Supplementary Online Content

Jackson TL, Soare C, Petrarca C, et al; MERLOT Study Group. Evaluation of month-24 efficacy and safety of epimacular brachytherapy for previously treated neovascular age-related macular degeneration: the MERLOT randomized clinical trial. *JAMA Ophthalmol.* Published online July 9, 2020. doi:10.1001/jamaophthalmol.2020.2309

This supplementary material has been provided by the authors to give readers additional
information about their work.

eAppendix 1. Eligibility Criteria

Inclusion criteria:

1. Subjects with subfoveal choroidal neovascularization (CNV) associated with wet age- related macular degeneration (AMD). Retinal Angiomatous Proliferation lesions not directly involving the fovea must be associated with contiguous foveal leakage demonstrated on fundus examination, Optical Coherence Tomography (OCT), or fluorescein angiography.
2. Subjects must have received anti-VEGF induction treatment, defined as the first three months of anti-VEGF therapy. Following this induction period, subjects must have received at least 4 additional injections of Lucentis® in no more than 12 months preceding enrollment, or 2 additional injections of Lucentis® in no more than 6 months preceding enrollment, given on an as needed basis.
3. At the time subjects commenced anti-VEGF therapy for wet age-related macular degeneration they were aged 50 years or older and met the NICE treatment criteria for Lucentis® therapy, as outlined in the Final Appraisal Determination (FAD). This states that all of the following circumstances must apply in the eye to be treated:
   - the best-corrected visual acuity is between 6/12 and 6/96 (24 to 69 ETDRS letters).
   - there is no permanent structural damage to the central fovea.
   - the lesion size is less than or equal to 12 disc areas in greatest linear dimension.
   - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes).

Exclusion criteria:

1. Patients who have not been treated in accordance with the National Institute for Health and Care Excellence (NICE) guidance.
2. Visual acuity worse than 6/96 (24 ETDRS letters) at the time of study enrollment.
3. Subjects with prior or concurrent subfoveal CNV therapy with

agents, surgery or devices (other than Macugen®, Avastin®, or Lucentis®) including thermal laser photocoagulation (with or without photographic evidence), photodynamic therapy, intravitreal or subretinal steroids, and transpupillary thermotherapy.

4. Subfoveal scarring.
5. Subjects with active concomitant disease in the study eye, including uveitis, presence of pigment epithelial tears or rips, acute ocular or periocular infection.
6. Subjects who have been previously diagnosed with Type 1 or Type 2 Diabetes Mellitus. Subjects who do not have a documented diagnosis, but have retinal findings consistent with Type 1 or Type 2 Diabetes Mellitus.
7. Subjects with advanced glaucoma (greater than 0.8 cup:disc or intraocular pressure ≥ 30 mmHg in the study eye.
8. Previous glaucoma filtering surgery in the study eye.
9. Subjects with inadequate pupillary dilation or significant media opacities in the study eye, including cataract, which may interfere with visual acuity or the evaluation of the posterior segment.
10. Current vitreous hemorrhage in the study eye.
11. History of rhegmatogenous retinal detachment or macular hole in the study eye.
12. Subjects who present with CNV due to causes other than AMD, including subjects with known or suspected idiopathic polypoidal choroidal vasculopathy, ocular histoplasmosis syndrome, angioid streaks, multifocal choroiditis, choroidal rupture, or pathologic myopia (spherical equivalent ≥ 8 Dioptre or axial length ≥25mm).
13. Subjects who have undergone any intraocular surgery in the study eye within 12 weeks prior to the screening visit, with the exception of cataract surgery as discussed in the Exclusion Criteria #14.
14. Previous cataract surgery within 2 months prior to enrollment into the study.
15. Subjects with known serious allergies to fluorescein dye used in angiography.
16. Subjects with known sensitivity or allergy to Lucentis®.
17. Subjects who underwent previous radiation therapy to the eye, head or neck.
18. Subjects with an intravitreal device or drug in the study eye.

19. Subjects with any other condition, which in the judgment of the investigator would prevent the subject from completing the study (e.g. documented diagnosis of dementia or serious mental illness).
20. Current participation in another drug or device clinical trial, or participation in such a clinical trial within the last year.
21. History of use of drugs with known retinal toxicity, including: chloroquine (Aralen – an anti-malarial drug), hydroxychloriquine (Plaquenil), phenothiazines, chlorpromazine (Thorazine), thioridazine (Mellaril), fluphenazine (Prolixin), perphenazine (Trilafon), and trifluoperazine (Stelazine).
22. Subjects who are unwilling or unable to return for scheduled treatment and follow- up examinations for three years.
23. Women must be post-menopausal 1 year unless surgically sterilized.

