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Cutaneous T-cell Lymphomas: 2022 update on diagnosis, risk-stratification, and management

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Disease overview: Cutaneous T-cell lymphomas are a heterogenous group of T-cell neoplasms involving the skin, the majority of which may be classified as Mycosis Fungoides (MF) or Sézary Syndrome (SS).
Diagnosis: The diagnosis of MF or SS requires the integration of clinical and histopathologic data.
Risk-adapted therapy: TNMB (tumor, node, metastasis, blood) staging remains the most important prognostic factor in MF/SS and forms the basis for a "risk-adapted," multi-disciplinary approach to treatment. For patients with disease limited to the skin, expectant management or skin-directed therapies is preferred, as both disease-specific and overall survival for these patients is favorable. In contrast, patients with advanced-stage disease with significant nodal, visceral or blood involvement are generally approached with systemic therapies, including biologic-response modifiers, histone deacetylase inhibitors, or antibody-based strategies, in an escalating fashion. In highly-selected patients, allogeneic stem-cell transplantation may be considered, as this may be curative in some patients.

Disease Overview

Primary cutaneous lymphomas are a heterogeneous group of extranodal non-Hodgkin lymphomas that, by definition, are confined to the skin at diagnosis. The European Organization for Research and Treatment of Cancer (EORTC) and World Health Organization (WHO) published a consensus classification for cutaneous lymphomas in 2005 (1) that was updated in 2018 (2). Additional refinements to this classification have been made by the WHO and the International Consensus Classification (3, 4). In contrast to nodal non-Hodgkin lymphoma, most of which are B-cell derived, approximately 75% of primary cutaneous lymphomas are T-cell derived, two-thirds of which may be classified as Mycosis fungoides (MF) or Sézary Syndrome (SS) (1, 5, 6). The incidence of cutaneous T-cell lymphomas (CTCL) has been increasing and is currently 6.4 per million persons, based on Surveillance, Epidemiology, and End Results (SEER) registry data, with the highest incidence rates being reported among men and African-Americans (5). Black patients with MF have key differences when compared to non-Black patients, including a female predominance, younger age of onset, and inferior outcomes (7, 8). While CTCL may occur in children and young adults, this is very uncommon and often associated with clinical and histopathologic variants of MF (9-12). The incidence of CTCL increases significantly with age, with a median age at diagnosis in the mid-50's and a four-fold increase in incidence appreciated in patients over 70 (5, 11). Patients with CTCL have a higher incidence of secondary malignancies, including other non-Hodgkin lymphomas, lung cancer, bladder cancer, and melanoma, thus meriting appropriate screening (13, 14).

While genetic evidence strongly implicates UV radiation as a risk-factor for CTCL (15-17), epidemiological studies have failed to consistently identify other environmental or virally associated risk factors for most CTCL subtypes, with the notable exception of HTLV-1 infection in adult T-cell leukemia/lymphoma (18). Recent studies, however, have suggested that medications may induce an antigen-driven T-cell lymphoproliferation or dyscrasia (19, 20). Moreover, as a variety of other medications may initiate a reaction mimicking MF, a careful medication history should be performed in these patients with a trial off any suspected offending drug. Individual genetic features have also been implicated in the development of CTCL. Rare reports of familial MF and the detection of specific HLA class II alleles in association with both sporadic and familial MF suggest that host genetic factors may contribute to MF development (21-23). While the role of environmental and host genetic factors in CTCL pathogenesis remains unclear, significant insights into disease ontogeny, molecular pathogenesis and disease-associated immune dysregulation have been realized (24-27). Recently performed next-generation sequencing studies have demonstrated a high frequency of C>T transitions, in contrast to the T>G transversions observed in B-cell lymphoproliferative disorders, within NpCpC trinucleotides, a signature associated with ultraviolet B (UVB) exposure in melanoma [reviewed in (15)].

The cell of origin, molecular pathogenesis, and genetic landscape associated with MF/SS have been elucidated [reviewed in (28)], and have significant therapeutic implications [reviewed in (15)].

Diagnosis

Mycosis fungoides. The definitive diagnosis of MF, particularly patch/plaque stage disease, is challenging, as many of its clinical and pathologic features are non-specific and overlap with reactive processes. Many patients will have had symptoms attributed to eczema, psoriasis or parapsoriasis for years prior to obtaining a definitive diagnosis. The median time from symptom onset to diagnosis in retrospective series is 3-4 years, but may exceed four decades (12, 29-31). Given the importance of clinicopathological correlation in the diagnosis of MF and the variable association of specific histologic findings with the diagnosis, biopsy reports are not infrequently "suggestive of" the diagnosis. This occasional uncertainty implied in biopsy reports and apparent lack of a more definitive histopathologic diagnosis may be a source of frustration for clinicians unfamiliar with the challenges associated with rendering a pathologic diagnosis of MF. Furthermore, treatment with skin-directed therapies at the time of biopsy, including topical corticosteroids, may diminish or eliminate neoplastic T-cells and other histopathologic findings, further compounding the diagnostic challenge, as these therapies diminish or eliminate neoplastic T cells and critical histopathologic findings for 2 to 4 weeks (32, 33). Drug reactions, chronic spongiotic dermatitis, connective tissue diseases, lichen sclerosus et atrophicus, and pigmented purpuric dermatoses are just a few of the conditions that may mimic MF (34, 35). While a definitive diagnosis of MF may be made based on clinical and histopathologic features alone, determination of T-cell clonality and assessment for the aberrant loss of T-cell antigen expression by immunohistochemical staining for CD2, CD3, CD5 and CD7 are useful ancillary studies in the diagnosis of MF (and SS). PCR-based methods are able to detect clonal rearrangements of the T-cell receptor (TCR) in formalin-fixed, paraffin-embedded biopsy specimens (36, 37). PCR-based methods, while sensitive, should be interpreted with caution, as clonal TCR gene rearrangements may be detected in normal elderly individuals and in patients with benign dermatoses or other disease states (38-42). However, detection of identical clones from two different sites is quite specific for MF (43). Even this feature is not without complications as rare reactive processes display what appears to be an identical T-cell clone by PCR-based gene rearrangement studies in multiple biopsies over time. Moreover, some MF cases may not have a detectable T-cell clone (44). Recent studies have suggested that next generation sequencing (NGS) may be more sensitive and/or specific for assessing T-cell clonality in MF/SS, but NGS is not yet widely available (45-47). Moreover, NGS may have similar pitfalls to PCR-based studies, as it may identify clonal T-cells in reactive infiltrates and may not identify clonal T-cell in CTCL (44, 48). The extent to which MF/SS may be preceded by a pre-malignant state, analogous to monoclonal B-cell lymphocytosis (MBL) or monoclonal gammopathy of undetermined significance (MGUS), is debatable and poorly defined (49). The malignant lymphocytes in

MF/SS are usually $CD3^+CD4^+$ and $CD8^-$, but frequently lose the expression of other pan-T-cell antigens. Therefore, demonstration of a significant population of $CD4^+$ cells lacking CD2, CD5, and/or CD7 expression is highly specific (specificity >90%) for MF in most reported series (50, 51). However, reactive dermatoses may also show a predominance of CD4-positive T-cells and loss to diminished expression of CD7, the T-cell antigen most frequently lost in MF, and these results must be interpreted with caution (35, 51). Finding a marked predominance of CD4-positive T-cells, especially by epidermotropic T-cells, helps to support a diagnosis of MF (35, 51). Similarly, finding extensive loss of CD7, preferential loss of pan T-cell antigens by epidermal T-cells, or loss of multiple pan T-cell markers favors a diagnosis of MF in challenging cases (35, 51). Clinically, patch/plaque stage MF is frequently characterized by persistent and progressive lesions that develop in a "bathing suit" distribution and vary in size, shape and color. These lesions are frequently large (>5 cm), pruritic and multifocal in "classical" MF. In skin of color (SoC), lesions are polymorphic, including hyper- and hypopigmented patches/plaques. Espinosa et. al. identified hyperpigmentation, lichenification and a silver hue as significantly more common in SoC (52). However, a broad range of MF variants have been described with differences in tropism (e.g. follicular MF), distribution (e.g. palmoplantar MF), pigmentation (e.g. hypo- and hyperpigmented variants) and focality (e.g. unilesional MF), some of which are formally recognized in the WHO-EORTC classification (1, 53). Histopathologically, patch/plaque MF is characterized by enlarged, epidermotropic lymphocytes with irregular nuclei that often show a band-like distribution in the dermis, where they are associated with dense strips of collagen ("wiry" fibrosis). Aggregates of neoplastic T-cells in the epidermis, termed Pautrier microabscesses, are seen in a minority of cases, but are a helpful clue to the diagnosis. Folliculotropism and/or syringotropism may be seen in a minority of cases. Given the need for uniform diagnostic criteria in MF, the International Society for Cutaneous Lymphoma (ISCL) proposed a point-based diagnostic algorithm which integrates clinical, histopathologic and immunophenotyping data with an assessment of T-cell clonality (34). Recent studies have demonstrated that the inclusion of clinical information, including photographs, improved the diagnostic accuracy of pathologists, thus highlighting the importance of clinical information for accurate histopathologic diagnosis (54, 55).

Sézary Syndrome. Traditionally, SS is defined as a leukemic form of CTCL associated with erythroderma, intractable pruritis, ectropion, and palmoplantar keratoderma. A series of studies in the early to mid-20th century, beginning with Sezary's initial landmark observation in 1938, identified a population of large lymphocytes in the peripheral blood with grooved, lobulated (that is, "cerebriform") nuclei in patients with MF or SS (56-61). As in other chronic lymphoproliferative disorders, the Sezary cell count is preferably expressed in absolute terms, with ≥1000 cells/μl classified as B2 disease in the current ISCL/EORTC TNMB staging classification. The morphologic detection of Sezary cells in the peripheral blood is not specific for CTCL, as Sezary cells may be found in peripheral blood from normal donors and in benign conditions (62-

64). The histopathologic findings in the skin often resemble those observed in MF, with less prominent epidermotropism, though findings in skin biopsies may be paradoxically subtle and non-specific. As in MF, immunohistochemical studies showing a CD4 predominance and loss of pan T-cell markers may be helpful. Lymph node involvement is characterized by complete effacement of the nodal architecture by infiltrating Sezary cells (65).

In SS, clonal T cells are generally $CD3^+CD4^+$ and $CD8^-$ by multi-color flow cytometry (66-69). As in MF, the aberrant loss of pan-T-cell antigens, including CD2, CD3, CD4, CD5, CD7 and/or CD26 is frequently observed (68, 70-73). Of these, the aberrant loss of CD7 and/or CD26 expression is most common, being observed in most cases (69, 70, 74-78). The loss of CD7 (≥40%) and/or CD26 (≥80%) is sensitive (>80%) and highly specific (100%) for SS (73). The International Society for Cutaneous Lymphomas (ISCL), United States Cutaneous Lymhoma Consortium (USCLC) and EORTC 2021 staging update have defined the B2 blood group as an absolute count of CD4+CD7-, CD4+CD26-, or other aberrant T-cell populations identified by flow cytometry T-cells ≥1000/μL (79-81), and further subclassifies B2 blood involvement based on the absence or presence of concordant T-cell clones in the blood and skin. The aberrant expression of the MHC class I-binding, killer immunoglobulin-like receptor (KIR) CD158κ (and less commonly CD158a or CD158b), normally expressed by natural killer cells, was described in the majority of patients examined with SS (73, 82, 83). Molecular studies, including detection of a clonal TCR gene rearrangement by PCR and the presence of a clonal cytogenetic abnormality, provide evidence of T-cell clonality. An alternative approach to demonstrate T-cell clonality incorporates multi-color flow cytometry using a panel of antibodies specific for various TCR beta-chain variable region family members (TCR-Vβ) (84-86). This approach is successful in identifying a clonal population of T cells if this population is significantly higher than the background frequency of polyclonal T cells harboring the same Vβ chain (84, 85, 87). The beta-chain constant region includes two gene segments (C1 and C2). In a manner analogous to kappa or lambda light chain restriction in B-cell lymphoproliferative disorders, over (or under) representation of beta-chain constant chain-1 region (TRBC1) is a sensitive and specific biomarker for αβ T-cell clonality (88-90).

The currently proposed ISCL criteria for SS integrate clinical, histopathologic, immunophenotyping and molecular studies. In patients with erythroderma, criteria recommended for the diagnosis of SS by the ISCL include the following: absolute sezary count ≥1000/μl, a CD4/CD8 ratio ≥10, (due to the clonal expansion of $CD4^+$ cells), aberrant expression of pan-T-cell antigens (i.e. loss of CD7 and/or CD26 expression in at least 40% or 30% of cells, respectively), demonstration of T-cell clonality by Southern blot or PCR-based methods, or cytogenetic demonstration of an abnormal clone (68). At a minimum, the WHO-EORTC recommends the demonstration of T-cell clonality in combination with the above-mentioned criteria for the diagnosis of SS (1). In addition to the ISCL criteria, the most recent WHO classification requires erythroderma, generalized lymphadenopathy, and clonally related T-cells (Sézary cells) in the skin, peripheral blood, and lymph nodes. On rare occasions, SS may

be preceded by a prior history of classic MF. The ISCL recommends that such cases be designated as SS preceded by MF or secondary erythrodermic CTCL Conversely, patients with MF, but without erythroderma, may meet hematologic criteria for SS. In these cases, the designation "MF with leukemic involvement" is recommended, although genetic features of both MF and SS have been recently described in patients with SS preceded by MF (17).

Non-MF/SS subtypes of CTCL. An important goal during a patient's initial diagnostic evaluation is to distinguish non-MF/SS CTCL subtypes from MF/SS, as the natural history, prognosis, and treatment approach for each of the non-MF/SS lymphomas is highly variable, including a recently described subset of primary cutaneous T-cell lymphomas with a T follicular helper immunophenotype with histopathologic and genetic characteristics similar to angioimmunoblastic T-cell lymphomas (91). A detailed description of these CTCL subtypes is beyond the scope of this update, but the salient features of each have been previously summarized (2, 92).

Risk-stratification

Staging. In contrast to many other lymphoproliferative disorders in which cytogenetic and laboratory findings play a prominent role in risk stratification, TNMB (tumor, node, metastasis, blood) staging remains an important prognostic factor in MF/SS and forms the basis for a "risk-adapted" approach to treatment. In 2007, the ISCL and EORTC revised the TNMB staging of MF/SS (93). Patients with only patches and plaques have stage I disease, but may be further divided into stage IA (<10% body surface area involved or T1) or stage IB (>10% body surface area involved or T2) based on the extent of skin involvement, and by the presence of patch- (T1a/T2a) or plaque-stage (T1b/T2b) disease. For practical purposes, the area of a patient's hand (including both palm and digits) represents approximately 1% of body surface area. Current staging and diagnostic recommendations do not require a biopsy of clinically normal lymph nodes; however, an excisional biopsy of any abnormal lymph nodes (≥1.5 cm in diameter or firm/fixed) is recommended, with preference being given either to the largest lymph node draining an area of skin involvement or to the node with the greatest standardized uptake value (SUV) on FDG-PET imaging(94-96). While radiologic examination of lymph nodes is considered optional for patients with T1 or T2 disease and no evidence of lymphadenopathy on physical examination (93), a recent international study found that physical examination may miss radiographically-enlarged lymph nodes leading to significant changes in staging in a minority of patients, particularly those with plaques (97). Patients with patch/plaque stage disease (T1/T2) and architectural preservation of any clinically abnormal lymph nodes are classified as stage IIA. Collectively, patients with stage I-IIA disease have "limited (or early)-stage" disease, as the overall survival in these patients is measured in decades, with survival in patients with stage IA disease resembling that of normal age-matched controls (11, 29, 30). At diagnosis, the majority of MF patients will have limited-stage disease (11). In contrast, patients with tumor stage disease (T3), erythroderma (T4), nodal involvement characterized by partial or complete architectural effacement (N3),

visceral metastases (M1), or significant leukemic involvement (B2) have "advanced (or late)-stage" disease. While the European Society for Medical Oncology (ESMO) an the EORTC have recommended peripheral blood flow cytometry for all MF/SS patients (79, 98), recent consensus recommendations support of the use of peripheral blood flow cytometry in specific patient groups: those with advanced-stage (≥IIB) disease, intractable pruritis, generalize patches/plaques, erythroderma, lymphocytosis, an elevated LDH, or a lack of response to skin-directed therapies (81). Detection of a clonal TCR gene rearrangement by PCR, which has been incorporated into the revised ISCL/EORTC node(N) and blood(B) staging classification, is an adverse prognostic factor (11, 99-102). Unfortunately, median survivals from approximately 1-5 years are observed in these patients with more extensive disease (11). The revised ISCL/EORTC staging for MF/SS is summarized in Table 1.

