



GUIDELINES

# 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

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## ABSTRACT

**Background:** Patients with treated solid tumours (TSTs) are a highly heterogeneous population at an increased risk for malignancy compared with the general population. When

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treating psoriasis in patients with a history of TSTs, clinicians are concerned about the immunosuppressive nature of psoriasis therapies, the possibility of augmenting cancer recurrence/progression, and infectious complications. No direct, high-level evidence exists to address these concerns.

**Objectives:** We aim to provide a structured framework supporting healthcare professional and patient discussions on the risks and benefits of systemic psoriasis therapy in patients with previously TSTs. Our goal was to address the clinically important question, “In patients with TSTs, does therapy with systemic agents used

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for psoriasis increase the risk of malignancy or malignancy recurrence?"

**Methods:** We implemented an inference-based approach relying on indirect evidence when direct clinical trial and real-world data were absent. We reviewed indirect evidence supporting inferences on the status of immune function in patients with TSTs. Recommendations on systemic psoriasis therapies in patients with TSTs were derived using an inferential heuristic.

**Results:** We identified five indirect indicators of iatrogenic immunosuppression informed by largely independent bodies of evidence: (1) overall survival, (2) rate of malignancies with psoriasis and systemic psoriasis therapies, (3) rate of infections with psoriasis and systemic psoriasis therapies, (4) common disease biochemical pathways for solid tumours and systemic psoriasis therapies, and (5) solid organ transplant outcomes. On the basis of review of the totality of this data, we provided inference-based conclusions and ascribed level of support for each statement.

**Conclusions:** Prior to considering new therapies for psoriasis, an understanding of cancer prognosis should be addressed. Patients with TSTs and a good cancer prognosis will have similar outcomes to non-TST patients when treated with systemic psoriasis therapies. For patients with TSTs and a poor cancer prognosis, the quality-of-life benefits of treating psoriasis may outweigh the theoretical risks.

## PLAIN LANGUAGE SUMMARY

Patients with previously treated cancer have a higher chance of cancer recurrence compared with the general population. With cancer incidence rising worldwide, doctors across medical specialities will need to treat other medical conditions, including inflammatory diseases such as psoriasis, in these patients. Effective systemic therapies for psoriasis reduce immune cell activity. Accordingly, there are concerns that treatments for psoriasis could worsen cancer recurrence/progression and infectious

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complications. There is not enough quality evidence to make broad recommendations for treating other inflammatory conditions in patients with a history of cancer. To guide patient and doctor discussions, we asked: what are effective and safe treatments when patients with treated solid tumours need systemic therapy (pills or injections) for their psoriasis? We focused on patients with solid tumours and excluded blood and skin cancers. Our panel of experts, including 12 dermatologists and 3 medical oncologists, reviewed direct and indirect evidence to answer this question. Considering the totality of evidence reviewed, the expert panel drafted and rated their level of support for opinion statements on important considerations in treating patients with psoriasis who have a history of solid tumours. By making inferences on systemic psoriasis therapies in this heterogeneous population, we take the onus off individual physicians to review the indirect data. This process may help answer questions in other disease populations where direct evidence is scarce or absent. To support treatment decisions, doctors should have a guided conversation with the patient and their family on a case-by-case basis about the risks and benefits of treatment.

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### Key Summary Points

Patients with treated solid tumours (TSTs) are a highly heterogeneous population that differ on the basis of cancer type, including stage and tissue of origin, mutational status of cancer, cancer prognosis and cancer treatment received.

Use of systemic psoriasis therapies in these patients is hindered by concerns about the possibility of augmenting cancer recurrence/progression or infectious complications.

Given the limited direct evidence to answer the clinical question, the present guidance document uses an inference-based approach to explore the risks and benefits imposed on patients with a history of TSTs when their psoriasis is treated with systemic psoriasis therapies to provide a structured framework that helps guide treatment decisions.

This framework supports a discussion between healthcare professionals and their patients about the risks and benefits of systemic psoriasis therapy in patients with previously TSTs.

The initiation of systemic psoriasis therapy after cancer treatment largely depends on immune reconstitution post-cancer treatment that depends primarily on the type of cancer treatment received rather than on the type of solid tumour or other factors (stage, mutational status, etc.).

