Use of Systemic Therapies for Treatment of Psoriasis in Patients with a History of Treated Solid Tumours: Inference-Based Guidance from a Multidisciplinary Expert Panel

Authors & Affiliations

Kim A Papp[1,2], Barbara Melosky*[3,4], Sandeep Sehdev*[5], Sebastien J Hotte*[6,7], Jennifer R Beecker[1,8,9,10], Mark G Kirchhof[8,9], Irina Turchin[1,11,12], Jan P Dutz[13, 14,15], Melinda J Gooderham[1,16], Robert Gniadecki[17], Chih-ho Hong[1,14,18], Jo Lambert[19, 20], Charles W Lynde[1,21,22], Vimal H Prajapati[1,23,24,25,26,27], Ronald B Vender[28,29]

*authors contributed equally after first author. All others are listed alphabetically.

[1] Probity Medical Research Inc., Waterloo, ON, Canada
[2] Alliance Clinical Research, Waterloo, ON, Canada
[3] Medical Oncology, BC Cancer Vancouver Centre, Vancouver, BC, Canada.
[4] Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada.
[5] Division of Medical Oncology, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada.
[6] Juravinski Cancer Centre, Hamilton, ON, Canada
[7] Department of Oncology, McMaster University, Hamilton, ON, Canada
[8] University of Ottawa, Ottawa, ON, Canada
[9] Division of Dermatology, The Ottawa Hospital, Ottawa, ON, Canada
[10] Ottawa Hospital Research Institute, Ottawa, ON, Canada
[11] Brunswick Dermatology Centre, Fredericton, NB, Canada
[12] Department of Medicine, Dalhousie University, Halifax, NS, Canada
[13] Skin Care Centre, Vancouver, BC, Canada
[14] Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada
[15] BC Children's Hospital Research Institute, Vancouver, BC, Canada
[16] SKiN Centre for Dermatology, Peterborough, ON, Canada
[17] Division of Dermatology, Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada
[18] Dr. Chih-ho Hong Medical Inc., Surrey, BC, Canada
[19] Department of Dermatology, Ghent University Hospital, Ghent, Belgium
[20] Dermatology Research Unit, Ghent University, Ghent, Belgium
[21] Lynde Institute for Dermatology, Markham, ON, Canada
[22] Division of Dermatology, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada
[23] Division of Dermatology, Department of Medicine, University of Calgary, Calgary, AB, Canada
[24] Section of Community Pediatrics, Department of Pediatrics, University of Calgary, Calgary, AB, Canada
[25] Section of Pediatric Rheumatology, Department of Pediatrics, University of Calgary, Calgary, AB, Canada
[26] Dermatology Research Institute, Calgary, AB, Canada
[27] Skin Health & Wellness Centre, Calgary, AB, Canada
[28] Department of Medicine, McMaster University, Hamilton, ON, Canada
[29] Dermatrials Research Inc., Hamilton, ON, Canada

Corresponding author: Kim A. Papp, MD, PhD, FRCPC, Waterloo. kapapp@probitymedical.com

Supplementary Material

Table of Contents:

*****Includes unformatted versions of the content that authors were provided with to accompany their statement voting, and unformatted references.

Supplementary Tables and Figures:

Table S1: Breakdown of Questions

Level	Question *Inference-based Conclusion*
1. Primary Question	*Are responses* to systemic psoriasis therapies for treatment of psoriasis in patients with previously or actively treated solid tumours (TST) similar to the general psoriasis population?* **responses include drug-related adverse events as well as drug-related benefits*
1.1	In patients with previously TST on systemic psoriasis therapy, is there suppression or augmentation of relevant immune function that may inhibit the efficacy of targeted therapies for TST, increase the risk of recurrence or metastasis, and/or increase the risk of infection compared to the general population?
1.1.1	What factors contribute to differences in overall survival between patients with TST and the general population?
1.1.2	In patients with TST and psoriasis, does systemic psoriasis treatment alter risk of progression or recurrence compared to the general TST population?
1.1.3	In patients with TST and psoriasis, does systemic psoriasis treatment alter risk of infection compared to the general TST population?
1.1.4	What role do chronic immunosuppression/immunomodulation, immune surveillance, and immunosenescence play in development of malignancies?
1.1.5	Do patients with a history of TST receiving allografts have a similar rate of complications including rejection, infections and malignancies compared to the general transplant population when treated with immunosuppressive therapies?

Table S2: Direct evidence in patients with psoriasis and previously treated cancer. Caveat small patient numbers with short follow-up time.

Reference (Author, year)	Study Type, N	Key Findings
Mastorino 2021[1]	Retrospective, single-centre, case series and literature review. 37 psoriasis patients with past cancer and subsequent biologic therapy. 38 case reports from literature review.	Use of biologics (TNFi, IL-17i, IL-23i, and IL-12/23i) appeared to be safe. Mean time from cancer diagnosis to biologic treatment onset was 112 months (range 0-480) for series, and 37.7 months (0-144) for literature review. Mean follow-up time for series was 33.1 months (5-132) and for literature review 35.7 months (2-180 months). Four cases developed cancer during previous TNFi treatment, which was paused and resumed.
Valenti 2021[2]	Retrospective, single-centre, case series. 16 patients with psoriasis and a history of malignancy in past 10 years (5/16 had cancer diagnosis in past 5 years).	Treatment with biologics (TNFi, IL-17i, IL-12/23i) for up to at least 96 weeks. Rapid decrease in PASI reaching 90% improvement in all patients and no worsening or recurrence of cancers noted.
Kahn 2019[3]	Retrospective chart review 16 psoriasis patients with history of malignancy (including 3/16 receiving concurrent cancer therapy and biologics).	Patients demonstrated improvement in psoriasis. None of the 16 patients had recurrence or progression of their cancer supporting safety of biologics (TNFi, IL-17i, IL-23i, IL-12/23i) and/or APR. Note, patients were on multiple therapies for various durations.
Fagerli 2019[4]	Retrospective study. 709 severely active PsA patients, 11/709 had cancer registered prior to baseline.	None of the 11 patients with previous cancer had a further incidence of cancer after receiving TNFi. Of note, 98% of the 709 patients had previous or current exposure to MTX at baseline; 45.6% had previous or current exposure to CsA.

APR, apremilast; CsA,cyclosporine A; IL-17i, interleukin-17 inhibitor; IL-23i, interleukin-23 inhibitor; IL-12/23i, interleukin-12/23 inhibitor; MTX, methotrexate; NMSC, non-melanoma skin cancer; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; TNFi, tumour necrosis factor-alpha inhibitor.

Table S3: Direct Evidence in Patients with Cancer and TNF Treatment for Other Immune Disorders (IBD, RA)

Reference (Author, year, journal)	Title	Study Type	N	Key Findings/Notes
Micic 2019[6]	Risk of Cancer Recurrence Among Individuals Exposed to Antitumor Necrosis Factor Therapy: A Systematic Review and Meta-Analysis of Observational Studies.	Systematic Review and Meta-Analysis of Observational Studies	3707 patients with inflammatory disorders exposed to **TNFi** therapy following a cancer diagnosis	Risk of new cancer or cancer recurrence among pts with history of cancer and use of TNFi therapy is similar to the risk with non-biological DMARDs. This supports use of TNFi therapy in select populations despite prior diagnosis of cancer. -Duration interval between original ca diagnosis and TNFi-prescription was 1.2-11.5 years Subgroup analysis by time to initiation of TNFi showed no increased risk of cancer recurrence. After TNF if started >5 years after ca diagnosis -only one study in this MA had a median time to anti TNF Rx of 1.2 years, but no increased risk in this study either. There is insufficient data *to estimate an optimal start-time for TNF-Rx following cancer therapy* *must be noted that could be selection bias in these observational studies (patients chosen for TNFs may have lower risk of recurrence), but conversely, detection bias may result in higher cancer rates as patients have closer follow-up (Shelton reference below)
Shelton 2016[7]	Cancer Recurrence Following Immune-Suppressive Therapies in Patients With Immune-Mediated Diseases: A Systematic Review and Meta-analysis.	A Systematic Review and Meta-analysis	11,702 patients with Immune-Mediated Diseases and prior cancer	Mainly IBD/RA. 16 studies, n=11702 pts with prior cancer, 31,258 person-years (p-y) of follow-up evaluation after a prior diagnosis of cancer. Only 1 study of severe psoriatic arthritis, Fagerli 2014 (referenced in direct evidence table) of TNF-i n=11 both new and recurrent cancers Using pooled incidence rates, similar rates of cancer relapse in patients with prior cancer receiving no immunosuppression, TNFi therapy, immune modulator or combination therapy; numerically higher among patients receiving combination immunosuppression. Reassuring data on restarting immunosuppressive therapy in pts with prior cancer. Caveat: unable to ascertain exact interval at which recommencement would be safe. Median recommencement of

				IS was 6 years. Note, an analysis of studies with median interval <6 years showed no risk in new or recurrent cancers
Raaschou 2018[8]	Tumor Necrosis Factor Inhibitors and Cancer Recurrence in Swedish Patients With Rheumatoid Arthritis: A Nationwide Population-Based Cohort Study	Cohort Study	467 RA patients who received **TNFi** therapy	The findings suggest that TNFi treatment is not associated with increased risk for cancer recurrence in patients with RA, although meaningful risk increases could not be ruled out completely. Among 467 patients who started TNFi treatment (mean time after cancer diagnosis, 7.9 years), 42 had cancer recurrences (9.0%; mean follow-up, 5.3 years); among 2164 matched patients with the same cancer history, 155 had recurrences (7.2%; mean follow-up, 4.3 years) (HR, 1.06 [95% CI, 0.73 to 1.54). Hazard ratios were close to 1 in analyses of patient subsets matched on cancer stage or with similar time from index cancer diagnosis to the start of TNFi treatment, as well as in unmatched analyses. Several CIs had upper limits close to 2. Limitation: The outcome algorithm was partly nonvalidated, and channeling bias was possible if patients with a better index cancer prognosis were more likely to receive TNFi.
Raaschou 2011[9]	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.	Cohort study	314 cancers in RA patients undergoing or history of **TNFi**	Relative risk of death with TNFi exposure same as biologics naïve group. * Reassuring to know from a Swedish study of Registries that when cancer develops on TNF rx, no increased risk of death or altered stage on TNfs vs nonbiologic controls
Xie 2020[10]	A meta-analysis of biologic therapies on risk of new or recurrent cancer in patients with rheumatoid arthritis and a prior malignancy	Meta-analysis	12 studies involving 13,598 patients and 32,473 patient-years of follow-up	Biologics were not associated with an increased risk of new or recurrent cancer compared with csDMARDs in patients with RA and prior cancer (**TNFi**: relative risk = 0.95, 95% CI = 0.83, 1.09). Secondary analyses of stratification of cancer types, the interval between initiation of TNFi and prior cancer diagnosis, and duration of TNFi exposure, found similar results

Waljee 2020[11]	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	Cohort study	434 patients who received TNFi therapy after their initial cancer were matched to 4328 patients in the control group.	Use of **TNFi** therapy was not associated with recurrent or new primary cancer development in patients with previous cancer. Timing of TNFi therapy after an initial cancer diagnosis did not influence recurrent or new primary cancer development.
Silva-Fernandez 2016[12]	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	Retrospective registry	425 patients with a prior malignancy from 18 000 RA patients, 101 patients developed a new malignancy.	Rates of incident malignancy: TNFi cohort: 33.3 events/1000 person-years (py) Rituximab cohort: 24.7 events/1000 py sDMARD cohort (**study does not specify which sDMARDs, mentions "such as AZA and MTX"*): 53.8 events/1000 py The age- and gender-adjusted hazard ratio was 0.55 (95% CI: 0.35, 0.86) for the TNFi cohort and 0.43 (95% CI: 0.10, 1.80) for the RTX cohort in comparison with the sDMARDs cohort. "Although numbers are still low, it seems that patients with RA and prior malignancy selected to receive either a TNFi or RTX in the UK do not have an increased risk of future incident malignancy."

Figure S1: Level of Support/Agreement/Confidence. A. Authors were asked to review the summary of direct and indirect evidence, and provide their level of support/agreement/confidence from **from 0-100%,** to the nearest decimal, using the scale below as a guide. Upper and lower values representing their level of uncertainty were also provided by authors. An open-ended text box to capture any caveats was also included. B. An example rating was provided to authors (red "x" on scale below). E.g., Your confidence/support/agreement for a statement is 90%, with a lower value of 75% and upper value of 95%.

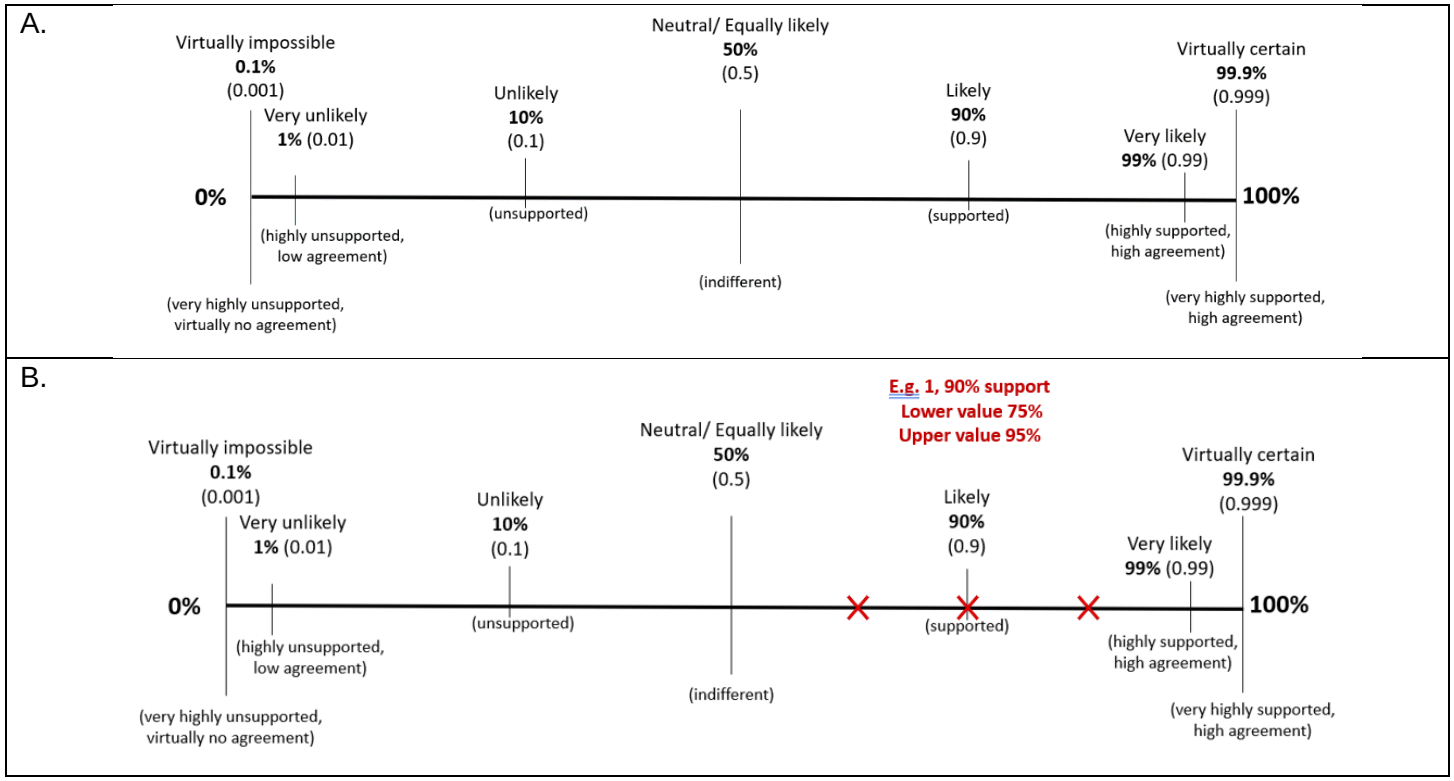
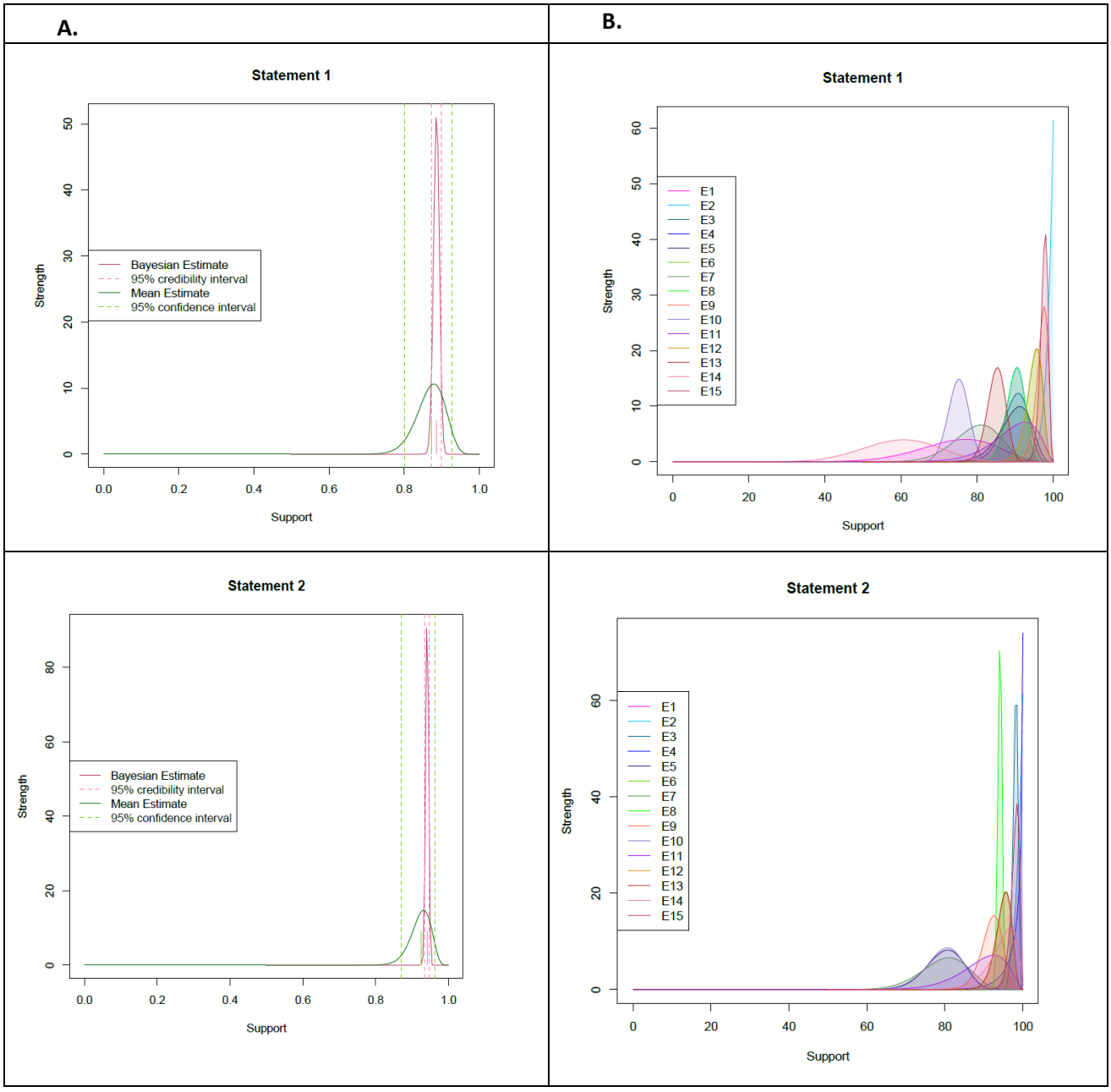


Figure S2: Consolidated and individual levels of support for core recommendation statements 1 to 4.
A. includes Bayesian and mean estimates of support, showing the strength of each method of consolidating individual expert ratings. B. represents individual expert ratings for level of support/agreement/confidence for each statement, including upper and lower values representing their confidence in their level of support. The 15 experts are represented at Expert 1, E1, through to Expert 15, E15.



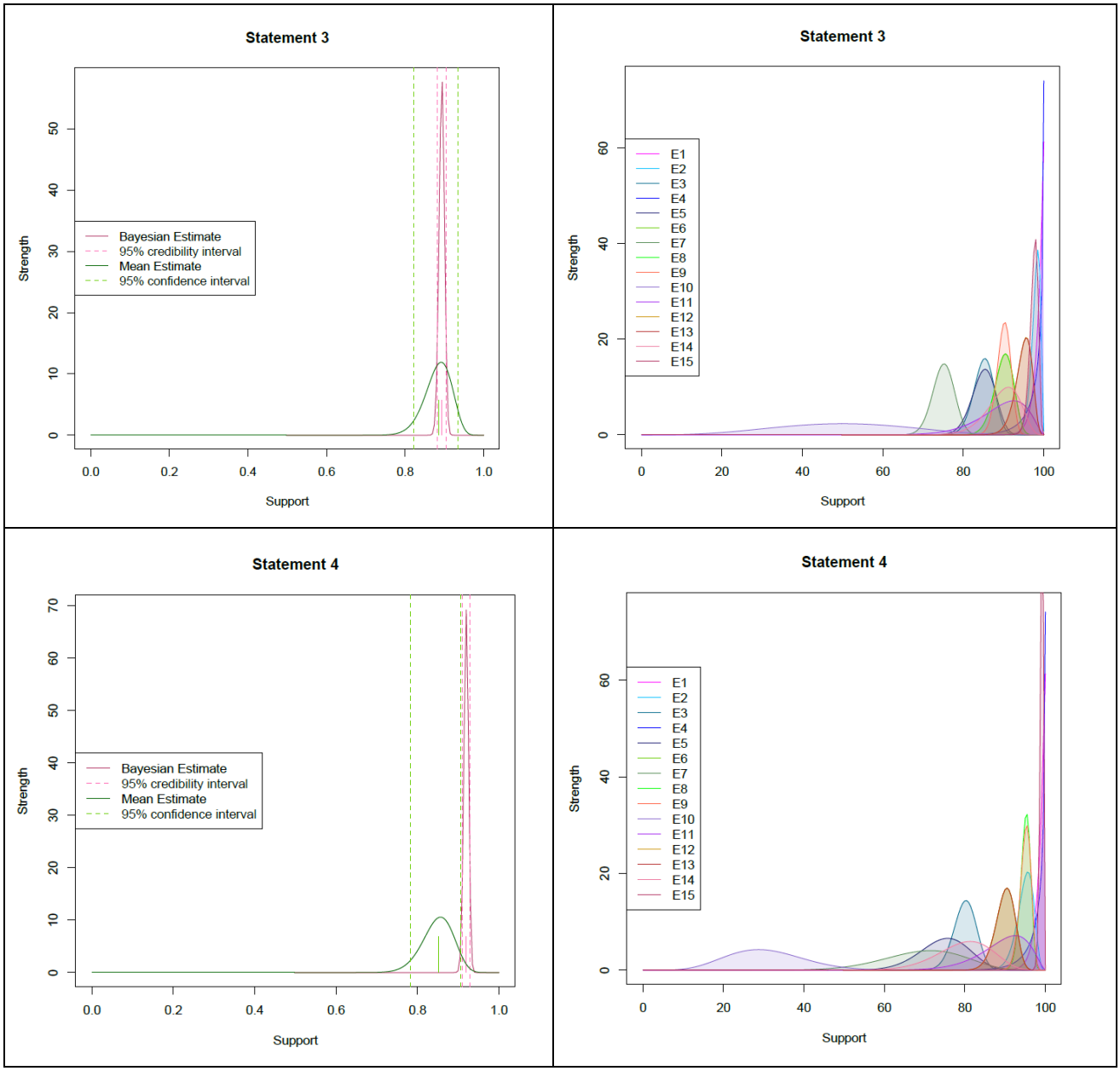
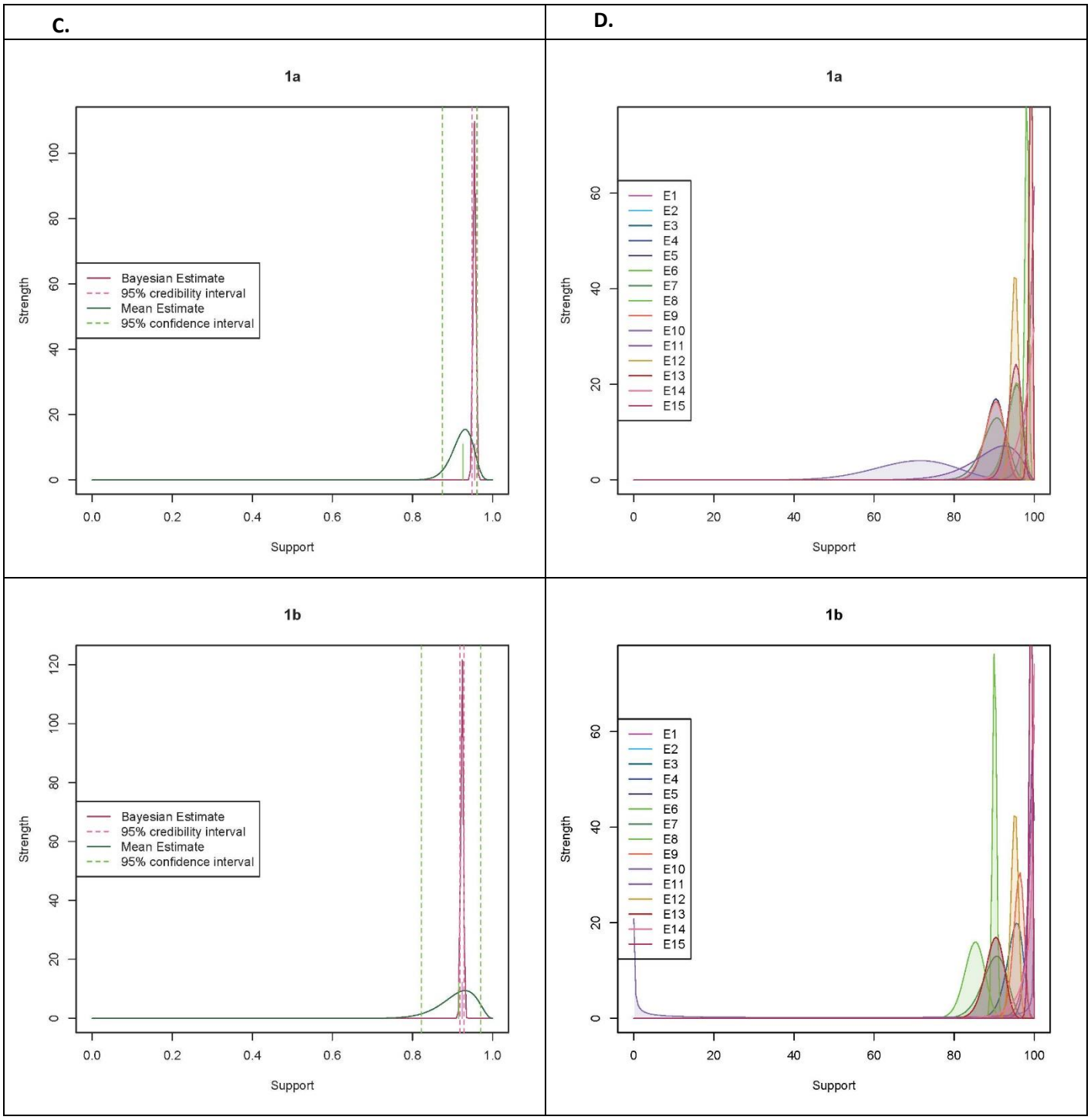
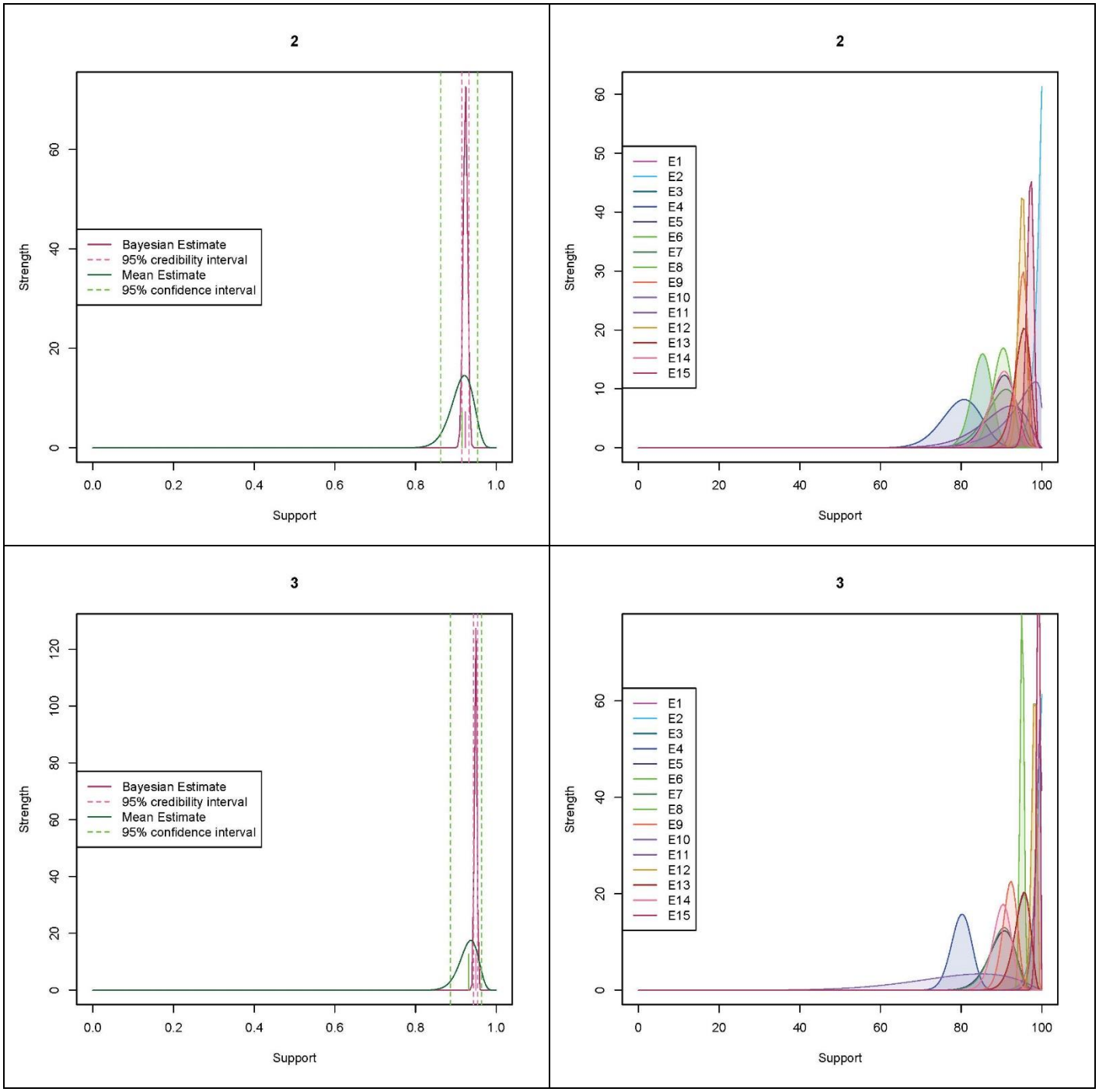
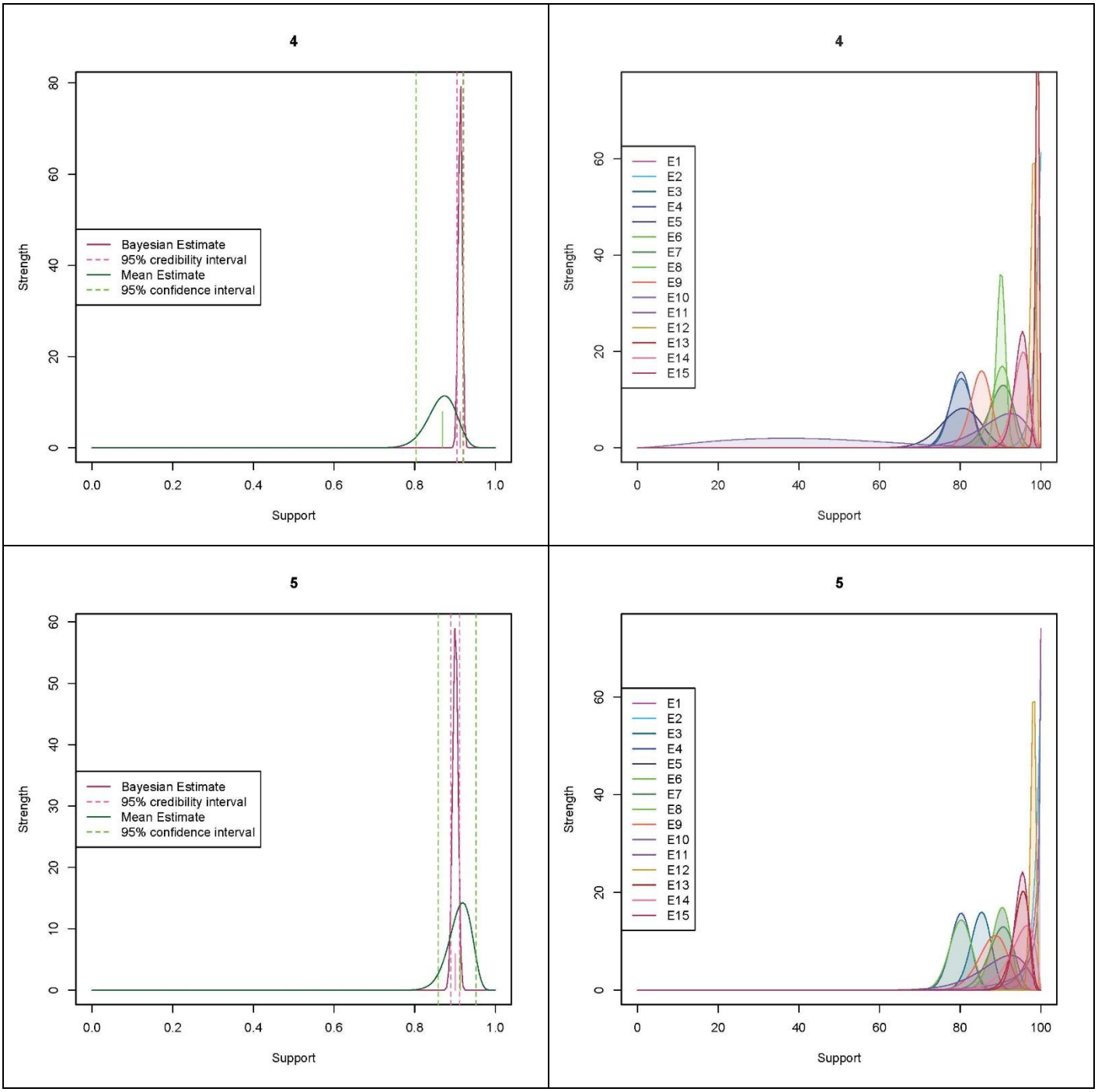

