

# Systemic pharmacological treatments for chronic plaque psoriasis : a network meta-analysis

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**EA 7379 EpiDermE – Epidemiology in Dermatology and Evaluation of therapeutics**



Any conflicts of interest to declare

# Psoriasis and randomised controlled trials

Psoriasis and RCT  
1972 - 2017

## Results by year

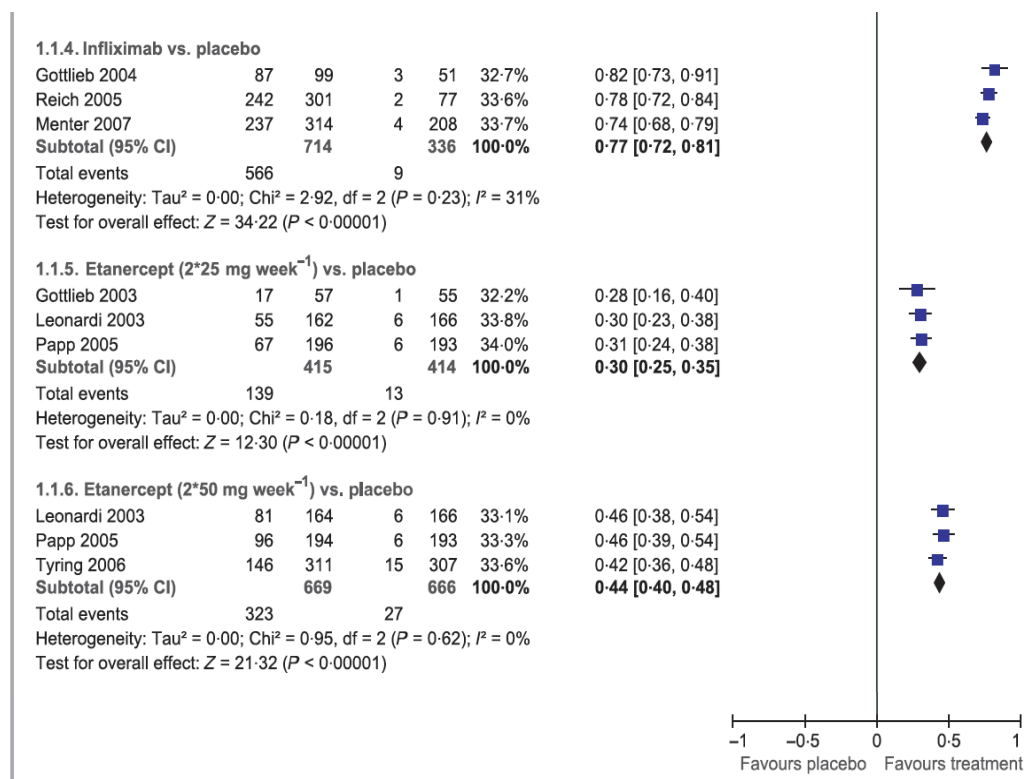


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# Psoriasis and randomised controlled trials

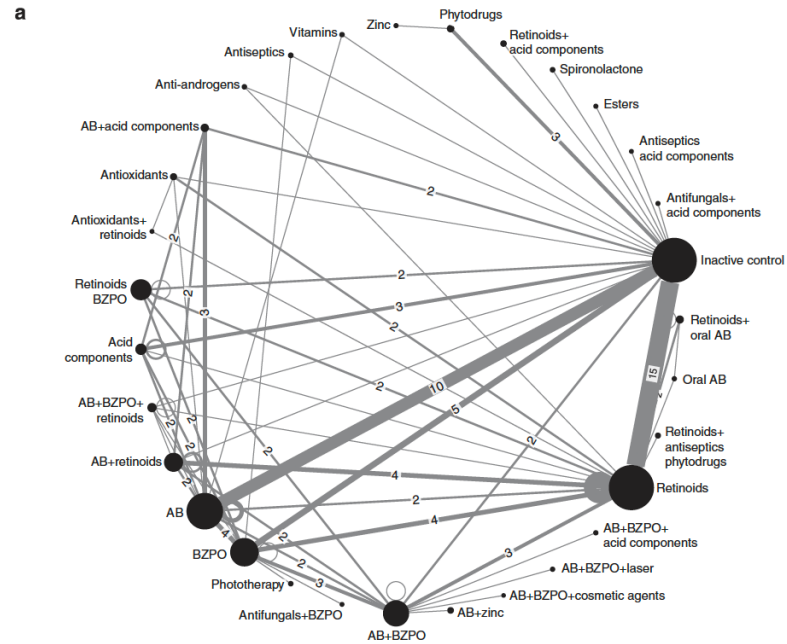
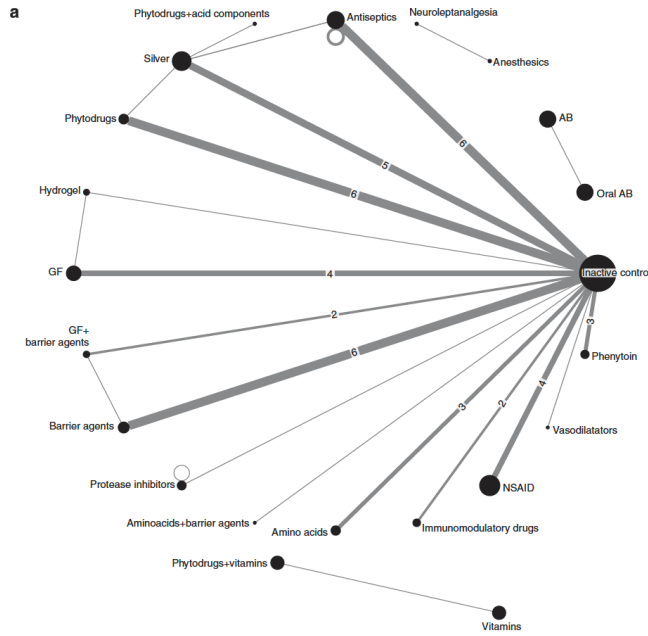
Schmitt et al, Br J Dermatol, 2008

- 2004 – 2007
- PASI 75
- Methotrexate, acitretin, ciclosporin, fumaric acid esters, etanercept, infliximab, adalimumab, alefacept and efalizumab
- 57 references, 16 included trials



Comparison between 2 different drugs are not allowed

# Network meta-analysis



Maruani et al, J Invest Dermatol, 2015

## Direct and indirect Comparaisons

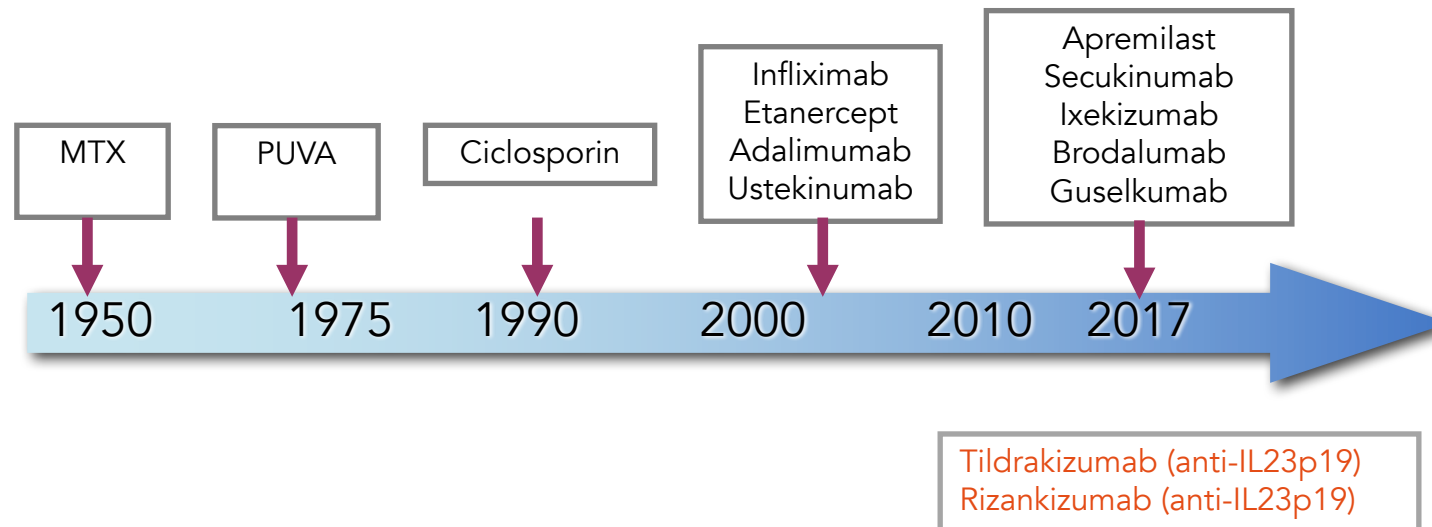
# Psoriasis and randomised controlled trials

