Supplementary Appendix

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Methods

Trial design

The randomisation sequence was determined by the sponsor and implemented using a vendor-operated interactive voice response system. To prevent potential unblinding of the efficacy assessor because of observed efficacy or laboratory changes, a dual assessor approach was used to evaluate efficacy and safety. Central laboratories (BioClinica, Inc., Newtown, PA, United States; and Covance, Geneva, Switzerland), blinded to treatment, were used to read x-rays.

The protocol was amended on 14 December 2009 to cap dosing of TCZ/placebo at 800 mg in patients weighing more than 100 kg and to remove the maximum weight limit of 150 kg. This was based on data from the sponsor's clinical development program in adult patients with rheumatoid arthritis, which indicated that additional benefit was not achieved when the TCZ dose was increased above 800 mg.

Patients

Disease-modifying anti-rheumatic drugs (DMARDs) had to be withdrawn for an appropriate washout period before baseline (leflunomide for ≥12 weeks or ≥14 days after standard cholestyramine or activated charcoal washout; azathioprine for ≥4 weeks). Intravenous or intramuscular corticosteroids were not permitted. Use of lipid-lowering agents in patients with elevated lipid levels was strongly encouraged in conjunction with the treating physician's clinical judgement and treatment guidelines. Patients had to have no evidence of active tuberculosis infection at enrolment, no active tuberculosis requiring treatment within the previous 3 years and no latent tuberculosis.

Sensitivity analyses

Sensitivity analyses were performed on the primary endpoint using last-observation-carried-forward imputation for missing data. Analysis of the observed data with no imputation for missing data was also performed. A Cochran-Mantel-Haenszel chi-squared test stratified by the stratification factors applied at randomisation was also performed as supportive analysis. Binary and categorical endpoints, including Disease Activity Score using 28 joints–erythrocyte sedimentation rate (DAS28-ESR) and American College of Rheumatology (ACR) remission, used non-responder imputation if remission status could not be determined. Last-observation-carried-forward was used for missing joint counts, and no imputation was used for missing ESR, patient or physician Visual Analogue Scale assessments or Health Assessment Questionnaire–Disability Index scores. If C-reactive protein data were not available, ESR was used instead. Linear extrapolation was used for missing radiographic data, provided a baseline and at least one post-baseline reading were available. Sensitivity analysis including observed data only was also performed.

Results

Patients

The study was conducted at 237 sites in 35 countries. Sites were located in Argentina, Australia, Austria, Brazil, Canada, China, Colombia, Denmark, Finland, France, Germany, Greece, Guatemala, Hong Kong, Hungary, Ireland, Israel, Italy, Macedonia, Mexico, New Zealand, Panama, Peru, Philippines, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Thailand, Turkey, United Kingdom and the United States. The first patient was screened on 30 September 2009, and the first patient was enrolled on 19 October 2009. The last patient completed week 52 on 23 May 2012.

Most patients increased their MTX dose to a 15-mg or 20-mg weekly regimen, as shown in table S2 (data related to dose excluded all patients randomly assigned to the TCZ monotherapy group because they did not receive active MTX). By baseline weight (which varied considerably among patients, though most were in the middle weight category; table S3), a consistent linear impact of weight on MTX dose was observed (table S4). The mean (SD) cumulative dose of MTX was 755.8 (276.16) mg, 725.6 (280.34) mg and 672.3 (297.31) mg in the placebo+MTX, 4-mg/kg TCZ+MTX and 8-mg/kg TCZ+MTX groups, respectively. The mean (SD) MTX dose per week was 15.6 (5.41), 15.2 (5.71) and 14.3 (6.19) mg, respectively, from baseline to week 24 and 16.4 (5.19), 15.7 (5.70) and 14.7 (6.17) mg, respectively, from baseline to week 52.

