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Release date: May 10, 2020; Expiration date: May 10, 2021

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Primary Cutaneous Lymphomas
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Primary Cutaneous Lymphomas

Disclosure of Relevant Financial Relationships

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Primary Cutaneous Lymphomas, Version 2.2020

Featured Updates to the NCCN Guidelines

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ABSTRACT

Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma (CTCL), and Sézary syndrome (SS) is a rare erythrodermic and leukemic subtype of CTCL characterized by significant blood involvement. Although early-stage disease can be effectively treated predominantly with skin-directed therapies, systemic therapy is often necessary for the treatment of advanced-stage disease. Systemic therapy options have evolved in recent years with the approval of novel agents such as romidepsin, brentuximab vedotin, and mogamulizumab. These NCCN Guidelines Insights discuss the diagnosis and management of MF and SS (with a focus on systemic therapy).

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*Provided content development and/or authorship assistance.

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TNMB		TNMB Classification and Staging of Mycosis Fungoides and Sézary Syndrome ^{m,n} See Clinical Staging of MF and SS on MFSS-4	
Skin	T1	Limited patches, ^o papules, and/or plaques ^p covering <10% of the skin surface	
	T2	Patches, papules, ^o and/or plaques ^o covering ≥10% of the skin surface	
	T2a	Patch only	
	T2b	Plaque ± patch	
	T3	One or more tumors ^q (≥1 cm in diameter)	
	T4	Confluence of erythema ≥80% body surface area	
Node	N0	No abnormal lymph nodes; biopsy not required	See NCI Lymph Node Classification on MFSS-5
	N1	Abnormal lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2	See Dutch Criteria for Lymph Nodes on MFSS-5
	N2	Abnormal lymph nodes; histopathology Dutch Gr 2 or NCI LN 3	
	N3	Abnormal lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4	
	NX	Abnormal lymph nodes; no histologic confirmation	
Visceral	M0	No visceral organ involvement	
	M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)	
	MX	Abnormal visceral site; no histologic confirmation	
Blood	B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes or <250/mcL atypical (Sézary) cells or <15% CD4+/CD26- or CD4+/CD7- cells of total lymphocytes	
	B1	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells or >15% CD4+CD26- or CD4+CD7- of total lymphocytes but do not meet the criteria of B0 or B2	
	B2	High blood tumor burden: ≥1000/mcL Sézary cells ⁿ determined by cytopathology or ≥1000 CD4+CD26- or CD4+CD7- cells/uL or other abnormal subset of T lymphocytes by flow cytometry with clone in blood same as that in skin. Other criteria for documenting high blood tumor burden in CD4+ MF/SS include CD4+/CD7- cells ≥40% and CD4+CD26- cells ≥30%.	

^m Adapted from Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722 and Olsen E, Whittaker S, Kim Y, et al. J Clin Oncol 2011;29:2598-2607.

ⁿ Sézary syndrome is defined by B2 blood involvement and a clonal rearrangement of *TCR* in the blood (clones should be relevant to clone in the skin).

^o Patch = Any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.

^p Plaque = Any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features such as folliculotropism or LCT (≥25% large cells), CD30+ or CD30-, and clinical features such as ulceration are important to document.

^q Tumor = at least one ≥1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of LCT has occurred. Phenotyping for CD30 is encouraged.

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MFSS-3

Overview

Cutaneous T-cell lymphomas (CTCLs) are a group of non-Hodgkin's lymphomas that primarily present in the skin but can involve lymph nodes, blood, and rarely visceral organs.¹⁻³ Mycosis fungoides (MF) is the most common subtype of CTCL and is usually associated with an indolent clinical course and intermittent, stable, or slow progression of the lesions.⁴ Extracutaneous involvement (lymph nodes, blood, or less commonly other organs) or large cell transformation (LCT) may be seen in advanced-stage disease. Sézary syndrome (SS) is a rare leukemic subtype of CTCL characterized by significant blood involvement, erythroderma, and often lymphadenopathy.^{5,6}

Folliculotropic MF (FMF), granulomatous slack skin, and pagetoid reticulosis are recognized as distinct clinicopathologic variants of MF in the WHO-EORTC classification.² FMF and LCT are histologic features that can occur irrespective of disease stage, but incidence of LCT is higher in patients with advanced-stage disease.⁷⁻⁹ Expert dermatopathology and/or hematopathology review is needed to confirm diagnosis, especially for the less common disease variants, which can be difficult to distinguish from other

lymphoproliferative disorders. Genomic studies have demonstrated further biologic diversity within MF.¹⁰

Due to the rarity and diversity of the condition and the need for an individualized approach, patients diagnosed with MF and SS should, if possible, be treated at specialized centers with expertise in the management of this disease.¹¹ These NCCN Guidelines Insights discuss the diagnosis and management of MF and SS as outlined in the NCCN Guidelines for Primary Cutaneous Lymphomas. Although this article predominantly discusses the role of systemic therapy, skin-directed therapies (eg, topical therapy, phototherapy, involved-site radiation therapy [RT], total skin electron-beam therapy [TSEBT]) also have an important role in the management of MF and SS. The complete and most recent version of these NCCN Guidelines is available at NCCN.org.

