



# International Literature Search in Rheumatology

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## **In this issue:**

**Highlights of the European League Against  
Rheumatism Annual Meeting 2011, London, England**



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# The ACQUIRE (Abatacept Comparison of sub[QU]cutaneous versus Intravenous in inadequate Responders to methotrexatE) Trial: A Large Phase IIIB Non-inferiority Study

Genovese MC, Covarrubias JA, Leon G, *et al.*

Presented at the 2011 European League Against Rheumatism (EULAR) Congress

Abstract #OP0023



# Study Design

Objective: To compare efficacy and safety of subcutaneous and intravenous abatacept in methotrexate (MTX)-inadequate responders (IR).

Subjects: 1,457 patients with inadequate response to MTX with active rheumatoid arthritis ( $\geq 10$  swollen and  $\geq 12$  tender joints, c-reactive protein  $\geq 0.8$  mg/dL).



# Methodology

- 6-month, double blind, double-dummy study
- Patients were randomized to:
  - weekly SC abatacept (ABA), fixed-dose 125 mg, with IV loading ( $\sim 10$  mg/kg) on Day 1 + methotrexate (MTX) ( $\geq 15$  mg/wk) or
  - IV ABA ( $\sim 10$  mg/kg, Days 1, 15, 29 and every 4 weeks thereafter) for 6 months + methotrexate (MTX) ( $\geq 15$  mg/wk).
- The primary endpoint was non-inferiority of SC to IV ABA by ACR 20 response at month 6 in the per protocol population; the intent to treat population was also assessed.
- HAQ response (increase from baseline  $\geq 0.3$ ) was a secondary endpoint, DAS28 (CRP) a tertiary endpoint.

SC: subcutaneous; IV: intravenous; ACR: American College of Rheumatology; HAQ-DI: Health Assessment Questionnaire – Disease Index; CRP: C-reactive protein; DAS: disease activity score; CRP: C-reactive protein.

Genovese MC, *et al.* Presented at EULAR 2011; Abstract #OP0023.

# Baseline Demographics and Clinical Characteristics

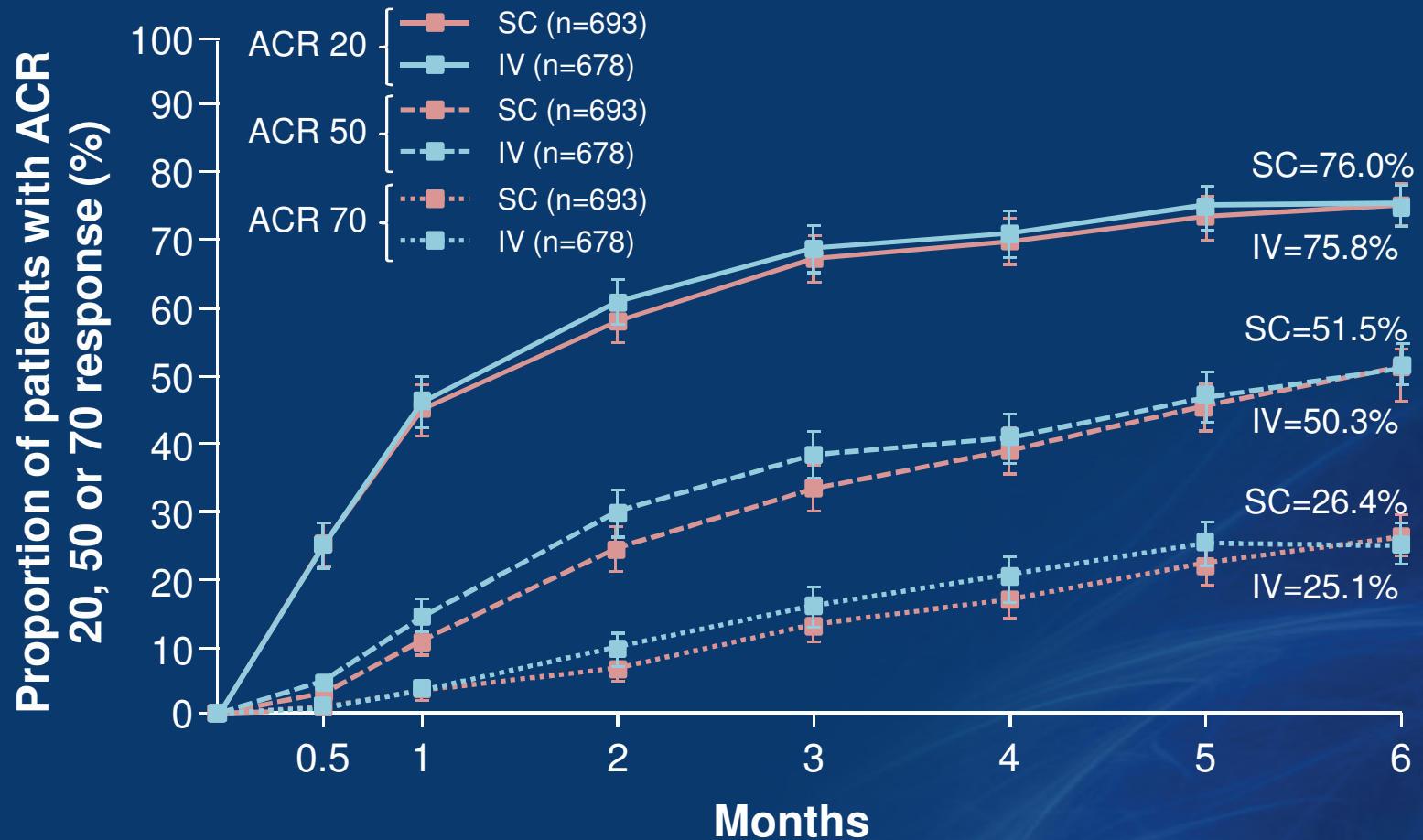
	ITT population		PP population	
	SC abatacept + MTX (n=736)	IV abatacept + MTX (n=721)	SC abatacept + MTX (n=696)	IV abatacept + MTX (n=683)
Age, years	49.9 (13.2)	50.1 (12.6)	49.9 (13.0)	49.9 (12.7)
Gender, % female	84.4	80.4	84.2	80.4
Race, % Caucasian	74.7	74.5	74.1	73.9
Disease duration, years	7.6 (8.1)	7.7 (7.8)	7.6 (8.0)	7.7 (7.9)
Tender joint count, n	30.1 (14.1)*	29.1 (13.3)	30.0 (14.1) <sup>¶</sup>	29.2 (13.1)
Swollen joint count, n	20.4 (9.6)*	19.4 (8.6)	20.5 (9.4) <sup>¶</sup>	19.6 (8.5)
HAQ-DI	1.7 (0.7)	1.7 (0.7)	1.7 (0.7)**	1.7 (0.7)
CRP levels, mg/dL	2.6 (2.9) <sup>†</sup>	2.7 (2.9)	2.7 (2.9)	2.7 (2.9)
DAS28 (CRP)	6.23 (0.85) <sup>‡</sup>	6.20 (0.84) <sup>  </sup>	6.25 (0.84) <sup>††</sup>	6.22 (0.83)
RF Status, % positive	84.8 <sup>§</sup>	85.9 <sup>  </sup>	85.1 <sup>‡‡</sup>	86.5 <sup>§ §</sup>

Data are mean ± standard deviation, unless otherwise stated; \*n=735; †n=734; ‡n=733; §n=724; ||n=711; ¶n=695; \*\*n=694; ††n=693; ‡‡n=684; § §n=674

ITT: intent to treat; PP: per protocol; SC: subcutaneous; IV: intravenous; MTX: methotrexate; HAQ-DI: Health Assessment Questionnaire – Disease Index; CRP: C-reactive protein; DAS: disease activity score; RF: rheumatoid factor.

Genovese MC, *et al.* Presented at EULAR 2011; Abstract #OP0023.

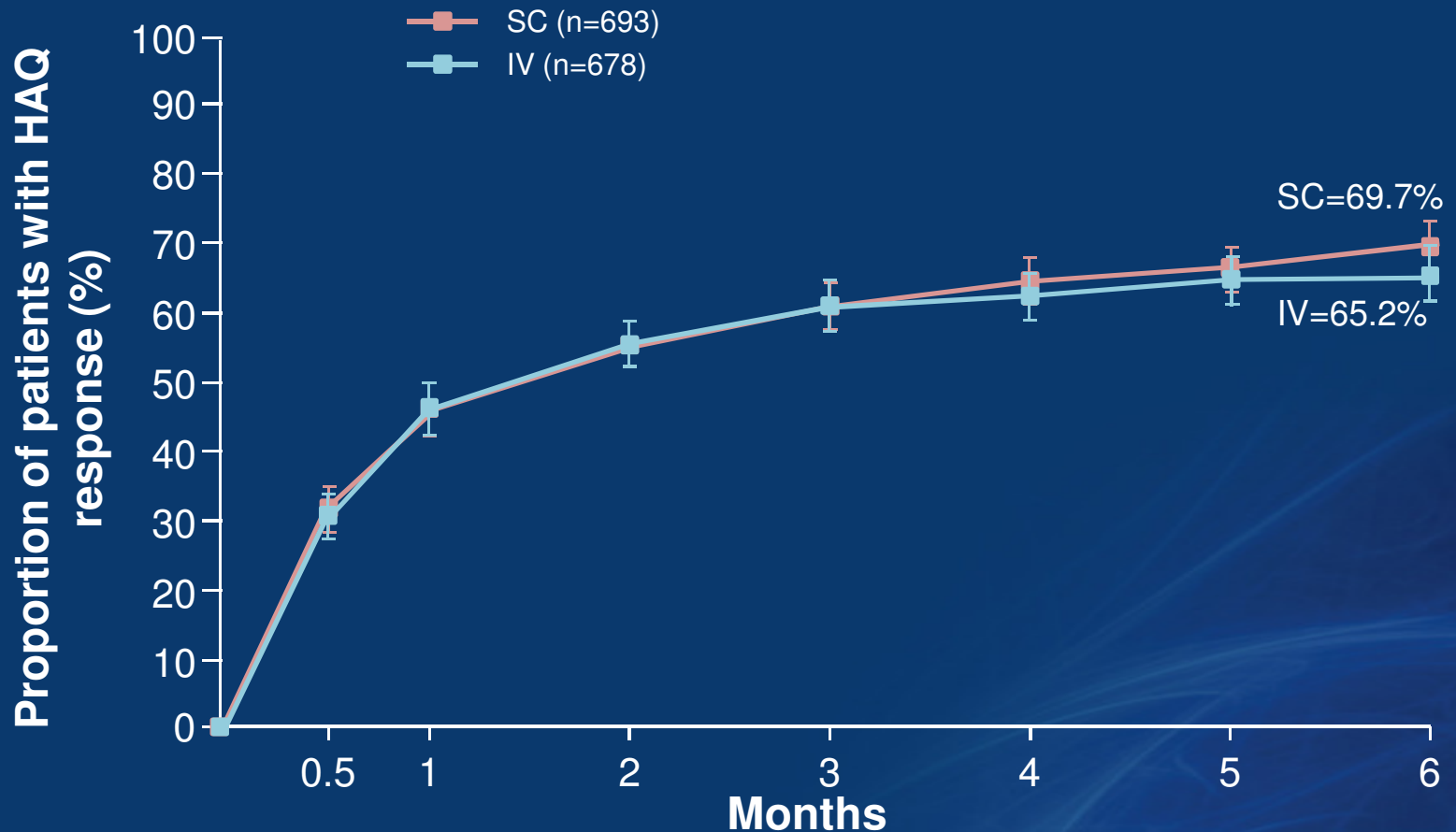
# ACR 20, 50 and 70 Responses Over 6 Months (PP Population)



Data exclude eight patients due to site non-compliance; PP population included all randomized and treated patients who received at least one dose of study medication, excluding patients with a protocol deviation; Patients who discontinued were considered non-responders; Error bars represent 95% CI; ACR: American College of Rheumatology; SC: subcutaneous; IV: intravenous.

Genovese MC, *et al.* Presented at EULAR 2011; Abstract #OP0023.

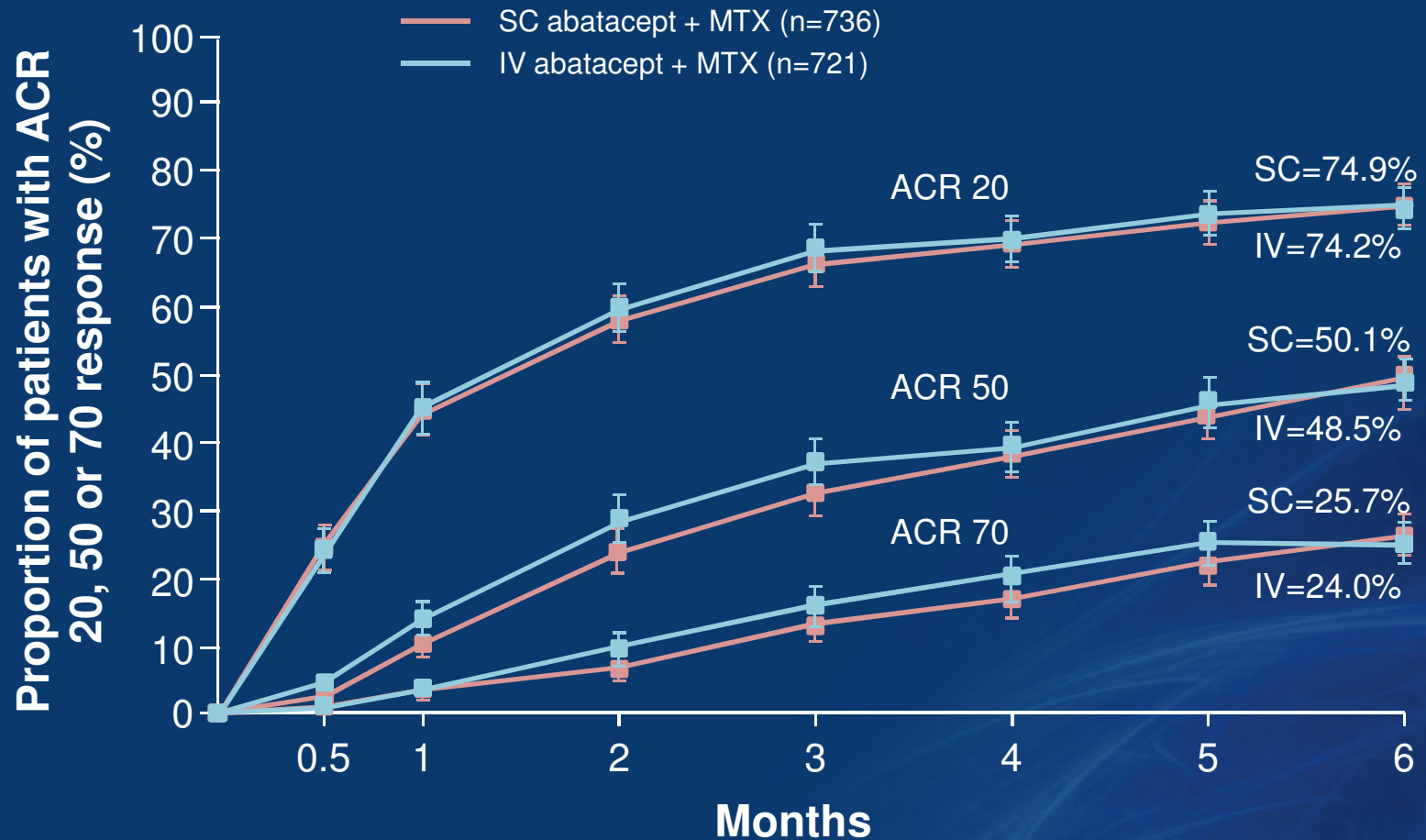
# HAQ-DI Response (Change from Baseline $\geq 0.3$ units) Over 6 Months



Data exclude eight patients due to site non-compliance; PP population included all randomized and treated patients who received at least one dose of study medication, excluding patients with a protocol deviation; Patients who discontinued were considered non-responders; Error bars represent 95% CI; HAQ-DI=Health Assessment Questionnaire-Disability Index; SC: subcutaneous; IV: intravenous.