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## INTRODUCTION

While cancer incidence is rising steadily worldwide [1], mortality rates and age-adjusted incidence rates of many solid tumours (STs) are declining [2]. Declining rates result from public health measures, lifestyle modification (especially the avoidance and cessation of cigarette smoking), and better treatments for both cancer and causative infectious diseases [2]. Accordingly, clinicians across medical specialities more frequently encounter patients with a history of treated solid tumours (TSTs). Lifespans of patients with TSTs remain shortened due to delayed cancer treatment toxicities: radiation therapy and certain chemotherapy regimens; secondary cancers; and comorbidities related to common risk factors [3]. Challenges arise in providing recommendations for treating other medical conditions in patients with TSTs due to the heterogeneity of cancer outcomes across different types and stages of solid tumours. In addition, cancer outcome data are skewed by various factors including country, access to resources, and socioeconomic status [4]. Socioeconomically deprived patients with cancer experience a higher loss of life expectancy, primarily from lung and stomach cancers, compared with non-socioeconomically deprived patients [5]. Owing to the heterogeneity and complexity of the topic, there is a need to provide guidance for treating other diseases, such as psoriasis, in patients with TSTs.

In patients with psoriasis, clinicians are concerned about the immunosuppressive nature of systemic psoriasis therapies. Specific concerns include possible augmentation of cancer recurrence/progression and infectious complications in patients with past or active malignancy. Additionally, there is a concern that poor outcomes in cancer survivors might be ascribed to the systemic psoriasis therapy. Notably, cancer survivors have a 14% increased risk of new or recurrent malignancies compared with the general population [6]. In addition, these patients have inherent risk for cancer-related death regardless of psoriasis status and treatment choices [3]. Anticipating that immune processes, treatment paradigms, and

risks may differ between broad tumour categories, we focused on patients with TSTs and excluded hematopoietic and cutaneous malignancies.

The objective of this work is to provide a structured framework exploring the risks and benefits for patients with TSTs when treating their psoriasis with systemic psoriasis therapies (which includes biologics and small molecules). A multidisciplinary panel of dermatologists and oncologists was convened to provide guidance on the main clinical question, "Are responses (including drug-related adverse effects and benefits) to systemic psoriasis therapies in patients with TSTs similar to the general psoriasis population?" Answering this question proved to be complex due to the limited direct evidence and heterogeneity of the TST patient population. Patients with TSTs are excluded from clinical trials of agents to treat psoriasis. Observational cohort studies in inflammatory disorders have too few patients with TST to provide meaningful results [7–9]. With very limited direct evidence available to answer the clinical question, the panel employed an inference-based approach reviewing indirect evidence relevant to the immune status of patients with TSTs. Levels of evidence and grading of evidence cannot, at this time, be ascribed to the recommendations herein. Rather than providing directive statements, the intended outcome is the development of statements supporting informed discussions between healthcare professionals and their patients regarding the risks and benefits of systemic psoriasis therapy in patients with TSTs. The expert panel defined solid tumours broadly and did not explore the complexities of specific types of solid tumours. Different cancer treatments were explored, with resultant recommendations dependent on the type of therapy received and cancer prognosis. The conclusions are agnostic to specific immune pathways and are therefore applicable to a larger audience of healthcare professionals who manage immune-mediated conditions.

## METHODS

A panel of 12 dermatologists and 3 medical oncologists (BM, SS, SH) convened following the framework of the New Psoriasis Guidelines group [10]. Through panel discussions directed towards identifying observable scenarios with addressable questions, the primary question was deconstructed in multiple revisions using a layered, inference-based approach (Table S1, Supplementary Material). Our original objective was to identify data assessing immune response in patients with previously and currently TSTs, thereby identifying the potential for altered risk or efficacy when treating psoriasis with a systemic psoriasis therapy. Structured systematic or scoping literature searches were conducted for each deconstructed question from December 2021 to January 2022. See Supplementary Material for literature search keywords. Working group authors summarised key evidence per topic and met in April and May of 2022 to discuss their summaries. Considering the totality of the evidence reviewed, the chairs (KAP, VP) reconstructed statements to address the overarching questions, where possible. Oncologists reviewed and revised the statements prior to all-author rating in September 2022. This study quantifies expert-elicited level of support for inference-based conclusions. A data summary of key evidence reviewed at the working group meetings was provided to all panel members (Supplementary Material), who then rated statements via online surveys, providing their level of support/confidence/agreement with upper and lower values to represent their range of uncertainty in the level of support. Experts provided their ratings on a scale of 0–100% based on approximate, verbal transformations of subjective probability for use in expert elicitation [11]. Here, rating 90% meant the statement was likely to be true, and 99% meant the statement was very likely to be true (Fig. S1, Supplementary Material). Ethics committee approval was not required per section 2.3b of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), as experts who participated in the surveys are

published authors on this work and therefore had no expectation of privacy.

