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Review

Dermatologic Perspectives on Primary Cutaneous Lymphomas: Clinicopathologic Spectrum, Molecular Insights, and Evolving Treatment Paradigms

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Abstract

Primary cutaneous lymphomas (PCLs) are a heterogeneous group of extranodal T- and B-cell neoplasms confined to the skin at diagnosis, characterised by distinct biological drivers, clinical behaviour, and therapeutic challenges compared with systemic lymphomas. Over the past decade, advances in genomic profiling, single-cell and spatial transcriptomics, and tumour microenvironment analysis have substantially refined the understanding of PCL pathogenesis, highlighting immune evasion, clonal heterogeneity, and compartment-specific disease dynamics as key determinants of outcome and treatment response. These insights have coincided with a rapidly evolving therapeutic landscape that includes immunomodulatory agents, targeted therapies, and ADCs, while also exposing persistent limitations related to diagnostic delay, response heterogeneity, resistance, and lack of validated predictive biomarkers. In this review, we provide a dermatology-focused synthesis of primary cutaneous lymphomas, integrating contemporary classification and clinicopathologic features with molecular pathogenesis and tumour microenvironmental insights of direct clinical relevance. We discuss current diagnostic and staging approaches, critically appraise established and emerging therapeutic strategies in cutaneous T- and B-cell lymphomas, and highlight unresolved clinical challenges and unmet needs, including biomarker integration, longitudinal disease monitoring, and translation of molecular advances into routine practice.

Keywords: primary cutaneous lymphomas; mycosis fungoides; Sézary syndrome; cutaneous T-cell lymphoma; cutaneous B-cell lymphoma; brentuximab vedotin; mogamulizumab; WHO–EORTC classification; dermatology

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1. Introduction

Primary cutaneous lymphomas (PCLs) comprise a heterogeneous group of T- and B-cell neoplasms confined to the skin at diagnosis, without evidence of extracutaneous disease. They are biologically and clinically distinct from systemic lymphomas with secondary cutaneous involvement, differing in cell of origin, tumour–microenvironment interactions, clinical course and prognosis, and therefore require dedicated diagnostic frameworks and

management strategies [1]. In the updated World Health Organization-European Organization of Research and Treatment of Cancer (WHO–EORTC) and International Consensus Classification (ICC) recognise, cutaneous T-cell lymphomas (CTCLs), notably mycosis fungoides (MF) and Sézary syndrome (SS), as the most prevalent entities, alongside three major subtypes of primary cutaneous B-cell lymphomas (PCBCLs): primary cutaneous follicle centre lymphoma (PCFCL), primary cutaneous marginal zone lymphoma/lymphoproliferative disorder (PCMZL/LPD) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) [1–4].

Epidemiologically, CTCLs are rare, with an annual incidence around 6–7 cases per million, and MF/SS accounts for approximately half of all CTCLs [5,6]. PCBCLs are less common but represent about one quarter of all PCLs in Western cohorts [3,7]. Despite their rarity, PCLs have a significant impact on quality of life due to chronic, often therapy-refractory skin disease, pruritus, and disfiguring lesions, and they require long-term follow-up by dermatologists.

Over the past decade, advances in next-generation sequencing, transcriptomics, and high-dimensional immune profiling have profoundly reshaped our understanding of PCL biology [4,6,8]. In CTCLs, recurrent alterations affecting T-cell receptor (TCR) signalling, JAK–STAT pathways, epigenetic regulation, and immune checkpoint networks have been linked to clonal evolution, immune evasion, and compartment-specific disease behaviour. In PCBCLs, particularly PCDLBCL-LT, molecular hallmarks such as MYD88 and CD79B mutations define a biologic program closely aligned with activated B-cell–type lymphomas and aggressive clinical behaviour [3,4,8,9]. These discoveries underpin a rapidly evolving therapeutic landscape that includes monoclonal antibodies, antibody-drug conjugates, and immune modulators.

Against this backdrop, clinicians face several unresolved challenges: persistent diagnostic delay in early MF, difficulty translating molecular findings into routine practice, limited availability of validated predictive biomarkers, and the need to balance disease control with long-term toxicity in largely chronic conditions. A contemporary, clinically grounded synthesis is therefore needed to bridge emerging biologic insights with everyday dermatologic practice.

In this review, we provide an integrated, dermatology-focused overview of primary cutaneous lymphomas. We first summarise current classification and clinicopathologic spectra, then discuss molecular pathogenesis and tumour microenvironment features with direct clinical relevance. We subsequently review diagnostic and staging approaches from a dermatologic perspective, followed by a critical appraisal of contemporary therapeutic strategies in CTCLs and PCBCLs. Throughout, we highlight unresolved clinical challenges, unmet needs, and future directions aimed at translating molecular advances into personalised, practical care for patients with PCLs.

To provide an integrated overview of the main clinicopathologic and therapeutic concepts emerging from the reviewed literature, we summarised key themes in Table 1.

Table 1. Conceptual synthesis of clinicopathologic, molecular, and therapeutic principles in primary cutaneous lymphomas.

Conceptual Domain	Integrated Insight	Clinical Relevance/Decision Point
Classification and clinicopathologic spectrum	WHO–EORTC/WHO5/ICC consolidate PCL as entities distinct from systemic lymphomas with secondary skin involvement and clarify borderline lymphoproliferative disorders.	Correct entity assignment prevents overtreatment of indolent disorders and ensures prompt escalation for aggressive variants (e.g., transformed CTCL, PCDLBCL-LT).
CTCL phenotypes and disease compartments (MF/SS)	MF and SS represent a spectrum in which skin and blood compartments can behave differently; variants carry distinct prognostic implications.	Treatment selection and response assessment should consider the dominant compartment (skin vs. blood), pace of progression, and symptom burden.

Table 1. *Cont.*

Conceptual Domain	Integrated Insight	Clinical Relevance/Decision Point
CTCL molecular drivers and clonal evolution	Recurrent alterations (TCR/JAK–STAT/PI3K, epigenetic dysregulation) converge on survival advantage, clonal heterogeneity, and adaptive resistance, rather than acting as isolated events.	Explains heterogeneous depth/durability of responses and supports combination/sequence strategies rather than prolonged monotherapy.
Tumour microenvironment and immune evasion (CTCL)	Th2/Treg skewing, exhausted cytotoxic infiltrates, macrophage enrichment, and checkpoint expression define an immunosuppressive niche; immune topography correlates with immunotherapy responsiveness.	Provides rationale for immune-based therapy but also explains primary resistance, compartment discordance, and "flare/pseudoprogression" during checkpoint blockade.
PCBCL biological spectrum and risk stratification	Indolent PCBCLs are often antigen-driven with restricted profiles; PCDLBCL-LT is driven by MYD88/CD79B–BCR/NF-κB dependence plus immune-escape features.	Guides intensity: local control for indolent subtypes vs. systemic, biology-driven approaches for PCDLBCL-LT and careful distinction from PCFCL with large-cell morphology.
Diagnosis: standards vs. adjunctive tools	The gold standard remains clinicopathologic correlation with adequate biopsies and immunophenotyping; flow cytometry is standard for SS; imaging/molecular tools can support challenging cases.	Non-invasive imaging and high-throughput clonotype sequencing are adjunctive/emerging, useful in selected centres but not replacements for histology and formal staging.
Staging and prognostic stratification	TNMB remains the cornerstone for MF/SS; additional clinical/lab factors refine risk; diagnostic delay persists as a major issue in early MF.	Reinforces the need for structured dermatologic algorithms, repeat biopsies when needed, and compartment-aware staging to guide therapy and monitoring.
Therapeutic principles in CTCLs	Most established options are cytostatic/immunomodulatory with frequent partial responses; toxicity and resistance constrain durability; no single therapy reliably cures advanced CTCLs.	Supports sequential, response-adapted management prioritising tolerability early and strategic escalation/combination in advanced disease.
Therapeutic principles in PCBCL	Indolent PCBCLs benefit from iterative local strategies; PCDLBCL-LT increasingly uses immune- and pathway-directed combinations, though evidence is often from small cohorts.	Highlights the need for multidisciplinary planning and biologically informed salvage strategies; underscores limits of generalisability and need for prospective validation.
Unmet needs and translation to practice	Biomarker integration, longitudinal monitoring, and practical deployment of molecular tools remain underdeveloped despite rapidly expanding datasets.	Priority areas: validated predictive biomarkers, monitoring across compartments (skin/blood), and standardised workflows to translate profiling into routine care.