Diagnosis and Workup

Initial workup of patients involves a history and complete physical examination, laboratory tests, and imaging studies in selected patients. The diagnosis and workup are outlined in MFSS-1 and MFSS-2 in the full NCCN Guidelines at NCCN.org.

Clinical Staging of MF and SS¹

Clinical Stage [†]	T (Skin)	N (Node)	M (Visceral)	B (Blood Involvement)	Guidelines Page
IA (Limited skin involvement)	T1 (patches, papules, and/or plaques covering <10% body surface area [BSA])	N0	M0	B0 or B1	MFSS-6
IB (Skin only disease)	T2 (patches, papules, and/or plaques covering ≥10% BSA)	N0	M0	B0 or B1	MFSS-7
IIA	T1–2	N1–2	M0	B0 or B1	MFSS-7
IIB (Tumor stage disease)	T3 (One or more tumors [≥1 cm in diameter])	N0–2	M0	B0 or B1	MFSS-8
IIIA (Erythrodermic disease)	T4 (Confluence of erythema ≥80% BSA)	N0–2	M0	B0	MFSS-10
IIIB (Erythrodermic disease)	T4 (Confluence of erythema ≥80% BSA)	N0–2	M0	B1	MFSS-10
IVA ₁	T1–4	N0–2	M0	B2	MFSS-11
IVA ₂	T1–4	N3	M0	B0 or B1 or B2	MFSS-11
IVB	T1–4	N0–3	M1	B0 or B1 or B2	MFSS-11
	Large-cell transformation (LCT) [§]				MFSS-12

¹ Olsen E, Vonderheid E, Pimpinelli N, et al. Blood 2007;110:1713-1722.

[†] Folliculotropism is a histologic feature that can occur irrespective of stage. Histologic evidence of folliculotropic MF is associated with higher risk of disease progression. In selected cases or inadequate response, consider primary treatment for stage IIB (tumor stage disease).

[§] LCT is a histologic feature that can occur irrespective of clinical stage. LCT often but not always corresponds to a more aggressive growth rate requiring systemic therapies.

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For TNMB Classification,
see MFSS-3

MFSS-4

Biopsy of suspicious skin sites along with immunohistochemistry (IHC) of biopsy specimens are essential to confirm the diagnosis. Biopsy of enlarged lymph nodes (ie, palpable nodes >1.5 cm in diameter and/or firm, irregular, clustered, or fixed nodes) or extracutaneous sites is recommended. Excisional biopsy is preferred but core needle biopsies can be used in certain circumstances. Fine-needle aspiration alone is not sufficient for the initial diagnosis. Bone marrow biopsy is not required for disease staging.¹²

Molecular analysis to detect clonal T-cell receptor (*TCR*) gene rearrangements is useful to support the diagnosis of MF and SS as well as to distinguish MF from inflammatory dermatoses, especially if identical clones are demonstrated in more than one skin site.^{13,14} However, results showing clonal *TCR* gene rearrangements should not be interpreted as the sole and defining test for malignancy, because clonal *TCR* gene rearrangements can occasionally be seen in nonmalignant conditions or may not be demonstrated in all cases of MF and SS. *TCR* analysis by high-throughput sequencing is a more sensitive and specific test of clonality that can identify the clones by the genetic sequence of the *TCR*.^{15,16} Demonstration of identical

clones in the skin, blood, and/or lymph nodes may be helpful both for diagnosis and differentiating MF and SS from benign inflammatory skin diseases.

Assessment of peripheral blood involvement optimally by flow cytometry is important for staging and is also useful to differentiate CTCL with peripheral blood involvement from other forms of leukemic T-cell lymphomas (eg, T-cell prolymphocytic leukemia, lymphocytic variant of hypereosinophilic syndrome, or adult T-cell leukemia/lymphoma). Flow cytometry allows for the assessment of a population of expanded CD4+ cells with abnormal immunophenotype (CD4+/CD26– or CD4+/CD7– or other aberrantly expressed phenotype).

The T (skin), N (node), M (visceral), and B (blood involvement) classification and clinical staging developed by the International Society for Cutaneous Lymphomas (ISCL) and EORTC¹² are outlined in MFSS-3 and MFSS-4 (page 524 and above, respectively). Blood involvement is classified into 3 groups—B0, B1, and B2—based on the number of immunophenotypically abnormal T cells in the blood (MFSS-3, page 524). B1 or B2 is best characterized by both flow cytometry and the presence of clonally related neoplastic T cells

† See Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1).

‡ Rebiopsy if suspect LCT; if histologic evidence of LCT, see MFSS-12.

§ In patients with histologic evidence of folliculotropic MF, skin disease may be less responsive to topical therapies.

¶ Patients with disease achieving a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration.

‡ See Principles of Radiation Therapy (LYMP-A).

§ Imaging indicated when suspicious of clinical extracutaneous disease with modalities used in workup.