### Data Analysis

Individual levels of support were fitted to beta-distributions assuming the lower, likely, and upper estimates were 2.5th, 50th, and 97.5th percentiles, respectively. The estimated beta-distributions were combined using averaging and Bayesian analyses to arrive at the estimated prevalence of psoriasis in the adult population. All analyses were performed using R statistics software [12]. Best fit beta-distribution using the quantile estimates provided by each expert was analysed using the `betaparms` function of the `riskDistributions` package (v2.1.2; Belgorodski 2017; <https://github.com/cran/riskDistributions>). Bayesian estimates were derived using one of the determined beta-distributions as the prior probability distribution. The averaged distribution parameters were determined by averaging the means and standard deviations of the panel member beta-distributions.

## RECOMMENDATIONS AND SUPPORTING EVIDENCE

We reviewed indirect evidence to support inferences on the status of immune function in patients with previously TSTs considering a systemic psoriasis therapy. Five indirect indicators of immune function were explored, informed by largely independent bodies of evidence: (1) overall survival (populations included general patients with TSTs and patients with TSTs and psoriasis), (2) rate of malignancies with psoriasis and systemic psoriasis therapies, (3) rate of infections with psoriasis and systemic psoriasis therapies, (4) common disease biochemical pathways for STs and systemic psoriasis therapies, and (5) solid organ transplant outcomes (including patients with TSTs pre-transplant and patients with post-transplant malignancy). The inference-based concluding statements made on the basis of review of the totality of these data and level of support for each statement are summarised below and

**Table 1** Core recommendations and level of support

Statements	Level of support for statements (0–100)	
	Mean support (0.025, 0.975 confidence intervals)	Bayes median support (0.025, 0.975 credibility intervals)
1. For patients with previously TST and a good cancer prognosis, initiating systemic therapy for psoriasis 1 month post-chemotherapy is not likely to alter the risk of cancer recurrence or progression	87.2 (80.1, 92.6)	88.6 (87.3, 89.8)
2. For patients with previously TST and a good cancer prognosis, initiating systemic therapy for psoriasis directly following radiation therapy is not likely to alter the risk of cancer recurrence or progression	92.5 (87.1, 96.2)	94.1 (93.4, 94.8)
3. For patients with previously TST and a good cancer prognosis, initiating systemic therapy for psoriasis directly following endocrine and targeted therapies (i.e. kinase or VEGF-targeting angiogenesis inhibitors) is not likely to alter the risk of cancer recurrence or progression	88.6 (82.2, 93.3)	89.3 (88.1, 90.4)
4. Patients with previously TST and a poor prognosis have an inherent increased risk for recurrence or progression associated with their cancer. Treating psoriasis is unlikely to change this prognosis	85.1 (78.1, 90.6)	91.9 (91.0, 92.9)

All authors provided their level of confidence/support/agreement as well as upper and lower values to represent their uncertainty in the level of confidence. Level of support was provided on a scale of 0–100, on the basis of approximate verbal transformations of subjective probability for use in expert elicitation, where 90% means the statement is likely to be true, and 99% means the statement is very likely to be true. The statements are based on low-level direct and indirect evidence and represent the beliefs of the expert panel members after reviewing the totality of this evidence

*TST* treated solid tumour, *VEGF* vascular endothelial growth factor

in Table 1 and Fig. S2 (Supplementary Material), with resultant recommendations summarised in Table 2 (and Fig. S3, Supplementary Material). See Supplementary Material for literature search output and data summaries. Of note, one respondent was an outlier with their assessments, as seen in the individual responses.

### Framing the Conclusions

Patients with TSTs are a highly heterogeneous population that differ on the basis of cancer type, including stage and tissue of origin, mutational status of cancer, cancer prognosis, and cancer treatment received. The initiation of

systemic psoriasis therapy after cancer treatment will depend largely on immune reconstitution post-cancer treatment. Cancer treatment is increasingly focused on specific oncogenic mutations rather than the tissue of origin, and consequently similar types of treatments are increasingly being received across cancer types [13]. Upon reviewing the evidence, the oncologists unanimously agreed that immune reconstitution following cancer treatment for patients with TSTs depends more on the type of treatment received than on the type of ST or any other factor (stage, mutational status, etc.). Accordingly, this document is relevant for a broad range of treated solid tumours and is not

**Table 2** Inference-based conclusion statements and level of support with range of uncertainty

Conclusion statements	Level of support for statements (0–100) Mean support (0.05,0.95 confidence intervals)	Bayes median support (0.05, 0.95 credibility intervals)
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	92.6 (87.5, 96.2)	95.5 (94.9, 96.1)
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	91.6 (82.2, 97.1)	92.4 (91.9, 92.9)
2. Systemic therapy for psoriasis is unlikely to cause increased risk of cancer recurrence in patients with previously TST 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	91.6 (86.2, 95.4)	92.4 (91.4, 93.2)
3. 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	93.2 (88.7, 96.4)	94.9 (94.4, 95.4)
4. In patients with previously TST and psoriasis, systemic treatment of psoriasis with a TNFi is unlikely to alter prognosis related to the previously TST	86.9 (80.3, 91.9)	91.3 (90.5, 92.1)
5. In patients with previously TST and psoriasis, systemic treatment of psoriasis with methotrexate is unlikely to alter prognosis related to the previously TST	91.3 (85.9, 95.3)	90.1 (89.0, 91.1)
6. a. In patients with previously TST and psoriasis, systemic treatment of psoriasis with cyclosporine A is unlikely to alter prognosis related to the previously TST	78.0 (69.2, 85.3)	80.9 (80.3, 81.6)

