Epimacular brachytherapy for previously treated neovascular age-related macular degeneration: month 36 results of the MERLOT randomised controlled trial

Timothy L Jackson ,[1,2] Cristina Soare ,[2] Caroline Petrarca,[1] Andrew Simpson,[1,2] James E Neffendorf,[1,2] Robert Petrarca,[1,2] Katherine Alyson Muldrew,[3] Tunde Peto ,[4] Usha Chakravarthy,[3] Luke Membrey,[5] Richard Haynes,[6] Mark Costen,[7] David H W Steel,[8,9] Riti Desai,[2] for the MERLOT Study Group

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjophthalmol-2021-320620).

For numbered affiliations see end of article.

Correspondence to
Timothy L Jackson, Ophthalmology, King's College London Faculty of Life Sciences and Medicine, London, London, UK; t.jackson1@nhs.net

Received 12 October 2021
Accepted 17 January 2022
Published Online First 25 February 2022

To cite: Jackson TL, Soare C, Petrarca C, *et al*. *Br J Ophthalmol* 2023;**107**:987–992.

ABSTRACT

Background/aim To assess the long-term safety and efficacy of epimacular brachytherapy (EMB) for chronic, active, neovascular age-related macular degeneration (nAMD).

Methods This pivotal, randomised, controlled surgical device trial recruited patients with chronic nAMD receiving intravitreal ranibizumab from 24 UK hospitals. Participants were randomised to either pars plana vitrectomy with 24 Gray EMB and *pro re nata* (PRN) ranibizumab (n=224) or PRN ranibizumab monotherapy (n=119). Although masking was not possible, masked clinicians assessed best-corrected visual acuity (BCVA) and imaging. After month 24, participants reverted to standard care, with either ranibizumab or aflibercept, returning for a month 36 study visit.

Results Of 363 participants, 309 (85.1%) completed month 36. The number of injections was 12.1±8.1 in the EMB group versus 11.4±6.1 in the ranibizumab group (difference 0.7, 95% CI of difference −0.9 to 2.3, p=0.41) between months 1 and 36, and 3.6±3.3 (n=200) versus 3.9±2.7 (n=102) (difference −0.3, 95% CI of difference −1.0 to 0.4, p=0.43) between months 25 and 36 (standard care). Over 36 months, BCVA change was −19.7±18.5 letters in the EMB group and −4.8±12.5 in the ranibizumab group (difference −14.9, 95% CI of difference −18.5 to −11.2, p<0.0001). The month 36 BCVA of 20 EMB-treated participants with microvascular abnormalities (MVAs) at month 24 was similar to EMB-treated participants without MVAs (−21.8 vs −19.4 letters, p=0.65).

Conclusion EMB does not reduce the number of anti-vascular endothelial growth factor (VEGF) injections, either within or outside of a trial setting, and is associated with worse BCVA than anti-VEGF monotherapy.

Trial registration number NCT01006538.

INTRODUCTION

Radiation is known to inhibit the actively proliferating cells involved in the pathogenesis of neovascular age-related macular degeneration (nAMD), including endothelial cells, inflammatory cells and fibroblasts.[1 2] Consequently, devices have been designed to deliver radiation to eyes with nAMD. These aim to reduce or eliminate disease activity, and thereby reduce the need for treatment with drugs targeting vascular endothelial growth factor (VEGF), the current standard of care.

Epimacular brachytherapy (EMB) uses a handheld surgical device positioned over the macula during vitrectomy, delivering 24 Gray over approximately 3 min.[3] Subsequently, a robotically controlled system was designed to deliver 16–24 Gray of stereotactic radiotherapy (SRT) via a non-surgical, transscleral approach (IRay, Carl Zeiss Meditec, Jena, Germany).[4] More recently, a handheld device has been developed to deliver 24 Gray of radiation over approximately 5 min, using a curved episcleral probe that is positioned behind the macula, via a conjunctival incision (Salutaris, Tucsan, AZ; ClinicalTrials.gov identifier: NCT02988895).[5 6]

The Macular Epiretinal Brachytherapy vs ranibizumab (Lucentis) Only Treatment (MERLOT) trial was a 24-centre, pivotal, randomised, controlled surgical device trial that investigated the safety and efficacy of EMB in patients with chronic, active nAMD. The trial compared EMB with as needed ranibizumab versus as needed ranibizumab monotherapy. The central hypothesis was that EMB would reduce the number of anti-VEGF injections, while maintaining stable vision. Results at month 12 and month 24 showed no reduction in the number of ranibizumab injections, and inferior best-corrected visual acuity (BCVA) compared with the control group.[7 8]

After month 24, MERLOT participants reverted to standard care, returning for a final study visit at month 36. The month 36 review was primarily to assess safety, as the microvascular changes caused by radiation treatment typically have delayed onset.[7–12] It also provides insight into the impact of EMB outside of a trial setting, and the long term efficacy of EMB, since the benefits of radiation therapy may have delayed onset. Herein, we report the month 36 results of the MERLOT study.

