Intravitreal ranibizumab therapy for diabetic macular oedema in routine practice: Two-year real-life data from a non-interventional, multicentre study in Germany - Supplementary Materials

Supplementary Tables

Supplementary Table S1. *Mean best-corrected visual acuity in participants of the OCEAN study who were treated with ranibizumab injections for DME by month window (FAS, n=1226)*

Month window	N	ETDRS letters		
		Mean	SD	95% CI
Baseline	1217	60.6	15.5	[59.7; 61.5]
1	1066	63.0	16.7	[62.0; 64.0]
2	1004	64.2	16.1	[63.2; 65.2]
3	874	65.7	15.7	[64.7; 66.7]
4	808	65.4	16.0	[64.3; 66.5]
5	781	65.3	16.8	[64.1; 66.4]
6	731	65.1	18.2	[63.8; 66.4]
7	732	65.3	16.5	[64.1; 66.5]
8	698	65.5	17.0	[64.2; 66.7]
9	683	65.1	17.9	[63.8; 66.5]
10	633	65.2	18.0	[63.8; 66.6]
11	664	65.7	17.5	[64.4; 67.1]
12	642	65.0	19.1	[63.5; 66.5]
13	580	65.7	17.9	[64.2; 67.1]
14	580	64.7	19.3	[63.1; 66.3]
15	576	65.2	19.3	[63.6; 66.8]
16	538	65.4	17.6	[63.9; 66.9]
17	531	65.8	17.3	[64.4; 67.3]
18	512	66.1	17.5	[64.5; 67.6]
19	501	67.2	16.6	[65.7; 68.6]
20	475	66.7	16.0	[65.3; 68.2]
21	487	66.4	18.0	[64.8; 68.0]
22	461	66.1	18.6	[64.4; 67.8]
23	429	66.5	19.1	[64.7; 68.3]
24	371	65.5	18.9	[63.5; 67.4]

CI, confidence interval; DME, diabetic macular oedema; ETDRS, Early treatment diabetic retinopathy study; FAS, full analysis set; SD, standard deviation.

Supplementary Table S2. *Mean best-corrected visual acuity in participants of the OCEAN study with DME at month 12 and month 24, by number of ranibizumab injections in the first year.*

Month window	**Best-corrected visual acuity (ETDRS letters)**					
	1-3 injections		**4-6 injections**		**≥7 injections**	
	n	**Mean [95% CI] n (%)**	**n**	**Mean [95% CI] n (%)**	**n**	**Mean [95% CI] n (%)**
Baseline	580	60.4 [59.1; 61.6]	432	61.7 [60.4; 63.0]	205	59.1 [56.7; 61.5]
Month 12*	211	64.1 [61.2; 66.9]	264	66.1 [64.0; 68.1]	167	64.4 [61.5; 67.4]
Month 24*	131	65.7 [62.3; 69.1]	154	66.2 [63.5; 68.8]	86	63.8 [59.2; 68.4]
Δ Mo 12 - BL*	209	+3.6 [1.6; 5.5]	262	+3.0 [1.0; 4.9]	167	+6.3 [4.1; 8.5]
Δ Mo 24 - BL*	130	+5.2 [3.0; 7.3]	154	+4.7 [2.6; 6.7]	86	+6.1 [1.9; 10.4]
Patients with a response (≥15 ETDRS letters gain)						
Month 12*		36 (17.2%)		56 (21.4%)		45 (27.0%)
Month 24*		27 (20.8%)		37 (24.0%)		23 (26.7%)

BL, baseline; CI, confidence interval, DME, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; Mo, month.
* Only patients with documented visual acuity within the respective month window were included.

Supplementary Table S3. *Patient-based incidences of adverse events (ocular and non-ocular) in participants of the OCEAN study who were treated with ranibizumab injections for DME (safety population, N=1250)*

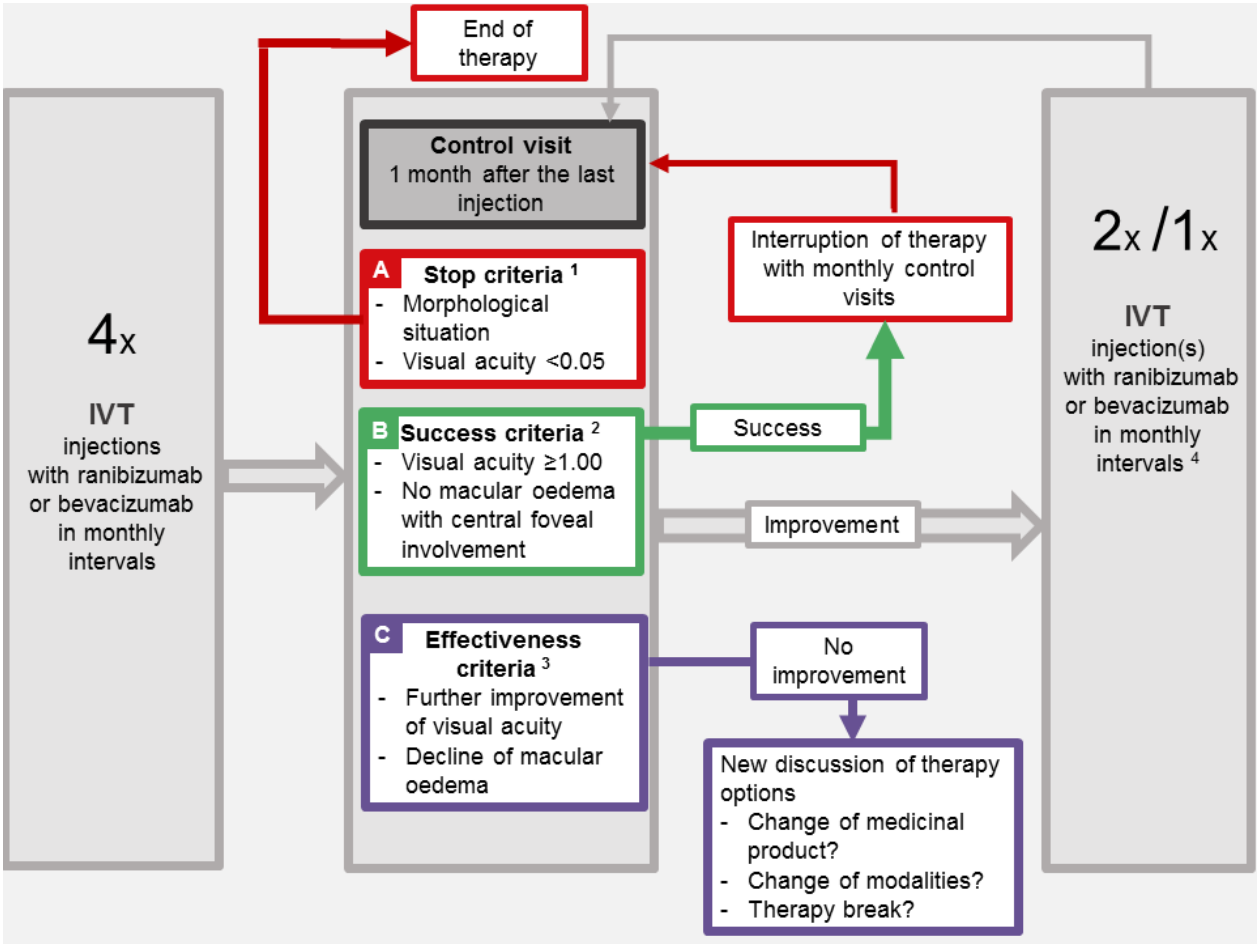
Population / Type of AE / MedDRA Preferred Term	**n (%)**
Participants in the safety population	1250 (100.0%)
Patients with any AE	256 (20.5%)
Patients with different types of AEs	
Patients with non-serious AE	170 (13.6%)
Patients with SAE	143 (11.4%)
AEs by MedDRA Preferred Term	
Ocular and non-ocular AEs occurring in ≥1.0% of patients	
Ocular AEs	
Intraocular pressure increased	32 (2.6%)
Visual acuity reduced	30 (2.4%)
Vitreous haemorrhage	18 (1.4%)
Cataract operation	18 (1.4%)
Posterior capsule opacification	13 (1.0%)
Non-ocular AEs	
Death	13 (1.0%)
SAEs by MedDRA Preferred Term	
Ocular and non-ocular SAEs occurring in ≥2 patients	
Ocular SAEs	
Vitreous haemorrhage	13 (1.0%)
Visual acuity reduced	12 (1.0%)
Intraocular pressure increased	6 (0.5%)
Posterior capsule opacification	4 (0.3%)
Diabetic retinopathy	4 (0.3%)
Cataract	3 (0.2%)
Retinal degeneration	3 (0.2%)
Vision blurred	3 (0.2%)
Cataract operation	3 (0.2%)
Vitrectomy	3 (0.2%)
Macular oedema	2 (0.2%)

