



Rheumatoid Arthritis: A growth opportunity for Roche

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IXIS RA Seminar, 11 April 2006



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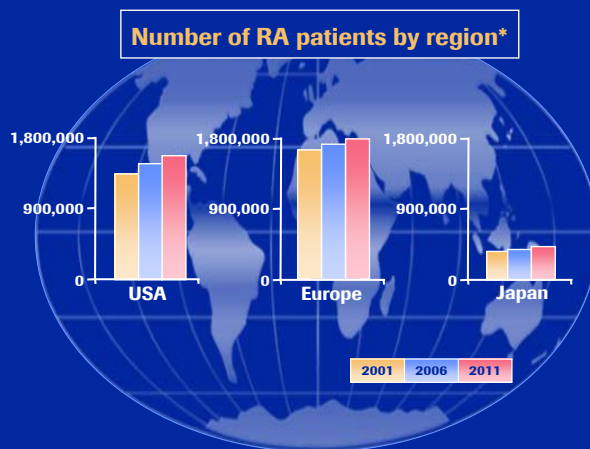
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Epidemiology of RA

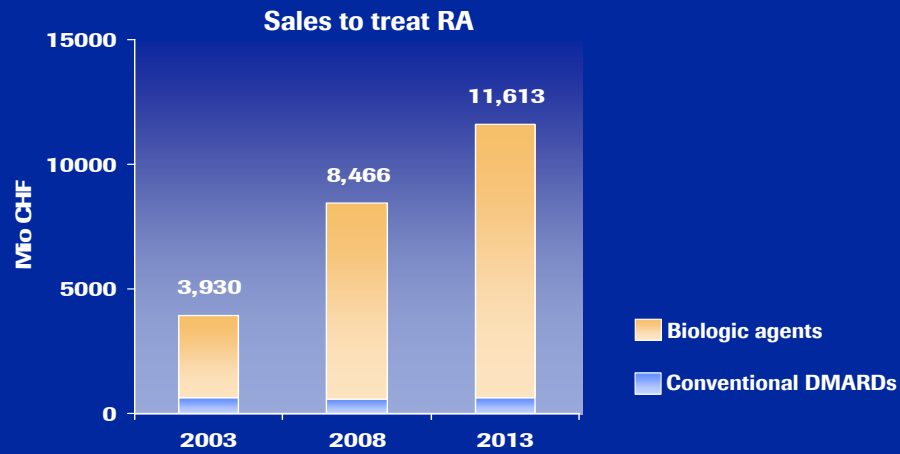
Current and predicted prevalence



- Overall prevalence is 0.5–1.0 %
- Approximately 3 times more prevalent in woman than in men
- Incidence increases with age until approximately 75 years and decreases thereafter

RA: Potential CHF 12 bn market by 2013

Biologics main driver

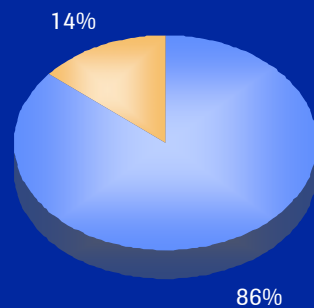


Source : Decision Resources March 2005, US/Top 5 EU/Japan; (1 USD=1.2737717 CHF)

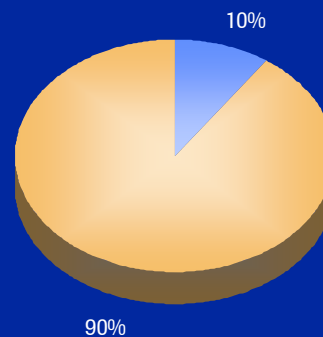
Majority patients still treated with DMARDs

Biologics account for majority sales

RA treated population in 2005



RA sales in 2005



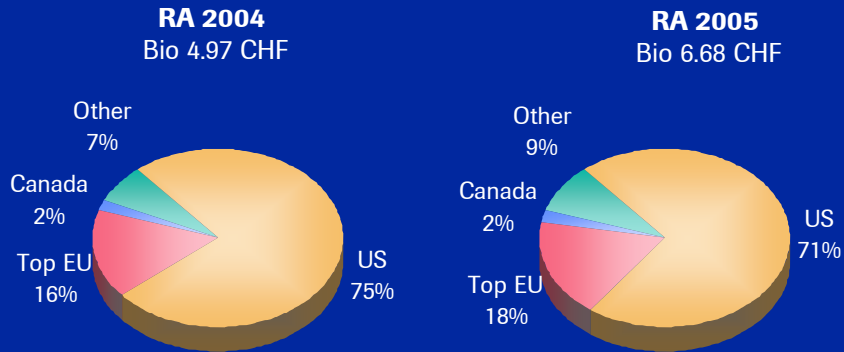
■ Conventional DMARDs ■ Biologics

Source : IMS PADDs, Sales in LC CHF; Biologic sales estimate from US PDDA Verispan, Conventional DMARDs Sales in M1C0 (Spec AntiRheum Agents), Estimated US/ Top5 EU/ Japan Patient Share from Decision Resources March 2005