Statement 3
Strength
Support
Bayesian Estimate
95% credibility interval
Mean Estimate
95% confidence interval
Statement 3
Strength
Support
E1
E2
E3
E4
E5
E6
E7
E8
E9
E10
E11
E12
E13
E14
E15
Statement 4
Strength
Support
Bayesian Estimate
95% credibility interval
Mean Estimate
95% confidence interval
Statement 4
Strength
Support
E1
E2
E3
E4
E5
E6
E7
E8
E9
E10
E11
E12
E13
E14
E15

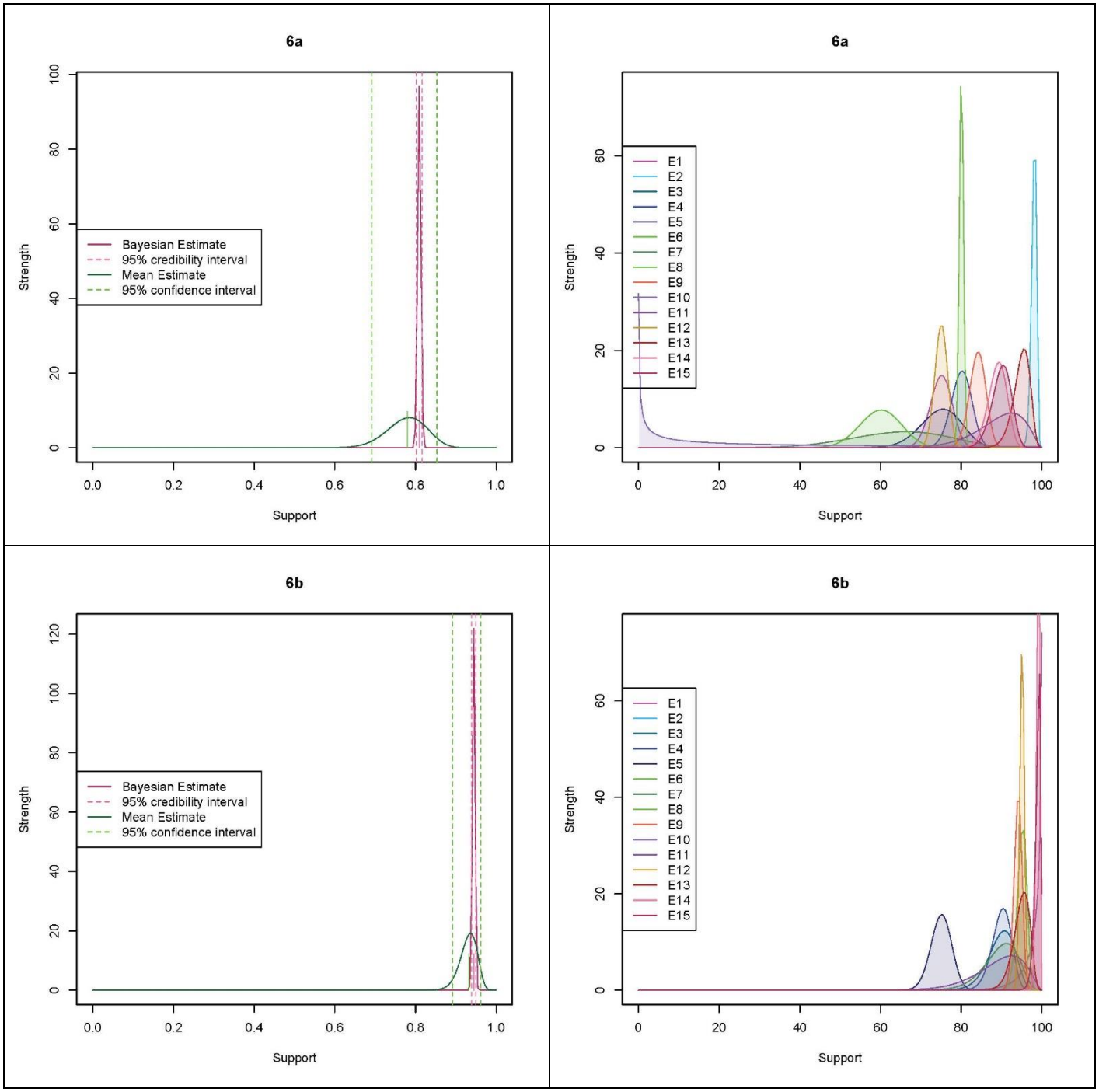
Figure S3: Consolidated and individual levels of support for inference-based conclusion statements 1-9. Correlated to statements in main text, Table 2.

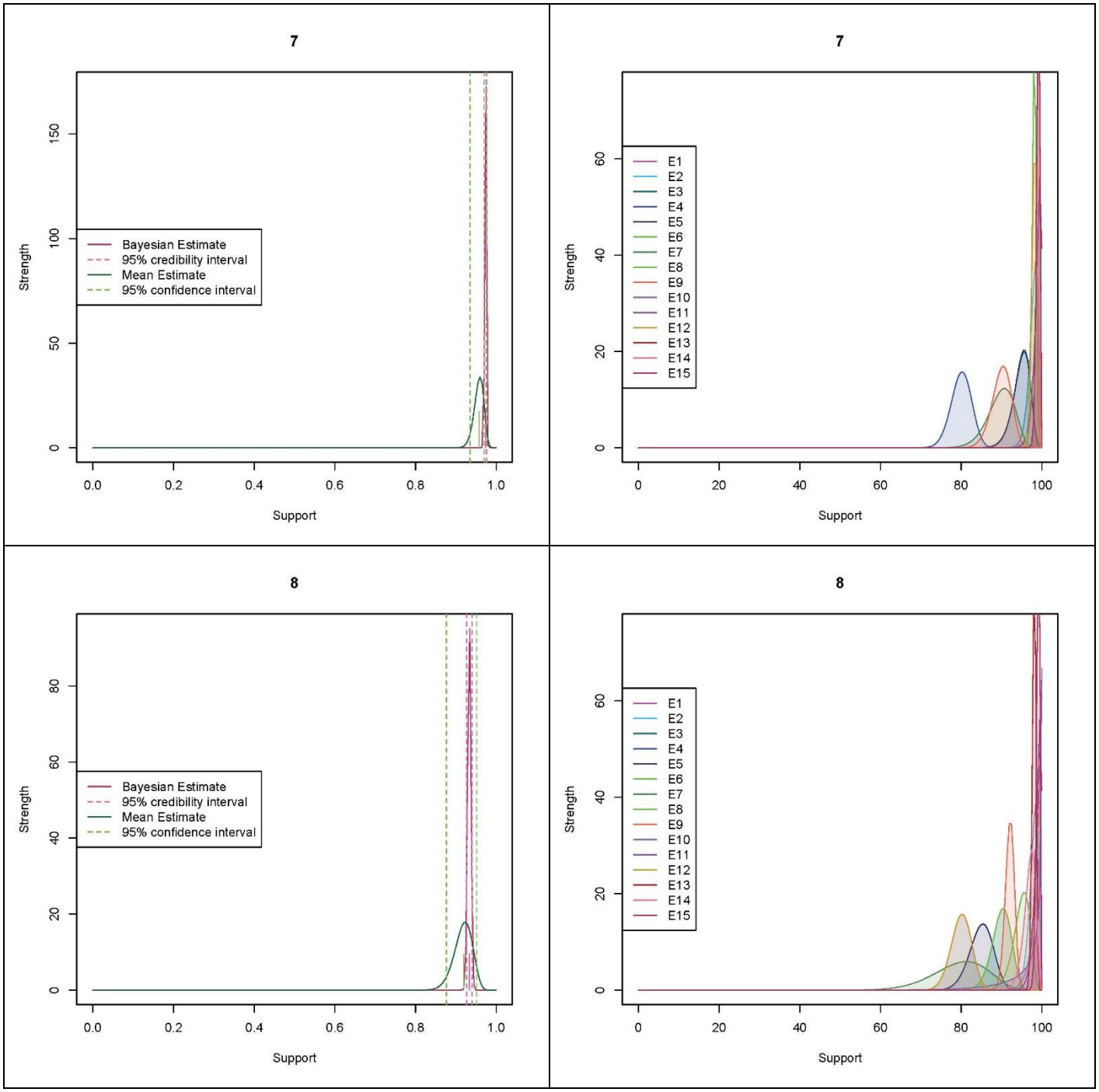
A. includes Bayesian and mean estimates of support, showing the strength of each method of consolidating individual expert ratings. **B.** represents individual expert ratings for level of support/agreement/confidence for each statement, including upper and lower values representing their confidence in their level of support. The 15 experts are represented at Expert 1, E1, through to Expert 15, E15.

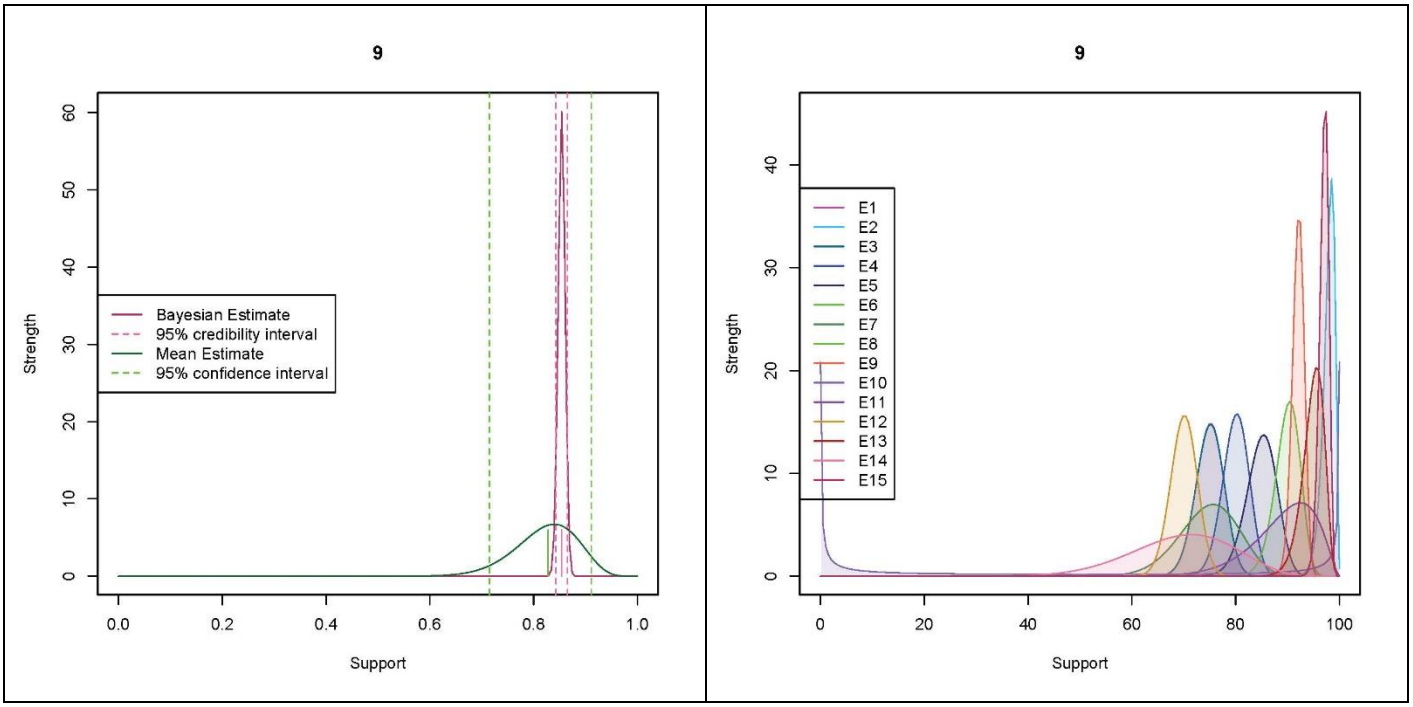



2
Strength
Support
Bayesian Estimate
95% credibility interval
Mean Estimate
95% confidence interval
2
E1
E2
E3
E4
E5
E6
E7
E8
E9
E10
E11
E12
E13
E14
E15
3
3


4
Strength
Support
Bayesian Estimate
95% credibility interval
Mean Estimate
95% confidence interval
4
Strength
Support
E1
E2
E3
E4
E5
E6
E7
E8
E9
E10
E11
E12
E13
E14
E15
5
Strength
Support
Bayesian Estimate
95% credibility interval
Mean Estimate
95% confidence interval
5
Strength
Support
E1
E2
E3
E4
E5
E6
E7
E8
E9
E10
E11
E12
E13
E14
E15


6a
Strength
Support
Bayesian Estimate
95% credibility interval
Mean Estimate
95% confidence interval
6a
Strength
Support
E1
E2
E3
E4
E5
E6
E7
E8
E9
E10
E11
E12
E13
E14
E15
6b
Strength
Support
Bayesian Estimate
95% credibility interval
Mean Estimate
95% confidence interval
6b
Strength
Support
E1
E2
E3
E4
E5
E6
E7
E8
E9
E10
E11
E12
E13
E14
E15


7
Strength
Support
Bayesian Estimate
95% credibility interval
Mean Estimate
95% confidence interval
7
Strength
Support
E1
E2
E3
E4
E5
E6
E7
E8
E9
E10
E11
E12
E13
E14
E15
8
Strength
Support
Bayesian Estimate
95% credibility interval
Mean Estimate
95% confidence interval
8
Strength
Support
E1
E2
E3
E4
E5
E6
E7
E8
E9
E10
E11
E12
E13
E14
E15


9
Strength
Support
Bayesian Estimate
95% credibility interval
Mean Estimate
95% confidence interval
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60
9
Strength
Support
E1
E2
E3
E4
E5
E6
E7
E8
E9
E10
E11
E12
E13
E14
E15
0
20
40
60
80
100
0
10
20
30
40

Literature Search Keywords and Methodology

Search parameters:

- English language articles only
- Consider presentations at international meetings be included for reference list review, where relevant and requested by authors
- Exclude:
    - Pediatrics/children/adolescents/infants
    - Haematologic cancers and cutaneous cancers (to be addressed in separate guidelines initiatives)
    - Animal studies and laboratory research *Note, basic science reviews may be consulted for some questions, where appropriate (e.g., question 1.1.5)
    - Medicinal herbs
    - Single case studies (excluded but categorize as case study for later reference, if needed). *Included case series and review articles of multiple case studies.

Psoriasis is defined as skin disease only. Where data is scarce, we will consult the literature for PsA and other inflammatory conditions where similar drugs are used (exclude abatacept).

General search strategy:

- Searches related to **general solid tumours population** were **scoping reviews (non-systematic) using PubMed and Google Scholar** to identify key articles of interest. Results were filtered by keywords and reference lists of key review articles were checked to identify additional articles of interest, where appropriate.
- Searches related to **(1) Psoriasis and solid tumours and (2) solid tumours and psoriasis drugs** (to capture studies in other populations) were **systematic PubMed searches (see below search terms and output)**. These searches were relevant to multiple clinical questions, and results were filtered using keywords to assign articles to the appropriate question.
- Authors could add additional articles for consideration at their discretion.

Search 1: Psoriasis AND Solid Tumours **PubMed, search date: 14 Dec 2021**		
No	**Search terms/description**	**Results** (No. of articles)
1	("solid tumour"[Title/Abstract] OR "solid tumor"[Title/Abstract] OR "solid tumours"[Title/Abstract] OR "solid tumors"[Title/Abstract] OR "malignant"[Title/Abstract] OR "malignancy"[Title/Abstract] OR "carcinoma"[Title/Abstract] OR "cancer"[Title/Abstract] OR "cancers"[Title/Abstract]	3,223,693
2	"psoriasis"[Title/Abstract]	45,130
3	1 AND 2	2827
4	Search No 3 Filters: search date 10 yrs	1399
5	Search No 4 Filters: search date 10 yrs	**1341**
	Excluded (reasons for exclusion below)	**1071**
	Non-relevant	973
	Case studies	42
	Cancer therapy-induced skin reactions	56
	Included for initial author review	**270**
	Common disease pathways/mechanisms	104
	Existing reviews/guidelines on similar topics	14
	General safety of psoriasis therapies (in psoriasis or other inflammatory diseases)	133
	Included for author review as possibly relevant	19

Search 2: Psoriasis Drugs/Classes AND Solid Tumours **PubMed, search date: 14 Dec 2021**		
No	**Search terms**	**Results** (No. of articles)
1	("solid tumour"[Title/Abstract] OR "solid tumor"[Title/Abstract] OR "solid tumours"[Title/Abstract] OR "solid tumors"[Title/Abstract] OR "malignant"[Title/Abstract] OR "malignancy"[Title/Abstract] OR "carcinoma"[Title/Abstract] OR "cancer"[Title/Abstract] OR "cancers"[Title/Abstract]	3,223,693
2	"Acitretin"[Title/Abstract] OR "Neotigason"[Title/Abstract] OR "Adalimumab"[Title/Abstract] OR "Cyltezo"[Title/Abstract] OR "Humira"[Title/Abstract] OR "Amgevita"[Title/Abstract] OR "Hulio"[Title/Abstract] OR "Hyrimoz"[Title/Abstract] OR "Idacio"[Title/Abstract] OR "Imraldi"[Title/Abstract] OR "Apremilast"[Title/Abstract] OR "Otezla"[Title/Abstract] OR "Deucravacitinib"[Title/Abstract] OR "Brodalumab"[Title/Abstract] OR "Kyntheum"[Title/Abstract] OR "Siliq"[Title/Abstract] OR "Certolizumab"[Title/Abstract] OR "Cimzia"[Title/Abstract] OR "Ciclosporin"[Title/Abstract] OR "Cyclosporin"[Title/Abstract] OR "Etanercept"[Title/Abstract] OR "Benepali"[Title/Abstract] OR "Brenzys"[Title/Abstract] OR "Enbrel"[Title/Abstract] OR "Erelzi"[Title/Abstract] OR "Eticovo"[Title/Abstract] OR "Tunex"[Title/Abstract] OR "Guselkumab"[Title/Abstract] OR "Tremfya"[Title/Abstract] OR "Infliximab"[Title/Abstract] OR "Avsola"[Title/Abstract] OR "Flixabi"[Title/Abstract] OR "Inflectra"[Title/Abstract] OR "Remicade"[Title/Abstract] OR "Remsima"[Title/Abstract] OR "Renflexis"[Title/Abstract] OR "Zessly"[Title/Abstract] OR "Ixekizumab"[Title/Abstract] OR "Taltz"[Title/Abstract] OR "Risankizumab"[Title/Abstract] OR "Skyrizi"[Title/Abstract] OR "Secukinumab"[Title/Abstract] OR "Cosentyx"[Title/Abstract] OR "Tildrakizumab"[Title/Abstract] OR "Ilumetri"[Title/Abstract] OR "Ilumya"[Title/Abstract] OR "Ustekinumab"[Title/Abstract] OR "Stelara"[Title/Abstract] *Note: The following biosimilar terms were not found in PubMed: Davictrel, Nepexto, Omvyence*	48,704
3	1 AND 2	3466
4	Search No 3 Filters: Search date 10 yrs	1433
5	Search No 4 Filters: English	**1390**
	Removing duplicates from (N=1343) Search No 5 NOT Search 1 (Psoriasis AND Solid Tumours)	**940**
	Excluded (reasons for exclusion below)	**820**
	Non-relevant	674
	Case studies	49
	Cancer therapy-induced adverse events	97
	Included for author review	**120**
	Transplant literature reviews	9
	General safety of psoriasis therapies (in psoriasis or other inflammatory diseases)	93
	Included for author review as possibly relevant	18

Final articles filtered for author review. Included articles from searches 1 and 2 above (N=390) were filtered by keywords (to corresponding clinical questions as per table S2) and included for author review.

Most of these articles were related to general safety of psoriasis treatments (excluding patients with TSTs). Additional articles were added from scoping review and by authors, as required.

Section/Clinical Question	**No. of articles**
1.1.1 Survival (3 from searches, 27 additional added from scoping review)	3 + 27
Final referenced by authors for data summaries	**15**
1.1.2.1 Recurrence/Metastasis (5 from searches, 47 additional from scoping searches)	5+ 47
1.1.2.2 Systematic reviews/pooled analysis (Psoriasis and PsA)	62
1.1.2.2 Clinical trials/real world/cohort studies (Psoriasis and PsA)	69
1.1.2.2 Systematic reviews/pooled analysis (Other indications)	43
1.1.2.2 Clinical trials/real world/cohort studies (Other indications)	62
1.1.3 Infection (General TST) from scoping search	26
1.1.3.2 Infection (psoriasis and TSTs)	14
1.1.2 and 1.1.3 Final referenced by authors for data summaries (combined due to overlap of studies across sections)	**63**
1.1.4 Inflammation (general scoping search on inflammation and cancer)	24
No conclusions could be made based on this evidence. No articles included.	0
1.1.5 Immune surveillance, immunosenescence, immunomodulation (from scoping review)	6 + 4 + 6
Common disease pathways (from literature searches above)	105
Final referenced by authors for data summaries	**86**
1.1.6 Transplant (scoping searches and articles added from literature searches above)	
Pre-transplant malignancy	16
Final referenced by authors for data summaries	**10**
Post-transplant malignancy	32
Final referenced by authors for data summaries	**12**

References (for above sections)

1. Mastorino L, Dapavo P, Avallone G, *et al.* Biologic treatment for psoriasis in cancer patients: should they still be considered forbidden? *J Dermatolog Treat* 2021;:1–8.

2. Valenti M, Pavia G, Gargiulo L, *et al.* Biologic therapies for plaque type psoriasis in patients with previous malignant cancer: long-term safety in a single- center real-life population. *J Dermatolog Treat* 2021;:1–5.

3. Kahn JS, Casseres RG, Her MJ, Dumont N, Gottlieb AB, Rosmarin D. Treatment of Psoriasis With Biologics and Apremilast in Patients With a History of Malignancy: A Retrospective Chart Review. *J Drugs Dermatol* 2019;**18**.

4. Fagerli, KM et al. Risk of Cancer in Patients with Severe Psoriatic Arthritis Requiring Tumour-Necrosis Factor Alpha Inhibition. 2014 ACR/ARHP Annual Meeting abstract No. 1848. .

5. 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.

6. Micic D, Komaki Y, Alavanja A, Rubin DT, Sakuraba A. Risk of Cancer Recurrence Among Individuals Exposed to Antitumor Necrosis Factor Therapy: A Systematic Review and Meta-Analysis of Observational Studies. *Journal of Clinical Gastroenterology* 2019;**53**:e1–11.

7. Shelton E, Laharie D, Scott FI, *et al.* Cancer Recurrence Following Immune-Suppressive Therapies in Patients With Immune-Mediated Diseases: A Systematic Review and Meta-analysis. *Gastroenterology* 2016;**151**:97-109.e4.

8. Raaschou P, Söderling J, Turesson C, Askling J. Tumor Necrosis Factor Inhibitors and Cancer Recurrence in Swedish Patients With Rheumatoid Arthritis. *Ann Intern Med* 2018;**169**:291–9.

9. Raaschou P, Simard JF, Neovius M, Askling J, Anti-Rheumatic Therapy in Sweden Study Group. 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. *Arthritis & Rheumatism* 2011;**63**:1812–22.

10. Xie W, Yang X, Huang H, Gao D, Ji L, Zhang Z. Risk of malignancy with non-TNFi biologic or tofacitinib therapy in rheumatoid arthritis: A meta-analysis of observational studies. *Seminars in Arthritis and Rheumatism* 2020;**50**:930–7.

11. 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.

12. 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 (Oxford)* 2016;**55**:2033–9.

Supplementary Data Summaries and Statements for Author Voting: The below summaries are unformatted versions of the content that authors were provided with to accompany their voting for statements. References are also unformatted.

