# AMD

## L'ARMAMENTARIO TERAPEUTICO SI ARRICCHISCE

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Napoli, 19 maggio 2014.

# AFLIBERCEPT

- Soluble fusion protein
- Human aminoacids sequence
- Penetrates to all retinal layers

- Molecular size: 115 kDa
(Ranibizumab 48 kDa; Bevacizumab 149 kDa)

- **IVT half-life: 4.7 days**
(Ranibizumab 2.88 days; Bevacizumab 4.32 days)

- **>100-fold higher affinity** than Ranibizumab and Bevacizumab

(Papadopoulos N, et al. Angiogenesis 2012)

- **VEGF-A pan-inhibitor**
- Also inhibits **VEGF-B** and **PIGF**
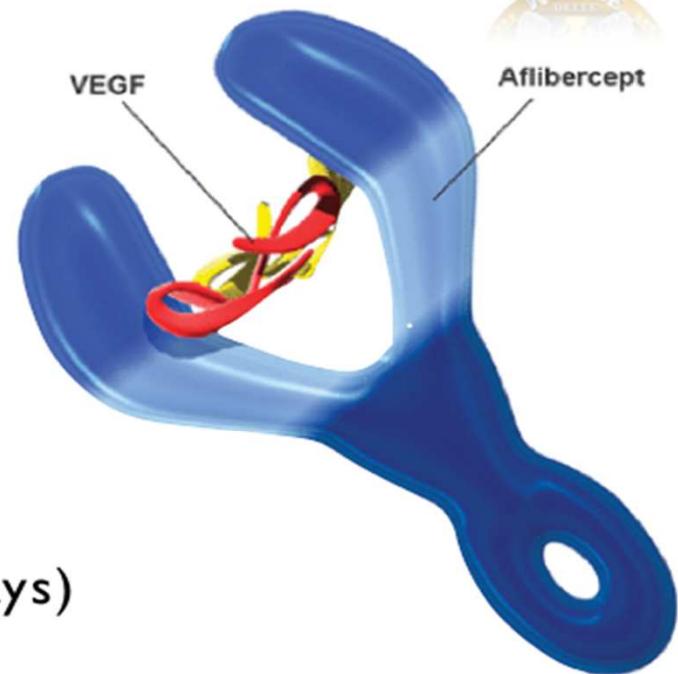
# AFLIBERCEPT IN AMD

- CLEAR           e.v.

- CLEAR-IT 1        IVT

- CLEAR-IT 2        IVT

- VIEW 1           IVT

- VIEW 2           IVT



Figure. Mean change in visual acuity from baseline to week 96; combined data from the VIEW 1 and VIEW 2 studies

- Aflibercept 2q8
- Ranibizumab 0.5q4

↓ 5.6 injections
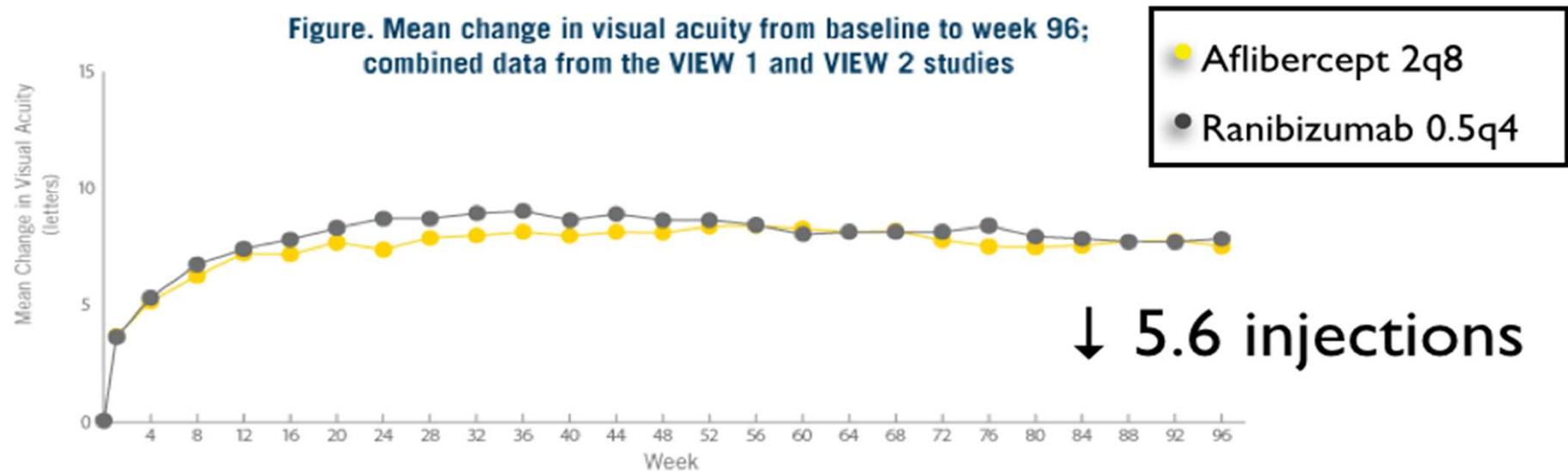
# AFLIBERCEPT IN AMD

2.0 mg di Aflibercept intravitreale:
attività biologica dai 48 agli 83 giorni
vs 30 giorni per 0.5 mg di Ranibizumab

(Stewart MW, et al. Br J Ophthalmol 2008)

VEGF      Aflibercept

↓ n° di iniezioni intravitreali

↓ il rischio di complicanze

direttamente legate all'iniezione:

- emovitreo
- distacco di retina
- endoftalmite
- ipertono

minor carico per pz e familiari

↓ i costi diretti e indiretti
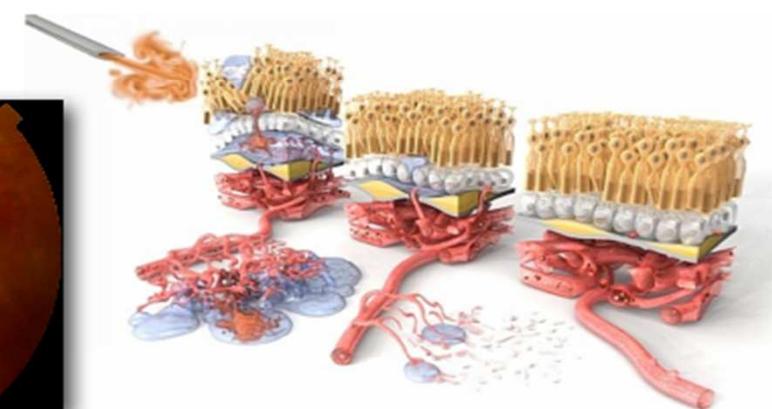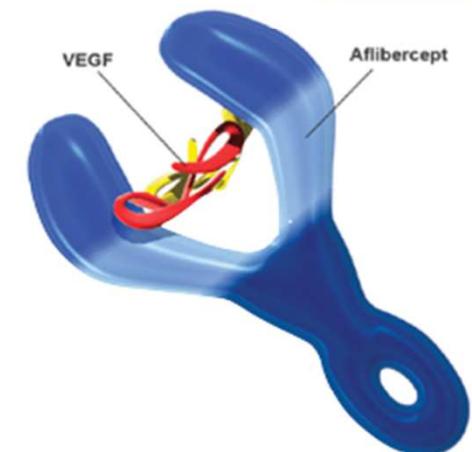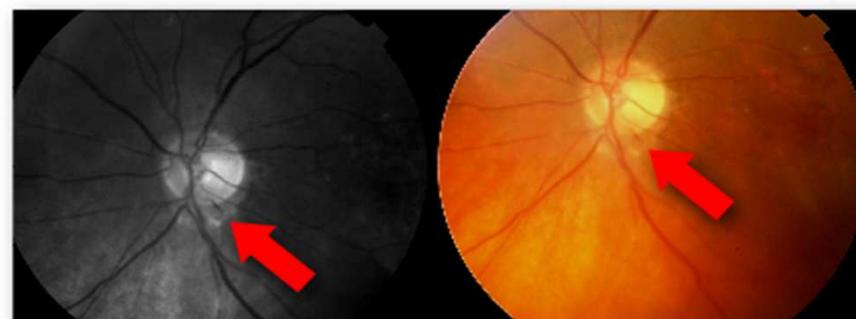
# AFLIBERCEPT IN AMD

Subgroup Analyses of the VIEW 1 and VIEW 2 Studies

- **Early persistent fluid (1815 patients)**

  - 595 for Ranibizumab 0.5 mg every 4 weeks (Rq4)

  - 613 for Aflibercept 2 mg every 4 weeks (2q4)

  - 607 for Aflibercept 2 mg every 8 weeks (2q8)

- Eyes with persistent fluid after 3 monthly Aflibercept injections benefitted from continued monthly injections of Aflibercept (2q4):

  - lowest in **18.8%** (2q4) vs **29.4%** in Rq4 and **20.3%** in 2q8.

