Cutaneous T-cell Lymphomas (CTCL)[1]

Disclaimer: *This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.*

TABLE OF CONTENTS

[1] This algorithm contains the following subtypes: mycosis fungoides, Sezary syndrome, and primary cutaneous anaplastic large-cell lymphoma (pcALCL).
See Peripheral T-cell Lymphomas (PTCL) algorithm for the following subtypes: PTCL - not otherwise specified, angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma, ALK+ and ALK- and enteropatic associated T-cell lymphoma (EATL).

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Cutaneous T-cell Lymphomas (CTCL)

Note: Consider Clinical Trials as treatment options for eligible patients.

PATHOLOGIC DIAGNOSIS[1]

ESSENTIAL:

- Pathology (dermatopathology or hematopathology) review of all slides with at least one paraffin block or 15 unstained slides representative of the tumor. Fresh punch biopsy if consult material is nondiagnostic or unavailable.
- Adequate morphology and immunophenotyping to establish diagnosis
  - Immunohistochemistry on formalin fixed paraffin embedded tissue: CD3, CD4, CD8, CD7, CD30

OF USE IN CERTAIN CIRCUMSTANCES TO DETERMINE SUBGROUP:

- Other IHC stains to consider in selected cases: CD5, CD2, TCRB, TCRD, TIA-1, Granzyme B, PD1, ICOS

STRONGLY RECOMMENDED:

- Molecular studies to detect clonality of the *TCR* genes
- NGS studies (end lymphoma panel) to assess the mutational landscape
- Fine needle aspiration (FNA) or core biopsy for tissue array/banking by protocol

INITIAL EVALUATION

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to of liver and spleen
  - Dermatology consult for comprehensive skin assessment including possible skin infections especially at sites of erosions and ulcerations[2]
  - Performance status
  - B symptoms (Unexplained fever > 38°C during the previous month; Recurrent drenching night sweats during the previous month; Weight loss > 10% of body weight ≤ 6 months of diagnosis)
  - Calculation of Cutaneous Lymphoma International Prognostic Index if indicated[3]
- CBC with differential, BUN, creatinine, albumin, AST, bilirubin, serum calcium, alkaline phosphatase, uric acid, LDH
- Beta-2-microglobulin
- Screening for HIV 1 and 2, hepatitis B and C (HBcAb, HBaAg, HCVAb)
- HTLV 1/2 serology
- Chest x-ray (AP & LAT)
- PET/CT if palpable nodes
- Lifestyle risk assessment[4]

OF USE IN SELECTED CASES:

- CT head or MRI brain with contrast
- Pregnancy test
- Unilateral or bilateral bone marrow biopsy with aspirate
- MUGA scan or echocardiogram
- Lumbar puncture, if paranasal sinus, testicular, parameningeal, orbit, CNS, paravertebral, bone marrow or HIV lymphoma
- Other work-up for patients at risk for hemophagocytic lymphohistiocytosis (HLH) including EBV by PCR, ferritin, fibrinogen, triglycerides, and cytokine 12 profile including IL-2sR
- Serum immunoelectrophoresis (SIEP)
- Discuss fertility options and sperm banking for patients of child bearing potential [refer to Fertility Preservation Prior to Cancer Treatment (Women) algorithm]

TREATMENT

- Mycosis Fungoides/ Sezary Syndrome: Stage IA, IB, IIA → Page 3
- Mycosis Fungoides/ Sezary Syndrome: Stage IIB → Page 4
- Mycosis Fungoides/ Sezary Syndrome: Stage III → Page 5
- Mycosis Fungoides/ Sezary Syndrome: Stage IV → Page 6
- Mycosis Fungoides/ Sezary Syndrome: Relapsed/ Refractory → Page 7
- Large Cell Transformation (LCT) → Page 8

[1] Review MD Anderson approved biomarkers

[2] See Appendix A for Supportive Therapies

[3] Refer to Benton, E. C., Crichton, S., Talpur, R., Agar, N. S., Fields, P. A., Wedgeworth, E., … Whittaker, S. J. (2013). A cutaneous lymphoma international prognostic index (CLIPi) for mycosis fungoides and Sezary syndrome. *European Journal of Cancer, 49*(13), 2859–2868. doi.org/10.1016/j.ejca.2013.04.018

[4] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

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Note: Consider Clinical Trials as treatment options for eligible patients.