Contents

Abbreviations

CsA, cyclosporine A

CTCL, cutaneous T-cell lymphoma

Il-12/23i, interleukin 12/23 inhibitor (includes UST, ustekinumab)

Il-23i, interleukin 23 inhibitor (includes GUS, guselkumab; RIS, risankizumab; TIL, tildrakizumab)

IL-17i, interleukin 17 inhibitor (includes SEC, secukinumab; BRO, brodalumab; IXE, ixekizumab)

JAKi, janus kinase inhibitor

MOA, mechanism of action

MTX, methotrexate

PDE4i, phosphodiesterase-4 inhibitor

SCC, squamous cell carcinoma

SOT, solid organ transplant

TNFi, tumour necrosis factor alpha inhibitor (includes ADA, adalimumab; CTZ, certolizumab pegol; ETN, etanercept; INF, infliximab, GOL, golimumab)

TYK2i, Tyrosine kinase 2 inhibitor (a type of JAKi, includes DEU, deucravacitinib)

TST: treated solid tumours

VEGFi, vascular endothelial growth factor inhibitor

PART A: Introduction/General Concepts/Framing Arguments

Patients with Treated Solid Tumours (TST) and Psoriasis Treatment

- In patients with past or actively TST, dermatologists are concerned about the immunosuppressive nature of psoriasis treatments, and possible augmentation of recurrence or progression. Drug-interactions are beyond the scope of the present investigation.
- Focusing on patients with solid tumours (excluding hematopoietic and cutaneous malignancies), we sought to provide guidance on the main guideline question "Are responses (including drug related adverse effects and benefits) to systemic psoriasis therapies in patients with treated solid-tumours (TST) similar to the general psoriasis population?" Answering this question proved complex due to the limited data and heterogeneity of the TST patient population. After a careful review of the literature and multiple revisions of clinical questions and data considered, we provide a framework for treating patients with previously TST that can be used to guide HCP and patient discussions.
- **Caution about categorical classifications and use of term "immunosuppressive agents" for psoriasis.** Immunomodulatory agents are categorized as immunosuppressant, instead we consider broad vs specific immunosuppression. There are many drugs that are functionally immunosuppressive even though they aren't classified as such. Effects are dose dependant and pathway dependant and can block or activate.
- **General caution for direct evidence:** Caution regarding reporting bias for the limited evidence available from case reports and series. RCTs exclude patients with a history of cancer in the past 5 yrs, and active malignancy. Observational studies of cancer incidence rates in psoriasis patients have biases.
- **Limited direct evidence exists in support of risk.** Nonetheless, clinical decisions are required. Consequently, we reviewed indirect evidence relevant to the immune status of patients with TST in order to guide treatment decisions. Since the evidence reviewed was low-level (case studies and series) and/or indirect, levels of evidence and grading of evidence are not ascribed to the recommendations herein, and the recommendations/statements are made based a review of the totality of evidence.

Patients with treated Solid Tumours (TST) and the Cancer Treatment Landscape

- Patients with treated solid tumours (TST) are a highly heterogeneous population with an increased risk of new or recurrent malignancies compared to the general population.
  - Outcome data is skewed by country, access to resources and socioeconomic status
  - Socioeconomically deprived patients: higher loss of life expectancy especially with lung and stomach cancers in UK compared to non-deprived patients (Syriopoulou et al. Br J Cancer 2017), while stomach cancer outcomes are better in Japan.
- Absolute numbers of TST patients are rising steadily with aging populations and population growth. The age adjusted incidence rates of several TSTs are declining as a result of public health measures, lifestyle modification (especially avoidance/cessation of cigarette smoking), and better treatments for cancer and causative infectious diseases.

- It is important to note that survivors of TST are at increased baseline risk for subsequent new primary neoplasms and the overall cancer rate in survivors is higher than the general population (NCN Survivorship Guidelines 3.2021). Healthy lifestyle and behavioral counselling are important, as well as screening for treatment-related AEs depending on type and intensity of anticancer treatment (radiation and chemotherapy).
    - SEER program analysis showed patients with previous malignancy have 14% increased risk of new malignancy in future than general population (Curtis REFM, Ron E. New malignancies among cancer survivors: SEER cancer registries, 1993-2000. NIH Publ. 2006:5 https://seer.cancer.gov/archive/publications/mpmono/MPMonograph_complete.pdf)
- Potential lifespans are reduced due to delayed cancer treatment toxicities (especially radiation therapy and certain chemotherapy regimens), second cancers, and comorbidities related to common risk factors
    - TST survivors have generally poorer health and more cardiovascular disease (some overlapping risk factors for both cancer and heart: obesity, smoking, inactivity, diet). E.g., Patients who are treated for lung cancer will have an increased risk of cardiac diseases related to smoking as a risk factor for both
    - E.g., patients who receive chemotherapy with alkylating agents (doxorubicin, anthracyclines) will have mildly increased lifetime risk of leukemia depending on dose received (from 0.5-1% increase)
- Clinicians across medical specialties will face increasing numbers of patients with a history of TSTs. Additionally, there is a trend in cancer treatment toward greater reliance on ICI, more focused or less exposure to radiation therapy, and less chemotherapy. These patients will have inherent risk for cancer-related death regardless of psoriasis status and treatment choices.
- **An understanding of the patient's cancer prognosis (Table 1: Common Solid Tumours and Survival by Stage at Diagnosis) and immune competence (Table 2: Immune Recovery Post-treatment for Solid Tumours, Stratified by Treatment Class) provides some context for discussing risk and benefit of therapy for inflammatory disorders.**
    - Disease-free survival is difficult to summarize because there are different outcomes from phase 3 clinical trials depending on the population studied (location, socioeconomic status, trial design including frequency of restaging etc.). Different clinical trials/databases use different staging and staging systems evolve and are updated frequently, so harder to interpret longer spans of data. Real world databases do not have encoded staging.
    - Most data does not have long-term follow-up beyond 10-20yrs (except SEER).
    - Cancer treatment is increasingly focused on specific oncogenic mutations, overexpression of key drivers, and immune signatures rather than the tissue of origin, and consequently similar types of therapies are increasingly being received across cancer types.
    - For patients with actively TST, the decision to initiate systemic therapy for psoriasis should be made on a case-by-case basis, considering the cancer prognosis, cancer therapy received, and potential adverse effects of that treatment.
    - **Accordingly, expert opinion is that immune reconstitution following cancer treatment depends more on the type of cancer therapy received than on the type of cancer.** The timing of systemic psoriasis therapy initiation after cancer treatment and effectiveness of psoriasis treatment will depend partly on immune reconstitution post-cancer therapy.

        - Note that ICI treatments may themselves cause or exacerbate psoriasis and, while many types of chemotherapy often induces remission of psoriasis, a rebound can occur post-chemo completion.
    - **Clinically, immune reconstitution during/after cancer treatment is primarily assessed by normalization of cell counts (see table 2).**
    - CAVEAT: Although white blood cell count recovery typically occurs within 1 month (table 2), it is important to note that many forms of cytostatic and broadly immunosuppressive chemotherapy agents may reduce lymphocyte and neutrophil competence, even after cell counts are normalized. Some studies indicate that CD4 T cells may be depleted beyond 1-month post-therapy, however the clinical significance to our topic is not known and this was not explored in detail here.
        - While CD4 lymphopenia is mostly detected in advanced or metastatic stages, functional impairment of immune cells (NK, monocytes, memory CD4+ and CD8+ T cells) can be detected in patients with localized primary tumors (BC, colon carcinoma, HCC). Ménétrier-Caux 2019 https://jitc.biomedcentral.com/articles/10.1186/s40425-019-0549-5
        - Flow-cytometry to assess circulating lymphocyte levels and phenotypes in 88 primary breast cancer patients before chemotherapy and at time-points from 2 weeks to 9 months after chemotherapy completion. **Levels of all cells recovered to some extent, although B and CD4+ T cells remained significantly depleted even 9 months post-chemotherapy ($p < 0.001$).** Phenotypes of repopulating B and CD4+ T cells were significantly different from, and showed no sign of returning to pre-chemotherapy profiles. Verma et al. Breast Cancer Research. 2016 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4727393/
- For patients with previously or actively TST requiring systemic therapy for psoriasis, a risk-benefit conversation with the patient that considers cancer prognosis, as well as type and intensity of cancer therapy received, should support all treatment decisions on a case-by-case basis.
- For patients with a poor prognosis, the quality-of-life benefits of treating psoriasis may outweigh the theoretical risks.

Table 1: Common Solid Tumours and Survival by Stage at Diagnosis

Tumours and stage at diagnosis	5-Year Relative Survival*, (%)
Breast cancer[†]	
Localized	99.0
Regional	85.8
Distant	29.0
Lung and Bronchus cancer[§]	
Localized	59.8
Regional	32.9
Distant	6.3
Colorectal cancer[§]	
Localized	90.6
Regional	72.2
Distant	14.7
Prostate cancer[¶]	
Localized	100.0
Regional	100.0
Distant	30.6
Stomach cancer[§]	
Localized	69.9
Regional	32.4
Distant	5.5
Esophageal cancer[§]	
Localized	46.4
Regional	25.6
Distant	5.2
Liver & Intrahepatic Bile duct cancer[§]	
Localized	35.3
Regional	12.3
Distant	2.7

*SEER reports relative survival, an estimate of the percentage of patients who would be expected to survive the effects of their cancer. It excludes the risk of dying from other causes. Based on data from SEER 18 areas from 2011-2017, all races, [†]females only, [§]both sexes, [¶]males only.

Localized, Cancer is confined to the primary site, i.e., organ of origin; **Regional**, Malignant cancer that extends beyond the primary site involving regional lymph nodes and surrounding tissue; **Distant**, malignant cancer that has metastasized to distant organs, tissues and distant lymph nodes

Table 2: Immune Recovery Post-treatment for Solid Tumours, Stratified by Treatment Class

Cancer Drug Classes	Expert opinion
Chemotherapy	Patients receiving chemotherapy will experience varying degrees of short-term impaired immunity, depending on the chemotherapy regimen used, the extent of steroid support required, and baseline patient characteristics[a]. Proliferating hematopoietic stem and progenitor cells (HSPCs) in the bone marrow are particularly susceptible to chemotherapy-induced damage (Lyman 2021). White blood cell count nadirs depend on the antineoplastic agent used and typically occur around 10 to 14 days after administration of therapy, with complete recovery by day 21 to 28 (Barreto 2014)[b].
Immune checkpoint inhibitors (e.g., CTLA or PD1-PDL1 inhibitors)	Do not usually cause immune deficits[c]. In contrast, they are designed to stimulate immune function by blocking inhibitory checkpoints, such as CTLA4 and PD1-PDL1. The extended duration of the therapeutic effects of ICIs (and their auto-immune toxicities) often far surpasses their pharmacokinetic half-life and is highly variable (Brahmer 2021, Maritaz 2022).
Radiation	Advances in radiation for the treatment of solid tumours have lead to improved tumour targeting with reduced impact on normal tissues. Immune deficits are uncommon post-treatment[d] (Kumari 2020).
Endocrine and targeted therapies (e.g., TKi, VEGF-targeting angiogenesis inhibitors)	Most of these therapies are not expected to have significant effects on immune deficits and/or immune reconstitution. Some kinase inhibitors can cause neutropenia and are taken daily for years (Jiang 2022, Ren 2017).

[a]In the setting of non-curative/palliative chemotherapy, patients may have some permanent immune suppression related to the chronic malignancy itself, receipt of multiple lines of chemotherapy, and long-term palliative use of steroids, with cumulative effects on neutrophils and neutrophil recovery (more suppression, longer time to recovery and sometimes long-lasting modest neutropenia). Further, patients may have had palliative radiation, and if a larger extent of their marrow is in the radiation field, the myelosuppression/neutropenia from chemotherapy may be more severe and long-lasting (Wang 2006).

[b] Some reports indicate that it could take up to 1 year for CD4+ T cells to recover. The repopulating cells have a reduced proportion of naïve cells and an increased memory component, however clinical significance to our topic is not known (Verma 2016 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4727393/pdf/13058_2015_Article_669.pdf).

[c]Some ICI patients require immunosuppressive therapy with long-term corticosteroids or mycophenolate to treat immune-related adverse events (Brahmer 2021).

[d]Should more than 1/3 of skeletal marrow reserve be radiated (mostly spine, pelvis, sternum), long-lasting cytopenia may occur. Moreover, radiation-suppressed marrow reserve may result in greater susceptibility to severe myelosuppression with chemotherapy (Wang 2006). At higher doses of radiation, immune suppression occurs, while lower levels of radiation have subtle but persistent immune function alterations that can be immunosuppressive or immunostimulatory (Carvalho 2018, Lumniczky 2018, Lumniczky 2021). In a small series of irradiated Stage I-III breast cancer patients, decreased TNF and lymphocyte counts persisted after ionizing radiation (Standish 2008).

Considering evidence from immunosuppressed transplant patients

- We can glean indirect evidence from transplant patients (with and without a history of cancer) who receive broadly immunosuppressive agents (see appendix 1.1.5.1 and 1.1.5.2 for summary of all evidence considered here).
- Cancer risk and cancer-related mortality is increased in solid organ transplant patients treated with broadly immunosuppressive agents, mainly due to the effects of immunosuppression and speculatively from a related decrease in cancer immunosurveillance and immunologic control over oncogenic infections/reactivation of latent infections.
    - The **broadly immunosuppressive** agents implicated in post-transplant malignancy **do not affect the same pathways** as **specific immunomodulating** agents used in psoriasis, and similar concerns are not warranted.
    - From the SOT literature, we can gather some of the reasons for increased cancer risk in immunosuppressed patients (i.e., the effects of immunosuppression, immunosenescence, increased susceptibility to oncogenic infections and the differential effects of these pathways on different types of cancer) and this helps frame the subsequent questions for psoriasis patients:
        - Is there evidence that the drugs/pathways targeted by psoriasis treatments are associated with an increase/decrease/neutral association with common solid tumours (question 1.1.4)? *(General conclusion: inconclusive evidence, depends on tumour microenvironment)*
        - What's the role of immunosenescence, immunosurveillance, immunomodulation in cancer and do psoriasis therapies affect these pathways question (1.1.4)? *(General conclusion: inconclusive evidence)*
        - Are infections, specifically oncogenic infections, increased with psoriasis treatments (question 1.1.3)? *(General conclusion: no evidence that oncogenic infections are increased from review below. Other infections may be increased which has implications for actively TST)*
- Some general comments to be made from transplant literature – role of immunosuppressive drugs in post-transplant malignancy and proposed MOAs:
    - SOT recipients have a higher risk of developing certain types of cancer (Kaposi sarcoma, nonmelanoma, skin cancer, non-Hodgkin lymphoma (NHL), Liver, Anus, Vulva, Lip)
    - Malignancy post-transplant is primarily due to the effects of immunosuppression (from treatment with broadly immunosuppressive agents) and speculatively from related decrease in cancer immunosurveillance and immunologic control over oncogenic infections/reactivation of latent infections.
    - There are theoretical concerns for immune suppression in viral transformative cancers such as HPV or EBV that may warrant additional caution (see below MOA section on following page).
- Pre-transplant malignancy is associated with an increased risk of all-cause mortality in SOT transplant patients. It is unclear if modified immunosuppressive regimens lead to increased all-cause mortality in SOT transplant patients. The mortality risk in SOT-transplant patients is highly influenced by type of malignancy, grade/stage, tumor specific characteristics, projected overall survival, time to transplant, and age.

General concepts of immunosuppression, immunomodulation, immune surveillance, and senescence in the development of malignancies:

- Chronic inflammation is carcinogenic and associated with various cancers (see appendix below for references). Chronic inflammation results in T-cell exhaustion thus providing a permissive environment for tumour development, growth, and metastasis.
    - IL-17 and Th17 cells are often associated with chronic inflammatory processes including those associated with malignancies.
    - T-cell exhaustion resulting from immunosenescence, chronic infection, or chronic inflammation provide an opportunity for tumour development, growth, and metastasis. Th17, IL17, IL23, and TNF are associated with chronic inflammation. The conclusion is that the treatments we use for psoriasis, except for CsA and UVB which promote the development of cutaneous SCC, are neither inducers nor promoters (of cancer) and may provide very small benefit by reducing the local inflammatory burden.
    - From a MOA perspective: with the exception of CsA and UVB which promote the development of cutaneous SCC, the treatments we use for psoriasis are neither inducers nor promoters of cancer pathways (see inference-based statements for psoriasis drug classes, below) and may provide very small benefit by reducing the local inflammatory burden. There is some uncertainty as the risk is cumulative and intervention at a late stage cannot result in a significant benefit (see Ridker CANTOS NEJM). The reported reduction in lung cancer is an incidental finding an very unlikely to be correct given the short observation period.
    - Brief note considering MOA of oncogenic viruses that cause cancer (HBV, EBV, KS, HPV) from working group summary:
        - Viral infections (HBV and HCV) alter cellular signalling. HBV in part by integrating viral DNA into host DNA, and both through viral proteins causing disruptive cellular signalling (chromosomal instability). Associated chronic inflammation resulting from immunological responses endeavouring to constrain the persistent infection, results in fibrosis and T-Cell exhaustion (see above) both of which result in a more permissive environment for the development, growth, and metastasis of malignancy. Chronic inflammation may result in chromatin breaks.
        - There is a small, theoretical risk of causing active infection with HBV but an anticipated benefit in treating patients infected with HCV with TNF antagonists (no references provided here).
        - HPV increases the risk of carcinogenesis by mechanisms similar to HBV and HCV.

Active Cancer Treatment (Brief mention)

- In general, there is a paucity of data on psoriasis treatments in patients with active treatment of solid tumours. This topic is complex and multi-factorial.
- For patients with actively TST, therapeutic decisions should be made on a case-by-case basis considering the cancer prognosis and cancer treatment being received.

- Chemotherapy may have broad immunosuppressive effects on inflammatory pathways and thereby suppress psoriasis. Consequently, psoriasis treatment may not be needed during active chemotherapy. Additionally, systemic corticosteroids may be used to control tumour related or chemotherapy-related adverse effects like nausea.
- "…risk of infection in patients with solid tumors, and the presence of multiple risk factors in the same patient is not uncommon. These include obstruction (most often caused by progression of the tumor), disruption of natural anatomic barriers such as the skin and mucosal surfaces, and treatment-related factors such as chemotherapy, radiation, diagnostic and/or therapeutic surgical procedures, and the increasing use of medical devices such as various catheters, stents, and prostheses. Common sites of infection include the skin and skin structures (including surgical site infections), the bloodstream (including infections associated with central venous catheters), the lungs, the hepato-biliary and intestinal tracts, and the urinary tract, and include distinct clinical syndromes such as post-obstructive pneumonia, obstructive uropathy, and neutropenic enterocolitis" Rolston et al. 2017. Infections in Cancer Patients with Solid Tumors: A Review. Infection Dis Ther. 10.1007/s40121-017-0146-1
- Need to consider effects of additive immunosuppression with multiple agents (more traditional chemotherapy):
  - Inferring from the info on psoriasis patients systemic agents: For TNFi, there is increased risk of bacterial (eg pneumonia) and skin infections (cellulitis), and potentially sepsis, which is an issue with cancer patients on chemotherapy given that skin and surgical site infections are common in cancer patients as well as bacteremia and sepsis (sometimes due to catheters/indwelling devices, etc.), (Rolston et al) and therefore theoretical heightened risk with both agents on board
  - Most TNFs and some biologics will reactivate TB, etanercept will not. Chemotherapy can also lead to TB reactivation.
  - IL-17 inhibitors will decrease interface between mucosal surfaces and candida, decreasing the integrity of the immune response that keep candida in check on mucosal surfaces (the vaginal mucosa is an exception in that there appears to be no dependence on IL-17). **The steroids given for nausea with chemo is what causes candida. If they are on steroids they are likely not needing treatment for RA, AD, Ps etc.

Timing Post-Cancer Treatment of Psoriasis Systemic Treatment Initiation

- **Is there any evidence to suggest that intervening earlier than 5 years will change overall survival?**
  - Theoretical concerns about increased risk of recurrence if patients with TST are treated early with immunosuppressive agents
  - There is no evidence on whether intervening earlier than 5 years will or will not change OS or cancer recurrence (from Capocaccia 2015 Annals of Oncology https://doi.org/10.1093/annonc/mdv131 :
    - Future life expectancy improves the further out from diagnosis, for survivors, slowly approaching general population life expectancy over time, fig 2.
    - Based on below curves, the later the onset of cancer, the closer to a normal life expectancy one can expect (reflective of Poisson process, event rates are strongly correlated with susceptibility)
    - There is a higher risk of recurrence in the first-year post-cancer (part of nature of malignancy)

- **Secondary question is – is there evidence that suggests intervening earlier than 5 years with psoriasis treatments will change the shape of these curves?**
- No evidence to suggest whether it will or will not (some evidence from RA literature that it it will not for TNFi)
- It is unlikely that any of the treatments we use for psoriasis will alter the risk of recurrence, i.e. alter the shape or slope of the curves for solid tumours.

- The overly cautious approach suggested by others (wait 5 years) is likely not warranted, and risk-benefit discussion with patients should guide treatment decisions
- Shelton 2016 (16 studies in IBD, RA, and only 1 pso study): "Random effects meta-analysis found similar pooled incidence values for new or primary cancers when immunosuppression was initiated within 6 years (33.6 per 1000 p-y for immunomodulatory agents and 43.7 per 1000 p-y for TNFi agents) vs more than 6 years after the index cancer (32.9 per 1000 p-y for immune-modulatory agents, P=0.86; and 21.0 per 1000 p-y for TNFi agents, P=0 .43)."
- According to expert recommendations Al-adra et al. Am J transplantation 2021 https://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.16318, many TST patients with a good prognosis can receive solid organ transplant (SOT) without a wait time, or with minimal wait time:
  - The guidelines are based on type of malignancy (breast, colorectal, anal, prostate, renal bladder, gyne), risk/stage, 5-year survival rate or recurrence free 5-year survival (except overall survival for prostate cancer and 2-year local recurrence from baseline trans urethral resection of bladder tumor). There are also cancer specific considerations that may determine lower or higher risk disease.

    CAVEATS:
    - In general, patients with high-risk disease as determined by stage (usually stage 4/metastatic disease) would not be SOT candidates.
    - Patients with cancer selected for transplant usually have good cancer prognosis which limits the ability to make strong biological and clinical inferences from comparisons with heterogeneous group of other patients with cancer in general population
    - HPV-related anal cancer where the risk of immunosuppression may lead to negative outcomes.

Indirect evidence (relevant for all psoriasis patients, regardless of treatment class):

- Pre-transplant malignancy is associated with an increased risk of all-cause mortality in SOT patients. It is unclear if modified immunosuppressive regimens lead to this outcome. Mortality risk is highly influenced by type of malignancy, grade/stage, tumor specific characteristics, projected overall survival, time to transplant, and age (in some studies), suggesting that increased risk is not a consequence of SOT (see appendix 1.1.5)

- Previously TST patients with a good prognosis can receive transplant and subsequent immunosuppressive therapy with similar outcomes as the general SOT population. Similar conclusions can be inferred for patients with psoriasis.
    - None of the therapies used in the advanced therapies for inflammatory conditions are as broadly immunosuppressive as anti-rejection regimens.
- Patients with a history of TST and a high-risk of recurrence or progression are either not considered candidates for transplantation or are considered after 3-5 years post-cancer. These patients have an inherent increased risk for progression and recurrence associated with their cancer and the psoriasis therapy is unlikely to change the prognosis. The quality-of-life benefits of treating psoriasis may outweigh the perceived risks, and a risk-benefit conversation with the patient should support treatment decisions.

PART B: Supporting Evidence for Inference-based Conclusion Statements

Statement 1: Baseline cancer risk in patients with psoriasis

1. a. In patients with psoriasis, the risk of cancer appears to be slightly increased for keratinocyte cancer (i.e., non-melanoma skin cancer) and possibly cutaneous T-cell lymphoma. The baseline risk of cancer in patients with psoriasis is difficult to assess due to inadequately powered studies with short follow-up times and confounding factors: prior use of phototherapy and immunosuppressive therapy.
1. b. When controlling for modifiable risk factors, the risk of cancer and mortality from cancer is similar in patients with psoriasis to that of the general population. Psoriasis is not causally associated with an increased risk of solid tumours. The risk of cancer is linked to modifiable risk factors including cigarette smoking and ultraviolet light exposure.

Caveats:

- Consider confounding effects of:
  - phototherapy and sun exposure
  - modifiable risk factors (e.g., smoking)
  - Aging (as age increases, SCC increases)
- Diagnostic confusion for CTCL – although patients may have both CTCL and psoriasis, there may be misdiagnosis. There is no direct evidence of a causal or direct relation between psoriasis and CTCL.
- Outmoded therapeutic options may be responsible for excess occurrence in cancer that may be seen
- Additional caveats to be populated from survey

Summary of Evidence:

Direct Evidence in Psoriasis:

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**

- systemic review and meta-analysis of over 2 million patients shows the risk of cancer overall as slightly increased in patients with psoriasis, particularly keratinocyte cancer (i.e.NMSC) and lymphomas (RR 1.21 CI 1.11-1.33) Vaengebjerg 2020 - baseline risk of cancer in PsO patients difficult to assess due to confounding from phototherapy and immunosupressive therapy (Geller 2018) - From UK retrospective cohort study looking at incident cancer diagnosis that included 198,366 patients with psoriasis (Chiesa Fuxench 2016): The association between psoriasis and cancer, albeit small, was present in this cohort of patients with psoriasis. This association was primarily driven by NMSC, lymphoma, and lung cancer. - The adjusted hazard ratios (aHRs) with 95% CIs for any incident cancer excluding nonmelanoma skin cancer (NMSC) were 1.06 (95% CI, 1.02-1.09), 1.06 (95% CI, 1.02-1.09), and 1.08 (95% CI, 0.96-1.22) in the overall, mild, and severe psoriasis group. The aHRs for incident lymphoma were 1.34 (95% CI, 1.18-1.51), 1.31 (95% CI, 1.15-1.49), and 1.89 (95% CI, 1.25-2.86); for NMSC, 1.12 (95% CI, 1.07-1.16), 1.09 (95% CI, 1.05-1.13), and 1.61 (95% CI, 1.42-1.84); and for lung cancer, 1.15 (95% CI, 1.03-1.27), 1.12 (95% CI, 1.01-1.25), and 1.62 (95% CI, 1.16-2.28) in the overall, mild, and severe psoriasis groups, respectively. No significant association was seen with cancer of the breast, colon, prostate, or leukemia.	Vaengebjerg S et al. 2020. Prevalence, Incidence, and Risk of Cancer in Patients With Psoriasis and Psoriatic Arthritis. JAMA Dermatol. Geller S et al. 2018. Malignancy risk and recurrence with psoriasis and its treatments: a concise update. Am J Clin Dermatol. Chiesa Fuxench Z.C. et al. 2016. https://pubmed.ncbi.nlm.nih.gov/26676102/ JAMA Dermatol.
• Risk of malignancy and risk of hospitalized infectious events (HIEs) from retrospective cohort study utilized data from MarketScan(®) databases (40 788 psoriasis patients). Cohorts included adult general population (GP), patients with psoriasis, and patients with psoriasis treated with nonbiologics, adalimumab, etanercept, infliximab or phototherapy • Malignancy rates were higher in patients with psoriasis than the GP, but these treatments did not appear to increase malignancy risk. patients with psoriasis were shown to have increased risk for some solid cancers (respiratory tract cancer, upper aerodigestive tract cancer, urinary tract cancer, liver cancer), haematological cancers (non-Hodgkin lymphoma) and skin cancers (squamous cell carcinoma, basal cell carcinoma) o Outcomes included incidence rates (IRs) per 10 000 person-years observation (PYO) for all malignancies excluding nonmelanoma skin cancer (NMSC), lymphoma, NMSC, and per 10 000 person-years of exposure (PYE) for HIEs. RESULTS: Incidence rates [95% confidence interval (CI)] for all malignancies except NMSC were 129 (127-130) and 142 (135-149) for GP (PYO = 51 071 587) and psoriasis (PYO = 119 432) cohorts, respectively; 10·9 (10·5-11·3) and 12·9 (10·9-14·8) for lymphoma; and 145 (144-147) and 180 (173-188) for NMSC. Rates for all malignancies excluding NMSC were similar among treatments but variable for lymphoma and NMSC. IRs (95% CI) for HIEs were 332 (256-408) for the	Kimball, AB et al. 2015. Cohort study of malignancies and hospitalized infectious events in treated and untreated patients with psoriasis and a general population in the United States. BJD. https://doi.org/10.1111/bjd.14068

nonbiologic cohort (PYE = 3528); 288 (206-370) for etanercept (PYE = 6563); 325 (196-455) for adalimumab (PYE = 2772); 521 (278-765) for infliximab (PYE = 1058); and 334 (242-427) for phototherapy (PYE = 1797). IRs for HIEs were lowest for etanercept and higher in patients on baseline systemic corticosteroids across treatment cohorts. CONCLUSIONS: Malignancy rates were higher in patients with psoriasis than the GP, but these treatments did not appear to increase malignancy risk.	
• Therapy has no effect, except NMSC which is not the question in this work: • Using a US claims database, we identified a general population, a psoriasis cohort, and four treatment cohorts [non-biologic systemics, etanercept, other TNF blockers (adalimumab, infliximab) and phototherapy] to assess the incidence of lymphomas, nonmelanoma skin cancer (NMSC), all malignancies (excluding NMSC), and HIEs, standardized for age and sex. RESULTS: Among 40 987 patients with psoriasis, 11% were prescribed non-biologics, 15% etanercept, 6% other TNF blockers and 11% phototherapy. For all cancers, the psoriasis population rate (114/10 000 person-years) was 20% greater than the rate found in the general population (95/10 000 person-years). For NMSC, the psoriasis population rate (129/10 000 person-years) was 65% greater than the general population rate (78/10 000 person-years). The incidence rate for each treatment modality was lower than the overall psoriasis cohort, except for phototherapy. There was little difference in the rates of lymphomas. NMSC rates were higher among patients treated with phototherapy. HIE rates ranged from 165/10 000 person-years for the phototherapy group to 262/10 000 person-years for the other TNFi group. CONCLUSIONS: Patients with psoriasis appear to have higher rates of malignancy and HIE than the general population, with little difference in rates between the treatment methods, except for a higher rate of cancer among those receiving phototherapy.	Kimball, AB et al. 2014. Incidence rates of malignancies and hospitalized infectious events in patients with psoriasis with or without treatment and a general population in the U.S.A.: 2005-09. BJD. https://doi.org/10.1111/bjd.12744
• minimal increase in colorectal cancer 1.16; 95% confidence interval [CI], 1.08-1.24. probably not significant clinically. Therapy not included, nor psoriasis severity ○ Included 9 cohort studies with 10,544,609 individuals. Found a significantly increased risk for CRC in patients with psoriasis (hazard ratio [HR], 1.16; 95% confidence interval [CI], 1.08-1.24). ○ Subgroups analysis according to sex found significantly increased risk for CRC in female patients with psoriasis (HR, 1.41; 95% CI, 1.16-1.72) but not in male patients (HR, 1.18; 95% CI, 0.92-1.50).	Fu, Y et al. 2021. Association of psoriasis with colorectal cancer. JAAD. https://doi.org/10.1016/j.jaad.2020.09.050
Inference-based conclusion (from points above):	Although malignancy rates may be slightly higher in patients with psoriasis than in the general population, overall, systemic treatments do not appear to increase malignancy risk.

