

Review

Cancer Therapy-Related Cutaneous Toxicities: Prognostic Biomarkers, Immunologic Endotypes, and Novel Therapeutic Strategies

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Simple Summary

Cutaneous adverse events are among the most frequent complications of modern cancer therapies and can negatively affect quality of life, treatment adherence, and clinical outcomes. As immunotherapy, targeted therapies, and antibody–drug conjugates become increasingly used, dermatologic toxicities are becoming more diverse and clinically relevant. This review summarizes the mechanisms underlying treatment-related skin toxicities and discusses their prognostic significance, particularly in patients receiving immune checkpoint inhibitors. We highlight emerging steroid-sparing biologic therapies, including dupilumab, omalizumab, anti-IL-17 agents, and Janus kinase inhibitors, as well as recent advances in immunologic endotyping and biomarker discovery. Particular attention is given to the growing role of precision oncodermatology, which aims to tailor management according to individual inflammatory pathways and molecular profiles. Improved collaboration between oncologists and dermatologists, together with biomarker-driven strategies, may optimize toxicity management while preserving the efficacy of anticancer treatments.

Abstract

Background/Objectives: Cutaneous adverse events (cAEs) are among the most common toxicities associated with modern anticancer therapies and can significantly affect quality of life, treatment adherence, and therapeutic outcomes. This narrative review aims to provide an updated overview of the mechanisms, clinical manifestations, prognostic implications, and management strategies of cancer therapy-related cutaneous toxicities, with a particular focus on precision oncodermatology. **Methods:** A narrative review of the recent literature was performed, integrating evidence from clinical studies, meta-analyses, pharmacovigilance investigations, consensus guidelines, and translational research. The review examines cutaneous toxicities associated with immune checkpoint inhibitors, targeted therapies, antibody–drug conjugates, and other emerging anticancer treatments. **Results:** Four major axes were identified: immune disinhibition, epithelial signaling inhibition, cytotoxic epithelial injury, and cytokine-driven immune activation. Cutaneous immune-related adverse events (cAEs) emerged as potential biomarkers of treatment efficacy, particularly vitiligo, lichenoid, and psoriasiform eruptions. Increasing evidence supports the use of steroid-sparing biologic therapies, including dupilumab, omalizumab, anti-IL-17 agents, and Janus kinase inhibitors, although prospective validation remains limited. Recent advances in immunologic endotyping have identified distinct inflammatory pathways that may enable personalized therapeutic approaches. Antibody–drug conjugates represent an expanding source of unique dermatologic toxicities requiring dedicated management



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strategies. Emerging biomarkers, including cytokine signatures and microRNAs, may further refine risk stratification and treatment selection. Conclusions: The management of cancer therapy-related cutaneous toxicities is evolving toward a precision medicine model integrating clinical phenotype, immunologic endotype, and biomarker profiling. Early multidisciplinary intervention and mechanism-based therapeutic strategies may improve patient outcomes while preserving anticancer efficacy. Prospective studies are needed to validate biomarker-guided and steroid-sparing approaches in oncodermatology.

Keywords: cutaneous toxicities; cutaneous immune-related adverse events; immune checkpoint inhibitors; epidermal growth factor receptor inhibitors; antibody–drug conjugates; steroid-sparing biologics; janus kinase inhibitors; prognostic biomarkers

1. Introduction

The skin is the organ most frequently affected by adverse events from anticancer therapy. Modern anticancer therapies comprise several major therapeutic classes with distinct mechanisms of action. ICIs restore antitumor T-cell activity by blocking inhibitory immune checkpoints such as CTLA-4 and PD-1/PD-L1. Targeted therapies selectively inhibit oncogenic signaling pathways involved in tumor proliferation and survival, including EGFR, BRAF, MEK, and other kinases. Antibody–drug conjugates combine tumor-specific monoclonal antibodies with cytotoxic payloads to deliver chemotherapy directly to malignant cells, whereas conventional chemotherapy induces nonspecific cytotoxic damage to rapidly proliferating tissues. More recently, cellular therapies and T-cell-engaging antibodies exert antitumor activity through immune-cell activation. These distinct mechanisms of action underlie the heterogeneous spectrum of cutaneous toxicities observed across different anticancer treatments that represent a major determinant of quality of life, treatment adherence, and dose intensity [1,2]. Among patients receiving ICI therapy, cutaneous toxicities are the most common immune-related adverse events (irAEs), reported in up to 71.5% of individuals, with onset as early as 3 weeks after initiation of anti-CTLA-4 therapy and within 6 weeks of anti-PD-1 therapy [3]. For EGFR inhibitors, up to 90% of patients experience cutaneous toxicities, including papulopustular eruptions, xerosis, pruritus, and paronychia [4,5]. BRAF inhibitor monotherapy induces proliferative cutaneous lesions in 15–26% of patients, while ADCs carry FDA boxed warnings for severe and potentially fatal skin reactions including Stevens–Johnson syndrome and toxic epidermal necrolysis [6,7]. A comprehensive analysis of the FDA Adverse Event Reporting System (FAERS) identified 113 anticancer drugs significantly associated with skin adverse events, with targeted therapies accounting for 49% of drug–AE pairs, cytotoxic chemotherapy for 36%, and immunotherapy for 11% [1,2]. Cutaneous toxicities can lead to dose reduction, treatment interruption, or permanent discontinuation of life-prolonging anticancer therapy—outcomes that may directly compromise oncologic efficacy [1–3]. ASCO guidelines emphasize that early identification and symptomatic or systemic management are pivotal to enhance compliance, treatment continuation, and ultimately therapeutic efficacy [3]. Findings from large clinical development programs suggest that cutaneous irAEs may serve as a surrogate for clinical benefit, making it critically important to correctly identify these skin changes so that ICI therapy is not unnecessarily discontinued in patients with favorable prognoses [3,8]. The impact on quality of life is substantial. Even mild skin toxicities elevate dermatology-specific quality of life measures, affecting mood, social function, and body image [9]. Dermatologic adverse events negatively impact quality of life through physical discomfort, changes to body image, decreased self-esteem, and effects on social interactions,

and decreased satisfaction with treatment can lead to discontinuation or dose reduction [8]. The integration of dermatologic care into oncology practice has been shown to minimize toxicity-associated anticancer interruptions [9].

The landscape of cancer treatment-related skin toxicity has undergone a fundamental transformation over the past decade. The approval of ICIs across an expanding range of tumor types has introduced a diverse spectrum of immune-mediated dermatologic toxicities that differ fundamentally from the predictable, dose-dependent skin reactions of conventional chemotherapy [1]. Simultaneously, the proliferation of targeted kinase inhibitors (EGFR, BRAF, MEK, mTOR, PI3K, and BTK inhibitors), the rapid expansion of the ADC pipeline (with over 15 FDA-approved agents), and the emergence of cellular therapies (CAR-T and bispecific antibodies) have each introduced distinct cutaneous toxicity profiles reflecting their unique mechanisms of action [7].

This expanding complexity has catalyzed the emergence of supportive oncodermatology as a subspecialty, with dedicated programs at major cancer centers providing urgent and follow-up dermatologic care for oncology patients. International guidelines now recommend early engagement of dermatologists in the management of cancer treatment-related skin toxicity, with the NCCN providing detailed, phenotype-specific management algorithms for maculopapular rash, pruritus, bullous dermatitis, lichenoid eruptions, psoriasisiform diseases, and oral mucositis [6].

This narrative review aims to synthesize these developments into an integrated framework that links clinical morphology to underlying biology, prognostic significance, and mechanism-directed therapeutic strategies across all major classes of anticancer therapy.

