Rehberg M et al. Identification of a rule to predict response to sarilumab in patients with rheumatoid arthritis using machine learning and clinical trial data

SUPPLEMENTARY MATERIAL

Table S1. Endpoints included in performance analysis of the anti-CCP+CRP rule (assessed at baseline and Week 24)

Measure	Endpoints	Studies
ACR	• Response rates (ACR20, ACR50, and ACR70)	MOBILITY, MONARCH, TARGET, ASCERTAIN
CDAI	• Response rates (REM: ≤2.8; LDA: ≤10.0) • Absolute values (CFB)	MOBILITY, MONARCH, TARGET
DAS28-CRP	• Response rates (REM: <2.6; LDA: <3.2) • Absolute values (CFB)	MOBILITY, MONARCH, TARGET, ASCERTAIN
DAS28-ESR	• Response rates (REM: <2.6; LDA: <3.2) • Absolute values (CFB)	MONARCH
HAQ-DI	• Response rates (MCID: ≥0.22) • Absolute values (CFB)	MONARCH, TARGET, ASCERTAIN

ACR20, ACR 20%; ACR50, ACR 50%; ACR70, ACR 70%; CDAI, Clinical Disease Activity Index; CFB, change from baseline; DAS28-CRP, 28-joint Disease Activity Score using C-reactive protein; DAS28-ESR, DAS28 using erythrocyte sedimentation rate; HAQ-DI; Health Assessment Questionnaire-Disability Index; LDA, low disease activity; MCID, minimal clinically important difference; REM, remission.

Table S2: Averaged metrics of different machine learning algorithms (10-fold cross-validated, MOBILITY training data - normalized, endpoint ACR20)

Model	Accuracy	AUC	Recall	Precision	F1	Kappa
Extra Trees Classifier	0.703	0.5833	0.9232	0.7184	0.8062	0.2053
Quadratic Discriminant Analysis	0.6758	0.5062	0.9875	0.6788	0.8039	0.0154
Light Gradient Boosting Machine	0.6758	0.543	0.8411	0.738	0.7717	0.1536
CatBoost Classifier	0.6742	0.6118	0.9214	0.6958	0.7907	0.0791
Gradient Boosting Classifier	0.6644	0.5604	0.8286	0.7214	0.7667	0.1588
Logistic Regression	0.6508	0.5606	0.7554	0.7617	0.7273	0.1823
Random Forest Classifier	0.647	0.5787	0.8018	0.7136	0.7504	0.1301
Ridge Classifier	0.6409	0	0.7554	0.7522	0.73	0.1459
K Neighbors Classifier	0.6402	0.5584	0.8821	0.6791	0.765	0.018
Ada Boost Classifier	0.622	0.453	0.7607	0.6949	0.7199	0.073
Linear Discriminant Analysis	0.6152	0.6497	0.7161	0.7365	0.7065	0.1069
SVM – Linear Kernel	0.6068	0	0.6911	0.7428	0.6939	0.1098
Decision Tree Classifier	0.5167	0.4753	0.5839	0.6596	0.6116	−0.0494
Naïve Bayes	0.4212	0.5692	0.2732	0.675	0.36	0.0038
Metrics Over Training Data for AntiCCP-CRP Rule						
GUIDE	0.644172		0.618182	0.809524	0.701031	0.280627

Table S3: Baseline characteristics of rule-positive and -negative patients in MONARCH

Parameter	Sarilumab 200 mg		Adalimumab	
	Rule-positive patients[a] (N = 62)	Rule-negative patients (N = 116)	Rule-positive patients[a] (N = 73)	Rule-negative patients (N = 107)
DAS28-CRP	6.6 ± 0.7	5.7 ± 0.8	6.4 ± 0.8	5.8 ± 0.9
DAS28-ESR	7.1 ± 0.8	6.7 ± 0.7	6.9 ± 0.9	6.7 ± 0.8
CDAI	46.3 ± 12.1	42.1 ± 11.6	41.6 ± 12.0	42.7 ± 12.0
HAQ-DI	1.8 ± 0.5	1.6 ± 0.6	1.9 ± 0.6	1.4 ± 0.6
ESR, mm/h	54.6 ± 25.5	41.1 ± 18.2	58.8 ± 26.8	38.6 ± 14.1
SJC28	14.4 ± 5.5	12.4 ± 5.4	12.1 ± 5.1	13.0 ± 5.7
Presence of RF, n (%)	52 (85.2)	66 (57.9)	61 (85.9)	54 (50.9)
Presence of anti-CCP, n (%)	62 (100)	72 (62.1)	73 (100)	65 (60.7)
RANKL, pmol/L	2401 ± 3959	1159 ± 2987	3853 ± 9607	822 ± 1178
OPG, pmol/L	6.8 ± 3.2	6.2 ± 2.2	7.7 ± 3.2	6.5 ± 2.6
OC, ng/mL	20.0 ± 10.0	21.9 ± 11.1	18.6 ± 8.7	21.6 ± 9.3
Prior DMARD use, n (%)	62 (100)	116 (100)	73 (100)	107 (100)