Sales of biologics in RA



Strong sales growth also outside the US



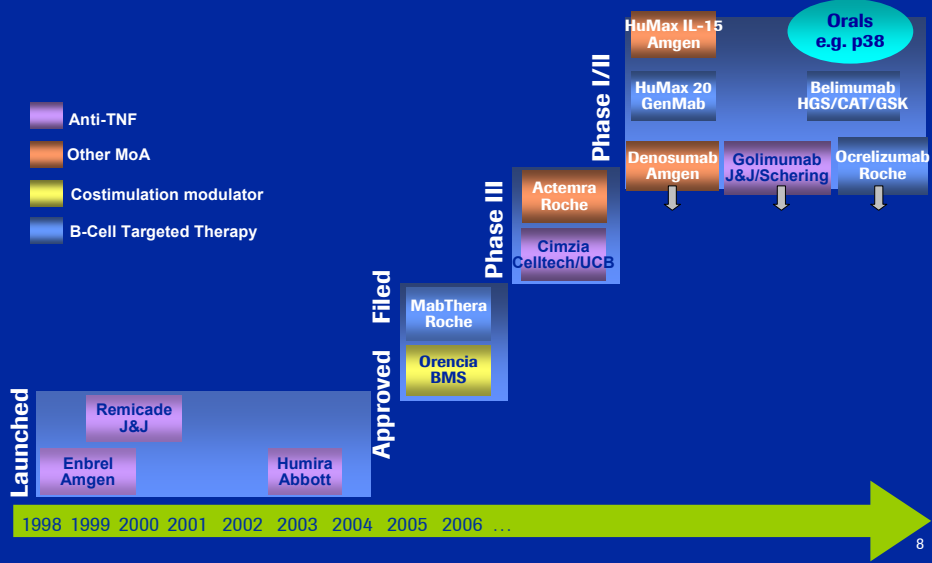
2004 vs. 05 sales growth:
US ~29 %, Canada ~31 %, Top 5 EU ~41 %, Other ~68 %

Source : IMS PADDS, Sales 2005 in LC CHF; Sales in RA estimated with US PDDA Verispan

Increasingly competitive environment ...



Opportunities remain for differentiated products



Roche in RA: A new therapeutic franchise

Urs Schleuniger
Business Director, Haematology and Autoimmune Diseases
IXIS RA Seminar, 11 April 2006



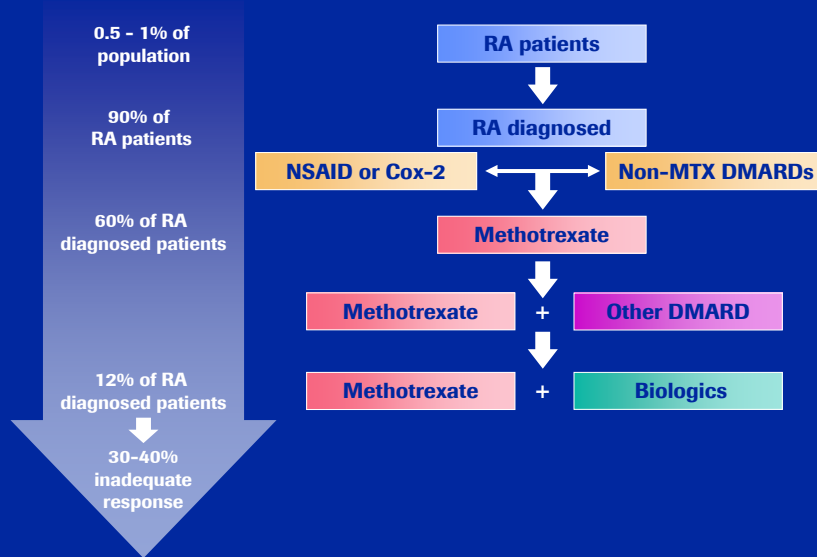
Rheumatoid Arthritis

A debilitating disease

- Affects about one per cent of population
- Progressive inflammation resulting in
 - Swollen and tender joints
 - Pain and fatigue
 - Disability
- Early Disease Progression:
 - Irreversible joint damage in 70% of patients within two years
 - 10% of patients stop working after one year



RA: Current treatment schedule



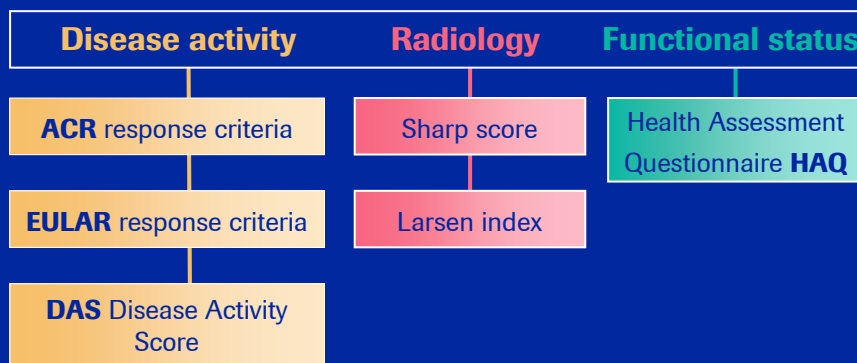
DMARD: Disease Modifying Anti Rheumatic Drugs, NSAIDs: Non-Steroidal Anti Inflammatory Drugs

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Assessment tools for RA



Commonly employed and validated tools include



ACR, 2002; Felson et al, 1995; Kirwan & Reeback, 1986; Sharp, 2000; van Gestel et al, 1996; www.das-score.nl

ACR: American College of Rheumatology
EULAR: European League against Rheumatism

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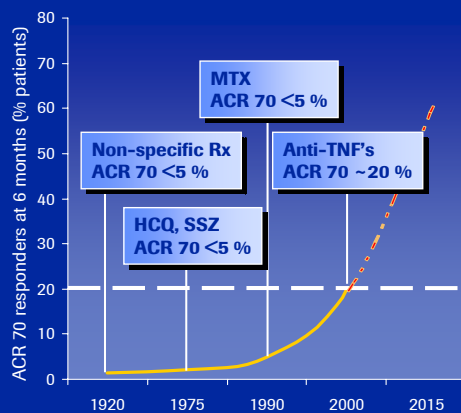
The Unmet Need

