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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# **Primary Cutaneous Lymphomas**

Version 1.2025 — November 11, 2024

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# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

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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](#).

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

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Updates in Version 1.2025 of the NCCN Guidelines for Primary Cutaneous Lymphomas from Version 3.2024 include:

### Global changes

- References updated throughout the guideline.

### New algorithm

- Added treatment algorithm for Subcutaneous Panniculitis-Like T-Cell Lymphoma

### Primary Cutaneous B-Cell Lymphomas

#### CUTB/INTRO-1

- Diagnosis
  - ▶ PCFCL
    - ◊ 1st sub-bullet revised: ...; surface Ig light chain typically positive but cytoplasmic Ig light chain is negative.
    - ◊ 3rd sub-bullet revised: PCFCL is most frequently germinal center B-cell (GCB) subtype. Germinal (or follicle) center phenotype with diffuse large cells in a skin lesion is may still be consistent with PCFCL with a diffuse population of large cells (PCFCL-LC) and should not be considered as DLBCL. PCFCL can also present with a mixed nodular/diffuse or purely diffuse pattern that similar to GCB immunophenotype that can be easily misdiagnosed as DLBCL.
  - ▶ PCDLBCL, leg type
    - ◊ 1st sub-bullet revised: ...FOXP1, IgM, and occasionally MYC. CD10 staining is usually negative. Immunophenotype may vary with poor correlation with Hans algorithm, but most cases are positive for MUM1 and BCL2 with variable expression of other markers.
    - ◊ 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. Gain-of-function mutations in MYD88 and CD79B co-occur in the so-called "MCD" subtype, and are specific to PCDLBCL, leg type.
    - ◊ Sub-bullet removed: Fluorescence in situ hybridization (FISH): frequently shows translocations of MYC, BCL6, and IGH genes.

#### CUTB-1

- Diagnosis
  - ▶ Useful in certain circumstances,
    - ◊ 1st bullet, 1st sub-bullet modified: ...kappa/lambda, MYC (IHC or ISH)
    - ◊ 3rd sub-bullet modified by adding: FISH for BCL2 and BCL6 rearrangements if MYC (IHC or ISH) is positive
    - ◊ 5th bullet added: Next generation sequencing (NGS) for MYD88 and CD79B mutations (to further help in distinguishing PC-DLBCL, leg type from PCFCL)
  - ▶ Footnote d added: IgM expression should be checked if MYD88 mutations are identified since these are the cases likely to have systemic involvement.

#### CUTB-3

- Footnote r revised from, "An FDA-approved biosimilar is an appropriate substitute for rituximab" to "An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines."

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# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

Updates in Version 1.2025 of the NCCN Guidelines for Primary Cutaneous Lymphomas from Version 3.2024 include:

### Mycosis Fungoides/Sézary Syndrome

#### MFSS/INTRO-1

- Definition, SS
  - 2nd sub-bullet revised: ...TRBC1 may contribute in detecting clonality and ~~is especially useful in cases where CD7 or CD26 are not lost~~ can improve the specificity of detecting Sézary cells when CD7 and CD26 are lost.

#### MFSS-1

- Diagnosis
  - Useful, 1st bullet,
    - ◊ 1st sub-bullet revised: Flow cytometry ~~and molecular analysis~~ to assess and quantitate an expanded T-cell population with aberrant immunophenotype
      - 1st sub-bullet: Text revised to include TRBC1 to flow cytometry panel and moved from footnote g. Flow cytometry panel may include CD3, CD4, CD7, CD8, CD26, CD45, TRBC1 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype, including loss of CD7 or CD26.
    - ◊ 2nd sub-bullet revised: Sézary cell preparation is less useful than flow cytometry due to the subjective nature of the process but may still be useful in cases where an aberrant immunophenotype is not detected.
  - Footnote g revised: TRBC1 may contribute in detecting clonality and ~~is especially useful in cases where CD7 or CD26 are not lost~~ can improve the specificity of detecting Sézary cells when CD7 and CD26 are lost.

#### MFSS-A (4 of 12)

- Treatment Considerations
  - 10th statement modified: LCT-MF was not an exclusion criteria for Study 302, which evaluated a reformulated version of denileukin diftitox, but no patients with LCT-MF were enrolled in the study. (Also for MFSS-A 5 of 12 and MFSS-A 6 of 12).

#### MFSS-A (9 of 12)

- Footnote c revised: 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.~~ Interpretation of CD30 expression is not universally standardized. Responses have been seen in patients with a low level of CD30 positivity and any level of CD30 positivity is acceptable for the use of brentuximab vedotin.

#### MFSS-B (1 of 2)

- Infections, Erythroderma
  - 6th bullet added: IV broad-spectrum antibiotics for S. aureus infection

#### MFSS-C

- Principles of Phototherapy added.

### Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

#### PCTL-D-4

- Footnote w revised: Peginterferon alfa-2a is the only interferon available for clinical use in the US and it may be substituted for other interferon preparations...

[Continued](#)



# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

Updates in Version 1.2025 of the NCCN Guidelines for Primary Cutaneous Lymphomas from Version 3.2024 include:

### Principles of Radiation Therapy

#### PCLYM-A 2 of 3

- General dose guidelines
  - ▶ PCMZL and PCFCL, 1st bullet modified: Alternatively, lower doses (eg, 4 Gy) may be used initially, with supplemental RT (4–20 Gy) for inadequate response or subsequent local relapse *though data with this approach are limited.*
  - ▶ MF/SS
    - ◊ 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 it may be less durable. 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.~~

#### PCLYM-A 3 of 3

- General dose guidelines
  - ▶ Added: SPTCL - RT for curative treatment: 36-45 Gy

### PMLYM-C

- Page reorganized by Viral reactivation and Anti-infective prophylaxis.
  - ▶ CMV reactivation
    - ◊ 1st sub-bullet revised: *Clinicians must be aware of the high risk of CMV reactivation in patients receiving alemtuzumab (anti-CD52 antibody).*
    - ◊ 4th sub-bullet added: Consultation with an infectious disease expert may be necessary.
- Anti-infective prophylaxis
  - ▶ 1st sub-bullet revised: *Recommended during treatment and thereafter (if tolerated) for patients receiving alemtuzumab (anti-CD52 antibody)*



## 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%),<sup>1,2</sup> 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.<sup>1,2</sup> 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%)<sup>1</sup> 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.<sup>1</sup>
  - 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%).<sup>2,3</sup>
  - Multiple skin lesions, inactivation of *CDKN2A*, and *MYD88 L265P* associated with inferior prognosis.

[Continued](#)

[References on CUTB/INTRO-A](#)

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



### PRINCIPLES FOR PRIMARY CUTANEOUS B-CELL LYMPHOMAS (PCBCL)

#### Diagnosis

- PCFCL: punch biopsy/incision/excision of skin lesion preferred to shave biopsy
  - ▶ Immunophenotype – cells express CD20, CD79a, and BCL6; surface Ig light chain typically positive but cytoplasmic Ig light chain 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.
  - ▶ PCFCL is most frequently germinal center B-cell (GCB) subtype.<sup>4</sup> Germinal (or follicle) center phenotype with diffuse large cells in a skin lesion may still be consistent with PCFCL. PCFCL can also present with a mixed nodular/diffuse or purely diffuse pattern that is similar to GCB immunophenotype, which can be easily misdiagnosed 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.<sup>5-8</sup> IgG class-switched subtype is a clonal chronic lymphoproliferative disorder (LPD), with indolent course.<sup>8,9</sup>
- 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, IgM, and occasionally MYC. CD10 staining is usually negative. Immunophenotype may vary with poor correlation with Hans algorithm, but most cases are positive for MUM1 and BCL2 with variable expression of other markers.
  - ▶ Gene expression profiling: PCDLBCL, leg type has been demonstrated to be most commonly activated B-cell (ABC) subtype. Gain-of-function mutations in *MYD88* and *CD79B* co-occur in the so-called "MCD" subtype, and are specific to PCDLBCL, leg type.<sup>4</sup>

#### General Principles

- PCFCL, PCMZL: If the pathology or clinical presentation is not typical, complete staging with chest/abdomen/pelvis 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](#))

References on [CUTB/INTRO-A](#)

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



**PRINCIPLES FOR PRIMARY CUTANEOUS B-CELL LYMPHOMAS (PCBCL)**  
**REFERENCES**

- <sup>1</sup> 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.
- <sup>2</sup> 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.
- <sup>3</sup> 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.
- <sup>4</sup> Zhang Y, LeWitt TM, Louissaint A Jr, et al. Disease-defining molecular features of primary cutaneous B-cell lymphomas: Implications for classification and treatment. *J Invest Dermatol* 2023;143:189-196.
- <sup>5</sup> 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.
- <sup>6</sup> 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.
- <sup>7</sup> 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.
- <sup>8</sup> 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.
- <sup>9</sup> Gibson SE, Swerdlow SH. How I diagnose primary cutaneous marginal zone lymphoma. *Am J Clin Pathol* 2020;154:428-449.

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



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## Primary Cutaneous B-Cell Lymphomas

**DIAGNOSIS<sup>a,b</sup>****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<sup>c</sup>
  - 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, MYC (IHC or ISH)
  - Assessment of IgM,<sup>d</sup> 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; FISH for BCL2 and BCL6 rearrangements if MYC (IHC or ISH) is positive
- If adequate biopsy material is available, flow cytometry or molecular analysis to detect IgH gene rearrangement can be useful in determining B-cell clonality
- Next generation sequencing (NGS) for *MYD88*<sup>d</sup> and *CD79B* mutations (to further help in distinguishing PC-DLBCL, leg type from PCFCL)

<sup>a</sup> A multidisciplinary team approach involving hematology/oncology, dermatology, pathology (with expertise in cutaneous lymphoma), and radiation oncology is often optimal for the diagnosis and management of patients with PCBCL

<sup>b</sup> 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.

<sup>c</sup> Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature NK/T-Cell Neoplasms (See [NCCN Guidelines for T-Cell Lymphomas](#)).

**WORKUP****ESSENTIAL<sup>e</sup>:**

- 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<sup>f</sup>
- Peripheral blood flow cytometry, if complete blood count (CBC) demonstrates lymphocytosis
- SPEP/quantitative immunoglobulins for PCMZL
- HIV testing
- Hepatitis B and C testing<sup>g</sup>
- Discuss fertility preservation<sup>h</sup>

[PCMZL \(CUTB-2\)](#)[PCFCL \(CUTB-2\)](#)

PC-DLBCL, Leg Type (See [NCCN Guidelines for B-Cell Lymphomas - DLBCL](#))

<sup>d</sup> IgM expression should be checked if *MYD88* mutations are identified since these are the cases likely to have systemic involvement.

<sup>e</sup> Rule out drug-induced cutaneous lymphoid hyperplasia.

<sup>f</sup> Often reserved for patients with unexplained cytopenias or if there is clinical suspicion of other subtypes (eg, PC-DLBCL, leg type).

<sup>g</sup> 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.

<sup>h</sup> Fertility preservation options include: sperm banking, semen cryopreservation, in vitro fertilization (IVF), or ovarian tissue or oocyte cryopreservation.

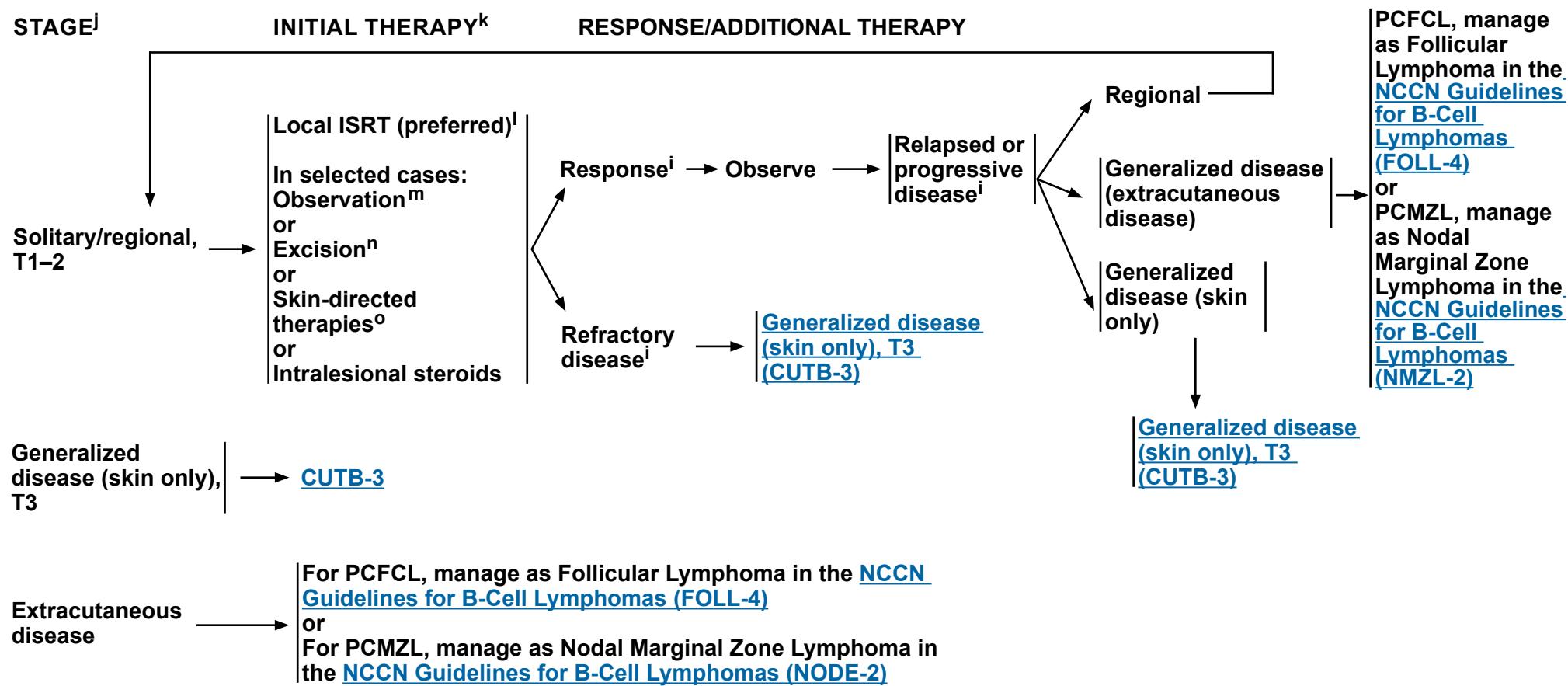
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## Primary Cutaneous B-Cell Lymphomas

### PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER LYMPHOMA<sup>j</sup>



<sup>i</sup> 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.

<sup>j</sup> [TNM Classification of Cutaneous Lymphoma other than MF/SS \(CUTB-A\)](#).

<sup>k</sup> [Treatment References \(CUTB-B\)](#).

<sup>l</sup> Local ISRT is the preferred initial treatment, but not necessarily the preferred treatment for relapse. See [Principles of Radiation Therapy \(PCLYM-A\)](#).

<sup>m</sup> When ISRT or surgical treatment is neither feasible nor desired.

<sup>n</sup> Small lesions may be excised with minimal non-disfiguring surgery.

<sup>o</sup> 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.



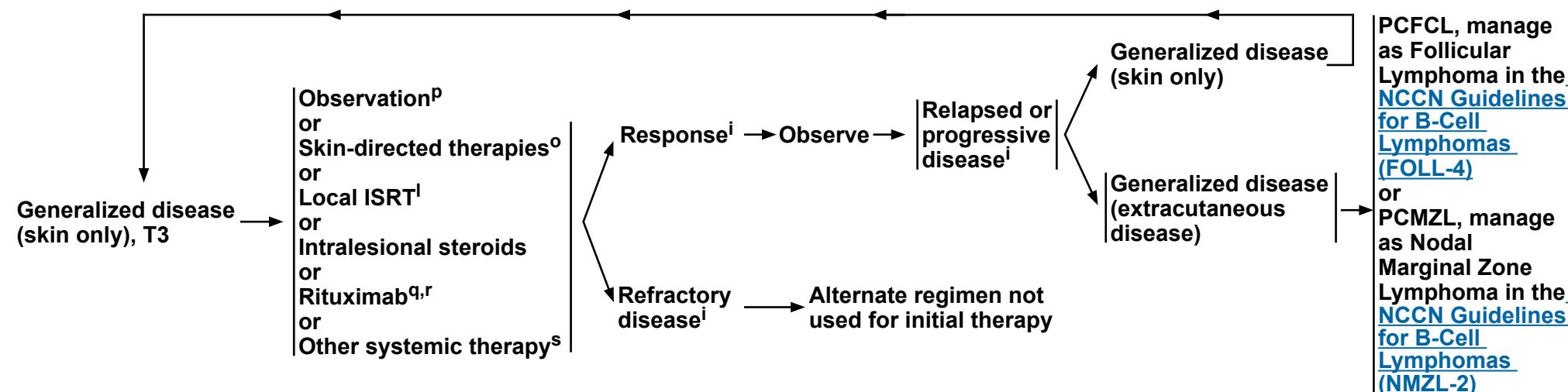
# NCCN Guidelines Version 1.2025

## Primary Cutaneous B-Cell Lymphomas

### PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER LYMPHOMA<sup>i</sup>

STAGE<sup>j</sup>INITIAL THERAPY<sup>k</sup>

RESPONSE/ADDITIONAL THERAPY



<sup>i</sup> 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.

<sup>j</sup> [TNM Classification of Cutaneous Lymphoma other than MF/SS \(CUTB-A\)](#).

<sup>k</sup> [Treatment References \(CUTB-B\)](#).

<sup>l</sup> Local ISRT is the preferred initial treatment, but not necessarily the preferred treatment for relapse. See [Principles of Radiation Therapy \(PCLYM-A\)](#).

<sup>o</sup> There are case reports showing efficacy of skin-directed therapies, which include topical steroids, imiquimod, nitrogen mustard, and bexarotene (useful in pediatric patients).

<sup>p</sup> Considered appropriate in asymptomatic patients.

<sup>q</sup> See monoclonal antibody and viral reactivation in the [NCCN Guidelines for B-Cell Lymphomas](#).

<sup>r</sup> 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 any recommended systemic biologic therapy in the NCCN Guidelines.

<sup>s</sup> 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.



# NCCN Guidelines Version 1.2025

## Primary Cutaneous B-Cell Lymphomas

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### TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS<sup>a,b</sup>

TNM		Size/location of lesions		
<b>T</b>				
$T_0^*$	Absence of clinically suspicious lesions			
$T_1$	Solitary lesion	$T_{1A}$	Solitary lesion <5 cm diameter	
		$T_{1B}$	Solitary <b>≥5 cm</b> diameter	
$T_2$	Multiple lesions limited to 1 body region or 2 contiguous body regions <sup>b</sup>	$T_{2A}$	All disease encompassing in a <15-cm-diameter circular area	
		$T_{2B}$	All disease encompassing a <b>15 to &lt;30 cm</b> diameter circular area	
		$T_{2C}$	All disease encompassing a <b>≥30 cm</b> diameter circular area	
$T_3$	Generalized skin involvement	$T_{3A}$	Multiple lesions involving 2 noncontiguous body regions <sup>b</sup>	
		$T_{3B}$	Multiple lesions involving <b>≥3</b> body regions <sup>b</sup>	
<b>N</b>				
$N_0$	No clinical or pathologic LN involvement			
$N_1$	Involvement of 1 peripheral LN region <sup>c</sup> that drains an area of current or prior skin involvement: biopsy positive for lymphoma			
$N_2$	Involvement of >2 peripheral LN regions <sup>c</sup> 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			
<b>M</b>				
$M_0$	No visceral involvement			
$M_1$	Visceral involvement			
$M_x$	Visceral involvement is neither confirmed nor refuted by available pathologic or imaging assessment			

<sup>a</sup> 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.

<sup>b</sup> For definition of body regions, see [Body Regions for the Designation of T \(Skin Involvement\) Category \(CUTB-A 2 of 2\)](#).

<sup>c</sup> 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.

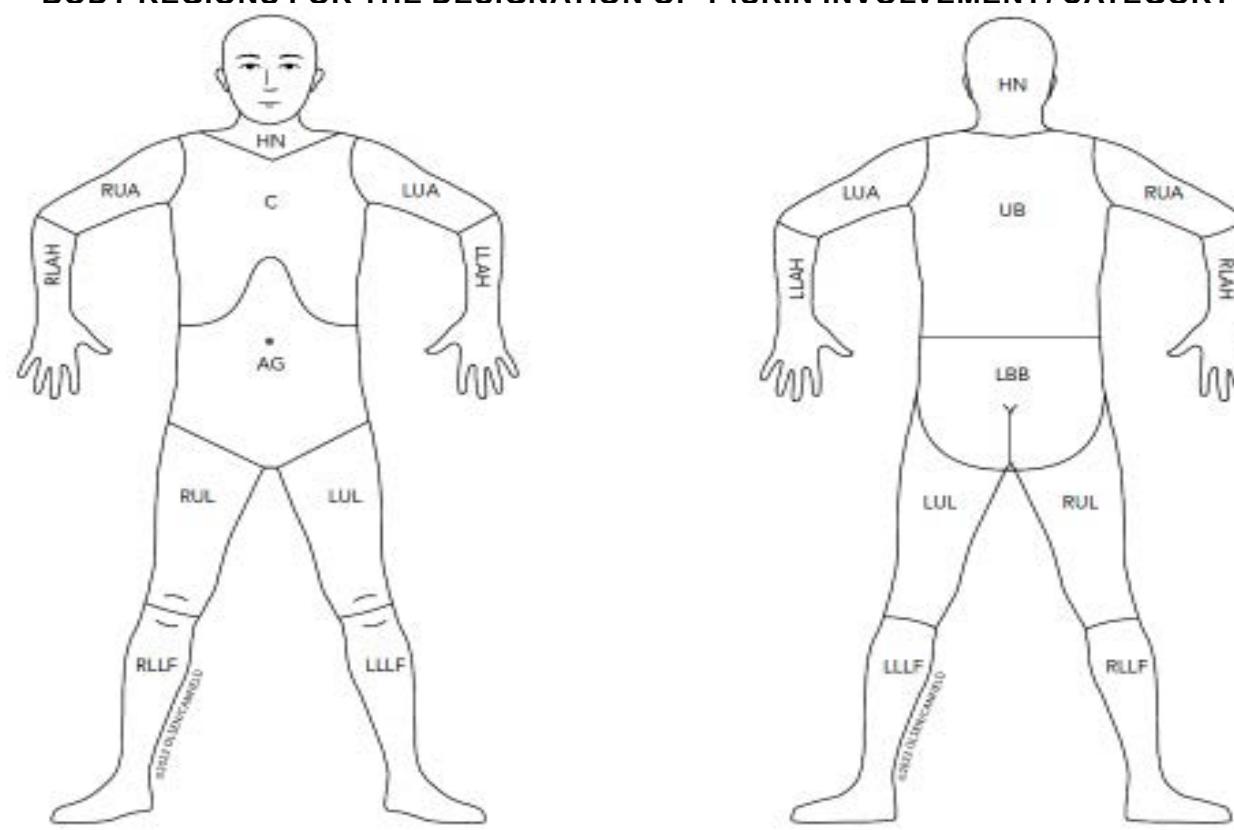
**Note:** All recommendations are category 2A unless otherwise indicated.



# NCCN Guidelines Version 1.2025

## Primary Cutaneous B-Cell Lymphomas

### BODY REGIONS FOR THE DESIGNATION OF T (SKIN INVOLVEMENT) CATEGORY<sup>a,d,e</sup>



<sup>a</sup> 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.

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

<sup>e</sup> 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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## Primary Cutaneous B-Cell Lymphomas

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### TREATMENT REFERENCES

#### **Skin-directed therapies**

##### *Topical/intralesional corticosteroids*

Bekkenk MW, Vermeer MH, Geerts ML, et al. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. *J Clin Oncol* 1999;17:2471-2478.

Perry A, Vincent BJ, Parker SR. Intralesional corticosteroid therapy for primary cutaneous B-cell lymphoma. *Br J Dermatol* 2010;163:223-225.

##### *Topical nitrogen mustard*

Bachmeyer C, Orlandini V, Aractingi S. Topical mechlorethamine and clobetasol in multifocal primary cutaneous marginal zone-B cell lymphoma. *B J Dermatol* 2006;154:1207-1209.

##### *Topical bexarotene*

Trent JT, Romanelli P, Kerdel FA. Topical targretin and intralesional interferon alfa for cutaneous lymphoma of the scalp. *Arch Dermatol* 2002;138:1421-1423.

##### *Topical imiquimod*

Coors EA, Schuler G, Von Den Driesch P. Topical imiquimod as treatment for different kinds of cutaneous lymphoma. *Eur J Dermatol* 2006;16:391-393.

Stavrakoglou A, Brown VL, Coutts I. Successful treatment of primary cutaneous follicle centre lymphoma with topical 5% imiquimod. *Br J Dermatol* 2007;157:620-622.

#### **Rituximab**

Morales AV, Advani R, Horwitz SM, et al. Indolent primary cutaneous B-cell lymphoma: experience using systemic rituximab. *J Am Acad Dermatol* 2008;59:953-957.

Heinzerling LM, Urbanek M, Funk JO, et al. Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. *Cancer* 2000;89:1835-1844.

Valencak J, Weihsgenreuber F, Rappersberger K, et al. Rituximab monotherapy for primary cutaneous B-cell lymphoma: Response and follow-up in 16 patients. *Ann Oncol* 2009;20:326-330.

Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood* 2008;112:1600-1609.

Heinzerling L, Dummer R, Kempf W, et al. Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous B-cell lymphoma. *Arch Dermatol* 2000;136:374-378.

#### **Chemotherapy/Chemoimmunootherapy**

Bekkenk MW, Vermeer MH, Geerts ML, et al. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. *J Clin Oncol* 1999;17:2471-2478.

Brice P, Cazals D, Mounier N, et al. Primary cutaneous large-cell lymphoma: analysis of 49 patients included in the LNH87 prospective trial of polychemotherapy for high-grade lymphomas. *Groupe d'Etude des Lymphomes de l'Adulte. Leukemia* 1998;12:213-219.

Hoefnagel JJ, Vermeer MH, Jansen PM, et al. Primary cutaneous marginal zone B-cell lymphoma: Clinical and therapeutic features in 50 cases. *Arch Dermatol* 2005;141:1139-1145.

Grange F, Beylot-Barry M, Courville P, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. *Arch Dermatol* 2007;143:1144-1150.

Grange F, Joly P, Barbe C, et al. Improvement of survival in patients with primary cutaneous diffuse large B-cell lymphoma, leg type, in France. *JAMA Dermatol* 2014;150:535-541.

Rijkenberg JU, Toonstra J, Meijer OW, et al. Treatment of primary cutaneous B-cell lymphomas of follicle center cell origin: A clinical follow-up study of 55 patients treated with radiotherapy or polychemotherapy. *J Clin Oncol* 1996;14:549-555.

Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood* 2008;112:1600-1609.

Vermeer MH, Geelen FA, van Hasselen CW, et al. Primary cutaneous large B-cell lymphomas of the legs. A distinct type of cutaneous B-cell lymphoma with an intermediate prognosis. *Dutch Cutaneous Lymphoma Working Group. Arch Dermatol* 1996;132:1304-1308.

#### **Palliative low-dose RT**

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.

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



# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

### 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.<sup>1,2</sup>
  - ▶ 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.<sup>1,2</sup>
- 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 can improve the specificity of detecting Sézary cells when CD7 and CD26 are lost).<sup>3</sup>
  - ▶ 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.<sup>4</sup> 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.<sup>5</sup>
- 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.<sup>1,2</sup>
- 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.<sup>6</sup>
- 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 (MF/SS)

#### 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.<sup>7,8,9</sup> 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.<sup>10,11</sup> 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.
- Patients having 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 (MF/SS)

- <sup>1</sup> WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. (WHO classification of tumours series, 5th ed.; vol. 11). Lyon (France): International Agency for Research on Cancer; 2024.
- <sup>2</sup> Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. *Blood* 2022;140:1229-1253.
- <sup>3</sup> Olsen E, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol* 2011;29:2598-2607.
- <sup>4</sup> Campbell JJ, Clark RA, Watanabe R, Kupper TS. Sézary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors. *Blood* 2010;116:767-771.
- <sup>5</sup> Pimpinelli N, Olsen EA, Santucci M, et al. Defining early mycosis fungoides. *J Am Acad Dermatol* 2005;53:1053-1063.
- <sup>6</sup> Talpur R, Sui D, Gangar P, et al. Retrospective Analysis of Prognostic Factors in 187 Cases of Transformed Mycosis Fungoides. *Clin Lymphoma Myeloma Leuk* 2016;16:49-56.
- <sup>7</sup> Hodak E, Amitay-Laish I, Atzmon L, et al. New insights into folliculotropic mycosis fungoides (FMF): A single-center experience. *J Am Acad Dermatol* 2016;75:347-355.
- <sup>8</sup> van Santen S, Roach RE, van Doorn R, et al. Clinical staging and prognostic factors in folliculotropic mycosis fungoides. *JAMA Dermatol* 2016;152:992-1000.
- <sup>9</sup> van Santen S, van Doorn R, Neelis KJ, et al. Recommendations for treatment in folliculotropic mycosis fungoides: report of the Dutch Cutaneous Lymphoma Group. *Br J Dermatol* 2017;177:223-228.
- <sup>10</sup> Vergier B, de Muret A, Beylot-Barry M, et al. Transformation of mycosis fungoides: clinicopathological and prognostic features of 45 cases. French Study Group of Cutaneous Lymphomas. *Blood* 2000;95:2212-2218.
- <sup>11</sup> Arulogun SO, Prince HM, Ng J, et al. Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. *Blood* 2008;112:3082-3087.