Genovese MC, *et al.* Presented at EULAR 2011; Abstract #OP0023.

# ACR 20, 50 and 70 Responses Over 6 Months (ITT)



Data exclude eight patients due to site non-compliance; PP population included all randomized and treated patients who received at least one dose of study medication, excluding patients with a protocol deviation; Patients who discontinued were considered non-responders; Error bars represent 95% CI; ACR: American College of Rheumatology; SC: subcutaneous; IV: intravenous.

Genovese MC, *et al.* Presented at EULAR 2011; Abstract #OP0023.

# Similar Safety Profile Between Abatacept IV and SC

Event, n (%)	SC abatacept + MTX (n=736)	IV abatacept + MTX (n=721)
Deaths	2 (0.3)	5 (0.7)
SAEs	31 (4.2)	35 (4.9)
Discontinued due to SAEs	8 (1.1)	14 (1.9)
AEs	493 (67.0)	470 (65.2)
Discontinued due to AEs	15 (2.0)	25 (3.5)
Infections	234 (31.8)	221 (30.7)
Serious infections	5 (0.7)	10 (1.4)
Malignancies	3 (0.4)	5 (0.7)
Autoimmune events	7 (1.0)	6 (0.8)

Safety profiles were similar across the different weight quartiles ( $\leq 59.4$  kg,  $>59.4$  to  $\leq 69$  kg,  $>69$  to  $\leq 81.9$  kg and  $>81.9$ )

Safety data are based on all patients who received at least one dose of abatacept and are reported up to 56 days post last study dose; Deaths occurring  $>56$  days post last study dose are also included ; SC: subcutaneous; IV: intravenous; MTX: methotrexate; SAE: severe adverse events.

Genovese MC, *et al.* Presented at EULAR 2011; Abstract #OP0023.



# Conclusions

- Subcutaneous (SC) abatacept (ABA) provides comparable efficacy and safety to intravenous ABA over 6 months, with high patient retention and low injection site reaction rates overall.
- Efficacy benefits were observed regardless of weight or rheumatoid arthritis (RA) duration.
- SC ABA can provide an additional treatment option for patients with RA.




## Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel

The efficacy and safety of IV abatacept in RA has been shown for both methotrexate and TNFi-inadequate responders.

This study confirms the efficacy and safety of the subcutaneous formulation of abatacept.

Once available, it will be the first biologic therapy to offer the option of a subcutaneous or intravenous formulation for the treatment of RA.



# Oral Solo (A3921045): Effects of the Oral JAK Inhibitor Tofacitinib (CP-690,550) Monotherapy on Patient Reported Outcomes in a Phase 3 Study of Active Rheumatoid Arthritis

Strand V, Kanik KS, Connell C, *et al.*

Presented at the 2011 European League Against Rheumatism (EULAR) Congress

Abstract #OP0063



# Study Design

Objective: To compare the effects of tofacitinib 5 and 10 mg BID, monotherapy vs placebo on patient reported outcomes in a 6-month, randomised, double-blind, placebo-controlled, parallel group Phase 3 study.

Subjects:

- 610 patients with a diagnosis of rheumatoid arthritis for at least 6 months
- $\geq 6$  tender/swollen joints
- ESR  $>28$  mm or CRP  $>7$  mg/L
- $\geq 1$  prior DMARD failure

BID: twice daily; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DMARD: disease-modifying anti-rheumatic drugs

Strand V *et al.* Presented at EULAR 2011; Abstract #OP0063.



# Methodology

Patients were randomized to 4, twice-daily treatment sequences:

1. Tofacitinib 5 mg months 0-6
2. Tofacitinib 10 mg months 0-6
3. Placebo months 0-3, tofacitinib 5 mg months 3-6
4. Placebo months 0-3, tofacitinib 10 mg months 3-6

After month 3, all placebo patients were blindly advanced to tofacitinib 5 or 10 mg bid with combined placebo



# Patient Demographics

	Placebo (N=122)	Tofacitinib 5 mg BID (N = 243)	Tofacitinib 10 mg BID (N = 245)
Female (%)	86.1	85.2	88.2
White (%)	72.1	63.0	68.6
Age (years, mean)	49.7	52.2	52.4
<b>Prior, concomitant meds (%)</b>			
Prior MTX	83.6	86.0	84.5
Prior DMARDs other than MTX	60.7	54.3	57.6
Prior TNF inhibitor	19.7	14.0	16.7
Prior non-TNFi biologics	8.2	4.9	7.8
Concomitant corticosteroids	63.1	57.4	60.4
Disease duration	7.7	8.0	8.6

BID: twice daily; MTX: methotrexate; DMARD: disease-modifying anti-rheumatic drugs; TNF: tumor necrosis factor

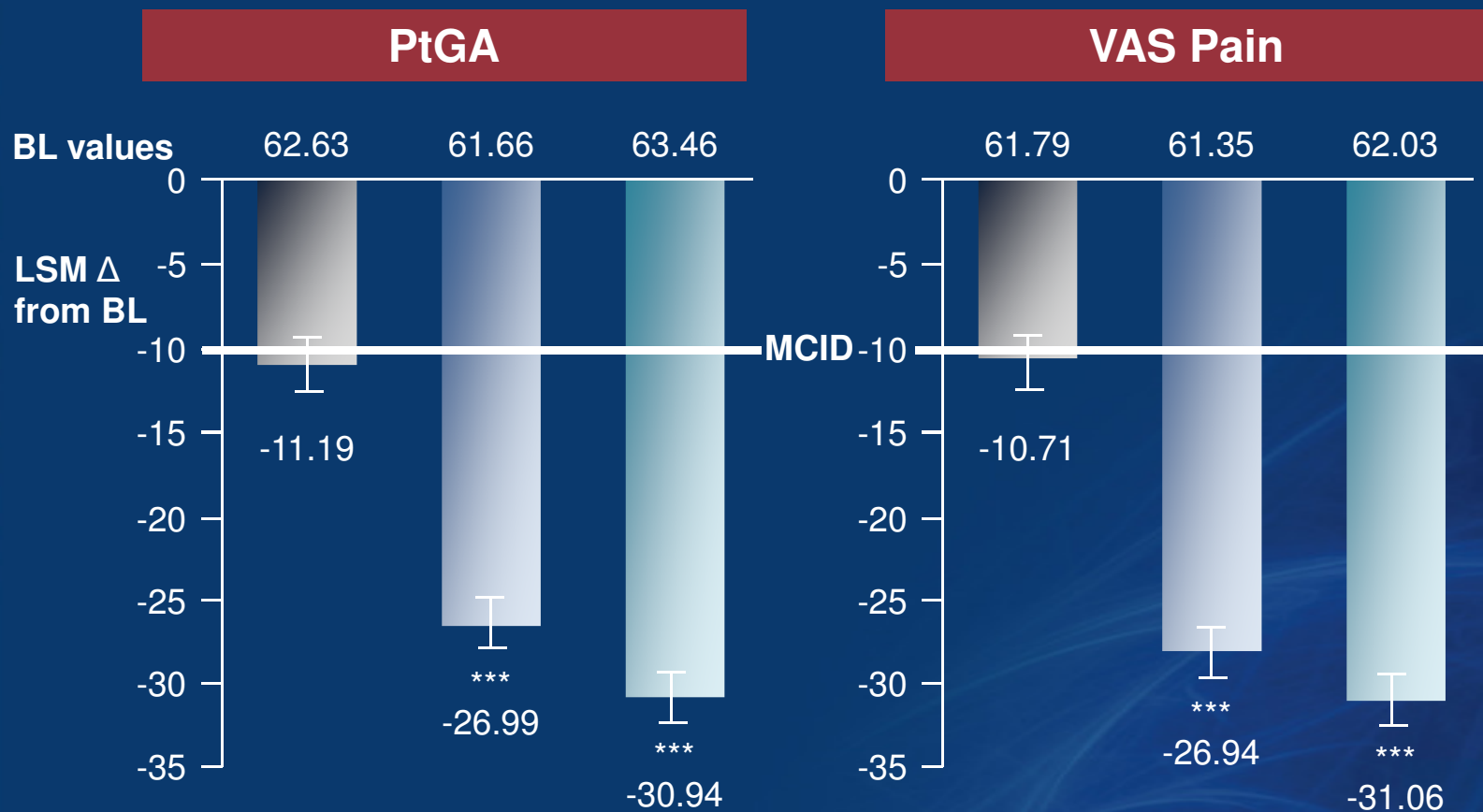
Strand V *et al.* Presented at EULAR 2011; Abstract #OP0063.

# PtGA and VAS Pain at Month 3

PBO

Tofacitinib 5 mg BID

Tofacitinib 10 mg BID

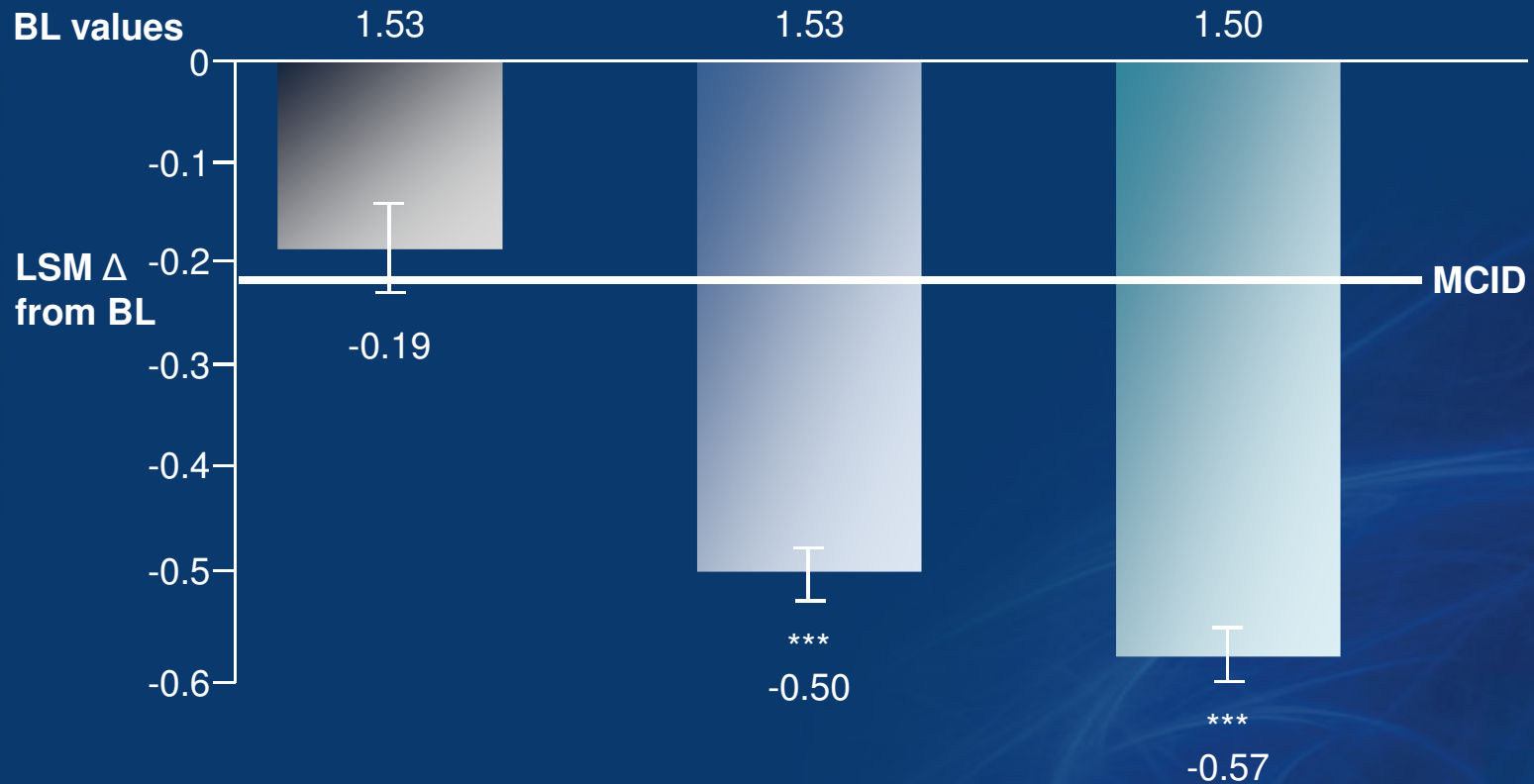


\*\*\* p<0.0001 vs placebo

MCID: minimum clinically important difference; PtGA: Patient global assessment; VAS: visual analog scale  
Strand V *et al.* Presented at EULAR 2011; Abstract #OP0063.

# HAQ Disability Response Rate at Month 3

■ PBO    ■ Tofacitinib 5 mg BID    ■ Tofacitinib 10 mg BID



\*\*\* p<0.0001

HAQ: health assessment questionnaire; LSM: least squares mean; MCID: minimum clinically important difference  
Strand V *et al.* Presented at EULAR 2011; Abstract #OP0063.

