
Στοχεύοντας την ύφεση στη
Ρευματοειδή αρθρίτιδα: Ποια είναι η
θέση των εκλεκτικών JAK αναστολέων;

Θάνος Κουτρούμπας
Βόλος.

Σύγκρουση συμφερόντων

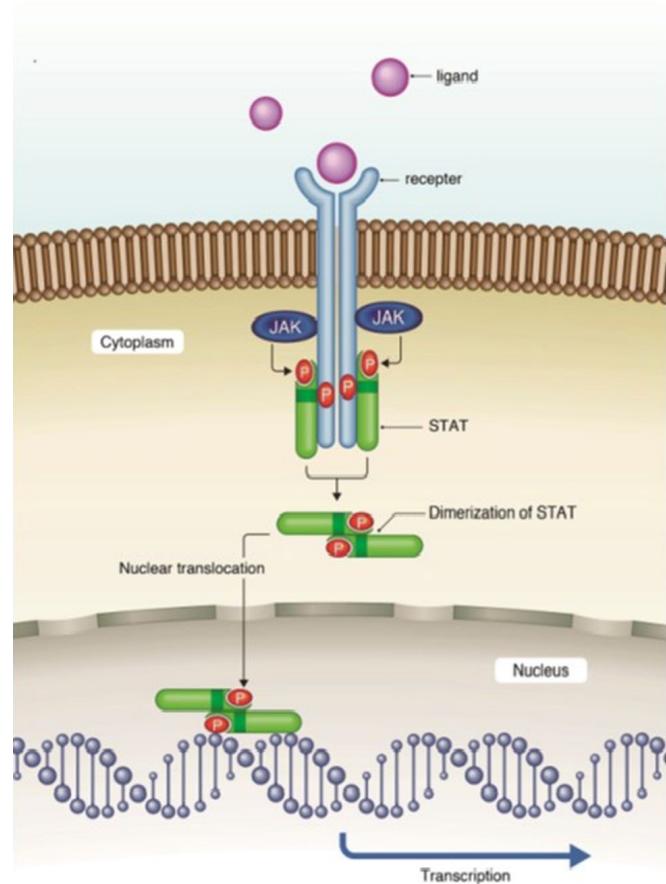
Τιμητική αμοιβή από την εταιρεία AbbVie

Την τελευταία διετία τιμητικές αμοιβές από τις εταιρείες Genesis Pharma, UCB, Roche

Το σύστημα JAK-STAT

Μετάδοση σημάτων (signal transducer) και ενεργοποίηση της μετάφρασης γονιδίων και σύνθεσης πρωτεΐνών

Μεταφέρει σήματα από τους υποδοχείς κυτταροκινών και αυξητικών παραγόντων της κυτταρικής μεμβράνης στον πυρήνα.

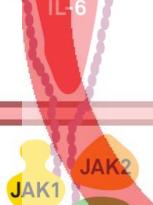
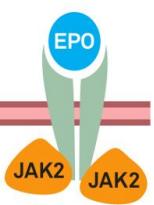


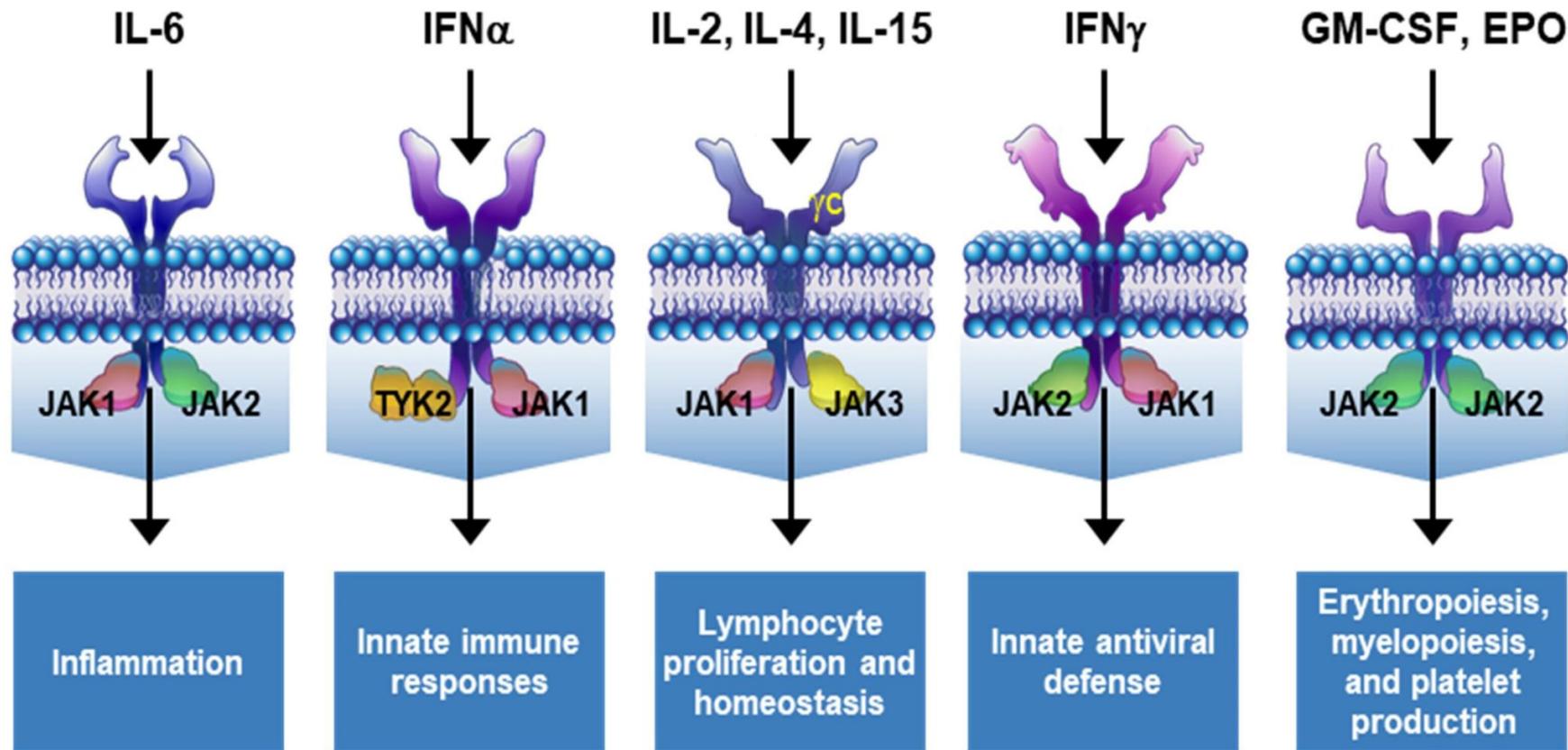


Πόσα είδη Jak υπάρχουν;

- ➔ **JAK 1,2,3**
- ➔ **TYK 2**
- ➔ **STAT 1,2,3,4,5A,5B,6**

Cytokine and cytokine receptor families	Cytokine receptor sharing the γ -chain (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21)	Cytokine receptor sharing the gp130 (IL-6, IL-11, IL-13, IL-25, IL-27, IL-31)	IFN- γ receptor	Type I IFN Receptor (IFN α/β)	IL-10 family receptor (IL-10, IL-22)	Receptors for Cytokine sharing the IL-12R β 1 (IL-12, IL-23)	Homo-dimeric cytokine receptor (GM-CSF, EPO, TP, IL-3, IL-5)
	STAT 1, 3, 5, 6	STAT 1, 3, 5	STAT 1, 3, 5	STAT 1, 2, 3	STAT 1, 3, 5	STAT 3, 4	STAT 5

Cytokine and cytokine receptor families	Cytokine receptor sharing the γ -chain (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21)	Cytokine receptor sharing the gp130 (IL-6, IL-11, IL-13, IL-25, IL-27, IL-31)	IFN- γ receptor	Type I IFN Receptor (IFN α/β)	IL-10 family receptor (IL-10, IL-22)	Receptors for Cytokine sharing the IL-12R β 1 (IL-12, IL-23)	Homo-dimeric cytokine receptor (GM-CSF, EPO, TP, IL-3, IL-5)
							
	STAT 1, 3, 5, 6	STAT 1, 3, 5	STAT 1, 3, 5	STAT 1, 2, 3	STAT 1, 3, 5	STAT 3, 4	STAT 5



-

Jak inhibitors

Tofacitinib- Jak 1, 2, 3

Baricitinib- Jak 1, 2

Upadacitinib- Jak 1

Filgotinib- Jak 1

Peficitinib- Jak 1, 2, 3

JAK inhibitors

Εκλεκτικότητα ή ειδικότητα;



Tip

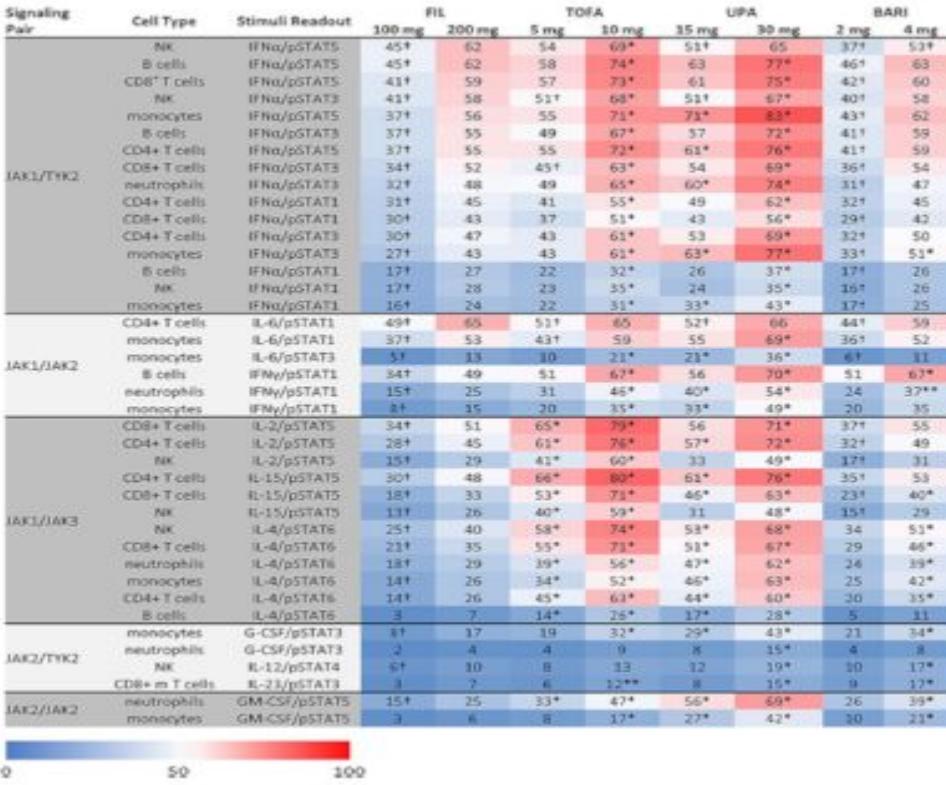
Εκλεκτικότητα: ο βαθμός με τον οποίο ένα φάρμακο συνδέεται σε ένα σημείο, σε σχέση με άλλα σημεία

Ειδικότητα: ο βαθμός στον οποίο ένα φάρμακο προκαλεί μία δράση σε ένα πληθυσμό κυττάρων

JAKis: εκλεκτικοί - όχι ειδικοί

Μερική, αναστρέψιμη
αναστολή

A.



JAKis: εκλεκτικοί - όχι ειδικοί

Μερική, αναστρέψιμη
αναστολή

A.

Signaling Pair	Cell Type	Stimuli Readout	FIL		TOFA			UPA		BARI	
			100 mg	200 mg	5 mg	10 mg	15 mg	30 mg	2 mg	4 mg	
JAK1/TYK2	NK	IFN γ /pSTAT5	45*	62	54	69*	51*	65	37*	53*	
	B cells	IFN γ /pSTAT5	45*	62	58	74*	63	77*	46*	63	
	CD8+ T cells	IFN γ /pSTAT5	43*	59	57	73*	61	75*	42*	60	
	NK	IFN γ /pSTAT3	41*	58	51*	68*	51*	67*	40*	58	
	monocytes	IFN γ /pSTAT5	37*	56	55	71*	71*	83*	43*	62	
	B cells	IFN γ /pSTAT3	37*	55	49	67*	57	72*	41*	59	
	CD4+ T cells	IFN γ /pSTAT5	37*	55	55	72*	61*	76*	41*	59	
	CD8+ T cells	IFN γ /pSTAT5	34*	52	45*	63*	54	69*	36*	54	
	neutrophils	IFN γ /pSTAT5	32*	48	49	65*	60*	74*	31*	47	
	CD4+ T cells	IFN γ /pSTAT1	31*	45	41	55*	49	62*	32*	45	
JAK1/JAK2	CD8+ T cells	IFN γ /pSTAT1	30*	43	37	53*	43	56*	29*	42	
	CD4+ T cells	IFN γ /pSTAT3	30*	47	43	61*	53	69*	32*	50	
	monocytes	IFN γ /pSTAT3	27*	43	43	61*	63*	77*	33*	51*	
	B cells	IFN γ /pSTAT1	17*	27	22	32*	26	37*	17*	26	
	NK	IFN γ /pSTAT1	17*	28	23	35*	24	35*	16*	26	
	monocytes	IFN γ /pSTAT1	16*	24	22	31*	33*	43*	17*	25	
	CD4+ T cells	IL-6/pSTAT1	49*	65	51*	65	52*	66	44*	59	
	monocytes	IL-6/pSTAT1	37*	53	43*	59	55	69*	36*	52	
	B cells	IL-6/pSTAT1	5*	—	—	—	23*	36*	6*	11	
	neutrophils	IFN γ /pSTAT1	—	—	—	—	—	70*	51	67*	
JAK3/JAK3	monocytes	IFN γ /pSTAT1	—	—	—	—	—	54*	24	37**	
	CD8+ T cells	IL-2/pSTAT1	—	—	—	—	—	49*	20	35	
	CD4+ T cells	IL-2/pSTAT1	—	—	—	—	—	71*	37*	55	
	NK	IL-2/pSTAT1	—	—	—	—	—	72*	32*	49	
	CD4+ T cells	IL-15/pSTAT1	—	—	—	—	—	49*	17*	31	
	CD8+ T cells	IL-15/pSTAT1	—	—	—	—	—	76*	35*	53	
	NK	IL-15/pSTAT1	—	—	—	—	—	63*	23*	40*	
	CD8+ T cells	IL-4/pSTAT1	—	—	—	—	—	48*	15*	29	
	CD4+ T cells	IL-4/pSTAT1	—	—	—	—	—	68*	34	51*	
	monocytes	IL-4/pSTAT1	—	—	—	—	—	67*	29	46*	
JAK2/TYK2	neutrophils	IL-4/pSTAT1	—	—	—	—	—	62*	24	39*	
	NK	IL-12/pSTAT1	—	—	—	—	—	63*	25	42*	
	CD8+ m T cells	IL-23/pSTAT1	—	—	—	—	—	60*	30	35*	
	monocytes	G-CSF/pSTAT1	—	—	—	—	—	28*	5	11	
JAK2/JAK2	neutrophils	G-CSF/pSTAT1	—	—	—	—	—	43*	23	34*	
	NK	IL-12/pSTAT1	—	—	—	—	—	15*	4	8	
	CD8+ m T cells	IL-23/pSTAT1	—	—	—	—	—	19*	30	17*	
	monocytes	GM-CSF/pSTAT1	—	—	—	—	—	15*	9	12*	



Tip

Δοσοεξαρτώμενη
Εξαρτώμενη από
τον τύπο του
κυττάρου

A.