Mycosis Fungoides (MF)/Sezary Syndrome (SS)

STAGE | **TREATMENT** | **EVALUATION AND TREATMENT**

Stage IA (skin only, < 10% BSA) → Skin-directed therapy (SDT) may be used alone or in combination of multiple SDTs[1,2]

- Complete or partial response[3] → Continue therapy as maintenance until progression or taper to optimize response duration; If disease progression or relapse, treat based on clinical stage
- Inadequate response[3] after radiation or after multiple SDTs → Clinical trial **or**; Systemic therapy (see Box A below)

Stage IB (skin only, ≥ 10% BSA)/ Stage IIA

- Predominantly patch → SDT alone or combination of multiple SDTs[1,2]; Consider systemic therapy
- Predominantly plaque → **A**

A

Systemic therapy **plus** SDT[1,2]
- Bexarotene (preferred)
- Brentuximab vedotin for CD30 positive disease[4]; preferred if unable to tolerate or unfavorable cost benefit from bexarotene or acitretin[5]
- Romidepsin preferred if unable to tolerate or does not qualify for interferon[5]
- Vorinostat
- Mogamulizumab preferred if blood involvement[6]
- Extracorporeal photopheresis (ECP) preferred if SS
- Acitretin[4]
- Interferons[4] (IFN alpha-2b, IFN gamma-1b, or pegylated IFN); preferred if unable to tolerate or does not qualify for bexarotene or acitretin **and** CD30 negative disease
- Consider methotrexate (dose ≤ 50 mg every week) if predominant symptom is pruritus
- Isotretinoin (13-cis-retinoic acid)

→
- Complete or partial response[3] → Continue therapy as maintenance until progression or taper to optimize response duration; If disease progression or relapse, treat based on clinical stage
- Inadequate response[3] after multiple SDT and systemic therapy → Clinical trial **or**; Total skin electron beam therapy (TSEBT)[2] **or**; Focal radiation therapy in combination with systemic or other topicals[1,2]

BSA = body surface area

[1] See Appendix B for Skin Directed Therapies
[2] See Appendix C for Principles of Radiation Therapy
[3] For response assessment, refer to: Olsen, E. A., Whittaker, S., Kim, Y. H., Duvic, M., Prince, H. M., Lessin, S. R., … Vonderheid, E. C. (2011). Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: A consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *Journal of Clinical Oncology, 29*(18), 2598. doi: 10.1200/JCO.2010.32.0630
[4] Excludes SS
[5] Not FDA approved
[6] Excludes large cell transformation