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



## DIAGNOSIS<sup>a</sup>

### 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<sup>b</sup>
- IHC panel of skin biopsy may include<sup>c,d,e</sup>:
  - CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30
- Molecular analysis to detect clonal T-cell receptor (TCR) gene rearrangements or other assessment of clonality<sup>a,f</sup>

→ [Workup \(MFSS-2\)](#)

### USEFUL IN CERTAIN CIRCUMSTANCES:

- Assessment of peripheral blood for Sézary cells (extensive skin disease where skin biopsy is not diagnostic, extensive patch or erythrodermic skin disease and/or strongly suggestive but not diagnostic of advanced-stage disease):
  - Flow cytometry to assess and quantitate an expanded T-cell population with aberrant immunophenotype.<sup>a,g</sup> See [MFSS-3](#) for specifics.
    - ◊ Flow cytometry panel may include CD3, CD4, CD7, CD8, CD26, CD45, TRBC1 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype, including loss of CD7 or CD26
  - Sézary cell preparation is less useful than flow cytometry due to the subjective nature of the process but may still be useful in cases where an aberrant immunophenotype is not detected.
- IHC panel of skin biopsy may include<sup>b,c</sup>:
  - CD25, CD56, TIA1, granzyme B, TCRβ, TCRδ; CCR4,<sup>h</sup> CXCL13, inducible T-cell co-stimulator (ICOS), and programmed cell death protein 1 (PD-1)
- Assessment of HTLV-1/2<sup>i</sup> by serology or other methods is encouraged as results can impact therapy.

<sup>a</sup> [Principles of Molecular Analysis in Primary Cutaneous Lymphomas \(PCLYM-B\)](#).

<sup>b</sup> Presence of LCT or areas of folliculotropism may have important implications for selection of therapy and outcome and should be included in pathology reports.

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

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

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

<sup>f</sup> 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 \(PCLYM-B\)](#).

<sup>g</sup> TRBC1 may contribute in detecting clonality and can improve the specificity of detecting Sézary cells when CD7 and CD26 are lost.

<sup>h</sup> 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).

<sup>i</sup> 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.



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## Mycosis Fungoides/Sezary Syndrome

### 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<sup>j</sup>:
  - ▶ CBC with differential and determination of absolute lymphocyte count
  - ▶ Flow cytometry to assess and quantitate an expanded T-cell population with aberrant phenotype (optional for T1<sup>k</sup>) ([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<sup>a</sup>
  - ▶ Comprehensive metabolic panel
  - ▶ LDH
- Imaging studies:
  - ▶ Chest/abdomen/pelvis (C/A/P) CT with contrast or integrated whole body FDG-PET/CT<sup>l</sup> for T3 or T4 (arms/legs included when disease assessment of entire body is needed)

For TNMB Classification, see [MFSS-3](#) and  
For Clinical Staging of MF and SS, see [MFSS-4](#)

#### 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 insufficient 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<sup>l</sup> 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<sup>m</sup>
- 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<sup>n</sup>
- Discuss fertility preservation<sup>o</sup>

<sup>a</sup> [Principles of Molecular Analysis in Primary Cutaneous Lymphomas \(PCLY-M-B\)](#).

<sup>j</sup> Sézary syndrome (B2) is as defined on [MFSS-3](#).

<sup>k</sup> See [Discussion](#) for when Sézary flow cytometric study is appropriate in T1 disease.

<sup>l</sup> Patients with cutaneous lymphomas have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.

<sup>m</sup> New significant adenopathy on clinical exam, abnormal laboratory results concerning of lymphoma, or accelerated skin disease.

<sup>n</sup> Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to full prescribing information for individual drugs.

<sup>o</sup> Fertility preservation options include: sperm banking, semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.

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



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## Mycosis Fungoides/Sezary Syndrome

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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 <sup>p,q,r,s,t,u</sup>			Clinical Staging of MF and SS ( <a href="#">MFSS-4</a> )					
Skin (T)	T <sub>0</sub> <sup>v</sup>	Absence of clinically suspicious lesions								
	T <sub>1</sub>	Patches, plaques, or papules <10% BSA	T <sub>1A</sub>	Patch only lesions						
			T <sub>1B</sub>	Plaque/papule ± patch lesions						
	T <sub>2</sub>	Patches, plaques, or papules ≥10% BSA	T <sub>2A</sub>	Patch only						
			T <sub>2B</sub>	Plaque ± patch						
T <sub>3</sub>		One or more tumors ≥1 cm in diameter								
T <sub>4</sub>		Confluence of erythema covering ≥80% BSA <sup>U</sup>								
Node (N) <sup>W</sup>	N <sub>0</sub>	No clinically abnormal LN; no biopsy necessary								
	N <sub>1</sub>	Pathology Dutch grade 1 or NCI LN 0-2: clone negative <b>or equivocal</b>		<a href="#">Dutch Criteria for Lymph Nodes on MFSS-5</a>						
	N <sub>1A</sub>									
	N <sub>1B</sub>	Pathology Dutch grade 1 or NCI LN 0-2: clone positive <b>and identical to skin</b>								
	N <sub>2</sub>	N <sub>2A</sub>	Dutch grade 2, NCI LN3: clone negative <b>or equivocal</b>							
		N <sub>2B</sub>	Dutch grade 2, NCI LN3: clone positive <b>and identical to skin</b>							
	N <sub>3W</sub>	N <sub>3A</sub>	Dutch grade 3-4, NCI LN4: clone negative or equivocal							
		N <sub>3B</sub>	Dutch grade 3-4, NCI LN4: clone positive <b>and identical to skin</b>							
N <sub>x</sub>		Clinically abnormal peripheral or central lymph node but no pathologic determination of representative LN. <b>Other surrogate means of determining involvement may be determined by Tri-Society consensus</b>								
Visceral (M)	M <sub>0</sub>	No visceral involvement								
	M <sub>1a</sub>	<b>BM only involvement</b>		<b>Clone positive and identical to skin</b>						
		<b>Clone negative or indeterminate</b>								
	M <sub>1b</sub>	<b>Non-BM visceral involvement</b>		<b>Clone positive and identical to skin</b>						
		<b>Clone negative or indeterminate</b>								
M <sub>x</sub>		Visceral involvement is neither confirmed nor refuted by available pathologic <b>or imaging assessment</b>								
Blood (B) <sup>X</sup>	B <sub>0</sub>	B <sub>0A</sub>	Clone negative <b>or equivocal</b>		Absence of significant blood involvement					
		B <sub>0B</sub>	Clone positive <b>and identical to skin</b>							
	B <sub>1</sub>	B <sub>1A</sub>	Clone negative <b>or equivocal</b>		Low blood tumor burden					
		B <sub>1B</sub>	Clone positive <b>and identical to skin</b>							
	B <sub>2</sub>	B <sub>2A</sub>	Clone negative <b>or equivocal</b>		High blood tumor burden					
		B <sub>2B</sub>	Clone positive <b>and identical to skin</b>							
	B <sub>x</sub>	B <sub>xA</sub>	Clone negative <b>or equivocal</b>		Unable to quantify blood involvement according to agreed upon guidelines					
B <sub>xB</sub>		Clone positive <b>and identical to skin</b>								

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

[Footnotes on MFSS-3A](#)



## FOOTNOTES

<sup>p</sup> 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.

<sup>q</sup> 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).

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

<sup>s</sup> 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 ( $\geq 25\%$  large cells), CD30+ or CD30-, and clinical features such as ulceration are important to document.

<sup>t</sup> Tumor = at least one  $\geq 1$  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.

<sup>u</sup> Patients with both erythroderma and tumors may be designated as T<sub>4</sub>(T<sub>3</sub>). 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.

<sup>v</sup> T<sub>0</sub> 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<sub>0</sub>.

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

<sup>x</sup> Blood staging for MF/SS is defined currently as B<sub>0</sub> = 250/ $\mu$ L of CD4+/CD26- or CD4+/CD7- cells, B<sub>1</sub> = does not meet criteria for B<sub>0</sub> or B<sub>2</sub>, and B<sub>2</sub> =  $\geq 1000/\mu$ L 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<sub>2</sub>) 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.



# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

## CLINICAL STAGING OF MF AND SSY

Clinical Stage <sup>z</sup>	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	<a href="#">MFSS-6</a>
IB (Skin only disease)	T2 (Patches, papules, and/or plaques covering ≥10% BSA)	N0	M0	B0 or B1	<a href="#">MFSS-7</a>
IIA	T1–2	N1–2	M0	B0 or B1	<a href="#">MFSS-7</a>
IIB (Tumor stage disease)	T3 (One or more tumors [≥1 cm in diameter])	N0–2	M0	B0 or B1	<a href="#">MFSS-8</a>
IIIA (Erythrodermic disease)	T4 (Confluence of erythema ≥80% BSA)	N0–2	M0	B0	<a href="#">MFSS-10</a>
IIIB (Erythrodermic disease)	T4 (Confluence of erythema ≥80% BSA)	N0–2	M0	B1	<a href="#">MFSS-10</a>
IV <sub>A</sub> <sub>1</sub> (Sézary syndrome)	T1–4	N0–2	M0	B2	<a href="#">MFSS-11</a>
IV <sub>A</sub> <sub>2</sub> (Sézary syndrome or Non-Sézary)	T1–4	N3	M0	B0 or B1 or B2	<a href="#">MFSS-11</a>
IVB (Visceral disease)	T1–4	N0–3	M1A or M1B	B0 or B1 or B2	<a href="#">MFSS-11</a>
	Large-cell transformation (LCT) <sup>aa</sup>				<a href="#">MFSS-12</a>

<sup>y</sup> Olsen EA, et al. Blood 2022;140:419-437.<sup>z</sup> 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).<sup>aa</sup> 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.[TNMB Classification on MFSS-3](#)

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



## LYMPH NODE (LN) 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.

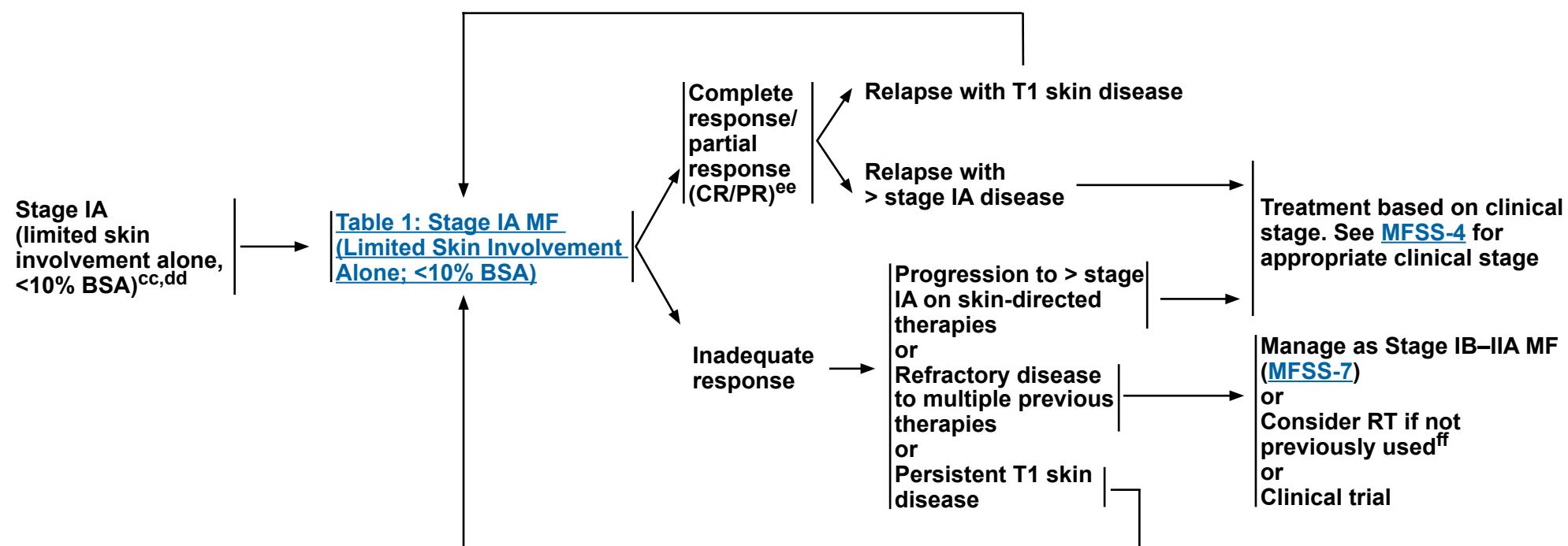


# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

STAGE<sup>bb</sup>  
([MFSS-3](#) and  
[MFSS-4](#))

### TREATMENT AND RESPONSE ASSESSMENT



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

<sup>cc</sup> In rare cases of confirmed unilesional MF, RT has been shown to provide long-term remission.

<sup>dd</sup> Rebiopsy if LCT is suspected; if histologic evidence of LCT, see [MFSS-12](#).

<sup>ee</sup> 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.

<sup>ff</sup> [Principles of Radiation Therapy \(PCLYM-A\)](#).

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



# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

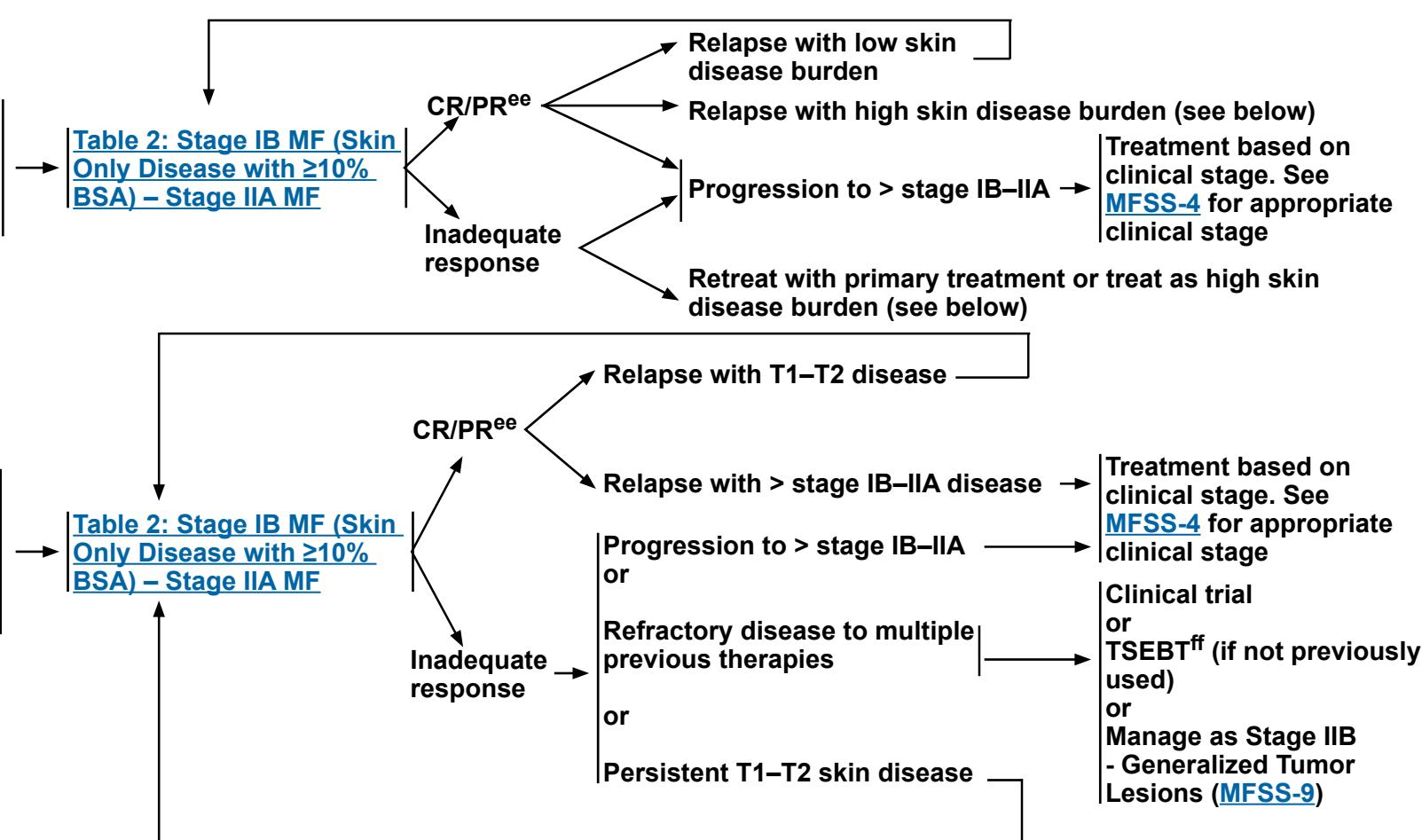
STAGE<sup>bb</sup>  
 (MFSS-3 and  
 MFSS-4)

Lower skin  
disease  
burden (eg,  
predominantly  
patch disease)

Stage IB (skin  
only disease  
with ≥10% BSA)  
- Stage IIA<sup>dd</sup>

Higher skin  
disease  
burden (eg,  
predominantly  
plaque  
disease)

### TREATMENT AND RESPONSE ASSESSMENT<sup>gg</sup>



<sup>bb</sup> 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).

<sup>dd</sup> Rebiopsy if LCT is suspected; if histologic evidence of LCT, see MFSS-12.

<sup>ee</sup> 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.

<sup>ff</sup> Principles of Radiation Therapy (PCLYM-A).

<sup>gg</sup> Imaging (with modalities used in workup) indicated when suspicious of clinical extracutaneous disease.

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



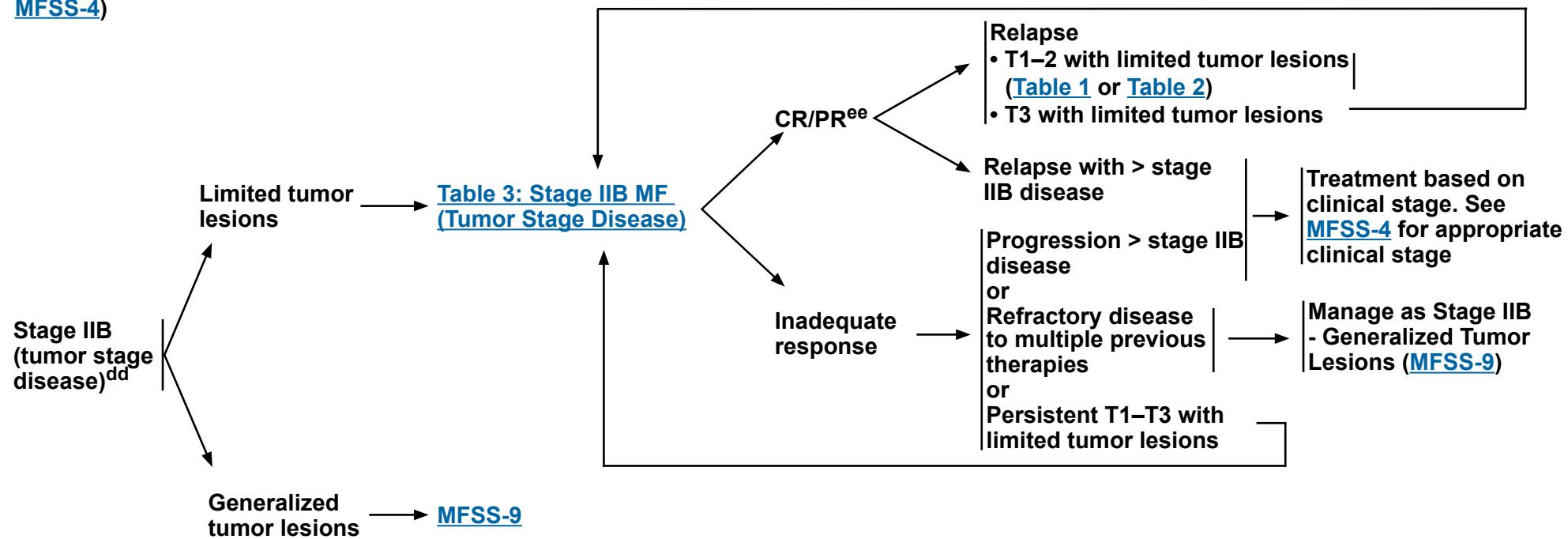
# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

### STAGE<sup>bb</sup>

(MFSS-3 and  
MFSS-4)

### TREATMENT AND RESPONSE ASSESSMENT<sup>gg</sup>



<sup>bb</sup> 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).

<sup>dd</sup> Rebiopsy if LCT is suspected; if histologic evidence of LCT, see MFSS-12.

<sup>ee</sup> 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.

<sup>gg</sup> Imaging (with modalities used in workup) indicated when suspicious of clinical extracutaneous disease.

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



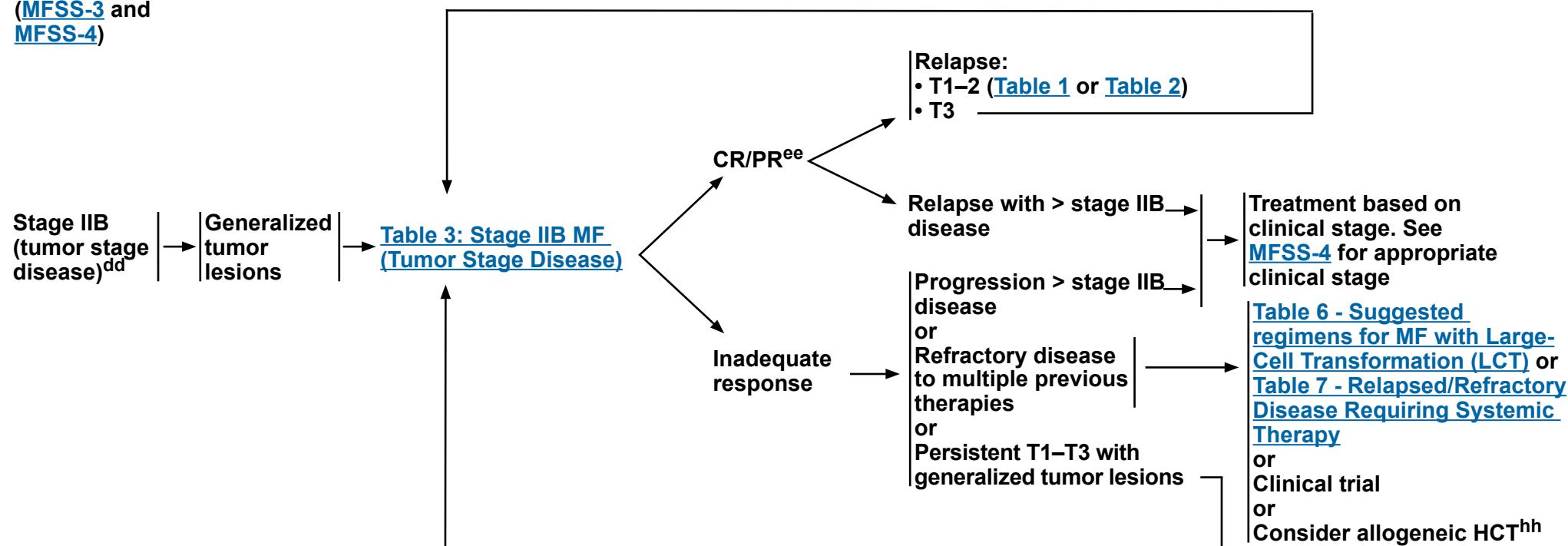
# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

STAGE<sup>bb</sup>

(MFSS-3 and  
MFSS-4)

### TREATMENT AND RESPONSE ASSESSMENT<sup>gg</sup>



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

<sup>dd</sup> Rebiopsy if LCT is suspected, if histologic evidence of LCT, see [MFSS-12](#).

<sup>ee</sup> 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.

<sup>gg</sup> Imaging (with modalities used in workup) indicated when suspicious of clinical extracutaneous disease.

<sup>hh</sup> 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.



# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

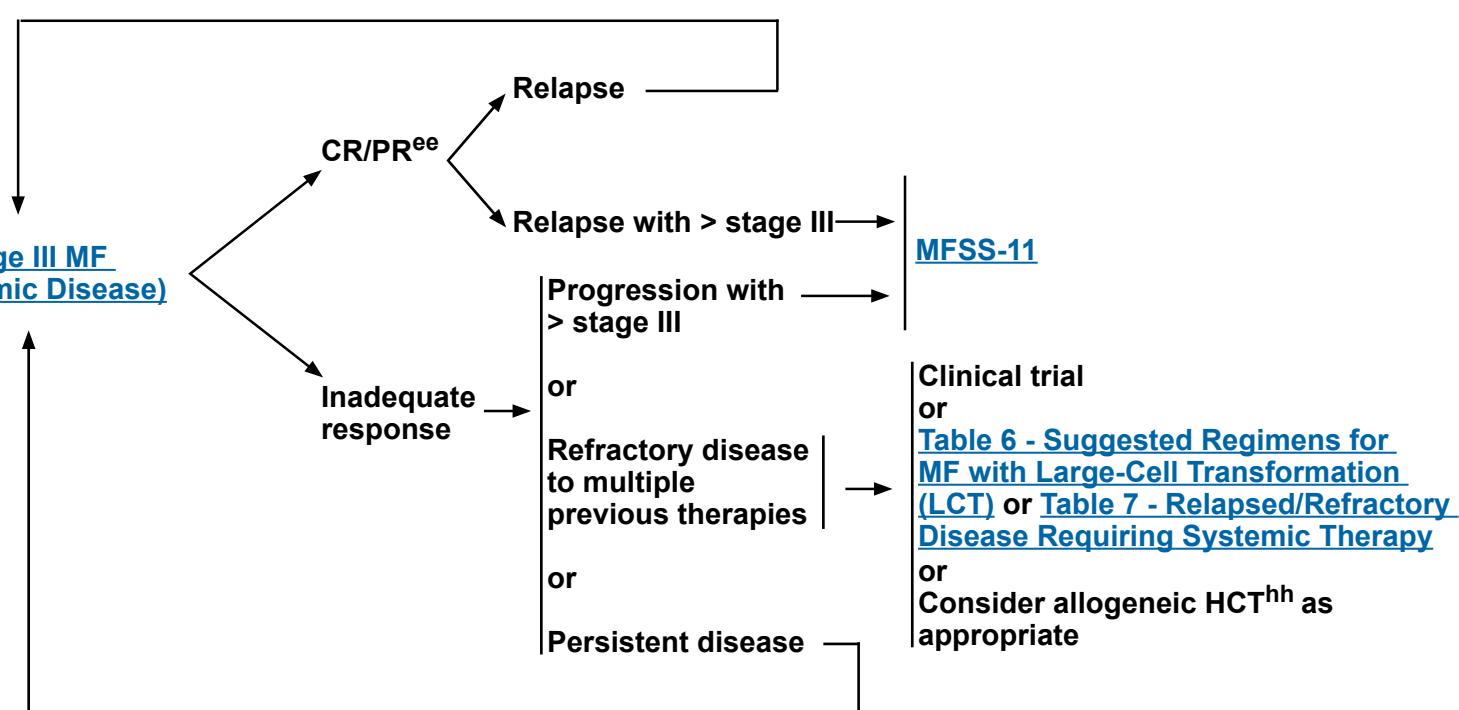
STAGE<sup>bb</sup>

(MFSS-3 and  
MFSS-4)

TREATMENT AND RESPONSE ASSESSMENT<sup>gg</sup>

Stage III  
(erythrodermic  
disease)<sup>dd</sup>

[Table 4: Stage III MF  
\(Erythrodermic Disease\)](#)



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

<sup>dd</sup> Rebiopsy if LCT is suspected; if histologic evidence of LCT, see [MFSS-12](#).

<sup>ee</sup> 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.

<sup>gg</sup> Imaging (with modalities used in workup) indicated when suspicious of clinical extracutaneous disease.

