Synovitis and the therapeutic management of psoriatic arthritis

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Psoriatic arthritis subtypes

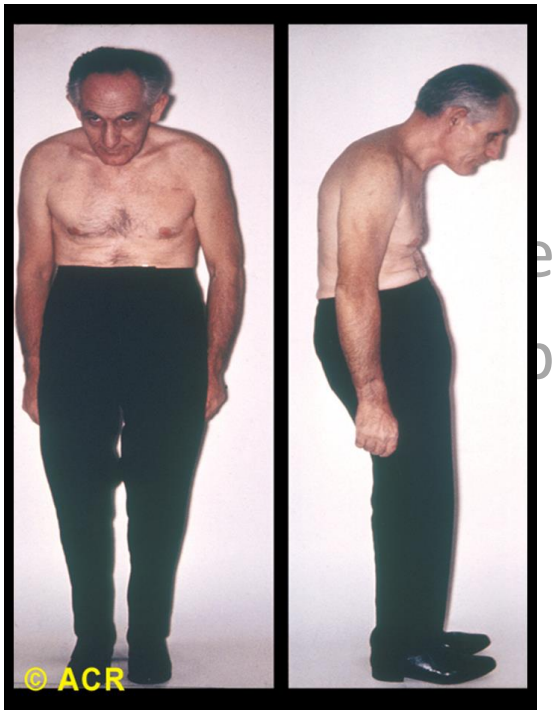
- Arthritis mutilans
- Ankylosing spondylitis +/- peripheral

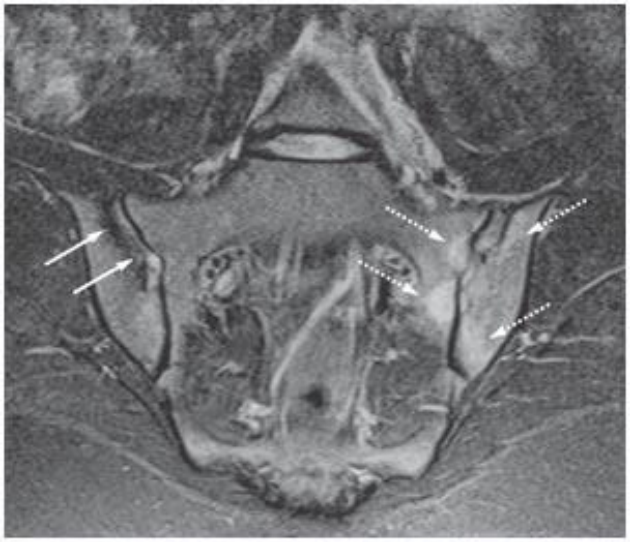
RA like)

r with dactylitis

Psoriatic arthritis subtypes

- Arthritis mutilans
- Ankylosing spondylitis +/- peripheral joints





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- Ankylosing spondylitis +/- peripheral jo

- DIP involvement
- Symmetrical polyart
- Asymmetrical oligoa

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- **Symmetrical polyarthritis (RA like)**
- Asymmetrical oligoarticular with dactylitis

Psoriatic arthritis subtypes

itis +/- p

thritis (RA like)

- Asymmetrical oligoarticular with dactylitis

Psoriatic arthritis subtypes

- Arthritis mutilans
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- DIP involvement
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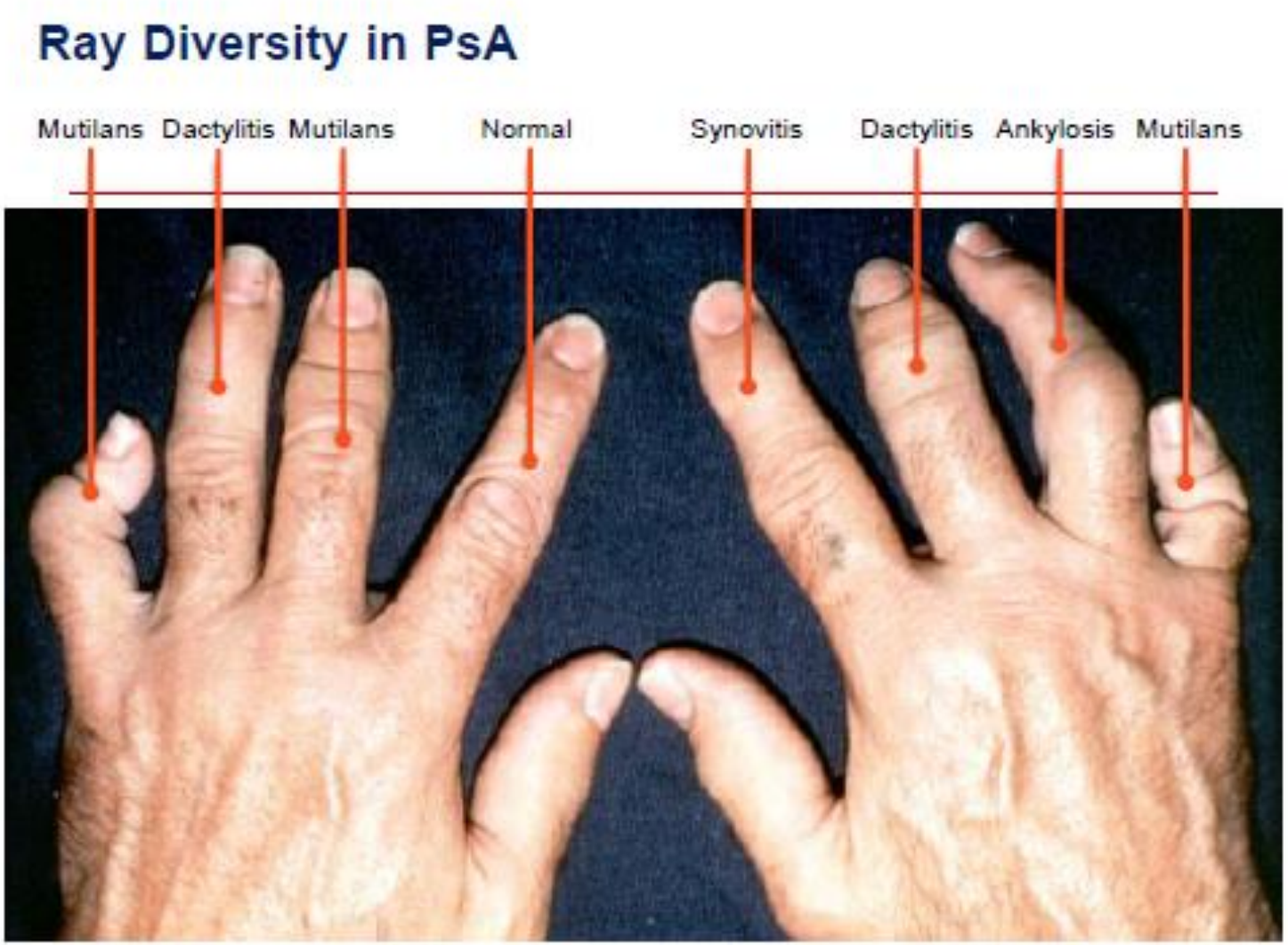
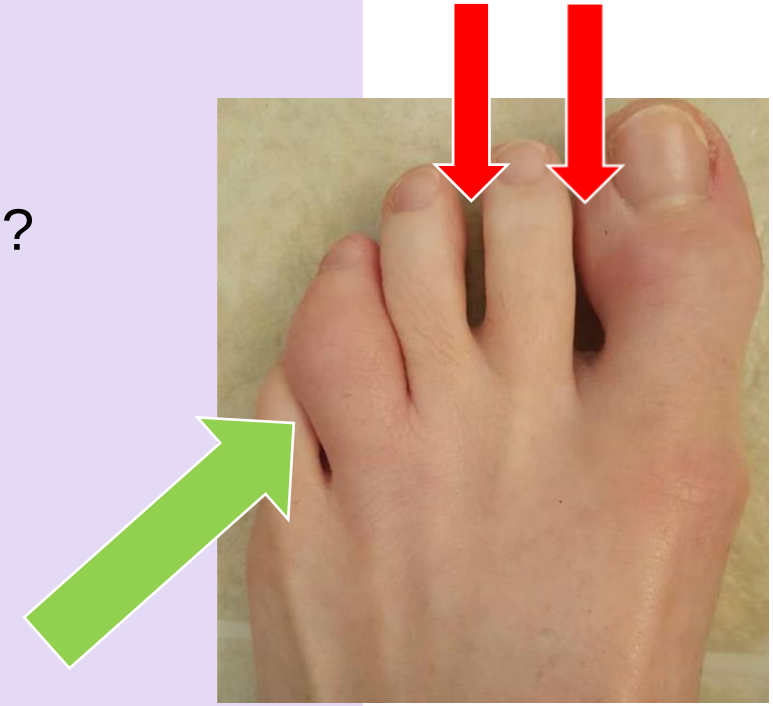
Disease heterogeneity in PsA



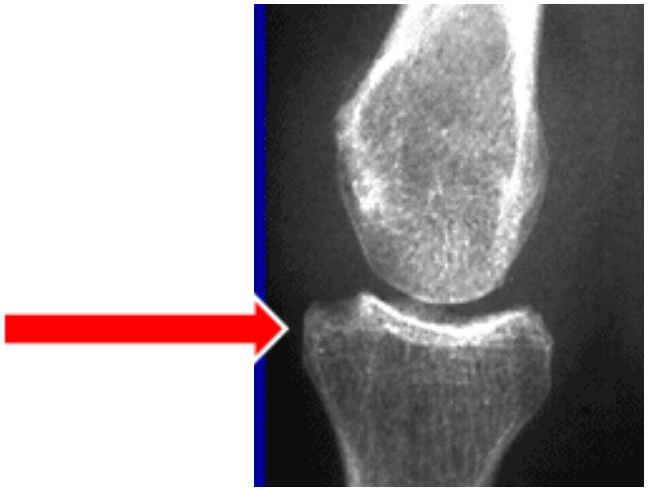
Modified from: Slide by Christopher Ritchlin, ACR 2012

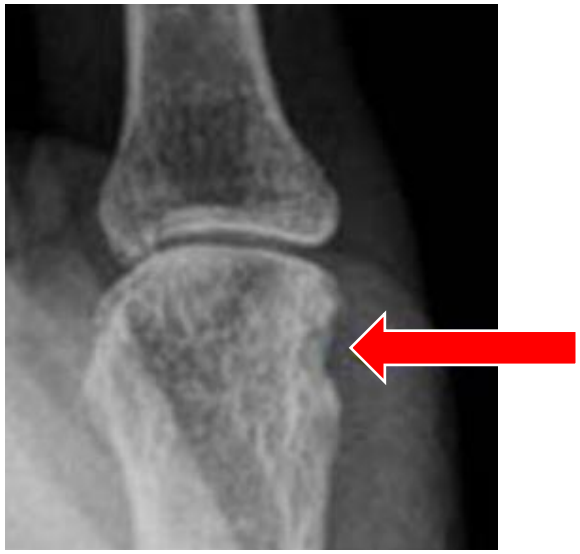
Synovitis

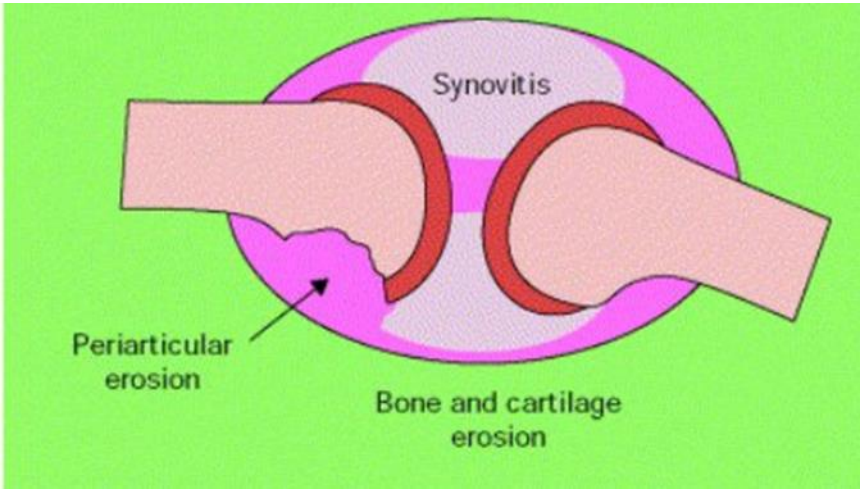
- Joint swelling / tenderness / (warmth)
  - Ankle
  - Subtalar
  - Mid-tarsal
  - MTP / IP
- Warmth (probably ankle only)
- Is it soft / spongy / squishy to palpation?
  - ‘Fullness’ at the MTPs
  - Toes may be separated by synovitis
  - Damage (NOT synovitis)
    - Bony hypertrophy/enlargement
    - MTP subluxation

