NCCN Guidelines Version 1.2013
Mycosis Fungoides/Sezary Syndrome

**DIAGNOSIS**

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

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- IHC of skin biopsy (CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granyme B, βF1)
- Molecular analysis for TCR gene rearrangements (assessment of clonality) of skin biopsy
- 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)
- Assessment of HTLV-1 serology in at-risk populations. HTLV-1 PCR if serology is indeterminate

**WORKUP**

**ESSENTIAL:**
- Complete physical examination
  - Examination of entire skin: assessment of %BSA (palm plus digits ≈ 1% BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)
  - Palpation of peripheral lymph node regions
  - Palpation for organomegaly/masses
- Laboratory studies:
  - 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

**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)
- Biopsy of suspicious lymph nodes for identical clones (recommend assessment of clonality for all but particularly NCI LN 2-3) or suspected extracutaneous sites
- Rebiopsy if suspicious of large cell transformation
- Neck CT

- TCR gene rearrangement of peripheral blood lymphocytes if blood involvement suspected
- Comprehensive metabolic panel
- LDH
- Imaging studies
  - Chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET-CT (≥ T2, large cell transformed or folliculotropic MF, or with palpable adenopathy or abnormal laboratory studies)
- Pregnancy testing in women of child-bearing age

**STAGE (MFSS-2 and MFSS-3)**

**Stage IA**
- See Primary Treatment (MFSS-4)

**Stage IB-IIA**
- See Primary Treatment (MFSS-5)

**Stage IIB**
- See Primary Treatment (MFSS-6)

**Stage III**
- See Primary Treatment (MFSS-7)

**Stage IV**
- See Primary Treatment (MFSS-8)

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bSee Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
cTypical immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+) CD30-/+ cytotoxic granule proteins negative.
dTCR 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 MF/SS. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.
eSee for prevalence of HTLV-1 by geographic region.
fSezary syndrome (B2) is as defined on MFSS-2.
gMany skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.
## TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome

<table>
<thead>
<tr>
<th>TNMB</th>
<th>Classification and Staging of Mycosis Fungoides and Sezary Syndrome&lt;sup&gt;h,i&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td><strong>T1</strong> Limited patches, papules, and/or plaques&lt;sup&gt;k&lt;/sup&gt; covering &lt;10% of the skin surface</td>
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<tr>
<td></td>
<td><strong>T2</strong> Patches, papules, and/or plaques&lt;sup&gt;k&lt;/sup&gt; covering ≥10% of the skin surface</td>
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<td><strong>T3</strong> One or more tumors&lt;sup&gt;l&lt;/sup&gt; (≥1 cm in diameter)</td>
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<tr>
<td></td>
<td><strong>T4</strong> Confluence of erythema ≥80% body surface area</td>
</tr>
<tr>
<td>Node</td>
<td><strong>N0</strong> No abnormal lymph nodes; biopsy not required</td>
</tr>
<tr>
<td></td>
<td><strong>N1</strong> Abnormal lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2</td>
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<tr>
<td></td>
<td><strong>N2</strong> Abnormal lymph nodes; histopathology Dutch Gr 2 or NCI LN 3</td>
</tr>
<tr>
<td></td>
<td><strong>N3</strong> Abnormal lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4</td>
</tr>
<tr>
<td></td>
<td><strong>NX</strong> Abnormal lymph nodes; no histologic confirmation</td>
</tr>
<tr>
<td>Visceral</td>
<td><strong>M0</strong> No visceral organ involvement</td>
</tr>
<tr>
<td></td>
<td><strong>M1</strong> Visceral involvement (must have pathology confirmation and organ involved should be specified)</td>
</tr>
<tr>
<td></td>
<td><strong>MX</strong> Abnormal visceral site; no histologic confirmation</td>
</tr>
<tr>
<td>Blood</td>
<td><strong>B0</strong> Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sezary) cells&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><strong>B1</strong> Low blood tumor burden: &gt;5% of peripheral blood lymphocytes are atypical (Sezary) cells but do not meet the criteria of B2</td>
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<tr>
<td></td>
<td><strong>B2</strong> High blood tumor burden: ≥1000/mcL Sezary cells&lt;sup&gt;i&lt;/sup&gt; or ≥40% CD4+/CD7- or ≥30% CD4+/CD26- cells&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
</tbody>
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<sup>i</sup>Sezary syndrome (B2) is defined as a clonal rearrangement of the TCR in the blood (clones should be relevant to clone in the skin) and either 1000/mcL or increased CD4 or CD3 cells with CD4/CD8 of ≥10 or increase in CD4 cells with an abnormal phenotype (≥40% CD4+/CD7- or ≥30% CD4+/CD26- of the total lymphocyte count).

