Cutaneous T cell lymphoma

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Abstract | Primary cutaneous T cell lymphomas (CTCLs) are a heterogeneous group of lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis. CTCL subtypes demonstrate a variety of clinical, histological, and molecular features, and can follow an indolent or a very aggressive course. The underlying pathogenetic mechanisms are not yet entirely understood. The pathophysiology of CTCL is complex and a single initiating factor has not yet been identified. Diagnosis is based on clinicopathological correlation and requires an interdisciplinary team. Treatment decision is made based on short-term and long-term goals. Therapy options comprise skin-directed therapies, such as topical steroids or phototherapy, and systemic therapies, such as monoclonal antibodies or chemotherapy. So far, the only curative treatment approach is allogeneic haematopoietic stem cell transplantation. Novel therapies, such as chimeric antigen receptor T cells, monoclonal antibodies or small molecules, are being investigated in clinical trials. Patients with CTCL have reduced quality of life and a lack of effective treatment options. Further research is needed to better identify the underlying mechanisms of CTCL development and course as well as to better tailor treatment strategies to individual patients.

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Primary cutaneous T cell lymphomas (CTCLs) are a heterogeneous group of T cell lymphomas that initially present in the skin with no evidence of extracutaneous disease[1]. Subtypes of CTCL vary widely in terms of biology, histopathology and clinical features (TABLE 1). After multiple studies found that primary cutaneous lymphomas and primary nodal lymphomas of the same histological subtype differ in clinical behaviour and prognosis, a new classification for cutaneous lymphomas was established in 1997. The most recent iteration of this classification was published in 2018 in the fourth edition of the WHO Classification of Skin Tumours Blue Book[2,3].

Mycosis fungoides (MF), the most common type of CTCL, usually presents with patches and plaques and generally has an indolent clinical course. MF has a tendency to progress over years or even decades to more infiltrated plaques and tumours[4]; progression occurs in 25% of patients with early-stage disease[5]. Extracutaneous disease develops in a minority of patients and varies according to the stage of disease at diagnosis; risk of extracutaneous spread was 0% in patients presenting with limited skin involvement at first diagnosis and was ~40% in those presenting with erythroderma at first diagnosis[5–8]. In the early stages of MF, that is, patch or plaque stage (or stage IA–IIA) disease, the differential diagnosis with benign inflammatory skin conditions can be difficult as neoplastic cells constitute only a minority of the infiltrate in the skin and clinical and histological findings may overlap[9].

Sézary syndrome (SS) is a rare and aggressive type of CTCL that is defined by the triad of erythroderma, generalized lymphadenopathy and the presence of neoplastic clonal T cells (Sézary cells) in skin, lymph nodes and peripheral blood. SS tends to progress more rapidly than MF and has a worse prognosis[2]. Upon disease progression, patients with MF and SS typically experience a worsening state of immune suppression with an increased risk for infections and a decreased antitumour immune response[10].

CD30-positive lymphoproliferative disorders (CD30$^+$ LPDs) are a spectrum of disorders including self-limiting lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large-cell lymphoma (pcALCL) (TABLE 1). CD30$^+$ LPDs usually have an indolent clinical course; however, patients have a higher risk for second lymphoid malignancies compared with the general population and therefore require regular follow-up and assessment.

This Primer discusses CTCL with a primary focus on the most common subtype (MF) and the most common aggressive subtype (SS). The Primer covers the epidemiology, pathogenesis, diagnosis, management and quality of life (QOL) of patients with MF and SS and briefly discusses other CTCL subtypes such as LyP or pcALCL.

Table 1 | **Common clinical presentations of WHO-EORTC CTCL subtypes**

CTCL subtype	Estimated frequency (% of CTCL)[2]	Clinical presentation	5-year DSS[2]	Refs
MF	39	Erythematous patches, plaques, tumours or erythroderma often with fine scaling and epidermal atrophy; may be hypopigmented and/or hyperpigmented lesions; pruritus is common; lesions occur in 'Bathing suit' distribution (non-sun-exposed areas)	88	2,222
FMF	5	Grouped, erythematous, follicular papules, erythematous papules and plaques with associated alopecia, and acneiform lesions; commonly affects face and neck (especially eyebrows)	75	2,223
PR	<1	Solitary, erythematous plaques that are verrucous and/or psoriasiform; commonly affects extremities and is slowly progressive	100	2,224
GSS	<1	Erythematous patches that evolve into pendulous, lax skin in flexural and intertriginous areas; pruritus is common; associated with preceding or concurrent Hodgkin disease and classical MF	100	2,225,226
SS	2	Generalized erythroderma with exfoliation, oedema and lichenification (often >80% of BSA); lymphadenopathy and pruritus are common; ≥1,000/μl Sézary cells with positive TCR clone	36	2,21,222
pcALCL	8	Solitary or grouped nodules or tumours that are rarely multi-focal; cutaneous relapse is common; possible spontaneous regression in some patients	95	2,161
LyP	12	Recurrent, dome-shaped papulonecrotic or nodular skin lesions occurring in cropped or generalized eruptions; lesions spontaneously regress after a few weeks; involution with crusting, ulceration and possible scarring; often presenting on the trunk and proximal extremities; chronic course	99	2,161
SPTCL	1	Subcutaneous plaques and nodulopapular lesions; overlying erythema; lesions may be self-healing and often involve lower extremities, upper extremities or trunk; associated with autoimmune disease in 20% of cases (possible overlap syndrome)	87	2,227,228
Extranodal NK/T cell lymphoma, nasal type	<1	EBV-associated form of CTCL; affects nasal cavity and mid-face regions; manifests as erythematous plaques, nodules and tumours with or without ulceration on trunk and extremities	16	2,229
Chronic active EBV infection	<1	Cutaneous manifestations of chronic EBV infection seen in childhood/adolescence; hydroa vacciniforme-like lesions and papulovesicular eruption on sun-exposed areas (especially face, ear lobes and back of hands) that heal with varioliform scars; systemic symptoms may be present (fever, lymphadenopathy, hepatosplenomegaly); causes hypersensitivity reactions to mosquito bites with clear or haemorrhagic bulla at the bite site that ulcerate and heal with scarring	NDA	2,230,231
Primary cutaneous γδ T cell lymphoma	<1	Ulceronecrotic plaques, subcutaneous nodules or tumours that often present on lower extremities, commonly the thighs and gluteal region; may involve hemophagocytic syndrome, especially when panniculitis-like	11	2,232,233
Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T cell lymphoma (provisional)	<1	Extensive annular patches or plaques with erosive features and ulceration, uncommonly tumours; variable distribution, can involve oral cavity; more common in elderly male patients; notable epidermal necrosis as disease progresses	31	2,187
Primary cutaneous $CD4^+$ small/medium T cell lymphoproliferative disorder (provisional)	6	Solitary nodules that commonly present on the head and neck	100	2,234
Primary cutaneous acral $CD8^+$ T cell lymphoma (provisional)	<1	Solitary papules or nodules that present on acral site, most commonly the ear, less commonly nose and foot; indolent, slow growing	100	2,235

BSA, body surface area; CTCL, cutaneous T cell lymphoma; DSS, disease-specific survival; EBV, Epstein–Barr virus; FMF, folliculotropic MF; GSS, granulomatous slack skin; LyP, lymphomatoid papulosis; MF, mycosis fungoides; NK, natural killer; pcALCL, primary cutaneous anaplastic large-cell lymphoma; PR, pagetoid reticulosis; SPTCL, subcutaneous panniculitis-like T cell lymphoma; SS, Sézary syndrome; TCR, T cell receptor.

Patches
Flat, erythematous, often scaly areas of the skin.

Plaques
Raised skin lesions that vary from pink to brownish colour and may often be scaly.

Epidemiology

The PROspective International Cutaneous Lymphoma International Index (PROCLIPI) Study provides global prospective data on MF and SS including clinical, pathological, genotypic, treatment, QOL and survival data[11–15]. The incidence of CTCL is <10 per 100,000 population per year, globally[16]. The prevalence is up to 10 times higher than the incidence owing to the survival of those presenting with early-stage disease[17]. The incidence of MF and SS does not vary between regions. These disorders occur with the same male predominance (1.7:1 male to female ratio[15,17,18]) and similar age of presentation (50–60 years in early stages and 60–70 years in advanced stages) globally but with a probable younger presentation in non-white individuals and possible higher incidence of MF in Asian populations[19,20]. This finding may be because early-stage hypopigmented MF is more recognizable and is therefore diagnosed earlier in non-white skin[17]. Some data have suggested a worse prognosis in Black individuals in the USA

Erythroderma
Widespread erythema and redness that affects >80% of the skin surface.

Lymphadenopathy
Increased size of the lymph nodes.

compared with white individuals but the latest data from PROCLIPI are conflicting[14]. The median age of diagnosis of MF and SS is lower in individuals presenting with early stages of disease (57 years) compared with those presenting with the advanced stages (63 years)[18]. This difference does not seem to be due to delayed diagnosis in patients with advanced disease as the diagnostic delay (from the onset of symptoms to diagnosis) is longer in patients with early-stage disease: advanced patients are typically diagnosed 12 months from the onset of symptoms compared with 36 months in patients with early-stage disease[15].

MF is the most common variant of CTCL and shares a staging system with SS (Supplementary Table 1)[21]. Different variants of MF, such as classic or folliculotropic MF, which present with different clinical features (TABLE 1), may coexist in the same patient. Additionally, different types of CTCL can coexist in the same patient, such as MF with LyP, and may share an identical T cell clone[22,23]. The incidence of second malignancies is high in patients with CTCL. Typically, secondary malignancies are other types of lymphoma, which occur with a standardized incidence ratio of >100 in patients with CTCL as reported in the SEER Registry and carry a worse outcome in this patient group[17,24].

Survival is largely stage dependent and the median 5-year and 10-year overall survival for MF is 49–100% and 45–100% for early stage, and 0–65% and 0–39% for advanced stage[5,7,25–27]. A large study comparing the global treatment of MF and SS found no difference in survival between the USA and other countries despite different prescribing patterns[28]. Aside from disease stage, other prognostic indicators for MF and SS include favourable features, such as poikilodermatous lesions, hypopigmented variant and association with LyP, and poor prognostic indicators such as older age at diagnosis (>60 years), large-cell transformation (LCT, defined as >25% of MF cells being four-times greater than a normal lymphocyte or clusters of large cells), folliculotropic plaques (plaques with follicular accentuation consistent with folliculotropic MF) and elevated serum lactate dehydrogenase (LDH)[18,29]. The PROCLIPI study aims to develop these factors into an international prognostic index to help stratify patients for management. In addition to identifying important prognostic markers for disease progression and survival, identifying molecular diagnostic markers to help differentiate early-stage MF from benign dermatoses would be highly valuable.

CD30$^+$ LPDs are the second most frequent subtype and account for 11% of CTCLs[2]. The disorders are a spectrum from LyP, in which the cutaneous lesions resolve spontaneously over weeks to months, to CD30$^+$ pcALCL, in which tumours enlarge and require localized treatment. The prognosis of pcALCL is excellent, with a 5-year survival of 95%[2].

Mechanisms and pathophysiology

T cells and the skin microenvironment

Normal adult skin contains a large number of phenotypically and clonally diverse memory T cells. These cells are essential in the cutaneous immune responses against microorganisms and cancer (FIG. 1); however, aberrant activation of these cells can lead to chronic inflammatory disorders[30]. Skin-tropic effector T cell clones are generated in skin draining lymph nodes. These T cells acquire the expression of glycosylated ligands for E-selectin and P-selectin, including cutaneous lymphocyte antigen (CLA) and CCR4, CCR8 and CCR10, which enables their tethering, arrest in dermal post-capillary venules and facilitates skin extravasation[30]. Chemokines CCL17, CCL22 and CCL27, released from keratinocytes and endothelium under normal conditions, are further involved in T cell migration into skin[30].