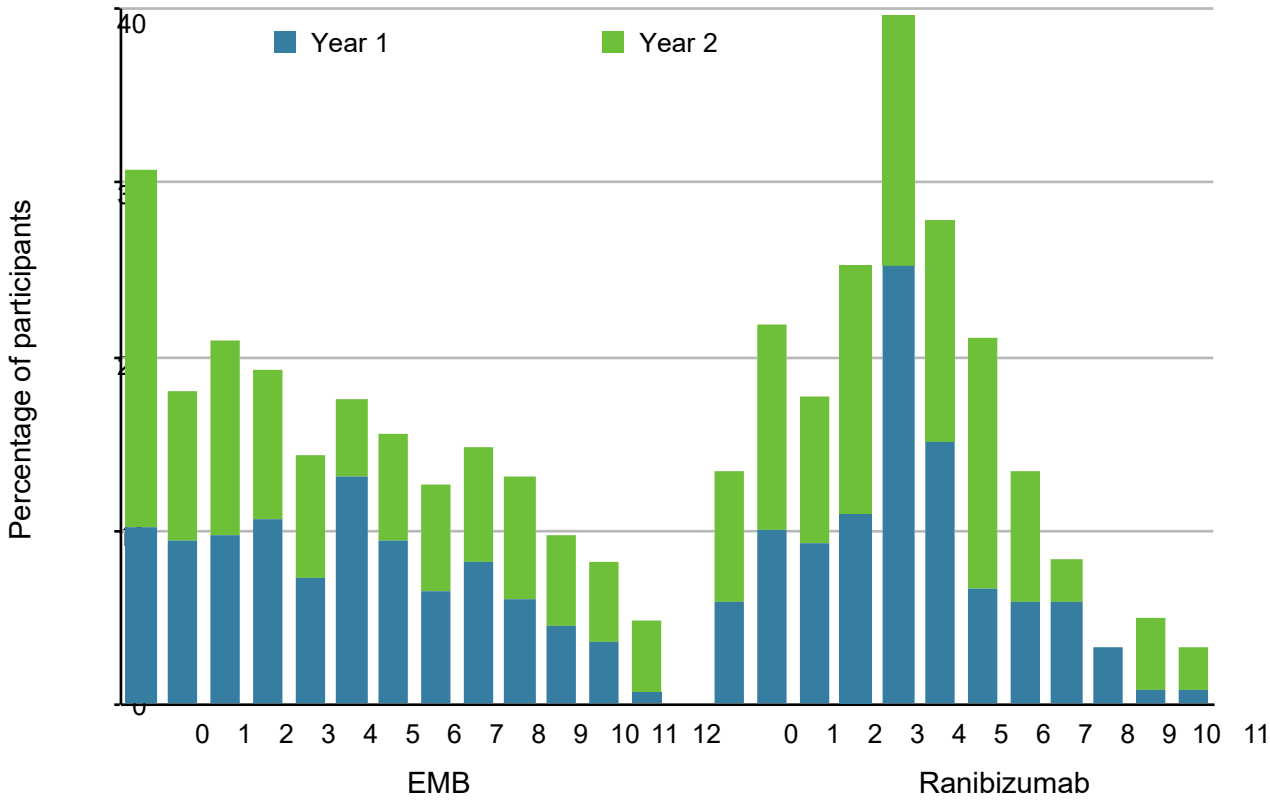
If more than one eye is eligible the patient may choose which eye they wish to have allocated as the study eye. The clinician should discuss all relevant clinical issues to help the patient make an informed decision. This discussion might consider issues such as the lens status, clinical response to ranibizumab, risk factors, visual acuity and visual potential.

eAppendix 2. Ranibizumab Retreatment Criteria

An intravitreal ranibizumab injection should be administered if at least one of the following retreatment criteria are met:

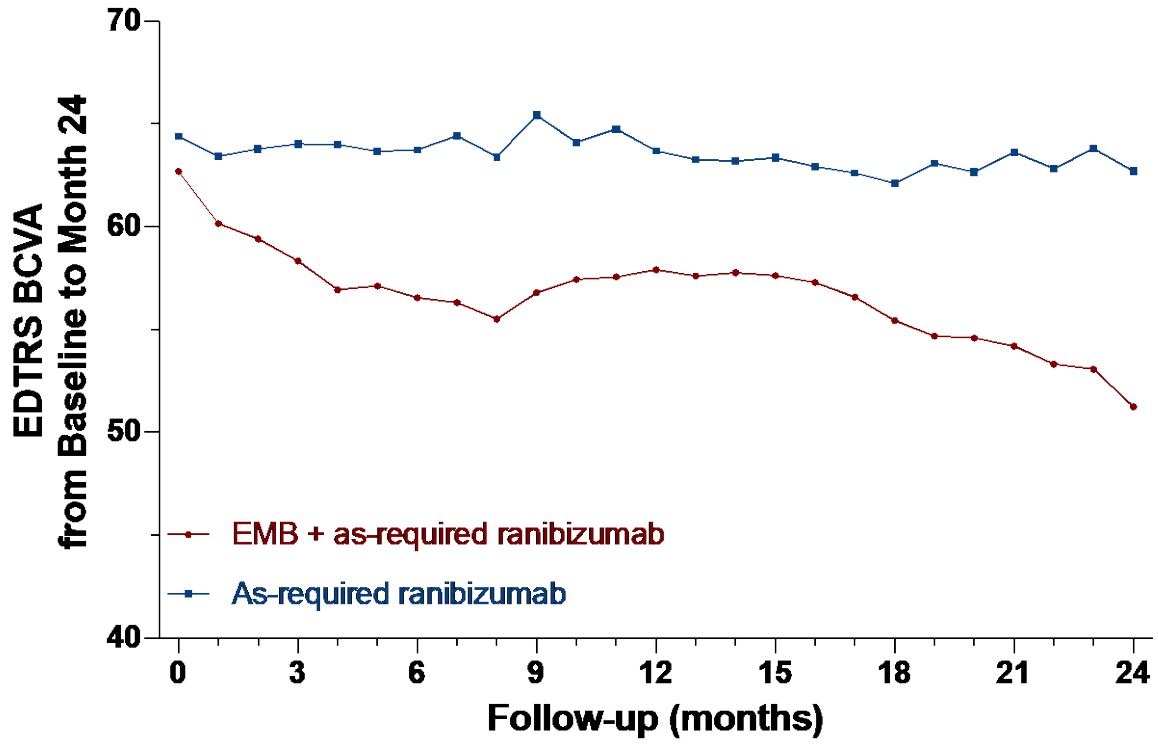
- A loss of > 5 ETDRS letters from baseline attributable to active wet age-related macular degeneration
- An increase of > 50 μm in optical coherence tomography central retinal thickness from the lowest measurement secondary to new or increased subretinal, intraretinal, or sub-retinal pigment epithelial fluid
- New or increased subretinal or intraretinal blood
- New neovascularization as confirmed by fluorescein angiography.