Major progress made but far from remission

- 30 – 40 % of patients don't have adequate control with current therapies
- 60 – 80 % of patients do not achieve **major** signs and symptoms control (ACR 70)
- No drug so far has gained regulatory approval for REMISSION

Future challenge

Improvement in efficacy



- ACR 70 is only achieved in ~20 % of patients with currently most effective therapies (MTX + biologics)
- The future - most patients on
 - Combination regimens
 - Individualized therapy
 - Intensive treatment in an early stage of the disease

MabThera/ Rituxan in Rheumatoid Arthritis

Actemra in Rheumatoid Arthritis

Potential roles of B Cells in the immunopathogenesis of RA

- Secretion of proinflammatory cytokines



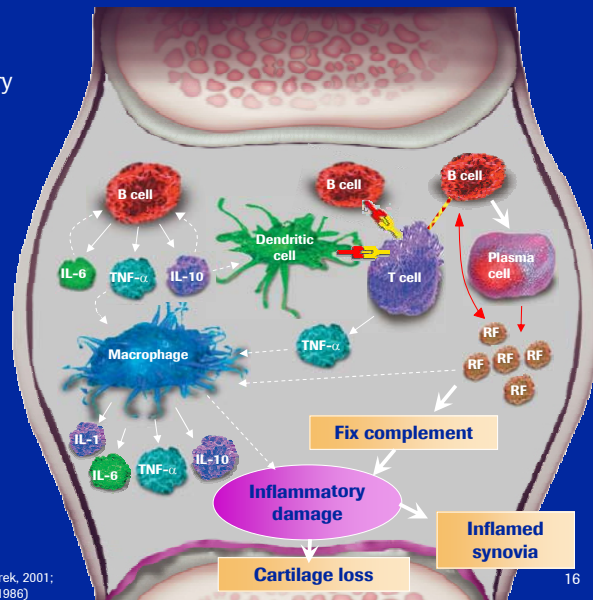
- Antigen presentation



- T-cell activation



- Autoantibody production and self-perpetuation



Global MabThera/ Rituximab development



A tri-company partnership

Biogen Idec

Phase III in anti-TNF
inadequate responders (IR)

reflex

Globally filed
US: Aug '05
EU: Sep '05

Approval
US: March '06

Roche

Phase IIb

dancer

**SERENE, MIRROR,
IMAGE**

Global filing
2007

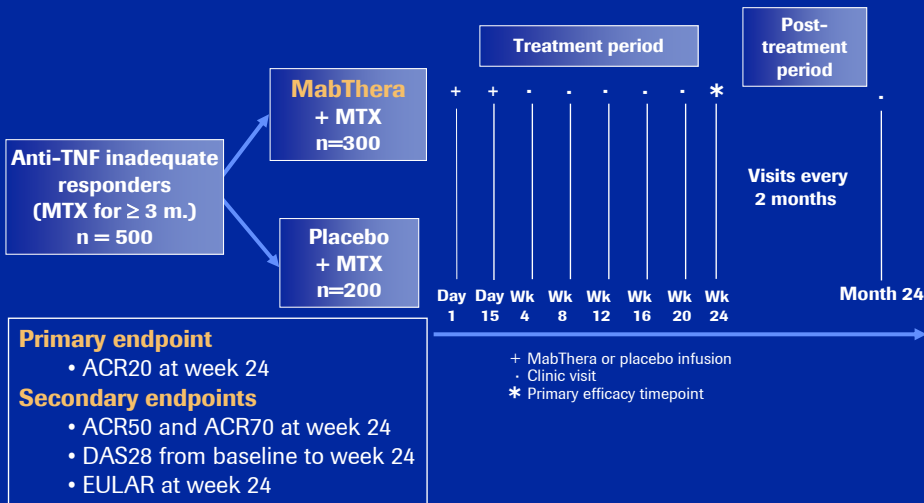
Genentech

Phase III in DMARD
IR and MTX naïve
patients

REFLEX



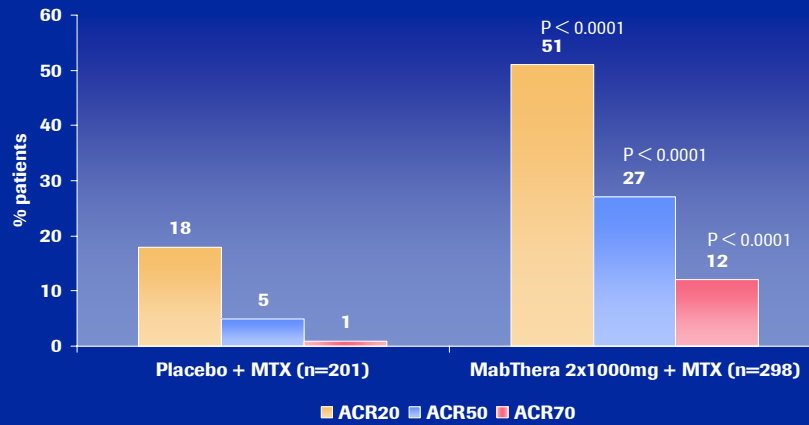
Study design in patients who failed anti-TNF therapy



REFLEX efficacy



ACR responses at 6 months (all patients)