Table 2 continued

Conclusion statements	Level of support for statements (0–100)	
	Mean support (0.05,0.95 confidence intervals)	Bayes median support (0.05, 0.95 credibility intervals)
6. b. Additional caution is warranted with CsA compared with other systemic treatment options as it may increase the risk of cutaneous squamous cell carcinoma	93.2 (89.2, 96.2)	94.5 (93.9, 95.0)
7. In patients with previously TST and psoriasis, systemic treatment of psoriasis with acitretin is unlikely to alter prognosis related to the previously TST	95.8 (93.5, 97.5)	97.4 (97.0, 97.7)
8. In patients with previously TST and psoriasis, systemic treatment of psoriasis with a PDE4i is unlikely to alter prognosis related to the previously TST	91.9 (87.7, 95.1)	93.3 (92.7, 94.0)
9. In patients with previously TST and psoriasis, systemic treatment of psoriasis with a TYK2i is unlikely to alter prognosis related to the previously TST	82.8 (71.5, 91.1)	85.4 (84.3, 86.5)

All authors provided their level of support as well as upper and lower values to represent their uncertainty in the level of confidence. Level of support was provided on a scale of 0–100, on the basis of approximate verbal transformations of subjective probability for use in expert elicitation, where 90% means the statement is likely to be true, and 99% means the statement is very likely to be true. The statements are based on low-level direct and indirect evidence and represent the beliefs of the expert panel members after reviewing the totality of this evidence

*IL-17i* interleukin 17 inhibitor, *IL-12/23i* interleukin 12/23 inhibitor, *IL-23i* interleukin 23 inhibitor, *PDE4i* phosphodiesterase 4 inhibitor, *TNFi* tumour necrosis factor- $\alpha$  inhibitor, *TST* treated solid tumour, *TYK2i* tyrosine kinase 2 inhibitor

limited to certain types of solid tumours. Physicians should consider the concepts herein as a guide in addition to considering any differences for specific types of solid tumours, which is beyond the scope of the present review. Clinically, immune reconstitution during or after cancer treatment is primarily assessed by normalisation of cell counts. The time frame of normalisation differs depending on the class of cancer treatment received (Table 3). Many types of chemotherapy may induce psoriasis remission [14], with possible recurrence of psoriasis post-completion of chemotherapy. There is a trend in cancer treatment paradigms towards less chemotherapy, less exposure to or more focused radiation therapy, and greater reliance on immune-checkpoint inhibitors (ICIs). ICI therapy has immunostimulatory effects that increase the risk of immune-

mediated adverse effects, including skin conditions such as psoriasis [15]. Due to the complexities of this topic, treating de novo psoriasis or psoriasis exacerbated by ICI therapy is not considered here. For patients on active or maintenance treatment for solid tumours, confounding from drug–drug interactions, paucity of direct data, and the complexity and multifactorial nature of this population prevents generalisable recommendations which are beyond the scope of the present investigation.

An understanding of the patient's cancer prognosis and immune competence provides some context for discussing risk and benefit of treatment for inflammatory disorders in patients with a history of TSTs. A summary of common STs and survival by stage at diagnosis based on the Surveillance, Epidemiology, and End Results (SEER) Program in the USA provides



**Table 3** Immune recovery post-cancer treatment for solid tumours stratified by cancer treatment class

Cancer treatment class	Expert opinion
Chemotherapy	<p>Patients receiving chemotherapy will experience varying degrees of short-term impaired immunity depending on the chemotherapy regimen used, the extent of systemic corticosteroid support required, and baseline patient characteristics<sup>a</sup>. Proliferating hematopoietic stem and progenitor cells (HSPCs) in the bone marrow are particularly susceptible to chemotherapy-induced damage [126]</p> <p>White blood cell count nadirs depend on the antineoplastic therapy used and typically occur around 10–14 days after administration of treatment, with complete recovery by day 21–28 [127]<sup>b</sup></p>
Immune checkpoint inhibitor therapies (e.g. CTLA4 or PD1-PDL1 inhibitors)	Do not usually cause immune deficits <sup>c</sup> . 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 [128, 129]
Radiation therapy	Advances in radiation for the treatment of solid tumours have led to improved tumour targeting with reduced impact on normal tissues. Immune deficits are uncommon post-treatment [130] <sup>d</sup>
Endocrine and targeted therapies (e.g. kinase or 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 [131, 132]