eFigure 1. The Percentage of Participants by Number of Ranibizumab Injections From Month 1 to Month 24



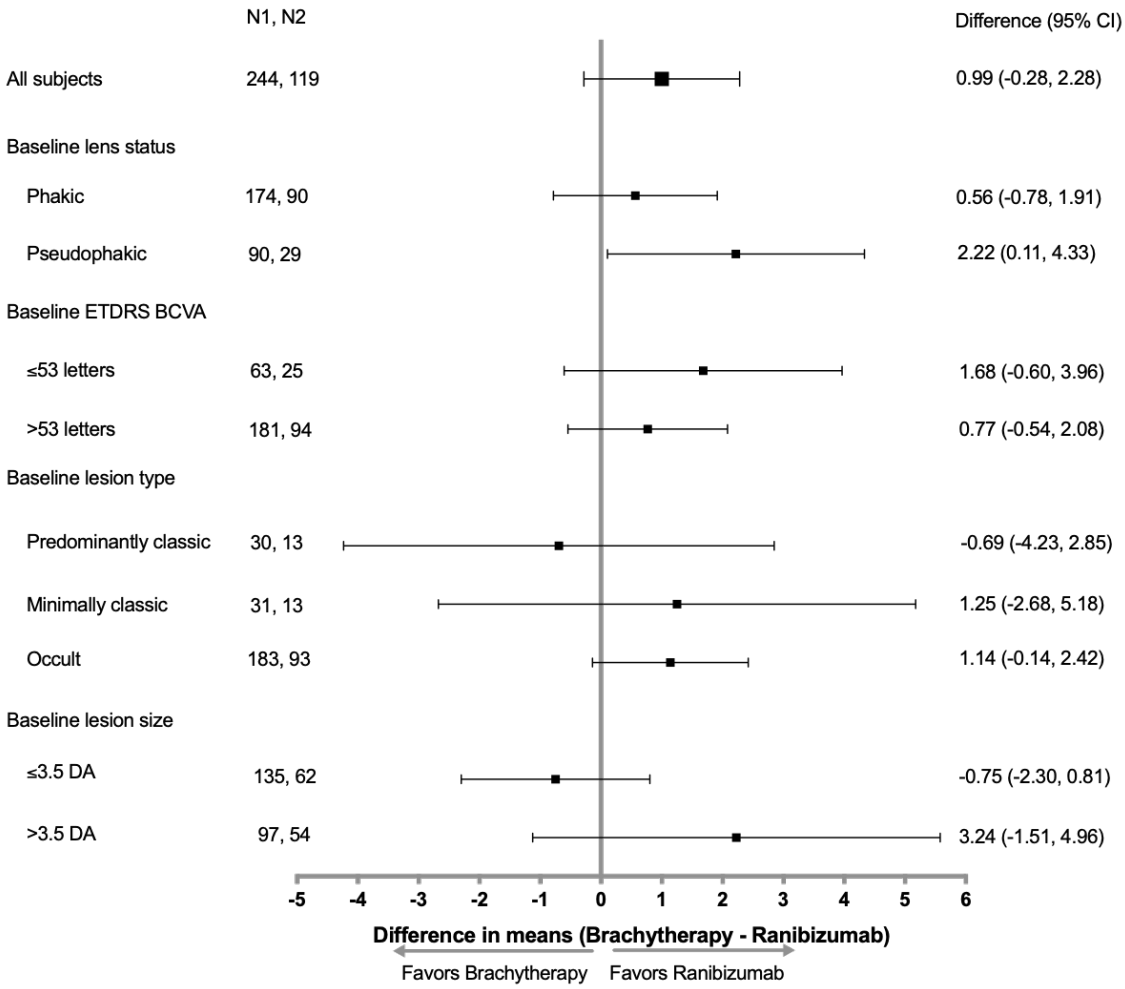
The number of ranibizumab injections is represented separately for year 1 and year 2 in both the epimacular brachytherapy (EMB) and ranibizumab monotherapy group. The ranibizumab injection given at baseline for pre-existing disease activity was excluded.

eFigure 2. The Mean Change in Best-Corrected Visual Acuity Over Time From
Baseline to Month 24 in the Epimacular Brachytherapy (EMB) and Ranibizumab Monotherapy Groups