<sup>k</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 large cell transformation (≥25% large cells), CD30+ or CD30-, and clinical features such as ulceration are important to document.

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

**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.
**Clinical Staging of MF and SS**

<table>
<thead>
<tr>
<th></th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>B</th>
</tr>
</thead>
<tbody>
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<td>IA</td>
<td>1</td>
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<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IB</td>
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<td>0</td>
<td>0,1</td>
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<td>IIA</td>
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<td>1,2</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IIB</td>
<td>3</td>
<td>0-2</td>
<td>0</td>
<td>0,1</td>
</tr>
<tr>
<td>IIIA</td>
<td>4</td>
<td>0-2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIB</td>
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<tr>
<td>IVB</td>
<td>1-4</td>
<td>0-3</td>
<td>1</td>
<td>0-2</td>
</tr>
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**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)" (MFSS-A)

- If B1 blood involvement, consider primary treatment for Stage III, B1 MFSS-7 (category 2B)

- If histologic evidence of folliculotropic or large-cell transformed MF

- Consider primary treatment for Stage IIB (See MFSS-6)

**Primary Treatment**

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

- Systemic therapy ± skin-directed therapy (see Stage IB on page MFSS-5)

  - or
  - Total skin electron beam therapy (TSEBT)

  - or
  - Clinical trial

**Response to Therapy**

- CR/PR or inadequate response

- Relapse with or persistent T1 skin disease

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**m**It is preferred that treatment occur at centers with expertise in the management of the disease.

**n**Unlike other NHL subtypes, response criteria for MF/SS has not been demonstrated to correlate with prognosis. Often decisions to continue or switch therapy are on a clinical basis. However, a proposal for detailed response criteria has been published (Olsen E, Whittaker S, Kim YH, et al. J Clin Oncol 2011;29:2598-2607).

**o**Patients achieving a response and/or a clinical benefit 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.

**p**Refractory or intolerant to multiple previous therapies.
**Stage IB-IIA**

- Generalized skin treatment
  - See Suggested Treatment Regimens "Skin-Directed Therapies (Skin-Generalized)" (MFSS-A)
  - ± adjuvant local skin treatment

If blood B1 involvement, consider primary treatment for Stage III B1 (category 2B)

If histologic evidence of folliculotropic or large-cell transformed MF

Consider primary treatment for Stage IIB

See MFSS-6

**Response to Therapy**

- CR/PR° or inadequate response
  - Relapse with or persistent T1-T2 disease:
    - T1 (see stage IA on MFSS-4)
    - T2 (see generalized skin treatment (MFSS-A))

- Refractory disease° or progression to > stage IB-IIA

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

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### Mycosis Fungoides/Sezary Syndrome

#### Stage IIIBr and/or histologic evidence of folliculotropic or large-cell transformation (LCT)

| Limited extent tumor disease ± patch/plaque disease | Generalized extent tumor, transformed, and/or folliculotropic disease

