APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

5ª edizione

REUMATOLOGIA E MALATTIE NEOPLASTICHE

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Safety delle terapie utilizzate in reumatologia:

Biotecnologici e neoplasie nei dati di real life dai Registri Nazionali

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DISCLOSURES

"This presentation may discuss unlicensed indications and/or use and/or products. Licensed indications may vary by country. Always refer to the prescribing information in your country before prescribing any drug"

Consultant for:

ACTELION

ABBVIE

BMS

CELLGENE

JANSSEN

MERCK

LILLY

PFIZER

UCB

WASSERMAN

CAVEATS

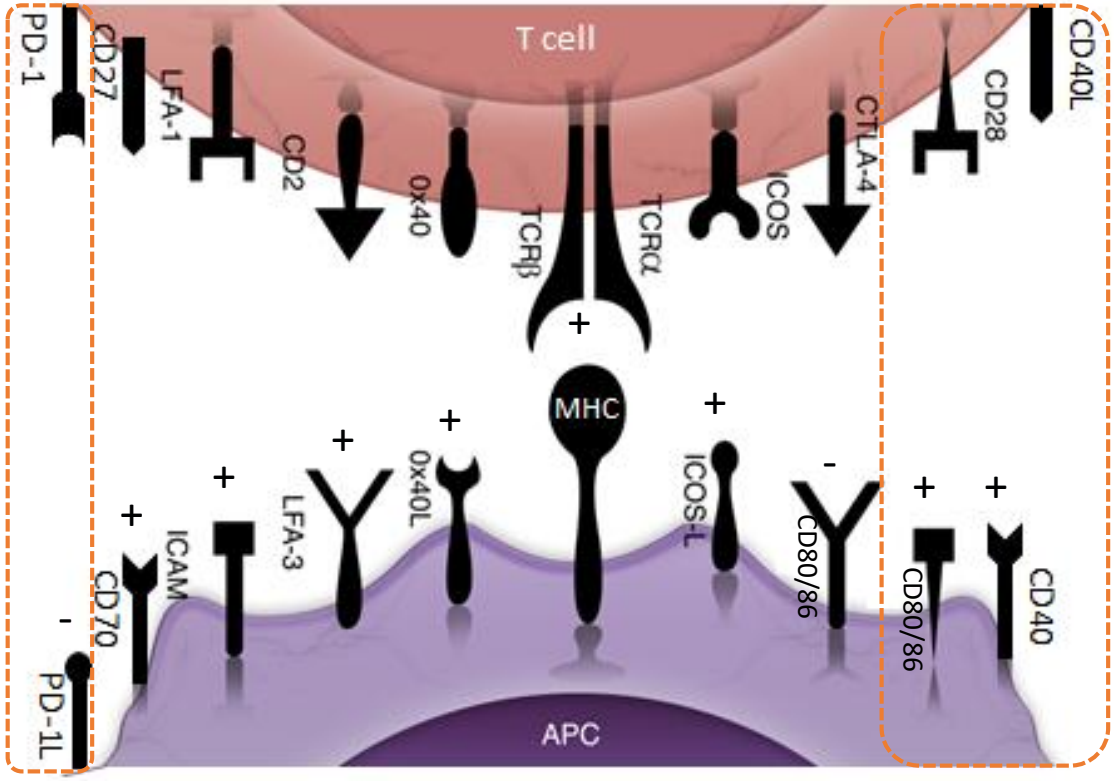
Epidemiologia (Standard Incidence Ratio)

Popolazione di controllo

Immunosorveglianza e terapia oncologia

Immune chekpoints e malattie reumatiche

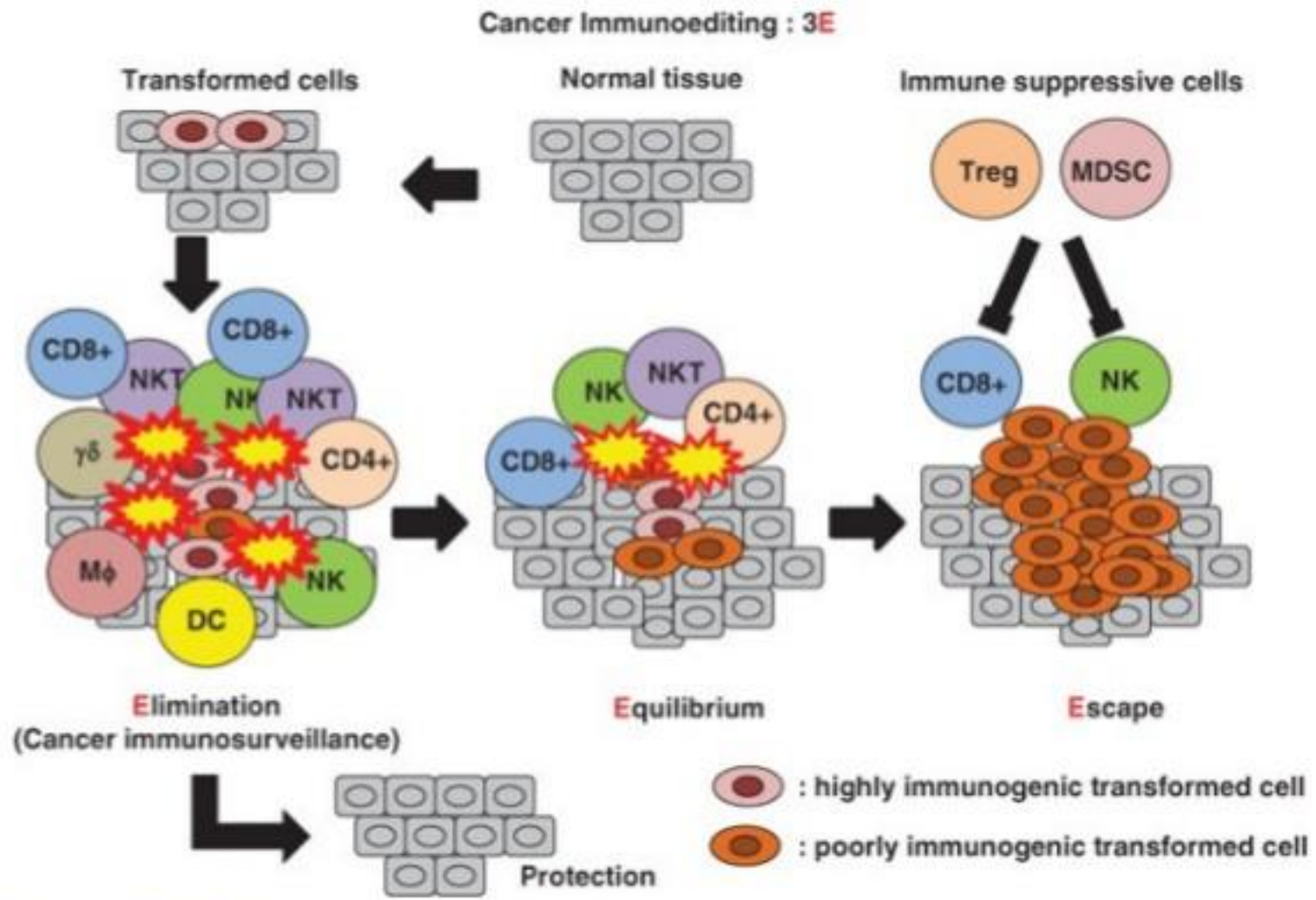
Co-stimulatory Pathways in T cell Activation



+ : co-stimulatory

- : co-inhibitory

Immune surveillance/editing of tumors



Prof. Mohamed Labib Salem

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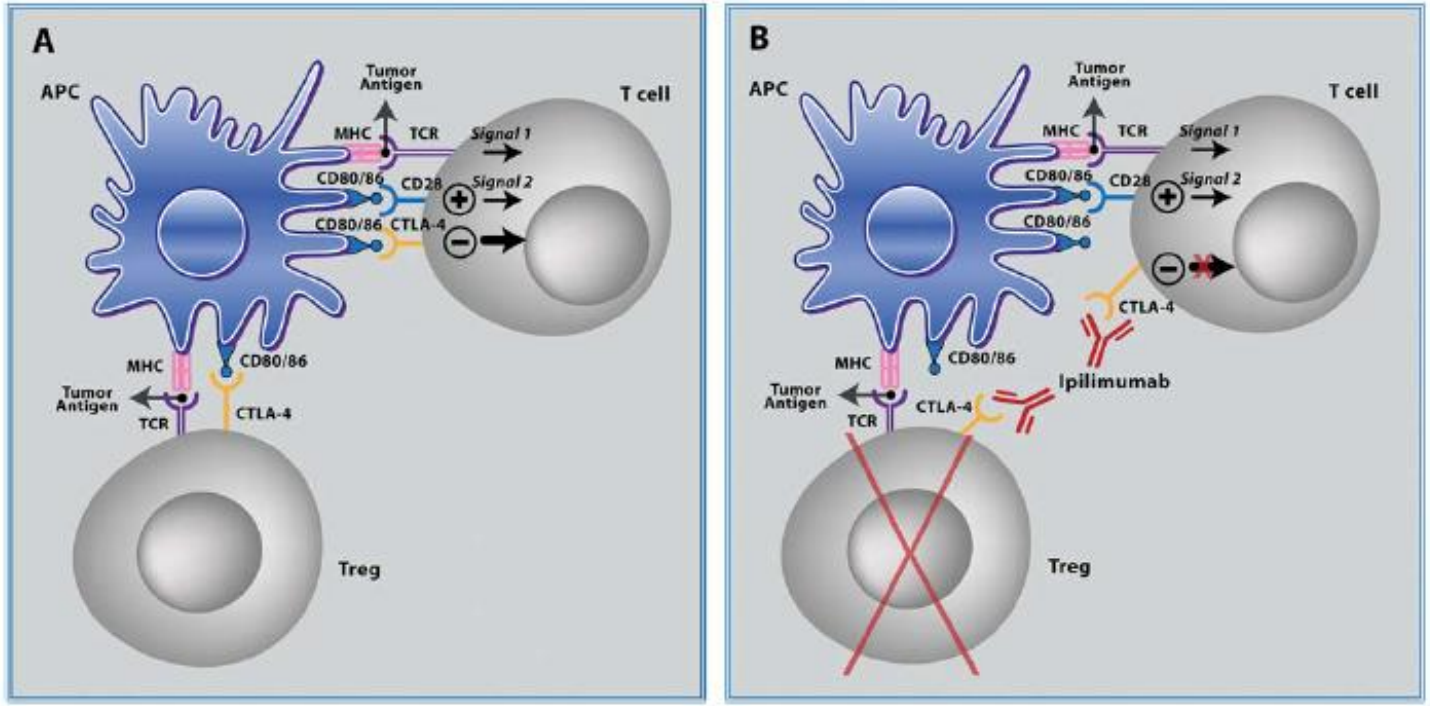


