

## CaSMO Management of Cutaneous Toxicities Associated with Immune Checkpoint Inhibitors: A Practical Primer

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### ABSTRACT

*The Canadian skin management in oncology (CaSMO) project was developed to improve cancer patients' (both active and survivors) quality of life by offering tools to healthcare professionals for preventing, reducing and/or managing cutaneous adverse events (cAEs).*

*Immunotherapy, specifically immune checkpoint inhibitors (ICIs), for cancer patients is both increasing in indications and use. Similarly, the incidence and onset of cutaneous immunotherapy-related adverse events (cirAEs) vary based on the class and dose of immunotherapy administered, the type of cancer, and factors related to the patients. Dermatologists will increasingly see side effects from immunotherapy.*

*The CaSMO advisors developed a practical primer on prevention, identification, and treatment, including skincare for cirAEs, focusing on isolated pruritus, psoriasiform eruptions, lichenoid eruptions, eczematous eruptions, and bullous pemphigoid.*

*A modified Delphi approach was used for the cirAEs practical primer's development. Recommendations given by the CaSMO advisors are based on information from the guidelines, algorithms, consensus papers, and systematic reviews coupled with their clinical experience and resulting from discussions.*

*According to the CaSMO group, the management of cirAEs starts with physician awareness and patient education on the occurrence of toxicities, preventive measures, and skincare using gentle cleansers, moisturizers, and sunscreen started before immunotherapy begins and ongoing thereafter as part of the lifestyle.*

**Keywords:** Immunotherapy, cutaneous adverse events, immune checkpoint inhibitor, skin toxicity, psoriasis, pruritus, morbilliform, eczema, bullous pemphigoid

## Introduction

In 2021 an estimated 229,200 Canadians were diagnosed with cancer.<sup>1</sup> In Canada, of the four most commonly diagnosed types of cancer (lung, breast, colorectal, and prostate), excluding non-melanoma skin cancer, lung cancer is the most lethal and expected to cause more deaths than the other types combined.<sup>2,3</sup>

Immunotherapy activates the body's immune system to fight cancer. Immune checkpoint inhibitors (ICIs) prevent the deactivating signal by blocking the T-cell shut-off receptors and ligands from binding to each other, thereby disrupting signaling so that T cells remain active and can then recognize and attack cancer cells.<sup>4,5</sup> ICIs are approved for treatment across almost every type of solid-organ tumors, many hematologic malignancies, and in many instances, first-line therapy.<sup>4,5</sup> In 2019, in the United States, approximately 40% of oncology patients were eligible for treatment with immunotherapy.<sup>6</sup> ICIs may be administered as a single agent (anti-CTLA-4 (ipilimumab), anti-PD-1 (pembrolizumab, nivolumab), anti-PD-L1 (atezolizumab, durvalumab, and avelumab)) or as combination immunotherapy (ipilimumab and nivolumab) and even as a combination with other agents.<sup>4,6</sup>

Oncology patients treated with immunotherapy may experience cutaneous immunotherapy-related adverse events (cirAEs) at any time during and after the cancer treatment, severely impacting the quality of life (QoL) and potentially cancer treatment outcomes.<sup>7-24</sup> The incidence and onset of cirAEs vary depending on the drug class, the type of cancer, and factors related to the patient.<sup>25</sup> Adverse skin reactions occur in 14%–47% of patients treated with ICIs, ranging from mild and localized to debilitating and widespread in 1%–3% of patients and even potentially causing death.<sup>15,16,26-30</sup> Nivolumab-related cirAEs, including isolated pruritus, occurred in approximately 13–20% of patients, of which 0.7% of patients reported grade three or higher cAEs.<sup>29-33</sup> Pembrolizumab-induced cirAEs occurred in 9%–27% of patients, of which 1%–4% of patients reported grade three or higher cirAEs.<sup>34,35</sup>

Frequently occurring cirAEs include pruritus without primary dermatologic findings (isolated pruritus), lichen planus or lichenoid drug eruptions, psoriasiform reactions, eczematoid eruptions, morbilliform eruptions, and bullous diseases, primarily bullous pemphigoid.<sup>7-24</sup>

The cirAEs may indicate a therapeutic response. A multicenter retrospective study on patients with non-small-cell lung carcinoma (NSCLC) receiving nivolumab showed that AEs and cirAEs were a strong predictor of survival outcomes, and those presenting with more than 2 AEs showed more benefit than patients with fewer AEs.<sup>14</sup> Vitiligo occurs in some patients with melanoma receiving ICIs (Figure 1), and this is significantly associated with both progression-free-survival (PFS) and overall survival (OS) which indicated a two to four times lower risk of disease progression and death.<sup>32,36</sup>

Major guidelines<sup>10-12</sup> recommend the use of systemic steroids for grade 2 or higher “rash” contrary to evidence showing the use of systemic steroids reduces the anticancer effect of ICIs.<sup>33</sup> A secondary analysis of a randomized trial on stage III melanoma patients with cirAEs showed that patients who received treatment with systemic steroids for 30 days or longer had lower OS than those without steroid treatment.<sup>33</sup> Another multicenter

retrospective analysis of patients treated with anti-PD-1 therapy showed that high-dose glucocorticoids used to treat AEs were associated with poorer PFS and OS.<sup>35</sup>

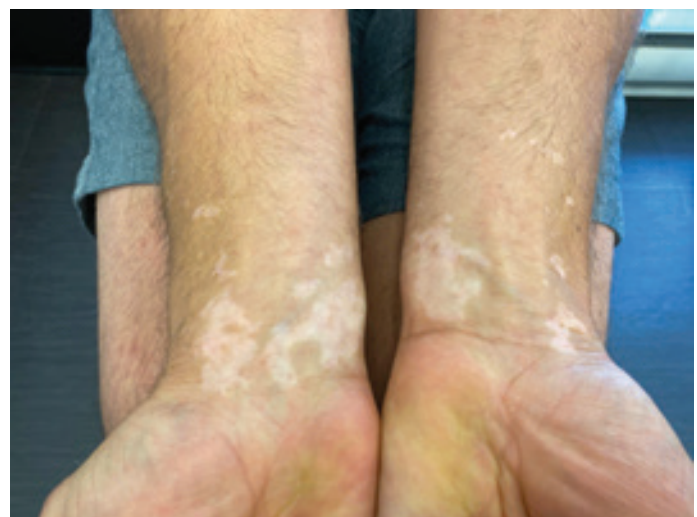
## Scope of the Canadian Skin Management in Oncology Project

