OPEN ACCESS

EULAR Points to Consider on the initiation of targeted therapies in patients with inflammatory arthritis and a history of cancer

Eden Sebbag ,[1] Kim Lauper ,[2] Juan Molina-Collada ,[3] Daniel Aletaha ,[4] Johan Askling ,[5] Karolina Gente,[6] Heidi Bertheussen,[7] Samuel Bitoun ,[8] Ertugrul Cagri Bolek ,[9,10] Gerd R Burmester ,[11] Helena M Canhão,[12] Katerina Chatzidionysiou ,[13] Jeffrey R Curtis,[14] Francois-Xavier Danlos,[15,16] Vera Guimarães,[17] Merete Lund Hetland ,[18] Florenzo Iannone ,[19] Marie Kostine ,[20] Tue Wenzel Kragstrup ,[21,22] Tore K Kvien ,[23] Anne Constanze Regierer ,[24] Hendrik Schulze-Koops ,[25] Lucia Silva-Fernandez,[26] Zoltan Szekanecz,[27] Maya H Buch ,[28] Axel Finckh ,[29] Jacques-Eric Gottenberg [30]

Handling editor Kimme L Hyrich

For numbered affiliations see end of article.

Correspondence to
Dr Jacques-Eric Gottenberg; jacques-eric.gottenberg@chru-strasbourg.fr

Received 16 April 2024
Accepted 5 November 2024

Check for updates

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ on behalf of EULAR.

To cite: Sebbag E, Lauper K, Molina-Collada J, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/ard-2024-225982

ABSTRACT

Background Potential associations between targeted therapies and a new cancer in patients with inflammatory arthritis (IA) and a previous malignancy are a frequent concern in daily rheumatology practice.

Objectives To develop points to consider (PTC) to assist rheumatologists when initiating a targeted therapy in the context of a previous malignancy.

Methods Following EULAR standardised operating procedures, a task force met to define the research questions for a systematic literature review and to formulate the overarching principles (OPs) and the PTC.

Results The group formulated five OPs; seven PTC were formulated concerning the initiation of targeted therapies in patients with active IA and a previous malignancy in remission and one PTC concerning patients with active IA who were not in cancer remission. Major themes included (a) the need to assess the individualised risk of cancer recurrence based on the characteristics of the patient, cancer and the underlying disease; (b) the importance of engaging with specialists caring for cancer and defining treatment based on a shared decision between the patient and the rheumatologist; (c) the value of initiating without delay an appropriate targeted therapy for the treatment of the IA in patients in remission of their cancer; (d) the proposal to use Janus kinase inhibitors and abatacept with caution and in the absence of therapeutic alternatives, based on the absence of any data concerning their use in the context of previous malignancy.

Conclusion The 2023 EULAR Points to Consider provide guidance on the management of targeted therapies in patients with IA and a previous malignancy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Potential associations between targeted therapies in patients with inflammatory arthritis (IA) and malignancy are a frequent concern in daily rheumatology practice.

⇒ No specific framework has been proposed to weigh the benefit/risk balance of initiating or reinitiating a targeted therapy in patients with IA and a history of cancer.

WHAT THIS STUDY ADDS

⇒ The 2023 EULAR Points to Consider provide practical guidance on the management of targeted therapies in patients with IA and a history of cancer. One of the main points is the importance of initiating without delay, an appropriate targeted therapy for the treatment of the IA in patients in remission of their cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this collaborative work will aid daily rheumatology practice and enhance therapeutic decision-making for patients with a history of cancer who are starting targeted therapy for IA. Patients may benefit from this initiative.

INTRODUCTION

In inflammatory arthritis (IA), the availability and use of targeted immune-modulatory therapies (biological and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs)) have been increasing since the approval of the first mechanism of action targeted therapy (a tumour necrosis factor (TNF) inhibitor) in the late 1990s.[1] The term 'IA' refers to rheumatoid arthritis (RA), spondyloarthritis and psoriatic arthritis.

Similar to several other autoimmune or inflammatory diseases, IA has been associated with an increased risk of malignant lymphomas. Indeed, IA has been linked to an increased risk of some cancers, directly due to inflammation or autoimmunity and indirectly via comorbidities and/or shared risk factors for IA and cancer, such as smoking. Targeted therapy drugs act to bring

AUTHOR PROOF

down disease activity in IA but might also confer specific risks of malignancy.[2]

For instance, corticosteroids and conventional synthetic DMARDs (csDMARDs) such as methotrexate and azathioprine may increase the risk of (most notably) non-melanoma skin cancers.[3] The putative association between b/tsDMARDs and cancer raises some concerns because the targeted treatments are more recent and thus less well studied in this respect but also because of the complex role of cytokines, lymphocytes and other aspects of immune competence in the pathogenesis of cancer, the clinical significance of which remains to be fully understood.[4]

For instance, TNF-α, targeted by TNF inhibitors, has a dual role in cancer with both anti- and pro-cancer effects, and TNF-α signalling plays a pathogenic role in some cancers.[5] Interleukin 6 (IL-6) directly stimulates the proliferation of cancer cells via activating signal transducer and activator of transcription 3 (STAT3) and subsequent promotion of cell-cycle progression. In human melanoma, IL-6-activated STAT3 enhances the proliferation of metastatic cells and contributes to invasion and angiogenesis.[6] Of note, neither TNF-α-[4] nor IL-6-knockout mice[7] seem at risk of cancer.

B lymphocytes play different roles depending on the type of malignancies. In B-cell lymphomas, tumorous B cells represent the target cells and B-cell depletion by anti-CD20 such as rituximab, approved for the treatment of lymphoma and also for the RA and ANCA-vasculitis, is a crucial part of the cancer treatment. In contrast, in solid malignancies, B cells might contribute to the antitumoral immunity. Presence of peritumoral B-cells, located within peritumoral germinal centres, before cancer treatment, is predictive of a better survival.[8 9] In addition, B-cell depletion decreases the efficacy of immune checkpoint inhibitors (ICIs) in animal models.[10] Presence of peritumoral B-cell infiltrates is associated with increased survival in patients treated with ICIs.[11]

Cytotoxic-T-lymphocyte-associated protein 4 (CTLA4)-Ig is established in the management of RA, but treatment with antibodies against CTLA4 is successful in patients with certain metastatic cancer entities by stimulating antitumoral immunity.[12–14]

Adding to the above uncertainties is the fact that with the improvement in cancer survival[15] (and an ageing population), the number of patients with IA and an ongoing or recent history of malignancy is increasing. Therefore, in clinical practice, the potential association between targeted antirheumatic therapies and the recurrence of a past cancer in patients with IA is a growing concern. These concerns extend to the initiation of b/tsDMARDs in patients who were previously naïve to such therapies (but with a history of cancer) and the re-initiation of b/tsDMARDs in patients who discontinued such treatment at the time of a cancer diagnosis.

