**DIAGNOSIS WORKUP**

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

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- IHC panel of skin biopsy \(a,b,c\)
  - CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD25, CD56, TIA1, granzyme B, βF1, TCR-CyM1
- Molecular analysis of skin biopsy: TCR gene rearrangements (assessment of clonality) \(d\) by PCR methods
- Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including:
  - Sezary cell prep
  - 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 \(e\) serology in at-risk populations. HTLV-1 PCR if blood involvement suspected

**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

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\(b\) See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NKT-Cell Neoplasms (NHODG-A).

\(c\) Typical immunophenotype: CD2+ CD3+ CD5+ CD7- CD4+ CD8- (rarely CD8+) CD30-/+ cytotoxic granule proteins negative.

\(d\) 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.

\(e\) See map for prevalence of HTLV-1 by geographic region.

\(f\) Sezary syndrome (B2) is as defined on MFSS-2.
## 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&lt;sup&gt;h,i&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| Skin | **T1**  
|      | Limited patches,<sup>j</sup>papules, and/or plaques<sup>k</sup> covering <10% of the skin surface |
|      | **T2**  
|      | Patches,<sup>j</sup>papules, and/or plaques<sup>k</sup> covering ≥10% of the skin surface  
|      | Patch only |
|      | **T2a**  
|      | Plaque ± patch |
|      | **T2b**  
|      | One or more tumors<sup>l</sup>(≥1 cm in diameter)  
|      | Confluence of erythema ≥80% body surface area |
| Node | **N0**  
|      | No abnormal lymph nodes; biopsy not required |
|      | **N1**  
|      | Abnormal lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2 |
|      | **N2**  
|      | Abnormal lymph nodes; histopathology Dutch Gr 2 or NCI LN 3 |
|      | **N3**  
|      | Abnormal lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4 |
|      | **NX**  
|      | Abnormal lymph nodes; no histologic confirmation |
| Visceral | **M0**  
|      | No visceral organ involvement |
|      | **M1**  
|      | Visceral involvement (must have pathology confirmation and organ involved should be specified) |
|      | **MX**  
|      | Abnormal visceral site; no histologic confirmation |
| Blood | **B0**  
|      | Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sezary) cells |
|      | **B1**  
|      | Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sezary) cells but do not meet the criteria of B2 |
|      | **B2**  
|      | High blood tumor burden: ≥1000/mcL Sezary cells<sup>i</sup>or CD4/CD8 ≥10 or ≥40% CD4+/CD7- or ≥30% CD4+/CD26- cells |


<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 (≥240% CD4+/CD7- or ≥30% CD4+/CD26- of the total lymphocyte count).

<sup>ii</sup>Sezary syndrome is defined by the presence of >1000/mcL of circulating T lymphocytes with >10% of lymphocytes showing CD4+ and <10% CD8+.

<sup>j</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>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>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.
### Clinical Staging of MF and SS<sup>h</sup>

<table>
<thead>
<tr>
<th></th>
<th>T</th>
<th>N</th>
<th>M</th>
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<td>IA</td>
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<tr>
<td>IB</td>
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<tr>
<td>IVB</td>
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<td>0–3</td>
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</tbody>
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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 (MFSS-2 and MFSS-3) PRIMARY TREATMENT\textsuperscript{m} RESPONSE TO THERAPY\textsuperscript{n}

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 folliculotrophic or large-cell transformed MF

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

CR/PR\textsuperscript{o} or inadequate response

Relapse with or persistent T1 skin disease

Refractory disease\textsuperscript{p} 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

\textsuperscript{m}It is preferred that treatment occur at centers with expertise in the management of the disease.

\textsuperscript{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).

\textsuperscript{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.

\textsuperscript{p}Refractory or intolerant to multiple previous therapies.

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**Mycosis Fungoides/Sezary Syndrome**

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

#### PRIMARY TREATMENT

| 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-4) |
| | If blood B1 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) |

#### 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 chemotherapy agents used in ≥ stage IIb disease |
| > See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT B)" (MFSS-A) |

° 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.

