DIAGNOSIS

ESSENTIAL:
• Biopsy of suspicious skin sites
  ▪ Multiple biopsies may be necessary to capture the pathologic variability of disease at diagnosis
• Dermatopathology review of slides

USEFUL UNDER CERTAIN CIRCUMSTANCES:
• IHC panel of skin biopsy
  ▪ CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyme B, βF1, TCR-CγM1
• Molecular analysis of skin biopsy: TCR gene rearrangements (assessment of clonality) by PCR methods
• Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including:
  ▪ Flow cytometry (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) 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

• Presence of transformation or areas of folliculotropism may have important implications for selection of therapy and outcome and should be included in pathology reports
• See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
• Typical immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+), CD30-/+ cytotoxic granule proteins negative.
• 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 MF/SS. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.
• See map for prevalence of HTLV-1 by geographic region.

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.
**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); 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 or large cell transformed or folliculotropic MF, or with palpable adenopathy or abnormal laboratory studies)
- Pregnancy testing in women of child-bearing age

**USEFUL IN SELECTED CASES:**
- Bone marrow biopsy in patients with unexplained hematologic abnormality
- Biopsy (FNA is often inadequate) of suspicious lymph nodes or suspected extracutaneous sites
- Rebiopsy skin if suspicious of large-cell transformation
- Neck CT

---

**STAGE (MFSS-3 and MFSS-4)**

- **Stage IA** → See Primary Treatment (MFSS-5)
- **Stage IB-IIA** → See Primary Treatment (MFSS-6)
- **Stage IIB** → See Primary Treatment (MFSS-7)
- **Stage III** → See Primary Treatment (MFSS-8)
- **Stage IV** → See Primary Treatment (MFSS-9)

---

Sezary syndrome (B2) is as defined on MFSS-3.

See Discussion for when Sezary flow cytometric study is appropriate in T1 disease.

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

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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^{i,k}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Patch = Any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted. 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.</td>
</tr>
<tr>
<td></td>
<td>Presence/absence of hypo- or hyperpigmentation, 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.</td>
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<td></td>
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</tr>
</tbody>
</table>


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 ≥40% CD4+/CD7- or ≥30% CD4+/CD26- cells.

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

{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.
# Mycosis Fungoides/Sezary Syndrome

## Clinical Staging of MF and SS\(^j\)

<table>
<thead>
<tr>
<th></th>
<th>T</th>
<th>N</th>
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<th>B</th>
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<td>0,1</td>
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<td>0–2</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>
</tbody>
</table>


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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. |
In rare cases of confirmed unilesional MF, RT has been shown to provide long-term remission.

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

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).

 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.

Refractory or intolerant to multiple previous therapies.

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

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**NCCN Guidelines Version 1.2016**

**Mycosis Fungoides/Sezary Syndrome**

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

**Stage IB-IIA**

**Generalized skin treatment**
- See Suggested Treatment Regimens "Skin-Directed Therapies (Skin-Generalized)" (MFSS-A)
- ± adjuvant local skin treatment (see stage IA on MFSS-5)

- If blood B1 involvement
  - Consider primary treatment for Stage III B1 MFSS-8 (category 2B)
- If histologic evidence of folliculotropic or large-cell transformed MF
  - In selected cases, consider primary treatment for Stage IIB (See MFSS-7)

**Primary Treatment**

- CR/PR or inadequate response

**Response to Therapy**

- Relapse with or persistent T1-T2 disease:
  - T1 (see stage IA on MFSS-5)
  - T2 (see generalized skin treatment (MFSS-A))

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

- CR/PR or inadequate response

- Refractory disease or progression

- Clinical trial
- TSEBT (if not previously administered)
  - Systemic chemotherapy agents used in ≥ stage IIB disease
  - See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT B)" (MFSS-A)

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Refractory or intolerant to multiple previous therapies.

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

Histologic evidence of folliculotropic or large-cell transformed MF is associated with higher risk of disease progression.

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Mycosis Fungoides/Sezary Syndrome

STAGE
(MFSS-2 and MFSS-3)

Stage IIB

Limited extent tumor disease ± patch/plaque disease

Generalized extent tumor, transformed, and/or folliculotropic disease

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

Primary Treatment

- Local RT for limited extent tumor, transformed, and/or folliculotropic disease²
- Systemic Therapies (SYST-CAT A) (MFSS-A) ± skin-directed therapies ± RT³

Response to Therapy

- CR/PR⁴ or inadequate response
  - Refractory disease¹ or progression
    - Relapse with or persistent T1-T3 limited:
      - T1-2 (see stage IA on MFSS-5 or stage IB-IIA on MFSS-6)
      - T3 limited extent

- TSEBT
  - See Suggested Treatment Regimens x,y ± skin-directed therapy
    - Systemic Therapies (SYST-CAT A) (MFSS-A)
    - Systemic Therapies (SYST-CAT B) (MFSS-A)
    - Systemic Therapies (SYST-CAT C) (MFSS-A)
    - Combination Therapies

- Refractory disease¹ or progression
  - Relapse with or persistent T1-T3:
    - T1-2 (see stage IA on MFSS-5 or stage IB-IIA on MFSS-6)
    - T3

- Multi-agent chemotherapy⁵
  - Consider allogeneic transplant⁶
  - Clinical trial

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

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**Stage III**

*If no blood involvement, consider skin-directed therapy*

- **See Suggested Treatment Regimens**
  - Skin-Directed Therapies (Skin-Generalized) *(MFSS-A)*

