Randomized Trial of Monthly Versus As-Needed Intravitreal Ranibizumab for Radiation Retinopathy–Related Macular Edema: 1-Year Outcomes

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• PURPOSE: To assess efficacy of intravitreal ranibizumab injections and targeted panretinal photocoagulation (TRP) for radiation retinopathy–related macular edema.
• DESIGN: Phase IIb, prospective, randomized clinical trial.
• METHODS: SETTING: Multicenter. SUBJECTS: Forty eyes in 40 treatment-naïve patients with radiation-induced macular edema and a resulting decrease in visual acuity ranging between 20/25 and 20/400 (Snellen equivalent). INTERVENTION: Patients either received intravitreal 0.5 mg ranibizumab monthly, monthly ranibizumab with TRP, or 3 monthly ranibizumab (loading doses) followed by as-needed (PRN) injections and TRP. After week 52, all subjects entered a treat-and-extend protocol for ranibizumab. MAIN OUTCOME MEASURES: Mean Early Treatment Diabetic Maculopathy Study (ETDRS) BCVA change from baseline.
• RESULTS: Mean patient age was 57 years (range, 22-80 years), ETDRS BCVA was 56.7 letters (20/74 Snellen equivalent), and central macular thickness (CMT) was 423 μm (range, 183-826 μm). Thirty-seven patients completed the month 12 visit (92.5%), at which time the change in mean BCVA was +4.0 letters, −1.9 letters, and +0.9 letters in the monthly, monthly plus laser, and PRN plus laser cohorts, respectively. There was a significant difference in mean BCVA at 1 year among all 3 cohorts ($P < .001$), as well as between cohorts in pairwise comparisons, with the most significant gains in the monthly group. A total of 82.5% of the patients retained visual acuity of 20/200 or better, and 20.0% improved 10 or more ETDRS letters.
• CONCLUSIONS: Ranibizumab may improve vision and anatomy in patients with radiation retinopathy–related macular edema and prevent vision loss through 48 weeks of therapy. Monthly injections were more effective than as-needed approach, and the addition of TRP yielded no therapeutic benefits. (Am J Ophthalmol 2020;216: 165–173. © 2020 Elsevier Inc. All rights reserved.)

RADIATION RETINOPATHY IS A COMMON AND devastating visual side effect of plaque brachytherapy or proton beam irradiation for the treatment of uveal melanoma, and of external beam radiotherapy for other intraocular or orbital cancers. Treatment methods for visual stabilization or improvement in these patients are sorely needed. Although local tumor control rates in the Collaborative Ocular Melanoma Study (COMS) and other reports were excellent for small-to-medium-sized choroidal melanoma,[1] long-term visual acuity outcomes were poor for many patients. In the COMS report examining visual outcomes at 3 years, 45% of patients had a visual acuity of 20/200 or worse and 49% had a loss of 6 or more lines from the pretreatment level at 3 years post treatment.[2] Furthermore, once poor visual outcomes were observed, improvement in vision was unlikely. Ocular radiation of any form can cause adverse effects, including radiation retinopathy, cataract, glaucoma, and optic neuropathy, all of which can significantly worsen patient vision.[3]

Radiation retinopathy, which typically manifests with signs of macular edema, cotton-wool spots, neovascularization, and/or vitreous hemorrhage between 6 months and 3 years post radiation therapy, significantly impairs vision.[4] Gunduz and associates reported that 42% of 1,300 patients who were treated for posterior uveal melanoma presented with nonproliferative radiation retinopathy at 5 years post brachytherapy based on Kaplan-Meier estimates.[5] Krema and associates reported that dose-dependent radiation retinopathy can occur in over 30% of melanoma patients at 24 months post plaque therapy.[6] Bianciotto and associates reported that radiation-induced retinopathy can further progress to proliferative radiation retinopathy with significant neovascularization in 5.6% of patients at 5 years after brachytherapy, with a mean presentation at 32 months.[7]

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Radiation retinopathy develops in a similar manner to retinal vascular diseases such as diabetic retinopathy, in that radiation triggers both retinal tissue damage and an inflammatory response.[8] Growth factors including fibroblast (FGF), epithelial (EGF), platelet-derived (PDGF), and vascular endothelial growth factor (VEGF) are released by epithelial and endothelial cells and fibroblasts in order to mediate the tissue repair process in the ischemic and nonperfused tissues. To prevent these devastating processes, several treatment options have been preemptively used in recent publications. Intravitreal injection of monoclonal antibodies against these factors, most notably anti-VEGF, can reduce the inflammatory response and subsequently minimize edema and neovascularization. Intravitreal triamcinolone acetonide also induces anti-inflammatory effects by reducing cytokine production. Laser photocoagulation, when used prophylactically, may prevent retinopathy in the ischemic retinal tissue post brachytherapy. Small retrospective studies examining these therapeutic options have been reported within the last 10 years with mostly favorable results.[8–22]