Signaling Pair	Cell Type	Stimuli Readout	FIL		TOFA			UPA		BARI	
			100 mg	200 mg	5 mg	10 mg	15 mg	30 mg	2 mg	4 mg	
JAK1/TYK2	NK	IFN α /pSTAT5	45 [†]	62	54	69 [*]	51 [†]	65	37 [†]	53 [†]	
	B cells	IFN α /pSTAT5	45 [†]	62	58	74 [*]	63	77 [*]	46 [†]	63	
	CD8 ⁺ T cells	IFN α /pSTAT5	43 [†]	59	57	73 [*]	61	75 [*]	42 [†]	60	
	NK	IFN α /pSTAT3	41 [†]	58	51 [†]	68 [*]	51 [†]	67 [*]	40 [†]	58	
	monocytes	IFN α /pSTAT5	37 [†]	56	55	71 [*]	71 [*]	83 [*]	43 [†]	62	
	B cells	IFN α /pSTAT3	37 [†]	55	49	67 [*]	57	72 [*]	41 [†]	59	
	CD4 ⁺ T cells	IFN α /pSTAT5	37 [†]	55	55	72 [*]	61 [*]	76 [*]	41 [†]	59	
	CD8 ⁺ T cells	IFN α /pSTAT3	34 [†]	52	45 [†]	63 [*]	54	69 [*]	36 [†]	54	
	neutrophils	IFN α /pSTAT5	32 [†]	48	49	65 [*]	60 [*]	74 [*]	31 [†]	47	
	CD4 ⁺ T cells	IFN α /pSTAT1	31 [†]	45	41	55 [*]	49	62 [*]	32 [†]	45	
JAK1/JAK2	CD8 ⁺ T cells	IFN α /pSTAT1	30 [†]	43	37	53 [*]	43	56 [*]	29 [†]	42	
	CD4 ⁺ T cells	IFN α /pSTAT3	30 [†]	47	43	61 [*]	53	69 [*]	32 [†]	50	
	monocytes	IFN α /pSTAT3	27 [†]	43	43	61 [*]	63 [*]	77 [*]	33 [†]	51 [†]	
	B cells	IFN α /pSTAT1	17 [†]	27	22	32 [*]	26	37 [*]	17 [†]	26	
	NK	IFN α /pSTAT1	17 [†]	28	23	35 [*]	24	35 [*]	16 [†]	26	
	monocytes	IFN α /pSTAT1	16 [†]	24	22	31 [*]	33 [*]	43 [*]	17 [†]	25	
	CD4 ⁺ T cells	IL-6/pSTAT1	49 [†]	65	51 [†]	65	52 [†]	66	44 [†]	59	
	monocytes	IL-6/pSTAT1	37 [†]	53	43 [†]	59	55	69 [*]	36 [†]	52	
	monocytes	IL-6/pSTAT3	51 [†]	33	30	23 [*]	23 [*]	36 [*]	6 [†]	11	
	B cells	IFN γ /pSTAT1	34 [†]	49	51	67 [*]	56	70 [*]	51	67 [*]	
JAK1/JAK3	neutrophils	IFN γ /pSTAT1	15 [†]	25	31	45 [*]	40 [*]	54 [*]	24	37 ^{**}	
	monocytes	IFN γ /pSTAT1	2 [†]	15	20	35 [*]	33 [*]	49 [*]	20	35	
	CD8 ⁺ T cells	IL-2/pSTAT5	34 [†]	51	65 [*]	79 [*]	56	71 [*]	37 [†]	55	
	CD4 ⁺ T cells	IL-2/pSTAT5	28 [†]	45	61 [†]	76 [*]	57 [*]	72 [*]	32 [†]	49	
	NK	IL-2/pSTAT5	15 [†]	29	41 [*]	60 [*]	33	49 [*]	17 [†]	31	
	CD4 ⁺ T cells	IL-15/pSTAT5	30 [†]	48	66 [*]	80 [*]	61 [*]	76 [*]	35 [†]	53	
	CD8 ⁺ T cells	IL-15/pSTAT5	18 [†]	33	53 [*]	73 [*]	46 [*]	63 [*]	23 [†]	40 [*]	
	NK	IL-15/pSTAT5	11 [†]	26	40 [*]	59 [*]	31	48 [*]	15 [†]	29	
	CD8 ⁺ T cells	IL-4/pSTAT5	25 [†]	40	58 [*]	74 [*]	53 [*]	68 [*]	34	51 [*]	
	monocytes	IL-4/pSTAT5	21 [†]	35	55 [*]	73 [*]	51 [*]	67 [*]	29	46 [*]	
JAK2/TYK2	neutrophils	IL-4/pSTAT6	18 [†]	29	39 [*]	56 [*]	47 [*]	62 [*]	24	39 [*]	
	monocytes	IL-4/pSTAT6	14 [†]	26	34 [*]	52 [*]	46 [*]	63 [*]	25	42 [*]	
	CD4 ⁺ T cells	IL-4/pSTAT6	14 [†]	26	45 [*]	63 [*]	44 [*]	60 [*]	30	35 [*]	
	B cells	IL-4/pSTAT6	3	7	14 [*]	26 [*]	17 [*]	28 [*]	5	11	
	monocytes	G-CSF/pSTAT3	8 [†]	17	19	32 [*]	29 [*]	43 [*]	23	34 [*]	
	neutrophils	G-CSF/pSTAT3	2	4	4	9	8	15 [*]	4	8	
	NK	G-CSF/pSTAT4	5 [†]	10	8	13	12	19 [*]	10	17 [*]	
	CD8 ⁺ T cells	G-CSF/pSTAT3	3	7	6	12 ^{**}	8	15 [*]	9	12 [*]	
	neutrophils	GM-CSF/pSTAT5	15 [†]	25	33 [*]	47 [*]	56 [*]	69 [*]	26	39 [*]	
	monocytes	GM-CSF/pSTAT5	3	6	8	17 [*]	27 [*]	42 [*]	10	23 [*]	



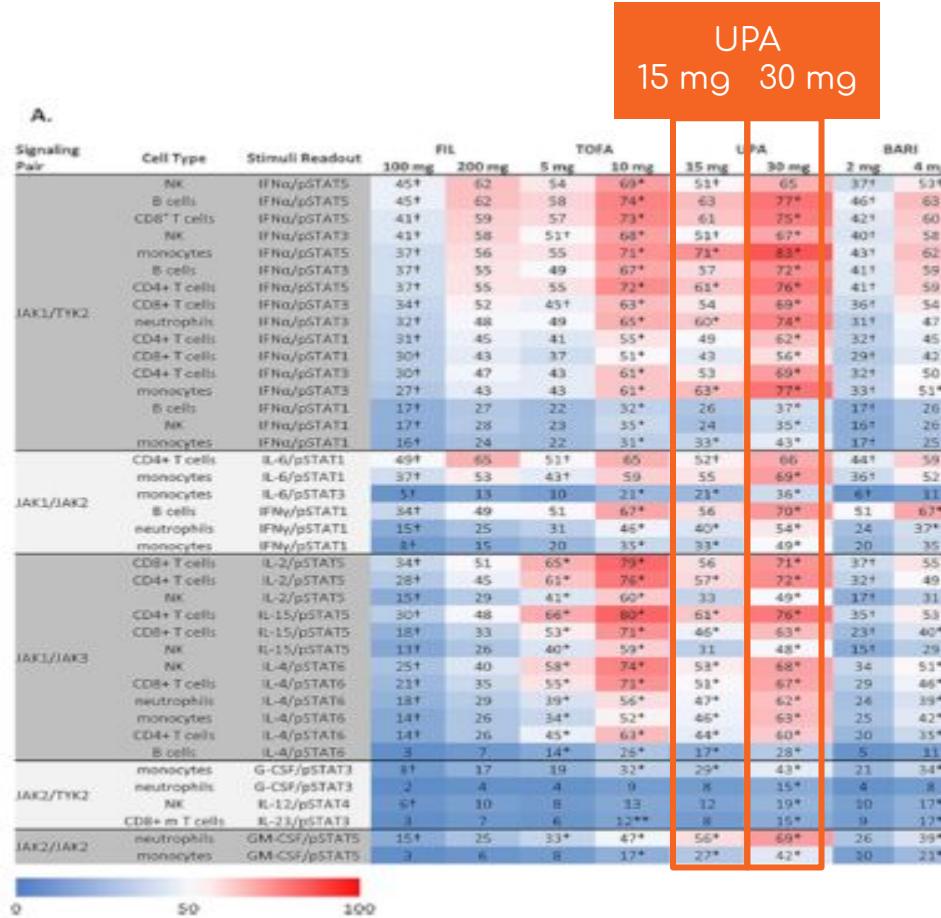
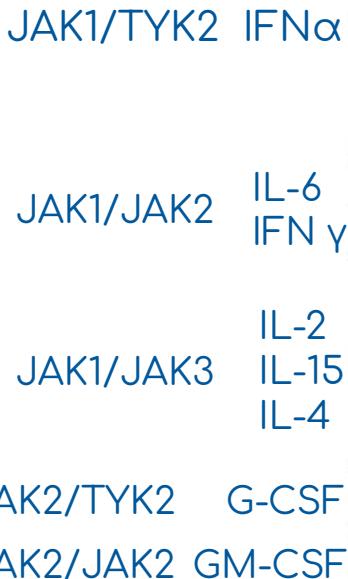
Calculated average target inhibition (AUC-24h +/- SD) over a 24h for selected JAKinibs for a given stimuli/cell type/pSTAT based on in vitro measurements in whole blood from healthy donors dose interval

JAK1/JAK2 IL-6
 IFN γ
 IL-2
 IL-15
 IL-4

 JAK1/JAK3

 JAK2/TYK2 G-CSF
 JAK2/JAK2 GM-CSF

Calculated average target inhibition (AUC-24h +/- SD) over a 24h for selected JAKinibs for a given stimuli/cell type/pSTAT based on in vitro measurements in whole blood from healthy donors dose interval



Calculated average target inhibition (AUC-24h +/- SD) over a 24h for selected JAKinibs for a given stimuli/cell type/pSTAT based on in vitro measurements in whole blood from healthy donors dose interval

JAK1/TYK2 IFN α
JAK1/JAK2 IL-6
IFN γ
JAK1/JAK3 IL-2
IL-15
IL-4
JAK2/TYK2 G-CSF
JAK2/JAK2 GM-CSF

A.

Signaling Pair	Cell Type	Stimuli Readout	Fil		TOFA		UPA		BARI	
			100 mg	200 mg	5 mg	10 mg	35 mg	30 mg	2 mg	4 mg
JAK1/TYK2	NK	IFN α /pSTAT5	45 \pm	62	54	69 \pm	51 \pm	65	37 \pm	53 \pm
	B cells	IFN α /pSTAT5	45 \pm	62	58	74 \pm	63	77 \pm	46 \pm	63
	CD8 \pm T cells	IFN α /pSTAT5	43 \pm	59	57	73 \pm	61	75 \pm	42 \pm	60
	NK	IFN α /pSTAT3	41 \pm	58	51 \pm	68 \pm	51 \pm	67 \pm	40 \pm	58
	monocytes	IFN α /pSTAT3	37 \pm	55	49	67 \pm	57	72 \pm	41 \pm	59
	B cells	IFN α /pSTAT3	37 \pm	55	55	72 \pm	61 \pm	76 \pm	41 \pm	59
	CD4 \pm T cells	IFN α /pSTAT3	34 \pm	52	45 \pm	63 \pm	54	69 \pm	36 \pm	54
	neutrophils	IFN α /pSTAT3	32 \pm	48	49	65 \pm	60 \pm	74 \pm	31 \pm	47
	CD4 \pm T cells	IFN α /pSTAT1	31 \pm	45	41	55 \pm	49	62 \pm	32 \pm	45
	CD8 \pm T cells	IFN α /pSTAT1	30 \pm	43	37	53 \pm	43	56 \pm	29 \pm	42
JAK1/JAK2	CD4 \pm T cells	IFN α /pSTAT1	30 \pm	47	43	61 \pm	53	69 \pm	32 \pm	50
	monocytes	IFN α /pSTAT3	27 \pm	43	43	61 \pm	63 \pm	77 \pm	33 \pm	51 \pm
	NK	IFN α /pSTAT1	17 \pm	27	22	32 \pm	26	37 \pm	17 \pm	26
	monocytes	IFN α /pSTAT1	16 \pm	24	22	31 \pm	33 \pm	43 \pm	17 \pm	25
	CD4 \pm T cells	IL-6/pSTAT1	49 \pm	65	51 \pm	65	52 \pm	66	44 \pm	59
	monocytes	IL-6/pSTAT1	37 \pm	53	43 \pm	59	55	69 \pm	36 \pm	52
	B cells	IL-6/pSTAT1	51	33	30	23 \pm	23 \pm	36 \pm	61	11
	neutrophils	IFN γ /pSTAT1	34 \pm	49	51	67 \pm	56	70 \pm	51	67 \pm
	monocytes	IFN γ /pSTAT1	31 \pm	25	31	45 \pm	40 \pm	54 \pm	24	37 \pm
	CD8 \pm T cells	IL-2/pSTAT5	34 \pm	51	65 \pm	79 \pm	56	71 \pm	37 \pm	55
JAK1/JAK3	CD4 \pm T cells	IL-2/pSTAT5	28 \pm	45	61 \pm	76 \pm	57 \pm	72 \pm	32 \pm	49
	NK	IL-2/pSTAT5	15 \pm	29	41 \pm	60 \pm	33	49 \pm	17 \pm	31
	CD4 \pm T cells	IL-15/pSTAT5	30 \pm	48	66 \pm	80 \pm	61 \pm	76 \pm	35 \pm	53
	CD8 \pm T cells	IL-15/pSTAT5	18 \pm	33	53 \pm	73 \pm	46 \pm	63 \pm	23 \pm	40 \pm
	NK	IL-15/pSTAT5	11 \pm	26	40 \pm	59 \pm	31	48 \pm	15 \pm	29
	CD8 \pm T cells	IL-4/pSTAT5	25 \pm	40	58 \pm	74 \pm	53 \pm	68 \pm	34	51 \pm
	B cells	IL-4/pSTAT5	21 \pm	35	55 \pm	73 \pm	51 \pm	67 \pm	29	46 \pm
	monocytes	IL-4/pSTAT5	18 \pm	29	39 \pm	56 \pm	47 \pm	62 \pm	24	39 \pm
	CD4 \pm T cells	IL-4/pSTAT5	14 \pm	26	34 \pm	52 \pm	46 \pm	63 \pm	25	42 \pm
	B cells	IL-4/pSTAT5	14 \pm	26	45 \pm	63 \pm	44 \pm	60 \pm	30	35 \pm
JAK2/TYK2	monocytes	G-CSF/pSTAT3	81	17	19	32 \pm	29 \pm	43 \pm	21	34 \pm
	neutrophils	G-CSF/pSTAT3	2	4	4	9	8	15 \pm	4	8
	NK	G-CSF/pSTAT4	51	10	8	13	12	19 \pm	10	17 \pm
	CD8 \pm T cells	G-CSF/pSTAT3	3	7	6	12 \pm	8	15 \pm	9	12 \pm
	neutrophils	GM-CSF/pSTAT5	15 \pm	25	33 \pm	47 \pm	56 \pm	69 \pm	26	39 \pm
JAK2/JAK2	monocytes	GM-CSF/pSTAT5	3	6	8	17 \pm	27 \pm	42 \pm	10	23 \pm



UPA
15 mg 30 mg

Δοσοεξαρτώμενη δράση
KAI εκλεκτικότητα

Calculated average target inhibition (AUC-24h +/- SD) over a 24h for selected JAKinibs for a given stimuli/cell type/pSTAT based on in vitro measurements in whole blood from healthy donors dose interval

JAK1/TYK2 IFN α
 JAK1/JAK2 IL-6
 IFN γ
 JAK1/JAK3 IL-2
 IL-15
 IL-4
 JAK2/TYK2 G-CSF
 JAK2/JAK2 GM-CSF



Calculated average target inhibition (AUC-24h +/- SD) over a 24h for selected JAKinibs for a given stimuli/cell type/pSTAT based on in vitro measurements in whole blood from healthy donors dose interval

JAK1/TYK2 IFN α

JAK1/JAK2 IL-6
IFN γ

JAK1/JAK3 IL-2
IL-15
IL-4

JAK2/TYK2 G-CSF

JAK2/JAK2 GM-CSF

A.

Signaling Pair	Cell Type	Stimuli Readout	FIL				TOFA		UPA		BARI	
			100 mg	200 mg	5 mg	10 mg	15 min	30 min	2 mg	4 mg	2 mg	4 mg
JAK1/TYK2	B cells	IFN α /pSTAT5	45 \pm	62	54	69*	--	--	37 \pm	53 \pm	37 \pm	63
	CD8 \pm T cells	IFN α /pSTAT5	45 \pm	62	58	74*	63	77*	46 \pm	63	42 \pm	60
	NK	IFN α /pSTAT5	43 \pm	59	57	73*	61	75*	42 \pm	60	40 \pm	58
	monocytes	IFN α /pSTAT5	41 \pm	58	51 \pm	68*	51 \pm	67*	40 \pm	58	39 \pm	58
	B cells	IFN α /pSTAT3	37 \pm	55	49	67*	57	72*	41 \pm	59	39 \pm	59
	CD4 \pm T cells	IFN α /pSTAT3	37 \pm	55	55	72*	61 \pm	76*	41 \pm	59	36 \pm	54
	CD8 \pm T cells	IFN α /pSTAT3	34 \pm	52	45 \pm	63*	54	69*	36 \pm	54	31 \pm	47
	neutrophils	IFN α /pSTAT3	32 \pm	48	49	65*	60*	74*	31 \pm	45	32 \pm	45
	CD4 \pm T cells	IFN α /pSTAT1	31 \pm	45	41	55*	49	62*	29 \pm	42	29 \pm	42
	CD8 \pm T cells	IFN α /pSTAT1	30 \pm	43	37	53*	43	56*	32 \pm	50	32 \pm	50
	monocytes	IFN α /pSTAT1	30 \pm	47	43	61*	53	69*	32 \pm	50	32 \pm	50
	B cells	IFN α /pSTAT1	27 \pm	43	43	61*	63*	77*	33 \pm	51*	33 \pm	51*
	NK	IFN α /pSTAT1	17 \pm	27	22	32*	26	37*	17 \pm	26	17 \pm	25
	CD4 \pm T cells	IFN α /pSTAT1	17 \pm	28	23	35*	24	35*	16 \pm	26	16 \pm	25
	monocytes	IFN α /pSTAT1	16 \pm	24	22	33*	33*	43*	17 \pm	25	17 \pm	25
JAK1/JAK2	CD4 \pm T cells	IL-6/pSTAT5	49 \pm	65	51 \pm	65	--	--	44 \pm	59	36 \pm	52
	monocytes	IL-6/pSTAT1	37 \pm	53	43 \pm	59	55	69*	36 \pm	52	36 \pm	52
	monocytes	IL-6/pSTAT5	51	33	30	23*	23*	36*	61	71	61	71
	B cells	IFN γ /pSTAT1	34 \pm	49	51	67*	56	70*	51	67*	51	67*
	neutrophils	IFN γ /pSTAT5	15 \pm	25	31	45*	40*	54*	24	37**	24	37**
	monocytes	IFN γ /pSTAT5	21 \pm	35	20	35*	33*	49*	20	35	20	35
	CD8 \pm T cells	IL-2/pSTAT5	34 \pm	51	65*	79*	56	71*	37 \pm	55	32 \pm	49
	CD4 \pm T cells	IL-2/pSTAT5	28 \pm	45	61*	76*	57*	72*	32 \pm	49	32 \pm	49
	NK	IL-2/pSTAT5	15 \pm	29	41*	60*	33	49*	17 \pm	31	17 \pm	31
	CD4 \pm T cells	IL-15/pSTAT5	30 \pm	48	66*	80*	61*	76*	35 \pm	53	35 \pm	53
JAK1/JAK3	CD8 \pm T cells	IL-15/pSTAT5	18 \pm	33	53*	73*	46*	63*	23 \pm	40*	23 \pm	40*
	NK	IL-15/pSTAT5	11 \pm	26	40*	59*	31	48*	15 \pm	29	15 \pm	29
	CD4 \pm T cells	IL-4/pSTAT5	25 \pm	40	58*	74*	53*	68*	34	51*	34	51*
	monocytes	IL-4/pSTAT6	21 \pm	35	55*	73*	51*	67*	29	46*	29	46*
	neutrophils	IL-4/pSTAT6	18 \pm	29	39*	56*	47*	62*	24	39*	24	39*
	monocytes	IL-4/pSTAT6	14 \pm	26	34*	52*	46*	63*	25	42*	25	42*
	CD4 \pm T cells	IL-4/pSTAT6	14 \pm	26	45*	63*	44*	60*	30	35*	30	35*
	B cells	IL-4/pSTAT6	3	7	14*	26*	17*	28*	5	11	5	11
	monocytes	G-CSF/pSTAT5	8 \pm	17	19	32*	29*	43*	23	34*	23	34*
	neutrophils	G-CSF/pSTAT3	2	4	4	9	8	15*	4	8	4	8
JAK2/TYK2	NK	IL-12/pSTAT4	5 \pm	10	8	13	12	19*	10	17*	10	17*
	CDB \pm T cells	IL-23/pSTAT3	3	7	6	12**	8	15*	9	12*	9	12*
	neutrophils	GM-CSF/pSTAT5	15 \pm	25	33*	47*	56*	69*	26	39*	26	39*
	monocytes	GM-CSF/pSTAT5	3	6	8	17*	27*	42*	10	23*	10	23*