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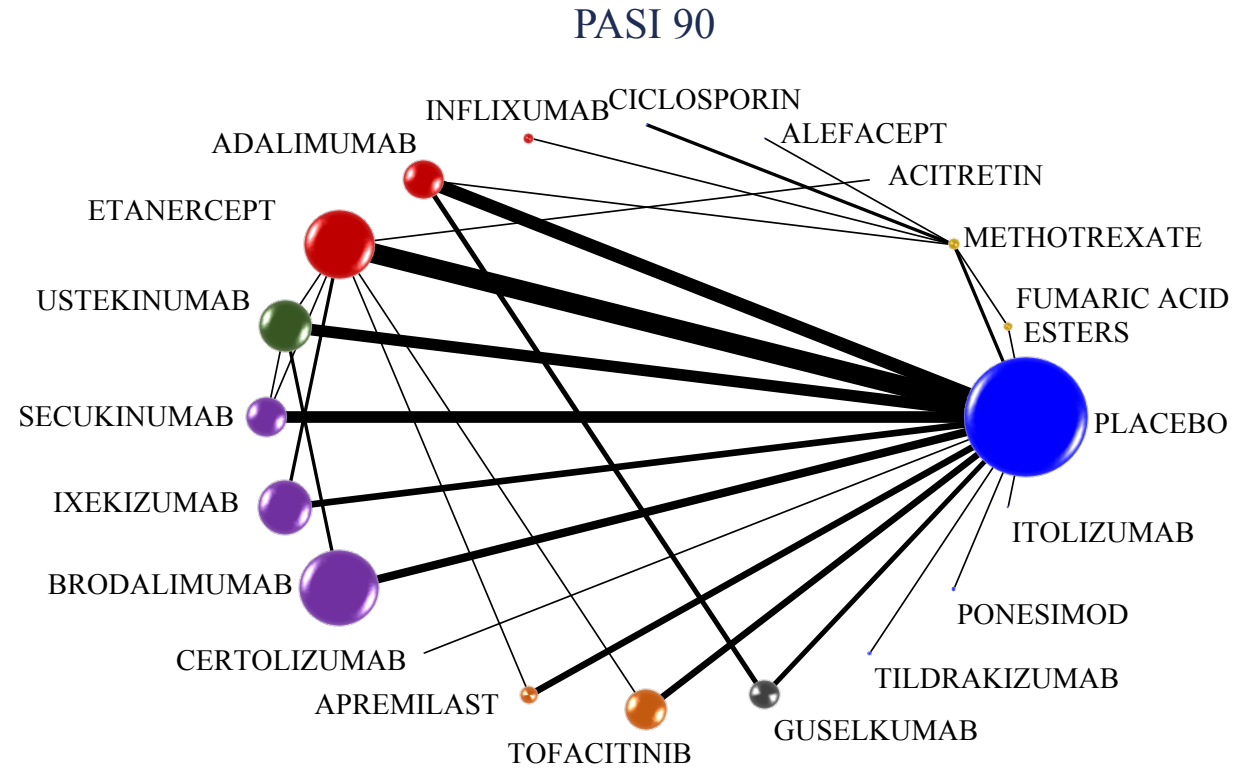
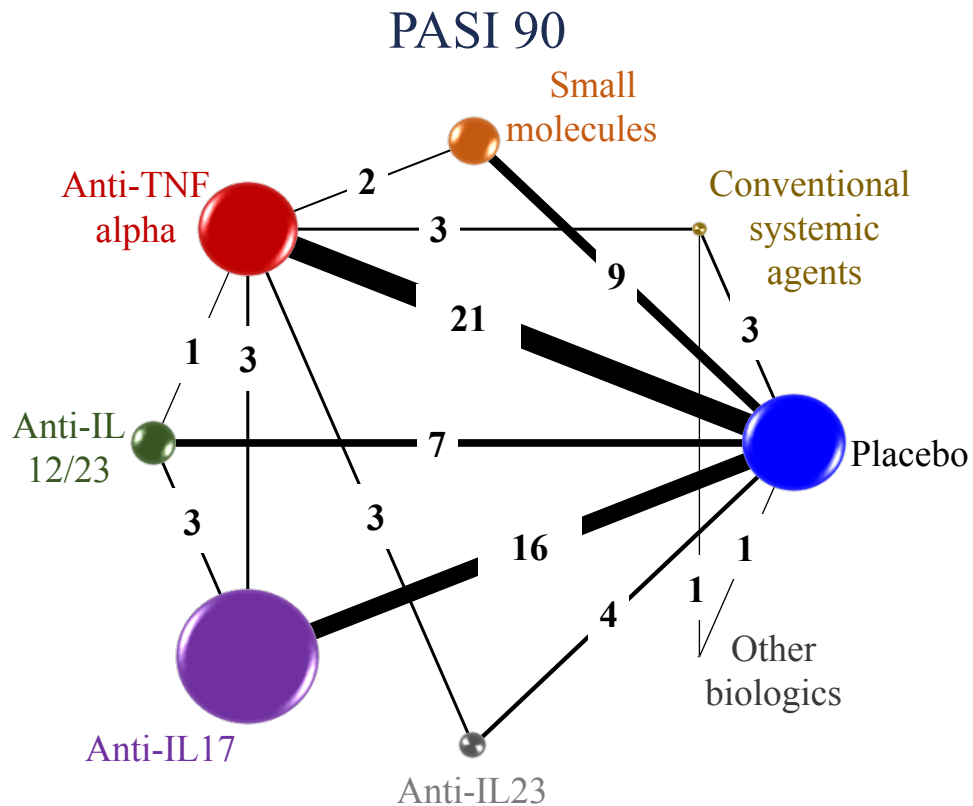