METHODS

Study design

The design of MERLOT trial has been previously published .[7 8] In summary, MERLOT was

an investigator-initiated, multicentre, pivotal, two-group, randomised controlled surgical device trial (ClinicalTrials.gov identifier: NCT01006538). From 10 November 2009 to 30 January 2012, 363 patients were recruited from 24 UK National Health Service hospitals. National Research Ethics Committee approval covered all sites, the study complied with the Declaration of Helsinki[13] and all participants provided written informed consent. The study protocol is available as online supplemental material.

Participants

To be eligible, participants had to have active neovascular AMD and to have completed a loading phase of three anti-VEGF injections followed by as-required anti-VEGF therapy, with a minimum of four ranibizumab injections in the previous 12 months or two ranibizumab injections in the previous 6 months prior to screening. Full inclusion and exclusion criteria are described in online supplemental eAppendix 1. Participants did not receive any incentives.

Randomisation, treatment and follow-up

Participants were randomised using a commercial system (MedSciNet Studies, MedSciNet AB) in a 2:1 ratio to EMB plus monthly as-required ranibizumab (n=244) or monthly as-required ranibizumab monotherapy (n=119). Participants randomised to EMB received 24 Gray of beta radiation, delivered via a strontium-90 probe (NeoVista) following a full pars plana vitrectomy (20, 23 or 25-gauge). The radiation was targeted at the area of maximal activity determined on fluorescein angiography (FFA).[3 7]

If at least one of the pre-defined anti-VEGF retreatment criteria (online supplemental eAppendix 2) was met at baseline, participants in either arm received an intravitreal ranibizumab injection (0.5 mg) (Lucentis, Novartis, Frimley, UK). Participants in both arms were then followed up monthly for 24 months, and received as-required intravitreal ranibizumab using the same retreatment criteria.

Thereafter, participants reverted to standard clinical care, but returned for one further study visit at month 36, mainly to assess safety, but also to analyse 'real-world' efficacy outcomes. During this interval, the retreatment criteria and anti-VEGF drug (ranibizumab or aflibercept (Eylea, Regeneron Pharmaceuticals, NY, USA)) were determined by the attending clinician according to their standard practice at that time. Protocol refraction and BCVA testing using the ETDRS chart and methodology, ocular examination and optical coherence tomography (OCT) were performed at month 36. The OCTs were assessed by the treating clinician at each study visit, with masked central Reading Centre analysis of OCT and FFA images from baseline, months 12 and 24.

Outcome measures

The outcome measures were the same as those used for months 12 and 24.[7 8] The co-primary outcome was the mean change in BCVA from baseline to month 36 and the mean number of as-required anti-VEGF injections per participant, per year. Secondary efficacy outcomes were the percentage of participants losing fewer than 15 ETDRS letters, gaining 0 or more letters and 15 or more letters.

Safety outcomes

Safety parameters included all adverse events (AEs) and serious AEs (SAEs) reported up to month 36. Study AEs and SAEs were coded using the Medical Dictionary for Regulatory Activities preferred terms, V.19.0. In addition to full ocular, dilated, slit-lamp examination, investigators were asked to grade any lens opacity using the LOCSII system,[14] and to record the presence or absence of radiation retinopathy.

Subgroup analysis

An exploratory subgroup analysis of the co-primary outcomes mirrored that undertake at months 12 and 24, considering baseline lens status (phakic or pseudophakic), BCVA (≤53 letters or >53 letters), lesion type (predominantly classic, minimally classic or occult) and lesion size (≤3.5 or >3.5 optic disc areas).[7 8]

Statistical analysis

Month 36 efficacy analysis replicated those of month 12 and month 24.[7 8] The BCVA outcome was tested for non-inferiority of the EMB group to the ranibizumab monotherapy group using a 5-letter margin, and the number of ranibizumab retreatments was tested for superiority (fewer injections). To reject the null hypothesis, the EMB group had to have both significantly fewer injections and non-inferior BCVA, hence there was no correction for multiplicity ($p<0.05$).

Analyses of co-primary and BCVA secondary outcomes included all randomised participants (regardless of the study treatment received) using an intent-to-treat approach. We used multiple imputations to impute the month 36 BCVA for the 57 participants missing the month 36 BCVA. Participants with a BCVA of counting fingers (CF) or worse at month 36 visit were not included in the calculation of mean VA for the co-primary VA outcome, but are discussed separately and are considered in the analysis of VA secondary outcomes. No imputation for the number of injections was made for participants who did not complete month 36 visit or had incomplete data.