This issue is shared by patients, primary care physicians, rheumatologists, dermatologists, gastroenterologists and oncologists. Observational data on the incidence of new cancer in patients with IA and a history of cancer who received b/tsDMARDs and those who received a csDMARD are limited. A recent study suggested that reluctance to use a targeted therapy in patients with RA and a history of cancer was associated with more frequent use of rituximab (reflecting a channelling bias with its use in the treatment of non-Hodgkin's lymphoma). The study also suggested that fear of cancer recurrence induced by b/tsDMARDs might result in undertreatment of some patients.[16]

International expert guidance regarding the use of b/tsDMARDs in patients with a history of cancer and inflammatory or autoimmune disease is limited.[17–19]

There is an unmet need for an evidence-based framework to guide clinicians on the benefit/risk balance when initiating or reinitiating b/tsDMARDs in patients with IA. EULAR Points to Consider offers a methodology and an opportunity to gather patients, clinicians, epidemiologists and onco-rheumatologists to formulate recommendations, overarching principles (OPs) and points to consider (PTC) for this topic. Hence, the current initiative aimed to develop PTC to assist rheumatologists when initiating/reinitiating b/tsDMARDs in the context of IA and a history of cancer.

METHODS

In line with the EULAR standardised operating procedures (SOP),[20] the Task Force consisted of 27 members of the required categories, including the steering committee, experts (with one oncologist), two EMerging EUlar NETwork representatives and two patient representatives. All members disclosed their potential conflicts of interest before starting the process. Due to the COVID-19 pandemic, the project initiation was delayed and the Task Force first met online to define the research questions for a systematic literature review (SLR). The SLR was set to encompass patients with a history of cancer, regardless of time since cancer diagnosis and regardless of the status of cancer (in remission or not in remission), treated with any targeted therapy for IA, inflammatory bowel disease (IBD) or inflammatory skin disease.

Two fellows (ES and JM-C) conducted the SLR under the guidance of the methodologist (AF) and co-methodologist (KL). Papers published from January 2010 to 15 July 2022 were considered. The evidence summarised in the SLR was presented to the Task Force using tables summarising the findings and assessing the risk of bias. The SLR is published separately but with the present manuscript, forms an integral and inseparable part and should be read as such.[21]

During the subsequent face-to-face meeting, the Task Force was informed by the SLR, which focused on the incidence of new or recurrent cancer in patients with IA and a history of cancer who received targeted therapies as opposed to csDMARDs. The Task Force also considered recent translational data on cancer immunopathogenesis, the incidence of cancer in patients receiving b/tsDMARDs and no history of cancer, and the use of b/tsDMARDs in patients with ICI-related flare of a pre-existing autoimmune disease or ICI-related induced inflammatory or autoimmune disease (in patients with no pre-existing autoimmune disease).

We included all b/tsDMARDs with European Medicines Agency (EMA) approval for any IA. The included drugs were the four TNF-α-specific monoclonal antibodies adalimumab, infliximab, golimumab and certolizumab pegol; the TNF-receptor fusion protein, etanercept; the anti-CD20 monoclonal antibody, rituximab; the IL-6 receptor (IL-6R)-specific monoclonal antibodies tocilizumab and sarilumab; the two IL-17A-specific monoclonal antibodies secukinumab and ixekizumab; the IL-17A/F-specific monoclonal antibody bimekizumab; the IL-12/23 (p40)-specific monoclonal antibody ustekinumab; the two IL-23 (p19)-specific monoclonal antibodies guselkumab and risankizumab; the CTLA4-Ig fusion protein, (inhibiting cluster of differentiation 80/86 (CD80/86)) abatacept; the IL-1 receptor antagonist anakinra; and the Janus kinase (JAK) inhibitors tofacitinib, baricitinib, filgotinib, upadacitinib.

The steering committee prepared proposals for OPs and PTCs that were discussed and refined by the entire group during the Task Force meeting. Following the EULAR SOP, consensus was accepted if >75% of the members voted in favour of the statement in the first round, >66% in the second round and >50%

AUTHOR PROOF

Table 1 EULAR Points to Consider for the initiation of targeted therapies in patients with active inflammatory arthritis and a history of cancer

		LoE	LoA mean (SD)	LoA ≥8/10 (%)
Overarching principles				
A	These PTC are underpinned by the EULAR recommendations for the management of inflammatory arthritis (ie, RA, SpA)	NA	9.6 (0.7)	96
B	New-onset or recurrent cancer can occur in patients with inflammatory arthritis with a history of cancer	NA	9.9 (0.2)	100
C	Individualised risk of cancer recurrence needs to be assessed based on the characteristics of the patient, cancer and the underlying inflammatory arthritis	NA	9.8 (0.6)	100
D	The rheumatologist is responsible for the management of patients with inflammatory arthritis and a history of cancer	NA	9.7 (0.7)	96
E	Treatment of patients with inflammatory arthritis and a history of cancer should aim at optimising outcomes and must be based on a shared decision between the patient and the rheumatologist	NA	9.7 (0.8)	96
Points to consider				
1	Treating inflammatory arthritis effectively in patients with a history of cancer is important to reduce the potential associated risk of malignancy	5	8.9 (2.1)	85
2	The risk of complications associated with undertreated inflammatory activity should be balanced against the potential risk of targeted antirheumatic therapy-related cancer recurrence	5	9.8 (0.5)	96
3	The rheumatologist should engage with other specialists caring for cancer for the co-management of patients with inflammatory arthritis and a history of cancer	5	9.5 (1.1)	96
4	Appropriate targeted antirheumatic treatment can be initiated without delay in patients with cancer in remission	4	9.4 (0.9)	92
5	In patients with a history of cancer, JAK inhibitors and Abatacept may be used with caution and only in the absence of therapeutic alternatives	5	8.9 (1.1)	84
6	When targeted antirheumatic therapy is indicated in patients with a history of solid cancer*, TNF inhibitors may be preferred over other treatment options	4	9.2 (1.3)	88
7	When targeted antirheumatic therapy is indicated in patients with a history of lymphoma, B-cell-depleting therapy may be preferred over other treatment options	5	9.3 (1.1)	92
8	In patients with a malignancy not in remission and active inflammatory arthritis, the decision to start targeted antirheumatic therapy should be based on a shared decision between the patient, the specialist caring for cancer and the rheumatologist	5	9.8 (0.5)	100

*This PTC does not concern melanoma.
JAK, Janus kinase; LoA, levels of agreement; LoE, level of evidence; PTC, points to consider; RA, rheumatoid arthritis; SpA, spondyloarthritis; TNF, tumour necrosis factor.

in the third round. The level of evidence (LoE) and grade of recommendation was based on the Oxford Levels of Evidence.[22]

Following the meeting, final PTC were then circulated among the Task Force members for an anonymous vote on the levels of agreement (LoA) to display the strengths of recommendation for each OP and PTC on a scale from 0 to 10 (with 0 indicating complete disagreement and 10 total agreement). In addition to the LoA, we present the mean (SD) LoA and percentage of votes that scored ≥8 for each entry.

New issues arising during the Task Force meeting were added to the research agenda presented in this paper. The final manuscript was reviewed and approved by all Task Force members and by the EULAR Council.

RESULTS

General aspects

The detailed findings of the SLR are presented in a separate publication.[21] However, pertinent results of the SLR will be presented in the detailed explanation of each PTC. Five OP and eight PTC were formulated (table 1). All OPs and PTCs concern patients with an active rheumatic disease, having insufficient control of disease activity. PTC 1–7 concern patients in cancer remission, PTC 8 concerns patients not in cancer remission.