See Supportive Care for MF/SS (MFSS-B)

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MFSS-7

as in the skin by *TCR* gene rearrangement analysis. A diagnosis of SS requires B2 level of blood involvement.¹²

Treatment Considerations

Although MF and SS are treatable, they are not curable with conventional systemic therapy, and symptoms have significant impact on quality of life. Patients with MF, particularly those with early-stage disease, can have very good prognosis and may live with the disease for decades.^{17,18}

Optimal treatment of any patient at any given time should be individualized based on overall goals of therapy (improve disease burden and quality of life, attain adequate response to reduce/control symptoms, and minimize the risk of progression), route of administration, and toxicity profile. Discussions regarding cumulative toxicity of therapy, impact of therapy on quality of life, and supportive care for symptom control are a key part of management of patients with MF and SS. Most treatment options do not result in durable remissions and are often given in an ongoing or maintenance fashion to achieve disease control with as little impact on quality of life as possible.

Patients with a clinical benefit and/or those with disease responding to primary treatment can be considered for maintenance or tapering of regimens to optimize response duration. Patients with disease that does not have adequate response to a systemic therapy regimen are generally treated with an alternative regimen recommended for primary treatment before moving onto treatment of refractory disease. This supports our therapeutic principle of initial treatment with less toxic regimens before moving on to treatment options that carry a higher risk of cumulative toxicity and/or immunosuppression. Along these lines, we have categorized systemic therapies with lower toxicity as SYST-CATA and therapies that we tend to use later in the disease course as SYST-CATB (see “Systemic Therapy Options for MF and SS,” page 529). Disease relapse (with the same stage) after discontinuation of therapy often responds well to retreatment with previous therapy.

Selection of Therapy Based on Clinical and Pathologic Features

In patients with early-stage disease and limited skin involvement (stage IA or IB–IIA), we recommend the use

[†] See Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1).

[‡] Rebiopsy if suspect LCT; if histologic evidence of LCT, see MFSS-12.

^w In patients with histologic evidence of folliculotropic MF, skin disease may be less responsive to topical therapies.

^x Patients with disease achieving a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration.

[‡] See Principles of Radiation Therapy (LYMP-A).

[‡] Imaging indicated when suspicious of clinical extracutaneous disease with modalities used in workup.

^{aa} RT is preferred for tumor lesions.

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MFSS-8

of skin-directed therapies (such as topical therapy, phototherapy, TSEBT) that can provide disease control without major cumulative toxicities. Although stage IB–IIA patch/plaque disease can be effectively treated predominantly with skin-directed therapies, systemic therapy can be considered for stage IB–IIA with higher skin disease burden, concerning pathologic features (eg LCT or FMF), predominantly plaque disease, and/or inadequate response to skin-directed therapy. Systemic therapy is recommended for advanced-stage disease (stage ≥IIB). On the other hand, patients with stage IIB disease with single or few T3 lesions can be treated with external-beam RT, with further delay of systemic therapy, and TSEBT may be used for patients with stage IB–IIB disease, with excellent response expected.^{19–22}

Systemic therapy can be and often is combined with skin-directed therapy to maximize clinical responses in the skin compartment and also to provide additive efficacy without cumulative toxicities (MFSS-A 3 of 6, page 533). For those who require systemic therapy, due to either advanced-stage disease or inadequate disease control on skin-directed therapy, there are many options; however, given the rare nature

of this disease, only a few have been evaluated in randomized studies, as discussed in “Systemic Therapy Options for MF and SS” (page 529). Therefore, we often consider enrollment in a clinical trial when appropriate and available.

Case 1: Stage IB (Lower Skin Disease Burden With Predominantly Patch Disease)

A 50-year-old man presents with a recent diagnosis of CTCL. Biopsy demonstrated epidermotropic atypical lymphocytes that express CD4 and CD3 but not CD7. Skin examination shows 30% body surface area (BSA) involvement with erythematous, scaling patches. He has used topical steroids without significant relief. Imaging and peripheral blood flow cytometry and TCR gene rearrangement analysis do not show evidence of lymph node or peripheral blood involvement.

In a patient with stage IB disease and lower skin disease burden (as illustrated in case 1; MFSS-7, page 526), we would consider skin-directed therapy (either alone or in combination with other skin-directed therapies or therapy that augments skin-directed therapy). Examples of this could include topical steroids, topical bexarotene, topical mechlorethamine,

[†] See Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1).

^v Rebiopsy if suspect LCT, if histologic evidence of LCT, see MFSS-12.

^w In patients with histologic evidence of folliculotropic MF, skin disease may be less responsive to topical therapies.

^x Patients with disease achieving a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration.

^y See Principles of Radiation Therapy (LYMP-A).

^z Imaging indicated when suspicious of clinical extracutaneous disease with modalities used in workup.

^{bb} Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should first be considered for therapies under SYST-CAT A before proceeding to treatments listed in SYST-CAT B. See MFSS-A (2 of 6).

^{cc} May consider adjuvant systemic biologic therapy (SYST-CAT A) after TSEBT to improve response duration. See MFSS-A (2 of 6).

