Visual Functional Loss in Geographic Atrophy (GA): Learnings From Lampalizumab Trial Data

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Disclosures

Financial Disclosures

- Usha Chakravarthy
  - Relevant: Consultant: Apellis, Iveric Bio, Roche
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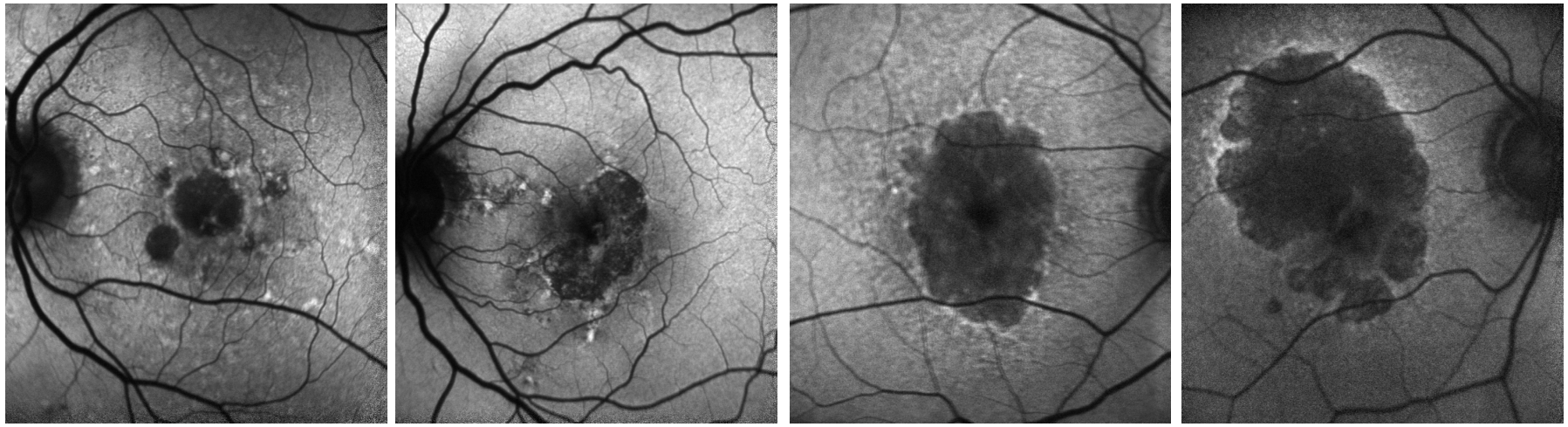
  - Data Safety Monitoring Board: Adverum, Oxurion

Study and Product Disclosures

- This presentation includes analyses of data from historical studies conducted in patients
- Institutional Review Board approval was obtained prior to study initiation
- Funding was provided by Genentech, Inc., a member of the Roche Group, for the study and third-party writing assistance, which was provided by Sara Molladavoodi, PhD, of Envision Pharma Group

Geographic Atrophy Is Pleomorphic

- GA lesions can vary in size, location, and appearance



Interventional trials have shown reductions in GA growth (measured by FAF) with no corresponding reduction in BCVA, a commonly used measure of retinal function

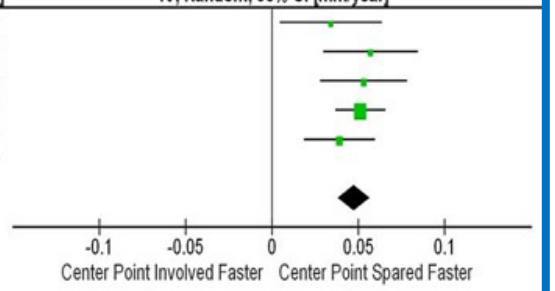
BCVA, best-corrected visual acuity; FAF, fundus autofluorescence; GA, geographic atrophy.

