

RANIBIZUMAB VERSUS VERTEPORFIN PHOTODYNAMIC THERAPY IN ASIAN PATIENTS WITH MYOPIC CHOROIDAL NEOVASCULARIZATION

BRILLIANCE, a 12-Month, Randomized, Double-Masked Study

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Purpose: To evaluate the efficacy and safety of 2 dosing regimens of ranibizumab 0.5 mg versus verteporfin photodynamic therapy in Asian patients with visual impairment due to myopic choroidal neovascularization.

Methods: Eligible patients (aged ≥ 18 years) were randomized 2:2:1 to Group I (n = 182; ranibizumab treatment guided by visual acuity stabilization criteria); Group II (n = 184; ranibizumab treatment guided by disease activity); or Group III (n = 91; verteporfin photodynamic therapy on Day 1; from Month 3, ranibizumab/verteporfin photodynamic therapy/both treatment guided by disease activity).

Results: The mean average best-corrected visual acuity change from baseline to Month 1 through Month 3 was significantly higher in Groups I/II versus Group III (Group I/II: +9.5/+9.8 letters vs. Group III: +4.5 letters; both $P < 0.001$). Group II was statistically noninferior to Group I for the mean average best-corrected visual acuity change from baseline to Month 1 through Month 6 (10.7 vs. 10.4 letters; $P < 0.001$). Over 12 months, the mean number of ranibizumab injections received by Groups I/II/III was 4.6/3.9/3.2.

Conclusion: In Asian patients, ranibizumab treatments demonstrated superior efficacy versus verteporfin photodynamic therapy at Month 3, and the beneficial treatment effects persisted at Month 12. Ranibizumab was well-tolerated and demonstrated a good safety profile.

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Choroidal neovascularization (CNV) secondary to pathologic myopia (myopic CNV) is the most common, irreversible bilateral sight-threatening complication of pathologic myopia.^{1,2} Myopic CNV is particularly prevalent in Asian countries and has a profound impact on patients' quality of life as it affects working-age adults.^{2–4} In patients with pathologic myopia, the risk of developing myopic CNV is 5% to 11%.^{3,5–7} Among patients with pre-existing myopic CNV, it was found that $>30\%$ will develop CNV in the fellow eye within a span of 8 years.^{3,7}

Anti-vascular endothelial growth factor (anti-VEGF) agents are approved for the treatment of visual impairment due to CNV secondary to pathologic myopia.^{8–10} Ranibizumab 0.5 mg (Lucentis; Novartis Pharma AG, Basel, Switzerland, and Genentech Inc, South San Francisco, CA) was the first anti-VEGF to be approved for the treatment of visual impairment due to CNV secondary to pathologic myopia in 2013 in the European Union and in 2017 in the United States,^{11,12} based on the results from the 12-month, Phase III RADIANCE (Ranibizumab And PDT [verteporfin] evaluation in myopic Choroidal neovascularization)

study.⁹ The RADIANCE study showed that treatment with ranibizumab 0.5 mg guided by either visual acuity stabilization criteria or disease activity criteria was superior to verteporfin photodynamic therapy (vPDT) in improving visual acuity up to Month 3 and in sustaining visual acuity gains over 12 months.⁹

In China, vPDT is the treatment approved by the State Food and Drug Administration (SFDA) for the

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treatment of myopic CNV, and ranibizumab is currently approved only for the treatment of neovascular age-related macular degeneration.¹³ The BRILLIANCE study (see **Table, Supplemental Digital Content 1** for the list of group members involved, <http://links.lww.com/IAE/A899>), with a design similar to the RADIANCE study,^{9,10} was conducted in Asian (primarily Chinese) patients to support the registration of ranibizumab for treating visual impairment due to myopic CNV in China.

Methods

Study Design

BRILLIANCE was a 12-month, Phase III, randomized, double-masked, multicenter, active-controlled clinical trial that was conducted across 48 centers in 5 countries (**Supplemental Digital Content 2**, <http://links.lww.com/IAE/A900>). The study was initiated in September 2013 and completed in September 2016. The study protocol was reviewed and approved by an independent ethics committee or institutional review board for each center, and the study was conducted in accordance with the Declaration of Helsinki. Patients provided written informed consent at screening. The study is registered with [Clinicaltrials.gov](http://www.clinicaltrials.gov) (identifier, NCT01922102).¹⁴

Patients

Patients aged 18 years and older were included if they had 1) active CNV secondary to pathologic myopia diagnosed using the following criteria: (a) spherical equivalent greater than -6 diopters and axial length measurement of ≥ 26.0 mm, (b) ocular ultrasonography or biometry demonstrating anteroposterior elongation measurement ≥ 26 mm, (c) presence of posterior changes compatible with pathologic myopia seen by fundus ophthalmoscopy and fundus photography, (d) presence of leakage from CNV seen by fluorescein angiography, and (e) presence of intraretinal edema or subretinal fluid (SRF) or increase of central subfield thickness (CSFT) seen by optical coherence tomography; 2) at least one of the following CNV lesion locations in the study eye at screening: (a) subfoveal, (b) juxtafoveal with involvement of the central macular area, (c) extrafoveal with involvement of the central macular area, and (d) margin of the optic disk with involvement of the central macular area; 3) best-corrected visual acuity (BCVA) in study eye of ≥ 24 to ≤ 78 Early Treatment Diabetic Retinopathy Study letters (approximate Snellen equivalent 20/320 to 20/32); and 4) visual loss only because of the presence of any eligible types of CNV due to pathologic myopia. If both eyes were eligible, the eye with the worse visual

acuity at screening was selected for study treatment, unless there were specific medical reasons and local ethical requirements.

