JAMA Ophthalmology | Original Investigation

Comparison of Ranibizumab With or Without Verteporfin Photodynamic Therapy for Polypoidal Choroidal Vasculopathy
The EVEREST II Randomized Clinical Trial

Tock H. Lim, MBBS; Timothy Y. Y. Lai, MD; Kanji Takahashi, MD; Tien Y. Wong, MD, PhD; Lee-Jen Chen, MD; Paisan Ruamviboonsuk, MD; Colin S. Tan, MD; Won Ki Lee, MD, PhD; Chui Ming Gemmy Cheung, MBBS; Nor Fariza Ngah, MS; Ramune Patalauskaite, MSc; Philippe Margaron, PhD; Adrian Koh, MD; for the EVEREST II Study Group

IMPORTANCE The 2-year efficacy and safety of combination therapy of ranibizumab administered together with verteporfin photodynamic therapy (vPDT) compared with ranibizumab monotherapy in participants with polypoidal choroidal vasculopathy (PCV) are unclear.

OBJECTIVE To compare treatment outcomes of ranibizumab, 0.5 mg, plus prompt vPDT combination therapy with ranibizumab, 0.5 mg, monotherapy in participants with PCV for 24 months.

DESIGN, SETTING, AND PARTICIPANTS This 24-month, phase IV, double-masked, multicenter, randomized clinical trial (EVEREST II) was conducted among Asian participants from August 7, 2013, to March 2, 2017, with symptomatic macular PCV confirmed using indocyanine green angiography.

INTERVENTIONS Participants (N = 322) were randomized 1:1 to ranibizumab, 0.5 mg, plus vPDT (combination therapy group; n = 168) or ranibizumab, 0.5 mg, plus sham PDT (monotherapy group; n = 154). All participants received 3 consecutive monthly ranibizumab injections, followed by a pro re nata regimen. Participants also received vPDT (combination group) or sham PDT (monotherapy group) on day 1, followed by a pro re nata regimen based on the presence of active polypoidal lesions.

MAIN OUTCOMES AND MEASURES Evaluation of combination therapy vs monotherapy at 24 months in key clinical outcomes, treatment exposure, and safety. Polypoidal lesion regression was defined as the absence of indocyanine green hyperfluorescence of polypoidal lesions.

RESULTS Among 322 participants (mean [SD] age, 68.1 [8.8] years; 225 [69.9%] male), the adjusted mean best-corrected visual acuity (BCVA) gains at month 24 were 9.6 letters in the combination therapy group and 5.5 letters in the monotherapy group (mean difference, 4.1 letters; 95% CI, 1.0–7.2 letters; P = .005), demonstrating that combination therapy was superior to monotherapy by the BCVA change from baseline to month 24. Combination therapy was superior to monotherapy in terms of complete polypoidal lesion regression at month 24 (81 of 143 [56.6%] vs 23 of 86 [26.7%] participants; P < .001). Participants in the combination group received fewer ranibizumab injections (median, 6.0 [interquartile range (IQR), 4.0-11.0]) than the monotherapy group (median, 12.0 [IQR, 7.0-17.0]) up to month 24. The combination group required a median of 2.0 (IQR, 1.0-3.0) vPDT treatments for 24 months, with 75 of 168 participants (44.6%) requiring only 1 vPDT treatment.

CONCLUSIONS AND RELEVANCE The 24-month data findings confirm that ranibizumab therapy, given as monotherapy or in combination with vPDT, is efficacious and safe for treatment of PCV. Combination therapy with vPDT added to ranibizumab achieved superior BCVA gain, increased odds of complete polypoidal lesion regression, and fewer treatment episodes compared with ranibizumab monotherapy.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01846273.

+ Invited Commentary

+ Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The EVEREST II study group members appear at the end of the article.

Corresponding Author: Tock H. Lim, MBBS, National Healthcare Group Eye Institute, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433 (tock_han_lim@nhg.com.sg).

Polypoidal choroidal vasculopathy (PCV) is generally recognized as a subtype of neovascular age-related macular degeneration characterized by the presence of aneurysmal polypoidal lesions with or without a branching vascular network, as observed using indocyanine green angiography (ICGA).[1-3]

In general, PCV is reported to be more prevalent in the East Asian population, with the prevalence ranging from 22.3% to 61.6%.[4-6] With increased use of multimodality imaging and ICGA, an increase in the frequency of the diagnosis of PCV has been observed across all patient groups, including Western populations.[4,7,8]

Currently, anti-vascular endothelial growth factor (anti-VEGF) agents administered as monotherapy or in combination with verteporfin photodynamic therapy (vPDT) are considered the 2 dominant treatments of choice for the management of PCV.[1,7,9] However, the optimal regimen for PCV is yet to be established. Emerging evidence has shown that PCV responds well to anti-VEGF monotherapy, resulting in a rapid resolution of subretinal fluid or subretinal pigment epithelial retinal fluid and thickening, exudate accumulation, and improvement in vision. However, the polypoidal lesions and associated branching vascular network complex often persist after treatment, resulting in the risk of recurrent bleeding and poor outcome.[10,11] Polypoidal lesion regression has therefore been suggested as an important end point in PCV management.[3]

Combination of anti-VEGF therapy with vPDT aims to achieve a synergistic treatment effect by combining photothrombosis of the polypoidal lesions with anti-vasoproliferative and anti-permeability therapy to maintain vision, close polypoidal lesions, and reduce recurrence. However, vPDT may have detrimental longer-term effects on visual acuity in eyes with recurrent disease.[12]

Few retrospective and case-control studies have investigated the efficacy of combination therapy in participants with PCV.[10,13-16] The first, to our knowledge, randomized, active clinical trial in participants with macular PCV, the EVEREST study,[10] showed that ranibizumab combined with vPDT or vPDT monotherapy was superior to ranibizumab monotherapy in achieving complete polypoidal lesion regression.[10] EVEREST II[11] showed that for 12 months, treatment of PCV with ranibizumab combined with vPDT resulted in greater best-corrected visual acuity (BCVA) improvement and a higher rate of complete resolution of polypoidal lesions, with fewer ranibizumab injections than ranibizumab monotherapy.[11] However, whether the visual outcomes, polypoidal lesion regression rates, and treatment burden were maintained beyond 12 months was unknown. The current study reports on the 24-month EVEREST II outcomes to generate further guidance on the management of symptomatic macular PCV.