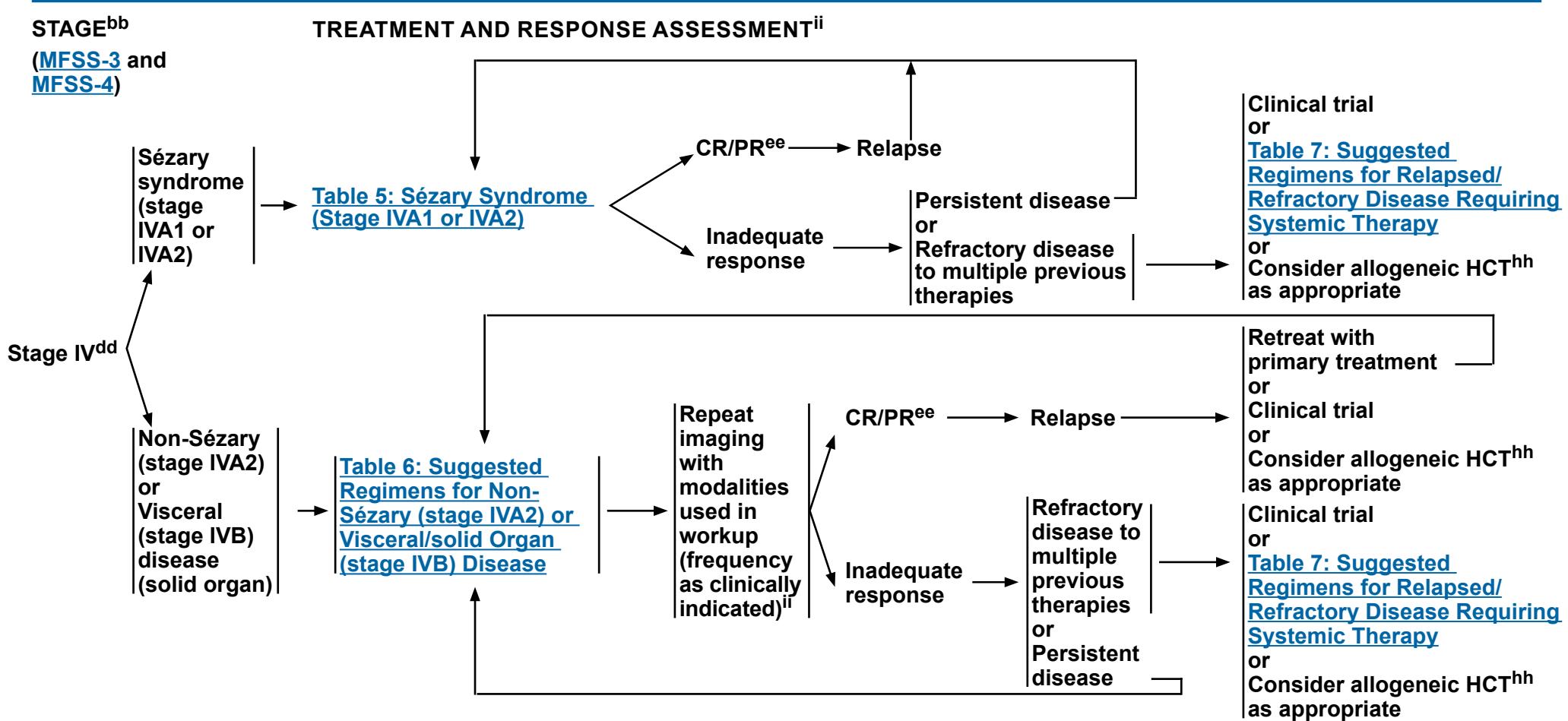
<sup>hh</sup> Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant. See [Discussion](#) for further details.

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



# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sézary Syndrome



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

<sup>dd</sup> Rebiopsy if LCT is suspected; if histologic evidence of LCT, see [MFSS-12](#).

<sup>ee</sup> 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.

<sup>hh</sup> Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant. See [Discussion](#) for further details.

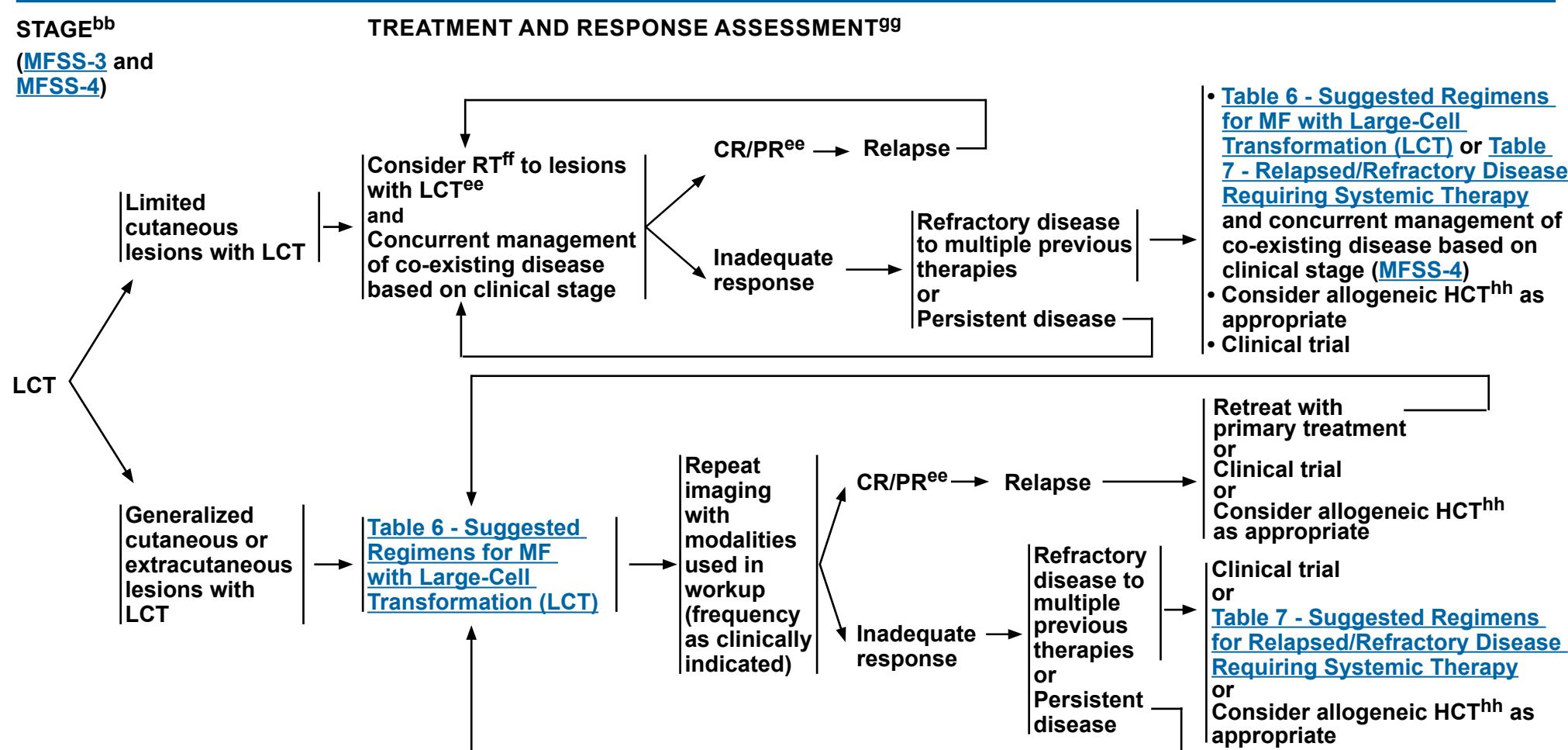
<sup>ii</sup> If disease in lymph nodes and/or viscera or suspicious of disease progression, imaging (with modalities used in workup) as clinically indicated based on distribution of disease.

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



# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome



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

<sup>ee</sup> 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.

<sup>ff</sup> [Principles of Radiation Therapy \(PCLYM-A\)](#).

<sup>gg</sup> Imaging (with modalities used in workup) indicated when suspicious of clinical extracutaneous disease.

<sup>hh</sup> 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.

**MFSS-A**  
**1 OF 12**



# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

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### SUGGESTED REGIMENS: SKIN-DIRECTED THERAPIES

SKIN-LIMITED/LOCAL (FOR LIMITED/LOCALIZED SKIN INVOLVEMENT)	TREATMENT CONSIDERATIONS
<ul style="list-style-type: none"> <li>• Local radiation (involved-site radiation therapy [ISRT])           <ul style="list-style-type: none"> <li>▶ 8–12 Gy; 24–30 Gy for unilesional presentation</li> </ul> </li> <li>• Phototherapy (See <a href="#">MFSS-C</a>)           <ul style="list-style-type: none"> <li>▶ UVB or narrowband UVB (NB-UVB)</li> </ul> </li> <li>• Topical corticosteroids</li> <li>• Topical imiquimod</li> <li>• Topical mechlorethamine (nitrogen mustard)</li> <li>• Topical retinoids (bexarotene, tazarotene)</li> <li>• Topical carmustine (category 2B)</li> </ul> <p><u>Useful in Certain Circumstances</u></p> <ul style="list-style-type: none"> <li>• Topical calcineurin inhibitor (pimecrolimus)</li> </ul>	<ol style="list-style-type: none"> <li>1. Skin-directed therapies can be used alone or in combination with other skin-directed therapies.</li> <li>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.</li> <li>3. TSEBT, and in certain cases PUVA or UVA1 may be considered for widespread thicker plaques or tumors.</li> <li>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.</li> <li>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.</li> <li>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.</li> <li>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.</li> <li>8. Topical retinoids can cause skin irritation including redness, peeling, and dermatitis when used on face and intertriginous body areas.</li> <li>9. Topical calcineurin inhibitors can be considered for perioral and periorbital affected areas of skin as a steroid-sparing treatment.</li> <li>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.</li> </ol>
<p><b>SKIN-GENERALIZED (FOR GENERALIZED SKIN INVOLVEMENT)</b></p> <ul style="list-style-type: none"> <li>• Phototherapy (See <a href="#">MFSS-C</a>)           <ul style="list-style-type: none"> <li>▶ UVB or NB-UVB</li> <li>▶ PUVA</li> <li>▶ UVA1 (if available)</li> </ul> </li> <li>• Topical corticosteroids</li> <li>• Topical mechlorethamine (nitrogen mustard)</li> <li>• Total skin electron beam therapy (TSEBT) (12–36 Gy)</li> </ul>	

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

**MFSS-A**  
**2 OF 12**



# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

[NCCN Guidelines Index](#)[Table of Contents](#)[Discussion](#)**TABLE 1: STAGE IA MF (Limited skin involvement alone; <10% BSA) - MFSS-6<sup>a,b</sup>**

SUGGESTED REGIMENS	TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON <a href="#">MFSS-A [1 of 12]</a> )
<ul style="list-style-type: none"> <li>Skin-directed therapies (alone or in combination with other skin-directed therapies) [See <a href="#">Skin-Limited/Local (for limited/localized skin involvement, MFSS-A 2 of 12)</a>]</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>Skin-directed therapy (<a href="#">Skin-Limited/Local</a>) in combination with systemic therapy (in selected cases)</li> </ul> <p><u>Preferred Regimens (alphabetical order)</u></p> <ul style="list-style-type: none"> <li>Systemic therapy + <a href="#">skin-directed therapy</a> (limited/local or generalized including phototherapy as indicated for stage of disease) <ul style="list-style-type: none"> <li>► Bexarotene</li> <li>► Interferon alfa<sup>b</sup></li> <li>► Methotrexate</li> </ul> </li> </ul> <p><u>Useful in Certain Circumstances (alphabetical order)</u></p> <ul style="list-style-type: none"> <li>Systemic therapy + <a href="#">skin-directed therapy</a> (limited/local or generalized including phototherapy as indicated for stage of disease) <ul style="list-style-type: none"> <li>► Acitretin</li> <li>► Extracorporeal photopheresis (ECP)</li> <li>► Interferon gamma-1b</li> <li>► Isotretinoin</li> </ul> </li> </ul>	<ol style="list-style-type: none"> <li>1. Stage IA MF most often can be treated with skin-directed therapies (alone or in combination with other skin-directed therapies).</li> <li>2. In patients with histologic evidence of FMF, skin disease may be less responsive to topical therapies.</li> <li>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).</li> <li>4. Alternative retinoids (acitretin or isotretinoin) could be considered in place of bexarotene.</li> <li>5. In stage IA, ECP is primarily reserved for the rare patient with stage IA MF with low level blood involvement (B1).</li> <li>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.</li> </ol>

[Footnotes on  
MFSS-A 9 of 12](#)

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

**MFSS-A  
3 OF 12**



# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

**TABLE 2: STAGE IB MF (Skin only disease with  $\geq 10\%$  BSA) – STAGE IIA MF - MFSS-7<sup>a,b,c</sup>**

SUGGESTED REGIMENS	TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON MFSS-A [1 of 12])
<ul style="list-style-type: none"> <li>• Skin-directed therapies (alone or in combination with other skin-directed therapies)           <ul style="list-style-type: none"> <li>▶ Lower skin disease burden (eg, predominantly patch disease): <a href="#">Skin-Limited/Local (for limited/localized skin involvement)</a></li> <li>▶ Higher skin disease burden (eg, predominantly plaque disease): <a href="#">Skin-Generalized (for generalized skin involvement)</a></li> </ul> </li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>• Systemic therapy + <a href="#">skin-directed therapy</a> (limited/local or generalized including phototherapy as indicated for stage of disease)</li> </ul> <p><u>Preferred Regimens</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>• Bexarotene</li> <li>• Brentuximab vedotin</li> <li>• Interferon alfa<sup>b</sup></li> <li>• Methotrexate</li> <li>• Mogamulizumab</li> <li>• Romidepsin</li> <li>• Vorinostat</li> </ul> <p><u>Useful in Certain Circumstances</u> (alphabetical order by category)</p> <ul style="list-style-type: none"> <li>• Acitretin</li> <li>• Denileukin diftitox-cxdl<sup>d</sup></li> <li>• ECP</li> <li>• Interferon gamma-1b</li> <li>• Isotretinoin</li> <li>• Alemtuzumab (category 2B)</li> <li>• Gemcitabine (category 2B)</li> <li>• Liposomal doxorubicin (category 2B)</li> <li>• Pembrolizumab (category 2B)</li> <li>• Pralatrexate (category 2B)</li> </ul>	<ol style="list-style-type: none"> <li>1. Stage IB-IIA MF can be treated with skin-directed therapies (alone or in combination with other skin-directed therapies).           <p><b>Limited patches/plaques:</b> Skin-directed therapy can be considered as monotherapy.</p> <p><b>Extensive skin involvement:</b> Phototherapy may be given alone or in combination with other skin-directed therapies. TSEBT maybe given alone or in combination with topical corticosteroids.</p> </li> <li>2. In patients with histologic evidence of FMF, skin disease may be less responsive to topical therapies.</li> <li>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.</li> <li>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 (<math>\geq</math> stage IB). Patients with SS were excluded from the ALCANZA trial.</li> <li>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 (<math>\geq</math> 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.</li> <li>6. Alternative retinoids (acitretin or isotretinoin) could be considered in place of bexarotene.</li> <li>7. In stage IB/IIA, ECP is primarily reserved for patients with low-level blood involvement (B1).</li> <li>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.</li> <li>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.</li> <li>10. LCT-MF was not an exclusion criteria for Study 302, which evaluated a reformulated version of denileukin diftitox, but no patients with LCT-MF were enrolled in the study.</li> </ol>

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

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**TABLE 3: STAGE IIB MF (Tumor stage disease)<sup>a,b,c</sup>**

LIMITED TUMOR DISEASE	GENERALIZED TUMOR DISEASE	TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON <u>MFSS-A [1 of 12]</u> )
<ul style="list-style-type: none"> <li>Local RT and/or <a href="#">skin-directed therapy</a></li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>Systemic therapy ± local RT ± <a href="#">skin-directed therapy</a> (limited/ local or generalized including phototherapy as indicated for stage of disease)</li> </ul> <p><u>Preferred Regimens</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Bexarotene</li> <li>Brentuximab vedotin</li> <li>Interferon alfa<sup>b</sup></li> <li>Methotrexate</li> <li>Mogamulizumab</li> <li>Romidepsin</li> </ul> <p><u>Other Recommended Regimen</u></p> <ul style="list-style-type: none"> <li>Vorinostat</li> <li>Pembrolizumab (category 2B)</li> </ul> <p><u>Useful in Certain Circumstances</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Acitretin</li> <li>Denileukin diftitox-cxdI<sup>d</sup></li> <li>ECP</li> <li>Interferon gamma-1b</li> <li>Isotretinoin</li> </ul>	<ul style="list-style-type: none"> <li>TSEBT OR</li> <li>Systemic therapy + <a href="#">skin-directed therapy</a> (limited/ local or generalized including phototherapy as indicated for stage of disease) OR</li> <li>Combination therapies</li> </ul> <p><u>Preferred Regimens</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Single agents <ul style="list-style-type: none"> <li>► Bexarotene</li> <li>► Brentuximab vedotin</li> <li>► Denileukin diftitox-cxdI<sup>d</sup></li> <li>► Gemcitabine</li> <li>► Interferon alfa<sup>b</sup></li> <li>► Retinoid + interferon alfa<sup>b</sup></li> </ul> </li> <li>Combination therapy</li> </ul> <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> <li>Pembrolizumab</li> <li>Vorinostat</li> </ul> <p><u>Useful in Certain Circumstances</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Single agents <ul style="list-style-type: none"> <li>► Acitretin</li> <li>► ECP</li> <li>► Interferon gamma-1b</li> <li>► Isotretinoin</li> </ul> </li> <li>Combination therapy <ul style="list-style-type: none"> <li>► ECP + interferon alfa<sup>b</sup> or retinoid</li> <li>► ECP + interferon alfa<sup>b</sup> + retinoid</li> </ul> </li> </ul>	<ol style="list-style-type: none"> <li>RT is preferred for limited tumor lesions. Topical therapies alone are often inadequate for tumor stage disease.</li> <li>In patients with histologic evidence of FMF, skin disease may be less responsive to topical therapies.</li> <li>Adjuvant systemic biologic therapy may be considered after TSEBT for generalized tumor lesions to improve response duration.</li> <li>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 (<math>\geq</math> stage IB). Patients with SS were excluded from the ALCANZA trial.</li> <li>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 (<math>\geq</math> 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 IIB/IIA disease. Patients with MF-LCT were excluded from the MAVORIC trial.</li> <li>Alternative retinoids (acitretin or isotretinoin) could be considered in place of bexarotene.</li> <li>ECP may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).</li> <li>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.</li> <li>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.</li> <li>LCT-MF was not an exclusion criteria for Study 302, which evaluated a reformulated version of denileukin diftitox, but no patients with LCT-MF were enrolled in the study.</li> </ol>

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



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## Mycosis Fungoides/Sezary Syndrome

[NCCN Guidelines Index](#)[Table of Contents](#)[Discussion](#)**TABLE 4: STAGE III MF (Erythrodermic disease) - MFSS-10<sup>a,b,c,e</sup>**

SUGGESTED REGIMENS	TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON <a href="#">MFSS-A [1 of 12]</a> )
<ul style="list-style-type: none"> <li>Systemic therapy + <a href="#">skin-directed therapy</a> (limited/local or generalized including phototherapy as indicated for stage of disease)</li> </ul> <p><u>Preferred Regimens</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Single agents <ul style="list-style-type: none"> <li>► Bexarotene</li> <li>► Brentuximab vedotin</li> <li>► ECP</li> <li>► Interferon alfa<sup>b</sup></li> <li>► Methotrexate</li> <li>► Mogamulizumab</li> <li>► Romidepsin</li> </ul> </li> <li>Combination therapy <ul style="list-style-type: none"> <li>► ECP + interferon alfa<sup>b</sup> or retinoid</li> <li>► ECP + interferon alfa<sup>b</sup> + retinoid</li> <li>► Retinoid + interferon alfa<sup>b</sup></li> </ul> </li> </ul> <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> <li>Vorinostat</li> </ul> <p><u>Useful in Certain Circumstances</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Single agents <ul style="list-style-type: none"> <li>► Acitretin</li> <li>► Alemtuzumab</li> <li>► Denileukin diftitox-cxdl<sup>d</sup></li> <li>► Gemcitabine</li> <li>► Interferon gamma-1b</li> <li>► Isotretinoin</li> <li>► Liposomal doxorubicin</li> <li>► Pembrolizumab</li> <li>► Pralatrexate</li> </ul> </li> <li>Skin-directed therapy <ul style="list-style-type: none"> <li>► Phototherapy</li> <li>► TSEBT (category 2B)</li> </ul> </li> </ul>	<ol style="list-style-type: none"> <li>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 (<math>\geq</math> stage IB). Patients with SS were excluded from the ALCANZA trial.</li> <li>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 (<math>\geq</math> 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 IIA disease. Patients with MF-LCT were excluded from the MAVORIC trial.</li> <li>Alternative retinoids (acitretin or isotretinoin) could be considered in place of bexarotene.</li> <li>ECP may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).</li> <li>Phototherapy and TSEBT may be associated with increased toxicity in patients with erythroderma and modification in dose/schedule may be considered.</li> <li>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.</li> <li>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.</li> <li>Patients with erythrodermic disease are at increased risk for secondary infection with skin pathogens and systemic antibiotic therapy should be considered. See <a href="#">MFSS-B</a>.</li> <li>LCT-MF was not an exclusion criteria for Study 302 LCT-MF was not an exclusion criteria for Study 302, which evaluated a reformulated version of denileukin diftitox, but no patients with LCT-MF were enrolled in the study.</li> </ol>

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

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## Mycosis Fungoides/Sezary Syndrome

**TABLE 5: SÉZARY SYNDROME (Stage IVA1 or IVA2) - MFSS-11<sup>a,b,c,e</sup>**

SUGGESTED REGIMENS		TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON <b>MFSS-A [1 of 12]</b> )
Low-Intermediate Burden (eg, ASC <5 K/mm <sup>3</sup> )	High Burden (eg, ASC >5 K/mm <sup>3</sup> )	
<ul style="list-style-type: none"> <li>Systemic therapy + <a href="#">skin-directed therapy</a> (limited/local or generalized including phototherapy as indicated for stage of disease)</li> </ul> <p><u>Preferred Regimens</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Single agents <ul style="list-style-type: none"> <li>Bexarotene</li> <li>ECP</li> <li>Interferon alfa<sup>b</sup></li> <li>Methotrexate</li> <li>Mogamulizumab</li> <li>Romidepsin</li> <li>Vorinostat</li> </ul> </li> <li>Combination therapy <ul style="list-style-type: none"> <li>ECP + interferon alfa<sup>b</sup> or retinoid</li> <li>ECP + interferon alfa<sup>b</sup> + retinoids</li> <li>Retinoid + interferon alfa<sup>b</sup></li> </ul> </li> </ul> <p><u>Other Recommended Regimens</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Alemtuzumab</li> <li>Brentuximab vedotin</li> <li>Gemcitabine</li> <li>Liposomal doxorubicin</li> <li>Pembrolizumab</li> <li>Pralatrexate</li> </ul> <p><u>Useful in Certain Circumstances</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Acitretin</li> <li>Interferon gamma-1b</li> <li>Isotretinoin</li> </ul>	<ul style="list-style-type: none"> <li>Systemic therapy + <a href="#">skin-directed therapy</a> (limited/local or generalized including phototherapy as indicated for stage of disease)</li> </ul> <p><u>Preferred Regimens</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Single agents <ul style="list-style-type: none"> <li>Mogamulizumab</li> <li>Romidepsin</li> </ul> </li> <li>Combination therapy <ul style="list-style-type: none"> <li>ECP + interferon alfa<sup>b</sup> or retinoid</li> <li>ECP + interferon alfa<sup>b</sup> + retinoids</li> <li>Retinoid + interferon alfa<sup>b</sup></li> </ul> </li> </ul> <p><u>Other Recommended Regimens</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Alemtuzumab</li> <li>Bexarotene</li> <li>Brentuximab vedotin</li> <li>ECP</li> <li>Gemcitabine</li> <li>Interferon alfa<sup>b</sup></li> <li>Liposomal doxorubicin</li> <li>Methotrexate</li> <li>Pembrolizumab</li> <li>Pralatrexate</li> <li>Vorinostat</li> </ul> <p><u>Useful in Certain Circumstances</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Acitretin</li> <li>Interferon gamma-1b</li> <li>Isotretinoin</li> </ul>	<ol style="list-style-type: none"> <li>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 (<math>\geq</math> stage IB). Patients with SS were excluded from the ALCANZA trial.</li> <li>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 (<math>\geq</math> 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.</li> <li>Alternative retinoids (acitretin or isotretinoin) could be considered in place of bexarotene.</li> <li>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.</li> <li>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.</li> </ol>

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

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

SUGGESTED REGIMENS		TREATMENT CONSIDERATIONS (SEE ALSO GENERAL CONSIDERATIONS ON <a href="#">MFSS-A [1 of 12]</a> )
<p><b>Non-Sézary (stage IVA2) or Visceral/Solid Organ (stage IVB) Disease (MFSS-11)</b></p> <ul style="list-style-type: none"> <li>Systemic therapy ± RT for local control</li> </ul> <p><u>Preferred Regimens</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Brentuximab vedotin</li> <li>Gemcitabine</li> <li>Liposomal doxorubicin</li> <li>Pralatrexate</li> <li>Romidepsin</li> </ul> <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> <li>Mogamulizumab</li> <li>Multiagent chemotherapy regimens (See <a href="#">NCCN Guidelines for T-Cell Lymphomas - PTCL-B 3 of 8</a> for regimens listed for PTCL- NOS)</li> </ul>	<p><b>MF-LCT (MFSS-12)</b></p> <ul style="list-style-type: none"> <li>TSEBT OR</li> <li>Systemic therapy + <a href="#">skin directed therapy</a></li> </ul> <p><u>Preferred Regimens</u> (alphabetical order)</p> <ul style="list-style-type: none"> <li>Brentuximab vedotin</li> <li>Gemcitabine</li> <li>Liposomal doxorubicin</li> <li>Pralatrexate</li> <li>Romidepsin</li> </ul> <p><u>Multiagent chemotherapy regimens</u> (See <a href="#">NCCN Guidelines for T-Cell Lymphomas - PTCL-B 3 of 8</a> for regimens listed for PTCL-NOS)</p> <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> <li>Pembrolizumab</li> </ul>	<ol style="list-style-type: none"> <li>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.</li> <li>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.</li> <li>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.</li> <li>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.</li> </ol>

**TABLE 7: RELAPSED OR REFRACTORY DISEASE TO MULTIPLE PRIOR THERAPIES**

SUGGESTED REGIMENS
<p><u>Useful in Certain Circumstances</u> (alphabetical order by category)</p> <ul style="list-style-type: none"> <li>Alemtuzumab</li> <li>Chlorambucil</li> <li>Cyclophosphamide</li> <li>Etoposide</li> <li>Pembrolizumab</li> <li>Pentostatin</li> <li>Temozolomide for central nervous system (CNS) involvement at some NCCN Member Institutions</li> <li>Bortezomib (category 2B)</li> <li>Multiagent chemotherapy regimens (See <a href="#">NCCN Guidelines for T-Cell Lymphomas - PTCL-B 3 of 8</a> for regimens listed for PTCL-NOS)</li> </ul>

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## FOOTNOTES

- <sup>a</sup>Laboratory studies for triglycerides, and thyroid function tests (with free thyroxine T4) are recommended for patients receiving bexarotene.
- <sup>b</sup>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).
- <sup>c</sup>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). Interpretation of CD30 expression is not universally standardized. Responses have been seen in patients with a low level of CD30 positivity and any level of CD30 positivity is acceptable for the use of brentuximab vedotin.
- <sup>d</sup>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.
- <sup>e</sup>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).
- <sup>f</sup>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.

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### SUGGESTED TREATMENT REGIMENS

#### REFERENCES

#### Skin-Directed Therapies

##### Topical corticosteroids

Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. *Arch Dermatol* 1998;134:949-954.

Zackheim HS. Treatment of patch stage mycosis fungoides with topical corticosteroids. *Dermatol Ther* 2003;16:283-287.

##### 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. Kim EJ, Guitart J, Querfeld C, et al. The PROVe Study: US Real-World Experience with Chlormethine/Mechlorethamine Gel in Combination with Other Therapies for Patients with Mycosis Fungoides Cutaneous T-Cell Lymphoma. *Am J Clin Dermato*. 2021;22: 407-414.

Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. *JAMA Dermatol* 2013;149:25-32.

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

Wilson LD, Kacinski BM, Jones GW. Local superficial radiotherapy in the management of minimal stage IA cutaneous T-cell lymphoma (Mycosis Fungoides). *Int J Radiat Oncol Biol Phys* 1998;40:109-115.

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.

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.

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.

Heald P, Mehlmauer M, Martin AG, et al. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. *J Am Acad Dermatol* 2003;49:801-815.

##### Tazarotene gel

Apisarthanarax 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.

Ponte P, Serrao V, Apetato M. Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides. *J Eur Acad Dermatol Venereol* 2010;24:716-721.

Olsen EA, Hodak E, Anderson T, et al. Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: A consensus statement of the United States Cutaneous Lymphoma Consortium. *J Am Acad Dermatol* 2018;74:27-58.

##### UVA1

Trovato E, Pellegrino M, Filippi F, et al. Clinical and histological evaluation in patients with mycosis fungoides treated with UVA1. *G Ital Dermatol Venereol* 2020;155:306-311.

Adıjen E, Tektaş V, Erduran F, et al. Ultraviolet A1 phototherapy in the treatment of early mycosis fungoides. *Dermatology* 2017;233:192-198.

Olek-Hrab K, Silny W, Dańczak-Pazdrowska A, et al. Ultraviolet A1 phototherapy for mycosis fungoides. *Clin Exp Dermatol* 2013;38:126-130.

Jang MS, Jang JY, Park JB, et al. Erratum: Folliculotropic mycosis fungoides in 20 Korean cases: Clinical and histopathologic features and response to ultraviolet A-1 and/or photodynamic therapy. *Ann Dermatol* 2018;30:510.

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.

Hoppe RT, Harrison C, Tavallaei M, et al. Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: results of a pooled analysis from 3 phase-II clinical trials. *J Am Acad Dermatol* 2015;72:286-292.

Morris S, Scarisbrick J, Frew J, et al. The results of low-dose total skin electron beam radiation therapy (TSEB) in patients with mycosis fungoides from the UK Cutaneous Lymphoma Group. *Int J Radiat Oncol Biol Phys* 2017;99:627-633.

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.

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

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# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

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### SUGGESTED TREATMENT REGIMENS

#### REFERENCES

## Systemic Therapies

### Alemtuzumab

Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. *Blood* 2003;101:4267-4272.

Bernengo MG, Quaglino P, Comessatti A, et al. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. *Haematologica* 2007;92:784-794.

Gautschi O, Blumenthal N, Streit M, et al. Successful treatment of chemotherapy-refractory Sezary syndrome with alemtuzumab (Campath-1H). *Eur J Haematol* 2004;72:61-63.

Querfeld C, Mehta N, Rosen ST, et al. Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. *Leuk Lymphoma* 2009;50:1969-1976.

### 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, Tavallaei 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.

Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet* 2017;390:555-566.