# SF-36 Physical and Mental Component Scores at Month 3

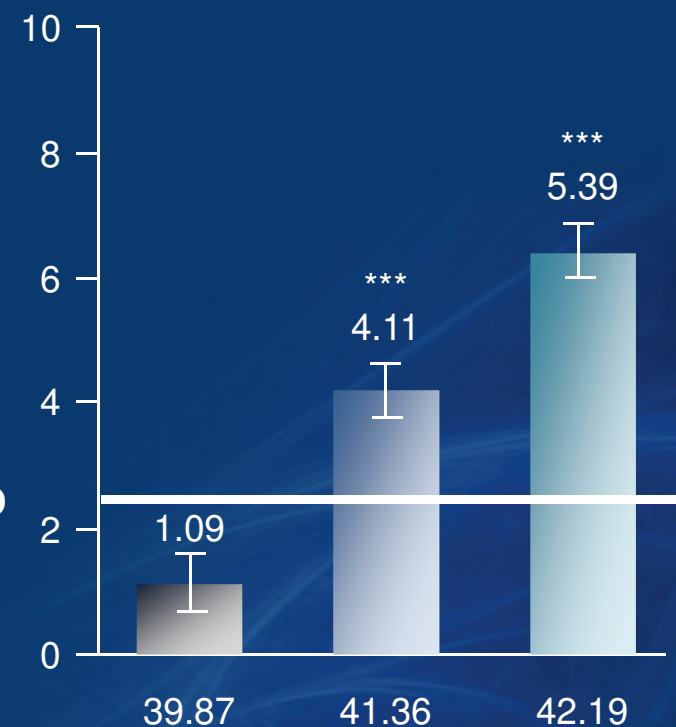
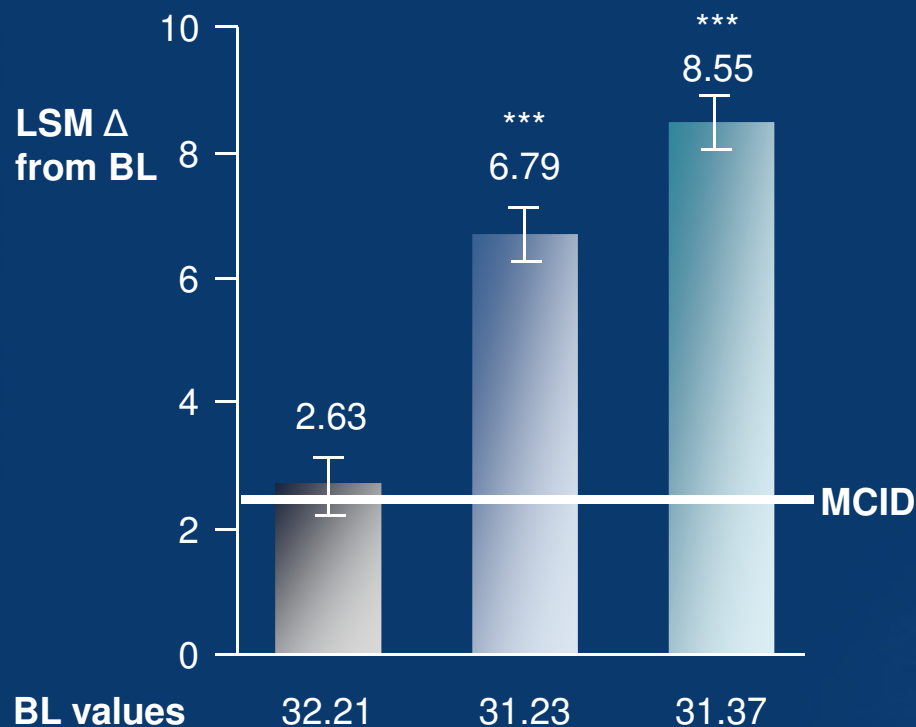
PBO

Tofacitinib 5 mg BID

Tofacitinib 10 mg BID

## Physical component score

## Mental component score



\*\*\* $p < 0.0001$

SF-36: medical outcomes survey short form 36; LSM: least squares mean; BL: baseline  
Strand V *et al.* Presented at EULAR 2011; Abstract #OP0063.



# Conclusions

- In this first Phase 3 study in patients with rheumatoid arthritis, those receiving tofacitinib monotherapy reported significant and clinically meaningful, dose-related improvements in patient-reported outcomes, relative to placebo, at month 3.



## Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel

Tafocitinib resulted in clinically significant improvement in all patient-reported outcomes.

These results are important as they compare favourably with standard biologic therapy in RA with monotherapy using an oral agent.

There are still some questions remaining as to safety and the positioning of these agents in our RA treatment armamentarium.



# Impact of Anti-TNF on Healthcare Utilization and Costs in Patients with Rheumatoid Arthritis in Alberta, Canada

Maksymowych WP, Thanh NX, Martin L, *et al.*

Presented at the 2011 European League Against Rheumatism (EULAR) Congress

Abstract #OP0151



# Study Design

Objective: To assess the impact of anti-TNF compared with standard DMARDs on healthcare utilization and costs in an inception cohort with RA in Alberta, Canada

Subjects: 1,222\* patients identified in administrative databases (Physician Claims, Ambulatory Care Classification System, and Hospital Discharged Abstract Database) between April 2004 and March 2009 who started on anti-TNF (n=1,041) or comparison DMARD (n=181).

\* 135 patients were excluded due to less than 3 months of administrative data.

TNF: tumor necrosis factor ; DMARD: disease-modifying anti-rheumatic drugs; RA: rheumatoid arthritis

Maksymowych WP, *et al.* Presented at EULAR 2011; Abstract #OP0151



# Methodology

- Measurement of clinical and self-reported data was done at baseline, 3 months and every 6 months.
- Subgroup analysis of patients who started their first anti-TNF and either continued for duration of follow up or who switched to another anti-TNF.
- DMARD patients stratified by whether they remained on the same therapy or switched to anti-TNF.
- 2008 Alberta costs of health services were used for costing analysis.
- Costs were categorized as RA and non-RA related.
- Physician visits included visits in the office, hospital or in the ER.

TNF: tumor necrosis factor; DMARD: disease-modifying anti-rheumatic drugs; RA: rheumatoid arthritis

Maksymowych WP, *et al.* Presented at EULAR 2011; Abstract #OP0151

# Annual Service Utilization/Costs per Patient in First anti-TNF-only Group and Differences From Other Study Groups

Total n=1087	Mean costs and visits	Difference to first anti-TNF-only group*		
	First anti-TNF-only (n=812)	Anti-TNF switch (n=133)	DMARD-only (n=48)	DMARD switch (n=94)
Total cost	4,929	+2,689 (Y)	+1561 (N)	+2118 (N)
Hospital cost	1,983	+1400 (N)	+376 (N)	+1049 (N)
ER cost	1,378	+840 (Y)	+813 (N)	+605 (Y)
Physician cost	1,568	+449 (Y)	+372 (N)	+464 (Y)
Hospitalizations	0.22	+0.21 (Y)	+0.04 (N)	+0.19 (N)
ER visits	6.7	+3.5 (Y)	-0.07 (N)	+2.3 (Y)
Physician visits	19.1	+4.4 (Y)	+6.0 (Y)	+3.4 (N)

\* Statistically significant 95% confidence intervals of differences from first anti-TNF-only group; Y: yes; N: no; TNF: tumor necrosis factor; DMARD: disease-modifying anti-rheumatic drugs

Maksymowych WP, *et al.* Presented at EULAR 2011; Abstract #OP0151



# Conclusions

Switching anti-TNF therapy is associated with significantly higher utilization and costs of health services compared to patients who remain on their first anti-TNF.

Treatment may therefore be less cost-effective and requires further study.



## Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel

The efficacy of biologic therapy on disease activity, function and radiologic progression has been well studied in RA; however, healthcare utilization is another important consideration in this chronic disease.

Cost-effectiveness data are needed to evaluate treatment strategies using biologics in RA.



# **Malignancies Associated with TNF Inhibitors in Registries and Prospective Observational Studies: A Systematic Review and Meta-analysis**

Taylor P, Mariette X, Matucci-Cerenic M, *et al.*

Presented at the 2011 European League Against Rheumatism (EULAR) Congress

Abstract #FRI0234



# Study Design

Background: Patients with rheumatoid arthritis are at increased risk of certain types of cancer including lymphoma. Tumour necrosis factor (TNF) plays a role in host defence against cancer but also plays a role in the spread of some cancers. Randomized controlled trials may not be able to ascertain risks associated with TNF inhibition due to limited patient numbers and relatively short duration of studies.

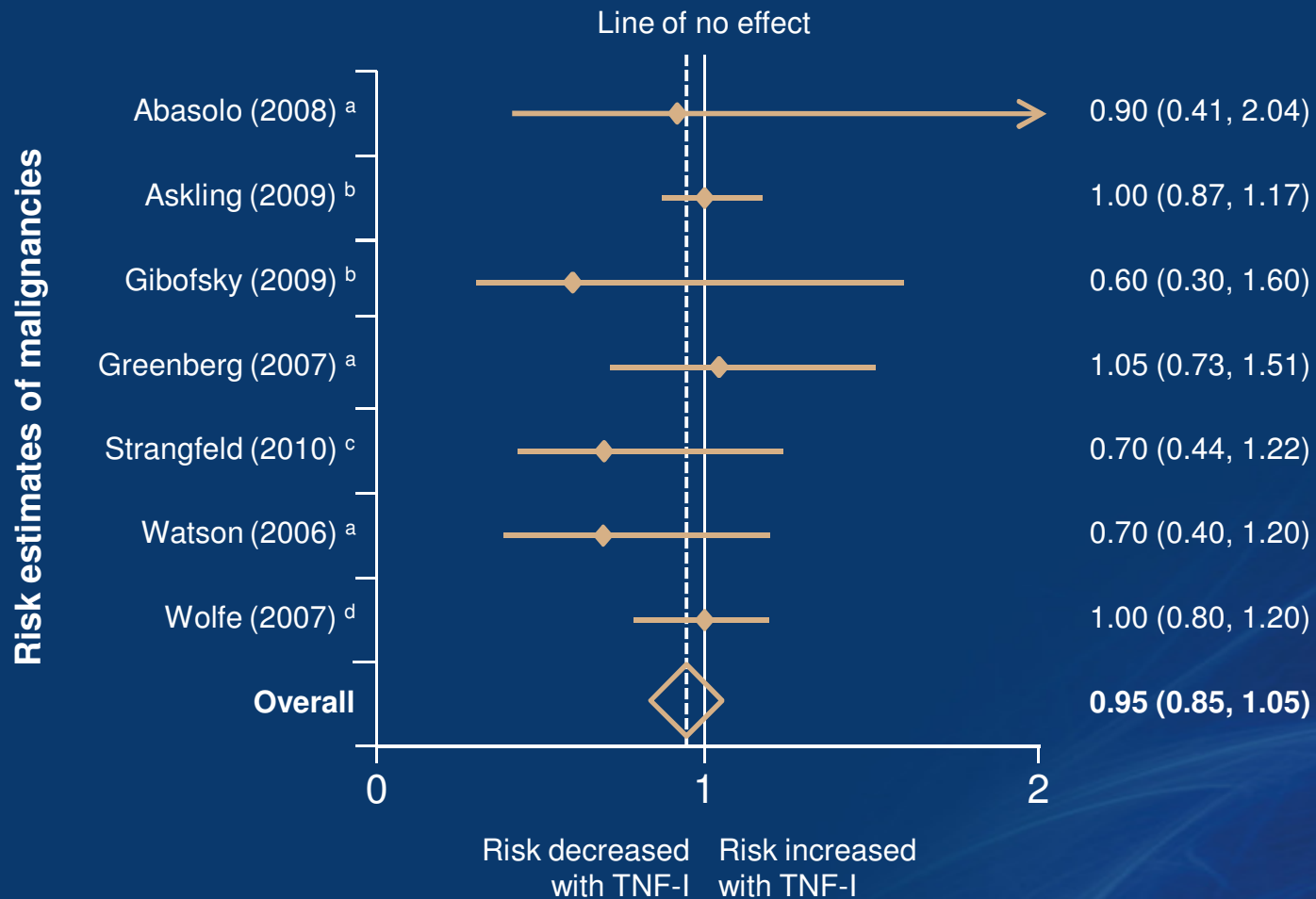
Objective: To assess the risk of malignancy in patients with rheumatoid arthritis treated with tumour necrosis factor inhibitors (TNF-I) in clinical practice, as recorded in prospective, observational studies.



# Methodology

- All prospective observational studies in patients with RA and including data on cancer and TNF-inhibitors were assessed for inclusion in the review.
- Comprehensive searches of Medline, EMBASE, the Cochrane Database of Systematic Reviews and ACR, EULAR and BSR conference abstracts were undertaken according to a pre-specified protocol.
- Publications that met the inclusion criteria were assessed for quality.
- Data on malignancy (including type, site, % of patients with malignancy, incidence rates, standardised incidence ratios and relative risks) were extracted and meta-analysis undertaken.