Only 2 prospective studies have been published on the use of anti-VEGF ranibizumab (Lucentis; Genentech, Inc, South San Francisco, California, USA) for radiation retinopathy. Finger and associates[8] reported in a phase I/II, open-label, nonrandomized prospective trial that high-dose (2.0 mg) ranibizumab use in 10 patients with recalcitrant radiation retinopathy achieved stable or improved visual acuity in 70% of patients. Kim and associates[23] reported a phase I, single-arm, open-label prospective study of 40 patients in which intravitreal ranibizumab treatment was initiated immediately after radiation completion, before clinical evidence of disease. The proportions of patients with visual acuity greater than or equal to 20/200 as well as greater than or equal to 20/40 were significantly improved compared to historical controls at 24 months ($P < .001$). Despite growing evidence that anti-VEGF can potentially treat radiation retinopathy effectively, there are currently no US Food & Drug Administration–approved therapies for radiation retinopathy. The purpose of this randomized phase II, prospective, 2-year multicenter clinical trial was to further investigate the tolerability and efficacy of ranibizumab with and without laser photocoagulation for radiation retinopathy–related macular edema.

METHODS

THE RANIBIZUMAB FOR RADIATION RETINOPATHY STUDY (RRR) is a phase IIb, multicenter, randomized controlled clinical trial (ClinicalTrials.gov identifier, NCT02222610; Sponsor, Retina Consultants of Houston; Collaborator, Genentech, Inc). Informed consent was obtained from every study subject for treatment and participation in the research. Institutional Review Board/Ethics Committee approval was prospectively obtained by the Houston Methodist Hospital. This study adhered to the tenets of the Declaration of Helsinki and was in accordance with Health Insurance Portability and Accountability Act regulations. Data were collected at the Retina Consultants of Houston (Houston, The Woodlands, and Katy, Texas, USA) as well as Texas Retina Associates (Dallas, Texas, USA). Subjects that met the following inclusion criteria were enrolled into this study: 18 years and older at the time of enrollment; active radiation retinopathy with macular edema detectable by spectral-domain optical coherence tomography (SDOCT) with a resulting decrease in visual acuity below 20/20 during standard postradiotherapy follow-up; history of any of the following forms of radiation treatment: ocular proton beam radiation, ocular plaque brachytherapy, ocular/orbital external beam radiation; and best-corrected visual acuity (BCVA) Snellen equivalent between 20/25 and 20/400 in the study eye. Exclusion criteria included but were not limited to the following: pregnancy or lactation at the time of enrollment; participation in other medical investigation or trial possibly involving investigational drugs within 30 days before enrollment; previous intravitreal injections with any anti-VEGF drug within 60 days of enrollment; previous intravitreal or subconjunctival treatment with corticosteroids within 90 days of enrollment; history of vitrectomy; history of more than 1 form of radiation to the eye; more than 7 disc diameter of ischemia in the central macula; history of panretinal photocoagulation in study eye.

At enrollment, patients were sequentially randomized to 1 of 3 cohorts by a masked study coordinator. At all visits, subjects underwent Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA testing at 4 m, slit-lamp and dilated ophthalmic examination, and SDOCT imaging using the Heidelberg Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany). The Heidelberg OCT acquisition protocol featured a volume scan (20 × 20, 49 lines, 768 A-scans per line) with 9 times image averaging.

Forty subjects from 4 study sites in the United States were enrolled. The subjects whose central vision was worse than 20/50 Snellen equivalent at screening were randomized into Cohorts A, B, and C in a 1:2:2 ratio. The reason for the 1:2:2 randomization ratio was that the monthly group would have less variability in terms of treatment course because each patient would uniformly receive an injection each month without alterations or additional factors to their treatment regimen, allowing for detection of the group's trend with a smaller cohort size. On the other hand, the other 2 cohorts could have different treatment schedules and therefore would require more patients to capture the trend. The exception to this randomization was that patients whose central vision of 20/50 or better at screening examination were randomized into the 3 cohorts in a 1:1:1 ratio so as to minimize a disproportionate population of subjects with good vision in any 1 group and to minimize the chance of significant difference in baseline

vision between groups. Randomization occurred on day 0 in which a randomly selected envelope containing a cohort assignment was chosen for each patient.

Cohort A (n = 8) patients received monthly intravitreal injections of 0.5 mg ranibizumab (RBZ) from day 1 through week 48, in which monthly treatment was defined as every 28 days ± 7 days. Cohort B (n = 16) patients received monthly RBZ injections of 0.5 mg for the first 48 weeks. One week (±3 days) after the initial RBZ injection, subjects in Cohort B also received targeted retinal photocoagulation (TRP) to areas of peripheral retinal ischemia determined by wide-field angiography. Cohort B patients underwent wide-field angiography at weeks 24 and 36 and received additional TRP at these 2 time points as needed (*pro re nata* [as needed], PRN) if ischemic areas persisted or new areas developed. Cohort C (n = 16) patients received a loading dose of 3 consecutive monthly RBZ injections of 0.5 mg followed by PRN monthly RBZ injections thereafter. Examination findings necessitating PRN treatment with RBZ injections included evidence of true subretinal or intraretinal fluid on SDOCT, increase in central macular thickness of 50 μm or more, and loss of 5 or more ETDRS letters from the previous measurement with corresponding evidence of active disease in the macula on SDOCT. One week (±3 days) after the first ranibizumab injection, patients in Cohort C received TRP to areas of peripheral retinal ischemia; subsequently, they underwent repeat wide-field angiogram at weeks 24 and 36 and received TRP PRN if ischemic areas persisted or new areas developed. Starting at week 52, subjects in all 3 cohorts entered a standardized treat-and-extend regimen for 48 additional weeks. Details of the study protocol for weeks 52-96 will be reported in a future manuscript. This report pertains to the first 48 weeks of the study.