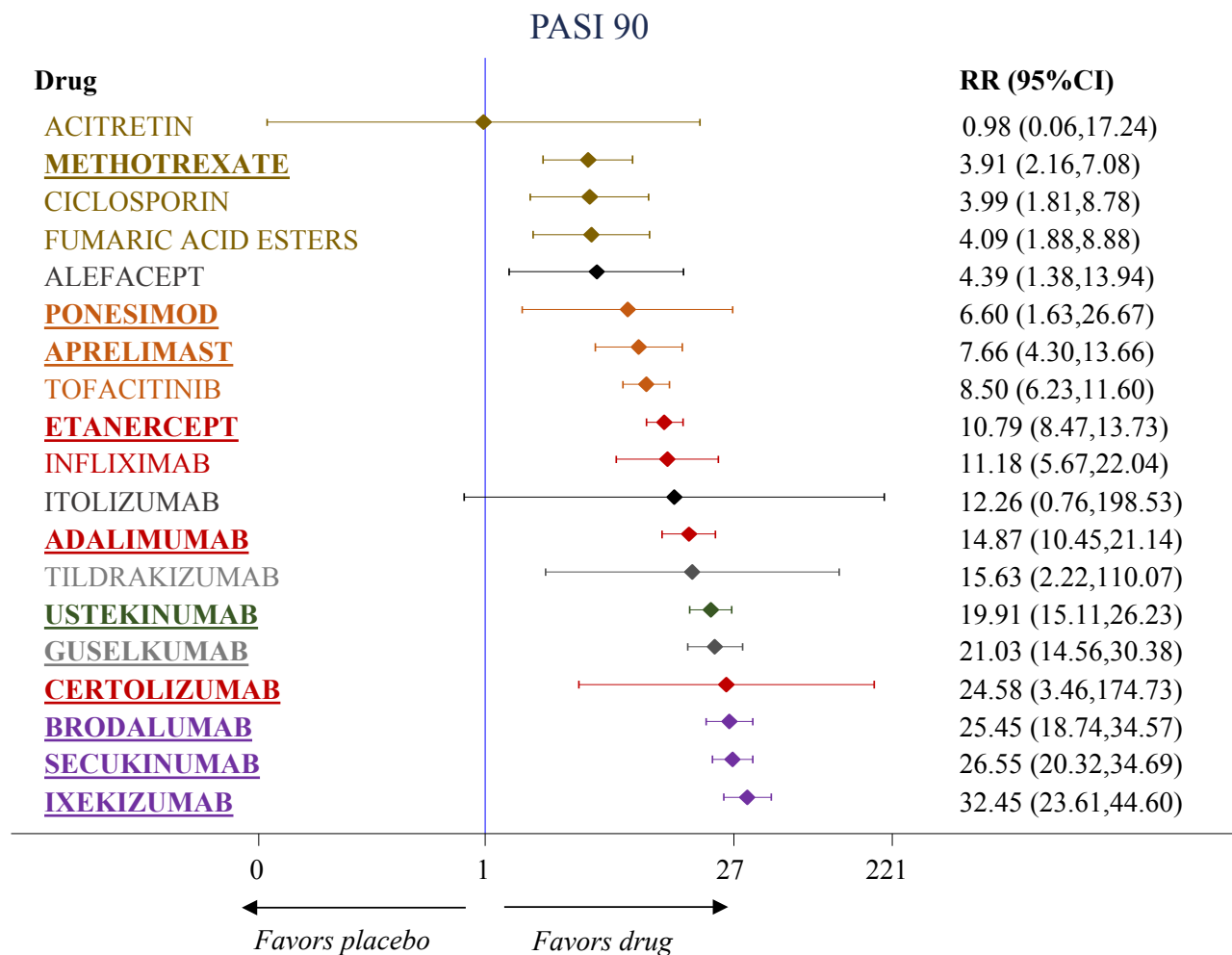
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# Psoriasis and network meta-analysis

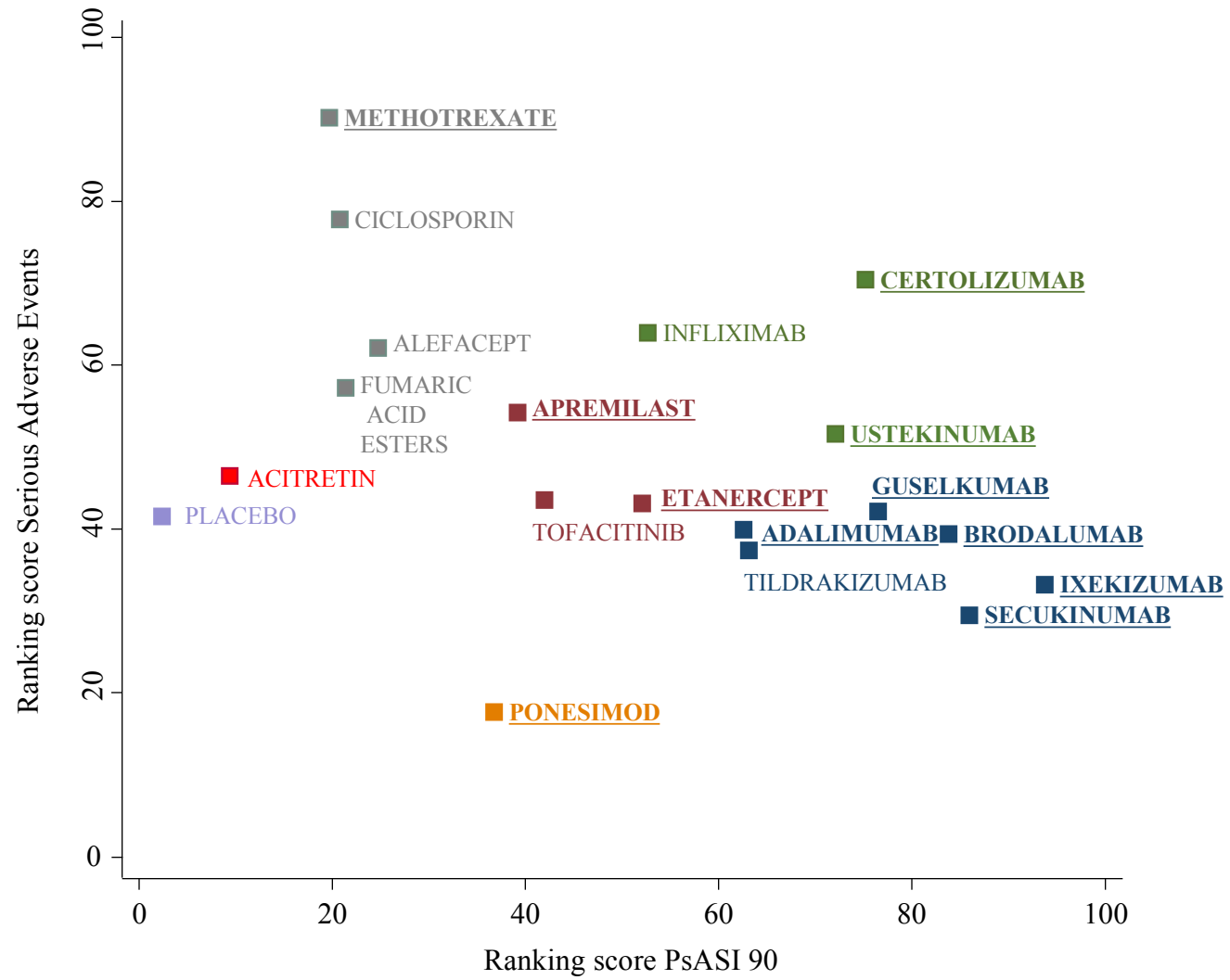
How helpfull is it ?