2. Materials and Methods

This study was conducted as a narrative review. A comprehensive literature search was conducted using PubMed/MEDLINE, Embase, the Cochrane Library, and ClinicalTrials.gov from database inception through June 2026. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords organized around the following thematic domains:

Cutaneous toxicity and cancer therapy: (“cutaneous adverse events” OR “dermatologic toxicity” OR “skin toxicity” OR “rash” OR “pruritus” OR “hand-foot syndrome” OR “bullous pemphigoid” OR “Stevens-Johnson syndrome” OR “toxic epidermal necrolysis” OR “vitiligo” OR “lichenoid” OR “psoriasiform” OR “eczematous” OR “acneiform”) AND (“cancer” OR “neoplasm” OR “oncology” OR “antineoplastic”);

Drug class-specific searches: (“immune checkpoint inhibitor” OR “anti-PD-1” OR “anti-PD-L1” OR “anti-CTLA-4” OR “nivolumab” OR “pembrolizumab” OR “ipilimumab” OR “atezolizumab”) AND (“cutaneous” OR “dermatologic” OR “skin”); (“EGFR inhibitor” OR “cetuximab” OR “erlotinib” OR “panitumumab”) AND (“rash” OR “skin toxicity”); (“BRAF inhibitor” OR “MEK inhibitor” OR “vemurafenib” OR “dabrafenib” OR “trametinib”) AND (“cutaneous” OR “skin”); (“antibody-drug conjugate” OR “ADC” OR “enfortumab vedotin” OR “trastuzumab deruxtecan” OR “sacituzumab govitecan”) AND (“cutaneous” OR “dermatologic” OR “skin toxicity”);

Steroid-sparing biologics and JAK inhibitors: (“dupilumab” OR “omalizumab” OR “secukinumab” OR “ixekizumab” OR “ustekinumab” OR “rituximab” OR “infliximab” OR “vedolizumab” OR “tocilizumab” OR “abatacept” OR “tofacitinib” OR “ruxolitinib” OR “baricitinib”) AND (“immune-related adverse event” OR “irAE” OR “checkpoint inhibitor” OR “cancer” OR “oncology”);

Immunologic endotyping and biomarkers: (“endotyping” OR “cytokine profiling” OR “immunophenotyping” OR “tape strip” OR “biomarker”) AND (“cutaneous immune-related adverse event” OR “cirAE” OR “checkpoint inhibitor” OR “skin toxicity”);

Prognostic significance: (“cutaneous adverse event” OR “skin toxicity” OR “vitiligo” OR “rash”) AND (“survival” OR “prognosis” OR “overall survival” OR “progression-free survival”) AND (“immune checkpoint inhibitor” OR “immunotherapy”);

Grading and classification: (“CTCAE” OR “Common Terminology Criteria for Adverse Events” OR “grading” OR “severity”) AND (“cutaneous” OR “dermatologic” OR “skin”) AND (“cancer” OR “oncology”).

The search was supplemented by manual review of reference lists from key articles, relevant conference abstracts from the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and American Academy of Dermatology (AAD) annual meetings (2020–2026), and the FDA Adverse Event Reporting System (FAERS) database analyses. Conference abstracts were considered only when peer-reviewed evidence, clinical practice guidelines, or position papers were unavailable, particularly for emerging therapeutic strategies. In these instances, they were used to illustrate evolving clinical experience rather than to support definitive clinical recommendations. Clinical practice guidelines from the National Comprehensive Cancer Network (NCCN), ASCO, the European Academy of Dermatology and Venereology (EADV), and the American Gastroenterological Association (AGA) were reviewed for management recommendations relevant to cutaneous toxicities.

Given the narrative review design, no formal risk-of-bias assessment was performed for individual studies; however, the level of evidence was considered when synthesizing findings, with emphasis placed on meta-analyses, randomized controlled trials, and large prospective cohorts over smaller retrospective series and case reports, consistent with established narrative review methodology. For several emerging biologic agents, published evidence is currently limited and formal guideline recommendations are not yet available; therefore, selected data from major international oncology and dermatology meetings were included to provide a comprehensive overview of the rapidly evolving therapeutic landscape, while clearly recognizing their preliminary nature.

3. Results and Discussion

3.1. Mechanistic Framework: Four Axes of Skin Toxicity

Immune disinhibition (immune checkpoint inhibitors): Blockade of CTLA-4, PD-1, or PD-L1 unleashes autoreactive T cells that target shared antigens expressed on both tumor cells and normal tissues, producing a diverse spectrum of inflammatory dermatoses. Cutaneous irAEs are reported in up to 71.5% of ICI-treated patients and are the most common irAE across all organ systems [3,10]. Presentations include maculopapular rash, eczematous eruptions, lichenoid dermatitis, psoriasiform reactions, bullous pemphigoid, vitiligo, and rare SCARs [3,10].

Epithelial signaling inhibition (EGFR inhibitors and BRAF/MEK inhibitors): EGFR inhibitors cause papulopustular (acneiform) rash in 43–85% of patients, along with paronychia, xerosis, and the “PRIDE” syndrome (Papulopustular rash, Regulatory hair changes, Itching, Dryness, EGFR inhibitors) [11,12]. BRAF inhibitors are associated with secondary cutaneous squamous cell carcinomas and keratoacanthomas arising from paradoxical MAPK pathway activation in keratinocytes harboring pre-existing RAS mutations; concurrent MEK inhibition substantially reduces these proliferative toxicities [13,14].

Cytotoxic epithelial injury (antibody–drug conjugates and classic chemotherapy): ADCs cause direct epithelial damage through payload-mediated mechanisms. Cutaneous AEs comprise a significant proportion of all ADC-related toxicities, with enfortumab vedotin showing disproportionately high cutaneous toxicity due to Nectin-4 expression in skin keratinocytes [15,16].

Cytokine-driven immune activation (CAR-T therapy and bispecific antibodies): These newer platforms introduce additional toxicity patterns mediated by massive cytokine release, including inflammatory eruptions that are only beginning to be systematically characterized [17,18].

3.2. Drug Class-Specific Dermatologic Signatures

3.2.1. Immune Checkpoint Inhibitors

ICI-associated cutaneous toxicities encompass a broad morphologic spectrum. The most common presentations include maculopapular rash, pruritus, eczematous dermatitis, lichenoid eruptions, psoriasiform reactions, and vitiligo [3,10]. Cutaneous irAEs are more frequently observed with CTLA-4 inhibitors alone or in combination with anti-PD-1 agents, and are most often reported in melanoma and NSCLC [3,10,19]. A critical advance has been the recognition that the nonspecific term “maculopapular rash” encompasses multiple distinct clinicopathologic entities—eczematous, lichenoid, psoriasiform, and granulomatous—each with different prognoses and treatment implications [8].

A systematic review and meta-analysis of 45 studies (26,817 patients) found that cirAEs were associated with prolonged OS (HR 0.54; 95% CI 0.46–0.63) and PFS (HR 0.51; 95% CI 0.43–0.60) [20]. Vitiligo showed the strongest prognostic signal, followed by rash, lichenoid eruptions, and psoriasiform reactions, while bullous pemphigoid and maculopapular rash did not show significant OS benefit [20]. A multi-institutional cohort study of 3731 ICI recipients confirmed that cirAE development was independently associated with decreased mortality (HR 0.87, $p = 0.027$), with the strongest associations for vitiligo, lichenoid eruptions, and psoriasiform eruptions [21]. The mechanistic basis for this association is the shared antigen theory. Cytotoxic T cells specific for melanocyte differentiation antigen (MDA) proteins (MART-1 and gp100) recognize peptides presented by both melanoma cells and normal melanocytes, mediating tumor destruction and vitiligo simultaneously [22–24]. More recently, keratinocyte differentiation antigens (KDAs) have been identified in NSCLC patients, where KDA-specific T cells recognize antigens shared between lung tumors and skin keratinocytes [23]. Shared TCR clones have been identified between vitiligo and metastatic melanoma tissues, supporting the concept of “on-target, off-tumor” damage [25,26]. Although the association between cirAEs and improved survival has been consistently reported, residual immortal time bias and guarantee-time effects may partially contribute to the observed prognostic advantage, warranting cautious interpretation of causality.