Key exclusion criteria were the presence of CNV secondary to any cause other than pathologic myopia (including idiopathic CNV) in the study eye such as neovascular age-related macular degeneration, histoplasmosis, polypoidal choroidal vasculopathy, and secondary to trauma; active infectious disease, intraocular inflammation, active or suspected periocular infection, or confirmed intraocular pressure ≥ 25 mmHg in either eye at the time of enrollment; ocular disorders, branch retinal vein occlusion, central retinal vein occlusion, diabetic macular edema, and severe diabetic retinopathy, in study eye at the time of enrollment; confirmed systolic blood pressure >150 mmHg or diastolic >90 mmHg at the time of enrollment; stroke or myocardial infarction within 3 months before screening; panretinal photocoagulation within 6 months before randomization or focal/grid laser photocoagulation with involvement of the macular area at any time in the study eye; intraocular treatment with any anti-VEGF or vPDT at any time in the study eye; intravitreal treatment with corticosteroids or intraocular surgery within 3 months before randomization in the study eye; use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever was longer; history of hypersensitivity to the study drugs (ranibizumab and verteporfin) or to drugs of similar chemical classes, and

fluorescein or any other component of fluorescein formulation; pregnant or nursing (lactating) women; and women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using effective methods of contraception during dosing of study treatment.

Randomization and Treatment

Eligible patients were randomized 2:2:1 to one of three treatment arms using an interactive response technology system (see **Figure, Supplemental Digital Content 3**, <http://links.lww.com/IAE/A901>, which shows treatment schedule and study design): Group I: Patients received ranibizumab 0.5 mg at Day 1 and Month 1. From Month 2, monthly injections were stopped if the stability criterion for visual acuity was fulfilled (defined as no change in BCVA as compared with the two preceding monthly visits). Monthly injections were resumed when there was a loss of visual acuity because of disease activity and continued until stable visual acuity was achieved again for three consecutive monthly assessments. Group II: Patients received ranibizumab 0.5 mg at Day 1. From Month 1, monthly injections were stopped if no disease activity was observed. Monthly injections were resumed based on disease activity (defined as vision impairment attributable to intraretinal fluid or SRF or active leakage secondary to pathologic myopia as assessed by optical coherence tomography and/or fluorescein