Standard ophthalmic sterile technique was used for every injection. If the patient had a treated intraocular tumor such as a uveal melanoma, the injection site was chosen in a meridian other than the meridian of the previously treated lesion. Prophylactic peri-intravitreal injection topical ophthalmic antibiotics were not used. Topical anesthetic was instilled and the use of subconjunctival anesthesia was optional at the investigator's discretion (2% lidocaine without epinephrine at the injection site). After topical anesthesia, the periocular skin, eyelids, and eyelashes were disinfected with povidone-iodine swabs, and povidone-iodine ophthalmic solution was applied to the ocular surface. After intravitreal injection, finger-counting testing was performed to confirm central retina artery perfusion, and intraocular pressure was measured 30 minutes after injection. Subjects were monitored until intraocular pressure measured 30 mm Hg or less.

The primary outcome measure for safety and tolerability was mean change in ETDRS BCVA at week 48. Secondary outcome measures included mean change in central macular thickness on SDOCT at week 48; mean number of patients with other manifestations of radiation retinopathy, such as macular hemorrhages and exudates; the mean number of intravitreal injections required for each subject per cohort; the percentage of subjects with persistent macular edema based on SDOCT at week 48; and the percentage of subjects avoiding the development of neovascular glaucoma and/or vitreous hemorrhage. ETDRS BCVA, intraocular pressure, slit-lamp examination, indirect ophthalmoscopy, and SDOCT were performed at every visit to monitor the progress of treatment and subject vision. Fundus photography and fluorescein angiography were performed at screen and at weeks 24, 36, 48, 78, and 104/early termination visit to assess the anatomic state of the retinal vasculature. To assess the severity of macular edema, central macular thickness, which is defined as the average macular thickness in the central 1-mm radius of the ETDRS grid, was obtained from the automated macular topographic information in the Heidelberg Eye Explorer OCT software.

Incidences of retinal hemorrhage, exudates, neovascularization, and new areas of ischemia were recorded on a standardized grading scale over the course of 12 months, all assessed via slit lamp and/or indirect ophthalmoscope by either the principal investigator or sub-investigator. For intraretinal hemorrhages, grade 0 represented no visible hemorrhages; grade 1, 0-5 individual dot-blot or flame-shaped hemorrhages; grade 2, 5-10 dot-blot or flame-shaped hemorrhages; grade 3, 10-20 dot-blot or flame-shaped hemorrhages; and grade 4, more than 20 dot-blot or flame-shaped hemorrhages. For hard exudates, grade 0 represented no visible exudates; grade 1, presence of non–visually significant hard exudates; and grade 2, visually significant hard exudate in the macula. For neovascularization, grade 0 represented no visible neovascularization; grade 1, early neovascularization including intraretinal microvascular abnormality, or non–clinically apparent neovascularization detectable on fluorescein angiography but minimally detectable on clinical examination; grade 2, clinically apparent neovascularization including neovascularization of the iris, neovascularization of the disc, and/or neovascularization everywhere else; and grade 3, neovascular glaucoma with documented elevated intraocular pressure requiring therapy. Retinal hemorrhage, neovascularization, and exudates were assessed during each visit by either the principal investigator or sub-investigator at each study site. All readers followed the standardized grading system as described above.

A priori power calculation was performed and revealed that a sample size of n = 41 was needed to achieve 80% power using single-factor analysis of variance (ANOVA) with a significance level (alpha) of 0.05. Based on this result, the final study size was 40. Patients were randomized in a 1:2:2 ratio. Sample size estimation was performed using RStudio (version 1.1.463; RStudio Inc, Boston, Massachusetts, USA). Statistical analyses were performed using Prism (GraphPad Software, San Diego, California, USA)

TABLE 1. Baseline Patient Demographics

Female sex, % (female/male)	40% (16/24)
Mean (median, range) age, years	57 (61.9, 22-80)
Right eye, % (right eye/left eye)	60% (24/16)
Mean (median, range) ETDRS BCVA	56.7 (56.5, 23-81)
Mean (median, range) Snellen equivalent	20/74 (20/74, 20/400 to 200/25)
Median (range) number of years since radiation, years	2.5 (6 months to 45 years)
% of patients who underwent radiation within 10 years of study	90% (36/40)

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.

and the data analysis function in Microsoft Excel (Microsoft Inc, Redmond, Washington, USA). For comparison of groups for primary and secondary outcomes, variables of interest were statistically analyzed using ANOVA, Student *t* test, χ^2 test, and Fisher exact test. ETDRS data were obtained for all 14 visits for all 40 of the participants. Bonferroni correction was applied to all pairwise comparison analyses for this study. There were no changes to the methods after trial commencement.