anism of anti–CTLA-4 checkpoint inhibitors. **A,** T cells require 2 signals for activation. Signal 1 is delivered via ngages with an antigen bound to the major histocompatibility complex (MHC) molecule on the antigen-presenting l via CD28 when it engages with CD80/86 on APCs. After activation, T cells express CTLA-4 on the surface that bi higher affinity, blocking T cell activation. Treg cells also constitutively express CTLA-4, as an inhibitory extrinsic n l escape. **B,** Anti–CTLA-4 agents prevent CTLA-4 from binding to CD80/86, reinvigorating the inhibited T cell. Tl tibody-dependent cell-mediated cytotoxicity.

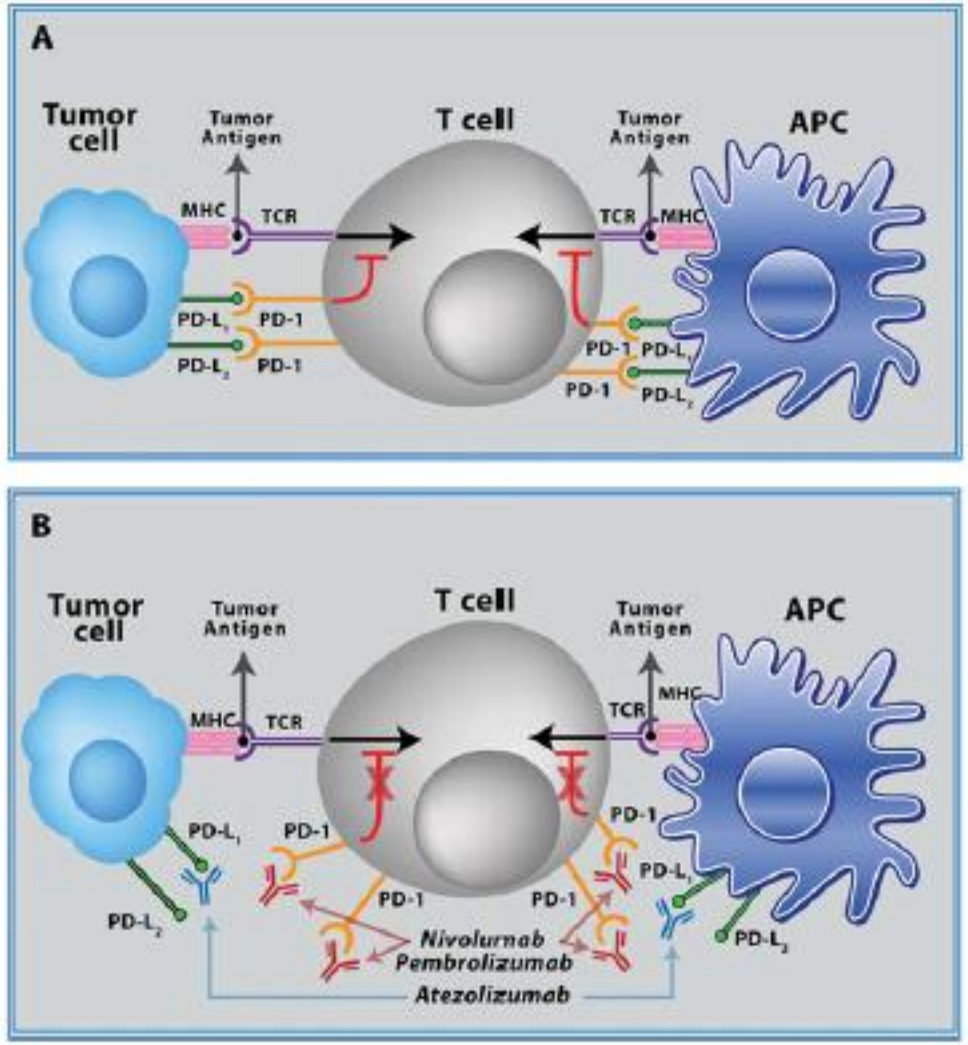


Figure 2. Mechanism of anti–programmed cell death 1 (anti–PD-1)/anti–PD ligand 1 (anti–PD-L1) checkpoint inhibitors. **A,** Engagement of PD-1 with PD-L1 down-modulates TCR signaling and leads to T cell exhaustion. **B,** Anti–PD-1/PD-L1 agents restore down-modulated TCR signaling and reinvigorate the exhausted T cell. See Figure 1 for

Cappelli LC, et al. Ann Rheum Dis 2017;76:43–50.

Table 1 Demographic features, cancer types and immunotherapy of included patients

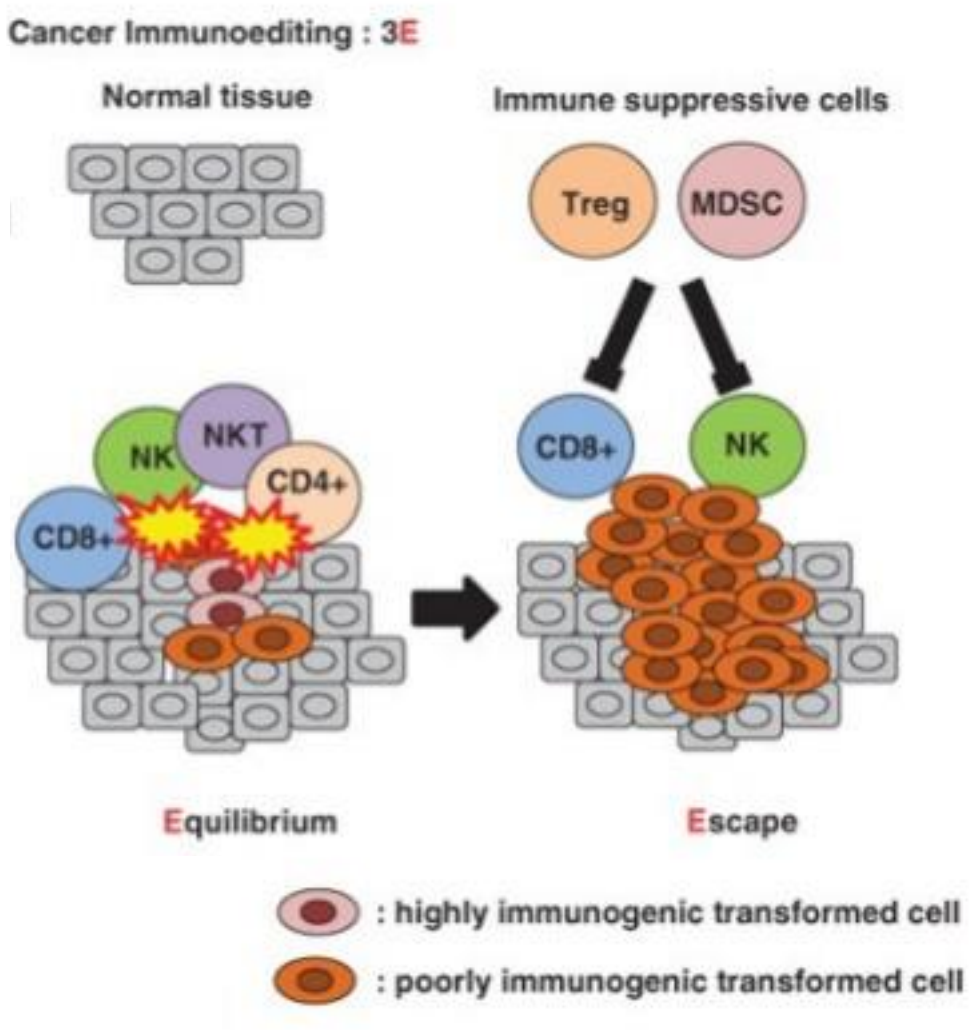
Patient	Age	Sex	Race	Type of malignancy	Cancer therapy	Rheumatic IRAE	Best overall response (RECIST 1.1)
1	58	Male	Caucasian	Renal cell carcinoma	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Stable disease
2	46	Female	Caucasian	Melanoma	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Partial response
3	62	Male	African American	Non-small cell lung cancer	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Stable disease
4	35	Male	Caucasian	Melanoma	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Stable disease
5	56	Male	Caucasian	Non-small cell lung cancer	Anti-PD-1	Inflammatory arthritis	Stable disease
6	66	Male	Caucasian	Melanoma	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Partial response
7	57	Male	Caucasian	Small cell lung cancer	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Partial response
8	42	Male	Caucasian	Non-small cell lung cancer	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Partial response
9	75	Female	Caucasian	Non-small cell lung cancer	Anti-PD-1	Inflammatory arthritis	Partial response
10	61	Male	Caucasian	Non-small cell lung cancer	Anti-PD-1	Sicca syndrome	Stable disease
11	57	Male	Caucasian	Melanoma	Anti-PD-1 Anti-CTLA-4	Sicca syndrome	Progressive disease
12	74	Male	Caucasian	Melanoma	Anti-CTLA-4	Sicca syndrome	Partial response
13	74	Female	Caucasian	Melanoma	Anti-PD-1	Sicca syndrome	No measureable disease by RECIST; tumour regression observed on clinical exam