Neoplastic cells in MF and SS typically express CLA and CCR4, exhibiting the phenotype of skin-homing CD4$^+$ T cells[31]. Additional investigations suggested that neoplastic cells in MF have a CCR4^{++}/CLA1$^+$/L-selectin$^-$/CCR7$^-$ phenotype resembling resident memory T cells, whereas neoplastic SS cells express CCR4^{++}/CLA1^{++}/L-selectin$^+$/CCR7$^+$, corresponding to a central memory T cell phenotype[31]. However, other studies found that neoplastic cells in SS and MF may have features of any of the major naive or memory T cell subsets[32,33].

Early-stage MF lesions are characterized by a low number of malignant T cells that are supported by the skin microenvironment, including the upregulation of dendritic cell function, a relative abundance of CD8$^+$ T cells and a T helper 1 (T_H1)-dominated microenvironment[34,35]. The T_H1 response promotes an antitumour response against malignant T cells[34], whereas colonization of the skin with *Staphylococcus aureus* may play a super-antigen role by binding directly to MHC class II molecules and T cell receptors, thereby promoting the clonal proliferation of malignant T cells[36,37]. In addition, staphylococcal enterotoxins can trigger crosstalk between malignant cells and reactive T cells resulting in positive selection, increased proliferation, cytokine production, IL-2 receptor alpha chain (IL-2Rα) expression and STAT3 activation in malignant cells[38].

As MF persists and progresses, an increase in malignant T cells is accompanied by a reduction in CD8$^+$ T cells and a shift towards a T_H2-dominated microenvironment driven by the neoplastic cells with a skewed T_H2 phenotype. The mechanism underlying this shift is not completely understood[35,39,40]. An increasing body of evidence suggests that cytokine and chemokine signalling between fibroblasts, keratinocytes and malignant T cells define the microenvironment in CTCL and may contribute to the progression of disease. In addition, other studies have reported the presence of cancer-associated fibroblasts (CAFs) in MF that may contribute to remodelling of the extracellular matrix and enhance cell motility and drug resistance of MF cells[41]. In addition, an increase in the number and/or function of inhibitory M2 macrophages, alteration of regulatory T cells/T_H17 balance, and the upregulation of CD47–SIRPα and PD1–PDL1 pathways have been reported in skin infiltrating cells[41–44]. Collectively, these changes in immune homeostasis of the CTCL microenvironment create an immune-suppressive profile and facilitate evasion of host immune surveillance. In line with these observations, non-malignant CD8$^+$ T cells from patients with SS demonstrate a decreased complexity of the

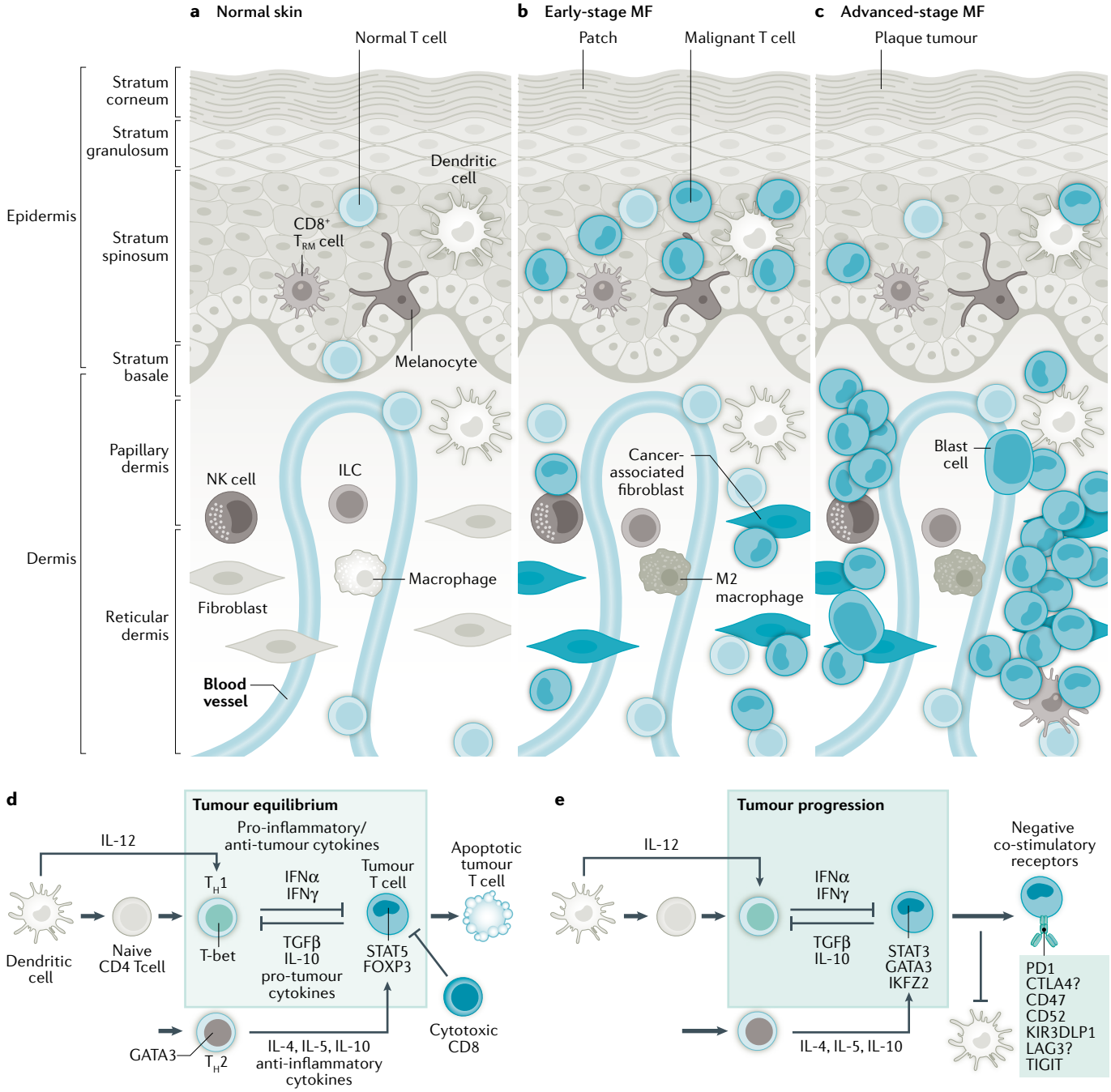

Fig. 1 | **Pathogenesis of mycosis fungoides.** The cellular composition of the skin varies between normal conditions (part **a**), early-stage cutaneous mycosis fungoides (MF; part **b**) and advanced-stage MF (part **c**). With the progression of disease, a shift is observed in the immune microenvironment from an equilibrium of tumour cells and reactive infiltrating cells to tumour progression (parts **d**,**e**). ILC, innate lymphoid cell; NK, natural killer; T_H, T helper; T_{RM}, T resident memory. Parts **a**–**c** adapted from REF.[30], Springer Nature Limited. Parts **d**,**e** adapted with permission from REF.[246], Karger.

T cell receptor (TCR) repertoire, expression of several exhausted T cell markers and decreased cytotoxicity, further promoting immune escape[45–47].

Genetic and molecular alterations

Advances in technology, including comparative genome hybridization and next-generation sequencing (NGS), have improved the understanding of the genetic and epigenetic alterations in CTCL. Despite the rareness of the disease, most studies on CTCL have focused on SS as large numbers of malignant T cells are accessible from the blood. Of note, because of challenges in collecting sufficient numbers of malignant T cells, only few studies have focused exclusively on MF[48,49]. Given that, in early stages of MF, the malignant cell infiltrate is scarce and lies superficially in the skin, the majority of studies have been performed on advanced (tumour) stage MF.

Early comparative genome hybridization studies in MF and SS found extensive copy number alterations, including losses in chromosomes 1, 5, 9, and 13 and gains in chromosomes 7 and 17 (REFS[50–55]). In addition, these studies demonstrated both overlapping and unique molecular features of MF and SS[50–52]. For instance, inactivation or deletion of the CDKN2A/B locus (encoding the tumour suppressor proteins P14/16) is the most commonly recurrent finding in MF but is less common in SS[53]. By contrast, loss of *TP53* is highly characteristic for SS (Supplementary Table 2). Fusion transcripts containing genes implicated in cancer (that is, *ATXN1-TP63*, *CCR7*$^{-}$*DOT1L*, *KDM6A-IL1RAPL1*, *LMF1-TAF15*, *TP53-GPR3* and *YTHDF3-LIFR*) have been observed in individual patients with MF[48].

NGS studies in patients with SS using whole exome, whole genome and targeted sequencing confirmed and expanded earlier observations on the potential importance of copy number alterations in this disorder. The average somatic mutation rate in SS cells was ~4 mutations/Mb[56,57], which is similar to the rate in solid tumours[58]. By contrast, 40–75% of somatic single-nucleotide substitutions in SS were C>T transitions[56,57,59], which is less frequent than in other haematological malignancies[57]. In-depth analyses show resemblance with so-called single-base substitution signatures SBS5 (which is associated with aging) and SBS7a/b (which is associated with exposure to UV radiation), although whether exposure to UV light has a causative role in the onset of SS is debated[60].

Single-cell RNA sequencing and flow cytometry studies found that neoplastic SS cells have a high degree of heterogeneity[61–63]. Understanding this heterogeneity in individual patients is important to understand the molecular mechanisms underlying the development of disease progression.

Although detailed knowledge regarding the initial drivers and promoting factors of CTCL remains unclear, combining NGS data from multiple studies and subjecting them to a uniform statistical analysis, a sample size of 225 patients with CTCL (including 186 patients with SS) allowed the identification of putative driver genes and pathways with reasonable certainty[58,64–70]. Despite a notable heterogeneity in the genomic and cellular features of MF and SS, ~45% of MF and SS demonstrate potentially targetable point mutations in genes that cluster into the following pathways and processes: TCR–NF-κB signalling, JAK–STAT signalling, MAP kinase signalling, chromatin modifications and cell cycle regulation (FIG. 2).

JAK–STAT signalling. Interferons and cytokines supporting T cell survival, such as IL-2, IL-7 and IL-15, function via the activation of the JAKs and their downstream STAT proteins, which affect proliferation, apoptotic pathways and immunogenicity due to alterations in intracellular protein processing and HLA-dependent antigen peptide presentation[71]. Increased JAK–STAT signalling has been reported in MF cells[71,72]. The activation of this pathway can be caused by the pro-tumorigenic inflammatory microenvironment and/or genetic changes in tumour cells. Deletion or unbalanced translocation of the tumour suppressor *SOCS1*, a member of the STAT-induced STAT inhibitor family, is observed in 35% of patients with MF[48]. In addition, upregulation of SOCS1-targeting microRNA-155 (miR-155) and methylation of the *SOCS1* promoter, both of which downregulate SOCS1 expression, have been observed in MF cells and may increase JAK–STAT signalling in MF[73–76]. Notably, *SOCS1* deletion is detected in early-stage MF, supporting its role in the early development of the disease[48]. Collectively, these observations suggest that hyperactivation of the JAK–STAT pathway is a founder event through a multitude of mechanisms leading to the evolution of tumour cells.

Gain-of-function single-nucleotide variants (SNVs) or point mutations in MF and SS are rare, with solitary or few cases being reported, including *RAS*, *JAK3*, *MAPK1*, *STAT3*, *PLCG1*, *TNFRSF1B* and *FGFR4* (REFS[48,64,67,77,78]). Of these, variants of *JAK3* and *STAT3* affect JAK–STAT signalling.