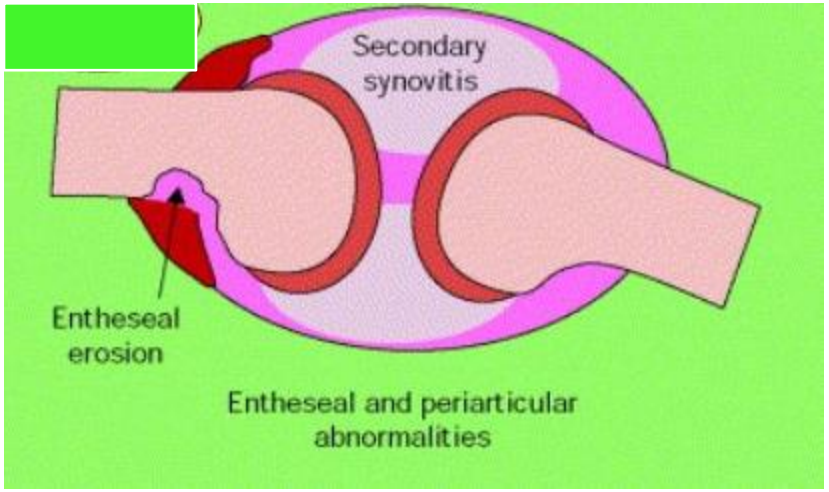


Joint erosions





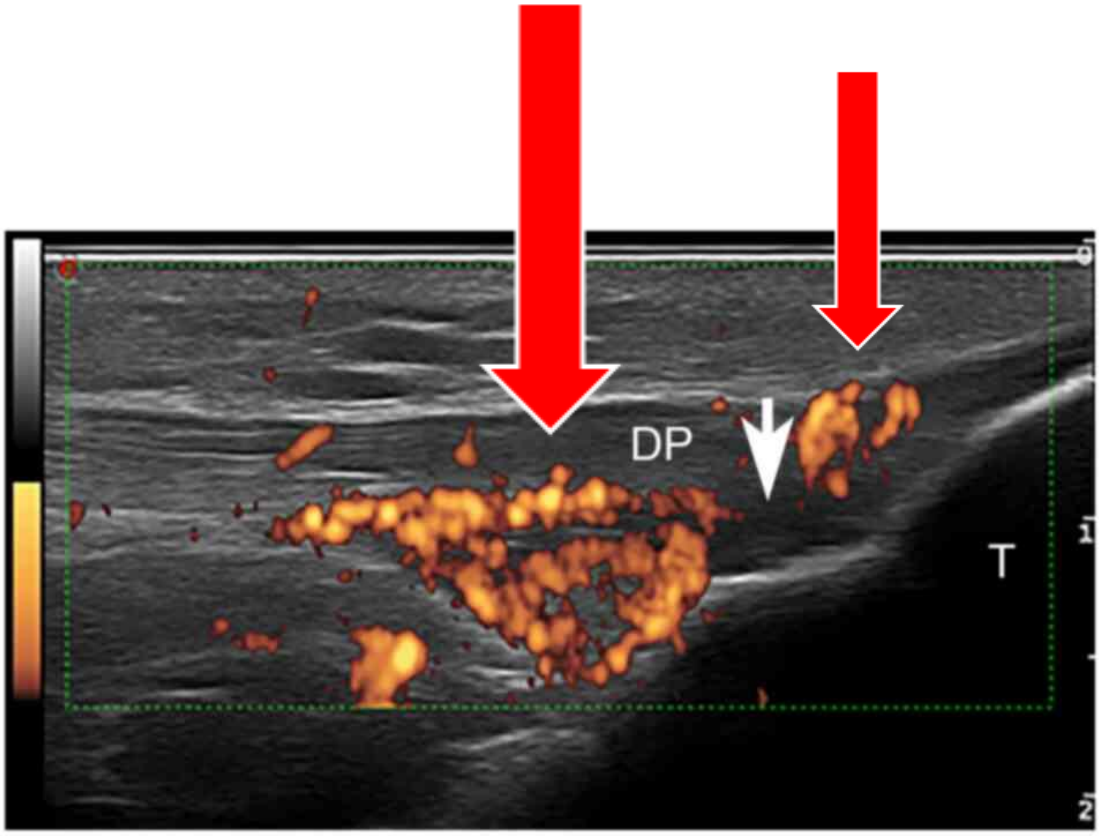




Rheumatoid arthritis

Psoriatic arthritis

Doppler Ultrasound



DMARDs used in PsA management:

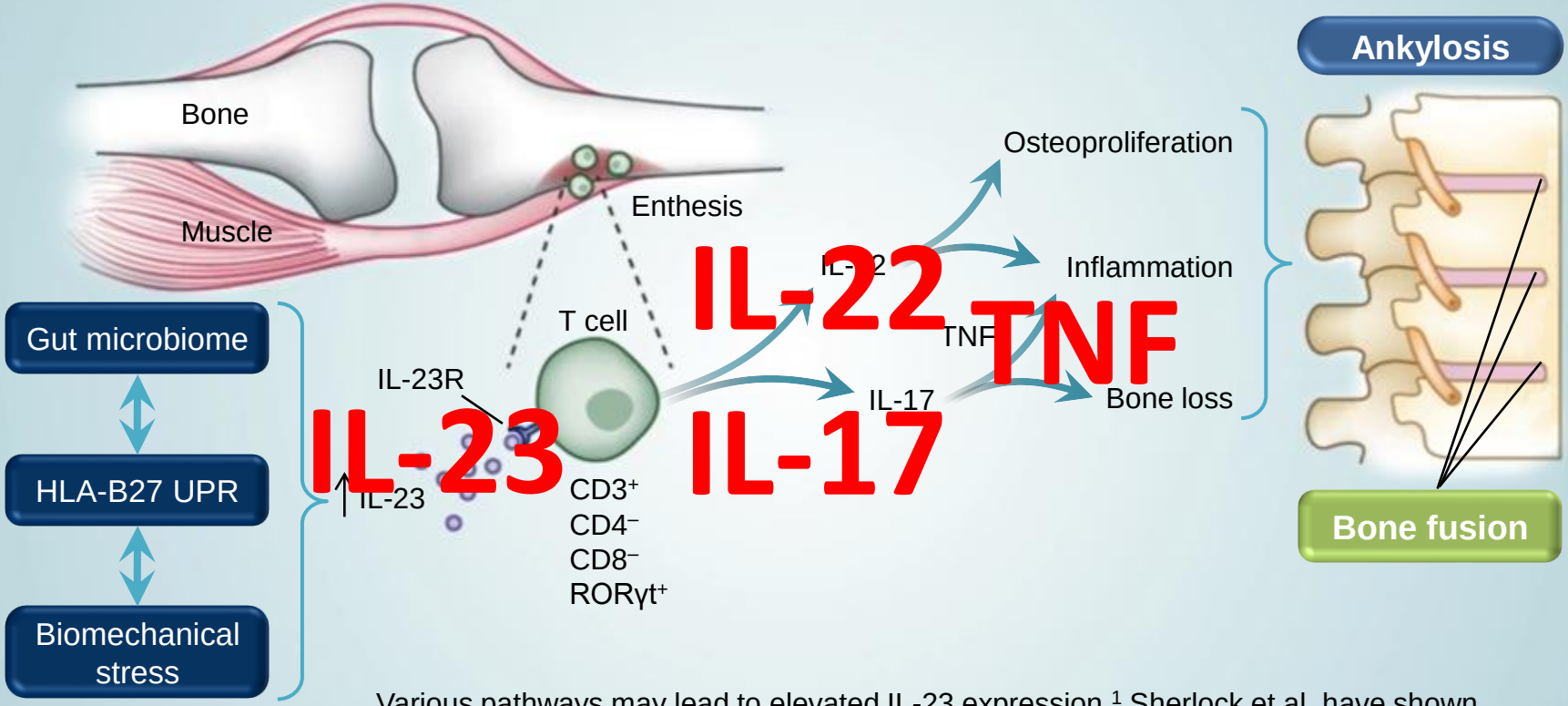
DMARDs

- Methotrexate – limited evidence; MIPA study[1]
- Leflunomide - 1 RCT[2]
- Sulfasalazine
- Hydroxychloroquine
- Cyclosporin

DMARDs are not considered effective for axial disease

1. Kingsley et al *Rheumatology* 2012;51:1368-77
2. Kaltwasser et al *Arthritis Rheum* 2004;50:1939-50

Proposed model linking inflammation, enthesitis, new bone formation and erosions



Various pathways may lead to elevated IL-23 expression.[1] Sherlock et al. have shown that IL-23 can activate resident T cells within the enthesis.[2]

HLA, human leukocyte antigen; UPR, unfolded protein response.

1. Lories RJ, McInnes IB. *Nat Med.* 2012;18:1018-1019.
2. Sherlock JP et al. *Nat Med.* 2012;18:1069-1076.

Towards molecular taxonomy in inflammation medicine

Psoriasis

IL-17/23

PsA

IL-12

SpA

RA

IL-6

GCA

JIA/AID

JAK

IL-1

Gout

CD

?

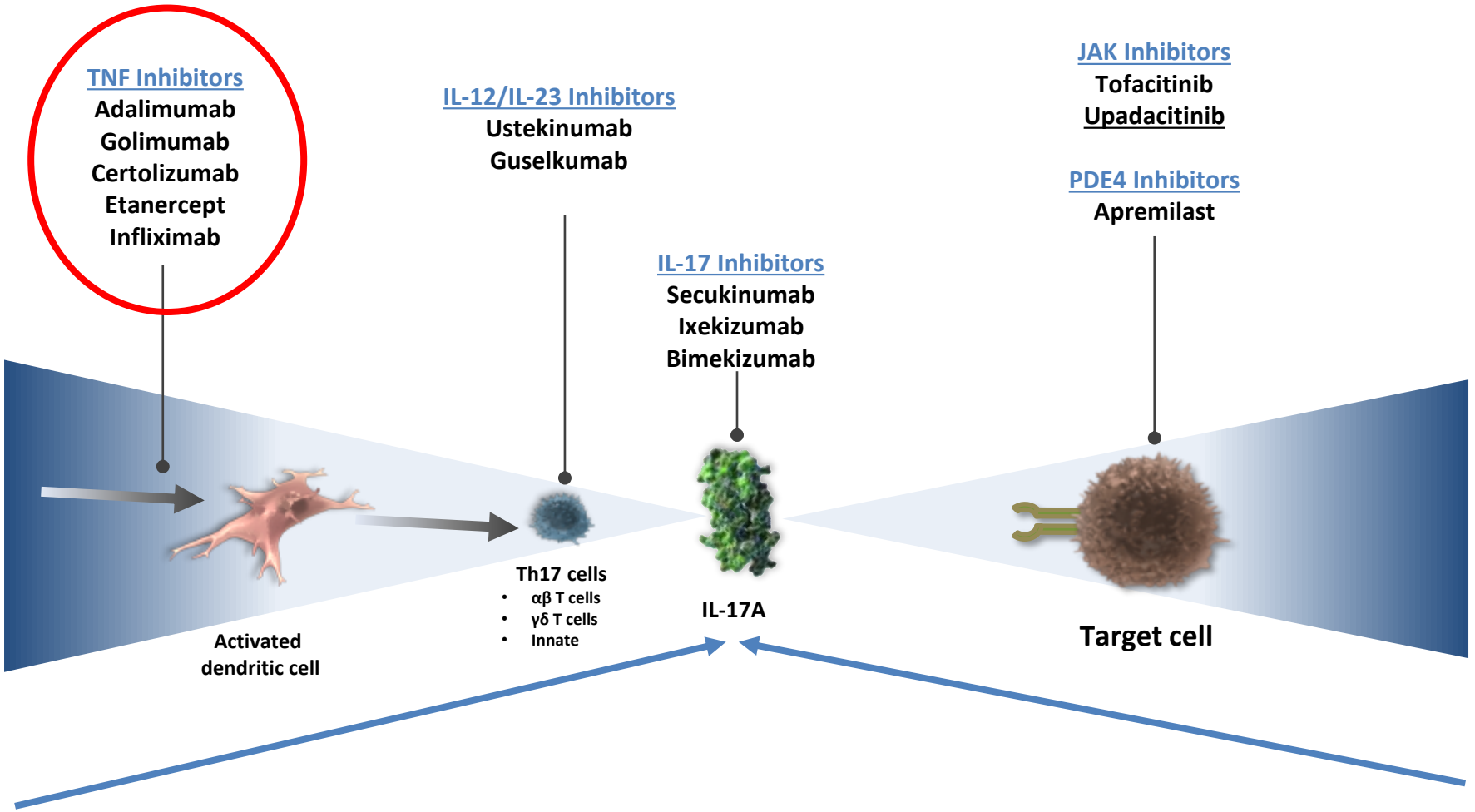
UC

TNF

AID: autoinflammatory disease including Still's disease; CD: Crohn's disease; GCA: giant cell arteritis; IL: interleukin; JIA: juvenile idiopathis arthritis; RA: rheumatoid arthritis; SpA: spondyloarthritis; TNF: tumour necrosis factor; UC: ulcerative colitis