0 50

Διαφορετική δράση σε διαφορετικά κύτταρα

Calculated average target inhibition (AUC-24h +/- SD) over a 24h for selected JAKinibs for a given stimuli/cell type/pSTAT based on in vitro measurements in whole blood from healthy donors dose interval

JAK1/TYK2 IFN α
 JAK1/JAK2 IL-6
 IFN γ
 JAK1/JAK3 IL-2
 IL-15
 IL-4
 JAK2/TYK2 G-CSF
 JAK2/JAK2 GM-CSF



Calculated average target inhibition (AUC-24h +/- SD) over a 24h for selected JAKinibs for a given stimuli/cell type/pSTAT based on in vitro measurements in whole blood from healthy donors dose interval

			JAK1/TYK2	IFNα		
			JAK1/JAK2	IL-6	IFN γ	
			JAK1/JAK3	IL-2	IL-15	IL-4
JAK2/TYK2	G-CSF					
JAK2/JAK2	GM-CSF					



Διαφορετική δράση του ίδιου JAK ανάλογα με τον συνδεδεμένο STAT

Calculated average target inhibition (AUC-24h +/- SD) over a 24h for selected JAKinibs for a given stimuli/cell type/pSTAT based on in vitro measurements in whole blood from healthy donors dose interval

JAK1/TYK2 IFN α
 JAK1/JAK2 IL-6
 IFN γ
 JAK1/JAK3 IL-2
 IL-15
 IL-4
 JAK2/TYK2 G-CSF
 JAK2/JAK2 GM-CSF

A.

Signaling Pair	Cell Type	Stimuli Readout	FIL		TOFA		UPA		BARI	
			100 mg	200 mg	5 mg	10 mg	15 mg	30 mg	2 mg	4 mg
JAK1/TYK2	NK	IFN α /pSTAT5	45 \pm	62	54	69 \pm	51 \pm	65	37 \pm	53 \pm
	B cells	IFN α /pSTAT5	45 \pm	62	58	74 \pm	63	77 \pm	46 \pm	63
	CD8 \pm T cells	IFN α /pSTAT5	43 \pm	59	57	73 \pm	61	75 \pm	42 \pm	60
	NK	IFN α /pSTAT3	41 \pm	58	51 \pm	68 \pm	51 \pm	67 \pm	40 \pm	58
	monocytes	IFN α /pSTAT5	37 \pm	56	55	71 \pm	71 \pm	83 \pm	43 \pm	62
	B cells	IFN α /pSTAT3	37 \pm	55	49	67 \pm	57	72 \pm	41 \pm	59
	CD4 \pm T cells	IFN α /pSTAT5	37 \pm	55	55	72 \pm	61 \pm	76 \pm	41 \pm	59
	CD8 \pm T cells	IFN α /pSTAT3	34 \pm	52	45 \pm	63 \pm	54	69 \pm	36 \pm	54
	neutrophils	IFN α /pSTAT5	32 \pm	48	49	65 \pm	60 \pm	74 \pm	31 \pm	47
	CD4 \pm T cells	IFN α /pSTAT1	31 \pm	45	41	55 \pm	49	62 \pm	32 \pm	45
JAK1/JAK2	CD8 \pm T cells	IFN α /pSTAT1	30 \pm	43	37	53 \pm	43	56 \pm	29 \pm	42
	CD4 \pm T cells	IFN α /pSTAT3	30 \pm	47	43	61 \pm	53	69 \pm	32 \pm	50
	monocytes	IFN α /pSTAT3	27 \pm	43	43	61 \pm	63 \pm	77 \pm	33 \pm	51 \pm
	B cells	IFN α /pSTAT1	17 \pm	27	22	32 \pm	26	37 \pm	17 \pm	26
	NK	IFN α /pSTAT1	17 \pm	28	23	35 \pm	24	35 \pm	16 \pm	26
	monocytes	IFN α /pSTAT1	16 \pm	24	22	31 \pm	33 \pm	43 \pm	17 \pm	25
	CD4 \pm T cells	IL-6/pSTAT1	49 \pm	65	51 \pm	65	52 \pm	66	44 \pm	59
	monocytes	IL-6/pSTAT1	37 \pm	53	43 \pm	59	55	69 \pm	36 \pm	52
	monocytes	IL-6/pSTAT3	51	33	30	23 \pm	23 \pm	36 \pm	61	11
	B cells	IFN γ /pSTAT1	34 \pm	49	51	67 \pm	56	70 \pm	51	67 \pm
JAK1/JAK3	neutrophils	IFN γ /pSTAT1	15 \pm	25	31	45 \pm	40 \pm	54 \pm	24	37 \pm
	monocytes	IFN γ /pSTAT1	21	15	20	35 \pm	33 \pm	49 \pm	20	35
	CD8 \pm T cells	IL-2/pSTAT5	34 \pm	51	65 \pm	79 \pm	56	71 \pm	37 \pm	55
	CD4 \pm T cells	IL-2/pSTAT5	28 \pm	45	61 \pm	76 \pm	57 \pm	72 \pm	32 \pm	49
	NK	IL-2/pSTAT5	15 \pm	29	41 \pm	60 \pm	33	49 \pm	17 \pm	31
	CD4 \pm T cells	IL-15/pSTAT5	30 \pm	48	66 \pm	80 \pm	61 \pm	76 \pm	35 \pm	53
	CD8 \pm T cells	IL-15/pSTAT5	18 \pm	33	53 \pm	73 \pm	46 \pm	63 \pm	23 \pm	40 \pm
	NK	IL-15/pSTAT5	11 \pm	26	40 \pm	59 \pm	31	48 \pm	15 \pm	29
	CD8 \pm T cells	IL-4/pSTAT5	25 \pm	40	58 \pm	74 \pm	53 \pm	68 \pm	34	51 \pm
	monocytes	IL-4/pSTAT5	21 \pm	35	55 \pm	73 \pm	51 \pm	67 \pm	29	46 \pm
JAK2/TYK2	neutrophils	IL-4/pSTAT6	18 \pm	29	39 \pm	56 \pm	47 \pm	62 \pm	24	39 \pm
	monocytes	IL-4/pSTAT6	14 \pm	26	34 \pm	52 \pm	46 \pm	63 \pm	25	42 \pm
	CD4 \pm T cells	IL-4/pSTAT6	14 \pm	26	45 \pm	63 \pm	44 \pm	60 \pm	30	35 \pm
	B cells	IL-4/pSTAT6	3	7	14 \pm	26 \pm	17 \pm	28 \pm	5	11
	monocytes	G-CSF/pSTAT3	81	17	19	32 \pm	29 \pm	43 \pm	21	34 \pm
	neutrophils	G-CSF/pSTAT3	2	4	4	9	8	15 \pm	4	8
	NK	G-CSF/pSTAT4	57 \pm	10	8	13	12	19 \pm	30	17 \pm
	neutrophils	GM-CSF/pSTAT5	15 \pm	25	33 \pm	47 \pm	56 \pm	69 \pm	26	39 \pm
	monocytes	GM-CSF/pSTAT5	3	6	8	17 \pm	27 \pm	42 \pm	10	23 \pm
	JAK2/JAK2	GM-CSF	15 \pm	25	33 \pm	47 \pm	56 \pm	69 \pm	26	39 \pm

Calculated average target inhibition (AUC-24h +/- SD) over a 24h for selected JAKinibs for a given stimuli/cell type/pSTAT based on in vitro measurements in whole blood from healthy donors dose interval

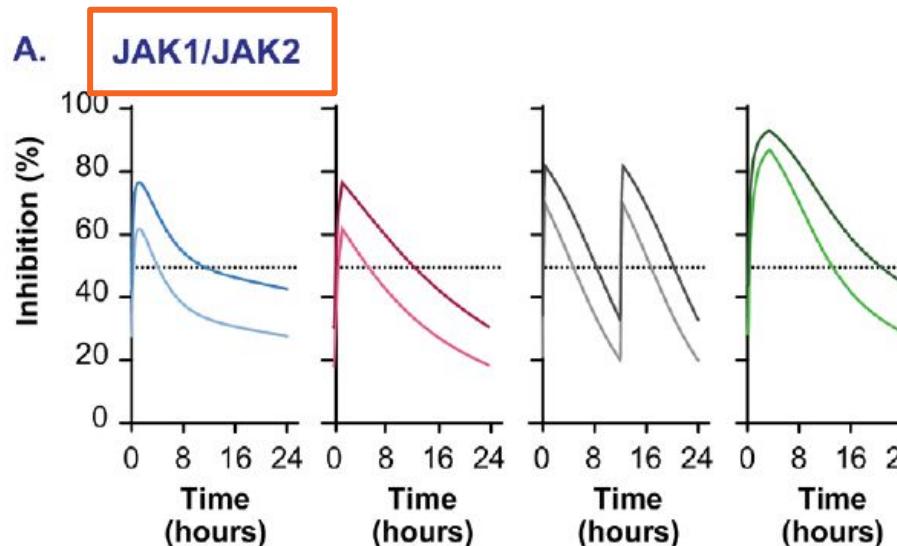
JAK1/TYK2 IFN α
 JAK1/JAK2 IL-6
 IFN γ
 JAK1/JAK3 IL-2
 IL-15
 IL-4
 JAK2/TYK2 G-CSF
 JAK2/JAK2 GM-CSF

A.

Signaling Pair	Cell Type	Stimuli Readout	Fil		TOFA			UPA		BARI	
			100 mg	200 mg	5 mg	10 mg	15 mg	30 mg	2 mg	4 mg	
JAK1/TYK2	NK	IFN α /pSTAT5	45 \pm	62	54	69 \pm	51 \pm	65	37 \pm	53 \pm	
	B cells	IFN α /pSTAT5	45 \pm	62	58	74 \pm	63	77 \pm	46 \pm	63	
	CD8 \pm T cells	IFN α /pSTAT5	43 \pm	59	57	73 \pm	61	75 \pm	42 \pm	60	
	NK	IFN α /pSTAT3	41 \pm	58	51 \pm	68 \pm	51 \pm	67 \pm	40 \pm	58	
	monocytes	IFN α /pSTAT5	37 \pm	56	55	71 \pm	71 \pm	83 \pm	43 \pm	62	
	B cells	IFN α /pSTAT3	37 \pm	55	49	67 \pm	57	72 \pm	41 \pm	59	
	CD4 \pm T cells	IFN α /pSTAT5	37 \pm	55	55	72 \pm	61 \pm	76 \pm	41 \pm	59	
	CD8 \pm T cells	IFN α /pSTAT3	34 \pm	52	45 \pm	63 \pm	54	69 \pm	36 \pm	54	
	neutrophils	IFN α /pSTAT5	32 \pm	48	49	65 \pm	60 \pm	74 \pm	31 \pm	47	
	CD4 \pm T cells	IFN α /pSTAT1	31 \pm	45	41	55 \pm	49	62 \pm	32 \pm	45	
JAK1/JAK2	CD8 \pm T cells	IFN α /pSTAT1	30 \pm	43	37	53 \pm	43	56 \pm	29 \pm	42	
	CD4 \pm T cells	IFN α /pSTAT3	30 \pm	47	43	61 \pm	53	69 \pm	32 \pm	50	
	monocytes	IFN α /pSTAT3	27 \pm	43	43	61 \pm	63 \pm	77 \pm	33 \pm	51 \pm	
	NK	IFN α /pSTAT1	17 \pm	27	22	32 \pm	26	37 \pm	17 \pm	26	
	monocytes	IFN α /pSTAT1	16 \pm	24	22	31 \pm	33 \pm	43 \pm	17 \pm	25	
	CD4 \pm T cells	IL-6/pSTAT1	49 \pm	65	51 \pm	65	52 \pm	66	44 \pm	59	
	monocytes	IL-6/pSTAT1	37 \pm	53	43 \pm	59	55	69 \pm	36 \pm	52	
	monocytes	IL-6/pSTAT3	51 \pm	33	30	23 \pm	23 \pm	36 \pm	61 \pm	11	
	B cells	IFN γ /pSTAT1	34 \pm	49	51	67 \pm	56	70 \pm	51	67 \pm	
	neutrophils	IFN γ /pSTAT1	15 \pm	25	31	45 \pm	40 \pm	54 \pm	24	37 \pm	
JAK1/JAK3	monocytes	IFN γ /pSTAT1	21 \pm	35	20	35 \pm	33 \pm	49 \pm	20	35	
	CD8 \pm T cells	IL-2/pSTAT5	34 \pm	51	65 \pm	79 \pm	56	71 \pm	37 \pm	55	
	CD4 \pm T cells	IL-2/pSTAT5	28 \pm	45	61 \pm	76 \pm	57 \pm	72 \pm	32 \pm	49	
	NK	IL-2/pSTAT5	15 \pm	29	41 \pm	60 \pm	33	49 \pm	17 \pm	31	
	CD4 \pm T cells	IL-15/pSTAT5	30 \pm	48	66 \pm	80 \pm	61 \pm	76 \pm	35 \pm	53	
	CD8 \pm T cells	IL-15/pSTAT5	18 \pm	33	53 \pm	73 \pm	46 \pm	63 \pm	23 \pm	40 \pm	
	NK	IL-15/pSTAT5	11 \pm	26	40 \pm	59 \pm	31	48 \pm	15 \pm	29	
	CD8 \pm T cells	IL-4/pSTAT5	25 \pm	40	58 \pm	74 \pm	53 \pm	68 \pm	34	51 \pm	
	CD4 \pm T cells	IL-4/pSTAT5	21 \pm	35	55 \pm	73 \pm	51 \pm	67 \pm	29	46 \pm	
	monocytes	IL-4/pSTAT5	18 \pm	29	39 \pm	56 \pm	47 \pm	62 \pm	24	39 \pm	
JAK2/TYK2	monocytes	IL-4/pSTAT5	14 \pm	26	34 \pm	52 \pm	46 \pm	63 \pm	25	42 \pm	
	CD4 \pm T cells	IL-4/pSTAT5	14 \pm	26	45 \pm	63 \pm	44 \pm	60 \pm	30	35 \pm	
	B cells	IL-4/pSTAT5	3 \pm	7	14 \pm	26 \pm	17 \pm	28 \pm	5	11	
	monocytes	G-CSF/pSTAT3	8 \pm	17	19	32 \pm	29 \pm	43 \pm	21	34 \pm	
JAK2/JAK2	neutrophils	G-CSF/pSTAT3	2 \pm	4	4	9	8	15 \pm	4	8	
	NK	G-CSF/pSTAT4	5 \pm	10	8	13	12	19 \pm	30	17 \pm	
JAK2/JAK2	neutrophils	GM-CSF/pSTAT5	15 \pm	25	33 \pm	47 \pm	56 \pm	69 \pm	26	39 \pm	
	monocytes	GM-CSF/pSTAT5	3 \pm	6	8	17 \pm	27 \pm	42 \pm	30	23 \pm	

Σχετική εκλεκτικότητα

Μερική και αναστρέψιμη αναστολή

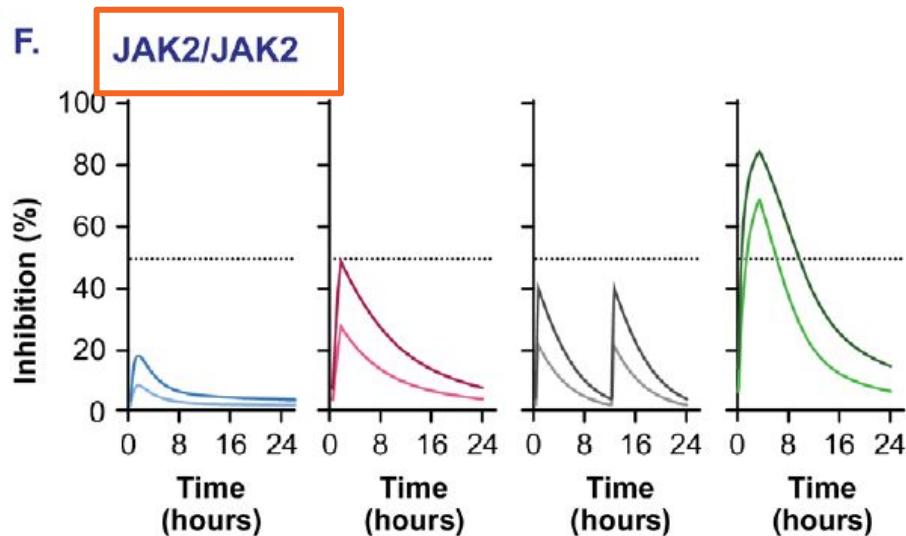


IL-6/pSTAT1/Monocytes

	FIL 100mg 200mg	BARI 2mg 4mg	TOFA 5mg 10mg	UPA 15mg 30mg
Average STAT inhibition (%)	37††† 53	36††† 52	43††† 59	55 69***
Time above IC ₅₀ (h)	5††† 15	5††† 13	9††† 17	13 21***

Μερική και αναστρέψιμη αναστολή

F.