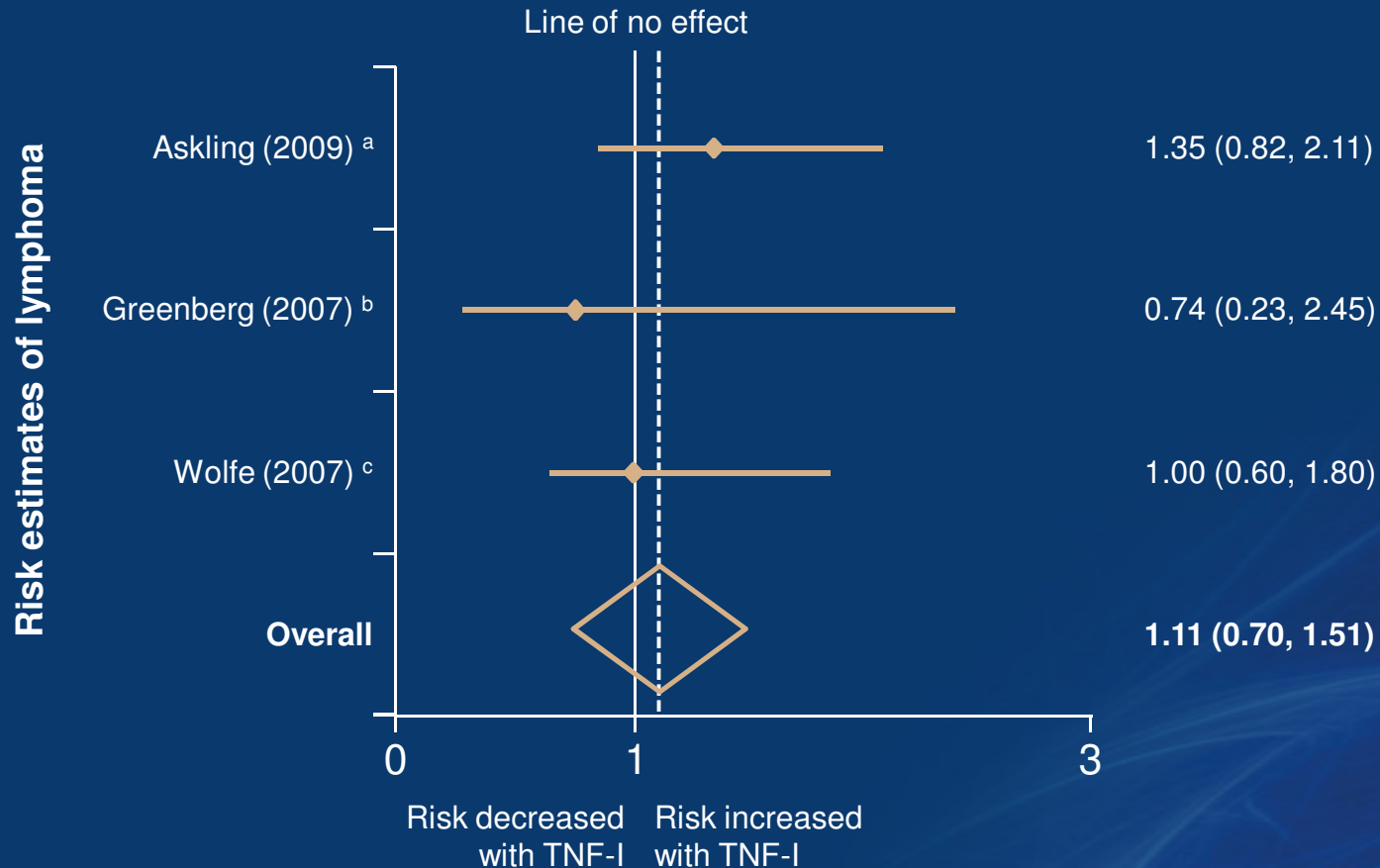
# Risk Estimates of Malignancies



I-squared = 0.0%, p = 0.529

<sup>a</sup> Incidence rate ratio; <sup>b</sup> relative risk; <sup>c</sup> hazard ratio; <sup>d</sup> odds ratio

# Risk of Lymphoma in RA Patients Treated with TNF-I



I-squared = 0.0%, p = 0.581

<sup>a</sup> Relative risk; <sup>b</sup> incidence rate ratio; <sup>c</sup> odds ratio




# Conclusions

- This systematic review and meta-analysis shows that TNF-I treatments do not increase the overall risk of malignancy, particularly lymphoma.
- There is evidence that the risk of skin cancer is increased relative to disease-modifying anti-rheumatic drug-treated RA patients.
- However, the confidence intervals do not preclude an effect of treatment on risk of malignancy.
- Similar results were reported from the recently published meta-analysis of individual patient data from randomised controlled trials.



## **Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel**

These data provide rheumatologists with further reassurance on the safety of biologics in relation to solid malignancies and lymphoma. The study confirms existing data on a higher risk of non-melanoma skin cancer.



# **Risk of Cancer in Patients Receiving Non-biologic Disease Modifying Therapy for Rheumatoid Arthritis: Results From the BSR Biologics Register (BSRBR)**

Mercer LK, Davies R, Lunt M, *et al.*

Presented at the 2011 European League Against Rheumatism  
(EULAR) Congress

Abstract #FRI0338



# Study Design

Objective: To compare the occurrence of cancer in a contemporary cohort of prevalent RA patients receiving nbDMARD to that in the general population.

Subjects: 3,727 biologic-naïve patients with RA enrolled in the British Society for Rheumatology Biologics Register. Patients were recruited from rheumatology departments around the UK between 2002 and 2008. Patients had active disease at recruitment (guideline DAS28  $\geq 4.2$ ) and were on treatment with at least one nbDMARD.

RA: rheumatoid arthritis; nbDMARD: non-biologic disease-modifying anti-rheumatic drugs; DAS: disease activity score


Mercer LK, *et al.* Presented at EULAR 2011; Abstract #FRI0338.



# Methodology

## Methods:

- Standardised incidence ratios (SIR) with 95% confidence intervals (CI) were calculated for overall cancer risk (excluding non-melanoma skin cancer) for the whole cohort and separately for men and women.
- SIR for solid cancers and for myelo- and lymphoproliferative malignancies were then calculated.
- Site-specific SIR were calculated for sites with  $\geq 5$  incident cancers in the British Society for Rheumatology Biologics Register cohort.



# Baseline Characteristics of Patients

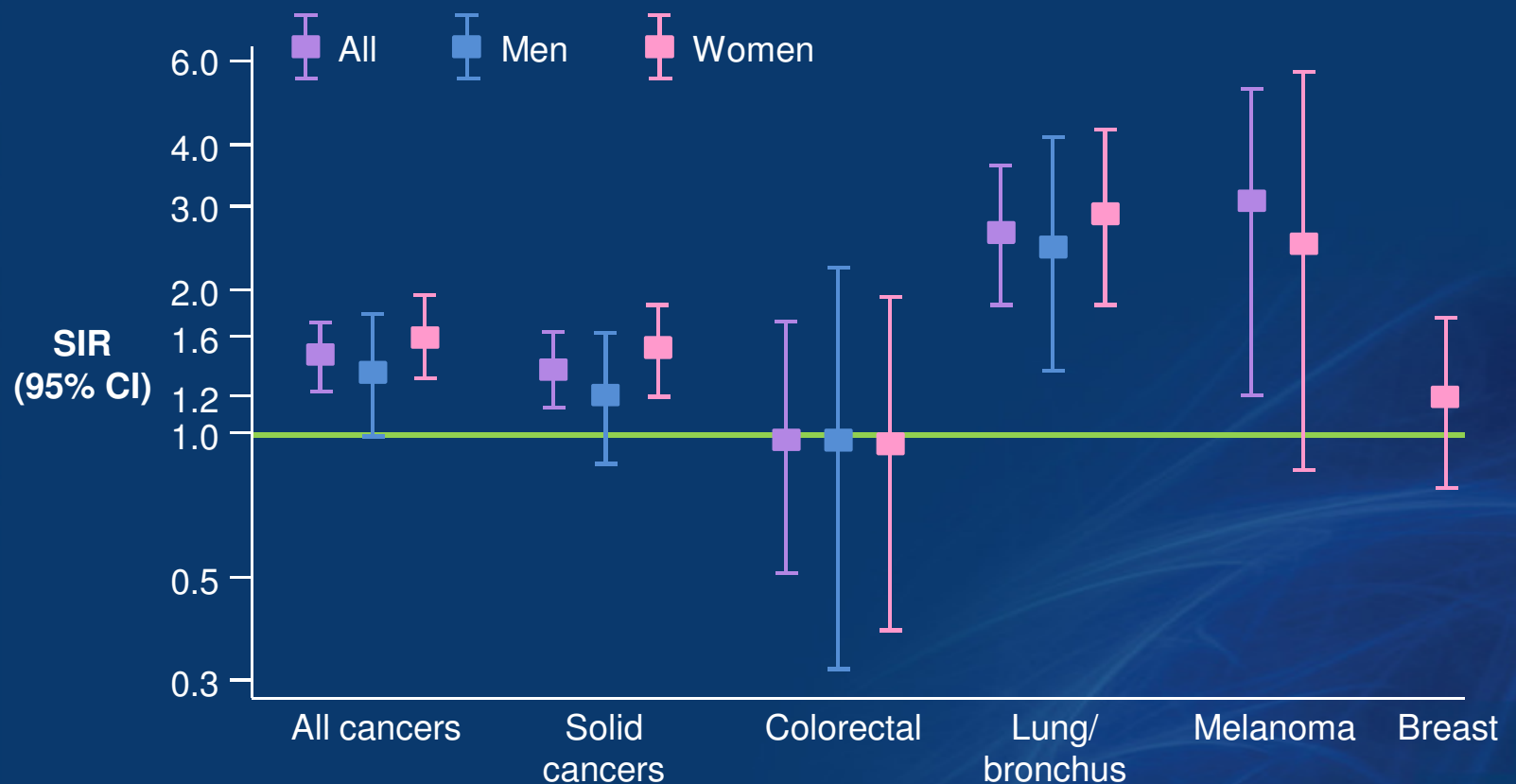
	<b>N=3,727</b>
Mean age: years (SD)	60 (12)
Female: number (%)	2701 (72)
Smoker: current/ever number (%)	881 (24)/2361 (63)
Prior cancer: number (%)	255 (7)
Median disease duration: Years (IQR)	6 (1-15)
Mean DAS28 (SD)	5.1 (1.3)
Mean HAQ (SD)	1.5 (0.7)
NSAID: number (%)	1997 (54)
Oral steroids: number (%)	847 (23)
Median number of prior DMARD (IQR)	2 (1-3)

SD: standard deviation; IQR: interquartile range; DAS: disease activity score; HAQ: Health Assessment Questionnaire; NSAID: Nonsteroidal anti-inflammatory drug; DMARD: disease-modifying anti-rheumatic drugs

Mercer LK, *et al.* Presented at EULAR 2011; Abstract #FRI0338.

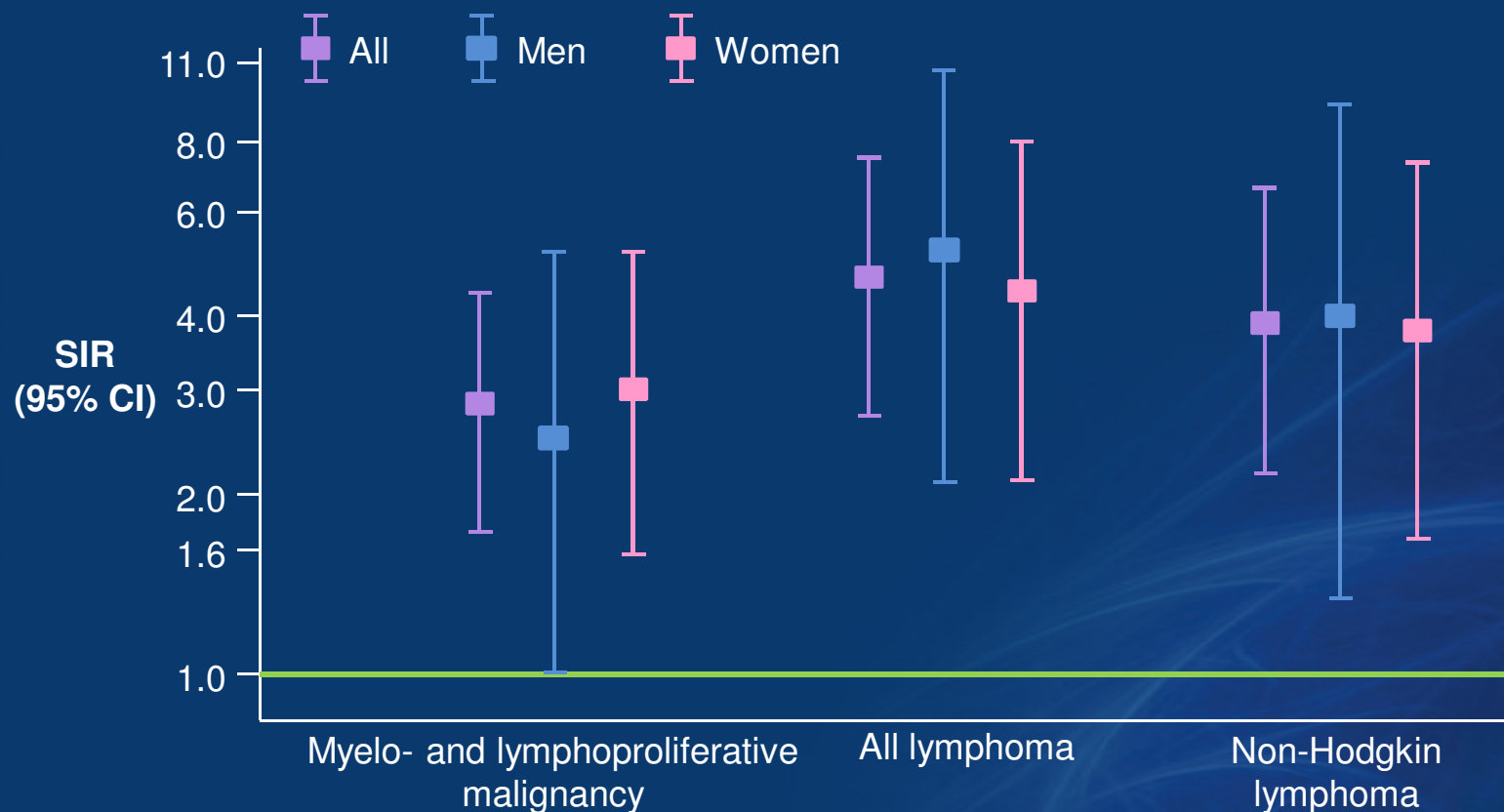
# Standardized Incidence Ratios of Solid Cancers

- 148 malignancies were observed equating to a rate of 1.4 per 100 patient years.



# Standardized Incidence Ratios of Myelo- and Lympho-proliferative Cancers

- Overall the SIR for lymphoma was 4.53 (95% CI 2.64, 7.25), suggesting that the risk of Hodgkin lymphoma was even higher than for non-Hodgkin lymphoma.





# Conclusions


- 148 malignancies were observed equating to an incidence of 1.4% per 100 patient years.
- Overall there was a 50% increased risk of cancer in these RA patients (SIR 1.48, 95% CI 1.25, 1.73) compared to the general population.
- The highest SIRs were seen for lymphomas, similar to findings in previous studies.
- The SIR for melanoma was also increased, which has not been previously reported in the UK where the background rate is low.
- The SIR for lung cancer was higher than previous studies but no increase in colorectal cancer was seen. The SIRs were comparable across genders.



## Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel

The results here may reflect the fact that most of the data for this analysis were collected in Manchester -- with a higher rate of malignancies than the whole of England -- which served to provide the SIRs.

There was also a high rate of present (24%) and previous (67%) smokers.



# Evaluation of Radiographic Progression over 1 Year in MTX-naive Patients with Early RA Treated with Abatacept + MTX Versus MTX Alone, According to Clinical Outcomes at Month 3

Smolen JS, Yazici Y, Durez P, *et al.*

Presented at the 2011 European League Against Rheumatism (EULAR) Congress

Abstract #FRI0368



# Study Design

Objective: To investigate the relationship between x-ray progression (total score over 1 year) and month 3 disease activity and functional outcomes in patients with early rheumatoid arthritis (RA) and poor prognostic factors treated with ABA+MTX or MTX alone.

Subjects: In AGREE, 256 and 253 MTX-naïve, early RA patients were randomized and treated with ABA + MTX or MTX alone, respectively. Baseline demographics were similar between the two groups and both groups had a high degree of disease activity and physical disability at baseline.

ABA: abatacept; MTX: methotrexate

Smolen JS, *et al.* Presented at EULAR 2011; Abstract #FRI0368.



