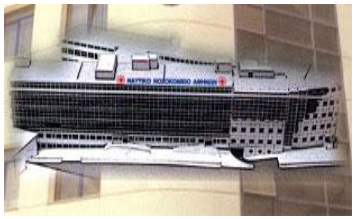


Νοσήματα Συνδετικού Ιστού
Year in Review

Γκ. Κατσιφής MD, PhD, RhMSUS
Διευθυντής Ρευματολογικής Κλινικής
Ναυτικού Νοσοκομείου Αθηνών

Εαρινές Ημέρες Ρευματολογίας 2018
Βόλος, 1-3 Ιουνίου 2018

The NET-effect of combining rituximab with belimumab in severe SLE

A phase 2A, open-label, single arm proof-of-concept study

- 16 SLE patients with severe, refractory disease were treated with a combination of CD20-mediated B-cell depletion with **rituximab** and sustained inhibition of B-cell activating factor BlyS with **belimumab.**

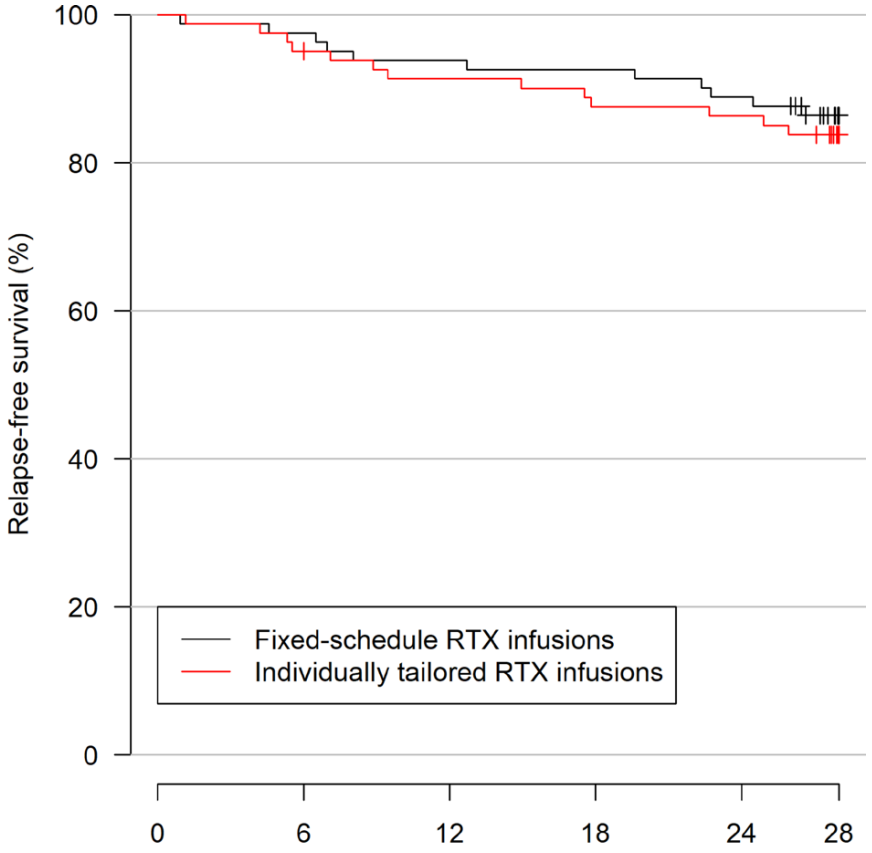
- **RTX + BLM** led to specific reductions in ANAs and regression of NET formation.

- **RTX + BLM** appeared to be safe and achieved clinically significant responses:

- Low lupus disease activity state was achieved in 10 patients,
- Renal responses in 11 patients and
- Concomitant immunosuppressive medication was tapered in 14 out of the 16 patients.

Kraaij T. et al J Autoimmun. 2018 Apr 7

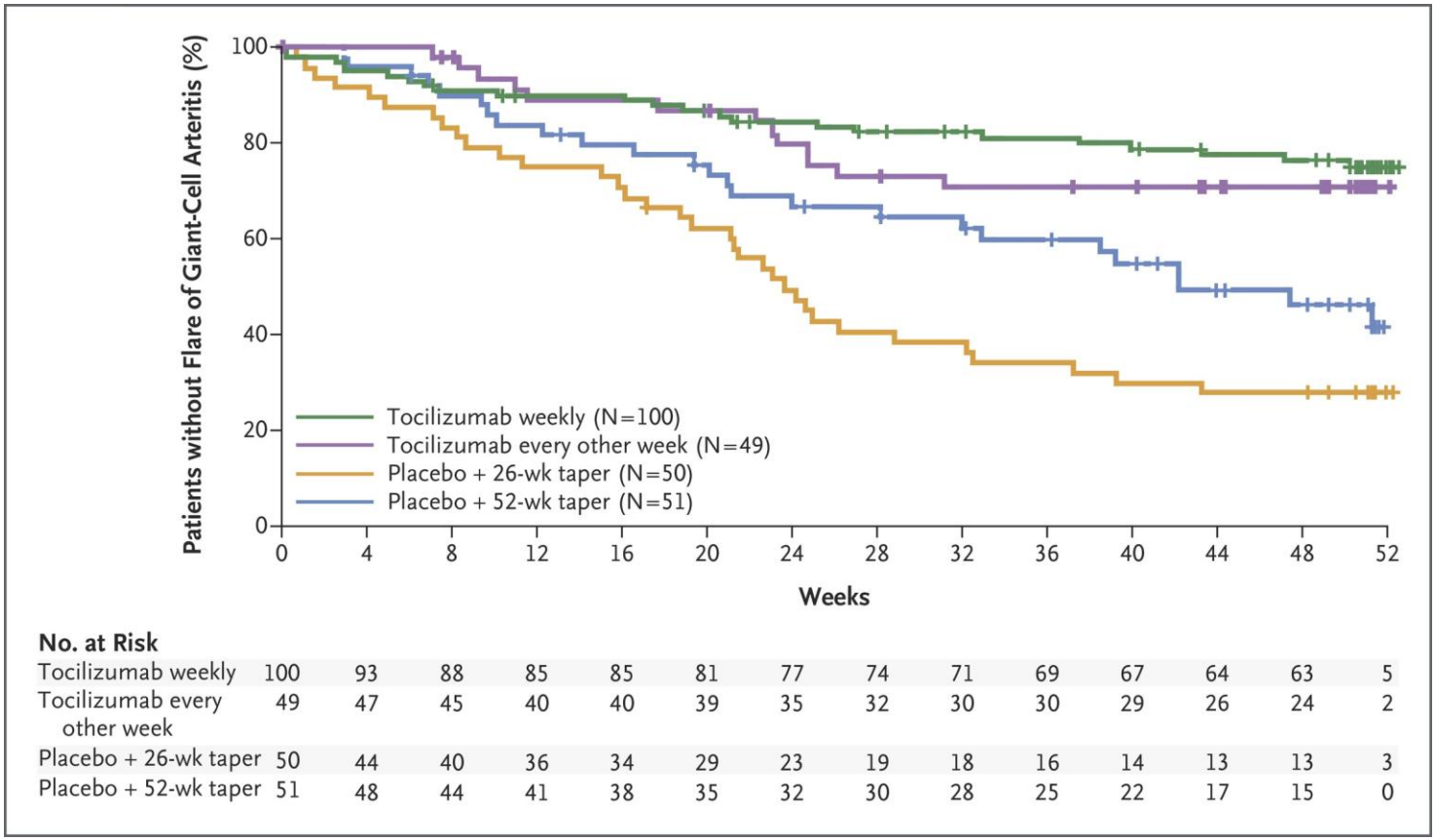
Comparison of individually tailored versus fixed schedule rituximab regimen to maintain ANCA associated vasculitis remission (MAINRITSAN2)