Methods

Study Design

The design of the EVEREST II randomized clinical trial (NCT01846273) is available elsewhere (trial protocol in

Key Points

Question What are the differences in treatment outcomes of combination therapy with intravitreal ranibizumab and verteporfin photodynamic therapy vs ranibizumab monotherapy in polypoidal choroidal vasculopathy at month 24?

Findings In the EVEREST II randomized clinical trial, combination therapy was superior to monotherapy in terms of adjusted mean best-corrected visual acuity gain and superior in achieving complete absence of indocyanine green hyperfluorescence of polypoidal lesions with fewer ranibizumab injections.

Meaning These data suggest that ranibizumab plus prompt verteporfin photodynamic therapy is more effective compared with ranibizumab monotherapy for polypoidal choroidal vasculopathy with reduced treatment burden.

Supplement 1).[11] EVEREST II was a 24-month, phase IV, multicenter, randomized, double-masked trial (Figure 1). The trial was conducted in accordance with the Declaration of Helsinki and Tripartite International Council on Harmonization Good Clinical Practice Guidelines,[17] considering applicable local regulations. The trial protocol was reviewed and approved by an independent ethics committee or institutional review board at each participating center. Participants provided written informed consent before entering the trial and received no payment to participate in the study. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

The study population consisted of treatment-naive participants with symptomatic macular PCV from 42 sites in Asia. The diagnosis of PCV in the study eye was confirmed by the Central Reading Center (Fundus Image Reading Center, National Healthcare Group Eye Institute at Tan Tock Seng Hospital, Singapore) using standardized multimodal imaging modified from the EVEREST grading criteria.[9,18]

Figure 1. CONSORT Diagram of Study Participants
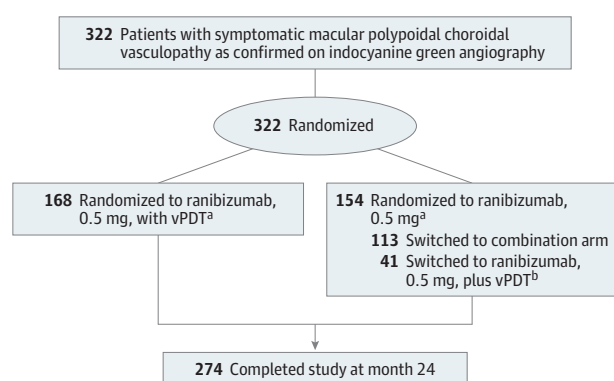
vPDT indicates verteporfin photodynamic therapy.

[a] Primary end point at month 12.

[b] Patients were at different levels of progression in the study at the therapy switch time point, which occurred after month 21 for half of the patients from the switched group.

Randomization and Treatment

All eligible participants were randomized 1:1 to receive ranibizumab, 0.5 mg, combined with standard fluence vPDT (combination therapy; n = 168) or ranibizumab, 0.5 mg, monotherapy with sham PDT (monotherapy; n = 154). The investigators were masked throughout the study. Participants were administered a ranibizumab, 0.5 mg, intravitreal injection on day 1 (baseline visit) and at months 1 and 2, followed by a pro re nata (PRN) regimen according to the protocol-specific retreatment criteria, with an interval between 2 ranibizumab treatments of at least 28 days. The vPDT treatment was based on the ICGA findings, which covered the whole lesion during the initial treatment and targeted only the active portions during subsequent treatments.

The participants in the monotherapy group were eligible to switch to combination therapy in year 2 for ethical reasons to offer therapeutic benefit. However, most (n = 113) of monotherapy group participants had completed the study before the month 12 analysis was concluded. Eligibility to switch for the remaining participants (n = 41) occurred between months 16 and 24, with half of the switch occurring after month 21. Thus, only 14 of 41 participants from the switched group actually received vPDT afterward. Most participants (140 of 154 [90.9%]) assigned to monotherapy at baseline received only ranibizumab therapy throughout 24 months despite the eligibility to switch. For this reason, data are presented for participants (n = 154) randomized to monotherapy at baseline. The data on the 113 participants from the monotherapy arm who completed the study before the implementation of the switch decision overall were similar to those for the randomized arm and are presented in eTables 1-5 and eFigures 1-15 in Supplement 2.

Study Objectives

The primary objectives were met at month 12.[11] For this article, the following prespecified secondary end points up to month 24 were analyzed, including (1) changes in BCVA during 24 months and categorization of these changes; (2) the proportion of participants with complete polypoidal lesion regression (assessed by ICGA) at month 24 and those with presence of leakage (assessed by fluorescein angiography) at month 24; (3) changes in central subfield thickness from baseline to month 24; (4) the number of ranibizumab injections and vPDT received in the study eye before month 24; and (5) safety and tolerability of both treatments up to month 24.