GM-CSF/pSTAT5 Monocytes

	FIL 100mg 200mg	BARI 2mg 4mg	TOFA 5mg 10mg	UPA 15mg 30mg
Average STAT inhibition (%)	3 6	10 21***	8 17***	27*** 42***
Time above IC ₅₀ (h)	0 0	0 0	0 0	5*** 9***

Αποτελεσματικότητα
και ασφάλεια:
Drug effect vs Class
effect?

Upadacitinib

Εκλεκτικός Jak-1 αναστολέας

Upadacitinib

Εκλεκτικός Jak-1 αναστολέας



Rationale:

Get the advantage of Jak-1 inhibition (on IL-6 & IFN- γ) without the risks of Jak-2 (erythropoiesis) & Jak-3 (lymphocyte development and immune homeostasis) inhibition



Upadacitinib JAK-1 Selectivity

Engineered Cellular Assays

Ba/F3 Cellular	IC50 nM	Fold selectivity vs. JAK1
JAK1	14	1
JAK2	593 +/- 118.7	42
JAK3	1860 +/- 207.2	133
TYK2	2715 +/- 548.7	194

JAk-is trials

MTX naive

MTX-IR

bDMARD-IR

Jak-is vs bDMARDs

Jak-is - dDMARDs switch

JAk-is trials

MTX naive

MTX-IR

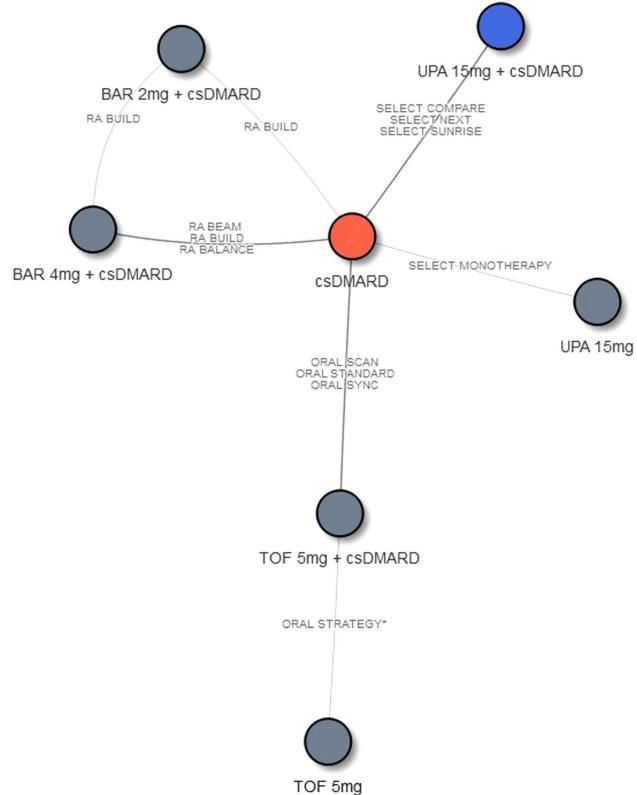
bDMARD-IR

Jak-is vs bDMARDs

Jak-is - dDMARDs switch

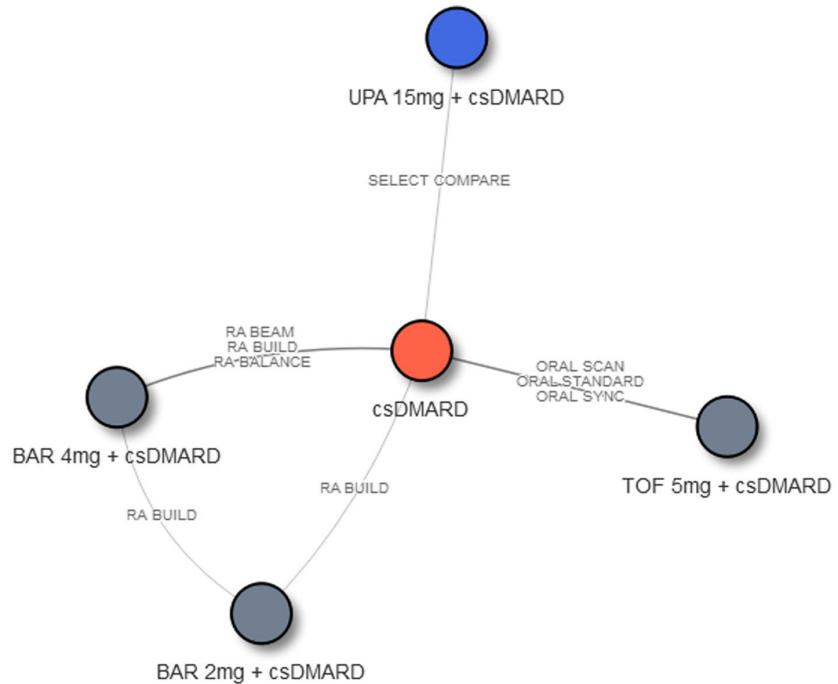
csDMARD-IR population- ACR 20/50/70 & DAS 28 remission

w12



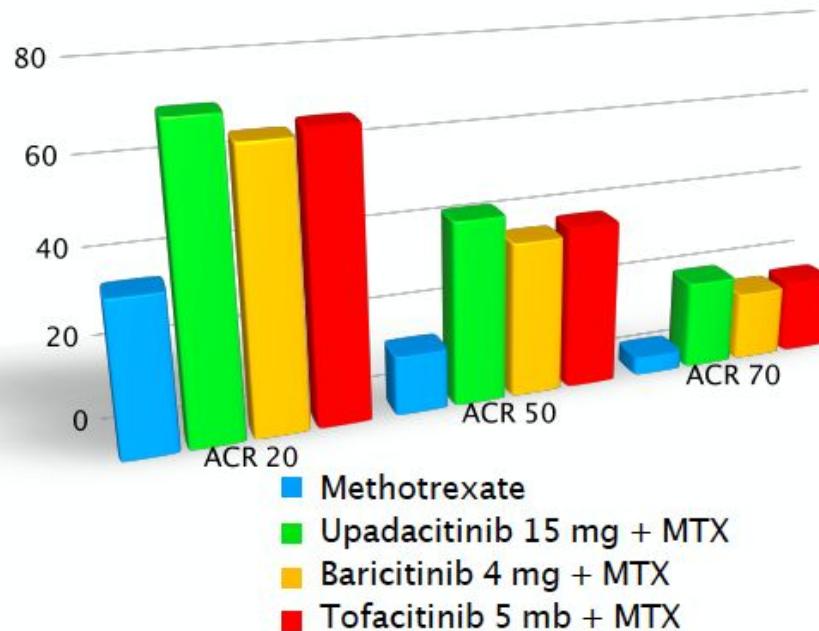
csDMARD-IR population- ACR 20/50/70 & DAS 28 remission

w24



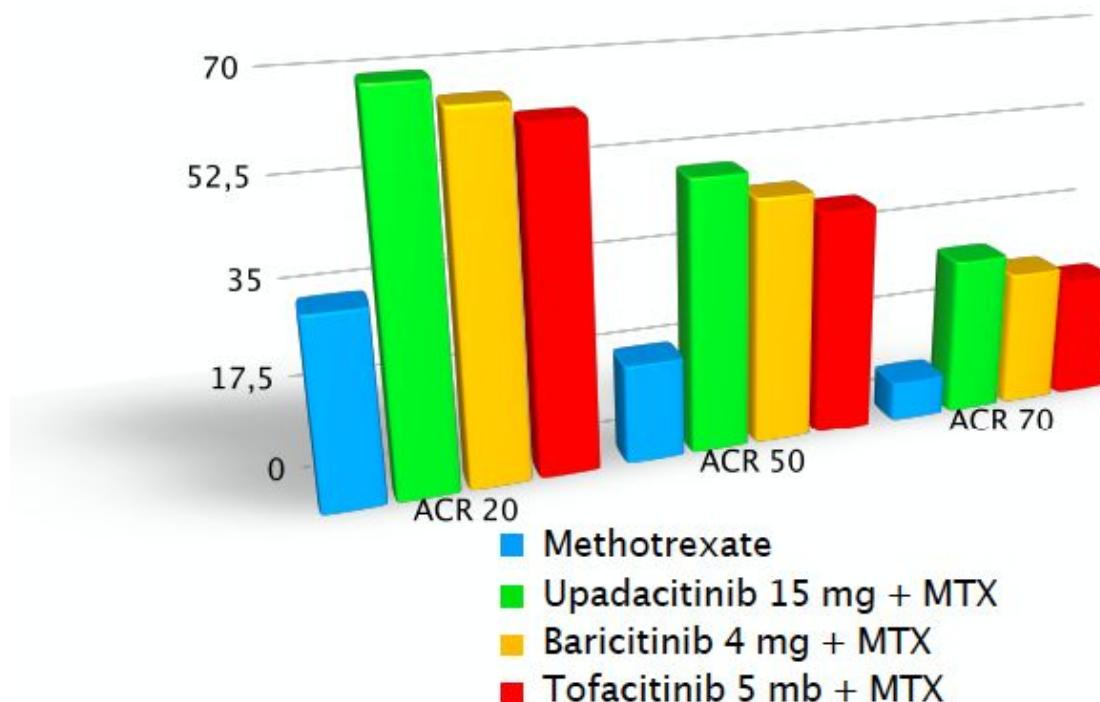
csDMARD-IR population- ACR 20/50/70

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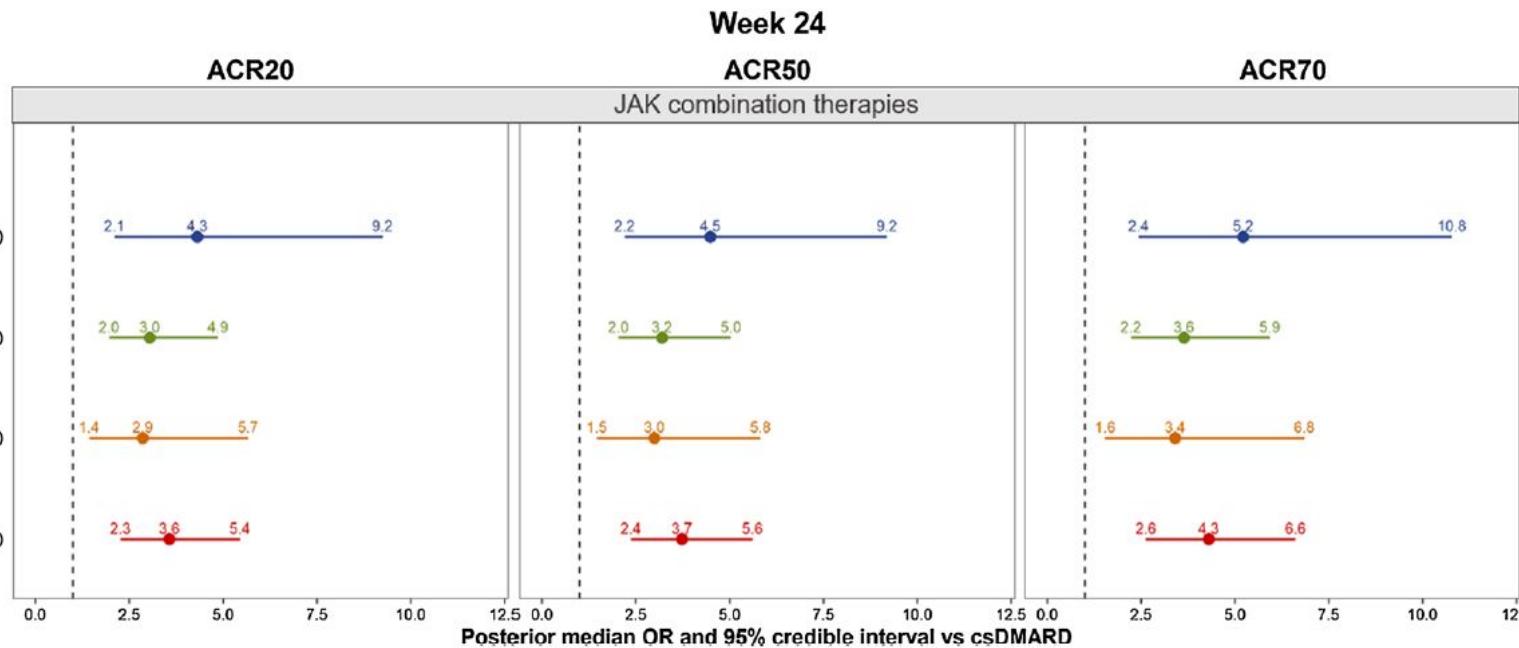


csDMARD-IR population- ACR 20/50/70

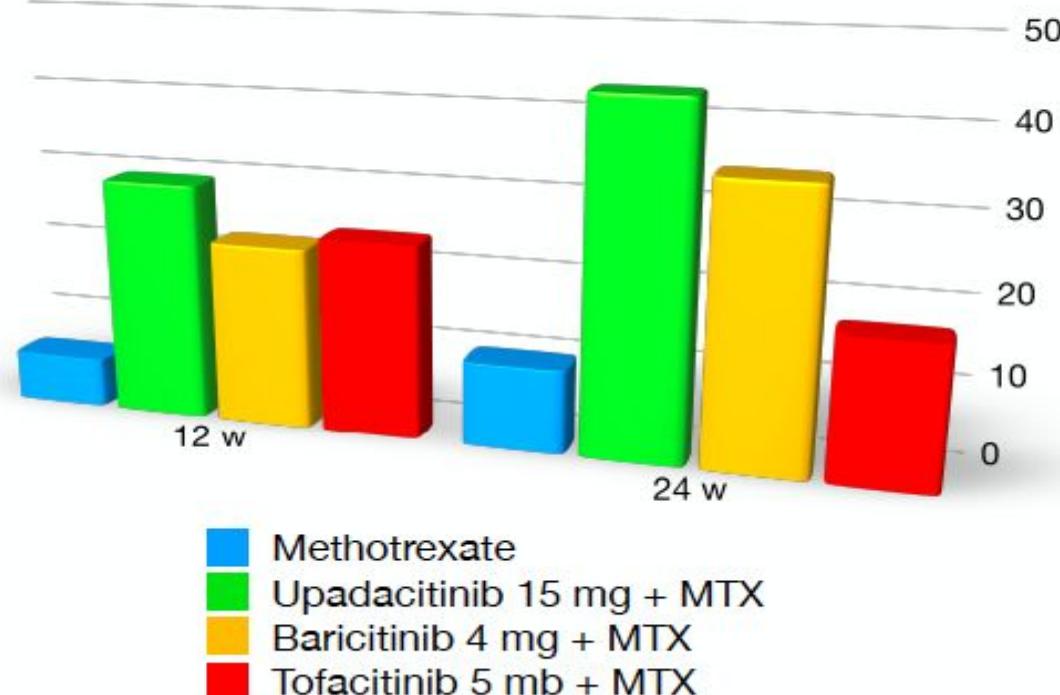
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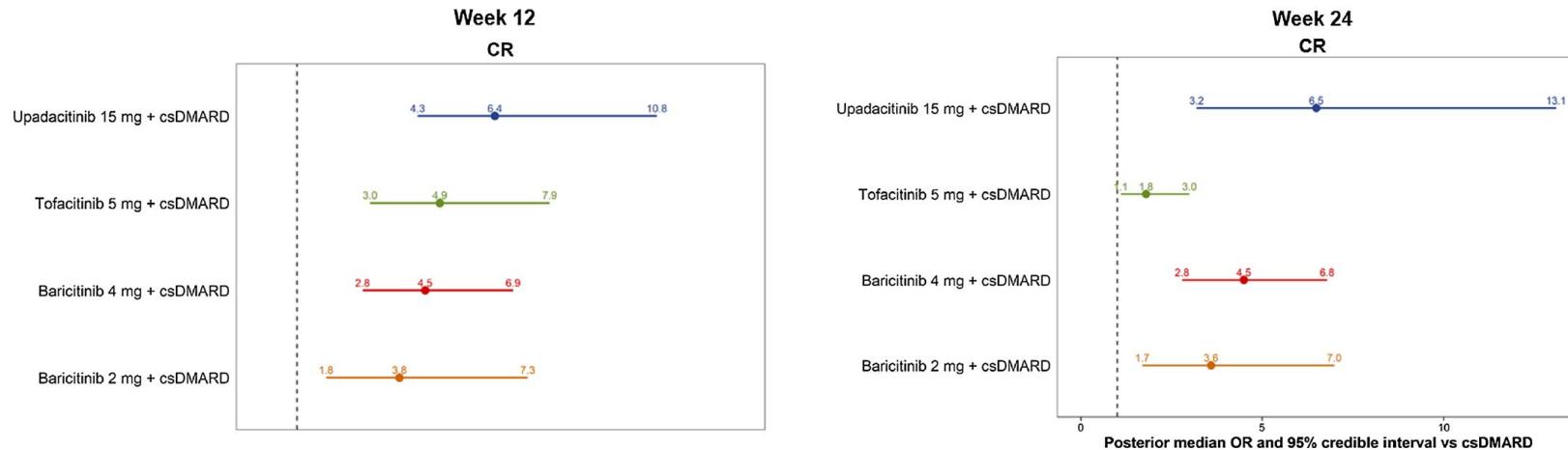
csDMARD-IR population- ACR 20/50/70