# Methodology

- In the 1-year, double-blind phase of AGREE, methotrexate (MTX)-naïve patients were randomized to abatacept (ABA) + MTX or MTX alone on days 1, 15 and 29 and every 28 days thereafter.
- MTX 7.5 mg/week was administered at study entry, increased to 15 mg/week at week 4 and to 20 mg/week at week 8.
- Mean change from baseline to year 1 in Genant-modified Sharp Total Score (primary endpoint) was assessed post-hoc by clinical outcomes at month 3 for patients with available data using DAS28, CDAI, MDAS, HDAS, RAPID3 and HAQ-DI.

DAS: disease activity score; CDAI: clinical disease activity index; MDAS: moderate disease activity score; HDAS: high disease activity score; RAPID: rheumatology assessment patient index data; HAQ-DI: health assessment questionnaire – disease index

Smolen JS, *et al.* Presented at EULAR 2011; Abstract #FRI0368.

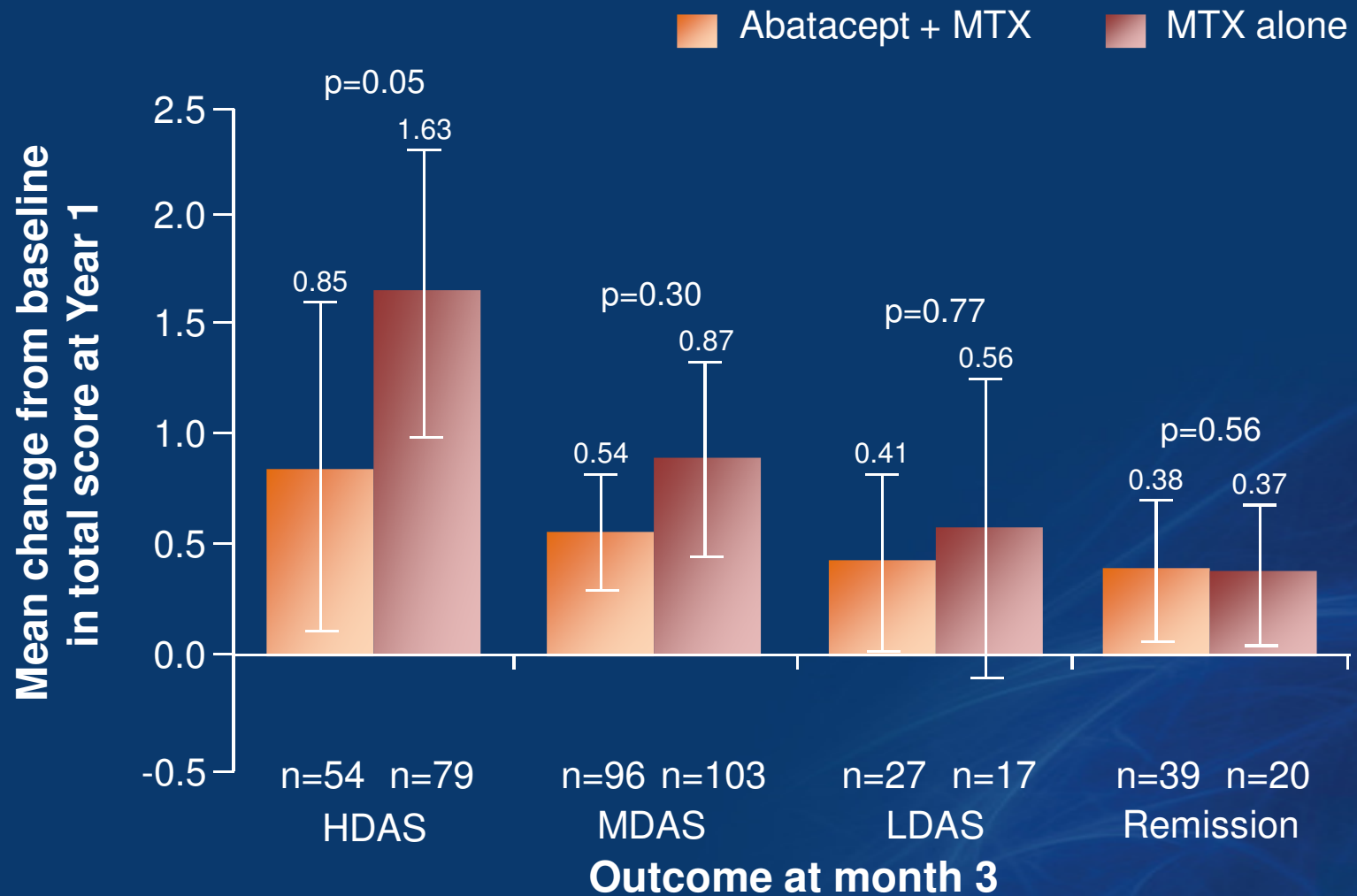
# Baseline Demographics and Clinical Characteristics at Randomization

	Abatacept + MTX, N=256	MTX alone, N=253
Age, years	50.1 ± 12.4	49.7 ± 13.0
Female, %	76.6	78.7
Caucasian, %	78.9	86.6
Disease duration, months	6.2 ± 7.5	6.7 ± 7.1
RF status, % positive	96.1	96.8
Anti CCP2 status, % positive	92.2	85.8
Tender joints	31.3 ± 14.8	30.8 ± 14.0
Swollen joints	22.9 ± 11.3	21.9 ± 10.1
Pain, 100 mm VAS*	66.6 ± 22.5	67.1 ± 22.6
Levels of CRP, mg/dL	3.1 ± 3.1	3.6 ± 5.0
Disease activity		
DAS28 (CRP)* (0 to 9.3)	6.3 ± 1.0	6.2 ± 1.0
CDAI□ (0.1 to 76)	45.6 ± 13.8	44.5 ± 12.8
SDAI□ (0.5 to -100)	48.7 ± 14.9	48.1 ± 14.5
RAPID3§ (0 to 30)	18.9 ± 5.4	18.7 ± 5.9
Physical function, HAQ-DI score (0 to 3)†	1.7 ± 0.7	1.7 ± 0.7
Radiographic total score^	7.5 ± 9.7	6.7 ± 9.8

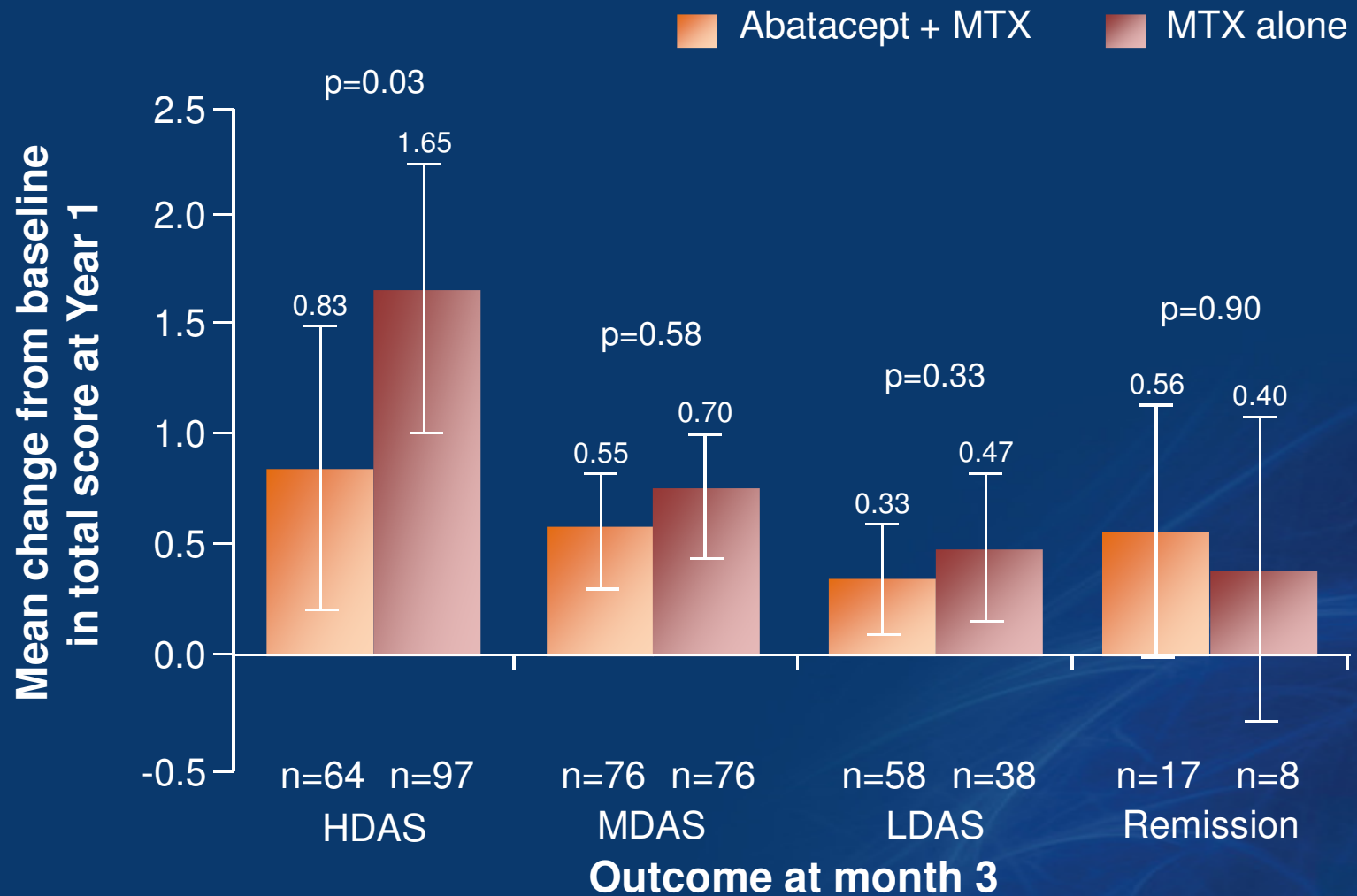
\*n=252 for MTX alone; †n=254 for abatacept + MTX, n=251 for MTX alone; □n=255 for abatacept + MTX and n=252 for MTX alone; §n=254 for abatacept +MTX and n=251 for MTX alone; ^n=253 for abatacept + MTX; data are mean ± standard deviation unless otherwise stated; VAS: visual analogue scale.

Smolen JS, *et al.* Presented at EULAR 2011; Abstract #FRI0368.

# Clinical Outcomes Over 1 Year and Associated Radiographic Progression (DAS28)

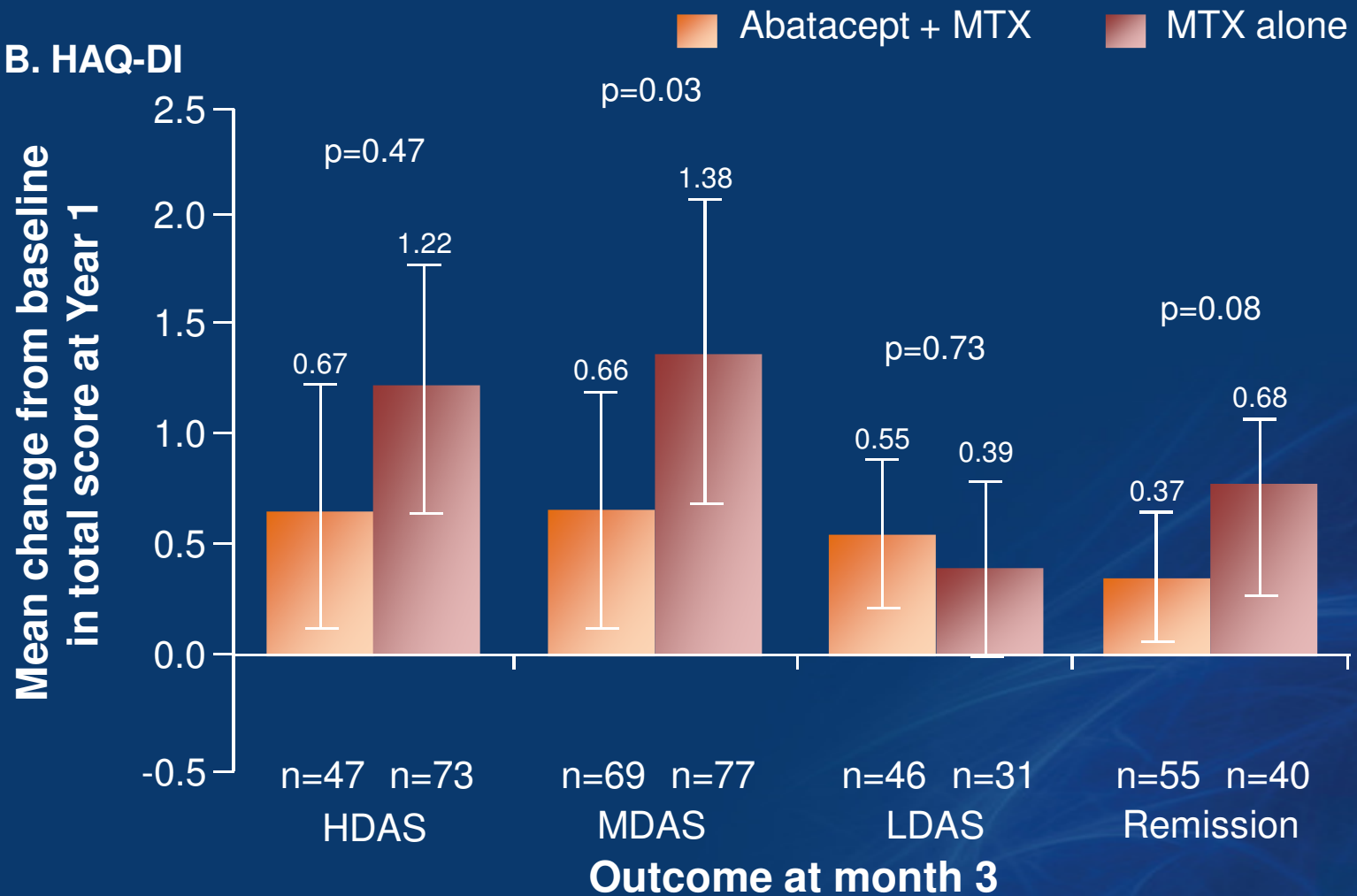


# Clinical Outcomes Over 1 Year and Associated Radiographic Progression (SDAI)



# Patient Reported Outcomes Over 1 Year and Associated Radiographic Progression (HAQ-DI)

## B. HAQ-DI





# Conclusions

- Overall, patients with early RA achieved better x-ray outcomes with combination therapy vs methotrexate (MTX) alone over 1 year, as previously shown in abatacept (ABA)-treated patients with established, refractory RA.
- The greatest difference between treatment groups was seen in patients with high/moderate disease activity.
- For patients with any level of disease activity, x-ray progression at year 1 was minimal with ABA + MTX.
- These data may support the use of ABA+MTX in patients with early, aggressive RA.




## Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel

“This post-hoc analysis of the AGREE study demonstrated that radiographic progression was minimal in patients treated with abatacept + methotrexate regardless of the degree of disease activity.

These data, in combination with previous observations with TNFi in other RA trials, suggest a dissociation between disease activity and radiographic progression in biologic treated patients.

The present results also demonstrate that patients should be in low disease activity or remission prior to using methotrexate alone, in order to prevent radiographic damage.



**Tofacitinib (CP-690,550), an Oral JAK Inhibitor, in Combination with Traditional DMARDs: Phase 3 Study in Patients with Active Rheumatoid Arthritis with Inadequate Response to DMARDs**

Kremer J, Li Z-G, Hall S, *et al.*

Presented at the 2011 European League Against Rheumatism (EULAR) Congress

Abstract #LB0005



# Study Design

Objective: To compare efficacy and safety of tofacitinib vs placebo in patients with active RA with inadequate response to  $\geq 1$  disease-modifying anti-rheumatic drugs (DMARDs).

Subjects: 792 pts on non-biologic background DMARDs. Patients had to have a diagnosis for  $> 6$  months; have active disease ( $\geq 4$  tender/swollen joints); ESR  $> 28$  mm/h or CRP  $> 7$  mg/L; prior inadequate response to 1 DMARD; patients remained on at least 1 background DMARD

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

Kremer J, *et al.* Presented at EULAR 2011; Abstract # LB0005.



# Methodology

- Over the 12-months of the study, patients on non-biologic background DMARDs were randomised (2:2:1) to tofacitinib 5 or 10 mg, twice daily or placebo for month 0 to 6.
- At month 3, non-responder placebo patients were advanced to tofacitinib 5 or 10 mg, twice daily.
- At month 6, remaining placebo patients were advanced to tofacitinib.

# Patient Demographics and Baseline Disease Characteristics

	5 mg BID n=315	10 mg BID n=318	PBO 5 mg BID n=79	PBO 10 mg BID n=80
Female n, %	264 (84)	258 (81)	63 (79.7)	60 (75)
White n, %	173 (54.9)	174 (54.7)	48 (60.8)	44 (55)
Age, years (mean)	52.7	51.9	50.8	53.3
Disease duration, years (mean)	8.1	9.2	9.5	10.2
Tender joints (68), mean	25	26.6	27.2	21.9
Swollen joints (66), mean	14.5	14.4	14.6	13.9
HAQ-DI, mean	1.44	1.43	1.45	1.24
DAS28-4(ESR), mean	6.29	6.36	6.44	6.16
ESR, mm/h, mean	50.46	51.94	51.04	49.29
DAS28-3 (CRP), mean	5.21	5.26	5.34	5.09
CRP, mg/L, mean	17.68	17.73	16.88	16.54
RF positive (%)	73.9	72.8	73.1	72.2
Anti-CCP positive (%)	76.7	76.3	75.6	76.3

BID: twice daily; HAQ-DI: health assessment questionnaire – disease index; DAS: disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; CCP: cyclic citrullinated peptide.

Kremer J, *et al.* Presented at EULAR 2011; Abstract # LB0005.



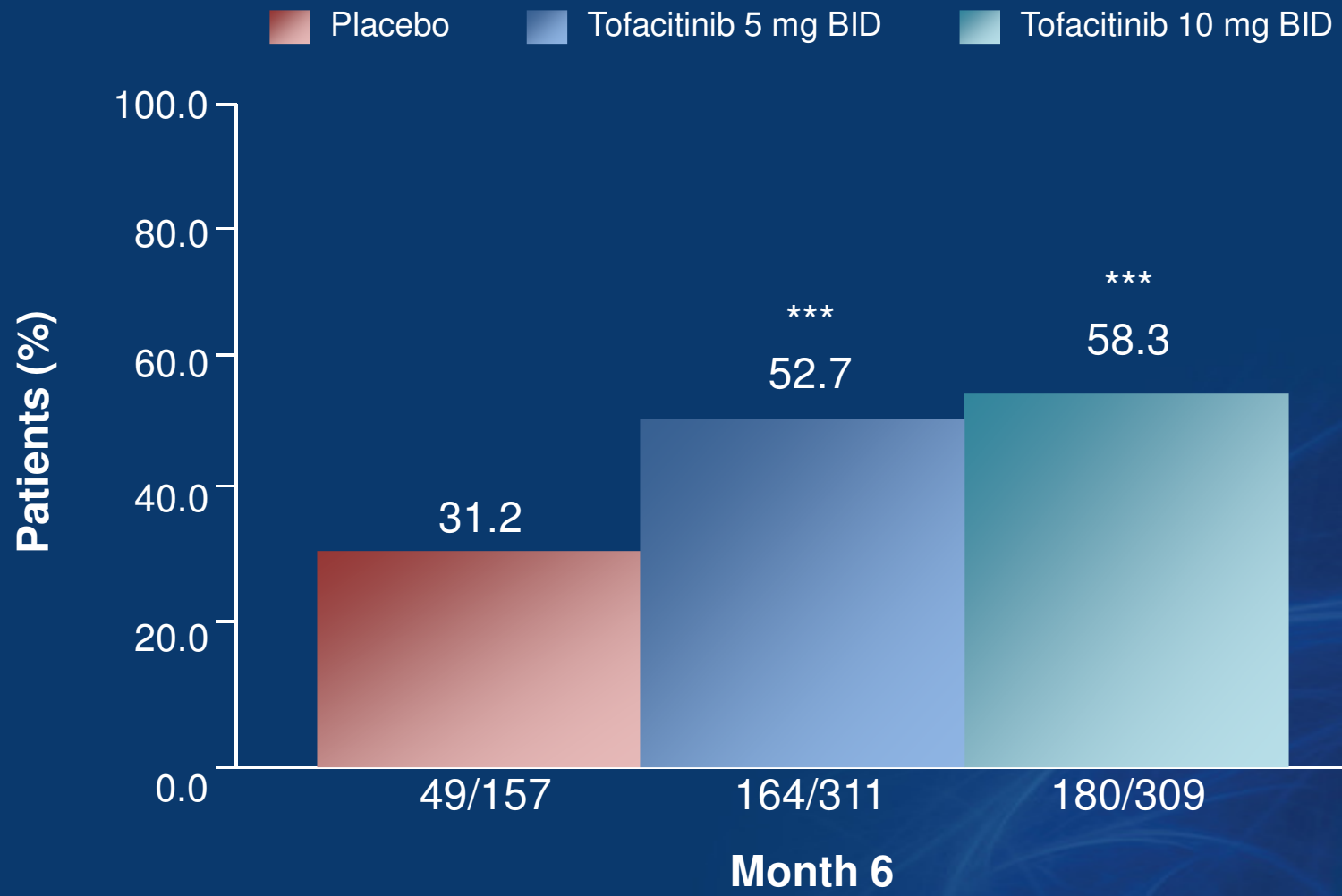
# Patient Demographics and Baseline Disease Characteristics (cont'd)

Prior DMARD use	5 mg BID n=315	10 mg BID n=318	PBO 5 mg BID n=79	PBO 10 mg BID n=80
MTX, %	86.7	82.7	83.5	82.5
Traditional DMARDS (not MTX), %	73.7	76.1	69.6	77.5
TNFi, %	7.3	6	6.3	6.3
Other biologic DMARD use, %	2.2	3.1	7.6	0

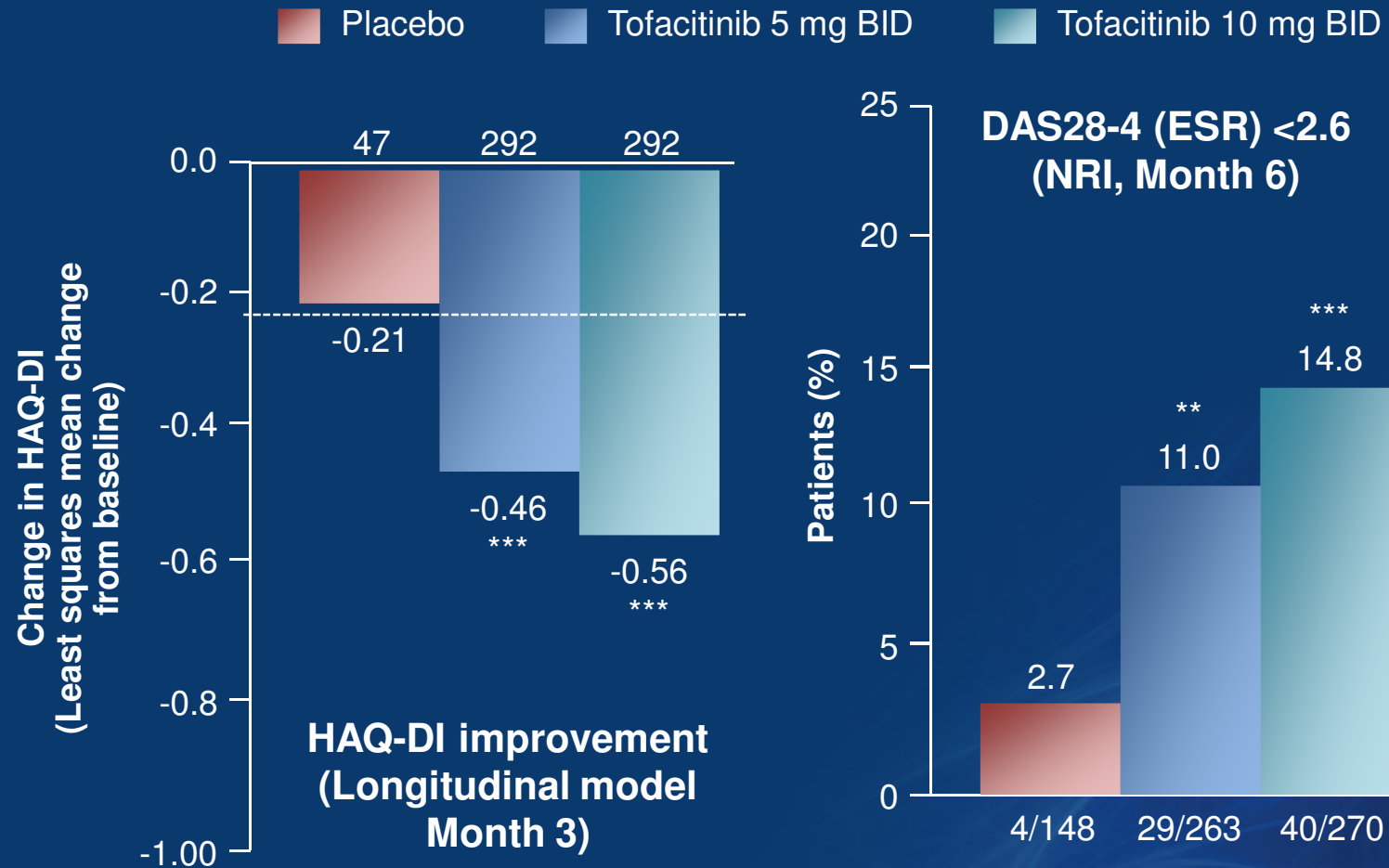
DMARD: disease-modifying anti-rheumatic drugs; BID: twice daily; MTX: methotrexate; TNFi: tumor necrosis factor inhibitor

Kremer J, *et al.* Presented at EULAR 2011; Abstract # LB0005.

# Primary Outcomes: ACR20



# Primary Outcomes: HAQ-DI and DAS28



\*\*p<0.001, \*\*\*p<0.0001  
 Kremer J, *et al.* Presented at EULAR 2011; Abstract # LB0005.

# Adverse Events

	Months 0 – 3			Months 3 – 6				Post month 6				
	5 mg BID n=315	10 mg BID n=318	PBO n=159	PBO n=81	5 mg BID n=315	10 mg BID n=318	PBO → 5 n=38	PBO → 10 n=40	5 mg BID n=315	10 mg BID n=318	PBO → 5 n=79	PBO → 10 n=80
AE, n (%)	166 (52.7)	173 (54.4)	97 (61.0)	21 (25.9)	121 (38.4)	124 (39.0)	16 (42.1)	18 (45.0)	104 (33.0)	135 (42.5)	34 (43.0)	29 (36.3)
Serious AE n (%)	9 (2.9)	8 (2.5)	6 (3.8)	0	5 (1.6)	7 (2.2)	0	0	7 (2.2)	9 (2.8)	2 (2.5)	0
Serious IE n (%)	2 (0.6)	4 (1.2)	0	0	0	0	1 (0.3)	1 (0.3)	3 (10)	8 (2.5)	0	0
D/Cs due to AEs n (%)	13 (4.1)	13 (4.1)	2 (1.3)	1 (1.2)	6 (1.9)	8 (2.5)	0	1 (2.5)	1 (0.3)	9 (2.8)	0	1 (1.3)

Note: 4 deaths and 4 causality related opportunistic infections were reported during the study.



# Conclusions

- This was the first Phase 3 study of tofacitinib in combination with background DMARDs in patients with active RA.
- Consistent with Phase 2 studies and a Phase 3 monotherapy study, tofacitinib demonstrated rapid, significant and clinically meaningful reductions in signs and symptoms of RA, and physical function.
- No new safety signals were detected.



## Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel

Two doses of tofacitinib (5 mg/10 mg BID) were given to 80% of randomized patients with significant DAS response (2.2/2.5), DAS remission (11%/14.8%), HAQ response (0.46/0.56), ACR20, 50 and 70 response (52.7%/58.3%; 33.8%/36.6%; 13.2%/16.2%) compared to placebo.

Clinical ACR20 responses were seen as early as 2 weeks in this trial.

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## Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel (cont'd)

Serious adverse events and discontinuations were seen in about 2% of treated patients, including 4 deaths and 4 opportunistic infections.

The exact place of JAK inhibition in active RA patients despite DMARD therapy will need to be addressed.

Radiological outcomes, long-term safety and predictive factors for major clinical response will ultimately guide physicians in the timely introduction of JAK inhibition in active RA.



# **The Association Between Systemic Glucocorticoid Therapy and the Risk of Infection in Patients with Rheumatoid Arthritis: Systematic Review and Meta-analysis**

Dixon WG, Suissa S, Hudson M

Presented at the 2011 European League Against Rheumatism (EULAR) Congress

Abstract # SAT0238



# Study Design

Objective: To perform a systematic review and meta-analysis of randomized controlled trials (RCTs) and observational studies to explore the relationship between glucocorticoid (GC) therapy and the risk of infection in patients with RA.

