

# Treat to a Target The New Paradigm in the Management of RA

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# Disclosure – Dr Boulos Haraoui

- Advisor/Research Grants/Speakers' Bureau:
  - Abbott
  - Amgen
  - Bristol-Myers Squibb
  - Merck/Schering
  - Pfizer/Wyeth
  - Roche
  - UCB
  - Conseil du médicament du Québec

# Objectives

- Treat to Target Concept
- Experience with etanercept
- Importance of rapid response
- How to translate clinical trial data to daily clinical practice

# Treating rheumatoid arthritis to target: recommendations of an international task force

Josef S Smolen,<sup>1,2</sup> Daniel Aletaha,<sup>1</sup> Johannes W J Bijlsma,<sup>3</sup> Ferdinand C Breedveld,<sup>4</sup> Dimitrios Boumpas,<sup>5</sup> Gerd Burmester,<sup>6</sup> Bernard Combe,<sup>7</sup> Maurizio Cutolo,<sup>8</sup> Maarten de Wit,<sup>9</sup> Maxime Dougados,<sup>10</sup> Paul Emery,<sup>11</sup> Alan Gibofsky,<sup>12</sup> Juan Jesus Gomez-Reino,<sup>13</sup> Boulos Haraoui,<sup>14</sup> Joachim Kalden,<sup>15</sup> Edward C Keystone,<sup>16</sup> Tore K Kvien,<sup>17</sup> Iain McInnes,<sup>18</sup> Emilio Martin-Mola,<sup>19</sup> Carlomaurizio Montecucco,<sup>20</sup> Monika Schoels,<sup>2</sup> Desirée van der Heijde,<sup>4</sup> for the T2T Expert Committee

**ARD Online First, published on March 9, 2010**

# Overarching Principles

- Treatment of RA must be based on a shared decision between patient and rheumatologist
- Primary goal of treating RA patient is to maximize long term HR-QoL through control of symptoms, prevention of progressive structural damage, normalization of function and social participation
- Abrogation of inflammation is the most important mean to achieve these goals
- Treatment to target by measuring disease activity and adjusting therapy accordingly optimizes outcomes in RA

# Recommendations 1-4

- The primary target for treatment should be a state of clinical remission
- Remission is defined as the absence of signs and symptoms of significant inflammatory disease activity
- While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established disease
- Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months

# Recommendations 5-7

- The use of **validated composite measures** of disease activity, **which include joint assessments**, is of utmost importance in routine clinical practice to guide treatment decisions
- Measures of disease activity must be obtained and **documented regularly**; as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3-6 months) for patients in sustained low disease activity or remission
- **Structural changes and functional impairment** should be considered when making clinical decisions, in addition to assessing composite measures of disease activity

# Recommendations 8-10

- The desired treatment target should be **sustained** throughout the remaining course of the disease
- The choice of the composite measure of disease activity and the level of the **target value may be influenced by considerations of co-morbidities, patient factors and drug related risks**
- The **patient has to be appropriately informed** by the rheumatologist about the treatment target and the strategy planned to reach this target

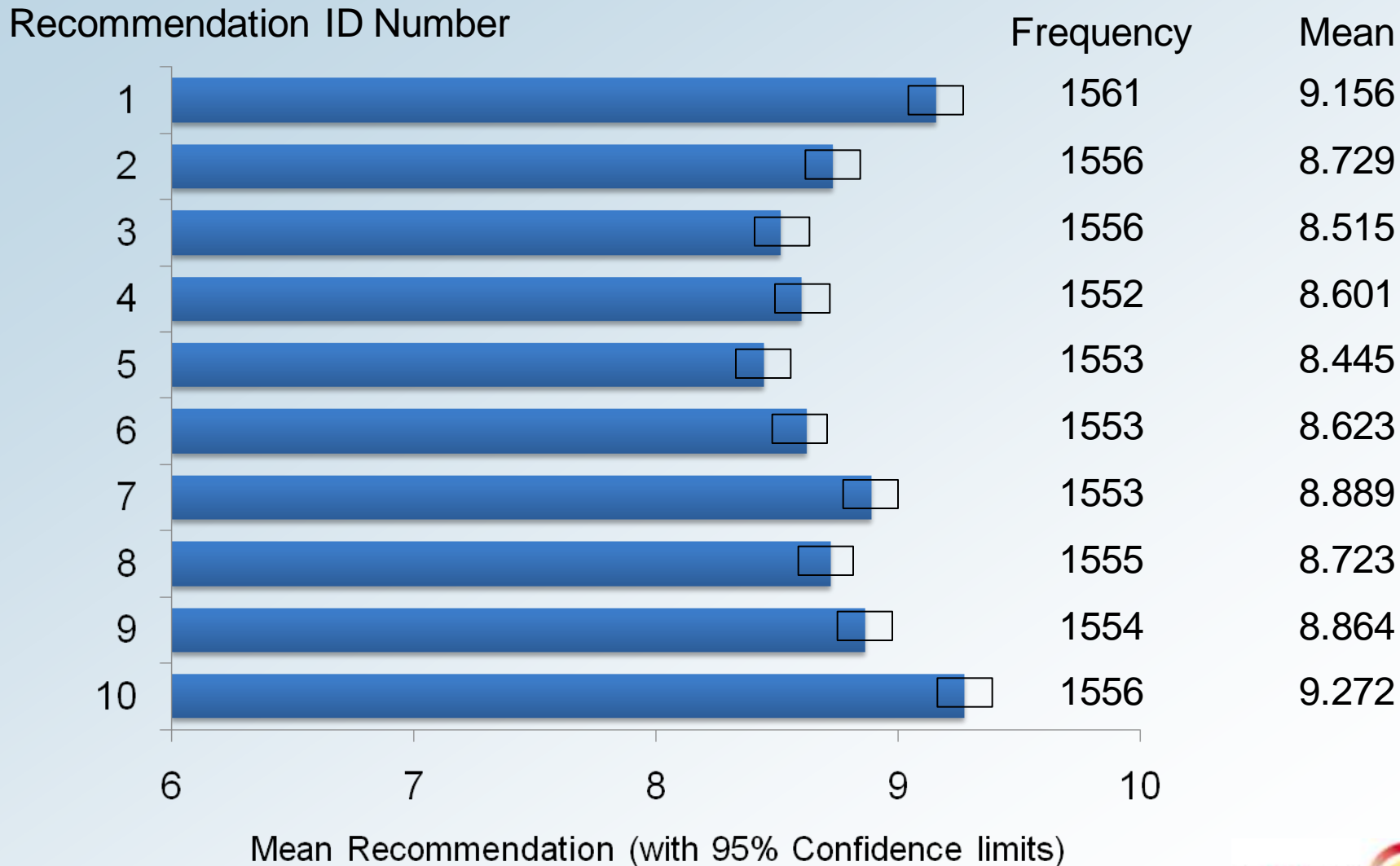
# International Survey

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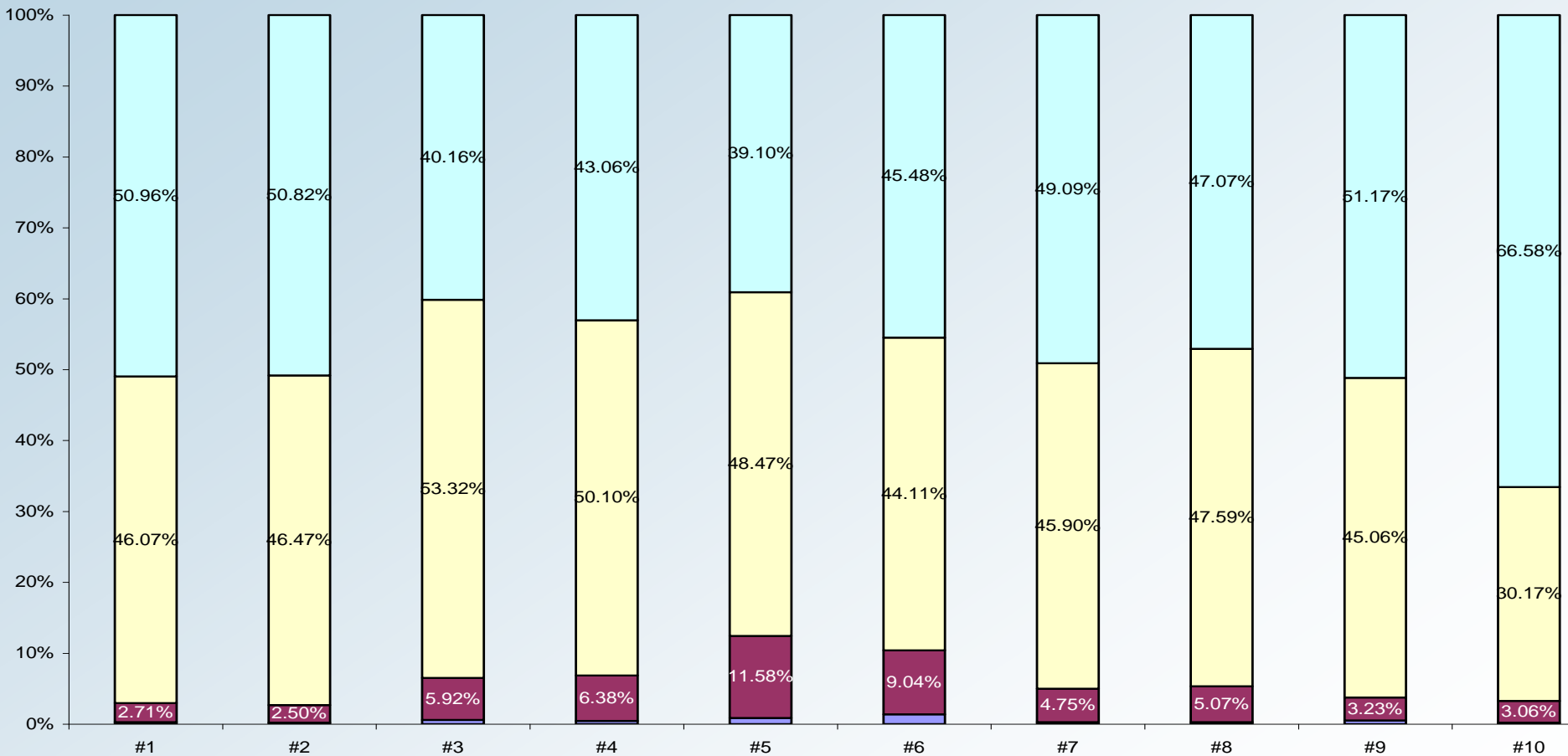
## *Demographics*

- A total of 1 568 physicians, representing 33 countries, participated.
- Practices in university hospitals, general hospitals, and private clinics were well represented with 37%, 31%, and 21% of respondents, respectively.
- The mean number of participants' years in practice was 18 ( $\pm 10.72$  SD)
- The average number of RA patients seen per month was 85 ( $\pm 88.99$  SD)