The Canadian skin management in oncology (CaSMO) project was developed to improve cancer patients' (both active and survivors) QoL by offering tools for preventing and managing cAEs.<sup>37-39</sup> A general management algorithm to reduce the incidence of all cutaneous toxicities and maintain healthy skin using general measures and over-the-counter agents<sup>38</sup> and an algorithm to reduce and treat acute radiation dermatitis<sup>39</sup> were previously published. These algorithms aim to support all healthcare providers treating oncology patients, including physicians, nurses, pharmacists, and other medical providers.<sup>38,39</sup> The next step in the project was to develop a practical primer on prevention, identification, and treatment for cirAEs, focusing on isolated pruritus, psoriasiform eruptions, lichenoid eruptions, eczematous eruptions, and bullous pemphigoid.

## Methods

For the CaSMO cirAEs practical primer's development, the advisors used a modified Delphi approach following the AGREE II instrument.<sup>40,41</sup> The modified Delphi method is a communication technique for interactive decision-making for medical projects.<sup>41</sup> The technique was adapted from face-to-face meetings to a virtual meeting to discuss the outcome of literature searches and reach a consensus on the practical primer based on the selected literature. The virtual discussion was followed by a virtual follow-up, replacing a questionnaire.<sup>41</sup> The process entailed preparing the project, selecting the advisors, and conducting systematic literature searches followed by two steps.

**Step 1:** Virtual panel meeting on November 20, 2021, to review the results of the systematic literature review addressing cirAEs prevention, treatment, and maintenance of cirAEs and to discuss and adopt a practical primer using evidence coupled with the panels' experience and opinion.



**Figure 1:** Vitiligo

Photo property of Joel Claveau

**Step 2:** Online process to fine-tune the practical primer and prepare and review the publication.

### Literature Review

The literature review included guidelines, consensus papers, publications on the prevention and management of cirAEs, and clinical and other research studies published in English from January 2010 to September 2021. Excluded were articles with no original data (unless a review article was deemed relevant), not dealing with cirAEs, and publication language other than English.

A dermatologist and a physician-scientist conducted the searches on September 26 and 27, 2021, on PubMed and Google Scholar as a secondary source of the English-language literature using the terms: *cirAEs; prevention and treatment of isolated pruritus, psoriasis, lichen planus, eczematous eruptions, bullous eruptions, QoL of patients with cirAEs; skincare and prescription treatment for the prevention, treatment, and maintenance of cirAEs; adjunctive skincare use; education of staff and patients; communication strategies; adherence; concordance; efficacy; safety; tolerability; skin irritation.*

The results of the searches were evaluated independently by two reviewers who resolved discrepancies by discussion. The searches yielded one hundred and six publications. Ninety-four papers remained after excluding duplicates (n = 12), and articles deemed not relevant (other subjects, low quality). Seven guidelines, eight systematic literature reviews, 16 reviews, and 37 clinical studies addressed cirAEs. Case reports were included as they provide valuable information in this fast-developing field. Moreover, cirAEs possess complex issues that are difficult to capture in randomized controlled trials (RCT). Ten consensus papers or algorithms and two clinical studies addressed cirAEs, treatment, and skincare. Finally, fourteen other publications addressed various subjects

(epidemiology studies, methodology, and general treatment of cirAEs or similar dermatological conditions). Two reviewers who graded the clinical publications evaluated the literature search results. Grading included study type and quality (RCT of high quality = A, B, or C) and level of evidence (level 1 to level 4) using the pre-established criteria.<sup>42</sup> The lack of studies on cirAEs treatment with prescription medications and skincare made grading irrelevant. However, the guidelines, systematic literature reviews, and consensus papers provided valuable information.