Overarching principles

The Task Force used OPs to provide insights into the general management of cancer in IA. The following principles pertain to fundamental understandings that require no specific evidence levels.

A. *These PTC are underpinned by the EULAR recommendations for the management of IA (LoE NA; LoA 9.6 (0.7)).*
This EULAR initiative focuses on the specifics of managing IA in the context of a history of cancer. All the present PTC are concordant with EULAR recommendations for RA, spondyloarthritis and psoriatic arthritis. For instance, EULAR recommendations for RA apply also to patients with RA and a history of cancer. The current point to consider thus aims to complement disease-specific EULAR recommendations and provide guidance on specific aspects related to treatment in light of a history of cancer.

B. *New-onset or recurrent cancer can occur in patients with IA with a history of cancer (LoE NA; LoA 9.9 (0.2)).*
In these PTC as in most publications on this topic, the Task Force suggested not to distinguish between the incidence of a new cancer, histologically distinct from the previous cancer, and a recurrent cancer. The Task Force further decided not to distinguish 'cancer' and 'malignancies', which were considered equivalent. The term cancer is used going forward. All OPs and PTC, except PTC 8, concern patients who were successfully treated for cancer and are considered in remission when antirheumatic therapy is discussed. That is, apart from PTC 8, the present initiative does not concern active cancer, cancers not in remission or indolent cancers.

C. *Individualised risk of cancer recurrence needs to be assessed based on the characteristics of the patient, cancer and the underlying inflammatory arthritide (LoE NA; LoA 9.8 (0.6)).*
The characteristics of the individual are crucial to take into account risk of recurrence and include comorbidities, lifestyle (eg, smoking, alcohol) and the patient's self-evaluation of disease activity and treatment goals for the IA (figure 1). The characteristics of cancer (such as type, histology, stage, anti-cancer treatment and any previous relapses) are also important to consider. Of note, the SLR showed that very

AUTHOR PROOF

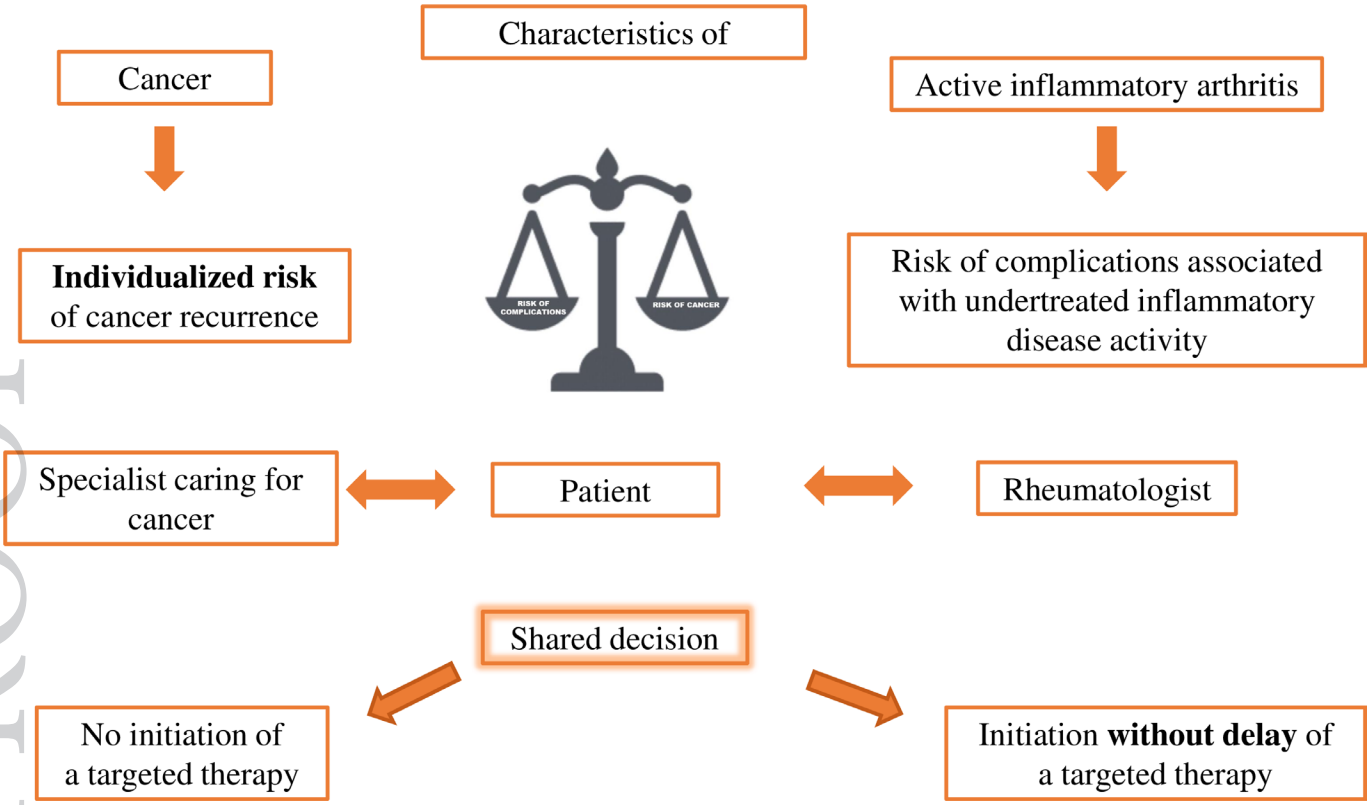

Figure 1 Initiation of a targeted therapy in a patient with active inflammatory arthritis of successfully treated cancer in remission.

AUTHOR PROOF

limited data were available regarding the risk of recurrent cancer in patients with specific cancer types/subsets such as melanomas. The SLR also showed that follow-up after initiation of a targeted therapy and duration of exposure to targeted therapies were limited. Finally, the type of IA including previous treatments, physician's assessment of disease activity, severity and prognosis (risk of damage), and the available therapeutic alternatives (other than targeted therapies) also need to be considered. The SLR showed limited data on IA other than RA.

D. *The rheumatologist is responsible for the management of patients with IA and a history of cancer (LoE NA; LoA 9.7 (0.7)).*

The Task Force highlighted the pivotal role of the rheumatologist. The responsibility of the rheumatologist includes expertise in the IA and antirheumatic drugs, the evaluation of IA disease activity, and the interactions with the patient, the patient's primary care physician and the specialist in charge of the cancer treatment.

E. *Treatment of patients with IA and a history of cancer should aim at optimising outcomes and must be based on a shared decision between the patient and the rheumatologist (LoE NA; LoA 9.7 (0.8)).*

The Task Force underscored the importance of optimising outcomes, which entails minimising the risk of cancer recurrence, enhancing the patient's quality of life, optimal control of disease activity and comorbidities, prevention of damage, and optimisation of comedications (aiming at decreasing/discontinuing non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids).