csDMARD-IR population- DAS 28 remission



csDMARD-IR population- DAS 28 remission



JAk-is trials

MTX naive

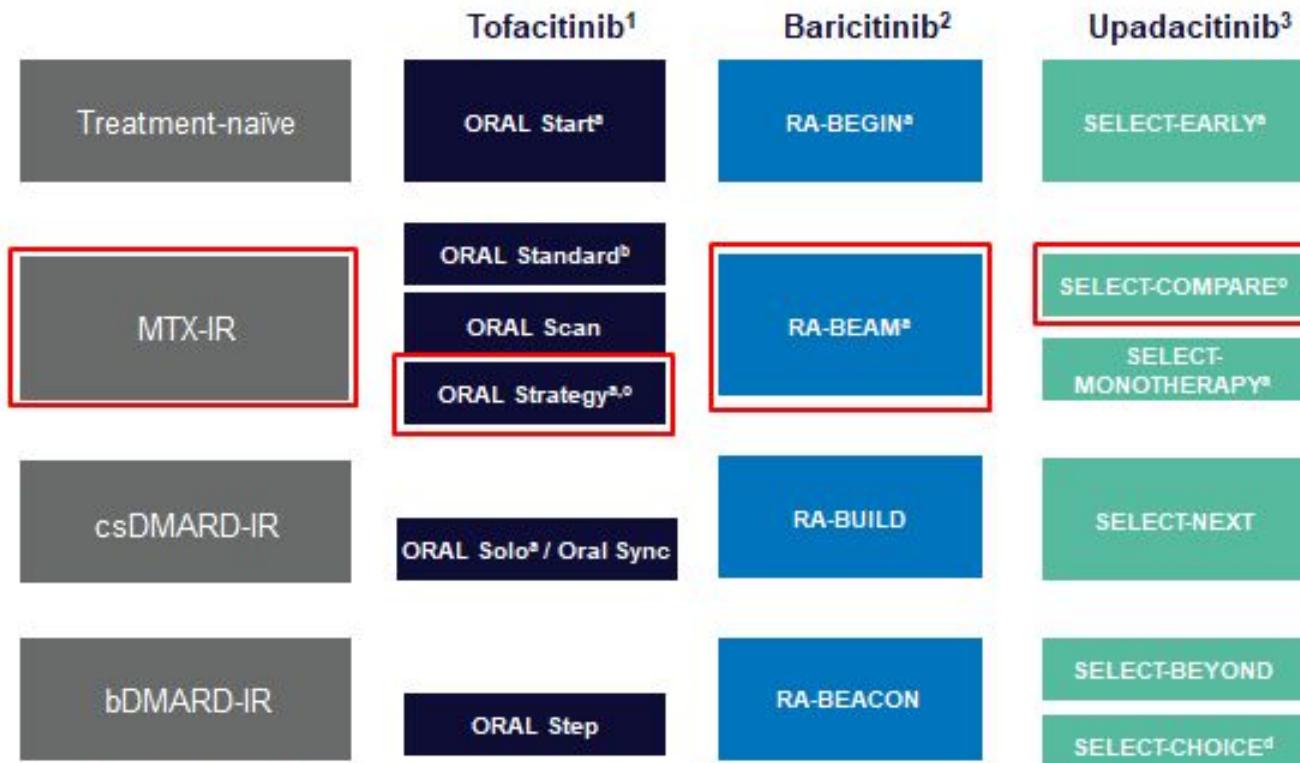
MTX-IR

bDMARD-IR

Jak-is vs bDMARDs

Jak-is - dDMARDs switch

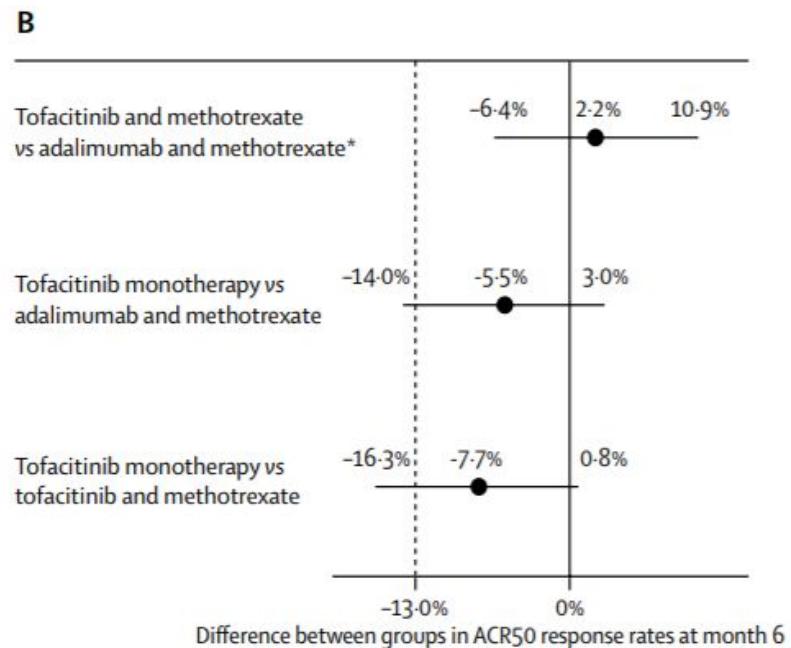
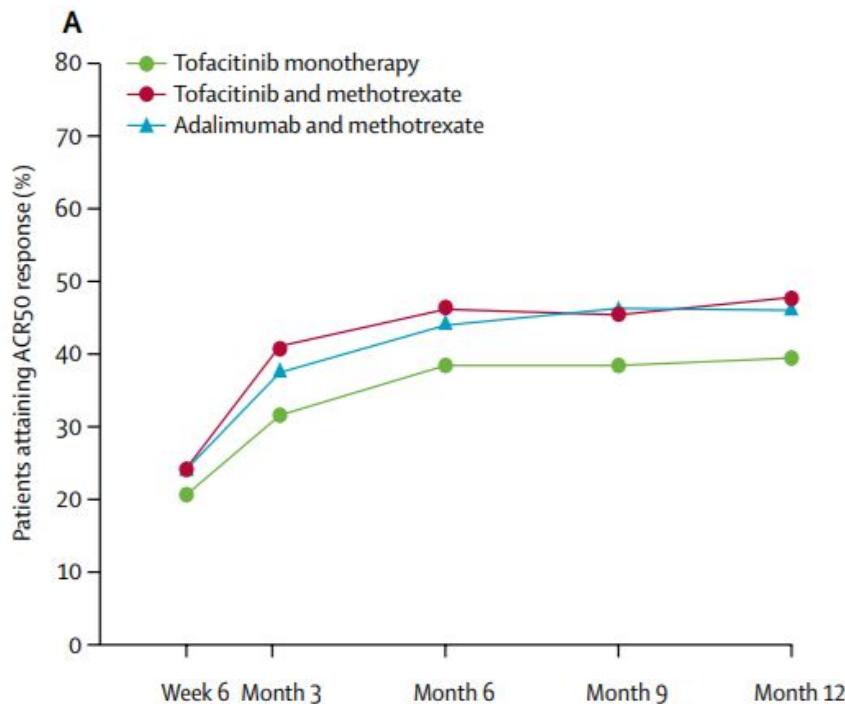
Phase III clinical trials comparing JAK inhibitors to adalimumab in patients with RA with an inadequate response to MTX



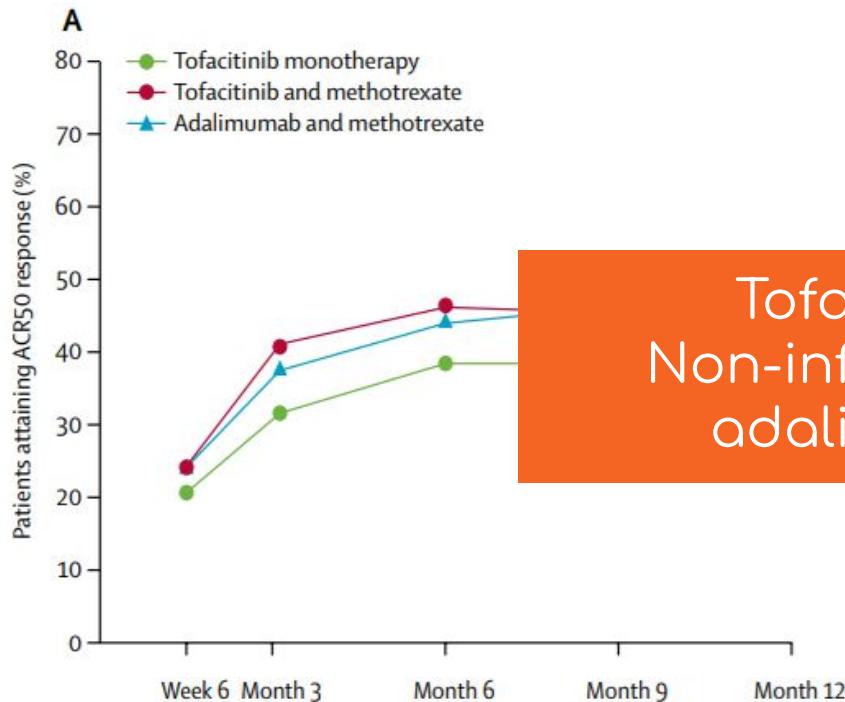
^aTrials with a monotherapy arm; ^bTrial with adalimumab arm without formal statistical comparisons between adalimumab and tofacitinib; ^cTrials with statistical comparison of JAK inhibitor vs adalimumab in MTX-IR patients; ^dTrial with statistical comparison of JAK inhibitor vs abatacept in bDMARD-IR patients
b/csDMARD, biologics/conventional synthetic drug modifying anti-rheumatic drugs; IR, Inadequate response; MTX, methotrexate

1. Xeljanz (tofacitinib) SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf (last accessed March 2021); 2. OLUMIANT (baricitinib) SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf (last accessed March 2021); 3. RINVOQ (upadacitinib) SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf (last accessed March 2021); 4. JYSLECA (filgotinib) SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/jysleca-epar-product-information_en.pdf (last accessed March 2021); 5. Rubin-Roth A. N Eng J Med 2020;383:1511-21