Analysis of safety outcomes included all participants and was conducted by actual treatment received. The month 36 safety analysis included all AEs and SAEs for the entire duration of the study. Means are presented ±SD unless noted otherwise. Missing data imputation and statistical analysis were performed using SAS software (North Carolina, USA), SPSS Statistics V.24 (IBM Chicago, Illinois, USA) and GraphPad Software (San Diego, California, USA).

RESULTS

Baseline characteristics

Of 363 randomised participants, 309 (85.1%) completed month 36 follow-up, including 207 of 244 (84.8%) in the EMB group and 102 of 119 (85.7%) in the ranibizumab group (online supplemental eFigure 1).

Mean age was 76.5±7.4 years (range 56–96 years): 76.9±7.2 years in the EMB group and 75.8±7.6 in the ranibizumab group. All participants were white, with a greater proportion of females in the EMB group compared with the ranibizumab group (63.5% vs 52.1%).[7 8] The two groups were balanced in terms of baseline ocular characteristics (online supplemental eTable 1).[7 8]

Number of anti-VEGF retreatments

From month 1 to month 36 inclusive (excluding the baseline injection for pre-existing disease activity), participants in the EMB group (n=244) received slightly more anti-VEGF injections than those in the ranibizumab group (n=119): 12.1±8.1 versus 11.4±6.1 (difference 0.7 injections, 95% CI of difference –0.9 to 2.3; p=0.41) (figure 1 and table 1).

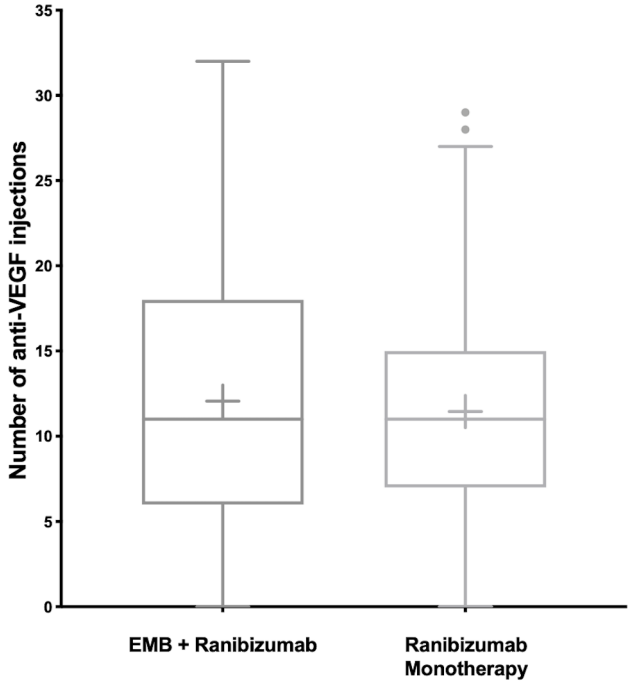

Figure 1 Number of anti-VEGF injections. The box-and-whisker plot shows the number of as-required anti-vascular endothelial growth factor (VEGF) injections given from month 1 to month 36. Until month 24, the anti-VEGF agent was exclusively ranibizumab, and after month 24, the anti-VEGF agent was either ranibizumab or aflibercept. The third and first quartiles are shown by the top and bottom of the box, the median by the line inside the box and the mean by the cross inside the box. The top and bottom error bar shows the values within 1.5 times of the upper and lower quartiles, respectively, with outliers represented as circles. EMB, epimacular brachytherapy; VEGF, vascular endothelial growth factor.

The mean number of anti-VEGF retreatments from months 25 to 36 inclusive, wherein participants were part of routine clinical care, was slightly lower in the EMB group, namely 3.6±3.3 versus 3.9±2.7 (difference −0.3 injections, 95% CI of difference −1.0 to 0.4, p=0.43; data available for 200 in the EMB group and 102 in the ranibizumab group) (table 1). The number of anti-VEGF injections per year, by group is shown in online supplemental eFigure 2.