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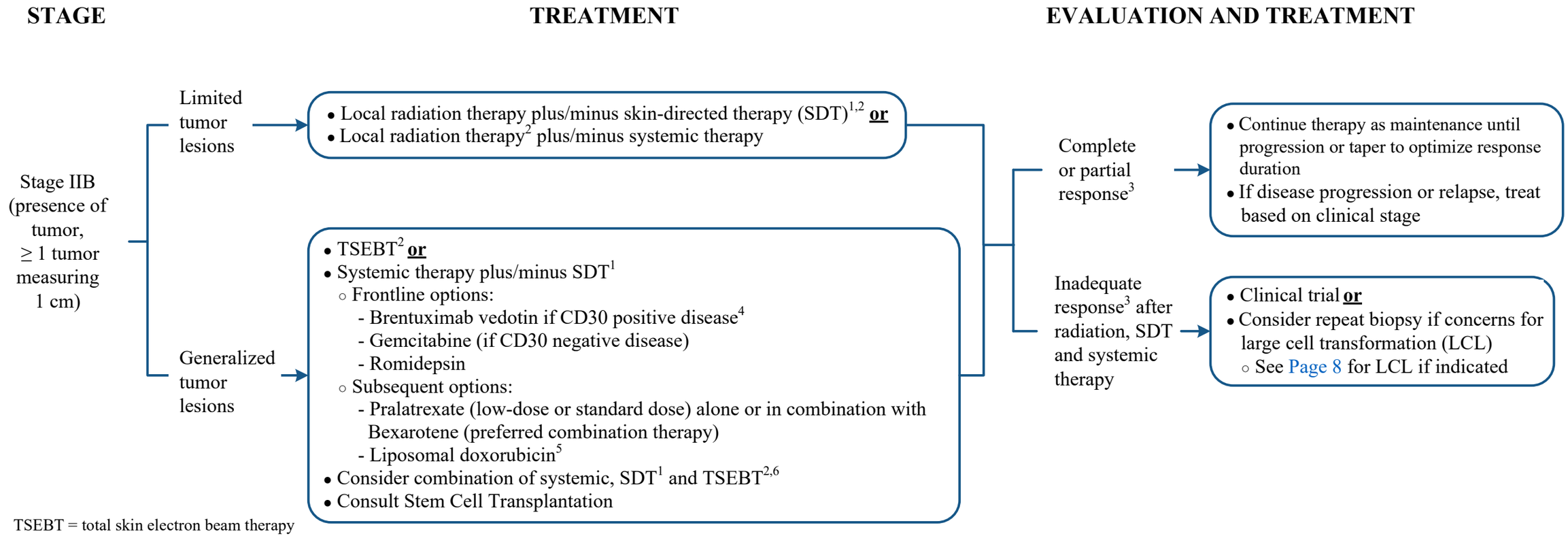
Cutaneous T-cell Lymphomas (CTCL)

Note: Consider Clinical Trials as treatment options for eligible patients.

Mycosis Fungoides (MF)/Sezary Syndrome (SS)



TSEBT = total skin electron beam therapy

[1] See Appendix B for Skin Directed Therapies
[2] See Appendix C for Principles of Radiation Therapy
[3] For response assessment, refer to: Olsen, E. A., Whittaker, S., Kim, Y. H., Duvic, M., Prince, H. M., Lessin, S. R., … Vonderheid, E. C. (2011). Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: A consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *Journal of Clinical Oncology, 29*(18), 2598. doi: 10.1200/JCO.2010.32.0630
[4] Excludes SS
[5] Final results of phase II trial did not benefit when bexarotene was added
[6] Limited data exists on the safety of these combinations. Institutional experience on the safety of drugs and combination with radiation:
- Therapies that appear safe: brentuximab vedotin, romidepsin, bexarotene, extracorporeal photopheresis (ECP)
- Concern for toxicity including radiation sensitization and/or radiation recall: gemcitabine, doxorubicin, pralatrexate, methotrexate

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Cutaneous T-cell Lymphomas (CTCL)

Note: Consider Clinical Trials as treatment options for eligible patients.

Mycosis Fungoides (MF)/Sezary Syndrome (SS)

STAGE	TREATMENT	EVALUATION AND TREATMENT
Stage III (erythrodermic) or any stage with blood (B1) involvement with aberrant cell count < 1000		
Skin-directed plus systemic	• Frontline options: ◦ Low symptom burden (responses expected 2-3 months after initiation) - Phototherapy plus interferon (IFN alfa-2bmor, IFN gamma-1b) - Phototherapy plus retinoid - Phototherapy plus ECP if blood involvement ◦ High symptom burden (need for immediate response) - TSEBT[1] alone if no blood involvement, or in combination with ECP if blood involvement • Subsequent options: Combinations of phototherapy plus: ◦ Brentuximab vedotin for CD30 positive disease[2] ◦ Gemcitabine (if CD30 negative disease) ◦ Romidepsin (preferred if unable to tolerate or not qualify for interferon) ◦ Pralatrexate (low-dose or standard dose) alone or in combination with Bexarotene (preferred combination therapy) ◦ Mogamulizumab preferred if blood involvement[3] ◦ Liposomal doxorubicin[4]	Complete or partial response[5] → • Continue therapy as maintenance[6] until progression or taper to optimize response duration • If disease progression or relapse, treat based on clinical stage • Stem cell transplant consolidation
Systemic	• ECP plus interferon (IFN alfa-2b, IFN gamma-1b, or pegylated IFN) • ECP plus retinoid • ECP plus retinoid plus interferon (IFN alfa-2b, IFN gamma-1b, or pegylated IFN) • Retinoid plus interferon (IFN alfa-2b, IFN gamma-1b, or pegylated IFN)	Inadequate response[5] after therapy → • Consider repeat biopsy • Clinical trial **or** • Treat as SS with ≥ 1000 aberrant cells (See Page 6) **or** • Consider allo-stem cell transplant if disease is controlled

