Skin cancers in patients treated with immunomodulating drugs

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Immunomodulating drugs used in inflammatory disorders

- Methotrexate
- Mycophenolate mofetil
- Calcineurin inhibitors (cyclosporin)
- Thiopurines (azathioprine, 6-mercaptopurine)
- Biologicals
    - TNF blockers (psoriasis, inflammatory rheumatisms, IBD)
    - Anti-IL12/IL23/ustekinumab (psoriasis, psoriatic arthritis, CD)
    - Anti-CD20/rituximab (RA, Wegener's disease, NHL, CLL)
    - Anti-IL1R/anakinra (RA, CAPS)
    - Anti-IL6R/tocilizumab (RA)
    - CTLA4 agonist/abatacept (RA)

Skin cancer risk and biologicals:

(1) TNF blockers

Initially: alarming signals regarding the risk of developing malignancy in RA patients receiving infliximab or adalimumab

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

Tim Bongartz, MD
Alex J. Sutton, PhD
Michael J. Sweeting, MSc
Iain Buchan, MD, MFPH
Eric L. Matteson, MD, MPH
Victor Montori, MD, MSc

JAMA. 2006;295:2275-2285

Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis

Xavier Mariette,[1] Marco Matucci-Cerinic,[2] Karel Pavelka,[3] Peter Taylor,[4] Ronald van Vollenhoven,[5] Rebecca Heatley,[6] Claire Walsh,[6] Richard Lawson,[6] Alan Reynolds,[7] Paul Emery[8]

Ann Rheum Dis 2011: 70:1895-1904

<u>Different methodology from meta analysis of RCT</u>:

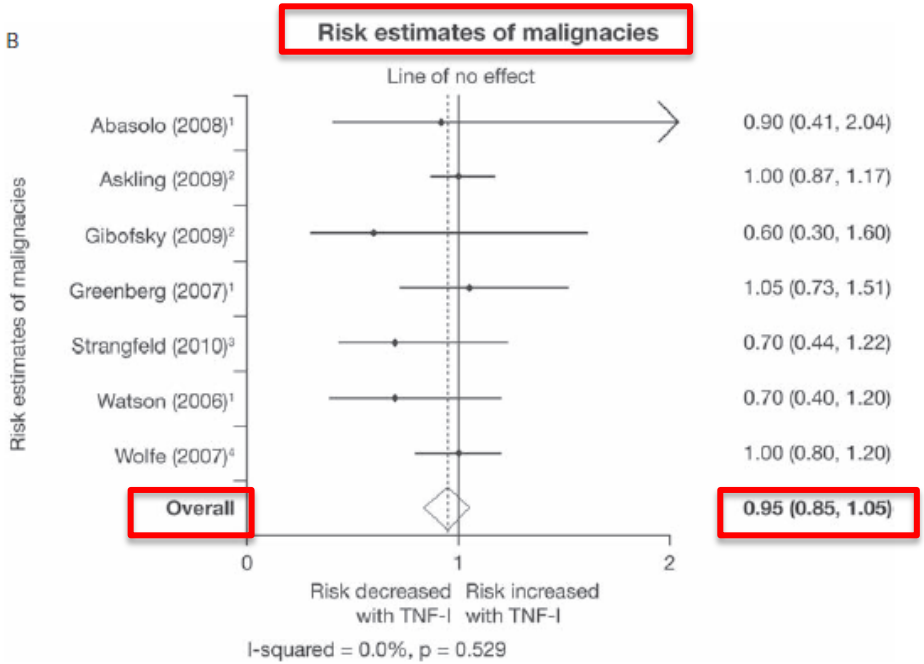
- **Published data from registries and prospective observational studies.**
- **RA and other rheumatic diseases patients.**
- **« Real life », « Usual clinical care ».**
- **Long term safety, higher number of patients.**

Results for all site malignancies

All site malignancies

7 publications with control arm (patients receiving DMARDs)

No increased risk of malignancy in patients exposed to TNF blockers RR<1 (0.95)



Mariette X et al. Ann Rheum Dis 2011

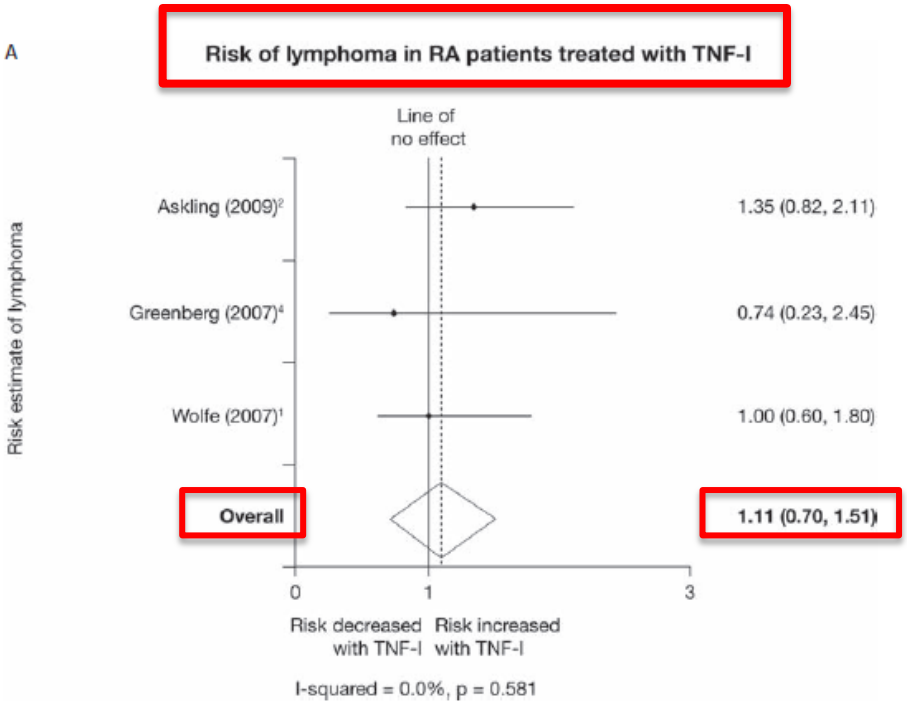
Results for lymphoma

Lymphoma

3 registries

Slight, non significant, increased RR (1.11)

