### NCCN Guidelines™ Version 4.2011 Panel Members

#### Non-Hodgkin’s Lymphomas

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### NCCN Guidelines Panel Disclosures

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

Classification and Staging (ST-1)

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Summary of the changes in the 4.2011 version of the Non-Hodgkin's Lymphoma guidelines from the 3.2011 version include:

**TCEL-B**

- "Brentuximab vedotin for nodal ALCL only (excluding cutaneous ALCL)" was added as a suggested treatment regimen for second-line therapy.

Summary of the changes in the 3.2011 version of the Non-Hodgkin's Lymphoma guidelines from the 2.2011 version include:

**MS-1**

- The following sections of the Discussion were updated to reflect the changes to the algorithm:
  - Lymphoblastic lymphoma
  - Primary cutaneous B-cell lymphoma
  - Peripheral T-cell lymphoma

**FOLL-B 1 of 3**

- Footnote "f" was modified by adding, “Updates as of 2010 suggest a trend towards an increased risk of MDS with RIT treatment”.

**MANT-A 1 of 3**

- Footnote b, “These regimens include first-line consolidation with high dose therapy and autologous stem cell rescue (HDT/ASCR)” is new to the page.

**MFSS-A 1 of 4**

- Footnote g, “Patients with large cell transformed (LCT) MF and stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. In general, agents listed in SYST-CAT C are preferred in these circumstances” is new to the page.

**NKTL-2**

- Induction therapy,
  - “Combined modality therapy with 50 Gy RT” was changed to “Concurrent chemoradiotherapy”. (Also for NKTL-B)
  - Stage I, no risk factors present, “clinical trial” was added as an option and the “RT alone” dose was changed from 54 Gy to ≥ 50 Gy.

**NKTL-3**

- Post RT response assessment, stage I with or without risk factors, additional therapy, for both PR and refractory disease, “candidate for transplant and non candidate for transplant” were removed.
  - For PR, the therapy was changed to “Hematopoietic stem cell transplant, if eligible”.
  - For refractory disease, the therapy was changed to “salvage chemotherapy or best supportive care” and after salvage chemotherapy, “Hematopoietic stem cell transplant, if eligible”.

**NKTL-B**

- Suggested treatment regimens, “or in sequence with chemotherapy” was added to “radiotherapy alone” and recommended tumor dose was changed from 54 Gy to ≥ 50 Gy.

**PTLD-2**

- Polymorphic, systemic disease, “rituximab” was added as a primary treatment option.

Continued on next page
Updates to the 1.2011 version of the Non-Hodgkin’s Lymphoma guidelines from the 1.2010 version include:

New Guidelines

**NKTL-1**
- Extramedullary NK/T-cell Lymphoma, nasal type is a new guideline.

**PTLD-1**
- Post-transplant lymphoproliferative disorders is a new guideline.

**Principles of Radiation Therapy**
- Principles of radiation therapy is new to the guidelines and links to this page were added throughout the guidelines.

**Global change**
- Clinical follow-up was modified as “Clinical follow-up every 3-6 mo for 5 y then yearly or as clinically indicated” throughout the guidelines.
- Workup sections, “MUGA scan/echocardiogram” was modified by adding “if anthracycline or anthracenediones-based regimen is indicated” which was previously in a footnote.

**Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**
- A new algorithm for CLL with deletion of 11q on  **CSLL-D 3 of 5** and the corresponding suggested regimens on  **CSLL-D 3 of 5** were added.

**CSLL-1**
- Diagnosis, the section title “informative for prognostic determination” was modified as “informative for prognostic and/or therapy determination”.

**CSLL-2**
- Workup, Hepatitis B testing bullet was modified as “if CD20 monoclonal antibody contemplated.”
- Workup, “PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter’s transformation is suspected” was added.

**CSLL-3**
- Evaluate for indications for treatment, “Progressive” was added to bulky disease.
- Footnote ‘j’ was modified by adding “... unless above 200-300 x 10^9/L or symptoms related to leukostatis.” Also for  **CSLL-5**.
- Footnote ‘m’ was modified by adding “... FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] is necessary to direct treatment.”
- Footnote n, “In addition to the regimens listed in BECEL-C, R-HyperCVAD has also been used in this setting” is new to the page.

**CSLL-4**
- CLL without a deletion 11q was added to the page.
- Age ≥ 70 y, “or younger patients with co-morbidities” was added as a qualifier.
- Footnotes ‘o’ and ‘p’ are new to the page.

**CSLL-5**
- Moved statement from footnote to a subbullet of clinical trial, “17p deletion is associated with low response rates with all treatments and there is no standard treatment, clinical trial is recommended”.
- Footnote r, “Patients with low positivity should be retested due to chance of false positive results” is new to the page.

**CSLL-6**
- Footnote b, “IGHV rearrangements involving VH3-21 carry a poor prognosis even if mutated” is new to the page.
- Percentages were added to outcome association for flow cytometry.

**CSLL-C**
- Sinopulmonary was added to recurrent infections.
- Recurrent sinopulmonary infections, 2nd subbullet was modified to “... nadir level of approximately 500 mg/dl”.
- Antiinfective prophylaxis, alemtuzumab subbullet was modified by adding, “Clinicians must be aware of the high risk of CMV reactivation. The current appropriate management is ... be measured by PCR quantitation at least every 2-3 wks. Consultation with an Infectious Disease expert may be necessary.”
- Autoimmune cytopenia, PRCA, “and bone marrow evaluation” was added.
- Vaccination, pneumococcal vaccine was modified by adding “Prevnar preferred”.
- Blood product support, “irradiate all blood products” was modified by adding “to avoid transfusion associated GVHD”.

**CSLL-D 1 of 5**
- CLL without del (11q) or del (17p)
  - First-line therapy, age ≥ 70 y or younger patients with co-morbidities
    - Vincristine was removed from combination with CP ± rituximab.
    - “+ rituximab” was added to bendamustine.
    - Cladribine was added.
  - First-line therapy, age < 70 y or older patients without significant co-morbidities
    - Bendamustine + rituximab was added.
    - “Alemtuzumab, chlorambucil, bendamustine, fludarabine” as monotherapies were removed.
  - Relapsed/refractory therapy, short response < 2 y for age ≥ 70 y:
    - Chlorambucil ± prednisone, “if used first-line” was added as a qualifier.
    - Alemtuzumab ± rituximab was added.

Continued on next page
Updates to the 1.2011 version of the Non-Hodgkin’s Lymphoma guidelines from the 1.2010 version include:

### Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (cont)

- **CSLL-D 2 of 5**
  - CLL with del (17p)
    - First-line therapy
      - “± rituximab” was added to alemtuzumab and ‘rituximab” was added to bendamustine.
    - Relapsed/refractory therapy
      - “± rituximab” was added to bendamustine and high-dose dexamethasone and corresponding footnote f, “Rituximab should be added unless patient is known to be refractory to rituximab” was added.
      - Footnote f, “This is not effective in patients with lymph nodes > 5 cm” was added to ofatumumab.

### Follicular Lymphoma

- **FOLL-1**
  - Diagnosis, useful under certain circumstances, “Paraffin section immunohistochemistry: Ki67” and corresponding footnote f, “There are reports showing Ki67 proliferation fraction of > 30 % may be associated with a more aggressive clinical behavior but no evidence this should guide treatment decisions” were added.

- **FOLL-2**
  - Stage I, II locoregional RT (preferred) was modified as “IFRT (preferred for clinical stage I or contiguous stage II)”. Bulky Stage II or abdominal disease was modified as “Stage IIX”.
  - Footnote q, “Consider clinical trials appropriate for patients on observation” is new to the page.

- **FOLL-B 1 of 3**
  - First-line therapy, “bendamustine + rituximab” the category was changed from a category 2A to a category 1 designation.
  - First-line therapy for elderly or infirm, “± rituximab” was added to single agent alkylators.
  - First-line consolidation or extended dosing, “rituximab maintenance” the category designation was changed from category 2B to a category 1 and “up to 2 y” was added as a qualifier.
  - “High dose therapy with autologous stem cell rescue” and “allo geneic stem cell transplant for highly selected patients” and “rituximab maintenance” were added to a new section titled “Second-line Consolidation or Extended Dosing”.

### Gastric MALT Lymphoma

- **MALT-1**
  - Workup
    - “Endoscopic ultrasound (if available)” was moved to essential with endoscopy.
    - “SPEP” was added to useful under certain circumstances. (Also for NGMLT-1)

- **MALT-2**
  - For Stage I_{E2} or Stage II_{E}, initial therapy of currently accepted antibiotic therapy for H. pylori followed by evaluation for H. pylori eradication with endoscopy was added.
  - Footnote h, “Involvement of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. If there is persistent disease after evaluation, RT may be considered earlier in the course” is new to the page.

- **MALT-3**
  - For Stage I_{E2} or Stage II_{E} early RT should be considered if there is no response to antibiotics” is new to the page.

- **MALT-4**
  - Restage after RT was changed from 3 mo to 3-6 mo.
  - For lymphoma positive and H. Pylori negative or positive, “locoregional RT, if not previously treated” was removed and directed to follicular lymphoma.

### Nongastric MALT lymphoma

- **NGMLT-1**
  - Workup, useful in selected cases, “SPEP” was added. Also for NODE-1.

### Nodal Marginal Zone Lymphoma

- **NODE-1**
  - Diagnosis, the section title “useful under certain circumstances” was modified by adding “for clarification of diagnosis”.

Continued on next page
Updates to the 1.2011 version of the Non-Hodgkin’s Lymphoma guidelines from the 1.2010 version include:

**Splenic Marginal Zone Lymphoma**

**SPLN-1**
- Diagnosis, essential, “peripheral blood, bone marrow, or tissue” was added to “cell surface marker analysis by flow cytometry”.
- Footnote ‘a’ is new to the page.
- Workup, useful in selected cases, “direct Coombs test” was added.

**SPLN-2**
- Hepatitis C, “assess” was added as a first decision in management and if no symptoms, then “observe” was added.
- Footnote, “Splenectomy is preferred in patients who are able to tolerate it” was removed and footnote e, “Vaccination should be performed at least 2 weeks before splenectomy” was added to the page.

**Mantle Cell Lymphoma**

**MANT-1**
- Footnote c, “Ki67 proliferation fraction of < 30% is associated with a more favorable prognosis. However, it is not used to guide treatment” is new to the page.
- Footnote ‘e’ was modified by adding, “essential for confirmation of stage I- II diseaseae”.
- Footnote ‘i’ is a new reference.

**MANT-A 1 of 3**
- Induction therapy,
  - Aggressive therapy, “CALGB regimen (rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone])” and “Sequential RCHOP/RICE (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (rituximab, ifosfamide, carboplatin, etoposide)” were added as treatment options.
  - Less aggressive therapy,
    - “CVP ± rituximab” was added as an option.
    - Cladribine was changed from “± rituximab” to “+ rituximab”.
- Second-line therapy
  - “± rituximab” was added to lenalidomide.
  - Cladribine was changed from “± rituximab” to “+ rituximab”.
  - “Temsirolimus” and “thalidomide + rituximab” were removed.

**Diffuse Large B-Cell Lymphoma**

**BCEL-1**
- Subtypes included with DLBCL were added:
  - Intravascular large B-cell lymphoma
  - DLBCL associated with chronic inflammation
  - ALK positive DLBCL
  - EBV positive DLBCL of the elderly
  - T-cell/histiocyte rich large B-cell lymphoma
- Subtypes not included with DLBCL were added:
  - Primary DLBCL of the CNS

**BCEL-3**
- Stage I - IV, “RCHOP 6 or 8 cycles” was revised to “RCHOP 6 cycles”. Also for follow-up on BCEL-5.
- Stage I, II, “locoregional RT” was changed to “RT”.
- Stage II, IV, “preferred” was removed from “clinical trial”.
- Footnote ‘k’ was modified by adding, “See AIDS-2 for HIV-positive DLBCL.”

**BCEL-4**
- Partial response, “± RT pre- or post-transplant” was added to “High dose therapy with autologous stem cell rescue” and “Clinical trial (may include allogeneic stem cell transplant).”
- For completion of planned course of treatment after a complete response, the algorithm has been directed to “clinical followup every 3-6 mo…” rather than “end of treatment restaging.”

**BCEL-5**
- For stage III, IV, interim restaging was changed from “after 3-4 cycles” to “after 2-4 cycles”.
- After completion of treatment with a complete response, “Observation (preferred)” and “For high risk patients, high dose therapy can be considered (category 2B)” were added as further options.

**BCEL-C 1 of 3**
- First-line therapy for patients with poor left ventricular function, “RCEOP” was added as a treatment option.
- Second-line therapy “for candidates for high dose therapy with autologous stem cell rescue” was clarified as “For patients with intention to proceed to high dose autologous stem cell rescue.”
- Second-line therapy for patients who are non-candidates for high dose therapy,
  - “CEOP ± rituximab” and “GDP ± rituximab” and “GemOx ± rituximab” were added.
  - “± rituximab” was added to lenalidomide.
- Footnote ‘e’ is new to the page.

Continued on next page
Updates to the 1.2011 version of the Non-Hodgkin's Lymphoma guidelines from the 1.2010 version include:

**Burkitt Lymphoma**

**BURK-1**
- Diagnosis, useful under certain circumstances, for additional immunohistochemical studies to establish lymphoma subtype, “Frozen: kappa/lambda” and “Paraffin panel: TdT; kappa/lambda” were removed.
- Workup, “flow cytometry of cerebrospinal fluid” was moved from useful under certain circumstances to essential. (Also for BLAST-1)

**BURK-2**
- “Second line chemotherapy followed by high dose chemotherapy with HSCT in selected patients” was added as a treatment option for relapse after consolidation in a clinical trial for the high risk category.
- “Second line therapy options for relapse for select patients with reasonable remission” was added with the following regimens:
  - Dose-adjusted EPOCH
  - R-IVAC if have not received previously
  - RGDP
  - HDAC

**AIDS-Related B-cell lymphoma**

**AIDS-1**
- Workup, “stool guaiac, if anemic” was removed.

**AIDS-2**
- Statement regarding antiretrovirals was added, “Antiretrovirals can be administered safely with chemotherapy, however some regimens have recommended discontinuation. Any change in antiviral therapy should be done in consultation with infectious disease specialist.” (Also for AIDS-3)
- For lymphoma-associated with Castleman's disease, DLBCL, and primary effusion lymphoma, “For DLBCL relapse, see BCEL-6” was added.

**AIDS-3**
- For primary CNS lymphoma, “For select patients with good performance status and on HAART, see NCCN CNS Guidelines- Primary CNS Lymphoma” was added.
- Footnote g, “Management can also apply to HIV negative plasmablastic lymphoma” was added to the page.

**Primary Cutaneous B-Cell Lymphoma**

**CUTB-1**
- “Locoregional RT” was clarified as “local RT” in the primary cutaneous B-cell lymphoma guidelines.
- Diagnosis, useful under certain circumstances, “Assessment of surface IgM and IgD expression (to further help in distinguishing DLBCL, leg type from FCL)” was added.
- Statement was added, “NOTE: A germinatal (or follicle) center phenotype and large cells in a skin lesion is NOT equivalent to DLBCL but is consistent with primary cutaneous germinatal/follicle center lymphoma.”
- Workup, peripheral blood flow cytometry, “if CBC demonstrates lymphocytosis” was added.
- Footnote 'c' with the typical immunophenotype was added.
- Footnote 'd' was modified, “Rule out drug-induced cutaneous lymphoid hyperplasia”.

**CUTB-2**
- Solitary/regional, initial therapy, “preferred” was added to local RT.
- Generalized disease, initial therapy:
  - “intralesional steroids” was added. Also for CUTB-3.
  - palliative chemotherapy, ± rituximab was added to “chlorambucil”.
  - Also for CUTB-3.
- Footnote j, was modified by adding “There are case reports showing efficacy of topicals which include...”. Also for CUTB-4.

**CUTB-4**
- For solitary/regional and generalized disease with a complete response after initial therapy, “observe” was added until relapse.
- Solitary/regional, secondary therapy, “local RT” was modified by adding “to previously unirradiated tumor”.

Continued on next page
Updates to the 1.2011 version of the Non-Hodgkin’s Lymphoma guidelines from the 1.2010 version include:

Peripheral T-Cell Lymphomas

**TCEL-1**
- Diagnosis, useful under certain circumstances: “PD1” and “βF1 and CD279” were added.

**TCEL-3**
- Induction therapy for “ALCL, ALK positive” subtype was added.

**TCEL-4**
- Partial response, follow-up therapy, “± RT” was added to “high dose therapy with stem cell transplant” and “clinical trial (may include allogeneic stem cell transplant”).

**TCEL-B 1 of 2**
- First-line therapy, the following list of “Other regimens that can be used” were added:
  - CHOEP
  - CHOP every 2 or 3 wks
  - CHOP followed by ICE
  - CHOP followed by IVE
  - HyperCVAD alternating with high-dose methotrexate and cytarabine
- Footnote b, “Standard induction for PTCL remains undefined with the exception of ALCL, ALK + for which CHOP remains the standard. Clinical trial is preferred for all other subtypes” is new to the page.
- Footnote c, “In AITL, pralatrexate has limited activity” is new to the page.
- Footnote e, “With close follow-up of renal function” is new to the page.

Mycosis Fungoides/Sezary Syndrome

**MFSS-1**
- Workup, useful in selected cases: “Rebiopsy if suspicious of large cell transformation” was added.
- Workup, essential, “chest x-ray” was removed from imaging studies.
- Footnote ‘a’ was modified by adding “clinically or histologically non-diagnostic cases”.
- Footnote ‘c’ was modified by adding “demonstration of identical clones in skin, blood and/or lymph node may be helpful in selected cases”.

**MFSS-2**
- Footnote ‘g’ was modified as “…defined as a clonal rearrangement of the TCR in the blood (clones should be relevant in clone in the skin) and either 1000/mcL or increased CD4 or CD3 cells with CD4/CD8 of 10 or more or increase in CD4 cells with an abnormal phenotype (40% CD4/CD7 or 30% CD4/CD26).”

**MFSS-4**
- Stage IA, for primary treatment, “If B1 blood involvement, consider primary treatment for Stage IIIB B1 (category 2B)” was added. Also for IB-IIA on MFSS-5.

**MFSS-6**
- “and/or histologic evidence of folliculotropucr or large cell transformation (LCT)” was added with “stage IIB.”
- Limited extent tumor, primary treatment with local RT for limited extent tumor, transformed, and/or folliculotropic disease, “± skin-directed therapies” was removed and “± skin-directed therapies” was added to “systemic therapies ± RT”.
- Footnotes s, “Rebiopsy if suspect large cell transformation” is new to the page.
- Footnote t, “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 category A or B are appropriate. If aggressive growth is seen, then agents listed in category C (SYST-CAT C) are preferred” is new to the page.
- Footnote u, “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” is new to the page. Also for MFSS-7 and MFSS-8.

