Optical coherence tomography risk factors for development of late age related macular degeneration in the fellow eyes of patients enrolled in the HARBOR Study.

Marco Nassisi[1,2], Jianqin Lei[1,2,3], Nizar Saleh Abdelfattah[1,2], Ayesha Karamat[1,2], Siva Balasubramanian[1,2], Wenying Fan[1,2,4], Akihito Uji[1,2], Kenneth M. Marion[1,2], Kirstie Baker[1,2], Xiwen Huang[1,2], Elizabeth Morgenthien[5], Srinivas R. Sadda[1,2].

1. Doheny Image Reading Center, Doheny Eye Institute, 1350 San Pablo St., DVRC211, Los Angeles, CA, 90033, USA.
2. Department of Ophthalmology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.
3. Department of Ophthalmology, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.
4. Beijing Tongren Eye Center, Beijing Tongren Hospital, Beijing Ophthalmology and Visual Sciences Key, Laboratory, Capital Medical University, Beijing, China.
5. Genentech, Inc., South San Francisco, CA, USA.

Corresponding Author:
SriniVas R. Sadda, MD
1355 San Pablo Street, Suite 211,
Los Angeles California 90033, United States
Tel: 323-342-6503 Fax: 323-442-6460
E-mail: SSadda@doheny.org

Keywords: age-related macular degeneration, optical coherence tomography, age-related macular degeneration progression

Short title: late AMD development in the fellow eyes of HARBOR

Abstract

Purpose: To evaluate the relationship between optical coherence tomography (OCT) features and the progression to late age related macular degeneration (AMD) in the fellow eyes of patients enrolled in the 24-month HARBOR study (NCT00891735) for neovascular AMD.

Design: post hoc analysis of a phase 3 multicenter, prospective, randomized, double-masked, active treatment-controlled clinical trial.

Participants: Evaluable subjects (N=501) with macular neovascularization (MNV) secondary to neovascular AMD and early or intermediate AMD in the fellow eye.

Methods: Volume OCT scans from 501 fellow eyes of 501 patients with MNV were reviewed. Baseline OCT features that were assessed included intraretinal hypereflective foci (IHRF), hyporeflective foci (hRF) within drusenoid lesions (DLs), subretinal drusenoid deposits (SDD) and drusen volume (DV) ≥ 0.03 mm^3. OCT images at months 6, 12, 18 and 24 were graded by masked graders for late AMD (defined as MNV and/or complete retinal pigment epithelium and photoreceptor atrophy (cRORA)). Subject demographic (age, gender, smoke exposure) characteristics and the baseline OCT features were correlated with progression to late AMD.

Main Outcome Measures: Incidence of late AMD, Hazard ratio (HR) for demographics and OCT risk factors.

Results: At month 24, 33.13% (166/501) eyes developed late AMD: 20.96% (105/501) developed cRORA while 12.18% (61/501) developed MNV. Baseline demographic factors were not significantly associated with development of late AMD while significant associations were identified for all OCT features. IHRF had a HR of 5.21 (95% confidence interval (CI): 3.29-8.26); hRF within DLs had a HR of 2.42 (95% CI: 1.74-3.38); SDD had a HR of 1.95 (95% CI: 1.34-2.82); DV ≥ 0.03 mm^3 had a HR of 1.46 (95% CI: 1.03-2.07). The correlation remained significant when considering only the progression to cRORA and MNV alone, except for DV which was not significantly associated with progression to MNV.

Conclusions: we confirmed that four previously reported OCT risk factors were associated with progression to late AMD in the fellow eyes of subjects newly diagnosed with MNV. Although outcomes > 2 years were not evaluated, these findings may help to identify high risk AMD patients.

Introduction

Age-related macular degeneration (AMD) is a progressive neuro-retinal disease. It is the leading cause of central vision loss among elderly individuals in the developed countries[1] and the probability of progression from intermediate stages to advanced AMD (i.e. macular neovascularization (MNV) and/or geographic atrophy (GA)) at 5 years can be as high as 27%, rising to 43% when subjects have advanced AMD in the fellow eye[2].