Schett et al. *Nature Med* 2013;19:822–824 (Updated version by Prof Packham)

“Novel” approaches to PsA management



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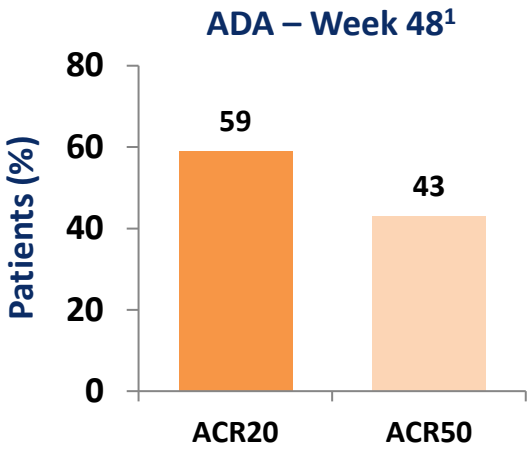
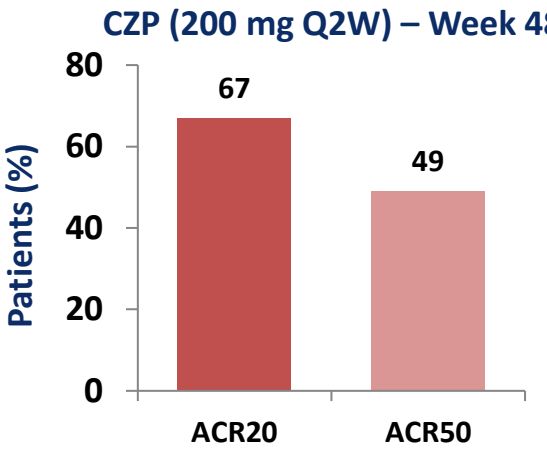
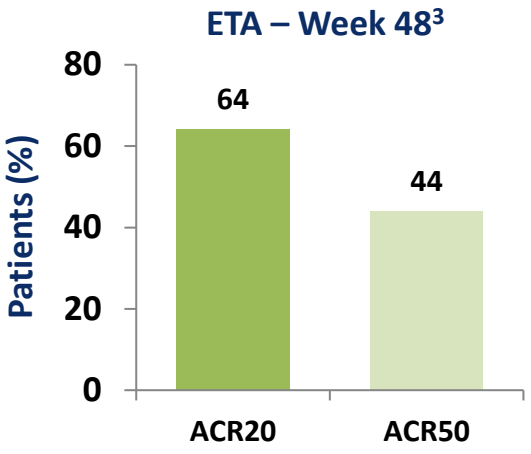
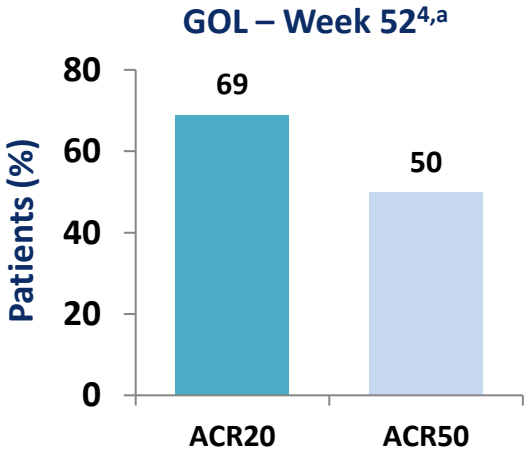
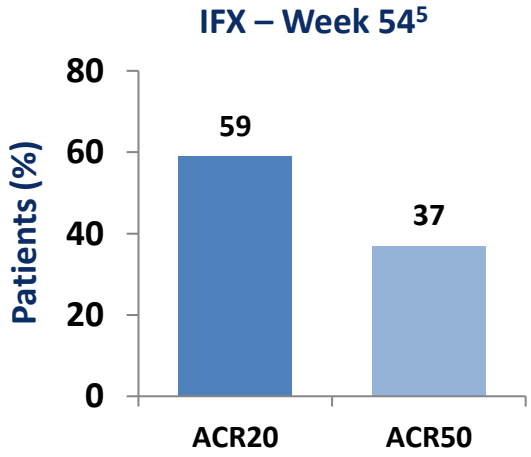
Biologics prior to 2015: anti-TNF











***Different studies:**
Not head-to-head comparisons

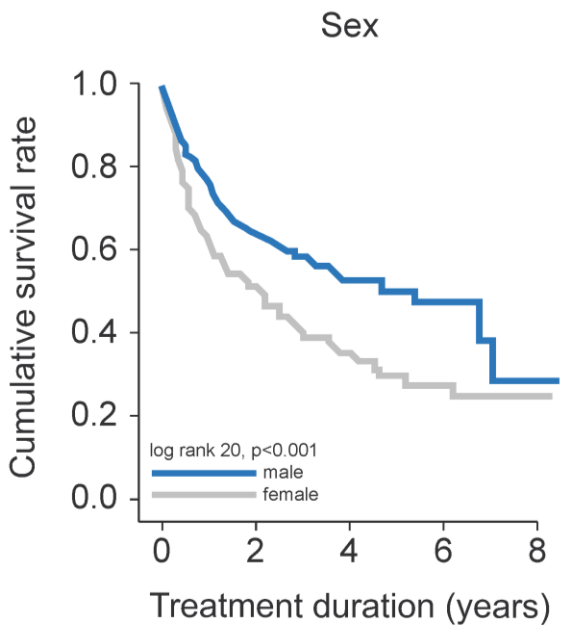
ADA; adalimumab,
CZP; certolizumab pegol,
ETA; etanercept,
GOL; golimumab,
IFX; infliximab

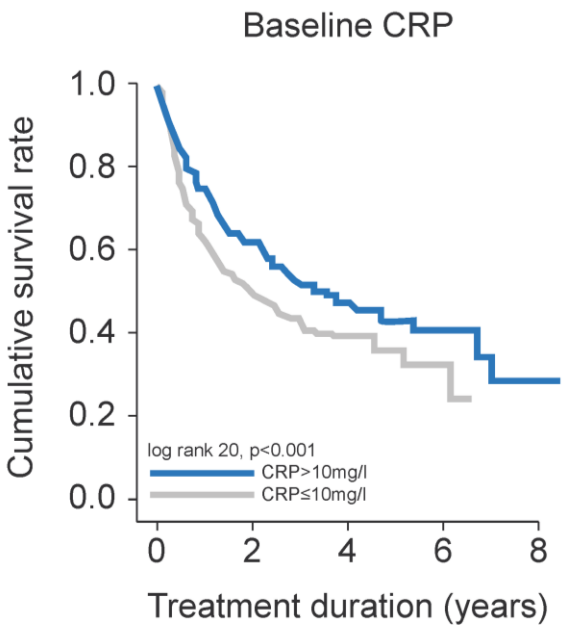
[a]Combined data from 50 and 100 mg dose groups

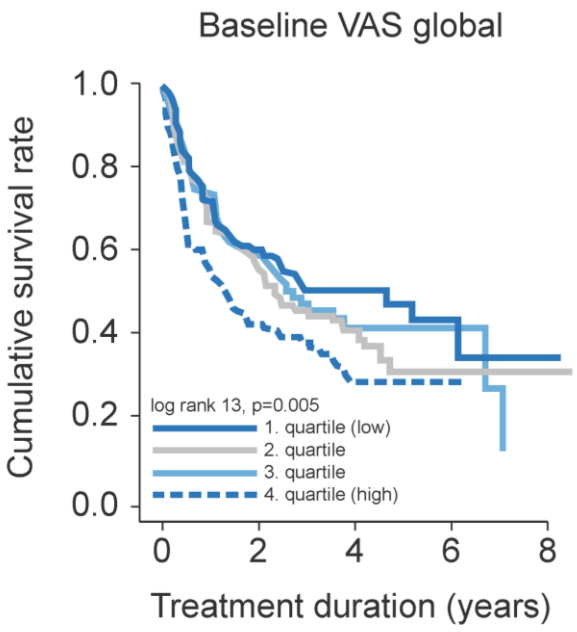
[1]Mease PJ, et al. Ann Rheum Dis 2009;68:702–9; [2]Mease PJ, et al. ACR 2013:Poster 312; [3]Mease PJ, et al. J Rheumatol 2006;33:712–21; [4]Kavanaugh A, et al. Arthritis Rheum 2012;64:2504-17; [5]Kavanaugh A, et al. Ann Rheum Dis 2007;66:498–505; [6]Kavanaugh A, et al. Ann Rheum Dis 2013;72:1777–85

Real-world drug survival of anti-TNF therapy in PsA

DANBIO Registry:
Drug Survival in 764 Patients with PsA treated with anti-TNF therapy

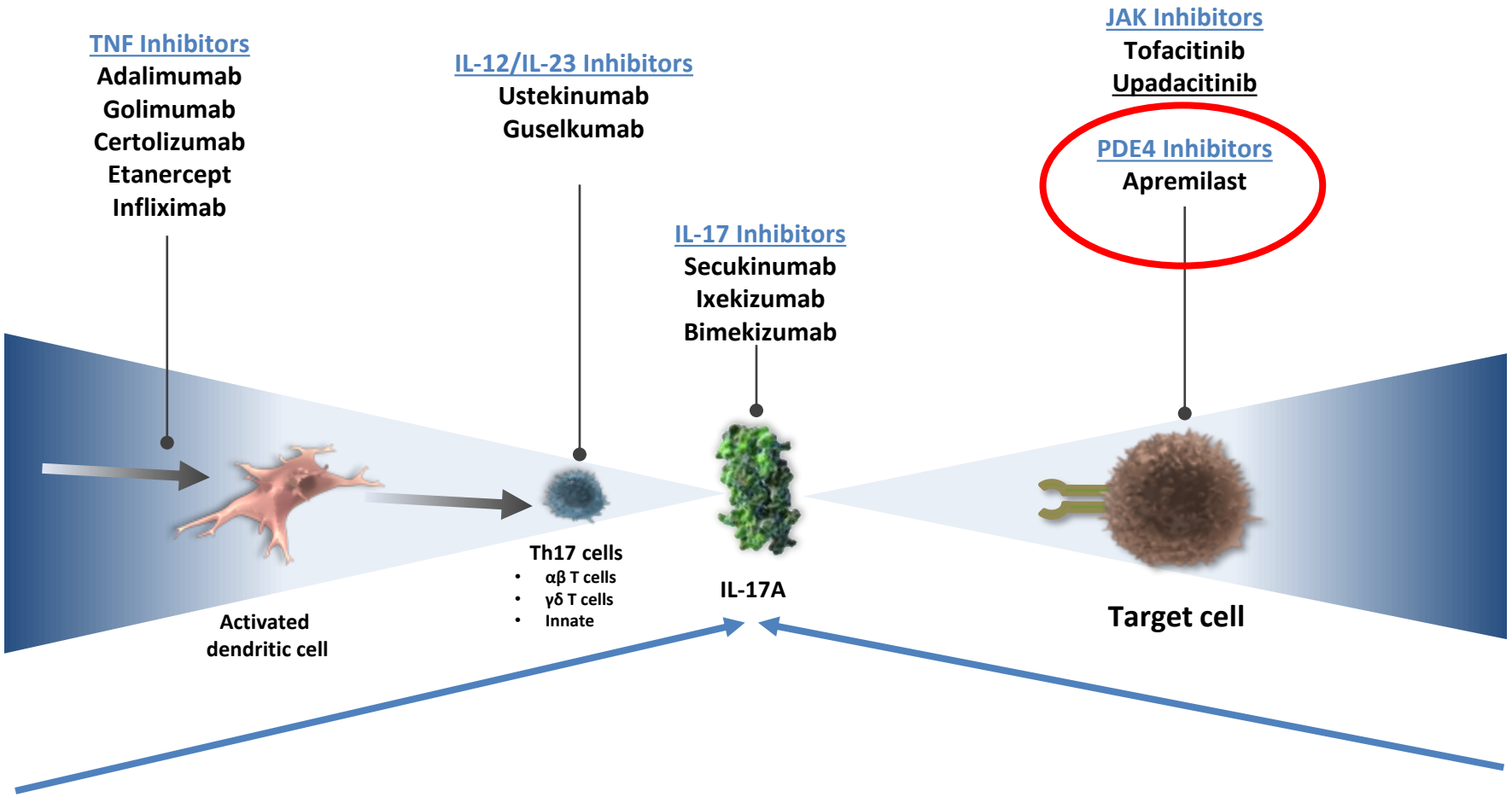






Glintborg et al. *Arthritis Rheum* 2011;63:382–90.