Abbreviations: PCL, primary cutaneous lymphoma; CTCL, cutaneous T-cell lymphoma; PCBCL, primary cutaneous B-cell lymphoma; MF, mycosis fungoides; SS, Sézary syndrome; PCFCL, primary cutaneous follicle centre lymphoma; PCMZL/LPD, primary cutaneous marginal zone lymphoma/lymphoproliferative disorder; PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type; TNMB, tumour–node–metastasis–blood; TCR, T-cell receptor; ICC, International Consensus Classification; WHO–EORTC, World Health Organization–European Organization for Research and Treatment of Cancer.

2. Classification and Clinicopathologic Spectrum

The 2018 WHO–EORTC update consolidated PCL entities and incorporated new lymphoproliferative disorders, reflecting their distinct clinical behaviour [1]. Notable changes include reclassification of primary cutaneous $CD4^+$ small/medium T-cell lymphoma as a lymphoproliferative disorder, expansion of the spectrum of lymphomatoid papulosis (LyP), and recognition of primary cutaneous acral $CD8^+$ T-cell lymphoma and EBV-positive mucocutaneous ulcer as provisional entities [1,2]. The International Consensus Classification and the 5th edition of the WHO haematologic neoplasm classification further harmonise cutaneous and systemic lymphoma taxonomy [2,10].

2.1. Cutaneous T-Cell Lymphomas

MF is the prototypic CTCL, typically presenting with slowly progressive patches and plaques on photoprotected sites. Histologically, it is characterised by epidermotropic atypical T cells, often $CD4^+$, with variable loss of pan-T-cell antigens and a clonal TCR gene rearrangement. Clinical variants include folliculotropic, pagetoid reticulosis, and granulomatous slack skin, each with distinct prognostic implications [5,6,11]. SS is defined by a triad of erythroderma, lymphadenopathy, and a leukaemic clone of neoplastic T cells in peripheral blood, often with prominent expression of PD-1 and other follicular helper T-cell markers [1,5,12].

Other CTCL entities of dermatologic relevance include primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders (LyP and primary cutaneous anaplastic large-cell lymphoma, C-ALCL), primary cutaneous γδ T-cell lymphoma, primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma, and primary cutaneous acral $CD8^+$

T-cell lymphoma [1,2,11]. CD30$^+$ disorders, while histologically malignant-appearing, often display indolent clinical behaviour and may regress spontaneously, making accurate clinicopathologic correlation essential [13].

2.2. Primary Cutaneous B-Cell Lymphomas

PCBCLs are confined to the skin at diagnosis and show a predilection for the head/neck and trunk. PCFCL typically presents as solitary or grouped plaques or tumours on the scalp or trunk, composed of centrocytes and centroblasts with a germinal centre B-cell phenotype (CD20$^+$, CD79a$^+$, BCL6$^+$, often BCL2-negative) [3,7]. PCMZL/LPD exhibits nodular or plaque-like lesions on the trunk or upper extremities, with marginal-zone B cells, plasma cells, and frequent evidence of chronic antigenic stimulation; it is now considered a lymphoproliferative disorder in some classifications due to its excellent prognosis [3,10].

PCDLBCL-LT, in contrast, is an aggressive lymphoma presenting as rapidly enlarging tumours on one or both legs, more common in elderly women and associated with frequent MYD88L265P and CD79B mutations and strong expression of BCL2 and MUM1/IRF4 [3,4,9]. Correct distinction between PCFCL with large-cell morphology and PCDLBCL-LT is crucial, as it dictates the need for systemic chemo-immunotherapy rather than local therapies alone.

3. Molecular Pathogenesis and Tumour Microenvironment

Because cutaneous T-cell and B-cell lymphomas display distinct cells of origin, oncogenic drivers, and tumour–host interactions, their molecular pathogenesis and microenvironmental features are discussed separately. Available data are more extensive for CTCLs, reflecting the greater depth of translational research in this field.

Over the last five years, high-throughput genomic, single-cell, and spatial transcriptomic studies have shifted the understanding of cutaneous lymphomas from descriptive pathway alterations to functionally relevant tumour–microenvironment interactions. In CTCLs, recent primary studies have identified immune topographic patterns and microenvironmental signatures that correlate with disease progression and response to immunotherapy, providing direct clinical relevance to molecular findings [14–17]. These mechanistic insights increasingly inform prognostic stratification and provide a biological rationale for targeted and immune-based therapies in clinical practice.

3.1. Molecular Pathogenesis of CTCLs

Genomic profiling has identified recurrent copy-number alterations and mutations affecting TCR signalling (PLCG1, CARD11), JAK–STAT pathway components (STAT3, STAT5B, JAK1, JAK3), NF-κB regulators, epigenetic modifiers (DNMT3A, TET2, ARID1A), and tumour suppressors (TP53, CDKN2A) in MF/SS [6,8,16]. These changes converge on abnormal survival and proliferation of malignant T cells, along with resistance to apoptosis and immune escape. Importantly, recent genomic and transcriptomic analyses have demonstrated that these alterations are not merely recurrent findings but actively shape immune evasion, blood involvement, and treatment sensitivity, as shown in primary translational studies integrating mutational data with clinical outcomes [14–16]. Collectively, these alterations converge on shared functional outputs—enhanced survival, immune evasion, and skin/blood compartmentalisation—rather than acting as isolated oncogenic events.

UV mutational signatures and chromosomal instability highlight the contribution of environmental and stochastic factors to clonal evolution in CTCLs, potentially contributing to genetic heterogeneity and variable therapeutic sensitivity [18].

The CTCL microenvironment is enriched in tumour-associated macrophages, regulatory T cells, Th2-skewed cytokines, and exhausted cytotoxic T cells, creating an immunosuppressive milieu [4,8,19]. Expression of PD-1/PD-L1, CTLA-4, and other checkpoints, as well as altered antigen presentation, contributes to tumour immune escape and may influence responsiveness to immunotherapies. Crosstalk between malignant T cells and stromal or dendritic cells via chemokines and cytokines shapes skin tropism and disease progression [8,19]. These microenvironmental features have direct clinical relevance, as they modulate responsiveness to immune checkpoint blockade, antibody-based therapies, and immunomodulatory agents, and help explain the heterogeneous activity of immunotherapies observed in MF and SS.

The key molecular drivers and microenvironmental interactions that sustain MF/SS pathogenesis are summarised in Figure 1.

