**DIAGNOSIS**

**ESSENTIAL:**
- Biopsy of suspicious skin sites
- Dermatopathology review of slides

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Immunohistochemical studies of skin biopsy\(^a\) (CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD26, CD56)
- Molecular study for T-cell receptor (TCR) gene rearrangements (assessment of clonality) of skin biopsy;\(^a\) PCR methods\(^b\)
- Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including Sezary cell prep, flow cytometry and PCR for TCR gene rearrangement
- Biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)

**WORKUP\(^c\)**

**ESSENTIAL:**
- Complete physical examination
  - Examination of entire skin: assessment of % BSA (palm plus digits \(\approx 1\%\) BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)
  - Palpation of peripheral lymph node regions
  - Palpation for organomegaly/masses
- Laboratory studies:\(^d\)
  - CBC with Sezary screen (manual slide review, "Sezary cell prep")
  - Sezary flow cytometric study (optional for T1); CD3, CD4, CD7, CD8, CD26 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype including loss of CD7 or CD26
  - TCR gene rearrangement of peripheral blood lymphocytes if Sezary Syndrome suspected
- Comprehensive metabolic panel
- LDH
- Imaging studies
  - Chest x-ray (in T1 or limited T2 where there is no indication of palpable adenopathy or blood involvement chest x-ray may be the only imaging study)
  - Neck/chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET/CT (\(\geq T2\), large cell transformed or folliculotropic MF, or with palpable adenopathy or abnormal laboratory studies)
- Biopsy of suspicious lymph nodes (recommend assessment of clonality for all but particularly NCI LN 2-3) or suspected extracutaneous sites

**USEFUL IN SELECTED CASES:**
- Bone marrow biopsy (not required for staging but used to document visceral disease in those suspected to have marrow involvement including B2 blood involvement and in patients with unexplained hematologic abnormality)
- TCR gene rearrangement results should be interpreted with caution. TCR clonal rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of Mycosis Fungoides/Sezary Syndrome.


\(^{b}\) TCR gene rearrangement results should be interpreted with caution. TCR clonal rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of Mycosis Fungoides/Sezary Syndrome.


\(^{d}\) Sezary syndrome (B2) defined by Sezary cell count \(\geq 1,000/mm^3\) (Sezary cell prep) or expanded CD4+ cells with CD4/CD8 ratio \(\geq 10\), CD4+/CD7- \(\geq 40\%), or CD4+/CD26- \(\geq 30\%\) of lymphs in the presence of a positive clonal TCR gene rearrangement.

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**NHL Table of Contents**

**Staging, MS, References**

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**Stage IA**

Skin-directed therapies (may be alone or in combination with other skin-directed therapies):

See Suggested Treatment Regimens "Skin-directed therapies (skin-limited/local)"

CR/PR

Refractory disease or progression to > stage IA on skin-directed therapies

Relapse with or persistent T1 disease

Systemic therapy ± skin-directed therapy (see Stage IB on page MFSS-3) or TSEBT or Clinical trial

**Stage IA with B1 blood involvement**

See Primary Treatment for Stage III, B1 MFSS-5

**Histologic evidence of folliculotropic or large cell transformed MF**

See Primary Treatment for Stage IIB Limited disease on page MFSS-4

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Referral to a multidisciplinary academic specialty center preferred.

Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

Folliculotropic, large cell transformed MF, or B1 involvement has been associated with worse outcome, thus, may be managed as "tumor (IIB)" disease (MFSS-4) or stage III with B1 involvement (MFSS-5), respectively.

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**STAGE PRIMARY TREATMENT**

**Stage IB-IIA**

- Generalized skin treatment
  - See Suggested Treatment Regimens "Skin-directed therapies (Skin-generalized)"
  - ± adjuvant local skin treatment (see stage IA on MFSS-2)

  → CR/PR

  → Relapse with or persistent T1-T2 disease:
    - T1 (see stage IA on MFSS-2)
    - T2 (see generalized skin treatment)

  → See Suggested Treatment Regimens
    - Systemic Therapies (SYST-CAT A)
    - Combination Therapies
    - ± skin-directed therapy
    - Clinical trial

  → CR/PR

  → Refractory disease or progression

**Stage IB-IIA with B1 blood involvement**

- See Primary Treatment for Stage III, B1 MFSS-5

**Histologic evidence of folliculotropic or large cell transformed MF**

- See Primary Treatment for Stage IIB Generalized disease on page MFSS-4 (except for SYST-CAT B)

  → Refractory disease or progression

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*Referral to a multidisciplinary academic specialty center preferred.

*Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

*Folliculotropic, large cell transformed MF, or B1 involvement has been associated with worse outcome, thus, may be managed as "tumor (IIB)" disease (MFSS-4) or stage III with B1 involvement (MFSS-5), respectively.

*For patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.

