



# Retinal Nonperfusion Extent and Its Relationship with Visual, Anatomic, and Disease State Outcomes Among Eyes Treated for DME

**Chirag Shah MD, MPH**

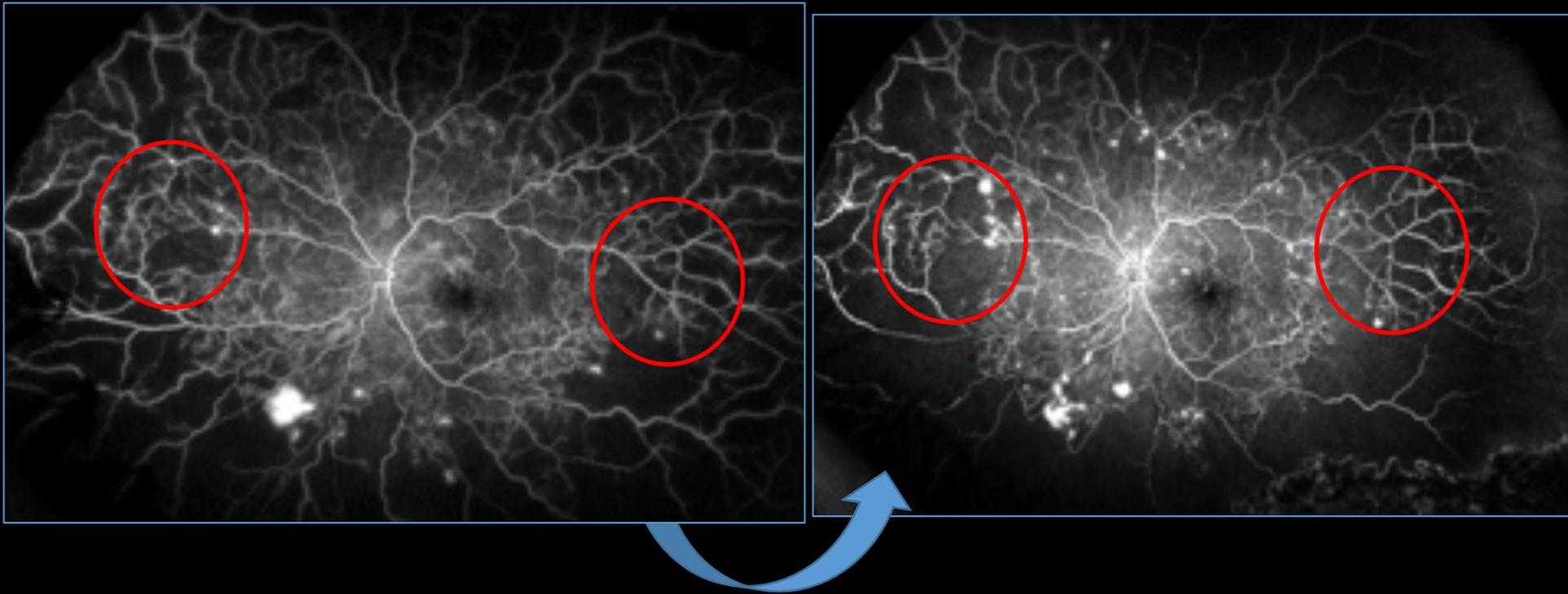
*on behalf of the VISTA study investigators*

**Ophthalmic Consultants of Boston**

# Disclosures

- This study was funded by Regeneron Pharmaceuticals, Inc., and Bayer HealthCare. The sponsor participated in the design and conduct of the study, analysis of the data, and preparation of this abstract.
- Dr Shah is a sub-investigator on clinical trials sponsored by Regeneron, Genentech, NIH, Apellis, Allergan, Novartis, Ellex, Alcon.
- Study disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation
- Medical writing support was provided by Lisa Heaney, PhD of Prime, Knutsford, UK according to Good Publication Practice guidelines and was funded by Regeneron Pharmaceuticals, Inc.