Established GA Growth Rate Modifiers

A. Effective Radius Growth Rate in Center Point Involved GA is Lower than Center Point Spared GA

Study or Subgroup	Center Point Spared Mean [mm/year]	SD [mm/year]	Total	Center Point Involved Mean [mm/year]	SD [mm/year]	Total	Weight	Mean Difference IV, Random, 95% CI [mm/year]
Domalpally 2013	0.186	0.164	212	0.152	0.158	265	10.1%	0.0340 [0.0049, 0.0631]
Holz 2018-Chroma Trial	0.237	0.12	134	0.18	0.107	140	11.8%	0.0570 [0.0300, 0.0840]
Holz 2018-Spectri Trial	0.232	0.115	125	0.179	0.095	166	14.0%	0.0530 [0.0282, 0.0778]
Keenan 2018	0.175	0.123	816	0.124	0.116	403	43.1%	0.0510 [0.0369, 0.0651]
Rosenfeld 2019	0.186	0.099	132	0.147	0.084	215	20.9%	0.0390 [0.0187, 0.0593]
Total (95% CI)			**1419**			**1189**	**100.0%**	**0.0478 [0.0385, 0.0570]**

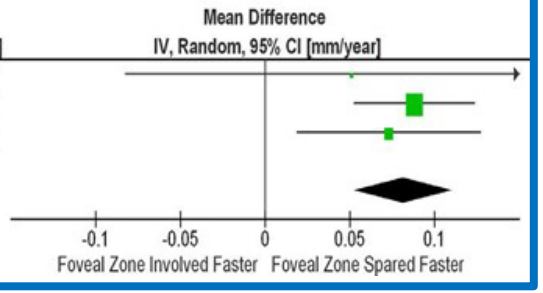
Heterogeneity: Tau² = 0.00; Chi² = 2.40, df = 4 (P = 0.66); I² = 0%
Test for overall effect: Z = 10.09 (P < 0.00001)



B. Effective Radius Growth Rate in Foveal Zone Involved GA is Lower than Foveal Zone Spared GA

Study or Subgroup	Foveal Zone Spared Mean [mm/year]	SD [mm/year]	Total	Foveal Zone Involved Mean [mm/year]	SD [mm/year]	Total	Weight	Mean Difference IV, Random, 95% CI [mm/year]
Allingham 2016	0.171	0.168	7	0.12	0.136	31	4.7%	0.0510 [-0.0823, 0.1843]
Mones 2018	0.224	0.131	75	0.136	0.072	53	66.6%	0.0880 [0.0526, 0.1234]
Schmitz-Valckenberg 2016	0.204	0.24	157	0.131	0.157	63	28.7%	0.0730 [0.0190, 0.1270]
Total (95% CI)			**239**			**147**	**100.0%**	**0.0820 [0.0530, 0.1109]**

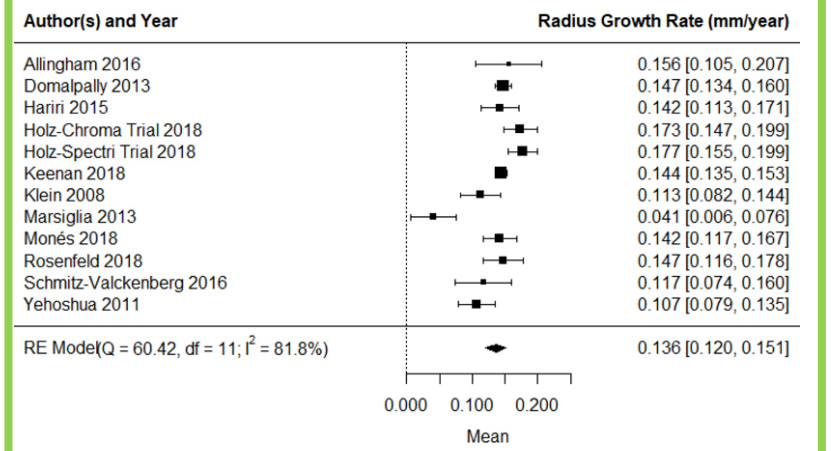
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 5.56 (P < 0.00001)



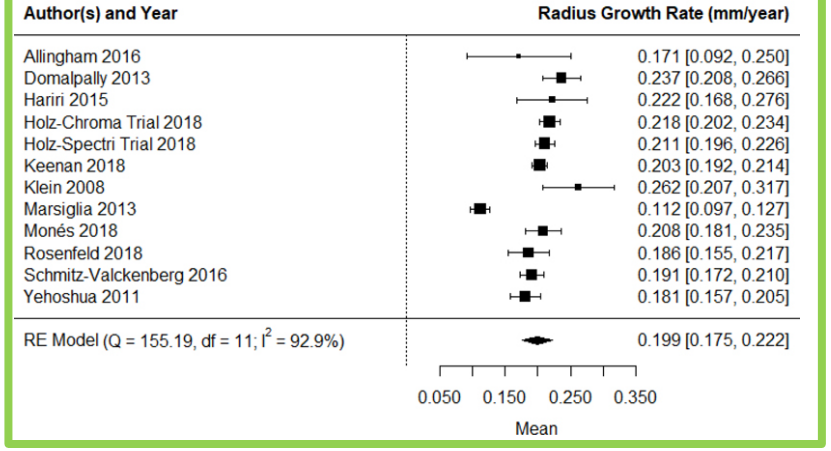
Published in Shen LL et al. *Invest Ophthalmol Vis Sci*. 2020.[1]