No evidence of an increased risk of lymphoma
in patients treated with TNF blockers



Mariette X et al. Ann Rheum Dis 2011

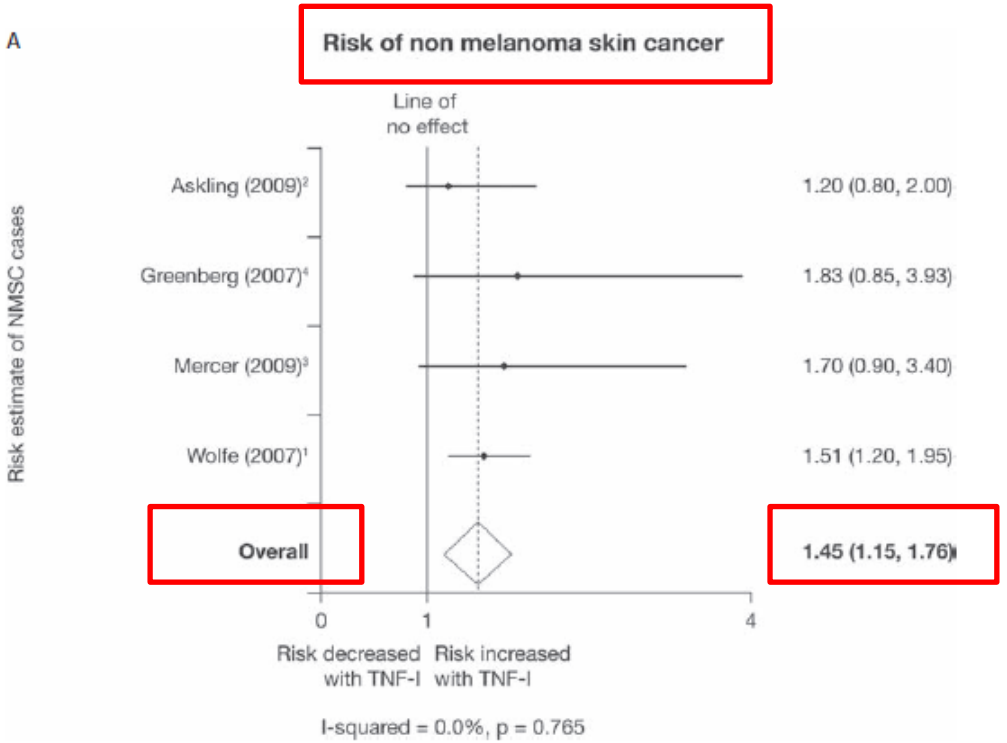
Results for Non Melanoma Skin Cancers (NMSC)

NMSC

(= BCC + SCC)

4 sources

Significant increased risk of developping NMSC (RR: 1.45)



Mariette X et al. Ann Rheum Dis 2011

The influence of anti-TNF therapy upon incidence of keratinocyte skin cancer in patients with rheumatoid arthritis: longitudinal results from the British Society for Rheumatology Biologics Register

Ann Rheum Dis 2012;**71**:869–874.

Louise K Mercer,[1] Adele C Green,[2,3] James B Galloway,[1] Rebecca Davies,[1] Mark Lunt,[1] William G Dixon,[1] Kath D Watson,[1] British Society for Rheumatology Biologics Register Control Centre Consortium*, Deborah PM Symmons,[1] Kimme L Hyrich,[1] on behalf of the British Society for Rheumatology Biologics Register

NMSC and anti TNF: BCC or SCC?

Table 3 Skin cancer reported in patients without previous history of skin cancer

	nbDMARD	Anti-TNF	Etanercept	Infliximab	Adalimumab
Number ever exposed to drug during follow-up	3523	11704	5086	3663	5035
Patients with cancer	38	139	54	49	36
Cancers	43	176	67	67	42
Patients with multiple cancers (%)	3 (8)	27 (19)	10 (18)	13 (27)	4 (11)
BCC (%)	38 (88)	150 (85)	57 (85)	59 (88)	34 (81)
SCC (%)	4 (9)	23 (13)	9 (13)	8 (12)	6 (14)
Basosquamous cell carcinoma (%)	0 (0)	1 (1)	0 (0)	0 (0)	1 (2)
Dermatofibrosarcoma protuberans	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Unclassified skin cancer (%)	1 (2)	1 (1)	0 (0)	0 (0)	1 (2)
First skin cancer reported by (%):					
NHS–IC	36 (95)	121 (87)	49 (91)	38 (78)	34 (94)
Physician and/or patient	17 (45)	85 (61)	35 (65)	33 (67)	17 (47)

BCC, basal cell carcinoma; nbDMARD, non-biological disease-modifying antirheumatic drug; NF, tumour necrosis factor; NHS–IC, National Health Service Information Centre; SCC, squamous cell carcinoma; TNF, tumour necrosis factor.

Clear predominance of BCC!