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Mycosis Fungoides/Sezary Syndrome
of the cutaneous T-cell lymphomas

STAGE

Limited extent tumor disease ± patch/plaque disease

Stage IIB

Generalized tumor disease or limited extent tumor disease with B1 or histologic evidence of folliculotropic or large cell transformed MF

PRIMARY TREATMENT

Relapse with or persistent T1-T3 limited:
- T1-2 (see stage IA on MFSS-2 or stage IB-IIA on MFSS-3)
- T3 limited extent

CR/PR

Refractory disease or progression

Local RT for limited tumor lesions + skin-directed therapies as in stages I-IIA

Systemic Therapies (SYST-CAT A) ± RT

- T1-2 (see stage IA on MFSS-2 or stage IB-IIA on MFSS-3)
- T3 limited extent

CR/PR

Referral to a multidisciplinary academic specialty center preferred.

Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

Skin-directed therapies are for patch or plaque lesions and not for tumor lesions.

Most patients are treated with multiple SYST-CAT A/B or Combination regimens before receiving multiagent chemotherapy.

Data on allogeneic HSCT, particularly using non-myeloablative conditioning, suggest the existence of a graft versus T-cell lymphoma effect. Success has been reported in highly selected patients. Patients with Stage ≥ IIB MF who have failed multiple systemic therapies + adequate trial of (or whose disease is not amenable to) skin-directed therapy, may be referred for a BMT consultation. Ideal time for allogeneic HSCT is when their disease is well controlled with induction therapy and before their disease has progressed to a state where the chance of response or survival with allogeneic HSCT is low. When appropriate, TSEBT may be considered as cytoreductive therapy before transplant.

CR/PR

Refectory disease or progression

- Multil-agent chemotherapy
- Consider allogeneic transplant

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Mycosis Fungoides/Sezary Syndrome of the cutaneous T-cell lymphomas

**Stage**

**Primary Treatment**

- **Stage IIm**
  - Skin-directed therapy
    - See Suggested Treatment Regimens "Skin-directed therapies (Skin-generalized)"
    - and/or
  - Systemic therapies
    - See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT A)"

- **Stage IIIIm**
  - Skin-directed therapy
    - See Suggested Treatment Regimens "Skin-directed therapies (Skin-generalized)"
  - and/or
  - Systemic therapies
    - See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT A)"
    ± skin-directed therapy

**CR/PR**

- Relapse or persistent disease
- Refractory disease or progression

**Referral to a multidisciplinary academic specialty center preferred.**

**Patients achieving a response should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.**

**Data on allogeneic HSCT, particularly using non-myeloablative conditioning, suggest the existence of a graft versus T-cell lymphoma effect. Success has been reported in highly selected patients. Patients with Stage ≥IIB MF who have failed multiple systemic therapies + adequate trial of (or whose disease is not amenable to) skin-directed therapy, may be referred for a BMT consultation. Ideal time for allogeneic HSCT is when their disease is well controlled with induction therapy and before their disease has progressed to a state where the chance of response or survival with allogeneic HSCT is low. When appropriate, TSEBT may be considered as cytoreductive therapy before transplant.**

**Generalized skin-directed therapies (other than topical steroids) may not be well-tolerated in stage III and should be used with caution. Phototherapy (PUVA or UVB) or TSEBT can be used successfully.**

**Mid-potency topical steroids should be included (± occlusive modality) with any of the primary treatment modalities to reduce skin symptoms. Erythrodermic patients are at increased risk for secondary infection with skin pathogens and systemic antibiotic therapy should be considered.**

**Combination therapy options can be considered earlier (primary treatment) depending on treatment availability or symptom severity.**

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**STAGE**

**PRIMARY TREATMENT**

- **Sezary syndrome ± lymph node disease**
  - See Suggested Treatment Regimens
    - Systemic Therapies (SYST-CAT A)
    - Combination Therapies

- **Stage IV**
  - Bulky lymph node disease
  - Visceral disease (solid organ)

  **CR/PR**

  **Relapse or persistent disease**

  - See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT B)"
  - Alemtuzumab
  - Clinical trial
  - Consider allogeneic transplant, as appropriate

  - Refractory disease or progression

  - Consider allogeneic transplant, as appropriate
  - Clinical trial

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**Guidelines Index**

Practice Guidelines in Oncology – v.1.2008

Mycosis Fungoides/Sezary Syndrome of the cutaneous T-cell lymphomas

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- 02/14/08
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## SUGGESTED TREATMENT REGIMENS

### SKIN-DIRECTED THERAPIES

**For limited/localized skin involvement (Skin-Limited/Local)**
- Topical corticosteroids<sup>a</sup>
- Topical chemotherapy (nitrogen mustard, BCNU)
- Local radiation (particularly unilesional presentation, 24-36 Gy)
- Topical retinoids (bexarotene)
- Phototherapy (UVB for patch/thin plaques; PUVA for thicker plaques)<sup>b</sup>

