</tr>
<tr>
<td>Initial glioblastoma surgery</td>
<td>Resection vs biopsy or debulking</td>
<td>0.93 (0.63-1.39)</td>
<td>.73</td>
</tr>
<tr>
<td>Age</td>
<td>(\geq 65) vs (&lt; 65) y</td>
<td>1.63 (1.02-2.63)</td>
<td>.04</td>
</tr>
<tr>
<td>Relapse</td>
<td>1 vs (&gt;2) or unknown</td>
<td>1.09 (0.73-1.62)</td>
<td>.69</td>
</tr>
<tr>
<td>eMRI</td>
<td>Progression vs not</td>
<td>3.85 (2.16-6.88)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; eMRI, early magnetic resonance imaging; HR, hazard ratio.

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**Figure 1.** Kaplan-Meier curves for overall survival comparing a complete or partial response (red), stable disease (green), and progressive disease (black) on 4-week magnetic resonance imaging. eMRI indicates early magnetic resonance imaging.

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**Figure 2.** Kaplan-Meier curves for overall survival comparing a complete or partial response (red), stable disease (green), and progressive disease (black) on 4-week magnetic resonance imaging. eMRI indicates early magnetic resonance imaging.
was assessed, regardless of any other radiological findings, the degree of the T2/FLAIR change, as documented with the 5-point modified RANO scale (Supporting Tables 1 and 2 [see online supporting information]), did not provide any additional information regarding OS beyond that obtained by the classification of T2/FLAIR changes as decreased, stable, or increased (the current RANO criteria classification).

Of the 17 patients who had eMRI disease progression, 6 had T1/contrast-enhancing progression alone, and 2 had a T2/FLAIR increase alone. OS differed according to the type of progression at week 4, although the small sample size limits formal statistical comparison. The median OS was 3.7 months for those with T1 progression and 1.8 months for those with T2/FLAIR progression (hazard ratio, 3.41; 95% confidence interval, 0.58-19.9).

**DISCUSSION**

This prospective study is one of the first in the setting of glioblastoma to show that eMRI during bevacizumab therapy may predict OS. The multivariate model showed disease progression on eMRI to be a strong predictor of mortality, even when it was adjusted for baseline risk factors. Knowing a patient’s likely prognosis during the early stages of a treatment is useful, especially because of the potential costs of therapy (both financial costs and toxicity risks) and because additional therapies, including clinical trial therapy, may be available to patients. Ceasing a treatment that is likely to be futile before the performance status deteriorates could facilitate easier access to alternative treatment options.

There is scant literature regarding the value of eMRI in this context. Kreisl et al, in their single-arm phase 2 trial of bevacizumab for recurrent glioblastoma, compared a 4-week partial response on MRI with stable disease (according to the MacDonald and Levin criteria), and reported that an early partial response was associated with improved PFS, although early disease progression was not evaluated. A retrospective study of eMRI as a prognostic marker for patients from the Radiation Therapy Oncology Group 0625 clinical trial of bevacizumab with irinotecan or temozolomide found that early progression shown by T1 (but not FLAIR) on 8- and 16-week scans was prognostic for OS. However, with respect to timing, 8-week MRI is more conventional for tumor assessment than our 4-week MRI. Huang et al in 2013 published a retrospective study of 91 patients with recurrent glioblastoma who were receiving bevacizumab. They analyzed the value of early posttreatment imaging (at approximately 30 days, which was similar to our MRI time frame), and reported that a posttreatment enhancing tumor volume and FLAIR volume were associated with both PFS and OS, although the FLAIR change did not remain statistically significant in a multivariate analysis. They concluded that eMRI volumetric analysis could identify patients who were more likely to benefit from bevacizumab therapy. Our study seems to support this, although we have not reported formal volumetric measurements, which may be a more sensitive tool and may potentially have identified even more patients with early progressive disease at the 4-week time point.

### TABLE 4. Overall Survival From Week 4 by T2/FLAIR at Week 4

<table>
<thead>
<tr>
<th>Week 4 T2/FLAIR</th>
<th>Overall Survival From Week 4 MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survival, Median (95% CI), mo</td>
</tr>
<tr>
<td>Any decrease (n = 49)</td>
<td>6.7 (4.7-8.1)</td>
</tr>
<tr>
<td>Stable (n = 62)</td>
<td>5.7 (4.3-7.1)</td>
</tr>
<tr>
<td>Any increase (n = 5)</td>
<td>2.3 (1.3-8.7)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FLAIR, fluid-attenuated inversion recovery; HR, hazard ratio; MRI, magnetic resonance imaging.