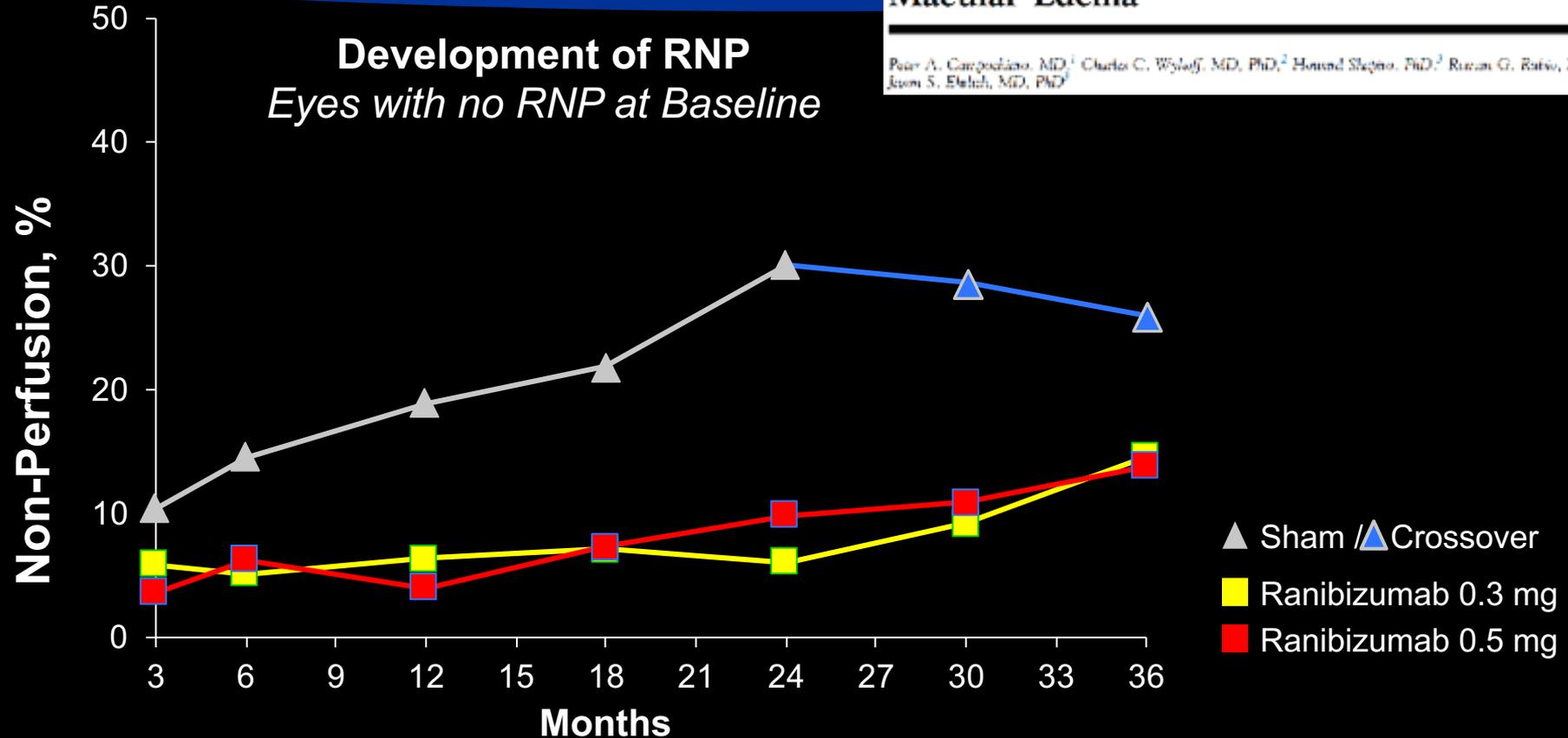
# Progressive Retinal Non-Perfusion



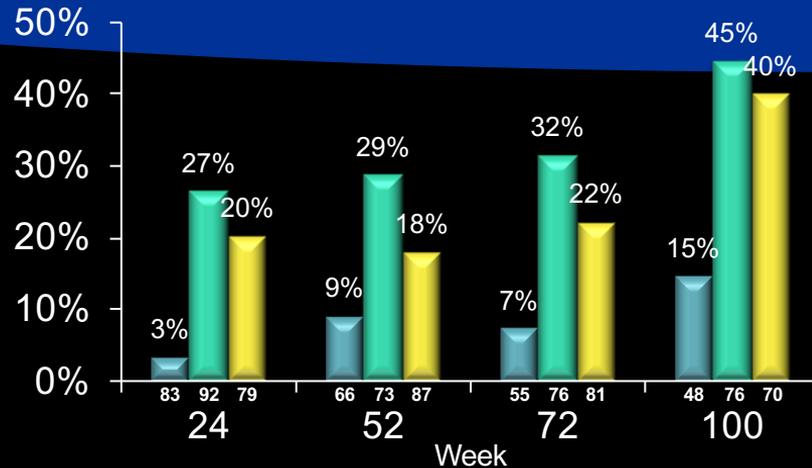
>4 Years Continuous Q 4-10 Week Anti-VEGF Dosing

# Neutralization of Vascular Endothelial Growth Factor Slows Progression of Retinal Nonperfusion in Patients with Diabetic Macular Edema