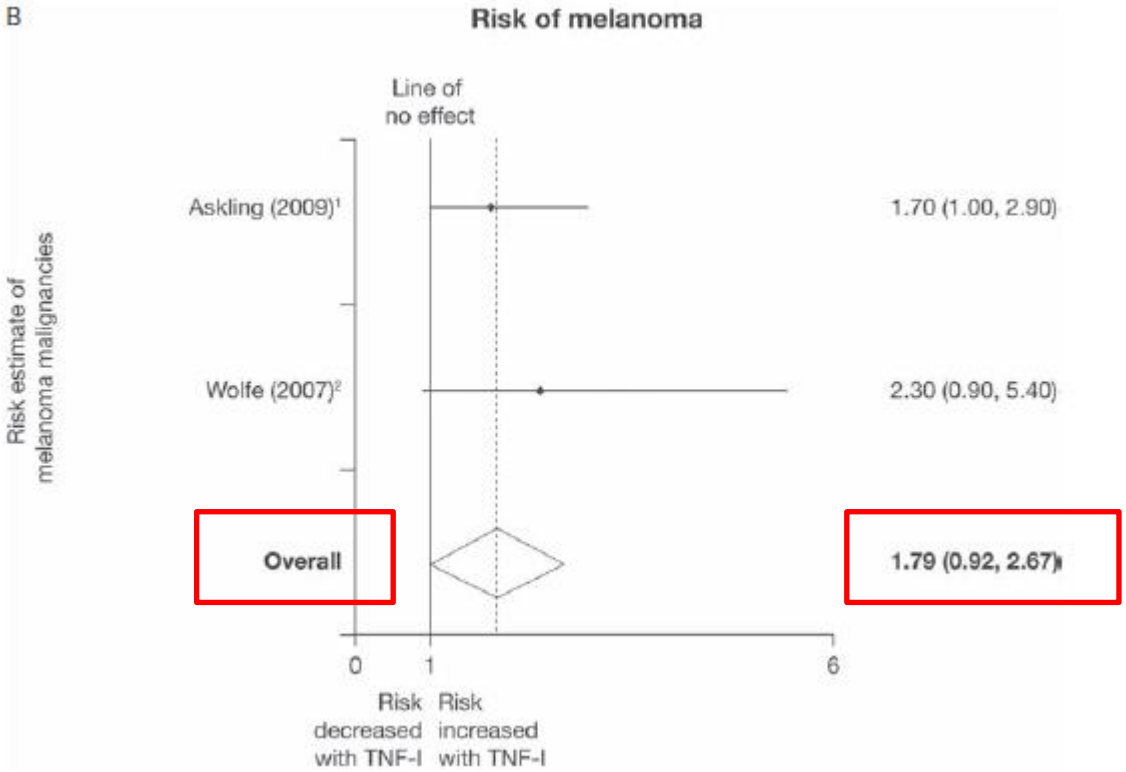
Results for Melanoma

Melanoma

Only 2 studies

Both reporting a trend toward increased risk of developing MM

Pooled analysis: RR 1.79 (wide CI)



Mariette X et al. Ann Rheum Dis 2011

A third recent study, not included in previous Mariette's meta analysis

Table 3| **Occurrence and hazard ratios of cancer outcomes in 10 878 Swedish rheumatoid arthritis patients starting tumour necrosis factor inhibitor compared with 42 198 not treated with biological drugs**

Outcome	Events/person year		Hazard ratio (95%CI)	
	Tumour necrosis factor inhibitor	No biological drug treatment	Stratified for sex and adjusted for age	Fully adjusted*
Invasive malignant melanoma†	38/57 223	113/203 345	1.6 (1.1 to 2.5)	1.5 (1.0 to 2.2)
In situ melanoma	11/56 080	57/197 754	1.1 (0.5 to 2.1)	—
Invasive all site cancer	558/55 947	2788/196 826	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.1)

*Stratified for year of inclusion and adjusted for sex, age, country of birth, personal history of non-melanoma skin cancer in situ, family history of melanoma, educational level, and comorbidities during follow-up (diabetes mellitus, ischaemic heart disease, chronic obstructive pulmonary disease, and joint surgery).
†Primary outcome.

Raaschou P, et al. Rheumatoid arthritis, anti-tumour necrosis factor therapy and risk of malignant melanoma : nationwide population based prospective cohort study from Sweden. BMJ 2013.

CONCISE COMMUNICATION

BJD
British Journal of Dermatology

Melanoma associated with tumour necrosis factor-α inhibitors: a Research on Adverse Drug events And Reports (RADAR) project

B. Nardone,[1] J.A. Hammel,[1] D.W. Raisch,[2] L.L. Weaver,[1] D. Schneider[3] and D.P. West[1]

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[2]College of Pharmacy, University of New Mexico, Albuquerque, NM, U.S.A.
[3]Northwestern University Clinical and Translational Sciences Institute, Northwestern University, Chicago, IL 60611, U.S.A.

For TNFαIs as a class of drugs, a safety signal was detectable in the FAERS database (EBGM 3·30, 95% CI 3·10–3·52) and RR was significant in the EMR database (RR 1·75, 95% CI 1·25–2·43, $P < 0·001$).

What does this study add?

- A safety signal was detected in the Food and Drug Administration Adverse Event Reporting System database.
- Enhanced monitoring for patients receiving TNFαIs is therefore warranted.

Increased risk of melanoma also identified in IBD patients receiving TNF blockers

Risk of Melanoma and Nonmelanoma Skin Cancer Among Patients With Inflammatory Bowel Disease

MILLIE D. LONG,[*,‡] CHRISTOPHER F. MARTIN,[*,‡] CLARE A. PIPKIN,[§] HANS H. HERFARTH,[*,‡] ROBERT S. SANDLER,[*,‡] and MICHAEL D. KAPPELMAN[‡,‖]

GASTROENTEROLOGY 2012;143:390–399

BACKGROUND & AIMS: Patients with inflammatory bowel disease (IBD) are at risk for certain malignancies. We aimed to determine the risk of melanoma and nonmelanoma skin cancer (NMSC) in patients with IBD and how medications affect these risks. **METHODS:** We performed retrospective cohort and nested case-control studies using administrative data from the LifeLink Health Plan Claims Database from 1997 to 2009. The cohort comprised 108,579 patients with IBD, and each was matched to 4 individuals without IBD. The risk of melanoma and NMSC was evaluated by incidence rate ratio (IRR) and by adjusted Cox proportional hazard ratio (HR) modeling. In nested case-control studies, patients with melanoma or NMSC were matched to 4 patients with IBD without melanoma or NMSC. Conditional logistic regression was used to determine associations between medications and both skin cancers. **RESULTS:** In the cohort, IBD was associated with an increased incidence of melanoma (IRR, 1.29; 95% confidence interval [CI], 1.09–1.53). Risk was greatest among individuals with Crohn's disease (IRR, 1.45; 95% CI, 1.13–1.85; adjusted HR, 1.28; 95% CI, 1.00–1.64). The incidence of NMSC also increased among patients with IBD (IRR, 1.46; 95% CI, 1.40–1.53) and was greatest among those with CD (IRR, 1.64; 95% CI, 1.54–1.74). In the nested case-control studies, therapy with biologics increased the risk of melanoma (odds ratio [OR], 1.88; 95% CI, 1.08–3.29). Patients who had been treated with thiopurines had an increased risk of NMSC (OR, 1.85; 95% CI, 1.66–2.05). **CONCLUSIONS: Immunosuppression increases the risk of melanoma and NMSC among patients with IBD. The risk of melanoma is increased by use of biologics, and the risk of NMSC is increased by use of thiopurines. Patients with IBD should be counseled and monitored for skin cancer.**

Odds Ratio 1.88 (IC95% : 1.08-3.29)

ARTHRITIS & RHEUMATISM
Vol. 63, No. 7, July 2011, pp 1812–1822
DOI 10.1002/art.30247

Does Cancer That Occurs During or After Anti–Tumor Necrosis Factor Therapy Have a Worse Prognosis?

