National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Primary Cutaneous Lymphomas

Version 3.2024 — August 22, 2024

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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‡ Hematology/Hematology oncology	ʘ Plastic surgery
Þ Internal medicine	§ Radiotherapy/Radiation oncology
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NCCN Guidelines Panel Disclosures

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 3.2024 of the NCCN Guidelines for Primary Cutaneous Lymphomas from Version 2.2024 include:

MFSS-A (1 of 12)
- 4th bullet revised: Bexarotene, brentuximab vedotin, *denileukin diftitox-cxdl,* mogamulizumab. romidepsin, and vorinostat are approved by the U.S. Food and Drug Administration (FDA)...

MFSS-A (4 of 12)
- Stage IB MF, Suggested Regimens
  - Useful in Certain Circumstances, denileukin diftitox-cxdl added as a category 2A recommendation.
- Treatment Considerations
  - 10th consideration added: Patients with MF-LCT were excluded from Study 302 that evaluated denileukin diftitox-cxdl in patients with relapsed or refractory CTCL. Also for MFSS-A (5 of 12) and (6 of 12).

MFSS-A (5 of 12)
- Stage IIB MF,
  - Limited Tumor Disease, Useful in Certain Circumstances, denileukin diftitox-cxdl added as a category 2A recommendation.
  - Generalized Tumor Disease, Preferred Regimens, denileukin diftitox-cxdl added as a category 2A recommendation.

MFSS-A (6 of 12)
- Stage III MF, Suggested Regimens
  - Useful in Certain Circumstances, denileukin diftitox-cxdl added as a category 2A recommendation.

MFSS-A (9 of 12)
- Footnote b modified: Peginterferon alfa-2a ~~is the only interferon available for clinical use in the US and it~~ may be substituted for other interferon preparations...
- Footnote d added: In Study 302, CD25-positiity was defined as detectable CD25 in ≥20% of total lymphoid cells in biopsy specimen by IHC. However, there was no correlation between the CD25 expression and the efficacy of denileukin diftitox.

MS-1
- Discussion section updated to reflect changes in the algorithm.

Continued
UPDATES

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Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 2.2024 of the NCCN Guidelines for Primary Cutaneous Lymphomas from Version 1.2024 include:

MS-1

• Discussion section updated to reflect changes in the algorithm.

Updates in Version 1.2024 of the NCCN Guidelines for Primary Cutaneous Lymphomas from Version 1.2023 include:

Global changes

• References updated throughout the guideline.

Primary Cutaneous B-Cell Lymphomas

CUTB/INTRO-1

• Overview & Definition
  ▸ 2nd subtype modified: Primary cutaneous marginal zone lymphoma (PCMZL)(WHO)/Primary cutaneous marginal zone lymphoproliferative disorder (ICC)
• Diagnosis
  ▸ PCMZL, 2nd bullet, 1st sub-bullet modified: Immunophenotype – cells are negative for CD10 and BCL6, but are often positive for BCL2, CD20, CD79a.
  ▸ PCDLBCL, leg type, 2nd bullet modified: Gene expression profiling: PCDLBCL, leg type has been demonstrated to be ~~always~~ most commonly activated B-cell (ABC) subtype.

CUTB-1

• Diagnosis
  ▸ Essential
    ◊ 1st bullet added: Biopsy of suspicious skin sites, Multiple biopsies may be necessary to capture the pathologic variability of disease at diagnosis
    ◊ 3rd bullet modified: Adequate biopsy (by punch, incisional, excisional) of all types of clinical lesions present will aid in final diagnosis
  ▸ Useful in certain circumstances,
    ◊ 1st bullet, 2nd sub-bullet modified: Assessment of IgM, IgD, ~~IgA, IgG, IgE~~, and FOXP1
    ◊ 4th bullet modified: If adequate biopsy material is available, flow cytometry or molecular analysis to detect IgH gene rearrangement ~~studies~~ can be useful in determining B-cell clonality

CUTB-A (1 of 2)

• Footnote removed: Patients with both erythroderma and tumors may be designated as T4(T3). The BSA of 80% is used to define erythroderma in MF/SS at study entry, but any decrease in BSA during the study does not affect the entry classification.

Mycosis Fungoides/Sézary Syndrome

MFSS-1

• Diagnosis
  ▸ Essential, 2nd bullet modified: Review of a sufficient number of slides with adequate material to perform a comprehensive work-up as described below and/or at least one paraffin block representative of the ~~tumor~~ lesion should be done by a pathologist...

MFSS-2

• Workup
  ▸ Useful in certain circumstances, 2nd bullet modified: ...~~Rebiopsy if consult material is nondiagnostic.~~ *Rebiopsy if pathological findings are non-diagnostic and/or discordant with the clinical presentation.*

MFSS-3

• Description added: Changes or confirmation of staging are noted in bold in table above and in further description below. Options for characterizing clonality further by designation as A (clone negative or equivocal) and B (clone positive and identical to skin) are presented. If a clone in LN or viscera is detected but different from that identified in the skin, another concurrent lymphoproliferative process should be considered.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Primary Cutaneous Lymphomas from Version 1.2023 include:

MFSS-3A
- Footnote x modified by adding: Patients with lymphopenia (defined as <1000 absolute lymphocytes) may potentially have an underestimation of aberrant lymphocyte burden if assessed only by the absolute number and not also by the percentage of immunophenotypically abnormal lymphocytes.

MFSS-4
- IVB (Visceral disease), M(visceral) cell modified: M1*A or M1B*
- Footnote y reference updated: ~~Olsen E, et al. Blood 2007;110:1713-1722~~ Olsen EA, et al. Blood 2022;140:419-437.

MFSS-7
- Stage IIB, Treatment and response assessment
  - Inadequate response, option modified: *Retreat with primary treatment or treat as* high skin disease burden (see below)

MFSS-8
- Stage IIB, Treatment and response assessment
  - CR/PR, relapse options modified:
    - ◊ T1–2 *with* limited tumor lesions See Table 1 or See Table 2)
    - ◊ T3 *with* limited tumor lesions
  - Inadequate response, option modified: Persistent T1–T3 *with* limited tumor lesions (also for MFSS-9)

MFSS-A (2 of 12)
- Treatment Considerations
  - 2nd option modified: Cumulative dose of UV, in particular PUVA, *which carries a higher risk than NBUVB*, is associated with increased risk of UV-associated skin neoplasms...
  - 7th option modified: Topical mechlorethamine *has no significant systemic absorption, and can be used alone or in combination with other skin directed therapies, in particular topical steroids. Topical mechlorethamine* use, in particular gel preparation, can be complicated by dermatitis, and can result in skin irritation when used on face and intertriginous body areas. ~~Consider initiating at less than daily use to determine tolerability. Slowly increase the application of topical mechlorethamine to once daily five times per week.~~ I*nitiating at less than daily use can be useful to determine tolerability and topical steroids can be considered as needed to alleviate skin reactions from topical mechlorethamine gel. If used with phototherapy, topical mechlorethamine gel should be applied after exposure to UVL*.

MFSS-A (3 of 12)
- Treatment Considerations
  - 5th option modified: In stage IA, ECP is primarily reserved for ~~the uncommon stage IA patients~~ *rare patient with stage IA MF* with low level blood involvement (B1).

MFSS-A (5 of 12)
- Limited Tumor Disease
  - 2nd bullet modified: Systemic therapy ± local RT ± *skin-directed therapy*

MFSS-A (9 of 12)
- Footnote b modified: ~~Interferon alfa (2a and 2b) and peginterferon alfa-2b have been discontinued. Peginterferon alfa-2a may be substituted for other interferon preparations (Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847).~~ *Peginterferon alfa-2a is the only interferon available for clinical use in the US and it may be substituted for other interferon preparations.(Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847; Patsatsi A, et al. J Eur Acad Dermatol Venereol 2022;36:e291-e293; Osman S, et al. Dermatologic Therapy 2023;2023:7171937).*

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Primary Cutaneous Lymphomas from Version 1.2023 include:

Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

PCTLD-1

- Diagnosis, essential
  - 3rd bullet modified: Complete skin examination ~~for evidence of MF~~ *for any sign of benign or malignant skin lesions*
  - 4th bullet,
    - 1st sub-bullet added: Multiple biopsies may be necessary to capture the pathologic variability of disease at diagnosis
    - 2nd sub-bullet modified: *Adequate* biopsy (*by* punch, incisional, or excisional) of all types of clinical lesions present will aid in final diagnosis

Principles of Radiation Therapy

PCLYM-A 1 of 3

- General principles
  - 2nd bullet modified: ~~Treatment~~ *External beam radiation therapy (EBRT)* with photons, electrons, or low-energy x-rays may all be appropriate, depending on clinical circumstances.

PCLYM-A 2 of 3

- General dose guidelines
  - PCMZL and PCFCL,1st bullet modified: Optimal initial management for solitary/regional disease is with 24–30 Gy external beam radiation therapy (EBRT). *Alternatively, lower doses (eg, 4 Gy) may be used initially, with supplemental RT (4-20 Gy) for inadequate response or subsequent local failure.*
  - MF/SS
    - 1st bullet modified: Treatment of individual *patches,* plaques or tumors
      - 1st sub-bullet modified: Optimal management for individual plaque and tumor lesions is with EBRT, 8–12 Gy given with palliative intent (usually as combined modality therapy; 8 Gy may be given in 1–2 fractions). *Even lower doses (4 Gy) may achieve a similar response, but these may be less durable.*
      - 2nd sub-bullet modified: For unilesional MF *at initial presentation*, 24–30 Gy.
    - TSEBT
      - 2nd bullet modified: ~~The dose range is 12–36 Gy, generally 4–6 Gy per week.~~ *The common dose is ~12 Gy, generally 4–6 Gy per week. Higher doses (24-36 Gy) have been used for more advanced or refractory disease.* The advantages of *a* lower ~~total~~ dose includes fewer short-term complications and better ability to retreat for relapsed disease

Supportive Care

PCLYM-C

- Monoclonal Antibody (mAb) Therapy and Viral Reactivation, bullet removed: Anti-CD20 Antibody Therapy - See NCCN Guidelines for B-Cell Lymphomas

PRINCIPLES FOR PRIMARY CUTANEOUS B-CELL LYMPHOMAS (PCBCL)

Overview & Definition

Three subtypes of PCBCL:

1. **Primary cutaneous follicle center lymphoma (PCFCL)**
   - **Most common subtype of PCBCL (57%),[1,2] located primarily in the scalp, face, forehead, and trunk, usually with indolent course and excellent prognosis (5-year overall survival [OS] rate is >95%).**
   - **Typically presents as solitary, firm, and pink to violaceous papules, nodules, plaques, or tumors. Multifocal skin lesions are seen in 15% of cases.[1,2] Ulceration is rare.**
   - **Dissemination to extracutaneous sites is extremely uncommon; cutaneous recurrences occur near the initial site in approximately 30% of cases.**
2. **Primary cutaneous marginal zone lymphoma (PCMZL) (WHO5)/Primary cutaneous marginal zone lymphoproliferative disorder (ICC)**
   - **Second most common subtype of PCBCL (24%–31%)[1] with distribution primarily on the trunk, upper extremities, and head. Typically presents as solitary or multiple erythematous to violaceous papules, small nodules, plaques, or tumors with indolent course and excellent prognosis (5-year survival rate is 99%).**
   - **Relapses in the skin occur in 50% of patients.**
3. **Primary cutaneous diffuse large B-cell lymphoma (PCDLBCL, leg type)**
   - **The rarest subtype of PCBCL (11%–19%), constituting 4% of all primary cutaneous lymphomas. It is distributed mostly to the leg, but not uncommonly (10%–15%) can be found in other sites.[1]**
   - **Typical clinical presentation is red to bluish plaques or tumors located on one or both legs that can ulcerate.**
   - **It is usually aggressive and associated with a poor prognosis (high frequency of extracutaneous relapses) (5-year OS rate is 50%).[2,3]**
   - **Multiple skin lesions, inactivation of *CDKN2A*, and *MYD88* L265P associated with inferior prognosis.**

Diagnosis

- **PCFCL: punch biopsy/incision/excision of skin lesion preferred to shave biopsy**
  - **Immunophenotype – cells express CD20, CD79a, and BCL6; surface Ig is negative. CD10 can be negative in cases with diffuse growth pattern. BCL2 is usually negative, or minimally expressed.**
  - **When CD10 and BCL2 are strongly expressed, or BCL2 is rearranged, consider a nodal follicular lymphoma (FL) with secondary skin involvement.**
  - **Germinal (or follicle) center phenotype with large cells in a skin lesion is consistent with PCFCL with a diffuse population of large cells (PCFCL-LC) and should not be considered as DLBCL.**
- **PCMZL: punch biopsy/incision/excision of skin lesion preferred to shave biopsy**
  - **Immunophenotype – cells are negative for CD10 and BCL6, but are often positive for BCL2, CD20, and CD79a. IgG4 can be expressed in about a third of cases.**
  - **Can be divided into 2 groups with different prognosis based on the immunoglobulin heavy chain *IgH* gene rearrangement: 1) CXCR3-negative and Ig class-switched subtype (IgG, IgA, and IgE), characterized by nodular infiltrates of plasma cells; and 2) a less common subtype that is CXCR3-positive and IgM positive (non class-switched), which may have extracutaneous extension.[4-7] IgG class-switched subtype is a clonal chronic lymphoproliferative disorder (LPD), with indolent course.[7,8]**
- **PCDLBCL, leg type: punch biopsy/incision/excision of skin lesion preferred to shave biopsy**
  - **Immunophenotype – cells express CD20, CD79a, monotypic immunoglobulins, BCL2 (strong), IRF/MUM1, FOXP1, and MYC. CD10 staining is usually negative.**
  - **Gene expression profiling: PCDLBCL, leg type has been demonstrated to be most commonly activated B-cell (ABC) subtype. Germinal center B-cell (GCB) subtype should be considered PCFCL, even if large cells are present.[9,10]**
  - **Fluorescence in situ hybridization (FISH): frequently shows translocations of *MYC*, *BCL6,* and *IGH* genes.**

Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES FOR PRIMARY CUTANEOUS B-CELL LYMPHOMAS (PCBCL)

General Principles

- **PCFCL, PCMZL: If the pathology or clinical presentation is not typical, complete staging with chest/abdominal/pelvic CT and/or FDG-PET/CT scan to rule out systemic involvement. Low-dose localized radiation therapy (RT), topical or intralesional steroids, or observation are excellent treatment options.**
- **PCDLBCL, leg type: Complete staging with FDG-PET/CT scan. Treat with chemoimmunotherapy and localized RT. (See NCCN Guidelines for B-Cell Lymphomas - DLBCL)**

[1] Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019;133:1703-1714.
[2] Zinzani PL, Quaglino P, Pimpinelli N, et al. Prognostic factors in primary cutaneous B-cell lymphoma: the Italian Study Group for Cutaneous Lymphomas. J Clin Oncol 2006;24:1376-1382.
[3] Felcht M, Klemke CD, Nicolay JP, et al. Primary cutaneous diffuse large B-cell lymphoma, NOS and leg type: Clinical, morphologic and prognostic differences. J Dtsch Dermatol Ges 2019;17:275-285.
[4] van Maldegem F, van Dijk R, Wormhoudt TA, et al. The majority of cutaneous marginal zone B-cell lymphomas expresses class-switched immunoglobulins and develops in a T-helper type 2 inflammatory environment. Blood 2008;112:3355-3361.
[5] Edinger JT, Kant JA, Swerdlow SH. Cutaneous marginal zone lymphomas have distinctive features and include 2 subsets. Am J Surg Pathol 2010;34:1830-1841.
[6] Kogame T, Takegami T, Sakai TR, et al. Immunohistochemical analysis of class-switched subtype of primary cutaneous marginal zone lymphoma in terms of inducible skin-associated lymphoid tissue. J Eur Acad Dermatol Venereol. 2019;33:e401-e403.
[7] Carlsen ED, Swerdlow SH, Cook JR, Gibson SE. Class-switched primary cutaneous marginal zone lymphomas are frequently IgG4-positive and have features distinct from IgM-positive cases. Am J Surg Pathol 2019;43:1403-1412.
[8] Gibson SE, Swerdlow SH. How I diagnose primary cutaneous marginal zone lymphoma. Am J Clin Pathol 2020;154:428-449.
[9] Hoefnagel JJ, Dijkman R, Basso K, et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 2005;105:3671-3678.
[10] Menguy S, Beylot-Barry M, Parrens M, et al. Primary cutaneous large B-cell lymphomas: relevance of the 2017 World Health Organization classification: clinicopathological and molecular analyses of 64 cases. Histopathology 2019;74:1067-1080.

Note: All recommendations are category 2A unless otherwise indicated.

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Primary Cutaneous B-Cell Lymphomas

DIAGNOSIS[a]

ESSENTIAL:

- **Biopsy of suspicious skin sites**
  - **Multiple biopsies may be necessary to capture the pathologic variability of disease at diagnosis**
- **Review of a sufficient number of slides with adequate material to perform a comprehensive workup as described below and/or at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of PCBCL. Rebiopsy if pathological findings are non-diagnostic and/or discordant with the clinical presentation**
- **Adequate biopsy (by punch, incisional, excisional) of all types of clinical lesions present will aid in final diagnosis**
- **Adequate immunophenotyping to establish diagnosis[b]**
  - **Immunohistochemistry (IHC) panel may include: CD20, CD3, CD10, BCL2, BCL6, IRF4/MUM1**

USEFUL IN CERTAIN CIRCUMSTANCES:

- **Additional immunohistochemical studies to establish lymphoma subtype**
  - **IHC panel may include: Ki-67, CD5, CD43, CD21, CD23, cyclin D1, kappa/lambda (IHC or ISH)**
  - **Assessment of IgM, IgD, and FOXP1 expression (to further help in distinguishing PC-DLBCL, leg type from PCFCL)**
- **EBER-ISH**
- **Cytogenetics (FISH and karyotype): t(14;18) if systemic FL is suspected**
- **If adequate biopsy material is available, flow cytometry or molecular analysis to detect IgH gene rearrangement can be useful in determining B-cell clonality**

WORKUP[c]

ESSENTIAL[d]:

- **History and physical exam, including complete skin exam**
- **CBC with differential**
- **Comprehensive metabolic panel**
- **Lactate dehydrogenase (LDH)**
- **Chest/abdominal/pelvic CT with contrast and/or FDG-PET/CT scan (may be omitted if clinically indicated)**
- **Pregnancy testing in patients of childbearing potential (if chemotherapy or RT planned)**

USEFUL IN CERTAIN CIRCUMSTANCES:

- **Bone marrow biopsy[e]**
- **Peripheral blood flow cytometry, if complete blood count (CBC) demonstrates lymphocytosis**
- **SPEP/quantitative immunoglobulins for PCMZL**
- **HIV testing**
- **Hepatitis B and C testing[f]**
- **Discuss fertility preservation[g]**

→ **PCMZL (CUTB-2)**

→ **PCFCL (CUTB-2)**

→ **PC-DLBCL, Leg Type (See NCCN Guidelines for B-Cell Lymphomas - DLBCL)**

[a] For non-cutaneous extranodal B-cell lymphomas, see Extranodal MZL of Nongastric Sites in the NCCN Guidelines for B-Cell Lymphomas. A germinal (or follicle) center phenotype and large cells in a skin lesion is not equivalent to DLBCL but is consistent with primary cutaneous germinal/follicle center lymphoma.

[b] Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See NCCN Guidelines for B-Cell Lymphomas).

[c] A multidisciplinary team approach involving hematology/oncology, dermatology, pathology (with expertise in cutaneous lymphoma), and radiation oncology is often optimal for the management of patients with PCBCL.

[d] Rule out drug-induced cutaneous lymphoid hyperplasia.

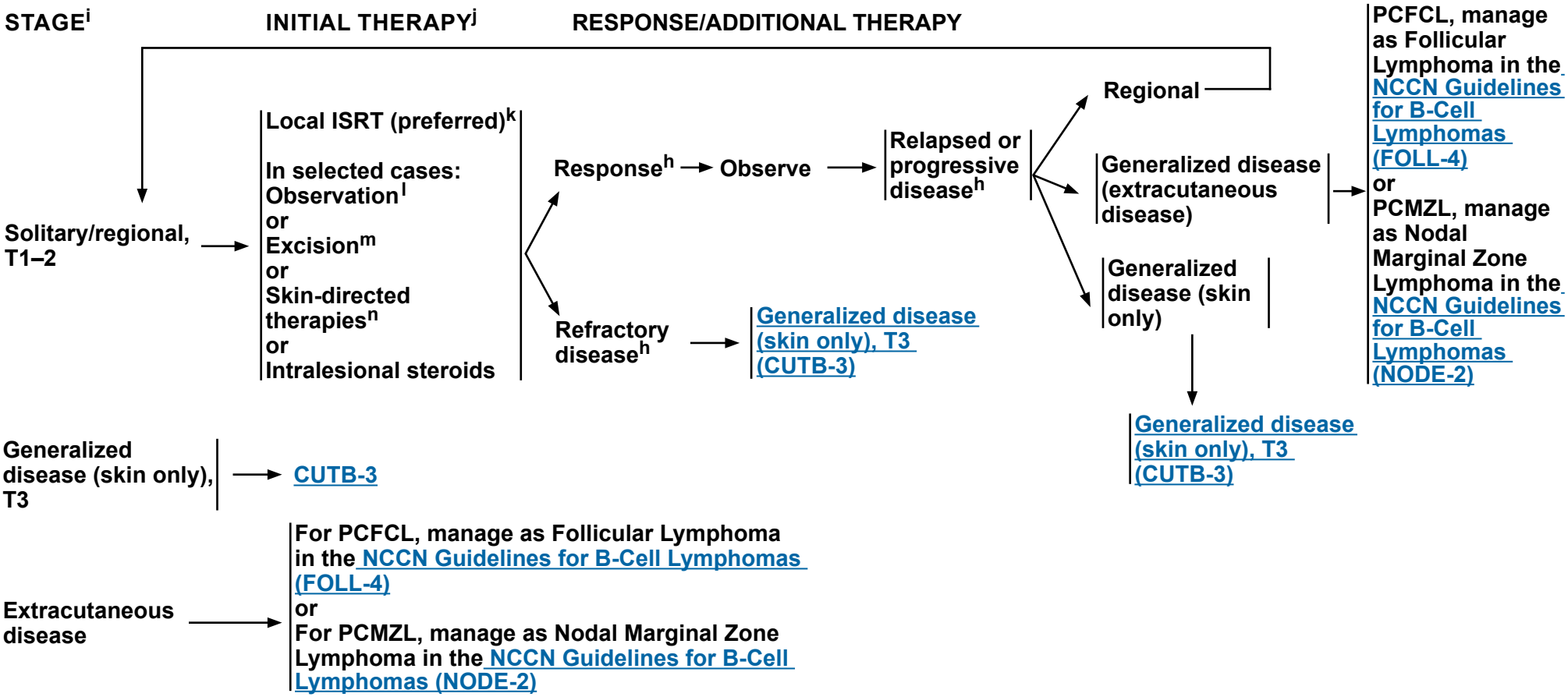
[e] Often reserved for patients with unexplained cytopenias or if there is clinical suspicion of other subtypes (eg, PC-DLBCL, leg type).

[f] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. See monoclonal antibody and viral reactivation in the NCCN Guidelines B-Cell Lymphomas. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with a gastroenterologist.

[g] Fertility preservation options include: sperm banking, semen cryopreservation, in vitro fertilization (IVF), or ovarian tissue or oocyte cryopreservation.

Note: All recommendations are category 2A unless otherwise indicated.

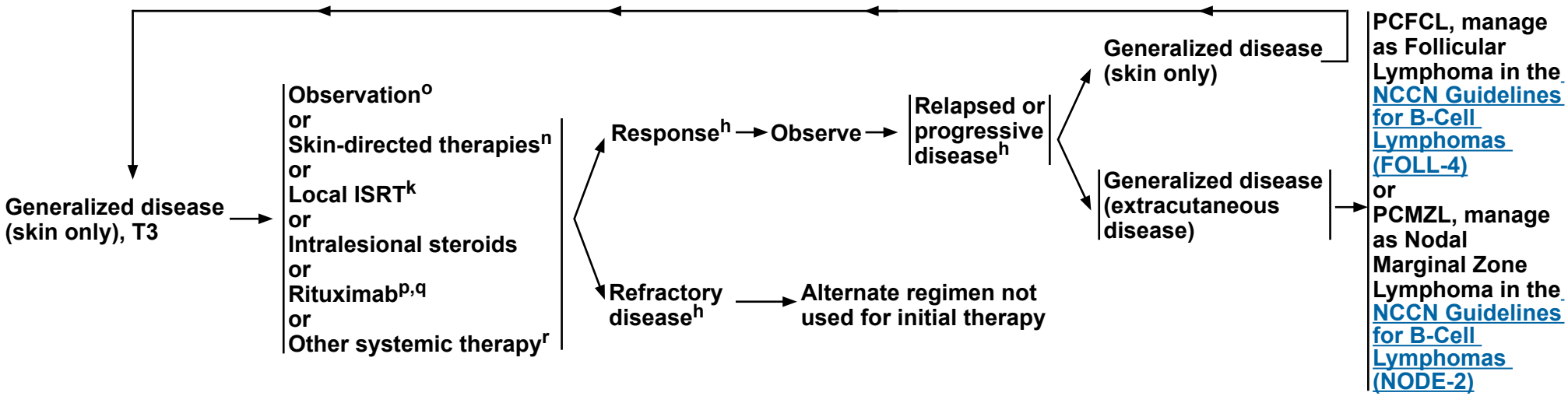
PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER LYMPHOMA[h]



[h] Additional imaging studies during the course of treatment are not needed. FDG-PET/CT or C/A/P CT with contrast at the end of treatment may be needed to assess response or if there is clinical suspicion of progressive disease.
[i] TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).
[j] Treatment References (CUTB-B).
[k] Local ISRT is the preferred initial treatment, but not necessarily the preferred treatment for relapse. See Principles of Radiation Therapy (PCLYM-A).
[l] When RT or surgical treatment is neither feasible nor desired.
[m] Small lesions may be excised with minimal non-disfiguring surgery.
[n] There are case reports showing efficacy of skin-directed therapies, which include topical steroids, imiquimod, nitrogen mustard, and bexarotene (useful in pediatric patients).

Note: All recommendations are category 2A unless otherwise indicated.

PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER LYMPHOMA[h]



[h] Additional imaging studies during the course of treatment are not needed. FDG-PET/CT or C/A/P CT with contrast at the end of treatment may be needed to assess response or if there is clinical suspicion of progressive disease.

[i] TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).

[j] Treatment References (CUTB-B).

[k] Local ISRT is the preferred initial treatment, but not necessarily the preferred treatment for relapse. See Principles of Radiation Therapy (PCLYM-A).

[n] There are case reports showing efficacy of skin-directed therapies, which include topical steroids, imiquimod, nitrogen mustard, and bexarotene (useful in pediatric patients).

[o] Considered appropriate in asymptomatic patients.

[p] See monoclonal antibody and viral reactivation in the NCCN Guidelines for B-Cell Lymphomas.

[q] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan. An FDA-approved biosimilar is an appropriate substitute for rituximab.

[r] In rare circumstances for very extensive or refractory disease, other combination chemoimmunotherapy regimens listed in NCCN Guidelines for B-Cell Lymphomas, FOLL-B can be used.

Note: All recommendations are category 2A unless otherwise indicated.

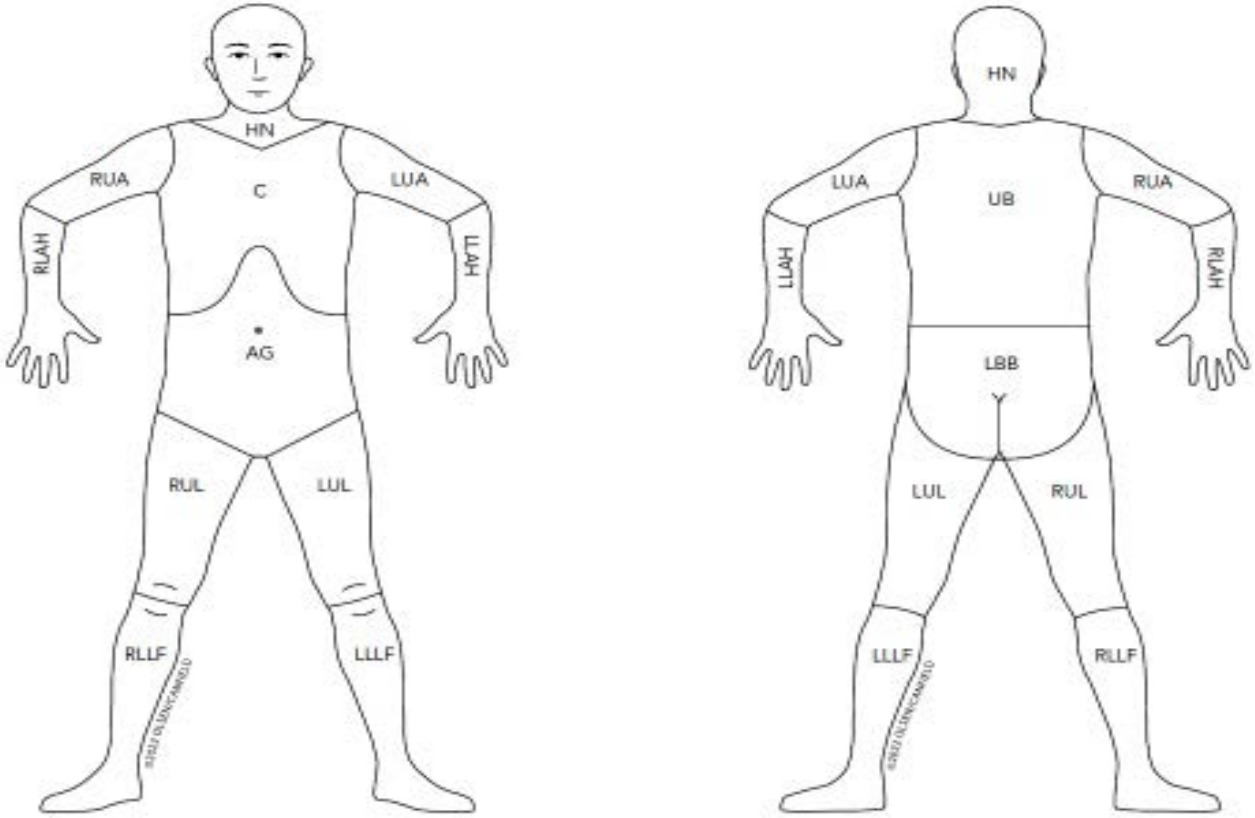
TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS[a,b]

TNM		Size/location of lesions		
T				
	T_0*	Absence of clinically suspicious lesions		
	T_1	Solitary lesion	T_{1A}	Solitary lesion <5 cm diameter
			T_{1B}	Solitary **≥5 cm** diameter
	T_2	Multiple lesions limited to 1 body region or 2 contiguous body regions[b]	T_{2A}	All disease encompassing in a <15-cm-diameter circular area
			T_{2B}	All disease encompassing a **15 to <30 cm** diameter circular area
			T_{2C}	All disease encompassing a **≥30 cm** diameter circular area
	T_3	Generalized skin involvement	T_{3A}	Multiple lesions involving 2 noncontiguous body regions[b]
			T_{3B}	Multiple lesions involving ≥3 body regions[b]
N				
	N_0	No clinical or pathologic LN involvement		
	N_1	Involvement of 1 peripheral LN region[c] that drains an area of current or prior skin involvement: biopsy positive for lymphoma		
	N_2	Involvement of >2 peripheral LN regions[c] or involvement of any LN region that does not drain an area of current or prior skin involvement: biopsy positive for lymphoma		
	N_3	Involvement of central lymph nodes: biopsy positive for lymphoma		
	N_X	Clinically abnormal peripheral or central LN but no pathologic determination. Other surrogate means of determining involvement may be determined by Tri-Society consensus		
M				
	M_0	No visceral involvement		
	M_1	Visceral involvement		
	M_X	Visceral involvement is neither confirmed nor refuted by available pathologic or imaging assessment		

[a] This work was originally published in Blood. Olsen EA, Whittaker S, Willemze R, et al. Primary cutaneous lymphoma: recommendations for clinical trial design and staging update from the ISCL, USCLC, and EORTC. Blood 2022;140:419-437. © The American Society of Hematology.
[b] For definition of body regions, see Body Regions for the Designation of T (Skin Involvement) Category (CUTB-A 2 of 2).
[c] Definition of lymph node regions is consistent with the Ann Arbor system: Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, paraaortic, and iliac.

