

ACR | Winter Rheumatology
SYMPOSIUM

Treatment for Lupus: Are We There Yet?

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AMERICAN COLLEGE
of RHEUMATOLOGY
Empowering Rheumatology Professionals

Joan T. Merrill, Disclosures

Companies	Consulting	Talks	Research	Treatment (*=approved)
Genentech/Roche			X (IST)	Rituximab, Rontalizaumab, Obinutuzumab
UCB	X	X	X	Epratuzumab, Dapi Pegol
GSK	X	X	X (IST)	Belimumab*
Provention	X			PRV 3279
EMD Serono	X	X	X	Atacicept, M2961, M5049
Pfizer	X		X	Anti-IL6
RemeGen	X			Telitacicept
Abbvie	X		X	Upadacitinib
Aurinia	X		X	Voclosporin
Bristol Myers Squibb	X	X	X (IST)	Abatacept, Lulizumab, Iberdomide, Deucravacitinib
Genelabs	X			Prasterone
Merck (MSD)	X			TBD
Lilly	X	X	X	Tabalumab, Baracitinib
Immunopharma	X			Lupuzor
Amgen	X		X	AMG 570
Janssen	X	X		Ustekinumab
Xencor, Zenas			X	Obexelimab
Sanofi	X			SAR441344
Astra Zeneca	X		X	Anifrolumab
Anthera	X			Blisibimod

■ = approved

■ = failed in Ph 3

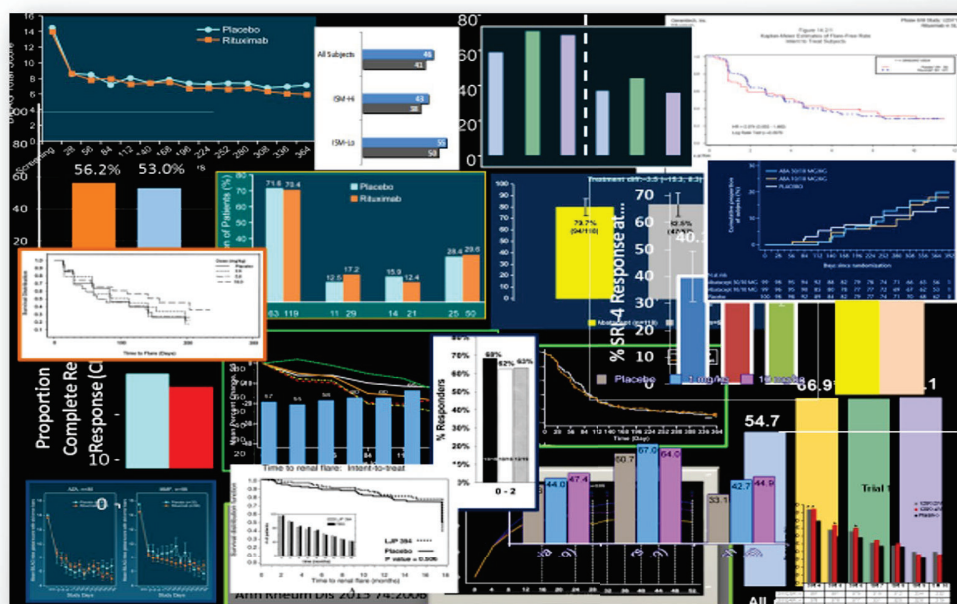
IST= investigator-initiated

Additionally, General Consulting for Biogen, Kezar, Ono, Takeda, Tenent

Key References

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- Merrill JT Tanaka Y, D'Cruz D, Vila-Rivera K, Siri D, Zen X, Saxena A, Aringer M, D'Silva K, Cheng L, Mohamed Efficacy and Safety of Upadacitinib or Elsubrutinib Alone or in Combination for SLE: A Phase 2 Randomized Controlled Trial *Arthritis Rheumatol*. 2024 Oct;76(10):1518-1529

30 Years of Treatment Development for SLE



If the Placebo response is high, why isn't the response to an effective treatment higher?



What is Lupus? Consult Respected Authorities

Lupus - Symptoms & causes - Mayo Clinic



<https://www.mayoclinic.org/diseases-conditions/lupus> ▼

Lupus is a disease that occurs when your immune system attacks your own tissues and organs. Symptoms may include **fatigue, fever, joint pain, skin lesions, butterfly-**



CDC

<https://www.cdc.gov/lupus/facts/detailed.html> ▼

Systemic Lupus Erythematosus (SLE) | CDC

Web Systemic **lupus** erythematosus (SLE), is the most common type of **lupus**. SLE is an autoimmune disease in which the **immune system attacks** its own tissues, causing ...



Johns Hopkins Medicine

<https://www.hopkinsmedicine.org/health/conditions-and-diseases/lupus> ▼

Lupus | Johns Hopkins Medicine

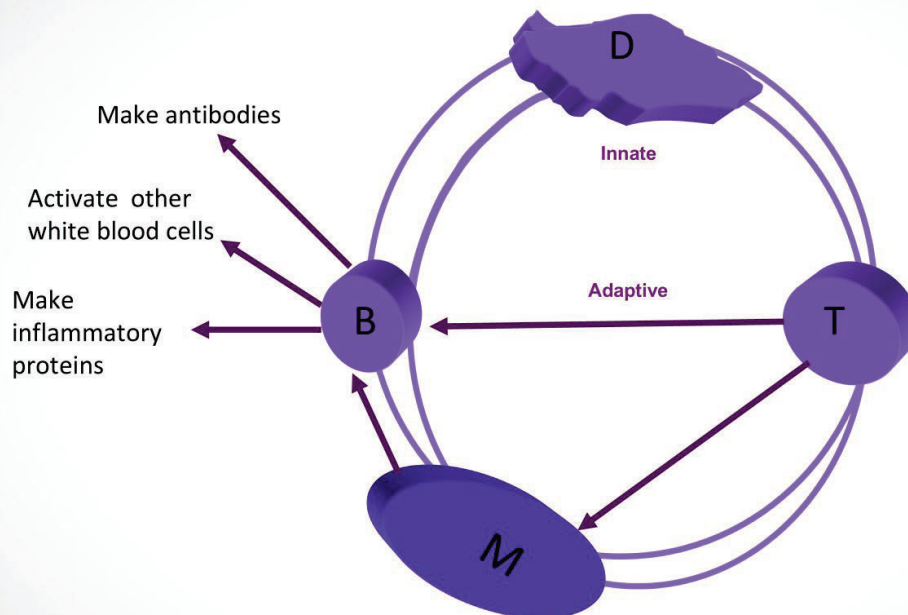


Web Systemic **lupus** erythematosus (**lupus**) is a disease that causes your body's **immune system** to **attack** its own cells and tissues. It causes periods of inflammation to various parts of ...