*CTLA4* cytotoxic T-lymphocyte-associated antigen 4, *ICI* Immune checkpoint inhibitor, *PDI* programmed cell death 1, *PDL1* programmed cell death ligand 1, *VEGF* vascular endothelial growth factor

<sup>a</sup>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 corticosteroids, 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 therapy, 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 [133]

<sup>b</sup>Some reports indicate that it could take up to 1 year for cluster of differentiation 4 (CD4)<sup>+</sup> 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 [134]

<sup>c</sup>Some patients with ICI require immunosuppressive therapy with long-term corticosteroids or mycophenolate to treat immune-related adverse effects [128]

<sup>d</sup>Should more than one-third of skeletal marrow reserve be radiated (mostly spine, pelvis, and sternum), long-lasting cytopenia may occur. Moreover, radiation-suppressed marrow reserve may result in greater susceptibility to severe myelosuppression with chemotherapy [133]. 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 [135–137]. In a small series of irradiated Stage I–III patients with breast cancer, decreased TNF and lymphocyte counts persisted after ionising radiation [138]

**Table 4** Common solid tumours and survival by stage at diagnosis

Tumours and stage at diagnosis	5-year relative survival <sup>a</sup> , (%)
Breast cancer <sup>b</sup>	
Localised	99.0
Regional	85.8
Distant	29.0
Lung and bronchus cancer <sup>c</sup>	
Localised	59.8
Regional	32.9
Distant	6.3
Colorectal cancer <sup>c</sup>	
Localised	90.6
Regional	72.2
Distant	14.7
Prostate cancer <sup>d</sup>	
Localised	100.0
Regional	100.0
Distant	30.6
Stomach cancer <sup>c</sup>	
Localised	69.9
Regional	32.4
Distant	5.5
Oesophageal cancer <sup>c</sup>	
Localised	46.4
Regional	25.6
Distant	5.2
Liver and intrahepatic bile duct cancer <sup>c</sup>	
Localised	35.3
Regional	12.3
Distant	2.7

Localised, cancer is confined to the primary site, that is, organ of origin; regional, malignant cancer that extends beyond the primary site involving regional lymph nodes and surrounding tissue; distant, malignant cancer that has metastasised to distant organs, tissues, and distant lymph nodes

<sup>a</sup>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. On the basis of data from SEER 18 areas from 2011 to 2017, all races, <sup>b</sup>females only, <sup>c</sup>both sexes, <sup>d</sup>males only

some guidance to dermatologists (Table 4). This table is included as a guide, and the present guideline is a broad exploration of concepts related to solid tumours, beyond these common STs. Clinical trials and databases in oncology use different staging systems that update frequently, making the interpretation of longitudinal data difficult. Real-world cancer databases lack encoded staging and longer-term follow-up beyond 10–20 years. As a result of the heterogeneity of outcomes from phase 3 oncology clinical trials, disease-free survival for patients with TSTs was not summarised here.

An informed risk–benefit conversation with patients with TST should support all treatment decisions on a case-by-case basis, considering cancer prognosis, the type and intensity of cancer treatment received, and patient preferences. For patients with a poor prognosis (i.e. high risk of recurrence/metastasis), quality-of-life benefits of treating psoriasis with a systemic psoriasis therapy may outweigh the theoretical risks. These patients have inherent risk for cancer-related death regardless of psoriasis status and treatment choices. The present review focused on patients with a good cancer prognosis, that is, those treated with a curative intent. These patients comprise a significant and growing population of patients seeking treatment for psoriasis who require guidance when considering systemic treatments for psoriasis.

### General Concepts of Immunosuppression, Immunomodulation, Immune Surveillance, and Senescence in the Development of Malignancies

Cancer formation is a complex of processes involving genetics, immune surveillance, comorbidities, environmental, dietary and lifestyle factors [16, 17]. Age is by far the greatest risk factor [18, 19], with minor contributions to overall cancer risk from environmental [excluding ultraviolet (UV) light exposure] and lifestyle factors [17, 20] as well as occupational exposure [21]. Chronic infections [16] and chronic inflammation [22, 23] contribute to various types of cancer including prostate