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

<table>
<thead>
<tr>
<th>PRIMARY TREATMENT</th>
<th>RESPONSE TO THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage IIA</strong>: Local RT for limited extent tumor, transformed, and/or folliculotropic disease</td>
<td>CR/PR(^o) or inadequate response</td>
</tr>
<tr>
<td><strong>Systemic Therapies (SYST-CAT A) (MFSS-A)</strong> ± skin-directed therapies ± RT</td>
<td>Relapse with or persistent T1-T3 limited:</td>
</tr>
<tr>
<td><strong>TSEBT</strong>(^w)</td>
<td>CR/PR(^o) or inadequate response</td>
</tr>
<tr>
<td><strong>See Suggested Treatment Regimens</strong>(^s,t)</td>
<td>Refractory disease(^p) or progression</td>
</tr>
<tr>
<td>&gt; <strong>Systemic Therapies (SYST-CAT A) (MFSS-A)</strong></td>
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<tr>
<td>&gt; <strong>Systemic Therapies (SYST-CAT B) (MFSS-A)</strong></td>
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<tr>
<td>&gt; <strong>Systemic Therapies (SYST-CAT C) (MFSS-A)</strong></td>
<td></td>
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<tr>
<td>&gt; <strong>Combination Therapies</strong> ± skin-directed therapy</td>
<td>Relapse with or persistent T1-T3:</td>
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<tr>
<td><strong>Multi-agent chemotherapy</strong>(^x)</td>
<td></td>
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<tr>
<td>&gt; <strong>Consider allogeneic transplant</strong>(^y)</td>
<td></td>
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<tr>
<td>&gt; <strong>Clinical trial</strong></td>
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\(^p\) Refractory or intolerant to multiple previous therapies.

\(^q\) Rebiopsy if suspect large cell transformation.

\(^r\) Histologic evidence of LCT often, but not always corresponds to a more aggressive growth rate. If there is no evidence of more aggressive growth, choosing systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

### Note

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\(^1\) Patients with indolent/plaque folliculotropic MF (without evidence of LCT) should first be considered for therapies under SYST-CAT A before resorting to treatments listed in SYST-CAT B or SYST-CAT C.

\(^2\) For non-radiated sites, see Stage I-IIA. After patient is rendered disease free by RT, may consider adjuvant systemic biologic therapy (SYST-CAT A) after RT to improve response duration.

\(^3\) Skin-directed therapies are for patch or plaque lesions and not for tumor lesions.

\(^4\) May consider adjuvant systemic biologic therapy (SYST-CAT A) after TSEBT to improve response duration.

\(^5\) Most patients are treated with multiple SYST-CAT A/B or combination therapies before receiving multiagent chemotherapy.

\(^6\) The role of allogeneic HSCT is controversial. See Discussion for further details.
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**STAGE**

(MFSS-2 and MFSS-3)

- **Sezary syndrome**
- **Non Sezary or Visceral disease (solid organ)**

### PRIMARY TREATMENT

- **Stage IV**
  - See Suggested Treatment Regimens
    - **Systemic Therapies (SYST-CAT A) (MFSS-A)**
    - **Combination Therapies**

### RESPONSE TO THERAPY

- **CR/PR or inadequate response**
  - Relapse or persistent disease
    - Consider allogeneic transplant,
      - as appropriate

- **Refractory disease or progression**
  - **See Suggested Treatment Regimens - Systemic Therapies (SYST-CAT B) (MFSS-A)**
  - Alemtuzumab
  - Clinical trial

- **See Suggested Treatment Regimens - Systemic Therapies (SYST-CAT C)**
  - or multi-agent chemotherapy ± RT for local control

- **CR/PR or inadequate response**
  - Relapse or persistent disease
    - Consider allogeneic transplant,
      - as appropriate

- **Refractory disease or progression**
  - Clinical trial
  - See Supportive Care for MF/SS (MFSS-B)
  - See monoclonal antibody and viral reactivation (NHODG-B)

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**Discussion**

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## SKIN-DIRECTED THERAPIES

### For limited/localized skin involvement (Skin-Limited/Local)
- Topical corticosteroids
- Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)
- Local radiation (12-36 Gy)
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, nbUVB for patch/thin plaques; PUVA for thicker plaques)
- Topical imiquimod