Population / Type of AE / MedDRA Preferred Term	n (%)
Ocular hypertension	2 (0.2%)
Retinal aneurysm	2 (0.2%)
Glaucoma	2 (0.2%)
Retinal detachment	2 (0.2%)
Retinal haemorrhage	2 (0.2%)
Non-ocular SAEs	
Death	13 (1.0%)
Cerebrovascular accident	9 (0.7%)
Cardiac failure	8 (0.6%)
Myocardial infarction	7 (0.6%)
Sepsis	5 (0.4%)
Fall	5 (0.4%)
Pneumonia	4 (0.3%)
Motor dysfunction	4 (0.3%)
Aphasia	3 (0.2%)
Hypertensive crisis	3 (0.2%)
Gastrointestinal carcinoma	3 (0.2%)
General physical health deterioration	2 (0.2%)
Hospitalisation	2 (0.2%)
Atrial fibrillation	2 (0.2%)
Cardiac arrest	2 (0.2%)
Coronary artery disease	2 (0.2%)
Dizziness	2 (0.2%)
Coordination abnormal	2 (0.2%)
Diabetic neuropathy	2 (0.2%)
Lung neoplasm malignant	2 (0.2%)
Dyspnoea	2 (0.2%)
Pulmonary embolism	2 (0.2%)
Renal failure	2 (0.2%)

AE, adverse event, DME, diabetic macular oedema; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.
AEs include patients with serious and/or non-serious events.

Supplementary Figures

Supplementary Figure S1. *Treatment and monitoring schedule for intravitreal injections with anti-VEGF medications for DME as recommended by the German medical societies*



DME, diabetic macular oedema; IVT, intravitreal treatment; OCT, optical coherence tomography; SD-OCT, spectral-domain optical coherence tomography; VEGF, vascular endothelial growth factor.

[1] The stop criteria for therapy are fulfilled if at least one of the following applies:
The morphological findings indicate no functional improvement:
Extensive photoreceptor atrophy (damage of outer retina layers confirmed by OCT);
Extensive central ischemia; OR
BCVA <0.05, not expected to improve significantly under therapy or spontaneously.

[2] The success criteria are fulfilled if at least one of the following applies:
Visual acuity of 1.0 or better; OR
No oedema with central foveal involvement confirmed by SD-OCT or fluorescein angiography.

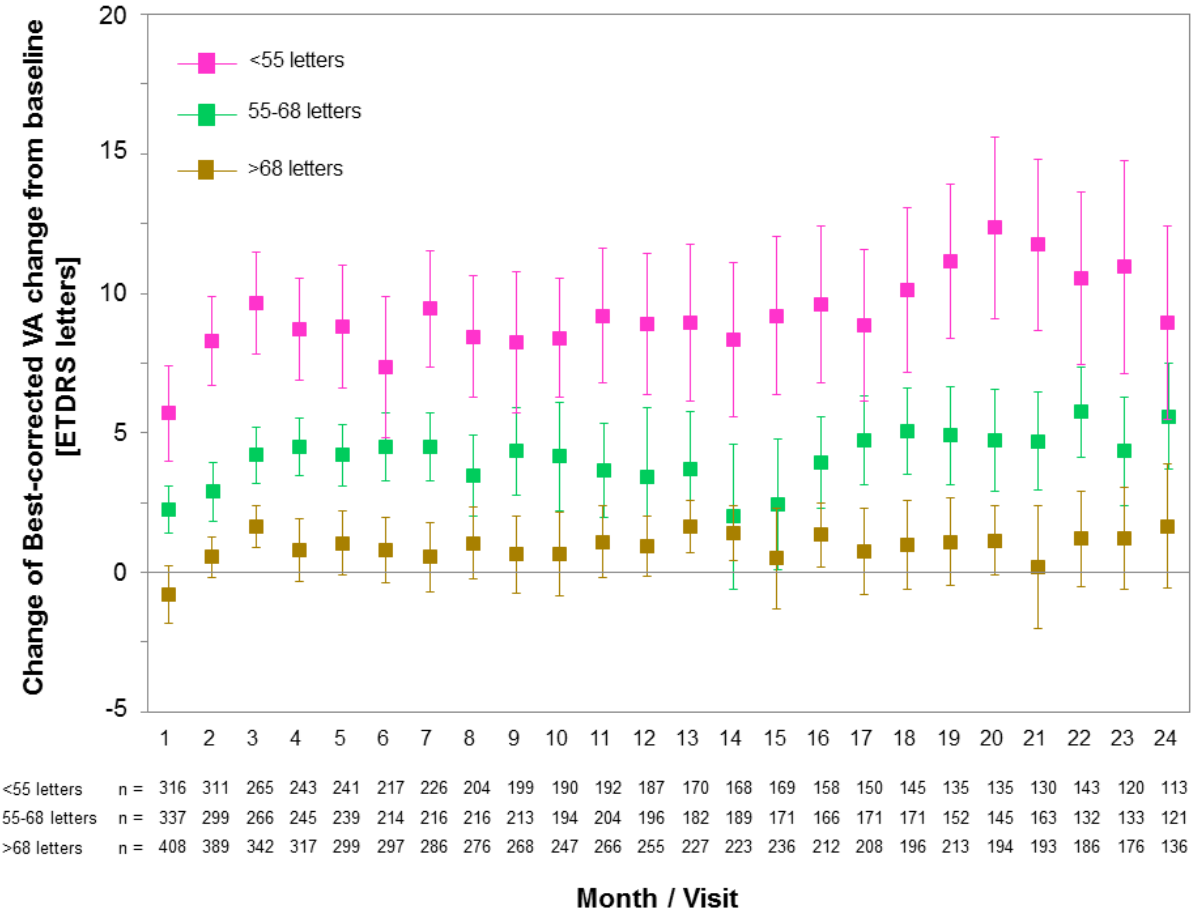
[3] Effectiveness criteria are fulfilled if at least one of the following applies:
Visual acuity improved by at least one line during the last three months; OR
Reduction of retina thickness by least 10% during the last three months confirmed by SD-OCT.