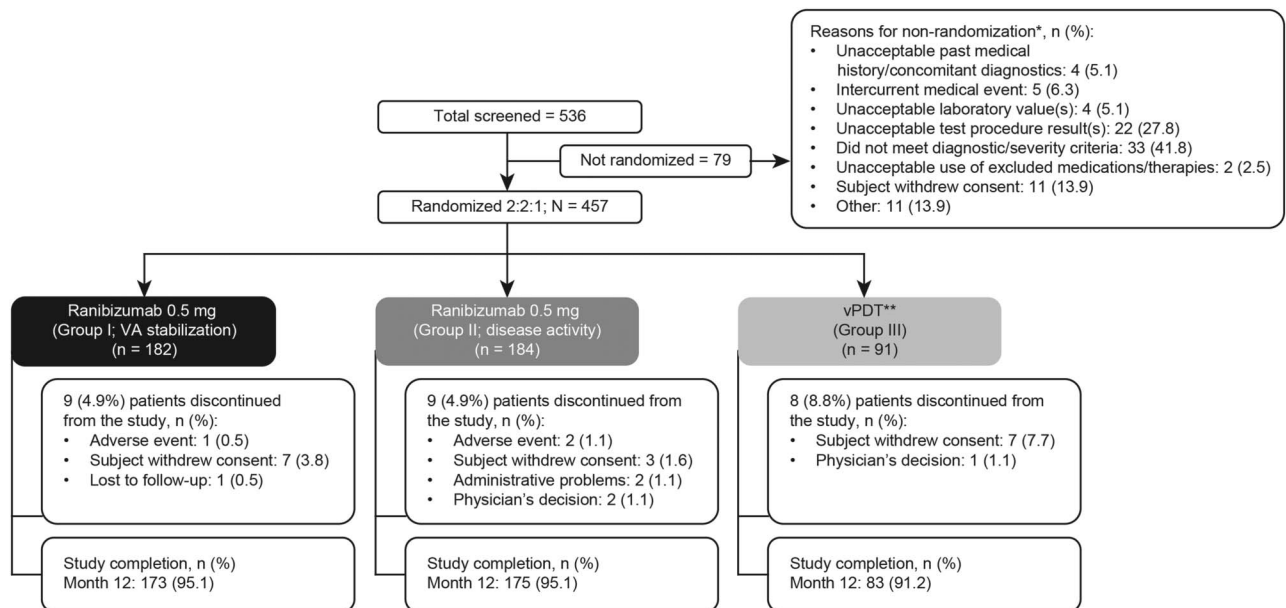


Fig. 1. Patient disposition. *Percentages are based on the total number of patients screened but not randomized. **Patients randomized to vPDT were allowed to receive vPDT at Day 1, and from Month 3 to Month 11, the investigator had the options to treat the patient's disease activity with ranibizumab 0.5 mg or vPDT (as per label) or both. VA, visual acuity.

angiography). Group III: Patients received vPDT on Day 1. From Month 3, patients could receive either vPDT, ranibizumab 0.5 mg, or a combination of both based on disease activity criteria. Dosing of verteporfin and laser light application was performed as per label¹⁵ and only at a minimum interval of 90 days. For masking purpose, sham ranibizumab or sham vPDT was applied. No rescue treatment was permitted in this study.

All patients were masked to the study treatment. In addition, to fulfill the masking, there were at least two investigators involved into the study: masked (assessing) investigator performing all assessments and capturing data; and an unmasked (treating) investigator administering the randomized study treatment when needed according to the protocol.

Objectives

The primary objective was to demonstrate the superiority of ranibizumab 0.5 mg guided by visual acuity stabilization and/or disease activity retreatment criteria versus vPDT, as assessed by the mean average change in BCVA from baseline to Month 1 through Month 3. The key secondary objective was to demonstrate the noninferiority (margin of -5 letters) of ranibizumab 0.5 mg guided by disease activity cri-

teria versus ranibizumab 0.5 mg guided by visual acuity stabilization criteria, as assessed by the mean average change in BCVA from baseline to Month 1 through Month 6.

Other secondary objectives were to assess 1) the mean change in BCVA from baseline to Month 12; 2) the mean average change in BCVA from baseline to Month 1 through Month 12; 3) the proportion of patients gaining ≥10 and ≥15 letters or reaching 84 letters at Months 3, 6, and 12; 4) the mean change in CSFT from baseline to Month 12; 5) the presence of active leakage at Month 12; 6) ranibizumab and vPDT treatment exposure; and 7) the safety of ranibizumab 0.5 mg and vPDT over 12 months.

Efficacy Assessments

Best-corrected visual acuity was tested at every visit using an Early Treatment Diabetic Retinopathy Study visual acuity testing protocol and at an initial distance of 4 m using Early Treatment Diabetic Retinopathy Study charts by masked assessors. Optical coherence tomography was performed before any study drug administration to assess the presence of intraretinal fluid or SRF, or increase in CSFT at all study visits. Fluorescein angiography was performed by a trained technician at screening, Months 6 and 12.

Table 1. Baseline Demographics and Ocular and Disease Characteristics (Randomized Set*)

Characteristics	Ranibizumab 0.5 mg		vPDT	Total (N = 457)
	Group I (VA Stabilization) (n = 182)	Group II (Disease Activity) (n = 184)	Group III (n = 91)	
Mean (SD) age, years	52.0 (12.0)	51.5 (12.1)	49.1 (14.8)	51.2 (12.7)
Female, n (%)	128 (70.3)	116 (63.0)	67 (73.6)	311 (68.1)
Ethnicity, n (%)				
Chinese	154 (84.6)	154 (83.7)	76 (83.5)	384 (84.0)
Indian (Indian subcontinent)	20 (11.0)	16 (8.7)	9 (9.9)	45 (9.8)
Others	8 (4.4)	14 (7.6)	6 (6.6)	28 (6.1)
Mean (SD) BCVA, letters	53.6 (12.6)	54.2 (13.0)	52.1 (12.7)	53.5 (12.8)
Mean (SD) IOP, mmHg	15.6 (3.1)	15.1 (3.1)	14.9 (2.7)	15.2 (3.0)
Mean (SD) axial length, mm	28.9 (1.7)	29.0 (1.8)	28.8 (1.7)	28.9 (1.7)
Mean (SD) refraction sphere, D†	12.7 (4.2)	12.6 (4.2)	13.4 (4.7)	12.8 (4.3)
Mean (SD) CSFT, μm	341.3 (88.2)	340.7 (101.8)	334.8 (101.4)	339.8 (96.3)
Mean (SD) CSFT, μm	321.4 (114.5)	323.6 (120.0)	320.4 (135.0)	322.1 (120.6)
Intraretinal edema, definite, n (%)	164 (90.1)	168 (91.3)	80 (87.9)	412 (90.2)
Intraretinal cysts present, n (%)	48 (26.4)	45 (24.5)	20 (22.0)	113 (24.7)
SRF, definite, n (%)	110 (60.4)	102 (55.4)	46 (50.5)	258 (56.5)
CNV location, n (%)				
Subfoveal	133 (73.1)	129 (70.1)	62 (68.1)	324 (70.9)
Juxtafoveal	16 (8.8)	22 (12.0)	14 (15.4)	52 (11.4)
Extrafoveal	30 (16.5)	32 (17.4)	12 (13.2)	74 (16.2)

Central subfield thickness and CFT represent all data irrespective of types of optical coherence tomography machines.