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LUPUS IS IMMUNE IMBALANCE

**Central and Peripheral Nervous System**

Seizures, Psychosis, Headaches,
Cognitive Dysfunction,
Neuropathies, Depression,
Low Grade Fever

Heart, Lungs

Pericarditis, Myocarditis,
Endocarditis, Pleuritis,
Pneumonitis

Kidneys

Edema, Hypertension,
Proteinuria, Cell Casts,
Renal Failure

Reproductive System

Pregnancy Complications,
Miscarriages,
Menstrual Cycle Irregularities

Blood

Anemia, Thrombocytopenia,
Leukopenia, Thrombosis,
Circulating Autoantibodies and
Immune Complexes

**Eyes and Mucous
Membranes**

Ulcers in the Eyes, Nose,
Mouth or Vagina,
Sjögren's Syndrome

Gastrointestinal

Nausea, Vomiting, Diarrhea,
Weight Changes

Musculoskeletal

Extreme Fatigue, Arthralgia,
Myalgia, Arthritis, Myositis

Skin

Butterfly Rash, Cutaneous
Lesions, Photosensitivity,
Alopecia, Vasculitis,
Raynaud's Phenomenon



Wallace DJ. In: Koopman DJ, ed. *Arthritis and Allied Conditions*. 13th ed. Vol 2 :1319.

Central and Peripheral Nervous System

Seizures, Psychosis, Headaches,
Cognitive Dysfunction,
Neuropathies, Depression,
Low Grade Fever

Heart, Lungs

Pericarditis, Myocarditis,
Endocarditis, Pleuritis,
Pneumonitis

**Eyes and Mucous
Membranes**

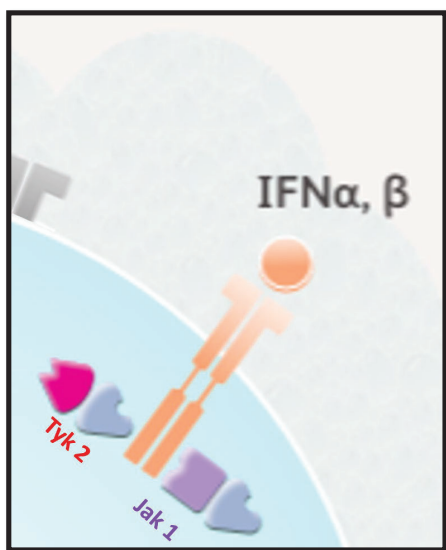
Ulcers in the Eyes, Nose,
Mouth or Vagina,
Sjögren's Syndrome





CLUES TO LOWER PLACEBO RESPONSE

Treatment	Target	Improved Treatment Effect Size with		Reference
		Sicker Subset	Less Polypharmacy	
Atacicept	BLyS/April		X	Isenberg ann rheu dis 2013 205067
Blisibimod	BLyS*	X		Furie ann rheu dis 2015 74:1667
Tabalumab	BLyS*	X		Merrill ann rheu dis 2016 15:332
Belimumab	BLys	X	X	VanVollenhoven ann rheu dis 2013 71:1343
Epratuzumab	CD22		X	Wallace ann rheu dis 2014 73:183
Rituximab	CD20	X	X	Merrill arth rheum 2010 62:222
Abatacept	B7	X	X	Furie arth rheum 2014 66:379
Ocrelizumab	CD20		X	Mysier arth rheum 2013 65:2368
PF-04236921	IL6	X	X	Wallace ACR 2014 (abstract)
Sifalimumab	IFN α	X		Khamashta ann rheu dis 2016 (epub)



humanized IgG1k monoclonal antibody binds to subunit 1 of IFNAR inhibiting formation of an IFN/IFNAR complex

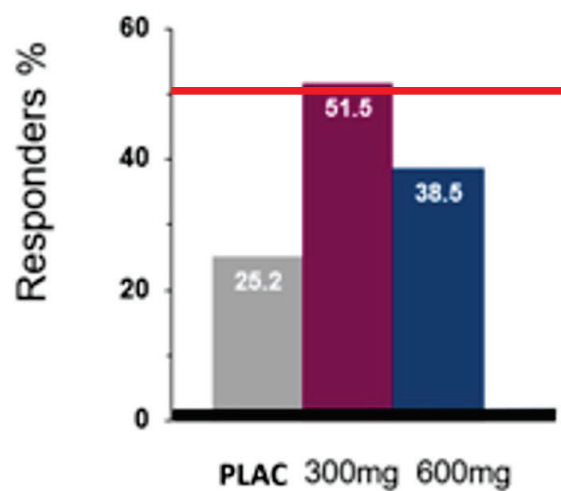


Figure from Furie ACR 2015
Full report in Furie Arth Rheum 2017 69:276-386

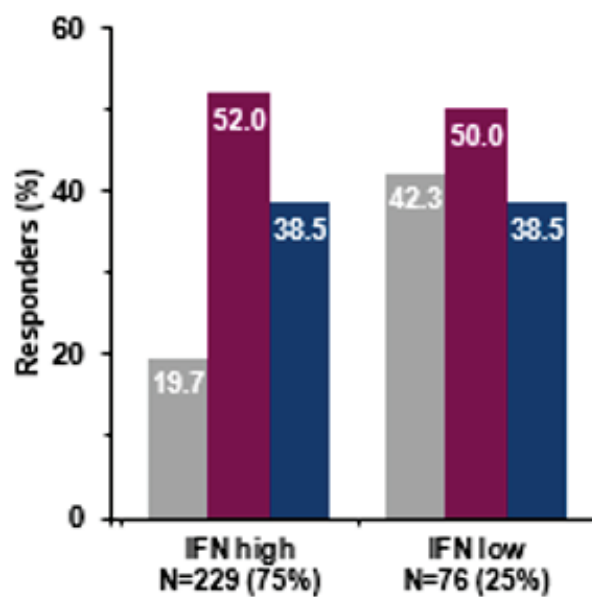
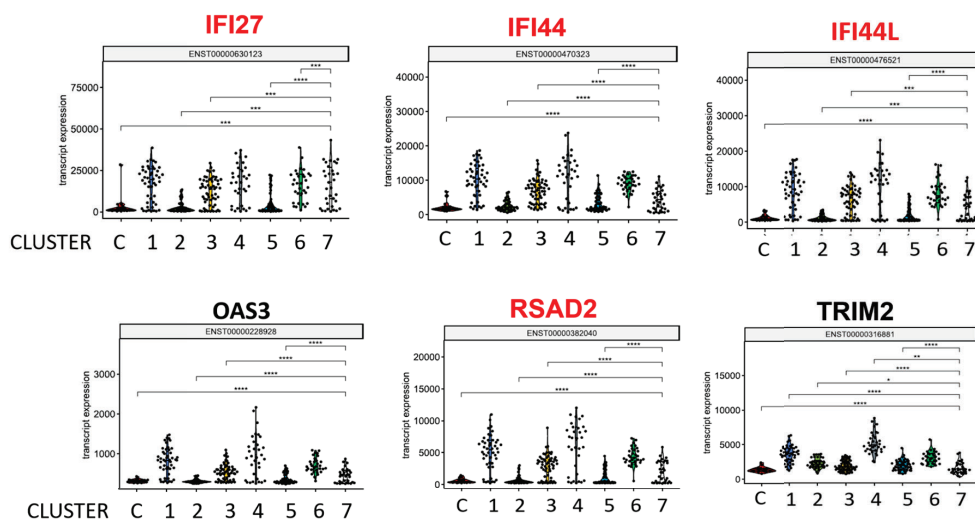
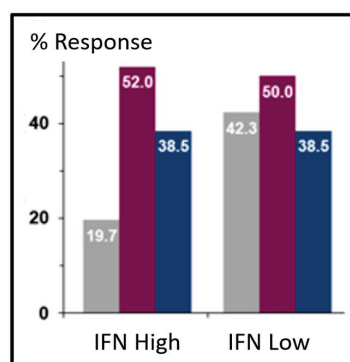