Three patients with unknown T2/FLAIR results for week 4 MRI were excluded.
Sorensen et al in 2009 described a vascular normalization index incorporating advanced MRI imaging that measured vascular permeability, microvessel volume, and circulating collagen IV levels after a single dose of cediranib, a pan-VEGF receptor tyrosine kinase inhibitor. This was able to predict the response to the drug. Several studies have found that early positron emission tomography imaging is more predictive than MRI of an early treatment response or progression in patients with recurrent glioblastoma on bevacizumab; however, 3-deoxy-3-[18F]fluorothymidine (FLT) positron emission tomography is not routine and currently has limited use outside clinical trials in this context in Australia.

The sample size of this study allows our ability to determine an association between early T2/FLAIR progression (alone or mixed with other change) and poorer outcomes. Other retrospective studies have resulted in conflicting findings related to whether T2/FLAIR tumor progression is adversely associated with survival. Although several have not found an association, a retrospective analysis of data from patients who participated in the recurrent glioblastoma AVF3708g clinical trial found that a T2/FLAIR assessment was significantly associated with differences in PFS and response rates. Our study has not incorporated advanced MRI techniques such as diffusion restriction, spectroscopy, and cerebral blood volume assessments; it is acknowledged that because of the conflicting studies on the prognostic significance of T2/FLAIR signal changes, advanced MRI may enlighten investigators and clinicians in this context.

We did not find an association between the steroid dose and the eMRI results. Nevertheless, almost 40% of the patients in the trial had decreased or ceased steroids after 4 weeks in the study. This highlights the important point that bevacizumab may be associated with a clinical benefit independent of radiographic findings. If bevacizumab is able to result in a reduction in steroid dose, this can be argued to be an example of a clinical benefit. Bevacizumab has been associated with reduced steroid requirements in multiple studies. This underpins the importance, when one is assessing any patient on treatment, of considering both the radiological findings and the clinical status when determining the potential benefit of therapy.

It is also interesting to note that the median PFS was similar when patients with an eMRI response and patients with stable disease were compared (Table 2). Although the exploratory nature of this analysis precludes robust statistical inference, the lack of a statistically significant association between response and PFS was also noted in a landmark analysis of scans for patients who participated in the BRAIN study, although the response was correlated with OS in their analysis. However, as previously noted, Kreisl et al did find an association between an eMRI response and PFS, although the RANO criteria were not used for this study. In the CABARET study, eMRI progression was the finding most strongly associated with survival outcomes, rather than an eMRI response.

There are several limitations to our study. Although 2-dimensional quantitation of abnormal enhancement was performed, formal volumetric assessments and advanced MRI sequences were not included. Seventeen patients showed progressive disease on eMRI, but only 5 had any T2/FLAIR increase at the 4-week mark, and only 2 had a solitary T2/FLAIR signal increase at this time; this means that robust statistical comparisons of survival for this group are not feasible. Furthermore, our findings apply to MRI after two 2-week bevacizumab treatments, and it is unclear how they would apply to bevacizumab given at a 3-week interval: whether 4 weeks would be an appropriate time point, or whether 2 treatment cycles are required. Nevertheless, strengths include the prospective study design, the uniformity of the centralized radiological assessment, and the fact that the majority of the patients who participated in the CABARET study had both 4- and 8-week scans available for assessment.

In summary, we found that early (4-week) MRI after the commencement of 2-week bevacizumab therapy correlated at least moderately with subsequent 8-week imaging. Compared with stable disease at 4 weeks, progressive disease was a significant prognostic marker for poorer survival, but a partial response at this time point was not a significant prognostic marker for better survival in this patient cohort.

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CONFLICT OF INTEREST DISCLOSURES
Anna K. Nowak reports research support from Roche Pharmaceuticals outside the submitted work.

AUTHOR CONTRIBUTIONS
Kathryn M. Field: Editing, revision, and approval of the final version of the manuscript; accountability for all aspects of the work; original trial conception and design; patient recruitment; trial
management; and interpretation of the results. **Pramit M. Phal**: Editing, revision, and approval of the final version of the manuscript; central radiological review of magnetic resonance imaging scans; and analysis and interpretation of the results. **Greg Fitz**: Editing, revision, and approval of the final version of the manuscript; central radiological review of magnetic resonance imaging scans; and analysis and interpretation of the results. **Christine Goh**: Editing, revision, and approval of the final version of the manuscript; central radiological review of magnetic resonance imaging scans; and analysis and interpretation of the results. **Anna K. Nowak**: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results. **Mark A. Rosenthal**: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results. **John Simes**: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results. **Elizabeth H. Barnes**: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results. **Kate Sawkins**: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results. **Lawrence M. Cher**: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results. **Elizabeth J. Hovey**: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results. **Helen Wheeler**: Editing, revision, and approval of the final version of the manuscript; original trial conception and design; patient recruitment; trial management; and interpretation of the results.

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