*Consisted of all randomized patients.

†Refraction-sphere values were collected as negative diopters but are presented as positive values to facilitate the interpretation.

BCVA, best-corrected visual acuity; CFT, central foveal thickness; CNV, choroidal neovascularization; CSFT, central subfield thickness; D, diopters; IOP, intraocular pressure; SD, standard deviation; SRF, subretinal fluid; VA, visual acuity; vPDT, verteporfin photodynamic therapy.

Treatment exposure. Data were collected for the overall number of ranibizumab 0.5 mg injections and vPDT treatments up to Month 12.

Safety Assessments

Safety assessments included the collection of adverse events (AEs) and serious AEs (SAEs) up to Month 12 based on their type, frequency, and severity.

Statistical Analysis

To fulfill the health authority requirement (300 patients for the registration of biologics), a total of 475 patients (a minimum of 375 Chinese patients) were planned to be randomized to the three arms in a ratio of 2:2:1 (190 patients in each of the ranibizumab treatment arms [minimum of 150 Chinese patients] and 95 patients in the vPDT arm [minimum of 75 Chinese patients]).

In the primary analysis, the mean of the primary efficacy variable in the two ranibizumab treatment arms were compared with vPDT treatment arm using the one-sided stratified Cochran–Mantel–Haenszel (CMH) test at an overall Type I error rate of 0.025 (Hochberg multiple testing procedure). Superiority could be claimed if the corresponding one-sided *P* value was 0.0125, or if both one-sided *P* values were ≤ 0.025 . The CMH test was stratified by baseline BCVA category (≤ 60 vs. > 60 letters) and used row mean score statistic with the observed values as scores. The primary analysis was performed on the full analysis set (FAS) which consisted of all patients to whom study treatment was assigned. The analysis on

FAS followed a modified last observation carried forward approach where the last missing values were replaced by carrying forward the previous postbaseline value, and values missing in between were replaced by the mean of the last value observed before and the first after the missing timepoint. The primary efficacy variable was also assessed by analysis of variance with treatment and baseline BCVA category (≤ 60 vs. > 60 letters) as factors using FAS. The two-sided 95% confidence intervals for the pairwise differences in mean change in BCVA between the arms were calculated and based on the analysis of variance model.

The key secondary efficacy variable was compared between ranibizumab treatment arms using a one-sided stratified CMH test with noninferiority margin of -5 letters, and two-sided 95% confidence interval for the difference between arms was calculated from analysis of variance model. All other efficacy variables were summarized descriptively.

Safety results were summarized descriptively on the safety set, which consisted of all patients who received at least one application of study treatment and had at least one postbaseline safety assessment.

Results

Patient Disposition and Baseline Characteristics

Of the 457 patients enrolled, 431 (94.3%) completed the study (Group I, 173 [95.1%]; Group II, 175 [95.1%]; and Group III, 83 [91.2%]) (Figure 1). The FAS consisted of 457 patients (Group I: 182; Group II: 184; and Group III: 91). The safety set consisted of 456 patients (Group I: 182; Group II: 185; Group III: 89; one patient randomized to Group III received one ranibizumab injection before Month 3, and hence, this patient was analyzed under Group II).

At baseline, the mean age (SD) of patients in the total population was 51.2 (12.7) years; most patients were women (68.1%), and the majority were Chinese (84.0%). Mean (SD) visual acuity and CSFT at baseline were 53.5 (12.8) letters and 339.8 (96.3) μm , respectively (Table 1). Patient demographics and ocular characteristics at baseline were comparable across treatment groups (Table 1).

Efficacy Outcomes

Best-corrected visual acuity. Ranibizumab treatment guided either by visual acuity stabilization or disease activity criteria was statistically superior to vPDT with respect to mean (SD) average change in BCVA from baseline to Month 1 through Month 3 (Group I: +9.5 [7.6] letters; Group II: +9.8 [8.5] letters vs. Group III:

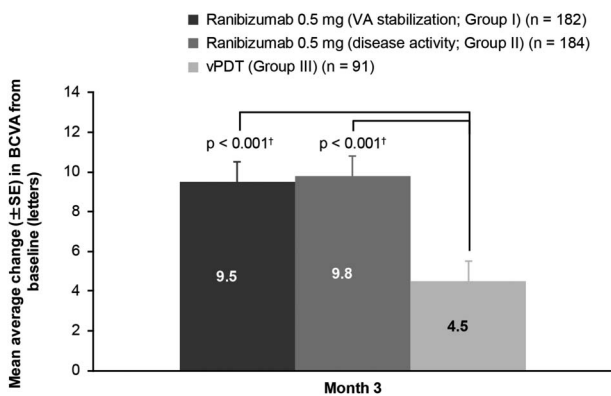


Fig. 2. Mean average change in BCVA from baseline to Month 1 through Month 3 (primary endpoint; FAS* [modified last observation carried forward]). *Consisted of all patients to whom study treatment were assigned. †One-sided *P* values for treatment difference are derived from the two-sided stratified CMH test using the row mean score statistics. Stratification is based on baseline visual acuity (≤ 60 , > 60 letters). BCVA, best-corrected visual acuity; CMH, Cochran–Mantel–Haenszel; FAS, full analysis set; SE, standard error; VA, visual acuity; vPDT, verteporfin photodynamic therapy.

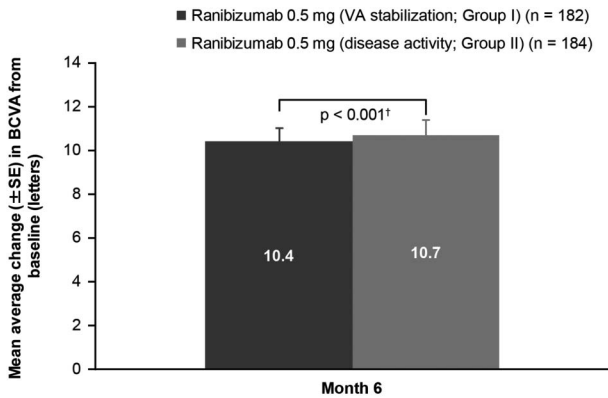


Fig. 3. Mean average change in BCVA from baseline to Month 1 through Month 6 (FAS* [modified last observation carried forward]). *Consisted of all patients to whom study treatment were assigned. Noninferiority was based on a prespecified margin of -5 letters. †P value for noninferiority is from a CMH test (stratified), is one-sided, and is based on the null hypothesis: Group II by disease activity is more than 5 letters worse than Group I by stabilization, against the alternative hypothesis: Group II by disease activity is not >5 letters worse than Group I by stabilization. Stratification is based on baseline visual acuity (≤ 60 , >60 letters). BCVA, best-corrected visual acuity; CMH, Cochran–Mantel–Haenzel; FAS, full analysis set; SE, standard error; VA, visual acuity.

+4.5 [7.8] letters; both $P < 0.001$; Figure 2). The difference in least-square mean values (95% confidence interval) versus vPDT in Group I was +5.2 (3.3, 7.1) letters and +5.6 (3.5, 7.6) letters in Group II.

Ranibizumab treatment guided by disease activity criteria was statistically noninferior (margin of -5 letters) to ranibizumab guided by visual acuity stabilization criteria with respect to mean [SD] average change in BCVA from baseline to Month 1 through Month 6 (Group I: +10.4 [8.2] letters vs. Group II: +10.7 [9.2] letters; $P < 0.001$; Figure 3). The difference in least-square mean values (95% confidence interval) versus Group I was +0.4 (-1.3 , 2.1) letters in Group II.

The mean change in BCVA from baseline to Month 12 was +12.0 letters, +13.1 letters, and +10.3 letters in

Groups I, II, and III, respectively (Figure 4). The mean average change in BCVA from baseline to Month 1 through Month 12 was similar in both ranibizumab groups (+11.2 and +11.7 letters in Groups I and II, respectively) compared with vPDT group (+8.6 letters). Most patients in both ranibizumab groups gained ≥ 10 letters from baseline or reached 84 letters at Months 3, 6, or 12 (Figure 5).

Anatomical outcomes. In both ranibizumab groups, a rapid and clinically relevant decrease in CSFT from baseline was observed during the first 3 months followed by a stabilization phase up to Month 12 (Figure 6). In the vPDT group, mean CSFT decreased from baseline to Month 1 and thereafter remained at a plateau level up to Month 3; the decrease was smaller than in any ranibizumab group. After Month 3, a further decrease in CSFT was achieved after patients in the vPDT group were allowed to receive ranibizumab (Figure 6).

In all treatment groups, the number of patients with definite SRF, intraretinal edema, or intraretinal cysts and CNV leakage decreased from baseline to Month 12 (see **Figure, Supplemental Digital Content 4A–D**, <http://links.lww.com/IAE/A902>). Similarly, in all groups, at Month 12, there was a reduction from baseline in the mean CNV leakage and lesion area (see **Table, Supplemental Digital Content 5**, <http://links.lww.com/IAE/A903>).