### Immunotherapy and Associated Cutaneous Adverse Events

#### Immunotherapy

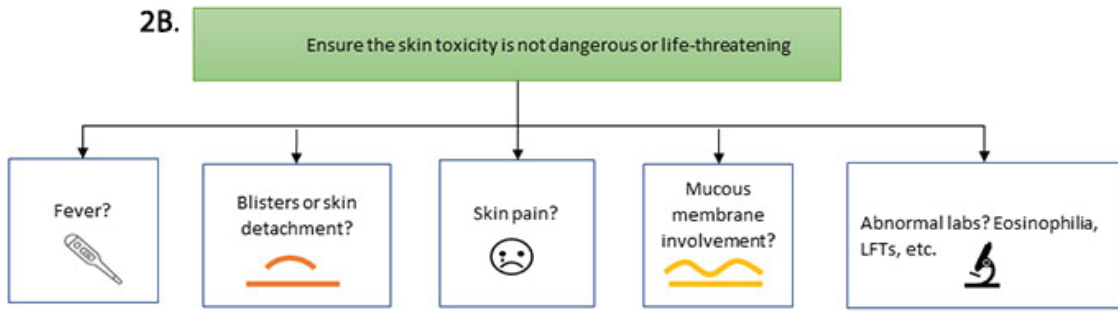
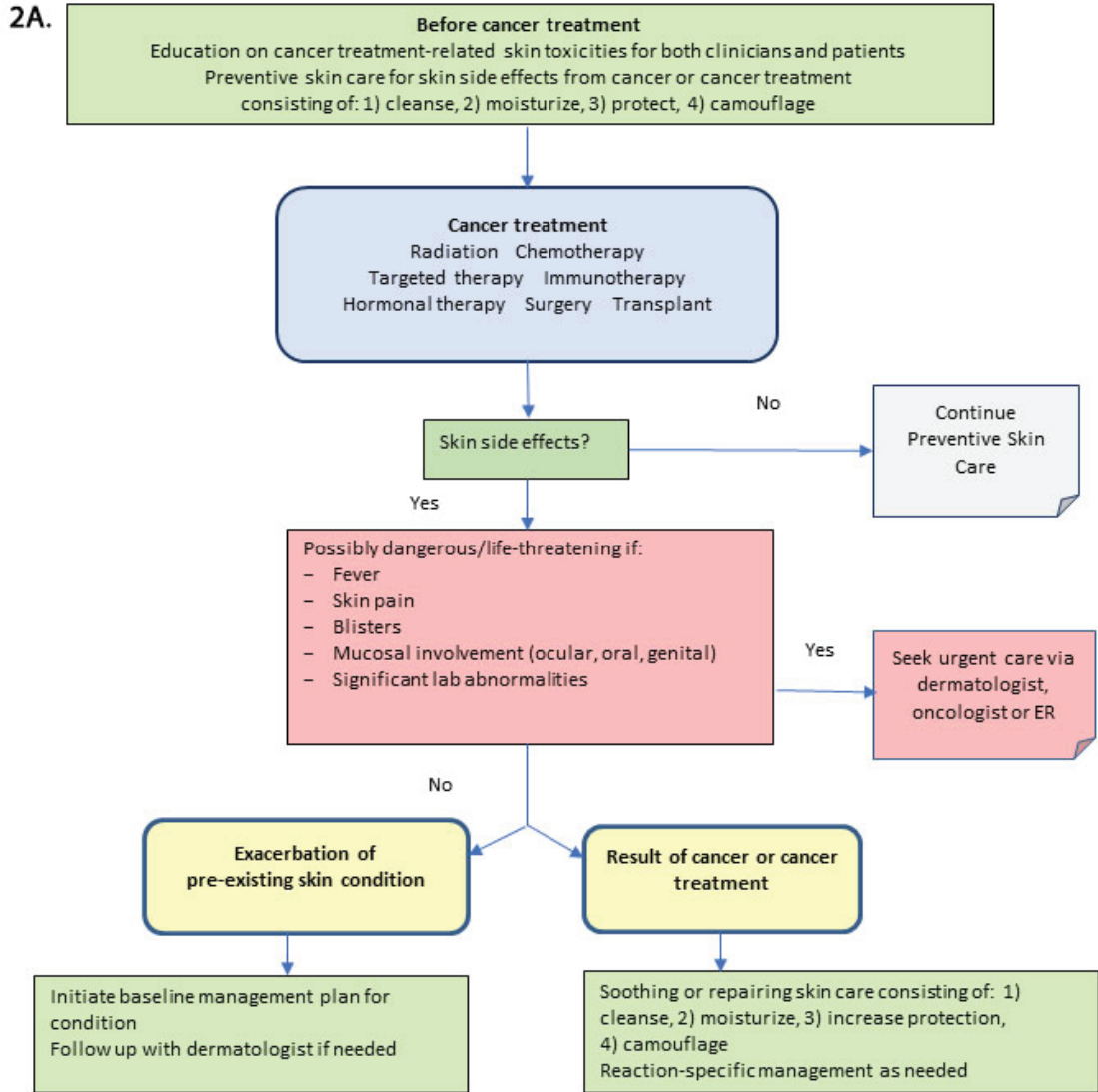
Immunotherapy uses immune checkpoint inhibitors, such as cytotoxic T-lymphocyte-antigen-4 (CTLA-4), inhibitors ipilimumab, programmed cell death receptor-1 (PD-1) inhibitors pembrolizumab, nivolumab, cemiplimab, and programmed death-ligand 1 (PD-L1) inhibitors atezolizumab, durvalumab, and avelumab (Table 1).<sup>4,5-11,43,44</sup>

CTLA-4 impinges on many features of T-cell biology.<sup>43,44</sup> The CTLA-4 signaling pathway and the PD-1/PD-L1/PD-L2 signaling pathway are critical checkpoints that are used to down-regulate the body's immune system that tumors often exploit and activate, thereby evading the body's immune system.<sup>43,44</sup> CTLA-4 dampens T-cell responses via cell-intrinsic and extrinsic pathways. Intrinsic events include, among others, inhibition of protein translation, recruitment of phosphatases, activation of ubiquitin ligases, inhibition of cytokine receptor signaling, and inhibition of lipid microdomain formation on the surface of T-cells. Cell extrinsic events include the competition for CD28 in binding to its ligands CD80/86, the removal of CD80/86, the release of suppressive indoleamine-dioxygenase, and the modulation of Treg function.

Drug Class	Name	Oncologic Indications
CTLA-4 inhibitors	Ipilimumab	Melanoma, renal cell, colorectal
	Tremelimumab	Not FDA approved; orphan drug designation for mesothelioma
PD-1 inhibitors	Nivolumab	Melanoma, lung, head and neck, Hodgkin's disease, bladder, colorectal, hepatocellular, renal cell
	Pembrolizumab	Melanoma, lung, head and neck, Hodgkin's disease, primary mediastinal large B-cell lymphoma, bladder, colorectal, gastric, cervical, hepatocellular, Merkel cell, renal cell
	Cemiplimab	Squamous cell carcinoma, basal cell carcinoma
PD-L1 inhibitors	Avelumab	Merkel cell, bladder, renal cell
	Atezolizumab	Bladder, lung, breast
	Durvalumab	Bladder, lung

**Table 1:** Immunotherapy classes, molecules, and indications

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), ipilimumab, programmed cell death 1 (PD-1) pembrolizumab, nivolumab, and programmed death-ligand 1 (PD-L1) atezolizumab, durvalumab, and avelumab.<sup>4,6,8-10</sup>