Immune surveillance/editing of tumors

TNF blocking

IL6 blocking

Anti-T cell therapy



BIOTECNOLOGICI E NEOPLASIE

JAMA. 2006;295:2275-2285

Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies. Systematic Review and Meta-analysis of Rare Harmful Effects in Randomized Controlled Trials

Table 1. Characteristics of Randomized Controlled Trials Included in the Meta-analysis

Source	No. of Randomized Participants	Disease Characteristics	Active Treatment Group (No. of Participants*)	Control Group (No. of Participants*)	Duration of Trial, wk
Maini et al,[32] 1998	101	Active RA with inadequate response to methotrexate	Placebo + 1 mg/kg infliximab every 4 wk (14) Methotrexate + 1 mg/kg infliximab every 4 wk (15) Placebo + 3 mg/kg infliximab every 4 wk (15) Methotrexate + 3 mg/kg infliximab every 4 wk (14) Placebo + 10 mg/kg infliximab every 4 wk (14) Methotrexate + 10 mg/kg infliximab every 4 wk (15)	Placebo + methotrexate (14)	26 (Last dose at wk 14)
Lipsky et al,[9] 2000	428	Active RA with inadequate response to methotrexate	Methotrexate + 3 mg/kg infliximab every 8 wk (88)† Methotrexate + 3 mg/kg infliximab every 4 wk (86) Methotrexate + 10 mg/kg infliximab every 8 wk (87) Methotrexate + 10 mg/kg infliximab every 4 wk (81)	Methotrexate + placebo (86)†	54
Furst et al,[8] 2003	636	Active RA	Adalimumab, 40 mg every other wk + DMARD (318) Rescue arm after 12 wk	Placebo + DMARD (318) Rescue arm after 12 wk	24
Van de Putte et al,[10] 2003	284	Active RA with inadequate response to ≥1 DMARD	Adalimumab, 20 mg/wk (72) Adalimumab, 40 mg/wk (70) Adalimumab, 80 mg/wk (72)	Placebo (70)	12
Weinblatt et al,[11] 2003	271	Active RA with inadequate response to methotrexate	Methotrexate + 20 mg adalimumab every other wk (69) Methotrexate + 40 mg adalimumab every other wk (67) Methotrexate + 80 mg adalimumab every other wk (73) Rescue arm after 16 wk	Methotrexate + placebo (62) Rescue arm after 16 wk	24
Keystone et al,[6] 2004	619	Active RA with inadequate response to methotrexate	Methotrexate + 20 mg adalimumab weekly (212) Methotrexate + 40 mg adalimumab every other wk (207) Rescue arm after 16 wk	Methotrexate + placebo (200) Rescue arm after 16 wk	52
St Clair et al,[7] 2004	1049	Active early RA <3 y (no previous methotrexate)	Methotrexate + 3 mg/kg infliximab every 8 wk (372)‡ Methotrexate + 6 mg/kg infliximab every 8 wk (377)‡	Methotrexate + placebo (291)‡	54
Van de Putte et al,[33] 2004	544	Active RA with inadequate response to ≥1 DMARD	Adalimumab, 20 mg every other wk (106) Adalimumab, 20 mg/wk (112) Adalimumab, 40 mg every other wk (113) Adalimumab, 40 mg/wk (103) Rescue arm after 8 wk	Placebo (110) Rescue arm after 8 wk	26
Westhovens et al,[34] 2004	1082	Active RA with inadequate response to methotrexate	Methotrexate + 3 mg/kg infliximab at wk 0, 2, 6, and 14 (360) Methotrexate + 10 mg/kg infliximab at wk 0, 2, 6, and 14 (361)	Methotrexate + placebo (361)	22

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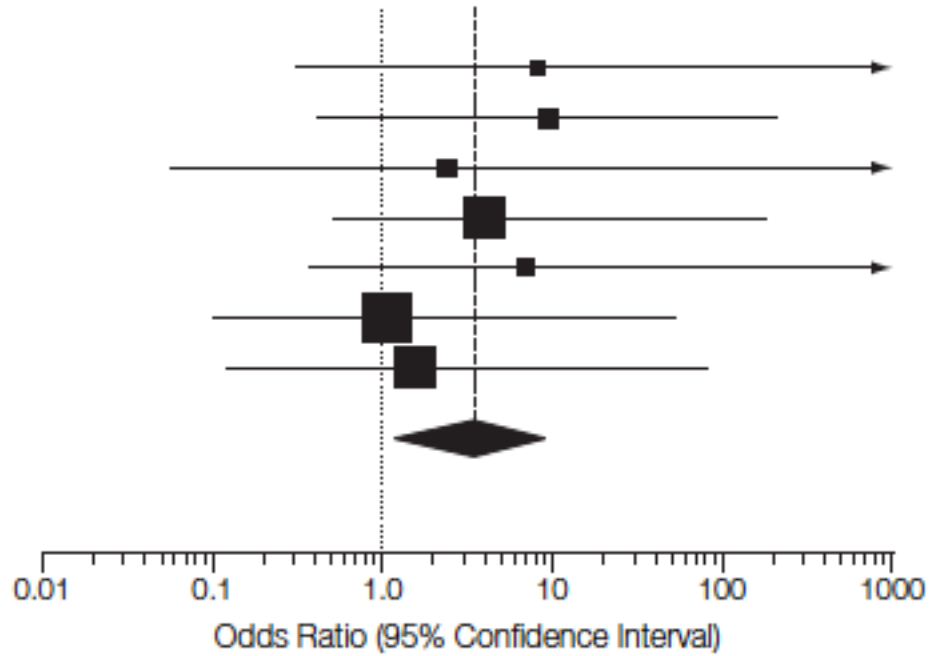
Figure 2. Effect of Anti-TNF Antibody Therapy vs Control Therapy on Occurrence of 1 or More Malignancies in Patients With Rheumatoid Arthritis

Source	Malignancies, No./Total		Odds Ratio (95% Confidence Interval)
	Anti-TNF	Placebo	
Lipsky et al,[9] 2000	5/342	0/86	7.57 (0.30-Infinity)
Furst et al,[8] 2003	4/318	0/318	9.11 (0.40-199.49)
Weinblatt et al,[11] 2003	1/209	0/62	2.29 (0.06-Infinity)
Keystone et al,[6] 2004	8/419	1/200	3.87 (0.51-172.73)
St Clair et al,[7] 2004	4/749	0/291	6.58 (0.36-Infinity)
Van de Putte et al,[33] 2004	4/434	1/110	1.01 (0.10-50.39)
Westhovens et al,[34] 2004	3/721	1/361	1.50 (0.12-79.18)
Total	**29/3192**	**3/1428**	**3.29 (1.19-9.08)**

Test for overall effect:
Mantel-Haenszel $\chi^2 = 5.2$; $P = .02$



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Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies. Systematic Review and Meta-analysis of Rare Harmful Effects in Randomized Controlled Trials

Conclusions

"There is evidence of an increased risk of serious infections and a dose dependent increased risk of malignancies in patients with rheumatoid arthritis treated with anti-TNF antibody therapy.

The formal meta-analysis with pooled sparse adverse events data from randomized controlled trials serves as a tool to assess harmful drug effects."

ARTHRITIS & RHEUMATOLOGY
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SPECIAL ARTICLE

2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

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ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 1, January 2016, pp 1–26

High-risk condition	Recommendation	Level of Evidence (evidence reviewed)
Past history of treated or untreated malignancy[4]		
Previously treated or untreated skin cancer (non-melanoma or melanoma)	*Use DMARDs over biologics in melanoma (PICO F.1).* *Use DMARDs over tofacitinib in melanoma (PICO F.2).* *Use DMARDs over biologics in non-melanoma (PICO F.3).* *Use DMARDs over tofacitinib in non-melanoma (PICO F.4).*	*Very low (104-106)*
Previously treated lymphoproliferative disorder	**Use rituximab over TNFI (PICO G.1).**	**Very low (105,107)**
Previously treated lymphoproliferative disorder	*Use combination DMARD or abatacept or tocilizumab over TNFi* (PICO G.2, G.3 and G.4)**.**	*Very low (105,107)*
Previously treated solid organ malignancy	*Same recommendations as in patients without this condition (PICO H.1)***.**	*Very low (105,108)*

Safety of synthetic and biological DMARDs:a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ramiro S, et al. Ann Rheum Dis 2017;76:1093-1101.