Statistical Analysis

The secondary efficacy analyses were conducted on the study eye of the participants in the full analysis set (all participants assigned to the treatment regimen). The first objective was to demonstrate that combination therapy was noninferior to monotherapy as assessed by the BCVA change from baseline at month 24 and superior with respect to complete polypoidal lesion regression at month 24 (at an overall 1-sided α level of .025). The chosen margin of 5 letters was consistent with other noninferiority trials of neovascular age-related macular degeneration.[19-21] After this condition was satisfied, a su-periority test with a 1-sided α level of .025 was performed with respect to BCVA change from baseline at month 24. With this hierarchical testing strategy, the overall 1-sided α (family-wise error rate) was maintained at .025.

An analysis of covariance model including treatment group as a factor and (centered) baseline BCVA as a continuous variable was used for testing noninferiority or superiority of adjusted mean BCVA change from baseline. The Fisher exact test was used to evaluate superiority with respect to complete polypoidal lesion regression. No missing data imputation method was applied.

Other efficacy assessments, safety analysis, exposure to treatment, demographics, and baseline characteristics are presented descriptively. Safety assessments (adverse events, deaths) were reported for the safety set (all participants who received at least 1 application of study drugs and had at least 1 postbaseline safety assessment). Safety assessments are presented for the monotherapy, combination, and switched groups.

Results

Participant Disposition and Baseline Characteristics

Baseline demographics were comparable between the treatment groups. Among 322 participants, the mean (SD) age of participants was 68.1 (8.8) years and 225 of 322 (69.9%) were male.

Of the 322 participants randomized to receive combination therapy (n = 168) or monotherapy (n = 154), 274 (85.1%) completed the 24-month study, including 146 of 168 (86.9%) in the combination therapy group and 128 of 154 (83.1%) in the monotherapy group. The most common reasons for study discontinuation were adverse events (16 of 322 [5.0%]) and consent withdrawal (13 of 322 [4.0%]) (eTable 1 in Supplement 2). The mean (SD) baseline BCVA letter score was 61.1 (approximate Snellen equivalent 20/63) (13.2), and the mean (SD) central subfield thickness was 413.3 (157.2) μm.[11]

Efficacy

Visual Outcomes

Mean BCVA improved in both combination and monotherapy groups from baseline to month 24. At month 24, the least-squares mean (SE) improvement from baseline was 9.6 (1.0) letters in the combination therapy and 5.5 (1.2) letters in the monotherapy, with between-group mean difference of 4.1 letters (95% CI, 1.0-7.2 letters), demonstrating both 1-sided noninferiority ($P < .001$) and superiority ($P = .005$) of combination therapy to monotherapy. The BCVA gains achieved at month 12 were maintained to 24 months (**Figure 2** and eFigure 1 in Supplement 2). Of 146 participants in the combination group, 75 (51.4%) and 45 (30.8%) showed a BCVA gain of at least 10 letters and at least 15 letters at month 24, respectively; of 128 participants in the monotherapy, 50 (39.1%) and 31 (24.2%) showed a BCVA gain of at least 10 letters and at least 15 letters at month 24, respectively (eFigures 2 and 3 in Supplement 2).

Figure 2. Mean Best-Corrected Visual Acuity (BCVA) Gain Up to Month 24 in the Combination and Monotherapy Groups
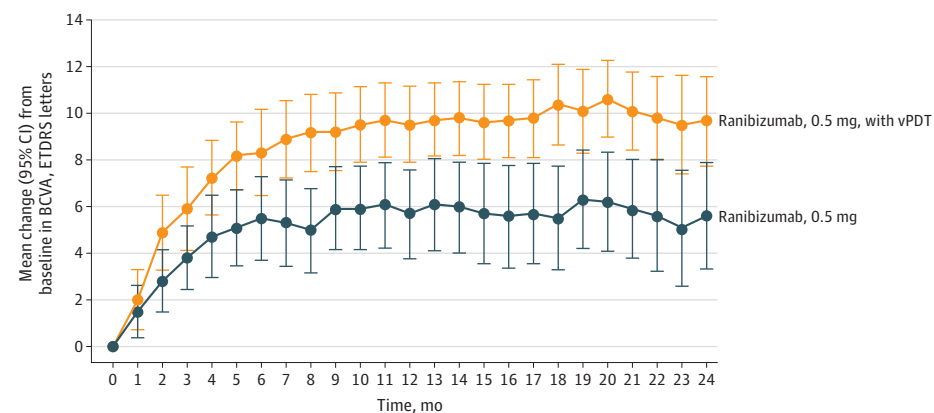
Data on the full analysis set are shown. Change from baseline was calculated as the number of participants with a value for both baseline and specific postbaseline visits. During year 2, 41 participants randomized to ranibizumab, 0.5 mg, were switched to ranibizumab, 0.5 mg, plus vPDT, but only 14 from the switched group had at least 1 treatment after the switch. ETDRS indicates Early Treatment Diabetic Retinopathy Study; vPDT, verteporfin photodynamic therapy.

Anatomical Outcomes

Improvements in complete polypoidal lesion regression were observed with both the combination and monotherapy groups. However, combination therapy was superior to monotherapy with respect to complete polypoidal lesion regression assessed by ICGA at month 24 (81 of 143 [56.6%] vs 23 of 86 [26.7%] participants; *P* < .001) (eTable 2 in Supplement 2). Complete polypoidal regression was achieved by month 3 in 115 of 161 participants (71.4%) in the combination therapy group (eFigures 4 and 5 in Supplement 2). At month 24, 19 of 40 switched group participants (47.5%) showed complete polypoidal lesion regression compared with 23 of 86 of those (26.7%) who were not switched (eFigure 5 in Supplement 2).

At month 24, the mean (SD) central subfield thickness reduction from baseline was greater in the combination group than in the monotherapy group (−152.9 [129.7] μm vs −109.3 [142.2] μm) (eFigures 6 and 7 in Supplement 2). A higher proportion of participants in the combination group showed absence of leakage on fluorescein angiography compared with the monotherapy group (84 of 146 [57.5%] vs 41 of 128 [32.0%]) (eFigures 8 and 9 in Supplement 2). Similarly, the proportion of participants with disease activity at month 23 was lower in the combination group (27.0% [40 of 148]) than in the monotherapy group (54.3% [69 of 127]) (eFigures 10 and 11 in Supplement 2).