AAV relapse rates did not differ significantly between individually tailored and fixed schedule rituximab regimens. Individually tailored-arm patients received fewer rituximab infusions.

Charles P. ARD Apr 2018

GiACTA: Pivotal phase 3 study investigated rates of GC-free remission GCA patients treated with tocilizumab vs placebo



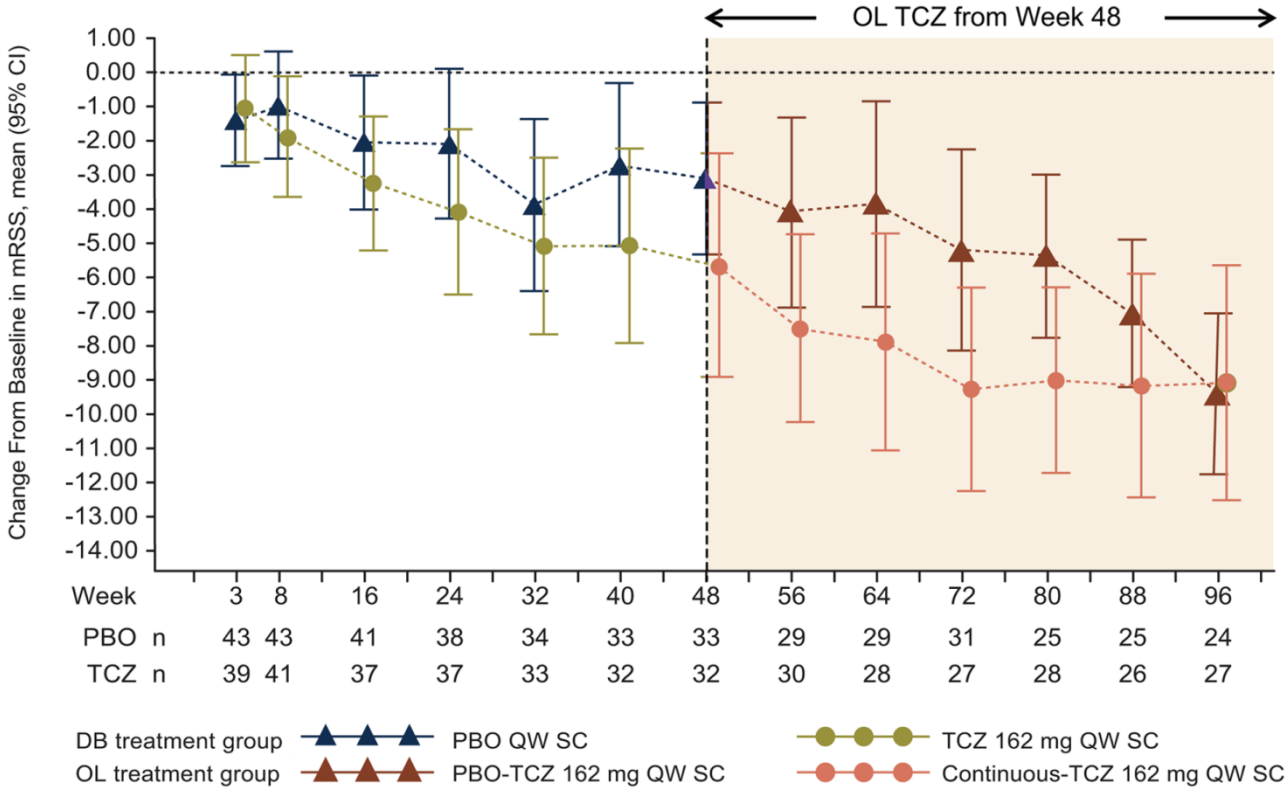
No. at Risk

Tocilizumab weekly	100	93	88	85	85	81	77	74	71	69	67	64	63	5
Tocilizumab every other week	49	47	45	40	40	39	35	32	30	30	29	26	24	2
Placebo + 26-wk taper	50	44	40	36	34	29	23	19	18	16	14	13	13	3
Placebo + 52-wk taper	51	48	44	41	38	35	32	30	28	25	22	17	15	0

Tocilizumab, received weekly or every other week, combined with a 26-week prednisone taper was superior to either 26-week or 52-week prednisone tapering plus placebo with regard to sustained glucocorticoid-free remission in GCA patients