However, data on changes in function by growth rate and by GA features at baseline are limited and come from small samples

A Effective radius growth rate in unifocal group



B Effective radius growth rate in multifocal group



Published in Shen LL et al. *Ophthalmol Retina*. 2020.[2]

1. Shen et al. *Invest Ophthalmol Vis Sci*. 2020;61(1):2. Licensed under CC-BY 4.0: https://creativecommons.org/licenses/by/4.0/. 2. Shen LL et al. *Ophthalmol Retina*. 2020;4(9):899-910. Figure reprinted from Shen LL et al. Ophthalmology Retina. 2020;4(9):899-910 © 2020, with permission from the American Academy of Ophthalmology. GA, geographic atrophy; IV, interval variable; RE, random-effects.

Lampalizumab Clinical Trial Data Used to Explore the Impact of GA Lesion Growth Rate on Retinal Function

Lampalizumab Program

The large, long-term lampalizumab clinical trials provide a rich and unique source of data to explore the impact of GA lesion growth rate on retinal function

Key Inclusion Criteria

- Age ≥ 50 years

Study Eye

- BCVA ≥ 49 letters (ETDRS)
- Well-demarcated area(s) of GA secondary to AMD with no active or prior CNV
- GA lesion size ≥ 2.54 mm^2 (1 DA) and ≥ 17.78 mm^2 (7 DAs)
- Banded or diffused hypoautofluorescence adjacent to GA area
- Sufficiently clear ocular media

Fellow Eye

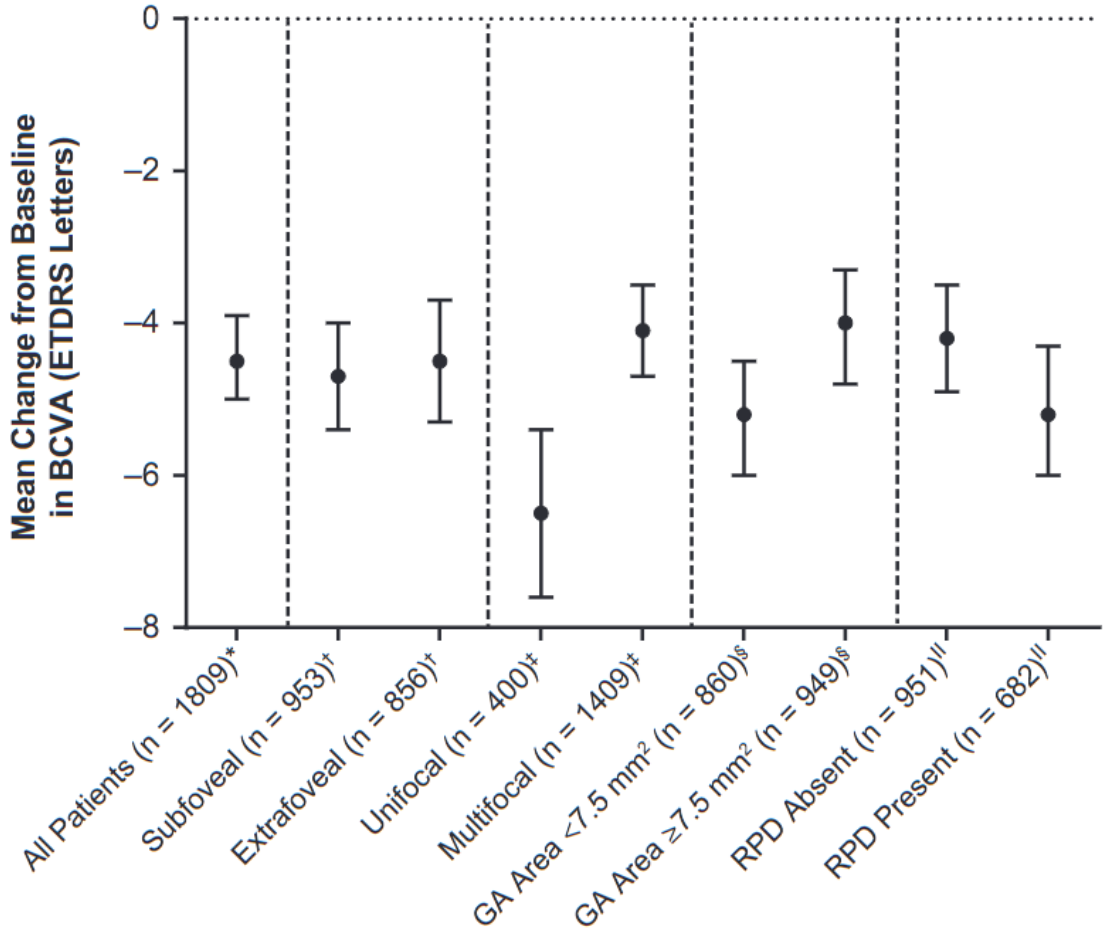
- GA secondary to AMD with no active or prior CNV