At month 24, serosanguinous hemorrhage was present in 16 of 146 participants (11.0%) in the combination therapy group and 17 of 127 participants (13.4%) in the monotherapy group (eFigures 12 and 13 in Supplement 2). Submacular hemorrhage in more than 4 disc areas was reported in 1 of 146 participants (0.7%) in the combination group and 1 of 127 (0.8%) in the monotherapy group (eFigures 14 and 15 in Supplement 2).

Treatment Exposure

The median number of ranibizumab injections administered up to month 24 was 6.0 in the combination group (interquartile range [IQR], 4.0-11.0) and 12.0 in the monotherapy group (IQR, 7.0-17.0). The mean (SD) number of ranibizumab injections administered up to month 24 was 8.1 (5.2) in the com-

bination group and 12.5 (6.7) in the monotherapy group. In the monotherapy group, 30 of 154 participants (19.5%) required 20 to 24 injections for 24 months compared with 7 of 168 participants (4.2%) in the combination group, whereas 51 of 168 participants (30.4%) in the combination group required 3 to 4 ranibizumab injections (0 or 1 additional injection with the mandatory 3 loading doses) compared with 20 of 154 participants (13.0%) in the monotherapy group (**Figure 3**A). The median number of ranibizumab injections between months 12 and 24 was 2.0 (IQR, 0-5.0) in the combination group and 5.0 (IQR, 0-9.0) in the monotherapy group. Between months 12 and 24, 63 of 168 participants (37.5%) required no ranibizumab injection in the combination therapy group compared with 41 of 154 participants (26.6%) in the monotherapy group. Only 7 of 168 participants (4.2%) in the combination group required 11 to 12 injections compared with 26 of 154 participants (16.9%) in the monotherapy group between months 12 and 24.

The median number of vPDT treatments up to 24 months in the combination group was 2.0 (IQR, 1.0-3.0), and the total of sham and vPDT treatments in the monotherapy group was 3.0 (IQR, 2.0-6.0). The mean (SD) number of vPDT treatments administered up to month 24 was 2.2 (1.4) in the combination group and the total of sham and vPDT treatments was 3.7 (2.3) in the monotherapy group. The median number of vPDT or sham PDT received from months 12 to 24 in the combination group was 0 (IQR, 0-1.0) and in the monotherapy group was 1.0 (IQR, 0-3.0). Overall, 75 of the 168 participants (44.6%) in the combination group needed vPDT only once during 24 months (Figure 3B).

Safety

Ocular adverse events of the study eye regardless of study drug relationship were reported in 64 of 172 participants (37.2%) in the combination group, 49 of 135 participants (36.3%) in the monotherapy group, and 8 of 14 (57.1%) in the switched group (eTable 3 in Supplement 2). No severe or sudden vision loss was reported among participants after vPDT treatment.

Nonocular adverse events regardless of study drug relationship were reported in 94 participants (54.7%) in the

Figure 3. Treatments Received Up to Month 24 in the Combination and Monotherapy Groups
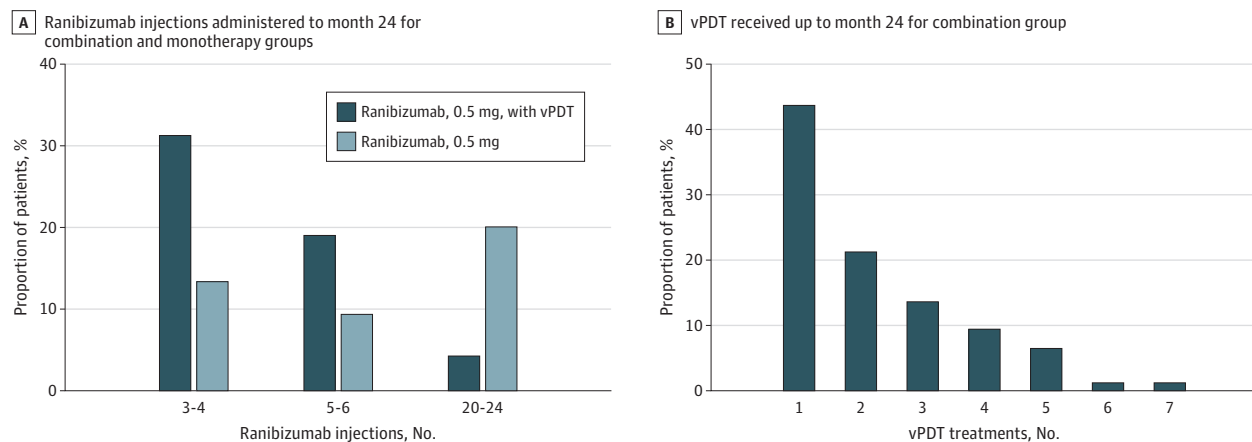
Data on the full analysis set are shown. A, Percentages are based on the total number of participants in the respective treatment group, with 168 in the combination treatment group and 154 in the monotherapy group. B,

Percentages are based on the total number of participants in the combination treatment group (n = 168). vPDT indicates verteporfin photodynamic therapy.

combination group, 72 (53.3%) in the monotherapy group, and 9 (64.3%) in the switched group (eTable 3 in Supplement 2).

Vitreous hemorrhage was the most common ocular serious adverse event, reported in 1 participant (0.6%) in the combination therapy and 3 participants (2.2%) in the monotherapy group. There were no cases of this adverse event in the switched group (eTable 4 in Supplement 2).

