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ONLINE SUPPLEMENTARY MATERIAL

SAFETY OF THE METHOTREXATE-LEFLUNOMIDE COMBINATION IN RHEUMATOID ARTHRITIS: RESULTS OF A MULTICENTRIC, REGISTRY-BASED, COHORT STUDY (BIOBADABRASIL).

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Supplementary Table 1. Description of the codification of adverse events using terms described in MEdDRA (Medical Dictionary for Regulatory Activities). Data were transferred to an Excel databank and analyzed using SPSS for Windows version 20.0. The variable SOC refers to 'System Organ Classes' and PtId to 'preferred terms'.

Cardiovascular adverse events (variable named CARDIOVASCULAR):

```
RECODE PtId ('Embolic stroke'=1) ('Ischaemic stroke'=1) ('Cerebral ischaemia'=1)
('Cerebral haemorrhage'=1) ('Cerebral infarction'=1) ('Cerebrovascular accident'=1)
('Cerebrovascular insuffciency'=1) ('Cerebellar artery occlusion'=1) INTO STROKE.
RECODE PtId ('Brain stem infarction'=1) ('Brain stem ischaemia'=1) ('Cerebral
haematoma'=1) ('Cerebrovascular disorder'=1) ('Ischaemic cerebral infarction'=1)
('Ischaemic stroke'=1) ('Ruptured cerebral aneurysm'=1) INTO STROKE.
RECODE STROKE (1=1) INTO CARDIOVASCULAR.
RECODE SOC ('Vascular disorders'=1) ('Cardiac disorders'=1) INTO
CARDIOVASCULAR.
RECODE PtId ('Carotid artery aneurysm'=1) ('Carotid artery stenosis'=1) INTO
CARDIOVASCULAR.
```

Gastrointestinal adverse events (variable named GASTRINT):

```
RECODE SOC ('Gastrointestinal disorders'=1) INTO GASTRINT.
```

Respiratory adverse events (variable named RESPIRATORY):

```
RECODE SOC ('Respiratory, thoracic and mediastinal disorders'=1) INTO
RESPIRATORY.
```

Hepatic adverse events (variable named HEPATIC):

```
RECODE PtId ('Hepatic enzyme abnormal'=1) ('Alanine aminotransferase
increased'=1)('Hepatic function abnormal'=1) ('Hepatotoxicity'=1) ('Hepatitis toxic'=1)
('Hepatitis'=1) INTO TGOTGP.
RECODE PtId ('Transaminases abnormal'=1) ('Biliary cirrhosis primary'=1)
('Transaminases increased'=1) ('Hepatocellular damage'=1) ('Hepatic necrosis'=1)
('Hepatic steatosis'=1) ('Hepatitis cholestatic'=1) INTO TGOTGP.
RECODE PtId ('Hepatic cirrhosis'=1) ('Hepatic fibrosis'=1) ('Hepatic lesion'=1) ('Hepatic
necrosis'=1)  ('Hepatic steatosis'=1)  ('Hepatic function abnormal'=1) ('Hepatotoxicity'=1)
('Hepatitis toxic'=1) ('Hepatitis'=1) INTO HEPATOCEL.
RECODE PtId ('Hepatic atrophy'=1) ('Alanine aminotransferase increased'=1) ('Hepatic
enzyme abnormal'=1) ('Hepatitis cholestatic'=1) ('Hepatobiliary disease'=1)
('Hepatocellular damage'=1) INTO HEPATOCEL.
RECODE PtId ('Biliary cirrhosis primary'=1) ('Autoimmune hepatitis'=1) ('Hepatic
steatosis'=1) INTO HEPATOCEL.
RECODE PtId ('Hepatic cirrhosis'=1) ('Hepatic fibrosis'=1) ('Hepatic necrosis'=1) ('Biliary
cirrhosis primary'=1) INTO CIRROSEGROUP.
EXECUTE.

COMPUTE HEPATIC=0.
RECODE TGOTGP (1=1)  INTO HEPATIC.
RECODE HEPATOCEL (1=1) INTO HEPATIC.
RECODE CIRROSEGROUP (1=1) INTO HEPATIC.
RECODE PtId ('Portal vein thrombosis'=1) INTO HEPATIC.
RECODE PtId ('Blood alkaline phosphatase abnormal'=1) ('Blood bilirubin increased'=1)
('Gamma-glutamyltransferase increased'=1) ('Hepatic adenoma'=1) ('Hepatic
arteriovenous malformation'=1) ('Hepatic atrophy'=1) ('Hepatic cyst'=1) INTO HEPATIC.
RECODE PtId ('Hepatosplenomegaly'=1) ('Hyperbilirubinaemia'=1)
('Hyperphosphatasaemia'=1) ('Jaundice cholestatic'=1) ('Liver disorder'=1) ('Mitochondrial
hepatopathy'=1) ('Polycystic liver disease'=1) ('Haemangioma of liver'=1) INTO HEPATIC.
IF (SOC= 'Infections and infestations') HEPATIC=0.
```

Elevation of hepatic transaminases (variable named TGOTGP):

```
RECODE PtId ('Hepatic enzyme abnormal'=1) ('Alanine aminotransferase
increased'=1)('Hepatic function abnormal'=1) ('Hepatotoxicity'=1) ('Hepatitis toxic'=1)
('Hepatitis'=1) INTO TGOTGP.
RECODE PtId ('Transaminases abnormal'=1) ('Transaminases increased'=1)
('Hepatocellular damage'=1) ('Hepatic necrosis'=1) INTO TGOTGP.
```

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Hematologic adverse events (variable named HEMATO):

```
RECODE PtId ('Acute leukaemia'=1) ('Acute myeloid leukaemia'=1) ('Anaemia'=1)
('Anaemia folate deficiency'=1) ('Anaemia macrocytic'=1)('Anaemia megaloblastic'=1)
INTO HEMATO.
RECODE PtId ('Anaemia of chronic disease'=1) ('Anaemia vitamin B12 deficiency'=1)
('Aplasia pure red cell'=1) ('Blood disorder'=1) ('Bone marrow depression'=1)('Bone
marrow disorder'=1) INTO HEMATO.
RECODE PtId ('Bone marrow toxicity'=1) ('Chronic lymphocytic leukaemia'=1) (''=1)
('Haematotoxicity'=1) ('Haemoglobin decreased'=1)('Haemolytic anaemia'=1) INTO
HEMATO.
RECODE PtId ('Haemorrhagic disorder'=1) ('Iron deficiency anaemia'=1) ('Leukopenia'=1)
('Lymphoma cutis'=1) ('Lymphopenia'=1)('Microcytic anaemia'=1) INTO HEMATO.
RECODE PtId ('Multiple myeloma'=1) ('Myelodysplastic syndrome'=1) ('Neutropenia'=1)
('Neutropenic infection'=1) ('Lymphopenia'=1)('Pancytopenia'=1) INTO HEMATO.
RECODE PtId ('Pernicious anaemia'=1) ('Platelet destruction increased'=1) ('Platelet
disorder'=1) ('Platelet production decreased'=1)
('Lymphopenia'=1)('Thrombocytopenia'=1) ('White blood cell disorder'=1) INTO HEMATO.
RECODE PtId ('Neutrophilia'=1) ('Leukocytosis'=1) ('Platelet disorder'=1) ('Platelet
production decreased'=1) ('Neutrophil count decreased'=1) INTO HEMATO.
RECODE PtId ('Thrombocythaemia'=1) ('Eosinophil count increased'=1) ('Eosinophilia'=1)
('Normochromic normocytic anaemia'=1) INTO HEMATO.
```

Neutropenia (variable named NEUTROPENIA):

```
RECODE PtId  ('Bone marrow depression'=1) INTO NEUTROPENIA.
RECODE PtId ('Bone marrow toxicity'=1)  ('Haematotoxicity'=1) INTO NEUTROPENIA.
RECODE PtId ('Leukopenia'=1)  INTO NEUTROPENIA.
RECODE PtId  ('Neutropenia'=1) ('Neutropenic infection'=1) ('Pancytopenia'=1) INTO
NEUTROPENIA.
RECODE PtId  ('White blood cell disorder'=1) INTO NEUTROPENIA.
RECODE PtId ('Neutrophil count decreased'=1) INTO NEUTROPENIA.
```

Anemia (variable named ANEMIA):

```
RECODE PtId  ('Anaemia'=1) ('Anaemia folate deficiency'=1) ('Anaemia
macrocytic'=1)('Anaemia megaloblastic'=1) INTO ANEMIA.
RECODE PtId ('Anaemia of chronic disease'=1) ('Anaemia vitamin B12 deficiency'=1)
('Aplasia pure red cell'=1) ('Pancytopenia'=1) INTO ANEMIA.
RECODE PtId ('Haemoglobin decreased'=1)('Haemolytic anaemia'=1) INTO ANEMIA.
RECODE PtId ('Iron deficiency anaemia'=1) ('Microcytic anaemia'=1) INTO ANEMIA.
RECODE PtId ('Pernicious anaemia'=1)   INTO ANEMIA.
RECODE PtId ('Normochromic normocytic anaemia'=1) INTO ANEMIA.
```

Infectious adverse events (variable named INFECTION):

```
RECODE SOC ('Infections and infestations'=1) INTO INFECTION.
```

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Supplementary Table 2. Description of primary and secondary outcomes.

Primary outcome	Secondary outcomes	Secondary outcomes of special interest	Other secondary outcomes
Serious adverse events (first SAE of any kind)	Fatal adverse events	Anemia (including pancytopenia)	Interruption of treatment course for any reason (except for pregnancy and disease remission)
	Total (any) adverse event (first AE event of any kind and degree of seriousness)	Neutropenia (including pancytopenia)	Interruption of therapy course due to inefficacy
	Cardiovascular events*: - First serious cardiovascular AE - First cardiovascular AE of any degree of seriousness	Elevation of hepatic transaminases	Interruption of treatment course due to adverse events or death
	Infectious events : - First serious infection - First infection of any degree of seriousness		
	Hepatic events*: - First hepatic serious AE - First hepatic AE of any degree of seriousness		
	Hematologic events: - First serious hematologic AE - First hematologic AE of any degree of seriousness		
	Respiratory tract events*: - First serious respiratory AE - First respiratory AE of any degree of seriousness		
	Gastrointestinal events*: - First serious gastrointestinal AE - First gastrointestinal AE of any degree of seriousness		

*Excluding infections. This exclusion does not apply to hematologic adverse because febrile

neutropenia/pancytopenia may be implicated in the etiology of infectious events. SAE: serious adverse event; AE: adverse event.