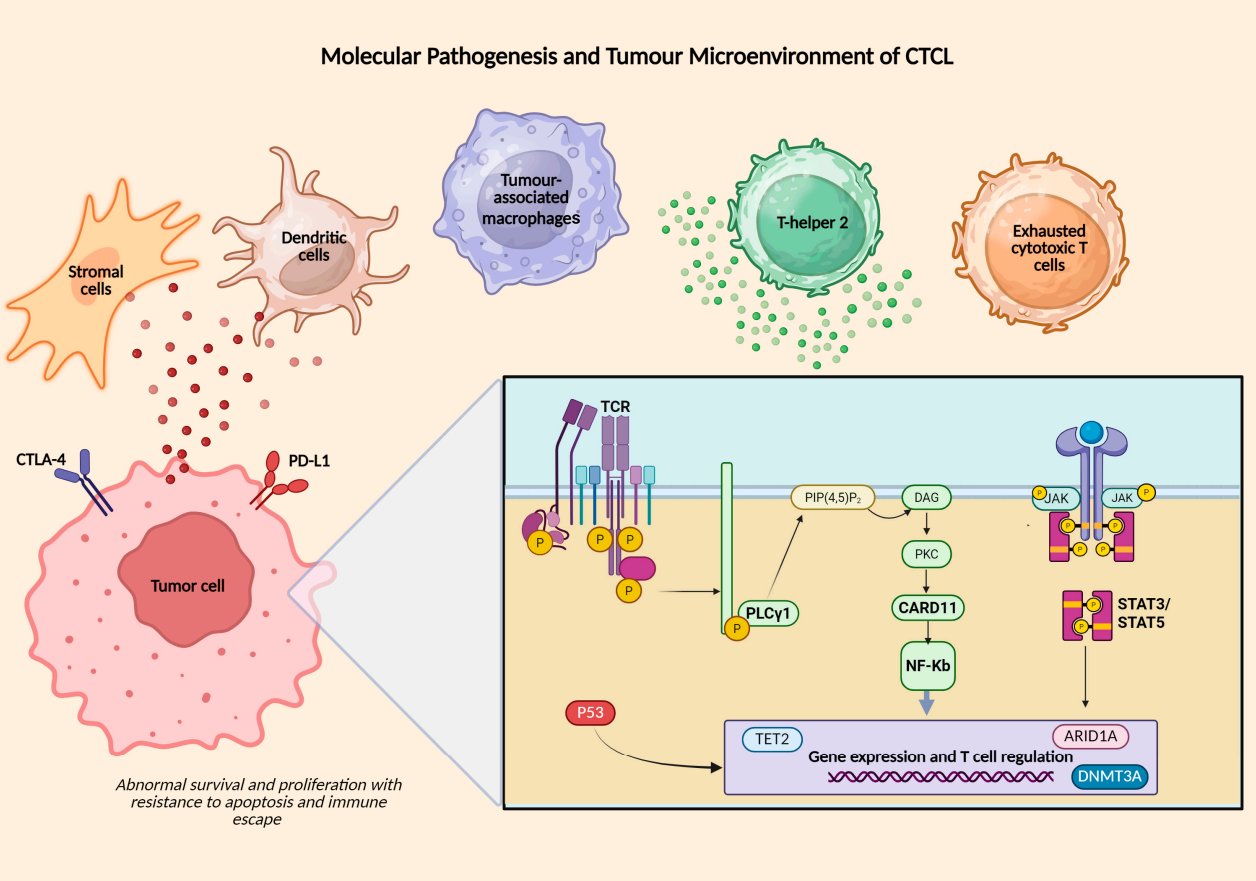


Figure 1. Molecular pathogenesis and tumour microenvironment of the CTCL.

CTCL progression is sustained by the interplay between tumour-intrinsic signalling abnormalities and an immunosuppressive microenvironment. Malignant T cells harbour alterations affecting TCR signalling, JAK/STAT, and NF-κB pathways, together with epigenetic dysregulation and loss of tumour suppressor function. The surrounding microenvironment is enriched in tumour-associated macrophages, regulatory T cells, and Th2 cytokines, with upregulation of immune checkpoints such as PD-1/PD-L1 and CTLA-4, promoting immune evasion and influencing response to immunotherapy [6,8,16,17,19].

3.2. Molecular Pathogenesis of PCBCLs

PCBCLs share some molecular features with their nodal counterparts but show distinctive patterns. PCFCL often lacks BCL2 translocations and exhibits a more restricted mu-

tational profile than nodal follicular lymphoma, whereas PCMZL/LPD is frequently associated with chronic antigenic drive (e.g., Borrelia in some geographic regions) and displays plasmacytic differentiation and class-switched immunoglobulin rearrangements [3,7,10]. These differences underpin the markedly distinct clinical behaviour of indolent versus aggressive PCBCLs and directly influence therapeutic intensity. PCDLBCL-LT shows frequent MYD88 and CD79B mutations, activation of NF-κB signalling, and an immune-privileged microenvironment enriched in M2 macrophages, supporting the use of rituximab-based chemo-immunotherapy and, potentially, novel targeted agents [3,4,9]. This biology explains both the aggressive clinical course of PCDLBCL-LT and its relative resistance to conventional chemotherapy alone. Recent molecular studies have refined this model by demonstrating that MYD88- and BCR-driven signalling is closely linked to immune-evasion programs, including PD-L1/PD-L2 overexpression and antigen-presentation defects, with direct implications for response to immunomodulatory and checkpoint-based therapies [20–22].

4. Diagnosis and Staging: A Dermatologic Approach

4.1. Clinical Assessment and Imaging

Early MF often mimics chronic eczematous or psoriasiform dermatoses, resulting in diagnostic delays of several years in many patients [23]. Dermatologists should maintain a high index of suspicion for persistent, therapy-refractory patches and plaques on photoprotected sites, especially when accompanied by poikiloderma, atrophy, or follicular involvement. Detailed full-body skin examination, photographic documentation, and severity scores (e.g., mSWAT) are essential for longitudinal assessment.

Adjunctive, non-invasive imaging techniques, such as dermatoscopy, high-frequency ultrasound, and line-field confocal optical coherence tomography, may assist in selected centres in distinguishing inflammatory dermatoses from early lymphoma and in guiding biopsy site selection. However, these modalities remain complementary tools and do not replace histopathologic confirmation [24]. In PCBCLs, clinical distribution (head/neck vs. leg), number of lesions, and growth kinetics provide important prognostic clues [3,7].

4.2. Histopathology, Immunophenotyping, and Molecular Studies

Multiple, adequately deep biopsies from representative lesions are often required. For MF/SS, classic features include epidermotropism, Pautrier microabscesses, and atypical cerebriform T cells, but early lesions may be subtle, and clinicopathologic correlation with repeated biopsies is often necessary [5,11]. Immunophenotyping typically demonstrates a $CD3^+$, $CD4^+$, $CD45RO^+$ phenotype with variable loss of CD7, CD26, or other pan-T antigens; CD30 expression, when present, must be interpreted in the broader context to differentiate large-cell transformation from co-existing $CD30^+$ lymphoproliferative disorders [5,13,25]. Histopathologic evaluation with clinicopathologic correlation, therefore, remains the diagnostic gold standard.

TCR gene rearrangement studies represent an established ancillary diagnostic tool in challenging cases. High-throughput sequencing of T-cell clonotypes is an emerging approach that can improve sensitivity for clonality detection and minimal blood involvement, but it is not yet required for routine diagnosis in all patients. Flow cytometry of peripheral blood is a standard component of SS evaluation and supports TNMB staging by quantifying aberrant circulating T-cells [12,25].