### For generalized skin involvement (Skin-Generalized)
- Topical corticosteroids
- Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)
- Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques)
- Total skin electron beam therapy (TSEBT) (12-36 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, isoretinoin [13-cis-retinoic acid], acitretin)
- Interferons (IFN-alpha, IFN-gamma)
- HDAC-inhibitors (vorinostat, romidepsin)
- Extracorporeal photopheresis
- Methotrexate (≤100 mg q week)

### Category B (SYST-CAT B)
- First-line therapies
  - Liposomal doxorubicin
  - Gemcitabine
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Bortezomib
  - Low-dose pralatrexate

### Category C (SYST-CAT C)
- Liposomal doxorubicin
- Gemcitabine
- Romidepsin
- Low- or standard-dose pralatrexate

## COMBINATION THERAPIES

- Phototherapy + retinoid
- Phototherapy + IFN
- Photopheresis + retinoid
- Photopheresis + IFN
- Photopheresis + retinoid + IFN

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Safety of combining TSEBT with systemic retinoids or HDAC-inhibitors, such as vorinostat or romidepsin or combining phototherapy with vorinostat or romidepsin is unknown.

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

Patients with large cell transformed (LCT) MF and stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. In general, agents listed in SYST-CAT C are preferred in these circumstances.

Combination regimens are generally reserved for patients with relapsed/refractory or extracutaneous disease.
Skin-directed Therapies
Topical corticosteroids

Carmustine

Nitrogen mustard (mechlorethamine hydrochloride)

Local radiation

Topical bexarotene

Tazarotene Gel

Topical imiquimod

Phototherapy (UVB and PUVA)

Total skin electron beam therapy (TSEBT)

Systemic Therapies
Alemtuzumab for Sezary Syndrome ± lymph node disease

Retinoids

Interferon

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Systemic Therapies Continued

Vorinostat

Romidepsin

Extracorporeal photopheresis (ECP)

Methotrexate

Liposomal doxorubicin

Gemcitabine

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Combination Therapies

**Skin-directed + Systemic**


**Systemic + Systemic**


Allogeneic stem cell transplant


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SUPPORTIVE CARE FOR MF/SS

Pruritus

• Assessment
  ▶ Pruritus should be assessed at each visit using consistent measurements
  ▶ Generalized pruritus and localized pruritus should be distinguished
  ▶ Correlation between sites of disease and localization of pruritus should be noted
  ▶ Other potential causes for pruritus should be ruled out

• Treatment
  ▶ Moisturizers, emollients, and barrier protection
  ▶ Topical steroid (appropriate strength for body region) ± occlusion
  ▶ Optimize skin-directed and systemic therapy
  ▶ Topical preparations - camphor/menthol formulations, pramoxine formulations
  ▶ Systemic agents
    ◦ First-line
      - Antihistamines
      - Doxepin
      - Gabapentin
    ◦ Second-line
      - Aprepitant
      - Mirtazapine
      - Selective serotonin reuptake inhibitors
    ◦ Third-line
      - Naltrexone

Infections

• Active or Suspected Infections
  ▶ Erythroderma:
    ◦ Skin swab and nares cultures for Staphylococcus aureus (S. aureus) infection or colonization
    ◦ Intranasal mupirocin
    ◦ Oral dicloxacillin or cephalaxin
    ◦ Sulfamethoxazole/trimethoprim, doxycycline if suspect MRSA
    ◦ Vancomycin if no improvement or bacteremia
    ◦ Bleach baths or soaks (if limited area)
  ▶ Ulcerated and necrotic tumors:
    ◦ Gram-negative rods (GNR) common in necrotic tumors may lead to bacteremia and sepsis
    ◦ If high suspicion for infection, obtain blood cultures, start antibiotics even if fever absent
    ◦ Role of wound cultures not clear due to colonization
    ◦ Empirical therapy for both GNR and gram-positive coccal infections is necessary initially

• Prophylaxis
  ▶ Optimize skin barrier protection
  ▶ Mupirocin for S. aureus colonization
  ▶ Bleach baths or soaks (if limited area)
  ▶ Avoid central lines (especially in erythrodermic patients)
  ▶ For patients receiving alemtuzumab, see NHODG-B.

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