MabThera significantly improves all ACR responses

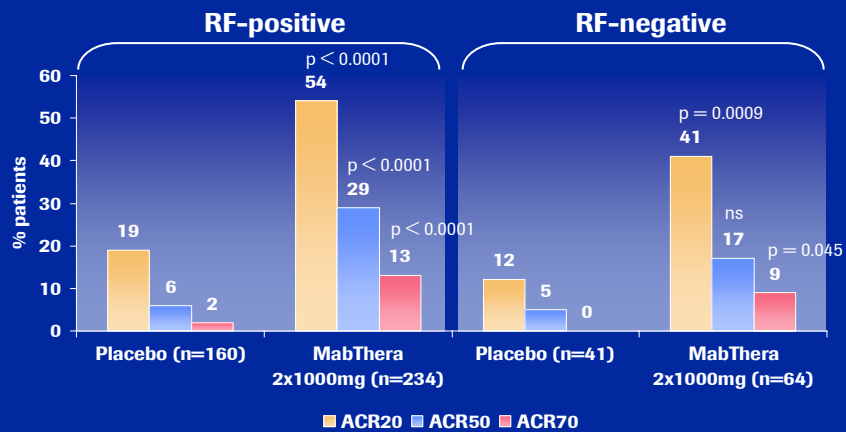
ACR: American College of Rheumatology

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REFLEX efficacy



ACR responses at 6 months



Magnitude of response similar and independent of Rheumatoid Factor

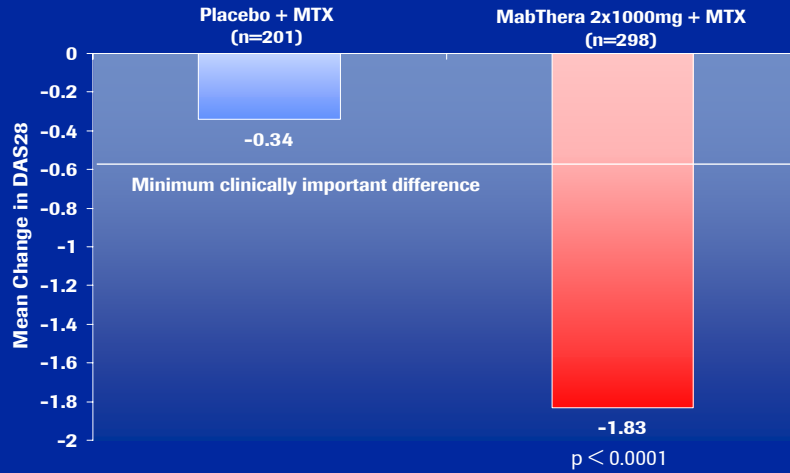
ACR: American College of Rheumatology

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REFLEX efficacy



Change in DAS28 at 6 months (all patients)



Impressive reduction in disease activity

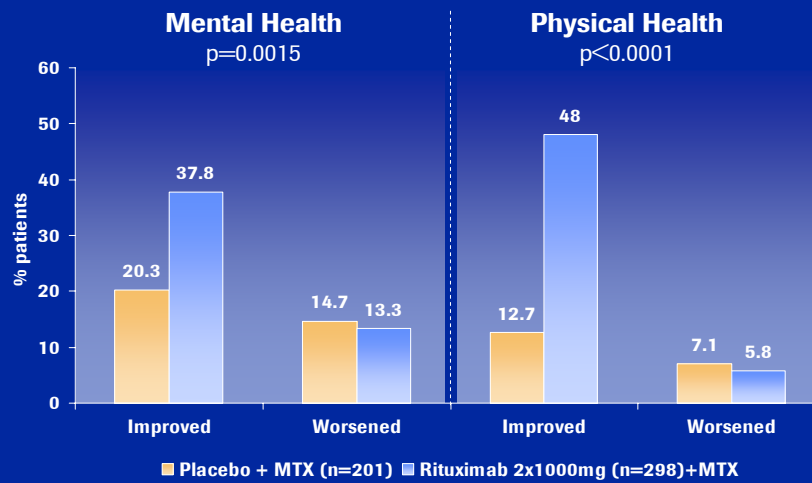
DAS: Disease Activity Score

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REFLEX efficacy



Changes in SF-36 categories (all patients)



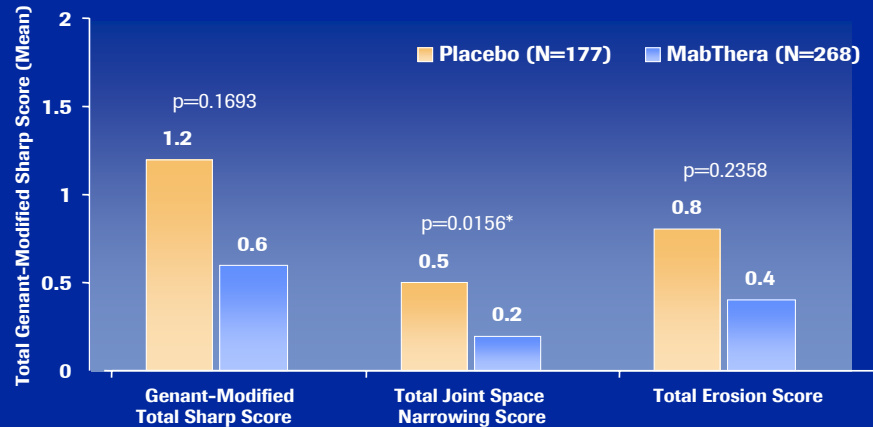
Substantial improvement in physical and mental health

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REFLEX efficacy



Radiographic endpoints at week 24



**Preliminary data suggest prevention of joint damage
1 year up-date EULAR June '06**

*Statistically significant at the 0.05 level
24 Placebo and 30 rituximab patients were missing x-rays at week 24