Table 3 Malignancies in patients on bDMARDs compared with patients on csDMARDs or general population (observational studies)

Year of publication	Study ID	Registry	Intervention	Control csDMARDs	Control general population	aHR (intervention vs comparator/control)	aHR (intervention vs general population)	Risk of bias
All types of cancer								
≤2013	Askling 2009 A&R[51]	ARTIS	3 TNFi	csDMARDs	General population	TNFi vs pts starting MTX: 1.0 (0.8 to 1.2); TNFi vs csDMARDs combination therapy 1.0 (0.7 to 1.4)	1.1 (1.0 to 1.3)	Low
	Carmona 2011 Semin Arthritis Rheum[52]	BIOBADASER	3 TNFi	csDMARDs	General population	0.5 (0.1 to 2.5)	**0.7 (0.5 to 0.9)**	Low
	Hayes 2013 A&R[53]	Claim database	3 TNFi	csDMARDs	NR	0.8 (0.6 to 1.1) Ever-analysis 0.9 (0.8 to 1.1)	NR	Moderate
	Pallavicini 2010 Autoimmunity Reviews[54]	LORHEN	3 TNFi	NR	General population	NR	Milan*: 0.9 (0.6 to 1.5) to Varese 1.1 (0.6 to 1.7)	Moderate
	Strangfeld 2010 AR&T[55]	RABBIT	3 TNFi	csDMARDs	General population	0.7 (0.4 to 1.1)	0.8 (0.5 to 1.0)	Low
			ANA			1.4 (0.6 to 3.5)	NR	
2013–2016	Berghen 2015 Clin Rheumatol[25]	Cases from the Leuven University Hospital	3 TNFi	NR	General population	NR	**♂163.5 (156.8 to 170.6)† ♀145.5 (137.2 to 154.3)**	Moderate
	Aaltonen 2015 J Rheum[10]	National Register for Biologic Treatment in Finland (ROB-FIN)	3 TNFi	csDMARDs	NR	1.2 (0.6 to 2.2)	NR	Low
			ADA			1.1 (0.5 to 2.2)		
			ETA			1.3 (0.7 to 2.6)		
			IFX			1.2 (0.4 to 3.1)		
			RTX			1.2 (0.5 to 3.2)		
	Morgan 2014 Rheumatology[14]	BSRBR	ETA	csDMARDs	NR	0.8 (0.7 to 1.0)	NR	Low
	Solomon 2014 Semin Arthr Rheum[9]	CORRONA	3 TNFi	MTX	NR	**0.3 (0.1 to 0.6)**	NR	Low
			RTX			0.4 (0.1 to 2.6)		
			ABA			1.6 (0.4 to 6.0)		
Patients with history of cancer								
≤2013	Dixon 2010 AC&R[68]	BSRBR	3 TNFi	csDMARDs	NR	0.5 (0.1 to 2.2); censoring after first cancer 0.5 (0.1 to 2.2)	NR	Low

Safety of synthetic and biological DMARDs:a systematic literature review informingthe 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ramiro S, et al. Ann Rheum Dis 2017;76:1093-1101.

Year of publication	Study ID	Registry	Intervention	Control csDMARDs	Control general population	aHR (intervention vs comparator/control)	aHR (intervention vs general population)	Risk of bias
Solid cancers								
2013–2016	Mercer 2015 ARD[26]	BSRBR	3 TNFi	csDMARDs	NR	0.8 (0.6 to 1.1)	NR	Low
			ADA			0.8 (0.6 to 1.1)		
			ETA			0.9 (0.7 to 1.2)		
			IFX			0.8 (0.6 to 1.1)		
	Solomon 2014 Semin Arthr Rheum[9]	CORRONA	3 TNFi	MTX	NR	0.2 (0.1 to 0.6)	NR	Low
			RTX			0.3 (0.0 to 3.4)		
			ABA			0.4 (0.1 to 2.2)		
Lymphoma								
≤2013	Askling 2009 ARD[69]	ARTIS	3 TNFi	csDMARDs	Gen population	1.4 (0.8 to 2.1)	2.7 (1.8 to 4.1)	Low
	Mariette 2010 ARD[70]	RATIO	3 TNFi	NR	Gen population	NR	2.3 (1.6 to 3.3)	Low
	Carmona 2011 Semin Arthritis Rheum[52]	BIOBADASER	3 TNFi	csDMARDs	General population	NR	Hodgkin's lymphoma 5.3 (0.1 to 29.5); non-Hodgkin's lymphoma 1.5 (0.31 to 4.4)	Low

Safety of synthetic and biological DMARDs:a systematic literature review informingthe 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ramiro S, et al. Ann Rheum Dis 2017;76:1093-1101.

Year of publication	Study ID	Registry	Intervention	Control csDMARDs	Control general population	aHR (intervention vs comparator/control)	aHR (intervention vs general population)	Risk of bias
Lymphoma								
	Haynes 2013 A&R[53]	Claim database	3 TNFi	csDMARDs	NR	0.8 (0.3 to 2.1) Ever-analysis 1.3 (0.7 to 2.2)	NR	Moderate
	Pallavicini 2010 Autoimmunity Reviews[54]	LOHREN	3 TNFi	NR	General population	NR	Milan 6.0 (1.6 to 15.4) to Varese 5.0 (1.3 to 12.7);	Moderate
2013–2016	Berghen 2015 Clin Rheumatol[25]	Cases from the Leuven University Hospital	3 TNFi	NR	General population	NR	♂ 423.6 (361.9-492.8)† ♀1135 (1003.1-1279.5)	Moderate
Non-melanoma skin cancer								
≤2013	Amari 2011 Rheumatology[71]	Claim database	3 TNFi	csDMARDs	NR	1.4 (1.2 to 1.6); TNFi vs MTX 1.4 (1.2 to 1.7)	NR	Moderate
	Mercer 2012 ARD[72]	BSRBR	3 TNFi	csDMARDs	General population	BCC 1.0 (0.5 to 1.7), SCC 1.2 (0.4 to 3.8); first cancer per subject BCC 0.8 (0. 5 to 1.5)	**1.7 (1.4 to 2.0)**	Low
	Haynes 2013 A&R[53]	Claim database	3 TNFi	csDMARDs	NR	0.8 (0.5 to 1.4) Ever-analysis 1.1 (0.8 to 1.5)	NR	Moderate
2013–2016	Solomon 2014 Semin Arthr Rheum[9]	CORRONA	3 TNFi	MTX	NR	0.4 (0.1 to 1.2)	NR	Low
			RTX			0.7 (0.0 to 13.6)		
			ABA			**15.3 (2.1 to 114.0)‡**		
Melanoma								
≤2013	Raaschou 2013 BMJ[56]	ARTIS	5 TNFi	csDMARDs	NR	1.5 (1.0 to 2.2)	NR	Low

Ann Rheum Dis 2017;76:386–391

Table 1 Means of age-standardised incidence rates of melanoma (years 2003–2012) using the European standard population aged 40–84 as reference