In SS cells, copy number alterations of *JAK2*, *STAT3* and *STAT5B* and activating mutations in *JAK1* and *JAK3* may play a role in the constitutive activation of the JAK–STAT pathway[79]. In line with these findings, constitutive activation of STAT3 was observed in SS cells and inhibiting this pathway resulted in the apoptosis of these cells[80,81]. Alterations of JAK–STAT signalling constitute a key mechanism for deficiencies in interferon signalling that may result in reduced antigen presentation, immune escape and increased susceptibility for viral infections.

TCR–NF-κB signalling. Activation of the TCR and co-stimulatory molecules trigger complex intracellular pathways, including NF-κB stimulation. This pathway regulates genes involved in innate and adaptive immunity, inflammation, stress responses, and B cell and lymphoid organ development[82]. NF-κB signalling is an essential link between the TCR and the BCR of adaptive immune responses and toll-like receptors, which are key sensors of innate immunity. This pathway is involved in the signalling of IL-1 or TNF family members (for example, CD40) or growth factors, including TGFs or EGFs. Increased NF-κB signalling supports T cell and B cell proliferation, activation and survival.

Mutations in the NF-κB pathway (for example, in *PLCG1*, *CARD11* and *TNFRSF1B*) and *TP53* are mutually exclusive in SS[83]. In addition, copy number alterations and, to a lesser extent, single-nucleotide variations have been observed in SS cells in genes involved in TCR-associated signalling (*PTPRN2* and *RLTPR*), co-stimulatory molecules (*CD28*) and in NF-κB signalling (*PRKCB* and *CSNK1A1*), which may contribute to the activation of this pathway[79]. Based on these observations, clinical trials with NF-κB-targeting therapies, such as the proteasome inhibitor bortezomib, which showed significant single-agent activity in patients with CTCL[84], have been performed.

MAP kinase signalling. Extracellular stimuli, including cytokines (such as IL-1 and TNF) and stress factors (including UV irradiation, heat shock, high osmotic stress and lipopolysaccharide), trigger surface receptor tyrosine kinases (RTKs), G protein-coupled receptors (GPCRs) and integrins that initiate protein kinase cascades termed MAP kinases, which include RAF, RAS and

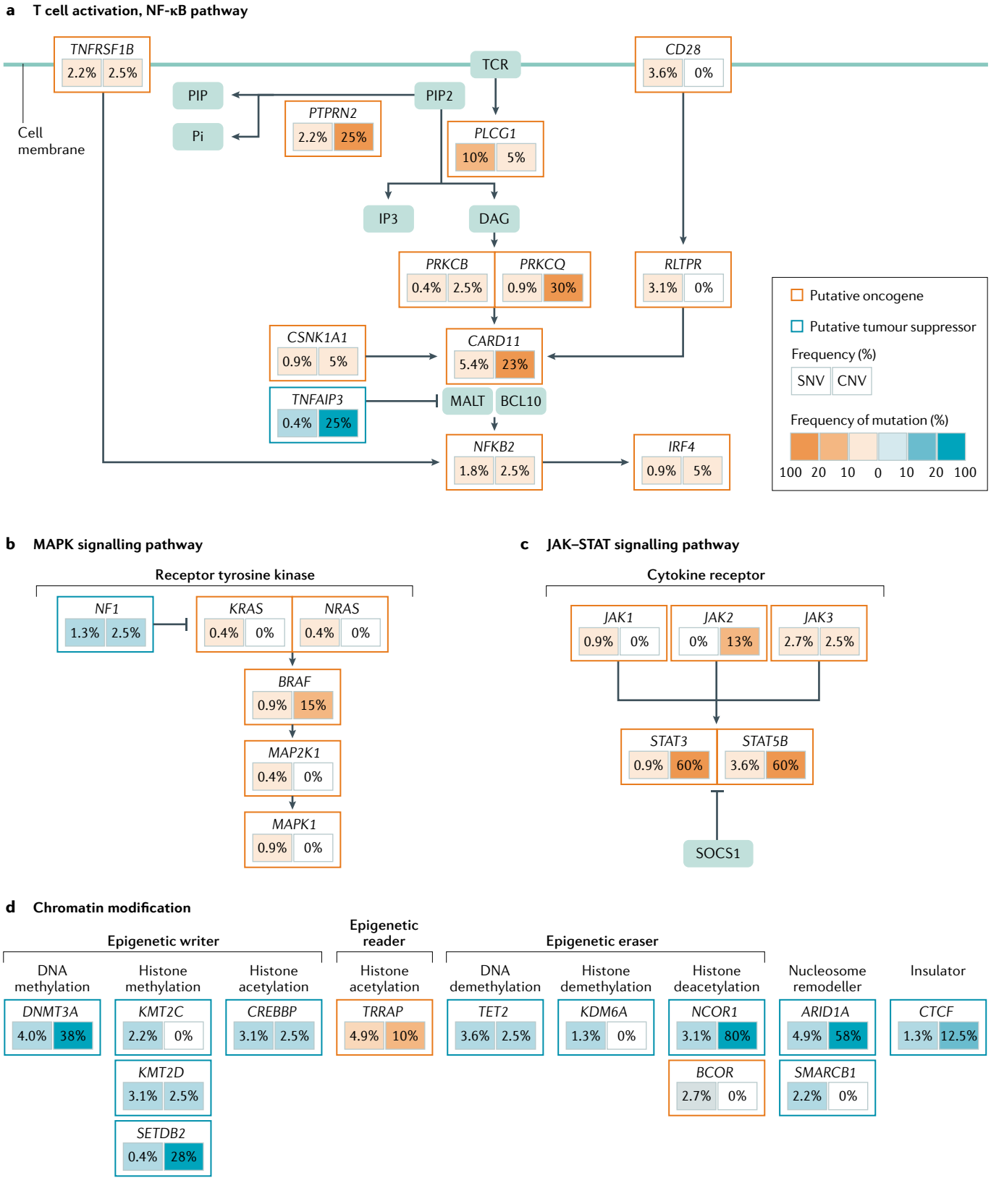

Fig. 2 | **Signalling pathways involved in mycosis fungoides and Sézary syndrome.** Genetic alterations in cutaneous T cell lymphoma can be broadly classified as those that affect TCR–NF-κB (part **a**), MAP kinase (MAPK; part **b**) or JAK–STAT (part **c**) signalling, chromatin modification (part **d**) and cell cycle control and apoptosis. CNV, copy number variant; SNV, single-nucleotide variant; TCR, T cell receptor. Figure adapted with permission from REF.[79], American Society of Hematology.

MEK family members. Activation of this pathway results in the transcription of multiple target genes that impact on proliferation, differentiation, survival, and migration and may also initiate the secretion of cytokines and growth factors. Multiple genetic alterations have been found in MF and SS cells that predispose to activation of the MAPK pathway, including variants in *MAP2K1*, *KRAS*, NRAS, *HNRNPK* and *NF1*. These variants might contribute to support the proliferation and survival of CTCL cells[78,79]. Of note, point mutations in MF and SS are infrequent; compared with other malignancies, only a few patients with MF or SS have activating mutations in *RAS*, *BRAF*, *MAPK1* and *FGFR4* (REFS[48,64,67,77–79]).

Cell cycle control and apoptosis. The cell cycle is orchestrated by cyclins, cyclin-dependent kinases (CDKs) and their substrate proteins and is controlled by CDK inhibitors, including P14/16 and the tumour-suppressor genes *TP53* and *RB*[53]. Inactivation or deletion of the CDKN2A/B locus (encoding the tumour suppressors $p16^{INK4a}$ and $p14^{ARF}$) is the most recurrent finding in MF but is rarely observed in SS[53]. $p16^{INK4a}$ blocks CDK4 and CDK6, whereas $p14^{ARF}$ facilitates cell cycle arrest and/or apoptosis via the p53 pathway[85]. By contrast, the deletion or loss of function of *TP53* (encoding p53, which regulates apoptosis, cell cycle arrest and DNA repair) located on chromosome 17p is highly characteristic for SS[53]. In addition, malignant cells isolated from epidermal clusters (Pautrier microabscesses) in patients with MF contained mutations in the FAS signalling pathway and were resistant to anti-FAS antibody, indicating that loss of Fas function may result in the accumulation of malignant cells[68].

Genome-wide methylation studies found hypermethylation of the promoter region of multiple tumour suppressor genes, including *BCL7a* and *CDKN2A/B*, in patients with CTCL[86,87].

MicroRNA. MiRNA profiling of MF tumours found upregulation of the functionally validated miR-93, miR-155 and miR-17-92 (REF.[76]). miR-155 is overexpressed in haematological and solid cancers and constitutive expression of miR-155 can be involved in the development of malignancies by increasing genomic instability and sustaining the proliferation and survival of malignant cells[88]. The oncogenic role of miR-155 in MF was confirmed by several studies[89] and miR-155 inhibitors are being tested in clinical trials[73,90,91]. The downregulation of miRNA expression was also linked to DNA methylation in MF tumours[75].

Several studies have investigated miRNA expression in SS using different microarray platforms and have consistently reported the upregulation of miR-214 and miR-199a[92,93]. Subsequent studies found that the miR-199a2/214 cluster within the DNM3OS transcript represents the vast majority of aberrantly expressed miRNAs in SS and antagomiR-214 can decrease the number of malignant T cells in a transgenic mouse model spontaneously overexpressing miR-214 (REFS[94,95]).

Chromatin modifications. Extensive alterations in genes encoding enzymes involved with DNA methylation (*DNMT3A* and *TET2*), histone modifications (*KMT2C* and *CREBBP*) and nucleosome remodelling (*ARID1A* and *SMARCB1*) have been found in SS cells[79]. In line with the alterations in enzymes involved in DNA methylation, the DNA methylome of patients with SS is characterized by widespread yet distinct DNA methylation patterns. Studies of individual genes found hypomethylation of *PLS3*, *TWIST1* and *GATA6* and hypermethylation of *SAMHD1* and *RUNX3* (REFS[96–100]). Another study reported consistent methylation of the promoter region of *CMTM2*, *C2orf40*, *G0S2*, *HSPB6*, *PROM1* and *PAM* but not in patients with inflammatory erythroderma, suggesting that these can be used clinically as epigenetic diagnostic markers[101].

Molecular classification. LCT is associated with a high mutation burden and represents an adverse prognostic factor in MF[72]. Early LCT identification could help optimize risk-stratified management approaches. One NGS study reported recurrent *PLCG1* alterations in patients with MF and LCT[68]. Furthermore, recent studies exploring the PD1–PDL1 axis show a possible link between PDL1 structural variants and LCT[102].

CTCL cytokine relevance in pruritus

Pruritus is a major debilitating symptom in CTCL. The underlying mechanism remains unknown. Potential mediators of pruritus in CTCL include histamine release from mast cells, substance P release from sensory nerve endings in skin, nerve growth factor produced by keratinocytes and T_H2 cytokines (IL-4, IL-5, IL-10, IL-13 and IL-31) produced by tumour cells[103]. In addition, serum IL-31 and peripheral blood mononuclear cell IL-31 mRNA have been found to be increased in patients with CTCL and levels correlate with the severity of CTCL-associated pruritus[104–106]. In support of a role of IL-31 in pruritus, in SS, in which severe itching is common, abnormal circulating T cells can produce IL-31 (REFS[106,107]). However, the role of IL-31 and the stimulatory signals underlying IL-31 production remain unclear, although antigens such as *S. aureus* have been associated with increased production of IL-31 (REF.[108]). Drugs targeting IL-31 and its pathways, such as nemolizumab, are in clinical trials in atopic dermatitis, where pruritus also plays a key role (NCT04921345).

