Disease Activity and Severity are reflected in serum tissue destruction markers

The Synoviomics cohort (The Netherlands)

	C1M	C2M	C3M
DAS28	0.57***	0.29	0.60***
SJC66	0.35**	0.19	0.37**
TJC	0.18	0.10	0.12
HAQ	0.38**	0.02	0.15
CRP	0.89***	0.23	0.66***
ESR	0.69***	0.29	0.69***

The correlation between baseline biomarkers and disease activity measures. Spearman's rho and significance given; **, p<0.01 and *** p<0.001. *Maijer KI, PLoS One. 2016.*

The Synoviomics cohort (AMC, NL): Ninety-two early arthritis patients (arthritis duration<1 year, DMARD naïve) were enrolled. Patients either fulfilled the ACR/EULAR2010 criteria for RA (n = 60) or had unclassified arthritis (UA) (n = 32). Patients fulfilling the RA criteria after 2 years follow-up were classified into non-erosive (n = 25), or erosive disease (n = 13). 64% female, mean age 50-year, 39% RF positive, 51% ACPA positive.

RA cohort from UOEB (Japan)

	C1M	C3M	C4M
DAS28	0.40***	0.36***	0.46***
CDAI	0.24**	0.23**	0.35***
SDAI	0.34***	0.30***	0.40***
HAQ	0.23**	0.14	0.28***
Erosion	0.17*	0.13	0.26**
Sharp (SHS)	0.15	0.12	0.30***

The correlation between baseline biomarkers and disease activity measures. Spearman's rho and significance given; **, p<0.01 and *** p<0.001. *Gudmann NS, Clin Exp Rheumatol. 2018*

RA cohort from UOEB (Japan); Mixed RA population (arthritis duration >3months) with active RA were enrolled. Patients fulfilled the ACR/EULAR2010 criteria for RA (N = 149). Patients were treated with MTX (n=23), Adalimumab+MTX (n=49), Tofacitinib+MTX (n=27) or tocilizumab+MTX (n=50) and followed for 1 year.

Response to treatment reflected in tissue destruction

- A 5 - 40% treatment dependent reduction in the collagen destruction markers were observed.

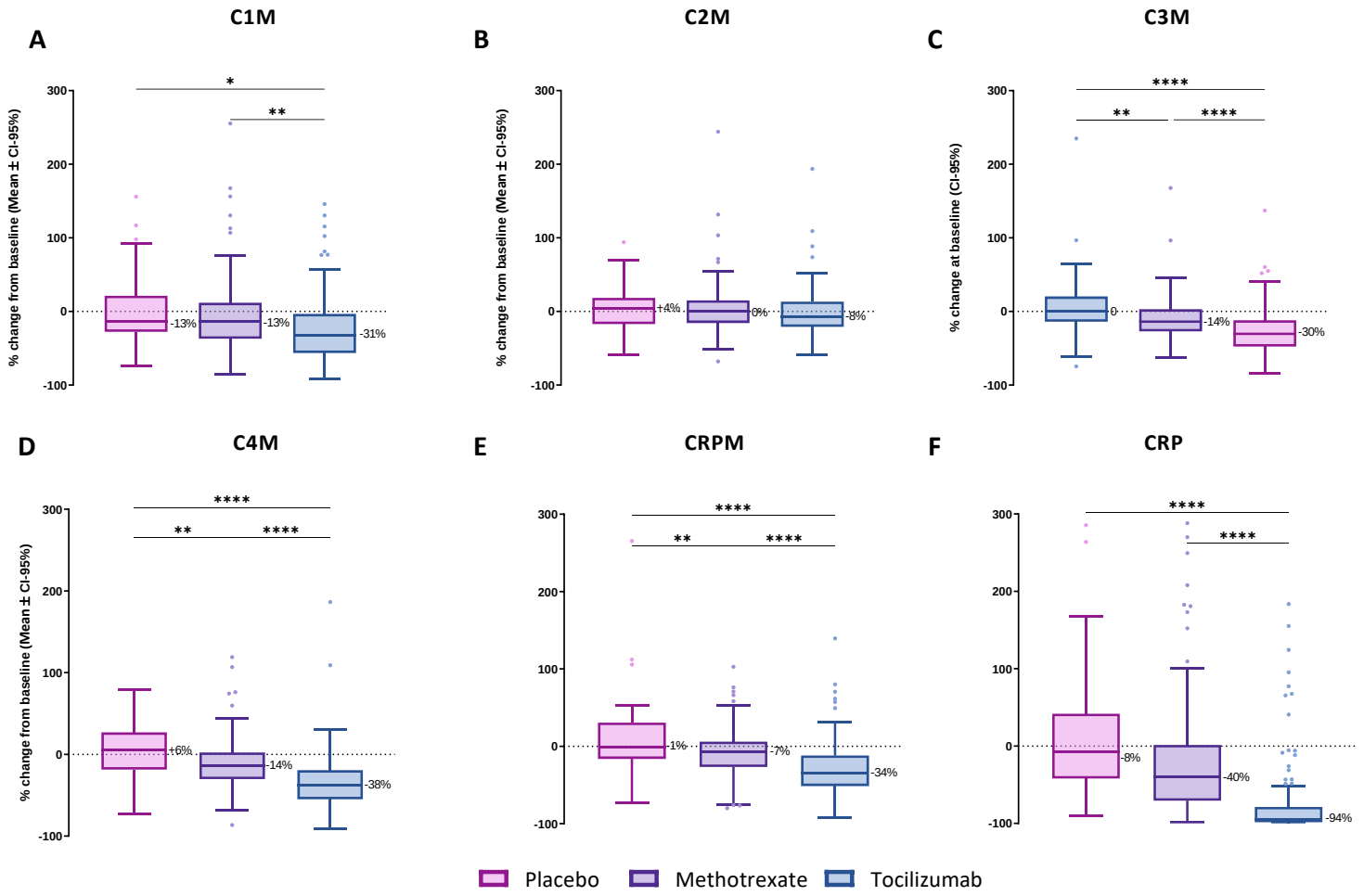
- Effective treatment suppress levels down to normal levels (typically 20-40% reduction)
- Fun fact: Only tofacitinib had an effect on the fibrosis marker PRO-C3