In PCBCLs, histology and immunophenotype (germinal centre vs. marginal zone vs. activated B-cell phenotype) are complemented by established molecular tests (e.g., IGH/IGK rearrangements) and, in selected cases, targeted assays such as MYD88 muta-

tion analysis, together with exclusion of systemic disease by imaging and bone marrow evaluation where appropriate [3,4,7].

4.3. Staging and Prognostic Stratification

The International Society for Cutaneous Lymphomas (ISCL)/EORTC TNMB staging system remains the cornerstone for MF/SS, with skin-limited early stages (IA–IIA) showing excellent disease-specific survival and advanced stages with nodal, visceral, or blood involvement carrying poorer outcomes [5,6,26]. While additional clinical and laboratory variables may refine risk stratification, they currently complement rather than replace formal TNMB staging. International registry efforts such as PROCLIPI have highlighted substantial diagnostic delay and identified clinical and laboratory predictors of progression in early MF [23,27]. In PCBCLs, subtype (indolent vs. aggressive), lesion multiplicity, leg involvement, and patient age are key prognostic factors [3,7]. Racial and ethnic disparities also influence outcomes in MF/SS. A large retrospective cohort from a major cancer referral centre demonstrated that African American/Black patients present with more advanced stages, have higher blood involvement, and experience worse overall survival compared with White patients, even after adjusting for stage and treatment variables [28].

5. Therapeutic Strategies

Therapeutic strategies in PCLs differ substantially between cutaneous T-cell and B-cell lymphomas, reflecting their distinct clinical behaviour, biological drivers, and prognosis. Across both CTCLs and PCBCLs, therapeutic efficacy is characterised by marked inter-patient heterogeneity, frequent incomplete responses, and the emergence of treatment resistance, making critical appraisal of benefits and limitations essential for clinical decision-making. For clarity, treatment approaches are discussed separately for CTCLs and PCBCLs. Recent molecular studies have refined this model by demonstrating that MYD88- and BCR-driven signalling is closely linked to immune-evasion programs, including PD-L1/PD-L2 overexpression and antigen-presentation defects, with direct implications for response to immunomodulatory and checkpoint-based therapies [20–22].

5.1. Therapeutic Strategies in CTCLs

The therapeutic management of CTCLs is guided by histotype, stage, symptom burden, and comorbidities, and must balance disease control with long-term toxicity in a largely chronic, relapsing setting. In MF and SS, early stages are typically managed with skin-directed treatments (topical corticosteroids, chlormethine, phototherapy, localised radiotherapy), whereas advanced stages require systemic agents, often administered sequentially, with allogeneic haematopoietic stem-cell transplantation reserved for selected fit patients with aggressive or refractory disease [1,5,27,29–33]. Recent prospective and real-world studies from the last five years emphasise that response depth and durability in CTCLs are highly heterogeneous and influenced by disease compartment (skin versus blood), tumour burden, and immune microenvironment, underscoring the need for biologically informed treatment sequencing rather than uniform escalation strategies [14,15,26,34]. In practice, this translates into selecting therapies not only by stage but also by dominant disease compartment (skin vs. blood), pace of progression, and the need for rapid symptom control versus long-term tolerability. Importantly, no currently available therapy reliably induces durable complete remission in advanced CTCLs, reinforcing the need for sequential, response-adapted strategies rather than fixed treatment algorithms. Consensus recommendations from EORTC, ISCL, and the National Comprehensive Cancer Network (NCCN) emphasise a risk-adapted strategy that prioritises skin-directed modalities and low-toxicity systemic agents in early disease, while reserving more intensive

or experimental therapies for advanced or transformed stages [1,3,29–33]. Within this framework, systemic therapies used in MF/SS include a spectrum of immunomodulatory and targeted agents that remain central to disease control. A randomised, controlled, multicentre trial demonstrated that 0.02% mechlorethamine (chlormethine) gel achieved overall response rates (ORRs) of approximately 60% in stage IA–IIA MF, with durable cutaneous responses and manageable local dermatitis [35]. Real-world and prospective data—including the MIDAS trial—show that proactive supportive care (e.g., topical corticosteroid co-treatment and schedule adjustment) reduces chlormethine-related dermatitis without compromising efficacy, thereby improving adherence in a chronic-use setting [36]. Clinical experience and guideline-based recommendations have confirmed its effectiveness and clarified the spectrum of irritant and allergic contact dermatitis, underscoring the need for proactive skin care, topical corticosteroids, and schedule modification to preserve adherence [5,29,30,32,33,37]. Mechanistic work demonstrates that chlormethine exerts cytotoxic activity not only through DNA alkylation but also through induction of immunogenic cell death and immune-microenvironment remodelling, as recently characterised in a detailed dermatopathologic and molecular study [38]. Among systemic options, retinoids continue to play a major role, particularly in advanced or erythrodermic disease. Oral bexarotene remains a backbone for advanced-stage MF/SS. In the pivotal multinational phase II–III trial of refractory advanced CTCLs, bexarotene produced an ORR of 45% with a median response duration of approximately nine months and meaningful improvement in pruritus in a subset of patients [39]. Its toxicity profile—dominated by hypertriglyceridaemia, central hypothyroidism, and hepatic enzyme elevation—requires close dermatologic and metabolic monitoring, but the drug is particularly attractive in pruritic erythrodermic disease and is frequently used in combination with phototherapy, interferon-α, or low-dose methotrexate [5,29,30,32,33,37]. Another cornerstone of systemic management in erythrodermic MF/SS is extracorporeal photopheresis (ECP), which exerts broad immunomodulatory effects. ECP represents a key immunomodulatory option for erythrodermic MF/SS, especially in patients with significant blood involvement or SS [5,29,32,33,37,40–43]. Early series and long-term follow-up studies demonstrated durable responses and favourable survival in subsets of patients, often when ECP is integrated into multimodality regimens that include interferon-α, bexarotene, or systemic corticosteroids [40–42]. Subsequent single-centre and multicentre experiences have confirmed that ECP can induce partial and complete remissions with an excellent safety profile, supporting repeated cycles over many months or years and making it particularly suitable for frail patients and those in whom cytotoxic chemotherapy is undesirable [40–43]. Collectively, skin-directed therapies, retinoids, and ECP remain foundational in early and erythrodermic CTCLs, not because of superior cytotoxic potency, but owing to their favourable long-term tolerability and ability to modulate tumour–immune interactions. However, their predominantly cytostatic and immunomodulatory mechanisms translate into partial responses in many patients, limited activity in bulky tumour-stage disease, and delayed onset of action. These features position them as optimal backbone or combination partners rather than definitive monotherapies in advanced CTCLs.

Epigenetic modulation has also emerged as an important therapeutic axis in relapsed or refractory CTCLs. Vorinostat and romidepsin are well-established systemic agents for relapsed/refractory MF/SS [30,37,44–47]. In the phase II trial of vorinostat 400 mg/day in refractory MF/SS, the ORR was approximately 30%, with clinically meaningful pruritus improvement and a safety profile characterised mainly by fatigue, diarrhoea, nausea, and thrombocytopenia [30]. A larger phase IIb multicentre trial confirmed the activity and safety of vorinostat, supporting its regulatory approval [46]. Romidepsin, evaluated in a pivotal multi-institutional phase II study, achieved an ORR of 34% (CR 6%) in heavily

pretreated CTCLs, with some responses lasting beyond one year [44]. A separate multi-institutional phase II trial corroborated these findings and highlighted sustained symptom relief in a proportion of patients [45]. Taken together, these data firmly position HDAC inhibitors as important systemic options in advanced-stage MF/SS, particularly in tumour-stage or folliculotropic disease where tumour debulking and rapid symptom control are priorities [30,37,44–47].