Stone JH et al. N Engl J Med 2017

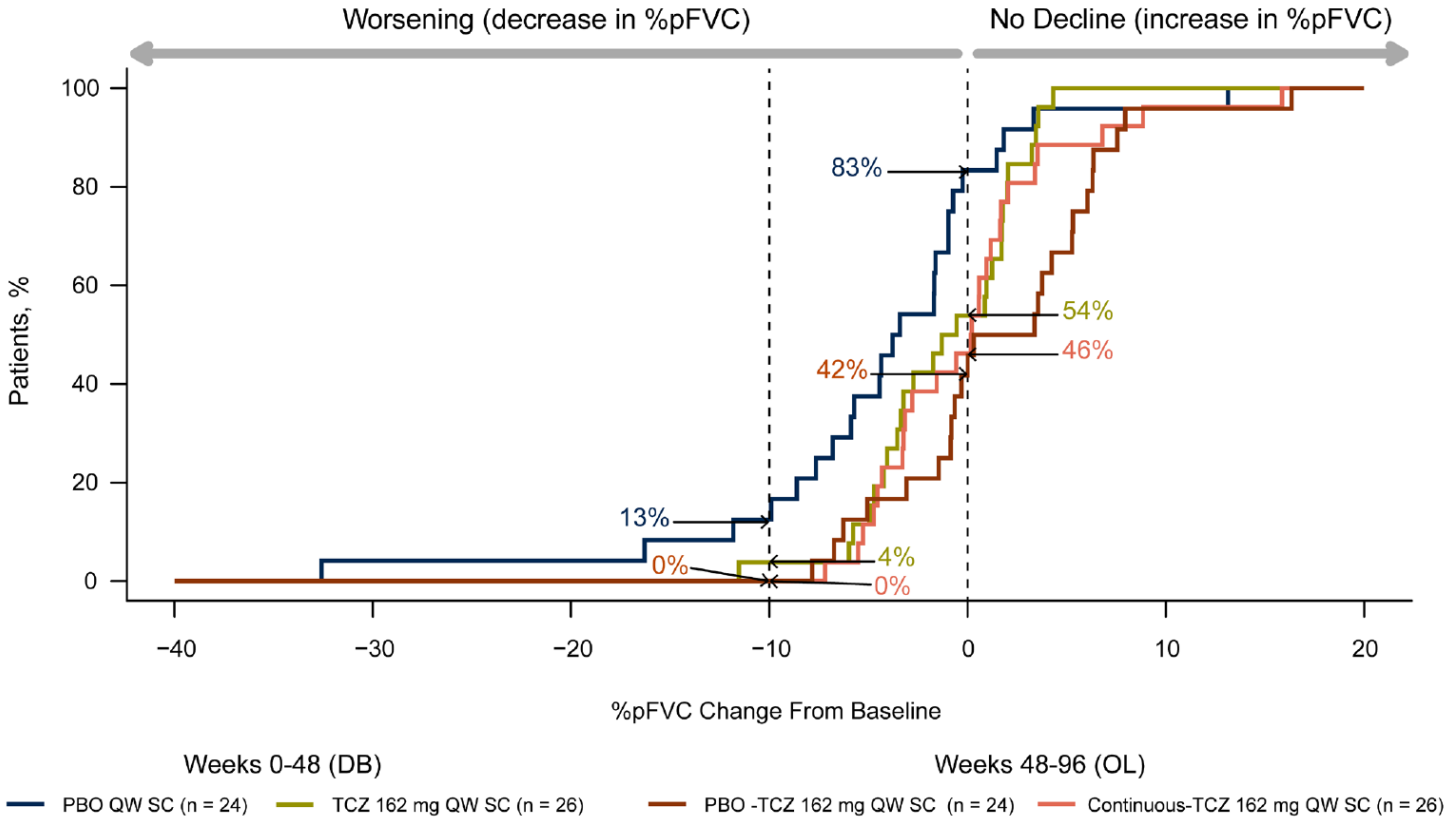
Safety and efficacy of sc tocilizumab in SScI: results from the open-label period of a phase II randomised controlled trial (faSScinate)



Skin score improvement in the double-blind period were observed in placebo-treated patients who transitioned to tocilizumab and were maintained in the open-label period

Khanna D et al. ARD 2017

Safety and efficacy of sc tocilizumab in SScI: results from the open-label period of a phase II randomised controlled trial (faSScinate)

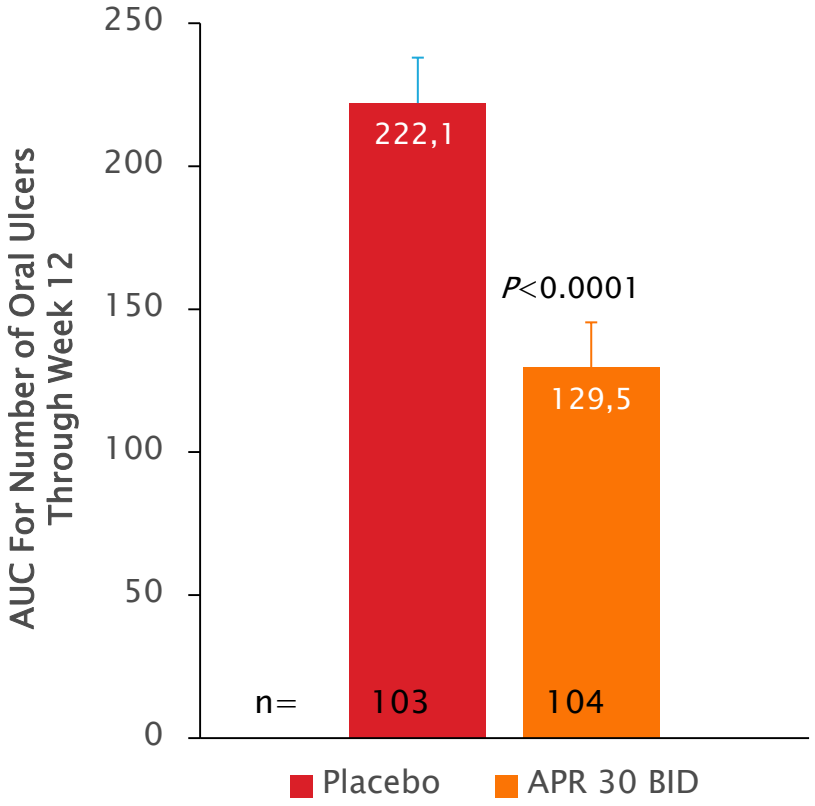


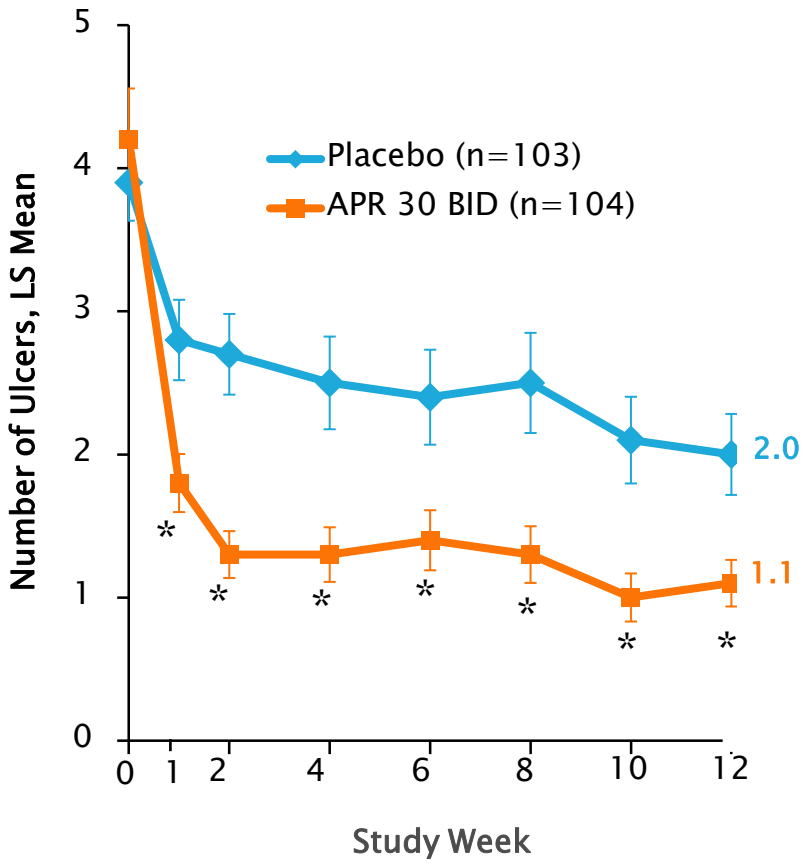
FVC stabilisation in the double-blind period were observed in placebo-treated patients who transitioned to tocilizumab and were maintained in the open-label period