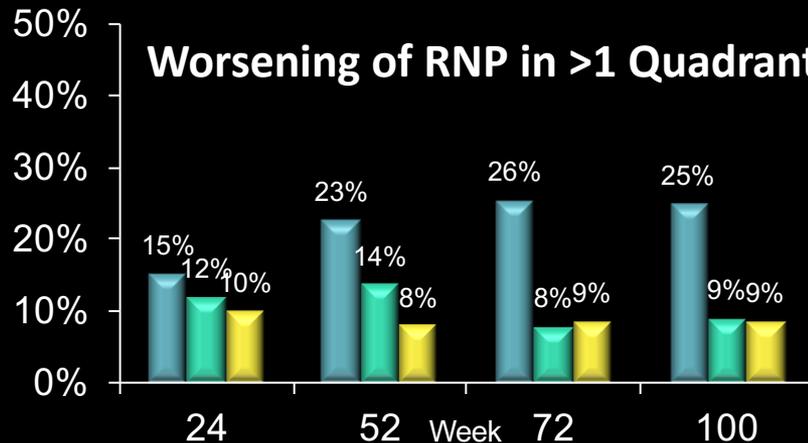
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## Improvement of RNP in >1 Quadrant



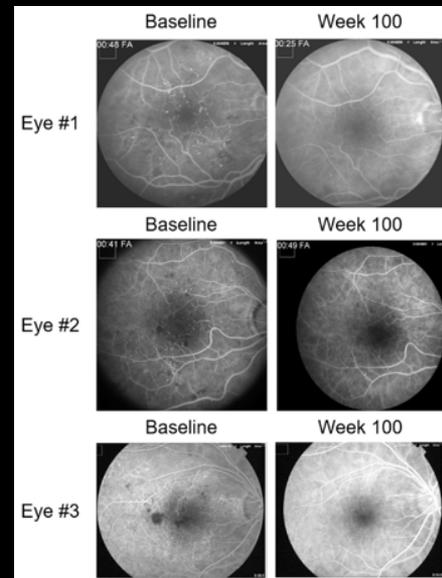
## Worsening of RNP in >1 Quadrant



## Longitudinal Retinal Perfusion Status in Eyes with Diabetic Macular Edema Receiving Intravitreal Aflibercept or Laser in VISTA Study

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- Sham
- Aflibercept 2mg Q4
- Aflibercept 2mg Q8



Observed cases. Compared with baseline  
For inclusion at each time point, patients must have FA with 4/4 graded quadrants at that time point and at baseline

# Background

Randomized, multicenter, double-masked trials in patients with clinically significant DME with central involvement and ETDRS BCVA 20/40 to 20/320  
 Randomized and treated: N = 406 (VIVID) and N = 466 (VISTA)

Patients randomized  
 1:1:1

IAI  
 2 mg q4 wks

IAI  
 2 mg q8 wks\*

Laser  
 photocoagulation

Primary endpoint:  
 mean change in BCVA

Primary endpoint:  
 week 52

Key secondary endpoints:  
 mean change in OCT  
 % with  $\geq 2$ -step DRSS  
 improvement

Continued treatment through year 3

- IAI given q4 weeks or q8 weeks (following 5 monthly doses) significantly improved visual and anatomic outcomes over laser at week 52. These improvements were sustained through week 100 with both IAI regimens
- In an integrated safety analysis, the most frequent serious ocular adverse event at week 100 was cataract (2.4%, 1.0%, and 0.3% for 2q4, 2q8, and control)

\*After 5 initial monthly doses. 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best-corrected visual acuity; DME, diabetic macular edema; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; IAI, intravitreal aflibercept injection; OCT, optical coherence tomography.

# Objectives

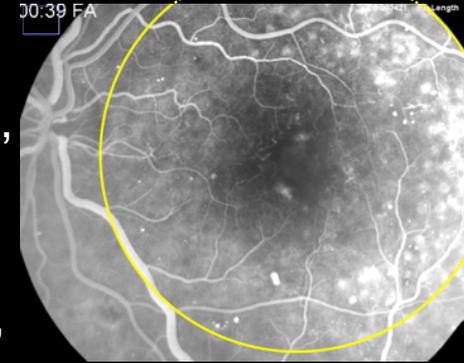


- To quantify macular RNP area in  $\text{mm}^2$  at baseline and through week 100
- To assess the relationship between changes from baseline in macular RNP area and the following outcomes at week 100:
  - BCVA
  - CST
  - DRSS score
- To evaluate the impact of baseline macular RNP area on the incidence of PDR events