RESULTS

• **DEMOGRAPHICS:** Forty patients were enrolled into this study. Patient demographics were well balanced among the 3 cohorts. Cohorts A, B, and C consisted of 8, 16, and 16 patients, respectively. Sixteen patients were female and 24 patients were male. One subject was of Asian descent, 38 patients were non-Hispanic white, and 1 patient was Hispanic white. At baseline, mean patient age was 57 (range, 22-80) years. Twenty-four eyes were right eyes and 16 eyes were left eyes (Table 1, Figure 1).

Mean ETDRS BCVA of all subjects at the time of enrollment was 56.7 letters (median, 56.5; Snellen equivalent, 20/74). Mean initial central macular thickness was 423 μm (median, 377 μm; range, 183-826 μm). Baseline central macular thickness (CMT) measurements were obtained from 39 patients; 1 patient (Subject 006) in Cohort C had a tumor too close to the macula that did not enable an accurate measurement of the macular thickness. The median number of years from the time of radiation therapy to the time of trial entry was 2.5 years (range, 6 months to 45 years). Of the 40 patients, 36 had completed radiation therapy within 10 years prior to the enrollment into this study. All data were obtained at a total of 14 visits from baseline visit through week 48. Thirty-seven patients (92.5%) completed the 48-week visit. There were no statistically significant differences in baseline ETDRS BCVA ($P = .72$), CMT ($P = .55$), age ($P = .16$), laterality of the study eye ($P = .78$), and sex ($P = .34$) among the 3 cohorts.

• **VISUAL ACUITY OUTCOMES:** Mean ETDRS BCVA letters were 56.9, 55.6 and 60.3 at baseline for the monthly injection cohort (Cohort A), monthly injection and TRP cohort (Cohort B), and PRN injections with TRP cohort (Cohort C), respectively (Snellen equivalent, 20/73, 20/77, 20/62). Mean ETDRS BCVA gains over first 48 weeks were 4.0, −1.9, and 0.9 letters for Cohort A, Cohort B, and Cohort C, respectively (Figure 2, Top left). Single-factor ANOVA demonstrated a statistically significant difference in mean BCVA values over the 1-year period among 3 cohorts ($P < .001$). Pairwise comparisons of the means demonstrated that all 3 pairs of mean BCVA values differed significantly from each other (Cohort A vs B, $P < .001$; B vs C, $P < .001$; A vs C, $P < .01$). In addition, there was a statistically significant difference in the mean change of BCVA from baseline values among the 3 cohorts (Cohort A vs B, $P < .0001$; B vs C, $P < .0001$; A vs C, $P = .008$). Cohort A (monthly ranibizumab injection group) saw the biggest gain in ETDRS letters during the study period. Repeated-measures ANOVA revealed that BCVA changes across the visits were independent of individual differences between subjects.

For the purpose of comparing these data with historical controls, ETDRS BCVA scores were also converted into Snellen equivalents. For patients in all 3 cohorts combined, at week 48, 82.5% of patients had vision of 20/200 or better; 30.0% of patients had vision of 20/40 or better; and 20.0% had improved 10 ETDRS letters or more from baseline. Only 17.5% of patients had 20/200 or worse vision at week 48. Given that the current study's patients presented with radiation retinopathy 2.5 years after radiation therapy on average and that this report analyzes visual outcomes 1 year after the initiation of ranibizumab therapy following the diagnosis of radiation retinopathy, it is therefore appropriate to compare the 1-year visual outcomes of this study to the outcomes at 36 months after the enrollment in the COMS study. At 3 years post brachytherapy in the COMS study, median visual acuity was 20/125, 34% of the patients remained at 20/40 or better, and 45% of the patients had 20/200 or worse.[2]

• **ANATOMIC OUTCOMES:** Mean CMT decreased in all 3 cohorts, resulting in improved macular edema over the

