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CLINICAL SCIENCE

Systematic literature review and meta-analysis informing the EULAR Points to Consider on the initiation of targeted therapies in patients with inflammatory arthritis and a history of cancer

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ABSTRACT

Background Targeted therapies have been associated with potential risk of malignancy, which is a common concern in daily rheumatology practice in patients with inflammatory arthritis (IA) and a history of cancer.

Objectives To perform a systematic literature review to inform a Task Force formulating EULAR Points to Consider on the initiation of targeted therapies in patients with IA and a history of cancer.

Methods Specific research questions were defined within the Task Force before formulating the exact research queries with a librarian. We included studies reporting a relative risk measure of patients with a history of cancer initiating a targeted therapy or a conventional synthetic disease-modifying antirheumatic drug (csDMARD), regardless of the time since diagnosis of cancer. All relevant studies included in PubMed or Embase up to 15 July 2022 were included. Two reviewers independently performed standardised article selection, data extraction, synthesis and risk of bias assessment.

Results 14 published articles and one ACR abstract fulfilled the inclusion criteria. All studies were high-quality observational studies, representing a median follow-up from treatment initiation of 4.52 years among 4428 patients and 15 062 patient-years of follow-up for new or recurrent cancer.

All patients had a history of cancer, most frequently solid cancer, most frequently receiving treatment for rheumatoid arthritis and most frequently treated with tumour necrosis factor-alpha inhibitors. Across these studies, the overall HR of cancer recurrence was 0.92 (95% CI 0.74 to 1.15) for patients receiving a targeted therapy versus a csDMARD.

Conclusion Overall, the targeted therapies and clinical contexts covered by the included studies were not associated with an increased risk of cancer recurrence as compared with csDMARDs.

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

⇒ This systematic literature review (SLR) and meta-analysis did not demonstrate any increased risk of cancer recurrence in patients with IA who were treated with targeted therapy compared with those who were treated differently after a history of cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this SLR can help clinicians improve therapeutic decision-making in the context of a patient with a history of cancer-initiating a targeted therapy for IA. The results have informed an international Task Force formulating EULAR Points to Consider.

INTRODUCTION

Targeted therapies, including biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), have considerably improved the long-term outcomes of patients with inflammatory arthritis (IA), improving quality of life and with remission as an attainable goal.[1–3] Potential associations between

targeted therapies in patients with IA and malignancy are a frequent concern in daily rheumatology practice. Cancer risks may be increased in patients with rheumatoid arthritis (RA) and other chronic inflammatory diseases as compared with the general population.[4 5] Because immunity plays an important role in tumour immunosurveillance, the use of b/tsDMARDs is a concern, also in the context of treating RA in individuals with a history of cancer.[6] Improvements in cancer therapy have led to major gains in survival.

For all the above reasons, including an ageing population, the number of patients with a history of cancer and a need for treatment with b/tsDMARDs is increasing. At the same time, the evidence to guide b/tsDMARD treatment in this context is limited. Patients with a history of cancer are routinely excluded from randomised controlled trials evaluating targeted therapies, and there are limited data on the risk of a new cancer or cancer recurrence in this setting. A recent study suggested that the reluctance to use a targeted therapy in patients with RA and a history of cancer might result in undertreatment of some patients and increased use of rituximab due to channelling bias.[7]

To inform the Task Force responsible for the EULAR Points to Consider (PTC) on the initiation of targeted therapies in patients with IA and a history of cancer, we performed a systematic literature review (SLR) and meta-analysis to investigate the risk of cancer in patients with IA treated with targeted therapies and a history of cancer.

METHODS

Literature search

At the first meeting, the Task Force for the EULAR PTC on the initiation of targeted therapies in patients with IA and a history of cancer defined the research points under supervision of one methodologist (AF) and a co-methodologist (KL). It also outlined the scope of the literature search according to the pre-specific Population, Intervention, Comparator and Outcomes (PICOs) format questions and defined the criteria for an eligible study. In a first meeting, the EULAR Task Force agreed to focus the SLR on clinical data in patients receiving any targeted therapy for an inflammatory or autoimmune rheumatic or skin or bowel disease, with a history of cancer regardless of the time since diagnosis of cancer.

The Task Force decided to include dermatological and gastrointestinal immune-mediated diseases, as these conditions are treated with the same therapies. The search was performed in PubMed via MEDLINE and Embase without language restrictions from 1 January 2010 to 15 July 2022 and included recent abstracts from large international congresses. Details on complete search strategies are in figure 1. The detailed search strategy is presented in online supplemental table 1.

Inclusion criteria for studies included the reporting of an outcome measure of the risk of cancer in patients with a history of cancer who initiated a targeted therapy for an inflammatory rheumatic, bowel or skin disease, regardless of the time since diagnosis of cancers. For the main analysis, studies were eligible if they included a comparator group and reported a relative risk