Supplementary Text 1. Data management and quality control

A 3-domain online platform was used for data entry: 1- demographics, disease characteristics, and comorbidities; 2- treatment course, recording the medications used in the therapy of RA and screening of contact with tuberculosis; 3- adverse events, with outcome information (Brazilian Society of Rheumatology. Manual BiobadaBrasil versão 2.1, available at https://biobadaser.ser.es/biobadamerica/Brasil/cgi-bin/upload/archivo.aspx?id=10). Data entry was responsibility of each center; data were compulsorily updated in case of an adverse event or treatment modification. A specifically trained monitor, employee of the Brazilian Society of Rheumatology, maintains a constant 3-level data quality control program: 1- digital, using the platform resources in a daily basis; 2- by phone, contacting all reachable registered patients at least once a year; 3- in loco, yearly, comparing registry data and medical files of 20% of patients randomly selected in each center (Cecconi et al. J Clin Rheum 2020;26:73-8). Adverse events identified during the annual phone contact should have its details verified during medical consultations.

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Supplementary Text 2. Additional information on statistical analysis

The assumption of proportional hazards was tested using log-minus-log plots using the variables of interest (the main study factors) as stratification variables in Cox models. Observing roughly parallelism between the curves of the strata confirms that the proportional hazards assumption is adequately fulfilled.

For propensity score matched analysis, which was performed including all potential confounding variables (see Methods) plus study center, we used greedy nearest neighbor matching without replacement using calipers of width equal to or less than 0.2 of the standard deviation of the logit of the propensity score.

Missing data (occurring exclusively in the variable baseline DAS28 in only 7 patients) were assumed to occur completely at random and were handled using replacement by the mean.

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Supplementary Table 3. Results of Cox proportional hazards models testing the associations of the MTX-LEF combo with adverse events in comparison to MTX. Results are expressed as hazards ratios, 95% confidence intervals, and P values.

		MTX-LEF combo (n=452) versus MTX (n=766; reference category) n=1671*	
Type of adverse event (number of events)		Crude analysis	Adjusted for covariates†
Total serious adverse events (298)		1.05 (0.80 to 1.39), P=0.712	1.02 (0.77 to 1.36), P=0.890
Fatal adverse events (26)		1.21 (0.49 to 3.02), P=0.676	1.23 (0.44 to 3.46), P=0.691
Any adverse event (854)		1.24 (1.06 to 1.45), P=0.009	1.29 (1.10 to 1.52), P=0.002
Cardiovascular‡	Serious (40)	1.07 (0.53 to 2.15), P=0.851	0.88 (0.41 to 1.89), P=0.740
	Total (106)	1.64 (1.06 to 2.52), P=0.025	1.45 (0.92 to 2.28), P=0.105
Infections	Serious (144)	1.18 (0.80 to 1.75), P=0.397	1.25 (0.83 to 1.87), P=0.281

	Total (458)	1.16 (0.94 to 1.44), P=0.170	1.28 (1.02 to 1.60), P=0.031
Hepatic‡	Serious (8)	ND	ND
	Total (42)	1.40 (0.71 to 2.79), P=0.330	1.35 (0.66 to 2.75), P=0.411
Hematologic	Serious (12)	1.35 (0.36 to 5.02), P=0.657	ND
	Total (49)	1.50 (0.76 to 2.94), P=0.238	1.33 (0.66 to 2.66), P=0.423
Respiratory tract‡	Serious (16)	0.74 (0.23 to 2.40), P=0.617	ND
	Total (57)	0.87 (0.46 to 1.66), P=0.669	1.00 (0.52 to 1.95), P=0.993
Gastrointestinal‡	Serious (15)	1.11 (0.31 to 3.93), P=0.872	ND
	Total (102)	1.10 (0.70 to 1.74), P=0.671	1.03 (0.64 to 1.65), P=0.896

*These analyses include 1671 patients, since 156 patients taking neither MTX nor LEF and 297 patients taking leflunomide were accounted for in the analyses. †Adjusted also for age, baseline DAS28, disease duration, gender, current smoking, seropositivity for RF or anti-CCP, history of malignancy, diabetes, hypertension, hypercholesterolemia, renal failure, ischemic cardiomyopathy, COPD, heart failure, use of sulfasalazine, antimalarials, biologic DMARDs/tofacitinib, corticosteroids, starting year, hypercholesterolemia, osteoporosis, hepatitis B and C. ‡Excluding infections of any kind. MTX: methotrexate; LEF: leflunomide; ND: not done due to small number of events (<10 for crude analysis and <20 for multivariate analysis); RF: rheumatoid factor; CCP: cyclic citrullinated peptide.

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Supplementary Table 4. Clinical and demographic features of the patients on therapy with the MTX-LEF combination and with biologic agents/JAK inhibitor combined with either MTX or LEF. Data are presented as number (percentage) of patients, except when indicated otherwise.

	MTX-LEF combination (without biologics or JAK inhibitor) (n=195)	Biologic agents/JAK inhibitor combined with MTX (n=535)	Biologic agents/JAK inhibitor combined with LEF (n=240)	P Value*
Female	168 (86.2)	452 (84.5)	210 (87.5)	0.526
Age (years) – mean (SD)	49.9 (12.7)	50.8 (11.6)	52.6 (11.6)	0.045
Disease duration (years) – median (IQR)	2.7 (0.5-10.2)	6.3 (2.8 to 13.0)	7.9 (3.9-14.9)	<0.001

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Seropositive RA (RF or anti-CCP)	166 (85.1)	477 (89.2)	204 (85.0)	0.161
DAS28 at baseline – mean (SD)	5.0 (1.4)	5.3 (1.5)	5.2 (1.4)	0.008
Current smoking	28 (14.4)	74 (13.8)	26 (10.8)	0.452
History of malignancy	4 (2.1)	4 (0.7)	4 (1.7)	0.269
Diabetes	20 (10.3)	59 (11.0)	42 (17.5)	0.024
Hypertension	72 (36.9)	182 (34.0)	110 (45.8)	0.007
Hypercholesterolemia	28 (14.4)	58 (10.8)	46 (19.2)	0.007
Osteoporosis	30 (15.4)	70 (13.1)	38 (15.8)	0.524
Hepatitis C	0 (0.0)	1 (0.2)	0 (0.0)	1.000
Hepatitis B	0 (0.0)	4 (0.7)	1 (0.4)	0.832
Kidney failure	1 (0.5)	4 (0.7)	2 (0.8)	1.000
Ischemic cardiomyopathy	3 (1.5)	9 (1.7)	5 (2.1)	0.895
COPD	4 (2.1)	10 (1.9)	7 (2.9)	0.661
Heart failure	2 (1.0)	3 (0.6)	2 (0.8)	0.675
Corticosteroid	169 (86.7)	418 (78.1)	189 (78.8)	0.033
Hydroxychloroquine or chloroquine	56 (28.7)	119 (22.2)	27 (11.2)	<0.001
Sulfasalazine	2 (1.0)	13 (2.4)	7 (2.9)	0.397
Anti-TNF agents	0 (0.0)	457 (85.4)	212 (88.3)	<0.001
Other biologics**	0 (0.0)	51 (9.5)	18 (7.5)	<0.001
JAK Inhibitor (tofacitinib)	0 (0.0)	27 (5.0)	10 (4.2)	0.007

Starting year – mean (SD)	2011.8 (2.8)	2012.4 (3.1)	2013.0 (3.0)	<0.001

*Pearson chi-square, Fisher's exact test, Student *t* test or Mann-Whitney test according to the nature and distribution of data. ** Other biologics are abatacept, rituximab or tocilizumab. MTX: methotrexate; LEF: leflunomide; SD: standard deviation; IQR: interquartile range; RA: rheumatoid arthritis; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; DAS28: Disease Activity Score in 28 joints; COPD: chronic obstructive pulmonary disease; TNF: tumor necrosis factor; JAK: Janus kinase.

Supplementary Table 5. Results of Cox proportional hazards models comparing the hazard of adverse events of the MTX-LEF combo (without biologics or JAK inhibitor) versus biologic agents/JAK inhibitor combined with MTX (without LEF). Results are expressed as hazards ratios, 95% confidence intervals, and P values.

	MTX-LEF (n=195) versus biologic agents/JAK inhibitor combined with MTX (n=535; reference category) n=730

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Type of adverse event (number of events)		Crude analysis	Adjusted for covariates†
Total serious adverse events (112)		0.64 (0.41 to 1.00), P= 0.049	0.58 (0.36 to 0.94), P=0.028
Fatal adverse events (9)		ND	ND
Any adverse event (380)		0.86 (0.68 to 1.08), P=0.191	0.82 (0.64 to 1.04), P=0.094
Cardiovascular‡	Serious (15)	1.12 (0.38 to 3.28), P=0.841	ND
	Total (40)	1.32 (0.69 to 2.51), P=0.397	0.95 (0.47 to 1.92), P=0.893
Infections	Serious (57)	0.54 (0.28 to 1.05), P=0.069	0.47 (0.23 to 0.95), P=0.035
	Total (213)	0.70 (0.51 to 0.96), P=0.025	0.69 (0.50 to 0.97), P=0.033
Hepatic‡	Serious (1)	ND	ND
	Total (20)	1.51 (0.62 to 3.70), P=0.368	1.86 (0.70 to 4.99), P=0.216
Hematologic	Serious (4)	ND	ND
	Total (22)	1.54 (0.66 to 3.60), P=0.323	1.58 (0.62 to 3.99), P=0.334
Respiratory tract‡	Serious (8)	ND	ND
	Total (25)	0.71 (0.28 to 1.77), P=0.459	0.73 (0.25 to 2.09), P=0.553
Gastrointestinal‡	Serious (4)	ND	ND
	Total (47)	1.00 (0.54 to 1.84), P=0.990	0.99 (0.52 to 1.92), P=0.985

†Adjusted also for age, baseline DAS28, disease duration, gender, current smoking, seropositivity for RF or anti-CCP, history of malignancy, diabetes, hypertension, hypercholesterolemia, renal failure, ischemic cardiomyopathy, COPD, heart failure, use of sulfasalazine, antimalarials, corticosteroids, starting year, hypercholesterolemia, osteoporosis, hepatitis B and C. ‡Excluding infections of any kind. MTX: methotrexate; LEF: leflunomide; ND: not done due to small number of events (<10 for crude analysis and <20 for multivariate analysis); RF: rheumatoid factor; CCP: cyclic citrullinated peptide.

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Supplementary Table 6. Clinical and demographic features of the patients in subgroup analysis comparing the MTX-LEF and MTX-SSZ combinations. Data are presented as number (percentage) of patients, except when indicated otherwise.