3.2.2. EGFR Inhibitors

The papulopustular eruption associated with EGFR inhibitors typically develops within the first 2 weeks of therapy; affects the face, scalp, and upper trunk; and is dose-dependent [11,27]. A meta-analysis of 35 RCTs comprising 16,151 patients confirmed significantly increased risk of all-grade rash (OR 12.21), paronychia (OR 31.97), dry skin (OR 6.15), and pruritus (OR 2.86) with EGFR-TKIs [28]. Importantly, the severity of EGFR inhibitor-associated rash correlates with improved oncologic outcomes: survival is significantly improved in patients experiencing at least grade 2 acneiform rash [4,29]. A German expert panel provided interdisciplinary recommendations for grade-specific and stage-adapted treatment, combining basic skin care with specific therapy adapted to stage and grade of skin reaction [30]. For grade 2 and above, specific treatment recommendations for early- and later-stage skin reactions were proposed [30]. Mild cases respond to topical anti-inflammatory therapy, whereas moderate to severe cases require tetracyclines [30]. A systematic review of 43 patients treated with systemic retinoids for EGFR inhibitor-induced acneiform eruptions found that 77% noted moderate to significant improvement with minimal adverse events,

suggesting retinoids as a safe and effective alternative when tetracyclines are insufficient [31]. The STEPP trial demonstrated a 50% reduction in grade ≥ 2 rash with preemptive doxycycline, topical corticosteroids, moisturizers, and sunscreen [4]. The Dana–Farber STAT program showed that prophylactically treated patients were 94% less likely to require rescue treatment and 79% less likely to experience dose changes or interruptions [4]. Prophylactic hydrocortisone acetate 1% with moisturizer, sunscreen, and doxycycline at a dose of 100 mg twice daily are recommended for the first 6 weeks of EGFR inhibitor therapy [32].

3.2.3. BRAF/MEK Inhibitors

BRAF inhibitor monotherapy is associated with a unique spectrum of proliferative cutaneous lesions arising from paradoxical MAPK pathway activation. A real-world pharmacovigilance analysis of 72,720 individual case safety reports from the WHO VigAccess database quantified that skin-related ADRs accounted for 39.78% of reports with vemurafenib, 16.49% with dabrafenib, and 14.62% with encorafenib; among MEK inhibitors, selumetinib (40.03%) and cobimetinib (34.31%) had the highest proportions [14]. A systematic review and meta-analysis comparing BRAF/MEK combination therapy versus BRAF monotherapy demonstrated significantly reduced risk of cutaneous SCC (RR 0.21), keratoacanthoma (RR 0.22), hyperkeratosis (RR 0.30), palmoplantar erythrodysesthesia (RR 0.21), and alopecia (RR 0.28) with combination therapy [33]. A meta-analysis of clinical trials reported pooled prevalence of rash at 39% with vemurafenib monotherapy, while that for rash and acneiform dermatitis was 24% and 12%, respectively, with dabrafenib plus trametinib [34,35].

The AAD guidelines recommend baseline dermatologic assessment and pre-BRAF inhibitor treatment of actinic keratoses [35]. Cutaneous SCC/keratoacanthoma can generally be managed with cryotherapy or shave/electrodesiccation rather than complete surgical excision [35]. Hyperkeratosis and hand–foot skin reaction can be managed with topical keratolytic agents (ammonium lactate 12%, urea 20–40%, or salicylic acid 6%) [35]. Acneiform eruptions during MEK inhibitor therapy can be managed with topical steroid ointments, topical or oral antibiotics (typically tetracyclines), and/or dilute bleach soaks; severe papulopustular eruptions may require isotretinoin or drug cessation [35]. The NCCN Cutaneous Melanoma guidelines recommend regular dermatologic evaluation for all patients receiving BRAF-based therapy, with prompt dermatologic consultation for severe and life-threatening skin toxicity, particularly drug-induced hypersensitivity syndrome following immune checkpoint blockade.

3.2.4. Antibody–Drug Conjugates

ADCs represent the newest frontier in cancer treatment-related dermatologic toxicity. Enfortumab vedotin shows disproportionately high cutaneous toxicity due to Nectin-4 expression in skin keratinocytes, with a FAERS reporting odds ratio of 55.4 for skin-related AEs. A pharmacovigilance study identified 44 positive cutaneous safety signals, including 10 not described in the EV label, with most events occurring within the first 2 weeks of treatment [15]. A broader FAERS analysis of all ADCs identified 3631 cutaneous AE cases, with 31 positive safety signals at the preferred term level, including SJS-TEN overlap and generalized exfoliative dermatitis [16]. Lacouture et al.'s practical management framework recommends monitoring for skin reactions, topical corticosteroids and antihistamines as clinically indicated, and withholding EV for persistent or recurrent grade 2 skin reactions until resolution to grade ≤ 1 [36]. Among patients who experienced skin reactions leading to dose interruption and then restarted EV, 24% experienced recurrent severe skin reactions regardless of whether they restarted at the same or reduced dose.

Unlike immune checkpoint inhibitors, whose cutaneous toxicities primarily arise from immune dysregulation, ADC-associated dermatologic adverse events result from a combination of target-dependent on-target/off-tumor effects [37]. Consequently, the clinical spectrum and biological mechanisms of ADC-related skin toxicities differ substantially across individual agents. For example, Nectin-4 expression in keratinocytes largely explains the characteristic toxicity profile of enfortumab vedotin, whereas ADCs carrying topoisomerase I inhibitor may induce distinct patterns of epithelial injury [36–38]. As the number of approved ADCs continues to expand, future guidelines may benefit from moving beyond management strategies extrapolated from immune checkpoint inhibitors or conventional chemotherapy toward ADC-specific classification systems and treatment algorithms that integrate target antigen biology, linker characteristics, and payload mechanism of action.

Data are fully displayed in Table 1.

Table 1. Cutaneous toxicity profiles across all major drug classes (ICI, EGFR inhibitors, BRAF/MEK inhibitors, and ADCs) with their mechanisms, key manifestations, and grading.