  - VA improvement for 2q4 group was greater than that of 2q8 and Rq4 groups *(p<0.05)*. Mean VA change in the 2q8 and Rq4 groups did not differ *(p=NS)*.

Rosenfeld et al, 2014.

# AFLIBERCEPT IN AMD

- **RPE elevation (1349 patients)**

  - 435 for Ranibizumab 0.5 mg every 4 weeks (Rq4)

  - 460 for Aflibercept 2 mg every 4 weeks (2q4)

  - 455 for Aflibercept 2 mg every 8 weeks (2q8)

- Cumulative flattening of RPE elevation at 52 weeks was significantly higher in Aflibercept groups (**59.6%** for 2q4 and **52.6%** in 2q8) than in Rq4 group (**45.7%**)

- Every two months and monthly regimes of intravitreal Aflibercept was **23-50%** more effective than monthly Ranibizumab in flattening RPE elevation in wet AMD.

Rosenfeld et al, 2014.

ZALTRAP is a recombinant fusion protein that combines the VEGFR-1 and VEGFR-2 binding domains and the Fc region of the human IgG1 antibody[1-3]

VEGF dimer

VEGFR2 binding domain 3

VEGFR1 binding domain 2
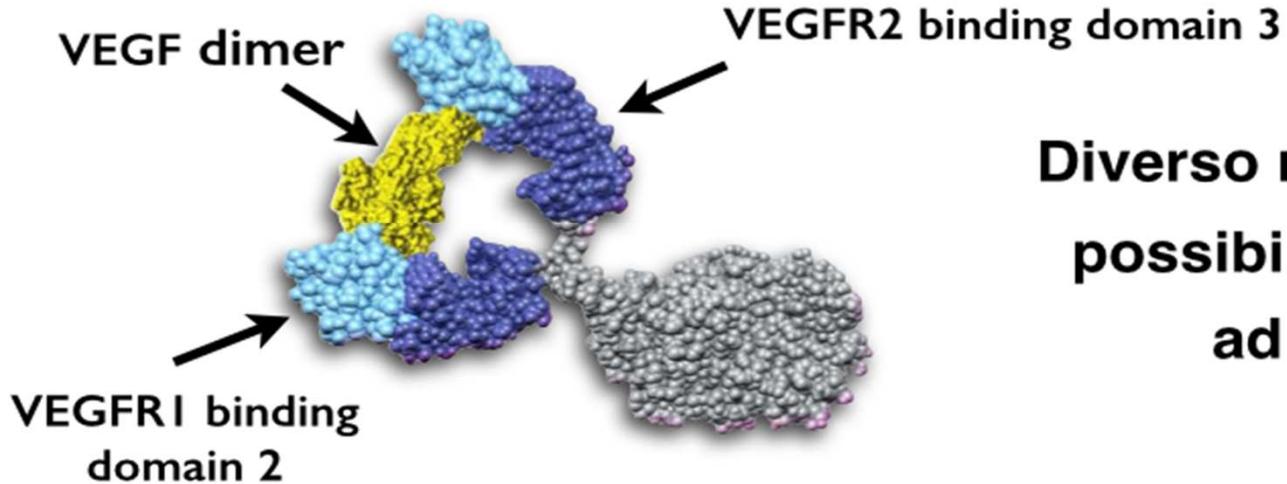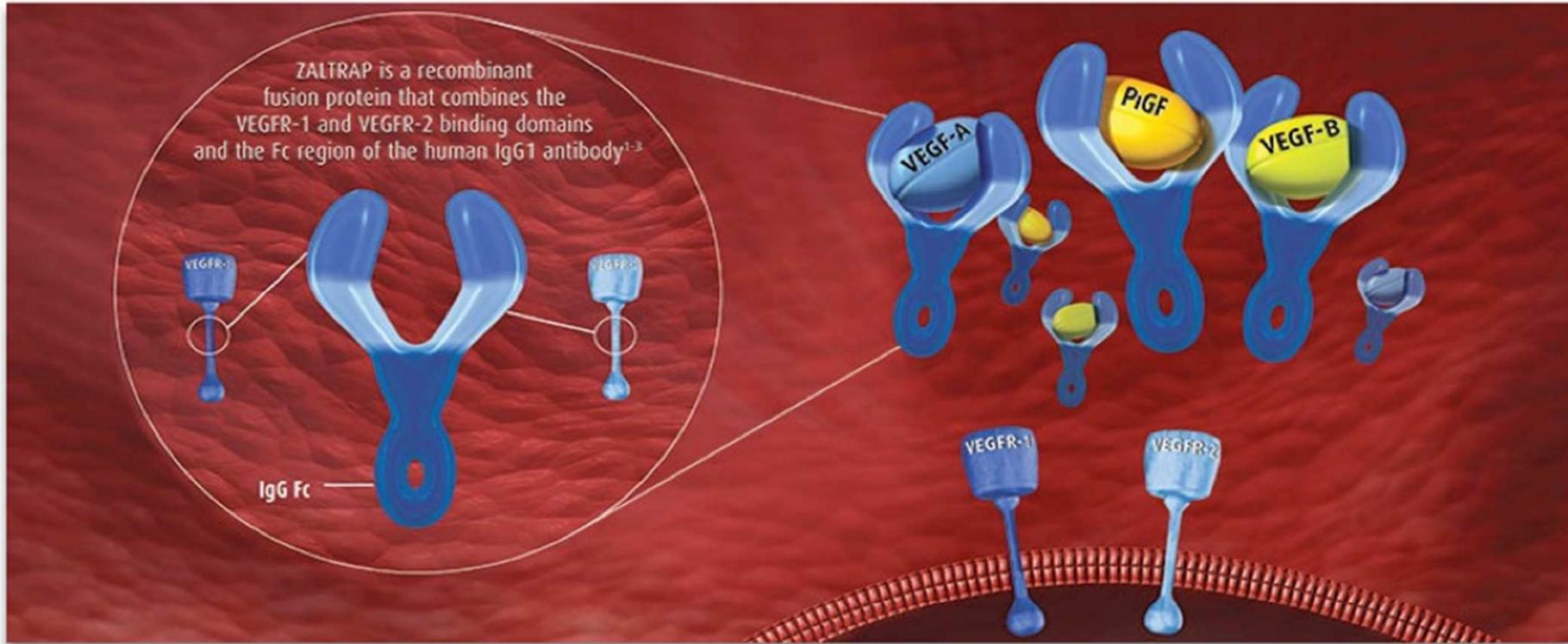
Diverso meccanismo d'azione: possibilità di **conversione** ad altro Anti-VEGF