Note: All recommendations are category 2A unless otherwise indicated.

BODY REGIONS FOR THE DESIGNATION OF T (SKIN INVOLVEMENT) CATEGORY[a,d,e]



[a] This work was originally published in Blood. Olsen EA, Whittaker S, Willemze R, et al. Primary cutaneous lymphoma: recommendations for clinical trial design and staging update from the ISCL, USCLC, and EORTC. Blood 2022;140:419-437. © The American Society of Hematology.

[d] Left and right extremities are assessed as separate body regions. The designation of these body regions is based on regional lymph node drainage patterns.

[e] Definition of body regions: Head and neck (HN), inferior borders = clavicles anterior and T1 spinous process posterior; left upper arm (LUA), superior border = glenohumeral joint (exclusive of axilla), inferior border = ulnar/radial/humeral (elbow) joint; left lower arm and hand (LLAH), superior border = ulnar/radial/humeral (elbow) joint; right upper arm (RUA), superior border = glenohumeral joint (exclusive of axilla), inferior border = ulnar/radial/humeral (elbow) joint; right lower arm and hand (RLAH), superior border = ulnar/radial/humeral (elbow) joint; chest (C), superior border = superior border clavicles, inferior border = inferior margin rib cage, lateral borders = midaxillary lines and glenohumeral joints (inclusive of axilla); abdomen/genital (AG), superior border = inferior margin rib cage, inferior border = inguinal folds and anterior perineum; upper back (UB), superior border = T1 spinous process, inferior border = inferior margin rib cage, lateral borders = midaxillary lines; lower back/buttocks (LBB), superior border = inferior margin rib cage, inferior border = inferior gluteal fold and anterior perineum (inclusive of perineum), lateral borders = midaxillary lines; left upper leg (LUL), superior border = inguinal fold and gluteal folds, inferior border = midpatella anterior and mid–popliteal fossa posterior; left lower leg and foot (LLLF), superior border = midpatella anterior and mid–popliteal fossa posterior; right upper leg (RUL), superior border = inguinal fold and gluteal folds, inferior border = midpatella anterior and mid–popliteal fossa posterior; right lower leg and foot (RLLF), superior border = midpatella anterior, and mid–popliteal fossa posterior.

Note: All recommendations are category 2A unless otherwise indicated.

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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES FOR MYCOSIS FUNGOIDES/SÉZARY SYNDROME (MF/SS)

Definition

- **Mycosis fungoides (MF)**
  - **MF is the most common cutaneous T-cell lymphoma (CTCL) and many clinicopathologic variants of MF have been described.[1,2]**
  - **Most patients with MF exhibit an indolent clinical course with intermittent, stable, or slow progression of the lesions.**
  - **Extracutaneous involvement may be seen in advanced stages, with involvement of lymph nodes, blood, or less commonly other organs.[1,2]**
- **Sézary syndrome (SS)**
  - **SS represents the leukemic variant of CTCL and is closely related to MF but has unique characteristics. SS is rare, accounting for less than 5% of cutaneous lymphomas and predominantly affects older individuals.**
  - **SS is characterized by the presence of atypical T cells (Sézary cells) in skin causing diffuse erythema (erythroderma) and significant blood involvement with abnormal T cells (>1000 abnormal cells/uL) defined as Sézary cells by cytopathologic assessment or flow cytometry (abnormal subsets including but not limited to CD4+CD7- or CD4+CD26- cells; TRBC1 may contribute in detecting clonality and is especially useful in cases where CD7 or CD26 are not lost).[3]**
  - **SS is thought to arise from thymic memory T cells, while skin resident effector memory T cells are the cells of origin of MF. This supports the contention that SS is a process distinct from MF.[4] Cases presenting clinically as an overlap of these two conditions exist.**

Diagnosis

- **The histopathologic findings of MF, even in cases showing classic features, need to be correlated with clinical presentation in order to reach a definitive diagnosis.[5]**
- **Patch lesions are often difficult for conclusive diagnosis; thus, in some instances multiple skin biopsies may be necessary for diagnosis. Stopping skin-directed therapy for 2–3 weeks or longer to individual lesions before obtaining a skin biopsy is advisable and may aid in diagnosis.[1,2]**
- **Awareness of specific clinicopathologic variants may aid in accurate diagnosis:**
  - **Lesions may be hyper- or hypopigmented.**
  - **Folliculotropic MF (FMF) may present as folliculocentric papules or nodules or areas of alopecia in any hair-bearing area of the body. A skin biopsy reaching the deep dermis may be required to assess adnexal structures.**
  - **Unilesional, pagetoid reticulosis and CD8+ MF variants tend to be associated with an indolent course.**
  - **Granulomatous slack skin is rare and presents with redundant skin resembling cutis laxa on flexural areas.**
- **By IHC, the tumor cells are usually CD3+, CD4+, and CD8-, although CD8+ variants are not uncommon. In selected cases, additional IHC markers and molecular studies to evaluate clonal TCR gene rearrangements are necessary for diagnosis.**
- **Large-cell transformation (LCT) of MF is defined histologically as greater than 25% of the tumor cells displaying large size. CD30 expression may be seen but is not included in the definition of LCT.[6]**
- **The histopathologic findings of SS in skin are generally similar to, but may be more subtle than those seen in MF. Correlation with clinical and laboratory findings in blood is essential for a definitive diagnosis.**

General Principles on MFSS/INTRO-2

References on MFSS/INTRO-A

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES FOR MYCOSIS FUNGOIDES/SÉZARY SYNDROME (MFSS)

General Principles

- Multidisciplinary team approach (hematology/oncology, dermatology, pathology, and radiation oncology) with expertise in CTCL is often optimal for the management of patients with MF/SS, particularly those with advanced disease.
- Given the rarity of the disease, it is preferred that treatment or consultation occur at centers with expertise in the management of CTCL.
- Evaluation of skin and/or nodal biopsies by a pathologist with expertise in CTCL at a referral center is recommended.
- Folliculotropism and LCT are histologic features that can occur irrespective of stage.
- Recent studies have reported that FMF presents with two distinct patterns of clinicopathologic features with different prognostic implications (early stage and advanced stage); in a subgroup of patients with early skin-limited disease, FMF has an indolent disease course and a favorable prognosis.[7,8,9] Early-stage cutaneous disease is associated with significantly higher disease-specific survival compared to advanced-stage cutaneous disease. Treatment may require skin-directed therapy that reaches the subcutaneous tissue (eg, psoralen plus ultraviolet A [PUVA], involved-site RT [ISRT]) or the addition of systemic therapy as used for stages I–IIB in patients with disease not responding to skin-directed therapy alone.
- The incidence of LCT is strongly dependent on the disease stage at diagnosis.[10,11] LCT often but not always corresponds to a more aggressive growth rate requiring systemic therapies (MFSS-12).
- Goals of therapy should be individualized but often include:
  - Attain adequate response in order to reduce and control symptoms and minimize risk of progression.
  - Most treatments for MF/SS do not result in durable remissions off of treatment.
  - Therapies with lower side-effect profiles and an absence of cumulative toxicity are often given in an ongoing or maintenance fashion to improve and maintain disease control and quality of life.
  - Other than allogeneic hematopoietic cell transplant (HCT), therapies are not given with curative intent.
- Generally, skin-directed therapies and systemic therapy regimens that can be tolerated for longer durations of therapy with lower rates of cumulative toxicity, less immunosuppression, and/or higher efficacy are used in earlier lines of therapy.
- In patients requiring chemotherapy, single agents are preferred over combination chemotherapy, due to the higher toxicity profiles associated with multi-agent regimens and the short-lived responses seen with time-limited combination chemotherapy.
- Responses can vary between the different compartments (ie, skin, blood, lymph nodes). Often decisions to continue or switch therapy are on a clinical basis.
- Disease relapse after discontinuation of therapy may respond to re-treatment with previous therapy.
- Partial responses with suboptimal quality of life should be treated with other or additional primary treatment options.
- Use of supportive care measures to minimize risk of skin infections and treat pruritus is an important part of disease and symptom control (MFSS-B).

References on MFSS/INTRO-A

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES FOR MYCOSIS FUNGOIDES/SÉZARY SYNDROME (MFSS)

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Note: All recommendations are category 2A unless otherwise indicated.

DIAGNOSIS[a]

ESSENTIAL:

- **Biopsy of suspicious skin sites**
  - **Multiple biopsies may be necessary to capture the pathologic variability of disease at diagnosis**
- **Review of a sufficient number of slides with adequate material to perform a comprehensive workup as described below and/or at least one paraffin block representative of the lesion should be done by a pathologist with expertise in the diagnosis of CTCLs. Rebiopsy if pathological findings are non-diagnostic and/or discordant with the clinical presentation[b]**
- **IHC panel of skin biopsy may include[c,d,e]:**
  - **CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30**
- **Molecular analysis to detect clonal T-cell receptor (*TCR*) gene rearrangements or other assessment of clonality[a,f]**

→ Workup (MFSS-2)

USEFUL IN CERTAIN CIRCUMSTANCES:

- **Assessment of peripheral blood for Sézary cells (in extensive skin disease where skin biopsy is not diagnostic in extensive patch or erythrodermic skin disease and/or strongly suggestive but not diagnostic of advanced-stage disease) including:**
  - **Flow cytometry and molecular analysis to assess and quantitate an expanded T-cell population with aberrant phenotype.[a,g] See MFSS-3 for specifics.**
  - **Sézary cell preparation is less useful than flow cytometry due to the subjective nature of the process.**
- **IHC panel of skin biopsy may include[b,c]:**
  - **CD25, CD56, TIA1, granzyme B, TCRß, TCRδ; CCR4,[h] CXCL13, inducible T-cell co-stimulator (ICOS), and programmed cell death protein 1 (PD-1)**
- **Assessment of HTLV-1/2[i] by serology or other methods is encouraged as results can impact therapy.**

[a] Principles of Molecular Analysis in Primary Cutaneous Lymphomas (PCLYM-B).

[b] Presence of LCT or areas of folliculotropism may have important implications for selection of therapy and outcome and should be included in pathology reports.

[c] Pimpinelli N, et al. Clinically suspicious and histologically non-diagnostic cases. J Am Acad Dermatol 2005;53:1053-1063.

[d] Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (see NCCN Guidelines for B-Cell Lymphomas).

[e] Typical immunophenotype: CD2+, CD3+, CD5+, CD7-, CD4+, CD8- (rarely CD8+), CD30-/+ cytotoxic granule proteins negative.

[f] Clonal *TCR* gene rearrangements alone are not sufficient for diagnosis, as these can also be seen in patients with non-malignant conditions. Results should be interpreted in the context of overall presentation. See Principles of Molecular Analysis in Primary Cutaneous Lymphomas (PCLYM-B).

[g] Flow cytometry panel may include CD3, CD4, CD7, CD8, CD26, CD45, to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype, including loss of CD7 or CD26. TRBC1 may contribute in detecting clonality and is especially useful in cases where CD7 or CD26 are not lost.

[h] The loss of CCR4 expression and emergence of CCR4 genomic alterations might be associated with resistance to mogamulizumab (Beygi S, et al. Blood 2022;139:3732-3736).

[i] See map for prevalence of HTLV-1/2 by geographic region. HTLV-1 has been described in patients in non-endemic areas.

Note: All recommendations are category 2A unless otherwise indicated.

WORKUP

ESSENTIAL:

- **History and complete physical examination:**
  - **Complete skin examination: assessment of % body surface area (BSA) (palm plus all 5 digits ≈1% BSA) and type of skin lesion (ie, patch/plaque, tumor, erythroderma)**
  - **Palpation of peripheral lymph node regions**
  - **Palpation for organomegaly/masses**
- **Laboratory studies:[j]**
  - **CBC with differential and determination of absolute lymphocyte count**
  - **Flow cytometric studies to assess and quantitate an expanded T-cell population with aberrant phenotype (optional for T1[k]) (MFSS-3)**
    - ◊ **Recommended for any patient with T2–4 skin classification, any suspected extracutaneous disease including adenopathy**
  - **Clonal *TCR* gene rearrangement in peripheral blood lymphocytes if blood involvement suspected[a]**
  - **Comprehensive metabolic panel**
  - **LDH**
- **Imaging studies:**
  - **Chest/abdomen/pelvis (C/A/P) CT with contrast or integrated whole body FDG-PET/CT[l] for T3 or T4 (arms/legs included when disease assessment of entire body is needed)**

USEFUL IN CERTAIN CIRCUMSTANCES:

- **Bone marrow biopsy in patients with unexplained hematologic abnormality**
- **Biopsy of enlarged lymph nodes or suspected extracutaneous sites. Excisional or adequate core needle biopsy is preferred. An fine-needle aspiration (FNA) biopsy alone is not sufficient for the initial diagnosis of lymphoma. Rebiopsy if pathological findings are nondiagnostic and/or discordant with the clinical presentation.**
- **Rebiopsy skin if suspicious of LCT or FMF and not previously confirmed pathologically or aggressive clinical behavior**
- **C/A/P CT with contrast or integrated whole body FDG-PET/CT[l] for ≥T2b or LCT or FMF, or with palpable adenopathy or abnormal laboratory studies; consider for T2a (patch disease with ≥10% BSA) or otherwise clinically indicated[m]**
- **Neck CT with contrast if whole body FDG-PET/CT not done**
- **Pregnancy testing in patients of childbearing potential if contemplating treatments that are contraindicated in pregnancy[n]**
- **Discuss fertility preservation[o]**

→ **For TNMB Classification, see MFSS-3 and For Clinical Staging of MF and SS, see MFSS-4**

[a] Principles of Molecular Analysis in Primary Cutaneous Lymphomas (PCLYM-B).
[j] Sézary syndrome (B2) is as defined on MFSS-3.
[k] See Discussion for when Sézary flow cytometric study is appropriate in T1 disease.
[l] Patients with cutaneous lymphomas have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
[m] New significant adenopathy on clinical exam, abnormal laboratory results concerning of lymphoma, or accelerated skin disease.
[n] Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to full prescribing information for individual drugs.
[o] Fertility preservation options include: sperm banking, semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.

Note: All recommendations are category 2A unless otherwise indicated.

Changes or confirmation of staging are noted in bold in table below and in further description on MFSS-3A. Options for characterizing clonality further by designation as A (clone negative or equivocal) and B (clone positive and identical to skin) are presented. If a clone in LN or viscera is detected but different from that identified in the skin, another concurrent lymphoproliferative process should be considered.

TNMB			TNMB Classification and Staging of Mycosis Fungoides and Sézary Syndrome[p,q,r,s,t,v]		Clinical Staging of MF and SS (MFSS-4)
Skin (T)	T_0[u]		Absence of clinically suspicious lesions		
	T_1		Patches, plaques, or papules <10% BSA	T_{1A}	Patch only lesions
				T_{1B}	Plaque/papule ± patch lesions
	T_2		Patches, plaques, or papules ≥10% BSA	T_{2A}	Patch only
				T_{2B}	Plaque ± patch
	T_3		One or more tumors ≥1 cm in diameter		
	T_4		Confluence of erythema covering ≥80% BSA[v]		
Node (N)[w]	N_0		No clinically abnormal LN; no biopsy necessary		
	N_1	N_{1A}	Pathology Dutch grade 1 or NCI LN 0-2: clone negative **or equivocal**		Dutch Criteria for Lymph Nodes on MFSS-5
		N_{1B}	Pathology Dutch grade 1 or NCI LN 0-2: clone positive **and identical to skin**		NCI Lymph Node Classification on MFSS-5
	N_2	N_{2A}	Dutch grade 2, NCI LN3: clone negative **or equivocal**		
		N_{2B}	Dutch grade 2, NCI LN3: clone positive **and identical to skin**		
	N_3w	N_{3A}	Dutch grade 3-4, NCI LN4: clone negative or equivocal		
		N_{3B}	Dutch grade 3-4, NCI LN4: clone positive **and identical to skin**		
	N_X		Clinically abnormal peripheral or central lymph node but no pathologic determination of representative LN. **Other surrogate means of determining involvement may be determined by Tri-Society consensus**		
Visceral (M)	M_0		No visceral involvement		
	M_{1a}	**BM only involvement**	**Clone positive and identical to skin**		
			Clone negative or indeterminate		
	M_{1b}	**Non-BM visceral involvement**	**Clone positive and identical to skin**		
			Clone negative or indeterminate		
	M_X		Visceral involvement is neither confirmed nor refuted by available pathologic **or imaging assessment**		
Blood (B)[x]	B_0	B_{0A}	Clone negative **or equivocal**	Absence of significant blood involvement	
		B_{0B}	Clone positive **and identical to skin**		
	B_1	B_{1A}	Clone negative **or equivocal**	Low blood tumor burden	
		B_{1B}	Clone positive **and identical to skin**		
	B_2	B_{2A}	Clone negative **or equivocal**	High blood tumor burden	
		B_{2B}	Clone positive **and identical to skin**		
	B_X	**B_{XA}**	Clone negative **or equivocal**	**Unable to quantify blood involvement according to agreed upon guidelines**	
		B_{XB}	Clone positive **and identical to skin**		

Note: All recommendations are category 2A unless otherwise indicated.

Footnotes on MFSS-3A

FOOTNOTES

[p] This work was originally published in Blood. Olsen EA, Whittaker S, Willemze R, et al. Primary cutaneous lymphoma: recommendations for clinical trial design and staging update from the ISCL, USCLC, and EORTC. Blood 2022;140:419-437. © The American Society of Hematology.

[q] 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).

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

[s] 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.

[t] 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.

[u] T_0 is used for clinical trials in order to track clearance of lesions in the skin compartment. No patient with PCL at time of diagnosis should be T_0.

[v] Patients with both erythroderma and tumors may be designated as $T_4(T_3)$. The BSA of 80% is used to define erythroderma in MF/SS at study entry, but any decrease in BSA during the study does not affect the entry classification.

[w] Abnormal LNs are those now >1.5 cm longest diameter (LDi) according to the Lugano classification and confirmed by imaging. The pathological findings of a representative abnormal LN may apply to all abnormal lymph nodes.

[x] Blood staging for MF/SS is defined currently as B_0 = 250/μL of CD4+/CD26- or CD4+/CD7- cells, B_1 = does not meet criteria for B_0 or B_2, and B_2 = ≥1000/μL of CD4+/CD26- or CD4+/CD7- cells or other aberrant population of lymphocytes identified by flow cytometry. It is expected that patients with high blood tumor burden (B_2) will have a clone in the blood that is identical to that in the skin. Nonidentical T-cell clones are often detected in peripheral blood with increasing age and are of unknown clinical significance. Patients with lymphopenia (defined as <1000 absolute lymphocytes) may potentially have an underestimation of aberrant lymphocyte burden if assessed only by the absolute number and not also by the percentage of immunophenotypically abnormal lymphocytes.

Note: All recommendations are category 2A unless otherwise indicated.

CLINICAL STAGING OF MF AND SS[y]

Clinical Stage[z]	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 (Sézary syndrome)	T1–4	N0–2	M0	B2	MFSS-11
IVA_2 (Sézary syndrome or Non-Sézary)	T1–4	N3	M0	B0 or B1 or B2	MFSS-11
IVB (Visceral disease)	T1–4	N0–3	M1A or M1B	B0 or B1 or B2	MFSS-11
	Large-cell transformation (LCT)[aa]				MFSS-12

[y] Olsen EA, et al. Blood 2022;140:419-437.
[z] Folliculotropism is a histologic feature that can occur irrespective of stage. Histologic evidence of FMF is associated with higher risk of disease progression. In selected cases or inadequate response, consider primary treatment for stage IIB (tumor stage disease).
[aa] 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.

Note: All recommendations are category 2A unless otherwise indicated.

TNMB Classification on MFSS-3

LYMPH NODE CLASSIFICATION IN MF AND SS

NCI-VA Lymph Node Classification

LN0: no atypical lymphocytes
LN1: occasional and isolated atypical lymphocytes (not arranged in clusters)
LN2: many atypical lymphocytes or in 3–6 cell clusters
LN3: aggregates of atypical lymphocytes; nodal architecture preserved
LN4: partial/complete effacement of nodal architecture by atypical lymphocytes or frankly neoplastic cells

Clendenning WE, Rappaport HW. Report of the Committee on Pathology of Cutaneous T Cell Lymphomas. Cancer Treat Rep 1979;63:719-724.

Dutch Criteria for Lymph Nodes

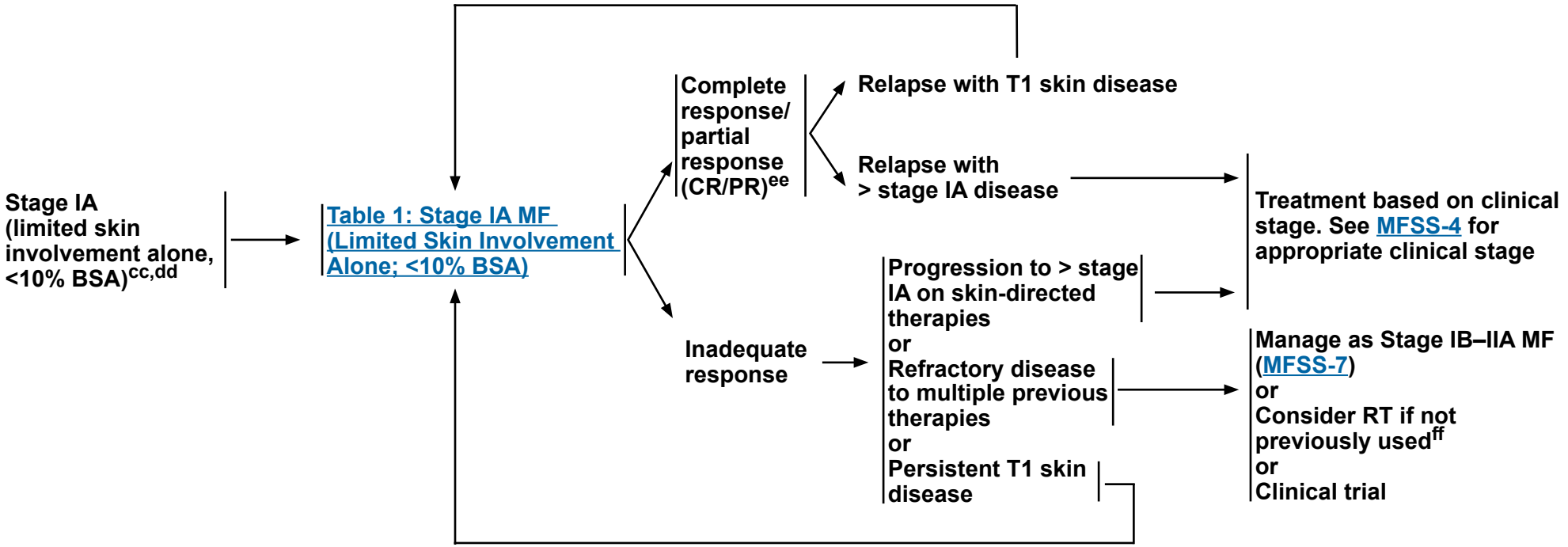
Grade 1: Dermatopathic lymphadenopathy
Grade 2: Early involvement by mycosis fungoides (presence of cerebriform nuclei >7.5 micrometers)
Grade 3: Partial effacement of lymph node architecture; many atypical cerebriform mononuclear cells
Grade 4: Complete effacement of lymph node architecture

Scheffer E, Meijer CJLM, van Vloten WA. Dermatopathic lymphadenopathy and lymph node involvement in mycosis fungoides. Cancer 1980;45:137-148.

Note: All recommendations are category 2A unless otherwise indicated.

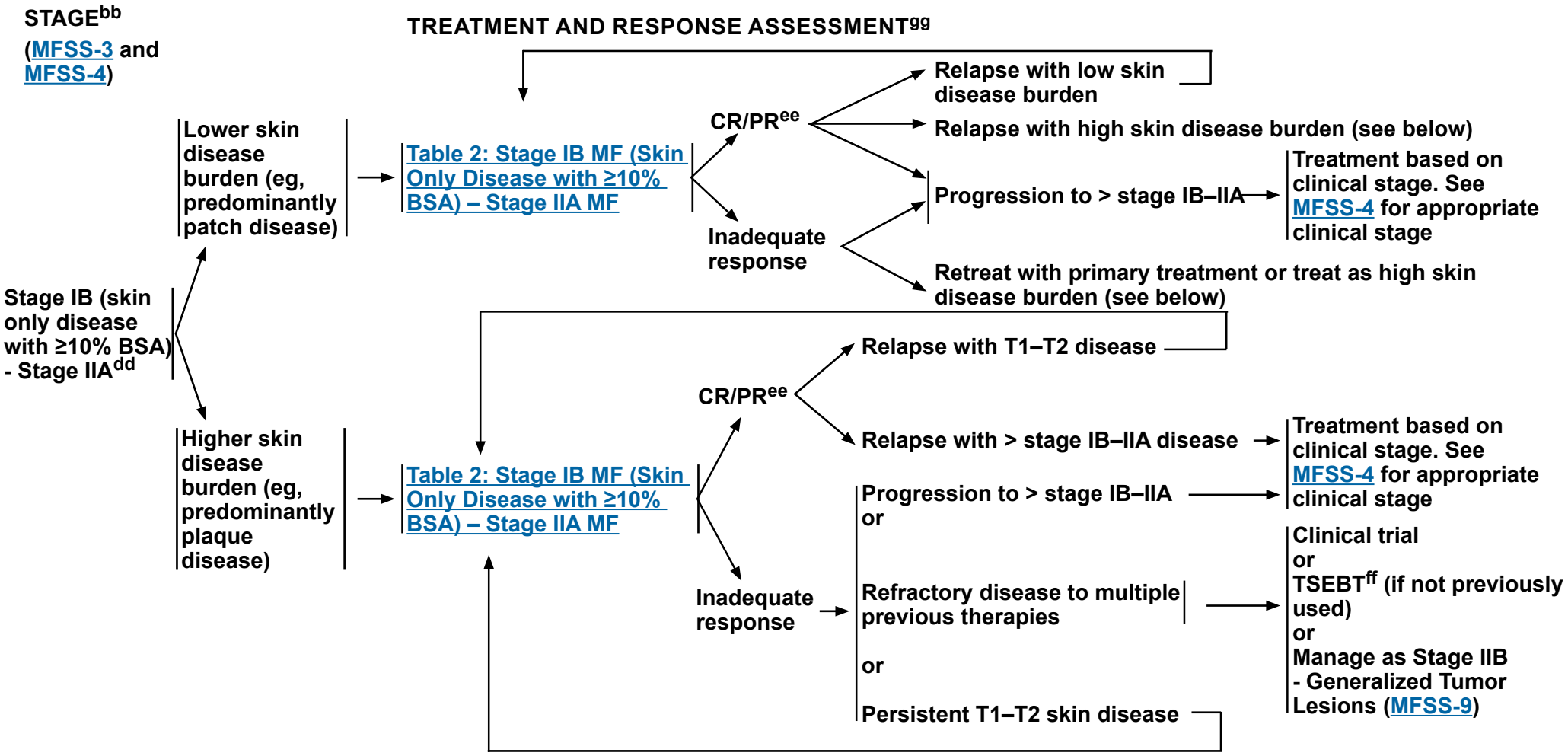
STAGE[bb] (MFSS-3 and MFSS-4)

TREATMENT AND RESPONSE ASSESSMENT



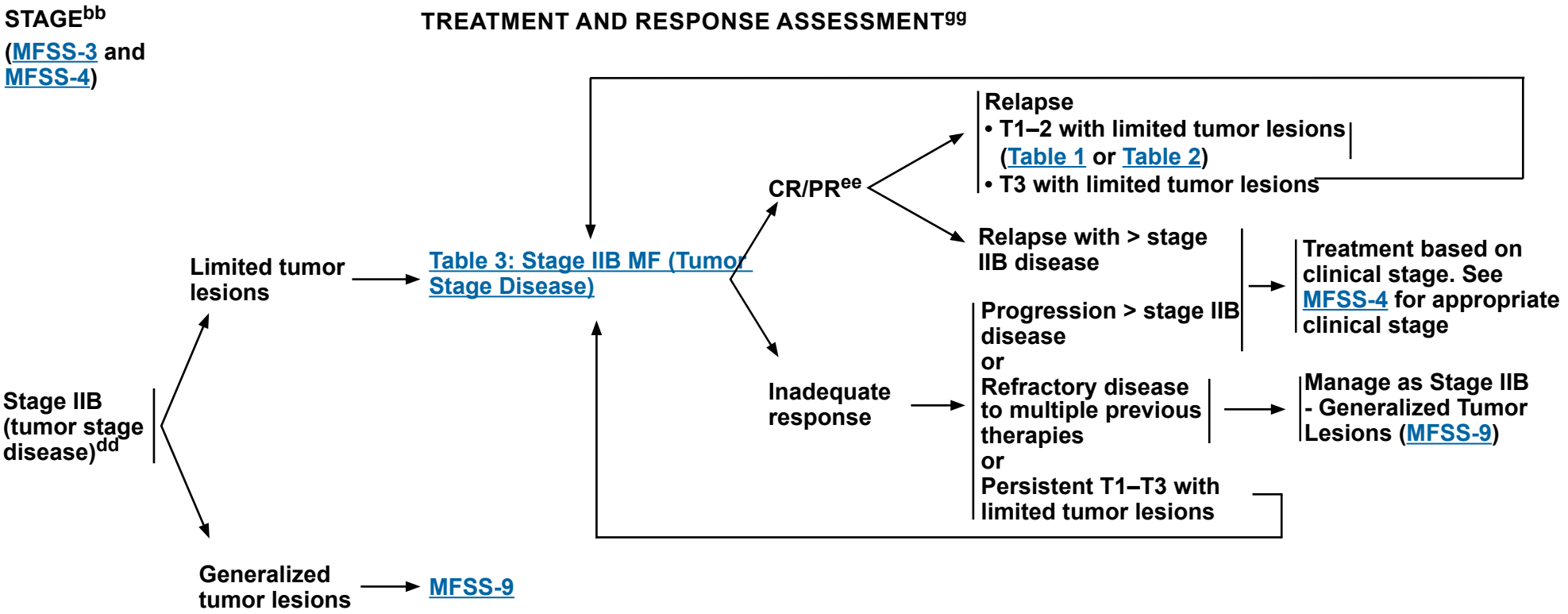
[bb] Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1) and General Considerations for the Treatment of Patients with MF and SS (MFSS-A 1 of 12).
[cc] In rare cases of confirmed unilesional MF, RT has been shown to provide long-term remission.
[dd] Rebiopsy if LCT is suspected; if histologic evidence of LCT, see MFSS-12.
[ee] 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.
[ff] Principles of Radiation Therapy (PCLYM-A).