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REFLEX



Conclusions of 6-month primary analyses

- MabThera is associated with highly significant and clinically meaningful improvement in all RA key outcome measures achieved after a single course of two MabThera administrations
- Significant efficacy irrespective of Rheumatoid Factor
- MabThera is well tolerated
- Preliminary data suggest prevention of structural damage

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DANCER



Study design in RF-positive patients (n=360)

	Placebo	Corticosteroid dose	
		2 x 100mg i.v.	2 x 100mg i.v. and p.o.*
Placebo + MTX	A (n=40/20)	B (n=40)	C (n=40)
Rituximab 2 x 500mg + MTX	D (n=40)	E (n=40)	F (n=40)
Rituximab 2 x 1000mg + MTX	G (n=40/20)	H (n=40/20)	I (n=40/20)

RF positive/RF negative

Primary endpoint

- ACR 20 response at week 24 for RF-positive patients

Patients

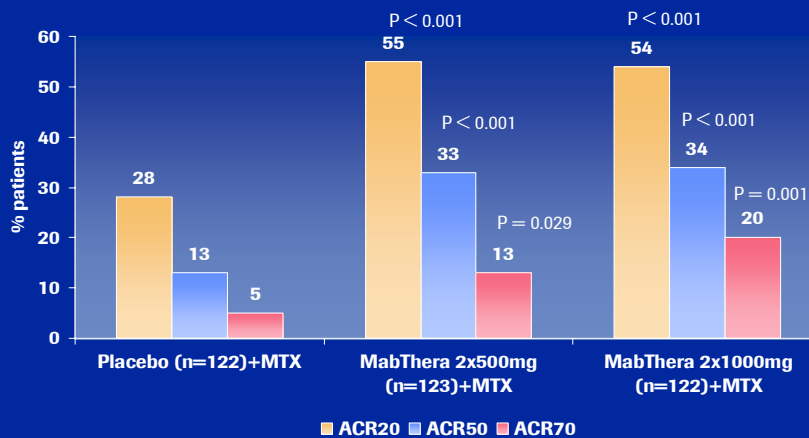
- stratified by region (US or non-US)
- failed at least one DMARD (other than MTX) but no more than 5

*770 mg total ACR: American College of Rheumatology
Dose-ranging Assessment: iNternational Clinical Evaluation of Rituximab in RA

DANCER efficacy



ACR responses at 6 months in RF-positive patients

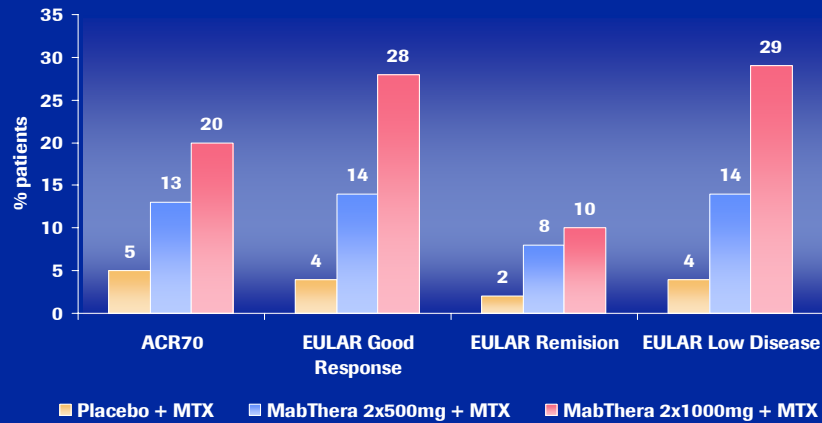


MabThera significantly improves all ACR responses

DANCER efficacy



High-hurdle endpoints at 6 months in RF-positive patients



High level of efficacy demonstrated with high dose of MabThera

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DANCER efficacy



ACR20 Logistic regression: Main effects model in RF-positive and RF-negative patients

Variable	DF	Wald Chi ²	Pr > Chi ²
MabThera	2	18.81	<0.001
Corticosteroids	2	2.85	0.241
Rheumatoid Factor	1	0.57	0.452

Efficacy not dependent on glucocorticoid use and Rheumatoid Factor

ACR: American College of Rheumatology; DF: Degrees of Freedom

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DANCER safety



Most frequently reported AE's in all patients

	Placebo + MTX (n=149)	MabThera 2 x 500mg + MTX (n=124)	MabThera 2 x 1000mg + MTX (n=192)
Exacerbation of RA	44 (30%)	21 (17%)	27 (14%)
Headache	19 (13%)	14 (11%)	21 (11%)
Nausea	13 (9%)	8 (6%)	19 (10%)
URTI	9 (6%)	10 (8%)	12 (6%)
Nasopharyngitis	8 (5%)	7 (6%)	10 (5%)
Arthralgia	5 (3%)	5 (4%)	11 (6%)
Diarrhoea	8 (5%)	7 (6%)	6 (3%)
Fatigue	8 (5%)	5 (4%)	8 (4%)
Hypertension	4 (3%)	5 (4%)	12 (6%)
Rigors	3 (2%)	5 (4%)	13 (7%)
Dizziness	6 (4%)	4 (3%)	10 (5%)

URTI: Upper Respiratory Tract Infection

MabThera is well tolerated

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DANCER



Conclusions from 6 months analyses

- MabThera is associated with highly significant and clinically meaningful improvement in all RA key outcome measures
 - Significant improvements in ACR response
 - Significant reductions in DAS
 - Clinically meaningful effects on EULAR responses, QOL, CRP, fatigue
- Both MabThera doses show significant efficacy, with the high dose showing greater high hurdle responses
- Efficacy not dependent on glucocorticoid use or Rheumatoid Factor
- Well tolerated
- Premedication with glucocorticoid administration reduces the frequency and severity of infusion reactions
- Slight increase in rate of infections