Eligibility criteria: Randomized controlled trials with:

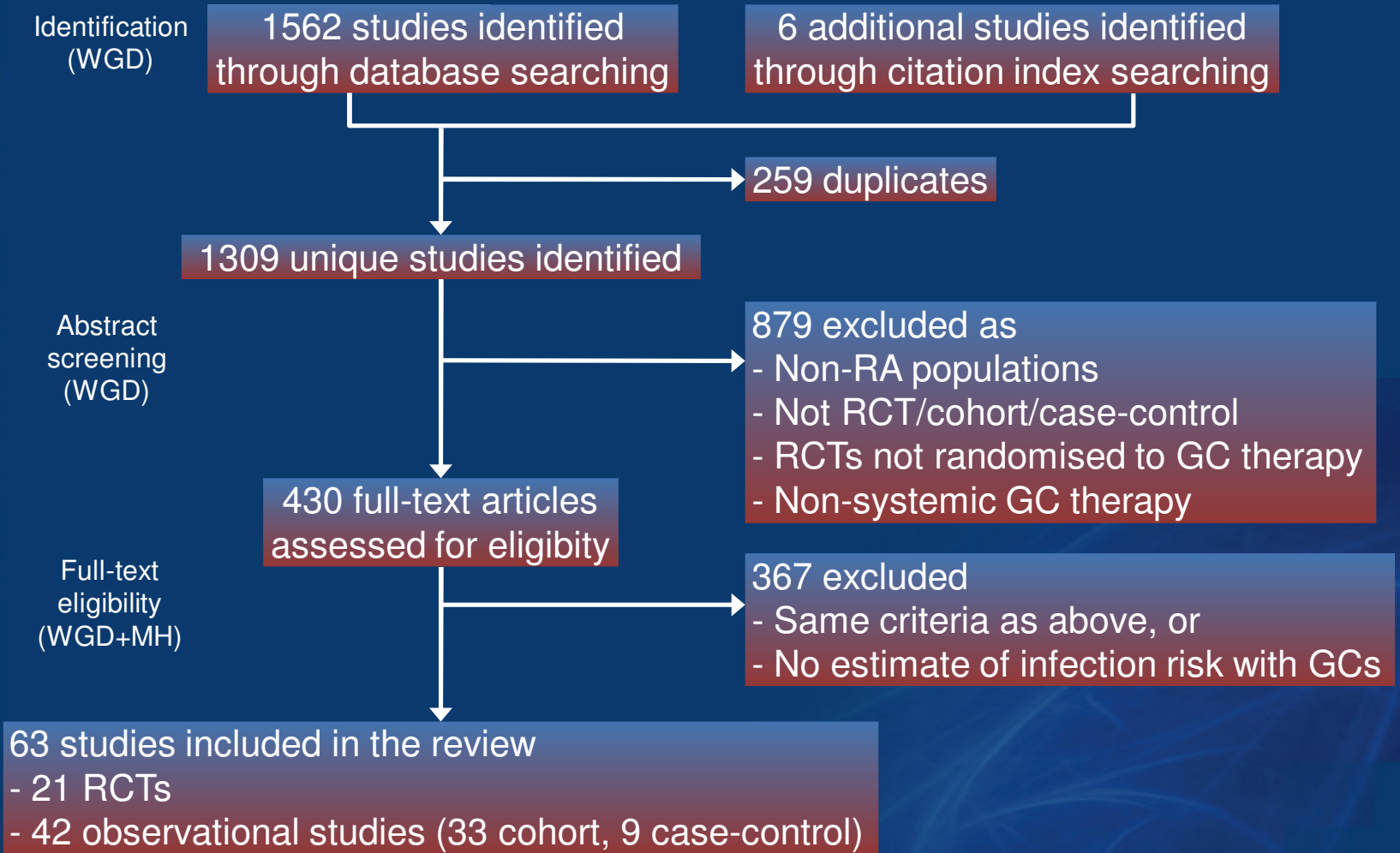
- Study population of patients with RA
- Exposure to systemic GC therapy in one arm and non-exposure in a further study arm
- Reporting of infection numbers or rates in both arms



# Methodology

- A systematic review of:
  - Patients with RA
  - Studies reporting comparison of infection incidence between glucocorticoid (GC)-exposed and non-GC-exposed patients.
  - Systemic GC therapy (intra-articular excluded)
  - MEDLINE, EMBASE, CINAHL and the Cochrane Centre of Controlled Trials to January 2010
  - English language publications
  - Separate searches for randomized controlled trials (RCTs) and observational studies

# Study Selection





# Results

- In this analysis of randomized controlled trials, glucocorticoid (GC) therapy was not associated with increased risk of infection (relative risk [RR] 0.97 [95% CI 0.69, 1.36]).
- Small numbers of events in the RCTs meant a clinically important increased or decreased risk could not be ruled out.
- The observational studies generated a RR of 1.67 (1.49, 1.87); there was significant heterogeneity between studies.
- A positive dose-response was seen with risk increasing with higher doses of GC therapy. The increased risk (and heterogeneity) persisted when analyses were stratified by varying definitions of exposure, outcome and adjustment for confounders.



# Conclusions

In this analysis, an increased risk of infection with GC therapy was seen in observational studies but not in randomized clinical trials.

Inconsistent reporting of safety outcomes in the RCTs, as well as marked heterogeneity, probable residual confounding and publication bias in the observational studies, limited the opportunity for a definitive conclusion. Nevertheless, neither meta-analysis excluded a clinically meaningful increased risk.


Clinicians should remain vigilant for infection in patients with RA treated with GC therapy



## Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel

Neither meta-analysis excluded a clinically meaningful increased risk.

Clinicians should remain vigilant for infection in RA patients treated with GC therapy.



# Induction Therapy with Methotrexate and Prednisone in Rheumatoid or Very Early Arthritic Disease: IMPROVED Study

de Boer K, Visser K, Roday H, *et al.*

Presented at the 2011 European League Against Rheumatism  
(EULAR) Congress

Abstract # SAT0244



# Study Design

Objective: To assess the rate of remission after 4 months of treatment with methotrexate (MTX) and a tapered high dose prednisone in patients with recent onset rheumatoid arthritis (RA) or undifferentiated arthritis (UA).

Subjects: 610 patients with recent onset (<2 years symptoms) RA and UA, with a baseline Disease Activity Score (DAS)  $\geq 1.6$ . The 1987 ARC criteria were used to classify patients with RA; UA was defined as arthritis >1 joint and at risk for developing RA by estimation of a rheumatologist.

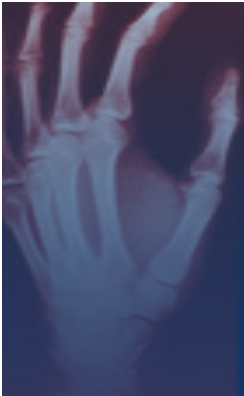


# Methodology

- Multicenter clinical study
- All patients started treatment with methotrexate 25 mg/wk and prednisone 60 mg/day tapered to 7.5 mg/day in 7 weeks, aimed at achieving a DAS <1.6.
- Clinical outcomes (% remission defined as DAS <1.6 and improvement in DAS) and functional ability were measured with the Dutch Health Assessment Questionnaire (HAQ) after 4 months of treatment.

DAS: disease activity score; HAQ: health assessment questionnaire

De Boer K, *et al.* Presented at EULAR 2011; Abstract # SAT0244.



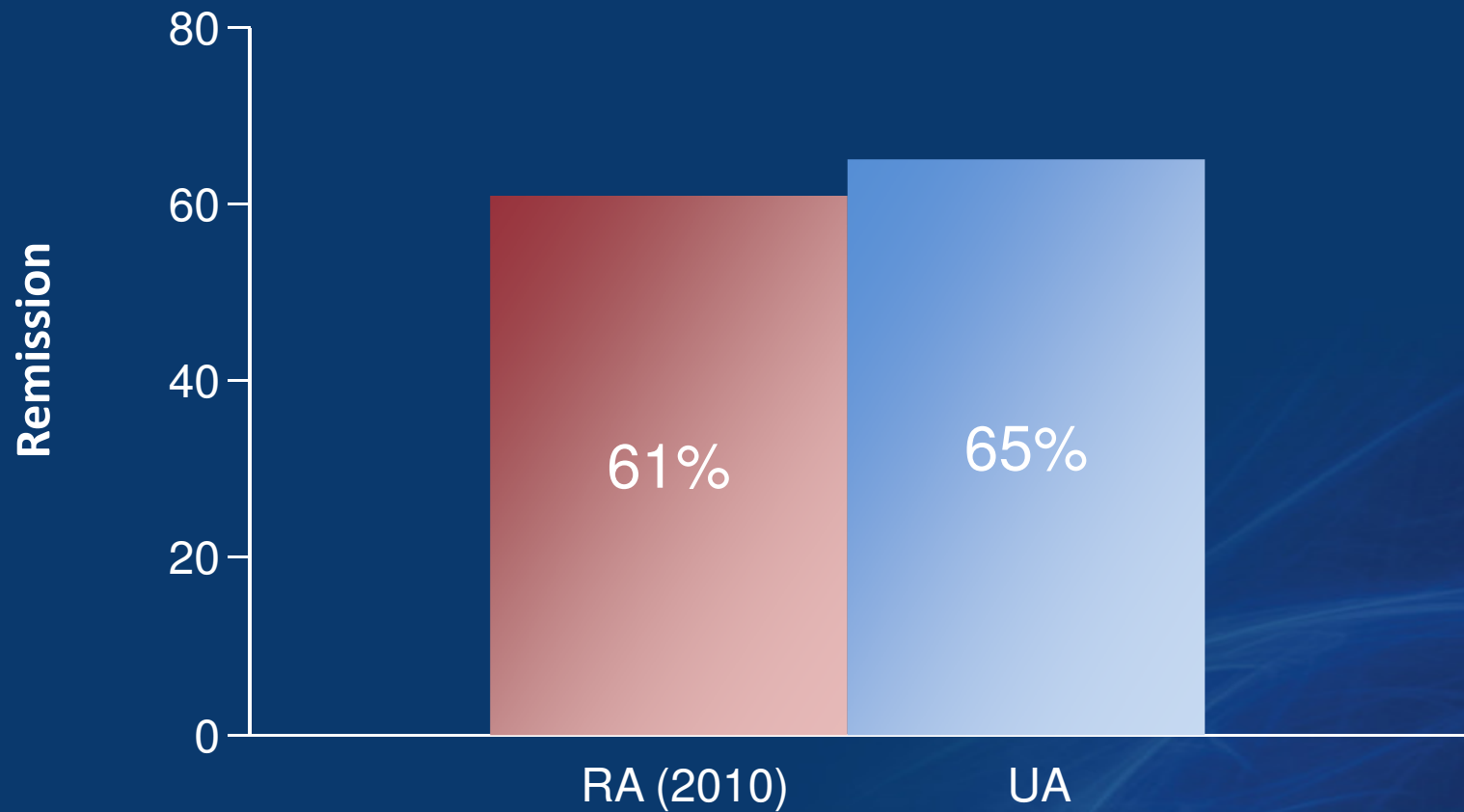
# Baseline Demographics of RA (2010) and UA (non-RA2010) Patients

	RA (2010), n=469	UA, n=134)	p value
Age , years (mean, SD)	53 (16)	52 (13)	0.53
% Female	61	69	0.08
Symptom duration, weeks (median IQR)	16 (8-29)	18 (9-34)	0.13
% RF positive	8	70	<0.001
% ACPA positive	4	56	<0.001
DAS (mean, SD)	2.71 (0.65)	3.35 (0.93)	<0.001
HAQ (mean, SD)	1.05 (0.65)	1.19 (0.67)	0.03

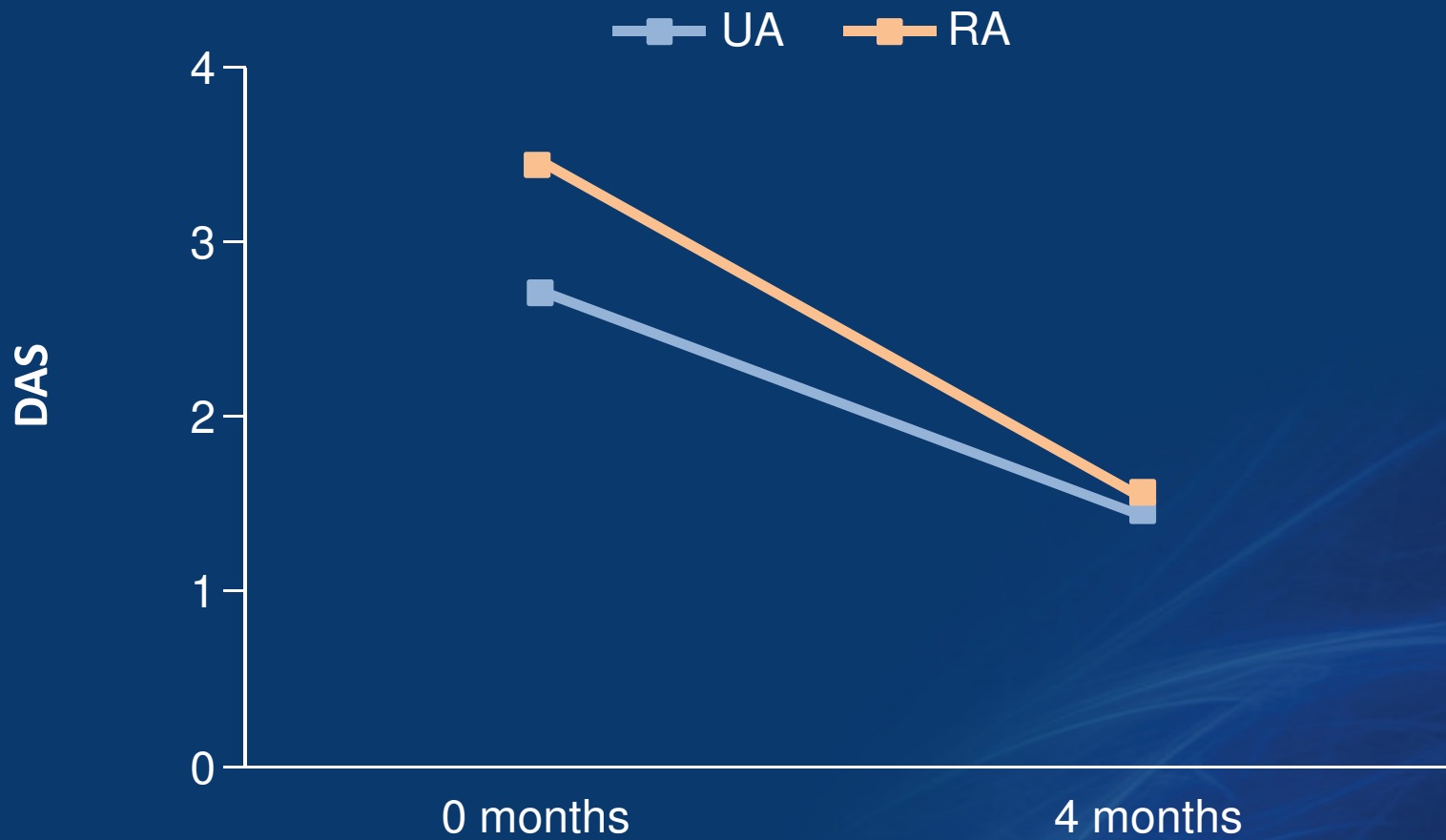
RA: rheumatoid arthritis; UA: undifferentiated arthritis; SD: standard deviation; IQR: interquartile range; RF: rheumatoid factor; ACPA: anticitrullinated protein antibody; DAS: disease activity score; HAQ: health assessment questionnaire

De Boer K, *et al.* Presented at EULAR 2011; Abstract # SAT0244.

