

# RANIBIZUMAB

**Maurizio Battaglia Parodi**

Clinica Oculistica

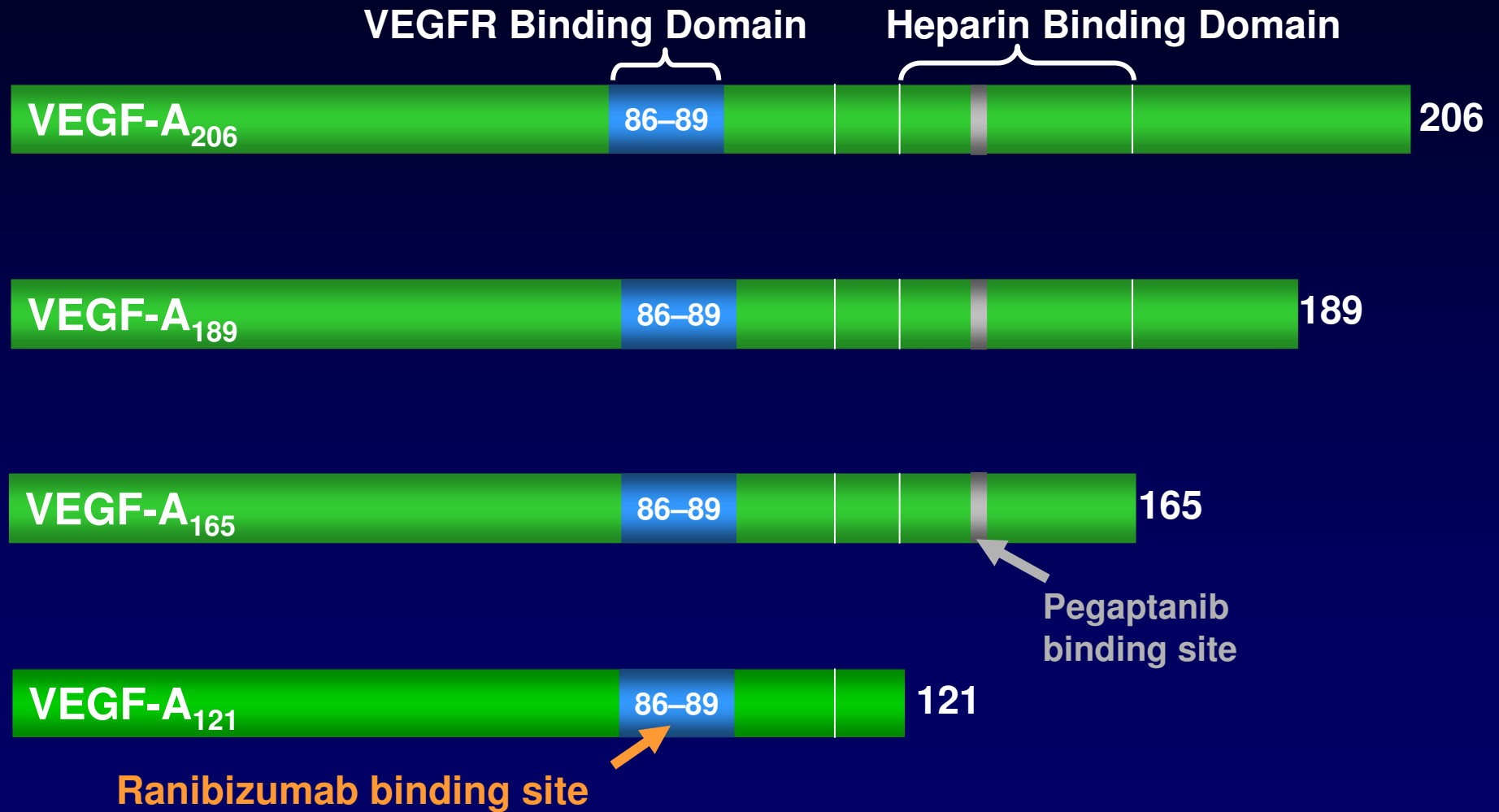
Azienda Ospedaliero-Universitaria di Trieste

Direttore: Prof. G. Ravalico

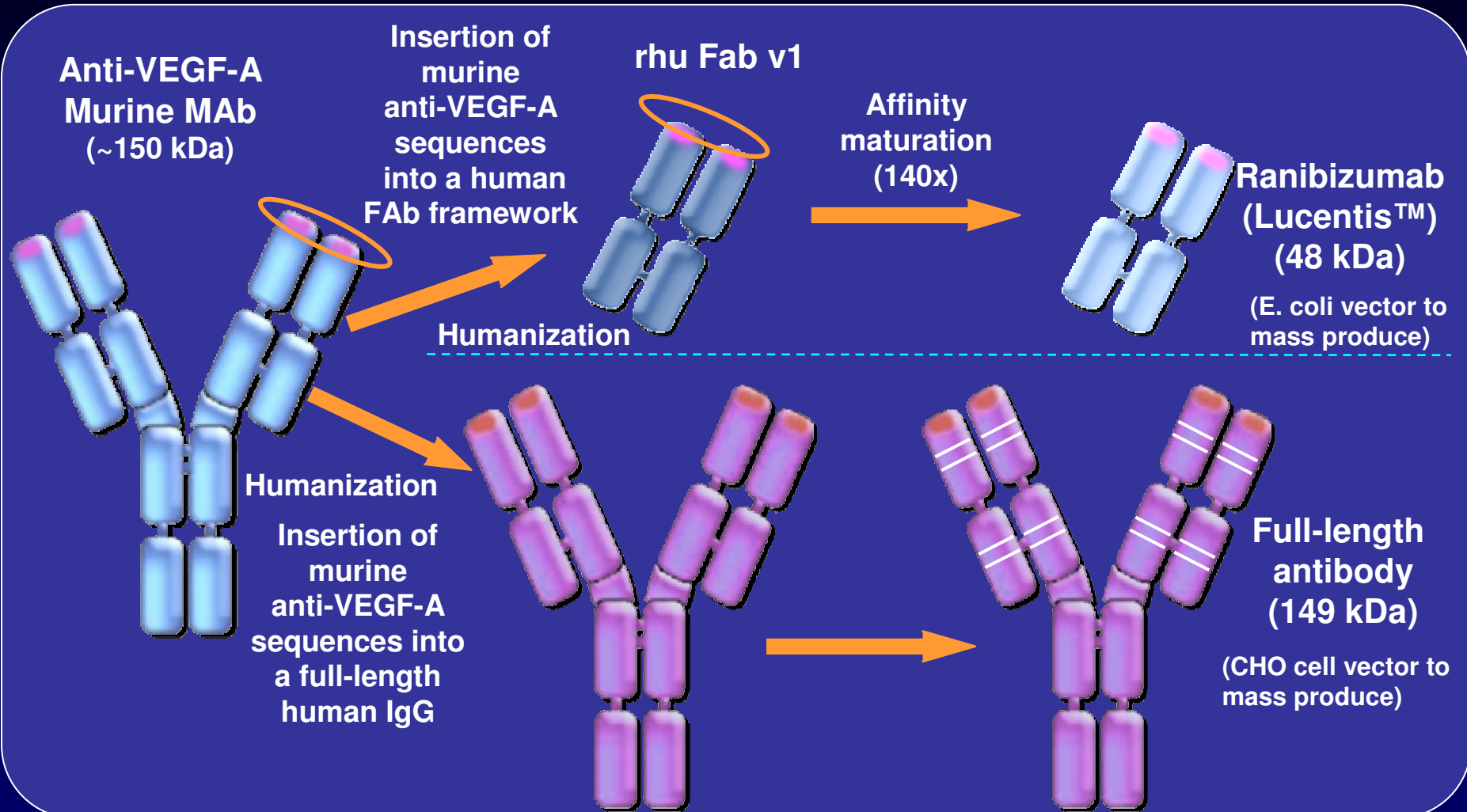
# Ranibizumab

- **Recombinant, humanized antibody antigen-binding fragment (Fab)**
- **Lucentis inactivates all the VEGF isoforms**
- **Intravitreal injection every 4 weeks**

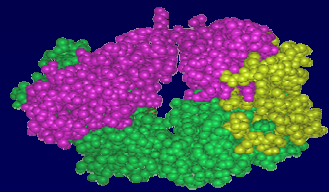
# Ranibizumab inhibits all biologically active VEGF-A isoforms



# Ranibizumab and full length antibody developed independently



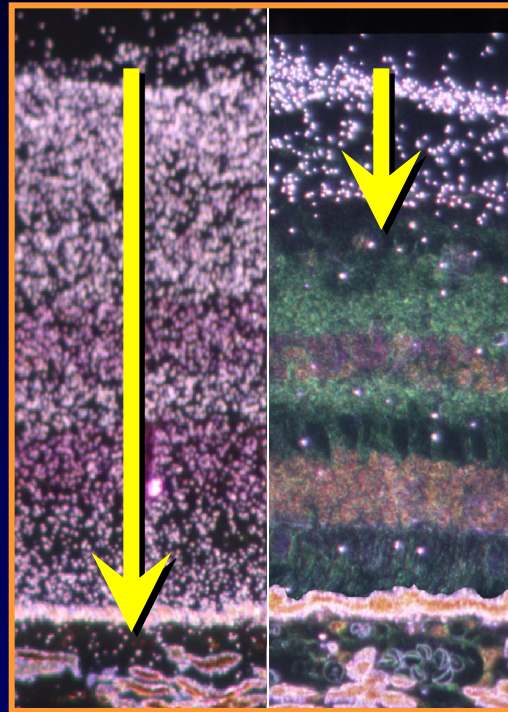
# Increased retinal penetration with antibody fragment



**RhuFab**  
48 kDa

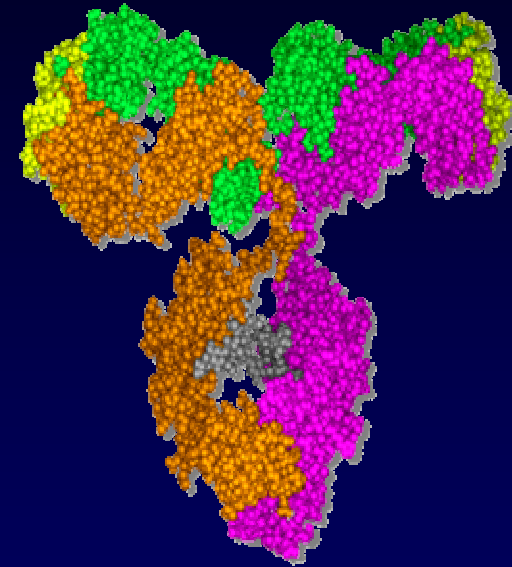
Inner  
retina

Outer  
retina



Fab

IgG



**Herceptin**  
150 kDa

- The smaller size and lower molecular weight of the antibody fragment allows increased retinal permeability compared to the complete IgG antibody