Figure from Furie ACR 2015
Full report in Furie Arth Rheum 2017 69:276-386



Mann – Whitney, Benjamini – Hochberg adjusted value.
**** $p < 0.0001$

Analysis of Anifrolumab

Furie R, Khamashta M, Merrill JT et al *Arthritis Rheum* 2017 69:376-386

Merrill JT, Furie R, Werth V et al *Lupus Sci Med* 2018 5(1):e000284

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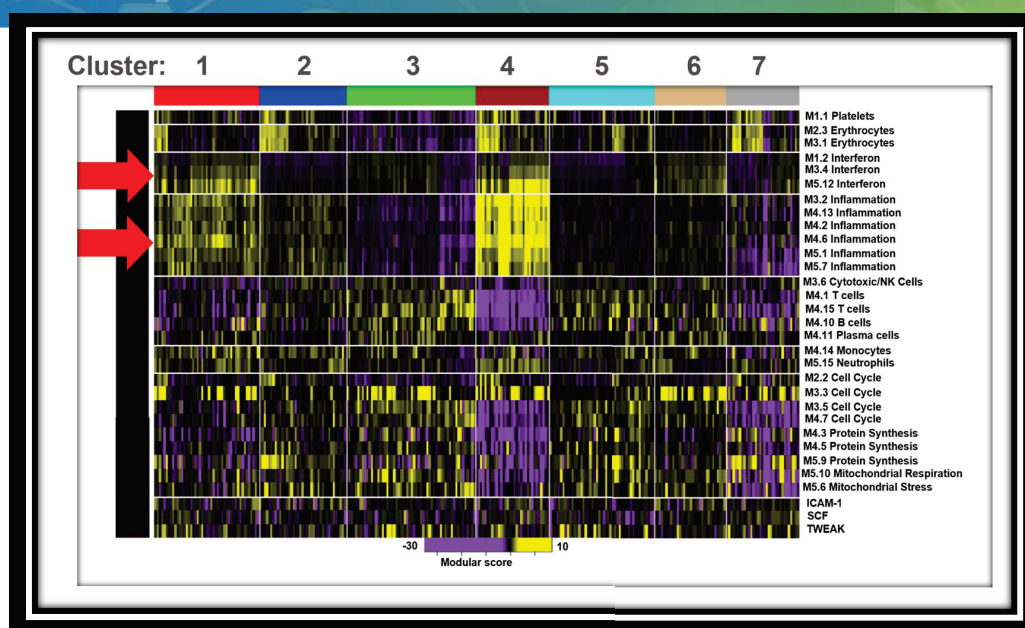


29 co-expression
module scores from
microarray gene-
expression data.

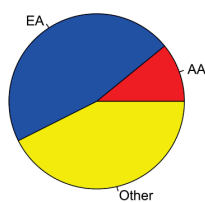
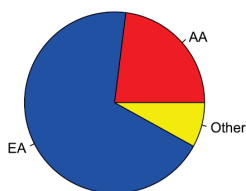
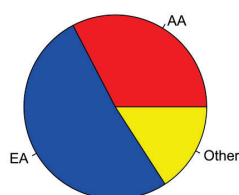
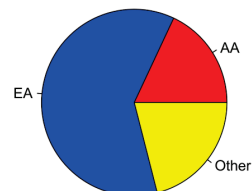
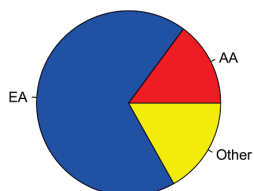
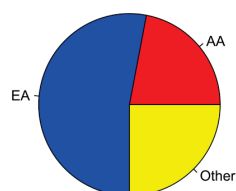
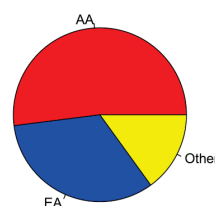
23 soluble mediators

13 autoantibodies

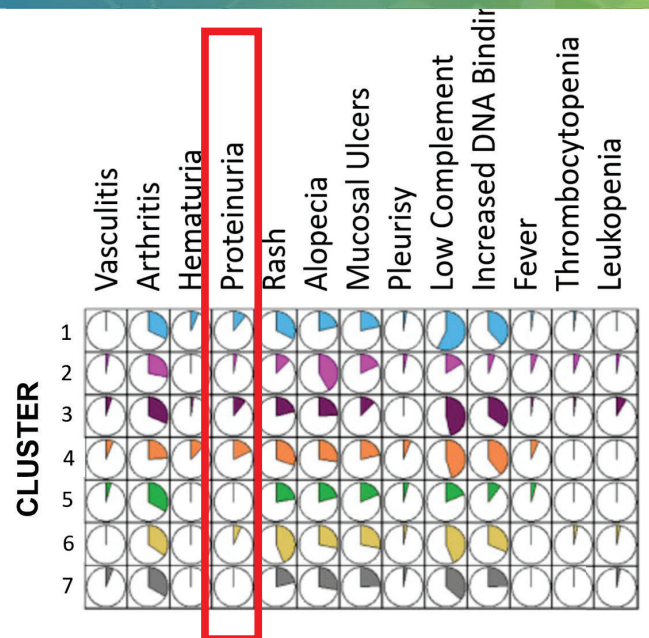
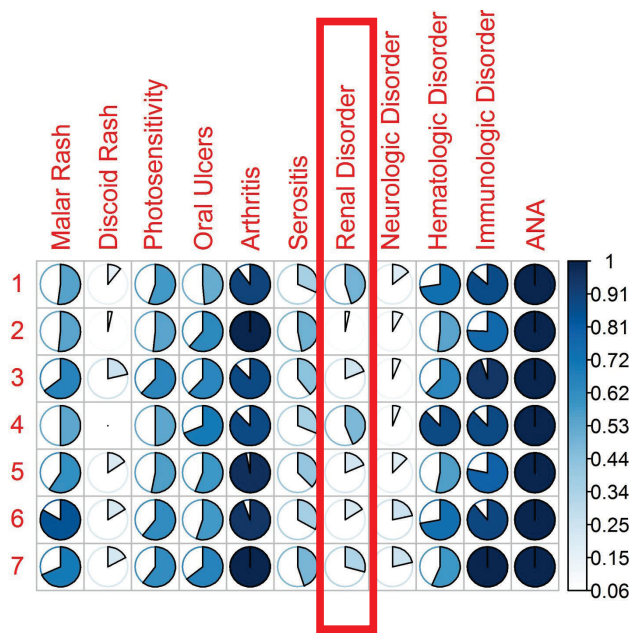
Patient clusters derived
by K-means clustering
and random forest
analysis of co-
expression module
scores and soluble
mediators.