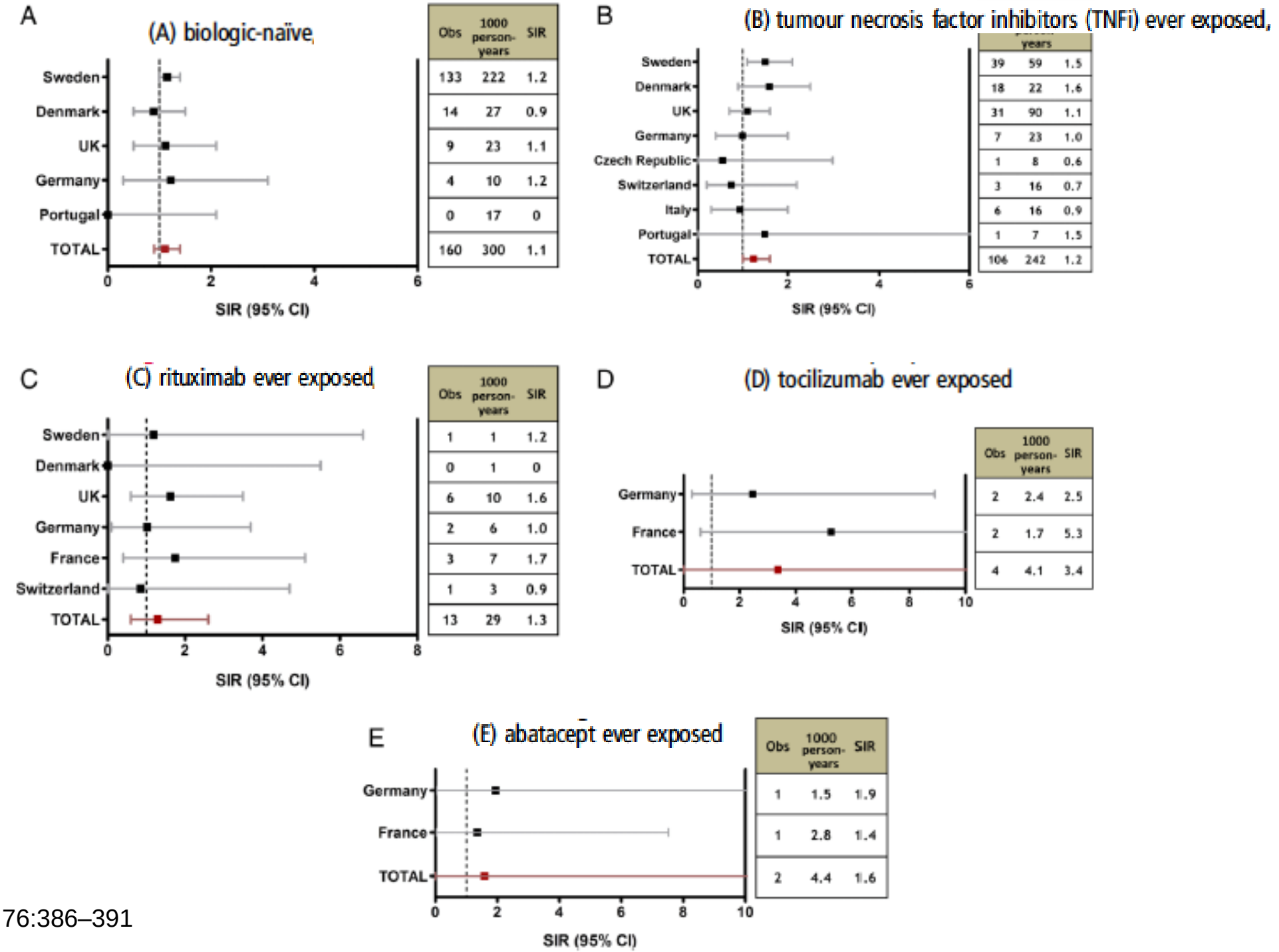
	Annual incidence of melanoma in the general population (per 100 000)		
	Total	Males	Females
Sweden	47.1	51.3	42.9
Denmark	52.2	53.3	51.2
UK	30.6	32.1	29.1
Germany	31.6	35.1	28.0
Czech Republic	34.0	40.0	28.0
France	22.9	23.3	22.5
Switzerland	48.6	54.5	42.7
Portugal	11.6	11.0	12.1
Italy	27.9	33.0	22.8

Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers

Louise K Mercer,[1] Johan Askling,[2,3] Pauline Raaschou,[2] William G Dixon,[1] Lene Dreyer,[4,5] Merete Lund Hetland,[6] Anja Strangfeld,[7] Angela Zink,[7,8] Xavier Mariette,[9] Axel Finckh,[10] Helena Canhao,[11] Florenzo Iannone,[12] Jakub Zavada,[13,14] Jacques Morel,[15] Jacques-Eric Gottenberg,[16] Kimme L Hyrich,[1] Joachim Listing[7]

Table 2 Baseline characteristics of biologic-naïve, TNFi rituximab, tocilizumab or abatacept ever-exposed RA patients

	Biologic-naïve	TNFi	Rituximab	Tocilizumab	Abatacept
Patients (n)	68 411	48 304	9431	2606	1563
Follow-up time (pyrs)	300 012	242 814	28 705	4053	4399
Female (%) (range)	72.1 (71–79)	75 (74.2–87)	78.4 (76.1–80.5)	78.8 (77–80.2)	78.4 (77–79.2)
Mean age (range)	61.1 (57–61.8)	55.0 (50.3–56.5)	58 (57.5–58.6)	56.5 (56–56.8)	57.4 (56–58.2)
Mean of median disease duration (range)	5.7 (4–13)	8.5 (6.2–12)	12.8 (8.6–17)	10.3 (6–13.5)	13.3 (8–16)
Mean DAS28 (range)	4.0 (3.6–5.1)	5.3 (3.8–6.6)	5.4 (4.3–5.7)	5.2 (5.1–5.3)	5.3 (5.3–5.4)
Mean HAQ (range)	1.0 (0.8–1.5)	1.4 (0.8–2)	1.5 (1.2–1.6)	1.4	1.5



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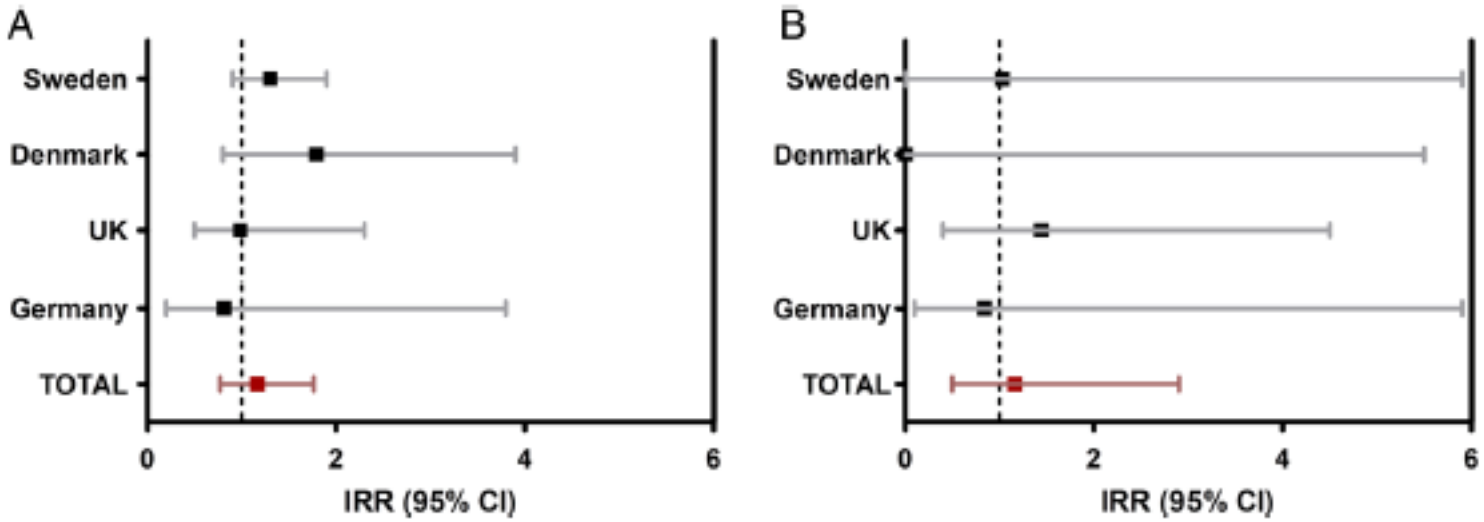

Figure 2 Melanoma incidence rate ratios (IRRs) of (A) tumour necrosis factor inhibitors (TNFi) ever exposed and (B) rituximab ever exposed patients compared with biologic-naïve patients.

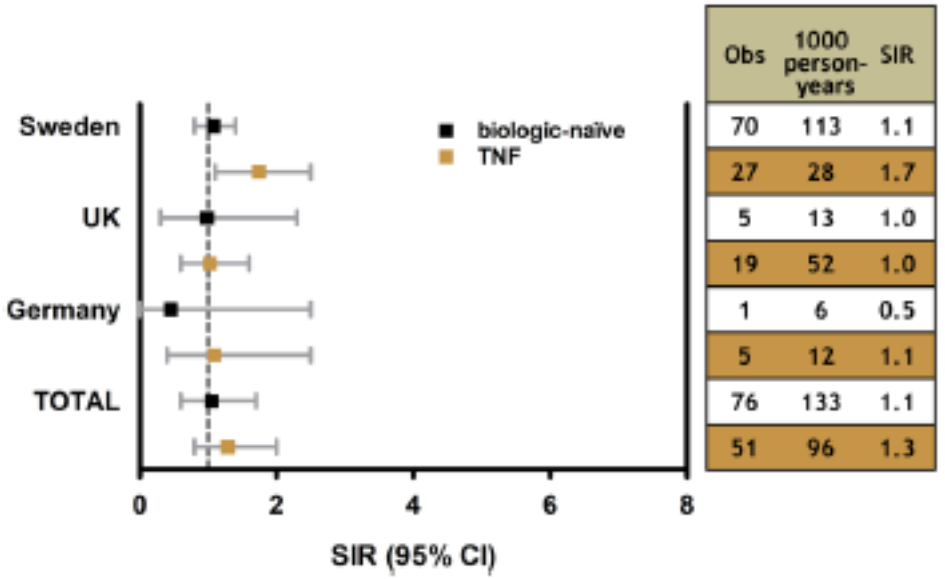

Figure 3 Subgroup analysis: standardised incidence ratios (SIRs) of melanomas in patients aged 50–74 years at the time of melanoma diagnosis. TNF, tumour necrosis factor.