A retrospective study including 1,398 MF patients, 71% with patch/plaque stage disease, and 104 SS patients has validated the revised ISCL/EORTC staging classification (11). On univariate and multivariate analyses, the revised T, N, M and B classification were significantly associated with overall and disease-specific survival. The median survival, disease-specific survival and risk of disease progression, by clinical stage, are summarized in Table 1. A recent metaanalysis reported a similar trend for 5-year survival (103). While the impact of recently approved agents on overall survival is uncertain, the rather durable responses observed in subsets of patients treated with these agents may provide ample reason for optimism. For those with early-stage disease, male gender, age >60, plaque-stage or folliculotropic disease, and nodal stage N1/Nx were adverse prognostic factors and were utilized to generate the cutaneous lymphoma international prognostic index (CLIPi) for patients with early-stage disease (104). Ten-year OS was 90.3% for those with low-risk (0-1 risk factors) disease and 48.9% for those with high-risk (3-5 risk factors) disease. Similarly, male gender, age >60, stage B1/B2 or N2/N3 disease, and visceral involvement were adverse prognostic factors for patients with late-stage disease. Ten-year OS was 53.2% for low-risk patients, and 15.0% for high-risk patients (104). In a large, international series (n=1,275) of late-stage MF/SS, stage IV disease, age >60, large-cell transformation, and elevated LDH were identified as independent adverse prognostic factors, and were similarly combined in a prognostic index (105). Patients with low-risk (0-1 risk factors) disease experienced superior 5-year OS (68%) compared with the 5-year OS observed (28%) among those with high-risk (3-4 risk factors) disease. (11, 106-110)An alternative staging system has been proposed for those with folliculotropic MF and identifies a subset of patients with limited cutaneous involvement and a more favorable prognosis (111, 112).Given the importance of the TNMB classification in risk stratification and defining disease burden, the ISCL/EORTC recommends its use in defining the initial, maximum and current burden of disease, which will ultimately play an important role in the selection of either skin-directed or systemic therapies (93). In the future, it is anticipated that improved understanding of the genetic

landscape will further improve risk-stratification and lead to a more personalized approach for treatment selection in CTCL (15).

Recognizing that the staging system used for MF/SS is less helpful for non-MF/SS cutaneous lymphomas, a new TNM classification was also proposed for these CTCL variants (113). Due to the significant heterogeneity of these lymphomas, this staging system does not provide prognostic information, but is intended to provide a uniform description of the disease burden.

Treatment of limited-stage MF

As the majority of CTCL patients present with patch/plaque stage MF and have an excellent prognosis, the initial goal of therapy is to improve symptoms and quality of life while avoiding treatment-related toxicity. For many patients, this may involve either expectant management (i.e. “watch and wait”) or skin-directed therapies. A randomized trial comparing early combined modality therapy, including both radiation and multiagent chemotherapy (cyclophosphamide, doxorubicin, etoposide, and vincristine), with sequential topical therapies demonstrated that combined-modality therapy, while associated with a superior complete response rate, did not translate into improvements in disease-free or overall survival and was associated with significant toxicity (114). Moreover, an international prospective study compared skin-directed therapies (topical steroids, ultraviolet B, psoralen and ultraviolet A, topical nitrogen mustard, topical carmustine and local radiotherapy) to systemic therapy (oral retinoids, oral bexarotene, methotrexate, interferon and extracorporeal photochemotherapy) in early-stage MF. Patients receiving skin-directed therapy had a superior overall response rate (115). The limited efficacy associated with chemotherapy has been highlighted in retrospective studies in which the median time to next treatment following single or multiagent chemotherapy was ≤4 months(116, 117). Therefore, patients with limited-stage disease who require therapy are best approached with skin-directed therapies, usually under the direction of a dermatologist and/or radiation oncologist. Excellent reviews and treatment guidelines are available (92, 118-123).

Topical therapies. The first-line treatment for limited stage MF is topical steroids. In an uncontrolled prospective study, topical clobetasol propionate was used in 85% of patients with stage 1A/B disease, had an overall response rate of 94%, and is associated with minimal to no toxicity (124, 125). An alternative topical medication is mechlorethamine 0.02% gel (126). In a phase 2 trial, patients with stage IA-IIA MF were treated with 0.02% gel daily for up to 12 months. A response was observed in 58.5% of patients, with 13.8% achieving a complete response. A sustained response was observed in 85.5% patients and the most common adverse effects are contact dermatitis and irritant dermatitis (127). For refractory and persistent cutaneous lesions, bexarotene 1 % topical gel may be considered. Prospective trials have demonstrated an ORR between 44% and 63% (128). Topical toll-like receptor (TLR) agonists, which lead to local production of interferons, and other cytokines, induce cell death and promote host anti-tumor immunity (129), and have demonstrated efficacy in limited stage MF. For example, 20 patients with stage 1A-2B disease were treated with 5%

Imiquimod, a TLR7 agonist, and an ORR of 80%, including 45% complete responses, were observed. Toxicities are limited, including localized pain, redness, ulceration, and pruritus. Systemic symptoms, including flu-like symptoms and fatigue, while reported, are rare. Most adverse events are self-limited and resolve after the first few weeks of treatment (129, 130). Resiquimod, a potent TLR7/8 agonist, was examined in a phase 1 trial using 0.03 and 0.06% topical resiquimod gel. Among the 12 patients treated, clinical improvement was observed in 75% of treated lesions and 90% of patients had a reduction in malignant T cell clones in the treated lesions, and an abscopal, and presumably immune-mediated, effect was observed (131).

Phototherapy. Phototherapy is an important treatment modality that may be used alone, or in combination with topical therapies, in patients with limited-stage disease, and includes narrowband UVB (NBUVB, 311nm) and 8-methoxypsoralen plus ultraviolet A (PUVA). NBUVB is used in both patch and plaque stage MF. PUVA is the modality of choice in skin of color. Phototherapy is widely available and has demonstrated efficacy in many retrospective and prospective studies (33, 132), and a comprehensive consensus statement on the use of phototherapy was recently published (133).

Radiation. MF/SS are radiosensitive, thus radiation therapy, with curative intent, may be considered in patients with localized, unilesional MF. For those with more widespread disease, palliative local radiation or low-dose total skin electron beam therapy (TSEBT) are effective [(134), reviewed in (135), (136)].

Treatment of advanced-stage MF/SS

Overview. Patients with advanced-stage MF/SS require a multidisciplinary approach, as various combinations of skin-directed therapies, biologic-response modifiers and ultimately the sequential use of systemic chemotherapeutic agents are frequently employed in the management of these patients. As for limited-stage disease, multiagent chemotherapy is not appropriate (114). Instead, a “risk-adapted” and stage-based approach, consistent with NCCN guidelines, incorporating biologic-response modifiers (e.g. bexarotene and interferon-alpha), histone deacetylase inhibitors (e.g. romidepsin), or monoclonal antibodies or antibody-drug conjugates (e.g. mogamulizumab, brentuximab vedotin) is generally preferred (137). Therapeutic decisions are individualized and based on a patient’s age, performance status, extent of disease burden, the rate of disease progression, and previous therapies (118-123).

Bexarotene. The endogenous retinoids all-*trans* retinoic acid and 9-*cis* retinoic acid (i.e. vitamin-A-derived compounds) regulate a diverse array of biologic processes, ranging from embryonic development to cell growth, differentiation and survival, upon binding two families of steroid hormone receptors, the retinoic acid receptors (RAR) and retinoid X receptors (RXR). Upon forming homo- or heterodimers, these receptors recruit various nuclear co-repressor or co-activator proteins depending whether or not they are bound by ligand. Multiple RAR retinoids have been used in MF/SS, either topically or systemically (reviewed in (138, 139)), with response rates exceeding 50%.

However, in 1999 the oral RXR-selective "rexinoid" bexarotene was FDA approved for CTCL and was later approved as a topical gel formulation. Laboratory studies demonstrate that bexarotene promotes cell cycle arrest and apoptosis in CTCL cell lines (140, 141). In a multicenter phase II-III study, 94 patients with advanced-stage CTCL who had been previously treated with a median of five prior therapies, the vast majority of whom had disease refractory to at least one prior systemic therapy, received at least 300 mg/m^2 of oral bexarotene daily (142). Among patients treated at the 300 mg/m^2 dose, an overall response rate of 45% was observed, only 2% of which were complete. While an improved overall response rate was noted with the use of higher doses, this difference was not statistically significant, and dose-limiting toxicity was far more common (50% vs. 89%) in these patients. While a dose-response relationship is likely, the 300 mg/m^2 dose appears to provide the optimal risk-benefit ratio. The most common toxicities associated with therapy were hypertriglyceridemia (in 82%) and central hypothyroidism (29%). Myelosuppression is infrequent and usually uncomplicated. Pancreatitis secondary to hypertriglyceridemia may be rarely observed, but is reversible upon discontinuation of treatment. Therefore, a baseline lipid panel and free T4/TSH should be obtained prior to the initiation of therapy. In one retrospective study, all patients treated with bexarotene developed hyperlipidemia and central hypothyroidism, frequently within weeks of initiating treatment (143). Consequently, use of lipid-lowering agents (e.g. fenofibrate) and low-dose levothyroxine (e.g. 50 micrograms) prior to initiating bexarotene is generally recommended (144-146). In clinical practice, bexarotene is frequently initiated at a lower dose of 150 mg/m^2 and subsequently titrated to full doses after 4 weeks of therapy, depending upon patient tolerability. Most responses occur within 2-3 months of treatment initiation, but may be delayed. Therefore, in the absence of disease progression or toxicity, treatment should be continued for up to 6 months. For responding patients, treatment should be continued until disease progression and, depending upon the quality of the response, adjunctive skin-directed therapies (e.g. NB-UVB, PUVA) should be considered (147). Guidelines describing appropriate laboratory monitoring, supportive care, and safe clinical prescribing of bexarotene have been recently published (146). Future studies clarifying the optimal use of bexarotene, either in combination or sequentially with other agents, are needed.

HDAC inhibitors. Histone deacetylases (HDACs) catalyze the removal of acetyl groups from both histone and non-histone proteins. As histone acetylation is associated with an open chromatin configuration associated with active gene transcription, HDACs contribute to histone deacetylation and the epigenetic repression of gene transcription. As HDACs regulate a wide variety of processes involved in carcinogenesis, multiple mechanisms may explain the clinical activity of HDAC inhibitors (148, 149), including altered gene expression of cell-cycle and apoptotic regulatory proteins (150-154), acetylation of non-histone proteins regulating cell growth and survival (155-158), angiogenesis (159, 160), aggresome formation (161) and DNA repair (162). In addition, HDAC inhibitors have profound effects on the tumor microenvironment in CTCL (163).

Vorinostat (suberoylanilide hydroxamic acid, SAHA) and romidepsin (depsipeptide) inhibit class I and II HDACs (i.e. pan-HDAC inhibitors), the former being widely expressed in various lymphoma subtypes (164). Early phase I studies of both vorinostat and romidepsin established their safety and potential efficacy in lymphoproliferative disorders, including CTCL (165), thus paving the way for larger phase II studies. An earlier phase II study established 400 mg of oral vorinostat once daily as the optimal dose that was investigated further in 74 previously treated patients with CTCL, most of whom (>80%) had advanced-stage disease (166, 167). The overall response rate was approximately 30% for patients with advanced-stage disease and was associated with a median duration of response estimated to exceed 185 days. However, it is noteworthy that the reported response rate observed with vorinostat, using updated response criteria, was considerably lower (i.e. <10%) in MAVORIC (168). Most responses were rapid (i.e. <2 months) and were also noted in patients with tumor-stage disease and Sézary syndrome (169). Patients who failed to achieve an objective response appeared to derive some clinical benefit, including stable disease, decreased lymphadenopathy and pruritis relief, with treatment. The most common non-hematologic adverse events, observed in almost 50% of patients, were gastrointestinal toxicities (nausea, vomiting, diarrhea). Hematologic toxicities, including anemia or thrombocytopenia, were observed in up to 20% of patients. Among responding patients, long-term therapy with vorinostat appears to be well tolerated (170). Prolongation of the QT interval was rarely observed, but monitoring and appropriate electrolyte replacement is recommended for those patients at risk for QT prolongation (171).

Romidepsin, administered as a 4-hour intravenous infusion (14 mg/m^2) days 1, 8 and 15 every 4 weeks, was evaluated in two phase II studies, the largest of which included 96 patients, most with advanced-stage disease(172, 173). The overall response rate was 38% for patients with advanced-stage disease, with a median duration of response that exceeded one year. A toxicity profile similar to that described for vorinostat was observed. Intensive cardiac monitoring in a subset of these patients failed to demonstrate any clinically significant cardiotoxicity (174). A subset of MF/SS patients, after induction with romidepsin at the standard dose, may anticipate a durable remission with attenuated “maintenance” (every 2- or 4-week) dosing. For example, among 38 MF/SS patients, 17 achieved a durable (>6 month) remission, 9 of which were maintained with an attenuated, dose-sparing schedule (175). Among the patients achieving a durable remission, the median duration of treatment was 15 months (range: 7-34 months).

Additional HDAC inhibitors, including potent pan-HDAC inhibitors, appear to have activity in CTCL (154, 176, 177). Further studies are needed to fully define the mechanisms of resistance to HDAC inhibition in CTCL (154, 178-182), enabling the development of rational therapeutic combinations incorporating HDAC inhibitors in CTCL (183, 184).

Interferons. Interferons (i.e. interferon alpha-2b, interferon gamma-1b), have pleiotropic and immunomodulatory effects in CTCL and are associated with an overall response rates as high as 50-70% and a complete response rate of

20-30%, particularly in patients with limited-stage disease (185-189). While often considered as second-line therapy for limited-stage CTCL, interferon-alpha, frequently at doses ranging from 3-10 million units daily to three times weekly, is a treatment to be considered in the first-line setting in patients with advanced-stage disease. Responses, which may be achieved within a few months, are observed in patients with tumor-stage MF and SS, and are occasionally durable(116, 190). Furthermore, interferon-alpha may be successfully combined with a number of other therapeutic modalities frequently utilized in the management of these patients, including PUVA, bexarotene, chemotherapy and ECP (191-204). For example, in a cohort of 51, mostly advanced-stage patients treated with single-agent, low-dose, interferon-alpha, responses were observed in 34 (67%), including 21 (41%) with a complete response and 9 with a long-term remission (188). Similarly, in a cohort of 47 patients with stage III/IV disease, 89% of whom had peripheral blood involvement, a response rate exceeding 80% was observed in those treated with a combination of ECP and interferon-alpha (204). Interferon-alpha is associated with myelosuppression, transaminitis and dose-limiting flu-like side effects, particularly at higher doses.

Extracorporeal photophoresis. During extracorporeal photophoresis (ECP) pooled leukapheresis and plasmapheresis products are exposed to 8-methoxypsoralen (8-MOP) prior to extracorporeal circulation through a 1 mm thick disposable cassette exposed to UVA radiation. The irradiated leukocytes, representing approximately 5% of peripheral blood leukocytes, are subsequently reinfused. Psoralen covalently binds and crosslinks DNA following UVA exposure, leading to the induction of apoptosis in the majority of treated lymphocytes by multiple mechanisms involving bcl-2 family members, disruption of the mitochondrial membrane potential and extrinsic cell death pathways (205-207). In contrast, ECP leads to monocyte activation, including significant changes in gene expression (208), and dendritic cell differentiation, which is thought to culminate in enhanced antigen presentation and the initiation of a host immune response (209).

