Università di Messina

Dipartimento di Scienze Sperimentali Medico-chirurgiche Specialistiche ed Odontostomatologiche

Sezione di Oftalmologia

"TREAT AND EXTEND" VS "PRN"

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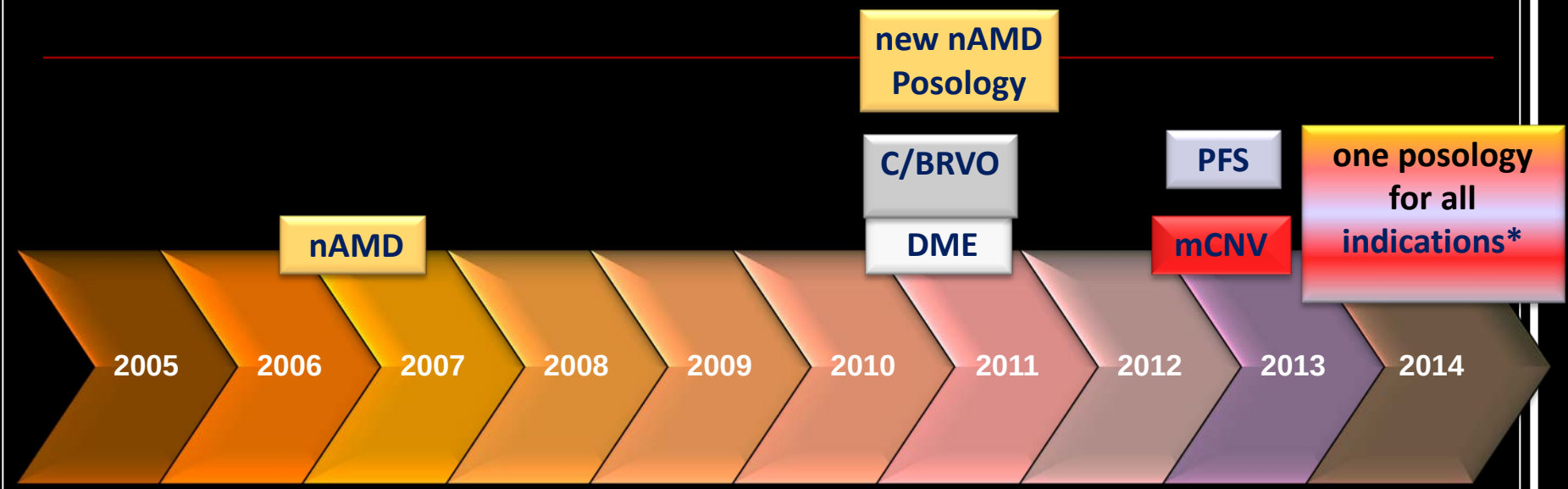
XLI Congresso SOSi, Campofelice di Roccella, 14-16 Aprile 2016

Evolution of EU ranibizumab posology



Continuing research, technological advances
and increased knowledge of retina's pathologies

VA → **VA + OCT**

Evolution of EU ranibizumab dosing posology: nAMD

	2007	2011	2014 (CHMP positive opinion)
Initiate	3 monthly injections	Treat monthly until maximum stable VA is achieved (i.e. VA is stable for 3 consecutive months)	Treatment initiated with one injection per month until maximum VA is achieved and/or no signs of disease activity
Monitor	Monitor VA monthly	Monitor VA monthly	Monitoring intervals based on disease activity as assessed by VA and/or anatomical parameters
Resume treatment	If there is a loss of > 5 letters	If there is a loss of VA due to disease activity	Based on disease activity as assessed by VA and/or anatomical parameters

RCP – Lucentis

Evolution of EU ranibizumab dosing posology

2007: nAMD – personalized treatment in maintenance phase (VA driven)

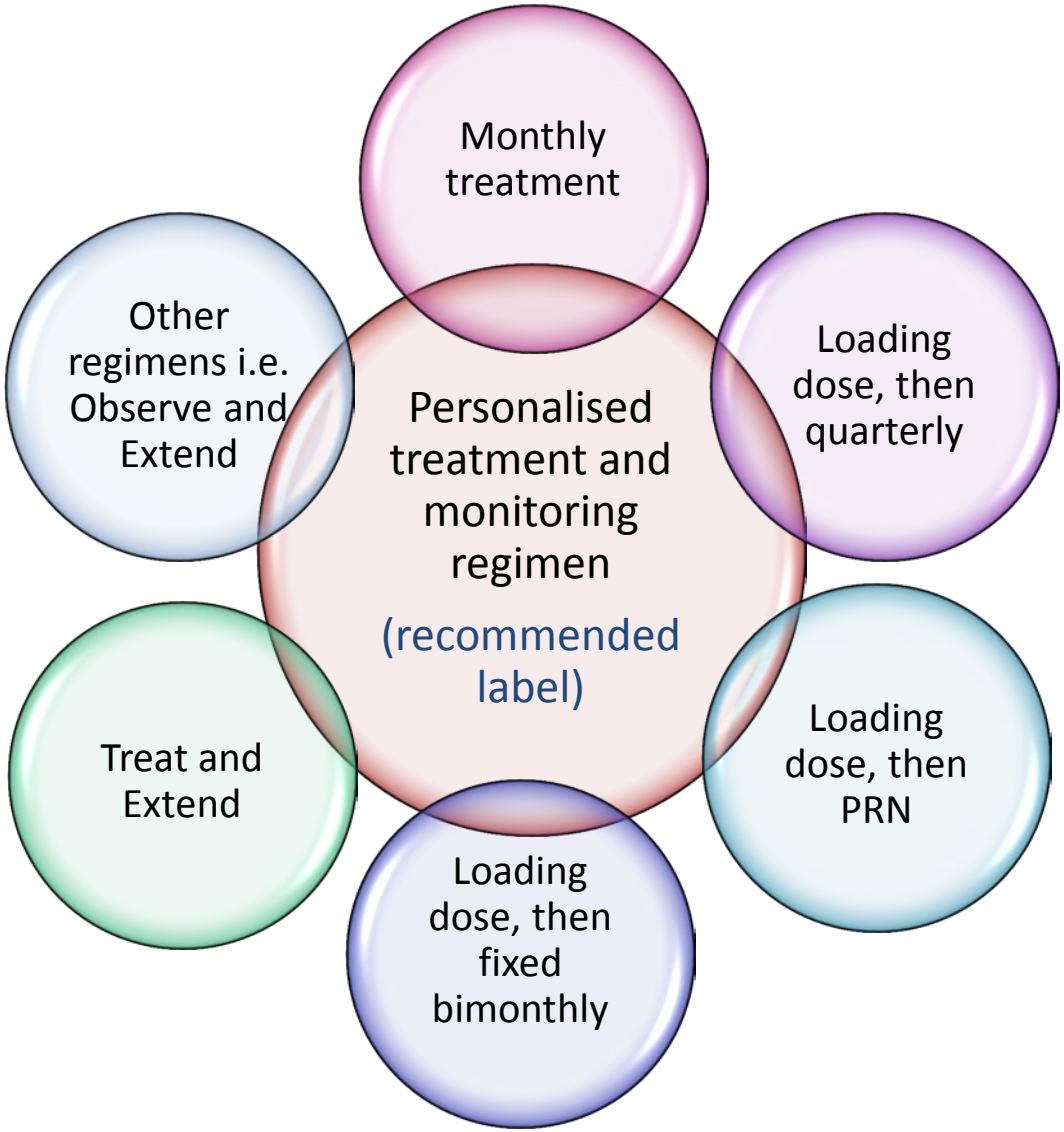
2011: nAMD, DME, RVO – personalized treatment in loading and maintenance phase (VA driven)