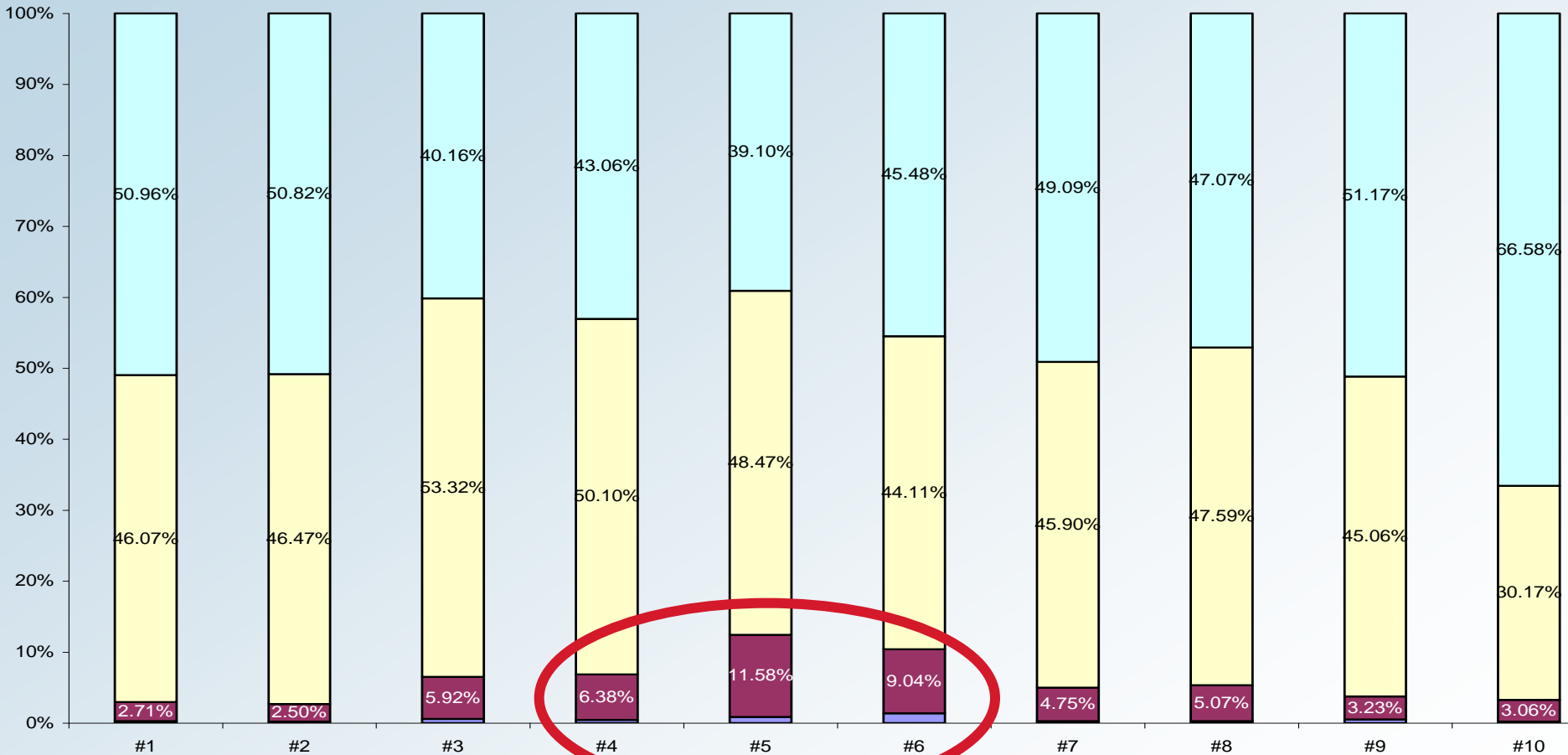
# Agreement with T2T Recommendations



# Application of T2T Recommendations to Daily Practice



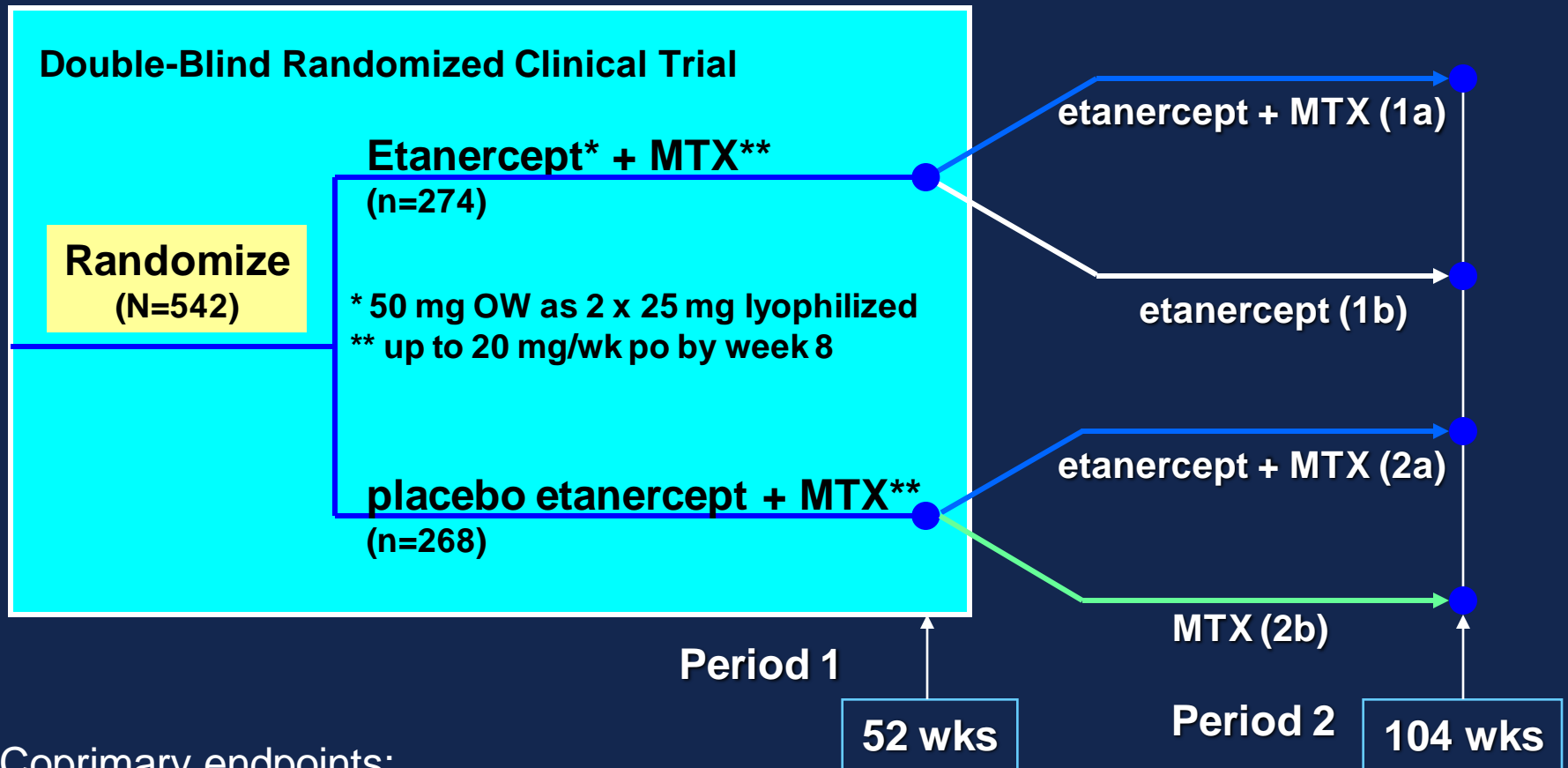
# Application of T2T Recommendations to Daily Practice



■ Never ■ Not very often ■ Very often ■ Always



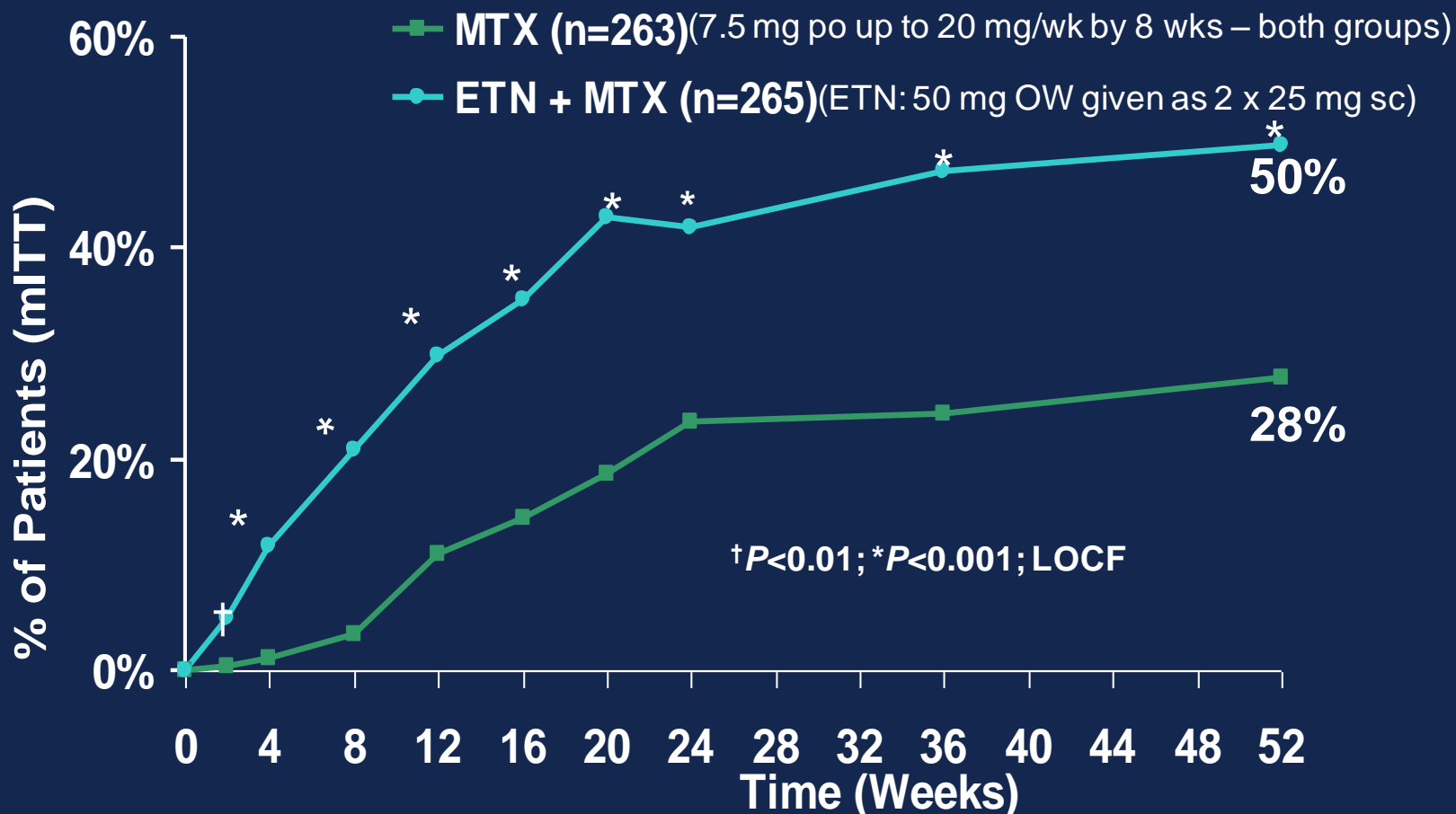
# COMET- Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis: Study Design



Coprimary endpoints:

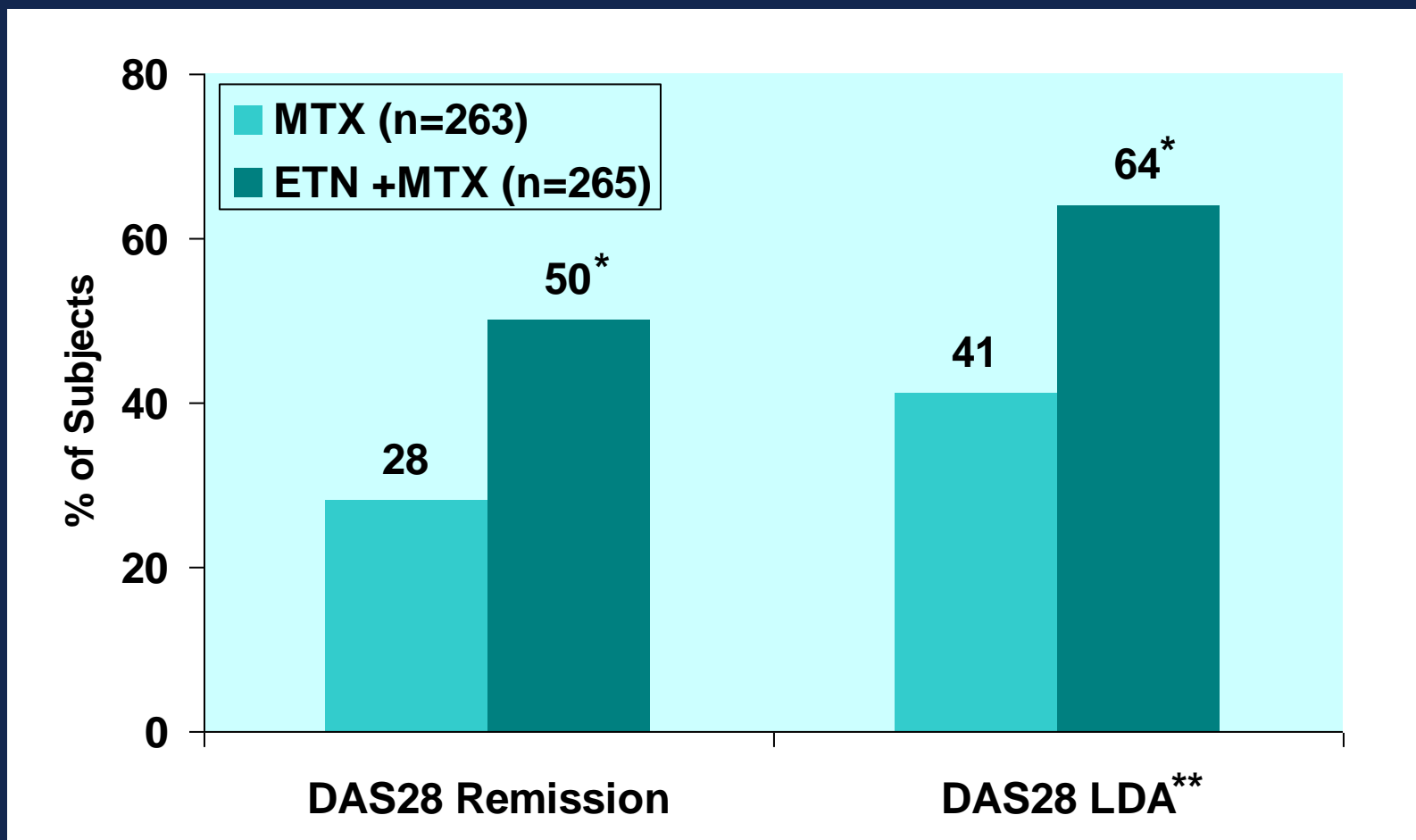
- 1) Proportion of patients with DAS28 remission at 52 weeks
- 2) Radiographic non-progression by modified total Sharp score (mTSS)

# COMET- Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis: Primary Endpoint - DAS28 Remission Over Time



More patients in ETN + MTX (80.7%) vs. MTX (70.5%) completed 52 wks largely because of lack of efficacy in MTX only arm.