### Denileukin diftitox-cxd1

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.

Prince HMM, Geskin LJ, Akilov OE, et al. Safety and tolerability 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;140:6577-6578.

### Extracorporeal photopheresis (ECP)

Talpur R, Demierre MF, Geskin L, et al. Multicenter photopheresis intervention trial in early-stage mycosis fungoides. *Clin Lymphoma Myeloma Leuk* 2011;11:219-227.

Knobler R, Duvic M, Querfeld C, et al. Long-term follow-up and survival of cutaneous T-cell lymphoma patients treated with extracorporeal photopheresis. *Photodermat Photoimmunol Photomed* 2012;28:250-257.

Atilla E, Atilla PA, Bozdag SC, et al. Extracorporeal photochemotherapy in mycosis fungoides. *Transfus Clin Biol* 2017;24:454-457.

Gao C, McCormack C, van der Weyden C, et al. Prolonged survival with the early use of a novel extracorporeal photopheresis regimen in patients with Sezary syndrome. *Blood* 2019;134:1346-1350.

### Gemcitabine

Duvic M, Talpur R, Wen S, et al. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. *Clin Lymphoma Myeloma* 2006;7:51-58.

Marchi E, Alinari L, Tani M, et al. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients. *Cancer* 2005;104:2437-2441.

Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. *J Clin Oncol* 2000;18:2603-2606.

Zinzani PL, Venturini F, Stefoni V, et al. Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. *Ann Oncol* 2010;21:860-863.

Awar O, Duvic M. Treatment of transformed mycosis fungoides with intermittent low-dose gemcitabine. *Oncology* 2007;73:130-135.

### Interferon

Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. *Dermatol Ther* 2003;16:311-321.

Kaplan EH, Rosen ST, Norris DB, et al. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. *J Natl Cancer Inst* 1990;82:208-212.

### 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.

Dummer R, Quaglino P, Becker JC, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. *J Clin Oncol* 2012;30:4091-4097.

Weiner D, Ly A, Talluru S, et al. Efficacy of single-agent chemotherapy with pegylated liposomal doxorubicin or gemcitabine in a diverse cohort of patients with recalcitrant cutaneous T-cell lymphoma. *Br J Dermatol* 2024;190:436-438.

Falkenhain-Lopez D, Fulgencio-Barbarin J, Puerta-Pena M, et al. Single-centre experience of using pegylated liposomal doxorubicin as maintenance treatment in mycosis fungoides. *Br J Dermatol* 2022;186:363-365.

### Methotrexate

Zackheim HS, Kashani-Sabet M, Hwang ST. Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients. *J Am Acad Dermatol* 1996;34:626-631.

Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. *J Am Acad Dermatol* 2003;49:873-878.

### Mogamulizumab

Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): An international, open-label, randomised, controlled phase 3 trial. *Lancet Oncol* 2018;19:1192-1204.

### Pembrolizumab

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.

Greiner D, Olsen EA, Petroni G. Pentostatin (2'-deoxycoformycin) in the treatment of cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1997;36:950-955.

Tsimberidou AM, Giles F, Duvic M, et al. Phase II study of pentostatin in advanced T-cell lymphoid malignancies. Update on an M.D. Anderson Cancer Center Series. *Cancer* 2004;100:342-349.

[Continued](#)

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

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**SUGGESTED TREATMENT REGIMENS**  
**REFERENCES**
**Systemic Therapies (continued)****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.

Foss F, Horwitz SM, Coiffier B, et al. Pralatrexate is an effective treatment for relapsed or refractory transformed mycosis fungoides: a subgroup efficacy analysis from the PROPEL study. *Clin Lymphoma Myeloma Leuk* 2012;12:238-243.

**Romidepsin**

Piekorz RL, Frye R, Turner M, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *J Clin Oncol* 2009;27:5410-5417.

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.

**Retinoids**

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

Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. *Arch Dermatol* 2001;137:581-593.

Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol* 2001;19:2456-2471.

**Temozolomide**

Tani M, Fina M, Alinari L, et al. Phase II trial of temozolomide in patients with pretreated cutaneous T-cell lymphoma. *Haematologica* 2005;90:1283-1284.

Querfeld C, Rosen ST, Guitart J, et al. Multicenter phase II trial of temozolomide in mycosis fungoides/sezary syndrome: correlation with O<sup>6</sup>-methylguanine-DNA methyltransferase and mismatch repair proteins. *Clin Cancer Res* 2011;17:5748-5754.

**Vorinostat**

Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). *Blood* 2007;109:31-39.

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.

Duvic M, Olsen EA, Breneman D, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. *Clin Lymphoma Myeloma* 2009;9:412-416.

**Combination Therapies****Systemic + skin-directed**

Rupoli S, Goteri G, Pulini S, et al. Long-term experience with low-dose interferon-alpha and PUVA in the management of early mycosis fungoides. *Eur J Haematol* 2005;75:136-145.

Kuzel T, Roenigk H Jr, Samuelson E, et al. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sézary syndrome. *J Clin Oncol* 1995;13:257-263.

McGinnis K, Shapiro M, Vittorio C, et al. Psoralen plus long-wave UV-A (PUVA) and bexarotene therapy: An effective and synergistic combined adjunct to therapy for patients with advanced cutaneous T-cell lymphoma. *Arch Dermatol* 2003;139:771-775.

Wilson LD, Jones GW, Kim D, et al. Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides. *J Am Acad Dermatol* 2000;43:54-60.

Stadler R, Otte HG, Luger T, et al. Prospective randomized multicenter clinical trial on the use of interferon alpha -2a plus acitretin versus interferon alpha -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. *Blood* 1998;92:3578-3581.

**Systemic + systemic**

Straus DJ, Duvic M, Kuzel T, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa-2b (Intron-A) for patients with cutaneous T-cell lymphoma. *Cancer* 2007;109:1799-1803.

Talpur R, Ward S, Apisarnthanarak N, et al. Optimizing bexarotene therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2002;47:672-684.

Suchin KR, Cucchiara AJ, Gottlieb SL, et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. *Arch Dermatol* 2002;138:1054-1060.

Raphael BA, Shin DB, Suchin KR, et al. High clinical response rate of Sezary syndrome to immunomodulatory therapies: prognostic markers of response. *Arch Dermatol* 2011;147:1410-1415.

**Allogeneic HCT**

de Masson A, Beylot-Barry M, Bouaziz JD, et al. Allogeneic stem cell transplantation for advanced cutaneous T-cell lymphomas: a study from the French Society of Bone Marrow Transplantation and French Study Group on Cutaneous Lymphomas. *Haematologica* 2014;99:527-534.

de Masson A, Beylot-Barry M, Ram-Wolff C, et al. Allogeneic transplantation in advanced cutaneous T-cell lymphomas (CUTALLO): a propensity score matched controlled prospective study. *Lancet* 2023;401:1941-1950.

Duarte R, Boumendil A, Onida F, et al. Long-term outcome of allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sézary syndrome: a European society for blood and marrow transplantation lymphoma working party extended analysis. *J Clin Oncol* 2014;32:3347-3348.

Duarte RF, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. *Bone Marrow Transplant* 2008;41:597-604.

Hosing C, Bassett R, Dabaja B, et al. Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution. *Ann Oncol* 2015;26:2490-2495.

Iqbal M, Reljic T, Ayala E, et al. Efficacy of allogeneic hematopoietic cell transplantation in cutaneous T-cell lymphoma: Results of a systematic review and meta-analysis. *Biol Blood Marrow Transplant* 2020;26:76-82.

Johnson WT, Mukherji R, Kartan S, et al. Allogeneic hematopoietic stem cell transplantation in advanced stage mycosis fungoides and Sezary syndrome: a concise review. *Chin Clin Oncol* 2019;8:12.

Lechowicz M, Lazarus HM, Carreras J, et al. Allogeneic hematopoietic cell transplantation for mycosis fungoides and Sezary syndrome. *Bone Marrow Transplant* 2014;49:1360-1365.

Weng WK, Arai S, Rezvani A, et al. Nonmyeloablative allogeneic transplantation achieves clinical and molecular remission in cutaneous T-cell lymphoma. *Blood Adv* 2020;4:4474-4482.

Wu PA, Kim YH, Lavori PW, et al. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. *Biol Blood Marrow Transplant* 2009;15:982-990.

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



# NCCN Guidelines Version 1.2025

## Mycosis Fungoides/Sezary Syndrome

### 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<sup>1</sup>
- Topical over-the-counter preparations
- Systemic agents
  - ◊ First-line
    - H1 antihistamines; single agent or combination of antihistamines from different classes<sup>2</sup>
    - Gabapentin<sup>3,4</sup>
    - Pregabalin
  - ◊ Second-line
    - Aprepitant<sup>5-8</sup>
    - Mirtazapine<sup>4</sup>
    - Selective serotonin reuptake inhibitors (SSRIs)<sup>9</sup>
  - ◊ Third-line
    - Naltrexone<sup>10</sup>
    - 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
- IV broad-spectrum antibiotics for *S. aureus* infection<sup>11</sup>
- 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**  
**REFERENCES**

- <sup>1</sup> Yosipovitch G, Szolar C, Hui XY, Maibach H. High-potency topical corticosteroid rapidly decrease histamine-induced itch but not thermal sensation and pain in human beings. *J Am Acad Dermatol* 1996;35:118-120.
- <sup>2</sup> Eschler D, Klein PA. An evidence-based review of the efficacy of topical antihistamines in the relief of pruritus. *J Drugs Dermatol* 2010;9:992-997.
- <sup>3</sup> Matsuda KM, Sharma D, Schonfeld AR, Kwatra SG. Gabapentin and pregabalin for the treatment of chronic pruritus. *J Am Acad Dermatol* 2016;75:619-625.
- <sup>4</sup> Demierre MF, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. *Am Acad Dermatol* 2006;55:543-544.
- <sup>5</sup> Jiménez Gallo D, Albarrán Planelles C, Linares Barrios M, et al. Treatment of pruritus in early-stage hypopigmented mycosis fungoides with aprepitant. *Dermatol Ther* 2014;27:178-182.
- <sup>6</sup> Duval A, Dubertret L. Aprepitant as an antipruritic agent? *N Engl J Med* 2009;361:1415-1416.
- <sup>7</sup> Booken N, Heck M, Nicolay JP, et al. Oral aprepitant in the therapy of refractory pruritus in erythrodermic cutaneous T-cell lymphoma. *Br J Dermatol* 2011;164:665-667.
- <sup>8</sup> Ladizinski B, Bazakas A, Olsen EA. Aprepitant: A novel neurokinin-1 receptor/substance P antagonist as antipruritic therapy in cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2012;67:e198-e199.
- <sup>9</sup> Ständer S, Böckenholt B, Schürmeyer-Horst F, et al. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. *Acta Derm Venereol* 2009;89:45-51.
- <sup>10</sup> Brune A, Metze D, Luger T, Ständer S. Antipruritic therapy with the oral opioid receptor antagonist naltrexone. Open, non-placebo controlled administration in 133 patients. *Hautarzt* 2004;55:1130-1136.
- <sup>11</sup> Lindahl LM, Willerslev-Olsen A, Gjerdum LMR, et al. Antibiotics inhibit tumor and disease activity in cutaneous T-cell lymphoma. *Blood* 2019;134:1072-1083.

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

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### PRINCIPLES OF PHOTOTHERAPY<sup>1</sup>

#### General Principles

- Phototherapy is used for several indications (including primary or adjuvant treatment for the lymphoma as well as to control pruritus) in cutaneous lymphomas, especially in MF, SS and lymphomatoid papulosis (LyP).
- Psoralen plus UVA (PUVA) carries an increased risk of melanoma and a higher risk of nonmelanoma skin cancers (NMSCs) than narrowband UVB (NBUVB). Therefore, the choice of whether to use PUVA is typically based on its deeper penetration in the skin, an important factor for patients with thick plaque disease or folliculotropism, particularly if phototherapy is used as sole therapy.
- NBUVB is available in many more offices than PUVA and also as a home panel or unit.
- Hand/foot PUVA is an office-based procedure that can be used at the end of a treatment with whole body PUVA or NBUVB. If using following NBUVB, this involves a topical psoralen applied 20-30 minutes prior to UVA exposure.
- UVA1 (available in limited centers) may offer deeper skin penetration without the need for psoralen and thus would allow for its use during pregnancy.
- Relative exclusions for NBUVB and PUVA include multiple NMSCs, photosensitivity (inherent, drug, or underlying condition) as well as physical and/or financial limitations.
- NBUVB and PUVA have certain exclusions for treatment based on medical conditions:
  - ▶ Xeroderma pigmentosa and photosensitive collagen vascular diseases such as systemic lupus erythematosus (SLE) for both PUVA and NBUVB
  - ▶ Melanoma and pregnancy for PUVA
  - ▶ Porphyria for NBUVB
  - ▶ Patients with a previously treated isolated thin melanoma that can be excluded from the field of UV light might be considered in certain circumstances for NBUVB.

#### Dosing Guidelines

- The Fitzpatrick skin prototype is typically used to determine the initial and incremental energy dose for an individual patient.
- When starting phototherapy, concomitant medications that are photosensitizers (such as the tetracyclines, amiodarone, and hydrochlorothiazide), a history of treatment that may have induced photosensitivity (such as mogamulizumab), recent TSEBT, or the presence of erythroderma should trigger consideration of decreasing the starting dose and reducing the rate of light escalation to prevent burning.
- If one of the retinoids (bexarotene, acitretin or isotretinoin; all photosensitizing) or systemic methotrexate is being added to phototherapy to enhance efficacy, consider lowering the current dose of light when starting the medication and taking the oral medication after, not immediately before, phototherapy.
- If phototherapy is being added to a treatment regimen that already includes a retinoid, the initial and incremental energy dose may need to be reduced and adjusted.
- Patients that do not have involvement of their face may help to prevent skin cancers and accelerated aging by covering their face during phototherapy, recognizing that doing so, like covering genitals (recommended in males), creates a “privileged” site.
- Topical medications, such as topical mechlorethamine or topical bexarotene, can be used with phototherapy but should be applied after, not before, phototherapy.
- Patients on long term phototherapy, alone or in combination with other systemic or topical agents, should be on the lowest dose/least frequent dosing to maintain response and carefully monitored for the development of actinic keratoses, NMSCs, and melanoma.

<sup>1</sup> Olsen, EA, Hodak E, Anderson T et al Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: A consensus statement of the United States Cutaneous Lymphoma Consortium. J Am Acad Dermatol 2016;74:27-58. Please see handout information for patients with MF/SS who you plan to treat with either NBUVB or PUVA.

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.<sup>a,b,c</sup>
- 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.<sup>a</sup>
- ▶ Unlike systemic ALCL, PC-ALCL typically follows an indolent course and although cutaneous relapses are common, an excellent prognosis is usually maintained.<sup>d,e</sup>
- ▶ Histologically characterized by diffuse, cohesive sheets of large CD30-positive (in >75%) cells with anaplastic, pleomorphic, or immunoblastic appearance.<sup>a</sup>
- ▶ 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.<sup>a</sup> 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.<sup>a</sup>
- ▶ LyP has been reported to be associated with other lymphomas such as MF, PC-ALCL, systemic ALCL, or Hodgkin lymphoma.<sup>f,g</sup>
- ▶ LyP is histologically heterogeneous with large atypical anaplastic, immunoblastic, or Hodgkin-like cells in a marked inflammatory background<sup>a</sup>; several histologic subtypes can be defined based on evolution of skin lesions.<sup>f</sup>
- ▶ LyP clinical features are characterized by chronic, recurrent, spontaneously regressing papulonodular (grouped or generalized) skin lesions.<sup>a,f</sup>

<sup>a</sup> WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. (WHO classification of tumours series, 5th ed.; vol. 11). Lyon (France): International Agency for Research on Cancer; 2024.; Campo E, et al. Blood 2022;140:1229-1253. See Classification ([ST-1](#)).

<sup>b</sup> Vergier B, et al. Am J Surg Pathol 1998;22:1192-1202.

<sup>c</sup> Liu HL, et al. J Am Acad Dermatol 2003;49:1049-1058.

<sup>d</sup> Benner MF, Willemze R. Arch Dermatol 2009;145:1399-1404.

<sup>e</sup> Woo DK, et al. Arch Dermatol 2009;145:667-674.

<sup>f</sup> Kempf W, et al. Blood 2011;118:4024-4035.

<sup>g</sup> 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).

**Diagnosis on  
PCTLTD-1**

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



# NCCN Guidelines Version 1.2025

## Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

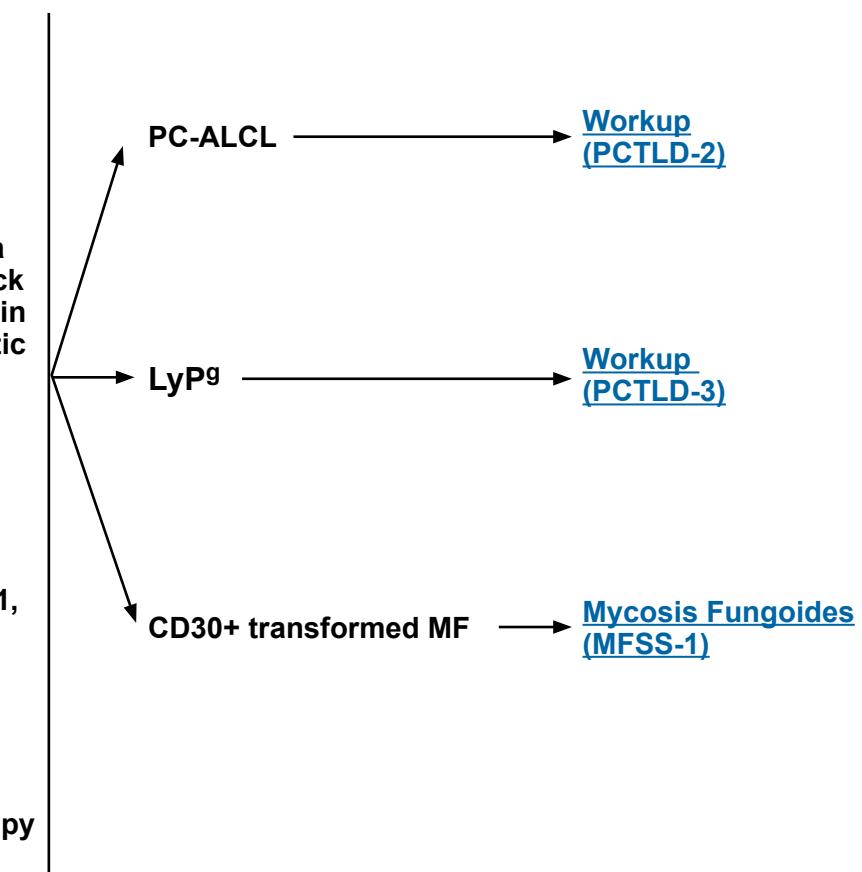
### DIAGNOSIS<sup>a</sup>

#### ESSENTIAL:

- Clinical presentation: see Overview and Definition ([PCTLTD/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<sup>b,c</sup> on skin biopsy:
  - IHC panel may include: CD3, CD4, CD8, CD20, CD30, CD56, ALK<sup>d</sup>

#### USEFUL IN CERTAIN CIRCUMSTANCES:

- On skin biopsy, expanded IHC panel may include: CD2, CD5, CD7, CD25, TIA1, granzyme B, perforin, IRF4/MUM1, EMA, TCR $\beta$ , TCR $\delta$
- EBER-ISH
- Molecular analysis to detect clonal TCR gene rearrangements or other assessment of clonality<sup>a,e</sup>
- FISH: ALK and DUSP22 gene rearrangements<sup>a</sup>
- Excisional or incisional biopsy of suspicious lymph nodes
- Assessment of HTLV-1/2 serology<sup>f</sup> is encouraged as results can impact therapy



<sup>a</sup> [Principles of Molecular Analysis in Primary Cutaneous Lymphomas \(PCLYM-B\)](#).

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

<sup>c</sup> Typical immunophenotype: CD30+ (>75% cells), CD4+ variable loss of CD2/CD5/CD3, CD8+ (<5%) cytotoxic granule proteins positive.

<sup>d</sup> ALK positivity and t(2;5) translocation is typically absent in PC-ALCL and LyP.

<sup>e</sup> 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 \(TCLYM-A\)](#).

<sup>f</sup> See [map](#) for prevalence of HTLV-1/2 by geographic region. HTLV-1 has been described in patients in non-endemic areas.

<sup>g</sup> 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

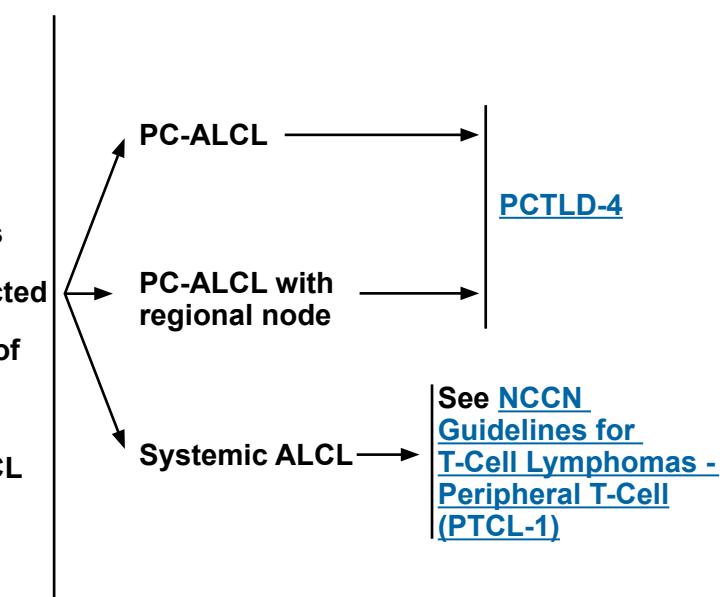
### ESSENTIAL:

- History and complete physical examination including complete skin examination<sup>h</sup>; 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)<sup>i</sup>
- Biopsy suspicious nodes<sup>j,k,l</sup>: 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.

PC-ALCL →

### 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<sup>m</sup>
- Discuss fertility preservation<sup>n</sup>



<sup>h</sup> Monitoring the size and number of lesions will assist with response assessment.

<sup>i</sup> 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.

<sup>j</sup> 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).

<sup>k</sup> Consider systemic ALCL, regional lymph node involvement with PC-ALCL, or lymph node involvement with transformed MF.

<sup>l</sup> Consider PC-ALCL if in draining lymph nodes only.

<sup>m</sup> Many skin-directed and systemic therapies are contraindicated or are of unknown safety in pregnancy. Refer to individual drug information.

<sup>n</sup> 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

### ESSENTIAL:

- History and complete physical examination including complete skin examination<sup>h</sup>; palpation of peripheral lymph node regions; liver or spleen enlargement
- CBC with differential
- Comprehensive metabolic panel
- LDH

LyP<sup>g</sup>

### USEFUL IN CERTAIN CIRCUMSTANCES:

- Pregnancy testing in patients of childbearing potential if contemplating treatments that are contraindicated in pregnancy<sup>m</sup>
- Discuss fertility preservation<sup>n</sup>
- C/A/P CT with contrast or integrated whole body FDG-PET/CT (arms/legs included when disease assessment of entire body is needed)<sup>g,i,o</sup> (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)<sup>g,o</sup>

[PCTL-D-5](#)

<sup>g</sup> 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.

<sup>h</sup> Monitoring the size and number of lesions will assist with response assessment.

<sup>i</sup> 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.

<sup>m</sup> Many skin-directed and systemic therapies are contraindicated or are of unknown safety in pregnancy. Refer to individual drug information.

<sup>n</sup> Fertility preservation options include: sperm banking, semen cryopreservation, IVF, or ovarian tissue or oocyte cryopreservation.

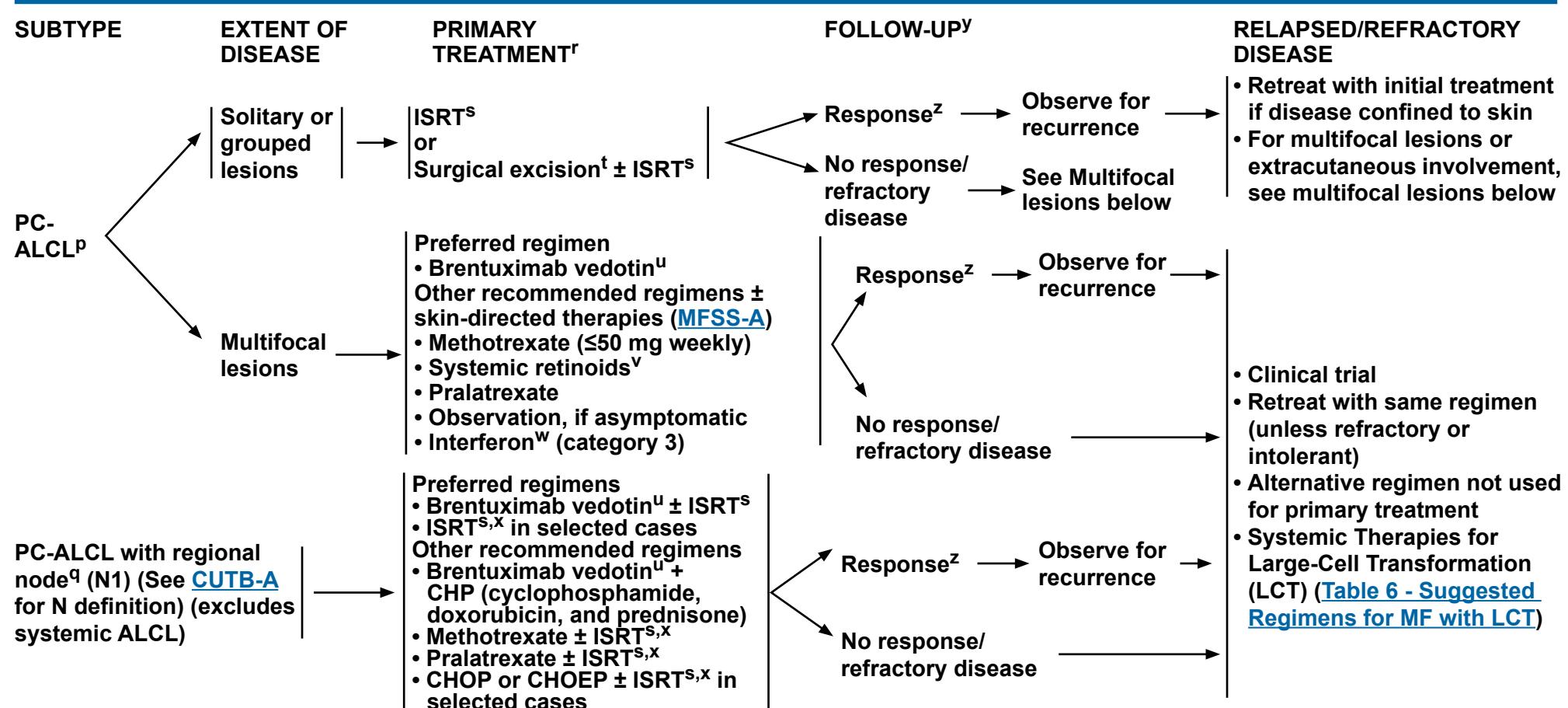
<sup>o</sup> Only done to exclude an associated lymphoma.

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



# NCCN Guidelines Version 1.2025

## Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders



<sup>p</sup> Regression of lesions may occur in up to 44% of cases.

<sup>q</sup> Biopsy-proven lymphoma in lymph node.

<sup>r</sup> [Therapy References \(PCTLDA\)](#).

<sup>s</sup> [Principles of Radiation Therapy \(PCLYM-A\)](#).

<sup>t</sup> Small lesions may be excised with minimal non-disfiguring surgery.

<sup>u</sup> [Supportive Care for Patients with Cutaneous Lymphomas \(PCLYM-C\)](#).

<sup>v</sup> Limited data from case reports (eg, bexarotene).

<sup>w</sup> Peginterferon may be substituted for other interferon preparations (Schiller M, et al. J Eur Acad Dermatol Venereol 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).

<sup>x</sup> ISRT to include lymph node(s) ± primary skin lesions.

<sup>y</sup> Mycosis fungoides can develop over time; continue to conduct thorough skin exam during follow-up.