**Figure 2A and 2B:** CaSMO algorithm for preventing or reducing cAEs using skincare  
 Permission for the reproduction of the algorithm was obtained.<sup>13</sup>

Antibodies to CTLA-4 may facilitate T-cell tumor entry and alter the movement in tumors and rates of egress.<sup>43,44</sup>

CirAEs can present as almost any dermatologic condition, but most are inflammatory dermatoses.<sup>7-11,26</sup> The median time to onset of cirAEs is four weeks but has a broad range from 2 to 150 weeks, including beyond treatment discontinuation.<sup>15,17,45</sup>

CirAEs of any grade have been reported at 30-40% of patients receiving PD-1/PD-L1 and approximately 50% of patients treated with ipilimumab.<sup>31</sup> Maculopapular rash and pruritus are common cirAEs related to these treatments.<sup>31</sup>

A systematic literature review on cancer treatment with pembrolizumab and nivolumab observed that the most frequently occurring cirAEs were inflammatory dermatitis, pruritus, and vitiligo.<sup>46</sup> The rate of any-grade cirAEs with pembrolizumab and nivolumab was reported at 16.7% (RR=2.6) and 14.3% (RR=2.5), respectively.<sup>46</sup> The cirAEs may be associated with pruritus and comprised of erythematous macules, papules, and plaques, predominantly low-grade and localized to the trunk and extremities.<sup>46</sup> Challenges with reports of cirAEs are accurate descriptions and diagnoses of the specific dermatoses as many are simply reported as “rash”. Additional cirAEs comprised pruritus [incidence pembrolizumab and nivolumab was 20.2% (RR=49.9) and 13.2% (RR=34.5) respectively] and vitiligo [incidence, 8.3% (RR=17.5) and 7.5% (RR=14.6) respectively].<sup>45</sup> The researchers noted that knowledge of cirAEs is critical in delivering optimal cancer treatment, maintaining therapeutic agent dose, and health-related QoL.<sup>46</sup>

The advisors agreed that cirAEs are likely an indicator of ICIs treatment efficacy and should be managed with topical treatment and judicious, ideally steroid-sparing systemic treatment where possible.<sup>33,35-38</sup>

### Approaches to the Most Common Immunotherapy-Related Caes

The advisors discussed and selected the most common cirAEs: isolated pruritus, psoriasiform eruptions, lichenoid eruptions, eczematous eruptions, morbilliform (maculopapular) eruptions, and bullous pemphigoid eruptions.<sup>7-25,27-30</sup>

According to the advisors, the management of cirAEs starts with patient education on the occurrence of cirAEs, preventive measures, and skincare using gentle cleansers, moisturizers, and sunscreen started before ICIs treatment begins and ongoing during survival as part of the lifestyle.<sup>9-25</sup>

### Diagnosis of cirAEs

When diagnosing the cirAEs, other etiologies such as an infection, an effect of other agents, or other skin conditions should be ruled out.<sup>8-11</sup>

Biopsies play a role in accurately diagnosing the cirAEs when morphology is not clear. Histopathologically, cirAEs can be categorized into four broad groups, group 1: Inflammatory skin disorders, which reflect acute, subacute, or chronic inflammation of various patterns associated with variable epidermal changes, including psoriasiform or lichenoid interface chronic dermatitis.<sup>16,50-53</sup> Group 2: ICIs-related bullous skin lesions such as bullous pemphigoid or dermatitis herpetiformis, group 3: Keratinocyte alteration—Grover’s disease<sup>54</sup>/acantholytic

dyskeratosis, and group 4: Immune-reaction mediated by alteration of melanocytes such as regression of nevi, tumoural melanosis, and vitiligo.<sup>29,36,48-52</sup> For this review, we will only be focusing on the selected cirAEs.

When assessing the severity of cirAEs, grading systems’ trial limitations need to be considered.<sup>9</sup> The Common Terminology Criteria for Adverse Events (CTCAE) classification is typically used; however, in the case of clinical trials, clinicians should be cognisant of the version the trial is using as different versions of CTCAE have different definitions and categorizations.<sup>26</sup>

A general approach to prevention or reduction of cirAEs as well as initial management of the previously published CaSMO algorithm is displayed (Figure 2) for reference.<sup>38</sup>

### Patient and Caregiver Education

Patient and caregiver education and information should occur before initiating therapy and continue throughout treatment and survivorship.<sup>9-11,37,38,47</sup> The patient should be informed that immunotherapy works differently than traditional chemotherapy and that therapeutic response and related cirAEs differ in timing, presentation, and response to treatment.<sup>48-57</sup>

Patients should be informed that cirAEs may continue even after discontinuation of the ICIs treatment.<sup>48-57</sup> Additionally, patients should be educated to inform all healthcare providers that they are receiving or have received ICIs therapy and to report any changes in health status.<sup>54</sup> Patients and caregivers need to be informed that cirAEs can often be managed effectively, especially when they are identified early. In addition, education should be provided on good hygiene, skincare, sun avoidance and protection, the safe handling of medications, and infection control is essential in preventing and supporting optimal management of cirAEs.<sup>38,48-57</sup>

### Severe Cutaneous Adverse Reactions (SCARs)

As described in the CaSMO algorithm, any drug eruption should be assessed if they are serious or life-threatening. Severe cutaneous adverse reactions (SCARs) require prompt clinical, urgent referral and triage.<sup>9-11,37-39,47</sup> Symptoms that raise suspicion of SCARs include fever, widespread rash, skin pain, skin sloughing, facial or upper-extremity edema, pustules, blisters, or erosions.<sup>9-11,38</sup> SCARs include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), overlap SJS-TEN, acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS).<sup>7,8,12-25,30,31,34,38,45-61</sup>