^{dd} Most patients are treated with multiple SYST-CAT A/B before receiving multiagent chemotherapy. See MFSS-A (2 of 6).

^{ee} Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant. See Discussion for further details.

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MFSS-9

and phototherapy (narrowband UVB or psoralen-ultraviolet A [PUVA]). Systemic agents such as bexarotene can be used in combination with skin-directed therapies in cases involving inadequate response to skin-directed therapy or higher skin disease burden. Narrowband UVB carries a lower risk of secondary skin cancers and is preferred over PUVA in patients with early patch-stage or thin-plaque disease. Increasingly, very low-dose TSEBT is also being considered for these patients.^{20–22}

Case 2: Stage IIB Generalized Tumor Stage Disease

A 62-year-old woman presents with a recent diagnosis of CTCL, 30% BSA involvement and predominantly tumors of MF. Imaging shows no evidence of peripheral lymphadenopathy. Biopsy of a skin tumor shows involvement with MF without LCT. Peripheral blood flow cytometry also shows no evidence of blood involvement.

TSEBT or systemic therapy is recommended for a patient with stage IIB generalized tumor stage disease as illustrated in case 2 (MFSS-9, above). Adjuvant systemic therapy (SYST-CAT A) may be used after TSEBT to improve response duration.

Special Considerations for Clinical Situations With Specific Pathologic Features

Folliculotropic MF

FMF is characterized by the infiltration of hair follicles by atypical T lymphocytes and resultant alopecia. Disease typically presents as plaques and tumors mainly on the head/neck and the risk profile varies with disease stage.^{23–27} Recent studies have reported that FMF presents with 2 distinct patterns of clinicopathologic features with different prognostic implications (early-stage and advanced-stage), and in a subgroup of patients with early skin-limited disease, FMF has been shown to have an indolent disease course and a favorable prognosis.^{28,29}

Patients with early-stage FMF may benefit from standard skin-directed therapies used for the treatment of early-stage MF, and those with generalized indolent/plaque FMF (without evidence of LCT) should initially be considered for options under SYST-CAT A before proceeding to options listed under SYST-CAT B.

LCT of MF

LCT is diagnosed when large cells are present in >25% of lymphoid/tumor cell infiltrates in a skin lesion biopsy,

[†] See Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1).

^v Rebiopsy if suspect LCT; if histologic evidence of LCT, see MFSS-12.

^x Patients with disease achieving a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration.

[‡] Imaging indicated when suspicious of clinical extracutaneous disease with modalities used in workup.

^{ee} Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant. See Discussion for further details.

^{ff} Patients with erythrodermic disease are at increased risk for secondary infection with skin pathogens and systemic antibiotic therapy should be considered.

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MFSS-10

and the incidence of LCT is strongly dependent on the disease stage at diagnosis (1% in early-stage disease vs 27% for stage IIB and 56% to 67% for stage IV disease).^{7–9} LCT is often, but not always, aggressive. CD30 expression is associated with LCT in MF or SS in 30% to 50% of cases and this finding may have potential implications for CD30-directed therapies.^{7–9} However, it should be noted that CD30 expression is variable in MF and SS, with the leukemic Sézary cells typically being CD30–.

Systemic therapy (brentuximab vedotin, gemcitabine, liposomal doxorubicin, pralatrexate, or romidepsin) with or without skin-directed therapies is the initial treatment of generalized cutaneous or extracutaneous lesions with LCT (MFSS-12, page 531). In addition, concurrent management of coexisting disease based on clinical stage is recommended. Selected patients with localized LCT (ie, restricted to one or few T3 lesions or stage IA–IIA plaque disease) could be treated with external-beam RT alone, with continuation of other treatment modalities used before transformation. Depending on the goals of treatment, multiagent chemotherapy regimens recommended for peripheral T-cell lymphomas (PTCLs) may be appropriate

for the management of LCT refractory to multiple prior therapies or when significant extracutaneous disease is present.

Systemic Therapy Options for MF and SS

The NCCN Guidelines are structured with systemic therapy regimens categorized into 2 groups: SYST-CAT A and SYST-CAT B (MFSS-A, 2 of 6, page 532). Selection of SYST-CAT A versus SYST-CAT B regimens is dependent on clinical (eg, extent of patch/plaques; disease burden profile in the skin, lymph nodes, and blood; prior therapies; and comorbidities) and pathologic features (eg, LCT or FMF) and IHC data (eg, CD30 positivity). In general, SYST-CAT A regimens should be considered first before proceeding to treatment with SYST-CAT B regimens.

SYST-CAT A includes regimens that can often be tolerated for longer periods with less cumulative toxicity, less immunosuppression, and/or higher efficacy. In a patient with stage IIB disease with limited tumor lesions (MFSS-8, page 527) or stage IIB generalized tumor stage disease (as illustrated in case 2 above; MFSS-9, page 528), we would consider a SYST-CAT A regimen, often following initial RT. SYST-CAT B

[†] See Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1).

^v Rebiopsy if suspect LCT; if histologic evidence of LCT, see MFSS-12.

^x Patients with disease achieving a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration.