# Methods



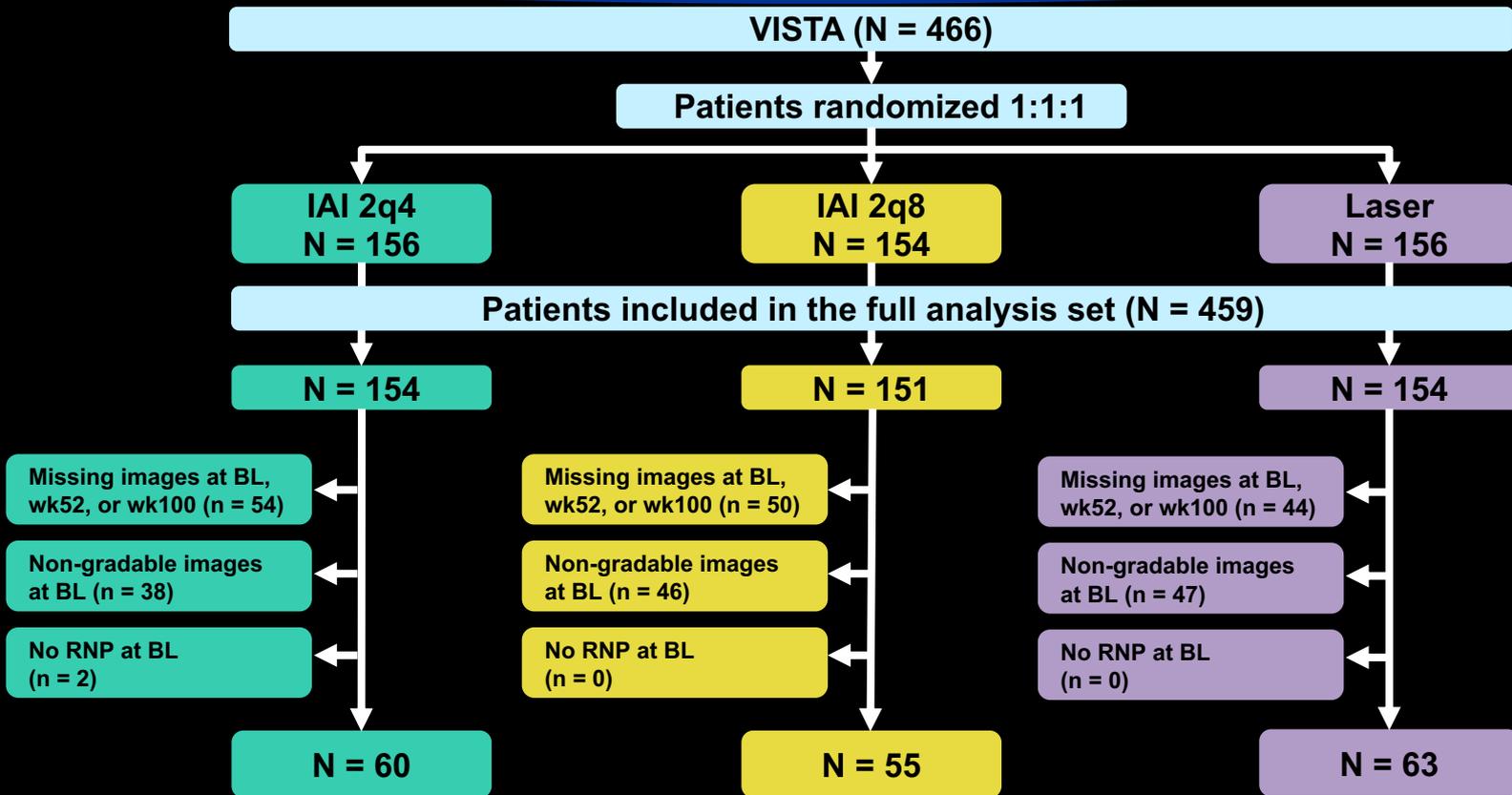
- Patients with macular RNP at baseline were included
- Macular RNP area was quantified at baseline, weeks 24, 52, and 100 by a reading center (Digital Angiography Reading Center [DARC], New York, NY)
- PDR events included PDR (graded by reading center), PRP, or vitrectomy
- Full analysis set and observed cases were used; data were censored after rescue treatment was given
- Statistical analyses included MMRM, Mantel-Haenszel weighting scheme, Pearson/Spearman correlation, Kaplan–Meier, Cox PH model
- *P*-values are considered nominal



Macula defined as the area inside the ETDRS grid\*

\*FAZ was included when it could be measured. Standard grid size of 7.2 mm for camera systems was used

# Patient Disposition



BL, baseline.

# Demographics and Baseline Characteristics



	● Laser	● IAI 2q4	● IAI 2q8	● Total
N	63	60	55	178
Mean age, years (SE)	60 (1.0)	59 (1.5)	62 (1.4)	60 (0.8)
Female, n %	29 (46)	24 (40)	26 (47)	79 (44)
Mean BMI (SE)	31 (0.9)	33 (0.9)	31 (0.8)	32 (0.5)
Mean HbA1c, % (SE)	7.5 (0.2)	7.8 (0.2)	7.9 (0.2)	7.7 (0.1)
>8%, n (%)	19 (30)	21 (35)	22 (40)	62 (35)
≤8%, n (%)	44 (70)	39 (65)	33 (60)	116 (65)