Following the landmark study by Edelson and colleagues describing responses in 27 out of 37 patients with erythrodermic CTCL treated with ECP, ECP was approved by the Food and Drug Administration of the USA for the treatment of CTCL and is now considered the treatment of choice in the first-line management of patients with Sézary syndrome in many centers (210). Furthermore, retrospective series demonstrate that ECP is associated with superior time to next treatment when compared with most systemic therapies, including HDAC inhibitors (117). While responses vary between case series, overall response rates hover around 60%, with a complete response rate of approximately 20% (211-214). As current treatment protocols no longer require the oral administration of 8-MOP, eliminating nausea, ECP is safe and generally very well tolerated. Long-term use of ECP may cause iron deficiency anemia due to the small residual blood volume that is not returned to the patient (215). While the precise mechanism of action is incompletely understood, evidence suggests that ECP has immunomodulatory effects which may augment host anti-tumor immunity (216, 217). It is not surprising then that the median time to response

following the initiation of ECP is approximately 6 months. Median survival exceeding 8 years has been observed in ECP treated patients and among complete responders, many experience durable responses which may permit, for some, weaning from CTCL-directed therapies (211, 218-220). In a retrospective study, patients treated with ECP early (i.e. within the first 3 lines of therapy) experienced superior median time to next treatment (approaching 4 years) when compared to either those treated with alternative agents or ECP later in the course of therapy (221). While patient- or disease-specific factors which may predict a response to therapy are imperfect (222), Sezary patients without significant nodal or visceral disease who initiate ECP promptly after diagnosis may be more likely to respond. In addition, patients without profound immune deficiencies, reflected by normal or near-normal cytotoxic T-cell and CD4/CD8 values and the absence of prior exposure to systemic chemotherapy, may be more likely to respond to therapy (211, 213, 219). While effective as monotherapy, ECP has also been combined with other therapeutic strategies, including interferon, bexarotene and TSEBT (194, 204, 218, 223-225).

Monoclonal antibodies and immunotoxins. In contrast to many B-cell lymphoproliferative disorders, where the incorporation of CD20-targeting monoclonal antibodies has become the standard of care, additional studies are needed to identify the optimal approach targeting T-cell specific antigens in advanced-stage MF/SS. Alemtuzumab is a humanized IgG1 monoclonal antibody directed against CD52, an antigen widely expressed by B-cells, T-cells and monocytes (226). In a phase II study in 22 patients with advanced-stage MF/SS, overall and complete response rates of 55% and 32%, respectively, were observed, with a median time to treatment failure of 1 year (227). Given the significant risk of infectious complications, low-dose subcutaneous alemtuzumab was investigated in 14 patients with SS, most of whom had relapsed/refractory disease (228). Most patients in this study received 3 mg of subcutaneous alemtuzumab on day 1 followed by a 10 mg dose on alternating days until the Sézary count was $<1000/mm^3$. With the exception of a single patient whose best response was stable disease, 9 out of 10 patients treated in this manner achieved a response, 3 of which were complete. For most patients, the time to treatment failure exceeded 12 months. What is notable, however, is that infectious complications were not observed in patients treated with the lowest dose (i.e. 10 mg) of alemtuzumab. Similar results, with no infectious complications, were recently reported in a small cohort of patients treated with modified, low-dose, subcutaneous alemtuzumab for six weeks (229). In addition to hematologic toxicity, conventionally dosed alemtuzumab in advanced-stage MF/SS is associated with a high incidence of infectious complications (227, 228, 230-233). Overall, infectious complications have been observed in two-thirds of treated patients, most of which are bacterial, including sepsis. Cytomegalovirus (CMV) reactivation is the most common viral infection. In addition, *Pneumocystis jirovecii* pneumonia and invasive fungal infections have also been observed. Therefore, trimethoprim-sulphamethoxazole and acyclovir should be routinely administered for PJP and HSV/VZV prophylaxis, respectively, in patients receiving alemtuzumab. In addition, CMV surveillance should be performed

every 1-2 weeks by quantitative PCR and suppressive therapy with ganciclovir or oral valganciclovir initiated in response to viral reactivation. Low-dose, subcutaneous alemtuzumab appears to be safe and efficacious in selected patients with advanced-stage MF/SS provided with appropriate supportive care. Monoclonal antibodies targeting additional T-cell specific antigens, including CD2 (234), CD4 (235), CD25 (236) and CCR4 (237-239) are being explored and appear promising. Resimmune, a second-generation immunotoxin in which the catalytic and translocation domains of diphtheria toxin (DT_{390}) have been fused to CD3-specific single chain antibody fragments [bisFv(UCHT1)], is associated with a response rate of 36% (16% complete), and is particularly active in patients with limited-stage disease (240). Much like its predecessor, resimmune is associated with a vascular leak syndrome (92).

Mogamulizumab. Mogamulizumab (KW-0761) is a humanized monoclonal antibody specific for the chemokine receptor CCR4 that has been defucosylated and is consequently associated with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). In a phase I/2 study, mogamulizumab was well tolerated and was associated with an overall response rate of 37%. A similar response rate of 29% (2/7), all partial, was observed in a phase II Japanese study (239, 241). In addition to ADCC-mediated clearance of malignant T cells, mogamulizumab may inhibit T_{reg}-mediate immune suppression (242, 243), and may warrant further investigation with immunomodulatory therapies, including immune checkpoint blockade (244). A randomized, phase III clinical trial comparing mogamulizumab and vorinostat in relapsed/refractory CTCL (MAVORIC) demonstrated a significant improvement in progression-free survival among MF/SS patients randomized to mogamulizumab (168). Overall responses in patients treated with mogamulizumab were higher in the blood compartment (68%) when compared with those observed in the skin (42%) or lymph nodes (17%). Not surprisingly then, the overall response rate was highest among Sezary syndrome patients (37%). Overall, treatment with mogamulizumab was well tolerated, with few ≥grade 3 adverse events (AE's). Infusion-related reactions were the most common grade 1 or 2 AE's and were observed in 32%. Mogamulizumab-associated rashes are observed, and may clinically and histopathologically mimic CTCL, but may be managed without discontinuation of therapy (245). Treatment-associated rashes are characterized by macrophage- and CD8+ T-cell-rich infiltrates and have been associated with superior disease control in Sezary patients (246). These positive findings led to mogamulizumab's approval by the FDA in 2018 for MF/SS patients who have failed at least one prior systemic therapy.

Brentuximab vedotin. Given the promising response rates observed with brentuximab vedotin (BV) in phase II studies (247, 248), a randomized, phase III clinical trial (ALCANZA) comparing BV with an investigator's choice (methotrexate or bexarotene) was performed, and demonstrated a significantly improved PFS (>12 months vs. 3.5 months) for patients randomized to BV, and led to its FDA approval in previously treated CTCL (249, 250). Among MF patients with limited-stage disease treated with BV, a response lasting at least 4 months (ORR4) was observed in 40%, whereas an ORR4 of 63% was observed

among patients with tumor-stage (stage IIB) disease. Consistent with prior experience in “CD30 high” lymphomas, an ORR4 of 89% was observed among patients with primary cutaneous ALCL with disease confined to the skin. More recently, and with a median follow-up of 46 months, the final ALCANZA data confirms the benefit associated with BV. Among MF patients, the median PFS in BV-treated patients was 16.1 months, compared with 3.5 months in these treated with either methotrexate or bexarotene (251). Not surprisingly then, one year following treatment, 34.5% of BV patients required treatment with an alternative systemic agent, whereas 86.6% of methotrexate or bexarotene treated patients required an alternative therapy. The benefit associated with BV was observed independent of CD30 expression or the presence of large cell transformation (250).

Checkpoint blockade. Durable remissions may be achieved with immunomodulatory therapies, including ECP and interferon-α. While largely anecdotal, these observations suggest that host immunity, when properly harnessed, can lead to durable responses in selected patients. These observations, coupled with high-level PD-L1 expression in a substantial minority of patients, provide a strong rationale for checkpoint blockade (CPB) in CTCL (252, 253). While few CTCL patients have been included in early phase clinical trials, durable responses have been observed, including two responding CTCL patients who achieved responses that were ongoing at 24+ and 50+ weeks (254). In a phase II study in heavily pretreated patients, an overall response rate of 38% was observed in advanced-stage patients treated with pembrolizumab (255). MF with large cell transformation (LCT) are genetically complex (with a high mutational burden), frequently downregulate MHC class I (256), and express PD-L1, including PD-L1 structural variants (257), all of which are consistent with immune evasion. While the experience in LCT patients is limited, anecdotal evidence supports the utility of checkpoint blockade in these patients (257). These encouraging results, in conjunction with the smorgasbord of currently available immunomodulatory agents, lend themselves to future and ongoing combinatorial strategies (253).

Systemic Chemotherapy. Responses to conventional chemotherapeutic agents are rarely durable in CTCL (92), being associated with a median time-to-next treatment that is measured in months (116, 117). Consequently, >90% of patients treated in this manner will require additional therapy within the first year of therapy. Furthermore, first-line treatment with systemic chemotherapy has been associated with increased mortality (258). Therefore, multiagent chemotherapy is rarely utilized. Therefore, novel therapeutic agents, including clinical trial participation, are preferred. As there is no standard of care for patients with MF/SS requiring systemic chemotherapy and the decision to initiate therapy is individualized, including consideration of responses and complications related to prior therapies, participation in a well-designed clinical trial is always worth consideration.

Pralatrexate, a novel antifolate with a high affinity for the reduced folate carrier (RFC-1) and novel mechanism of resistance when compared with methotrexate (259-261), was associated with an overall response rate of 29% in

the PROPEL study. This study was comprised largely of peripheral T-cell lymphoma patients, most of whom had refractory disease (262). Notably, twelve patients with transformed MF were included in the study (263). Many of these patients had received more than 5 prior systemic therapies, including CHOP or CHOP-like regimens. With only a single exception, these patients were refractory to their most recent therapy. Responses, as assessed by the study investigators, were observed in 58% of patients with a median duration of response and progression-free survival of 4-5 months. Results of a dose-finding study were reported in a larger cohort of CTCL patients (264). In this study, the optimal dose was identified as 15 mg/m^2, given weekly 3 weeks out of 4, and was associated with an overall response rate of 43%. In an effort to reduce the incidence of mucositis, folic acid and vitamin B12 supplementation is routinely provided in these patients (265). Additional therapeutic approaches, including proteasome inhibition (266), immunomodulatory strategies (267), and more targeted approaches warrant further investigation (268, 269).

High-dose chemotherapy and hematopoietic stem cell transplantation. The available experience with high-dose chemotherapy and autologous stem cell transplantation, largely confined to case series, suggests that responses following treatment are frequently transient. In contrast, the durable remissions observed following allogeneic transplantation may be explained by the graft versus lymphoma immune response (270, 271). A retrospective analysis of 60 patients with advanced-stage MF/SS who underwent allogeneic stem cell transplantation was recently reported (272). In this series, patients had received a median of 4 prior therapies prior to undergoing either reduced-conditioning (73%) or myeloablative (27%) conditioning prior to related (75%) or matched-unrelated donor (25%) transplantation. Non-relapse mortality at 1 year was 14% for patients receiving reduced-intensity conditioning or HLA identical/related donor stem cells and 38-40% for those undergoing myeloablative conditioning or receiving match-unrelated donor grafts. Transplantation during an early phase of disease (defined as first or second remission or relapse following 3 or fewer systemic therapies) was associated with lower relapse rates (25% vs. 44% at 1 year) and a statistically insignificant increase in 3-year overall survival (68% vs. 46%). Given the differences in non-relapse mortality, both reduced-intensity conditioning and use of matched-related donors were associated with superior overall survival (63% at 3 years). Seventeen out of 26 patients who relapsed received donor-lymphocyte infusions. Of these, 47% achieved a complete remission, thus providing evidence for a graft-versus-lymphoma effect in MF/SS. The estimated 3-year progression-free and overall survival were 34% and 53%, respectively. A more recent update of the EBMT experience again demonstrates that allogeneic stem-cell transplantation is curative in a minority of patients, but non-relapse mortality and disease progression remain challenging (273).Similar outcomes have been observed in a large series from the CIBMTR (n=129), as non-relapse mortality and disease progression at 1 year were 19% and 50%, respectively, and 5-year PFS and OS were 17% and 32%, respectively (274). A systematic review and meta-analysis, pooling data from five studies (and 266 patients), demonstrated a

relapse rate following allogeneic transplantation of 47% and a non-relapse mortality rate of 19% (275). Given the possibility of complete and durable remissions, allogeneic stem-cell transplantation may be considered in highly selected patients(190, 276, 277).

Summary. Establishing a definitive diagnosis of CTCL, accurate disease staging and risk-stratification, and the selection of appropriate therapy requires a multidisciplinary approach. While high response rates may be achieved with systemic chemotherapy, these responses are frequently short-lived and associated with significant toxicities. As treatment of advanced-stage MF/SS is largely palliative, a stage-based approach utilizing sequential therapies in an escalated fashion is preferred. Participation in a well-designed clinical trial is encouraged, as the introduction of novel agents will continue to expand the therapeutic options available in the management of CTCL.

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Conflict of Interest

The authors declare no potential conflicts of interest.

References

1. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, Ralfkiaer E, Chimenti S, Diaz-Perez JL, Duncan LM, Grange F, Harris NL, Kempf W, Kerl H, Kurrer M, Knobler R, Pimpinelli N, Sander C, Santucci M, Sterry W, Vermeer MH, Wechsler J, Whittaker S, Meijer CJ. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-3785.
2. Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH, Jaffe ES. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019;133:1703-1714.
3. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, Bhagat G, Borges AM, Boyer D, Calaminici M, Chadburn A, Chan JKC, Cheuk W, Chng WJ, Choi JK, Chuang SS, Coupland SE, Czader M, Dave SS, de Jong D, Du MQ, Elenitoba-Johnson KS, Ferry J, Geyer J, Gratzinger D, Guitart J, Gujral S, Harris M, Harrison CJ, Hartmann S, Hochhaus A, Jansen PM, Karube K, Kempf W, Khoury J, Kimura H, Klapper W, Kovach AE, Kumar S, Lazar AJ, Lazzi S, Leoncini L, Leung N, Leventaki V, Li XQ, Lim MS, Liu WP, Louissaint A, Jr., Marcogliese A, Medeiros LJ, Michal M, Miranda RN, Mitteldorf C, Montes-Moreno S, Morice W, Nardi V, Naresh KN, Natkunam Y, Ng SB, Oschlies I, Ott G, Parrens M, Pulitzer M, Rajkumar SV, Rawstron AC, Rech K, Rosenwald A, Said J, Sarkozy C, Sayed S, Saygin C, Schuh A, Sewell W, Siebert R, Sohani AR, Tooze R, Traverse-Glehen A, Vega F, Vergier B, Wechalekar AD, Wood B, Xerri L, Xiao W. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720-1748.
4. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, Brousset P, Cerroni L, de Leval L, Dirnhofer S, Dogan A, Feldman A, Fend F, Friedberg JW, Gaulard P, Ghia P, Horwitz SM, King RL, Salles GA, San-Miguel JF, Seymour JF, Treon SP, Vose J, Zucca E, Advani R, Ansell SM, Au WY, Barrionuevo C, Bergsagel PL, Chan WC, Cohen JI, d'Amore F, Davies AJ, Falini B, Ghobrial IM, Goodlad JR, Gribben JG, Hsi ED, Kahl BS, Kim WS, Kumar SK, LaCasce AS, Laurent C, Lenz G, Leonard JP, Link MP, Lopez-Guillermo A, Mateos MV, Macintyre EA, Melnick AM, Morschhauser F, Nakamura S, Narbaitz M, Pavlovsky A, Pileri SA, Piris MA, Pro B, Rajkumar SVV, Rosen ST, Sander B, Sehn LH, Shipp MA, Smith SM, Staudt LM, Thieblemont C, Tousseyn T, Wilson WH, Yoshino T, Zinzani PL, Dreyling M, Scott DW, Winter JN, Zelenetz AD. The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee. Blood 2022.
5. Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973-2002. Arch Dermatol 2007;143:854-859.
6. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood 2009;113:5064-5073.
7. Johnson WT, Kartan S, Sokol K, Nikbakht N, Porcu P. Clinical characteristics and outcomes of black patients with mycosis fungoides and Sezary syndrome: a subgroup analysis of the phase III MAVORIC trial. Leuk Lymphoma 2021:1-8.
8. Geller S, Lebowitz E, Pulitzer MP, Horwitz SM, Moskowitz AJ, Dusza S, Myskowski PL. Outcomes and prognostic factors in African American and black patients with mycosis fungoides/Sezary syndrome: Retrospective analysis of 157 patients from a referral cancer center. J Am Acad Dermatol 2020;83:430-439.
9. Burns MK, Ellis CN, Cooper KD. Mycosis fungoides--type cutaneous T-cell lymphoma arising before 30 years of age. Immunophenotypic, immunogenotypic and clinicopathologic analysis of nine cases. J Am Acad Dermatol 1992;27:974-978.