Number of Eyes Per Study: Chroma (n = 858; NCT02247479), Spectri (n = 935; NCT02247531) and Proxima A (n = 269; NCT02479386)

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; DA, disc area; ETDRS, Early Treatment Diabetic Retinopathy Study; GA, geographic atrophy.

BCVA Fall Is More Pronounced in Unifocal vs Multifocal Lesions

- In a previous analysis of data from the Chroma and Spectri trials, Heier et al[1] showed that the magnitude of the fall in BCVA was similar in subfoveal and extrafoveal lesions but more pronounced in unifocal vs multifoveal lesions



1. Heier JS et al. *Ophthalmol Retina*. 2020 Jul;4(7):673-688. Figure reprinted from Heier JS et al. Visual Function Decline Resulting from Geographic Atrophy: Results from the Chroma and Spectri Phase 3 Trials. Ophthalmol Retina. 2020 Jul;4(7):673-688, Copyright 2020, with permission from the American Academy of Ophthalmology.

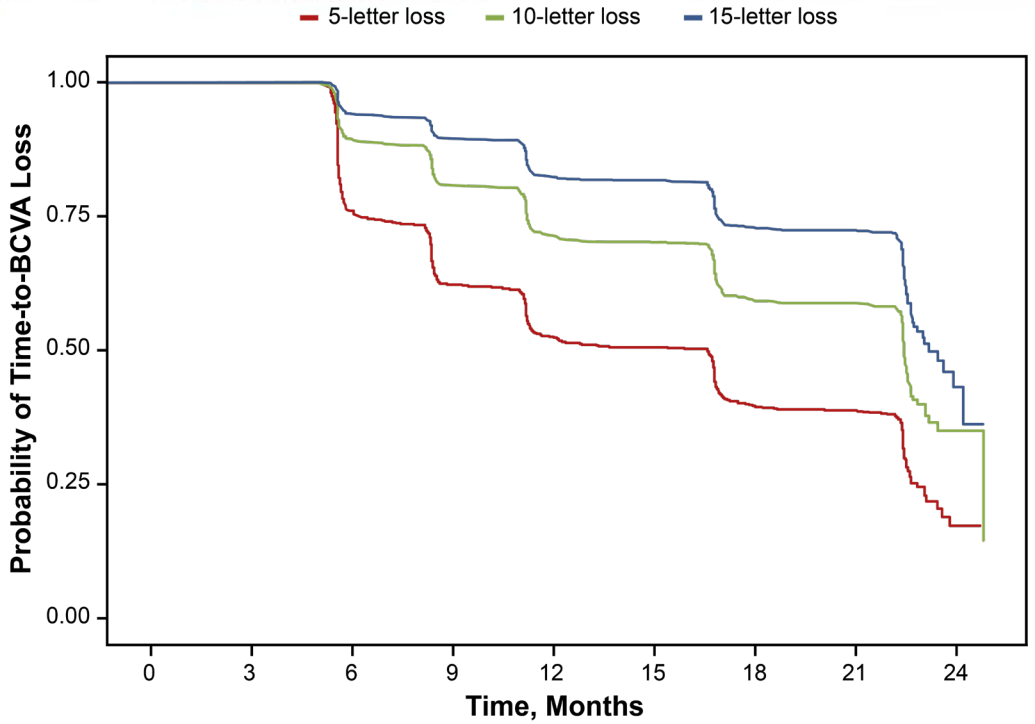
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; GA, geographic atrophy; RPD, reticular pseudodrusen.