Abbreviations: ETDRS = Early Treatment of Diabetic Retinopathy Study

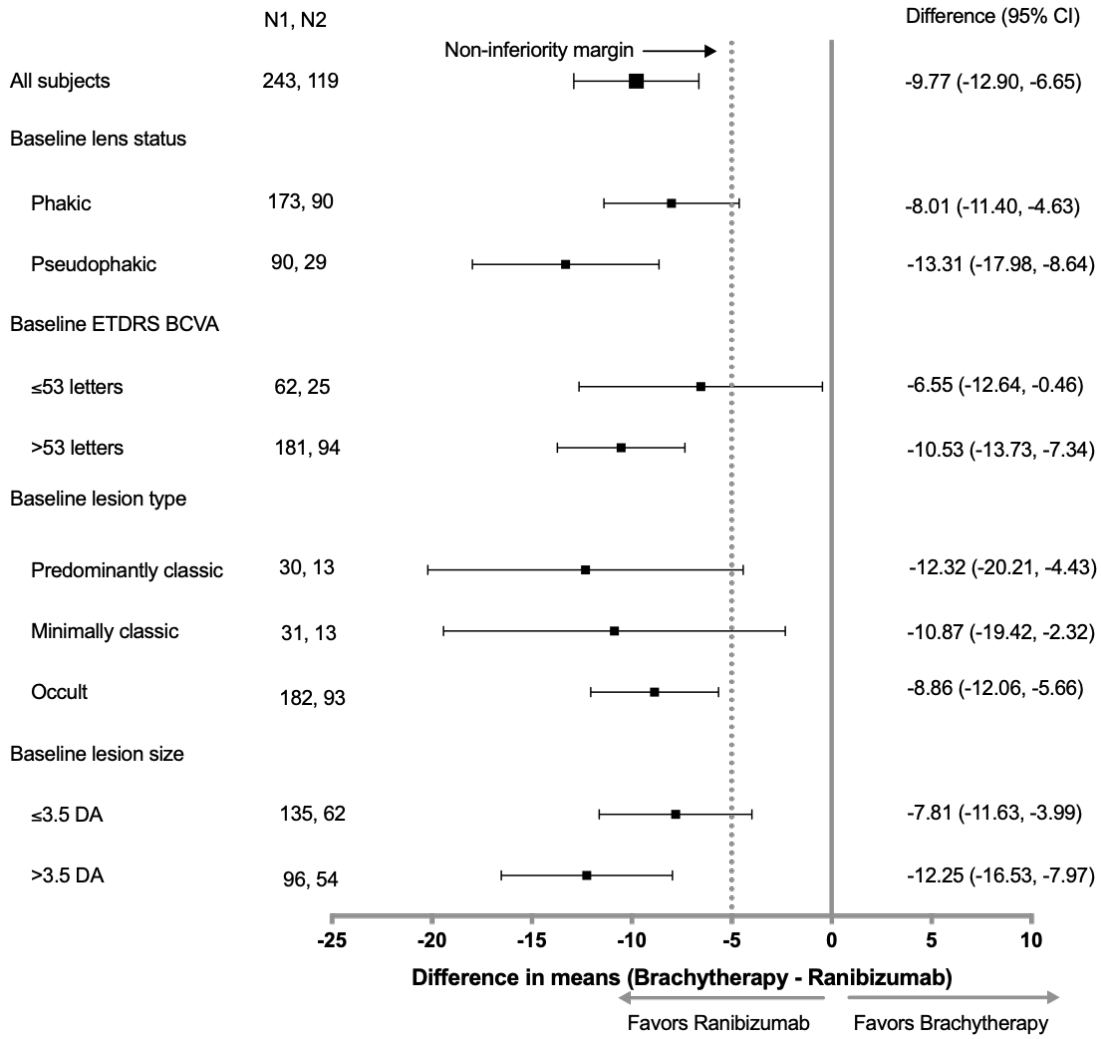
eFigure 3. Subgroup Analysis of the Number of As-Required Ranibizumab Injections From Month 1 to Month 24 Inclusive, Comparing the Epimacular Brachytherapy Group to the Ranibizumab Monotherapy Group



For each subgroup N1 represents the number of participants in the epimacular brachytherapy group, and N2 the number in the ranibizumab monotherapy group. The “All participants” difference and 95% confidence interval are derived from an analysis of covariance (ANCOVA) model of the number of ranibizumab injections, adjusted for baseline lens status and lesion type. Differences and 95% confidence intervals within subgroups are from t-tests comparing the treatment group means. With the exception of predominantly classic lesions and small lesions, all other subgroups favored the ranibizumab monotherapy group. The sub-group analyses were not corrected for multiplicity.

Abbreviations: BCVA = Best-Corrected Visual Acuity; DA = Disc Areas; ETDRS = Early Treatment of Diabetic Retinopathy Study; CI = Confidence Interval

eFigure 4. Subgroup Analysis of the Change in Best-Corrected Visual Acuity From
Baseline to Month 24 Comparing the Epimacular Brachytherapy Group to the Ranibizumab Monotherapy Group



For each subgroup N1 represents the number of participants in the epimacular brachytherapy group, and N2 the number in the ranibizumab monotherapy group. The “All participants” difference and 95% confidence interval are derived from an analysis of covariance (ANCOVA) model of the number of ranibizumab injections, adjusted for baseline lens status, lesion type and baseline best-corrected visual acuity (BCVA). Differences and 95% confidence intervals within subgroups are from t-tests comparing the treatment group means. For all subgroups the VA was inferior in the EMB group compared with ranibizumab only group. The sub-group analyses were not corrected for multiplicity.