2013: mCNV – personalized treatment in loading and monitoring phase (VA + OCT/FFA driven)

2014: all indications – personalized treatment and monitoring throughout (VA + OCT/FFA driven)

RCP – Lucentis

Possible treatment regimens



Variation in re-treatment needs indicates that monthly monitoring not necessary for all patients

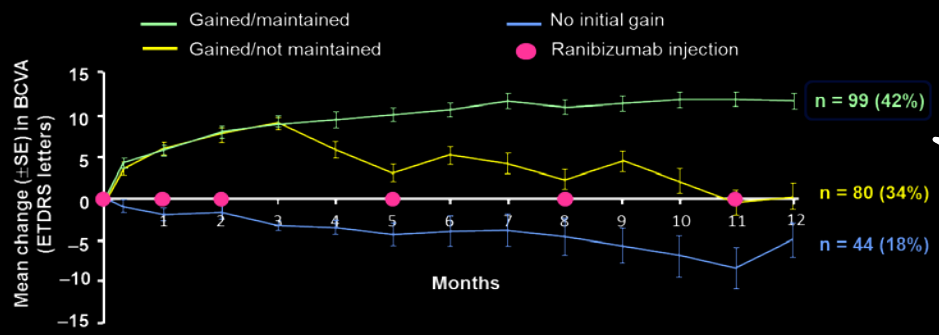
Re-treatment frequencies across indications and therapies

Indication	Trial	Year 1 (ini)	Year 2	Year 3
AMD	HARBOR[1,2]	7.7 (3)	5.6	N/A
	CATT[3,4]	6.9 (1)	5.7	N/A
	IVAN[5,6]	7 (3)	6	N/A
	LUCAS (RBZ, T&E)[7]	8 (1)	N/A	N/A
	VIEW 1&2 (RBZ)[8,9]	12	4.7	N/A
	VIEW 1&2 (VTEq8)[8,9]	7 (3)	4.2	N/A
DME	RESTORE[10]	7.4 (3)	3.9	2.9

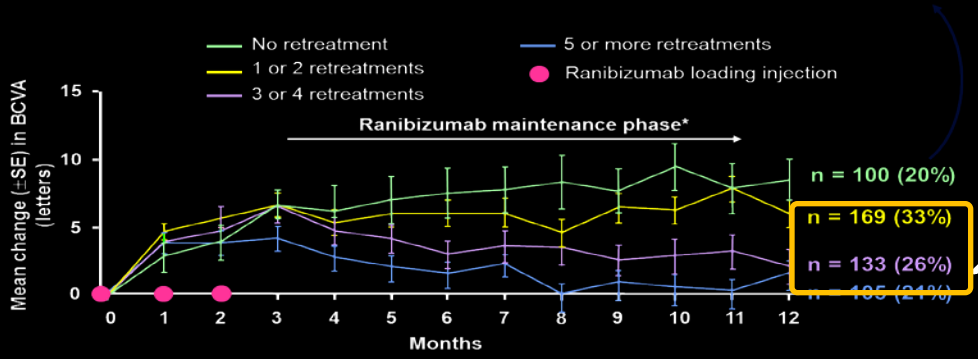
*monitoring was mandated to occur at least quarterly; initial VA gains not maintained; Ini, no. of monthly injections for treatment initiation

1. Faber D, et al. ARVO 2013 2. Busbee, 2013 3. Martin, CATT 4. Martin, 2012 .5. Chakravarthy, 2012 IVAN 6. Chakravarthy, 2013 7. Berg K et al, 2014 8. Schmidt-Erfurth, 2014 VIEW 9. Heier, 2012 10. Mitchell, 2013 11. DRCR network, 2012 12. Campochiaro, BRAVO 13: Heier 2012; 14. Brown, 2010 CRUISE 15. Brown, COPERNICUS 16. Novartis Data onfile

Patients' need for re-treatment is highly variable: nAMD



EXCITE[1] – 42% of initial gainers maintained vision with quarterly dosing; Initial gain not maintained with quarterly injections in 34% patients



SUSTAIN[2] – >50% of patients maintained initial VA gain with 0-2 injections in the PRN phase and therefore have potential for less frequent monitoring