# COMET: 1 Year Clinical Results for DAS28 Remission and Low Disease Activity



\* $p < 0.001$ , ANCOVA

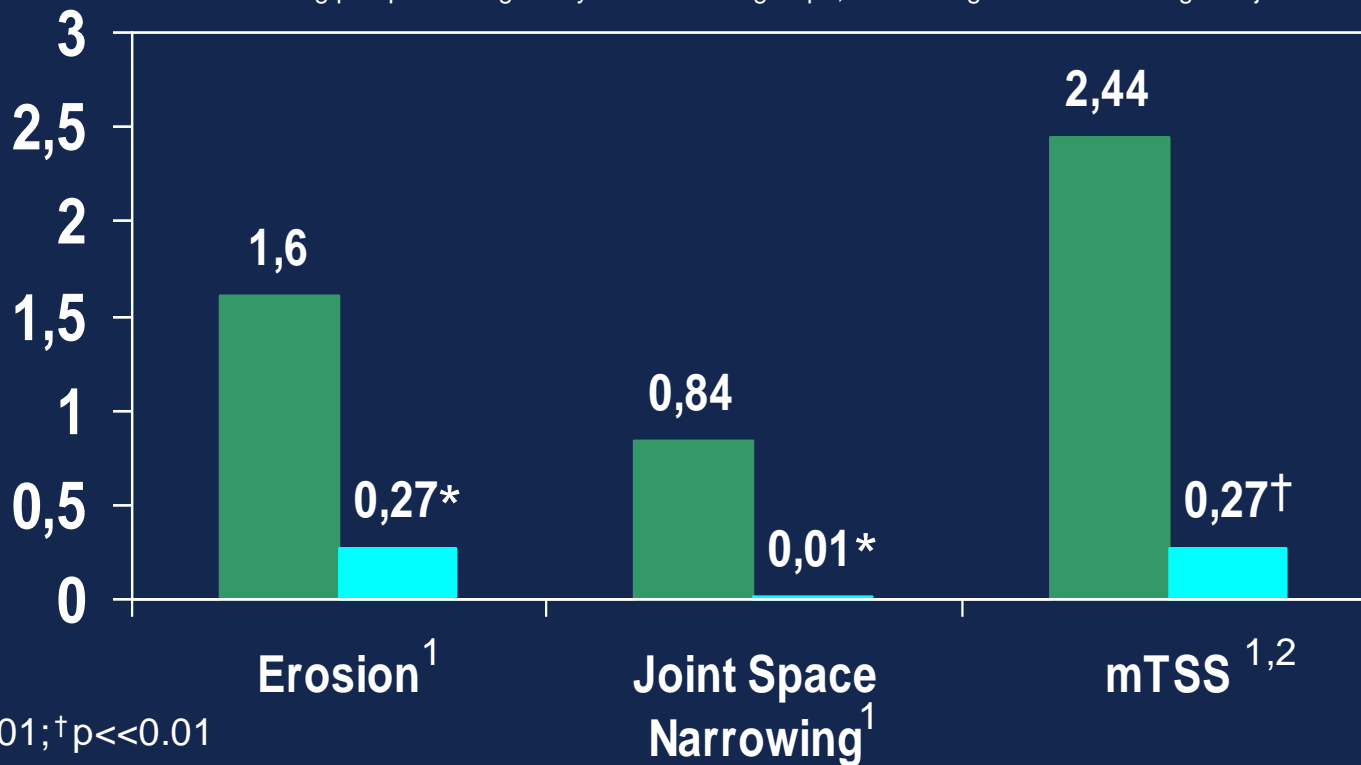
\*\* DAS28 LDA =  $DAS28 \leq 3.2$

# COMET: Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis: Primary Endpoint -Radiographic Outcomes

## Radiographic Outcomes at 52 Weeks

■ MTX<sup>†</sup> (n=230) ■ ETN<sup>†</sup>+ MTX (n=246)

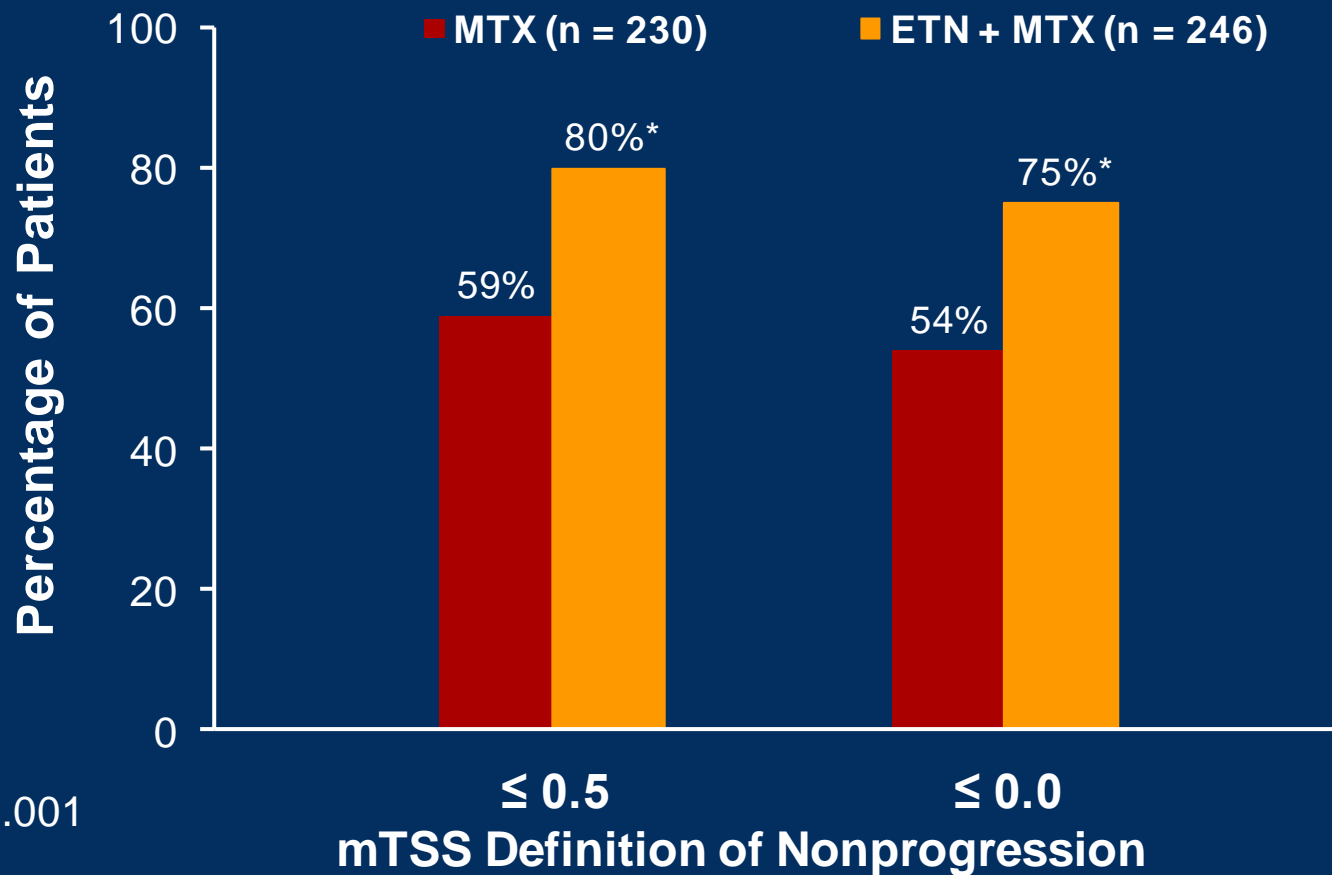
<sup>†</sup> MTX 7.5 mg po up to 20 mg/wk by 8 wks – both groups; ETN 50 mg OW as 2 x 25 mg sc injections



1. Emery P, et al. Ann Rheum Dis 2008;67(Suppl II):50 Abstract OP-0008 (EULAR 2008).

2. Emery P, et al. Lancet, 2008: e-Pub July 16, 2008.

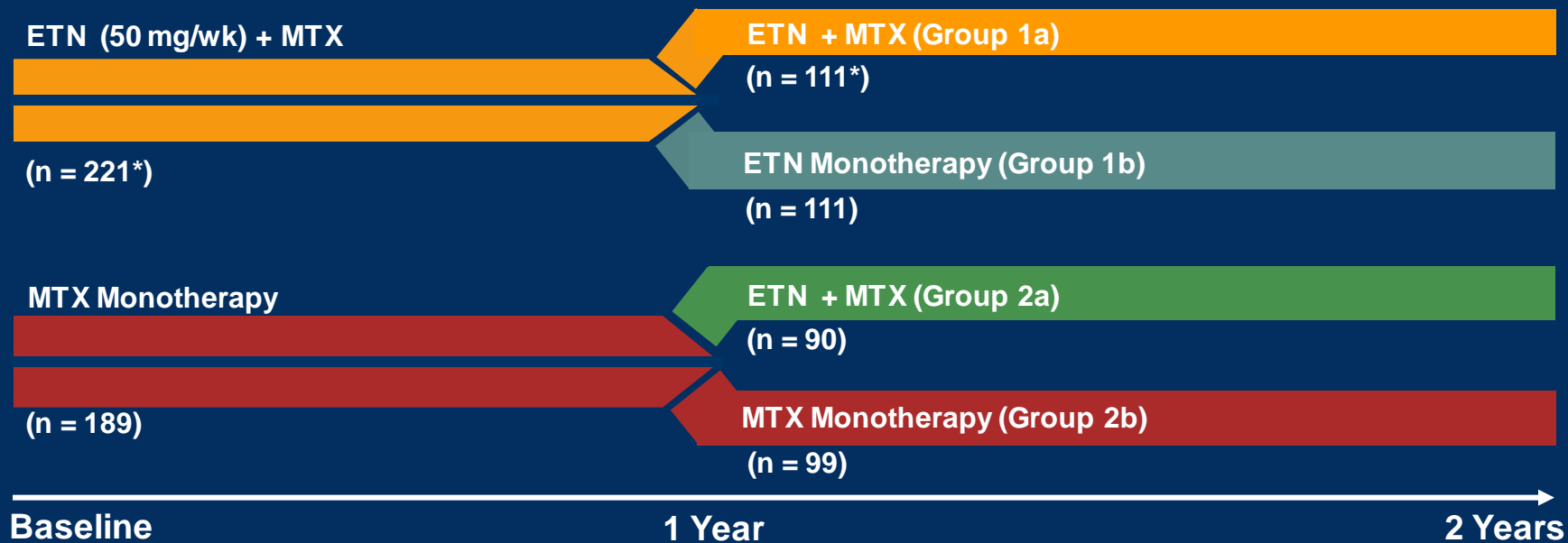
# Radiographic Non - progression Through Period 1: Initial Treatment Arms



\* $P < 0.001$

# Study Design: Double-Blind, Randomized Clinical Trial (N = 411)

## Period 2



**Period 2: (weeks 52 to 104) MTX dose†**

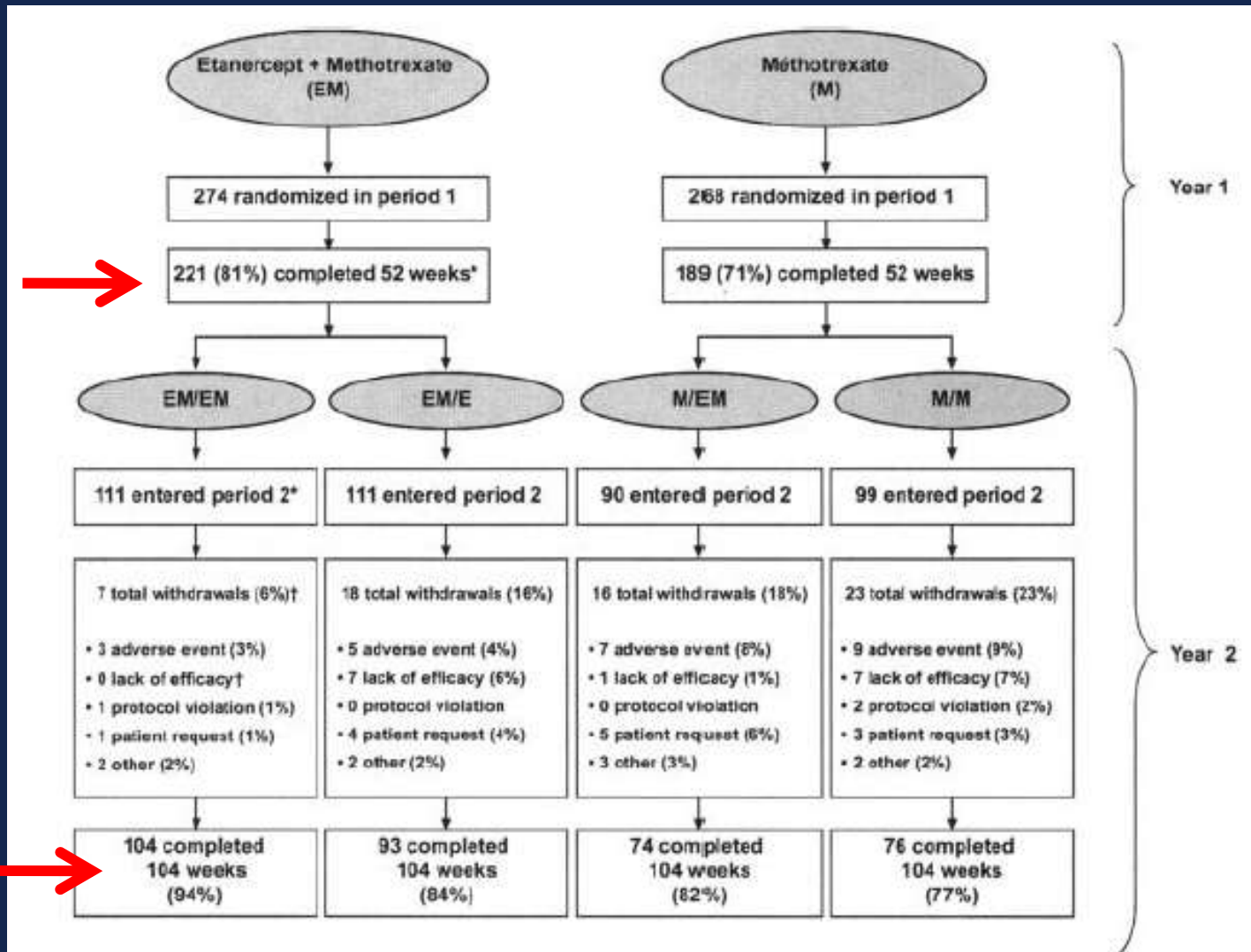
<i>ETN + MTX</i> → <i>ETN + MTX</i> : mean 16 mg/wk	<i>MTX</i> → <i>ETN + MTX</i> : mean 18 mg/wk
<i>ETN + MTX</i> → <i>ETN</i> : mean 16 mg/wk	<i>MTX</i> → <i>MTX</i> : mean 18 mg/wk

