Interrelationships Between Macular Neovascularization Lesion Type, Retinal Fluid Location, and Visual Outcomes in the HARBOR Trial

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• **SB, MT, SG**: Employee: Genentech, Inc.

Study Disclosures

• This study includes research conducted on human subjects
• Institutional Review Board approval was obtained prior to study initiation
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Key Takeaways

• This post hoc analysis of HARBOR represents the first application of CONAN Study Group criteria to a major nAMD dataset

• We aimed to evaluate the relationship between baseline MNV lesion type, retinal fluid location, and vision outcomes among eyes receiving ranibizumab therapy for nAMD

• Vision outcomes over 24 months were associated with MNV lesion type at baseline, and the location/presence of retinal fluid over time

• Anatomic classification of MNV lesion type and a nuanced assessment of retinal fluid should be considered in the management of nAMD

CONAN, Consensus on Neovascular Age-Related Macular Degeneration Nomenclature; MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration.
• In 2010, we proposed a classification for macular neovascularization (MNV) based on anatomic localization ascertained by multimodal imaging.

• In 2015, we reported “Long-term Visual Outcomes for a Treat-and-Extend Anti-VEGF Regimen in Eyes With nAMD”\(^1\)

- 210 treatment-naïve eyes
- Mean follow-up of 3.5 years
- Anatomic classification was an independent predictor of visual acuity at 6 months and years 1, 2, 3, and 4
- Eyes with Type 1 MNV lesions had better visual outcomes


logMAR, logarithm of the minimum angle of resolution; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.
CONAN Study Group Definitions

Type 1 MNV
Neovascularization located between the RPE and Bruch’s membrane

Type 2 MNV
Neovascularization in the subretinal space above the RPE

Type 3 MNV
Intraretinal neovascularization originating from the deep vascular complex

CONAN, Consensus on Neovascular Age-Related Macular Degeneration Nomenclature; MNV, macular neovascularization; RPE, retinal pigment epithelium.
Objective

To evaluate the relationship between baseline MNV lesion type, retinal fluid location, and vision outcomes among eyes receiving ranibizumab for nAMD in HARBOR

MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration.
HARBOR Compared Monthly and PRN Ranibizumab Therapy for nAMD Over 24 Months

Treatment-naïve patients with nAMD and active subfoveal MNV (N = 1097)

Current Analysis (n = 700)
Post hoc analysis of pooled data from study eyes with:
• Multimodal assessment of baseline MNV (SD-OCT, FA, CFP)
• Retinal fluid (SRF and/or IRF) at baseline, screening, or week 1
• SD-OCT follow-up over 24 months

Outcomes of Interest:
1. Baseline MNV lesion type
   - Classified using CONAN Study Group criteria\(^1\)
     • Type 1
     • Type 2/Mixed Type 1 and 2 (Type 2/M)
     • Any Type 3
2. SRF and/or IRF over 24 months
   - Identified by SD-OCT
   - Location (central/noncentral) classified using a modified ETDRS grid
3. BCVA outcomes over 24 months
   - Assessed using standard ETDRS protocols

NCT00891735. *Re-treatment criteria for PRN arms: ≥ 5-letter decrease in BCVA from previous visit, or any evidence of disease activity on SD-OCT (SRF, IRF, or subretinal pigment epiretinal fluid). 1. Spaide RF et al. Ophthalmology. 2020;127(5):616-636. BCVA, best-corrected visual acuity; CFP, color fundus photography; CONAN, Consensus on Neovascular Age-Related Macular Degeneration Nomenclature; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; IRF, intraretinal fluid; LD, loading dose; MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration; PRN, as-needed; RBZ, ranibizumab; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal fluid.
Distribution of Lesion Types at Baseline

- **Any Type 3**
  - n = 150 (21%)
- **Type 2/M***
  - n = 287 (41%)
- **Type 1**
  - n = 263 (38%)

*Type 2/Mixed Type 1 and 2.*
Type 1 Eyes Had the Best Mean BCVA Profile Over 24 Months, While Type 2/M* Eyes Had the Worst

BCVA Over Time by Baseline Lesion Type

HARBOR (Pooled Treatment Arms)

Mrejen et al, 2015¹

Mean BCVA, ETDRS Letters

*Type 2/Mixed Type 1 and 2. Error bars represent 95% CI.

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; logMAR, logarithm of the minimum angle of resolution.
Mean Vision Gains Over 24 Months Were Numerically Greatest Among Monthly-Treated Type 2/M* Eyes

**Type 1**

<table>
<thead>
<tr>
<th>Month 12</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly</td>
<td>10.1</td>
</tr>
<tr>
<td>PRN</td>
<td>8.4</td>
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</table>

**Type 2/M***

<table>
<thead>
<tr>
<th>Month 12</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly</td>
<td>12.6</td>
</tr>
<tr>
<td>PRN</td>
<td>9.3</td>
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</table>

**Any Type 3**

<table>
<thead>
<tr>
<th>Month 12</th>
<th>Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly</td>
<td>10.6</td>
</tr>
<tr>
<td>PRN</td>
<td>9.2</td>
</tr>
</tbody>
</table>

*Type 2/Mixed Type 1 and 2. Error bars represent 95% CI.

