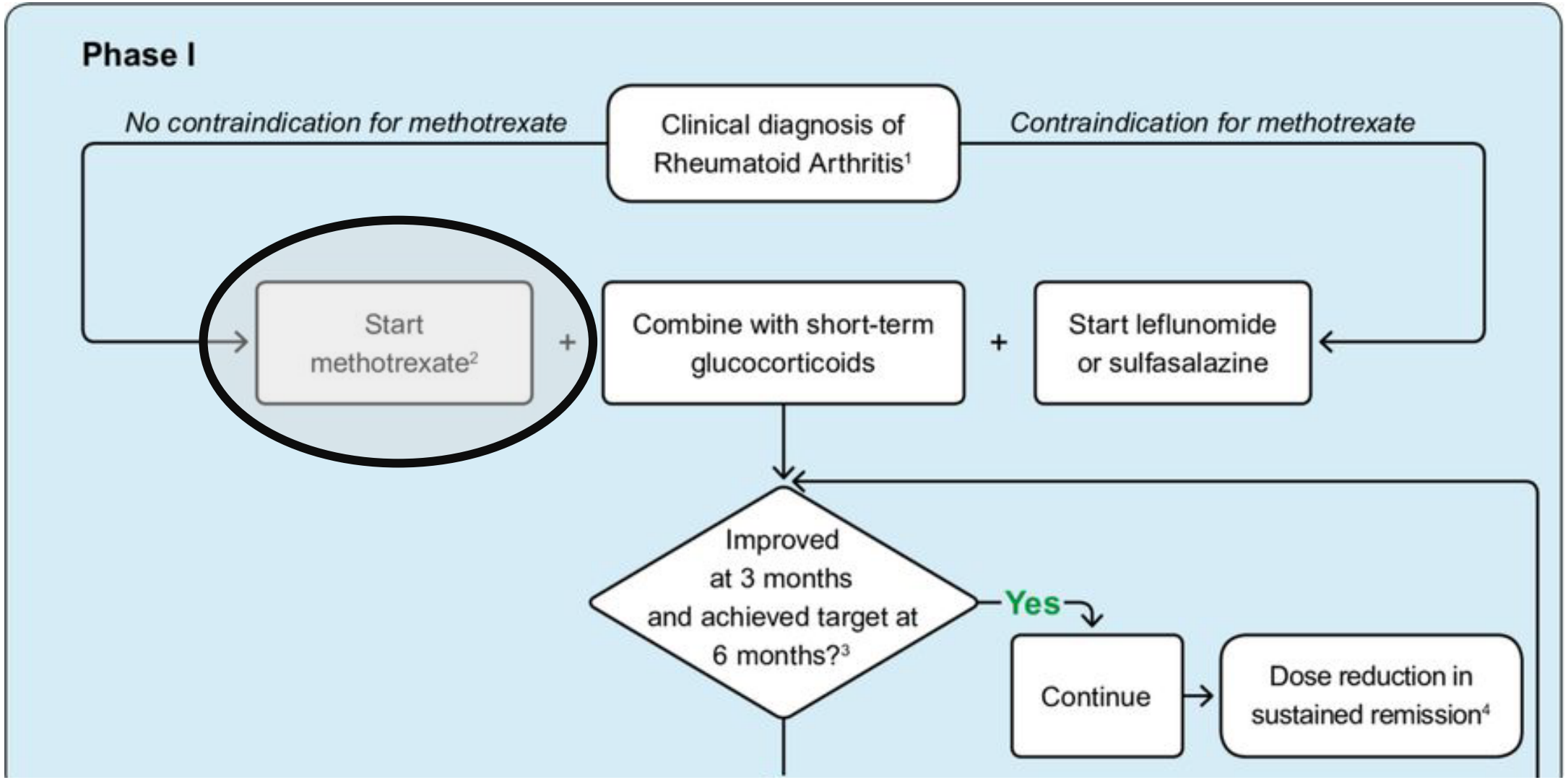
USZ Universitäts Spital Zürich

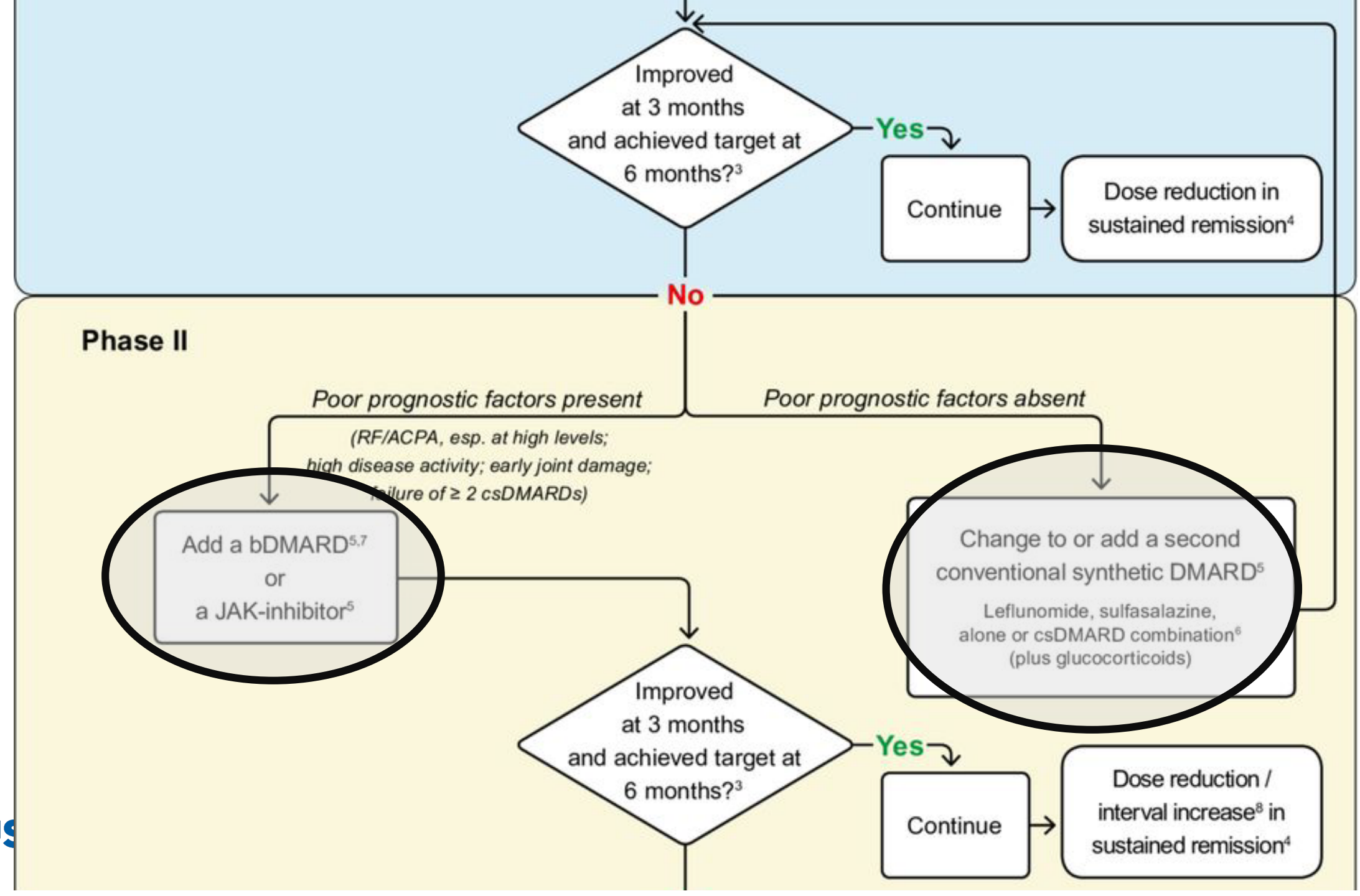
Rheumatoide Arthritis: Therapiekombinationen