General Statements:	Although risk of dying from cancer may be increased in psoriasis patients, this appears to be linked to modifiable risk factors.
Implications for treatment of psoriasis in TST patients:	This highlights the importance of patient counselling on modifiable risk factors. This helps set framework: Psoriasis itself is not causally associated with increased risk of ST. If there is indeed a risk in this population it's likely due to lifestyle factors than the disease itself.

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• Although preliminary studies have suggested little to no increased risk of cancer incidence in patients with psoriasis receiving biologic therapies, further study allowing greater follow-up and increased power is required to properly examine the potential cancer risk, particularly for site-specific cancers.	Trafford 2019 JAMA https://doi.org/10.1001/jamadermatol.2019.3056
• Studies (refs 2-8) have previously demonstrated that patients with **more severe psoriasis are at an increased risk of cancer-related mortality**, and psoriasis has been associated with an increased risk of cancer, including lymphoma. However, these studies have generally not controlled for important confounders, and have often failed to examine the rates of specific cancers or the impact of disease severity on cancer risk. Comment on length of time of follow-up: many studies have short-term follow-up. • The 2016 UK-based cohort study doesn't report on mortality rather incident cancer diagnosis, but does note increased risk of NMSC, lymphoma and lung cancer in psoriasis patients (excludes medical history of HIV, SOT, cancer)	Chiesa Fuxench 2016 JAMA https://jamanetwork.com/journals/jamadermatology/fullarticle/2475006 Trafford 2019 JAMA https://doi.org/10.1001/jamadermatol.2019.3056
• The increased prevalence of known cancer risk factors in people with psoriasis, such as smoking, excessive alcohol consumption, and obesity, has also been posited as a plausible explanation for an association with cancer. The potential role of these lifestyle factors is strengthened by the attenuation of risk in those studies that adjusted estimates for lifestyle factors and the increased risk of site-specific cancers, such as esophageal cancer and liver cancer, which have been reported to be independently associated with obesity, smoking, and higher alcohol consumption.	
• Pooled cohort and case control studies: included 58 observational studies; 50 examined cancer risk, 15 assessed cancer mortality, and 7 evaluated both.	Trafford 2019 JAMA https://doi.org/10.1001/jamadermatol.2019.3056

• People with psoriasis had an 18% increased risk of developing cancer compared with people who don't have psoriasis
• People with severe psoriasis had a **22% increased risk of dying of cancer** compared with those who were psoriasis free, but no increased mortality risk was reported for all severities combined
  ○ Overall cancer mortality risk was higher in patients with severe psoriasis (RR, 1.22; 95% CI, 1.08-1.38 [4 studies])
• The investigators found that 3 cancers— esophageal, liver, and pancreatic—were associated with an elevated risk of death among people with severe psoriasis
  ○ liver (RR, 1.43 [95% CI, 1.09-1.88]), esophageal (RR, 2.53 [95% CI, 1.87-3.41]), and pancreatic (RR, 1.31 [95% CI, 1.02-1.69]) cancer mortality were found to be elevated in those with severe psoriasis.
• Although people with psoriasis have additional, modifiable risks—they're more likely to smoke, drink alcohol, and have weight control issues than people without the condition—**cancer risks declined when the investigators controlled for these lifestyle factors.** Subgroup analysis by level of adjustment for confounders found marked attenuation of all cancer incidence and mortality risks in studies that additionally controlled for smoking, alcohol consumption, and obesity.
• Authors discussed possible reasons for increased cancer risk:
  ○ Link between chronic inflammation and cancer
  ○ Immunomodulatory agents and potentially carcinogenic therapies? (esp. lymphoma) It was noted that in RA - a meta-analysis of the association between rheumatoid arthritis and cancer suggested a lower risk of all cancer (standardized incidence ratio, 1.05; 95% CI, 1.01-1.09) compared with that found in psoriasis.
	Voelker 2019 JAMA (letter commenting on above) https://doi.org/10.1001/jama.2019.18582

• Cutaneous squamous cell carcinoma risk is primarily from UVB exposure (1) • Broad and generally profound immunosuppression is associated with an increased risk of development and metastatic risk (2,3,4) – risk increases by more than one order of magnitude (40 – 200 fold increase). The implications of this – small increases are more likely the result of inadequate correction for risk, observational or selection bias • Somatic mutations are associated with high risk of metastasis (5) https://www.jci.org/articles/view/57415 (references herein)	Gandhi Med Clin North Am. 2015 Skin Cancer Epidemiology, Detection, and Management PMID 26476255 Tessari Dermatol Surg 2012 Nonmelanoma skin cancer in solid organ transplant recipients: update on epidemiology, risk factors, and management PMID 22805312 Zwald JAAD 2011 Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipients PMID 21763561

	Kuschal Exp Dermatol 2012 Skin cancer in organ transplant recipients: effects of immunosuppressive medications on DNA repair PMID 22151386 Zilberg Nature 2017 Analysis of clinically relevant somatic mutations in high-risk head and neck cutaneous squamous cell carcinoma https://www.nature.com/articles/modpathol2017128

Statement 2: Solid Organ Transplants

2. Systemic therapy for psoriasis is unlikely to cause increased risk of cancer recurrence in previously TST patients with a good prognosis, based on evidence from patients with a history of TSTs who have undergone solid organ transplantation and broadly immunosuppressive therapy. The type of organ transplant and regimen of immunosuppressive therapy after transplant does not appear to affect outcomes for cancers with a good prognosis.

Caveats:

- This is not the case for HPV-related anal cancer where immune suppression may increase the risk of disease progression and recurrence and may not be the case for cancers with poor prognosis.
- This may be relevant for psoriatic agents with broad T-cell immunosuppression such as Cyclosporine but not the case for immunomodulating agents inhibiting Th17 pathway (IL-17/23inhibitors) and TNF-alpha inhibitors (RaashouP et al. Ann Intern Med 2018; 169:291-299).
- *Additional caveats may be added from survey results.*

Summary of Evidence:

Summary statement: Inference-based conclusion (from points below):	Overall, patients with history of malignancy receiving SOT have higher risk of overall mortality and possibly cancer-specific mortality compared to the general transplant population. This risk is highly influenced by type of malignancy, grade/stage, tumor specific characteristics, projected overall survival, time to transplant, age (in some studies). Patients selected for transplantation generally have good cancer prognosis which limits the ability to make reliable inferences about true risks. Patients with pre-transplant malignancy had decreased graft survival (one study). It is unclear if they had modified immunosuppressive regimens leading to this outcome. None of the studies looked at specific risks of infection.
Implications for treatment of psoriasis in TST patients:	Type of transplantation and immune suppression regimen after transplantation did not appear to affect outcomes for tumors with good prognosis suggesting that immunosuppressive treatments used for patients with psoriasis should not lead to increased risk of cancer recurrence. The foregoing is not the case for HPV-related anal cancer where immune suppression may increase the risk of disease progression and recurrence and may not be the case for cancers with poor prognosis. This may be relevant for psoriatic agents with broad T-cell immunosuppression such as Cyclosporine but not the case for immunomodulating agents inhibiting Th17 pathway (IL-17/23inhibitors) and TNF-alpha inhibitors (RaashouP et al. Ann Intern Med 2018; 169:291-299).

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• **Patients with prior history of malignancy can receive SOT after a time interval, with caveats.** The guidelines are based on type of malignancy (breast, colorectal, anal, prostate, renal bladder, gyne), risk/stage, 5-year survival rate or recurrence free 5-year survival (except overall survival for prostate cancer and 2-year local recurrence from baseline trans urethral resection of bladder tumor). There are also cancer specific considerations that may determine lower or higher risk disease. CAVEATS: ○ In general, patients with high-risk disease as determined by stage (usually stage 4/metastatic disease) would not be SOT candidates. ○ Patients with cancer selected for transplant usually have good cancer prognosis which limits the ability to make strong biological and clinical inferences from comparisons with heterogeneous group of other patients with cancer in general population	Al-adra et al. Am J transplantation 2021 https://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.16318

○ HPV-related anal cancer where the risk of immunosuppression may lead to negative outcomes.	
The risk of cancer <u>deaths</u> post-transplant among those with a <u>prior history of cancer</u> is increased vs those without prior cancer diagnosis. • the risk of cancer deaths among those with a <u>prior history of cancer</u> is increased at least 15-fold in comparison with those without a prior cancer diagnosis, with the majority of deaths attributed to renal cancers, presumably from the native kidneys • Recipients with pretransplant history of cancer had higher risk of post-transplant death from malignancy compared with those without any previous history (17.6% vs. 1.9%, P<0.001). * Only 74 recipients (0.4%) in this cohort had a pre-transplantation history of malignancy. Recipients with pretransplant history of cancer were more likely to die from renal malignancy compared with those without pretransplant cancer history (9.5% vs. 0.2%, P<0.001). Indeed over half of all malignancy-related deaths in recipients with pretransplant cancer history were renal in origin (53.8%) compared with 8.3% for those with no pretransplant cancer history (P<0.001). We were unable to ascertain pretransplant cancer location from HES data so were unable to determine if they corresponded to post-transplant cancer death locations • A history of cancer prior to kidney transplantation in the recipient increases the risk of death by 30% [57]. These findings were also confirmed in another study showing that kidney transplant recipients with a pre-transplant cancer are 3.7 times more likely to die of cancer post-transplantation [5]. Acuna et al. [58] performed an interesting meta-analysis including 32 cohort studies on solid organ transplant recipients with a pre-transplant malignancy in remission. **They demonstrated that pre-transplant malignancy is associated with an increased risk of all-cause mortality (pooled hazard ratio 1.51), cancer-specific mortality (pooled hazard ratio 3.13) and of developing de novo malignancies (pooled hazard ratio 1.92) after transplantation compared with solid organ transplant recipients without a pre-transplant malignancy** [58]. These studies clearly identify kidney transplant recipients with pre-transplant cancer as a high-risk patient population requiring tailored screening and management strategies.	Wong 2014 **https://doi.org/10.1038/ki.2013.494** Farrugia 2014 **https://doi.org/10.1038/ki.2013.458** Sprangers 2018 **https://doi.org/10.1093/ckj/sfx122**
• **CAVEAT: Some studies also note increased cancer-specific mortality, whereas others do not (inconclusive and likely related to selection bias).** • **Patients with prior malignancy generally have high cure probabilities when selected to receive SOT. Older age, advanced tumor stage and shorter interval between diagnosis and**	

transplantation are prognostic factors for low cure probability and have increased risk of post-transplant mortality due to cancer. ○ The study included 10,524,326 patients with cancer, with 17 cancer types; 5,425 (0.05%) subsequently underwent solid organ transplantation. ○ At the time of transplantation, the median cure probability was 94% (IQR 86-98%) ▪ Tumors with low cure probability: lung, stomach, ovarian, myeloma ▪ Tumors with high cure probability: testicular, thyroid, melanoma ○ Most common malignancies among transplanted patients: prostate, breast, colorectum, NHL ○ Most common transplanted organs: kidney and liver ○ Patients in the low cure probability tertile were less likely to receive induction immunosuppression or maintenance immunosuppression limited to tacrolimus and/or MMF and were more likely to receive MTOR inhibitor for maintenance ○ Patients in the low tertile of cure probability at transplantation had greater cancer-specific mortality HR 2.06; 95 CI 1.47-2.88; adjusted HR 2.08 95% CI 1.48-2.93 and lower than predicted; medium and high cure probability tertiles, the cumulative cancer-specific mortality was higher than predicted ○ Cancer cure probability was not predictive of mortality from non-cancer causes	Engels et al. J Clin Oncology 2022 https://ascopubs.org/doi/abs/10.1200/JCO.21.01195 *Note: 2 studies published with same dataset*
• <u>IT comments: No clear associations between transplanted organs or immune-suppressive medications and cancer-specific mortality; may suggest that immunosuppressants used in derm (ex. Cyclosporine) may not portend higher risk of cancer recurrence.</u> • Solid organ transplantation and survival among individuals with a history of cancer –> among patients with cancer, subsequent organ transplantation was associated with reduced overall survival, likely due to end-stage organ disease and transplant-related complications. <u>There were no adverse associations with cancer-specific survival, partly reflecting careful candidate selection</u> ○ Same study as above (10,524,326 patients with cancer, with 17 cancer types; 5,425 (0.05%) subsequently underwent solid organ transplantation). ○ This study did not demonstrate detrimental effect of immunosuppression on cancer-specific survival ○ The median time from cancer diagnosis to transplantation was 5.7 years. ○ Transplantation was associated with reduced overall survival for most cancers, especially cervical, testicular, and thyroid cancers [adjusted hazard ratios (aHR) for overall mortality, 3.43–4.88]. ○ In contrast, transplantation was not associated with decreased cancer-specific survival for any cancer site; inverse associations for patients with breast cancer (aHRs for cancer-specific	Engels et al. Cancer Epidemiol Biomarkers Prev 2021 https://doi.org/10.1158/1055-9965.EPI-21-0044

mortality, 0.65–0.67), non-Hodgkin lymphoma (0.50–0.51), and myeloma (0.39–0.42) were observed. ○ Transplanted patients were more likely to have localized stage cancer at diagnosis and less likely to have regional disease than untransplanted patients ○ The strongest elevations in overall mortality were seen for cervical, testicular and thyroid cancers (aHR 3.43-4.88) ○ The only cancer for which overall mortality following transplant was not at least borderline increased was myeloma (aHR 0.89)	Liauw et al. JNCI 2019 https://doi.org/10.1093/jnci/djz221
• In men aged 66+ with prostate cancer, transplantation is associated with higher overall mortality (OM) but no difference in prostate cancer specific mortality (PCSM) suggesting that management of men with prostate cancer and previous or future organ transplantation should proceed per usual standard of care ○ 620 men with SOT up to 10 years before or 5 years after prostate cancer diagnosis were compared to 3100 men with no history of transplant. At 10 years, in the transplant cohort OM was 55.7% and PCSM was 6.0% compared to non-transplanted cohort OM was 42.4% and PCSM was 7.6%. Adjusted models showed no difference in PCSM in men with transplant; there were no differences by prostate cancer therapy. Among 334 transplanted men with low-risk prostate cancer, PCSM was similar for treated and untreated men.	Acuna et al. Transplantation 2018 https://doi.org/10.1097/TP.0000000000002178
• SOT in patients with pre-existing malignancies in remission -> Transplant recipients with pre-transplant malignancies (PTM) had worse overall survival (OS) compared with transplant recipients without PTM (median OS, 10.3 years vs 13.4 years). ○ Recipients with PTM were not only at **increased risk of cancer-specific mortalit**y (cause-specific HR, 1.85; 95% CI, 1.2-2.86) but also at increased risk of non-cancer death (cause -specific HR, 1.81; 95% CI, 1.47-2.23) and recurrence ○ Recipients of low risk PTM were not at increased risk (HR 1.06, 95%CI 0.86-1.31) ○ GI PTM were associated with the highest risk of mortality, followed by melanoma, hematologic and breast.	Livingston-Rosanoff et al. J AM Coll Surg 2019 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6879822/
• Patients with pre-transplant malignancies (PTM) are at increased risk of post-transplant malignancy, graft loss and decreased OS.	

○ Pre-TM was associated with development of post-TM (HR 1.77 CI 1.68, 1.86), all cause (HR 1.22 CI 1.18, 1.27) and death censored graft failure (HR 1.08 CI 1.02, 1.15) between 2004 and 2016. ○ The 5-y all cause graft failure rate was 28% for pre-TM patients and 22% for non-pre-TM patients. 5 year rate of post-TM was almost three times higher than in patients without pre-TM (21.3% vs 7.3%). ○ Pre-TM was associated with decreased patient survival (5y 80% vs. 88% and HR 1.23 CI 1.18, 1.28). More patients with pre-TM died of malignancy related complications than those without a history of pre-TM (19 vs 11%). Of the patients with pre-TM who died of cancer, 16% experienced recurrence of their cancer prior to death. ○ Pre-TM – non-melanoma skin cancer (NMSC) >renal cell cancer>breast>prostate>hem ; NMSC, melanoma and hem pre-TM all had higher risk of developing post-TM. Most common post-TM was NMSC ○ Pre-TM was independently associated with worse patient survival; Patients with history of Hem malignancy had worse survival than patients with history of solid organ tumors. ○ CAVEAT: <u>melanomas were not associated with differences in patient survival</u>. • Swedish Cohort: Overall and cause specific mortality in transplant recipients (SOT) with a pre-transplantation cancer history -> organ transplant recipients with cancer history are at moderately increased rate of death after transplantation, driven primarily by death due to cancer recurrence. ○ Mortality among cancer history recipients was 30% increased after transplantation, compared with other recipients (aHR 1.3, 95% CI 1.1-1.5), driven by cancer-specific death with no increase in CV, infectious or other non-cancer mortality ○ An increased rate of death due to cancer history was primarily observed among non-kidney recipients (aHR 1.8, 95% CI 1.3-2.5) ○ Rates were greatest for patients with waiting times of 5 years or less but persisted with waiting times more than 10 years among kidney and non-kidney recipients with prior aggressive cancer types (GI, breast, kidney/urothelial and hematologic) ○ After kidney transplantation, 77% of patients with history of cancer and 80% of patients with no history of cancer were still alive at 5 years. After 10 years, survival estimated dropped to 55% (prior cancer) and 61% (no prior cancer).	BratTSTrom et al. Transplantation 2013 https://doi.org/10.1097/tp.0b013e31829854b7

○ After non-kidney transplantation, 5 year survival was 49% in cancer history group and 71% in patients with no prior cancer history, dropping to 27% and 52% at 10 years and were parallel thereafter ○ Cancer recurrence causing patient death was estimated to be 9.4% ○ Patients with cancer history were at 30% increased rate to die from all causes and at more than three fold increase rate to die from cancer compared to other transplanted patients ○ Overall mortality among transplanted patients with prior cancer history was 63.4/1000person-years vs 48.8/1000person-years in the absence of cancer history ○ There was no increased mortality from non-cancer causes in patients with prior history of cancer pre-transplant ○ Age, sex, follow up time did not affect all-cause and cancer-specific mortality; significantly increased rates of all cause and cancer specific deaths were confined to the first 9 years after transplantation ○ There was 20% increase in overall mortality in kidney recipients and 80% increased among non-kidney recipients with cancer history	Boissier et al. Eur J Urol 2018 https://doi.org/10.1016/j.eururo.2017.07.017
• The risk of cancer recurrence in end-stage renal disease (ESRD) patients after previous treatment for urological cancer. Immunosuppression after kidney transplantation does not affect the outcomes and natural history of low-risk renal cell carcinomas and prostate cancer; waiting time from successful treatment for these cancers to transplantation could be reduced (exception aristolochic acid nephropathy) ○ For renal cell carcinomas, the risks of recurrence, cancer-specific, and overall survival were similar between transplantation and dialysis; mean waiting period before transplantation was 0-10yrs; 5-year cancer specific survival rates for transplantation vs dialysis were 79-100% vs 77-100%. OS rates for transplantation vs dialysis were 80-100% vs 76-100%. Stage, grade, histological subtype, and solid/cystic component of the tumor were the main prognostic factors for recurrence. ○ For prostate cancer, most of the tumors had favourable prognosis; mean interval between cancer treatment and transplantation ranged from 3mo-4yrs. Recurrence rates for transplanted patients at <1yr were 0-9% and at >5years were 4-20%. The 1-5year survival rates for transplanted patients ranged from 62%-100%. Overall sparse data. Registry studies included patients with low-risk disease.	Stockle et al. European Urology Focus 2018 https://doi.org/10.1016/j.euf.2018.07.003 Acuna S et al. Transplantation 2017 https://doi.org/10.1097/TP.0000000000001192

○ Urothelial carcinomas, mainly upper urinary tract urothelial carcinomas were in context of aristolochic acid nephropathy that has risks of synchronous bilateral tumor and high recurrence. Data on bladder urothelial carcinoma were sparse. ○ Data on testicular cancer were sparse; Cancer specific and OS of 100% at 1-5yrs • No evidence that kidney transplantation and immunosuppression are associated with an increased prostate cancer related risk, neither in incidence nor aggressiveness • Screening for and treatment of prostate cancer in patient considering kidney transplantation or in patients after kidney transplantation should be performed in individualized manner based on the lifetime risk calculations. Untreated or incurable low-risk prostate cancer (presumed life expectancy >10 years) cannot be regarded as strict. • In patients who received SOT, pretransplant malignancy (PTM) is associated with **increased risk of all-cause mortality, cancer-specific mortality and of developing de novo malignancies after transplantation, compared without PTM.** ○ The association of all-cause mortality in SOTR with PTM did not vary by the type of transplanted organ; HR 1.51 (95% CI, 1.28-1.8). Observed hazard was similar for kidney and non-kidney transplant recipients. ○ Cancer-specific mortality – patients with PTM were at greater risk of cancer specific mortality compared to those without PTM; pooled HR 3.13; 95% CI, 2.29-4.27 • SOTR with PTM were more likely to develop post-transplant de novo malignancy compared to those without; HR, 1.92; 95% CI, 1.52-2.42; I2, 30%; observed hazard for kidney transplant recipients was similar to non-kidney transplant recipients ; PTMs were significantly associated with an increased risk of post-transplant NMSC. ○ One study – patients with pretransplant melanoma had an increased incidence of melanoma after transplant: HR, 5.38, 95% CI, 2.9-9.8. ○ One study – PTM was an independent risk factor for the development of posttransplant lymphoproliferative disorder (PTLD), adjusted HR 3.54, 95% CI, 2.31-5.43, but not for death after PTLD, adjusted HR 2.04, CI 0.96-4.3)	

Statement 3: IL-17i, IL12/23i, or IL-23i

In patients with previously TST and psoriasis, systemic treatment of psoriasis with an IL-17i, IL-12/23i, or IL-23i is unlikely to alter prognosis related to the previously TST.

Summary of Evidence:

Direct Evidence in Psoriasis:

*Caution regarding reporting bias for this evidence, small numbers, short follow-up time.

Reference (Author, year, journal)	**Title**	**Study Type**	**N**	**Key Findings/Notes:**
Mastorino 2021 The Journal of Dermatological Treatment	Biologic treatment for psoriasis in cancer patients: should they still be considered forbidden?	Case series	37 Psoriatic patients from single Italian centre with past cancer and subsequent biologic therapy. Retrospective analysis. 38 case reports from literature search.	Use of biologics against TNFα, IL17, IL-23, and IL12 appear to be safe in psoriatic patients with previously diagnosed cancer. **<u>Cases from single center</u>:** **9 patients on IL-12/23i, IL-23i**: 8 GUS, 1 RIS, 0 TIL, 0 UST **24 patients on IL17i:** 15 SEC, 4 BRO, 5 IXE **4 patients on TNFi**: 4 ADA **<u>Case reports from literature review</u>:** **5 IL12/23i, IL23i**: 4 UST, 1 GUS **18 IL17i:** SEC, IXE **8 TNFi**: ADA, INF and/or ETN **7** received combination of above categories. Caveat: Evidence for safety of biologics weak due to limited number of studies and reports, and follow-up time.

Valenti 2021 The Journal of Dermatological Treatment	Biologic therapies for plaque type psoriasis in patients with previous malignant cancer: long-term safety in a single- center real-life population.	Retrospective real-life single-center study	16 psoriasis patients with history of malignancy in previous 10 years, (5/16 had cancer diagnosis in previous 5 years). Tx with biologics for up to at least 96 weeks	**2 TNFi**: ETN **9 IL-17i:** 5 IXE, 1 RIS, 3 SEC **5 IL12/23i:** 1 GUS, 4 UST Rapid decrease in PASI reaching 90% improvement in all patients and no worsening or recurrence of cancers noted. Caveat: small study but consistent with other series
Bellinato 2021 Dermatologic therapy (referenced in Mastorino 2021)	**IL-17A** inhibitors in patients with chronic plaque psoriasis and history of malignancy: A case series with systematic literature review.	Case Series and lit review	Case series: 12 patients, at start of il-17i therapy 9 were in clinical remission, 3 had advanced cancer) From literature: 10 cases treated with SEC, IXE, or both (sequentially). Stage I-IV cancers but most were early-stage. IL-17A inhibitor was initiated after a median of 10 months, interquartile range (IQR) 5-30 (range 0-144) from the diagnosis of malignancy.	No malignancy recurrence was reported within a median of 12 (IQR 6-23) and 46 (IQR 36-48) months follow up in case series from literature and our experience, respectively. Caveat: small study

Kahn 2019 Journal of Drugs in Dermatology	Treatment of Psoriasis With Biologics and Apremilast in Patients With a History of Malignancy: A Retrospective Chart Review.	Retrospective Chart Review	16 psoriasis patients with history of malignancy	None of the 16 patients (including 3/16 receiving concurrent cancer therapy and biologic Tx) had recurrence or progression of their cancer supporting safety or **biologics & Apremilast**. They also demonstrated improvement in psoriasis. *Note: Patients were on multiple therapies for various durations. The longest duration therapy is noted below. **2 IL12/23i, IL23i** **4 IL17i** **5 TNFi** **5 APR**

Indirect Evidence (for above treatment class):

- Risk of solid tumours is not increased in patients with psoriasis treated with **IL-17i, IL12/23i, or IL-23i**. No likely altered risk of progression or recurrence compared to the general TST population.
- No increased risk of serious infection.