	MTX-SSZ combination (n=31)	MTX-LEF combination (n=440)	P Value*

Female	26 (83.9)	382 (86.8)	0.589
Age (years) – mean (SD)	43.5 (12.9)	50.7 (11.6)	0.001
Disease duration (years) – median (IQR)	2.6 (0.8-7.6)	5.7 (1.8-12.3)	0.024
Seropositive RA (RF or anti-CCP)	26 (83.9)	358 (81.4)	0.728
DAS28 at baseline – mean (SD)	5.4 (1.5)	5.1 (1.4)	0.227
Current smoking	5 (16.1)	78 (17.7)	0.821
History of malignancy	3 (9.7)	6 (1.4)	0.017
Diabetes	3 (9.7)	57 (13.0)	0.784
Hypertension	7 (22.6)	173 (39.3)	0.064
Hypercholesterolemia	2 (6.5)	67 (15.2)	0.290
Osteoporosis	4 (12.9)	74 (16.8)	0.571
Hepatitis C	0 (0.0)	1 (0.2)	1.000
Hepatitis B	0 (0.0)	2 (0.5)	1.000
Kidney failure	0 (0.0)	1 (0.2)	1.000
Ischemic cardiomyopathy	0 (0.0)	5 (1.1)	1.000
COPD	2 (6.5)	12 (2.7)	0.233
Heart failure	1 (3.2)	4 (0.9)	0.290
Corticosteroid	27 (87.1)	371 (84.3)	0.803
Hydroxychloroquine or chloroquine	22 (71.0)	105 (23.9)	<0.001
Anti-TNF agents	13 (41.9)	233 (53.0)	0.235

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Other biologics**	0 (0.0)	11 (2.5)	1.000
JAK Inhibitor (tofacitinib)	0 (0.0)	3 (0.7)	1.000
Starting year – mean (SD)	2011.9 (2.3)	2012.1 (2.7)	0.707

*Pearson chi-square, Fisher's exact test, Student *t* test or Mann-Whitney test according to the nature and distribution of data. ** Other biologics are abatacept, rituximab or tocilizumab. MTX: methotrexate; LEF: leflunomide; SSZ: sulfasalazine; SD: standard deviation; IQR: interquartile range; RA: rheumatoid arthritis; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; DAS28: Disease Activity Score in 28 joints; COPD: chronic obstructive pulmonary disease; TNF: tumor necrosis factor; JAK Janus kinase.

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Supplementary Table 7. Results of Cox proportional hazards models (subgroup analysis) comparing the hazard of adverse events between the MTX-LEF combo and the MTX-SSZ combination*.

Type of adverse event (number of events)		MTX + LEF (n=440) Rate per 100 PY (95% CI)	MTX + SSZ (n=31) Rate per 100 PY (95% CI)	Hazards ratios, 95% confidence intervals, and P values.	
				Crude analysis	Adjusted for covariates†
Total serious adverse events (90)		5.2 (4.2 to 6.4)	18.1 (10.8 to 30.2)	0.32 (0.18 to 0.59), P<0.001	0.33 (0.16 to 0.65), P=0.002
Fatal adverse events (7)		0.4 (0.2 to 0.9)	0 (NA)	ND	ND
Any adverse event (259)		25.7 (23.0 to 28.6)	33.3 (22.6 to 49.1)	0.88 (0.54 to 1.44), P=0.618	0.80 (0.46 to 1.37), P=0.408
Cardiovascular events‡	Serious (15)	0.8 (0.5 to 1.3)	2.5 (0.6 to 9.9)	0.31 (0.07 to 1.38), P=0.123	ND
	Total (41)	2.4 (1.8 to 3.3)	2.5 (0.6 to 9.9)	1.01 (0.24 to 4.21), P=0.987	0.64 (0.14 to 2.98), P=0.574
Infections	Serious (46)	2.6 (1.9 to 3.5)	6.5 (2.8 to 15.1)	0.45 (0.18 to 1.14), P=0.090	0.61 (0.21 to 1.73), P=0.352
	Total (138)	10.4 (8.8 to 12.2)	11.3 (5.9 to 21.7)	1.0 (0.49 to 2.04), P=0.997	0.94 (0.43 to 2.03), P=0.868
Hepatic events‡	Serious (3)	0.2 (0.1 to 0.5)	0 (NA)	ND	ND
	Total (14)	0.8 (0.5 to 1.4)	0 (NA)	††	ND

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Hematologic events	Serious (3)	0.2 (0.1 to 0.6)	0 (NA)	ND	ND
	Total (18)	0.9 (0.6 to 1.5)	3.6 (1.2 to 11.0)	0.26 (0.08 to 0.90), P=0.033	ND
Respiratory tract events‡	Serious (3)	0.2 (0.1 to 0.6)	0 (NA)	ND	ND
	Total (12)	0.7 (0.4 to 1.3)	0 (NA)	††	ND
Gastrointestinal events‡	Serious (4)	0.2 (0.1 to 0.6)	1.1 (0.2 to 8.3)	ND	ND
	Total (33)	1.8 (1.3 to 2.6)	3.6 (1.2 to 10.9)	0.54 (0.16 to 1.77), P=0.307	0.38 (0.10 to 1.45), P=0.156

*See description of patients` features in Supplementary Table 6. †Adjusted also for age, baseline DAS28, disease duration, gender, current smoking, seropositivity for RF or anti-CCP, history of malignancy, diabetes, hypertension, hypercholesterolemia, renal failure, ischemic cardiomyopathy, COPD, heart failure, antimalarials, biologic DMARDs/tofacitinib, corticosteroids, starting year, hypercholesterolemia, osteoporosis, hepatitis B and C. ‡Excluding infections of any kind. †† Analysis rendered extreme limits of 95% CI ranging from <0.01 to >100000. MTX: methotrexate; LEF: leflunomide; SSZ: sulfasalazine; ND: not done due to small number of events (<10 for crude analysis and <20 for multivariate analysis); RF: rheumatoid factor; CCP: cyclic citrullinated peptide; NA: not applicable.

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Supplementary Table 8. Results of Cox proportional hazards models comparing the hazard of interruption of treatment. Results are expressed as hazards ratios, 95% confidence intervals, and P values.

Cause of treatment interruption (number of events)	**Crude analysis**	**Adjusted for covariates***
	MTX-LEF combo versus a category representing use of either MTX or LEF (reference)** n=1671	
For any reason, except for pregnancy or disease remission (921)	1.04 (0.90 to 1.21), P=0.552	1.11 (0.96 to 1.29), P=0.174
Due to inefficacy (450)	1.06 (0.87 to 1.31), P=0.557	1.12 (0.90 to 1.38), P=0.311
Due to adverse events or death (232)	1.04 (0.77 to 1.39), P=0.819	1.18 (0.87 to 1.60), P=0.275

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	MTX-LEF combo versus biologic agents/JAK inhibitor (combined with either MTX or LEF; reference category) n=970	
For any reason, except for pregnancy or disease remission (542)	0.80 (0.65 to 0.99), P=0.043	0.76 (0.61 to 0.95), P=0.016
Due to inefficacy (274)	0.90 (0.67 to 1.19), P=0.448	0.84 (0.62 to 1.12), P=0.237
Due to adverse events or death (130)	0.34 (0.19 to 0.62), P<0.001	0.31 (0.17 to 0.58), P<0.001
	MTX-LEF combo versus MTX-SSZ combo (reference category) n=471	
For any reason, except for pregnancy or disease remission (287)	0.62 (0.41 to 0.96), P=0.031	0.62 (0.39 to 0.98), P=0.042
Due to inefficacy (144)	0.71 (0.38 to 1.36), P=0.306	0.75 (0.37 to 1.53), P=0.431
Due to adverse events or death (66)	0.59 (0.26 to 1.38), P=0.224	0.38 (0.15 to 0.96), P=0.040
	Patients on treatment with biologic agents or tofacitinib: MTX-LEF combo versus MTX or LEF (reference category) n=1032	
For any reason, except for pregnancy or disease remission (595)	1.14 (0.96 to 1.37), P=0.142	1.19 (0.99 to 1.44), P=0.064

Due to inefficacy (287)	1.07 (0.82 to 1.39), P=0.631	1.12 (0.85 to 1.46), P=0.428
Due to adverse events or death (171)	1.37 (0.99 to 1.89), P=0.058	1.40 (1.00 to 1.96), P=0.053

*Adjusted for age, baseline DAS28, disease duration, gender, current smoking, seropositivity for RF or anti-CCP, history of malignancy, diabetes, hypertension, hypercholesterolemia, renal failure, ischemic cardiomyopathy, COPD, heart failure, use of sulfasalazine (if appropriate), antimalarials, biologic DMARDs/tofacitinib (if appropriate), corticosteroids, starting year, hypercholesterolemia, osteoporosis, hepatitis B and C. **Adjusted for a category representing absence of MTX and LEF. MTX: methotrexate; LEF: leflunomide; JAK: Janus kinase; SSZ: sulfasalazine; RF: rheumatoid factor; CCP: cyclic citrullinated peptide.

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Supplementary Table 9. Clinical and demographic features of the patients in exploratory analysis comparing treatment with the MTX-LEF combo with MTX or LEF (but not combined) among patients treated with biologic agents or JAK inhibitors. Data are presented as number (percentage) of patients, except when indicated otherwise.

	Either MTX or LEF (plus Biologic agents/JAK inhibitor) (n=775)	MTX-LEF combination (plus Biologic agents/JAK inhibitor) (n=257)	P Value*
Female	662 (85.4)	225 (87.5)	0.395
Age (years) – mean (SD)	51.4 (11.7)	51.4 (10.7)	0.966
Disease duration (years) – median (IQR)	7.0 (3.1-13.4)	7.6 (4.1-13.1)	0.245
Seropositive RA (RF or anti-CCP)	681 (87.9)	201 (78.2)	<0.001
DAS28 at baseline – mean (SD)	5.3 (1.5)	5.2 (1.3)	0.196
Current smoking	100 (12.9)	51 (19.8)	0.006
History of malignancy	8 (1.0)	2 (0.8)	1.000
Diabetes	101 (13.0)	38 (14.8)	0.475
Hypertension	292 (37.7)	104 (40.5)	0.426

hypercholesterolemia	104 (13.4)	43 (16.7)	0.188
Osteoporosis	108 (13.9)	44 (17.1)	0.212
Hepatitis C	1 (0.1)	1 (0.4)	0.436
Hepatitis B	5 (0.6)	2 (0.8)	0.687
Kidney failure	6 (0.8)	0 (0 0)	0.346
Ischemic cardiomyopathy	14 (1.8)	2 (0.8)	0.383
COPD	17 (2.2)	8 (3.1)	0.406
Heart failure	5 (0.6)	2 (0.8)	0.687
Corticosteroid	607 (78.3)	211 (82.1)	0.195
Hydroxychloroquine or chloroquine	146 (18.8)	51 (19.8)	0.722
Sulfasalazine	20 (2.6)	10 (3.9)	0.279
Anti-TNF agents	669 (86.3)	243 (94.6)	<0.001
Other biologics**	69 (8.9)	11 (4.3)	0.016
JAK Inhibitor (tofacitinib)	37 (4.8)	3 (1.2)	0.009
Starting year – mean (SD)	2012.6 (3.1)	2012.3 (2.6)	0.212

*Pearson chi-square, Fisher's exact test, Student *t* test, or Mann-Whitney test according to the nature and distribution of data. ** Other biologics are abatacept, rituximab or tocilizumab. MTX: methotrexate; LEF: leflunomide; SD: standard deviation; IQR: interquartile range; RA: rheumatoid arthritis; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; DAS28: Disease Activity Score in 28 joints; COPD: chronic obstructive pulmonary disease; TNF: tumor necrosis factor; JAK: Janus kinase.