SJS-TEN occurs in up to 2% of patients treated with ICIs exceedingly rare.<sup>31,43</sup> SJS-TEN is characterized by extensive epidermal loss (<10% SJS, >30% TEN, 10-30% SJS-TEN overlap) with mucous membrane erosions.<sup>31,37-39,43-49</sup> Classically, this is an acute reaction; however, a slower and more indolent presentation may occur.<sup>31,52</sup> ICIs-related DRESS is rare and is mostly reported in case studies. Common DRESS features are fever, eosinophilia, lymphocyte activation, multiorgan involvement, and reactivation of herpes viruses, especially HHV6.<sup>60,61</sup> Patients usually develop two or three features of symptoms followed by a stepwise development of other symptoms.<sup>60,61</sup>

AGEP is a rare, severe, potentially fatal, acute cirAEs with systemic involvement, including abnormal liver function and acute respiratory distress.<sup>62</sup> Patients with AGEP may develop multiple

organ failure or sepsis. We found one case report on AGEPE caused by a combination of PD-1 and chemotherapy therapy.<sup>62</sup>

SCARs tend to occur more commonly with combination ICI therapy. Management and treatment of SCARs vary and is beyond the scope of this paper.<sup>31,59</sup> Permanent discontinuation of ICIs treatment is recommended for grade 4 cirAEs.<sup>31,43,47</sup>

### Isolated Pruritus

Immunotherapy-related isolated pruritus occurs frequently and has a significant impact on QoL (Figure 3).<sup>7-25,31,46,55-57</sup> Diagnostic criteria for pruritus have been described as core symptoms, including duration of pruritus (more than six weeks) and a history of signs of scratching.<sup>63,64</sup> Associated criteria comprise a range of clinical manifestations, symptoms, functions, and emotions. The function includes the extent of impaired QoL, sleep loss, and days of absence from work. Emotions include possible psychological reactions such as, depression, anxiety, anger, and helplessness.<sup>64</sup>

Isolated pruritus should be a diagnosis of exclusion once other causes such as pre-bullous pemphigoid, bites, or other drug reactions are ruled out.

A stepwise approach includes starting with over-the-counter topical agents, topical prescription agents, systemic drugs, and phototherapy.<sup>63,64</sup> General principles before starting topical and/or systemic treatment comprise skincare using gentle cleansers and moisturizers, especially in the presence of xerosis.<sup>63,48</sup>

The CaSMO algorithm educates on general measures such as avoiding skin irritants, scented products, temperature extremes, sun, and the use of sun-protective clothing (e.g., brim hats and sunglasses). The information should be provided before immunotherapy starts, and this is especially important for isolated pruritus.<sup>38</sup> The daily skincare regimen should be reinforced with emphasis on gentle cleansers, skin moisturization, and sun protection – similar counseling to a patient with atopic dermatitis.<sup>37,38,47</sup>



**Figure 3:** Pruritus without primary dermatologic finding

TDC – RA – 77-year-old male with metastatic non-small cell lung cancer treated with pembrolizumab (PD1 inhibitor) and binimetinib (MEK inhibitor) experiencing generalized pruritus with excoriated papules and nodules. a. left arm; b. back

Photo property of MB Sauder

A prurigo nodularis 4-tier treatment ladder<sup>64</sup> addresses neural and immunologic mechanisms that may be applicable to ICIs-induced pruritus.<sup>64</sup> Immunologic mechanisms are more likely to be the underlying mechanism in ICIs-induced pruritus. Patients can enter the treatment ladder at any tier and move up or down the ladder based on their clinical presentation.<sup>64</sup> Immunologic tier 1 is more likely mechanisms can be treated with TCS, TCI, or topical calcipotriol.<sup>64</sup> Moisturizers, including antipruritics such as pramoxine 1% or formulations with menthol or camphor, may be used as an adjunct therapy.<sup>64</sup>

For tier 2 neural mechanisms of pruritus medications include selective norepinephrine reuptake inhibitors (SNRIs) (i.e., mirtazapine) and gabapentinoids (gabapentin and pregabalin), which have antipruritic properties.<sup>63,64</sup> Second-generation histamine H1 receptor antagonists were shown to be effective and safe for patients receiving ICIs.<sup>64</sup>

Additional second-line systemic therapies such as neurokinin 1 inhibitors (i.e., aprepitant) and inhibitors of interleukins (ILs) 4, 13 may be considered for the tier 3 immunologic mechanisms approach.<sup>64</sup> When evaluating the need for systemic or topical treatment, possible interactions with cancer therapy are assessed together with concomitant conditions and cirAEs.<sup>9-11,15,16,23,24,37,38,47</sup>

Clinicians should take caution using systemic steroids and immunomodulators for patients receiving cancer treatment with ICIs (Table 2).<sup>9-11</sup>

### Psoriasisiform Eruptions

T helper (Th) cells producing interleukin (IL)-17, IL-22, and tumor necrosis factor (TNF) drive the pathogenesis of psoriasis by orchestrating inflammation in the skin triggering proliferation of keratinocytes and endothelial cells.<sup>65</sup> Besides Th17 cells, other immune cells that are capable of producing IL-17-associated cytokines participate in psoriatic inflammation.<sup>66-70</sup> ICIs are thought to be driven through the TH17 pathway, and this may have implications on the development of psoriasis but also on the use of systemic psoriasis medications.<sup>64,65,71,72</sup>

Immunotherapy with anti-PD1 and anti-PDL1 can exacerbate psoriasis, although more severe flares were noted in patients treated with durvalumab.<sup>65-68,70,71</sup>

A personal or family history of psoriasis is a significant risk factor that should be identified before starting immunotherapy.<sup>65,66,68</sup> These patients require regular skin monitoring enabling early diagnosis and treatment of psoriatic exacerbations.<sup>65,66,68</sup> Prompt diagnosis can prevent a severe impact on QoL of this cirAE that may compromise therapeutic protocols and final cancer prognosis (Figure 4).<sup>53,65,66</sup> A skin biopsy to confirm the diagnosis, although not required, includes parakeratosis, hypogranulosis, regular acanthosis, suprapapillary plate thinning, and neutrophils at various layers of the epidermis.<sup>68,70</sup>