[4] Number of re-treatments:
Immediate re-treatment after initial upload or re-treatment after therapy break of 2 to 23 months:
2 IVTs, otherwise 1 IVT
After therapy break of at least 24 months: 4 IVTs (as initial upload)

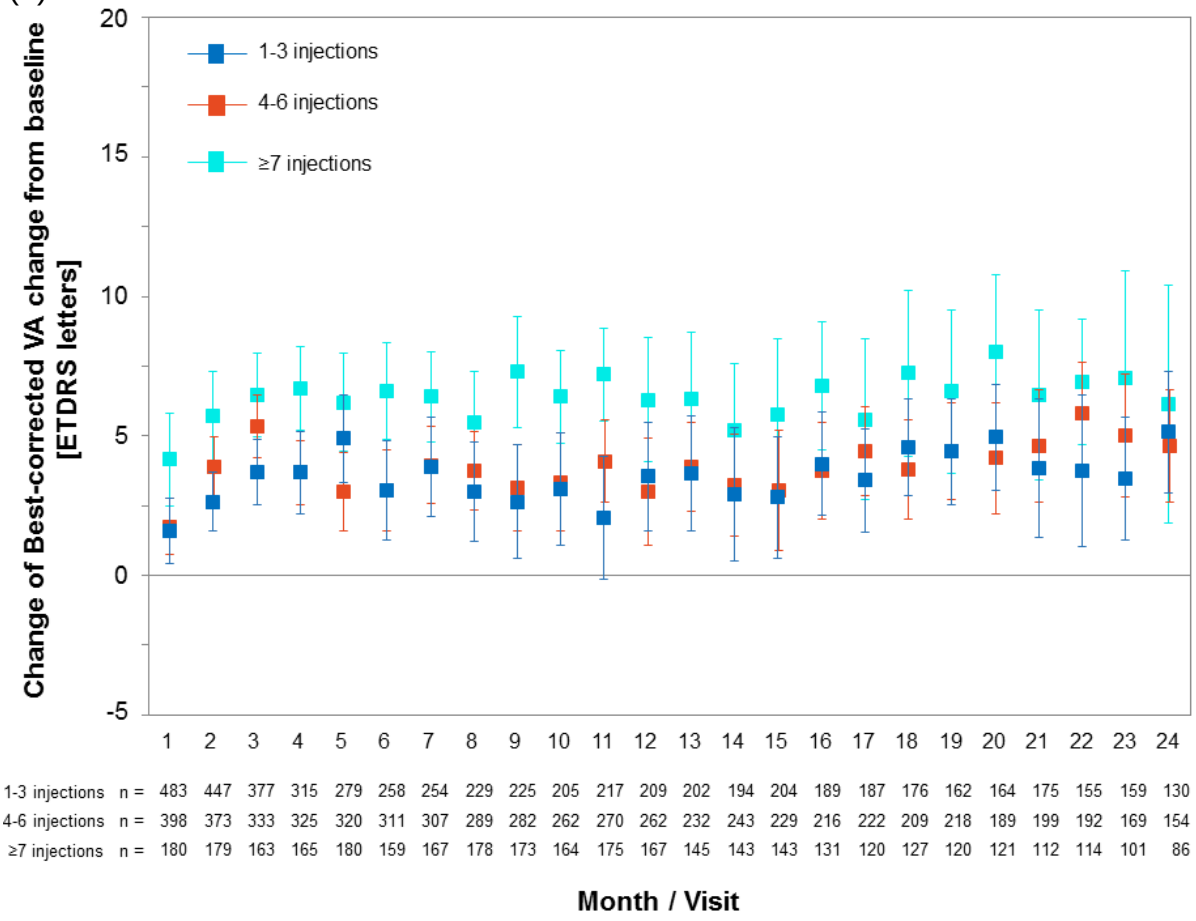
The figure was modified from: DOG, RG, BVA. Stellungnahme der Deutschen Ophthalmologischen Gesellschaft, der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands: Therapie der diabetischen Makulopathie. Stand April 2013. 2013.

Supplementary Figure S2. *Mean best-corrected VA change from baseline during the 24-months observational period (a) by baseline VA and (b) by number of injections in the first 12 months of the study.*

(a)



(b)

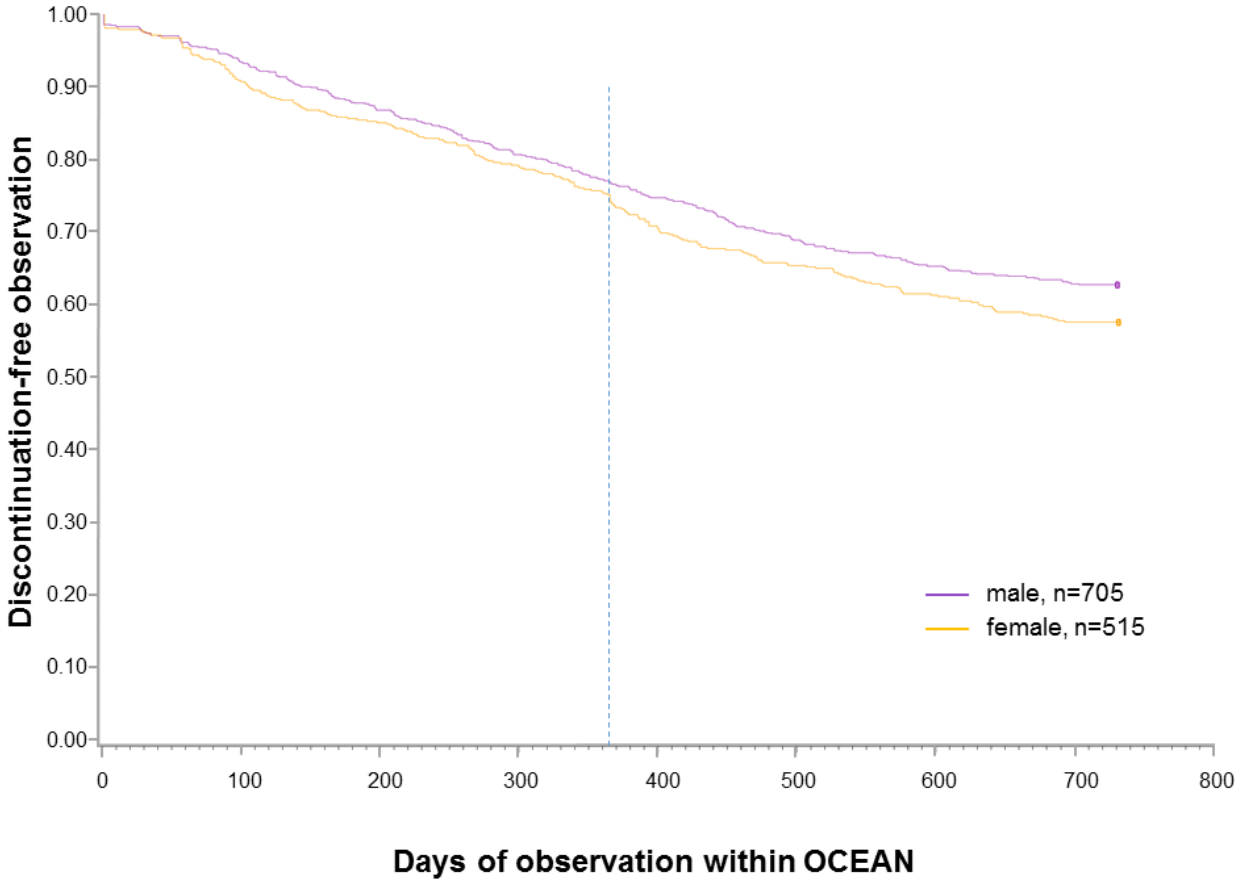


DME, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity. Boxes represent mean changes and error bars represent 95% confidence intervals.