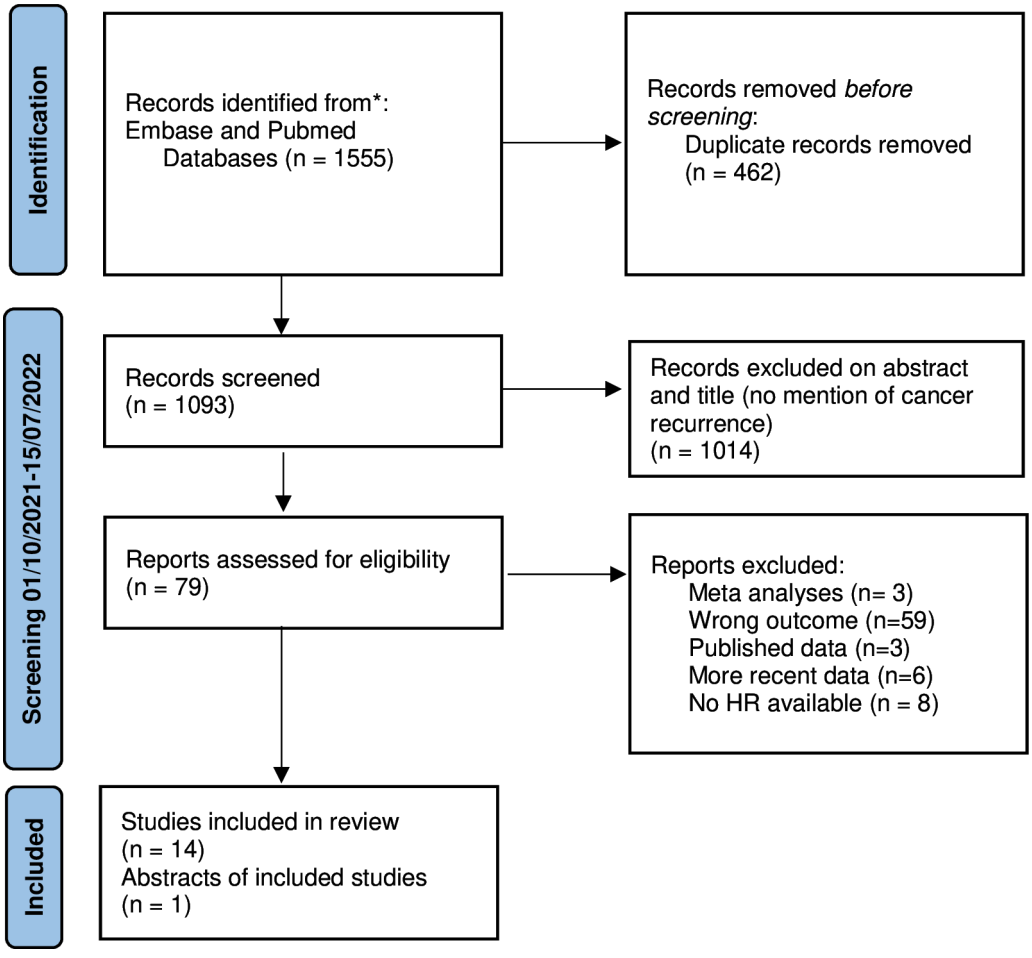


Figure 1 Flow chart of the study.

measure (eg, HR) of new cancer or cancer recurrence between groups. Studies reporting incidence data without HRs were not included in the meta-analysis. In the case of several publications from the same registry, only the most recent article was selected, unless the main outcome was specified to be different (eg, new breast cancer/breast cancer recurrence in patients with a history of breast cancer, new non-melanoma skin cancer (NMSC)/NMSC recurrence in patients with a history of NMSC). Stratified analyses considered the histological type of the initial cancer, the time from the initial cancer diagnosis to the initiation of targeted therapy, and the duration of targeted therapy. Several sensitivity analyses were performed to study specific treatments, to analyse only the most recent study from registries that had published multiple reports, and to analyse only patients with RA.

Selection of studies, data extraction and assessment of risk of bias

Two independent reviewers (ES and JM-C) screened titles and abstracts to assess eligibility. Subsequently, all potentially eligible articles were read in full text to decide whether they fulfilled the inclusion criteria. The reviewers used a standardised data extraction form with the Rayyan online tool[8] to extract data from eligible studies regarding study and population characteristics, inclusion/exclusion criteria, drug exposure time, interventions and outcome definition. Any disagreement between reviewers was resolved by discussion. Tables including the summary of findings of the studies included were generated. The risk of bias (RoB) of each included study was assessed with the ROBINS-I tool.[9] The quality of the studies was graded according to the Newcastle-Ottawa Scale for quality assessment. Discrepancies between reviewers regarding study selection, data extraction and RoB assessment were resolved by discussion with the methodologists.

Statistical analysis

The included studies were used for a meta-analysis to assess the association between targeted therapy (b/tsDMARD) and new cancer or cancer recurrence after prior cancer, the primary outcome of all included studies. Heterogeneity between studies was assessed with the I^2 calculation. Heterogeneity as well as differences in the treatment used for every study (tumour necrosis factor (TNF) inhibitor, rituximab, vedolizumab or other) led to the choice of a random-effects model to produce a combined relative risk and its corresponding 95% CI. Given the limited number of studies available for analysis, the Hartung-Knapp-Sidik-Jonkman approximation was employed as a means of mitigating potential bias. Publication bias was assessed with a funnel plot. When needed, the statistical results of the studies were pooled and weighted according to their sample size. All analyses were performed with R V.4.1.2. $P<0.05$ was considered statistically significant.

RESULTS

Primary analysis

Fifteen articles were included in the primary analysis, representing (disregarding any overlap between studies) 4428 patients and 15 062 patient-years in the group receiving targeted therapy, and 13 698 patients and 41 160 patient-years in the control group (typically receiving a csDMARD; table 1). The flow chart of articles in the SLR is available in figure 1. Nine studies used data from European registries, four studies used data from US healthcare databases, one study was a retrospective single-centre study and one study was a retrospective multicentric study. According to the Newcastle-Ottawa Scale, the overall quality of the studies was considered good, with a calculated score of >6 for all studies (online supplemental table 1).

The median age at cancer diagnosis was 52.5 years (min–max range 49–57). In the 13 studies reporting the follow-up duration, the median follow-up was 4.52 years (min–max range 9.8 months–8.8 years). The reported median time from the index cancer to the initiation of b/tsDMARD treatment was 4 years. Six out of fifteen studies adjusted the reported HR for general risk factors such as smoking, age and sex, and four studies additionally adjusted for specific cancer risk factors such as cancer type and index cancer stage.

For all included studies, the primary objective was to analyse cancer recurrence or new incident cancer in patients with a history of cancer-initiating a targeted therapy. In most studies (>90%), previous cancers were solid tumours. Two studies focused on breast cancer,[10 11] one study on melanoma,[12] two studies on NMSC[13 14] and one study on squamous cell carcinomas of the head and neck.[15]

12 studies included patients with RA exclusively and 2 studies included patients with inflammatory bowel disease (IBD). One study included RA, IBD and psoriasis. The details of the targeted therapies included are in table 2.