# ANTI-VEGF IN REAL-LIFE

1) No Responders ab initio

2) "Acquired No Responders"
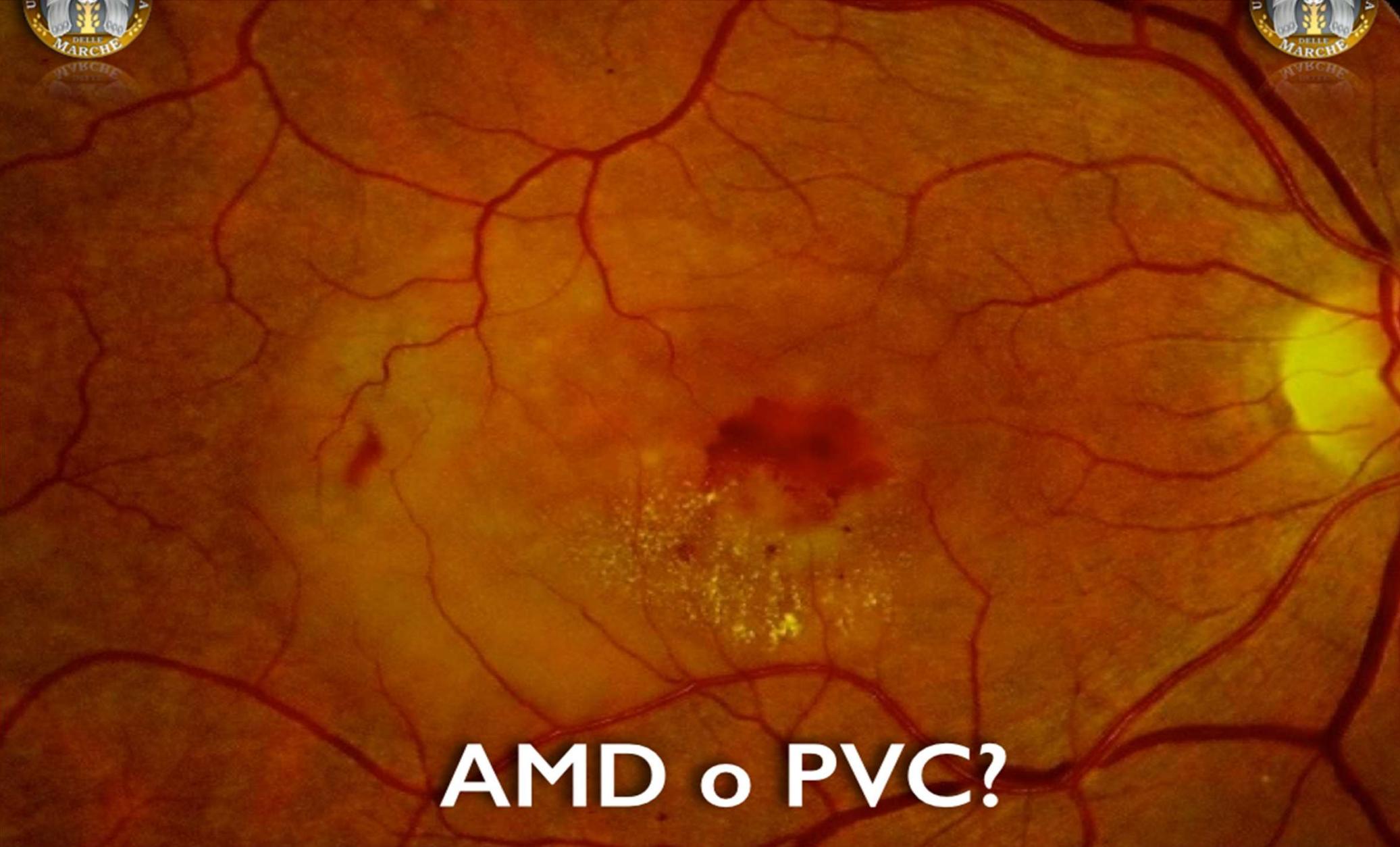
3) Brief Responders

AMD o PVC?

# NO RESPONDERS AB INITIO

## ICG IS MANDATORY!
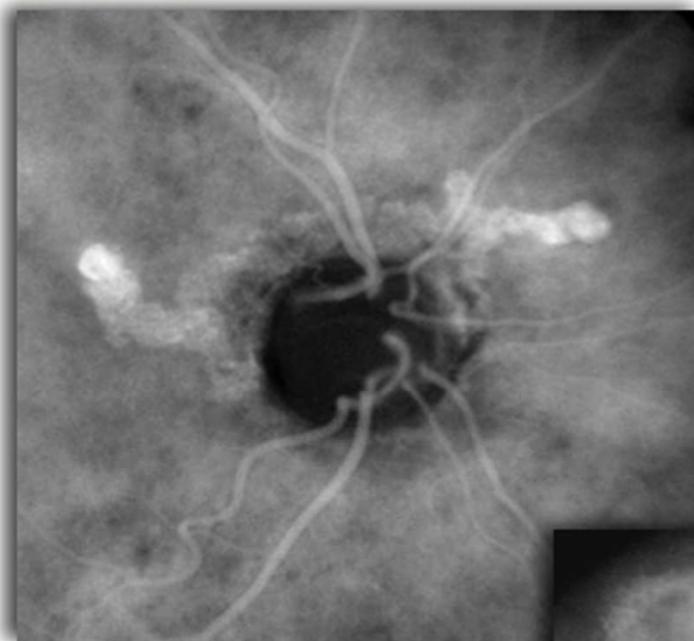
Peripapillary
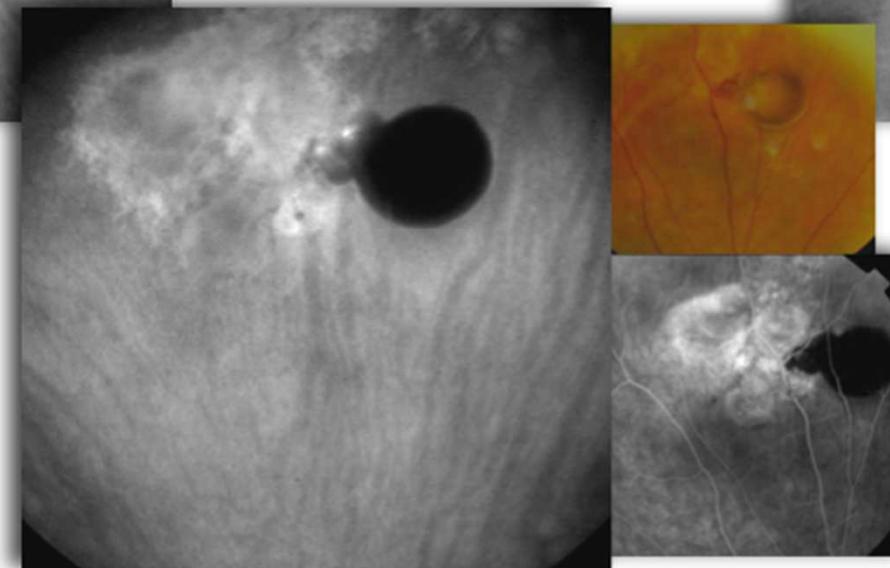
Peripheral
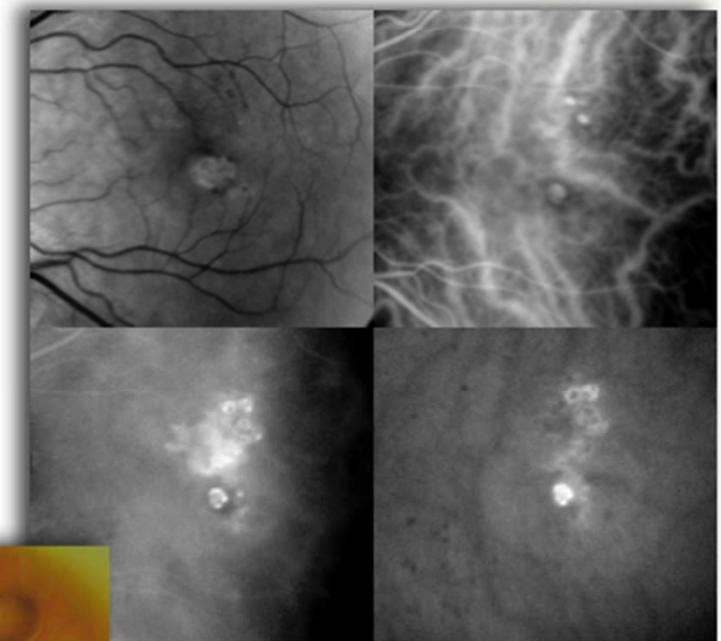
Macular:
- extra-foveal
- sub/iuxta-foveal