ECP = extracorporeal photopheresis
TSEBT = total skin electron beam therapy

Note: Patients with extensive skin lesions (*e.g.*, erythrodermic disease, ulcerative lesions) are at increased risk for secondary infection with skin pathogens; systemic antibiotic therapy should be considered

[1] See Appendix C for Principles of Radiation Therapy

[2] Excludes SS

[3] Excludes large cell transformation

[4] Final results of phase II trial did not benefit when Bexarotene was added

[5] For response assessment, refer to: Olsen, E. A., Whittaker, S., Kim, Y. H., Duvic, M., Prince, H. M., Lessin, S. R., … Vonderheid, E. C. (2011). Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: A consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *Journal of Clinical Oncology, 29*(18), 2598. doi: 10.1200/JCO.2010.32.0630

[6] For patients treated with TSEBT, maintenance options may include phototherapy with or without oral regimens

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Note: Consider Clinical Trials as treatment options for eligible patients.

Mycosis Fungoides (MF)/Sezary Syndrome (SS)

STAGE	TREATMENT	EVALUATION AND TREATMENT
Stage IVA1 or any stage with blood (B2) involvement with aberrant cell count > 1000	• ECP plus retinoid plus/minus interferon • Mogamulizumab preferred if significant symptomatic leukocytosis for ECP not feasible • For high symptom burden (need for immediate response), TSEBT[1] alone plus systemic therapy options • Subsequent options: Combinations of skin directed therapy[2] plus: ◦ Brentuximab vedotin for CD30 positive disease[3] ◦ Gemcitabine (if CD30 negative disease) ◦ Romidepsin (preferred if unable to tolerate or not qualify for interferon) ◦ Pralatrexate (low-dose or standard dose) alone or in combination with Bexarotene (preferred combination therapy) ◦ Liposomal doxorubicin[4]	Complete or partial response[5] → • Continue therapy as maintenance until progression or taper to optimize response duration • Stem cell transplant consolidation
Stage IVA2 and IVB	Systemic therapy plus or minus skin directed therapy is the preferred treatment option [see Page 8 for large cell transformation (LCT)]	Inadequate response[5] after therapy → • Consider repeat biopsy • Clinical trial **or** • Regimens for advanced relapsed/refractory disease, • Consider allo-stem cell transplant if disease is controlled • Discuss Goal Concordant Care (GCC) with patient or if clinically indicated, with Surrogate Decision-Maker (SDM)[6]

ECP = extracorporeal photopheresis
TSEBT = total skin electron beam therapy

[1] See Appendix C for Principles of Radiation Therapy
[2] See Appendix B for Skin Directed Therapies
[3] Excludes SS
[4] Final results of phase II trial did not benefit when bexarotene was added
[5] For response assessment, refer to: Olsen, E. A., Whittaker, S., Kim, Y. H., Duvic, M., Prince, H. M., Lessin, S. R., …Vonderheid, E. C. (2011). Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: A consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *Journal of Clinical Oncology, 29*(18), 2598. doi: 10.1200/JCO.2010.32.0630
[6] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients or if clinically indicated, the SDM should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

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Cutaneous T-cell Lymphomas (CTCL)

Note: Consider Clinical Trials as treatment options for eligible patients.