A National Assessment of Overall and Site-Specific Cancer Survival in Rheumatoid Arthritis Patients Treated With Biologic Agents

Pauline Raaschou,[1] Julia F. Simard,[2] Martin Neovius,[2] and Johan Askling,[1] for the Anti-Rheumatic Therapy in Sweden Study Group

Table 2. Match comparison: incident first primary cancers, deaths following cancer diagnosis, TNM stage at cancer diagnosis, and difference in stage distribution for the 302 cancers occurring in 8,562 Swedish RA patients treated with biologic agents during 1999–2007 and in 586 matched first primary cancers occurring in patients with RA not exposed to biologic agents*

	Cancers in biologics-exposed RA patients (n = 302)						Cancers in biologics-naive RA patients (n = 586)						
			TNM stage, % of cancers†						TNM stage, % of cancers†				
Cancer site	No. of cancers	No. of patients who died	I	II	III	IV	No. of cancers	No. of patients who died	I	II	III	IV	Adjusted HR (95% CI) for death following cancer diagnosis‡
All sites combined	302	113	43	14	20	20	586	256	45	17	9	29	1.1 (0.8–1.6)
Breast	48	8	63	33	0	4	96	7	63	37	0	0	0.7 (0.05–10.2)
Lung	39	30	29	6	38	26	78	69	19	10	10	60	1.0 (0.45–2.39)
Colorectal	25	13	0	17	50	33	50	32	13	25	38	25	0.7 (0.34–1.58)
Prostate	21	2	100	0	0	0	42	6	40	0	0	60	0.6 (0.11–2.93)
Malignant melanoma	21	3	71	14	0	14	41	7	100	0	0	0	1.3 (0.31–5.29)
All hematologic	35	17	NA	NA	NA	NA	60	30	NA	NA	NA	NA	0.9 (0.70–1.19)
All other sites	113	40	42	8	19	31	219	105	48	14	10	28	0.8 (0.51–1.17)

* Of the first primary cancers occurring in rheumatoid arthritis (RA) patients treated with biologic agents, 300 were in those taking anti–tumor necrosis factor, and 2 were in those taking other biologic agents. The control group was matched (1:2 ratio) for age, sex, calendar year, and cancer type. Relative risk is presented as the hazard ratio (HR) for death following the diagnosis of cancer, using the cancer cases in the controls as the reference group. NA = not applicable.

† The tumor-node-metastasis (TNM) stage of cancers for which information was available (34% of cancers in the biologics-exposed patients and 28% of cancers in the biologics-naive patients; see Table 1 for details).

‡ HRs and 95% confidence intervals (95% CIs) were determined by Cox proportional hazards regression. For the analysis of all sites, the model was stratified for age, sex, type of cancer, and stage at cancer diagnosis and was adjusted for the year of cancer diagnosis. Because of power restraints, site-specific models were adjusted for sex and age only, except for lung cancers and malignant melanomas, which were also adjusted for stage.

Arthritis Care & Research
Vol. 62, No. 6, June 2010, pp 755–763
DOI 10.1002/acr.20129

Influence of Anti–Tumor Necrosis Factor Therapy on Cancer Incidence in Patients With Rheumatoid Arthritis Who Have Had a Prior Malignancy: Results From the British Society for Rheumatology Biologics Register

W. G. DIXON, K. D. WATSON, M. LUNT, L. K. MERCER, BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS REGISTER CONTROL CENTRE CONSORTIUM, K. L. HYRICH, AND D. P. M. SYMMONS, ON BEHALF OF THE BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS REGISTER

Table 1. Baseline characteristics*

	DMARD (n = 117)	All anti-TNF (n = 177)	*P*
Age, mean ± SD years	66 ± 10	62 ± 10	0.002
Women, %	74	81	0.110
DAS28, mean ± SD	5.0 ± 1.3	6.7 ± 1.2	0.0001
HAQ score, mean ± SD	1.6 ± 0.7	2.2 ± 0.5	0.0001
Disease duration, median (IQR) years	9 (2–18)	11 (6–18)	0.0083
Prior DMARDs, median (IQR)	2 (1–4)	4 (3–5)	0.0001
Baseline steroid use	39 (33)	90 (51)	0.003
Smoking			
Current	25 (21)	32 (18)	0.011
Former	61 (52)	67 (38)	
Never	31 (27)	77 (44)	
Entry year			
Pre-2003	0	15 (8)	< 0.0001
2003	6 (5)	57 (32)	
2004	27 (23)	49 (28)	
2005	41 (35)	28 (16)	
2006 or after	43 (37)	28 (16)	
Prior malignancy			
Solid	96 (82)	147 (83)	0.795
Lymphoproliferative	11 (9)	13 (7)	
Melanoma	10 (8)	17 (10)	
Time from most recent prior malignancy to registration			
Median (IQR) years	8.5 (4.7–14.1)	11.5 (5.8–17.1)	0.027
>10 years preregistration	46 (39)	102 (58)	0.002

* Values are the number (percentage) unless otherwise indicated. DMARD = disease-modifying antirheumatic drug; anti-TNF = anti–tumor necrosis factor; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; IQR = interquartile range.