Objective

The present analysis explored the effect of lesion characteristics and GA growth rate quartiles on BCVA loss using a time-to-event approach

BCVA, best-corrected visual acuity; GA, geographic atrophy.

KM Plots of Time to 5-, 10-, and 15-Letter Loss



Number at Risk									
Visit, months	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**
5-letter loss	2044	2044	1535	1228	948	898	582	559	7
10-letter loss	2044	2044	1799	1590	1293	1245	854	824	11
15-letter loss	2044	2044	1895	1760	1475	1434	1040	1005	13

METHODS

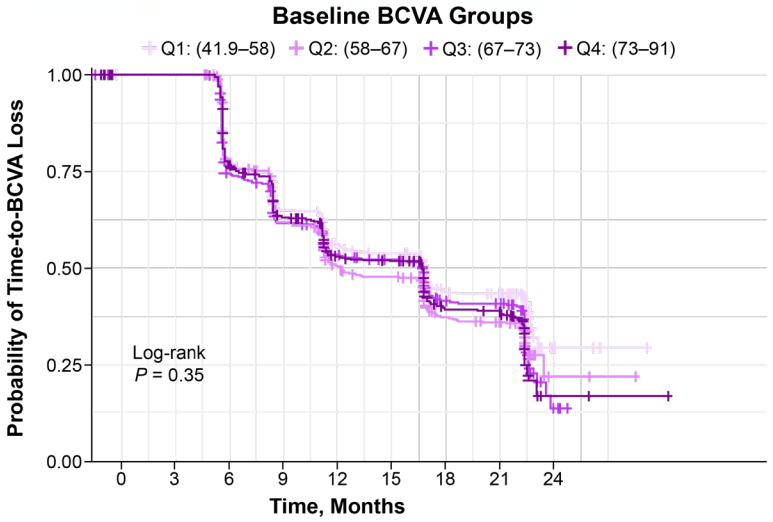
Cox regression model adjusted for baseline characteristics, including **BCVA**, **GA area**, **foveal involvement**, and **focality**