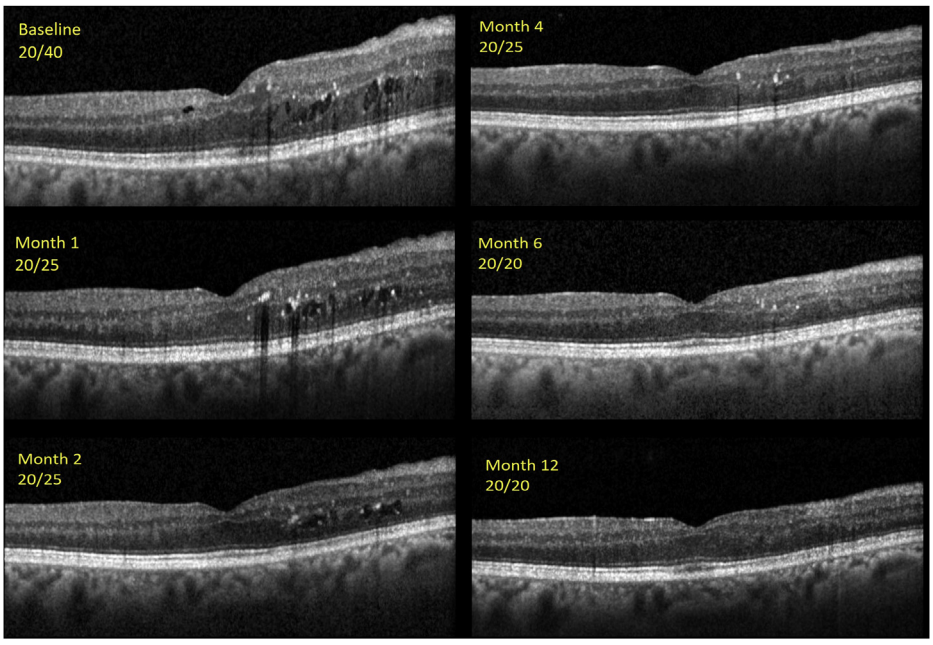

FIGURE 1. Serial optical coherence tomography images of the right eye of a 60-year-old man (Subject 034) in the monthly injection with targeted retinal photocoagulation cohort (Cohort B). The patient had a baseline best-corrected visual acuity of 74 Early Treatment Diabetic Retinopathy Study (ETDRS) letters that improved to 83 letters at 1 year.

study period. Mean CMT values were 423.1 μm, 456.3 μm, and 388.2 μm at baseline for Cohorts A, B, and C, respectively. Single-factor ANOVA demonstrated that the mean CMT values among 3 cohorts over the 12-month study period had a statistically significant difference ($P < .001$). Cohorts A, B, and C experienced mean changes in CMT of −97.0 μm, −104.9 μm, and −71.0 μm from baseline over the first 12 months (Figure 2, Top right). Regarding the mean CMT change from baseline over the study period, a statistically significant difference was observed among the cohorts ($P < .001$). Pairwise comparisons demonstrated that the mean CMT change differed significantly between Cohorts A and C ($P < .001$) and between Cohorts B and C ($P < .001$) but not between Cohorts A and B ($P = .75$). Repeated-measures ANOVA demonstrated a significant difference in means of the visits for CMT value for Cohort A ($P = .012$), but not for Cohort B ($P = .21$) or C ($P = .52$), indicating that differences in CMT values from the baseline across the follow-up visits were significantly related to the visit sequence independent of individual differences among subjects.

At the baseline visit, a total of 75% (n = 6), 81.25% (n = 13), and 87.5% (n = 14) of patients had any degree of retinal hemorrhage in Cohorts A, B, and C, respectively. At week 48, 0%, 6.25% (n = 1), and 12.5% (n = 2) of patients had persistent retinal hemorrhage in Cohorts A, B, and C, respectively (Figure 2, Bottom left). All cohorts reported a statistically significant improvement during the study period (Cohort A, $P = .0019$; Cohort B, $P < .0001$; Cohort C, $P = .0001$), with no statistically significant inter-cohort differences in the percentage of patients with persistent retinal hemorrhages ($P = .519$) on single-factor ANOVA analysis. Therefore, no further pairwise comparisons were conducted. Of note, no patients developed vitreous hemorrhages during the first year of study.

The percentage of patients who demonstrated the presence of intraretinal exudates on fundus examination improved from 25% (n = 2), 37.5% (n = 6), and 62.5% (n = 10) at the initial visit to 0%, 6.25% (n = 1), and 25% (n = 4) at week 48 in Cohorts A, B, and C, respectively (Figure 2, Bottom right). A single-factor ANOVA showed a significant difference between percent incidence of exudates in the cohorts across visits ($P < .001$). Pairwise comparisons demonstrated that there was a statistically significant difference in percent incidence between Cohorts A and C ($P = .003$) and between Cohorts B and C ($P = .0002$), but not between Cohorts A and B ($P = .62$).

Neovascularization was only observed in 1 patient in Cohort B and another patient in Cohort C at baseline, and week 48 incidence of neovascularization remained the same. Therefore, no statistical analysis was performed.

• **ADVERSE EVENTS:** Ocular and serious systemic adverse events are listed in Table 2. There were no serious ocular adverse events. There were no cases of endophthalmitis or intraocular inflammation. Two patients did develop metastatic uveal melanoma during the study period, and 1 developed a local recurrence of uveal melanoma, neither thought to be related to the injection or laser protocol.