Descriptive summary: 19 papers selected as relevant with regards to the safety of the use of IL17 and IL12-23 agents in patients with prior or current solid tumors. These papers were either pooled analyses or clinical trials. As all clinical trials exclude patients with active malignancy or malignancy within the past 5 years, the relevance of these papers to the study question is assessed at marginal. Overall, clinical follow up in clinical trials extended to 5 years for guselkumab, secukinumab, brodalumab, ixekizumab and ustekinumab and 2.9 years on average for risankizumab. In none of the studies was the risk of serious infection or malignancy increased. The incidence rates for guselkumab were similar to other agents and were listed as: serious infections (0.85/100 PY), nonmelanoma skin cancer (0.34/100 PY), malignancies other than nonmelanoma skin cancer (0.45/100 PY).	
• A single real-world registry has longitudinally assessed risk of malignancy of ustekinumab compared to TNF inhibitors and found no increased risk of malignancy with ustekinumab	Fiorentino, D et al. 2017. Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry. JAAD. https://doi.org/10.1016/j.jaad.2017.07.013
Summary of papers and results:	Blauvelt, A et al. 2021. Consistent safety profile with up to 5 years of continuous treatment with guselkumab: Pooled analyses from the phase

Blauvelt, Guselkumab – voyage 1and 2 – 5 year data = 264 weeks. serious infections (0.85/100 PY), nonmelanoma skin cancer (0.34/100 PY), malignancies other than nonmelanoma skin cancer (0.45/100 PY) Gordon , risankizumab – 17 trials –1306 patients – av 2.9 years rates of serious adverse events were 7.8 per 100 PY, serious infections 1.2 per 100 PY, nonmelanoma skin cancer (NMSC) 0.7 per 100 PY, malignant tumours excluding NMSC 0.5 per 100 PY Rahmna P Guselkumab PsA 1 year No new signals V der Kerkhof – 10 pooled secukinumab studies - Over 52 weeks, for secukinumab 300 mg, 150 mg, and etanercept, respectively, exposure- adjusted incidence rates (IRs) per 100 SYs serious infections (1.4, 1.1, and 1.4, respectively); malignant or unspecified tumors (0.77, 0.97, and 0.68, respectively) Armstrong – Ixekizumab 5 yrs, 17000 patients: serious infections (range 1.3–1.7/100 p-y); nonmelanoma skin cancer (ranging from 0.5/100 p-y in year 1 to 0.2/100 p-y in years 4–5); other malignancies (range 0.4–0.6/100 p-y); Lebwohl – secukinumab multiple indications: 49 trails 10685 patient : the EAIR of malignancy was 085 per100 PTY [95% confidence interval (CI) 074–098] Mease – Ixekizumab and PsA for serious infections, the frequencies were 1.3% and 0%, respectively; Candida infections, 2.6% and 0.4%; confirmed major adverse cardiac events, 0% and 0%; malignancy, 0.4% and 0%; Gottlieb – 3 brodalumab studies: Exposure-adjusted event rates per 100 PY at 52 weeks were lower with brodalumab (n = 4019; 3446 total PY of exposure) than with ustekinumab (n = 613; 495 total PY of exposure), including adjudicated malignancies (0.9 vs 2.6) and Surveillance, Epidemiology, and End Results (SEER)-adjudicated malignancies (0.3 vs 0.4). Megna – Real world study of secukinumab in elderly – no rates published	3 VOYAGE 1 and VOYAGE 2 trials of patients with moderate-to-severe psoriasis. Journal of the American Academy of Dermatology. https://doi.org/10.1016/j.jaad.2021.11.004 Gordon, KB et al. 2021. Long-term safety of risankizumab from 17 clinical trials in patients with moderate-to-severe plaque psoriasis. The British journal of dermatology. https://doi.org/10.1111/bjd.20818 Rahmna, P et al. 2021. Pooled Safety Results Through 1 Year of 2 Phase III Trials of Guselkumab in Patients With Psoriatic Arthritis. The Journal of rheumatology. https://doi.org/10.3899/jrheum.201532 van de Kerkhof, P et al. 2016. Secukinumab long-term safety experience: A pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. Journal of the American Academy of Dermatology. https://doi.org/10.1016/j.jaad.2016.03.024 Armstrong, A et al. 2020. Safety of Ixekizumab Treatment for up to 5 Years in Adult Patients with Moderate-to-Severe Psoriasis: Results from Greater Than 17,000 Patient-Years of Exposure. Dermatology and therapy. https://doi.org/10.1007/s13555-019-00340-3 Lebwohl, M. 2021. The risk of malignancy in patients with secukinumab-treated psoriasis, psoriatic arthritis and ankylosing spondylitis: analysis of clinical trial and postmarketing surveillance data with up to five years of follow-up. The British journal of dermatology. https://doi.org/10.1111/bjd.20136 Mease, P. et al. 2019. Safety of Ixekizumab in Patients With Psoriatic Arthritis: Results From a Pooled Analysis of Three Clinical Trials. Arthritis care & research. https://doi.org/10.1002/acr.23738

Ustekinumab – Papp – 5 years follow up – At year 5, event rates (45 mg, 90 mg, respectively) serious infections (0·98, 1·19), NMSCs (0·64, 0·44), other malignancies (0·59, 0·61) and MACE (0·56, 0·36) Ustekinumab – Reich – 4 years follow up cumulative rates were generally comparable between patients who received 45 mg and 90 mg of ustekinumab. The rates of AEs of interest also remained stable over time, and cumulative rates per 100 patient-years were 0.80 and 1.32 (serious infections), 0.70 and 0.53 (nonmelanoma skin cancer), 0.63 and 0.61 (other malignancies)	Gottlieb, A et al. 2020. Malignancy Rates in Brodalumab Clinical Studies for Psoriasis. American journal of clinical dermatology. https://doi.org/10.1007/s40257-020-00512-4 Megna, M et al. 2020. Guselkumab in moderate to severe psoriasis in routine clinical care: an Italian 44-week real-life experience. The Journal of dermatological treatment. https://doi.org/10.1080/09546634.2020.1800577 Papp, KA et al. 2013. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. The British journal of dermatology. https://doi.org/10.1111/bjd.12214 Reich, K et al. 2012. An update on the long-term safety experience of ustekinumab: results from the psoriasis clinical development program with up to four years of follow-up. Journal of drugs in dermatology : JDD. https://pubmed.ncbi.nlm.nih.gov/22395580/
Inference-based conclusion (from points above):	Serious risk of infection or malignancies is not increased in psoriasis patients treated with IL-inhibitors. For patients with previously or actively TST, there is no data suggesting that patients on IL-inhibitor therapy would have clinically important increased risk of recurrence, metastasis or infections.

Serious infection, nasopharyngitis, URTI, and sinusitis with ustekinumab → no analysis of statistical significance performed. No cases of active TB with ustekinumab. Additional notes: - systematic review (included 17 clinical trials, 2 OLE studies, and 8 meta-analyses) - only included data for adalimumab, etanercept, and ustekinumab	Sorenson, E et al. 2015. Evidence-based adverse effects of biologic agents in the treatment of moderate-to-severe psoriasis: Providing clarity to an opaque topic. The Journal of dermatological treatment. https://doi.org/10.3109/09546634.2015.1027167
Inference-based conclusion (from points above):	Ustekinumab is not associated with a greater frequency of TB reactivation.

- MOA – Depending on the tumour microenvironment, the cytokines may or may not inhibit or promote tumour pathways. Evidence is not clear, conclusions cannot be made as the effect size is likely small.

Inference-based conclusion (from points below):	Mechanistically, it's possible that IL-17 inhibitors could suppress or promote cancer, depending on the tumour microenvironment. Th17 cells, IL-17 and its receptors are expressed in various types of solid tumours and are associated with poor prognosis. Conversely targeting IL-17 is being studied as therapeutic option for treating cancer. Mechanistic studies seem to support the oncogenic role of IL-17. Notably, there are discrepancies in the data with some data suggesting an anti-tumour role of IL-17. Reasons for the discrepancies may be due to tumour microenvironments, methods of measuring IL-17 and model of cancer being studied. *Mention effect size** Generally, totality of the evidence examined indicated the overall, general risk is low. Discussion needs to take place with patients based on anxiety level, their risk, how long ago the cancer was etc."**

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• Several studies have demonstrated that IL-17A is highly expressed within tumors, for instance, IL-17A is overexpressed in gastric carcinoma, medulloblastoma, ovarian cancer, colorectal carcinoma, Non-Small-Cell Lung Cancer (NSCLC), breast cancer, hepatocellular carcinoma (HCC) and thyroid cancer.	Santibanez, JF, and Bjelica, S. 2018. Novel Patents Targeting Interleukin-17A; Implications in Cancer and Inflammation. Recent Pat Anticancer Drug Discov. 10.2174/1574892813666180220105958
• Increased IL-17A peripheral blood levels correlate with the aggressiveness of malignant thyroid tumor, Pancreatic Adenocarcinoma (PA), NSCLC, laryngeal squamous cell carcinoma; colorectal cancer	Santibanez, JF, and Bjelica, S. 2018. Novel Patents Targeting Interleukin-17A; Implications in Cancer and Inflammation. Recent Pat Anticancer Drug Discov. 10.2174/1574892813666180220105958
• IL-17RA expression has been reported in cancer cells, including gliomas, non-Hodgkin B cell lymphoma, Breast cancer, Prostate cancer, Colorectal cancer, Skin cancer, NSCLC, Osteosarcoma, Lung adenocarcinoma.	Santibanez, JF, and Bjelica, S. 2018. Novel Patents Targeting Interleukin-17A; Implications in Cancer and Inflammation. Recent Pat Anticancer Drug Discov. 10.2174/1574892813666180220105958
• IL-17RA has been associated with cancer progression and poor prognosis gastric cancer patients	Santibanez, JF, and Bjelica, S. 2018. Novel Patents Targeting Interleukin-17A; Implications in Cancer and Inflammation. Recent Pat Anticancer Drug Discov. 10.2174/1574892813666180220105958

• Elevated IL17B expression has a strong correlation with poor prognosis of breast cancer.	Alinejad, V et al. 2017. The role of IL17B-IL17RB signaling pathway in breast cancer. Biomed Pharmacother. 10.1016/j.biopha.2017.01.120
• Th17 cells can promote tumor growth, and the function of Th17 cells is suggested to be dependent on several host factors such as the type of cancer and the respective therapeutic approach, and the stimuli to which the cells are exposed during activation	Joerger, M et al. 2016. The IL-17-Th1/Th17 pathway: an attractive target for lung cancer therapy? Expert Opin Ther Targets. 10.1080/14728222.2016.1206891
• The utility of anti-IL-17 mAb CJM112 alone or in combination with anti-PD1 in multiple myeloma patients is being studied in a phase I clinical trial (NCT 03111992).	Ruiz de Morales, JMG et al. 2019. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: An updated review of the evidence focusing in controversies. Autoimmun Rev. 10.1016/j.autrev.2019.102429
Inference-based conclusion (from points above):	Th17 cells, IL-17 and its receptors are expressed in various types of solid tumours and are associated with poor prognosis. Conversely targeting IL-17 is being studied as therapeutic option for treating cancer.

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• IL-17 is a double-edged cytokine that acts in a cancer-type depending manner as an anti- or protumor cytokine	Ruiz de Morales, JMG et al. 2019. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: An updated review of the evidence focusing in controversies. Autoimmun Rev. 10.1016/j.autrev.2019.102429
• The oncogenic role of IL-17 is supported by studies that demonstrated an anti-apoptotic effect in mouse breast cancer models and sustaining self-renewal properties of ovarian cancer stem cells	Ruiz de Morales, JMG et al. 2019. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: An updated review of the evidence focusing in controversies. Autoimmun Rev. 10.1016/j.autrev.2019.102429
• IL-17 decreases the presence of CD4 and CD8 infiltrating cells in tumor sites, to diminish the secretion of interferon gamma (IFN-γ) by CD8 T cells, to increase infiltrating T-regs	Ruiz de Morales, JMG et al. 2019. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: An updated review of the evidence

and to promote angiogenesis, invasion and metastasis recruiting tumor associated macrophages (TAM) and myeloid-derived suppressor cells (MDSC).	focusing in controversies. Autoimmun Rev. 10.1016/j.autrev.2019.102429
• Some studies have shown opposite effects. This likely stems from the heterogeneity in how the IL-17 is measured in the different reports and the fact that it has been studied mostly in in vitro cell models and human xenografts	Ruiz de Morales, JMG et al. 2019. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: An updated review of the evidence focusing in controversies. Autoimmun Rev. 10.1016/j.autrev.2019.102429
• Some reports showed that Th17 cells eradicate tumors, while others revealed that they promote the initiation and early growth of tumors and these discrepancies are due to the tumour microenvironment. The generation of Th17 cells with different phenotypes in response to tumor microenvironment would explain the conflicting observations.	Bernardini N et al. 2020. IL-17 and its role in inflammatory, autoimmune, and oncological skin diseases: state of art. Int J Dermatol. 10.1111/ijd.14695
Inference-based conclusion (from points above):	Mechanistic studies seem to support an oncogenic role of IL-17. Several studies show discrepant results with data suggesting an anti-tumour role of IL-17. Reasons for the differing observations may be related to tumour microenvironments, methods of measuring IL-17, and model of cancer being studied.

Inference-based conclusion (from points below):	IL23 plays a role in the tumor microenvironment, which can be immunologic and non-immunologic. Increased expression of IL23 promotes tumor growth. Its impact is influenced by host characteristics as well: genetic background, STAT3 expression, and also by the cause of tumor formation. Certain tumours behave differently to IL-12 (melanoma, UV induced skin cancer). Mechanistically, it's possible that IL-23 inhibitors could suppress cancer, while the role of IL12/23 inhibitors is less clear (could promote or supress), depending on the tumour microenvironment. *Mention effect size. Generally, totality of the evidence examined indicated the overall, general risk is low. Discussion needs to take place with patients based on anxiety level, their risk, how long ago the cancer was etc."**

Key points	**References**

• IL23 is an important molecular link between tumour-promoting pro-inflammatory processes and the failure of the adaptive immune surveillance to infiltrate tumours, as it upregulates MMP9 and increases angiogenesis but reduces CD8 T cell infiltration. • Expression of IL23 (but not of IL12) is increased in human tumours. • Genetic deletion of IL23 is protective against chemically induced carcinogenesis. • Transplanted tumours are growth-restricted in hosts depleted for IL23 or in IL23 R deficient mice. • 'Anti-IL23 p19 therapy may prove efficacious for tumour treatment'	Langowski JL et al, Nature 2006
• In vitro and animal studies have suggested that IL12 and IL23 may have distinct roles in contributing to protective immune responses to tumors. • Thus, therapies targeted to IL12 and IL23 carry a theoretical risk of decreased tumor surveillance. • Increased levels of IL23 are associated with unfavourable outcomes in various malignancies in humans. • Murine models of IL23 deficiency show prevention of tumor growth and enhance tumor rejection. (Table 4) • Except: may increase risk of melanoma, may increase risk of UV radiation induced skin cancer.	Ergen E, Exp Dermatol 2018
• IL23 and its ability to manipulate host immune responses, its role in modulating the activities of cell and molecules in the tumor microenvironment, and its capacity to directly affect a variety of (pre)malignant tumours. • The local balance between IL12 and IL23 has repeatedly been shown to play an important role in determining whether a pro- and antitumor immune response develops. • Whether IL23 acts in a pro-or anticarcinogenic manner may depend on the genetic background, the type of tumor, the cause (eg UV, chemical, virus…) and the critical balance of STAT3 signaling (constitutive STAT3 activation eg.) in both the tumor and the tumor cell microenvironment. • IL23 has a number of non-immunologic effects which may impact tumorigenesis : it interferes with the antitumour function of NK cells by blocking the IFNg and perforin-mediated effects ; supports neoangiogenesis (via VEGF ; effect on type-2 pericytes) ; inhibits CD8 T cell infiltration into the tumor tissue. • It also activates DNA repair pathways • They advise continued investigation into the relationship of IL23 and its downstream pathways with regard to carcinogenesis.	Subhadarshani S et al, Tumor Microenvironment, 2021

Statement 4: TNFi

In patients with previously TST and psoriasis, systemic treatment of psoriasis with a TNFi is unlikely to alter prognosis related to the previously TST.

Systematic reviews/meta-analyses show risk of cancer recurrence is similar to non-biologic therapies and those who did not receive immunosuppression.

Summary of Evidence:

*Caution regarding reporting bias for this evidence. Systematic reviews/meta-analyses show risk of cancer recurrence is similar to non-biologic therapies and those who did not receive immunosuppression.

Reference (Author, year, journal)	**Title**	**Study Type**	**N**	**Key Findings/Notes:**
Mastorino 2021 The Journal of Dermatological Treatment	Biologic treatment for psoriasis in cancer patients: should they still be considered forbidden?	Case series	37 Psoriatic patients from single Italian centre with past cancer and subsequent biologic therapy. Retrospective analysis. 38 case reports from literature search.	Use of biologics against TNFα, IL17, IL-23, and IL12 appear to be safe in Psoriatic patients with previously diagnosed cancer. **<u>Cases from single center</u>:** **9 patients on IL-12/23i, IL-23i**: 8 GUS, 1 RIS, 0 TIL, 0 UST **24 patients on IL17i:** 15 SEC, 4 BRO, 5 IXE **4 patients on TNFi**: 4 ADA **<u>Case reports from literature</u>:** **5 IL12/23i, IL23i**: 4 UST, 1 GUS **18 IL17i:** SEC, IXE **8 TNFi**: ADA, INF and/or ETN **7** received combination of above categories. Caveat: Evidence for safety of biologics weak due to limited number of studies and reports, and follow-up time.
Valenti 2021 The Journal of	Biologic therapies for	Retrospective real-life	16 psoriasis patients with	**2 TNFi**: ETN

Dermatological Treatment	plaque type psoriasis in patients with previous malignant cancer: long-term safety in a single-center real-life population.	single-center study	history of malignancy in previous 10 years, (5/16 had cancer diagnosis in previous 5 years). Tx with biologics for up to at least 96 weeks	**9 IL-17i:** 5 IXE, 1 RIS, 3 SEC **5 IL12/23i:** 1 GUS, 4 UST Rapid decrease in PASI reaching 90% improvement in all patients and no worsening or recurrence of cancers noted. Caveat: small study but consistent with other series
Kahn 2019 Journal of Drugs in Dermatology	Treatment of Psoriasis With Biologics and Apremilast in Patients With a History of Malignancy: A Retrospective Chart Review.	Retrospective Chart Review	16 psoriasis patients with history of malignancy	None of the 16 patients (including 3/16 receiving concurrent cancer therapy and biologic Tx) had recurrence or progression of their cancer supporting safety or **biologics & Apremilast**. They also demonstrated improvement in psoriasis. *Note: Patients were on multiple therapies for various durations. The longest duration therapy is noted below. **2 IL12/23i, IL23i** **4 IL17i** **5 TNFi** **5 APR**
Fagerli et al, 2019 Arthritis Rheum 2014 ACR/ARHP Annual Meeting abstract No. 1848	Risk of Cancer in Patients with Severe Psoriatic Arthritis Requiring Tumour-Necrosis	Retrospective study	709 psoriasis patients: **11**/709 had cancer registered prior to baseline, none of which had a further	"In this population of severely active PsA patients recruited early in the TNFi-era, the overall incidence of malignancy was reassuringly similar to that of the general population. Incidence of NMSC was increased, which may be related to PsA itself, skin psoriasis, phototherapy and/or immune-modulatory treatment."

	Factor Alpha Inhibition		cancer; 98% had previous or current exposure to MTX at baseline; 45.6% had previous or current exposure to CsA	

Direct evidence in other immune disorders (IBD, RA)

Reference (Author, year, journal)	**Title**	**Study Type**	**N**	**Key Findings/Notes**
Ytterberg et al, 2022 NEJM	Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis	Randomized, open-label, noninferiority, post authorization, safety end-point trial	1455 patients received tofacitinib at a dose of 5 mg twice daily, 1456 received tofacitinib at a dose of 10 mg twice daily, and 1451 received a TNF inhibitor	During a median follow-up of 4.0 years, the incidences of MACE and cancer were higher with the combined tofacitinib doses (3.4% [98 patients] and 4.2% [122 patients], respectively) than with a TNF inhibitor (2.5% [37 patients] and 2.9% [42 patients]). The hazard ratios were 1.33 (95% confidence interval [CI], 0.91 to 1.94) for MACE and 1.48 (95% CI, 1.04 to 2.09) for cancers; the noninferiority of tofacitinib was not shown. The incidences of adjudicated opportunistic infections (including herpes zoster and tuberculosis), all herpes zoster (nonserious and serious), and adjudicated nonmelanoma skin cancer were higher with tofacitinib than with a TNF inhibitor. Efficacy was similar in all three groups, with improvements from month 2 that were sustained through trial completion.

Micic 2019 Journal of Clinical Gastroenterology	Risk of Cancer Recurrence Among Individuals Exposed to Antitumor Necrosis Factor Therapy: A Systematic Review and Meta-Analysis of Observational Studies.	Systematic Review and Meta-Analysis of Observational Studies	3707 patients with inflammatory disorders exposed to **TNFi** therapy following a cancer diagnosis	Risk of new cancer or cancer recurrence among pts with history of cancer and use of TNFi therapy is similar to the risk with non-biological DMARDs. This supports use of TNFi therapy in select populations despite prior diagnosis of cancer. -Duration interval between original ca diagnosis and TNFi- rx was 1.2-11.5 years Subgroup analysis by time to initiation of TNFi showed no increased risk of cancer recur. After TNF if started >5 years after ca diagnosis -only one study in this MA had a median time to anti TNF Rx of 1.2 years, but no increased risk in this study either. There is insufficient data *to estimate an optimal start-time for TNF-Rx following cancer therapy* *must be noted that could be selection bias in these observational studies (patients chosen for TNFs may have lower risk of recurrence), but conversely, detection bias may result in higher cancer rates as patients have closer follow-up (Shelton reference below)
Shelton 2016 Gastroenterology	Cancer Recurrence Following Immune-Suppressive Therapies in Patients With Immune-Mediated Diseases: A Systematic Review and Meta-analysis.	A Systematic Review and Meta-analysis	11,702 patients with Immune-Mediated Diseases and prior cancer	Mainly IBD/RA. 16 studies, n=11702 pts with prior cancer, 31,258 person-years (p-y) of follow-up evaluation after a prior diagnosis of cancer. Only 1 study of severe psoriatic arthritis, Fagerli 2014 (referenced in direct evidence table) of TNF-i n=11 both new and recurrent cancers Using pooled incidence rates, similar rates of cancer relapse in patients with prior cancer receiving no immunosuppression, TNFi therapy, immune modulator or combination therapy; numerically higher among patients receiving combination immunosuppression. Reassuring

				data on restarting immunosuppressive therapy in pts with prior cancer. Caveat: unable to ascertain exact interval at which recommencement would be safe. Median recommencement of IS was 6 years. Note, an analysis of studies with median interval <6 years showed no risk in new or recurrent cancers
Raaschou 2018 Annals of Int Med	Tumor Necrosis Factor Inhibitors and Cancer Recurrence in Swedish Patients With Rheumatoid Arthritis: A Nationwide Population-Based Cohort Study	Cohort Study	467 RA patients who received **TNFi** therapy	The findings suggest that TNFi treatment is not associated with increased risk for cancer recurrence in patients with RA, although meaningful risk increases could not be ruled out completely. Among 467 patients who started TNFi treatment (mean time after cancer diagnosis, 7.9 years), 42 had cancer recurrences (9.0%; mean follow-up, 5.3 years); among 2164 matched patients with the same cancer history, 155 had recurrences (7.2%; mean follow-up, 4.3 years) (HR, 1.06 [95% CI, 0.73 to 1.54). Hazard ratios were close to 1 in analyses of patient subsets matched on cancer stage or with similar time from index cancer diagnosis to the start of TNFi treatment, as well as in unmatched analyses. Several CIs had upper limits close to 2. Limitation: The outcome algorithm was partly nonvalidated, and channeling bias was possible if patients with a better index cancer prognosis were more likely to receive TNFi.
Raaschou 2011 Arthritis Rheum.	Does cancer that occurs during or after anti-tumor necrosis factor therapy have a worse prognosis? A	Cohort study	314 cancers in RA patients undergoing	Relative risk of death with TNFi exposure same as biologics naïve group. * Reassuring to know from a Swedish study of Registries that when cancer develops on TNF rx, no increased risk of death or altered stage on TNfs vs nonbiologic controls

	national assessment of overall and site-specific cancer survival in rheumatoid arthritis patients treated with biologic agents.		or history of **TNFi**	
Xie 2020 Rheumatology (Oxford)	A meta-analysis of biologic therapies on risk of new or recurrent cancer in patients with rheumatoid arthritis and a prior malignancy	Meta-analysis	12 studies involving 13,598 patients and 32,473 patient-years of follow-up	Biologics were not associated with an increased risk of new or recurrent cancer compared with csDMARDs in patients with RA and prior cancer (**TNFi**: relative risk = 0.95, 95% CI = 0.83, 1.09). Secondary analyses of stratification of cancer types, the interval between initiation of TNFi and prior cancer diagnosis, and duration of TNFi exposure, found similar results
Waljee 2020 Lancet Gastroenterol Hepatol.	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	Cohort study	434 patients who received TNFiα therapy after their initial cancer were matched to 4328 patients in the control group.	Use of **TNFiα** therapy was not associated with recurrent or new primary cancer development in patients with previous cancer. Timing of TNFiα therapy after an initial cancer diagnosis did not influence recurrent or new primary cancer development.
Silva-Fernandez 2016	The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab:	Retrospective registry	425 patients with a prior malignancy from 18 000 RA patients, 101 patients	Rates of incident malignancy: TNFi cohort: 33.3 events/1000 person-years (py) Rituximab cohort: 24.7 events/1000 py sDMARD cohort (**study does not specify which sDMARDs, mentions "such as AZA and MTX"*): 53.8 events/1000 py

	results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis		developed a new malignancy.	The age- and gender-adjusted hazard ratio was 0.55 (95% CI: 0.35, 0.86) for the TNFi cohort and 0.43 (95% CI: 0.10, 1.80) for the RTX cohort in comparison with the sDMARDs cohort. "Although numbers are still low, it seems that patients with RA and prior malignancy selected to receive either a TNFi or RTX in the UK do not have an increased risk of future incident malignancy."

Indirect Evidence (for above treatment class):

- **Risk of solid tumours is not increased in patients with psoriasis treated with TNFi.** No likely altered risk of progression or recurrence compared to the general TST population. Overall, data reported up to 8.2 years of long term OLE/ real world Rx and RCT data for TNFs in psoriasis suggested development of new solid tumours is low, similar to SEER data. Inferring from the data available (SRs and meta-analyses of mainly observational studies with biases in both directions), patients with previously treated solid cancers who receive systemic treatment of psoriasis, are unlikely to experience an increased risk of recurrence. Nonetheless, these data alone are insufficient to inform on when treatment with TNFi or other systemic therapies can be re-commenced following cessation of cancer therapy. The limited available data, 1.2 years median time to re-introduction of TNFi following completion of cancer therapy, is reassuring

Risk of cancer with TNF-i treatments: General comments: -Data from RCTs with TNFs in psoriasis excludes patients with cancer, so only report incident cancers -some published data from registries *exclude* patients with previous cancers (eg. PSOLAR *Fiorentino*) -Overall, rates of new cancer development with TNFis (excluding NMSC and sometimes melanoma depending on publication, does not appear elevated compared to general population (SEER database often used for comparison) or controls/matched controls	Fiorentino, D et al. 2017. Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry. JAAD. https://doi.org/10.1016/j.jaad.2017.07.013
Studies of malignancy with TNFs across indications (eg. RA, IBDs etc.) are contaminated by the fact that many of them received concomitant immunosuppressive medications- *eg. Burmester safety analysis of 71 clinical trials found 53% of patients received concomitant IS agent (3% of patients with psoriasis),* therefore likely not reflective of pso patients on monotherapy with TNFi - and diff conditions have diff baseline risk of cancer (Saliba et al)	Burmester et al. 2013. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Annals of the rheumatic diseases. https://doi.org/10.1136/annrheumdis-2011-201244

eg. *Chen's systematic Review of 59 TNFi studies, mostly RA and IBD studies, found increased cancer in patients on TNFs exposed to immunosuppressants(DMARDs) vs not exposed, despite the fact TNFs used (cancer risks no higher than the control group in both pso studies)* *Also, looking at other indications further contaminated by the fact that increased risk of malignancy by disease state/chronic inflammation (eg RA)* *Chronic inflammation an established risk factor for cancer*	Salibaa, L et al. 2018. Tumor necrosis factor inhibitors added to nonbiological immunosuppressants vs. Nonbiological immunosuppressants alone. Fundamental & clinical pharmacology. 10.1111/fcp.12171 Chen, Y et al. 2018. Do tumor necrosis factor inhibitors increase cancer risk in patients with chronic immune-mediated inflammatory disorders? Cytokine. https://doi.org/10.1016/j.cyto.2016.09.013
Rates of solid tumours in RCTs and RWE for TNFs for psoriasis: *Studies have up to 8.2 years of data overall published (up to 8.2 for PSOLAR, 8 for Costa 2016 prospective observation on PsA (important to consider when thinking about the timelines for cancer development, which can be prolonged)* ***RWE in pso adalimumab:*** Strober's systematic review of RWE of adalimumab specifically in psoriasis patients found 3/10 studies reported on malignancy (excluding NMSC) and risk is low (0.3-0.6events /100PY) and consistent with the clinical trials, also c/w other biologics/systemic treatments for pso (0.5-0.7/100py) ***Pooled RCT data pso adal*** -this is consistent with RCTs- Leonardi's review of adalimumab's safety data for pso from 18 clinical trials, with maximum exposure of 5.5 years, average 1.5 patient years: "The incidence of malignancies excluding NMSC in patients treated with adalimumab for all body sites combined was comparable with the expected rate of diagnosed cancer for this demographic population, with an SIR of 0_86 [95% confidence interval (CI) 0_58–1_23; Fig. 3]" ***Pso RWE TNFs****:* PSOLAR: one of the larger registries, 12, 090 pts, 252 malignancy cases and 1008 controls matched	Strober, B et al. 2018. Systematic review of the real-world evidence of adalimumab safety in psoriasis registries. Journal of the European Academy of Dermatology and Venereology. JEADV. 10.1111/jdv.15203 Leonardi, C et al. 2019. Comprehensive long-term safety of adalimumab from 18 clinical trials in adult patients with moderate-to-severe plaque psoriasis. The British journal of dermatology. 10.1111/bjd.17084

-median follow-up 4.17 years and maximum follow-up 8.2 years, 48, 870 total patient years -after adjusting for confounders such as multiple exposures (to different medications)TNF-I's not associated with increased malignancy (NB- despite conclusion in abstract-text details the details of multiple exposures)	Fiorentino, D et al. 2017. Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry. JAAD. https://doi.org/10.1016/j.jaad.2017.07.013
PSOLAR poster: RWE -a median 2.5 years of follow-up, a descriptive summary suggests that patients with a history of malignancy (other than skin cancer) had higher rates of malignancy than patients who did not, approximately 5 fold • Taking into account the limitations, the descriptive data suggest **malignancy rates are generally comparable in patients treated with biologics to patients treated with non-biologic therapies, whether or not there was a history of malignancy**	**EADV 2015 Poster** P1777: Experience in Patients With a History of Malignancy in the Psoriasis Longitudinal Assessment and Registry (PSOLAR) Study R.G. Langley,1 K. Goyal,2 D. Fiorentino,3 J. Bagel,4 M. Lebwohl,5 B. Strober,6 V. Ho,7 W. Langholff,8 S. Calabro,2 S. Fakharzadeh2
Other studies also support these conclusions that TNFi's not an increased risk for malignancy (excluding NMSC): *Burmester et al 2013 : overall malignancy rates were as expected for the general population for adlimumab (up to 2013)* *Certolizumab the same: 7.8 years of maximum exposure, no increased risk of mailg. c/w gen population* *Other studies similar:* Observe -5 (etanercept), ESPRIT 10 year post marketing (adalimumab)- same conclusions • Added from Dr. Gniadecki's section (supports above): TNF vs non-TNF treated. Overall cancer risk the same, but solid tumors not specifically analyzed.	Burmester et al. 2013. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Annals of the rheumatic diseases. https://doi.org/10.1136/annrheumdis-2011-201244 Burmester et al. 2011. Long-term safety of certolizumab pegol in rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis and Crohn's disease: a pooled analysis of 11 317 patients across clinical trials. Ammrheumdis. 10.1136/annrheumdis-2011-201244 Curtis JR, et al. 2019. Long-term safety of certolizumab pegol in rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis and Crohn's disease: a pooled analysis of 11 317 patients across clinical trials. RMD Open. 10.1136/rmdopen-2019-000942

Sought to estimate the overall malignancy rate (excluding NMSC) and NMSC rate among 5889 patients with systemically treated psoriasis. Cohort of adult Kaiser Permanente Northern California health plan members with psoriasis diagnosed from 1998 to 2011 and treated with at least 1 systemic antipsoriatic agent and categorized them into ever-biologic or nonbiologic users. RESULTS: Most biologic-exposed members were treated with TNF-alfa inhibitors (n = 2214, 97%). Overall incident cancer rates were comparable between ever-biologic as compared to nonbiologic users (aHR 0.86, 95% CI 0.66-1.13). NMSC rates were 42% higher among individuals ever exposed to a biologic (aHR 1.42, 95% CI 1.12-1.80), largely driven by increased cutaneous squamous cell carcinoma risk (aHR 1.81, 95% CI 1.23-2.67).	Asgari, MM et al. 2017. Malignancy rates in a large cohort of patients with systemically treated psoriasis in a managed care population. JAAD. https://doi.org/10.1016/j.jaad.2016.10.006

- Patients with psoriasis on TNFi are at an increased risk of infection, including SI, although RWE suggests rates are lower than those seen in clinical trials. Given TNFs have rare risk of opportunistic infection as many chemo agents do, need to be cautious about adding these therapies together in active treatment of malignancy. Patients at high risk of new TB infection or other opportunistic infections may be less ideal candidates for TNFi while on CA Rx/chemo. Special consideration must also be given to cancers secondary to oncogenic viruses such as cervical CA and HCC, as limited mechanistic data suggest possible negative effect on TNF inhibition, despite reassuring clinical data in psoriasis patients without malignancy/additional immunosuppression.