Abbreviations: DA = Disc Areas; ETDRS = Early Treatment of Diabetic Retinopathy Study; CI = Confidence Interval

eTable 1. Baseline Ocular Characteristics

	Epimacular brachytherapy *N=244*	Ranibizumab monotherapy *N=119*	Total *N=363*
Baseline ETDRS letters			
n	244	119	363
Mean (SD)	62.7 (13.7)	64.4 (12.9)	63.3 (13.5)
Range (min, max)	13, 86	34, 88	13, 88
Quartiles (25th, median, 75th)	53, 66, 73	56, 67, 74	54, 66, 73
Baseline lens status, n (%)			
Phakic	174 (71)	90 (76)	264 (73)
Pseudophakic	70 (29)	29 (24)	99 (27)
Baseline lesion type, n (%)			
Occult with no classic	180 (74)	91 (76)	271 (75)
Minimally classic	31 (13)	13 (11)	44 (12)
Predominantly classic	30 (12)	13 (11)	43 (12)
RAP	2 (1)	2 (2)	4 (1)
Baseline total lesion size (mm^2)			
n	232	116	348
Mean (SD)	9.4 (7.6)	9.7 (7.0)	9.5 (7.4)
Range (min, max)	0.5, 45	0.5, 43	0.5, 45
Quartiles (25th, median, 75th)	4, 8, 13	4, 8, 14	4, 8, 13
Baseline total lesion size category, n (%)			
n	232	116	348
≤ 3.5 DA	135 (58)	62 (53)	197 (57)
> 3.5 DA	97 (42)	54 (47)	151 (43)
Baseline total CNV size (mm^2)			
n	232	116	348
Mean (SD)	6.1 (6.9)	6.1 (6.8)	6.1 (6.8)
Range (min, max)	0, 45	0, 43	0, 45
Quartiles (25th, median, 75th)	0, 5, 9	1, 4, 9	1, 4, 9
Baseline foveal thickness (μm)			
n	236	115	351
Mean (SD)	364 (145)	363 (145)	363 (145)
Range (min, max)	60, 937	119, 760	60, 937
Quartiles (25th, median, 75th)	255, 340, 441	252, 328, 446	254, 337, 441

	Epimacular brachytherapy *N=244*	Ranibizumab monotherapy *N=119*	Total *N=363*
Prior anti-VEGF injections			
n	244	119	363
Mean (SD)	11.7 (5.5)	10.6 (5.1)	11.4 (5.4)
Range (min, max)	5, 36	5, 30	5, 36
Quartiles (25th, median, 75th)	8, 10, 15	7, 9, 14	7, 10, 14

Abbreviations: ETDRS = Early Treatment of Diabetic Retinopathy Study; SD = Standard Deviation; RAP = Retinal Angiomatous Proliferation; DA = Disc Areas; CNV = Choroidal Neovascularization; VEGF = Vascular Endothelial Growth Factor

eTable 2. Study Eye Adverse Events

	Epimacular brachytherapy *N=244*		Ranibizumab monotherapy *N=119*	
	Events	**%**	**Events**	**%**
Anterior chamber cell	1	0.4		
Anterior chamber flare	3	1.2		
Asthenopia	1	0.4		
Blepharitis	5	2.0	4	3.4
Blindness transient			1	0.8
Cataract	158	64.8	24	20.2
Cataract nuclear	3	1.2		
Cataract operation	43	17.6	10	8.4
Charles Bonnet syndrome			1	0.8
Choroidal effusion	1	0.4		
Choroidal hemorrhage	2	0.8		
Choroidal neovascularization	1	0.4		
Conjunctival granuloma	1	0.4		
Conjunctival hemorrhage	18	7.4	3	2.5
Conjunctival hyperemia	2	0.8		
Conjunctival irritation			1	0.8
Conjunctivitis	9	3.7	1	0.8
Conjunctivitis allergic	1	0.4		
Corneal abrasion	6	2.5	1	0.8
Corneal erosion	1	0.4		
Corneal infection	1	0.4		
Corneal edema	2	0.8		
Cyst drainage	1	0.4		
Cystoid macular edema	3	1.2		
Dacryoadenitis acquired	1	0.4		
Detachment of retinal pigment epithelium	2	0.8	1	0.8
Device malfunction	1	0.4		
Diplopia	1	0.4		

Drug hypersensitivity	1	0.4		
Dry eye	3	1.2		
Episcleritis	1	0.4		
Eye contusion	3	1.2	1	0.8
Eye discharge	2	0.8		
Eye hemorrhage	1	0.4		
Eye infection	1	0.4		
Eye inflammation	5	2.0		
Eye irritation	5	2.0	1	0.8
Eye operation complication	6	2.5	1	0.8
Eye pain	21	8.6	5	4.2
Eye pruritus	2	0.8		
Eyelid ptosis	1	0.4		
Foreign body sensation in eyes	3	1.2	1	0.8
Glaucoma	2	0.8	1	0.8
Intraocular pressure increased	12	4.9	8	6.7
Iodine allergy			1	0.8
Iridocyclitis	2	0.8		
Iritis	1	0.4		
Lacrimation increased	5	2.0	1	0.8
Lenticular opacities	2	0.8		
Macular fibrosis	2	0.8		
Macular scar	1	0.4		
Meibomianitis	1	0.4		
Metamorphopsia			1	0.8
Neovascular age-related macular degeneration	1	0.4		
Ocular discomfort	5	2.0		
Ocular hyperemia	2	0.8	2	1.7
Open-angle glaucoma	2	0.8		
Ophthalmic herpes simplex	1	0.4		
Paracentesis eye	1	0.4	2	1.7

Photopsia	3	1.2	2	1.7
Polypoidal choroidal vasculopathy	1	0.4		
Posterior capsule opacification	3	1.2	3	2.5
Posterior capsule rupture	2	0.8		
Radiation retinopathy	1	0.4		
Retinal aneurysm	1	0.4		
Retinal artery embolism	1	0.4		
Retinal cyst	2	0.8		
Retinal degeneration	1	0.4		
Retinal exudates	1	0.4		
Retinal fibrosis	1	0.4		
Retinal hemorrhage	16	6.6	3	2.5
Retinal ischemia	1	0.4		
Retinal pigment epithelial tear	5	2.0	2	1.7
Retinal tear	19	7.8		
Retinal vein occlusion	2	0.8		
Retinoschisis	2	0.8		
Skin abrasion	1	0.4		
Subretinal fluid	2	0.8		
Suture related complication	1	0.4		
Ulcerative keratitis	1	0.4		
Uveitis	2	0.8		
Vision blurred	4	1.6		
Visual acuity reduced	30	12.3	6	5.0
Visual field defect			1	0.8
Visual impairment	4	1.6	1	0.8
Vitreous detachment			1	0.8
Vitreous floaters	4	1.6	2	1.7
Vitreous hemorrhage	3	1.2		
Vitreous opacities			1	0.8
Total	**477**		**94**	

eTable 3. Ocular Serious Adverse Events in Study Eye, and Relatedness to Treatment