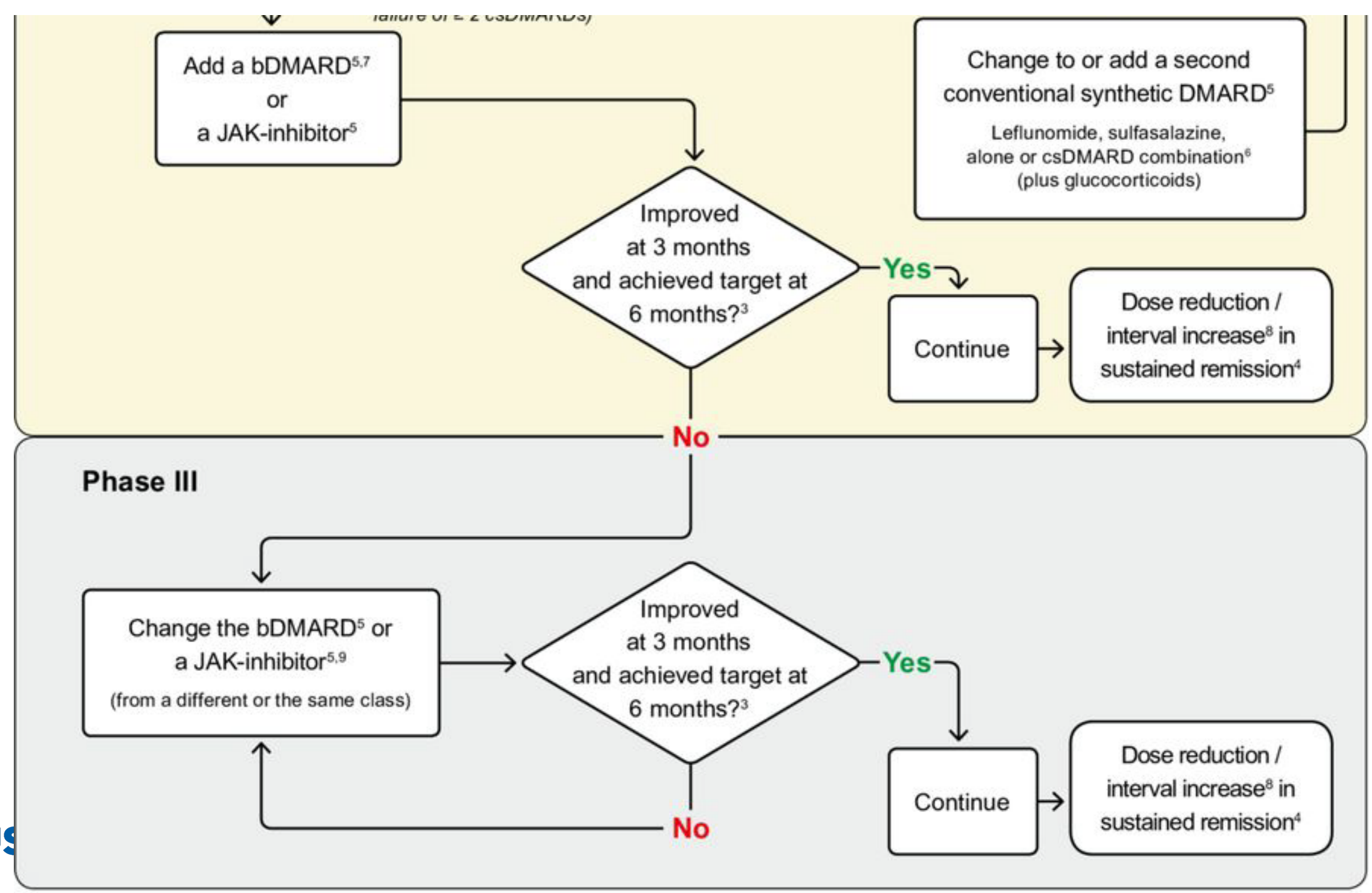
Dr. med. Raphael Micheroli, Oberarzt

Rheumaworkshop, 02.12.2021



Smolen et al, ARD, 2020


Improved
at 3 months
and achieved target at
6 months?[3]
Yes
Continue
Dose reduction in
sustained remission[4]
No
Phase II
Poor prognostic factors present
(RF/ACPA, esp. at high levels;
high disease activity; early joint damage;
failure of ≥ 2 csDMARDs)
Poor prognostic factors absent
Add a bDMARD[5,7]
or
a JAK-inhibitor[5]
Change to or add a second
conventional synthetic DMARD[5]
Leflunomide, sulfasalazine,
alone or csDMARD combination[6]
(plus glucocorticoids)
Improved
at 3 months
and achieved target at
6 months?[3]
Yes
Continue
Dose reduction /
interval increase[8] in
sustained remission[4]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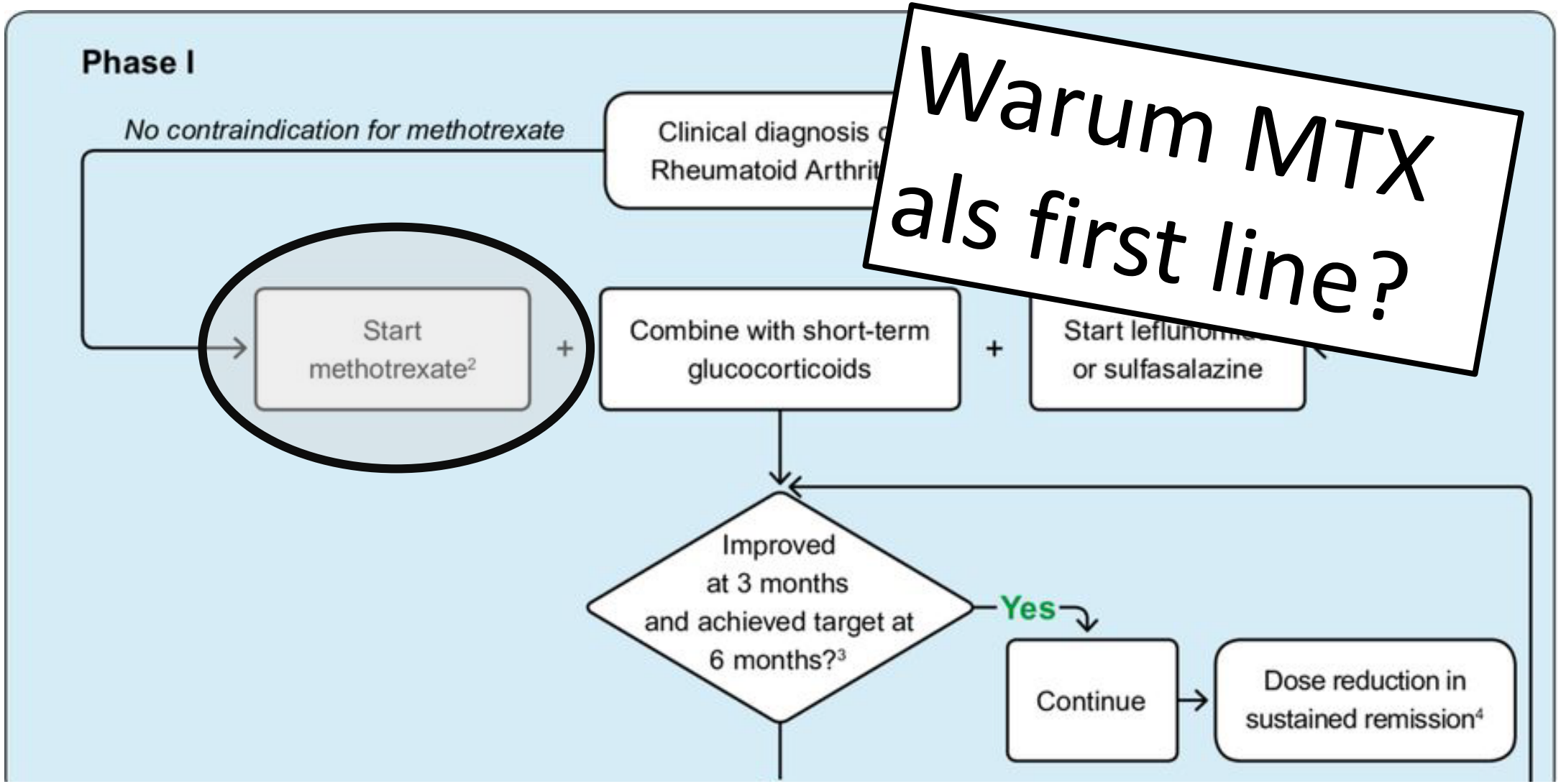
or
a JAK-inhibitor[5]
Change to or add a second conventional synthetic DMARD[5]
Leflunomide, sulfasalazine, alone or csDMARD combination[6] (plus glucocorticoids)
Improved at 3 months and achieved target at 6 months?[3]
Yes
Continue
Dose reduction / interval increase[8] in sustained remission[4]
No
Phase III
Change the bDMARD[5] or a JAK-inhibitor[5,9]
(from a different or the same class)
Improved at 3 months and achieved target at 6 months?[3]
Yes
Continue
Dose reduction / interval increase[8] in sustained remission[4]
No



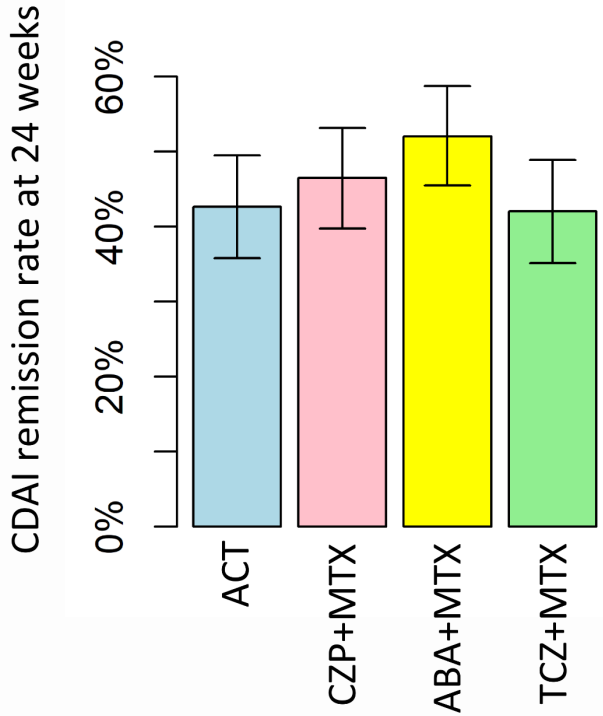
Warum MTX als first line?

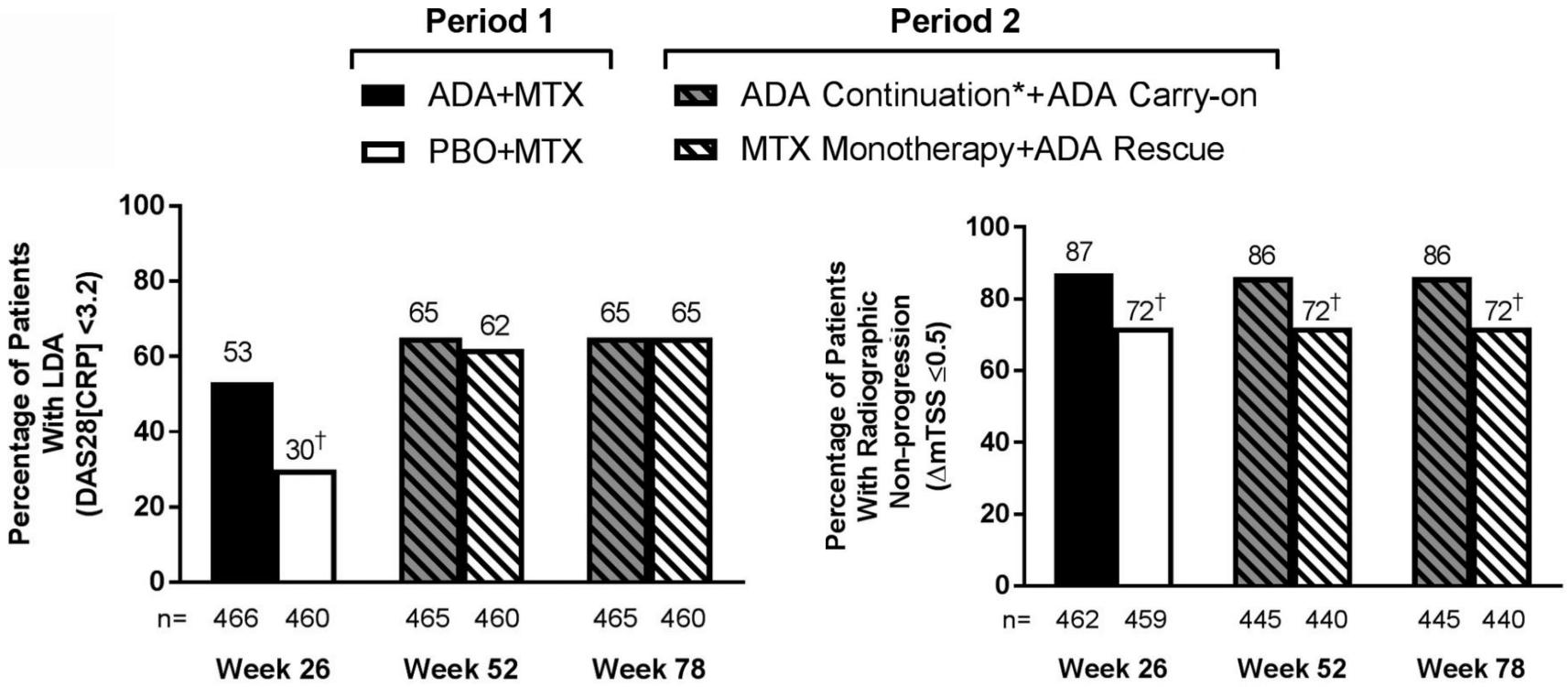
Smolen et al, ARD, 2020

Warum MTX als Anchor Drug?

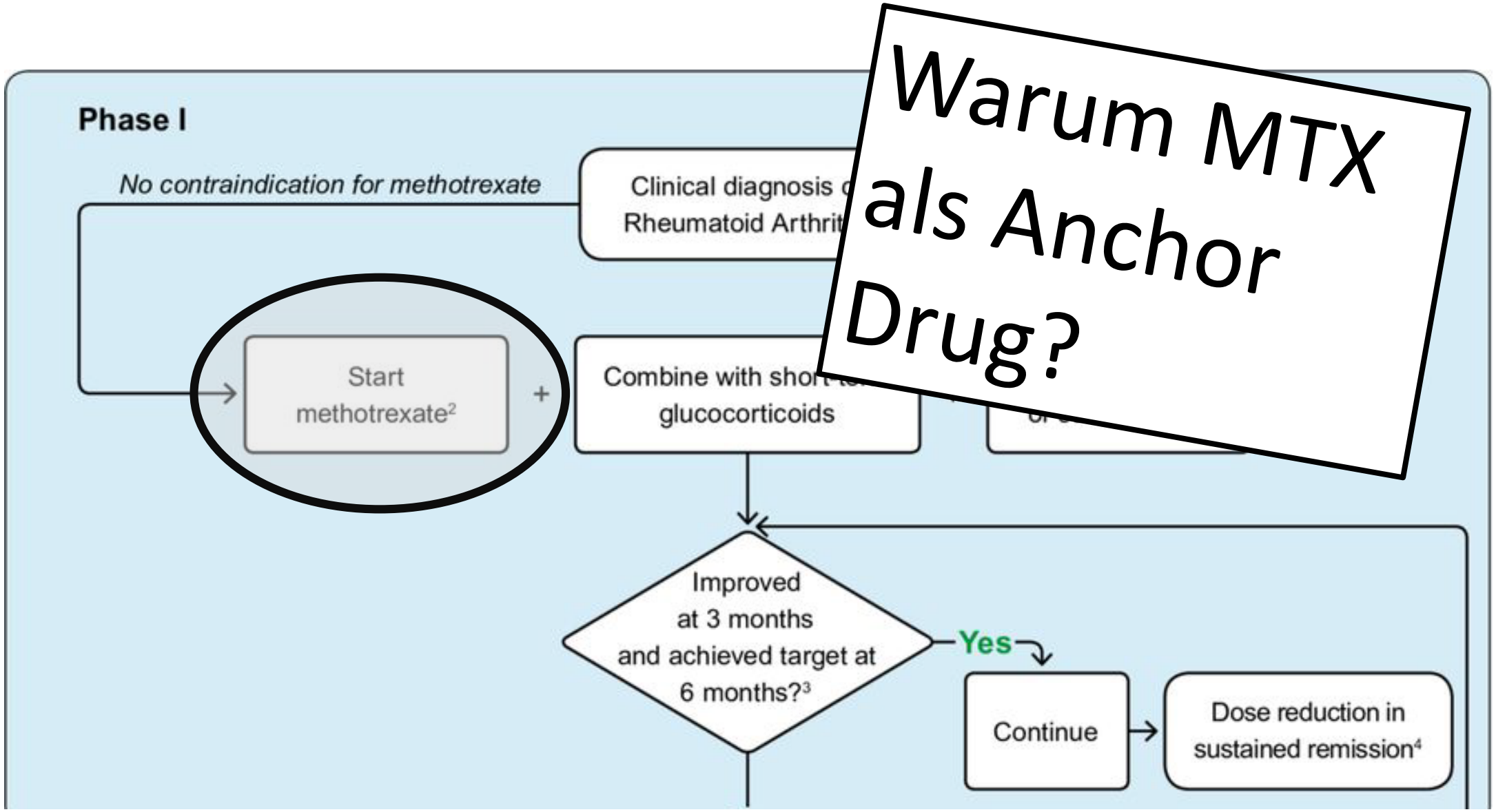
- **Längste Erfahrung – auch in Kombination**
- **Tiefe AE-Rate im Vergleich zu tsDMARD/bDMARD**
- **Flexible Dosierung**
- **Tiefe Kosten**

Warum nicht direkt Kombitherapie?