Risk of infection with TNFs: *infections are commonly AEs reported in clinical trials with TNFi's, and the increased risk of infection is noted in the prescribing information/monograph, but infection rate in RWE/Registries is generally lower than reported in clinical trials, eg. Adalimumab clinical trial 88.8/100 Py vs <1.0-2.0/100Py in RW registries)-* ***Strober et al,***	Strober, B et al. 2018. Systematic review of the real-world evidence of adalimumab safety in psoriasis registries. JAMA Dermatol. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7042857/
Increased risk of infections, including opportunistic infections and serious infections have been observed with TNF-I's but a metananalysis of RWE/Registry data with 23 358 PY-no diff between TNFi and systemics incl. mtx for bacterial infection, granulomatous infection or serious infection- ***Garcia et al***	Garcia-Doval I et al. 2017. Risk of serious infections, cutaneous bacterial infections, and granulomatous infections in patients with psoriasis treated with anti-tumor necrosis factor agents versus classic therapies: prospective meta-analysis of Psonet registries. J Am Acad Dermatol. 10.1016/j.jaad.2016.07.039
*-****pneumonia and cellulitis*** *most common serious infections with adalimumab, consistent with clinical trial experience in systematic review of adalimumab studies, (****Strober et al),*** *and PSOLAR showed this as well with pneumonia and cellulitis being the most common Sis reported****(Kalb et al-PSOLAR)***	

-Results from PSOLAR suggest a higher risk of serious infections with adalimumab and infliximab compared with nonmethotrexate and nonbiologic therapies. No increased risk was observed with ustekinumab or ***etanercept (kalb et al)*** *-The cumulative incidence rate of serious infections was 1.45 per 100 patient-years (n = 323) across treatment cohorts, and the rates were 0.83, 1.47, 1.97, and 2.49 per 100 patient-years in the ustekinumab, etanercept, adalimumab, and infliximab cohorts, respectively, and 1.05 and 1.28 per 100 patient-years in the nonmethotrexate/nonbiologics and methotrexate/nonbiologics cohorts, respectively.* ***(kalb et all- PSOLAR)***	Kalb, RE et al. 2015. Risk of Serious Infection with Biologic and Systemic Treatment of Psoriasis: Results From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol. 10.1001/jamadermatol.2015.0718
*-of the tnfi, infliximab had the highest rate of serious infection (PSOLAR) in pso-****Papp et al, and Gottlieb et al, and Kalb et al (expanded on below)*** Infliximab is highest infection risk (PSOLAR) with etanercept the least of the TNF-is *By indication, pso has the lowest rate of TNF-I associated infections (compared with RA, Crohns)-****(Strober et al)***	Papp, K et al. 2015. Safety Surveillance for Ustekinumab and Other Psoriasis Treatments From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JDD. https://pubmed.ncbi.nlm.nih.gov/26151787/ Gottlieb, AB et al. Safety observations in 12095 patients with psoriasis enrolled in an international infliximab and other systemic and biologic therapies. Journal of Drugs and Dermatology. https://pubmed.ncbi.nlm.nih.gov/25607786/
-combination therapy with methotrexate and adalimumab in BIOBADADERM had higher risk of infection versus monotherapy, ***and this may be relevant to patients on chemotherapy, and other IS agents such as corticosteroids for their cancer Rx*** *(smaller numbers in this publication limit generalizability)-* ***Davila et al*** *Certolizumab –similar to other TNFs had infections as most common cause of SAE* *-risk of infections with certolizumab highest in first 3 months after Rx initiation*	Davila-Seijo, P et al. 2017. Infections in moderate to severe psoriasis patients treated with biological drugs compared to classic systemic drugs: findings from the BIOBADADERM registry. J Invest Dermatol. 10.1016/j.jid.2016.08.034
	Curtis 2019. Long-term safety of certolizumab pegol in rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis and Crohn's disease: a pooled analysis of 11 317 patients across clinical trials. RMD Open. 10.1136/rmdopen-2019-000942
- systematic review (included 17 clinical trials, 2 OLE studies, and 8 meta-analyses) - only included data for adalimumab, etanercept, and ustekinumab **Adalimumab** is associated with a greater frequency of upper respiratory tract infections, but not serious infections or nasopharyngitis. Upper respiratory tract infection with adalimumab → statistically significant.	Sorenson, E et al. 2015. Evidence-based adverse effects of biologic agents in the treatment of moderate-to-severe psoriasis: Providing clarity to an opaque topic. The Journal of dermatological treatment.

Serious infection and nasopharyngitis with adalimumab → not statistically significant. **Etanercept** is not associated with a greater frequency of serious infections, upper respiratory tract infections, nasopharyngitis, sinusitis or TB reactivation. Serious infection, URTI, nasopharyngitis, and sinusitis with etanercept → not statistically significant. No cases of active TB with etanercept.	https://doi.org/10.3109/09546634.2015.1027167
PSOLAR is now fully enrolled at 12095 patients followed for 31818PY. The cumulative rate was 1.50/100PY for serious infections. Increasing age was a significant predictor. A history significant infection was associated with a higher risk of serious infection. Exposure to infliximab (HR=3.101, P<0.001) and exposure to other biologics (HR=1.736, P<0.001) were significant predictors of serious infections. **The data suggest that infliximab was associated with serious infections.** Additional notes: - PSOLAR is a large, ongoing, observational study of patients receiving, or eligible to receive biologic or systemic therapy for psoriasis - cumulative incidence rates of AEs per 100 patient-years (PY) are reported across treatment cohorts: (1) infliximab, (2) ustekinumab, (3) other biologics (e.g., adalimumab and etanercept) and (4) non-biologic agents There were 478 serious infections (1.50/100PY) reported during the data collection period (Table 2). Serious infections occurred more frequently in the infliximab group (2.73/100PY) compared with the other biologics (1.80/100PY), ustekinumab (1.00/100PY), and non-biologic (1.26/100PY) cohorts (Table 2; Figure 2). Significant predictors of serious infection were increasing age (HR=1.465; 95% CI: 1.348-1.593, *P*<0.001), a history of significant infection (HR=1.896; 95% CI: 1.519-2.366, *P*<0.001), baseline Physician's Global Assessment (PGA) of 4 or 5 (HR=1.773; 95% CI: 1.246-2.522, p=0.001), and exposure to infliximab (HR=3.101; 95% CI: 2.187-4.397, *P*<0.001), as well as exposure to biologics other than infliximab (HR=1.736; 95% CI: 1.355-2.226, *P*<0.001;Table 3). **Infliximab can be associated with serious infections in psoriasis patients, with increasing age and prior history of significant infections being risk factors.** **Rates of serious infection are higher with infliximab (TNF inhibitor) and other biologics compared with ustekinumab (IL12/23 inhibitor).** -	Gottlieb, AB et al. 2014. Safety observations in 12095 patients with psoriasis enrolled in an international registry (PSOLAR): experience with infliximab and other systemic and biologic therapies. Journal of drugs in dermatology : JDD. https://pubmed.ncbi.nlm.nih.gov/25607786/
PSOLAR is now fully enrolled at 12093 patients followed for 40388PY. The cumulative rate was 1.60/100PY for serious infection. Unadjusted rates of serious infection for infliximab (2.91/100PY) and other biologics (1.91/100PY) were numerically higher compared with ustekinumab (0.93/100PY). Exposure to the combined groups of biologics other than ustekinumab was significantly associated with serious infection (HR=0.96).	Papp, K et al. 2015. Safety Surveillance for Ustekinumab and Other Psoriasis Treatments From the Psoriasis Longitudinal

Cumulative incidence rates for serious infection in the ustekinumab group were numerically lower or comparable with other biologic and non-biologic cohorts in PSOLAR. Of note, a significant association between history of PsA and risk of serious infection (HR=1.30, 95% CI: 1.07-1.59, - P=.009) was newly observed in the current 2014 Ustekinumab Safety Analysis. Smoking and diabetes were added as covariates in the current analyses; smoking was found to be a significant risk factor for serious infection, while diabetes was significantly associated with serious infection.	Assessment and Registry (PSOLAR). Journal of drugs in dermatology : JDD. https://pubmed.ncbi.nlm.nih.gov/26151787/
Opportunistic and other infections with TNFi: TNF alpha inhibitors may interfere with the maintenance/containment of granulomas, and therefore have a particular risk in granulomatous infections such as TB (by inhibiting CD8+ and CD 4 + cells and lymphocytes (all of which produce IFN gamma),deregulating IL-10-producing Treg cells) -Tb reactivation or development is a risk with tNFi's -the introduction of latent TB infection screening prior to initiation of therapy led to a decrease in the instant TB, closer should the background population, but new cases of TB are still being reported despite appropriate measures (**Jauregi et al and Pereira et al)** **-**the risk of endemic mycosis such as histoplasmosis, coccidiomycosis come on blastomycosis as well as TB varies with geography and baseline risk, therefore the overall risk of opportunistic infections should be considered- **-**atypical manifestion as of infection such as cytomegalovirus infection, histoplasmosis, pneumocystis jirovecci pneumonia, and aspergillosis are rarely reported -meta analysis showed increased risk of zoster in patients receiving anti TNF-I therapies. The absolute risk remains low. Furthermore, zoster may be prophylaxed with vaccination -HBV reactivation related to TNFi is possible. Nonetheless, TNFi therapy appears to be safe option in chronic HBV infection when combined with appropriate anti viral therapy or with close monitoring in HBc positive patients	Talotta et al 2018. Biological Agents in Rheumatoid Arthritis: A Cross-Link Between Immune Tolerance and Immune Surveillance. Curr Rheumatol Rev. 10.2174/1573397112666161230125317 Pereira, R et al. 2015. Safety of Anti-TNF Therapies in Immune-Mediated Inflammatory Diseases: Focus on Infections and Malignancy. Drug Dev Res. 10.1002/ddr.21285 Jauregui-Amezga, A et al. 2013. Risk of developing tuberculosis under TNFi treatment despite latent infection screening. J Crohns Colitis. 10.1016/j.crohns.2012.05.012
HPV (as oncogenic)- ***I didn't find much mentioned clinically in the larger registries etc. on HPV infection in the lit search provided, but a few reports of cervical SCC, so patients on TNFs should be screened as per guidelines for HPV and cervical cancer- maybe the mechanistic section will speak more to this? (NMSC a separate manuscript so trying to stick to solid tumours)	Bessaleli, E et al. 2018. Squamous cell carcinoma of the cervix arising in a patient on adalimumab a need for cervical screenings in patients on tumor necrosis factor inhibitors. Dermatology Online

	Journal. https://pubmed.ncbi.nlm.nih.gov/30142745/
HPV-study on HPV DNA prevalence in healthy skin of psoriasis patients treated with TNF inhibitors - data demonstrate that TNFi agents have no impact on the prevalence of HPV DNA in healthy skin and on the number of HPV types. - Despite the small number of patients in the cohort, results are quite encouraging in view use of TNFi agents in different autoimmune or inflammatory diseases, but modification in HPV DNA prevalence after several years of exposure cannot be ruled out.	Bellaud, G et al. 2013. Prevalence of human Papillomavirus DNA in eyebrow hairs plucked from patients with psoriasis treated with TNF inhibitors. J Eur Acad Dermatol Venereol. https://doi.org/10.1111/jdv.12308
HPV MOA of TNF-alpha cont'd: TNF- plays an important role in the immune response to infection. When it is inhibited, the production of cytokines and chemokines, the expression of cell surface MHC class I and II as well as the proliferation and apoptosis of T lymphocytes may be affected. Thus, the recognition of microorganisms by phagocytes and dendritic cells as well as the activation of T lymphocytes may be impaired. Furthermore, TNF- is involved in signaling apoptosis in infected cells, a mechanism employed in an effort to stop viral replication and spread. E6 protein of HPV-16 is known to directly bind to TNF receptor 1 and abrogate TNF-induced apoptosis of the host cell [4	Antoniou, C et al. Genital HPV Lesions and Molluscum Contagiosum Occurring in Patients Receiving Anti-TNF- Therapy. Dermatology. 10.1159/000117709
HPV: cervical cancer might be an exception, although appears to be case reports mainly: **"**The HPV16 *E6* and *E7* transcripts were found to be sharply upregulated in CaCx cases strongly inversely correlated with the TNF-*α* expression. Significant role of TNF-*α* downregulation associated with insufficient IFN-*γ* and total NF-*κβ*p65 modulation and the resulting significant upregulation of viral transcripts *E6* and *E7* are key to the HPV16 infection mediated CaCx pathogenesis in northeast Indian patients"	Chandana Ray Das et al. 2018. Deregulated TNF-Alpha Levels Along with HPV Genotype 16 Infection Are Associated with Pathogenesis of Cervical Neoplasia in Northeast Indian Patients**.** Viral Immunology. https://doi.org/10.1089/vim.2017.0151
HCV The safety profile of TNFi agents in the setting of HCV infection seems to be acceptable (but most in this review on etanercept)-2011 But some recent (2017) basic science data suggests TNF-i protective against spread of HCV amongst liver cells	Alexandra M. G. Brunasso et al. 2011. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic. Rheumatology https://doi.org/10.1093/rheumatology/ker190 Volodymyr Nechyporuk-Zloy et al. 2017. Tumor Necrosis Factor Inhibits Spread of Hepatitis C Virus Among Liver Cells, Independent From Interferons. Gastroenterology.

	https://doi.org/10.1053/j.gastro.2017.04.021
Biologic therapies pose minimal risk for reactivation in low-risk patients without hepatitis seropositivity for HCV or HBV core. Serology indicated HCV infection in 4 patients, past HBV infection in 17 patients, isolated core antibody in 8 patients, and chronic HBV infection in 1 patient. During follow-up (mean 4.85 6 3.1 years), no patients experienced hepatitis or viral reactivation. The systematic review of the literature included 49 studies comprising 312 patients followed for a mean of 30.9 months. Viral reactivation occurred in 2/175 patients who were seropositive for core antibody and 3/97 with HCV infection (yearly rates, 0.32% and 2.42%, respectively) compared with 8/40 patients with chronic HBV infection (yearly rate, 13.92%). Three of these 8 patients with reactivated HBV infection received antiviral prophylaxis. Biologic therapies pose minimal risk for viral reactivation in low-risk patients without hepatitis seropositive for HCV or HBV core antibody but are a considerable risk in patients with chronic HBV infection, highlighting the necessity of antiviral prophylaxis. Additional notes: - retrospective cohort study design was used → clinical and laboratory data for 30 patients - undergoing biologic therapy who were seropositive for HBV or HCV were evaluated - systematic review was performed → primary outcomes were hepatitis and viral reactivation during therapy; treatment duration and antiviral prophylaxis were also recorded limitations: we pooled heterogeneous studies evaluating different biologic therapies	Snast, I et al. 2017. Risk for hepatitis B and C virus reactivation in patients with psoriasis on biologic therapies: A retrospective cohort study and systematic review of the literature. Journal of the American Academy of Dermatology. https://www.sciencedirect.com/science/article/pii/S0190962217301305
KS- case report with infliximab	Brambilla, L et al. 2021. Kaposi's sarcoma, biologics and small molecules: Navigating the complex interplay between host immunity and viral biology. A case series with focused review of the literature. Dermaol Ther. https://doi.org/10.1111/dth.15278

- MOA – Cytokine tumour inhibition, promotion, or neutrality are depending on the tumour microenvironment and the specific cytokine. Clinical evidence is suggestive but firm conclusions cannot be made. Given the complexity of cytokine engagement and the varied roles in tumorigenesis, the effect size of any cytokine is likely to be small.

Inference-based conclusion (from points below):	TNF plays a role in the tumour microenvironment, although it can promote cancer cell survival or cancer cell death under different conditions. TNFs also play an essential role in combatting infection. Mechanistically, it's possible that TNF inhibitors could promote or suppress cancer, and result in an increased rate of infections.

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
Theoretical cancer risk with TNFs (background) *-Biological possibility for cancer development proposed due to MOA of TNF inhibition, as TNF is an important cytokine regulating inflammation and therefore potentially cancer development, particularly for cancers that may be more immune mediated* *-TNF has different functions/complexity re: cancer biology* *-Under different conditions, TNF can promote cancer cell survival or cancer cell death: (Chen et al, Waters, Talotta)* *-TNF can activate proliferation pathways, trigger inflammatory cell infiltration of tumours and promote angiogenesis and tumour cell migration and invasion* *-Cancer risk is proposed to be possibly from impaired immune surveillance, facilitation of oncogenic viruses, alteration of DNA (Shelton)*	Chen, Y et al. 2018. Do tumor necrosis factor inhibitors increase cancer risk in patients with chronic immune-mediated inflammatory disorders? Cytokine. https://doi.org/10.1016/j.cyto.2016.09.013 Tallota et al. 2018. Biologics and RA: Immunosurveillance. Current Rheumatology Reviews. 10.2174/1573397112666161230125317 Waters, JP et al. 2013. Tumour necrosis factor and cancer. Journal of pathology. https://doi.org/10.1002/path.4188 Shelton, E. 2016. Cancer Recurrence Following Immune-Suppressive Therapies in Patients with Immune-Mediated Diseases. Gastroenterology. 10.1053/j.gastro.2016.03.037
Added by medical writer (as per Dr. Lambert's suggestion from intro of Bongartz 2006): • Basic science research suggests that infectious complications and malignancies should be seriously considered as possible adverse effects of TNF antagonists.	Bongartz 2006 JAMA ttps://jamanetwork.com/journals/jama/article-abstract/202873

• Animal models indicate an essential role of TNF in combating infection.2-4 • In addition, TNF is important in natural killer cell– and CD8 lymphocyte–mediated killing of tumor cells, although tumor-promoting effects of TNF have also been described.5	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 2. Nakane A, Minagawa T, Kato K. Endogenous tumor necrosis factor (cachectin) is essential to host resistance against Listeria monocytogenes infection. Infect Immun. 1988;56:2563-2569. 3. Kato K, Nakane A, Minagawa T, et al. Human tumor necrosis factor increases the resistance against Listeria infection in mice. Med Microbiol Immunol (Berl). 1989;178:337-346. 4. Mastroeni P, Villarreal-Ramos B, Hormaeche CE. Effect of late administration of TNFi antibodies on a Salmonella infection in the mouse model. Microb Pathog. 1993;14:473-480. 5. Balkwill F. Tumor necrosis factor or tumor promoting factor? Cytokine Growth Factor Rev. 2002;13:135- 141.

Caveats:

- Additional caveats may be added from survey results.

Statement 5: Systemic Agent (MTX)

In patients with previously TST and psoriasis, systemic treatment of psoriasis with methotrexate is unlikely to alter prognosis related to the previously TST.

Summary of Evidence:

Direct Evidence in Psoriasis:

*Caution regarding reporting bias for this evidence

Reference (Author, year, journal)	**Title**	**Study Type**	**N**	**Key Findings/Notes:**
Aydin 2014 Cutaneous and Ocular Toxicology	Cancer-free survival of psoriasis patients treated with methotrexate and cyclosporine combination.	Retrospective study	17/20 psoriasis patients on **MTX & CsA** combination therapy followed up for development of malignancy (3/20 patients lost to follow-up)	No increased cancer risk seen in the median 76 months follow-up time Caveat: small study, selection bias, combination of CsA AND MTX is rarely used in clinical practice, short duration of therapy.

Indirect Evidence (for above treatment class):

- Risk of solid tumours is not increased in patients with psoriasis treated with **MTX**. No likely altered risk of progression or recurrence compared to the general TST population.
- Although MTX may also increase risk of infection, this is debatable and MTX as a cancer treatment slows the growth of cancer cells, so concerns are likely not warranted.

Observations or findings from the literature related to the baseline risk of malignancy in psoriasis patients treated with MTX, CyA, Acitretin *What are outcomes of interest, caveats and considerations.*	**References**
• Use of methotrexate in psoriasis patients does not appear to increase risk of subsequent malignancy	Fiorentino, D et al. 2017. Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry. JAAD. 10.1016/j.jaad.2017.07.013 Pouplard, C et al. 2013 Risk of cancer in psoriasis: a systematic review and meta-analysis of epidemiological studies. JEADV 10.1111/jdv.12165 Mazaud, C and Fardet L. 2017. Relative risk of and determinants for adverse events of methotrexate prescribed at a low dose: a systematic review and meta-analysis of randomized placebo-controlled trials. Br J Dermatol. 10.1111/bjd.15377
• Methotrexate was used at high doses to treat solid tumours. Low dose methotrexate is not an inducer nor a promoter of malignancy. Studies have not shown an increased risk of malignancy associated with the use of low dose mtx. • There may be a small in the risk of skin cancer associated with low dose mtx. (10.1177/0192623311427711 ; https://www.sciencedirect.com/science/article/abs/pii/S0049017213001704; 10.7326/M19-3369; https://doi.org/10.1093/rheumatology/kes283). • No difference in malignancy risk is observed in patient treated with MTX compared to biologics (https://doi.org/10.1007/s12254-019-0506-5	Weaver 2011 Establishing the Carcinogenic Risk of Immunomodulatory Drugs https://journals.sagepub.com/doi/10.1177/0192623311427711 Solomon 2014 Comparative cancer risk associated with methotrexate, other non-biologic and biologic disease-modifying anti-rheumatic drugs https://www.sciencedirect.com/science/article/abs/pii/S0049017213001704 Solomon 2020 Adverse Effects of Low-Dose Methotrexate: A Randomized Trial https://pubmed.ncbi.nlm.nih.gov/32066146/ Ruderman 2012 Overview of safety of non-biologic and biologic DMARDs

	https://academic.oup.com/rheumatology/article/51/suppl_6/vi37/1787789 Rudzki 2019 Risk of cancer after long-term therapy of autoimmune disorders with glucocorticoids or DMARDs—a controversial issue https://link.springer.com/article/10.1007/s12254-019-0506-5

- **Methotrexate is reported to be associated with an increased risk of infection, although the risk of MTX monotherapy alone being associated is debatable.**

• Methotrexate is reported to be associated with an increased risk of infection, although the risk of MTX monotherapy alone being associated is debatable. • Opportunistic infection reported (but typically in patients treated with MTX and another systemic agent, often prednisone)	Naldi L and Griffiths, CEM. 2005. Traditional therapies in the management of moderate to severe chronic plaque psoriasis: an assessment of the benefits and risks. BJD. https://doi.org/10.1111/j.1365-2133.2005.06563.x Kaushik, SB and Lebwohl, MG. 2019. Review of safety and efficacy of approved systemic psoriasis therapies. Int J Dermatol. 10.1111/ijd.14246

Caveats:

- Additional caveats may be added from survey results.

Statement 6: Systemic Agent (CsA)

6.a. In patients with previously TST and psoriasis, systemic treatment of psoriasis with cyclosporine A (CsA) is unlikely to alter prognosis related to the previously TST.
6.b. Additional caution is warranted with CsA compared to other systemic treatment options as it may increase the risk of cutaneous squamous cell carcinoma.

Summary of Evidence:

Direct Evidence in Psoriasis:

Reference (Author, year, journal)	**Title**	**Study Type**	**N**	**Key Findings/Notes:**
Aydin 2014 Cutaneous and Ocular Toxicology	Cancer-free survival of psoriasis patients treated with methotrexate and cyclosporine combination.	Retrospective study	17/20 psoriasis patients on **MTX & CsA** combination therapy followed up for development of malignancy (3/20 patients lost to follow-up)	No increased cancer risk seen in the median 76 months follow-up time Caveat: small study, selection bias, combination of CsA AND MTX is rarely used in clinical practice, short duration of therapy.

Indirect Evidence (for above treatment class):

- **Risk of solid tumours is not increased in patients with psoriasis treated with CsA. No likely altered risk of progression or recurrence compared to the general TST population.**

- **For patients with actively TST, physicians should be cautious about adding CsA together in active treatment of malignancy given that it may increase skin cancer and infections.**

• Use of cyclosporine may be associated with an increased risk in malignancies, particularly cutaneous SCC, especially in patients with prior exposure to systemic PUVA • Use of CyA in solid organ transplant has been shown to increase risk of malignancy	Balak, DMW et al. 2020. Long-term Safety of Oral Systemic Therapies for Psoriasis: A Comprehensive Review of the Literature. Dermatol Ther (Heidelb). 10.1007/s13555-020-00409-4 Naldi L and Griffiths, CEM. 2005. Traditional therapies in the management of moderate to severe chronic plaque psoriasis: an assessment of the benefits and risks. BJD. https://doi.org/10.1111/j.1365-2133.2005.06563.x

- **Cyclosporine is associated with an increased risk of infection**

• Cyclosporine is associated with an increased risk of infection • In a multicenter prospective cohort, CyA had a 58% higher rate of infection than MTX over a 3.3 yr period	Kaushik, SB and Lebwohl, MG. 2019. Review of safety and efficacy of approved systemic psoriasis therapies. Int J Dermatol. 10.1111/ijd.14246 Davila-Seijo, P et al. 2017. Infections in Moderate to Severe Psoriasis Patients Treated with Biological Drugs Compared to Classic Systemic Drugs: Findings from the BIOBADADERM Registry. Invest Dermatol. 10.1016/j.jid.2016.08.034
• Long-term **ciclosporin** treatment is associated with renal toxicity, hypertension, non-melanoma skin cancer, neurological AEs and GI AEs (caution for active malignancy?)	Balak, DMW et al. 2020. Long-term Safety of Oral Systemic Therapies for Psoriasis: A Comprehensive Review of the Literature. Dermatol Ther (Heidelb). 10.1007/s13555-020-00409-4

- **MOA:**

• CsA (and other calcineurin inhibitors) is a promoter of tumour formation – mechanisms of SCC occurrence in patients on CsA is less likely attributable to immune suppression	Hojo et al. Nature 1999 Cyclosporine induces cancer progression by a cell-autonomous mechanism https://pubmed.ncbi.nlm.nih.gov/10028970/ Wu et al. Nature 2010. Opposing roles for calcineurin and ATF3 in squamous skin cancer. https://pubmed.ncbi.nlm.nih.gov/20485437/ Hofbauer et al. Exp Dermatol. 2010 Organ transplantation and skin cancer: basic problems and new perspectives https://pubmed.ncbi.nlm.nih.gov/20482618/

Caveats:

- Additional caveats may be added from survey results.

Statement 7: Acitretin

In patients with previously TST and psoriasis, systemic treatment of psoriasis with acitretin is unlikely to alter prognosis related to the previously TST.

Summary of Evidence:

Direct Evidence in Psoriasis:

Not studies/no direct evidence. Because acitretin is not categorized as an immunosuppressive or immune-modulating agent, it is not considered at "at risk" agent for cancer and is therefore not studied. Some guidelines recommend acitretin in immunocompromised patients (e.g., patients with HIV, patients with history of malignancy, due to its categorical classification as a non-immunosuppressive agent).