**MFSS-7**
- Footnote cc, “Alemtuzumab can be administered by IV or subcutaneously. Lower doses administered subcutaneously have shown lower incidence of infectious complications” is new to the page. Also for MFSS-8.

**MFSS-8**
- For primary treatment of non sezary or visceral disease, a link to the new category C treatment options for systemic therapies was added.

**MFSS-A 1 of 3**
- Systemic therapies, a new group titled “Category C” was added with corresponding footnote g, “Combination regimens are generally reserved for patients with relapsed/refractory or extracutaneous disease.”
Updates to the 1.2011 version of the Non-Hodgkin’s Lymphoma guidelines from the 1.2010 version include:

**Adult T-cell Leukemia/Lymphoma**

**ATLL-1**
- Diagnosis, useful under certain circumstances, “Molecular analysis HTLV-1 clonal integration is encouraged in all cases of mature T-cell lymphoma/leukemia in HTLV-1 seropositive individuals: Southern blot or inverse PCR” was removed.

**ATLL-2**
- Chronic/smoldering subtype, after persistent or progressive disease “discontinue treatment” was removed and “clinical trial or best supportive care” were added as additional treatment options.

**ATLL-3**
- Acute subtype, after complete response “consider allogeneic stem cell transplant” was added as an additional treatment option.
- Both acute and lymphoma subtypes, after persistent or progressive disease “best supportive care” was added as an additional treatment option.

**Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms**

**NHODG-A**
- Footnote c, “Rare cases of both cyclin D1 and t(11;14) negative MCL have been reported. This diagnosis should be made with extreme caution and with expert consultation” was added.

**Tumor Lysis Syndrome**

**NHODG-B**
- High risk features for tumor lysis syndrome were added.
- Indications for rasburicase use were added.
DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor, if the diagnosis was made on a lymph node or bone marrow biopsy. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IGHV and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis. This is particularly true for the diagnosis of CLL/SLL.
- Flow cytometry of blood adequate for diagnosis of CLL/SLL (biopsy not required).

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:

- Adequate immunophenotyping to establish diagnosis
  - Recommended panel for paraffin section immunohistochemistry: CD3, CD5, CD10, CD20, CD23, cyclin D1
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
  - Absolute monoclonal B lymphocyte count

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

- Cytogenetics and/or FISH to detect: t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)
- Molecular genetic analysis to detect: immunoglobulin heavy chain variable gene (IGHV) mutation status
- Determination of CD38 and Zap 70 expression by flow cytometry or immunohistochemistry

Evaluation of ZAP 70 expression can be challenging and ZAP 70 is not recommended outside the setting of a clinical trial.

See Prognostic Information for CLL (CSLL-A).

- Absolute monoclonal B lymphocyte count < 5000/mm^3
  - All lymph nodes < 1.5 cm
  - No anemia
  - No thrombocytopenia

Observe

- Monoclonal B lymphocytosis (MBL)
  - Absolute monoclonal B lymphocyte count < 5000/mm^3
  - All lymph nodes < 1.5 cm
  - No anemia
  - No thrombocytopenia

Observe

- CLL/SLL

See Workup for CLL/SLL (CSLL-2)

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.

a CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma. Cases diagnosed as B-PLL are excluded from this guideline.
b Typical immunophenotype: CD5+, CD23+, CD43+/−, CD10−, CD19+, CD20 dim, sIg dim+ and cyclin D1+. Note: Some cases may be sIg bright+, CD23- or dim and some MCL may be CD23++; cyclin D1 immunohistochemistry or FISH for t(11;14) should be considered in all cases and should be done in cases with an atypical immunophenotype (CD23 dim or negative, CD20 bright, sIg bright).

c See Use of Immunophenotyping and Genetic Testing in Differential Diagnosis of Mature B-cell and T/NK-cell Neoplasms (NHODG-A).
d Absolute monoclonal B lymphocyte count < 5000/mm^3 in the absence of adenopathy or other clinical features of lymphoproliferative disorder is monoclonal B lymphocytosis (MBL).
e See Prognostic Information for CLL (CSLL-A).
f Evaluation of ZAP 70 expression can be challenging and ZAP 70 is not recommended outside the setting of a clinical trial.
WORKUP

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Hepatitis B testing if CD20 monoclonal antibody contemplated
- MUGA scan/echocardiogram if anthracycline or anthracenediones-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Quantitative immunoglobulins
- Reticulocyte count, haptoglobin, and direct Coombs’ test
- Chest/abdominal/pelvic CT should be done prior to initiation of therapy (particularly when peripheral adenopathy is present and symptoms suggest bulky lymph nodes)
- Beta-2-microglobulin
- Uric acid
- Unilateral bone marrow biopsy (± aspirate) at initiation of therapy
- Discussion of fertility issues and sperm banking
- PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected

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.

9Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
NCCN Guidelines™ Version 4.2011
CLL/SLL

PRESENTATION

SLL/Localized (Ann Arbor Stage I)\(^h\) → Locoregional RT (if indicated) → Observe

Evaluate for indications for treatment:\(^j\)

- Eligible for clinical trial\(^k\)
- Significant disease-related symptoms:
  - Fatigue (severe)
  - Night sweats
  - Weight loss
  - Fever without infection
- Threatened end-organ function
- Progressive bulky disease
  - (spleen > 6 cm below costal margin, lymph nodes > 10 cm)
  - Lymphocyte doubling time (LDT) ≤ 6 mo
- Progressive anemia
- Progressive thrombocytopenia\(^l\)

No indication

\(\text{SLL} \rightarrow \text{CLL} \rightarrow \text{Rai Low (0)}\) and Intermediate (I-II) risk\(^i\)

\(\text{CLL} \rightarrow \text{Rai High (III-IV)}\) Risk\(^i\)

Indication present

- Evaluate FISH\(^m\)
- Imaging as appropriate

\(\text{CLL Without Deletion of 11q or 17p (See CSLL-4)}\)

\(\text{CLL With Deletion of 17p (See CSLL-5)}\)

\(\text{CLL With Deletion of 11q (See CSLL-6)}\)

Histologic transformation to diffuse large-cell/ Hodgkin lymphoma → Manage as aggressive lymphoma (See BCEL-C)\(^n\) → Consider allogeneic stem cell transplant (See BCEL-C)

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.

\(^h\) See Supportive Care For Patients With CLL (CSLL-C).
\(^i\) See Rai and Binet Classification Systems (CSLL-B).
\(^j\) Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10^9/L or symptoms related to leukostatis.
\(^k\) Given incurability with conventional therapy, consider a clinical trial as first line of treatment.
\(^l\) Platelet counts >100,000 cells/mm\(^3\) are typically not associated with clinical risk.
\(^m\) Re-evaluation of FISH \([t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)]\) is necessary to direct treatment.
\(^n\) In addition to the regimens listed in BCEL-C, R-HyperCVAD has also been used in this setting.
CLL WITHOUT DELETION OF 11q or 17p

Frail patient, significant co-morbidity\(^o\) (not able to tolerate purine analogs)

Age \(\geq 70\) y or younger patients with co-morbidities\(^o\)

Age < 70 y or older without significant co-morbidities\(^o\)

FIRST-LINE THERAPY

- See Suggested Regimens (CSLL-D 1 of 5)

RESPONSE TO THERAPY\(^p\)

- See Suggested Regimens\(^q\) (CSLL-D 1 of 5)

- Long response > 3 y, repeat FISH, if del (17p) see CSLL-5, or del (11q) see CSLL-6

- Short response < 2 y, repeat FISH, if del (17p) see CSLL-5, or del (11q) see CSLL-6

- Long response > 3 y, repeat FISH, if del (17p) see CSLL-5, or del (11q) see CSLL-6

- Short response < 2 y, repeat FISH, if del (17p) see CSLL-5, or del (11q) see CSLL-6

- See Suggested Regimens (CSLL-D 1 of 5) (relapsed/refractory therapy)

- Retreat with first-line therapy until a short response

- Consider allogeneic stem cell transplant, if without significant co-morbidities\(^p\)

- Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

- Consider risk for CMV reactivation (See CSLL-C)

- Allogeneic stem cell transplant
CLL WITH DELETION OF 17p

FIRST-LINE THERAPY

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

Consider risk for CMV reactivation (See CSLL-C)

• Clinical trial
  ▶ 17p deletion is associated with low response rates with all treatments and there is no standard treatment, clinical trial is recommended.
  • See Suggested Regimens (CSLL-D 2 of 5)

RESPONSE TO THERAPY

CR/PRs

CRs

Observe or Clinical trial

Observe or Clinical trial

Allogeneic stem cell transplant

PRs

Non-candidate for transplant

Candidate for transplant

No response

No response

Clinical trial or Relapsed/refractory therapy (See Suggested Regimens CSLL-D 2 of 5)

CLL with del (17p)h,j,r

Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10^9/L or symptoms related to leukostasis.

Patients with low positivity should be retested due to chance of false positive results.

See Supportive Care For Patients With CLL (CSLL-C).

See Response Criteria: CLL (CSLL-E) or SLL (NHODG-C).

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.
**CLL WITH DELETION OF 11q**

### FIRST-LINE THERAPY

- **Consider prophylaxis for tumor lysis syndrome** (See NHODG-B)
- **Consider risk for CMV reactivation** (See CSLL-C)

### OUTCOMES

- **Outcomes are more favorable in patients with 11q deletion who receive regimens containing an alkylator.**

### RESPONSE TO THERAPY

- **CR**
  - Candidate for transplant
  - Consider allogeneic stem cell transplant

- **PR**
  - Non-candidate for transplant
  - Disease progression
  - Observe or Clinical trial

- **No response**
  - Observe or Clinical trial
  - See Suggested Regimens (CSLL-D 3 of 5)

- **CR**
  - Observe or Clinical trial

- **PR**
  - Observe or Clinical trial
  - See Suggested Regimens (CSLL-D 3 of 5)

### CLINICAL TRIAL

- **Consider allogeneic stem cell transplant**
- **Candidate for transplant**

### OBSERVATION OR CLINICAL TRIAL

- **Observe or Clinical trial**

### CANDIDATE FOR TRANSPLANT

- **No transplant**

### NON-CANDIDATE FOR TRANSPLANT

- **Disease progression**
- **Observe or Clinical trial**

### RELAPSED/REFRACTORY

- **Clinical trial or Relapsed/refractory therapy** (See Suggested Regimens CSLL-D 3 of 5)

### RESPONSE CRITERIA

- **CR**
- **PR**

### SUPPORTIVE CARE

- **See Supportive Care For Patients With CLL (CSLL-C).**

### CMV REACTIVATION

- **See Risk for CMV Reactivation (CSLL-C).**

### LYSIS SYNDROME

- **See Tumor Lysis Syndrome (CSLL-D 3 of 5).**

### ALKYLATOR

- **See Response Criteria: CLL (CSLL-E) or SLL (NHODG-C).**

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

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---

**h** See Supportive Care For Patients With CLL (CSLL-C).

**j** Absolute lymphocyte count alone is not an indication for treatment unless above 200-300 x 10^9/L or symptoms related to leukostasis.

**s** See Response Criteria: CLL (CSLL-E) or SLL (NHODG-C).
PROGNOSTIC INFORMATION FOR CLL\textsuperscript{a}

Immunoglobulin Variable Region (IGHV) Gene Mutation and Surrogates by Flow Cytometry

<table>
<thead>
<tr>
<th>Outcome Association</th>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA sequencing\textsuperscript{b}</td>
<td>&gt; 2% mutation</td>
<td>≤ 2% mutation</td>
</tr>
<tr>
<td>IGHV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow Cytometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD38</td>
<td>&lt; 30 %</td>
<td>≥ 30 %</td>
</tr>
<tr>
<td>Zap 70</td>
<td>&lt; 20 %</td>
<td>≥ 20 %</td>
</tr>
</tbody>
</table>

Interphase Cytogenetics (FISH)\textsuperscript{c}

<table>
<thead>
<tr>
<th>Unfavorable</th>
<th>Neutral</th>
<th>Favorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(11q) del(17p)</td>
<td>Normal +12</td>
<td>del(13q) (as a sole abnormality)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}This table provides useful prognostic information relative to the time to progression where therapy is required and survival. The presence of del(11q) and/or del(17p) are associated with short progression free survival to chemotherapy and chemoimmunotherapy approaches. Alemtuzumab or high dose steroids have anecdotal response in del(17p) disease.

\textsuperscript{b}IGHV rearrangements involving VH3-21 carry a poor prognosis even if mutated.

\textsuperscript{c}Formal studies identifying the percentage of abnormal cells identified by FISH are ongoing although populations less than 10% appear to not have the clinical impact as noted in the table.

\textsuperscript{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.}
**CLL STAGING SYSTEMS**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Risk Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis, lymphocytes in blood &gt; 15,000/mcL and &gt; 40% lymphocytes in the bone marrow</td>
<td>Low</td>
</tr>
<tr>
<td>I</td>
<td>Stage 0 with enlarged node(s)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>II</td>
<td>Stage 0-I with splenomegaly, hepatomegaly, or both</td>
<td>Intermediate</td>
</tr>
<tr>
<td>IIIc</td>
<td>Stage 0-II with hemoglobin &lt; 11.0 g/dL or hematocrit &lt; 33%</td>
<td>High</td>
</tr>
<tr>
<td>IVc</td>
<td>Stage 0-III with platelets &lt; 100,000/mcL</td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hemoglobin ≥ 10 g/dL and Platelets ≥ 100,000/mm³ and &lt; 3 enlarged areas</td>
</tr>
<tr>
<td>B</td>
<td>Hemoglobin ≥ 10 g/dL and Platelets ≥ 100,000/mm³ and ≥ 3 enlarged areas</td>
</tr>
<tr>
<td>Cc</td>
<td>Hemoglobin &lt; 10 g/dL and/or Platelets &lt; 100,000/mm³ and any number of enlarged areas</td>
</tr>
</tbody>
</table>

---

**Rai System**


**Binet System**


Immune-mediated cytopenias are not the basis for these stage definitions.

---

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

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**SUPPORTIVE CARE FOR PATIENTS WITH CLL**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Recurrent Sinopulmonary Infections** (requiring IV antibiotics or hospitalization) | • Antimicrobials as appropriate  
• Evaluate serum IgG, if < 500 mg/dl  
  ➤ begin monthly IVIG 0.3-0.5 g/kg,  
  ➤ adjust dose/interval to maintain nadir level of approximately 500 mg/dl |
| **Antiinfective Prophylaxis**                   | • Recommended for patients receiving purine-analog and/or alemtuzumab during treatment and thereafter, if tolerated  
  ➤ Herpes virus (acyclovir or equivalent)  
  ➤ PCP (sulfamethoxazole/trimethoprim or equivalent)  
• Alemtuzumab: Clinicians must be aware of the high risk of CMV reactivation. The current appropriate management is controversial, some use ganciclovir (oral or IV) prophylactically if viremia present, others only if viral load is rising. CMV viremia should be measured by PCR quantitation at least every 2-3 wks. Consultation with an Infectious Disease expert may be necessary. |
| **Autoimmune Cytopenias**                       | • Auto-immune hemolytic anemia (AIHA): Diagnosis with reticulocyte count, haptoglobin, DAT  
  ➤ AIHA that develops in setting of treatment with fludarabine, stop, treat, and avoid subsequent fludarabine  
• Immune thrombocytopenia purpura (ITP): Evaluate bone marrow for cause of low PLT  
• Pure red blood cell aplasia (PRCA): Evaluate for parvo B19 and bone marrow evaluation  
• Treatment: Corticosteroids; rituximab; IVIG; cyclosporin A; splenectomy; eltrombopag or romiplostim (ITP) |
| **Vaccination**                                  | • Annual Influenza vaccine\(^a\)  
• Pneumococcal vaccine (Prevnar preferred) every 5 yrs  
• Avoid all live vaccines, including Zoster |
| **Blood Product Support**                       | • Transfuse according to institutional or published standards  
• Irradiate all blood products to avoid transfusion associated GVHD |

\(^a\)In patients who have received rituximab, B-cell recovery occurs by approximately 9 months. Prior to B-cell recovery, patients generally do not respond to influenza vaccine and if given should not be considered vaccinated.

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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.
### SUGGESTED TREATMENT REGIMENS

#### (in order of preference)

<table>
<thead>
<tr>
<th>Frail patient, significant co-morbidity (not able to tolerate purine analogs)</th>
<th>First-line therapy</th>
<th>Relapsed/Refractory therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chlorambucil ± prednisone</td>
<td>• Age ≥ 70 y or younger patients with co-morbidities</td>
<td>• Long response &gt; 3 y</td>
</tr>
<tr>
<td>• Rituximab (single)</td>
<td>• Chlorambucil ± prednisone</td>
<td>▶ Retreat as in first line therapy until short response</td>
</tr>
<tr>
<td>• Pulse corticosteroids</td>
<td>• BR (bendamustine, rituximab)</td>
<td>• Short response &lt; 2 y for age ≥ 70 y</td>
</tr>
<tr>
<td></td>
<td>• Cyclophosphamide, prednisone ± rituximab</td>
<td>▶ Chemoimmunotherapy</td>
</tr>
<tr>
<td></td>
<td>• Alemtuzumab</td>
<td>▶ Reduced-dose FCR</td>
</tr>
<tr>
<td></td>
<td>• Rituximab</td>
<td>▶ Reduced-dose PCR</td>
</tr>
<tr>
<td></td>
<td>• Fludarabine ± rituximab</td>
<td>▶ Bendamustine ± rituximab</td>
</tr>
<tr>
<td></td>
<td>• Cladribine</td>
<td>▶ HDMP (high-dose methylprednisolone) + rituximab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age &lt; 70 y or older patients without significant co-morbidities</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chemoimmunotherapy</td>
<td>• Age &lt; 70 y or older patients without significant co-morbidities</td>
<td></td>
</tr>
<tr>
<td>▶ FCR (fludarabine, cyclophosphamide, rituximab)</td>
<td>▶ Chemoimmunotherapy</td>
<td></td>
</tr>
<tr>
<td>▶ FR (fludarabine, rituximab)</td>
<td>▶ Reduced-dose FCR</td>
<td></td>
</tr>
<tr>
<td>▶ PCR (pentostatin, cyclophosphamide, rituximab)</td>
<td>▶ Reduced-dose PCR</td>
<td></td>
</tr>
<tr>
<td>▶ BR</td>
<td>▶ Bendamustine ± rituximab</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ HDMP (high-dose methylprednisolone) + rituximab</td>
</tr>
</tbody>
</table>

**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.
SUGGESTED TREATMENT REGIMENS
(in order of preference)

**CLL with del (17p)**

- **First-line therapy**
  - FCR (fludarabine, cyclophosphamide, rituximab)
  - FR (fludarabine, rituximab)
  - HDMP (high-dose methylprednisolone) + rituximab
  - Alemtuzumab + rituximab
  - Bendamustine + rituximab

- **Relapsed/Refractory therapy**
  - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
  - CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab)
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
  - OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)
  - Ofatumumab
  - Alemtuzumab ± rituximab
  - High-dose dexamethasone ± rituximab
  - Bendamustine ± rituximab

---

*See references for regimens CSL-D 4 of 5 and CSL-D 5 of 5.*

*b* Antibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy.