Pathophysiology of CD30⁺ LPDs

The molecular mechanisms of cutaneous $CD30^+$ LPDs are largely unknown. Systemic ALCL can be divided into subgroups with distinct molecular and clinical findings characterized by translocations involving *ALK*, *DUSP22*/*IRF4*, *TP63* and *TYK2* (REFS[109,110]). In pcALCL, rearrangements affecting *ALK* are found in ~3% of patients, translocations affecting *DUSP22* are found in ~20% of patients, whereas *TP63* and *TYK2* rearrangements have been described in case reports[109,110].

Frequent large-scale chromosomal imbalances in patients with pcALCL include losses of chromosome 6q (containing *PRDM1*) and chromosome 13 and gains of chromosome 7q (containing *EZH2*)[111]. Single-nucleotide variants presumed as pathogenetic in *JAK1*, *MSC* and *STAT3* have been reported in a few cases[112,113].

No consistent genetic abnormalities are found in lymphomatoid papulosis. Rearrangement of the

Follicular involvement
A hallmark of folliculotropic mycosis fungoides and defines the infiltration of hair follicles through malignant cells.

DUSP22-IRF4 locus was found in a small subset of patients, correlated with the presence of small cerebriform lymphocytes in the epidermis and larger transformed lymphocytes in the dermis[114].

Diagnosis, screening and prevention

General principles

Several diagnostic guidelines for CTCL have been produced by professional societies such as the EORTC, ISCL and NCCN[2,21,115,116]. Although minor differences exist between these guidelines, the general consensus is a comprehensive physical examination, skin biopsy, peripheral blood flow cytometry, radiological imaging and, as indicated, lymph node and bone marrow biopsies. Clinical and pathological features of selected CTCL subtypes are shown in FIG. 3.

The physical examination should evaluate the type of lesion (patch, plaque, tumour or erythroderma), the body areas affected and the extent of the lesions (that is, total body surface area (BSA)). In addition, all peripheral lymph node groups (cervical, clavicular, axillary and inguinal) should be examined along with an abdominal examination for hepatosplenomegaly.

For skin biopsy, punch biopsy is preferred from more than one area to evaluate for deep components, such as follicular involvement and depth of involvement. The evaluation of skin biopsies should preferentially be conducted by a pathologist specialized in cutaneous lymphomas and biopsies should include at least a standard set of immunohistochemical biomarkers and evaluation for clonality (see below). Biopsy of only clearly enlarged nodes is recommended to assess for lymph node involvement or to rule out other conditions. Lymph node biopsy should include assessment of the overall architecture, immunohistochemistry and clonality (see below). Bone marrow biopsy is usually performed only in clinical trials as, in clinical practice, blood involvement is characterized by expansion of malignant cells in the peripheral blood.

TCR clonality in CTCL is typically assessed by polymerase chain reaction (PCR) of *TCRG* (encoding TCRγ)

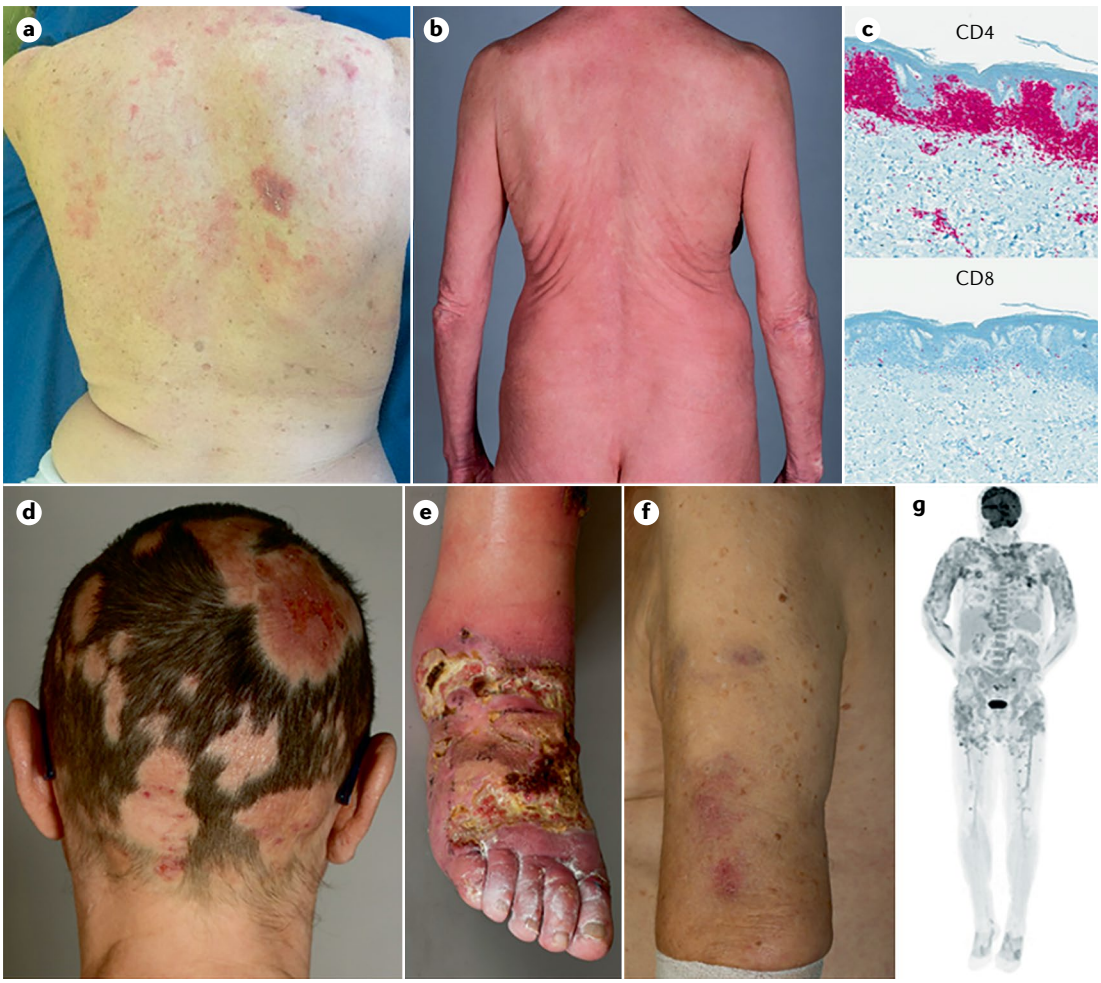

Fig. 3 | **Clinical and pathological presentation of selected cutaneous T cell lymphoma subtypes. a** | Mycosis fungoides in patch and plaque stage. **b** | Erythrodermia in a patient with Sézary syndrome. **c** | Immunohistochemistry of a biopsy of a patient with Sézary syndrome showing predominant $CD4^+$ T cell infiltration with scarce $CD8^+$ T cells. **d** | Areas of alopecia in a patient with folliculotropic mycosis fungoides. **e** | Ulcerated skin lesion in a patient with primary cutaneous anaplastic large-cell lymphoma. **f** | Violaceous lesions in a patient with subcutaneous panniculitis-like T cell lymphoma. **g** | PET–CT scan of a patient with subcutaneous panniculitis-like T cell lymphoma, showing metabolically active subcutaneous lesions in the extremities.

on tissue obtained from skin biopsy. *TCRB* (encoding TCRβ) PCR was found to show at least comparable results to *TCRG* in clonality assessment of early MF lesions[117]; accordingly, the addition of *TCRB* assessment to the CTCL work-up could be considered in the future. Of note, the sensitivity of PCR-based assays may be 50–90% depending on disease stage, type of PCR assay, primer selection and associated reagents[118–126]. The use of standardized primers can improve sensitivity as can using capillary gel electrophoresis rather than polyacrylamide gel-based assays. NGS and high-throughput sequencing may also improve sensitivity, with levels approaching >80% in some studies[123,125]. It is important to note that clonality should always be evaluated in the context of clinical and pathological findings as an isolated finding is not sufficient for the diagnosis of CTCL (with the exception of SS, where clonality is imperative for diagnosis). Indeed, TCR clones can be detected in otherwise healthy elderly patients and in those with chronic benign dermatoses, including pityriasis lichenoides et varioliformis acuta, lichen planus, pigmented purpura, lichen sclerosis and reactive pseudolymphomas[127–131].

Laboratory assessment, radiological examination and peripheral flow cytometry are also used for the diagnosis of CTCL. Routine laboratory studies comprise a complete blood count, LDH and complete metabolic profile. Radiological evaluation comprises whole-body (neck to upper thighs) CT or PET–CT, depending on institutional guidelines. Peripheral flow cytometry should comprise at least a standard set of immunohistochemical biomarkers (see below), evaluation for a clonal population by PCR analysis and an absolute number of atypical cell count. CTCL staging is conducted according to the tumour-node-metastasis-blood (TNMB) classification (Supplementary Table 3[2,132]). Of note, separate staging criteria are available for MF, SS and non-MF CTCLs.

Mycosis fungoides

Clinical features. Patients with MF may have a wide variety of clinical presentations ranging from patches, papules and plaques to tumours and, rarely, erythrodermic MF (without or with minimal blood involvement, not meeting criteria for leukaemia) (TABLE 1). MF lesions most commonly present as erythematous patches with fine scaling (loss of the upper layer of the epidermis in small flakes) and epidermal atrophy[16,133]. Patches may be hypopigmented and/or hyperpigmented and often occur in non-sun-exposed areas, although presentation in any skin area is possible. Lesions are often pruritic (itchy). Of note, BSA may not always reflect the severity of MF as the presence of few tumours may signify an inferior prognosis compared with patches and plaques taking up the same BSA. The Modified Severity Weighted Assessment Tool (mSWAT) was created to overcome these shortcomings (Supplementary Table 4) and was found to better correlate with prognosis[116,134,135]. The mSWAT involves multiplying the measured BSA of CTCL skin lesions by a factor based on their respective clinical morphology (by 1 for patches, by 2 for plaques and by 4 for tumours). As the clinical presentation of MF can change over years, routine monitoring, set according to the disease stage and activity (new lesions occurring, stable or after achieving complete clinical response), is crucial following diagnosis.

Inflamed and excoriated skin is associated with localized or systemic infections. Late-stage MF is associated with declining immunocompetence, resulting in severe life-threatening infections and a high incidence of secondary malignancies[136]. The latter increase is not attributable to prior treatment with carcinogenic agents alone. Skin infection vigilance is extremely important in the overall management of patients with CTCL and bacterial decolonization is exceptionally important in those with advanced disease[137–140].

Laboratory evaluation. Diagnosing MF requires a clinical and pathological correlation as the use of histopathology alone, without clinical correlation of further molecular tests such as TCR rearrangement, has a 40% false-negative and a 44% false-positive rate[141]. The false negatives result in delay in diagnosis for years or even decades[142]. The PROCLIPI database found a diagnostic delay in 85.6% of patients (with a median duration of 36 months), highlighting the difficulties in accurate diagnosis[15]. Owing to the tendency for MF to mimic benign dermatoses clinically and pathologically, multiple skin biopsies may be necessary over time[128–130,134,143,144]. In addition, supplementary biopsies are recommended in all patients with confirmed MF with clinical suspicion for LCT or folliculotropism to ascertain if lesions may have acquired more aggressive features.

The standard initial immunohistochemical assessment for individuals with suspected MF should include T cell markers, for example, CD2, CD3, CD4, CD5 and CD8, in addition to T cell maturation markers such as CD7 and CD30 (REFS[130,145,146]). Identifying $CD4^+$ or $CD8^+$ T cell subtypes can narrow the differential diagnosis as can aberrancy in the expression of certain T cell antigens; for example, in MF, T cells frequently have diminished expression of CD7 and sometimes of CD2 and CD5, with retention of CD3 and CD4, in addition to a decreased number of $CD8^+$ cells[130,147]. Indeed, detecting a population of $CD4^+CD2^-CD5^-$ and/or $CD4^+CD7^-$ cells with a CD4 to CD8 ratio of >6:1 in a lesion had a 90% specificity for MF in retrospective studies[130,145,146,148,149]. To aid assessment of histologically uncertain cases and to inform prognosis, immunohistochemical assessment of CD25, CD56, TIA1, granzyme B, CXCL13, ICOS and PD1 are also recommended[130,145,146]. These markers are important as some may help in prognostication ($CD8^+CD56^+$, TIA1 and granzyme B) and others may be considered as targets for therapies (PD1 and PDL1, denileukin diftitox (CD25)); however, so far, apart from CD30 in treatment with brentuximab vedotin, there are no universally accepted markers to guide treatment choices. TCR clonality should also be evaluated as part of the diagnostic work-up for MF.