Indirect Evidence (for above treatment class):

- Acitretin is used as a way to prevent or minimize keratinocyte carcinoma in high-risk patients (eg solid organ transplant) (Cohen, E et al. 2022. Low-Dose Acitretin for Secondary Prevention of Keratinocyte Carcinomas in Solid-Organ Transplant Recipients. Dermatology). 10.1159/000515496
- Acitretin is not categorized as immunosuppressive, so is thought to not alter risk of infection in psoriasis patients (Davila-Seijo, P et al. 2017. Infections in Moderate to Severe Psoriasis Patients Treated with Biological Drugs Compared to Classic Systemic Drugs: Findings from the BIOBADADERM Registry. Invest Dermatol. 10.1016/j.jid.2016.08.034)
- Risk of solid tumours is not increased in patients with psoriasis treated with **acitretin**. No likely altered risk of progression or recurrence compared to the general TST population.

• Long-term treatment with **acitretin** could be associated with skeletal toxicity and hepatotoxicity, although evidence for skeletal toxicity is mixed and hepatotoxicity is rare, particularly at low doses. Other safety issues include hyperlipidemia and potential	Balak, DMW et al. 2020. Long-term Safety of Oral Systemic Therapies for Psoriasis: A Comprehensive Review of the Literature. Dermatol Ther (Heidelb). 10.1007/s13555-020-00409-4

for teratogenicity up to 2-3 years after discontinuation of treatment. (caution for active malignancy?)	

Caveats:

- Additional caveats may be added from survey results.

Statement 8: PDE4i (apremilast)

In patients with previously TST and psoriasis, systemic treatment of psoriasis with a PDE4i is unlikely to alter prognosis related to the previously TST.

Summary of Evidence:

Direct Evidence in Psoriasis:

Reference (Author, year, journal)	**Title**	**Study Type**	**N**	**Key Findings/Notes:**
Kahn 2019 Journal of Drugs in Dermatology	Treatment of Psoriasis With Biologics and Apremilast in Patients With a History of Malignancy: A Retrospective Chart Review.	Retrospective Chart Review	16 psoriasis patients with history of malignancy	None of the 16 patients (including 3/16 receiving concurrent cancer therapy and biologic Tx) had recurrence or progression of their cancer supporting safety or **biologics & Apremilast (PDE4i)**. They also demonstrated improvement in psoriasis. *Note: Patients were on multiple therapies for various durations. The longest duration therapy is noted below. **2 IL12/23i, IL23i** **4 IL17i** **5 TNFi** **5 APR**

Indirect Evidence (for above treatment class):

- Risk of solid tumours is not increased in patients with psoriasis treated with **apremilast (PDE4i)**. No likely altered risk of progression or recurrence compared to the general TST population. PDE4i, at doses used in dermatology, the effect size anticipated in terms of inflammation and potential effect of ST is modest to small. **Even with more potent PDE4i (roflumilast), there is no increased risk of solid tumours, so concerns for apremilast area likely not warranted.**

• In a small retrospective observational study of 95 PsA/PsC patients, no impact of apremilast on malignancy rates ○ More than 2 comorbidities, history of malignancy and previous biologic treatment negatively influenced PASI responses.	Balato, A et al. 2020. Long-term efficacy and safety of apremilast in psoriatic arthritis: Focus on skin manifestations and special populations. Dermatologic therapy. https://doi.org/10.1111/dth.13440
• Meta-analysis of relationship b/w malignancy and therapy for PsA. Overall cancer increase HR 1.29, more in classic DMARDS than biologics ○ 9 cohort studies were included, corresponding to a total of 43,115 PsA patients undergoing therapy. A significant positive association between therapy and increased risk for overall malignancy was found relative to the general population as the reference group (pooled RR, 1.29; 95% CI: 1.04-1.60). High heterogeneity was found (I(2) = 71.37%). Subgroup analysis reported that PsA patients treated with conventional synthetic disease modifying antirheumatic drugs (csDMARDs) presented increased cancer risk (pooled RR, 1.75; 95% CI: 1.40-2.18) but patients treated with biological disease modifying antirheumatic drugs (bDMARDs) did not (pooled RR, 0.957; 95% CI: 0.80-1.14). Compared to controls, patients with PsA undergoing treatment specifically are at increased risk for non-melanoma skin cancers (pooled RR, 2.46; 95% CI: 1.84-3.28). • Limitation **One working group author commented in the include/exclude sheet: insufficient power and inadequate control	Luo, X et al. 2019. Malignancy development risk in psoriatic arthritis patients undergoing treatment: A systematic review and meta-analysis. Seminars in arthritis and rheumatism. https://doi.org/10.1016/j.semarthrit.2018.05.009

- Based on very limited data, there is a small increased risk of serious infection associated with apremilast use in psoriasis patients.
  - For patients with actively TST, physicians should be cautious about adding apremilast together in active treatment of malignancy given that it may increase serious infections.

• Continued exposure to **apremilast** does not seem to increase the incidence of common AEs, such as gastrointestinal (GI) AEs, upper respiratory tract infections and headache, while the long-term risks for depression, suicidal thoughts and weight loss are unknown.	Balak, DMW et al. 2020. Long-term Safety of Oral Systemic Therapies for Psoriasis: A Comprehensive Review of the Literature. Dermatol Ther (Heidelb). 10.1007/s13555-020-00409-4
• Review of infections in real world associated with biologic and small molecule therapies in PsA and Ps. • Useful review with good citations supporting small increase in risk of serious infection in psoriasis, HR approx 1.5, Ps severity dependent, TNF slightly higher risk but apremilast and newer biologics are safe.	Siegel, SAR et al. 2019. In the Real World: Infections Associated with Biologic and Small Molecule Therapies in Psoriatic Arthritis and Psoriasis. Current Rheumatology Reports. https://doi.org/10.1007/s11926-019-0832-y
• large network meta-analysis pf Ps and PsA RCTs comparing efficacy, primarily, number of AE very low, no power to look at cancer. ○ Did not look at comparison of specific AEs (only total number of AEs) ○ ranked treatments according to their effectiveness (as measured by the PASI 90 score) and acceptability (the inverse of serious adverse effects)	Spidian, E et al. 2020. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Reviews. https://doi.org/10.1002/14651858.CD011535.pub3

Inference-based conclusion (from points below):	There is no data for apremilast, however there is some data for roflumilast, a more potent PDE4i used in other diseases. *Mention effect size** Generally, totality of the evidence examined indicated the overall, general risk is low. Discussion needs to take place with patients based on anxiety level, their risk, how long ago the cancer was etc."** Roflumilast, a more potent blocker of PDE4 than apremilast, doesn't show increase in ST, so arguably there are no concerns for apremilast.

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• There is no increase in solid tumours. • From Dr. Papp: At meeting, Dr. Kirchhof brought up a study, likely study cited in https://journals.sagepub.com/doi/10.4137/CCRPM.S7049 but I believe inappropriately citing https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2010.181.1_MeetingAbstracts.A4441. And even if it is correct, 12 months, 1500 patients in each arm, the statement is "numerical difference" • And then there is https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60304-3/fulltext#:~:text=The%20incidence%20of%20cancer%20was,group%20than%20the%20placebo%20group.&text=Analysis%20of%20malignancy%20for%20roflumilast%20500%20mcg%20group%20vs%20placebo.&text=Studies%20in%20animals%20also%20showed%20an%20increase%20in%20cancer%20on%20roflumilast. A lancet publication that suggested otherwise. • https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022522Orig1s000MedR.pdf which clearly indicates the tumours had nothing to do with Roflumilast. • https://www.ema.europa.eu/en/documents/assessment-report/daxas-epar-public-assessment-report_en.pdf a more sensible review – animal studies with olfactory tumours are irrelevant to humans • **Conclusion: even with more potent PDE4i (roflumilast), there is no increased risk of solid tumours, so concerns for apremilast area likely not warranted.**	• https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3085868/

Note: No articles came up in the search with PDE4i and solid tumours/cancer pathways. PDE4i, at doses used in dermatology, do not profoundly impact inhibitor pathways. Effect size anticipated in terms of inflammation and potential effect of ST is modest to small.

Caveats:

- Additional caveats may be added from survey results.

Statement 9: TYK2i

In patients with previously TST and psoriasis, systemic treatment of psoriasis with a TYK2i is unlikely to alter prognosis related to the previously TST.

Summary of Evidence:

Direct Evidence in Psoriasis:

Reference (Author, year, journal)	**Title**	**Study Type**	**N**	**Key Findings/Notes:**
No data – newer treatment, not yet approved for psoriasis.				

Indirect Evidence (for above treatment class):

- Based on limited data (emerging treatment, no long term studies) the risk of solid tumours is not increased in patients with psoriasis treated with **TYK2i**. No likely altered risk of progression or recurrence compared to the general TST population. JAKis were tested as a treatment for solid tumours, with no benefit shown to date.
- No increased risk of serious infection.
- Mechanistically, it's possible but unlikely that JAK-inhibitors, including TYK2i, could suppress or promote cancer, depending on the tumour microenvironment.

Inference-based conclusion (from points below):	TYKi blocks a specific JAK (TYK2) implicated in the JAK-STAT pathway. NOTE: Although the JAK-STAT pathway, and STAT3 activation specifically, is implicated in tumour progression, our focus here is on JAK blockade as STAT3 is activated by many different pathways (activation is further upstream). JAKis are being developed for testing as a treatment for solid tumours, however most of the trials testing JAKi for solid tumours (ex. Ruxolitinib) were either terminated early or did not show a benefit; one explanation is that JAKi is impeding immune cell function counteracting the drug's other anti-cancer effects – it is likely only a subset of solid tumours that will respond to JAKi

	Mechanistically, it's possible but unlikely that JAK-inhibitors, including TYK2i, could suppress or promote cancer, depending on the tumour microenvironment. *Mention effect size** Generally, totality of the evidence examined indicated the overall, general risk is low. Discussion needs to take place with patients based on anxiety level, their risk, how long ago the cancer was etc."**

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• STAT3 activation is associated with many cancers, including both hematologic malignancies and solid tumours	Pencik, Jet al. 2016. JAK-STAT signaling in cancer: From cytokines to non-coding genome. Cytokine. 10.1016/j.cyto.2016.06.017
• Hematologic malignancies with clear JAK mutations make JAKi logical, but targeting JAK/STAT pathway in solid tumours is less clear since they are not usually associated with JAK mutations ○ Difficult to target STAT3 directly, so targeting upstream (JAK) is more practical and many JAKi in development or being tested in solid tumours	Qureshy et al 2020. Targeting the JAK/STAT pathway in solid tumors. J Cancer Metastasis Treat. 10.20517/2394-4722.2020.58
• From Dr. Papp: *Sent review on STAT3 activation, talks about the cells, doesn't specifically mention all pathways STAT3 mediates.* • Stat3 mediates signaling from multiple receptors. • The role of stat3 is obvious dependent on mechanism of activation https://www.nature.com/articles/bjc2011246; https://www.nature.com/articles/srep17663 • Activation is complex in malignancy https://www.frontiersin.org/articles/10.3389/fonc.2018.00287/full • And then there is the whole canonical and non-canonical discussion https://www.frontiersin.org/articles/10.3389/fimmu.2017.00029/full which may not be true anyway (sited the IFN story because there is a large and confusing literature on canonical vs non canonical stat3)	Wook Jin. Role of JAK/STAT3 Signaling in the Regulation of Metastasis, the Transition of Cancer Stem Cells, and Chemoresistance of Cancer by Epithelial–Mesenchymal Transition. Cells 2020, 9, 217; doi:10.3390/cells9010217

• https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3063716/pdf/0110018.pdf an overview but, true to form, never went anywhere because stat3 was a tag-along signal	
• Most of the trials testing JAKi for solid tumours (ex. Ruxolitinib) were either terminated early or did not show a benefit; one explanation is that JAKi is impeding immune cell function counteracting the drug's other anti-cancer effects – it is likely only a subset of solid tumours that will respond to JAKi	Qureshy et al 2020. Targeting the JAK/STAT pathway in solid tumors. J Cancer Metastasis Treat. 10.20517/2394-4722.2020.58

Appendix (additional data considered at working group meetings, not summarized in detail above):

1.1.1.1 General ST population: What are the differences in overall survival for patients with TST in the general population? What factors contribute to differences in overall survival between patients with TST and the general population?

General Statements:	**TST patients are a heterogeneous group made up of different cancer diagnoses, heavily affected by country and socioeconomic status.** **Absolute numbers of TST patients are rising steadily with aging demographics, population growth though often age adjusted incidence rates are declining with public health measures, smoking avoidance, and better treatments for cancer and causative infectious diseases.** **Shortening of future lifespans may be related to delayed treatment toxicities (especially radiation, but also chemotherapies), second cancers, and comorbidities related to common risk factors.** **Much as we have become accustomed to treating patients with past histories of treated heart disease (bypass surgery, etc.) which might have been fatal in previous years, we will face increasing numbers of patients across medical specialties who have had histories of treated solid tumours. There is a trend to more ICI in more cancers (possibly 1/3 of all cancers by 2025 will be treated with CPI), maybe less chemo, more focused or less radiation.**
Implications for treatment of psoriasis in TST patients:	Increasingly, patients seeking treatments for Ps will have a history of ST and these patients will have inherent risk for cancer-related death regardless of psoriasis status and treatment choices. With increased ICI therapy in more cancers, there are implications for increased exacerbation of and new onset psoriasis or psoriatic arthropathy (sets up rationale for this work).

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• Higher death rates after TST. In part due to higher smoking rates in TST pts • Death rates improving over time esp for non small cell lung cancer (fig 1 and fig 6)	Siegel. Cancer Status 2021 CA CANCER J CLIN https://onlinelibrary.wiley.com/doi/10.3322/caac.21654

Estimated New Cases

Males			Females		
Prostate	248,530	26%	Breast	281,550	30%
Lung & bronchus	119,100	12%	Lung & bronchus	116,660	13%
Colon & rectum	79,520	8%	Colon & rectum	69,980	8%
Urinary bladder	64,280	7%	Uterine corpus	66,570	7%
Melanoma of the skin	62,260	6%	Melanoma of the skin	43,850	5%
Kidney & renal pelvis	48,780	5%	Non-Hodgkin lymphoma	35,930	4%
Non-Hodgkin lymphoma	45,630	5%	Thyroid	32,130	3%
Oral cavity & pharynx	38,800	4%	Pancreas	28,480	3%
Leukemia	35,530	4%	Kidney & renal pelvis	27,300	3%
Pancreas	31,950	3%	Leukemia	25,560	3%
All Sites	**970,250**	**100%**	**All Sites**	**927,910**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	69,410	22%	Lung & bronchus	62,470	22%
Prostate	34,130	11%	Breast	43,600	15%
Colon & rectum	28,520	9%	Colon & rectum	24,460	8%
Pancreas	25,270	8%	Pancreas	22,950	8%
Liver & intrahepatic bile duct	20,300	6%	Ovary	22,950	5%
Leukemia	13,900	4%	Uterine corpus	12,940	4%
Esophagus	12,410	4%	Liver & intrahepatic bile duct	9,930	3%
Urinary bladder	12,260	4%	Leukemia	9,760	3%
Non-Hodgkin lymphoma	12,170	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,500	3%	Brain & other nervous system	8,100	3%
All Sites	**319,420**	**100%**	**All Sites**	**289,150**	**100%**

FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2021. Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from the most recent observed data.

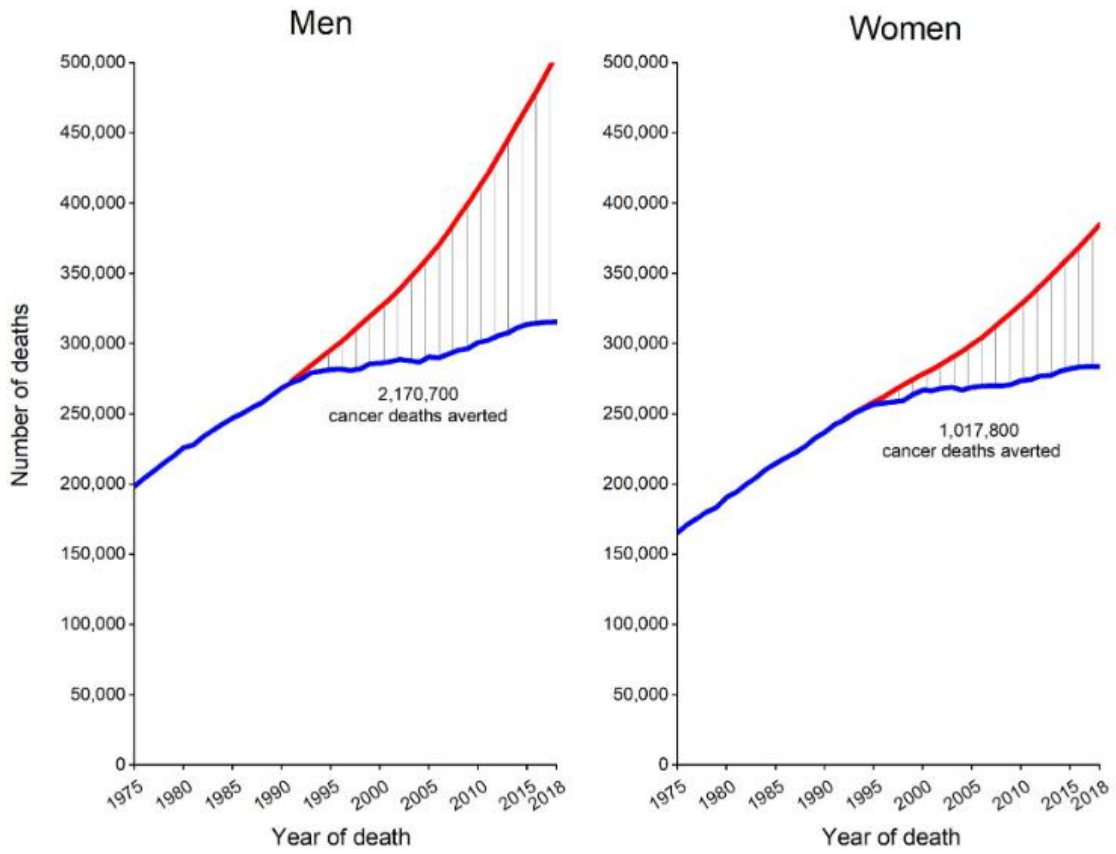


FIGURE 6. Total Number of Cancer Deaths Averted During 1991 to 2018 in Men and 1992 to 2018 in Women, United States. The blue line represents the actual number of cancer deaths recorded in each year; the red line represents the number of cancer deaths that would have been expected if cancer death rates had remained at their peak.

• Future life expectancy improves the further out from diagnosis, for survivors, slowly approaching general population life expectancy over time, fig 2.	https://doi.org/10.1093/annonc/mdv131

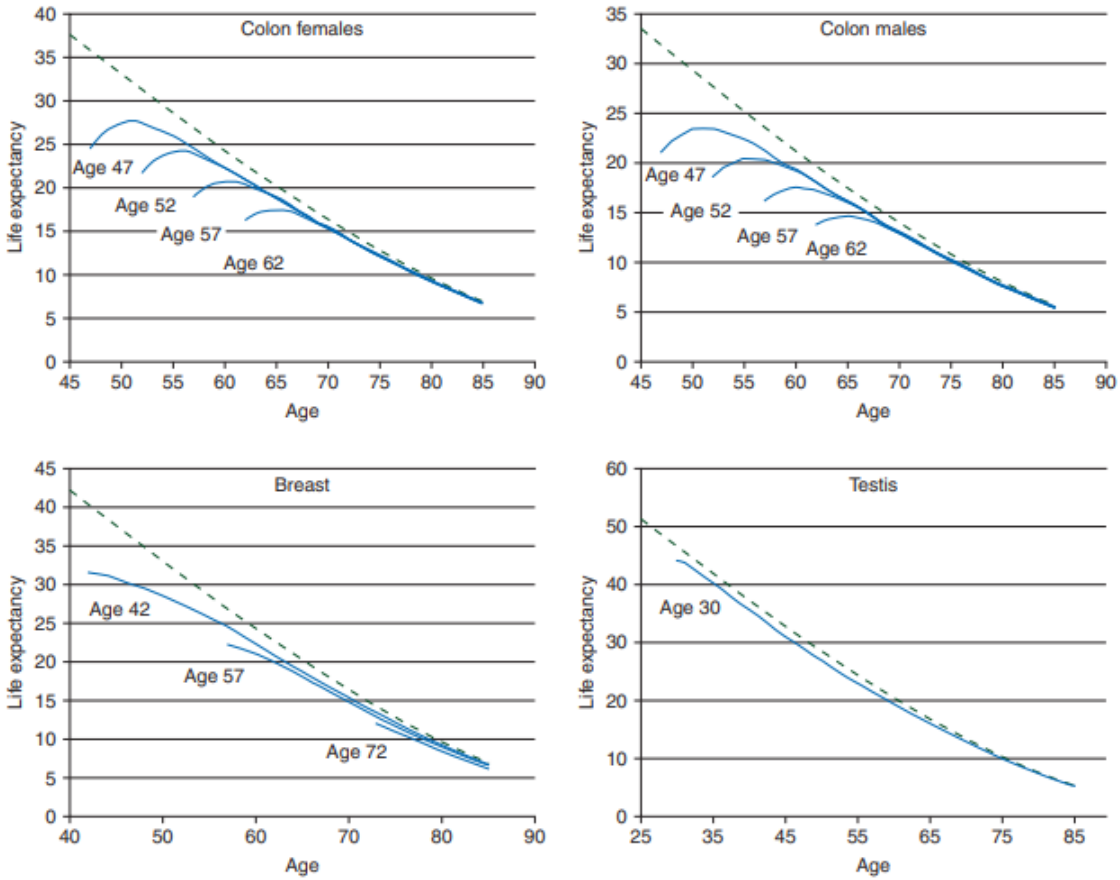


Figure 2. Life expectancy of the general population (dashed line) and of cancer patients according to attained age, by cancer type, and age at diagnosis. Analysis of SEER 9-registries data, period 2009–2011.

- TST survivors have generally poorer health, more cardiovascular disease (some overlapping risk factors for both cancer and heart: obesity, smoking, inactivity, diet)
- Long term risks of cytotoxic chemo and radiation treatments can lead to secondary cancers far in the future. Most data doesn't have long-term follow-up beyond 10-20yrs (except SEER).

- Global health statistics studies all suggest increased deaths numerically from cancers over time, driven by aging demographics and population growth but many cancers showing decreased age adjusted numbers

• Patterns of cancers reflect differences between higher and lower SEC countries • Cancer = leading cause now of premature mortality in developed countries (and 3-5th cause in developing nations)	https://linkinghub.elsevier.com/retrieve/pii/S0140673616310121 https://onlinelibrary.wiley.com/doi/10.3322/caac.21660 https://doi.org/10.1001/jamaoncol.2018.2706
• For pediatric and young adult cancer survivors, increased future incidence of other cancers but tied to radiation - less when radiation exposure minimized in modern protocols (Post-radiation cancers include: sarcomas (e.g. breast or angiosarcomas), numerically most are epithelial)	http://www.nejm.org/doi/10.1056/NEJMoa1510795 https://jamanetwork.com/journals/jamaoncology/fullarticle/2757844
• Socioeconomically deprived patients: higher loss of life expectancy esp with lung and stomach cancers in UK (Outcome data is skewed by country, access to resources and SEC)	http://www.nature.com/articles/bjc2017300
• With demographic changes, largest group of cancer survivors now >65 yo – unique survivorship issues and comorbidities (Shorter natural lifespan to develop other problems and unique survivorship challenges related to other pre-existing conditions that cancer treatment can exacerbate, e.g., heart disease, lipid/glucose imbalances with hormonal therapies)	https://doi.org/10.1158/1055-9965.EPI-16-0133

May also consider general principles from NCCN Survivorship Guidelines. V3.2021.
Additional comment from Oncologist: Patients who receive with chemo: Alkylating agents, doxorubicin, anthracyclines will have mildly increased lifetime risk of leukemia depending on dose received (from 0.5-1% increase)

Note on below table: Disease-Free Survival would answer question regarding tumour recurrence rates is important to ask, but hard to summarize. Disease free survival data is clinical trial/treatment specific. In phase 3 trials, different outcomes because of differences in the population, so below overview is more useful and accurate. The same trials repeated in UK or America will have different outcomes because of differences in the population that make it hard to summarize. Different databases use different staging that SEER - Staging systems evolve and get updated frequently, so looking at long spans of data it would be hard to interpret. Real world databases don't have encoded staging. Every cancer you see is not 1 disease, lung is 20 diseases, breast is 6. Movement in the next decade to treat based on molecular drivers instead of organ of origin, so representing the data this way makes the guidelines more malleable.

In table 1, oncologist included stomach cancer, esophageal cancer, liver cancer to represent low-income countries. The same cancer will have different outcomes based on country. E.g., Stomach cancer outcomes are better in Japan. Numbers will be different from jurisdiction to jurisdiction, rapidly evolving, definitions with new treatments.

1.1.4 What role do immunosuppression/immunomodulation, inflammation, and immunosurveillance play in oncogenesis? Do psoriasis treatments modify any of these pathways?

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• Net outcome of tumour associated inflammation depends on the dominance of either tumor promoting or tumor suppressive action. Chemotherapy and radiation can cause inflammatory responses. In depth article but no conclusion.	Chow et al Seminars in Cancer Biology 2012 22 23-32 https://doi.org/10.1016/j.semcancer.2011.12.004
• Immune surveillance is accepted as a host defense for malignancy. • Immunosuppressed patient have a higher incidence of tumors. • Immunoediting three phases : elimination, equilibrium and escape phase leading to a immunosuppressive tumor microenvironment	Ribatti Oncotarget 2017 https://doi.org/10.18632/oncotarget.12739
• Tumors elicit and inflammatory environment supporting their growth and suppressing tumor specific immune reaction.	Candeias and Gaipl Anti Cancer Agency 2016, 16, 101-107 https://doi.org/10.2174/1871520615666150824153523
• Mechanism of immune evasion breast cancer. • Breast microenvironment key. TIL's and subtypes may be prognostic. Ongoing trial by ECOG	Bates et al BMC Cancer 2018 18:556 https://doi.org/10.1186/s12885-018-4441-3
Inference-based conclusion (from points above):	None.

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• Chronic inflammation is a common cause of malignancy • Tumours take advantage of inflammatory response to evade immune surveillance – local and eventually general T-cell fatigue	Gonzalez, H et al. 2018. Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes and Dev. http://genesdev.cshlp.org/content/32/19-20/1267 Liu, Y and Cao, X. 2015. Immunosuppressive cells in tumor immune escape and metastasis. Journal of Molecular Medicine. https://link.springer.com/article/10.1007/s00109-015-1376-x
• Blocking immunosuppressive cells may enhance tumour detection and elimination • IL-17 and Th17 cells are thought to be involved in recruitment of immune suppressive cells	Liu, Y and Cao, X. 2015. Immunosuppressive cells in tumor immune escape and metastasis. Journal of Molecular Medicine. https://link.springer.com/article/10.1007/s00109-015-1376-x
• immunoediting and inflammation are independent and concurrent players in carcinogenesis. (note, myD88 is dispensible in humans and is more commonly associated with hematological malignancies in humans) supporting the roles of inflammation as a tumour inducer and tumour promoter	Swann, JB et al. 2007. Demonstration of inflammation-induced cancer and cancer immunoediting during primary tumorigenesis. PNAS. https://www.pnas.org/doi/pdf/10.1073/pnas.0708594105
• Numerous T-cells, T-regs in particular, are associated with tumours. Local t-cell exhaustion – the result of chronic inflammation, provides a permissive environment for malignant growth	Zheng, L et al. 2021. Pan-cancer single-cell landscape of tumor-infiltrating T cells. Science. https://www.science.org/doi/10.1126/science.abe6474
• Liver cancer as a paradigm of chronic inflammation inducing malignancy (infectious, lifestyle, toxins associated). Adaptive and innate immune processes are drivers. Note the presence of CD8+, Th17, and B cells.	Yang, YM et al. 2019. Inflammation and Liver Cancer: Molecular Mechanisms and Therapeutic Targets. Semin Liver Dis. https://www.thieme-connect.de/products/ejournals/abstract/10.1055/s-0038-1676806
• Inflammation while an inducer of malignancy, is necessary to eliminate malignancy. Chronic inflammation is immunosuppressive.	Shalapour, S and Karin, M. 2015. Immunity, inflammation, and cancer: an eternal fight between good and evil. JCI. https://www.jci.org/articles/view/80007 https://www.dovepress.com/the-association- Sacdalan, DB and Lucero, JA. 2021. The Association Between Inflammation and Immunosuppression: Implications for ICI Biomarker Development. OncoTargets and Therapy. https://www.dovepress.com/the-association-between-inflammation-and-immunosuppression-implication-peer-reviewed-fulltext-article-OTT

• IL17 appears to be an important modulator and plays a dual role in pro- and anti-tumor immune response. • IL17 is associated with several common malignancies that are driven by chronic inflammation (ovarian, prostate, lung cancer, gastric cancer, pancreatic, colorectal, liver, SCC skin cancer, melanoma, cervical, breast)	Marques, HS et al. 2021. Relationship between Th17 immune response and cancer. World J Clin Oncol. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8546660/ Asadzadeh, Z et al. 2017. The paradox of Th17 cell functions in tumor immunity. Cell Immunol. https://pubmed.ncbi.nlm.nih.gov/29103586/ Marchall, EA et al. 2016. Emerging roles of T helper 17 and regulatory T cells in lung cancer progression and metastasis. Mol Cancer. https://pubmed.ncbi.nlm.nih.gov/27784305/ Najafi, S and Mirshafiey, A. 2019. The role of T helper 17 and regulatory T cells in tumor microenvironment. Immunopharmacol Immunotoxical. https://pubmed.ncbi.nlm.nih.gov/30714422/
Inference-based conclusion (from points above):	Chronic inflammation is carcinogenic. Chronic inflammation results in T-cell exhaustion thus providing a permissive environment for tumour development, growth, and metastasis. IL-17 and Th17 cells are often associated with chronic inflammatory processes including those associated with malignancies.