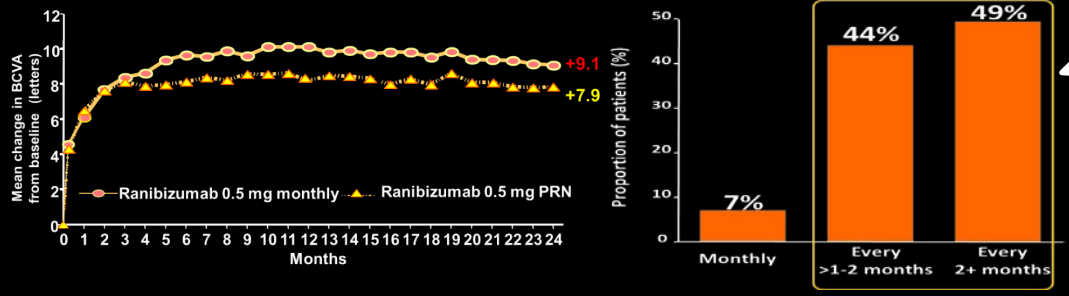
1. Schmidt-Erfurt U Ophthalmology 2011; 2. Holz FG et al. Ophthalmology 2011; 118;

Initial treatment response may predict final outcome

- Patients who maintain stable vision at first treatment interruption following 3 loading doses maintain BCVA through to 12 months with quarterly dosing (EXCITE[1])
- Patients losing >5 letters at first treatment interruption likely to continue to lose vision with quarterly dosing (EXCITE[1])
- Longer the duration of anatomical improvements, more likely the BCVA improvements were to persist with quarterly dosing (PIER[2])
- Differentiation between patients maintaining and losing vision apparent at first treatment interruption (SUSTAIN[3])

1. Schmidt-Erfurt U Ophthalmology 2011; 2. P Abraham et. al. Am J Ophthalmol 2010; 3. Holz FG et al. Ophthalmology 2011

Patients' need for re-treatment is highly variable: nAMD



HARBOR 2 year[1] – 93% of patients in the PRN arm did not require monthly dosing

Integrated Analysis: pts receiving Tx at 12 wks interval		
	RBZ (N=557)	VTE q8 (N=558)
N (%)	218 (39)	245 (44)

VIEW 2 year[2] – 40% of patients sufficiently treated with quarterly treatment when treatment was applied PRN

1. Ho AC, Ophthalmology 2014; 2.Schmidt-Erfurth U et al. Ophthalmology 2014; 121

AMD Treatment Protocols

- Monthly injections: standard of care.
- Alternative individualized treatment strategies:

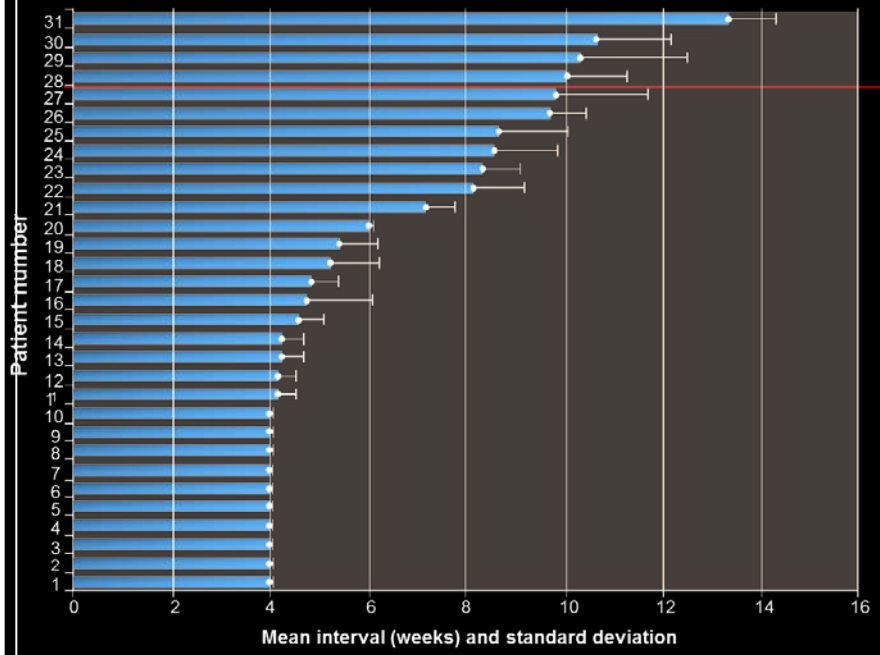
  PRN (treat and observe).

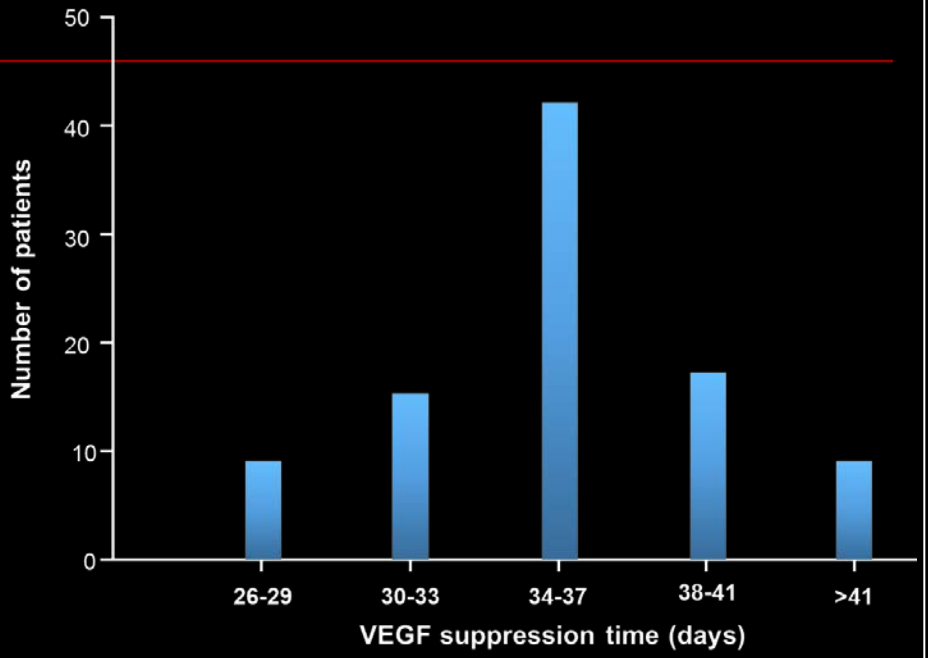
  PrONTO protocol (treat and observe).