Despite reproducible response rates across trials, HDAC inhibitors illustrate a recurring theme in CTCL therapeutics: modest overall efficacy, limited durability, and marked inter-patient variability. Emerging translational and real-world data suggest that epigenetic plasticity and clonal heterogeneity contribute to both primary and acquired resistance, supporting their use as immunomodulatory sensitizers in rational combination strategies rather than as prolonged monotherapy [48,49].

More recently, increasing attention has focused on targeting intracellular signalling pathways involved in CTCL pathogenesis. The PI3K–AKT axis is increasingly recognised as a pathogenic driver in CTCLs, with both tumour-intrinsic and microenvironmental effects [17,37,48,50–52]. Tenalisib (RP6530), an oral dual PI3K-δ/γ inhibitor, demonstrated promising activity in a phase I/Ib study including patients with relapsed/refractory peripheral and CTCLs: among evaluable CTCL patients, the ORR approached 45%, with transaminase elevations as the most common grade $\geq$3 adverse event [50,51]. In a subsequent phase I/II study combining tenalisib with romidepsin, the ORR across the peripheral T-cell lymphoma and CTCL was approximately 60%, including durable responses in MF/SS and manageable overlapping haematologic toxicity [48]. Duvelisib, another oral PI3K-δ/γ inhibitor, has also shown relevant activity in T-cell lymphomas. In a phase I trial, duvelisib produced an ORR of 50% in the CTCL, with evidence from preclinical models that the drug not only directly kills malignant T cells but also reprograms tumour-associated macrophages from an immunosuppressive M2 phenotype to a pro-inflammatory M1 state [17,37,52]. Real-world data on duvelisib combined with romidepsin suggest that this doublet is feasible and active in relapsed/refractory CTCLs, supporting the rationale for PI3K–HDAC inhibitor combinations in future prospective trials [49]. Importantly, recent translational studies suggest that PI3K inhibition exerts both direct anti-tumour and microenvironmental effects, but may also select for resistant immune and malignant clones, contributing to heterogeneous clinical benefit and reinforcing the need for rational combinatorial approaches and careful patient selection [49,52]. Clinically, this argues for time-limited, combination-based use in selected patients rather than prolonged monotherapy, particularly given overlapping infectious and haematologic risks when paired with other systemic agents. Accordingly, PI3K inhibitors are best viewed as high-impact but biologically fragile agents, whose benefit is constrained by immune-mediated toxicity and adaptive resistance. Collectively, these agents provide a therapeutic platform onto which newer immunotherapies and antibody–drug conjugates (ADCs) are now being layered [5,29,30,32,33,37,48–52].

Beyond small molecules, ADCs have significantly reshaped the management of selected CTCL subtypes. Brentuximab vedotin (BV), an anti-CD30 monoclonal antibody conjugated to the microtubule toxin monomethyl auristatin E, has significantly transformed the management of CD30-positive cutaneous lymphomas. In a phase II trial of patients with $CD30^+$ CTCLs and lymphomatoid papulosis, BV yielded an ORR of approximately 70%, with complete responses in 16–20% of patients and meaningful improvements in pruritus and quality of life [53]. These results have been corroborated by real-world and small-case series, including reports of rapid and deep clinical responses in primary C-ALCL treated with BV [54].

These results were confirmed and extended by the randomised phase III ALCANZA trial, which compared BV with a physician's choice (methotrexate or bexarotene) in patients with CD30-expressing MF or primary C-ALCL requiring systemic therapy [55,56]. BV significantly improved the primary endpoint of objective response lasting ≥4 months (ORR4 56.3% vs. 12.5%), prolonged progression-free survival (median 16.7 vs. 3.5 months; HR 0.27), and improved patient-reported symptom burden [55,56].

From a dermatologic viewpoint, BV's toxicity profile is dominated by peripheral neuropathy and mild cutaneous adverse events [37,53,55,56]. The neuropathy is often cumulative but at least partially reversible; thus, early recognition, dose modification, and treatment interruption are critical. Infusion-related reactions and alopecia are typically manageable. The main challenge in practice is to integrate BV into therapeutic sequences that also include skin-directed therapies—such as pairing BV with localised RT for bulky plaques or tumours—to maximise local control while limiting systemic exposure [3,30,32,33,37,53,55,56]. The clinical success of BV underscores the value of antigen-directed therapy in CTCLs, particularly when tumour biology offers a clear therapeutic anchor such as CD30 expression. However, its benefit remains confined to a molecularly defined subset of patients, and cumulative neurotoxicity constrains prolonged exposure. These factors emphasise the importance of strategic integration—rather than indiscriminate use—within multimodal treatment pathways.

Immunotherapy represents another major advance, reflecting the profound immune dysregulation characteristic of MF and SS. CTCLs are characterised by profound immune dysregulation: malignant T cells coexist with an exhausted, PD-1–high cytotoxic infiltrate and an immunosuppressive microenvironment enriched in regulatory T cells and tumour-associated macrophages [5,14,17,37,44]. This biology provides a compelling rationale for PD-1/PD-L1 blockade. In a multicentre phase II study, pembrolizumab (200 mg every three weeks) in 24 patients with relapsed/refractory MF/SS resulted in an ORR of 38%, including two complete and seven partial responses, with some responses exceeding 12 months; activity was observed in both MF and SS [15]. A subset of patients experienced transient "flare" reactions, with erythema and pruritus in pre-existing lesions, highlighting the importance of dermatologic expertise in distinguishing immune activation from true disease progression [15,37].

At a mechanistic level, single-cell and spatial transcriptomic analyses have shown that CTCL lesions responding to PD-1 blockade are enriched in clonally expanded, granzyme-B–positive $CD8^+$ T cells and exhibit a "hot" immune cell topography, whereas non-responders display immune exclusion and enrichment of PD-L1–positive myeloid cells [14]. These findings support combinatorial strategies (for example, with RT, HDAC, or PI3K inhibitors) to remodel the tumour microenvironment and sensitise otherwise "cold" tumours to PD-1/PD-L1 blockade [14,17,37]. Case reports of pembrolizumab combined with palliative radiotherapy in refractory MF further illustrate potential synergy between immune checkpoint blockade and localised radiation [15,57].

Early experiences with nivolumab and durvalumab in CTCLs, mostly in basket trials and small series, suggest similar response rates, but also underscore the potential for immune-related adverse events (colitis, hepatitis, endocrinopathies), which require prompt recognition and multidisciplinary management [22,37]. Checkpoint blockade has revealed a dichotomy within CTCLs, wherein a subset of patients derives durable benefit while others experience primary resistance or immune-mediated flares. Spatial and single-cell profiling studies suggest that pre-existing immune activation and cytotoxic T-cell infiltration are key determinants of response, reframing PD-1 inhibition as a biomarker-dependent rather than broadly applicable strategy. This paradigm reinforces the need for microenvironmental profiling and biomarker-guided positioning of PD-1/PD-L1 blockade,

especially in immunologically "cold" disease. This dichotomous activity underscores both the promise and the current limitations of immunotherapy in CTCLs, highlighting the unmet need for validated predictive biomarkers.

Targeting immune cell trafficking has further expanded therapeutic options. Mogamulizumab is a defucosylated humanised IgG1 monoclonal antibody targeting CCR4, which is abundantly expressed on Sézary cells and on subsets of MF cells, as well as on regulatory T cells. In the phase III MAVORIC trial, mogamulizumab significantly improved progression-free survival compared with vorinostat (median 7.7 vs. 3.1 months; HR 0.53) and more than quintupled the ORR (28% vs. 5%) in previously treated MF/SS, with the greatest benefit seen in patients with high blood tumour burden [34]. Post hoc analyses confirmed that patients with B2 blood involvement derive the most pronounced benefit, reinforcing the role of detailed blood staging in therapeutic decision-making [14,17,34,58].