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MabThera further courses

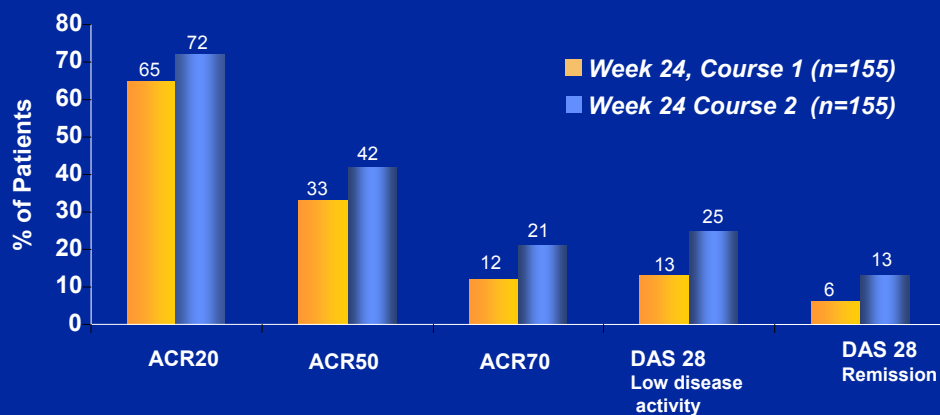


Study outline

- Patients received MabThera infusion with background MTX
- Second course was permitted at anytime post 24 weeks of initial treatment
 - required evidence of returning disease
- Protocol ongoing with continual accrual of patients from phase IIa and DANCER (cohort now > 250 patients)

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MabThera — ACR Efficacy



Repeat courses provide improved ACR efficacy over the first treatment course

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Proportion of adverse events by treatment course



No evidence for additional safety signals with repeat courses

AEs	Placebo N = 103 N (%)	First N = 1039 N (%)	Second N = 570 N (%)	Third N = 191 N (%)	Fourth N = 40 N (%)
Any	86 (88%)	911 (88%)	404 (71%)	121 (63%)	22 (55%)
Serious	23 (22%)	161 (15%)	60 (11%)	11 (6%)	3 (8%)

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MabThera further courses



Conclusions

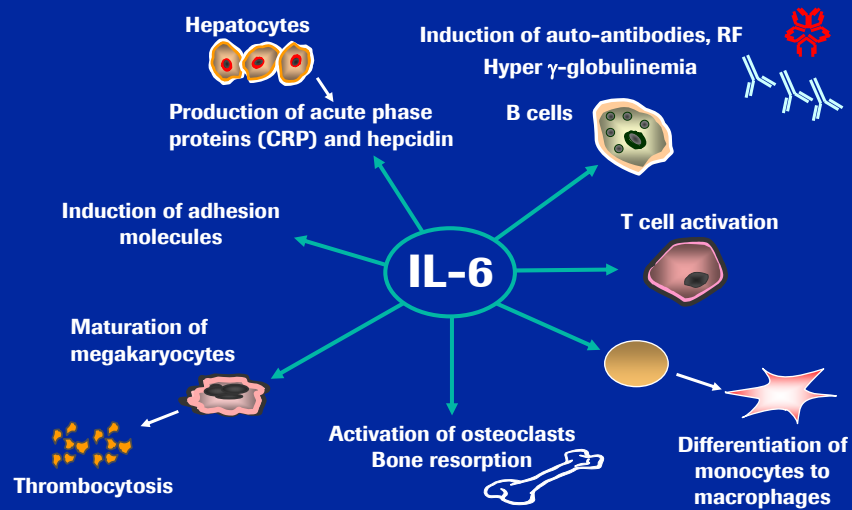
- Repeated courses of MabThera are further improving signs and symptoms control and are well tolerated
- No long term safety signal identified to date
- Time course of DAS-CRP and RF would suggest a 2nd course is required for a large part of the patients before the 12 months mark after the 1st infusion

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MabThera/ Rituxan in Rheumatoid Arthritis