Most of the b/tsDMARDs studied evaluated TNF inhibitors (4162 patients and 13 519 patient-years), but data on other bDMARDs were also studied: vedolizumab (130 patients and 1087 patient-years), ustekinumab (66 patients and 228 patient-years) and rituximab (100 patients and 261 patient-years). No studies included tsDMARDs.

In total, 460 new cancers or cancer recurrences (46.2/1000 patient-years) were reported in the bDMARD-treated group: 428 in the TNF-inhibitor group (47.6/1000 patient-years), 9 in the rituximab group (35.7/1000 patient-years), 19 in the vedolizumab group (17.1/1000 patient-years) and 3 in the ustekinumab group. A total of 1394 new cancers or cancer recurrences were reported in the control csDMARD group (42.3/1000 patient-years, 423/100 patient-years). The pooled HR for new incidents or recurrent cancer between the bDMARD and control group was 0.90 (95% CI 0.74 to 1.10) (figure 2).

In analyses by drug exposure, the pooled adjusted HR was 0.94 (95% CI 0.76 to 1.18)) for the TNF inhibitor group, 0.81 (0.35 to 1.89) for the rituximab group (figure 3) and 0.49 (0.14 to 1.65) for the vedolizumab group (online supplemental figure 1).

Stratified analyses

Stratified analyses considered the histological type of initial cancer, the time from the initial cancer diagnosis to the initiation of targeted therapy and the duration of targeted therapy.

Six studies specifically studied patients with a history of solid cancer (excluding NMSCs and melanomas). All compared the occurrence of new incident cancer or cancer recurrence in patients with a history of solid cancer who received a TNF inhibitor or csDMARD. Two studies specifically studied breast cancer,[10 11] one study focused on squamous cell carcinomas of the head and neck[15] and three studies evaluated different types of solid cancers.[16–18] The pooled adjusted random effects meta-analysis HR for new cancer/cancer recurrence was 0.89 (95% CI 0.66 to 1.21) for patients with a history of solid cancer who received a TNF inhibitor versus a csDMARD (online supplemental figure 1).

Three studies specifically analysed patients with a history of NMSC[13 14 16] who received a TNF inhibitor. The pooled

Table 1 Details of the studies included in the systematic literature review

Author	Year	Country	Group	Number	Patient-years	Cancer endpoint	Inflammatory disease studied	Events*	Rate/1000 patient-years	HR (95% CI)	Crude HR	Adjusted HR	Adjustments
Waljee *et al*[16]	2019	Denmark	TNF inhibitors	434	2376	Mixed cancer type	RA, Pso, IBD	72	30.3	0.82 (0.51 to 1.11)	0.86 (0.66 to 1.12)	0.82 (0.51 to 1.11)	(1)
			Biologic-naive	4328	16376			563	34.4	Reference			
Mamtani *et al*[10]	2016	USA	TNF inhibitors	291	764	Breast cancer	RA	17	22.3	1.13 (0.65 to 1.97)		1.13 (0.65 to 1.97)	No covariates needed
			csDMARDs	1164	2466			48	19.5	Reference			
Strangfeld *et al*[19]	2010	Germany	TNF inhibitors	59	198	Mixed cancer type	RA	9	45.5	1.4 (0.5 to 5.55)	1.4 (0.5 to 5.55)		None
			csDMARDs	56	159			5	31.4	Reference			
Strangfeld *et al*[22]	2013	Germany	Rituximab	77	180	Mixed cancer type	RA	7	38.9	1.1 (0.4 to 2.7)	1.1 (0.4 to 2.7)		None
			csDMARDs	112	361			13	36	Reference			
Scott *et al*[13]	2015	USA	TNF inhibitors	1839	1465	NMSC	RA	109	74.4	1.49 (1.03 to 2.16)		1.49 (1.03 to 2.16)	(2)
			csDMARDs	4414	4631			335	72.3	Reference			
Silva-Fernández *et al*[23]	2016	UK	TNF inhibitors	243	1591	Mixed cancer type	RA	53	33.3	0.56 (0.36 to 0.88)	0.51 (0.33 to 0.79)	0.56 (0.36 to 0.88)	(3)
			Rituximab	23	81			2	24.7	0.44 (0.11 to 1.82)	0.45 (0.11 to 1.97)	0.44 (0.11 to 1.82)	
			csDMARDs	159	855			46	53.8	Reference			
Raaschou *et al*[17]	2018	Sweden	TNF inhibitors	467	2471	Mixed cancer type	RA	42	17.0	1.06 (0.73 to 1.54)		1.06 (0.73 to 1.54)	(4)
			Biologic-naive	2164	9394			155	16.5	Reference			
Philipps *et al*[15]	2015	USA	TNF inhibitors	40	256	Head and neck cancer	RA	7	27.3	0.9 (0.4 to 2.1)	0.9 (0.4 to 2.1)		None
			csDMARDs	190	1195			35	29.3	Reference			
Aaltonen *et al*[18]	2015	Finland	TNF inhibitors	100	233	Mixed cancer type	RA	3	12.9	2.2 (0.2 to 20.7)	2.2 (0.2 to 20.7)		None
			csDMARDs	77	169			1	5.9	Reference			
Raaschou *et al*[12]	2013	Sweden	TNF inhibitors	54	271	Melanoma	RA	3	11.1	3.2 (0.8 to 13.1)		3.2 (0.8 to 13.1)	(5)
			Biologic-naive	295	1370			10	7.3	Reference			
Mercer *et al*[14]	2012	UK	TNF inhibitors	177	627	NMSC	RA	29	46.3	0.7 (0.26 to 1.94)		0.7 (0.26 to 1.94)	(6)
			Biologic-naive	106	276			23	79.9	Reference			
Raaschou *et al*[11]	2014	Sweden	TNF inhibitors	120	592	Breast cancer	RA	9	15	1.1 (0.4 to 2.8)	0.8 (0.3 to 2.1)	1.1 (0.4 to 2.8)	(7)
			csDMARDs	120	550			9	16	Reference			
Axelrad *et al*[20]	2016	USA	TNF inhibitors	55	285	Mixed cancer type	IBD	7	24.6	0.35 (0.09 to 1.09)		0.35 (0.09 to 1.09)	(8)
			csDMARDs	149	852			46	852	Reference			
Vedamurthy *et al*[21]	2022	USA	Vedolizumab	96	821	Mixed cancer type	IBD	18	22	0.72 (0.38 to 1.39)		0.72 (0.38 to 1.39)	(9)
			TNF inhibitors	184	1452			61	42	1.03 (0.65 to 1.64)		1.03 (0.65 to 1.64)	
			csDMARDs	183	1378			78	56	Reference			

