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# Epimacular Brachytherapy for Previously Treated Neovascular Age-Related Macular Degeneration (MERLOT)

## A Phase 3 Randomized Controlled Trial

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***Purpose:*** To assess the safety and efficacy of epimacular brachytherapy (EMB) for patients with chronic, active, neovascular age-related macular degeneration (AMD).

***Design:*** Phase 3 randomized controlled trial.

***Participants:*** Patients (n = 363) with neovascular AMD already receiving intravitreal ranibizumab injections.

***Intervention:*** Either pars plana vitrectomy with 24-gray EMB and ongoing pro re nata (PRN) ranibizumab (n = 224) or ongoing PRN ranibizumab monotherapy (n = 119).

***Main Outcome Measures:*** The coprimary outcomes, at 12 months, were the number of PRN ranibizumab injections and Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (VA). Secondary outcomes included the proportion of participants losing fewer than 15 ETDRS letters, angiographic total lesion size, choroidal neovascularization (CNV) size, and optical coherence tomography (OCT) foveal thickness. A predefined subgroup analysis tested the influence of baseline ocular characteristics on the response to EMB.

***Results:*** The mean number of PRN ranibizumab injections was 4.8 in the EMB arm and 4.1 in the ranibizumab monotherapy arm ($P = 0.068$). The mean VA change was −4.8 letters in the EMB arm and −0.9 letters in the ranibizumab arm (95% confidence interval of difference between groups, −6.6 to −1.8 letters). The proportion of participants losing fewer than 15 letters was 84% in the EMB arm and 92% in the ranibizumab arm ($P = 0.007$). In the EMB arm, the mean total lesion size increased by 1.2 $mm^2$ versus 0.4 $mm^2$ in the ranibizumab arm ($P = 0.27$). The CNV size decreased by 0.5 $mm^2$ in the EMB arm and by 1.3 $mm^2$ in the ranibizumab arm ($P = 0.27$). The OCT foveal thickness decreased by 1.0 μm in the EMB arm and by 15.7 μm in the ranibizumab arm ($P = 0.43$). Most subgroups favored ranibizumab monotherapy, some significantly so. One participant showed retinal vascular abnormality attributed to radiation, but otherwise safety was acceptable.

***Conclusions:*** These results do not support the use of EMB for chronic, active, neovascular AMD. Safety is acceptable out to 12 months, but radiation retinopathy can occur later, so further follow-up is planned. *Ophthalmology 2016;123:1287-1296 Crown Copyright © 2016 Published by Elsevier Inc. on behalf of American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

*Supplemental material is available at www.aaojournal.org.

Epimacular brachytherapy (EMB) uses radiation to treat neovascular age-related macular degeneration (AMD).[1] Radiation is known to preferentially damage the proliferating vascular endothelium and fibroblastic and inflammatory cells that cause tissue damage in neovascular AMD.[2–4] The EMB devices use a strontium 90 source housed in an endoscopic probe. Patients undergo a pars plana vitrectomy, and then the device is held over the AMD lesion for about 3 to 4 minutes to deliver 24 gray of β radiation. Because of the short range of strontium β particles in tissue, neighboring structures such as the optic nerve and lens receive a dose well below the safety threshold.[5] Therefore, EMB has the ability to deliver radiation directly to the AMD lesion, with stabilized eye position and with low off-target dosing.

The initial results with EMB were encouraging. An uncontrolled study of 34 treatment-naïve participants reported that 91% lost fewer than 15 Early Treatment of Diabetic Retinopathy (ETDRS) letters over 1 year, despite the fact that



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26 required no ongoing anti−vascular endothelial growth factor (VEGF) therapy after 2 mandated induction injections of bevacizumab.[1] No cases of radiation retinopathy were reported. As a result, the Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration Treated with Beta Radiation Epiretinal Therapy (CABERNET) study was established to test EMB in a phase 3 randomized controlled trial of treatment-naïve neovascular AMD.[6,7] The study failed to replicate the early results, missing both its primary visual acuity (VA) end points.[6]

However, the CABERNET study was not designed to test whether EMB reduced the demand for anti-VEGF therapy, or whether it was suitable as a second-line treatment. Specifically, those in the EMB arm received ranibizumab at baseline then monthly pro re nata (PRN), whereas those in the ranibizumab arm received 3 consecutive monthly injections from baseline, then quarterly mandated injections with PRN dosing in the intervening months. Thus, it was not possible to determine if EMB reduces the demand for anti-VEGF therapy; moreover, the increased dosing in the control arm may well have improved the VA in that group, given that increased dosing may be associated with better visual outcomes.[8] Therefore, it was unknown if EMB may be suitable as a second-line intervention when used as an adjunct to anti-VEGF therapy and if it reduces the demand for anti-VEGF therapy.