Follow-up during 2 years of 27 RA patients with past history of melanoma

Table 4. Prior and incident cancers, clinical table*

Cohort and patient number	Age band, years	Sex	Prior cancer: Site of prior cancer	Prior cancer: Time preregistration, years	Incident cancer: Site of incident cancer	Incident cancer: Definite/ probable/ possible	Incident cancer: Time postregistration, years
Anti-TNF cohort							
1	60–69	Female	Lung	0.5	Spinal and liver metastases	Definite	0.9
2	40–49	Female	Melanoma	2.9	CNS metastases	Probable	0.5
3	50–59	Male	Melanoma	3.5			
First incident cancer					Bladder	Definite	2.4
Second incident cancer					Pleural melanoma	Definite	3.9
4	50–59	Female	Breast	4.6	Neck lump	Probable	2.6
5	60–69	Female	Melanoma	7.5	Multiple metastases (adenocarcinoma)	Definite	3.1
6	50–59	Female	Digestive organ	8.9	Colon	Definite	1.0
7	60–69	Male	Cecum	10.3	Colon	Definite	0.9
8	70–79	Female	Breast	10.9	Colon	Definite	2.6
9	60–69	Female	Kidney	12.8	Kidney with spread to inferior vena cava	Probable	2.5
10	60–69	Female	Breast	15.3			
First incident cancer					Low-grade CLL	Definite	2.7
Second incident cancer					Lung with liver metastases	Definite	2.9
11	70–79	Female	Appendix adenocarcinoma	21	Cholangiocarcinoma	Definite	0.05
DMARD cohort							
12	70–79	Male	Prostate	2.6	Prostate with bony metastases	Probable	1.9
13	50–59	Female	Uterus	4.7	Frontal lobe of brain	Definite	1.0
14	60–69	Female	Breast	5.4	Pancreatic adenocarcinoma with pleural and peritoneal metastases	Definite	0.5
15	60–69	Male	Prepuce	5.9	Penis with metastases	Probable	2.8
16	50–59	Female	Breast	8.6	Anal	Definite	1.6
17	50–59	Female	Thyroid	9.7	Kidney	Definite	1.4
18	70–79	Male	Kidney	9.7	Transitional cell carcinoma of bladder	Definite	2.1
19	60–69	Female	Breast	10.6	Breast with liver and bone metastases	Probable	2.8
20	70–79	Male	Lip	15.2	Lung	Definite	2.0

* Anti-TNF = anti–tumor necrosis factor; CNS = central nervous system; CLL = chronic lymphocytic leukemia; DMARD = disease-modifying antirheumatic drug.

Relapse of melanoma only observed in the TNF cohort

Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT

Strangfeld *et al. Arthritis Research & Therapy* 2010, **12**:R5

Anja Strangfeld*[1], Franka Hierse[1], Rolf Rau[2], Gerd-Ruediger Burmester[3], Brigitte Krummel-Lorenz[4], Winfried Demary[5], Joachim Listing[1] and Angela Zink[1,3]

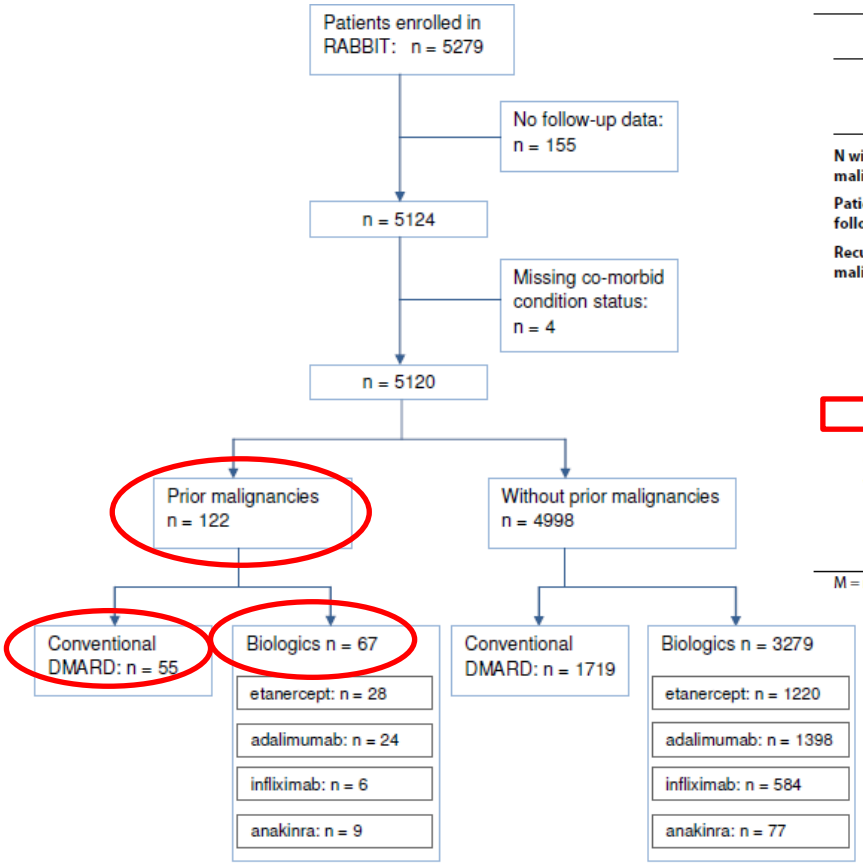


Figure 1 Flow chart of patients included in the analysis.