Patients were randomized at baseline visit equally into 4 groups: Group 1a, ETN + MTX in periods 1 and 2; Group 1b, ETN + MTX in period 1 and ETN in period 2; Group 2a, MTX alone in period 1 and ETN + MTX in period 2; Group 2b; MTX in periods 1 and 2

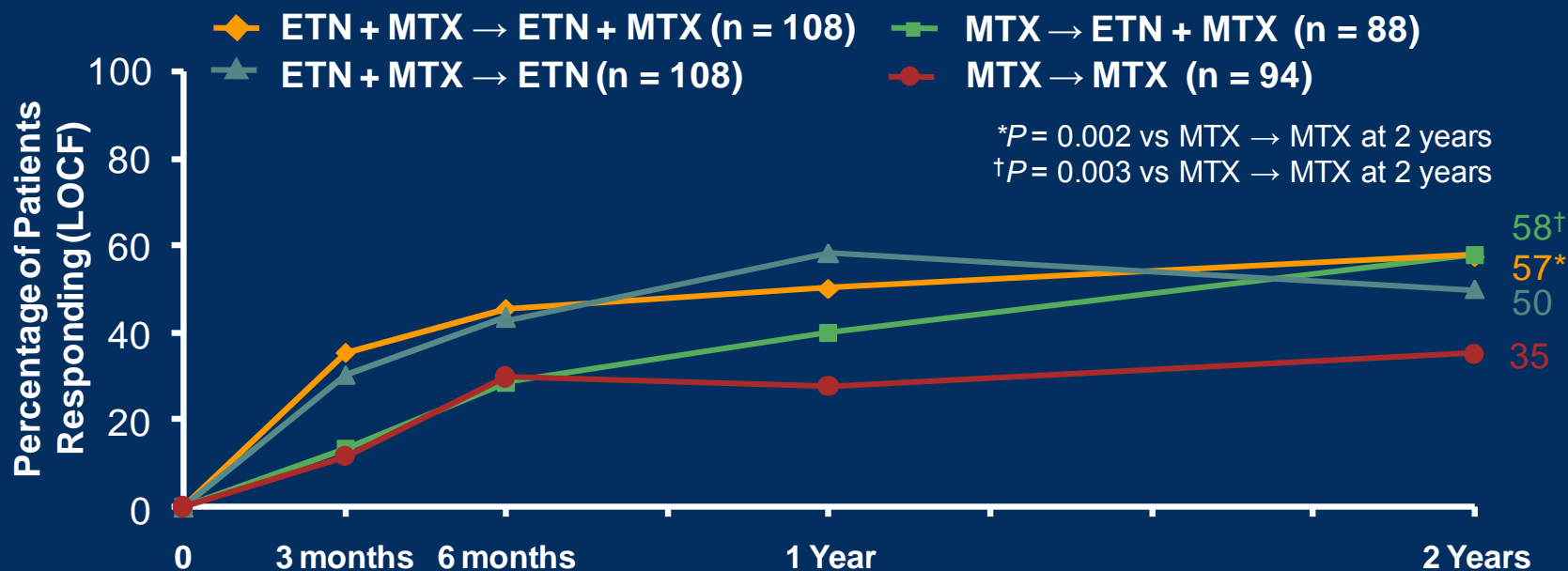
\*1 subject discontinued at final period 1 visit but received 1 dose of study drug in period 2 (included in period 2 population)  
 †ETN+MTX→ETN patients had MTX titrated down in 2-week intervals; mean doses are for weeks 1-4 before complete discontinuation

1. Emery P, et al. Presented at: EULAR; June 10-13, 2009; Copenhagen, Denmark. Abstract and oral presentation OP-0149.  
 2. Data on file, Pfizer Inc.

# Patient disposition at Y1 and Y2



# DAS 28 Clinical Remission\* Through Period 2



Period 2 DAS 28 NRI Based on Period 1 Baseline (N = 528)	3 months	6 months	Year 1	Year 2
ETN + MTX → ETN + MTX (n = 131) <sup>‡§</sup>	32%	40%	41%	45%
MTX → MTX (n = 130)	11%	23%	23%	22%
ETN + MTX → ETN (n = 134)	27%	40%	50%	37%
MTX → ETN + MTX (n = 133)	12%	22%	27%	36%

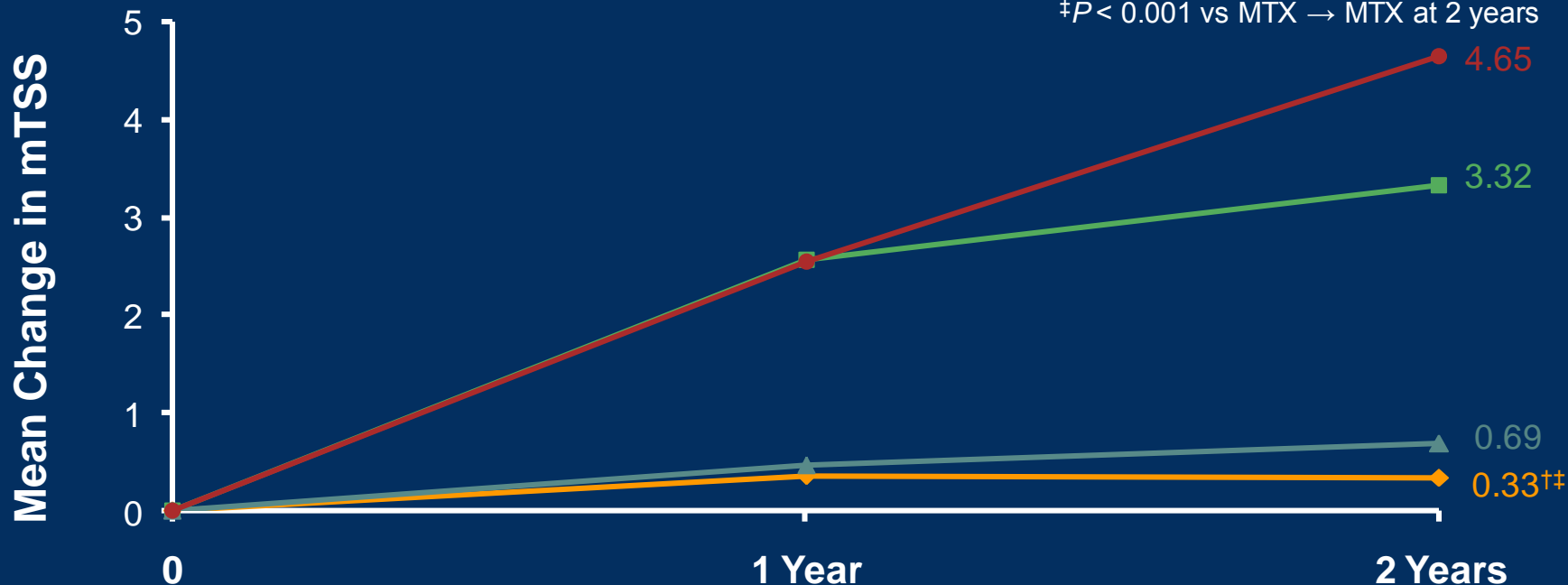
<sup>‡</sup>P ≤ 0.005 vs MTX → MTX at all time points except week 36 (P = 0.006); <sup>§</sup>P ≤ 0.05 vs MTX → ETN + MTX at all time points except week 80 (P = 0.099) and week 104 (P = 0.168); P = 0.015 vs MTX → MTX at week 104

<sup>\*</sup>In this study, a modified DAS (DAS 28) was also utilized based on the 28-joint count (tender 28 and swollen 28) rather than 44 joints. Clinical remission is defined as DAS 28 < 2.6 units

# Change in mTSS Through Period 2

◆ ETN + MTX → ETN + MTX (n = 99)    ■ MTX → ETN + MTX (n = 79)  
▲ ETN + MTX → ETN (n = 99)    ● MTX → MTX (n = 83\*)

†P < 0.001 vs MTX → ETN + MTX at 2 years  
 ‡P < 0.001 vs MTX → MTX at 2 years

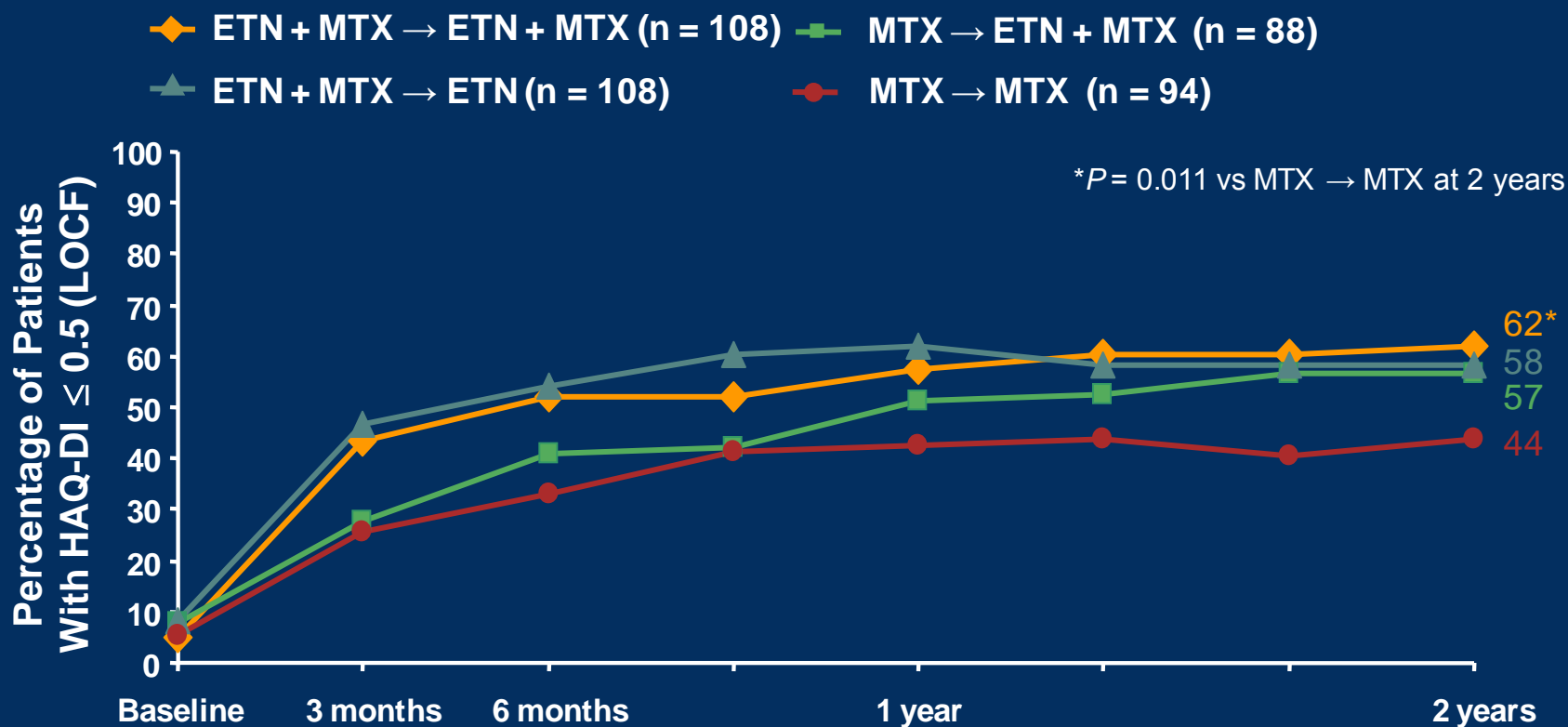


- The radiographic ITT population included patients who received at least 1 dose of study drug and provided data at baseline, period 1, and during period 2 or early termination visit
- The radiographic ITT population evaluated for radiographic progression (n = 361) differed from the period 2 ITT population (n = 411) due to patients discontinuing the trial or radiographs that were either unreadable or not obtained

\*n = 84 at year 2

1. Emery P, et al. Presented at: EULAR; June 10-13, 2009; Copenhagen, Denmark. Abstract and oral presentation OP-0149. 2. Data on file, Pfizer Inc.