Ann Rheum Dis 2017;76:386–391

Table 3 Association between exposure to TNFi and lymphoma

	csDMARD N=3367	TNFi N=11 931
Total follow-up time (pyrs)	19 473	95 126
Lymphomas	30	84
Incidence rate per 100 000 pyrs (95% CI)	154 (104 to 220)	88 (70 to 109)
Unadjusted HR (95% CI)	Referent	0.61 (0.40 to 0.92)
Age-adjusted and sex-adjusted HR (95% CI)	Referent	0.75 (0.49 to 1.15)
PD-adjusted HR (95% CI)	Referent	1.00 (0.56 to 1.80)
On TNFi (plus 90 days)*		
Follow-up time (pyrs)	15 167	57 949
Lymphomas	25	63
PD-adjusted HR (95% CI)	Referent	1.17 (0.60 to 2.26)
Excluded time after switched to second biological drug*		
Follow-up time (pyrs)	15 167	55 167
Lymphomas	25	52
PD-adjusted HR (95% CI)	Referent	1.12 (0.58 to 2.18)
Cancer registry-only reported lymphomas		
Follow-up time (pyrs)	19 473	95 126
Lymphomas	27	76
PD-adjusted HR (95% CI)	Referent	1.02 (0.55 to 1.90)
Hodgkin's lymphomas (HL)		
Incidence rate of HL per 100 000 pyrs (95% CI)	26 (8 to 60)	13 (7 to 22)
PD-adjusted HR for HL (95% CI)	Referent	0.54 (0.12 to 2.50)
Non-Hodgkin's lymphomas (NHL)		
Incidence rate of NHL per 100 000 pyrs (95% CI)	128 (83 to 190)	75 (58 to 94
PD-adjusted HR for NHL (95% CI)	Referent	1.10 (0.58 to 2.08)
DLBCL		
Incidence rate of DLBCL per 100 000 pyrs (95% CI)	67 (36 to 114)	56 (42 to 73)
PD-adjusted HR for DLBCL (95% CI)	Referent	1.54 (0.60 to 3.95)

*Time after last received consultant follow-up form excluded from this analysis.
DLBCL, diffuse large B cell lymphoma; pyrs, patient-years; TNFi, tumour necrosis factor

Risk of lymphoma in patients exposed to antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

Louise K Mercer,[1] James B Galloway,[2] Mark Lunt,[1] Rebecca Davies,[1] Audrey L S Low,[1] William G Dixon,[1,3] Kath D Watson,[1] BSRBR Control Centre Consortium[1] Deborah P M Symmons,[1,3] Kimme L Hyrich[1,3]

Ann Rheum Dis 2017;76:497–503

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Table 4 Association between exposure to adalimumab (ADA), etanercept (ETA) or infliximab (INF) and lymphoma

	ADA N=4288	ETA N=4144	INF N=3499
First TNFi received (censored when second biological drug started)*			
Total follow-up time (pyrs)	22 361	26 838	17 688
Number of lymphomas	20	20	18
Incidence rate per 100 000 pyrs (95% CI)	89 (55 to 138)	75 (45 to 115)	102 (60 to 161)
PD-adjusted HR (95% CI) (csDMARD referent)	1.00 (0.49 to 2.03)	1.02 (0.45 to 2.33)	0.91 (0.39 to 2.13)
Most recently received TNFi			
Follow-up time (pyrs)	33 354	40 618	21 149
Number of lymphomas	34	29	21
Incidence rate per 100 000 pyrs (95% CI)	102 (71 to 143)	71 (48 to 103)	99 (62 to 152)
PD-adjusted HR (95% CI) (csDMARD referent)	0.99 (0.52 to 1.88)	0.78 (0.37 to 1.66)	0.82 (0.37 to 1.82)
On drug (plus 90 days)*†			
Follow-up time (pyrs)	18 818	24 984	12 328
Number of lymphomas	23	10	10
Incidence rate per 100 000 pyrs (95% CI)	122 (77 to 183)	40 (19 to 74)	81 (39 to 149)
PD-adjusted HR (95% CI) (csDMARD referent)	0.77 (0.37 to 1.61)	0.41 (0.14 to 1.19)	0.75 (0.27 to 2.09)

Spectrum of lymphomas across different drug treatment groups in rheumatoid arthritis: a European registries collaborative project

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Table 1 Baseline characteristics and crude incidence rate of lymphomas among biologic-naïve, TNFi, rituximab, tocilizumab or abatacept-treated patients with RA

	Bionaïve	TNFi	Rituximab	Tocilizumab	Abatacept	Total
No. of patients	71 088	47 864*	9094	2029	1708*	124 997*
Follow-up time (pyrs)	322 167	242 260*	29 810	2827	3352*	584 236*
Female (%)	72.1	74.8	79.0	80.1	78.0	73.7
Age mean (mean range)	61.1 (57–62)	55.0 (50–57)	57.9 (58–58)	55.9 (55–57)	57.5 (56–58)	58.5 (50–62)
No. of lymphomas	288	230	6	6	3	533
Incidence per 100 000 pyrs (95% CI)	89 (79–100)	81 (70–94)	20 (7–44)	177 (57–413)	60 (7–216)	85 (77–92)

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Table 2 Lymphoma subtype distribution (Hodgkin's, B-cell and T-cell lymphomas) in patients with RA in treatment groups. ARTIS and BSRBR-RA, both with more than 30 lymphomas in the bionaïve and TNFi groups, are shown separately to describe the robustness of the results

		Hodgkin's			B cell			T cell			NOS
	N total	n	%	95% CI	n	%	95% CI	n	%	95% CI	N excluded
Bionaïve											
ARTIS	197	13	6.6	3.3 to 11.8	174	88.3	82.1 to 93.0	10	5.1	2.6 to 8.8	19
BSRBR	30	5	16.7	5.1 to 37.0	22	73.3	50.9 to 88.6	3	10.0	1.8 to 29.1	4
Other	31	3	9.7	1.8 to 28.6	24	77.4	55.3 to 91.2	4	12.9	3.2 to 32.5	7
Total	258	21	8.1	4.7 to 12.9	220	85.3	79.3 to 90.0	17	6.6	3.6 to 11.2	30
TNFi											
ARTIS	52	6	11.5	4.0 to 26.2	40	76.9	61.1 to 88.3	6	11.5	4.0 to 26.2	7
BSRBR	77	11	14.3	6.5 to 25.9	63	81.8	69.4 to 90.6	3	3.9	0.7 to 12.1	10
Other	73	7	9.6	3.6 to 20.4	61	83.6	71.3 to 91.8	5	6.9	2.0 to 17.0	11
Total	202	24	11.9	7.0 to 18.3	164	81.2	74.1 to 87.3	14	6.9	3.3 to 12.3	28
Rituximab	6	0	0	0 to 50.0	5	83.3	32.9 to 99.7	1	16.7	0.3 to 67.2	0
Tocilizumab	5	0	0	0 to 56.0	5	100	44.0 to 100	0	0	0 to 56.0	1
Abatacept	3	0	0	0 to 74.4	3	100	25.6 to 100	0	0	0 to 74.4	0
RA total	474	45	9.5	6.6 to 13.2	397	83.8	79.3 to 87.6	32	6.8	4.3 to 10.0	59

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Table 3 B-cell non-Hodgkin's lymphoma subtypes

		Chronic lymphocytic leukemia/ smallcell lymphoma		Lymphoplasmocytic lymphoma (Waldenstrom macroglobulinaemia)		Marginal zone lymphoma		Follicular lymphoma		Mantle cell lymphoma		Diffuse large B-cell lymphoma		Burkitt lymphoma	
	N total	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Bionaïve	184	28	15.2 (9.2 to 23.2)	4	2.2 (0.4 to 6.8)	1	0.5 (0 to 4.1)	33	17.9 (11.3 to 26.6)	5	2.7 (0.6 to 7.6)	113	61.4 (51.5 to 70.8)	0	0 (0 to 3.0)
TNFi	151	26	17.2 (10.1 to 26.8)	6	4.0 (1.1 to 10.1)	10	6.6 (2.6 to 13.6)	34	22.5 (14.3 to 32.6)	0	0 (0 to 3.6)	75	49.7 (38.6 to 60.8)	0	0 (0 to 3.6)
RTX	5	1	20.0 (1.4 to 79.6)	1	20.0 (1.4 to 79.6)	0	0 (0 to 62.9)	1	20.0 (1.4 to 79.6)	0	0 (0 to 62.9)	2	40.0 (2.8 to 90.6)	0	0 (0 to 62.9)
TOC	5	2	40.0 (2.8 to 90.6)	0	0 (0 to 62.9)	0	0 (0 to 62.9)	0	0 (0 to 62.9)	0	0 (0 to 62.9)	3	60.0 (9.4 to 97.3)	0	0 (0 to 62.9)
ABA	3	0	0 (0 to 80.7)	0	0 (0 to 80.7)	0	0 (0 to 80.7)	2	66.7 (5.0 to 99.8)	0	0 (0 to 80.7)	1	33.3 (0.2 to 95.0)	0	0 (0 to 80.7)
RA total	348	57	16.4 (11.6 to 22.2)	11	3.2 (1.3 to 6.4)	11	3.2 (1.3 to 6.4)	70	20.1 (14.7 to 26.4)	5	1.4 (0.3 to 4.0)	194	55.8 (48.4 to 62.9)	0	0 (0 to 1.6)
General population	28 747	11 019	38.3 (37.6 to 39.1)	1859	6.5 (6.1 to 6.9)	950	3.3 (3.0 to 3.6)	4881	17.0 (16.4 to 17.6)	1012	3.5 (3.2 to 3.8)	8538	29.7 (29.0 to 30.4)	488	1.7 (1.5 to 1.9)

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Rheumatoid Arthritis and Risk of Malignant Lymphoma

Is the Risk Still Increased?

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Objective. Patients with rheumatoid arthritis (RA) are at increased risk of malignant lymphomas with a strong correlation with RA disease severity. Given the changes in RA therapy over recent decades, this study was undertaken to assess whether lymphoma risk remains increased, and if so, to explore risk predictors and lymphoma subtypes.