Note: All recommendations are category 2A unless otherwise indicated.



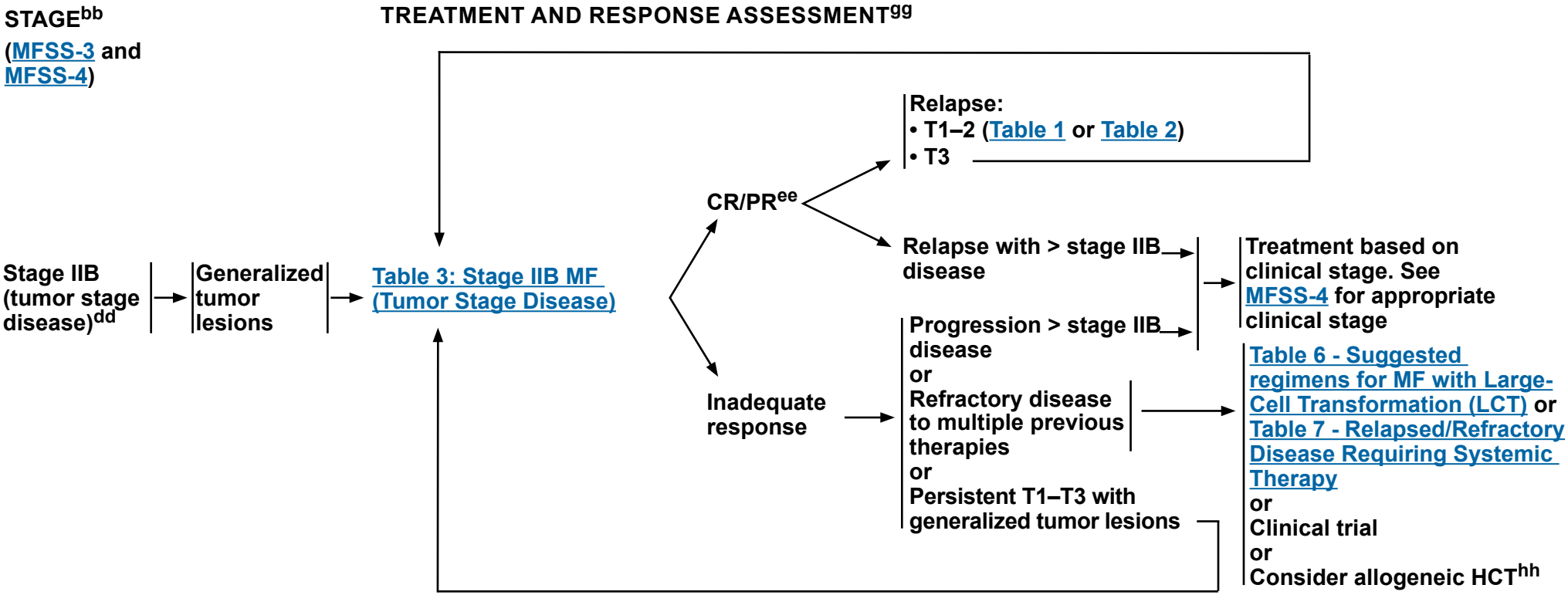
[bb] Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1) and General Considerations for the Treatment of Patients with MF and SS (MFSS-A 1 of 12).
[dd] Rebiopsy if LCT is suspected; if histologic evidence of LCT, see MFSS-12.
[ee] Patients with disease achieving a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration.
[ff] Principles of Radiation Therapy (PCLYM-A).
[gg] Imaging (with modalities used in workup) indicated when suspicious of clinical extracutaneous disease.

Note: All recommendations are category 2A unless otherwise indicated.



[bb] Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1) and General Considerations for the Treatment of Patients with MF and SS (MFSS-A 1 of 12).
[dd] Rebiopsy if LCT is suspected; if histologic evidence of LCT, see MFSS-12.
[ee] 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.
[gg] Imaging (with modalities used in workup) indicated when suspicious of clinical extracutaneous disease.

Note: All recommendations are category 2A unless otherwise indicated.

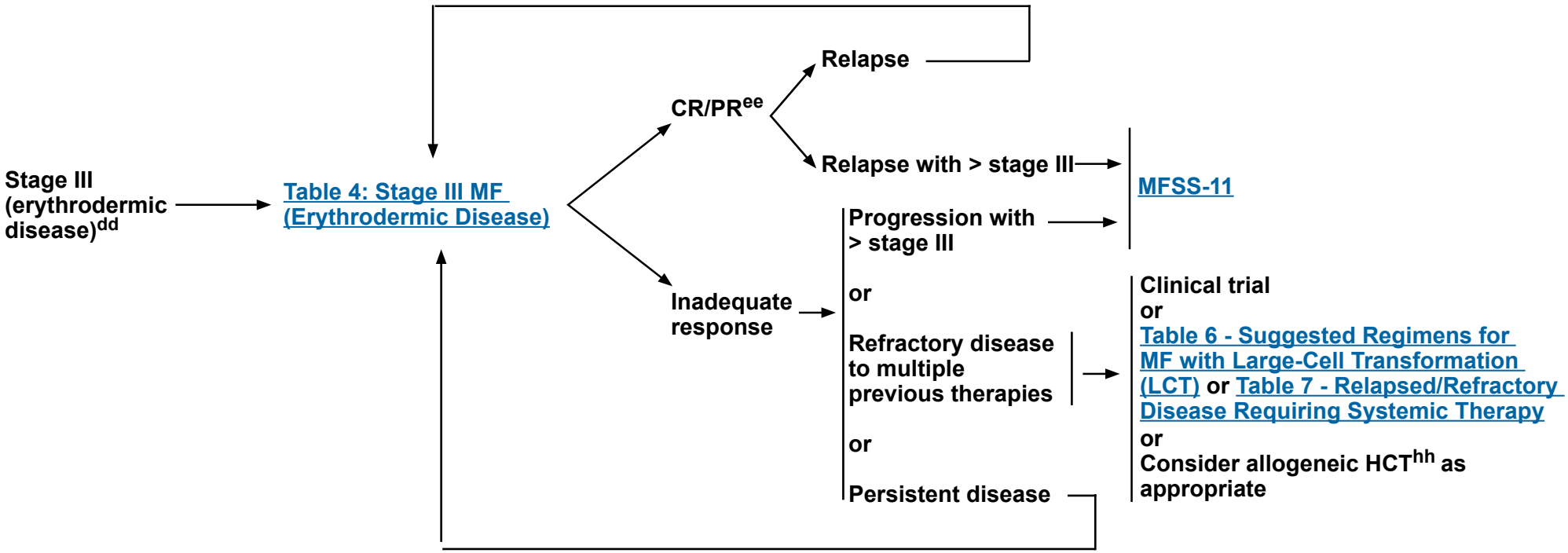


[bb] Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1) and General Considerations for the Treatment of Patients with MF and SS (MFSS-A 1 of 12).
[dd] Rebiopsy if LCT is suspected, if histologic evidence of LCT, see MFSS-12.
[ee] Patients with disease achieving a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration.
[gg] Imaging (with modalities used in workup) indicated when suspicious of clinical extracutaneous disease.
[hh] Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant. See Discussion for further details.

Note: All recommendations are category 2A unless otherwise indicated.

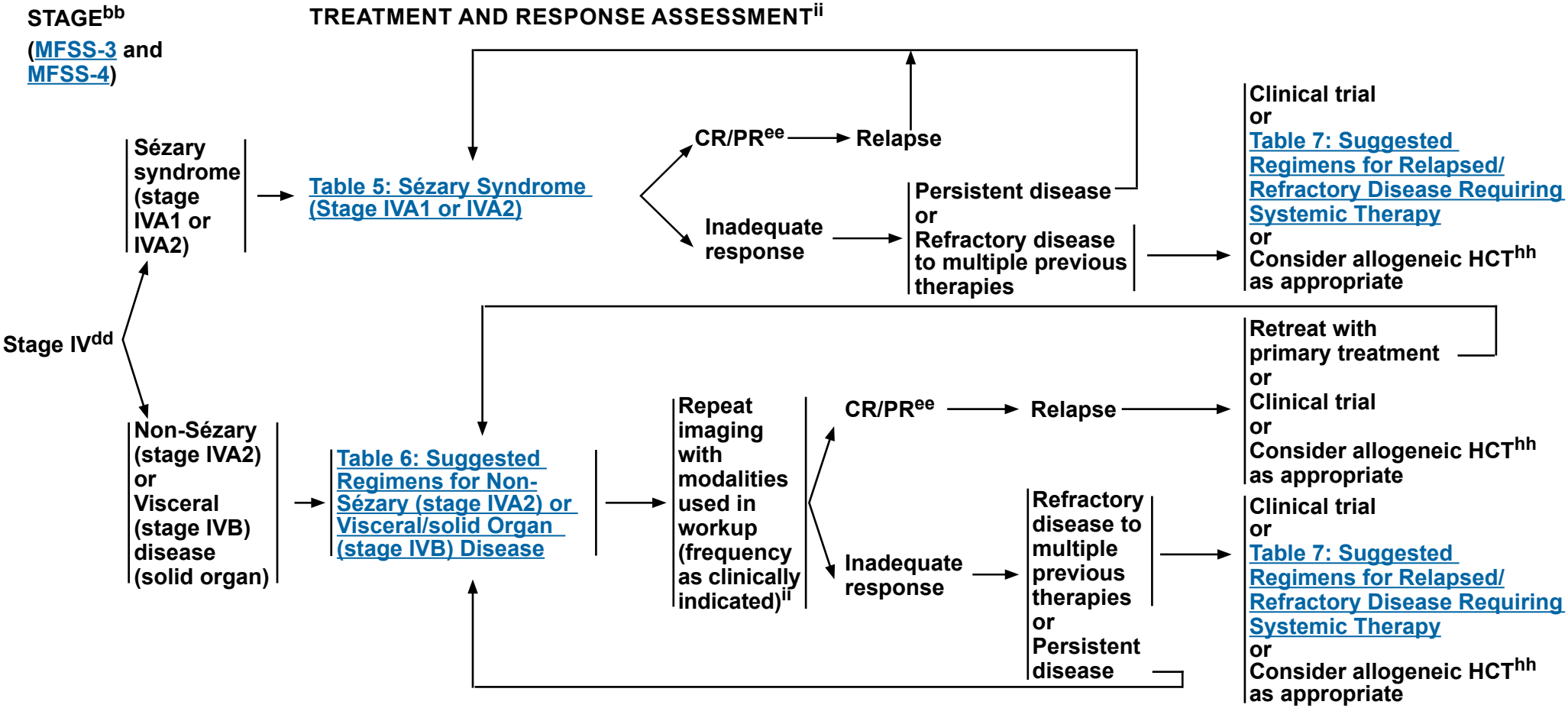
STAGE[bb]
(MFSS-3 and MFSS-4)

TREATMENT AND RESPONSE ASSESSMENT[gg]



[bb] Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1) and General Considerations for the Treatment of Patients with MF and SS (MFSS-A 1 of 12).
[dd] Rebiopsy if LCT is suspected; if histologic evidence of LCT, see MFSS-12.
[ee] 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.
[gg] Imaging (with modalities used in workup) indicated when suspicious of clinical extracutaneous disease.
[hh] Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant. See Discussion for further details.

Note: All recommendations are category 2A unless otherwise indicated.



[bb] Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1) and General Considerations for the Treatment of Patients with MF and SS (MFSS-A 1 of 12).

[dd] Rebiopsy if LCT is suspected; if histologic evidence of LCT, see MFSS-12.

[ee] 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.

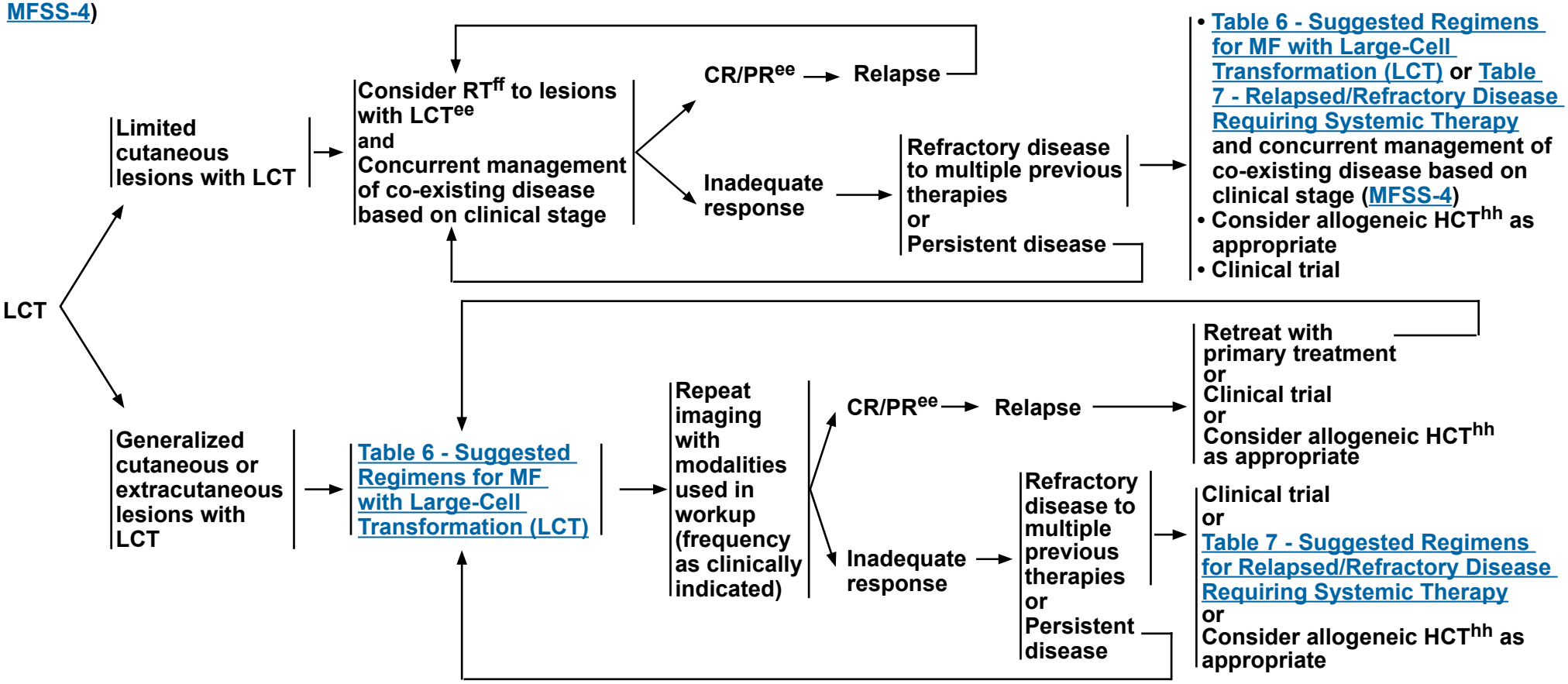
[hh] Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant. See Discussion for further details.

[ii] If disease in lymph nodes and/or viscera or suspicious of disease progression, imaging (with modalities used in workup) as clinically indicated based on distribution of disease.

Note: All recommendations are category 2A unless otherwise indicated.

STAGE[bb]
(MFSS-3 and MFSS-4)

TREATMENT AND RESPONSE ASSESSMENT[gg]



[bb] Principles for Mycosis Fungoides/Sézary Syndrome (MFSS/INTRO-1) and General Considerations for the Treatment of Patients with MF and SS (MFSS-A 1 of 12).
[ee] 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.
[ff] Principles of Radiation Therapy (PCLYM-A).
[gg] Imaging (with modalities used in workup) indicated when suspicious of clinical extracutaneous disease.
[hh] Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant. See Discussion for further details.

Note: All recommendations are category 2A unless otherwise indicated.

GENERAL CONSIDERATIONS FOR THE TREATMENT OF PATIENTS WITH MF AND SS

- **Generally, skin-directed therapies and systemic therapy regimens that can often be tolerated for longer durations of therapy with lower rates of cumulative toxicity, less immunosuppression, and/or higher efficacy are used in earlier lines of therapy before moving on to treatment options that carry a higher risk of cumulative toxicity and/or immunosuppression.**
- **Therapies with lower side effect profiles and an absence of cumulative toxicity are often given in an ongoing or maintenance fashion to improve and maintain disease control and quality of life.**
- **Systemic therapy is often combined with skin-directed therapy to maximize clinical responses in the skin compartment and to provide additive efficacy without cumulative toxicities.**
- **Bexarotene, brentuximab vedotin, denileukin diftitox-cxdl, mogamulizumab, romidepsin, and vorinostat are approved by the U.S. Food and Drug Administration (FDA) for the treatment of MF and SS. Other systemic therapies such as interferons (alfa and gamma), methotrexate, and other retinoids (acitretin and isotretinoin) also offer clinical benefit but have only been evaluated in small studies.**
- **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.**
- **Use of supportive care measures to minimize risk of skin infections and treat pruritus is an important part of disease and symptom control (MFSS-B).**

Note: All recommendations are category 2A unless otherwise indicated.

SUGGESTED REGIMENS: SKIN-DIRECTED THERAPIES

SKIN-LIMITED/LOCAL (FOR LIMITED/LOCALIZED SKIN INVOLVEMENT)	TREATMENT CONSIDERATIONS
• Local radiation (involved-site radiation therapy [ISRT]) ▸ 8–12 Gy; 24–30 Gy for unilesional presentation • Phototherapy ▸ UVB or narrowband UVB (NB-UVB) • Topical corticosteroids • Topical imiquimod • Topical mechlorethamine (nitrogen mustard) • Topical retinoids (bexarotene, tazarotene) • Topical carmustine (category 2B) Useful in Certain Circumstances • Topical calcineurin inhibitor (pimecrolimus)	1. Skin-directed therapies can be used alone or in combination with other skin-directed therapies. 2. Cumulative dose of UV, in particular PUVA, which carries a higher risk than NBUVB, is associated with increased risk of UV-associated skin neoplasms; thus, phototherapy use should be balanced against these risks in patients with a history of extensive squamoproliferative skin neoplasms or basal cell carcinomas or who have had melanoma. 3. TSEBT, and in certain cases PUVA or UVA1 may be considered for widespread thicker plaques or tumors. 4. Low-dose local RT (8–12 Gy) is given with palliative intent (usually as combined modality therapy). Some Member Institutions are exploring the use of lower dose options (eg, 4 Gy). Up to 8 Gy can be given in a single fraction, although lower dose per fraction (3–5 Gy) may be preferred depending on skin condition, irradiation volume, and prior RT. For rare initial unilesional presentations, RT (24–30 Gy) is given as monotherapy with curative intent. 5. Optimal use of topical steroids is often dependent on lesion type and location of disease. This is best done in consultation with a dermatologist or physician with experience in the use of topical steroids. In general, high-potency steroids may be less well-tolerated intertriginous body areas or other areas such as the face. Potency of steroid and extent/duration of skin treated can result in systemic absorption and/or skin atrophy. 6. Topical imiquimod can be considered (often in consultation with a dermatologist or physician with experience in its safety and use) for areas with few patches/plaques/small tumors that are recalcitrant to treatment or on sun-damaged skin such as forearms, scalp, and face. 7. Topical mechlorethamine has no significant systemic absorption, and can be used alone or in combination with other skin directed therapies, in particular topical steroids. Topical mechlorethamine use, in particular gel preparation, can be complicated by dermatitis, and can result in skin irritation when used on face and intertriginous body areas. Initiating at less than daily use can be useful to determine tolerability and topical steroids can be considered as needed to alleviate skin reactions from topical mechlorethamine gel. If used with phototherapy, topical mechlorethamine gel should be applied after exposure to UVL. 8. Topical retinoids can cause skin irritation including redness, peeling, and dermatitis when used on face and intertriginous body areas. 9. Topical calcineurin inhibitors can be considered for perioral and periorbital affected areas of skin as a steroid-sparing treatment. 10. It is common practice to follow TSEBT with systemic therapies to maintain response. There is limited safety data for the use of TSEBT in combination with systemic retinoids, histone deacetylase (HDAC) inhibitors (such as vorinostat or romidepsin), or mogamulizumab, or combining phototherapy with vorinostat or romidepsin.
SKIN-GENERALIZED (FOR GENERALIZED SKIN INVOLVEMENT)	
• Phototherapy ▸ UVB or NB-UVB ▸ PUVA ▸ UVA1 (if available) • Topical corticosteroids • Topical mechlorethamine (nitrogen mustard) • Total skin electron beam therapy (TSEBT) (12–36 Gy)	

Note: All recommendations are category 2A unless otherwise indicated.

TABLE 1: STAGE IA MF (Limited skin involvement alone; <10% BSA) - MFSS-6[a,b]

SUGGESTED REGIMENS	TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON MFSS-A [1 of 12])
• Skin-directed therapies (alone or in combination with other skin-directed therapies) [See Skin-Limited/Local (for limited/localized skin involvement, MFSS-A 2 of 12)] OR • Skin-directed therapy (Skin-Limited/Local) in combination with systemic therapy (in selected cases) Preferred Regimens (alphabetical order) • Systemic therapy + skin-directed therapy (limited/local or generalized including phototherapy as indicated for stage of disease) ▸ Bexarotene ▸ Interferon alfa[b] ▸ Methotrexate Useful in Certain Circumstances (alphabetical order) • Systemic therapy + skin-directed therapy (limited/local or generalized including phototherapy as indicated for stage of disease) ▸ Acitretin ▸ Extracorporeal photopheresis (ECP) ▸ Interferon gamma-1b ▸ Isotretinoin	1. Stage IA MF most often can be treated with skin-directed therapies (alone or in combination with other skin-directed therapies). 2. In patients with histologic evidence of FMF, skin disease may be less responsive to topical therapies. 3. Systemic therapies (single agents or combination therapies) should be reserved for patients with blood involvement or for whom skin-directed therapies do not provide sufficient disease control or who have disease that is not amenable to skin-directed therapy (eg, in regions where topical therapies are difficult to apply regularly). 4. Alternative retinoids (acitretin or isotretinoin) could be considered in place of bexarotene. 5. In stage IA, ECP is primarily reserved for the rare patient with stage IA MF with low level blood involvement (B1). 6. 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.

Note: All recommendations are category 2A unless otherwise indicated.

Footnotes on MFSS-A 9 of 12

TABLE 2: STAGE IB MF (Skin only disease with ≥10% BSA) – STAGE IIA MF - MFSS-7[a,b,c]

SUGGESTED REGIMENS	TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON MFSS-A [1 of 12])
• Skin-directed therapies (alone or in combination with other skin-directed therapies) ▸ Lower skin disease burden (eg, predominantly patch disease): Skin-Limited/Local (for limited/localized skin involvement) ▸ Higher skin disease burden (eg, predominantly plaque disease): Skin-Generalized (for generalized skin involvement) OR • Systemic therapy + skin-directed therapy (limited/local or generalized including phototherapy as indicated for stage of disease) Preferred Regimens (alphabetical order) • Bexarotene • Brentuximab vedotin • Interferon alfa[b] • Methotrexate • Mogamulizumab • Romidepsin • Vorinostat Useful in Certain Circumstances (alphabetical order by category) • Acitretin • Denileukin diftitox-cxdl[d] • ECP • Interferon gamma-1b • Isotretinoin • Alemtuzumab (category 2B) • Gemcitabine (category 2B) • Liposomal doxorubicin (category 2B) • Pembrolizumab (category 2B) • Pralatrexate (category 2B)	1. Stage IB–IIA MF can be treated with skin-directed therapies (alone or in combination with other skin-directed therapies). ***Limited patches/plaques:*** Skin-directed therapy can be considered as monotherapy. ***Extensive skin involvement:*** Phototherapy may be given alone or in combination with other skin-directed therapies. TSEBT maybe given alone or in combination with topical corticosteroids. 2. In patients with histologic evidence of FMF, skin disease may be less responsive to topical therapies. 3. Systemic therapies (single agents or combination therapies) should be considered for patients with extensive skin involvement, higher skin disease burden, predominantly plaque disease, blood involvement, and/or inadequate response to skin-directed therapy. 4. In the randomized ALCANZA trial (Prince HM, et al. Lancet 2017;390:555-566), brentuximab vedotin was more effective than methotrexate or bexarotene in patients with previously treated MF (≥ stage IB). Patients with SS were excluded from the ALCANZA trial. 5. In the randomized MAVORIC trial (Kim YH, et al. Lancet Oncol 2018;19:1192-1204), mogamulizumab was more effective than vorinostat in patients with previously treated MF (≥ stage IB) and SS. Responses were higher in patients with blood involvement (stage III or stage IV disease) than those with stage IIB or stage IB/IIA disease. Patients with MF-LCT were excluded from the MAVORIC trial. 6. Alternative retinoids (acitretin or isotretinoin) could be considered in place of bexarotene. 7. In stage IB/IIA, ECP is primarily reserved for patients with low-level blood involvement (B1). 8. There is limited safety data for the use of TSEBT in combination with systemic retinoids, HDAC inhibitors (such as vorinostat or romidepsin), or mogamulizumab, or combining phototherapy with vorinostat or romidepsin. 9. Patients with disease achieving a clinical benefit and/or those with disease responding to treatment should be considered for maintenance or tapering of regimens to optimize response duration. 10. LCT-MF was not an exclusion criteria for Study 302 but no patients with LCT-MF were enrolled in the study.

Footnotes on MFSS-A 9 of 12

Note: All recommendations are category 2A unless otherwise indicated.

TABLE 3: STAGE IIB MF (Tumor stage disease)[a,b,c]

LIMITED TUMOR DISEASE	GENERALIZED TUMOR DISEASE	TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON MFSS-A [1 of 12])
• Local RT and/or skin-directed therapy OR • Systemic therapy ± local RT ± skin-directed therapy (limited/ local or generalized including phototherapy as indicated for stage of disease) Preferred Regimens (alphabetical order) • Bexarotene • Brentuximab vedotin • Interferon alfa[b] • Methotrexate • Mogamulizumab • Romidepsin Other Recommended Regimen • Vorinostat • Pembrolizumab (category 2B) Useful in Certain Circumstances (alphabetical order) • Acitretin • Denileukin diftitox-cxdl[d] • ECP • Interferon gamma-1b • Isotretinoin	• TSEBT OR • Systemic therapy + skin-directed therapy (limited/ local or generalized including phototherapy as indicated for stage of disease) OR • Combination therapies Preferred Regimens (alphabetical order) • Single agents ▸ Bexarotene ▸ Brentuximab vedotin ▸ Denileukin diftitox-cxdl[d] ▸ Gemcitabine ▸ Interferon alfa[b] ▸ Liposomal doxorubicin ▸ Methotrexate ▸ Mogamulizumab ▸ Pralatrexate ▸ Romidepsin • Combination therapy ▸ Retinoid + interferon alfa[b] Other Recommended Regimens • Pembrolizumab • Vorinostat Useful in Certain Circumstances (alphabetical order) • Single agents ▸ Acitretin ▸ ECP ▸ Interferon gamma-1b ▸ Isotretinoin • Combination therapy ▸ ECP + interferon alfa[b] or retinoid ▸ ECP + interferon alfa[b] + retinoid	1. RT is preferred for limited tumor lesions. Topical therapies alone are often inadequate for tumor stage disease. 2. In patients with histologic evidence of FMF, skin disease may be less responsive to topical therapies. 3. Adjuvant systemic biologic therapy may be considered after TSEBT for generalized tumor lesions to improve response duration. 4. In the randomized ALCANZA trial (Prince HM, et al. Lancet 2017;390:555-566), brentuximab vedotin was more effective than methotrexate or bexarotene in patients with previously treated MF (≥ stage IB). Patients with SS were excluded from the ALCANZA trial. 5. In the randomized MAVORIC trial (Kim YH, et al. Lancet Oncol 2018;19:1192-1204), mogamulizumab was more effective than vorinostat in patients with previously treated MF (≥ stage IB) and SS. Responses were higher in patients with blood involvement (stage III or stage IV disease) than those with stage IIB or stage IB/IIA disease. Patients with MF-LCT were excluded from the MAVORIC trial. 6. Alternative retinoids (acitretin or isotretinoin) could be considered in place of bexarotene. 7. ECP may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2). 8. There is limited safety data for the use of TSEBT in combination with systemic retinoids, HDAC inhibitors (such as vorinostat or romidepsin), or mogamulizumab, or combining phototherapy with vorinostat or romidepsin. 9. Patients with disease achieving a clinical benefit and/or those with disease responding to treatment should be considered for maintenance or tapering of regimens to optimize response duration. 10. LCT-MF was not an exclusion criteria for Study 302 but no patients with LCT-MF were enrolled in the study.

Footnotes on MFSS-A 9 of 12

Note: All recommendations are category 2A unless otherwise indicated.