# Proportion of Subjects With Improvement in Physical Function Through Period 2



- LOCF data represents the mITT population (N = 398) who received study drug during period 2 and provided at least 1 post-baseline period 2 evaluation

# Safety Summary Through Period 1

	<b>MTX n = 268</b>	<b>ETN + MTX n = 274</b>
<b>Any AE, n (%)</b>	246 (91.8)	247 (90.2)
<b>Total infections, n (%)</b>	125 (46.6)	143 (52.2)
<b>SAEs, n (%)</b>	34 (12.7)	33 (12.0)
<b>Death, n (%)</b>	0 (0.0)	1 (0.4)*
<b>Malignancy, n (%)</b>	4 (1.5)	4 (1.5)
<b>Serious infection, n (%)</b>	8 (3.0)	5 (1.8)

\*Patient died from moderate to severe pneumonia

- There were no reported cases of tuberculosis, demyelinating disease, or lymphoma

SAEs = serious adverse events.

## Safety Summary: End of Period 1 to End of Period 2

	ETN + MTX → ETN + MTX (n = 111)	MTX → ETN + MTX (n = 90)	ETN + MTX → ETN (n = 111)	MTX → MTX (n = 99)	Total (N = 411)
All AEs, n (%)	91 (82.0)	71 (78.9)	89 (80.2)	79 (79.8)	330 (80.3)
All SAEs, n (%)	8 (7.2)	11 (12.2)	10 (9.0)	12 (12.1)	41 (10.0)
<b>SAEs of Interest</b>					
• Death, n (%)	0	0	0	1 (1.0)*	1 (0.2)*
• Malignancy, n (%)	0	5 (5.6)	1 (0.9)	3 (3.0)	9 (2.2)
• SIs, n (%)	1 (0.9)	1 (1.1)	2 (1.8)	2 (2.0)	6 (1.5)

\*Patient died who was diagnosed with pneumonia and adenocarcinoma of the lungs with metastasis

- Safety for period 2 was analyzed using the ITT population (N = 411), which was defined as all patients who received at least one dose of study medication during period 2.
- SAEs of interest not necessarily the sum of all SAEs (all types of SAEs that occurred are not listed as subcategories)
- A patient may also have reported more than 1 different SAE
- There were no reported cases of tuberculosis, demyelinating disease, or lymphoma

SIs = serious infections.

# Messages

- Early combination of ETN + MTX is superior but cannot be used.
- Realise that MTX alone has limitations:
  - < 30% remission and < 50% low disease activity
- Decision needs to be made at most 6 months after starting MTX
- Benefit of early combination is maintained even when ETN is stopped: Clinical, X-rays, Function.

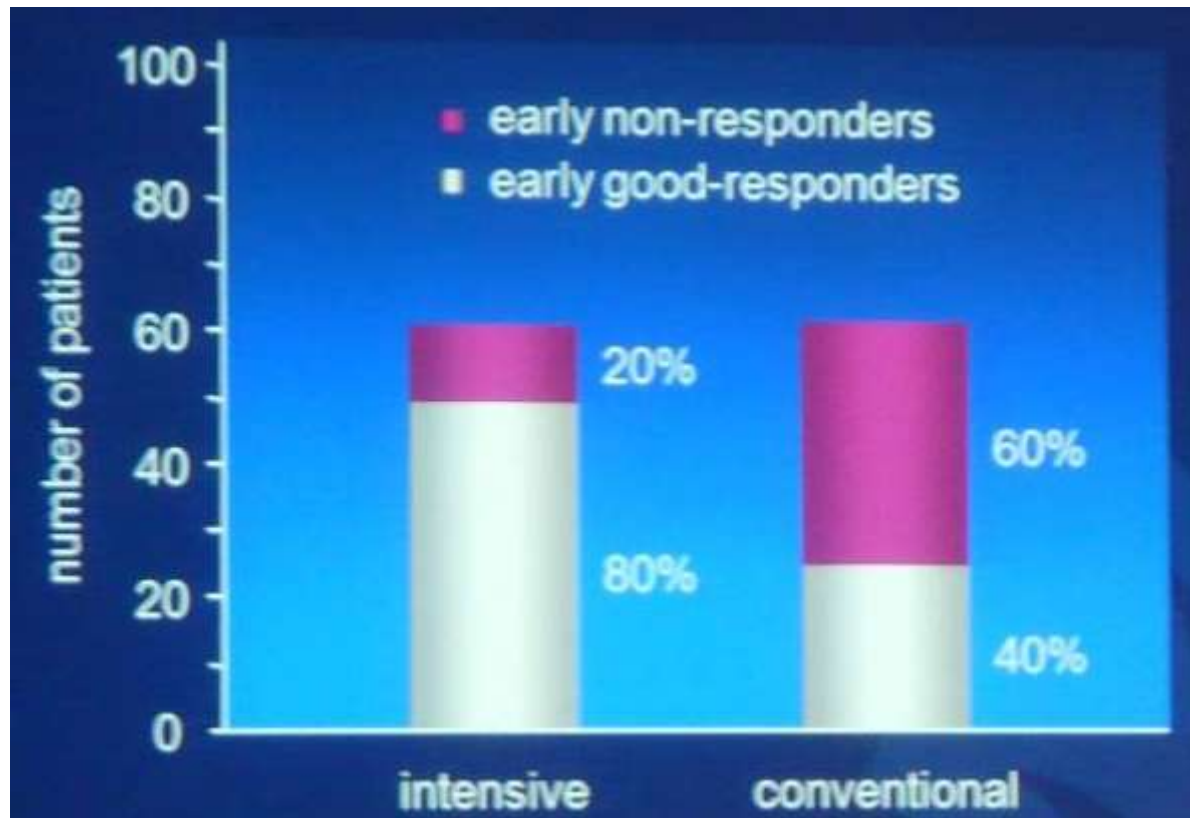
# IMPORTANCE OF EARLY GOOD RESPONSE

**A Better Long-Term Clinical Course and Less Radiographic Joint Damage Can Be Predicted by an Early Good Response to Therapy in RA Patients**

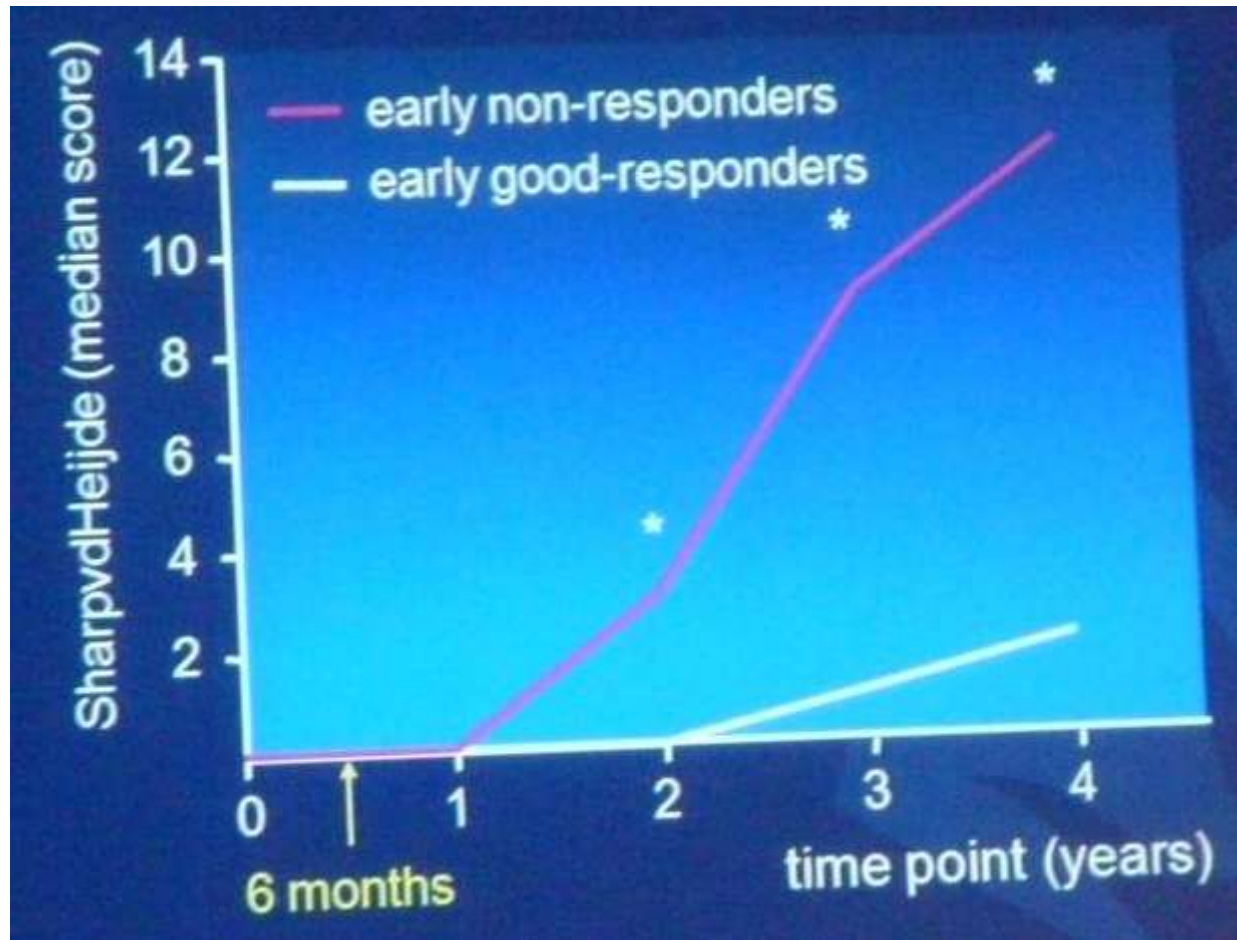
# CAMERA Study Population

- 299 patients in total
- Intensive treatment strategy MTX (n=151)
  - Monthly
  - Computer decision model
- Conventional treatment strategy MTX (n=148)
  - 3-monthly
  - Usual care based on SJC

# 6 Months Good Responders vs. Non-Responders by Treatment Group



# Results – Disease Severity



# Take-Home Messages

- Early responders had better outcomes
  - Clinical
  - Radiographic
  - Reduced requirement of MTX (data not shown)
- Target-steered therapy allowed a larger number of early responders
- It does not matter what type of treatment is used to achieve an early response, only that an early response is achieved

# Application in Daily Practice

- See the patient as early as possible
  - Referral process
  - Early synovitis clinics
- Systematically collect joint count/composite index
  - Paper/electronic records
- Be convinced that “adherence” to the proposed recommendations is of benefit for the patient
  - Tight control

# Treat to Target

## Application in daily practice

**Stable Remission of Early Rheumatoid Arthritis During Tight Control and Treatment Per Protocol Is Achieved in Ninety Percent on either Methotrexate Alone or in Combination with Other DMARDS**

# Methods

- Prospective observational cohort study in daily clinical practice
- 330 consecutive patients with a clinical diagnosis of RA (duration of arthritis symptoms  $\leq 1$  years)
- Goal of treatment: remission, defined as DAS28  $< 2.6$
- Treatment per protocol, including DMARDs and biologicals
- Tight control: medication was adjusted when DAS28  $\geq 2.6$

# Treatment Strategy

Week 0	MTX 15 mg/week
Week 8	MTX 25 mg/week
Week 12	MTX 25 mg/week + SSZ 2 g/day
Week 20	MTX 25 mg/week + SSZ 3 g/day
Week 24	MTX 25 mg/week + ADA 40 mg/2 weeks
Week 36	MTX 25 mg/week + ADA 40 mg/week
Weeks 48-52	MTX 25 mg/week + ETN 50 mg/week
1 year + 3 months	MTX 25 mg/week + IFX 3 mg/kg/8 weeks
1 year + 6 months	MTX 25 mg/week + IFX 40 mg/4 weeks

# Results

- 67% of patients achieved remission at  $\geq 1$  visit
  - Median time to 1<sup>st</sup> remission was 25 weeks
- Stable remission was seen in 40.4% of these patients
- In the majority of patients not achieving stable remission, fluctuations between remission and low disease activity (DAS28 2.6-3.2) were rather common

<b>Medication at time of achieving stable remission</b>	<b>40.4%</b>
MTX	50.0%
MTX+SSZ	24.3%
MTX + prednisolone	13.5%
MTX+ADA	4.1%
No medication	4.1%
Other	4.1%

# **Outcome Measures to Assess Remission**

ARTHRITIS & RHEUMATISM

Vol. 63, No. 3, March 2011, pp 573–586

DOI 10.1002/art.30129

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# Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology  
[www.arthritisrheum.org](http://www.arthritisrheum.org) and [wileyonlinelibrary.com](http://wileyonlinelibrary.com)

American College of Rheumatology/European League Against  
Rheumatism Provisional Definition of Remission in  
Rheumatoid Arthritis for Clinical Trials

# Background: Definitions of Remission

*Remission should have predictive validity and be able to predict later good outcome*

- Good x-ray outcome: change  $\leq 0$  in modified Sharp or Sharp-van der Heijde score
- Good function outcome: change  $\leq 0$  in HAQ and HAQ score  $\leq 5$  throughout 2<sup>nd</sup> year