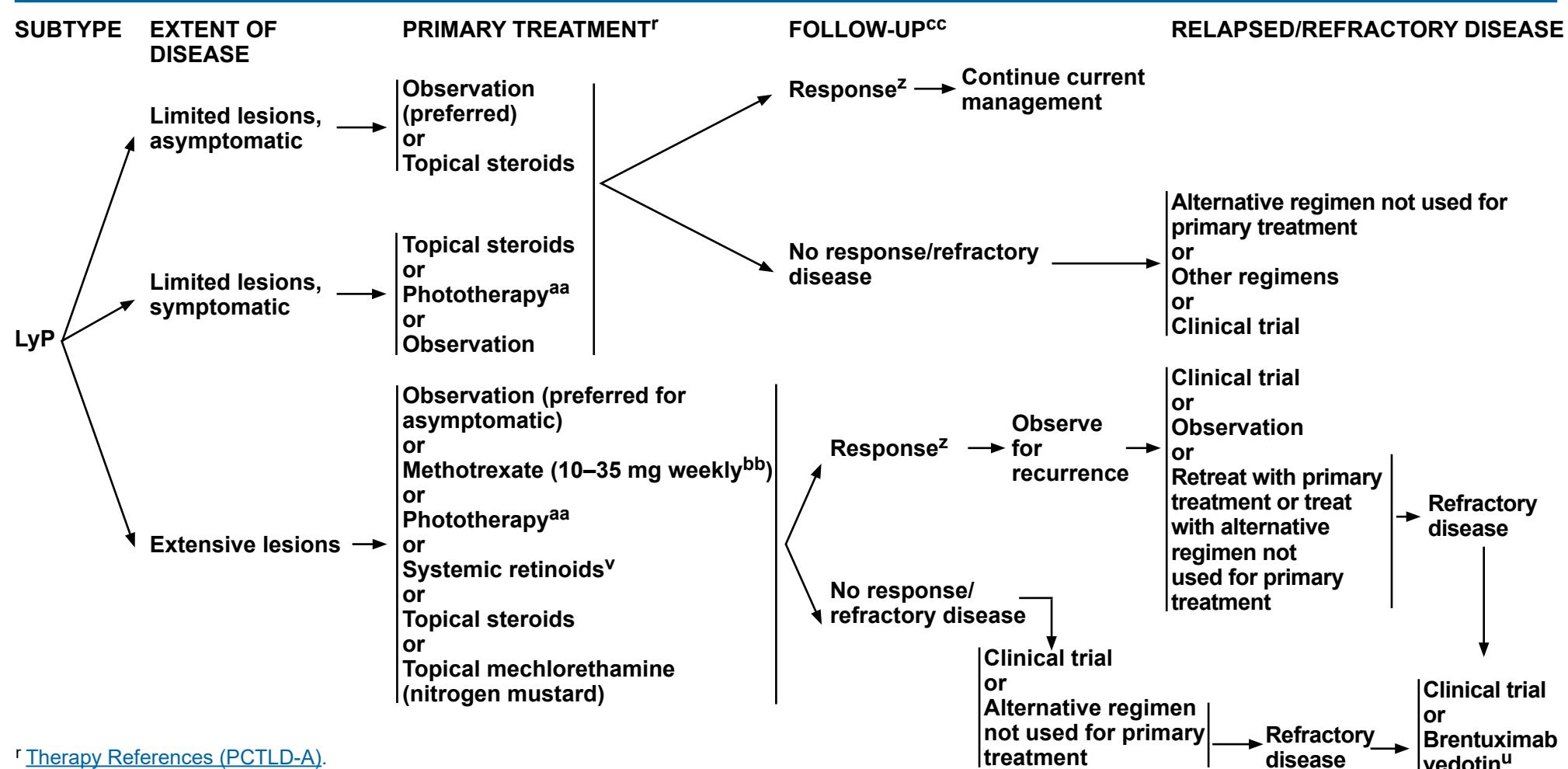
<sup>z</sup> Patients with a clinical benefit and/or those with disease responding to primary treatment should be considered for maintenance or tapering of regimens to optimize response duration. Relapsed disease often responds well to the same treatment. Partial response should be treated with other 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.



# NCCN Guidelines Version 1.2025

## Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

<sup>r</sup> [Therapy References \(PCTLDA\).](#)<sup>u</sup> [Supportive Care for Patients with Cutaneous Lymphomas \(PCLYM-C\).](#)<sup>v</sup> Limited data from case reports (eg, bexarotene).<sup>z</sup> 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.<sup>aa</sup> NB-UVB is generally preferred over PUVA.<sup>bb</sup> Kempf W, et al. Blood 2011;118:4024-4035.<sup>cc</sup> 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

Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet* 2017;390:555-566.

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.

Lewis DJ, Talpur R, Huen AO, et al. Brentuximab Vedotin for Patients With Refractory Lymphomatoid Papulosis: An Analysis of Phase 2 Results. *JAMA Dermatol* 2017;153:1302-1306.

#### 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.

### Systemic Therapies (continued)

#### Interferons

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

Schmutz 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, Sajjad 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.

Krathon 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 FOR SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA (SPTCL)

- There is only modest evidence for the management of SPTCL. The following guidelines are based on expert consensus. Treatment options are based on the presence of HLH and tumor burden as outlined in [SPTCL-2](#) and [SPTCL-3](#).
- SPTCL is a very rare condition characterized by mature medium size CD8+ activated T-cells with tropism towards adipocytes in the subcutaneous tissue and in extraordinary cases involving adipocytes at other sites, like mesentery.
- Patients with SPTCL tend to be young, often with a personal or family history of systemic lupus erythematosus (SLE) or other autoimmune disorders.
- The presentation includes non-ulcerated deep nodules typically involving legs and other sites. The process may resolve with areas of lipodystrophy and hyperpigmentation.
- Fever and malaise are commonly observed at presentation. Signs and symptoms of hemophagocytic lymphohistiocytosis (HLH) may occasionally lead to severe morbidity or mortality. Markers of HLH should be checked when SPTCL is suspected with ferritin levels as a reliable marker to assess disease evolution (See [NCCN Guidelines for T-Cell Lymphomas \(TCLYM-B \[4 of 4\]\)](#)).
- Rimming of bone marrow adipocytes by CD8+ T-cells may be observed, but tumoral growth in nodal, bone marrow, or mesenchymal organs is not typically seen. This limited growth potential, along with the lack of common lymphoma driver mutations and the frequent detection of germline mutations in the *HAVCR2* gene suggest an immune dysregulation characterized by unchecked activated T-cells driving the process. *HAVCR2* encodes for T-cell immunoglobulin and Mucin-domain protein 3 (TIM-3), a membrane modulator of immune response resulting in hemophagocytosis and uncontrolled activation of the innate immune system. *HAVCR2* mutations appears to be more prevalent in patients of Asian ancestry.

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



# NCCN Guidelines Version 1.2025

## Subcutaneous Panniculitis-Like T-Cell Lymphoma

### DIAGNOSIS<sup>a</sup>

#### ESSENTIAL:

- Deep subcutaneous skin biopsy with adequate amount of adipose tissue (wedge excision or deep telescope punch biopsy) of clinical lesions:
  - ▶ Multiple biopsies may be necessary to confirm diagnosis
  - ▶ 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 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 immunophenotyping to establish diagnosis<sup>b</sup>
  - ▶ IHC panel may include: TCRβ, TCRδ, CD2, CD3, CD20, CD4, CD5, CD7, CD8, CD30, CD56
- EBER-ISH
- Molecular analysis to detect clonal T-cell receptor (TCR) gene rearrangements or other assessment of clonality

#### USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Additional IHC markers may include: Ki67, CD123, TIA1, perforin, granzyme-B, CD1a, TdT, TCL1
- Consider peripheral blood flow cytometry to rule out other T-cell lymphoma subtypes
- Germline testing for *HAVCR2* mutation
- Comprehensive genomic profiling

### WORKUP

#### ESSENTIAL:

- History and complete physical examination:
  - ▶ Complete skin examination
  - ▶ Palpation of peripheral lymph node regions
  - ▶ Palpation for organomegaly/masses
  - ▶ Potential triggers for recent infections
  - ▶ Personal or family history of autoimmunity, consanguinity, ancestry, etc
- CBC with differential
- Comprehensive metabolic panel
- LDH, ferritin
- HLH workup if B symptoms or HLH is suspected (See [NCCN Guidelines for T-Cell Lymphomas](#) [TCLYM-B])
- Whole body FDG-PET/CT scan<sup>c</sup> to assess the extent of subcutaneous involvement and exclude systemic involvement

→ [SPTCL-2](#)

#### USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Pregnancy testing in patients of childbearing potential if contemplating treatments that are contraindicated in pregnancy
- Consider quantitative Epstein-Barr virus (EBV) polymerase chain reaction (PCR)
- Antinuclear antibody (ANA) with reflex, rheumatoid factor (RF), TSH, and primary immunodeficiency (PID) gene panel to rule out other autoimmune conditions that closely resemble SPTCL
- Consider bone marrow biopsy, if unexplained cytopenias or HLH
- Consider biopsy of enlarged lymph nodes or other suspected FDG-PET–avid extracutaneous sites

<sup>a</sup> Borderline or low grade presentations that may overlap with lupus panniculitis and evolve into SPTCL (eg, adipotrophic LPD, necrotizing, infectious or granulomatous panniculitis and other cutaneous lymphomas [primary cutaneous gamma-delta T-cell lymphoma, primary cutaneous NKTL or PTCL] should be included in the differential diagnosis.

<sup>b</sup> Typical immunophenotype: CD3+ CD8+ βF1+ CD2+ CD5+ CD7+.

<sup>c</sup> Patients have extranodal disease, which may be inadequately imaged by CT. PET scan is preferred.

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



# NCCN Guidelines Version 1.2025

## Subcutaneous Panniculitis-Like T-Cell Lymphoma

## CLINICAL PRESENTATION

FIRST-LINE THERAPY<sup>d,e,f</sup>

## RESPONSE ASSESSMENT AND ADDITIONAL THERAPY

SPTCL with HLH, systemic disease, or high tumor burden (widespread subcutaneous disease)

- Consider single agents with or without prednisone:
  - Cyclosporine ( $\geq 5$  mg/kg/day)<sup>g</sup>
  - Pralatrexate
  - Romidepsin
- or
- Consider etoposide-based combination chemotherapy<sup>f</sup>
  - CHOEP
  - DA-EPOCH
  - ESHA + platinum (cisplatin or oxaliplatin)
  - ICE

CR or PR

Inadequate response

- Observation or Maintenance therapy with single agents<sup>h</sup>
  - Cyclosporine
  - Pralatrexate
  - Romidepsin
  - Methotrexate (PO/SC/IM)
  - Bexarotene (PO) or Consider allogeneic HCT in selected patients

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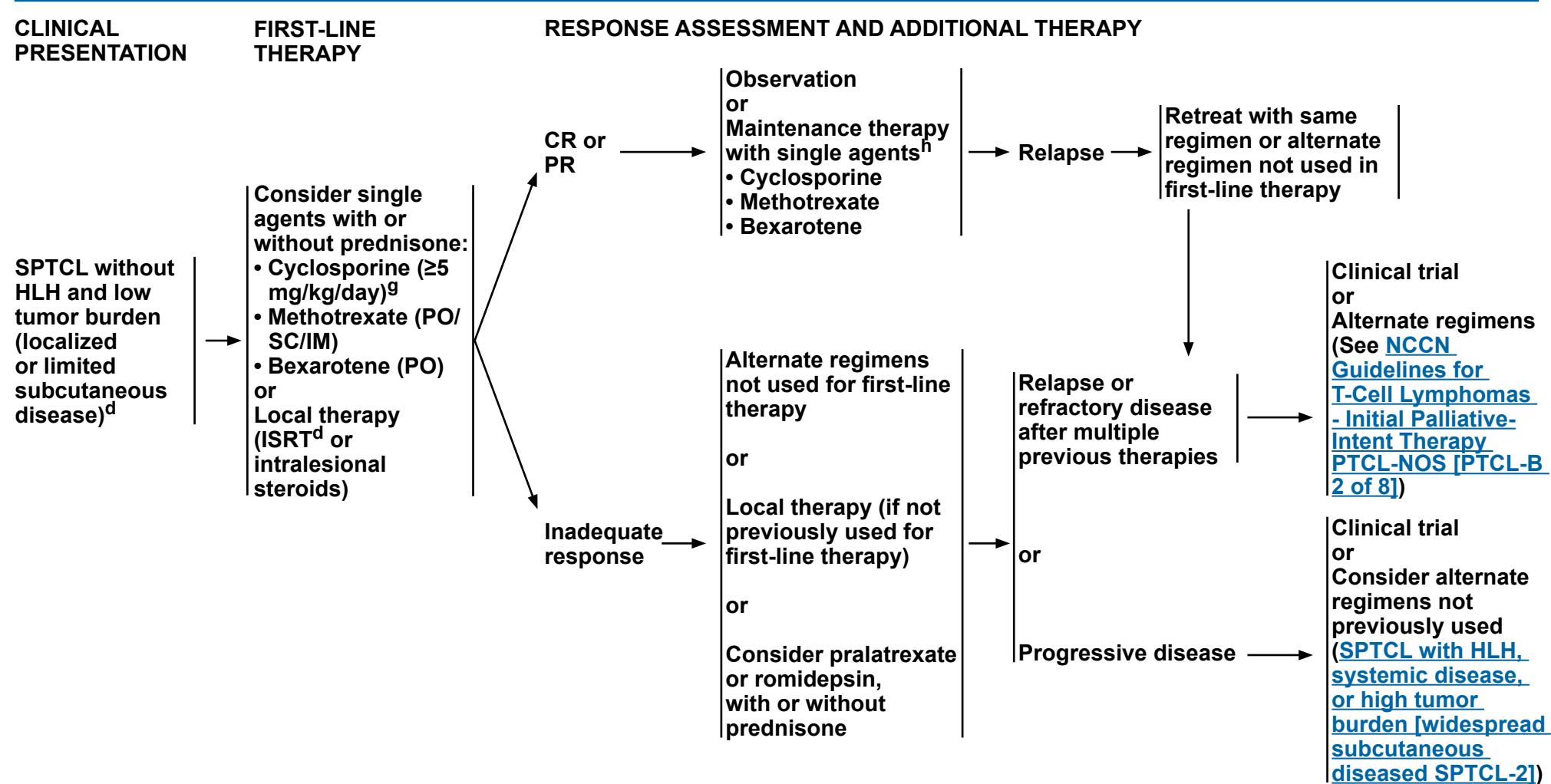
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# NCCN Guidelines Version 1.2025

## Subcutaneous Panniculitis-Like T-Cell Lymphoma



<sup>d</sup> Consider ISRT for single lesion or limited disease with or without symptoms or HLH.

<sup>g</sup> Oral cyclosporine is typically initiated at 3–5 mg/kg/day in divided doses. Higher dosage may be necessary to achieve disease control. Dose adjustment is based on response and tolerance. In patients with disease responding to first-line therapy, consider slow tapering as tolerated or cyclosporine maintenance.

<sup>h</sup> Patients with disease achieving a clinical benefit and/or those with disease responding to first-line therapy should be considered for maintenance or tapering of regimens to optimize response duration.

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



### PRINCIPLES OF RADIATION THERAPY<sup>a</sup>

#### 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](#)

<sup>a</sup> [References on PCLYM-A 3 of 3.](#)

**Continued**

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

**PCLYM-A  
1 OF 3**



### PRINCIPLES OF RADIATION THERAPY<sup>a</sup>

#### 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 though data with this approach are limited.
    - ◊ 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. 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 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.

[Continued](#)

<sup>a</sup> [References on PCLYM-A 3 of 3.](#)

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



## PRINCIPLES OF RADIATION THERAPY

### General Dose Guidelines: (RT in conventional fraction sizes) (continued)

- 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

- SPTCL

- RT for curative treatment: 36-45 Gy

### 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.

Hoppe RT, Harrison C, Tavallaee M, et al. Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: results of a pooled analysis from 3 phase-II clinical trials. J Am Acad Dermatol 2015;72:286-292.

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.

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.

Patel AM, West L, Atluri PS, et al. Optimizing palliative focal radiation therapy dose in cutaneous T-cell lymphoma: How low can you Go? Pract Radiat Oncol 2023;13:e192-e199.

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.

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.

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.

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

**PCLYM-A**  
**3 OF 3**



### PRINCIPLES OF MOLECULAR ANALYSIS IN PRIMARY CUTANEOUS LYMPHOMAS<sup>a</sup>

- 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 DUSP22-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.

<sup>a</sup> [References on PCLYM-B 2 of 2](#).

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



**PRINCIPLES OF MOLECULAR ANALYSIS IN CUTANEOUS LYMPHOMAS**  
**REFERENCES**

- Chiarle R, Voena C, Ambrogio C, et al. The anaplastic lymphoma kinase in the pathogenesis of cancer. *Nat Rev Cancer* 2008;8:11-23.
- De Schouwer PJ, Dyer MJ, Brito-Babapulle VB, et al. T-cell prolymphocytic leukaemia: antigen receptor gene rearrangement and a novel mode of MTCP1-B1 activation. *Br J Haematol* 2000;110:831-838.
- Hu Z, Medeiros LJ, Fang L, et al. Prognostic significance of cytogenetic abnormalities in T-cell prolymphocytic leukemia. *Am J Hematol* 2017;92:441-447.
- Karai LJ, Kadin ME, Hsi ED, et al. Chromosomal rearrangements of 6p25.3 define a new subtype of lymphomatoid papulosis. *Am J Surg Pathol* 2013;37:1173-1181.
- Morris SW, Kirstein MN, Valentine MB, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's Lymphoma. *Science* 1994;263:1281-1284.
- Odejide O, Weigert O, Lane AA, et al. A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. *Blood* 2014;123:1293-1296.
- Onaindia A, Montes-Moreno S, Rodriguez-Pinilla SM, et al. Primary cutaneous anaplastic large cell lymphomas with 6p25.3 rearrangement exhibit particular histological features. *Histopathology* 2015;66:846-855.
- Pedersen MB, Hamilton-Dutoit SJ, Bendix K, et al. *DUSP22* and *TP63* rearrangements predict outcome of ALK-negative anaplastic large cell lymphoma: a Danish cohort study. *Blood* 2017;130:554-557.
- Wada DA, Law ME, Hsi ED, et al. Specificity of IRF4 translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies. *Mod Pathol* 2011;24:596-605.

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

**PCLYM-B**  
**2 OF 2**



## SUPPORTIVE CARE FOR PATIENTS WITH CUTANEOUS LYMPHOMAS

### Viral Reactivation

#### • CMV Reactivation:

- ▶ Clinicians must be aware of the high risk of CMV reactivation in patients receiving alemtuzumab (anti-CD52 antibody).
- ▶ The current recommendations for appropriate screening and management are controversial; some NCCN Member Institutions use ganciclovir (PO or IV) preemptively if viremia is present, others only if viral load is rising.
- ▶ CMV viremia should be measured by quantitative PCR at least every 2–3 weeks.
- ▶ Consultation with an infectious disease expert may be necessary.
- ▶ Consider evaluating CD52 expressions before initiating treatment with alemtuzumab-based regimens.

#### • John Cunningham virus (JC) Reactivation

- ▶ Brentuximab vedotin (anti-CD30 antibody-drug conjugate) can cause JC reactivation and progressive multifocal leukoencephalopathy (PML).
- ▶ PML is usually fatal. Clinical indications may include changes in behavior such as confusion, dizziness or loss of balance, difficulty talking or walking, and vision problems.
- ▶ Diagnosis is made by PCR of CSF and in some cases brain biopsy.
- ▶ There is no known effective treatment.

### Anti-infective Prophylaxis

#### • Recommended during treatment and thereafter (if tolerated) for patients receiving alemtuzumab (anti-CD52 antibody)

- ▶ Herpes simplex virus (HSV) prophylaxis with acyclovir or equivalent.
- ▶ Pneumocystis jirovecii pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent.
- ▶ Consider screening and treatment (if needed) for strongyloidiasis in patients with ATLL.
- ▶ Consider antifungal prophylaxis.

◊ Consultation with an infectious disease expert may be necessary. See [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#).

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, 2024)
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 \(ST-2\)](#)

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.  
 With permission, WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. (WHO classification of tumours series, 5th ed.; vol. 11). Lyon (France): International Agency for Research on Cancer; 2024.



# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

### 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, 2024)
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 gamma-delta T-cell lymphoma • Primary cutaneous acral CD8-positive T-cell lymphoma (provisional) • Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (provisional) • Primary cutaneous peripheral T-cell lymphoma, NOS	Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder Primary cutaneous gamma-delta T-cell lymphoma Primary cutaneous acral CD8-positive lymphoproliferative disorder Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma Not included	Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder Primary cutaneous gamma/delta T-cell lymphoma Primary cutaneous acral CD8-positive lymphoproliferative disorder Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma Primary cutaneous peripheral T-cell lymphoma, NOS

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.  
 With permission, WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. (WHO classification of tumours series, 5th ed.; vol. 11). Lyon (France): International Agency for Research on Cancer; 2024.



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## Primary Cutaneous Lymphomas

### ABBREVIATIONS

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

[Continued](#)



# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

### ABBREVIATIONS

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



# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

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### NCCN Categories of Evidence and Consensus

<b>Category 1</b>	Based upon high-level evidence ( $\geq 1$ randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ( $\geq 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 2A</b>	Based upon lower-level evidence, there is uniform NCCN consensus ( $\geq 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 2B</b>	Based upon lower-level evidence, there is NCCN consensus ( $\geq 50\%$ , but $< 85\%$ support of the Panel) that the intervention is appropriate.
<b>Category 3</b>	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

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

All recommendations are considered appropriate.



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# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

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

## Discussion

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# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

### Overview

Primary cutaneous lymphomas (PCL) are a heterogeneous 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.<sup>1</sup>

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.<sup>2,3</sup> The most common subtypes of PCL that are covered in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) 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 (PCTL)

### Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at [www.NCCN.org](http://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.<sup>2,3</sup> 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%).<sup>4,5</sup>

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.<sup>6,7</sup> 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.<sup>3</sup>



# National Comprehensive Cancer Network® NCCN Guidelines Version 1.2025 Primary Cutaneous Lymphomas

PCFCL is more prevalent in the scalp, face, and the forehead, whereas the trunk and extremities are the most common sites for PCMZL.<sup>4,5</sup> 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).<sup>8,9</sup> In the ICC, PCMZL are defined as primary cutaneous marginal zone lymphoproliferative disorders because of their indolent disease course.<sup>9</sup>

PCDLBCL, leg type is found most commonly on the leg, although it can arise at other sites.<sup>4,5</sup> PCDLBCL, leg type is usually aggressive and associated with a generally poorer prognosis (mainly due to the higher frequency of extracutaneous relapses).<sup>4,5</sup> 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.<sup>4</sup> 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;  $P < .0001$ ).<sup>4</sup> 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).<sup>4</sup> 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.<sup>5</sup> 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.<sup>10</sup>

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.<sup>11-14</sup> Emerging data suggest that Ig class-switched subtype may be categorized as a clonal chronic lymphoproliferative disorder due to its indolent disease course.<sup>14,15</sup>

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.<sup>16</sup> 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.<sup>16</sup> 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.<sup>17-19</sup> However, these algorithms may be of limited utility in the differentiation of PC-DLBCL, leg type and PCFCL-LC.<sup>19</sup> 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 heterogeneous in patients with PC-DLBCL, leg type.<sup>19</sup>



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A high prevalence of *MYD88* L265P mutation has been reported in patients with PCDLBCL, leg type and is associated with inferior clinical outcomes.<sup>17,20</sup> 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.<sup>20</sup> 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%).<sup>17</sup> 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.<sup>21</sup>

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](http://www.NCCN.org).

## Diagnosis

PCMZL are negative for BCL6 and CD10, but are often positive for CD20 and BCL2.<sup>22</sup> 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.<sup>23-26</sup>

PCDLBCL, leg type tumors express CD20, IRF4/MUM1, FOXP1, and BCL2; many cases express BCL6 and lack expression of CD10.<sup>5,16,17,27-29</sup> PCDLBCL, leg type also has a high incidence of *MYC* rearrangements and *MYC* rearrangements are not detected in PCFCL.<sup>30</sup> In addition, PCFCL is usually IRF4/MUM1-negative while PCDLBCL, leg type is usually IRF4/MUM1-positive and shows strong expression of FOXP1.<sup>28,29</sup> Assessment of FOXP1 expression is helpful to distinguish PCDLBCL, leg type from PCFCL since all cases of PCFCL are FOXP1-negative.<sup>29</sup> 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.<sup>17,18</sup>

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



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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)<sup>31-33</sup> and in the differential diagnosis of intravascular large B-cell lymphoma, which often manifests in skin and is associated with a poor prognosis.<sup>34</sup>

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.<sup>28,29,35</sup> 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.<sup>3</sup>

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).<sup>25,36</sup> 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.<sup>33</sup> 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.<sup>37</sup> 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.<sup>38</sup>

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.<sup>39</sup> However, it can be omitted if clinically indicated in patients with low-grade indolent PCBCL.<sup>40</sup> PET/CT may have higher sensitivity in the detection of both local and distant metastases than CT.<sup>41</sup> 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.<sup>38,40,42</sup> 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.<sup>42</sup> 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.<sup>42</sup>

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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).<sup>38</sup>

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.<sup>43-47</sup>

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.<sup>44</sup> 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.<sup>45</sup> 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).<sup>45</sup>

In another retrospective study of 42 patients with biopsy-proven PCFCL and PCMZL, RT resulted in CR in all patients.<sup>47</sup> 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.<sup>48</sup> 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).<sup>49</sup>

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.<sup>4,50-53</sup> 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.<sup>4</sup> 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



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confirmed both for patients with single or regional lesions treated with RT and for patients with disseminated cutaneous involvement treated with chemotherapy.<sup>4</sup> 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).<sup>52</sup> 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<sup>54-58</sup> and intralesional<sup>59-61</sup>) 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.<sup>54-58</sup> 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.<sup>57</sup> 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.<sup>58</sup> 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.<sup>59</sup> 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.<sup>62</sup>

Several case reports have shown the effectiveness of skin-directed therapy (steroids, imiquimod, and nitrogen mustard or bexarotene gel) for patients with multifocal lesions.<sup>63-67</sup> Interlesional steroids have also been used in the management of PCFCL or PCMZL, although only limited data are available.<sup>50,68,69</sup> 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.<sup>54-58,63,70-72</sup>

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.<sup>73</sup> 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

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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.<sup>39</sup> 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.<sup>48,49,69</sup> 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.<sup>70–72</sup>

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.<sup>70–72</sup>

### **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.<sup>74–79</sup> 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.<sup>74</sup> Among 12 patients treated with anthracycline-based chemoimmunotherapy, the CR rate was 92%



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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.<sup>77-79</sup> 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.<sup>77</sup> 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;  $P = .04$ ).<sup>79</sup>

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.

Discussion  
update in  
progress

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## References

1. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood* 2009;113:5064-5073. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19279331>.
2. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005;105:3768-3785. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15692063>.
3. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30635287>.
4. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16492713>.
5. Senff NJ, Hoefnagel JJ, Jansen PM, et al. Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. *J Clin Oncol* 2007;25:1581-1587. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17353548>.
6. Lucioni M, Berti E, Arcaini L, et al. Primary cutaneous B-cell lymphoma other than marginal zone: clinicopathologic analysis of 161 cases: Comparison with current classification and definition of prognostic markers. *Cancer Med* 2016;5:2740-2755. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27665744>.
7. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30851152>.

8. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35732829>.
9. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of mature lymphoid neoplasms: A report from the clinical advisory committee. *Blood* 2022;140:1229-1253. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35653592>.
10. Zhang Y, LeWitt TM, Louissaint A, Jr., et al. Disease-defining molecular features of primary cutaneous B-cell lymphomas: implications for classification and treatment. *J Invest Dermatol* 2023;143:189-196. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36163302>.
11. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18687986>.
12. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21107089>.
13. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31124191>.
14. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31464711>.



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# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

15. Gibson SE, Swerdlow SH. How I diagnose primary cutaneous marginal zone lymphoma. *Am J Clin Pathol* 2020;154:428-449. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32808967>.
16. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15308563>.
17. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30715765>.
18. Cretella P, Peluso AL, Picariello C, et al. Immunohistochemical algorithms and gene expression profiling in primary cutaneous B-cell lymphoma. *Pathol Res Pract* 2022;231:153804. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35183824>.
19. Schrader AMR, de Groen RAL, Willemze R, et al. Cell-of-origin classification using the Hans and Lymph2Cx algorithms in primary cutaneous large B-cell lymphomas. *Virchows Arch* 2022;480:667-675. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35028710>.
20. Pham-Ledard A, Beylot-Barry M, Barbe C, et al. High frequency and clinical prognostic value of MYD88 L265P mutation in primary cutaneous diffuse large B-cell lymphoma, leg-type. *JAMA Dermatol* 2014;150:1173-1179. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25055137>.
21. PubMed Overview. Available at: <https://pubmed.ncbi.nlm.nih.gov/about/>. Accessed March 10, 2024.
22. Hoefnagel JJ, Vermeer MH, Jansen PM, et al. Bcl-2, Bcl-6 and CD10 expression in cutaneous B-cell lymphoma: further support for a follicle centre cell origin and differential diagnostic significance. *Br J Dermatol* 2003;149:1183-1191. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14674895>.
23. de Leval L, Harris NL, Longtine J, et al. Cutaneous B-cell lymphomas of follicular and marginal zone types: use of Bcl-6, CD10, Bcl-2, and CD21 in differential diagnosis and classification. *Am J Surg Pathol* 2001;25:732-741. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11395550>.
24. Pham-Ledard A, Cowppli-Bony A, Doussau A, et al. Diagnostic and prognostic value of BCL2 rearrangement in 53 patients with follicular lymphoma presenting as primary skin lesions. *Am J Clin Pathol* 2015;143:362-373. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25696794>.
25. Servitje O, Climent F, Colomo L, et al. Primary cutaneous vs secondary cutaneous follicular lymphomas: A comparative study focused on BCL2, CD10, and t(14;18) expression. *J Cutan Pathol* 2019;46:182-189. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30511443>.
26. Pileri A, Grandi V, Agostonelli C, et al. BCL-2 expression in primary cutaneous follicle center lymphoma is associated with a higher risk of cutaneous relapses: A study of 126 cases. *J Eur Acad Dermatol Venereol* 2022;36:e811-e813. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35648475>.
27. Kodama K, Massone C, Chott A, et al. Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients. *Blood* 2005;106:2491-2497. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15947086>.
28. Hoefnagel JJ, Mulder MM, Dreef E, et al. Expression of B-cell transcription factors in primary cutaneous B-cell lymphoma. *Mod Pathol* 2006;19:1270-1276. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16778825>.
29. Espinet B, Garcia-Herrera A, Gallardo F, et al. FOXP1 molecular cytogenetics and protein expression analyses in primary cutaneous large B cell lymphoma, leg-type. *Histol Histopathol* 2011;26:213-221. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21154235>.

# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

30. Schrader AMR, Jansen PM, Vermeer MH, et al. High incidence and clinical significance of *MYC* rearrangements in primary cutaneous diffuse large B-cell lymphoma, leg type. *Am J Surg Pathol* 2018;42:1488-1494. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30113335>.
31. Baldassano MF, Bailey EM, Ferry JA, et al. Cutaneous lymphoid hyperplasia and cutaneous marginal zone lymphoma: comparison of morphologic and immunophenotypic features. *Am J Surg Pathol* 1999;23:88-96. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9888708>.
32. Leinweber B, Colli C, Chott A, et al. Differential diagnosis of cutaneous infiltrates of B lymphocytes with follicular growth pattern. *Am J Dermatopathol* 2004;26:4-13. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14726817>.
33. Schafernak KT, Variakojis D, Goolsby CL, et al. Clonality assessment of cutaneous B-cell lymphoid proliferations: a comparison of flow cytometry immunophenotyping, molecular studies, and immunohistochemistry/in situ hybridization and review of the literature. *Am J Dermatopathol* 2014;36:781-795. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24335516>.
34. Murase T, Yamaguchi M, Suzuki R, et al. Intravascular large B-cell lymphoma (IVLBCL): a clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. *Blood* 2007;109:478-485. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16985183>.
35. Koens L, Vermeer MH, Willemze R, Jansen PM. IgM expression on paraffin sections distinguishes primary cutaneous large B-cell lymphoma, leg type from primary cutaneous follicle center lymphoma. *Am J Surg Pathol* 2010;34:1043-1048. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20551823>.
36. Child FJ, Russell-Jones R, Woolford AJ, et al. Absence of the t(14;18) chromosomal translocation in primary cutaneous B-cell lymphoma. *Br J Dermatol* 2001;144:735-744. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11298531>.
37. Wehkamp U, Pott C, Unterhalt M, et al. Skin involvement of mantle cell lymphoma may mimic primary cutaneous diffuse large B-cell lymphoma, leg type. *Am J Surg Pathol* 2015;39:1093-1101. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26034867>.
38. Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007;110:479-484. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17339420>.
39. Kheterpal MK, Dai J, Geller S, et al. Role of imaging in low-grade cutaneous B-cell lymphoma presenting in the skin. *J Am Acad Dermatol* 2019;81:970-976. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30703460>.
40. Vachhani P, Neppalli VT, Cancino CJ, et al. Radiological imaging and bone marrow biopsy in staging of cutaneous B-cell lymphoma. *Br J Haematol* 2019;184:674-676. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29468663>.
41. Kumar R, Xiu Y, Zhuang HM, Alavi A. 18F-fluorodeoxyglucose-positron emission tomography in evaluation of primary cutaneous lymphoma. *Br J Dermatol* 2006;155:357-363. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16882175>.
42. Senff NJ, Kluin-Nelemans HC, Willemze R. Results of bone marrow examination in 275 patients with histological features that suggest an indolent type of cutaneous B-cell lymphoma. *Br J Haematol* 2008;142:52-56. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18422781>.
43. Eich HT, Eich D, Micke O, et al. Long-term efficacy, curative potential, and prognostic factors of radiotherapy in primary cutaneous B-cell lymphoma. *Int J Radiat Oncol Biol Phys* 2003;55:899-906. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12605967>.

# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

44. Smith BD, Glusac EJ, McNiff JM, et al. Primary cutaneous B-cell lymphoma treated with radiotherapy: a comparison of the European Organization for Research and Treatment of Cancer and the WHO classification systems. *J Clin Oncol* 2004;22:634-639. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14966086>.
45. Senff NJ, Hoefnagel JJ, Neelis KJ, et al. Results of radiotherapy in 153 primary cutaneous B-Cell lymphomas classified according to the WHO-EORTC classification. *Arch Dermatol* 2007;143:1520-1526. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18087001>.
46. Pedretti S, Urpis M, Leali C, et al. Primary cutaneous non-Hodgkin lymphoma: results of a retrospective analysis in the light of the recent ILROG guidelines. *Tumori* 2018;104:394-400. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28218382>.
47. De Felice F, Grapulin L, Pieroni A, et al. Radiation therapy in indolent primary cutaneous B cell lymphoma: a single institute experience. *Ann Hematol* 2018;97:2411-2416. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30094511>.
48. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18834672>.
49. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25860237>.
50. Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood* 2008;112:1600-1609. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18567836>.
51. Pashtan I, Mauch PM, Chen YH, et al. Radiotherapy in the management of localized primary cutaneous B-cell lymphoma. *Leuk Lymphoma* 2013;54:726-730. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22916994>.
52. Servitje O, Muniesa C, Benavente Y, et al. Primary cutaneous marginal zone B-cell lymphoma: response to treatment and disease-free survival in a series of 137 patients. *J Am Acad Dermatol* 2013;69:357-365. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23796549>.
53. Olszewska-Szopa M, Sobas M, Laribi K, et al. Primary cutaneous indolent B-cell lymphomas - a retrospective multicenter analysis and a review of literature. *Acta Oncol* 2021;60:1361-1368. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34346830>.
54. Heinzerling LM, Urbanek M, Funk JO, et al. Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. *Cancer* 2000;89:1835-1844. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11042581>.
55. Heinzerling L, Dummer R, Kempf W, et al. Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous B-cell lymphoma. *Arch Dermatol* 2000;136:374-378. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10724200>.
56. Gellrich S, Muche JM, Wilks A, et al. Systemic eight-cycle anti-CD20 monoclonal antibody (rituximab) therapy in primary cutaneous B-cell lymphomas—an applicational observation. *Br J Dermatol* 2005;153:167-173. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16029344>.
57. Morales AV, Advani R, Horwitz SM, et al. Indolent primary cutaneous B-cell lymphoma: experience using systemic rituximab. *J Am Acad Dermatol* 2008;59:953-957. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18817999>.
58. Valencak J, Weihsgenreber F, Rappersberger K, et al. Rituximab monotherapy for primary cutaneous B-cell lymphoma: response and follow-up in 16 patients. *Ann Oncol* 2009;20:326-330. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18836086>.



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# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

59. Penate Y, Hernandez-Machin B, Perez-Mendez LI, et al. Intralesional rituximab in the treatment of indolent primary cutaneous B-cell lymphomas: an epidemiological observational multicentre study. The Spanish Working Group on Cutaneous Lymphoma. Br J Dermatol 2012;167:174-179. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22356294>.
60. Vakeva L, Ranki A, Malkonen T. Intralesional rituximab treatment for primary cutaneous B-cell lymphoma: Nine finnish cases. Acta Derm Venereol 2016;96:396-397. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26525093>.
61. Eberle FC, Holstein J, Scheu A, et al. Intralesional anti-CD20 antibody for low-grade primary cutaneous B-cell lymphoma: Adverse reactions correlate with favorable clinical outcome. J Dtsch Dermatol Ges 2017;15:319-323. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28177583>.
62. Kerl K, Prins C, Saurat JH, French LE. Intralesional and intravenous treatment of cutaneous B-cell lymphomas with the monoclonal anti-CD20 antibody rituximab: report and follow-up of eight cases. Br J Dermatol 2006;155:1197-1200. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17107389>.
63. Bekkenk MW, Vermeer MH, Geerts ML, et al. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. J Clin Oncol 1999;17:2471-2478. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10561311>.
64. Trent JT, Romanelli P, Kerdel FA. Topical targretin and intralesional interferon alfa for cutaneous lymphoma of the scalp. Arch Dermatol 2002;138:1421-1423. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12437444>.
65. Bachmeyer C, Orlandini V, Aractingi S. Topical mechlorethamine and clobetasol in multifocal primary cutaneous marginal zone-B cell lymphoma. Br J Dermatol 2006;154:1207-1209. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16704661>.
66. Coors EA, Schuler G, Von Den Driesch P. Topical imiquimod as treatment for different kinds of cutaneous lymphoma. Eur J Dermatol 2006;16:391-393. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16935796>.
67. Stavrakoglou A, Brown VL, Coutts I. Successful treatment of primary cutaneous follicle centre lymphoma with topical 5% imiquimod. Br J Dermatol 2007;157:620-622. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17553050>.
68. Perry A, Vincent BJ, Parker SR. Intralesional corticosteroid therapy for primary cutaneous B-cell lymphoma. Br J Dermatol 2010;163:223-225. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20394622>.
69. Kollipara R, Hans A, Hall J, Lisle A. A case report of primary cutaneous marginal zone lymphoma treated with intralesional steroids. Dermatol Online J 2015;21:13030/qt13039s15929m. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26437162>.
70. Rijlaarsdam JU, Toonstra J, Meijer OW, et al. Treatment of primary cutaneous B-cell lymphomas of follicle center cell origin: a clinical follow-up study of 55 patients treated with radiotherapy or polychemotherapy. J Clin Oncol 1996;14:549-555. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8636770>.
71. Brice P, Cazals D, Mounier N, et al. Primary cutaneous large-cell lymphoma: analysis of 49 patients included in the LNH87 prospective trial of polychemotherapy for high-grade lymphomas. Groupe d'Etude des Lymphomes de l'Adulte. Leukemia 1998;12:213-219. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9519784>.
72. Wang S, Perlmutter JW, Johnston J, et al. Rituximab treatment of primary cutaneous follicle center lymphoma: A retrospective review. J Cutan Med Surg 2022;26:604-612. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36134749>.
73. Haverkos B, Tyler K, Gru AA, et al. Primary cutaneous B-cell lymphoma: management and patterns of recurrence at the multimodality cutaneous lymphoma clinic of the Ohio State University. Oncologist



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# NCCN Guidelines Version 1.2025

## Primary Cutaneous Lymphomas

2015;20:1161-1166. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26306900>.

74. Grange F, Beylot-Barry M, Courville P, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. Arch Dermatol 2007;143:1144-1150. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/17875875>.

75. Posada Garcia C, Florez A, Pardavila R, et al. Primary cutaneous large B-cell lymphoma, leg type, successfully treated with rituximab plus chemotherapy. Eur J Dermatol 2009;19:394-395. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/19467966>.

76. Grange F, Maubec E, Bagot M, et al. Treatment of cutaneous B-cell lymphoma, leg type, with age-adapted combinations of chemotherapies and rituximab. Arch Dermatol 2009;145:329-330. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/19289772>.

77. Grange F, Joly P, Barbe C, et al. Improvement of survival in patients with primary cutaneous diffuse large B-cell lymphoma, leg type, in France. JAMA Dermatol 2014;150:535-541. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/24647650>.

78. Kim MJ, Hong ME, Maeng CH, et al. Clinical features and treatment outcomes of primary cutaneous B-cell lymphoma: a single-center analysis in South Korea. Int J Hematol 2015;101:273-278. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25552248>.

79. Kraft RM, Ansell SM, Villasboas JC, et al. Outcomes in primary cutaneous diffuse large B-cell lymphoma, leg type. Hematol Oncol 2021;39:658-663. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/34453851>.



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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.<sup>1-3</sup>

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.<sup>4</sup> 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.<sup>4-6</sup> 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.<sup>5</sup> 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.<sup>2</sup> 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.<sup>7-9</sup> 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.<sup>4,10</sup>

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.<sup>11</sup>

### 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.<sup>12</sup>

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](http://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](#).<sup>13</sup>



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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 ( $\geq 1$  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.<sup>13</sup> 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.<sup>14-20</sup> 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.<sup>15</sup> 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.<sup>17,18</sup>

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.<sup>21</sup> 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.<sup>22</sup>

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



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significantly different survival outcomes.<sup>20</sup> 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 [PROCLIP]) 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.<sup>23-25</sup>

## 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.<sup>26</sup> 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.<sup>27-29</sup> 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.<sup>30</sup> 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).<sup>31,32</sup> Identification of these markers along with other clinical and histopathologic features would be useful to distinguish MFSS from CTCL of TFH origin.<sup>33,34</sup>

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.<sup>35,36</sup> 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.<sup>37,38</sup> 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



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(CD4+/CD26- or CD4+/CD7- or other aberrantly expressed phenotype).<sup>39</sup> 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.<sup>40-42</sup> Human T-cell lymphotropic 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.<sup>13</sup>

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  $\geq 10\%$  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 PROCLIP 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.<sup>24</sup>

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.<sup>43</sup> 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.<sup>17,18</sup>

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



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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 ( $\geq$  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-IIIB disease, with excellent response expected. In the PROCLIP study, the use of systemic therapy was significantly associated with higher clinical stage, presence of plaques, and FMF.<sup>25</sup> 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.<sup>44-46</sup>

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



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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.<sup>47</sup> 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.<sup>48</sup> 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.<sup>49</sup> 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).<sup>50</sup>

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).<sup>51,52</sup>

### ***Topical Imiquimod***

Imiquimod has also demonstrated activity in a small number of patients with early-stage MF refractory to other therapies.<sup>53-56</sup> 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.<sup>57,58</sup> Topical carmustine is included with a category 2B recommendation.



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## **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).<sup>59</sup> 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%.<sup>60,61</sup> Recent studies have shown that low-dose involved-field RT (IFRT) also results in high response rates without any toxicity in patients with MF.<sup>61–63</sup> 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%.<sup>62</sup> 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.<sup>63</sup>

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).<sup>61,63</sup>

## **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.<sup>64–67</sup> 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.<sup>66,67</sup> 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 ( $\geq$ 30 Gy).<sup>65</sup> The OS and progression-free survival (PFS) rates were not significantly different by dose groups and were comparable to that of standard-dose TSEBT ( $\geq$ 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.<sup>68–73</sup> 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).<sup>69</sup> 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.<sup>72</sup> 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).<sup>71,74,75</sup> 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



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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.<sup>76,77</sup>

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)<sup>78–82</sup> and psoralen plus ultraviolet A1 (PUVA/UVA-1)<sup>83–86</sup> 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),<sup>87–89</sup> others have reported that UVB is as effective as PUVA for the treatment of early-stage MF.<sup>90,91</sup> 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.<sup>92</sup> 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.<sup>93,94</sup>

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.<sup>92,95,96</sup> 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



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has been demonstrated in phase III randomized trials (ALCANZA and MAVORIC, respectively).<sup>97-99</sup> The safety and efficacy of reformulated version of denileukin diftitox was demonstrated in study 302.<sup>100,101</sup> Bexarotene,<sup>102,103</sup> vorinostat,<sup>104-106</sup> romidepsin,<sup>107-109</sup> and other systemic therapies such as pralatrexate,<sup>110-112</sup> alemtuzumab,<sup>113-118</sup> and pembrolizumab<sup>119</sup> 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.<sup>120-122</sup> Peginterferon alfa-2a is the only IFN available for clinical use in the United States and it may be substituted for other IFN preparations.<sup>123-125</sup>

Extracorporeal photopheresis (ECP) is an immunomodulatory therapy in which patient's leukocytes are removed by leukapheresis, treated extracorporeally with 8-methoxysoralen and UVA, and then returned to the patient.<sup>126-128</sup> ECP may be a more appropriate systemic therapy for patients with some level of blood involvement (B1 or B2).

Gemcitabine<sup>129-136</sup> and pegylated liposomal doxorubicin<sup>136-141</sup> 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.<sup>142,143</sup> 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.<sup>102,103</sup> In phase II-III studies, oral bexarotene ( $\geq 300 \text{ mg/m}^2$ ) was well tolerated, resulting in an ORR of 45% to 67% in patients with early-stage and advanced-stage disease.<sup>102,103</sup> 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.<sup>144-147</sup> 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.<sup>148-150</sup> 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).<sup>149</sup>

## **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 ( $\geq \text{stage IB}$ ).<sup>97</sup> 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.<sup>98</sup> Peripheral neuropathy was the most common adverse event reported in 44 (69%) patients. At the

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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  $\geq 10\%$  of total lymphoid cells in at least 1 skin biopsy (43% of patients had at least 1 sample with CD30 <10%).<sup>97</sup> The results of an exploratory analysis showed that brentuximab vedotin resulted in higher ORR and improved PFS in patients with  $\geq 10\%$  CD30 expression, regardless of LCT status.<sup>151</sup> The ORR (41% vs. 10% for <10% CD30<sub>min</sub> expression; 57% vs. 10% for  $\geq 10\%$  CD30<sub>min</sub> expression) and median PFS (17 months vs. 2 months for <10% CD30<sub>min</sub> expression; 16 months vs. 4 months for  $\geq 10\%$  CD30<sub>min</sub> 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.<sup>152,153</sup> 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.<sup>152,153</sup> 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.<sup>154,155</sup>

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.<sup>156</sup> 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.<sup>157</sup>

### ***Mogamulizumab***

In the MAVORIC trial, mogamulizumab, a humanized anti-CCR4 monoclonal antibody, was more effective than vorinostat in patients with previously treated MF ( $\geq$  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%).<sup>99</sup> 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.<sup>158</sup> 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.<sup>159</sup>

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.<sup>99,160,161</sup> 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.<sup>99</sup> Mogamulizumab also resulted in higher ORR than vorinostat across all



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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.<sup>162</sup> 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.<sup>160,161</sup> The ORRs were 26% and 37%, respectively, for patients with B1 and B2 blood involvement compared to 16% for those with B0 blood involvement.<sup>160</sup> 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.<sup>161</sup> 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.<sup>161</sup> 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.<sup>99,163-166</sup> Mogamulizumab-associated skin rash has also been identified as a potential marker for tumor response.<sup>167</sup> 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.<sup>165,168</sup>

### **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%.<sup>105</sup> 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.<sup>106</sup> 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.<sup>107-109</sup> The median duration of response is 13 to 15 months for patients with disease responding to romidepsin.<sup>107,108</sup> 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.<sup>109</sup> 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,<sup>169,170</sup> 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-positivity was defined as detectable CD25 in ≥20% of total lymphoid cells in biopsy specimen by IHC.

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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.<sup>100</sup> The ORR were higher for stage IIIB 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.<sup>101</sup>

Denileukin diftitox is included as a preferred systemic therapy option for stage IIIB (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.<sup>113-118</sup> 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.<sup>114,118</sup> 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.<sup>115</sup> 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.<sup>119</sup> 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.<sup>110-112</sup> In a multicenter dose-finding study that evaluated pralatrexate (10–30 mg/m<sup>2</sup> 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).<sup>110</sup> Among the 29 patients who received the recommended dose (15 mg/m<sup>2</sup> weekly for 3 weeks of a 4-week cycle), the ORR was 45% (3% CR).<sup>110</sup> In the subgroup of patients with relapsed/refractory LCT of MF treated on the PROPEL trial, pralatrexate (30 mg/m<sup>2</sup>) resulted in an ORR of 58% (25% by independent review).<sup>111</sup> 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.<sup>129-136</sup> 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.<sup>133</sup> 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.<sup>136</sup> Retrospective studies have also reported favorable clinical outcomes (ORR and PFS) with low-dose gemcitabine in patients with previously treated MF and SS.<sup>134,135</sup>

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#### **Liposomal Doxorubicin**

Pegylated liposomal doxorubicin has shown single-agent activity in patients with pretreated, advanced, or refractory MF and SS.<sup>136-141</sup>

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.<sup>139</sup>

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).<sup>136</sup> 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.<sup>141</sup>

#### **Extracorporeal Photopheresis**

ECP has been demonstrated as an effective treatment option in many retrospective studies, resulting in an ORR of 42% to 74%.<sup>127,171-178</sup> 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.<sup>172</sup> 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).<sup>175</sup> 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).<sup>177</sup>

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.<sup>126,127,179</sup> 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).<sup>172,178</sup>

#### **Combination Therapies**

##### **Skin-Directed + Systemic Therapies**

Phototherapy is most commonly used in combination with either IFN<sup>180-183</sup> or systemic retinoid.<sup>144,150,184-186</sup>

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%).<sup>180</sup> 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).<sup>182</sup>

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



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71% (22% CR) for PUVA alone; the median duration of response was 6 months and 10 months, respectively.<sup>144</sup> 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.<sup>144</sup> 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.<sup>184</sup> 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.<sup>150</sup> 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.<sup>187,188</sup> 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.<sup>187</sup> 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.<sup>145–147,189–191</sup> 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.<sup>145</sup> 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.<sup>190,191</sup> Other systemic combination therapy regimens have also been studied.<sup>192–194</sup>

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.<sup>195</sup> The decisions to continue with or switch treatment regimens are often made



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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.<sup>20,196–199</sup> 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.<sup>200–202</sup>

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.<sup>203</sup> 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).<sup>7–9</sup> 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.<sup>7–9,204</sup> 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



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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.<sup>205-212</sup>

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.<sup>205</sup>

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.<sup>206</sup> 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  $\geq 3$  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.<sup>210</sup>

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.<sup>208</sup> 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.<sup>212</sup> 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.<sup>213,214</sup>

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).<sup>215</sup> 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



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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.<sup>216</sup> 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%).<sup>205-209</sup>

The use of TSEBT with non-myeloablative allogeneic HCT has also been evaluated in patients with advanced MF and SS.<sup>217-219</sup> 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%.<sup>217</sup> 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.<sup>220,221</sup> 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.<sup>220</sup> 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.<sup>221</sup> 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.<sup>217,220</sup> 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.<sup>222</sup> 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



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for patients.<sup>223-225</sup> 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.<sup>225,226</sup> First-line options include H1 antihistamines (single-agent or combination of antihistamines from different classes) or the anticonvulsant gabapentin.<sup>223,227,228</sup> Neurokinin-1 (NK-1) receptor antagonist aprepitant,<sup>229-231</sup> the tetracyclic antidepressant mirtazapine, or selective serotonin reuptake inhibitors (SSRIs) may be considered in the second-line setting.<sup>232,233</sup> Treatment with the oral opioid receptor antagonist naltrexone may be considered if symptoms of pruritus do not resolve with the above agents.<sup>234</sup>

## ***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).<sup>235</sup> 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.<sup>235</sup> 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 cephalaxin. 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.



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**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) <sup>98</sup>	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 <sup>a</sup> (≥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/m <sup>2</sup> once per day) for 48 weeks							
MAVORIC trial (Phase III RCT) <sup>99</sup>	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 <sup>100</sup>	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) <sup>b</sup>	ECOG PS 0-2; Adequate organ function; ≥18 years with recurrent or persistent CD25-positive MF and SS <sup>c</sup> (≥1 prior systemic therapy; no prior denileukin diftitox);	—	42% (36% by IRC);	—		
Phase II and III <sup>102</sup>	Bexarotene	300 mg/m <sup>2</sup> /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/m <sup>2</sup> /day	Stage IA-IIA (n = 15)		—	67%		
Phase II and III <sup>103</sup>	Bexarotene	300 mg/m <sup>2</sup> /day	Stage IIB–IVB (n = 56)	≥18 years with refractory or persistent MF and SS	—	45%		
		>300 mg/m <sup>2</sup> /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 positivity 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 fungoïdes; 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](#)



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**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
<b>Phase II<sup>B105</sup></b>	<b>Vorinostat</b> (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%	
<b>Phase II<sup>108</sup></b>	<b>Romidepsin</b> (14 mg/m <sup>2</sup> 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)	
<b>PDX-010 (Dose-escalation study)<sup>110</sup></b>	<b>Pralatrexate</b> (15 mg/m <sup>2</sup> , 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
<b>Phase II<sup>114</sup></b>	<b>Alemtuzumab</b> (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)	
<b>Subcutaneous alemtuzumab<sup>115</sup></b>	<b>Alemtuzumab</b> (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)
<b>Phase II (CITN-10)<sup>119</sup></b>	<b>Pembrolizumab</b> (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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### References

1. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood* 2009;113:5064-5073. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19279331>.
2. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30635287>.
3. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA Cancer J Clin* 2016;66:443-459. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27618563>.
4. Dummer R, Vermeer MH, Scarisbrick JJ, et al. Cutaneous T cell lymphoma. *Nat Rev Dis Primers* 2021;7:61. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34446710>.
5. Campbell JJ, Clark RA, Watanabe R, Kupper TS. Sezary syndrome and mycosis fungoïdes arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors. *Blood* 2010;116:767-771. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20484084>.
6. Olsen EA, Rook AH, Zic J, et al. Sezary syndrome: immunopathogenesis, literature review of therapeutic options, and recommendations for therapy by the United States Cutaneous Lymphoma Consortium (USCLC). *J Am Acad Dermatol* 2011;64:352-404. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21145619>.
7. Diamandidou E, Colome-Grimmer M, Fayad L, et al. Transformation of mycosis fungoïdes/Sezary syndrome: clinical characteristics and prognosis. *Blood* 1998;92:1150-1159. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9694702>.

8. Vergier B, de Muret A, Beylot-Barry M, et al. Transformation of mycosis fungoïdes: clinicopathological and prognostic features of 45 cases. French Study Group of Cutaneous Lymphomas. *Blood* 2000;95:2212-2218. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10733487>.
9. Arulogun SO, Prince HM, Ng J, et al. Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. *Blood* 2008;112:3082-3087. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18647960>.
10. Choi J, Goh G, Walradt T, et al. Genomic landscape of cutaneous T cell lymphoma. *Nat Genet* 2015;47:1011-1019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26192916>.
11. Kann BH, Park HS, Yeboa DN, et al. Annual facility treatment volume and patient survival for mycosis fungoïdes and Sezary syndrome. *Clin Lymphoma Myeloma Leuk* 2017;17:520-526.e522. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28655598>.
12. PubMed Overview. Available at: <https://pubmed.ncbi.nlm.nih.gov/about/>. Accessed March 10, 2024.
13. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34758074>.
14. de Coninck EC, Kim YH, Varghese A, Hoppe RT. Clinical characteristics and outcome of patients with extracutaneous mycosis fungoïdes. *J Clin Oncol* 2001;19:779-784. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11157031>.
15. Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoïdes and Sezary syndrome: clinical prognostic factors and risk for disease progression. *Arch Dermatol* 2003;139:857-866. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12873880>.



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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

16. Vidulich KA, Talpur R, Bassett RL, Duvic M. Overall survival in erythrodermic cutaneous T-cell lymphoma: an analysis of prognostic factors in a cohort of patients with erythrodermic cutaneous T-cell lymphoma. *Int J Dermatol* 2009;48:243-252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19261011>.
17. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol* 2010;28:4730-4739. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20855822>.
18. Talpur R, Singh L, Daulat S, et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sezary syndrome from 1982 to 2009. *Clin Cancer Res* 2012;18:5051-5060. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22850569>.
19. Alberti-Violette S, Talpur R, Schlichte M, et al. Advanced-stage mycosis fungoides and Sezary syndrome: survival and response to treatment. *Clin Lymphoma Myeloma Leuk* 2015;15:e105-112. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25817937>.
20. Scarisbrick JJ, Prince HM, Vermeer MH, et al. Cutaneous Lymphoma International Consortium study of outcome in advanced stages of mycosis fungoides and Sezary syndrome: Effect of specific prognostic markers on survival and development of a prognostic model. *J Clin Oncol* 2015;33:3766-3773. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26438120>.
21. Bontoux C, de Masson A, Thonnart N, et al. Large-cell transformation is an independent poor prognostic factor in Sezary syndrome: analysis of 117 cases. *Br J Dermatol* 2022;187:815-817. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35791764>.
22. Jairath NK, Bardhi R, Runge JS, et al. Predictors of large cell transformation in patients with Sezary Syndrome-A retrospective analysis.
23. Scarisbrick JJ, Quaglino P, Prince HM, et al. The PROCLIP international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients. *Br J Dermatol* 2019;181:350-357. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30267549>.
24. Hodak E, Sherman S, Papadavid E, et al. Should we be imaging lymph nodes at initial diagnosis of early-stage mycosis fungoides? Results from the PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIP) international study. *Br J Dermatol* 2021;184:524-531. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32574377>.
25. Quaglino P, Prince HM, Cowan R, et al. Treatment of early-stage mycosis fungoides: results from the PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIP) study. *Br J Dermatol* 2021;184:722-730. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32479678>.
26. Kim EJ, Hess S, Richardson SK, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. *J Clin Invest* 2005;115:798-812. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15841167>.
27. Martinez Villarreal A, Gantchev J, Lagace F, et al. Hypopigmented mycosis fungoides: loss of pigmentation reflects antitumor immune response in young patients. *Cancers (Basel)* 2020;12. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32707930>.
28. Jayasinghe DR, Dissanayake K, de Silva MVC. Comparison between the histopathological and immunophenotypical features of hypopigmented and nonhypopigmented mycosis fungoides: A retrospective study. *J Cutan Pathol* 2021;48:486-494. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32965737>.
29. Jung JM, Lee MY, Won CH, et al. Hyperpigmented mycosis fungoides: a retrospective and comparative analysis with other subtypes of mycosis



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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

fungoides. Leuk Lymphoma 2022;63:1598-1606. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35201905>.

30. Beygi S, Duran GE, Fernandez-Pol S, et al. Resistance to mogamulizumab is associated with loss of CCR4 in cutaneous T-cell lymphoma. Blood 2022;139:3732-3736. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35436328>.

31. Battistella M, Beylot-Barry M, Bacheler H, et al. Primary cutaneous follicular helper T-cell lymphoma: a new subtype of cutaneous T-cell lymphoma reported in a series of 5 cases. Arch Dermatol 2012;148:832-839. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22508770>.

32. Wang JY, Nguyen GH, Ruan J, Magro CM. Primary cutaneous follicular helper T-cell lymphoma: A case series and review of the literature. Am J Dermatopathol 2017;39:374-383. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28375859>.

33. Bosisio FM, Cerroni L. Expression of T-follicular helper markers in sequential biopsies of progressive mycosis fungoides and other primary cutaneous T-cell lymphomas. Am J Dermatopathol 2015;37:115-121. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25406852>.