A substantial reduction in the number of circulating $CD8^+$ T cells (<600/ml) portends a poorer prognosis in MF[150,151], whereas enlarged lymphocytes (especially a size greater than four times that of normal lymphocytes) should be assessed for LCT in the skin biopsy[145].

Lichenification
Secondary skin lesion, defined as a thickening of the skin with exaggerated skin lines and sometimes hyperpigmentation.

Flow cytometry is recommended at initial diagnosis of MF as well as at disease progression to establish peripheral clonality and the presence of neoplastic cells[116,152–155].

Imaging. Imaging is recommended for any patient with suspected MF and clinically palpable adenopathy as well as in those with stage T3 disease, LCT, folliculotropic MF or abnormal haematological results[135]. CT or PET–CT including at least the neck, chest, abdomen and pelvis are recommended (Supplementary Table 1).

Sézary syndrome

Clinical features. SS usually presents as a triad of pruritic erythroderma (involvement of >80% of BSA), generalized lymphadenopathy and clonally related neoplastic T cells in the skin, lymph nodes and peripheral blood. Pruritic erythroderma presents with exfoliation, oedema and lichenification. The clinical features of SS can be difficult to distinguish from those of erythrodermic inflammatory dermatoses; therefore, assessment for peripheral blood involvement is the gold standard for diagnosis. As patients with SS have an increased risk for relapse, mostly cutaneous infections, this should also be assessed at the time of diagnosis and during each clinical visit.

Laboratory evaluation. In addition to routine laboratory assessments, flow cytometry must be sent to confirm clonality in the peripheral blood and assess the phenotype of potential neoplastic cells. Malignant SS cells are clonal and often have a $CD3^+CD4^+$ and $CD8^-$ phenotype. They also commonly lose expression of CD7 and/or CD26 (REFS[155–157]). In fact, in peripheral blood, a loss of CD26 in >80% of $CD4^+$ T cells has a sensitivity of 83% for SS, whereas loss of CD7 in >40% of $CD4^+$ T cells has a sensitivity of 98%, with both metrics achieving 100% specificity[158].

KIRDL2 (CD158k) is a natural killer cell marker recently found to have a sensitivity of 88.6% and specificity of 96.3% in detecting SS cells and may be useful in supporting a diagnosis[159]. In addition, numerous driver genes have been identified that may provide future opportunities for further diagnostic specificity (see 'Genetic and molecular alterations' above). For the diagnosis and staging of SS, WHO-EORTC and ISCL guidelines require both confirmation of a TCR clone in the blood or skin as well as the following findings: an absolute Sézary cell count of >1,000/μl or an expanded $CD4^+$ T cell population with a CD4 to CD8 ratio of ≥10:1 and either ≥40% $CD4^+CD7^-$ cells or ≥30% $CD4^+CD26^-$ cells in peripheral blood (Supplementary Table 1). As the clinical and histological presentation of SS is not specific for SS, flow cytometry and identification of clonally related neoplastic T cell populations are crucial for diagnosis.

$CD30^+$ LPDs

Clinical features. LyP typically presents as recurrent, erythematous dome-shaped papules occurring in cropped or generalized eruptions on the trunk or proximal extremities. The lesions often spontaneously regress after a few weeks, during which time they may involute, ulcerate and possibly scar. LyP typically has a chronic course. In addition, LyP has a 10-year disease-specific survival of nearly 100%, although ~20% of patients may develop a second lymphoid malignancy such as MF, pcALCL or Hodgkin lymphoma and, therefore, routine monitoring is required[160]. By contrast, pcALCL typically presents as solitary or grouped nodules or tumours. pcALCL can occur anywhere on the body with brownish to violaceous nodules or tumours, ranging in number from solitary (most commonly) to numerous with generalized involvement. Similar to LyP, there is a chance of spontaneous regression with pcALCL, but cutaneous recurrence is common[161]. Extracutaneous dissemination of pcALCL is rare and occurs in only 10% of cases, wherein the disease will typically spread to regional lymph nodes[162]. Although pcALCL generally has an excellent prognosis, advanced-stage pcALCL (at least T3) has a 5-year survival of 77%[163] and therefore treatment rather than observatory monitoring is indicated.

Biopsy and laboratory evaluation. By definition, $CD30^+$ LPDs present with $CD30^+$ T cells detectable using immunohistochemistry. As subtypes of MF, LyP and pcALCL may all present with $CD30^+$ T cell infiltration, further immunohistochemical labelling, such as cytotoxic markers TIA1 and granzyme B, both of which can be expressed in pcALCL and LyP, and clinicopathological correlation are key to a correct diagnosis. LyP and pcALCL do not show blood involvement; however, patients with these disorders should undergo regular monitoring (comprising complete blood count, a comprehensive metabolic panel and LDH) owing to their increased risk of second lymphoproliferative malignancies.

For a diagnosis of pcALCL, histopathologically, at least 75% of the neoplastic cells should express CD30 in tissue from lesion biopsy[164]. Most neoplastic cells in pcALCL are $CD4^+$[165] but, in rare cases, the neoplastic cells are $CD8^+CD30^+$[166]. In contrast to systemic anaplastic large-cell lymphoma, pcALCL T cells are negative for CD15 and epithelial membrane antigen[162,167]. Importantly, pcALCL usually does not express anaplastic lymphoma kinase 1 (ALK1) or the t(2;5) chromosomal translocation found in nodal ALCL[168].

The three main histological subtypes of LyP are A, B and C. The infiltrate is usually wedge-shaped with ulcer formation. The large, atypical cells of type A LyP resemble Reed–Sternberg cells. These cells are surrounded by neutrophils and eosinophils. Type B cells resemble MF, with lichenoid lymphocytic infiltration of cells with cerebriform nuclei and some epidermotropism[169]. The neoplastic cells in type C LyP resemble ALCL, with sheets of large $CD30^+$ cells in the infiltrate[169]. The histological distinction between LyP and other histologically similar lymphoproliferative conditions may be difficult and clinical correlation is required[169]. About 10% of patients with LyP develop another lymphoma, often MF. In addition, a higher incidence of lymphoid and non-lymphoid malignancies is observed in patients with LyP[170–172]. In some cases, the distinction between LyP and pcALCL cannot be made because of discrepancies between clinical features and histological appearance. These cases are referred to as borderline lesions

and their classification should consider their clinical behaviour and appearance.

Rare aggressive CTCLs

Other CD30⁻ non-MF/SS subtypes of CTCL are rare (TABLE 1). These disorders comprise less than 1% of total CTCL diagnoses but may be highly aggressive and therefore important to consider in any CTCL work-up. The workflow for diagnosis of these subtypes is generally consistent with that described above. Staging occurs via ISCL/EORTC TNM guidelines for non-MF/SS subtypes[173].

Management

Basic principles

Treatment strategies for CTCL vary widely from 'wait-and-see' approaches, skin-directed therapies (SDTs; namely, topical steroids, chlormethine gel, phototherapy and local radiotherapy) and systemic therapies. Systemic therapies include immune-modifiers (interferon, extracorporeal photopheresis (ECP) wherein patient blood is extracted and separated leucocytes undergo irradiation in the presence of a photosensitizing agent, followed by reinfusion into the patient), retinoids, low-dose methotrexate, total-skin radiotherapy, monochemotherapy (gemcitabine, pegylated liposomal doxorubicin), multi-agent chemotherapy (CHOP/CHOEP regimens) and allogeneic haematopoietic stem cell transplantation (HSCT). Treatment choice depends on disease subtype, patient age, the presence of comorbidities, disease extension, and staging and treatment availability[21,174] (BOX 1; FIG. 4). A multidisciplinary group of different specialties (dermatologists, pathologists, onco-haematologists and radiotherapists) is required particularly in advanced stages and aggressive subtypes.

Box 1 | **The cornerstones of CTCL management**

To treat or wait-and-see

In indolent cases, in the presence of limited skin involvement, for example, early-stage T1a mycosis fungoides (MF) or lymphomatoid papulosis, the decision can be 'wait-and-see' also based on the site of the lesions, disease evolution, age of the patient and symptoms associated. A wait-and-see approach has not been demonstrated to be associated with a worsening of disease course and survival.

Treat what you see

There is no evidence that aggressive treatments could modify the disease course and survival when given in the early stage of disease; therefore, the indication is to tailor the treatment focusing on disease extension in the skin and extracutaneous sites. Thus, accurate staging procedures should be developed according to the disease entity to allow the correct management of the patient.

SDTs versus systemic therapies

Skin-directed therapies (SDTs) represent very active and well-tolerated treatment options that need to be performed in all cases whenever indicated, alone and before systemic therapies. In advanced stages or aggressive subtypes, SDTs can be given in association with systemic therapies to improve the response or to better manage localized cutaneous lesions.

Up-grade and down-grade of treatments

The majority of cutaneous T cell lymphoma (CTCL) (in particular MF) show an indolent disease course spanning over decades; therefore, it is important to carefully evaluate treatment options to preserve potentially active treatments when they are really needed. In progressive cases, an up-grade of treatments needs to be conducted (that is, in MF, from phototherapy to treat patches and plaques to interferons, retinoids and total skin electron therapy, up to monoclonal antibodies and chemotherapy for treatment in the tumour stage); however, in case of response, a down-grade of treatments is warranted (that is, phototherapy to treat residual patches after response).

Re-challenge/re-treatment

In contrast to what occurs in nodal lymphomas, in CTCLs, there is the possibility of re-challenge (that is, the use of a treatments already performed in the clinical history of the patient after other approaches) or simply re-treatment (the use of the same last treatment performed) (FIG. 3).

Quality of life

As these diseases primarily involve the skin and have a long duration and, in the majority of patients, skin represents the only site of involvement, the impact of cutaneous lesions on visible parts of the body is fundamental for the patient and implies that the maintenance and preservation of quality of life is a cornerstone in the treatment strategy.

Mycosis fungoides

International guidelines for the treatment of MF (EORTC 2017, ESMO 2018, BAD2018 and NCCN) divide treatments into first-line options and treatments to be considered after but do not recommend any particular order of individual therapies owing to lack of evidence from clinical trials[16,59,175,176] (FIG. 5; TABLE 2).

The distinct features of early versus advanced MF drives the treatment strategy. In early MF, the decision to treat relies on patient age, lesion site, symptoms and disease kinetics. The aim of therapy is to substantially improve clinical and health-related QOL (HRQOL), rather than the complete eradication of skin lesions. Real-world data from patients with early-stage MF[13] showed that the SDTs with topical steroids and phototherapy were the first-line therapy in 81.6% of patients, whereas the wait-and-see approach was used in 7.3% of patients. Other patients (11.1%) received first-line retinoids, IFN or combination with phototherapy, most of whom had plaque stage or folliculotropic MF[13]. Of note, the response rate to first-line SDTs (73%) is superior to that of systemic treatments (57%), meaning that it is conceivable to start with an SDT even in patients with worse prognostic factors[18,25].