Treatment Exposure. Ranibizumab injections. Up to Month 3, the mean (SD) number of ranibizumab injections in Groups I and II was 2.4 (0.5) and 2.1 (0.8), respectively. The mean (median) number of ranibizumab injections received before Month 12 was 4.6 (4.0) and 3.9 (3.0) in Groups I and II, respectively (Table 2). In Group III, the mean (median) number of ranibizumab injections received from Month 3 up to Month 11 was 3.2 (3.0; Table 2). Approximately 24%

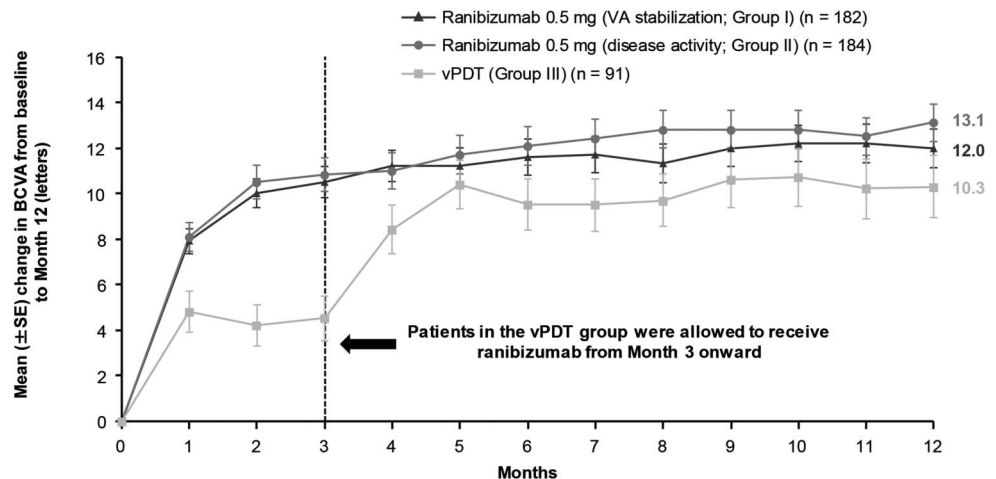


Fig. 4. Mean change in BCVA from baseline to Month 12 (FAS* [modified last observation carried forward]). *Consisted of all patients to whom study treatment were assigned. BCVA, best-corrected visual acuity; FAS, full analysis set; SE, standard error; VA, visual acuity; vPDT, verteporfin photodynamic therapy.

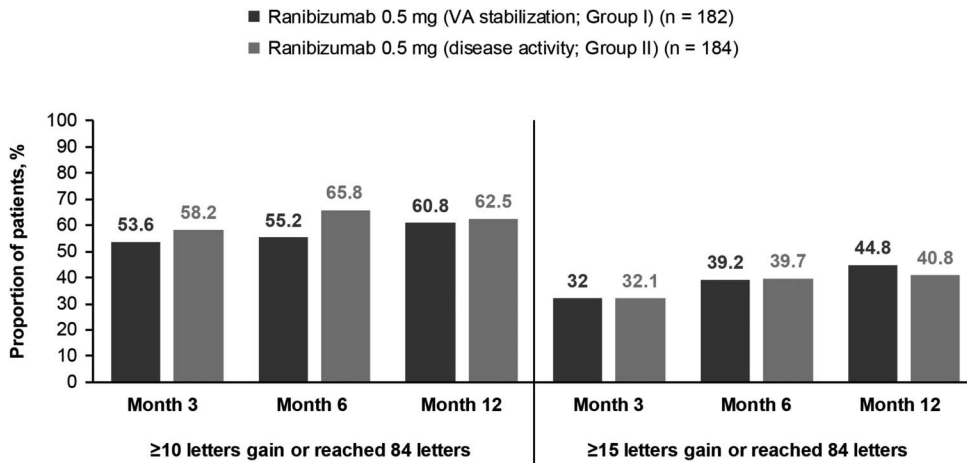


Fig. 5. Proportion of patients who gained ≥ 10 or ≥ 15 letters in BCVA from baseline (or reached 84 letters) at Months 3, 6, and 12 (FAS* [modified last observation carried forward]). *Consisted of all patients to whom study treatment were assigned. BCVA, best-corrected visual acuity; FAS, full analysis set; VA, visual acuity.

and 20% of patients in Groups I and II received 2 ranibizumab injections within 12 months (Table 2).

Verteporfin photodynamic therapy. The mean (median) number of vPDT treatment received in Group III up to Month 3 was 1.0 (1.0). Of the 75 patients in Group III who received ranibizumab from Month 3, 3 (4%) patients received a second vPDT between Months 3 and 12. Of the 14 patients in Group III who did not receive ranibizumab from Month 3, none received a second vPDT treatment.

Safety Outcomes

Serious adverse events. Up to Month 12, ocular (study eye) SAEs were reported in three patients: one patient in each of the three groups: Group I and Group II (retinal detachment, n = 1 [0.5%] each) and Group III with ranibizumab (endophthalmitis, n = 1 [1.3%]; considered to be related to study drug). Up to Month 12, there were 24 patients with nonocular SAEs re-

ported: Group I (6 patients, 3.3%), Group II (13 patients, 7.0%), and Group III with ranibizumab (6 patients, 8.0%), and none were considered to be related to study drug (see **Table, Supplemental Digital Content 6**, <http://links.lww.com/IAE/A904>).