Early detection and prompt intervention in eyes with active exudative AMD has been shown to improve visual outcomes; therefore, it would appear to be important to identify the development of MNV at the earliest stage possible[3,4]. Although effective treatments are now available for MNV, there is no effective therapy for GA, with several agents having failed trials or still under assessment for preventing progression of GA[5]. Rather than attempting to intervene after GA or MNV have already developed, it may be preferable to prevent the development of late AMD. As such, though there are currently no treatments to prevent early AMD from progressing to GA, it is hoped that such therapeutics may be available in the near future. Optical coherence tomography (OCT) is a critical diagnostic tool for the evaluation of patients with AMD. The ease of acquisition and high axial resolution allow excellent visualization of the retinal morphology. Several previous retrospective studies have identified features on OCT which may be associated with a higher risk for progression to late AMD. These features include intraretinal hyperreflective foci (IHRF)[6,7], hyporeflective foci (hRF) within drusenoid lesions (DLs)[6], subretinal drusenoid deposits (SDD)[8–11], and higher drusen volume[12]. Recently *Lei et al.* proposed a simple OCT-based scoring system for progression of AMD considering all those features together in a context of a retrospective cohort study[13].

In order to validate these presumed OCT risk factors in the context of a longitudinal prospective study, we performed a post hoc grading of images from the fellow eyes of subjects enrolled in HARBOR, a large, 2-year prospective phase 3 multicenter randomized clinical trial that evaluated the efficacy and safety of ranibizumab for neovascular AMD.

Methods

This study was a retrospective, post hoc analysis of the HARBOR trial (ClinicalTrials.gov identifier: NCT00891735), a phase 3 multicenter, prospective, randomized, double-masked, active treatment controlled clinical trial whose study design and primary 12-month and 24-month outcomes were reported previously[14,15].

Briefly, HARBOR evaluated the efficacy and safety of 2 doses and 2 regimens of ranibizumab in 1097 patients aged 50 years with new diagnosis of subfoveal neovascular AMD. Study eye inclusion criteria included BCVA of 20/40 to 20/320 (Snellen equivalent) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts; active subfoveal MNV lesions (regardless of classic or occult composition); total area of lesion < 12 disc areas or 30.48 mm^2 ; and total MNV area constituting at least 50% of total lesion area based on fluorescein angiography (FA). Regarding the fellow eye, exclusion criteria were: (1) previous treatment or participation in a clinical trial involving anti-angiogenic drugs (Avastin®, anecortave acetate, protein kinase C inhibitors, etc.) within 3 months of Day 0; (2) prior injection of Lucentis® or Macugen® in the non-study eye within 7 days of Day 0; (3) prior treatment with Visudyne® in the non-study eye < 7 days preceding Day 0.

All participants in HARBOR provided written informed consent, and the study protocol was approved by institutional review boards before the study start. The study was conducted in accordance with Good Clinical Practice (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E6), applicable U.S. Food and Drug Administration regulations, the Health Insurance Portability and Accountability Act, and the tenets of the Declaration of Helsinki.

The population of randomized HARBOR patients (n=1097) was the starting cohort for this analysis. In particular we focused on the fellow eyes of these patients where data were available (n=941). All available OCT images from fellow eyes of HARBOR study patients acquired with a Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA; 512x128 macular cube; 6x6mm; centered on fovea) at baseline, month 6, month 12, month 18 and month 24 were re-read by masked graders at the Doheny Image Reading Center (DIRC; Los Angeles, CA).

OCT Grading Protocol

Baseline OCT scans were first reviewed to identify subjects eligible for this analysis. Eyes with presence of either complete or incomplete retinal pigment epithelium (RPE) and outer retinal atrophy (cRORA and iRORA respectively) or MNV were excluded from the analysis. The cRORA was defined using the Classification of Atrophy Meeting (CAM)[16] criteria as hypertransmission of OCT signal into the choroid (at least 250 microns in diameter) with an overlying RPE defect and thinning of the outer retina[16]. For iRORA, some hypertransmission is evident but it is discontinuous as the overlying RPE band is present but irregular or interrupted. Interruptions in the continuity of the ELM and EZ may be present and the inner nuclear layer (INL) and outer plexiform layer (OPL) may demonstrate subsidence but criteria for cRORA are not met[16]. A pigment epithelial detachment (PED) was considered suspicious for MNV (Type 1 NV) based on its shape (irregular elevation), heterogeneous internal reflectivity and/or presence of exudation (intraretinal, subretinal, sub-RPE fluid)[17]. Other features suggestive of Type 2 NV (subretinal hyperflective material-SHRM) or Type 3 NV (intraretinal hyper-reflective features with associated cystoid macular edema overlying a PED with an apical defect) were also evaluated for[18,19] . All subjects with iRORA, cRORA and MNV (of any type) at baseline were excluded from this post hoc analysis.