*c* Less effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.

*d* Monitor for myelosuppression.

*e* Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

*f* This is not effective in patients with lymph nodes > 5 cm.

*g* Rituximab should be added unless patient is known to be refractory to rituximab.

---

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**SUGGESTED TREATMENT REGIMENS**

**(in order of preference)**

**CLL with del (11q)**

**First-line therapy**

- Age ≥ 70 y or younger patients with co-morbidities
  - Chlorambucil ± prednisone
  - BR (bendamustine, rituximab)\(^b\)
  - Cyclophosphamide, prednisone ± rituximab
  - Reduced-dose FCR (fludarabine,\(^c\) cyclophosphamide, rituximab)
  - Alemtuzumab\(^c\)
  - Rituximab

- Age < 70 y or older patients without significant co-morbidities
  - Chemoimmuno therapy\(^d\)
    - FCR
    - BR
    - PCR (pentostatin, cyclophosphamide, rituximab)

**Relapsed/Refractory therapy**

- Long response > 3 y
  - Retreat as in first line therapy until short response

- Short response < 2 y for age ≥ 70 y
  - Chemoimmuno therapy\(^d\)
    - Reduced-dose FCR\(^e\)
    - Reduced-dose PCR
    - Bendamustine ± rituximab
    - HDMP (high-dose methylprednisolone) + rituximab
    - Chlorambucil ± prednisone (if used first line)
  - Ofatumumab
  - Alemtuzumab ± rituximab
  - Dose-dense rituximab (category 2B)

- Short response < 2 y for age < 70 y or older patients without significant co-morbidities
  - Chemoimmuno therapy\(^d\)
    - FCR\(^e\)
    - PCR\(^e\)
    - BR
    - Fludarabine\(^e\) + alemtuzumab
    - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
    - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
    - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
    - OFAR (oxaliplatin, fludarabine,\(^c\) cytarabine, rituximab)
  - Ofatumumab
  - Alemtuzumab ± rituximab
  - HDMP + rituximab

---

**See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)**

**See Suggested Regimens for CLL without del (11q) or del (17p) (1 of 5)**

**See Suggested Regimens for CLL with del (17p) (2 of 5)**

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\(^a\) See references for regimens [CSLL-D 4 of 5](#) and [CSLL-D 5 of 5](#).

\(^b\) Antibiotic prophylactic therapy for shingles and pneumocystis is recommended in purine analog-based and/or alemtuzumab combination therapy.

\(^c\) Less effective for bulky (> 5 cm) lymphadenopathy; monitor for CMV reactivation.

\(^d\) Monitor for myelosuppression.

\(^e\) Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

---

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SUGGESTED TREATMENT REGIMENS

REFERENCES

Alemtuzumab


Alemtuzumab + rituximab

Bendamustine

Bendamustine + rituximab

Chlorambucil


Chlorambucil + prednisone

Cyclophosphamide, Fludarabine, Alemtuzumab, and Rituximab (CFAR)

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)

FCR (fludarabine, cyclophosphamide, rituximab)


SUGGESTED TREATMENT REGIMENS

REFERENCES

Fludarabine + alemtuzumab

Fludarabine + rituximab

HDMP (high-dose methylprednisolone) + rituximab


Ofatumumab


OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)


PCR (pentostatin, cyclophosphamide, rituximab)


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.
## RESPONSE DEFINITION AFTER TREATMENT FOR CLL\(^a\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Progressive Disease</th>
<th>Stable Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy(^b)</td>
<td>None above 1.0 cm</td>
<td>Decrease ≥ 50%</td>
<td>Increase ≥ 50%</td>
<td>Change from -49% to +49%</td>
</tr>
<tr>
<td>Liver and/or spleen size</td>
<td>Normal size</td>
<td>Decrease ≥ 50%</td>
<td>Increase ≥ 50%</td>
<td>Change from -49% to +49%</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>&gt; 1500/mm(^3)</td>
<td>&gt; 1500/mm(^3) or &gt; 50% improvement</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Circulating B lymphocytes</td>
<td>Normal</td>
<td>Decrease ≥ 50% over baseline</td>
<td>Increase ≥ 50%</td>
<td>Change from -49% to +49%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&gt; 100,000/mm(^3)</td>
<td>&gt; 100,000/mm(^3) or increase ≥ 50% over baseline</td>
<td>Decrease ≥ 50% over baseline</td>
<td>Change from -49% to +49%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt; 11.0 g/dL (untransfused)</td>
<td>&gt; 2 g/dL from baseline</td>
<td>Decrease of &gt; 2 g/dL from baseline</td>
<td>Increase &lt; 11.0 g/dL or &lt; 50% over baseline, or decrease &lt; 2 g/dL</td>
</tr>
<tr>
<td>Marrow</td>
<td>Normocellular, &lt; 30% lymphocytes, no B-lymphoid nodules</td>
<td>Hypocellular, or ≥ 30% lymphocytes, or B-lymphoid nodules, or not done</td>
<td>Increase of lymphocytes to more than 30% from normal</td>
<td>No change of marrow infiltrate</td>
</tr>
</tbody>
</table>

\(^a\) Eichhorst B and Hallek M. Revision of the guidelines for diagnosis and therapy of chronic lymphocytic leukemia (CLL). Best Practice & Research Clinical Haematology. 2007;20:469-477.

\(^b\) Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical exam or ultrasound in general practice).

---

**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.
Diagnosis

Essential:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis. Histologic grading cannot be performed on an FNA.
- Adequate immunophenotyping to establish diagnosis.
  - Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD5, CD10, BCL2, BCL6, cyclin D1, CD21 or CD23, or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Useful under certain circumstances:
  - Molecular genetic analysis to detect: antigen gene receptor rearrangements; BCL2 rearrangement
  - Cytogenetics or FISH: t(14;18); t(8;14) or variants
  - Paraffin section immunohistochemistry: Ki67

Follicular lymphoma, grade 1-2. Follicular lymphoma, grade 3 is an area of controversy. The distinction between follicular grade 3a and 3b has not been shown to have clinical significance to date. Follicular lymphoma, grade 3 is commonly treated according to the NCCN Diffuse Large B-Cell Lymphoma Guideline (BCEL-1). Any area of diffuse large B-cell lymphoma (DLBCL) in a follicular lymphoma of any grade should be diagnosed and treated as a DLBCL.

Workup

Essential:
- Physical exam: attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Hepatitis B testing
- Bone marrow biopsy + aspirate to document clinical stage I-II disease
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

Useful in selected cases:
- MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated
- Neck CT
- Beta-2-microglobulin
- PET-CT scan
- Uric acid
- Discussion of fertility issues and sperm banking
- SPEP and/or quantitative immunoglobulin levels
- Hepatitis C testing

There are reports showing Ki67 proliferation fraction of > 30 % may be associated with a more aggressive clinical behavior but no evidence this should guide treatment decisions.

Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

Bilateral or unilateral provided core biopsy is > 2 cm. If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. If observation is initial therapy, bone marrow biopsy may be deferred.

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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.
# NCCN Guidelines™ Version 4.2011
## Follicular Lymphoma (grade 1-2)

### STAGE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I, II</td>
<td>IFRT (preferred for clinical stage I or contiguous stage II) or Immunotherapy + chemotherapy (See FOLL-B) ± RT (category 2B for chemotherapy + RT) or Observation (selected cases)</td>
</tr>
<tr>
<td>Stage II, III, IV</td>
<td>Indications for treatment: Candidate for clinical trial, Symptoms, Threatened end-organ function, Cytopenia secondary to lymphoma, Bulky disease, Steady progression, Patient preference</td>
</tr>
</tbody>
</table>

### Indicators for Treatment
- Complete response or partial response
- Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated
- Progressive disease

### Follow-up
- Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated
- Progressive disease

### 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.
INITIAL RESPONSE

Complete response ³ or partial response ⁴ → Consolidation or extended therapy (See FOLL-B) or Observe → Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated ³ → Progressive disease ³, ⁴ (For transformation see FOLL-4) → Indications for treatment: ⁶
- Candidate for clinical trial
- Symptoms
- Threatened end-organ function
- Cytopenia secondary to lymphoma
- Bulky disease
- Steady progression
- Patient preference

No indication → Observe

No response or progressive disease ³, ⁴ (For transformation see FOLL-4) → Follow-up includes repeat diagnostic tests, including imaging (based on site of disease and clinical presentation) as clinically indicated (about every 6 mo).

Progressive disease should be histologically documented to rule out transformation (preferentially, biopsy or marked increase in FDG uptake on PET), especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, new B symptoms develop, or there is marked heterogeneity or sites of intense FDG avidity on PET scan. A directed biopsy should be performed of a suspicious area. If transformation is histologically confirmed, treat with anthracycline-based therapy. Positive functional imaging does not replace biopsy to diagnose transformation. See Management of Transformation (FOLL-4).

Clinical trials may involve novel agents, regimens, or transplantation.

ADDITIONAL THERAPY

See Principles of Radiation Therapy (NHODG-E).
See GELF criteria (FOLL-A).
See Response Criteria for Lymphoma (NHODG-C).

Follow-up includes repeat diagnostic tests, including imaging (based on site of disease and clinical presentation) as clinically indicated (about every 6 mo).

Progressive disease should be histologically documented to rule out transformation (preferentially, biopsy or marked increase in FDG uptake on PET), especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, new B symptoms develop, or there is marked heterogeneity or sites of intense FDG avidity on PET scan. A directed biopsy should be performed of a suspicious area. If transformation is histologically confirmed, treat with anthracycline-based therapy. Positive functional imaging does not replace biopsy to diagnose transformation. See Management of Transformation (FOLL-4).

Clinical trials may involve novel agents, regimens, or transplantation.

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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.
Histological transformation to diffuse large B-cell lymphoma

**Multiple prior therapies**
- Clinical trial or Radioimmunotherapy or Chemotherapy (See BCEL-C) ± rituximab or IFRT or Best Supportive Care (See NCCN Palliative Care Guidelines)
- Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant

**Minimal or no prior chemotherapy**
- Chemotherapy (anthracycline-based chemotherapy preferred unless contraindicated) (See BCEL-C) + rituximab ± RT
- Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant

- **Responsive disease**
  - Observation or Clinical trial or Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant
  - Consider radioimmunotherapy

- **Complete response**
  - Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant
  - Clinical trial or Consider radioimmunotherapy

- **Partial response**
  - No response or progressive disease
    - Consider high-dose therapy with autologous stem cell rescue or allogeneic stem cell transplant
    - Clinical trial or Consider radioimmunotherapy

- **Observation**
  - Clinical trial or Radioimmunotherapy or Palliative or best supportive care

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†Involved-field RT alone or one course of single agent therapy including rituximab.

‡If locoregional transformation, consider adding RT.

§Strongly recommend this treatment be given in the context of a clinical trial; nonmyeloblative approaches may also be considered.

See Response Criteria for Lymphoma (NHODG-C).
GELF CRITERIA<sup>a,b</sup>

- Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm
- Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L
- Leukemia (> 5.0 x 10^9/L malignant cells)

FLIPI - 1 CRITERIA<sup>a,c</sup>

<table>
<thead>
<tr>
<th>Age</th>
<th>≥ 60 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Arbor stage</td>
<td>III-IV</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>&lt; 12 g/dL</td>
</tr>
<tr>
<td>Serum LDH level</td>
<td>&gt; ULN (upper limit of normal)</td>
</tr>
<tr>
<td>Number of nodal sites</td>
<td>≥ 5</td>
</tr>
</tbody>
</table>

Risk group according to FLIPI chart

<table>
<thead>
<tr>
<th>Number of factors</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-1</td>
<td>2</td>
<td>≥ 3</td>
</tr>
</tbody>
</table>

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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.

<sup>a</sup>This provides useful prognostic information which may be used to guide therapeutic decisions.


<sup>c</sup>This research was originally published in Blood. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258-1265. (c) the American Society of Hematology.

<sup>d</sup>The map is used to determine number of nodal sites in FLIPI-1 criteria and is different than the conventional Ann Arbor site map.
**SUGGESTED TREATMENT REGIMENS**

**(in alphabetical order)**

**First-line Therapy**
- Bendamustine + rituximab (category 1)
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- Fludarabine + rituximab
- RFND (rituximab, fludarabine, mitoxantrone, dexamethasone)
- Radioimmunotherapy (category 2B)
- Rituximab

**First-line Therapy for Elderly or Infirm**
- Radioimmunotherapy
- Rituximab, preferred
- Single agent alkylators ± rituximab (eg, chlorambucil or cyclophosphamide)

For patients with locally bulky or symptomatic disease, consider IFRT 4-30 Gy ± additional systemic therapy.

**First-line Consolidation or Extended Dosing**
- Chemotherapy followed by radioimmunotherapy (category 1)
- Rituximab maintenance up to 2 y (category 1)

**Second-line and Subsequent Therapy**
- Chemoimmunotherapy (as in first-line therapy)
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (category 1)
- Radioimmunotherapy (category 1)
- See Second-line Therapy for DLBCL (BCEL-C 1 of 3)

**Second-line Consolidation or Extended Dosing**
- High dose therapy with autologous stem cell rescue
- Allogeneic stem cell transplant for highly selected patients
- Rituximab maintenance (category 1)

See **Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)**

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**FOLL-B**

**FOLLCULAR LYMPHOMA**

**SUGGESTED TREATMENT REGIMENS**

### First-line therapy

**Bendamustine + rituximab:**

**Cyclophosphamide**

**CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab**

### Cyclophosphamide + doxorubicin, vincristine, prednisone + rituximab

**CVP (cyclophosphamide, vincristine, prednisone) + rituximab**

### Fludarabine + rituximab

**FND (fludarabine, mitoxantrone, dexamethasone) + rituximab**

### Rituximab


### Radioimmunotherapy


### First-line Consolidation or Extended Dosing

**Chemotherapy followed by radioimmunotherapy**


**Chemotherapy followed by rituximab**

Continued on next page
SUGGESTED TREATMENT REGIMENS

References

Second-line therapy

Bendamustine


FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)

Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared to FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas - results of a prospective randomized study of the German low grade lymphoma study group (GLSG). Blood 2004;104:3064-3071.

Radioimmunotherapy


Second-line extended dosing

Rituximab maintenance


Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

- Gastric: See Diagnosis and Workup (MALT-1)
- Nongastric: See Diagnosis and Workup (NGMLT-1)

Nodal marginal zone lymphoma: See Diagnosis and Workup (NODE-1)

Splenic marginal zone lymphoma: See Diagnosis and Workup (SPLN-1)

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**DIAGNOSIS**

**ESSENTIAL:**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.\(^a,b\)
- Diagnosis of Gastric MALT lymphoma requires an endoscopic biopsy and an FNA is never adequate.
- Adequate immunophenotyping to establish diagnosis\(^c,d\)
  - Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1, BCL6 or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Helicobacter Pylori stain (gastric), if positive, then PCR or FISH for t(11;18)\(^e\)

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Molecular genetic analysis to detect: antigen receptor gene rearrangements
- Cytogenetics or FISH: t(1;14), t(14;18), t(3;14)

**WORKUP**

**ESSENTIAL:**
- Physical exam with attention to nongastric sites (eyes, skin)
- Performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- If H. pylori negative by histopathology, then use noninvasive H. pylori testing (stool antigen test, urea breath test, blood antibody test)
- Hepatitis B testing\(^f\) if rituximab contemplated
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Endoscopy with ultrasound (if available) with multiple biopsies of anatomical sites
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

**USEFUL IN SELECTED CASES**
- Bone marrow biopsy ± aspirate
- MUGA scan/echocardiogram if anthracycline or anthracenediones-based regimen is indicated
- Hepatitis C testing
- Discussion of fertility issues and sperm banking
- SPEP

---

\(^a\)Nondiagnostic atypical lymphoid infiltrates that are H. Pylori positive, should be rebiopsied to confirm or exclude lymphoma prior to treatment of H. Pylori.

\(^b\)Any area of DLBCL should be treated according to the NCCN Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1).

\(^c\)Typical immunophenotype: CD10-, CD5-, CD20+, cyclin D1-, BCL2 follicles-.

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

\(^e\)Locally advanced disease is more likely in patients with gastric MALT lymphoma with t(11;18).