34. Park JH, Han JH, Kang HY, et al. Expression of follicular helper T-cell markers in primary cutaneous T-cell lymphoma. Am J Dermatopathol 2014;36:465-470. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24162385>.

35. Thurber SE, Zhang B, Kim YH, et al. T-cell clonality analysis in biopsy specimens from two different skin sites shows high specificity in the diagnosis of patients with suggested mycosis fungoides. J Am Acad Dermatol 2007;57:782-790. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17646032>.

36. Zhang B, Beck AH, Taube JM, et al. Combined use of PCR-based TCRG and TCRB clonality tests on paraffin-embedded skin tissue in the differential diagnosis of mycosis fungoides and inflammatory dermatoses.

J Mol Diagn 2010;12:320-327. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20203005>.

37. Kirsch IR, Watanabe R, O'Malley JT, et al. TCR sequencing facilitates diagnosis and identifies mature T cells as the cell of origin in CTCL. Sci Transl Med 2015;7:308ra158. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26446955>.

38. de Masson A, O'Malley JT, Elco CP, et al. High-throughput sequencing of the T cell receptor beta gene identifies aggressive early-stage mycosis fungoides. Sci Transl Med 2018;10:eaar5894. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29743350>.

39. Horna P, Wang SA, Wolniak KL, et al. Flow cytometric evaluation of peripheral blood for suspected Sezary syndrome or mycosis fungoides: International guidelines for assay characteristics. Cytometry B Clin Cytom 2021;100:142-155. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32319723>.

40. Martin-Moro F, Martin-Rubio I, Garcia-Vela JA. TRBC1 expression assessed by flow cytometry as a novel marker of clonality in cutaneous alphabeta T-cell lymphomas with peripheral blood involvement. Br J Dermatol 2022;187:623-625. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35606929>.

41. Castillo F, Morales C, Spralja B, et al. Integration of T-cell clonality screening using TRBC-1 in lymphoma suspect samples by flow cytometry. Cytometry B Clin Cytom 2024;106:64-73. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38010106>.

42. Nguyen PC, Nguyen T, Wilson C, et al. Evaluation of T-cell clonality by anti-TRBC1 antibody-based flow cytometry and correlation with T-cell receptor sequencing. Br J Haematol 2024;204:910-920. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38098188>.

43. Tsai EY, Taur A, Espinosa L, et al. Staging accuracy in mycosis fungoides and sezary syndrome using integrated positron emission tomography and computed tomography. Arch Dermatol



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Network®

# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

2006;142:577-584. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16702495>.

44. Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol

1998;134:949-954. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/9722724>.

45. Zackheim HS. Treatment of patch-stage mycosis fungoides with topical corticosteroids. Dermatol Ther 2003;16:283-287. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/14686970>.

46. Kartan S, Shalabi D, O'Donnell M, et al. Response to topical corticosteroid monotherapy in mycosis fungoides. J Am Acad Dermatol 2021;84:615-623. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32428610>.

47. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. Arch Dermatol 2003;139:165-173. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12588222>.

48. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol 2013;149:25-32. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23069814>.

49. 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. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11902983>.

50. Heald P, Mehlmauer M, Martin AG, et al. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol 2003;49:801-815. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/14576658>.

51. Apisarnthanarak 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. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15034511>.

52. Besner Morin C, Roberge D, Turchin I, et al. Tazarotene 0.1% cream as monotherapy for early-stage cutaneous T-cell lymphoma. J Cutan Med Surg 2016;20:244-248. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26742957>.

53. 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. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15692473>.

54. Coors EA, Schuler G, Von Den Driesch P. Topical imiquimod as treatment for different kinds of cutaneous lymphoma. Eur J Dermatol 2006;16:391-393. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16935796>.

55. Martinez-Gonzalez MC, Verea-Hernando MM, Yebra-Pimentel MT, et al. Imiquimod in mycosis fungoides. Eur J Dermatol 2008;18:148-152. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18424373>.

56. Lewis DJ, Byekova YA, Emge DA, Duvic M. Complete resolution of mycosis fungoides tumors with imiquimod 5% cream: a case series. J Dermatolog Treat 2017;28:567-569. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28635518>.

57. Zackheim HS. Topical carmustine (BCNU) for patch/plaque mycosis fungoides. Semin Dermatol 1994;13:202-206. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/7986689>.

58. Zackheim HS. Topical carmustine (BCNU) in the treatment of mycosis fungoides. Dermatol Ther 2003;16:299-302. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/14686972>.

59. Ortiz-Romero PL, Maronas Jimenez L, Muniesa C, et al. Activity and safety of topical pimecrolimus in patients with early stage mycosis



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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

fungoides (PimTo-MF): a single-arm, multicentre, phase 2 trial. Lancet Haematol 2022;9:e425-e433. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/35654076>.

60. Piccinno R, Caccialanza M, Cuka E, Recalcati S. Localized conventional radiotherapy in the treatment of Mycosis Fungoides: our experience in 100 patients. J Eur Acad Dermatol Venereol 2014;28:1040-1044. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/23998331>.

61. 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. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25863751>.

62. 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. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/18834672>.

63. 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. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/22818412>.

64. Ysebaert L, Truc G, Dalac S, et al. Ultimate results of radiation therapy for T1-T2 mycosis fungoides (including reirradiation). Int J Radiat Oncol Biol Phys 2004;58:1128-1134. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/15001254>.

65. Harrison C, Young J, Navi D, et al. Revisiting low-dose total skin electron beam therapy in mycosis fungoides. Int J Radiat Oncol Biol Phys 2011;81:e651-657. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/21489711>.

66. Navi D, Riaz N, Levin YS, et al. The Stanford University experience with conventional-dose, total skin electron-beam therapy in the treatment of generalized patch or plaque (T2) and tumor (T3) mycosis fungoides.

Arch Dermatol 2011;147:561-567. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/21576575>.

67. Elsayad K, Kriz J, Moustakis C, et al. Total skin electron beam for primary cutaneous T-cell lymphoma. Int J Radiat Oncol Biol Phys 2015;93:1077-1086. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/26581145>.

68. Kamstrup MR, Lindahl LM, Gniadecki R, et al. Low-dose total skin electron beam therapy as a debulking agent for cutaneous T-cell lymphoma: an open-label prospective phase II study. Br J Dermatol 2012;166:399-404. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/21967035>.

69. Hoppe RT, Harrison C, Tavallaee M, et al. Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: results of a pooled analysis from 3 phase-II clinical trials. J Am Acad Dermatol 2015;72:286-292. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25476993>.

70. Kamstrup MR, Gniadecki R, Iversen L, et al. Low-dose (10-Gy) total skin electron beam therapy for cutaneous T-cell lymphoma: an open clinical study and pooled data analysis. Int J Radiat Oncol Biol Phys 2015;92:138-143. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25863761>.

71. Kroeger K, Elsayad K, Moustakis C, et al. Low-dose total skin electron beam therapy for cutaneous lymphoma : Minimal risk of acute toxicities. Strahlenther Onkol 2017;193:1024-1030. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/28785772>.

72. Morris S, Scarsbrick J, Frew J, et al. The results of low-dose total skin electron beam radiation therapy (TSEB) in patients with mycosis fungoides from the UK cutaneous lymphoma group. Int J Radiat Oncol Biol Phys 2017;99:627-633. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/28843374>.

73. Georgakopoulos I, Papadavid E, Platoni K, et al. Low dose total skin electron beam therapy for the management of T cell cutaneous



National  
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Cancer  
Network®

# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

lymphomas. *Dermatol Ther* 2020;33:e13478. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32391976>.

74. Song A, Gochoco A, Zhan T, et al. A prospective cohort study of condensed low-dose total skin electron beam therapy for mycosis fungoides: Reduction of disease burden and improvement in quality of life. *J Am Acad Dermatol* 2020;83:78-85. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32004646>.

75. Elsayad K, Kroeger K, Greve B, et al. Low-dose total skin electron beam therapy: Quality of life improvement and clinical impact of maintenance and adjuvant treatment in patients with mycosis fungoides or Sezary syndrome. *Strahlenther Onkol* 2020;196:77-84. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31591658>.

76. Kudelka MR, Switchenko JM, Lechowicz MJ, et al. Maintenance therapy for cutaneous T-cell lymphoma after total skin electron irradiation: Evidence for improved overall survival with ultraviolet therapy. *Clin Lymphoma Myeloma Leuk* 2020;20:757-767 e753. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32703750>.

77. Elsayad K, Rolf D, Sunderkotter C, et al. Low-dose total skin electron beam therapy plus oral bexarotene maintenance therapy for cutaneous T-cell lymphoma. *J Dtsch Dermatol Ges* 2022;20:279-285. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34984837>.

78. Gathers RC, Scherschun L, Malick F, et al. Narrowband UVB phototherapy for early-stage mycosis fungoides. *J Am Acad Dermatol* 2002;47:191-197. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12140464>.

79. Dereure O, Picot E, Comte C, et al. Treatment of early stages of mycosis fungoides with narrowband ultraviolet B. A clinical, histological and molecular evaluation of results. *Dermatology* 2009;218:1-6. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18832806>.

80. Gokdemir G, Barutcuoglu B, Sakiz D, Koslu A. Narrowband UVB phototherapy for early-stage mycosis fungoides: evaluation of clinical and histopathological changes. *J Eur Acad Dermatol Venereol*

2006;20:804-809. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16898902>.

81. Drucker AM, Baibergenova A, Rosen CF, Shear NH. Narrowband UVB as an effective substitute for psoralen plus UVA: lessons from a psoralen shortage. *Photodermat Photoimmunol Photomed* 2012;28:267-268. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22971194>.

82. Elcin G, Duman N, Karahan S, et al. Long-term follow-up of early mycosis fungoides patients treated with narrowband ultraviolet B phototherapy. *J Dermatolog Treat* 2014;25:268-273. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23030414>.

83. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15781671>.

84. Pavlotsky F, Hodak E, Ben Amitay D, Barzilai A. Role of bath psoralen plus ultraviolet A in early-stage mycosis fungoides. *J Am Acad Dermatol* 2014;71:536-541. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24836546>.

85. Amitay-Laish I, Prag-Naveh H, Dalal A, et al. Treatment of early folliculotropic mycosis fungoides with special focus on psoralen plus ultraviolet A. *Acta Derm Venereol* 2018;98:951-955. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30085321>.

86. Vieyra-Garcia P, Fink-Puches R, Porkert S, et al. Evaluation of low-dose, low-frequency oral psoralen-UV-A treatment with or without maintenance on early-stage mycosis fungoides: A randomized clinical trial. *JAMA Dermatol* 2019;155:538-547. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30892603>.

87. Almohideb M, Walsh S, Walsh S, et al. Bath psoralen-ultraviolet A and narrowband ultraviolet B phototherapy as initial therapy for early-stage mycosis fungoides: A retrospective cohort of 267 cases at the University of



National  
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Cancer  
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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

Toronto. Clin Lymphoma Myeloma Leuk 2017;17:604-612. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28711574>.

88. Nikolaou V, Sachlas A, Papadavid E, et al. Phototherapy as a first-line treatment for early-stage mycosis fungoides: The results of a large retrospective analysis. Photodermatol Photoimmunol Photomed 2018;34:307-313. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29533478>.

89. Phan K, Ramachandran V, Fassihi H, Sebaratnam DF. Comparison of narrowband UV-B With psoralen-UV-A phototherapy for patients with early-stage mycosis fungoides: a systematic review and meta-analysis. JAMA Dermatol 2019;155:335-341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30698622>.

90. Ahmad K, Rogers S, McNicholas PD, Collins P. Narrowband UVB and PUVA in the treatment of mycosis fungoides: a retrospective study. Acta Derm Venereol 2007;87:413-417. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17721648>.

91. Ponte P, Serrao V, Apetato M. Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides. J Eur Acad Dermatol Venereol 2010;24:716-721. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19929938>.

92. Hearn RM, Kerr AC, Rahim KF, et al. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. Br J Dermatol 2008;159:931-935. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18834483>.

93. Ahad T, Wang EY, Liu YA, et al. Incidence of skin cancers in patients with eczema treated with ultraviolet phototherapy. J Am Acad Dermatol 2022;87:387-389. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34864113>.

94. Wang E, Ahad T, Liu YA, et al. Incidence and profile of skin cancers in patients following ultraviolet phototherapy without psoralens: A retrospective cohort study. J Am Acad Dermatol 2024;90:759-766. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38070541>.

95. Diederken PV, van Weelden H, Sanders CJ, et al. Narrowband UVB and psoralen-UVA in the treatment of early-stage mycosis fungoides: a retrospective study. J Am Acad Dermatol 2003;48:215-219. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12582391>.

96. Olsen EA, Hodak E, Anderson T, et al. Guidelines for phototherapy of mycosis fungoides and Sezary syndrome: A consensus statement of the United States Cutaneous Lymphoma Consortium. J Am Acad Dermatol 2016;74:27-58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26547257>.

97. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet 2017;390:555-566. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28600132>.

98. Horwitz SM, Scarisbrick JJ, Dummer R, et al. Randomized phase 3 ALCANZA study of brentuximab vedotin vs physician's choice in cutaneous T-cell lymphoma: final data. Blood Adv 2021;5:5098-5106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34507350>.

99. Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol 2018;19:1192-1204. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30100375>.

100. Foss FM, Kim YH, Prince HMM, et al. Efficacy and safety of E7777 (improved purity denileukin dititox [ONTAK]) in patients with relapsed or refractory cutaneous T-cell lymphoma: Results from pivotal study 302 [abstract]. Blood 2022;140:1491-1492. Available at: <https://doi.org/10.1182/blood-2022-166916>.

101. Prince HMM, Geskin LJ, Akilov OE, et al. Safety and Tolerability of E7777 (improved purity Denileukin dititox [ONTAK]) in Patients with Relapsed or Refractory Cutaneous T-Cell Lymphoma: Results from Pivotal



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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

Study 302 [abstract]. Blood 2022;140:6577-6578. Available at:  
<https://doi.org/10.1182/blood-2022-167564>.

102. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol 2001;137:581-593. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/11346336>.

103. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol 2001;19:2456-2471. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11331325>.

104. Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007;109:31-39. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/16960145>.

105. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17577020>.

106. Duvic M, Olsen EA, Breneman D, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009;9:412-416. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19951879>.

107. Piekarz RL, Frye R, Turner M, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol 2009;27:5410-5417. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19826128>.

108. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20697094>.

109. Kim EJ, Kim YH, Rook AH, et al. Clinically significant responses achieved with romidepsin across disease compartments in patients with cutaneous T-cell lymphoma. Leuk Lymphoma 2015;56:2847-2854. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25791237>.

110. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22394596>.

111. Foss F, Horwitz SM, Coiffier B, et al. Pralatrexate is an effective treatment for relapsed or refractory transformed mycosis fungoïdes: a subgroup efficacy analysis from the PROPEL study. Clin Lymphoma Myeloma Leuk 2012;12:238-243. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/22542448>.

112. Talpur R, Thompson A, Gangar P, Duvic M. Pralatrexate alone or in combination with bexarotene: long-term tolerability in relapsed/refractory mycosis fungoïdes. Clin Lymphoma Myeloma Leuk 2014;14:297-304. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24589156>.

113. Kennedy GA, Seymour JF, Wolf M, et al. Treatment of patients with advanced mycosis fungoïdes and Sezary syndrome with alemtuzumab. Eur J Haematol 2003;71:250-256. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/12950233>.

114. Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoïdes/Sezary syndrome. Blood 2003;101:4267-4272. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12543862>.

115. Bernengo MG, Quaglino P, Comessatti A, et al. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. Haematologica 2007;92:784-794. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17550851>.

116. Alinari L, Geskin L, Grady T, et al. Subcutaneous alemtuzumab for Sezary Syndrome in the very elderly. Leuk Res 2008;32:1299-1303. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18096224>.



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Cancer  
Network®

# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

117. Querfeld C, Mehta N, Rosen ST, et al. Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. *Leuk Lymphoma* 2009;50:1969-1976. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19860617>.
118. de Masson A, Guitera P, Brice P, et al. Long-term efficacy and safety of alemtuzumab in advanced primary cutaneous T-cell lymphomas. *Br J Dermatol* 2014;170:720-724. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24438061>.
119. Khodadoust MS, Rook AH, Porcu P, et al. Pembrolizumab in relapsed and refractory mycosis fungoïdes and Sézary syndrome: A multicenter phase II study. *J Clin Oncol* 2020;38:20-28. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31532724>.
120. Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. *Dermatol Ther* 2003;16:311-321. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14686974>.
121. Kaplan EH, Rosen ST, Norris DB, et al. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. *J Natl Cancer Inst* 1990;82:208-212. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2104937>.
122. Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoïdes: a retrospective study in 69 patients. *J Am Acad Dermatol* 2003;49:873-878. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14576667>.
123. Schiller M, Tsianakas A, Sterry W, et al. Dose-escalation study evaluating pegylated interferon alpha-2a in patients with cutaneous T-cell lymphoma. *J Eur Acad Dermatol Venereol* 2017;31:1841-1847. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28557110>.
124. Patsatsi A, Papadavid E, Kyriakou A, et al. The use of pegylated interferon α-2a in a cohort of Greek patients with mycosis fungoïdes. *J Eur Acad Dermatol Venereol* 2022;36:e291-e293. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34753217>.
125. Osman S, Chia JC, Street L, Hardin J. Transitioning to pegylated interferon for the treatment of cutaneous T-cell lymphoma: Meeting the challenge of therapy discontinuation and a proposed algorithm. *Dermatologic Therapy* 2023;2023:7171937. Available at: <https://doi.org/10.1155/2023/7171937>.
126. McGirt LY, Thoburn C, Hess A, Vonderheid EC. Predictors of response to extracorporeal photopheresis in advanced mycosis fungoïdes and Sézary syndrome. *Photodermatol Photoimmunol Photomed* 2010;26:182-191. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20626820>.
127. Quaglino P, Knobler R, Fierro MT, et al. Extracorporeal photopheresis for the treatment of erythrodermic cutaneous T-cell lymphoma: a single center clinical experience with long-term follow-up data and a brief overview of the literature. *Int J Dermatol* 2013;52:1308-1318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23786842>.
128. Knobler R, Arenberger P, Arun A, et al. European dermatology forum - updated guidelines on the use of extracorporeal photopheresis 2020 - part 1. *J Eur Acad Dermatol Venereol* 2020;34:2693-2716. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33025659>.
129. Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. *J Clin Oncol* 2000;18:2603-2606. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10893292>.
130. Marchi E, Alinari L, Tani M, et al. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients. *Cancer* 2005;104:2437-2441. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16216001>.
131. Duvic M, Talpur R, Wen S, et al. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. *Clin Lymphoma Myeloma* 2006;7:51-58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16879770>.



National  
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Network®

# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

132. Jidar K, Ingen-Housz-Oro S, Beylot-Barry M, et al. Gemcitabine treatment in cutaneous T-cell lymphoma: a multicentre study of 23 cases. *Br J Dermatol* 2009;161:660-663. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19438862>.
133. Pellegrini C, Stefoni V, Casadei B, et al. Long-term outcome of patients with advanced-stage cutaneous T cell lymphoma treated with gemcitabine. *Ann Hematol* 2014;93:1853-1857. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24908331>.
134. Blazejak C, Stranzenbach R, Gosman J, et al. Clinical outcomes of advanced-stage cutaneous lymphoma under low-dose gemcitabine treatment: Real-life data from the German Cutaneous Lymphoma Network. *Dermatology* 2022;238:498-506. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34474414>.
135. Di Raimondo C, Vaccarini S, Nunzi A, et al. Continuous low-dose gemcitabine in primary cutaneous T cell lymphoma: A retrospective study. *Dermatol Ther* 2022;35:e15482. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35373414>.
136. Weiner D, Ly A, Talluru S, et al. Efficacy of single-agent chemotherapy with pegylated liposomal doxorubicin or gemcitabine in a diverse cohort of patients with recalcitrant cutaneous T-cell lymphoma. *Br J Dermatol* 2024;190:436-438. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37655919>.
137. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17488695>.
138. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18559761>.
139. Dummer R, Quaglino P, Becker JC, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. *J Clin Oncol* 2012;30:4091-4097. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23045580>.
140. Falkenhain-Lopez D, Fulgencio-Barbarin J, Puerta-Pena M, et al. Single-centre experience of using pegylated liposomal doxorubicin as maintenance treatment in mycosis fungoides. *Br J Dermatol* 2022;186:363-365. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34528240>.
141. Falkenhain-Lopez D, Puerta-Pena M, Fulgencio-Barbarin J, et al. Real-life experience of using pegylated liposomal doxorubicin in primary cutaneous T-cell lymphomas. *Clin Exp Dermatol* 2022;47:1712-1715. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35426448>.
142. Hughes CF, Khot A, McCormack C, et al. Lack of durable disease control with chemotherapy for mycosis fungoides and Sezary syndrome: a comparative study of systemic therapy. *Blood* 2015;125:71-81. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25336628>.
143. Quaglino P, Maule M, Prince HM, et al. Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium. *Ann Oncol* 2017;28:2517-2525. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28961843>.
144. Whittaker S, Ortiz P, Dummer R, et al. Efficacy and safety of bexarotene combined with psoralen-ultraviolet A (PUVA) compared with PUVA treatment alone in stage IB-IIA mycosis fungoides: final results from the EORTC Cutaneous Lymphoma Task Force phase III randomized clinical trial (NCT00056056). *Br J Dermatol* 2012;167:678-687. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22924950>.
145. Duvic M, Apisarnthanarak N, Cohen DS, et al. Analysis of long-term outcomes of combined modality therapy for cutaneous T-cell lymphoma. *J*



National  
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Network®

# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

Am Acad Dermatol 2003;49:35-49. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/12833006>.

146. Straus DJ, Duvic M, Kuzel T, et al. Results of a phase II trial of oral bexarotene (Targretin) combined with interferon alfa-2b (Intron-A) for patients with cutaneous T-cell lymphoma. Cancer 2007;109:1799-1803. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17366595>.

147. Siakantaris MP, Tsirigotis P, Stavroyianni N, et al. Management of cutaneous T-Cell lymphoma patients with extracorporeal photopheresis. The Hellenic experience. Transfus Apher Sci 2012;46:189-193. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22178592>.

148. Cheeley J, Sahn RE, DeLong LK, Parker SR. Acitretin for the treatment of cutaneous T-cell lymphoma. J Am Acad Dermatol 2013;68:247-254. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/22917895>.

149. Amitay-Laish I, Reiter O, Prag-Naveh H, et al. Retinoic acid receptor agonist as monotherapy for early-stage mycosis fungoides: does it work? J Dermatolog Treat 2019;30:258-263. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/29889596>.

150. Nikolaou V, Patsatsi A, Sidiropoulou P, et al. Monotherapy and combination therapy with acitretin for mycosis fungoides: results of a retrospective, multicentre study. J Eur Acad Dermatol Venereol 2020;34:2534-2540. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/32364303>.

151. Kim YH, Prince HM, Whittaker S, et al. Response to brentuximab vedotin versus physician's choice by CD30 expression and large cell transformation status in patients with mycosis fungoides: An ALCANZA sub-analysis. Eur J Cancer 2021;148:411-421. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/33794441>.

152. 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. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/26261247>.

153. Kim YH, Tavallaei 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26195720>.

154. Papadavid E, Kapniari E, Pappa V, et al. Multicentric EORTC retrospective study shows efficacy of brentuximab vedotin in patients who have mycosis fungoides and Sezary syndrome with variable CD30 positivity. Br J Dermatol 2021;185:1035-1044. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/34137025>.

155. Barta SK, Liu N, DerSarkissian M, et al. Real-world treatment patterns and clinical outcomes with brentuximab vedotin or other standard therapies in patients with previously treated cutaneous T-cell lymphoma in the United States. Clin Lymphoma Myeloma Leuk 2024;24:e21-e32 e24. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37919137>.

156. Dummer R, Prince HM, Whittaker S, et al. Patient-reported quality of life in patients with relapsed/refractory cutaneous T-cell lymphoma: Results from the randomised phase III ALCANZA study. Eur J Cancer 2020;133:120-130. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/32502876>.

157. Lewis DJ, Haun PL, Samimi SS, et al. Brentuximab vedotin for relapsed or refractory Sezary syndrome. JAMA Dermatol 2021;157:317-321. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/33377934>.

158. Horwitz S, Zinzani PL, Bagot M, et al. Lack of impact of type and extent of prior therapy on outcomes of mogamulizumab therapy in patients with cutaneous T cell lymphoma in the MAVORIC trial. Leuk Lymphoma 2021;62:3109-3118. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/34304674>.

159. Porcu P, Hudgens S, Horwitz S, et al. Quality of life effect of the anti-CCR4 monoclonal antibody mogamulizumab versus vorinostat in patients with cutaneous T-cell lymphoma. Clin Lymphoma Myeloma Leuk



National  
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Network®

# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

2021;21:97-105. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/33158772>.

160. Cowan RA, Scarisbrick JJ, Zinzani PL, et al. Efficacy and safety of mogamulizumab by patient baseline blood tumour burden: a post hoc analysis of the MAVORIC trial. *J Eur Acad Dermatol Venereol* 2021;35:2225-2238. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/34273208>.

161. Beylot-Barry M, Booken N, Weishaupt C, et al. Impact of blood involvement on efficacy and time to response with mogamulizumab in mycosis fungoides and Sezary syndrome. *J Eur Acad Dermatol Venereol* 2023;37:311-316. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/35993803>.

162. Bagot M, Dalle S, Sokol L, et al. Long-term disease control and safety with the anti-CCR4 antibody mogamulizumab: Post-hoc analyses from the MAVORIC trial of patients with previously treated cutaneous T-cell lymphoma. *Dermatol Ther* 2022;35:e15634. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/35695215>.

163. Hirotsu KE, Neal TM, Khodadoust MS, et al. Clinical characterization of mogamulizumab-associated rash during treatment of mycosis fungoides or Sezary syndrome. *JAMA Dermatol* 2021;157:700-707. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/33881447>.

164. Trum NA, Zain J, Martinez XU, et al. Mogamulizumab efficacy is underscored by its associated rash that mimics cutaneous T-cell lymphoma: a retrospective single-centre case series. *Br J Dermatol* 2022;186:153-166. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/34427917>.

165. Wang JY, Hirotsu KE, Neal TM, et al. Histopathologic characterization of mogamulizumab-associated rash. *Am J Surg Pathol* 2020;44:1666-1676. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32976123>.

166. Wang J, de Masson A, Ram-Wolff C, et al. Granulomatous rash associated with mogamulizumab mimicking mycosis fungoides: a case

series. *Eur J Cancer* 2021;156 Suppl 1:S49. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/34649659>.

167. Chen L, Carson KR, Staser KW, et al. Mogamulizumab-associated cutaneous granulomatous drug eruption mimicking mycosis fungoides but possibly indicating durable clinical response. *JAMA Dermatol* 2019;155:968-971. Available at:

168. Musiek ACM, Rieger KE, Bagot M, et al. Dermatologic events associated with the anti-CCR4 antibody mogamulizumab: characterization and management. *Dermatol Ther (Heidelb)* 2022;12:29-40. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/34816383>.

169. Prince HM, Duvic M, Martin A, et al. Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. *J Clin Oncol* 2010;28:1870-1877. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20212249>.

170. Duvic M, Geskin L, Prince HM. Duration of response in cutaneous T-cell lymphoma patients treated with denileukin diftitox: results from 3 phase III studies. *Clin Lymphoma Myeloma Leuk* 2013;13:377-384. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23770157>.

171. Bisaccia E, Gonzalez J, Palangio M, et al. Extracorporeal photochemotherapy alone or with adjuvant therapy in the treatment of cutaneous T-cell lymphoma: a 9-year retrospective study at a single institution. *J Am Acad Dermatol* 2000;43:263-271. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10906649>.

172. Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. *Dermatol Ther* 2003;16:337-346. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/14686977>.

173. Arulogun S, Prince HM, Gambell P, et al. Extracorporeal photopheresis for the treatment of Sezary syndrome using a novel treatment protocol. *J Am Acad Dermatol* 2008;59:589-595. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18656282>.