10. Pope E, Weitzman S, Ngan B, Walsh S, Morel K, Williams J, Stein S, Garzon M, Knobler E, Lieber C, Turchan K, Wargon O, Tsuchiya A. Mycosis fungoides in the pediatric population: report from an international Childhood Registry of Cutaneous Lymphoma. J Cutan Med Surg 2010;14:1-6.
11. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, Robson A, Calonje E, Stefanato CM, Wain EM, Wilkins B, Fields PA, Dean A, Webb K, Scarisbrick J, Morris S, Whittaker SJ. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol 2010;28:4730-4739.
12. Jung JM, Lim DJ, Won CH, Chang SE, Lee MW, Lee WJ. Mycosis Fungoides in Children and Adolescents: A Systematic Review. JAMA Dermatol 2021;157:431-438.
13. Goyal A, O'Leary D, Goyal K, Patel K, Pearson D, Janakiram M. Cutaneous T-cell lymphoma is associated with increased risk of lymphoma, melanoma, lung cancer, and bladder cancer: A systematic review and meta-analysis. J Am Acad Dermatol 2020.
14. Goyal A, O'Leary D, Goyal K, Rubin N, Bohjanen K, Hordinsky M, Chen ST, Pongas G, Duncan LM, Lazaryan A. Increased risk of second primary hematologic and solid malignancies in patients with mycosis fungoides: A Surveillance, Epidemiology, and End Results analysis. J Am Acad Dermatol 2020;83:404-411.
15. Elenitoba-Johnson KS, Wilcox R. A new molecular paradigm in mycosis fungoides and Sezary syndrome. Semin Diagn Pathol 2017;34:15-21.
16. Jones CL, Degasperi A, Grandi V, Amarante TD, Genomics England Research C, Mitchell TJ, Nik-Zainal S, Whittaker SJ. Spectrum of mutational signatures in T-cell lymphoma reveals a key role for UV radiation in cutaneous T-cell lymphoma. Sci Rep 2021;11:3962.
17. Park J, Daniels J, Wartewig T, Ringbloom KG, Martinez-Escala ME, Choi S, Thomas JJ, Doukas PG, Yang J, Snowden C, Law C, Lee Y, Lee K, Zhang Y, Conran C, Tegtmeyer K, Mo SH, Pease DR, Jothishankar B, Kwok PY, Abdulla FR, Pro B, Louissaint A, Boggon T, Sosman J, Guitart J, Rao DA, Ruland J, Choi J. Integrated Genomic Analyses of Cutaneous T Cell Lymphomas Reveal the Molecular Bases for Disease Heterogeneity. Blood 2021.
18. Whittemore AS, Holly EA, Lee IM, Abel EA, Adams RM, Nickoloff BJ, Bley L, Peters JM, Gibney C. Mycosis fungoides in relation to environmental exposures and immune response: a case-control study. J Natl Cancer Inst 1989;81:1560-1567.
19. Magro CM, Crowson AN, Kovatich AJ, Burns F. Drug-induced reversible lymphoid dyscrasia: a clonal lymphomatoid dermatitis of memory and activated T cells. Hum Pathol 2003;34:119-129.
20. Jahan-Tigh RR, Huen AO, Lee GL, Pozadzides JV, Liu P, Duvic M. Hydrochlorothiazide and cutaneous T cell lymphoma: prospective analysis and case series. Cancer 2013;119:825-831.
21. Hodak E, Klein T, Gabay B, Ben-Amitai D, Bergman R, Gdalevich M, Feinmesser M, Maron L, David M. Familial mycosis fungoides: report of 6 kindreds and a study of the HLA system. J Am Acad Dermatol 2005;52:393-402.
22. Hodak E, Lapidoth M, Kohn K, David D, Brautbar B, Kfir K, Narinski N, Safirman S, Maron M, Klein K. Mycosis fungoides: HLA class II associations among Ashkenazi and non-Ashkenazi Jewish patients. Br J Dermatol 2001;145:974-980.
23. Jackow CM, McHam JB, Friss A, Alvear J, Reveille JR, Duvic M. HLA-DR5 and DQB1*03 class II alleles are associated with cutaneous T-cell lymphoma. J Invest Dermatol 1996;107:373-376.
24. Tuyp E, Burgoyne A, Aitchison T, MacKie R. A case-control study of possible causative factors in mycosis fungoides. Arch Dermatol 1987;123:196-200.

25. Wohl Y, Tur E. Environmental risk factors for mycosis fungoides. Curr Probl Dermatol 2007;35:52-64.
26. Morales Suarez-Varela MM, Olsen J, Kaerlev L, Guenel P, Arveux P, Wingren G, Hardell L, Ahrens W, Stang A, Llopis-Gonzalez A, Merletti F, Guillen-Grima F, Johansen P. Are alcohol intake and smoking associated with mycosis fungoides? A European multicentre case-control study. Eur J Cancer 2001;37:392-397.
27. Morales-Suarez-Varela MM, Olsen J, Johansen P, Kaerlev L, Guenel P, Arveux P, Wingren G, Hardell L, Ahrens W, Stang A, Llopis A, Merletti F, Guillen-Grima F, Masala G. Occupational sun exposure and mycosis fungoides: a European multicenter case-control study. J Occup Environ Med 2006;48:390-393.
28. Wilcox RA. Cutaneous T-cell lymphoma: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol 2017;92:1085-1102.
29. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol 2003;139:857-866.
30. van Doorn R, Van Haselen CW, van Voorst Vader PC, Geerts ML, Heule F, de Rie M, Steijlen PM, Dekker SK, van Vloten WA, Willemze R. Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. Arch Dermatol 2000;136:504-510.
31. Arulogun SO, Prince HM, Ng J, Lade S, Ryan GF, Blewitt O, McCormack C. Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. Blood 2008;112:3082-3087.
32. Hurabielle C, Ingen-Housz-Oro S, Ortonne N, Cornillet-Lefebvre P, Merah A, D'Incan M, Joly P, Franck N, Esteve E, Maubec E, Grange F, Machet L, Laroche L, Barete S, Dalac S, Mortier L, Michel C, Quereux G, Saiag P, Ram-Wolff C, Lenormand B, Wechsler J, Bastuji-Garin S, Bagot M, Delfau-Larue MH. Frequency and prognostic value of cutaneous molecular residual disease in mycosis fungoides: a prospective multicentre trial of the Cutaneous Lymphoma French Study Group. Br J Dermatol 2015;173:1015-1023.
33. Dereure O, Picot E, Comte C, Bessis D, Guillot B. Treatment of early stages of mycosis fungoides with narrowband ultraviolet B. A clinical, histological and molecular evaluation of results. Dermatology 2009;218:1-6.
34. Pimpinelli N, Olsen EA, Santucci M, Vonderheid E, Haeffner AC, Stevens S, Burg G, Cerroni L, Dreno B, Glusac E, Guitart J, Heald PW, Kempf W, Knobler R, Lessin S, Sander C, Smoller BS, Telang G, Whittaker S, Iwatsuki K, Obitz E, Takigawa M, Turner ML, Wood GS. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1053-1063.
35. Song SX, Willemze R, Swerdlow SH, Kinney MC, Said JW. Mycosis fungoides: report of the 2011 Society for Hematopathology/European Association for Haematopathology workshop. Am J Clin Pathol 2013;139:466-490.
36. Morgan SM, Hodges E, Mitchell TJ, Harris S, Whittaker SJ, Smith JL. Molecular analysis of T-cell receptor beta genes in cutaneous T-cell lymphoma reveals Jbeta1 bias. J Invest Dermatol 2006;126:1893-1899.
37. Ponti R, Quaglino P, Novelli M, Fierro MT, Comessatti A, Peroni A, Bonello L, Bernengo MG. T-cell receptor gamma gene rearrangement by multiplex polymerase chain reaction/heteroduplex analysis in patients with cutaneous T-cell lymphoma (mycosis fungoides/Sezary syndrome) and benign inflammatory disease: correlation with clinical, histological and immunophenotypical findings. Br J Dermatol 2005;153:565-573.
38. Guitart J, Magro C. Cutaneous T-cell lymphoid dyscrasia: a unifying term for idiopathic chronic dermatoses with persistent T-cell clones. Arch Dermatol 2007;143:921-932.

39. Posnett DN, Sinha R, Kabak S, Russo C. Clonal populations of T cells in normal elderly humans: the T cell equivalent to "benign monoclonal gammapathy". J Exp Med 1994;179:609-618.
40. Epling-Burnette PK, Painter JS, Rollison DE, Ku E, Vendron D, Widen R, Boulware D, Zou JX, Bai F, List AF. Prevalence and clinical association of clonal T-cell expansions in Myelodysplastic Syndrome. Leukemia 2007;21:659-667.
41. Martinez A, Pittaluga S, Villamor N, Colomer D, Rozman M, Raffeld M, Montserrat E, Campo E, Jaffe ES. Clonal T-cell populations and increased risk for cytotoxic T-cell lymphomas in B-CLL patients: clinicopathologic observations and molecular analysis. Am J Surg Pathol 2004;28:849-858.
42. Kohler S, Jones CD, Warnke RA, Zehnder JL. PCR-heteroduplex analysis of T-cell receptor gamma gene rearrangement in paraffin-embedded skin biopsies. Am J Dermatopathol 2000;22:321-327.
43. Thurber SE, Zhang B, Kim YH, Schrijver I, Zehnder J, Kohler S. T-cell clonality analysis in biopsy specimens from two different skin sites shows high specificity in the diagnosis of patients with suggested mycosis fungoides. J Am Acad Dermatol 2007;57:782-790.
44. Rojansky R, Fernandez-Pol S, Wang E, Rieger KE, Novoa RA, Zehnder JL, Kunder CA, Kim YH, Khodadoust MS, Brown RA. Cutaneous T-cell lymphomas with pathogenic somatic mutations and absence of detectable clonal T-cell receptor gene rearrangement: two case reports. Diagnostic pathology 2020;15:122.
45. Sufficool KE, Lockwood CM, Abel HJ, Hagemann IS, Schumacher JA, Kelley TW, Duncavage EJ. T-cell clonality assessment by next-generation sequencing improves detection sensitivity in mycosis fungoides. J Am Acad Dermatol 2015;73:228-236 e222.
46. Rea B, Haun P, Emerson R, Vignali M, Farooqi M, Samimi S, Elenitsas R, Kirsch I, Bagg A. Role of high-throughput sequencing in the diagnosis of cutaneous T-cell lymphoma. J Clin Pathol 2018;71:814-820.
47. Gibbs JD, Ma S, Kim A, Seminario-Vidal L, Sokol L, Zhang H, Zhang X, Sagatys E, Chen PL, Messina JL. Utility of flow cytometry and gene rearrangement analysis in tissue and blood of patients with suspected cutaneous Tcell lymphoma. Oncol Rep 2021;45:349-358.
48. Raghavan SS, Wang JY, Gru AA, Marqueling AL, Teng JMC, Brown RA, Novoa RA, Kim Y, Zehnder J, Zhang BM, Rieger KE. Next-generation sequencing confirms T-cell clonality in a subset of pediatric pityriasis lichenoides. J Cutan Pathol 2022;49:252-260.
49. Gniadecki R, Lukowsky A. Monoclonal T-cell dyscrasia of undetermined significance associated with recalcitrant erythroderma. Arch Dermatol 2005;141:361-367.
50. Ormsby A, Bergfeld WF, Tubbs RR, Hsi ED. Evaluation of a new paraffin-reactive CD7 T-cell deletion marker and a polymerase chain reaction-based T-cell receptor gene rearrangement assay: implications for diagnosis of mycosis fungoides in community clinical practice. J Am Acad Dermatol 2001;45:405-413.
51. Michie SA, Abel EA, Hoppe RT, Warnke RA, Wood GS. Discordant expression of antigens between intraepidermal and intradermal T cells in mycosis fungoides. Am J Pathol 1990;137:1447-1451.
52. Espinosa ML, Walker CJ, Guitart J, Mhlaba JM. Morphology of Mycosis Fungoides and Sezary Syndrome in Skin of Color. Cutis 2022;109:E3-E7.
53. Kazakov DV, Burg G, Kempf W. Clinicopathological spectrum of mycosis fungoides. J Eur Acad Dermatol Venereol 2004;18:397-415.

54. Hadi R, Miller TI, May C, Lehman JS, Bennett DD, Piliang M, Chang O, Shinohara MM. Impact of clinical photographs on the accuracy and confidence in the histopathological diagnosis of mycosis fungoides. J Cutan Pathol 2021;48:842-846.
55. Dittmer M, Brown-Joel ZO, Smith HL, Liu V. Influence of clinical information on the histopathological diagnosis of mycosis fungoides: A follow-up study using scanned slide image review. J Cutan Pathol 2021;48:719-720.
56. Sezary A, Bouvrain Y. Erythrodermie avec presence de cellules monstrueses dans le derme et le sang circulant. Bull Soc Fr Derm Syph 1938;45:254-260.
57. Main RA, Goodall HB, Swanson WC. Sezary's syndrome. Br J Dermatol 1959;71:335-343.
58. Taswell HF, Winkelmann RK. Sezary syndrome--a malignant reticulemic erythroderma. Jama 1961;177:465-472.
59. Lutzner MA, Emerit I, Durepaire R, Flandrin G, Grupper C, Prunieras M. Cytogenetic, cytophotometric, and ultrastructural study of large cerebriform cells of the Sezary syndrome and description of a small-cell variant. J Natl Cancer Inst 1973;50:1145-1162.
60. Lutzner MA, Jordan HW. The ultrastructure of an abnormal cell in Sezary's syndrome. Blood 1968;31:719-726.
61. Edelson RL, Lutzner MA, Kirkpatrick CH, Shevach EM, Green I. Morphologic and functional properties of the atypical T lymphocytes of the Sezary syndrome. Mayo Clin Proc 1974;49:558-566.
62. Lutzner MA, Hobbs JW, Horvath P. Ultrastructure of abnormal cells in Sezary syndrome, mycosis fungoides, and parapsoriasis en plaque. Arch Dermatol 1971;103:375-386.
63. Matutes E, Robinson D, O'Brien M, Haynes BF, Zola H, Catovsky D. Candidate counterparts of Sezary cells and adult T-cell lymphoma-leukaemia cells in normal peripheral blood: an ultrastructural study with the immunogold method and monoclonal antibodies. Leuk Res 1983;7:787-801.
64. Reinhold U, Herpertz M, Kukel S, Oltermann I, Uerlich M, Kreysel HW. Induction of nuclear contour irregularity during T-cell activation via the T-cell receptor/CD3 complex and CD2 antigens in the presence of phorbol esters. Blood 1994;83:703-706.
65. Scheffer E, Meijer CJ, van Vloten WA, Willemze R. A histologic study of lymph nodes from patients with the Sezary syndrome. Cancer 1986;57:2375-2380.
66. Willemze R, van Vloten WA, Hermans J, Damsteeg MJ, Meijer CJ. Diagnostic criteria in Sezary's syndrome: a multiparameter study of peripheral blood lymphocytes in 32 patients with erythroderma. J Invest Dermatol 1983;81:392-397.
67. Boumsell L, Bernard A, Reinherz EL, Nadler LM, Ritz J, Coppin H, Richard Y, Dubertret L, Valensi F, Degos L, Lemerle J, Flandrin G, Dausset J, Schlossman SF. Surface antigens on malignant Sezary and T-CLL cells correspond to those of mature T cells. Blood 1981;57:526-530.
68. Vonderheid EC, Bernengo MG, Burg G, Duvic M, Heald P, Laroche L, Olsen E, Pittelkow M, Russell-Jones R, Takigawa M, Willemze R. Update on erythrodermic cutaneous T-cell lymphoma: report of the International Society for Cutaneous Lymphomas. J Am Acad Dermatol 2002;46:95-106.
69. Hristov AC, Vonderheid EC, Borowitz MJ. Simplified flow cytometric assessment in mycosis fungoides and Sezary syndrome. Am J Clin Pathol 2011;136:944-953.
70. Bernengo MG, Quaglino P, Novelli M, Cappello N, Doveil GC, Lisa F, De Matteis A, Fierro MT, Appino A. Prognostic factors in Sezary syndrome: a multivariate analysis of clinical, haematological and immunological features. Ann Oncol 1998;9:857-863.