Drug Class	Key Agents	Primary Mechanism of Cutaneous Toxicity	Most Common Cutaneous AEs (Incidence)	Distinctive/Pathognomonic Features	CTCAE Grading Landmarks	References
Anti-PD-1/PD-L1	Pembrolizumab, nivolumab, atezolizumab	T cell activation against shared tumor/skin antigens; loss of peripheral tolerance	Maculopapular rash (20–40%), pruritus (13–25%), vitiligo (3–11% in melanoma), lichenoid dermatitis (5–15%)	Vitiligo-like depigmentation (associated with improved OS in melanoma); lichenoid interface dermatitis on biopsy; late-onset psoriasiform eruptions	G1: 10% BSA, asymptomatic; G2: 10–30% BSA, limiting iADL; G3: >30% BSA, limiting self-care ADL; G4: SJS/TEN, life-threatening	[1,3,39]
Anti-CTLA-4	Ipilimumab	Treg depletion, enhanced T cell priming); higher irAE rates than anti-PD-1	Maculopapular rash (24–68%), pruritus (25–35%); higher rates of severe (G3–4) cutaneous irAEs with combination ICI	More frequent bullous pemphigoid; DRESS/DIHS; higher rate of combination-specific toxicities	Same CTCAE framework; combination ICI increases G3–4 cutaneous irAE rate to 5–10%	[1,3,39]
EGFR Inhibitors	Erlotinib, gefitinib, afatinib, osimertinib, cetuximab	Epithelial signaling inhibition: EGFR blockade disrupts keratinocyte differentiation, barrier function, and follicular homeostasis	Papulopustular/acneiform rash (25–85%), xerosis (10–35%), paronychia (OR 31.97 vs. controls), skin fissures, hair changes	PRIDE syndrome (Papulopustular rash, Regulatory hair changes, Itching, Dryness, EGFR inhibitors); acneiform rash correlates with treatment response; IL-36 γ -mediated neutrophil recruitment via C. acnes synergy	G1: papules/pustules 10% BSA; G2: 10–30% BSA, limiting iADL, associated with psychosocial impact; G3: >30% BSA, limiting self-care ADL, superinfection risk	[5,40–42]
BRAF Inhibitors (monotherapy)	Vemurafenib, dabrafenib, encorafenib	Paradoxical MAPK activation in BRAF-wild-type keratinocytes via CRAF-mediated ERK signaling	Photosensitivity (vemurafenib 30–63%), squamoproliferative lesions (cSCC/KA 6–26%), hand-foot skin reaction, keratosis pilaris, eruptive nevi	UVA-specific photosensitivity (vemurafenib); cSCC/KA within 8 weeks, decreasing after 4–6 months; new BRAF-WT primary melanomas; panniculitis/erythema nodosum	Photosensitivity: G1 painless erythema, G2 painful erythema, G3 blistering/desquamation; cSCC: managed by excision/cryotherapy without dose modification	[5,14,35]
BRAF + MEK Inhibitors	Dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib	MEK inhibition attenuates paradoxical MAPK activation but introduces EGFR-like epithelial toxicity	Acneiform rash (MEK component), pyrexia (~55%), reduced cSCC/KA rates vs. BRAF monotherapy; dermatitis, peripheral edema	Pyrexia with rash (onset 2–4 weeks); severe DIHS after sequential ICI-BRAF inhibitor; MEK-driven acneiform eruption resembles EGFR inhibitor toxicity	Pyrexia: hold at $\geq 38.5^{\circ}\text{C}$, resume at full dose after resolution; skin: standard CTCAE dermatologic grading	[14,35]

Table 1. Cont.

Drug Class	Key Agents	Primary Mechanism of Cutaneous Toxicity	Most Common Cutaneous AEs (Incidence)	Distinctive/Pathognomonic Features	CTCAE Grading Landmarks	References
Antibody–Drug Conjugates (ADCs)	Trastuzumab deruxtecan (T-DXd), enfortumab vedotin, sacituzumab govitecan	Cytotoxic epithelial injury: payload-mediated keratinocyte damage (topoisomerase I inhibitors, MMAE); bystander effect on skin	Rash (30–50%), alopecia, stomatitis; enfortumab vedotin: SJS/TEN risk (FDA boxed warning); sacituzumab govitecan: neutropenic skin infections	SJS/TEN with enfortumab vedotin (requires immediate discontinuation); maculopapular rash distinct from ICI pattern (cytotoxic interface on biopsy vs. immune-mediated); photosensitivity with some payloads	Standard CTCAE; SJS/TEN: any grade = permanent discontinuation for enfortumab vedotin	[1,3,39]

3.3. Potential Impact of Corticosteroids on Oncologic Outcomes

A post hoc analysis of six registrational phase II/III trials (CheckMate-067, -142, -214, -648, -743, -9LA; $n = 1959$) found that higher corticosteroid peak dose for treatment-related AEs was associated with worse PFS (HR 1.43 for 2 vs. 0.5 mg/kg) and OS (HR 1.66 for 2 vs. 0.5 mg/kg), while cumulative dose was not significantly associated with survival [43]. A large real-world TriNetX analysis ($n = 43,282$) confirmed a “corticosteroid timing paradox”: baseline and early intercurrent steroid use (within 56 days of ICI initiation) were associated with significantly worse OS, whereas late use (57–180 days) was not [44]. A JAMA Network Open study further demonstrated that any glucocorticoid dosage ≥ 1 mg/d prednisone equivalent was associated with shorter survival, with dosages ≥ 60 mg/d associated with 37% shorter survival time [45].

The NCCN guidelines explicitly recommend that “steroid-sparing measures with secondary agents may be appropriate to minimize steroid exposure and expedite resumption of ICI therapy” [6].

These findings should be interpreted with caution. Patients requiring high-dose or prolonged corticosteroid therapy frequently have more severe immune-related adverse events, higher inflammatory burden, or additional comorbidities that may independently contribute to poorer oncologic outcomes. Consequently, the observed association between corticosteroid exposure and reduced survival cannot be interpreted as evidence of a direct causal detrimental effect of corticosteroids on antitumor immunity. Rather, corticosteroid use may represent a surrogate marker of disease severity in at least a proportion of patients. Prospective studies specifically designed to account for disease severity, timing, indication, and cumulative corticosteroid exposure are needed to clarify this relationship.

3.4. Steroid-Sparing Biologic Therapies

3.4.1. Dupilumab (Anti-IL-4R α)

Dupilumab currently represents the biologic agent supported by the largest body of evidence in cirAEs and is now incorporated into NCCN guidelines for multiple cirAE subtypes [6]. For bullous pemphigoid, dupilumab is recommended as a steroid-sparing measure for severe (G3/G4) confirmed irBP. A retrospective series of 17 patients showed 75% complete response and 12% partial response, with 62% achieving CR with dupilumab as the only systemic agent [46]. A Spanish multicenter series of 19 patients reported 84% complete remission, with 82% discontinuing systemic corticosteroids [47]. A systematic review of 25 publications (136 patients) confirmed high response rates across eczematous, bullous pemphigoid, and maculopapular phenotypes [48]. For pruritus, the NCCN guidelines recommend dupilumab for moderate-to-severe pruritus refractory to gabapentinoids [6]. For lichenoid eruptions, dupilumab is listed as a consideration for severe ($>30\%$ BSA) disease [6].

3.4.2. Omalizumab (Anti-IgE)

A multicenter retrospective analysis of 34 patients with refractory grade 2/3 pruritus from ICIs and anti-HER2 therapies showed an 82% response rate with omalizumab, with oral corticosteroid use decreasing from 50% to 9% ($p = 0.001$) [49]. The NCCN guidelines recommend omalizumab specifically for severe pruritus with elevated IgE levels [6]. For bullous pemphigoid, a systematic review comparing rituximab ($n = 122$), omalizumab ($n = 53$), and dupilumab ($n = 36$) found similar complete remission rates (67–71%), but rituximab had notably higher recurrence rates (20.5% vs. 5.6–5.7%), adverse events, and mortality [50].

3.4.3. Anti-IL-17 Agents (Secukinumab, Ixekizumab)

Anti-IL-17 agents are mechanistically supported by selective IL-17A mRNA upregulation in psoriasiform, lichenoid, and bullous dermatitis phenotypes [51]. The NCCN guidelines list IL-17 inhibitors among the approved biologics for moderate-to-severe psoriasiform irAEs. However, data remain limited to case reports and small series.

3.4.4. Infliximab and Vedolizumab

Infliximab remains the most widely prescribed biologic for irAEs overall. Its primary role is in ICI-induced colitis, recommended as a first-line biologic alongside vedolizumab for steroid-refractory disease at 5 mg/kg IV. Key limitations include contraindication in ICI hepatitis and avoidance in ICI myocarditis.

3.4.5. Abatacept (CTLA-4-Ig)

Abatacept has emerged for ICI myocarditis. Two phase 3 randomized controlled trials (ATRIUM, NCT05335928; NCT05195645) are actively evaluating abatacept for ICI myocarditis. It is important to note that the evidence base for biologic therapies in irAE management remains predominantly retrospective, consisting of case series, single-center cohorts, and systematic reviews of observational data. No randomized controlled trials have compared any biologic agent head-to-head or against corticosteroids for cutaneous irAEs. Response rates reported in these studies (e.g., 75–87% with dupilumab and 82% with omalizumab) should be interpreted with caution given the inherent selection bias, publication bias, and lack of standardized outcome measures in retrospective series. While these data suggest a potential shift toward steroid-sparing management, this transition remains in its early stages and requires prospective validation.

