

Investor event at EULAR 2009 Copenhagen, 12 June 2009



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- 7 interruptions in production
- 8 loss of or inability to obtain adequate protection for intellectual property rights;
- 9 litigation;
- 10 loss of key executives or other employees; and
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Agenda



Overview of Roche's Inflammation/ RA franchise

- Richard Erwin, *Actemra Task Force Leader, Roche, Switzerland*

Actemra data presented at EULAR

- Andrea Rubbert-Roth, *Head of Rheumatology, University of Cologne, Germany*

MabThera/ Rituxan data presented at EULAR

- Paul-Peter Tak, *Professor of Medicine, Academic Medical Center/University of Amsterdam, The Netherlands*

Questions & Answers

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Fighting Inflammation – Rebuilding Patients' Lives

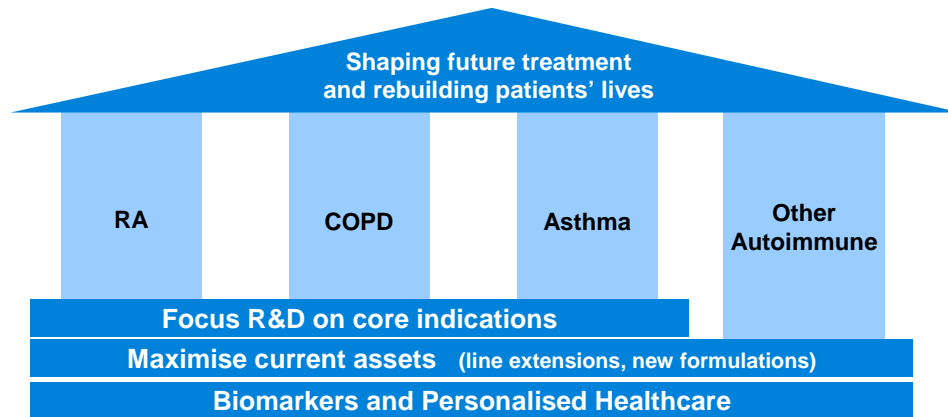
*Richard Erwin,
Actemra Task Force Leader, Roche*



Inflammation strategy



Focus on core areas – complement with line extensions in other autoimmune diseases

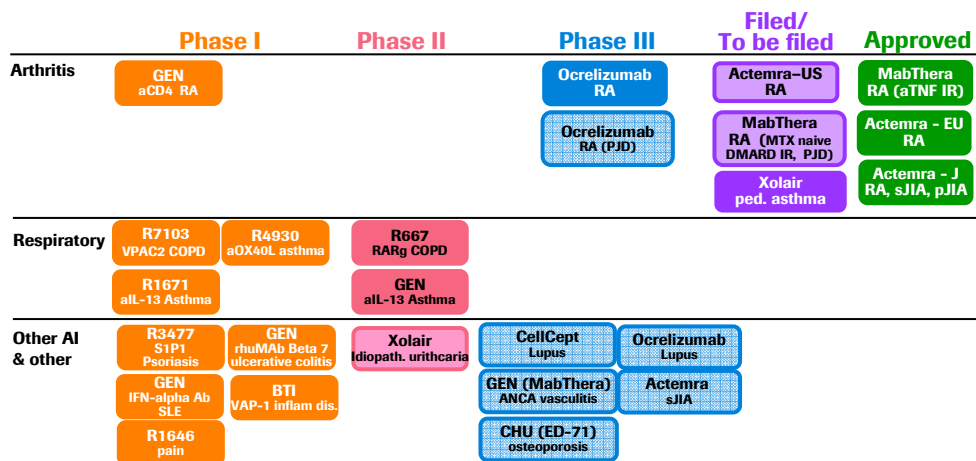


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Roche's Inflammation portfolio



Innovative molecules with diversity of mechanisms



NME Additional Indications GEN=Genentech managed, CHU=Chugai managed, BTI=BioTie opt-in

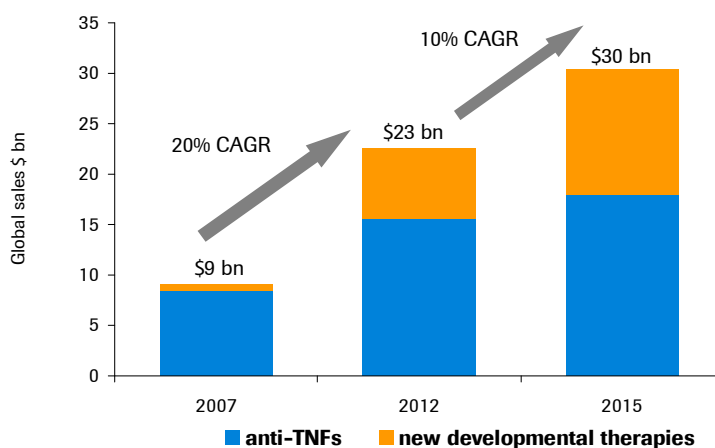
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Status as of March 31, 2009

Rheumatoid arthritis (RA): an attractive market

Substantial growth both in anti-TNFs & new therapies

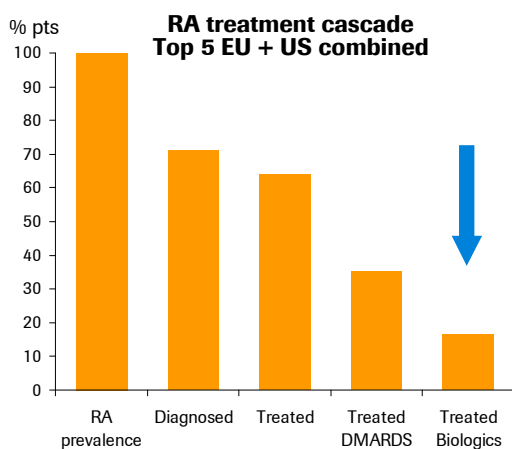
RA Biologic Therapy Market development 2007-2015E (\$m)



Source: J.P. Morgan estimates

< 20% of treated patients are prescribed biologics

Increasing data supporting positive effects of aggressive & early treatment with biologics

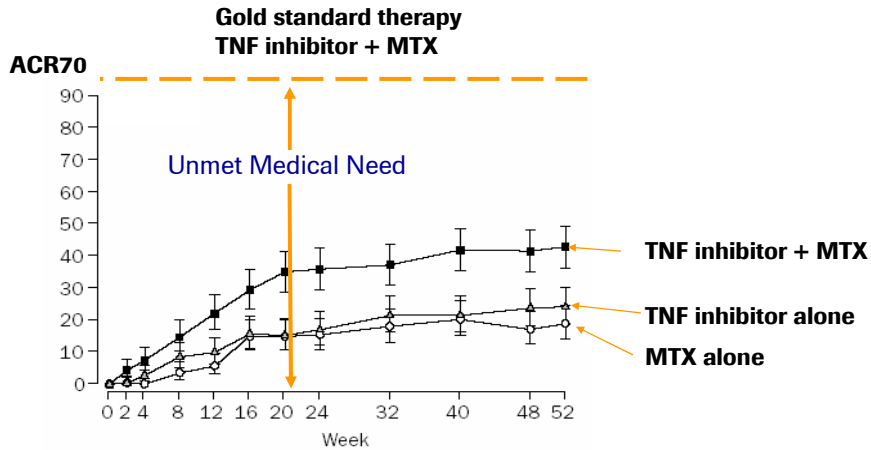


- Biologics use limited by cost, convenience, adverse reactions
- Increasing evidence suggests joint destruction occurs early in disease
- Recognised need to identify inadequate response sooner and switch therapy

Sources: Decision Resources, GfK Performance Tracker, Roche analysis, RA Registries

Not all patients respond to current therapy

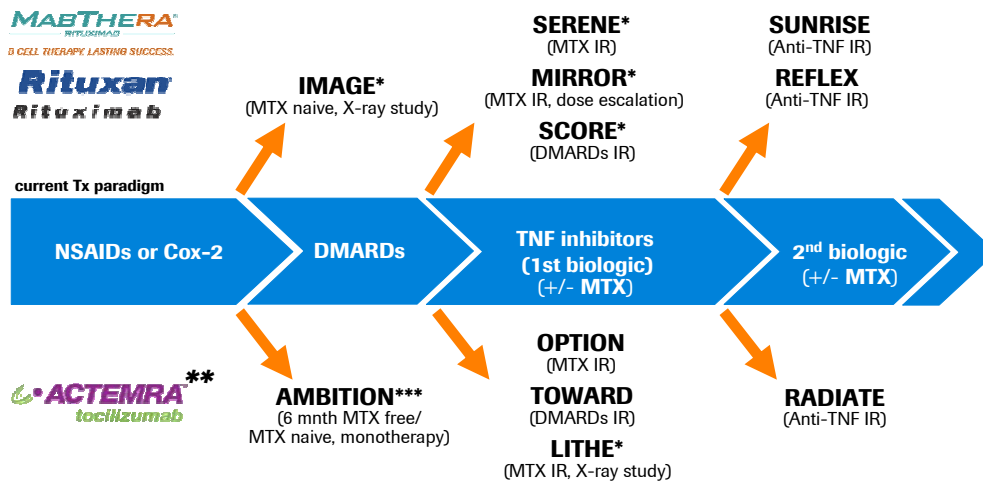
Need for new therapies with different modes of action



Breedveld et al, 2006

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Comprehensive development program targeting all treatment stages



* Indication not yet approved, awaiting filing or regulatory approval
 ** Not approved for use in the USA
 *** Approved in EU for monotherapy use in patients who are MTX intolerant

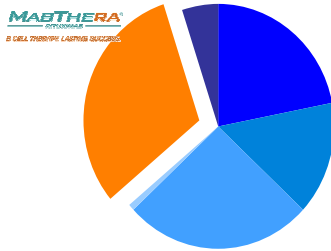
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MabThera/ Rituxan: first & only B cell therapy in RA

Leading biologic for anti-TNF-IRs in Europe



**Patient Share anti-TNF-IRs
Top 5 EU (2008)**



- Achieved ~800 m CHF sales globally in 2008 in RA (in labelled indication)
- Moving up the treatment line:
 - US submitted sBLA Q3 '08 (DMARD-IR), 2nd filing 2009 (MTX-naïve, PJD)
 - EU filing 2009 (MTX-naïve, DMARD-IR, PJD)
- Strong additional data:
 - Inhibition of radiographic progression in MTX naïve pts (IMAGE)^{1, 2}
 - Identify patients with enhanced response³
 - Efficacy maintained or increased over time; no increase in safety concerns⁴

Sources: Decision Resources, GfK Performance Tracker, Roche analysis, RA Registries

¹ Tak et al., EULAR 2009, Abstract OP-0022

² Rigby et al., EULAR 2009, Abstract SAT0121

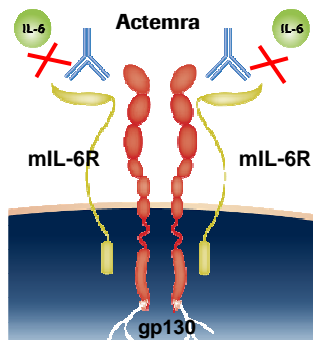
³ Isaacs et al., EULAR 2009, Abstract FRI0256

⁴ van Vollenhoven et al., EULAR 2009, Abstract OP-0026

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Actemra: first IL-6 receptor inhibitor

Consistently high and durable remission rates - across all disease stages



- Largest clinical programme of any biologic in RA
- Approved in EU (RA broad label) & Japan (RA, sJIA, pJIA); US re-submission on track Q3 '09
- Subcutaneous dose form in development
- Continued strong efficacy data:
 - Demonstrated long-term safety with increasing efficacy over time^{1,2,3,5}
 - Only biologic to have demonstrated superiority vs. methotrexate as monotherapy⁴
 - Significant inhibition in progression of joint damage⁵ with benefits maintained at 2 yrs⁶

¹ Smolen et al., EULAR 2009, Abstract FRI0133

² Keystone et al., EULAR 2009, Abstract THU0165

³ van Vollenhoven et al., EULAR 2009, Abstract SAT0111

⁴ Jones et al., EULAR 2009, Abstract FRI0252 ann Rheum Dis 2009, Mar 17

⁵ Kremer et al., EULAR 2009, Abstracts OP-0157 & FRI0262

⁶ Data to be presented at an upcoming conference

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Roche's portfolio: innovative and first-in-class
Designed to further reduce unmet medical need in RA



MABTHERA
RITUXIMAB
B CELL THERAPY. LASTING SUCCESS.