Eye disorders	Events	%	Intensity	Epimacular brachytherapy	Vitrectomy	Ranibizumab monotherapy	Intravitreal injection
Epimacular brachytherapy ***N=244***							
Retinal detachment	4	1.6	Severe	Unlikely	Likely	Possibly	Possibly
			Moderate	Not Related	Likely	Not Related	Not Related
			Moderate	Not Related	Definitely	Not Related	Not Related
			Severe	Possibly	Possibly	Possibly	Possibly
Retinal hemorrhage	2	0.8	Severe	Unlikely	Unlikely	Unlikely	Unlikely
			Severe	Unlikely	Not Related	Not Related	Not Related
Retinal tear	1	0.4	Moderate	Not Related	Likely	Not Related	Not Related
Vision blurred	1	0.4	Severe	Possibly	Possibly	Possibly	Possibly
Blindness	1	0.4	Severe	Unlikely	Not Related	Not Related	Not Related
Corneal perforation	1	0.4	Severe	Not Related	Possibly	Not Related	Not Related
Endophthalmitis	1	0.4	Severe	Possibly	Possibly	Unlikely	Possibly
Hallucination, visual	1	0.4	Mild	Not Related	Likely	Not Related	Not Related
Hypopyon	1	0.4	Severe	Possibly	Likely	Unlikely	Unlikely
Uveitis	2	0.8	Severe	Possibly	Likely	Unlikely	Unlikely
			Severe	Not Related	Possibly	Not Related	Not Related
Visual acuity reduced	3	1.2	Severe	Possibly	Likely	Unlikely	Unlikely
			Severe	Possibly	Possibly	Unlikely	Possibly
			Severe	NA	NA	NA	NA
Vitreous floaters	1	0.4	Severe	Possibly	Possibly	Unlikely	Possibly
Ranibizumab monotherapy ***N=119***							
Blindness	1	0.8	Moderate	N/A	N/A	Unlikely	Unlikely
Retinal hemorrhage	1	0.8	Moderate	N/A	N/A	Unlikely	Unlikely
Visual field defect	1	0.8	Moderate	N/A	N/A	Unlikely	Unlikely

NA - not available, N/A - not applicable

The most serious adverse event (SAE) in the EMB group was one case of endophthalmitis related to cataract surgery which occurred in the first year, as previously reported.[13] Retinal detachment was the most frequent SAE in the study eye, occurring in four participants in the epimacular brachytherapy (EMB) group. Submacular hemorrhage requiring tissue plasminogen activator with or without vitrectomy occurred in two participants in the EMB group and one in the ranibizumab group.

eTable 4. Adverse Events, Excluding Those in the Study Eye

System Organ Class	Epimacular brachytherapy *N=244*		Ranibizumab monotherapy *N=119*	
	Events	%	Events	%
Cardiac disorders	15	6.1	1	0.8
Ear and labyrinth disorders	14	5.7	5	4.2
Endocrine disorders	4	1.6		
Eye disorders	91	37.3	30	25.2
Gastrointestinal disorders	55	22.5	31	26.1
General disorders and administration site conditions	28	11.5	13	10.9
Hepatobiliary disorders	2	0.8		
Immune system disorders	5	2.0		
Infections and infestations	168	68.9	75	63.0
Injury, poisoning and procedural complications	86	35.2	31	26.1
Investigations	22	9.0	13	10.9
Metabolism and nutrition disorders	41	16.8	34	28.6
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	4	1.6	2	1.7
Nervous system disorders	36	14.8	24	20.2
Product issues	1	0.4		
Psychiatric disorders	8	3.3	3	2.5
Renal and urinary disorders	11	4.5	2	1.7
Reproductive system and breast disorders	3	1.2	4	3.4
Respiratory, thoracic and mediastinal disorders	42	17.2	15	12.6
Skin and subcutaneous tissue disorders	38	15.6	9	7.6
Social circumstances	1	0.4		
Surgical and medical procedures	31	12.7	14	11.8
Vascular disorders	13	5.3	6	5.0
Total	729		319	

eTable 5. All Serious Adverse Events Excluding Those in the Study Eye

System organ class	Epimacular brachytherapy *N=244*		Ranibizumab monotherapy *N=119*	
	Events	**%**	**Events**	**%**
Blood and lymphatic system disorders				
Anemia	1	0.4	1	0.8
Cardiac disorders				
Atrial fibrillation	8	3.3	2	1.7
Bradycardia	1	0.4		
Bundle branch block left	1	0.4		
Cardiac failure	1	0.4		
Cardiac failure congestive	2	0.8		
Cardiac murmur	1	0.4		
Cyanosis	1	0.4		
Left ventricular dysfunction	2	0.8		
Mitral valve incompetence	1	0.4		
Myocardial infarction	2	0.8	1	0.8
Myocardial ischemia	1	0.4	1	0.8
Palpitations	2	0.8		
Supraventricular tachycardia	1	0.4		
Tachycardia	1	0.4		
Tricuspid valve incompetence	1	0.4		
Eye disorders (non-study eye)				
Atrophy of globe	1	0.4		
Charles Bonnet syndrome	1	0.4		
Endophthalmitis	1	0.4		
Eye discharge	1	0.4		
Eye pain	1	0.4		
Eyelid edema	1	0.4		