3.5. JAK Inhibitors

3.5.1. Tofacitinib (JAK1/3)

Tofacitinib accounts for 82% of all reported JAK inhibitor use for irAEs [52]. A multi-center observational study of 53 patients demonstrated clinical remission rates of 54.5% in life-threatening cases, 96.7% in steroid-resistant cases, and 100% in steroid taper failure [53]. The largest prospective cohort (24 evaluable patients) showed clinical response in 70.8%, with highest rates for arthritis (100%) and myocarditis (75%), though thrombotic events occurred in 10.3% [54].

3.5.2. Ruxolitinib (JAK1/2)

A phase 2 RCT of add-on ruxolitinib for severe checkpoint inhibitor pneumonitis demonstrated significantly higher resolution rates than corticosteroids alone at 8 weeks (66.7% vs. 36.7%, $p = 0.038$) [55]. A phase I trial in relapsed/refractory Hodgkin lymphoma showed that ruxolitinib combined with nivolumab yielded a 53% best overall response rate in patients who had already progressed on checkpoint inhibitor therapy, suggesting that JAK inhibition may paradoxically enhance ICI efficacy [56].

3.5.3. Oncologic Safety of JAK Inhibitors

A literature review found tumor progression in 38% of JAK inhibitor-treated patients, though these patients had severe/refractory irAEs and were heavily pretreated [52]. Whether JAK inhibition can be safely integrated into routine irAE management remains controversial. While available data suggest that short-term treatment may not substantially impair antitumor immunity, concerns regarding thrombotic risk, infectious complications, and potential effects on long-term tumor control warrant careful patient selection and prospective evaluation [52,55,57].

Data are fully displayed in Table 2.

Table 2. Therapeutic management landscape integrating steroid-sparing biologics and JAK inhibitors.

Therapeutic Strategy/Diagnostic Tool	Mechanism of Action	Key Evidence	Clinical Application in Oncodermatology	Limitations	References
Dupilumab (anti-IL-4R α)	Blocks IL-4/IL-13 signaling; reduces Th2-driven inflammation and IgE	NCCN recommends for confirmed bullous pemphigoid (G2–G4) as steroid-sparing measure; effective in corticosteroid-refractory irAEs; highest response rates for cutaneous irAEs among biologics	ICI-induced bullous pemphigoid, eczematous dermatitis, refractory pruritus (G2–G3 after gabapentinoid failure)	Case reports of cancer progression in some dupilumab-treated patients	[1,3,39]
Rituximab (anti-CD20)	B cell depletion; reduces autoantibody production	NCCN recommends as alternative for ICI-induced bullous pemphigoid (G2–G4); effective in corticosteroid-refractory cases as adjunct to IVIG	ICI-induced bullous pemphigoid, severe autoantibody-mediated cutaneous irAEs	Prolonged B cell depletion; infection risk; delayed onset of action (weeks)	[1,3,39]
Anti-IL-17 agents (secukinumab, ixekizumab)	Block IL-17A; suppress Th17-driven inflammation	NCCN lists as option for ICI-induced psoriasis/psoriasiform diseases (moderate-severe); systematic review: 75% complete response rate for cutaneous irAEs	ICI-induced psoriasiform eruptions (moderate-severe, BSA > 10%); refractory to topical steroids and phototherapy	Theoretical concern for reduced antitumor immunity (IL-17 role in tumor surveillance); limited oncology-specific safety data	[1,3,39]
Anti-IL-23 agents (guselkumab, risankizumab)	Block IL-23p19; suppress Th17 differentiation upstream	Highest complete resolution rates for cutaneous irAEs alongside anti-IL-17; NCCN lists as option for ICI-induced psoriasis	ICI-induced psoriasiform eruptions; potential advantage of less frequent dosing	Very limited case series in ICI setting	[1,3,39]
Omalizumab (anti-IgE)	Binds free IgE; reduces mast cell/basophil degranulation	NCCN recommends for ICI-induced pruritus (G2–G3) with elevated IgE, after gabapentinoid failure	ICI-induced refractory pruritus with elevated serum IgE	Requires IgE elevation for optimal response;	[1,3,39]
Tofacitinib (JAK1/3 inhibitor)	Blocks JAK1/3-STAT signaling; suppresses multiple cytokine pathways (IL-6, IFN- γ , IL-2, IL-15)	Most prescribed JAKi for irAEs (82% of published cases); 100% complete response rate for cutaneous irAEs in systematic review; prospective cohort: 70.8% clinical response across irAE types	Corticosteroid-refractory irAEs (myocarditis, arthritis, colitis, hepatitis, cutaneous); second-line or later	Thrombotic events in 10.3% of prospective cohort; FDA boxed warning for VTE/MACE in RA population; predominantly case report evidence	[1,3,39]
Upadacitinib (selective JAK1 inhibitor)	Selective JAK1 blockade; rapid suppression of IFN- γ , IL-6 signaling	First clinical trial of oral JAKi for ICI-dermatitis: pruritus resolution within 1 day, rash improvement within 4 days, near-complete resolution ($G \leq 1$) within 7 days vs. 55 days with corticosteroids	ICI-induced dermatitis (rapid symptom control); potential first-line steroid-sparing agent	Single-arm trial, small sample size, no long-term follow-up; low dose/short regimen may explain favorable safety	[1,3,39]
Ruxolitinib (JAK1/2 inhibitor, topical)	Topical JAK1/2 inhibition; local anti-inflammatory without systemic exposure	Case reports for ICI-induced vitiligo, localized lichenoid dermatitis; FDA-approved for atopic dermatitis and vitiligo	Localized ICI-induced cutaneous irAEs where systemic therapy is not warranted; vitiligo-like depigmentation	Limited to localized disease; no prospective irAE data	[1,3,39]

3.6. Oncologic Safety of Steroid-Sparing Biologics

A multi-institutional retrospective cohort study (53 dupilumab-treated patients vs. matched controls) found that dupilumab did not adversely impact overall survival (HR 0.74 vs. cirAE controls, $p = 0.5$), while systemic glucocorticoid use within 2 years of ICI initiation was independently associated with poorer OS (HR 2.03–2.21) [58]. A JAMA Oncology study confirmed these findings, reporting that dupilumab for cirAEs was associated with

improved survival compared with both control groups, aligning with evidence implicating IL-4 signaling in tumorigenesis and immune evasion [59].

A 2026 ASCO abstract from a prospective oncodermatology cohort (n = 159) confirmed that biologic-treated patients had comparable oncologic outcomes to non-biologic patients (31% vs. 28% CR/PR; 43% stable disease), with only 13% requiring systemic steroids and 60% successfully rechallenged with ICI [60]. Mechanistically, IL-4 blockade may even enhance antitumor immunity: preclinical studies show that IL-4 signaling within monocyte-derived macrophages promotes tumor progression, and a phase 1b study is investigating combined dupilumab + cemiplimab in early-stage resectable NSCLC [61].