Furthermore, the Task Force felt it was crucial to promote shared decision-making (figure 1). This ensures that the patient is clearly informed by the rheumatologist and oncologist of the prognosis of the IA and the potential risk of new cancer. The patient's information and perception of the balance between potential benefits of targeted therapy and potential risks of new cancer must be taken into account.

Individual PTC

The Task Force proposes eight specific PTC.

1. *Treating IA effectively in patients with a history of cancer is important to reduce the potential associated risk of malignancy (LoE 5; LoA 8.9 (2.1)).*

The Task Force stressed the significance of understanding that chronic inflammation can increase the risk of some cancers.[23] Autoimmunity, if left untreated or undertreated due to a history of cancer, also represents a risk factor for cancer. This is particularly well demonstrated for lymphoma in patients with RA, indicating that the risk increases with disease activity but not with the use of DMARDs.[24] Therefore, the Task Force emphasised that treating IA effectively might contribute to decreasing the risk of new malignancy or malignancy recurrence in patients with a history of cancer.

2. *The risk of complications associated with undertreated inflammatory activity should be balanced against the potential risk of targeted antirheumatic therapy-related cancer recurrence (LoE 5; LoA 9.8 (0.5)).*

The Task Force emphasised the importance of recognising the multifaceted risks conveyed by undertreated IAs, beyond the risk of cancer-related to chronic inflammation and ongoing autoimmunity. Specifically, undertreatment of IA leads to irreversible joint damage and function with consequent impaired quality of life. In addition, persistent inflammation is associated with wider comorbidity, notably, increased risk and mortality due to cardiovascular complications, infection risk and complications related to increased use of analgesics, NSAIDs and corticosteroids.

Therefore, the risk of cancer associated with treatment must be balanced against the risk of undertreating chronic inflammation.

3. *The rheumatologist should engage with other specialists caring for cancer for the co-management of patients with IA and a history of cancer (LoE 5; LoA 9.5 (1.1)).*

The Task Force underscored the importance of the rheumatologist establishing connections with specialists caring for cancer (ie, oncologist, haematologists, cancer organ specialists such as pulmonologists, dermatologists, gastroenterologists). The rheumatologist should inform the oncologist of the characteristics of the patient and the underlying IA, risk of damage and other complications if the IA is left undertreated, and available therapeutic options. The term 'co-management' also emphasises the role of the oncologist, who best appreciates the risk of new incident cancer/cancer recurrence according to cancer-specific prognostic factors[25 26] and patient characteristics. This co-management aims at reaching a consensus on the benefit/risk ratio of initiating (or re-initiating in case of treatment discontinuation at the time of cancer diagnosis) a targeted therapy in patients with a history of cancer, including a consensus on the choice of the targeted therapy drug, that will be presented to the patient for shared decision.

4. *Appropriate targeted antirheumatic treatment can be initiated without delay in patients with cancer in remission (LoE 4; LoA 9.4 (0.9)).*

The Task Force strongly believed that a cancer in remission should not delay the initiation of targeted antirheumatic treatment, when indicated for the treatment of active IA (figure 1). This was underpinned by previous considerations about the importance of controlling the IA disease activity but also by findings of the SLR. In patients for whom an antirheumatic treatment was initiated less than 5 years after the diagnosis of cancer, no significant difference was observed in the risk of new cancer between targeted therapies and csDMARDs.[27–30]

The four studies on IA included in the SLR concerned TNF-inhibitor therapy for patients with RA. Of note, a selection bias cannot be ruled out in these observational studies: patients chosen to receive a bDMARD early after cancer diagnosis (<5 years) might be different from those with later treatment in terms of staging and histopathological type, which might influence the risk for recurrence.

5. *In patients with a history of cancer, JAK inhibitors and abatacept may be used with caution, and only in the absence of therapeutic alternatives (LoE 5; LoA 8.9 (1.1)).*

The Task Force highlighted the need for caution when considering the use of JAK inhibitors and abatacept in patients with a history of cancer because no specific data are available with JAK inhibitors and abatacept for patients with a history of cancer. In addition, the ORAL surveillance trial, a randomised controlled study, comparing the occurrence of MACEs and cancers between tofacitinib and TNF-inhibitor therapy in RA patients without a history of cancer but enriched for some key risk factors, reported a significant increase in the incidence of cancer.[31] According to all available evidence and a defined procedure within the EMA, the EMA recently recommended that JAK inhibitors should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (eg, heart attack or stroke), those who smoke or have done so for a long time and those at increased risk of cancer.

In the case of abatacept, the Task Force's deliberation was shaped by its mechanism of action and insights from the SLR. Abatacept has a mechanism of action converse to that of ipilimumab and other ICIs, used in cancer immunotherapy. Five of seven observational studies reported an increase in cancer incidence with abatacept compared with other targeted therapies in patients with RA and no history of cancer. These studies showed a small but significant increase in incidence of cancer (any cancer in one study,[32] melanoma in one study,[33] squamous cell skin cancer in one study compared with tocilizumab and rituximab,[34] non-melanoma skin cancer[35] and all invasive cancers excluding skin cancer in patients receiving abatacept for 2–5 years[36]) compared with other bDMARDs. In contrast, two studies showed no significant difference between abatacept and other bDMARDs in the incidence of cancer in patients with RA and no history of cancer.[37 38]

Thus, when treating patients with a history of cancer, the Task Force recommends exploring alternative therapeutic options, if available, before using JAK inhibitors and abatacept. Collecting observational data on abatacept and JAK inhibitors in patients with a history of cancer will be of specific interest (see research agenda, box 1). Therapeutic choice will integrate cancer risk but also other risks of targeted therapies, such as serious infections, taking into account comorbidities, such as diabetes, chronic obstructive pulmonary disease and a history of severe or recurrent infections.

6. *When targeted antirheumatic therapy is indicated in patients with a history of solid cancer (this PTC does not concern melanoma), TNF inhibitors may be preferred over other treatment options (LoE 4; LoA 9.2 (1.3)).*

Regarding solid cancers, this PTC also includes non-melanoma skin cancers but not melanomas because only one study compared TNF-inhibitor therapy to csDMARDs in patients with a history of melanoma, with no significant difference but large CIs.[39] In addition, immunity plays a major role in melanoma cancer surveillance. Therefore, the Task Force excluded melanoma from this PTC and added the issue of targeted therapies in patients with a history of melanoma to the research agenda (box 1).

Current knowledge indicates that TNF-inhibiting treatment may be preferred over other treatment options because it has the best body of available evidence (14 available studies).

All the publications included in the SLR compared RA patients with a history of solid cancer who received TNF-inhibitor drugs

Box 1 Research agenda

How can we improve the management of patients with a history of cancer who require biological antirheumatic treatments?
Do differences in safety data for targeted therapy exist among histological cancer types, particularly for melanomas and lymphomas?
Is it possible to standardise the collected data for future studies?
What is the safety profile of targeted therapies in other types of IA than rheumatoid arthritis?
What is the safety profile of non-TNF targeted therapy in patients with a history of cancer?
Would a longer follow-up period have led to the observation of more cancers in patients receiving a b/tsDMARD than a csDMARD?
Is it safe to administer targeted therapies to patients with indolent cancer?

b/tsDMARDs, biological and targeted synthetic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; IA, inflammatory arthritis; TNF, tumour necrosis factor.