From a dermatologic standpoint, mogamulizumab-associated rashes are common (up to 40%), often eczematous or psoriasiform, and may histologically mimic graft-versus-host disease (GVHD). Interestingly, the emergence of these immune-mediated eruptions has been associated with better systemic responses, similar to observations with other immune therapies [17,37,58,59]. However, prior mogamulizumab exposure increases the risk of severe acute GVHD after allogeneic transplant, making careful timing and adequate wash-out before transplantation critical [14,17,29,32,33].

Recent real-world studies further indicate that prior treatment history, blood tumour burden, and immune-related toxicity profiles substantially influence outcomes with mogamulizumab, underscoring both its clinical value and the importance of strategic sequencing in advanced disease [58,59].

Finally, emerging strategies continue to broaden the therapeutic horizon in advanced CTCLs. Hyperactivation of JAK/STAT and SYK signalling is a hallmark of many T-cell lymphomas, including CTCLs, often driven by autocrine and paracrine cytokine loops [17,37]. Cerdulatinib, a dual SYK/JAK inhibitor, has produced ORRs of roughly one-third in relapsed/refractory peripheral and CTCLs in early-phase studies, with particularly encouraging responses in T-follicular helper–type nodal lymphomas and symptom relief (notably pruritus) in CTCL patients [37]. Although still investigational, such data highlight cytokine and BCR-proximal signalling as promising therapeutic targets.

Preclinical models suggest that HDAC inhibition can increase tumour immunogenicity by upregulating MHC and co-stimulatory molecules, potentially enhancing sensitivity to PD-1 blockade [17,37,44,46,47]. Clinically, combinations of HDAC inhibitors (romidepsin or vorinostat) with PI3K inhibitors (tenalisib, duvelisib) are emerging in early-phase trials and real-world series, where they appear to deepen responses compared with either agent alone, albeit at the cost of increased haematologic toxicity and infectious risk [17,37,49–52]. Frequent dermatologic assessment is essential to distinguish drug-related exanthems and immune phenomena from CTCL progression.

Allogeneic haematopoietic cell transplantation remains the only established curative-intent strategy for advanced MF/SS, with registry data showing long-term disease control in a subset of high-risk patients but at the price of significant transplant-related morbidity and mortality [27,29,31–33,60]. Early-phase trials of CD30-targeted and CD5-directed CAR-T cells in T-cell lymphomas have demonstrated proof-of-concept responses, including in CTCLs, but issues such as fratricide, prolonged T-cell aplasia, and antigen-negative relapse remain major challenges [37].

Innate immune engagement and macrophage reprogramming are also emerging as therapeutic concepts. Preclinical data indicate that agents targeting the CD47–SIRPα "don't-eat-me" axis and PI3K-δ/γ can re-educate tumour-associated macrophages and enhance phagocytosis of CTCL cells [17,37,48,51,52]. Early-phase clinical trials of anti-CD47

antibodies and SIRPα-Fc fusion proteins in T-cell lymphomas will provide critical insights; dermatologic endpoints—such as ulceration, re-epithelialisation, and inflammation in heavily infiltrated plaques—are likely to be particularly informative in CTCLs.

5.2. Therapeutic Strategies in PCBCLs

In PCBCLs, indolent entities such as PCFCL and PCMZL/LPD generally respond to localised radiotherapy or surgical excision and have an excellent prognosis, with skin-limited relapses that are amenable to repeat local treatment [1,4,20,61–65]. In contrast, PCDLBCL-LT behaves as an aggressive lymphoma, often requiring anthracycline-based immunochemotherapy and, increasingly, novel immunomodulatory and B-cell receptor (BCR)/BTK-inhibitor–based strategies in the relapsed setting [4,20–22,32,61–69].

Recent molecularly annotated clinical series from the last five years confirm that outcomes in PCBCLs—particularly in PCDLBCL-LT—are driven more by underlying genetic and immune-evasion features than by histology alone, supporting a shift toward biologically stratified therapeutic approaches [32,34,35].

Clinically, this implies that relapse management in PCDLBCL-LT should prioritise pathway/immune-based combinations when chemoresistance or frailty limits further cytotoxic therapy, whereas indolent PCBCLs can often be managed with iterative, skin-directed approaches focused on local control and quality of life.

Dermatologists are central to this landscape: they frequently determine the initial diagnostic pathway, longitudinally assess cutaneous response and toxicity, and often coordinate multidisciplinary care with haematologists, radiation oncologists, and transplant teams.

Beyond conventional chemoimmunotherapy, therapeutic innovation in PCDLBCL-LT has increasingly drawn on advances developed for nodal diffuse large B-cell lymphoma (DLBCL). Case reports and small series describe responses to ADCs (such as CD79b-targeted polatuzumab vedotin) and other novel agents in multiply relapsed PCDLBCL-LT, particularly in patients harbouring MYD88 and BCR-pathway mutations [20–22,61–63,65–68]. Although clinical data remain limited, the biological parallels between PCDLBCL-LT and activated B-cell-type DLBCL—especially their addiction to the BCR–MYD88–NF-κB axis—support further exploration of ADCs and related targeted approaches in this setting [20–22,61–70].

Immune modulation has also emerged as a key therapeutic dimension in aggressive PCBCLs. PCDLBCL-LT is strongly enriched in immune-evasion mechanisms, including overexpression of PD-L1/PD-L2 and recurrent alterations in antigen presentation pathways [20–22,63,64]. A small series suggests that integrating PD-1 blockade into salvage regimens can achieve meaningful responses. A case series combining rituximab, lenalidomide, and pembrolizumab in multiply relapsed PCDLBCL-LT reported durable complete responses in patients who had progressed after R-CHOP and radiotherapy [67]. Another cohort treated with rituximab, lenalidomide, and ibrutinib achieved high response rates with acceptable toxicity, suggesting that dual immunomodulation plus BTK inhibition can re-sensitise chemoresistant disease [68]. These experiences, together with mechanistic data on PD-L1/PD-L2 expression and MYD88/BCR pathway activation, support a conceptual shift in PCDLBCL-LT from purely cytotoxic approaches toward immune- and pathway-directed combinations [20–22,61–68].

Lenalidomide has emerged as a rational partner for rituximab in PCDLBCL-LT, leveraging both direct anti-lymphoma effects and T-cell/macrophage activation [32,61–64,66,67]. In a multicentre, single-arm phase II trial of relapsed/refractory PCDLBCL-LT, lenalidomide monotherapy achieved an ORR of 26% at six months, with some durable complete remissions in an elderly, frail population; cytopenias and infections were the main toxicities [66]. Real-world case reports confirm the activity of lenalidomide, including

impressive responses after multiple prior lines of therapy and in combination with rituximab, supporting its use as a palliative yet potentially disease-modifying option in selected patients [66,67,71].

Nonetheless, recent studies underline modest response durability and marked interpatient heterogeneity, reinforcing the role of lenalidomide as part of combination or sequential strategies rather than as a standalone long-term solution [66,67,71].