[24–26], breast [27–30], lung [31–35], colorectal [36–40], and pancreatic [41] cancers. Chronic inflammation results in T-cell exhaustion, thus providing a permissive environment for tumour development, growth and metastasis [42]. T-cell exhaustion resulting from immunosenescence, chronic infection or chronic inflammation provides an opportunity for tumour development, growth and metastasis [43]. Although we reviewed the literature on mechanisms of action of systemic psoriasis therapies to identify any associations with cancer pathways, the evidence was unclear and the effect sizes are likely small; thus, meaningful conclusions could not be made on the basis of this evidence. Depending on the tumour microenvironment, the pathways and cytokines blocked by systemic psoriasis therapies may inhibit, promote or have no effect on tumourigenesis. Interleukin (IL)-17 and T helper 17 (Th17) cells are often associated with chronic inflammatory processes, including those associated with malignancies [42]. Inflammation, while an inducer of malignancy, is also necessary to eliminate malignancy, whereas chronic inflammation is immunosuppressive [44, 45].

Generally, systemic psoriasis therapies are neither inducers nor promoters of cancer pathways and may provide very small benefit by reducing the local inflammatory burden. The exceptions are cyclosporine A (CsA), which may promote the development of cutaneous squamous cell carcinoma (SCC), and UVB light, which is both an inducer and promoter of cutaneous SCC and basal cell carcinoma [46]. Conversely, the benefit of reducing local or systemic inflammatory burden in inflammation-associated malignancies is uncertain, and increasingly so at a later stage. The risk of effect is cumulative; therefore, intervening at a late stage cannot result in a significant benefit [47]. The reported reduction in lung cancer associated with IL-1 inhibition in the CANTOS study is, almost certainly, an incidental finding given the short observation period [47].

### Indirect Evidence from Transplant Patients with Immunosuppression

We considered indirect evidence from patients with solid organ transplant (SOT), with and without a history of cancer, who were treated post-transplant with broadly immunosuppressive therapies. In general, SOT recipients have a higher risk of developing certain types of cancer, including Kaposi sarcoma, non-melanoma skin cancer, non-Hodgkin lymphoma, and cancers of the liver, anus, vulva, and lip [48–56]. Cancer risk and cancer-related mortality are increased in patients with SOT possibly due to the effects of broad immunosuppression. The nature of tumours developing in patients with SOT suggests the elevated risk is related to a decrease in immunologic control over oncogenic infections or reactivation of latent infections [48, 52]. In general, pre-transplant malignancy is associated with an increased risk of all-cause mortality in transplant patients with SOT, and possibly cancer-specific mortality [50, 54, 57–62]. This is likely due to end-stage organ disease and transplant-related complications, but is highly influenced by type of malignancy, grade/stage, tumour-specific characteristics, projected overall survival, time to transplant, and age [50, 54, 57–62]. It is unclear if modified immunosuppressive regimens lead to increased all-cause mortality in transplant patients with SOT. However, some studies suggest there is no increase in all-cause mortality for cancers with a good prognosis [59].

Recent guidelines indicate that patients with previously TST with a good prognosis can receive a transplant (and subsequent broad immunosuppressive therapy) with minimal-to-no wait time and similar outcomes as the general SOT population [63]. Similar conclusions can be inferred for patients with psoriasis. Patients at high risk for metastasis, including stage IV and some high-risk stage II–III, are not considered candidates for transplantation until at least 3–5 years post-cancer; therefore, no inference could be drawn from this subpopulation [63].

## Considerations for Virus-Associated Cancers

Certain viral infections, including hepatitis B virus (HBV) and hepatitis C virus (HCV), alter cellular signalling and can lead to malignancy [64–67]. Associated chronic inflammation resulting from immunological responses endeavoring to constrain the persistent infection results in fibrosis and T-cell exhaustion, both of which result in a more permissive environment for the development, growth, and metastasis of malignancy [43]. Chronic inflammation may result in chromatin breaks. Human papillomavirus (HPV) increases the risk of carcinogenesis by mechanisms similar to HBV and HCV [68–70]. In general, we found no evidence from our review that oncogenic infections are increased with systemic psoriasis therapy. Other types of infections may be increased with certain systemic psoriasis therapies, which has implications for actively TSTs.

In SOT populations, additional caution is warranted for viral transformative cancers such as HPV or Epstein–Barr virus (EBV), where immune suppression may increase the risk of disease progression and recurrence [48, 51, 71]. This may be relevant for systemic psoriatic therapies with broad T-cell immunosuppression (e.g. CsA), but not the case for systemic psoriasis therapies that immunomodulate by inhibiting Th17 pathway [e.g. IL-17 inhibitors (IL-17i), IL-23 inhibitors (IL-23i) and tumour necrosis factor- $\alpha$  inhibitors (TNFi)] [72]. For treatment of psoriasis with TNFi, there is a small theoretical risk of causing active infection with HBV but an anticipated benefit in treating patients infected with HCV. Special consideration should be given to cancers secondary to oncogenic viruses such as cervical cancer and hepatocellular carcinoma, as limited mechanistic data suggest possible negative effect of TNF inhibition [73]. Clinical data in patients with psoriasis that show no significant increase in STs is reassuring.