AUTHOR PROOF

and csDMARDs. Data from the SLR demonstrated no increased risk of new cancer associated with the use of TNF inhibitors compared with csDMARDs in patients with a history of solid cancer in six studies: two concerning non-melanoma skin cancers,[40 41] two breast cancer,[42 43] one head and neck squamous cell carcinoma[44] and three various types of cancer.[29 45 46]

Regarding rituximab, the SLR found only two published studies of patients with a history of solid cancer who received rituximab[47] compared with six studies in patients treated with TNF-inhibitor agents. The Task Force took also into account the emerging role of B lymphocytes in cancer surveillance in some translational studies.[48] Therefore, despite the absence of clinical evidence of inferiority of rituximab to TNFi in such a setting, the Task Force consensually preferred the use of TNF-inhibitor agents to that of rituximab in patients with a history of solid cancer. Regarding IL-6 inhibition, only translational research data were available. IL-6 tissue and serum levels are increased in numerous cancers.[6] IL-6 knockout mice have no increased risk of cancer. Of note, targeting IL-6 in cancer might de-couple autoimmunity from antitumour immunity.[38] Interestingly, ongoing randomised controlled trials are combining ICIs and IL-6R inhibitor for inducing tumour response and for preventing immune-related adverse events in patients receiving ICIs. Data on IL-12/23, IL-17 and IL-23 inhibitors remain also scarce. It is therefore important to emphasise that the preference in patients with a history of cancer for TNF inhibitors over IL-6, IL-12/23, IL-17 and IL-23 inhibitors is based on the strength of the available evidence with TNF inhibition and not on any specific safety concerns. Abatacept and JAK inhibitors were not discussed in the context of history of solid cancer because of the issues discussed in PTC 5.

Data concerning IL-12/23 inhibitor, IL-23 inhibitor, anti-IL-17 inhibitor in patients with a history of cancer are currently too limited.

7. *When targeted antirheumatic therapy is indicated in patients with a history of lymphoma, B-cell-depleting therapy may be preferred over other treatment options (LoE 5; LoA 9.3 (1.1)).*

Although no specific studies addressed this situation directly, given the effectiveness of B-cell-depleting therapy (ie, rituximab) in lymphoma and previous recommendations,[49] the Task Force considered that B-cell depletion may be preferred in patients with a history of lymphoma. The knowledge gap regarding all targeted therapies and patients with a history of lymphoma is considerable and needs addressing. The Task Force added this specific issue to the research agenda (box 1).

8. *In patients with a malignancy not in remission and an active IA, the decision to start targeted antirheumatic therapy should be based on a shared decision between the patient, the specialist caring for cancer and the rheumatologist (LoE 5; LoA 9.8 (0.5)).*

This PTC addresses a different situation from the previous PTCs, which exclusively related to cancers in remission, because the Task Force felt that it was important to also provide some insights on this clinical context. This PTC captures patients with an active IA and indolent cancers (such as chronic lymphocytic leukaemia, smouldering myeloma or other haematological cancers), patients with disease flare that may be due to discontinuation of an effective antirheumatic treatment following cancer diagnosis, ICI-induced flare of pre-existing IA and/or ICI-induced de novo IA. The ICI-induced flare of pre-existing IA and ICI-induced de novo IA, which have specific PTC,[50] may not have the same immunological background, the same mechanisms or the same response to therapy. In addition, regarding ICI-induced arthritis and ongoing ICI treatment, the effect of immunomodulatory treatment on the antitumoral effect of ICI is still unknown. Discordant results exist on the impact of overall survival or event-free survival of targeted therapies versus csDMARDs in patients with cancer not in remission treated for IA in ICI-treated patients.[51–55] Considering that data on patients with a malignancy not in remission and active IA remain particularly limited, the Task Force emphasised the importance of a shared decision approach and co-management with the specialist caring for cancer. The Task Force added this specific issue to the research agenda.

DISCUSSION

The EULAR Task Force formulated five OPS and eight PTC relevant to the initiation of targeted therapies in patients with IA and a history of cancer. Seven out of eight PTC concern patients in cancer remission. PTC 8 concerns patients not in cancer remission. Patients treated with checkpoint inhibitors for their cancer, who experience IA or flare of a pre-existing IA are also subject to specific PTC.[50]

Major themes included (a) the need to assess the individualised risk of new cancer/cancer recurrence based on the characteristics of the patient, cancer and the underlying disease; based on a shared decision between the patient and the rheumatologist; (b) the need to take into account the balance between the potential risk of new cancer and potential risks of leaving IA undertreated; (c) the importance of engaging with specialists caring for cancer and to decide treatment and (d) the value of initiating without delay an appropriate targeted therapy for treating the IA in patients in cancer remission. The voices of the patient representatives were crucial in formulating some of the OPs and PTC. Of note, the patient representatives emphasised the importance of the shared decision approach and increased awareness of the potential risks of leaving IA undertreated because of a history of cancer.

To date, there is no evidence of an increased risk of cancer recurrence with b/tsDMARDs in patients with IA and a history of cancer. However, the absence of evidence does not mean evidence of absence. Some recent translational data in cancer reported the role of some targeted pathways and cell populations in cancer surveillance. The present initiative focuses on targeted therapies in patients with a history of cancer, but corticosteroids[56] and some csDMARDs such as methotrexate[3] have been shown to increase the incidence of cancer in patients with no history of cancer. Most of the studies included in our SLR concern RA, and some on IBD. Since all inflammatory joint diseases share some commonalities regarding pathogenesis, association with cancer, safety concerns and therapeutic strategies, the findings from the SLR may be extrapolated beyond RA. However, studies on other types of IA than RA are needed, as mentioned in the research agenda.

The SLR highlighted the very limited data available regarding the risk of recurrent cancer in patients with specific cancer types/subsets (notably melanoma), in patients receiving a b/tsDMARD other than a TNF-inhibitor agent (eg, IL-12/23 inhibitor, IL-23 inhibitor and IL-17 inhibitor, IL-6R inhibitor, abatacept, B-cell-depleting agents, belimumab, JAK inhibitors), and for an IA other than RA. Among the eligible studies in the SLR, data on specific cancers were very limited (two studies on a history of breast cancer,[42 43] one on a history of head and neck cancer,[44] two on non-melanoma skin cancers[40 41] and one on melanoma[39]), and cancer-related prognostic factors were usually not reported.

In addition, the median follow-up in studies included in the SLR was <3 years. This limited follow-up must be considered for two reasons: (a) some cancer recurrences (eg, metastatic

AUTHOR PROOF

breast cancer) are observed more than 10 years after cancer diagnosis and (b) most of the publications only included patients with a limited time of exposure to targeted therapy. Only four studies, all evaluating TNF-inhibitor agents, reported a duration of bDMARD exceeding 5 years.[29 39 44 47] Supporting the hypothesis for time-dependent risk, some evidence exists that malignancy risk manifests only after a minimum duration of use (eg, JAK inhibitors >18 months[57]).