Advanced MF has a lack of effective treatments, as available treatment options have a low response rate, and a short duration of response. Moreover, there is a lack of effective maintenance treatments, and the available treatments should be assessed for the relevance of adverse effects in elderly patients and severe HRQOL impairment[177]. A wide range of treatments for advanced MF was reported in one retrospective international study, with more than 25 different first-line treatments and 38.9% of patients receiving 4 or more therapies[28]. Stage IIB disease was most frequently treated by SDTs, bexarotene and gemcitabine, patients with erythrodermic MF or SS were most frequently treated with ECP, and patients with stage IVA2 were most frequently treated by polychemotherapy[28]. Multivariate analysis identified age and stage as prognostic factors and monochemotherapy or polychemotherapy as first-line treatment were associated with an increased risk of death and/or a change of therapy, suggesting that chemotherapy should be used only after failure or relapse of previous approaches in those with aggressive disease and where other options are not indicated[28]. However, the retrospective nature of this analysis poses a risk of selection bias and should be interpreted with caution.

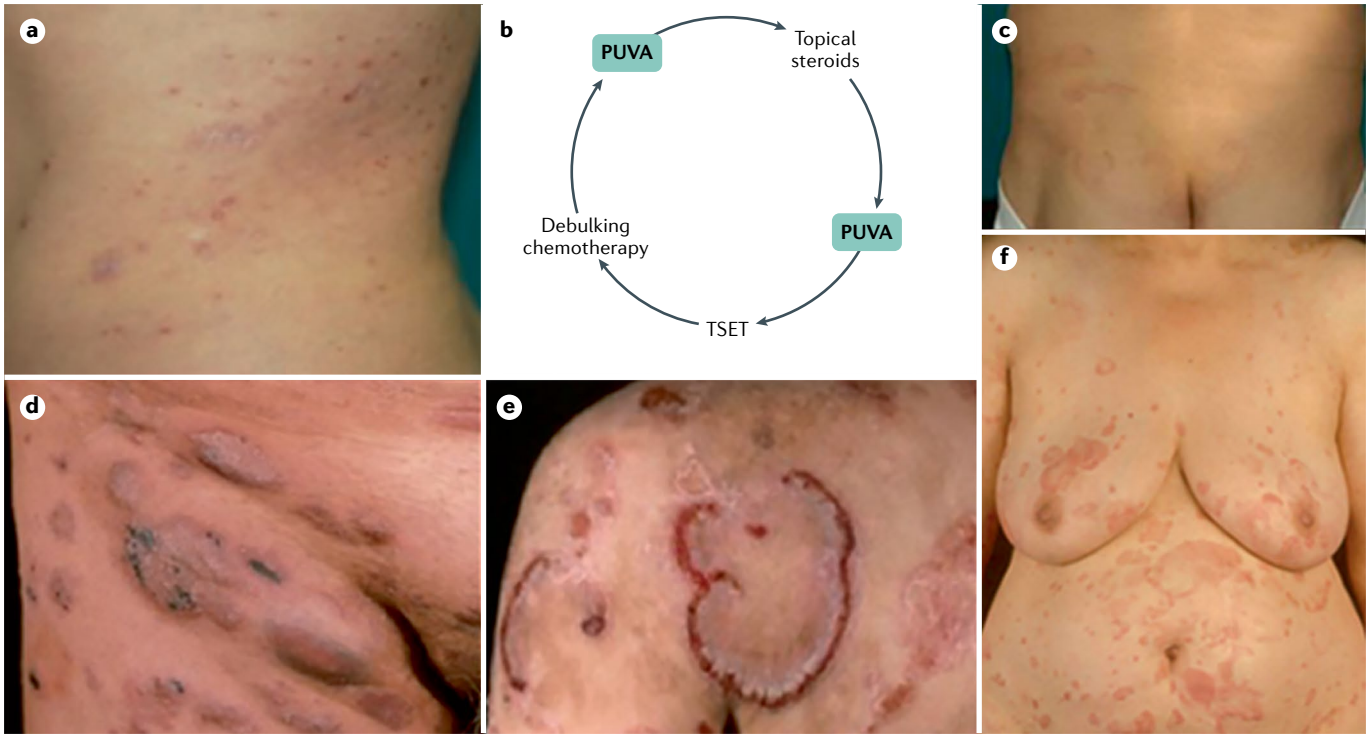

Fig. 4 | **The re-challenge paradigm of mycosis fungoides therapy. a** | Mycosis fungoides (MF) presenting as patch and solitary papules. **b** | Re-challenge paradigm of MF therapy. **c** | MF in patch stage. **d** | MF in tumour stage. **e** | Ulcerated MF patches. **f** | Widespread MF patches and plaques. Re-challenge (that is, the use of treatments already performed in the clinical history of the patient after other approaches) or simply re-treatment (the use of the same last treatment performed) can be used for cutaneous T cell lymphoma when deemed suitable. PUVA, psoralen plus UVA; TSET, total skin electron therapy.

Two recent multicenter randomized trials led to the approval of two new drugs for CTCL: brentuximab and mogamulizumab. The ALCANZA trial enrolled 128 pre-treated patients with CD30$^+$ MF or pcALCL to receive brentuximab, methotrexate or bexarotene[178]. This study found a higher ORR4 (that is, overall response lasting for at least 4 months) in the brentuximab group (56.3% vs 12.5%), with a higher response in a subgroup analysis of those with tumour-stage MF. The other multicentre registrative study was the phase III MAVORIC, which compared the anti-CCR4 treatment mogamulizumab with vorinostat[179]. In this study, progression-free survival was significantly higher in the mogamulizumab group compared with the vorinostat group, with better responses in patients with SS (37%) and patients developing a response in the blood (68%) associated with a significant duration (median 25.5 months in the blood and 20.6 months in the skin)[179]. In a post hoc analysis, patients with a B1 and B2 blood-score responded better than those with B0 scores in terms of cutaneous mSWAT[180]. A third compound, topical chemotherapy chlormethine gel, has also been approved by the EMA for the treatment of early phases of disease or, in those with advanced disease, in combination with systemic therapies[181].

Sézary syndrome

Treatment of SS is challenging owing to the aggressive disease course, risk of relapsing infections (which can be increased by chemotherapy and immunosuppressive regimens), itching and severe QOL impairment[2,59,175,176,182]. The recommendations for the treatment of SS include ECP as first-line therapy, where possible, in patients with a low tumour burden in the blood and as maintenance therapy after remission with more aggressive therapies[183], alone or in combination with other agents such as bexarotene or other retinoids, IFN, and TSET. The recently approved drug mogamulizumab was demonstrated to induce significant responses particularly in patients with SS and in the blood compartment[179] and can thus be used as a debulking agent and as a bridge towards transplantation. Other therapies for SS include mogamulizumab (which can induce a high response rate particularly in the blood) and chemotherapy (namely, gemcitabine and liposomal doxorubicin). Multi-agent chemotherapy treatments do not lead to a significant increase in response rate compared with monochemotherapy, resulting instead in burden by greater systemic toxicity[16,59,175,176]. Allogeneic HSCT, albeit in selected patients, is the only available treatment with a truly curative intent[184].

CD30$^+$ LPDs

Management of indolent CD30$^+$ LPDs is highly dependent on the spread of the lesions. In those with solitary and infrequent LyP, a wait-and-see approach, surgery or radiotherapy can be used[185]. In those with widespread or recurrent LyP lesions, weekly low-dose methotrexate achieves responses in up to 100% with complete response in 34%; however, relapses occur

in over half of the patients and methotrexate does not seem to reduce the recurrence rate[185]. Brentuximab, an antibody–drug conjugate, composed of CD30-antibody linked to an anti-tubulin agent monomethyl auristatin E, showed an overall response rate of 100% and complete response of 58% in refractory LyP[185].

Similar to LyP, surgery or radiotherapy are the treatments of choice for those with solitary pcALCL lesions. Radiotherapy with a 30–40 Gy dose can achieve responses in up to 95% of patients[2,16,59,175,176]. Although responses can be durable, relapses are common[185,186]. In those with widespread or recurrent disease, systemic treatment is recommended. As with LyP, low-dose weekly methotrexate is a safe and effective strategy for pcALCL; however, brentuximab demonstrated a 75% overall response rate and a 31% complete response rate, compared with 33% overall response rate and 7% complete response rate for either methotrexate or bexarotene[178].

Rare aggressive CTCLs

Other rare CTCL subtypes, such as primary cutaneous aggressive epidermotropic cytotoxic $CD8^+$ T cell lymphoma or primary cutaneous γδ T cell lymphoma, are aggressive and have a poor prognosis[16]. Interdisciplinary approaches with dermato-oncologists, haematologists and radiation oncologists are crucial to achieve best outcomes in these patients. Multi-agent chemotherapy, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and CHOP-like regimens are the preferred first-line treatments and, in eligible patients, such as young patients with aggressive advanced relapsed CTCL without comorbidities and a good performance status (ECOG), allogeneic HSCT should be considered. However, even with treatment, most cases are fatal[2,187,188]. In selected patients, high-throughput molecular analysis with possible identification of molecular targets, such as CD30 or PD1, for off-label treatment attempts should be discussed. Palliation using radiotherapy of single lesions can be applied[189].

Allogeneic haematopoietic stem cell transplantation

Allogeneic HSCT is a potentially curative treatment for advanced-stage MF and SS. In one series of 113 patients, allogeneic HSCT induced a sustained clinical benefit in a significant percentage of patients, with a 5-year overall survival of 38% and 5-year progression-free survival of 26%[190]. Adverse prognostic factors were advanced-phase disease, refractory, relapsing or progressive disease after repeated therapy lines, and an unrelated donor[190]. Similar results were reported in other studies[191], with a 5-year progression-free survival of 17% and overall survival of 32% in 129 patients with relapsed or refractory MF or SS and a 2-year progression-free survival of 31% and overall survival of 57% in 37 pretreated patients in another study[192]. Patients with MF as well as SS were suggested to present long-term outcome benefit[191].

Owing to the high post-transplant relapse rate and the adverse effects of the procedure, allogeneic HSCT is a treatment option in young patients with aggressive advanced relapsed CTCL without comorbidities. Open challenges are the timing of allogeneic HSCT in the disease course, the early identification of best candidates and the relevance of disease control before transplantation[184].