Hypopyon	1	0.4		
Ocular hyperemia	1	0.4		
Hallucination, visual	1	0.4		
Visual acuity reduced	1	0.4		
Retinal detachment			2	1.7
Gastrointestinal disorders				
Abdominal pain	3	1.2	1	0.8
Abdominal pain upper	1	0.4		
Diarrhea	2	0.8	2	1.7
Gastric ulcer			1	0.8
Gastrointestinal hemorrhage			1	0.8
Hematemesis	1	0.4		
Hematochezia	1	0.4		
Intestinal ischemia	1	0.4		
Irritable bowel syndrome	1	0.4		
Pancreatitis			1	0.8
Rectal hemorrhage	2	0.8		
Vomiting	1	0.4		
General disorders and administration site conditions				
Asthenia			1	0.8
Chest pain	6	2.5	1	0.8
Death	9	3.7	4	3.4
Edema peripheral	2	0.8		
Exercise tolerance decreased	2	0.8		
Fatigue			1	0.8
Gait disturbance	1	0.4		
Malaise	1	0.4	1	0.8
Multiple organ dysfunction syndrome			1	0.8
Organ failure			1	0.8
Pyrexia	1	0.4	2	1.7
Swelling	1	0.4		
Hepatobiliary disorders				
Cholecystitis			1	0.8
Cholelithiasis	1	0.4		
Jaundice	1	0.4		
Liver disorder			2	1.7
Portal vein thrombosis			1	0.8
Immune system disorders				
Drug hypersensitivity			1	0.8

Immunosuppression			1	0.8
Infections and infestations				
Abscess			1	0.8
Cystitis			1	0.8
Cytomegalovirus colitis			1	0.8
Enteritis infectious			1	0.8
Gastric infection			1	0.8
Herpes zoster			1	0.8
Incision site abscess	1	0.4		
Influenza			1	0.8
Liver abscess			1	0.8
Lower respiratory tract infection	3	1.2	1	0.8
Pneumonia	7	2.9	1	0.8
Sepsis	2	0.8	2	1.7
Urinary tract infection	3	1.2	4	3.4
Wound infection	2	0.8	1	0.8
Injury, poisoning and procedural complications				
Ankle fracture	2	0.8	1	0.8
Fall	15	6.1	7	5.9
Femoral neck fracture	3	1.2		
Foot fracture			1	0.8
Head injury	2	0.8		
Hip fracture			1	0.8
Intentional overdose	1	0.4		
Joint dislocation	3	1.2		
Joint injury	1	0.4	1	0.8
Laceration			1	0.8
Limb injury	1	0.4	1	0.8
Rib fracture	1	0.4		
Upper limb fracture	1	0.4		
Wound dehiscence	1	0.4		
Investigations				
Biopsy			1	0.8
Biopsy breast			1	0.8
Biopsy thyroid gland	1	0.4		
C-reactive protein increased			1	0.8
Cardiac output decreased	1	0.4		
Coma scale abnormal	1	0.4		
Cystoscopy	1	0.4		

Electrocardiogram abnormal	2	0.8		
Endoscopic retrograde colangiopancreatography	1	0.4		
Esophagogastroduodenoscopy			1	0.8
Heart rate increased			1	0.8
International normalized ratio increased	1	0.4		
Lumbar puncture	1	0.4		
Weight decreased	1	0.4	1	0.8
Metabolism and nutrition disorders				
Decreased appetite	1	0.4	1	0.8
Dehydration			1	0.8
Electrolyte imbalance	1	0.4		
Gout			1	0.8
Musculoskeletal and connective tissue disorders				
Arthralgia	3	1.2	2	1.7
Back pain	1	0.4	1	0.8
Clubbing	1	0.4		
Joint stiffness	2	0.8		
Joint swelling			1	0.8
Mobility decreased	2	0.8	1	0.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Bladder cancer recurrent	1	0.4		
Bone cancer	1	0.4		
Breast cancer			1	0.8
Cervix carcinoma			1	0.8
Colon cancer	2	0.8		
Colon cancer metastatic	1	0.4		
Chronic myeloid leukemia			1	0.8
Endometrial cancer	1	0.4	1	0.8
Esophageal carcinoma	1	0.4	1	0.8
Gastric cancer			1	0.8
Leukemia			1	0.8
Lung carcinoma cell type unspecified recurrent	1	0.4		
Metastases			1	0.8
Metastatic neoplasm			1	0.8
Metastases to liver	1	0.4		
Metastases to lung	1	0.4		
Neoplasm malignant			1	0.4
Prostate cancer	3	1.2	1	0.8
Rectosigmoid cancer	1	0.4		