Continued

Table 1 Continued

Author	Year	Country	Group	Number	Patient-years	Cancer endpoint	Inflammatory disease studied	Events*	Rate/1000 patient-years	HR (95% CI)	Crude HR	Adjusted HR	Adjustments
Hasan *et al*[34]	2022	Canada	Vedolizumab	34	266	Mixed cancer type	IBD	1	4	0.18 (0.03 to 1.35)		0.18 (0.03 to 1.35)	(10)
			Ustekinumab	27	164			3	18	0.88 (0.25 to 3.03)		0.88 (0.25 to 3.03)	
			TNF inhibitors	99	938			7	7	0.47 (0.20 to 1.12)		0.47 (0.20 to 1.12)	

Adjustments when done: (1) adjusted for sex; initial primary cancer type; diagnosis of inflammatory bowel disease (IBD), rheumatoid arthritis or psoriasis; age at diagnosis of IBD, rheumatoid arthritis or psoriasis; age at initial cancer diagnosis; number of baseline hospital admissions; and number of baseline outpatient visits; (2) TNF exposure; (3) age-, sex- and smoking status-adjusted HR; (4) adjusted for the matching variables sex, birth year (±10 years), year of diagnosis (±5 years) of the index cancer, cancer type and index cancer stage; (5) age and sex; (6) age, sex, smoking, exposure to cyclosporine or azathioprine, NSAIDs and baseline characteristics; (7) adjusted for breast cancer characteristics (nodal state, type of surgery, chemotherapy) and comorbidities (diabetes mellitus, ischaemic heart disease, chronic obstructive pulmonary disease and joint surgery); (8) adjusted by recurrence risk type of prior cancer; (9) adjusted for age at index cancer, IBD subtype, smoking history, antimetabolite exposure, cancer category, cancer stage and time to biological. Time to biological for the no immunosuppressant group was set as the median of the anti-TNF group; (10) adjusted for recurrence risk, type of primary cancer, baseline demographics and disease characteristics.
*New incident cancer or recurrence of a previous cancer.
csDMARD, conventional synthetic disease-modifying antirheumatic drug; IBD, inflammatory bowel disease; NMSC, non-melanoma skin cancer; Pso, psoriasis; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

Table 2 Details of the targeted therapies included in the study

Targeted therapy	Patients	Patient-years
TNF inhibitors	4162	13 519
Vedolizumab	130	1087
Ustekinumab	66	228
Rituximab	100	261

TNF, tumour necrosis factor.

adjusted random effects meta-analysis HR was 1.23 (95% CI 0.90 to 1.70) as compared with csDMARD users (online supplemental figure 3).

Five studies,[17 19–22] reported a median time from the initial cancer diagnosis to the initiation of bDMARDs of less than 5 years. One study focused on patients with an IBD, and the other four studies focused on patients with RA. One study[21] reported data with vedolizumab and TNF inhibitors, the other studies reported on TNF inhibitors only. When analysing the risk of cancer resurgence on bDMARDs initiated within 5 years of cancer diagnosis, the pooled adjusted random effects meta-analysis HR was 0.88 (95% CI 0.64 to 1.21) as compared with csDMARD users (figure 4). Three studies[11 17 23] reported a time from the initial cancer diagnosis to the initiation of biological therapy of more than 5 years. One study[23] reported rituximab and TNF-inhibitor data; the other two studies reported TNF-inhibitor data only. When analysing the risk of cancer recurrence on bDMARDs initiated after more than 5 years of cancer diagnosis, the pooled adjusted random effects meta-analysis HR was 0.82 (95% CI 0.47 to 1.44) as compared with csDMARD users (online supplemental figure 4).

Four studies[12 15 17 23] reported a mean duration of bDMARD exposure exceeding 5 years. All these studies focusses on treatment with TNF inhibitors. The pooled adjusted random effects meta-analysis HR was 0.87 (95% CI 0.63 to 1.19) as compared with csDMARD users (online supplemental figure 5). For the 11 studies with a duration of TNF-inhibitor exposure of less than 5 years, the pooled adjusted random effects meta-analysis HR was 0.93 (95% CI 0.71 to 1.20) as compared with csDMARD users (online supplemental figure 6).