\(^f\)Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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**NCCN Guidelines™ Version 4.2011**

**Extranodal Marginal Zone B-Cell Lymphoma**

**Gastric MALT Lymphoma**

### STAGE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Initial Therapy</th>
</tr>
</thead>
</table>
| I<sub>E1</sub><sup>h</sup>  
H. pylori positive | Currently accepted antibiotic therapy for H. pylori<sup>i</sup>  
Evaluate for H. pylori eradication with endoscopy (<small>MALT-3</small>) |
| I<sub>E2</sub><sup>h</sup>  
or II<sub>E</sub><sup>h</sup>  
H. pylori positive | Currently accepted antibiotic therapy for H. pylori<sup>i</sup>  
Evaluate for H. pylori eradication with endoscopy (<small>MALT-3</small>) |
| I<sub>E</sub> or II<sub>E</sub>  
H. pylori negative | RT<sup>j,k</sup> (preferred)  
Rituximab (if RT is contraindicated)  
Endoscopy for restaging, as per <small>MALT-4</small> |
| III<sub>E</sub>/IV<sub>E</sub>  
(advanced-stage disease uncommon) | Indications for treatment:  
- Candidate for clinical trial<sup>l</sup>  
- Symptoms  
- GI bleeding  
- Threatened end-organ function  
- Bulky disease  
- Steady progression  
- Patient preference |

- **Indication present<sup>m</sup>**  
  - Induction chemo-immunotherapy<sup>n</sup>  
  - or  
  - Locoregional RT in specific settings<sup>k</sup>  
  - Endoscopy for restaging, if evidence of recurrence, manage per follicular lymphoma (see <small>FOLL-3</small>) |

- **No indication**  
  - Observe |

---

<sup>g</sup>See Lugano Staging System for gastrointestinal lymphoma (<small>MALT-A</small>).  
<sup>h</sup>Involvement of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. If there is persistent disease after evaluation, RT may be considered earlier in the course.  
<sup>i</sup>(11;18) is a predictor for lack of response to antibiotics. These patients should be considered for alternative therapy.  
<sup>j</sup>If negative by both histology and serum antibodies, RT recommended.  
<sup>k</sup>See Principles of Radiation Therapy (<small>NHODG-E</small>).  
<sup>l</sup>Given incurability with conventional therapy, consider investigational therapy as first line of treatment.  
<sup>m</sup>Surgical resection is generally limited to specific clinical situations, ie, life-threatening hemorrhage.  
<sup>n</sup>See Suggested Treatment Regimens (<small>FOLL-B</small>).
### 3-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

**AFTER ANTIBIOTICS**

- **H. pylori negative, Lymphoma negative**
  - Observe

- **H. pylori positive, Lymphoma positive**
  - Asymptomatic
    - Observe for another 3 mo or RT
  - Symptomatic
    - RT

- **H. pylori negative, Lymphoma positive**
  - Asymptomatic
    - Observe for another 3 mo or RT
  - Symptomatic
    - RT

**ADDITIONAL THERAPY**

- **Second-line antibiotic treatment**
  - Second-line antibiotic treatment

---

**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.

---

**See Principles of Radiation Therapy (NHODG-E).**

- Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the NCCN Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1).
- If re-evaluation suggests slowly responding disease or asymptomatic nonprogression, continued observation may be warranted. RT can be considered as early as 3 mo after observation but can be prolonged to 18 mo (category 2B).
- If patient originally had clinical Stage I_E2 or Stage II_E, early RT should be considered if there is no response to antibiotics.
3-6 MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

AFTER RT

- **H. pylori negative**
  - **Lymphoma negative**: Observe
  - **Lymphoma positive**: See FOLL-2

- **H. pylori positive**
  - **Lymphoma negative**: Consider antibiotic treatment
    - **See Follow-up Endoscopy (MALT-5)**
  - **Lymphoma positive**: See FOLL-2

Restage at 3-6 mo with endoscopy and biopsy\(^o\) after RT

\(^o\)Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the [Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1)](https://www.nccn.org/professionals/physician_gls/pdf/dlbcl.pdf).

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**FOLLOW-UP ENDOSCOPY**

- **Complete response**
  - Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated

- **No response**
  - Previous RT
  - Previous antibiotic treatment

- **Recurrence post RT**
  - See follicular lymphoma indications for treatment (FOLL-3)

- **Recurrence post antibiotics**
  - Systemic
  - Locoregional RT

- **Repeat endoscopy after 3 mo**

---

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---

- **See Principles of Radiation Therapy (NHODG-E).**
- **See Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1).**
- **Optimal interval for follow-up endoscopy and imaging is not known.** Follow-up endoscopy and imaging at NCCN institutions is driven by symptoms.
### STAGING OF GASTRIC MALT LYMPHOMA: COMPARISON OF DIFFERENT SYSTEMS

<table>
<thead>
<tr>
<th>Lugano Staging System for gastrointestinal lymphomas</th>
<th>Ann Arbor Stage</th>
<th>TNM Staging System adapted for gastric lymphoma</th>
<th>Tumor extension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I_E</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confined to GI tract&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I_E&lt;sub&gt;1&lt;/sub&gt; = mucosa, submucosa</td>
<td>I_E</td>
<td>T1 N0 M0</td>
<td>Mucosa, submucosa</td>
</tr>
<tr>
<td>I_E&lt;sub&gt;2&lt;/sub&gt; = muscularis propria, serosa</td>
<td>I_E</td>
<td>T2 N0 M0</td>
<td>Muscularis propria</td>
</tr>
<tr>
<td></td>
<td>I_E</td>
<td>T3 N0 M0</td>
<td>Serosa</td>
</tr>
<tr>
<td><strong>Stage II_E</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extending into abdomen</td>
<td>II_E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I_&lt;sub&gt;E&lt;/sub&gt;1 = local nodal involvement</td>
<td>II_E</td>
<td>T1-3 N1 M0</td>
<td>Perigastric lymph nodes</td>
</tr>
<tr>
<td>I_&lt;sub&gt;E&lt;/sub&gt;2 = distant nodal involvement</td>
<td>II_E</td>
<td>T1-3 N2 M0</td>
<td>More distant regional lymph nodes</td>
</tr>
<tr>
<td><strong>Stage III-IV&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement</td>
<td>III_E</td>
<td>T1-4 N3 M0</td>
<td>Lymph nodes on both sides of the diaphragm/distant metastases (eg, bone marrow or additional extranodal sites)</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>T1-4 N0-3 M1</td>
<td></td>
</tr>
</tbody>
</table>


<sup>a</sup>Single primary or multiple, noncontiguous.

<sup>b</sup>Involvement of multiple extranodal sites in MALT lymphoma appears to be biologically distinct from multiple extranodal involvement in other lymphomas, and these patients may be managed by treating each site separately with excision or RT. In contrast, cases with disseminated nodal involvement appear to behave more like nodal MZL or like disseminated FL.

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.
### DIAGNOSIS

**ESSENTIAL:**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- Adequate immunophenotyping to establish diagnosis c,d
  - Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD5, CD10, BCL2, kappa lambda, CD21 or CD23, cyclin D1 or
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Molecular genetic analysis to detect: antigen receptor gene rearrangements; PCR for t(11;18)
- Cytogenetics or FISH: t(11;18); t(11;14); t(3;14);

### WORKUP

**ESSENTIAL:**
- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing if rituximab contemplated
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

**USEFUL IN SELECTED CASES**
- MUGA scan/echocardiogram if anthracycline or anthracenediones-based regimen is indicated
- Bone marrow biopsy ± aspirate (for patients with multifocal disease)
- Endoscopy with multiple biopsies of anatomical sites
- PET-CT scan
- MRI
- Hepatitis C testing
- Discussion of fertility issues and sperm banking
- SPEP

### 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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a Typical sites of extranodal marginal zone lymphoma other than the stomach include the following: bowel (small and large), breast, head and neck, lung, ocular adnexa, ovary, parotid, prostate, and salivary gland. Infectious agents have been reported to be associated with many nongastric sites but testing for these agents is not required for management.

b Non-cutaneous, for cutaneous marginal zone B-cell lymphoma, see CUTB.

c Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+, cyclin D1-, BCL2 follicles-

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

e Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
NCCN Guidelines™ Version 4.2011
Extranodal Marginal Zone B-Cell Lymphoma
Nongastric MALT Lymphoma

STAGE  TREATMENT

Stage I-II
- RT or
- Surgery may be considered for certain sites (eg, lung, breast [lumpectomy], thyroid, colon/small bowel or
- Observation in selected cases
- Extranodal (multiple sites)
- Stage III, IV: extranodal disease and multiple nodal sites
- Stage I-IV, MALT lymphomas coexistent with large cell lymphoma

- Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated
- Systemic recurrence

Extranodal (multiple sites)
- RT or
- Observation in selected cases

Stage III, IV: extranodal disease and multiple nodal sites
- Manage per NCCN Follicular Lymphoma Guidelines for advanced stage (FOLL-2)

Stage I-IV, MALT lymphomas coexistent with large cell lymphoma
- Treat per NCCN Diffuse Large B-Cell Lymphoma Guidelines (BCEL-1)

- Local recurrence
- Manage per NCCN Follicular Lymphoma Guidelines for advanced stage (FOLL-2)

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.

Dose is site dependent with lower dose reserved for eye involvement.
See Principles of Radiation Therapy (NHODG-E).
Surgical excision for adequate diagnosis may be appropriate treatment for disease.
Observation may be considered for patients whose diagnostic biopsy was excisional or involved-field RT or systemic treatment could result in significant comorbidity.
Follow-up includes diagnostic tests and imaging as clinically indicated.

Treatment of each site may be indicated (eg, bilateral conjunctiva) both at diagnosis and at relapse.
DLBCL coexistent with MALT cell lymphoma is managed as DLBCL.
Based on anecdotal responses to antibiotics in ocular and cutaneous marginal zone lymphomas, some physicians will give an empiric course of doxycycline prior to initiating other therapy.
## Nodal Marginal Zone Lymphoma

### Diagnosis

**Essential:**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis. Histologic grading cannot be performed on an FNA.
- Adequate immunophenotyping to establish diagnosis:
  - Paraffin panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Pediatric nodal marginal zone lymphoma should be considered with localized disease in a young patient.

**Useful under certain circumstances for clarification of diagnosis:**
- Molecular genetic analysis to detect: antigen receptor gene rearrangements; PCR for t(11;18)
- Cytogenetics or FISH: t(11;18); t(1;14); t(14;18); del(13q); del(7q)

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### Workup

**Essential:**
- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing if rituximab contemplated
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Bone marrow biopsy + aspirate to document clinical stage I-II disease
- Evaluation to rule out extranodal primary sites
  - Neck nodes: ocular, parotid, thyroid, and salivary gland
  - Axillary nodes: lung, breast, and skin
  - Mediastinal/hilar nodes: lung
  - Abdominal nodes: splenic and GI
  - Inguinal/iliaic nodes: GI and skin
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

**Useful in selected cases:**
- MUGA scan/echocardiogram if anthracycline or anthracenediones-based regimen is indicated
- Additional imaging as appropriate
- PET-CT scan
- Hepatitis C testing
- Discussion of fertility issues and sperm banking
- SPEP

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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.
NCCN Guidelines™ Version 4.2011
Splenic Marginal Zone Lymphoma

**DIAGNOSIS**

**ESSENTIAL:**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.  

- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.

- Adequate immunophenotyping to establish diagnosis
  - Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1, IgD, CD43, annexin-1
  - Cell surface marker analysis by flow cytometry (peripheral blood, bone marrow, or tissue): kappa/lambda, CD19, CD20, CD5, CD23, CD10, CD43, CD103

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Molecular genetic analysis to detect: antigen receptor gene rearrangements; PCR for t(11;18)
- Cytogenetics or FISH: CLL panel; t(11;18); t(11;14); t(14;18); del(7q)

**WORKUP**

**ESSENTIAL:**
- Physical exam with performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B testing if rituximab contemplated
- Hepatitis C testing
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Bone marrow biopsy ± aspirate
- SPEP and/or quantitative immunoglobulin levels
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

**USEFUL IN SELECTED CASES**
- Additional imaging as appropriate
- PET-CT scan
- Discussion of fertility issues and sperm banking
- Immunofixation of blood (for elevated immunoglobulins or positive SPEP)
- Cryoglobulins
- Directs Coombs testing

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*SMZL* is most definitively diagnosed at splenectomy, since the immunophenotype is nonspecific and morphologic features on the bone marrow may not be diagnostic. However, the diagnosis of SMZL may be made on the basis of bone marrow +/- peripheral blood involvement by small lymphoid cells with immunoglobulin (Ig) light chain restriction that lack characteristic features of other small B-cell neoplasms (CD5, CD10, cyclin D1). Plasmacytoid differentiation with cytoplasmic Ig detectable on paraffin sections may occur. In such cases, the differential diagnosis may include lymphoplasmacytic lymphoma. With a characteristic intrasinusoidal lymphocytic infiltration of the bone marrow, the diagnosis can strongly be suggested on bone marrow biopsy alone, if the immunophenotype is consistent.

[b] Typical immunophenotype: CD10-, CD5-, CD20+, CD23/-, CD43/- and cyclin D1-, BCL2 follicles-, annexin-1, CD103- (distinction from hairy cell leukemia) with expression of both IgM and IgD.


d] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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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.
**SPLN-2**

### CLINICAL PRESENTATION

- **Asymptomatic, without progressive cytopenia, no splenomegaly**
  - Observe

- **Hepatitis C positive**
  - Hepatology consult
  - No contraindications for treatment of hepatitis → Appropriate treatment
  - Contraindications for treatment of hepatitis

- **Hepatitis C negative**
  - Assess
  - Cytopenias
  - Symptoms
  - Splenectomy or Rituximab
  - No symptoms → Observe

### MANAGEMENT

- **Splenomegaly**
  - Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated

- **If progression of disease, manage per NCCN Follicular Lymphoma Guidelines for advanced stage (FOLL-2)**

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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.

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**References:**

- Pneumococcal and meningococcal vaccination should be performed at least 2 weeks before splenectomy.
- Follow-up includes diagnostic tests and imaging as clinically indicated.
**MANT-1**

**DIAGNOSIS**

**ESSENTIAL:**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis
  - Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD5, cyclin D1, CD10, CD21, CD23, BCL2, BCL6, Ki67
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Molecular genetic analysis to detect: antigen receptor gene rearrangements; BCL1 rearrangements
- Cytogenetics or FISH: t(11;14); t(14;18); CLL panel

**WORKUP**

**ESSENTIAL:**
- Physical exam: Attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- Bone marrow biopsy ± aspirate
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Hepatitis B testing if rituximab contemplated
- MUGA scan/echocardiogram if anthracycline or anthracenediones-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)
- Evaluation of fertility issues and sperm banking
- Lumbar puncture (for blastic variant or CNS symptoms)
- Beta-2-microglobulin
- PET-CT scan

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Endoscopy/colonoscopy
- Neck CT
- Uric acid
- Discussion of fertility issues and sperm banking
- Lumbar puncture (for blastic variant or CNS symptoms)
- Beta-2-microglobulin
- PET-CT scan

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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.

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**See Induction Therapy (MANT-2)**
**INDUCTION THERAPY**

- **Stage I, II** (localized presentation, extremely rare)
  - See Suggested Regimens (MANT-A) ± RT
  - or
  - RT

- **Stage IIX, III, IV**
  - Clinical trial
  - See Suggested Regimens (MANT-A)
  - or
  - Observation in highly selected cases

**INITIAL RESPONSE**

- Complete response → Relapse → Clinical trial or Second-line treatment
  - RT
  - See Suggested Regimens (MANT-A)

- Partial response → Progression

**RELAPSE**

- Clinical trial or Second-line treatment
  - RT
  - See Suggested Regimens (MANT-A)

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^f Early referral for high dose therapy with stem cell rescue is advisable for planning purposes.


^h See Principles of Radiation Therapy (NHODG-E).


^j See Response Criteria for Lymphoma (NHODG-C).

^k Option for clinical trials of adjuvant therapy or for relapsed disease involving high dose therapy with autologous or allogeneic stem cell rescue, immunotherapy with nonmyeloablative stem cell rescue, or evaluation of treatment with new agents are appropriate.

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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.
SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

**Induction Therapy**

**Aggressive therapy**
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
- NORDIC regimen\(^b\) (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine
- CALGB regimen\(^b\) (rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone]) (rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone])
- Sequential RCHOP/RICE\(^b\) (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (rituximab, ifosfamide, carboplatin, etoposide)
- Alternating RCHOP/RDHAP\(^b\) (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cisplatin, cytarabine)

**Less aggressive therapy**
- Bendamustine + rituximab
- CHOP + rituximab\(^c\)
- Cladribine + rituximab
- CVP (cyclophosphamide, vincristine, prednisone) + rituximab
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
- Modified rituximab-HyperCVAD with rituximab maintenance in patients older than 65 y

**First-line Consolidation\(^d\)**
- Clinical trial
- High dose therapy with autologous stem cell rescue\(^e\)

**Second-line Therapy**
- Bendamustine ± rituximab
- Bortezomib ± rituximab
- Cladribine + rituximab
- FC (fludarabine, cyclophosphamide) ± rituximab
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)
- FMR (fludarabine, mitoxantrone, rituximab)
- Lenalidomide ± rituximab
- PCR (pentostatin, cyclophosphamide, rituximab)
- PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab
- See Second-line Therapy for DLBCL (BCEL-C 1 of 3)\(^f\)

**Second-line Consolidation**
- Allogeneic stem cell transplant (nonmyeloablative or myeloablative)

**See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)**

\(a\)See references for regimens MANT-A 2 of 3 and MANT-A 3 of 3.

\(b\)These regimens include first-line consolidation with high dose therapy and autologous stem cell rescue (HDT/ASCR).

\(c\)There is a randomized trial that demonstrated that RCHOP was not superior to CHOP.

\(d\)Typically patients will receive an aggressive induction regimen prior to consolidation; however, less aggressive regimens followed by consolidation with high dose therapy may also result in a good long-term outcome.

\(e\)Randomized data with anthracycline-containing regimens suggest an improvement in progression free survival with the addition of first-line high dose therapy with autologous stem cell consolidation.

\(f\)These agents can be administered without restriction for transplantability.

**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.
**SUGGESTED TREATMENT REGIMENS**

**References**

**Induction Therapy**

**Aggressive therapy**

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine) + rituximab


**Nordic trial regimen** (Dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine


CALGB regimen (rituximab + methotrexate with augmented CHOP):


RChOP/Rice


RChOP/RDHP


**Less aggressive therapy**

Bendamustine + rituximab


CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab


Cladribine + rituximab


CVP + rituximab


**Modified HyperCVAD with rituximab maintenance**


**First-line consolidation**

High dose therapy with autologous stem cell rescue


SUGGESTED TREATMENT REGIMENS

References

**Second-line Therapy**

**Bendamustine**

**Bortezomib**

**Cladribine**

**FC (fludarabine and cyclophosphamide) ± rituximab**

**FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)**

**FMR (fludarabine, mitoxantrone, rituximab)**

**Lenalidomide**

**Lenalidomide + rituximab**

**PEP-C (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab**

**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.
Diffuse Large B-Cell Lymphoma

DIAGNOSIS 

ESSENTIAL:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis
  - Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Additional immunohistochemical studies to establish lymphoma subtype
  - Paraffin panel: cyclin D1, kappa/lambda, CD138, EBV, ALK, HTLV
- Molecular genetic analysis to detect: antigen receptor gene rearrangements; BCL1, BCL2, MYC rearrangements
- Cytogenetics or FISH: t(14;18); t(3;v); t(8;14)

Subtypes included:
- Diffuse large B-cell lymphoma (DLBCL), NOS
- DLBCL coexistent with follicular lymphoma of any grade
- DLBCL coexistent with gastric MALT lymphoma
- DLBCL coexistent with nongastric MALT lymphoma
- Follicular Lymphoma grade 3
- Intravascular large B-cell lymphoma
- DLBCL associated with chronic inflammation
- ALK positive DLBCL
- EBV positive DLBCL of the elderly
- T-cell/histiocyte rich large B-cell lymphoma

Subtypes not included:
- Cutaneous B-cell lymphoma (See CUTB-1)
- Primary DLBCL of the CNS

Primary Mediastinal Large B-Cell Lymphoma (PMBL), see BCEL-B.

\[ \text{See Workup (BCEL-2)} \]

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.