Overall, the rates of nonocular serious adverse events reported were comparable between the 3 treatment groups (23 [13.4%] in the combination therapy group, 18 [13.3%] in the monotherapy group, and 2 [14.3%] in the switched group) (eTable 5 in Supplement 2). Two deaths [1.2%] in the combination therapy group and 1 [0.7%] in the monotherapy group were reported but were not suspected to be related to the study treatment.

Discussion

The 24-month results of the EVEREST II trial confirmed that ranibizumab, administered as monotherapy or in combination with vPDT, is efficacious and safe for treatment of PCV. Combination therapy was superior to monotherapy in improving BCVA and superior in achieving complete polypoidal lesion regression in participants with symptomatic macular PCV, with fewer injections for 24 months. These results were consistent with month 12, demonstrating a sustained treatment effect for combination therapy.[11]

In the 12-month Fujisan study (n = 72),[14] participants receiving combination therapy of vPDT with ranibizumab had a BCVA gain of 8.1 letters at baseline and 8.8 letters with deferred vPDT. In contrast, in the Dragon study,[22] participants (n = 139) showed a BCVA gain of 12.3 and 9.7 letters over 24 months with monthly and PRN ranibizumab monotherapy, respectively.[22] The 24-month BCVA gains in the Aflibercept in Polypoidal Choroidal Vasculopathy (PLANET) study[23,24]

(n = 284) were 10.7 letters in aflibercept monotherapy group and 9.1 letters in aflibercept with rescue PDT group. Differences in VA gains across various studies[25] could be attributable to differences in study design and baseline BCVA, an important factor associated with numerical change in BCVA. The baseline BCVA for the ranibizumab monotherapy arm in EVEREST II (61.1 letters) was numerically higher than that in the ranibizumab PRN arm in the Dragon study (54.6 letters) and the aflibercept monotherapy (with sham rescue PDT) arm in the PLANET study (57.7 letters).[11,23] It is therefore possible that the opportunity to gain more letters in EVEREST II may have been limited by a ceiling effect.

A key outcome of the EVEREST trials is the effect on polypoidal lesion regression. In the EVEREST trial, combination therapy was superior to ranibizumab monotherapy in achieving complete polypoidal lesion regression for 6 months (77.8% vs 28.6%, P = .002).[10] Similarly, in EVEREST II, the rates of complete polypoidal lesion regression at months 3, 6, 12, and 24 were consistently higher for combination therapy than for monotherapy at months 3 (71.4% vs 23.3%), 6 (71.3% vs 28.0%), 12 (69.7% vs 33.8%), and 24 (56.6% vs 33.3%). In the Fujisan study, the proportion of participants with complete polypoidal lesion regression at month 12 was in broad agreement with EVEREST II, whether vPDT was given at baseline (62.1%) or deferred (54.8%) (P = .53).[14] These findings strengthen the concept that combination therapy is more efficacious than anti-VEGF monotherapy in achieving higher polypoidal lesion regression rates and superior BCVA outcomes in participants with PCV.

The 24-month results of EVEREST II demonstrated that the switched group participants showed better complete polypoidal lesion regression than did those who were not switched (47.5% vs 26.7%) (eFigure 5 in Supplement 2). These results suggest that vPDT can still be applied even later in the treatment course initiated with ranibizumab monotherapy to achieve polypoidal lesion regression.

In EVEREST II, the occurrence of serosanguinous hemorrhage and submacular hemorrhage decreased over time in both treatment groups, showing that combination therapy did not increase the rates of posttreatment hemorrhage and that the hemorrhage was effectively controlled with regular monitoring and ranibizumab treatment. Participants in the combination group demonstrated either better or similar efficacy than those in the monotherapy group for all other secondary and exploratory outcomes.

In terms of treatment burden, the median number of ranibizumab injections was lower in the combination group (2.0) than the monotherapy group (5.0) even in year 2. This reduction in injection number in the combination group was similar to other studies evaluating combination therapies for the management of PCV.[14,26] Prompt combination therapy may help reduce the treatment burden, which is particularly important in countries where there is limited national financial coverage for anti-VEGF therapies. In the present study, 44.6% of participants in the combination group needed a single initial vPDT treatment for 24 months and 21.4% of participants required 2 vPDT treatments. This number is lower when compared with 5.6 and 5.0 vPDT treatments, respectively, reported by the Treatment of Age-related Macular Degeneration With Photodynamic Therapy and Verteporfin in Photodynamic Therapy study groups[20,27] for 24 months.

In EVEREST II, investigators were encouraged to limit laser application to active portions of the PCV lesion using ICGA guidance in the vPDT retreatment protocol to minimize post-PDT complications. No new safety concerns were identified in this study.

The involvement of a central reading center and the use of predefined criteria for participant identification and diagnosis of PCV was one of the main strengths of EVEREST II. Difficulties in diagnosing PCV, even on ICGA, are reflected by the high rates of screening failure.[28] Focal ICGA hyperfluorescence may be present in cases of retinal angiomatous proliferation, type 2 choroidal neovascularization, central serous chorioretinopathy, and focal retinal pigment epithelial defect, mimicking PCV. Some patients with PCV do not have well-defined polypoidal lesions or have extensive bleeding or large lesion size, making diagnosis difficult.

Limitations

One of the limitations of this trial is that the retreatment in the second year was based on disease activity as assessed by the investigators, which can be subjective. Regular ICGA was not mandated during the second year except the final ICGA performed at the end of study; thus, it is possible that the polypoidal lesion regression rate might not have decreased in the second year if investigators diagnosed active polypoidal lesions, which might have required additional combination therapy. Furthermore, the use of the 3 initial monthly injections is presumptive and based on age-related macular degeneration protocol or treatment guidelines, which may not be necessary in a PCV treatment algorithm. In addition, few participants in the monotherapy arm who were eligible to switch therapy actually received vPDT in the second year. The small numbers preclude adequate analyses of the effect of delayed vPDT on PCV treatment outcomes.