Guthridge JM, Lu R, Tran LT, Arriens C, Aberle T, Kamp S, Munroe ME, Dominguez N, Gross T, DeJager W, Macwana SR, Bourn RL, Apel S, Thanou A, Chen H, Chakravarty EF, Merrill JT, James JA. *EClinicalMedicine* 2020 Mar 4;20:100291

**Cluster 1****Cluster 2****Cluster 3****Cluster 4****Cluster 5****Cluster 6****Cluster 7**

Racial Distribution in Each Molecular Phenotype Cluster



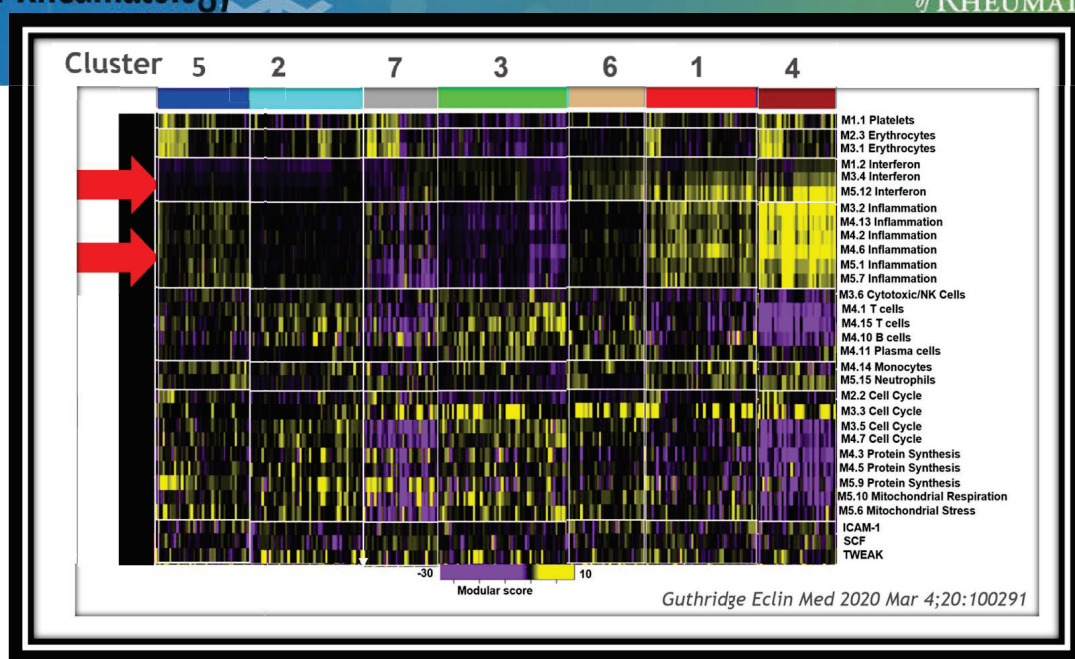
Guthridge JM, Lu R, Tran LT, Arriens C, Aberle T, Kamp S, Munroe ME, Dominguez N, Gross T, DeJager W, Macwana SR, Bourn RL, Apel S, Thanou A, Chen H, Chakravarty EF, Merrill JT, James JA. *EClinicalMedicine* 2020 Mar 4;20:100291