Sensitivity analyses and RoB assessment

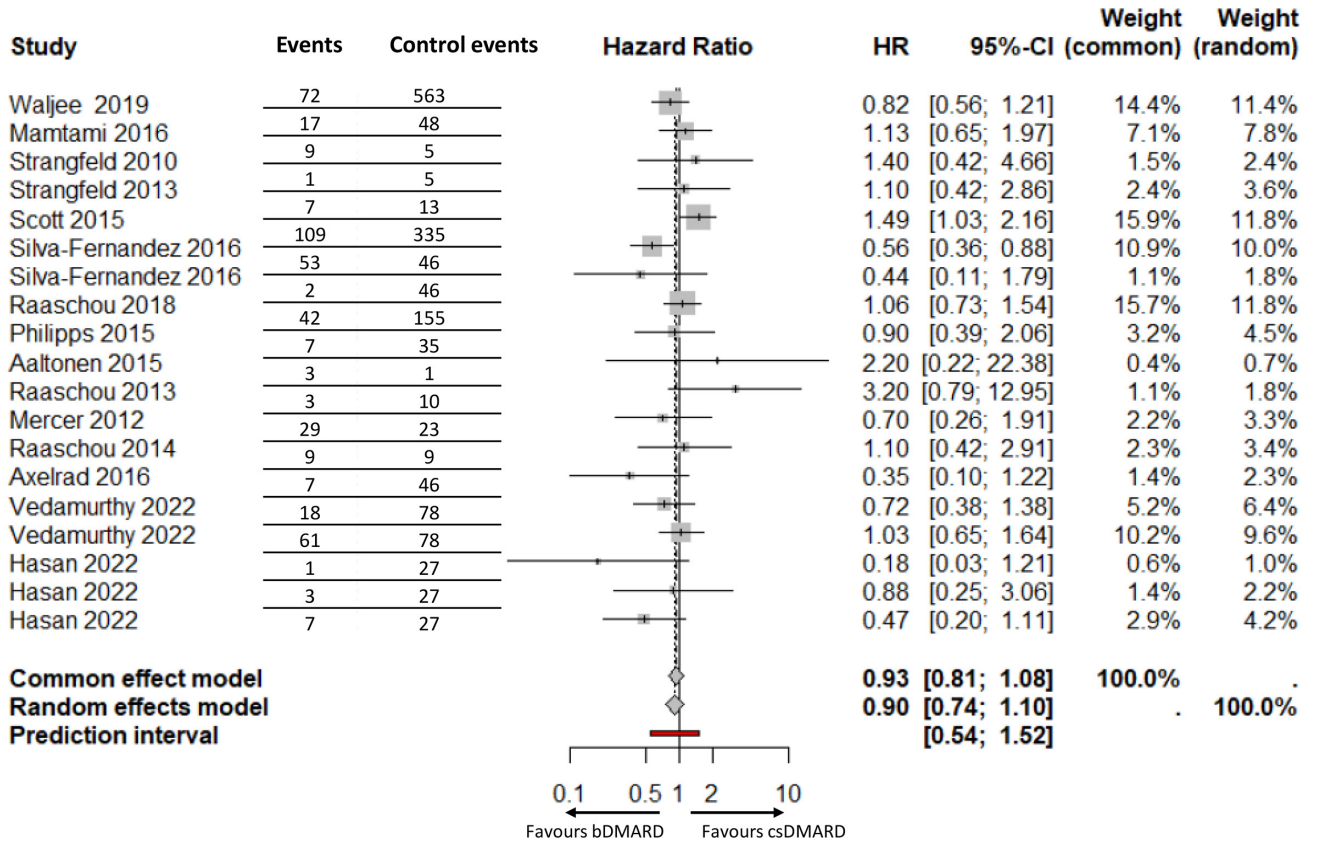
Furthermore, several sensitivity analyses were conducted.

A sensitivity analysis was conducted on the data set comprising only patients with IA (12 studies), all of them having RA. The overall risk of new incidents or recurrent cancer in RA patients with a history of cancer treated with bDMARDs versus csDMARDs was 1.03 (95% CI 0.79 to 1.34) (figure 5).

In another sensitivity analysis, we retained only the most recent study from each registry to limit the risk of taking into account the same patients several times when the same registry had published multiple reports. The following studies were removed in this sensitivity analysis: Strangfeld *et al*[22] and Raaschou *et al*.[11 12] The overall risk of new incident or recurrent cancer in the sensitivity analysis was 0.87 (95% CI 0.70 to 1.09) (online supplemental figure 7).

In the last sensitivity analysis, we combined only RA patients with the latest registry data available. The pooled adjusted HR of new incidents or recurrent cancer in this sensitivity analysis was 0.99 (95% CI 0.72 to 1.37) (online supplemental figure 8).

The RoB, evaluated with the ROBINS-I tool, was considered low. However, heterogeneity could have been impacted by a lot more factors (besides the ones included in the I^2 calculation): the studies were intrinsically heterogeneous because they addressed