New drugs and trials

As frequent targetable driver mutations in CTCL have not been identified, most of the new systemic therapeutic agents under investigation are monoclonal antibodies, histone deacetylase inhibitors, proteasome inhibitors, immune-checkpoint inhibitors or chimeric antigen T cell receptor strategies, administered alone or in combination (TABLE 3)[193–195]. Due to the rarity of the disease, randomized clinical trials are still uncommon in CTCL[+]; therefore, homogeneity among trials is extremely important to allow consolidation or comparison of trial data on specific treatments. Accordingly, the ISCL has proposed a consensus statement for clinical endpoints and response criteria in MF and SS[196] and EORTC proposed new flow cytometry-based criteria

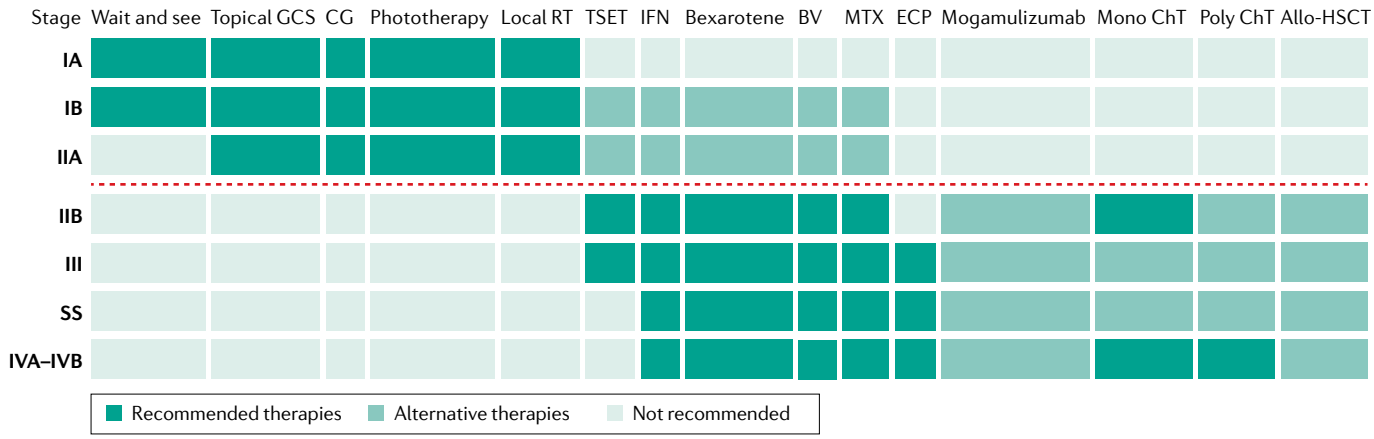

Fig. 5 | **Recommendations for MF/SS treatment, based on EORTC guidelines.** The dark green boxes identify treatments recommended for the respective stage; lighter green boxes identify subsequent and alternative choice; and grey boxes represent treatment options that are not generally recommended. The red bar separates early vs advanced-stage mycosis fungoides (MF). Allo-HSCT, allogeneic haematopoietic stem cell transplantation; BV, brentuximab vedotin (in cases with CD30 expression, approved for patients with relapsed or refractory disease who received at least one prior systemic therapy); CG, chlormethine gel; ChT, chemotherapy; ECP, extracorporeal photopheresis; GCS, glucocorticosteroids; IFN, interferon; MTX, methotrexate; RT, radiotherapy; SS, Sézary syndrome; TSET, total skin electron therapy. Mogamulizumab is approved for patients with relapsed or refractory disease who received at least one prior systemic therapy.

Table 2 | **Summary of MF treatment results from the main studies**

Drug	Phase	No of patients	Inclusion	Response rate	Disease outcome	Drug approval
Narrow-band UVB	Review[236]	251	IA–IIA	87.6%; CR 62.2	35% at average follow-up of 77 weeks	Not applicable
	Review[237]	>300	IA–IIA	54–90% (median 87%)	29–80% relapses	Not applicable
PUVA	Review[236]	527	IA–IIA	90.9%; CR 73.8	20–100% relapse	Not applicable
	Review[237]	400	IA–IIA	65–85% superior to UVB in plaques	40–50% relapses	Not applicable
Low-dose TSET	Pooled three phase II trials[238]	33	IB–IIIA	88%; CR 27%	Median duration of clinical benefit: 70.7 weeks	Not applicable
PUVA plus IFNα2a vs acitretin plus IFNα2a	Randomized clinical trial[239]	98	IA–IIB (82 patients evaluable)	CR 70% in PUVA plus IFNα2a vs 38% in IFNα2a plus acitretin	Shorter time to CR in PUVA plus IFNα2a	FDA and EMA
Bexarotene	Phases II–III[240]	58	IA–IIA	54–67%; CR 7–27%	Duration of response up to 64.7 weeks	FDA and EMA
Bexarotene	Phases II–III[201]	94	IIB–IV	45–55%; CR 2–13%	Duration of response 42–55 weeks	FDA and EMA
Bexarotene/MTX	Phase III randomized control arm (ALCANZA trial)[29]	64	$CD30^+$ MF or pcALCL	12.5% (ORR4)	mPFS 3.5 months	FDA and EMA
Bexarotene plus PUVA	Phase III randomized vs PUVA alone[241]	93	IB–IIA	77% in combination vs 71% in PUVA alone; trend towards fewer PUVA sessions to CR in the combination (median 22 sessions)	mDOR 9.7 months for PUVA vs 5.8 months for the combination	Combination not approved
Brentuximab vedotin	Phase III randomized vs bexarotene or MTX (ALCANZA trial)[178]	64	$CD30^+$ MF or pcALCL	56.3% vs 12.5% (ORR4); MF IIB: 63%; $CD30^+$ anaplastic: 75%	mPFS: 16.7 months vs 3.5 months	FDA and EMA
Pegylated liposomal doxorubicin	Prospective multicentre phase II[242]	49	IIB, IVA, IVB	40.8%; CR 6.1%	mTTP: 7.43 months; mDOR: 6 months	FDA and EMA
Gemcitabine	Phase II multicentre[243]	32	IB–IV MF/SS, PTCLU	75%; CR 2%	Median duration of CR was 10 months (range, 4–22 months)	Not approved
ECP	Review[183]	407	SS/erythrodermic MF	Median response rate 63% (range 31–86%); median CR 20% (0–62%)	mDOR 22 months (up to 11 years)	Not applicable
Mogamulizumab	Phase III randomized vs vorinostat[179]	372	MF/SS stage IB–IV with at least one systemic therapy	28% vs 5%; response rate in SS 37%; 68% in the blood	mPFS 7.7 months vs 3.1 months; $P<0.0001$	FDA and EMA
Vorinostat	Open-label phase IIb trial[244]	74	IB–IVA MF and SS, pretreated with at least two lines, one with bexarotene	29.7% (32% pruritus relief)	mDOR NR (>185 days); mTTP 4.9 months, 9.8 months stage IIB or higher responders	FDA
Romidepsin	Pivotal, single-arm, open-label, phase II[245]	96	Stage IB–IVA pretreated	34%, 38% IIB–IV pruritus relief 43%	mDOR 15 months	FDA
Mechlorethamine gel	Randomized, observer-blinded, trial mechlorethamine gel vs ointment[181]	260	IA–IIA	Gel vs ointment 58.5% vs 47.7% (non-inferiority)	90% of responses maintained for at least 10 months, no treatment difference	FDA and EMA

CR, complete response; ECP, extracorporeal photopheresis; mDOR, median duration of response; MF, mycosis fungoides; mPFS, median progression-free survival; mTTP, median time to progression; MTX, methotrexate; NR, not reported; ORR4, overall response lasting for at least 4 months; pcALCL, primary cutaneous anaplastic large-cell lymphoma; PTCLU, peripheral T cell lymphoma unspecified; PUVA, psoralen plus UVA; SS, Sézary syndrome; TSET, total skin electron therapy.

for responses in the blood, which still need prospective verification[158].

Given that, with the exception of curative-indent allogeneic HSCT, available treatments lead to incomplete responses and disease palliation, time to next treatment has been suggested as a meaningful endpoint for CTCL trials. Time to next treatment represents the interval from the initiation of one treatment to that of the next line of therapy and can be used as a surrogate for the duration of clinical benefit[197]. Furthermore, the evaluation of QOL could be incorporated as an endpoint in clinical trials.

As the tumour microenvironment and the host immune response (in particular with new immune-checkpoint inhibitors) is modulated by the tumour itself and can contribute to the different disease course, future treatment approaches should target not only the tumour cells but also the tumour microevnironment. Moreover, the finding of multiple neoplastic circulating clones using whole-exome sequencing in early-stage MF and which continuously replenish the skin lesions increasing their heterogeneity with a tumour seeding mechanism, could constitute the rationale for the clinical use of systemic treatments even in the early stage of disease. Circulating neoplastic clones could represent a potential biomarker and a promising new target for therapy[198].

Adverse effects and QOL

Short-term and long-term toxicity should always be considered when planning treatment. Of note, SDTs are related to local, mostly transient, manageable adverse events[199]. When choosing a systemic therapy, comorbidities (for example, interferon or liposomal doxorubicin should be avoided in patients with cardiovascular diseases) and treatment availability should be considered[200]. Patient education and regular follow-up allows the

Table 3 | **Summary of main new drugs investigated in CTCL**

Agent	Mechanism of action	Route of administration	Ongoing trials
TLR7 and TLR8 agonist (resiquimod)	↑ IFNα production by pDCs and increased TH1 response	Topical	Phase II – NCT03292406
SGX301 (a synthetic hypericin, 'FLASH')	Visible light-induced phototherapy with synthetic hypericin	Topical	Phase III – NCT02448381
Microneedle array – doxorubicin (MNA-D)	Direct tumour cell killing through DNA damage	Topical	Phase I – NCT02192021
Talimogene laherparepvec	Oncolysis, induction of host antitumour immune responses	il	Phase I – NCT03458117, Phase II – NCT02978625
Anti-CD47-ab (TTI-621)	ADCP	il, iv	Phase I – NCT02890368, Phase II – NCT03763149
Anti-KID3DL2-ab (IPH4102, latucamab)	ADCC and ADCP	iv	Phase II – NCT03902184
Recombinant cytotoxic fusion protein comprising DT and hIL-2 (E7777)	Cell protein synthesis inhibition	il	Phase III – NTC10871727
MRG-106 (cobomarsen)	Inhibits miR-155 and T cell proliferation	il, iv	Phase I – NCT02580552 (il), Phase II – NCT03713320 (iv)
Anti-PDL1-ab (atezolizumab)	Immune-checkpoint inhibition	iv	Phase II – NCT03357224
Autologous CAR T cells (ATLCAR.CD30.CCR4/ATLCAR.CD30)	Cell-therapy through CD30-directed and CCR4-directed allogenous CAR T cells	iv	Phase I – NCT03602157
Anti-PD1 (sintilimab) and HDACi (chidamide)	Immune-checkpoint inhibition; histone deacetylase enzyme inhibition	iv or oral	Phase II – NCT04296786
AFM13 (CD30/CD16A bispecific ab)	Redirects NK cells to CD30-expressing tumour cells	iv	Phase II – NCT04101331
PI3K inhibitor (duvelisib) with HDACi (romidepsin) or proteasome inhibitor (bortezomib)	PI3K inhibitor: cell cycle regulation, apoptosis, DNA repair, senescence, angiogenesis and cell metabolism	oral, iv, sc	Phase I – NCT02783625
PI3K inhibitor (duvelisib) and anti-PD1-ab (nivolumab)	Cell cycle regulation, apoptosis, DNA repair, senescence, angiogenesis and cell metabolism; immune-checkpoint inhibition	oral, iv	Phase I – NCT04652960
CPI-818 (IL-2-ITKi)	Inhibition of TCR signal transduction	oral	Phase I – NCT03952078
Proteasome inhibitor (bortezomib) and dexamethasone	Induces apoptosis; may inhibit malignant cell migration by suppressing TGFβ1 and IL-10 through NF-κB inhibition	iv	Phase II – NCT03487133
exoIL-12, engineered exosome therapy	exoIL-12; analysis of skin punch biopsies bordering the subcutaneous injection site of exoIL-12 revealed local retention of immunologically detectable IL-12 at the injection site	il	Placebo-controlled, double-blind; phase I trial complete; phase II planned

ADCC, antibody-dependent cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CAR T, chimeric antigen receptor T; HDACi, histone deacetylase inhibitor; il, intralesional; iv, intravenous; NK, natural killer; PI3K, phosphatidylinositol 3-kinase; sc, subcutaneous; TCR, T cell receptor; T_H1, type 1 helper; pDCs, plasmacytoid dendritic cells.

early recognition of adverse effects (such as central hypothyroidism with bexarotene[201]) and management.

Quality of life

CTCL has a multidimensional effect on patient QOL due to cutaneous symptoms and impairment of emotional well-being[12]. An improvement in HRQOL has been found in both patients with responsive and stable disease, further supporting less aggressive therapies in some cases[13]. QOL reductions are more frequent and pronounced in patients with MF or SS compared with control populations with general dermatology concerns, with largest decrements in social functioning and physical and emotional health[202]. Pruritus is one of the major factors contributing to poor HRQOL in patients with CTCL but most commonly in patients with SS[203]. In addition, disease entity, stage and sociodemographic factors were associated with a reduction in QOL in those with advanced disease[204]. Significant differences were found between patients with early or advanced MF or SS by the Skindex-29 tool, which found that patients with advanced MF or SS are compromised in their daily life routine procedures[204]. Advanced age, worse disease stage, alopecia and non-university education have an incremental effect on QOL, and social deprivation was frequently observed[204].