Therefore, there was insufficient evidence for the Task Force to draw any conclusions on the time on DMARDs to inform its PTC. In addition, most of the studies did not distinguish between recurrence and new incident cancer. Finally, progression-free and overall survival outcomes were usually not reported. Therefore, all PTC should be appreciated in light of the limited data available, which calls for more efforts to generate and collect observational data in patients with a history of cancer (see research agenda). These factors emphasise the need to remain cautious and continue the collaborative effort to collect data on patients on targeted therapy for IA and a history of cancer.

In the SLR, the median delay between cancer diagnosis and initiation of targeted therapy was 4 years. No evidence-based delay exists in patients in tumour remission. Therefore, the Task Force decided to recommend that the clinician, with the help of the specialist in charge of the cancer, decide the appropriate timing based on disease activity and cancer-related prognostic factors, without stating a minimal delay since cancer diagnosis.

The Task Force insisted on the importance of initiating the 'appropriate' targeted therapy in patients with a history of cancer. According to the results of the SLR and the available data, in patients with a history of solid cancer, TNF inhibitors may be preferred over a B-cell-depleting agent. In patients with cancer, presence of peritumoral B-cells before cancer treatment is predictive of better survival in patients with cancer, notably in patients treated with ICIs.[9 11] Translational research data do not suggest safety concerns with IL-6R inhibition in patients with a history of solid cancer. Clinical data on the safety of IL-12/23, IL-17 and IL-23 inhibitors in the context of malignancy is also very limited and was thus added to the research agenda. In patients with a history of lymphoma, a B-cell-depleting agent may be preferred over other targeted therapies, but no formal comparison of the risk of new cancer was identified in the SLR between patients with a history of lymphoma treated with B-cell depleting agents and other targeted therapies. Therefore, the Task Force added this specific issue to the research agenda. Rituximab used to be the preferred treatment for RA patients with a history of cancer irrespective of the type of cancer in the previous decade, because rituximab is the only bDMARD used in the treatment of RA and lymphoma. The Task Force proposed in PTC 6 and 7 to change this current practice prioritising rituximab in RA patients with a history of any cancer to now prioritise rituximab to patients with a history of lymphoma specifically.

The use of JAK inhibitors and abatacept may be restricted to patients with no other therapeutic alternatives. The point to consider is supported by one randomised controlled trial for JAK inhibitors and some observational studies for abatacept, all concerning patients with no history of cancer. Taking into account the risks of un(der)-treated IA, these targeted therapies may be used in selected patients regarding their comorbidities aside from the history of cancer or refractory to other targeted therapies. Comparison of the incidence of new cancer/cancer recurrence in patients with a history of cancer who receive JAK inhibitors or abatacept and those who receive other targeted therapies is absolutely needed (see research agenda).

Implementation of these PTC is a critical next step,[58] which requires a collaborative approach. We have first presented these PTC at the EULAR Congress 2023 and in national congresses, promoted by the Task Force members residing in different EULAR countries, and they will be discussed again at the EULAR recommendation session in 2024. The Task Force proposed to disseminate PTC in oncology in multidisciplinary tumour boards, to integrate them in continuous medical education programmes and to provide them to patient representatives and associations of patients.

We also plan to evaluate potential barriers and facilitators to identify points for improvement.

CONCLUSION

The 2023 EULAR Points to Consider provide urgently needed guidance on the care of patients with active IA and a history of cancer. The research agenda highlights the need for studies to evaluate targeted therapies other than TNF inhibitors and rituximab to address the evidence gaps in this setting, as well as the need to further study the impact of targeted therapies on IA induced by immune-checkpoint inhibitors in the context of active cancer.

Author affiliations
[1]Rheumatology, Les Hopitaux Universitaires de Strasbourg Hopital de Hautepierre, Strasbourg, France
[2]Department of Medicial Specialities, University Hospitals of Geneva, Geneva, Switzerland
[3]Hospital General Universitario Gregorio Marañón, Madrid, Spain
[4]Department of Rheumatology, Medical University of Vienna, Vienna, Austria
[5]Karolinska Institutet, Stockholm, Sweden
[6]Division of Rheumatology, Department of Medicine V, Hematology, Oncology and Rheumatology, University Hospital Heidelberg, Heidelberg, Germany
[7]null, Oslo, Norway
[8]APHP hopital Bicêtre, Le Kremlin Bicêtre, France
[9]Division of Rheumatology, Department of Internal Medicine, Hacettepe University, Ankara, Turkey
[10]Hacettepe University Vasculitis Research Centre, Hacettepe University, Ankara, Turkey
[11]Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany
[12]Comprehensive Research Center, CHRC, EpicDoC Unit, CEDOC – NOVA Medical School– NOVA University of Lisbon, Lisboa, Portugal
[13]Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
[14]University of Alabama at Birmingham Department of Medicine, Birmingham, Alabama, USA
[15]Département d'Innovation Thérapeutique et d'Essais Précoces, Gustave Roussy, Villejuif, France
[16]Translationnal Immunotherapy Team, INSERM U1015, Villejuif, France
[17]Liga Portuguesa Contra as Doenças Reumáticas, Lisbon, Portugal
[18]Center for Rheumatology and Spine Diseases, Rigshospitalet Glostrup, Glostrup, Denmark
[19]School of Medicine, University of Bari, Bari, Italy
[20]Rheumatology, Centre Hospitalier Universitaire de Bordeaux Groupe hospitalier Pellegrin, Bordeaux, France
[21]Department of Biomedicine, Aarhus University, Aarhus C, Denmark
[22]Department of Rheumatology, Aarhus Universitetshospital, Aarhus, Denmark
[23]Center for Treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway
[24]Epidemiology, Deutsches Rheuma-Forschungszentrum Berlin, Berlin, Germany
[25]Division of Rheumatology and Clinical Immunology, Internal Medicine IV, Ludwig-Maximilians-Universitat Munchen, Munchen, Germany
[26]Complejo Hospitalario Universitario de Ferrol, Ferrol, Spain
[27]Department of Rheumatology, University of Debrecen, Debrecen, Hungary
[28]Centre for Musculoskeletal Research, The University of Manchester, Manchester, UK
[29]Division of Rheumatology, University of Geneva, Geneva, Switzerland
[30]Department of Rheumatology, Hôpital de Hautepierre-Hôpitaux Universitaires de Strasbourg, Strasbourg, France

X Kim Lauper @k_lauper, Juan Molina-Collada @jmolinacollada, Ertugrul Cagri Bolek @ertugrul_cagri, Marie Kostine @MarieKostine and Tue Wenzel Kragstrup @KragstrupTW

AUTHOR PROOF

Acknowledgements The Task Force would like to thank EULAR for the financial and logistical support it has provided. These Points to Consider were presented at the 2023 EULAR Congress.[59]

Contributors ES and J-EG wrote the first draft of the manuscript, with help from KL and AF. All authors participated in the work of the Task Force, revised the manuscript and approved the final manuscript. J-EG, as guarantor, accept full responsibility for the work, had access to the data and control the decision to publish.

Funding This project was funded by European Alliance of Associations for Rheumatology.

Competing interests No.