71. Harmon CB, Witzig TE, Katzmann JA, Pittelkow MR. Detection of circulating T cells with CD4+CD7- immunophenotype in patients with benign and malignant lymphoproliferative dermatoses. J Am Acad Dermatol 1996;35:404-410.
72. Klemke CD, Booken N, Weiss C, Nicolay JP, Goerdt S, Felcht M, Geraud C, Kempf W, Assaf C, Ortonne N, Battistella M, Bagot M, Knobler R, Quaglino P, Arheiliger B, Santucci M, Jansen P, Vermeer MH, Willemze R. Histopathological and immunophenotypical criteria for the diagnosis of Sezary syndrome in differentiation from other erythrodermic skin diseases: a European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force Study of 97 cases. Br J Dermatol 2015;173:93-105.
73. Boonk SE, Zoutman WH, Marie-Cardine A, van der Fits L, Out-Luiting JJ, Mitchell TJ, Tosi I, Morris SL, Moriarty B, Booken N, Felcht M, Quaglino P, Ponti R, Barberio E, Ram-Wolff C, Jantti K, Ranki A, Bernengo MG, Klemke CD, Bensussan A, Michel L, Whittaker S, Bagot M, Tensen CP, Willemze R, Vermeer MH. Evaluation of Immunophenotypic and Molecular Biomarkers for Sezary Syndrome Using Standard Operating Procedures: A Multicenter Study of 59 Patients. J Invest Dermatol 2016;136:1364-1372.
74. Bogen SA, Pelley D, Charif M, McCusker M, Koh H, Foss F, Garifallou M, Arkin C, Zucker-Franklin D. Immunophenotypic identification of Sezary cells in peripheral blood. Am J Clin Pathol 1996;106:739-748.
75. Ginaldi L, Matutes E, Farahat N, De Martinis M, Morilla R, Catovsky D. Differential expression of CD3 and CD7 in T-cell malignancies: a quantitative study by flow cytometry. Br J Haematol 1996;93:921-927.
76. Jones D, Dang NH, Duvic M, Washington LT, Huh YO. Absence of CD26 expression is a useful marker for diagnosis of T-cell lymphoma in peripheral blood. Am J Clin Pathol 2001;115:885-892.
77. Pierson DM, Jones D, Muzzafar T, Kersh MJ, Challagundla P, Medeiros LJ, Jorgensen JL. Utility of CD26 in flow cytometric immunophenotyping of T-cell lymphomas in tissue and body fluid specimens. Cytometry B Clin Cytom 2008;74:341-348.
78. Sokolowska-Wojdylo M, Wenzel J, Gaffal E, Steitz J, Roszkiewicz J, Bieber T, Tuting T. Absence of CD26 expression on skin-homing CLA+ CD4+ T lymphocytes in peripheral blood is a highly sensitive marker for early diagnosis and therapeutic monitoring of patients with Sezary syndrome. Clin Exp Dermatol 2005;30:702-706.
79. Scarisbrick JJ, Hodak E, Bagot M, Stranzenbach R, Stadler R, Ortiz-Romero PL, Papadavid E, Evison F, Knobler R, Quaglino P, Vermeer MH. Blood classification and blood response criteria in mycosis fungoides and Sezary syndrome using flow cytometry: recommendations from the EORTC cutaneous lymphoma task force. Eur J Cancer 2018;93:47-56.
80. Olsen EA, Whittaker S, Willemze R, Pinter-Brown L, Foss FM, Geskin LJ, Schwartz LH, Horwitz SM, Guitart J, Zic J, Kim YH, Wood GS, Duvic M, Ai WZ, Girardi M, Gru A, Guenova E, Hodak E, Hoppe RT, Kempf W, Kim EJ, Lechowicz MJ, Ortiz-Romero PL, Papadavid E, Quaglino P, Pittelkow MR, Prince HM, Sanches JA, Sugaya M, Vermeer MH, Zain J, Knobler R, Stadler R, Bagot M, Scarisbrick JJ. Primary Cutaneous Lymphoma: Recommendations for Clinical Trial Design and Staging Update from the ISCL, USCLC, and EORTC. Blood 2021.
81. Vermeer MH, Moins-Teisserenc H, Bagot M, Quaglino P, Whittaker S. Flow cytometry for the assessment of blood tumour burden in cutaneous T-cell lymphoma: towards a standardized approach. Br J Dermatol 2022;187:21-28.

82. Bahler DW, Hartung L, Hill S, Bowen GM, Vonderheid EC. CD158k/KIR3DL2 is a useful marker for identifying neoplastic T-cells in Sezary syndrome by flow cytometry. Cytometry B Clin Cytom 2008;74:156-162.
83. Poszepczynska-Guigne E, Schiavon V, D'Incan M, Echchakir H, Musette P, Ortonne N, Boumsell L, Moretta A, Bensussan A, Bagot M. CD158k/KIR3DL2 is a new phenotypic marker of Sezary cells: relevance for the diagnosis and follow-up of Sezary syndrome. J Invest Dermatol 2004;122:820-823.
84. Klemke CD, Brade J, Weckesser S, Sachse MM, Booken N, Neumaier M, Goerdt S, Nebe TC. The diagnosis of Sezary syndrome on peripheral blood by flow cytometry requires the use of multiple markers. Br J Dermatol 2008;159:871-880.
85. Morice WG, Kimlinger T, Katzmann JA, Lust JA, Heimgartner PJ, Halling KC, Hanson CA. Flow cytometric assessment of TCR-Vbeta expression in the evaluation of peripheral blood involvement by T-cell lymphoproliferative disorders: a comparison with conventional T-cell immunophenotyping and molecular genetic techniques. Am J Clin Pathol 2004;121:373-383.
86. Schwab C, Willers J, Niederer E, Ludwig E, Kundig T, Grob P, Burg G, Dummer R. The use of anti-T-cell receptor-Vbeta antibodies for the estimation of treatment success and phenotypic characterization of clonal T-cell populations in cutaneous T-cell lymphomas. Br J Haematol 2002;118:1019-1026.
87. Clark RA, Shackelton JB, Watanabe R, Calarese A, Yamanaka K, Campbell JJ, Teague JE, Kuo HP, Hijnen D, Kupper TS. High-scatter T cells: a reliable biomarker for malignant T cells in cutaneous T-cell lymphoma. Blood 2011;117:1966-1976.
88. Horna P, Otteson GE, Shi M, Jevremovic D, Yuan J, Olteanu H. Flow Cytometric Evaluation of Surface and Cytoplasmic TRBC1 Expression in the Differential Diagnosis of Immature T-Cell Proliferations. Am J Clin Pathol 2022;157:64-72.
89. Horna P, Shi M, Jevremovic D, Craig FE, Comfere NI, Olteanu H. Utility of TRBC1 Expression in the Diagnosis of Peripheral Blood Involvement by Cutaneous T-Cell Lymphoma. J Invest Dermatol 2021;141:821-829 e822.
90. Horna P, Shi M, Olteanu H, Johansson U. Emerging Role of T-cell Receptor Constant beta Chain-1 (TRBC1) Expression in the Flow Cytometric Diagnosis of T-cell Malignancies. Int J Mol Sci 2021;22.
91. Wang L, Rocas D, Dalle S, Sako N, Pelletier L, Martin N, Dupuy A, Tazi N, Balme B, Vergier B, Beylot Barry M, Carlotti A, Bagot M, Battistella M, Chaby G, Ingen-Housz-Oro S, Gaulard P, Ortonne N. Primary cutaneous peripheral T-cell lymphomas with a T follicular helper phenotype: An integrative clinical, pathological, and molecular case series study. Br J Dermatol 2022.
92. Wilcox RA. Cutaneous T-cell lymphoma: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol 2011;86:928-948.
93. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, Zackheim H, Duvic M, Estrach T, Lamberg S, Wood G, Dummer R, Ranki A, Burg G, Heald P, Pittelkow M, Bernengo MG, Sterry W, Laroche L, Trautinger F, Whittaker S. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713-1722.
94. Scheffer E, Meijer CJ, Van Vloten WA. Dermatopathic lymphadenopathy and lymph node involvement in mycosis fungoides. Cancer 1980;45:137-148.
95. Sausville EA, Worsham GF, Matthews MJ, Makuch RW, Fischmann AB, Schechter GP, Gazdar AF, Bunn PA, Jr. Histologic assessment of lymph nodes in mycosis fungoides/Sezary syndrome (cutaneous T-cell lymphoma): clinical correlations and prognostic import of a new classification system. Hum Pathol 1985;16:1098-1109.

96. Clendenning WE, Rappaport HW. Report of the Committee on Pathology of Cutaneous T Cell Lymphomas. Cancer Treat Rep 1979;63:719-724.
97. Hodak E, Sherman S, Papadavid E, Bagot M, Querfeld C, Quaglino P, Prince HM, Ortiz-Romero PL, Stadler R, Knobler R, Guenova E, Estrach T, Patsatsi A, Leshem YA, Prague-Naveh H, Berti E, Alberti-Violetti S, Cowan R, Jonak C, Nikolaou V, Mitteldorf C, Akilov O, Geskin L, Matin R, Beylot-Barry M, Vakeva L, Sanches JA, Servitje O, Weatherhead S, Wobser M, Yoo J, Bayne M, Bates A, Dunnill G, Marschalko M, Buschots AM, Wehkamp U, Evison F, Hong E, Amitay-Laish I, Stranzenbach R, Vermeer M, Willemze R, Kempf W, Cerroni L, Whittaker S, Kim YH, Scarisbrick JJ, Cutaneous Lymphoma International Consortium i. Should we be imaging lymph nodes at initial diagnosis of early-stage mycosis fungoides? Results from the PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) international study. Br J Dermatol 2021;184:524-531.
98. Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M, Committee EG. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv30-iv40.
99. Fraser-Andrews EA, Mitchell T, Ferreira S, Seed PT, Russell-Jones R, Calonje E, Whittaker SJ. Molecular staging of lymph nodes from 60 patients with mycosis fungoides and Sezary syndrome: correlation with histopathology and outcome suggests prognostic relevance in mycosis fungoides. Br J Dermatol 2006;155:756-762.
100. Assaf C, Hummel M, Steinhoff M, Geilen CC, Orawa H, Stein H, Orfanos CE. Early TCR-beta and TCR-gamma PCR detection of T-cell clonality indicates minimal tumor disease in lymph nodes of cutaneous T-cell lymphoma: diagnostic and prognostic implications. Blood 2005;105:503-510.
101. Scarisbrick JJ, Whittaker S, Evans AV, Fraser-Andrews EA, Child FJ, Dean A, Russell-Jones R. Prognostic significance of tumor burden in the blood of patients with erythrodermic primary cutaneous T-cell lymphoma. Blood 2001;97:624-630.
102. Fraser-Andrews EA, Woolford AJ, Russell-Jones R, Seed PT, Whittaker SJ. Detection of a peripheral blood T cell clone is an independent prognostic marker in mycosis fungoides. The Journal of investigative dermatology 2000;114:117-121.
103. Mourad A, Gniadecki R. Overall Survival in Mycosis Fungoides: A Systematic Review and Meta-Analysis. J Invest Dermatol 2020;140:495-497 e495.
104. Benton EC, Crichton S, Talpur R, Agar NS, Fields PA, Wedgeworth E, Mitchell TJ, Cox M, Ferreira S, Liu P, Robson A, Calonje E, Stefanato CM, Wilkins B, Scarisbrick J, Wain EM, Child F, Morris S, Duvic M, Whittaker SJ. A cutaneous lymphoma international prognostic index (CLIPi) for mycosis fungoides and Sezary syndrome. Eur J Cancer 2013;49:2859-2868.
105. Scarisbrick JJ, Prince HM, Vermeer MH, Quaglino P, Horwitz S, Porcu P, Stadler R, Wood GS, Beylot-Barry M, Pham-Ledard A, Foss F, Girardi M, Bagot M, Michel L, Battistella M, Guitart J, Kuzel TM, Martinez-Escala ME, Estrach T, Papadavid E, Antoniou C, Rigopoulos D, Nikolaou V, Sugaya M, Miyagaki T, Gniadecki R, Sanches JA, Cury-Martins J, Miyashiro D, Servitje O, Muniesa C, Berti E, Onida F, Corti L, Hodak E, Amitay-Laish I, Ortiz-Romero PL, Rodriguez-Peralto JL, Knobler R, Porkert S, Bauer W, Pimpinelli N, Grandi V, Cowan R, Rook A, Kim E, Pileri A, Patrizi A, Pujol RM, Wong H, Tyler K, Stranzenbach R, Querfeld C, Fava P, Maule M, Willemze R, Evison F, Morris S, Twigger R, Talpur R, Kim J, Ognibene G, Li S, Tavallaee M, Hoppe RT, Duvic M, Whittaker SJ, Kim YH. Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sezary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. J Clin Oncol 2015;33:3766-3773.

106. Vergier B, de Muret A, Beylot-Barry M, Vaillant L, Ekouevi D, Chene G, Carlotti A, Franck N, Dechelotte P, Souteyrand P, Courville P, Joly P, Delaunay M, Bagot M, Grange F, Fraitag S, Bosq J, Petrella T, Durlach A, De Mascarel A, Merlio JP, Wechsler J. Transformation of mycosis fungoides: clinicopathological and prognostic features of 45 cases. French Study Group of Cutaneious Lymphomas. Blood 2000;95:2212-2218.
107. Greer JP, Salhany KE, Cousar JB, Fields JP, King LE, Graber SE, Flexner JM, Stein RS, Collins RD. Clinical features associated with transformation of cerebriform T-cell lymphoma to a large cell process. Hematol Oncol 1990;8:215-227.
108. Salhany KE, Cousar JB, Greer JP, Casey TT, Fields JP, Collins RD. Transformation of cutaneous T cell lymphoma to large cell lymphoma. A clinicopathologic and immunologic study. The American journal of pathology 1988;132:265-277.
109. Diamandidou E, Colome M, Fayad L, Duvic M, Kurzrock R. Prognostic factor analysis in mycosis fungoides/Sezary syndrome. J Am Acad Dermatol 1999;40:914-924.
110. Diamandidou E, Colome-Grimmer M, Fayad L, Duvic M, Kurzrock R. Transformation of mycosis fungoides/Sezary syndrome: clinical characteristics and prognosis. Blood 1998;92:1150-1159.
111. Charli-Joseph Y, Kashani-Sabet M, McCalmont TH, Kornak J, Allen I, Ai WZ, LeBoit PE, Pincus LB. Association of a Proposed New Staging System for Folliculotropic Mycosis Fungoides With Prognostic Variables in a US Cohort. JAMA Dermatol 2021;157:157-165.
112. van Santen S, Roach RE, van Doorn R, Horvath B, Bruijn MS, Sanders CJ, de Pooter JC, van Rossum MM, de Haas ER, Veraart JC, Bekkenk MW, Vermeer MH, Willemze R. Clinical Staging and Prognostic Factors in Folliculotropic Mycosis Fungoides. JAMA Dermatol 2016;152:992-1000.
113. Kim YH, Willemze R, Pimpinelli N, Whittaker S, Olsen EA, Ranki A, Dummer R, Hoppe RT, EORTC Iat. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:479-484.
114. Kaye FJ, Bunn PA, Jr., Steinberg SM, Stocker JL, Ihde DC, Fischmann AB, Glatstein EJ, Schechter GP, Phelps RM, Foss FM, et al. A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. N Engl J Med 1989;321:1784-1790.
115. Quaglino P, Prince HM, Cowan R, Vermeer M, Papadavid E, Bagot M, Servitjie O, Berti E, Guenova E, Stadler R, Querfeld C, Busschots AM, Hodak E, Patsatsi A, Sanches J, Maule M, Yoo J, Kevin M, Fava P, Ribero S, Zocchi L, Rubatto M, Fierro MT, Wehkamp U, Marshalko M, Mitteldorf C, Akilov O, Ortiz-Romero P, Estrach T, Vakeva L, Enz PA, Wobser M, Bayne M, Jonak C, Rubeta M, Forbes A, Bates A, Battistella M, Amel-Kashipaz R, Vydianath B, Combalia A, Georgiou E, Hauben E, Hong EK, Jost M, Knobler R, Amitay-Laish I, Miyashiro D, Cury-Martins J, Martinez X, Muniesa C, Prag-Naveh H, Stratigos A, Nikolaou V, Quint K, Ram-Wolff C, Rieger K, Stranzenbach R, Szepesi A, Alberti-Violetti S, Felicity E, Cerroni L, Kempf W, Whittaker S, Willemze R, Kim Y, Scarisbrick JJ. Treatment of early-stage mycosis fungoides: results from the PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study. Br J Dermatol 2021;184:722-730.
116. Hughes CF, Khot A, McCormack C, Lade S, Westerman DA, Twigger R, Buelens O, Newland K, Tam C, Dickinson M, Ryan G, Ritchie D, Wood C, Prince HM. Lack of durable disease control with chemotherapy for mycosis fungoides and Sezary syndrome: a comparative study of systemic therapy. Blood 2015;125:71-81.