Efficacy

Logistic regression analysis demonstrated that patients receiving the TCZ regimens were 2.7 to 4.8 times more likely to achieve DAS28-ESR remission at week 24 than those receiving MTX monotherapy; however, the comparison with placebo+MTX occurred after the break in hierarchical testing for the 4-mg/kg TCZ+MTX group (Table 2). Observed case and last-observation-carried-forward sensitivity analyses reached similar conclusions (table S5). Identical values to those of the primary analysis were obtained for each treatment group using the Cochran-Mantel-Haenszel chi-squared test supportive analysis: higher proportion of patients achieved DAS28 remission in the TCZ treatment group (44.8% [8 mg/kg TCZ+MTX], 38.7% [8 mg/kg TCZ+placebo] and 31.9% [4 mg/kg TCZ+MTX]) compared with 15% [placebo+MTX]. The observed analysis results for changes in radiographic score (mTSS), for which no imputation was made for missing results, were similar to the linearly extrapolated results (figure S2). Last-observation-carried-forward was used to impute missing data for some components of certain secondary endpoints and in sensitivity analysis of the primary endpoint; however, this method has known limitations.[1] Nevertheless, observed case sensitivity analysis of the primary endpoint provided consistent results.

Safety

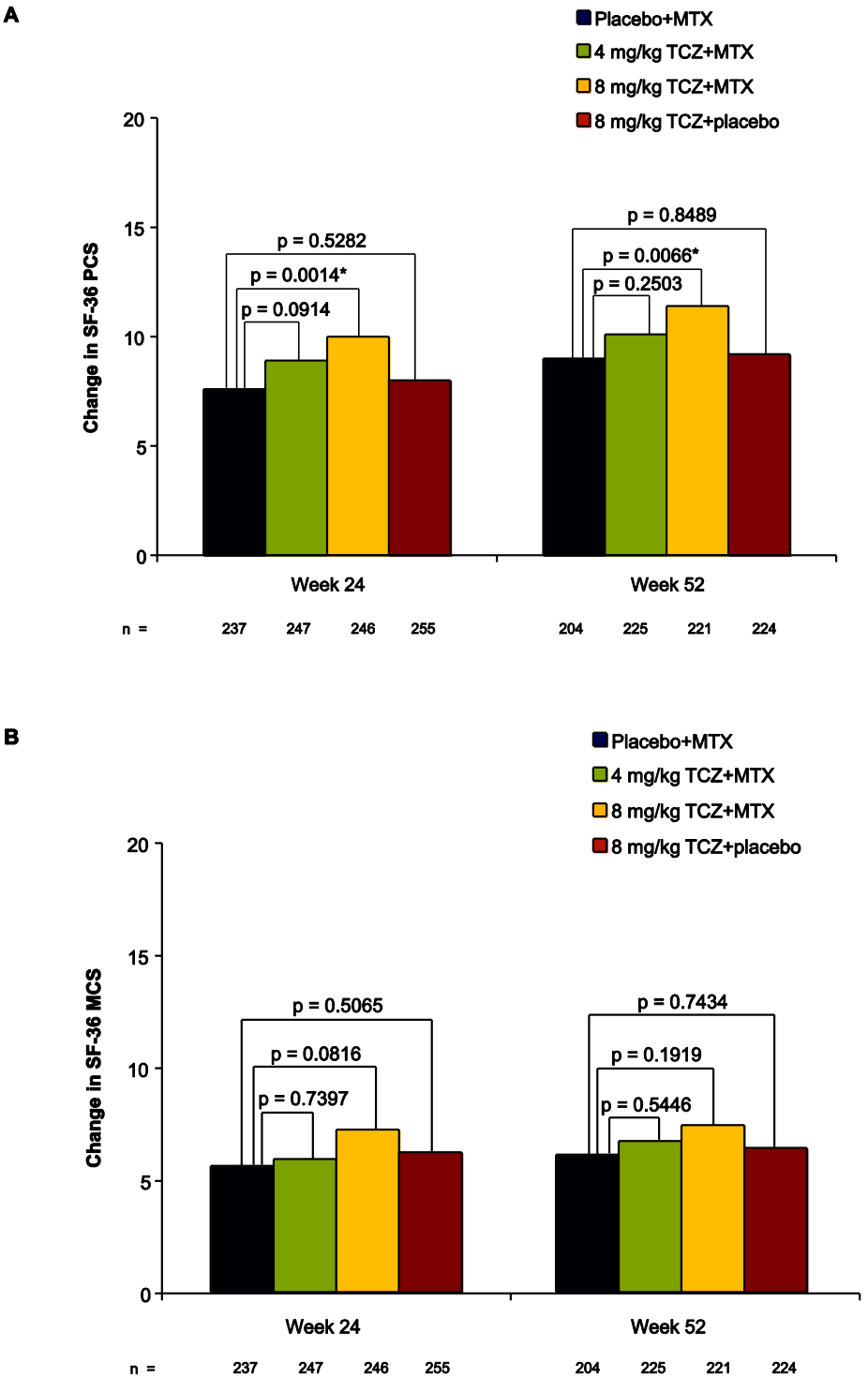
Five serious myocardial infarctions developed: one each in the 8-mg/kg TCZ+MTX and the 8-mg/kg TCZ+placebo groups and three in the 4-mg/kg TCZ+MTX group. All five patients had cardiovascular risk factors that might have contributed to the myocardial infarction event.