Patient and public involvement statement Patients and/or the public were involved in the design, conduct, reporting, and dissemination plans of this research. Two patient representatives (HB and VG) were part of the Task Force. A preliminary meeting, before the 1st Task Force meeting, was fully dedicated to introduce the subject to patient representatives. The patient representatives attended the two Task Force meeting, and provided their insights during meetings, contributed to revise the manuscript and approved the manuscript.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Eden Sebbag http://orcid.org/0000-0003-3045-7725
Kim Lauper http://orcid.org/0000-0002-4315-9009
Juan Molina-Collada http://orcid.org/0000-0001-5191-7802
Daniel Aletaha http://orcid.org/0000-0003-2108-0030
Johan Askling http://orcid.org/0000-0003-0433-0616
Samuel Bitoun http://orcid.org/0000-0003-0891-2269
Ertugrul Cagri Bolek http://orcid.org/0000-0003-3886-2813
Gerd R Burmester http://orcid.org/0000-0001-7518-1131
Katerina Chatzidionysiou http://orcid.org/0000-0002-2669-1247
Merete Lund Hetland http://orcid.org/0000-0003-4229-6818
Florenzo Iannone http://orcid.org/0000-0003-0474-5344
Marie Kostine http://orcid.org/0000-0002-6729-6200
Tue Wenzel Kragstrup http://orcid.org/0000-0002-6439-397X
Tore K Kvien http://orcid.org/0000-0002-8441-3093
Anne Constanze Regierer http://orcid.org/0000-0003-2456-4049
Hendrik Schulze-Koops http://orcid.org/0000-0002-1681-491X
Maya H Buch http://orcid.org/0000-0002-8962-5642
Axel Finckh http://orcid.org/0000-0002-1210-4347
Jacques-Eric Gottenberg http://orcid.org/0000-0002-9469-946X

REFERENCES

1 Smolen JS, Landewé RBM, Bergstra SA, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023;82:3–18.
2 Szekanecz Z, Gomez I, Soós B, *et al*. Eight pillars of oncorheumatology: Crossroads between malignancies and musculoskeletal diseases. *Autoimmun Rev* 2020;19:102658.
3 Yan MK, Wang C, Wolfe R, *et al*. Association Between Low-Dose Methotrexate Exposure and Melanoma: A Systematic Review and Meta-analysis. *JAMA Dermatol* 2022;158:1157–66.
4 Burke F. Cytokines (IFNs, TNF-alpha, IL-2 and IL-12) and animal models of cancer. *Cytokines Cell Mol Ther* 1999;5:51–61.
5 Balkwill F. TNF-alpha in promotion and progression of cancer. *Cancer Metastasis Rev* 2006;25:409–16.
6 Kang S, Tanaka T, Narazaki M, *et al*. Targeting Interleukin-6 Signaling in Clinic. *Immunity* 2019;50:1007–23.
7 Scheller J, Garbers C, Rose-John S. Interleukin-6: from basic biology to selective blockade of pro-inflammatory activities. *Semin Immunol* 2014;26:2–12.
8 Petitprez F, de Reyniès A, Keung EZ, *et al*. B cells are associated with survival and immunotherapy response in sarcoma. *Nature New Biol* 2020;577:556–60.
9 Germain C, Gnjatic S, Tamzalit F, *et al*. Presence of B cells in tertiary lymphoid structures is associated with a protective immunity in patients with lung cancer. *Am J Respir Crit Care Med* 2014;189:832–44.
10 Küçükköse E, Heesters BA, Villaudy J, *et al*. Modeling resistance of colorectal peritoneal metastases to immune checkpoint blockade in humanized mice. *J Immunother Cancer* 2022;10:e005345.
11 Helmink BA, Reddy SM, Gao J, *et al*. B cells and tertiary lymphoid structures promote immunotherapy response. *Nature New Biol* 2020;577:549–55.
12 Owonikoko TK, Park K, Govindan R, *et al*. Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: CheckMate 451. *J Clin Oncol* 2021;39:1349–59.
13 Shitara K, Ajani JA, Moehler M, *et al*. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. *Nature New Biol* 2022;603:942–8.
14 Choueiri TK, Powles T, Albiges L, *et al*. Cabozantinib plus Nivolumab and Ipilimumab in Renal-Cell Carcinoma. *N Engl J Med* 2023;388:1767–78.
15 Hemminki K, Försti A, Hemminki A. Survival in colon and rectal cancers in Finland and Sweden through 50 years. *BMJ Open Gastroenterol* 2021;8:e000644.
16 Chatzidionysiou K, Delcoigne B, Frisell T, *et al*. How do we use biologics in rheumatoid arthritis patients with a history of malignancy? An assessment of treatment patterns using Scandinavian registers. *RMD Open* 2020;6:e001363.
17 Thatiparthi A, Martin A, Liu J, *et al*. Biologic Treatment Algorithms for Moderate-to-Severe Psoriasis with Comorbid Conditions and Special Populations: A Review. *Am J Clin Dermatol* 2021;22:425–42.
18 Amatore F, Villani AP, Tauber M, *et al*. Psoriasis Research Group of the French Society of Dermatology (Groupe de Recherche sur le Psoriasis de la Société Française de Dermatologie). French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults. *J Eur Acad Dermatol Venereol* 2019;33:464–83.
19 Yazici H, Ozguler Y, Hatemi G, *et al*. Recommendations in the American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis Related to the Use of Biologic Agents in Patients With a History of Cancer Need Reconsideration: Comment on the Article by Singh et al. *Arthritis Care Res (Hoboken)* 2016;68:724.
20 van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
21 Sebbag E, Molina Collada J, Lauper K, *et al*. Systematic literature review and metanalysis informing the EULAR Points to Consider task force on the initiation of targeted therapies in patients with inflammatory arthritis and a history of cancer. 2023.
22 OCEBM Levels of Evidence Working Group. The oxford 2011 levels of evidence. n.d. Available: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ ocebm-levels-of-evidence
23 Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nat Rev Clin Oncol* 2018;15:234–48.
24 Baecklund E, Iliadou A, Askling J, *et al*. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum* 2006;54:692–701.
25 Pan H, Gray R, Braybrooke J, *et al*. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *N Engl J Med* 2017;377:1836–46.
26 Wu C-F, Fu J-Y, Yeh C-J, *et al*. Recurrence Risk Factors Analysis for Stage I Non-small Cell Lung Cancer. *Medicine (Baltimore)* 2015;94:e1337.
27 Vedamurthy A, Gangasani N, Ananthakrishnan AN. Vedolizumab or Tumor Necrosis Factor Antagonist Use and Risk of New or Recurrent Cancer in Patients With Inflammatory Bowel Disease With Prior Malignancy: A Retrospective Cohort Study. *Clin Gastroenterol Hepatol* 2022;20:88–95.
28 Strangfeld A, Hierse F, Rau R, *et al*. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. *Arthritis Res Ther* 2010;12:R5.
29 Raaschou P, Söderling J, Turesson C, *et al*. Tumor Necrosis Factor Inhibitors and Cancer Recurrence in Swedish Patients With Rheumatoid Arthritis: A Nationwide Population-Based Cohort Study. *Ann Intern Med* 2018;169:291–9.
30 Axelrad J, Bernheim O, Colombel J-F, *et al*. Risk of New or Recurrent Cancer in Patients With Inflammatory Bowel Disease and Previous Cancer Exposed to Immunosuppressive and Anti-Tumor Necrosis Factor Agents. *Clin Gastroenterol Hepatol* 2016;14:58–64.
31 Ytterberg SR, Bhatt DL, Mikuls TR, *et al*. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N Engl J Med* 2022;386:316–26.
32 Simon TA, Boers M, Hochberg M, *et al*. Comparative risk of malignancies and infections in patients with rheumatoid arthritis initiating abatacept versus other biologics: a multi-database real-world study. *Arthritis Res Ther* 2019;21:228.
33 de Germay S, Bagheri H, Despas F, *et al*. Abatacept in rheumatoid arthritis and the risk of cancer: a world observational post-marketing study. *Rheumatol (Oxford)* 2020;59:2360–7.
34 Wadström H, Frisell T, Askling J. Malignant Neoplasms in Patients With Rheumatoid Arthritis Treated With Tumor Necrosis Factor Inhibitors, Tocilizumab, Abatacept, or Rituximab in Clinical Practice: A Nationwide Cohort Study From Sweden. *JAMA Intern Med* 2017;177:1605–12.
35 Montastruc F, Renoux C, Dell'Aniello S, *et al*. Abatacept initiation in rheumatoid arthritis and the risk of cancer: a population-based comparative cohort study. *Rheumatology (Oxford)* 2019;58:683–91.
36 Huss V, Bower H, Wadström H, *et al*. Short- and longer-term cancer risks with biologic and targeted synthetic disease-modifying antirheumatic drugs as used against rheumatoid arthritis in clinical practice. *Rheumatology (Oxford)* 2022;61:1810–8.
37 Ozen G, Pedro S, Schumacher R, *et al*. Safety of abatacept compared with other biologic and conventional synthetic disease-modifying antirheumatic drugs in patients