^y See Principles of Radiation Therapy (LYMP-A).

^{dd} Most patients are treated with multiple SYST-CAT A/B before receiving multiagent chemotherapy. See MFSS-A (2 of 6).

^{ee} Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant. See Discussion for further details.

⁹⁹ Patients with stage IV non-Sézary/visceral disease may present with more aggressive growth characteristics. If there is no evidence of more aggressive growth, systemic therapies from SYST-CAT B are appropriate. If aggressive growth is seen, then systemic therapies listed for LCT are preferred. See MFSS-A (2 of 6).

^{hh} If disease in lymph nodes and/or viscera or suspicious of disease progression, imaging indicated with modalities used in workup as clinically indicated based on distribution of disease.

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MFSS-11

includes regimens that can have more significant cumulative toxicity, but in our experience, can be effective for stage IIB generalized tumor disease (MFSS-9, page 528), stage III erythrodermic disease (MFSS-10, page 529), or stage IV disease (MFSS-11, above).

Brentuximab vedotin, bexarotene, histone deacetylase (HDAC) inhibitors (vorinostat and romidepsin), methotrexate, pralatrexate, mogamulizumab, alemtuzumab, and pembrolizumab are effective systemic therapy options for patients with advanced MF and SS. Bexarotene, brentuximab vedotin, mogamulizumab, vorinostat, and romidepsin are FDA-approved for treatment of MF and SS. The efficacy of brentuximab vedotin and mogamulizumab compared with standard therapy has been demonstrated in phase III randomized trials (ALCANZA and MAVORIC, respectively).^{30,31} Bexarotene,^{32,33} vorinostat,^{34–36} romidepsin,^{37–39} and other systemic therapies, such as pralatrexate,^{40–42} alemtuzumab,^{43–48} and pembrolizumab,⁴⁹ have been evaluated only in phase II studies. Interferons (alfa and gamma) and methotrexate also offer clinical benefit but have not been studied in phase II studies in the era of modern staging of MF and SS.^{50–52}

Extracorporeal photopheresis (ECP) is an immunomodulatory therapy in which patient's leukocytes are removed by leukapheresis, treated extracorporeally with 8-methoxypsoralen and UVA, and then returned to the patient.^{53–55} ECP may be a more appropriate systemic therapy for patients with some level of blood involvement (B1 or B2).

Gemcitabine^{56–59} and pegylated liposomal doxorubicin^{60–62} also have substantial activity in patients with advanced MF and SS. Multiagent chemotherapy regimens used for the treatment of systemic PTCL have activity but are associated with greater toxicity and a potentially higher risk of death when used in earlier lines of treatment.^{63,64} Therefore, multiagent chemotherapy regimens are generally reserved only for disease refractory to multiple prior therapies or for bulky lymph node or solid organ disease, and/or as a bridge to allogeneic hematopoietic cell transplant (HCT).

Data supporting the use of some of these agents in patients with MF and SS, particularly those studied in larger prospective phase II and III studies, are outlined as follows and are also summarized in Table 1.

† See Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1).

^w In patients with histologic evidence of folliculotropic MF, skin disease may be less responsive to topical therapies.

^x Patients with disease achieving a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration.

^y See Principles of Radiation Therapy (LYMP-A).

^z Imaging indicated when suspicious of clinical extracutaneous disease with modalities used in workup.

^{ee} Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant. See Discussion for further details.

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Bexarotene

Bexarotene, an oral retinoid, can have prolonged disease control without cumulative toxicity and is often considered for patients with higher skin burden with plaque disease.^{32,33} In phase II/III studies, oral bexarotene (≥ 300 mg/m²) was well tolerated, resulting in overall response rates (ORRs) of 45% to 67% in patients with early-stage and advanced-stage disease.^{32,33} Given the favorable tolerability profile without significant cumulative toxicity, the NCCN Guidelines recommend consideration of bexarotene for patients with early-stage MF who have insufficient disease control with skin-directed therapy. Bexarotene is also used in combination with phototherapy or ECP for early-stage disease with inadequate response to single-agent therapy and in patients with advanced-stage disease.^{65–68} It is important to note that bexarotene is associated with hypertriglyceridemia and central hypothyroidism, which necessitates laboratory monitoring for triglycerides, and serum levels of free thyroxine (T₄), often requiring additional management.

Brentuximab Vedotin

In the ALCANZA trial, brentuximab vedotin, an anti-CD30 antibody drug conjugate, resulted in significantly

improved ORR lasting at least 4 months (56% vs 13%), median progression-free survival (PFS; 17 vs 4 months), and patient-reported symptom burden compared with methotrexate or bexarotene in patients with CD30+ MF.³⁰ Peripheral neuropathy was the most common adverse event reported in 67% of patients.

