

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)

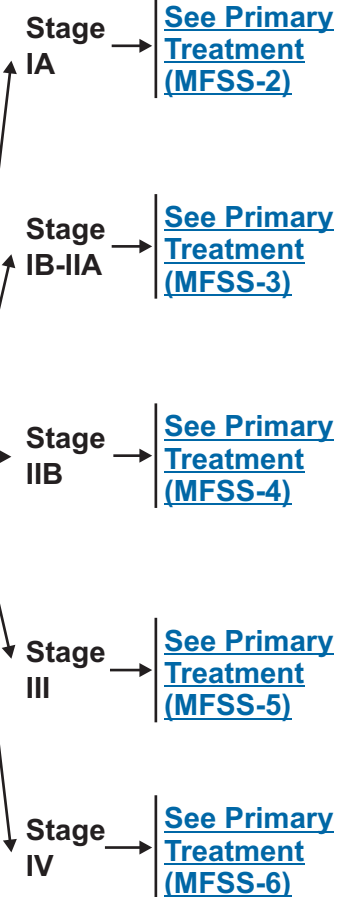
WORKUP^c

ESSENTIAL:

- Complete physical examination
 - ▶ Examination of entire skin: assessment of %BSA (palm plus digits ≈ 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 (≥ 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)



^aPimpinelli N, Olsen EA, Santucci M, et al., for the International Society for Cutaneous Lymphoma. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1053-1063

^bTCR 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.

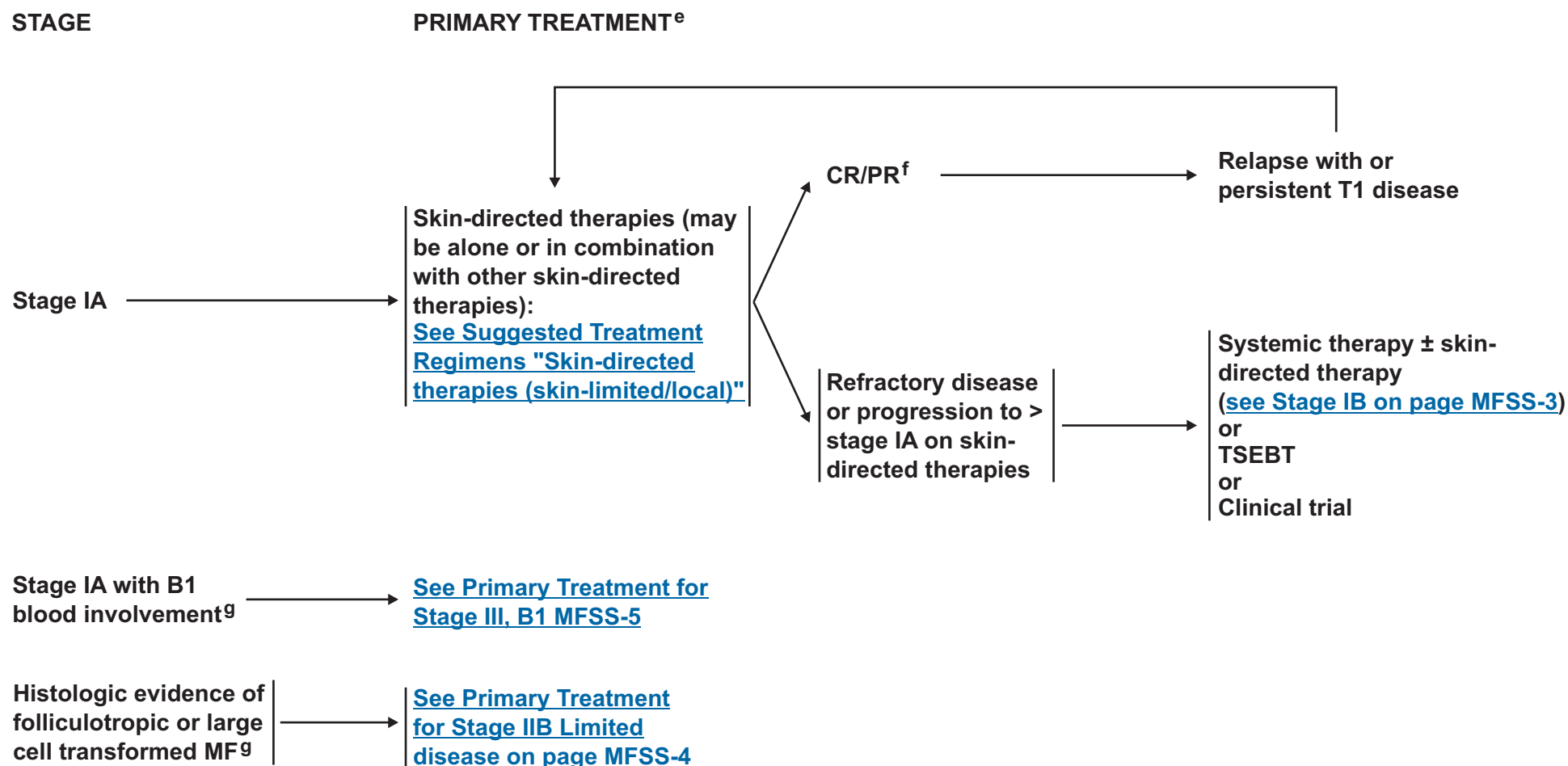
^cOlsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the Staging and Classification of Mycosis Fungoides and Sezary Syndrome: A Proposal of the International Society for

Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713-22. (MFSS-B).

^dSezary syndrome (B2) defined by Sezary cell count ≥ 1,000/mm³ (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.

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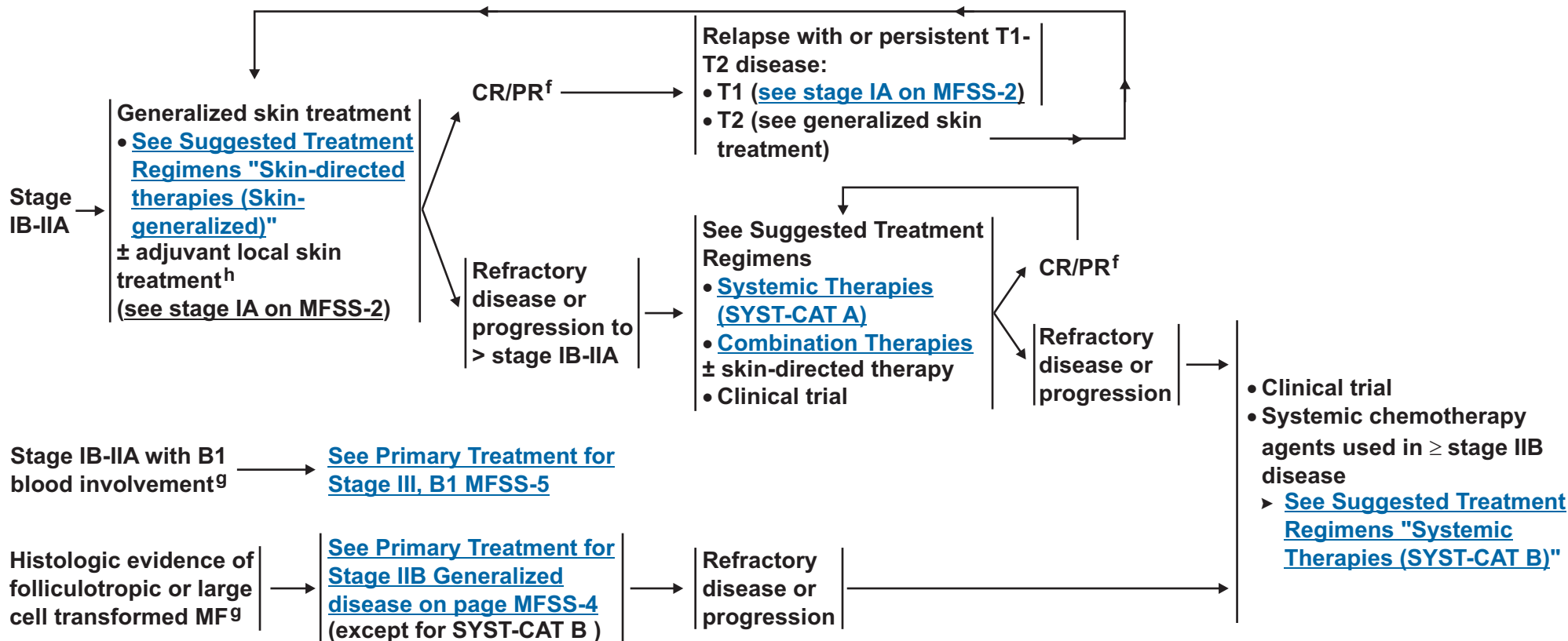
^eReferral to a multidisciplinary academic specialty center preferred.

^fPatients 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.