Visual acuity

As previously reported, the mean change in BCVA was −4.8±10.8 letters in the EMB groupand −0.9±9.7 letters in the ranibizumab group at month 12, and −11.2±15.7 letters in the EMB group and −1.4±10.9 letters in the ranibizumab group at month 24.[7 8] The mean change in BCVA from baseline to month 36 was −19.7±18.5 letters in the EMB group (n=238) and −4.8±12.5 letters in the ranibizumab group (n=119) (difference −14.9 letters, 95% CI of difference −18.5 to −11.2, p<0.0001) (table 1, figure 2 and online supplemental eFigure 3). The mean change in BCVA between month 24 and month 36 was −8.9±12.9 letters in the EMB group (n=238) and −3.4±8.6 letters in the ranibizumab group (n=119) (difference −5.5 letters, 95% CI of difference −8.1 to −2.9 letters, p<0.0001) (table 1). At month 36, six participants in the EMB group had a BCVA of CF or worse: three were hand movement, two perception of light and one no perception of light.

The percentage of participants losing fewer than 15 letters from baseline was 43.9% (107 of 244) in the EMB group versus 79.8% (95 of 119) in the ranibizumab group (difference 35.9%, 95% CI of difference 25.7% to 44.7%, p<0.0001). The percentage of participants gaining 0 or more letters from baseline was 14.3% (35 of 244) in the EMB group versus 34.5% (41 of 119) in the ranibizumab group (difference 20.2%, 95% CI of difference 10.8% to 29.8%, p<0.0001). The percentage of participants gaining 15 or more letters from baseline was 0% (0 out of 244) in the EMB group versus 2.5% (3 of 119) in the ranibizumab group (difference 2.5%, 95% CI of difference 0.2% to 7.2%, p=0.002) (table 1).

Between month 24 and month 36, 75.8% (185 of 244) in the EMB group versus 93.3% (111 of 119) in the ranibizumab group lost fewer than 15 letters (difference 17.5%, 95% CI 10.5% to 24.5%, p<0.0001), 22.1% (54 of 244) versus 38.6% (46 of 119) gained 0 or more letters (difference 16.5%, 95% CI of difference 6.3% to 26.7%, p=0.004) and 0.8% (2 of 244) versus 1.7% (2 of 119) gained 15 letters or more (difference 0.9%, 95% CI of difference −1.7% to 3.4%, p=0.6) (table 1).

Table 1 Primary and secondary outcomes (visual acuity and number of anti-VEGF injections) at month 36

	Baseline to month 36					Month 24 to month 36				
	EMB+ranibizumab group		Ranibizumab monotherapy group			EMB+ranibizumab group		Ranibizumab monotherapy group		
	n	Mean (SD)	n	Mean (SD)	Difference (95% CI)	n	Mean (SD)	n	Mean (SD)	Difference (95% CI)
Co-primary outcomes										
BCVA change, ETDRS letters	238	−19.7 (18.5)	119	−4.8 (12.5)	−14.9 (−18.5 to −11.2)	238	−8.9 (12.9)	119	−3.4 (8.6)	−5.5 (−8.1 to −2.9)
Number of anti-VEGF retreatments*	244	12.1 (8.1)	119	11.4 (6.1)	0.7 (−0.9 to 2.3)	200	3.6 (3.3)	102	3.9 (2.7)	−0.3 (−1.0 to 0.4)
Secondary BCVA outcomes										
<15 ETDRS letter loss (%)	244	107 (43.9%)	119	95 (79.8%)	35.9% (25.7 to 44.7)	244	185 (75.8%)	119	111 (93.3%)	17.5% (10.5 to 24.5)
≥0 ETDRS letter gain (%)	244	35 (14.3%)	119	41 (34.5%)	20.2% (10.8 to 29.8)	244	54 (22.1%)	119	46 (38.6%)	16.5% (6.3 to 26.7)
≥15 ETDRS letter gain (%)	244	0 (0.0%)	119	3 (2.5%)	2.5% (0.2 to 7.2)	244	2 (0.8%)	119	2 (1.7%)	0.9% (−1.7 to 3.4)

Results for co-primary outcomes are based on analysis of covariance model of the change in visual acuity, adjusting for baseline visual acuity, baseline lens status and baseline lesion type.
*Ranibizumab was the anti-VEGF agent administered until month 24. After month 24 when the participants returned to standard care, the anti-VEGF drug was either ranibizumab or aflibercept.
BCVA, best-corrected visual acuity; EMB, epimacular brachytherapy; VEGF, vascular endothelial growth factor.