[a]Patients who were anti-CCP-positive and had CRP >12.3 mg/L. Values are mean ± SD, unless otherwise indicated. Anti-CCP, anti-cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; DAS28-CRP, 28-joint Disease Activity Score using C-reactive protein; DAS28-ESR, DAS28 using erythrocyte sedimentation rate; HAQ-DI; Health Assessment Questionnaire-Disability Index; OC, osteocalcin; OPG, osteoprotegerin; RANKL, receptor activator of NF-kappa B ligand; RF, rheumatoid factor; SJC, swollen joint count.

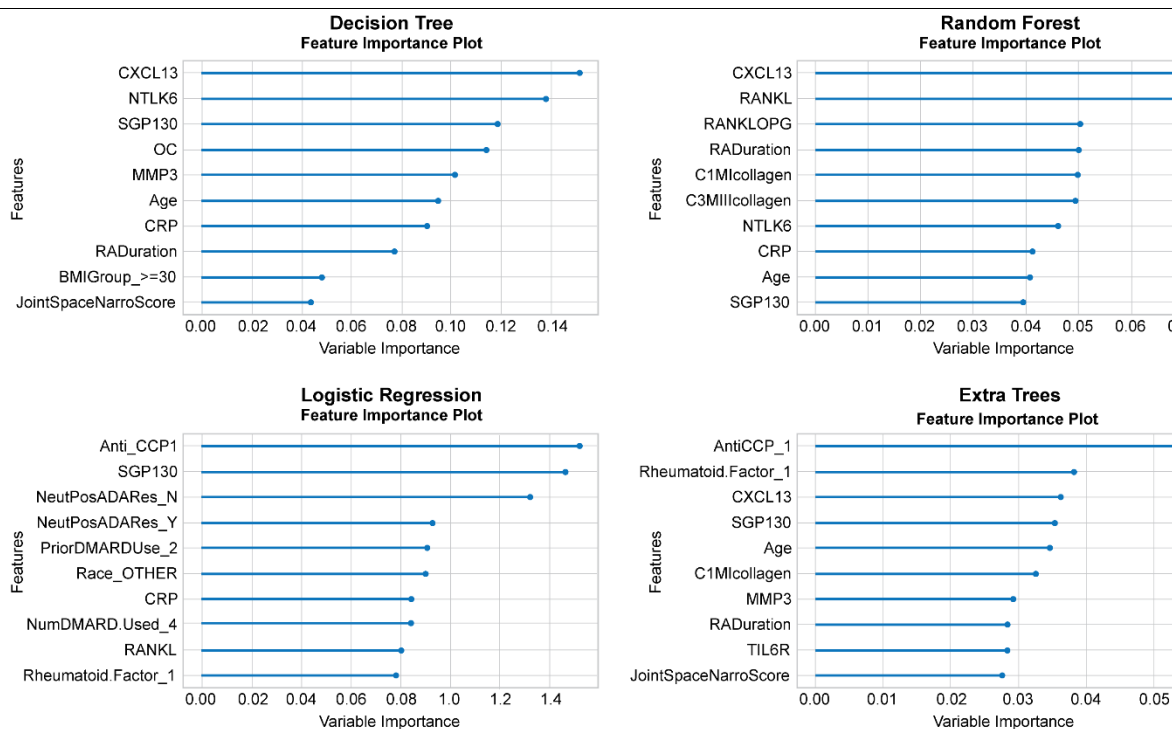**Table S4:** Baseline characteristics of rule-positive and -negative patients in TARGET