“Novel” approaches to PsA management



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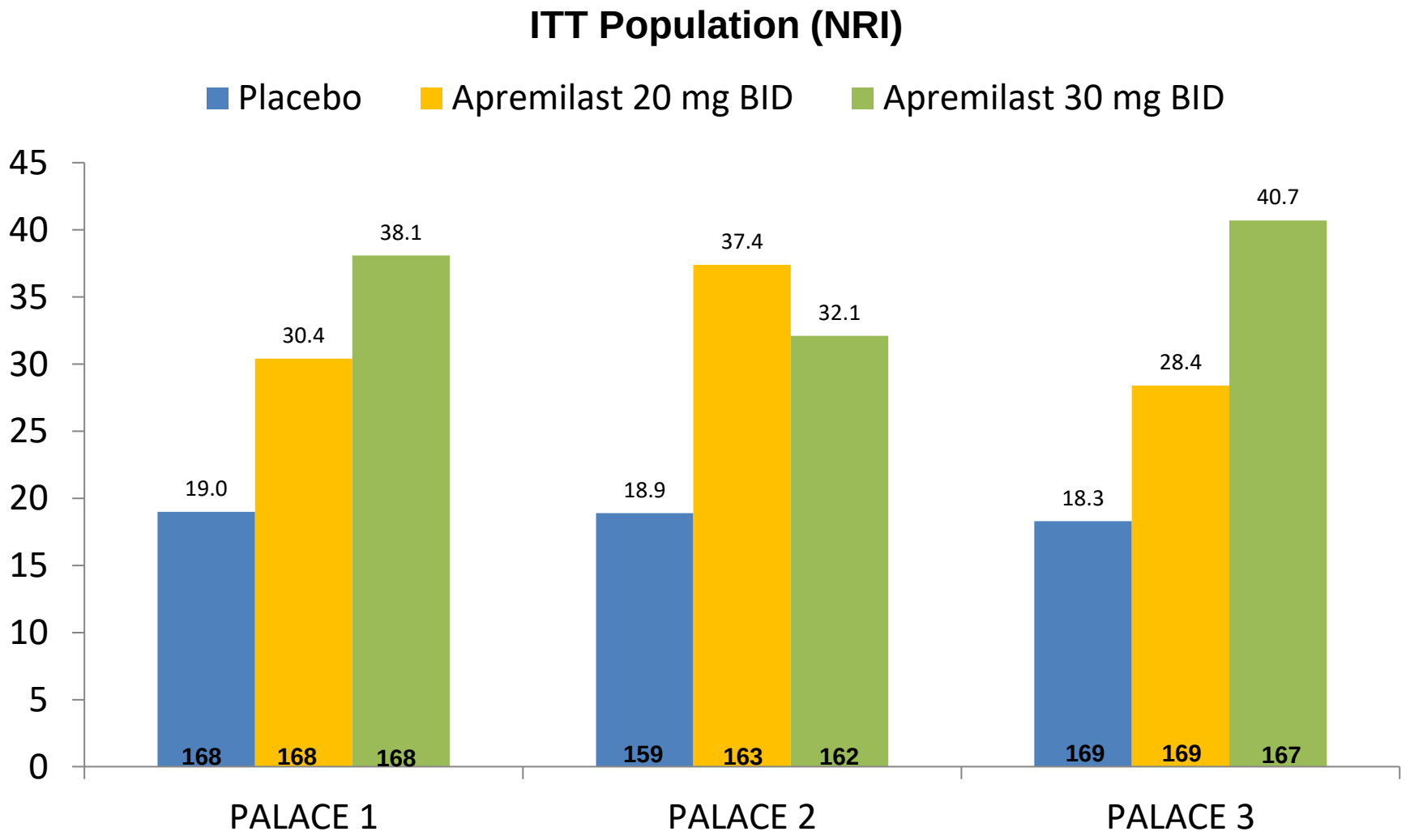
Apremilast (PDE4i) in PsA: ACR20 primary end point



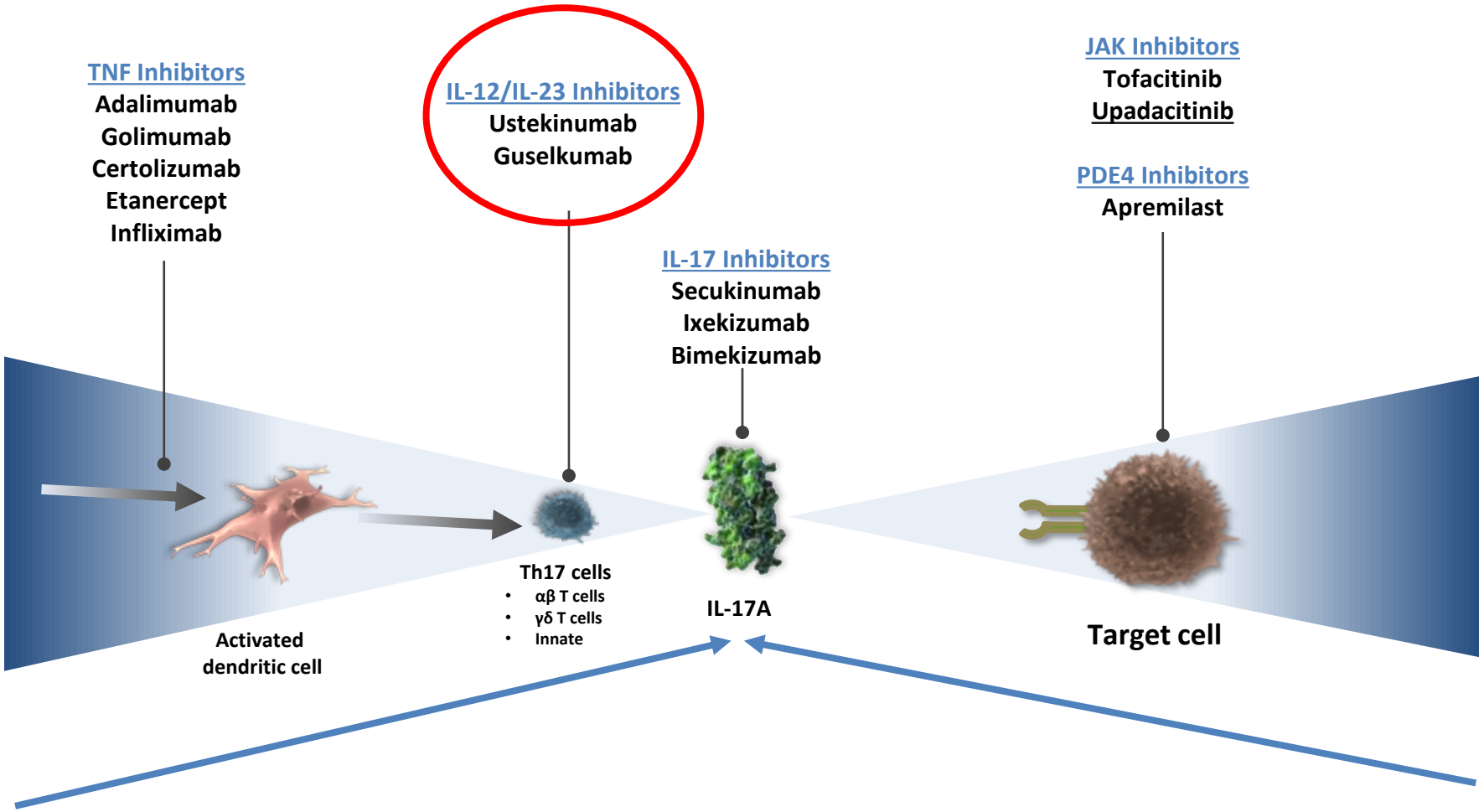
*P<0.05; §P<0.005; ‡P≤0.0001 vs. placebo.

ACR20=American College of Rheumatology 20; ITT=intent to treat; NRI=non-responder imputation.

Kavanaugh A, et al. EULAR 2014 [oral presentation]

Apremilast 20 mg is not licensed

“Novel” approaches to PsA management



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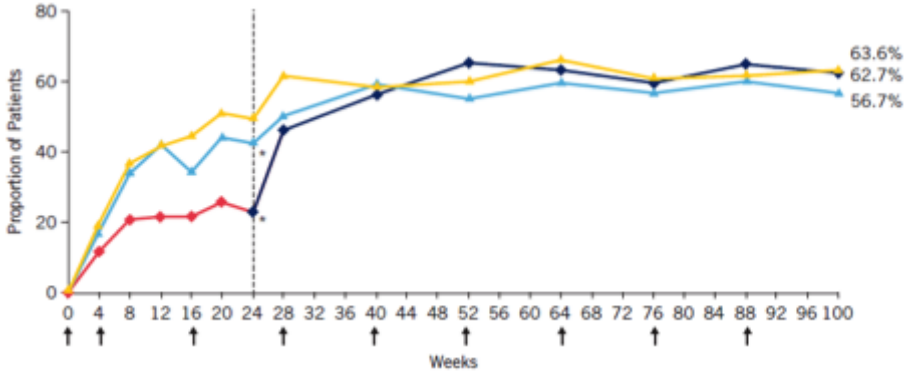
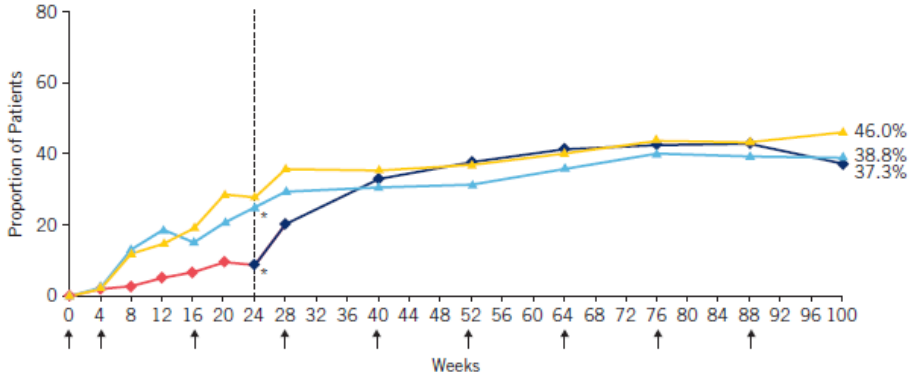
Ustekinumab Phase III – to week 100