<b>Ixekizumab</b>	0.9 (0.4-1.9)	1.1 (0.5-2.3)	1.1 (0.5-2.7)	2.3 (0.4-12)	1.3 (0.7-2.5)	1.1 (0.5-2.3)	1.1 (0.7-1.9)	1.3 (0.6-2.9)	0.4 (0.05-3.5)	4.9 (1-22.9)
1.2 (0.9-1.6)	<b>Secukinumab</b>	1.2 (0.6-2.4)	1.2 (0.5-2.9)	2.4 (0.5-12.7)	1.3 (0.7-2.4)	1.2 (0.6-2.5)	1.2 (0.4-2.3)	1.4 (0.6-3.1)	0.5 (0.06-3.8)	5.1 (1.1-24.3)
1.3 (0.9-1.7)	1.0 (0.8-1.3)	<b>Brodalumab</b>	1 (0.4-2.5)	2.1 (0.4-11)	1.2 (0.6-2.1)	1 (0.4-2.1)	1.1 (0.6-2)	1.2 (0.6-2.7)	0.4 (0.05-3.4)	4.5 (0.9-21)
1.5 (0.9-2.5)	1.3 (0.8-2)	1.2 (0.7-2)	<b>Guselkumab</b>	2 (0.4-11.4)	1.1 (0.5-2.6)	0.9 (0.1-2.5)	1 (0.4-2.3)	1.2 (0.5-3)	0.2 (0.01-2.5)	4.4 (0.9-21.3)
1.3 (0.2-9.6)	1.1 (0.2-7.8)	1.0 (0.1-7.5)	0.9 (0.1-6.3)	<b>Certolizumab</b>	0.6 (0.1-2.8)	0.5 (0.1-2.5)	0.5 (0.1-2.5)	0.6 (0.1-3.1)	0.2 (0.01-2.5)	2.1 (0.3-18.1)
1.6 (1.3-2.1)	1.3 (1.1-1.6)	1.3 (1.1-1.5)	1.1 (0.7-1.7)	1.2 (0.2-9)	<b>Ustekinumab</b>	0.9 (0.4-1.7)	0.9 (0.5-1.6)	1.1 (0.5-2.2)	0.3 (0.04-2.8)	3.9 (0.8-17.7)
2.2 (1.4-3.5)	1.8 (1.2-2.8)	1.7 (1.1-2.7)	1.4 (1.2-1.7)	1.7 (0.2-12.1)	1.3 (0.9-2.1)	<b>Adalimumab</b>	1 (0.5-2)	1.2 (0.6-3.9)	0.4 (0.05-3.2)	4.4 (0.9-19.8)
3.0 (2.5-3.7)	2.5 (2-3)	2.4 (1.8-3)	2 (1.3-3)	2.3 (0.3-16.4)	1.9 (1.5-2.3)	1.4 (0.9-2.1)	<b>Etanercept</b>	1.2 (0.6-2.4)	0.4 (0.05-3.1)	4.3 (0.9-19.5)
4.2 (2.3-7.8)	3.5 (1.9-6.3)	3.3 (1.8-6.1)	2.8 (1.4-5.5)	3.2 (0.4-24.8)	2.6 (1.4-4.7)	1.9 (0.9-3.8)	1.4 (0.8-2.5)	<b>Apremilast</b>	0.3 (0.04-2.7)	3.6 (0.8-17.5)
4.9 (1.2-20.6)	4 (0.9-16.7)	3.9 (0.9-16)	3.2 (0.8-13.5)	3.7 (0.3-41.4)	3 (0.7-12.5)	2.3 (0.5-9.5)	1.6 (0.4-6.8)	1.2 (0.3-5.3)	<b>Ponesimod</b>	11.2 (0.9-137)
8.3 (4.2-16.5)	6.8 (3.5-13.1)	6.5 (3.3-13)	5.4 (3.2-9.1)	6.3 (0.8-48.8)	5.1 (2.6-9.9)	3.8 (2.3-6.4)	2.8 (1.5-5.3)	2 (0.9-4.5)	1.7 (0.4-7.7)	<b>Methotrexate</b>



# Psoriasis and network meta-analysis

~ 10 published network meta-analyses

## Quantitative Evaluation of Biologic Therapy Options for Psoriasis: A Systematic Review and Network Meta-Analysis

Zarif K. Jabbar-Lopez<sup>1</sup>, Zenas Z.N. Yiu<sup>2</sup>, Victoria Ward<sup>3</sup>, Lesley S. Exton<sup>4</sup>, M. Firouz Mohd Mustapa<sup>4</sup>, Eleanor Samarasekera<sup>5</sup>, A. David Burden<sup>6</sup>, Ruth Murphy<sup>7</sup>, Caroline M. Owen<sup>8</sup>, Richard Parslew<sup>9</sup>, Vanessa Venning<sup>10</sup>, Richard B. Warren<sup>2</sup> and Catherine H. Smith<sup>11</sup>



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**Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis (Review)**

Sbidian E, Chaimani A, Garcia-Doval I, Do G, Hua C, Mazaud C, Droitcourt C, Hughes C, Ingram JR, Naldi L, Chosidow O, Le Cleach L



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# PICO criteria



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Any age limitation – any severity

Biologics (adalimumab, etanercept, infliximab, ixekizumab, ustekinumab, and secukinumab)

Placebo or biologics or methotrexate

PASI 90 / PGA 0-1 - withdrawal due to adverse events

DLQI

PASI 75

Short-term (<16 weeks)

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Adults 18 years old and older – moderate to severe type-plaque psoriasis

Systemic treatments (conventionals, small molecules, anti-TNF, anti IL12/23, anti-IL17, anti-IL23, others biologics)

Placebo or systemic treatments

PASI 90 – Serious adverse events

PASI 75, PGA 0-1, QoL, AEs

Short-term (<16 weeks)

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# Descriptive results



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Several electronic databases  
Independent dual screening

Other sources (registration databases, FDA)  
Independent dual abstraction

- 41 RCTs
- 20,561 participants

- 109 RCTs
- 39,882 participants (67% males)
- 44 years old
- Mean PASI 20

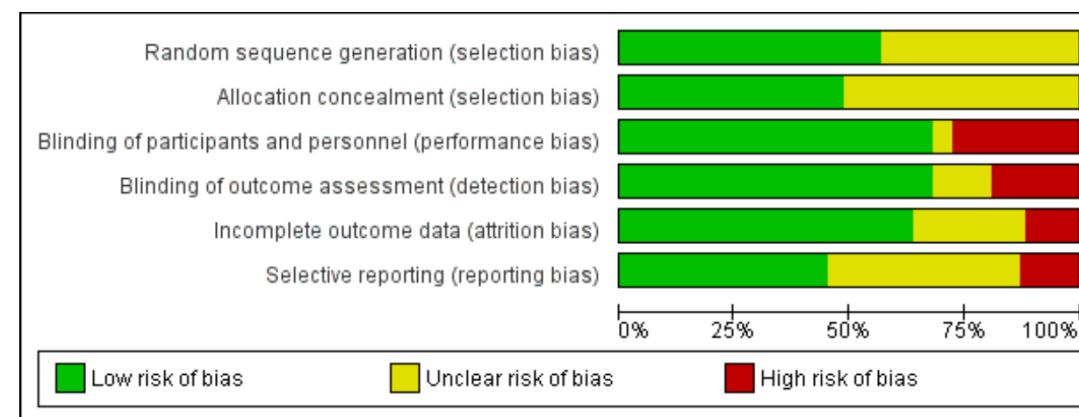
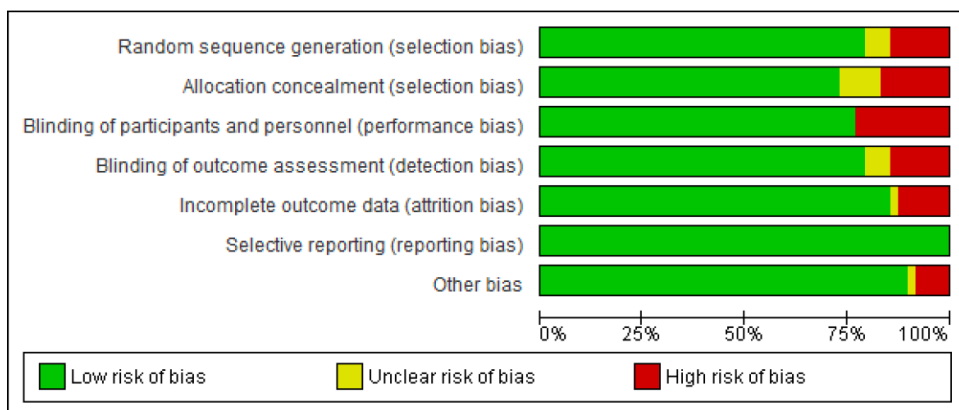
# Risk of Bias Tool