**For generalized skin involvement (Skin-Generalized)**
- Topical corticosteroids<sup>a</sup>
- Topical chemotherapy (mechlorethamine, BCNU)
- Phototherapy (UVB, nbUVB, or PUVA for patch/thin plaques; PUVA for thicker plaques)<sup>b</sup>
- Total skin electron beam therapy (30-36 Gy)
- (reserved for those with severe skin symptoms or generalized thick plaque or tumor disease, or poor response to other therapies)

### SYSTEMIC THERAPIES

**Category A (SYST-CAT A)**
- Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid])
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat)
- Extracorporeal photopheresis<sup>c</sup>
- Denileukin diftitox
- Methotrexate (<100 mg q week)

**Category B (SYST-CAT B)**
- First-line therapies
  - Liposomal doxorubicin
  - Gemcitabine
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphomide
  - Temozolomide
  - Methotrexate (>100 mg q week)

### COMBINATION THERAPIES

**Skin-directed + Systemic**
- Phototherapy + retinoid
- Phototherapy + IFN
- Photopheresis + photopheresis<sup>c</sup>
- Total skin electron beam + photopheresis<sup>c</sup>

**Systemic + Systemic**
- Retinoid + IFN
- Bexarotene + denileukin diftitox
- Photopheresis<sup>c</sup> + retinoid
- Photopheresis<sup>c</sup> + IFN
- Photopheresis<sup>c</sup> + retinoid + IFN

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<sup>a</sup>Long-term use of topical steroid may be associated with skin atrophy and/or striae formation. This risk worsens with increased potency of the steroid. High-potency steroid used on large skin surfaces may lead to systemic absorption.

<sup>b</sup>Cumulative dose of UV is associated with increased risk of UV-associated skin neoplasms; thus, phototherapy may not be appropriate in patients with history of extensive squamoproliferative skin neoplasms or basal cell carcinomas or who have had melanoma.

<sup>c</sup>Photopheresis may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).

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### TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome

<table>
<thead>
<tr>
<th>TNMB</th>
<th>TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Limited patches,(^b) papules and/or plaques(^c) covering &lt; 10 % of the skin surface</td>
</tr>
<tr>
<td>T2</td>
<td>Patches, papules and/or plaques covering ≥ 10 % of the skin surface</td>
</tr>
<tr>
<td>T3</td>
<td>One or more tumors(^d) (≥ 1 cm in diameter)</td>
</tr>
<tr>
<td>T4</td>
<td>Confluence of erythema ≥ 80 % body surface area</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Node</th>
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<tbody>
<tr>
<td>N0</td>
<td>No clinically abnormal peripheral lymph nodes; biopsy not required(^e)</td>
</tr>
<tr>
<td>N1</td>
<td>Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2</td>
</tr>
<tr>
<td>N2</td>
<td>Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 2 or NCI LN 3</td>
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<td>N3</td>
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</tr>
<tr>
<td>NX</td>
<td>Clinically abnormal peripheral lymph nodes; no histologic confirmation</td>
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<table>
<thead>
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<th>Visceral</th>
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<tr>
<td>M0</td>
<td>No visceral organ involvement</td>
</tr>
<tr>
<td>M1</td>
<td>Visceral involvement (must have pathology confirmation(^f) and organ involved should be specified)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood</th>
<th></th>
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<tbody>
<tr>
<td>B0</td>
<td>Absence of significant blood involvement: ≤ 5 % of peripheral blood lymphocytes are atypical (Sezary) cells(^g)</td>
</tr>
<tr>
<td>B1</td>
<td>Low blood tumor burden: &gt; 5 % of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2</td>
</tr>
<tr>
<td>B2</td>
<td>High blood tumor burden: ≥ 1000/mcL Sezary cells(^g) with positive clone(^h)</td>
</tr>
</tbody>
</table>

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

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

\(^d\) Tumor = at least one > 1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histological evidence of large cell transformation has occurred. Phenotyping for CD30 is encouraged.

\(^e\) Abnormal peripheral lymph node(s) = any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or ≥ 1.5 cm in diameter. Node groups examined on physical examination = cervical, supraclavicular, epitrochlear, axillary and inguinal. Central nodes, which are not generally amenable to pathologic assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically.

\(^f\) Spleen and liver may be diagnosed by imaging criteria.

\(^g\) Sezary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sezary cells are not able to be used to determine tumor burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead. (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio ≥ 10, (2) expanded CD4+ cells with abnormal immunophenotype including loss of CD7 or CD26.

\(^h\) A T cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.
### Clinical Staging/Classification of MF and SS<sup>a</sup>

<table>
<thead>
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<th>T</th>
<th>N</th>
<th>M</th>
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<tr>
<td>IVB</td>
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<td>0-3</td>
<td>1</td>
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</tbody>
</table>


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