ACTEMRA
tocilizumab

Ocrelizumab

Two first-in-class biologics with different modes of action:

- MabThera/ Rituxan
- Actemra

+

Extensive development program:

- Lifecycle management (Ocrelizumab)
- Line extensions (new indications, new formulations)
- New products (orals)

Well positioned to shape future therapy standards:

- New combinations
- Sequential treatment algorithms
- Biomarker guided therapy

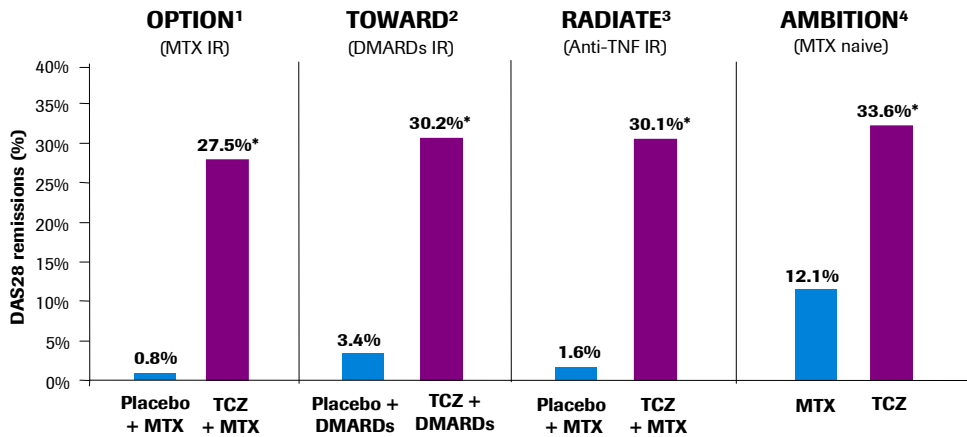
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Tocilizumab: Long Term Extensions Studies, LITHE
Data presented at EULAR 2009

*Andrea Rubbert-Roth,
Head of Rheumatology,
University of Cologne, Germany*



Actemra phase III trials: unsurpassed efficacy
Around 30% of patients achieved DAS28 remission at week 24 – regardless of concomitant or prior therapy



¹ Smolen JS, et al. Lancet 2008;371:987-97

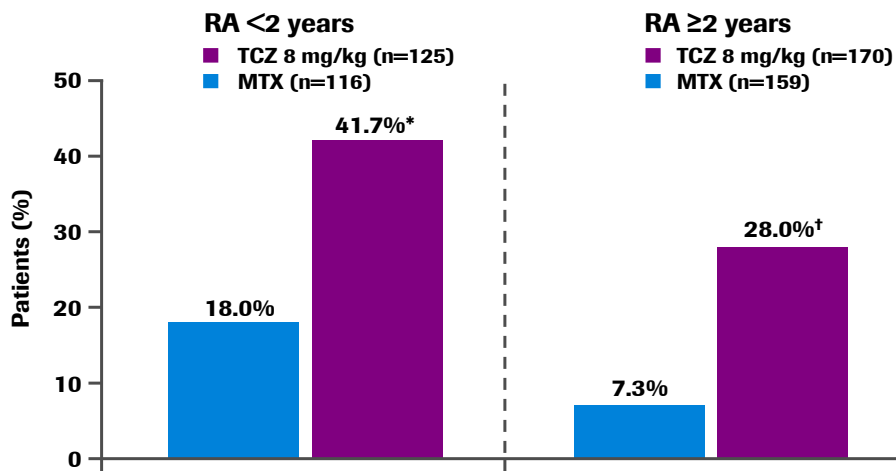
³ Emery et al., Ann Rheum Dis 2008, 67,1516-1523

² Genovese et al., Arthritis & Rheumatism, vol 58, no 10, 2008, 2968-2980

⁴ Jones et al., Ann Rheum Dis 2009, Mar 17

* p ≤ 0.0001; TCZ dose 8 mg/kg

AMBITION: Patients with RA for <2 yrs had 42% remission (DAS28 <2.6) at wk 24 when treated with TCZ monotherapy



* Mean difference vs. MTX (95% CI) = 24% (11-37)

† Mean difference vs. MTX (95% CI) = 24% (14-34)

Genovese M, et al. ACR 24-29 October, 2008; Poster:988.

Efficacy of tocilizumab in rheumatoid arthritis: Interim analysis of long-term extension trials of up to 2.5 years

Josef Smolen

Medical University of Vienna, Vienna, Austria

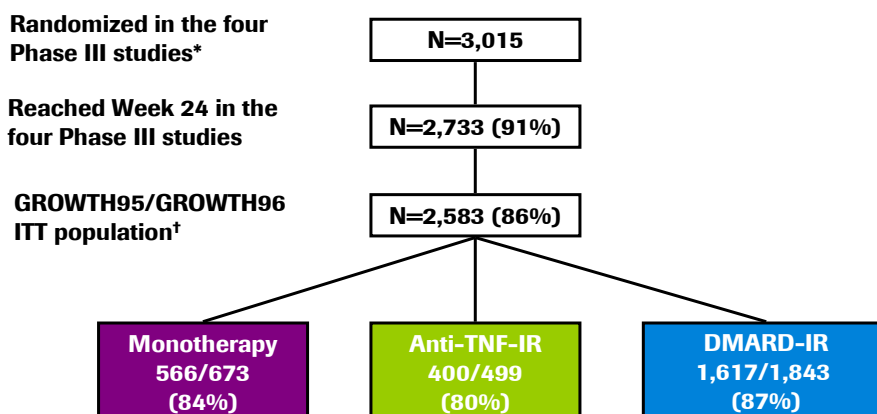
**R Alten, J Gomez-Reino, W Rizzo,
C Davies, E Alecock, R van Vollenhoven**

Poster FRI0133

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Patient population

Close to 90% of eligible patients entered the long-term extension (LTE) trials

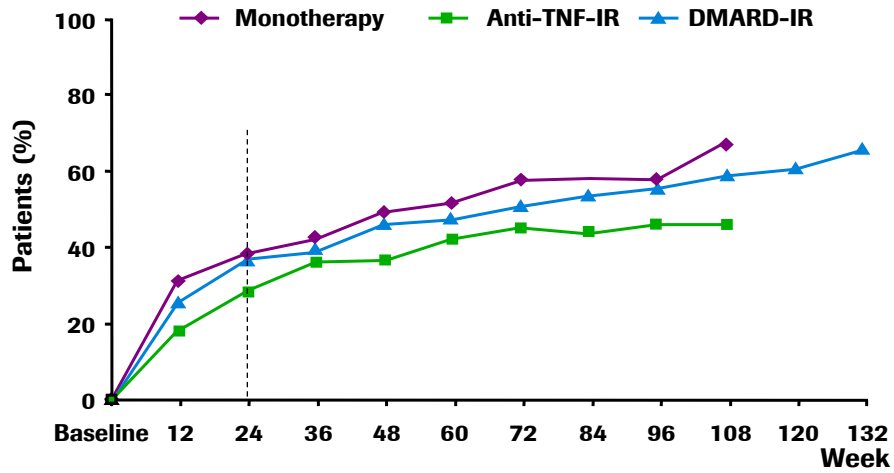


* OPTION, AMBITION, TOWARD and RADIATE

† Comprises all patients who received ≥1 dose of tocilizumab

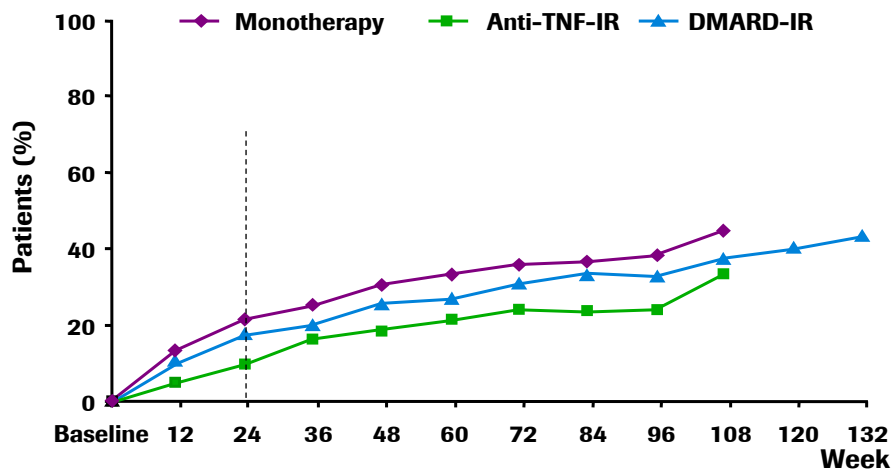
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ACR50 response rates: rapid improvement which is maintained over time in all RA populations (ITT)



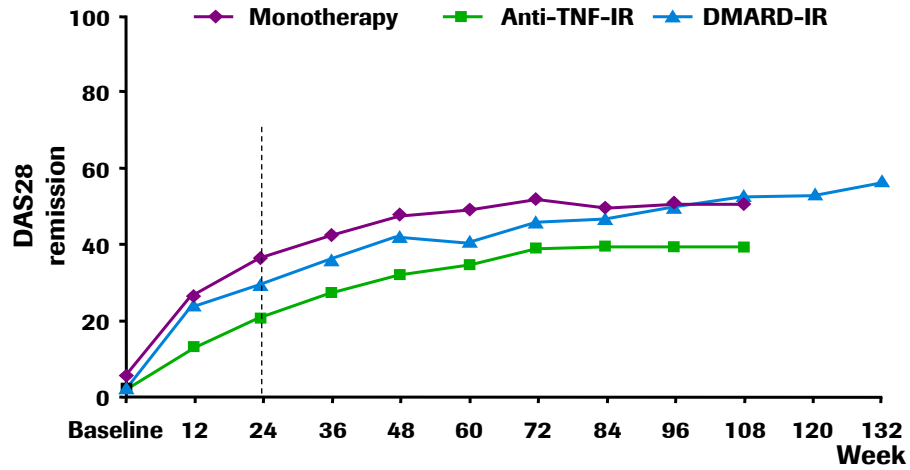
Monotherapy	n = 566	546	538	504	486	415	360	252	166	84		
Anti-TNF-IR	n = 400	391	389	367	354	318	295	295	170	103		
DMARD-IR	n = 1,617	1,578	1,551	1,441	1,421	1,373	1,279	1,156	948	653	403	228