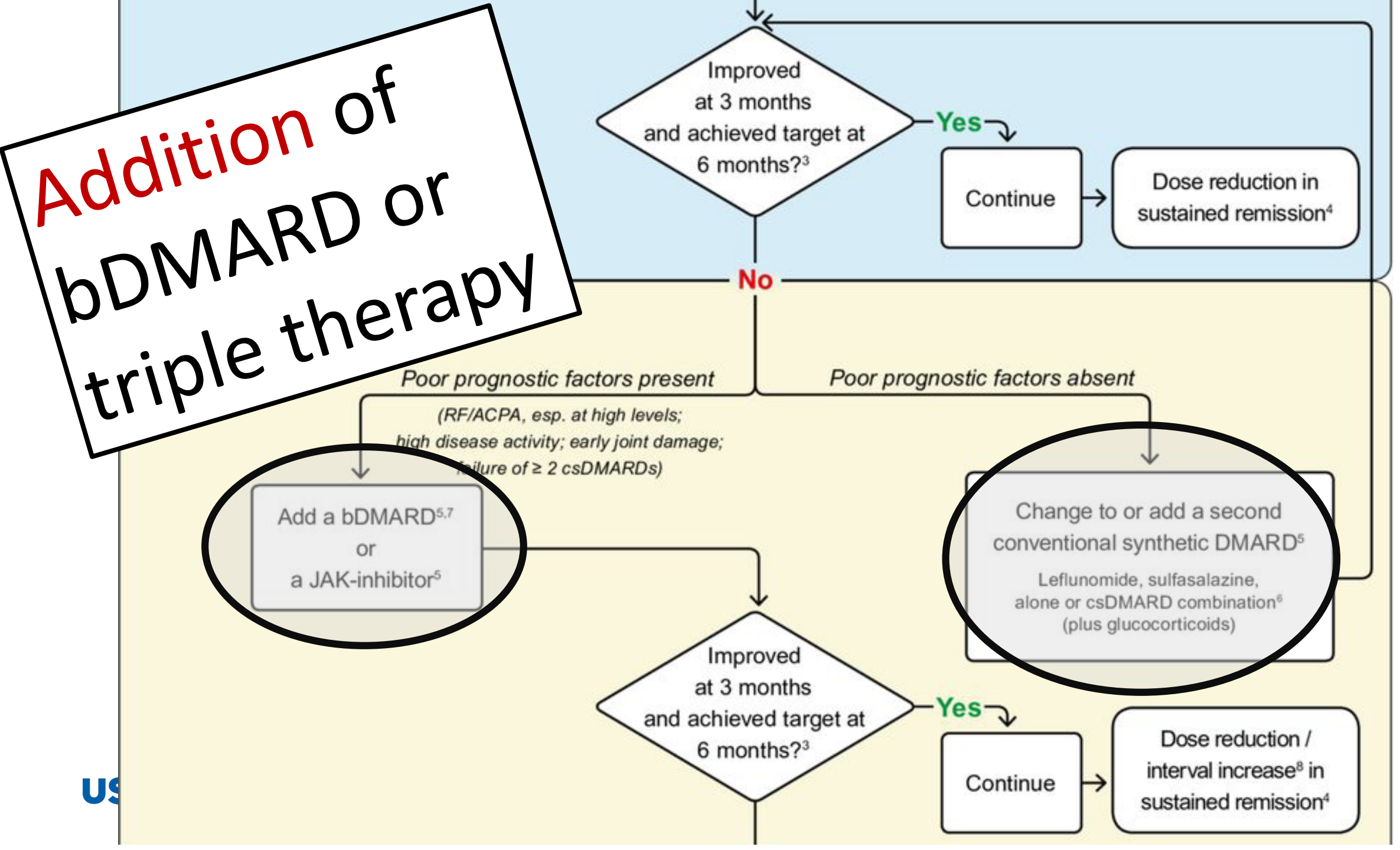


Lund et al, ACR, 2019 & Kavanaugh et al, ARD, 2018



Warum MTX als Anchor Drug?

Smolen et al, ARD, 2020


Addition of bDMARD or triple therapy
Improved at 3 months and achieved target at 6 months?[3]
Yes
Continue
Dose reduction in sustained remission[4]
No
Poor prognostic factors present
(RF/ACPA, esp. at high levels; high disease activity; early joint damage; failure of ≥ 2 csDMARDs)
Poor prognostic factors absent
Add a bDMARD[5,7] or a JAK-inhibitor[5]
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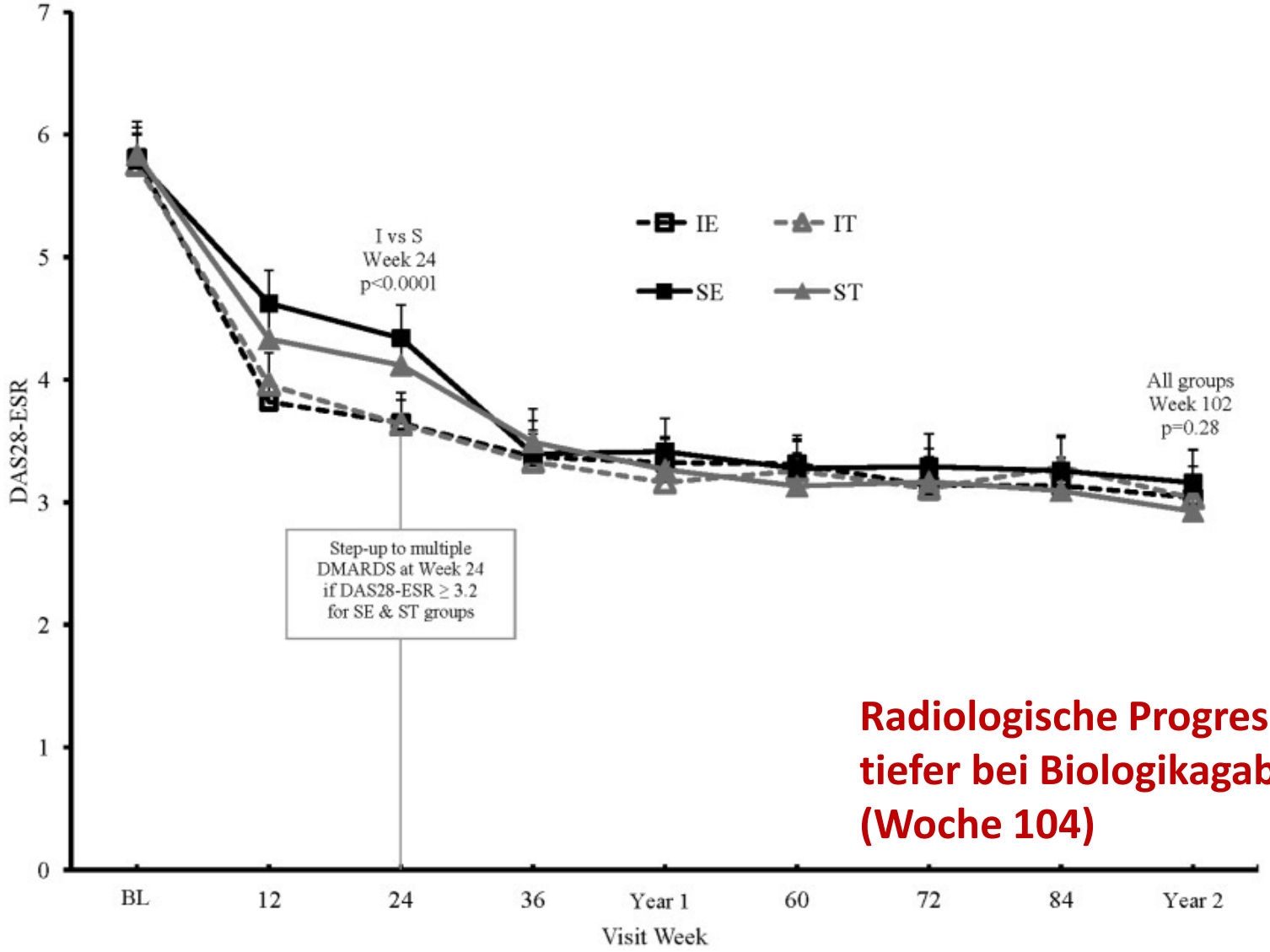
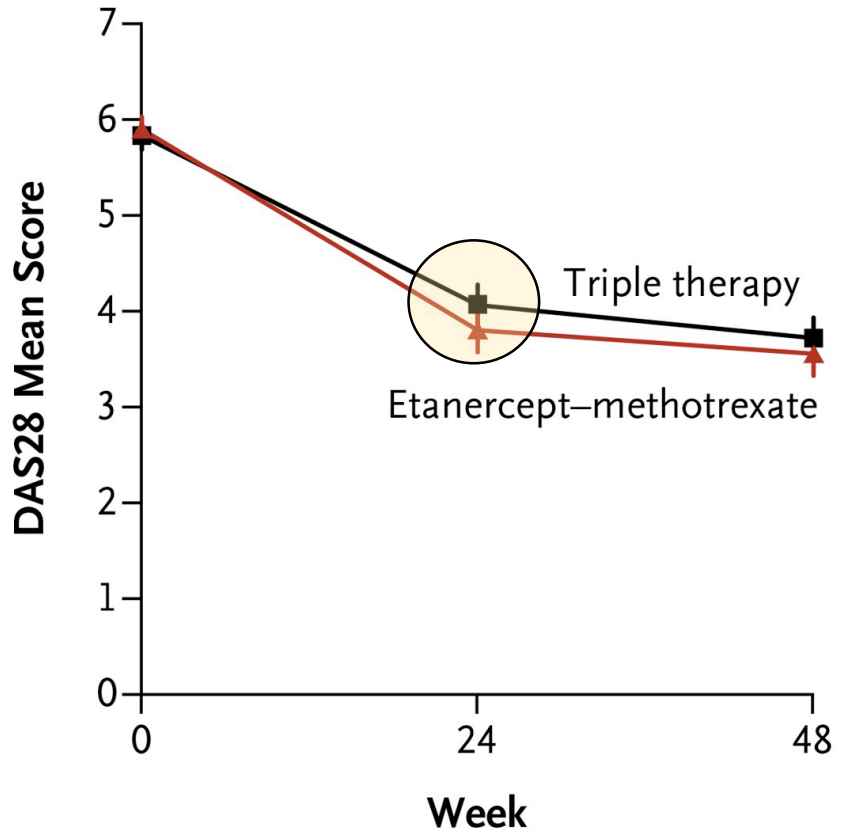
Triple (T)
vs.
MTX/ETN (E)



Radiologische Progression tiefer bei Biologikagabe (Woche 104)

Moreland et al, A&R, 2012

A Change in DAS28 According to Initial Treatment



No. Evaluated			
Triple therapy	178	157	154
Etanercept–methotrexate	175	161	155

O'Dell, NEJM, 2013

Table 3. Most Frequently Reported Adverse Events.*

Variable	Triple Therapy (N=222)	Etanercept (N=219)
	no. of patients (%)	
Death	0	1 (0.5)
Discontinuation of treatment owing to adverse event	12 (5.4)	5 (2.3)
Any adverse event	170 (76.6)	165 (75.3)
Adverse events in ≥5% of patients†		
Eye disorder	21 (9.5)	17 (7.8)
Gastrointestinal disorder‡	66 (29.7)	47 (21.5)
General disorder or administration-site condition	38 (17.1)	41 (18.7)
Infection or infestation§	56 (25.2)	82 (37.4)
Injury, poisoning, or procedural complication	18 (8.1)	21 (9.6)
Laboratory abnormalities	29 (13.1)	26 (11.9)
Musculoskeletal or connective-tissue disorder	44 (19.8)	39 (17.8)
Nervous system disorder	33 (14.9)	41 (18.7)
Respiratory, thoracic, or mediastinal disorder	28 (12.6)	24 (11.0)
Skin or subcutaneous tissue disorder‡	22 (9.9)	36 (16.4)
Any serious adverse event	25 (11.3)	26 (11.9)
Serious adverse events in ≥1% of patients		
Gastrointestinal disorder	4 (1.8)	4 (1.8)
Infection or infestation	4 (1.8)	9 (4.1)
Renal or urinary disorder	0	3 (1.4)
Surgical or medical procedure	3 (1.4)	4 (1.8)
Vascular disorder	3 (1.4)	4 (1.8)
Cardiac disorder	4 (1.8)	0
Respiratory, thoracic, or mediastinal disorder	3 (1.4)	0
Other	6 (2.7)	3 (1.4)

* The adverse events are listed according to the therapy that the participant was receiving at the time of the event.
† A total of 561 adverse events were reported in 5% or more of the patients in the triple-therapy group, and 614 in the etanercept–methotrexate group.
‡ $P<0.05$ for the between-group comparison, assuming equal follow-up time and independent treatment groups.
§ $P=0.006$ for the between-group comparison, assuming equal follow-up time and independent treatment groups.