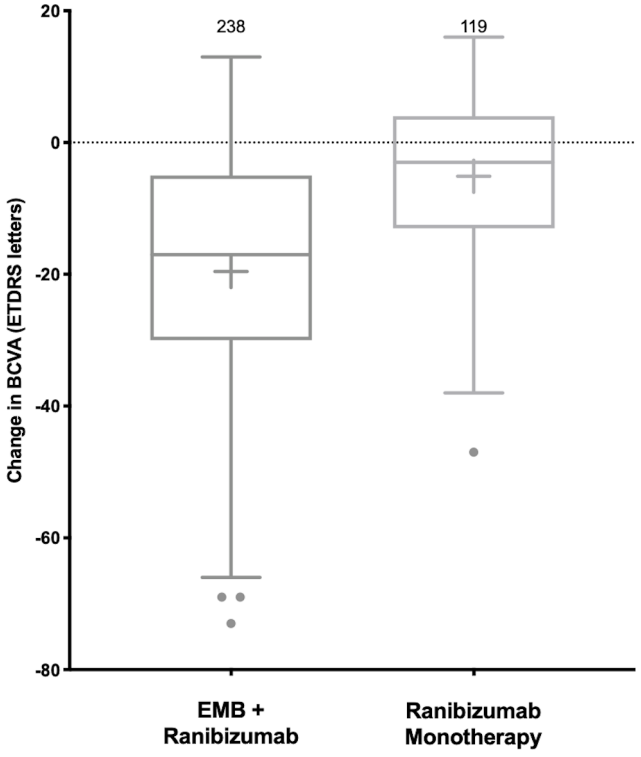

Figure 2 Visual acuity. The image shows a box-and-whisker plot of the change in ETDRS best-corrected visual acuity (BCVA) at month 36, in the epimacular brachytherapy and ranibizumab monotherapy groups. The box conventions are the same as for figure 1. EMB, epimacular brachytherapy.

Subgroup analysis

Subgroup analysis of the number of injections received from month 1 to month 36 (including study and standard care injections) shows that most subgroups favoured the ranibizumab monotherapy, with the exception of predominantly classic and small lesions (online supplemental eFigure 4).

With respect to the mean BCVA co-primary outcome, at month 36 participants in the EMB group lost significantly more letters compared with participants in the ranibizumab group irrespective of the pre-defined subgroup (online supplemental eFigure 5).

Post hoc analysis

In view of the worse BCVA in the EMB compared with ranibizumab group within and outside trial settings, we performed a post hoc analysis of several angiographic characteristics between the two groups at month 24. We found no significant difference between month 24 change in the area of fibrosis (0.8±5.4 vs 1.6±6.1 mm^2, p=0.36), atrophic scar (1.2±5.1 vs 0.5±3.9 mm^2, p=0.79) or geographic atrophy (0.1±0.9 vs 0.03±0.23 mm^2, p=0.59) between the EMB and ranibizumab groups.

Safety

Study eye AEs up to month 36 are listed in online supplemental eTable 2. Clinically significant cataract was the most frequently recorded study eye AE, occurring in 167 out of 174 (95.9%) phakic eyes in the EMB group and 29 of 90 (32.2%) phakic eyes in the ranibizumab group. Cataract surgery occurred in 147 out of 174 (84.5%) phakic eyes in the EMB group and in 20 out of 90 (22.2%) phakic eyes in the ranibizumab group.

Study eye SAEs occurring during the study period and their relatedness to treatment are shown in online supplemental eTable 3. The most frequent study eye SAE was retinal detachment which occurred in five participants in the EMB group, followed by significant retinal haemorrhage occurring in four participants in the EMB group versus one participant in the ranibizumab group. One case of endophthalmitis in the EMB group occurred following cataract surgery, as detailed previously.[7]

All other AEs, including those occurring in the non-study eye, are described in online supplemental eTable 4. The proportion of non-ocular AEs and non-study eye AEs was similar between the two treatment groups. Online supplemental eTable 2 shows all SAEs, excluding those that occurred in the study eye. During the study period, there were 15 deaths in the EMB group (6.1%) and 8 deaths in the ranibizumab group (6.7%). The incidence of malignant tumours (including metastases) was similar between the EMB and ranibizumab groups (11.1% vs 10.9%).

Radiation retinopathy was reported by investigators in 3 out of 244 participants (1.2%) in the EMB group (one case at month 24 also reported by the Reading Centre, and two cases at the month 36 visit). The BCVA for the two participants with investigator-reported radiation retinopathy at month 36 improved by 3 ETDRS letters in one participant and decreased by 23 ETDRS letters in the other.

The BCVA for the 20 EMB-treated participants who were identified by the Reading Centre as having retinal microvascular abnormalities (MVAs) at month 24 visit[8] did not differ significantly at month 36 compared with EMB-treated participants without MVAs at month 24 (−21.8 vs −19.4 letters, p=0.65). All nine of the participants with foveal MVAs at month 24 lost 15 ETDRS letters or more by month 36, compared with 3 out of 11 of those with extrafoveal MVAs. Out of the six participants with BCVA worse than CF at month 36, only one participant (HM at month 36) had Reading Centre reported MVAs at month 24.