**Patients Move
From Cluster to
Cluster**

**Disease activity?
Medications?**

**Implications of
Fluidity:
Is Lupus a problem
of balance rather
than a preset static
abnormality?**

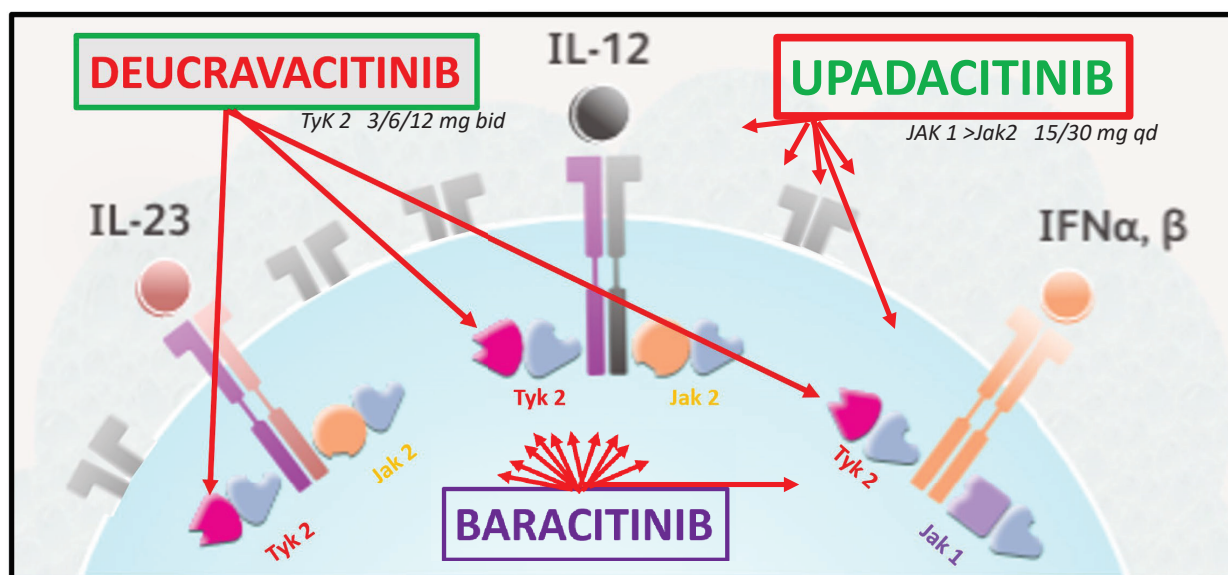


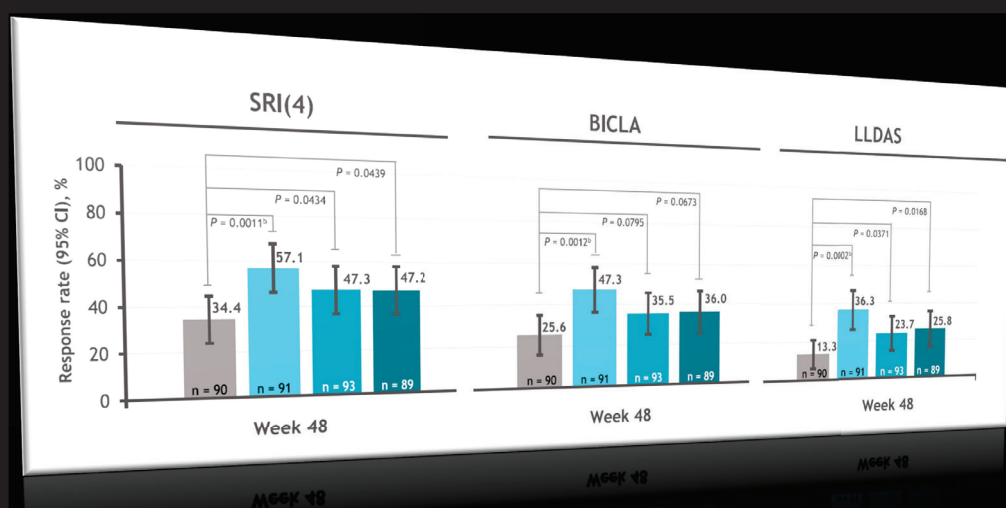
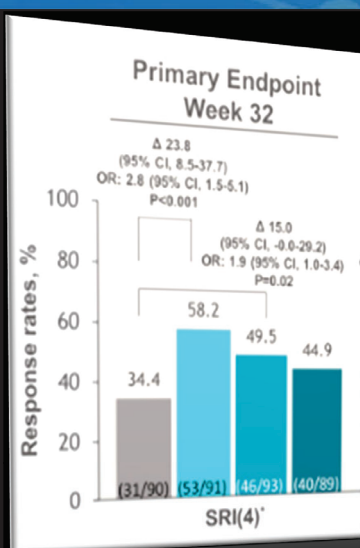
There may be Complicated Clinical and Pathophysiologic Conditions and Medication Immune Modulating Effects Causing Patients to Move From Cluster to Cluster.

Impact of Immunosuppressants on Gene Expression

Detector	IFN High AZA - no d IS LS mean delta		IFN Low AZA - no IS LS mean delta		IFN High MMF - no IS LS mean delta		IFN Low MMF - no IS LS mean delta		IFN High MTX - no IS LS mean delta		IFN Low MTX - no IS LS mean delta	
	Cts	p-value	Cts	p-value	Cts	p-value	Cts	p-value	Cts	p-value	Cts	p-value
FCER1A	0.26	0.6170	-0.96	0.0533	-1.19	0.0197	-0.81	0.3124	-1.14	0.0507	-1.78	0.0008
FCGR3A	0.74	0.0427	0.38	0.2625	-0.08	0.8272	0.79	0.1567	0.57	0.1594	0.05	0.8981
FOXP3	-0.05	0.9147	-0.42	0.3403	-0.04	0.9304	1.42	0.0499	1.18	0.0240	-0.21	0.6509
HJURP	-0.27	0.6333	-0.16	0.7591	0.49	0.3642	0.17	0.8408	1.24	0.0490	1.73	0.0026
ICOSLG	0.34	0.2859	0.15	0.6155	-0.68	0.0326	0.58	0.2525	-0.04	0.9073	0.24	0.4605
IL17RA	0.26	0.1523	-0.01	0.9323	0.08	0.6569	0.91	0.0015	0.19	0.3481	0.33	0.0693
IL17RC	0.25	0.4289	-0.17	0.5803	-0.59	0.0597	1.08	0.0303	-0.36	0.3138	0.05	0.8818
IL1RL1	0.64	0.1820	-1.15	0.0130	-0.10	0.8350	-0.28	0.7075	0.10	0.8505	-1.44	0.0032
IL23A	-0.65	0.0287	-0.01	0.9630	-0.51	0.0753	0.16	0.7314	0.02	0.9636	-0.37	0.2049
IL3RA	0.80	0.0264	-0.92	0.0083	0.23	0.5052	0.56	0.3153	0.06	0.8778	-0.43	0.2344
ITGAM	0.35	0.0434	-0.03	0.8653	0.17	0.3262	0.76	0.0059	0.10	0.5944	0.26	0.1393
LGALS3BP	-0.43	0.2597	-0.37	0.3065	-0.10	0.7933	-0.04	0.9515	1.47	0.0009	-0.09	0.8180
OAS1	0.05	0.8663	-0.29	0.2786	0.05	0.8621	0.36	0.4190	0.78	0.0161	0.16	0.5795
OAS2	0.05	0.8292	-0.13	0.5086	-0.05	0.7979	0.51	0.1268	0.85	0.0006	0.00	0.9842
TNFSF13	0.05	0.7822	-0.09	0.6252	-0.44	0.0183	-0.05	0.8741	-0.13	0.5428	0.04	0.8489

Merrill ACR 2016

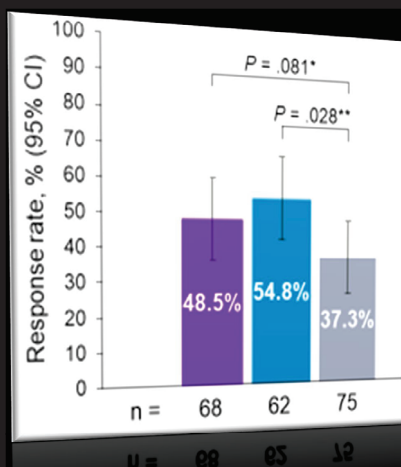




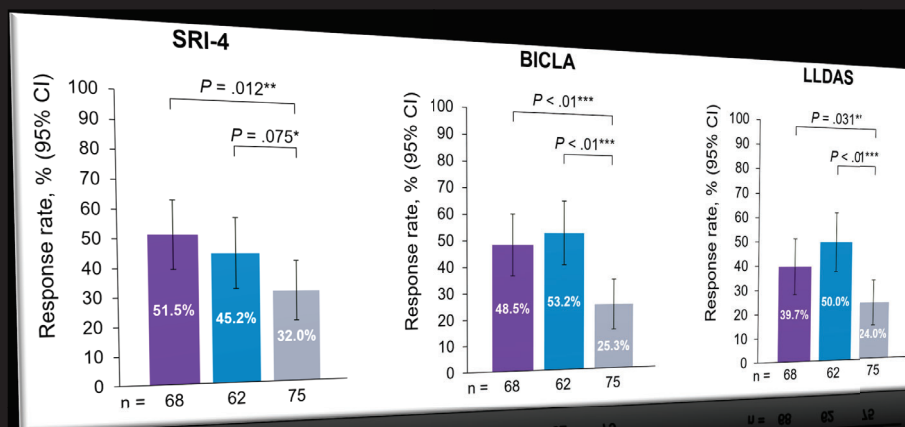
■ Placebo ■ Deucravacitinib 3 mg BID ■ Deucravacitinib 6 mg BID ■ Deucravacitinib 12 mg QD