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Supplementary Table 10. Results of Cox proportional hazards models comparing, among patients on biologic or janus kinase inhibitor treatment, the hazard of adverse events between the MTX-LEF combo and use of either MTX or LEF. Results are expressed as hazards ratios, 95% confidence intervals, and P values.

	Patients on treatment with biologic agents or tofacitinib: MTX-LEF combo (n=257) versus MTX or LEF (n=775; reference category) n=1032*	
Type of adverse event (number of events)	Crude analysis	Adjusted for covariates†
Total serious adverse events (189)	1.41 (1.03 to 1.92), P=0.030	1.36 (0.98 to 1.87), P=0.066
Fatal adverse events (13)	1.93 (0.63 to 5.91), P=0.248	ND
Any adverse event (562)	1.24 (1.03 to 1.49), P=0.024	1.21 (1.00 to 1.46), P=0.050

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Cardiovascular events‡	Serious (19)	2.20 (0.88 to 5.47), P=0.090	ND
	Total (63)	2.19 (1.33 to 3.62), P=0.002	2.04 (1.21 to 3.41), P=0.007
Infections	Serious (99)	1.50 (0.99 to 2.29), P=0.058	1.40 (0.90 to 2.19), P=0.138
	Total (319)	1.22 (0.95 to 1.56), P=0.116	1.18 (0.91 to 1.52), P=0.207
Hepatic events‡	Serious (5)	ND	ND
	Total (22)	1.44 (0.59 to 3.54), P=0.422	1.68 (0.66 to 4.23), P=0.273
Hematologic events	Serious (4)	ND	ND
	Total (27)	1.07 (0.45 to 2.53), P=0.881	1.03 (0.42 to 2.51), P=0.949
Respiratory tract events‡	Serious (9)	ND	ND
	Total (33)	1.01 (0.46 to 2.24), P=0.979	0.96 (0.42 to 2.24), P=0.933
Gastrointestinal events‡	Serious (9)	ND	ND
	Total (60)	1.13 (0.64 to 2.00), P=0.679	1.14 (0.64 to 2.04), P=0.651

*See description of patients` features in Supplementary Table 9. †Adjusted also for age, baseline DAS28, disease duration, gender, current smoking, seropositivity for RF or anti-CCP, history of malignancy, diabetes, hypertension, hypercholesterolemia, renal failure, ischemic cardiomyopathy, COPD, heart failure, use of sulfasalazine, antimalarials, corticosteroids, starting year, hypercholesterolemia, osteoporosis, hepatitis B and C. ‡Excluding infections of any kind. MTX: methotrexate; LEF: leflunomide; SSZ: sulfasalazine; ND: not done due to small number of events (<10 for crude analysis and <20 for multivariate analysis); RF: rheumatoid factor; CCP: cyclic citrullinated peptide; CI: confidence interval.

Supplementary Text 3. Additional information on Results (sensitivity analyses and tests of proportional hazards assumptions).

We performed sensitivity analysis excluding patients with less than 6 months of follow-up, and so eliminating adverse events that could have possibly been be recorded retrospectively. The results of multivariate analysis for serious adverse events (SAEs) were similar to the original analysis (MTX-LEF combo versus MTX or LEF, 220 SAEs, adj. HR, 1.14, 0.83 to 1.55, P=0.422, n=1470; MTX-LEF combo versus biologics/tofacitinib (plus MTX or LEF), 118 SAE, adj. HR, 0.66, 0.40 to 1.07, P=0.094, n=867).

We also performed a sensitivity analysis for the primary outcome (SAEs) in which we compared patients on the MTX-LEF combo with biologics/tofacitinib with MTX or LEF, but excluding patients receiving treatment with sulfasalazine, cyclosporin, or antimalarials. Considering that patients could only be included at the start of treatment with a biologic, JAK inhibitor, or escalation of treatment by the addition of a new non-biologic DMARD, excluding patients on sulfasalazine, cyclosporin or antimalarials would guaranty that the MTX-LEF combo represent a new simultaneous use of both drugs. The results are shown in Supplementary Table 11. Supplementary Table 12 shows the results for SAEs controlled for study center. In another sensitivity analysis (Supplementary Table 13), we

adjusted the results for biologics agents/JAK inhibitor considering these medications individually as different categorical variables, and not as a single binary variable as previously done. In all these sensitivity analyses, the overall results were not significantly changed in relation to those demonstrated before.

Supplementary Table 14 shows the comparison of hazard of SAEs between the MTX-LEF combo and individual biologics or tofacitinib (in association or not with MTX or LEF), adjusted and not adjusted for possible confounding variables. There was a significantly higher hazard of SAEs with infliximab, adalimumab, and tocilizumab comparing to MTX plus LEF. Comparing the MTX-LEF combo with biologics/tofacitinib (again as a single group, but independent from the use or not of MTX or LEF; reference category), the adjusted hazard ratio for SAEs is 0.50, 95% CI, 0.32 to 0.78, P=0.002.

The test of the proportional hazards assumption (PHA) was made for multivariate survival analyses whose outcome was SAEs (Tables 1 and 2 and Supplementary Tables 7 and 10). The log-minus-log plots relative to the analyses enumerated before in this paragraph are shown in Supplementary Figure A to D, confirming the fulfillment of the PHA.

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Supplementary Table 11. Results of Cox proportional hazards models comparing the hazard of serious adverse events considering only patients with new combinations of methotrexate and leflunomide and new combinations of cs- and bDMARDs/janus kinase inhibitor (schemes including antimalarials, cyclosporin or sulfasalazine were excluded from this analysis). Results are expressed as hazards ratios, 95% confidence intervals, and P values.

Type of adverse event (number of events)	**Crude analysis**	**Adjusted for covariates***
	MTX-LEF combo (n=335) versus a category representing use of either MTX or LEF (n=807; reference) n=1245**	
Serious adverse events (219)	1.02 (0.76 to 1.38), P=0.873	0.98 (0.71 to 1.35), P=0.892
	MTX-LEF combo (without biologics or JAK inhibitor; n=137) versus biologic agents/JAK inhibitor combined with either MTX or LEF (n=618; reference category) n=755	

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Serious adverse events (125)	0.61 (0.37 to 1.01), P=0.055	0.50 (0.29 to 0.84), P=0.010
	Patients on treatment with biologic agents or tofacitinib: MTX-LEF combo (n=198) versus MTX or LEF (n=618; reference category) n=816	
Serious adverse events (151)	1.36 (0.96 to 1.94), P=0.086	1.30 (0.90 to 1.88), P=0.161
*Adjusted for age, baseline DAS28, disease duration, gender, current smoking, seropositivity for RF or anti-CCP, history of malignancy, diabetes, hypertension, hypercholesterolemia, renal failure, ischemic cardiomyopathy, COPD, heart failure, antimalarials, biologic DMARDs/tofacitinib (if appropriate), corticosteroids, starting year, hypercholesterolemia, osteoporosis, hepatitis B and C. **These analyses are adjusted for a category representing absence of MTX and LEF (n=103), and so the total number of patients is 1245. DMARDs: disease modifying anti-rheumatic drugs; Cs- and bDMARDs: conventional synthetic and biologic DMARDs; MTX: methotrexate; LEF: leflunomide; JAK: Janus kinase; RF: rheumatoid factor; CCP: cyclic citrullinated peptide.		

Supplementary Table 12. Results of Cox proportional hazards models comparing the hazard of serious adverse events controlling for study center (represented by 28 categories). Results are expressed as hazards ratios, 95% confidence intervals, and P values.

Type of adverse event (number of events)	Crude analysis*	Adjusted for covariates**

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	MTX-LEF combo (n=452) versus a category representing use of either MTX or LEF (n=1063; reference) n=1671†	
Serious adverse events (298)	0.85 (0.64 to 1.12), P=0.249	0.87 (0.66 to 1.17), P=0.362
	MTX-LEF combo (without biologics or JAK inhibitor; n=195) versus biologic agents/JAK inhibitor combined with either MTX or LEF (n=775; reference category) n=970	
Serious adverse events (156)	0.48 (0.30 to 0.76), P=0.002	0.46 (0.28 to 0.74), P=0.001
	MTX-LEF combo (n=440) versus MTX-SSZ combo (n=31; reference category) n=471	
Serious adverse events (90)	0.50 (0.20 to 1.21), P=0.124	0.50 (0.19 to 1.26), P=0.141
	Patients on treatment with biologic agents or tofacitinib: MTX-LEF combo (n=257) versus MTX or LEF (n=775; reference category) n=1032	
Serious adverse events (189)	1.08 (0.76 to 1.56), P=0.660	1.06 (0.73 to 1.54), P=0.748

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*Adjusted for study center. **Adjusted for age, baseline DAS28, disease duration, gender, current smoking, seropositivity for RF or anti-CCP, history of malignancy, diabetes, hypertension, renal failure, ischemic cardiomyopathy, heart failure, chronic pulmonary obstructive disease, and concomitant use of sulfasalazine (where appropriate), biologics/tofacitinib (if appropriate), antimalarials, corticosteroids, starting year, hypercholesterolemia, osteoporosis, hepatitis B and C, and study center. †These analyses include 1671 patients and are adjusted for a category representing absence of MTX and LEF (n=156). MTX: methotrexate; LEF: leflunomide; JAK: Janus kinase; SSZ: sulfasalazine; RF: rheumatoid factor; CCP: cyclic citrullinated peptide.

Supplementary Table 13. Results of Cox proportional hazards models comparing the hazard of serious adverse events adjusting for concomitant use of different biologic agents or JAK inhibitor taken as individual categorical variables. Results are expressed as hazards ratios, 95% confidence intervals, and P values.

Type of adverse event (number of events)	**Crude analysis***	**Adjusted for covariates****
	MTX-LEF combo (n=452) versus a category representing use of either MTX or LEF (n=1063; reference) n=1671†	
Serious adverse events (298)	1.05 (0.81 to 1.37), P=0.707	0.97 (0.74 to 1.28), P=0.849
	MTX-LEF combo (n=440) versus MTX-SSZ combo (n=31; reference category) n=471	
Serious adverse events (90)	0.25 (0.13 to 0.47), P<0.001	0.25 (0.12 to 0.51), P<0.001

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*Adjusted for use of infliximab, etanercept, adalimumab, golimumab, certolizumab, abatacept, rituximab, tocilizumab, and tofacitinib. **Adjusted for age, baseline DAS28, disease duration, gender, current smoking, seropositivity for RF or anti-CCP, history of malignancy, diabetes, hypertension, renal failure, ischemic cardiomyopathy, heart failure, chronic pulmonary obstructive disease, and concomitant use of infliximab, etanercept, adalimumab, golimumab, certolizumab, abatacept, rituximab, tocilizumab, tofacitinib, sulfasalazine (where appropriate), antimalarials, corticosteroids, starting year, hypercholesterolemia, osteoporosis, hepatitis B and C. †These analyses include 1671 patients and are adjusted for a category representing absence of MTX and LEF (n=156). MTX: methotrexate; LEF: leflunomide; JAK: Janus kinase; SSZ: sulfasalazine; RF: rheumatoid factor; CCP: cyclic citrullinated peptide.