117. Hanel W, Briski R, Ross CW, Anderson TF, Kaminski MS, Hristov AC, Wilcox RA. A retrospective comparative outcome analysis following systemic therapy in Mycosis fungoides and Sezary syndrome. Am J Hematol 2016;91:E491-E495.
118. Trautinger F, Knobler R, Willemze R, Peris K, Stadler R, Laroche L, D'Incan M, Ranki A, Pimpinelli N, Ortiz-Romero P, Dummer R, Estrach T, Whittaker S. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. European Journal of Cancer 2006;42:1014-1030.
119. Lansigan F, Foss FM. Current and emerging treatment strategies for cutaneous T-cell lymphoma. Drugs 2010;70:273-286.
120. Horwitz SM, Olsen EA, Duvic M, Porcu P, Kim YH. Review of the treatment of mycosis fungoides and sezary syndrome: a stage-based approach. J Natl Compr Canc Netw 2008;6:436-442.
121. Prince HM, Whittaker S, Hoppe RT. How I treat mycosis fungoides and Sezary syndrome. Blood 2009;114:4337-4353.
122. Whittaker SJ, Marsden JR, Spittle M, Russell Jones R. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. Br J Dermatol 2003;149:1095-1107.
123. Jones GW, Kacinski BM, Wilson LD, Willemze R, Spittle M, Hohenberg G, Handl-Zeller L, Trautinger F, Knobler R. Total skin electron radiation in the management of mycosis fungoides: Consensus of the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group. J Am Acad Dermatol 2002;47:364-370.
124. Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol 1998;134:949-954.
125. Demierre MF, Kim YH, Zackheim HS. Prognosis, clinical outcomes and quality of life issues in cutaneous T-cell lymphoma. Hematol Oncol Clin North Am 2003;17:1485-1507.
126. Kim EJ, Guitart J, Querfeld C, Girardi M, Musiek A, Akilov OE, Angello JT, Bailey WL, Geskin LJ. The PROVe Study: US Real-World Experience with Chlormethine/Mechlorethamine Gel in Combination with Other Therapies for Patients with Mycosis Fungoides Cutaneous T-Cell Lymphoma. Am J Clin Dermatol 2021;22:407-414.
127. Lessin SR, Duvic M, Guitart J, Pandya AG, Strober BE, Olsen EA, Hull CM, Knobler EH, Rook AH, Kim EJ, Naylor MF, Adelson DM, Kimball AB, Wood GS, Sundram U, Wu H, Kim YH. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol 2013;149:25-32.
128. Breneman D, Duvic M, Kuzel T, Yocum R, Truglia J, Stevens VJ. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma. Arch Dermatol 2002;138:325-332.
129. Huen AO, Rook AH. Toll receptor agonist therapy of skin cancer and cutaneous T-cell lymphoma. Curr Opin Oncol 2014;26:237-244.
130. Shipman AR, Scarisbrick J. New Treatment Options for Mycosis Fungoides. Indian J Dermatol 2016;61:119.
131. Rook AH, Gelfand JM, Wysocka M, Troxel AB, Benoit B, Surber C, Elenitsas R, Buchanan MA, Leahy DS, Watanabe R, Kirsch IR, Kim EJ, Clark RA. Topical resiquimod can induce disease regression and enhance T-cell effector functions in cutaneous T-cell lymphoma. Blood 2015;126:1452-1461.

132. Gathers RC, Scherschun L, Malick F, Fivenson DP, Lim HW. Narrowband UVB phototherapy for early-stage mycosis fungoides. J Am Acad Dermatol 2002;47:191-197.
133. Olsen EA, Hodak E, Anderson T, Carter JB, Henderson M, Cooper K, Lim HW. Guidelines for phototherapy of mycosis fungoides and Sezary syndrome: A consensus statement of the United States Cutaneous Lymphoma Consortium. J Am Acad Dermatol 2016;74:27-58.
134. Fong S, Hong EK, Khodadoust MS, Li S, Hoppe RT, Kim YH, Hiniker SM. Low-Dose Total Skin Electron Beam Therapy Combined With Mogamulizumab for Refractory Mycosis Fungoides and Sezary Syndrome. Adv Radiat Oncol 2021;6:100629.
135. Specht L, Dabaja B, Illidge T, Wilson LD, Hoppe RT, International Lymphoma Radiation Oncology G. Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2015;92:32-39.
136. Hoppe RT, Harrison C, Tavallaee M, Bashey S, Sundram U, Li S, Million L, Dabaja B, Gangar P, Duvic M, Kim YH. Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: results of a pooled analysis from 3 phase-II clinical trials. J Am Acad Dermatol 2015;72:286-292.
137. Wilcox RA. Cutaneous T-cell lymphoma: 2014 update on diagnosis, risk-stratification, and management. Am J Hematol 2014;89:837-851.
138. Kempf W, Kettelhack N, Duvic M, Burg G. Topical and systemic retinoid therapy for cutaneous T-cell lymphoma. Hematol Oncol Clin North Am 2003;17:1405-1419.
139. Zhang C, Duvic M. Retinoids: therapeutic applications and mechanisms of action in cutaneous T-cell lymphoma. Dermatol Ther 2003;16:322-330.
140. Nieto-Rementeria N, Perez-Yarza G, Boyano MD, Apraiz A, Izu R, Diaz-Perez JL, Asumendi A. Bexarotene activates the p53/p73 pathway in human cutaneous T-cell lymphoma. Br J Dermatol 2009;160:519-526.
141. Zhang C, Hazarika P, Ni X, Weidner DA, Duvic M. Induction of apoptosis by bexarotene in cutaneous T-cell lymphoma cells: relevance to mechanism of therapeutic action. Clin Cancer Res 2002;8:1234-1240.
142. Duvic M, Hymes K, Heald P, Breneman D, Martin AG, Myskowski P, Crowley C, Yocum RC. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol 2001;19:2456-2471.
143. Abbott RA, Whittaker SJ, Morris SL, Russell-Jones R, Hung T, Bashir SJ, Scarisbrick JJ. Bexarotene therapy for mycosis fungoides and Sezary syndrome. Br J Dermatol 2009;160:1299-1307.
144. Assaf C, Bagot M, Dummer R, Duvic M, Gniadecki R, Knobler R, Ranki A, Schwandt P, Whittaker S. Minimizing adverse side-effects of oral bexarotene in cutaneous T-cell lymphoma: an expert opinion. Br J Dermatol 2006;155:261-266.
145. Gniadecki R, Assaf C, Bagot M, Dummer R, Duvic M, Knobler R, Ranki A, Schwandt P, Whittaker S. The optimal use of bexarotene in cutaneous T-cell lymphoma. Br J Dermatol 2007;157:433-440.
146. Scarisbrick JJ, Morris S, Azurdia R, Illidge T, Parry E, Graham-Brown R, Cowan R, Gallop-Evans E, Wachsmuth R, Eagle M, Wierzbicki AS, Soran H, Whittaker S, Wain EM. U.K. consensus statement on safe clinical prescribing of bexarotene for patients with cutaneous T-cell lymphoma. Br J Dermatol 2013;168:192-200.
147. Huber MA, Kunzi-Rapp K, Staib G, Scharffetter-Kochanek K. Management of refractory early-stage cutaneous T-cell lymphoma (mycosis fungoides) with a combination of oral bexarotene and psoralen plus ultraviolet bath therapy. J Am Acad Dermatol 2004;50:475-476.

148. Schrump DS. Cytotoxicity mediated by histone deacetylase inhibitors in cancer cells: mechanisms and potential clinical implications. Clin Cancer Res 2009;15:3947-3957.
149. Lemoine M, Younes A. Histone deacetylase inhibitors in the treatment of lymphoma. Discov Med 2010;10:462-470.
150. Gui CY, Ngo L, Xu WS, Richon VM, Marks PA. Histone deacetylase (HDAC) inhibitor activation of p21WAF1 involves changes in promoter-associated proteins, including HDAC1. Proc Natl Acad Sci U S A 2004;101:1241-1246.
151. Richon VM, Sandhoff TW, Rifkind RA, Marks PA. Histone deacetylase inhibitor selectively induces p21WAF1 expression and gene-associated histone acetylation. Proc Natl Acad Sci U S A 2000;97:10014-10019.
152. Sandor V, Senderowicz A, Mertins S, Sackett D, Sausville E, Blagosklonny MV, Bates SE. P21-dependent g(1)arrest with downregulation of cyclin D1 and upregulation of cyclin E by the histone deacetylase inhibitor FR901228. Br J Cancer 2000;83:817-825.
153. Zhang C, Richon V, Ni X, Talpur R, Duvic M. Selective induction of apoptosis by histone deacetylase inhibitor SAHA in cutaneous T-cell lymphoma cells: relevance to mechanism of therapeutic action. J Invest Dermatol 2005;125:1045-1052.
154. Shao W, Growney JD, Feng Y, O'Connor G, Pu M, Zhu W, Yao YM, Kwon P, Fawell S, Atadja P. Activity of deacetylase inhibitor panobinostat (LBH589) in cutaneous T-cell lymphoma models: Defining molecular mechanisms of resistance. Int J Cancer 2010;127:2199-2208.
155. Tang Y, Zhao W, Chen Y, Zhao Y, Gu W. Acetylation is indispensable for p53 activation. Cell 2008;133:612-626.
156. Zhao Y, Lu S, Wu L, Chai G, Wang H, Chen Y, Sun J, Yu Y, Zhou W, Zheng Q, Wu M, Otterson GA, Zhu WG. Acetylation of p53 at lysine 373/382 by the histone deacetylase inhibitor depsipeptide induces expression of p21(Waf1/Cip1). Mol Cell Biol 2006;26:2782-2790.
157. Dai Y, Rahmani M, Dent P, Grant S. Blockade of histone deacetylase inhibitor-induced RelA/p65 acetylation and NF-kappaB activation potentiates apoptosis in leukemia cells through a process mediated by oxidative damage, XIAP downregulation, and c-Jun N-terminal kinase 1 activation. Mol Cell Biol 2005;25:5429-5444.
158. Zhang XD, Gillespie SK, Borrow JM, Hersey P. The histone deacetylase inhibitor suberic bishydroxamate regulates the expression of multiple apoptotic mediators and induces mitochondria-dependent apoptosis of melanoma cells. Mol Cancer Ther 2004;3:425-435.
159. Kim SH, Jeong JW, Park JA, Lee JW, Seo JH, Jung BK, Bae MK, Kim KW. Regulation of the HIF-1alpha stability by histone deacetylases. Oncol Rep 2007;17:647-651.
160. Heider U, Kaiser M, Sterz J, Zavrski I, Jakob C, Fleissner C, Eucker J, Possinger K, Sezer O. Histone deacetylase inhibitors reduce VEGF production and induce growth suppression and apoptosis in human mantle cell lymphoma. Eur J Haematol 2006;76:42-50.
161. Catley L, Weisberg E, Kiziltepe T, Tai YT, Hideshima T, Neri P, Tassone P, Atadja P, Chauhan D, Munshi NC, Anderson KC. Aggresome induction by proteasome inhibitor bortezomib and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. Blood 2006;108:3441-3449.
162. Munshi A, Kurland JF, Nishikawa T, Tanaka T, Hobbs ML, Tucker SL, Ismail S, Stevens C, Meyn RE. Histone deacetylase inhibitors radiosensitize human melanoma cells by suppressing DNA repair activity. Clin Cancer Res 2005;11:4912-4922.

163. Qu K, Zaba LC, Satpathy AT, Giresi PG, Li R, Jin Y, Armstrong R, Jin C, Schmitt N, Rahbar Z, Ueno H, Greenleaf WJ, Kim YH, Chang HY. Chromatin Accessibility Landscape of Cutaneous T Cell Lymphoma and Dynamic Response to HDAC Inhibitors. Cancer Cell 2017;32:27-41 e24.
164. Gloghini A, Buglio D, Khaskhely NM, Georgakis G, Orlowski RZ, Neelapu SS, Carbone A, Younes A. Expression of histone deacetylases in lymphoma: implication for the development of selective inhibitors. Br J Haematol 2009;147:515-525.
165. Prince HM, Bishton MJ, Harrison SJ. Clinical studies of histone deacetylase inhibitors. Clin Cancer Res 2009;15:3958-3969.
166. Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, Chiao JH, Reilly JF, Ricker JL, Richon VM, Frankel SR. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007;109:31-39.
167. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, Frankel SR, Chen C, Ricker JL, Arduino JM, Duvic M. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:3109-3115.
168. Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, Whittaker S, Tokura Y, Vermeer M, Zinzani PL, Sokol L, Morris S, Kim EJ, Ortiz-Romero PL, Eradat H, Scarisbrick J, Tsianakas A, Elmets C, Dalle S, Fisher DC, Halwani A, Poligone B, Greer J, Fierro MT, Khot A, Moskowitz AJ, Musiek A, Shustov A, Pro B, Geskin LJ, Dwyer K, Moriya J, Leoni M, Humphrey JS, Hudgens S, Grebennik DO, Tobinai K, Duvic M, Investigators M. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol 2018;19:1192-1204.
169. Kim E, Rook A, Kim Y, Demierre MF, Lerner A, Duvic M, Robak T, Becker JC, McCulloch W, Whittaker S. Romidepsin activity in all three disease compartments (skin, blood, lymph nodes) in patients with cutaneous T-cell lymphoma (CTCL). J Clin Oncol 2010;28:abstract 8047.
170. Duvic M, Olsen EA, Breneman D, Pacheco TR, Parker S, Vonderheid EC, Abuav R, Ricker JL, Rizvi S, Chen C, Boileau K, Gunchenko A, Sanz-Rodriguez C, Geskin LJ. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009;9:412-416.
171. Sager PT, Balser B, Wolfson J, Nichols J, Pilot R, Jones S, Burris HA. Electrocardiographic effects of class 1 selective histone deacetylase inhibitor romidepsin. Cancer medicine 2015;4:1178-1185.
172. Whittaker SJ, Demierre MF, Kim EJ, Rook AH, Lerner A, Duvic M, Scarisbrick J, Reddy S, Robak T, Becker JC, Samtsov A, McCulloch W, Kim YH. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol 2010;28:4485-4491.
173. Piekarz RL, Frye R, Turner M, Wright JJ, Allen SL, Kirschbaum MH, Zain J, Prince HM, Leonard JP, Geskin LJ, Reeder C, Joske D, Figg WD, Gardner ER, Steinberg SM, Jaffe ES, Stetler-Stevenson M, Lade S, Fojo AT, Bates SE. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol 2009;27:5410-5417.
174. Piekarz RL, Frye AR, Wright JJ, Steinberg SM, Liewehr DJ, Rosing DR, Sachdev V, Fojo T, Bates SE. Cardiac studies in patients treated with depsipeptide, FK228, in a phase II trial for T-cell lymphoma. Clin Cancer Res 2006;12:3762-3773.
175. Martinez-Escala ME, Kuzel TM, Kaplan JB, Petrich A, Nardone B, Rosen ST, Guitart J. Durable Responses With Maintenance Dose-Sparing Regimens of Romidepsin in Cutaneous T-Cell Lymphoma. JAMA Oncol 2016;2:790-793.