Conclusions

The EVEREST II 24-month results confirmed that the combination of ranibizumab with prompt vPDT was superior in achieving improvement in BCVA and superior in achieving complete polypoidal lesion regression (2 key clinical outcomes for PCV management) compared with monotherapy. These functional and anatomical outcomes were achieved with fewer ranibizumab injections for 24 months, thereby reducing the treatment burden.

Author Affiliations: National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore (Lim, Tan); Fundus Image Reading Centre, National Healthcare Group Eye Institute, Singapore (Lim, Tan); Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, China (Lai); Department of Ophthalmology, Kansai Medical University, Osaka, Japan (Takahashi); Singapore Eye Research Institute, Singapore National Eye Centre, Duke-NUS Medical School, National University of Singapore, Singapore (Wong, Cheung); Department of Ophthalmology, Mackay Memorial Hospital, Taipei, Taiwan (Chen); Department of Ophthalmology, Rajavithi Hospital, Bangkok, Thailand (Ruamviboonsuk); Department of Ophthalmology,

Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, Korea (Lee); Department of Ophthalmology, Hospital Shah Alam, Malaysia (Ngah); Novartis Ireland Ltd, Dublin, Ireland (Patalauskaite); Novartis Pharma AG, Basel, Switzerland (Margaron); Eye & Retina Surgeons, Camden Medical Centre, Singapore (Koh).

Author Contributions: Drs Patalauskaite and Margaron had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Lim, Lai, Wong, Chen, Tan, Lee, Ngah, Koh.
Acquisition, analysis, or interpretation of data: Lim, Lai, Takahashi, Wong, Chen, Ruamviboonsuk, Tan, Lee, Cheung, Patalauskaite, Margaron, Koh.
Drafting of the manuscript: Lim, Wong, Chen, Tan, Patalauskaite.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Patalauskaite, Margaron.
Administrative, technical, or material support: Chen, Ruamviboonsuk, Cheung, Ngah, Patalauskaite, Margaron, Koh.

study; receiving grants and personal fees from Bayer Healthcare and Genentech; receiving personal fees from Roche and Samsung outside the submitted work; being a co-inventor and cofounder of Plano and EyRiS; and being a consultant for Allergan, Bayer Healthcare, Boehringer-Ingelheim, Genentech, Merck, Novartis Pharma AG, Oxurion (formerly ThromboGenics), Roche, and Samsung. Dr Chen reported receiving lecture fees from Bayer Healthcare and personal fees from Novartis Pharmaceuticals outside the submitted work. Dr Ruamviboonsuk reported receiving grants and consulting fees from Bayer Healthcare, Novartis Pharma AG, and Roche. Dr Tan reported receiving personal fees from Novartis Pharma AG during the conduct of the study; receiving nonfinancial support from Heidelberg Engineering; receiving personal fees and nonfinancial support from Bayer Healthcare and Novartis Pharma AG outside the submitted work; and receiving conference support from Allergan, Bayer, and Novartis Pharma AG. Dr Lee reported receiving consulting fees from Allergan, Bayer Healthcare, Boehringer Ingelheim, Novartis Pharma AG, Roche, and Santen outside the submitted work. Dr Cheung reported receiving grants, personal fees, and nonfinancial support from Novartis Pharma AG during the conduct of the study; receiving grants, personal fees, and nonfinancial support from Bayer Healthcare, Boehringer Ingelheim, Topcon, and Carl Zeiss; and receiving personal fees and nonfinancial support from Allergan and Roche during the conduct of the study. Dr Ngah reported receiving lecture fees from Allergan, Bayer Healthcare, and Novartis Pharma AG and receiving research grants from Novartis for the study. Dr Patalauskaite reported being an employee of Novartis Ireland Ltd during the conduct of the study. Dr Margaron reported being an employee of Novartis Pharma AG, Basel, Switzerland, during the conduct of the study. Dr Koh reported receiving consulting fees and honoraria from Alcon, Allergan, Apellis, Bayer, Boehringer Mannheim, Carl Zeiss Meditec, Heidelberg, Novartis Pharma AG, and Topcon.

Funding/Support: This trial was supported by Novartis Pharma AG.

Role of the Funder/Sponsor: In conjunction with the EVEREST II study group, Novartis Pharma AG participated in the design of the study; analysis and interpretation of the data; preparation, review, and approval of the manuscript; the decision to submit the manuscript for publication; the conduct of the study; and oversight of the collection and management of data.

Group Information: The EVEREST II Study Group members include Kanji Takahashi, MD, Kansai Medical University Hospital, Hirakata-city, Osaka, Japan; Kunihiko Shiraki, MD, Osaka City University Hospital, Osaka-city, Osaka, Japan; Yasuo Yanagi, MD, The University of Tokyo Hospital, Bunkyo-ku, Tokyo, Japan; Satoshi Kato, MD, PhD, The University of Tokyo Hospital, Bunkyo-ku, Tokyo, Japan; Hiroko Terasaki, MD, Nagoya University Hospital, Nagoya-city, Aichi, Japan; Masahito Ohji, MD, Shiga University of Medical Science Hospital, Ohtsu-city, Shiga, Japan; Tetsuju Sekiryu, MD, Fukushima Medical University Hospital, Fukushima-city, Fukushima, Japan; Shoji Kishi, MD, Gunma University Hospital, Maebashi-city, Gunma, Japan; Masahiro Morimoto, MD, Gunma University Hospital, Maebashi-city, Gunma, Japan; Tatsuro Ishibashi, MD, Kyushu University Hospital, Fukuoka