Eyes with non-visually significant vitreoretinal interface disease, such as a subtle epiretinal membrane, were not excluded; however, those with evidence of any other pathology involving the macula, such as high myopia, central serous chorioretinopathy, macular hole, or retinal vascular disease, were excluded. After applying these criteria, 501 subjects were eligible for further analysis (figure 1).

In this cohort of eligible subjects, all 128 B-scans of the baseline OCT were reviewed for the presence of three qualitative features (IHRF, hRF within DL and SDD) as previously described[13]. Briefly, IHRF were defined as discrete, well-circumscribed hyperreflective lesions within the neurosensory retina, with a minimum size of 3 pixels and a reflectivity equal or higher than the RPE band[15]. To identify hRF, graders scrutinized drusen with a height of at least 40 μm[17], as a sufficient number of pixels inside a drusen must be present to reliably determine internal hRF. Subretinal drusenoid deposits were identified as medium-reflective hyper-reflective mounds or cones, either at the level of the ellipsoid zone or between the ellipsoid zone and the RPE surface. At least three lesions had to be identified on one B-scan in order for SDD to be deemed to be definitively present. The topographic organization of SDD, with multiple deposits commonly present at regularly spaced intervals within a region of the retina, also aided in recognition of these lesions.

Using conventional reading-center practices, a lesion was deemed present if the grader had a >90% confidence that it was present in at least one B-scan. The standard Cirrus Advanced RPE analysis software (version 8.0) was used to automatically generate drusen volume within a 3-mm circle centered on the fovea. All images were randomly assigned to two masked, independent graders for evaluation. The grading process consisted of three steps: first, all 941 baseline images of patients with available data were graded for eligibility; second, all 501 eligible baseline images were graded for the presence of IHRF, hRF and SDD; third, the set of visits at months 6, 12, 18 and 24 for each subject was graded for progression to late AMD (whether cRORA or MNV). Discrepancies between graders were resolved by open adjudication. If no consensus was reached, a final decision was made by the medical director of the reading center (SRS).

Study Outcomes and Statistical Analysis

The primary outcome measure was progression to late AMD, defined as the appearance of MNV or cRORA at any of the follow-up visits. A multivariable Cox regression model was fit to determine if the baseline retinal anatomic features in these eyes and demographic characteristics (i.e. age, gender and smoking status) were risk factors for developing late AMD. Hazard ratios (HRs) and 95% confidence intervals (CI)

were calculated. Patients with no MNV or cRORA detected during follow-up were censored at the last on-study assessment (24 month visit).

All subjects were grouped in different categories of risk according to the scoring system elaborated by *Lei et al*[13]. Briefly, this scoring system assigns one point for the presence of each feature (i.e. IHRF, hRF, SDD and DV), in each eye. By summing the score from both eyes, the final total score (TS) could range from 0 to 8 points for each subject. When one of the two eyes has atrophy or MNV, it is automatically awarded 4 points. Finally the TS values are combined and collapsed into four severity categories based on the total score: categories I (score 0, 1, 2), II (score 3, 4), III (score 5, 6), and IV (score 7, 8). Since in our analysis all eligible subjects had one eye with MNV (inclusion criteria for the HARBOR trial), all subjects had a starting score of 4 , and thus no subjects were assigned to category I. Kaplan-Meier survival curves were plotted and logistic regression analysis performed to test the effectiveness of the scoring system. For cases with a 0 response in any category, the odds ratio, 95% confidence limits and p-value were estimated after adding 0.5 to each cell.

Results

From the initial cohort of 1097 subjects enrolled in the HARBOR study, 501 were eligible for the evaluation of the fellow eye in this post hoc analysis (figure 1). A summary of the demographics and baseline characteristics is provided in Table 1.

Baseline Risk Factors for late age related macular degeneration development

At the baseline visit, IHRF were found in 219 (43.7%) eyes , hRF within DLs were evident in 94 (18.8 %) eyes, while 257 (51.3%) eyes had SDD within the 6x6mm macular scans. A total of 82 (16.4%) eyes had a drusen volume ≥ 0.03 mm^3 within the 3-mm circle. Among the cohort of 501 subjects with neovascular AMD in one eye, 105 (21.0%) fellow eyes progressed to cRORA while 61 (12.2%) progressed to neovascular AMD within 24 months (figure 2).