176. Ellis L, Pan Y, Smyth GK, George DJ, McCormack C, Williams-Truax R, Mita M, Beck J, Burris H, Ryan G, Atadja P, Butterfoss D, Dugan M, Culver K, Johnstone RW, Prince HM. Histone deacetylase inhibitor panobinostat induces clinical responses with associated alterations in gene expression profiles in cutaneous T-cell lymphoma. Clin Cancer Res 2008;14:4500-4510.
177. Pohlman B, Advani RH, Duvic M, Hymes K, Intragumtornchai T, Lekhakula A, Shpilberg O, Lerner A, Ben-Yehuda D, Beylot-Barry M, Hillen U, Fagerberg J, Foss F. Final Results of a Phase II Trial of Belinostat (PXD101) in Patients with Recurrent or Refractory Peripheral or Cutaneous T-Cell Lymphoma. Blood 2009;114:abstract 920.
178. Fantin VR, Loboda A, Paweletz CP, Hendrickson RC, Pierce JW, Roth JA, Li L, Gooden F, Korenchuk S, Hou XS, Harrington EA, Randolph S, Reilly JF, Ware CM, Kadin ME, Frankel SR, Richon VM. Constitutive activation of signal transducers and activators of transcription predicts vorinostat resistance in cutaneous T-cell lymphoma. Cancer Res 2008;68:3785-3794.
179. Robey RW, Zhan Z, Piekarz RL, Kayastha GL, Fojo T, Bates SE. Increased MDR1 expression in normal and malignant peripheral blood mononuclear cells obtained from patients receiving depsipeptide (FR901228, FK228, NSC630176). Clin Cancer Res 2006;12:1547-1555.
180. Karpova MB, Gunz D, Okoniewski MJ, Cozzio A, Schad K, Baumann Conzett K, Dummer R. Transcriptome adaptation caused by vorinostat/bexarotene combination therapy in advanced cutaneous T-cell lymphoma. J Clin Oncol 2010;28:abstract 8050.
181. Khan O, Fotheringham S, Wood V, Stimson L, Zhang C, Pezzella F, Duvic M, Kerr DJ, La Thangue NB. HR23B is a biomarker for tumor sensitivity to HDAC inhibitor-based therapy. Proc Natl Acad Sci U S A 2010;107:6532-6537.
182. Chakraborty AR, Robey RW, Luchenko VL, Zhan Z, Piekarz RL, Gillet JP, Kossenkov AV, Wilkerson J, Showe LC, Gottesman MM, Collie NL, Bates SE. MAPK pathway activation leads to Bim loss and histone deacetylase inhibitor resistance: rationale to combine romidepsin with an MEK inhibitor. Blood 2013;121:4115-4125.
183. Heider U, Rademacher J, Lamottke B, Mieth M, Moebs M, von Metzler I, Assaf C, Sezer O. Synergistic interaction of the histone deacetylase inhibitor SAHA with the proteasome inhibitor bortezomib in cutaneous T cell lymphoma. Eur J Haematol 2009;82:440-449.
184. Dummer R, Hymes K, Sterry W, Steinhoff M, Assaf C, Kerl H, Ahern J, Rizvi S, Ricker JL, Whittaker S. Vorinostat in combination with bexarotene in advanced cutaneous T-cell lymphoma: A phase I study. J Clin Oncol 2009;27:abstract 8572.
185. Olsen EA, Rosen ST, Vollmer RT, Variakojis D, Roenigk HH, Jr., Diab N, Zeffren J. Interferon alfa-2a in the treatment of cutaneous T cell lymphoma. J Am Acad Dermatol 1989;20:395-407.
186. Sun WH, Pabon C, Alsayed Y, Huang PP, Jandeska S, Uddin S, Platanias LC, Rosen ST. Interferon-alpha resistance in a cutaneous T-cell lymphoma cell line is associated with lack of STAT1 expression. Blood 1998;91:570-576.
187. Bunn PA, Jr., Foon KA, Ihde DC, Longo DL, Eddy J, Winkler CF, Veach SR, Zeffren J, Sherwin S, Oldham R. Recombinant leukocyte A interferon: an active agent in advanced cutaneous T-cell lymphomas. Ann Intern Med 1984;101:484-487.
188. Jumbou O, N'Guyen JM, Tessier MH, Legoux B, Dreno B. Long-term follow-up in 51 patients with mycosis fungoides and Sezary syndrome treated by interferon-alfa. Br J Dermatol 1999;140:427-431.
189. Kaplan EH, Rosen ST, Norris DB, Roenigk HH, Jr., Saks SR, Bunn PA, Jr. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 1990;82:208-212.

190. Polansky M, Talpur R, Daulat S, Hosing C, Dabaja B, Duvic M. Long-Term Complete Responses to Combination Therapies and Allogeneic Stem Cell Transplants in Patients With Sezary Syndrome. Clinical lymphoma, myeloma & leukemia 2015;15:e83-93.
191. Olsen EA, Bunn PA. Interferon in the treatment of cutaneous T-cell lymphoma. Hematol Oncol Clin North Am 1995;9:1089-1107.
192. Kuzel TM, Gilyon K, Springer E, Variakojis D, Kaul K, Bunn PA, Jr., Evans L, Roenigk HH, Jr., Rosen ST. Interferon alfa-2a combined with phototherapy in the treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 1990;82:203-207.
193. Straus DJ, Duvic M, Kuzel T, Horwitz S, Demierre MF, Myskowski P, Steckel S. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa-2b (Intron-A) for patients with cutaneous T-cell lymphoma. Cancer 2007;109:1799-1803.
194. Dippel E, Schrag H, Goerdt S, Orfanos CE. Extracorporeal photopheresis and interferon-alpha in advanced cutaneous T-cell lymphoma. Lancet 1997;350:32-33.
195. Foss FM, Ihde DC, Breneman DL, Phelps RM, Fischmann AB, Schechter GP, Linnoila I, Breneman JC, Cotelingam JD, Ghosh BC, et al. Phase II study of pentostatin and intermittent high-dose recombinant interferon alfa-2a in advanced mycosis fungoides/Sezary syndrome. J Clin Oncol 1992;10:1907-1913.
196. Fritz TM, Kleinhans M, Nestle FO, Burg G, Dummer R. Combination treatment with extracorporeal photopheresis, interferon alfa and interleukin-2 in a patient with the Sezary syndrome. Br J Dermatol 1999;140:1144-1147.
197. Zachariae H, Thestrup-Pedersen K. Interferon alpha and etretinate combination treatment of cutaneous T-cell lymphoma. J Invest Dermatol 1990;95:206S-208S.
198. Papa G, Tura S, Mandelli F, Vegna ML, Defazio D, Mazza P, Zinzani PL, Simoni R, DePita O, Ferranti G, et al. Is interferon alpha in cutaneous T-cell lymphoma a treatment of choice? Br J Haematol 1991;79 Suppl 1:48-51.
199. Rupoli S, Barulli S, Guiducci B, Offidani M, Mozzicafreddo G, Simonacci M, Filosa G, Giacchetti A, Ricotti G, Brandozzi G, Cataldi I, Serresi S, Ceschini R, Bugatti L, Offidani A, Giangiacomi M, Brancorsini D, Leoni P. Low dose interferon-alpha2b combined with PUVA is an effective treatment of early stage mycosis fungoides: results of a multicenter study. Cutaneous-T Cell Lymphoma Multicenter Study Group. Haematologica 1999;84:809-813.
200. Kuzel TM, Roenigk HH, Jr., Samuelson E, Herrmann JJ, Hurria A, Rademaker AW, Rosen ST. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sezary syndrome. J Clin Oncol 1995;13:257-263.
201. Roenigk HH, Jr., Kuzel TM, Skoutelis AP, Springer E, Yu G, Caro W, Gilyon K, Variakojis D, Kaul K, Bunn PA, Jr., et al. Photochemotherapy alone or combined with interferon alpha-2a in the treatment of cutaneous T-cell lymphoma. J Invest Dermatol 1990;95:198S-205S.
202. Chiarion-Sileni V, Bononi A, Fornasa CV, Soraru M, Alaibac M, Ferrazzi E, Redelotti R, Peserico A, Monfardini S, Salvagno L. Phase II trial of interferon-alpha-2a plus psolaren with ultraviolet light A in patients with cutaneous T-cell lymphoma. Cancer 2002;95:569-575.
203. Foss FM, Ihde DC, Linnoila IR, Fischmann AB, Schechter GP, Cotelingam JD, Steinberg SM, Ghosh BC, Stocker JL, Bastian A, et al. Phase II trial of fludarabine phosphate and interferon alfa-2a in advanced mycosis fungoides/Sezary syndrome. J Clin Oncol 1994;12:2051-2059.
204. Suchin KR, Cucchiara AJ, Gottleib SL, Wolfe JT, DeNardo BJ, Macey WH, Bromley PG, Vittorio CC, Rook AH. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. Arch Dermatol 2002;138:1054-1060.

205. Bladon J, Taylor PC. Lymphocytes treated by extracorporeal photopheresis demonstrate a drop in the Bcl-2/Bax ratio: a possible mechanism involved in extracorporeal-photopheresis-induced apoptosis. Dermatology 2002;204:104-107.
206. Bladon J, Taylor PC. Extracorporeal photopheresis: a focus on apoptosis and cytokines. J Dermatol Sci 2006;43:85-94.
207. Osella-Abate S, Zaccagna A, Savoia P, Quaglino P, Salomone B, Bernengo MG. Expression of apoptosis markers on peripheral blood lymphocytes from patients with cutaneous T-cell lymphoma during extracorporeal photochemotherapy. J Am Acad Dermatol 2001;44:40-47.
208. Berger C, Hoffmann K, Vasquez JG, Mane S, Lewis J, Filler R, Lin A, Zhao H, Durazzo T, Baird A, Lin W, Foss F, Christensen I, Girardi M, Tigelaar R, Edelson R. Rapid generation of maturationally synchronized human dendritic cells: contribution to the clinical efficacy of extracorporeal photochemotherapy. Blood 2010;116:4838-4847.
209. Berger CL, Xu AL, Hanlon D, Lee C, Schechner J, Glusac E, Christensen I, Snyder E, Holloway V, Tigelaar R, Edelson RL. Induction of human tumor-loaded dendritic cells. Int J Cancer 2001;91:438-447.
210. Edelson R, Berger C, Gasparro F, Jegasothy B, Heald P, Wintroub B, Vonderheid E, Knobler R, Wolff K, Plewig G, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med 1987;316:297-303.
211. Knobler R, Jantschitsch C. Extracorporeal photochemoimmunotherapy in cutaneous T-cell lymphoma. Transfus Apher Sci 2003;28:81-89.
212. Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. Dermatol Ther 2003;16:337-346.
213. Quaglino P, Knobler R, Fierro MT, Savoia P, Marra E, Fava P, Bernengo MG. Extracorporeal photopheresis for the treatment of erythrodermic cutaneous T-cell lymphoma: a single center clinical experience with long-term follow-up data and a brief overview of the literature. Int J Dermatol 2013;52:1308-1318.
214. Knobler R, Berlin G, Calzavara-Pinton P, Greinix H, Jaksch P, Laroche L, Ludvigsson J, Quaglino P, Reinisch W, Scarisbrick J, Schwarz T, Wolf P, Arenberger P, Assaf C, Bagot M, Barr M, Bohbot A, Bruckner-Tuderman L, Dreno B, Enk A, French L, Gniadecki R, Gollnick H, Hertl M, Jantschitsch C, Jung A, Just U, Klemke CD, Lippert U, Luger T, Papadavid E, Pehamberger H, Ranki A, Stadler R, Sterry W, Wolf IH, Worm M, Zic J, Zouboulis CC, Hillen U. Guidelines on the use of extracorporeal photopheresis. J Eur Acad Dermatol Venereol 2014;28 Suppl 1:1-37.
215. Sanford KW, Anderson J, Roseff S, McPherson RA. Iron Deficiency Anemia in Patients Undergoing Extracorporeal Photopheresis for Cutaneous T-Cell Lymphoma. Lab Med 2019;50:29-33.
216. Tatsuno K, Yamazaki T, Hanlon D, Han P, Robinson E, Sobolev O, Yurter A, Rivera-Molina F, Arshad N, Edelson RL, Galluzzi L. Extracorporeal photochemotherapy induces bona fide immunogenic cell death. Cell Death Dis 2019;10:578.
217. Ventura A, Vassall A, Yurter A, Robinson E, Filler R, Hanlon D, Meeth K, Ezaldein H, Girardi M, Sobolev O, Bosenberg MW, Edelson RL. Novel Protocol for Generating Physiologic Immunogenic Dendritic Cells. J Vis Exp 2019.
218. Gottlieb SL, Wolfe JT, Fox FE, DeNardo BJ, Macey WH, Bromley PG, Lessin SR, Rook AH. Treatment of cutaneous T-cell lymphoma with extracorporeal photopheresis monotherapy and in combination with recombinant interferon alfa: a 10-year experience at a single institution. J Am Acad Dermatol 1996;35:946-957.
219. Heald P, Rook A, Perez M, Wintroub B, Knobler R, Jegasothy B, Gasparro F, Berger C, Edelson R. Treatment of erythrodermic cutaneous T-cell lymphoma with extracorporeal photochemotherapy. J Am Acad Dermatol 1992;27:427-433.

220. Zic JA, Stricklin GP, Greer JP, Kinney MC, Shyr Y, Wilson DC, King LE, Jr. Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. J Am Acad Dermatol 1996;35:935-945.
221. Gao C, McCormack C, van der Weyden C, Goh MS, Campbell BA, Twigger R, Buelens O, Harrison SJ, Khoo C, Lade S, Prince HM. Prolonged survival with the early use of a novel extracorporeal photopheresis regimen in patients with Sezary syndrome. Blood 2019;134:1346-1350.
222. Wilcox RA. ECP in the spotLIGHT. Blood 2019;134:1275-1277.
223. Wilson LD, Jones GW, Kim D, Rosenthal D, Christensen IR, Edelson RL, Heald PW, Kacinski BM. Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides. J Am Acad Dermatol 2000;43:54-60.
224. Wilson LD, Licata AL, Braverman IM, Edelson RL, Heald PW, Feldman AM, Kacinski BM. Systemic chemotherapy and extracorporeal photochemotherapy for T3 and T4 cutaneous T-cell lymphoma patients who have achieved a complete response to total skin electron beam therapy. Int J Radiat Oncol Biol Phys 1995;32:987-995.
225. Tsirigotis P, Pappa V, Papageorgiou S, Kapsimali V, Giannopoulou V, Kaitsa I, Girkas K, Papageorgiou E, Stavrianeas N, Economopoulos T, Dervenoulas J. Extracorporeal photopheresis in combination with bexarotene in the treatment of mycosis fungoides and Sezary syndrome. Br J Dermatol 2007;156:1379-1381.
226. Ginaldi L, De Martinis M, Matutes E, Farahat N, Morilla R, Dyer MJ, Catovsky D. Levels of expression of CD52 in normal and leukemic B and T cells: correlation with in vivo therapeutic responses to Campath-1H. Leuk Res 1998;22:185-191.
227. Lundin J, Hagberg H, Repp R, Cavallin-Stahl E, Freden S, Juliusson G, Rosenblad E, Tjonnfjord G, Wiklund T, Osterborg A. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 2003;101:4267-4272.
228. Bernengo MG, Quaglino P, Comessatti A, Ortoncelli M, Novelli M, Lisa F, Fierro MT. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. Haematologica 2007;92:784-794.
229. Fisher DC, Tawa M, Walsh M, Clark RA, Kupper TS. Low-dose alemtuzumab is uniquely effective in refractory leukemic cutaneous T-cell lymphoma (L-CTCL). Blood 2009;114:abstract 3748.
230. Thursky KA, Worth LJ, Seymour JF, Miles Prince H, Slavin MA. Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab*. Br J Haematol 2006;132:3-12.
231. Enblad G, Hagberg H, Erlanson M, Lundin J, MacDonald AP, Repp R, Schetelig J, Seipelt G, Osterborg A. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. Blood 2004;103:2920-2924.
232. Gautschi O, Blumenthal N, Streit M, Solenthaler M, Hunziker T, Zenhausern R. Successful treatment of chemotherapy-refractory Sezary syndrome with alemtuzumab (Campath-1H). Eur J Haematol 2004;72:61-63.
233. Kennedy GA, Seymour JF, Wolf M, Januszewicz H, Davison J, McCormack C, Ryan G, Prince HM. Treatment of patients with advanced mycosis fungoides and Sezary syndrome with alemtuzumab. Eur J Haematol 2003;71:250-256.
234. O'Mahony D, Morris JC, Moses L, O'Hagan D, Gao W, Stetler-Stevenson M, Taylor M, Hammershaimb L, Waldman TA, Janik JE. Phase I Trial of Siplizumab in CD2-Positive Lymphoproliferative Disease. Blood 2005;106:abstract 3353.
235. Kim YH, Duvic M, Obitz E, Gniadecki R, Iversen L, Osterborg A, Whittaker S, Illidge TM, Schwarz T, Kaufmann R, Cooper K, Knudsen KM, Lisby S, Baadsgaard O,