## Baseline Risk of Cancer in Patients with Psoriasis and Its Treatments

Psoriasis and its treatments are not causally associated with an increased risk of STs. Patients with psoriasis may have an increased incidence of lymphomas and non-melanoma skin cancer [74–79]. Cutaneous SCC risk, possibly increased in the psoriasis population, is primarily from UVB light exposure [80]. Some studies have suggested that risk of dying from cancer may be increased in patients with more severe psoriasis [74, 81]. However, modifiable risk factors strongly confound the association between psoriasis and cancer death, thus highlighting the importance of patient counselling on weight control, smoking cessation, and moderating alcohol consumption [74, 81].

For each category of systemic psoriasis therapy, we reviewed the limited direct evidence of systemic psoriasis therapy in patients with solid tumours and indirect evidence from the general psoriasis population, and other indications, where available. Direct evidence from cases of psoriasis treatments in patients with a history of malignancy are reassuring, with no worsening or recurrence of cancers noted for any of the treatments studied (Table S2, Supplementary Material) [7]; however, these data should be considered with caution due to reporting bias, with small patient numbers and short follow-up times. The most data exist for risk of cancer recurrence in patients with a history of cancer treated with TNFi for other immune-mediated conditions, including rheumatoid arthritis and inflammatory bowel disease (Table S3, Supplementary Material). These data include meta-analyses of up to 13,598 patients and 32,473 patient-years of follow-up, with no increased risk of cancer recurrence observed [82–84]. Although clinical trials exclude patients with a history of TSTs, long-term extensions and meta-analyses estimate baseline cancer risk with systemic treatments. Biologics targeting IL-17, IL-12/23, and IL-23 do not show an increased risk of malignancy or serious infection in the general psoriasis population with up to 5 years of follow-up [85–96]. Likewise, biologics targeting TNF- $\alpha$  have up to 8.2 years of long-term extension, real-world and randomised controlled trial

data, suggesting that the development of new solid tumours in patients with psoriasis is similar to the SEER database population [85, 97–102]. Although preliminary studies have suggested little-to-no increased risk of cancer incidence in patients with psoriasis treated with biologics, longer follow-up periods and increased power are required to properly examine the potential cancer risk, particularly for site-specific cancers [103]. Of note, patients with psoriasis on TNFi are at an increased risk of infection, including serious infection, although real-world evidence suggests that rates are lower than those seen in clinical trials [97, 104]. Clinicians should be cautious about adding TNFi to patients with actively TST on immunosuppressive chemotherapies.

In addition to biologics, systemic psoriasis therapies include traditional systemics and newer emerging small molecules. There are insufficient numbers of patients with psoriasis treated with these specific psoriasis therapies to suggest altered risk for the development of solid tumours. Methotrexate (MTX) is not an inducer or promoter of malignancy [105, 106]. At higher doses, oncologists use MTX to treat solid tumours. Compared with biologics, studies have not shown an increased risk of malignancy associated with the use of low-dose MTX [85, 107–110], however, there may be a small risk of skin cancer associated with its use [111]. CsA is not known to be an inducer nor a promoter of solid tumours [106], with the possible exception of keratinocyte malignancies [112]. There are several reports suggesting an increased risk of cutaneous SCC in patients receiving CsA [113, 114]. CsA is also associated with a higher risk of infections [115, 116], which has implications for actively TSTs. One study followed 17 patients with psoriasis who were treated with CsA and MTX for 9.5 weeks and reported no occurrences of cancer after a median of 76 months of follow-up [117]. Acitretin is not known to be an inducer or promoter of malignancy [113]. Interestingly, it may be used to prevent or minimise keratinocyte carcinoma in high-risk patients post-transplant [118], though the effect size is uncertain. Neither apremilast [a phosphodiesterase-4 inhibitor (PDE4i)] nor deucravacitinib [an emerging

tyrosine kinase 2 inhibitor (TYK2i) with limited long-term data] are known to promote or induce malignancy [119].