However, caution is warranted. A systematic review found that while dupilumab was associated with high response rates, most studies reported subsequent cancer progression in treated patients, though this likely reflects the natural history of advanced malignancy rather than a drug effect [48]. A FAERS pharmacovigilance analysis detected a disproportionality signal for cutaneous T-cell lymphoma with dupilumab (ROR 6.1), though causality cannot be established from spontaneous reporting data [62]. An integrative epidemiology and immunotranscriptomics study found that dupilumab had 30.0 times the proportional reporting ratio for CTCL compared to all other medications in FAERS, with the highest risk in men aged 45–65, and proposed that IL-13 receptor blockade may unmask or promote CTCL progression via increased IL-13 availability in the local milieu [63]. A retrospective cohort study using TriNetX confirmed an increased relative risk of CTCL in dupilumab-treated AD patients (RR 4.59, *p* 0.0001), with the majority of cases diagnosed within the first year [64]. The EORTC Cutaneous Lymphoma Tumour Group consensus recommends that dupilumab should be avoided if mycosis fungoides or Sézary syndrome is suspected or confirmed, and clinicians should maintain a high index of suspicion for CTCL in atypical or treatment-refractory disease, particularly adult-onset AD without atopic history [65]. Importantly, dupilumab can cause a reversible and benign lymphoid reaction (LR) that mimics CTCL but has distinctive histopathologic features, including sprinkled distribution of small hyperchromatic lymphocytes in the upper epidermal section, a dysregulated CD4:CD8 ratio, and CD30 overexpression without loss of CD2/CD3/CD5 [66].

Balancing effective toxicity control with preservation of antitumor immunity remains one of the major challenges in oncodermatology. Unlike systemic corticosteroids, which broadly suppress multiple immune pathways, steroid-sparing biologics offer the potential advantage of selectively targeting specific inflammatory axes. However, not all immunologic targets are expected to have the same implications for tumor immune surveillance. IL-4/IL-13 blockade primarily attenuates type 2 inflammation while largely preserving cytotoxic T-cell responses, providing a biologic rationale for its increasing use in cutaneous irAEs [58,65]. In contrast, inhibition of the IL-17/IL-23 axis may theoretically interfere with both protumor and antitumor immune mechanisms, reflecting the complex and context-dependent role of Th17 immunity in cancer [67]. TNF- α inhibition remains highly effective for selected severe irAEs but has historically raised concerns regarding potential impairment of antitumor immune responses, although current clinical evidence remains inconclusive [68,69]. JAK inhibitors represent an additional challenge because they simultaneously suppress multiple cytokine pathways, including interferon signaling, potentially affecting both inflammatory toxicity and antitumor immunity [56,68]. Consequently, therapeutic selection should not rely solely on clinical phenotype but also consider the underlying immunologic endotype and the potential consequences of pathway-specific immune modulation. Although current evidence is encouraging, prospective studies integrating mechanistic biomarkers with long-term oncologic outcomes are needed to determine which targeted immunomodulatory strategies best preserve the efficacy of immune checkpoint blockade while effectively controlling cutaneous toxicity.

3.7. Immunologic Endotyping: Toward Precision Oncodermatology

3.7.1. Two Fundamental Inflammatory Axes

The Lacouture et al. (2024) study enrolled 200 patients (139 with cirAEs, 61 controls) and evaluated cytokines across skin biopsies [51], skin tape strip extracts, and plasma. The central finding is that cirAEs segregate into two dominant inflammatory axes [51].

Type 2 (Th2)-dominant phenotypes—pruritus, eczema, urticaria, and maculopapular rash—collectively account for approximately 74% of all cirAEs, characterized by elevated IL-4, IL-13, IL-5, and IL-31. These phenotypes are amenable to dupilumab (IL-4/IL-13) and omalizumab (IgE-mediated pathways) [51].

Type 1/Type 17 (Th1/Th17)-dominant phenotypes, psoriasiform, lichenoid, bullous dermatitis, and vitiligo, account for approximately 26% of cirAEs but tend to be more severe [1,6,41]. These showed highest IFN γ mRNA upregulation in lichenoid (p 0.0001) and psoriasiform (p 0.01) dermatitis, with selective IL-17A increases. These observations provide a biologic rationale for targeting the IL-17/IL-23 axis; however, prospective validation of endotype-guided treatment selection remains lacking [51].

3.7.2. Challenging the Binary Model

Azin et al. (2025) found that ICI-induced lichenoid eruptions showed increased CD4 $^{+}$ /CD8 $^{+}$ T-cell ratios and Th2/Th1 ratios compared to spontaneous lichenoid dermatitis, making ICI-induced LE immunologically more similar to eczematous eruptions than to its spontaneous counterpart [70]. This finding underscores that cirAEs should not be managed identically to their spontaneous dermatologic counterparts.

3.7.3. Regimen-Dependent Molecular Signatures

Kraehenbuehl et al. (2025) demonstrated distinct transcriptomic clustering between anti-PD-1 monotherapy cirAEs (resembling TEN, with cytotoxic/type 1 signatures) and combination therapy cirAEs (resembling maculopapular drug rash, with mixed inflammatory profiles) [71]. This has implications for biologic selection: monotherapy cirAEs may respond better to JAK inhibitors or IFN γ -targeted approaches, while combination therapy cirAEs may be more amenable to type 2-targeted strategies.

3.7.4. Noninvasive Biomarkers

The Lacouture study validated that cytokine profiles identified in skin biopsies were confirmed in skin tape strip extracts and plasma, establishing proof-of-concept for non-invasive endotyping [51,72]. A prospective pan-tumor cohort study found that early changes in Th17 (IL-6, IL-17f), type 2 (IL-5, IL-13, IL-25), and type 1 (TNF- α) cytokine signatures were positively associated with the development of grade ≥ 2 irAEs [67]. Multi-dimensional immune profiling has identified a baseline proinflammatory, autoimmune-like state—characterized by increased plasmablasts, elevated ANA, heightened IFN- γ /CXCL10/CXCR3 axis, and amplified TNF signaling—as a driver of irAE development [73,74]. MicroRNAs (miRNAs), small non-coding RNA molecules (19–25 nucleotides) that regulate gene expression post-transcriptionally, have emerged as a layer of the precision oncodermatology framework. Their structural stability, presence in accessible biofluids, and conservation across species make them attractive candidates as noninvasive biomarkers for predicting, monitoring, and potentially modulating cancer treatment-related cutaneous toxicity [75–78]. The most extensively characterized miRNA in the context of irAEs is miR-146a, which functions as a negative regulator of NF- κ B-dependent inflammatory responses in keratinocytes and immune cells. In a landmark preclinical study, mice lacking miR-146a developed markedly more severe irAEs compared with wild-type mice in two different murine ICI models, exhibiting increased T-cell activation, enhanced effector

function, and elevated neutrophil infiltration in the spleen and inflamed intestine [79,80]. The therapeutic potential of miRNA modulation in cancer treatment-related skin toxicity remains largely preclinical. The demonstration that miR-146a mimics reduce irAE severity in murine models and ameliorate psoriasiform skin inflammation provides a rationale for developing topical or intradermal miRNA-based therapies for cirAEs [80,81]. Despite their promise, no miRNA signature has yet been prospectively validated or incorporated into routine clinical decision-making for cancer therapy-related cutaneous toxicities.

3.7.5. Uncoupling Toxicity from Efficacy

A landmark study in immunity demonstrated that baseline IFN- γ signatures may guide personalized ICI regimen selection: in IFN- γ -high subgroups, high-dose anti-CTLA-4 increased toxicity but not efficacy, while in IFN- γ -low subgroups, it increased efficacy while toxicity remained low [82]. This suggests that baseline immune signatures could enable de-escalation in immunologically “hot” tumors and escalation in “cold” tumors [83–86]. A longitudinal immune profiling study further confirmed that toxicity-associated programs (reflecting baseline susceptibility amplified by early on-treatment immune trajectories) are at least partly dissociable from response-associated programs, which emerge later and reflect a distinct Tfh/B cell-activated CD8 axis [87].

3.8. Preventive Strategies

3.8.1. EGFR Inhibitor-Associated Rash

Prophylactic strategies using tetracycline- or macrolide-based antibiotics combined with topical corticosteroids consistently reduce grade ≥ 2 events [88,89]. The STEPP trial demonstrated a 50% reduction in grade ≥ 2 rash with preemptive doxycycline, topical corticosteroids, moisturizers, and sunscreen [4,90–92]. A comprehensive skin toxicity program at Dana–Farber showed that prophylactically treated patients were 94% less likely to require rescue treatment and 79% less likely to experience dose changes or interruptions [4]. Prophylactic management of skin reactions is recommended for all patients treated with EGFR inhibitors [93–95].