Inhibition of Tyk 2
IFNAR +IL10, 12, 23

Morand et al EULAR 2022
Data since published as Morand Arth Rheum 75:242 2023

PRIMARY ENDPOINT AT WEEK 24
SRI-4 + $\leq$ 10mg Prednisone

SECONDARY ENDPOINTS AT WEEK 48



■ ABBV-599HD (elsubrutinib 60 mg + upadacitinib 30 mg) ■ Upadacitinib 30 mg ■ Placebo

Inhibition of Jak 1 Jak 1 +/- BTK
IFNAR + IFNg IL2, 4, 6

Merrill Arth Rheum 2024 76:1518

Phase 2

	PBO (N=105)	Bari 2-mg (N=105)	Bari 4-mg (N=104)
Efficacy measure		Week 24	
Resolution of arthritis or rash (SLEDAI-2K)	56 (53.3)	61 (58.1)	70 (67.3)*
SRI-4	50 (47.6)	54 (51.4)	67 (64.4)*
Flare (SFI, any severity)	54 (51.4)	45 (42.9)	34 (32.7)*
Flare (SFI, severe)	12 (11.4)	10 (9.5)	6 (5.8)
LLDAS	27 (25.7)	35 (33.3)	40 (38.5)*
ΔTJC	-5.59	-6.50	-6.86*
ΔSJC	-4.60	-4.12	-4.76
ΔCLASI activity score	-2.80	-1.66	-2.27
ΔWorst pain	-0.56	-1.17	-1.31*
ΔWorst fatigue	-1.18	-1.13	-1.52
Safety measure		Weeks 0-24‡	
TEAEs	68 (64.8)	75 (71.4)	76 (73.1)
SAEs	5 (4.8)	11 (10.5)	10 (9.6)
Serious infections	1 (1.0)	2 (1.9)	6 (5.8)
Deep vein thrombosis	0	0	1 (1.0)

Data are n (%) patients, unless otherwise indicated. Δ=least squares mean change from baseline.
‡Includes up to 30 days post treatment. CLASI=Cutaneous Lupus Erythematosus Disease Area and Severity Index; N=number of patients in the analysis population; n=number of patients in the specified category; TEAE=treatment-emergent adverse event.*p≤0.05.

Wallace ACR 2018 abs 970
Full report in Wallace Lancet 2018 282:222

Phase 3

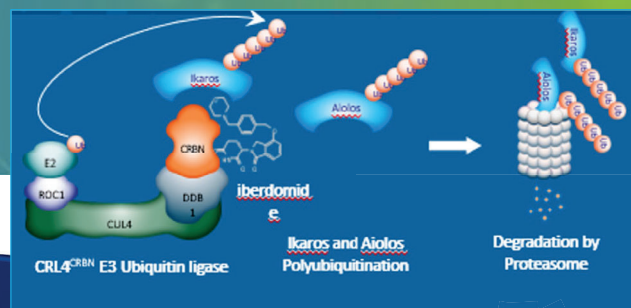
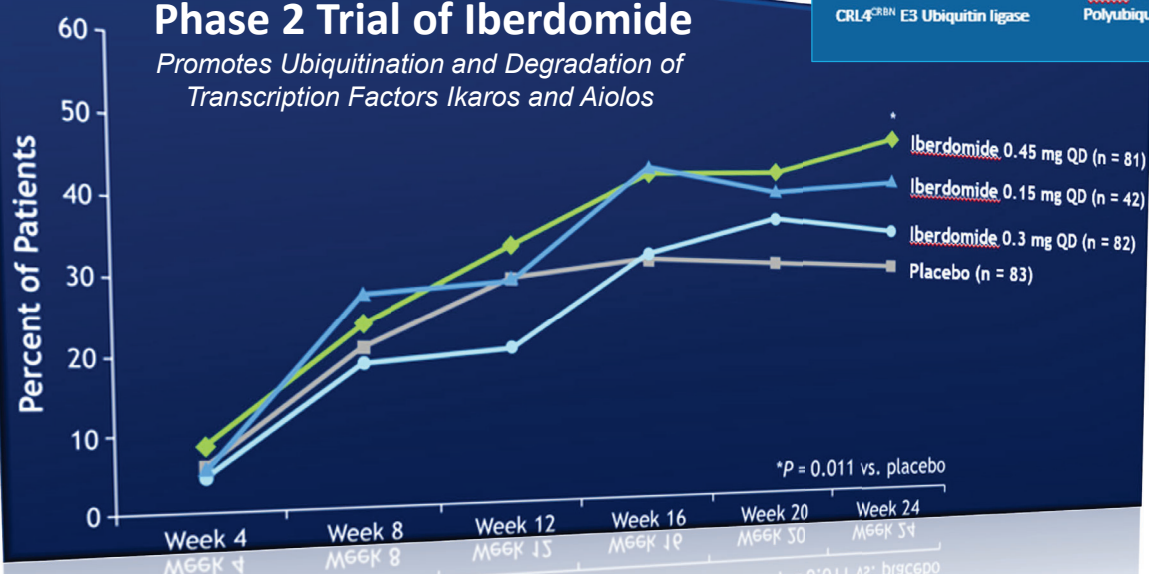
	SLE-BRAVE-1 PBO (N=253)	BARI 2-mg (N=255)	BARI 4-mg (N=252)
Efficacy measure			
SRI-4 (W52)	116 (45.9)	26 (49.8)	142 (56.7)*
SRI-4 (W24)	99 (39.1)	14 (44.8)	117 (46.5)
Severe Flares (n, events)	38 (15.0)	4 (13.3)	26 (10.3)
HR for time to first severe flare (SFI) HR [CI]	NA	0.8 [0.52, 1.32]	0.65 [0.40, 1.08]
Glucocorticoid sparing	36 (30.8)	1 (29.2)	36 (34.0)
LLDAS (W52)	66 (26.2)	5 (25.7)	74 (29.7)
Safety measure			
TEAE	210 (83.0)	10 (82.4)	208 (82.5)
SAE	18 (7.1)	4 (9.4)	26 (10.3)
Data are n (%) patients, unless otherwise indicated. BARI=baricitinib; CI=confidence interval; HR=hazard ratio; NA=not applicable; *p≤0.05 vs PBO.			
	SLE-BRAVE-1 PBO (N=256)	BARI 2-mg (N=261)	BARI 4-mg (N=258)
Efficacy measure			
SRI-4 (W52)	116 (45.6)	20 (46.3)	121 (47.1)
SRI-4 (W24)	98 (38.6)	10 (40.0)	108 (42.1)
Severe Flares (n, events)	26 (10.2)	29 (11.1)	29 (11.2)
HR for time to first severe flare (SFI) HR [CI]	NA	1.1 [0.65, 1.89]	1.1 [0.67, 1.94]
Glucocorticoid sparing	33 (31.7)	24 (29.8)	36 (34.3)
LLDAS (W52)	59 (23.2)	32 (24.0)	65 (25.4)
Safety measure			
TEAE	198 (77.3)	99 (76.2)	200 (77.5)
SAE	22 (8.6)	5 (13.4)	29 (11.2)