Heterogeneity : I^2 = 62.17%, τ^2 = 0.19, p-value = 0.9

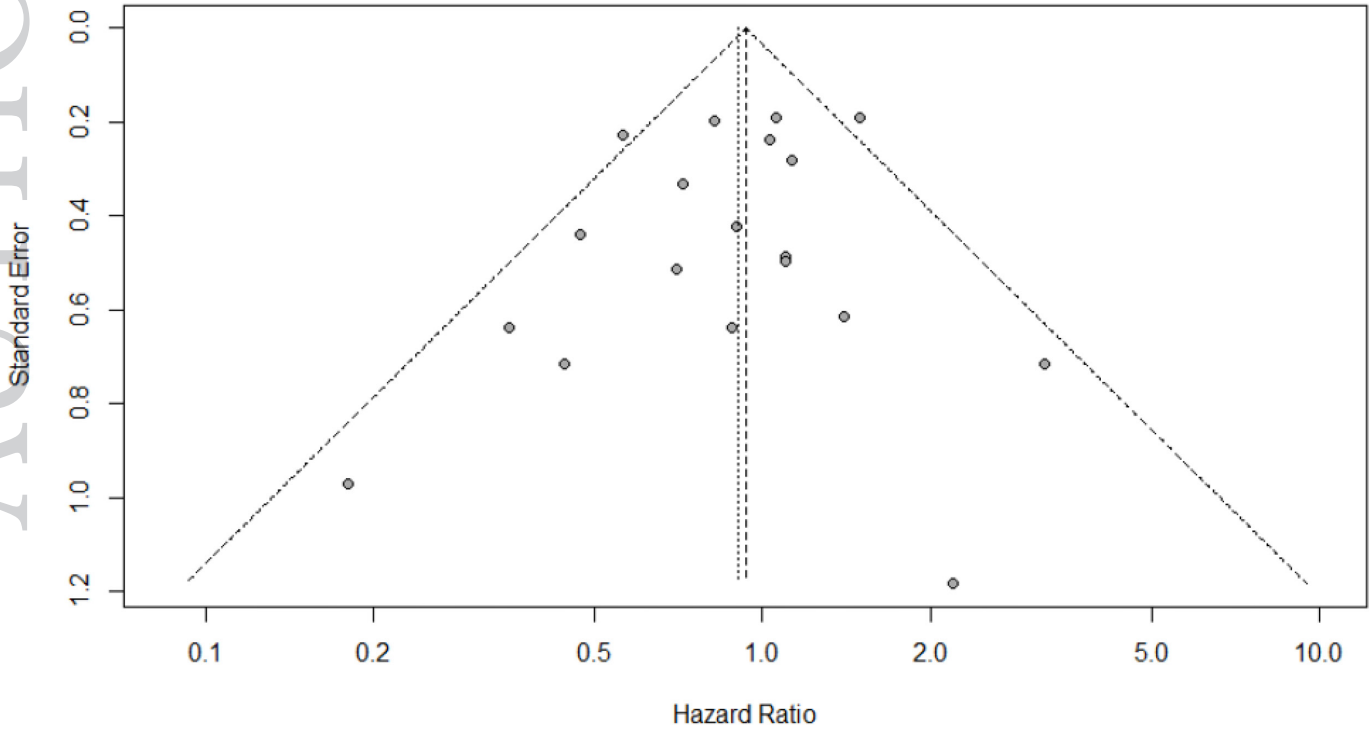


Figure 2 Overall risk of new cancer or cancer recurrence for patients receiving biologic disease-modifying anti-rheumatic drugs (bDMARDs) versus conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) with the respective funnel plot of the studies. All bDMARDs versus csDMARDs in patients with a history of cance r.

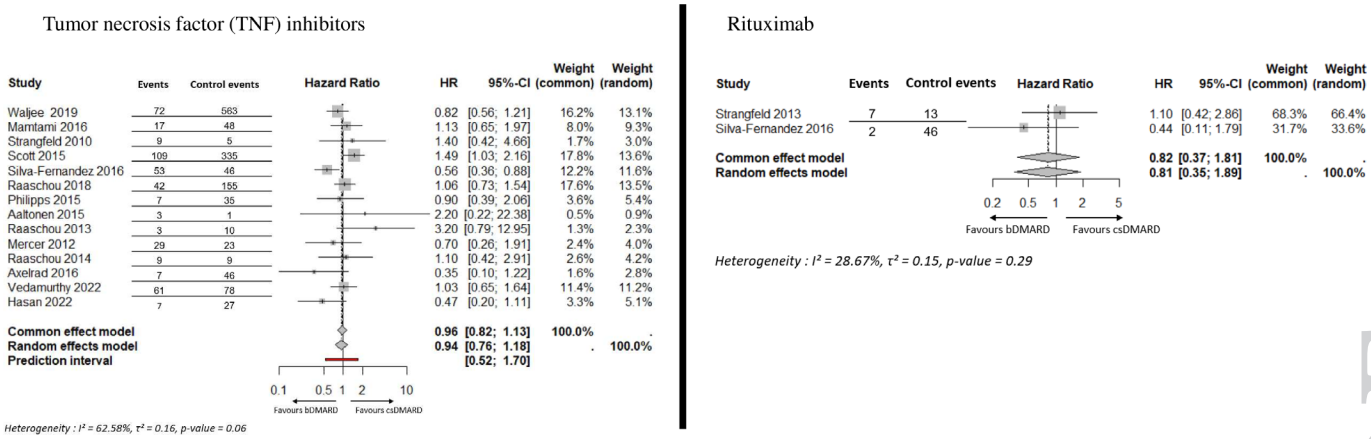


Figure 3 Overall risk of new cancer or cancer recurrence in patients receiving biologic synthetic disease-modifying antirheumatic drugs (bDMARDs) versus conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), stratified by type of bDMARD used (TNF inhibitors or rituximab).

different treatments and different diseases, and some of them included a limited sample size, which affects the I^2 calculation.

DISCUSSION

In this SLR and meta-analysis including a total of 15 studies covering 4428 patients and 15 062 patient-years in the groups receiving targeted therapies and 13 698 patients and 41 160 patient-years in the control groups, we found no indication of increased risk of new cancer or cancer recurrence in patients receiving targeted therapy.

The SLR aimed to analyse cancer recurrence not only in IA but also in inflammatory skin and bowel diseases, yet it mainly identified data for patients with IA. Among patients with IA, all patients had RA. The systematic review aimed to collect data on all targeted therapies, but most studies enrolled only patients with a history of cancer receiving TNF inhibitors. No study analysed patients for whom the cancer was not in remission or presumed to be in remission at the time of the initiation of targeted therapy. This study aimed to assess the incidence of cancer between targeted therapies and csDMARDs. However, some csDMARDs might increase the risk of cancer in patients as compared with healthy individuals, such as methotrexate for NMSCs.[24] Independent of treatments, some rheumatic diseases are associated with increased risk of some cancers,[25 26] notably via disease activity, autoimmunity, inflammation and comorbidities such as smoking. Therefore, these results should not be extrapolated to all clinical situations and need to be adapted individually to each patient.

The limitations of this study are inherent in the use of observational data, with their higher RoB than randomised clinical trials. The selected studies were all good quality, with a Newcastle-Ottawa Scale score >6. No study on rheumatic diseases was published after 2019, which may be related to the impact of the pandemic on research priorities. All included studies were observational studies, with their risk of confounding by indication (eg, more patients with a history of cancer-initiated rituximab vs other bDMARDs), confounding by other factors, under-reporting or misclassification. Although such biases are certainly possible, the results of our meta-analysis are homogenous and do not suggest large variations in different settings. Of note, most of the studies adjusted the reported HR on cancer-related prognostic factors such as stage, metastatic status, alcohol consumption and