  Treat and extend or Inject and extend.

  Observe and plan.

Initial response may predict re-treatment interval





Mantel et al., 2013 (N=31)

- High intra-individual predictability of retreatment need
- The first interval after the initial three loading doses was a good predictor of the following intervals

Muether et al., 2013 (N=83)

- Intra-individual suppression time was stable within a period of up to 3 years

1. Mantel I et al, Graefes Arch Clin Exp Ophthalmol 2013 251:697–704
2. Muether PS, Am J Ophthalmol 2013;156:989–993

What is treat and extend ?

- The dosing strategy consists of an initial induction or ‘‘loading’’ sequence of at least three initial monthly injections

- If stable visual acuity, an absence of macular hemorrhage, and a dry OCT have been achieved at this point, patients continue to receive regular maintenance injections at increasing intervals.

- At 6 weeks after the last of the 3 initial monthly injections, visual acuity, clinical findings, and OCT changes are recorded again, and patients receive an injection regardless of the presence or absence of disease activity.

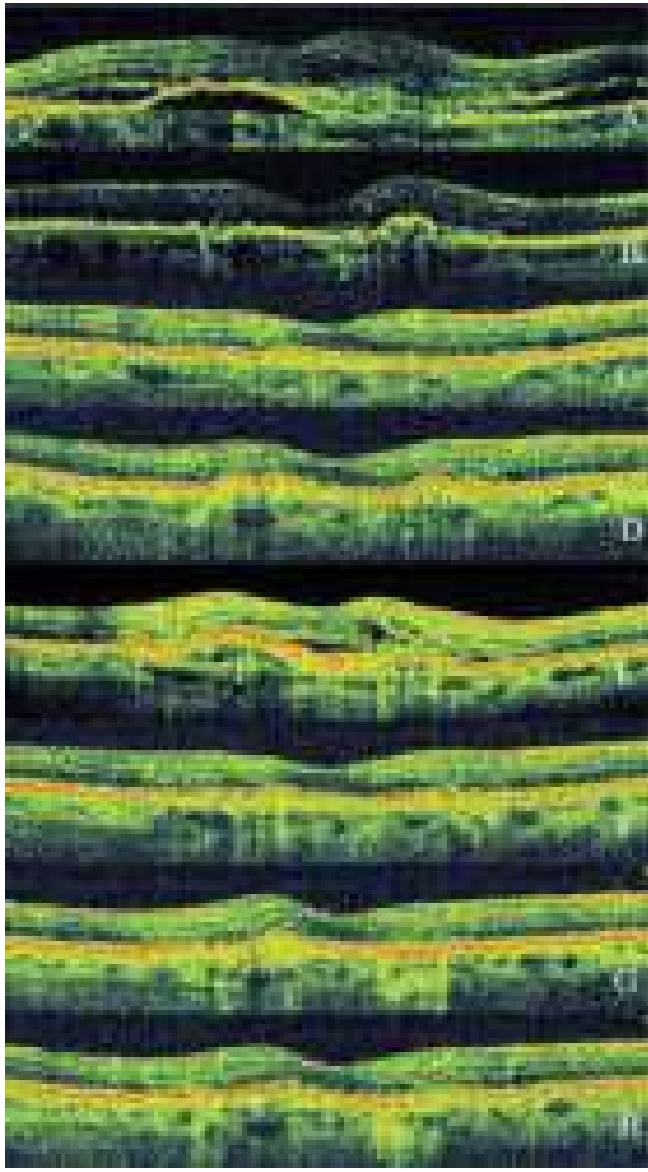
- However, the interval to the next visit (and scheduled injection) is based on an observed change in these parameters.

- If there are no changes, the next visit for examination and injection is scheduled for 8 weeks. If there is a change, the patient returns for another scheduled injection and examination after 4 weeks.

- The observation and scheduled treatment interval is extended (hence the phrase ‘‘**treat and extend’’)**

- 10 weeks and sometimes 12 weeks was chosen as the longest interval between office visits and treatments.

- Baseline
- After 3 monthly (4 weeks) injections
- Extended to 6 weeks intervals
- Extended to 8 weeks intervals
- Extended to 10 weeks intervals
- Back to 8 weeks



What are the disadvantages of treat and observe (PRN/PrONTO)

- This strategy does require monthly visits, clinical examinations, and OCTs. This means more frequent visits which is a huge burden on the patient (elderly) and their families and health care system!

- Patients uncertain (and doctors too!) if or when they will need treatment?! And this may be a reason for some patients to skip visits!

- Some patients managed with this strategy will return for assessments having already developed hemorrhages in the injection-free interval with irreversible vision loss!
- You treat only when you see fluid!. Unlike DME and RVO, AMD is unforgiving disease! Each time fluid accumulates, this means CNV is growing and more photoreceptors loss!!
- In theory, a dosing regimen that does not maintain the macula in a “dry” state could deny some patients the opportunity for further visual recovery!

What are the Advantages of Treat and Extend protocol?

- To put it in a nutshell :The “Treat and Extend” dosing regimen is a strategy intended to resolve macular exudation and maintain the macula in this “dry” state indefinitely with, when possible, fewer patient visits and treatments than monthly dosing.
- Reduction of treatment burden by reducing the number of patient visits and the number of imaging studies performed by eliminating the need for the monthly visits necessitated by alternative dosing strategies.

- Effective giving similar results to monthly injections but with fewer injections.
- Just as effective and even better than PrONTO protocol! patients on a ‘‘treat and extend’’ dosing regimen receive a mandated injection at each visit, their eyes receive slightly more injections in 1st year, but a similar number of injections as received by patients who completed 24- month follow-up in the PrONTO study.
- The significant reduction in patient visits of nearly 50% without an increase in the number of treatments could potentially decrease the burden on patients, practitioners, and the healthcare system as a whole.