DISCUSSION

The month 36 visit of the MERLOT trial was primarily intended to monitor safety, but a description of the efficacy outcomes (BCVA and number of injections) was performed to explore the effects of EMB in the context of standard care, and to assess longer term efficacy.

At month 36, participants in the EMB group had significantly worse BCVA than those in the control group (−19.4 vs −4.7 letters). Further, EMB failed to reduce the number of anti-VEGF injections that participants required (12.1 in the EMB group vs 11.4 in the ranibizumab monotherapy group, p=0.41), although there were slightly fewer injections in the EMB group during standard care (3.6 vs 3.9, p=0.43). The greater decline in the visual acuity in the EMB group compared with the control group may be partially explained by the greater increase in total lesion size and choroidal neovascularisation (CNV) size (4.1 vs 2.1 mm^2, p=0.04, and 2.6 vs 0.04 mm^2, p=0.02, respectively) observed at month 24.[15] While FFA was not performed at month 36, it is expected that the increase in TLS and CNV size at month 24 persisted during the third year and partially explains the visual decline in the EMB group. Although other angiographic characteristics were not pre-defined outcomes, in a post hoc analysis there was no significant difference between the change in area of fibrosis, atrophy or atrophic scar at month 24 between the two groups.

There were more AEs and SAEs in the EMB group, driven largely by a greater incidence of cataract. The dose of radiation

received by ocular tissue decreases exponentially with increasing distance from the strontium source. Thus, the dose of radiation received by the lens is very low, and it seems likely that the higher incidence of cataract was due to vitrectomy, which is known to cause cataract in a majority of phakic eyes.[16] The proportion of participants with neoplasia was similar between the two arms, which is expected given the very low dose of radiation beyond the treatment zone. The rate of retinal detachment (2%) was similar to that reported following vitrectomy for macular surgery.[17] Thus, the AEs and SAEs in MERLOT did not identify any unexpected safety concerns.

The main risk of EMB is retinal MVAs. These are often hard to detect on fundus examination, with investigators detecting retinal radiation damage in only one case in year 2 and two in year 3, giving an overall incidence of 1.2%. By contrast, the reading centre detected MVAs on FFA in 8% of cases. Overall, those with MVAs had very similar BCVA to those who did not, although in 3.7% of the EMB group the MVAs involved the foveal area, and these participants had all lost vision by month 36.

EMB safety after 36 months has been previously reported in a small, prospective, non-randomised clinical study.[18] Thirty-four participants received EMB, with 19 followed up to month 36. EMB was found to be safe, with BCVA improved by +3.9 letters compared with baseline. Only one case developed MVAs, but these did not affect vision. The difference in VA between MERLOT and this small study might be partially explained by the fact that MERLOT enrolled patients with chronic, active nAMD, compared with the treatment-naïve participants enrolled in the uncontrolled study.[18]

Similar results to MERLOT have been reported when EMB was used outside of a clinical trial setting. A retrospective, single-centre report of EMB for unresponsive nAMD showed a −8 letters change in BCVA and 5.5 anti-VEGF injections throughout 1 year.[19]

Unlike EMB, SRT was shown to benefit patients with chronic, active nAMD in the IRay in conjunction with Anti-VEGF treatment for Patients with Wet AMD (INTREPID) study.[4 20] The INTREPID study recruited similar patients to MERLOT and met its primary outcome—participants in the radiotherapy arms received significantly fewer ranibizumab retreatments than those in the sham arm.

The main difference between MERLOT and INTREPID is the technology used to deliver radiation. With EMB, the effective dose of radiation delivered to tissue relies on accurate positioning of the strontium source in the area of maximal disease activity determined on FFA, which may be difficult to locate, particularly for occult lesions, representing the majority of those in the MERLOT population. Also, SRT avoids vitrectomy which causes cataract[16] and decreases the half-life of anti-VEGF agents which may reduce their therapeutic effect.[21 22]

Strengths of our study include its size and multicentre, randomised design, long-term follow-up with good retention rate, an independent reading centre analysis of angiography and OCTs at the study milestones (baseline, months 12 and 24) and an estimate of the effect of EMB in the real world at month 36. Limitations include a lack of masking of patients and investigators, as it was not possible to mask participants or doctors to vitrectomy. The lack of FFA and reading centre analysis of MVAs at month 36 means subclinical MVAs may have gone unnoticed.

In conclusion, long-term follow-up at 36 months indicates that EMB is associated with significantly worse vision than standard of care, and it does not reduce the number of anti-VEGF injections that patients require either within, or outside of a trial setting. These findings do not support the use of EMB for chronic active nAMD.