Reference

1. Molenberghs G. What to do with missing data [editorial]? *J R Stat Soc: Series A* (Statistics in Society) 2007;170:861-63.

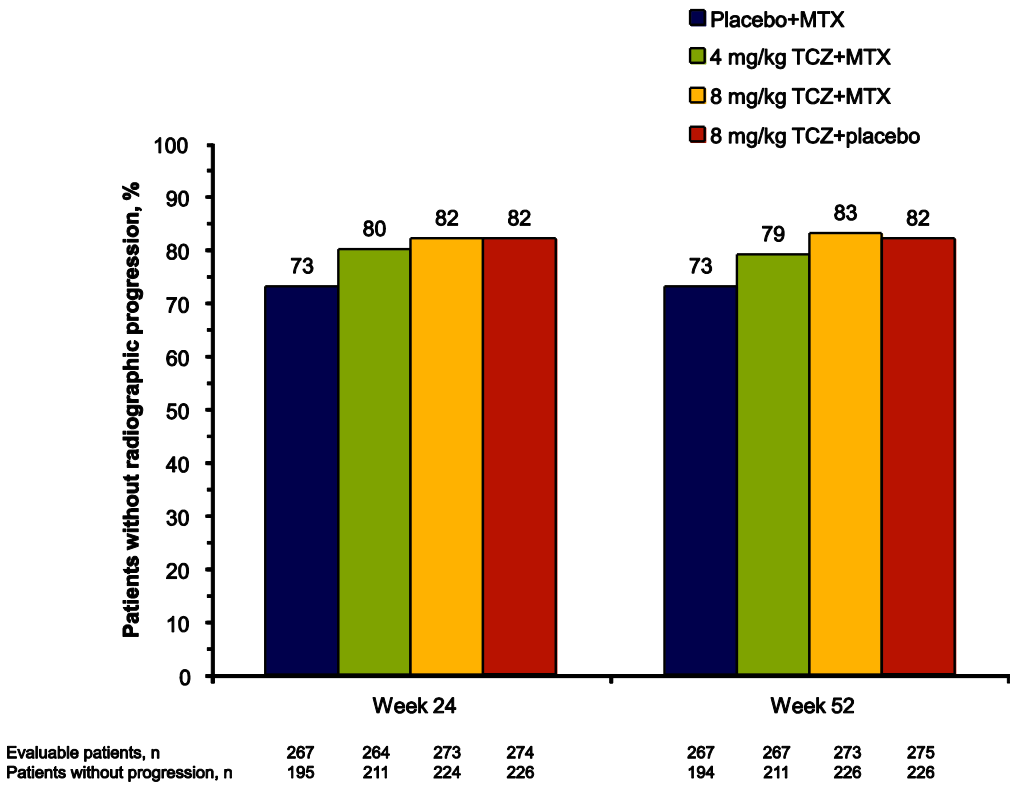
Supplementary Figure S1 Change from baseline in SF-36 (A) PCS and (B) MCS (ITT population).

MCS, Mental Component Summary score; MTX, methotrexate; PCS, Physical Component Summary score; SF-36, Short Form 36; ITT, intent-to-treat TCZ, tocilizumab.