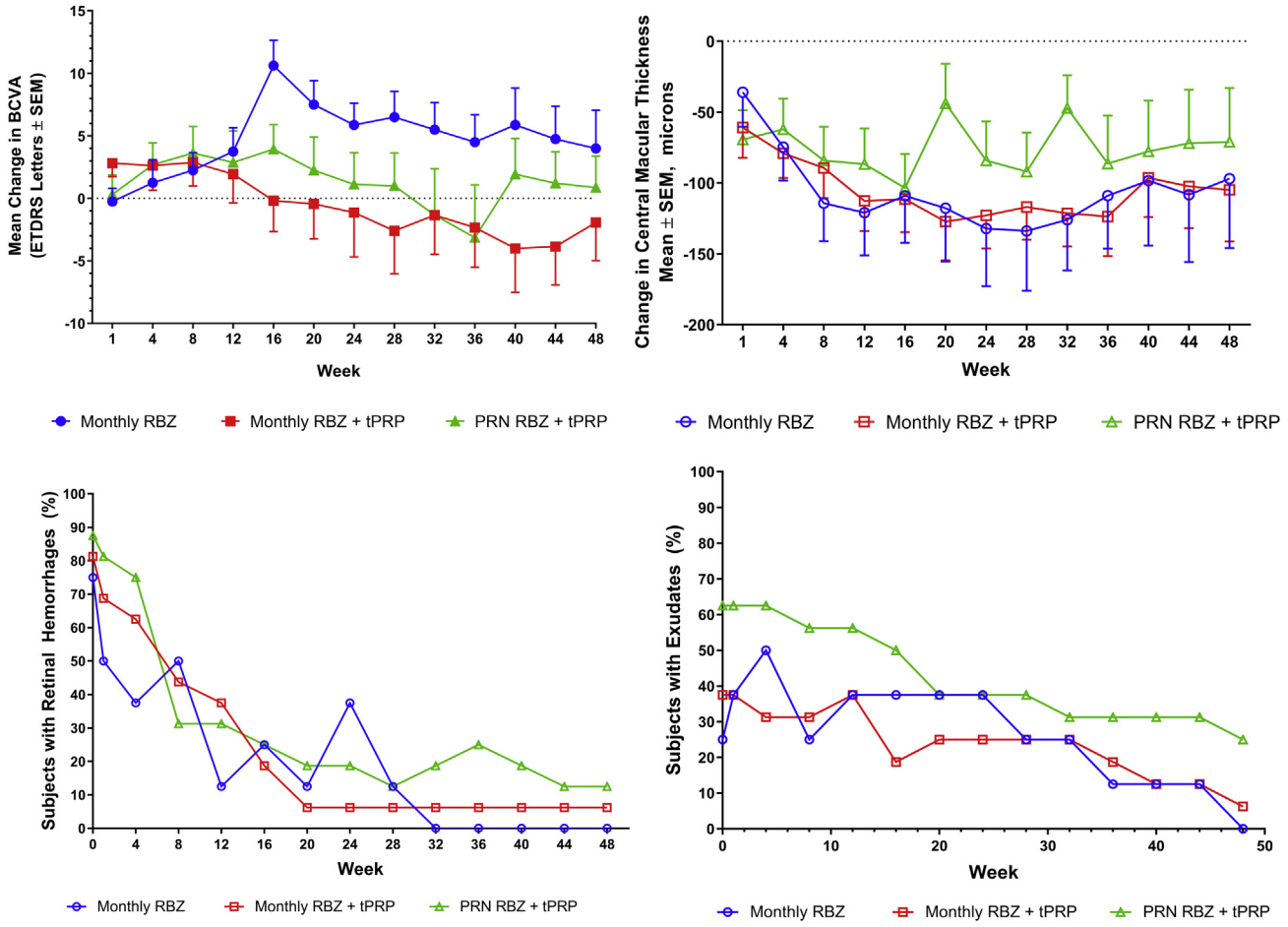

FIGURE 2. Visual outcomes and ocular adverse events over the first year of study. Top left. Mean changes in best-corrected visual acuity (BCVA) over the first year of study. Baseline BCVA was 56.9, 55.6, and 60.3 ETDRS letters for the monthly injection cohort, monthly injection with targeted retinal photocoagulation (TRP) cohort, and as-needed (PRN) injections with TRP cohort, respectively. The graphs demonstrate that the monthly injection cohort experienced a statistically significant gain in visual acuity compared to the monthly injection with TRP cohort ($P < .0001$) and PRN injections with TRP cohort ($P < .008$). Top right. Mean changes in central macular thickness (CMT) over the first year of study. Mean CMT values were 423.1 μm, 456.3 μm, and 388.2 μm at baseline for the monthly, monthly with TRP, and PRN injections with TRP, respectively. The graphs demonstrate that all 3 cohorts experienced an overall decrease in CMT at 1 year, with a statistically significant difference between the PRN injections cohort and the other 2 cohorts (both $P < .001$ in pairwise comparisons), but not between the monthly injections and the monthly injections with TRP cohorts ($P = .75$). Bottom left. Percentage of subjects with retinal hemorrhage per cohort over the first year of study. Zero patients, 1 patient, and 2 patients in Cohorts A, B, and C, respectively, had persistent retinal hemorrhages at 1 year. Bottom right. Percentage of subjects with intraretinal exudates over the first year of study. Zero patients, 1 patient, and 4 patients in Cohorts A, B, and C, respectively, had persistent retinal exudates at 1 year.