The results of the multivariable Cox regression analysis performed on the baseline OCT features and demographics characteristics to determine the risk of developing late AMD are summarized in Figure 3. All the OCT features considered in this study were significantly associated with an increased risk of developing either cRORA or MNV within the 2 years of the study. IHRF had a HR of 5.21 (95% CI: 3.29-8.26, p<0.01); hRF within DLs had a HR of 2.42 (95% CI: 1.74-3.38, p<0.01); SDD had a HR of 1.95 (95% CI: 1.34-2.82, p<0.01); DV ≥ 0.03 mm^3 had a HR of 1.46 (95% CI: 1.03-2.07, p=0.03). The correlation remained significant when considering only the progression to cRORA: HR was 10.66 (95% CI: 4.96-22.89 p<0.01) for IHRF; 2.83 (95% CI: 1.89-4.26, p<0.01) for hRF within DLs; 2.05 (95% CI: 1.26-3.32, p<0.01) for SDD; 1.74 (95% CI: 1.14-2.66, p=0.01) for DV ≥ 0.03 mm^3. However, for progression to MNV alone, IHRF (HR, 2.84; 95% CI: 1.5-5.36, p<0.01), hRF within DLs (HR, 1.83; 95% CI: 1.02-3.28, p=0.04) and SDD (HR, 1.9; 95% CI: 1.05-3.44, p=0.03) remained significant risk factors, DV ≥ 0.03 mm^3 was not. Other evaluated baseline factors were not significantly associated with development of late AMD or either MNV or cRORA alone at 2 years (i.e. age, gender and smoking exposure) (Figure 3).

Effectiveness of the composite OCT scoring system

Given the presence of MNV in the study eyes, the variability in a given subjects score was driven by the OCT characteristics of the fellow eye, ranging among three possible categories: category II (score 4) when no risk features were present, category III (scores 5-6) when one or two features were present, and category IV (scores 7-8) when three or all risk features were present. In the analyzed cohort of 501 fellow eyes, 166 (33.1%) were assigned to category II, 245 (48.9%) to category III and 90 (18%) to category IV. The progression rate to late AMD, and cRORA and MNV alone by category, are shown in Table 2.

Kaplan-Meier survival curves showing the cumulative incidence of either late AMD or MNV and cRORA alone were plotted for each category (Figure 4). A *log rank* test revealed a strongly significant difference among the curves for each outcome ($p<0.001$).

Repeatability

The unweighted kappa values for intergrader repeatability were 0.96 (903/941) for eligibility criteria, 0.9 (450/501) for IHRF, 0.84 (421/501) for hRF, 0.8 (402/501) for SDD and 0.94 (470/501) for progression to late AMD. Agreement was reached for all discrepancies after adjudication between graders.

Discussion

In this study, we confirmed that four previously reported OCT risk factors were associated with progression to late AMD in the fellow eyes of subjects newly diagnosed with MNV. Drusen volume ≥ 0.03 mm^3 within the central 3-mm circle and the presence of IHRF, hRF within a DL, and SDD were all associated with an overall progression to any late AMD. Specifically, we observed that IHRF was the strongest individual predictor for progression to late AMD in accordance with previous literature[13]. Recent studies demonstrated that the association or co-localization of IHRF with the drusen apex in AMD showed an increased correlation with RPE atrophy at baseline[20] or, if atrophy was not already present, with an increased risk of developing atrophy at that location[6].

In this study, the presence of IHRF was also associated with a greater risk for progression to both atrophy and MNV alone. Our finding that IHRF were a risk factor for MNV is consistent with our previous work showing that IHRF commonly precede the development of type 3 NV (retinal angiomatous proliferation)[21].

Hyporeflective foci within DLs were also suggested to be a risk factor for atrophy in our previous studies[6,13]. We have previously hypothesized that increased heterogeneity of the internal structure of the drusenoid lesion might represent further impairment of the RPE overlying the drusen and a greater likelihood of the drusen's collapse[6]. Subretinal drusenoid deposits (or reticular pseudodrusen)[11] were a consistent risk factor for progression to both atrophy and MNV in our analysis in accordance with previous literature[9,10].