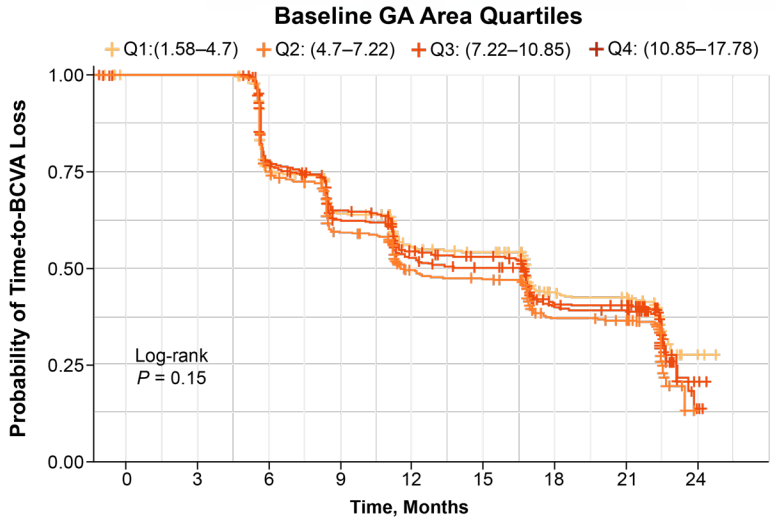
RESULTS

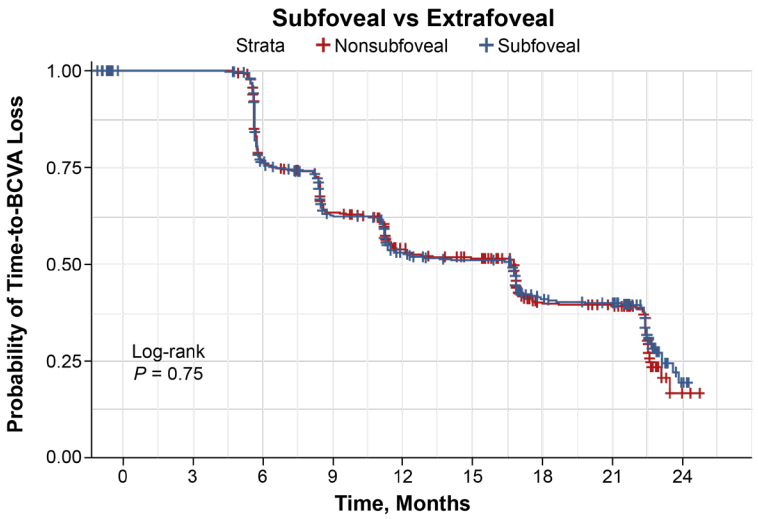
- **5-letter** loss occurred in **50%** of study eyes by 12 months and **75%** by 24 months
- **10-letter** loss occurred in **50%** by 24 months
- **15-letter** loss occurred in **25%** by 24 months

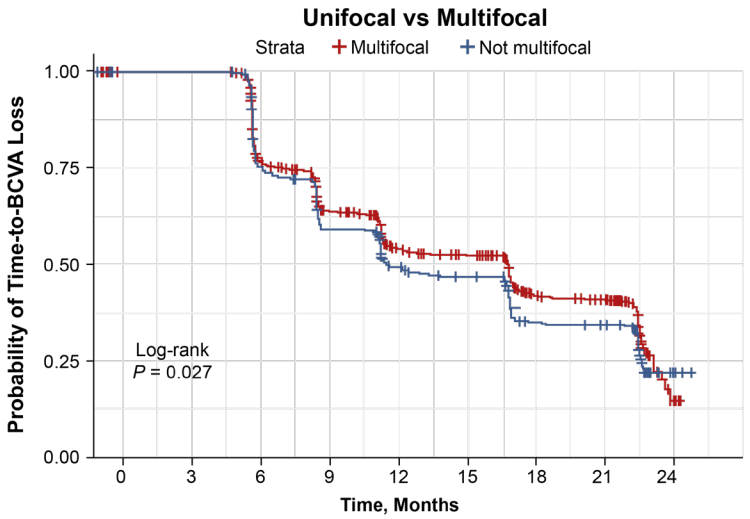
BCVA, best-corrected visual acuity; GA, geographic atrophy; KM, Kaplan–Meier.

KM Plots by Baseline Characteristics









Time-to-BCVA loss for 5 letters is shown in the above figures.
BCVA, best-corrected visual acuity; GA, geographic atrophy; KM, Kaplan–Meier; Q, quarter.