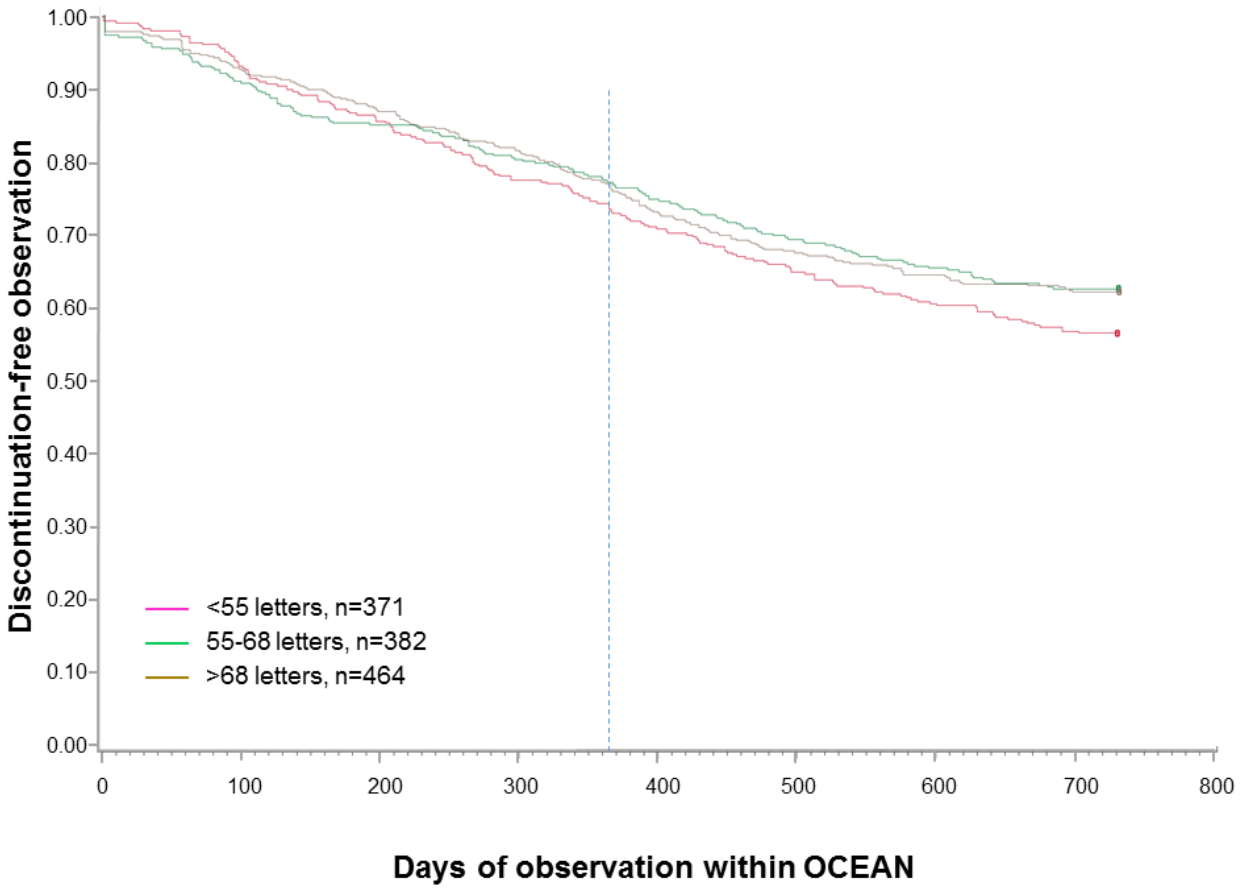
Supplementary Figure S3. *Time to premature discontinuation of patients with DME in the OCEAN study for the entire observational period stratified by (a) sex, (b) visual acuity at baseline, and (c) number of ranibizumab injections in the first year of the study*

Time-to-discontinuation, FAS (n=1226)

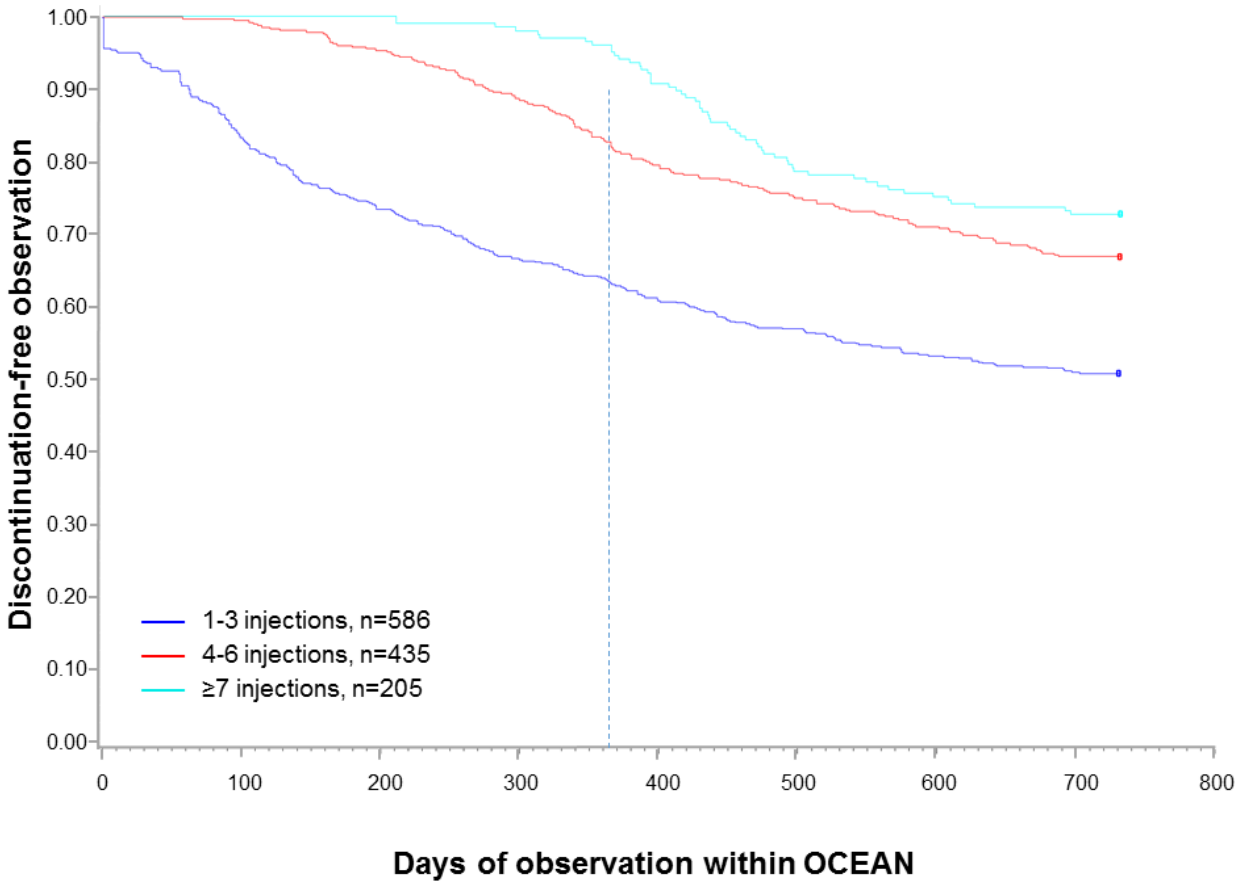
(a) Stratified by sex



(b) Stratified by baseline visual acuity (ETDRS letters)