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Network®

# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

174. Talpur R, Demierre MF, Geskin L, et al. Multicenter photopheresis intervention trial in early-stage mycosis fungoides. *Clin Lymphoma Myeloma Leuk* 2011;11:219-227. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21575927>.
175. Knobler R, Duvic M, Querfeld C, et al. Long-term follow-up and survival of cutaneous T-cell lymphoma patients treated with extracorporeal photopheresis. *Photodermat Photoimmunol Photomed* 2012;28:250-257. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22971190>.
176. Knobler R, Berlin G, Calzavara-Pinton P, et al. Guidelines on the use of extracorporeal photopheresis. *J Eur Acad Dermatol Venereol* 2014;28 Suppl 1:1-37. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24354653>.
177. Atilla E, Atilla PA, Bozdag SC, et al. Extracorporeal photochemotherapy in mycosis fungoides. *Transfus Clin Biol* 2017;24:454-457. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28578935>.
178. Gao C, McCormack C, van der Weyden C, et al. Prolonged survival with the early use of a novel extracorporeal photopheresis regimen in patients with Sezary syndrome. *Blood* 2019;134:1346-1350. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31467061>.
179. Stevens SR, Baron ED, Masten S, Cooper KD. Circulating CD4+CD7- lymphocyte burden and rapidity of response: predictors of outcome in the treatment of Sezary syndrome and erythrodermic mycosis fungoides with extracorporeal photopheresis. *Arch Dermatol* 2002;138:1347-1350. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12374541>.
180. Stadler R, Otte HG, Luger T, et al. Prospective randomized multicenter clinical trial on the use of interferon -2a plus acitretin versus interferon -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. *Blood* 1998;92:3578-3581. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9808550>.
181. Chiarion-Sileni V, Bononi A, Fornasa CV, et al. Phase II trial of interferon-alpha-2a plus psolarex with ultraviolet light A in patients with cutaneous T-cell lymphoma. *Cancer* 2002;95:569-575. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12209749>.
182. Rupoli S, Goteri G, Pulini S, et al. Long-term experience with low-dose interferon-alpha and PUVA in the management of early mycosis fungoides. *Eur J Haematol* 2005;75:136-145. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16000130>.
183. Olisova OY, Megna M, Grekova EV, et al. PUVA and interferon alpha2b combined therapy for patients with mycosis fungoides at different stages of the disease: a seven-year retrospective study in Russia. *J Eur Acad Dermatol Venereol* 2019;33:e72-e74. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30102807>.
184. Rupoli S, Canafoglia L, Goteri G, et al. Results of a prospective phase II trial with oral low-dose bexarotene plus photochemotherapy (PUVA) in refractory and/or relapsed patients with mycosis fungoides. *Eur J Dermatol* 2016;26:13-20. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26678311>.
185. Fujimura T, Sato Y, Tanita K, et al. Case series of cutaneous T-cell lymphomas treated with bexarotene-based therapy. *J Dermatol* 2020;47:636-640. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32207181>.
186. Morita A, Tateishi C, Muramatsu S, et al. Efficacy and safety of bexarotene combined with photo(chemo)therapy for cutaneous T-cell lymphoma. *J Dermatol* 2020;47:443-451. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32189402>.
187. Wilson LD, Jones GW, Kim D, et al. Experience with total skin electron beam therapy in combination with extracorporeal photopheresis in the management of patients with erythrodermic (T4) mycosis fungoides. *J Am Acad Dermatol* 2000;43:54-60. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10863224>.



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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

188. Atzmony L, Amitay-Laish I, Gurion R, et al. Erythrodermic mycosis fungoides and Sezary syndrome treated with extracorporeal photopheresis as part of a multimodality regimen: A single-centre experience. *J Eur Acad Dermatol Venereol* 2015;29:2382-2389. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26299651>.
189. Wollina U, Looks A, Meyer J, et al. Treatment of stage II cutaneous T-cell lymphoma with interferon alfa-2a and extracorporeal photochemotherapy: a prospective controlled trial. *J Am Acad Dermatol* 2001;44:253-260. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11174383>.
190. Suchin KR, Cucchiara AJ, Gottlieb SL, et al. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy: a 14-year experience at a single institution. *Arch Dermatol* 2002;138:1054-1060. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12164743>.
191. Raphael BA, Shin DB, Suchin KR, et al. High clinical response rate of Sezary syndrome to immunomodulatory therapies: prognostic markers of response. *Arch Dermatol* 2011;147:1410-1415. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21844430>.
192. Straus DJ, Duvic M, Horwitz SM, et al. Final results of phase II trial of doxorubicin HCl liposome injection followed by bexarotene in advanced cutaneous T-cell lymphoma. *Ann Oncol* 2014;25:206-210. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24285015>.
193. Ninosu N, Melchers S, Kappenstein M, et al. Mogamulizumab combined with extracorporeal photopheresis as a novel therapy in erythrodermic cutaneous T-cell lymphoma. *Cancers (Basel)* 2023;16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/38201568>.
194. Campbell BA, Dobos G, Haider Z, et al. International study of treatment efficacy in SS shows superiority of combination therapy and heterogeneity of treatment strategies. *Blood Adv* 2023;7:6639-6647. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37648672>.
195. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol* 2011;29:2598-2607. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21576639>.
196. van Doorn R, Scheffer E, Willemze R. Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis: a clinicopathologic and follow-up study of 51 patients. *Arch Dermatol* 2002;138:191-198. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11843638>.
197. Gerami P, Rosen S, Kuzel T, et al. Folliculotropic mycosis fungoides: an aggressive variant of cutaneous T-cell lymphoma. *Arch Dermatol* 2008;144:738-746. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18559762>.
198. Lehman JS, Cook-Norris RH, Weed BR, et al. Folliculotropic mycosis fungoides: single-center study and systematic review. *Arch Dermatol* 2010;146:607-613. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20566923>.
199. Wieser I, Wang C, Alberti-Violette S, et al. Clinical characteristics, risk factors and long-term outcome of 114 patients with folliculotropic mycosis fungoides. *Arch Dermatol Res* 2017;309:453-459. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28516243>.
200. Hodak E, Amitay-Laish I, Atzmony L, et al. New insights into folliculotropic mycosis fungoides (FMF): A single-center experience. *J Am Acad Dermatol* 2016;75:347-355. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27245278>.
201. van Santen S, Roach RE, van Doorn R, et al. Clinical staging and prognostic factors in folliculotropic mycosis fungoides. *JAMA Dermatol* 2016;152:992-1000. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27276223>.
202. Charli-Joseph Y, Kashani-Sabet M, McCalmont TH, et al. Association of a proposed new staging system for folliculotropic mycosis fungoides



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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

with prognostic variables in a US cohort. *JAMA Dermatol* 2021;157:157-165. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/33295938>.

203. van Santen S, van Doorn R, Neelis KJ, et al. Recommendations for treatment in folliculotropic mycosis fungoides: report of the Dutch Cutaneous Lymphoma Group. *Br J Dermatol* 2017;177:223-228. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28132406>.

204. Lansigan F, Horwitz SM, Pinter-Brown LC, et al. Outcomes of patients with transformed mycosis fungoides: Analysis from a prospective multicenter US cohort study. *Clin Lymphoma Myeloma Leuk* 2020;20:744-748. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32532611>.

205. de Masson A, Beylot-Barry M, Bouaziz JD, et al. Allogeneic stem cell transplantation for advanced cutaneous T-cell lymphomas: a study from the French Society of Bone Marrow Transplantation and French Study Group on Cutaneous Lymphomas. *Haematologica* 2014;99:527-534. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24213148>.

206. Duarte RF, Boumendil A, Onida F, et al. Long-term outcome of allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: a European society for blood and marrow transplantation lymphoma working party extended analysis. *J Clin Oncol* 2014;32:3347-3348. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25154828>.

207. Lechowicz MJ, Lazarus HM, Carreras J, et al. Allogeneic hematopoietic cell transplantation for mycosis fungoides and Sezary syndrome. *Bone Marrow Transplant* 2014;49:1360-1365. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25068422>.

208. Hosing C, Bassett R, Dabaja B, et al. Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution. *Ann Oncol* 2015;26:2490-2495. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26416896>.

209. Shiratori S, Fujimoto K, Nishimura M, et al. Allogeneic hematopoietic stem cell transplantation following reduced-intensity conditioning for mycosis fungoides and Sezary syndrome. *Hematol Oncol* 2016;34:9-16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25312300>.

210. Domingo-Domenech E, Duarte RF, Boumedil A, et al. Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides and Sezary syndrome. An updated experience of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2021;56:1391-1401. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/33420392>.

211. Cengiz Seval G, Sahin U, Bozdag SC, et al. Allogeneic hematopoietic stem cell transplantation for heavily pretreated patients with mycosis fungoides and Sezary syndrome. *Dermatol Ther* 2022;35:e15447. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35289037>.

212. Elliott J, Ahlawat S, Prince HM, et al. Long-term outcomes for allogeneic bone marrow transplantation in Sezary syndrome and mycosis fungoides. *Bone Marrow Transplant* 2022;57:1724-1726. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/36028756>.

213. Johnson WT, Mukherji R, Kartan S, et al. Allogeneic hematopoietic stem cell transplantation in advanced stage mycosis fungoides and Sezary syndrome: a concise review. *Chin Clin Oncol* 2019;8:12. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/30525754>.

214. Iqbal M, Reljic T, Ayala E, et al. Efficacy of allogeneic hematopoietic cell transplantation in cutaneous T cell lymphoma: Results of a systematic review and meta-analysis. *Biol Blood Marrow Transplant* 2020;26:76-82. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31494227>.

215. de Masson A, Beylot-Barry M, Ram-Wolff C, et al. Allogeneic transplantation in advanced cutaneous T-cell lymphomas (CUTALLO): a propensity score matched controlled prospective study. *Lancet* 2023;401:1941-1950. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/37105210>.



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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

216. Duarte RF, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. *Bone Marrow Transplant* 2008;41:597-604. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18176611>.
217. Duvic M, Donato M, Dabaja B, et al. Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome. *J Clin Oncol* 2010;28:2365-2372. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20351328>.
218. Isufi I, Seropian S, Gowda L, et al. Outcomes for allogeneic stem cell transplantation in refractory mycosis fungoides and primary cutaneous gamma Delta T cell lymphomas. *Leuk Lymphoma* 2020;61:2955-2961. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32643494>.
219. Thompson LL, Pan CX, Chang MS, et al. Alemtuzumab, total skin electron beam, and non-myeloablative allogeneic haematopoietic stem-cell transplantation in advanced sezary syndrome: a retrospective cohort study. *J Eur Acad Dermatol Venereol* 2021;35:e373-e375. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33545747>.
220. Weng WK, Arai S, Rezvani A, et al. Nonmyeloablative allogeneic transplantation achieves clinical and molecular remission in cutaneous T-cell lymphoma. *Blood Adv* 2020;4:4474-4482. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32941647>.
221. Morris SL, Thomas BR, Palanicawandar R, et al. Long term outcomes of nonmyeloablative allogeneic stem cell transplantation with TSEB TLI and ATG for Mycosis Fungoides and Sezary Syndrome. *Bone Marrow Transplant* 2024. Available at:
222. Mori T, Shiratori S, Suzumiya J, et al. Outcome of allogeneic hematopoietic stem cell transplantation for mycosis fungoides and Sezary syndrome. *Hematol Oncol* 2020;38:266-271. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32011008>.
223. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. *Cancer* 2006;107:2504-2511. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17048251>.
224. Sampogna F, Frontini M, Baliva G, et al. Quality of life and psychological distress in patients with cutaneous lymphoma. *Br J Dermatol* 2009;160:815-822. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19120325>.
225. Meyer N, Paul C, Misery L. Pruritus in cutaneous T-cell lymphomas: frequent, often severe and difficult to treat. *Acta Derm Venereol* 2010;90:12-17. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20107719>.
226. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. *Eur J Cancer* 2006;42:1014-1030. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16574401>.
227. Eschler DC, Klein PA. An evidence-based review of the efficacy of topical antihistamines in the relief of pruritus. *J Drugs Dermatol* 2010;9:992-997. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20684150>.
228. Matsuda KM, Sharma D, Schonfeld AR, Kwatra SG. Gabapentin and pregabalin for the treatment of chronic pruritus. *J Am Acad Dermatol* 2016;75:619-625.e616. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27206757>.
229. Duval A, Dubertret L. Aprepitant as an antipruritic agent? *N Engl J Med* 2009;361:1415-1416. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19797294>.
230. Booken N, Heck M, Nicolay JP, et al. Oral aprepitant in the therapy of refractory pruritus in erythrodermic cutaneous T-cell lymphoma. *Br J Dermatol* 2011;164:665-667. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21039410>.



National  
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Cancer  
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## NCCN Guidelines Version 3.2024 Primary Cutaneous Lymphomas

231. Jimenez Gallo D, Albaran Planelles C, Linares Barrios M, et al. Treatment of pruritus in early-stage hypopigmented mycosis fungoides with aprepitant. *Dermatol Ther* 2014;27:178-182. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24517320>.

232. Demierre MF, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2006;55:543-544. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16908377>.

233. Stander S, Bockenholt B, Schurmeyer-Horst F, et al. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. *Acta Derm Venereol* 2009;89:45-51. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19197541>.

234. Bigliardi PL, Stammer H, Jost G, et al. Treatment of pruritus with topically applied opiate receptor antagonist. *J Am Acad Dermatol* 2007;56:979-988. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17320241>.

235. Axelrod PI, Lorber B, Vonderheid EC. Infections complicating mycosis fungoides and Sezary syndrome. *JAMA* 1992;267:1354-1358. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1740857>.

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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.<sup>1,2</sup> Primary cutaneous disease, spontaneous regression, and absence of extracutaneous spread are associated with a better prognosis.<sup>3,4</sup>

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.<sup>5</sup> 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.<sup>6-8</sup> 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.<sup>7</sup> 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.<sup>9-11</sup>

LyP is histologically heterogeneous with large atypical anaplastic, immunoblastic, or Hodgkin-like cells in a marked inflammatory background.<sup>2</sup> 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.<sup>8</sup> 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.<sup>12-17</sup> Older age, positive TCR gene rearrangement, or diagnosis of mixed-type LyP have been reported as prognostic indicators of disease progression to lymphoma.<sup>13,15</sup>

### 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.<sup>18</sup>

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](http://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.<sup>5</sup> Clinical and pathologic correlation is essential for distinguishing within the spectrum of PCTLD as well as distinguishing PCTLD from other



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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 PCTL 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 PCTL than previously thought; however, coexpression of CD30 and CD15 in these T-cell lymphomas may lead to a mistaken diagnosis of CHL.<sup>19</sup> 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 PCTL 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.<sup>20</sup> 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.

PCTL 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+

PCTL.<sup>21,22</sup> ALK positivity and differential expression of t(2;5) can help to distinguish between CD30+ PCTL and ALCL of nodal origin. GATA3 expression by IHC has been proposed to be useful to differentiate between MF-LCT and CD30+ PCTL.<sup>23</sup> MF-LCT was associated with a strong/diffuse expression of GATA3 while the CD30+ PCTL 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.<sup>24</sup>

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.<sup>25</sup>

*DUSP22-IRF4* (6p25.3) gene rearrangement has been described in patients with PC-ALCL and LyP but is not associated with prognostic significance.<sup>26-28</sup> 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.<sup>26</sup> 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).



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### 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.<sup>29</sup> 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.<sup>7</sup> 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.<sup>30</sup> 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 ( $\leq$ 20 Gy) for the treatment of solitary or localized PC-ALCL was also confirmed in other recent reports.<sup>31–33</sup>

Involved-site RT (ISRT) alone or surgical excision (with or without ISRT) are recommended for patients with solitary or grouped lesions.<sup>6–8,34–37</sup> ISRT alone is an appropriate option in selected patients with cutaneous ALCL regional lymph node involvement  $\pm$  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



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

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.<sup>39</sup> 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 PCTL, 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%).<sup>7</sup> 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.<sup>40</sup> 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 ( $\pm$  skin-directed therapy) and for those with regional node involvement ( $\pm$  ISRT). Brentuximab vedotin is the preferred systemic treatment option based on the results of the ALCANZA study.<sup>38</sup> Low-dose methotrexate (50 mg weekly),<sup>41,42</sup> pralatrexate,<sup>43</sup> systemic retinoids (bexarotene for multifocal lesions),<sup>44-47</sup> and interferon (multifocal lesions)<sup>44,48-50</sup> 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.<sup>51-53</sup> 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.<sup>40</sup> 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.<sup>7,54</sup>

### 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



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56% and 35% of patients, respectively.<sup>7</sup> 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%.<sup>55</sup> 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 ( $\leq 25$  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.<sup>56</sup> 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.<sup>41</sup>

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.<sup>7,45,57-59</sup> 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.<sup>41,55,56,60-65</sup> Systemic retinoids (bexarotene) are included as an option based on limited available data mainly from case reports.<sup>44-47</sup>

### 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.<sup>66,67</sup> 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%.<sup>67</sup> 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.<sup>55,68</sup> 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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### References

1. Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007;110:479-484. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17339420>.
2. Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Blood* 2011;118:4024-4035. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21841159>.
3. Paulli M, Berti E, Rosso R, et al. CD30/Ki-1-positive lymphoproliferative disorders of the skin—clinicopathologic correlation and statistical analysis of 86 cases: a multicentric study from the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma Project Group. *J Clin Oncol* 1995;13:1343-1354. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7751878>.
4. Vergier B, Beylot-Barry M, Pulford K, et al. Statistical evaluation of diagnostic and prognostic features of CD30+ cutaneous lymphoproliferative disorders: a clinicopathologic study of 65 cases. *Am J Surg Pathol* 1998;22:1192-1202. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9777981>.
5. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30635287>.
6. Beljaards RC, Kaudewitz P, Berti E, et al. Primary cutaneous CD30-positive large cell lymphoma: definition of a new type of cutaneous lymphoma with a favorable prognosis. A European Multicenter Study of 47 patients. *Cancer* 1993;71:2097-2104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8382999>.
7. Bekkenk MW, Geelen FA, van Voorst Vader PC, et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. *Blood* 2000;95:3653-3661. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10845893>.
8. Liu HL, Hoppe RT, Kohler S, et al. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. *J Am Acad Dermatol* 2003;49:1049-1058. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14639383>.
9. Woo DK, Jones CR, Vanoli-Storz MN, et al. Prognostic factors in primary cutaneous anaplastic large cell lymphoma: characterization of clinical subset with worse outcome. *Arch Dermatol* 2009;145:667-674. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19528422>.
10. Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. *Arch Dermatol* 2009;145:1399-1404. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20026848>.
11. Fernandez-de-Misa R, Hernandez-Machin B, Combalia A, et al. Prognostic factors in patients with primary cutaneous anaplastic large cell lymphoma: a multicentric, retrospective analysis of the Spanish Group of Cutaneous Lymphoma. *J Eur Acad Dermatol Venereol* 2020;34:762-768. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31591786>.
12. Wang HH, Myers T, Lach LJ, et al. Increased risk of lymphoid and nonlymphoid malignancies in patients with lymphomatoid papulosis. *Cancer* 1999;86:1240-1245. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10506709>.
13. de Souza A, el-Azhary RA, Camilleri MJ, et al. In search of prognostic indicators for lymphomatoid papulosis: a retrospective study of 123



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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

patients. J Am Acad Dermatol 2012;66:928-937. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/21982062>.

14. Nikolaou V, Papadavid E, Ekonomidi A, et al. Association of clinicopathological characteristics with secondary neoplastic lymphoproliferative disorders in patients with lymphomatoid papulosis. Leuk Lymphoma 2015;56:1303-1307. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25242096>.

15. Cordel N, Tressieres B, D'Incan M, et al. Frequency and risk factors for associated lymphomas in patients with lymphomatoid papulosis. Oncologist 2016;21:76-83. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/26668250>.

16. Wieser I, Oh CW, Talpur R, Duvic M. Lymphomatoid papulosis: Treatment response and associated lymphomas in a study of 180 patients. J Am Acad Dermatol 2016;74:59-67. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/26518172>.

17. AbuHilal M, Walsh S, Shear N. Associated hematolymphoid malignancies in patients with lymphomatoid papulosis: A Canadian retrospective study. J Cutan Med Surg 2017;21:507-512. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/28614957>.

18. PubMed Overview. Available at:  
<https://pubmed.ncbi.nlm.nih.gov/about/>. Accessed March 10, 2024.

19. Eberle FC, Song JY, Xi L, et al. Nodal involvement by cutaneous CD30-positive T-cell lymphoma mimicking classical Hodgkin lymphoma. Am J Surg Pathol 2012;36:716-725. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/22367293>.

20. Thurber SE, Zhang B, Kim YH, et al. T-cell clonality analysis in biopsy specimens from two different skin sites shows high specificity in the diagnosis of patients with suggested mycosis fungoides. J Am Acad Dermatol 2007;57:782-790. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/17646032>.

21. DeCoteau JF, Butmarc JR, Kinney MC, Kadin ME. The t(2;5) chromosomal translocation is not a common feature of primary cutaneous CD30+ lymphoproliferative disorders: comparison with anaplastic large-cell lymphoma of nodal origin. Blood 1996;87:3437-3441. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8605362>.

22. Melchers RC, Willemze R, van de Loo M, et al. Clinical, histologic, and molecular characteristics of anaplastic lymphoma kinase-positive primary cutaneous anaplastic large cell lymphoma. Am J Surg Pathol 2020;44:776-781. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/32412717>.

23. Collins K, Gu J, Aung PP, et al. Is immunohistochemical expression of GATA3 helpful in the differential diagnosis of transformed mycosis fungoides and primary cutaneous CD30-positive T cell lymphoproliferative disorders? Virchows Arch 2021;479:377-383. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/33604757>.

24. Kempf W, Kutzner H, Cozzio A, et al. MUM1 expression in cutaneous CD30+ lymphoproliferative disorders: a valuable tool for the distinction between lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Br J Dermatol 2008;158:1280-1287. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/18410414>.

25. Fauconneau A, Pham-Ledard A, Cappellen D, et al. Assessment of diagnostic criteria between primary cutaneous anaplastic large-cell lymphoma and CD30-rich transformed mycosis fungoides: a study of 66 cases. Br J Dermatol 2015;172:1547-1554. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25645336>.

26. Wada DA, Law ME, Hsi ED, et al. Specificity of IRF4 translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies. Mod Pathol 2011;24:596-605. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/21169992>.

27. Karai LJ, Kadin ME, Hsi ED, et al. Chromosomal rearrangements of 6p25.3 define a new subtype of lymphomatoid papulosis. Am J Surg



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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

Pathol 2013;37:1173-1181. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23648461>.

28. Onaindia A, Montes-Moreno S, Rodriguez-Pinilla SM, et al. Primary cutaneous anaplastic large cell lymphomas with 6p25.3 rearrangement exhibit particular histological features. *Histopathology* 2015;66:846-855. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25131361>.

29. Benner MF, Willemze R. Bone marrow examination has limited value in the staging of patients with an anaplastic large cell lymphoma first presenting in the skin. Retrospective analysis of 107 patients. *Br J Dermatol* 2008;159:1148-1151. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/18782320>.

30. 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. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/27315663>.

31. Melchers RC, Willemze R, Daniels LA, et al. Recommendations for the optimal radiation dose in patients with primary cutaneous anaplastic large cell lymphoma: a report of the Dutch Cutaneous Lymphoma Group. *Int J Radiat Oncol Biol Phys* 2017;99:1279-1285. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/28958772>.

32. 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. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/29114604>.

33. Piccinno R, Damiani G, Rossi LC, Berti E. Radiotherapy of primary cutaneous anaplastic large cell lymphoma: our experience in 30 cases. *Int J Dermatol* 2020;59:469-473. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/31916593>.

34. Yu JB, McNiff JM, Lund MW, Wilson LD. Treatment of primary cutaneous CD30+ anaplastic large-cell lymphoma with radiation therapy.

*Int J Radiat Oncol Biol Phys* 2008;70:1542-1545. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18037577>.

35. Booken N, Goerdt S, Klemke CD. Clinical spectrum of primary cutaneous CD30-positive anaplastic large cell lymphoma: an analysis of the Mannheim Cutaneous Lymphoma Registry. *J Dtsch Dermatol Ges* 2012;10:331-339. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/22525148>.

36. Huang BS, Chen WY, Wang CW, et al. Relapse pattern and treatment outcome of curative radiotherapy for primary cutaneous CD30+ anaplastic large-cell lymphoma: A retrospective cohort study. *Acta Derm Venereol* 2016;96:394-395. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/26463467>.

37. Hapgood G, Pickles T, Sehn LH, et al. Outcome of primary cutaneous anaplastic large cell lymphoma: a 20-year British Columbia Cancer Agency experience. *Br J Haematol* 2017;176:234-240. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/27766622>.

38. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet* 2017;390:555-566. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/28600132>.

39. Melchers RC, Willemze R, Bekkenk MW, et al. Evaluation of treatment results in multifocal primary cutaneous anaplastic large cell lymphoma: report of the Dutch Cutaneous Lymphoma Group. *Br J Dermatol* 2018;179:724-731. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/29494757>.

40. 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. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/30522922>.



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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

41. Bruijn MS, Horvath B, van Voorst Vader PC, et al. Recommendations for treatment of lymphomatoid papulosis with methotrexate: a report from the Dutch Cutaneous Lymphoma Group. *Br J Dermatol* 2015;173:1319-1322. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25998985>.
42. Park JB, Yang MH, Kwon DI, et al. Low-dose methotrexate treatment for solitary or localized primary cutaneous anaplastic large cell lymphoma: A long-term follow-up study. *Acta Derm Venereol* 2020;100:adv00069. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31996929>.
43. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22394596>.
44. Wyss M, Dummer R, Dommann SN, et al. Lymphomatoid papulosis—treatment with recombinant interferon alfa-2a and etretinate. *Dermatology* 1995;190:288-291. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7655107>.
45. Krathon RA, Ward S, Duvic M. Bexarotene is a new treatment option for lymphomatoid papulosis. *Dermatology* 2003;206:142-147. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12592082>.
46. Sheehy O, Catherwood M, Pettengell R, Morris TC. Sustained response of primary cutaneous CD30 positive anaplastic large cell lymphoma to bexarotene and photopheresis. *Leuk Lymphoma* 2009;50:1389-1391. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19544141>.
47. Fujimura T, Furudate S, Tanita K, et al. Successful control of phototherapy-resistant lymphomatoid papulosis with oral bexarotene. *J Dermatol* 2018;45:e37-e38. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28971510>.
48. Proctor SJ, Jackson GH, Lennard AL, Marks J. Lymphomatoid papulosis: response to treatment with recombinant interferon alfa-2b. *J Clin Oncol* 1992;10:170. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1727920>.
49. Yagi H, Tokura Y, Furukawa F, Takigawa M. Th2 cytokine mRNA expression in primary cutaneous CD30-positive lymphoproliferative disorders: successful treatment with recombinant interferon-gamma. *J Invest Dermatol* 1996;107:827-832. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8941669>.
50. Schmuth M, Topar G, Illersperger B, et al. Therapeutic use of interferon-alpha for lymphomatoid papulosis. *Cancer* 2000;89:1603-1610. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11013377>.
51. Schiller M, Tsianakas A, Sterry W, et al. Dose-escalation study evaluating pegylated interferon alpha-2a in patients with cutaneous T-cell lymphoma. *J Eur Acad Dermatol Venereol* 2017;31:1841-1847. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28557110>.
52. Patsatsi A, Papadavid E, Kyriakou A, et al. The use of pegylated interferon a-2a in a cohort of Greek patients with mycosis fungoides. *J Eur Acad Dermatol Venereol* 2022;36:e291-e293. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34753217>.
53. Osman S, Chia JC, Street L, Hardin J. Transitioning to pegylated interferon for the treatment of cutaneous T-cell lymphoma: Meeting the challenge of therapy discontinuation and a proposed algorithm. *Dermatologic Therapy* 2023;2023:7171937. Available at: <https://doi.org/10.1155/2023/7171937>.
54. Brice P, Cazals D, Mounier N, et al. Primary cutaneous large-cell lymphoma: analysis of 49 patients included in the LNH87 prospective trial of polychemotherapy for high-grade lymphomas. *Groupe d'Etude des Lymphomes de l'Adulte. Leukemia* 1998;12:213-219. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9519784>.
55. Fernandez-de-Misa R, Hernandez-Machin B, Servitje O, et al. First-line treatment in lymphomatoid papulosis: a retrospective multicentre study. *Clin Exp Dermatol* 2018;43:137-143. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28994134>.



National  
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# NCCN Guidelines Version 3.2024

## Primary Cutaneous Lymphomas

56. Vonderheide EC, Sajadian A, Kadin ME. Methotrexate is effective therapy for lymphomatoid papulosis and other primary cutaneous CD30-positive lymphoproliferative disorders. *J Am Acad Dermatol* 1996;34:470-481. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8609262>.

57. Zackheim HS, Epstein EH, Jr., Crain WR. Topical carmustine therapy for lymphomatoid papulosis. *Arch Dermatol* 1985;121:1410-1414. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/4051529>.

58. Thomsen K, Wantzin GL. Lymphomatoid papulosis. A follow-up study of 30 patients. *J Am Acad Dermatol* 1987;17:632-636. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2889756>.

59. Calzavara-Pinton P, Venturini M, Sala R. Medium-dose UVA1 therapy of lymphomatoid papulosis. *J Am Acad Dermatol* 2005;52:530-532. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15761440>.

60. Everett MA. Treatment of lymphomatoid papulosis with methotrexate. *Br J Dermatol* 1984;111:631. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6498098>.

61. Christensen HK, Thomsen K, Vejlsgaard GL. Lymphomatoid papulosis: a follow-up study of 41 patients. *Semin Dermatol* 1994;13:197-201. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7986688>.

62. Yazawa N, Kondo S, Kagaya M, et al. Successful treatment of a patient with lymphomatoid papulosis by methotrexate. *J Dermatol* 2001;28:373-378. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11510505>.

63. Fujita H, Nagatani T, Miyazawa M, et al. Primary cutaneous anaplastic large cell lymphoma successfully treated with low-dose oral methotrexate. *Eur J Dermatol* 2008;18:360-361. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18474486>.

64. Cornejo CM, Novoa RA, Krisch RE, Kim EJ. Low-dose radiotherapy for primary cutaneous anaplastic large-cell lymphoma while on low-dose

methotrexate. *Cutis* 2016;98:253-256. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27874877>.

65. Newland KM, McCormack CJ, Twigger R, et al. The efficacy of methotrexate for lymphomatoid papulosis. *J Am Acad Dermatol* 2015;72:1088-1090. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25981010>.

66. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26261247>.

67. Lewis DJ, Talpur R, Huen AO, et al. Brentuximab vedotin for patients with refractory lymphomatoid papulosis: An analysis of phase 2 results. *JAMA Dermatol* 2017;153:1302-1306. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28980004>.

68. Melchers RC, Willemze R, Bekkenk MW, et al. Frequency and prognosis of associated malignancies in 504 patients with lymphomatoid papulosis. *J Eur Acad Dermatol Venereol* 2020;34:260-266. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31715046>.