Morand E Lancet 2023 401(10381):1001
Petri M Lancet 2023 401(10381):1011



Phase 2 Trial of Iberdomide

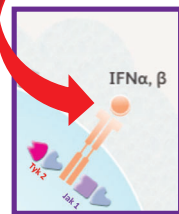
Promotes Ubiquitination and Degradation of
Transcription Factors Ikaros and Aiolos



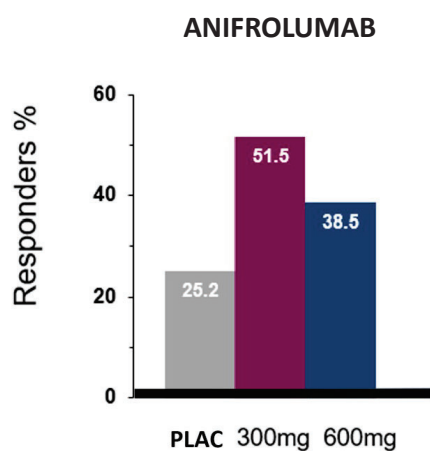
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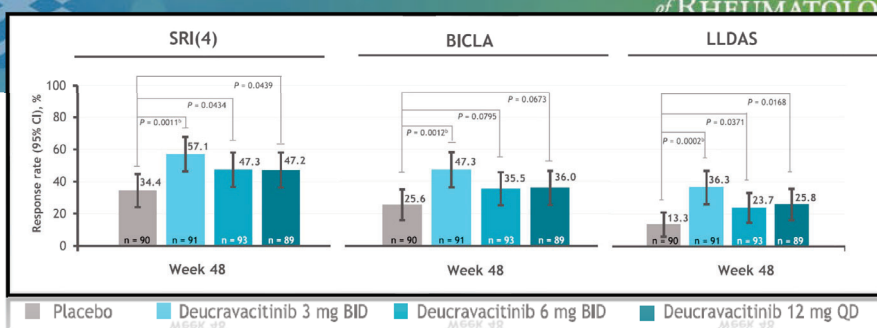


Merrill N Engl J Med 2022 386:1034

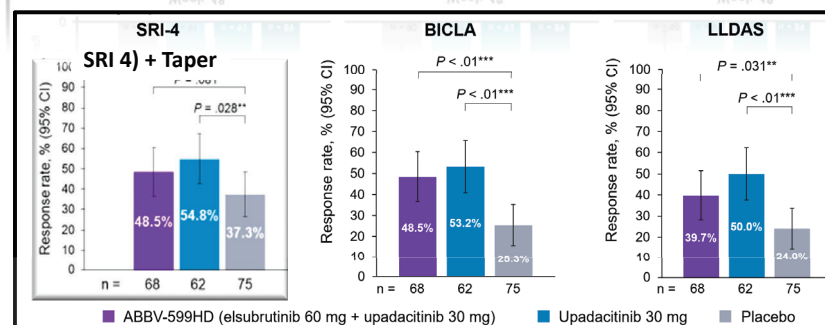


Left: Fig from Furie ACR 2015
Full report in Furie Arth Rheum 2017 69:276-386

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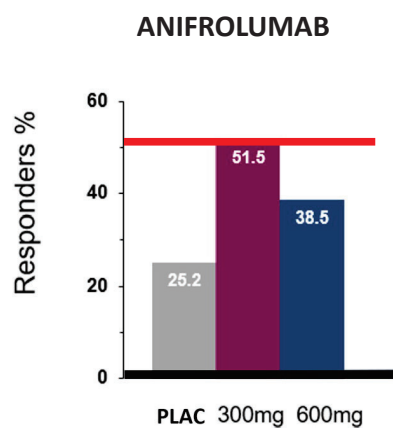


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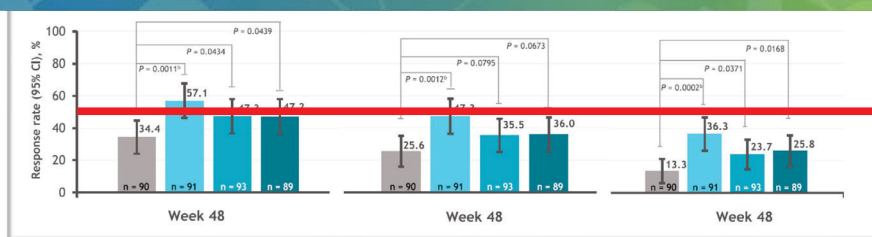


Upper Right: Fig from Morand EULAR 2022
Full report in Morand Arth Rheum 2023 75:242

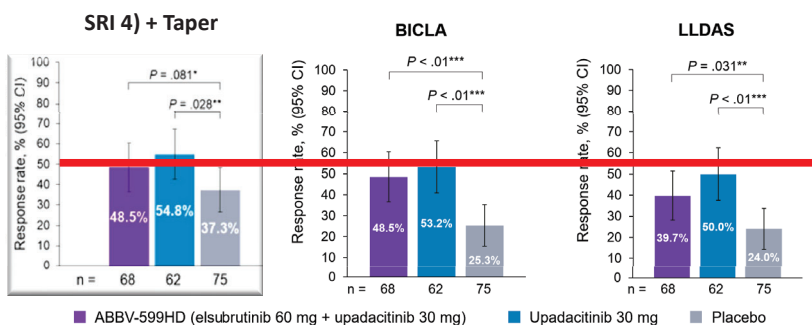
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Full data in Merrill Arth Rheum 2024 76:1518