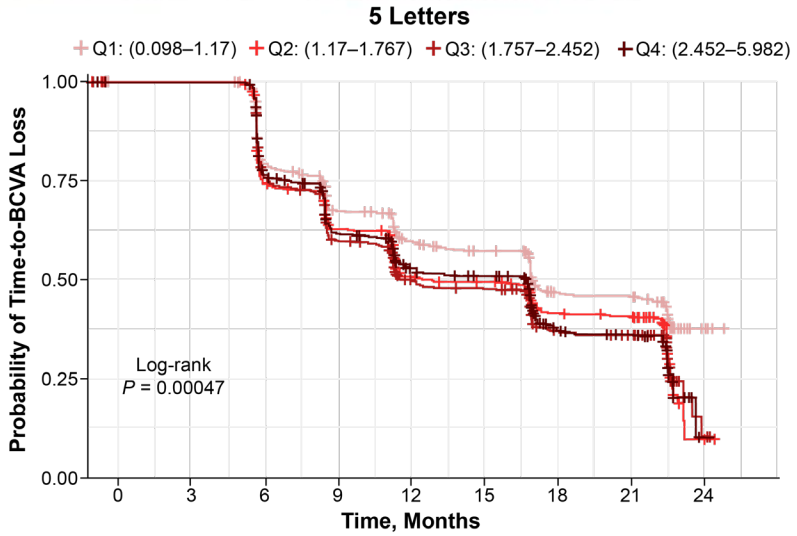
METHODS

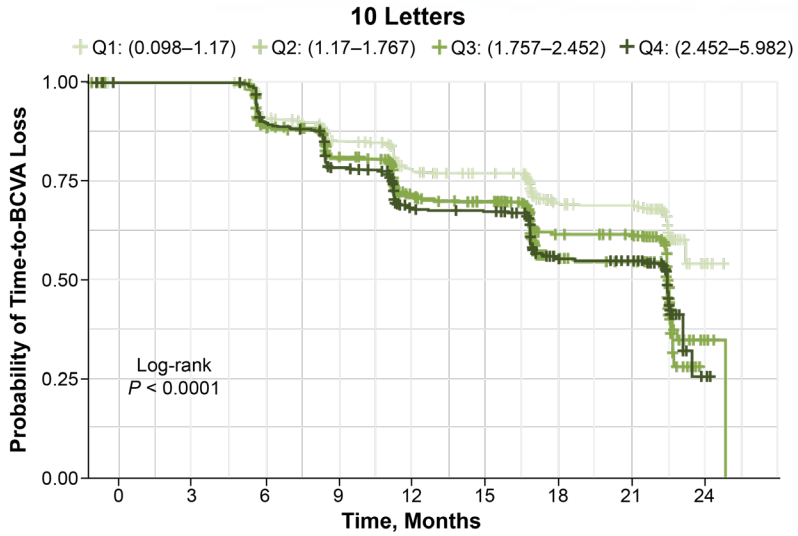
The probability of loss of 5, 10, and 15 letters was generated by KM analysis for baseline **BCVA, GA size, foveal involvement and focality**

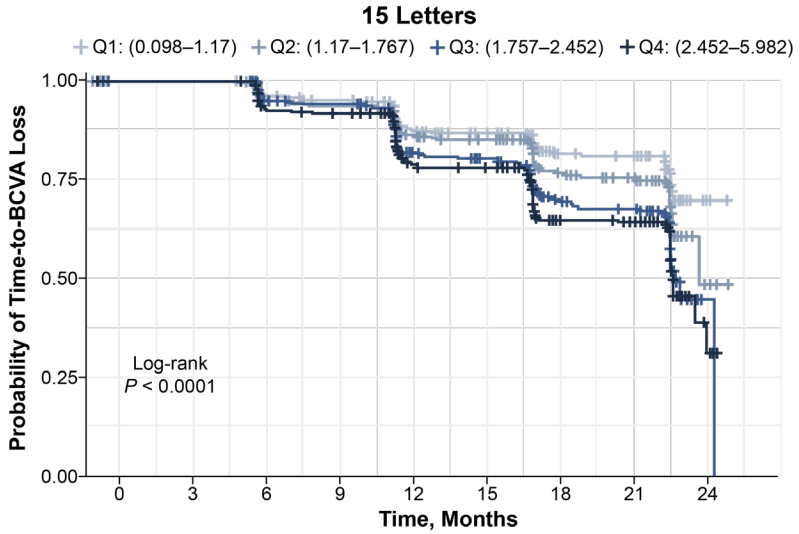
RESULTS

- **Baseline BCVA, GA area, and foveal involvement did not influence the rate of BCVA loss**
- **Time-to-BCVA loss of 5 letters was faster in unifocal compared with multifocal lesions**

KM Plots of Time To 5-, 10-, and 15-Letter Loss by GA Growth Rate Quartiles







BCVA, best-corrected visual acuity; GA, geographic atrophy; KM, Kaplan–Meier; Q, quarter.

METHODS

- GA growth rate was calculated for each eye and took into account all area measurements during the 2-year follow-up
- Growth rate quartiles were generated KM curves and plotted for 5-, 10-, and 15-letter loss

RESULTS

- **Study eyes classified in higher GA growth rate quartiles experienced shorter times to 5-, 10-, and 15-letter losses**

Take-Home Messages

- 2 years after enrollment into studies of GA, some three-quarters of eyes will have lost 5 letters of BCVA and one-quarter will have lost 15 letters
- Most baseline features did not influence rapidity of BCVA loss except for focality, with unifocal lesions losing BCVA at a faster rate
- Fast-growing lesions in higher quartiles of GA growth experienced more rapid losses of BCVA compared with slow-growing lesions
- Time-to-event analyses based on pragmatic measures of vision have the potential to discriminate between eyes with slower versus more rapid GA lesion growth

BCVA, best-corrected visual acuity; GA, geographic atrophy.

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Principal Statistical Scientist

Daniela Ferrara, MD, PhD, FASRS
Principal Medical Director