*Mordenti et al, Toxicol Pathol 1999; 27: 536*  
*Mordenti et al, Toxicol Pathol 1999; 27: 14*

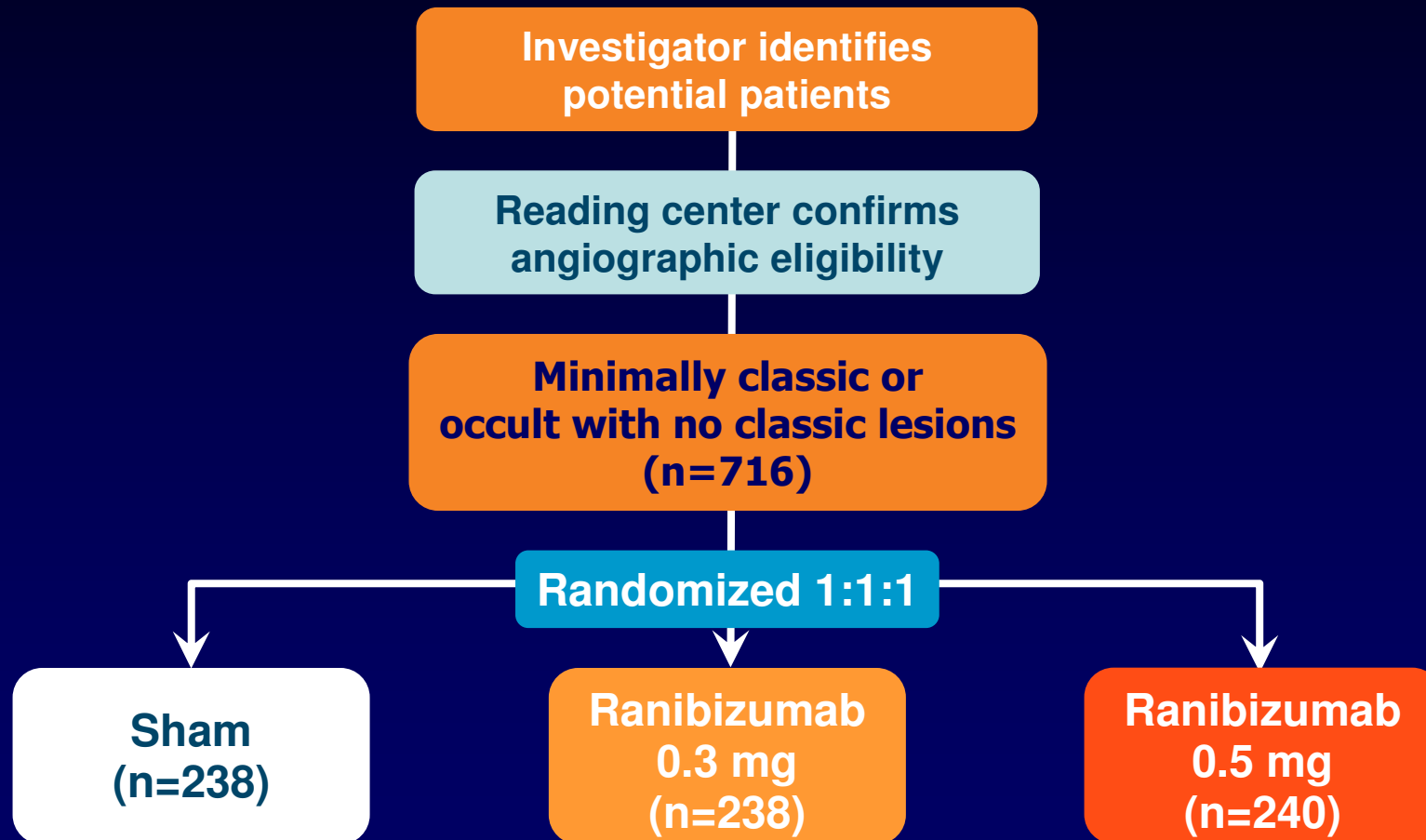
# Ranibizumab Clinical Trials

- MARINA
- ANCHOR
- FOCUS
- SAILOR
- PIER
- PRONTO

## **MARINA study**

**A Phase III, multicentre, randomized, double-masked, study of the efficacy and safety of ranibizumab in patients with **minimally classic** or **occult** subfoveal neovascular age-related macular degeneration**

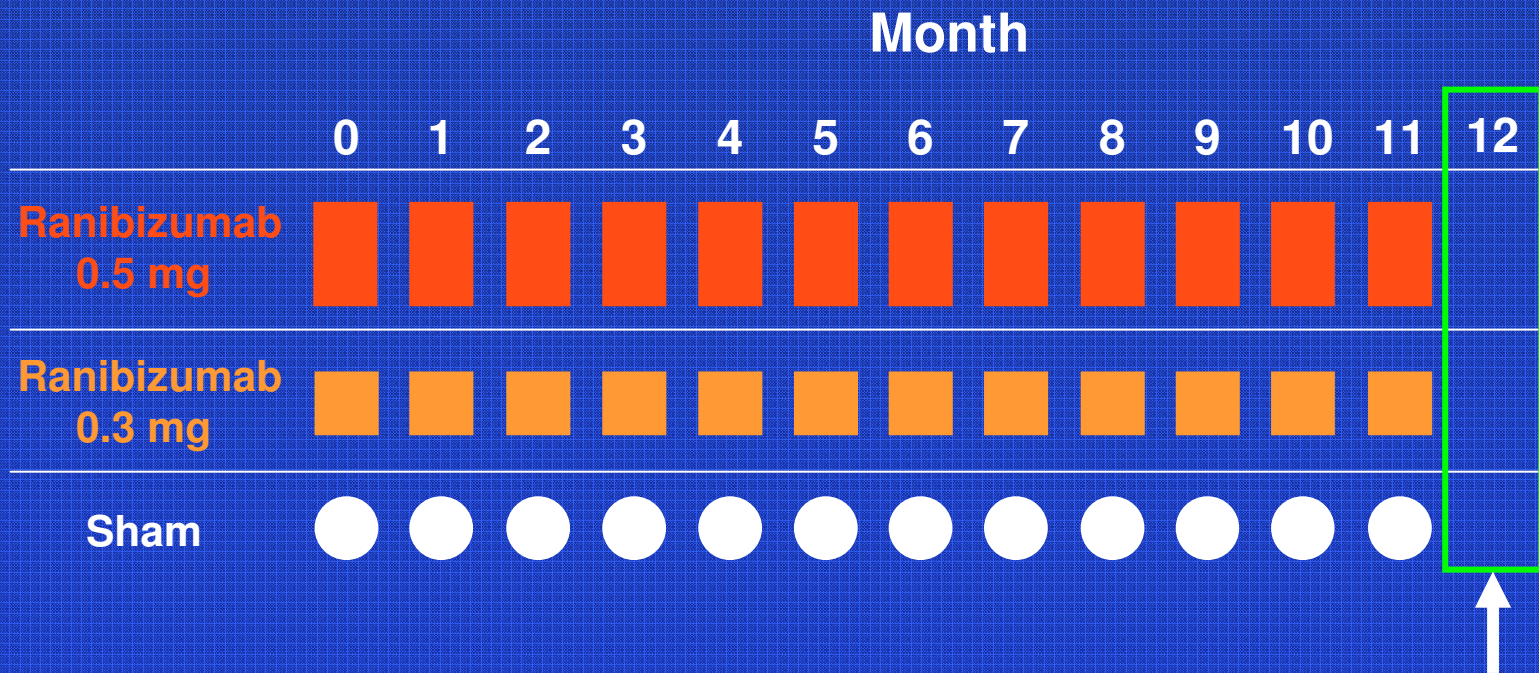
# MARINA trial design



# Inclusion criteria

- Subfoveal **choroidal neovascularization (CNV)** secondary to AMD
- Lesion composition by fluorescein angiography
  - area of CNV must be  $\geq 50\%$  of total lesion
  - **minimally classic or occult** with no classic
- Age  $\geq 50$  years
- BCVA of **20/40 to 20/320**
- No prior verteporfin
- Lesion size  $\leq 12$  DA
- Evidence of presumed recent disease progression
  - blood, growth by FA, or recent VA loss

# Treatment schema: Year 1



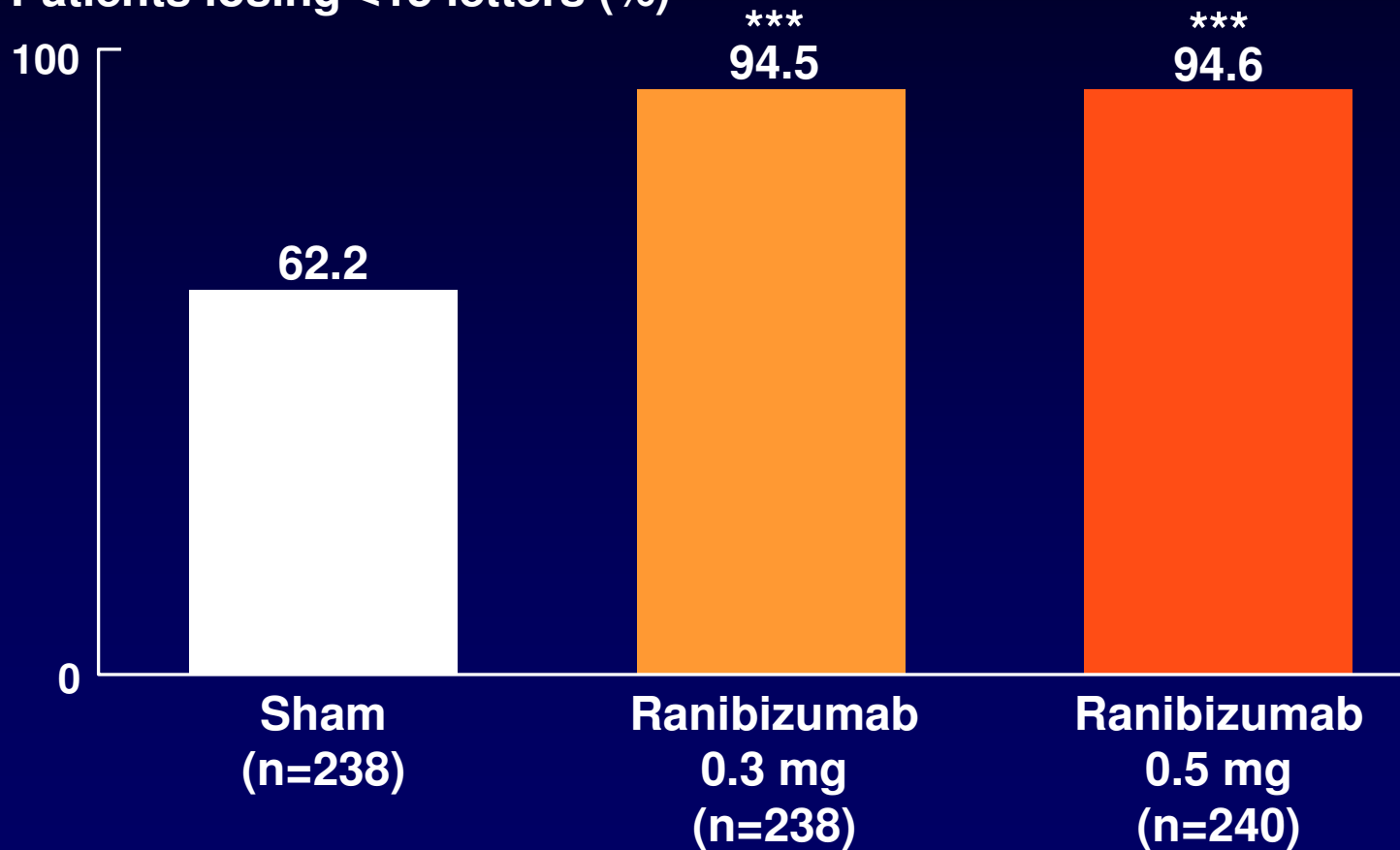
**Primary  
endpoint**

PDT at investigator discretion if:

- Conversion to predominantly classic CNV, or
- Loss of  $\geq 20$  letters on 2 consecutive visits and small ( $\leq 4$  DA), minimally classic or occult with no classic lesions, with presumed recent disease progression

# Primary endpoint: Ranibizumab prevents vision loss

Patients losing <15 letters (%)

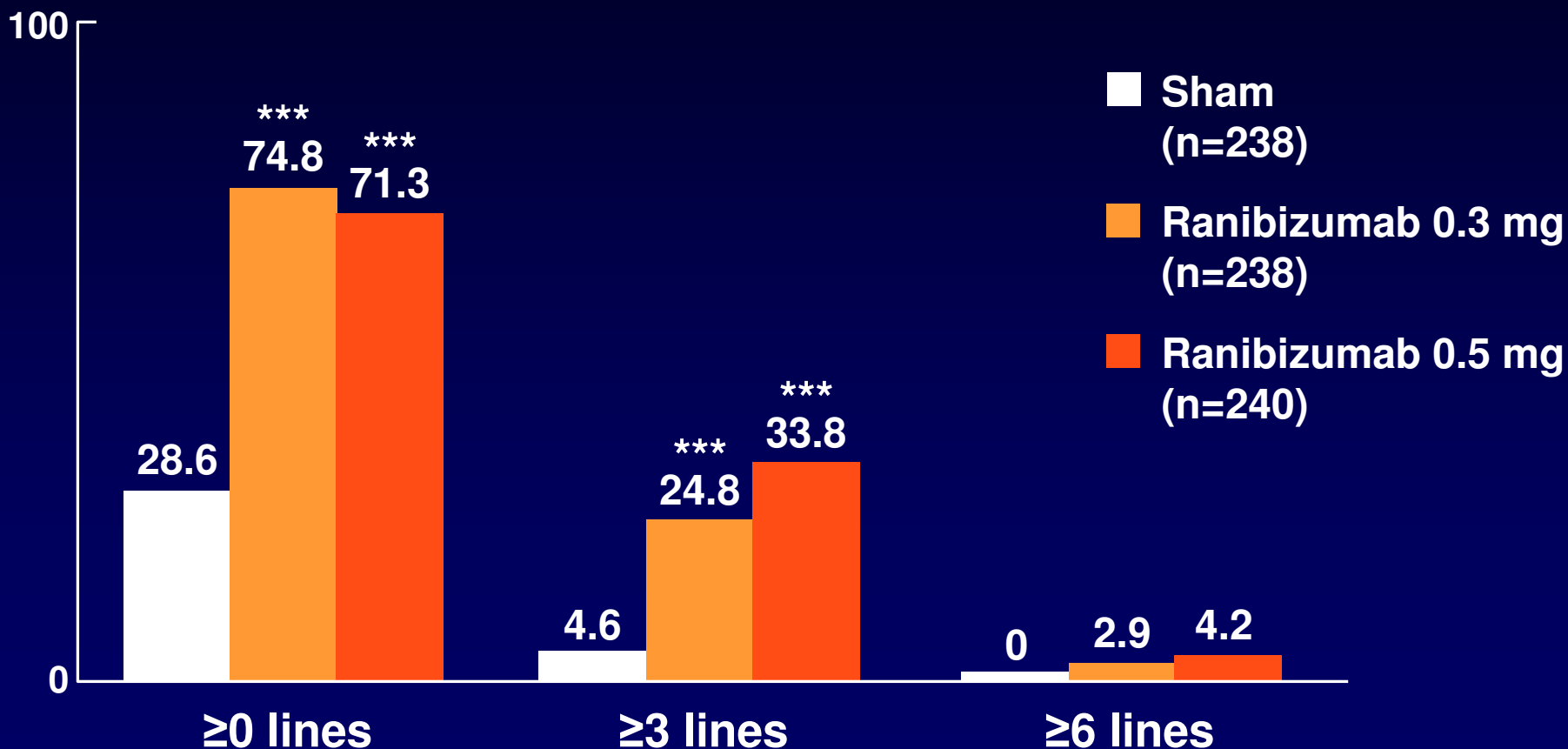


\*\*\*p<0.0001 vs sham

MARINA study MONTH 12

# Secondary endpoint: Ranibizumab provides visual gains

Patients with gain (%)



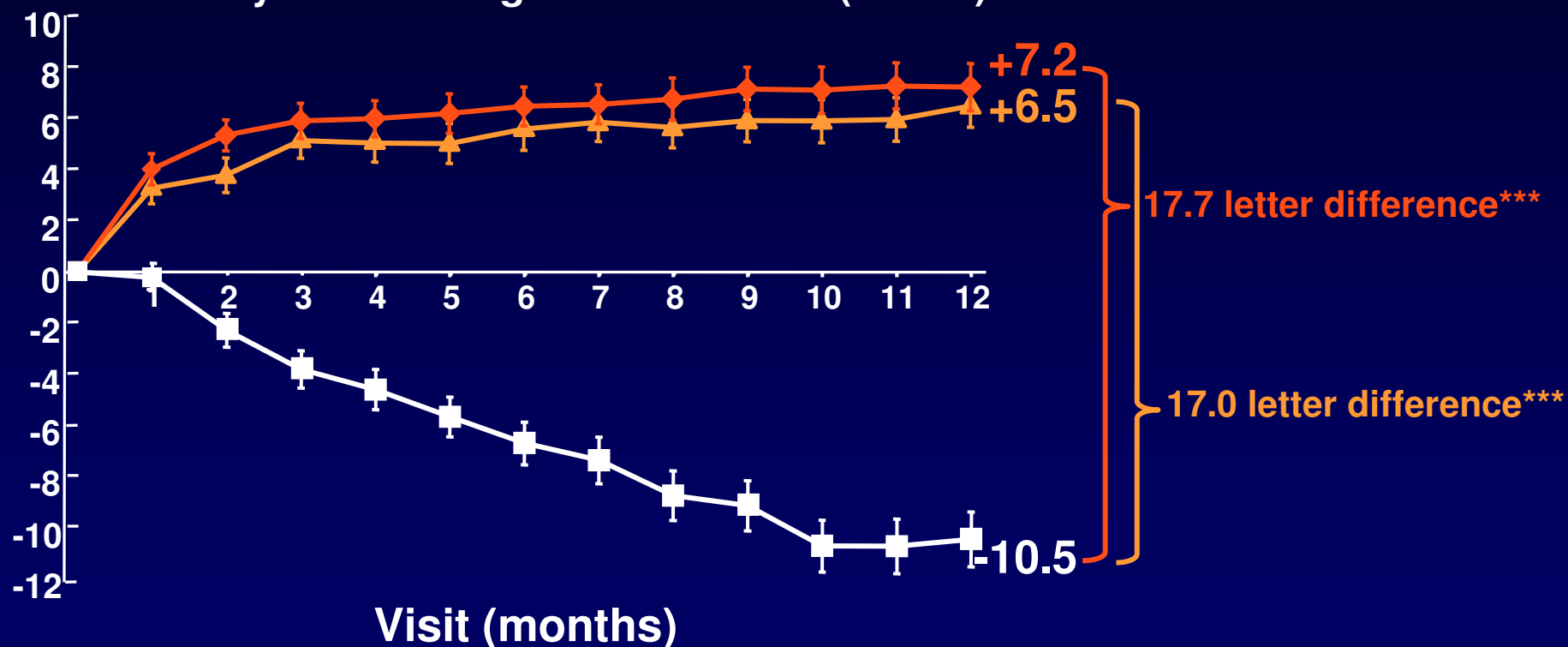
\*\*\* $p < 0.0001$  vs sham

MARINA study MONTH 12

# Secondary endpoint: Ranibizumab improves vision

■ Sham (n=238) ▲ Ranibizumab 0.3 mg (n=238) ◆ Ranibizumab 0.5 mg (n=240)

Visual acuity mean change from baseline (letters)