TABLE 4: STAGE III MF (Erythrodermic disease) - MFSS-10[a,b,c,e]

SUGGESTED REGIMENS	TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON MFSS-A [1 of 12])
• Systemic therapy + skin-directed therapy (limited/local or generalized including phototherapy as indicated for stage of disease) Preferred Regimens (alphabetical order) • Single agents ▸ Bexarotene ▸ Brentuximab vedotin ▸ ECP ▸ Interferon alfa[b] ▸ Methotrexate ▸ Mogamulizumab ▸ Romidepsin • Combination therapy ▸ ECP + interferon alfa[b] or retinoid ▸ ECP + interferon alfa[b] + retinoid ▸ Retinoid + interferon alfa[b] Other Recommended Regimens • Vorinostat Useful in Certain Circumstances (alphabetical order) • Single agents ▸ Acitretin ▸ Alemtuzumab ▸ Denileukin diftitox-cxdl[d] ▸ Gemcitabine ▸ Interferon gamma-1b ▸ Isotretinoin ▸ Liposomal doxorubicin ▸ Pembrolizumab ▸ Pralatrexate • Skin-directed therapy ▸ Phototherapy ▸ TSEBT (category 2B)	1. In the randomized ALCANZA trial (Miles Prince H, et al. Lancet 2017;390:555-566), brentuximab vedotin was more effective than methotrexate or bexarotene in patients with previously treated MF (≥ stage IB). Patients with SS were excluded from the ALCANZA trial. 2. In the randomized MAVORIC trial (Kim YH, et al. Lancet Oncol 2018;19:1192-1204), mogamulizumab was more effective than vorinostat in patients with previously treated MF (≥ stage IB) and SS. Responses were higher in patients with blood involvement (stage III or stage IV disease) than those with stage IIB or stage IB/IIA disease. Patients with MF-LCT were excluded from the MAVORIC trial. 3. Alternative retinoids (acitretin or isotretinoin) could be considered in place of bexarotene. 4. ECP may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2). 5. Phototherapy and TSEBT may be associated with increased toxicity in patients with erythroderma and modification is dose/schedule may be considered. 6. There is limited safety data for the use of TSEBT in combination with systemic retinoids, HDAC inhibitors (such as vorinostat or romidepsin), or mogamulizumab, or combining phototherapy with vorinostat or romidepsin. 7. Patients with disease achieving a clinical benefit and/or those with disease responding to treatment should be considered for maintenance or tapering of regimens to optimize response duration. 8. Patients with erythrodermic disease are at increased risk for secondary infection with skin pathogens and systemic antibiotic therapy should be considered. See MFSS-B. 9. LCT-MF was not an exclusion criteria for Study 302 but no patients with LCT-MF were enrolled in the study.

Note: All recommendations are category 2A unless otherwise indicated.

Footnotes on MFSS-A 9 of 12

TABLE 5: SÉZARY SYNDROME (Stage IVA1 or IVA2) - MFSS-11[a,b,c,e]

SUGGESTED REGIMENS		TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON MFSS-A [1 of 12])
Low-Intermediate Burden (eg, ASC <5 K/mm³)	**High Burden (eg, ASC >5 K/mm³)**	
• Systemic therapy + skin-directed therapy (limited/local or generalized including phototherapy as indicated for stage of disease) Preferred Regimens (alphabetical order) • Single agents ▸ Bexarotene ▸ ECP ▸ Interferon alfa[b] ▸ Methotrexate ▸ Mogamulizumab ▸ Romidepsin ▸ Vorinostat • Combination therapy ▸ ECP + interferon alfa[b] or retinoid ▸ ECP + interferon alfa[b] + retinoids ▸ Retinoid + interferon alfa[b] Other Recommended Regimens (alphabetical order) • Alemtuzumab • Brentuximab vedotin • Gemcitabine • Liposomal doxorubicin • Pembrolizumab • Pralatrexate Useful in Certain Circumstances (alphabetical order) • Acitretin • Interferon gamma-1b • Isotretinoin	• Systemic therapy + skin-directed therapy (limited/local or generalized including phototherapy as indicated for stage of disease) Preferred Regimens (alphabetical order) • Single agents ▸ Mogamulizumab ▸ Romidepsin • Combination therapy ▸ ECP + interferon alfa[b] or retinoid ▸ ECP + interferon alfa[b] + retinoids ▸ Retinoid + interferon alfa[b] Other Recommended Regimens (alphabetical order) • Alemtuzumab • Bexarotene • Brentuximab vedotin • ECP • Gemcitabine • Interferon alfa[b] • Liposomal doxorubicin • Methotrexate • Pembrolizumab • Pralatrexate • Vorinostat Useful in Certain Circumstances (alphabetical order) • Acitretin • Interferon gamma-1b • Isotretinoin	1. In the randomized ALCANZA trial (Miles Prince H, et al. Lancet 2017;390:555-566), brentuximab vedotin was more effective than methotrexate or bexarotene in patients with previously treated MF (≥ stage IB). Patients with SS were excluded from the ALCANZA trial. 2. In the randomized MAVORIC trial (Kim YH, et al. Lancet Oncol 2018;19:1192-1204), mogamulizumab was more effective than vorinostat in patients with previously treated MF (≥ stage IB) and SS. Responses were higher in patients with blood involvement (stage III or stage IV disease) than those with stage IIB or stage IB/IIA disease. Patients with MF-LCT were excluded from the MAVORIC trial. 3. Alternative retinoids (acitretin or isotretinoin) could be considered in place of bexarotene. 4. There is limited safety data for the use of TSEBT in combination with systemic retinoids, HDAC inhibitors (such as vorinostat or romidepsin), or mogamulizumab, or combining phototherapy with vorinostat or romidepsin. 5. Patients with disease achieving a clinical benefit and/or those with disease responding to treatment should be considered for maintenance or tapering of regimens to optimize response duration.

Footnotes on MFSS-A 9 of 12

Note: All recommendations are category 2A unless otherwise indicated.

TABLE 6: STAGE IV MF (Non-Sézary/Visceral organ disease) AND MF WITH LARGE CELL TRANSFORMATION (MF-LCT)[c,e,f]

SUGGESTED REGIMENS		TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON MFSS-A [1 of 12])
Non-Sézary (stage IVA2) or Visceral/Solid Organ (stage IVB) Disease (MFSS-11)	**MF-LCT (MFSS-12)**	
• Systemic therapy ± RT for local control Preferred Regimens (alphabetical order) • Brentuximab vedotin • Gemcitabine • Liposomal doxorubicin • Pralatrexate • Romidepsin Other Recommended Regimens • Mogamulizumab • Multiagent chemotherapy regimens (See NCCN Guidelines for T-Cell Lymphomas - PTCL-B 3 of 8 for regimens listed for PTCL- NOS)	• TSEBT OR • Systemic therapy + skin directed therapy Preferred Regimens (alphabetical order) • Brentuximab vedotin • Gemcitabine • Liposomal doxorubicin • Pralatrexate • Romidepsin • Multiagent chemotherapy regimens (See NCCN Guidelines for T-Cell Lymphomas -PTCL-B 3 of 8 for regimens listed for PTCL-NOS) Other Recommended Regimens • Pembrolizumab	1. In the MAVORIC trial (Kim YH, et al. Lancet Oncol 2018;19:1192-1204), mogamulizumab was more effective than vorinostat in patients with previously treated MF and SS. Response rates were higher in the blood compartment than in lymph nodes or viscera. Patients with MF-LCT were excluded from the MAVORIC trial. 2. There is limited safety data for the use of TSEBT in combination with systemic retinoids, HDAC inhibitors (such as vorinostat or romidepsin), or mogamulizumab, or combining phototherapy with vorinostat or romidepsin. 3. In patients requiring chemotherapy, single agents are preferred over combination chemotherapy, due to the higher toxicity profiles associated with multi-agent regimens and the short-lived responses seen with time-limited combination chemotherapy. 4. Multiagent chemotherapy regimens are generally reserved for patients with relapsed/refractory or extracutaneous disease. Most patients are treated with multiple single-agent systemic therapies before receiving multiagent chemotherapy.

TABLE 7: RELAPSED OR REFRACTORY DISEASE TO MULTIPLE PRIOR THERAPIES

SUGGESTED REGIMENS
Useful in Certain Circumstances (alphabetical order by category) • Alemtuzumab • Chlorambucil • Cyclophosphamide • Etoposide • Pembrolizumab • Pentostatin • Temozolomide for central nervous system (CNS) involvement at some NCCN Member Institutions • Bortezomib (category 2B) • Multiagent chemotherapy regimens (See NCCN Guidelines for T-Cell Lymphomas - PTCL-B 3 of 8 for regimens listed for PTCL-NOS)

Footnotes on MFSS-A 9 of 12

Note: All recommendations are category 2A unless otherwise indicated.

FOOTNOTES

[a] Laboratory studies for triglycerides, and thyroid function tests (with free thyroxine T4) are recommended for patients receiving bexarotene.

[b] Peginterferon alfa-2a may be substituted for other alpha interferon preparations (Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847; Patsatsi A, et al. J Eur Acad Dermatol Venereol 2022;36:e291-e293; Osman S, et al. Dermatologic Therapy 2023;2023:7171937).

[c] In the ALCANZA trial, brentuximab vedotin was associated with superior clinical outcome in patients with previously treated CD30+ MF (CD30 positivity was defined as CD30 expression in ≥10% of total lymphoid cells). In other clinical studies, clinical responses with brentuximab vedotin have been reported across all CD30 expression levels including negligible CD30 expression.

[d] In Study 302, CD25-positiity was defined as detectable CD25 in ≥20% of total lymphoid cells in biopsy specimen by IHC. However, there was no correlation between the CD25 expression and the efficacy of denileukin diftitox.

[e] Rapid progression has been reported in patients, who are positive for human t-lymphotropic virus (HTLV), receiving pembrolizumab. Disease flare is seen in some patients (especially in erythrodermic skin/Sézary patients) and should be distinguished from disease progression (Khodadoust MS, et al. J Clin Oncol 2020:38:20-28).

[f] Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications. While alemtuzumab is no longer commercially available, it may be obtained for clinical use. Recommend CMV monitoring or prophylaxis (see PCLYM-C).

Note: All recommendations are category 2A unless otherwise indicated.

SUGGESTED TREATMENT REGIMENS
REFERENCES

Skin-Directed Therapies

Topical corticosteroids

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Mechlorethamine hydrochloride (nitrogen mustard)

Alexander-Savino CV, Chung CG, Gilmore ES, et al. Randomized Mechlorethamine/Chlormethine Induced Dermatitis Assessment Study (MIDAS) Establishes Benefit of Topical Triamcinolone 0.1% Ointment Cotreatment in Mycosis Fungoides. Dermatol Ther (Heidelb). 2022;12:643-654.

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Querfeld C, Geskin LJ, Kim EJ, et al. Lack of Systemic Absorption of Topical Mechlorethamine Gel in Patients with Mycosis Fungoides Cutaneous T-Cell Lymphoma. J Invest Dermatol. 2021;141:1601-1604.e2.

Local radiation

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Neelis KJ, Schimmel EC, Vermeer MH, et al. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. Int J Radiat Oncol Biol Phys 2009;74:154-158.

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Thomas TO, Agrawal P, Guitart J, et al. Outcome of patients treated with a single-fraction dose of palliative radiation for cutaneous T-cell lymphoma. Int J Radiat Oncol Biol Phys 2013;85:747-753.

Topical bexarotene

Breneman D, Duvic M, Kuzel T, et al. 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.

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Tazarotene gel

Apisarnthanarax N, Talpur R, Ward S, et al. Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. J Am Acad Dermatol 2004;50:600-607.

Topical imiquimod

Deeths MJ, Chapman JT, Dellavalle RP, et al. Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. J Am Acad Dermatol 2005;52:275-280.

Topical calcineurin inhibitor (pimecrolimus)

Ortiz-Romero PL, Jiménez LM, Muniesa C, et al, Activity and safety of topical pimecrolimus in patients with early stage mycosis fungoides (PimTo-MF): a single-arm, multicentre, phase 2 trial. Lancet Haematol 2022;9:e425-433.

Phototherapy (UVB and PUVA)

Gathers RC, Scherschun L, Malick F, et al. Narrowband UVB phototherapy for early-stage mycosis fungoides. J Am Acad Dermatol 2002;47:191-197.

Querfeld C, Rosen ST, Kuzel TM, et al. Long-term follow-up of patients with early-stage cutaneous T-cell lymphoma who achieved complete remission with psoralen plus UV-A monotherapy. Arch Dermatol 2005;141:305-311.

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Zane C, Leali C, Airò P, et al. "High-dose" UVA1 therapy of widespread plaque-type, nodular, and erythrodermic mycosis fungoides. J Am Acad Dermatol 2001;44:629-633.

Total skin electron beam therapy (TSEBT)

Chinn DM, Chow S, Kim YH, Hoppe RT. Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides. Int J Radiat Oncol Biol Phys 1999;43:951-958.

Ysebaert L, Truc G, Dalac S, et al. Ultimate results of radiation therapy for T1-T2 mycosis fungoides. Int J Radiat Oncol Biol Phys 2004;58:1128-1134.

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Bortezomib

Zinzani PL, Musuraca G, Tani M, et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007;25:4293-4297.

Brentuximab vedotin

Kim YH, Tavallaee M, Sundram U, et al. 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.

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Foss FM, Kim YH, Prince HMM, et al. Efficacy and Safety of E7777 (improved purity Denileukin diftitox [ONTAK]) in patients with relapsed or refractory cutaneous T-Cell Lymphoma: Results from Pivotal Study 302 [abstract]. Blood 2022;140:1491-1492.

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Liposomal doxorubicin

Pulini S, Rupoli S, Goteri G, et al. Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas. Haematologica 2007;92:686-689

Quereux G, Marques S, Nguyen JM, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. Arch Dermatol 2008;144:727-733.

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Khodadoust MS, Rook AH, Porcu P, et al. Pembrolizumab in relapsed and refractory mycosis fungoides and Sezary syndrome: A multicenter phase II study. J Clin Oncol 2020;38:20-28.

Pentostatin

Cummings FJ, Kim K, Neiman RS, et al. Phase II trial of pentostatin in refractory lymphomas and cutaneous T-cell disease. J Clin Oncol 1991;9:565-571.

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SUGGESTED TREATMENT REGIMENS
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Romidepsin

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Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol 2010;28:4485-4491.

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Zhang C, Duvic M. Treatment of cutaneous T-cell lymphoma with retinoids. Dermatol Ther 2006;19:264-271.

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Vorinostat

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Olsen EA, Kim YH, Kuzel TM, et al. 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.

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Combination Therapies

Systemic + skin-directed

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Systemic + systemic

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Allogeneic HCT

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Note: All recommendations are category 2A unless otherwise indicated.

SUPPORTIVE CARE FOR PATIENTS WITH MF/SS

Collaboration with dermatologist for supportive care is essential.

Pruritus

- Assessment
  - Pruritus should be assessed
  - Correlation between sites of disease and localization of pruritus may be useful in tailoring therapy
  - For severe or persistent pruritus despite therapeutic response other potential causes for pruritus should be investigated

- Treatment
  - Co-management with a dermatologist with expertise in skin care and CTCL
  - Optimized skin-directed and systemic therapy for MF/SS
  - Mild, unscented soaps for bathing are gentle and optimal to prevent skin dryness
  - Moisturizers/emollients
  - Topical steroid application (appropriate strength for body region) ± occlusion[1]
  - Topical over-the-counter preparations
  - Systemic agents
    - ◊ First-line
      - – H1 antihistamines; single agent or combination of antihistamines from different classes[2]
      - – Gabapentin[3,4]
      - – Pregabalin
    - ◊ Second-line
      - – Aprepitant[5-8]
      - – Mirtazapine[4]
      - – Selective serotonin reuptake inhibitors (SSRIs)[9]
    - ◊ Third-line
      - – Naltrexone[10]
      - – Systemic steroids

Infections

- Active or suspected infections
  - Cutaneous viral infections
    - ◊ High risk for skin dissemination of localized viral infections herpes simplex virus (HSV)/varicella zoster virus (VZV).
    - ◊ HSV prophylaxis with acyclovir or equivalent should be considered for patients with frequent recurrence of HSV infection.
  - Erythroderma:
    - ◊ Swab of skin, nares, or other areas for cultures of *Staphylococcus aureus* infection or colonization
    - ◊ Intranasal mupirocin for *S. aureus* carriers
    - ◊ Oral dicloxacillin or cephalexin
    - ◊ Sulfamethoxazole/trimethoprim, doxycycline, minocycline, or clindamycin if suspected methicillin-resistant *staphylococcus aureus* (MRSA)
    - ◊ Vancomycin if no improvement or documented bacteremia
    - ◊ Bleach baths [1/2 cup of regular strength bleach (5%–6%) in full tub of water] or for limited areas, soaks (1 tsp of bleach in 1 gallon of water). Bleach baths should be taken for 5 to 10 minutes two to three times a week maximum followed by tap water to rinse off the bleach water. Moisturizer should be put on immediately following the bleach bath or soak.
  - Ulcerated and necrotic tumors:
    - ◊ Infection or colonization with Gram-negative rods should be considered in addition to the more common gram-positive organisms.
    - ◊ Ulcer will not heal unless disease is treated. Consider local RT if feasible.
- Prophylaxis
  - Optimize skin barrier protection with moisturizing of skin
  - Consider mupirocin to the nares for *S. aureus* carriers
  - Diluted bleach baths or soaks (if limited area) as noted above
  - Minimize use of central lines when possible
  - For patients receiving alemtuzumab, see PCLYM-C

Note: All recommendations are category 2A unless otherwise indicated.

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SUPPORTIVE CARE FOR PATIENTS WITH MF/SS
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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PRIMARY CUTANEOUS CD30+ T-CELL LYMPHOPROLIFERATIVE DISORDERS (LPD)

Overview & Definition

- Primary cutaneous CD30+ T-cell LPDs represent a spectrum that includes primary cutaneous anaplastic large cell lymphoma (ALCL), lymphomatoid papulosis (LyP), and "borderline" cases with overlapping clinical and histopathologic features.[a,b,c]
- Clinical correlation with histopathologic features is essential for establishing the diagnosis of primary cutaneous CD30+ T-cell LPDs; diagnosis cannot be made based on pathology review alone.

Differential Diagnosis

- It is critical to distinguish CD30+ T-cell LPDs from other processes involving skin that may express CD30:
  - Systemic T-cell lymphomas (eg, ALCL, adult T-cell leukemia/lymphoma [ATLL], peripheral T-cell lymphoma [PTCL]);
  - Other CD30+ cutaneous lymphomas such as MF, especially MF with LCT
  - Benign disorders such as lymphomatoid drug reactions, arthropod bites, viral infections, and others.
- Lymphomatoid drug reactions have been linked with certain drugs (eg, amlodipine, carbamazepine, cefuroxime, valsartan) and may be associated with CD30+ atypical large cells in histology.
- MF and primary cutaneous CD30+ T-cell LPD can coexist in the same patient.

- Primary cutaneous ALCL (PC-ALCL)
  - Represents about 8% of cutaneous lymphoma cases.[a]
  - Unlike systemic ALCL, PC-ALCL typically follows an indolent course and although cutaneous relapses are common, an excellent prognosis is usually maintained.[d,e]
  - Histologically characterized by diffuse, cohesive sheets of large CD30-positive (in >75%) cells with anaplastic, pleomorphic, or immunoblastic appearance.[a]
  - Clinical features typically include solitary or localized nodules or tumors (often ulcerated); multifocal lesions occur in about 20% of cases. Extracutaneous disease occurs in about 10% of cases, usually involving regional lymph nodes.[a] Patches and plaques may also be present and some degree of spontaneous remittance in lesions may also be seen.

- Lymphomatoid papulosis (LyP)
  - LyP is included under the classification system for lymphomas (WHO-EORTC) but may be best classified as an LPD as it is a frequently spontaneously regressing process.[a]
  - LyP has been reported to be associated with other lymphomas such as MF, PC-ALCL, systemic ALCL, or Hodgkin lymphoma.[f,g]
  - Lyp is histologically heterogeneous with large atypical anaplastic, immunoblastic, or Hodgkin-like cells in a marked inflammatory background[a]; several histologic subtypes can be defined based on evolution of skin lesions.[f]
  - Lyp clinical features are characterized by chronic, recurrent, spontaneously regressing papulonodular (grouped or generalized) skin lesions.[a,f]

[a] Alaggio R, et al. Leukemia 2022;36:1720-1748; Campo E, et al. Blood 2022;140:1229-1253. See Classification (ST-1).
[b] Vergier B, et al. Am J Surg Pathol 1998;22:1192-1202.
[c] Liu HL, et al. J Am Acad Dermatol 2003;49:1049-1058.
[d] Benner MF, Willemze R. Arch Dermatol 2009;145:1399-1404.
[e] Woo DK, et al. Arch Dermatol 2009;145:667-674.
[f] Kempf W, et al. Blood 2011;118:4024-4035.
[g] Due to overlapping immunophenotype and morphology, need to use caution to *not* diagnose CD30+ T-cell in lymph nodes as HL (Eberle FC, et al. Am J Surg Pathol 2012;36:716-725).

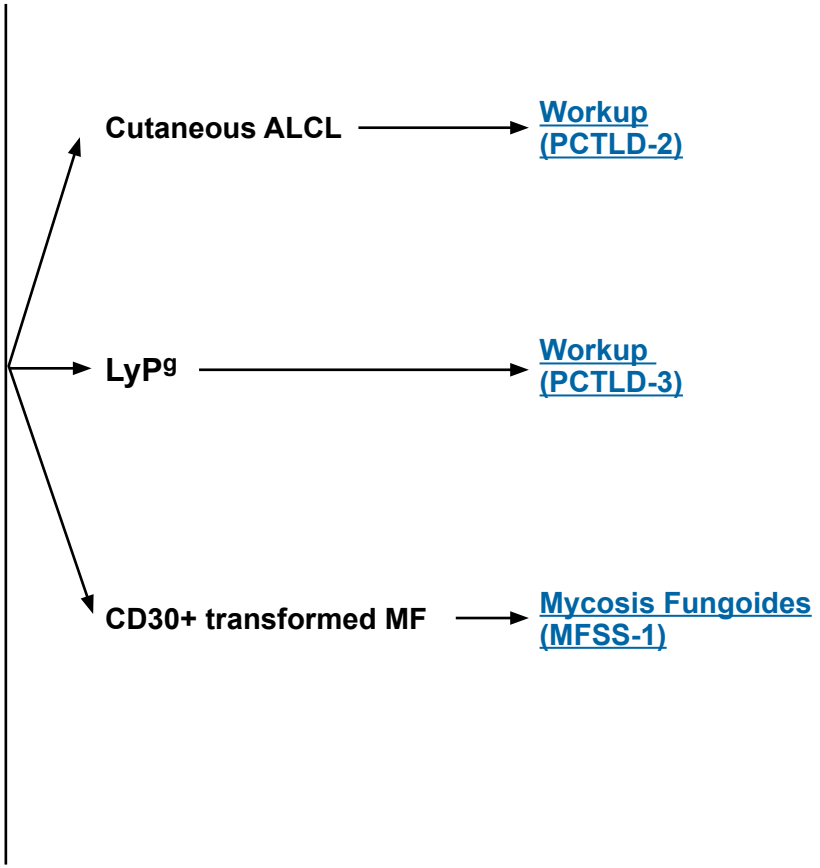
Note: All recommendations are category 2A unless otherwise indicated.

Diagnosis on PCTLD-1

DIAGNOSIS[a]

ESSENTIAL:
- **Clinical presentation: see Overview and Definition (PCTLD/INTRO-1)**
- **Clinical pathologic correlation is essential**
- **Complete skin examination for any sign of benign or malignant skin lesions**
- **Biopsy of suspicious skin sites**
  - **Multiple biopsies may be necessary to capture the pathologic variability of disease at diagnosis**
  - **\Review of a sufficient number of slides with adequate material to perform a comprehensive workup as described below and/or at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of CTCLs. Rebiopsy if pathological findings are non-diagnostic and/or discordant with the clinical presentation**
  - **Adequate biopsy (by punch, incisional, or excisional) of all types of clinical lesions present will aid in final diagnosis**
- **Adequate immunophenotyping to establish diagnosis[b,c] on skin biopsy:**
  - **IHC panel may include: CD3, CD4, CD8, CD20, CD30, CD56, ALK[d]**

USEFUL IN CERTAIN CIRCUMSTANCES:
- **On skin biopsy, expanded IHC panel may include: CD2, CD5, CD7, CD25, TIA1, granzyme B, perforin, IRF4/MUM1, EMA, TCRβ, TCRδ**
- **EBER-ISH**
- **Molecular analysis to detect clonal *TCR* gene rearrangements or other assessment of clonality[a,e]**
- **FISH: *ALK* and *DUSP22* gene rearrangements[a]**
- **Excisional or incisional biopsy of suspicious lymph nodes**
- **Assessment of HTLV-1/2 serology[f] is encouraged as results can impact therapy**



[a] Principles of Molecular Analysis in Primary Cutaneous Lymphomas (PCLYM-B).
[b] Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (See NCCN Guidelines for B-Cell Lymphomas).
[c] Typical immunophenotype: CD30+ (>75% cells), CD4+ variable loss of CD2/CD5/CD3, CD8+ (<5%) cytotoxic granule proteins positive.
[d] ALK positivity and t(2;5) translocation is typically absent in PC-ALCL and LyP.
[e] Clonal TCR gene rearrangements alone are not sufficient for diagnosis, as these can also be seen in patients with non-malignant conditions. Results should be interpreted in the context of overall presentation. See Principles of Molecular Analysis in T-Cell Lymphomas (TCLYM-A).
[f] See map for prevalence of HTLV-1/2 by geographic region. HTLV-1 has been described in patients in non-endemic areas.
[g] LyP is not considered a malignant disorder; however, there is an association with other lymphoid malignancy (MF or PC-ALCL). Staging studies are done in LyP only if there is suspicion of systemic involvement by an associated lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.

WORKUP

Cutaneous ALCL →

ESSENTIAL:
- **History and complete physical examination including complete skin examination[h]; palpation of peripheral lymph node regions; liver or spleen enlargement**
- **CBC with differential**
- **Comprehensive metabolic panel**
- **LDH**
- **C/A/P CT with contrast or integrated whole body FDG-PET/CT (arms/legs included when disease assessment of entire body is needed)[i]**
- **Biopsy suspicious nodes[j,k,l]: Biopsy of enlarged lymph nodes or suspected extracutaneous sites. Excisional or adequate core needle biopsy is preferred. An FNA biopsy alone is not sufficient for the initial diagnosis of lymphoma. Rebiopsy if consult material is nondiagnostic.**

USEFUL IN CERTAIN CIRCUMSTANCES
- **Bone marrow aspiration and biopsy (optional for solitary cutaneous ALCL or cutaneous ALCL without extracutaneous involvement on imaging)**
- **Pregnancy testing in patients of childbearing potential if contemplating treatments that are contraindicated in pregnancy[m]**
- **Discuss fertility preservation[n]**

→ **PC-ALCL** → **PCTLD-4**

→ **Cutaneous ALCL with regional node** → **PCTLD-4**

→ **Systemic ALCL** → **See NCCN Guidelines for T-Cell Lymphomas - Peripheral T-Cell (PTCL-1)**

[h] Monitoring the size and number of lesions will assist with response assessment.
[i] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. FDG-PET scan may be preferred in these instances.
[j] Due to overlapping immunophenotype and morphology, need to use caution to avoid diagnosing CD30+ T-cell in lymph nodes as HL (Eberle FC, et al. Am J Surg Pathol 2012;36:716-725).
[k] Consider systemic ALCL, regional lymph node involvement with PC-ALCL, or lymph node involvement with transformed MF.
[l] Consider PC-ALCL if in draining lymph nodes only.
[m] Many skin-directed and systemic therapies are contraindicated or are of unknown safety in pregnancy. Refer to individual drug information.
[n] Fertility preservation options include: sperm banking, semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.

Note: All recommendations are category 2A unless otherwise indicated.