# Demographics and Baseline Characteristics



	Laser	IAI 2q4	IAI 2q8	Total
N	63	60	55	178
Mean BCVA, letters (SE)	61 (1.4)	61 (1.3)	59 (1.5)	60 (0.8)
Mean CRT, $\mu\text{m}$ (SE)	496 (17)	486 (16)	502 (23)	495 (11)
Mean duration of DM, years (SE)	15 (1.2)	15 (1.1)	19 (1.3)	16 (0.7)
DRSS level, n (%)				
10	0	2 (3.3)	1 (1.8)	3 (1.7)
20	2 (3.2)	2 (3.3)	1 (1.8)	5 (2.8)
35	1 (1.6)	1 (1.7)	3 (5.5)	5 (2.8)
43	21 (33.3)	17 (28.3)	21 (38.2)	59 (33.1)
47	13 (20.6)	10 (16.7)	12 (21.8)	35 (19.7)
53	20 (31.7)	23 (38.3)	15 (27.3)	58 (32.6)
61	0	1 (1.7)	0	1 (0.6)
65	6 (9.5)	2 (3.3)	1 (1.8)	9 (5.1)
71	0	2 (3.3)	1 (1.8)	3 (1.7)

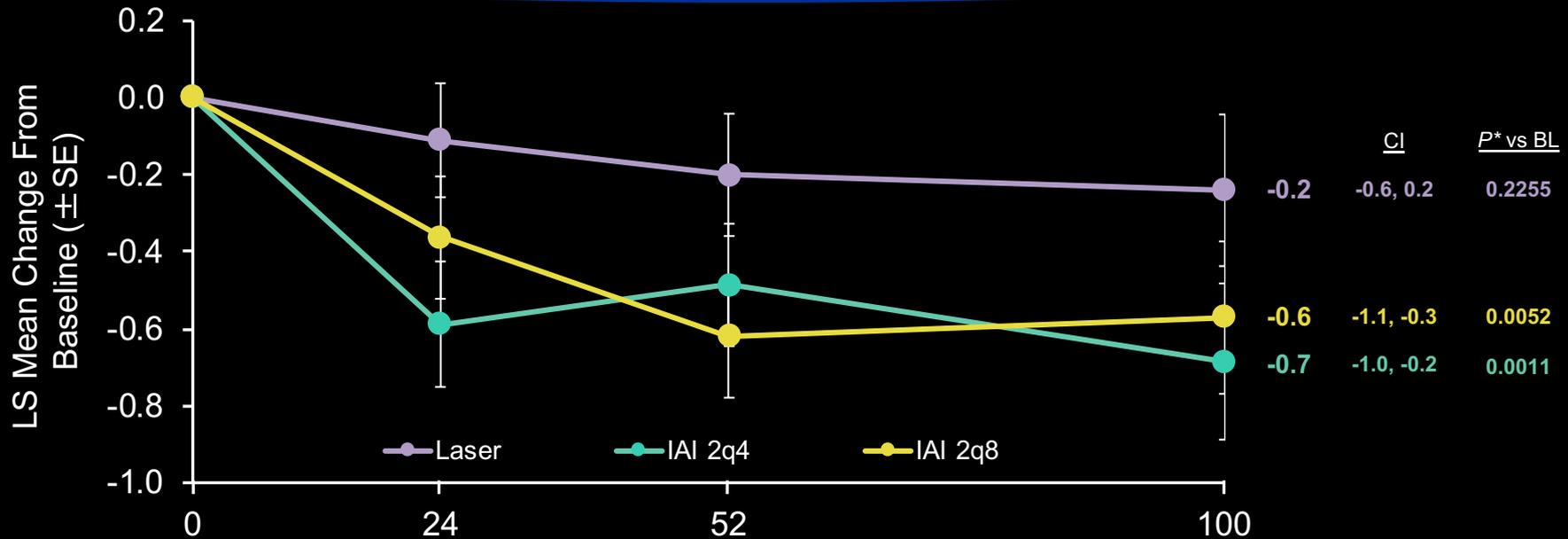
# Baseline Macular RNP Area

	<span style="color: purple;">●</span> Laser	<span style="color: teal;">●</span> IAI 2q4	<span style="color: yellow;">●</span> IAI 2q8	<span style="color: white;">●</span> Total
N	63	60	55	178
Mean baseline RNP, mm <sup>2</sup> (SD)	1.5 (1.7)	1.7 (2.5)	1.5 (1.5)	1.6 (1.9)
Median	0.9	0.8	0.8	0.9
Min, Max	0.1, 7.7	0.1, 13.8	0.2, 6.5	0.1, 13.8



Red tracing outlines area of 1.495 mm<sup>2</sup> of RNP

# Macular RNP Area Change Through Week 100



	0	24	52	100
Laser, n	63	40	29	26
2q4, n	60	31	33	23
2q8, n	55	33	31	25

	CI	P* vs BL
Laser	-0.2, -0.6, 0.2	0.2255
IAI 2q4	-1.1, -0.3	0.0052
IAI 2q8	-1.0, -0.2	0.0011

\*Nominal

Full analysis set, VISTA (censor after rescue, OC); error bars represent standard error  
 BL = baseline; CI = confidence interval; LS = Least Square; SE = standard error