# Results: Predictive Validity of Candidate Remission Definitions for Later Good X-ray and HAQ Outcomes – Indices

	Percent in remission with good outcome	Percent not in remission with good outcome	Positive likelihood ratio	p value
TJC28, SJC28, CRP + PtGA ≤1	66%	17%	7.2	<0.0001
Indices				
DAS28 <2.6	38%	18%	2.2	0.01
DAS28 <2.0	56%	20%	4.5	0.01
SDAI ≤3.3	56%	17%	4.8	<0.0001



**Table 6.** American College of Rheumatology/European League Against Rheumatism definitions of remission in rheumatoid arthritis clinical trials\*

*Boolean-based definition:*

At any time point, patient must satisfy all of the following:

Tender joint count  $\leq 1$ †

Swollen joint count  $\leq 1$ †

C-reactive protein  $\leq 1$  mg/dl

Patient global assessment  $\leq 1$  (on a 0–10 scale)‡

*Index-based definition:*

At any time point, patient must have a

Simplified Disease Activity Index score of  $\leq 3.3$ §

Definitions without CRP (for clinical practice)

TJC28, SJC28, PhGA, PtGA $\leq 1$	68 (21/31)	17 (53/321)	7.9 (3.9–16.0)	<0.0001
TJC28, SJC28, PtGA $\leq 1$	66 (23/35)	16 (51/318)	7.2 (3.8–13.9)	<0.0001
CDAI $\leq 2.8$ §	63 (22/35)	16 (52/317)	6.4 (3.4–12.0)	<0.0001



# Assessment Instruments

## ACR Recommendations

Saag et al. *Arthritis Rheum* 2008;59:762

Table 1. Instruments used to measure rheumatoid arthritis disease activity\*

Instrument (ref.)	Score range	Thresholds of disease activity		
		Low	Moderate	High
Disease Activity Score in 28 joints (253)	0–9.4	≤3.2	>3.2 and ≤5.1	>5.1
Simplified Disease Activity Index (103)	0.1–86.0	≤11	>11 and ≤26	>26
Clinical Disease Activity Index (103)	0–76.0	≤10	>10 and ≤22	>22
Rheumatoid Arthritis Disease Activity Index (254)	0–10	<2.2	≥2.2 and ≤4.9	>4.9†
PAS or PASII (14)	0–10	<1.9	≥1.9 and ≤5.3	>5.3
Routine Assessment Patient Index Data (255)	0–30	<6	≥6 and ≤12	>12

\* Methods for calculating various instrument scores are shown in Appendix E (available at the *Arthritis Care & Research* Web site at <http://www.interscience.wiley.com/jpages/0004-3591:1/suppmat/index.html>). PAS = Patient Activity Scale.

† Median.

**Table III.** Cutoff values for different disease activity states.

Index	Disease activity state	Original definition	Newly proposed definition
SDAI	Remission	$\leq 5$	$\leq 3.3$
	Low disease activity	$\leq 20$	$\leq 11$
	Moderate disease activity	$\leq 40$	$\leq 26$
	High disease activity	$> 40$	$> 26$
CDAI	Remission	-	$\leq 2.8$
	Low disease activity	-	$\leq 10$
	Moderate disease activity	-	$\leq 22$
	High disease activity	-	$> 22$
DAS28	Remission	$\leq 2.6$	$\leq 2.4$
	Low disease activity	$\leq 3.2$	$\leq 3.6$
	Moderate disease activity	$\leq 5.1$	$\leq 5.5$
	High disease activity	$> 5.1$	$> 5.5$

## EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs

Josef S Smolen,<sup>1,2</sup> Robert Landewé,<sup>3</sup> Ferdinand C Breedveld,<sup>4</sup> Maxime Dougados,<sup>5</sup> Paul Emery,<sup>6</sup> Cecile Gaujoux-Viala,<sup>5,7</sup> Simone Gorter,<sup>3</sup> Rachel Knevel,<sup>4</sup> Jackie Nam,<sup>6</sup> Monika Schoels,<sup>2</sup> Daniel Aletaha,<sup>1</sup> Maya Buch,<sup>6</sup> Laure Gossec,<sup>5</sup> Tom Huizinga,<sup>4</sup> Johannes W J W Bijlsma,<sup>8</sup> Gerd Burmester,<sup>9</sup> Bernard Combe,<sup>10</sup> Maurizio Cutolo,<sup>11</sup> Cem Gabay,<sup>12</sup> Juan Gomez-Reino,<sup>13</sup> Marios Kouloumas,<sup>14</sup> Tore K Kvien,<sup>15</sup> Emilio Martin-Mola,<sup>16</sup> Iain McInnes,<sup>17</sup> Karel Pavelka,<sup>18</sup> Piet van Riel,<sup>19</sup> Marieke Scholte,<sup>14</sup> David L Scott,<sup>20</sup> Tuulikki Sokka,<sup>21</sup> Guido Valesini,<sup>22</sup> Ronald van Vollenhoven,<sup>23</sup> Kevin L Winthrop,<sup>24</sup> John Wong,<sup>25</sup> Angela Zink,<sup>26</sup> Désirée van der Heijde<sup>4</sup> *Ann Rheum Dis* 2010;**69**:964–975.

# EULAR Recommendations: Start Soon

1. Therapy with synthetic DMARDs should be started as soon as the diagnosis of RA is made
  - → Early diagnosis
  - → Consequences of delayed DMARD start

# How Do We Define RA?

JOINTS (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
SEROLOGY (0-3)	
Negative RF <u>AND</u> negative ACPA	0
Low positive RF <u>OR</u> low positive ACPA	2
High positive RF <u>OR</u> high positive ACPA	3
SYMPTOM DURATION (0-1)	
<6 weeks	0
>=6 weeks	1
ACUTE PHASE REACTANTS (0-1)	
Normal CRP <u>AND</u> normal ESR	0
Abnormal CRP <u>OR</u> abnormal ESR	1

# EULAR Recommendations: MTX Is the Anchor Drug

3. MTX should be part of the first treatment strategy in patients with active RA
  - MTX is today's anchor drug by virtue of
    - Large array of data
    - Unsurpassed by other DMARDs or TNF-inhibitor monotherapies
    - Synergy with biological DMARDs

# EULAR Recommendations: Glucocorticoids

6. Glucocorticoids at low to moderately high doses added to synthetic DMARD mono- or combination-therapy provide benefit as initial short term treatment, but should be tapered as rapidly as clinically feasible

# EULAR Recommendations: First Biological

8. In patients with insufficient response to MTX or other synthetic DMARDs, a biological DMARD should be started; current practice is to start a TNF inhibitor plus MTX
- Why are TNFi currently employed first?
    - Largest, long-term experience/safety data
    - Expert opinion/statement which may change with time
    - Statement does not preclude use of other biologics
  - Why combination with MTX?
    - Superior efficacy compared with monotherapy for all biologics
    - Note: Tocilizumab monotherapy has shown superiority to MTX monotherapy

# EULAR Recommendations: Subsequent Biologicals

9. Patients who failed a first TNF inhibitor therapy should receive another TNF inhibitor, abatacept, rituximab or tocilizumab
  - Phase III trials for ABT, RTX, TCZ, GLM
  - Registry data for 3 TNF-inhibitors and RTX

# Insights into the safety of the anti-TNF agents

# Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Review)

Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E, Tugwell P



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# Biologics for RA: An overview of the Cochrane Database

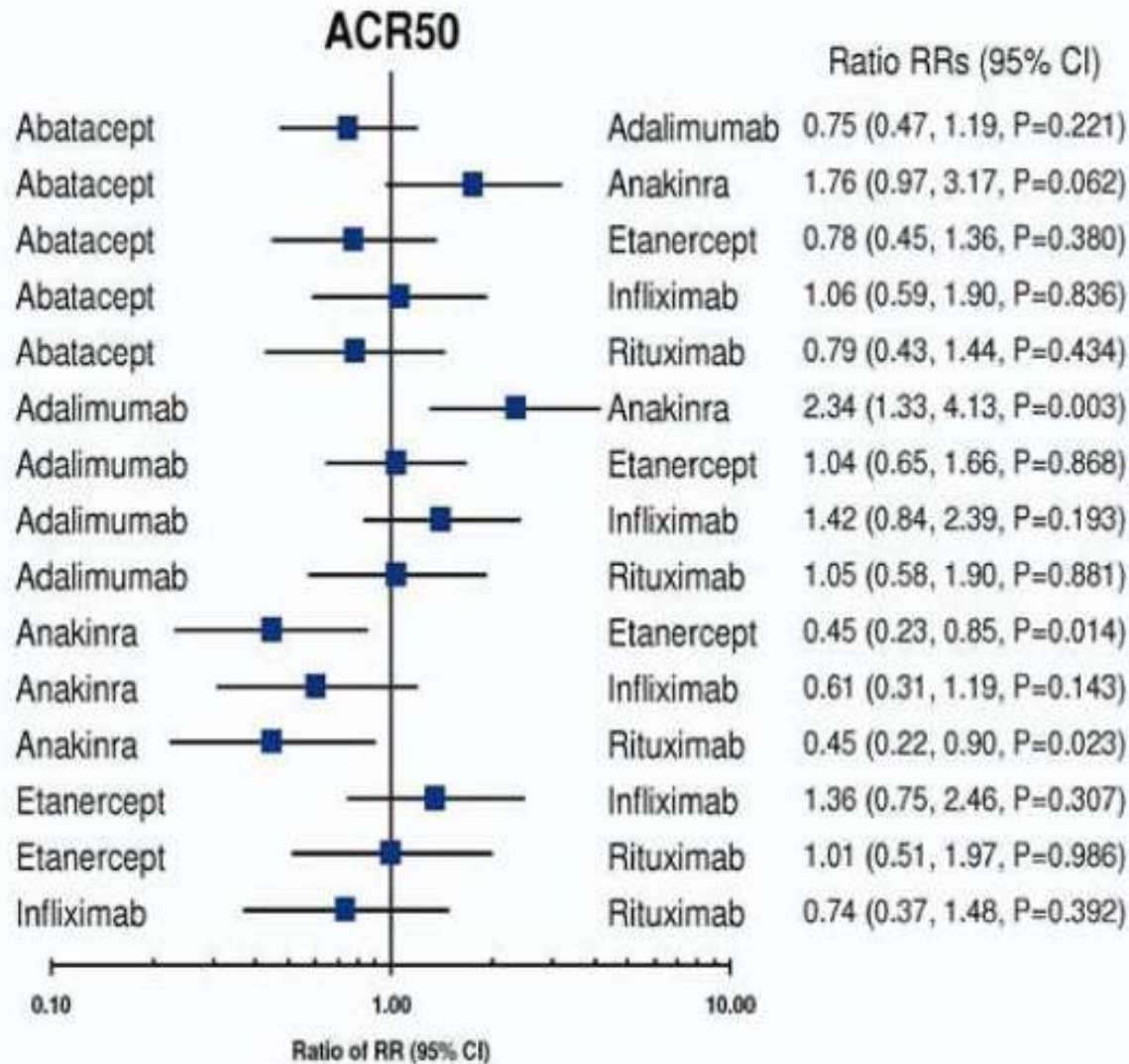
## Purpose

To directly compare efficacy and safety of ABA, ADA, ANA, ETN, IFX, and RTX in RA patients and calculate the NNT for benefit and harm

# Biologics for RA: An Overview of the Cochrane Database - Methods

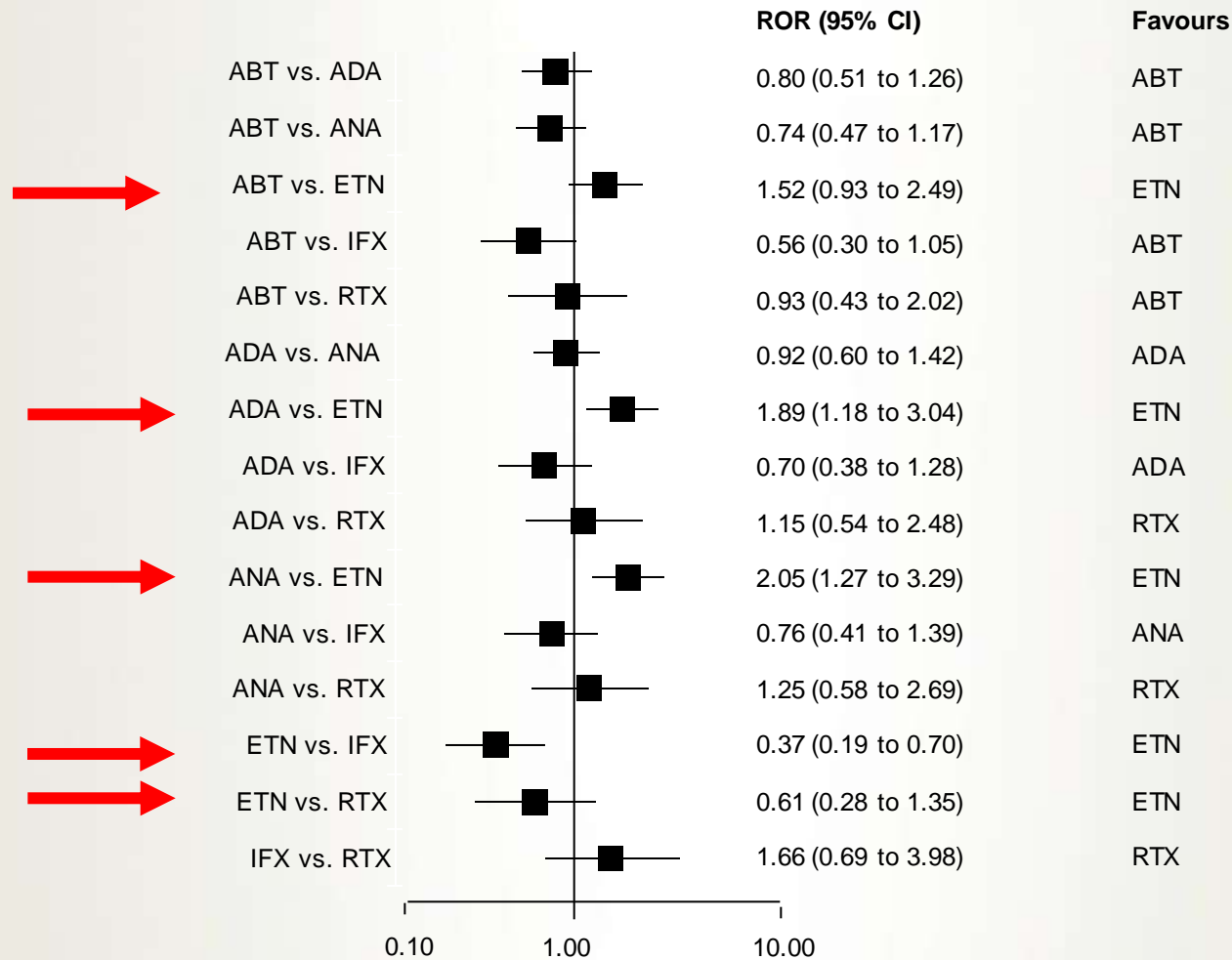
- Primary efficacy outcome is ACR 50
- Number of withdrawals due to AE was the primary Safety outcome
- 7 studies on ABA, 8 on ADA, 5 on ANA, 5 on ETN, 4 on IFX and 3 on RTX