AUTHOR PROOF

with rheumatoid arthritis: data from an observational study. *Arthritis Res Ther* 2019;21:141.
38 Simon TA, Suissa S, Boers M, *et al*. Malignancy outcomes in patients with rheumatoid arthritis treated with abatacept and other disease-modifying antirheumatic drugs: Results from a 10-year international post-marketing study. *Semin Arthritis Rheum* 2024;64:152240.
39 Raaschou P, Simard JF, Holmqvist M, *et al*. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. *BMJ* 2013;346:f1939bmj.f1939.
40 Scott FI, Mamtani R, Brensinger CM, *et al*. Risk of Nonmelanoma Skin Cancer Associated With the Use of Immunosuppressant and Biologic Agents in Patients With a History of Autoimmune Disease and Nonmelanoma Skin Cancer. *JAMA Dermatol* 2016;152:164.
41 Mercer LK, Green AC, Galloway JB, *et al*. 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;71:869–74.
42 Mamtani R, Clark AS, Scott FI, *et al*. Association Between Breast Cancer Recurrence and Immunosuppression in Rheumatoid Arthritis and Inflammatory Bowel Disease: A Cohort Study. *Arthritis Rheumatol* 2016;68:2403–11.
43 Raaschou P, Frisell T, Askling J, *et al*. TNF inhibitor therapy and risk of breast cancer recurrence in patients with rheumatoid arthritis: a nationwide cohort study. *Ann Rheum Dis* 2015;74:2137–43.
44 Phillips C, Zeringue AL, McDonald JR, *et al*. Tumor Necrosis Factor Inhibition and Head and Neck Cancer Recurrence and Death in Rheumatoid Arthritis. *PLoS ONE* 2015;10:e0143286.
45 Waljee AK, Higgins PDR, Jensen CB, *et al*. Anti-tumour necrosis factor-α therapy and recurrent or new primary cancers in patients with inflammatory bowel disease, rheumatoid arthritis, or psoriasis and previous cancer in Denmark: a nationwide, population-based cohort study. *Lancet Gastroenterol Hepatol* 2020;5:276–84.
46 Aaltonen KJ, Joensuu JT, Virkki L, *et al*. Rates of Serious Infections and Malignancies Among Patients with Rheumatoid Arthritis Receiving Either Tumor Necrosis Factor Inhibitor or Rituximab Therapy. *J Rheumatol* 2015;42:372–8.
47 Silva-Fernández L, Lunt M, Kearsley-Fleet L, *et al*. The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. *Rheumatology (Sunnyvale)* 2016;55:2033–9.
48 Federico L, McGrail DJ, Bentebibel S-E, *et al*. Distinct tumor-infiltrating lymphocyte landscapes are associated with clinical outcomes in localized non-small-cell lung cancer. *Ann Oncol* 2022;33:42–56.
49 Buch MH, Smolen JS, Betteridge N, *et al*. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70:909–20.
50 Kostine M, Finckh A, Bingham CO, *et al*. EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors. *Ann Rheum Dis* 2021;80:36–48.
51 Braaten TJ, Brahmer JR, Forde PM, *et al*. Immune checkpoint inhibitor-induced inflammatory arthritis persists after immunotherapy cessation. *Ann Rheum Dis* 2020;79:332–8.
52 Zou F, Faleck D, Thomas A, *et al*. Efficacy and safety of vedolizumab and infliximab treatment for immune-mediated diarrhea and colitis in patients with cancer: a two-center observational study. *J Immunother Cancer* 2021;9:e003277.
53 Verheijden RJ, May AM, Blank CU, *et al*. Association of Anti-TNF with Decreased Survival in Steroid Refractory Ipilimumab and Anti-PD1-Treated Patients in the Dutch Melanoma Treatment Registry. *Clin Cancer Res* 2020;26:2268–74.
54 van Not OJ, Verheijden RJ, van den Eertwegh AJM, *et al*. Association of Immune-Related Adverse Event Management With Survival in Patients With Advanced Melanoma. *JAMA Oncol* 2022;8:1794–801.
55 Bass AR, Abdel-Wahab N, Reid PD, *et al*. Comparative safety and effectiveness of TNF inhibitors, IL6 inhibitors and methotrexate for the treatment of immune checkpoint inhibitor-associated arthritis. *Ann Rheum Dis* 2023;82:920–6.
56 Oh TK, Song IA. Long-Term Glucocorticoid Use and Cancer Risk: A Population-Based Cohort Study in South Korea. *Cancer Prev Res (Phila)* 2020;13:1017–26.
57 Curtis JR, Yamaoka K, Chen Y-H, *et al*. Malignancy risk with tofacitinib versus TNF inhibitors in rheumatoid arthritis: results from the open-label, randomised controlled ORAL Surveillance trial. *Ann Rheum Dis* 2023;82:331–43.
58 Loza E, Carmona L, Woolf A, *et al*. Implementation of recommendations in rheumatic and musculoskeletal diseases: considerations for development and uptake. *Ann Rheum Dis* 2022;81:1344–7.
59 Sebbag E, Lauper K, Molina Collada J, *et al*. OP0045 EULAR points to consider on the initiation of targeted therapies in patients with inflammatory arthritides and a history of cancer. 2023.

AUTHOR PROOF