DISCUSSION

IN THIS RANDOMIZED PHASE II, PROSPECTIVE, MULTICENTER clinical trial, the primary goal of the 1-year report was to statistically evaluate the tolerability and efficacy of ranibizumab and/or TRP laser for radiation retinopathy–related macular edema. Based on the analyses, patients in Cohort A who received monthly intravitreal ranibizumab injections had the largest improvement in ETDRS BCVA from baseline to week 48, with a statistically significant difference in change of BCVA from the other 2 study arms. The difference in ETDRS BCVA between Cohorts A and C mirrors many previous publications on the efficacy of monthly intravitreal anti-VEGF injections compared to PRN regimens for other VEGF-driven diseases such as neovascular age-related macular degeneration (ARMD).[24] As with neovascular ARMD, the challenge for this group of patients is establishing best practice patterns for the frequency and duration of injections needed to maintain visual acuity in the long term. The second year of this trial will address the number of injections required by patients undergoing a treat-and-extend

TABLE 2. Ocular and Serious Systemic Adverse Events During the First Year of Study

Ocular Adverse Events	Number (%) of Patients (N = 40)
Worsening of cataract	8 (20%)
Worsening of posterior capsular opacity	4 (10%)
Posterior vitreous detachment	5 (12.5%)
Corneal abrasion	1 (2.5%)
Subconjunctival hemorrhage	3 (7.5%)
Central retinal artery occlusion	1 (2.5%)
Serious Systemic Adverse Events	
Metastatic uveal melanoma	2 (5%)
Local recurrence of uveal melanoma	1 (2.5%)
Worsening hypertension	2 (5%)

treatment approach in order to maintain a dry macula and to preserve vision. Nonetheless, when compared to the patients undergoing brachytherapy in the COMS trials, patients in this cohort with good vision have retained their visual acuity.[2] In the COMS study, at 3 years post brachytherapy, which is approximately equivalent to 1 year after the initiation of ranibizumab therapy in the current study in terms of time elapsed since radiotherapy, 34% of the patients had Snellen visual acuity of 20/40 or better, comparable to 30% in the present study at the 48-week time point. However, it is important to note that patients with peripapillary tumors were not included in the COMS study, and these are the patients who tend to have the worst outcomes with respect to radiation retinopathy. Nonetheless, significant preservation of baseline visual acuity was achieved in all study subjects that were stratified based on their baseline visual acuity (Figure 3), in contrast to the gradual decline observed in the COMS report.[2] As a result, only 17.5% of the RRR cohort had visual acuity worse than 20/200 at a median of 3.5 years since radiation (2.5 years at entry into the study plus 1 year in the study), compared to 45% at 3 years post brachytherapy in the COMS trial. Moreover, patients who received monthly ranibizumab injections saw a 7% improvement in BCVA (56.9 at baseline to 60.9 ETDRS letters at 1 year), indicating potential benefits for visual acuity with monthly injections. In the following 2-year report, the efficacy of prospective ranibizumab injections will be further analyzed in the setting of a treat-and-extend protocol, which would allow us to provide insights into how extending the interval impacts visual outcomes as well as cost and treatment burdens for the patients.

Anatomic results also mirrored many previous publications in the ARMD and diabetic macular edema literature. Patients in all 3 cohorts had a significant improvement in retinal thickness over the course of the study time period; however, the mean change in macular thickness was significantly better in the monthly ranibizumab cohorts than in the PRN cohort. Figure 2 (Top right) demonstrates the typical "sawtooth-ing" OCT pattern often seen in previously published ARMD trials in which patients' anatomy worsens after each month in which an injection is skipped.[24]

It was notable that adding TRP laser to the treatment regimen did not result in additional therapeutic benefits at the 12-month time point in this study. This phenomenon might be explained by the fact that laser photocoagulation can induce an inflammatory response with macular edema that might have countered the visual benefit of anti-VEGF therapy. Several studies have reported that TRP treatment can upregulate the release of inflammatory cytokines including VEGF, therefore causing a transient worsening of macular edema.[25–27] In this study, TRP laser was administered to patients in Cohorts B and C at baseline as well as when needed at weeks 24 and 36. Regardless of the exact mechanism, the addition of laser photocoagulation seems not to be beneficial, or even potentially harmful in this population, as visual outcomes of Cohorts B and C were inferior to that of Cohort A. This finding is consistent with recent data indicating that targeted laser to areas of ischemic peripheral retina in diabetics did not result in decreased frequency of anti-VEGF injections for diabetic macular edema.[28] Given that it is yet uncertain what the exact mechanism is behind the development of radiation retinopathy, adding TRP laser could have further augmented the inflammatory reactions and worsened the damages to microvascular structures.

Radiation-induced damage to the retina can manifest not only as macular edema, but also in the form of hemorrhages, telangiectasias, microaneurysms, cotton-wool spots, capillary nonperfusion, and retinal pigment epithelium and retinal atrophy. As another measure of retinopathy improvement in response to anti-VEGF therapy, we examined the change in retinal hemorrhages and exudation in the cohorts over time, and patients in all cohorts had significant improvement in these measures at week 48. As in diabetic retinopathy, anti-VEGF therapy does seem to modify other manifestations of retinal vascular damage (nonproliferative and proliferative changes) other than edema, although the effect of these changes on visual recovery and maintenance of visual acuity over time remain unknown.