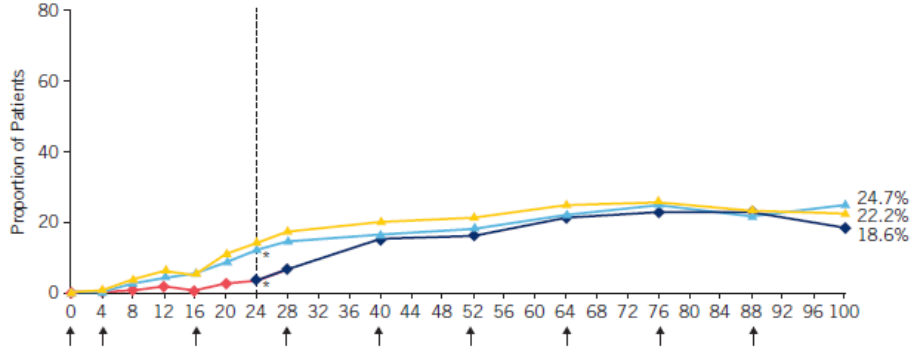
ACR 20



ACR 50



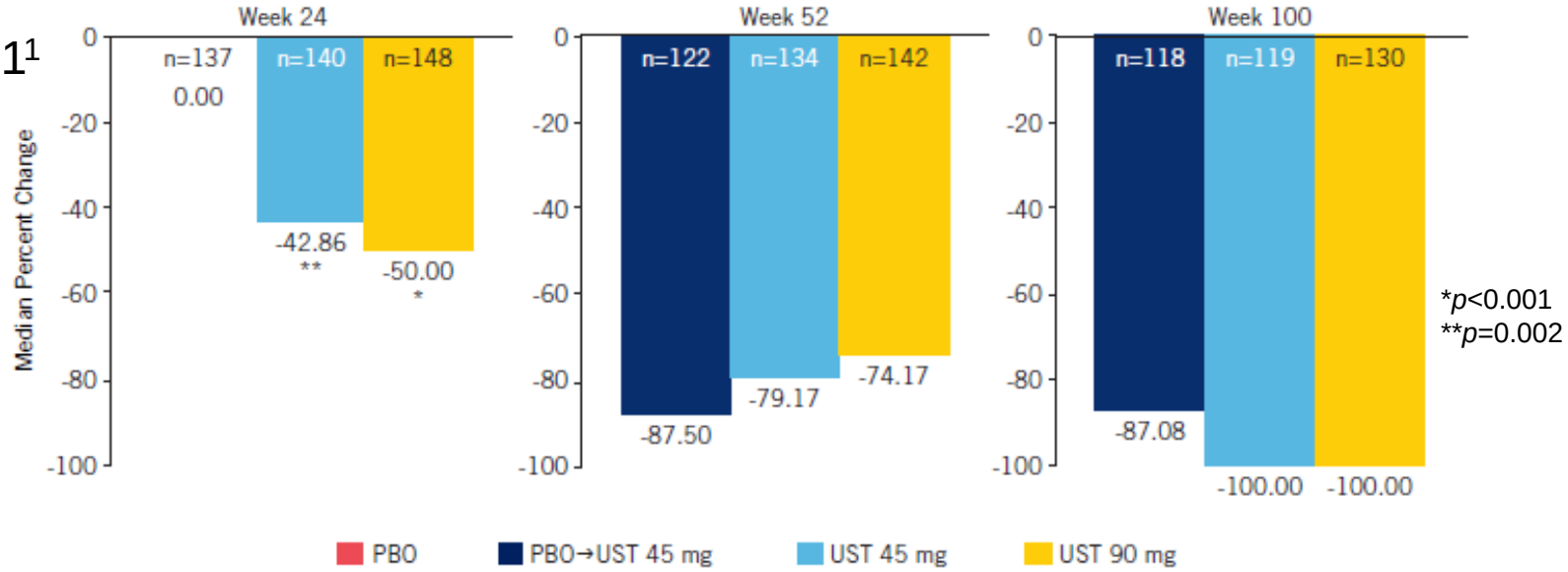
ACR 70



Kavanaugh A et al. Poster presented at EULAR 2014; SAT0396.

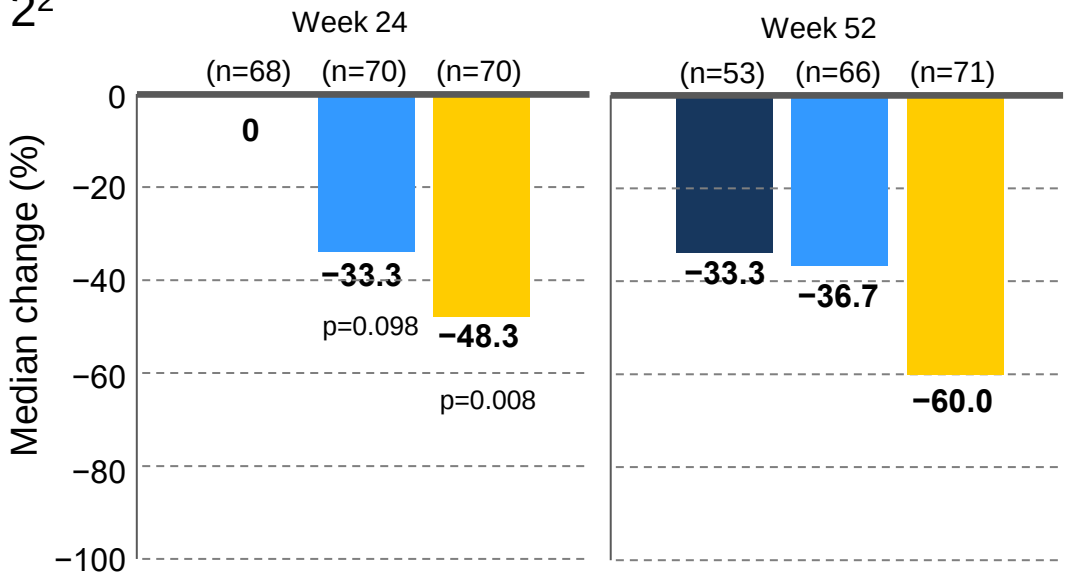
Ustekinumab Phase III – Enthesitis

PSUMMIT 1[1]



*p<0.001
**p=0.002

PSUMMIT 2[2]

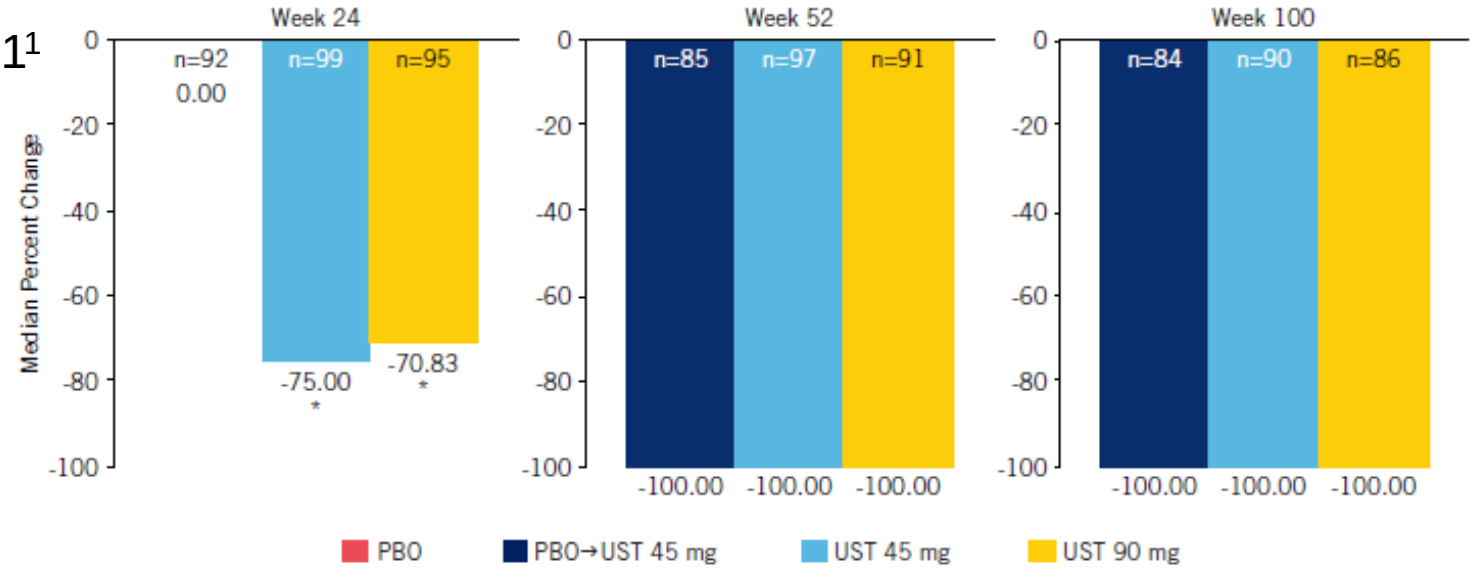


Enthesitis scoring based on Modified MASES Index. Includes only randomised patients with enthesitis at baseline.

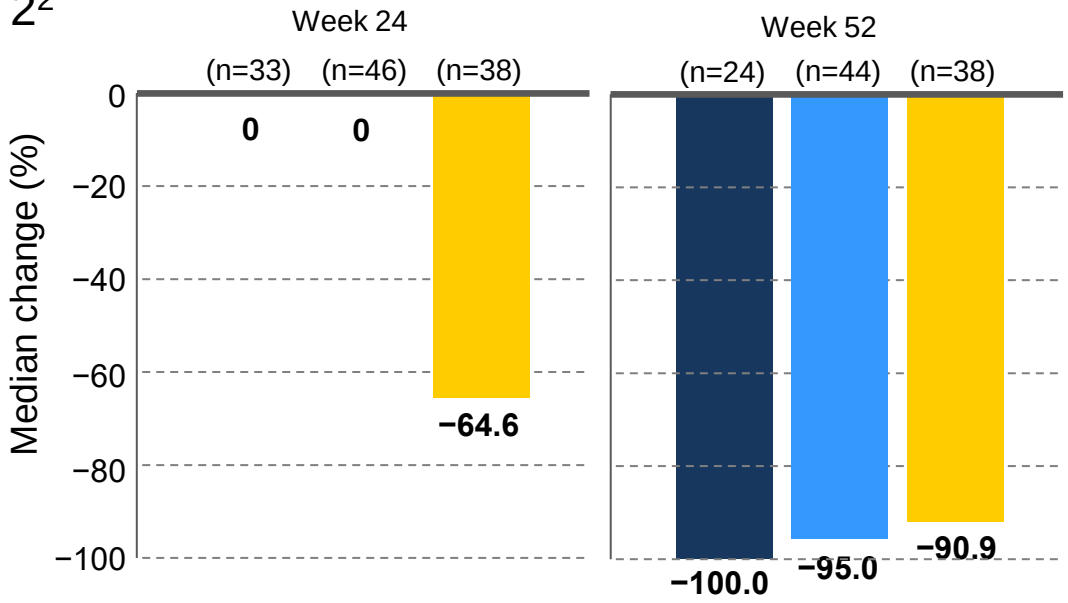
1. Kavanaugh A et al. Poster presented at EULAR 2014; SAT0396. 2. Ritchlin et al. Ann Rheum Dis 2014;73(6):990-9 Supplementary data.

Ustekinumab Phase III – Dactylitis

PSUMMIT 1[1]



PSUMMIT 2[2]



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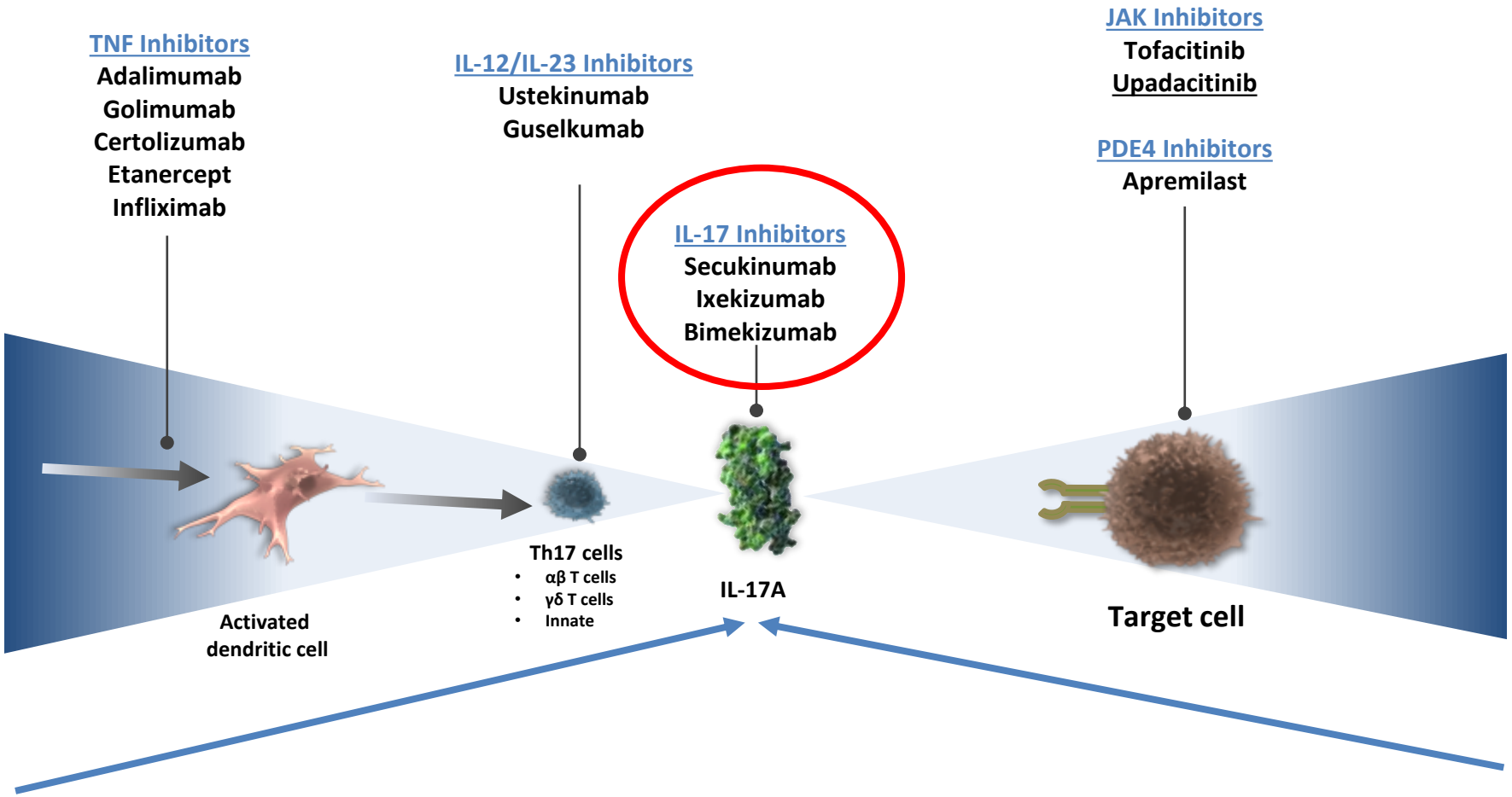
“Novel” approaches to PsA management