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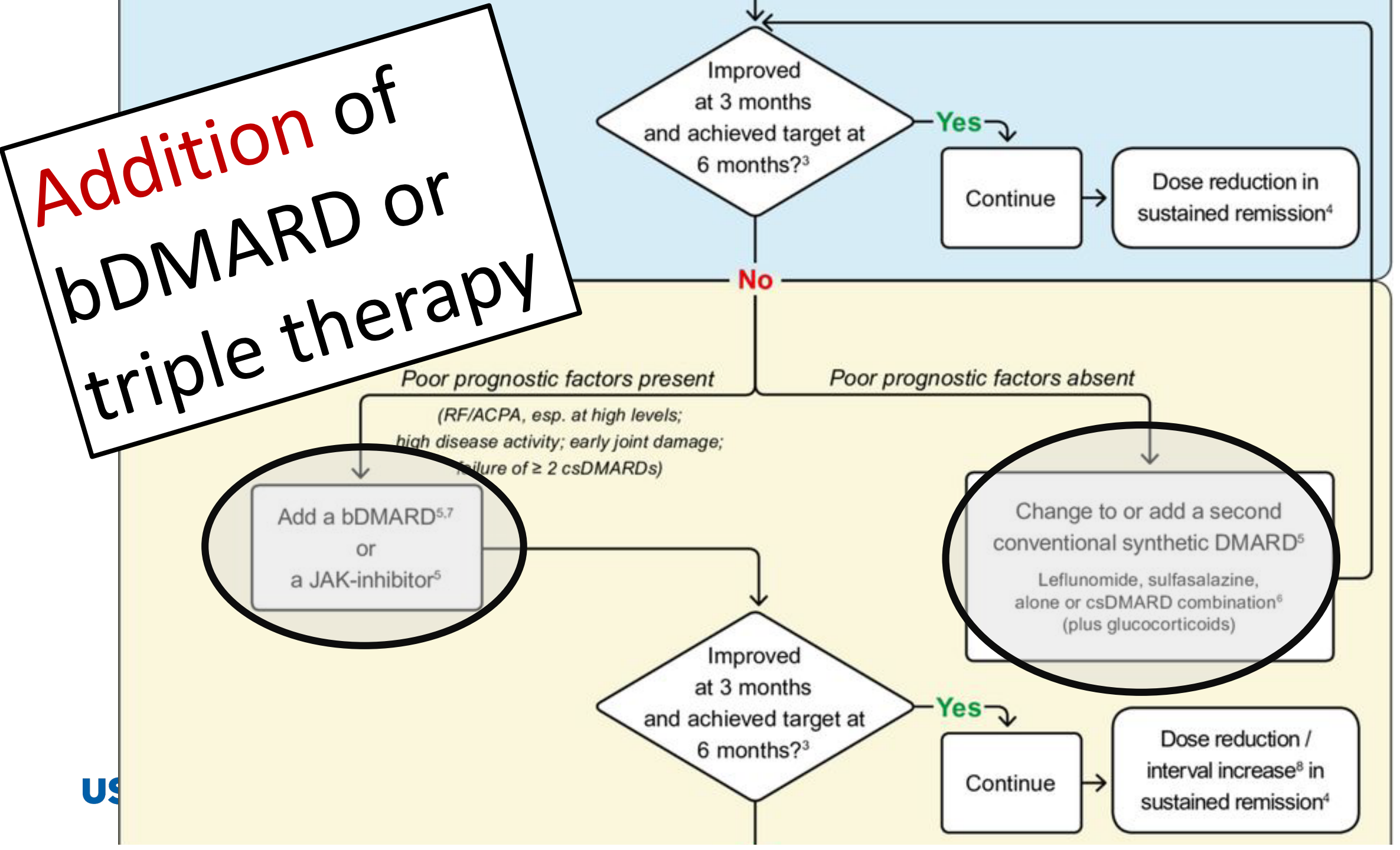
Triple Therapie
→ Kosteneffektiv!

Table 4. Treatment modification*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
A TTT approach is **strongly** recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs.	Low	PICO 12.a	p. 191
A TTT approach is **conditionally** recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs.	Very low	PICO 12.b	p. 199
A minimal initial treatment goal of low disease activity is **conditionally** recommended over a goal of remission.	Low	PICO 13	p. 201
Addition of a bDMARD or tsDMARD is **conditionally** recommended over triple therapy for patients taking maximally tolerated doses of methotrexate who are not at target.	Very low	PICO 19.C2–C6†	p. 240–1
Switching to a bDMARD or tsDMARD of a different class is **conditionally** recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target.	Very low	PICO 24–27†	p. 293–338
Addition of/switching to DMARDs is **conditionally** recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target.	Very low	PICO 23	p. 292
Addition of/switching to DMARDs (with or without IA glucocorticoids) is **conditionally** recommended over the use of IA glucocorticoids alone for patients taking DMARDs who are not at target.	Very low	PICO 28.C1–C2	p. 339–40

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; TTT = treat-to-target; bDMARDs = biologic disease-modifying antirheumatic drugs; tsDMARDs = targeted synthetic DMARDs; IA = intraarticular.
† The original PICO included individual DMARDs as comparators. The recommendation considers bDMARDs as a group.

Fraenkel et al, AC&R, 2021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Improved at 3 months and achieved target at 6 months?[3]
Yes
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Dose reduction in sustained remission[4]
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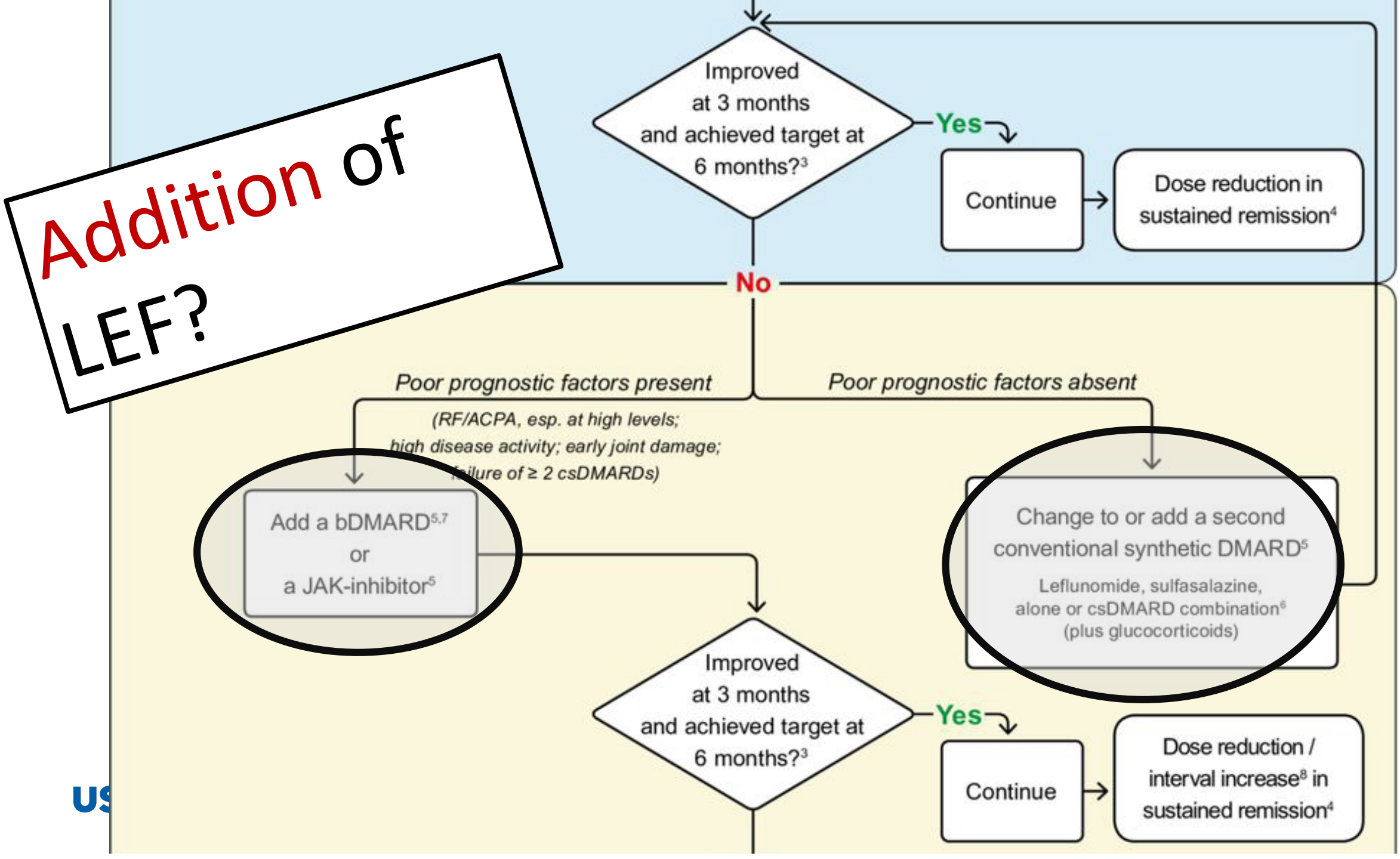
Addition of LEF?
Improved at 3 months and achieved target at 6 months?[3]
Yes
Continue
Dose reduction in sustained remission[4]
No
Poor prognostic factors present
(RF/ACPA, esp. at high levels; high disease activity; early joint damage; failure of ≥ 2 csDMARDs)
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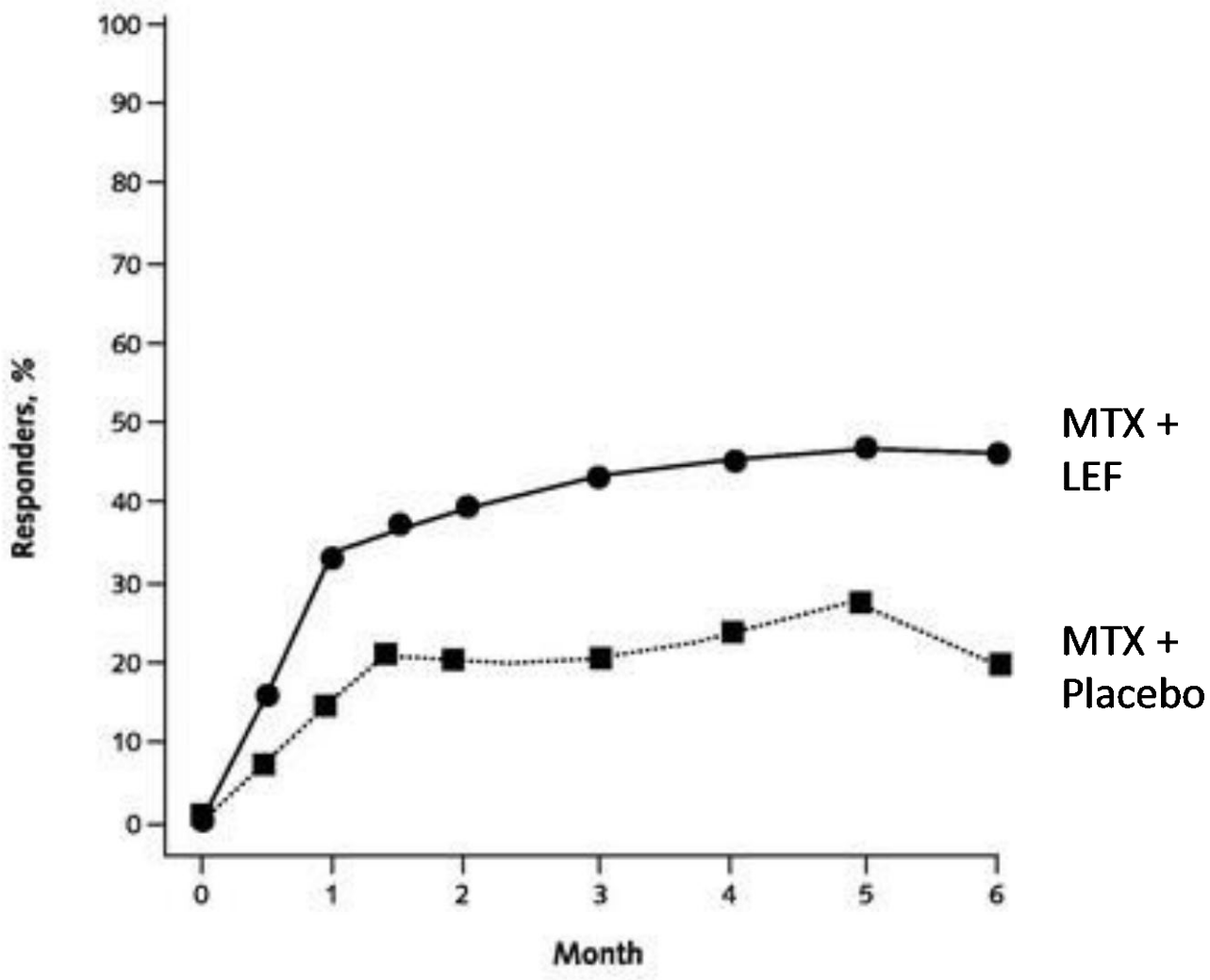
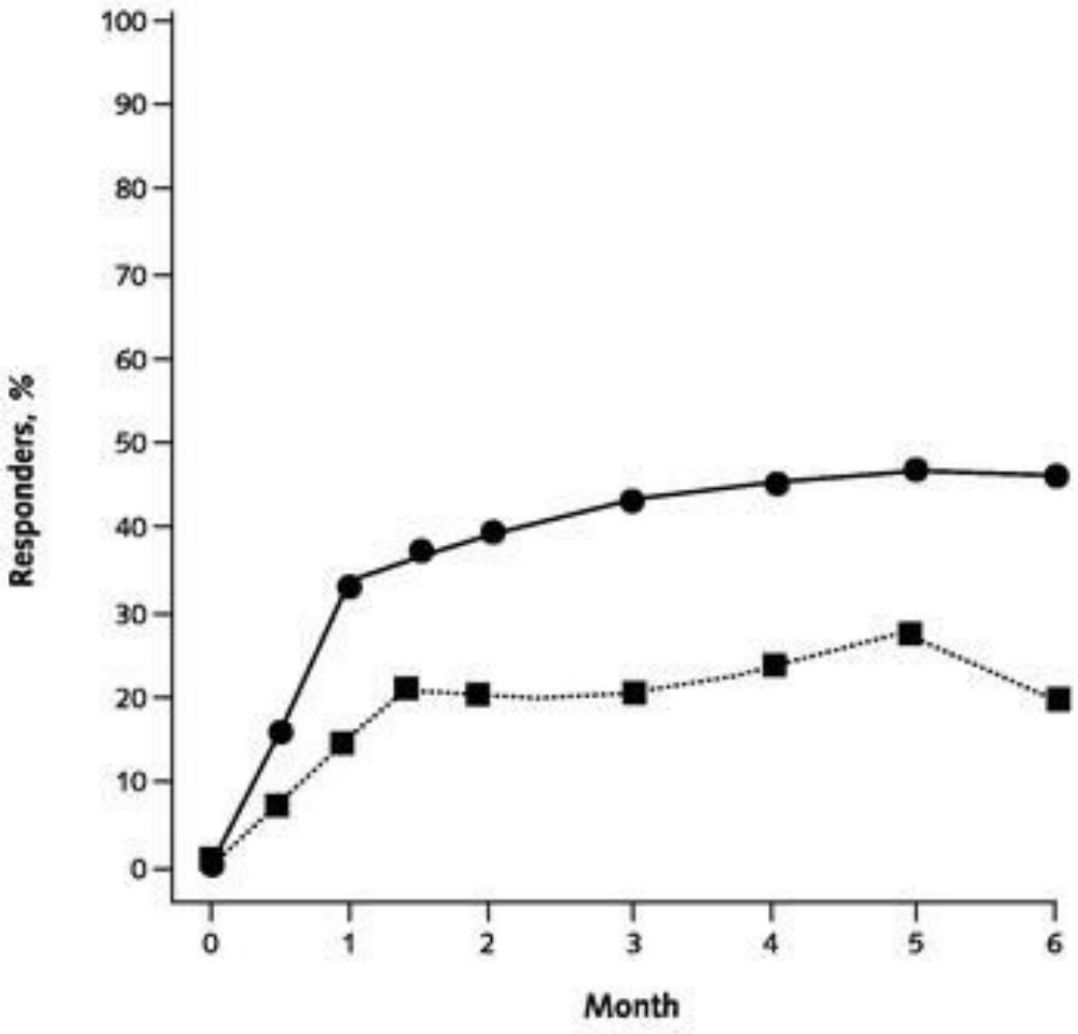
Addition of LEF?