# Proportion of Patients in Remission After 4 Months



# DAS at Baseline and After 4 Months





# Conclusions

Although there were significant differences at baseline between patients with RA and patients with UA, after 4 months of treatment with MTX and a tapered high dose of prednisone, both groups achieved clinical remission (DAS <1.6) in similar proportions (average 61%), with similar outcomes for mean DAS and HAQ.



## Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel

With the new 2010 EULAR-ACR classification criteria, many patients not meeting the 1987 criteria are considered to have RA. This allows a re-examination of undifferentiated arthritis (UA).

When compared to RA patients, and with only 8% ACPA and 6% RF positivity, these newly defined undifferentiated arthritis patients have shorter disease duration, lower DAS and HAQ at baseline, yet have similar DAS response, HAQ response, and DAS remission rates with MTX and a tapered high dose of prednisone.

The similar response and remission rates in RA and in UA according to these new 2010 EULAR classification criteria argue strongly for a window of opportunity for optimal treatment of early arthritis.



# Improvements in Disease Activity and Physical Function in Patients with RA Receiving Subcutaneous Abatacept in the Presence or Absence of an Initial IV Loading Dose

Nash P, Ludivico C, Delaet I, *et al.*

Presented at the 2011 European League Against Rheumatism (EULAR) Congress

Abstract #SAT0287



# Study Design

Objective: To utilize open-label data from two Phase 3 trials in order to examine efficacy in patients with established disease-modifying antirheumatic drug (DMARD)-refractory RA receiving subcutaneous (SC) abatacept (125 mg/week) with or without an IV loading dose.

Subjects: A total of 167 patients entered ALLOW and received SC abatacept plus an IV loading dose (SC + IV load), and 100 patients entered ACCOMPANY and received SC abatacept, with no IV loading dose (SC only)



# Methodology

- In the initial 3-month open-label period of the ALLOW trial, patients received subcutaneous (SC) abatacept + methotrexate (MTX) with an IV loading dose on day 1.
- In the 4-month, open-label ACCOMPANY trial, patients were stratified to SC abatacept  $\pm$  MTX, with no IV loading dose.
- Patients in both trials had active RA and an inadequate response to disease-modifying antirheumatic drugs.
- Data from these trials were examined up to month 3 to assess mean changes from baseline in disease activity and physical function based on patients with available data at the visit of interest.

# Baseline Demographics and Clinical Characteristics

	ALLOW SC + IV load (n=167)	ACCOMPANY SC only (n=100)
Age , years	50.1 ± 13.4	54.0 ± 10.9
Female, %	84	75
Caucasian %	92	76
Disease duration, years	7.5 ± 8.0	10.1 ± 11.1
RF status, % positive	81	67
Tender joints	14.3 ± 10.3	24.1 ± 16.2
Swollen joints	11.0 ± 5.7	17.2 ± 12.1
Pain, 100 mm VAS	54.1 ± 22.7	66.8 ± 19.6
HAQ-DI score (0-3)	1.3 ± 0.7	1.4 ± 0.7
Levels of CRP, mg/dL	1.3 ± 1.9*	2.0 ± 2.9
DAS28 (CRP)	4.7 ± 0.9	5.4 ± 1.4
Prior treatment, n (%)		
MTX	167 (100)	81 (81)
Corticosteroids	83 (50)	47 (47)
NSAIDs	138 (83)	69 (69)
Other DMARDs	66 (40)	49 (49)
Biologics	18 (11)	23 (23)

Data are mean ± SD unless otherwise stated. \*Based on hsCRP; standard deviation; SC: subcutaneous; RF: rheumatoid factor; VAS: visual analog scale; HAQ-DI: health assessment questionnaire – disease index; DAS: disease activity score; CRP: c-reactive protein; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; DMARD: disease-modifying anti-rheumatic drugs

Nash P, *et al.* Presented at EULAR 2011; Abstract # SAT0287.

# Clinical Efficacy through 3 Months of Treatment with or without IV Loading

Mean (SD)	ALLOW SC + IV load		ACCOMPANY SC only	
	DAS28 (CRP)	HAQ-DI	DAS28 (CRP)	HAQ-DI
Baseline	4.7 (0.9) n=167	1.3 (0.07) n=167	5.4 (1.4) n=98	1.4 (0.7) n=99
Month 1	3.7 (1.2) n=165	1.0 (0.7) n=166	4.6 (1.4) n=95	1.2 (0.7) n=94
Month 2	3.4 (1.2) n=164	0.8 (0.6) n=163	4.0 (1.4) n=96	1.1 (0.8) n=93
Month 3	3.2 (1.3) n=161	0.7 (0.7) n=163	3.8 (1.4) n=94	1.1 (0.7) n=92

As observed data; SD: standard deviation; SC: subcutaneous; DAS: disease activity score; HAQ-DI: health assessment questionnaire – disease index

Nash P, *et al.* Presented at EULAR 2011; Abstract # SAT0287.



# Results

- Baseline disease was less severe in patients receiving subcutaneous (SC) + intravenous (IV) load versus those receiving SC only
- Mean % changes (SE) in DAS28 at Month 3 were generally comparable with and without IV loading.
- A similar pattern was seen for physical function; HAQ-DI improved from 1.3 to 0.7 in patients receiving SC + IV load, and from 1.5 to 1.1 in patients receiving SC only.
- Occurrence of serious adverse events, including infections, was similar with or without IV loading dose.

DAS: disease activity score; HAQ-DI: health assessment questionnaire – disease index

Nash P, *et al.* Presented at EULAR 2011; Abstract # SAT0287.



# Conclusions

Improvements in disease activity and physical function were observed with SC abatacept treatment over three months, with and without a loading dose. The magnitude of improvements was generally similar in both studies

SC abatacept was well tolerated in ALLOW (with IV loading) and in ACCOMPANY (without IV loading).

Target therapeutic PK values were achieved by Day 15 of SC abatacept treatment, regardless of IV loading.

Observations on clinical efficacy, tolerability and PK support the use of SC abatacept, both with and without an IV abatacept loading dose.



## Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel

With the arrival of SC abatacept, the pertinence of an initial intravenous loading dose is being reexamined.

Analysis of open-label data from two Phase III trials of SC abatacept failed to show a clinical or a pharmacokinetic advantage of an initial IV dose, yet these two strategies were not compared directly, in a head to head trial.

A direct comparison on disease activity and long-term responses of newly initiated SC abatacept, with or without IV loading, in a randomized cohort should answer this question more thoroughly.



# Comparison of Drug Retention Between New Biological Agents and Classic Anti-TNF Agents in TNF Inadequate Responder Rheumatoid Arthritis Patients

Martin-du-Pan Prujim S, Scherer A, Gabay C, *et al.*

Presented at the 2011 European League Against Rheumatism (EULAR)  
Congress

Abstract #SAT0298



# Study Design

Objective: To compare drug retention rates of the newer biologics (non-anti-TNF group: rituximab, tocilizumab, abatacept) with those of alternative anti-TNF (etanercept, adalimumab, infliximab) prescribed in second or third intention.

Subjects: All patients were diagnosed with RA by a board-certified rheumatologist and were treated with an alternative biological, after a first inadequate response to an anti-TNF agent.

TNF: tumor necrosis factor

Martin-du-Pan S, *et al.* Presented at EULAR 2011; Abstract # SAT0298.



# Methodology

- Longitudinal population-based Swiss RA cohort (SCQM-RA).
- Drug survival was analyzed using a Cox proportional hazards model, adjusting for potential confounders such as disease-modifying anti-rheumatic drug and glucocorticoid co-medication, number of previous biologic failures, calendar year, and various disease characteristics.

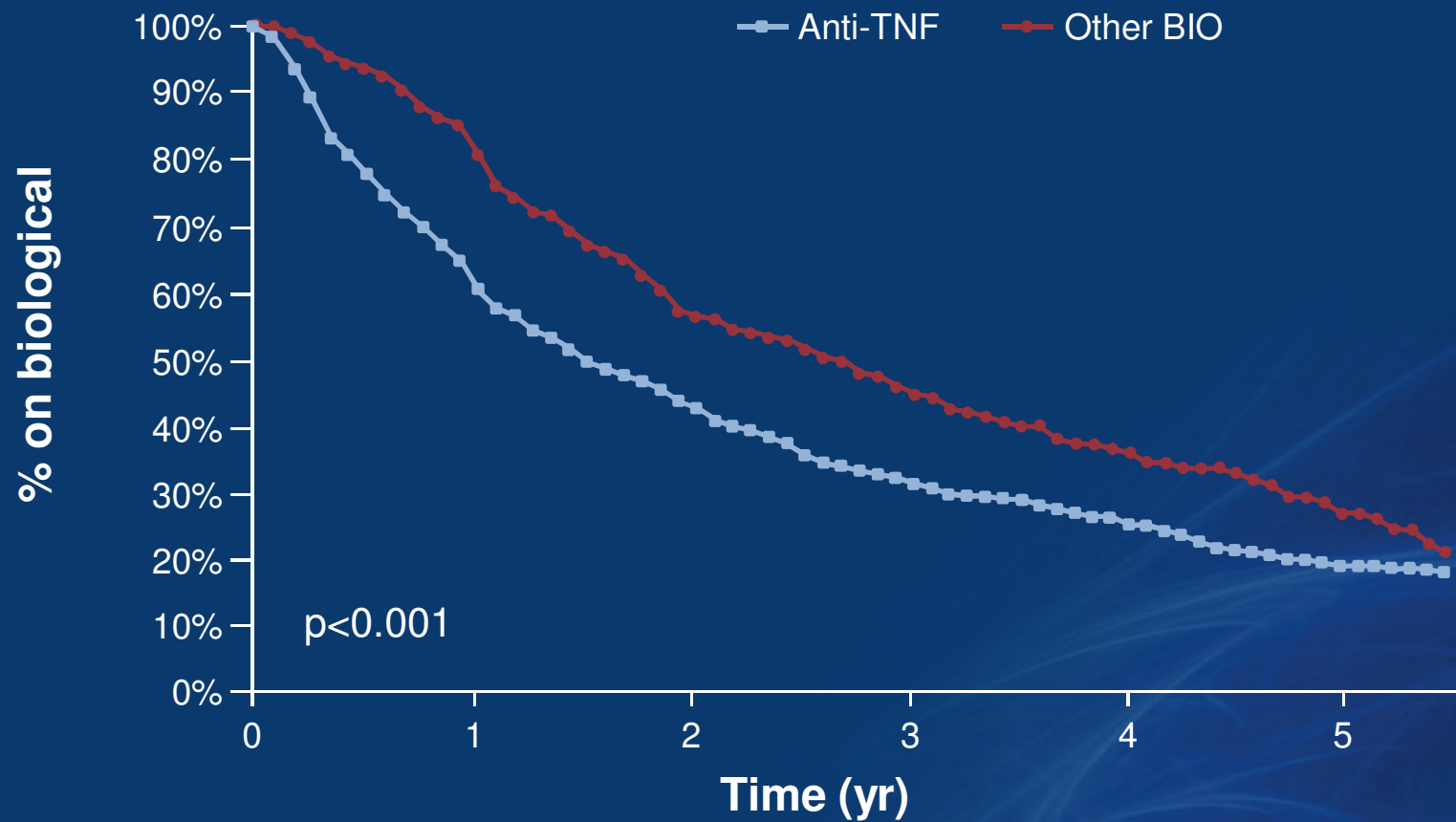
# Study Population (Treatment Courses)

Baseline characteristics	Alternative anti-TNF (n=858)	Other biologics (n=629)	P value
Number of tt courses	858	629	
Age, years	54 (14)	57 (12)	0.07
Gender, male (%)	22	20	0.363
Disease duration, years	10 (9)	11 (9)	0.16
RF, %	82	78	0.065
Number failed biologics	2.7 (0.8)	2 (0.4)	<0.001
Disease activity (DAS28)	4.3 (1.45)	4.18 (1.55)	0.52
Functional capacity (HAQ)	1.30 (0.67)	1.32 (0.70)	0.67
RADAI	3.93 (2.1)	4.35 (2.32)	0.53
<b>DMARDS (%)</b>			
Methotrexate	47	43	0.2
Leflunomide	15	17	0.27
Other	10	8	0.32
Combination DMARD	6	4	0.03
No DMARD	36	37	0.71
Prednisone	44	45	0.73

TNF: tumor necrosis factor; RF: rheumatoid factor; DAS: disease activity score; HAQ: health assessment questionnaire; RADAI: Rheumatoid Arthritis Disease Activity Index; DMARD: disease-modifying anti-rheumatic drugs

Martin-du-Pan S, *et al.* Presented at EULAR 2011; Abstract # SAT0298.

# Time to Discontinuation of Biologic Agents





# Results

We identified 1,487 biologic treatment courses in anti-tumor necrosis factor (TNF) inadequate responders – 858 with an alternative anti-TNF and 629 with a biologic agent having a different mode of action.

A second biological was administered 1,046 times, a third biological 331 times, a fourth 88 times, and a fifth 20 times.

Baseline characteristics were similar in both study groups except for a higher frequency of glucocorticoid and methotrexate use in the anti-TNF group.

Overall, drug retention was lower in the anti-TNF group.

Median treatment retention was 25 months for alternative anti-TNFs and 32 months on non-anti-TNF biologics.



# Conclusions

In patients having experienced at least one inadequate response to a previous anti-tumor necrosis factor (TNF) agent, there was significantly higher drug retention for biologics of a different mode of action compared to alternative anti-TNF agents.



## Commentary from the International Literature Search in Rheumatology's Canadian Editorial Panel

Patients who failed an anti-TNF were more likely to continue therapy if they switched to another biologic with a different mode of action; however, reasons for discontinuation were not analysed.

The reason for failing a TNFi is important when deciding to switch to another anti-TNF with a different mode of action.

Gullick et al. (FRI0217) presented clinical responses for 158 patients who switched to a different TNFi following discontinuation. Their analysis showed that another TNFi was an effective treatment option after a secondary failure to a TNFi; however, an alternative mode of action is preferable after a primary failure.