(c) Stratified by number of ranibizumab injections in the first year of the study

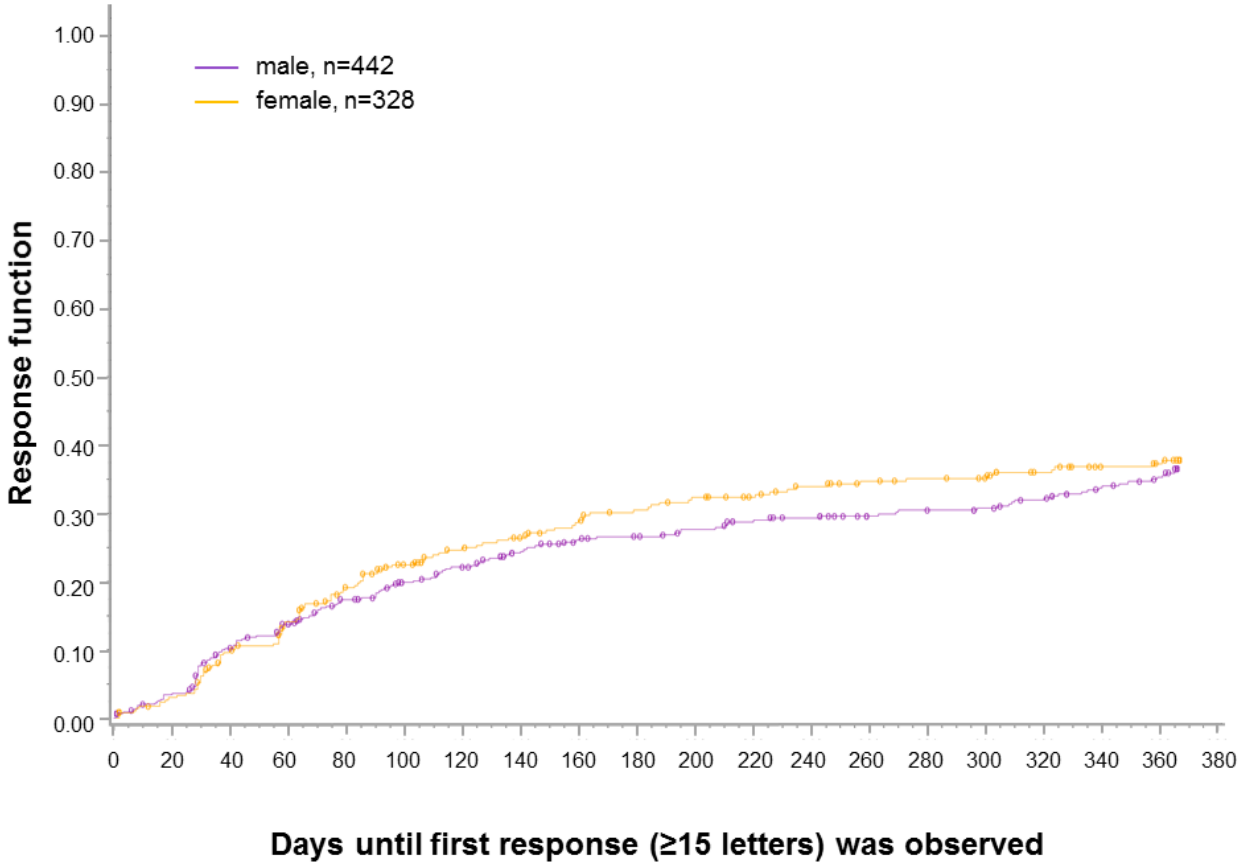


DME, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set.

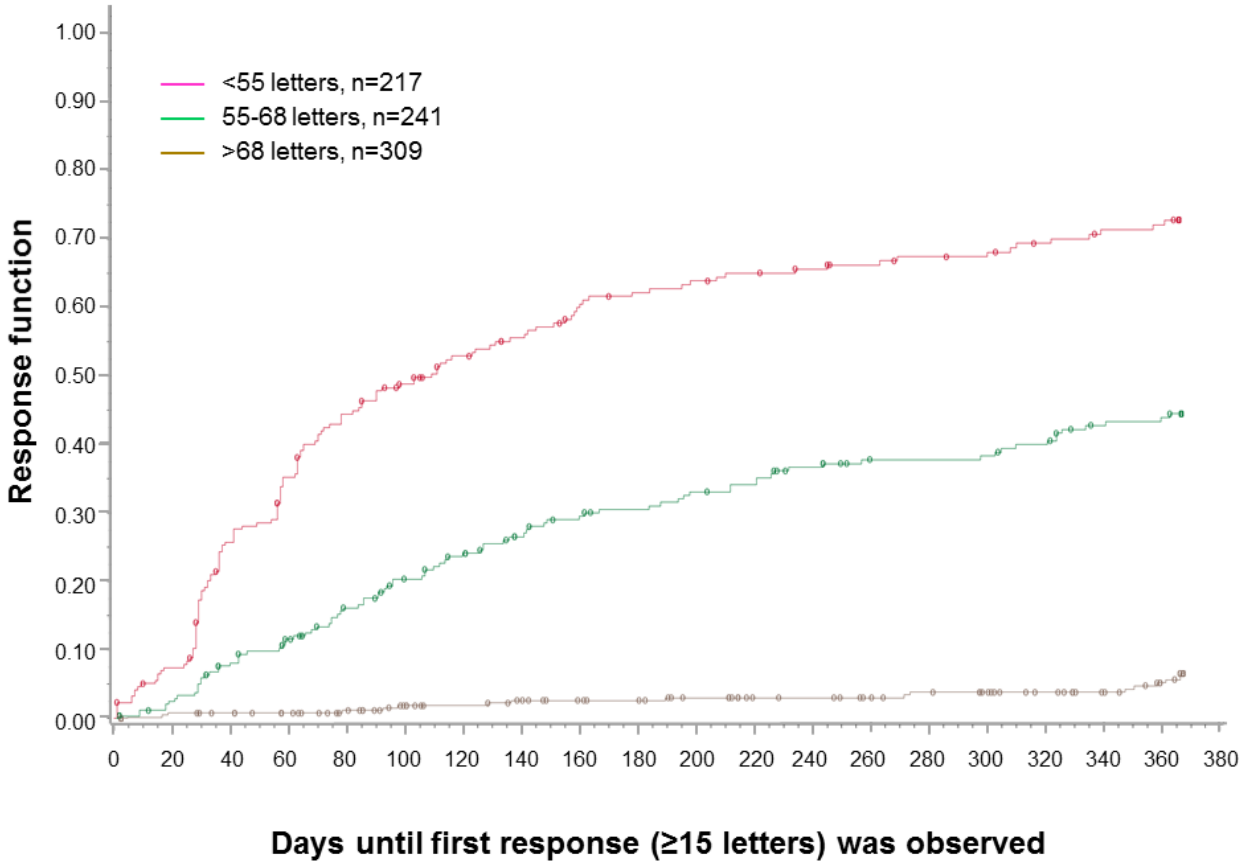
Supplementary Figure S4. *Time-to-response (time to first ≥15 letters gain from baseline) of participants with DME in the OCEAN study for the first 12 months of the observational period, for treatment-naive patients by (a) sex and (b) baseline visual acuity, and for pre-treated patients by (c) sex and (d) baseline visual acuity*