Table 2: Recurrence of prior malignancy by type and treatment

		Ever exposed to		
	Total	Anti-TNFα	Anakinra	Conventional DMARD only
N with prior malignancy	122	72	11	43
Patient-years of follow-up	379	198	31	159
Recurrent malignancies	15	9 (5 f, 4 m)	1 (m)	5 (4 f, 1 m)
Breast cancer	5	4 (f)	-	1(f)
Lung cancer	3	1 (m)	1 (m)	1 (f)
Bladder cancer	2	1 (m)#	-	1 (f)
Liposarcoma	1	1 (m)	-	-
Melanoma	1	1 (f)		
Signet-ring cell carcinoma	1	-	-	1 (f)
Testicular cancer	1	1 (m)#	-	-
Metastasis of unknown origin	1			1 (m)

M = male, f = female, #testicular cancer and bladder cancer in one patient

Incidence rate ratio anti TNF vs DMARDs: 1,4 (95% CI: 0,5 to 5,5), p: 0,63

Skin cancer risk and biologicals:

(2) Anti-IL12/IL23 (ustekinumab)

THERAPEUTICS

BJD
British Journal of Dermatology

Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up

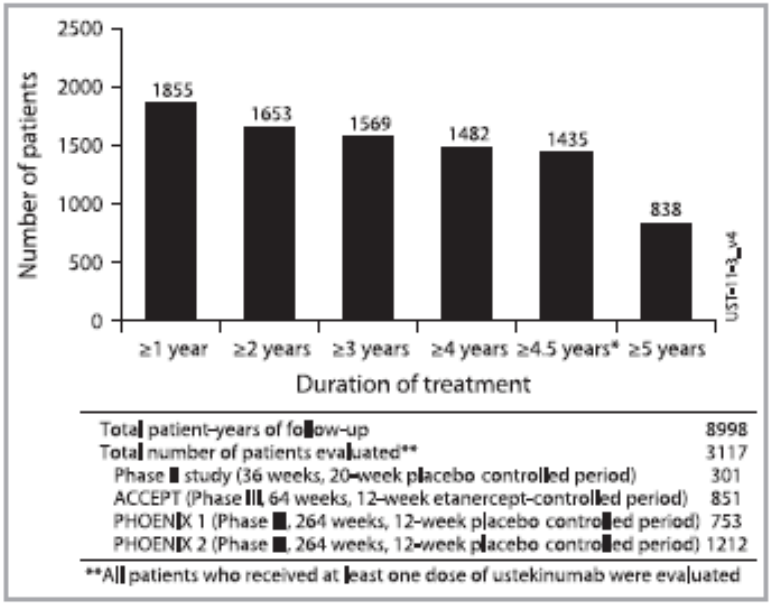
K.A. Papp,[1] C.E.M. Griffiths,[2] K. Gordon,[3] M. Lebwohl,[4] P.O. Szapary,[5] Y. Wasfi,[5] D. Chan,[5] M.-C. Hsu,[5] V. Ho,[6] P.D. Ghislain,[7] B. Strober[1,8] and K. Reich[9]; on behalf of the PHOENIX 1, PHOENIX 2 and ACCEPT Investigators

British Journal of Dermatology (2013) **168**, pp844–854

Pooled data from 4 phase II and III studies

3.117 patients having received at least 1 dose
1.482 patients treated≥ 4 y.
838 patients≥ 5 y.

Rates of cancers compared to those observed in the US population (except for NMSC)

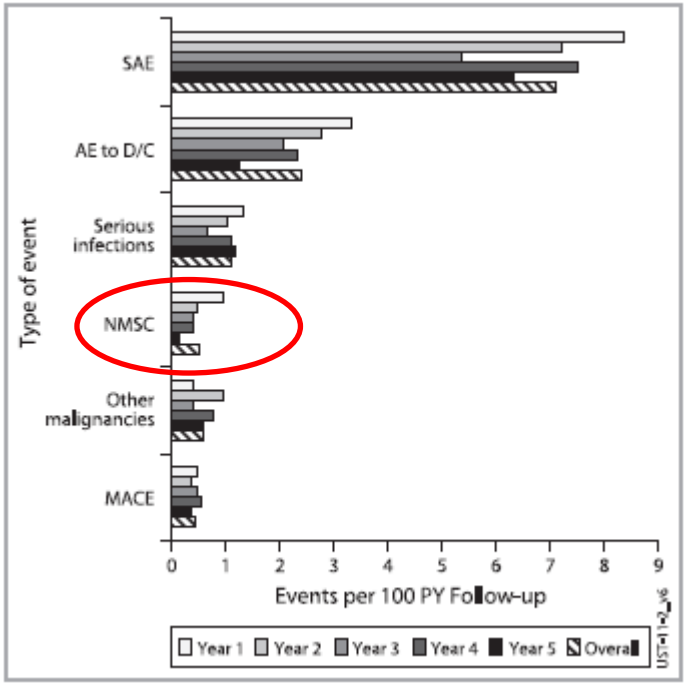


Total patient-years of follow-up	8998
Total number of patients evaluated**	3117
Phase II study (36 weeks, 20-week placebo controlled period)	301
ACCEPT (Phase III, 64 weeks, 12-week etanercept-controlled period)	851
PHOENIX 1 (Phase III, 264 weeks, 12-week placebo controlled period)	753
PHOENIX 2 (Phase III, 264 weeks, 12-week placebo controlled period)	1212

**All patients who received at least one dose of ustekinumab were evaluated

NMSCs

	Ustekinumab		
	45 mg	90 mg	Combined
Patients treated, n	1319	2001	3117
Patients with NMSC, n	24	23	47
Basal cell carcinoma	21	19	40
Squamous cell carcinoma	5	5	10



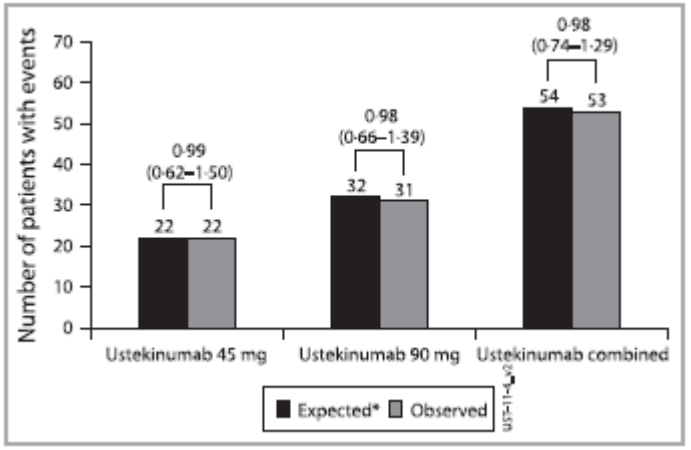
47 NMSC: BCC/SCC ratio 4/1

Same rate of NMSC at 45 or 90 mg. No increase other time.