Kremer et al, AIM, 2002

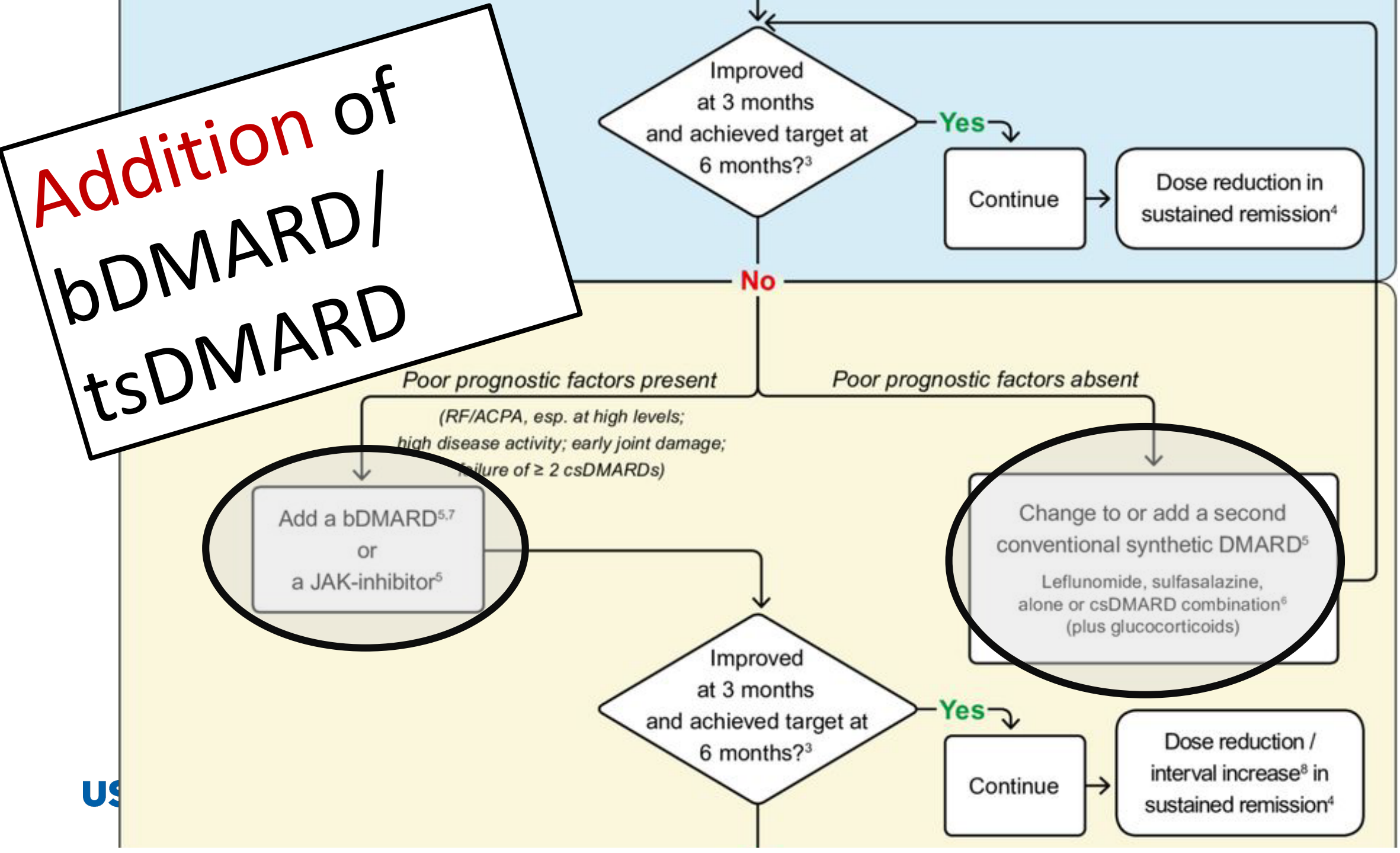


Mehr milde Nebenwirkungen MTX/LEF und engmaschige Leberwertbestimmung notwendig!

MTX + LEF

MTX + Placebo

Kremer et al, AIM, 2002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Improved at 3 months and achieved target at 6 months?[3]
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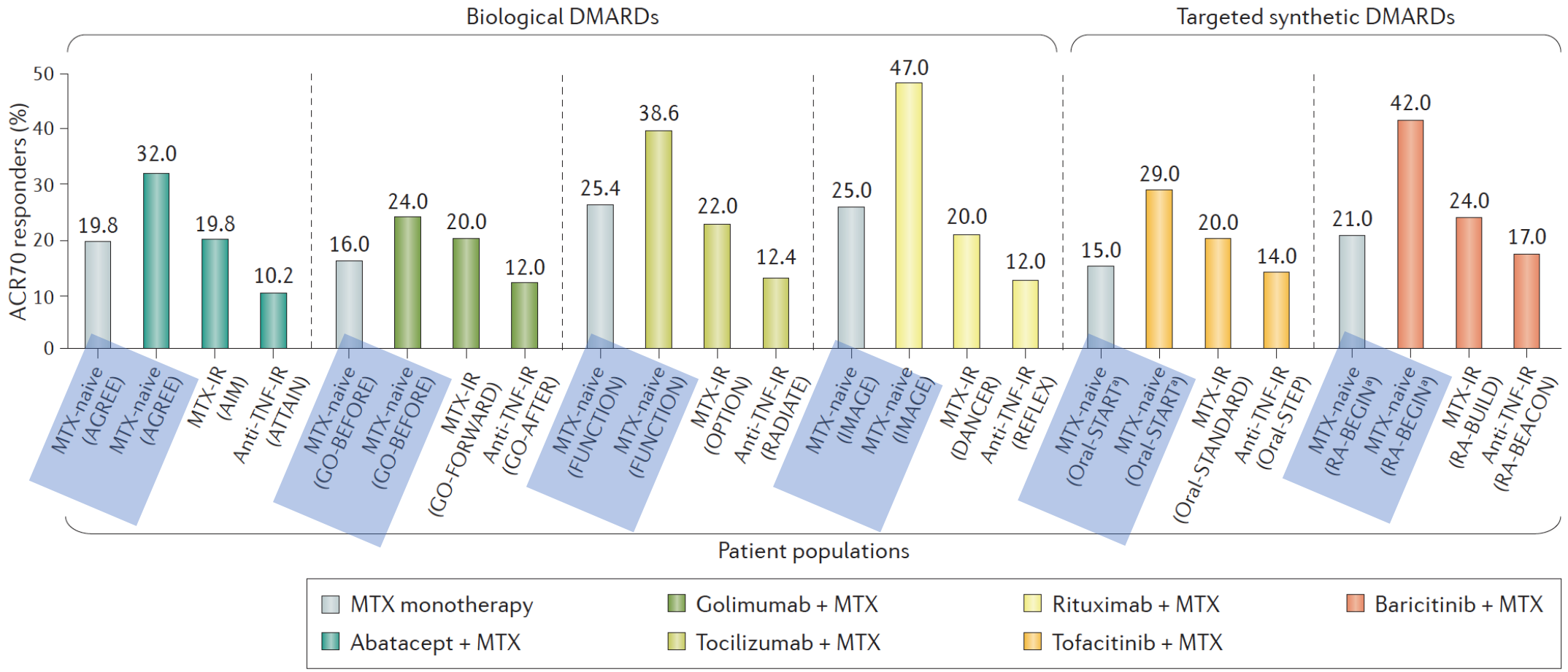
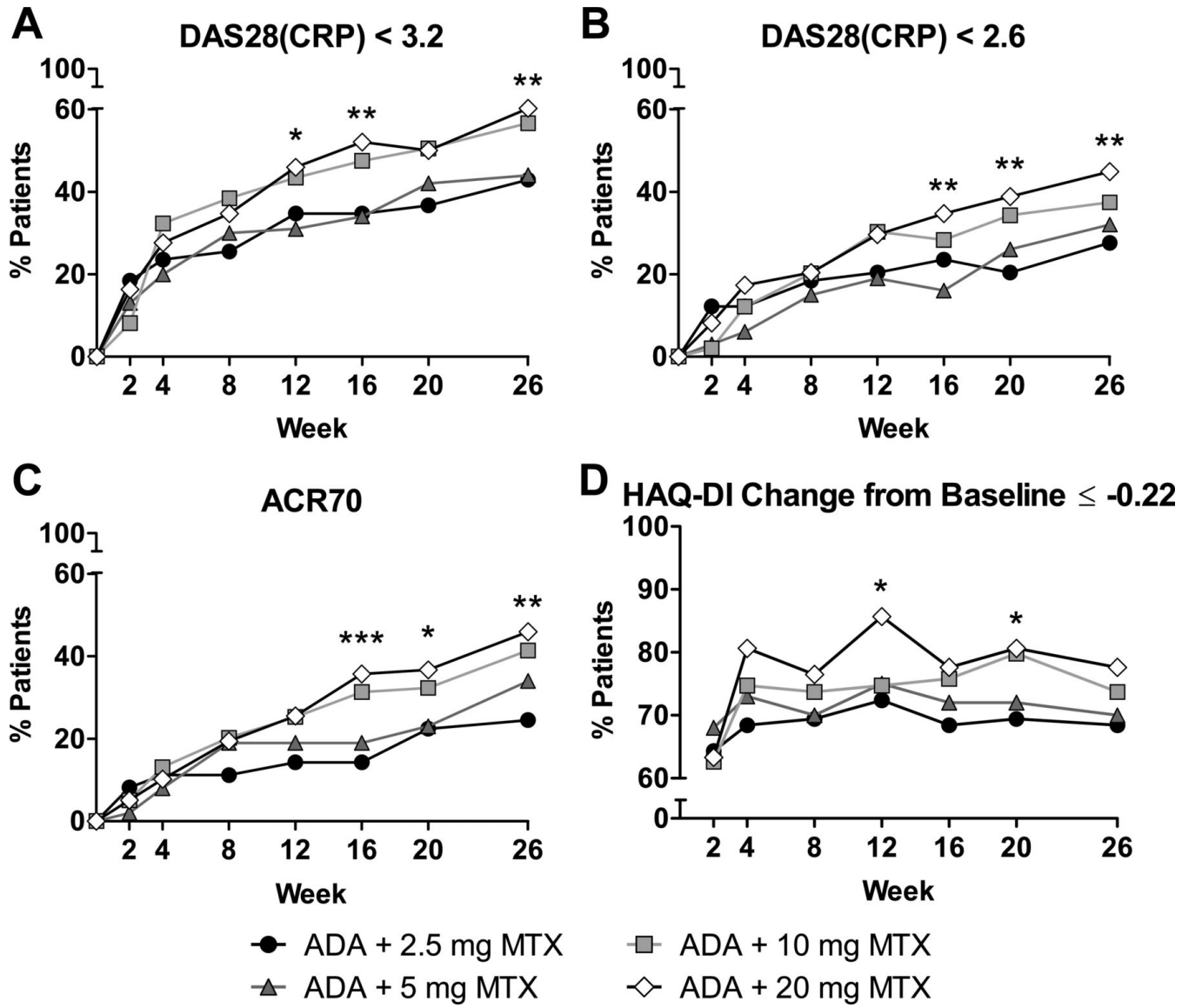
Improved at 3 months and achieved target at 6 months?[3]
Yes
Continue
Dose reduction / interval increase[8] in sustained remission[4]

Welches bDMARD/tsDMARD dazu?