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

\[ \text{See International Prognostic Index (BCEL-A).} \]

Typical immunophenotype: CD20+, CD45+, CD3-; other markers used for subclassification.

\[ \text{See } \text{BCEL-1} \]
WORKUP

ESSENTIAL:
- Physical exam: attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Unilateral or bilateral bone marrow biopsy (1-2 cm) ± aspirate
- Calculation of International Prognostic Index (IPI)\textsuperscript{b}
- Hepatitis B testing\textsuperscript{g}
- MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated
- PET-CT scan
- Pregnancy testing in women of child-bearing age
- Beta-2-microglobulin (category 2B)

USEFUL IN SELECTED CASES:
- Neck CT, Head CT, or MRI
- Discussion of fertility issues and sperm banking
- HIV
- Lumbar puncture, if paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or \( \geq 2 \) extranodal sites

\textsuperscript{b}See International Prognostic Index (BCEL-A).

\textsuperscript{g}Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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.
## Diffuse Large B-Cell Lymphoma

### Induction Therapy

**Stage I, II**
- Nonbulky (< 10 cm)
  - Adverse risk factors present:
    - Elevated LDH
    - Stage II
    - Age > 60 y
    - Performance status ≥ 2
  - RCHOP x 3 cycles + RT
- Bulky (≥ 10 cm)
  - Adverse risk factors not present
  - RCHOP x 6 cycles ± RT (category 2B for RT)

**Stage III, IV**
- Clinical trial
- RCHOP x 6 cycles ± RT (category 1)

### Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

**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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**Adverse risk factors present:**
- Elevated LDH
- Stage II
- Age > 60 y
- Performance status ≥ 2

**Adverse risk factors not present:**
- RCHOP x 6 cycles ± RT (category 2B for RT)

**In patients who are not candidates for chemotherapy:** Involvement field radiation therapy (IFRT) is recommended.

**In testicular lymphoma:** After completion of chemotherapy, RT should be given to contralateral testis (30-36 Gy).

**In selected settings:** (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or ≥ 2 extranodal sites), CNS prophylaxis should be given (4-8 doses of intrathecal methotrexate and/or cytarabine during the course of treatment). Recent data regarding Stage IE DLBCL of breast has been suggested as a potential risk for CNS disease.

**See AIDS-2 for HIV-positive DLBCL**, **See Principles of Radiation Therapy (NHODG-E)**, **May include high-dose therapy**, **Based on current clinical trials, CHOP is preferable due to reduced toxicities, but other comparable anthracycline-based regimens are acceptable**, **For other regimens, see BCEL-C**, **In selected cases, RT to initially bulky sites of disease may be beneficial (category 2B)**.
**Pre RT Evaluation**

- **Stage I, II:**
  - Pre RT evaluation, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.
  - **Complete response** (PET negative) → Complete planned course of treatment
  - **Partial response** (PET positive) → Complete course of therapy with higher RT dose
  - **No response or progressive disease** → See Additional Therapy for Relapse (BCEL-6)

**Follow-up Therapy**

- **Complete response** (PET negative)
  - Complete planned course of treatment

- **Partial response** (PET positive)
  - Complete course of therapy with higher RT dose
  - High dose therapy with autologous stem cell rescue ± RT pre- or post-transplant
  - Clinical trial (may include allogeneic stem cell transplant ± RT pre- or post-transplant)

**End of Treatment Restaging**

- At completion of treatment, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.
- At completion of treatment, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.

**Initial Response**

- Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated
- Partial response
- No response or progressive disease

**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.
### Diffuse Large B-Cell Lymphoma

#### INTERIM RESTAGING

**Stage III, IV:**
- After 2-4 cycles, repeat all positive studies

**Partial response (PET positive)**
- Continue RCHOP\(^o\) to a total of 6 cycles or Clinical trial

**No response or progressive disease\(^q\)**
- See Additional Therapy for Relapse (BCEL-6) or RT in select patients who are not candidates for chemotherapy

**Complete response (PET negative)**
- Continue RCHOP\(^o\) to a total of 6 cycles

### FOLLOW-UP THERAPY

**END OF TREATMENT RESTAGING\(^t\)**

- At completion of treatment, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.

**Partial response (PET positive)**
- Continue RCHOP\(^o\) to a total of 6 cycles or Clinical trial

**No response or progressive disease\(^q\)**
- See Additional Therapy for Relapse (BCEL-6) or RT in select patients who are not candidates for chemotherapy

### INITIAL RESPONSE

**Observation (preferred) or Consider RT to initially bulky disease (category 2B) or Consider high dose therapy with autologous stem cell rescue in high risk patients (category 2B)**

**Complete response (PET negative)**
- At completion of treatment, repeat all positive studies.

**Partial response (PET positive)**
- Continue RCHOP\(^o\) to a total of 6 cycles

**No response or progressive disease\(^q\)**
- See Additional Therapy for Relapse (BCEL-6) or RT in select patients who are not candidates for chemotherapy

### END OF TREATMENT RESTAGING

**Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated**

**Relapse, See Relapse or Refractory Disease (BCEL-6)**

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\(o\) For other regimens, see BCEL-C.

\(q\) See Response Criteria for Lymphoma (NHODG-C).

\(t\) Documented PR includes a biological measure of disease: positive PET-CT scan, or ideally positive biopsy.

\(^\dagger\) There is evidence that the addition of maintenance rituximab does not improve survival.

\(^u\) Patients in first remission may be candidates for consolidation trials including high dose therapy with autologous stem cell rescue.

\(^v\) PET-CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET-CT scan performed and positive, rebiopsy before changing course of treatment.

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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.
Relapse/refractory disease

For patients with intention to proceed to high-dose therapy
- Second-line therapy
  - See Suggested Regimens (BCEL-C)

For patients without intention to proceed to high-dose therapy
- Clinical trial
  - or
  - Second-line therapy
    - See Suggested Regimens (BCEL-C)
    - or
    - Palliative RT

Response #2
- Complete response or partial response

Consolidation/additional therapy
- High dose therapy with autologous stem cell rescue (category 1 for CR, category 2A for all others) ± involved field RT or Clinical trial or Allogeneic stem cell transplant in selected cases

Relapse #2 or greater
- Clinical trial

Additional therapy

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.
### INTERNATIONAL PROGNOSTIC INDEX

**ALL PATIENTS:**
- Age > 60 years
- Serum LDH > 1 x normal
- Performance status 2-4
- Stage III or IV
- Extranodal involvement > 1 site

**INTERNATIONAL INDEX, ALL PATIENTS:**
- Low
- Low intermediate
- High intermediate
- High
- 0 or 1
- 2
- 3
- 4 or 5

### AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX

**PATIENTS ≤ 60 YEARS:**
- Stage III or IV
- Serum LDH > 1 x normal
- Performance status 2-4

**INTERNATIONAL INDEX, PATIENTS ≤ 60 YEARS:**
- Low
- Low/intermediate
- High/intermediate
- High
- 0
- 1
- 2
- 3

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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.
Primary Mediastinal Large B-Cell Lymphoma (PMBL)

PMBL can be defined as a clinical entity presenting with primary site of disease in mediastinum with or without other sites and has histology of DLBCL.

- Clinical pathologic correlation is required to establish diagnosis.

- Optimal first-line therapy is more controversial than other subtypes of NHL.

- Because of relative rarity of PMBL, the role of R-CHOP-21 is not established as the definitive treatment option for this disease. However, R-CHOP-21 is widely used in NCCN institutions based on data in DLBCL and other regimens have been used (see BCEL-C). There are data suggesting that more intense therapy may be better based on non-randomized comparisons.

- Role of RT is controversial; if PET-CT scan negative at the end of treatment, may be observed.

- Residual mediastinal masses are common. PET-CT scan is essential post-treatment. Biopsy of PET-CT scan positive mass is recommended if additional treatment is contemplated.
**Diffuse Large B-Cell Lymphoma**

**First-line Therapy**
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- Dose-dense RCHOP 14 (category 2B)
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (category 2B)

**First-line Therapy for patients with poor left ventricular function**
- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- RCNOP (rituximab, cyclophosphamide, mitoxantrone, vincristine, prednisone)
- DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
- RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)

**First-line Consolidation**
- High dose therapy with autologous stem cell rescue in high risk patients (category 2B)

**SUGGESTED TREATMENT REGIMENS** (in alphabetical order)

**Second-line Therapy** (For patients with intention to proceed to high dose therapy with autologous stem cell rescue)
- DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab
- GemOx (gemcitabine, oxaliplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

**Second-line Therapy** (non candidates for high dose therapy)
- Clinical trial
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV
- DA-EPOCH ± rituximab
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- GDP ± rituximab
- GemOx ± rituximab
- Lenalidomide ± rituximab
- Rituximab

---

**See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)**

- See references for regimens BCEL-C 2 of 3 and BCEL-C 3 of 3.
- Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
- There is limited published data regarding the use of these regimens, however, they are used at NCCN institutions for the first-line treatment of DLBCL for patients with poor ventricular left function.
- If upward dose adjustment is necessary, doxorubicin should be maintained at base dose and not increased.
- If additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.
- Rituximab would be included in second line therapy if there is relapse after a reasonable remission (> 6 mo); however, rituximab would often be omitted in patients with primary refractory disease.

---

**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.
SUGGESTED TREATMENT REGIMENS

First-line Therapy

**CHOP** (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab


**Dose-adjusted EPOCH** (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab


**Dose-dense CHOP 14 + rituximab**


**References**


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.
Second-line Therapy

**DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab**


**ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab**


**GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab**


**GemOX (gemcitabine, oxaliplatin) + rituximab**


**ICE (ifosfamide, carboplatin, etoposide) ± rituximab**


**Lenalidomide**


**CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab**


**EPOCH + rituximab**


**RGemOx (rituximab, gemcitabine, oxaliplatin)**


**NCCN Guidelines™ Version 4.2011**  
**Burkitt Lymphoma**

### DIAGNOSIS

**ESSENTIAL:**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.

**Workup:**

- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.

- Adequate immunophenotyping to establish diagnosis:
  - Paraffin panel: CD45 (LCA), CD20, CD3, CD10, Ki-67, BLC2, BCL6, TdT
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD20, CD3, CD5, CD19, CD10, TdT
  - Cytogenetics or FISH: t(8;14) or variants; MYC; IgH; BCL2; BCL6 rearrangements

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**

-ISH for EBV EBER
- Molecular genetic analysis to detect: antigen receptor gene rearrangements; MYC rearrangement

---

### WORKUP

**ESSENTIAL:**

- Physical exam: attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Lumbar puncture
- Flow cytometry of cerebrospinal fluid
- Unilateral or bilateral bone marrow biopsy ± aspirate
- HIV testing
- Hepatitis B testing
- MUGA scan/echocardiogram if anthracycline or anthracenediones-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

**USEFUL IN SELECTED CASES:**

- Neck CT
- Discussion of fertility issues and sperm banking
- Beta-2-microglobulin
- PET-CT scan

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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.

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**RISK ASSESSMENT**

- **Low risk**
  - Normal LDH
  - Completely resected abdominal lesion or single extra-abdominal mass < 10 cm

- **High risk**

**INDUCTION THERAPY**

- **Low risk**
  - Clinical trial
  - See Suggested Regimens (BURK-A)

- **High risk**
  - Clinical trial
  - See Suggested Regimens (BURK-A)

**INITIAL RESPONSE**

- **Complete response**
  - Follow-up after complete response: every 2-3 mo for 1 y, then every 3 mo for 1 y, then every 6 mo

- **< Complete response**
  - Follow-up after complete response: every 2-3 mo for 1 y, then every 3 mo for 1 y, then every 6 mo

**RELAPSE**

- Clinical trial
- Second-line chemotherapy (BURK-A)
- Followed by high dose chemotherapy with HSCT in selected patients
- Best supportive care

- Clinical trial
- Individual approach
- Palliative RT

---

**Prophylaxis for tumor lysis syndrome is mandatory**

*(See NHODG-B)*

- **Complete response**
  - Consolidation in clinical trial

- **< Complete response**

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9Clinical trials may include high dose therapy with allogeneic or autologous stem cell rescue.

hSee Response Criteria for Lymphoma (NHODG-C).

iRelapse after 2 y is rare, therefore, follow-up should be individualized according to patient characteristics.

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.
SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

CHOP is not adequate therapy.

Induction therapy

Low Risk- Combination Regimens

• CALGB 9251 regimen (cyclophosphamide and prednisone followed by cycles containing either ifosfamide or cyclophosphamide; high-dose methotrexate, leucovorin, vincristine, dexamethasone, and either doxorubicin or etoposide or cytarabine; or intrathecal triple therapy [methotrexate, cytarabine and hydrocortisone]).
• CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) ± rituximab (3 cycles)
• Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data is for patients without CNS disease.)
• HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)

High Risk- Combination Regimens

• CALGB 9251 regimen (cyclophosphamide and prednisone followed by cycles containing either ifosfamide or cyclophosphamide; high-dose methotrexate, leucovorin, vincristine, dexamethasone, and either doxorubicin or etoposide or cytarabine; or intrathecal triple therapy [methotrexate, cytarabine and hydrocortisone] with prophylactic CNS irradiation in select patients)
• CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) alternating with IVAC (ifosfamide, cytarabine, etoposide and intrathecal methotrexate) ± rituximab
• Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (For high risk patients not able to tolerate aggressive treatments) (regimen includes intrathecal methotrexate) (Data is for patients without CNS disease.)
• HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)

Second-line therapy (select patients with reasonable remission)

• Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data is for patients without CNS disease.)
• RIVAC (rituximab, ifosfamide, cytarabine, etoposide and intrathecal methotrexate) if have not received previously
• RGDP (rituximab, gemcitabine, dexamethasone, cisplatin)
• HDAC (high-dose cytarabine)

\(^a\)See references for regimens [BURK-A 2 of 2].

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.
SUGGESTED TREATMENT REGIMENS

References

Low Risk- Combination Regimens

CALGB 9251 regimen
CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) ± rituximab
Dose-adjusted EPOCH plus rituximab (regimen includes IT methotrexate)
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab

High Risk- Combination Regimens

CALGB 9251 regimen
CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) alternating with IVAC (ifosfamide, cytarabine, etoposide and intrathecal methotrexate) ± rituximab
Dose-adjusted EPOCH plus rituximab (regimen includes IT methotrexate)
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab

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.
**DIAGNOSIS**

**ESSENTIAL:**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Additional immunohistochemical studies to establish lymphoma subtype
  - Frozen: kappa/lambda
  - Paraffin panel: CD22, CD4, CD8, cyclin D1
- Molecular genetic analysis to detect: antigen receptor gene rearrangements
- Cytogenetics or FISH: MYC; t(8;14) and variants

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

**WORKUP**

**ESSENTIAL:**
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid, phosphate
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Lumbar puncture
- Flow cytometry of cerebrospinal fluid
- Bilateral or unilateral bone marrow biopsy ± aspirate with flow and cytogenetics
- Hepatitis B testing
- MUGA scan/echocardiogram if anthracycline or anthracenediones-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

**USEFUL IN SELECTED CASES:**
- Head MRI
- Discussion of fertility issues and sperm banking
- Beta-2-microglobulin
- PET-CT scan

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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.
**CLINICAL ASSESSMENT**

- Stage I–IV (disease is considered to be systemic)

**INDUCTION THERAPY**

<table>
<thead>
<tr>
<th>Initial Response</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completeresponse &lt;sup&gt;g&lt;/sup&gt; (PET negative)</td>
<td>Observe or Clinical trial &lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Partialresponse &lt;sup&gt;g&lt;/sup&gt; (PET positive)</td>
<td>Rebiopsy to confirm disease</td>
</tr>
</tbody>
</table>

- Clinical trial <sup>f</sup> or See Suggested Regimens (BLAST-A)

**RELAPSE**

- Allogeneic HSCT or Clinical trial
- Attempt reinduction with combination chemotherapy or Allogeneic HSCT or Clinical trial

<sup>g</sup>For poor risk patients, consideration of high dose therapy with autologous or allogeneic stem cell rescue is appropriate.

<sup>f</sup>Prophylaxis for tumor lysis syndrome is mandatory (See NHODG-B).

<sup>See Response Criteria for Lymphoma (NHODG-C).</sup>

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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.
SUGGESTED TREATMENT REGIMENS\textsuperscript{a}  
(in alphabetical order)

BFM (Berlin–Frankfurt–Munster)
- **Standard BFM regimen:**
  - **Induction phase:**
    - Vincristine, daunomycin, prednisone, L-asparaginase, cytarabine (IT), and methotrexate (IT).
  - **Consolidation phase (5 weeks):**
    - Prednisone, cyclophosphamide, mercaptopurine, vincristine, cytarabine, IT methotrexate, and RT.
  - **Interim Maintenance phase (8 weeks):**
    - Mercaptopurine and methotrexate (PO)
  - **Delayed intensification (7 weeks):**
    - *Reinduction phase (4 weeks):*
      - Dexamethasone, vincristine, and doxorubicin.
    - *Reconsolidation phase (3 weeks):*
      - L-asparaginase, vincristine, cyclophosphamide, thioguanine, cytarabine, and intrathecal methotrexate.
  - **Long-term maintenance (12 weeks):**
    - Vincristine, prednisone, mercaptopurine, methotrexate (PO and IT).
- **Augmented BFM regimen:**
  - **Induction I:**
    - Prednisone, vincristine, daunorubicin, L-asparaginase, methotrexate (IT).
  - **Induction II:**
    - Cyclophosphamide, cytarabine, 6-mercaptopurine, methotrexate (IT)
  - **Consolidation I:**
    - Cytarabine, mitoxantrone, methotrexate, asparaginase, 6-mercaptopurine
  - **Reinduction I**
    - Prednisolone, vincristine, doxorubicin
    - Triple prophylaxis: methotrexate, cytarabine, dexamethasone
  - **Reinduction II**
    - Cyclophosphamide, cytarabine, 6-thioguanine
    - Triple prophylaxis: methotrexate, cytarabine, dexamethasone
  - **Consolidation II**
    - Etoposide, cytarabine
    - Cyclophosphamide, cytarabine

\textsuperscript{a}See references for regimens BLAST-A 3 of 3.