- Reduces the risk of new sight-threatening submacular hemorrhages (maintained VEGF suppression/more aggressive than PrONTO).
- Rare progression of GA overlying the neovascular lesions suggest additional long-term benefits of the ‘‘treat and extend’’ dosing regimen (less aggressive than monthly Rx).
- Patients and doctors are more compliant because both parties know when will be the next scheduled injection. No place for uncertainty!.
- Patient will be less inclined to skip visits... because they know they will have an injection!

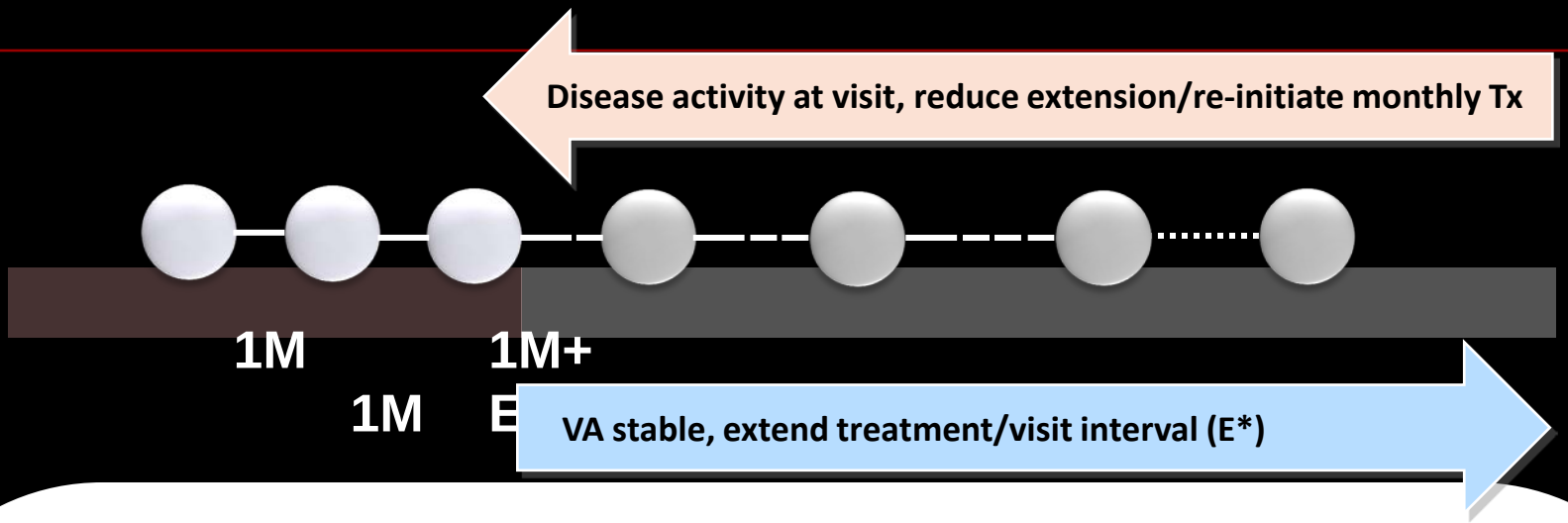
- You can know what is optimal injection free interval for each individual patient without macular exudation.

- Some patients could be 6 weeks, others 8 or 10 weeks.

Thus Treat and Extend is:

- Effective.
- Indefinite strict control of AMD.
- Practical to patient and doctor in every day practice.
- More compliance.
- Clear schedule.
- More Economic (less visits, injections and imaging)

Regime Treat and extend



E*: al raggiungimento della massima acuità visiva e/o in assenza di segni di attività della patologia, gli intervalli di trattamento possono essere gradualmente estesi fino a che non si ripresentino i segni della patologia o si evidenzi un peggioramento della funzione visiva. L'intervallo di trattamento deve essere gradualmente esteso di al massimo due settimane in pazienti con AMD essudativa, e può essere esteso fino ad un mese nei pazienti con DME. Gli intervalli di trattamento possono essere gradualmente estesi anche nel trattamento dell'RVO, tuttavia non ci sono dati sufficienti per stabilire la durata di questi intervalli. Al reinsorgere dell'attività di malattia, l'intervallo di trattamento deve essere ridotto di conseguenza.

- Monthly treatment until disease stability
- T&E visit: Mandatory treatment including a decision point to extend/reduce visit interval

‘The 2012 American Society of Retinal Specialists Preference and Trends Survey revealed the majority of Retina Specialists members have turned to non-monthly regimens, with 66.7% using TAE and 23.7% TAO’.

Calvo et al., J Clin Exp Ophthalmol 2014, 5:1

Evidence in literature

- *“TREAT AND EXTEND” DOSING OF INTRAVITREAL ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR TYPE 3 NEOVASCULARIZATION/RETINAL ANGIOMATOUS PROLIFERATION*

MICHAEL ENGELBERT, MD, PHD, SANDRINE A.

ZWEIFEL, MD,K. BAILEY FREUND, MD

RETINA 29:1424–1431, 2009

- *“INJECT AND EXTEND DOSING VERSUS DOSING AS NEEDED.*

A Comparative Retrospective Study of Ranibizumab in Exudative Age-Related Macular Degeneration.

HASSIBA OUBRAHAM, MD, SALOMON Y. COHEN, MD, PHD, SEPIDEH SAMIMI, MD,DAVID MAROTTE, MD, INES BOUZAHER, MD, PIERRE BONICEL, MD,FRANCK FAJNKUCHEN, MD, RAMIN TADAYONI, MD, PHD

RETINA 31:26–30, 2011

- *LONG-TERM FOLLOW-UP FOR TYPE 1 (SUBRETINAL PIGMENT EPITHELIUM) NEOVASCULARIZATION USING A MODIFIED ‘‘TREAT AND EXTEND’’ DOSING REGIMEN OF INTRAVITREAL ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY*

MICHAEL ENGELBERT, MD, PHD, SANDRINE A. ZWEIFEL, MD, K. BAILEY FREUND, MD

RETINA 30:1368–1375, 2010

A Treat and Extend Regimen Using Ranibizumab for Neovascular Age-Related Macular Degeneration

Clinical and Economic Impact

Omesh P. Gupta, MD, MBA, Gary Shienbaum, MD, Avni H. Patel, MD, Christopher Fecarotta, MD, Richard S. Kaiser, MD, Carl D. Regillo, MD