Mycosis Fungoides (MF)/Sezary Syndrome (SS)

STAGE	TREATMENT
Clinically aggressive / relapsed and refractory MF/SS requiring systemic therapy	• Clinical trial preferred • **Outside of a trial, institutional practice**: ○ Mogamulizumab preferred if blood involvement[1] • Regimens for Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) if intention is for transplant (see Page 8 for LCT) • Alemtuzumab • Pembrolizumab • Discuss GCC with patient or if clinically indicated, with SDM[2]

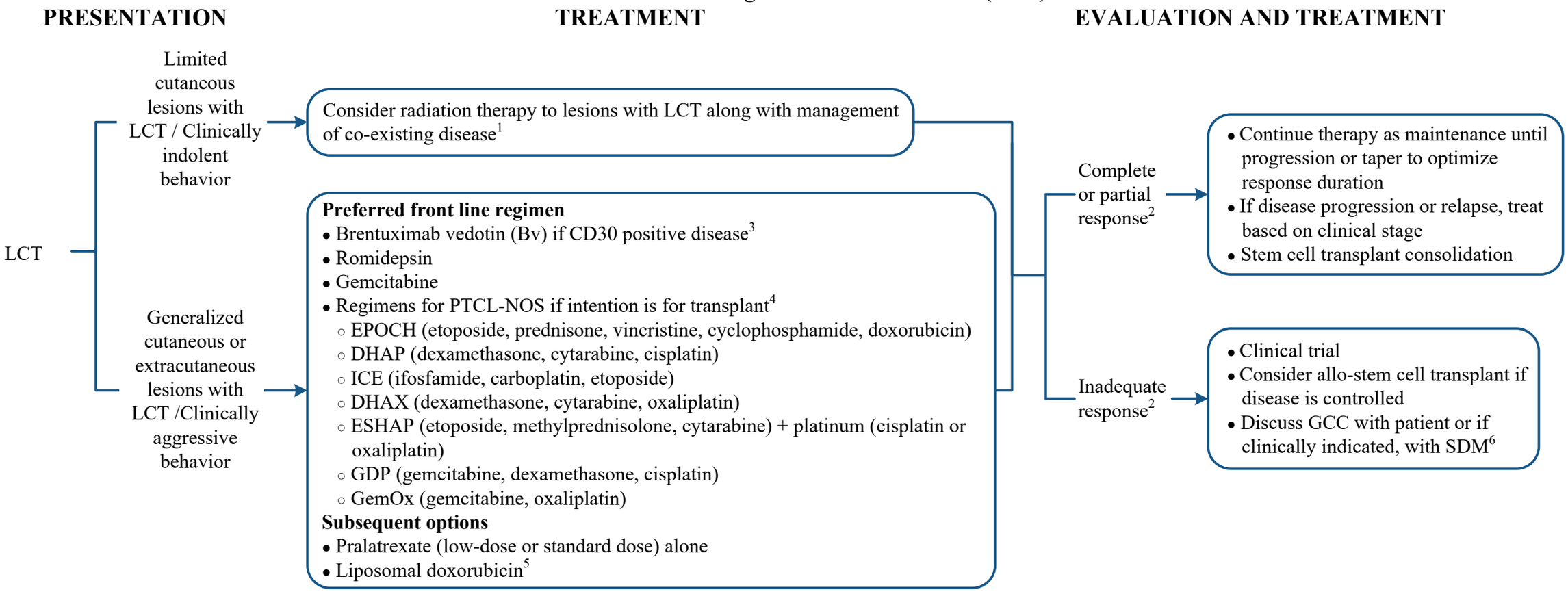
[1] Concern for increased risk for acute GVHD in patients receiving therapy approximately 80 days prior to transplant

[2] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients or if clinically indicated, the SDM should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

Cutaneous T-cell Lymphomas (CTCL)

Note: Consider Clinical Trials as treatment options for eligible patients.

Large Cell Transformation (LCT)



[1] See Appendix C for Principles of Radiation Therapy

[2] For response assessment, refer to: Olsen, E. A., Whittaker, S., Kim, Y. H., Duvic, M., Prince, H. M., Lessin, S. R., … Vonderheid, E. C. (2011). Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: A consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *Journal of Clinical Oncology, 29*(18), 2598. doi: 10.1200/JCO.2010.32.0630

[3] If intention is for transplant, institutional practice is Bv + CHP

[4] Non-CHOP preferred over CHOP-like regimens; however, overall data is limited to guide optimal therapy

[5] Final results of phase II trial did not benefit when bexarotene was added

[6] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients or if clinically indicated, the SDM should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

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APPENDIX A: Supportive Therapies