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.
SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

• **CALGB ALL regimen**
  - Induction therapy (4 weeks):
    - Cyclophosphamide, daunorubicin, vincristine, prednisone, and L-asparaginase.
    - For patients 60 years and older: the doses of cyclophosphamide, daunorubicin, and prednisone are modified (see reference for details).
  - Early intensification (4 weeks):
    - Intrathecal methotrexate, cyclophosphamide, 6-mercaptopurine, cytarabine, vincristine, and L-asparaginase.
  - CNS prophylaxis and interim maintenance:
    - Cranial irradiation in select cases, intrathecal methotrexate, 6-mercaptopurine, and methotrexate (PO).
  - Late intensification (8 weeks):
    - Doxorubicin, vincristine, dexamethasone, cyclophosphamide, 6-thioguanine, and cytarabine.
  - Prolonged maintenance (until 24 months from diagnosis):
    - Vincristine, prednisone, methotrexate (PO), and 6-mercaptopurine.

• **HyperCVAD** \(^b\) (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with methotrexate + cytarabine, including intrathecal methotrexate
  - Maintenance therapy
    - 6-mercaptopurine, methotrexate, vincristine, and prednisone (POMP)
  - In the cases of CD20 positive (≥ 20%) acute lymphoblastic lymphoma (ALL), the addition of rituximab should be considered.
  - In cases of Philadelphia chromosome positive ALL, imatinib should be incorporated into regimen.

• **LMB-86 regimen**
  - Cytoreductive therapy
    - COP (cyclophosphamide, vincristine, and prednisone)
  - Induction therapy
    - COPADM (cyclophosphamide, vincristine, prednisone, doxorubicin, and high-dose methotrexate)
  - Consolidation therapy
    - CYVE (cytarabine and etoposide; regimen includes high-dose cytarabine)

• **Maintenance chemotherapy**
  - Up to 2 y of maintenance based on the treatment protocol is recommended.

\(^a\) See references for regimens **BLAST-A 3 of 3**.

\(^b\) For T-cell lymphoblastic lymphomas with primary mediastinal presentation, residual masses are irradiated.

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.
SUGGESTED TREATMENT REGIMENS

References

BFM (Berlin–Frankfurt–Munster)

**Standard BFM**


**Augmented BFM**


CALGB ALL regimen


**HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate-cytarabine)**

followed by **POMP (mercaptopurine, methotrexate, vincristine, and prednisone) maintenance**


LMB-86 regimen


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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.
**NCCN Guidelines™ Version 4.2011**

**AIDS-Related B-Cell Lymphomas**

**DIAGNOSIS**

**ESSENTIAL:**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis\(^a\)
  - Recommended panel for paraffin section immunohistochemistry: CD45 (LCA), CD20, CD3, CD10, BCL2, BCL6, Ki-67, CD138, kappa/lambda, HHV8
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, TdT, CD14, CD20
- Epstein-Barr virus (EBER-ISH)

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Additional immunohistochemical studies to establish lymphoma subtype
  - DLBCL, Burkitt, Plasmablastic, Primary effusion: CD10, BCL2, Ki-67, BCL6, CD138
- Molecular genetic analysis to detect: antigen receptor gene rearrangements; BCL2, BCL6, MYC rearrangements
- Cytogenetics or FISH: BCL2; BCL6; MYC

**WORKUP**

**ESSENTIAL:**
- Physical exam: attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid, phosphate
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- PET-CT scan
- Bone marrow biopsy ± aspirate
- CD4 count
- LP
- Viral load
- Hepatitis B testing\(^b\)
- MUGA scan/echocardiogram if anthracycline or anthracenediones- based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

**USEFUL IN SELECTED CASES**
- UGI/barium enema/endoscopy
- Neck CT
- Plain bone radiographs and bone scan
- Discussion of fertility issues and sperm banking
- Beta-2-microglobulin
- Brain MRI with gadolinium, or head CT

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

\(^b\)Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
**TREATMENT AND FOLLOW-UP**

Antiretrovirals can be administered safely with chemotherapy, however some regimens have recommended discontinuation. Any change in antiviral therapy should be done in consultation with an infectious disease specialist.

- **Suggested regimens:**
  - **d** CODOX-M/IVAC: cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine ± rituximab
  - **e** Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) ± rituximab (+ rituximab is for favorable presentation)
  - **d** CDE (cyclophosphamide, doxorubicin, etoposide) ± rituximab (+ rituximab is for favorable presentation)
  - **e** Consider CHOP with high-dose methotrexate ± rituximab (+ rituximab is for favorable presentation) Avoid methotrexate dose > 3 g/m²
  - **GCSF for all patients**

- **Suggested regimens:**
  - **d** Dose-adjusted EPOCH
  - **CDE**
  - **CHOP**
  - **CDOP** (cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
  - **GCSF for all patients**
  - **Intrathecal therapy (IT)**
  - **If CD20+, add rituximab with chemotherapy**

- **For DLBCL relapse,** see BCEL-6

---

**See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)**

- Most cases are CD20 negative and addition of rituximab is not indicated.
- dSee references for regimens AIDS-A.
- fProphylactic IT methotrexate is used at some NCCN institutions for all patients. At other NCCN institutions, patients with HIV-associated DLBCL receive IT methotrexate in selective settings (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV-lymphoma, or ≥ 2 extranodal sites).

**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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TREATMENT AND FOLLOW-UP

Antiretrovirals can be administered safely with chemotherapy however some regimens have recommended discontinuation. Any change in antiviral therapy should be done in consultation with an infectious disease specialist.

Plasmablastic lymphoma\textsuperscript{9}

- Suggested regimens:\textsuperscript{d}
  - CODOX-M/IVAC
  - Dose-adjusted EPOCH
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine)
- Standard CHOP is not adequate therapy

Primary CNS lymphoma

- Consider high-dose methotrexate
- Consider RT alone
- For select patients with good performance status on HAART, see NCCN CNS Guidelines - Primary CNS Lymphoma
- Best Supportive Care (See NCCN Palliative Care Guidelines)

\textsuperscript{d}See references for regimens AIDS-A.

\textsuperscript{9}Management can also apply to HIV negative plasmablastic lymphoma.

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

\textsuperscript{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.}
SUGGESTED TREATMENT REGIMENS

References

CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine)

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)

CDE (cyclophosphamide, doxorubicin, and etoposide)

CDE + rituximab

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)

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.
**Primary Cutaneous B-Cell Lymphoma**

### DIAGNOSIS

**ESSENTIAL:**
- Review of all slides with at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of primary cutaneous B-cell lymphoma. Rebiopsy if consult material is nondiagnostic.
- Histopathology review of adequate biopsy (punch, incisional, excisional).
- Adequate immunophenotyping to establish diagnosis.
  - Recommended panel for paraffin section immunohistochemistry: CD20, CD79a, CD3, CD5, CD10, BCL2, BCL6, Ki-67, kappa/lambda, IRF4/MUM1

**USEFUL IN CERTAIN CIRCUMSTANCES:**
- Additional immunohistochemical studies to establish lymphoma subtype
  - Paraffin panel: cyclin D1
  - Assessment of surface IgM and IgD expression (to further help in distinguishing DLBCL, leg type from follicle center lymphoma)
- Molecular genetic analysis to detect: antigen receptor gene rearrangements; IgH gene rearrangement by PCR
- Cytogenetics or FISH: t(14;18)

**NOTE:** A germinal (or follicle) center phenotype and large cells in a skin lesion is not equivalent to DLBCL but is consistent with primary cutaneous germinal/follicle center lymphoma.

### WORKUP

**ESSENTIAL:**
- Complete history and physical examination including complete skin exam
- CBC, differential, comprehensive metabolic panel
- LDH
- Hepatitis B testing if rituximab considered
- Chest/abdominal/pelvic CT
- Bone marrow biopsy, if PC-DLBCL, Leg type
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

**USEFUL IN SELECTED CASES:**
- PET-CT scan
- Bone marrow biopsy
  - Consider if PCFCL
  - Optional if PCMZL
- Peripheral blood flow cytometry, if CBC demonstrates lymphocytosis
- SPEP/quantitative immunoglobulins for PCMZL

### PC-DLBCL, Leg type: Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg type

### PCMZL: Primary Cutaneous Marginal Zone B-cell Lymphoma

### PCFCL: Primary Cutaneous Follicle Center B-cell Lymphoma

**Rule out drug-induced cutaneous lymphoid hyperplasia.**

**Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.**
Primary Cutaneous B-Cell Lymphoma

**INITIAL THERAPY**

- **Solitary/regional, T1-2 (Ann Arbor Stage IE)**
  - Local RT (preferred) or Excision or Observation in selected cases
  - CR/PR -> Persistent or progressive disease
  - Generalized disease (extracutaneous disease)
  - Generalized disease (skin only)

- **Generalized disease (skin only), T3**
  - Observation or Rituximab or Topicals or Local RT for palliation of symptoms or Intrallesional steroids or Palliative chemotherapy such as chlorambucil ± rituximab or CVP ± rituximab
  - CR/PR -> Persistent or progressive disease
  - Generalized disease (extracutaneous disease)
  - Generalized disease (skin only)
  - Relapsed disease

- **Extracutaneous disease**
  - Manage as per FOLL-2

**SECONDARY THERAPY**

- **Regional**
  - Observation or Excision or Topicals or Injected steroids or Local RT

- **Relapsed disease, See CUTB-3**

---

**Notes:**
- 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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**References:**
- See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).
- See Treatment References (CUTB-B).

---

**特殊情况：**
- If RT or surgical treatment is neither feasible nor desired.
- There are case reports showing efficacy of topicals which include steroids, imiquimod, nitrogen mustard, bexarotene.
- In rare circumstances for very extensive disease, other combination chemotherapy regimens listed in FOLL-B are used.
Relapsed disease

Solitary/regional, T1-2 (Ann Arbor Stage IE)
Observation or Excision or Topicals
or Intrallesional steroids or Local RT
CR/PR
Persistent or progressive disease
Regional
Generalized disease (extracutaneous disease)
Generalized disease (skin only)

Extracutaneous disease

Generalized disease (skin only), T3
Observation or Rituximab or Topicals
or Local RT for palliation of symptoms or Intrallesional steroids or Palliative chemotherapy such as chlorambucil ± rituximab or CVP ± rituximab
CR/PR
Refractory

Relapsed disease

CR/PR
Persistent or progressive disease
Manage as per FOLL-2

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.

†Unless clinically indicated, additional imaging studies during the course of treatment is not needed.

§See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).

hSee Treatment References (CUTB-B).

††There are case reports showing efficacy of topicals which include steroids, imiquimod, nitrogen mustard, bexarotene.

kIn rare circumstances for very extensive disease, other combination chemotherapy regimens listed in FOLL-B are used.

lRefractory to all previous treatments.
### PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE

<table>
<thead>
<tr>
<th>STAGE</th>
<th>INITIAL THERAPY</th>
<th>SECONDARY THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary regional, T1-2 (Ann Arbor Stage IE)</td>
<td>R-CHOP&lt;sup&gt;m&lt;/sup&gt; + local RT or Local RT&lt;sup&gt;n&lt;/sup&gt; or Clinical trial</td>
<td>CR → Observe → Relapse → R-CHOP (if not previously received) or Manage as per BCEL-6 or Local RT to previously unirradiated tumor</td>
</tr>
<tr>
<td>Generalized disease (skin only), T3</td>
<td>R-CHOP ± local RT or Clinical trial</td>
<td>CR → Observe → Relapse → Manage as per BCEL-6 or Local RT for palliation or Radioimmunotherapy</td>
</tr>
<tr>
<td>Extracutaneous disease</td>
<td>Manage as per BCEL-3</td>
<td>See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)</td>
</tr>
</tbody>
</table>

<sup>g</sup>See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).

<sup>m</sup>For alternate regimens, see BCEL-C.

<sup>n</sup>For patients not able to tolerate chemotherapy.

**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.
### TNM CLASSIFICATION OF CUTANEOUS LYMPHOMA OTHER THAN MF/SS\(^a,b\)

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
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</table>
| **T** | Solitary skin involvement  
T1a: a solitary lesion < 5 cm diameter  
T1b: a solitary > 5 cm diameter  
Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions\(^b\)  
T2a: all-disease-encompassing in a < 15-cm-diameter circular area  
T2b: all-disease-encompassing in a > 15- and < 30-cm-diameter circular area  
T2c: all-disease-encompassing in a > 30-cm-diameter circular area  
Generalized skin involvement  
T3a: multiple lesions involving 2 noncontiguous body regions\(^b\)  
T3b: multiple lesions involving ≥ 3 body regions\(^b\) |
| **N** | No clinical or pathologic lymph node involvement  
N0 | Involvement of 1 peripheral lymph node region\(^c\) that drains an area of current or prior skin involvement  
N1 | Involvement of 2 or more peripheral lymph node regions\(^c\) or involvement of any lymph node region that does not drain an area of current or prior skin involvement  
N2 | Involvement of central lymph nodes  
N3 | |
| **M** | No evidence of extracutaneous non–lymph node disease  
M0 | Extracutaneous non-lymph node disease present  
M1 |

---

\(^a\)This work was originally published in Blood. Kim YH, Willemze R, Pimpinell Ni, et al, for the ISCL and the EORTC. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary 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;110:479-484. ©the American Society of Hematology.

\(^b\)For definition of body regions, see Body Regions for the Designation of T (skin involvement) Category (CUTB-A 2 of 2).

\(^c\)Definition of lymph node regions is consistent with the Ann Arbor system: Peripheral sites: antecubital, cervical, supraclavicular, axillary, inguinal-femoral, and popliteal. Central sites: mediastinal, pulmonary hilar, paraaortic, iliac.

---

**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.
BODY REGIONS FOR THE DESIGNATION OF T (SKIN INVOLVEMENT) CATEGORY

**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.

---

**Definition of Body Regions:**

- **Head and Neck:** inferior border—superior border of clavicles; lateral borders—midaxillary lines, glenohumeral joints (inclusive of axillae).
- **Chest:** superior border—superior border of clavicles; inferior border—inferior margin of rib cage; lateral borders—mid-axillary lines.
- **Abdominal & Genital:** superior border—superior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—mid-axillary lines.
- **Right Upper Arm:** superior border—superior border of clavicles; inferior border—inferior margin of rib cage; lateral borders—mid-axillary lines.
- **Right Lower Arm & Hand:** superior border—superior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—mid-axillary lines.
- **Right Upper Leg:** superior border—superior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—mid-axillary lines.
- **Right Lower Leg & Feet:** superior border—superior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—mid-axillary lines.
- **Left Upper Arm:** superior border—superior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—mid-axillary lines.
- **Left Lower Arm & Hand:** superior border—superior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—mid-axillary lines.
- **Left Upper Leg:** superior border—superior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—mid-axillary lines.
- **Left Lower Leg & Feet:** superior border—superior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—mid-axillary lines.
- **Upper Back:** superior border—superior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—mid-axillary lines.
- **Lower Back & Buttock:** superior border—superior margin of rib cage; inferior border—inferior gluteal fold, anterior perineum (inclusive of perineum); lateral borders—mid-axillary lines.

---

**Left and right extremities are assessed as separate body regions. The designation of these body regions are based on regional lymph node drainage patterns.**

---

**References:**


- Left and right extremities are assessed as separate body regions. The designation of these body regions are based on regional lymph node drainage patterns.

**Rituximab**

**Chemotherapy**

**Topicals**
Topical/intralesional corticosteroids

Topical nitrogen mustard

Topical bexarotene

Topical imiquimod
**DIAGNOSIS**

**ESSENTIAL:**
- Review of all slides with at least one paraffin block representative of the tumor should be done by a hematopathologist with expertise in the diagnosis of PTCL. Rebiopsy if consult material is nondiagnostic.
- An FNA alone is not sufficient for the initial diagnosis of peripheral T-cell lymphoma.
- Adequate immunophenotyping to establish diagnosis\(^a,b\)
  - Recommended panel for paraffin section immunohistochemistry: CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, CD57, CD21, CD23, EBER, ALK
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20, CD30, CD4, CD8, CD7, CD2

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Molecular genetic analysis to detect: antigen receptor gene rearrangements; t(2;5) and variants
- Additional immunohistochemical studies to establish lymphoma subtype: βF1, CD279
- Cytogenetics or FISH
- CXCL-13, PD-1

**SUBTYPES**

**Subtypes included:**
- Peripheral T-cell lymphoma (PTCL), NOS
- Angioimmunoblastic T-cell lymphoma (AITL)\(^c\)
- Anaplastic large cell lymphoma (ALCL), ALK positive
- Anaplastic large cell lymphoma (ALCL), ALK negative
- Enteropathy associated T-cell lymphoma (EATL)

**Subtypes not included:**
- Primary cutaneous ALCL
- All other T-cell lymphomas

**Extranodal NK/T-cell lymphoma, nasal type** (See NKTL-1)

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\(^a\)Molecular diagnosis for T-cell receptor rearrangements should be done in most circumstances to confirm clonality. T-cell receptors rearrangements alone are not sufficient for diagnosis.

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

\(^c\)AITL may occasionally present with concurrent DLBCL. EBV and appropriate immunohistochemistry should be performed.

---

**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:
- Physical exam: attention to node-bearing areas, including Waldeyer’s ring, size of liver and spleen, skin rash and nasopharynx
- Performance status
- B symptoms
- CBC, differential, platelets
- Bone marrow biopsy
- LDH
- Comprehensive metabolic panel
- Uric acid
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Calculation of International Prognostic Index (IPI)<sup>e</sup>
- MUGA scan/echocardiogram if anthracycline or anthracenediones-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- PET-CT scan
- Neck CT
- Head CT or MRI
- Skin biopsy
- Discussion of fertility issues and sperm banking
- HIV, HTLV-1

<sup>d</sup>The role of intrathecal prophylaxis in PTCL is largely unknown.

<sup>e</sup>See International Prognostic Index (TCEL-A).

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** | **INDUCTION THERAPY** | **Consider prophylaxis for tumor lysis syndrome (See NHODG-B)**
---|---|---

**ALCL, ALK +**

- **Stage I, II**
  - aIPI<sup>e</sup> low/low-intermediate
  - Clinical trial (preferred) or Multiagent chemotherapy<sup>g</sup> 4 - 6 cycles + locoregional RT (30-40 Gy to involved region)
  - Interim restaging: repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.
  - At completion of treatment, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.

- **Stage III, IV**
  - aIPI<sup>e</sup> high/high-intermediate
  - Clinical trial (preferred) or Multiagent chemotherapy<sup>g</sup> 6 - 8 cycles ± RT<sup>h</sup>
  - Complete response<sup>i</sup> → Clinical trial or Consider high dose therapy with stem cell rescue<sup>j</sup> or Observe
  - Partial response or no response or progressive disease<sup>i</sup> → Relapse, See Additional Therapy (TCEL-5)

**See International Prognostic Index (TCEL-A).**

<sup>1</sup>For selected patients (elderly, comorbid conditions), a trial of single agent corticosteroid may be considered for symptom management.