3.8.2. Hand-Foot Syndrome/Skin Reaction

A systematic review and network meta-analysis of 18 RCTs found that diclofenac and celecoxib were effective in the prevention of grade 2 or higher HFS, with diclofenac yielding the best point estimates among nonherbal agents [96]. Diclofenac has a favorable safety profile with no reported systemic adverse effects, positioning it as the most appealing option for routine clinical practice [96]. Pyridoxine at 400 mg showed significant efficacy but raises concerns about decreased tumor response and shorter median OS at this dose [96]. Topical silymarin showed the lowest odds for HFS prevention but was studied in small cohorts with wide confidence intervals [96].

3.8.3. General Skin Care

Evidence supports pH-balanced cleansers (pH close to 5), ceramide-based moisturizers, and broad-spectrum photoprotection (SPF ≥ 30) as baseline interventions for all patients on anticancer therapy [97–99]. The NECOM and USCOM multidisciplinary algorithms provide practical frameworks for prevention and management of cAEs across drug classes [100–102].

3.9. Quality of Life and Treatment Adherence

Cutaneous toxicities are a major determinant of quality of life, treatment adherence, and dose intensity. Even mild skin toxicities elevate dermatology-specific QoL measures, affecting mood and social function [98]. A cross-sectional study of 1004 patients found that itching was the most frequently reported problem, and 78% emphasized the need for

multidisciplinary approaches [9]. Prospective data show that early dermatology referral and tailored management significantly improve DLQI and EORTC QLQ-C30 scores over 3 months [103]. A review of the literature confirmed that dermatologic adverse events negatively impact quality of life through physical discomfort, changes to body image, decreased self-esteem, and effects on social interactions, and that decreased satisfaction with treatment can lead to discontinuation or dose reduction [104]. Existing QoL tools may not fully capture the unique burden of cancer-related dAEs, representing an unmet need [104].

3.10. *The Role of Multidisciplinary Oncodermatology*

The emergence of supportive oncodermatology as a subspecialty reflects the growing complexity of cancer treatment-related skin toxicity. Dermatology consultation significantly reduces cirAE severity (mean CTCAE grade from 1.74 to 0.71; p 0.001) [39]. Both ASCO and NCCN guidelines recommend early engagement of dermatologists, with the NCCN algorithms specifying “urgent dermatology consultation” for moderate-to-severe bullous dermatitis, SJS/TEN, and refractory presentations across all cirAE subtypes [3,6,73].

The clinical heterogeneity of cancer treatment-related cutaneous adverse events poses significant diagnostic challenges. While histopathology remains the gold standard for definitive diagnosis, noninvasive imaging modalities including dermoscopy, reflectance confocal microscopy (RCM), line-field confocal optical coherence tomography (LC-OCT), optical coherence tomography (OCT), and high-frequency ultrasound (HFUS) offer complementary capabilities for differential diagnosis, biopsy site optimization, and longitudinal treatment monitoring without the risks of pain, infection, scarring, or the isomorphic Koebner phenomenon associated with biopsy in conditions such as psoriasiform cirAEs [105–111]. In patients with cutaneous immune-related adverse events, longitudinal imaging could facilitate early recognition of progression or resolution, support treatment escalation or de-escalation decisions, and improve assessment of steroid-sparing biologic efficacy. Furthermore, integration of imaging features with cytokine profiling, circulating microRNAs, and other molecular biomarkers may enable the development of composite multimodal signatures capable of predicting toxicity trajectories and therapeutic responses. Future prospective studies should investigate whether imaging-derived biomarkers can contribute to personalized management algorithms and reduce the need for invasive diagnostic procedures [112–115].

The NCCN guidelines provide detailed, phenotype-specific management algorithms for maculopapular rash, pruritus, bullous dermatitis/SJS/TEN, lichenoid eruptions, psoriasiform diseases, and oral mucositis—each with grading criteria based on body surface area (BSA) involvement and functional impact, and stepwise management escalating from topical therapies to systemic immunosuppression and biologic agents [6]. A consistent principle across all algorithms is that mild (G1) disease generally permits continuation of immunotherapy with topical management, moderate (G2) disease may require holding immunotherapy and initiating systemic corticosteroids, and severe (G3/G4) disease mandates holding or discontinuing immunotherapy with urgent dermatology consultation and consideration of biologic agents [6].

The NCCN Cutaneous Melanoma guidelines further recommend regular dermatologic evaluation for all patients receiving BRAF-based therapy, with prompt dermatologic consultation for severe and life-threatening skin toxicity [116,117]. The USCOM and NECOM multidisciplinary algorithms extend this framework to targeted therapy-related cAEs, providing practical recommendations for acneiform rash, pruritus, xerosis, paronychia, hyperpigmentation, and hand-foot skin reaction [67,102,118].

The clinical decision algorithm (Figure 1) integrates guideline recommendations into a stepwise management approach:

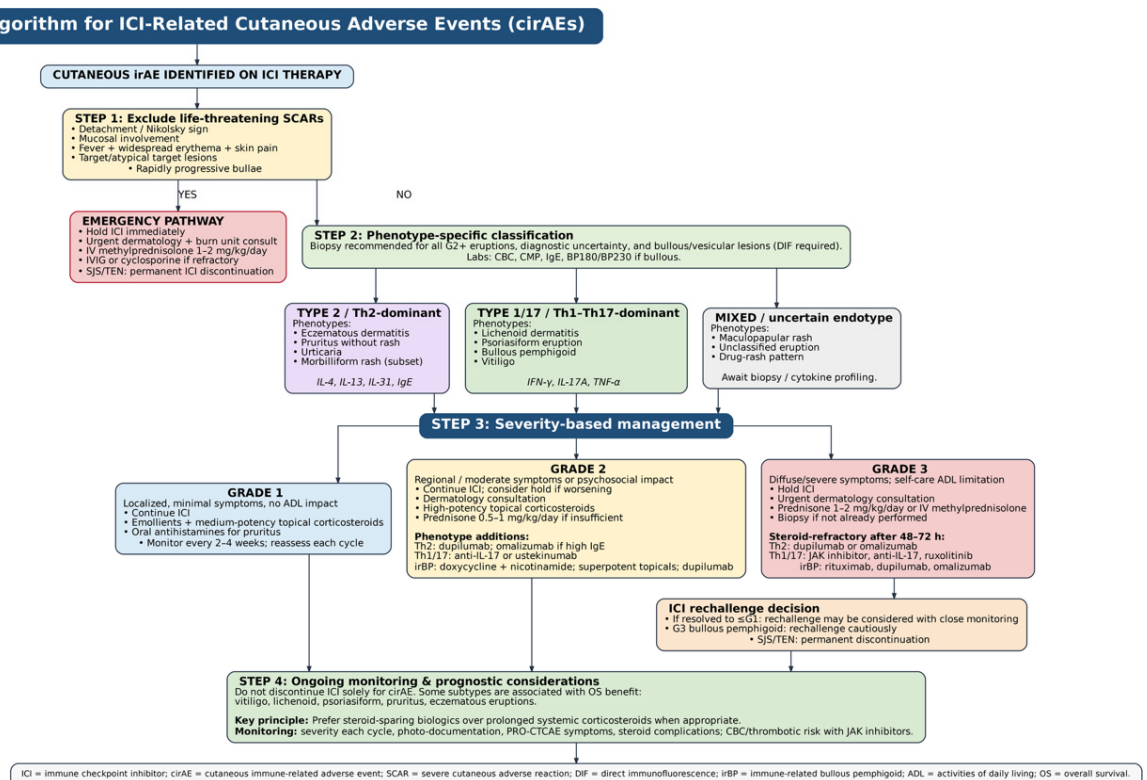


Figure 1. Evidence-Based Clinical Decision Algorithm for the Management of Immune Checkpoint Inhibitor-Related Cutaneous Adverse Events (cirAEs). This algorithm provides a stepwise, evidence-based framework for the evaluation and management of cutaneous immune-related adverse events (cirAEs) arising during immune checkpoint inhibitor (ICI) therapy. Abbreviations: ICI, immune checkpoint inhibitor; cirAE, cutaneous immune-related adverse event; SCAR, severe cutaneous adverse reaction; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; irBP, immune-related bullous pemphigoid; DIF, direct immunofluorescence; ADL, activities of daily living; BSA, body surface area; CS, corticosteroids; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; HR, hazard ratio; OS, overall survival; CR, complete response; IVIG, intravenous immunoglobulin; CBC, complete blood count; CMP, comprehensive metabolic panel.