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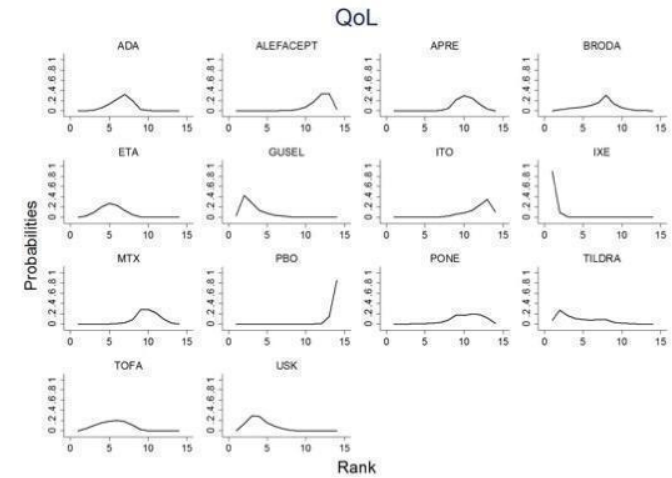
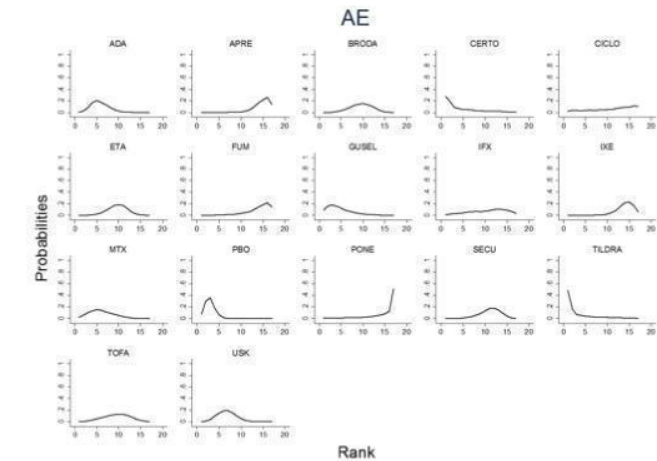
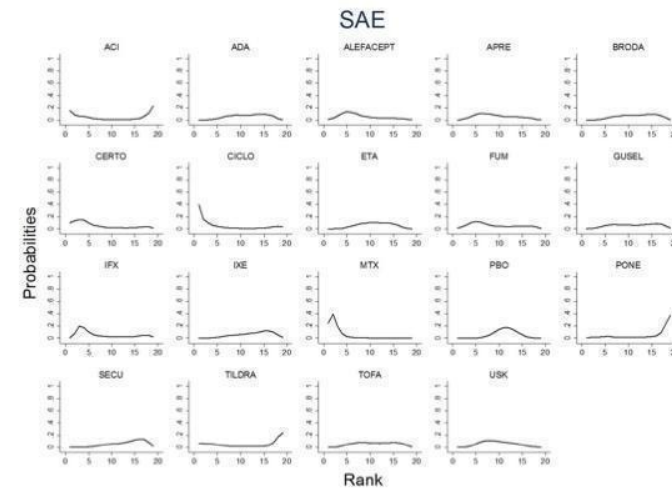
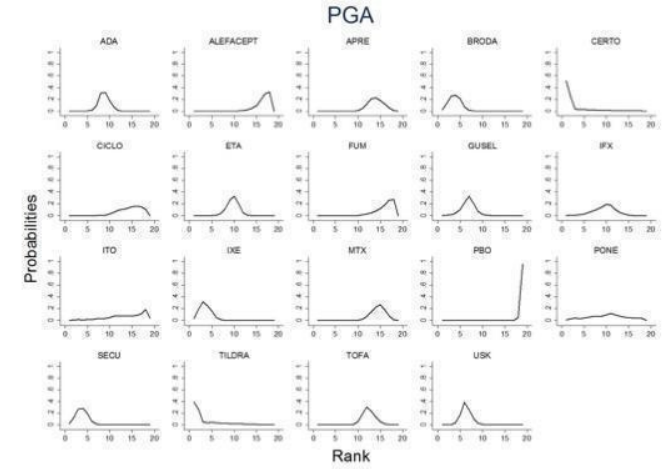
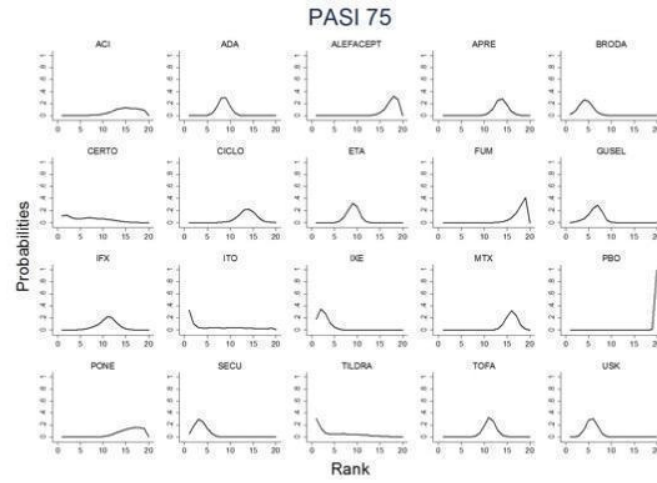
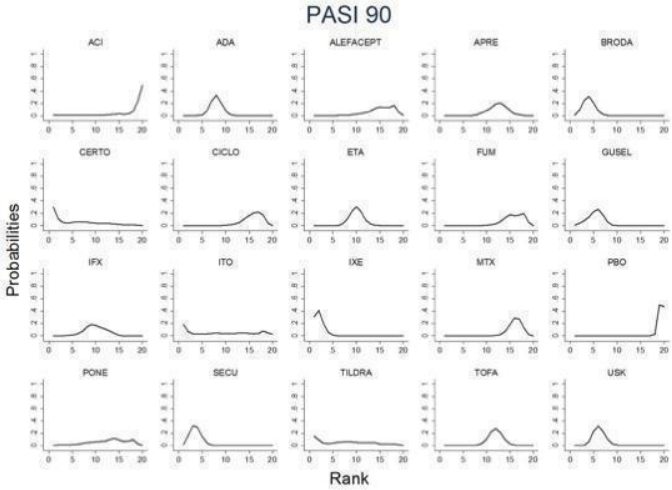
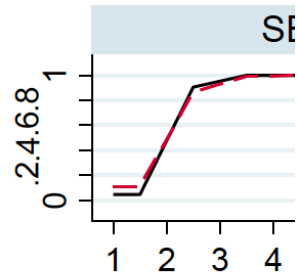
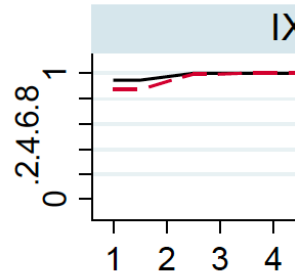
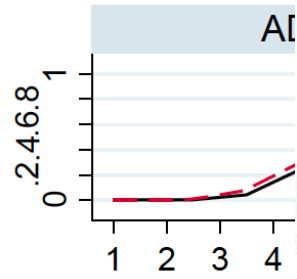


38 trials included in both reviews

10 of the 38 trials with the same ratings for all domains

Justification for the ratings

# Analysis outputs



Graphs by Treatment

# Key NMA assumptions

Heterogeneity (variation in the true treatment effect between the studies)

- Study ID
- CSA - PBO
- Warren
- Mrowietz3
- Saurat1
- Subtotal (I-squared = 64.5%, p = 0.060)
- SM - PBO
- Paul1
- Papp7
- Papp5
- Reich5
- Papp11
- Vaclavkova
- Bachelez
- Papp8
- Papp2
- Subtotal (I-squared = 0.0%, p = 0.607)