*If blood B1 involvement, systemic therapies*

- **See Suggested Treatment Regimens**
  - "Systemic Therapies (SYST-CAT A)" ± skin-directed therapy

### Response to Therapy

- **CR/PR** or inadequate response → Relapse or persistent disease
- Refractory disease or progression
  - **Combination therapies**
    - **See Suggested Treatment Regimens - Combination Therapies** *(MFSS-A)*
  - **Clinical trial**

### Stage III**

*Refractory or intolerant to multiple previous therapies.*

- Alemtuzumab
  - Consider nonmyeloablative allogeneic transplant, as appropriate

---

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Sezary syndrome
(MFSS-2 and MFSS-3)

Stage IV

Sezary syndrome

Non Sezary or Visceral disease (solid organ)

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

CR/PR or inadequate response

Relapse or persistent disease
- Consider allogeneic transplant, as appropriate

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

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

See monoclonal antibody and viral reactivation (NHODG-B)

CR/PR or inadequate response

Relapse or persistent disease
- Consider allogeneic transplant, as appropriate

Refactory disease or progression
- Clinical trial

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

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).

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Refractory or intolerant to multiple previous therapies.

The role of allogeneic HSCT is controversial. See Discussion for further details.

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

Patients with stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. If there is no evidence of more aggressive growth, systemic therapies from SYST-CAT B are appropriate. If aggressive growth is seen, then agents listed in SYST-CAT C are preferred.

Consider adjuvant systemic biologic therapy (SYST-CAT A) after chemotherapy to improve response duration.

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### Mycosis Fungoides/Sezary Syndrome

#### SUGGESTED TREATMENT REGIMENS

**SKIN-DIRECTED THERAPIES**

**For limited/localized skin involvement (Skin-Limited/Local)**
- Topical corticosteroids
- Topical chemotherapy (mechlorethamine [nitrogen mustard])
- Local radiation (8–36 Gy)
- Topical retinoids (bexarotene, tazarotene)
- Phototherapy (UVB, NB-UVB for patch/thin plaques; PUVA for thicker plaques)
- Topical imiquimod

**For generalized skin involvement (Skin-Generalized)**
- Topical corticosteroids
- Topical chemotherapy (mechlorethamine [nitrogen mustard])
- Phototherapy (UVB, NB-UVB, 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)

<table>
<thead>
<tr>
<th>Category A (SYST-CAT A)</th>
</tr>
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<tbody>
<tr>
<td>Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [13-cis-retinoic acid], acitretin)</td>
</tr>
<tr>
<td>Interferons (IFN-alpha, IFN-gamma)</td>
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<tr>
<td>HDAC-inhibitors (vorinostat, romidepsin)</td>
</tr>
<tr>
<td>Extracorporeal photopheresis</td>
</tr>
<tr>
<td>Methotrexate (≤100 mg q week)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Category B (SYST-CAT B)</th>
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<tbody>
<tr>
<td>First-line therapies (alphabetical order)</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
</tr>
<tr>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
</tr>
<tr>
<td>Low-dose pralatrexate</td>
</tr>
<tr>
<td>Second-line therapies</td>
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<tr>
<td>Chlorambucil</td>
</tr>
<tr>
<td>Pentostatin</td>
</tr>
<tr>
<td>Etoposide</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Temozolomide</td>
</tr>
<tr>
<td>Methotrexate (&gt;100 mg q week)</td>
</tr>
<tr>
<td>Bortezomib (category 3)</td>
</tr>
</tbody>
</table>

**SYSTEMIC THERAPIES**

**Category A (SYST-CAT A)**
- Retinoids (bexarotene, all-trans retinoic acid, isotretinoin [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 (alphabetical order)
  - Brentuximab vedotin
  - Gemcitabine
  - Liposomal doxorubicin
  - Low-dose pralatrexate
- Second-line therapies
  - Chlorambucil
  - Pentostatin
  - Etoposide
  - Cyclophosphamide
  - Temozolomide
  - Methotrexate (>100 mg q week)
  - Bortezomib (category 3)

**SYSTEMIC THERAPIES (continued)**

**Category C (SYST-CAT C)**
- Brentuximab vedotin
- Gemcitabine
- Liposomal doxorubicin
- Low- or standard-dose pralatrexate
- Romidepsin
- See regimens listed on TCEL-B 2 of 5 (PTCL-NOS)

**COMBINATION THERAPIES**

**Skin-directed + Systemic**
- Phototherapy + retinoid
- Phototherapy + IFN
- Photopheresis
- Total skin electron beam + photopheresis

**Systemic + Systemic**
- Retinoid + IFN
- Photopheresis + retinoid
- Photopheresis + IFN
- Photopheresis + retinoid + IFN

---

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**MFSS-A 1 OF 4**
Skin-directed Therapies

Topical corticosteroids

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

Bortezomib

Brentuximab vedotin

Retinoids
### SUGGESTED TREATMENT REGIMENS

#### References

**Systemic Therapies Continued**

**Interferon**


**Vorinostat**


**Romidepsin**


**Extracorporeal photopheresis (ECP)**


**Methotrexate**


**Liposomal doxorubicin**


**Gemcitabine**


**Pentostatin**


**Temozolomide**


**Pralatrexate**


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Combination Therapies
Skin-directed + Systemic
Systemic + Systemic

Allogeneic stem cell transplant

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### 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 and emollients
  - 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**
  - Cutaneous viral infections
    - High risk for skin dissemination of localized viral infections (HSV/VZV)
  - 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.