Psoriasisiform cirAEs can affect skin, nails, and joints and significantly impact QoL.<sup>65-71</sup> Psoriasis can be associated with arthritis as patients have a greater-than-expected incidence of psoriatic arthritis when it occurs as a cirAE of cancer treatment.<sup>33,65,66</sup> The choice of therapy takes many factors into account, including the extent and area of involvement, lifestyle, other health issues, and medications. First-line treatments include topical treatment with TCS, TCI, calcitriol, or a combination of a

super potent TCS with calcipotriol or tazarotene can be given.<sup>65-71</sup> For recalcitrant cases, consider adjuvant narrowband ultraviolet B therapy or oral treatment such as systemic retinoids [acitretin] or apremilast.<sup>72-75</sup> Although there is no direct evidence in ICIs treated cancer patients, methotrexate is immunosuppressive and may reduce the therapeutic effect of ICIs, similar to systemic steroids that have been shown to reduce RFS and OS.<sup>32,33,35</sup>

Acitretin or apremilast is preferred over methotrexate; however, there is an absence of data for apremilast on the effect it may have on the anticancer treatment.<sup>68-75</sup> If the lesions persist, treatment with biologics may be required to treat psoriasiform cAEs. IL-23 agents (guselkumab, risankizumab, tildrakizumab) are considered most targeted and have the least direct evidence of immunosuppression (e.g. infection and TB reactivation). However, the risk/benefit needs to be considered before starting treatment with biologics (Table 3).<sup>76-86</sup>

## Lichen Planus

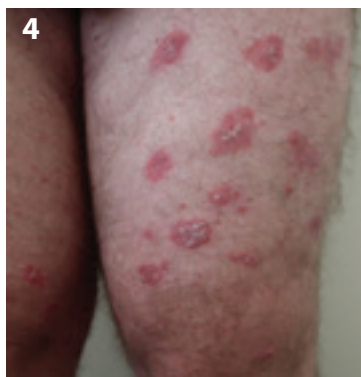
Immunotherapy-induced lichen planus is a pruritic, papulosquamous disease that can affect skin, hair, and nails (Figure 5). Treatment is required, especially if pruritic when it can severely impact QoL.<sup>7-19,27,33,46,63,77,78</sup> When examining the patient exclude guttate psoriasis, mucositis, and bullous disease. Specific investigations include a detailed medical history and medication use, liver function tests including hepatitis C status, and, if required, a skin biopsy.<sup>79</sup>

Pruritus may be treated with second-generation histamine H1 receptor antagonists (e.g., bilstane, rupatadine, cetirizine and fexofendadine).<sup>63,64,79</sup> A retrospective analysis of clinical data investigating if commonly used medications might influence responses to checkpoint inhibitors. The researchers found that concurrent use of second-generation histamine H1 receptor antagonists correlated with significantly improved

Isolated Pruritus			
Treatment recommendations	First-line	Second-line	Third-line
	Moisturization and sun avoidance Antipruritic additives: pramoxine, menthol, camphor Second-generation H1 antihistamine TCS, TCI, PDE4 inhibitors TCA (i.e. doxepin) SNRIs (i.e., mirtazapine) and gabapentinoids (gabapentin and pregabalin)	Neurokinin 1 inhibitors (i.e., aprepitant), inhibitors of ILs 4, 13, (i.e., dupilumab, tralokinumab) Phototherapy	Methotrexate Inhibitors of IL31 (i.e. nemolizumab – only in trials)
Other comments	Take caution using systemic steroids Consider biopsy if pruritus is extreme or non-responsive to treatments to rule out pre-bullous pemphigoid Look for alternative diagnoses (e.g., scabies)		

**Table 2:** Isolated pruritus

Quality of life (QoL), Selective nor-epinephrine reuptake inhibitors (SNRIs), Interleukins (ILs), Topical corticosteroids (TCS), Topical calcineurin inhibitors (TCI), Not applicable (n.a.)



**Figure 4:** Psoriasiform cAEs



**Figure 5:** Lichenoid cAEs

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**Figure 6:** Eczematous eruptions

Photo property of Joel Claveau

Psoriasis			
Treatment recommendations	First-line	Second-line	Third-line
	Moisturization and avoidance of sun exposure TCS, TCI Combination steroid products Vitamin D analogues	Phototherapy Systemic retinoids (acitretin) Apremilast	Methotrexate Biologics: consider most targeted biologics such as IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab)
Other comments	Differential diagnosis: lichen planus Avoid cyclosporine Consider biopsy if extensive, atypical, or non-responsive to therapy		

**Table 3:** Psoriasiform eruption

Quality of life (QoL), Interleukin (IL), Body surface area (BSA), Topical corticosteroids (TCS), Topical calcineurin inhibitors (TCI)

Lichen Planus			
Treatment recommendations	First-line	Second-line	Third-line
	Moisturization and skincare TCS, TCI Second-generation H1 antihistamine	Metronidazole, Hydroxychloroquine (especially for scalp or presentation with arthritis) Systemic retinoids (acitretin) nbUVB PDE4 inhibitors	Sulfasalazine, Griseofulvin, Calcipotriol ointment Low-dose corticosteroid
Other comments	Differential diagnosis: psoriasis, mucositis, bullous disease Avoid cyclosporine Consider concomitant conditions and immune-related AEs Consider biopsy if extensive, atypical, or non-responsive to therapy; biopsy can help distinguish lichen planus from guttate psoriasis		

**Table 4:** Lichen planus

Psoralen and ultraviolet A (PUVA), Body surface area (BSA), Topical corticosteroids (TCS), Topical calcineurin inhibitors (TCI), Phosphodiesterase (PDE)