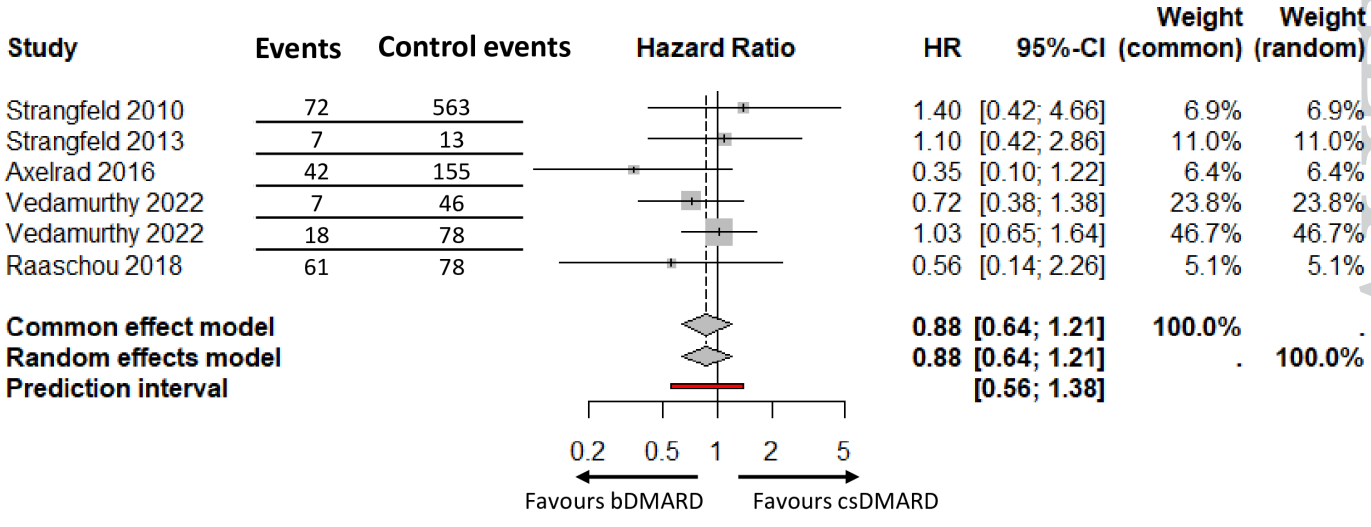
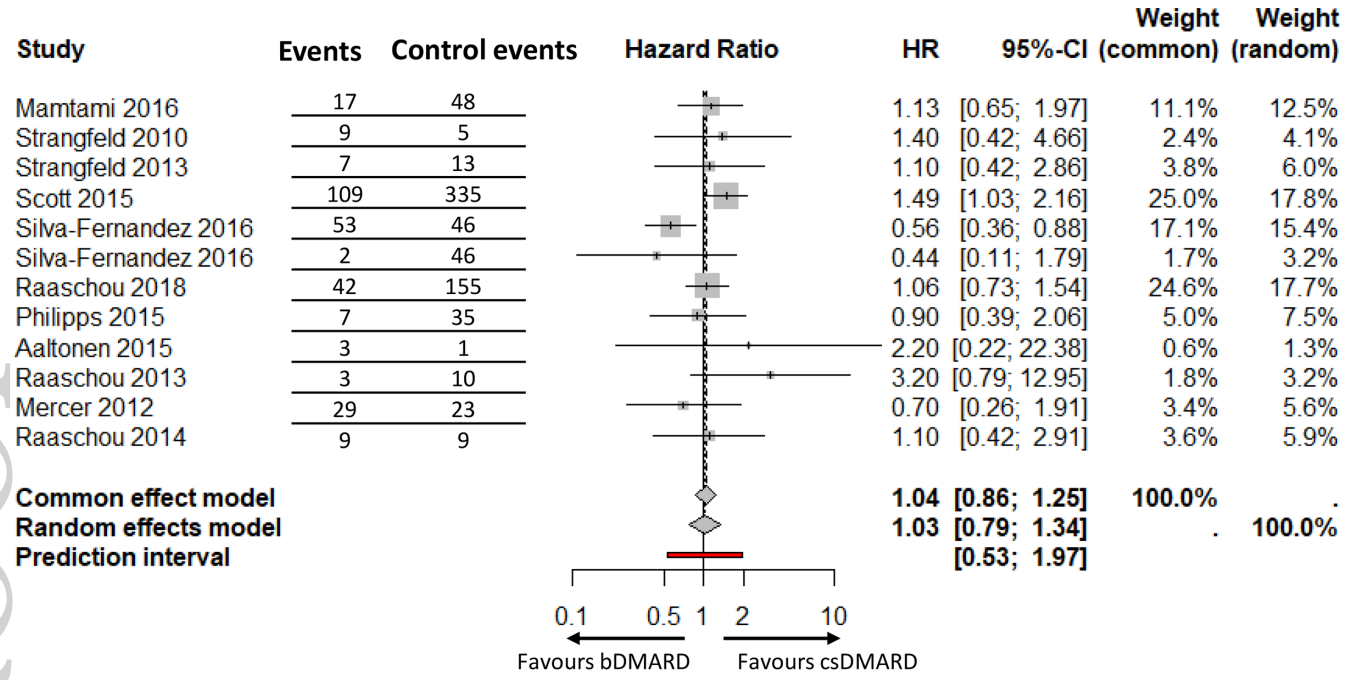


Figure 4 Risk of new cancer or cancer recurrence for patients receiving biologic synthetic disease-modifying antirheumatic drugs (bDMARDs) versus conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) less than 5 years after initial cancer diagnosis. Use of bDMARD within 5 years of cancer diagnosis.