city, Fukuoka, Japan; Yuji Oshima, MD, Kyushu University Hospital, Fukuoka city, Fukuoka, Japan; Koh Hei Sonoda, MD, Kyushu University Hospital, Fukuoka-city, Fukuoka, Japan; Rvusaburo Mori, MD, Surugadai Nihon University Hospital, Kanda Surugadai, Chiyoda, Tokyo, Japan; Ayame Annabelle Okada, MD, Kyorin University Hospital, Shinkawa, Mitaka, Tokyo, Japan; Tomohiro Iida, MD, Tokyo Women's Medical University Hospital, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan; Takayuki Baba, MD, Chiba University Hospital, Inohana Chuo-ku Chiba-shi Chiba, Japan; Fumio Shiraga, MD, Okayama University Hospital, Shikata-cho, Kita-ku, Okayama, Okayama, Japan; Hideyasu Oh, MD, Hyogo Prefectural Amagasaki General Medical Center, Higashinaniwa-cho, Amagasaki-city, Hyogo, Japan; Toshiya Sakurai, MD, Tane Memorial Eye Hospital, Sakaigawa, Nishi-ku, Osaka, Japan; Nagako Kondo, MD, Miyake Eye Hospital, Ozone, Kita-ku, NagOya City, Japan; Shigeru Honda, MD, Kobe University Hospital, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe, Hyogo, Japan; Mineo Kondo, MD, Mie University Hospital, 2-174, Edobashi, Tsu, Mie, Japan; Masahiro Miura, MD, Tokyo Medical University Ibaraki Medical Center, Inashiki-gun Ibaraki, Japan; Chieko Shiragami, MD, Kagawa University Hospital, Kita-gun, Kagawa Japan; Yasuo Kurimoto, MD, Kobe City Medical Center General Hospital, Kobe-city, Hyogo, Japan; Yuk Yau Timothy Lai, MD, Chinese University of Hong Kong, Hong Kong; Ian Y. H. Wong, MMed, Queen Mary Hospital, Hong Kong; Wonki Lee, MD, The Catholic University of Korea Seoul, St. Mary's Hospital, Seoul, Korea; Hakyoung Kim, MD, PhD, Kangnam Sacred Heart Hospital, Seoul, Korea; Kyu Hyung Park, MD, Seoul National University Bundang Hospital, Bundang Seongnam, Korea; Hyung-Woo Kwak, MD, PhD, Kyung Hee University Hospital, Seoul, Korea; Eung Suk Kim, MD, PhD, Kyung Hee University Hospital, Seoul, Korea; Dongwon Lee, MD, PhD, Kim's Eye Hospital, Seoul, Korea; Taegon Lee, MD, Kim's Eye Hospital, Seoul, Korea; Nikolle Tan, MMed, Tan Tock Seng Hospital, Ophthalmology, Singapore; Rajesh Rajagopalan, MBBS, Tan Tock Seng Hospital Ophthalmology, Singapore; Gemmy Cheung, MBBS, Singapore National Eye Centre, Singapore; Caroline Ka Lin Chee, MMed, National University Hospital, Singapore; Shih-Jen Chen, MD, PhD, Taipei Veterans General Hospital, Taipei, Taiwan; Chi-Chun Lai, MD, Chang Gung Memorial Hospital Linkou, Lin-Ko, Taiwan; Lee-Jen Chen, MD, MacKay Memorial Hospital, Taipei, Taiwan; Chung-May Yang, MD, National Taiwan University Hospital, Taipei, Taiwan; San-Ni Chen, MD, Changhua Christian Hospital, Changhua, Taiwan; Shwu-Jiuan Sheu, MD, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; Paisan Ruamviboonsuk, MD, Rajavithi Hospital, Bangkok, Thailand; Prut Hanutsaha, MD, Ramathibodi Hospital, Bangkok, Thailand; Patama Bhurayanontachai, MD, Songklanagarind Hospital, Songkla, Thailand; Nor Fariza Ngah, MBBS, Hospital Selayang, Batu Caves, Selangor, Malaysia; and Kenneth Choong Sian Fong, Sunway Medical Centre, Petaling Jaya Selangor Darul Ehsan, Malaysia.

Data Sharing Statement: See Supplement 3.

Additional Contributions: Steven Cartmell, PhD (Product Lifestyle Services, Novartis Ireland Ltd, Dublin, Ireland), and Shridevi Venkataramani, PhD (Scientific Services Practice, PLS, Novartis Healthcare Private Limited, Hyderabad, India), assisted with medical writing and editorial assistance toward the development of this article.

REFERENCES

1. Wong RLM, Lai TYY. Polypoidal choroidal vasculopathy: an update on therapeutic approaches. *J Ophthalmic Vis Res*. 2013;8(4):359-371.

2. Laude A, Cackett PD, Vithana EN, et al. Polypoidal choroidal vasculopathy and neovascular age-related macular degeneration: same or different disease? *Prog Retin Eye Res*. 2010;29(1):19-29. doi:10.1016/j.preteyeres.2009.10.001

3. Cheung CMG, Lai TYY, Ruamviboonsuk P, et al. Polypoidal choroidal vasculopathy: definition, pathogenesis, diagnosis, and management. *Ophthalmology*. 2018;125(5):708-724. doi:10.1016/j.ophtha.2017.11.019

4. Honda S, Matsumiya W, Negi A. Polypoidal choroidal vasculopathy: clinical features and genetic predisposition. *Ophthalmologica*. 2014;231(2):59-74. doi:10.1159/000355488

5. Iida T. Polypoidal choroidal vasculopathy with an appearance similar to classic choroidal neovascularisation on fluorescein angiography. *Br J Ophthalmol*. 2007;91(9):1103-1104. doi:10.1136/bjo.2007.116160