Eczematous Eruptions			
Treatment recommendations (grouped into 1st, 2nd, and 3rd line)	First-line	Second-line	Third-line
	Moisturization and sun avoidance TCS TCI Topical PDE4 inhibitor (crisaborole) Second-generation H1 antihistamine	Dupilumab Tralokinumab nbUVB	Methotrexate Systemic steroids
Other comments	Look for a classic presentation Consider previous history or family history of atopy JAK inhibitors are not recommended (pending further data) Consider biopsy if extensive or non-responsive to therapy		

**Table 5:** Eczematous eruptions

Quality of life (QoL), Body surface area (BSA), Janus kinase (JAK), Topical corticosteroids (TCS), Topical calcineurin inhibitors (TCI), Phosphodiesterase (PDE)



survival outcomes in those with melanoma or lung cancer. In addition, the antihistamine was effective for treating pruritus in cirAEs.<sup>63,64,79</sup> The choice of therapy takes many factors into account, including the extent and area of involvement, other health issues, and medications.<sup>8-11,67-69,78,80</sup> First-line treatment includes moisturization and sun avoidance, antihistamines, TCS, and TCI.<sup>80,81</sup> Other second-line treatments include oral retinoids (acitretin), apremilast, sulfasalazine, metronidazole, hydroxychloroquine (especially for scalp or presentation with arthritis).<sup>80</sup> Additionally, narrowband or broadband UVB or PUVA may be used. Treatment with cyclosporine should be avoided as it may exert effects on the immune system (Table 4).<sup>25,31,78</sup>

### **Eczematous Eruptions**

Eczematous eruptions (EE) are associated with altered immune function, epidermal barrier dysfunction, genetic and environmental factors, and poorly understood interaction between these factors.<sup>82-85</sup> EE presents clinically as relapsing erythematous and pruritic patches of skin with varying severity (Figure 6).<sup>9-11,82-85</sup> Skin biopsies may be taken if the condition is extensive or not responding to therapy or if the diagnosis is in doubt.<sup>9-11</sup> Canadian and US guidelines for topical treatment of atopic dermatitis include education and avoiding triggers, routine skincare with gentle cleansers and moisturizers, and EE management foundation regardless of disease severity and prescription treatment.<sup>82,83</sup> Conventional moisturizers contain occlusives, humectants, and emulsions. Newer moisturizers designed to restore skin barrier defects include distinct ratios of lipids that resemble physiological compositions.<sup>36,38,47,82,83</sup> If EE is not controlled with a moisturizer alone, TCS, TCI, or crisaborole ointment, an anti-inflammatory inhibitor of PDE4, is recommended while continuing skincare.<sup>9-11,82-86</sup> Treatment with crisaborole ointment achieved early sustained control of atopic dermatitis flares (reduced pruritus, erythema, exudation, excoriation, induration/papulation, and lichenification).<sup>84,85</sup> The topical PDE4 inhibitor offered a safe alternative to TCS and TCI.<sup>84,85</sup>

For those not adequately controlled with topical treatment, nbUVB may be considered.<sup>82,83</sup> Dupilumab is a humanized monoclonal antibody against the shared alpha subunit of IL-4 and IL-13 receptors, blocking these cytokines commonly found in atopic dermatitis-affected skin. The use of dupilumab may be considered for extensive, moderate-to-severe EE. Two large, long-term RCTs demonstrated its efficacy and safety.<sup>9-11,82,83,86</sup>

Another option is tralokinumab (IL-13 inhibitor) which was shown to be effective and safe for the treatment of severe atopic dermatitis.<sup>87</sup>

Treatment with the biologic is preferred to methotrexate which is an immunosuppressive and may reduce the anticancer effect.<sup>9-11</sup> TCS, TCI, and crisaborole can be used with any systemic treatment to address an EE flare (Table 5).<sup>82-85,93</sup>

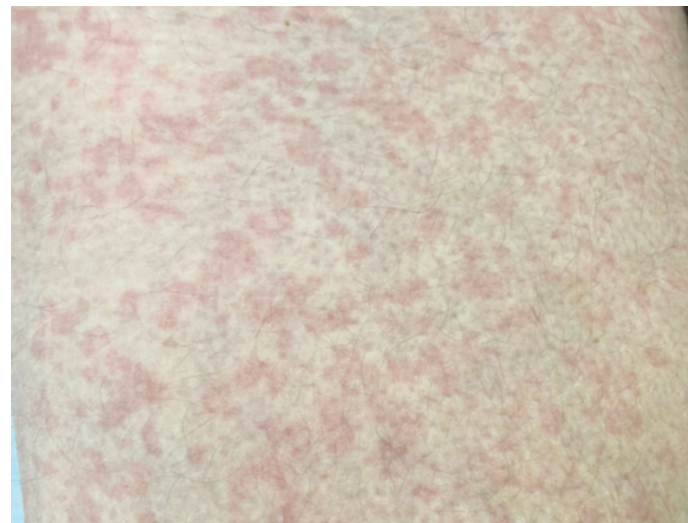
### **Morbilloform (maculopapular) Eruptions**

These cirAEs may present as pruritic, nontender, erythematous papular, and macular eruptions on various body locations.<sup>37,38,46,47</sup> Physical examination focusing on the morphology and the distribution, starting on the trunk and then spreading to limbs, of the presented morbilliform eruptions is required to distinguish between the various cirAEs (Figure 7).<sup>37,38,46,47</sup> Laboratory tests

may be needed and include a complete blood count, electrolytes, renal and liver function, and inflammatory markers.<sup>37,38,46,47</sup> Peripheral blood eosinophilia ( $\geq 500$  eosinophils/microL) may be caused by numerous conditions, including allergic, infectious, inflammatory, and neoplastic disorders (Table 6).<sup>37,38,46,47</sup> Mild to moderate conditions may be treated with general skin care measures, TCS, TCI, and oral histamine H1 receptor antagonists to reduce pruritus.<sup>63,64,94</sup> Generally, this condition can be managed with aggressive topical treatment; however, for very severe and symptomatic cases, ICIs-treatment may be held, and a short course of systemic corticosteroids may be indicated.<sup>94</sup>