Supplementary Table 14. Results of Cox proportional hazards models comparing the hazard of serious adverse events of different biologics/JAK inhibitor in comparison to the MTX + LEF combination (reference category; n=195). Results are expressed as hazards ratios, 95% confidence intervals, and P values.

Biologic agent/JAK inhibitor (always in combination with either MTX or LEF)	Crude analysis*	Adjusted for covariates*†
Infliximab (n=172)	2.64 (1.62 to 4.31), P<0.001	2.68 (1.61 to 4.47), P<0.001

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Adalimumab (n=246)	1.56 (0.95 to 2.57), P=0.077	1.49 (0.88 to 2.50), P=0.135
Etanercept (n=158)	1.35 (0.77 to 2.36), P=0.297	1.43 (0.80 to 2.54), P=0.230
Golimumab (n=37)	0.85 (0.26 to 2.84), P=0.797	1.16 (0.33 to 4.06), P=0.818
Certolizumab (n=56)	0.89 (0.31 to 2.56), P=0.823	1.11 (0.35 to 3.46), P=0.861
Rituximab (n=30)	1.32 (0.46 to 3.78), P=0.612	1.70 (0.56 to 5.17), P=0.348
Abatacept (n=17)	1.17 (0.28 to 4.94), P=0.834	1.89 (0.43 to 8.40), P=0.401
Tocilizumab (n=22)	2.71 (1.17 to 6.26), P=0.020	3.63 (1.50 to 8.78), P=0.004
Tofacitinib (n=37)	††	††
Biologic agent/JAK inhibitor (in combination or not with MTX or LEF)	Crude analysis€	Adjusted for covariates€†
Infliximab (n=199)	2.58 (1.60 to 4.18), P<0.001	2.91 (1.76 to 4.79), P<0.001
Adalimumab (n=277)	1.65 (1.02 to 2.67), P=0.043	1.78 (1.07 to 2.94), P=0.026
Etanercept (n=189)	1.67 (1.00 to 2.79), P=0.051	1.69 (0.99 to 2.91), P=0.056
Golimumab (n=40)	0.79 (0.24 to 2.61), P=0.694	1.15 (0.33 to 4.00), P=0.822
Certolizumab (n=63)	0.95 (0.36 to 2.50), P=0.923	1.29 (0.46 to 3.63), P=0.628
Rituximab (n=45)	1.52 (0.66 to 3.51), P=0.330	1.31 (0.53 to 3.22), P=0.554
Abatacept (n=24)	1.27 (0.38 to 4.23), P=0.693	1.76 (0.50 to 6.13), P=0.376
Tocilizumab (n=27)	2.66 (1.20 to 5.89), P=0.016	3.26 (1.40 to 7.56), P=0.006
Tofacitinib (n=56)	0.19 (0.03 to 1.42), P=0.105	0.31 (0.04 to 2.40), P=0.262

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*Includes 970 patients who suffered 156 events. †Adjusted also for age, baseline DAS28, disease duration, gender, current smoking, seropositivity for RF or anti-CCP, history of malignancy, diabetes, hypertension, hypercholesterolemia, renal failure, ischemic cardiomyopathy, COPD, heart failure, use of sulfasalazine, antimalarials, corticosteroids, starting year, hypercholesterolemia, osteoporosis, hepatitis B and C. ††Analysis rendered extreme limits of 95% CI ranging from <0.01 to >100000. €Includes 1115 patients who suffered 187 events. MTX: methotrexate; LEF: leflunomide; SSZ: sulfasalazine; ND: not done due to small number of events (<10 for crude analysis and <20 for multivariate analysis); RF: rheumatoid factor; CCP: cyclic citrullinated peptide; CI: confidence interval.

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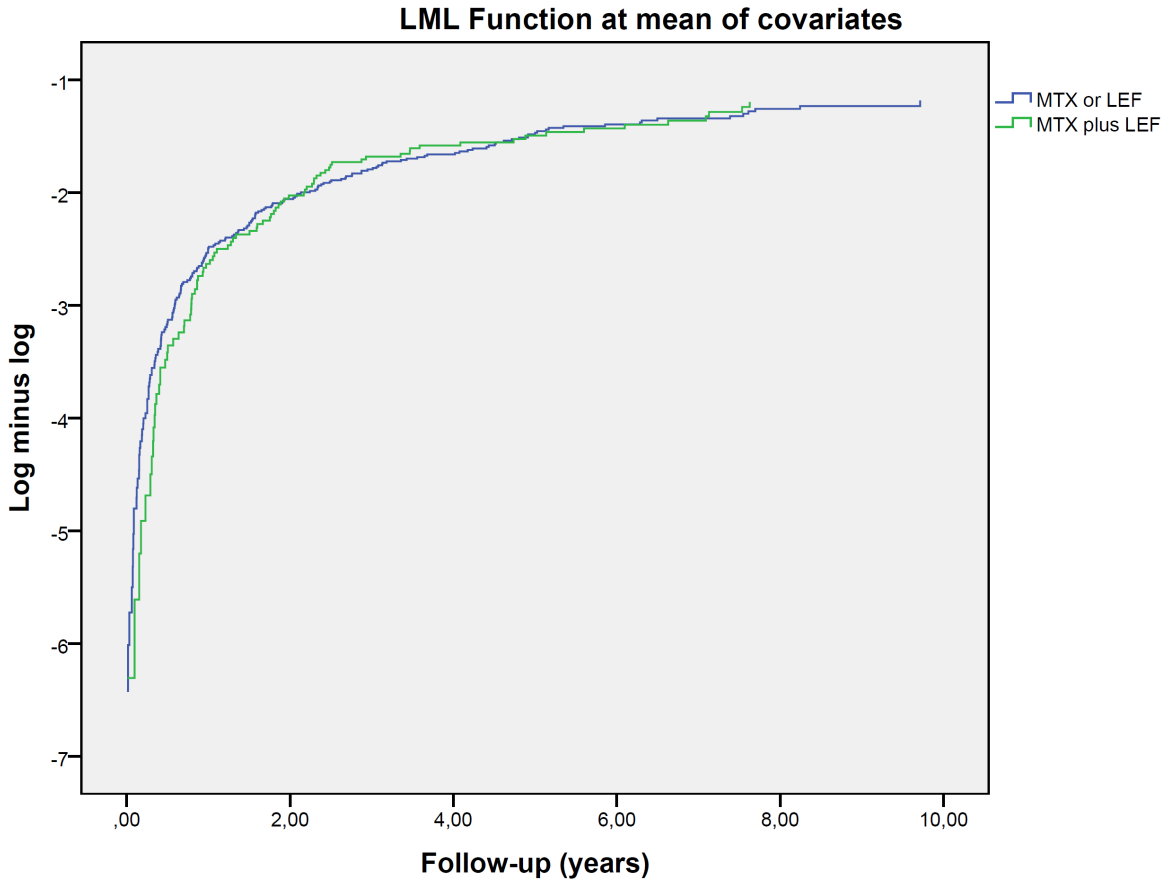
Supplementary Figure 1. Log-minus-log (LML) versus time plots testing the assumption of proportional hazards of the analysis on serious adverse events presented in Table 1 (A), Table 2 (B), Supplementary Table 7 (C), and Supplementary Table 10 (D). MTX: methotrexate; LEF: leflunomide; JAKi: Janus kinase inhibitor; SSZ: sulfasalazine.

A



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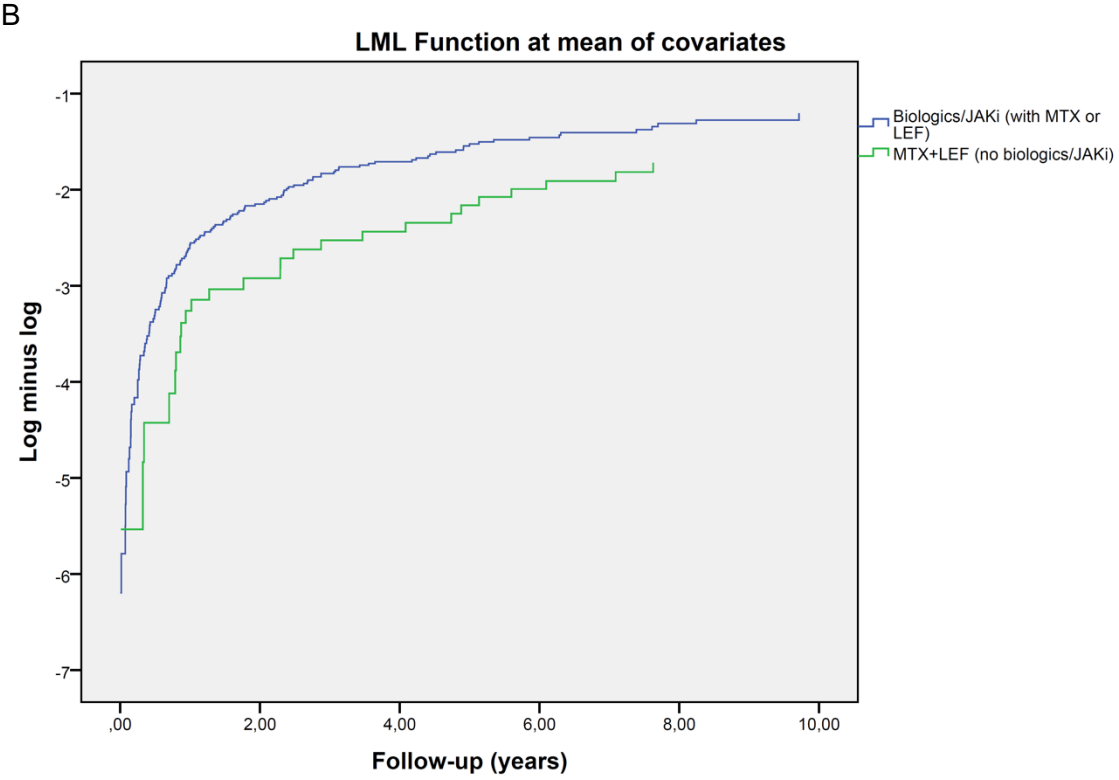
B