Patients with SS were excluded from this trial, and CD30 positivity was defined as CD30 expression in $\geq 10\%$ of total lymphoid cells. However, in other phase II studies, clinical responses with brentuximab vedotin were observed across all CD30 expression levels (including negligible CD30 expression) and in patients with high blood Sézary cell count.^{63,64} Lesions with $< 5\%$ CD30 expression had a lower likelihood of global response than those with $\geq 5\%$ expression ($P < .005$), but responses were still seen in those with CD30 positivity of $\geq 1\%$.^{69,70} Although responses were observed in patients with very low or absent CD30 expression, the likelihood and/or depth of response may be lower in these situations and further studies are needed to define the activity of brentuximab vedotin in this setting. Brentuximab vedotin is a more effective treatment option than methotrexate

SUGGESTED TREATMENT REGIMENS^{a,b}

SYSTEMIC THERAPIES			
	Preferred Regimens (alphabetical order)	Other Recommended Regimens	Useful Under Certain Circumstances
SYST-CAT A	<ul style="list-style-type: none"> • Brentuximab vedotin^{i,j,k} • Bexarotene^h • Extracorporeal photopheresis (ECP)^l • Interferons (IFN-alfa-2b^m or IFN-gamma 1b) • Methotrexate (≤50 mg q week) • Mogamulizumabⁿ • Romidepsinⁿ • Vorinostatⁿ 	<ul style="list-style-type: none"> • Acitretin^h • All-trans retinoic acid^h • Isotretinoin [13-cis-retinoic acid]^h 	
SYST-CAT B	<ul style="list-style-type: none"> • Brentuximab vedotin^{i,j,k} • Gemcitabine • Liposomal doxorubicin • Pralatrexate (low-dose or standard dose) 		<ul style="list-style-type: none"> • Relapsed/refractory disease requiring systemic therapy; alphabetical order by category) <ul style="list-style-type: none"> ▶ Alemtuzumab^{k,p} ▶ Chlorambucil ▶ Cyclophosphamide ▶ Etoposide ▶ Pentostatin ▶ Temozolomide for CNS involvement ▶ Bortezomib (category 2B) ▶ Pembrolizumab (category 2B)^{q,r} • See TCEL-B 2 of 5 for regimens listed for PTCL-NOS^o
Large-cell transformation (LCT)	<ul style="list-style-type: none"> • Brentuximab vedotin^{i,j,k} • Gemcitabine • Liposomal doxorubicin • Pralatrexate (low-dose or standard dose) • Romidepsin • See TCEL-B 2 of 5 for regimens listed for PTCL-NOS^o 		

^a See references for regimens MFSS-A 4 of 6, MFSS-A 5 of 6, and MFSS-A 6 of 6.

^b The optimal treatment for any patient at any given time is often individualized based on symptoms of disease, route of administration, toxicities, and overall goals of therapy.

^h Safety of combining TSEBT with systemic retinoids, HDAC inhibitors (such as vorinostat or romidepsin), or mogamulizumab, or combining phototherapy with vorinostat or romidepsin is unknown.

ⁱ In the ALCANZA trial (Prince HM, et al. Lancet 2017;390:555-566) brentuximab vedotin (BV) was associated with superior clinical outcome in patients with CD30+ MF and pcALCL. CD30 positivity was defined as CD30 expression ≥10% of total lymphoid cells. However, in other clinical studies, clinical responses with BV have been reported across all CD30 expression levels including negligible CD30 expression.

^j Patients with Sézary syndrome were excluded from the ALCANZA trial.

^k See Supportive Care for Brentuximab Vedotin and Alemtuzumab (LYMP-C).

^l ECP may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).

^m Peginterferon alfa-2a may be substituted for other interferon preparations. Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847.

ⁿ Patients with LCT were excluded from the MAVORIC trial.

^o Multiagent chemotherapy regimens are generally reserved for patients with relapsed/refractory or extracutaneous disease. Most patients are treated with multiple SYST-CAT A/B before receiving multiagent chemotherapy.

^p Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

^q Preliminary phase II data in patients with MF and SS. Disease flare is seen in some patients (especially in erythrodermic skin/Sézary patients) and should be distinguished from disease progression. Khodadoust MS, Rook AH, Porcu P, et al. Pembrolizumab in relapsed and refractory mycosis fungoides and Sézary syndrome: A multicenter phase II study. J Clin Oncol 2019;[Epub ahead of print].

^r Rapid progression has been reported in HTLV positive patients receiving pembrolizumab.

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or bexarotene for patients with CD30+ MF but carries greater risk, particularly a cumulative risk of peripheral neuropathy.

Mogamulizumab

In the MAVORIC trial, the humanized anti-CCR4 monoclonal antibody mogamulizumab resulted in a significantly higher ORR (28% vs 5%) and median PFS (8 vs 3 months) compared with vorinostat, and the ORR was higher in patients with SS than in those with MF (37% vs 21%).³¹ Patients with LCT were excluded from this trial. Grade 1–2 infusion-related reactions, skin eruptions, and diarrhea were the most common adverse events.

In the post hoc subgroup analysis, the ORR for mogamulizumab was higher for patients with stage III (23%) or IV disease (36%) than for those with stage IIB (16%) or IB/IIA disease (19%). Mogamulizumab also resulted in higher ORR than vorinostat across all disease compartments. Compartment-specific ORRs were 42% (vs 16%), 68% (vs 19%), and 17% (vs 4%), respectively, for involvement of skin, blood, and lymph nodes. Mogamulizumab is included as a preferred regimen for patients with SS with high Sézary cell burden.