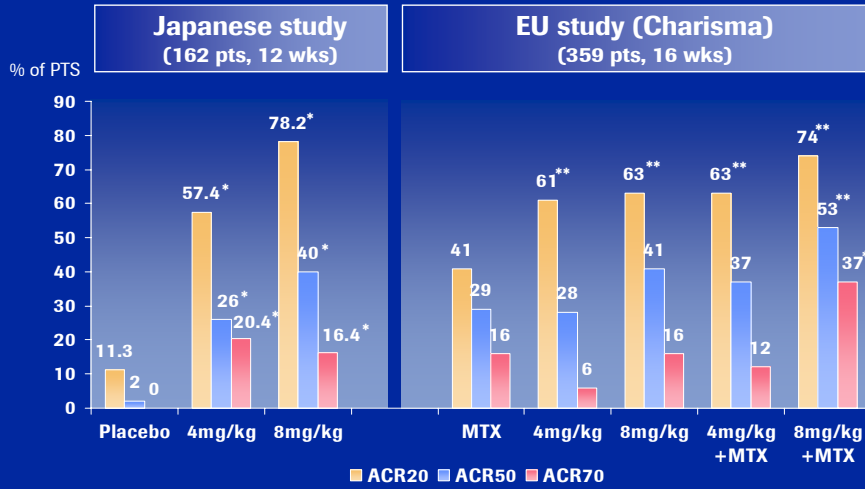
Actemra in Rheumatoid Arthritis

IL-6: A new target in the treatment of RA



Actemra: Phase II efficacy

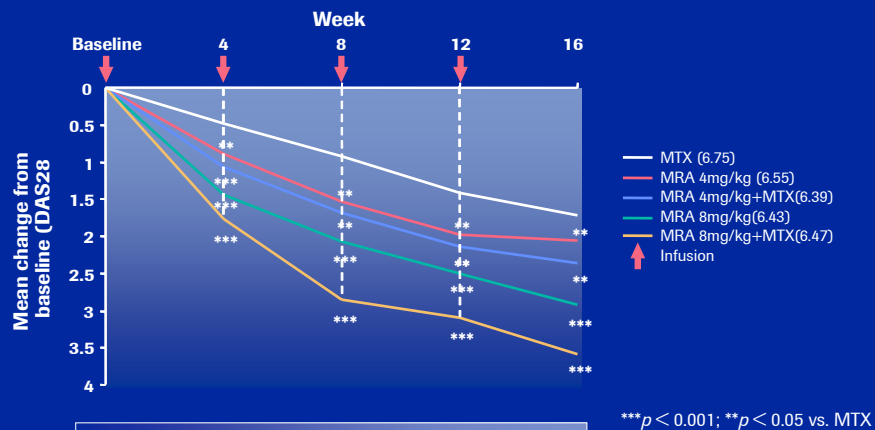
ACR scores improved in mono- and combination therapy in different populations



* Statistically different from placebo ** Statistically different from MTX

Actemra: Phase II efficacy (Charisma)

Effects on DAS 28



Fast onset of action

Actemra: Phase II safety (Charisma)



Liver enzymes profile

- Elevations of liver enzymes (mainly ALT)
 - Mild, transient and reversible
 - No evidence of clinical hepatitis in any patients with ALT elevations
- Periodicity of elevations
 - Coincides with frequency of Tocilizumab administration (monthly infusions), especially at beginning of treatment
- The liver appears to adapt over time
 - Linked to mechanism of action of the drug

	# of patients	Patients with ALT > 2.5 ULN	Patients withdrawn due to ALT changes
Actemra mono	159	3 (2 %)	0
Actemra + MTX	151	17 (11 %)	5 (3 %)
MTX	49	0	0

ALT: Alanin Aminotransferase

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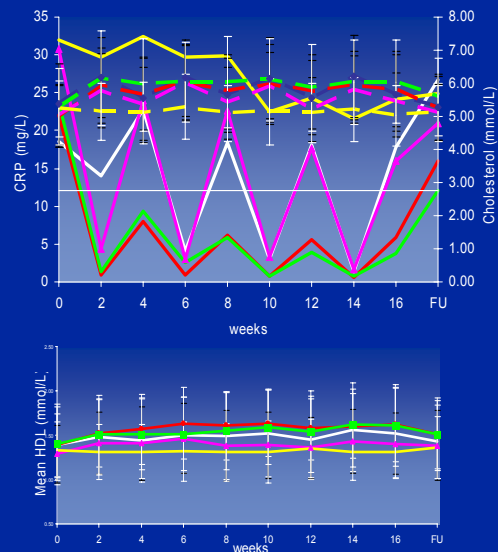
Actemra: Phase II safety (Charisma)



Lipid profile

- Mild non-fasting elevations of total cholesterol, HDL cholesterol and triglycerides, with no change in atherogenic index
- Lipid elevations reported in patients with RA successfully treated with DMARDs
- No clear temporal association with ALT increases
- Temporally related to CRP levels

— 4 mg Actemra
 — 4 mg Actemra + MTX
 — 8 mg Actemra
 — MTX
 — 8 mg Actemra + MTX



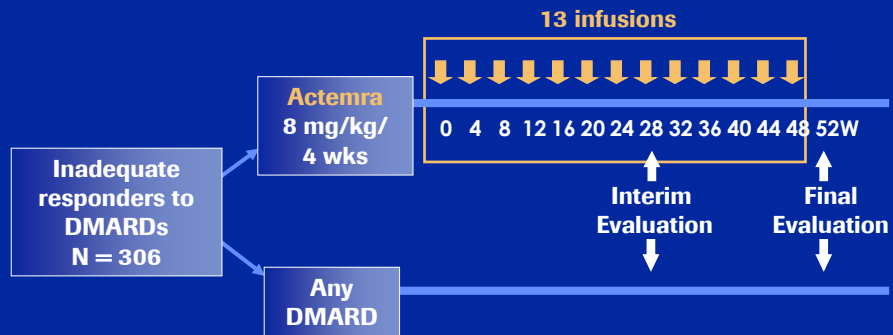
CRP: C Reactive protein

ALT: Alanin Aminotransferase

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Actemra : Japanese PJD phase III trial