ACR70 response rates



Monotherapy	n = 566	546	538	504	486	415	360	252	166	84		
Anti-TNF-IR	n = 400	391	389	367	354	318	295	295	170	103		
DMARD-IR	n = 1,617	1,578	1,551	1,441	1,421	1,373	1,279	1,156	948	653	403	228

DAS28 remission rate (DAS28 <2.6): early and durable remission across range of RA patients (ITT population)



Monotherapy	n = 564	552	531	494	466	402	344	239	160	81		
Anti-TNF-IR	n = 399	384	377	353	334	292	270	232	159	93		
DMARD-IR	n = 1,609	1,566	1,526	1,401	1,382	1,331	1,236	1,119	898	620	386	211

Over one third of patients showed no clinical activity in ACR core set components at Week 96

Patients had an average of 30 tender joints and 20 swollen joints at baseline

Patients, %	Group		
	Monotherapy (N=226)	DMARD-IR (N=1,053)	Anti-TNF-IR (N=213)
0 SJC	38.1	34.9	22.5
0 TJC and SJC	16.8	19.0	8.9
	(N=167)	(N=951)	(N=169)
Patient global VAS = 0 mm	13.2	4.5*	3.0
Physician global VAS = 0 mm	10.8*	8.4†	2.4
HAQ-DI = 0	24.6	17.1*	8.9*

* Data missing for one patient
† Data missing for three patients

SJC = swollen joint count
TJC = tender joint count

Summary: Long-term Remission/ Efficacy Data

Tocilizumab delivers a rapid onset of action and an efficacy that continues improving over time

- Efficacy with long-term tocilizumab treatment was maintained over >2 years, in all three patient groups
 - ACR response rates
 - DAS28
- Major improvements in ACR core components at week 96
- Major clinical response (maintenance of ACR70 response for 24 consecutive weeks)
- Low rate of withdrawal (3%) due to insufficient response
- Sustained efficacy in monotherapy

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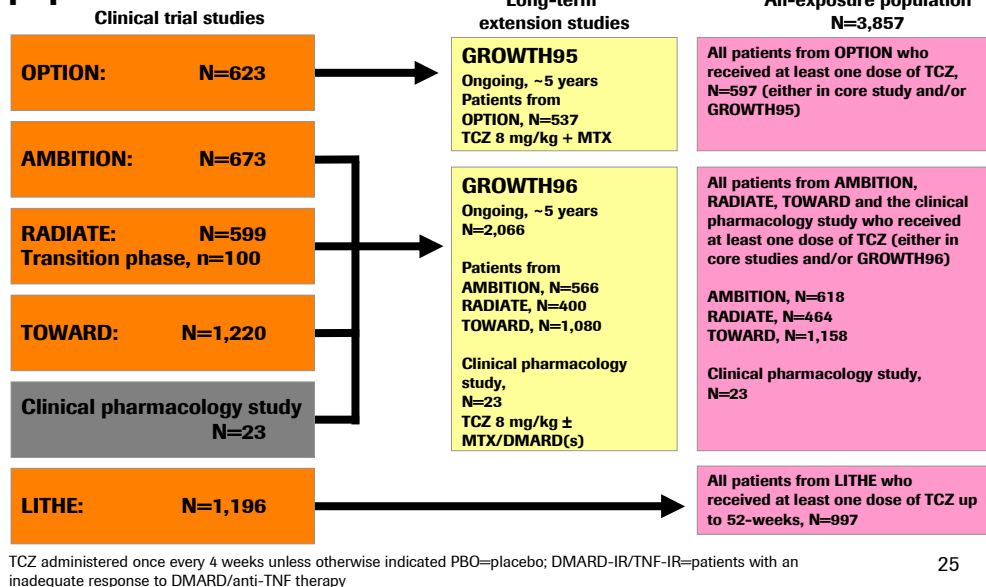
Long-term safety and tolerability of tocilizumab in patients with a mean treatment duration of 1.5 years

RF van Vollenhoven, A Rubbert-Roth, A Cantagrel,
D Ridley, J Dudler, D Grimaldi, E Alecock, J Smolen

Poster SAT0111

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Summary of clinical trials and patients in the all-exposure population



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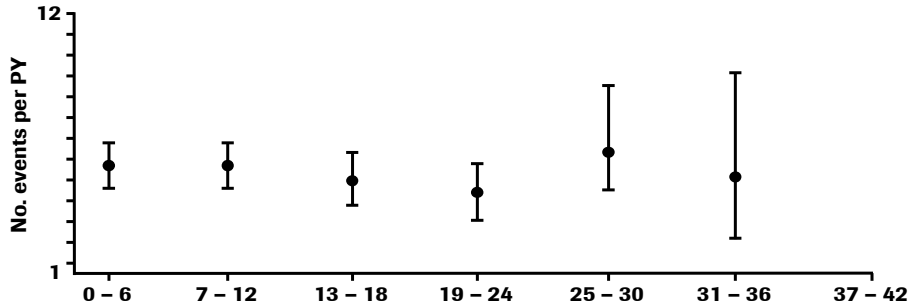
Adverse events in tocilizumab Phase III trials (safety population)

	Combination treatment*		Monotherapy	
	TCZ 8 mg/kg + DMARD (n=1,582)	Placebo + DMARD (n=1,170)	TCZ 8 mg/kg (n=288)	MTX (n=284)
Total PY	754	507	140	134
Rate per 100 PY (95% CI)				
Overall AEs	462 (447, 478)	377 (361, 395)	492 (456, 530)	450 (415, 487)
Serious AEs	15 (13, 18)	15 (12, 19)	9 (4, 15)	11 (6, 19)
Infections	118 (110, 126)	104 (95, 113)	107 (90, 125)	109 (92, 129)
Serious infections	5.2 (3.7, 7.1)	3.8 (2.3, 5.9)	2.9 (0.8, 7.3)	1.5 (0.2, 5.4)
Malignancies	1.3	1.4	1.4	2.2
Incidence, n (%)				
Infusion-related events [†]	6 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
AEs leading to withdrawal	74 (4.7)	28 (2.4)	11 (3.8)	15 (5.3)
Treatment-related AEs	756 (47.8)	401 (34.3)	163 (56.6)	141 (49.6)

AE=adverse event; CI=confidence interval; MTX=methotrexate; PY=patient-years; SAE=serious adverse event
*Included patients who had previous inadequate responses to DMARDs or anti-TNF therapy
[†]Includes infusion-related reactions, hypersensitivity reactions and anaphylactic reactions

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Rates of serious infections did not increase with continued treatment with TCZ

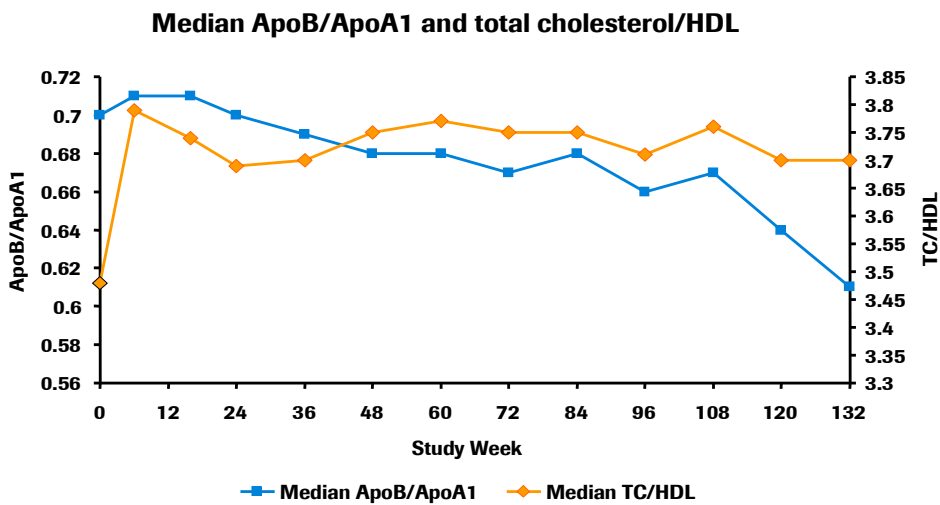


- Most common infections were pneumonia (n=66) and cellulitis (n=31)
- Nine opportunistic infections were reported (0.2/100 PY)
 - *M. avium* complex infection, TB (n=2), mycobacterial urinary tract infection, *P. jiroveci* pneumonia, *Candida* osteomyelitis, GI candidiasis, fungal oesophagitis and fungal sinusitis
- Overall rate of serious infections = 4.37/100 PY (n=249), rate of deaths attributed to infections = 0.18/100 PY (n=10)

All-exposure population

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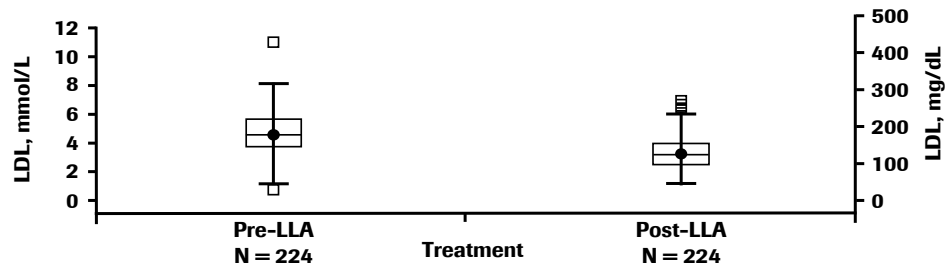
Atherogenic indices during long-term TCZ treatment



September 2008 safety update to FDA

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Normalisation of LDL cholesterol in patients receiving concomitant lipid-lowering agents



- Mean and fasting total LDL and HDL cholesterol levels and triglyceride levels were increased at 6 weeks and remained relatively stable during subsequent assessments

All-exposure population

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Serious Cardiac events (cumulative)*

	Control (628 PY)	Tocilizumab 4 mg/kg (435 PY)	Tocilizumab 8 mg/kg (3,707 PY)
Event	n (rate/100 PY)	n (rate/100 PY)	n (rate/100 PY)
Total	8 (1.27)	4 (0.92)	45 (1.20)
MI/ACS	4 (0.64)	2 (0.46)	12 (0.32)
Ischaemic heart disease	1 (0.16)	-	13 (0.35)
Arrhythmia	2 (0.32)	1 (0.23)	13 (0.35)
Cardiac failure	-	1 (0.23)	3 (0.08)
Cardio-respiratory arrest	1 (0.16)	-	1 (0.03)

*Evaluated at 4-month safety update after BLA filing
PY = patient years
Excludes 3 events diastolic dysfunction, stress cardiomyopathy, mixed aortic valve disease

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Cardiovascular events: Long-term follow-up

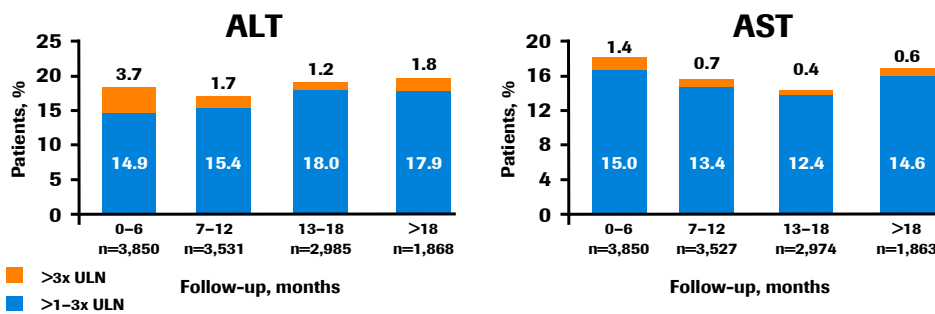
The most frequent cardiovascular events were arrhythmias and ischaemic events