Knox SJ. Clinical efficacy of zanolimumab (HuMax-CD4): two phase 2 studies in refractory cutaneous T-cell lymphoma. Blood 2007;109:4655-4662.
236. Kreitman RJ, Wilson WH, White JD, Stetler-Stevenson M, Jaffe ES, Giardina S, Waldmann TA, Pastan I. Phase I trial of recombinant immunotoxin anti-Tac(Fv)-PE38 (LMB-2) in patients with hematologic malignancies. J Clin Oncol 2000;18:1622-1636.
237. Suzuki R. Dosing of a phase I study of KW-0761, an anti-CCR4 antibody, for adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. J Clin Oncol 2010;28:e404-405; author reply e406.
238. Yamamoto K, Utsunomiya A, Tobinai K, Tsukasaki K, Uike N, Uozumi K, Yamaguchi K, Yamada Y, Hanada S, Tamura K, Nakamura S, Inagaki H, Ohshima K, Kiyoi H, Ishida T, Matsushima K, Akinaga S, Ogura M, Tomonaga M, Ueda R. Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. J Clin Oncol 2010;28:1591-1598.
239. Duvic M, Pinter-Brown L, Foss F, Sokol L, Jorgensen J, Spitalny GL, Kim YH. Results of a phase 1/2 Study for KW-0761, a Monoclonal Antibody Directed Against CC Chemokine Receptor Type 4 (CCR4), In CTCL Patients. Blood 2010;116:Abstract 285.
240. Frankel AE, Woo JH, Ahn C, Foss FM, Duvic M, Neville PH, Neville DM. Resimmune, an anti-CD3epsilon recombinant immunotoxin, induces durable remissions in patients with cutaneous T-cell lymphoma. Haematologica 2015;100:794-800.
241. Ogura M, Ishida T, Hatake K, Taniwaki M, Ando K, Tobinai K, Fujimoto K, Yamamoto K, Miyamoto T, Uike N, Tanimoto M, Tsukasaki K, Ishizawa K, Suzumiya J, Inagaki H, Tamura K, Akinaga S, Tomonaga M, Ueda R. Multicenter Phase II Study of Mogamulizumab (KW-0761), a Defucosylated Anti-CC Chemokine Receptor 4 Antibody, in Patients With Relapsed Peripheral T-Cell Lymphoma and Cutaneous T-Cell Lymphoma. J Clin Oncol 2014;32:1157-1163.
242. Ni X, Jorgensen JL, Goswami M, Challagundla P, Decker WK, Kim YH, Duvic MA. Reduction of regulatory T cells by Mogamulizumab, a defucosylated anti-CC chemokine receptor 4 antibody, in patients with aggressive/refractory mycosis fungoides and Sezary syndrome. Clin Cancer Res 2015;21:274-285.
243. Ni X, Langridge T, Duvic M. Depletion of regulatory T cells by targeting CC chemokine receptor type 4 with mogamulizumab. Oncoimmunology 2015;4:e1011524.
244. Wilcox RA. Mogamulizumab: 2 birds, 1 stone. Blood 2015;125:1847-1848.
245. Hirotsu KE, Neal TM, Khodadoust MS, Wang JY, Rieger KE, Strelo J, Hong E, Kim YH, Kwong BY. Clinical Characterization of Mogamulizumab-Associated Rash During Treatment of Mycosis Fungoides or Sezary Syndrome. JAMA Dermatol 2021;157:700-707.
246. de Masson A, Darbord D, Dobos G, Boisson M, Roelens M, Ram-Wolff C, Cassius C, Le Buanec H, de la Grange P, Jouenne F, Louveau B, Sadoux A, Bouaziz JD, Marie-Cardine A, Bagot M, Moins-Teisserenc H, Mourah S, Battistella M. Macrophage-derived CXCL9 and CXCL11, T-cell skin homing, and disease control in mogamulizumab-treated CTCL patients. Blood 2022;139:1820-1832.
247. Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphoma and Lymphomatoid Papulosis. J Clin Oncol 2015;33:3759-3765.
248. Kim YH, Tavallaee M, Sundram U, Salva KA, Wood GS, Li S, Rozati S, Nagpal S, Krathen M, Reddy S, Hoppe RT, Nguyen-Lin A, Weng WK, Armstrong R, Pulitzer M, Advani RH, Horwitz SM. Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides and Sezary Syndrome With Variable CD30 Expression Level: A Multi-Institution Collaborative Project. J Clin Oncol 2015;33:3750-3758.

249. Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, Zinzani PL, Wolter P, Sanches JA, Ortiz-Romero PL, Akilov OE, Geskin L, Trotman J, Taylor K, Dalle S, Weichenthal M, Walewski J, Fisher D, Dreno B, Stadler R, Feldman T, Kuzel TM, Wang Y, Palanca-Wessels MC, Zagadailov E, Trepicchio WL, Zhang W, Lin HM, Liu Y, Huebner D, Little M, Whittaker S, Duvic M, group As. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet 2017;390:555-566.
250. Kim YH, Prince HM, Whittaker S, Horwitz SM, Duvic M, Bechter O, Sanches JA, Stadler R, Scarisbrick J, Quaglino P, Zinzani PL, Wolter P, Eradat H, Pinter-Brown LC, Ortiz-Romero PL, Akilov OE, Trotman J, Taylor K, Weichenthal M, Walewski J, Fisher D, McNeeley M, Gru AA, Brown L, Palanca-Wessels MC, Lisano J, Onsum M, Bunn V, Little M, Trepicchio WL, Dummer R. Response to brentuximab vedotin versus physician's choice by CD30 expression and large cell transformation status in patients with mycosis fungoides: An ALCANZA sub-analysis. Eur J Cancer 2021;148:411-421.
251. Horwitz SM, Scarisbrick JJ, Dummer R, Whittaker S, Duvic M, Kim YH, Quaglino P, Zinzani PL, Bechter O, Eradat H, Pinter-Brown L, Akilov OE, Geskin L, Sanches JA, Ortiz-Romero PL, Weichenthal M, Fisher DC, Walewski J, Trotman J, Taylor K, Dalle S, Stadler R, Lisano J, Bunn V, Little M, Prince HM. Randomized phase 3 ALCANZA study of brentuximab vedotin vs physician's choice in cutaneous T-cell lymphoma: final data. Blood Adv 2021;5:5098-5106.
252. Wilcox RA, Feldman AL, Wada DA, Yang ZZ, Comfere NI, Dong H, Kwon ED, Novak AJ, Markovic SN, Pittelkow MR, Witzig TE, Ansell SM. B7-H1 (PD-L1, CD274) suppresses host immunity in T-cell lymphoproliferative disorders. Blood 2009;114:2149-2158.
253. Phillips T, Devata S, Wilcox RA. Challenges and opportunities for checkpoint blockade in T-cell lymphoproliferative disorders. J Immunother Cancer 2016;4:95.
254. Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, Millenson MM, Cohen AD, Schuster SJ, Lebovic D, Dhodapkar M, Avigan D, Chapuy B, Ligon AH, Freeman GJ, Rodig SJ, Cattry D, Zhu L, Grosso JF, Bradley Garelik MB, Shipp MA, Borrello I, Timmerman J. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. J Clin Oncol 2016;34:2698-2704.
255. Khodadoust MS, Rook AH, Porcu P, Foss F, Moskowitz AJ, Shustov A, Shanbhag S, Sokol L, Fling SP, Ramchurren N, Pierce R, Davis A, Shine R, Li S, Fong S, Kim J, Yang Y, Blumenschein WM, Yearley JH, Das B, Patidar R, Datta V, Cantu E, McCutcheon JN, Karlovich C, Williams PM, Subrahmanyam PB, Maecker HT, Horwitz SM, Sharon E, Kohrt HE, Cheever MA, Kim YH. Pembrolizumab in Relapsed and Refractory Mycosis Fungoides and Sezary Syndrome: A Multicenter Phase II Study. J Clin Oncol 2020;38:20-28.
256. Song X, Chang S, Seminario-Vidal L, de Mingo Pulido A, Tordesillas L, Song X, Reed RA, Harkins A, Whiddon S, Nguyen JV, Segura CM, Zhang C, Yoder S, Sayegh Z, Zhao Y, Messina JL, Harro CM, Zhang X, Conejo-Garcia JR, Berglund A, Sokol L, Zhang J, Rodriguez PC, Mule JJ, Futreal AP, Tsai KY, Chen PL. Genomic and Single-Cell Landscape Reveals Novel Drivers and Therapeutic Vulnerabilities of Transformed Cutaneous T-cell Lymphoma. Cancer Discov 2022;12:1294-1313.
257. Beygi S, Fernandez-Pol S, Duran G, Wang EB, Stehr H, Zehnder JL, Ramchurren N, Fling SP, Cheever MA, Weng WK, Kim YH, Khodadoust MS. Pembrolizumab in mycosis fungoides with PD-L1 structural variants. Blood Adv 2021;5:771-774.

258. Quaglino P, Maule M, Prince HM, Porcu P, Horwitz S, Duvic M, Talpur R, Vermeer M, Bagot M, Guitart J, Papadavid E, Sanches JA, Hodak E, Sugaya M, Berti E, Ortiz-Romero P, Pimpinelli N, Servitje O, Pileri A, Zinzani PL, Estrach T, Knobler R, Stadler R, Fierro MT, Alberti Violetti S, Amitay-Laish I, Antoniou C, Astrua C, Chaganti S, Child F, Combalia A, Fabbro S, Fava P, Grandi V, Jonak C, Martinez-Escala E, Kheterpal M, Kim EJ, McCormack C, Miyagaki T, Miyashiro D, Morris S, Muniesa C, Nikolaou V, Ognibene G, Onida F, Osella-Abate S, Porkert S, Postigo-Llorente C, Ram-Wolff C, Ribero S, Rogers K, Sanlorenzo M, Stranzenbach R, Spaccarelli N, Stevens A, Zugna D, Rook AH, Geskin LJ, Willemze R, Whittaker S, Hoppe R, Scarisbrick J, Kim Y. Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium. Ann Oncol 2017;28:2517-2525.
259. O'Connor OA, Hamlin PA, Portlock C, Moskowitz CH, Noy A, Straus DJ, Macgregor-Cortelli B, Neylon E, Sarasohn D, Dumetrescu O, Mould DR, Fleischer M, Zelenetz AD, Sirotnak F, Horwitz S. Pralatrexate, a novel class of antifol with high affinity for the reduced folate carrier-type 1, produces marked complete and durable remissions in a diversity of chemotherapy refractory cases of T-cell lymphoma. Br J Haematol 2007;139:425-428.
260. Serova M, Bieche I, Sablin MP, Pronk GJ, Vidaud M, Cvitkovic E, Faivre S, Raymond E. Single agent and combination studies of pralatrexate and molecular correlates of sensitivity. Br J Cancer 2011;104:272-280.
261. Zain J, O'Connor O. Pralatrexate: basic understanding and clinical development. Expert Opin Pharmacother 2010;11:1705-1714.
262. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, Jo Lechowicz M, Savage KJ, Shustov AR, Gisselbrecht C, Jacobsen E, Zinzani PL, Furman R, Goy A, Haioun C, Crump M, Zain JM, Hsi E, Boyd A, Horwitz S. Pralatrexate in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results From the Pivotal PROPEL Study. J Clin Oncol 2011;29:1182-1189.
263. Foss F, Horwitz S, Pinter-Brown L, Goy A, Pro B, Coiffier B, Popplewell L, Savage KJ, Shustov AR, Zain J, Koutsoukos T, Fruchtman SM, O'Connor OA. Pralatrexate Is An Effective Treatment for Heavily Pretreated Patients with Relapsed/Refractory Transformed Mycosis Fungoides (tMF). Blood 2010;116 Abstract 1762.
264. Horwitz S, Kim YH, Foss F, Zain JM, Myskowski P, Lechowicz MJ, Fisher DC, Shustov AR, Bartlett N, Delioukina M, Koutsoukos T, Fruchtman SM, O'Connor OA, Duvic M. Identification of An Active, Well-Tolerated Dose of Pralatrexate In Patients with Relapsed or Refractory Cutaneous T-cell Lymphoma (CTCL): Final Results of a Multicenter Dose-Finding Study. Blood 2010;116:Abstract 2800.
265. Rueda A, Casanova M, Quero C, Medina-Perez A. Pralatrexate, a new hope for aggressive T-cell lymphomas? Clin Transl Oncol 2009;11:215-220.
266. Zinzani PL, Musuraca G, Tani M, Stefoni V, Marchi E, Fina M, Pellegrini C, Alinari L, Derenzini E, de Vivo A, Sabattini E, Pileri S, Baccarani M. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:4293-4297.
267. Querfeld C, Rosen ST, Guitart J, Duvic M, Kim YH, Dusza SW, Kuzel TM. Results of an open-label multicenter phase 2 trial of lenalidomide monotherapy in refractory mycosis fungoides and Sezary syndrome. Blood 2014;123:1159-1166.
268. Wilcox RA. A three signal model of T-cell lymphoma pathogenesis. Am J Hematol 2015.
269. Devata S, Wilcox RA. Cutaneous T-Cell Lymphoma: A Review with a Focus on Targeted Agents. Am J Clin Dermatol 2016;17:225-237.

270. Wu PA, Kim YH, Lavori PW, Hoppe RT, Stockerl-Goldstein KE. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biology of Blood & Marrow Transplantation 2009;15:982-990.
271. Duarte RF, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. Bone Marrow Transplantation 2008;41:597-604.
272. Duarte RF, Canals C, Onida F, Gabriel IH, Arranz R, Arcese W, Ferrant A, Kobbe G, Narni F, Deliliers GL, Olavarria E, Schmitz N, Sureda A. Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2010;28:4492-4499.
273. Domingo-Domenech E, Duarte RF, Boumedil A, Onida F, Gabriel I, Finel H, Arcese W, Browne P, Beelen D, Kobbe G, Veelken H, Arranz R, Greinix H, Lenhoff S, Poire X, Ribera JM, Thompson J, Zuckerman T, Mufti GJ, Cortelezzi A, Olavarria E, Dreger P, Sureda A, Montoto S. Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides and Sezary syndrome. An updated experience of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant 2021.
274. Lechowicz MJ, Lazarus HM, Carreras J, Laport GG, Cutler CS, Wiernik PH, Hale GA, Maharaj D, Gale RP, Rowlings PA, Freytes CO, Miller AM, Vose JM, Maziarz RT, Montoto S, Maloney DG, Hari PN. Allogeneic hematopoietic cell transplantation for mycosis fungoides and Sezary syndrome. Bone Marrow Transplant 2014;49:1360-1365.
275. Iqbal M, Reljic T, Ayala E, Sher T, Murthy H, Roy V, Foran J, Tun H, Kumar A, Kharfan-Dabaja MA. Efficacy of Allogeneic Hematopoietic Cell Transplantation in Cutaneous T Cell Lymphoma: Results of a Systematic Review and Meta-Analysis. Biol Blood Marrow Transplant 2020;26:76-82.
276. Schlaak M, Theurich S, Pickenhain J, Skoetz N, Kurschat P, von Bergwelt-Baildon M. Allogeneic stem cell transplantation for advanced primary cutaneous T-cell lymphoma: a systematic review. Crit Rev Oncol Hematol 2013;85:21-31.
277. Hosing C, Bassett R, Dabaja B, Talpur R, Alousi A, Ciurea S, Popat U, Qazilbash M, Shpall EJ, Oki Y, Nieto Y, Pinnix C, Fanale M, Maadani F, Donato M, Champlin R, Duvic M. Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution. Ann Oncol 2015;26:2490-2495.

TABLE 1. ISCL/EORTC Staging

Stage	TNMB Classification T	N	M	B	Median OS (years)	OS (%)	10-year(11) DSS (%)	RDP (%)
IA	1	0	0	0,1	35.5	88	95	12
IB	2	0	0	0,1	21.5	70	77	38
IIA	1, 2	1	0	0,1	15.8	52	67	33
IIB	3	0-2	0	0,1	4.7	34	42	58
IIIA	4	0-2	0	0	4.7	37	45	62
IIIB	4	0-2	0	1	3.4	25	45	73
IVA1	1-4	0-2	0	2	3.8	18	20	83
IVA2	1-4	3	0	0-2	2.1	15	20	80
IVB	1-4	0-3	1	0-2	1.4	18 (5 year)	18 (5 year)	82 (5 year)

OS, overall survival; DSS, disease-specific survival; RDP, risk of disease progression