- I<sup>2</sup> for the dir
- Estimated h
- Prediction ir
- relative effe

	SAE, $\tau = 0$																					
I <sup>2</sup> E	0.95	1.08	1.12	2.28	1.26	0.82	1.10	2.01	1.14	1.14	1.34	0.43	1.55	1.46	4.97	4.86	1.14	1.12				
1.22	SECU	1.15	1.18	2.42	1.33	0.87	1.16	2.13	1.20	1.21	1.41	0.46	1.64	1.55	5.26	5.14	1.20	1.19				
1.28	1.04	BRODA	1.03	2.11	1.16	0.76	1.01	1.86	1.05	1.05	1.23	0.40	1.43	1.35	4.59	4.48	1.05	1.04				
1.54	1.26	1.21	GUSEL	2.04	1.13	0.74	0.98	1.80	1.02	1.02	1.20	0.39	1.39	1.31	4.45	4.35	1.02	1.00				
1.32	1.08	1.04	0.86	CERTO	0.55	0.36	0.48	0.88	0.50	0.50	0.58	0.19	0.68	0.64	2.18	2.13	0.50	0.49				
1.63	1.33	1.28	1.06	1.23	USK	0.55	0.87	1.60	0.90	0.91	1.06	0.34	1.23	1.16	3.95	3.86	0.90	0.89				
2.08	1.70	1.63	1.35	1.57	1.27	1.27	1.33	2.45	1.38	1.39	1.62	0.53	1.89	1.78	6.04	5.91	1.38	1.36				
2.18	1.79	1.71	1.41	1.65	1.34	1.05	ADA	1.83	1.04	1.04	1.22	0.40	1.42	1.33	4.53	4.43	1.04	1.02				
2.65	2.17	2.08	1.72	2.00	1.62	1.27	1.21	ITO	-	-	-	-	-	-	-	-	-	-				
2.90	2.38	2.28	1.88	2.20	1.78	1.40	1.33	1.10	IFX	0.56	0.57	0.66	0.22	0.77	0.73	2.47	2.41	0.56	0.56			
3.01	2.46	2.36	1.95	2.28	1.85	1.45	1.38	1.14	1.04	ETA	1.01	1.18	0.38	1.37	1.29	4.38	4.28	1.00	0.99			
3.82	3.12	2.99	2.47	2.89	2.34	1.84	1.75	1.44	1.32	1.27	TOFA	1.17	0.38	1.36	1.28	4.35	4.25	0.99	0.98			
4.24	3.47	3.32	2.75	3.21	2.60	2.04	1.94	1.46	1.41	1.11	APRE	0.32	1.16	1.09	3.72	3.64	0.85	0.84				
4.92	4.03	3.86	3.19	3.73	3.02	2.37	2.25	1.86	1.69	1.29	1.16	0.37	1.36	1.28	4.35	4.25	0.99	0.98				
7.40	6.05	5.80	4.80	5.60	4.54	3.56	3.39	2.80	2.55	2.46	1.94	1.75	1.50	ALEFACEPT	0.94	3.20	3.13	0.73	0.72			
7.94	6.49	6.22	5.14	6.01	4.87	3.82	3.64	3.00	2.73	2.64	2.08	1.87	1.61	1.07	FUM	3.40	3.32	0.78	0.77			
8.14	6.65	6.38	5.28	6.17	4.99	3.92	3.73	3.08	2.80	2.71	1.13	1.92	1.65	1.10	1.03	CICLO	0.98	0.23	0.23			
8.30	6.79	6.51	5.38	6.29	5.09	4.00	3.80	3.14	2.86	2.76	2.17	1.96	1.69	1.12	1.05	1.02	MTX	0.23	0.23			
33.10	27.08	25.95	21.45	25.07	20.31	15.94	15.16	12.51	11.40	11.00	8.67	7.81	6.73	4.47	4.07	3.59	3.59	ACI	0.99			
32.45	26.55	25.45	21.03	24.58	19.91	15.63	14.87	12.26	11.18	10.79	8.50	7.66	6.60	4.39	4.09	3.99	3.91	0.98	PRO			

27.53 (16.68,45.44) (13.30,56.97)  
43.27 (22.73,82.38) (18.64,100.43)  
8.88 (4.30,18.35) (3.57,22.12)  
37.14 (26.06,51.16) (26.20,67.00)

PASI 90,  $\tau = 0.09$



# Key NMA assumptions

Inconsistency (how the direct and indirect estimates of a particular comparison agree)



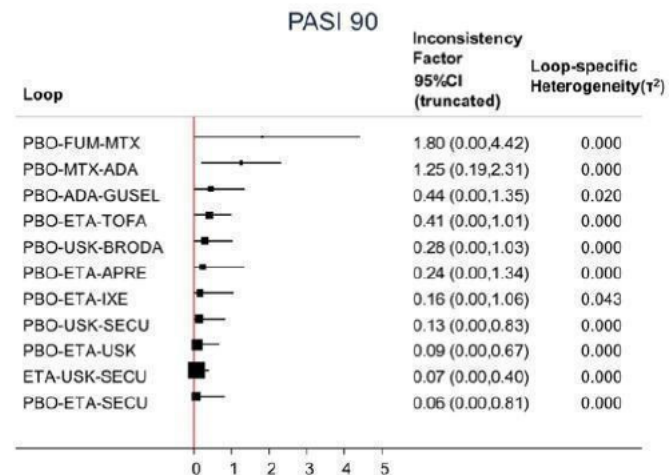
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## Specific and global inconsistency

- Loop-specific approach
- Side splitting method
- Interaction model



# Key NMA assumptions

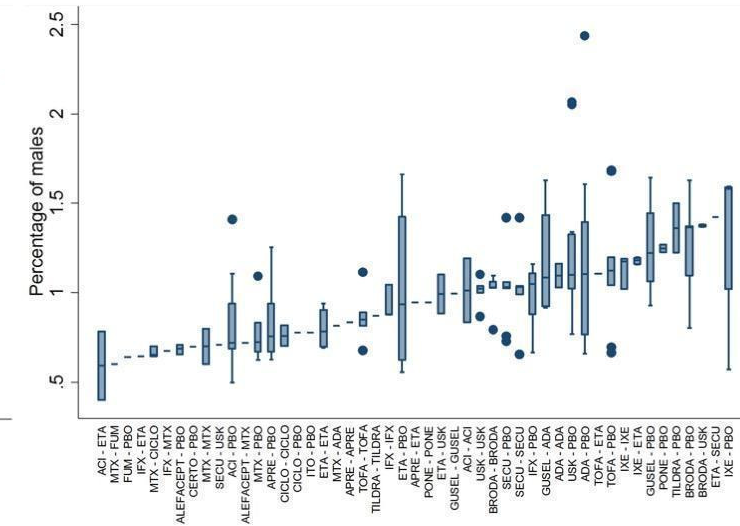
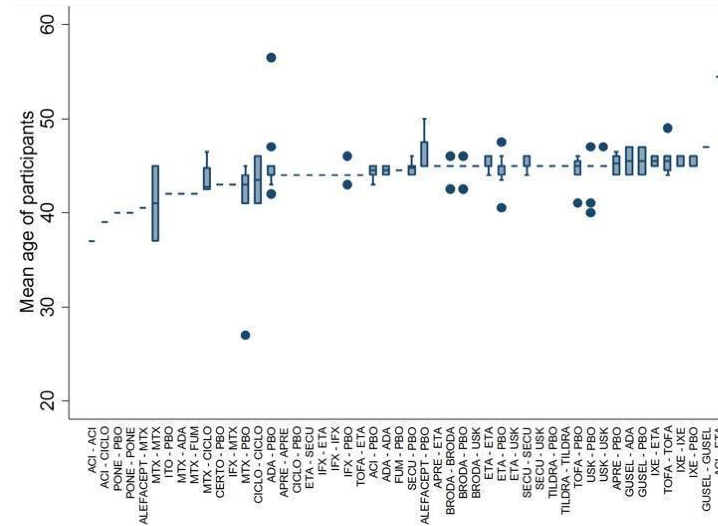
Transitivity (important differences between the trials other than the treatments)