Author affiliations
[1]Faculty of Life Sciences and Medicine, King's College London, London, UK
[2]King's Ophthalmology Research Unit (KORU), King's College Hospital, London, UK
[3]NetwORC UK, Central Angiographic Reading Centre, Queen's University Belfast, Belfast, UK
[4]Reading Centre, Moorfields Eye Hospital NHS Foundation Trust, London, UK
[5]Department of Ophthalmology, Maidstone Hospital, Maidstone, UK
[6]Department of Ophthalmology, Bristol Eye Hospital, Bristol, UK
[7]Department of Ophthalmology, Hull Royal Infirmary, Hull, UK
[8]Department of Ophthalmology, Sunderland Eye Infirmary, Sunderland, UK
[9]Biosciences Institute, Newcastle University, Newcastle Upon Tyne, UK

Twitter Cristina Soare @cris_soare11

Acknowledgements We thank the members of the MERLOT study group, the Reading Centre Clinicians, the Data Monitoring Committee and Trial Steering Committee members and Trial Participants.

Collaborators The MERLOT Study Group Collaborators: Fiona Bishop, St James' University Hospital, Leeds. Edward Doyle, Torbay Hospital, Devon. Ibraheem Elghrably, James Cook University Hospital, Middlesbrough. Rajen Gupta, Royal Victoria Infirmary, Newcastle. Simon Harding, NetwORC UK, University of Liverpool, Liverpool. Heinrich Heimann, Royal Liverpool Hospital, Liverpool. Edward Hughes, Sussex Eye Hospital, Brighton. Afsar Jafree, William Harvey Hospital, Ashford. Niral Karia, Southend University Hospital, Southend. Pauline Lenfesty, NetwORC UK, University of Liverpool, Liverpool. Vineeth Kumar, Arrowe Park Hospital, Merseyside. Andrew Lotery, Southampton General Hospital, Southampton. Anthony O'Driscoll, Warwick Hospital, Warwick. Jignesh Patel, Essex County Hospital, Essex. Wallace Poon, William Harvey Hospital, Ashford. Som Prasad, Arrowe Park Hospital, Merseyside. Michael Quinn, Central Angiographic Reading Centre, Queen's University of Belfast, Belfast, United Kingdom. Vasant Raman, Royal Eye Infirmary, Plymouth. Steven Rowley, Royal Bournemouth Hospital, Bournemouth. Jayashree Sahni, NetwORC UK, University of Liverpool, Liverpool. David Schultz, William Harvey Hospital, Ashford. Richard Sheard, Royal Hallamshire Hospital, Sheffield. Peter Simcock, Royal Devon&Exeter Hospital, Wonford. Paulo Stanga, Manchester Royal Eye Hospital, Manchester. Saju Thomas, Darlington Memorial Hospital, Darlington. Yit Fung Yang, Queen Alexandra Hospital, Portsmouth

Contributors TLJ was Chief Investigator, wrote the MERLOT protocol and drafted the manuscript. CS undertook the statistical analysis and helped prepare the manuscript. AS, JEN and RP were consecutive MERLOT clinical fellows who helped design and implement trial amendments, execute the trial and helped prepare the manuscript. KAM, TP and UC designed the image analysis protocol, and oversaw the image analysis. LM, RH, MC and DHWS were the principal investigators at the four best recruiting sites. RD managed the trial and helped prepare the manuscript. TLJ is the guarantor.

Funding Funded by an unrestricted research grant from NeoVista and supported by the National Institute of Health Research Comprehensive Clinical Research Network.

Competing interests TLJ received conference support and his employer received unrestricted research grant support from NeoVista. NeoVista had no role in data collection, analysis, or in the preparation or review of this manuscript. TLJ's employer received free use of equipment from Oraya for an investigator-initiated trial of SRT, and his employer received research funding from Novartis for an unrelated project. His employer receives site payments for participants enrolled in various commercial clinical trials of AMD.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by South West Research Ethics Committee (REC)(Research Ethics Service, Royal Devon and Exeter Hospital, Gladstone Road, Exeter, EX1 2ED), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation. REC No: 09/HO206/21. Prior to recruitment of any subjects into the study at each participating site, Site Specific Approval (SSA) and NHS Research and Development approval was also obtained. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Not applicable.

of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Timothy L Jackson http://orcid.org/0000-0001-7618-1555
Cristina Soare http://orcid.org/0000-0002-4533-0105
Tunde Peto http://orcid.org/0000-0001-6265-0381