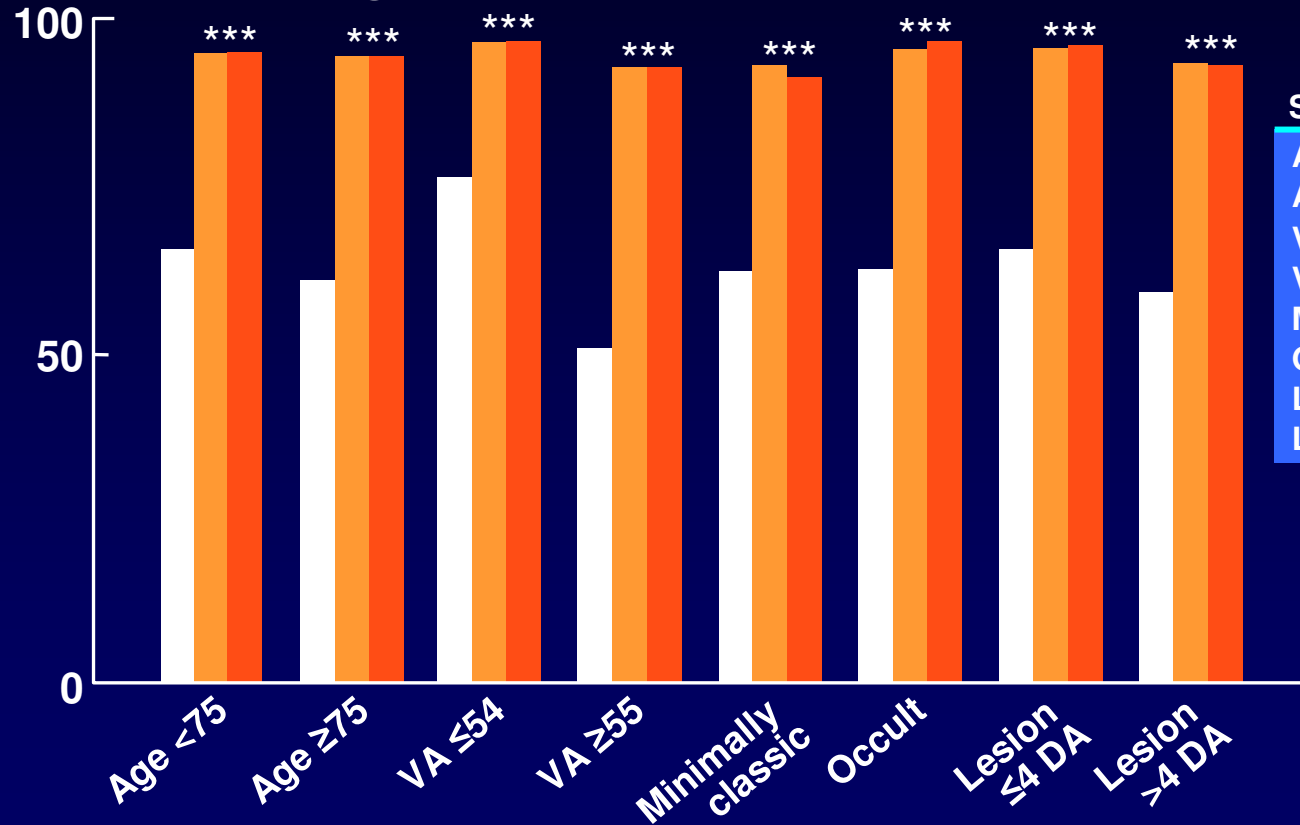


\*\*\*p<0.0001 for all ranibizumab comparisons vs sham from month 1 to month 12

MARINA study MONTH 12

# Results are comparable among pre-defined subgroups

Patients losing <15 letters (%)



Subgroup	Sample sizes		
	Sham	0.3mg	0.5mg
Age <75	78	77	80
Age ≥75	160	161	160
VA ≤54	109	115	117
VA ≥55	129	123	123
Min. Classic	87	86	91
Occult	151	151	148
Lesion ≤4DA	124	134	125
Lesion >4DA	114	104	115

Sham
  Ranibizumab 0.3 mg
  Ranibizumab 0.5 mg

\*\*\*p<0.0001 ranibizumab vs sham

MARINA study MONTH 12

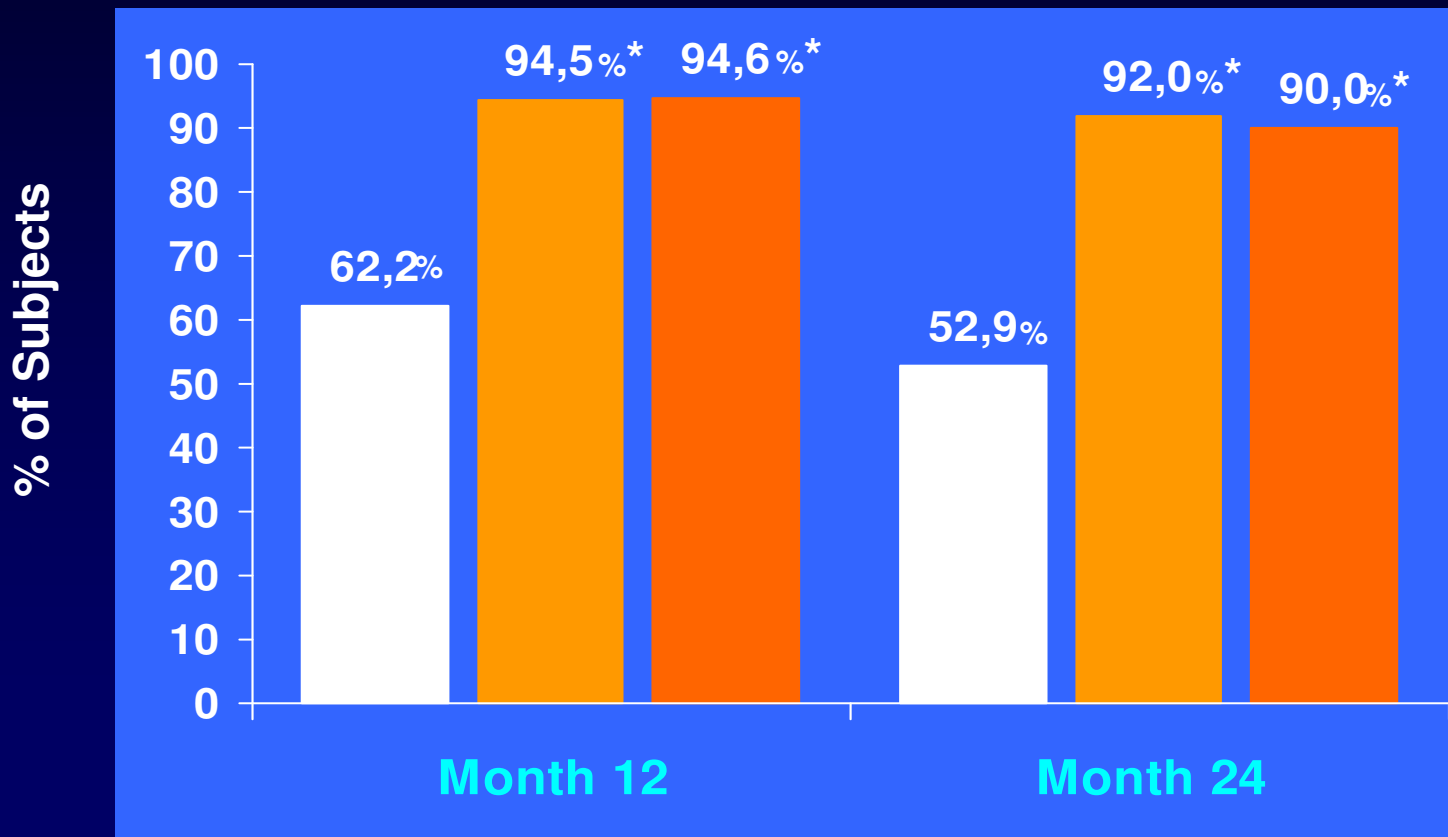
# MARINA 2 year results

# Subjects Losing <15 Letters from Baseline

■ Sham  
(n=238)

■ Ranibizumab 0.3 mg  
(n=238)

■ Ranibizumab 0.5 mg  
(n=240)

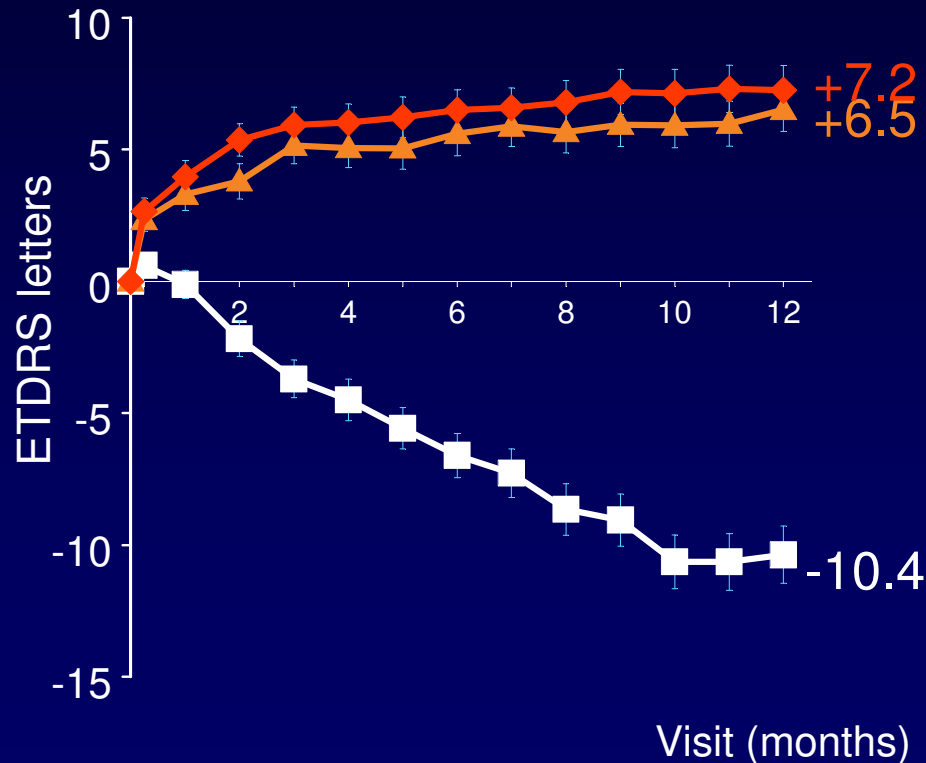


\*P < 0.0001 vs. Sham

# Visual Acuity Mean Change from Baseline over Time

- ◆ Ranibizumab 0.5 mg (n=240)
- ▲ Ranibizumab 0.3 mg (n=238)
- Sham (n=238)