<sup>g</sup>See Suggested Treatment Regimens (TCEL-B).

<sup>h</sup>Patients with locoregional disease receive RT.

<sup>i</sup>See Response Criteria for Lymphoma (NHODG-C).

<sup>j</sup>Localized areas can be irradiated before or after high dose therapy.

---

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.
NCCN Guidelines™ Version 4.2011
Peripheral T-Cell Lymphoma

STAGE I/II, LOW/LOW- INTERMEDIATE

INTERIM RESPONSE  FOLLOW-UP THERAPY  END OF TREATMENT RESTAGING

Complete response\(^1\) → Complete planned course of treatment (RT) → At completion of treatment, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.  
Partial response\(^1\) → RT (30-40 Gy) or High dose therapy with stem cell rescue ± RT or Clinical trial (may include allogeneic stem cell transplant ± RT)  
No response or progressive disease\(^1\) → RT or See Additional Therapy for Relapse (TCEL-5)

Clinical follow-up every 3-6 mo for 5 y and then yearly or as clinically indicated

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.

\(^1\)See Response Criteria for Lymphoma (NHODG-C).
**NCCN Guidelines™ Version 4.2011**

**Peripheral T-Cell Lymphoma**

**RELAPSE/REFRACTORY DISEASE**

- **Non-candidate for transplant**
  - Clinical trial or Second-line therapy
  - See Suggested Regimens (TCEL-B) or Palliative RT

- **Candidate for transplant**
  - Clinical trial preferred or Second-line therapy
  - See Suggested Regimens (TCEL-B)

**ADDITIONAL THERAPY**

- **Complete response**
  - Clinical trial preferred or Second-line therapy
  - See Suggested Regimens (TCEL-B)

- **Partial response**
  - Clinical trial preferred or Second-line therapy
  - See Suggested Regimens (TCEL-B)

- **No response**
  - Clinical trial preferred or Second-line therapy
  - See Suggested Regimens (TCEL-B)

**CONSOLIDATION/ADDITIONAL THERAPY**

- **Clinical trial** or Allogeneic stem cell transplant (non myeloablative or ablative) or High dose therapy with autologous stem cell rescue

**RELAPSE #2 OR GREATER**

- **Clinical trial** or Allogeneic stem cell transplant (non myeloablative or ablative) or High dose therapy with autologous stem cell rescue

- **Clinical trial** or Best supportive care or Palliative RT

---

1 See Response Criteria for Lymphoma (NHODG-C).
2 Localized areas can be irradiated before or after high dose therapy.

**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.
**INTERNATIONAL PROGNOSTIC INDEX\textsuperscript{a}**

**ALL PATIENTS:**
- Age > 60 years
- Serum LDH > 1 x normal
- Performance status 2-4
- Stage III or IV
- Extranodal involvement > 1 site

**INTERNATIONAL INDEX, ALL PATIENTS:**
- Low
- Low intermediate
- High intermediate
- High

**PATIENTS \leq 60 YEARS:**
- Stage III or IV
- Serum LDH > 1 x normal
- Performance status 2-4

**INTERNATIONAL INDEX, PATIENTS \leq 60 YEARS:**
- Low
- Low/intermediate
- High/intermediate
- High

**RISK FACTORS:**
- Age > 60 years
- Serum LDH > 1 x normal
- Performance status 2-4
- Bone marrow involvement

**PROGNOSTIC RISK:**
- Group 1
- Group 2
- Group 3
- Group 4

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**Prognostic Index for PTCL-U (PIT)\textsuperscript{b}**

**RISK FACTORS:**
- Age > 60 years
- Serum LDH > 1 x normal
- Performance status 2-4
- Bone marrow involvement

**PROGNOSTIC RISK:**
- Group 1
- Group 2
- Group 3
- Group 4

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\textsuperscript{a}International Prognostic Index for (PIT)\textsuperscript{b}PTCL-U

**RISK FACTORS:**
- Age > 60 years
- Serum LDH > 1 x normal
- Performance status 2-4
- Bone marrow involvement

**PROGNOSTIC RISK:**
- Group 1
- Group 2
- Group 3
- Group 4

---

**AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX\textsuperscript{a}**

**ALL PATIENTS:**
- Age > 60 years
- Serum LDH > 1 x normal
- Performance status 2-4
- Stage III or IV
- Extranodal involvement > 1 site

**INTERNATIONAL INDEX, ALL PATIENTS:**
- Low
- Low intermediate
- High intermediate
- High

**PATIENTS \leq 60 YEARS:**
- Stage III or IV
- Serum LDH > 1 x normal
- Performance status 2-4

**INTERNATIONAL INDEX, PATIENTS \leq 60 YEARS:**
- Low
- Low/intermediate
- High/intermediate
- High

**RISK FACTORS:**
- Age > 60 years
- Serum LDH > 1 x normal
- Performance status 2-4
- Bone marrow involvement

**PROGNOSTIC RISK:**
- Group 1
- Group 2
- Group 3
- Group 4

---


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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.
SUGGESTED TREATMENT REGIMENS\textsuperscript{a}

(in alphabetical order)

**First-line therapy:**\textsuperscript{b}
- Clinical trial preferred
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) appropriate for ALCL, ALK+.
- Other regimens that can be used include:
  - CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone)
  - CHOP every 2 or 3 wks
  - CHOP followed by ICE (ifosfamide, carboplatin, etoposide)
  - CHOP followed by IVE (ifosfamide, etoposide and epirubicin) alternating with intermediate dose methotrexate [New Castle Regimen]
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine

**Second-line therapy (candidate for transplant):**
- Clinical trial preferred
- Brentuximab vedotin for nodal ALCL only (excluding cutaneous ALCL)
- DHAP (dexamethasone, cisplatin, cytarabine)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
- GDP (gemcitabine, dexamethasone, cisplatin)
- GemOx (gemcitabine, oxaliplatin)
- ICE (ifosfamide, carboplatin, etoposide)
- MINE (mesna, ifosfamide, mitoxantrone, etoposide)
- Pralatrexate (category 2B)\textsuperscript{c}
- Romidepsin

**Second-line therapy (non-candidate for transplant):**
- Clinical trial preferred
- Alemtuzumab\textsuperscript{d}
- Bortezomib\textsuperscript{d}
- Brentuximab vedotin for nodal ALCL only (excluding cutaneous ALCL)
- Cyclosporine forAITL only\textsuperscript{e}
- Denileukin diftitox
- Gemcitabine
- Pralatrexate\textsuperscript{c}
- Radiation therapy
- Romidepsin

---

\textsuperscript{a}See references for regimens TCEL-B 2 of 2.

\textsuperscript{b}Standard induction for PTCL remains undefined with the exception of ALCL, ALK+ for which CHOP remains the standard. Clinical trial is preferred for all other subtypes.

\textsuperscript{c}In AITL, pralatrexate has limited activity.

\textsuperscript{d}Activity has been demonstrated in small clinical trials and additional larger trials are needed.

\textsuperscript{e}With close follow-up of renal function.

---

**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.
First-line therapy

**CHOP**

**CHOP or CHOP-14 with or without etoposide**

**CHOP followed by ICE**

**CHOP followed by IVE**

**HyperCVAD alternating with high-dose methotrexate and cytarabine**

Second-line therapy

**Alemtuzumab**

**Brentuximab**

**Cyclosporine for AILT**

**Denileukin diftitox**


**DHAP (dexamethasone, cisplatin, cytarabine)**


**ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)**

**Gemcitabine**

**GDP (gemcitabine, dexamethasone, cisplatin)**

**GemOX (gemcitabine, oxaliplatin)**

**ICE (ifosfamide, carboplatin, etoposide)**

**Pralatrexate**

**Romidepsin**
**NCCN Guidelines™ Version 4.2011**

**Mycosis Fungoides/Sezary Syndrome**

**DIAGNOSIS WORKUP**

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

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Immunohistochemical studies of skin biopsy (CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD26, CD56, TIA1, granzyme B, TIA1)
- Molecular study for T-cell receptor (TCR) gene rearrangements (assessment of clonality) of skin biopsy
- Assessment of peripheral blood for Sezary cells, including Sezary cell prep, flow cytometry, and PCR for TCR gene rearrangement
- Biopsy of suspicious lymph nodes (in absence of definitive skin diagnosis)
- Assessment of ATLL serology or PCR in at-risk populations

**WORKUP 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 or 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

**STAGE (MFSS-2)**

- Stage IA: See Primary Treatment (MFSS-4)
- Stage IB-IIA: See Primary Treatment (MFSS-5)
- Stage IIB: See Primary Treatment (MFSS-6)
- Stage III: See Primary Treatment (MFSS-7)
- Stage IV: See Primary Treatment (MFSS-8)

---

**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.

---


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

**c:** 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. Demonstration of identical clones in skin, blood and/or lymph node may be helpful in selected cases.

**d:** Sezary syndrome (B2) is as defined on MFSS-2.

**e:** Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.
## TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome

<table>
<thead>
<tr>
<th>TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
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<tr>
<td>B1</td>
</tr>
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<td>B2</td>
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</table>


<sup>g</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 more or increase in CD4 cells with an abnormal phenotype (40% CD4/CD7 or 30% CD4/CD26).

<sup>h</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>i</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>k</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>l</sup>Spleen and liver may be diagnosed by imaging criteria.

<sup>m</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.

---

**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.
### Clinical Staging/Classification of MF and SS

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<th>T</th>
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<th>M</th>
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</tbody>
</table>


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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.
**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)

**Histologic evidence of folliculotropic or large cell transformed MF**

See Primary Treatment for Stage IIB on page MFSS-6

---

**CR/PR** or inadequate response

- Relapse with or persistent T1 skin disease

- Refractory disease 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

---

**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.

---

**n:** Folliculotropic, large cell transformed MF, or B1 involvement has been associated with worse outcome, thus, may be managed as "tumor (IIB)" disease (MFSS-6) or stage III with B1 involvement (MFSS-7), respectively.

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

**p:** 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.

**q:** 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
  - See stage IA on MFSS-4
- If blood B1 involvement, consider primary treatment for Stage IIIIB B1 (MFSS-7) (category 2B)

### Histologic evidence of folliculotropic or large cell transformed MF

- See Primary Treatment for Stage IIB on page MFSS-6

---

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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.
NCCN Guidelines™ Version 4.2011
Mycosis Fungoides/Sezary Syndrome

STAGE (MFSS-2)

Limited extent tumor disease ± patch/plaque disease

Generalized extent tumor, transformed, and/or folliculotrophic disease

Stage IIBs and/or histologic evidence of folliculotrophic or large cell transformation (LCT)

PRIMARY TREATMENT

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

CR/PR or inadequate response

Relapse with or persistent T1-T3 limited:
- T1-2 (see stage IA on MFSS-4 or stage IB-IIA on MFSS-5)

Refractory disease or progression

Relapse with or persistent T1-T3:
- T1-2 (see stage IA on MFSS-4 or stage IB-IIA on MFSS-5)
- T3

TSEBT

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

CR/PR or inadequate response

Refractory disease or progression

Multi-agent chemotherapy
- Consider allogeneic transplant
- Clinical trial

CR/PR or inadequate response

Relapse with or persistent T1-T3:
- T1-2 (see stage IA on MFSS-4 or stage IB-IIA on MFSS-5)
- T3

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 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

CR/PR or inadequate response → Relapse or persistent disease

- Combination therapies
  - See Suggested Treatment Regimens - Combination Therapies (MFSS-A)
  - Clinical trial

Refractory disease or progression

- Clinical trial
  - See Suggested Treatment Regimens "Systemic Therapies (SYST-CAT B)"
  - Alemtuzumab
  - Consider non-ablative allogeneic transplant

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.

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.

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

Alemtuzumab can be administered by IV or subcutaneously. Lower doses administered subcutaneously have shown lower incidence of infectious complications.
STAGE (MFSS-2)

Stage IV

Sezary syndrome

Non Sezary or Visceral disease (solid organ)

Primary Treatment

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

- See Suggested Treatment Regimens - Systemic Therapies (SYST-CAT B) or (SYST-CAT C) or multi-agent chemotherapy ± RT for local control

CR/PR or inadequate response

CR/PR or inadequate response

Relapse or persistent disease

Relapse or persistent disease

- Consider allogeneic transplant, as appropriate

- Consider allogeneic transplant, as appropriate

Refractory disease or progression

Refractory disease or progression

Clinical trial

- Alemtuzumab
- 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.

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.

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

Alemtuzumab can be administered by IV or subcutaneously. Lower doses administered subcutaneously has 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.
SUGGESTED TREATMENT REGIMENS

SKIN-DIRECTED THERAPIES

For limited/localized skin involvement (Skin-Limited/Local)
- Topical corticosteroids
- Topical chemotherapy (mechlorethamine [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 [nitrogen mustard], 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 (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
- 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)
  - Bortezomib
  - Low dose pralatrexate

SYSTEMIC THERAPIES (continued)

Category C (SYST-CAT C)
- Liposomal doxorubicin
- Gemcitabine
- Denileukin diftitox
- Romidepsin
- Low or standard dose pralatrexate
- See regimens listed on TCEL-B

COMBINATION THERAPIES

Skin-directed + Systemic
- Phototherapy + retinoid
- Phototherapy + IFN
- Photopheresis + photopheresis

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

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

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

Patients with large cell transformed (LCT) MF and stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. In general, agents listed in SYST-CAT C are preferred in these circumstances.

Combination regimens are generally reserved for patients with relapsed/refractory or extracutaneous disease.

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.

See references for regimens MFSS-A 2 of 4, MFSS-A 3 of 4, and MFSS-A 4 of 4
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.
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 squamous proliferative skin neoplasms or basal cell carcinomas or who have had melanoma.

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

Safety of combining TSEBT with systemic retinoids or HDAC-inhibitors, such as vorinostat or romidepsin or combining photopheresis with vorinostat or romidepsin is unknown.
Photopheresis may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).
Patients with large cell transformed (LCT) MF and stage IV non-Sezary/visceral disease may present with more aggressive growth characteristics. In general, agents listed in SYST-CAT C are preferred in these circumstances.
SUGGESTED TREATMENT REGIMENS

References

Skin-directed therapies

Topical corticosteroids

Carmustine

Nitrogen mustard (mechlorethamine hydrochloride)

Local radiation

Topical bexarotene

Tazarotene Gel

Topical imiquimod

Phototherapy (UVB and PUVA)

Total skin electron beam therapy (TSEBT)

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.
SUGGESTED TREATMENT REGIMENS

References


Extracorporeal photopheresis (ECP)

Denileukin diftitox

Methotrexate

Liposomal doxorubicin

Gemcitabine

Continued on next page
**SUGGESTED TREATMENT REGIMENS**

**References**


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ATLL-1

**DIAGNOSIS**

**ESSENTIAL:**
- HTLV-1 serology: ELISA and confirmatory Western Blot if ELISA is positive
- Peripheral blood smear analysis for atypical cells
- Flow cytometry on peripheral blood

**USEFUL IN CERTAIN CIRCUMSTANCES:**
- Biopsy of lymph nodes (excisional), skin biopsy, GI tract, or bone marrow biopsy is required if:
  - Diagnosis is not established on peripheral blood, or
  - Ruling out an underlying infection (tuberculosis, histoplasmosis, toxoplasmosis, etc.)
- If biopsy performed, the recommended panel for paraffin section immunohistochemistry:

**WORKUP**

**ESSENTIAL:**
- Complete history and physical examination-including complete skin exam
- CBC and blood smear: lymphocytosis (ALC > 4000/μL in adults) in acute and chronic subtypes
- Electrolytes, BUN, creatinine, serum calcium, serum LDH
- Chest/abdominal/pelvic/neck CT scan
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

**USEFUL IN SELECTED CASES:**
- Upper gastrointestinal endoscopy
- Skeletal survey in symptomatic patients
- Stool examination for parasites (strongyloides is most likely)
- PET-CT scan
- Central nervous system evaluation: CT scan, MRI and/or lumbar puncture in all patients with acute or lymphoma subtypes or in patients with neurologic manifestations

---

*a* The diagnosis of ATLL requires histopathology and immunophenotyping of tumor lesion, or morphology and immunophenotyping of peripheral blood, and/or HTLV serology.

*b* Typical ATL cells (“flower cells”) have distinctly polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli and agranular and basophilic cytoplasm but multiple morphological variations can be encountered. Presence of ≥ 5% atypical cells by morphology in peripheral blood is required for diagnosis in the absence of other criteria.

*c* Presence of ≥ 5% T-lymphocytes with an abnormal immunophenotype in peripheral blood is required for diagnosis.

*d* Bone marrow involvement is an independent poor prognostic factor.

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

*f* Usually CD4+ T-cells with expression of CD2, CD5, CD25, CD45RO, CD29, T-cell receptor αβ and HLA-DR. Most cases are CD7 - and CD26 - with low CD3 expression. Rare cases are CD8 + or CD4/CD8 double positive or double negative.
### NCCN Guidelines™ Version 4.2011
#### Adult T-cell Leukemia/Lymphoma

<table>
<thead>
<tr>
<th>ATLL SUBTYPE&lt;sup&gt;g&lt;/sup&gt;</th>
<th>PRIMARY THERAPY&lt;sup&gt;h&lt;/sup&gt;</th>
<th>INITIAL RESPONSE (at 2 mo)</th>
<th>ADDITIONAL THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic/Smoldering</td>
<td>Clinical trial or Observation or Skin-directed therapies as clinically indicated (See Mycosis Fungoides/Sezary Syndrome MFSS-A) or Zidovudine and interferon&lt;sup&gt;i,j&lt;/sup&gt;</td>
<td>Complete response&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Continue treatment with zidovudine and interferon</td>
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<tr>
<td></td>
<td></td>
<td>Persistor or progressive disease&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Chemotherapy (See Suggested Treatment Regimens ATLL-C) or Clinical trial or Best supportive care</td>
</tr>
</tbody>
</table>

<sup>g</sup>See Diagnostic Criteria for Clinical Subtype of ATLL (ATLL-A).

<sup>h</sup>Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis prophylaxis is recommended.

<sup>i</sup>Outside of a clinical trial, if a patient is not responding or is progressing, treatment with zidovudine and interferon should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. If life threatening manifestations, treatment can be discontinued before the two months period.

<sup>j</sup>See references for zidovudine and interferon (ATLL-D).

<sup>k</sup>See Response Criteria for ATLL (ATLL-B).