ORAL-STRATEGY: Tofa vs Ada+MTX

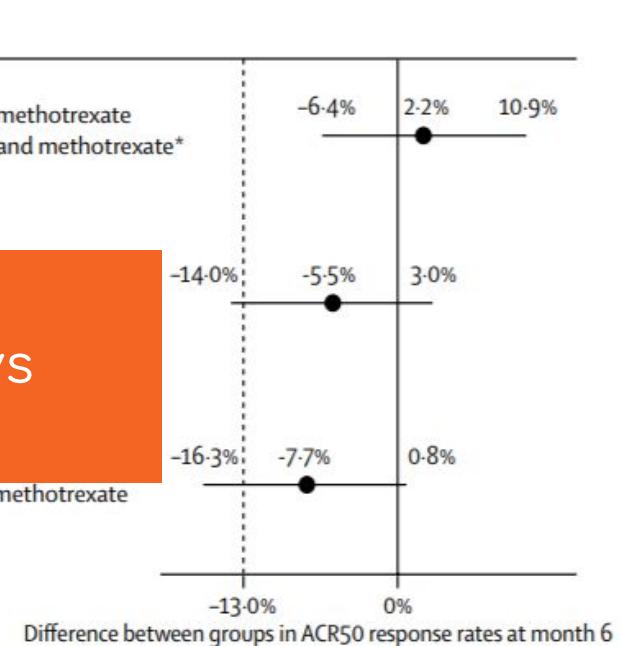


ORAL-STRATEGY: Tofa vs Ada+MTX

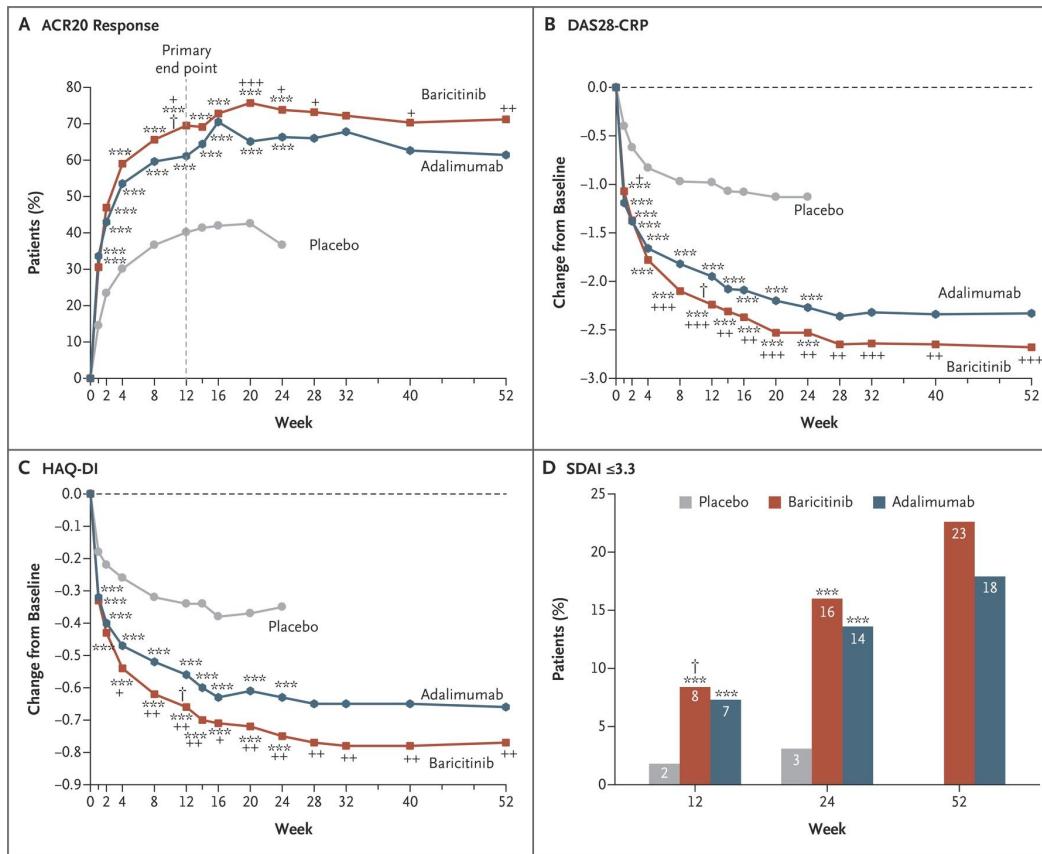


Tofacitinib:
Non-inferiority vs
adalimumab

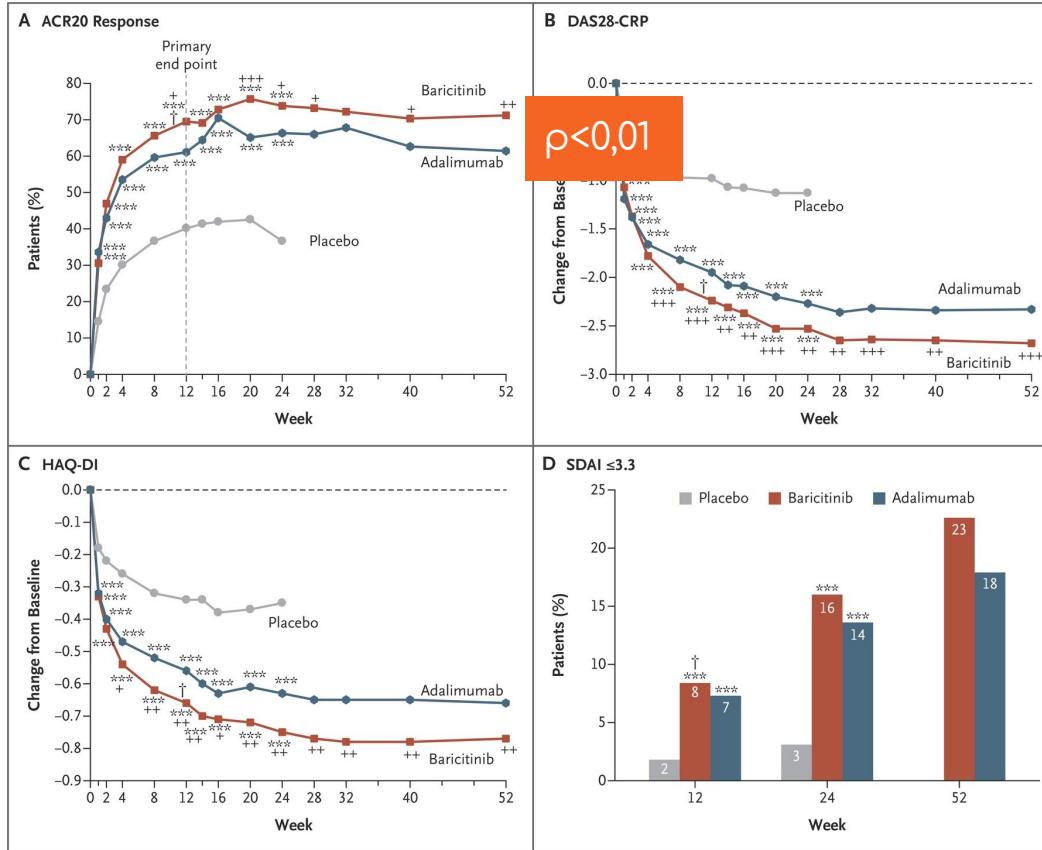
tofacitinib and methotrexate



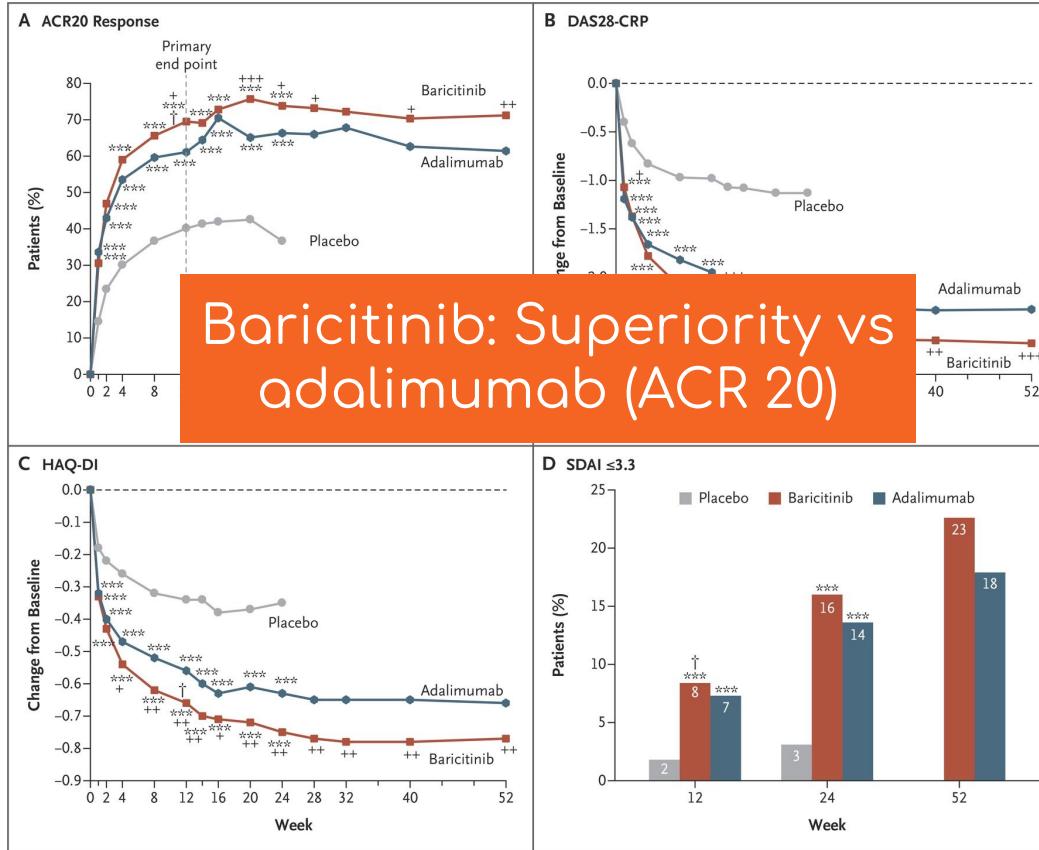
RA-BEAM: Baricitinib+MTX vs Adalimumab+MTX



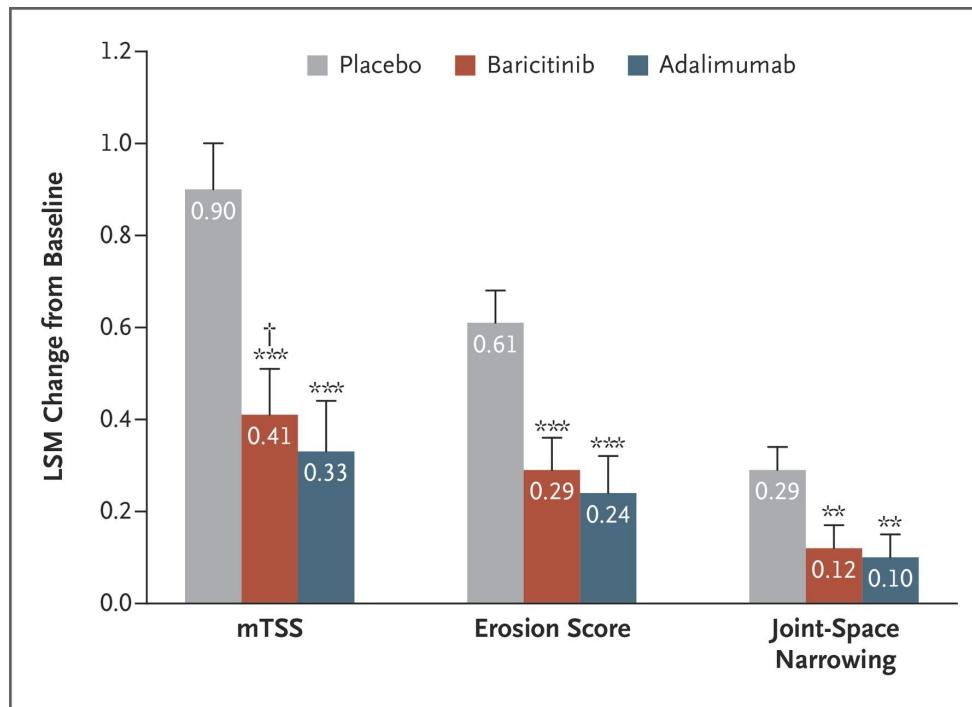
RA-BEAM: Baricitinib+MTX vs Adalimumab+MTX



RA-BEAM: Baricitinib+MTX vs Adalimumab+MTX

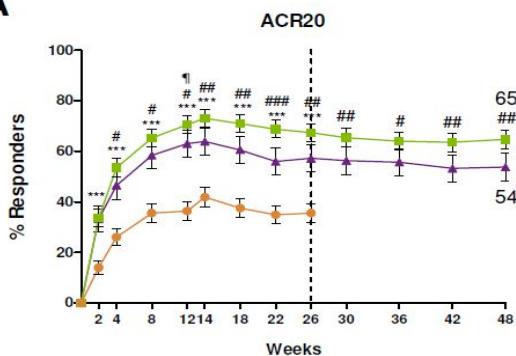


RA-BEAM: Baricitinib+MTX vs Adalimumab+MTX

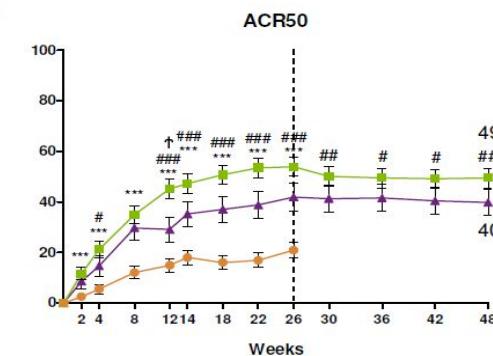


SELECT-COMPARE: Upadacitinib vs Adalimumab+MTX

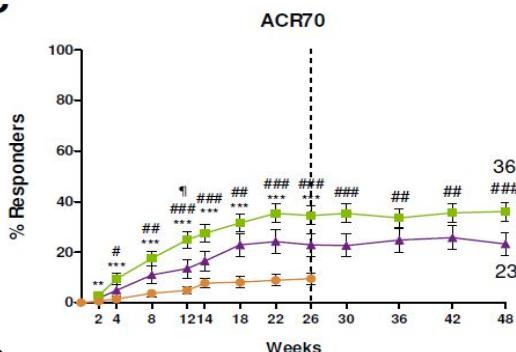
A



B

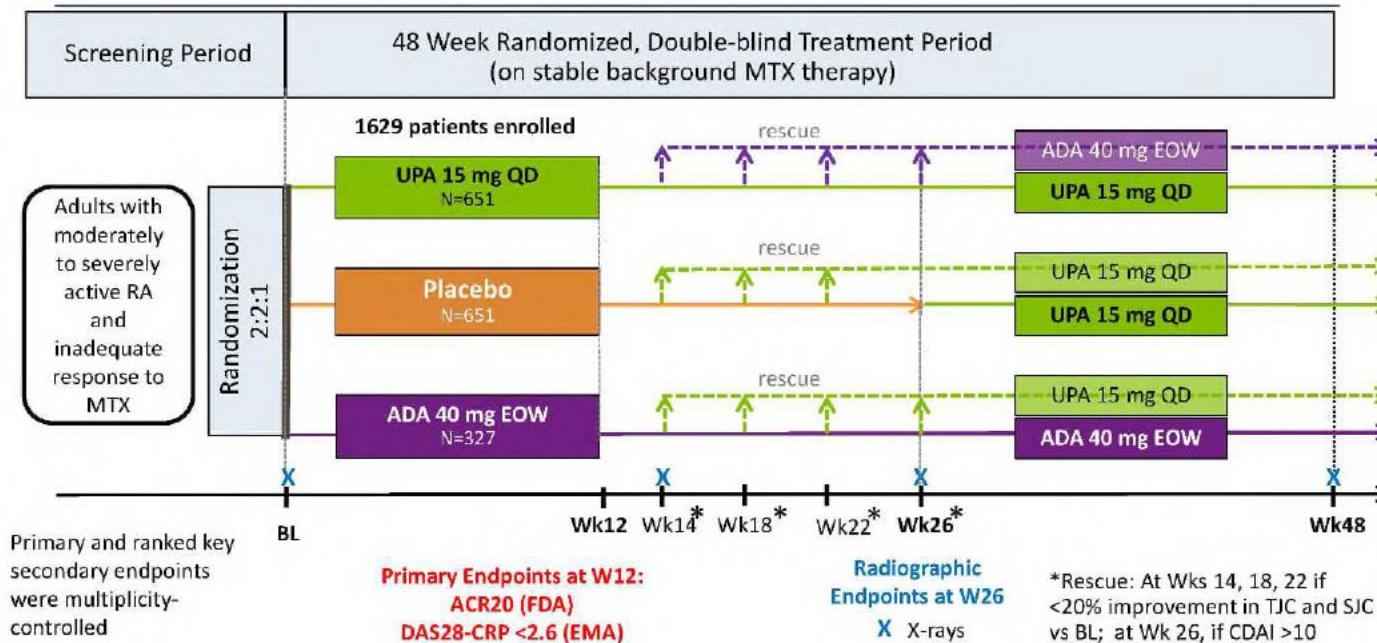


C



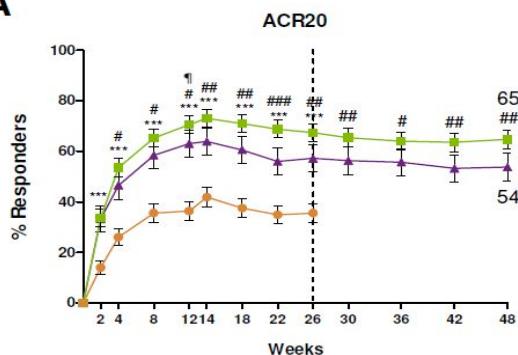
- PBO + background MTX, N=651
- UPA 15 mg QD + background MTX, N=651
- ADA + background MTX, N=327

SELECT-COMPARE: Upadacitinib vs Adalimumab+MTX

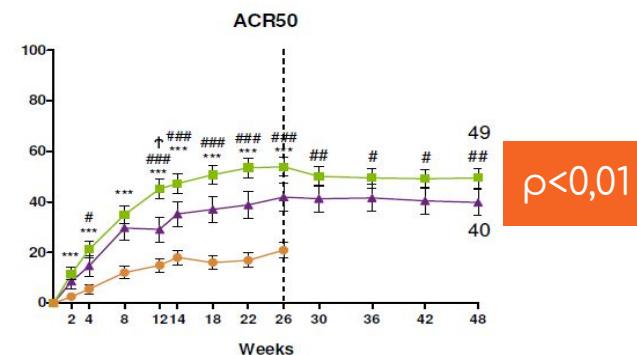


SELECT-COMPARE: Upadacitinib vs Adalimumab+MTX

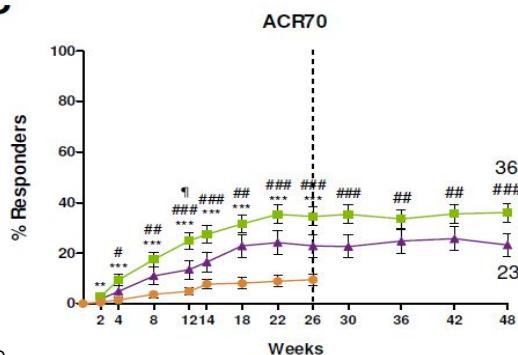
A



B

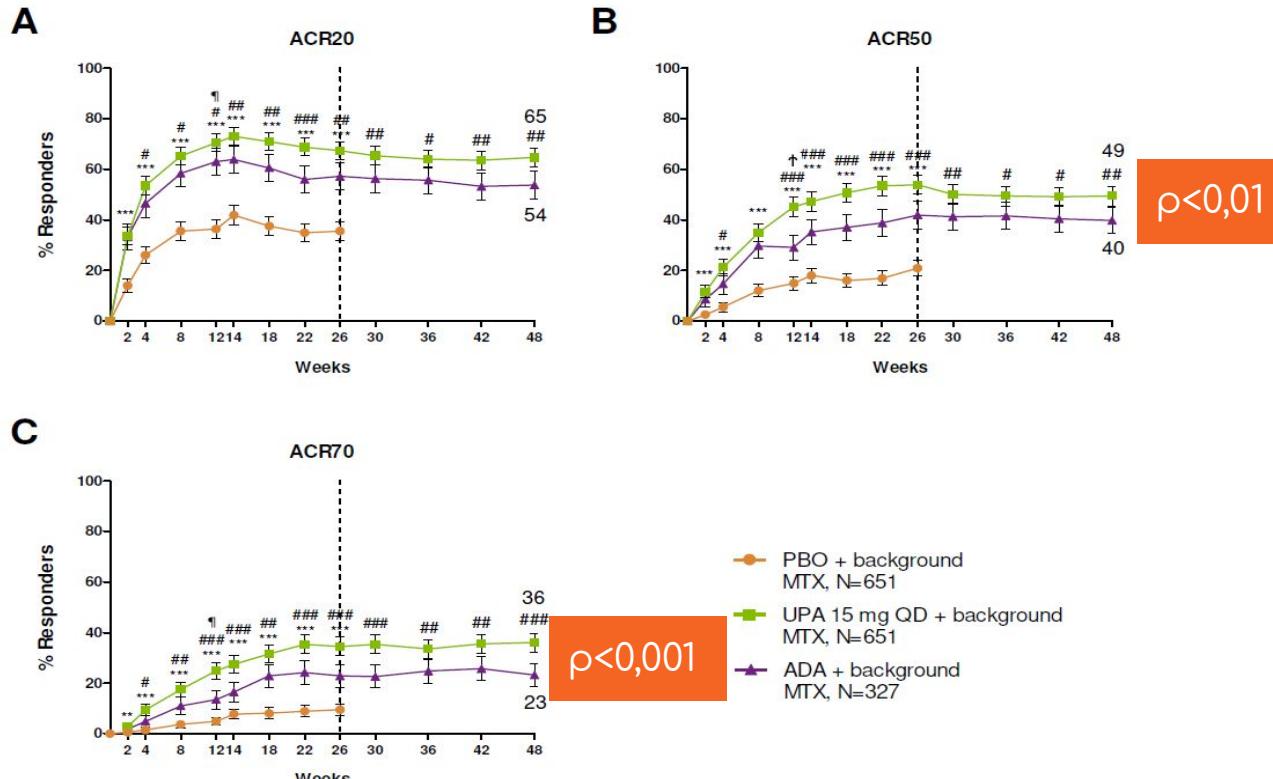


C



- PBO + background MTX, N=651
- UPA 15 mg QD + background MTX, N=651
- ADA + background MTX, N=327

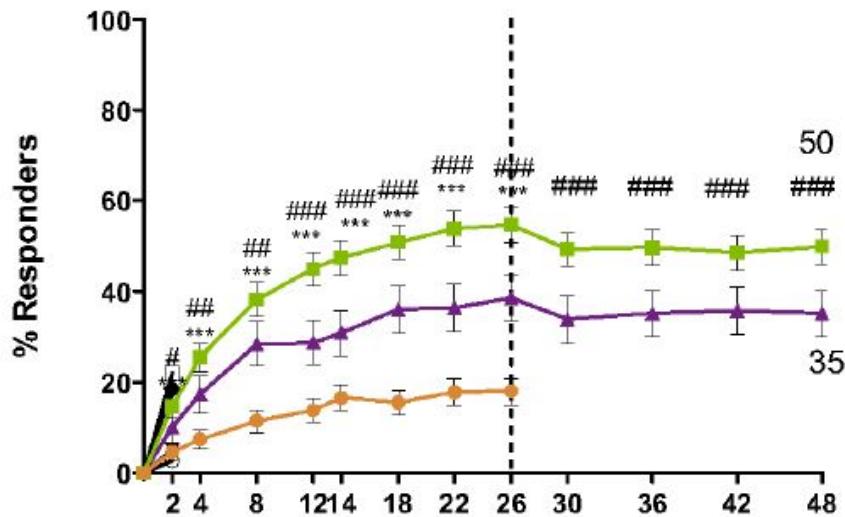
SELECT-COMPARE: Upadacitinib vs Adalimumab+MTX