\*  $P < 0.0001$



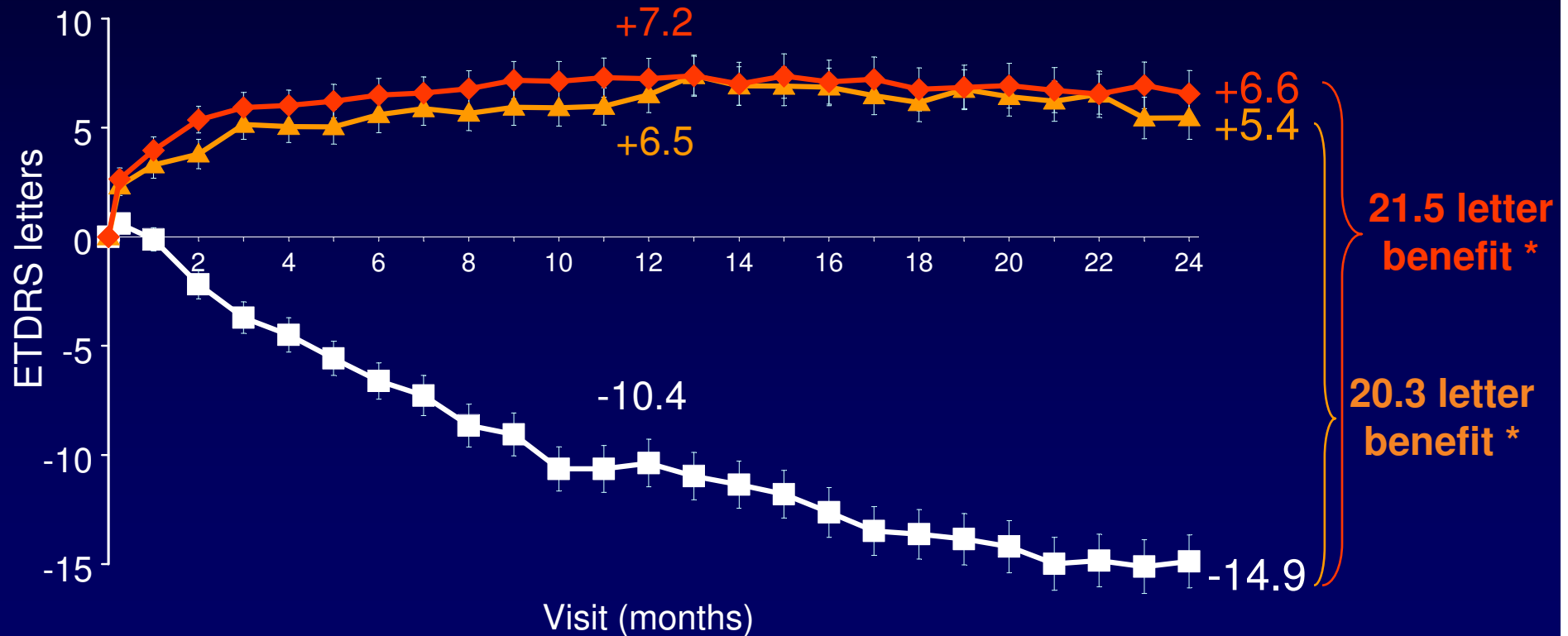
17.7 letter benefit \*

17 letter benefit \*

# Visual Acuity Mean Change from Baseline over Time

- ◆ Ranibizumab 0.5 mg (n=240)
- ▲ Ranibizumab 0.3 mg (n=238)
- Sham (n=238)

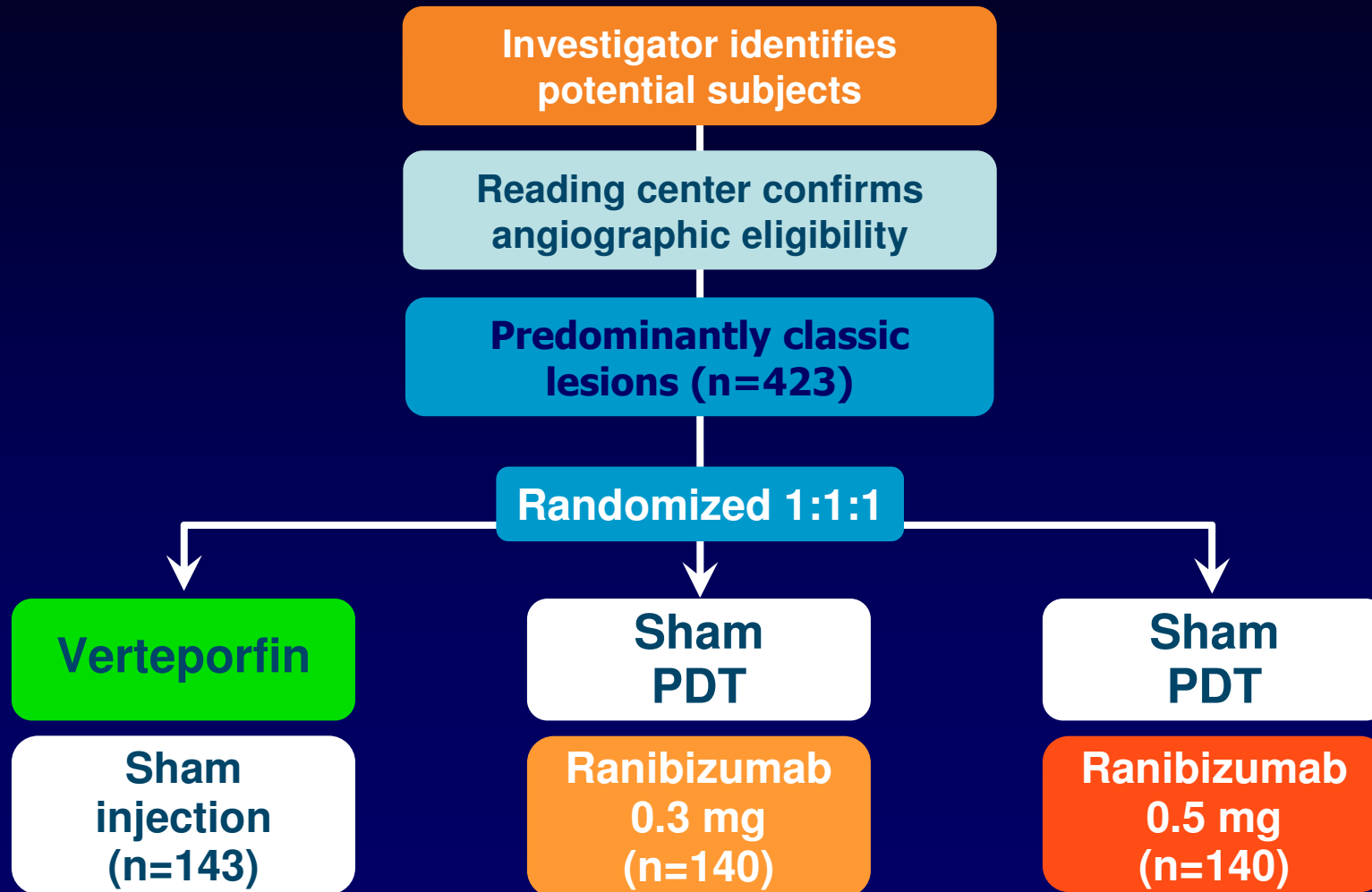
\*  $P < 0.0001$



## **ANCHOR study**

**A Phase III, multicentre, randomized, double-masked active treatment controlled study comparing the efficacy and safety of the investigational drug **ranibizumab** with **verteporfin** in subjects with **predominantly classic subfoveal CNV** due to AMD**

# Trial design

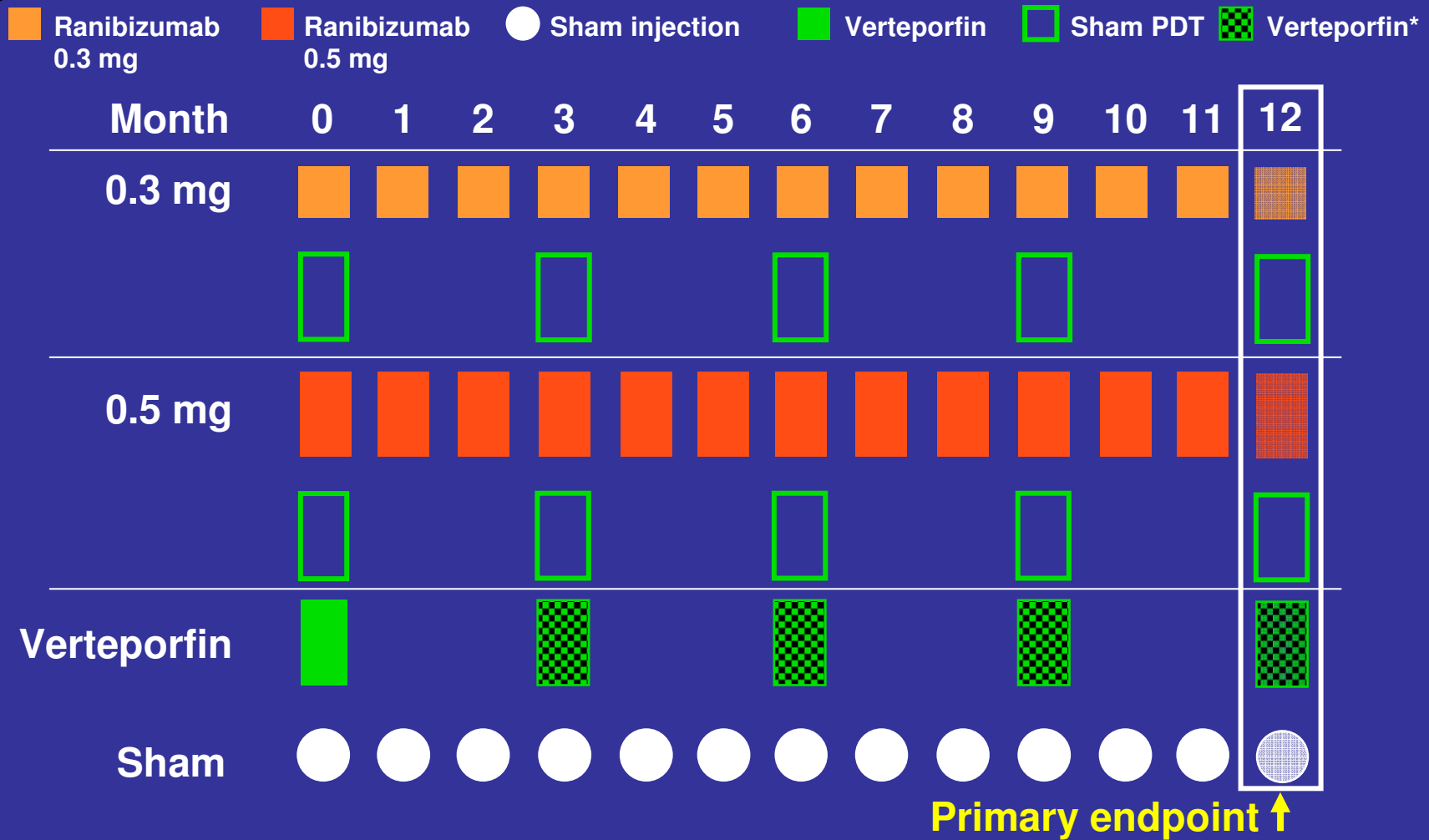


# Inclusion criteria

- **Primary or recurrent** subfoveal choroidal neovascularization (CNV\*) secondary to AMD
- **Predominantly classic** lesions
  - classic CNV  $\geq 50\%$  of the total lesion size
- Age  $\geq 50$  years
- BCVA in study eye of **20/40 to 20/320**
- Total lesion area  $\leq 5400 \mu\text{m}$  in GLD

CNV\* = CNV by FA + subretinal hemorrhage + blocked fluorescence + serous PED + fibrosis