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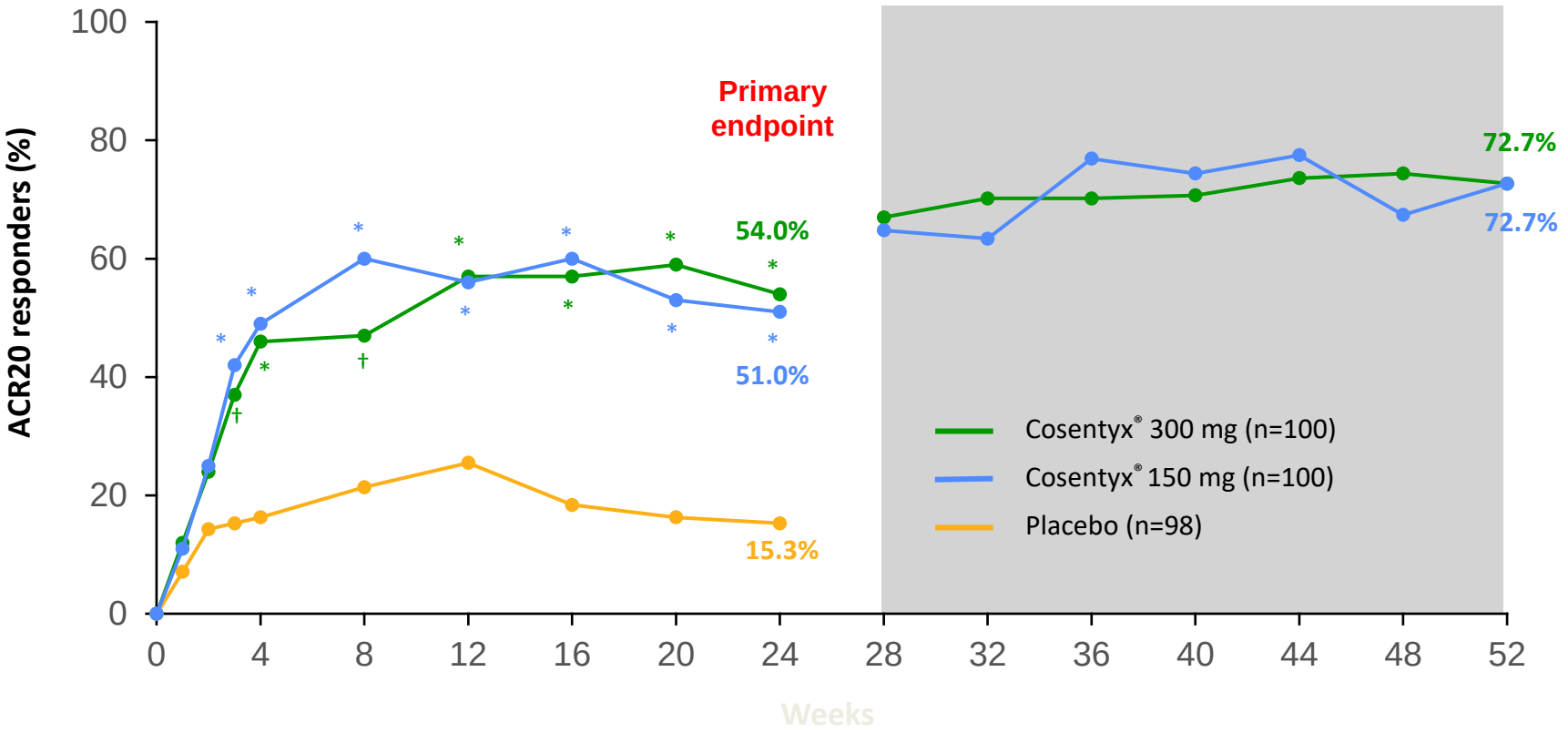
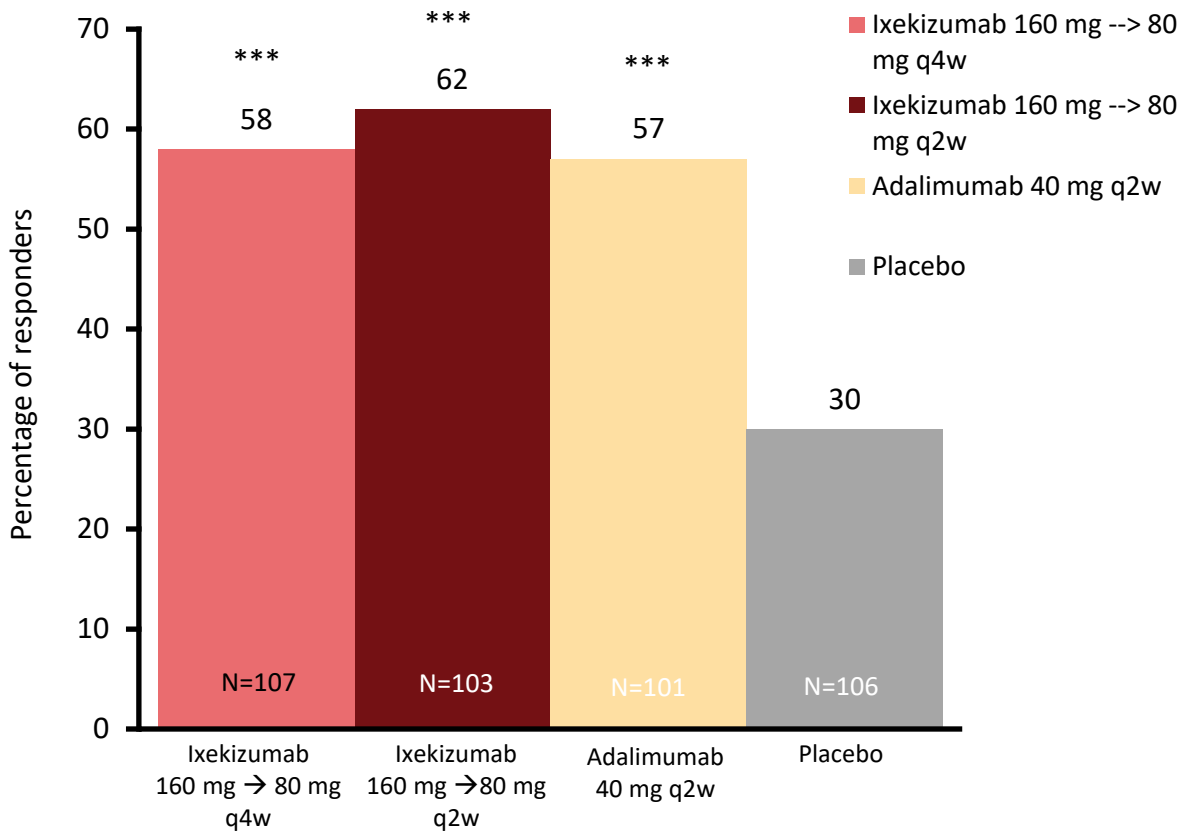
Secukinumab: FUTURE 2 study



*P < 0.0001 vs. placebo (P-values at Week 24 adjusted for multiplicity of testing).
Missing values were imputed as nonresponse (non-responder imputation) up to Week 24. Observed data from Week 28–52.

1. Mease P and McInnes IB. *Rheumatol Ther* 2016;3:5-29; 2. Rheumatology DOF UK 1; 3. Rheumatology DOF UK 102.

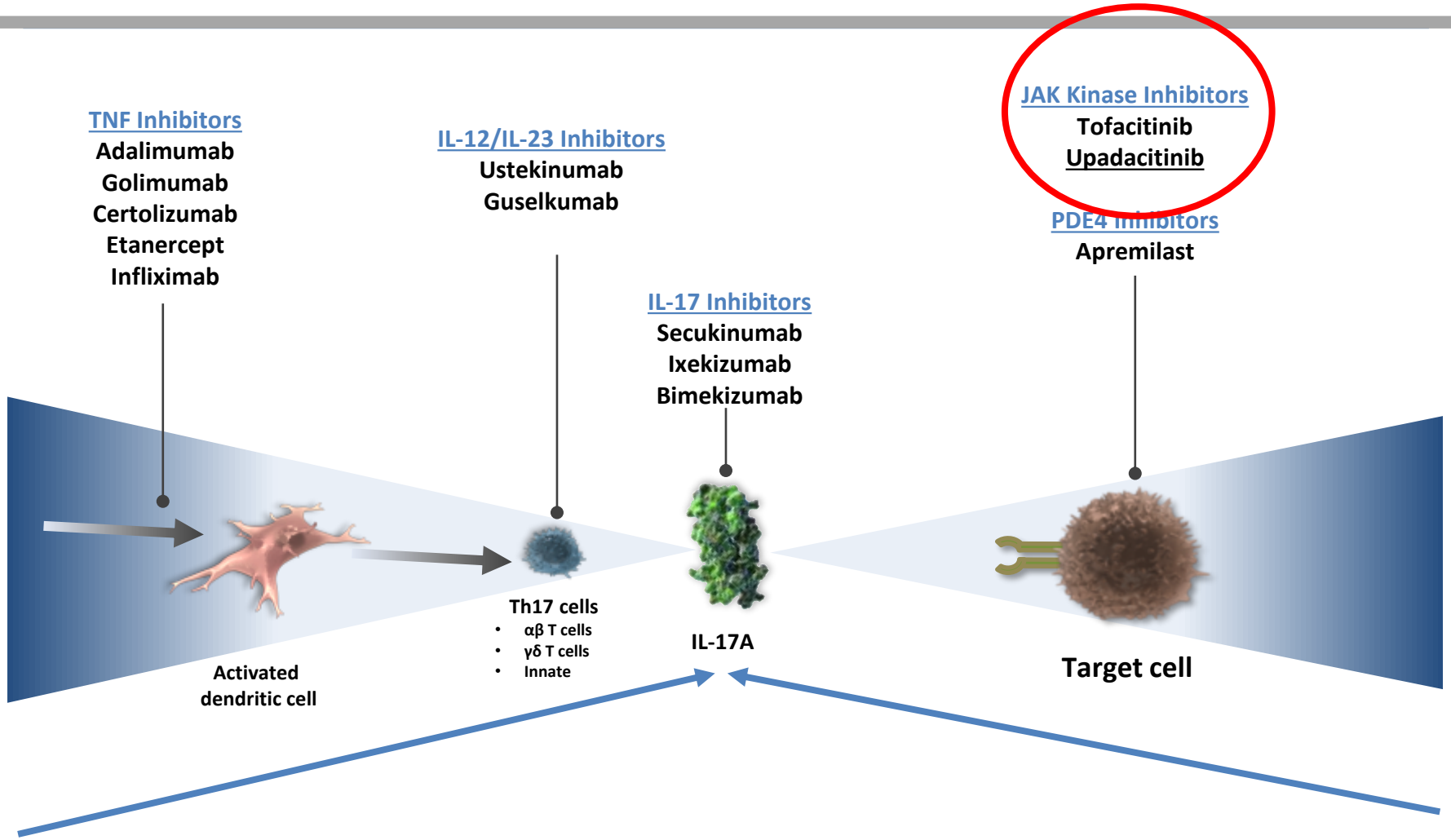
Ixekizumab: ACR20 Responses at Week 24 (SPIRIT-P1; Primary Endpoint)