No deaths were reported during the study.

Adverse events. Up to Month 12, ocular (study eye) AEs were reported in similar proportion of patients in the 3 groups: 28.6% and 29.7% of patients in Groups I and II, respectively; in Group III with ranibizumab 0.5 mg and without ranibizumab 0.5 mg, the ocular AEs were reported in 30.7% and 28.6% of patients, respectively (see **Table, Supplemental Digital Content 7**, <http://links.lww.com/IAE/A905>). The most frequently reported ocular AE was conjunctival hemorrhage (Group I: 4.4%, Group II: 7.6%, Group III with ranibizumab: 2.7%, and none in Group III without ranibizumab; see **Table, Supplemental Digital Content 7**, <http://links.lww.com/IAE/A905>).

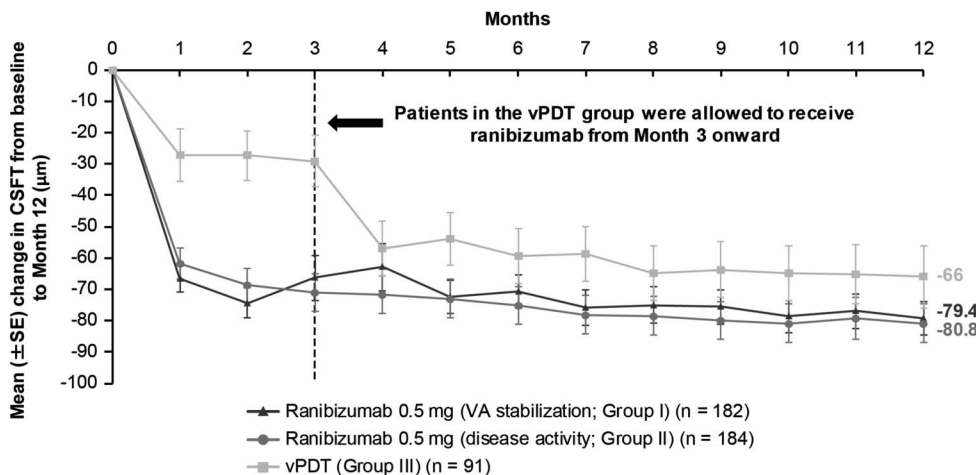


Fig. 6. Mean change in CSFT from baseline to Month 12 (FAS* [modified last observation carried forward]). *Consisted of all patients to whom study treatment were assigned. CSFT, central subfield thickness; FAS, full analysis set; SE, standard error; VA, visual acuity; vPDT, verteporfin photodynamic therapy.

Table 2. Ranibizumab 0.5 mg Treatment Exposure up to Month 11 (Safety Set*)

	Ranibizumab 0.5 mg		vPDT
	Group I (VA Stabilization) (n = 182)	Group II (Disease Activity) (n = 185)	Group III (With Ranibizumab 0.5 mg From Month 3) (n = 75)
No. of injections			
Total	831	716	240
Mean (SD)	4.6 (2.4)	3.9 (2.5)	3.2 (2.3)
Median	4.0	3.0	3.0
Frequency of injections, n (%)			
0	0	0	0
1	3 (1.6)	32 (17.3)	22 (29.3)
2	44 (24.2)	36 (19.5)	15 (20.0)
3	31 (17.0)	30 (16.2)	10 (13.3)
4	23 (12.6)	24 (13.0)	10 (13.3)
5	24 (13.2)	17 (9.2)	6 (8.0)
6	16 (8.8)	22 (11.9)	3 (4.0)
7	14 (7.7)	7 (3.8)	5 (6.7)
8	13 (7.1)	5 (2.7)	1 (1.3)
9	7 (3.8)	4 (2.2)	3 (4.0)
10	4 (2.2)	4 (2.2)	0
11	2 (1.1)	4 (2.2)	0
12	1 (0.5)	0	0

One patient in Group III received a ranibizumab injection before Month 3, which was recorded as a protocol deviation. This patient was analyzed as part of Group II in the safety set.

*Consisted of all patients who received at least one application of study treatment and had at least one postbaseline safety assessment.

SD, standard deviation; VA, visual acuity; vPDT, verteporfin photodynamic therapy.

Nonocular AEs were reported in 51.1% of patients in Group I, 50.8% in Group II, 56.0% in group III with ranibizumab, and 35.7% in group III without ranibizumab (see **Table, Supplemental Digital Content 7**, <http://links.lww.com/IAE/A905>). The nonocular AE with the highest incidence across all groups was nasopharyngitis (Group I: 9.3%, Group II: 10.8%, and 10.7 and 7.1% in Group III with ranibizumab and without ranibizumab, respectively; see **Table, Supplemental Digital Content 7**, <http://links.lww.com/IAE/A905>).