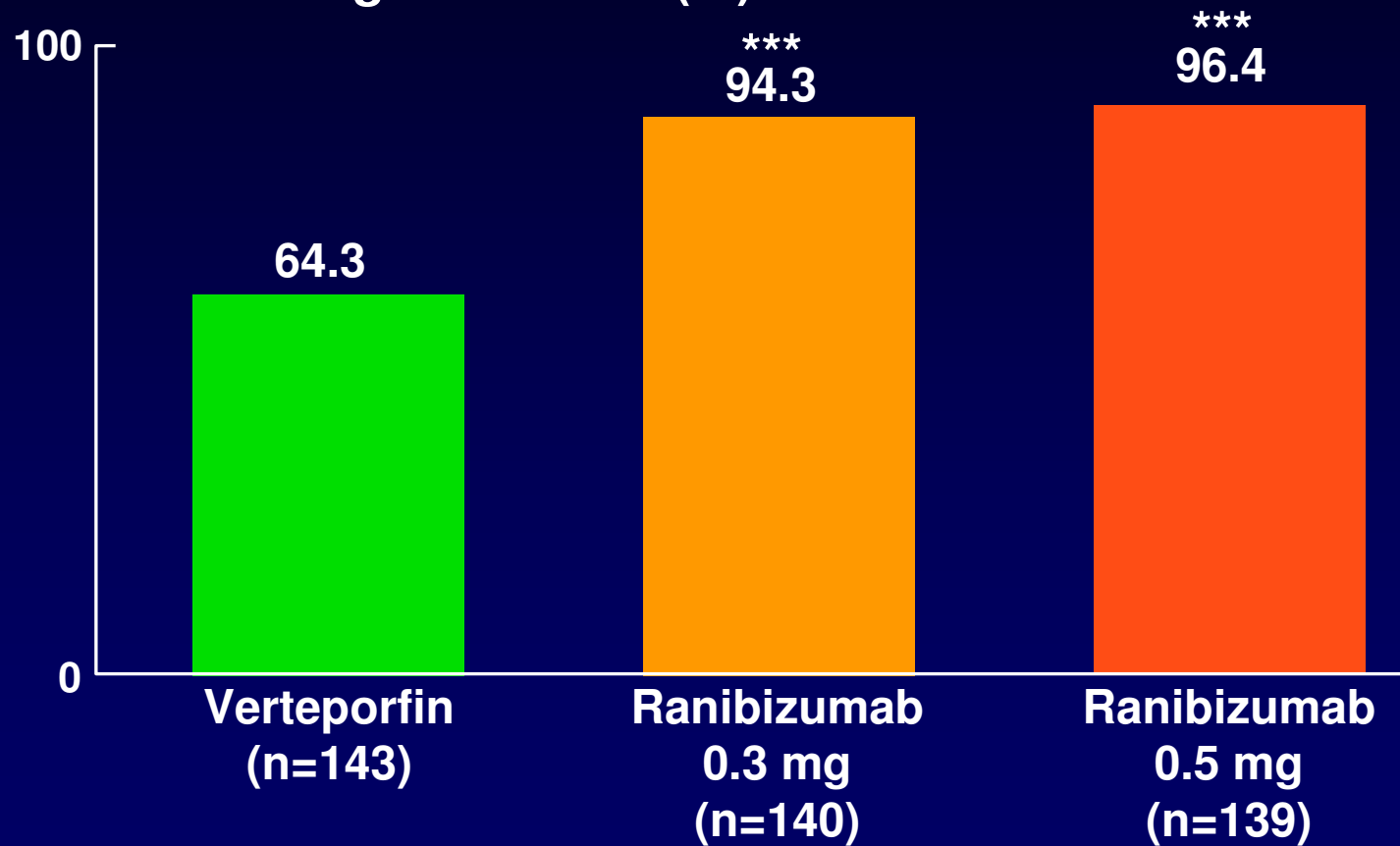
# Treatment schema: Year 1



\*Verteporfin treatment if angiographic leakage present

# Primary endpoint: Ranibizumab preserves vision

Patients losing <15 letters (%)

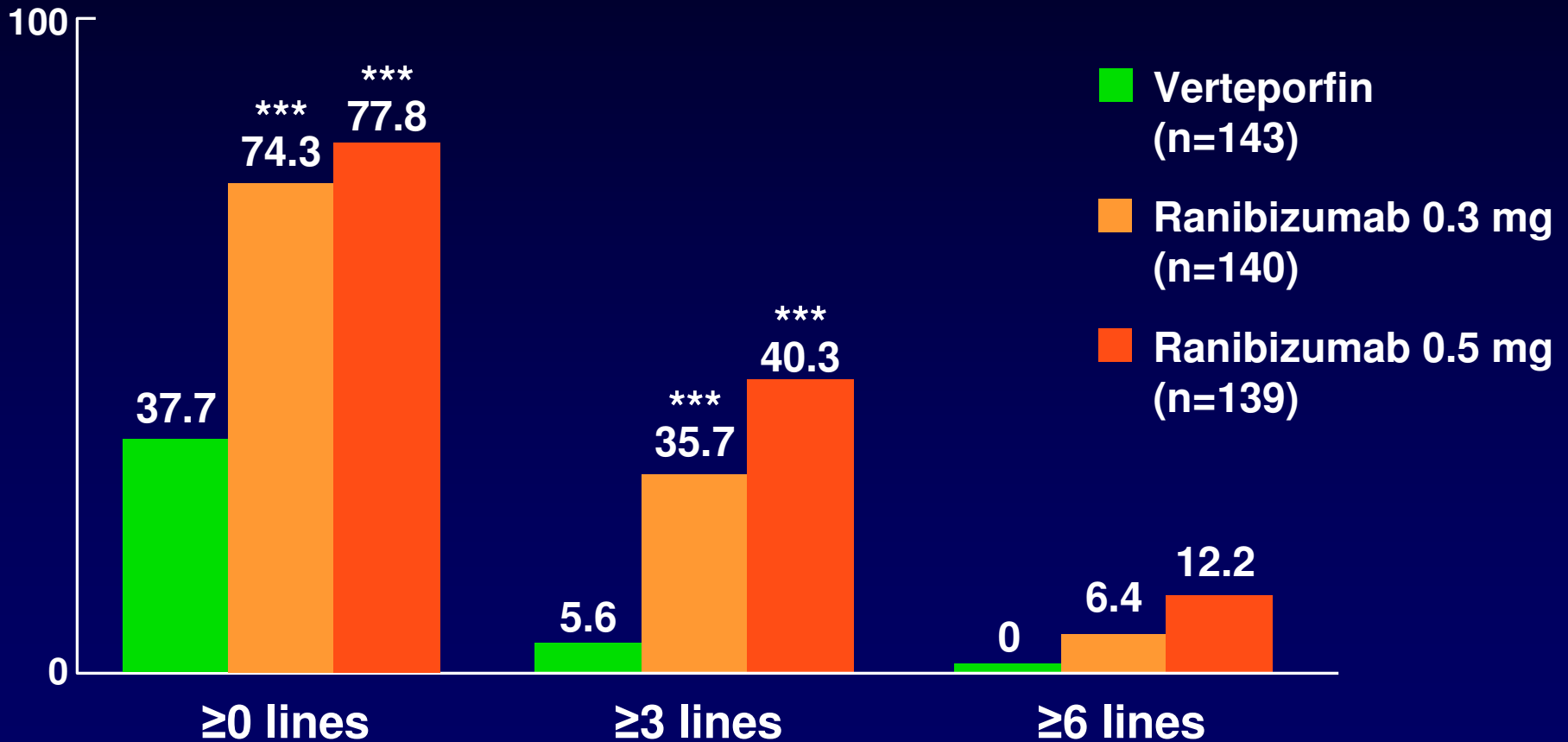


\*\*\*p<0.0001 vs verteporfin

ANCHOR study MONTH 12

# Secondary endpoint: Ranibizumab provides visual gains

Patients with gain (%)



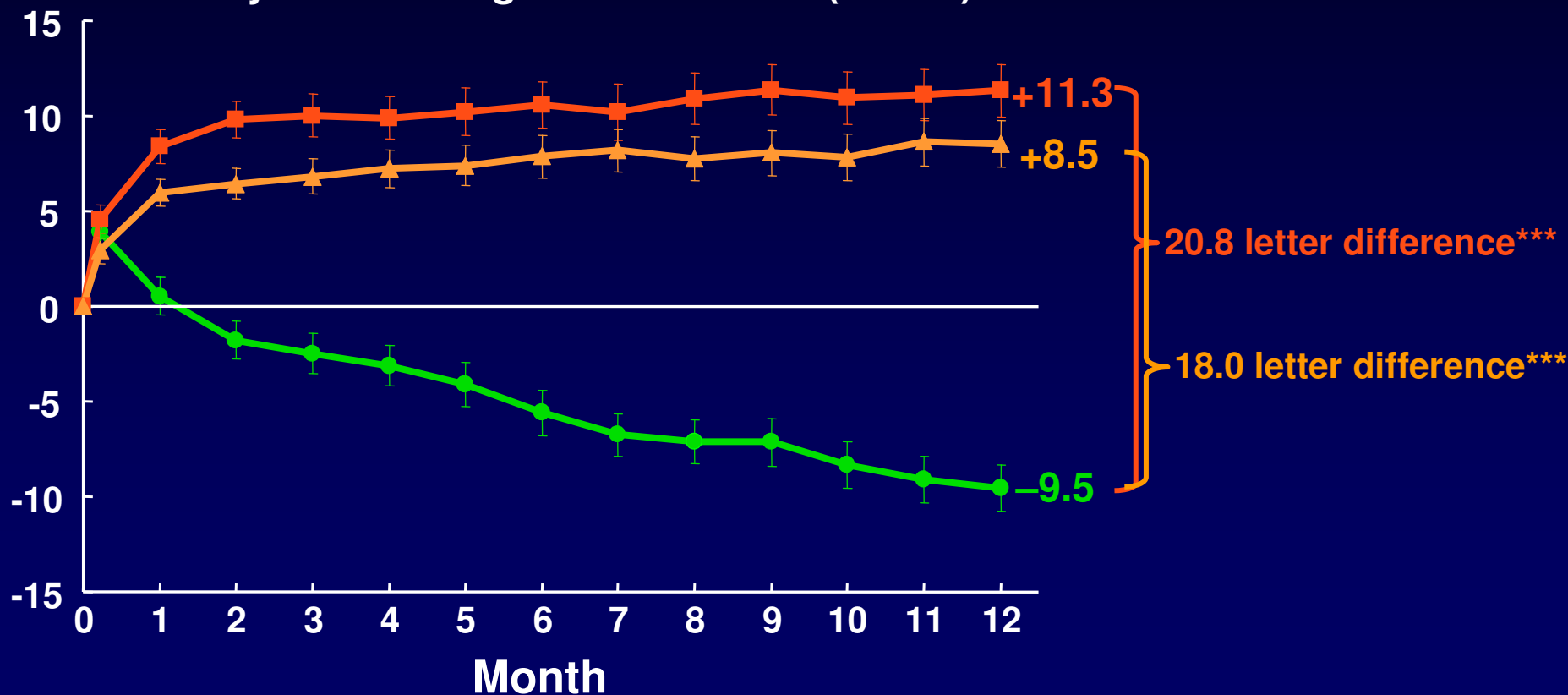
\*\*\*p<0.0001 vs sham

ANCHOR study MONTH 12

# Secondary endpoint: Ranibizumab improves vision

● Verteporfin (n=143) ▲ Ranibizumab 0.3 mg (n=140) ■ Ranibizumab 0.5 mg (n=139)