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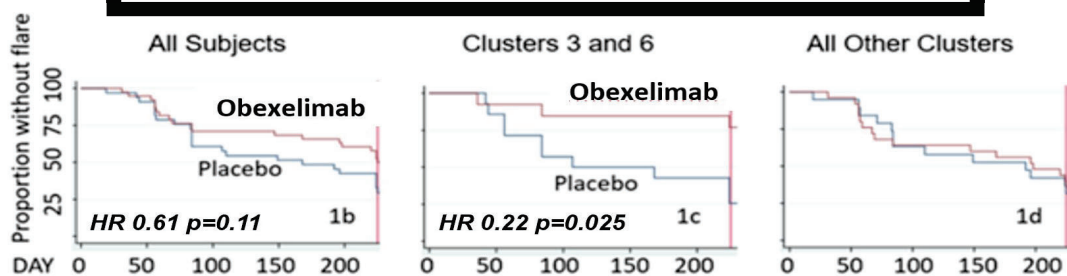
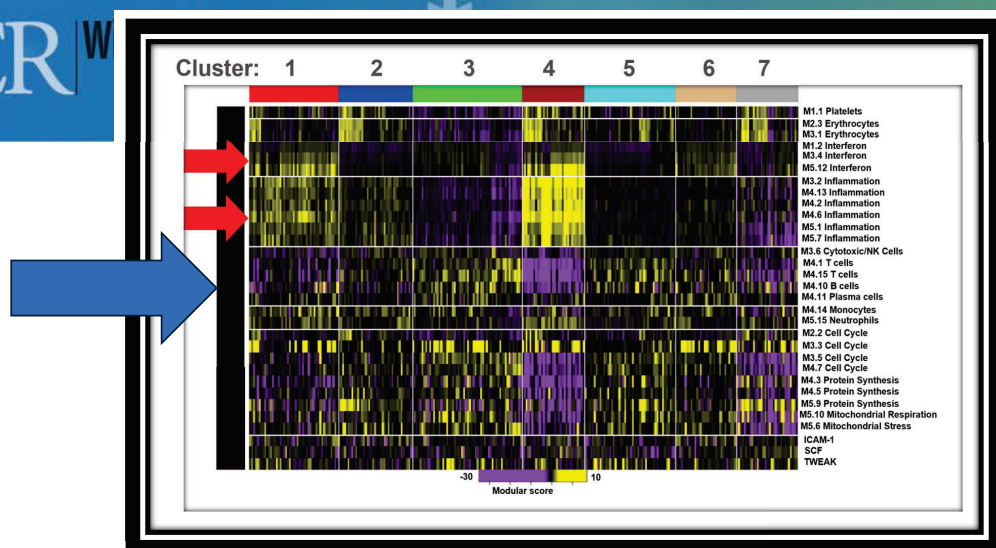
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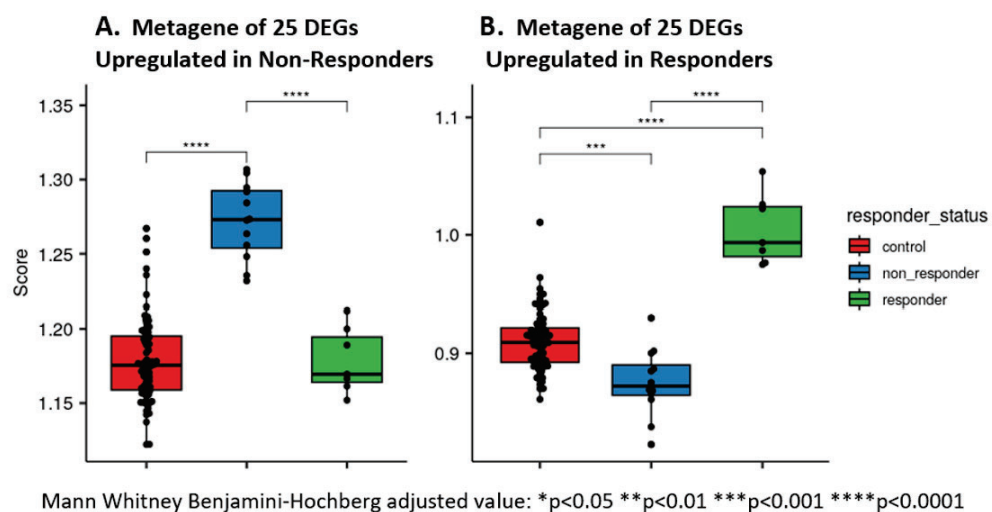


Left: Fig from Furie ACR 2015
Full report in Furie Arth Rheum 2017 69:276-386

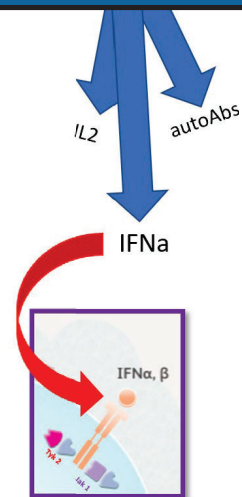
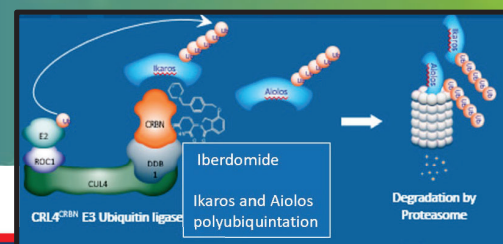
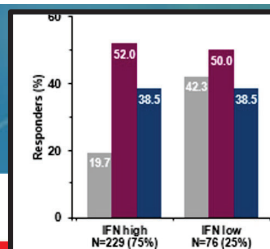
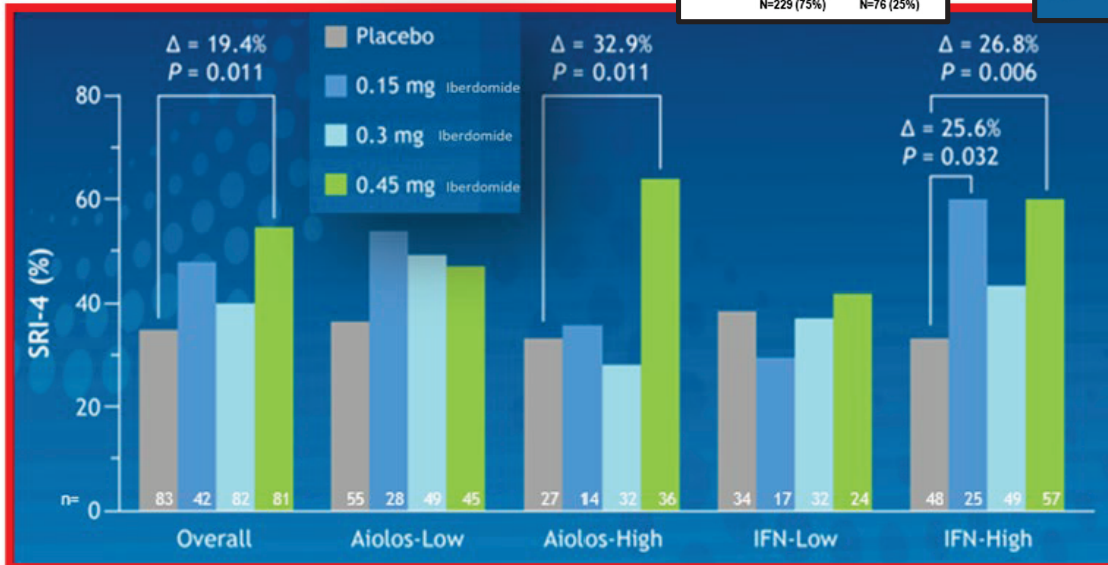
Upper Right: Fig from Morand EULAR 2022
Full report in Morand Arth Rheum 2023 75:242

Lower Right: Fig from Merrill EULAR 2023
Full data in Merrill Arth Rheum 2024 76:1518





**Figure: No overlap between pre-treatment metagene module scores
In SLE patients who do vs do not respond to belimumab**



How To Get There?

More Precise Approach to Understanding Immunologic Impact of
Treatments And Treatment Interactions

Use of Clinical Clues About Types of Patients Most Likely to Respond to
Targeted Treatments