**MFSS-1**

**DIAGNOSIS**

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

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Immunohistochemical studies of skin biopsy, immunohistochemistry of skin biopsy (CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD26, CD56, TIA1, granzyme B, βF1)
- Molecular study for T-cell receptor (TCR) gene rearrangements (assessment of clonality) of skin biopsy; PCR methods

**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
  - TCR gene rearrangement of peripheral blood lymphocytes if Sezary Syndrome suspected
  - Comprehensive metabolic panel
  - LDH

**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)
- 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 (> 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
- Pregnancy testing in women of child-bearing age

**STAGE**

- Stage IA → See Primary Treatment (MFSS-2)
- Stage IB-IIA → See Primary Treatment (MFSS-3)
- Stage IIB → See Primary Treatment (MFSS-4)
- Stage III → See Primary Treatment (MFSS-5)
- Stage IV → See Primary Treatment (MFSS-6)

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See Use of Immunophenotyping in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).

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.

Sezary syndrome (B2) is as defined on MFSS-B (1 of 2).

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

See TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome (MFSS-B).
Mycosis Fungoides/Sezary Syndrome

STAGE

PRIMARY TREATMENT

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)

- CR/PR or inadequate response

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

Relapse with or persistent T1 disease

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

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

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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.

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

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.

Refractory or intolerant to multiple previous therapies.
STAGE PRIMARY TREATMENT

Stage IB-IIA

Generalized skin treatment
- See Suggested Treatment Regimens "Skin-directed therapies (Skin-generalized)" (MFSS-A)
± adjuvant local skin treatment (MFSS-A)

CR/PR or inadequate response

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

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 to > stage IB-IIA

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

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

Clinical trial
- TSEBT (if not previously administered)
- Systemic chemotherapy agents used in ≥ stage IIB disease

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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.
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

CR/PR\(^i\) or inadequate response

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

Local RT for limited tumor lesions + skin-directed therapies\(^i\) as in stages I-IIA
- Systemic Therapies (SYST-CAT A) (MFSS-A) ± RT

Refactory disease\(^j\) or progression

Refractory disease\(^j\) or progression

\(\text{Limited extent tumor disease ± patch/plaque disease} \)

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

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

MULTIPLE AGENT CHEMOTHERAPY\(^n\)
- Consider allogeneic transplant\(^o\)
- Clinical trial

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

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

\(\text{Refractory or intolerant to multiple previous therapies.} \)

\(\text{Skin-directed therapies are for patch or plaque lesions and not for tumor lesions.} \)

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

\(\text{It is preferred that treatment occur at centers with expertise in the management of the disease.} \)

\(\text{Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.} \)

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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.

Refractory or intolerant to multiple previous therapies.

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 ≥ IIIB 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.

Combination therapy options can be considered earlier (primary treatment) depending on treatment availability or symptom severity.
**Mycosis Fungoides/Sezary Syndrome**

**STAGE**

- **Stage IV**
  - Sezary syndrome ± lymph node disease
  - Lymph node disease (not Sezary)
  - Visceral disease (solid organ)

**PRIMARY TREATMENT**

- **Stage IV**
  - **Sezary syndrome ± lymph node disease**
    - 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

  - **Lymph node disease (not Sezary)**
    - See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT B)" or multi-agent chemotherapy ± RT for local control
    - CR/PR or inadequate response
      - Refractory disease or progression
        - Consider allogeneic transplant, as appropriate

  - **Visceral disease (solid organ)**
    - See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT B)" or multi-agent chemotherapy ± RT for local control
    - CR/PR or inadequate response
      - Refractory disease or progression
        - Clinical trial

**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.

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**Guidelines Index**

- NCCN® Practice Guidelines in Oncology – v.1.2010
- NHL Table of Contents
- Staging, Discussion, References

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### Suggested Treatment Regimens