Treatment-naïve participants

(a) Stratified by sex

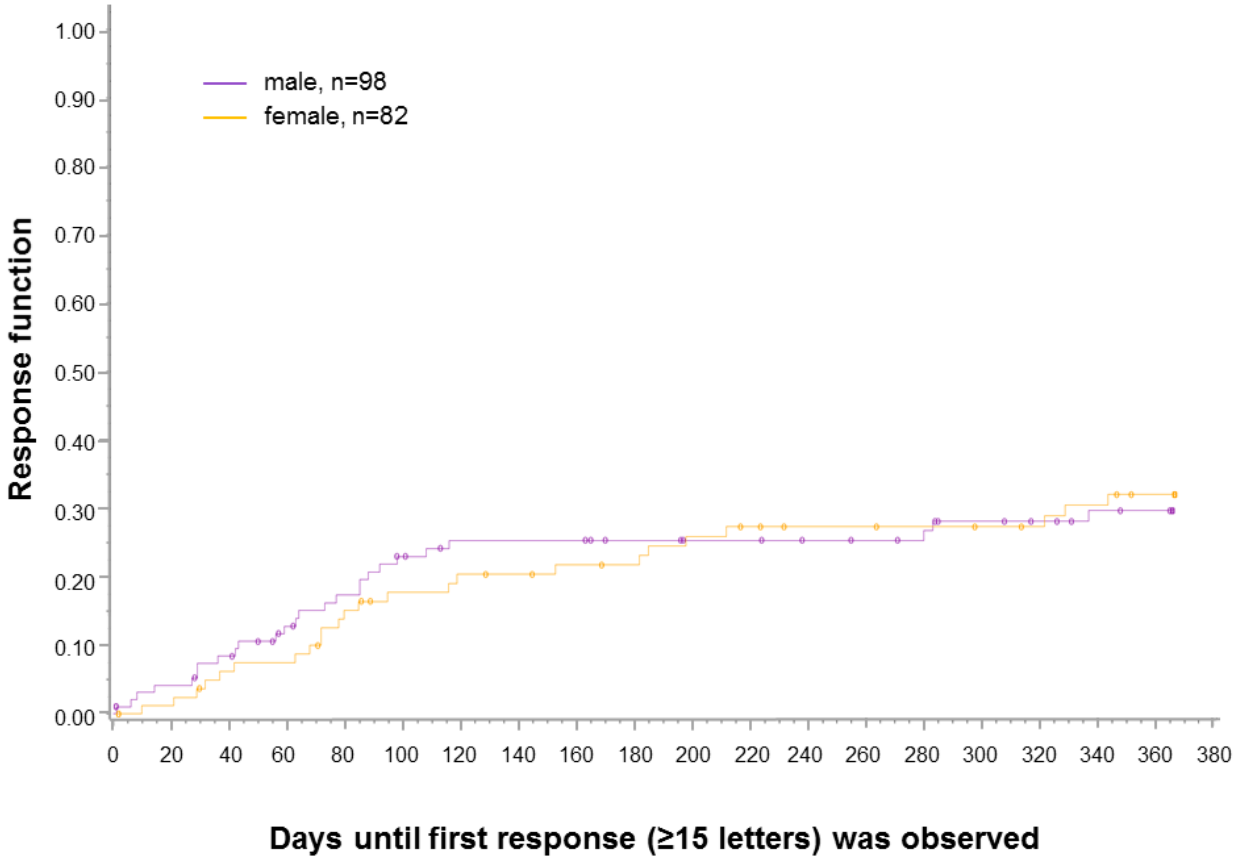


(b) Stratified by baseline visual acuity (ETDRS letters)

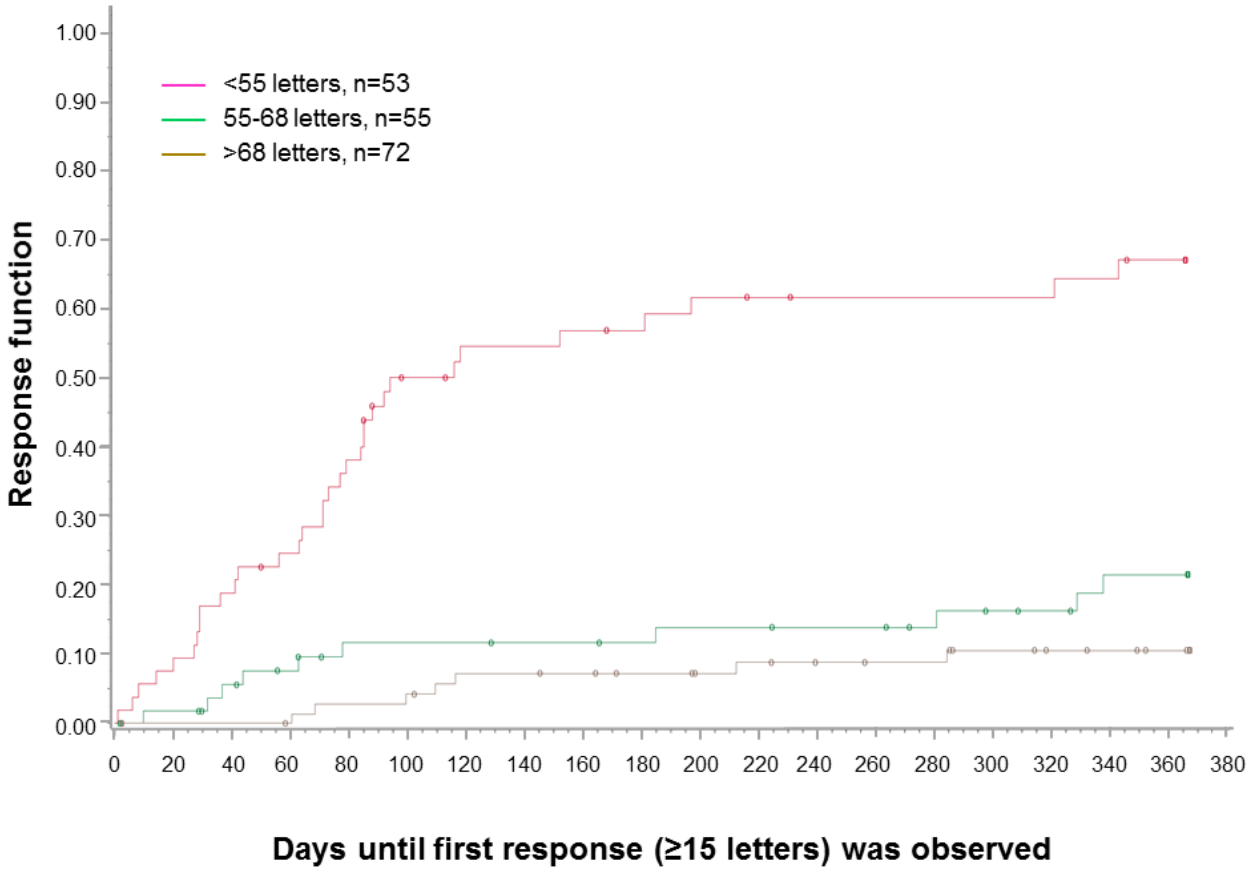


Pre-treated participants

(c) Stratified by sex



(d) Stratified by baseline visual acuity (ETDRS letters)