These clinical observations are strongly supported by molecular insights into BCR-driven oncogenesis. PCDLBCL-LT is characterised by high frequencies of MYD88 L265P and CD79B mutations, underpinning dependence on chronic active BCR signalling and NF-κB activation [20–22,62–64]. This biology translates into clinical sensitivity to BTK inhibition. A landmark case report of low-dose ibrutinib documented a rapid and deep remission in a patient with PCDLBCL-LT harbouring MYD88 and CD79B mutations, after failure of anthracycline-based therapy and lenalidomide [69]. Subsequent small series combining rituximab, lenalidomide, and ibrutinib in relapsed/refractory PCDLBCL-LT reported high response rates with acceptable tolerability, suggesting that simultaneous BCR blockade and immunomodulation may overcome chemoresistance in some patients [68,71].

Translational and mechanistic studies suggest that secondary resistance to BTK inhibition can involve acquisition of downstream lesions (including PIM1 and other NF-κB–related alterations), supporting next-generation and combinatorial targeted strategies rather than sequential single-agent BTK inhibition [21,22,70].

Finally, immune checkpoint blockade and microenvironmental targeting continue to shape emerging treatment paradigms. Genomic and immunohistochemical studies demonstrate frequent loss-of-function alterations in antigen-presentation genes (for example, B2M), high PD-L1/PD-L2 expression, and a complex immune microenvironment in PCDLBCL-LT, often with abundant PD-L1–positive macrophages [20–22,62–64]. These features support the use of checkpoint inhibitors, particularly in biologically selected patients and in combination regimens. Although numbers remain small, these observations hint at a therapeutic paradigm in which immune-directed combinations—rather than purely cytotoxic escalation—become the preferred salvage strategy in selected patients [4,20,32,61–65,67].

However, the limited size of available cohorts and the biological heterogeneity of immune escape mechanisms remain major challenges, underscoring the need for biomarker-driven patient selection in future clinical trials [20,21,67]. Overall, recent comprehensive reviews and molecular studies emphasise that PCBCL management is moving toward biologically tailored regimens for PCDLBCL-LT based on BCR/MYD88 mutation status and immune-evasion signatures; de-escalation of systemic therapy in indolent PCBCLs using localised RT, intralesional agents, and conservative systemic regimens; and integration of targeted agents (lenalidomide, BTK inhibitors, and potentially BCL2 and EZH2 inhibitors) for relapse and peri-transplant management [4,20,32,61–66]. For dermatologists, this evolution underscores the importance of high-quality diagnostic biopsies (including molecular profiling), long-term surveillance for relapse, and close partnership with lymphoma centres experienced in rare cutaneous entities.

These therapeutic principles are summarised schematically in Figure 2.

Management strategies differ according to lymphoma subtype and disease stage. In MF and SS, early disease is treated with skin-directed therapies, whereas advanced stages require sequential systemic treatments, with allogeneic stem-cell transplantation reserved for selected refractory cases [3,26,29,46].

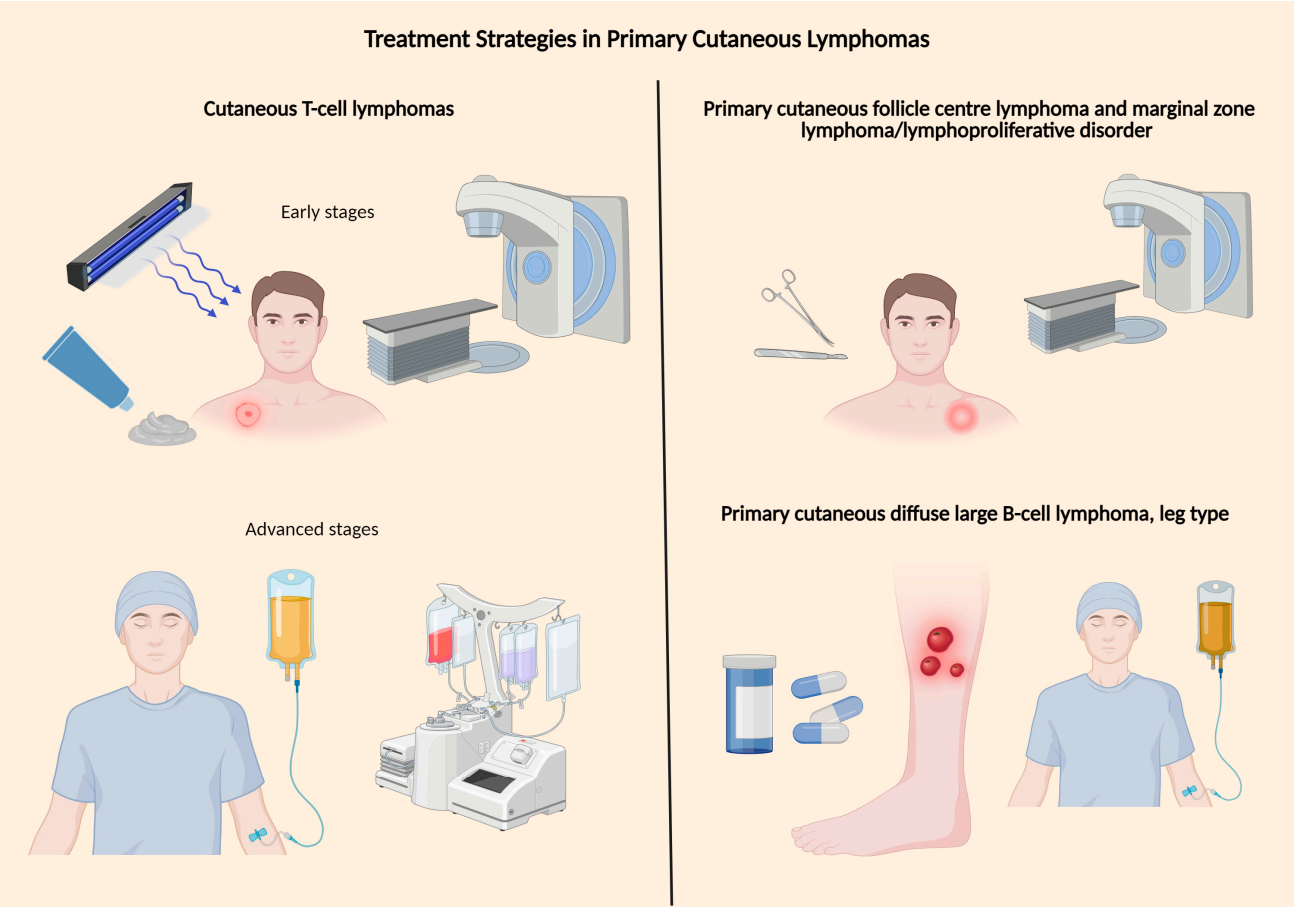


Figure 2. Treatment strategies in primary cutaneous lymphomas.

In PCBCLs, indolent subtypes (PCFCL, PCMZL/LPD) are effectively managed with localised therapies, whereas PCDLBCL-LT requires systemic chemo-immunotherapy and, increasingly, immune- and pathway-directed approaches in relapse [3,61,62,66–68].

6. Discussion

PCLs constitute a clinically and biologically heterogeneous group of lymphoid neoplasms that increasingly require molecularly informed diagnostic and therapeutic strategies. Advances in sequencing technologies and high-dimensional immune profiling have clarified central pathogenic mechanisms in CTCLs, including dysregulated TCR signalling, JAK/STAT activation, PI3K pathway involvement, and robust immune-evasion programs, which help explain treatment resistance, blood involvement, and the immunosuppressive microenvironment characteristic of advanced MF and SS [1,6,16,19]. However, a major unresolved clinical challenge is translating these immune-evasion frameworks into reliable bedside decisions: immune escape may manifest as compartment-specific disease behaviour (skin versus blood), variable depth and durability of response, and clinically ambiguous inflammatory flares that can mimic progression during immune-based therapies.