Methods. We identified 12,656 cases of incident RA in the Swedish Rheumatology Quality Register 1997–2012 and obtained information on therapy and inflammatory activity during the first year after diagnosis. Each patient was matched to 10 population comparator subjects. Through linkage to the Swedish Cancer Register, lymphomas, including subtypes, were identified. We assessed hazard ratios (HRs) using Cox regression.

Results. Overall, the HR for lymphoma was increased in RA, to 1.6 (95% confidence interval [95% CI] 1.2–2.1). Taking RA duration into account, risks did not appear to have declined over successive calendar years of RA diagnosis. Neither use of methotrexate the first year after RA diagnosis nor ever use of tumor necrosis factor inhibitors (TNFi) increased lymphoma risk (HR 0.9 [95% CI 0.4–1.9]). Use of oral corticosteroids the first year after RA diagnosis was associated with a reduced risk (HR 0.5 [95% CI 0.3–0.9]). Inflammatory activity during the first year after RA diagnosis did not predict future lymphoma risk. Chronic lymphocytic leukemia occurred less frequently, and Hodgkin's lymphoma occurred more frequently, in RA patients than in the general population.

Conclusion. The average lymphoma risk in recently diagnosed RA is similar in magnitude to that reported in historical cohorts. Standard antirheumatic treatment including TNFi did not predict future lymphoma risk. Distribution of lymphoma subtypes warrants further investigation.

In rheumatoid arthritis (RA) an increased risk of malignant lymphoma, an average doubling of the risk compared with the general population, is well established (1–4). Although the mechanisms underlying this risk increase are not understood (4–7), available data suggest a strong association with RA disease severity and accumulated inflammatory activity. Further, we have noted a particularly increased risk of diffuse large B cell lymphoma (DLBCL) (8) during the period 1964–1995

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Table 2. HRs for lymphoma in the patients with incident RA 1997–2012 (n = 12,656) versus their individually matched comparator subjects (n = 124,161), with respect to disease characteristics and inflammatory activity 1 year after RA diagnosis

	Lymphomas, no. (%)	HR (95% CI)*
Overall	62 (100)	1.6 (1.2–2.1)
Women	35 (56)	1.5 (1.1–2.2)
Men	27 (44)	1.7 (1.1–2.6)
Age at diagnosis of RA, years†		
18–50	5 (8)	1.6 (0.6–4.1)
51–74	49 (79)	1.9 (1.4–2.5)
≥75	8 (13)	0.8 (0.4–1.7)
Rheumatoid factor status at diagnosis of RA†		
Positive	41 (66)	1.7 (1.2–2.4)
Negative	17 (27.5)	1.2 (0.7–2.0)
Unknown	4 (6.6)	ND‡
Inflammatory activity at diagnosis of RA§		
High (DAS28 >5.1)	31 (50)	1.6 (1.1–2.4)
Moderate (DAS28 3.2–5.1)	20 (32)	1.6 (1.0–2.6)
Low (DAS28 2.6–3.1)	2 (3)	ND‡
Remission (DAS28 <2.6)	1 (2)	ND‡
No information	8 (13)	1.7 (0.8–3.4)
Inflammatory activity at 1 year¶		
High (DAS28 >5.1)	4 (7)	2.3 (0.9–6.2)
Moderate (DAS28 3.2–5.1)	17 (31)	2.1 (1.3–3.4)
Low (DAS28 2.6–3.1)	4 (7)	1.0 (0.4–2.6)
Remission (DAS28 <2.6)	19 (35)	1.7 (1.1–2.7)
No information	11 (20)	1.1 (0.6–2.1)

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Table 4. HRs for lymphoma in the patients with incident RA 1997–2012 versus all other RA patients, with respect to inflammatory activity and therapy*

	Lymphomas, no. (%) (n = 55)	RA patients, no. (%) (n = 11,638)	HR (95% CI)†	HR (95% CI)‡
Inflammatory activity during the first year after RA diagnosis§				
DAS28 ≥3.2	8 (14)	1,271 (11)	1.2 (0.5–2.6)	–
DAS28 <3.2	7 (13)	1,481 (13)	0.9 (0.4–2.0)	–
Other DAS28¶	40 (73)	8,886 (76)	1 (reference)	–
Therapy				
Methotrexate during the first year after RA diagnosis (yes versus no)	40 (72)	8,739 (75)	0.9 (0.8–1.0)	0.9 (0.9–1.0)
Oral corticosteroids during the first year after RA diagnosis (yes versus no)	22 (40)	7,339 (63)	0.5 (0.3–0.9)	0.5 (0.3–0.9)
TNFi during follow-up (yes versus no)#	12 (19)	3,072 (24)	0.9 (0.4–1.9)	1.2 (0.6–2.4)

Table 3. HRs for lymphoma in the patients with incident RA 1997–2012 (n = 12,656) versus their individually matched comparator subjects (n = 124,161), with respect to time since RA diagnosis and calendar period of RA diagnosis*

	Time since RA diagnosis, years		
Year of RA diagnosis	0–<6	6–16	Total follow-up period
1997–2003	1.3 (0.7–2.2) (14)	1.9 (1.2–3.1) (22)	1.8 (1.3–2.6) (36)
2004–2012	1.4 (0.9–2.2) (21)	2.7 (1.1–6.7) (5)	1.4 (0.9–2.0) (26)
Entire study period	1.3 (0.9–1.8) (35)	2.4 (1.6–3.6) (27)	1.6 (1.2–2.1) (62)

* Values are the hazard ratio (HR) (95% confidence interval [95% CI]), adjusted for age and sex (no. of lymphomas). All HRs were determined in comparison with the general population comparator subjects. *P* for time since diagnosis of rheumatoid arthritis (RA) = 0.01; *P* for calendar period = 0.3.

Accepted Manuscript

Title: Incidence of cancer in patients with spondyloarthritis treated with anti-tnf drugs

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Table IV. Risk for neoplasias in patients with SpA treated with anti-TNF drugs

	HR (95% CI)	P value
Sex*		
	0.8 (0.5-1.34)	0.429
TNFi	1.04 (1.01-1.06)	0.001
Disease duration	1 (0.96-1.03)	0.89
Combidities*	2.5 (1.2-5.2)	0.012
Anti-TNF drugs*		
Adalimumab	1.56 (0.8-3.2)	0.221
Etanercept	1.05 (0.5-2.0)	0.89
Corticosteroids*	1.18 (0.7-2.1)	0.58
DAS-28	1.32 (0.92-1.90)	0.137
HAQ-DI	2.82 (1.5-5.3)	0.002
BASDAI	1.02 (0.92-1.14)	0.703
BASFI	1.01 (0.9-1.2)	0.882

*Female sex, no comorbidities, no previous DMARDs , infliximab, no steroids are reference groups.

Table VI. Hazard ratio by type of comorbidity and neoplasia

	HR	95% CI		P value
Others	1.8	1.0	3.2	0.059
Thyroid diseases	3.1	1.5	6.2	0.002
Dyslipidemia	3.0	1.1	8.3	0.039
Prostatic hypertrophy	4.1	1.3	13.3	0.018
Neoplasias	10.6	4.2	27.0	**<0.001**

Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. Ann Rheum Dis 2017;76:105–111.

From the Swedish (Anti-Rheumatic Therapy in Sweden (ARTIS)) and Danish (DANBIO) biologics registers, we assembled 8703 (ARTIS=5448, DANBIO=3255) patients with SpA initiating a first TNFi 2001–2011

From the Swedish National Patient and Population Registers we assembled a TNFi-naïve SpA cohort (n=28,164)

Swedish age-matched and sex-matched general population comparator cohort (n=131 687)

We identified incident cancers by linkage with the nationwide Swedish and Danish Cancer Registers 2001 2011, and calculated age-standardised and sex-standardised incidence ratios as measures of relative risk (RR)

Ann Rheum Dis 2017;76:105–111.

Table 1 Seminal studies on risks of cancer in patients with AS and PsA treated with TNF inhibitors (TNFi)

Type of condition	Author (ref) publication year	Type of study	N cancers/N study population	Relative risks of cancer overall (HR, OR, IRR, SIR, 95% CI)
AS/PsA	Burmester 2012[16]	RCT Median duration of exposure 0.4 years	N cancers not available 1684 patients with AS 837 patients with PsA	SIR AS 0.51 (0.16 to 1.19) PsA 0.68 (0.22 to 1.59)
PsA/psoriasis	Dommasch 2011[15]	Meta-analysis Of 20 RCTs Mean duration follow-up 17.8 weeks	N cancer TNFi exposed; 28 Placebo group; 4 /Total 6810 patients 20% PsA, 80% Psoriasis	OR for entire group 1.48 (0.71 to 3.09)
AS/PsA	Haynes 2012[18]	Cohort study	N solid cancer TNFi exposed: 6/783 AS 17/1036 PsA TNFi naïve: 11/703 AS 30/1462 PsA	HR AS 0.15 (0.03 to 0.76) PsA 0.88 (0.39 to 1.98)
AS/PsA	Carmona 2011[19]	Cohort study	N cancer not available 761 patients with AS 727 patients with PsA	SIR* AS 0.92 (0.44 to 1.70) PsA 0.73 (0.33 to 1.39)
PsA	Saad 2011[20]	Cohort study	N cancers TNFi exposed:14/596 PsA TNFi naïve: 67/1115	IRR 1.0 (0.5 to 2.2)
AS	van der Heijde 2014[13]	Pooled analysis from 5 RCTs	N cancer 6/1074	SIR 1.47 (0.54 to 3.21)

Ann Rheum Dis 2017;76:105–111.