## PVC himmunochemical features

➤ Lack of a VEGF positivity in the vascular endothelial cells of PCV

➤ Higher levels of aqueous VEGF in PVC when compared to normal controls but significantly lower than eyes with AMD

➤ PVC = vascular maturity

# AFLIBERCEPT IN PVC (#1)

PRE: già 6 Anti-VEGF (Bevacizumab e Ranibizumab)
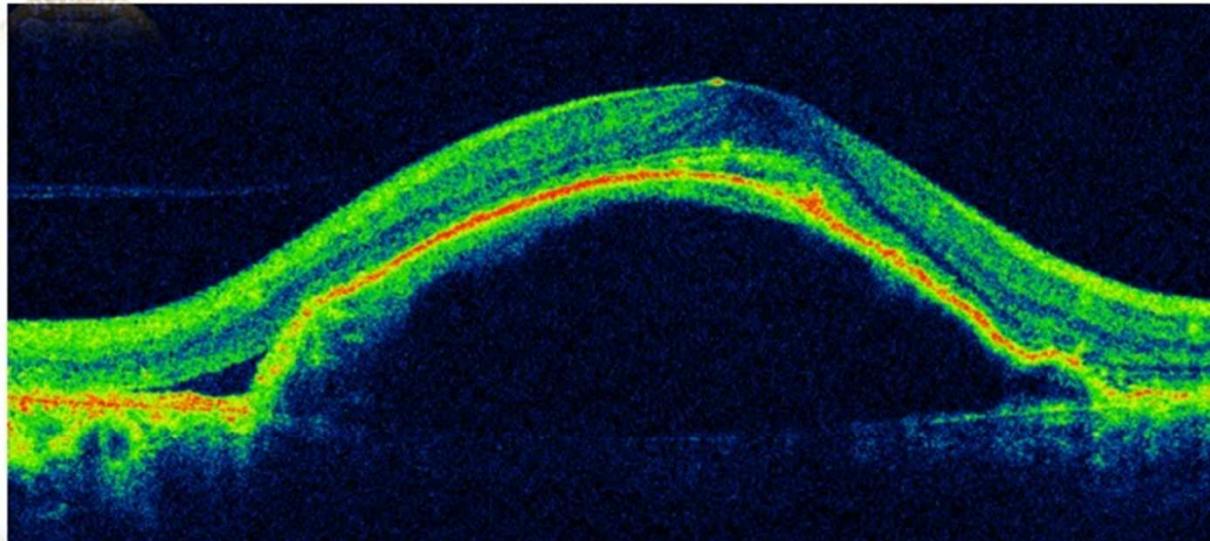


POST 1 Aflibercept
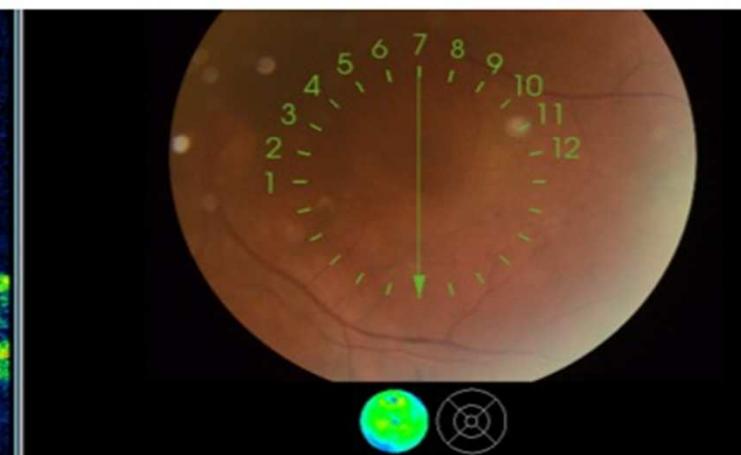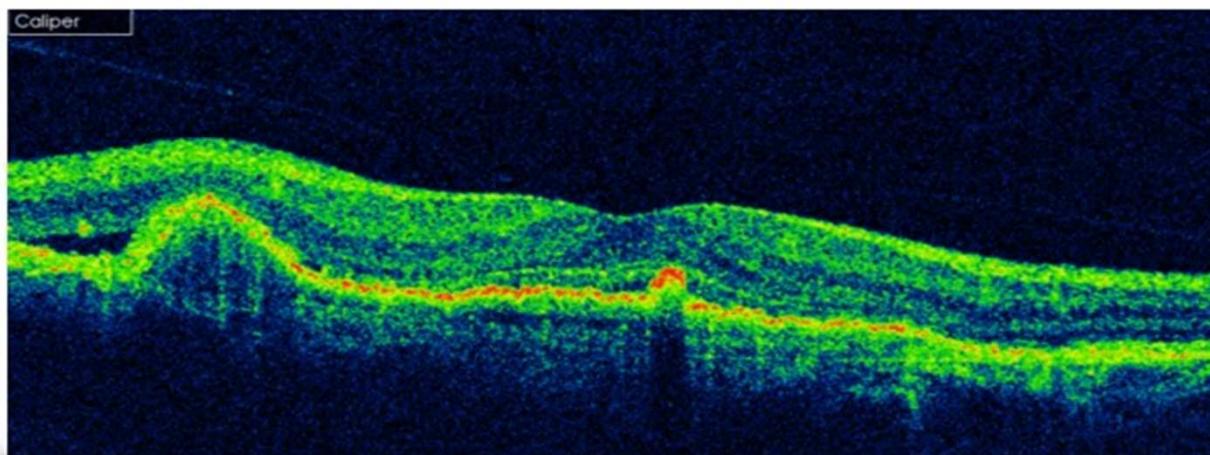
# AFLIBERCEPT IN PVC (#2)

PRE: già 21 trattamenti endovitreali in 9 anni.
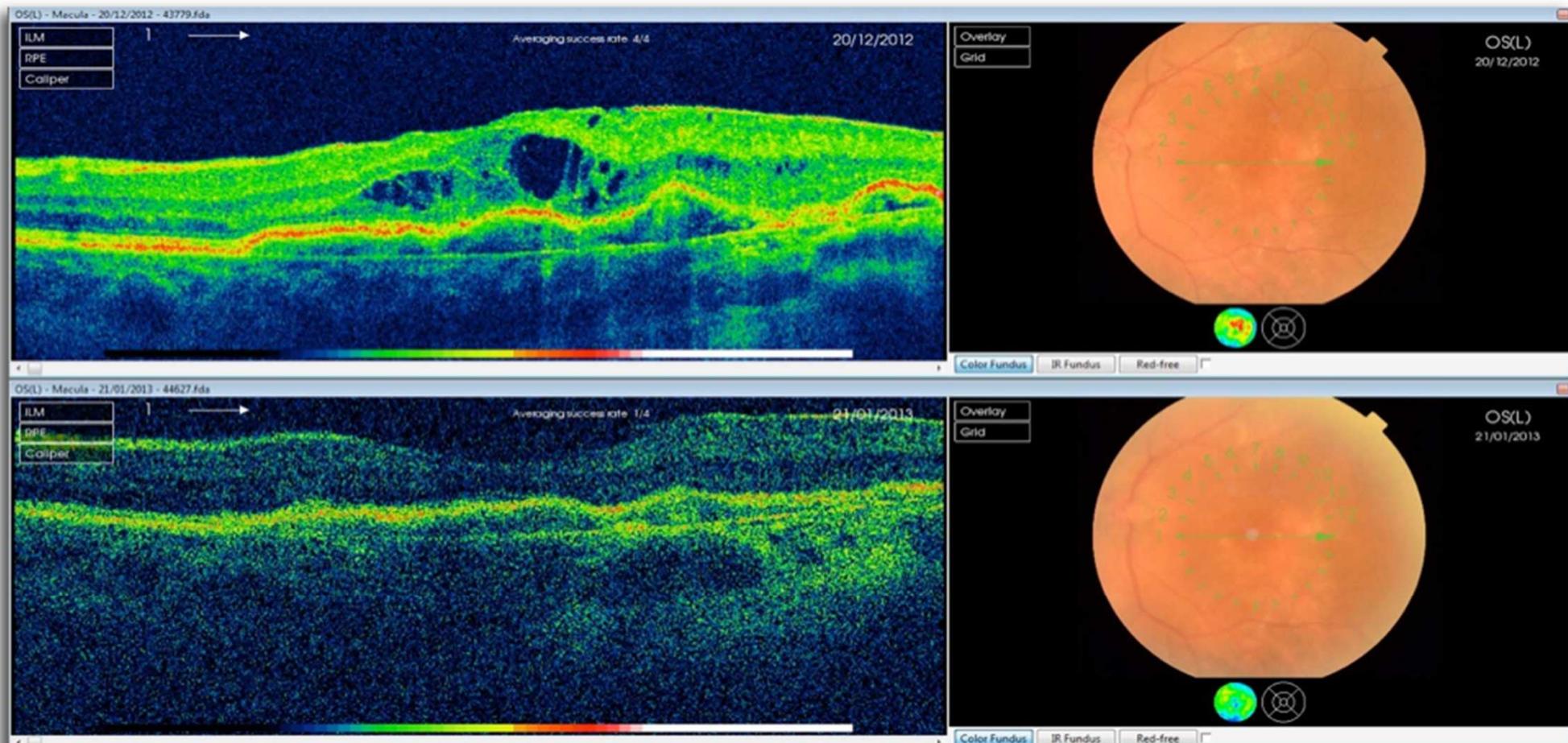