HDAC Inhibitors (Vorinostat and Romidepsin)

Vorinostat was the first HDAC inhibitor to be approved for the treatment of MF and SS. In the initial phase IIB registration study, vorinostat resulted in an ORR of 30%.³⁵ A post hoc subset analysis of patients who experienced clinical benefit with ≥2 years of vorinostat therapy in the phase IIB study provided some evidence for its long-term safety and efficacy in patients with heavily pretreated MF and SS, regardless of previous treatment failures.³⁶ Although cumulative toxicities were rare, patients must be monitored for gastrointestinal toxicity, including nausea, diarrhea, and resultant dehydration, which could be more detrimental for elderly patients.

Romidepsin has demonstrated clinical activity across all disease compartments,^{37–39} with a median response duration of 13 to 15 months.^{37–39} Importantly, romidepsin was associated with a high rate of reduction in pruritus score irrespective of clinical objective response.³⁸ The compartment-specific ORRs were 40%, 35%, 32%, and 27%, respectively, for skin involvement, erythroderma, blood involvement, and lymphadenopathy.³⁹ It is important to initially monitor for QTc prolongation when administering romidepsin, particularly with concomitant use

SUGGESTED TREATMENT REGIMENS^{a,b}

COMBINATION THERAPIES (alphabetical order)		
Skin-directed + systemic	<ul style="list-style-type: none"> • Phototherapy + ECP^l • Phototherapy + Interferon (IFN-alfa-2b^m or IFN-gamma 1b) • Phototherapy + retinoid • TSEBT + ECP^l 	
Systemic + systemic	<ul style="list-style-type: none"> • ECP^l + Interferon (IFN-alfa-2b^m or IFN-gamma 1b) • ECP^l + retinoid • ECP^l + retinoid + Interferon (IFN-alfa-2b^m or IFN-gamma 1b) • Retinoid + Interferon (IFN-alfa-2b^m or IFN-gamma 1b) 	

ERYTHRODERMIC DISEASE/SÉZARY SYNDROME		
	Preferred Regimens	Other Recommended Regimens
Low-intermediate burden (eg, absolute Sézary cell [ASC] count <5 K/mm ³)	<ul style="list-style-type: none"> • Combination therapies (see above) • SYST-CAT A ± skin-directed therapies (skin-generalized) (See MFSS-A 2 of 6) 	<ul style="list-style-type: none"> • SYST-CAT B ± skin-directed therapies (skin-generalized) (See MFSS-A 2 of 6) • Alemtuzumab^{k,p} • Pembrolizumab^{q,r}
Higher burden (eg, ASC >5 K/mm ³)	<ul style="list-style-type: none"> • Combination therapies (see above) • Mogamulizumab ± skin-directed therapies (skin-generalized)^h • Romidepsin ± skin-directed therapies (skin-generalized)^h 	<ul style="list-style-type: none"> • SYST-CAT A (options not listed under preferred regimens) (See MFSS-A 2 of 6) • SYST-CAT B (See MFSS-A 2 of 6) • Alemtuzumab^{k,p} • Pembrolizumab^{q,r}

^a See references for regimens MFSS-A 4 of 6, MFSS-A 5 of 6, and MFSS-A 6 of 6.

^b The optimal treatment for any patient at any given time is often individualized based on symptoms of disease, route of administration, toxicities, and overall goals of therapy.

^h Safety of combining TSEBT with systemic retinoids, HDAC inhibitors (such as vorinostat or romidepsin), or mogamulizumab, or combining phototherapy with vorinostat or romidepsin is unknown.

^k See Supportive Care for Brentuximab Vedotin and Alemtuzumab (LYMP-C).

^l ECP may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).

^m Peginterferon alfa-2a may be substituted for other interferon preparations. Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847.

^p Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

^q Preliminary phase II data in patients with MF and SS. Disease flare is seen in some patients (especially in erythrodermic skin/Sézary patients) and should be distinguished from disease progression. Khodadoust MS, Rook AH, Porcu P, et al. Pembrolizumab in relapsed and refractory mycosis fungoides and Sézary syndrome: A multicenter phase II study. J Clin Oncol 2019;[Epub ahead of print].

^r Rapid progression has been reported in HTLV-positive patients receiving pembrolizumab.

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of antiemetics that also prolong QTc. Romidepsin is included as a preferred regimen for patients with SS with high Sézary cell burden.

Alemtuzumab

Alemtuzumab (a humanized anti-CD52 monoclonal antibody) has significant clinical activity in patients with previously treated advanced MF and SS.^{43,44,46-48} The ORR with alemtuzumab (30 mg intravenously) was higher in patients with erythroderma or SS than in those with advanced MF; however, it was associated with myelotoxicities and infectious complications.^{44,48} Reduced-dose subcutaneous alemtuzumab (3–15 mg per administration) given for a shorter duration was equally effective, with a lower incidence of infectious complications in patients with SS.⁴⁵ Although alemtuzumab is no longer commercially available, it may be obtained for compassionate use in patients with CTCL and other hematologic malignancies.