# Indirect comparison of RCTs in RA - Efficacy



# Indirect comparison of RCTs in RA

## - Safety

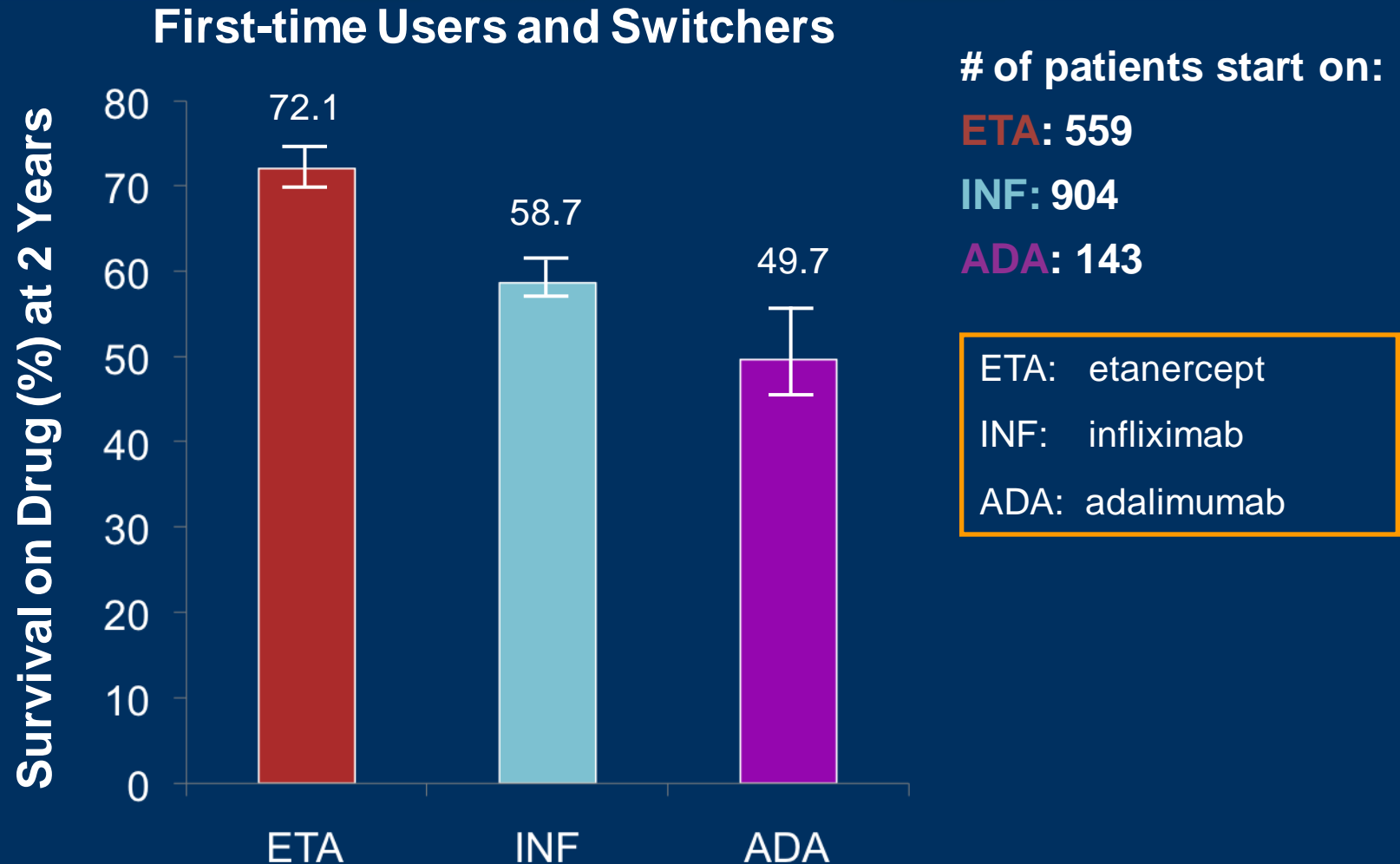


**Retention of Patients on  
Anti-TNF Therapies:  
European Biologics Registry Data**

# Long-term Retention in Biologic Registries

- Drug survival can be taken as a sensible indicator of its effectiveness in the clinical setting
- Surrogate marker for effectiveness
  - Clinical response
  - Tolerability/absence of side effects
  - Patient and physician satisfaction

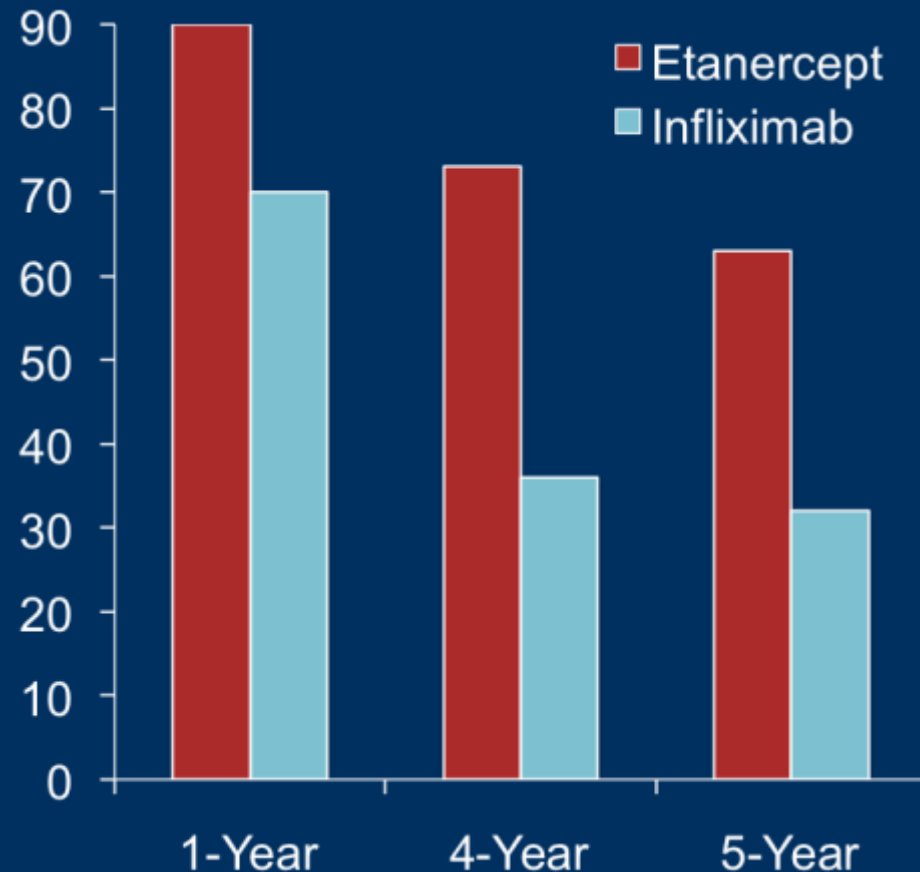
# Survival on Anti-TNF- $\alpha$ Therapy: STURE Registry at 2 Years



# Adherence to Therapy Over 5 Years

## Infliximab and Etanercept with Concomitant Methotrexate

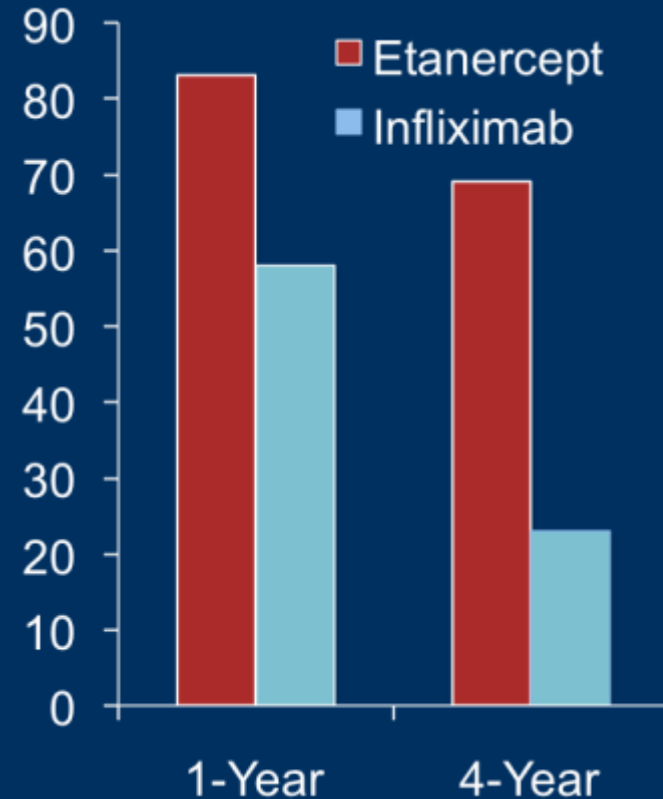
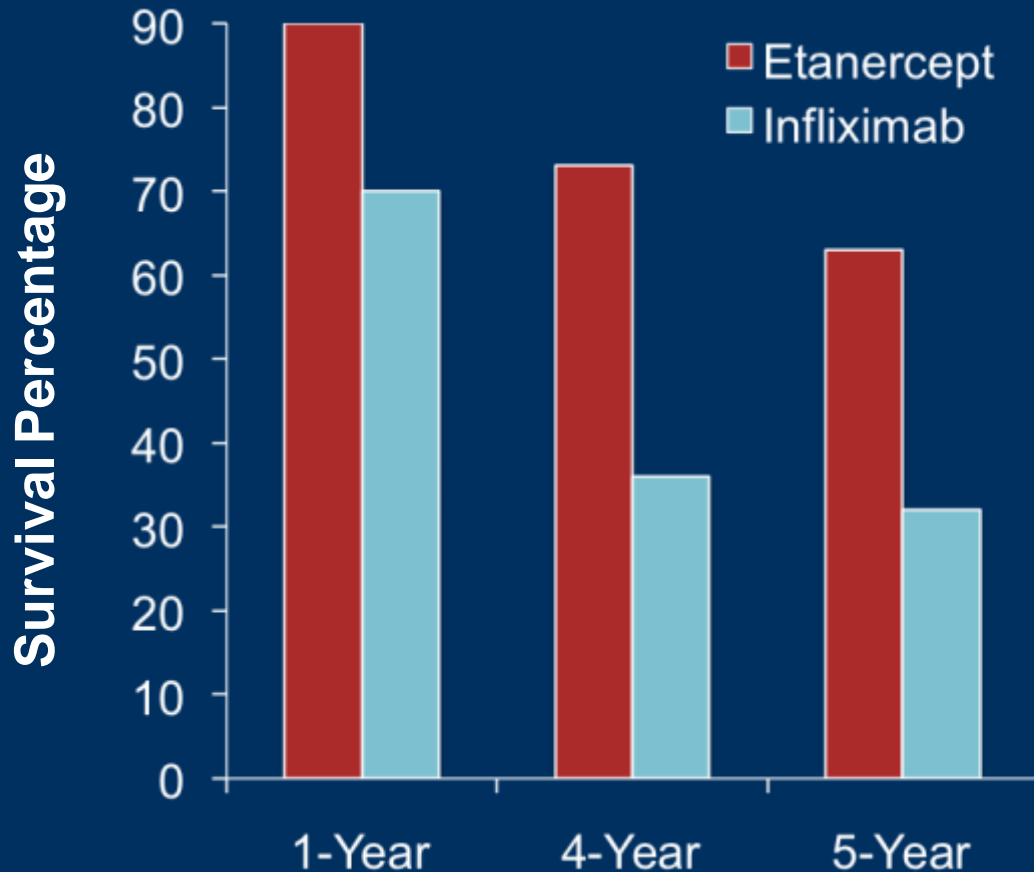
### Biologic-naïve RA Patients