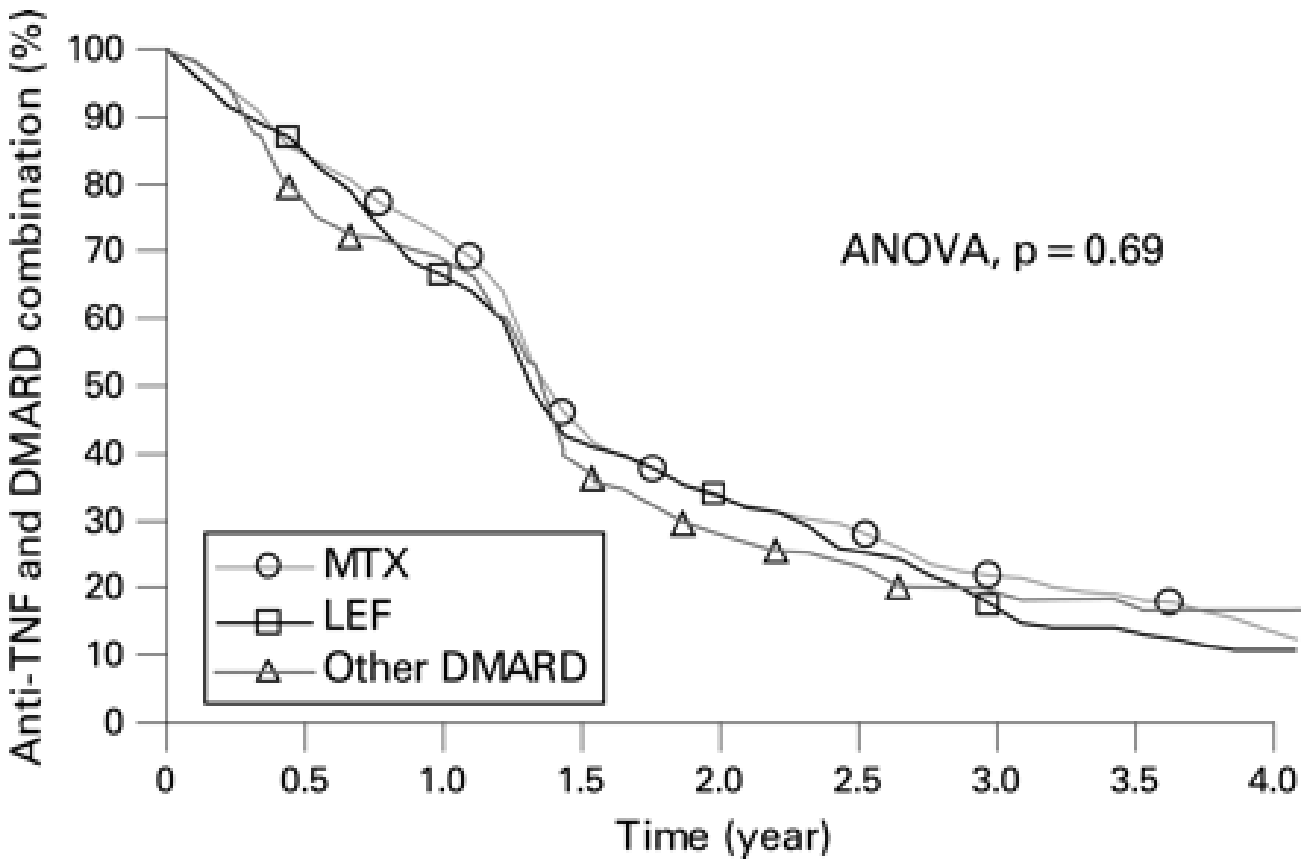
Smolen et al, Nature Reviews Disease Primer, 2017

TNF-Hemmer – Dosierung MTX



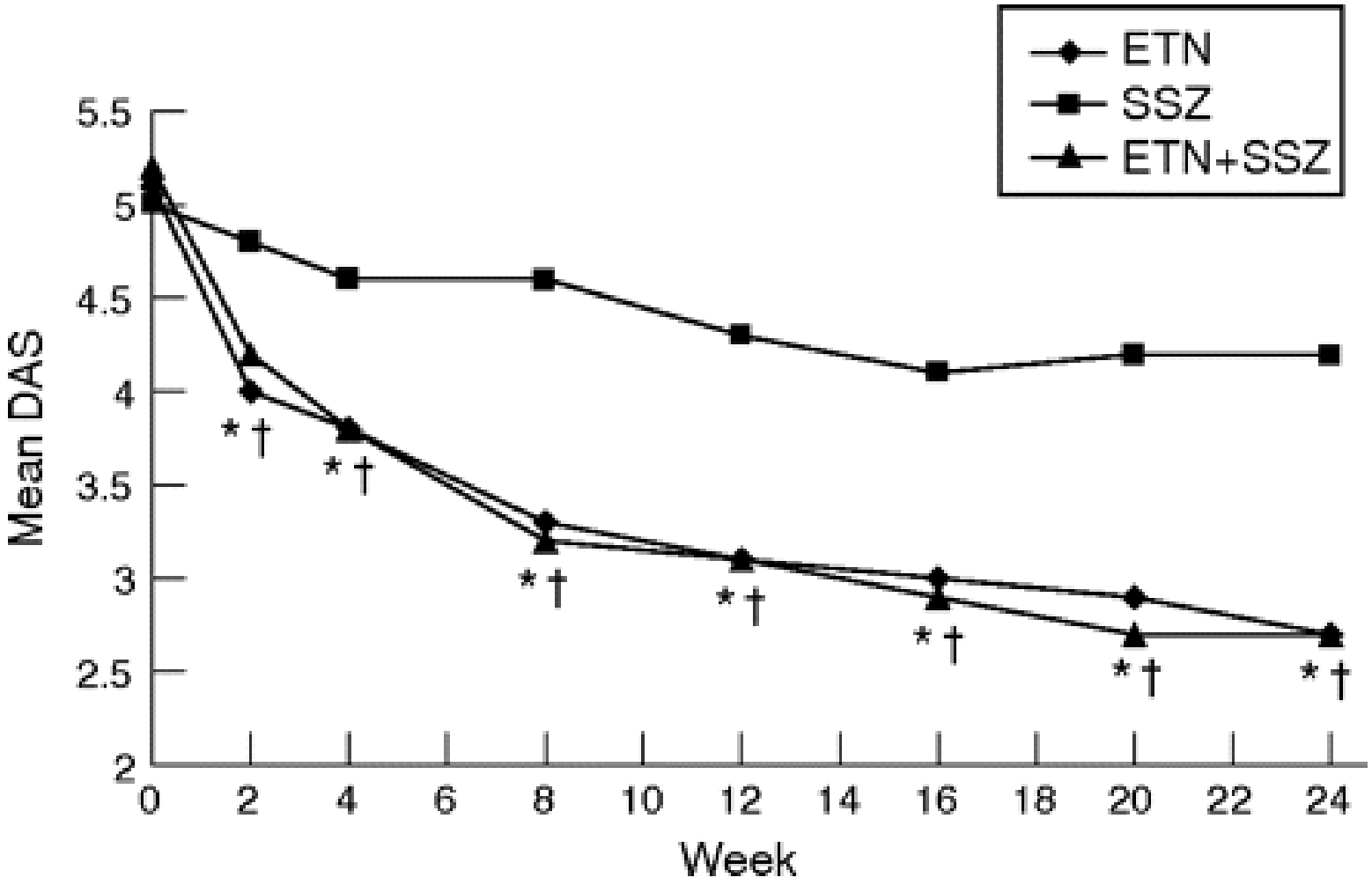
Burmester et al, ARD, 2015

TNF-Hemmer + cDMARD

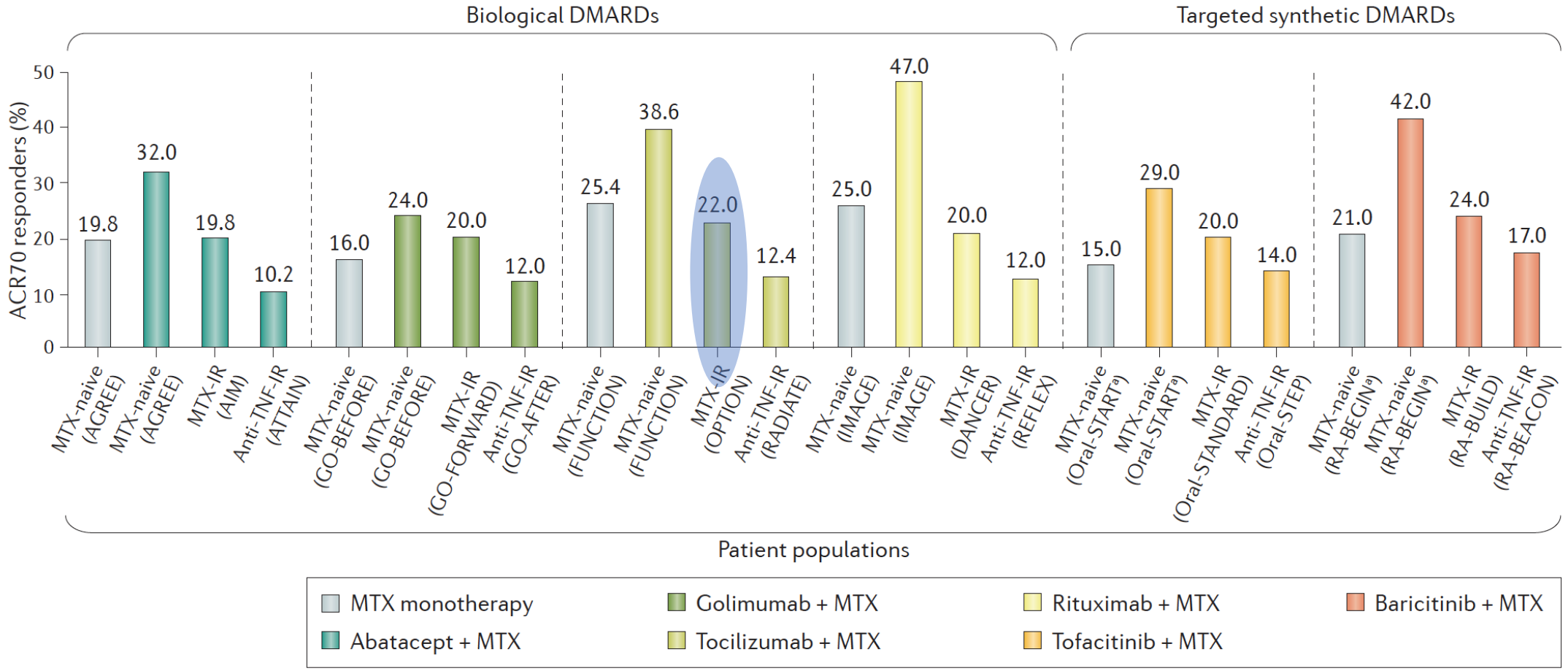


Finckh, ARD, 2007

TNF-Hemmer – SSZ als alternative?