POST Aflibercept: 1 mese

# AFLIBERCEPT IN PVC (#2)

POST Aflibercept: 3 mesi…
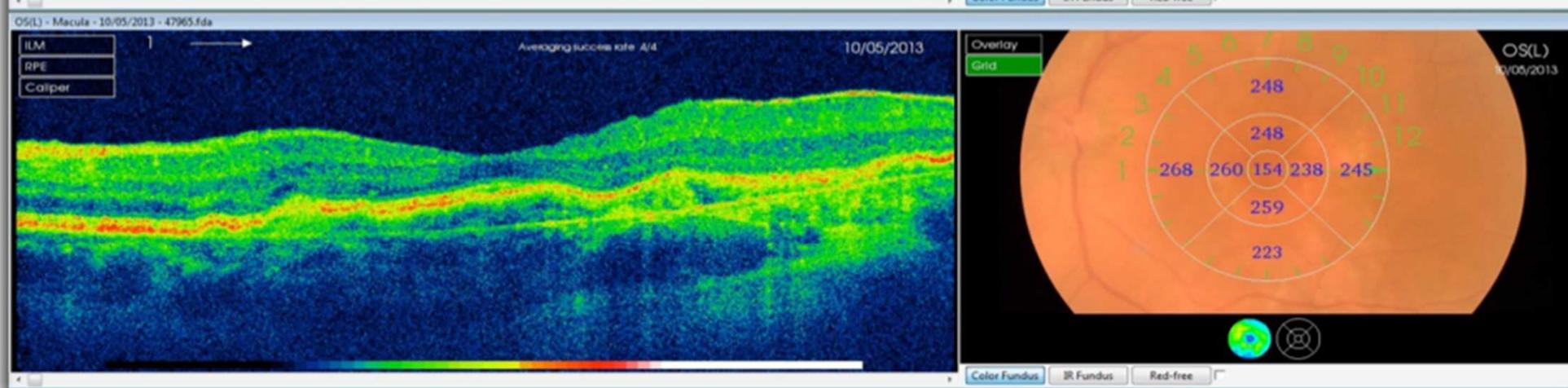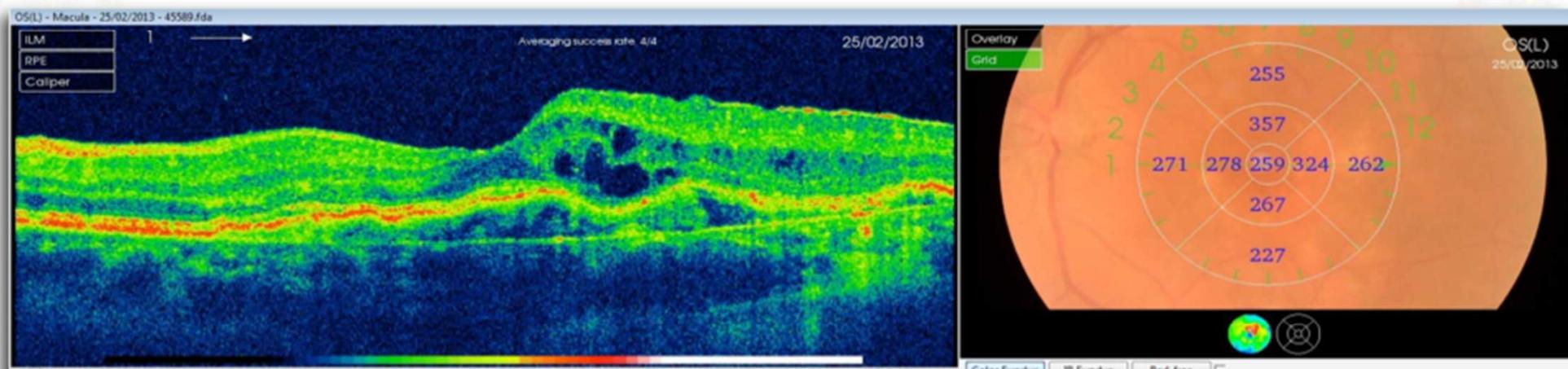


POST 2° Aflibercept: 1 mese

# NO RESPONDERS AB INITIO

## REFRACTORY AMD

- Different clinical features
- Different CNV subtypes
- Different stage

⬇

*Different VEGF sensibility!*

## REFRACTORY AMD

- Super Dose (ARBOR Study - SAVE Study): **WARNING!!!!**

- Terapia combinata:

PDT    +    Anti-VEGF ± Steroidi    + ...?
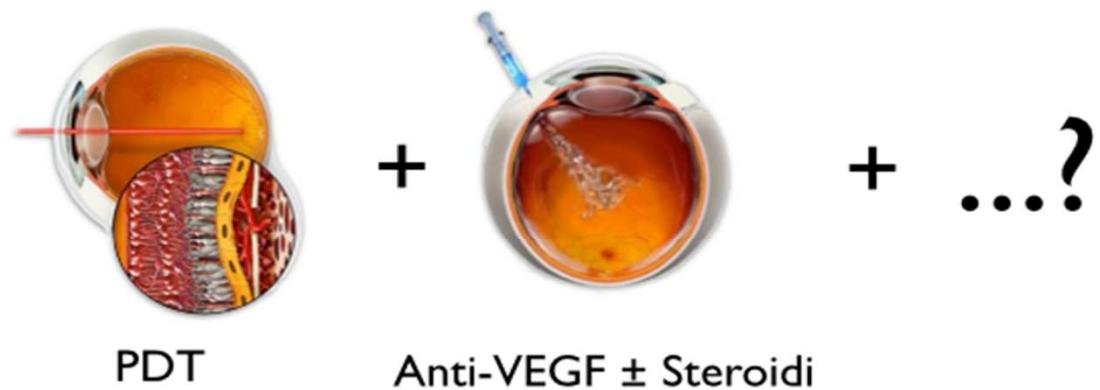
- Conversione ad altro Anti-VEGF:
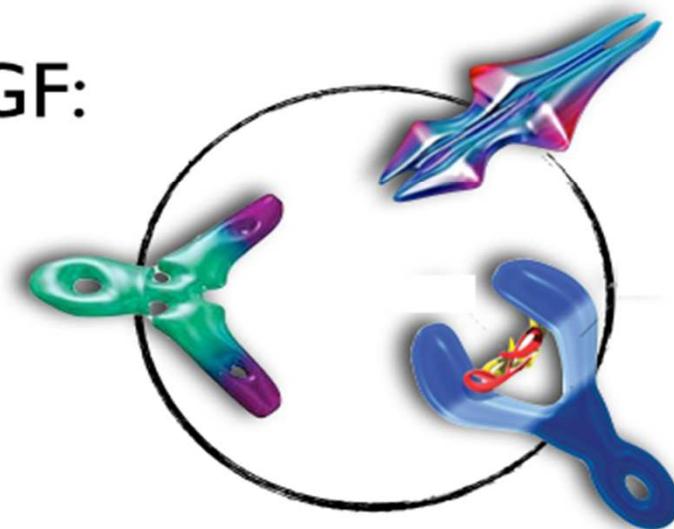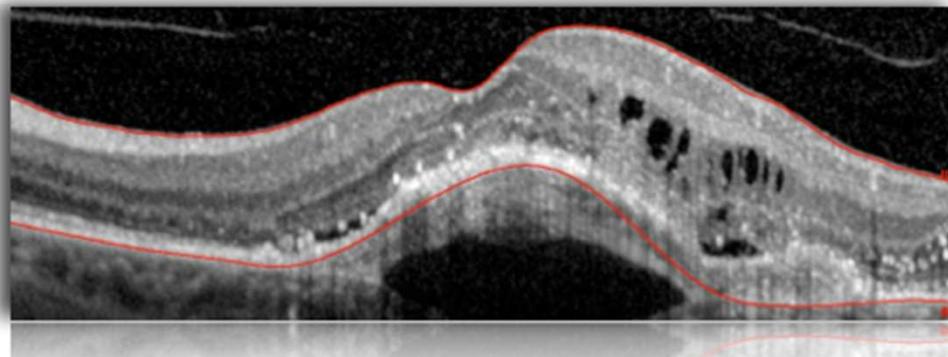
# ACQUIRED NO RESPONDERS

- **Bevacizumab** (Shaal S, et al. 2008)

- **Ranibizumab** (Keane I, et al. 2008)
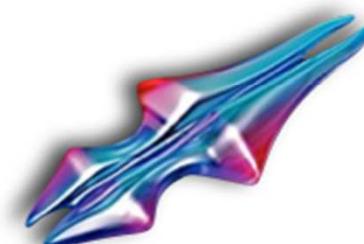
n° mediano di iniezioni per Bevacizumab:

**8**

(range 5-10)

(Forooghian F, et al. Retina 2009)

# ACQUIRED NO RESPONDERS

## POSSIBILI CAUSE

- Tachifilassi (Gasperini JL, et al. Br J Ophthalmol 2012)

- Attivazione di altre pathways angiogeniche

- "Maturazione" della NC (Darland DC, et al. J Clin Invest 1999)

- Interazione con "Anti-Therapeutic Antibodies" (ATA)
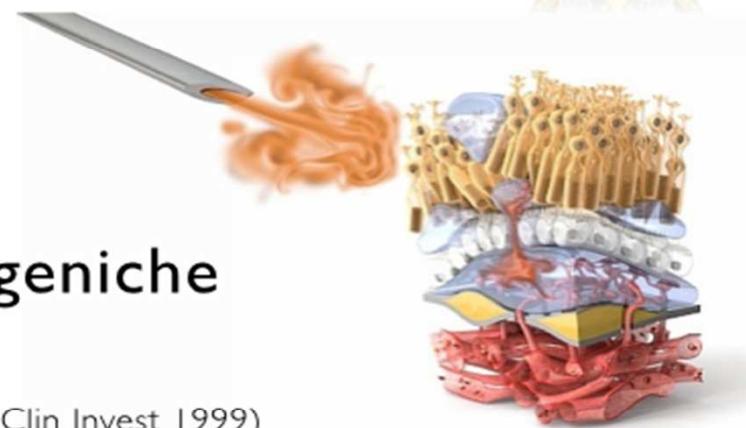
(Rosenfeld PJ, et al. N Engl J Med 2006)

- Diminuita efficacia dell'EPR

- Sviluppo di alterazioni infiammatorie croniche

(Sakurai E, et al. Invest Ophthalmol Vis Sci 2003)

# ACQUIRED NO RESPONDERS

- Tachifilassi

- Attivazione di altre pathways angiogeniche

- Interazione con "Anti-Therapeutic Antibodies" (ATA)

**Successo della <u>conversione</u> ad altro Anti-VEGF**

# AFLIBERCEPT FOR AMD



- Sub-optimally responsive to...

- Patients recalcitrant to...

- ... with persistent exudation...

- ... requiring frequent retreatment...

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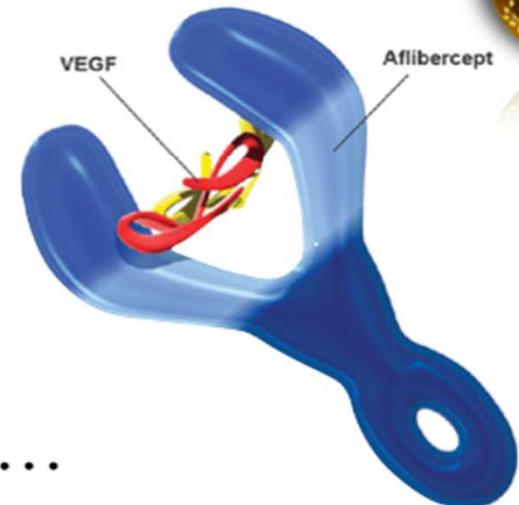
### Thorell MR et al, 2014.

- 73 eyes of 65 patients with V-PED (follow-up 6 months)
- Mean duration of anti-VEGF therapy (44.9 months; range 13.8-104.7)
- Previous treatments: 30.7 (9.8 for the 12 months prior to the switch)

CRT decreased ($p<0.001$)

Reduction PED volume ($p=0.009$)

N° of injections decreased ($p<0.001$)

# AFLIBERCEPT IN AMD

## 28 occhi (28 pz)

n° medio iniezioni B e/o R: 20 (range 7-37)

n° medio iniezioni Aflibercept: 4.4 (range 3-6)

| Table 2 Characteristics following initial aflibercept injection | |
| --- | --- |
| Total aflibercept injections, average (range) | 4.4 (3–6) |
| Central retinal thickness, mean (microns) | |
| Baseline | 295 |
| 1 month post aflibercept* | 272, p<0.001 |
| 6 months post aflibercept* | 274, p=0.008 |
| LogMAR visual acuity, mean (Snellen) | |
| Baseline | 0.52 (20/67) |
| 1 month post aflibercept* | 0.54 (20/69), p=0.64 |
| 6 months post aflibercept* | 0.57 (20/76), p=0.49 |

"25% of eyes (7 of 28 eyes) were completely dry at the 6-month follow-up visit."

Cho H, et al. Br J Ophthalmol 2013.

# AFLIBERCEPT IN AMD

## 96 occhi (85 pz)

n° medio iniezioni B e/o R: 17 (range 1-60)

n° medio iniezioni Aflibercept: 2.6 (range 2-4)

... dopo 4 mesi...

| SD OCT Segmentation | Baseline No. of Eyes | Worse (%) | Unchanged (%) | Partial Resolution (%) | Complete Resolution (%) | |
|---|---|---|---|---|---|---|
| Intraretinal fluid | 31 | 2 (6) | 10 (32) | 6 (19) | 13 (42) | 61% |
| Subretinal fluid | 49 | 9 (18) | 11 (22) | 12 (25) | 17 (35) | 60% |
| PED | 73 | 4 (5) | 50 (69) | 17 (23) | 2 (3) | 26% |
| Subretinal hemorrhage | 18 | 0 (0) | 4 (22) | 3 (17) | 11 (61) | 78% |
| Overall | 82 | 12 (14) | 26 (32) | 40 (49) | 4 (5) | 54% |

Ho V, et al. Am J Ophthalmol 2013.