Visual acuity mean change from baseline (letters)

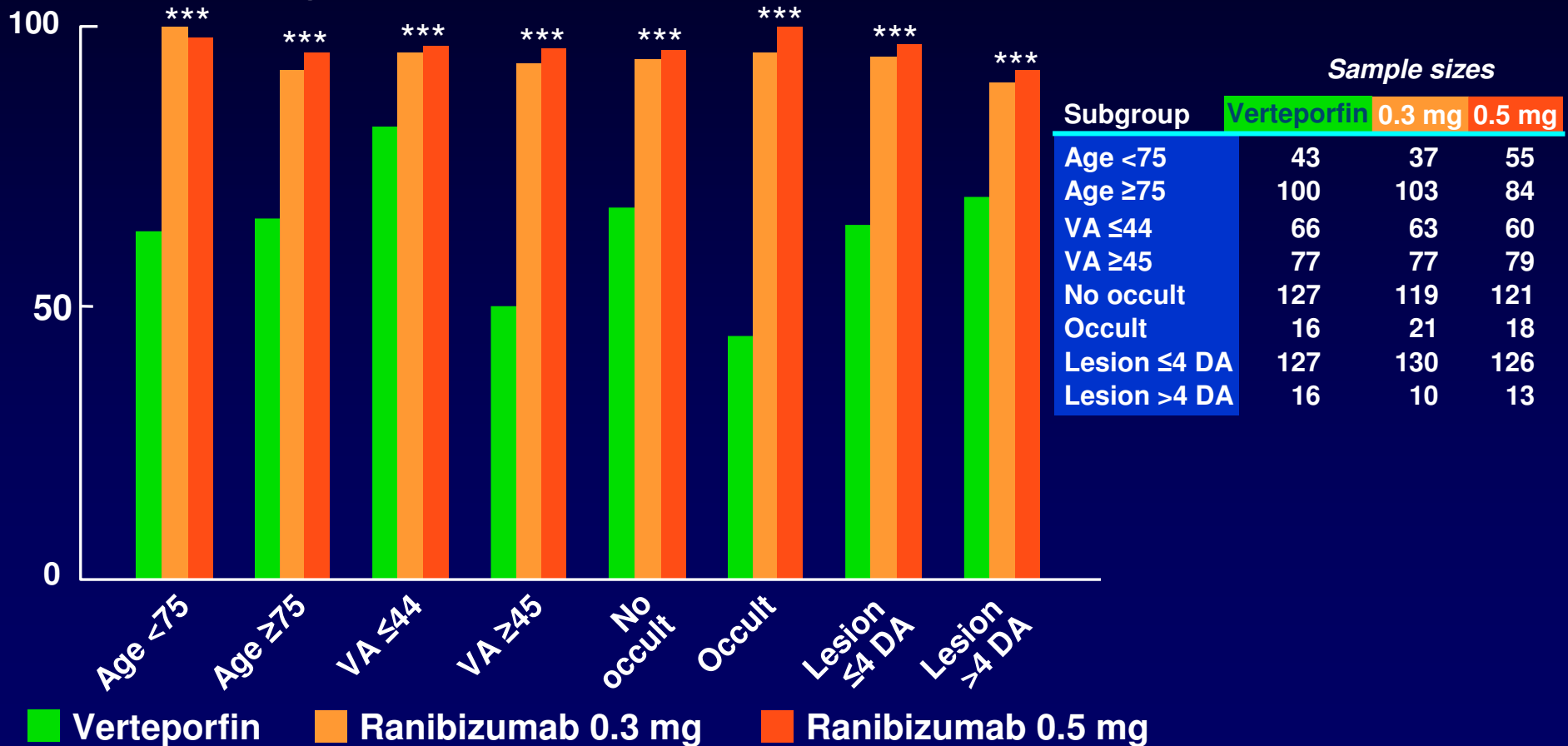


\*\*\* $p < 0.0001$  for all ranibizumab comparisons vs verteporfin from month 1 to month 12

ANCHOR study MONTH 12

# Results are comparable among subgroups

Patients losing <15 letters (%)



\*\*\*p<0.0001 ranibizumab vs verteporfin

ANCHOR study MONTH 12

**Summary of MARINA and ANCHOR:  
Safety**

# Integrated safety analysis: ANCHOR and MARINA

- **754 ranibizumab-treated patients** with neovascular AMD
- Large, randomized double-masked, controlled trials in neovascular AMD
- Control groups:
  - MARINA: Sham injected (n=236)
  - ANCHOR: Verteporfin (n=143)
- **9220 ranibizumab injections** and 4476 control treatments (2765 sham and 1711 verteporfin) in year 1

# Overview of key ocular serious adverse events

	MARINA			ANCHOR		
	Sham (n=236)	Ranibizumab 0.3 mg (n=238)	Ranibizumab 0.5 mg (n=239)	Verteporfin (n=143)	Ranibizumab 0.3 mg (n=137)	Ranibizumab 0.5 mg (n=140)
<b>Presumed endophthalmitis*</b>						
Culture positive	0	0	0	0	0	1 (0.7%)
Culture not done	0	1 (0.4%)	2 (0.8%)	0	0	1 (0.7%)
Intraocular inflammation	0	2 (0.8%)	2 (0.8%)	0	0	1 (0.7%)
IOP	0	1 (0.4%)	1 (0.4%)	0	0	0
Rheg. retinal detachment	0	0	0	1 (0.7%)	1 (0.7%)	0
Retinal tear	0	1 (0.4%)	1 (0.4%)	0	0	0
Vitreous hemorrhage	0	1 (0.4%)	1 (0.4%)	0	1 (0.7%)	0
Lens damage	0	0	1 (0.4%)	0	0	0

\*One culture not done

*Integrated safety summary*

# Deaths on study (MARINA and ANCHOR)

	Sham (n=236)	Verteporfin (n=143)	Ranibizumab 0.3 mg (n=375)	Ranibizumab 0.5 mg (n=379)
<b>Death</b>	0	2 (1.4%)	4 (1.1%)	4 (1.1%)
<b>Cause of death</b>		<ul style="list-style-type: none"> <li>■ Cardiac arrest</li> <li>■ COPD</li> </ul>	<ul style="list-style-type: none"> <li>■ Myocardial infarction</li> <li>■ Cardiac arrest</li> <li>■ Respiratory arrest</li> <li>■ Viral syndrome</li> </ul>	<ul style="list-style-type: none"> <li>■ Small bowel infarct</li> <li>■ Chronic asthma / COPD</li> <li>■ Cardiac failure</li> <li>■ Chronic heart failure</li> </ul>




- No deaths reported as related to ranibizumab

# Incidence of hypertension

	MARINA			ANCHOR		
	Sham (n=236)	Ranibizumab 0.3 mg (n=238)	Ranibizumab 0.5 mg (n=239)	Verteporfin (n=143)	Ranibizumab 0.3 mg (n=137)	Ranibizumab 0.5 mg (n=140)
Hypertension	23 (9.7%)	20 (8.4%)	20 (8.4%)	12 (8.4%)	3 (2.2%)	9 (6.4%)
Mean change in SBP / DBP (mmHg)	-2 / -2	-1 / -2	-4 / -1	0.1 / 0.3	-2 / -2	-2 / 1

# **Ranibizumab and Quality-of-Life**

# Definitions of subscales using the NEI-VFQ-25 questionnaire

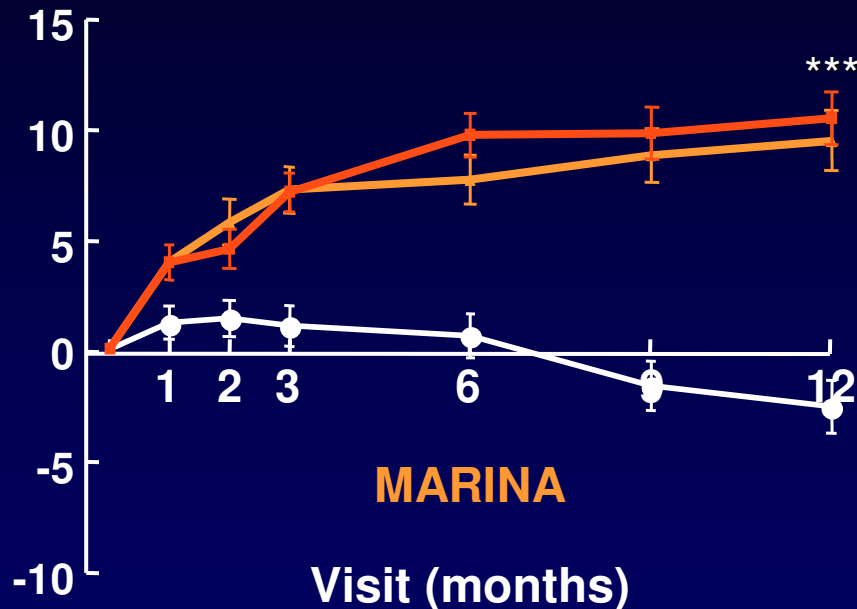
Subscale	Disability assessment items	
Near vision	<ul style="list-style-type: none"><li>■ Reading ordinary print in newspaper</li><li>■ Seeing well close up to do activities such as cooking and sewing etc.</li><li>■ Difficulty finding something on a crowded shelf</li></ul>	
Distance vision	<ul style="list-style-type: none"><li>■ Going out to see movies, plays or sports events</li><li>■ Reading street signs or names of stores</li><li>■ Going down steps, stairs or curbs at night</li></ul>	
Vision-specific dependency	<ul style="list-style-type: none"><li>■ Stay at home most of the time</li><li>■ Rely too much on others to help</li><li>■ Relying on what other people tell me</li></ul>	

Pre-defined secondary endpoints in MARINA and ANCHOR trials from a standard list of eleven subscales