- Wound care assessment by Dermatology
- Whirlpool Therapy consultation for extensive wounds
- Infections
  - Swab and culture
  - Topical and oral treatment as indicated
    - Empiric therapy with anti-staphylococcus aureus coverage if erythrodermic
    - Gram negative coverage for tumors
  - Infectious Diseases consult for multi-drug resistant lesions
  - Assess erosions for herpes simplex virus (HSV) and varicella zoster virus (VZV) reactivation
  - For colonization, diluted bleach baths and hibiclens wash at least weekly
- Physical Therapy and Occupational Consult, as indicated
- Puritis: consider gabapentin, pregabalin, antihistamines, and/or mirtazapine
- Supportive Care consult and/or Psychiatry consult, as indicated (*e.g.*, depression, anxiety)

APPENDIX B: Skin-Directed Therapies (SDT)

- Radiation Therapy (See Appendix B: Principles of Radiation Therapy)
- Phototherapy (UVB, NB-UVB for patch/thin plaques; PUVA/UVA1 for thicker plaques)
  - Preferred in widespread lesions
  - Localized therapy if thicker plaques or tumors, followed by radiation
- Topical management
  - First-line: high-potency corticosteroids
  - Second-line: topical mechlorethamine (nitrogen mustard)
  - Third-line: topical imiquimod
  - Less preferred
    - Topical carmustine (concern for toxicity)
    - Topical retinoids (bexarotene, tazarotene) (unfavorable cost:benefit ratio)

APPENDIX C: Principles of Radiation Therapy

- Dosing
  - Patch/plaque disease is typically treated with 4-8Gy in 2-4 fractions
  - Plaque/tumor disease is typically treated with 8-12 Gy in 3-6 fractions
  - Refractory disease resistant to prior radiation therapy courses may require higher dose
  - Treatment is typically delivered with superficial electrons
- Focal versus total skin electron beam therapy (TSEBT)
  - Focal therapy can be given for individual lesions or groups of lesions when TSEBT is not indicated
  - Decision for TSEBT should be made based on multidisciplinary discussion and is typically reserved for patients with higher BSA involvement
  - TSEBT is typically given as 12 Gy delivered over 2-3 weeks. Boost dose is given to shielded areas (*e.g.*, axillae, perianal region, perineum)
  - Patients intended to undergo allogeneic stem cell transplant often receive pre-transplant TSEBT to a dose of 28-32 Gy over 6-8 weeks

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SUGGESTED READINGS

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Continued on next page

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MD Anderson Institutional Policy #CLN1202 - Advance Care Planning Policy
Advance Care Planning (ACP) Conversation Workflow (ATT1925)

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Piekarz, R. L., Frye, R., Turner, M., Wright, J. J., Allen, S. L., Kirschbaum, M. H., … Bates, S. E. (2009). Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *Journal of Clinical Oncology*, *27*(32), 5410-5417. doi: 10.1200/JCO.2008.21.6150

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DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Lymphoma Center Faculty at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

Core Development Team Lead

Auris Huen, MD, PharmD (Dermatology)
Swaminathan P. Iyer, MD (Lymphoma/Myeloma)

Workgroup Members

Luis Malpica Castillo, MD (Lymphoma/Myeloma)
Sheree E. Chen, PharmD (Pharmacy Clinical Programs)
Bouthaina S. Dabaja, MD (Radiation Oncology)
Julia Dai, MD (Dermatology)
Bryan Do, PharmD (Pharmacy Clinical Programs)
Madeleine Duvic, MD (Dermatology)
Olga N. Fleckenstein, BS♦
Chistopher Flowers, MD (Lymphoma/Myeloma)
Chistopher Flowers, MD (Lymphoma/Myeloma)
Jillian Gunther, MD (Radiation Oncology)
Chitra Hosing, MD (Stem Cell Transplantation)
Hun Lee, MD (Lymphoma/Myeloma)
Ranjit Nair, MD (Lymphoma/Myeloma)
Samer Srour, MBCHB (Stem Cell Transplantation)
Francisco Vega, MD, PhD (Hematopathology Administration)
Mary Lou Warren, DNP, APRN, CNS-CC♦

♦ Clinical Effectiveness Development Team