# Adherence to Therapy

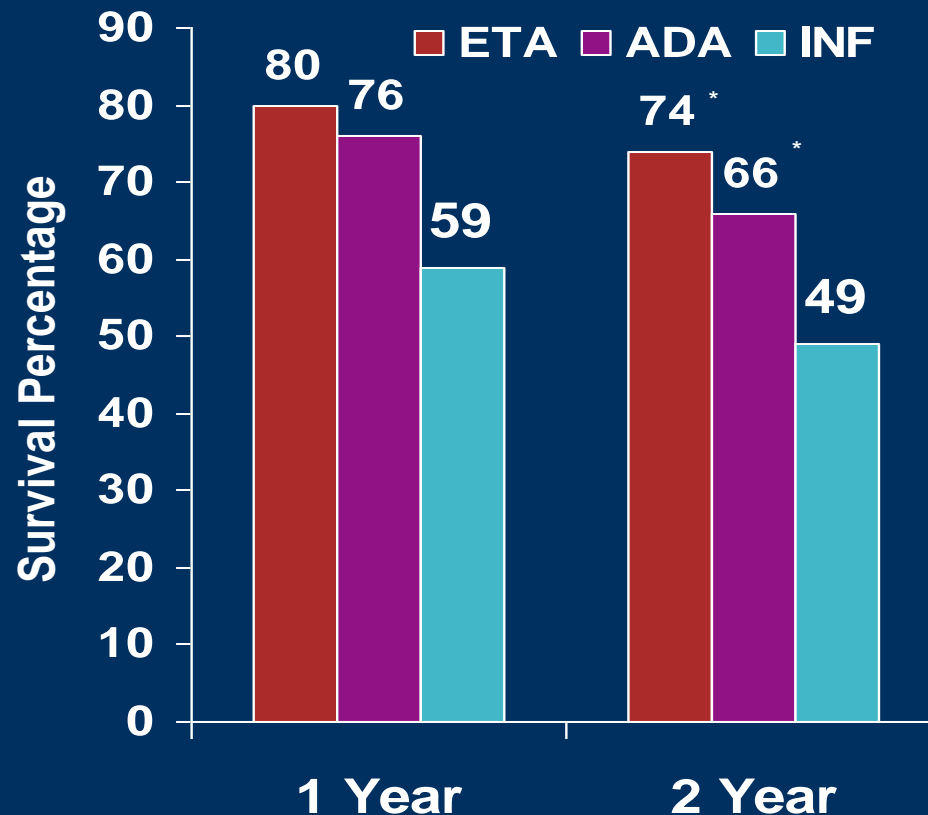
## Infliximab and Etanercept with Concomitant Methotrexate or Other DMARDs

### Biologic-naïve RA Patients



# Drug Survival of Anti-TNF Therapy in RA Patients in Daily Clinical Practice: DREAM Registry at 2 Years

## Biologic-naïve RA Patients

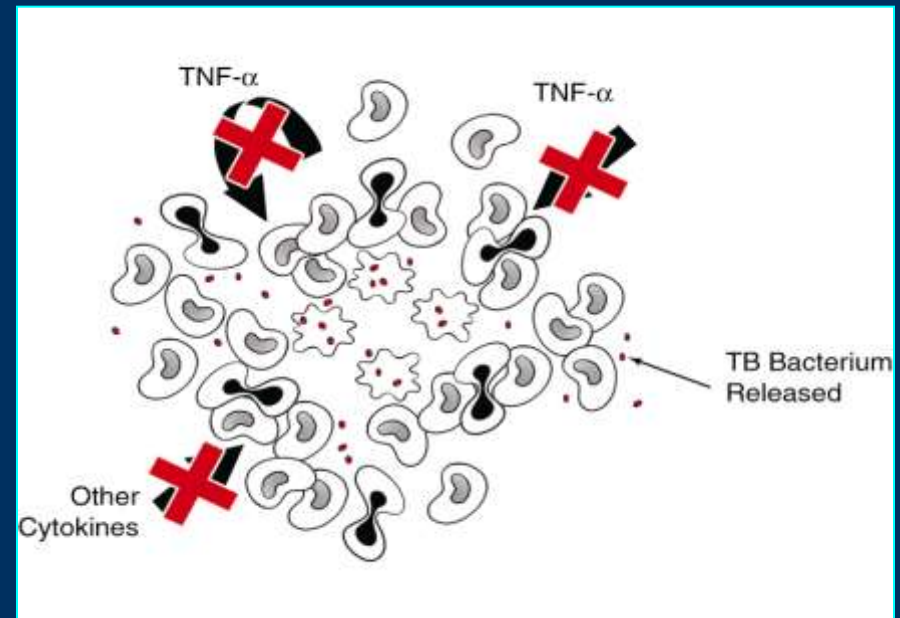
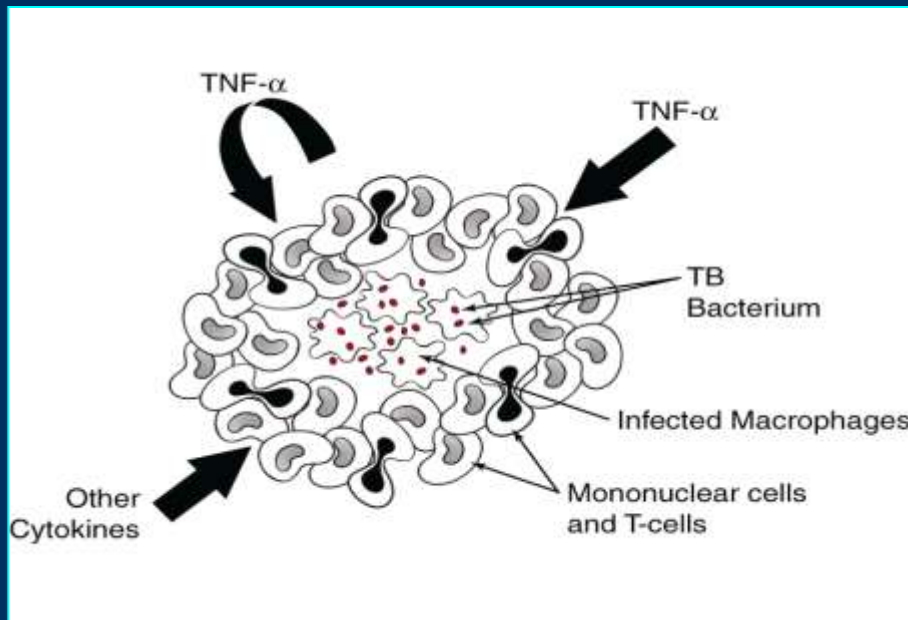


\*Drug survival of INF was significantly lower compared with: ADA (log rank  $p = 0.0019$ ) and ETA (log rank  $p = 0.0001$ ). ADA and ETA showed an equal survival percentage (log rank  $p = 0.039$ )

# Tuberculosis

# TNF- $\alpha$ Plays a Crucial, Positive Role in Host Defense During Primary TB Infection and in Maintaining TB Latency

TNF necessary for granuloma homeostasis and especially membrane TNF on monocytes and lymphocytes



# *Mycobacterium tuberculosis* in Rheumatoid Arthritis Patients with Tumour Necrosis Factor Antagonists, Post Approval

		Etanercept*	Infliximab†
<b># of Patients Treated</b>		230,000	277,000
<b>Exposure (patient-years)</b>		423,000	466,000
<b>Use (%)</b>	USA	90	64
	EU/Norway	10	36
<b>M. TB reports</b>		38	242
<b>Geography</b>	USA	26	90
	Outside USA	1	152
<b>Time to onset</b>		Median 11.2 months	By 3 infusions: 60% By 7 months: 97%
<b>Characteristics (%)</b>	Extrapulmonary	34	30-45
	Miliary	16	

EU = European Union; M. TB = *Mycobacterium tuberculosis*

\*As of December 2003

†As of October 2003

# Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: Results from the British Society for Rheumatology Biologics Register (BSRBR)

W G Dixon, K L Hyrich, K D Watson, M Lunt, J Galloway, A Ustianowski and D P M Symmons

*Ann Rheum Dis* published online 22 Oct 2009;

**Table 2.** Numbers and rates of incident tuberculosis, switchers included

Number of patients ever received the drug	DMARD n=3232	All Anti-TNF n=10712	ETA n=5521	INF n=3718	ADA n=4857
<b>On drug*</b>					
Person years	7345	28447	12744	8069	7634
Cases of TB	0	27	5	11	11
Rate / 100,000 pyrs (95% CI)	0	95 (63, 138)	39 (13, 92)	136 (68, 244)	144 (72, 258)
IRR, adjusted for age, gender and entry year (95% CI)			Referent	3.1 (1.0, 9.5)	4.2 (1.4, 12.4)
<b>Most recent drug*</b>					
Person years	7345	34025	15070	9730	9224
Cases of TB	0	40	8	12	20
Rate / 100,000 pyrs (95% CI)	0	118 (84, 160)	53 (23,105)	123 (64,215)	217 (132,335)
IRR, adjusted for age, gender and entry year (95% CI)			Referent	2.2 (0.9, 5.8)	4.2 (1.8, 9.9)

Patients could switch between anti-TNF therapies, but all TB cases were attributable to 1 drug only

\*The two models of risk attribution are illustrated in Figure 1

# Risk for Tuberculosis Following Treatment of Rheumatoid Arthritis with Anti-TNF Therapy

## The Swedish Experience 1998-2008

- 3 groups tracked in TB register

- 471,047 general population

- 161 cases TB
- **Crude rate 5/100,00**

- 67,705 biologic-naïve RA patients

- 64 cases TB
- Crude rate 20/100,000
- **RR to general population = 3.2 (95% CI 2.4-4.3)**

- 6,603 RA patients on TNFi
  - 25 cases TB
  - All on Rx or within 3 months
  - Median duration on Rx: 20 months
  - Crude rate 77/100,000
  - **RR to biologic naïve = 4.3 (95% CI 2.6-7.3)**
  - **RR to general population = 15 (95% CI 9.6-24)**
  - ETN: 5 cases, RR=2.55 (95% CI 2.7-11)
  - ADA: 17 cases, RR=3.1 (95% CI 1.1-8)
  - IFX: 5 cases, RR=5.2 (95% CI 1.1-8)

# *Mycobacterium tuberculosis* in Clinical Trials with Tumour Necrosis Factor Antagonists

			Adalimumab‡	
	Etanercept*	Infliximab†	Prescreen	Postscreen
# of pts treated	3,839	1,298	9,460	
Exposure (pt-yrs)	8,336	2,458	534	9,360
# of TB cases	0	5	7	14
<b>Geography</b>				
USA		NA		3
Outside USA		NA	7	11
<b>Characteristics:</b>				
Time to onset				3-8 mo
Extrapulmonary				NA

NA = not available; TB = tuberculosis

\*Includes psoriatic arthritis and juvenile rheumatoid arthritis (as of Dec. 2003).

† Includes ASPIRE Trial (as of October 2003).

‡ Includes pivotal extension trials, ACT and REACT (as of Dec. 2003).

# Screening for TB

- Chest X-ray
- PPD (5 units): 5 mm of induration
- If active TB
  - Do not use antiTNF
  - Treat TB as required
- If latent TB
  - Give prophylaxis as per local guidelines (INH for 9 months)
  - Start anti-TNF from 0 to 4 weeks after initiation of INH

# Opportunistic infections

# Opportunistic Infections With TNF Antagonists: Post-Approval

	Etanercept	Infliximab*
# Treated	>150,000	198,235
Pt-yrs exposure	>230,000	227,559
- Pneumocystis carinii	4	14
- Histoplasmosis*	1	18
- Listeriosis	3	16
- Atypical mycobacteria	10	23
- Aspergillus	5	14
- Cytomegalovirus	5	9
- Nocardia	2	?
- Systemic Candidiasis	7	4
- Coccidioidomycosis*	-	4

\* RA Only

# Risk of Herpes Zoster with Anti- TNF- $\alpha$ Agents in RA Treated Patients: RABBIT Registry

	Etanercept	Infliximab/ Adalimumab	Total Anti-TNFs	Controls (DMARDs)
Observed pt-yrs	2588	3524	6112	4291
Herpes zoster	23	39	62	24
Crude Incidence Rate (95% CI)	8.9/1000 pt-yrs (5.6 – 13.3)	11.1/1000 pt-yrs (7.9 – 15.1) <sup>a</sup>	10.1/1000 pt-yrs (7.8-13.0) <sup>a</sup>	5.6 /1000 pt-yrs (3.6 – 8.3)
Adjusted Hazard Ratio* (95% CI)	1.36 (0.73 – 2.55) p=0.33	1.82 (1.05- 3.15) p=0.03	1.63 (0.97-2.74) p=0.07	1.0 Referent

CI=Confidence interval

<sup>a</sup> Significantly different ( $p < 0.05$ ) compared with controls; \*Multivariate analysis



Treatment with monoclonal anti-TNF- $\alpha$  antibodies may be associated with increased risk of herpes zoster. Further studies are required.

# Take Home Message

- RA is a **TREATABLE** Condition
- **EARLY CONTROL** yields better outcome
- Use validated **COMPOSITE** assessment tools (SDAI)
- Aim for **REMISSION**
- Chose the treatment with the best **RETENTION / SAFETY PROFILE**