The Macular Epiretinal Brachytherapy in Treated Age-Related Macular Degeneration (MERITAGE) study was a multicenter phase 2 trial of 53 previously treated patients who underwent EMB. The trial suggested that EMB may reduce demand for anti-VEGF therapy with acceptable visual results out to 1 year.[9,10] However, because this study was not controlled, it was not possible to conclude whether EMB caused the apparent reduction in anti-VEGF therapy. We therefore initiated the phase 3 Macular Epiretinal Brachytherapy versus Ranibizumab (Lucentis) Only Treatment (MERLOT) trial, which was designed to investigate whether EMB was a safe and efficacious second-line treatment for chronic, active neovascular AMD. Specifically, we aimed to test the hypothesis that EMB reduces the ongoing need for anti-VEGF therapy in those who had already commenced intravitreal injections, while maintaining a noninferior visual outcome compared with anti-VEGF monotherapy.

## Methods

### Study Design

The MERLOT study was an investigator-initiated, multicenter, phase 3 randomized controlled trial sponsored by a United Kingdom university hospital. Multicenter research ethics committee approval was obtained to cover all 24 sites, all participants provided written informed consent, and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

### Participants

The study enrolled 363 participants with chronic, active neovascular AMD who were receiving ranibizumab therapy at the time of screening. Enrollment ran from November 10, 2009, through January 30, 2012. Inclusion criteria included completion of a loading phase of 3 anti-VEGF induction injections, followed by ongoing monthly PRN therapy, with a minimum of 4 ranibizumab treatments in the previous 12 months or 2 ranibizumab treatments in the previous 6 months. Exclusion criteria included VA worse than 24 letters (20/80), prior AMD treatment other than anti-VEGF injections, subfoveal scarring, known diabetes or features suggesting diabetic retinopathy, intraocular surgery within the prior 12 weeks, and previous radiation therapy to the eye, head, or neck (Appendix 2, available at www.aaojournal.org). If both eyes were eligible, the patient could elect which eye to treat, in discussion with the clinical investigator, who should address lens status, clinical response to ranibizumab, risk factors, VA, visual potential, and other relevant factors.

### Randomization and Masking

Participants were randomized in a 2:1 ratio to pars plana vitrectomy and 24-gray EMB with ongoing monthly PRN ranibizumab (n = 224) or to ongoing monthly PRN ranibizumab monotherapy (n = 119). Online electronic randomization was undertaken immediately after eligibility was confirmed by recruiting sites using a commercial system (MedSciNet, Stockholm, Sweden) and was stratified by lens status (phakic or pseudophakic) and angiographic lesion type (predominantly classic, minimally classic, or occult) as determined at the baseline visit. It was not feasible to mask surgery, but VA testing and macular imaging (which were the most commonly used criteria to necessitate ranibizumab retreatment) were undertaken by masked assessors.

### Study Treatment

Epimacular brachytherapy could involve either a 20-, 23-, or 25-gauge full pars plana vitrectomy, but the EMB probe (NeoVista, Freemont, CA) was 20 gauge, and therefore, if necessary, a smaller-gauge port was enlarged to insert the probe. The EMB device houses a strontium source in a shielded handpiece (Fig 1, available at www.aaojournal.org). One end of the handpiece is connected to a remote handheld actuator by a thin actuator cable. The other end of the handpiece has a steel, 20-gauge endoprobe that is inserted into the eye after vitrectomy. The probe is positioned over the area of greatest disease activity and the actuator is depressed, causing the strontium source to leave the handpiece and travel down the probe to near the tip. The probe then is held in position for the requisite time needed to deliver 24 gray (the exact time, which is calibrated for each probe, is typically within a range from 3 to 4 minutes).

Intravitreal 0.5 mg ranibizumab (Lucentis, Novartis, Frimley, UK) was administered to participants in both study groups using a monthly PRN dosing regimen if the attending clinical investigator determined that at least 1 of the following retreatment criteria was met: a loss of more than 5 ETDRS letters from baseline attributable to active neovascular AMD; an increase of more than 50 μm in optical coherence tomography (OCT) central retinal thickness from the lowest measurement secondary to new or increased subretinal fluid, intraretinal fluid, or subretinal pigment epithelial fluid; new or increased subretinal or intraretinal blood; and new neovascularization as confirmed by fluorescein angiography (FA).

### Study Examinations, Optical Coherence Tomography, and Fluorescein Angiography

Participants attended monthly visits with protocol refraction and testing of best-corrected VA (BCVA) using the ETDRS chart and methodology, ocular examination, and OCT. Three sites used time-domain OCT, 14 sites used spectral-domain OCT, and 7 sites used a mixture of both over the course of the study. Fundus photography