Table 2 Characteristics of patients with SpA from ARTIS and DANBIO treated with TNFi (n=8703), Swedish TNFi-naïve SpA patients (n=28 164) and age-matched and sex-matched Swedish general population comparator subjects (n=131 687) 2001 to 2011

	TNFi-treated patients DANBIO	TNFi-treated patients ARTIS	TNFi-treated patients DANBIO+ARTIS	TNFi-naïve patients Sweden	General population comparator cohort Sweden
All SpA, N	3255	5448	8703	28,164*	131 687†
AS, N (%)	1491 (46)	1587 (29)	3078 (35)	7023 (23)*	32 706 (23)†
PsA, N (%)	1342 (41)	2491 (46)	3833 (44)	15 908 (51)*	74 010 (51)†
SpA undifferentiated, (UNS) N (%)	422 (13)	1370 (25)	1792 (21)	8066 (26)*	38 534 (26)†
Gender, men, N (%)					
All SpA	1907 (58)	3115 (57)	5022 (58)	13 708 (49)	64 273 (49)
Median age (IQR)					
All SPA	43 (34–52)	45 (36–55)	44 (35–54)	49 (38–59)	49 (38–58)

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Table 3 Relative risk* of cancer overall in TNFi-treated patients with SpA from ARTIS and DANBIO (n=8703)† versus Swedish TNFi-naïve SpA patients (n=28 164)† and Swedish general population comparator subjects (n=131 687)† overall and in AS, PsA and SpA undifferentiated (UNS) separately 2001 to 2011

	TNFi (DANBIO and ARTIS)-treated patients with SpA versus TNFi-naïve		TNFi-treated (DANBIO and ARTIS) patients with SpA versus general population		TNFi-naïve patients with SpA versus the general population	
	N cancers TNFi-treated/TNFi-naïve	RR (95% CI)	N cancers TNFi-treated/general population	RR (95% CI)	N cancers TNFi naïve/general population	RR (95% CI)
All SpA	147/1188	0.8 (0.7 to 1.0)	147/5153	0.9 (0.7 to 1.0)	1188/5153	1.1 (1.0 to 1.2)
AS	53/310	0.8 (0.6 to 1.1)	53/1296	0.9 (0.7 to 1.2)	310/1296	1.1 (1.0 to 1.3)
PsA	71/722	0.9 (0.7 to 1.1)	71/3227	0.9 (0.7 to 1.1)	722/3227	1.0 (0.9 to 1.1)
SpA UNS	23/200	0.9 (0.6 to 1.3)	23/979	0.8 (0.6 to 1.3)	202/979	1.0 (0.8 to 1.2)

Ann Rheum Dis 2017;76:105–111.

Table 4 Relative risk* of six site-specific cancers in patients with SpA treated with TNFi (n=8703)† versus TNFi-naïve Swedish patients with SpA (n=28 164)† and Swedish general population comparator subjects (n=131 687)† 2001 to 2011

	TNFi-treated (DANBIO and ARTIS) patients with SpA versus TNFi-naïve		TNFi-treated (DANBIO and ARTIS) patients with SpA versus the general population		TNFi-naïve patients with SpA versus the general population	
Cancer site	N cancers TNFi-treated/ TNFi-naïve	RR (95% CI)	N cancers TNFi-treated/general population	RR (95% CI)	N cancers TNFi naïve/general population	RR (95% CI)
Prostate	23/296	**0.5 (0.3 to 0.8)**	23/1125	**0.6 (0.4 to 0.9)**	296/1125	**1.2 (1.1 to 1.4)**
Lung	7/76	0.6 (0.3 to 1.3)	7/357	0.6 (0.3 to 1.2)	76/357	1.0 (0.7 to 1.2)
Colorectal	11/86	1.0 (0.5 to 2.0)	11/580	0.7 (0.4 to 1.2)	86/580	**0.7 (0.5 to 0.8)**
Malignant lymphoma	9/54	0.8 (0.4 to 1.8)	9/258	0.8 (0.4 to 1.7)	54/258	1.0 (0.7 to 1.3)
Breast	30/179	1.3 (0.9 to 2.0)	30/837	1.3 (0.9 to 1.9)	179/837	1.0 (0.8 to 1.2)
Malignant melanoma	13/57	1.4 (0.7 to 2.6)	13/275	1.3 (0.7 to 2.3)	57/275	1.0 (0.7 to 1.3)

Ankylosing Spondylitis, Psoriatic Arthritis, and Risk of Malignant Lymphoma
A Cohort Study Based on Nationwide Prospectively Recorded Data From Sweden

ARTHRITIS & RHEUMATOLOGY Vol. 66, No. 5, May 2014, pp 1282–1290

Through the Swedish National Patient Register we assembled nationwide prevalence cohorts of patients with AS (n 8,707) and patients with PsA (n 19,283) for whom data were obtained between 2001 and 2010.

Each cohort member was matched to 5 population comparator subjects.

Linkage with the nationwide Cancer Register identified all lymphomas recorded from 2001 to 2010.

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Table 3. HRs of malignant lymphoma in the Swedish cohorts of patients with AS (n = 8,707) and patients with PsA (n = 19,283) compared with their comparator subjects with data recorded between 2001 and 2010, overall and stratified by sex, age, calendar period, and duration of followup time*

	No. of lymphomas among AS patients/no. of lymphomas among general population	HR (95% CI)	No. of lymphomas among PsA patients/no. of lymphomas among general population	HR (95% CI)
Overall	14/75	0.9 (0.5–1.6)	45/175	1.2 (0.9–1.7)
Stratified by sex				
Female	2/18	0.5 (0.1–2.3)	21/79	1.3 (0.8–2.0)
Male	12/57	1.0 (0.5–1.8)	24/96	1.2 (0.8–1.9)
Stratified by age at start of followup				
18–49 years	2/21	0.4 (0.1–1.9)	6/22	1.3 (0.5–3.2)
50–74 years	11/51	1.2 (0.5–2.0)	33/136	1.2 (0.8–1.7)
≥75 years	1/3	1.5 (0.2–15)	6/17	1.6 (0.6–4.0)
Stratified by calendar period at start of followup				
2001–2004	12/65	0.9 (0.5–1.6)	36/126	1.3 (0.9–2.0)
2005–2010	2/10	1.0 (0.2–4.4)	9/49	1.0 (0.6–2.0)
Stratified by duration of followup				
≤1 year	3/13	1.1 (0.3–3.1)	8/24	1.2 (0.6–2.6)
>1 year	11/62	0.8 (0.5–1.6)	37/151	1.2 (0.8–1.7)
Ever RA diagnosis excluded†	11/75	0.8 (0.4–1.5)	28/175	1.0 (0.6–1.4)

Ankylosing Spondylitis, Psoriatic Arthritis, and Risk of Malignant Lymphoma
A Cohort Study Based on Nationwide Prospectively Recorded Data From Sweden

ARTHRITIS & RHEUMATOLOGY Vol. 66, No. 5, May 2014, pp 1282–1290

Table 4. HRs of lymphoma in the Swedish cohorts of patients with AS (n = 6,415) and PsA (n = 14,088) compared with their comparator subjects with respect to treatment with DMARDs and oral glucocorticoids*

	No. of lymphomas among AS patients (person-time)†	HR (95% CI)	No. of lymphomas among PsA patients (person-time)†	HR (95% CI)
Overall	11 (39,640)	0.9 (0.5–1.6)	37 (83,468)	1.3 (0.9–1.9)
DMARDs‡	3 (10,261)	1.2 (0.3–4.3)	14 (39,131)	1.7 (1.0–3.1)
Oral glucocorticoids§	0 (5,604)	–	3 (19,668)	0.6 (0.2–2.0)

* Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were determined in a Cox regression analysis taking sex and age (linear variable within the regression model) into account. Analyses were based on a stricter definition of case exposure, i.e., requiring ≥2 outpatient specialist visits with a diagnosis of ankylosing spondylitis (AS) or psoriatic arthritis (PsA). DMARDs = disease-modifying antirheumatic drugs.

Table 5. Crude incidences of lymphoma in the Swedish cohorts of patients with AS (n = 6,415) and PsA (n = 14,088) compared with their comparator subjects with respect to treatment with a TNFi*

	No. of lymphomas among patients with AS (person-time)†	Crude incidence (95% CI) per 100,000 person-years	No. of lymphomas among patients with PsA (person-time)†	Crude incidence (95% CI) per 100,000 person-years
Overall	11 (39,640)	28 (14–50)	37 (83,468)	44 (31–61)
TNFi-treated patients‡	2 (7,028)	28 (3–102)	5 (9,600)	52 (17–122)
Non–TNFi-treated patients	9 (32,882)	27 (12–52)	32 (74,230)	43 (29–61)

Take home messages

- ✓ RA but not SpA or PsA increases the risk of lymphoma
- ✓ TNFi does not further increase the risk of lymphoma
- ✓ Data from registries do not confirm an higher incidence of melanoma in RA patient on TNFi
- ✓ Previous cancer seems to be the only predictor of cancer occurrence in patients on TNFi

Life is striking a balance