Ophthalmology 2010;117:2134–2140

nAMD: Extended monitoring intervals (case series)

Source	Gupta, 2010	Shienbaum, 2012	Toalster, 2013
N	92	73	45
Mean Follow up (years)	1.52	1.41	1
Extension based on	No fluid on OCT	No fluid on OCT	No fluid on OCT
Max. av. visit free interval (days)	80	92	64
Mean number of injections	Yr 1: 8.36	Yr 1: 7.94	8
0-1 Recurrence (successful)	76.1%	82.4%	71.1%

1. Gupta OP et.al Ophthalmology 2010; **117:** 2134-2140; 2. Shienbaum G et.al AJO 2012; **153:** 468-473 e461; 3. Toalster N et.al Retina 2013; **33:** 1351-1358

LUCAS study

- *“Lucentis Compared to Avastin Study. A Randomized, Double Blind, Prospective Multicenter Study Comparing the Effect of Intravitreal Injection of Bevacizumab (Avastin)to Ranibizumab (Lucentis)When Given to Patients With Exudative (Wet) Age-related Macular Degeneration”.*

•A total of 420 patients with objective evidence of wet AMD will be randomized to a double-blind treatment with ranibizumab or bevacizumab over the course of 2 years (still recruiting).

•The treatment interval will be determined by protocol called "**inject and extend." The shortest interval will be 4 weeks and the longest 12 weeks.**

wAMD: LUCAS, first large study confirming validity of individualized monitoring in wAMD

Head to Head ranibizumab/bevacizumab study examining Treat and Extend regimen. Patients treated during each visit regardless of disease activity. No sign of activity, treatment intervals are extended gradually; when there are signs of recurrence, the intervals are shortened. In the study, the shortest interval was 4 weeks, and the longest was 12 weeks.

	Ranibizumab 0.5mg
N	218
Duration (month)	12
Extension based on	No fluid on OCT
Average no. of injections	8
Average no. of visits	8
VA gain at M12	8.2 letters

Results shown for ranibizumab treatment arm only.

10 – 20% patients needed 3 or less injections in year 1

Berg K et al, Ophthalmology, 2014

Recommended label wording (RCP – Lucentis , 2014)

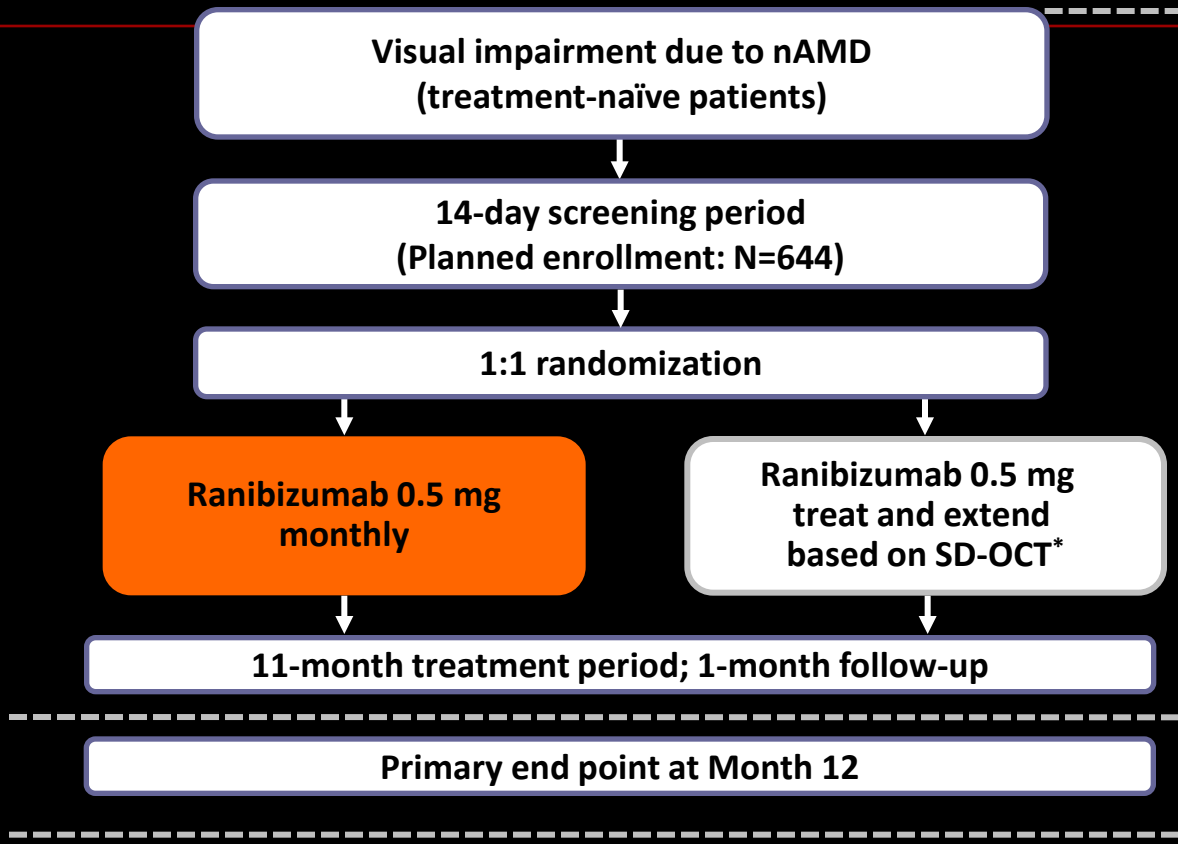
Inizio del trattamento: Il trattamento è iniziato con una iniezione al mese fino a che è ottenuta la massima acuità visiva e/o non ci sono segni di attività della patologia, quali variazioni nell'acuità visiva e alterazioni di altri segni e sintomi della patologia durante il trattamento continuativo. Nei pazienti con AMD essudativa, DME e RVO, potrebbe essere necessario iniziare la terapia con tre o più iniezioni mensili consecutive.