No specific validated QOL questionnaire for CTCL is available; therefore, several generic, dermatology-specific and/or oncology-specific QOL instruments are used in this patient population. Whether the existing HRQOL or skin-related QOL instruments effectively meet the specific problems of these conditions is unclear; thus there is an urgent need to develop improved tools that focus on the specific aspects of the CTCL-related cutaneous and extracutaneous problems to identify the most meaningful aspects from a patient's perspective.

Several clinical studies of denileukin diftitox, oral and topical bexarotene, and ECP alone or with adjuvant therapy have investigated QOL as a secondary endpoint. However, early reports on treatment outcome used unvalidated QOL assessment tools allowing only limited conclusions. Further insights in the complexity and relevance of QOL resulted in the integration of validated QOL tools in the drug development of brentuximab[178,205] and mogamulizumab[179,206]. Mogamulizumab resulted in a significant improvement of QOL compared with vorinostat using two different assessment tools, reflecting the clinical benefits[205].

Superior reductions in cutaneous symptom burden (skin itching, burning, pain, irritation and bleeding) but not in emotional or functional domains were associated with an improvement in QOL with brentuximab in a large multicenter trial that included patients with MF and pcALCL. There was a more rapid and durable reduction from baseline in symptom burden (symptom domain) with brentuximab compared with physician's choice unrelated to response status. Interestingly, the development of polyneuropathy did not influence the benefits on QOL. In addition, the histone deacetylase inhibitor romidepsin was reported to improve symptoms in patients with intractable pruritus, thus contributing to improved QOL[207,208]. The differences between the patient populations with a predominance of SS in the mogamulizumab trial and the substantial population of pcALCL in the brentuximab trial might account for the differences in QOL improvement observed.

Outlook

Current gaps in research

Compared with other cutaneous malignancies, stable representative cell cultures for the subtypes of CTCL and animal models that would allow the study of key molecular mechanisms or drive the development of therapeutic interventions are lacking. The malignant cell population in CTCL is difficult to identify as there is no reliable and stable surface marker with the exception of CD30 in $CD30^+$ LPDs. Thus, biopsies or blood samples used for translational research may contain variable concentrations of malignant cells.

Priorities for the next 5–10 years

Routine treatments for CTCL, such as narrow-band UVB irradiation, radiotherapy or ECP, have not been investigated in large multicenter randomized trials. International groups, such as ISCL or the EORTC Cutaneous Lymphoma working groups, are developing prospective randomized clinical trial programmes accompanied by a harmonized concept to collect pretreatment and on-treatment samples for translational research, which should be the focus in the next years. These projects must consider the ultimate goal of long-term disease control with minimal toxicity and distinguish between short-term aggressive tumour debulking versus maintenance therapy strategies, with special attention on allogeneic HSCT. Finally, the results of these trials will contribute to refined evidence-based treatment algorithms considering disease subtype, stage, tumour load and potential biomarkers.

Long-term priorities

The skin is easily accessible for biopsy and biopsy tissue from early and advanced lesions could be used to generate a biobanking for CTCL, allowing sophisticated work-ups. These work-ups could include the use of high-throughput molecular biology techniques and multichannel imaging procedures such as CyTOF. The generated huge datasets need a careful bioinformatics analysis. Information from these analyses will provide a detailed description of the individual tumour microenvironment, involved signalling networks, and cell communications and could allow the development of specific therapeutic interventions.

Drug candidates

Surface molecules with a selective or at least preferential expression on the malignant CTCL population are potential targets for monoclonal antibodies; however, as most CTCLs have a mature T cell phenotype, it is challenging to find such surface targets. Early CTCL targets, such as CD4, CD25 and CD52, are widely expressed by T cells and other cell types. CD30 and CCR4 appear preferentially expressed on the malignant T cell populations and, thus, the clinical development of the monoclonal antibody mogamulizumab and the fusion

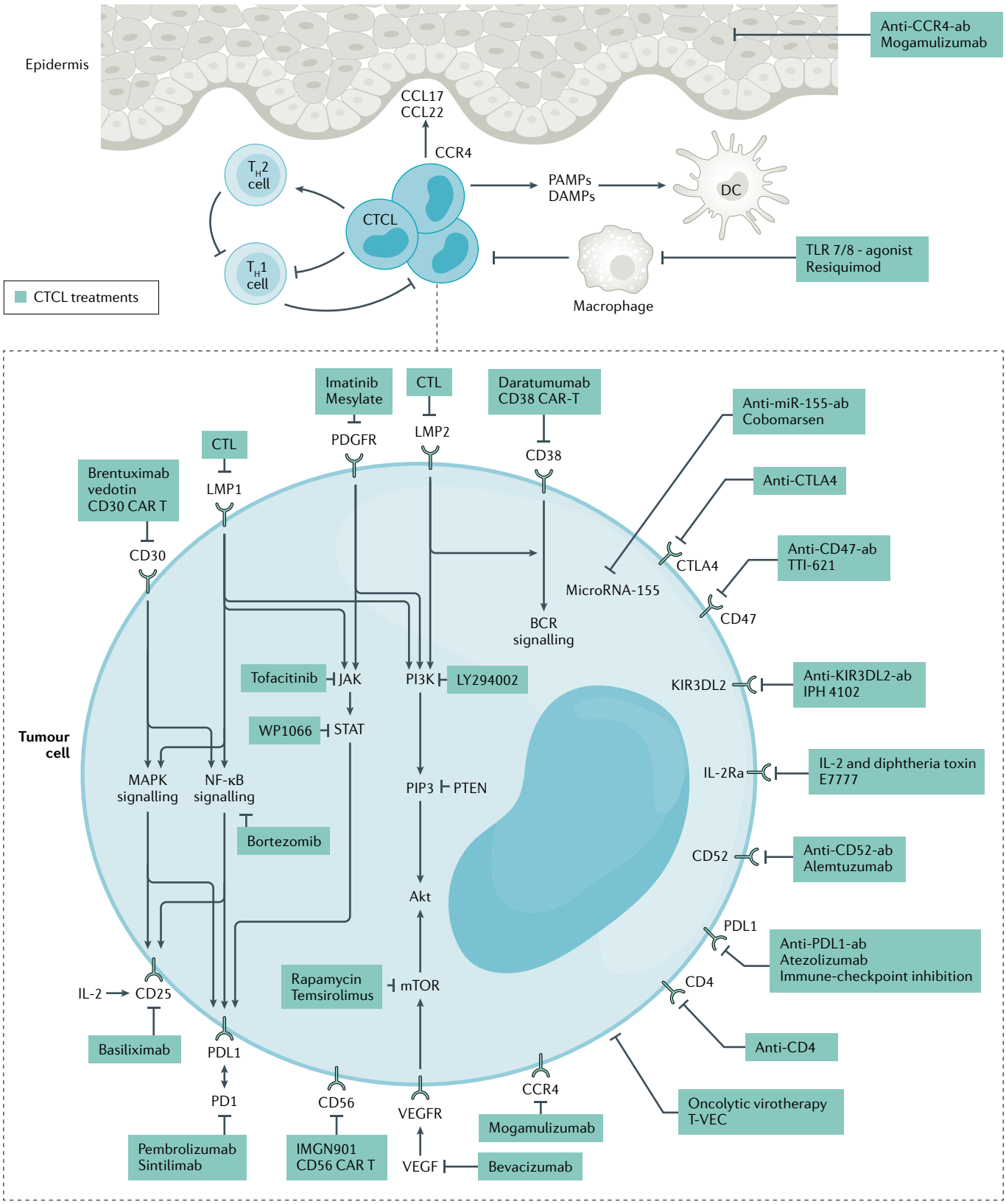

Fig. 6 | **Targets for future directions for CTCL therapy.** New therapeutic approaches in mycosis fungoides focus on both surface molecules and intracellular targets and involve a variety of agents, including antibodies, small molecules or microRNAs. CAR T, chimeric antigen receptor T; CTCL, cutaneous T cell lymphoma; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DAMPs, damage-associated molecular patterns; MAPK, mitogen-activated protein kinase; PAMPs, pathogen-associated molecular patterns; PI3K, phosphatidylinositol 3-kinase; TH, T helper. Figure adapted with permission from REF.[195], Taylor and Francis and REF.[247], Elsevier.

toxin brentuximab resulted in the approval of these agents (FIG. 6). We cannot yet anticipate how monoclonal antibodies targeting CD47, which is a glycoprotein providing a signal to inhibit phagocytosis and which is ubiquitously expressed on the surface of most cells, will impact on the disease manifestation in CTCL.

Another promising surface target is KIR3DL2 (CD158k), which belongs to the family of killer immunoglobulin-like receptors. By binding to major histocompatibility complex (MHC) class I, it provides an inhibitory signal, the blocking of which results in cell death. After extensive preclinical work, IPH4102 is the first-in-class anti-KIR3DL2-antibody, which is in early clinical development with some early signals of clinical efficacy in SS[209].

The phosphatidylinositol 3-kinase (PI3K) pathway is a key regulator of proliferation and activation in many cell types and altered in many malignancies, including lymphomas. Early trials are investigating various molecules, such as tenalisib (RP6530) and duvelisib (IPI-145 in NCT02783625), in relapsed/refractory peripheral T cell lymphoma and CTCL. Both tenalisib and duvelisib are double PI3Kδ and PI3Kγ inhibitors and have demonstrated reasonable activity[210,211], justifying further trials alone or in combination with other approaches.

Immunotherapy using monoclonal antibodies interfering with checkpoints during T cell activation have dramatically influenced the treatment landscape in many malignancies. In CTCL, a disease of proliferating T cells, interfering with immune checkpoints might be a double-edged sword[212].

PD1 is a transmembrane protein, which transduces immune-inhibitory signals after binding to its ligands PDL1/PDL2 (REF.[213]). In mouse models, deletion of PD1 led to enhanced T cell growth and development of lymphomas, suggesting a tumour-suppressive role in lymphomagenesis[112]. The anti-PD1 antibody pembrolizumab resulted in an attractive response rate of 38% in patients with SS and advanced MF[102,214]. Moreover, at a follow-up of 58 weeks, median duration of response was not reached, suggesting that lasting responses could be achieved with anti-PD1 inhibitors[102,214]. Clinical responses were not associated with known prognostic/predictive biomarkers, including PDL1 expression, mutation burden or IFNγ gene expression signature, illustrating the need for high-resolution translational research. However, as PD1 inhibition was also reported to induce T cell neoplasms[215–217] and may also induce the development of CTCL in humans, anti-PD1 approaches should be developed with caution in these entities.

Viruses (wild type or genetically modified) can substantially modify the cutaneous microenvironment by inducing innate interferon-driven immune responses, switching resident reactive T cells to a T_H1 phenotype and recruiting other cell populations such as NK cells, M1 polarized macrophages and plasmacytoid dendritic cells. Since at least some CTCL malignant cell populations are characterized by interferon signalling deficiencies, viruses may replicate preferentially in the malignant cells. Again, larger trials need to be initiated given promising data in small patient populations treated with talimogene laherparepvec (T-VEC), a replicating attenuated herpes simplex virus, replicating measles vaccine virus and a non-replicating adenoviral vector carrying a human IFNγ (TG1042)[218–220].

Besides immunotherapy, small molecules, which interfere with signal transduction pathway targets, including Janus kinase-signal transducer and activator of transcription (JAK–STAT), epigenetic modifiers (combined approaches to impact on histone acetylation and methylation)[221] and miRNAs must also be explored[195].

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