# Correlations Between RNP and Visual and Anatomic Changes from Baseline at Week 100

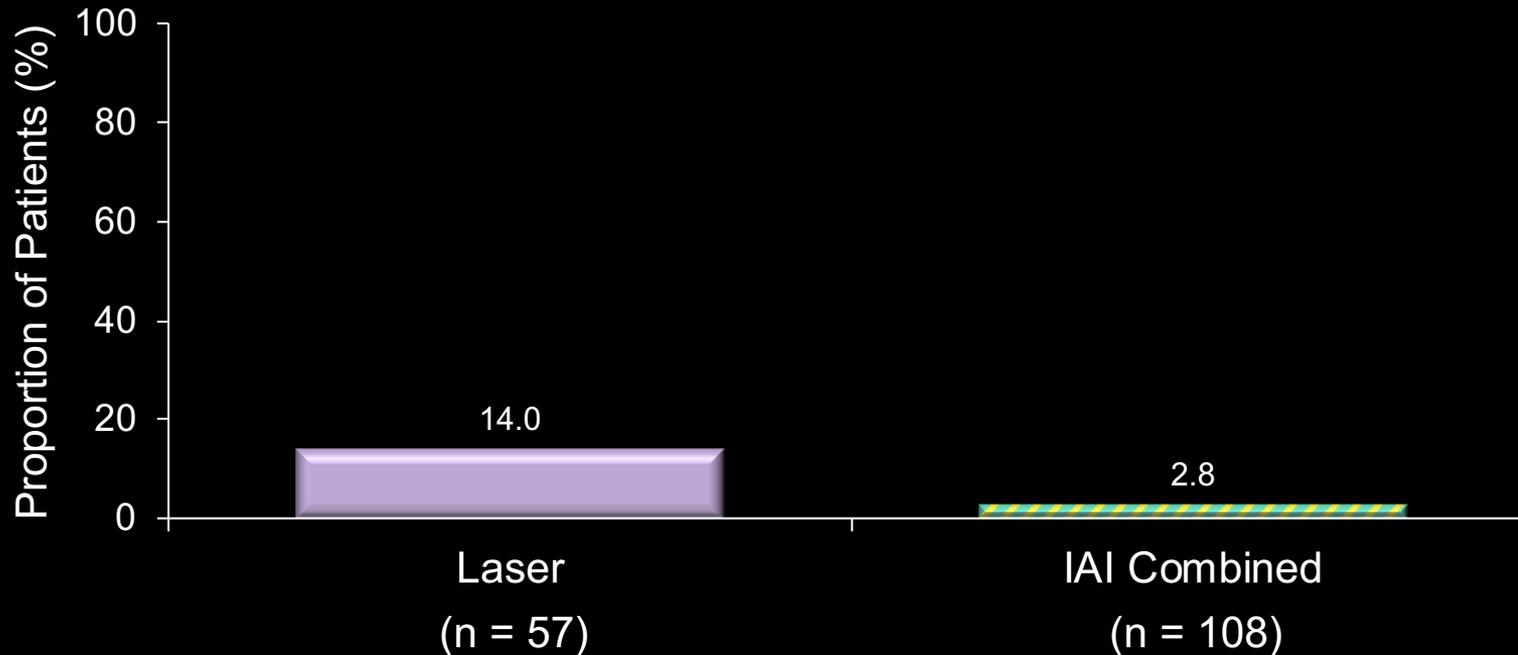


	● Laser	● IAI 2q4	● IAI 2q8
<b>N</b>	26	23	25
<b>BCVA</b>			
Correlation coefficient (95% CI)	0.1 (-0.3, 0.5)	-0.6 (-0.8, -0.2)	-0.5 (-0.7, -0.1)
<i>P</i> value	0.5084	0.0045	0.0230
<b>CST</b>			
Correlation coefficient (95% CI)	-0.1 (-0.5, 0.3)	0.7 (0.4, 0.9)	0.4 (0.04, 0.7)
<i>P</i> value	0.5656	0.0002	0.0288
<b>DRSS score</b>			
Correlation coefficient (95% CI)	-0.1 (-0.5, 0.3)	0.4 (-0.04, 0.7)	0.1 (-0.32, 0.5)
<i>P</i> value	0.6670	0.0680	0.6840