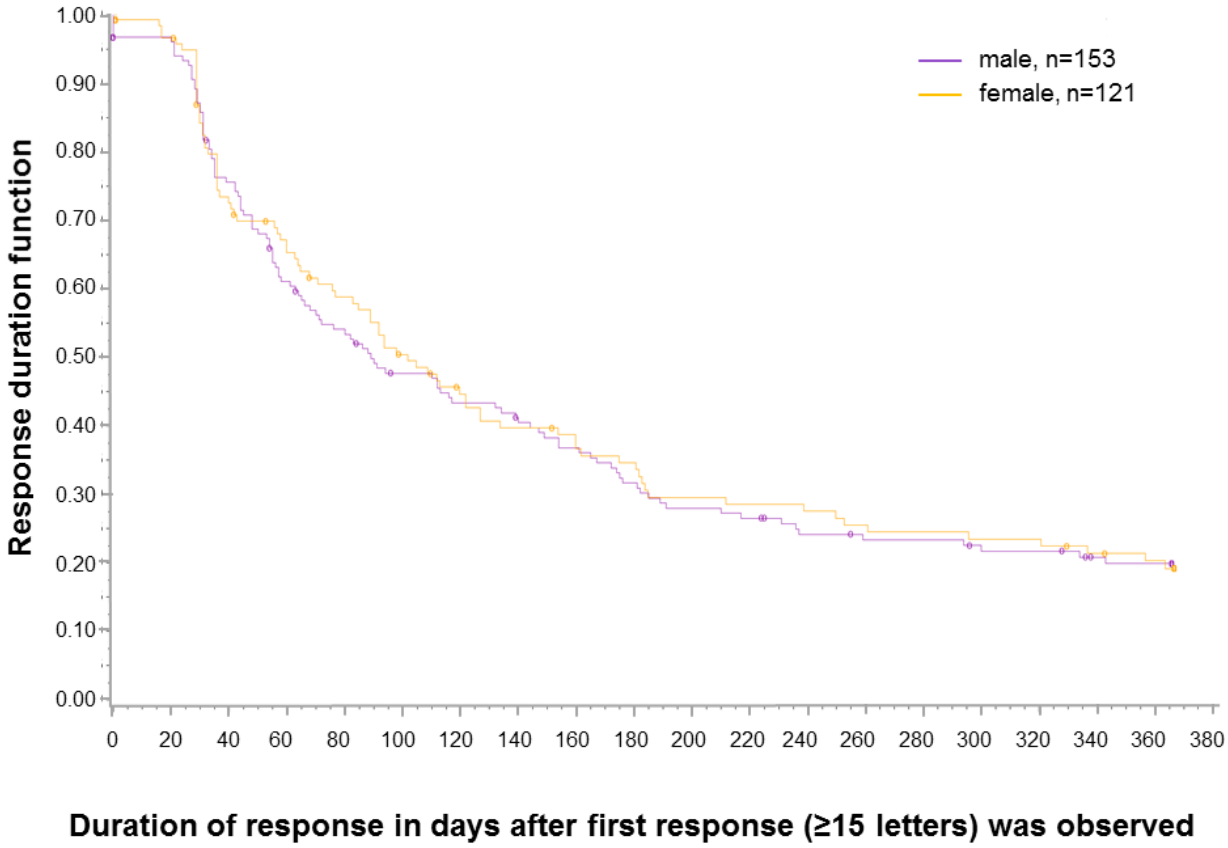


DME, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study.

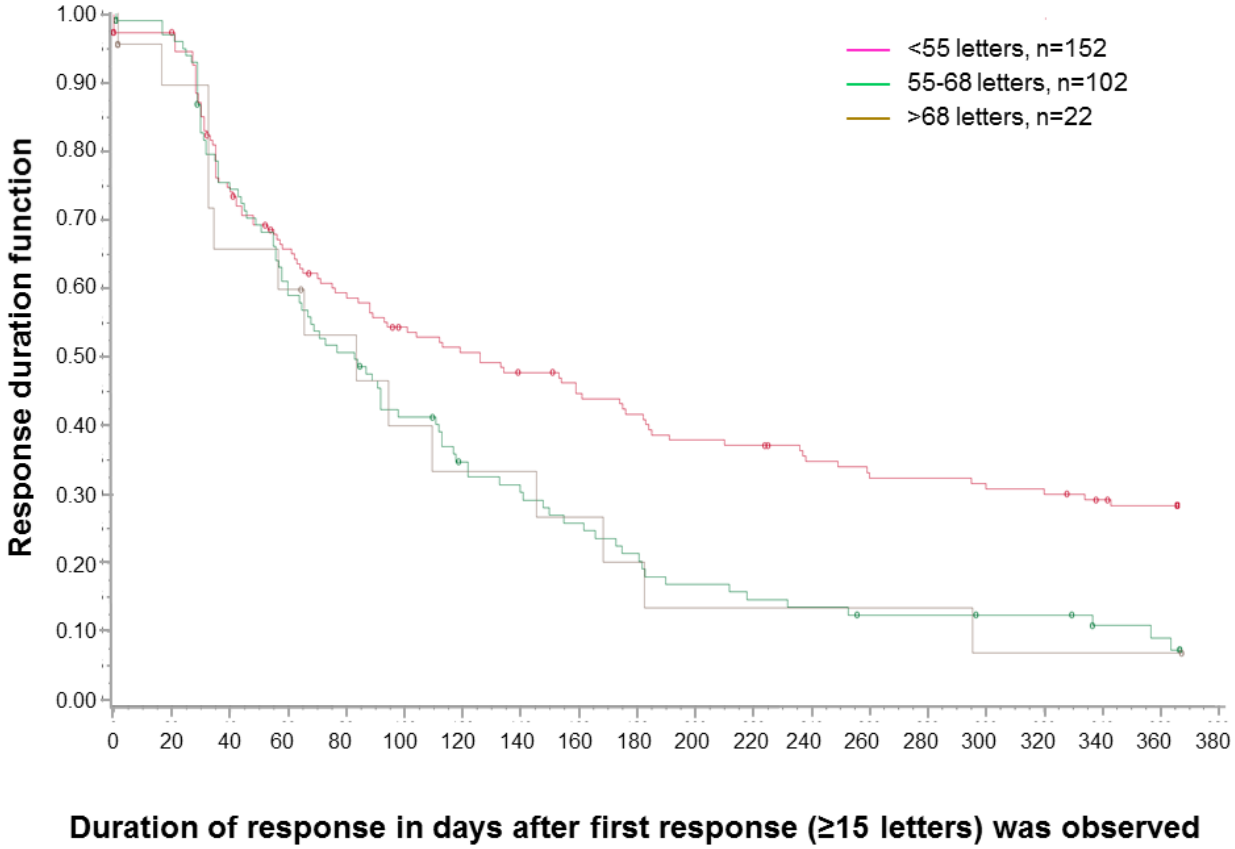
Supplementary Figure S5. *Duration-of-response (time from first ≥15 letters gain to first time point of losing this improvement) in participants with response in the first 12 months of the observational period, for treatment-naïve patients by (a) sex and (b) baseline visual acuity, and for pre-treated patients by (c) sex and (d) baseline visual acuity*