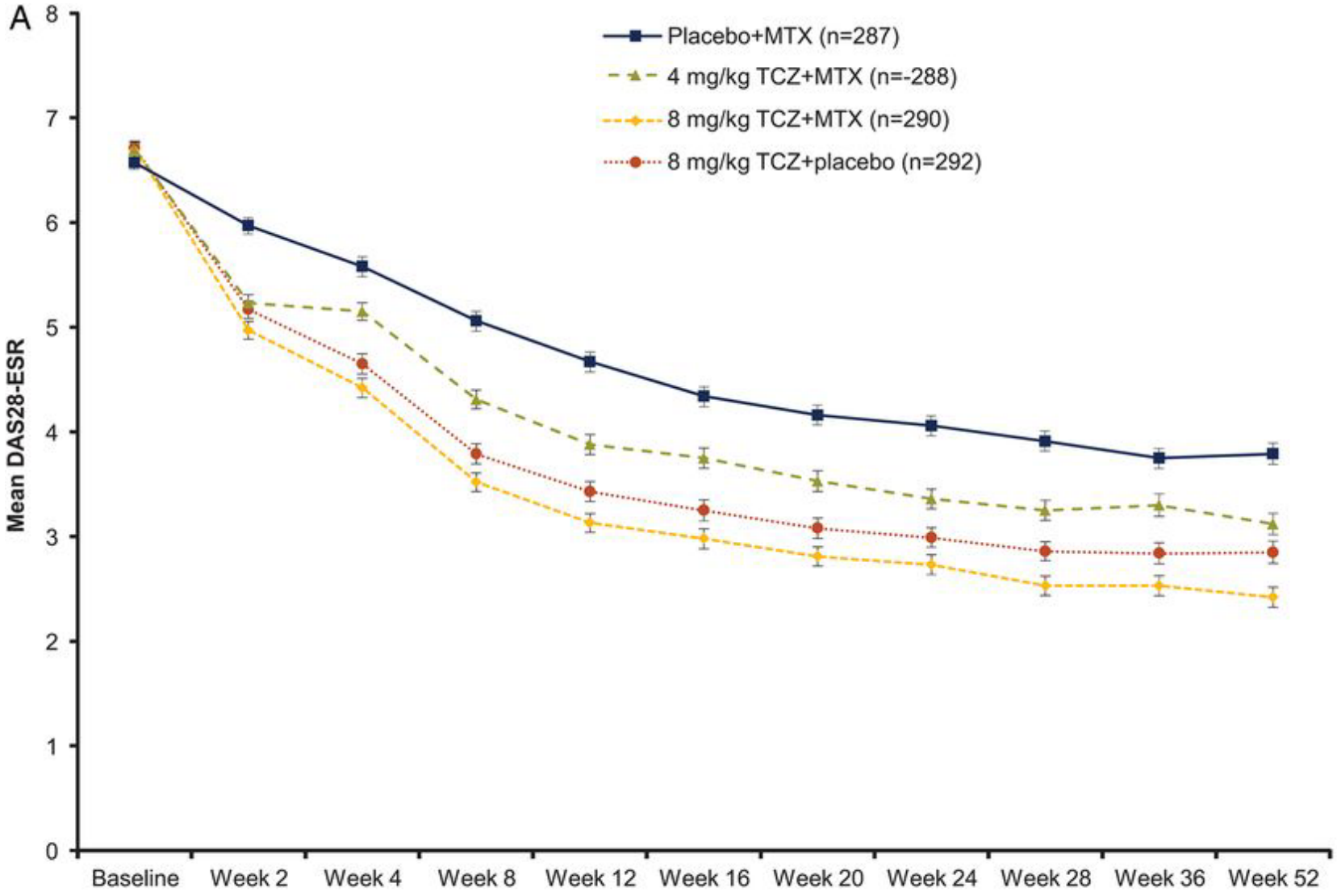


Combe, ARD, 2005



Smolen et al, Nature Reviews Disease Primer, 2017

Tocilizumab in MTX naive patients



Burmester, ARD, 2015

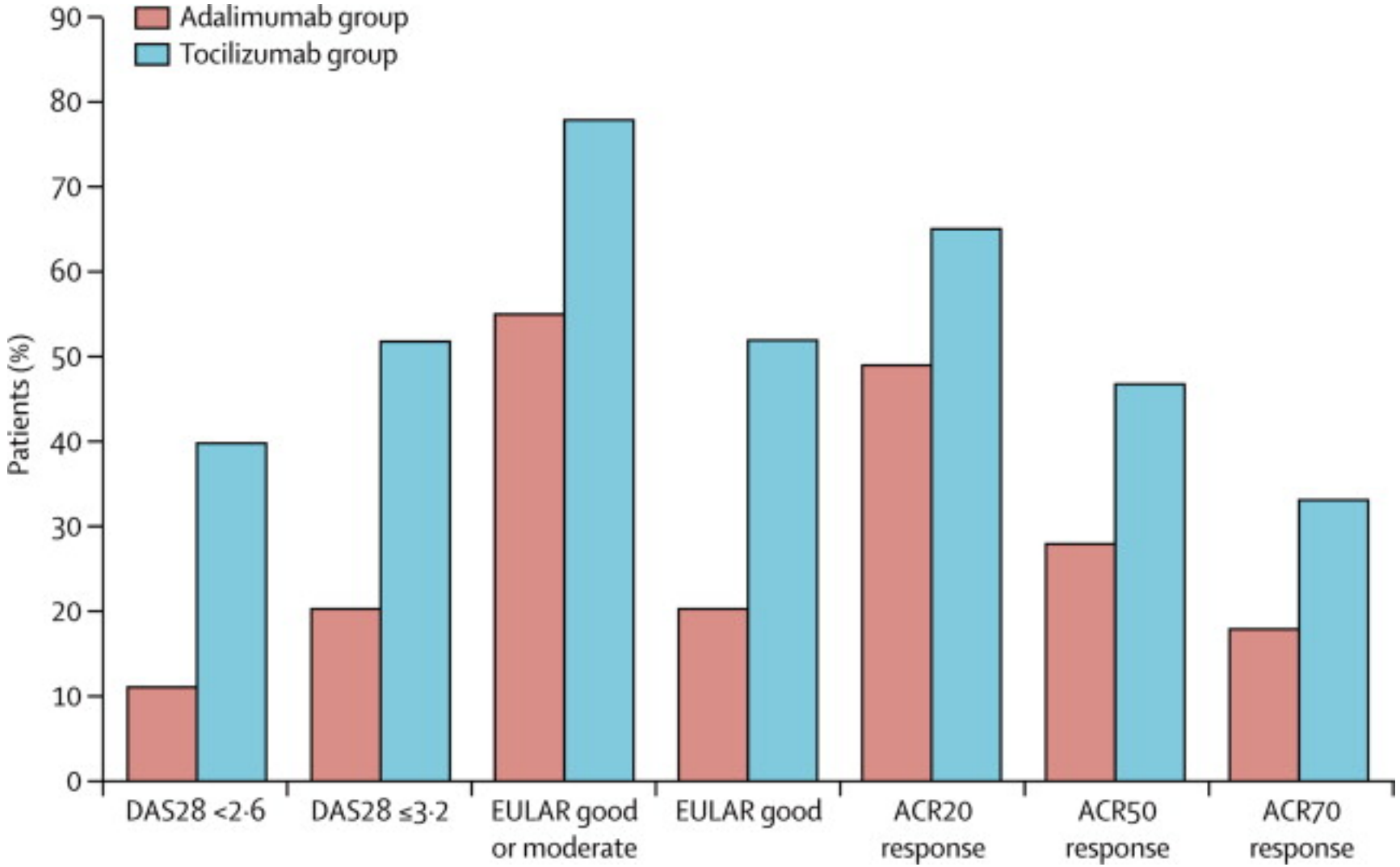
Tocilizumab vs. TNFi (mit/ohne MTX)

Multivariable analysis of CDAI over time

	Overall		
	coeff	**95%CI**	**p**
Treatment at baseline			
TNFi-combo (comparator)	–	–	–
TNFi-mono	1.13	0.32–1.94	0.006
TCZ-combo	−2.08	−3.25–0.91	<0.001
TCZ-mono	0.29	−1.61–2.18	0.77

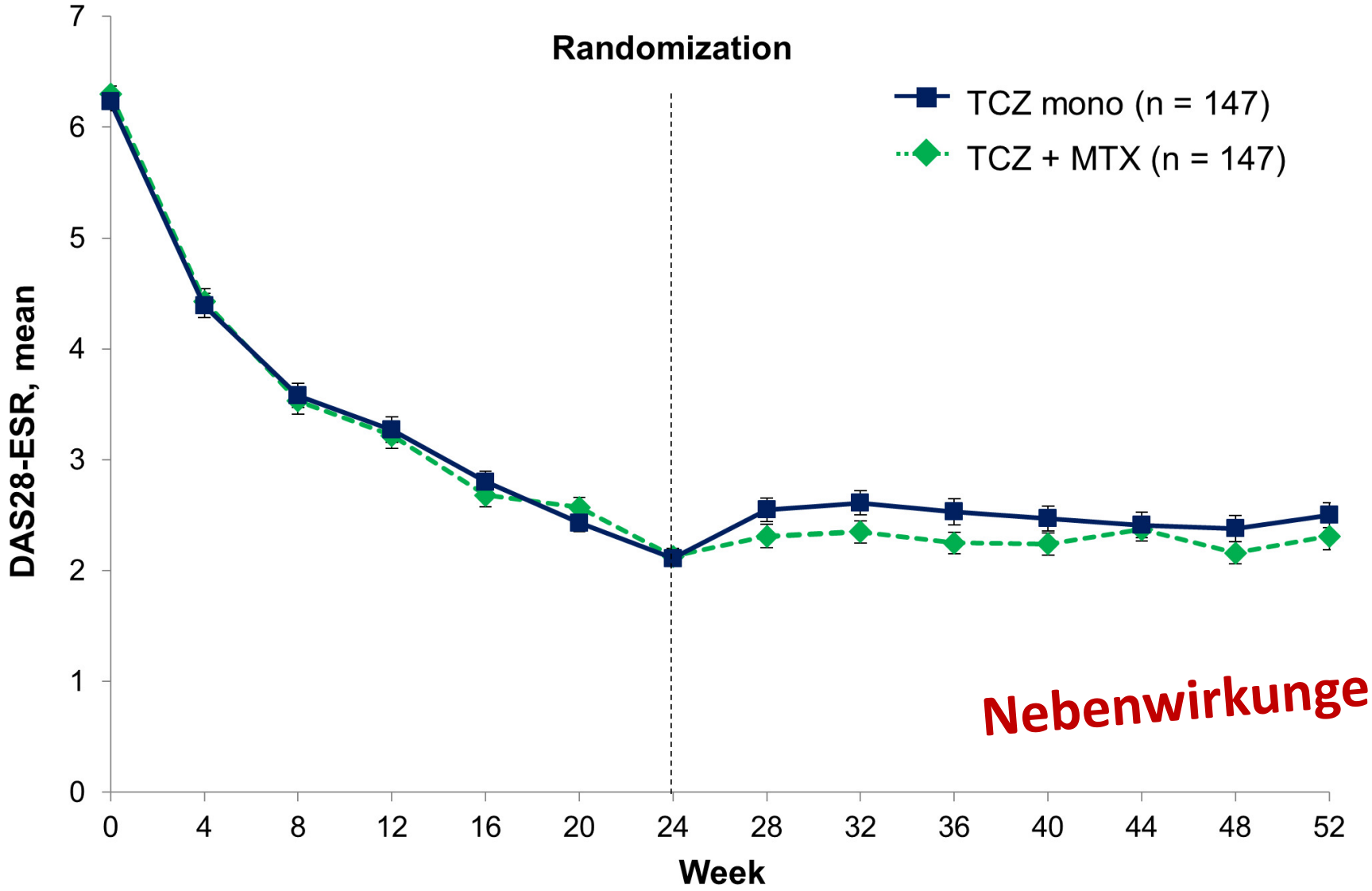
Lauper et al, SAR, 2020

Tocilizumab vs. TNFi (Mono)



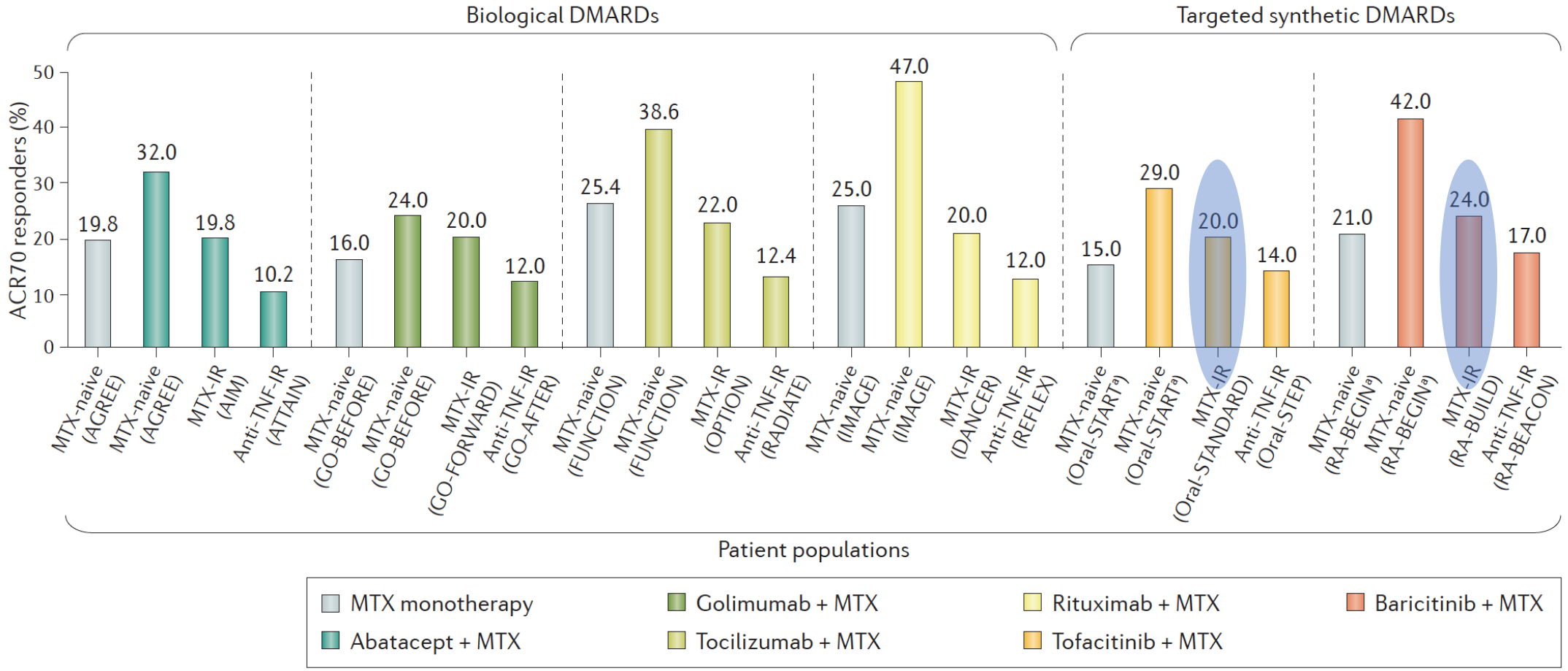
Gabay, Lancet, 2013

Tocilizumab mono bei Remission



Nebenwirkungen gleich!