In PCBCLs, and especially in PCDLBCL-LT, recurrent MYD88 L265P and CD79B mutations and alterations in antigen-presentation genes establish a biologic profile deeply reliant on BCR–NF-κB signalling and enriched in immune-escape signatures [20–22,63]. These insights increasingly guide not only prognosis but also therapeutic selection, supporting the use of BTK inhibitors, lenalidomide-containing regimens, and emerging checkpoint-based combinations [66–69]. Nevertheless, most evidence derives from small cohorts and case-

based experiences, and key questions remain unresolved regarding biomarker thresholds, sequencing, and durability of benefit in real-world populations.

Despite these advances, diagnostic delay remains a pervasive issue, particularly in early MF, where clinical overlap with benign dermatoses and subtle early histopathology frequently hinder timely recognition [11,23,28]. Dermatologists remain central in identifying persistent or atypical dermatoses, coordinating repeat biopsies and incorporating molecular testing when indicated [25,32]. Accurate subclassification of PCBCLs is equally essential: while PCFCL and PCMZL typically benefit from conservative, skin-directed approaches, PCDLBCL-LT mandates systemic therapy informed by its aggressive molecular profile [61–63].

Therapeutically, the landscape for CTCLs continues to broaden. Skin-directed therapy remains foundational in early MF, with chlormethine gel demonstrating consistent efficacy across randomised and real-world settings, and mechanistic studies suggesting additional immunogenic effects beyond direct alkylation [35,36,38]. Systemic therapies (including retinoids, ECP, HDAC, and PI3K inhibitors) offer benefits that vary by disease compartment, burden, and symptom profile [29,30,37,39–43]. HDAC inhibitors, such as vorinostat and romidepsin, retain particular value in tumour-stage or folliculotropic MF, and early-phase data support the synergistic potential of combinations with PI3K inhibitors [44–48,50–52].

BV represents one of the most significant therapeutic advances in CD30-positive CTCLs, with the ALCANZA trial demonstrating superior and durable responses compared with physician's choice, along with meaningful symptom improvement [53–56]. Its activity in primary cutaneous ALCL is further supported by case-based evidence [54], though peripheral neuropathy remains a major dose-limiting toxicity. Immunotherapy has also expanded treatment options: pembrolizumab provides durable benefit in a subset of MF/SS patients [15], and immune-topographic profiling has begun to identify microenvironmental signatures predictive of response [14]. Yet, routine implementation remains limited by the lack of validated, widely available predictive biomarkers, and by practical challenges in response assessment—particularly distinguishing immune-related flare or pseudoprogression from true progression in skin, where clinical morphology can be misleading. However, immune-related adverse events and flare reactions require careful dermatologic assessment to avoid misinterpretation as progression [24,26].

Immune-directed strategies extend to mogamulizumab, which shows substantial benefit—particularly in SS with high blood tumour burden—but its association with drug-related rashes and increased risk of post-transplant GVHD demands careful sequencing, especially in transplant-eligible patients [34,58,59]. This exemplifies a broader unmet need in CTCLs: immune-directed therapies may improve disease control while simultaneously complicating subsequent curative-intent strategies (e.g., allogeneic transplant), requiring evidence-based sequencing frameworks that are currently lacking.

In PCDLBCL-LT, combinations such as rituximab–lenalidomide–pembrolizumab and rituximab–lenalidomide–ibrutinib have shown encouraging activity in relapsed settings, reinforcing the role of immunomodulation and targeted therapy in a disease with limited chemoresponsiveness [66–69]. Mechanistic studies describing ibrutinib-induced resistance via PIM1 and related pathways suggest avenues for future rational combinations with downstream inhibitors [70].

Looking ahead, biomarker-driven treatment selection remains underdeveloped across both the CTCL and PCBCL. A key unmet need is the integration of candidate biomarkers (e.g., tumour clonality dynamics, immune-topographic signatures, and immune-evasion markers) into standardised, clinically actionable assays with defined thresholds, reproducibility across centres, and prospective validation. In parallel, longitudinal disease monitoring remains challenging: the CTCL is spatially and temporally heterogeneous, and

response may differ across compartments (skin, blood, nodes), underscoring the need for monitoring strategies that combine clinical scoring with serial blood-based assessments and, where feasible, repeat tissue sampling. Finally, translating molecular insights into routine practice will require harmonised workflows for specimen acquisition, sequencing/immune profiling, turnaround times, and access, particularly outside specialised centres [23,24].

Trials exploring rational therapeutic combinations and optimal sequencing are urgently needed, as are more robust translational models that reflect the unique biology of cutaneous lymphomas. As therapeutic options expand, multidisciplinary collaboration across dermatology, haematology, pathology, immunology and computational biology will become increasingly essential. Equally important is the development of clinically meaningful endpoints for cutaneous disease—capturing symptom burden, quality of life and compartment-specific responses—so that translational biomarkers can be linked to outcomes that matter in routine practice. Overall, the rapidly expanding therapeutic armamentarium offers genuine potential to improve outcomes in PCL, though personalization of therapy remains the central challenge.

Key clinical and translational studies informing current practice are summarised in Supplementary Table S1.

7. Methods

This manuscript was prepared as a narrative review synthesising current evidence on the biology, diagnosis, and management of primary cutaneous lymphomas. A structured, non-systematic search of PubMed/MEDLINE, Embase, and Web of Science was performed from database inception through March 2025, using combinations of keywords related to the CTCL (e.g., mycosis fungoides, Sézary syndrome, cutaneous T-cell lymphoma), PCBCL (e.g., PCFCL, PCMZL, PCDLBCL-LT), pathogenesis (JAK/STAT, MYD88, CD79B, TCR signalling, epigenetics), and treatment (chlormethine, bexarotene, HDAC inhibitors, PI3K inhibitors, brentuximab vedotin, mogamulizumab, pembrolizumab, lenalidomide, ibrutinib). Reference lists of pivotal clinical trials, molecular studies, and major reviews were examined for additional sources.

Eligible publications included clinical trials, prospective and retrospective cohorts, translational studies, case series with mechanistic relevance, and authoritative consensus guidelines. We excluded non–peer-reviewed material and reports unrelated to cutaneous disease. Study characteristics and findings were extracted manually and synthesised narratively; no meta-analysis or quantitative pooling was undertaken.

No new data were generated, and no human, animal, or institutional datasets were collected; therefore, ethics approval was not required. All information derives from publicly available peer-reviewed literature. In accordance with journal guidelines, we disclose that generative AI tools were used only for language refinement under direct author supervision, and all scientific interpretations, the literature selection, and synthesis were performed solely by the authors.

8. Conclusions

PCLs require nuanced, multidisciplinary, and stage-specific management. Advances in genomic profiling and immune characterisation have refined diagnostic criteria and therapeutic decision-making, particularly in MF/SS and PCDLBCL-LT [6,8,20,22,26,27,37,63,64]. Novel systemic agents—including PI3K and HDAC inhibitors, BV, mogamulizumab, immunomodulatory drugs, and checkpoint inhibitors—have expanded treatment options and improved outcomes in selected patients [15,29–31,37,39,45,55,58,59].

Future progress will rely on biomarker-guided therapy, rational combination strategies, and deeper integration of molecular diagnostics into routine dermatologic practice. Because

the skin provides unparalleled access for serial tissue analysis, dermatologists will continue to play a central role in advancing precision medicine for these rare lymphomas.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/lymphatics4010011/s1, Table S1: Key clinical and translational studies in primary cutaneous lymphomas.

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