WORKUP

LyP[g] →

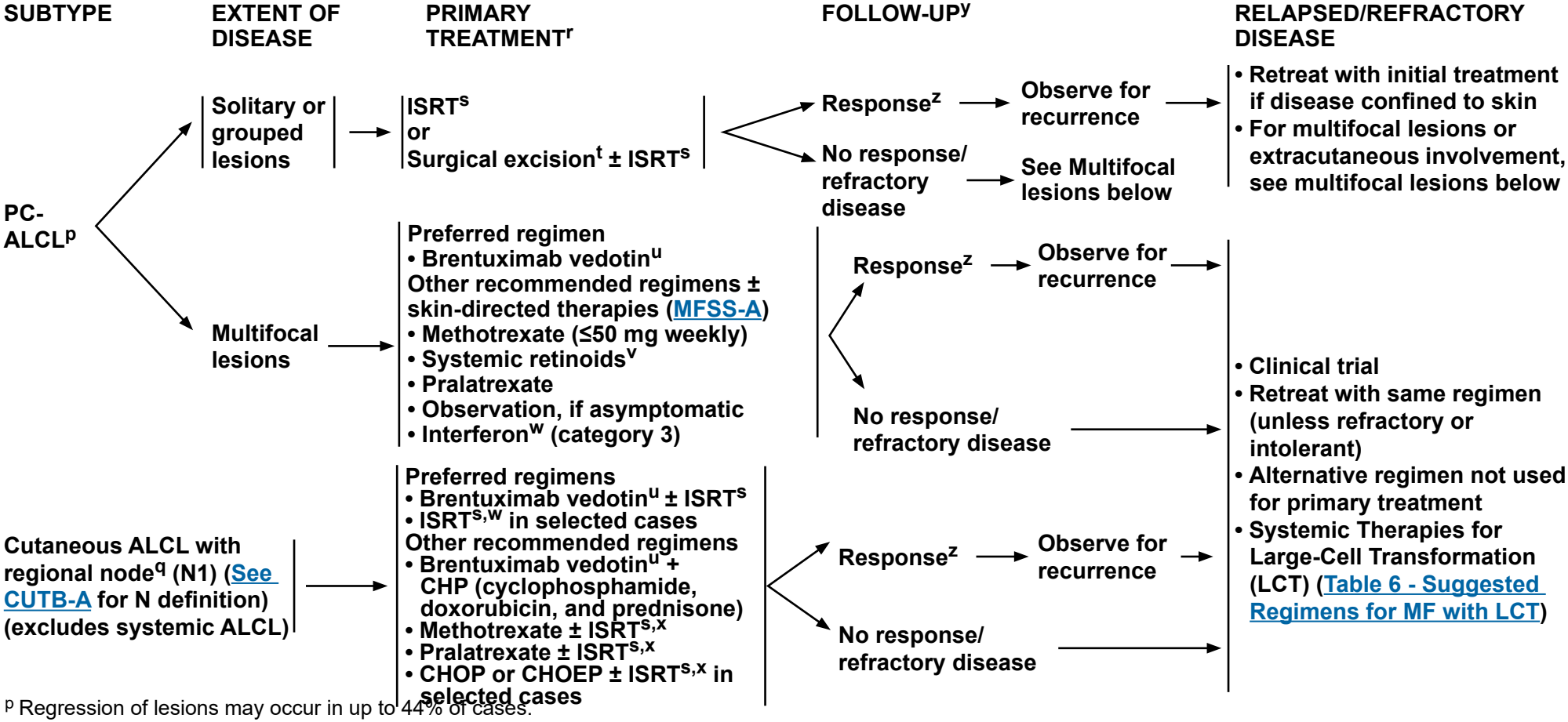
ESSENTIAL:
- History and complete physical examination including complete skin examination[h]; palpation of peripheral lymph node regions; liver or spleen enlargement
- CBC with differential
- Comprehensive metabolic panel
- LDH

USEFUL IN CERTAIN CIRCUMSTANCES:
- Pregnancy testing in patients of childbearing potential if contemplating treatments that are contraindicated in pregnancy[m]
- Discuss fertility preservation[n]
- C/A/P CT with contrast or integrated whole body FDG-PET/CT (arms/legs included when disease assessment of entire body is needed)[g,i,o] (not done for typical LyP)
- Neck CT with contrast if whole body FDG-PET/CT not done (not done for typical LyP)
- Bone marrow aspiration and biopsy (not done for typical LyP)[g,o]

→ PCTLD-5

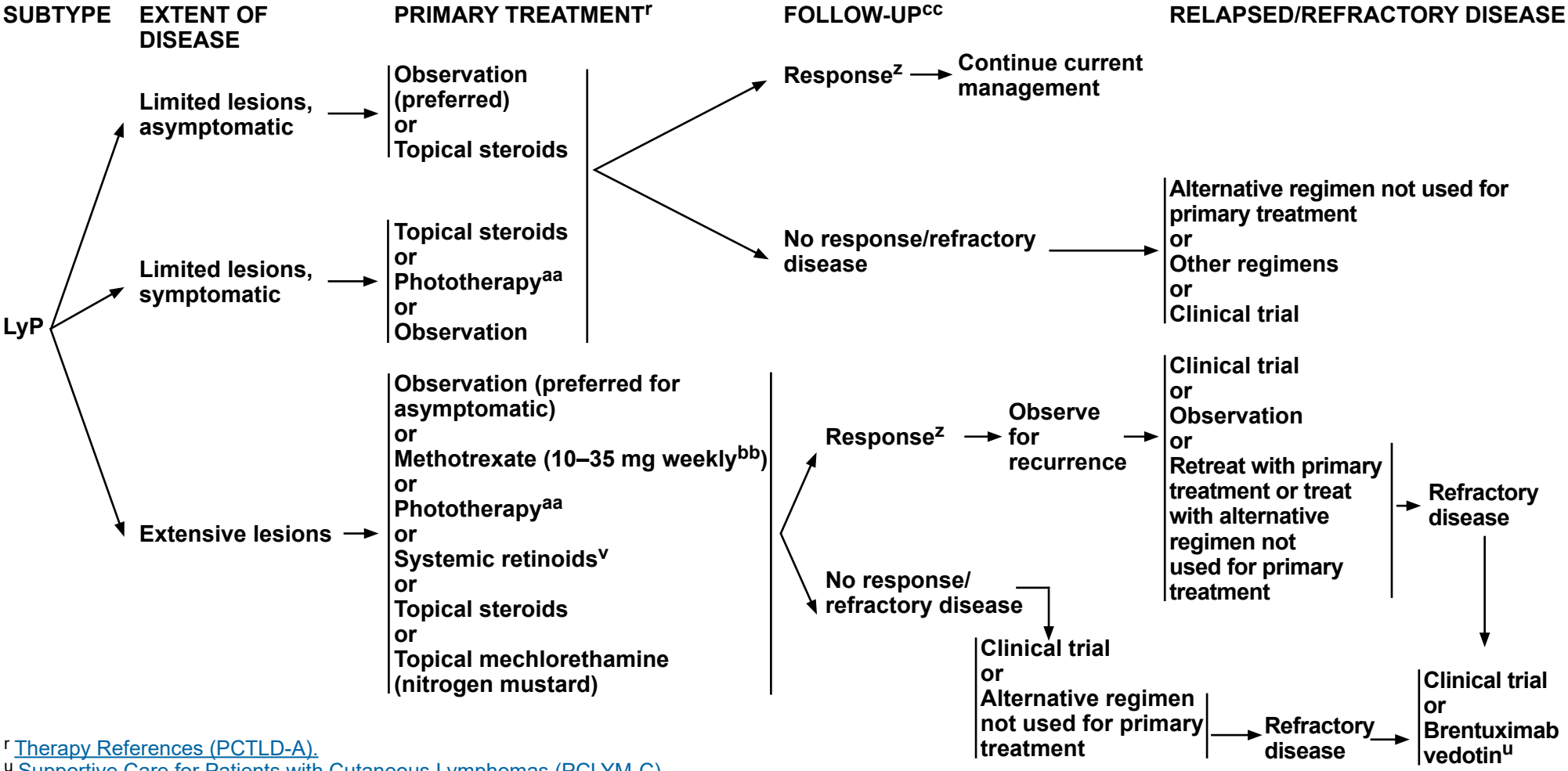
[g] LyP is not considered a malignant disorder; however, there is an association with other lymphoid malignancy (MF or PC-ALCL). Staging studies are done in LyP only if there is suspicion of systemic involvement by an associated lymphoma.
[h] Monitoring the size and number of lesions will assist with response assessment.
[i] Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. FDG-PET scan may be preferred in these instances.
[m] Many skin-directed and systemic therapies are contraindicated or are of unknown safety in pregnancy. Refer to individual drug information.
[n] Fertility preservation options include: sperm banking, semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.
[o] Only done to exclude an associated lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.



[p] Regression of lesions may occur in up to 44% of cases.
[q] Biopsy-proven lymphoma in lymph node.
[r] Therapy References (PCTLD-A).
[s] Principles of Radiation Therapy (PCLYM-A).
[t] Small lesions may be excised with minimal non-disfiguring surgery.
[u] Supportive Care for Patients with Cutaneous Lymphomas (PCLYM-C).
[v] Limited data from case reports (eg, bexarotene).
[w] Peginterferon alfa-2a is the only interferon available for clinical use in the US and it may be substituted for other interferon preparations (Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847; Patsatsi A, et al. J Eur Acad Dermatol Venereol 2022;36:e291-e293; Osman S, et al. Dermatologic Therapy 2023;2023:7171937).
[x] ISRT to include lymph node(s) ± primary skin lesions.
[y] Mycosis fungoides can develop over time; continue to conduct thorough skin exam during follow-up.
[z] Patients with 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. Relapsed disease often responds well to the same treatment. Partial response should be treated with other primary treatment options not received before to improve response before moving onto treatment for refractory disease. Patients with disease relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

Note: All recommendations are category 2A unless otherwise indicated.



[r] Therapy References (PCTLD-A).
[u] Supportive Care for Patients with Cutaneous Lymphomas (PCLYM-C).
[v] Limited data from case reports (eg, bexarotene).
[z] Patients with 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. Relapsed disease often responds well to the same treatment. Partial response should be treated with the other primary treatment options not received before to improve response before moving onto treatment for refractory disease. Patients with disease relapse or persistent disease after initial primary treatment may be candidates for clinical trials.
[aa] NB-UVB is generally preferred over PUVA.
[bb] Kempf W, et al. Blood 2011;118:4024-4035.
[cc] Life-long follow-up is warranted due to high risk for second lymphoid malignancies; continue to conduct thorough skin exam during follow-up.

Note: All recommendations are category 2A unless otherwise indicated.

THERAPY REFERENCES

Skin-Directed Therapies

Topical steroids

Paul MA, Krowchuk DP, Hitchcock MG, Jorizzo JL. Lymphomatoid papulosis: successful weekly pulse superpotent topical corticosteroid therapy in three pediatric patients. Pediatr Dermatol 1996;13:501-506.

Phototherapy

Wantzin GL, Thomsen K. PUVA-treatment in lymphomatoid papulosis. Br J Dermatol 1982;107:687-690.

Topical nitrogen mustard

Vonderheid EC, Tan ET, Kantor AF, et al. Long-term efficacy, curative potential, and carcinogenicity of topical mechloethamine chemotherapy in cutaneous T cell lymphoma. J Am Acad Dermatol 1989;20:416-428.

Radiation therapy

Million L, Yi EJ, Wu F, et al. Radiation therapy for primary cutaneous anaplastic large cell lymphoma: An International Lymphoma Radiation Oncology Group Multi-institutional Experience. Int J Radiat Oncol Biol Phys 2016;95:1454-1459.

Specht L, Dabaja B, Illidge T, et al. 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.

Smith GL, Duvic M, Yehia ZA, et al. Effectiveness of low-dose radiation for primary cutaneous anaplastic large cell lymphoma. Adv Radiat Oncol 2017;2:363-369.

Systemic Therapies

Brentuximab vedotin

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Duvic M, Tetzlaff MT, Gangar P, et al. 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.

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Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone)

Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet 2019;393:229-240.

Interferons

Proctor SJ, Jackson GH, Lennard AL, Marks J. Lymphotoid papulosis: response to treatment with recombinant interferon alfa-2b. J Clin Oncol 1992;10:170.

Schmuth M, Topar G, Illersperger B, et al. Therapeutic use of interferon-alpha for lymphomatoid papulosis. Cancer 2000;89:1603-1610.

Methotrexate

Everett MA. Treatment of lymphomatoid papulosis with methotrexate. Br J Dermatol 1984;111:631.

Vonderheid EC, Sajjadian A, Kaden ME. Methotrexate is effective for lymphomatoid papulosis and other primary cutaneous CD30+ lymphoproliferative disorders. J Am Acad Dermatol 1996;34:470-481.

Fujita H, Nagatani T, Miyazawa M, et al. Primary cutaneous anaplastic large cell lymphoma successfully treated with low-dose methotrexate. Eur J Dermatol 2008;18:360-361.

Pralatrexate

Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma. Blood 2012;119:4115-4122.

Systemic retinoids

Nakamura S, Hashimoto Y, Nishi K, et al. Primary cutaneous CD30+ lymphoproliferative disorder successfully treated with etretinate. Eur J Dermatol 2012;22:709-710.

Krathen RA, Ward S, Duvic M. Bexarotene is a new treatment option for lymphomatoid papulosis. Dermatology 2003;206:142-147.

Wyss M, Dummer R, Dommann SN, et al. Lymphomatoid papulosis--treatment with recombinant interferon alfa-2a and etretinate. Dermatology 1995;190:288-291.

Sheehy JM, Catherwood M, Pettengell R, Morris TCC. Sustained response of primary cutaneous CD30+ anaplastic large cell lymphoma to bexarotene and photopheresis. Leuk Lymphoma 2009;50:1389-1391.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY[a]

General Principles

- The general intent of RT is to treat the evident skin disease with adequate margin both circumferentially and in depth.
- External beam radiation therapy (EBRT) with photons, electrons, or low-energy x-rays may all be appropriate, depending on clinical circumstances.

Target Volumes

- ISRT for cutaneous lesions:
  - ISRT is recommended as the appropriate field for treating primary cutaneous lymphomas.
  - Planning to define the clinical target volume (CTV) may often only require a careful physical exam. However, when the depth of disease is not evident or when disease extends around curved surfaces, treatment planning may be facilitated by ultrasound imaging or CT-based simulation and planning. Incorporating other modern imaging like PET and MRI may enhance treatment volume determination in some cases.
  - ISRT targets the site of skin involvement. The volume encompasses the clinically evident disease with adequate margins.
  - The visible or palpable disease defines the gross tumor volume (GTV) and provides the basis for determining the CTV. If using CT-based planning, delineating tumor boundary with wire for CT simulation will guide treatment volumes. Concerns for questionable subclinical disease and uncertainties in original imaging accuracy or localization will lead to expansion of the CTV and are determined individually using clinical judgment but generally include a margin of 1–2 cm both circumferentially and in depth. The CTV need not be expanded into intact bone.
  - The planning target volume (PTV) is an additional expansion of the CTV that accounts only for setup variations (see ICRU definitions).
  - The treatment plan is designed using conventional or 3-D conformal techniques using clinical treatment planning considerations of coverage and dose reductions for organs at risk (OARs).
- ISRT for nodal disease:
  - Principles of Radiation Therapy for T-Cell Lymphomas (Target Volumes: ISRT for nodal disease).
  - Principles of Radiation Therapy for B-Cell Lymphomas (Target Volumes: ISRT for nodal disease).
- Radiation Dose Constraints – Recommendations for normal tissue dose constraints can be found in the Principles of Radiation Therapy NCCN Guidelines for Hodgkin Lymphoma

[a] References on PCLYM-A 3 of 3.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY[a]

General Dose Guidelines: (RT in conventional fraction sizes)

- **PCMZL and PCFCL:**
  - **Optimal initial management for solitary/regional disease is with 24–30 Gy EBRT. Alternatively, lower doses (eg, 4 Gy) may be used initially, with supplemental RT (4–20 Gy) for inadequate response or subsequent local relapse.**
    - ◊ **Surface margins beyond area of clinically evident disease will vary depending on lesion size and body site and must take into account dosimetry of the beam being used. Surface margins of 1.0–1.5 cm are generally adequate.**
    - ◊ **Margins in depth should include the volume at risk for involvement.**
    - ◊ **Generally, treatment with 6–9 MeV electrons (with surface bolus) provides an adequate depth of treatment. Alternatively, low-energy x-rays (~100 Kv) may be used.**
    - ◊ **Doses as low as 4 Gy are used occasionally, but data are limited regarding response and duration.**
  - **RT for relapsed disease: 4 Gy EBRT may be adequate.**

- **MF/SS**
  - **Treatment of individual patches, plaques, or tumors**
    - ◊ **Optimal management for individual plaque and tumor lesions is with EBRT, 8–12 Gy given with palliative intent (usually as combined modality therapy; 8 Gy may be given in 1–2 fractions). Even lower doses (4 Gy) may achieve a similar response, but it may be less durable.**
    - ◊ **For unilesional MF at initial presentation, the definitive RT dose is 24–30 Gy.**
    - ◊ **Surface margins beyond area of clinically evident disease will vary depending on lesion size and body site and must take into account dosimetry of the beam being used. Surface margins of 1.0–1.5 cm are generally adequate.**
    - ◊ **Margins in depth should include the volume at risk for involvement.**
    - ◊ **Generally, treatment with 6–9 MeV electrons (with surface bolus) provides an adequate depth of treatment. Alternatively, low-energy x-rays (~100 Kv) may be used.**
    - ◊ **For certain body surfaces, higher energy photon fields and opposed-field treatment (with bolus) may be required.**
  - **TSEBT**
    - ◊ **A variety of techniques may be utilized to cover the entire cutaneous surface. Patients are generally treated in the standing position on a rotating platform or with multiple body positions to ensure total skin coverage.**
    - ◊ **The common dose is ~12 Gy, generally 4–6 Gy per week. Higher doses (24–36 Gy) have been used for more extensive or refractory disease. The advantages of a lower dose includes fewer short-term complications and better ability to retreat for relapsed disease**
    - ◊ **“Shadowed” areas may need to be supplemented with individual electron fields.**
    - ◊ **Individual tumors may be boosted with doses of 4–12 Gy.**
    - ◊ **For patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.**

- **PC-ALCL:**
  - **RT for curative treatment: 24–30 Gy**
  - **Doses as low as 6 Gy are used at some Member Institutions, but data are limited regarding response and duration.**
  - **Palliative RT: 2 Gy x 2 or 4 Gy x 1**

[a] References on PCLYM-A 3 of 3.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY
REFERENCES

Akhtari M, Reddy JP, Pinnix CC, et al. Primary cutaneous B-cell lymphoma (non-leg type) has excellent outcomes even after very low dose radiation as single-modality therapy. Leuk Lymphoma 2016;57:34-38.

Goyal A, Carter JB, Pashtan I, et al. Very low-dose versus standard dose radiation therapy for indolent primary cutaneous B-cell lymphomas: A retrospective study. J Am Acad Dermatol 2018;78:408-410.

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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF MOLECULAR ANALYSIS IN PRIMARY CUTANEOUS LYMPHOMAS[a]

- **Genetic testing, including high-throughput sequencing (HTS), array-based comparative genomic hybridization (CGH), next-generation sequencing (NGS), karyotype, or FISH to detect somatic mutations or genetic abnormalities are often informative and in some cases essential for an accurate and precise diagnostic and prognostic assessment of primary cutaneous lymphomas (PCL).**

T-Cell Antigen Receptor (*TCR*) Gene Rearrangements

- ***TCR* gene rearrangement testing is recommended to support a diagnosis of PCL.**
- **Diseases:**
  - **MF/SS; primary cutaneous CD30+ T-cell LPDs**
- **Description:**
  - ***TCR* gene rearrangement is indicative of T-cell clonal expansion. The test targets the gamma and/or beta *TCR* genes using PCR methods with capillary or gel electrophoresis detection methods. Alternatively, HTS methods are increasingly utilized. HTS methods are more sensitive, precise, and capable of providing a unique sequence of the T-cell clone, which allows for comparison and confirmation of disease evolution and monitoring during remission. Clonal T-cell expansions can also be detected using V beta families in blood or tissue with flow cytometry methods.**
- **Diagnostic value:**
  - **Clonal *TCR* gene rearrangements without cytologic histopathologic and immunophenotypic evidence of abnormal T-cell population does not constitute a diagnosis of T-cell lymphoma since it can be identified in patients with non-malignant conditions. Conversely, a negative result does not exclude the diagnosis of T-cell lymphoma, which occasionally may fail *TCR* amplification. Nonetheless, it often provides essential information and increased precision for many of these complex diagnoses.**
- **Prognostic value:**
  - **Identification of clonal *TCR* gene rearrangement has no definitive established prognostic value; however, it could be helpful when used to determine clinical staging or assess relapsed or residual disease.**

***DUSP22-IRF4* Gene Rearrangement**

- **Testing for *DUSP22* (dual-specificity phosphatase 22) rearrangement is considered useful under certain circumstances for the diagnosis of primary cutaneous CD30+ T-cell LPDs.**
- **Diseases:**
  - **Primary cutaneous CD30+ T-cell LPDs**
- **Description:**
  - ***DUSP22* is a tyrosine/threonine/serine phosphatase that may function as a tumor suppressor gene. *DUSP22* inactivation contributes to the development of PTCLs.**
- **Detection:**
  - **FISH using probes to *DUPS22-IRF4* gene region at 6p25.3**
- **Diagnostic value:**
  - ***DUSP22* rearrangement has been described in patients with PC-ALCL and LyP but is not associated with prognostic significance.**

[a] ~~See~~ References on PCLYM-B 2 of 2.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF MOLECULAR ANALYSIS IN CUTANEOUS LYMPHOMAS

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Note: All recommendations are category 2A unless otherwise indicated.

SUPPORTIVE CARE FOR PATIENTS WITH CUTANEOUS LYMPHOMAS

For other immunosuppressive situations, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Monoclonal Antibody (mAb) Therapy and Viral Reactivation

- **Brentuximab vedotin (anti-CD30 antibody-drug conjugate)**
  - **Progressive multifocal leukoencephalopathy (PML):**
    - ◊ **Caused by reactivation of the John Cunningham (JC) virus and is usually fatal.**
    - ◊ **Diagnosis made by PCR of cerebrospinal fluid (CSF) and in some cases brain biopsy.**
    - ◊ **Clinical indications may include changes in behavior such as confusion, dizziness or loss of balance, difficulty talking or walking, and vision problems.**
    - ◊ **No known effective treatment.**
- **Alemtuzumab (anti-CD52 mAb)**
  - **Cytomegalovirus (CMV) reactivation:**
    - ◊ **CMV viremia should be measured by quantitative PCR at least every 2 to 3 weeks**
    - ◊ **The current recommendations for the appropriate management is controversial; some clinicians use ganciclovir (PO or IV) preemptively if viremia is present, others only if viral load is rising.**
  - **Antiinfective prophylaxis**
    - ◊ **HSV prophylaxis with acyclovir or equivalent.**
    - ◊ **Pneumocystis jirovecii pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent.**
    - ◊ **Consider antifungal prophylaxis.**
    - ◊ **Consultation with an infectious disease expert may be necessary. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**

Adverse Events Associated with Mogamulizumab

- **Graft-Versus-Host Disease (GVHD): A retrospective study showed a particularly high risk of developing GVHD in patients proceeding to allogeneic HCT within 50 days of mogamulizumab.[a]**
- **Mogamulizumab-associated rash (MAR): Mogamulizumab has been associated with a drug eruption (termed as MAR) that can clinically mimic CTCL. Skin biopsy is recommended to distinguish progression of disease versus drug eruption.[b,c]**

Pralatrexate-Induced Mucositis[d,e,f]

- **Vitamin B12 (cyanocobalamin) at a dose of 1000 mcg intramuscular to be started no more than 10 weeks prior to starting therapy with pralatrexate and then every 8 to 10 weeks.**
- **Oral folic acid 1 to 1.25 mg daily to be started within 10 days of starting therapy and continuing for 30 days after the last dose of pralatrexate.**
- **Consider use of oral leucovorin 25 mg three times daily for two consecutive days (total of 6 doses), starting 24 hours after each dose of pralatrexate.**

[a] Fuji S, et al. J Clin Oncol 2016;34:3426-3433.
[b] Chen L, et al. JAMA Dermatol 2019;155:968-971.
[c] Hirotsu KE, et al. JAMA Dermatol 2021;157:700-707.
[d] Mould DR, et al. Clin Pharmacol Ther 2009;86:190-196.
[e] Shustov AR, et al. Blood 2018;132:2910.
[f] Koch E, et al. Leuk Lymphoma 2013;54:2448-2451.

Note: All recommendations are category 2A unless otherwise indicated.

Classification

Table 1: Classification of Cutaneous B-Cell Lymphomas

WHO-EORTC classification for Primary Cutaneous Lymphomas (2018)	The International Consensus Classification (ICC) of Mature Lymphoid Neoplasms (2022)	WHO Classification of Hematolymphoid Tumors: Lymphoid Neoplasms (5th edition, 2022)
Cutaneous B-Cell Lymphomas	**Mature B-cell Neoplasms**	**Mature B-cell Neoplasms**
Primary cutaneous marginal zone lymphoma	Primary cutaneous marginal zone lymphoproliferative disorder	Marginal zone lymphoma • Primary cutaneous marginal zone lymphoma
Primary cutaneous follicle center lymphoma	Primary cutaneous follicle center lymphoma	Cutaneous follicle center lymphoma • Primary cutaneous follicle center lymphoma
Primary cutaneous DLBCL, leg type	Primary cutaneous DLBCL, leg type	Large B-cell lymphomas • Primary cutaneous DLBCL, leg type • Intravascular large B-cell lymphoma
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma	
EBV+ mucocutaneous ulcer (provisional)	EBV-positive mucocutaneous ulcer	Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation • EBV-positive mucocutaneous ulcer

Table 2: Classification of Cutaneous T-Cell Lymphomas (ST-2)

With permission, Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019;133:1703-1714.
The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee. Blood 2022;140:1229-1253.
Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720-1748.

Classification

Table 2: Classification of Cutaneous T-Cell Lymphomas

WHO-EORTC classification for Primary Cutaneous Lymphomas (2018)	The International Consensus Classification (ICC) of Mature Lymphoid Neoplasms (2022)	WHO Classification of Hematolymphoid Tumors: Lymphoid Neoplasms (5th edition, 2022)
Cutaneous T-Cell Lymphomas	**Mature T-cell and NK-cell neoplasms**	**Mature T-cell and NK-cell neoplasms**
Sézary syndrome	Sézary syndrome	Sézary syndrome
		Primary cutaneous T-cell lymphoid proliferations and lymphomas
Mycosis fungoides (MF)	Mycosis fungoides	Mycosis fungoides
MF Variants • Folliculotropic MF • Pagetoid reticulosis • Granulomatous slack skin	Not included	Not included
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders • Lymphomatoid papulosis • Cutaneous anaplastic large cell lymphoma	Primary cutaneous CD30-positive T-cell lymphoproliferative disorders • Lymphomatoid papulosis • Primary cutaneous anaplastic large cell lymphoma	Primary cutaneous CD30-positive T-cell lymphoproliferative disorders: • Lymphomatoid papulosis • Primary cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous peripheral T-cell lymphoma, rare subtypes		
• Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (provisional)	Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder	Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder
• Primary cutaneous gamma-delta T-cell lymphoma	Primary cutaneous gamma-delta T-cell lymphoma	Primary cutaneous gamma/delta T-cell lymphoma
• Primary cutaneous acral CD8-positive T-cell lymphoma (provisional)	Primary cutaneous acral CD8-positive lymphoproliferative disorder	Primary cutaneous acral CD8-positive lymphoproliferative disorder
• Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (provisional)	Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma	Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
• Primary cutaneous peripheral T-cell lymphoma, NOS	Not included	Primary cutaneous peripheral T-cell lymphoma, NOS

With permission, Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019;133:1703-1714.
The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee. Blood 2022;140:1229-1253.
Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720-1748.

ABBREVIATIONS

ABC	activated B-cell
ALCL	anaplastic large cell lymphoma
ANA	antinuclear antibody
ASC	absolute Sézary cell
ATLL	adult T-cell leukemia/lymphoma
BSA	body surface area
CSF	cerebrospinal fluid
C/A/P	chest/abdomen/pelvis
CGH	comparative genomic hybridization
CBC	complete blood count
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CTCL	cutaneous T-cell lymphoma
CTV	clinical target volume
DLBCL	diffuse large B-cell lymphoma
EBER-ISH	Epstein-Barr encoding region-in situ hybridization
EBRT	external beam radiation therapy
EBV	Epstein-Barr virus
ECP	extracorporeal photopheresis
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
FMF	follicular folliculotropic mycosis fungoides
FNA	fine-needle aspiration
GCB	germinal center B-cell
GVHD	graft-versus-host disease
GTV	gross tumor volume
GVHD	graft-versus-host disease
HCT	hematopoietic cell transplant
HLH	hemophagocytic lymphohistiocytosis
HSV	herpes simplex virus
HTLV	human T-cell lymphotropic virus
HTS	high-throughput sequencing
IHC	immunohistochemistry
ICOS,	inducible T-cell co-stimulator
ISH	in situ hybridization
ISRT	involved-site radiation therapy
IVF	in vitro fertilization
JC	John Cunningham
LCT	large-cell transformation
LDH	lactate dehydrogenase
LDi	longest diameter
LN	lymph node
LPD	lymphoproliferative disorder
LyP	lymphomatoid papulosis
MRSA	methicillin-resistant *Staphylococcus aureus*
MF	mycosis fungoides
NKTL	natural killer T-cell lymphoma
NB-UVB	narrowband ultraviolet B
NGS	next-generation sequencing;
NOS	not otherwise specified
OARS	organ(s) at risk
OS	overall survival

Continued

ABBREVIATIONS

PC-ALCL	primary cutaneous anaplastic large cell lymphoma
PC-BCL	primary cutaneous B-cell lymphoma
PC-DLBCL	primary cutaneous diffuse large B-cell lymphoma
PC-FCL	primary cutaneous follicle center lymphoma
PCL	primary cutaneous lymphoma
PC-MZL	primary cutaneous marginal zone lymphoma
PCR	polymerase chain reaction
PD-1	programmed cell death protein 1
PID	primary immunodeficiency
PJP	pneumocystis jirovecii pneumonia
PML	progressive multifocal leukoencephalopathy
PR	partial response
PTCL-NOS	peripheral T-cell lymphoma not otherwise specified
PTV	planning target volume
PUVA	psoralen plus ultraviolet A
RF	RF, rheumatoid factor
SPEP	serum protein electrophoresis
SS	Sézary syndrome
TCR	T-cell antigen receptor
TSEBT	total skin electron beam therapy
UVB	ultraviolet B
VZV	varicella zoster virus

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

This discussion corresponds to the NCCN Guidelines for Primary Cutaneous Lymphomas. Last updated: August 22, 2024.

Discussion

Table of Contents

Overview

Primary cutaneous lymphomas (PCL) are a heterogenous group of extranodal B-cell and T-cell non-Hodgkin lymphomas (NHL) originating in and usually confined to the skin. In the Surveillance, Epidemiology, and End Results (SEER) database population-based analysis of 3884 cases of PCL diagnosed in the United States from 2001 to 2005, the incidence of cutaneous B-cell lymphomas (CBCL) and cutaneous T-cell lymphomas (CTCL) accounted for 29% and 71%, respectively.[1]

The World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification for cutaneous lymphomas was first published in 2005 and was subsequently updated in 2018.[2,3] The most common subtypes of PCL that are covered in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are listed below:

- Cutaneous B-Cell Lymphomas
  - Primary cutaneous marginal zone lymphoma (PCMZL)
  - Primary cutaneous follicle center lymphoma (PCFCL)
  - Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, leg type)
- Cutaneous T-Cell Lymphomas
  - Mycosis fungoides (MF) and Sézary syndrome (SS)
  - Primary cutaneous CD30+ T-cell lymphoproliferative disorders (PCTLD)

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Primary Cutaneous B-Cell Lymphomas

Primary cutaneous B-cell lymphomas (PCBCL) account for mainly three subtypes: PCMZL, PCFCL, and PCDLBCL, leg type.[2,3] PCFCL is the most common subtype of the CBCL, diagnosed in 57% of patients followed by PCMZL (24%–31%) and PCDLBCL, leg type (11%–19%).[4,5]

In addition to these three subtypes, PCDLBCL, not otherwise specified (PCDLBCL-NOS) with clinicopathologic features intermediate between PCFCL and PCDLBCL, leg type has also been described.[6,7] In the revised 2018 WHO-EORTC classification, rare cases that cannot be classified as either PCDLBCL, leg type or PCFCL are classified as PCDLBCL-NOS.[3]

PCFCL is more prevalent in the scalp, face, and the forehead, whereas the trunk and extremities are the most common sites for PCMZL.[4,5] PCMZL and PCFCL are generally indolent or slow growing and both are associated with excellent prognosis. PCMZL is now recognized as a distinct entity from other mucosa-associated lymphoid tissue (MALT) lymphomas in both the International Consensus Classification (ICC) and the updated 2022 WHO classification (WHO5).[8,9] In the ICC, PCMZL are defined as primary cutaneous marginal zone lymphoproliferative disorders because of their indolent disease course.[9]

PCDLBCL, leg type is found most commonly on the leg, although it can arise at other sites.[4,5] PCDLBCL, leg type is usually aggressive and associated with a generally poorer prognosis (mainly due to the higher frequency of extracutaneous relapses).[4,5] In a large Italian series of 467 patients with PCBCL, extracutaneous involvement was reported in 17% with PCDLBCL, leg type compared to 6% of patients with PCMZL and 11% with PCFCL.[4] The 5-year overall survival (OS) rate was significantly higher for patients with PCMZL and PCFCL than for patients with PCDLBCL, leg type (97%, 96%, and 73%, respectively; $P < .0001$).[4] In patients with PCMZL and PCFCL, the disease-free survival (DFS) and OS rates were significantly higher for patients with single lesions compared with those with regional or disseminated lesions (5-year DFS, 62% vs. 44%; 5-year OS, 97% vs. 85%), whereas the difference in outcomes between single and regional or disseminated lesions was not significant in patients with PCDLBCL, leg type (5-year DFS rate 55% vs. 44%; 5-year OS rate 79% vs. 67% for single and regional or disseminated lesions, respectively).[4] In the report from the Dutch Cutaneous Lymphoma Registry that included 300 patients with PCBCL, the incidence of extracutaneous relapse was 47% among patients with PCDLBCL, leg type compared to 11% and 9%, respectively, for patients with PCFCL and PCMZL.[5] The 5-year disease-specific survival rates in this series were 95%, 98%, and 50% for PCFCL, PCMZL, and PCDLBCL, leg type, respectively.