Overall, drusen volume was the least predictive of the four parameters and also the only one not significantly associated with the development of MNV. There could be several explanations for this finding: (1) drusen are known to grow and recede; and a sharp reduction in drusen volume has been reported prior to the development of advanced AMD; (2) volume alone may be insufficient for characterization of a drusen's risk for atrophy. *De Sisternes et al.*[22] reported an automated prediction model for the development of neovascular AMD based not only on DV but also on the number, morphology and reflectivity properties of the drusen. Therefore a severity or prognostic scale including only drusen volume may be insufficient. DV does have an important advantage in that it is automatically generated and does not require clinician review of the OCT B-scans.

Among the demographic factors, age, gender and smoking exposure did not impact the 2-year progression to late AMD.

We decided to apply the score proposed in our previous work to test its reliability in a larger cohort, given its ease of use and potential application for patient counseling in clinical practice[13]. The severity categories appeared to correlate well with progression risk to late AMD, with approximate progression rates of 5, 33, and 84% for category II, III and IV respectively. The identification of subgroups with especially high progression rates (≥70%) could be of particular value, especially since these high risk patients may benefit from enrollment in future early intervention clinical trials.

When assessing our results and progression rates, it is important to note that our study did not include subjects with early or intermediate AMD, as they all had MNV in one eye. Compared to the Age-related Eye Disease Study (AREDS) which reports a rate of progression of 24.4% for the fellow eyes of MNV in 2 years, we report an overall higher rate of 33.2%[2]. At the same time, the rate of progression to MNV in our study is 12.2%, while the post-hoc analysis of the fellows eyes of the Comparison of Age-related Macular Degeneration Treatments Trials (CATT), the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study and the Minimally Classic/ Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA), report a 2-years progression rate to MNV of 18.6%, 30.4% and 23.8% respectively[23,24]. A possible explanation to these discrepancies is that we only used structural OCT to identify the late AMD endpoints. For example, while color fundus photos were used to evaluate for progression to advanced AMD in the AREDS trial, structural volume OCT used in our HARBOR analysis may have yielded a higher sensitivity for detecting cRORA in our study. At the same time, the lack of dye-based angiography in our HARBOR OCT analysis, may explain the lower incidence of MNV compared to other trials.

As regards the OCT scoring system, we previously tested it for subjects with intermediate AMD. Compared with the previous study, we observed a lower rate of progression for eyes assigned to category II (5% versus 14% in the previous study) and a slightly higher rate for category IV (84% versus the previous 73%)[13]. The differences, especially the lower risk in “Category II ” eyes in our cohort, are perhaps not surprising since the Category II fellow eyes in our cohort would have had no OCT risk features (all 4 points would have come from the presence of MNV in the other eye). Of note, after 24 months, only 9 eyes in Category II developed late AMD and in particular only MNV. This observation highlights the fact that the presence of MNV in one eye is an important risk factor for the development of MNV in the second eye. As we did not evaluate imaging modalities aside from OCT, we cannot completely exclude that factors other than AMD may have contributed to the development of MNV in these Category II eyes. However, even though these

eyes had no risk factors according to our classification, they did have evidence of drusen on OCT, but at a volume below the threshold of 0.3 mm^3.

Our study has some limitations that must be considered when evaluating our results. First of all, as previously stated, our cohort consists of only patients with MNV in the other eye, therefore the rates of progression and the odds ratios related to the risk factors described can only be applied to this group of participants and may differ if cRORA rather than MNV is present in the fellow eye. However, prediction of progression in the "good eye" might be particularly relevant for the overall visual prognosis of these patients and might help the clinician to better assess their pathology, inform them of the risks and plan their follow-up.

Although HARBOR trial was a prospective trial with two years of follow-up, this could be still considered a relatively short time in the context of a chronic disease such as AMD.Another limitation is that we only used structural OCT to identify both risk factors as well as progression to the late AMD endpoint. FA or OCTA were not available for this post hoc analysis to confirm the presence or absence of MNV. However, as structural OCT is a ubiquitously obtained diagnostic test in clinical practice, the use of OCT and identification of OCT risk factors may be of greatest clinical relevance. Finally, we elected to exclude eyes with iRORA at baseline, reducing the number of eligible patients for this analysis [16]. Since the presence of iRORA constitutes an important risk factor for developing cRORA in a relatively short time[26], this inclusion of cases with iRORA at baseline could have potentially confounded the odds ratio of the other OCT risk factors.