Khanna D et al. ARD 2017

Apremilast for Behçet's Syndrome: A Phase III Randomized, Placebo-Controlled, Double-Blind Study (RELIEF)

Primary Endpoint: Oral Ulcers Through week 12

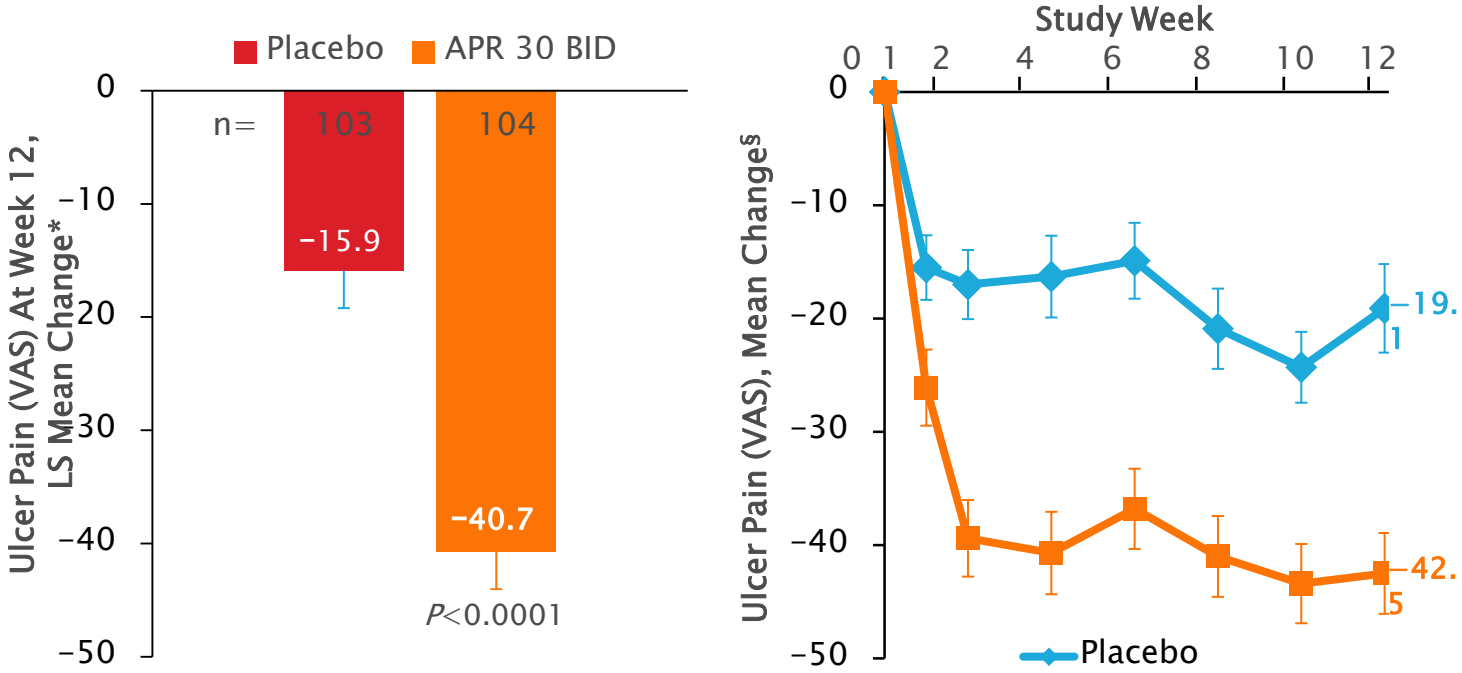




Presented at: the 2018 AAD Annual Meeting; February 16–20, 2018; San Diego, CA.

Apremilast for Behçet's Syndrome: A Phase III Randomized, Placebo-Controlled, Double-Blind Study (RELIEF)