The limitations of this study include the relatively small number of patients and lack of a true control group. Nonetheless, patient retention in the study was excellent through week 48, and the follow-up time since radiation is significant, since the median time from radiation to time of enrollment in the study was 2.5 years. Given that the peak incidence of clinically evident radiation retinopathy occurs between 2 and 3 years after radiation, we felt that a study design that addressed retinopathy once it was visually significant with objective OCT-based evidence was the most appropriate and mirrored the current treatment approach for other retinal diseases. Furthermore, we

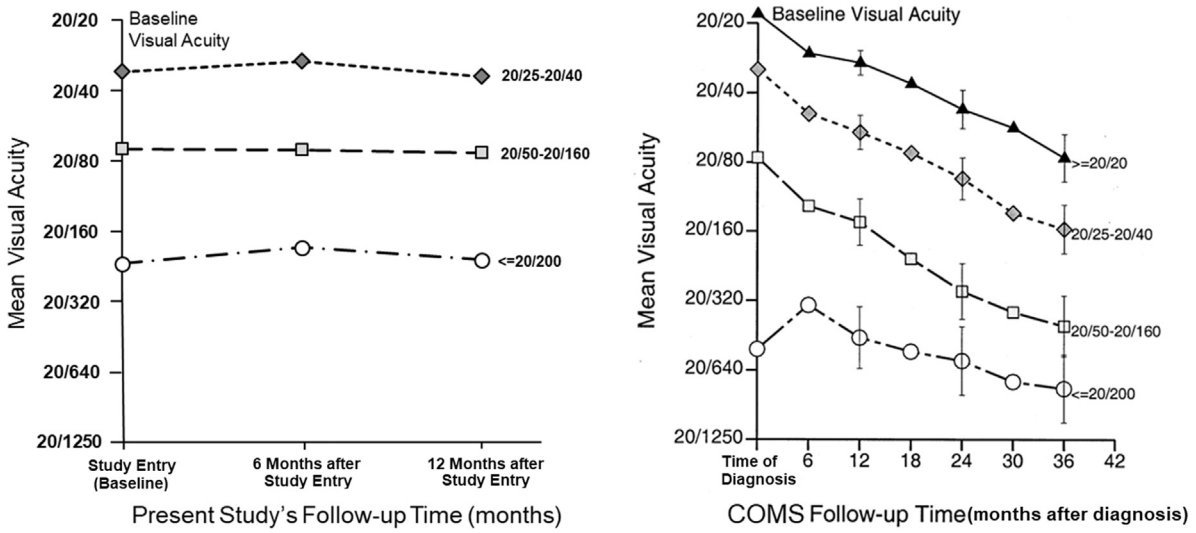

FIGURE 3. Side-by-side comparison of the present study and the Collaborative Ocular Melanoma Study (COMS)[2] (adapted from COMS; request for permission for reuse granted) in terms of mean visual acuity performance over the follow-up period, stratified by baseline visual acuity. Of note, T = 0 for the present study (left) corresponds to the time of enrollment in this study, which may not necessarily coincide with the time of cancer diagnosis. On the other hand, T = 0 for COMS (right) represents the time of melanoma diagnosis.

chose monthly injections for 2 of the cohorts in this study rather than the bimonthly injections in the study by Kim and associates[23] with a belief that such an approach would likely lead to best visual outcomes. Year 2 of the study will reflect a more real-world, practical, treat-and-extend approach. Another limitation of the study is the fact that patients presented with a wide range of disease states, including different tumor locations as well as radiation types and doses. Such variability in baseline patient characteristics could have impacted how each patient would fare over the course of study follow-up in terms of visual outcomes. Had patient selection been more uniform in terms of tumor geometry and location, radiation type and dosage, and involvement of critical structures including the macula and optic nerve, then treatment efficacy for each cohort could have been more clearly delineated.

Despite its limitations, this is one of the only prospective, randomized studies investigating the use of 0.5 mg intravitreal ranibizumab therapy for the treatment of radiation retinopathy–related macular edema. The results suggest that intravitreal ranibizumab, when given at the time of decreased vision due to macular edema, is effective at improving vision and anatomy and preventing vision loss through 48 weeks of therapy. Monthly injections were more effective than a PRN approach, and the additional of targeted PRP did not seem to have a visual benefit. It would be beneficial to investigate the efficacy of ranibizumab by comparing visual outcomes between monthly injections, as-needed injections without TRP, and true control patients. Therefore, additional randomized, controlled clinical trials on a larger scale of monthly ranibizumab injections for clinically evident macular edema should be performed so as to further elucidate the long-term clinical utility of ranibizumab in the management of radiation retinopathy.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

AMY C. SCHEFLER: CONCEPTUALIZATION, METHODOLOGY, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Dwain Fuller:** Investigation, Methodology, Data curation. **Rajiv Anand:** Investigation, Methodology, Data curation. **Timothy Fuller:** Investigation, Methodology, Data curation. **Chelsey Moore:** Investigation, Data curation, Supervision, Project administration. **Jose Munoz:** Investigation, Data curation, Supervision, Project administration. **Ryan S. Kim:** Data curation, Writing - original draft, Writing - review & editing.

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