#### Skin-Directed Therapies

**For limited/localized skin involvement (Skin-Limited/Local)**
- Topical corticosteroids
- Topical chemotherapy (nitrogen mustard, carmustine)
- Local radiation (particularly unilesional presentation, 24-36 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, carmustine)
- Phototherapy (UVB, nbUVB, for patch/thin plaques; PUVA for thicker plaques)
- 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** (SYS-T-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
- Denileukin diftitox
- Methotrexate (≤ 100 mg q week)

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

#### Combination Therapies

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

**Systemic + Systemic**
- Retinoid + IFN
- Bexarotene + denileukin diftitox
- Photopheresis + retinoid
- Photopheresis + IFN
- Photopheresis + retinoid + IFN

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**a** See references for regimens MFSS-A 2 of 4, MFSS-A 3 of 4, and MFSS-A 4 of 4

**b** 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.

**c** 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.

**d** It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response.

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

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

References

**Skin-directed therapies**

*Topical corticosteroids*


*Carmustine*


**Nitrogen mustard (mechlorethamine hydrochloride)**


**Local radiation**


*Topical bexarotene*


*Zazarotene Gel*


*Topical imiquimod*


**Phototherapy (UVB and PUVA)**


**Total skin electron beam therapy (TSEBT)**


Continued on next page
SUGGESTED TREATMENT REGIMENS

**References**

**Romidepsin**


**Extracorporeal photopheresis (ECP)**

**Denileukin diftitox**


**Methotrexate**


Continued on next page
**SYSTEMIC THERAPIES CONTINUED**

**Liposomal doxorubicin**

**Gemcitabine**


**Pentostatin**

**Temozolomide**

**Bortezomib**

**COMBINATION THERAPIES**

**Skin-directed + Systemic**


**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(9):1799-1803.**


<table>
<thead>
<tr>
<th>TNMB&lt;sup&gt;a&lt;/sup&gt;</th>
<th>TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>Skin</strong></td>
<td></td>
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<tr>
<td>T1</td>
<td>Limited patches&lt;sup&gt;c&lt;/sup&gt;, papules and/or plaques&lt;sup&gt;d&lt;/sup&gt; covering &lt; 10% of the skin surface</td>
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<tr>
<td>T2</td>
<td>Patches&lt;sup&gt;c&lt;/sup&gt;, papules and/or plaques&lt;sup&gt;d&lt;/sup&gt; covering ≥ 10% of the skin surface</td>
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<td>T3</td>
<td>One or more tumors&lt;sup&gt;e&lt;/sup&gt; (≥ 1 cm in diameter)</td>
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<tr>
<td>T4</td>
<td>Confluence of erythema ≥ 80% body surface area</td>
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<tr>
<td><strong>Node</strong></td>
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<td>N0</td>
<td>No clinically abnormal peripheral lymph nodes; biopsy not required&lt;sup&gt;f&lt;/sup&gt;</td>
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<td><strong>Visceral</strong></td>
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<td>M0</td>
<td>No visceral organ involvement</td>
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<tr>
<td>M1</td>
<td>Visceral involvement (must have pathology confirmation&lt;sup&gt;g&lt;/sup&gt; and organ involved should be specified)</td>
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<tr>
<td><strong>Blood</strong></td>
<td></td>
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<tr>
<td>B0</td>
<td>Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sezary) cells&lt;sup&gt;h&lt;/sup&gt;</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&lt;sup&gt;g&lt;/sup&gt; with positive clone&lt;sup&gt;i&lt;/sup&gt;</td>
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</table>


<sup>b</sup>Sezary syndrome (B2) is defined by Sezary cell count ≥ 1,000/mm<sup>3</sup> (Sezary cell prep) or expanded CD4+ cells with CD4/CD8 ratio ≥ 10, CD4+/CD7- ≥ 40%, or CD4+/CD26- ≥ 30% of lymphs in the presence of a positive clonal TCR gene rearrangement.

<sup>c</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>d</sup>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.

<sup>e</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 histological evidence of large cell transformation has occurred. Phenotyping for CD30 is encouraged.

<sup>f</sup>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.

<sup>g</sup>Spleen and liver may be diagnosed by imaging criteria.

<sup>h</sup>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.

<sup>i</sup>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\(^a\)

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