# AFLIBERCEPT IN AMD

## 102 occhi (94 pz)

n° medio iniezioni B e/o R: 20.4 (range 3-65)

n° medio iniezioni Aflibercept: 3.8 (range 1-8)

**TABLE 2.** Treatment Response After Converting to Aflibercept in Patients With Chronic Neovascular Age-Related Macular Degeneration

|  | All | P | Refractory | P | Recurrent | P |
|---|---|---|---|---|---|---|
| Mean visual acuity (logMAR)[a] |  |  |  |  |  |  |
| Before conversion (SD) | 0.42 (0.30) |  | 0.44 (0.33) |  | 0.38 (0.23) |  |
| After 1 injection (SD) | 0.44 (0.36) | .723 | 0.46 (0.41) | .897 | 0.39 (0.25) | .778 |
| Final (SD) | 0.38 (0.27) | .253[b] | 0.38 (0.28) | .215 | 0.38 (0.25) | .811 |
| Mean CMT (μm) |  |  |  |  |  |  |
| Before conversion (SD) | 305.07 (80.65) |  | 311.57 (77.83) |  | 288.83 (86.86) |  |
| After 1 injection (SD) | 274.05 (68.98) | <.001 | 283.33 (66.97) | <.001 | 250.83 (69.82) | <.001 |
| Final (SD) | 276.20 (69.82) | <.001 | 283.01 (68.73) | <.001 | 260.97 (70.00) | .001 |
| Injection intervals (weeks) |  |  |  |  |  |  |
| Previous (SD) | 5.86 (2.55) |  | 5.18 (1.59) |  | 7.21 (3.44) |  |
| Aflibercept (SD) | 7.27 (2.94) | <.001 | 6.15 (2.18) | .003 | 9.47 (3.03) | .001 |

"The intravitreal injection intervals were able to be extended in all groups after converting to Aflibercept."

Yonekawa Y, et al. Am J Ophthalmol 2013.

# AFLIBERCEPT IN AMD

## 34 occhi (33 pz)

n° medio iniezioni B e/o R: 28.6 (range 8-49)

n° medio iniezioni Aflibercept: 5.3 (range 4-6)

Table 2. Visual and Anatomical Results

| | Baseline<br>Mean ± SD (IQR) | After 3 IVA<br>Mean ± SD (IQR) | P (Baseline Compared with After Third IVA) | At the Final Follow-up<br>Mean ± SD (IQR) | P (Baseline Compared with the Final Follow-up) |
|---|---|---|---|---|---|
| Visual acuity (logMAR) | 0.57 ± 0.36 (0.30–1.00) | 0.52 ± 0.34 (0.30–0.70) | 0.24 | 0.47 ± 0.32 (0.30–0.60) | 0.004 |
| mCFT | 416 ± 217 (263–487) | 351 ± 172 (224–445) | <0.001 | 348 ± 171 (235–419) | <0.001 |
| Subfoveal distance between Bruch membrane and RPE | 187 ± 158 (85–275) | 161 ± 131 (78–225) | 0.002 | 149 ± 125 (64–200) | 0.002 |
| Subfoveal distance between RPE and IS/OS junction line | 32 ± 48 (0–58) | 17 ± 28 (0–31) | 0.02 | 14 ± 27 (0–0) | 0.01 |
| Subfoveal distance between IS/OS line and ILM | 198 ± 150 (122–202) | 173 ± 103 (107–178) | 0.11 | 186 ± 101 (121–207) | 0.44 |
| Subfoveal PED height | 260 ± 162 (129–368) | 228 ± 140 (114–340) | 0.001 | 215 ± 142 (111–305) | <0.001 |
| Subfoveal PED diameter | 3,265 ± 1,622 (2,354–4,555) | 3,188 ± 1,599 (2,091–4,487) | 0.51 | 2,949 ± 1,634 (1,721–4,484) | 0.04 |

"Intravitreal injections of Aflibercept resulted in a significant improvement in visual and anatomical outcomes in eyes with persistent subfoveal fluid."

Kumar N, et al. Retina 2013

# AFLIBERCEPT IN V-PED

## ROLL Study

HiPED Study: anti-VEGF veterans

Mean 2 mg Ranibizumab injections: 17

Switch to 2 mg Aflibercept monthly x 3

then q8wk ± q4wk if PRN criteria met

Anatomic regression in 10/30 (**33%**) patients

after 2nd Aflibercept injection

Fung A, et al. 2014

# OUR SERIES
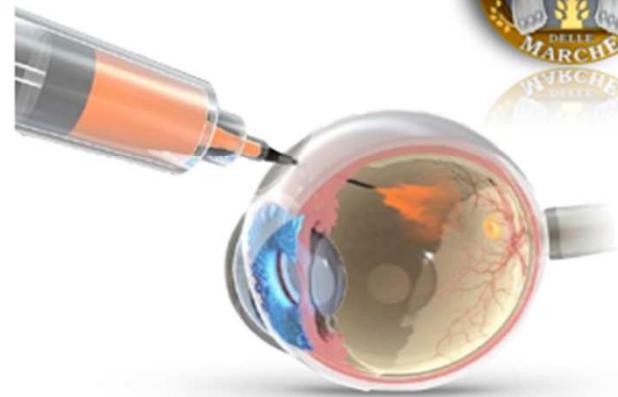


## AMD: 18 eyes (10 male and 8 female)

- mean age: 70 years (range 61÷83)

- mean follow-up: 9 months

- n° previous injections: 11.4 (Bevacizumab - Ranibizumab)

- n° injections of Aflibercept: 4.9

- mean CMT before: 458 μm ⇒ 371 μm at last follow-up

- mean VA before: 20/100 ⇒ unchanged at last follow-up

- patients with shorter disease duration (<12 months) had ↑ in VA post conversion: from a mean of 20/63 before to 20/40 at last follow-up