	Event rates per 100 PY (95% CI)	Event rates per 100 PY by 6-month periods (95% CI)						
		0-6	7-12	13-18	19-24	25-30	31-36	37-42
Myocardial infarction	0.26 (0.15, 0.43)	0.35 (0.13, 0.76)	0.39 (0.14, 0.85)	0.18 (0.02, 0.66)	0.13 (0.0, 0.70)	—	—	—
Stroke	0.18 (0.08, 0.32)	0.35 (0.13, 0.76)	0.13 (0.20, 0.47)	0.18 (0.02, 0.66)	0	—	—	—

All-exposure population

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The incidence of elevations in ALT/AST levels did not increase after prolonged administration of TCZ



- 67 (1.7%) patients discontinued treatment because of elevations in transaminase levels
- Incidence of elevations in ALT/AST levels did not increase after prolonged administration of TCZ
- In the AMBITION study, shifts in ALT and AST levels were similar for TCZ 8mg/Kg as monotherapy and MTX treatment groups, regardless of previous MTX or DMARD exposure
- Elevations in transaminase levels were not associated with clinical hepatic events

All-exposure population

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Tocilizumab: Safety summary

Well-defined and manageable safety profile

- No new safety signals emerged after prolonged exposure to TCZ
 - Incidences and types of AEs reported after long-term exposure to TCZ were similar to those reported in controlled 6-month studies
- Rates of serious infections, malignancy and other SAEs did not increase with continued treatment with TCZ
 - With >10,000 patient-years of TCZ exposure, six cases of *Mycobacterium tuberculosis* infection have been reported
- The incidence of elevations in ALT/AST levels did not increase after prolonged administration of TCZ
- Elevations in lipid levels were observed with TCZ treatment and decreased when statins were prescribed
- Rates of MI/stroke were comparable with those reported for RA patients receiving biologics (<0.5 per 100 PY) and remained stable over time

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Summary: Consistent results across all trials

Maintained over long-term

- 86% of eligible patients from four controlled 24-week studies entered the LTE programme, suggesting that these patients and their physicians consider ongoing treatment with ACTEMRA has a favourable benefit/risk profile
- Response rates to therapy with ACTEMRA 8 mg/kg (+ DMARD) were maintained from the preceding 24-week core studies and tended to improve further with increasing duration of treatment
- The adverse events reported are consistent with the known mode of action of Actemra and were manageable with existing guidelines and practice
- Tocilizumab is efficacious in the long term

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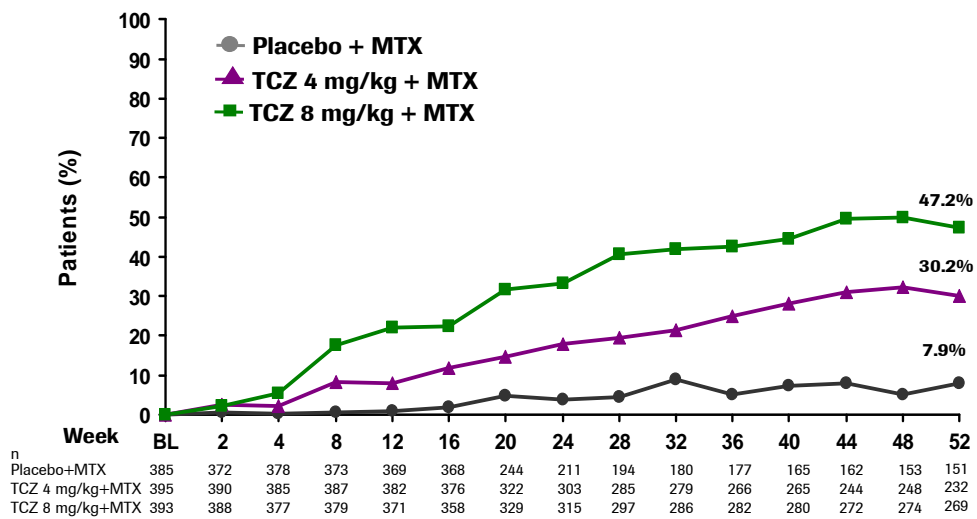
TOCILIZUMAB INHIBITS STRUCTURAL JOINT DAMAGE, IMPROVES PHYSICAL FUNCTION, AND INCREASES DAS28 REMISSION RATES IN RA PATIENTS WHO RESPOND INADEQUATELY TO METHOTREXATE: THE LITHE STUDY

J. Kremer et al.

ORAL PRESENTATION **OP-0157**

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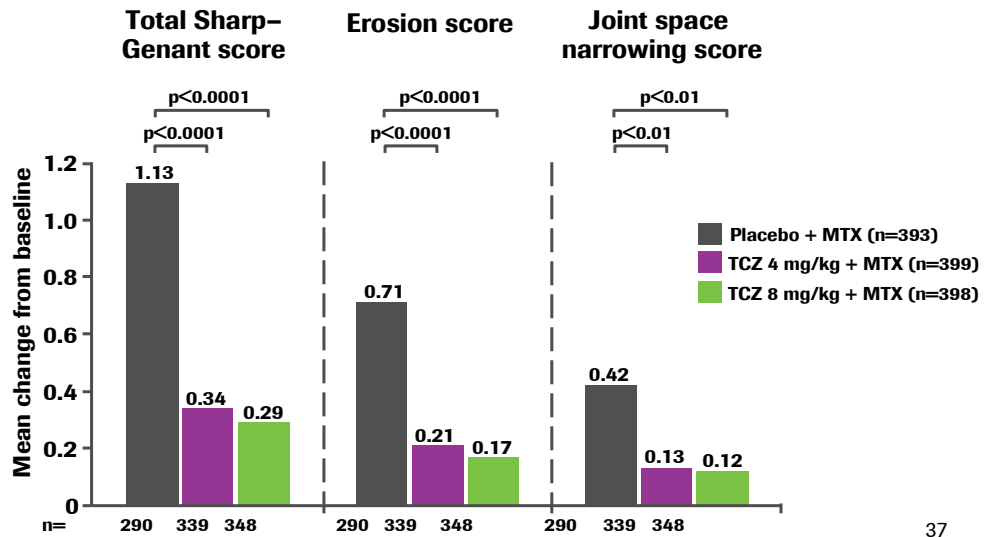
LITHE: Significantly increased DAS28 remission rate (DAS28 <2.6) at Week 52 (ITT)



LOCF used for TJC and SJC; No imputation used for ESR and Patient's Global Assessments of Disease Activity VAS.

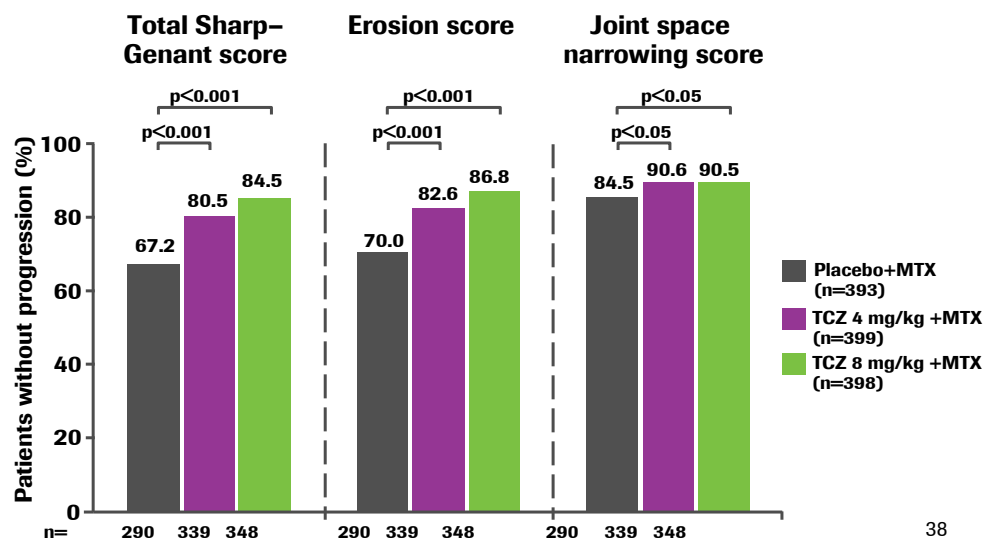
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LITHE: Significant inhibition of radiographic progression at Week 52 (linear extrapolation method; ITT)



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LITHE: Significantly greater proportion of patients without progression at Week 52 (linear extrapolation method; ITT)



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LITHE: Summary

- Tocilizumab 8 mg/kg showed substantial (74%) inhibition of radiographic progression at Week 52
- Continuous growth of effects over time in DAS28 and ACR scores
- Rapid and sustained improvement in HAQ-DI with tocilizumab, significantly superior to control
- Safety profile without new signals as compared to earlier studies

Rituximab: IMAGE, Long Term Safety, Biomarkers Data presented at EULAR 2009

*Paul P. Tak, Professor of Medicine
Academic Medical Center/University of Amsterdam
The Netherlands*



**Inhibition of joint damage and improved clinical outcomes with a combination of rituximab and methotrexate in patients with early active rheumatoid arthritis who are naive to MTX:
A randomised active comparator placebo- controlled trial (IMAGE)**

*P. P. Tak, W. Rigby, A. Rubbert, C. Peterfy,
R. F. van Vollenhoven, W. Stohl, E. Hessey,
A. Chen, H. Tyrrell, T. Shaw*

On behalf of the IMAGE Study Group

Presentation # OP-0022

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The IMAGE study

Objectives

- Determine effectiveness of rituximab in prevention of progression in structural joint damage in patients with active RA initiating treatment with MTX
- Evaluate efficacy of rituximab in improving signs and symptoms of RA and patients' physical function
- Evaluate safety in patients with active RA initiating treatment with MTX

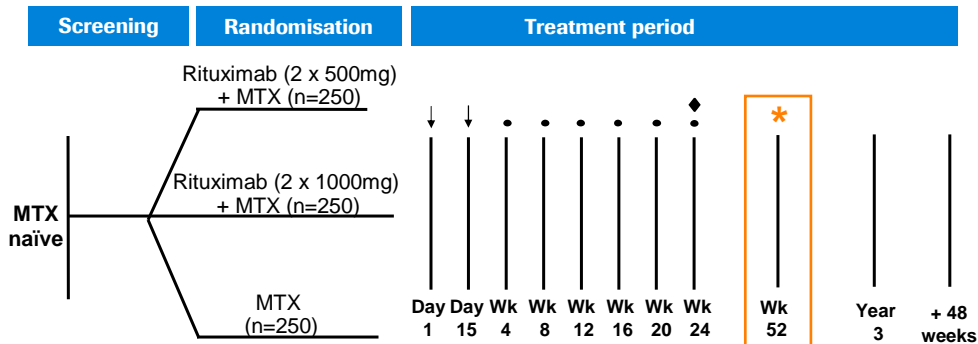
Key inclusion criteria

- RA diagnosed for ≥ 8 weeks but ≤ 4 years
- Naïve to, and considered to be candidates for, MTX
- Active disease, defined as;
 - SJC ≥ 8 TJC ≥ 8 (66/68 joint count) at screening and baseline
 - CRP ≥ 1.0 mg/dL (10mg/L) at screening
- For rheumatoid factor (RF)-negative patients: radiographic evidence of at least one joint with definite erosion attributable to RA