Parameter	Sarilumab 200 mg		Placebo	
	Rule-positive patients[a] (N = 97)	Rule-negative patients (N = 83)	Rule-positive patients[a] (N = 93)	Rule-negative patients (N = 87)
DAS28-CRP	6.6 ± 0.9	5.9 ± 1.0	6.4 ± 0.8	5.9 ± 0.7
CDAI	46.6 ± 13.6	41.0 ± 12.7	43.5 ± 13.4	41.8 ± 10.7
HAQ-DI	1.9 ± 0.6	1.7 ± 0.7	1.9 ± 0.6	1.6 ± 0.6
SJC28	14.4 ± 6.4	11.8 ± 5.9	13.1 ± 5.8	13.2 ± 5.6
Presence of RF, n (%)	87 (89.7)	44 (53.0)	84 (91.3)	57 (65.5)
Presence of anti-CCP, n (%)	97 (100)	40 (48.2)	93 (100)	57 (65.5)
RANKL, pmol/L	2937 ± 3263	2108 ± 3341	2796 ± 5844	1697 ± 2848
OPG, pmol/L	6.2 ± 3.4	6.9 ± 4.0	6.8 ± 2.7	6.1 ± 2.2
OC, ng/mL	21.7 ± 10.8	20.0 ± 10.3	18.8 ± 7.3	18.1 ± 9.8
Prior TNFi use, n (%)				
≥1 prior TNFi	97 (100)	83 (100)	93 (100)	87 (100)
>1 prior TNFi	29 (29.9)	20 (24.1)	28 (30.1)	20 (23.0)

[a]Patients who were anti-CCP-positive and had CRP >12.3 mg/L. Values are mean ± SD, unless otherwise indicated. Anti-CCP, anti-cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; DAS28-CRP, 28-joint Disease Activity Score using C-reactive protein; HAQ-DI; Health Assessment Questionnaire-Disability Index; OC, osteocalcin; OPG, osteoprotegerin; RANKL, receptor activator of NF-kappa B ligand; RF, rheumatoid factor; SJC, swollen joint count; TNFi, tumor necrosis factor inhibitor.

Table S5: Baseline characteristics of rule-positive and -negative patients in ASCERTAIN

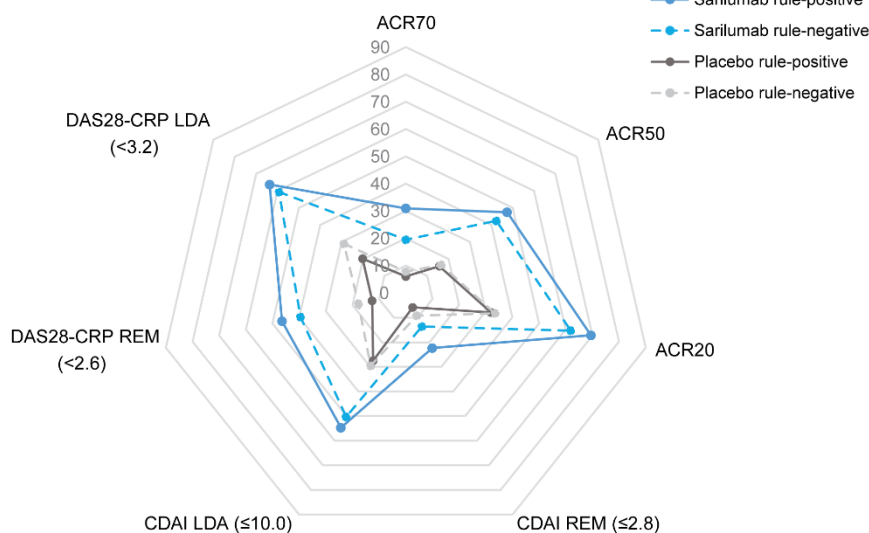| Parameter	Sarilumab 200 mg		Tocilizumab	
	Rule-positive patients[a] (N = 18)	Rule-negative patients (N = 33)	Rule-positive patients[a] (N = 45)	Rule-negative patients (N = 52)
DAS28-CRP	6.4 ± 0.9	5.7 ± 0.8	6.3 ± 1.0	5.5 ± 0.9
HAQ-DI	1.7 ± 0.6	1.8 ± 0.5	1.9 ± 0.6	1.7 ± 0.7
SJC28	12.8 ± 5.4	11.3 ± 4.9	12.1 ± 5.9	11.3 ± 4.9
Presence of RF, n (%)	16 (88.9)	13 (40.6)	41 (91.1)	37 (71.2)
Presence of anti-CCP, n (%)	18 (100)	18 (54.5)	45 (100)	37 (71.2)
Prior DMARD use, n (%)	18 (100)	33 (100)	45 (100)	52 (100)