# #1: M.G. (69 anni) - AMD

## PRE: già 8 Anti-VEGF
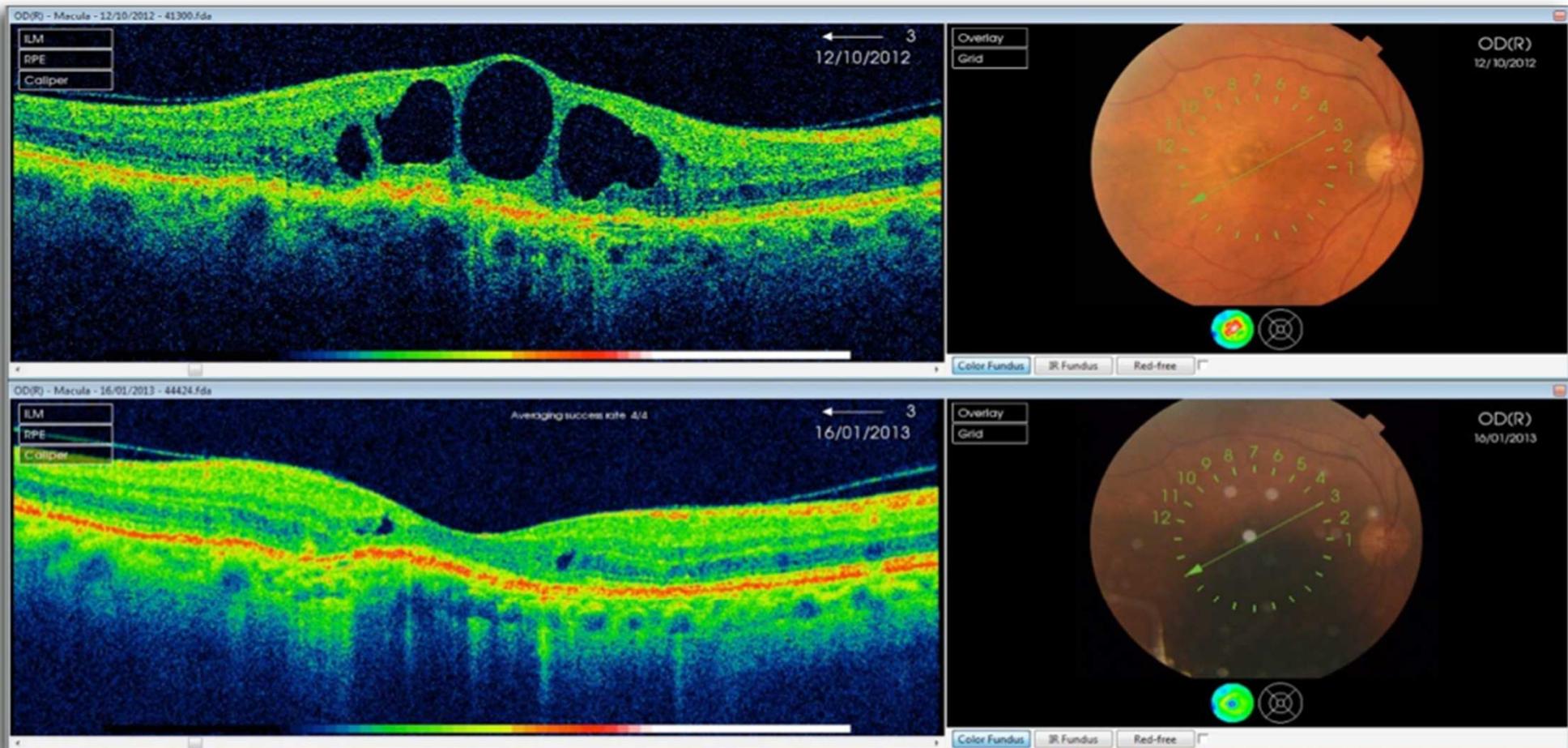
## POST Aflibercept

# #2: F.C. (83 anni) - AMD

PRE: già 10 Anti-VEGF
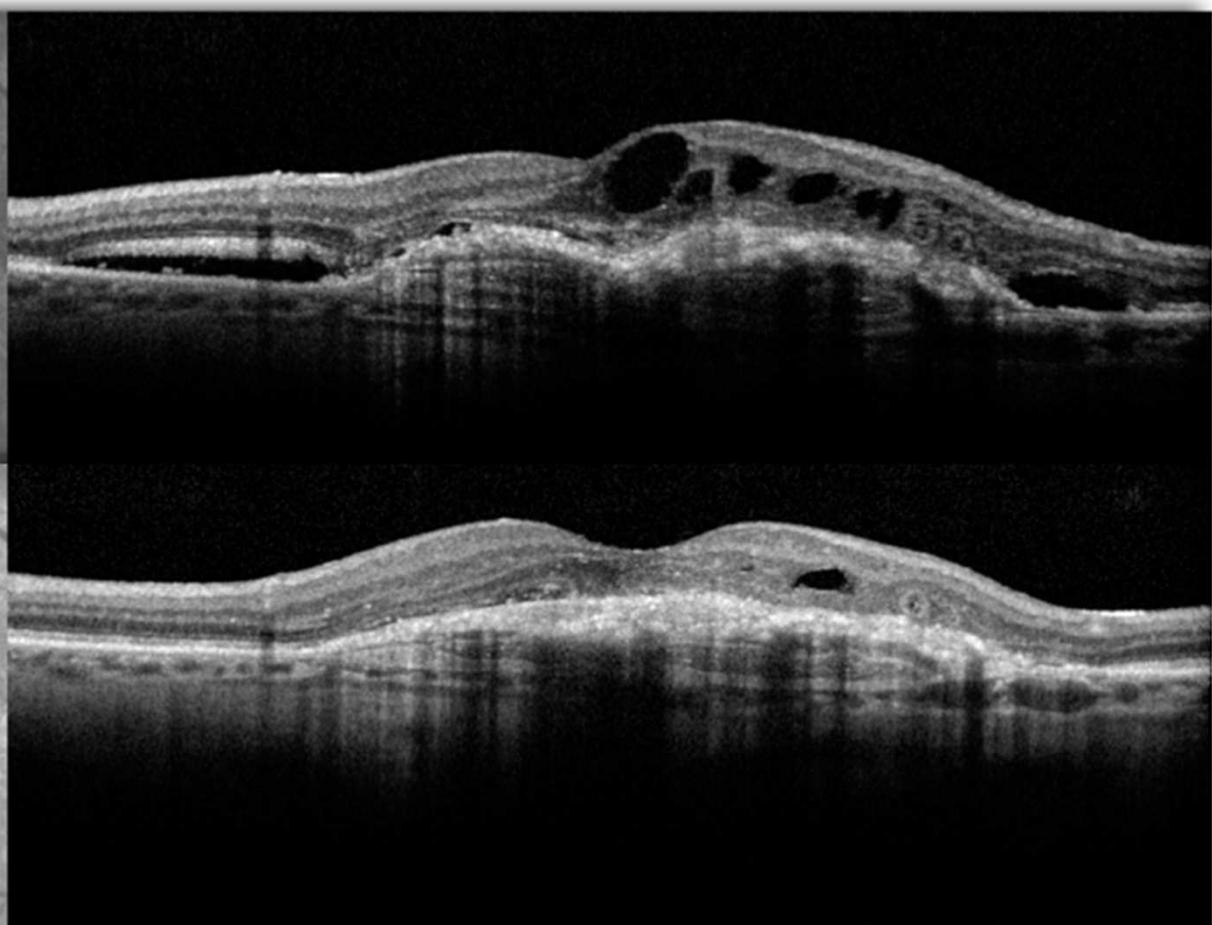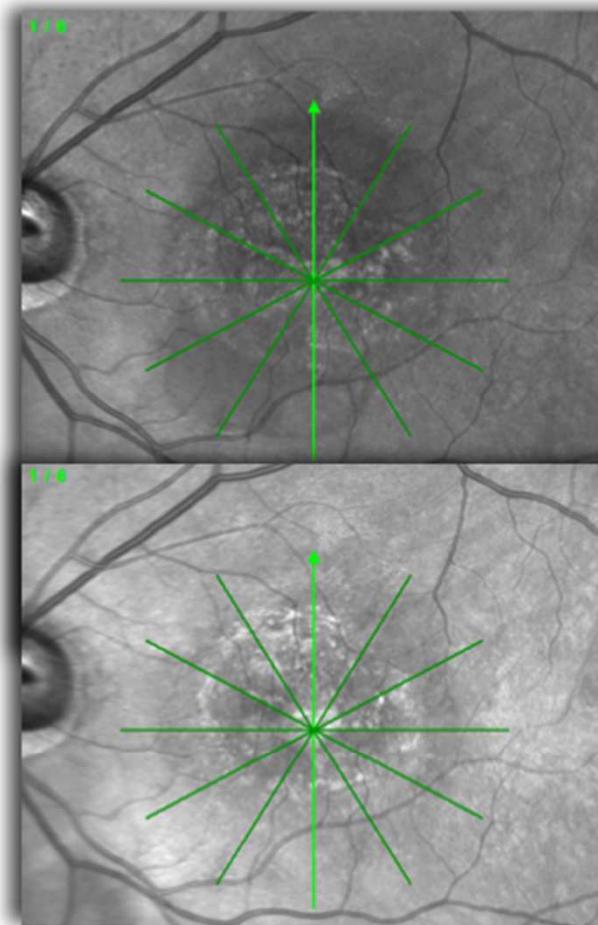
POST Aflibercept

# BRIEF RESPONDERS

Impiegare Anti-VEGF con maggior durata d'azione
(Aflibercept)



Yonekawa Y, et al. Am J Ophthalmol 2013.

# CONCLUSIONI

L'introduzione nella pratica clinica dell'Aflibercept:



• Aumenta le possibilità terapeutiche a nostra disposizione

• Appare essere un'efficace "rescue-therapy" per pazienti con risposta sub-ottimale o resistenti ad altri anti-VEGF (diverso meccanismo d'azione, blocca anche il PIGF...)

• Minor numero di trattamenti

• Importanza di disporre di un anti-VEGF "diverso" (conversione/riconversione)