### **Bullous Pemphigoid**

Bullous pemphigoid (BP) is an autoimmune bullous dermatosis caused by a variety of medications. One of the more common medications to cause BP now are ICIs.<sup>88,90,91</sup> A skin biopsy may be required to confirm BP, including direct immunofluorescence to identify the presence of antibodies in the skin, typically demonstrating linear IgG and C3. Further studies on serum can detect circulating autoantibodies (anti-BP180 or anti-BP230)



**Figure 7:** Morbilliform eruptions  
Photo from MB Sauder



**Figure 8:** Bullous eruptions  
Severe bullous pemphigoid associated with pembrolizumab therapy  
Photo from MB Sauder

with either ELISA or indirect immunofluorescence. Clinically, BP classically presents with pruritic tight tense bullae filled with serous fluid on erythematous skin on various body locations (Figure 8).<sup>88,90,91</sup> The pre-bullous phase presents as intense pruritic urticoid plaques that can be diagnostically challenging and may be mistaken for the more common cirAE of isolated pruritus or urticaria.<sup>88,90,91</sup> The post-bullous phase presents as hemorrhagic crusts on a background of erythema representing ruptured bullae.

CirAE BP can occur at any time, including after discontinuation of ICI. The onset to developing BP is within days or weeks of ICI exposure or may be delayed several months after starting ICI.<sup>31</sup> Upon diagnosis ICIs is to be held and may require permanent discontinuation.<sup>3,15,46</sup> In milder cases, aggressive topical treatments with class I TCS may be as effective as systemic steroids.<sup>92</sup> CirAE BP may require systemic treatment and temporary, if not permanent, cessation of immunotherapy.<sup>3,15,46</sup> Systemic corticosteroids may be used to achieve control quickly while waiting for steroid-sparing treatments to take effect.<sup>88,90-92</sup> Non-immunosuppressive systemic treatment includes oral tetracycline-class antibiotics combined with oral niacinamide 500 mg twice a day, omalizumab, IVIg, and dupilumab.<sup>31,88,90-92</sup> However, steroid-sparing agents that are immunosuppressive may be required in order to control BP ongoing, including methotrexate, mycophenolate mofetil or rituximab.<sup>91</sup> While rituximab may be immunosuppressive, it works on B-cells and may not hinder the T-cell activation from ICIs. In patients with cirAE BP, obtaining disease control as quickly as possible is ideal not only for improved QoL, and decreased morbidity but also if treatment is to be reinitiated (Table 7).<sup>93,95</sup>

## Limitations

The details provided on the mode of action of ICIs were limited to what is clinically relevant for this primer on cirAEs. Clinical studies on prescription medications and skin care for cirAEs frequently are case reports, case series, or have small sample sizes. For this reason, grading the evidence resulting from the literature searches was irrelevant. Therefore, recommendations given by the CaSMO project advisers are based on information from the guidelines, algorithms, consensus papers, and systematic reviews coupled with their clinical experience and resulting from discussions. More work is required to identify the best practice evidence-based management of cirAEs.

## Summary and Conclusions

Immunotherapy for cancer patients is fast-developing into the standard of care for many malignancies. Although many publications are available on cirAEs, publications on the treatment using prescription medications and skincare are scarce.

The CaSMO practical primer focuses on isolated pruritus, psoriasiform eruptions, lichenoid eruptions, eczematous eruptions, and bullous pemphigoid. The practical primer addresses the need for physician awareness, patient education on the occurrence of cirAEs, prompt diagnosis, prevention, treatment, and ongoing skincare started before ICI.

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## Morbilloform (Maculopapular) Eruptions

Diagnosis	<p>Drug eruptions can range from a mild lesion involving only the skin to severe complex eruptions with systemic involvement, such as TEN. Systemic involvement should be explored even in a mild cutaneous eruption due to a drug because skin manifestation does not necessarily mirror the severity of the systemic involvement.</p> <p>Ensure another drug does not cause symptoms; take a drug history, looking for medications started 2-3 weeks before the eruption.</p> <p>Consider biopsy if the eruptions are extreme or non-responsive to treatment.</p>		
Treatment recommendations (grouped into 1st, 2nd, and 3rd line)	First-line	Second-line	Third-line
	<p>Moisturization and skincare TCS</p> <p>If accompanied by itch: pramoxine, menthol, camphor</p> <p>Second-generation H1 antihistamine</p>	Systemic corticosteroids	
Other comments			

**Table 6:** Morbilliform Eruptions  
Topical corticosteroids (TCS)

## Bullous Eruptions

Diagnosis	<p>Prompt clinical/pathologic workup is essential (urgent referral &amp; triage within 2-3 days), including biopsy &amp; blood work.</p> <p>Biopsy can help determine if the eruption is bullous pemphigoid, bullous lichen planus, or TEN and blood work can identify pemphigus and pemphigoid antibodies</p>		
Treatment recommendations (grouped into 1st, 2nd, and 3rd line)	First-line	Second-line	Third-line
	<p>High-dose TCS</p> <p>Tetracycline &amp; nicotinamide</p> <p>Systemic corticosteroids</p>	<p>Methotrexate</p> <p>Dapsone</p> <p>Cellcept (with caution)</p>	<p>Rituximab (some evidence); off-label, Intravenous immunoglobulin,</p> <p>Omalizumab</p> <p>Dupilumab</p>
Other comments	<p>With mild symptoms, consider holding immunotherapy and consult a dermatologist to determine resuming treatment.</p> <p>In severe cases, immediately hold immunotherapy and seek urgent care from a dermatologist, oncologist, or ER.</p> <p>Immunotherapy is usually discontinued until eruptions are under control,</p> <p>Avoid azathioprine &amp; cyclosporine</p>		

**Table 7:** Bullous eruptions

Cutaneous adverse events (cAEs), Quality of life (QoL), Toxic epidermal necrolysis (TEN), Topical corticosteroids (TCS)

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