SELECT-COMPARE: Upadacitinib vs Adalimumab+MTX

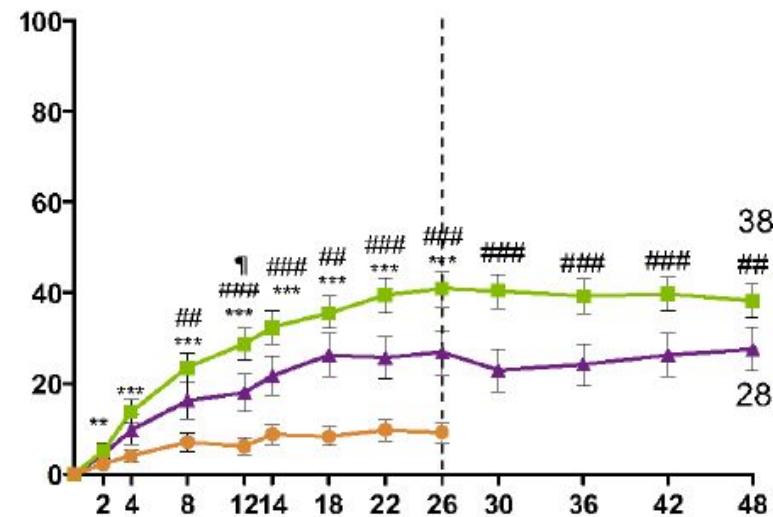
A

DAS28(CRP) \leq 3.2



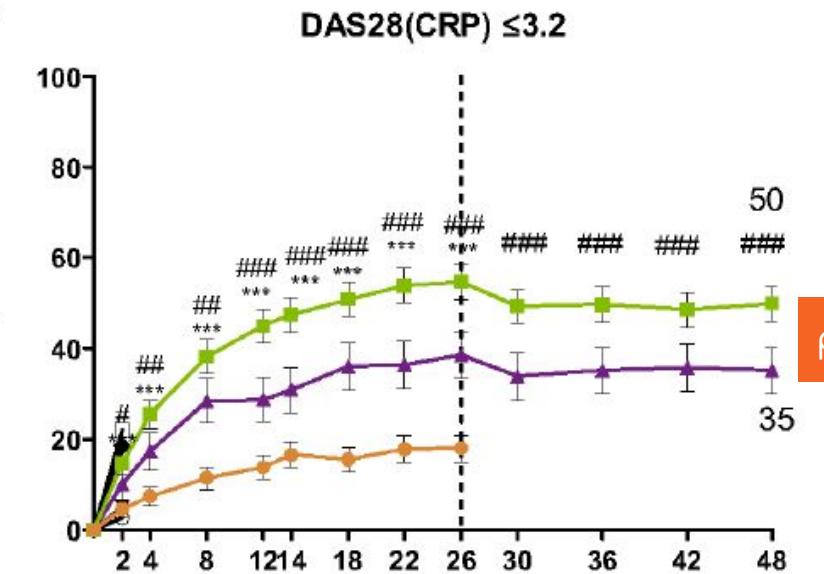
B

DAS28(CRP) <2.6

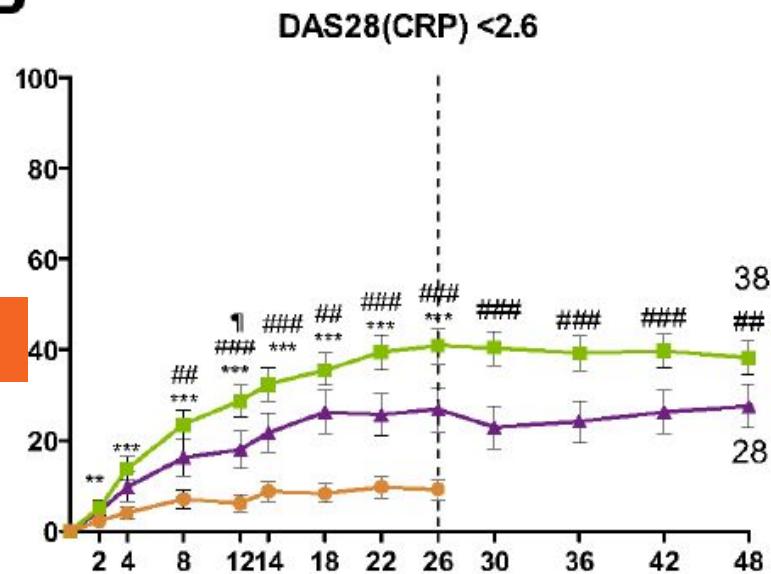


SELECT-COMPARE: Upadacitinib vs Adalimumab+MTX

A

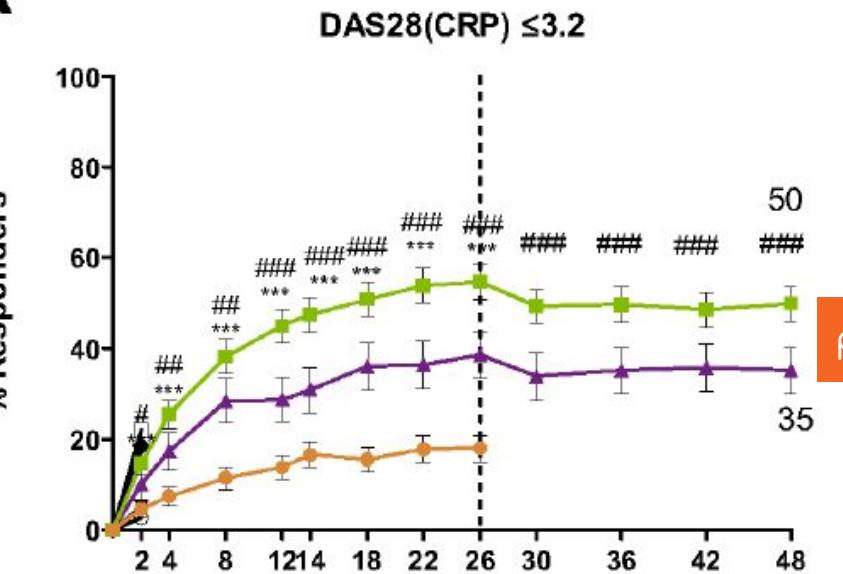


B

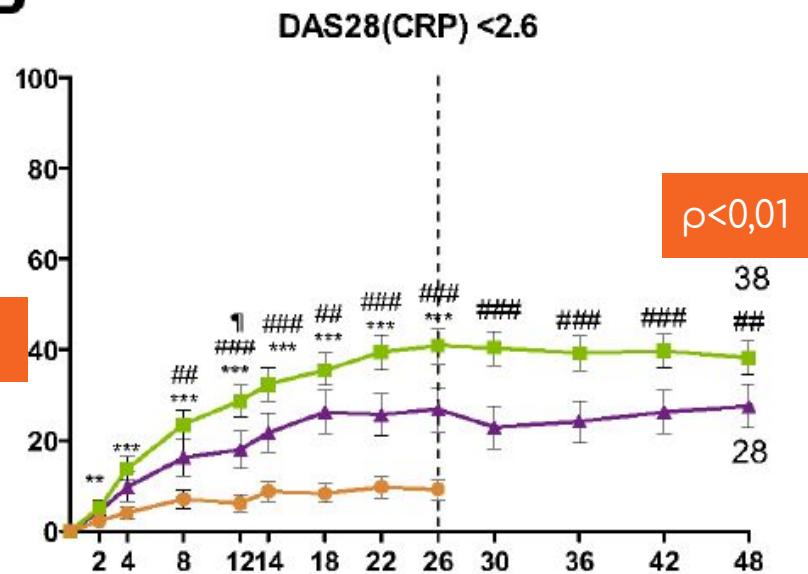


SELECT-COMPARE: Upadacitinib vs Adalimumab+MTX

A



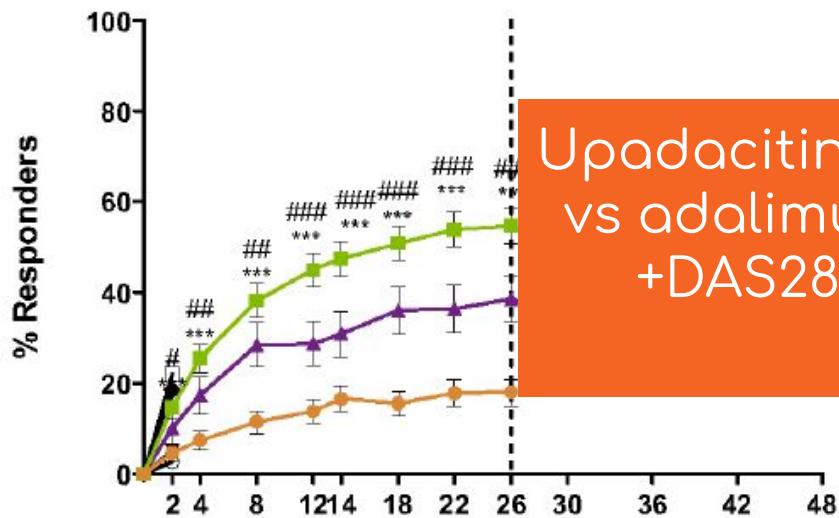
B



SELECT-COMPARE: Upadacitinib vs Adalimumab+MTX

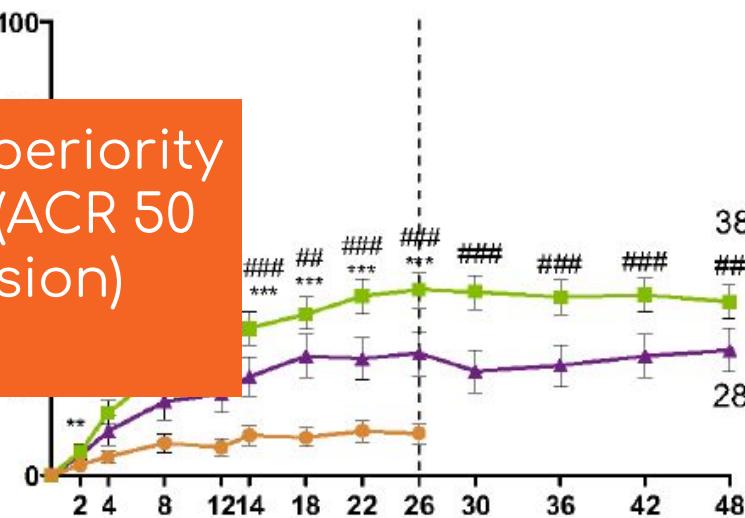
A

DAS28(CRP) ≤ 3.2



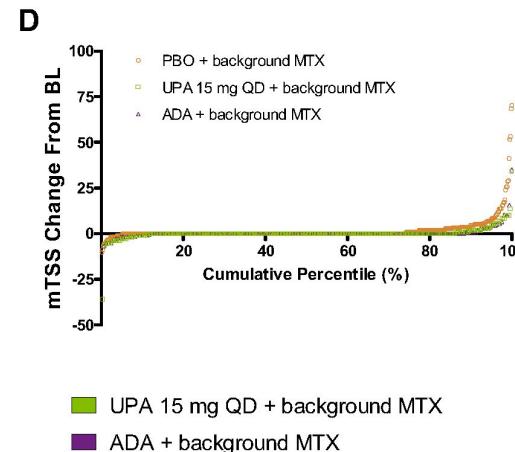
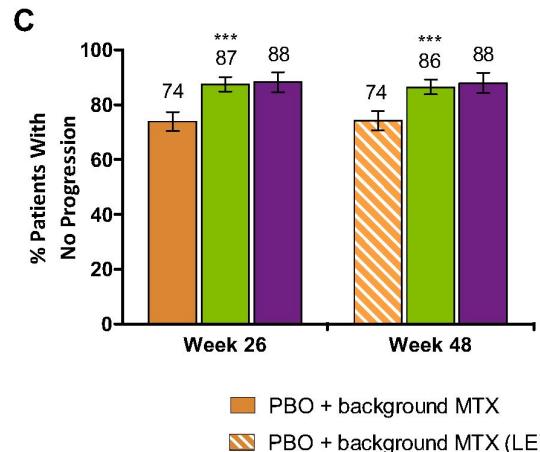
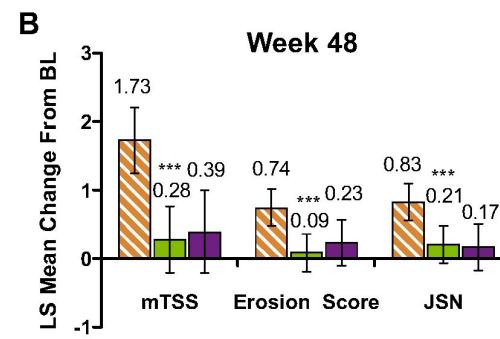
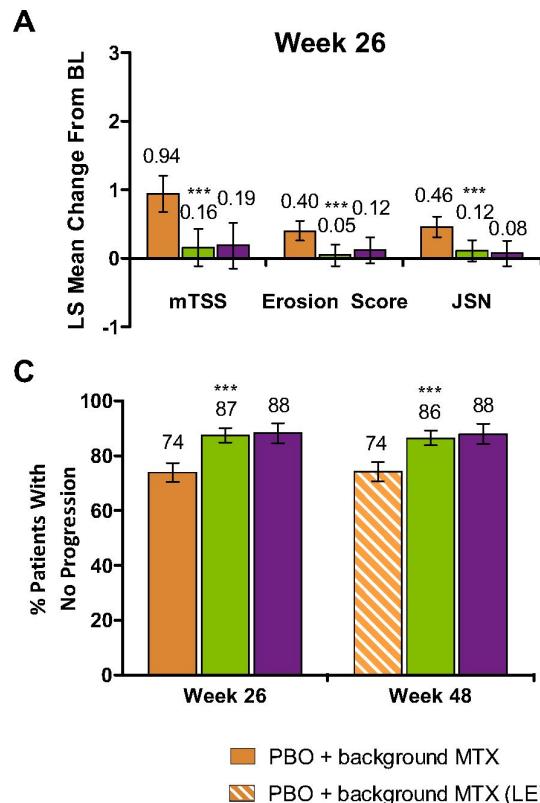
B

DAS28(CRP) < 2.6

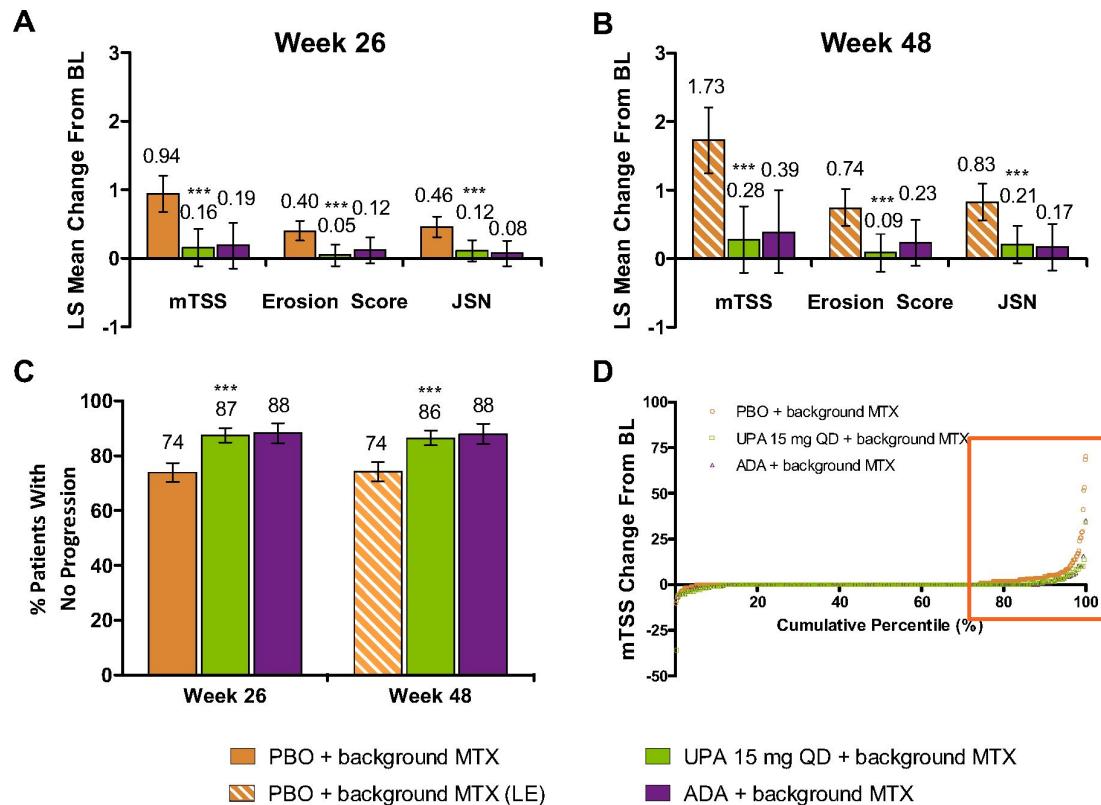


Upadacitinib: Superiority
vs adalimumab (ACR 50
+DAS28 remission)

SELECT-COMPARE: Upadacitinib vs Adalimumab+MTX



SELECT-COMPARE: Upadacitinib vs Adalimumab+MTX



JAk-is trials

MTX naive

MTX-IR

bDMARD-IR

Jak-is vs bDMARDs

Jak-is - dDMARDs switch

Jak-i to TNFi and TNFi to Jak-i switch: evidence from SELECT-COMPARE

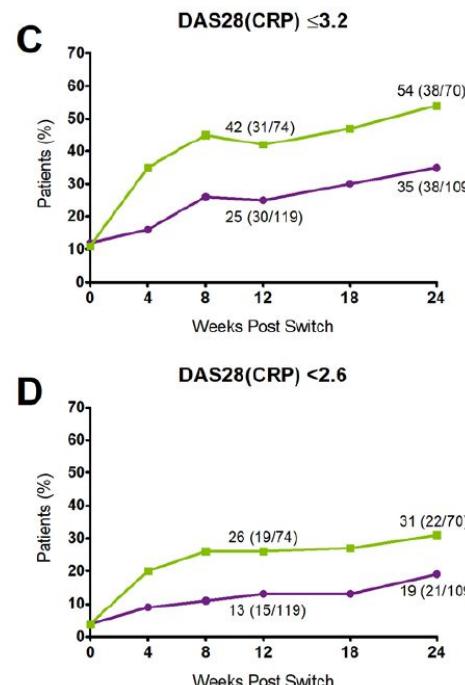
ADA
↓
UPA

54/57% of non responders/incomplete responders to adalimumab had LDA+REM after switching to upadacitinib