While the diagnosis of PCMZL is generally straightforward and reproducible among pathologists, it is more difficult to distinguish between PCFCL and PCDLBCL, leg type, partly because the cell size (large vs. small) is not a defining feature as it is in nodal B-cell lymphomas. Disease-specific characteristics identified by molecular and gene expression profiling (GEP) studies (as described below) may be helpful to distinguish the subtypes of CBCL.[10]

PCMZL can be divided into two subgroups with different prognosis based on the immunoglobulin (Ig) heavy chain usage, with the vast majority being CXCR3-negative and Ig class-switched subtype (IgG, IgA, and IgE) and a small subset being CXCR3-positive and IgM-positive.[11-14] Emerging data suggest that Ig class-switched subtype may be categorized as a clonal chronic lymphoproliferative disorder due to its indolent disease course.[14,15]

GEP studies have shown that PCFCL is characterized by a germinal center B-cell (GCB) phenotype and PCDLBCL, leg type is most commonly characterized by activated B-cell (ABC) phenotype.[16] Thus, a germinal (or follicle) center phenotype and large cells in a skin lesion is consistent with PCFCL with a diffuse population of large cells (PCFCL-LC) and not with DLBCL.[16] In nodal DLBCL, the GCB phenotype is associated with a better prognosis than the ABC phenotype. Immunohistochemical and GEP-based algorithms used to classify nodal DLBCL into GCB or non-GCB subtypes based on cell of origin (COO) have also shown to be useful to distinguish PCFCL from PCDLBCL, leg type.[17-19] However, these algorithms may be of limited utility in the differentiation of PC-DLBCL, leg type and PCFCL-LC.[19] While all cases of PCFCL-LC were uniformly classified as GCB phenotype by both immunohistochemical and GEP-based algorithms, the classification based on COO was heterogenous in patients with PC-DLBCL, leg type.[19]

A high prevalence of *MYD88* L265P mutation has been reported in patients with PCDLBCL, leg type and is associated with inferior clinical outcomes.[17,20] In a retrospective analysis of 61 patients (58 patients with interpretable results) diagnosed with PCDLBCL, leg type, *MYD88* L265P mutation was detected in 59% of patients.[20] It was also associated with shorter disease-specific survival and was an independent adverse prognostic factor for OS. The 3-year and 5-year disease-specific survival rates for those with *MYD88* L265P mutation were 66% and 60%, respectively, compared to 85% and 72%, respectively, for patients with the wild-type allele. In the aforementioned report that evaluated the clinicopathologic and molecular characteristics of patients with PCFCL (25 patients) and PCDLBCL, leg type (32 patients), *MYD88* L265P mutation was detected only in patients with PCDLBCL, leg type (n = 22; 69%).[17] These findings suggest that determination of *MYD88* L265P mutation status could be helpful to further distinguish PCDLBCL, leg type from PCFCL.

Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines for Primary Cutaneous Lymphomas, a literature search was performed to obtain key literature on PCBCL published since the previous Guidelines update, using the following search terms: cutaneous diffuse large B-cell lymphoma, cutaneous follicle center lymphoma, and cutaneous marginal zone lymphoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[21]

The search results were narrowed by selecting studies in humans published in English. The data from key PubMed articles deemed as relevant to these guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Diagnosis

PCMZL are negative for BCL6 and CD10, but are often positive for CD20 and BCL2.[22] PCFCL is consistently BCL6-positive, whereas CD10 and BCL2 are expressed in only a few cases with a follicular growth pattern and the detection of *BCL2* rearrangement is generally associated with extracutaneous spread.[23-26]

PCDLBCL, leg type tumors express CD20, IRF4/MUM1, FOXP1, and BCL2; many cases express BCL6 and lack expression of CD10.[5,16,17,27-29] PCDLBCL, leg type also has a high incidence of *MYC* rearrangements and *MYC* rearrangements are not detected in PCFCL.[30] In addition, PCFCL is usually IRF4/MUM1-negative while PCDLBCL, leg type is usually IRF4/MUM1-positive and shows strong expression of FOXP1.[28,29] Assessment of FOXP1 expression is helpful to distinguish PCDLBCL, leg type from PCFCL since all cases of PCFCL are FOXP1-negative.[29] GEP-based algorithms and modified Hans immunohistochemical algorithm including CD10 and MUM1 have been shown to be useful to distinguish PCFCL from PCDLBCL, leg type with optimal diagnostic value without the need for BCL-6.[17,18]

The diagnosis of PCBCL is established by adequate biopsy of skin lesions. Multiple biopsies may be necessary to capture the pathologic variability of disease at diagnosis. Incisional, excisional, or punch biopsy is preferred to shave biopsy, as PCBCL have primarily dermal infiltrates, often deep, which are less well-sampled and can be missed by a shave biopsy. Review of the slides by a pathologist with expertise in the diagnosis of PCBCL is recommended. Adequate immunophenotyping of

the biopsy sample is essential for the diagnosis of the exact subtype of PCBCL. In addition, immunophenotyping is also useful to rule out cutaneous lymphoid hyperplasia (also known as pseudolymphoma or lymphocytoma cutis)[31-33] and in the differential diagnosis of intravascular large B-cell lymphoma, which often manifests in skin and is associated with a poor prognosis.[34]

The initial immunohistochemistry (IHC) panel should include CD20, CD3, CD5, CD10, BCL2, BCL6, and IRF4/MUM1. Under certain circumstances, evaluation of additional immunohistochemical markers such as Ki-67, CD43, CD21, CD23, cyclin D1, and kappa/lambda may be useful to further establish the lymphoma subtype. Additionally, assessment of surface IgM, IgD, and FOXP1 expression may also be helpful in distinguishing PCDLBCL, leg type from PCFCL.[28,29,35] Epstein-Barr virus (EBV)-positive mucocutaneous ulcer is also included as a new provisional entity in the updated WHO-EORTC classification and Epstein-Barr encoding region-in situ hybridization (EBER-ISH) may be useful under selected circumstances.[3]

The t(14;18) translocation on FISH analysis has been observed only in a small number of cases with PCFCL, and the detection of a t(14;18) translocation suggests the presence of systemic follicular lymphoma (FL).[25,36] Cytogenetics or FISH to detect t(14;18) may be useful if systemic FL is suspected. The feasibility of flow cytometric immunophenotyping of skin biopsies for the assessment of B-cell clonality has been reported, although it has not been widely used.[33] If adequate biopsy material is available, molecular analysis to detect Ig heavy chain gene rearrangement or flow cytometry could be useful to determine B-cell clonality.

Mantle cell lymphoma (MCL) is not a cutaneous lymphoma and finding it in the skin requires a careful search for extracutaneous disease. Clinical presentation on the leg and blastoid cytology along with high proliferative index and expression of BCL2, IRF4/MUM1, and IgM would often represent MCL with skin involvement.[37] The use of cyclin D1 may be useful to differentiate PCMZL (negative for CD5 and cyclin D1) from MCL (positive for CD5 and cyclin D1).

Workup

The absence of extracutaneous disease at diagnosis is part of the definition of PCBCL. The initial workup is geared toward evaluating extent of disease on the skin and seeking extracutaneous disease.[38]

The initial workup should include a complete physical examination, a comprehensive skin examination, complete blood count (CBC) with differential, comprehensive metabolic panel, and CT and/or PET/CT of the chest, abdomen, and pelvis. Peripheral blood flow cytometry will be useful in selected cases, if CBC demonstrates lymphocytosis. Imaging is effective in identifying systemic involvement in patients with indolent CBCL.[39] However, it can be omitted if clinically indicated in patients with low-grade indolent PCBCL.[40] PET/CT may have higher sensitivity in the detection of both local and distant metastases than CT.[41] However, this is not validated and the higher rates of false-positive findings can create confusion.

Bone marrow biopsy is essential for PCDLBCL, leg type, since this is an aggressive lymphoma that will probably require systemic treatment; however, it appears to have a more limited value in PCFCL and PCMZL, and may be considered only in selected patients.[38,40,42] Senff et al evaluated 275 patients with histologic features consistent with marginal zone lymphoma (MZL; n = 82) or follicle center lymphoma (FCL; n = 193) first presenting in the skin.[42] Bone marrow involvement was seen in approximately 11% of patients in the FCL group compared with 2% in the MZL group. Among patients with FCL, a positive bone marrow was associated with significantly worse prognosis compared with those with skin lesions only; the 5-year OS rate was 44% and 84%, respectively.[42]

The International Society of Cutaneous Lymphomas (ISCL) and the EORTC Task Force recommend that bone marrow biopsy be obtained for cutaneous lymphomas with intermediate to aggressive behaviors and should be considered for cutaneous lymphomas with indolent behavior and when there is any evidence of extracutaneous disease, as indicated by other staging assessments (eg, radiographic evidence or serologic clues such as elevated monoclonal or polyclonal Ig).[38]

The NCCN Guidelines recommend considering bone marrow biopsy for patients with unexplained cytopenias or if there is a clinical suspicion of PCDLBCL, leg type.

Treatment Options

Involved-site radiation therapy (ISRT) is very effective when used as initial therapy as well as for cutaneous relapses in most patients with indolent PCBCL.[43-47]

In a retrospective study of 34 patients with PCBCL treated with RT, 5-year relapse-free survival (RFS) rates ranged from 62% to 73% for PCFCL and PCMZL but were only 33% for patients with PCDLBCL, leg type.[44] The 5-year OS rate was 100% for PCFCL and PCMZL but was 67% for PCDLBCL, leg type. Senff et al evaluated the outcome of 153 patients with PCBCL (25 with PCMZL; 101 with PCFCL; and 27 with PCDLBCL) who were initially treated with RT with a curative intent.[45] Overall, 45% of patients had single lesions while localized or disseminated lesions were seen in 43% and 12% of patients, respectively. Complete response (CR) was obtained in 151 of 153 patients (99%). Relapse rates for PCMZL, PCFCL, and PCDLBCL, leg type were 60%, 29%, and 64%, and the 5-year disease-specific survival rates were 95%, 97%, and 59%, respectively. The PCFCLs presenting on the legs also had a higher relapse rate (63%) and a lower 5-year disease-specific survival (44%) compared with PCFCLs occurring at other sites (25% and 99%, respectively).[45]

In another retrospective study of 42 patients with biopsy-proven PCFCL and PCMZL, RT resulted in CR in all patients.[47] The 10-year RFS and OS rates were 71% and 87%, respectively, for the entire cohort, after a median follow-up of 9.5 years. The 5-year RFS rate was higher for patients with trunk lesions and single lesions (89% and 84%, respectively) compared to those with extra-trunk lesions and multiple lesions (67% and 57%, respectively). Low-dose ISRT (4 Gy in 2 fractions) is an effective treatment option for palliation of symptoms in patients with persistent (initial) lesions or recurrent symptomatic disease.[48] The results of a more recent retrospective study also showed that RT less than or equal to 12 Gy (4 Gy for relapsed disease) was equally effective as RT greater than 12 Gy in patients with indolent PCBCL (42 patients; 16 patients had PCFCL).[49]

ISRT and excision result in higher response rates compared to chemotherapy in patients with indolent histologies, but were generally used for those with more limited disease; therefore, a direct comparison cannot be made.[4,50-53] In a large retrospective analysis by the Italian Study Group for Cutaneous Lymphomas involving 467 patients with PCBCL, the CR rate and the 5- and 10-year OS rates for all patients with PCFCL and PCMZL who received first-line treatment (RT in 53%, with total dose of 35–45 Gy; chemotherapy in 25%, mainly with CHOP; surgery in 23%) were 92% to 95%, 96% to 97%, and 89% to 91%, respectively.[4] The relapse rate was 44% to 47% and extracutaneous spread was observed in 6% to 11% of patients. Relapse rate did not vary by the type of initial therapy. In patients with PCDLBCL, leg type, the CR rate and 5- and 10-year OS rates were 82%, 73%, and 47%, respectively. PCDLBCL, leg type was associated with higher relapse rates (55%) and higher incidences of extracutaneous spread (17%)—a higher relapse rate was

confirmed both for patients with single or regional lesions treated with RT and for patients with disseminated cutaneous involvement treated with chemotherapy.[4] In a retrospective analysis of 137 patients with PCMZL, initial treatment with surgical excision, RT, or a combination of both resulted in a CR rate of 88% (93% for patients with solitary or localized disease and 71% for those with multifocal lesions).[52] Although there were no significant differences in the rate of recurrences between the treatment modalities, surgery alone was associated with more recurrences at the initial site.

Rituximab monotherapy (intravenous[54-58] and intralesional[59-61]) has been shown to be effective for PCMZL and PCFCL. Intravenous rituximab may be more effective for patients with multiple lesions that cannot be managed effectively with local therapy.[54-58] In a retrospective analysis of 15 patients with indolent PCBCL, rituximab resulted in an overall response rate (ORR) of 87% (60% CR). The ORR was 100% for patients with PCFCL and 60% for PCMZL. With a median follow-up of 36 months, the median duration of response was 24 months.[57] In another series of 16 patients with PCBCL, 14 patients (88%) achieved a CR with rituximab monotherapy; 35% of these patients with CR eventually relapsed between 6 and 37 months.[58] In an observational multicenter study conducted by the Spanish Working Group on Cutaneous Lymphoma (17 patients with PCMZL and 18 patients with PCFCL), intralesional rituximab induced CR and partial response (PR) in 71% and 23% of patients, respectively, with a median DFS of 114 weeks.[59] The response rates were similar among patients with PCMZL and PCFCL. In a small series that evaluated the efficacy of intravenous and intralesional rituximab in treatment of patients with PCMZL and PCFCL, although intralesional rituximab resulted in response rates similar to that of intravenous rituximab, within a 12-month follow-up period, relapses were more frequent among patients treated with intralesional rituximab.[62]

Several case reports have shown the effectiveness of skin-directed therapy (steroids, imiquimod, and nitrogen mustard or bexarotene gel) for patients with multifocal lesions.[63-67] Interlesional steroids have also been used in the management of PCFCL or PCMZL, although only limited data are available.[50,68,69] Systemic therapy (rituximab monotherapy or combination chemoimmunotherapy) is often more appropriate for those with generalized disease (skin only; T3) in patients with PCFCL or PCMZL.[54-58,63,70-72]

Because there are no data from randomized clinical trials, the treatment recommendations included in the NCCN Guidelines are derived from the management practices of patients with PCBCL at NCCN Member Institutions based on the limited data from retrospective analyses and studies involving a small cohort of patients.

Primary Cutaneous Marginal Zone Lymphoma and Primary Cutaneous Follicle Center Cell Lymphoma

While PCMZL and PCFCL respond to initial therapy, disease relapse is common in the majority of patients with regional or generalized disease, regardless of type of initial treatment. However, relapses are generally confined to the skin in which case survival does not appear to be affected. In a retrospective analysis that assessed the efficacy of various treatment modalities (55 patients; majority of patients had indolent PCBCL; 25 patients with PCMZL and 24 patients with PCFCL), the type of treatment modality (skin-directed vs. definitive RT with or without systemic therapy) did not affect the time to first recurrence among patients with T1 and T2/T3 lesions.[73] The rates of recurrence were higher for T2/T3 lesions compared to T1 lesions (58% and 31%, respectively). The time to first recurrence for T1 lesions was 33% and 29%, respectively, for patients with PCMZL and PCFCL; however, the difference was not significant. Among patients with T2/T3 lesions, there was a non-significant trend toward

higher rate of recurrence for PCMZL than PCFCL (73% and 38%, respectively).

Additional imaging studies during the course of treatment are not needed after negative initial staging for systemic involvement and clinical follow-up without routine imaging may be appropriate for patients with PCMZL.[39] PET/CT (preferred) or CT with contrast may be repeated at the end of treatment for assessment of response and can be repeated if there is clinical suspicion of progressive disease.

Solitary or Regional Lesions (T1–T2)

Local ISRT (24–30 Gy) is a preferred initial treatment option. Excision or skin-directed therapy or intralesional steroids may be used for selected patients. Observation is an option when RT or excision is neither desired nor feasible (eg, lesions on the scalp where hair loss is a major concern).

Observation is also recommended for patients with disease responding to initial therapy, and those with refractory disease should be treated as described for generalized disease below.

Low-dose RT (4 Gy) may be adequate for relapsed or refractory disease.[48,49,69] Patients with regional relapse should be treated with an alternate initial treatment option and those with generalized disease relapse confined to the skin should receive treatment options recommended for generalized disease at presentation.

Patients with extracutaneous relapse or those with cutaneous relapse that is not responding to any of the initial treatment options should be treated according to the FL or nodal MZL as outlined in the NCCN Guidelines for B-Cell Lymphomas.

Generalized Disease (skin only; T3)

Skin-directed therapy, local ISRT (24–30 Gy) for palliation of symptoms, intralesional steroids, or rituximab are included as options for initial treatment. Observation is appropriate in asymptomatic patients. In patients with very extensive or symptomatic disease, other combination chemotherapy regimens recommended for FL or nodal MZL may be used.[70-72]

Observation is recommended for patients with disease responding to initial therapy, and those with refractory disease should be treated with an alternate initial treatment option.

Patients with relapse localized to skin should be treated with an alternate initial treatment option. Patients with extracutaneous relapse or those with cutaneous relapse that is not responding to any of the initial treatment options should be treated as described for extracutaneous disease.

Extracutaneous Disease

Extracutaneous disease should be managed according to FL or nodal MZL as outlined in the NCCN Guidelines for B-Cell Lymphomas.[70-72]

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

RT alone is less effective in patients with PCDLBCL, leg type. While these lesions do respond to RT, remissions are often short-lived and higher rates of dissemination to extracutaneous sites may occur.

The potential utility of chemoimmunotherapy for the treatment of PCDLBCL, leg type has been described only in retrospective analyses and case reports.[74-79] In a retrospective multicenter study from the French Study Group on 60 patients with PCDLBCL, leg type, patients treated with anthracycline-based chemoimmunotherapy had a more favorable short-term outcome, although no particular therapy (RT or multiagent chemotherapy with or without rituximab) was significantly associated with improved survival outcomes.[74] Among 12 patients treated with anthracycline-based chemoimmunotherapy, the CR rate was 92%

compared to 62% for patients who received other therapies. The 2-year OS rate for these two groups was 81% and 59%, respectively.

Multiagent chemoimmunotherapy regimens have been associated with excellent outcomes.[77-79] In a report from the French Study Group (115 patients), the 3- and 5-year survival rates were 80% and 74%, respectively, for patients who received multiagent chemoimmunotherapy compared to 48% and 38%, respectively, for patients who received less-intensive therapies.[77] In a more recent retrospective analysis involving 28 patients with PCDLBCL, leg type treated in a single center, R-CHOP with ISRT resulted in significantly longer median PFS compared to R-CHOP without ISRT as front-line therapy (58 vs. 14 months; P = .04).[79]

PCDLBCL, leg type has a poorer prognosis than other types of PCBCL and is generally treated with more aggressive chemoimmunotherapy regimens used for systemic DLBCL as outlined in the NCCN Guidelines for B-Cell Lymphomas.

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Mycosis Fungoides and Sézary Syndrome

Overview

Cutaneous T-cell lymphomas (CTCL) are a group of non-Hodgkin lymphomas (NHL) that primarily present in the skin, and at times progress to involve lymph nodes, blood, and visceral organs.[1-3]

Mycosis fungoides (MF) is the most common subtype and is usually associated with an indolent clinical course with 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 erythrodermic, leukemic variant characterized by significant blood involvement, erythroderma, and often lymphadenopathy.[4-6] MF is caused by the malignant transformation of skin-resident effector memory T cells while SS is thought to arise from thymic memory T cells, supporting the contention that SS is a process distinct from MF.[5] Cases presenting as an overlap of these two conditions also exist.

Folliculotropic MF (FMF), hypopigmented MF, granulomatous slack skin, and pagetoid reticulosis are recognized as distinct clinicopathologic variants of MF in the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification.[2] FMF and LCT are histologic features that can occur irrespective of stage, but the incidence of LCT is higher in patients with advanced-stage disease.[7-9] Expert dermatopathology and/or hematopathology review is needed to confirm the diagnosis. This is especially true for the less common variants of the disease, which can be difficult to distinguish from other lymphoproliferative disorders. Genomic studies have demonstrated further biologic diversity within MF.[4,10]

Due to the rarity and diversity of the condition and the need for an individualized approach, the NCCN Guidelines Panel recommends that patients diagnosed with MF and SS be treated at specialized centers with expertise in the management of this disease.[11]

Literature Search Criteria

Prior to the update of this version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Primary Cutaneous Lymphomas, an electronic search of the PubMed database was performed to obtain key literature on MF and SS published since the previous Guidelines update using the following search terms: cutaneous T-cell lymphomas, mycosis fungoides, and Sézary syndrome. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[12]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Randomized Controlled Trial; Phase II; Clinical Trial, Phase III; Guideline; Meta Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles deemed as relevant to these guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Staging

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 EORTC are outlined on MFSS-3 and MFSS-4.[13]

The extent of skin involvement is based on the percentage of body surface area (BSA) where the patient's palm (without digits) is equivalent to 0.5% BSA and the palm with all five digits is approximately 1% BSA. In the revised staging system, T1 disease (limited skin involvement) is defined as patches, papules, and/or plaques covering less than 10% BSA. T2 (skin-only disease) is defined as patches, papules, and/or plaques covering 10% or greater BSA. Patch diagnosis is noted as T1a or T2a and plaque diagnosis is noted as T1b or T2b. T3 (tumor-stage disease) is defined by the presence of one or more tumors (≥1 cm in diameter with nodular quality). T4 (erythrodermic disease) is defined as confluence of erythema covering 80% or greater BSA. However, this criterion of 80% is subjective and the BSA can fluctuate in patients with erythrodermic MF or SS. Thus, other features including keratoderma, ectropion, or leg edema should also be evaluated in patients with erythrodermic MF or SS.

Lymph node biopsy for staging is recommended only for clinically abnormal nodes (>1.5 cm in longest diameter). Lymphadenopathy can be clinically reactive or dermatopathic; thus, not all enlarged lymph nodes are sampled. The designation "Nx" may be used for abnormal lymph nodes without histologic evaluation. The designation "Mx" can be used for presence of abnormal visceral sites without histologic evaluation. Visceral disease with the involvement of an organ (eg, spleen, liver) other than the skin, nodes, or blood should be documented using imaging studies.

Blood involvement is classified into three groups: B0, B1, and B2 based on the number of immunophenotypically abnormal T cells in the blood (MFSS-3). Patients with lymphopenia (defined as <1000 absolute lymphocytes) may potentially have an underestimation of aberrant lymphocyte burden if assessed only by the absolute number and not also by the percentage of immunophenotypically abnormal lymphocytes.[13] B1 or B2 is best characterized by both flow cytometry and the presence of clonally related neoplastic T cells as in the skin by *TCR* gene rearrangement analysis. A diagnosis of SS requires B2 level of blood involvement.

Prognosis

Age at presentation, overall stage, extent and type of skin involvement (T classification), presence of extracutaneous disease, extent of peripheral blood involvement (as defined by flow cytometric measurements of Sézary cell counts), elevated lactate dehydrogenase (LDH), and presence of LCT have been identified as the most significant factors for disease progression and/or survival in patients with MF.[14-20] In a retrospective cohort study of 525 patients with MF or SS, patient age, T classification, and presence of extracutaneous disease retained independent prognostic value in a multivariate analysis.[15] The risk of disease progression, development of extracutaneous disease, or death due to MF correlated with initial T classification. Limited patch or plaque disease has an excellent prognosis compared to patients with widespread plaque-type or tumor-type skin disease or erythrodermic skin involvement, and extracutaneous disease is associated with a poor prognosis.[17,18]

LCT is also an independent prognostic factor of shorter overall survival (OS) in patients with SS. In an analysis of 117 patients with SS, LCT was present in 6% of patients at the time of diagnosis and the median OS was 35 months for those with LCT compared to 80 months for those without LCT.[21] The presence of ulceration, decreased levels of CD8+ cells in peripheral blood, maximum total BSA, and peak LDH were predictors for LCT in patients with SS.[22]

In the Cutaneous Lymphoma International Consortium (CLIC) study that evaluated the relevance of prognostic markers on OS in 1275 patients with advanced-stage MF and SS, stage IV disease, aged 60 years, LCT and LDH levels were identified as independent prognostic markers that could be used together in a prognostic model to identify three risk groups with

significantly different survival outcomes.[20] The 5-year survival rates were 68%, 44%, and 28%, respectively, for low-risk, intermediate-risk, and high-risk groups. A prospective international study by CLIC (Prospective Cutaneous Lymphoma International Prognostic Index [PROCLIPI] international study) is underway to identify any new prognostic markers and validate the refined prognostic index model to optimize the risk-stratified approach for the treatment of patients with MF or SS.[23-25]

Diagnosis

Biopsy of suspicious skin sites along with immunohistochemistry (IHC) of biopsy specimen 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 or incisional biopsy is preferred over core needle biopsy. Fine-needle aspiration (FNA) alone is not sufficient for the initial diagnosis. Bone marrow biopsy is not required for disease staging, but may be helpful in those with an unexplained hematologic abnormality.

MF and SS cells are typically characterized by the following immunophenotype: CD2+, CD3+, CD5+, CD4+, CD8-, CCR4+, TCR-beta+, and CD45RO+ and they lack certain T-cell markers, CD7 and CD26.[26] However, there are variants of MF that are CD8+ (especially the hypopigmented variant) or CD4/CD8 dual negative (in those with LCT and hypopigmented variant), although rare.[27-29] The IHC panel of skin biopsy should include CD2, CD3, CD4, CD5, CD7, CD8, CD20, and CD30.

Additional immunohistochemical markers such as CD25, CD56, TIA1, granzyme B, TCR beta, and TCR delta may be useful in selected circumstances. The loss of CCR4 expression and emergence of CCR4 genomic alterations might be associated with resistance to mogamulizumab.[30] IHC for CCR4 may be useful to confirm resistance to mogamulizumab in patients with progressive or refractory disease while on treatment with mogamulizumab.

Primary cutaneous follicular helper T-cell (TFH) lymphoma is a recently described variant of peripheral T-cell lymphoma (PTCL)-not otherwise specified. This variant usually presents as a sudden onset of multiple plaques and nodules characterized by the expression TFH markers such as CXCL13, ICOS, and programmed cell death protein 1 (PD-1).[31,32] Identification of these markers along with other clinical and histopathologic features would be useful to distinguish MFSS from CTCL of TFH origin.[33,34]

Molecular analysis to detect clonal *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.[35,36] However, results showing clonal *TCR* gene rearrangements should not be interpreted as the sole and defining test for malignancy since clonal *TCR* rearrangements can at times be seen in non-malignant conditions or may not be demonstrated in all cases of MF and SS. *TCR* rearrangement analysis by high throughput sequencing (or next-generation sequencing) is a more sensitive and specific test of clonality that can identify the clones by the genetic sequence of the *TCR*.[37,38] 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, adult T-cell leukemia/lymphoma [ATLL]). Flow cytometry allows for the assessment and quantitation of an expanded population of CD4+ cells with abnormal immunophenotype

(CD4+/CD26- or CD4+/CD7- or other aberrantly expressed phenotype).[39] Assessment of TRBC1 expression by flow cytometry is also useful for the detection of clonality, especially in cases where CD7 or CD26 are not lost.[40-42] Human T-cell lymphotrophic virus (HTLV)-1 status, assessed either by HTLV-1 serology or other methods, may be useful in populations at risk to exclude the diagnosis of ATLL (which is usually HTLV-1-positive).

Workup

The initial workup of patients diagnosed with MF or SS involves a history and complete skin examination (assessment of the extent of disease [ie, percent of BSA] and type of skin lesion [eg, patch/plaque, tumor, erythroderma]), palpation of peripheral lymph nodes, and palpation for organomegaly.[13]

Laboratory studies should include a complete blood count (CBC), Sézary flow cytometric study (optional for T1 disease), comprehensive metabolic panel, and assessment of LDH levels. Analysis of clonal *TCR* gene arrangement of peripheral blood lymphocytes is recommended if blood involvement is suspected.

CT with contrast of the chest, abdomen, and pelvis or integrated whole-body PET/CT scan is recommended for patients with T3 or T4 disease and should be considered for patients with T2a (patch disease with ≥10% BSA), T2b (widespread plaque-type skin disease), FMF or LCT, palpable adenopathy, or abnormal laboratory studies. In an analysis of 375 patients with stage T1/T2 MF enrolled in the PROCLIPI international study, the presence of plaques was associated with a significant increase in the identification of radiologically enlarged or involved lymph nodes in patients with early-stage MF.[24]

A CT scan of the neck may be useful in some circumstances. Integrated PET/CT was found to be more sensitive for the detection of lymph node involvement than CT alone and can help direct biopsies.[43] PET scan may also be preferred in patients with extranodal disease that may be inadequately imaged by CT. Many skin-directed and systemic therapies are contraindicated or are of unknown safety in pregnancy. Therefore, pregnancy testing is recommended for individuals of childbearing age.

Treatment Considerations

While MF and SS are treatable, they are not curable with conventional systemic therapy and the symptoms of the disease have significant impact on the 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]

The optimal treatment for any patient at any given time should be individualized based on overall goals of therapy (improve the 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 the treatment of patients with MF and SS. Most of the 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 on to treatment for refractory disease. This supports the 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. Disease relapse (with the same

stage) after discontinuation of therapy often responds well to re-treatment with previous therapy.

Selection of Therapy Based on Clinical and Pathologic Features

Skin-directed therapies (topical therapy, phototherapy, radiation therapy [RT], or total skin electronic beam therapy [TSEBT]) that can provide disease control without major cumulative toxicities are recommended for patients with early-stage disease and limited skin involvement (stage IA or stage IB–IIA). Stage IA MF most often can be treated with skin-directed therapies (alone or in combination with other skin-directed therapies). While 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). However, stage IIB patients with single or few T3 lesions can be treated with external beam RT (EBRT) with further delay of systemic therapy and TSEBT may be used for patients with stage IB–IIB disease, with excellent response expected. In the PROCLIPI study, the use of systemic therapy was significantly associated with higher clinical stage, presence of plaques, and FMF.[25] In a multivariate analysis, the presence of plaques and FMF were significantly associated with the use of systemic therapy and skin-directed therapy was superior to systemic therapy even in patients with these disease characteristics. The overall response rate (ORR) to first-line skin-directed therapy was 73% compared to 57% for systemic therapy.

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. 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 the section *Systemic Therapies*. Therefore, a clinical trial should be considered when appropriate and available.

Data from clinical trials that have evaluated various treatment strategies (skin-directed therapy, systemic therapy, and combination therapies) are discussed below.

Skin-Directed Therapies

Topical therapy with corticosteroids, mechlorethamine (nitrogen mustard), topical retinoids or topical imiquimod, or RT are indicated for patients with localized disease. Phototherapy and TSEBT are indicated for patients with widespread skin involvement. Topical retinoids are not recommended for generalized skin involvement because these treatments can cause substantial irritation.