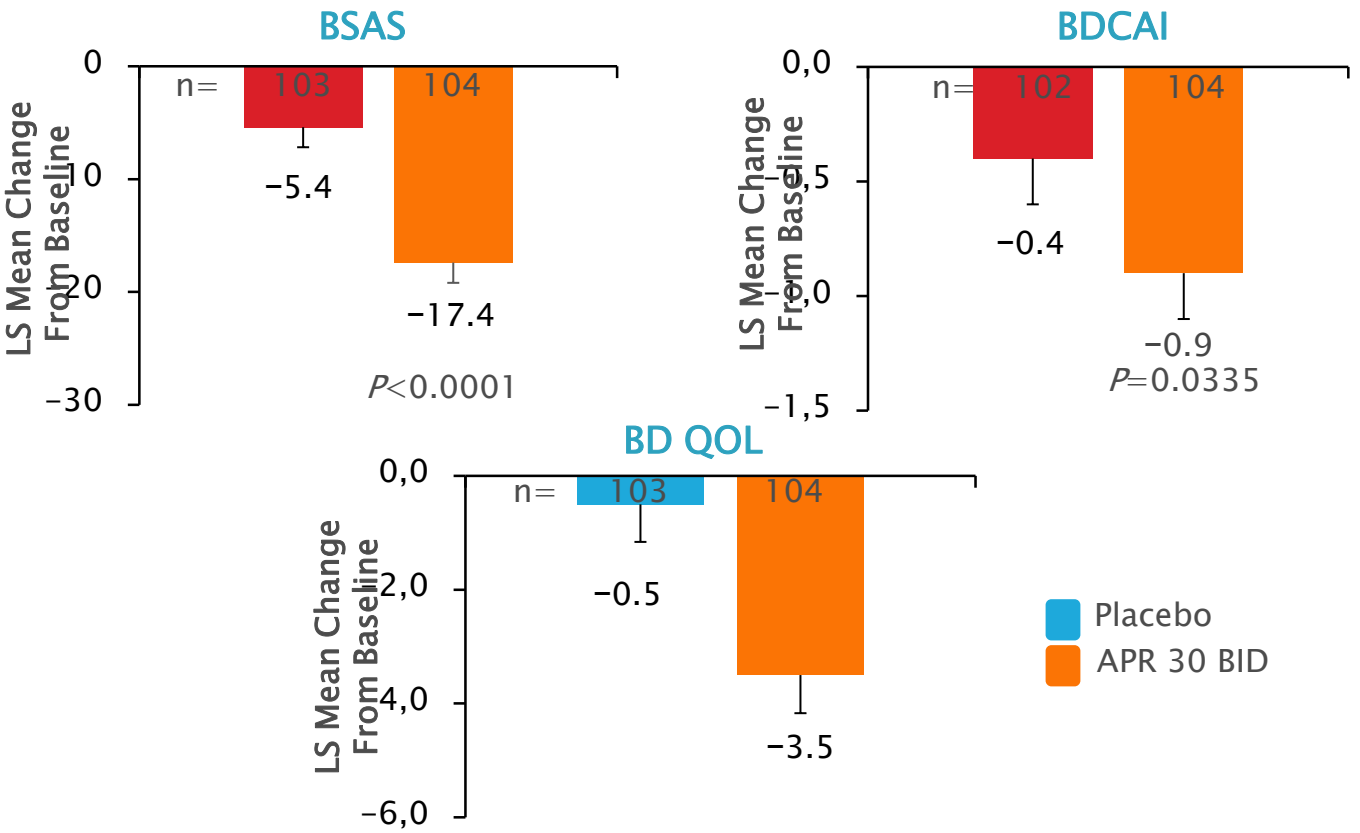
Mean Change From Baseline in Oral Ulcer Pain VAS



Presented at: the 2018 AAD Annual Meeting; February 16–20, 2018; San Diego, CA.

Apremilast for Behçet's Syndrome: A Phase III Randomized, Placebo-Controlled, Double-Blind Study (RELIEF)

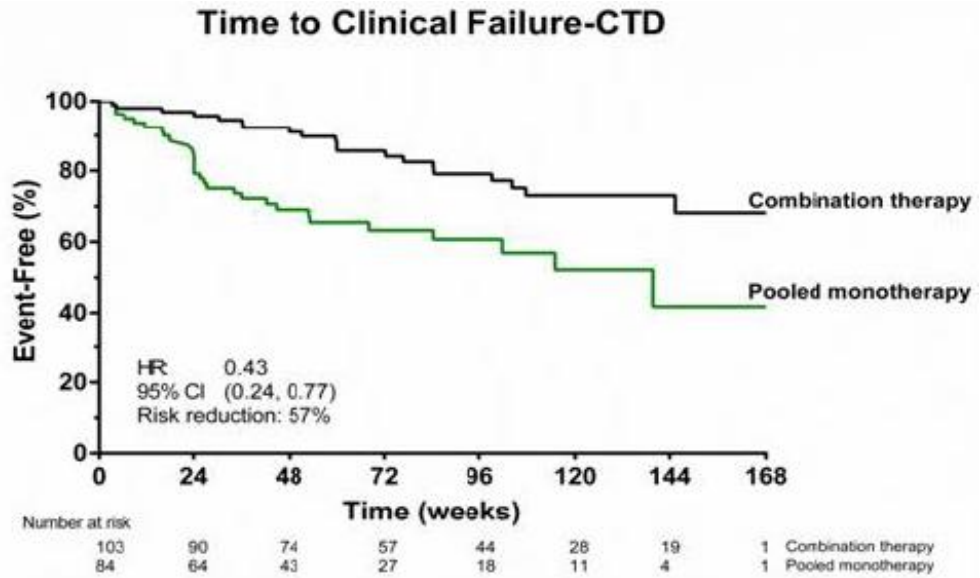
Improvement in disease activity and QoL at week 12

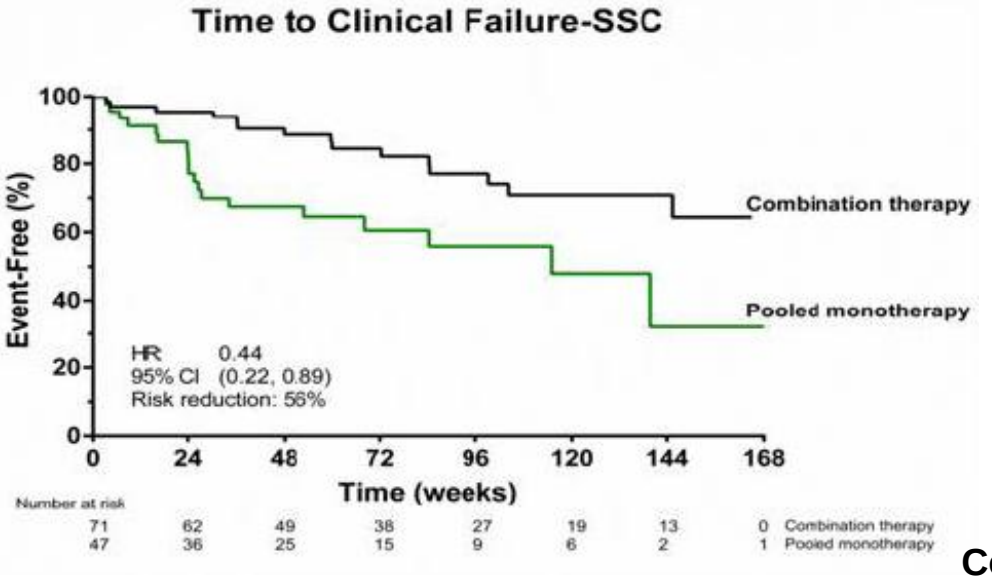


Presented at: the 2018 AAD Annual Meeting; February 16–20, 2018; San Diego, CA.