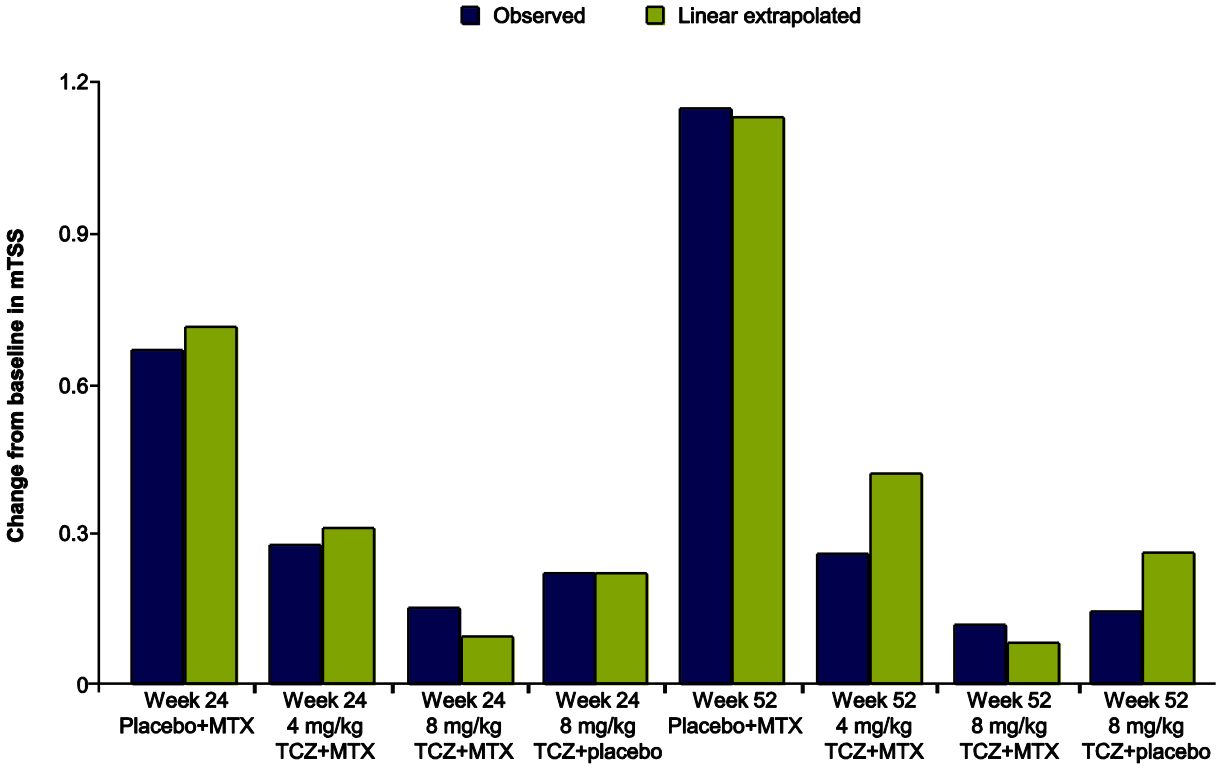


*Comparison occurred after the break in hierarchically ordered testing sequence.

Supplementary Figure S2 Percentages of patients with no radiographic progression (change from baseline ≤0 in mTSS) at week 24 and week 52 (ITT population).
ITT, intent-to-treat; mTSS, van der Heijde–modified total Sharp score; MTX, methotrexate; TCZ, tocilizumab.



Supplementary Figure S3 Observed and linearly extrapolated change from baseline in mTSS (ITT population). ITT, intent-to-treat; mTSS, modified total Sharp score; MTX, methotrexate; TCZ, tocilizumab.