Topical Corticosteroids

Topical corticosteroids are effective for early-stage MF (especially for the treatment of patch-stage MF), resulting in measurable improvement in BSA involvement and high ORR of 94% (63% complete response [CR]; 13% partial response [PR]) and 82% (25% CR; 57% PR) in patients with stage T1 and T2 disease, respectively.[44-46]

Optimal use of topical steroids is often dependent on lesion type and disease site. This is best done in consultation with a dermatologist or physician with experience in the use of topical steroids. In general, high-potency steroids may be less well-tolerated in intertriginous body areas or other areas such as the face. Long-term use of a topical steroid may lead to skin atrophy or striae formation and the risk becomes greater

with increased potency of the steroid. Moreover, high-potency steroids used on large skin surfaces may lead to systemic absorption.

Topical Mechlorethamine (nitrogen mustard)

Topical mechlorethamine has been used for the management of MF for many decades resulting in an ORR of 83% (50% CR). Patients with T1 disease had a higher ORR (93% vs. 72%), CR rate (65% vs. 34%), longer median OS (21 vs. 15 months), and higher 5-year OS rate (97% vs. 72%) than those with T2 disease.[47] The efficacy was similar for aqueous and ointment preparations, although the ointment was associated with reduced hypersensitivity reactions.

A topical gel formulation of mechlorethamine was approved by the U.S. Food and Drug Administration (FDA) in 2013 based on the results of a multicenter, randomized, phase II trial that demonstrated the non-inferiority of topical gel formulation compared to the compounded ointment formulation for the treatment of stage IA or IIA MF in patients (n = 260) who had not been treated with topical mechlorethamine within 2 years of study enrollment and had not received prior therapy with topical mechlorethamine.[48] Response rate based on Composite Assessment of Index Lesion Severity was 59% for the topical gel formulation compared to 48% for the ointment formulation. No study treatment-related serious adverse events were reported, and no systemic absorption was detected.

Topical mechlorethamine has no significant systemic absorption, and can be used alone or in combination with other skin directed therapies, in particular topical steroids. The use of topical gel formulation of mechlorethamine can be complicated by dermatitis and can result in skin irritation when used on the face and intertriginous body areas. Initiation at less than daily use can be useful to determine tolerability. Topical steroids can be considered as needed to alleviate skin reactions from topical gel formulation. If used in combination with phototherapy, topical mechlorethamine gel should be applied after exposure to ultraviolet light. Topical mechlorethamine is prohibited in the genital skin.

Topical Retinoids

Bexarotene gel is the only FDA-approved synthetic topical retinoid for the treatment of MF and SS. In the phase I–II trial of 67 patients with early-stage MF, the ORR was 63% (21% CR) and the estimated median response duration was 99 weeks.[49] Response rates were higher among the patients who had had no prior therapy compared with those who had received prior topical therapies (75% vs. 67%). In the phase III multicenter study of 50 patients with early-stage refractory MF, the ORR was 44% (8% CR).[50]

Tazarotene 0.1% topical gel/cream was reported to be a well-tolerated and active adjuvant therapy by clinical and histologic assessments in a small series of patients with early patch or plaque MF lesions (stable or refractory to therapy).[51,52]

Topical Imiquimod

Imiquimod has also demonstrated activity in a small number of patients with early-stage MF refractory to other therapies.[53-56] Topical imiquimod can be considered (often in consultation with a dermatologist or physician with experience in its safety and use) for areas with few patches/plaques/small tumors that are recalcitrant to treatment or on sun-damaged skin such as forearms, scalp, and face.

Topical Carmustine

Topical carmustine is an effective treatment for patch/plaque early-stage MF resulting in high response rates of 92% and 64% in patients with T1 and T2 disease, respectively, at 36 months.[57,58] Topical carmustine is included with a category 2B recommendation.

Topical Calcineurin Inhibitors

In a phase II multicenter study of 39 patients with stage IA–IIA MF, topical pimecrolimus (1% cream) resulted in an ORR of 56% and was well tolerated (grade 1 transient mild burning or pruritus was the most common adverse event reported in 21% of patients).[59] Topical calcineurin inhibitors can be considered for patients with early-stage MF as a steroid-sparing treatment for early-stage skin lesions in the perioral and periorbital areas.

Radiation Therapy

MF is extremely radiosensitive and unilesional or stage IA MF may be treated effectively with local RT alone (without adjuvant therapy), resulting in an ORR of 97% to 100%.[60,61] Recent studies have shown that low-dose involved-field RT (IFRT) also results in high response rates without any toxicity in patients with MF.[61-63] In a study that included 31 patients with MF, low-dose RT (4 Gy in 2 fractions) resulted in a CR rate of only 30%, whereas increasing the dose to 8 Gy in two fractions yielded a CR rate of 92%.[62] Patients with disease not responding to low-dose RT were re-treated with 20 Gy in eight fractions. In a large series of 58 patients treated with 8 Gy in a single fraction, the CR rate was 94% for individual lesions after a median follow-up of 41 months.[63]

Optimal management of individual plaque and tumor lesions is with EBRT (8–12 Gy, 8 Gy may be given in a single-fraction; 24–30 Gy is recommended for more durable duration of response or for unilesional presentation).[61,63]

Total Skin Electron Beam Therapy

TSEBT (conventional dose [30–36 Gy] or low dose [<30 Gy]) either alone or in combination with adjuvant therapy has been shown to be effective for the treatment of early-stage MF.[64-67] TSEBT at a conventional dose of greater than or equal to 30 Gy was associated with a non-significant trend towards better clinical benefit and was also associated with better outcomes in patients with T2 disease compared to those with T3 disease.[66,67] In a retrospective study that evaluated low-dose TSEBT in 102 patients with T2 to T4 disease (excluding those with extracutaneous disease), TSEBT doses of 10 Gy to less than 20 Gy and 20 Gy to less than 30 Gy resulted in ORRs of 98% and 97%, respectively, which were comparable to the ORRs achieved with standard-dose TSEBT (≥30 Gy).[65] The OS and progression-free survival (PFS) rates were not significantly different by dose groups and were comparable to that of standard-dose TSEBT (≥30 Gy).

Lower-dose TSEBT (10–12 Gy over a period of 2–3 weeks) is shown to be sufficiently active and may also be associated with fewer short-term complications and better ability to re-treat progressive disease (PD) or cutaneous relapses.[68-73] A pooled analysis of three phase II clinical trials that evaluated low-dose TSEBT (12 Gy; 1 Gy per fraction over 3 weeks) in 33 patients with MF reported an ORR of 88% (including 9 patients with a CR).[69] The median time to response and median duration of clinical benefit were 8 weeks and 71 weeks. In a cohort of 103 patients with MF treated with low-dose TSEBT (12 Gy in 8 fractions for 2 weeks; the majority of patients had stage IB or IIB disease), after a median follow-up of 21 months, the ORR was 87% (18% CR and 69% PR) and the median PFS was 13 months.[72] The median PFS was significantly longer for patients with stage IB disease (27 months) compared to 11 months and 10 months, respectively, for those with stage IIB or stage III disease. Low-dose TSEBT (12 Gy in 6–7 fractions) was also associated with favorable outcomes and significantly fewer grade 2 acute toxicities compared with conventional-dose TSEBT (30 Gy).[71,74,75] Further studies are warranted to confirm these findings and the use of low-dose TSEBT in combined modality regimens.

The recommended dose range for TSEBT is 12–36 Gy (generally 4–6 Gy per week). Lower total dose is associated with fewer short-term complications and better ability to re-treat relapsed disease. It is common

practice to follow TSEBT with systemic therapies such as interferon (IFN) or bexarotene to maintain response, for patients with stage IB–IIA disease with higher skin disease burden. Adjuvant systemic therapy can be considered to improve response rate and PFS in patients with stage IIB (tumor stage) disease receiving TSEBT.[76,77]

TSEBT may not be well tolerated in patients with erythrodermic disease and should be used with caution. In these patients, TSEBT may be used with lower doses and slower fractionation. Antibiotic therapy should be considered since patients with erythrodermic disease are at increased risk of developing secondary infections.

Phototherapy

Ultraviolet B (UVB including narrowband-UVB)[78-82] and psoralen plus ultraviolet A1 (PUVA/UVA-1)[83-86] are effective treatment options for patients with early-stage MF. Narrowband UVB is the most common phototherapy approach and less skin damaging than PUVA/UVA-1. While some retrospective studies have reported that PUVA results in better responses and improved disease-free survival (DFS),[87-89] others have reported that UVB is as effective as PUVA for the treatment of early-stage MF.[90,91] However, these modalities have not been compared in randomized clinical trials.

PUVA may be associated with a small increase in the risk of developing basal cell carcinoma (BCC), while there was no significant association between the use of narrowband UVB and the risk of developing BCC, squamous cell carcinoma (SCC), or melanoma.[92] More recent reports also confirmed that the use of UV radiation (including UVA and narrowband UVB) was not associated with an increased risk of developing BCC, SCC, or melanoma except in patients receiving immunosuppressive therapy.[93,94]

It may be more beneficial to start with narrowband UVB than PUVA in patients with early patch-stage or thin-plaque disease, since narrowband UVB has less skin toxicity than broadband UVB and PUVA.[92,95,96] Phototherapy should be used with caution in patients with a history of immunosuppressive medication due to the increased risk of UV radiation-associated skin malignancies in this patient population. The risk and benefits of phototherapy should be considered in patients with a history of BCC, SCC, or melanoma. There are limited safety data for the use of phototherapy in combination with vorinostat or romidepsin.

Systemic Therapies

The selection of systemic therapy 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, systemic therapy regimens that can be tolerated for longer durations of therapy with lower rates of cumulative toxicity, less immunosuppression, and/or higher efficacy are used in earlier lines of therapy. Regimens with lower side-effect profiles and an absence of cumulative toxicity are often given in an ongoing or maintenance fashion to improve and maintain disease control and quality of life. In patients requiring chemotherapy, single agents are preferred over combination chemotherapy, due to the higher toxicity profiles associated with multiagent regimens and the short-lived responses seen with time-limited combination chemotherapy.

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, romidepsin and denileukin diftitox are approved by the FDA for the treatment of MF and SS. The efficacy of brentuximab vedotin and mogamulizumab compared to standard therapy

has been demonstrated in phase III randomized trials (ALCANZA and MAVORIC, respectively).[97-99] The safety and efficacy of reformulated version of denileukin diftitox was demonstrated in study 302.[100,101] Bexarotene,[102,103] vorinostat,[104-106] romidepsin,[107-109] and other systemic therapies such as pralatrexate,[110-112] alemtuzumab,[113-118] and pembrolizumab[119] have been evaluated only in phase II studies. IFNs (alfa and gamma) and methotrexate also offer clinical benefit but have not been evaluated in phase II studies in the era of modern staging of MF and SS.[120-122] Peginterferon alfa-2a is the only IFN available for clinical use in the United States and it may be substituted for other IFN preparations.[123-125]

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.[126-128] ECP may be a more appropriate systemic therapy for patients with some level of blood involvement (B1 or B2).

Gemcitabine[129-136] and pegylated liposomal doxorubicin[136-141] also have substantial activity in patients with advanced MF and SS. Multiagent chemotherapy regimens used for the treatment of systemic PTCLs have activity but are associated with greater toxicity and a potentially higher risk of death when used in earlier lines of treatment.[142,143] Therefore, multiagent chemotherapy regimens are generally reserved only for refractory disease to multiple prior therapies or 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 are discussed below. The data for systemic therapy agents, particularly those studied in larger prospective phase II and III studies, are also summarized in Table 1.

Systemic Retinoids

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.[102,103] In phase II–III studies, oral bexarotene (≥300 mg/m^2) was well tolerated, resulting in an ORR of 45% to 67% in patients with early-stage and advanced-stage disease.[102,103] Given the favorable tolerability profile without significant cumulative toxicity, we consider 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.[144-147] It is important to note that bexarotene is associated with hypertriglyceridemia and central hypothyroidism, which necessitates laboratory monitoring for triglycerides, and free thyroxine (T4), often requiring additional management.

Retinoic-acid receptor (RAR) agonists such as acitretin and isotretinoin (13-cis-retinoic acid) have also been shown to be effective for the treatment of early-stage MF.[148-150] In a small cohort of 35 patients with early-stage MF, acitretin and isotretinoin resulted in ORRs of 64% and 80%, respectively (although the CR rates were low at 4% and 8%, respectively).[149]

Brentuximab Vedotin

In the ALCANZA trial, brentuximab vedotin, an anti-CD30 antibody drug conjugate, was more effective than methotrexate or bexarotene in patients with previously treated MF (≥ stage IB).[97] The final analysis confirmed that brentuximab vedotin resulted in significantly improved ORR lasting for at least 4 months (ORR4; 55% vs.13%), median PFS (17 vs. 4 months), and patient-reported symptom burden compared to methotrexate or bexarotene in patients with CD30-positive MF.[98] Peripheral neuropathy was the most common adverse event reported in 44 (69%) patients. At the

median follow-up of 46 months, 86% (38 of 44) of patients had complete resolution or improvement to grades 1 and 2.

In the ALCANZA trial, CD30 positivity was defined as CD30 expression in ≥10% of total lymphoid cells in at least 1 skin biopsy (43% of patients had at least 1 sample with CD30 <10%).[97] The results of an exploratory analysis showed that brentuximab vedotin resulted in higher ORR4 and improved PFS in patients with ≥10% CD30 expression, regardless of LCT status.[151] The ORR4 (41% vs. 10% for <10% $CD30_{min}$ expression; 57% vs. 10% for ≥10% $CD30_{min}$ expression) and median PFS (17 months vs. 2 months for <10% $CD30_{min}$ expression; 16 months vs. 4 months for ≥10% $CD30_{min}$ expression) were significantly higher for brentuximab vedotin compared to vorinostat across all CD30 expression levels.

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.[152,153] Lesions with less than 5% CD30 expression had a lower likelihood of global response than those with greater than or equal to 5% CD30 expression ($P < .005$), but responses are still seen in those with CD30 positivity of greater than or equal to 1% or non-detectable CD30 by IHC using light microscopy.[152,153] While 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 in this setting. Real world cohort studies have also reported favorable outcomes with brentuximab vedotin in patients with previously treated MF and SS and variable CD30 positivity.[154,155]

Brentuximab vedotin is a more effective treatment option than methotrexate or bexarotene for patients with CD30-positive MF but carries greater risk, particularly a cumulative risk of peripheral neuropathy.[156] Patients with SS were excluded from the ALCANZA trial and the efficacy of brentuximab vedotin in patients with SS in the setting of refractory disease or low CD30 skin expression has only been demonstrated in a small case series of 13 patients.[157]

Mogamulizumab

In the MAVORIC trial, mogamulizumab, a humanized anti-CCR4 monoclonal antibody, was more effective than vorinostat in patients with previously treated MF (≥ stage IB) and SS. Mogamulizumab resulted in 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 those with MF (37% vs. 21%).[99] Patients with LCT at study entry were excluded from this trial. In a post hoc analysis, the number of prior therapies did not impact the ORR, PFS, and duration of response observed with mogamulizumab.[158] Among the 186 patients randomly assigned to vorinostat, 136 patients (109 patients with disease progression and 27 patients after intolerable toxicity) crossed over to mogamulizumab. The ORR was 31% for the 133 patients who crossed over from vorinostat to mogamulizumab and subsequently received mogamulizumab. The most common adverse events associated with mogamulizumab were mostly grade 1–2 and manageable (infusion-related reactions [37%], skin eruptions [25%], and diarrhea [14%]). Pyrexia (4%) and cellulitis (3%) were the most common grade 3 adverse events in the mogamulizumab group. Patients with the greatest symptom burden and functional impairment derived the most benefit from mogamulizumab in terms of quality of life.[159]

The clinical benefit with mogamulizumab was higher in patients with stage III or stage IV disease, especially in patients with B1 and B2 blood involvement.[99,160,161] In the post-hoc subgroup analysis by clinical stage, the ORRs for mogamulizumab were 23% and 36%, respectively, for patients with stage III or stage IV disease compared to 19% and 16%, respectively, for patients with stage IB/IIA disease or stage IIB disease.[99] Mogamulizumab also resulted in higher ORR than vorinostat across all

disease compartments. The compartment-specific ORRs for mogamulizumab were 42%, 68%, and 17%, respectively, for skin, blood involvement, and lymph nodes. The corresponding ORRs for vorinostat were 16%, 19%, and 4%, respectively. The overall disease control rate was 79% (76% for MF and 82% for SS) and improved with long-term exposure to mogamulizumab.[162] This trial, however, was not powered to detect OS differences between the two groups within the defined follow-up period.

The post-hoc analyses that evaluated the efficacy of mogamulizumab based on blood tumor burden showed that blood involvement was associated with improved ORRs, PFS, and time to next treatment (TTNT) for patients treated with mogamulizumab.[160,161] The ORRs were 26% and 37%, respectively, for patients with B1 and B2 blood involvement compared to 16% for those with B0 blood involvement.[160] The median PFS was 11 months and 8 months, respectively, for patients with B2 and B1 blood involvement compared to 5 months for those with B0 blood involvement.[161] The TTNT was 20 months for those with B2 blood involvement compared to 12 months and 7 months, respectively, for those with B1 and B0 blood involvement.[161] Mogamulizumab also was associated with sustained reductions seen in CD4+ CD26- cell counts and CD4:CD8 ratios in patients for all B classes of blood involvement.

A drug-induced skin eruption that has variable clinical and pathologic features (and can mimic CTCL) was the most frequent adverse event leading to treatment discontinuation in the MAVORIC trial.[99,163-166] Mogamulizumab-associated skin rash has also been identified as a potential marker for tumor response.[167] Skin biopsy (with adequate immunohistochemical stains and clonality assessment) is recommended to rule out disease progression in patients experiencing drug-induced skin eruptions or mogamulizumab-associated skin rash.[165,168]

Histone Deacetylase Inhibitors

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%.[105] A *post-hoc* subset analysis of patients who experienced clinical benefit with greater than or equal to 2 years of vorinostat therapy in the phase IIB study provided some evidence for the long-term safety and efficacy of vorinostat in patients with heavily pretreated MF and SS.[106] While cumulative toxicities were rare with vorinostat, patients need to be monitored for gastrointestinal toxicity, including nausea, diarrhea, and resultant dehydration, which could be more detrimental for older patients.

Romidepsin has demonstrated clinical activity across all disease compartments.[107-109] The median duration of response is 13 to 15 months for patients with disease responding to romidepsin.[107,108] Importantly, romidepsin was associated with a high rate of reduction in pruritus score irrespective of clinical objective response. The compartment-specific ORRs were 40%, 35%, 32%, and 27%, respectively, for skin involvement, erythroderma, blood involvement, and lymphadenopathy.[109] It is important to initially monitor for QTc prolongation when administering romidepsin, particularly with the concomitant use of antiemetics that also prolong QTc. Romidepsin is included as a preferred regimen for patients with SS with high Sézary cell burden.

Denileukin Diftitox

Denileukin diftitox (a recombinant human interleukin-2 diphtheria toxin fusion protein), initially approved for relapsed/refractory CTCL,[169,170] was withdrawn from the market in 2014 due to manufacturing difficulties. A reformulated version of denileukin diftitox was evaluated in Study 302 for patients with relapsed or refractory MF and SS. LCT-MF was not an exclusion criteria but no patients with LCT-MF were enrolled in the study. CD25-positiity was defined as detectable CD25 in ≥20% of total lymphoid cells in biopsy specimen by IHC.

The primary efficacy analysis included 69 patients with MF (stage IA to stage IIIB). The majority of the patients had stage IB-IIA (n =25) or stage IIB (n = 24) disease. Denileukin diftitox resulted in an ORR of 36% (as assessed by an independent review committee) and the median duration of response was 6.5 months.[100] The ORR were higher for stage IIB disease (46%) compared to those with stage IA-IIA disease (37%) or stage III disease (20%). There was no correlation between the CD25 expression and the efficacy of denileukin diftitox.

Reduction in skin disease burden was observed across all stages (84%; 54 out of the 64 evaluable patients). Treatment-related adverse events including capillary leak syndrome (CLS; typically occurring during the first 2 cycles), infusion-related reactions, visual impairment and hepatotoxicity were mostly grade 1-2, with no evidence of cumulative toxicity.[101]

Denileukin diftitox is included as a preferred systemic therapy option for stage IIB (generalized tumor disease) and as an option under useful in certain circumstances for stage IB-IIA, stage IIB (limited) and stage III disease.

Alemtuzumab

Alemtuzumab (a humanized anti-CD52 monoclonal antibody) has significant clinical activity in patients with previously treated advanced MF and SS.[113-118] The ORR with alemtuzumab (30 mg IV) was higher in patients with erythroderma or SS than those with advanced MF; however, it was associated with myelotoxicities and infectious complications.[114,118] Reduced-dose subcutaneous alemtuzumab (3–15 mg per administration) given for a shorter duration was equally effective with lower incidence of infectious complications in patients with SS.[115] While alemtuzumab is no longer commercially available, it may be obtained for compassionate use for 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.[119] Pembrolizumab was associated with a skin flare reaction, occurring exclusively in patients with SS; the flare reaction correlated with high PD-1 expression on Sezary cells and it should be distinguished from disease progression.

Pralatrexate

Pralatrexate is a folate analog with demonstrated activity in patients with heavily pretreated MF and SS.[110-112] In a multicenter dose-finding study that evaluated pralatrexate (10–30 mg/m^2 given weekly for 2 of 3 weeks or 3 of 4 weeks) in 54 patients with relapsed or refractory MF and SS, the ORR for all evaluable patients was 41% (6% CR).[110] Among the 29 patients who received the recommended dose (15 mg/m^2 weekly for 3 weeks of a 4-week cycle), the ORR was 45% (3% CR).[110] In the subgroup of patients with relapsed/refractory LCT of MF treated on the PROPEL trial, pralatrexate (30 mg/m^2) resulted in an ORR of 58% (25% by independent review).[111] The median PFS and OS were 5 months and 13 months, respectively.

Gemcitabine

Gemcitabine monotherapy is an effective treatment option for patients with heavily pretreated advanced-stage MF and SS.[129-136] In a retrospective observational study of 25 patients with advanced MF and SS, after a long-term follow-up of 15 years, the estimated OS, PFS, and DFS rates were 47%, 9%, and 40%, respectively.[133] In a single-center study of 14 patients with heavily pretreated MF (n = 12) and SS (n = 2), gemcitabine resulted in an ORR of 57% (all were in the skin compartment) and the median time-to-next treatment was 12 months.[136] Retrospective studies have also reported favorable clinical outcomes (ORR and PFS) with low-dose gemcitabine in patients with previously treated MF and SS.[134,135]

Liposomal Doxorubicin

Pegylated liposomal doxorubicin has shown single-agent activity in patients with pretreated, advanced, or refractory MF and SS.[136-141]

In a phase II EORTC multicenter trial of 49 patients with relapsed/refractory advanced MF (stage IIB, IVA, or IVB) after at least two prior systemic therapies, pegylated liposomal doxorubicin resulted in an ORR of 41% (6% CR), with a median duration of response and median time to progression (TTP) of 6 months and 7 months, respectively.[139] Pegylated liposomal doxorubicin was well tolerated with no grade 3 or 4 hematologic toxicities; the most common grade 3 or 4 toxicities included dermatologic toxicity other than hand and foot reaction (6%), constitutional symptoms (4%), gastrointestinal toxicities (4%), and infection (4%).

In a single-center study of 32 patients (MF, n = 25; SS, n = 7) treated with pegylated liposomal doxorubicin for heavily pretreated MF (n = 25) and SS (n = 7), the ORR was 58% for the entire study population (71% in skin, 44% in blood, and 33% in lymph nodes).[136] The toxicity profile was also consistent with that reported in the phase II study, with fatigue, peripheral edema, anemia, hyperpigmentation, and hand-foot syndrome being the most common toxicities of all grades. Another real-life cohort study (36 patients; MF, n = 34; SS, n = 2) also confirmed the activity of pegylated liposomal doxorubicin for advanced MF and SS, especially in patients with tumor stage disease.[141]

Extracorporeal Photopheresis

ECP has been demonstrated as an effective treatment option in many retrospective studies, resulting in an ORR of 42% to 74%.[127,171-178] In a meta-analysis involving more than 400 patients with MF and SS, ECP as monotherapy resulted in a 56% ORR with a 15% CR.[172] The corresponding response rates were 58% (15% CR) for erythrodermic disease (T4) and 43% (10% CR) for SS. In one retrospective study of 39 patients with MF and SS (31 patients with T4 disease and 8 patients with T2 disease), ECP resulted in a skin ORR of 74% (33% of patients achieved ≥50% partial skin response and 41% of patients achieved ≥90% improvement).[175] After a median follow-up of 72 months, the median OS was 9 years from diagnosis and 7 years from the initiation of treatment with ECP. Another retrospective study of 50 patients with MF reported an ORR of 42% and an OS of 72 months with no statistically significant differences in OS among patients with early-stage and late-stage disease (77 months and 69 months, respectively; $P = .077$).[177]

The degree of blood involvement, CD4/CD8 ratio, and amount of circulating CD3+CD8+ cells or CD4(+)CD7(-) lymphocytes have been identified as predictors of clinical response.[126,127,179] ECP is generally given for at least 6 months and may be more appropriate as systemic therapy for patients with or at risk of blood involvement (B1 or B2; erythrodermic stage III disease or IVA with SS).[172,178]

Combination Therapies

Skin-Directed + Systemic Therapies

Phototherapy is most commonly used in combination with either IFN[180-183] or systemic retinoid.[144,150,184-186]

In a prospective randomized study that evaluated IFN combined with PUVA versus IFN combined with retinoids in patients with stage I or II CTCL (n = 82 evaluable), the combination of IFN with PUVA resulted in significantly higher CR rates in this patient population (70% vs. 38%).[180] In another prospective phase II trial in patients with early-stage MF (stages IA–IIA; n = 89), the combination of low-dose IFN alfa with PUVA resulted in an ORR of 98% (84% CR).[182]

In a phase III randomized study from the EORTC that evaluated the combination of bexarotene with PUVA compared with PUVA alone in patients with early-stage MF (stage IB and IIA; n = 93), the ORR for the combination of bexarotene with PUVA was 77% (31% CR) compared to

71% (22% CR) for PUVA alone; the median duration of response was 6 months and 10 months, respectively.[144] A trend towards fewer PUVA sessions and lower UVA doses to achieve CR was observed with the combination arm, although the differences were not significant.[144] This trial was closed prematurely due to low patient accrual.

A small prospective study evaluated the combination of low-dose bexarotene in combination with PUVA maintenance in 21 patients with MF and SS (stages IB–IV) resistant or intolerant to previous therapies.[184] The ORR was 86% after induction therapy with bexarotene (93% for early-stage disease and 66.6% for advanced disease). At the end of maintenance, the ORR was 76% (33% CR) and the median event-free survival (EFS) for the whole group was 31 months.

In a retrospective analysis of 128 patients with MF (118 patients had early-stage disease; stage ≤IIA), acitretin (either as monotherapy or in combination with phototherapy or topical steroids) resulted in an ORR of 77% (44% CR and 33% PR) with a trend towards better response rate in the combination arm compared to monotherapy.[150] The median duration of response was 24 months.

ECP used in combination with TSEBT or phototherapy (narrowband UVB or PUVA) has also resulted in high durable clinical response in patients with erythrodermic MF and SS.[187,188] In a retrospective study of 44 patients with erythrodermic MF, the combination of TSEBT with ECP (concurrent or sequential following TSEBT) significantly improved PFS compared with TSEBT alone.[187] The 2-year PFS and OS rates were 36% and 63%, respectively, for patients treated with TSEBT alone compared with 66% and 88% for those treated with TSEBT + ECP.

There are limited efficacy and safety data for the use of TSEBT in combination with systemic retinoids, HDAC inhibitors (vorinostat or romidepsin), or mogamulizumab.

Systemic Combination Therapies

Systemic combination therapy regimens have been shown to improve response rates in patients with early-stage disease with inadequate response to single-agent therapy or those with advanced-stage CTCL.

ECP with IFN and/or systemic retinoid and IFN with systemic retinoid are the most commonly evaluated combination therapies for patients with CTCL.[145-147,189-191] The combination of oral isotretinoin and IFN alfa resulted in an ORR of 85% and the estimated 5-year OS rate was 94% for patients with early-stage MF and 35% for advanced-stage MF.[145] ECP in combination with IFN and/or systemic retinoids resulted in a response rate of 84% in patients with advanced CTCL and the 5-year OS rates for the subgroups of patients with stage IIIB, IVA1, IVA2, and IVB were 80%, 80%, 76%, and 0%, respectively.[190,191] Other systemic combination therapy regimens have also been studied.[192-194]

However, aforementioned studies that have evaluated the systemic combination regimens are limited by small sample size and there are no data from prospective randomized clinical studies to support the use of a specific systemic combination therapy regimen.

Additional Therapy Based on Response to Primary Treatment

Historically, the response criteria for MF and SS were poorly defined and validated response assessments were lacking. Response criteria for MF and SS have not been demonstrated to correlate with prognosis, and responses can vary between the different disease compartments (ie, skin, blood, lymph nodes).

More recent studies have incorporated consensus response assessments and newer FDA-approved agents have undergone central review for efficacy outcomes. A proposal for the standardization of definition of response in skin, nodes, blood, and viscera has been published.[195] The decisions to continue with or switch treatment regimens are often made

based on clinical parameters. Imaging with the same modalities used in workup is indicated when there is suspicion of disease progression or extracutaneous disease.

All patients (stage IA–IV) with 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. Disease relapse (with the same stage) after discontinuation of therapy often responds well to re-treatment with previous therapy. Patients with persistent disease following completion of primary treatment should be treated with the other primary treatment options not received before to improve response before moving onto treatment for refractory disease.

Currently there is no definitive treatment for refractory disease that can produce reliable durable remissions or curative results. Participation in a clinical trial is recommended for all patients with refractory disease. Multiagent chemotherapy regimens recommended for PTCL can be considered for the treatment of refractory disease to multiple prior therapies.

Special Considerations for Clinical Situations with Specific Pathologic Features

Folliculotropic Mycosis Fungoides

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 stage of the disease.[20,196-199] Recent studies have reported that FMF presents with two distinct patterns of clinicopathologic features with different prognostic implications (early stage and advanced stage). In a subgroup of patients with early skin-limited disease, FMF has an indolent disease course and a favorable prognosis, with early-stage cutaneous disease associated with significantly higher disease-specific survival compared to advanced-stage cutaneous disease.[200-202]

In a report from the Dutch Cutaneous Lymphoma Group that evaluated the treatment outcomes in patients with FMF (203 patients; 84 patients with early-stage FMF, 102 patients with advanced-stage FMF, and 17 patients with extracutaneous FMF), treatment with topical steroids and phototherapy with UVB or PUVA were more effective in patients with early-stage FMF resulting in an ORR of 83% (28% CR), 83%, and 88%, respectively.[203] Local RT, TSEBT, and PUVA combined with RT were more effective in patients with advanced-stage FMF resulting in an ORR of 100% (63% CR), 100% (59% CR), and 75% (5% CR), respectively.