A Randomised, Multicenter Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension

AMBITION

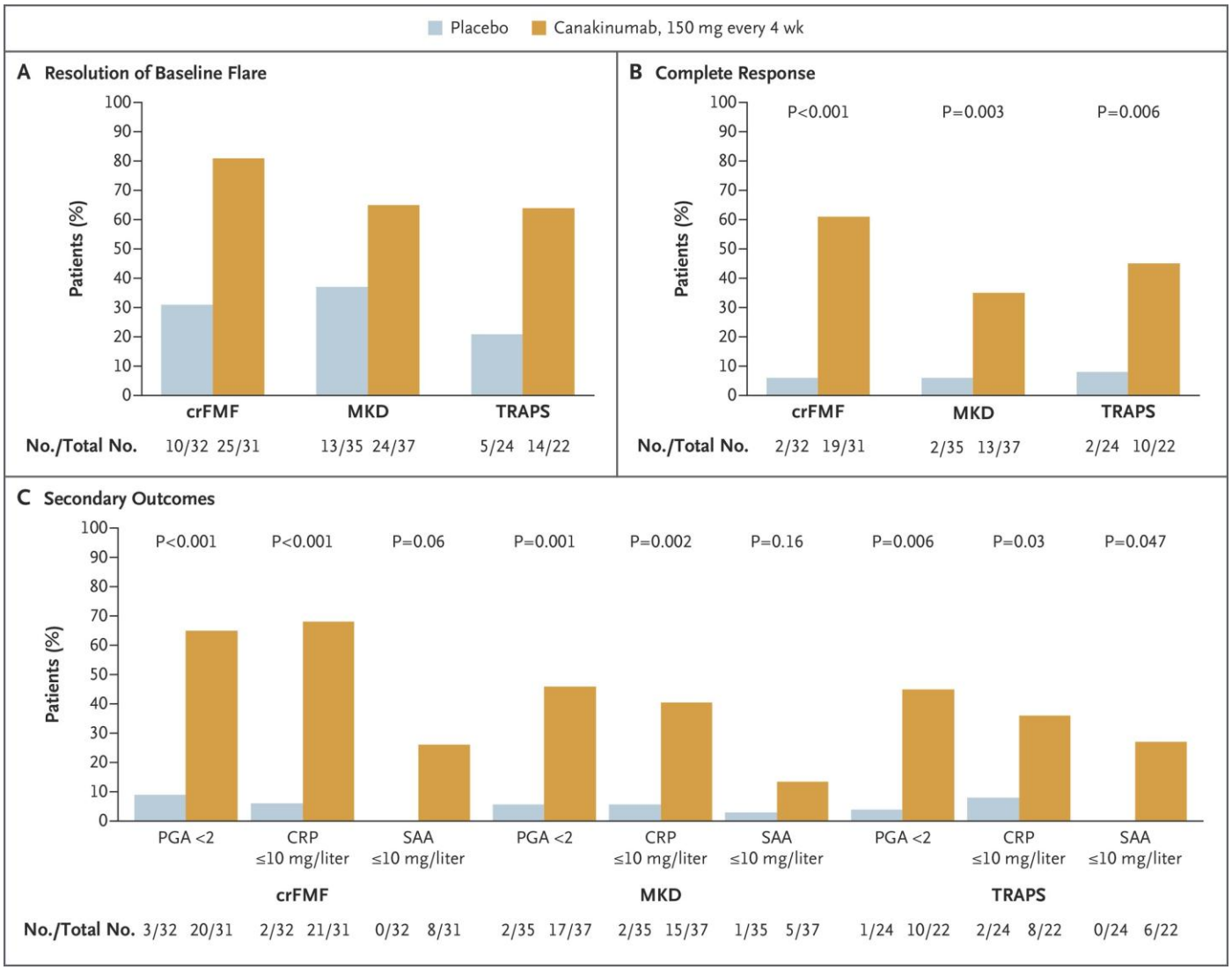




CTD-PAH subgroup analysis

Coghlan et al. Ann Rheum Dis 2016

Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes



Resolution of Baseline Flare and Response Rate of Primary and Secondary Outcomes at Week 16

De Benedetti F et al. N Engl J Med 2018

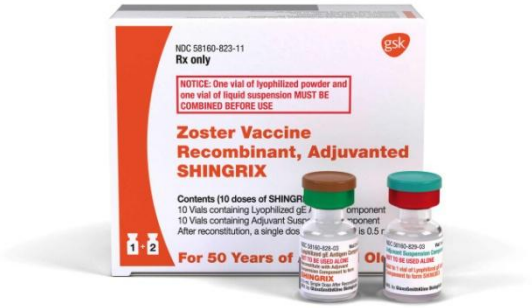
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2017 VOL. 377 NO. 12

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

- **Με 150 mg/3μηνο** μείωση των καρδιαγγειακών νοσημάτων, ανεξάρτητη της μείωσης των λιπιδίων
- Μείωση της θνησιμότητας από καρκίνο, ιδιαίτερα του πνεύμονα
- Μεγαλύτερη συχνότητα λοιμώξεων απειλητικών για τη ζωή και σηψαιμίας