***P<0.001 vs. placebo
All patients were naïve to anti-TNF treatment; non-responder imputation at Week 24
q2w, every two weeks; q4w, every 4 weeks

Mease PJ et al. *Arthritis Rheumatol* 2015;67(suppl 10):Abstract 977

“Novel” approaches to PsA management



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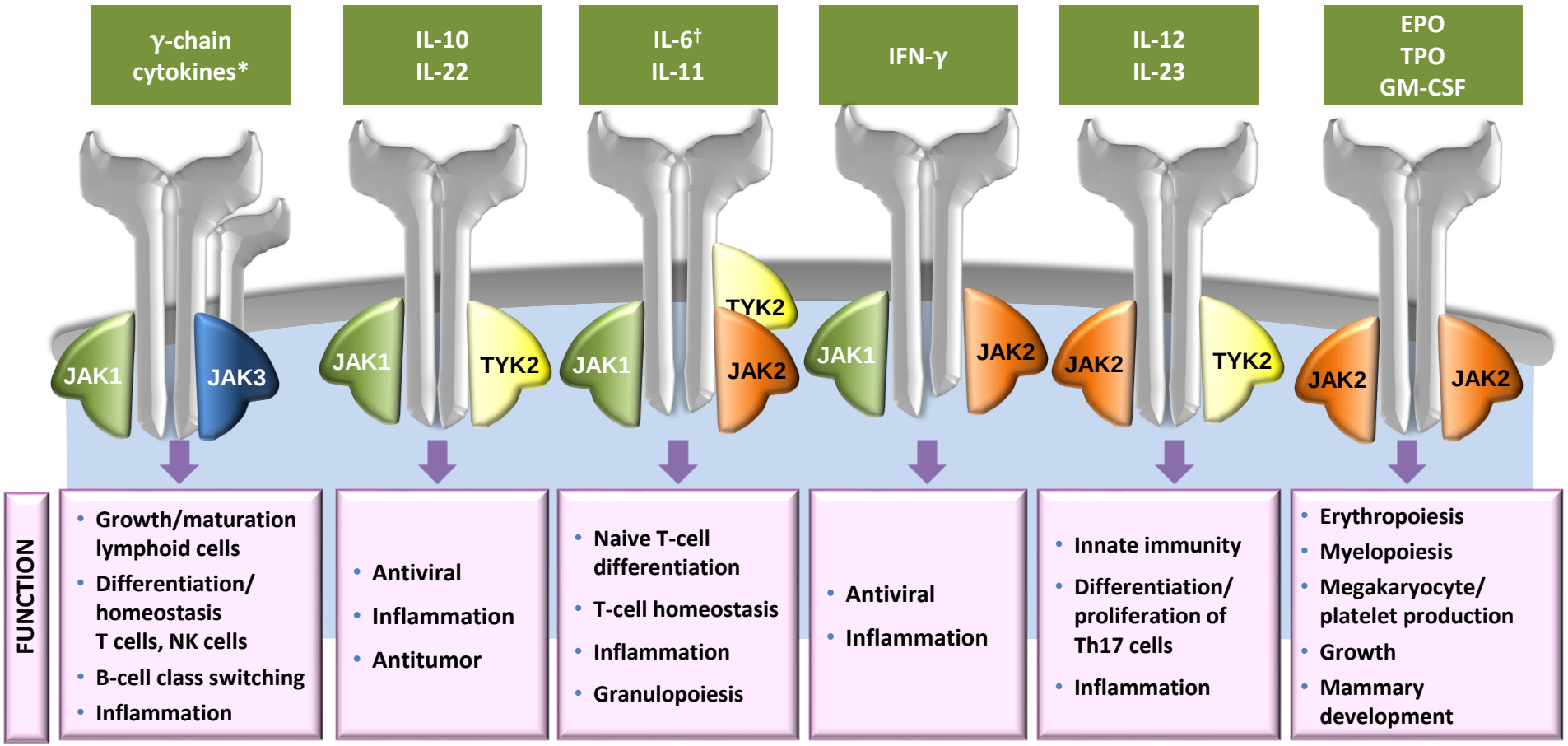
The biological significance of signaling through different JAK combinations



*Type II cytokine receptors such as those for IL-10, IL-19, IL-20, and IL-22 as well as gp130 subunit sharing receptors for IL-6 and IL-11 mainly signal through JAK1, but also associate with JAK2 and TYK2.[2]

†IL-10/IL-22 may have pro- or anti-inflammatory activities depending on the cellular environment and/or disease state.[4]

JAK=Janus kinase; NK=natural killer; Th=T helper; TYK=tyrosine kinase.

1. O'Sullivan LA, et al. *Mol Immunol.* 2007;44(10):2497-506; 2. Ghoreschi K, et al. *Immunol Rev.* 2009;228:273-287; 3. Vijayakrishnan L, et al. *Trends Pharmacol Sci*. 2011;32:25-34; 4. Sanjabi S, et al. *Curr Opin Pharmacol*. 2009;9(4):447-453.

JAK inhibitors

- MHRA warning April 2023
  - Cardiovascular events
  - Malignancy
  - Thromboembolism
  - Serious infections
  - Increased mortality
- Avoid unless no alternatives in:
  - Age over 65
  - Current or past smoker
  - Other cardiovascular or cancer risk factors
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  - Tofacitinib post authorisation: 4362 patients
    → 2020 MHRA/FDA/EMEA warning for tofacitinib
  - Baracitinib phase 3 study: 290 patients
    → 2023 MHRA/FDA/EMEA warning for <u>all</u> JAK inhibitors

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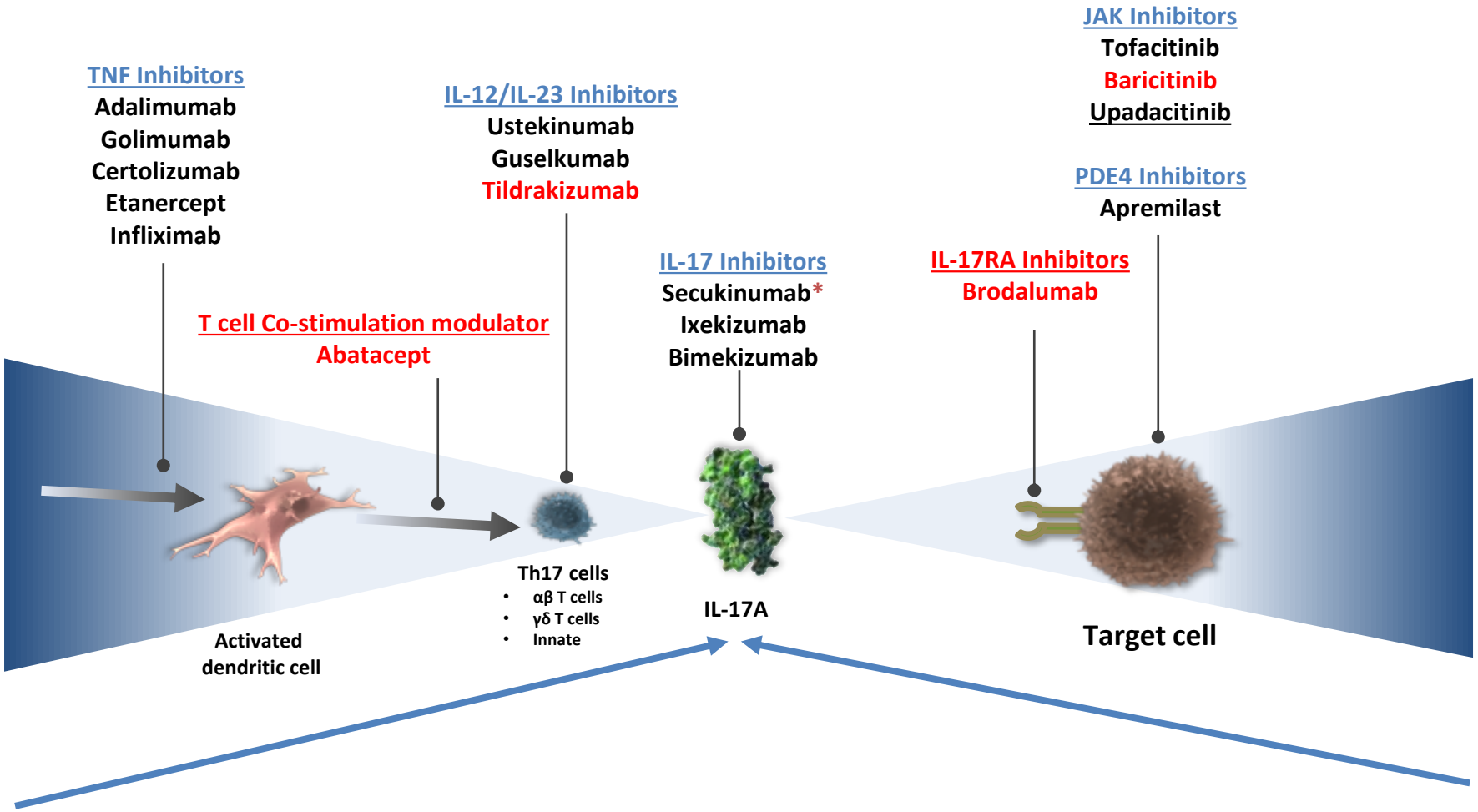
“Novel” approaches to PsA management - Future



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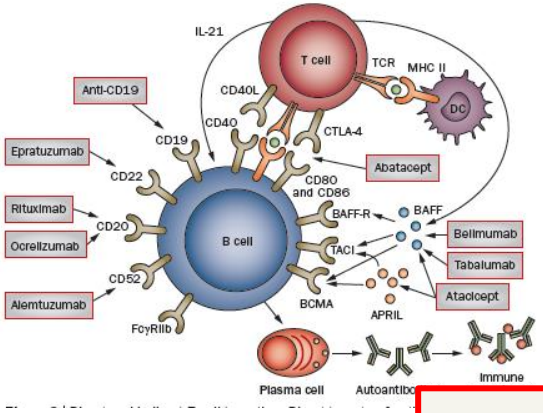
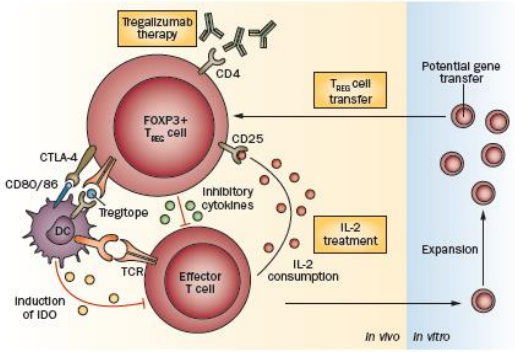
NICE and PsA treatment

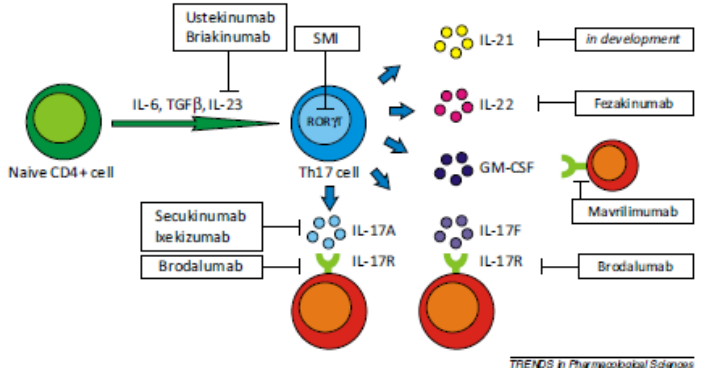
TA199 – Aug 2010	Etanercept/Infliximab/Adalumimab
TA220 – Feb 2011	Golumimab
TA340 – June 2015	Ustekinumab
TA433 – Feb 2017	Aprelimast
TA445 – May 2017	Certolizumab
	Secukinumab
TA537 - August 2018	Ixekizumab
TA543 - October 2018	Tofacitinib
TA803 - July 2022	Risankizumab
TA815 - August 2022	Guselkumab
TA768 - February 2022	Upadacitinib
TA916 - October 2023	Bimekizumab