^gFolliculotropic, 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^e



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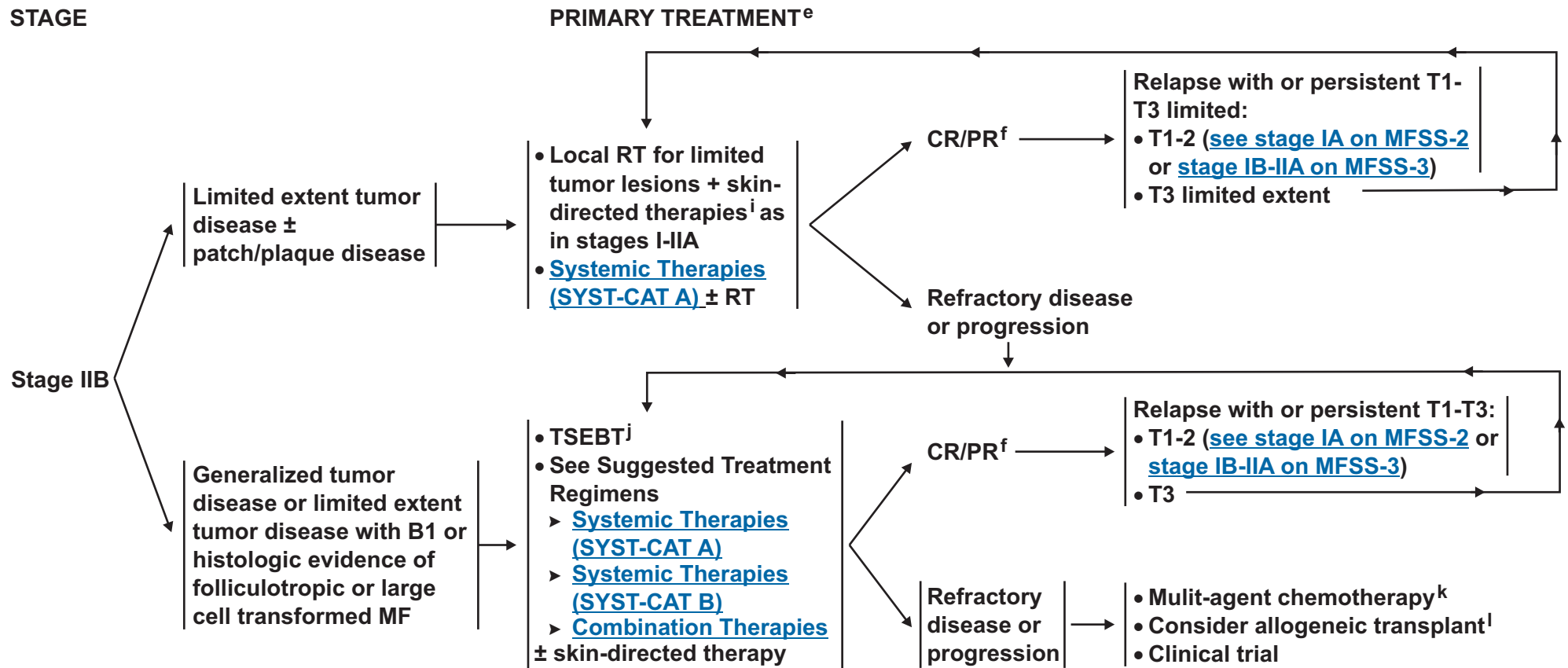
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^hFor patients with recalcitrant sites after generalized skin treatment, additional local treatment may be needed.