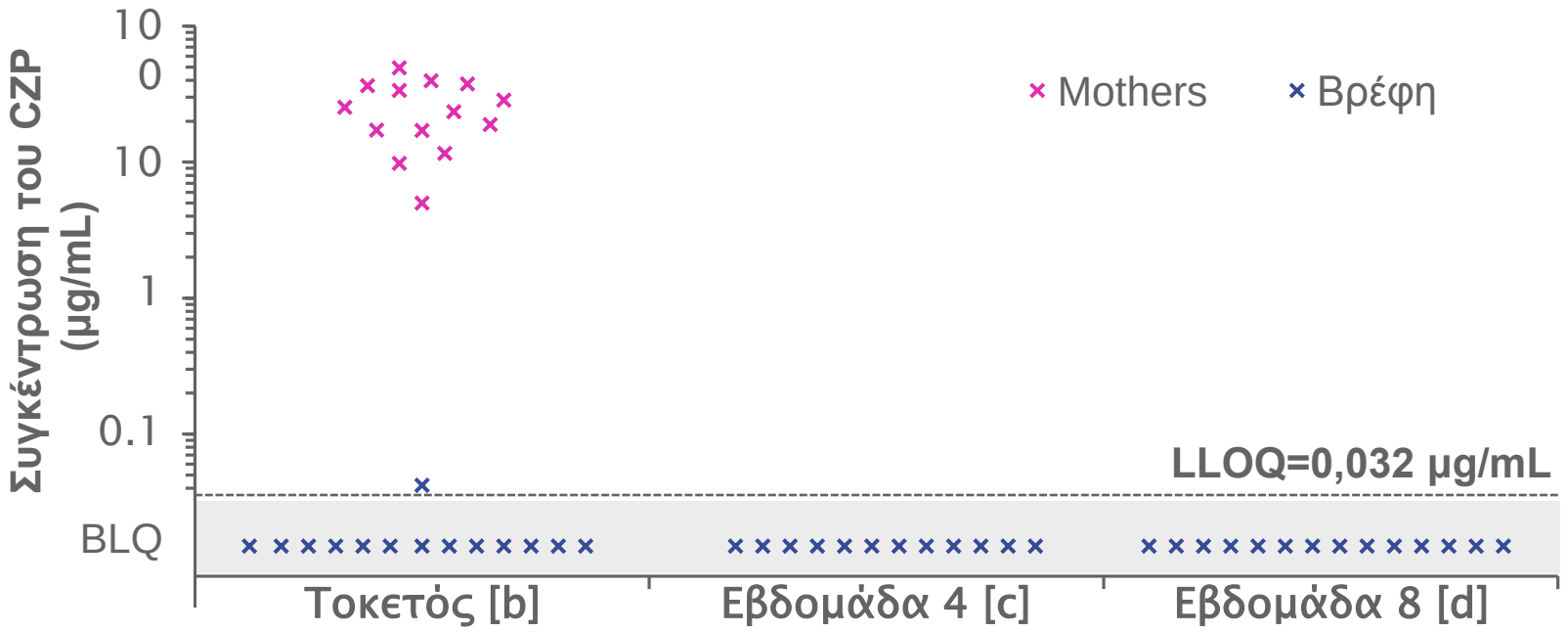
New Shingles Vaccine Is Here

- At October 2017 FDA approved a new herpes zoster vaccine (Shingrix).
- Unlike Zostavax, which is a live attenuated vaccine, Shingrix consists of a recombinant zoster glycoprotein along with a potent adjuvant.
- The new vaccine's efficacy seems to be substantially better than that of its predecessor.
- A booster dose is required at 2 months.
- Both injections commonly elicit substantial local reactions.

NEJM JW Infect Dis Jun 2015
NEJM May 2015

Συγκέντρωση Certolizumab pegol στο πλάσμα σε μητέρες και βρέφη στην CRIB

13/14 βρέφη δεν είχαν ανιχνεύσιμα επίπεδα CZP κατά τη γέννηση

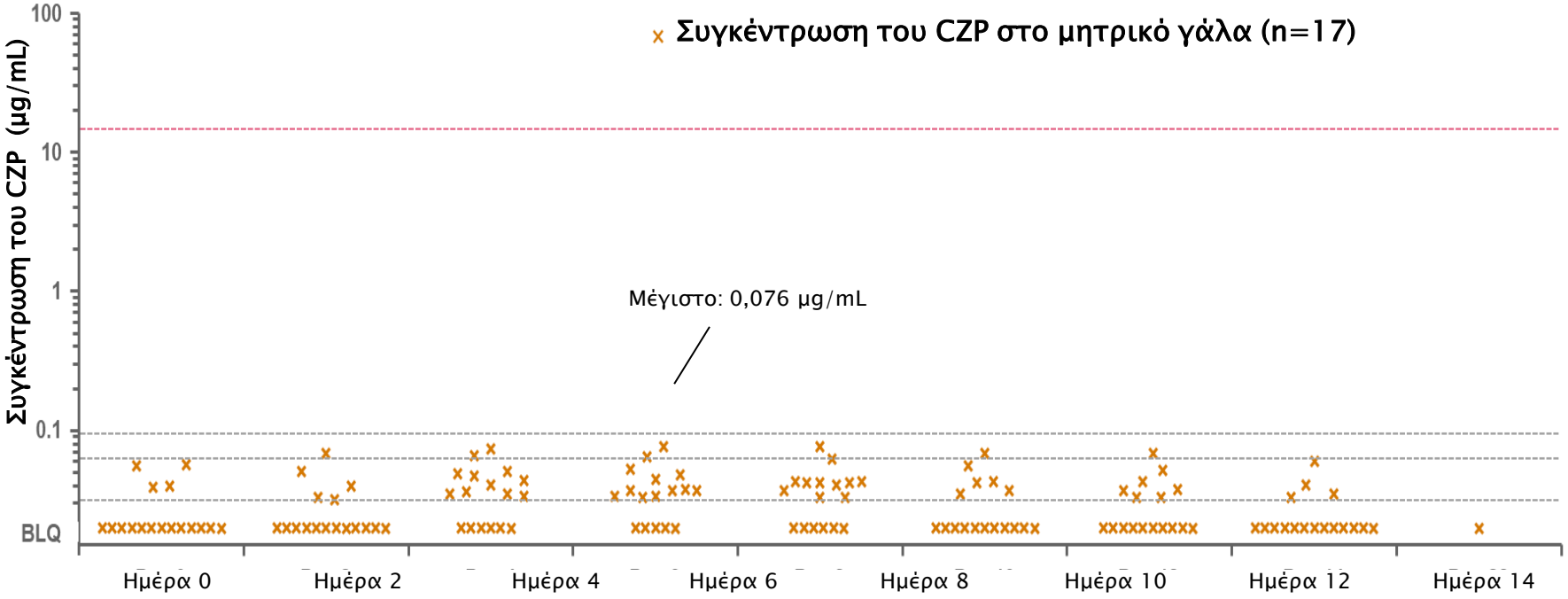


Κατά τη διάρκεια της εγκυμοσύνης, το Cimzia θα πρέπει να χορηγείται μονό εάν χρειάζεται από κλινική άποψη

Mariette X et al. Ann Rhem Dis. 2017

Συγκεντρώσεις του CZP (μg/mL) στο μητρικό γάλα στην CRADLE

- **77 (56%)** από τα δείγματα δεν είχαν ανιχνεύσιμα επίπεδα CZP, **52 (38%)** είχαν ελάχιστα αλλά μετρήσιμα επίπεδα CZP (<0,064μg/mL) και **8 (6%)** είχαν χαμηλά επίπεδα CZP (<0,096μg/mL)
- **Η διάμεση RID του CZP** ήταν 0,15%. Μια RID <10% θεωρείται **απίθανο να προκαλέσει κλινική ανησυχία**



Το Cimzia μπορεί να χρησιμοποιηθεί κατά την διάρκεια του θηλασμού

Clowse MEB et al. Ann Rhem Dis. 2017

Rules for Pregnancy Management

- Plan all pregnancies – discuss contraception, Pre-Preg planning
- Optimally – get pregnant only with low Dz activity or remission
- Prepare for upcoming pregnancy by:
  - Getting off MTX, LEF, cytotoxics (OK to be on HCQ, SSZ, AZA)
    Women must be off MTX for 1 month (per PI); others for >3 mos before conceiving
  - Use TNF inhibitors (Pregnancy Category B) to achieve LDAS/remission
  - OK to get pregnant on TNFi (certolizumab or etanercept preferred)
    (insufficient data on Cat C biologics – RTX, TCZ, ABA or Tofa)
- If on mAb TNFi (INFLX, ADA) during Preg stop at wk 32 if possible
  - To avoid transplacental transfer to child at birth
  - (note: most pregnant IBD patients take TNFi or 6MP throughout Preg)