[a]Patients who were anti-CCP-positive and had CRP >12.3 mg/L. Values are mean ± SD, unless otherwise indicated. Anti-CCP, anti-cyclic citrullinated peptide; DAS28-CRP, 28-joint Disease Activity Score using C-reactive protein; HAQ-DI; Health Assessment Questionnaire-Disability Index; RF, rheumatoid factor; SJC, swollen joint count.

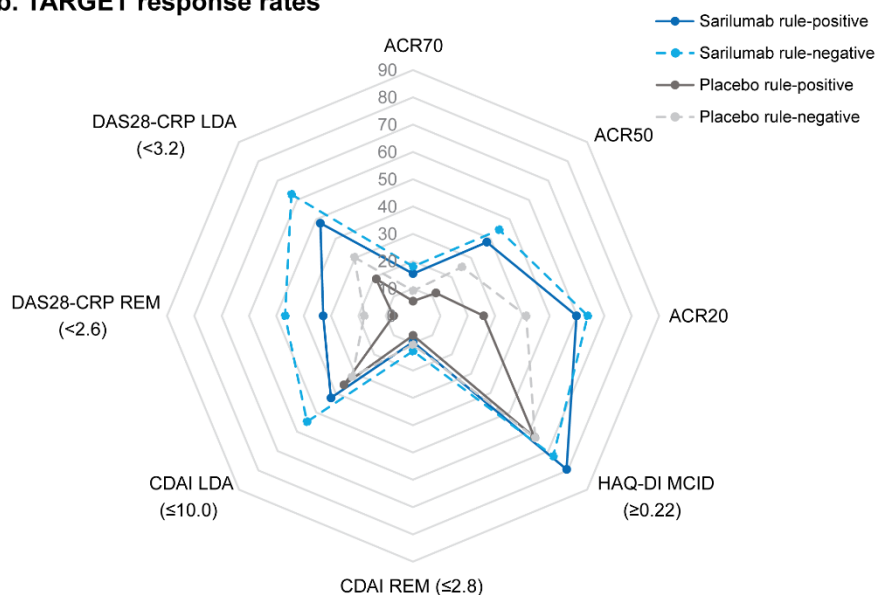**Figure S1.** Relative importance of variables, by model

Anti-CCP, anti-cyclic citrullinated peptide; BMI, body-mass index; C1M, MMP-degraded type 1 collagen; C3M, MMP-degraded type 3 collagen; CRP, C-reactive protein; CXCL13, C x C motif chemokine ligand 13; DMARD, disease-modifying antirheumatic drug; MMP, matrix metalloproteinase; Neut Pos ADA Res, neutralizing positive anti-drug-antibodies response; Num DMARD Used, number of DMARDs used; OC, osteocalcin; OPG, osteoprotegerin; RA, rheumatoid arthritis; RANKL, receptor activator of NF-kappa B ligand; SGP130, soluble glycoprotein 130; TIL6R, total IL-6-receptor.