Discussion

The BRILLIANCE study design was similar to that of the RADIANCE study.⁹ The RADIANCE study had both Asian and white populations, whereas BRILLIANCE study contained a purely Asian (majority Chinese) population. The other baseline characteristics were comparable between the two studies. The number of female patients in BRILLIANCE was higher than the number of men, and most patients had subfoveal CNV.

The BRILLIANCE study results demonstrate that ranibizumab treatment in Asian (primarily Chinese) patients, irrespective of the retreatment criteria, resulted in superior BCVA gains compared with vPDT

up to Month 3. The mean average change in BCVA from baseline to Month 1 through Month 3 of +9.5, +9.8, and +4.5 letters in Groups I, II, and III, respectively, in the BRILLIANCE study was similar to that observed in the RADIANCE study⁹ (Group I: 10.5 letters; Group II: 10.6 letters; and Group III: 2.2 letters). The increase in mean BCVA with the two ranibizumab treatment regimens was clinically relevant and comparable with those obtained in the pivotal RADIANCE study.⁹

Also, consistent with findings from the RADIANCE study, ranibizumab retreatment guided by disease activity was noninferior to retreatment guided by visual acuity stabilization criterion; the mean average change in BCVA from baseline to Month 1 through Month 6 was +10.4 letters and +10.7 letters in Groups I and II, respectively, in BRILLIANCE and was +11.9 letters in Group I and +11.7 letters in Group II in RADIANCE.⁹

Over 12 months, the mean change in BCVA in BRILLIANCE (Group I: +12.0 letters; Group II: +13.1 letters; and Group III: +10.3 letters) was comparable with that of the RADIANCE study (Group I: 14.4 letters; Group II: 13.8 letters; and Group III: 9.3 letters).⁹ Patients who received ranibizumab only as of Month 3 (Group III) were not able to catch up with the patients who received ranibizumab from Day 1; early treatment with ranibizumab is therefore the prerequisite for optimal visual acuity gains. This finding is

consistent with the guidance and consensus statement on management of myopic CNV, which recommends that once a diagnosis of myopic CNV has been confirmed, treatment should be initiated immediately with anti-VEGF agents as the first-line therapy.¹⁶ The anatomical outcomes in mean CSFT reduction were also favorable for the ranibizumab groups compared with vPDT group, and the results were comparable with those observed in RADIANCE.⁹

The comparable efficacy observed in the two ranibizumab groups between the BRILLIANCE and RADIANCE studies was achieved with a similar mean number of ranibizumab injections (BRILLIANCE: 4.6 [Group I] and 3.9 injections [Group II] and RADIANCE: 4.6 [Group I] and 3.5 injections [Group II]).⁹ The mean of 4 injections over 12 months is further supported by previous myopic CNV studies.^{11,17,18}

The results from BRILLIANCE further support the current ranibizumab European Union label recommendations on retreatment criteria, which states one injection at baseline and retreatment as needed, guided by disease activity criteria.¹⁹

Overall, the results from the BRILLIANCE study corroborate those from the RADIANCE study and confirm the efficacy of ranibizumab, irrespective of retreatment criteria, in the treatment of Asian (primarily Chinese) patients with myopic CNV. The results from BRILLIANCE are also consistent with other studies evaluating the use of anti-VEGF agents for myopic CNV studies such as the REPAIR²⁰ and MYRROR⁸ studies.

The strength of BRILLIANCE is that this was the first large randomized study with ranibizumab 0.5 mg in myopic CNV that was conducted in a predominantly Chinese population. For patients with myopic CNV, vPDT has been the treatment of choice among retina specialists in China because of the lack of approved anti-VEGF therapy for myopic CNV. The use of vPDT as a control group also has an important limitation. It is evident from the RADIANCE study that ranibizumab treatment, irrespective of the treatment regimen, was superior to vPDT up to Month 3, and the patients initially randomized in the vPDT group could not catch up with the visual acuity gains observed in the other two ranibizumab groups at Month 12.⁹ Moreover, previous studies have shown that vPDT stabilizes vision in the short-term, and the improvement in visual acuity in the long-term is limited.^{21–23}

Over 12 months, the frequency of AEs and SAEs were low, and there were no deaths reported in the study. The safety profile of ranibizumab 0.5 mg was consistent with the previous studies.^{9,20,24} Ranibizumab treatment was found to be efficacious and well-tolerated in patients with visual impairment secondary to myopic CNV.

In conclusion, ranibizumab treatment, irrespective of retreatment criteria, provided superior efficacy versus vPDT up to Month 3 for patients with visual impairment secondary to myopic CNV. Ranibizumab treatment guided by disease activity criteria was statistically noninferior to treatment guided by visual acuity stabilization criteria up to Month 6. Ranibizumab administered over 12 months was effective and well-tolerated in Asian patients. These results confirm the findings from other ranibizumab studies performed in primarily white patients.

Key words: choroidal neovascularization, myopia, anti-VEGF, ranibizumab, photodynamic therapy, clinical trial, Asian patients.

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