	Methotraxate						Adalimumab						Tocilizumab						Tofacitinib					
	N	Median conc. At baseline	IQR	Median Change	IQR	P value	N	Median	IQR	Median Change	IQR	P value	N	Median	IQR	Median Change	IQR	P value	N	Median	IQR	Median Change	IQR	P value
C1M	21	32.9	20.7-49.7	80.8	50.1-101	0.019	49	48.9	30.9-70.4	66.8	22.3-44.5	0.0005	49	45.1	21.1-62.4	66.9	37.3-119	0.029	27	46.6	29.6-71.1	64.2	27.9-111	0.012
C3M	21	32.7	18.7-61.5	81.5	61.4-104	0.0052	49	26.8	21.1-35.4	84.8	66.0-110	0.021	49	36.5	19.2-50.4	72.5	54.0-89.6	<0.0001	27	34.1	28.9-50.3	68.1	34.4-77.2	0.0001
C4M	21	57.7	47.3-70.9	78.6	71.0-89.4	0.0011	49	57.2	39.2-75.2	79.5	64.0-112	0.0009	49	73.7	52.9-93.0	64	46.5-80.5	<0.0001	27	75.9	64.0-102	65.4	55.4-75.7	<0.0001
PRO-C3	21	15.4	11.3-18.3	116.9	99.0-131	ns	49	17.8	11.1-25.4	99.5	62.7-150	ns	49	14.6	11.3-23.5	116	68.5-165	ns	27	19.4	15.8-21.8	72.6	60.5-106	0.017
CRPM	21	2.44	1.96-3.59	78.7	45.4-114	0.058	49	2.21	1.57-2.79	123.6	76.2-221	0.011	49	2.54	1.79-3.77	87.3	44.7-136	0.012	27	2.4	1.97-3.34	81.9	44.8-127	ns

RA cohort from UOEB (Japan); Mixed RA population (arthritis duration >3months) with active RA were enrolled. Patients fulfilled the ACR/EULAR2010 criteria for RA (N = 149). Patients were treated with MTX (n=21), adalimumab+MTX (n=49), tocilizumab+MTX (n=49) or Tofacitinib+MTX (n=27) and followed for 1 year. Paired t-test using log-transformed data from baseline and FU. Data is shown as median with interquartile ranges (IQR). Alpha = 0.05.