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IMAGE: Study design

Primary endpoint week 52, followed for 3 yrs



↓ Rituximab or placebo infusion (with GC pre-medication)

◆ Retreatment (from 24 weeks in pts with DAS28>2.6)

* Primary efficacy timepoint

MTX initiated at 7.5mg p.o./wk and escalated to 20mg p.o./wk by Week 8 as tolerated

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IMAGE: Endpoints at 52 weeks

- **Primary endpoint**

- Change in Genant modified Total Sharp Score (mTSS) from baseline to wk 52

- **Secondary endpoints**

- Radiographic
 - Change in erosion and joint space scores
 - Proportion of patients with change in mTSS ≤ 0
- Clinical Outcome
 - ACR and EULAR responses
 - Major Clinical Response (ACR70 maintained for ≥ 6 months)
 - Change in DAS28-ESR

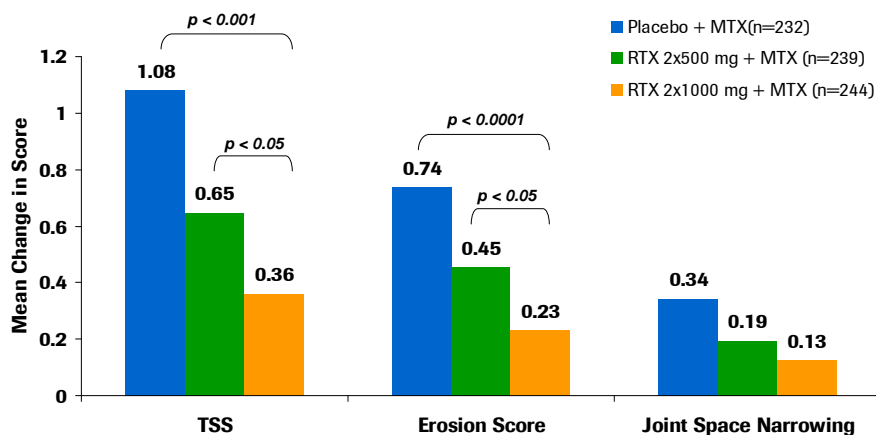
- **Safety throughout the 52-week period**

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IMAGE: Patient disease characteristics

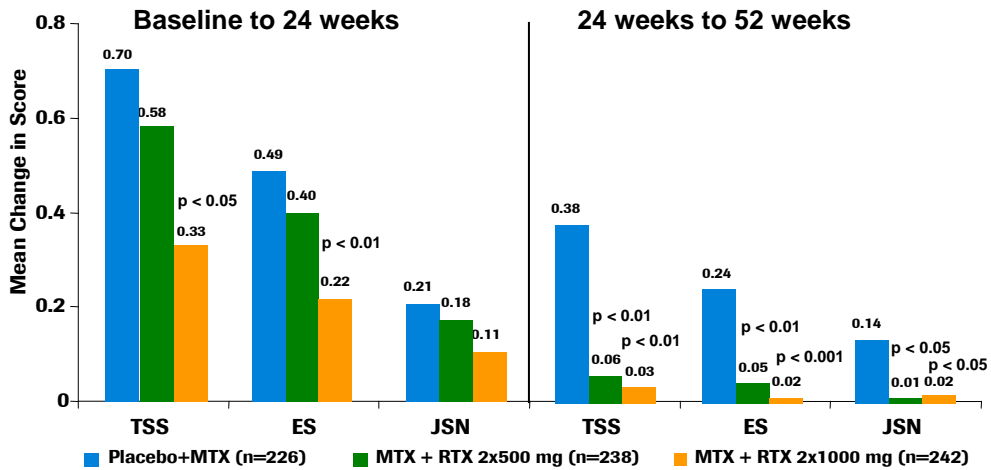
	Placebo + MTX n=249	RTX 2 x 500mg + MTX n=249	RTX 2 x 1000mg + MTX n=250
Disease duration			
mean, yrs	0.91	0.99	0.92
median, yrs	0.42	0.45	0.40
% pts with duration < 2 yr	86	80	83
SJC, mean	20.0	22.4	21.6
TJC, mean	32.7	34.0	33.2
RF positive, %	87	87	85
CRP, mean, mg/dL	3.2	3.4	3.0
ESR, mean, mm/h	62.2	57.9	57.3
HAQ-DI, mean score	1.84	1.77	1.73
DAS28-ESR, mean score	7.07	7.11	7.04
mTSS, mean score	7.35	7.67	6.88

IMAGE: Changes in Radiographic scores at wk52 (mITT) RTX 2x1000mg + MTX significantly inhibited joint damage as a first-line biologic



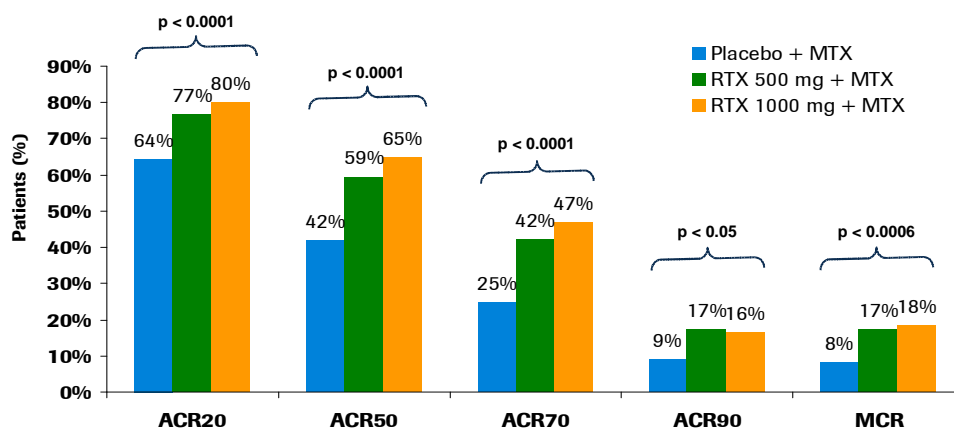
Missing values were imputed using linear extrapolation using baseline and wk 24 radiographs
Adjusted p-values comparing RTX+MTX groups to MTX alone
Unadjusted P-values comparing RTX (2 x 1000mg) to RTX (2 x 500mg)

IMAGE: Change in radiographic scores (6-month periods)
Over 90% inhibition of bone damage after second treatment



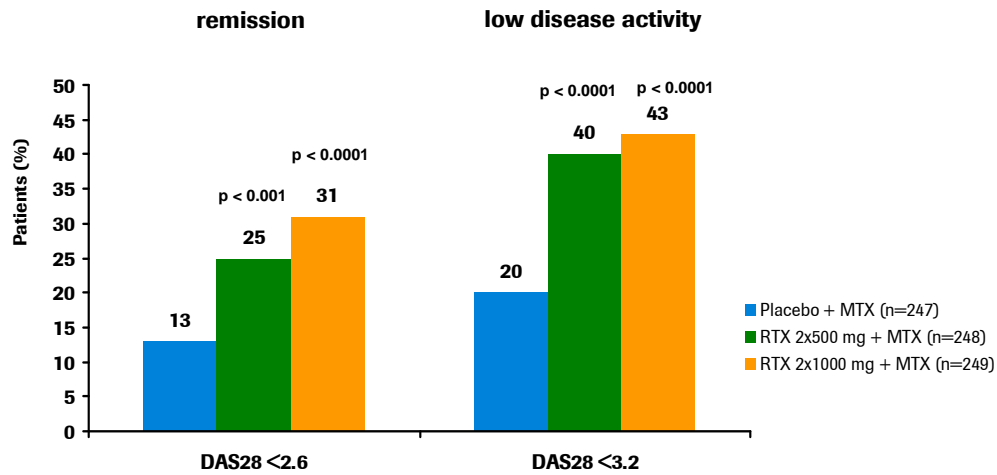
Missing values were imputed using linear extrapolation using baseline and wk 24 radiographs
 Adjusted p-values comparing RTX+MTX groups to MTX alone

IMAGE: ACR & Major Clinical Response (MCR) at week 52
All analyses between RTX and placebo statistically significant



Major Clinical Response (MCR) = ACR70 response maintained for at least 6 consecutive months
 P-values from CMH test, comparing the placebo group with each rituximab group
 Adjusted p-values comparing RTX+MTX groups to MTX alone
 Patients with insufficient data to calculate an ACR response are classed as non-responders

IMAGE: Significantly more patients on Rituximab reached DAS remission and low disease activity at week 52



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Infection rate was equal across treatment arms

	Placebo + MTX n=250	RTX 2 x 500mg + MTX n=249	RTX 2 x 1000mg + MTX n=249
Total pt-years	229.75	238.77	241.06
All infections			
No. infections	264	248	305
Infections per 100 pt-year	115	104	127
95% CI	102, 130	92, 118	113, 142
Serious infections (SIEs)			
No. SIEs	14	11	9
SIEs per 100 pt-year	6.09	4.61	3.73
95% CI	3.61, 10.29	2.55, 8.32	1.94, 7.18

Infections as per MedDRA basket terms, plus investigator classification
All events counted, including duplicates in the same individual
*Serious and/or those requiring i.v. anti-infectives

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IMAGE: Conclusions

- In patients with early, active RA, RTX (2 x 1000mg) + MTX significantly inhibited joint damage compared with MTX alone
 - Inhibition of joint damage evident at 6 months
- RTX (2 x 500mg) improved clinical outcomes but did not significantly slow the rate of joint damage over the full 52-week period
- Safety outcomes are consistent with previous data, with no new signals identified

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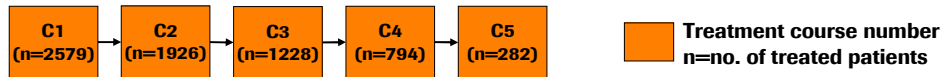
Long-term Safety of Rituximab: Follow-up of the RA Clinical Trials and Re-treatment Population

RF van Vollenhoven,¹ P Emery,² CO Bingham III,³ E Keystone,⁴ R Fleischmann,⁵ DE Furst,⁶ KM Macey,⁷ MT Sweetser,⁸ A Kelman,⁹ R Rao⁷

*European League Against Rheumatism OP0026
Thu 11 Jun, 10.15-11.45, Auditorium 1*