Order	Endpoint	TCZ dose (mg/kg) compared with placebo+MTX
1	Proportion of patients with DAS28 remission response (DAS28 <2.6) at week 24	8+MTX
2	Proportion of patients with ACR50 response at week 24	8+MTX
3	Proportion of patients with ACR70 response at week 24	8+MTX
4	Proportion of patients with ACR20 response at week 24	8+MTX
5	Change from baseline in mTSS at week 52	8+MTX
6	Change from baseline in modified Sharp erosion score at week 52	8+MTX
7	Proportion of patients with a DAS28 remission response (DAS28 <2.6) at week 52	8+MTX
8	Proportion of patients with ACR50 response at week 52	8+MTX
9	Proportion of patients with ACR70 response at week 52	8+MTX
10	Proportion of patients with ACR20 response at week 52	8+MTX
11	Change from baseline in HAQ-DI score at week 52	8+MTX
12	Change from baseline in HAQ-DI score at week 24	8+MTX
13	Proportion of patients with DAS28 remission response (DAS28 <2.6) at week 24	8 (monotherapy)
14	Proportion of patients with ACR50 response at week 24	8 (monotherapy)
15	Proportion of patients with ACR70 response at week 24	8 (monotherapy)
16	Change from baseline in mTSS at week 52	8 (monotherapy)
17	Change from baseline in modified Sharp erosion score at week 52	8 (monotherapy)
18	Proportion of patients with DAS28 remission response (DAS28 <2.6) at week 24	4+MTX
19	Proportion of patients with ACR50 response at week 24	4+MTX
20	Proportion of patients with ACR70 response at week 24	4+MTX
21	Change from baseline in mTSS at week 52	4+MTX
22	Change from baseline in modified Sharp erosion score at week 52	4+MTX
23	Proportion of patients with ACR20 response at week 24	8 (monotherapy)
24	Proportion of patients with DAS28 remission response (DAS28 <2.6) at week 52	8 (monotherapy)
25	Proportion of patients with ACR50 response at week 52	8 (monotherapy)
26	Proportion of patients with ACR70 response at week 52	8 (monotherapy)
27	Proportion of patients with ACR20 response at week 52	8 (monotherapy)
28	Change from baseline in HAQ-DI score at week 52	8 (monotherapy)
29	Change from baseline in HAQ-DI score at week 24	8 (monotherapy)
30	Proportion of patients with ACR20 response at week 24	4+MTX
31	Proportion of patients with DAS28 remission response (DAS28 <2.6) at week 52	4+MTX
32	Proportion of patients with ACR50 response at week 52	4+MTX
33	Proportion of patients with ACR70 response at week 52	4+MTX
34	Proportion of patients with ACR20 response at week 52	4+MTX
35	Change from baseline in HAQ-DI score at week 52	4+MTX
36	Change from baseline in HAQ-DI score at week 24	4+MTX
37	Major clinical response (defined as achieving continuous 6-month period of success by the ACR70) at week 52	8+MTX
38	Change from baseline in modified Sharp JSN score at week 52	8+MTX
39	Major clinical response at week 52	8 (monotherapy)
40	Change from baseline in modified Sharp JSN score at week 52	8 (monotherapy)
41	Major clinical response at week 52	4+MTX
42	Change from baseline in modified Sharp JSN score at week 52	4+MTX

43	Change from baseline in SF-36 Physical Component score at week 24	8+MTX
44	Change from baseline in SF-36 Physical Component score at week 52	8+MTX
45	Change from baseline in SF-36 Physical Component score at week 24	8 (monotherapy)
46	Change from baseline in SF-36 Physical Component score at week 52	8 (monotherapy)
47	Change from baseline in SF-36 Physical Component score at week 24	4+MTX
48	Change from baseline in SF-36 Physical Component score at week 52	4+MTX

Supplementary Table S1 Hierarchical chain of efficacy endpoints for statistical testing. Endpoints were evaluated sequentially in a fixed hierarchy of statistical testing (with prioritisation of the primary comparator group, 8 mg/kg TCZ+MTX) to reduce the occurrence of false-positive conclusions resulting from multiple testing.
ACR, American College of Rheumatology; DAS28, Disease Activity Score using 28 joints; HAQ-DI, Health Assessment Questionnaire–Disability Index; JSN, joint space narrowing; mTSS, modified total Sharp score; MTX, methotrexate; SF-36, Short Form 36; TCZ, tocilizumab.

Highest MTX dose recorded (mg/week)	Frequency (number of patients)	Percentage (%)
7.5	33	3.8
10	1	0.1
15	120	13.9
18.75	1	0.1
20	699	80.9
22.5	1	0.1
25	4	0.5
30	1	0.1
40	2	0.2
52.5	1	0.1
60	1	0.1

Supplementary Table S2 Frequency of patients by highest dose recorded (n=864). Data related to MTX dose excluded all patients randomly assigned to the TCZ monotherapy group because they did not receive active MTX. Five patients took a high dose of MTX (>25 mg/week) in error for 1 week only; patients returned to their usual dose after the deviation.
MTX, methotrexate.

Weight Category	n	Mean	SD	Median	Min	Max
<60 kg	257	52.81	5.16	54.0	36.7	59.8
60-100 kg	804	76.15	10.59	75.0	60.0	100.0
>100 kg	101	116.47	14.36	111.4	101.0	167.3
Overall	1162	74.49	18.99	71.8	36.7	167.3

Supplementary Table S3 Descriptive summary statistics of baseline weight (kg).
Max, maximum; Min, minimum; SD, standard deviation.