Gudmann NS, Clin Exp Rheumatol. 2018

Tissue destruction markers are decreased in response to tocilizumab

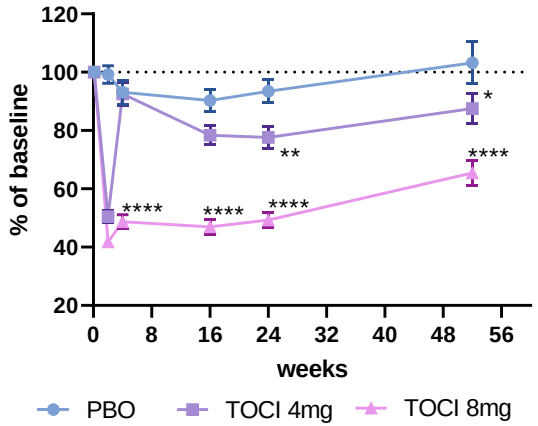


- The AMBITION study (Phase III, Roche-Genentech)
- Changes in biomarkers from baseline to week 8, biological naïve RA patients
- Tissue destruction markers are decreased in response to tocilizumab compared to placebo more significantly than MTX

Drobinski et al. ART 2021

Profiling of dose-response of different drug

Tocilizumab



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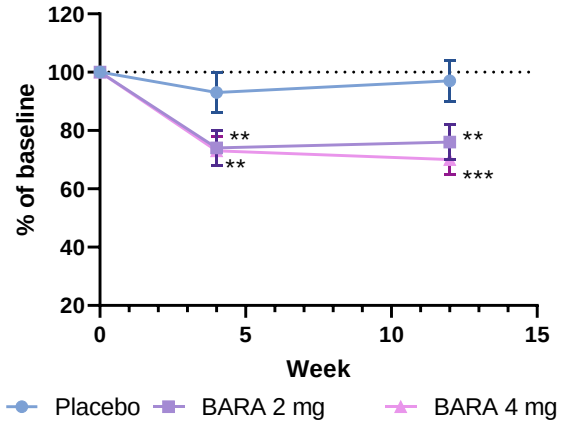
Baricitinib



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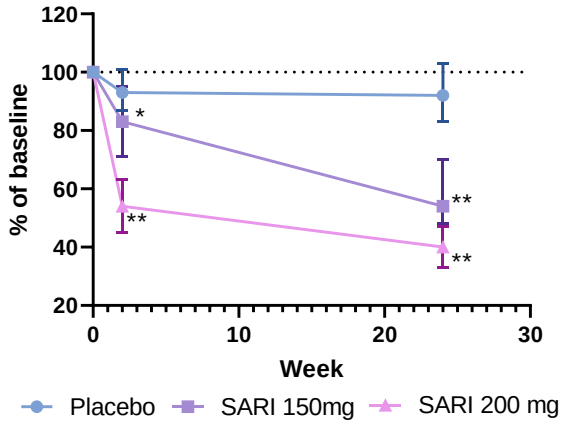
Sarilumab



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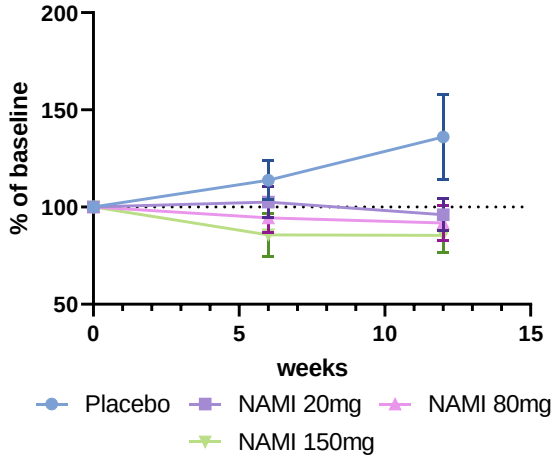
Namilumab



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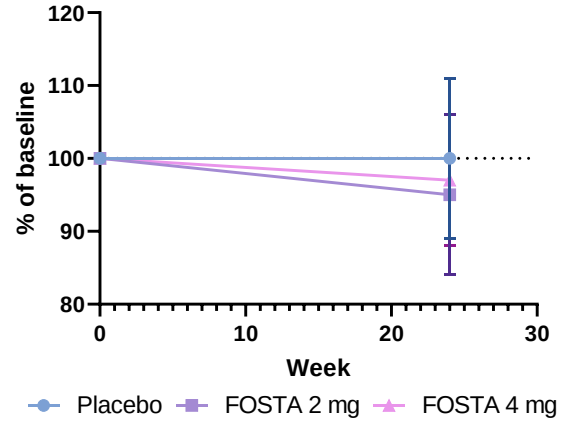
Fostamatinib