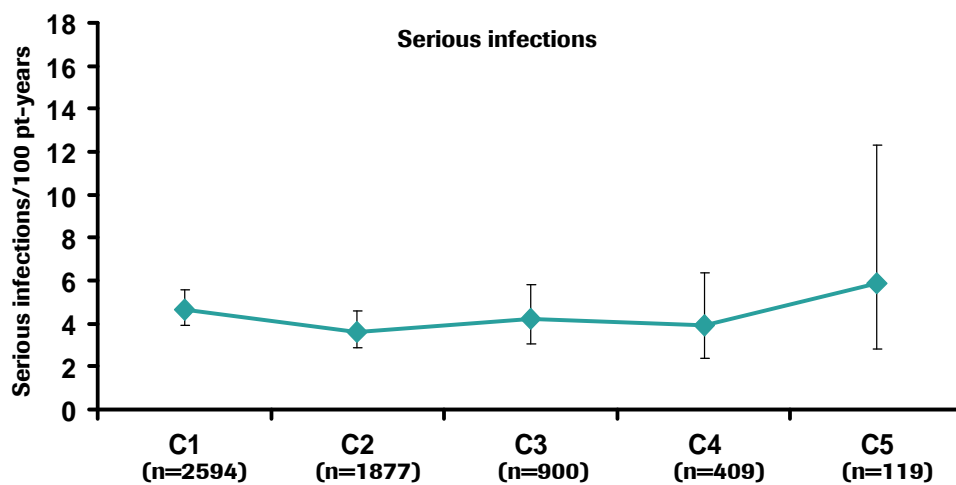
52

Duration of rituximab exposure (as of April 2008)

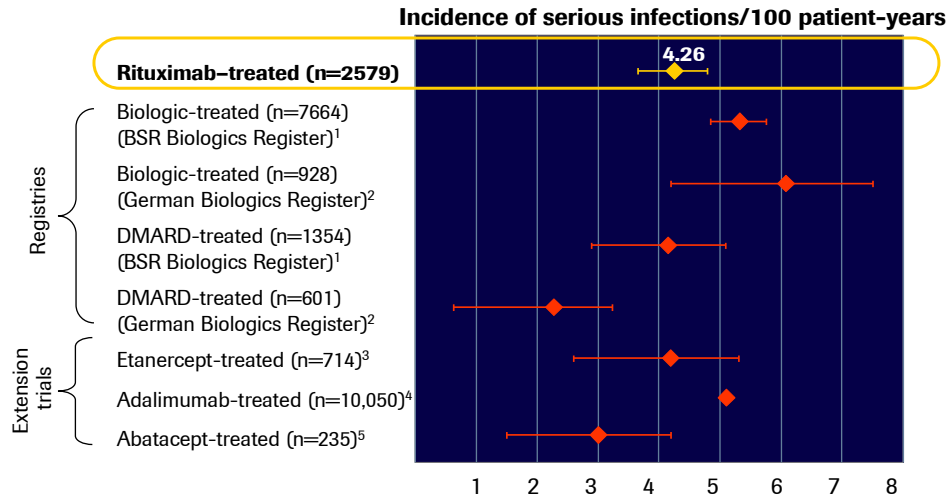


Duration of observation	Patients (n=2579)
>1 year	2417
>2 years	1198
>3 years	743
>4 years	564
>5 years	109
Total exposure (patient-years)	5964

Rates of serious infection remained constant with repeated courses of rituximab



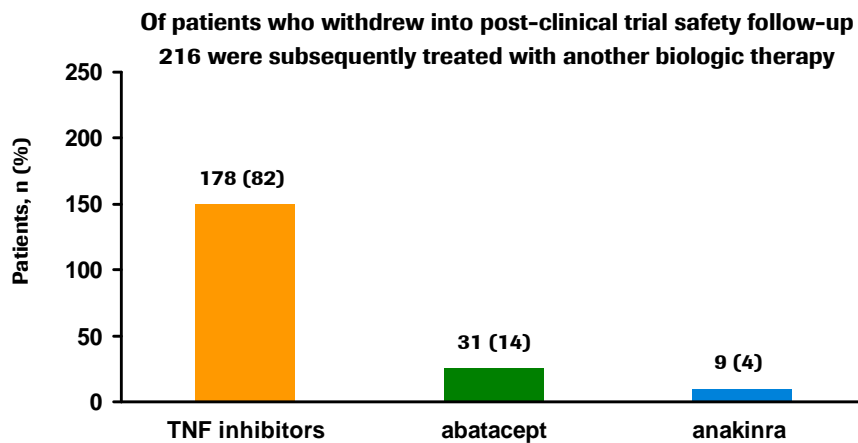
Long-term Safety: Serious Infections per 100 Patient-years



1. Dixon et al, Arthritis Rheum 2006;54:2368-76;
 3. Moreland et al, J Rheum 2006 33:854-61;
 5. Westhovens et al, J Rheum 2009;36(4):1-7.

2. Listing et al, Arthritis Rheum 2005;52:3403-12;
 4. Schiff Ann Rheum Dis 2006 65(7): 889-94;

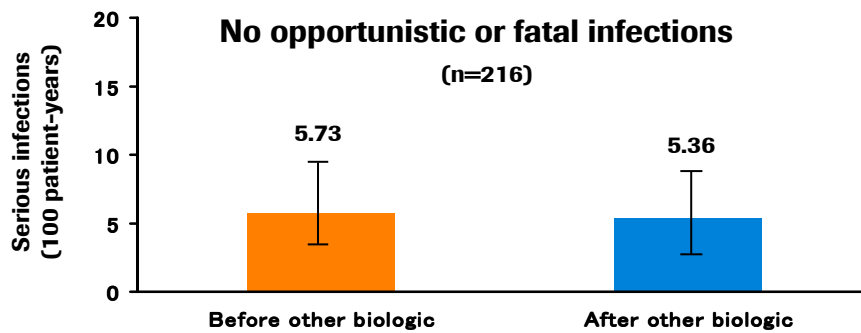
Biologic treatment following rituximab



Genovese M et al. EULAR 2009 [Abstract 2333]

No increased rate of serious infections when biologics are used after rituximab

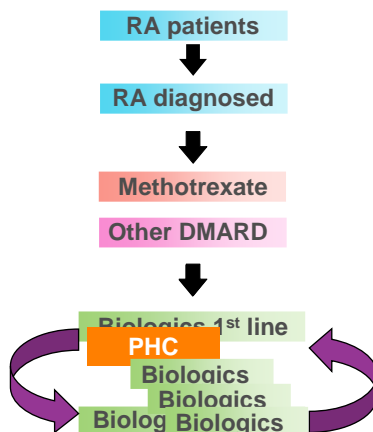
Median follow-up 11 months (range 0–45 months) after initiating another biologic



Of 216 patients, 13 SIEs were reported during the follow-up period

RA is a heterogeneous condition

Not all patients respond to available treatments leading to cycling



- Biomarkers in the management of RA:
 - Early diagnosis
 - Early treatment decisions
- Biomarkers as predictors of response to:
 - TNF inhibitors
 - Rituximab

Biomarkers and Personalised Healthcare can help optimise therapeutic outcome

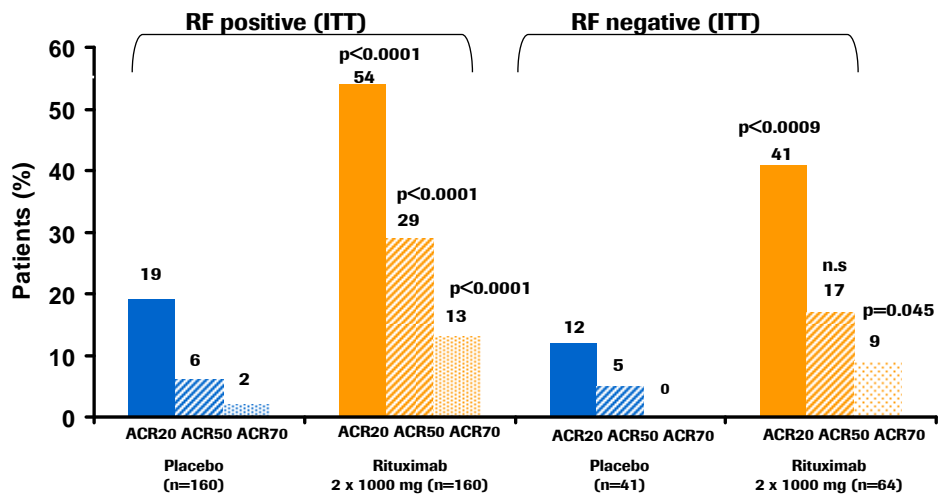
Autoantibody-positive rheumatoid arthritis patients have enhanced clinical response to rituximab when compared with seronegative patients

JD Isaacs, E Olech, PP Tak, A Deodhar, E Keystone, P Emery, D Yocum, E Hessey, S Read

Poster # FRI0256

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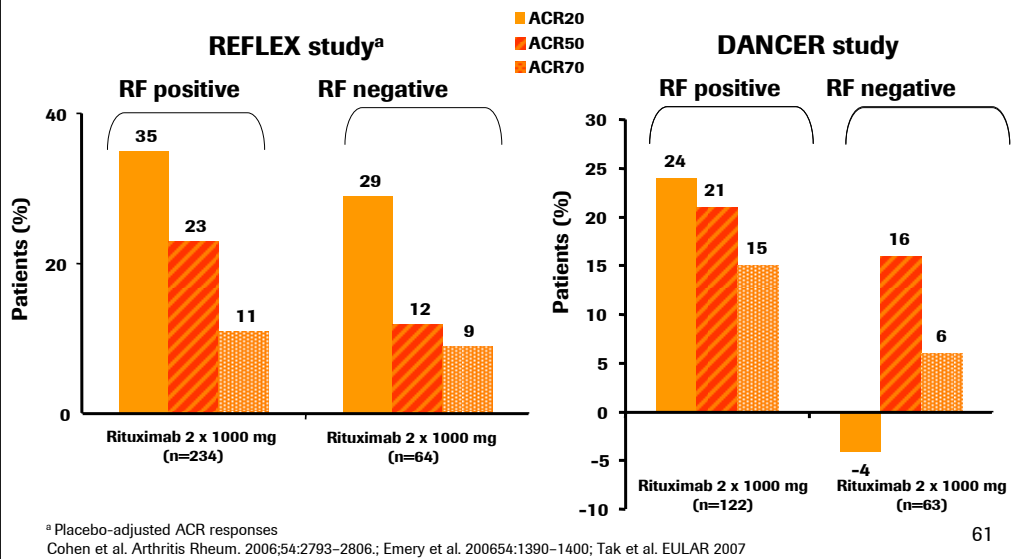
REFLEX: ACR responses at Week 24 in RF+ve versus RF-ve patients (ITT)



Cohen et al. 2006; Tak et al. 2007

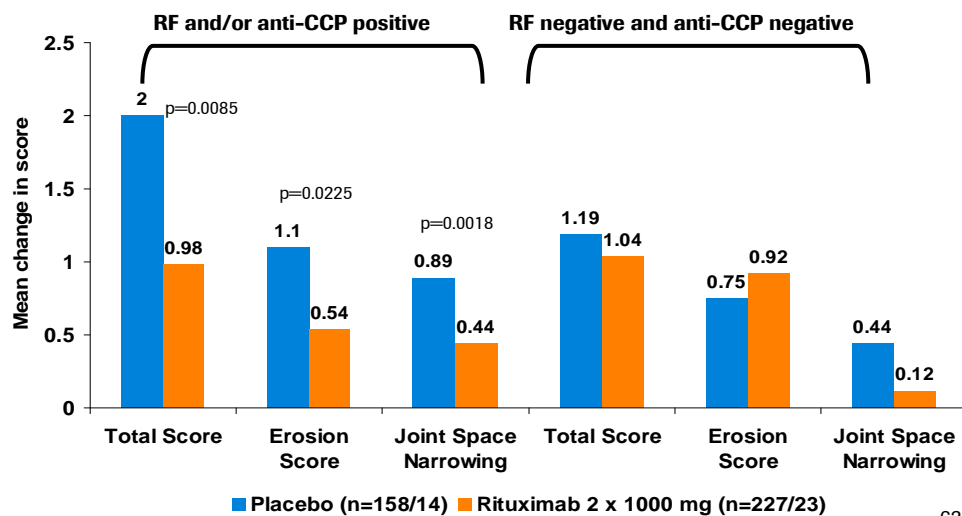
60

Placebo-adjusted ACR responses with rituximab at week 24 are greater in RF positive patients