~~Abatacept TA568~~	- March 2019 not resubmitted
Tildrakizumab / Brodalumab	- psoriasis only (to date)
Baricitinib	- rheumatoid arthritis only (to date)

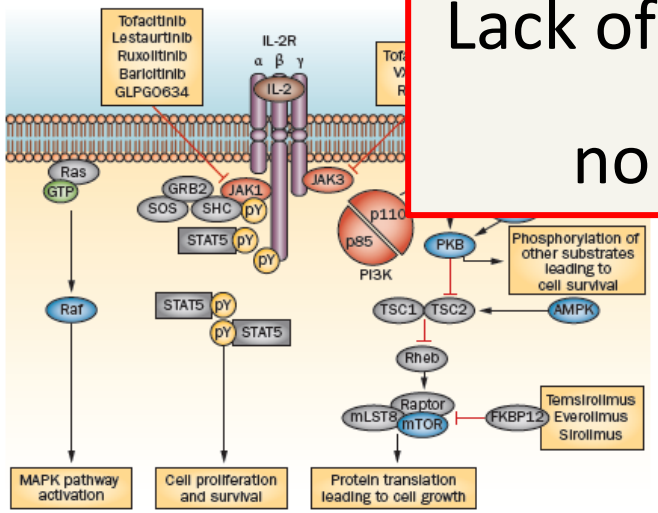
Novel targets and therapies+++++++





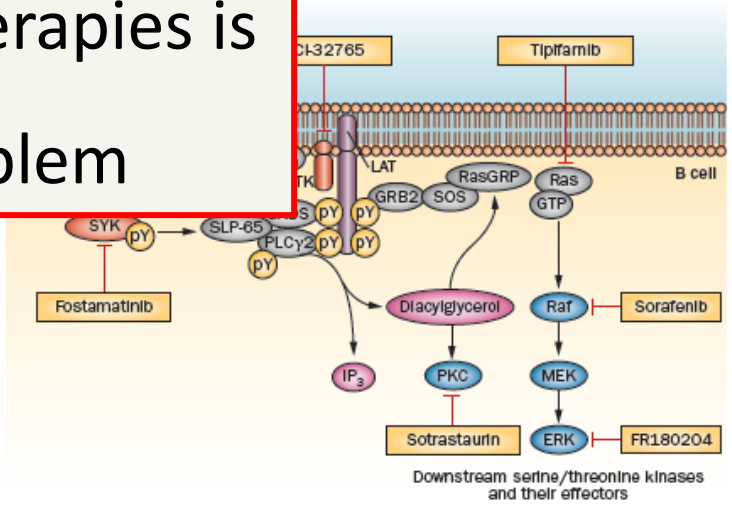


Lack of targets and therapies is no longer the problem



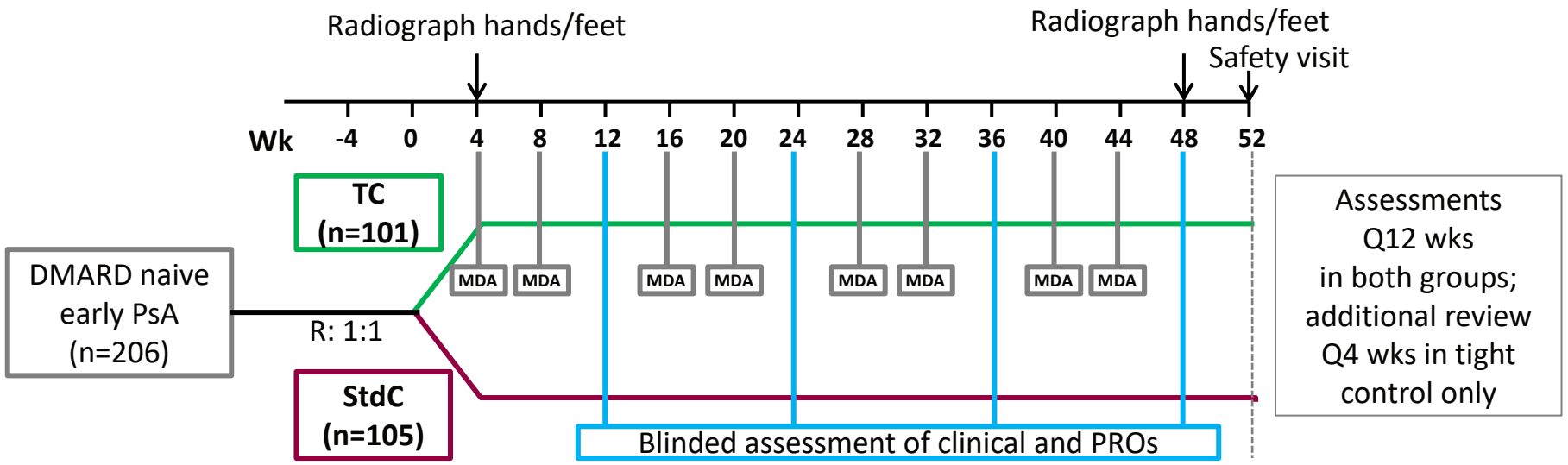
		Essential thrombocythaemia Acute leukaemia, lymphoma Multiple myeloma Prostate cancer Breast cancer	Phase II Phase II Phase I–II Phase II Phase II terminated
INCB18424 (topical formulation)	JAK1, JAK2	Psoriasis	Phase II
Baricitinib (LY3009104 or INCB28050)	JAK1, JAK2	RA Psoriasis Diabetic nephropathy	Phase II Phase IIb Phase II
CYT387	JAK1, JAK2	Myelofibrosis	Phase I– II
GLPG0634	JAK1, JAK2, TYK2	RA	Phase II
SAR302503 (TG101348)	JAK1, JAK2	Myelofibrosis	Phase I–II
Pacritinib (SB1518)	JAK2	Myelofibrosis	Phase II

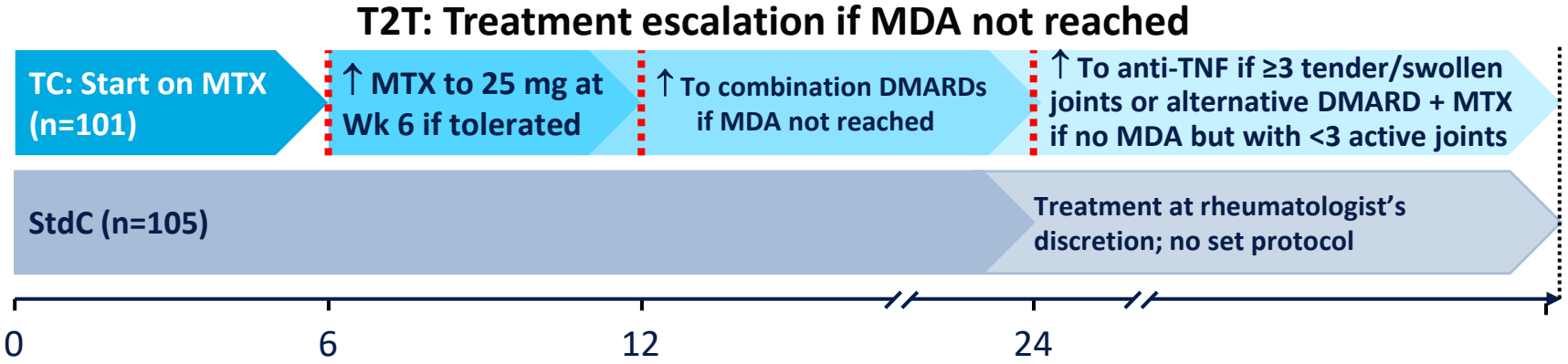
Abbreviations: JAK, Janus kinase; jakinibs, JAK inhibitors; JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis; TYK2, tyrosine kinase 2.



Burmeister *Nat Rev Rheum* 2014;10:77-88
Koenders *Trends in Pharmacol Sci* 2015
O'Shea *Nat Rev Rheum* 2013;9:173-82

TICOPA: Tight control in PsA – study design



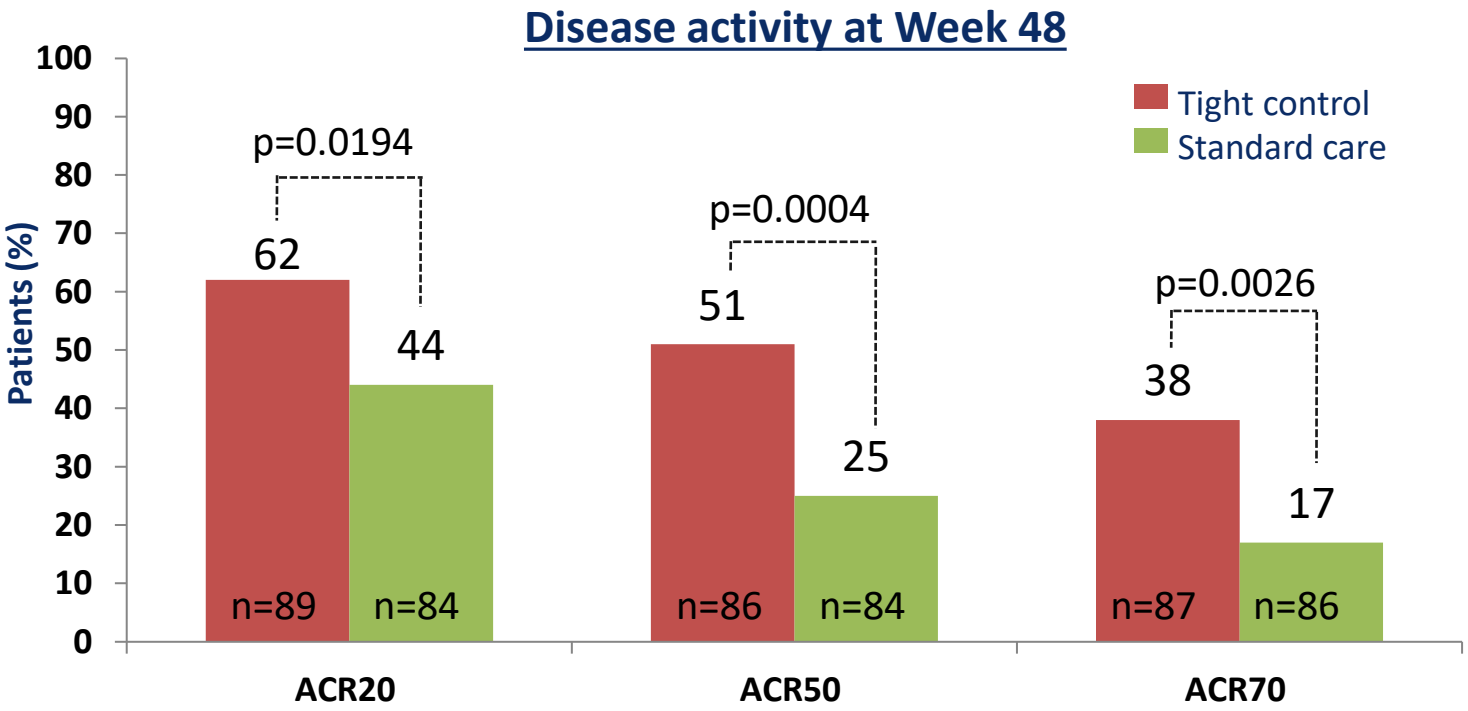


MDA, minimum disease activity; MTX, methotrexate; R, randomisation; StdC, standard care; TC, tight control; T2T, treat to target

Coates et al. *Lancet* 2015;386;2489–98

T2T in PsA - TICOPA study

- **Recruitment:** N=206; early PsA
- **Primary outcome:** ACR20 at Week 48
  - Tight control using T2T improved outcomes



Coates et al. *Lancet* 2015;386;2489–98

Unmet need in PsA treatment

- RCTs based on polyarticular PsA (except methotrexate studies)
- Mono/oligoarthritis
  - Limited data; not included in phase III RCTs
  - Therefore, effectively excluded by most biologic guidelines
- Enthesitis and dactylitis
  - Limited data, usually secondary outcomes
- Juvenile PsA = limited data
  - Classification issues
  - Often part of Juvenile SpA
- What order to use drugs
  (TNF→IL-17 may not be same as IL-17→TNF)
- Cost of therapies. Correct dose?

1. Reviewed in: Katsicas & Russo Pediatr Rheumatol Online J 2016;14:17