Monitoraggio e ritrattamento: Pertanto, gli intervalli di monitoraggio e di trattamento devono essere decisi dal medico e devono essere basati sull'attività della patologia, come accertato mediante valutazione dell'acuità visiva e/o dei parametri anatomici. Se, secondo l'opinione del medico, i parametri anatomici e visivi indicano che il paziente non trae beneficio dal trattamento continuativo, Lucentis deve essere interrotto. Il monitoraggio dell'attività della patologia può comprendere esame clinico, valutazioni funzionali o tecniche di imaging (ad esempio tomografia a coerenza ottica o angiografia con fluoresceina).

Guida al Treat and extend : Se i pazienti sono in trattamento secondo un regime "treat-and-extend", al raggiungimento della massima acuità visiva e/o in assenza di segni di attività della patologia, gli intervalli di trattamento possono essere gradualmente estesi fino a che non si ripresentino i segni della patologia o si evidenzi un peggioramento della funzione visiva. L'intervallo di trattamento deve essere gradualmente esteso di al massimo due settimane in pazienti con AMD essudativa, e può essere esteso fino ad un mese nei pazienti con DME. Gli intervalli di trattamento possono essere gradualmente estesi anche nel trattamento dell'RVO, tuttavia non ci sono dati sufficienti per stabilire la durata di questi intervalli. Al reinsorgere dell'attività di malattia, l'intervallo di trattamento deve essere ridotto di conseguenza. Nel trattamento della diminuzione visiva causata da CNV secondaria a PM, molti pazienti potrebbero necessitare solo di una o due iniezioni durante il primo anno, mentre alcuni di un trattamento più frequente

wAMD: Future T&E evidence (TREND)