REFERENCES

1 Kirwan JF, Constable PH, Murdoch IE, *et al*. Beta irradiation: new uses for an old treatment: a review. *Eye* 2003;17:207–15.
2 Chakravarthy U, Houston RF, Archer DB. Treatment of age-related subfoveal neovascular membranes by teletherapy: a pilot study. *Br J Ophthalmol* 1993;77:265–73.
3 Dugel PU, Petrarca R, Bennett M, *et al*. Macular epiretinal brachytherapy in treated age-related macular degeneration: MERITAGE study: twelve-month safety and efficacy results. *Ophthalmology* 2012;119:1425–31.
4 Jackson TL, Chakravarthy U, Kaiser PK, *et al*. Stereotactic radiotherapy for neovascular age-related macular degeneration: 52-week safety and efficacy results of the INTREPID study. *Ophthalmology* 2013;120:1893–900.
5 Hamilton R, Cetas T, Gordon J, *et al*. SU-E-T-308: dosimetry of a new minimally invasive episcleral brachytherapy device. *Med Phys* 2012;39:3774.
6 Balaggan KSR, Joffe L, Patel P. Novel Minimally-Invasive episcleral brachytherapy for the treatment of neovascular age-related macular degeneration (nAMD): results of a twelve month prospective phase I safety and tolerability evaluation. ARVO Annual Meeting, Seattle, USA, 2013.
7 Jackson TL, Desai R, Simpson A, *et al*. Epimacular brachytherapy for previously treated neovascular age-related macular degeneration (MERLOT): a phase 3 randomized controlled trial. *Ophthalmology* 2016;123:1287–96.
8 Jackson TL, Soare C, Petrarca C, *et al*. Evaluation of month-24 efficacy and safety of epimacular brachytherapy for previously treated neovascular age-related macular degeneration. *JAMA Ophthalmol* 2020;138:835.
9 Dugel PU, Bebchuk JD, Nau J, *et al*. Epimacular brachytherapy for neovascular age-related macular degeneration: a randomized, controlled trial (Cabernet). *Ophthalmology* 2013;120:317–27.
10 Petrarca R, Dugel PU, Bennett M, *et al*. Macular epiretinal brachytherapy in treated age-related macular degeneration (MERITAGE): month 24 safety and efficacy results. *Retina* 2014;34:874–9.
11 Jackson TL, Dugel PU, Bebchuk JD, *et al*. Epimacular brachytherapy for neovascular age-related macular degeneration (Cabernet): fluorescein angiography and optical coherence tomography. *Ophthalmology* 2013;120:1597–603.
12 Petrarca R, Dugel PU, Nau J, *et al*. Macular epiretinal brachytherapy in treated age-related macular degeneration (MERITAGE): month 12 optical coherence tomography and fluorescein angiography. *Ophthalmology* 2013;120:328–33.
13 World Medical Association. World Medical association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–4.
14 Chylack LT, Leske MC, Khu P, *et al*. Strategies for measuring the rate of age-related cataract formation in vivo. *Lens Eye Toxic Res* 1989;6:515–22.
15 Jackson TL, Soare C, Petrarca C, *et al*. 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* 2020;138:835–42.
16 Jackson TL, Donachie PHJ, Sparrow JM, *et al*. United Kingdom national ophthalmology database study of vitreoretinal surgery: report 1; case mix, complications, and cataract. *Eye* 2013;27:644–51.
17 Jackson TL, Donachie PHJ, Sparrow JM, *et al*. United Kingdom national ophthalmology database study of vitreoretinal surgery: report 2, macular hole. *Ophthalmology* 2013;120:629–34.
18 Avila MP, Farah ME, Santos A, *et al*. Three-year safety and visual acuity results of epimacular 90 strontium/90 yttrium brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2012;32:10–18.
19 Zur D, Loewenstein A, Barak A. One-year results from clinical practice of epimacular strontium-90 brachytherapy for the treatment of subfoveal choroidal neovascularization secondary to AMD. *Ophthalmic Surg Lasers Imaging Retina* 2015;46:338–43.
20 Jackson TL, Chakravarthy U, Slakter JS, *et al*. Stereotactic radiotherapy for neovascular age-related macular degeneration: year 2 results of the INTREPID study. *Ophthalmology* 2015;122:138–45.
21 Kakinoki M, Sawada O, Sawada T, *et al*. Effect of vitrectomy on aqueous VEGF concentration and pharmacokinetics of bevacizumab in macaque monkeys. *Invest Ophthalmol Vis Sci* 2012;53:5877–80.
22 Chen Y-Y, Chen P-Y, Chen F-T, *et al*. Comparison of efficacy of intravitreal ranibizumab between non-vitrectomized and vitrectomized eyes with diabetic macular edema. *Int Ophthalmol* 2018;38:293–9.