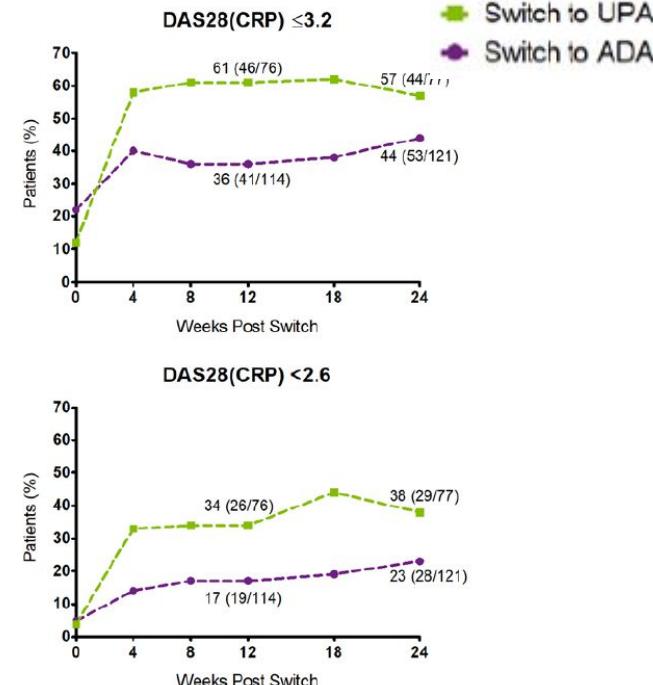
UPA
↓
ADA

35/44% of non responders/incomplete responders to upadacitinib had LDA+REM after switching to adalimumab

Non-responders



Incomplete-responders

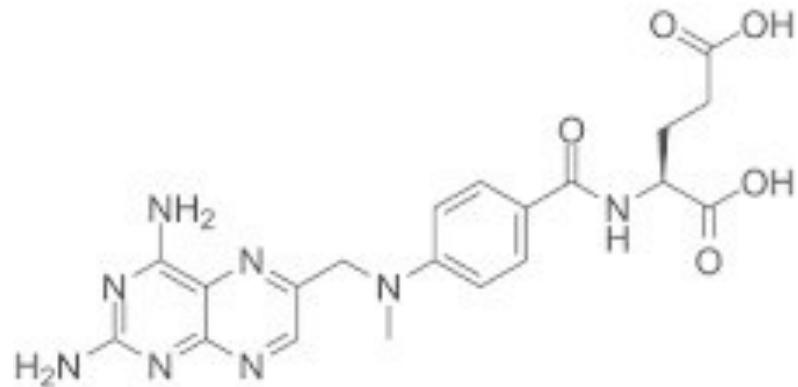


Jak-i to TNFi and TNFi to Jak-i switch: evidence from SELECT-COMPARE



20% of patients were double non-responders

Μονοθεραπεία ή με μεθοτρεξάτη;



JAk-is trials

MTX naive

MTX-IR

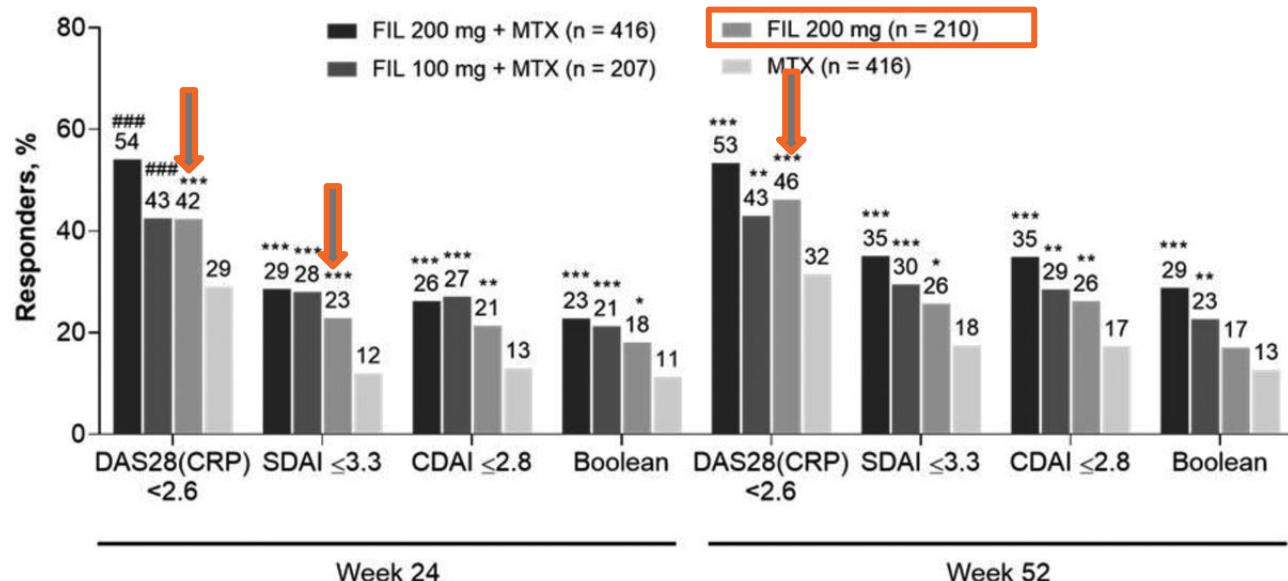
bDMARD-IR

Jak-is vs bDMARDs

Jak-is - dDMARDs switch

Filgotinib + MTX vs Filgotinib monotherapy in MTX-naive patients

Figure. Patients in clinical remission at week 52



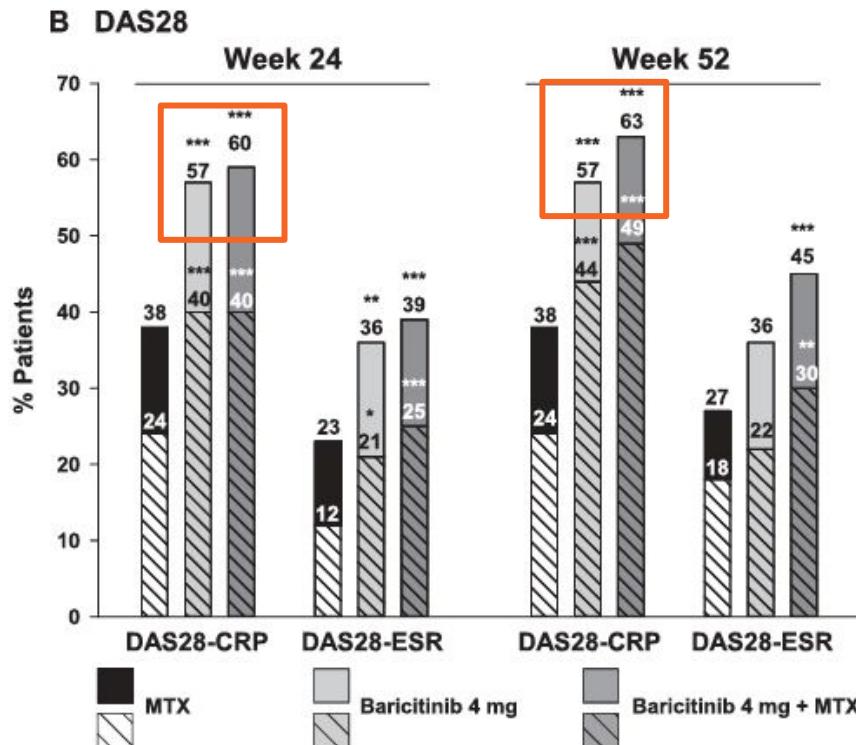
###, p <0.001 vs MTX alone adjusted for multiplicity.

*, p <0.05; **, p <0.01; ***, p <0.001 vs MTX alone; not adjusted for multiplicity.

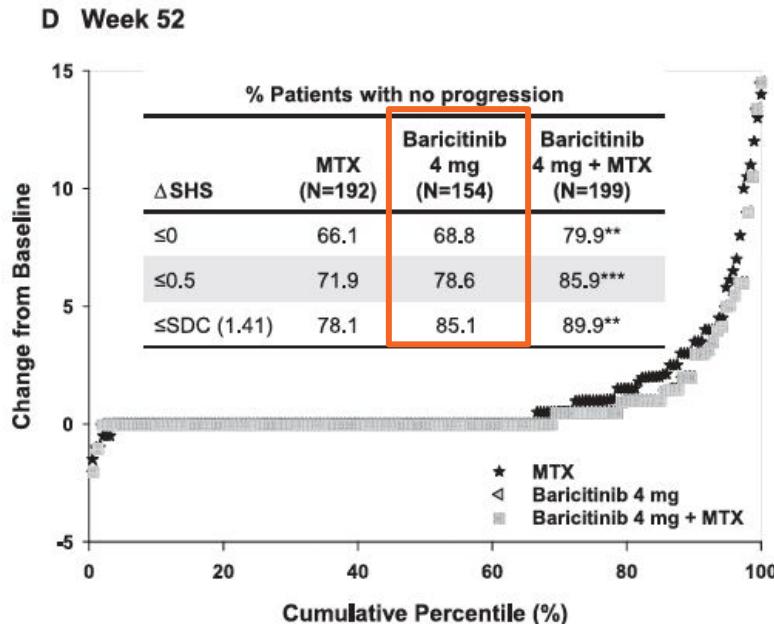
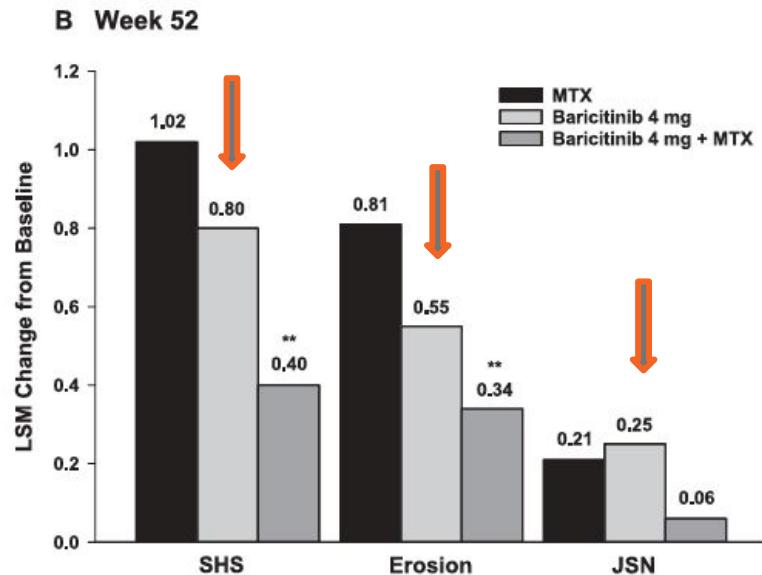
CDAI, Clinical Disease Activity Index; DAS28(CRP), Disease Activity Score in 28 joints with C-reactive protein; FIL, filgotinib; MTX, methotrexate; SDAI, Simplified Disease Activity Index.

Baricitinib + MTX vs Baricitinib monotherapy in MTX-naive patients

Percentage of pts achieving DAS 28 low disease activity and remission in 24 and 52 weeks

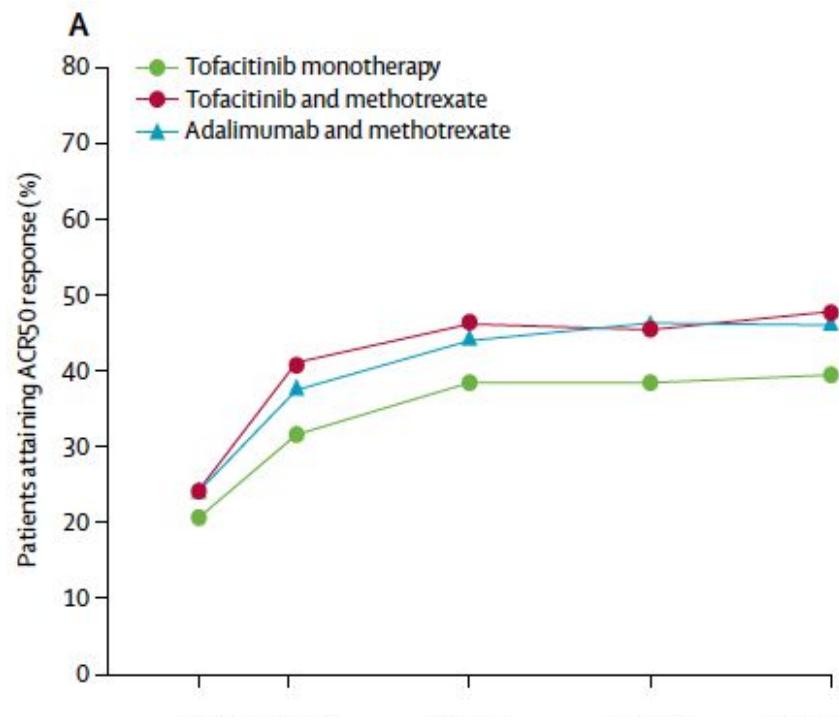


Baricitinib + MTX vs Baricitinib monotherapy in MTX-naive patients

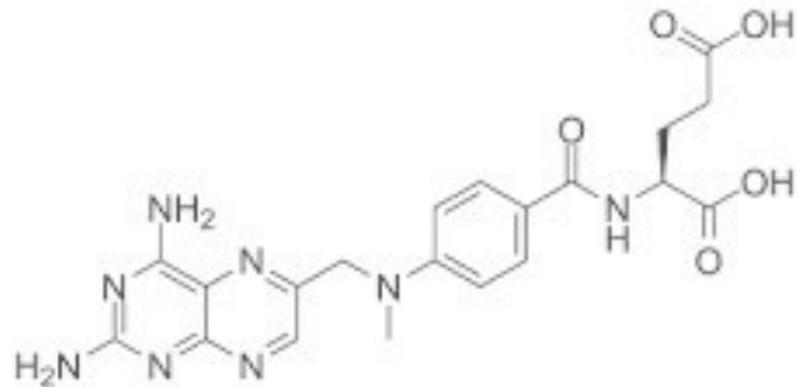


Radiographic progression evaluation

ORAL-STRATEGY: Tofa mono vs Tofa+MTX vs Ada+MTX in MTX-IR



Μονοθεραπεία ή με μεθοτρεξάτη;



EULAR: with MTX, unless in contraindicated or not tolerated

ACR: addition of a tsDMARD or a bDMARD



Research Agenda

- Switch between JAK-is
- AEs- class effect?
- Predictors of response- personalised medicine
- Effect on comorbidities (eg CV disease, malignancy)
- Pregnancy-lactation
- Elective surgery
- Combination with biologics

Recommendation



Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement

Peter Nash ,¹ Andreas Kerschbaumer ,² Thomas Dörner ,³ Maxime Dougados,⁴ Roy M Fleischmann ,⁵ Klaus Geissler,⁶ Iain McInnes,⁷ Janet E Pope ,⁸ Désirée van der Heijde ,⁹ Michaela Stoffer-Marx,¹⁰ Tsutomu Takeuchi,¹¹ Michael Trauner,¹² Kevin L Winthrop ,¹³ Maarten de Wit ,¹⁴ Daniel Aletaha ,² Xenofon Baraliakos,¹⁵ Wolf-Henning Boehncke,¹⁶ Paul Emery ,¹⁷ John D Isaacs,¹⁸ Joel Kremer,¹⁹ Eun Bong Lee ,²⁰ Walter P Maksymowych ,²¹ Marieke Voshaar,¹⁴ Lai-Shan Tam,²² Yoshiya Tanaka ,²³ Filip van den Bosch,²⁴ René Westhovens ,²⁵ Ricardo Xavier,²⁶ Josef S Smolen ,²

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For numbered affiliations see end of article.

Correspondence to
Professor Josef S Smolen,
Division of Rheumatology,
Department of Medicine 3,
Medical University of Vienna,
1090 Vienna, Austria,
josef.smolen@meduniwien.ac.at
and Professor Peter Nash,
Griffith University School of
Medicine, Herston, Gold Coast,
QLD 9726, Australia; drpnash@tpg.com.au

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ABSTRACT

Objectives Janus kinase inhibitors (JAKi) have been approved for use in various immune-mediated inflammatory diseases. With five agents licensed, it was timely to summarise the current understanding of JAKi use based on a systematic literature review (SLR) on efficacy and safety.

Methods Existing data were evaluated by a steering committee and subsequently reviewed by a 29 person expert committee leading to the formulation of a consensus statement that may assist the clinicians, patients and other stakeholders once the decision is made to commence a JAKi. The committee included patients, rheumatologists, a gastroenterologist, a haematologist, a dermatologist, an infectious disease specialist and a health professional. The SLR informed the Task Force on controlled and open clinical trials, registry data, phase 4 trials and meta-analyses. In addition, approval of new compounds by, and warnings from

(PaA), axial spondyloarthritis/ankylosing spondylitis (AxSpA/AS), systemic lupus erythematosus (SLE), psoriasis (PsO), atopic dermatitis (AD), Crohn's disease (CD), ulcerative colitis (UC) and others, have significantly improved over the past two decades. This results primarily from the introduction of several novel medications, in particular biological (b) disease-modifying antirheumatic drugs (DMARDs), as reflected in recent management recommendations.^{1–6} Improved strategic utilisation of drugs has similarly impacted positively on outcomes.

Among all therapies developed for IMIDs over the last two decades, only tumor necrosis factor (TNF)-inhibitors exhibit a very broad efficacy across many diseases: RA, PsA, axSpA, juvenile idiopathic arthritis, PsO, CD, UC and uveitis.⁷ Even though targeting just a single cytokine, no other treatment modality has yet been approved for such