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REFLEX: Superior radiographic outcomes with rituximab in RF and/or anti-CCP seropositive patients at week 56



62

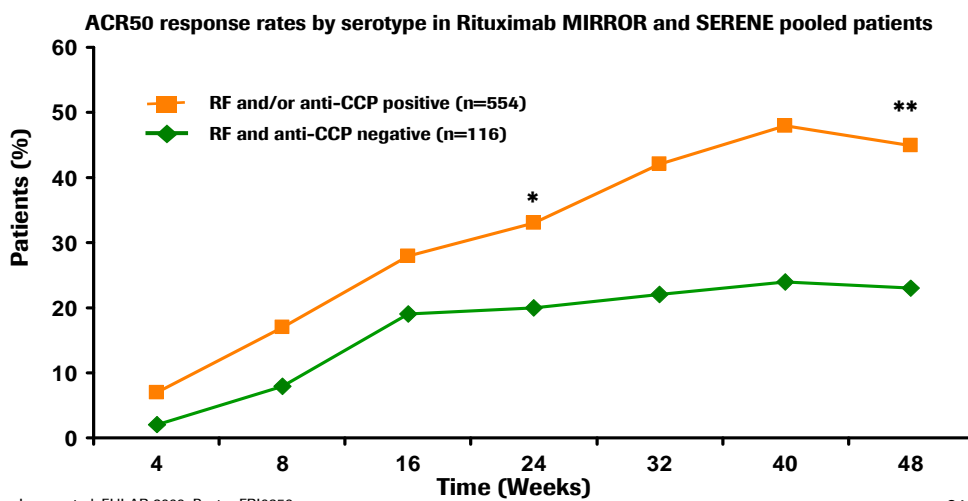
To examine in two DMARD-IR rituximab trials whether baseline seropositivity (RF and/or anti-CCP) enriches clinical responses versus patients seronegative for both autoantibodies

Baseline characteristics pooled patient cohort from SERENE and MIRROR studies

Patient baseline characteristics	RF+ and/or anti-CCP+ (n=554)	RF- and anti-CCP- (n=116)
Age, years	52.1	52.0
RA disease duration, years	8.2	6.2
DAS28-ESR	6.6	6.5
DAS28-CRP	6.0	5.9
Baseline RF _{TOTAL} IU/ml	324	15.1
Baseline anti-CCP, IU/ml	270	2.1

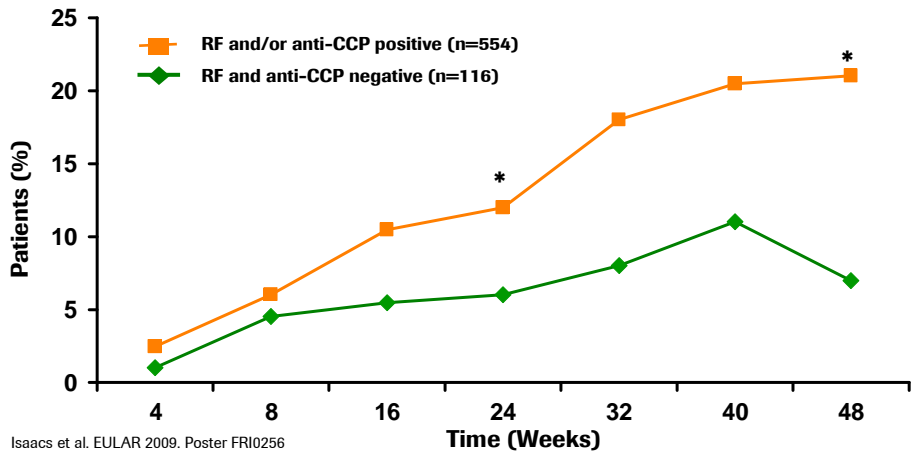
Isaacs et al. *EULAR* 2009. Poster FRI0256
 RF+: >20 IU/mL; anti-CCP+: >5 U/mL, Diastat™, AxisShield

More patients seropositive for RF and/or anti-CCP had an ACR50 response compared with seronegative patients



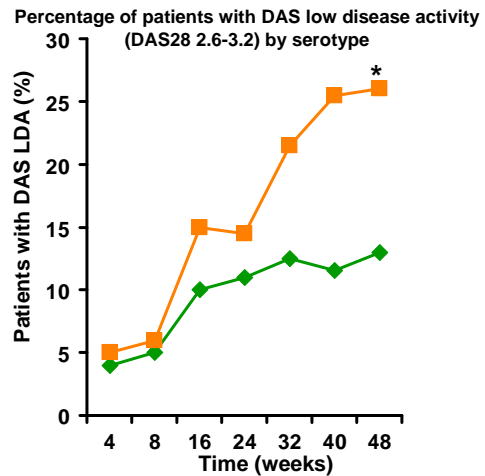
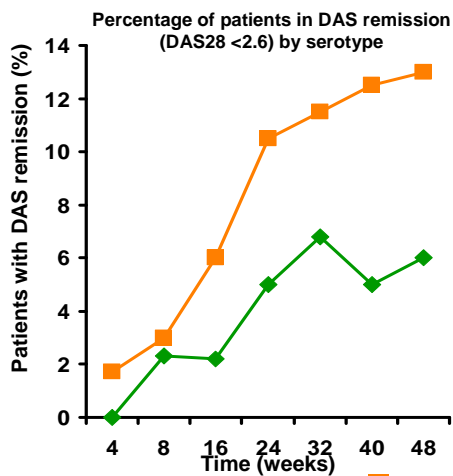
More patients seropositive for RF and/or anti-CCP had an ACR70 response compared with seronegative patients

ACR70 response rates by serotype in Rituximab MIRROR and SERENE pooled patients



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More patients seropositive for RF and/or anti-CCP achieved DAS remission or low disease activity compared with seronegative patients

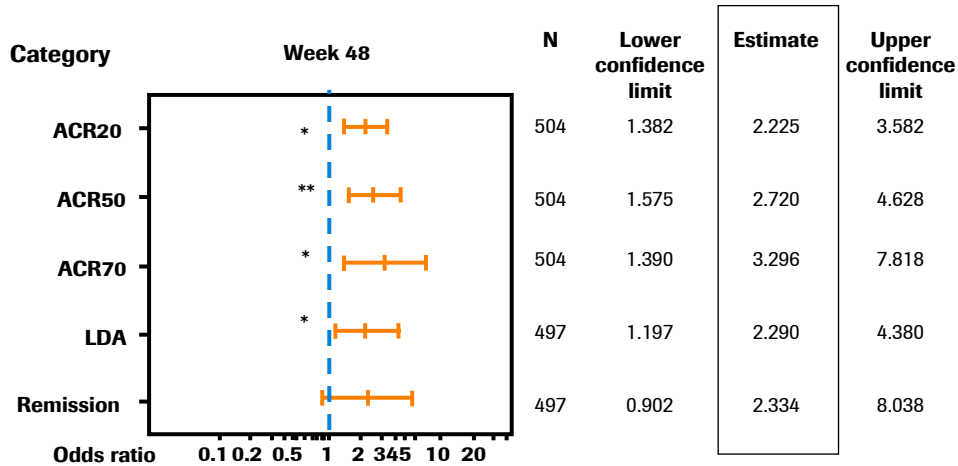


Isaacs et al. EULAR 2009. Poster FRI0256
*p<0.05 vs seronegative patients

RF and/or anti-CCP +ve (n=554)
RF and anti-CCP -ve (n=116)

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Patients seropositive for RF and/or anti-CCP were more likely to achieve a clinical response at Week 48 versus seronegative patients



Statistical analysis was carried out by logistic regression, fitting serotype as covariate and using observed clinical data only (no imputation) *p<0.05, **p<0.001

Isaacs et al. EULAR 2009. Poster FRI0256

Conclusions

- At week 48 in this pooled analysis of rituximab treated DMARD IR patients;
 - Responses in those patients who were seropositive for RF and/or anti-CCP were significantly enhanced compared to seronegative patients
 - Seropositive patients were 2–3 times more likely to achieve ACR responses compared with patients seronegative for both autoantibodies
- Further identification of biomarkers for RA prognosis and treatment response promise personalised strategies to achieve optimal therapeutic outcomes

Questions & Answers



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IL-6 Receptor Inhibition: Actemra (tocilizumab)



Trial	Patient population	Treatment	Size	Endpoints	Status
OPTION	MTX IR	TCZ 4mg/kg + MTX TCZ 8mg/kg + MTX MTX	623	ACR 20 (24 wks)	Filed Q4 '07
TOWARD	DMARD IR	TCZ 8mg/kg + DMARDs DMARDs	1,200	ACR 20 (24 wks)	Filed Q4 '07
RADIATE	anti-TNF IR	TCZ 4mg/kg + MTX TCZ 8mg/kg + MTX MTX	499	ACR 20 r(24 wks)	Filed Q4 '07
AMBITION	MTX naive	TCZ 8mg/kg (esc. dose) MTX	673	ACR 20 (24 wks)	Filed Q4 '07
LITHE	MTX IR	TCZ 4mg/kg + MTX TCZ 8mg/kg + MTX MTX	1,196	ACR 20 (24 wks) Sharp Score (52, 104 wks) Physical function (104 wks)	met 1 ^o endpoint
GROWTH95 LTE	pts from OPTION	TCZ 8mg/kg + standard anti-rheumatic therapy	537	Open-label long-term extension studies for safety and efficacy	ongoing
GROWTH96 LTE	pts from AMBITION, RADIATE, TOWARD	TCZ 8mg/kg + standard anti-rheumatic therapy	1,902	Open-label long-term extension studies for safety and efficacy	ongoing
TENDER Ph III	Systemic juvenile idiopathic arthritis (sJIA)	TCZ 8dosed by body weight ranges (8 or 12mg/kg x6) Placebo	108		Initiated Q2 '08

LTE = long term extensions studies

Anti-CD20: MabThera/ Rituxan (rituximab) in RA

Roche's ongoing phase III program



Trial	Patient population	Treatment	Size	Endpoints	Status
REFLEX	anti-TNF IR	MTX MTX +RTX 2 x 1g	521	ACR 20 (24 wks) Radiographic Progression	marketed US, EU
SERENE	DMARD-IR	MTX MTX +RTX 2 x 0.5g MTX +RTX 2 x 1g	509	ACR 20 (24 wks)	Met primary endpoint Q1 '08 US: submitted sBLA Q3 '08 EU: filing planned 2009
MIRROR	DMARD-IR Dose escalation	MTX +RTX 2 x 0.5g retx 2 x 0.5g MTX +RTX 2 x 0.5g retx 2 x 1g MTX +RTX 2 x 1g retx 2 x 1g	375	ACR 20 (48 wks) Effect of further courses and dose escalation	Met primary endpoint Q1 '08 US: submitted sBLA Q3 '08 EU: filing planned 2009
SCORE	DMARD-IR	MTX MTX +RTX 2 x 0.5g MTX +RTX 2 x 1g	180	MRI changes at 6 months	Data expected 2010
IMAGE	MTX naïve (X-ray study)	MTX MTX+RTX 2x0.5g MTX+RTX 2x1g	750	Inhibition of structural joint damage (52wks)	Met primary endpoint Q4 '08 EU: filing planned 2009