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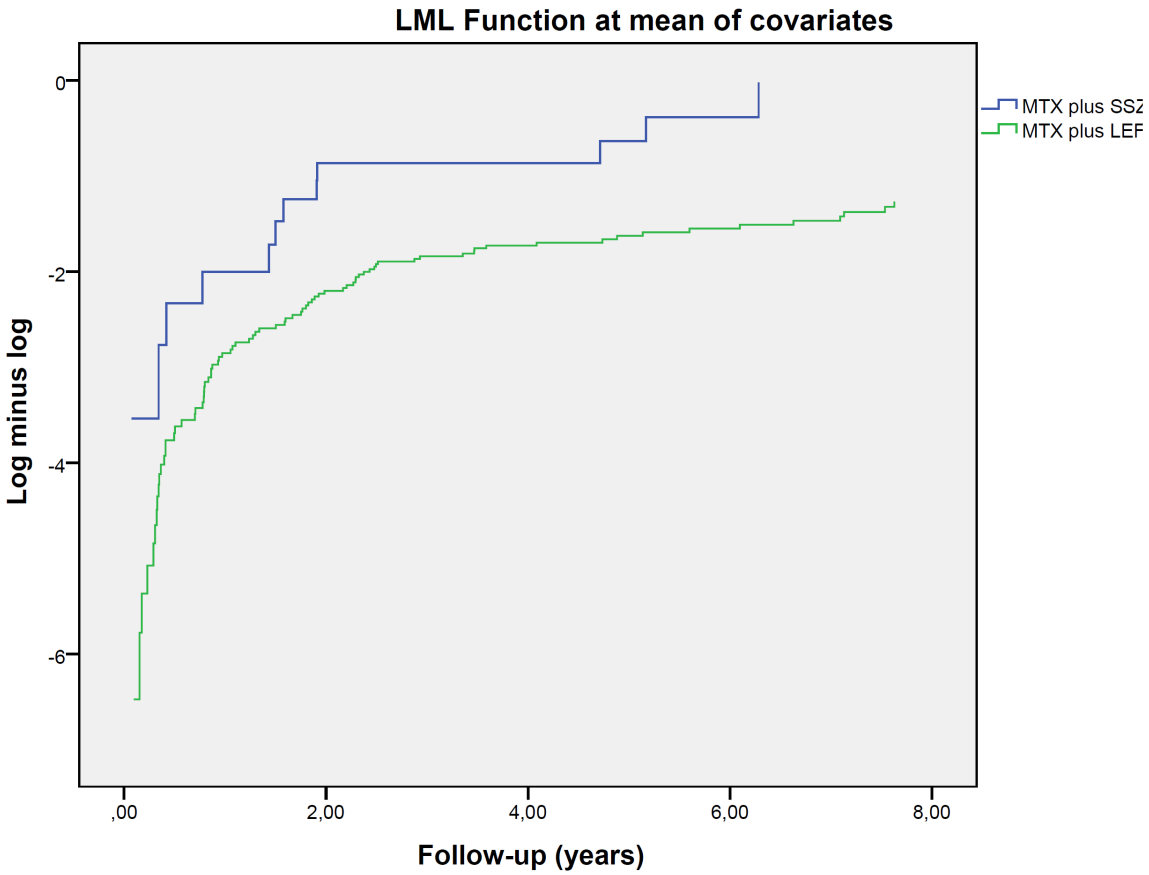
C



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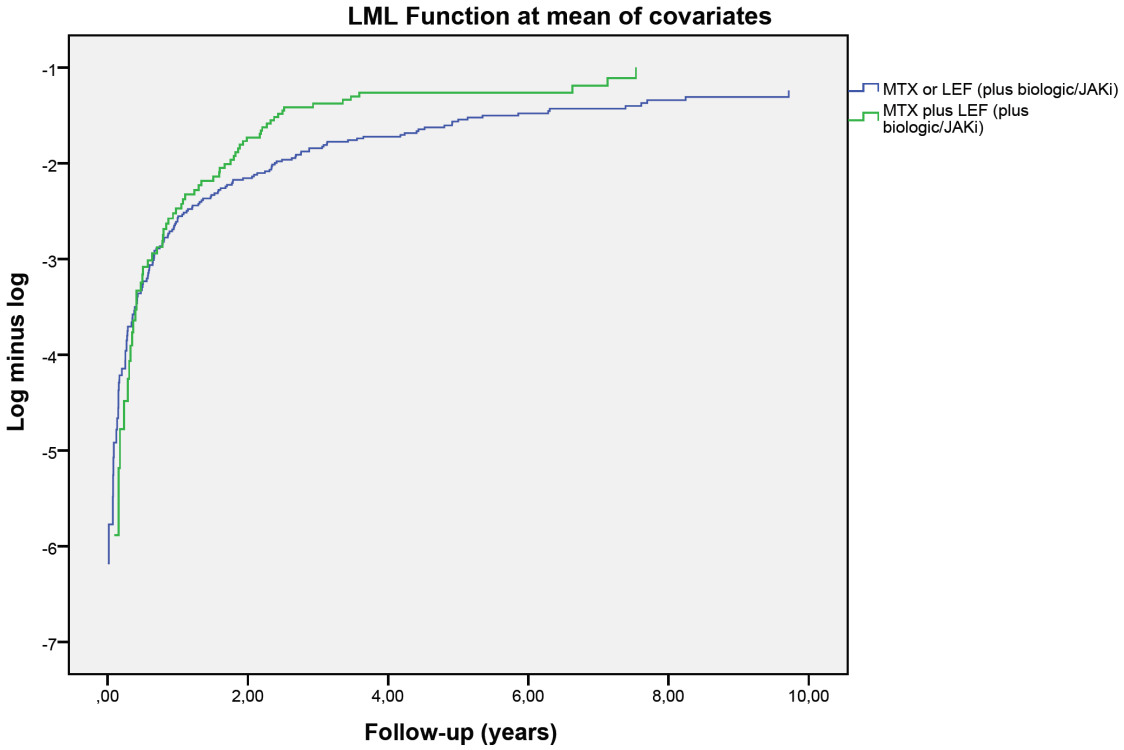
D



Supplementary Data 1. Propensity Score Matched Analysis Supplement.

SAFETY OF THE METHOTREXATE-LEFLUNOMIDE COMBINATION IN RHEUMATOID ARTHRITIS: RESULTS OF A MULTICENTRIC, REGISTRY-BASED, COHORT STUDY (BIOBADABRASIL).

1- PROPENSITY SCORE MATCHED ANALYSIS (PSMA) USING R COMPARING THE HAZARD OF SERIOUS ADVERSE EVENTS (SAE) OF THE MTX-LEF COMBO (N=452) VERSUS A CATEGORY REPRESENTING USE OF EITHER MTX OR LEF (N=1063; REFERENCE).

Sample sizes:

	Control	Treated
All	1063	452
Matched	569	397
Unmatched	494	55
Discarded	0	0

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Comparison of groups generated by propensity score matching (p.c: proportion in controls; p.t: proportion in treated, stfdiff: standardized difference between the groups; mean.c and sd.c: mean and standard deviation in control group, respectively; mean.t and sd.t: mean and standard deviation in treated group, respectively)

Categorical variables

	p.c	**p.t**	missing.c	missing.t	**stddiff**	stddiff.l	stddiff.u
CORTICOSTEROID	0.822	0.829	0	0	0.016	-0.112	0.145
SULFASALAZINE	0.021	0.028	0	0	0.043	-0.085	0.171
ANTIMALARIALS	0.188	0.217	0	0	0.071	-0.057	0.199
FEMALE	0.872	0.877	0	0	0.015	-0.113	0.143
SERONEGATIVE	0.158	0.174	0	0	0.042	-0.086	0.170
CANCER	0.012	0.010	0	0	0.021	-0.107	0.149
HYPERCHOLESTEROLEMIA	0.137	0.139	0	0	0.004	-0.124	0.132
HEPATITIS B	0.009	0.005	0	0	0.045	-0.083	0.173
HEPATITIS C	0.002	0.003	0	0	0.016	-0.112	0.145
OSTEOPOROSIS	0.146	0.154	0	0	0.022	-0.106	0.150
ISQUEMIC CARDIOMYOPATHY	0.012	0.008	0	0	0.048	-0.080	0.176
DIABETES	0.139	0.121	0	0	0.053	-0.075	0.182
SMOKING	0.151	0.169	0	0	0.048	-0.080	0.176
RENAL FAILURE	0.002	0.003	0	0	0.016	-0.112	0.145
HEART FAILURE	0.005	0.003	0	0	0.044	-0.084	0.172
COPD	0.023	0.028	0	0	0.031	-0.097	0.159
HYPERTENSION	0.388	0.390	0	0	0.004	-0.124	0.132
BIOLOGIC/JAKi	0.627	0.589	0	0	0.078	-0.050	0.206

Continuous variables

	mean.c	sd.c	**mean.t**	sd.t	missing.c	missing.t	**stddiff**
Age (days)	18527.174	4303.850	18425.013	4251.795	0	0	0.024