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

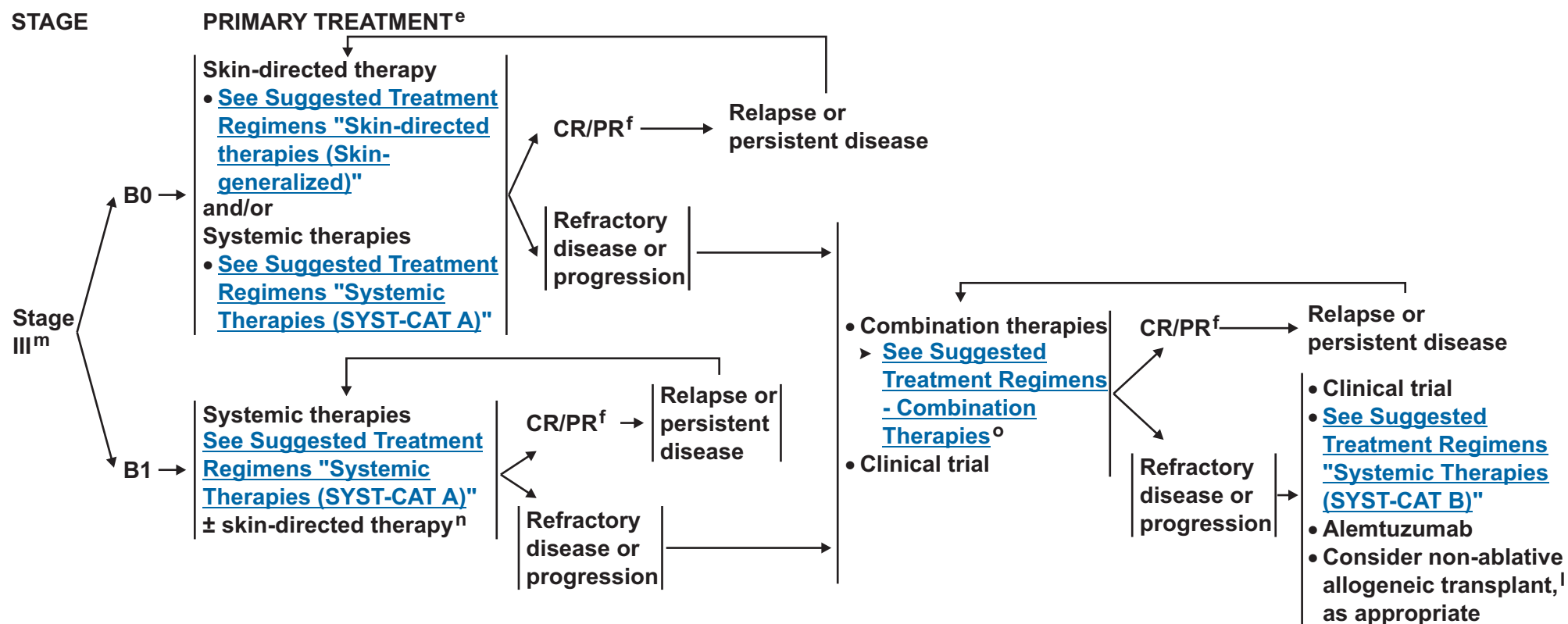
^jMay consider adjuvant systemic biologic therapy (SYST-CAT A) after TSEBT to improve response duration.

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

^lData 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.

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^mGeneralized 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.

ⁿMid-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.

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

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SUGGESTED TREATMENT REGIMENS

SKIN-DIRECTED THERAPIES

For limited/localized skin involvement (Skin-Limited/Local)

- Topical corticosteroids^a
- 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)^b

For generalized skin involvement (Skin-Generalized)

- Topical corticosteroids^a
- Topical chemotherapy (mechlorethamine, BCNU)
- Phototherapy (UVB, nbUVB, or PUVA for patch/thin plaques; PUVA for thicker plaques)^b
- 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^c
- Denileukin diftitox
- 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)

COMBINATION THERAPIES

Skin-directed + Systemic

- Phototherapy + retinoid
- Phototherapy + IFN
- Phototherapy + photopheresis^c
- Total skin electron beam + photopheresis^c

Systemic + Systemic

- Retinoid + IFN
- Bexarotene + denileukin diftitox
- Photopheresis^c + retinoid
- Photopheresis^c + IFN
- Photopheresis^c + retinoid + IFN

^aLong-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.

^bCumulative 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.

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

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TNMB ^a		TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome
Skin	T1	Limited patches, ^b papules and/or plaques ^c covering < 10 % of the skin surface
	T2	Patches, papules and/or plaques covering ≥ 10 % of the skin surface
	T3	One or more tumors ^d (≥ 1 cm in diameter)
	T4	Confluence of erythema ≥ 80 % body surface area
Node	N0	No clinically abnormal peripheral lymph nodes; biopsy not required ^e
	N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2
	N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 2 or NCI LN 3
	N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4
	NX	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation ^f and organ involved should be specified)
Blood	B0	Absence of significant blood involvement: ≤ 5 % of peripheral blood lymphocytes are atypical (Sezary) cells ^g
	B1	Low blood tumor burden: > 5 % of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2
	B2	High blood tumor burden: ≥ 1000/mcL Sezary cells ^g with positive clone ^h

^aOlsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the Staging and Classification of Mycosis Fungoides and Sezary Syndrome: A Proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007;110:1713-22.

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

^cPlaque = 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.

^dTumor = 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.

^eAbnormal 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.

^fSpleen and liver may be diagnosed by imaging criteria.

^gSezary 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.

^hA T cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.

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Clinical Staging/Classification of MF and SS^a

	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
II	1-2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA ₁	1-4	0-2	0	2
IVA ₂	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

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