Study design

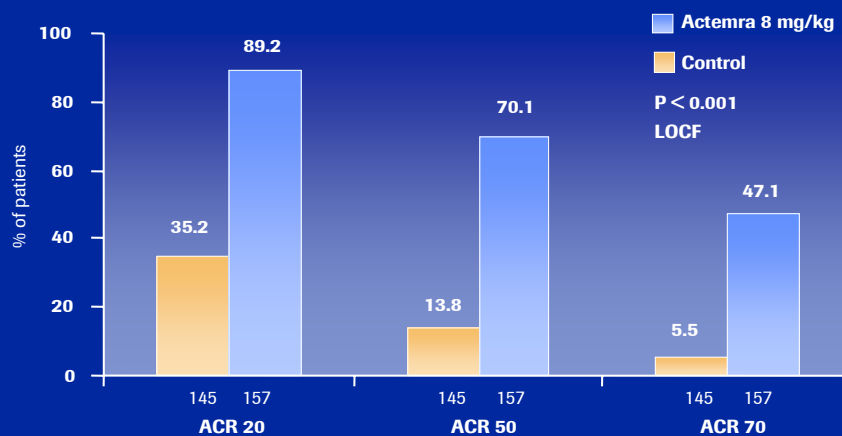


Primary endpoints

- Sharp score at week 52
- ACR response

Japanese phase III efficacy

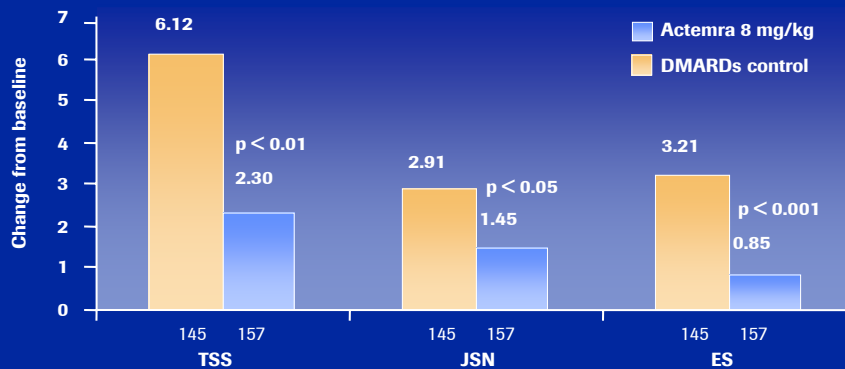
Impressive ACR responses in monotherapy at week 52



Actemra significantly improves ACR responses

Japanese phase III efficacy

Actemra can prevent joint damage



Significantly less radiographic progression with Actemra

TSS: Total Sharp Score; JSN: Joint Space Narrowing; ES: Erosion Score

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Japanese phase III safety

Preliminary results



- Treatment-emergent AEs: 96 % in Actemra vs. 87 % in DMARDs group
- Treatment-emergent SAEs: 19 % in Actemra vs. 13 % in DMARDs group
- The most frequently reported infectious event was nasopharyngitis
- Mild, transient increases in LFTs were observed in both groups
- Lipid increases were mainly reported in the Actemra group: mean total cholesterol levels became stable (217 ± 39.3 mg/dl) at around the normal upper limit

LFT: Liver Function Test

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Japanese phase III

Conclusions

- IL-6 is an important pro-inflammatory cytokine in the pathogenesis of RA
- Blocking the IL-6 receptor with Actemra leads to significant improvement in signs and symptoms and reduce the progression of joint damage
- Adverse events are within expectations
- First trial showing superiority of Actemra compared to conventional DMARDs in preventing joint damage

Roche RA portfolio summary

MabThera phase III program in DMARD failures

Three trials to start end 2005/ early 2006



Trial	Treatment	Sample Size	Endpoints
MTX-IR SERENE	MTX + placebo vs. MTX + MabThera 1g vs. MTX + MabThera 2g	495	Reduction in signs and symptoms
MTX active comparator (X-ray study) IMAGE	MTX vs. MTX + MabThera 1g vs. MTX + MabThera 2g	852	Reduction in signs and symptoms Inhibition of structural joint damage Improvement in physical function
MTX-IR Dose Escalation MIRROR	Rituximab 1g retx 1g vs. Rituximab 1g retx 2g vs. Rituximab 2g no retx	375	Effect of further courses and dose escalation

EU Filing 2007

IR: Inadequate Responders

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Actemra phase III program in Roche territories

Five trials ongoing



Treatment	Sample Size	Patient population	Endpoints
Actemra 4 mg + MTX Tocilizumab 8mg + MTX MTX OPTION	630	MTX partial responders	ACR 20 response at Wk 24
Actemra 4 mg + MTX Actemra 8 mg + MTX MTX LITHE	1'170	MTX partial responders	ACR 20 at Wk 24 Sharp Score at Wk 52 Sharp Score at Wk 104 Physical function at Wk 104
Actemra 8 mg + DMARDs DMARDs TOWARD	1'200	DMARD partial responders	ACR 20 response at Wk 24
Actemra 4 mg + MTX Actemra 8 mg + MTX MTX RADIATE	570	Anti-TNF α failures	ACR 20 response at Wk24
Actemra 8 mg MTX AMBITION	550	MTX naive	ACR 20 response at Wk 24

Filing 2007

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Summary of Roche RA Phase III *Biologics*



Description	MabThera/ Rituxan	Actemra/ Tocilizumab
Target	CD20 on B cells	Humanized anti-IL-6 receptor
Mechanism	B cell reduction	Inhibition of IL-6 signaling
Dose Regimen	IV days 1 & 15 Q 6-12 mo	IV every 4 weeks
Treatment Strategy	Combo MTX	Mono & Combo MTX and other DMARDs
Target Population	Anti-TNF failures; General RA patients	General RA patients, including anti-TNF failures
Efficacy	ACR20/50/70; EULAR response supports joint protection	ACR20/50/70; EULAR response joint protection shown
Safety	Manageable infusion reactions Slight increase infections	Manageable infusion reactions; Chol, LFT, CBC changes Slight increase infections

ACR: American College of Rheumatology; EULAR: European League Against Rheumatism

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Roche RA portfolio



Diversified and exciting

- Roche is well-positioned to enter RA market with biologics and small molecules
- Secondary indications/ claims extension offer relatively low risk/ low investment way to leverage our emerging RA portfolio

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2006: Roche in Rheumatoid Arthritis



The first products in the autoimmune franchise