Weight Category	n	Mean	SD	Median	Min	Max
<60 kg	197	0.36	0.077	0.36	0.13	0.80
60-100 kg	589	0.26	0.063	0.26	0.08	0.88
>100 kg	78	0.16	0.030	0.17	0.05	0.20
Overall	864	0.27	0.085	0.27	0.05	0.88

Supplementary Table S4 Descriptive summary statistics of MTX dose by weight (mg/week/kg). Data related to dose excluded all patients randomly assigned to the TCZ monotherapy group because they did not receive active MTX.
Max, maximum; Min, minimum; MTX, methotrexate; SD, standard deviation; TCZ, tocilizumab.

Reference: placebo+MTX n=287[*]	**4 mg/kg TCZ+MTX n=288[†]**	**8 mg/kg TCZ+MTX n=290[‡]**	**8 mg/kg TCZ+placebo n=292[§]**
DAS28-ESR remission			
LOCF sensitivity analysis	2.71 [1.81, 4.07][¶]	5.01 [3.37, 7.46]‖	3.78 [2.54, 5.64]‖
Observed case sensitivity analysis	2.74 [1.80, 4.18][¶]	5.12 [3.38, 7.76]‖	3.63 [2.40, 5.49]‖

Supplementary Table S5 Odds ratios from sensitivity analyses of DAS28-ESR remission status at week 24 compared with placebo+MTX (ITT population).
Data are odds ratio [95% CI]. If ESR=0, then ESR=1 is substituted into the DAS28-ESR calculation to enable a non-missing DAS28-ESR. Odds ratios were derived from logistic regression analyses. The stratification factors *region* and *serologic status* were included in the model.
[*]n=250 for observed case sensitivity analysis.
[†]n=257.
[‡]n=256.
[§]n=267 for observed case sensitivity analysis.
[¶]p<0.0001 vs placebo+MTX after the break in the hierarchically ordered testing sequence.
‖p<0.0001 vs placebo+MTX.
CI, confidence interval; DAS28, Disease Activity Score using 28 joints; DAS28-ESR remission, DAS28-ESR <2.6; ESR, erythrocyte sedimentation rate; ITT, intent-to-treat; LOCF, last-observation-carried-forward; MTX, methotrexate; TCZ, tocilizumab.

	Placebo+MTX n=282	4 mg/kg TCZ+MTX n=289	8 mg/kg TCZ+MTX n=290	8 mg/kg TCZ+placebo n=292
Patients with ≥1 event, n (%)				
All body systems Patients with ≥1 AE	3 (1.1)	4 (1.4)	3 (1.0)	3 (1.0)
Neoplasms benign, malignant and unspecified, including cysts and polyps				
Basal cell carcinoma	0	0	1 (0.3)	1 (0.3)
Breast cancer in situ	0	0	1 (0.3)	0
Breast cancer	1 (0.4)*	0	1 (0.3)*	0
Colon cancer	1 (0.4)*	0	0	0
Endometrial cancer	0	1 (0.3)*	0	0
Endometrial cancer stage I	0	0	0	1 (0.3)*
Hepatic neoplasm malignant	0	1 (0.3)*	0	0
Lung neoplasm	0	0	0	1 (0.3)*
Metastatic bronchial carcinoma	0	1 (0.3)*	0	0
Renal cancer stage II	0	1 (0.3)*	0	0
Renal cell carcinoma	1 (0.4)*	0	0	0
Total number of AEs	3	4	3	3

Supplementary Table S6 Malignancy AEs by body system and MedDRA preferred term (version 15.0). Multiple occurrences of the same AE in one individual were counted only once.
*Serious AE.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MTX, methotrexate; TCZ, tocilizumab.

Treatment group	Age, years	Sex	Underlying cause of death
Placebo+MTX n=282	64 64	F M	Sepsis Pneumonia, influenza
4 mg/kg TCZ+MTX n=289	51 83 83 82	F M F M	Cerebral haemorrhage aneurysm Lung infection Pneumonia malnutrition Arteriosclerosis
8 mg/kg TCZ+MTX n=290	60 41	M F	Pneumothorax mechanical ventilation Hypoglycaemic coma diabetes mellitus
8 mg/kg TCZ+placebo n=292	70	M	Lung neoplasm pneumonia

Supplementary Table S7 Patient deaths and underlying causes of death. Underlying causes of death were encoded using MedDRA version 15.0.
F, female; M, male; MedDRA, Medical Dictionary for Regulatory Activities; MTX, methotrexate; TCZ, tocilizumab.