Skin cancer	1	0.4		
Thyroid adenoma	1	0.4		
Uterine cancer	1	0.4		
Nervous system disorders				
Amnesia			1	0.8
Cerebrovascular accident	3	1.2		
Dizziness	2	0.8		
Dysstasia	1	0.4		
Generalized tonic-clonic seizure	1	0.4		
Headache	1	0.4	1	0.8
Hemiparesis			1	0.8
Lacunar infarction	1	0.4		
Lethargy	2	0.8		
Loss of consciousness	5	2.0	1	0.8
Migraine	1	0.4		
Myastenia gravis			2	1.7
Nystagmus	1	0.4		
Paresthesia	1	0.4		
Presyncope	1	0.4		
Seizure	1	0.4		
Transient ischemic attack	1	0.4		
Psychiatric disorders				
Confusional state	6	2.5	2	1.7
Delirium	1	0.4		
Dementia			1	0.8
Depression	1	0.4		
Disorientation	1	0.4		
Renal and urinary disorders				
Acute kidney injury	1	0.4		
Hematuria	1	0.4		
Nocturia	1	0.4		
Pollakiuria	1	0.4		
Renal colic	1	0.4		
Stress urinary incontinence	1	0.4		
Urinary incontinence	1	0.4		
Urinary retention	1	0.4		
Reproductive system and breast disorders				
Breast mass			1	0.8
Breast pain	1	0.4		

Prostate disorder	1	0.4		
Prostatomegaly	1	0.4		
Vaginal hemorrhage	1	0.4	2	1.7
Vaginal prolapse	1	0.4		
Respiratory, thoracic and mediastinal disorders				
Aspiration	1	0.4		
Chronic obstructive pulmonary disease	5	2.0		
Cough	1	0.4		
Dyspnea	10	4.1		
Emphysema	4	1.6		
Epistaxis	1	0.4		
Pleural effusion	1	0.4		
Pneumothorax	1	0.4		
Pulmonary edema	2	0.8		
Pulmonary embolism	1	0.4	1	0.8
Skin and subcutaneous tissue disorders				
Erythema			1	0.8
Skin ulcer			1	0.8
Surgical and medical procedures				
Aneurysm repair			1	0.8
Ankle operation	2	0.8		
Arthroscopic surgery	1	0.4		
Cardiac pacemaker insertion	1	0.4		
Cholecystectomy	1	0.4		
Colectomy	2	0.8		
Cholelithotomy			1	0.8
Coronary arterial stent insertion	1	0.4		
Debridement	1	0.4	1	0.8
Hernia repair	1	0.4		
Hip arthroplasy	3	1.2	2	1.7
Hysterectomy	1	0.4		
Hysterosalpingo-oopherectomy	1	0.4		
Intraocular lens implant	1	0.4		1
Knee arthroplasty	3	1.2	1	3
Knee operation			2	
Laparoscopy			1	
Laparotomy	1	0.4		1
Lesion excision	1	0.4		1
Mastectomy			1	

Mitral valve replacement	1	0.4		1
Prostatic operation	1	0.4		
Resuscitation	1	0.4		
Shoulder operation	1	0.4		
Skin graft	1	0.4		
Thoracostomy	1	0.4		
Transurethral prostatectomy	1	0.4		
Tricuspid valve repair	1	0.4		
Vaginal operation	1	0.4		
Vascular graft	1	0.4		
Vitrectomy	1	0.4		
Wound closure	1	0.4		
Wound treatment	1	0.4		
Vascular disorders				
Aortic aneurysm			1	0.8
Blood pressure increased	1	0.4		
Circulatory collapse	5	2.0	2	1.7
Hemorrhage	1	0.4		
Hypotension	2	0.8		
Orthostatic hypotension			1	0.8
Total	**276**		**115**	

eTable 6. Retinal Vascular Abnormalities in the Epimacular Brachytherapy Group

	Study Eye, n (%)		
Retinal Vascular Abnormality	**Baseline** ***N=244***	**Month 12** ***N=244***	**Month 24** ***N=244***
Microaneurysms	0 (0)	0 (0)	1 (0.4)
Dilated or tortuous vessels	2 (0.8)	3 (1.2)	8 (3.3)
Retinal vessel staining or leakage	1 (0.4)	1 (0.4)	14 (5.7)
Intraretinal hemorrhage	0 (0)	0 (0)	7 (2.9)
Retinal vessels sheathing or narrowing	1 (0.4)	1 (0.4)	5 (2.0)
Capillary nonperfusion	0 (0)	1 (0.4)	10 (4.1)
Capillary infarcts	0 (0)	0 (0)	4 (1.6)
Total	**4 (1.6)**	**6 (2.0)**	**49 (20.1)**

At month 24, the Reading Center identified microvascular abnormalities (MVAs) in 20/207 (10%) eyes in the epimacular brachytherapy (EMB) group and 1/97 (1%) eyes in the ranibizumab monotherapy group (P = .003, Fisher exact test). The MVAs were attributed to radiation in 17/20 (85%) eyes in the EMB group, but in 3/20 (15%) the cause could not be decided despite additional expert review by two Reading Center clinicians (U.C. and T.P.). The main features were retinal vessels staining or leakage and capillary non-perfusion.

In the only participant who had MVAs by month 12, these progressed through month 24 when pruning, shunting and leakage of retinal vessels were present, and the best-corrected visual acuity (BCVA) decreased from 54 letters at baseline to 34 letters at month 12 and 5 letters at month 24.

The majority of MVAs were extra-foveal (55%), and of those involving the fovea, none was present in the center of the fovea. The mean change in BCVA at month 24 in study eyes with definite or possible radiation-induced MVAs was -15.3 (23.1) letters, versus -10.1 (15.8) in those who received radiation but did not show MVAs (P=.33). Eight of the 20 eyes with MVAs lost >15 letters, but this was not necessarily attributable to radiation, as it did not reliably correspond to foveal involvement, occurring in 5/9 eyes with foveal MVAs and 3/11 eyes with extrafoveal MVAs.

Radiation-induced choroidopathy was suspected in 1/207 (<1%) eye in the EMB group.