### Timing of Systemic Psoriasis Therapy Initiation Post-cancer Treatment

There are theoretical concerns about the increased risk of recurrence for patients with TSTs treated with immunosuppressive therapies following chemotherapy. On the basis of our analysis of the literature, a 5-year interval post-cancer treatment [120, 121] is overly cautious and generally unwarranted. The present recommendations (Table 1) are based on anticipated time to immune reconstitution post-cancer treatment, with a 1-month period post-chemotherapy, and no wait time warranted for radiation or endocrine and targeted therapies [i.e. kinase or vascular endothelial growth factor (VEGF)-targeting angiogenesis inhibitors] for STs with a good prognosis. A risk–benefit discussion with patients should always guide treatment decisions. In general, the highest risk of recurrence occurs in the first year post-cancer, with future life expectancy for survivors improving further out from diagnosis and slowly approaching general population life expectancy over time [122]. On the basis of the survival curves for solid tumours, the later the onset of cancer, the closer to a normal life expectancy one can expect [122]. It is unlikely that any of the systemic psoriasis therapies will alter the risk of recurrence or alter the shape or slope of the curves for solid tumours. There is no evidence suggesting that intervening earlier than 5 years with systemic psoriasis therapies will change overall survival or cancer recurrence. One random effects meta-analysis pooling 16 studies of patients with inflammatory bowel disease, rheumatoid arthritis, and psoriasis found similar pooled incidence values for new or primary cancers when immunosuppression was initiated within 6 years versus more than 6 years after the index cancer [83]. In addition, recall that patients with SOT with a history of TST and a good prognosis can receive transplantation and subsequent broad immunosuppression without a wait time or

with minimal wait time [63]. A more cautious approach may be warranted for cancers with a poor prognosis or with viral transformative cancers such as HPV and EBV.

## DISCUSSION/LIMITATIONS

The present guidance document demonstrates a formal inference-based process, novel to clinical medicine, guiding practice where high-level evidence is lacking [10, 123]. In addition to recommendation statements, we provide inference-based conclusions supporting healthcare professional discussions and shared decision making. This approach is useful when guidance is needed but direct evidence is lacking. Clinical trials require small, well-defined populations. Real-world data, while reporting on larger populations, are confounded by inclusion and observation biases. An inference-based approach provides guidance on clinical scenarios for populations in which clinical trial and real-world studies are unlikely to be conducted [124, 125]. Practical clinical decisions are often made in the face of limited evidence. The process of considering indirect evidence provides reflective, critical and structured support for care providers. Implementing a formalised methodology reduces the burden on individual physicians to review and assess available data while encouraging clinicians to engage patients in an informed manner [10]. Deconstructing the main question into components and addressing the sub-components permits restructuring of evidence supporting, or refuting, a conclusion. The result is a statement of confidence in the recommendations based on the totality of evidence. The responses of expert dermatologists and oncologists indicated significant support with high levels of confidence regarding the risks of treating psoriasis with systemic psoriasis therapies in patients with TSTs. One participant was an outlier in their assessments. Regardless of whether their evaluations reflect personal beliefs, their considered assessment of the evidence, or their comfort with the process, the summary stands apparent and transparent.

It is impractical and ill-considered to provide comprehensive or directive statements. The uniqueness of each clinical situation and each patient requires a holistic approach based on a reasonable understanding of the facts. Significant clinical heterogeneity and knowledge gaps characterise malignancy. The authors have attempted to provide informed guidance based on limited data. Our observations do not address patients with TSTs on active or maintenance cancer treatment. The present framework notes that the type of cancer treatment received will impact immune reconstitution more than other cancer-related factors, suggesting there are few differences across ST types. Optimal patient care demands dermatologists consult with treating oncologists regarding cancer prognosis, concerns related to cancer type and stage, and systemic psoriasis therapy should it be necessary.

Generalisations made here may not be relevant for all tumour types. Previously published guidance on systemic psoriasis therapy use in patients with TSTs were based on weak evidence that was subject to reporting and observer bias: case reports or case series [78]. Previous guidance suggests a 5-year interval post-remission before introducing systemic psoriasis therapy for psoriasis in patients with TSTs [120, 121]. Previous guidelines may reflect an unwarranted, overly cautious approach. Immune reconstitution is realised soon after stopping cancer treatment in most patients with a good cancer prognosis (see Table 3). Inferring from indirect data, our multidisciplinary group, consisting of dermatologists and oncologists, concurred that patients with a good cancer prognosis will likely experience similar responses to systemic therapies as those in the general population. Additional caution should be taken for those who have a poor prognosis.

## CONCLUSIONS

We reviewed indirect evidence supporting inferences on additional risks and benefits imposed on patients with TSTs requiring systemic therapies for the treatment of psoriasis. On the basis of our review, we expect that

patients with TSTs and a good prognosis will have similar drug-related adverse effects and benefits to non-TST patients when treated with systemic psoriasis therapies. Prior to considering new therapies for psoriasis, an understanding of cancer prognosis should be addressed with the treating oncologist and patient. All treatment decisions should be made on a case-by-case basis after an informed discussion with the treating physician and patient.

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