6. Kokame GT. Polypoidal choroidal vasculopathy—an important diagnosis to make with therapeutic implications. *Retina*. 2012;32(8):1446-1448. doi:10.1097/IAE.0b013e3182695bf8

7. Wong CW, Yanagi Y, Lee W-K, et al. Age-related macular degeneration and polypoidal choroidal vasculopathy in Asians. *Prog Retin Eye Res*. 2016;53:107-139. doi:10.1016/j.preteyeres.2016.04.002

8. Yadav S, Parry DG, Beare NAV, Pearce IA. Polypoidal choroidal vasculopathy: a common type of neovascular age-related macular degeneration in Caucasians. *Br J Ophthalmol*. 2017;101(10):1377-1380. doi:10.1136/bjophthalmol-2016-310074

9. Koh AHC, Chen L-J, Chen S-J, et al; Expert PCV Panel. Polypoidal choroidal vasculopathy: evidence-based guidelines for clinical diagnosis and treatment. *Retina*. 2013;33(4):686-716. doi:10.1097/IAE.0b013e3182852446

10. Koh A, Lee WK, Chen L-J, et al. EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina*. 2012;32(8):1453-1464. doi:10.1097/IAE.0b013e31824f91e8

11. Koh A, Lai TYY, Takahashi K, et al; EVEREST II study group. Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: a randomized clinical trial. *JAMA Ophthalmol*. 2017;135(11):1206-1213. doi:10.1001/jamaophthalmol.2017.4030

12. Wong CW, Cheung CMG, Mathur R, et al. Three-year results of polypoidal choroidal vasculopathy treated with photodynamic therapy: retrospective study and systematic review. *Retina*. 2015;35(8):1577-1593. doi:10.1097/IAE.0000000000000499

13. Lai TYY, Chan W-M, Liu DTL, Luk FOJ, Lam DSC. Intravitreal bevacizumab (Avastin) with or without photodynamic therapy for the treatment of polypoidal choroidal vasculopathy. *Br J Ophthalmol*. 2008;92(5):661-666. doi:10.1136/bjo.2007.135103

14. Gomi F, Oshima Y, Mori R, et al. Initial versus delayed photodynamic therapy in combination with ranibizumab for treatment of polypoidal choroidal vasculopathy: the Fujisan study. *Retina*. 2015;35(8): 1569-1576. doi:10.1097/IAE.0000000000000526

15. Tang K, Si J-K, Guo D-D, et al. Ranibizumab alone or in combination with photodynamic therapy vs photodynamic therapy for polypoidal choroidal vasculopathy: a systematic review and meta-analysis. *Int J Ophthalmol*. 2015;8(5):1056-1066.

16. Wang W, He M, Zhang X. Combined intravitreal anti-VEGF and photodynamic therapy versus photodynamic monotherapy for polypoidal choroidal vasculopathy: a systematic review and meta-analysis of comparative studies. *PLoS One*. 2014;9(10):e110667. doi:10.1371/journal.pone.0110667

17. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

18. Tan CS, Ngo WK, Chen JP, Tan NW, Lim TH, Group ES; EVEREST Study Group. EVEREST study report 2: imaging and grading protocol, and baseline characteristics of a randomised controlled trial of polypoidal choroidal vasculopathy. *Br J Ophthalmol*. 2015;99(5):624-628. doi:10.1136/bjophthalmol-2014-305674

19. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report 1 [published correction appears in *Arch Ophthalmol*. 2000;118(4):488]. *Arch Ophthalmol*. 1999;117(10): 1329-1345. doi:10.1001/archopht.117.10.1329

20. Bressler NM; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials—Tap report 2. *Arch Ophthalmol*. 2001;119(2):198-207.

21. Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419-1431. doi:10.1056/NEJMoa054481

22. Chen S-N, Cheng C-K, Yeung L, et al. One-year real-world outcomes of ranibizumab 0.5 mg treatment in Taiwanese patients with polypoidal choroidal vasculopathy: a subgroup analysis of the REAL study. *Int J Ophthalmol*. 2018;11(11):1802-1808.

23. Lee WK, Iida T, Ogura Y, et al; PLANET Investigators. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy in the PLANET study: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(7):786-793. doi:10.1001/jamaophthalmol.2018.1804

24. Wong TY, Ogura Y, Lee WK, et al; PLANET Investigators. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy: two-year results of the Aflibercept in Polypoidal Choroidal Vasculopathy Study. *Am J Ophthalmol*. 2019;204:80-89. doi:10.1016/j.ajo.2019.02.027

25. Zhang X, Lai TYY. Baseline predictors of visual acuity outcome in patients with wet age-related macular degeneration. *Biomed Res Int*. 2018;2018: 9640131. doi:10.1155/2018/9640131

26. Akaza E, Yuzawa M, Matsumoto Y, Kashiwakura S, Fujita K, Mori R. Role of photodynamic therapy in polypoidal choroidal vasculopathy. *Jpn J Ophthalmol*. 2007;51(4):270-277. doi:10.1007/s10384-007-0452-3

27. Verteporfin In Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization—verteporfin in photodynamic therapy report 2. *Am J Ophthalmol*. 2001;131(5):541-560. doi:10.1016/S0002-9394(01)00967-9

28. Tan CS, Ngo WK, Lim LW, Tan NW, Lim TH, Group ES; EVEREST Study Group. EVEREST study report 3: diagnostic challenges of polypoidal choroidal vasculopathy: lessons learnt from screening failures in the EVEREST study. *Graefes Arch Clin Exp Ophthalmol*. 2016;254(10):1923-1930. doi:10.1007/s00417-016-3333-y