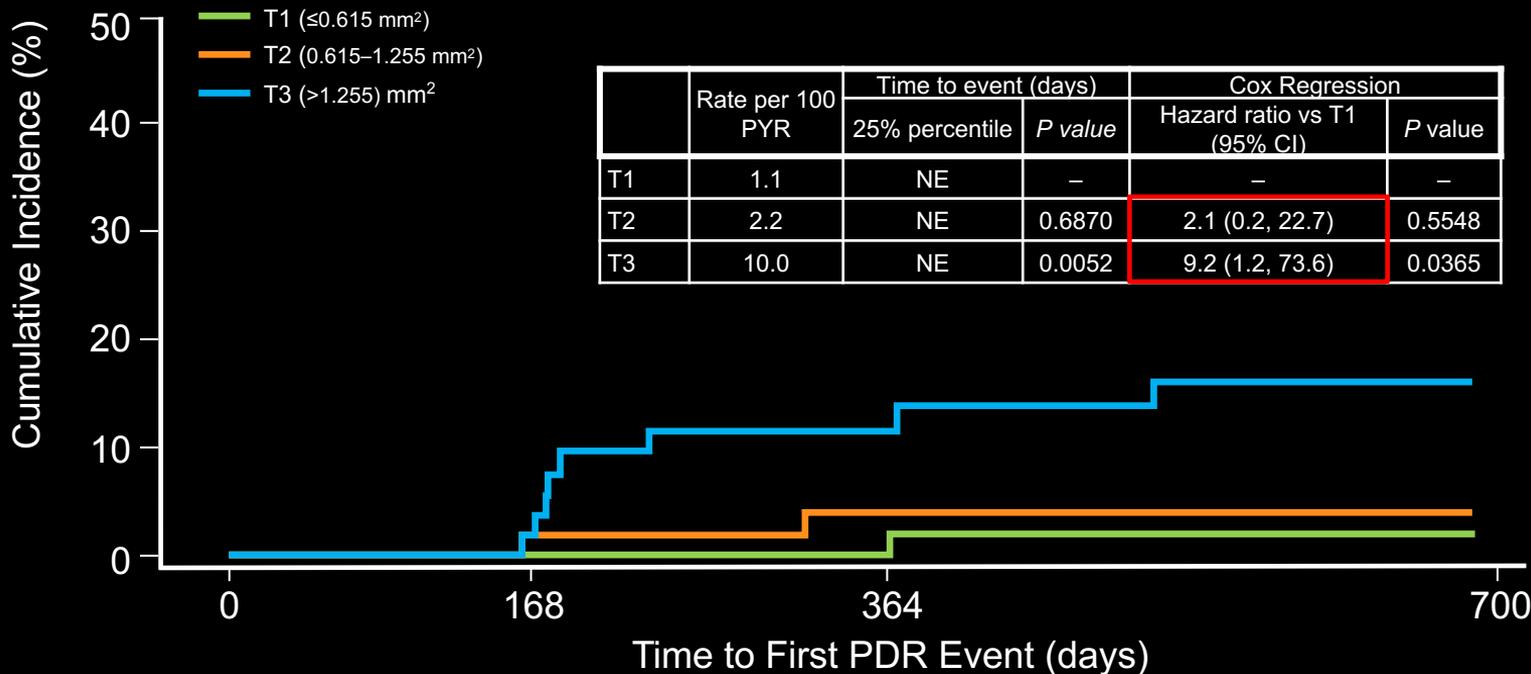
# Development of PDR Events By the Extent of Baseline RNP

# Proportion of Patients who Developed PDR Events Through Week 100



PDR events = PDR, PRP, or vitrectomy  
Patients with baseline macular RNP and NPDR included.  
NPDR, nonproliferative diabetic retinopathy.