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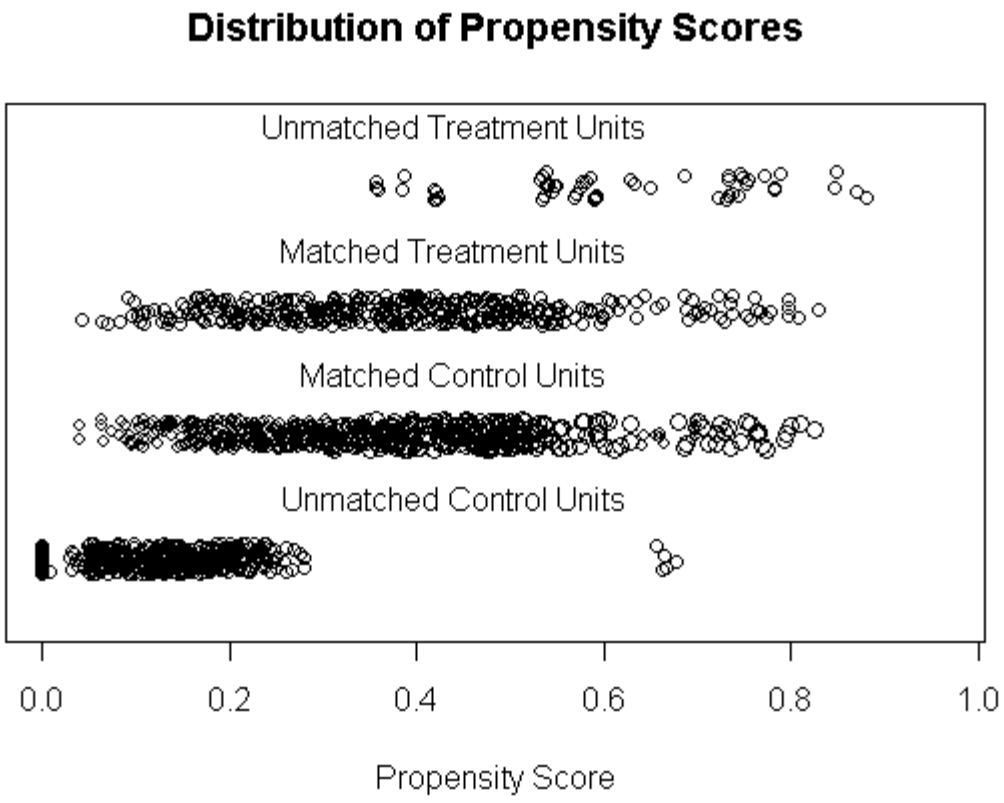
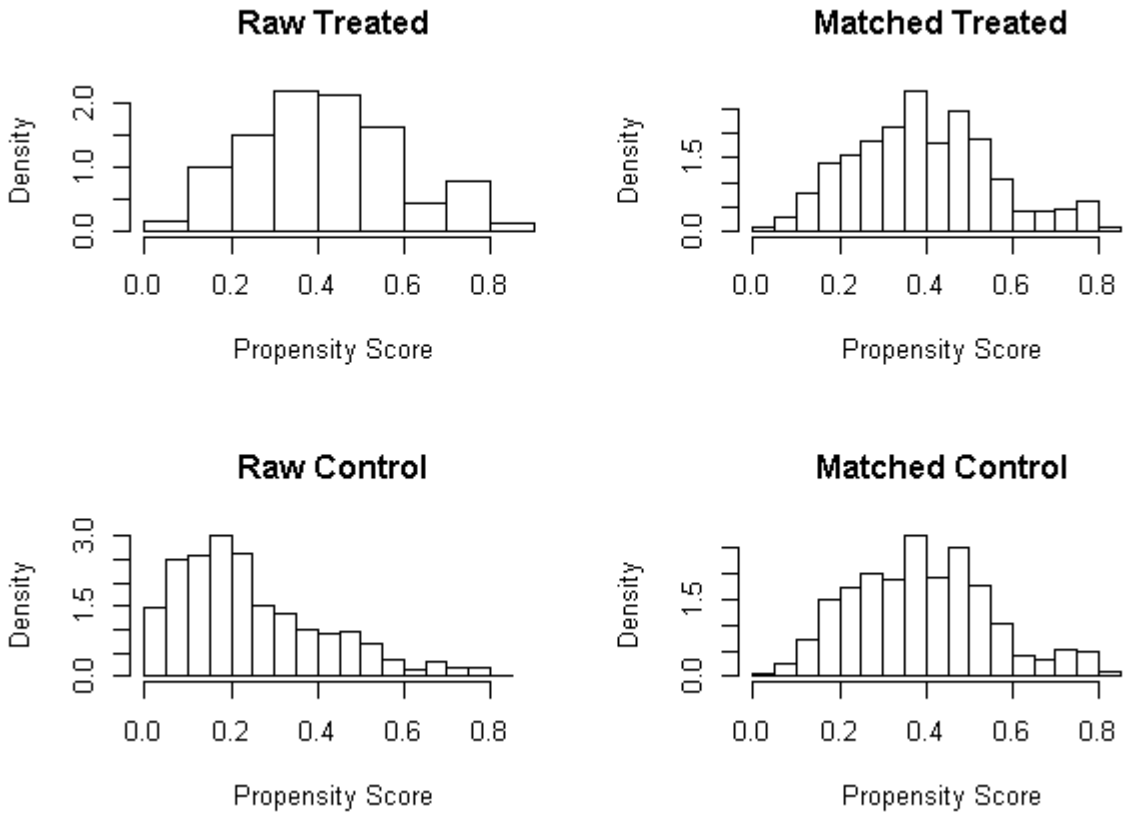
Disease duration (days)	2779.116	2877.369	2972.680	2907.921	0	0	0.067
Starting year	12.408	3.059	12.222	2.750	0	0	0.064
DAS28	5.153	1.552	5.081	1.376	0	0	0.049





Results of this PSMA:

```
coxph(formula = Surv(FOLLOW, EF_ADV) ~ MTXpLEFLU, data = matched.def1,
    method = "breslow")

  n= 966, number of events= 177

             coef exp(coef) se(coef)      z Pr(>|z|)
MTXpLEFLU -0.05507   0.94641  0.15374 -0.358     0.72

          exp(coef) exp(-coef) lower .95 upper .95
MTXpLEFLU    0.9464      1.057    0.7002     1.279
```

FINAL RESULT:

HAZARD RATIO: 0.95, 95% confidence interval: 0.70 to 1.28, P= 0.720.

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2- PROPENSITY SCORE MATCHED ANALYSIS (PSMA) USING R COMPARING THE HAZARD OF SERIOUS ADVERSE EVENTS (SAE) OF THE MTX-LEF COMBO (N=195) VERSUS BIOLOGIC AGENTS/JAK INHIBITOR (COMBINED WITH EITHER MTX OR LEF; N=775)..

Sample sizes:

	Control	Treated
All	775	195
Matched	257	157
Unmatched	518	38
Discarded	0	0

Comparison of groups generated by propensity score matching (p.c: proportion in controls; p.t: proportion in treated, stfdiff: standardized difference between the groups; mean.c and sd.c: mean and standard deviation in control group, respectively; mean.t and sd.t: mean and standard deviation in treated group, respectively)

Categorical variables

	p.c	**p.t**	missing.c	missing.t	**stddiff**	stddiff.l	stddiff.u
CORTICOSTEROID	0.837	0.841	0	0	0.011	-0.187	0.210
SULFASALAZINE	0.012	0.013	0	0	0.010	-0.189	0.208
ANTIMALARIALS	0.222	0.229	0	0	0.018	-0.181	0.217
FEMALE	0.875	0.860	0	0	0.046	-0.152	0.245
SERONEGATIVE	0.125	0.153	0	0	0.082	-0.117	0.281
CANCER	0.019	0.013	0	0	0.053	-0.145	0.252
HYPERCHOLESTEROLEMIA	0.156	0.146	0	0	0.026	-0.173	0.224

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HEPATITIS B	0.000	0.000	0	0	NaN	NaN	NaN
HEPATITIS C	0.000	0.000	0	0	NaN	NaN	NaN
OSTEOPOROSIS	0.160	0.159	0	0	0.001	-0.198	0.199
ISQUEMIC CARDIOMYOPATHY	0.012	0.019	0	0	0.060	-0.138	0.259
DIABETES	0.125	0.108	0	0	0.051	-0.148	0.249
SMOKING	0.152	0.140	0	0	0.033	-0.166	0.231
RENAL FAILURE	0.004	0.006	0	0	0.035	-0.164	0.233
HEART FAILURE	0.004	0.013	0	0	0.098	-0.101	0.296
COPD	0.031	0.025	0	0	0.034	-0.164	0.233
HYPERTENSION	0.374	0.369	0	0	0.009	-0.190	0.207

Continuous variables

	mean.c	sd.c	**mean.t**	sd.t	missing.c	missing.t	**stddiff**
Age (days)	18367.307	4103.220	18307.484	4677.722	0	0	0.014
Disease duration (days)	2763.677	2283.391	2590.045	3167.834	0	0	0.063
Starting year	12.058	3.145	11.892	2.861	0	0	0.055
DAS28	5.082	1.475	4.975	1.414	0	0	0.074

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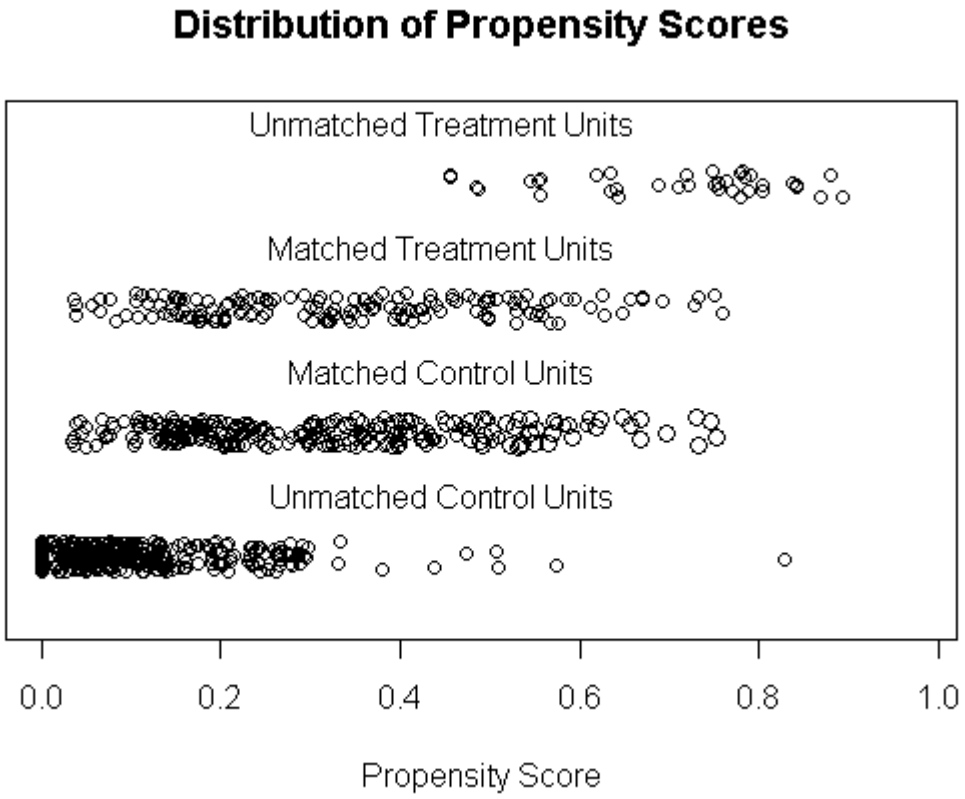