Pembrolizumab

In a phase II trial, pembrolizumab (an immune checkpoint inhibitor) resulted in durable responses in both MF and SS, with an ORR of 38% and median duration of

response not reached at a median follow-up of 58 weeks.⁴⁹ Pembrolizumab was associated with a skin flare reaction, occurring exclusively in patients with SS; the flare reaction correlated with high PD-1 expression on Sézary cells and should be distinguished from disease progression.

Role of HCT in MF and SS

Currently there is no definitive treatment that can produce reliable durable remissions or curative results for disease that is refractory to multiple prior therapies. There is a role for allogeneic HCT in a subset of patients with advanced-stage MF and SS who have received multiple lines of therapy, as shown in retrospective studies and small prospective series.⁷¹⁻⁷⁵ Recent systematic review and meta-analysis have reported pooled PFS and OS rates of 36% and 59%, respectively.^{76,77} Autologous HCT is not recommended for patients with CTCL, due to short duration of response despite its toxicity, thus limiting its utility.⁷⁸

Allogeneic HCT may be considered for appropriate patients with stage IIB–IV disease refractory to multiple primary treatment options. Based on the limited evidence, patients with erythrodermic MF and SS appear to

Table 1. Systemic Therapy for MF and SS

Trial	Regimen/Dose		Disease Stage and Number of Patients	ORR	Median PFS
ALCANZA trial (phase III RCT) ^{a,30}	Brentuximab vedotin (1.8 mg/kg every 3 weeks; up to 16 3-week cycles)		Stage IA–IVB MF (n=48)	65% (10% CR)	17 mo
	Oral methotrexate (5–50 mg once per week) for up to 48 weeks or Oral bexarotene (300 mg/m ² once per day) for up to 48 weeks		Stage IA–IVB MF (n=49)	16%	4 mo
MAVORIC trial (phase III RCT) ^{b,31}	Mogamulizumab (1 mg/kg intravenously on a weekly basis for the first 28-day cycle, then on days 1 and 15 of subsequent cycles)		Stage IB–IVA (n=186)	28% (23% by IR)	8 mo (7 mo by IR)
	Vorinostat (400 mg daily)		Stage IB–IVA (n=186)	5% (4% by IR)	3 mo (4 mo by IR)
Phase II and III ³²	Bexarotene	300 mg/m ² /d	Stage IA–IIA (n=28)	54%	
		>300 mg/m ² /d	Stage IA–IIA (n=15)	67%	
Phase II and III ³³	Bexarotene	300 mg/m ² /d	Stage IIB–IVB (n=56)	45%	
		>300 mg/m ² /d	Stage IIB–IVB (n=38)	55% (13% CR)	
Phase IIB ³⁵	Vorinostat (400 mg daily)		Stage IB–IVA (n=74)	30%	
Phase II ³⁸	Romidepsin (14 mg/m ² as a 4-hour IV infusion on days 1, 8, and 15 of each 28-day cycle for up to 6 cycles)		Stage IB–IVA (n=96)	34% (6% CR)	
PDX-010 (dose-escalation study) ⁴⁰	Pralatrexate (15 mg/m ² , weekly for 3 out of 4 weeks)		Stage IB–IVA (n=29)	45%	Not reached
Phase II ⁴⁴	Alemtuzumab (IV 30 mg)		Stage III or IV (n=22)	55% (32% CR)	
Trial of low-dose SC alemtuzumab ⁴⁵	Alemtuzumab (SC 10 mg maximum per administration) ^{45,c}		SS (n=14)	86% (21% CR)	Median survival (35 mo)
Phase II (CITN-10) ⁴⁹	Pembrolizumab (2 mg/kg IV, every 3 weeks)		Stage IIB–IVB (n=24)	38%	65% (1-year PFS rate)

Abbreviations: CR, complete response; IR, independent review; IV, intravenous; MF, mycosis fungoides; LCT, large cell transformation; ORR, overall response rate; PFS, progression-free survival; RCT, randomized controlled trial; SC, subcutaneous; SS, Sézary syndrome.

^aPatients with SS were excluded from ALCANZA trial; median follow-up 23 months.

^bPatients with LCT of MF were excluded from MAVORIC trial; median follow-up 17 months.

^cSC alemtuzumab at lower doses given for shorter duration based on Sézary cell levels was associated with a more favorable toxicity profile.

receive the most benefit from allogeneic HCT, despite a high posttransplant relapse rate. Allogeneic HCT is generally reserved for patients with systemic disease and/or extensive skin involvement that is refractory to or progressive after multiple lines of systemic therapy options.

The ideal timing for allogeneic HCT is when the disease is well controlled with induction therapy and before it has progressed to a state in which the chance of

response or survival with allogeneic HCT is low.⁷⁹ A transplant decision requires careful counseling to weigh the significant risks of this procedure against the likelihood of long-term benefits and availability of alternate treatments.

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