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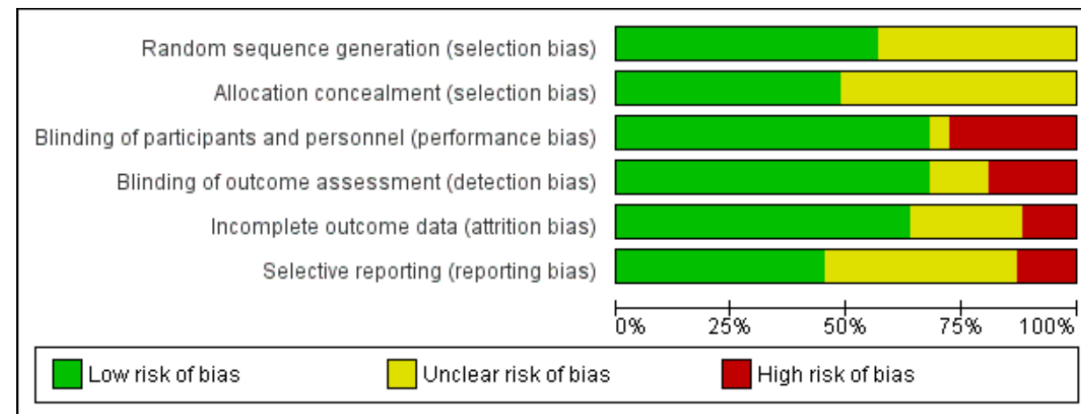
# Psoriasis and network meta-analyses

## Limits

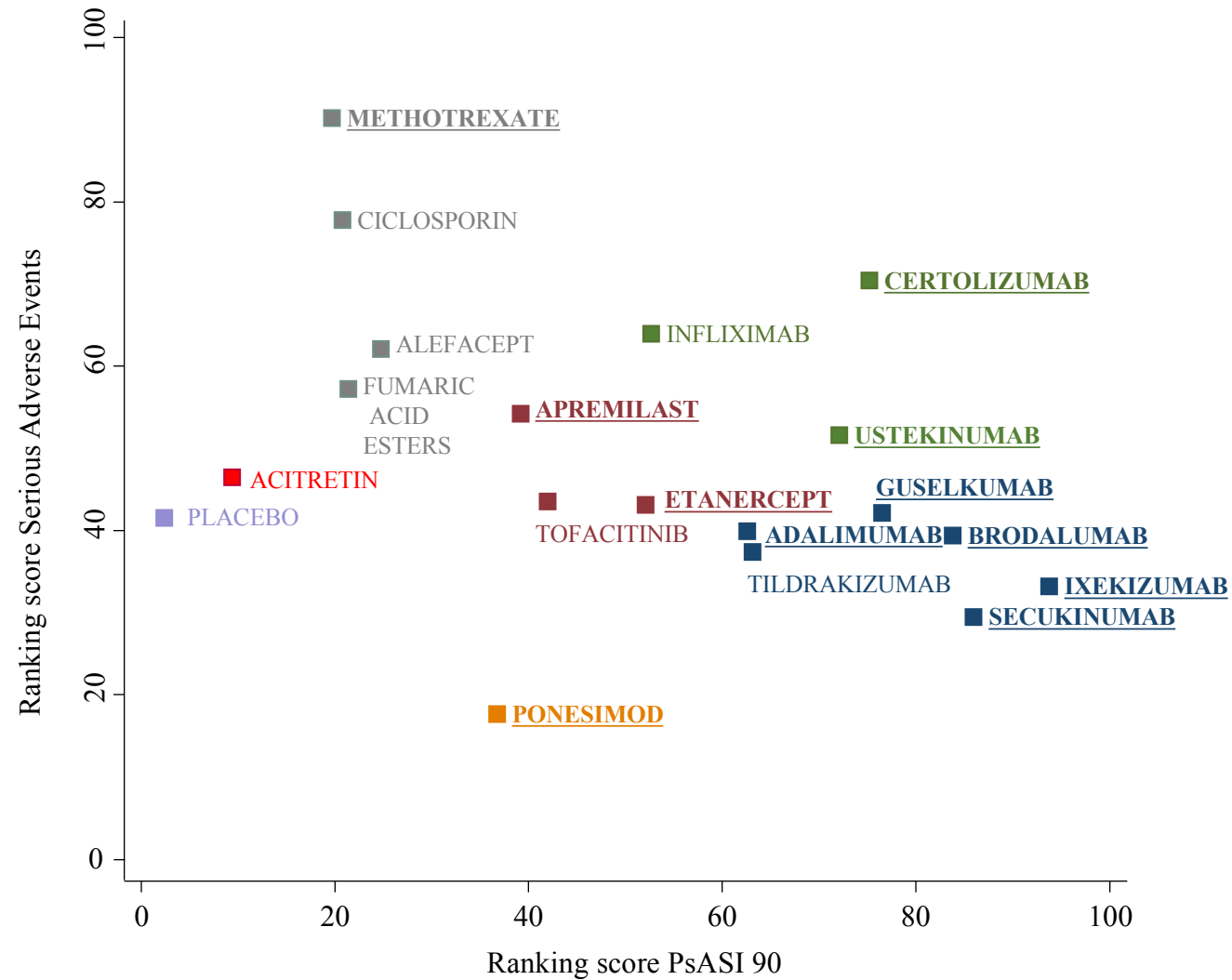
GRADE scale – For each primary outcomes, 4 levels of certainty of evidence could be assigned : high, moderate, low, very low

1. Risk of bias (blinding, randomisation, ITT, missing data...)
2. Imprecision (IC95%)
3. Heterogeneity
4. Indirect comparisons
5. Publication bias