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Anti-CD20: Ocrelizumab in RA



Trial	Patient population	Treatment	Size	Endpoints	Status
STAGE Ph III	MTX-IR	MTX MTX + Ocrelizumab	1,000	ACR 20 (24&48 wks) Inhibition of structural joint damage	Initiated Q4 '06 Data expected Q4 '09
SCRIPT Ph III	anti-TNF IR	DMARD DMARD + Ocrelizumab	800	ACR 20 (24 and 48 wks) Inhibition of structural joint damage	Initiated Q2 '07 Data expected 2010
FEATURE Ph III	MTX-IR anti-TNF IR	MTX MTX + Ocrelizumab	300	ACR 20 (24 and 48 wks)	Ongoing Data expected 2010
FILM Ph III	MTX naïve	MTX MTX + Ocrelizumab	600	Inhibition of structural joint damage at 52 and 104 Wks	Initiated Q2 '07 Data expected 2010
CINEMA Ph II	Anti-TNF IR (cycling study)	Ocrelizumab infliximab	290	Mean change from baseline in DAS28	Initiated Q4 '08 Data expected 2011

Global Phase III program in RA by Roche and Genentech

- Fully humanised
- Potential clinical benefits - less immunogenicity, better tolerability, shorter infusion time, single infusion

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Anti-CD20: Ocrelizumab in other Automimmune



Trial	Patient population	Treatment	Size	Endpoints	Status
BELONG Ph III	Lupus Nephritis	SOC SOC + Ocrelizumab (2x 400mg, 2x1000mg)	369	Renal response at 52 wks	Initiated Q4 '07 Data expected 2011
Dose finding study Ph II	Relapsing Remitting Multiple Sclerosis	1st cycle placebo, then ocrelizumab 1st cycle IFN b-1a, then ocrelizumab Ocrelizumab (600mg) Ocrelizumab (1000mg)	200	Total number gadolinium-enhancing T1 lesions observed on MRI scans of the brain at wks 12, 16, 20 & 24	Completed enrolment Q2 '09 Data expected Q4 '09

Anti-CD20: MabThera/ Rituxan in other Automimmune

Trial	Patient population	Treatment	Size	Endpoints	Status
RAVE Ph II/ III	ANCA-Associated Vasculitis	conventional therapy (cyclophosphamide) RTX + glucocorticoids	197	Non-inferiority efficacy and safety	Initiated Q4 '04

Xolair Development Program



Patient Population	Asthma			Urticaria
	Asthma	Pediatric Asthma (Children ages 6 to 11)	Asthma	Chronic Idiopathic Urticaria
Study	Phase II AQUA <i>Liquid Formulation Study</i>	Phase III <i>Novartis Study</i>	Phase IIIb EXTRA <i>Add-on therapy to high-dose ICS and LABA</i>	Phase II
# of Patients	N=61	N=570	N=850	N=76
Status	• Expect data Q2 2009	• Data presented at the 2008 European Respiratory Society meeting • Submitted sBLA Q4 2008 • PDUFA date October 5, 2009	• Completed enrollment Q3 2008 • Expect data Q4 2009	• FPI Q1 2009

In collaboration with Novartis

sBLA = supplemental Biologics License Applications; PDUFA = Prescription Drug User Fee Act; ICS = Inhaled Corticosteroids; LABA = Long-Acting Beta-Agonists; IND = Investigational New Drug.

Other Early-stage Programs



	Inflammation				
Molecule	Anti-Beta7	Anti-CD4 In collaboration with TolereX	Anti-IFN alpha	Anti-IL13	Anti-OX40L
Patient Population	Ulcerative Colitis	Rheumatoid Arthritis	Systemic Lupus Erythematosus	Asthma	Asthma
Study	Phase I <i>Global Study</i> N=70	Phase I N=65	Phase II	Phase II N=24	Phase I
Status	• FPI Q3 2008	• FPI Q3 2008 • Expect to complete enrollment H2 2009	• Phase Ia/b study completed enrollment Q3 2008 • Expect FPI mid-2009	• FPI Q4 2008 • Expect data Q3 2009	• Phase I studies completed enrollment Q4 2008 • Expect Phase II 'go/no go' decision Q2 2009

FPI = first-patient-in.

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TCZ LTE: Baseline RA characteristics (ITT population)

	AMBITION (n=449)	RADIATE (n=382)	OPTION, TOWARD (n=1,431)
Rheumatoid factor positive, %	70	75	76
RA duration, yrs	6.5	11.9	9.42
No. of previous DMARDs/ anti-TNFs	1.1	4.0	1.7
No. of background DMARDs, %			
0	88	-	<1
1	12	100	84
2	-	<1	12
>3	-	-	3
Oral steroid use, %	46	57	52
DAS28	6.1	6.7	6.4

Data shown as mean except where indicated

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Tocilizumab (TCZ) exposure during the clinical trial programme (Roche and Chugai) up to 30 June 2008



Indication	Dose	Roche		Chugai		Roche + Chugai	
		N	PY*	N	PY*	N	PY*
RA	<8 mg/kg	1,181	662	289	85	1,470	747
	≥8 mg/kg [†]	3,242	6,962	683	2,239	3,925	9,201
Total RA	All doses [‡]	3,778	7,624	972	2,324	4,750	9,948
Non-RA	8 mg/kg	–	–	338	604	338	604
Total all indications	All doses	3,778	7,624	1,310	2,928	5,088	10,552

* Patient-years of exposure are estimated

[†] For Roche, this included a drug-drug interactions study in RA patients (23 patients dosed at 10 mg/kg)

[‡] Some patients received 4 mg/kg and 8 mg/kg and are accounted for twice in the number for '<8' and '≥8' but only once in the 'total all doses' category

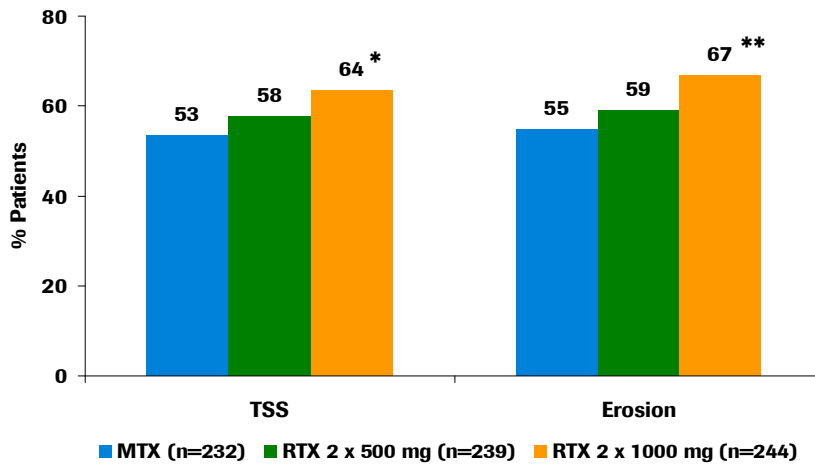
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IMAGE: Summary of patient disposition at week 52

	Placebo + MTX	RTX 2 x 500mg + MTX	RTX 2 x 1000mg + MTX
Randomised	252 (100%)	252 (100%)	251 (100%)
Treated	250 (99.2%)	249 (98.8%)	249 (99.2%)
Completed Wk 52	213 (84.5%)	227 (90.1%)	230 (91.6%)
Withdrew before Wk 52	39 (15.5%)	25 (9.9%)	21 (8.4%)
AE/intercurrent illness	5 (2%)	3 (1.2%)	3 (1.2%)
Death	3 (1%)	–	–
Insufficient therapeutic response	19 (7.5%)	9 (3.6%)	4 (1.6%)
Failure to return	4 (1.6%)	2 (0.8%)	4 (1.6%)
Protocol violation	2 (0.8%)	2 (0.8%)	–
Refused treatment	3 (1.2%)	1 (0.4%)	1 (0.4%)
Withdrew consent	5 (2%)	8 (3.2%)	4 (1.6%)
Admin/other	1 (0.4%)	–	5 (2.0%)

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IMAGE: Patients with no radiographic change (change mTTS_{≤0})



Missing values were imputed using linear extrapolation using baseline and Wk 24 radiographs
* p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 comparing RTX+MTX groups to MTX alone

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IMAGE: Overview of safety

	Placebo + MTX n=250	RTX 2 x 500mg + MTX n=249	RTX 2 x 1000mg + MTX n=249
Any adverse event	203 (81%)	189 (76%)	197 (79%)
Grade 3	29 (12%)	18 (7%)	22 (9%)
Grade 4	1 (<1%)	4 (1.6%)	-
Any Serious AE	26 (10%)	23 (9%)	24 (10%)
Infusion-related reaction	45 (18%)	43 (17%)	58 (23%)
Serious infusion reactions	-	-	1 (<1%)
Infectious AE	124 (50%)	127 (51%)	129 (52%)
Serious infection	13 (5%)	6 (2%)	8 (3%)
AEs leading to withdrawal	12 (5%)	4 (2%)	5 (2%)
Deaths	3 (1%)	-	-

Number of patients (%)

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Adverse events observed with rituximab with repeat treatment courses – stable over time

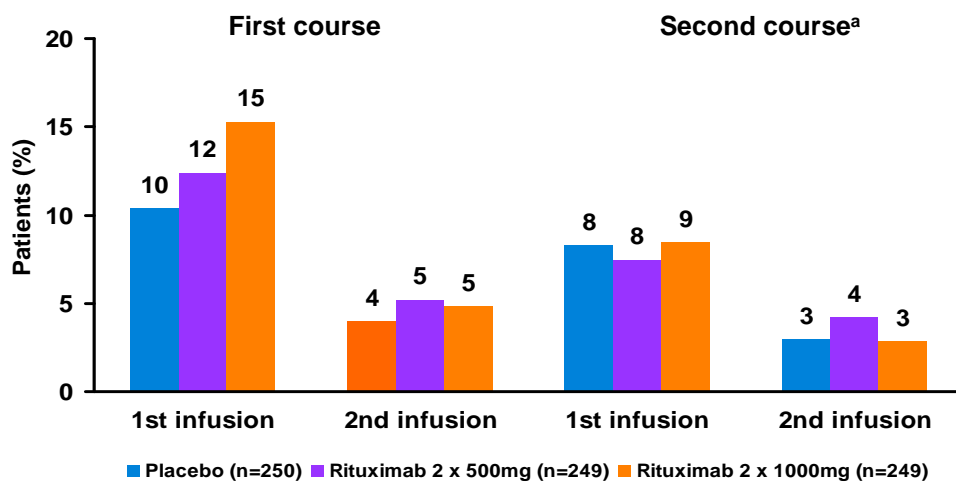


	C1 (n=2579)	C2 (n=1926)	C3 (n=1228)	C4 (n=794)	C5 (n=282)
Exposure (pt-yrs)	2594	1877	900	409	119
AEs Rate/100 pt-yrs	379	313	319	329	330
Serious AEs Rate/100 pt-yrs	18.3	17.4	16.6	12.0	13.4

van Vollenhoven et al. EULAR 2009 [Abstract 2363]

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Rituximab Infusion-related reactions (courses 1 and 2)



^aOne of the IRRs in the rituximab 2 x 1000mg group was reported as serious

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