Treatment-naïve participants

(a) Stratified by sex

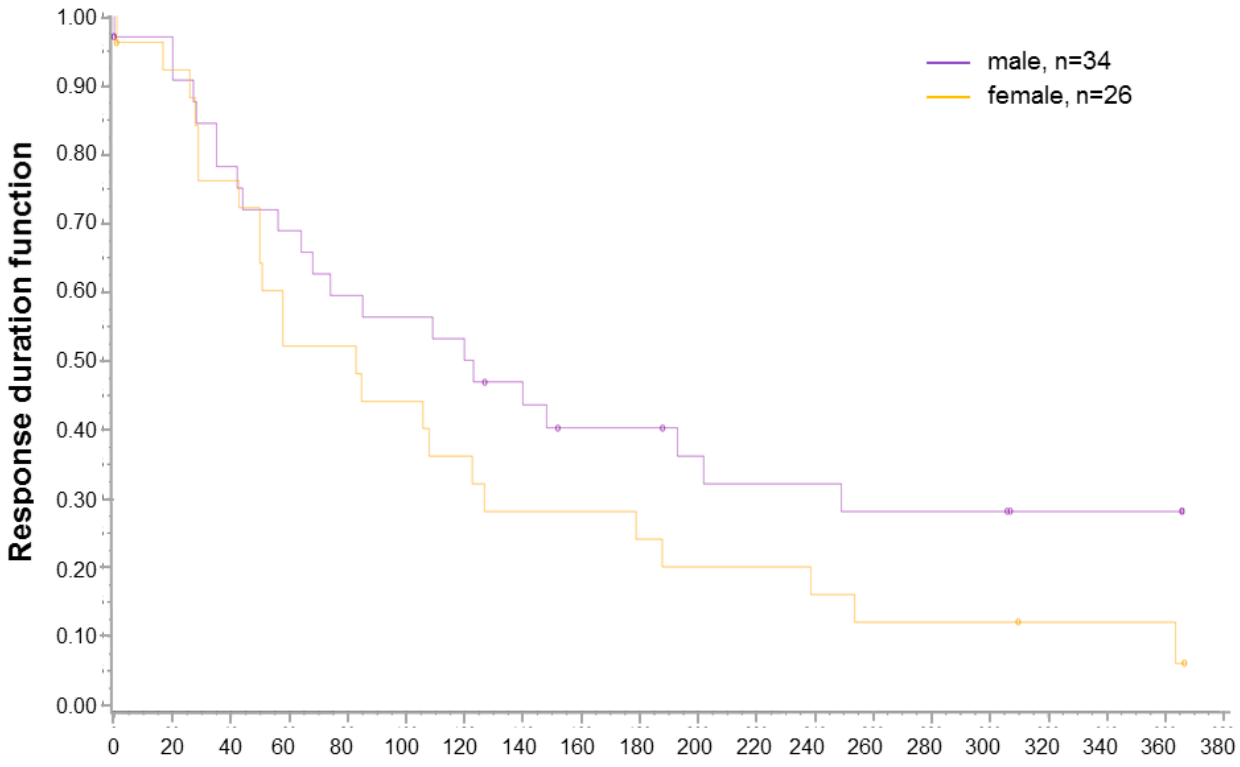


(b) Stratified by baseline visual acuity (ETDRS letters)



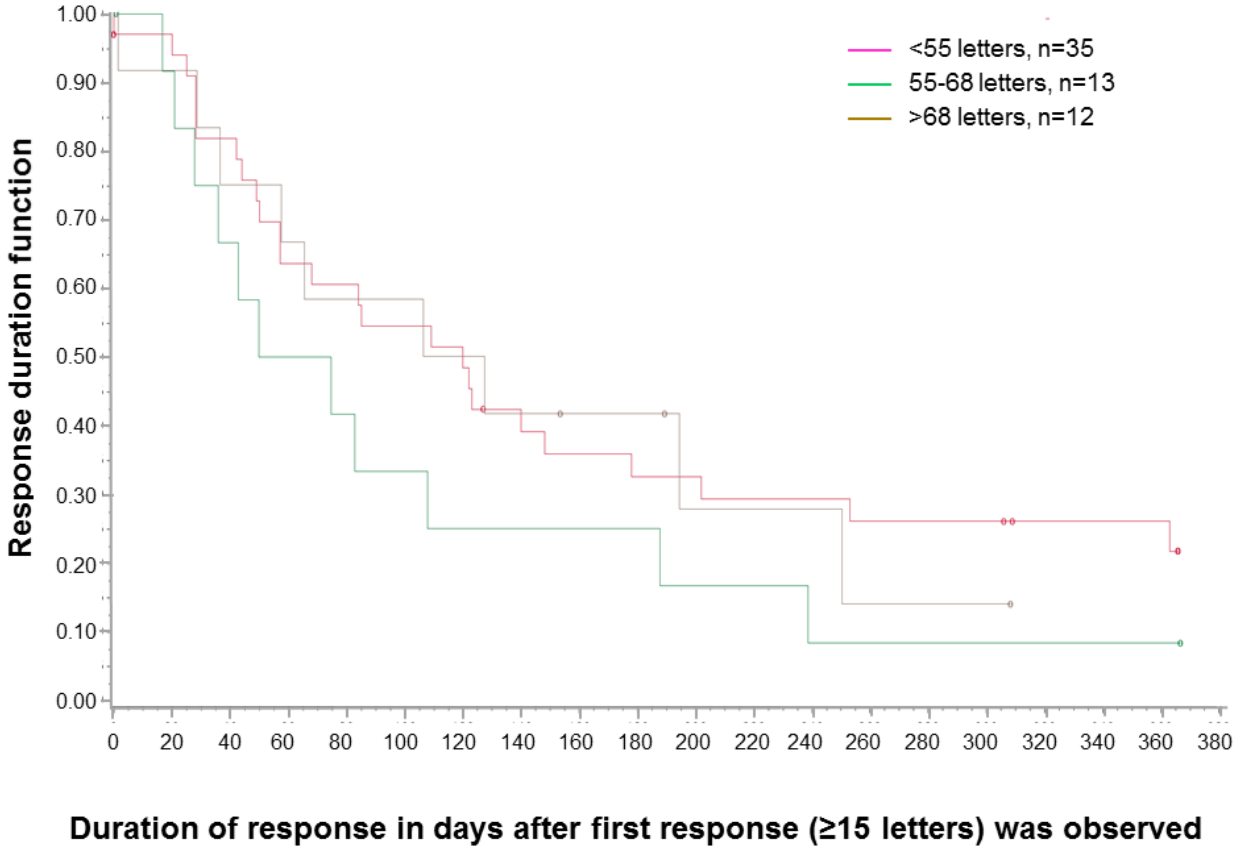
Pre-treated participants

(c) Stratified by sex



Duration of response in days after first response (≥15 letters) was observed

(d) Stratified by baseline visual acuity (ETDRS letters)



ETDRS, Early Treatment Diabetic Retinopathy Study.