Our study also has strengths, including the use of standardized data collected in the context of a large prospective trial, the use of a standardized assessment protocol and the use of two masked, independent, experienced reading center graders for each image..

In summary, this post hoc analysis of the fellow eyes of subjects enrolled in the HARBOR trial, validates previously proposed OCT risk factors for progression to late AMD, with IRHF, hRF within DLs, SDD, and DV ≥ 0.03 mm^3 (in diminishing order of importance) all confirmed to be of relevance. These

observations may be used to guide patient prognostication in clinical practice, establishment of follow-intervals for re-assessment, and selection and randomization of eyes at the highest risk for future early intervention trials.

References

1. Bressler NM, Bressler SB, Congdon NG, et al. Potential public health impact of Age-Related Eye Disease Study results: AREDS report no. 11. *Arch Ophthalmol Chic Ill 1960*. 2003;121(11):1621-1624.

2. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol Chic Ill 1960*. 2001;119(10):1417-1436.

3. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1997;104(1):7-21.

4. Wong RW, Richa DC, Hahn P, Green WR, Dunaief JL. Iron toxicity as a potential factor in AMD. *Retina Phila Pa*. 2007;27(8):997-1003.

5. Jack LS, Sadiq MA, Do DV, Nguyen QD. Emixustat and Lampalizumab: Potential Therapeutic Options for Geographic Atrophy. *Dev Ophthalmol*. 2016;55:302-309.

6. Ouyang Y, Heussen FM, Hariri A, Keane PA, Sadda SR. Optical coherence tomography-based observation of the natural history of drusenoid lesion in eyes with dry age-related macular degeneration. *Ophthalmology*. 2013;120(12):2656-2665.

7. Nassisi M, Fan W, Shi Y, et al. Quantity of Intraretinal Hyperreflective Foci in Patients With Intermediate Age-Related Macular Degeneration Correlates With 1-Year Progression. *Invest Ophthalmol Vis Sci*. 2018;59(8):3431-3439.

8. Finger RP, Chong E, McGuinness MB, et al. Reticular Pseudodrusen and Their Association with Age-Related Macular Degeneration: The Melbourne Collaborative Cohort Study. *Ophthalmology*. 2016;123(3):599-608.

9. Marsiglia M, Boddu S, Bearelly S, et al. Association between geographic atrophy progression and reticular pseudodrusen in eyes with dry age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2013;54(12):7362-7369.

10. Zhou Q, Daniel E, Maguire MG, et al. Pseudodrusen and Incidence of Late Age-Related Macular Degeneration in Fellow Eyes in the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2016;123(7):1530-1540.

11. Spaide RF, Ooto S, Curcio CA. Subretinal Drusenoid Deposits AKA Pseudodrusen. *Surv Ophthalmol*. May 2018.

12. Abdelfattah NS, Zhang H, Boyer DS, et al. Drusen Volume as a Predictor of Disease Progression in Patients With Late Age-Related Macular Degeneration in the Fellow Eye. *Invest Ophthalmol Vis Sci*. 2016;57(4):1839-1846.

13. Lei J, Balasubramanian S, Abdelfattah NS, Nittala MG, Sadda SR. Proposal of a simple optical coherence tomography-based scoring system for progression of age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 2017;255(8):1551-1558.

14. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(5):1046-1056.

15. Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2014;121(11):2181-2192.

16. Sadda SR, Guymer R, Holz FG, et al. Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT: Classification of Atrophy Report 3. *Ophthalmology*. November 2017.

17. Lee SY, Stetson PF, Ruiz-Garcia H, Heussen FM, Sadda SR. Automated characterization of pigment epithelial detachment by optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2012;53(1):164-170.

18. Kim JH, Chang YS, Kim JW, Lee TG, Kim HS. DIAGNOSIS OF TYPE 3 NEOVASCULARIZATION BASED ON OPTICAL COHERENCE TOMOGRAPHY IMAGES. *Retina Phila Pa*. 2016;36(8):1506-1515.

19. Jung JJ, Chen CY, Mrejen S, et al. The incidence of neovascular subtypes in newly diagnosed neovascular age-related macular degeneration. *Am J Ophthalmol*. 2014;158(4):769-779.e2.

20. Leuschen JN, Schuman SG, Winter KP, et al. Spectral-domain optical coherence tomography characteristics of intermediate age-related macular degeneration. *Ophthalmology*. 2013;120(1):140-150.