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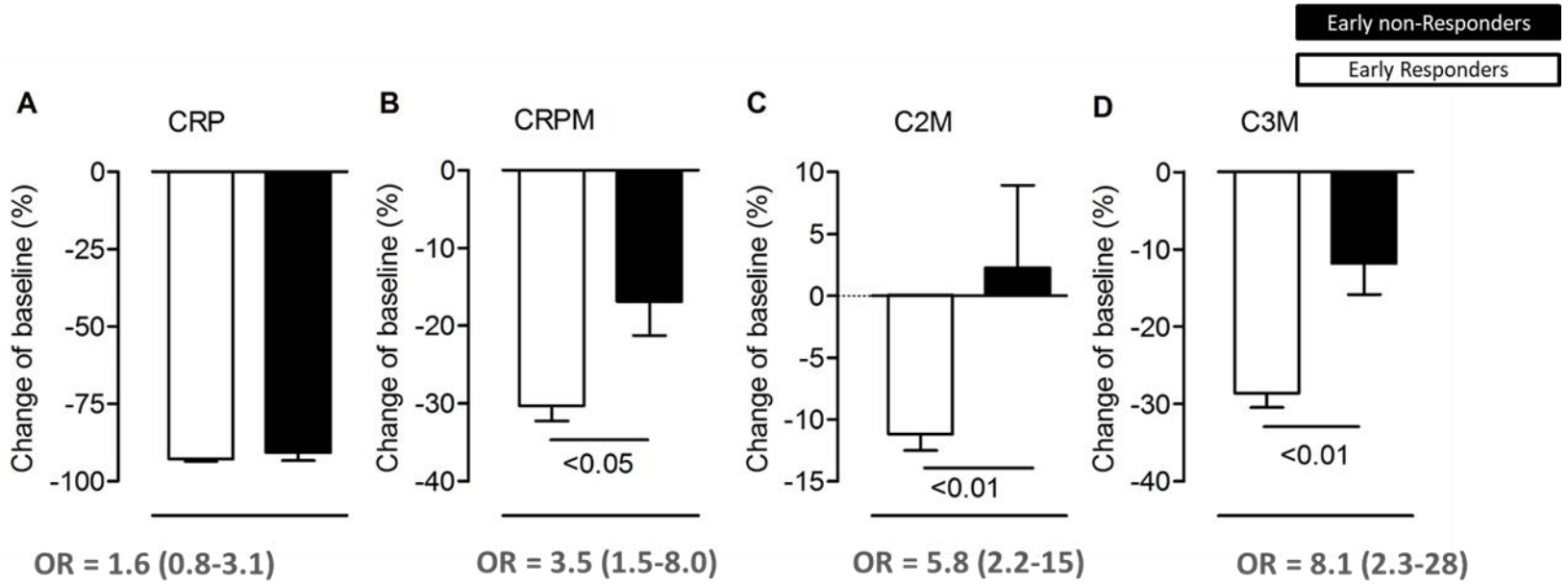
Level of suppression is reflective of drug response in phase II and III

Drug	Indication	Suppression tissue destruction marker	Public disclosed results
Forstamatinib (Syk)	RA	0%	Discontinued
Tocilizumab (IL-6)	RA	40 %	Success
Sarilumab (IL-6)	RA	50%	Success
Baracitinib (Jak)	RA	30%	Pending
Mavrilimumab (GM-CSF)	RA	25%	Discontinued
Namilumab (GM-CSF)	RA	0%	Discontinued
Guselkumab	PSA	60%	Success
Deucravacitinib (tyk2)	PSA	15%	Development ongoing
Anti-TNFs (multiple)	RA, AS, PSA	30-50%	Success

Fibrolysis fragments predict treatment response

- Change in biomarker from baseline to week 4 and Response to 8mg/kg tocilizumab + MTX at week 16 in DMARD-IR patients



Bay-Jensen AC, Semin Arthritis Rheum. 2014