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• Cancer formation is a complex of processes involving genetics, immune pathways, environment, diet, and lifestyle.	Canadian Cancer Society. https://cancer.ca/en/cancer-information/what-is-cancer/what-causes-cancer Ames, BN et al. 1995. The causes and prevention of cancer. Proc. Natl. Acad. Sci. USA. https://www.pnas.org/doi/pdf/10.1073/pnas.92.12.5258 Blackadar, CB. 2016. Historical review of the causes of cancer. World J Clin Oncol. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4734938/
• Age is by far the greatest risk factor • (for an interesting comparison, compare to age associated mortality of covid)	National Cancer Institute. https://www.cancer.gov/about-cancer/causes-prevention/risk/age DePinho, RA. 2000. The age of cancer. Nature. https://www.nature.com/articles/35041694 White, MC et al. 2014. Age and Cancer Risk: A Potentially Modifiable Relationship. American Journal of Preventative Medicine. https://www.sciencedirect.com/science/article/pii/S0749379713006429
• Environmental and lifestyle factors, excluding UV exposure, are minor contributors to overall cancer risk	Danaei, G et al. 2005. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. The Lancet.

	https://www.sciencedirect.com/science/article/pii/S0140673605677252 Ames, BN et al. 1995. The causes and prevention of cancer. Proc. Natl. Acad. Sci. USA. https://www.pnas.org/doi/pdf/10.1073/pnas.92.12.5258
• Occupational exposure is an important but minor contributor	Doll, R and Peto R. 1981. The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today. JNCI. https://academic.oup.com/jnci/article-abstract/66/6/1192/1076736
• Infectious causes – chronic infections, like chronic inflammation, are a common cause of malignancy	Blackadar. 2016 Historical review of the causes of cancer World J Clin Oncol. Feb 10; 7(1): 54–86. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4734938/
• Cancer mortality accounts for 28% of deaths. Skin cancers are the most common malignancy though they are rarely fatal. Epithelial cancers are the most common cancers (see references above on age and ca)	Canadian Cancer Society. https://cancer.ca/en/research/cancer-statistics/cancer-statistics-at-a-glance#:~:text=Chances%20(probability)%20of%20developing%20or,expected%20to%20die%20from%20cancer. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/cancer
• Most frequent causes of death – malignant solid tumours. Lung, colon/rectum, pancreas, breast, prostate	National Cancer Institute, Surveillance, Epidemiology and End results Program. https://seer.cancer.gov/statfacts/html/common.html
Inference-based conclusion (from points above):	T-cell exhaustion resulting from immunosenescence, chronic infection, or chronic inflammation provide an opportunity for tumour development, growth, and metastasis. Th17, IL17, IL23, and TNF are associated with chronic inflammation

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• Chronic Inflammation is associated with cancer risk	Greten, FR and Grivennikov, SI. 2019. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. Immunity. https://www.cell.com/immunity/fulltext/S1074-7613(19)30295-X
• Chronic inflammation and prostate cancer	De Marzo, AM et al. 2007. Inflammation in prostate carcinogenesis. Nature Reviews Cancer. https://www.nature.com/articles/nrc2090 Sfanos, KS and De Marzo, AM. 2012. Prostate cancer and inflammation: the evidence. Histopathology. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4029103/

	deBono, JS et al. 2020. Prostate carcinogenesis: inflammatory storms. Nature Reviews Cancer. https://www.nature.com/articles/s41568-020-0267-9
• Breast cancer and associated inflammation is more complex	Picon-Ruiz, M et al. 2017. Obesity and Adverse Breast Cancer Risk and Outcome: Mechanistic Insights and Strategies for Intervention. CA A Cancer J Clinicains. https://acsjournals.onlinelibrary.wiley.com/doi/pdfdirect/10.3322/caac.21405 Howe, LR. 2007. Inflammation and breast cancer. Cyclooxygenase/prostaglandin signaling and breast cancer. Breast Cancer Research. https://breast-cancer-research.biomedcentral.com/articles/10.1186/bcr1678 DeNardo DG and Coussens, LM. 2007. Inflammation and breast cancer. Balancing immune response: crosstalk between adaptive and innate immune cells during breast cancer progression. Breast Cancer Research. https://link.springer.com/article/10.1186/bcr1746 Cole, SW. 2009. Chronic inflammation and breast cancer recurrence. J Clin Oncol. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4828958/
• Lung cancer is associated with chronic inflammation	Engels, EA. 2014. Inflammation in the development of lung cancer: epidemiological evidence. Expert Review of Anticancer Therapy. https://www.tandfonline.com/doi/abs/10.1586/14737140.8.4.605 Walser, T et al. 2008. Smoking and Lung Cancer. Proc Am Thorac Soc. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4080902/ Brenner, DR et al. 2011. Previous Lung Diseases and Lung Cancer Risk: A Systematic Review and Meta-Analysis. PLOS One. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0017479 Conway, EM et al. 2015. Macrophages, Inflammation, and Lung Cancer. American Journal of Respiratory and Critical Care Medicine. https://www.atsjournals.org/doi/full/10.1164/rccm.201508-1545CI Engels, EA et al. 2017. Systematic Evaluation of Genetic Variants in the Inflammation Pathway and Risk of Lung Cancer. CA A Cancer J Clinicians. https://www.medpagetoday.com/upload/2007/7/5/0008-5472.CAN-07-0370v1.pdf
• Inflammation is associated with colorectal cancer risk	Givennikov, SI. 2013. Inflammation and colorectal cancer: colitis-associated neoplasia. Seminars in Immunopathology. https://link.springer.com/article/10.1007/s00281-012-0352-6

	Wang, S et al. 2009. NF-KB Signaling Pathway, Inflammation and Colorectal Cancer. Cellular and Molecule Immunology. https://www.nature.com/articles/cmi200943.pdf?origin=ppub Rhodes, JM and Campbell, BJ. 2002. Inflammation and colorectal cancer: IBD-associated and sporadic cancer compared. Trends in Molecular Medicine. https://www.sciencedirect.com/science/article/abs/pii/S1471491401021943 Kraus, S and Arber, N. 2009. Inflammation and colorectal cancer. Current Opinion in Pharmacology. https://www.sciencedirect.com/science/article/abs/pii/S1471489209000812 Canavan, C. et al. 2006. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. AP&T. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2036.2006.02854.x
• Inflammation is associated with pancreatic cancer	Juan-Juan, D et al. 2017. Inflammation-Related Pancreatic Carcinogenesis. Pancreas. https://journals.lww.com/pancreasjournal/Abstract/2017/09000/Inflammation_Related_Pancreatic_Carcinogenesis_.2.aspx
Inference-based conclusion (from points above):	

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**
• Viral infections (HBV and HCV) alter cellular signalling. HBC in part by integrating viral DNA into host DNA, and both through viral proteins causing disruptive cellular signalling (chromosomal instability). Associated chronic inflammation resulting from immunological responses endeavouring to constrain the persistent infection, results in fibrosis and T-Cell exhaustion(see above) both of which result in a more permissive environment for the development, growth, and metastasis of malignancy. Chronic inflammation may result in chromatin breaks.	Tsai, WL and Chung, RT. 2010. Viral hepatocarcinogenesis. Oncogene. https://www.nature.com/articles/onc201036 Lemon, SM and McGivern, DR. 2012. Is Hepatitis C Virus Carcinogenic? HHA Author Manuscripts. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4422399/ Kremsdorf, D et al. 2006. Hepatitis B virus-related hepatocellular carcinoma: paradigms for viral-related human carcinogenesis. Oncogene. https://www.nature.com/articles/1209559 Levrero, M and Zucman-Rossi, J. 2016. Mechanisms of HBV-induced hepatocellular carcinoma. Journal of Hepatology.

There is a small, theoretical risk of causing active infection with HBV virus but an anticipated benefit in treating patients infected with HVC with TNF antagonists (no references provided here).	https://www.journal-of-hepatology.eu/article/S0168-8278(16)00152-5/fulltext Fung, J et al. 2009. Hepatitis B and C virus-related carcinogenesis. CMI. https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(14)61803-6/fulltext Cougot, D et al, 2008. Carcinogenesis Induced by Hepatitis B Virus. Transl Res Biomed. https://www.karger.com/Article/PDF/141035#:~:text=Epidemiological%20studies%20have%20established%20that,humans%20%5B1%2C%202%5D. Tarocchi, M et al. 2014. Molecular mechanism of hepatitis B virus-induced hepatocarcinogenesis. WJD. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4155355/ Mas, VR et al. 2009. Genes Involved in Viral Carcinogenesis and Tumor Initiation in Hepatitis C Virus-Induced Hepatocellular Carcinoma. Molecular Medicine. https://molmed.biomedcentral.com/articles/10.2119/molmed.2008.00110 Uehara, T et al 2013. Molecular Mechanisms of Fibrosis-Associated Promotion of Liver Carcinogenesis. Toxicological Sciences. https://academic.oup.com/toxsci/article/132/1/53/1650419
• HPV increases the risk of carcinogenesis by mechanisms similar to HBV and HCV.	Williams, VM et al. 2010. HPV-DNA integration and carcinogenesis: putative roles for inflammation and oxidative stress. Future Virology. https://www.futuremedicine.com/doi/10.2217/fvl.10.73 Castellsague, X et al. 2002. Environmental co-factors in HPV carcinogenesis. Virus Research. https://hdgo.hr/userFiles/upload/documents/ginekologija/upalne_bolesti/HPV/5a_environmental-risk-HPV.pdf Chan, CK et al. 2019. Human Papillomavirus Infection and Cervical Cancer: Epidemiology, Screening, and Vaccination—Review of Current Perspectives. Journal of Oncology. https://www.hindawi.com/journals/jo/2019/3257939/ Narisawa-Saito, M and Kiyono, T. 2007. Basic mechanisms of high-risk human papillomavirus-induced carcinogenesis: Roles of E6 and E7 proteins. Cancer Science.

	https://onlinelibrary.wiley.com/doi/full/10.1111/j.1349-7006.2007.00546.x Wany, X et al. 2018. Involvement of Human Papillomaviruses in Cervical Cancer. Frontiers in Microbiology. https://www.frontiersin.org/articles/10.3389/fmicb.2018.02896/full
• Cutaneous squamous cell carcinoma risk is primarily from UVB exposure (1) • Broad and generally profound immunosuppression is associated with an increased risk of development and metastatic risk (2,3,4) – risk increases by more than one order of magnitude (40 – 200 fold increase). The implications of this – small increases are more likely the result of inadequate correction for risk, observational or selection bias • Somatic mutations are associated with high risk of metastasis (5) https://www.jci.org/articles/view/57415 (references herein)	Gandhi Med Clin North Am. 2015 Skin Cancer Epidemiology, Detection, and Management PMID 26476255 Tessari Dermatol Surg 2012 Nonmelanoma skin cancer in solid organ transplant recipients: update on epidemiology, risk factors, and management PMID 22805312 Zwald JAAD 2011 Skin cancer in solid organ transplant recipients: advances in therapy and management: part I. Epidemiology of skin cancer in solid organ transplant recipients PMID 21763561 Kuschal Exp Dermatol 2012 Skin cancer in organ transplant recipients: effects of immunosuppressive medications on DNA repair PMID 22151386 Zilberg Nature 2017 Analysis of clinically relevant somatic mutations in high-risk head and neck cutaneous squamous cell carcinoma https://www.nature.com/articles/modpathol2017128
Inference-based conclusion (from points above):	• Uncertainty: risk is cumulative. Intervention at a late stage cannot result in a significant benefit (see Ridker CANTOS NEJM). (The reported reduction in lung cancer is an incidental finding an very unlikely to be correct given the short observation period). • The conclusion, with the exception of csa and UVB which promote the development of cutaneous SCC, the treatments we use for ps are neither inducers nor promoters and may provide very small benefit by reducing the local inflammatory burden. Less clear, what is the effect size of reducing inflammation over a long period – say 2 decades or more – and at what cost? (not relevant to this exposition)

1.1.5.1 Do patients with a history of treated solid tumors (TST) receiving allografts have a similar mortality rates compared to the general transplant population when treated with immunosuppressive therapies?

	Some concerns warranted in TST psoriasis patients treated with systemic Pso therapies: **-Inflammation vs. infection-induced cancers- Perhaps extra caution if past cancer is infection-induced cancer? What are primary drivers/issues with oncogenic viruses? Appear to be 2-fold: 1) inflammation can provide environment for development of tumours 2) inflammation or incorporation of viral genetic material that results in genotoxocity that gives rise to malignancy. Whatever mechanisms, is there evidence that the pathways we're blocking are related to those phenomenon? For most part, we can say generically that no, but we should pursue this question. Dr. Sehdev: Speculative – and gets more and more speculative (H.Pylori, lymphomas of macular glands) that may be different mediated by chronic inflammation, getting out there. Rectal cancer may be related to retrovirus.** **-All cause-mortality is increased - what could this imply?** - **There is a pre-loaded risk associated with previous malignancy.** - **Always balance of risk/benefit. Whats the severity of psoriasis relative to risk.** - **Risk management: Stratify by prognosis from cancer – if good prognosis, concerns are lessened/no need to wait for 5 years (low risk). Worse prognosis cancers are not considered for transplant – so can't make direct inferences – but if underlying risk is there, how much additional risk will there by with pso treatment (we don't think there's not much of a risk, but we don't know VS we don't know for sure but we're pretty confident that there isn't much additional risk, patient decides). And can make better decision balancing QoL. Severity/symptomotology of psoriasis. Unlikely to make the prognosis worse. If prognosis is good we should not worry, if prognosis is bad, we should have risk/benefit discussion – <u>may be increased risk but not large risk</u> (*if we can get to this that would be ideal).** **Sehdev: Do we know if current biologics affect EBV/HPS/viral-related cancer? SCC/melanoma slightly increased with TNFi. MOA associated with HPV-related or viral-related cancers, or maintaining the viruses in check? Current biologics – do they affect HPV/EBV related cancers? What are the primary drivers of oncogenic infections? Imflammation can provide an environment for development of tumours. Incorporation of viral genetic material gives rise to malignancy. Is there evidence that pathways we're blocking are related to any of those phenomenon? **Theoretical concerns for viral transformative cancers.**

1.1.5.2 For patients who receive a transplant and subsequent immunosuppressive drugs, what is the risk of post-transplant malignancy?

Summary statement: Inference-based conclusion (from points below):	**In general, SOT recipients treated with broadly immunosuppressive agents have a higher risk of developing and dying from malignancy due to the effects of immunosuppression and increased susceptibility to oncogenic infections.**
Implications for treatment of psoriasis in TST patients:	**The immunosuppressive agents implicated in post-transplant malignancy do not affect the same pathways as immunomodulating agents used in psoriasis, and similar concerns are not warranted.** **From the SOT literature, we can glean some of the reasons for increased cancer risk in immunosuppressed patients (effects of immunosuppression, immunosenescence, increased susceptibility to oncogenic infections and the differential effects of these pathways on different types of cancer) and this helps frame the subsequent questions for psoriasis patients: is there evidence that the drugs/pathways targeted by psoriasis treatments are associated with an increase/decrease/neutral association with common solid tumours (question 1.1.4)? What's the role of immunosenescence, immunosurveillance, immunomodulation in cancer and do psoriasis therapies affect these pathways? Are infections, specifically oncogenic infections, increased with psoriasis treatments (question 1.1.3)?**

Observations or findings from the literature related to the clinical question of interest. *What are outcomes of interest, caveats and considerations.*	**References**	**RATING (to be rated by working group authors after meeting).**
SOT recipients have a <u>higher risk of developing</u> certain types of cancer. • Following is the list of various cancers associated with the organ transplant: **Kaposi sarcoma, Skin (nonmelanoma, nonepithelial), Non-Hodgkin lymphoma (NHL), Liver, Anus, Vulva, Lip** • Other common malignancies with a statistically significant ($p<0.001$) increase included: Lung, Kidney, Colon and rectum, Pancreas, Hodgkin's lymphoma, Melanoma • For recipients aged >50 years, the 5-year cumulative incidence was higher for colorectal cancer (CRC) (range, 0.33%-1.94%) than for the general population at the recommended screening age (aged 50 years: range, 0.25%-0.33%). For recipients aged >50 years, the 5-year cumulative incidence was high for lung cancer among thoracic organ recipients (range, 1.16%-3.87%) and for kidney cancer among kidney recipients (range, 0.53%-0.84%). The 5-year cumulative incidence for prostate cancer and breast cancer was similar or lower in transplantation recipients than at the recommended ages of screening in the general population.	Gogna 2021 **http://www.ncbi.nlm.nih.gov/books/NBK537256/** Hall 2013 **https://doi.org/10.1002/cncr.28043**	DO NOT RATE

• In kidney transplant recipients, the incidence of cancer is generally increased 2- to 3-fold compared with the general population. This increased cancer risk is not spread evenly over all types of cancers; while some cancer incidences are not increased (breast, prostate, ovarian, brain and cervical cancer), others are **increased substantially (lung, colon, liver, lymphoma, melanoma and non-melanoma skin cancer).** • An extensive cohort study with 175,732 SOT recipients showed cancers with the highest risk relative to the general population included Kaposi sarcoma (SIR [standardized incidence ratio] 61.5), lip (SIR 16.8), nonmelanoma skin (SIR 13.9), liver (SIR 11.6), vulvar (SIR 7.6), NHL (SIR 7.5), and anal (SIR 5.8). Interestingly, risk of breast and prostate cancers was lower in the transplant population (SIR 0.85 and SIR 0.92 respectively); Risk of cervical cancer was not increased (SIR 1.03). • Skin cancers are the most frequent malignancy observed in the transplant population, ultimately occurring in 8% of recipients and accounting for more than 40% of posttransplant malignancies. Lung transplant recipients have a twofold increase in NHL compared with kidney, liver, or heart transplant recipients. Additionally, lung cancer was most common in lung transplant recipients; the incidence of liver and kidney cancers is highest in the liver and kidney transplant recipients, respectively. • Kidney transplant recipients consistently show a 2- to 4-fold increased risk of cancer compared with the age and gender matched general population. The increased risk of malignancy is type specific, with the greatest risk being for KS (80-500 times more frequent), non-melanocytic and melanocytic skin cancers, NHL, CRC (2- to 3-fold), renal cell cancer and cancers of the anogenital tract (cervical cancer incidence is 2- to 3-times greater). Peak incidence is 3-5 years post-transplant; however, this varies with the age of the recipient and type of cancer. • The most common cancers in lung transplant recipients are non-melanoma skin cancers with Squamous cell carcinoma (SCC) being the most common with a 100-200-fold increased risk, followed by lung cancer and PTLD. Merkel cell carcinoma is 24-fold more common in transplant recipients. An increased risk for malignant melanoma with a relative risk of 2.7 compared to non-transplant patients was reported. SOT recipients are also at an increased risk for CRC. ○	Sprangers 2018 https://doi.org/10.1093/ckj/sfx122 Rossi 2019 https ://doi.org/10.1016/j.suc.2018.09.004 Rossi 2019 https ://doi.org/10.1016/j.suc.2018.09.004 Manickavasagar 2020 https://doi.org/10.7861/clinmed.2019-0423 Shtraichman 2020 https://doi.org/10.21037/atm.2020.02.126	
In general, malignancy-related <u>mortality rates post-transplant</u> are higher vs the general population stratified by age and gender. • Cancer Standardized mortality ratios (SMRs) varied substantially with age group; cancer SMRs were 23-fold and 4.4-fold higher in patients <20 years and 20–39 years of age, respectively, while cancer SMRs were lower in patients >60 years of age [5]. The cancer death rates were	Sprangers 2018 https://doi.org/10.1093/ckj/sfx122	

>500/100 000 patient-years for patients >60 years of age compared with 13/100 000 patient-years for patients 20–39 years of age [5]. So in older patients who are at the highest risk to die from cancer, there is no increased risk to die from cancer in kidney transplant recipients. • Caveat/note: **The data regarding standardized mortality rates (SMRs) have been conflicting**. While some studies have suggested that the cancer related SMR has increased with the same magnitude as the SIR in transplant recipients [224], other studies have shown a more nuanced picture [5]. • Among 19,103 kidney transplant procedures analyzed (median follow-up 4.4 years), 2085 deaths occurred, of which 376 (18.0%) were due to malignancy (crude mortality rate 361 malignancy-related deaths per 100,000 person-years). Common sites of malignancy-related death were lymphoma (18.4%), followed by lung (17.6%) and renal (9.8%), with 14.1% unspecified. The risk of malignancy-related death increased with age: under 50 (0.8%), 50–59 (2.5%), 60–69 (4.8%), 70–79 (6.5%) and over 80 years (9.1%). Age- and gender-stratified malignancy-related mortality risk difference was higher in the transplant compared with the general population. • De novo malignancies in SOT recipients are associated with worse outcomes compared to the general population. An Australian study of liver and cardiothoracic transplant recipients showed a twofold-increased mortality risk compared with the matched general population (SMR 2.83) Excess risk was observed regardless of transplanted organ, recipient age, or gender. (From Rossi, but references from Na R et al, *Am J Trans*. 2013;13(5):1296-304) • Post-transplant malignancy currently represents the 2nd most common cause of death in lung transplant recipients 5-10 years after transplant (17.3%) and for patients who were more than 10-years after the procedure (17.9%). The rates of nonmelanoma skin cancer and death from this malignancy are highest after lung transplantation. The incidence of Post-transplant lymphoproliferative disorders (PTLD) after lung transplantation has been reported to be between 3-9% and is associated with worse long-term survival and high mortality. Late-onset PTLD is generally associated with worse prognosis and a worse overall and chronic lung allograft dysfunction (CLAD)-free survival compared to the thoracic organ transplant recipients without PTLD.	Shtraichman 2020 https://doi.org/10.21037/atm.2020.02.126 Farrugia 2014 https://doi.org/10.1038/ki.2013.458 Rossi 2019 https ://doi.org/10.1016/j.suc.2018.09.004 Shtraichman 2020 https://doi.org/10.21037/atm.2020.02.126	
Malignancy post-transplant is primarily due to the effects of immunosuppression (from treatment with broadly immunosuppressive agents) and related decrease in cancer immunosurveillance and immunologic control over oncogenic infections/reactivation of latent infections. • **Immunosuppressive agents and oncogenesis**: The **immunosuppressive drugs impair immunosurveillance of neoplastic cells** and increase the incidence of virally induced malignancies. The type, intensity, and duration of immunosuppressive therapy all influence the	Gogna 2021 http://www.ncbi.nlm.nih.gov/books/NBK537256/	Do not complete.

rate of carcinogenesis. These immunosuppressive drugs, for example, biologic agents (anti-thymocyte globulin, basiliximab), corticosteroids, antimetabolites (azathioprine, mycophenolate mofetil), calcineurin inhibitors (cyclosporine, tacrolimus), and mTOR inhibitors (rapamycin [sirolimus], everolimus) all have been implicated (from Gogna 2021 but references Stallone 2015) ○ Calcineurin inhibitors (CNIs) stimulate carcinogenesis by inhibiting DNA repair mechanisms, apoptosis, and enhancing the production of interleukin 2 (IL-2), transforming growth factor (TGF), and vascular endothelial growth factor (VEGF). Transforming growth factor promotes tumor growth by regulating tumor cell invasion, metastatic potential, and VEGF stimulates neo-angiogenesis. Azathioprine increases cancer risk by causing post-replicative DNA mismatch repair. Sirolimus, everolimus and mycophenolate mofetil are not associated with an increased risk of cancer; they actually have antiproliferative properties. • Antibody therapies against T lymphocytes such as ATG and alemtuzumab, increase the risk of posttransplant malignancies; they are linked to an increased risk of posttransplant lymphoproliferative disorder (PTLD), melanoma, CRC, and thyroid cancer. PTLD is the 3rd most common malignancy in SOT recipients. CNIs in addition to the above are linked to increased IL-6 production, promoting B-cell activation, growth, and possible immortalization, facilitating oncogenic viral replication of EBV, HHV-8, and HPV. Use of Azathioprine after SOT found to be associated with an increased risk of squamous cell skin carcinoma (SCSC). Belatacept, which selectively blocks costimulation of T cells, showed an increased risk of PTLD in clinical trials. • Immunosuppression is considered the most important risk factor for post-transplant cancer development via multiple mechanisms, including decreased immune surveillance of cancers, decreased antiviral response facilitating unchecked replication of oncogenic viruses, interference with normal deoxyribonucleic acid repair mechanism, and possibly direct carcinogenic effect of immunosuppressive agents such as ciclosporin and azathioprine. • Lung transplant recipients receive more immunosuppression than other SOT populations, likely contributing to the observed higher rates of cancer in this population. Induction agents that deplete T-lymphocytes have been associated with an increased risk of cancer after SOT. Azathioprine is associated with increased risk for skin cancer; CNIs promote tumor development. In contrast, mTOR inhibitors may interfere with cancer cell proliferation and angiogenesis and	Stallone 2015 (Post kidney transplant malignancies) **https://doi.org/10.1093/ckj/sfv054** Rossi 2019 **https ://doi.org/10.1016/j.suc.2018.09.004** Manickavasagar 2020 **https://doi.org/10.7861/clinmed.2019-0423** Shtraichman 2020 **https://doi.org/10.21037/atm.2020.02.126**	

are associated with lower incidence of certain cancers such as KS, mantle cell lymphoma and nonmelanoma skin cancer. • **Viral Infection and oncogenesis**: Transplant patients are vulnerable to viral infection or reactivation of latent infection (EBV, Varicella, CMV, (HHV)-8, etc.) ○ EBV promotes the oncogenesis by reduced lymphocyte regulation, a lack of control of the oncogenic virus by EBV-specific CD81 cytotoxic T-cells, and proliferation of EBV-infected B cells. The mechanism by which HHV-8 induces oncogenesis has not been completely elucidated. HHV-8's proinflammatory proteins might directly inhibit apoptosis and promote cell transformation.[11] ○ Chronic viral infections are well-recognized mediators of specific cancers post-transplantation: HHV-8 and KS; HPV found in 64% to 90% of SCSC, though its role in post-transplant malignancy remains to be elucidated; anogenital, and head and neck cancers; EBV and PTLD, nasopharyngeal cancers; hepatitis B or C and hepatocellular carcinoma; Merkel cell polyomavirus detectable in more than 80% of Merkel cell carcinomas. ○ Viruses associated with carcinogenesis in the post-transplant setting include EBV associated with PTLD; HHV-8 associated with KS, multiple myeloma, multicentric Castleman disease and primary effusion lymphoma; HPV associated with cervical, vaginal, anal, head and neck cancers; Merkel cell polyomavirus associated with Merkel cell carcinoma; hepatitis B and hepatitis C associated with hepatocellular carcinoma. ○ In the setting of impaired cell-mediated immunity, oncogenic viruses such as EBV, HPV and others have emerged as major risk factors for cancer development, with majority of squamous cell cancers in the transplant population associated with HPV infection. • During 2000-2018, 2,852 Welsh patients underwent solid organ transplantation. A total of 13,527 controls were matched from the general population. The incidence of skin cancer within the OTR cohort was 1203.2 per 100,000 PYAR vs 133.9 in the matched control group. **Age, male gender and azathioprine use were all associated with an increased risk of skin cancer.** Contemporary immunomodulators such as tacrolimus and mycophenolate were associated with a reduction in skin cancer risk when compared to their predecessors, cyclosporin and azathioprine. The highest adjusted IRR was observed in heart transplant recipients (IRR: 10.82; 95% CI: 3.64-32.19) and the lowest in liver transplant recipients (IRR: 2.86; 95% CI: 1.15-7.13).	Gogna 2021 **http://www.ncbi.nlm.nih.gov/books/NBK537256/** Martinez et al, 2008 **https://onlinelibrary.wiley.com/doi/10.1111/j.1600-6143.2008.02368.x** Rossi 2019 **https ://doi.org/10.1016/j.suc.2018.09.004** Manickavasagar 2020 **https://doi.org/10.7861/clinmed.2019-0423** Gibson 2021 **https://doi.org/10.1684/ejd.2021.4108**	

• Among the gynecologic cancers, including uterine, cervical, vaginal, vulvar, and ovarian, the HPV-related cancers are known to increase among women posttransplant compared to women in the general population, but less is known about the risk of uterine and ovarian cancers. Two of the gynecologic cancers, uterine and ovarian cancers, are primarily hormone-regulated cancers.5 The other three gynecologic cancers—cervical, vulvar, and vaginal cancers, and their high-grade precursor lesions that require treatment to avoid progression—are often related to persistent high-risk human papillomavirus (HPV) infection in the setting of immune suppression.6 **Data on the direct effect of specific immunosuppressants on gynecologic, including oncogenic virus-related, cancers is sparse and often conflicting**.	Liao 2019 **https ://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.15292**	