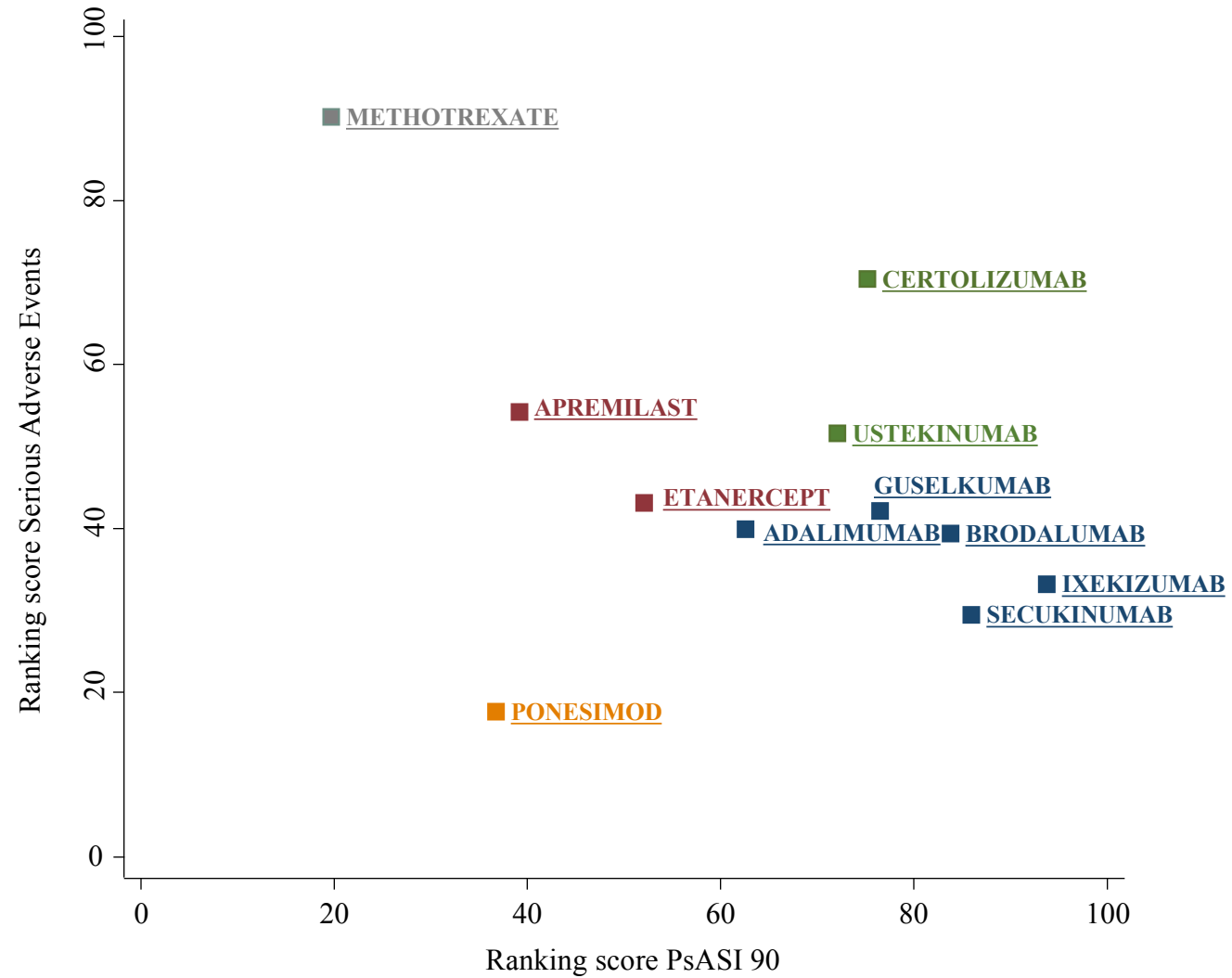
Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies



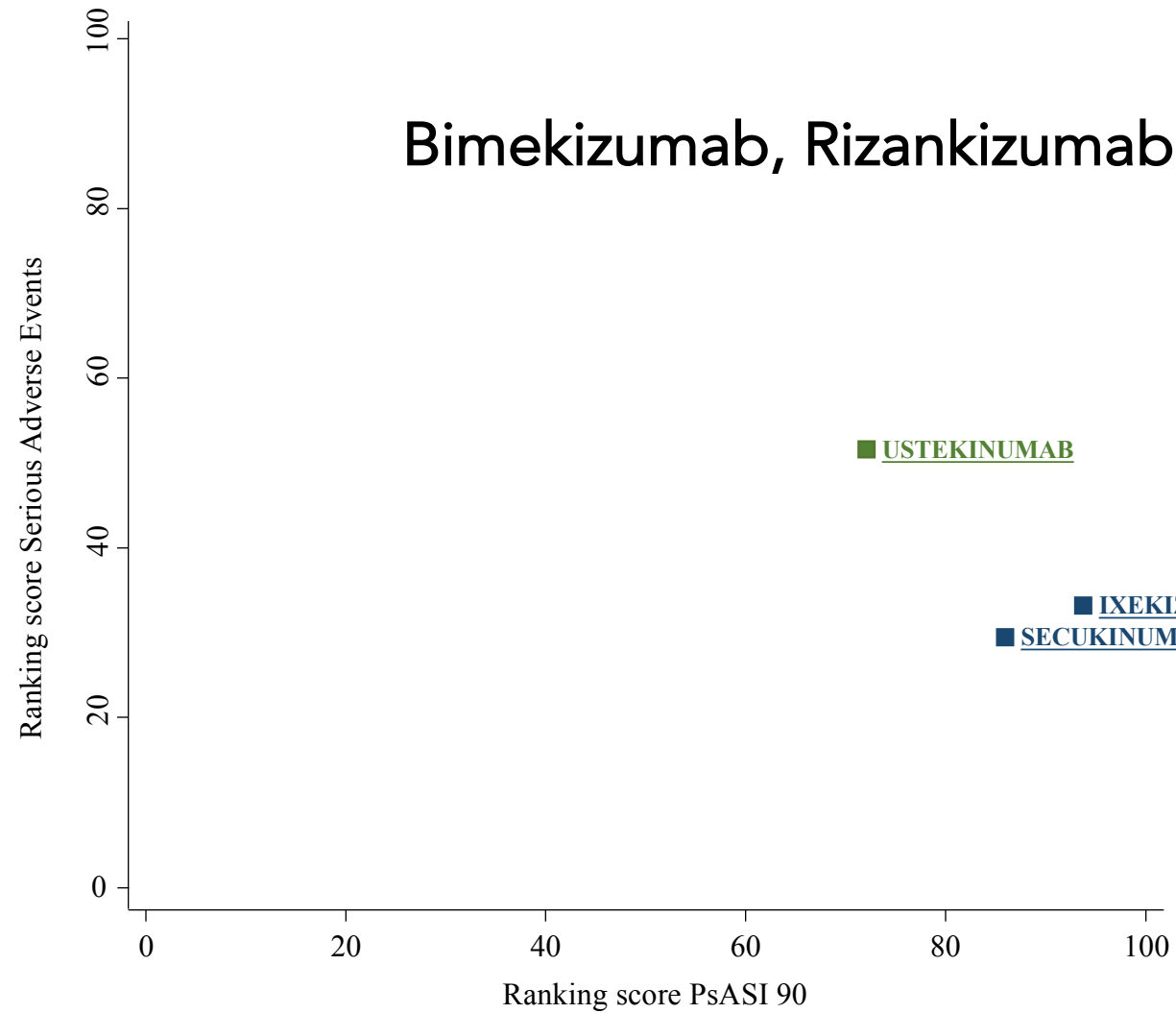
# All the interventions regardless of the level of certainty of evidence



# All the interventions with moderate to high level certainty of evidence



# All the interventions with high certainty of evidence



Bimekizumab, Rizankizumab, Mirikizumab... ?

# Living cumulative network meta-analyses



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# Outstanding issue

- Which treatment for which patient ?
  - Baseline characteristics
  - Psoriatic arthritis
  - Previous lines
- Such data are available !
  - Not (systematically) reported in the RCT
  - **Individual Patient Data (IPD) network meta-analysis**
- Campaigns promoting data sharing



“The right to search for truth implies also a duty; one must not conceal any part of what one has recognized to be true.”

*Albert Einstein*

# How to Request Data

## Data Request Process Diagram

### Instructions:

1. Review the [YODA Project Policies and Procedures](#)
2. Identify data of interest in the [Trial List](#)
  - a. If data of interest are not listed, [submit an Inquiry](#)
3. Log in
4. Complete the data request requirements. These include:
  - a. Names, degrees, and SCOPUS IDs (if available) for all Key Personnel
  - b. Project funding source (if applicable)
  - c. Conflict of Interest statement for the PI and Key Personnel ([form provided here](#))
  - d. Data Use Agreement Training ([training provided here](#))
  - e. Research Proposal ([instructions provided here](#))
  - f. Specify the type of data requested for identified trials: redacted full CSRs or IPD
5. Certify that all information provided is true, and that the requested data will not be used in pursuit of litigation or for commercial interests
6. Submit data request

# Take home messages

- Not a network meta-analysis but network meta-analyses
- Pay attention to PICO criteria
- Check for inconsistency, heterogeneity and level of certainty of evidence