A 12-month, phase IIIb, randomized, multicenter (n=102), interventional study



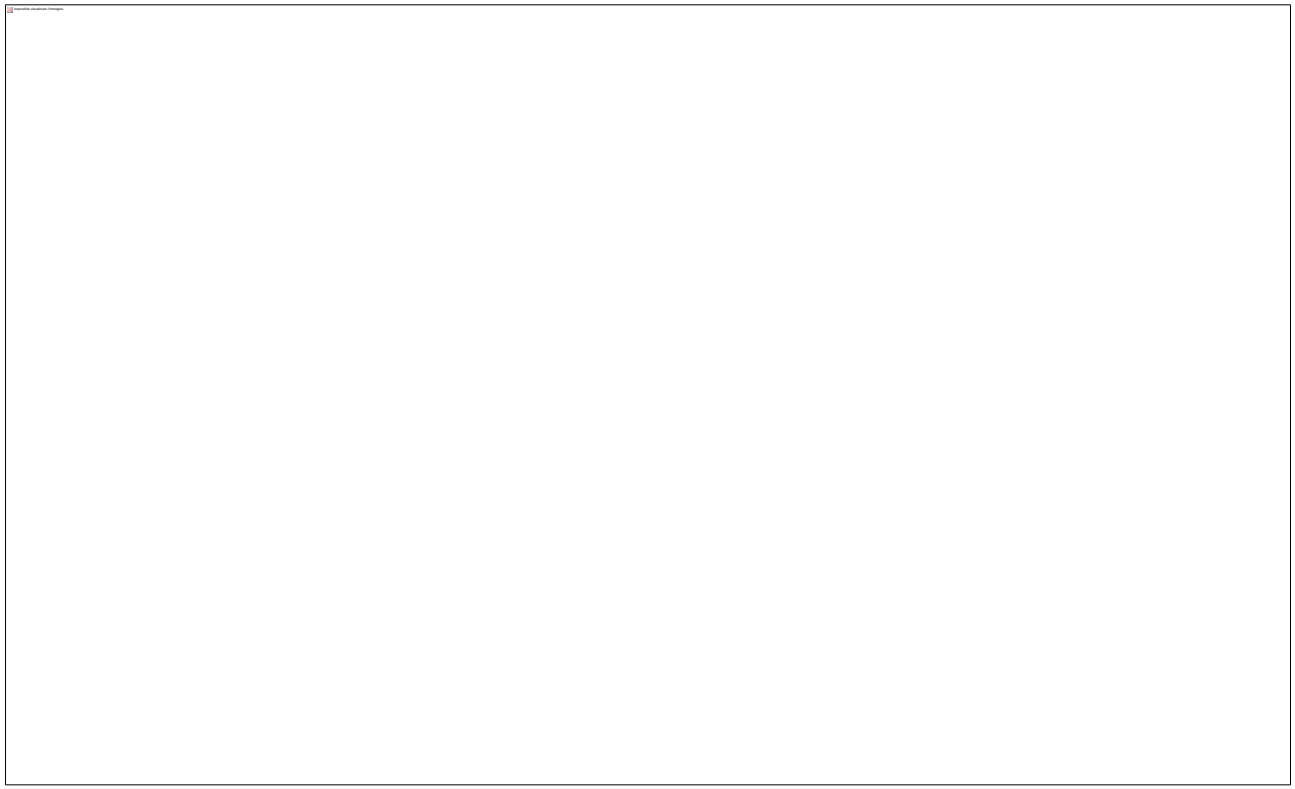
Study start date
December 2013

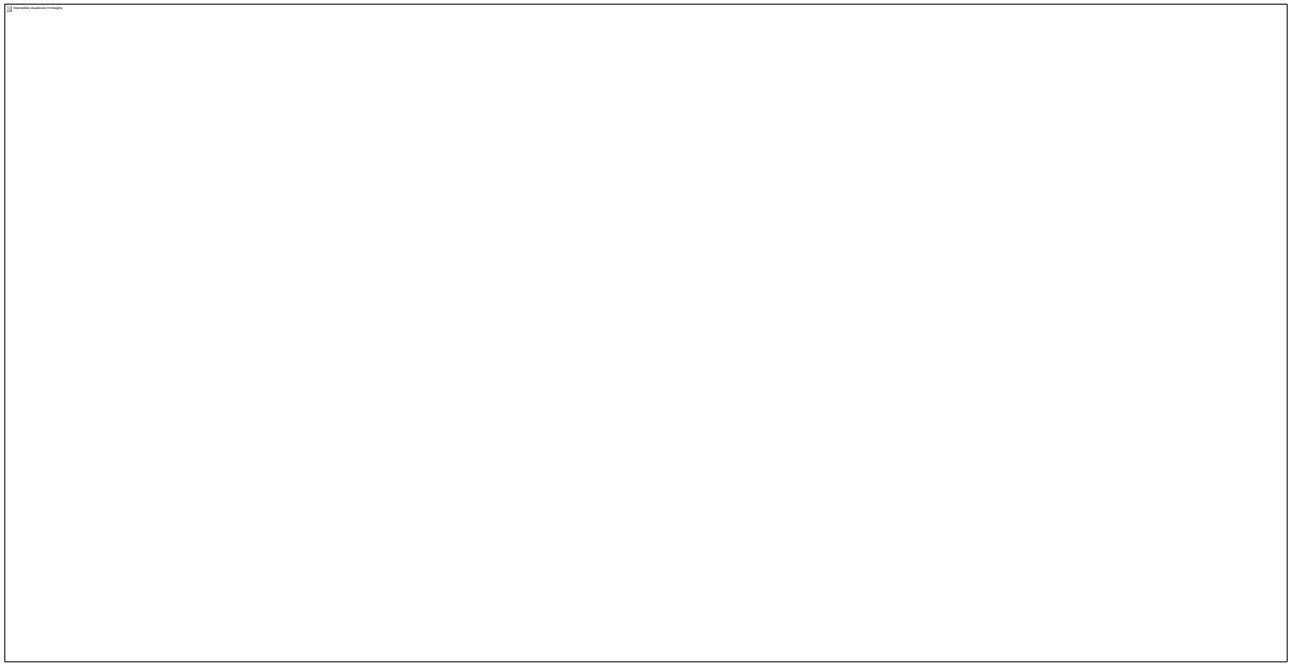
Estimated study completion date
October 2015

*Disease activity based on SD-OCT (i.e., signs of exudation) as evaluated by the investigator. In the absence of disease activity, each visit will be extended by 2 weeks, with a maximum of a 12-week interval

nAMD, neovascular age-related macular degeneration; SD-OCT, spectral domain optical coherence tomography

http://clinicaltrials.gov/ct2/show/record/NCT01948830 (TREND; Last accessed July 2014)


Interaktiver visualisierter Chirurgiekurs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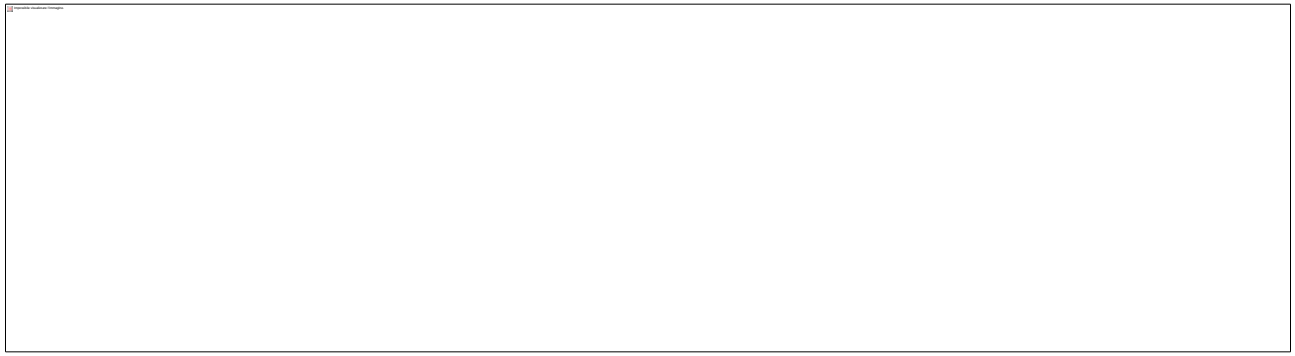
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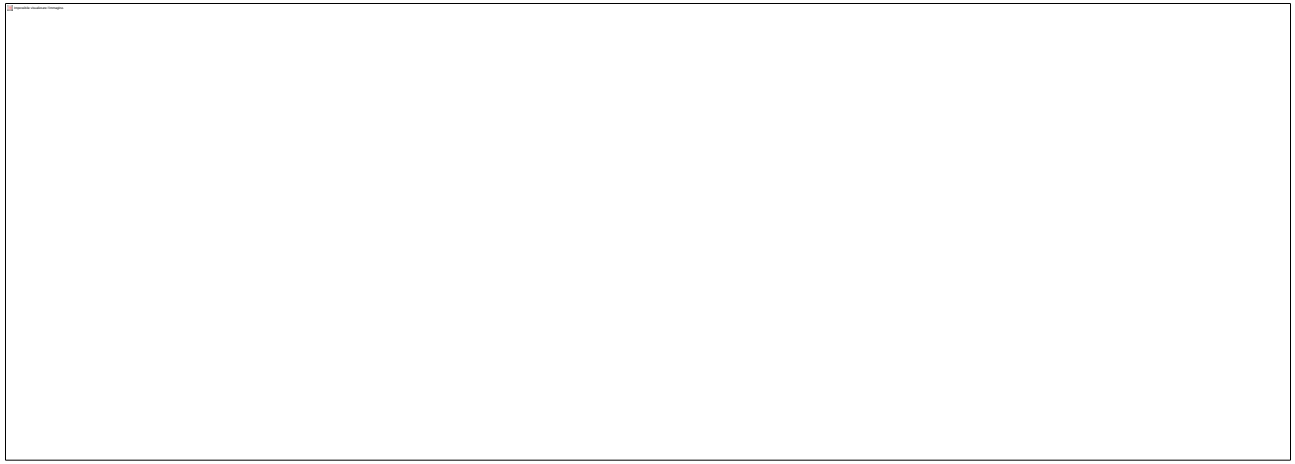


Impossible visualizare Omnigine

‘The paradox of the clinical trial is that it is the best way to assess whether an intervention works, but is arguably the worst way to assess who will benefit from it.’

Mant, D, Can randomized trials inform clinical decisions about individual patients?

The Lancet, 953, 9154 (743-746), 1999