Disease Activity is more Hazardous than the Drugs

Paternal use of antirheumatic drugs on pregnancy

Drug	Spermatogenesis	Male Counseling
NSAIDS	Not fully investigated	No link between paternal drug exposure and adverse pregnancy outcomes
Steroids	Limited data; no correlation with infertility in men	No harmful effects have emerged for low (<10 mg prednisone/day) doses.
AZA	No impairment	No increased risk of congenital abnormalities in offspring of fathers treated with thiopurines and male fertility not affected
TNF inhibitors	No impairment	TNFi do not influence male fertility or harm offspring. Risks are the same as female exposure and thus should be continued to avoid flare

Micu MC. et al. Sem Arthr Rheum 2018

Paternal use of antirheumatic drugs on pregnancy

Drug	Spermatogenesis	Male Counseling
MTX	Studies showed alterations in sperm DNA after MTX exposure	Some believe it is ok to maintain MTX therapy in men throughout the disease course to avoid unnecessary flares, as controlled studies have not shown increased malformation rates with male exposure
SSZ	Oligospermia, reduced mobility and increase of pathologic sperm morphology	Stop SSZ 3 months before conception
MMF	Limited data; but no effect on sperm in rat studies	MMF is a known, clear teratogen in women. But 3 studies in men have failed to show any increase risk of malformations with male use of MMF.

Micu MC. et al. Sem Arthr Rheum 2018

ACR/AAHKS Guidelines for Perioperative Management

- 7 low evidence recommendations for arthroplasty in RA, JIA, PsA, SpA and SLE:

1. Continue synthetic DMARDs thru THA or TKA surgery
2. Hold Biologics for surgery – hold for one dosing cycle before surgery
3. Hold tofacitinib for 7 days before surgery
4. Severe SLE: Continue immunosuppressives thru surgery
5. Non-Severe SLE: Hold immunosuppressives for 7 days before surgery
6. Restart biologics with start of wound healing, sutures out, no infection (~14days)
7. Continue daily steroids (rather than stress dosing)

Goodman S. et al. Athr Care & Res 2017

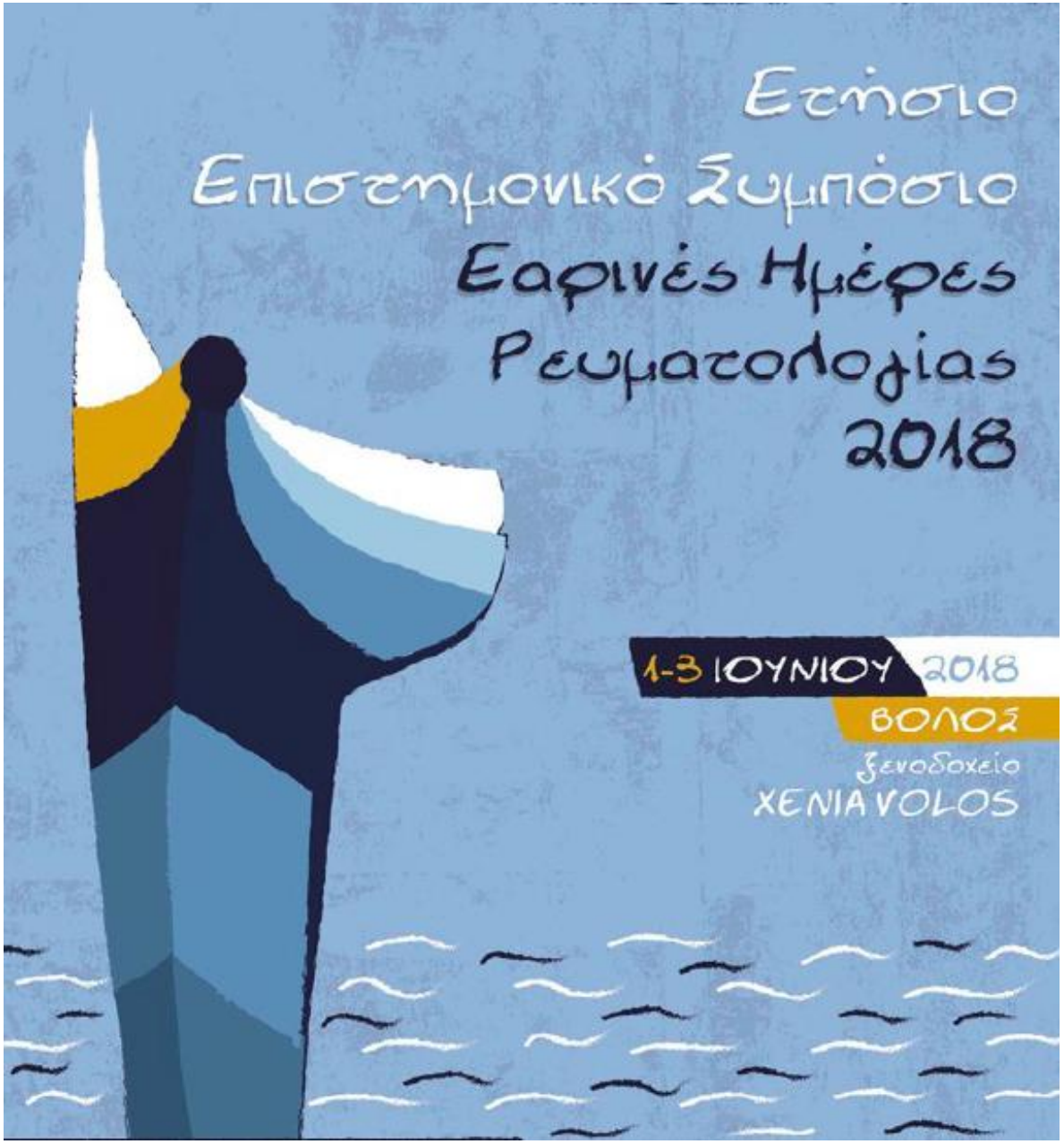
ASCO/NCCN Guidelines for Checkpoint Inhibitor Immune-Related Adverse Events

Grade 1 toxicities: ICPis should be continued with close monitoring

Grade 2 toxicities: ICPis therapy may be suspended, resuming when symptoms revert to grade 1 or less. Corticosteroids may be administered.

Grade 3 toxicities: Suspension of ICPis and initiation of corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy.

Grade 4 toxicities: Permanent discontinuation of ICPis is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement.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