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

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

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

- Limited extent tumor disease ± patch/plaque disease
- Generalized extent tumor, transformed, and/or folliculotropictumor disease

**Stage IIBr and/or histologic evidence of folliculotrophic or large-cell transformation (LCT)**

<table>
<thead>
<tr>
<th>PRIMARY TREATMENT</th>
<th>RESPONSE TO THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Local RT for limited extent tumor, transformed, and/or folliculotrophic disease</td>
<td>CR/PR or inadequate response</td>
</tr>
<tr>
<td>• Systemic Therapies (SYST-CAT A) (MFSS-A) ± skin-directed therapies ± RT</td>
<td>Refractory disease or progression</td>
</tr>
<tr>
<td>• TSEBT</td>
<td>CR/PR or inadequate response</td>
</tr>
<tr>
<td>• See Suggested Treatment Regimens</td>
<td>Refractory disease or progression</td>
</tr>
<tr>
<td>• Systemic Therapies (SYST-CAT A) (MFSS-A)</td>
<td>Multi-agent chemotherapy</td>
</tr>
<tr>
<td>• Systemic Therapies (SYST-CAT B) (MFSS-A)</td>
<td>Consider allogeneic transplant</td>
</tr>
<tr>
<td>• Systemic Therapies (SYST-CAT C) (MFSS-A)</td>
<td>Clinical trial</td>
</tr>
<tr>
<td>• Combination Therapies</td>
<td></td>
</tr>
</tbody>
</table>

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

- 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.
- Rebiopsy if suspect large cell transformation.
- 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.

1. Patients with indolent/plaque folliculotrophic 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. RT is preferred 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.

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

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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*[^aa]

### Response to Therapy[^n]

**CR/PR[^o] or inadequate response**

Relapse or persistent disease

**CR/PR[^o] or inadequate response**

Relapse or persistent disease

- Combination therapies
  - *See Suggested Treatment Regimens - Combination Therapies[^bb] (MFSS-A)*
  - Clinical trial

- Clinical trial
  - *See Suggested Treatment Regimens Systemic Therapies (SYST-CAT B)*
  - Alemtuzumab[^cc]
  - Consider nonmyeloablative allogeneic transplant[^y]

[^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.

[^q]: The role of allogeneic HSCT is controversial. See Discussion for further details.

[^r]: 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.

[^s]: 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.

[^t]: Combination therapy options can be considered earlier (primary treatment) depending on treatment availability or symptom severity.

[^u]: Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications.

[^aa]: Refractory or intolerant to multiple previous therapies.

[^bb]: Combination therapy options can be considered earlier (primary treatment) depending on treatment availability or symptom severity.

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**STAGE**

(MFSS-2 and MFSS-3)

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

**PRIMARY TREATMENT**

- 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 B) or (SYST-CAT C)**

- or multi-agent chemotherapy ± RT for local control

**Refractory disease or progression**

- 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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---

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**P** Refractory or intolerant to multiple previous therapies.

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

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

**dd** 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.

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

**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)

**SYSTEMIC THERAPIES (continued)**

Category C (SYST-CAT C) (alphabetical order)
- Brentuximab vedotin
- Gemcitabine
- Liposomal doxorubicin
- Low- or standard-dose pralatrexate
- Romidepsin
- See regimens listed on TCEL-B

**COMBINATION THERAPIES**

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

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

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

References

**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**


**Brentuximab vedotin**


**Retinoids**


**Interferon**


Continued on next page
SUGGESTED TREATMENT REGIMENS

**References**

**Gemcitabine**


**Pentostatin**


**Romidepsin**


**Extracorporeal photopheresis (ECP)**


**Methotrexate**


**Liposomal doxorubicin**


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

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Combination Therapies

Skin-directed + Systemic


Systemic + Systemic


Allogeneic stem cell transplant


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**
  - 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 cephalexin
    - 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.