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 single-agent systemic therapy regimens before receiving multiagent chemotherapy regimens.

Large-Cell Transformation

LCT is diagnosed when large cells are present in greater than 25% of lymphoid/tumor cell infiltrates in a skin lesion biopsy, and the incidence of LCT is strongly dependent on the disease stage at diagnosis (1% for early-stage disease, compared with 27% for stage IIB disease and 56%–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.[7-9,204] However, it should be noted that CD30 expression is variable in MF and SS, with the leukemic Sézary cells typically being CD30-negative.

Systemic therapy (brentuximab vedotin, gemcitabine, liposomal doxorubicin, pralatrexate, romidepsin, or pembrolizumab) with skin-directed therapies is the initial treatment for generalized cutaneous or extracutaneous lesions with LCT. 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 EBRT alone, with continuation of other treatment modalities used prior to transformation. Depending on the goals of treatment, multiagent chemotherapy regimens recommended for PTCL may be appropriate for the management of LCT that is refractory to multiple prior therapies or when significant extracutaneous disease is present.

Role of Allogeneic Hematopoietic Cell Transplant in MFSS

Allogeneic HCT has a role 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 of patients with advanced MF and SS.[205-212]

In a multicenter retrospective analysis of 37 patients with advanced-stage primary CTCL treated with allogeneic HCT (24 patients [65%] had stage IV MFSS or disseminated nodal or visceral involvement), after a median follow-up of 29 months, the incidence of relapse was 56% and the estimated 2-year OS and PFS rates were 57% and 31%, respectively.[205]

In a retrospective analysis of patients with advanced-stage MF and SS in the European Group for Blood and Marrow Transplantation (EBMT) database (n = 60) treated with allogeneic HCT, the 5-year PFS and OS rates were 32% and 46%, respectively. The corresponding 7-year survival rates were 44% and 30%, respectively.[206] The non-relapse mortality (NRM) rate at 7 years was 22%. Outcomes were not significantly different between histology types. However, patients with advanced-stage disease had an increased risk of relapse or progression as well as lower PFS, and myeloablative conditioning was associated with poorer NRM and OS. In an updated analysis, advanced-stage disease (refractory disease or PD after ≥3 lines of systemic therapy prior to transplant), a short interval between diagnosis, and transplant (<18 months) were independent adverse prognostic factors for PFS; advanced-stage disease and the use of unrelated donors were independent adverse prognostic factors for OS.[210]

In a case series of 47 patients with advanced-stage MF and SS who underwent allogeneic HCT after disease progression on conventional therapy, the estimated 4-year OS and PFS rates were 51% and 26%, respectively.[208] While there was no statistical difference in the OS in patients who had MF without LCT, SS, MF with LCT, or SS with LCT, the 4-year PFS rate was superior in patients who had SS versus those who did not (52% vs.10%; $P = .02$). Another multicenter retrospective study, although limited by small sample size (26 patients; MF, n = 17; SS, n = 9), reported superior outcomes with allogeneic HCT in patients with SS compared to MF.[212] After a median follow-up of 5 years, patients with SS had lower relapse rates (11% at 5 years), longer TTNT (not reached), higher treatment-free survival (89% at 5 years) and OS (5-year OS rate was 100%) compared to those with MF (74%, 24 months, 16% and 52%, respectively). Other systematic review and meta-analysis have reported pooled PFS and OS rates of 36% and 59%, respectively, following allogeneic HCT in patients with advanced-stage MF and SS.[213,214]

The survival benefit of allogeneic HCT in patients with advanced MF and SS was confirmed in a prospective, multicenter, propensity score-matched, controlled trial (99 patients with advanced MF and SS; 55 patients assigned to the allogeneic HCT group and 44 patients assigned to the non-allogeneic HCT treatment option of investigator's choice).[215] After a median follow-up of 13 months, the median PFS was significantly longer in the allogeneic HCT group (9 months vs. 3 months in the non-allogeneic HCT group; $P < .0001$). The 1-year PFS rates were 51% and 14%, respectively, for patients in the allogeneic HCT group and non-allogeneic HCT group. The 1-year cumulative incidence of relapse

was also lower in the allogeneic HCT group (45% compared to 86% in the non-allogeneic HCT group).

Autologous HCT is not recommended for patients with CTCL, due to short duration of response despite its toxicity, thus limiting its utility.[216] While the majority of the deaths among patients undergoing autologous HCT may be attributable to PD, deaths associated with allogeneic HCT may be more due to NRM (the incidence of 1-year NRM in published reports with allogeneic HCT is approximately 11%–25%).[205-209]

The use of TSEBT with non-myeloablative allogeneic HCT has also been evaluated in patients with advanced MF and SS.[217-219] In a study of 19 patients with advanced CTCL, the use of TSEBT prior to allogeneic HCT provided improved disease control with an ORR of 68% (58% CR) with median OS not reached at the time of the report; the treatment-related mortality (TRM) rate was 21%.[217] The safety and efficacy of a non-myeloablative conditioning regimen consisting of TSEBT and total lymphoid irradiation (TLI) + anti-thymocyte globulin (ATG) has also been demonstrated in prospective clinical studies.[220,221] In a prospective clinical study of 35 patients with advanced-stage disease (13 patients with MF and 22 patients with SS), this regimen was associated with 1-year and 2-year NRM of 3% and 14%, respectively.[220] The 2-year incidence of moderate/severe chronic graft-versus-host disease (GVHD) was 32%. With a median post-transplant follow-up of 5 years, the 2-year, 3-year, and 5-year OS rates were 68%, 62%, and 56%, respectively. The 5-year PFS rate was 41%. Patients >65 years at the time of transplant had similar clinical outcomes compared with younger patients. This study also evaluated the utilization of high-throughput sequencing (HTS) to monitor minimal residual disease (MRD), and molecular remission after allogeneic HCT (achieved in 43% of patients) was associated with a lower incidence of PD or relapse. In another prospective study that evaluated the same non-myeloablative conditioning regimen (TSEBT + TLI + ATG) in 41 patients with advanced-stage disease (34 patients with MF and 7 patients with SS), the 1-year and 2-year NRM rates were 10% and 13%, respectively.[221] Grade ≥2 acute and chronic GVHD were reported in 32% and 24% of patients, respectively. After a median follow-up of 5 years after transplant, the 5-year OS rate was 38% for the entire study population (37% for MF and 57% for SS). The 5-year cumulative incidence of disease progression or relapse was 53% for all patients and these rates were significantly lower for patients achieving CR following transplant (21% compared to 71% in those not in CR; P = .006).

Allogeneic HCT may be considered for appropriate patients with stage IIB–IV disease that is refractory to multiple primary treatment options. Based on the limited evidence, patients with erythrodermic MF and SS appear to receive the most benefit from allogeneic HCT, despite high post-transplant 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. When appropriate, TSEBT may be considered as cytoreductive therapy before transplant.[217,220] Novel conditioning regimens are being explored to provide improved disease control while limiting transplant-related complications.

The ideal timing for allogeneic HCT is when the disease is well controlled with induction therapy and before the disease has progressed to a state where the chance of response or survival with allogeneic HCT is low.[222] A transplant decision requires careful counseling to weigh the significant risks of this procedure versus the likelihood of long-term benefits and availability of alternate treatments.

Supportive Care

Management of Pruritus

Symptoms of pruritus can be present in a large majority (nearly 90%) of patients with CTCL, and may be associated with decreased quality of life

for patients.[223-225] Patients should be evaluated for pruritus at each visit. Other potential causes of pruritus (eg, contact dermatitis, atopic dermatitis, psoriasis, other inflammatory skin conditions) should be ruled out. The extent of pruritus (localized vs. generalized) and potential correlation between disease site and localization of pruritus should be noted.

The treatment of pruritus requires optimizing skin-directed and systemic treatments. Daily use of moisturizers and emollients are helpful in maintaining and protecting the skin barrier. Topical steroids (with or without occlusion) can be effective in managing the disease and accompanying pruritus in early-stage disease.[225,226] First-line options include H1 antihistamines (single-agent or combination of antihistamines from different classes) or the anticonvulsant gabapentin.[223,227,228] Neurokinin-1 (NK-1) receptor antagonist aprepitant,[229-231] the tetracyclic antidepressant mirtazapine, or selective serotonin reuptake inhibitors (SSRIs) may be considered in the second-line setting.[232,233] Treatment with the oral opioid receptor antagonist naltrexone may be considered if symptoms of pruritus do not resolve with the above agents.[234]

Prevention and Treatment of Infections

Infectious complications are frequent among patients with MF and SS, particularly cutaneous bacterial infections and cutaneous herpes viral infections (eg, herpes simplex virus [HSV] or herpes zoster virus [HZV] infections).[235] Bacteremia/sepsis and bacterial pneumonia were reported as the major cause of death due to infections in a retrospective cohort study of patients with MF and SS.[235] Several preventive measures such as maintaining/protecting the skin barrier (routine use of skin moisturizers and/or emollients), bleach baths or soaks (for limited areas only), avoidance of central lines (particularly for erythrodermic patients), and prophylactic use of mupirocin in cases of *Staphylococcus aureus* colonization can be incorporated to minimize infectious complications. HSV prophylaxis with acyclovir or equivalent should be considered for patients with frequent recurrence of HSV infection. Patients undergoing treatment with alemtuzumab-containing regimens should be closely monitored for cytomegalovirus (CMV) reactivation and preemptively treated with antivirals to avoid overt CMV disease.

Cultures from skin swab and nares (nostrils) should be taken to evaluate for *S. aureus* colonization/infection in patients with erythroderma and an active or suspected infection. Antimicrobial treatments may include intranasal mupirocin and/or oral dicloxacillin or cephalexin. Bleach baths or soaks may be helpful if the affected area is limited. Doxycycline or trimethoprim/sulfamethoxazole (TMP/SMX) should be considered for patients with suspected methicillin-resistant *S. aureus* (MRSA) infection. If no improvements in infection status are observed with the above agents, or if bacteremia is suspected, vancomycin should be initiated.

Infection with Gram-negative rods is common in necrotic tumors, and may lead to serious complications such as bacteremia/sepsis. For active or suspected infections in patients with ulcerated and necrotic tumors, blood cultures should be obtained and empiric therapy with antibacterials should be considered even in the absence of a fever. An antimicrobial agent with broad-spectrum coverage (including coverage for both Gram-negative rods and Gram-positive cocci) should be chosen initially. The role of skin/wound culture is not clear in this setting.

Further information on empiric therapy in patients with cancer at risk for infections is included in the NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections.

Table 1. Systemic Therapy for MF and SS

Trial	Regimen/Dose		Disease Stage and No. of Patients (n)	Patient Characteristics	Median Follow-up	ORR	Median PFS
ALCANZA trial (Phase III RCT)[98]	**Brentuximab vedotin** (1.8 mg/kg every 3 weeks; 16 3-week cycles)		Stage IA–IVB MF (n = 48)	ECOG PS 0-2; ≥18 years with relapsed or refractory CD30-expressing MF[a] (≥1 prior systemic therapy or RT); Patients with MF and B1 blood involvement were considered eligible; Patients with SS (B2 blood involvement) and those with disease progression on prior methotrexate and bexarotene were excluded.	46 months	55% (17% CR)	17 months
	Oral methotrexate (5–50 mg once per week) for 48 weeks		Stage IA–IVB MF (n = 49)			13% (2% CR)	4 months
	Oral bexarotene (300 mg/m² once per day) for 48 weeks						
MAVORIC trial (Phase III RCT)[99]	**Mogamulizumab** (1 mg/kg IV on a weekly basis for the first 28-day cycle, then on days 1 and 15 of subsequent cycles)		Stage IB–IVA (n = 186)	ECOG PS 0-1; ≥18 years with relapsed or refractory MF and SS (≥1 prior systemic therapy); Patients with LCT at study entry were excluded. CCR4 expression was not a requirement for participation in the trial.	17 months	28% (23% by IRC)	8 months (7 months by IR)
	Vorinostat (400 mg daily)		Stage IB–IVA (n = 186)			5% (4% by IRC)	3 months (4 months by IR)
Study 302[100]	**Denileukin diftitox (reformulated)** (9 mcg/kg/day IV over 60 min for 5 days every 21 days up to 8 cycles).		Stage IA -IIIB MF (n = 69)[b]	ECOG PS 0-2; Adequate organ function; ≥18 years with recurrent or persistent CD25-positive MF and SS[c] (≥1 prior systemic therapy; no prior denileukin diftitox);	—	42% (36% by IRC);	—
Phase II and III[102]	**Bexarotene**	300 mg/m²/day	Stage IA–IIA (n = 28)	≥18 years with refractory or persistent MF (after ≥2 prior therapies: phototherapy or TSEBT or topical mechlorethamine)	—	54%	—
		>300 mg/m²/day	Stage IA–IIA (n = 15)		—	67%	—
Phase II and III[103]	**Bexarotene**	300 mg/m²/day	Stage IIB–IVB (n = 56)	≥18 years with refractory or persistent MF and SS	—	45%	—
		>300 mg/m²/day	Stage IIB–IVB (n = 38)		—	55% (13% CR)	—

a. CD30 expression in ≥10% of total lymphoid cells in at least one skin biopsy. b. Patients with stage IV disease were enrolled in the study but not included in the primary efficacy analysis. c. CD25-positiity was defined as detectable CD25 in ≥20% of total lymphoid cells in biopsy specimen by IHC.

CR, complete response; IRC, independent review committee; LCT, large cell transformation; MF, mycosis fungoides; ORR, overall response rate; PFS, progression-free survival; PS, performance status; RT, radiation therapy; RCT, randomized control trial; SS, Sézary syndrome; TSEBT, total skin electronic beam therapy; Continued on next page

Table 1. Systemic Therapy for MF and SS

Trial	Regimen/Dose	Disease Stage and No. of Patients (n)	Patient Characteristics	Median Follow-up	ORR	Median PFS
Phase IIB[105]	**Vorinostat** (400 mg daily)	Stage IB–IVA (n = 74)	ECOG PS 0–2; ≥18 years with progressive, persistent, or recurrent MF and SS (after ≥2 prior systemic therapies including bexarotene)	—	30%	
Phase II[108]	**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)	ECOG PS 0–1; ≥18 years with relapsed or refractory MF and SS (≥1 prior systemic therapy)	—	34% (6% CR)	
PDX-010 (Dose-escalation study)[110]	**Pralatrexate** (15 mg/m^2, weekly for 3 out of 4 weeks)	Stage IB–IVA (n = 29)	ECOG PS 0–2; ≥18 years with progressive MF and SS (after ≥1 prior systemic therapy)	—	45%	Not reached
Phase II[114]	**Alemtuzumab** (IV 30 mg)	Stage II or IV (n = 22)	WHO PS ≤2; ≥18 years with CD52-positive relapsed or refractory MF and SS (≤5 prior systemic therapy)	—	55% (32% CR)	
Subcutaneous alemtuzumab[115]	**Alemtuzumab** (SC 10 mg maximum per administration)	SS (n = 14)	Median age 72 years; Previously untreated (n = 3) or relapsed/refractory (n = 11) SS with high counts of circulating Sézary cells	—	86% (21% CR)	Median survival (35 months)
Phase II (CITN-10)[119]	**Pembrolizumab** (2 mg/kg IV, every 3 weeks)	Stage IIB–IVB (n = 24)	ECOG PS 0–1; ≥18 years with relapsed or refractory MF and SS (≥1 prior systemic therapy)	—	38%	65% (1-year PFS rate)

CR, complete response; MF, mycosis fungoides; ORR, overall response rate; PFS, progression-free survival; PS, performance status; SS, Sézary syndrome;

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Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

Primary cutaneous CD30+ T-cell lymphoproliferative disorders (PCTLD) represent a spectrum that includes primary cutaneous anaplastic large-cell lymphoma (PC-ALCL), lymphomatoid papulosis (LyP), and "borderline" cases with overlapping clinical and histopathologic features.[1,2] Primary cutaneous disease, spontaneous regression, and absence of extracutaneous spread are associated with a better prognosis.[3,4]

PC-ALCL represents approximately 8% of all cutaneous T-cell lymphomas (CTCL) and is histologically characterized by diffuse, cohesive sheets of large CD30-positive (in >75%) cells with anaplastic, pleomorphic, or immunoblastic appearance.[5] Patches and plaques may also be present, and some degree of spontaneous remittance in lesions may also be seen. PC-ALCL typically follows an indolent course with an excellent prognosis, although cutaneous relapses are more common.[6-8] Clinical features typically include solitary or localized nodules or tumors (often ulcerated); multifocal lesions occur in approximately 20% of cases. Extracutaneous disease occurs in approximately 10% of cases, usually involving regional lymph nodes.[7] The presence of multiple cutaneous lesions at presentation, extensive skin lesions on the leg, disease progression to extracutaneous disease, early cutaneous relapse, and nodal progression are associated with poorer outcomes.[9-11]

LyP is histologically heterogenous with large atypical anaplastic, immunoblastic, or Hodgkin-like cells in a marked inflammatory background.[2] Several histologic subtypes have been defined based on the evolution of skin lesions. Clinical features include chronic, recurrent, spontaneously regressing papulonodular (grouped or generalized) skin lesions. LyP is not considered a malignant disorder and has an excellent prognosis with an overall survival (OS) rate of 92% at 5 and 10 years.[8] However, LyP has also been reported to be associated with an increased risk of secondary lymphomas such as mycosis fungoides (MF), PC-ALCL, systemic ALCL, or Hodgkin lymphoma.[12-17] Older age, positive *TCR* gene rearrangement, or diagnosis of mixed-type LyP have been reported as prognostic indicators of disease progression to lymphoma.[13,15]

Literature Search Criteria

Prior to the update of this version of the "NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), an electronic search of the PubMed database was performed to obtain key literature on PCTLD published since the previous Guidelines update using the following search terms: primary cutaneous anaplastic large cell lymphoma and LyP. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[18]

The search results were narrowed by selecting studies in humans published in English. The data from key PubMed articles deemed as relevant to these guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Diagnosis

As described earlier, PCTLD is a spectrum of clinical presentation including LyP (mostly papular and always regressing), PC-ALCL (mostly nodular and persistent), and also "borderline" presentations where lesions regress but take longer or are larger and not papular as in LyP.[5] Clinical and pathologic correlation is essential for distinguishing within the spectrum of PCTLD as well as distinguishing PCTLD from other

cutaneous CD30+ disorders (ie, systemic ALCL, adult T-cell leukemia/lymphoma [ATLL], peripheral T-cell lymphoma [PTCL], MF with large cell transformation (MF-LCT) and benign disorders such as lymphomatoid drug reactions, arthropod bites, viral infections, and others. MF and PCTLD can coexist in the same patient. Lymphomatoid drug reactions have been linked with certain drugs (eg, amlodipine, carbamazepine, cefuroxime) and may be associated with CD30+ atypical large cells in histology. Classic Hodgkin lymphoma (CHL) is less often associated with MF and PCTLD than previously thought; however, coexpression of CD30 and CD15 in these T-cell lymphomas may lead to a mistaken diagnosis of CHL.[19] It is therefore important not to diagnose CD30+ T-cell lymphomas in lymph nodes as Hodgkin lymphoma.

Complete skin examination (for any sign of benign or malignant skin lesions), adequate biopsy (punch, incisional, or excisional) of suspicious skin lesions, and immunohistochemistry (IHC) of skin biopsy specimen are essential to confirm the diagnosis. Molecular analysis to detect clonal *TCR* gene rearrangements, excisional or incisional biopsy of suspicious lymph nodes, and assessment of human T-cell lymphotropic virus type 1 (HTLV-1) serology to identify CD30+ ATLL would be helpful in selected circumstances. However, *TCR* gene rearrangement may not be demonstrated in all cases of PCTLD and *TCR* rearrangements can also be seen in patients with non-malignant conditions. Demonstration of identical clones in skin, blood, and/or lymph nodes may be helpful in selected cases.[20] Identification of clonal *TCR* gene rearrangement has no definitive established prognostic value; however, it could be helpful to determine clinical staging or assess relapsed or residual disease.

PCTLD are characterized by the following immunophenotype: CD30+ (>75% cells), CD4+, variable loss of CD2/CD5/CD3, and CD8+ (<5%) cytotoxic granule-associated proteins positive. ALK-positive PC-ALCL is extremely uncommon and t(2;5) translocation is typically absent in CD30+ PCTLD.[21,22] ALK positivity and differential expression of t(2;5) can help to distinguish between CD30+ PCTLD and ALCL of nodal origin. GATA3 expression by IHC has been proposed to be useful to differentiate between MF-LCT and CD30+ PCTLD.[23] MF-LCT was associated with a strong/diffuse expression of GATA3 while the CD30+ PCTLD showed variable/moderate expression of GATA3. MUM1 expression is valuable to distinguish between LyP and PC-ALCL, since the majority of cases of LyP (87%) are positive for MUM1 staining compared to only 20% of cases with PC-ALCL.[24]

The IHC panel may include CD3, CD4, CD8, CD20, CD30, CD56, and ALK. Additional markers such as CD2, CD5, CD7, CD25, TIA1, granzyme B, perforin, TCR beta, and TCR delta, IRF4/MUM1, and EMA may be useful in selected circumstances. Abnormal T-cell phenotype and perforin expression are significantly more frequent in PC-ALCL than in transformed MF and may be useful for the differential diagnosis between PC-ALCL and CD30-expressing transformed MF.[25]

DUSP22-IRF4 (6p25.3) gene rearrangement has been described in patients with PC-ALCL and LyP but is not associated with prognostic significance.[26-28] In a large multicenter study that investigated the clinical utility of detecting *IRF4* translocations in skin biopsies of T-cell lymphoproliferative disorders, fluorescence in situ hybridization (FISH) for *IRF4* had a specificity and positive predictive value of 99% and 90%, respectively, for cutaneous ALCL.[26] FISH to detect *ALK* and *DUSP22-IRF4* rearrangements would be useful in selected circumstances. HTLV-1 status, assessed either by HTLV-1 serology or other methods, may be useful in populations at risk to exclude the diagnosis of CD30-positive ATLL (which is usually HTLV-1 positive).

Workup

The initial workup involves a history and complete physical examination including entire skin, palpation of peripheral lymph node regions, and liver or spleen. Laboratory studies should include complete blood count (CBC) with differential, a comprehensive metabolic panel, and assessment of lactate dehydrogenase (LDH) levels. Many skin-directed and systemic therapies are contraindicated or are of unknown safety in pregnancy. Therefore, pregnancy testing is recommended for individuals of childbearing age.

Biopsy of enlarged lymph nodes or extracutaneous sites is recommended if biopsy of skin is non-diagnostic. Fine-needle aspiration (FNA) biopsy alone is not sufficient for the initial diagnosis. Excisional or incisional biopsy is preferred over core needle biopsy. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core needle biopsy and FNA biopsy in conjunction with appropriate ancillary techniques may be sufficient for diagnosis. Bone marrow evaluation has limited value in the staging of patients with PC-ALCL and is not required for disease staging.[29] Bone marrow aspiration and biopsy may be considered for solitary PC-ALCL or PC-ALCL without extracutaneous involvement on imaging.

Contrast-enhanced CT scan of the chest, abdomen, and pelvis or integrated whole-body PET/CT is recommended for PC-ALCL. PET scan may be preferred for patients with extranodal disease, which is inadequately imaged by CT. In LyP, imaging studies and bone marrow evaluation are done only if there is suspicion of systemic involvement by an associated lymphoma.

Primary Cutaneous ALCL

Radiation Therapy

In a report from the Dutch Cutaneous Lymphoma Group that evaluated the long-term outcome of patients with PCTLD (118 patients with LyP, 79 patients with PC-ALCL, and 11 patients with PC-ALCL with regional node involvement), radiation therapy (RT) or surgical excision as initial therapy (given for 48% and 19% of patients, respectively) resulted in a complete response (CR) rate of 100% in patients with PC-ALCL.[7] After a median follow-up of 61 months, subsequent skin-only relapse and extracutaneous disease were reported in 41% and 10% of patients, respectively.

A multicenter retrospective analysis of patients with PC-ALCL (n = 56) eligible to receive RT (primary therapy or after surgical excision) reported a clinical complete response (cCR) rate of 95% and a local control rate of 98% after a median follow-up of 4 years.[30] Although the median RT dose was 35 Gy (range, 6–45 Gy), CRs were seen with doses as low as 6 Gy and the achievement of cCR was independent of the RT dose, suggesting that lower RT dose of less than 30 Gy may be appropriate for the management of localized lesions. The efficacy of low-dose RT (≤20 Gy) for the treatment of solitary or localized PC-ALCL was also confirmed in other recent reports.[31-33]

Involved-site RT (ISRT) alone or surgical excision (with or without ISRT) are recommended for patients with solitary or grouped lesions.[6-8,34-37] ISRT alone is an appropriate option in selected patients with cutaneous ALCL regional lymph node involvement ± primary skin lesions.

Systemic Therapy

In the ALCANZA study that included 31 patients with previously treated PC-ALCL, overall response rate (ORR) lasting for 4 months or more was significantly higher for brentuximab vedotin compared to the physician's choice of treatment with methotrexate or bexarotene (75% vs. 20%), and

the proportion of patients achieving CR was also higher with brentuximab vedotin than with physician's choice (31% vs. 7%).[38]

In a multicenter study that evaluated the efficacy of treatment options in patients with multifocal lesions included in the Dutch Registry for Cutaneous Lymphomas prior to the FDA approval of brentuximab vedotin (24 patients with initial presentation and 17 patients with relapsed disease), RT (n = 21), systemic chemotherapy (n = 9), and low-dose methotrexate (n = 7) were the most common treatment options resulting in ORRs of 100% (100% CR), 100% (78% CR), and 57% (43% CR), respectively.[39] The presence of greater than 5 skin lesions was associated with a higher risk of extracutaneous relapse (56% vs. 20% for the presence of 2–5 skin lesions).

In the aforementioned report from the Dutch Cutaneous Lymphoma Group that evaluated the long-term outcome of 219 patients with PCTLD, 9 of 11 patients (82%) with PC-ALCL and regional node involvement received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like multiagent chemotherapy as initial therapy (82%), resulting in a CR in eight patients (88%).[7] However, five out of these eight patients experienced skin relapses during follow-up. After a median follow-up of 58 months, disease-related 5-year survival rate was 91%.

In November 2018, the FDA approved brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) for the treatment of previously untreated systemic ALCL or other CD30-positive PTCL based on the results of the ECHELON-2 trial, which showed that brentuximab vedotin + CHP was superior to CHOP for patients with CD30-positive PTCL as shown by a significant improvement in progression-free survival (PFS) and OS.[40] This trial, however, excluded patients with PC-ALCL. However, since CHOP is included as an option for primary treatment (other recommended regimens) for cutaneous ALCL with regional nodes, the panel acknowledged that brentuximab vedotin + CHP would also be an appropriate option for these patients.

Systemic therapy is indicated only for multifocal lesions (± skin-directed therapy) and for those with regional node involvement (± ISRT). Brentuximab vedotin is the preferred systemic treatment option based on the results of the ALCANZA study.[38] Low-dose methotrexate (50 mg weekly),[41,42] pralatrexate,[43] systemic retinoids (bexarotene for multifocal lesions),[44-47] and interferon (multifocal lesions)[44,48-50] are included as options for other recommended regimens based on the limited available data. Peginterferon alfa-2a is the only interferon available for clinical use in the United States and it may be substituted for other interferon preparations.[51-53] Observation (if asymptomatic) is appropriate for patients with multifocal lesions.

Brentuximab vedotin + CHP is included as an option under other recommended regimens for the primary treatment for patients with cutaneous ALCL with regional nodes.[40] Multiagent chemotherapy (CHOP or CHOEP [cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone]) with or without ISRT is included as an option for selected patients with regional lymph node involvement.[7,54]

Lymphomatoid Papulosis

It is important to be reminded that LyP is not a malignant disorder but a recurrent, benign, self-regressing lymphoid proliferation. Although multiagent chemotherapy often leads to reduction or clearance of lesions, rapid recurrence shortly after or even during treatment is a consistent finding in patients with LyP.

In the aforementioned report from the Dutch Cutaneous Lymphoma Group that included 118 patients with LyP, topical steroids and phototherapy were the most common skin-directed therapies used as initial treatment in

56% and 35% of patients, respectively.[7] Although CR or partial response (PR) were common, none of these therapies resulted in sustained CR. In a retrospective multicenter study of 252 patients with LyP, topical steroids and phototherapy were the most common first-line treatments (prescribed in 35% and 14% of the patients, respectively) resulting in a CR rate of 48%.[55] The overall estimated median disease-free survival (DFS) was 11 months, but the DFS was longer for patients treated with phototherapy (23 months; $P < .03$). The presence of type A LyP and the use of first-line treatment other than phototherapy were significantly associated with increased risk of early cutaneous relapse.

In a retrospective study of 45 patients with LyP and other CD30+ PCTLD, low-dose methotrexate (≤25 mg) resulted in satisfactory disease control in 87% of patients, and the median total duration of treatment was greater than 39 months for all patients.[56] After discontinuation, 25% of patients remained free of disease relapse during the follow-up period of 24 to 227 months. Another study that evaluated the efficacy of low-dose methotrexate in a cohort of 28 patients with LyP reported that satisfactory disease control could be achieved at 7.5-mg to 10-mg weekly doses of methotrexate.[41]

Observation is preferred for patients with asymptomatic disease. Topical steroids or phototherapy are appropriate initial treatment options for limited lesions (in symptomatic patients) or extensive lesions.[7,45,57-59] In patients receiving phototherapy, narrowband ultraviolet B (UVB) is generally preferred over psoralen plus ultraviolet A (PUVA). Systemic therapy is indicated only for patients with extensive lesions. Methotrexate is widely used for the treatment of LyP.[41,55,56,60-65] Systemic retinoids (bexarotene) are included as an option based on limited available data mainly from case reports.[44-47]

Follow-Up and Treatment for Relapsed/Refractory Disease

Patients with a clinical benefit and/or those with disease responding to initial treatment can be considered for maintenance or tapering of regimens to optimize response duration. Patients with disease that does not have adequate response to initial treatment are generally treated with an alternative regimen recommended for initial treatment before moving on to treatment for refractory disease. Disease relapse often responds well to the same treatment. In patients with PC-ALCL, refractory disease to multiple prior therapies should be managed with systemic therapy options recommended for MF with LCT.

Brentuximab vedotin is included as an option for LyP that is refractory to multiple primary treatment options.[66,67] In a phase II study of 12 patients with refractory LyP, brentuximab vedotin resulted in an ORR of 100% and a CR rate of 58%.[67] The median duration of response was 20 weeks. Grade 1 or 2 peripheral neuropathy was the most common adverse event reported in 10 patients (83%). Further studies are needed to optimize the dosing to minimize the incidences of peripheral neuropathy.

Regular follow-up (including complete skin examination) is essential during observation since these patients can develop associated hematologic malignancies (particularly MF or ALCL) over time.[55,68] Life-long follow-up (including thorough skin examination) is warranted for patients with LyP (even for patients with disease responding to initial treatment) due to high risks for second lymphoid malignancies.

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