Heterogeneity : I^2 = 51.32%, τ^2 = 0.12, p-value = 0.13

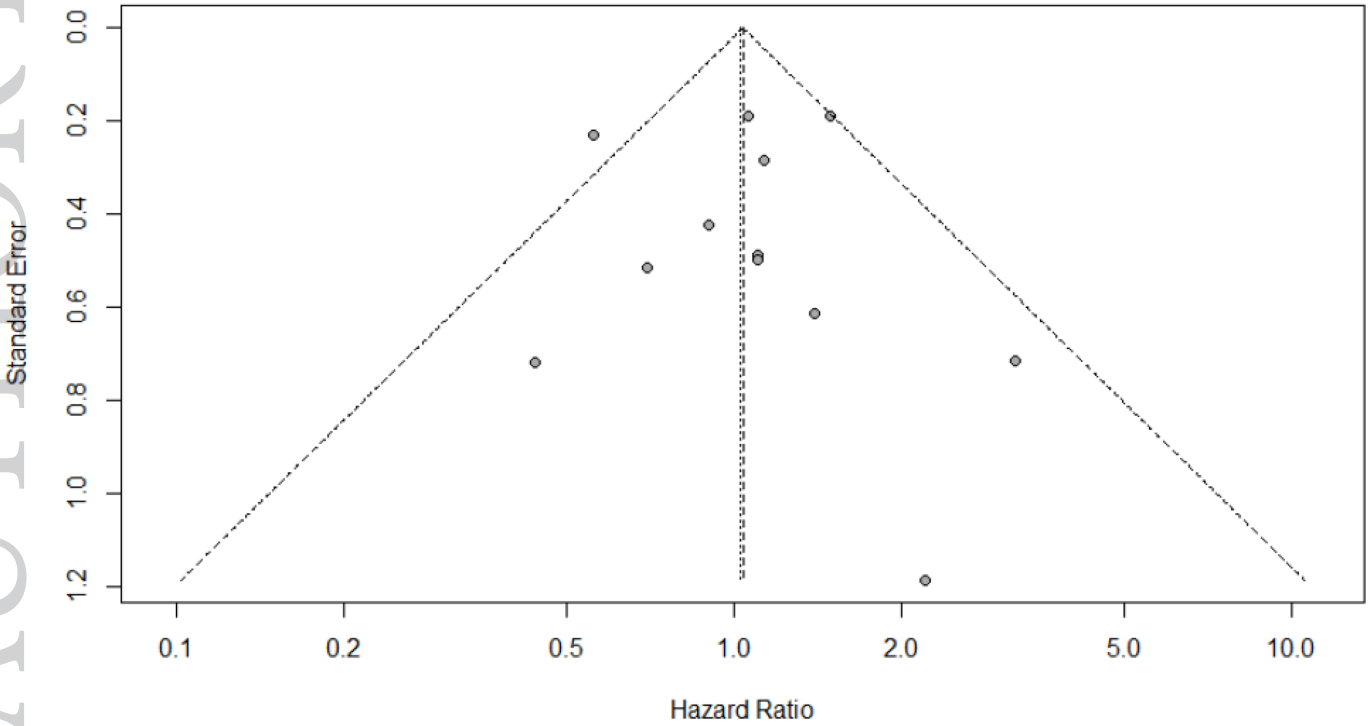


Figure 5 Sensitivity analysis restricted to patients with rheumatoid arthritis. bDMARDs, biologic synthetic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs.

smoking persistence. A few studies focused on a specific cancer, notably lymphomas. Some important data were missing. 12 of 17 studies reported the time from cancer diagnosis to the initiation of a bDMARD. Only 4 of 17 studies reported follow-ups on targeted therapy for longer than 5 years. Furthermore, the duration of the follow-up was limited, considering the risk of cancer recurrence in the long term, ranging from 9.8 months to 8.8 years. Considering the clinical context covered by the SLR and the current limitations of the literature, we emphasise that the absence of evidence of increased risk of new cancer with targeted therapies versus csDMARDs is not evidence of absence of increased risk.

Notwithstanding these limitations, data on TNF inhibitors in patients with a history of cancer are consistent and reassuring. Data in the literature allowed for comparing the risk of new cancer with a TNF inhibitor versus csDMARDs based on the

time from the cancer diagnosis to the initiation of treatment (<5 or ≥5 years). Of note, we found no significant difference between therapies in new cancer occurrence, even in patients treated less than 5 years since the diagnosis of cancer. This result is particularly important because some previous guidelines recommended avoiding the use of targeted therapies in patients with a recent cancer[27 28] which, as a consequence, may make any selection away from b/tsDMARDs stronger the shorter the time interval between the cancer and the start of a b/tsDMARD. When evaluating the benefit/risk of initiating or re-initiating a targeted therapy in patients with a history of cancer, prioritising cancer-related risk factors for recurrence might hold greater significance than focusing solely on the time elapsed since the initial cancer diagnosis. In addition, from the collected data, longer exposure to a TNF inhibitor >5 years was not associated with increased risk of a new cancer as compared with csDMARD treatment.

Unexpectedly, despite the wide use of this bDMARD in current practice,[7] in patients with a history of cancer, limited data were available for rituximab in patients with IA and a history of cancer. This absence of epidemiological data, along with recent translational results showing the role of B lymphocytes in tumour surveillance, should serve as an incentive to generate more data on rituximab in this setting.[29] The limited or lack of data on interleukin 12/23 (IL-12/23), IL-23 and IL-17 inhibitors in patients with a history of cancer should also be added to the collective research agenda. Data on abatacept and Janus kinase/signal regulator and activator of transcription (JAK/STAT) inhibitors in patients with a history of cancer will be of specific interest, given the results of some studies, out of scope for this SLR because these studies reported data on patients without a history of cancer. In the context of RA without a history of cancer, some observational studies reported an increased risk of cancer with abatacept versus other targeted therapies.[30–32] Of note, the mechanism of action of abatacept is the opposite of that of ipilimumab used in cancer immunotherapy, which warrants some heightened monitoring. JAK/STAT inhibitors have also raised concerns regarding the risk of cancer after the Oral-Surveillance study, which excluded patients with a history of cancer.[33]

In summary, this SLR informing the EULAR PTC on the initiation of targeted therapies in patients with IA and a history of cancer shows that overall, the targeted therapies and clinical context covered by the included studies were not associated with increased risk of cancer recurrence as compared with csDMARDs. We further found no significant risk by type of cancer, time from cancer to the initiation of a bDMARD and treatment duration.

Results of the present meta-analysis based on studies evaluating the risk of recurrent or new cancer after targeted therapy initiation with a very limited follow-up should be interpreted with caution. Additional data are needed regarding inflammatory rheumatic diseases other than RA, treatments other than TNF inhibitors as well as longer durations of follow-up and exposure to targeted therapies. Improving the data collection, notably on non-TNF targeted therapies, and improving the reporting, differentiating relapses of a previous cancer from new incident cancers, and extending the follow-up of patients are needed in future studies, for patients and clinicians.

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