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, as-needed.
The Majority of Type 1 Eyes Had SRF Only at Baseline

Type 1

- 37% IRF only
- 57% SRF only
- 6% IRF and SRF

Type 2/M*

- 59% IRF only
- 34% SRF only
- 7% IRF and SRF

Any Type 3

- 59% IRF only
- 38% SRF only
- 3% IRF and SRF

*Type 2/Mixed Type 1 and 2.
IRF, intraretinal fluid; SRF, subretinal fluid.
Across All Lesion Types, BCVA Outcomes Over 24 Months Were Similar Regardless of SRF Location at Baseline

**Type 1**

**Type 2/M**

**Any Type 3**

*Type 2/Mixed Type 1 and 2. Error bars represent 95% CI.

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SRF, subretinal fluid.
Mean Vision Gains Were Similar in Type 1 Eyes With and Without Residual SRF Over 24 Months

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Residual SRF</th>
<th>No SRF</th>
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</thead>
<tbody>
<tr>
<td>Month 12</td>
<td>9.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Month 24</td>
<td>8.1</td>
<td>8.8</td>
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<table>
<thead>
<tr>
<th>Type 2/M*</th>
<th>Residual SRF</th>
<th>No SRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 12</td>
<td>13.2</td>
<td>10.5</td>
</tr>
<tr>
<td>Month 24</td>
<td>15.5</td>
<td>9.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any Type 3</th>
<th>Residual SRF</th>
<th>No SRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 12</td>
<td>4.3</td>
<td>10.2</td>
</tr>
<tr>
<td>Month 24</td>
<td>1.6</td>
<td>9.3</td>
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</table>

*Type 2/Mixed Type 1 and 2. Error bars represent 95% CI.
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SRF, subretinal fluid.
Mean Vision Gains Were Significantly Better in Type 2/M* Eyes With Residual SRF at Month 24

**Type 1**

<table>
<thead>
<tr>
<th>Residual SRF</th>
<th>No SRF</th>
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</thead>
<tbody>
<tr>
<td><strong>Month 12</strong></td>
<td>9.6, 9.1</td>
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<tr>
<td><strong>Month 24</strong></td>
<td></td>
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**Type 2/M***

<table>
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<th>Residual SRF</th>
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</thead>
<tbody>
<tr>
<td><strong>Month 12</strong></td>
<td>13.2, 10.5</td>
</tr>
<tr>
<td><strong>Month 24</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Any Type 3**

<table>
<thead>
<tr>
<th>Residual SRF</th>
<th>No SRF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Month 12</strong></td>
<td>4.3, 10.2</td>
</tr>
<tr>
<td><strong>Month 24</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Type 2/Mixed Type 1 and 2. Error bars represent 95% CI.
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SRF, subretinal fluid.
In Type 1 and Type 2/M* Eyes, BCVA Outcomes Over 24 Months Were Generally Worse When Central IRF Was Present at Baseline

*Type 2/Mixed Type 1 and 2. Error bars represent 95% CI.

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; IRF, intraretinal fluid.
Mean Vision Gains Were Significantly Worse in Type 2/M* Eyes With Residual IRF at Months 12 and 24

**Type 1**
- Residual IRF: Month 12: 6.8, Month 24: 6.9
- No IRF: Month 12: 10.1, Month 24: 9.3

**Type 2/M***
- Residual IRF: Month 12: 6.1, Month 24: 12.9
- No IRF: Month 12: 5.6, Month 24: 12.7

**Any Type 3**
- Residual IRF: Month 12: 8.6, Month 24: 10.5
- No IRF: Month 12: 5.5, Month 24: 10.5

*Type 2/Mixed Type 1 and 2. Error bars represent 95% CI.

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; IRF, intraretinal fluid.
Conclusions

- In this first application of CONAN Study Group criteria to a major nAMD dataset, MNV lesion type correlated with visual and anatomic endpoints in HARBOR

- Regardless of regimen, eyes with **Type 1** lesions had the best BCVA profile over 24 months, while **Type 2/M** eyes had the worst

- Vision gains over 24 months were numerically greatest among monthly-treated **Type 2/M** eyes, and better in **Type 2/M** eyes with residual versus no SRF

- In eyes with **Type 1** lesions, vision outcomes over 24 months were similar regardless of concurrent residual SRF

- Central IRF at baseline and residual IRF at month 24 correlated with poor vision across MNV lesion types

**Anatomic classification of MNV lesion type and a nuanced assessment of retinal fluid should be considered in the management of nAMD**

BCVA, best-corrected visual acuity; CONAN, Consensus on Neovascular Age-Related Macular Degeneration Nomenclature; IRF, intraretinal fluid; MNV, macular neovascularization; nAMD, neovascular age-related macular degeneration; PRN, as-needed; SRF, subretinal fluid; Type 2/M, Type 2/Mixed Type 1 and 2.