Figure S2. Response rates in rule-positive and rule-negative patients from MOBILITY and TARGET
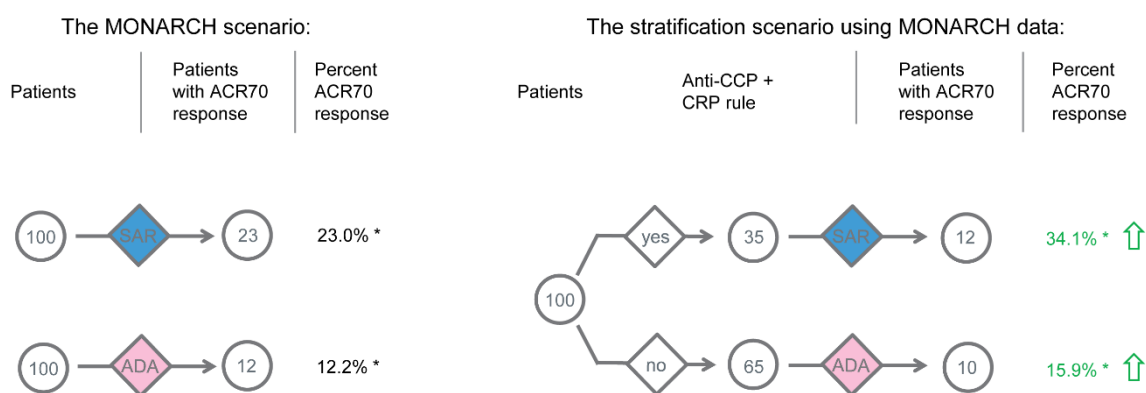

The patient stratification rule was the combined presence of anti-CCP and CRP >12.3 mg/L.
ACR20, ACR 20%; ACR50, ACR 50%; ACR70, ACR 70%; anti-CCP, anti-cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; DAS28-CRP, 28-joint Disease Activity Score using C-reactive protein; DAS28-ESR, DAS28 using erythrocyte sedimentation rate; HAQ-DI; Health Assessment Questionnaire-Disability Index; LDA, low disease activity; MCID, minimal clinically important difference; REM, remission.
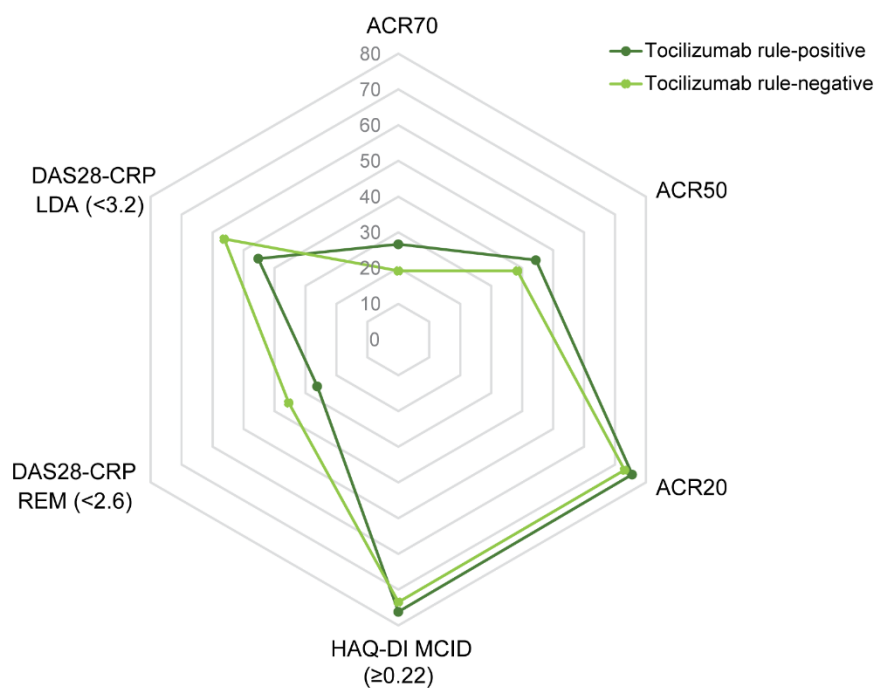
Figure S3. Clinical rule application scenario

The patient stratification rule was the combined presence of anti-CCP and CRP >12.3 mg/L.

*Calculated from MONARCH 200 mg study.

ACR70, ACR 70%; ADA, adalimumab; anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; SAR, sarilumab.

Figure S4. ASCERTAIN: Response rates in rule-positive and rule-negative tocilizumab-treated patients

The patient stratification rule was the combined presence of anti-CCP and CRP >12.3 mg/L.

ACR20, ACR 20%; ACR50, ACR 50%; ACR70, ACR 70%; DAS28-CRP, 28-joint Disease Activity Score using C-reactive protein; HAQ-DI; Health Assessment Questionnaire-Disability Index; LDA, low disease activity; MCID, minimal clinically important difference; REM, remission.