Step 1: SCAR Screening. All patients presenting with new cutaneous symptoms during ICI therapy should first be evaluated for life-threatening SCARs (SJS/TEN, DRESS, and AGEP). The presence of skin pain, mucosal involvement, Nikolsky sign, or >10% BSA epidermal detachment mandates immediate ICI discontinuation, urgent dermatology consultation, and emergency management per NCCN guidelines [24].

Step 2: Immunologic Endotype Classification. After excluding SCARs, eruptions are classified by immunologic endotype based on clinical morphology, histopathology, and—when available—cytokine profiling. Type 2 (Th2)-dominant phenotypes (~74% of cirAEs; pruritus, eczema, and urticaria) are distinguished from Type 1/17 (Th1/Th17)-dominant phenotypes (~26%; lichenoid, psoriasiform, bullous pemphigoid, and vitiligo) [11].

Step 3: Severity-Graded Management. Within each endotype, management follows NCCN severity grading (G1–G3/G4) with endotype-directed steroid-sparing biologic selection at Grade 2–3 decision points. For Th2-dominant phenotypes, dupilumab and omalizumab are recommended; for Th1/Th17-dominant phenotypes, anti-IL-17, anti-IL-12/23, or JAK inhibitors are considered.

Step 4: Prognostic Integration and Monitoring. The algorithm incorporates prognostic data (vitiligo HR 0.23 for OS; lichenoid HR 0.51) to inform the risk–benefit discussion regarding immunotherapy continuation versus discontinuation, and recommends ongoing monitoring with PRO-CTCAE instruments.

4. Future Directions and Critical Gaps

Despite the rapid advances outlined in this review, several critical gaps remain:

Prospective validation of steroid-sparing biologics: The evidence base for biologics in cirAE management remains largely retrospective. No randomized controlled trials have compared biologic agents head-to-head or against corticosteroids for cutaneous irAEs. Prospective studies are needed to validate the oncologic safety and efficacy signals observed in retrospective cohorts [48,58,60].

Standardization of immunologic endotyping: While Lacouture et al.’s study established proof-of-concept for cytokine-guided biologic selection, the clinical implementation of endotyping requires standardized assay platforms, validated cutoffs, and prospective demonstration that endotype-directed therapy improves outcomes compared with empiric management [51,119].

ADC-specific dermatologic management: As the ADC pipeline expands, there is an urgent need for ADC-specific supportive care guidelines. Current management is largely extrapolated from ICI or chemotherapy, which may not adequately address the unique mechanisms of ADC-mediated cutaneous toxicity [15,16].

Biomarker-guided ICI regimen selection: The demonstration that baseline IFN- γ signatures can uncouple toxicity from efficacy opens the door to personalized ICI dosing strategies, but prospective validation in diverse tumor types is needed [74,82,120–124].

Long-term safety monitoring of dupilumab in oncology: The emerging signal for CTCL unmasking/progression with dupilumab requires ongoing pharmacovigilance and prospective studies, particularly in patients with cancer who may have altered immune surveillance [62,63,65].

Quality of life instruments: Development and validation of cancer treatment-specific dermatologic QoL instruments that capture the unique burden of cAEs across drug classes remains an unmet need [9,103,104,125,126].

5. Conclusions

The landscape of cancer treatment-related cutaneous toxicity has evolved from a peripheral concern to a central challenge in supportive oncology. The mechanistic framework presented, including immune disinhibition, epithelial signaling inhibition, cytotoxic epithelial injury, and cytokine-driven immune activation, provides a rational basis for understanding the diverse dermatologic manifestations of modern anticancer therapy and for selecting mechanism-directed interventions.

The recognition that cirAEs serve as prognostic biomarkers of ICI efficacy, coupled with growing evidence that corticosteroids may compromise antitumor immunity, has catalyzed a shift toward steroid-sparing biologic therapies. Dupilumab, omalizumab, anti-IL-17 agents, ustekinumab, and JAK inhibitors have demonstrated promising efficacy across multiple cirAE phenotypes, with reassuring oncologic safety data from retrospective cohorts and early prospective studies. The emerging field of immunologic endotyping, using skin biopsy, tape strip, and plasma cytokine profiling to classify cirAEs into actionable inflammatory axes, may provide a practical framework for future biomarker-guided management strategies [72].

However, the field remains in its early stages. The evidence base is dominated by case series, retrospective cohorts, and pharmacovigilance analyses. Prospective randomized

trials comparing steroid-sparing biologics to standard corticosteroid-based management are urgently needed to establish definitive efficacy, safety, and oncologic impact. Until such data are available, a multidisciplinary oncodermatology approach—integrating early dermatology consultation, phenotype-specific management algorithms, and judicious use of targeted biologics—represents the best available strategy for preserving both skin health and anticancer efficacy.

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Abbreviations

The following abbreviations are used in this manuscript:

cAE	Cutaneous Adverse Event
ICI	Immune Checkpoint Inhibitor
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
EGFR	Epidermal Growth Factor Receptor
BRAF	v-Raf Murine Sarcoma Viral Oncogene Homolog B1
MEK	Mitogen-Activated Protein Kinase Kinase
ADC	Antibody–Drug Conjugate
FDA	U.S. Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
ASCO	American Society of Clinical Oncology
NSCLC	Non-Small Cell Lung Cancer
NCCN	National Comprehensive Cancer Network
AAD	American Academy of Dermatology
CAR-T	Chimeric Antigen Receptor T-cell
CTCAE	Common Terminology Criteria for Adverse Events
ESMO	European Society for Medical Oncology
EADV	European Academy of Dermatology and Venereology
AGA	American Gastroenterological Association
MeSH	Medical Subject Headings
irAE	Immune-Related Adverse Event
SCARs	Severe Cutaneous Adverse Reactions
PRIDE	Papulopustular Rash, Regulatory Hair Changes, Itching, Dryness, and EGFR Inhibitors

MAPK	Mitogen-Activated Protein Kinase
TCR	T-Cell Receptor
OS	Overall Survival
PFS	Progression-Free Survival
HR	Hazard Ratio
RCT	Randomized Controlled Trial
OR	Odds Ratio
SJS	Stevens–Johnson Syndrome
TEN	Toxic Epidermal Necrolysis
BSA	Body Surface Area
TKI	Tyrosine Kinase Inhibitor
KA	Keratoacanthoma
MMAE	Monomethyl Auristatin E
IL	Interleukin
JAK	Janus Kinase
IL-4R α	Interleukin-4 Receptor Alpha
irBP	Immune-Related Bullous Pemphigoid
IgE	Immunoglobulin E
IV	Intravenous
STAT	Signal Transducer and Activator of Transcription
VTE	Venous Thromboembolism
MACE	Major Adverse Cardiovascular Events
CTCL	Cutaneous T-Cell Lymphoma
ROR	Reporting Odds Ratio
TNF- α	Tumor Necrosis Factor Alpha

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