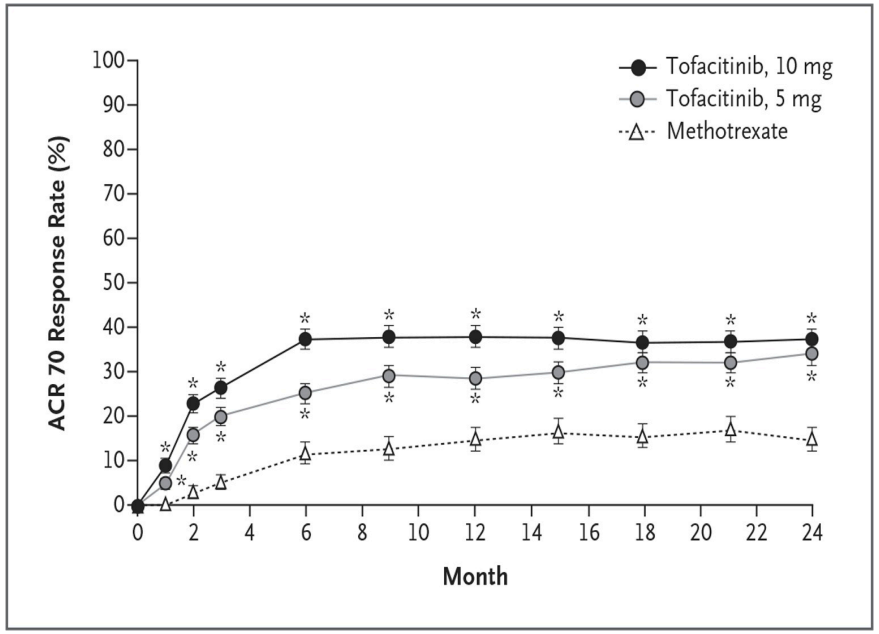
Kremer et al. A&R, 2018



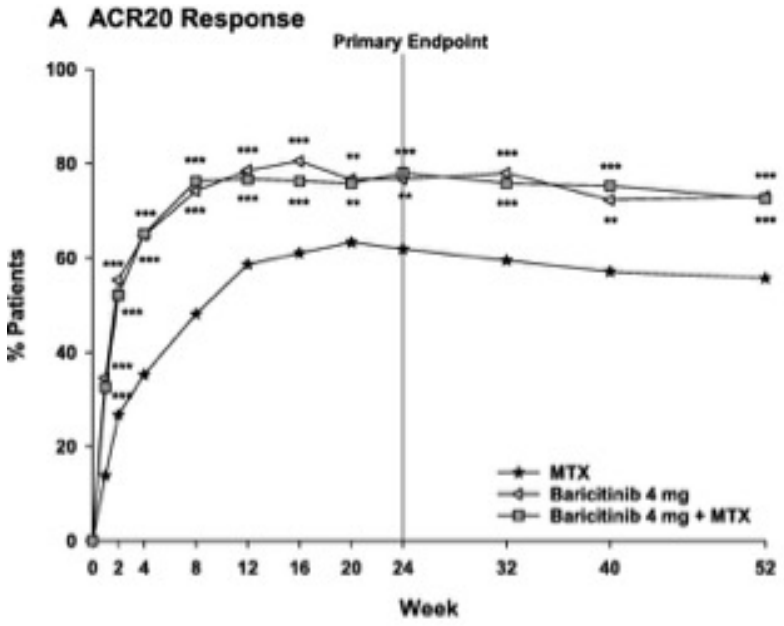
Smolen et al, Nature Reviews Disease Primer, 2017

Jak-Monotherapie?

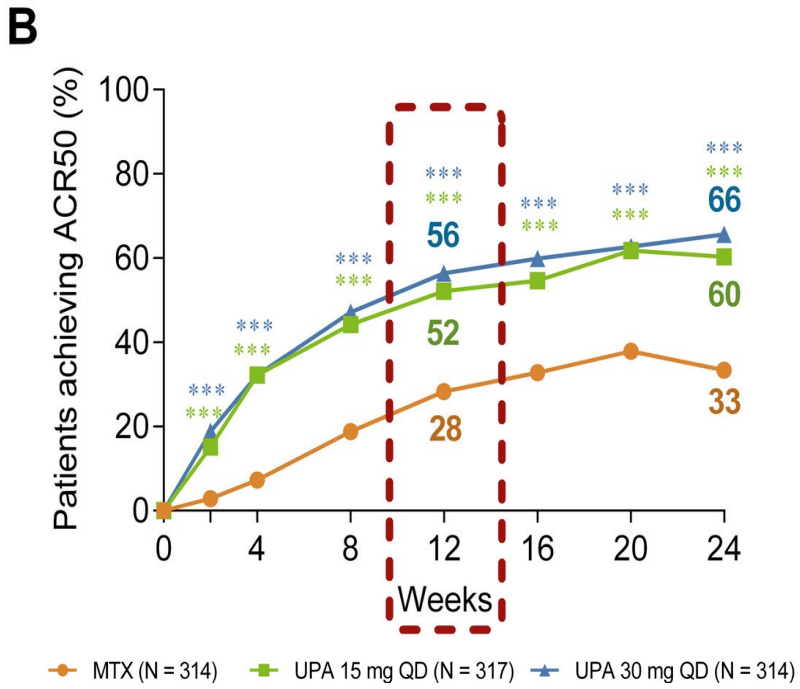
Tofacitinib



Baricitinib

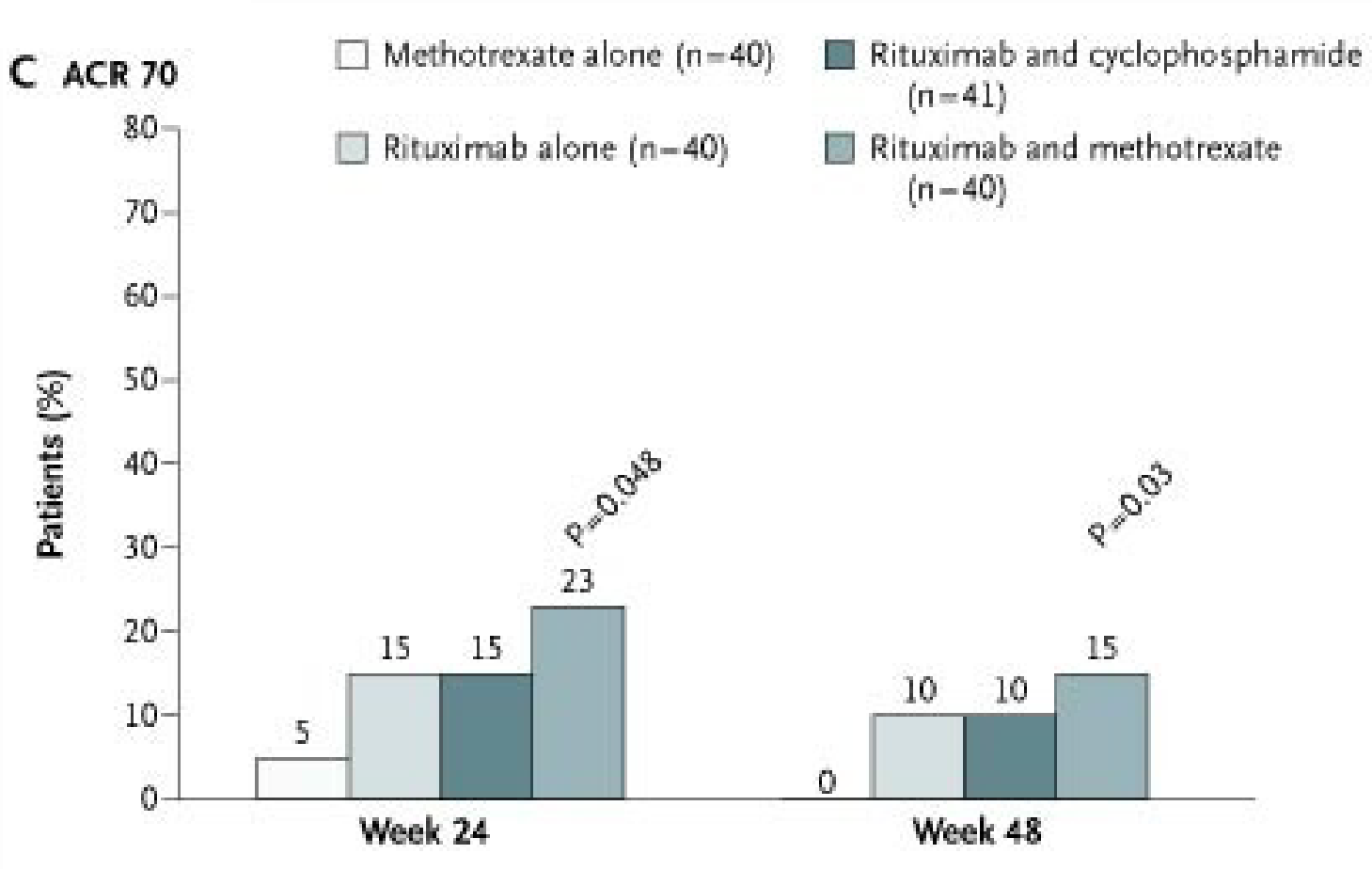


Upadacitinib



Fleischmann et al, AR, 2017 & Lee et al, NEJM, 2014 & van Vollenhofen,, AR, 2020

Rituximab



Edwards et al, NEJM, 2004

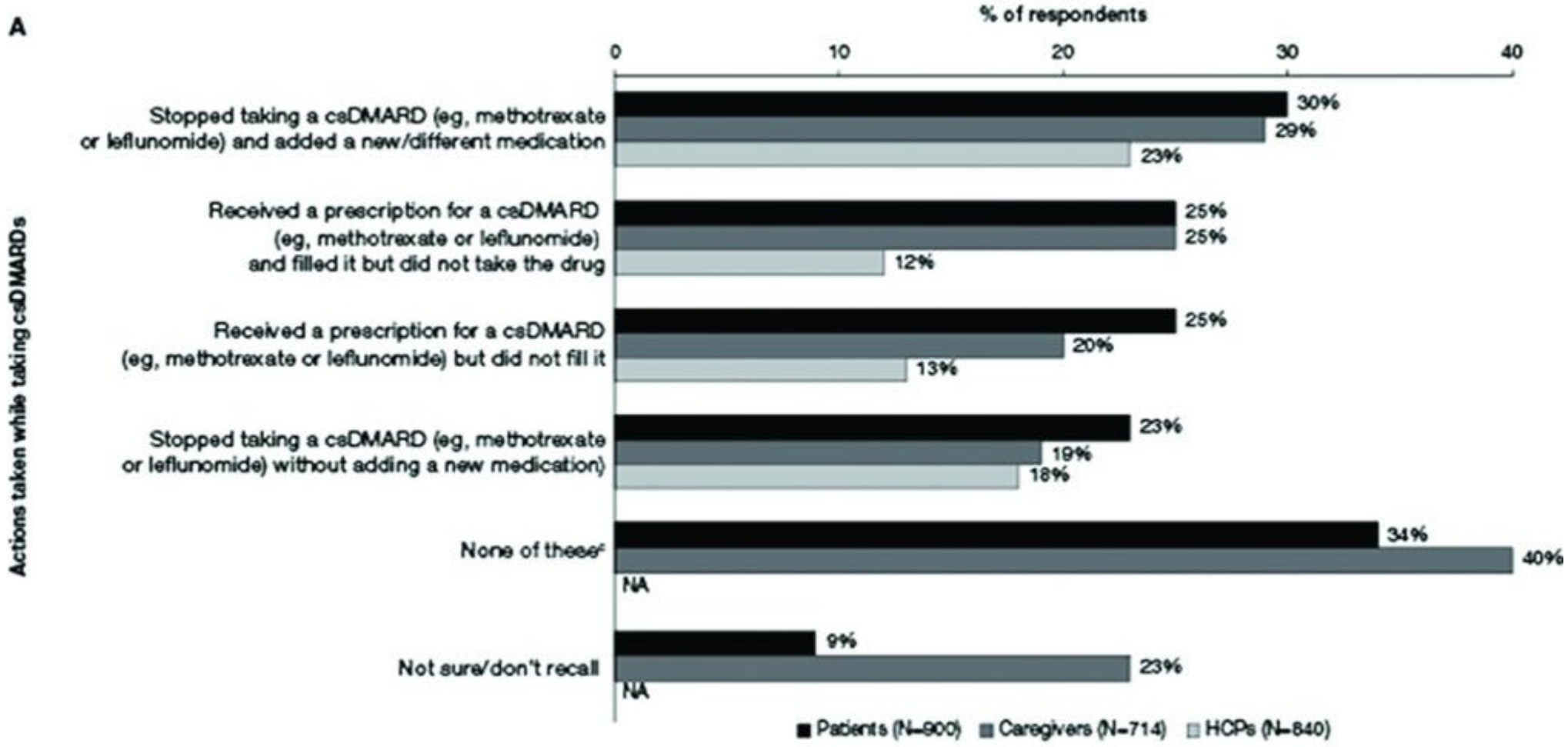
Rituximab – MTX oder LEF?

Nebenwirkungen gleich!

Treatment Response Rates at 6 months of Therapy

	RTX + MTX (*N* = 45)	**RTX + LEF (*N* = 32)**	***P* Value**
DAS28	4.24 (1.52)	3.85 (1.61)	0.28[b]
Change in DAS 28	−1.68 (1.38)	−1.72 (1.43)	0.31[b]
Change% in DAS28	−28.85 (−73, 35)	−26.41 (−92, 7)	0.71[c]

Patientenmeinung - Realität



Galloway, ARD Abstract, 2019

Zusammenfassung

- cDMARD in Kombi mit bDMARD einer Monotherapie überlegen
- Falls Monotherapie: IL-6 Hemmer oder Jak-Inhibitoren
- Patienten informieren!

USZ Universitäts Spital Zürich

Vielen Dank für Ihre Aufmerksamkeit!