21. Nagiel A, Sarraf D, Sadda SR, et al. Type 3 neovascularization: evolution, association with pigment epithelial detachment, and treatment response as revealed by spectral domain optical coherence tomography. *Retina Phila Pa*. 2015;35(4):638-647.

22. de Sisternes L, Simon N, Tibshirani R, Leng T, Rubin DL. Quantitative SD-OCT imaging biomarkers as indicators of age-related macular degeneration progression. *Invest Ophthalmol Vis Sci*. 2014;55(11):7093-7103.

23. Maguire MG, Daniel E, Shah AR, et al. Incidence of choroidal neovascularization in the fellow eye in the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2013;120(10):2035-2041.

24. Barbazetto IA, Saroj N, Shapiro H, Wong P, Ho AC, Freund KB. Incidence of New Choroidal Neovascularization in Fellow Eyes of Patients Treated in the MARINA and ANCHOR Trials. *Am J Ophthalmol*. 2010;149(6):939-946.e1.

25. Talks J, Koshy Z, Chatzinikolas K. Use of optical coherence tomography, fluorescein angiography and indocyanine green angiography in a screening clinic for wet age-related macular degeneration. *Br J Ophthalmol*. 2007;91(5):600-601.

26. Wu Z, Luu CD, Ayton LN, et al. Optical Coherence Tomography–Defined Changes Preceding the Development of Drusen-Associated Atrophy in Age-Related Macular Degeneration. *Ophthalmology*. 2014;121(12):2415-2422.

Financial Disclosure

Financial Disclosure(s): M.N., none. J.L., none. N.S.A., none. A.K., none, S.B., none, W.F., none. A.U., none. K.M.M., none. K.B., none. X.H., none. S.R.S., Allergan (C,F), Carl Zeiss Meditec (F), CenterVue (C), Genentech (C,F), Heidelberg Engineering (C), Iconic (C), NightstarX (C), Novartis (C), Optos (C,F), Thrombogenics (C), Topcon (C).

E.M.: Employee - Genentech, Inc.

Figure 1. Flow chart diagram explaining the selection process of eligible eyes for this post hoc analysis. Among the initial cohort of 1097 subjects with macular neovascularization (MNV) in the study eye, only 941 subjects had available and complete data for the fellow eye. Among these, 440 subjects had evidence of macular atrophy (either geographic atrophy or secondary to previous MNV) or MNV (either active or inactive) in the fellow eye, hence they were excluded from the analysis. Ultimately, the fellow eyes of 501 subjects were analyzed.

Figure 2. Rates of complete retinal pigment epithelium and outer retina atrophy (cRORA) and macular neovascularization (MNV) development in the analyzed cohort (overall) and in the subset of subjects with no optical coherence tomography risk factors, or with intraretinal hyper-reflective foci (IHRF), subretinal drusenoid deposits (SDD), hyporeflective foci within drusenoid lesions (hRF) and drusen volume (DV) ≥ 0.03 mm^3 at baseline. Since patients could show multiple features at the same time, they might have been included in more than one column in the graph. All numbers represent the percentage of the cohort included in the analysis

Figure 3. Risk of developing late age-related macular degeneration (AMD), complete RPE and photoreceptor atrophy (cRORA), or macular neovascularization (MNV) after two years of follow-up. The top row shows the hazard ratio (HR) and 95% confidence interval (CI) for the baseline presence of optical coherence tomography (OCT) features such as intraretinal hyper-reflective foci (IHRF), hyporeflective foci (hRF) within drusenoid lesions (DLs), subretinal drusenoid deposits (SDD) and drusen volume (DV) ≥ 0.03 mm^3. The bottom row shows the HR and 95% CI for demographic characteristics (i.e. age, gender and exposure to smoking [previous/current or none]).

Figure 4. Kaplan-Meier curves showing the cumulative incidence of late age related macular degeneration (AMD) or either complete retinal pigment epithelium and outer retina atrophy (cRORA) or macular neovascularization (MNV) alone in fellow eyes of MNV patients. The curves were built for each category according to the optical coherence tomography (OCT)-based scoring system used in this study: category II (score 4) for eyes with no OCT risk features at baseline; category III (scores 5-6) for eyes with one or two OCT risk features at baseline; category IV (scores 7-8) for eyes with three or four OCT risk features at baseline.