# Time to Development of PDR Events Through Week 100 by the Extent of Baseline Macular RNP

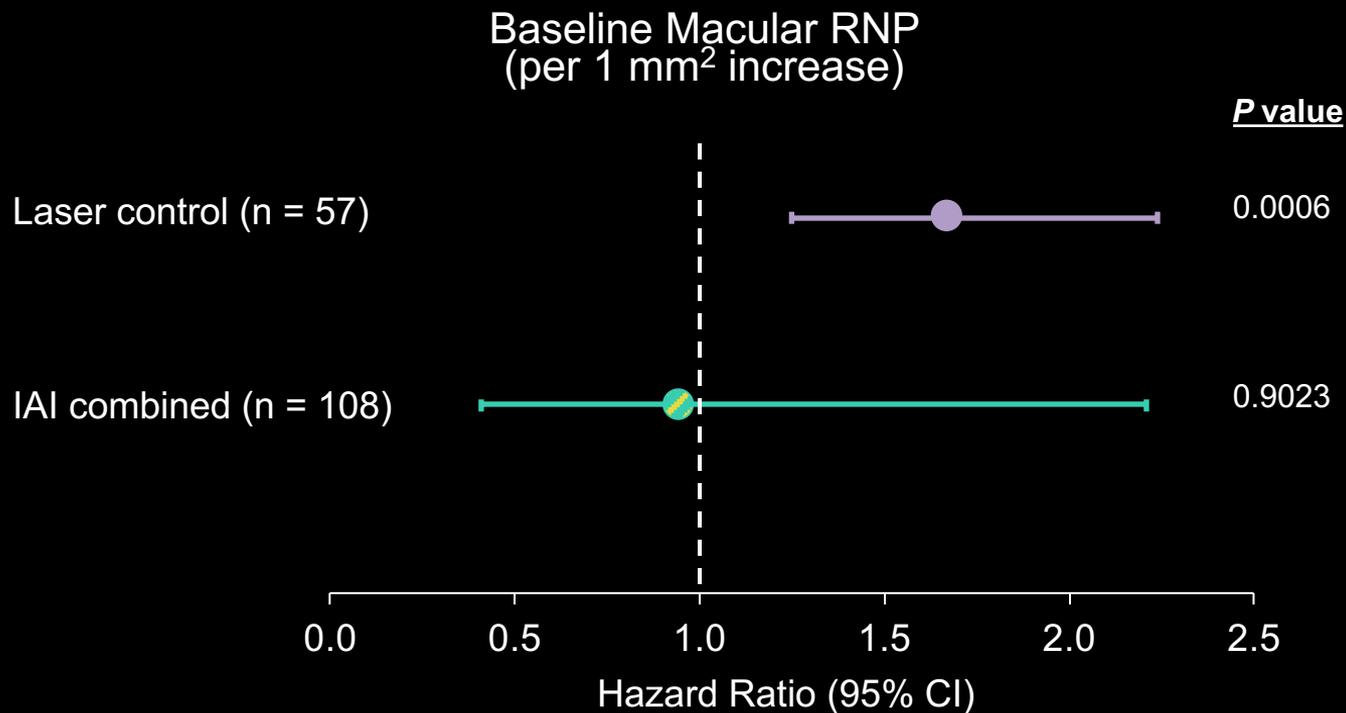


T1 (n = 55)	0	0	0	1
T2 (n = 55)	0	1	2	2
T3 (n = 55)	0	1	6	8

Full analysis set, VISTA (censor after rescue, OC).

PDR events = PDR, PRP or Vitrectomy. NE = not estimable; PYR = person-years at risk; T = tertile.

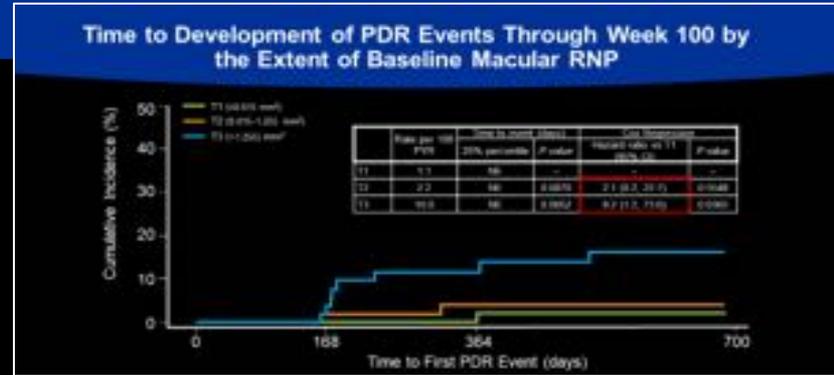
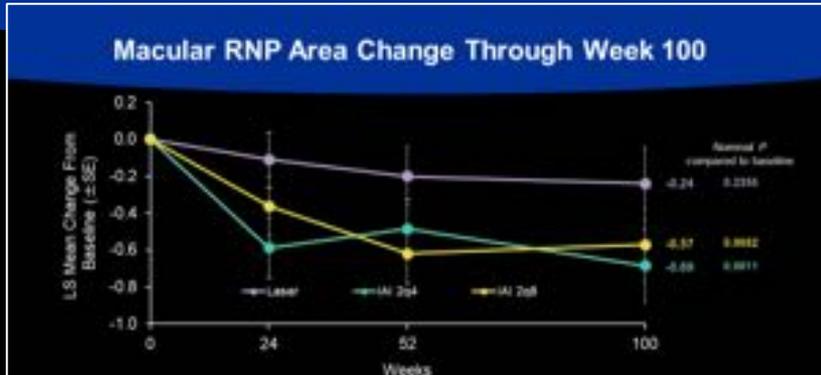
# Hazard Ratio of PDR Event Incidence by Extent of Baseline Macular RNP Area Through Week 100



# Limitations

- Post hoc analysis
- High missing number of FA images primarily due to the inclusion requirement for having complete set of assessments at baseline and weeks 52 and 100
- Absence of peripheral nonperfusion assessment

# Conclusions



- Mean area of RNP at baseline was small, approximately 1.6 mm<sup>2</sup>
- There were small decreases in RNP from baseline through week 100 across all arms:
  - Decreases in RNP from baseline with IAI was statistically significant at week 100
  - These changes were not statistically different between arms
- Moderate correlations identified between RNP reduction and BCVA increase and CST decrease from baseline at week 100 among IAI-treated patients
- Similar to PANORAMA, lower proportion of patients treated with IAI developed PDR compared to laser
- Extent of baseline RNP associated with increased risk of development of a PDR event, particularly among laser-treated patients.