*NEI-VFQ-25 questionnaire*

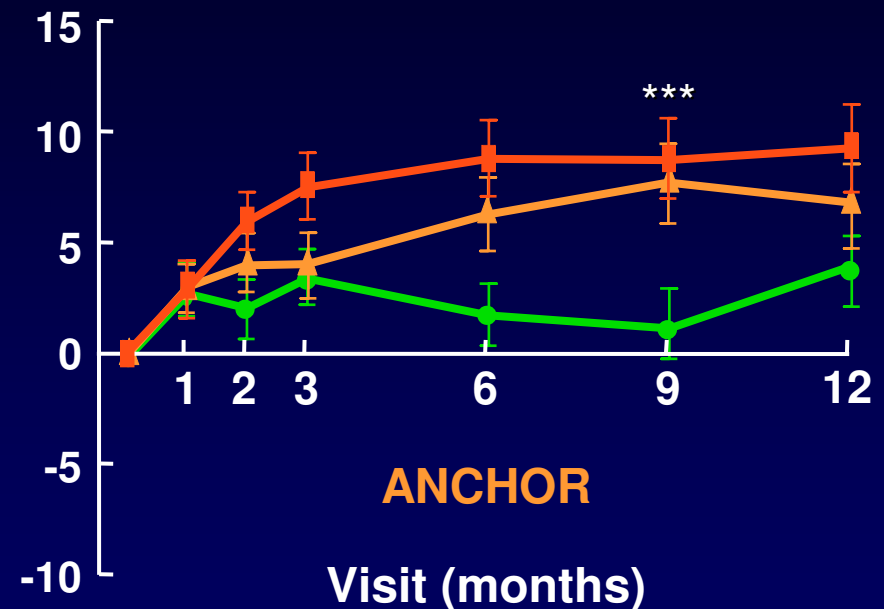
# Ranibizumab improves near activities

Mean change in near activities



- Ranibizumab 0.5 mg (n=240)
- ▲ Ranibizumab 0.3 mg (n=238)
- Sham (n=238)

Mean change in near activities

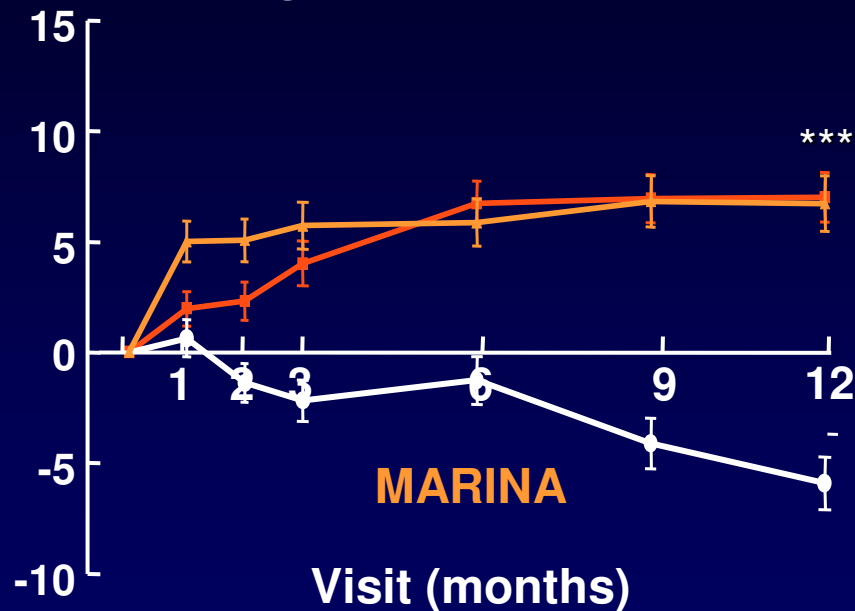


- Ranibizumab 0.5 mg (n=139)
- ▲ Ranibizumab 0.3 mg (n=137)
- Verteporfin (n=142)

\*\*\*p<0.0001 vs control

# Ranibizumab improves distance activities

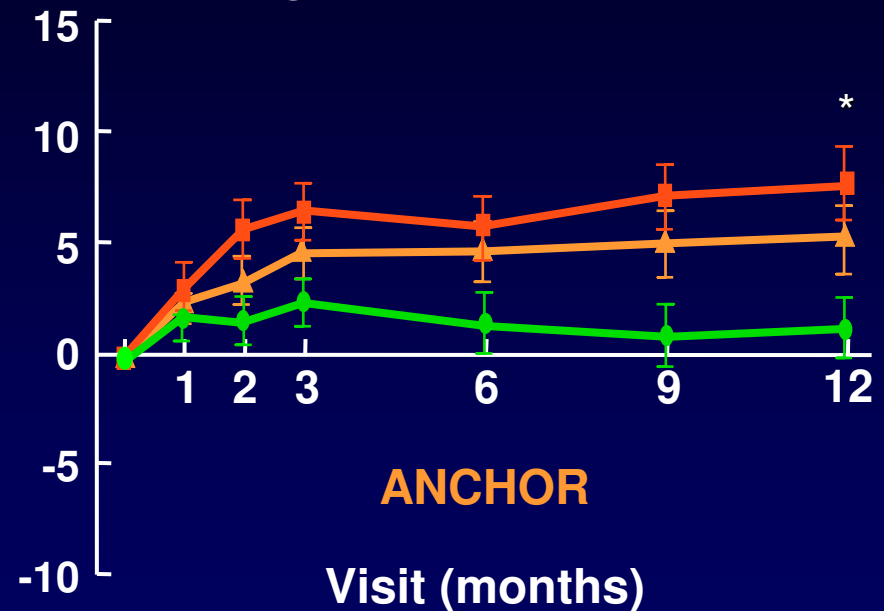
Mean change in distance activities



- Ranibizumab 0.5 mg (n=240)
- ▲ Ranibizumab 0.3 mg (n=238)
- Sham (n=238)

\*\*\*p<0.0001 vs control

Mean change in distance activities

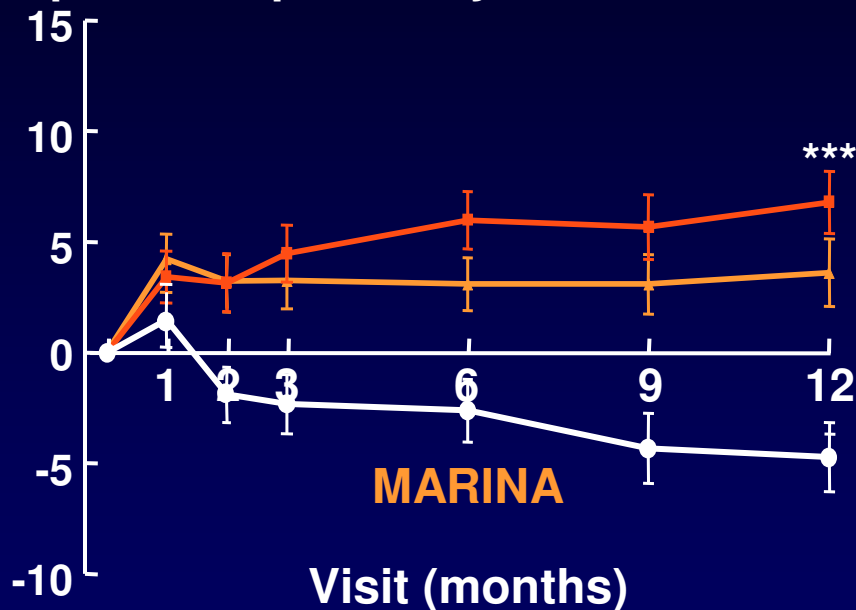


- Ranibizumab 0.5 mg (n=139)
- ▲ Ranibizumab 0.3 mg (n=137)
- Verteporfin (n=142)

\*p<0.01 vs verteporfin

# Ranibizumab improves vision-specific dependency

Mean change in vision-specific dependency



- Ranibizumab 0.5 mg (n=240)
- ▲ Ranibizumab 0.3 mg (n=238)
- Sham (n=238)

Mean change in vision-specific dependency



- Ranibizumab 0.5 mg (n=139)
- ▲ Ranibizumab 0.3 mg (n=137)
- Verteporfin (n=142)

\*\*\*p<0.0001 vs control

# Summary

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- Quality-of-life outcomes **help describe visual benefits** and add to the overall assessment of efficacy
  - Ranibizumab-treated patients reported **significant improvements** in near activities, distance activities and vision-specific dependency
-

# FOCUS Study

Phase I/II study designed to evaluate safety, efficacy, tolerability of **ranimizumab treatment in conjunction with verteporfin PDT** compared with **verteporfin PDT alone** in patients with subfoveal predominantly classic CNV secondary to AMD

# FOCUS Study

- **Primary or recurrent** subfoveal CNV secondary to AMD
- **Predominantly classic** lesions
  - classic CNV  $\geq 50\%$  of the total lesion size
- Age  $\geq 50$  years
- BCVA in study eye of **20/40 to 20/320**
- Total lesion area  $\leq 5400 \mu\text{m}$  in GLD

# FOCUS Study

	<b>PDT Alone</b>	<b>Lucentis/PDT</b>
<b>VA loss &lt;15 L</b>	<b>67.9%</b>	<b>90.5%</b>
<b>VA gain ≥15 L</b>	<b>5.4%</b>	<b>23.8%</b>
<b>Letter score</b>	<b>-13.1</b>	<b>+4.9</b>
<b>Repeated PDT</b>	<b>91.1%</b>	<b>27.6%</b>

# PrONTO Study

- **Interventional, Open Label, Uncontrolled, Single Group Assignment, Efficacy Study**
- **40 Patients**
- **Study completion: June 2008**
- **Minimally Classic or Occult or Predominantly Classic CNV**
- **Ranibizumab dose (500 micrograms) at baseline and every 30 days for the first 2 mos**
- **No further injection if VA stable/improved from the previous visit, and no evidence of leakage from CNV as determined by FA and OCT**

# PrONTO Study

To undergo reinjection:

- vision loss  $\geq 5$  letters associated with:
- evidence of leakage from CNV as determined by OCT or FA
- or a new-onset macular hemorrhage
- or new onset classic CNV
- or an increase in central macular thickness  $\geq 100$  microns

# PrONTO Study

## Results

- Study ongoing
- Gain of 5.5 letters by day 14 in the first 30 pts
- Gain of 8.5 letters by day 90
- VA improvement associated with decrease in central retinal thickness
- 50 $\mu$  decrease in CRT on day 1
- 175 $\mu$  decrease in CRT on day 90
- 40% pts needed further injections

# PrONTO Study

## Results

- **Mean number of injections in 12 mos: 5.6**
- **Gain of 9.3 letters by 12-mos examination**
- **95% pts lost less than 15 letters**
- **35% pts gained at least 15 letters**
- **Tendency for OCT to show return of fluid before loss of vision, allowing re-treatment with ranibizumab without loss of vision**
- **the PrONTO study will likely guide clinicians to use variable dosing of ranibizumab, potentially sparing patients the additional risks of intravitreal injection and long-term VEGF inhibition**

**grazie per l'attenzione**