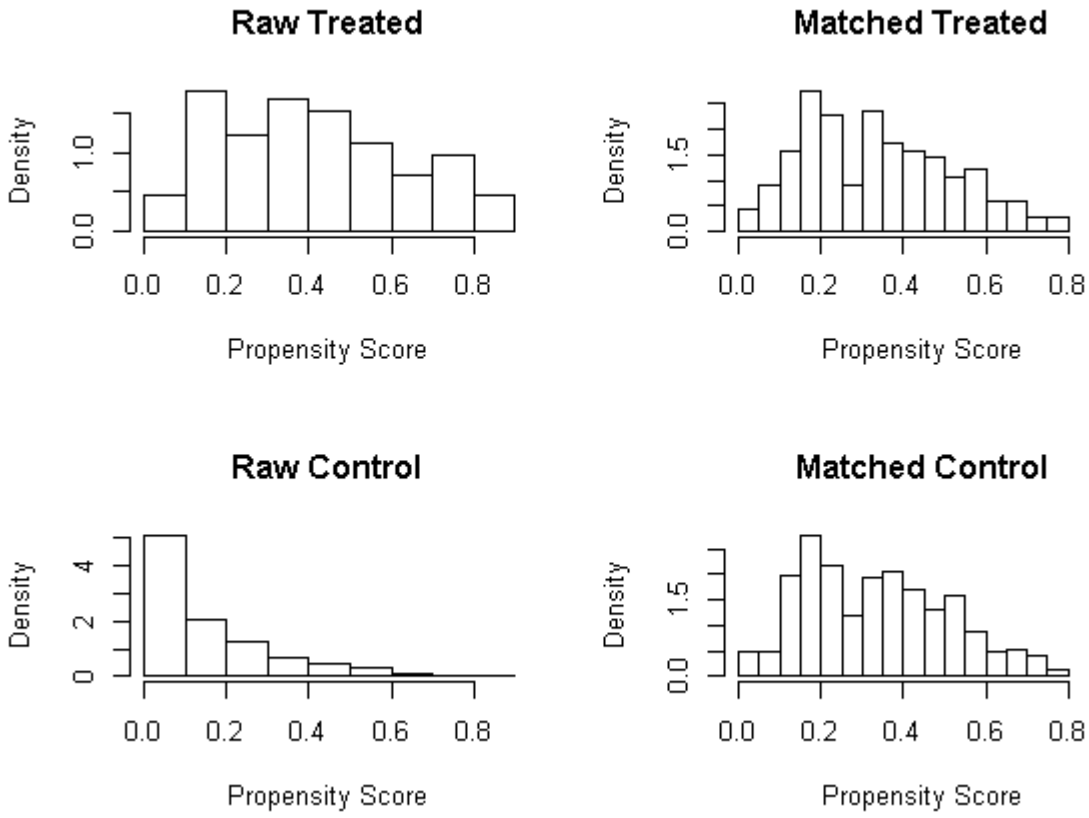

Results of this PSMA:

```
coxph(formula = Surv(FOLLOW, EF_ADV) ~ MTXLEFBIO, data = matched.def1,
    method = "breslow")

  n= 414, number of events= 77

              coef exp(coef) se(coef)      z Pr(>|z|)
MTXLEFBIO -0.7113    0.4910   0.2538 -2.802  0.00507 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

           exp(coef) exp(-coef) lower .95 upper .95
MTXLEFBIO     0.491      2.037    0.2986    0.8075
```

FINAL RESULT:

HAZARD RATIO: 0.49, 95% confidence interval: 0.30 to 0.81, P=0.005.

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3-PROPENSITY SCORE MATCHED ANALYSIS (PSMA) USING R COMPARING THE HAZARD OF SERIOUS ADVERSE EVENTS (SAE) OF THE MTX-LEF COMBO VERSUS THE MTX-SSZ COMBO.

Matching was not adequate due to the reduced number of patients in the MTX-SSZ group, generating standardized differences up to 0.7 for some explanatory variables compounding the propensity scores.

4-PROPENSITY SCORE MATCHED ANALYSIS (PSMA) USING R COMPARING THE HAZARD OF SERIOUS ADVERSE EVENTS (SAE) BETWEEN THE MTX-LEF COMBO AND USE OF MTX OR LEF AMONG PATIENTS ON TREATMENT WITH BIOLOGIC AGENT OR JANUS KINASE INHIBITOR.

Sample sizes:

	Control	Treated
All	775	257
Matched	306	200
Unmatched	469	57
Discarded	0	0

Comparison of groups generated by propensity score matching (p.c: proportion in controls; p.t: proportion in treated, stfdiff: standardized difference between the groups; mean.c and sd.c: mean and standard deviation in control group, respectively; mean.t and sd.t: mean and standard deviation in treated group, respectively)

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Categorical variables

p.c	**p.t**	missing.c	missing.t	**stddiff**	stddiff.l	stddiff.u
CORTICOSTEROID	0.784	0.800	0	0	0.039	-0.140	0.217
SULFASALAZINE	0.033	0.040	0	0	0.039	-0.139	0.217
ANTIMALARIALS	0.137	0.170	0	0	0.091	-0.087	0.269
FEMALE	0.876	0.880	0	0	0.013	-0.165	0.191
SERONEGATIVE	0.167	0.175	0	0	0.022	-0.156	0.200
CANCER	0.010	0.010	0	0	0.002	-0.176	0.180
HYPERCHOLESTEROLEMIA	0.154	0.145	0	0	0.024	-0.154	0.202
HEPATITIS B	0.007	0.010	0	0	0.038	-0.140	0.216
HEPATITIS C	0.003	0.000	0	0	0.081	-0.097	0.259
OSTEOPOROSIS	0.147	0.175	0	0	0.076	-0.102	0.254
ISQUEMIC CARDIOMYOPATHY	0.010	0.005	0	0	0.056	-0.122	0.234
DIABETES	0.137	0.160	0	0	0.064	-0.114	0.242
SMOKING	0.137	0.130	0	0	0.021	-0.157	0.200
RENAL FAILURE	0.000	0.000	0	0	NaN	NaN	NaN
HEART FAILURE	0.003	0.005	0	0	0.027	-0.151	0.205
COPD	0.016	0.020	0	0	0.027	-0.151	0.206
HYPERTENSION	0.379	0.400	0	0	0.043	-0.135	0.221

Continuous variables

mean.c	sd.c	**mean.t**	sd.t	missing.c	missing.t	**stddiff**
Age (days)	18534.405	4197.968	18903.390	3769.770	0	0	0.092
Disease duration (days)	3681.745	3055.755	3626.360	2912.342	0	0	0.019
Starting year	12.605	3.010	12.515	2.755	0	0	0.031
DAS28	5.235	1.429	5.155	1.307	0	0	0.059

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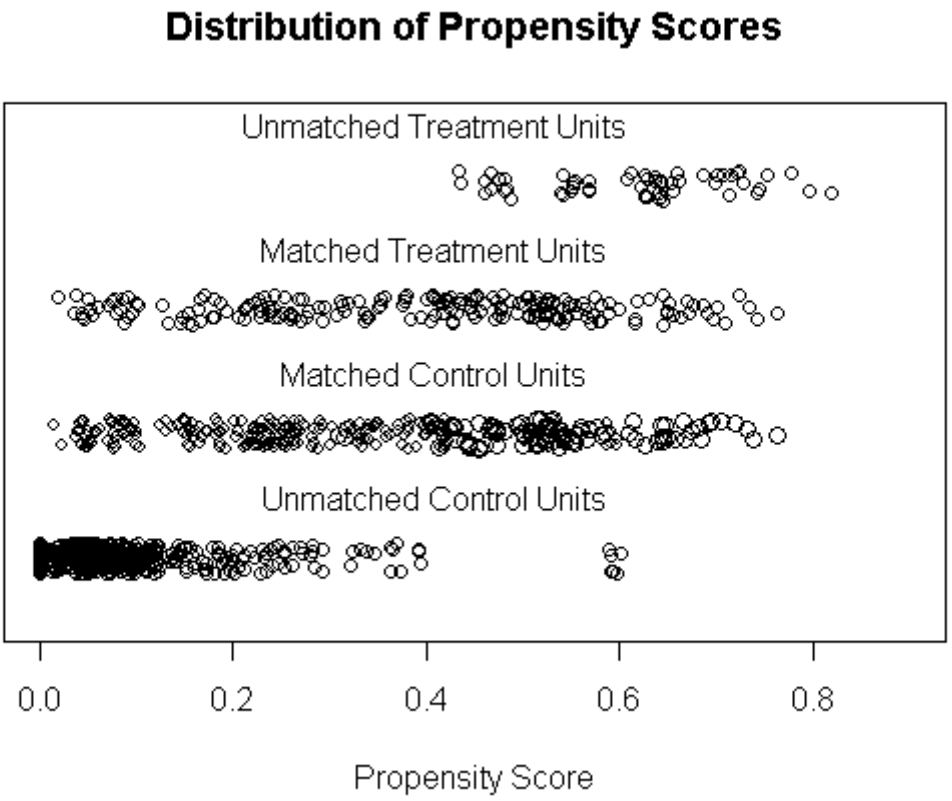

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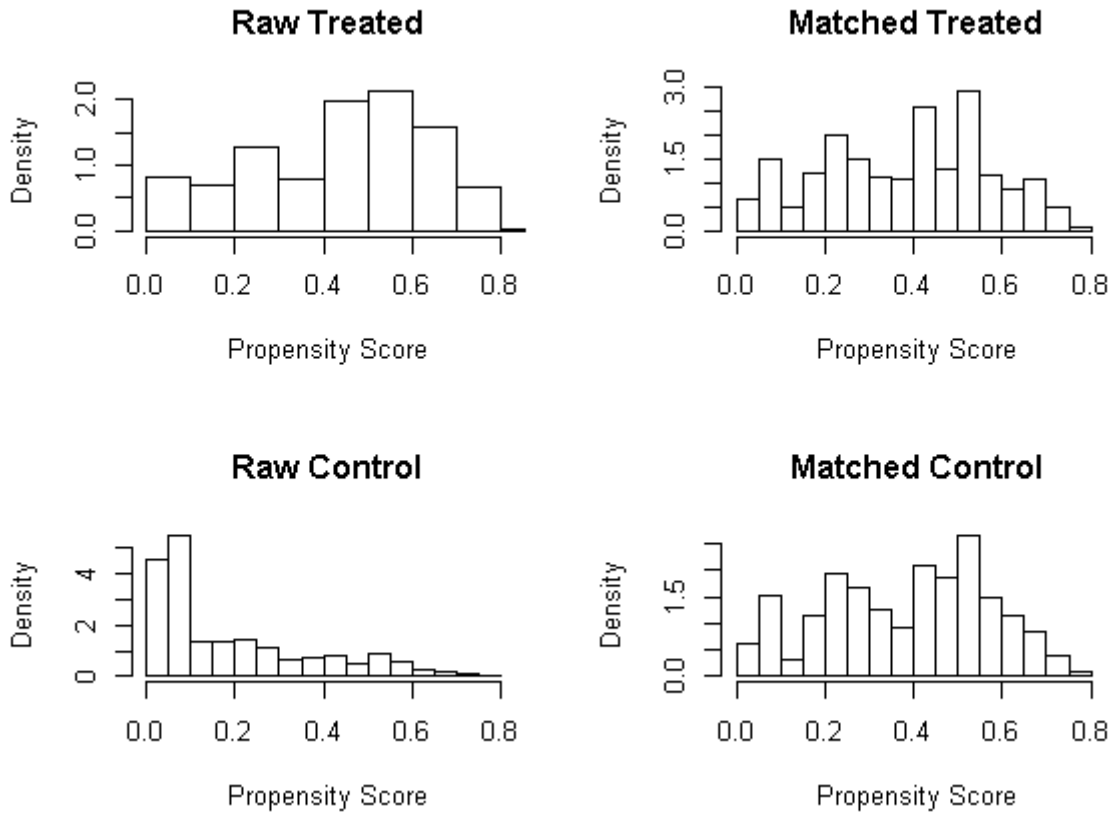

Results of this PSMA:

```
coxph(formula = Surv(FOLLOW, EF_ADV) ~ TTO2, data = matched.def1,
   method = "breslow")

  n= 506, number of events= 88

       coef exp(coef) se(coef)     z Pr(>|z|)
TTO2 0.08307   1.08661  0.21700 0.383    0.702

     exp(coef) exp(-coef) lower .95 upper .95
TTO2     1.087     0.9203    0.7102     1.663
```

FINAL RESULT:
HAZARD RATIO: 1.09, 95% confidence interval: 0.71 to 1.66, P=0.702.