Proportion of patients more important if previous treatment with PUVA (2.9% vs 1%, p<0.001)

Other cancers than NMSCs

	Ustekinumab		
	45 mg	90 mg	Combined
Patients treated, n	1319	2001	3117
Patients with NMSC, n	24	23	47
Basal cell carcinoma	21	19	40
Squamous cell carcinoma	5	5	10
Patients with ≥ 1 malignancy other than NMSC, n	22	32	54
Prostate	8	6	14
Melanoma	2	4	6
Melanoma in situ	2	3	5
Invasive melanoma[a]	0	1	1
Colorectal	2	3	5
Breast	3	1	4
Head and neck	1	2	3
Renal	1	2	3
Bladder	2	0	2
Leukaemia	0	2	2
Lymphoma[b]	0	2	2
Myeloma	0	2	2
Pancreatic	1	1	2
Adenocarcinoma, unknown primary	0	1	1
Cervical	0	1	1
Endometrial	0	1	1
Oesophageal	0	1	1
Lung	1	0	1
Ovarian	0	1	1
Squamous cell carcinoma, unknown primary	0	1	1
Testicular	0	1	1
Thyroid	1	0	1



54 other cancers

No significative difference between 45 and 90 mg

Pooled rate comparable to the one expected in US population

Melanoma SIR 1.42 (95%CI: 0.52-3.09)

« Spectrum of malignancies observed consistent to the one expected in the general population »
« More frequent and early detection of melanoma because of greater access to routine dermatological care? »

Skin cancer risk and biologicals:

(3) Anti-CD20 (rituximab)

Rituximab (anti CD20)

Table 3. Information available in the EudraVigilance database on the 13 rituximab-treated patients with melanoma

Patient	Age	Sex	Country	Melanoma							Indication for rituximab
				stage at diagnosis	Breslow thickness	Clark level	histoclinical type	location	delay before excision	evolution	
1	UK	F	Australia	UK	UK	UK	UK	UK	UK	UK	UK
2	UK	M	Germany	III lymph node	UK	UK	UK	UK	UK	UK	systemic B-cell lymphoma
3	UK	F	Germany	UK	UK	UK	UK	UK	UK	UK	rheumatoid arthritis
4	UK	M	Germany	3 primary melanomas	UK	UK	UK	UK	UK	UK	cutaneous B-cell lymphoma
5	70	M	Germany	III lymph node	UK	UK	UK	UK	UK	death	chronic lymphocytic leukaemia
6	55	F	France	II	3.25 mm	IV	nodular	back	12 months	UK	rheumatoid arthritis
7	51	F	France	II	2.2 mm	III	nodular	leg	5 months	UK	rheumatoid arthritis
8	UK	M	France	UK	UK	UK	UK	UK	UK	escape to chemo-therapy	systemic B-cell lymphoma
9	43	M	Great Britain	UK	UK	UK	UK	UK	UK	death	spondylarthritis
10	UK	F	Great Britain	UK	UK	UK	UK	UK	UK	UK	UK
11	48	F	Italy	I	UK	II	UK	UK	UK	UK	rheumatoid arthritis
12	59	F	United States	III lymph node	UK	IV	on congenital nevus	leg	17 months	UK	rheumatoid arthritis
13	65	M	United States	IV bone	not found					death	EBV-induced brain lymphoma

F = Female; M = male; UK = unknown.

RTX treatment duration: 12,5 mo.
In 3 cases: < 3 mo.

Peuvrel L, et al. Dermatology 2013; 226: 274-278.
Velter C, et al. Melanoma Res 2014; 24: 401-3.

Risk Factors for Melanoma Among Survivors of Non-Hodgkin Lymphoma

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ABSTRACT

Purpose

Previous studies have reported that survivors of non-Hodgkin lymphoma (NHL) have an increased risk of developing cutaneous melanoma; however, risks associated with specific treatments and immune-related risk factors have not been quantified.

Patients and Methods

We evaluated second melanoma risk among 44,870 1-year survivors of first primary NHL diagnosed at age 66 to 83 years from 1992 to 2009 and included in the Surveillance, Epidemiology, and End Results-Medicare database. Information on NHL treatments, autoimmune diseases, and infections was derived from Medicare claims.

Results

A total of 202 second melanoma cases occurred among survivors of NHL, including 91 after chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and 111 after other NHL subtypes (cumulative incidence by age 85 years: CLL/SLL, 1.37%; other NHL subtypes, 0.78%). Melanoma risk after CLL/SLL was significantly increased among patients who received infused fludarabine-containing chemotherapy with or without rituximab (n = 18: hazard ratio [HR], 1.92; 95% CI, 1.09 to 3.40; n = 10: HR, 2.92; 95% CI, 1.42 to 6.01, respectively). Significantly elevated risks also were associated with T-cell activating autoimmune diseases diagnosed before CLL/SLL (n = 36: HR, 2.27; 95% CI, 1.34 to 3.84) or after CLL/SLL (n = 49: HR, 2.92; 95% CI, 1.66 to 5.12). In contrast, among patients with other NHL subtypes, melanoma risk was not associated with specific treatments or with T-cell/B-cell immune conditions. Generally, infections were not associated with melanoma risk, except for urinary tract infections (CLL/SLL), localized scleroderma, pneumonia, and gastrohepatic infections (other NHLs).

Conclusion

Our findings suggest immune perturbation may contribute to the development of melanoma after CLL/SLL. Increased vigilance is warranted among survivors of NHL to maximize opportunities for early detection of melanoma.

Skin cancer risk and biologicals:

(4) CTLA-4 agonist (abatacept)

Abatacept (CTLA-4 agonist)

- No safety signal regarding skin cancers (melanoma and NMSC) at this time.

- 1 case of multiple eruptive KAs and SCCs, exclusively during abatacept treatment, in a 45 y.-old RA patient.
  - 3 years of treatment with abatacept.
  - 7 SCC (2 SCC/y.) and > 100 KA (33KA/y.)!
  - No additional SCC and KA during the year following abatacept discontinuation.

Corcorran et al. J Am Acad Dermatol 2013; 69: e178-e179.

Skin cancer risk and biologicals:

(5) Anti-IL6R (tocilizumab) and anti-IL1R (anakinra)

Rapidly progressive malignant melanoma in a patient treated with tocilizumab

Michiel Bonny, MD,[a] *Veronique Buyse, MD,*[b,c] *and Erwin Suys, MD*[d]

J Am Acad Dermatol
August 2012

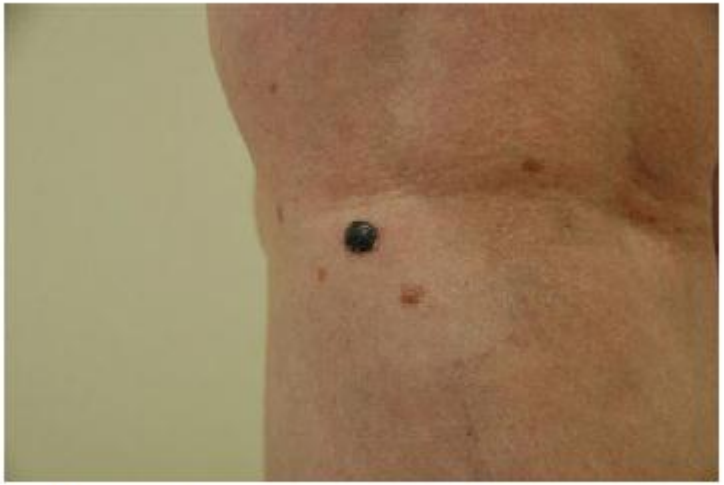

Fig 1. Melanoma at time of diagnosis.

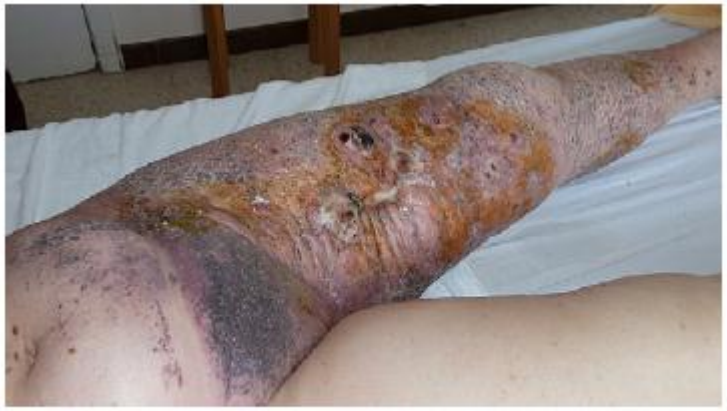

Fig 2. Extensive locoregional progression.

Nodular progression of lentigo malignant melanoma during a treatment with tocilizumab: cause or coincidence?

A. Finet · M. Amini-Adle · B. Balme · F. Colson · L. Thomas

Clin Rheumatol (2013) 32:277–280

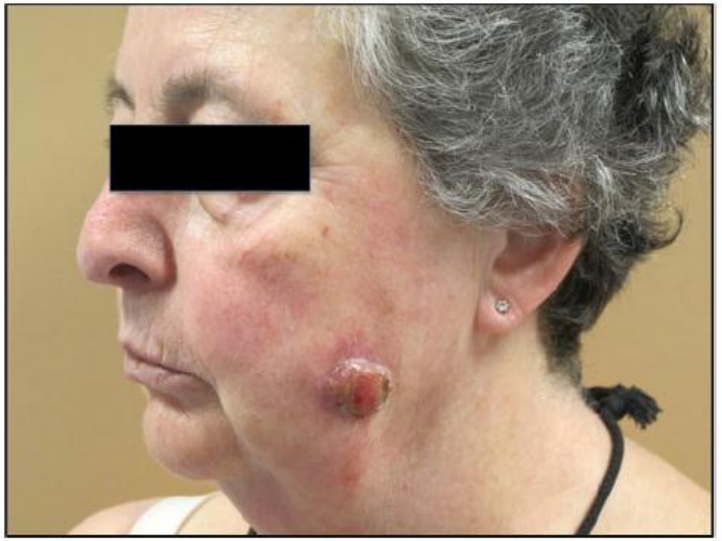

Fig. 1 Two-centimeter ulcerated nodule of the left cheek

Wendling D, et al. Metastatic malignant melanoma in a patient taking interleukin-1 receptor antagonist. Joint Bone Spine 2006

Cancer risk with biologicals: Summary

- No increased risk for solid tumor and for lymphoma with TNF blockers.
- But: several studies suggest an increased risk for NMSC and for melanoma with TNF blockers
  - In RA and IBD.
  - Nevertheless:
    - Risk slightly increased (<2)
    - Limited studies +++
    - Most of the NMSC are BCC
- This modestly elevated risk does not outweigh the benefit of TNF blockers.
- Limited studies for psoriasis patients (past history of PUVA) and for ustekinumab and other biologicals.
- Photoprotection and regular dermatology check-up.

Teach your colleagues!

PLOS | ONE

RESEARCH ARTICLE

Online Training on Skin Cancer Diagnosis in Rheumatologists: Results from a Nationwide Randomized Web-Based Survey

Manuelle Viguier[1]*, Stéphanie Rist[2], François Aubin[3], Marie-Thérèse Leccia[4], Marie-Aleth Richard[5], Marina Esposito-Farèse[6], Philippe Gaudin[7], Thao Pham[8], Pascal Richette[9], Daniel Wendling[10], Jean Sibilia[11], Florence Tubach[6], Club Rhumatismes et Inflammation[¶]

What to do in patients requiring immunomodulating drugs with previous history of skin cancer?

- **BCC:** no drug restriction, secondary prevention.

- **SCC**: secondary prevention; be aware of the prognostic markers; no absolute contra indication for treatment unless unfavourable prognostic markers.

- **Melanoma:** the black box…

  Personal opinion: contra-indication for cyclosporin A, azathioprine, mycophenolate mofetil, anti-TNFα.

- **Cutaneous lymphoma:**

  Personal opinion: contra indication for cyclosporin A, azathioprine, anti-TNF. MTX sometimes used as a treatment.