---

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## ATLL Subtype

### Acute

<table>
<thead>
<tr>
<th>Initial Response (after 2 cycles)</th>
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<tr>
<td>Complete response&lt;sup&gt;k&lt;/sup&gt;</td>
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<tr>
<td>Persistent or progressive disease&lt;sup&gt;k&lt;/sup&gt;</td>
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</tbody>
</table>

**Primary Therapy**
- Clinical trial or Zidovudine and interferon<sup>ij</sup> or Chemotherapy (See Suggested Treatment Regimens (ATLL-C))

**Additional Therapy**
- Continue treatment with zidovudine and interferon or Consider allogeneic stem cell transplant

**Lymphoma<sup>l,m,n</sup>**

<table>
<thead>
<tr>
<th>Initial Response (after 2 cycles)</th>
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</thead>
<tbody>
<tr>
<td>Complete response&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td>Persistent or progressive disease&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Primary Therapy**
- Clinical trial or Chemotherapy (See Suggested Treatment Regimens ATLL-C)

**Additional Therapy**
- Consider allogeneic stem cell transplant

---

<sup>g</sup>See Diagnostic Criteria for Clinical Subtype of ATLL (ATLL-A).

<sup>h</sup>Supportive care: anti-infectious prophylaxis with sulfamethoxazole/trimethoprim + strongyloidosis prophylaxis is recommended.

<sup>i</sup>Outside of a clinical trial, if a patient is not responding or is progressing, treatment with zidovudine and interferon should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. If life threatening manifestations, treatment can be discontinued before the two months period.

<sup>j</sup>See References for zidovudine and interferon (ATLL-D).

<sup>k</sup>See Response Criteria for ATLL (ATLL-B).

<sup>l</sup>Efficacy of long term treatment is limited. There are small series where transplant is beneficial. There is no defined treatment.

<sup>m</sup>Antiviral therapy is not effective.

<sup>n</sup>CNS prophylaxis: intrathecal chemotherapy is recommended (methotrexate and cytarabine and corticosteroids).

---

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### Diagnostic Criteria and Classification of Clinical Subtypes of ATLL\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Healthy carrier</th>
<th>Smoldering ATL</th>
<th>Chronic ATL</th>
<th>Acute ATL</th>
<th>ATL Lymphoma</th>
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<td>Bone marrow or spleen involvement</td>
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</table>


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### RESPONSE CRITERIA FOR ATLL\(^a\)

<table>
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<tr>
<th>Response</th>
<th>Definition</th>
<th>Lymph Nodes</th>
<th>Extranodal Masses</th>
<th>Spleen, Liver</th>
<th>Skin</th>
<th>Peripheral Blood</th>
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<tr>
<td><strong>Complete remission(^*)</strong></td>
<td>Disappearance of all disease</td>
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<td>Normal</td>
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<td>Normal</td>
<td>Normal(^†)</td>
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<tr>
<td><strong>Uncertified complete remission(^*)</strong></td>
<td>Stable residual mass in bulky lesion</td>
<td>≥ 75% decrease(^‡)</td>
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<td>Normal</td>
<td>Normal(^†)</td>
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<tr>
<td><strong>Partial remission(^*)</strong></td>
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<td>≥ 50% decrease</td>
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<td><strong>Stable disease(^*)</strong></td>
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<td>No change in size</td>
<td>No change in size</td>
<td>No change in size</td>
<td>No change in size</td>
<td>No change</td>
</tr>
<tr>
<td><strong>Relapsed disease or progressive disease</strong></td>
<td>New or increased lesions</td>
<td>New or ≥ 50% increase(^§)</td>
<td>New or ≥ 50% increase(^§)</td>
<td>New or ≥ 50% increase</td>
<td>≥ 50% increase</td>
<td>New or ≥ 50% increase(^#)</td>
<td>Reappearance</td>
</tr>
</tbody>
</table>

\(^*\)Required that each criterion to be present for a period of at least 4 weeks.
\(^†\)Provided that < 5% of flower cells remain, complete remission is judged to have been attained if the absolute lymphocyte count, including flower cells, is < 4 x 10[^9]L.
\(^‡\)Calculated by the sum of the products of the greatest diameters of measurable disease.

\(^§\)Defined by ≥ 50% increase from nadir in the sum of the products of measurable disease.
\(^#\)Defined by ≥ 50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of > 4 x 10[^9]L.

SUGGESTED TREATMENT REGIMENS

- Chemotherapy\textsuperscript{a}
  - CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)
  - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine

\textsuperscript{a}There is not published data regarding the use of these regimens, however, they are used at NCCN member institutions for the treatment of ATLL.

\textbf{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.
REFERENCES FOR ZIDOVUDINE AND INTERFERON

**Zidovudine and interferon**


NCCN Guidelines™ Version 4.2011
Extranodal NK/T-cell Lymphoma, nasal type

DIAGNOSIS

ESSENTIAL:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is non-diagnostic.
- A FNA or core needle biopsy alone is not suitable for the initial diagnosis of lymphoma.\textsuperscript{b}
- In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis\textsuperscript{c}
  - Recommended immunohistochemistry (IHC) panel: B cell: CD20; T lineage antigens: CD2, CD7, CD8, CD4, CD5. cCD3\textsubscript{ε}; NK lineage markers: CD56; Ki-67 (nuclear antigen marker).
  - \textit{in situ} hybridization (ISH) for (EBER-1/2)\textsuperscript{d}

\textsuperscript{a}It is preferred that treatment occur at centers with expertise in the management of this disease.
\textsuperscript{b}Necrosis is very common in diagnostic biopsies and may delay diagnosis significantly. Biopsy should include the edges of lesions, to increase the odds of having viable tissue. Useful to perform multiple nasopharyngeal biopsies even in areas not clearly involved.
\textsuperscript{c}Typical NK/T-cell immunophenotype: CD20\textsuperscript{-}, CD2\textsuperscript{+}, cCD3\textsubscript{ε} (surface CD3\textsuperscript{-}), CD7\textsuperscript{+}, CD8\textsuperscript{+} CD45RO\textsuperscript{+}, CD43\textsuperscript{+}, CD56\textsuperscript{+}, T-cell receptor (TCR)\textgamma\textbeta, TCR\textgamma\textdelta, TCR and Ig genes are usually germline (NK lineage).
\textsuperscript{d}Negative result should prompt pathology review for alternative diagnosis.

SUBTYPES

Subtypes included:
- Extranodal NK/T-cell, nasal type

Subtypes not included:
- NK-cell leukemias
- Precursor NK-cell neoplasm

WORKUP

ESSENTIAL:
- Physical exam; attention to complete ENT evaluation nasopharynx involvement (including Waldeyer's ring), testicles and skin
- Performance status
- B symptoms
- CBC, differential platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Bone marrow biopsy + aspirate\textsuperscript{e}
- Chest/abdominal/pelvic CT with contrast of diagnostic quality or PET-CT scan with diagnostic quality CT
- Dedicated CT of the nasal cavity, hard palate, anterior fossa or MRI nasopharynx
- Calculation of NK/T-cell PI\textsuperscript{f}
- MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenediones
- EBV viral load\textsuperscript{g}

USEFUL IN SELECTED CASES:
- Pregnancy testing in women of child-bearing age
- Discussion of fertility and sperm banking
- HIV

\textsuperscript{e}BM aspirate - lymphoid aggregates rare, considered involved if EBER-1 positive, hemophagocytosis may be present.
\textsuperscript{f}See NK/T-cell Lymphoma Prognostic Index (NKTL-\textsuperscript{A}).
\textsuperscript{g}EBV viral load is important in diagnosis and possibly in monitoring of disease. A positive result is consistent with NK/T-cell, nasal type. Lack of normalization of EBV viremia should be considered indirect evidence of persistent disease.

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.
NCCN Guidelines™ Version 4.2011
Extranodal NK/T-cell Lymphoma, nasal type

**INDUCTION THERAPY**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>No risk factors present</th>
<th>Presence of ANY risk factor</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Assess risk factors</td>
<td>Clinical trial or RT alone (≥ 50 Gy) or Concurrent chemoradiotherapy&lt;sup&gt;h&lt;/sup&gt;</td>
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<tr>
<td>Stage II</td>
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<td>Clinical trial or Concurrent chemoradiotherapy&lt;sup&gt;h&lt;/sup&gt;</td>
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<tr>
<td>Stage III/IV</td>
<td></td>
<td>Clinical trial or Concurrent chemoradiotherapy&lt;sup&gt;h&lt;/sup&gt; or Combination chemotherapy regimen (L-asparaginase based)&lt;sup&gt;h&lt;/sup&gt; ± RT</td>
</tr>
</tbody>
</table>

**Risk factors** (includes elements of NK/T-cell Lymphoma PI on NKTL-A)

- Age > 60 y
- B symptoms
- ECOG PS ≥ 2
- Elevated LDH
- Regional node involvement
- Local tumor invasion (LTI); bone or skin
- Histological evidence of high Ki-67 staining
- EBV DNA titer ≥ 6.1 x 10<sup>7</sup> copies/ml


<sup>h</sup>See Suggested Treatment Regimens (NKTL-B).

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.
NCCN Guidelines™ Version 4.2011
Extranodal NK/T-cell Lymphoma, nasal type

POST RT EVALUATION

Nasal
Extranasal

Stage I, with or without risk factors
Stage II- IV

CR

CR or PR

Hematopoietic stem cell transplant, if eligible
Salvage chemotherapy, or Best supportive care

POST RT evaluation
- Repeat initial imaging of CT, MRI, or PET-CT scan
- Endoscopy with visual inspection and repeat biopsies
- EBV viral load

RESPONSE ASSESSMENT

CR

Observe

Hematopoietic stem cell transplant, if eligible
Salvage chemotherapy, or Best supportive care

ADDITIONAL THERAPY

Refractory disease


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.

See Response Criteria for Lymphoma (NHODG-C).
Includes a negative ENT evaluation.
Allogeneic preferred, if matched donor available.
Combination chemotherapy regimen (L-asparaginase based) See Suggested Treatment Regimens (NKTL-B).

The role of PET scan in this disease is not well established.

# NK/T CELL LYMPHOMA PROGNOSTIC INDEX

### ALL PATIENTS

- Serum LDH > 1 x normal
- B symptoms
- Lymph nodes, N1 to N3, not M1
- Ann Arbor Stage III

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<tr>
<td>High</td>
<td>3 or 4</td>
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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.
SUGGESTED TREATMENT REGIMENS

Combination chemotherapy regimen (L-asparaginase based)
- SMILE (steroid [dexamethasone], methotrexate, ifosfamide, L-asparaginase, and etoposide)

Concurrent chemoradiotherapy (CCRT)
- CCRT (radiation 50 Gy and 3 courses of DeVIC [dexamethasone, etoposide, ifosfamide, and carboplatin])
- CCRT (radiation 40 to 52.8 Gy and cisplatin) followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)

Radiotherapy alone (or in sequence with chemotherapy)
- Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal-type, in the upper aerodigestive tract. The recommended tumor dose was ≥ 50 Gy. Up-front RT may yield more benefits on survival in patients with stage I disease.

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.
SUGGESTED TREATMENT REGIMENS

References

Combination chemotherapy regimen (L-asparaginase based)

Concurrent chemoradiotherapy

Radiotherapy alone
### DIAGNOSIS

**ESSENTIAL:**
- Histopathology and adequate immunophenotype to establish diagnosis. Rebiopsy if consult material is nondiagnostic.
  - Recommended panel for paraffin section immunohistochemistry: CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, Ki67
  - Cell surface marker analysis by flow cytometry: CD3, CD5, CD7, CD4, CD8, CD19, CD20, CD10, Kappa, lambda
- Epstein-Barr virus (EBV-ISH). If the less sensitive EBV-LMP1 stain is positive, EBER in situ hybridization is not required.

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Panel for paraffin section immunohistochemistry: CD15, CD30, CD45, CD7, CD4, CD8, ALK, TIA-1, Granzyme B, CD57, CD56, CD138
- Cell surface marker analysis by flow cytometry: CD138, cytoplasmic Kappa and lambda, CD30, CD57, CD56, CD16, CD25, CD52.
- Molecular genetic analysis to detect gene rearrangements: IgH by PCR
- BCL6 gene mutation analysis

### WORKUP

**ESSENTIAL:**
- Performance status
- Albumin
- Immunosuppressive regimen
- LDH, electrolytes, BUN, creatinine
- CBC, differential
- Hepatitis B testing
- Chest/abdomen/pelvis CT

**USEFUL IN SELECTED CASES:**
- MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenediones
- Bone marrow evaluation
- PET-CT scan
- EBV PCR, CMV PCR
- Brain MRI

**Early lesions**
- Polymorphic

**Monomorphic**
- Classic Hodgkin lymphoma

---

**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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*a* BCL6 gene mutation positivity has been associated with a poor response to reduction in immunosuppressive therapy.

*b* Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
PTLD SUBTYPE

Early lesions

- Reduction of immunosuppressive (RI)
- If EBV positive, treat with gancyclovir

Polymorphic

- RI, if possible
- If EBV positive, treat with gancyclovir
- Rituximab
- Chemoimmunotherapy

RT or Surgery or Rituximab alone

Monomorphic

- RI or Chemoimmunotherapy
- Rituximab alone

Classic Hodgkin lymphoma

Treat as Hodgkin lymphoma

(See NCCN Hodgkin Lymphoma Guidelines)

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.
NCCN Guidelines™ Version 4.2011
Post-Transplant Lymphoproliferative Disorder

SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
- RCHOEP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (for frail patients who cannot tolerate anthracycline)

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)

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.
USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND T/NK-CELL NEOPLASMS
(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)

Small cells:

- Chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL)
- Mantle cell lymphoma (MCL)
- Splenic marginal zone lymphoma
- Hairy cell leukemia (HCL)
- Lymphoplasmacytic lymphoma (LPL)
- Extranodal marginal zone lymphoma (MALT lymphoma)
- Nodal marginal zone lymphoma
- Follicular lymphoma (FL)

Panel: CD5, CD10, CD23, cyclin D1, BCL2, BCL6 (CD25, CD103)

CD23 + → CLL → cyclin D1 - t(11;14) -
CD5 +
CD23 - → cyclin D1 + t(11;14) + → MCL
cyclin D1 - t(11;14) - → CLL
CD5 -
CD10 + → FL → BCL6 + BCL2 + t(14;18) +
CD103 + → HCL → annexin 1 +
CD25 +
CD103 -
CD10 -
Cytoplasmic Ig - → LPL vs MZL → Cytoplasmic Ig +

- Morphology (MZ pattern)
- Clinical features (extranodal, splenic)
- Pseudofollicular pattern, clinical features (BM)
- Morphology (MZ pattern, plasmacytoid features, genetics (del 7q))
- Clinical features (splenomegaly, bone marrow involvement, paraprotein)

CD5 -
CLL
HCL

85% of Follicular Lymphoma will be BCL2 + or t(14;18) +.

Rare cases of both cyclin D1 and t(11;14) negative MCL have been reported. This diagnosis should be made with extreme caution and with expert consultation.

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.
Medium cells
- Burkitt lymphoma (BL)
- Diffuse large B-cell lymphoma (DLBCL)
- Mantle cell lymphoma (MCL), blastoid variant
- B-cell lymphoma (BCL), unclassifiable, intermediate between DLBCL and BL (U-DLBCL/BL)

B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)

Panel: CD5, CD10, BCL2, BCL6, cyclin D1, Ki67

CD5 +
- cyclin D1 + blastoid MCL
- BCL6 +/- IRF4/MUM1 +/-
  - CD5 + DLBCL
- Cyclin D1 - Ki67 95%
  - BCL6 + BCL2 -
  - MYC + BCL2 - BCL6 -
  - MYC +/- BCL2 + BCL6 +/
  - BL

CD5 -
- CD10 +
- BCL6 + BCL2 +
  - Fish for MYC, BCL2, BCL6
  - U-DLBCL/BL
- BCL6 + BCL2 - IRF4/MUM1 - Ki67 > 90%
  - Fish for MYC, BCL2, BCL6
  - U-DLBCL/BL

CD10 -
- BCL6 +/- BCL2 + IRF4/MUM1 +/- Ki67 60-90%
  - U-DLBCL/BL
  - Fish for MYC, BCL2, BCL6 to check for “double hit”

MYC + BCL2 - BCL6 -

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.

These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND T/NK-CELL NEOPLASMS

(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

**B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)**

Large cells:

- Diffuse large B-cell lymphoma (DLBCL), NOS
  - T-cell/histiocyte rich large B-cell lymphoma (THRLBCL)
  - Primary DLBCL of the CNS
  - Primary cutaneous DLBCL, leg type
  - EBV positive DLBCL of the elderly (EBV + DLBCL)
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma (PMBL)
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease (LBCL in HHV8 + MCD)
- Primary effusion lymphoma
- B-cell lymphoma, unclassifiable, intermediate between DLBCL (U-DLBCL) and classical Hodgkin lymphoma (CHL)
- Mantle cell lymphoma (MCL), pleomorphic variant

**GCB= Germinal center B-cell like**

- cyclin D1 + pleomorphic MCL
- CD5 +
- cyclin D1 - BCL6 +/- IRF4/MUM1 +/
- CD5 + DLBCL, NOS
- CD5 - DLBCL or U-DLBCL/CHL
- CD10+ DLBCL, NOS GCB type (BCL6+)
- CD10- BCL6 + IRF4/MUM1 - DLBCL, NOS GCB type
- BCL6 + IRF4/MUM1 - Non-GCB
- BCL6 - IRF4/MUM1 + Post-GCB

Panel: CD5, CD10, BCL6, IRF4/MUM1

**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.
USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND T/NK-CELL NEOPLASMS

(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

Large cells (continued)

- **CD30 -**
  - **EBER - HHV8 -**
    - **CD30 +**
      - **EBER + HHV8 -**
        - **CD30 +**
          - **Elderly or immunosuppressed**
            - **EBV + DLBCL**
        - **CD15 -**
          - **PMBL**
      - **Morphologically borderline with CHL**
        - **CD15 +**
          - **U-DLBCL/CHL**
    - **EBR +/ HHV8 -**
      - **EBR - HHV8 +**
        - **LBCL in HHV8 + multicentric Castleman disease (IgM lambda +)** confirm by morphology
      - **EBR + HHV8 -**
        - **Plasmablastic lymphoma**
      - **EBR +/- HHV8 +**
        - **PEL (CD30+)**
      - **EBR - ALK+**
        - **ALK + DLBCL**
          - **IgA lambda + EMA +**
      - **EBR - ALK - HHV8 -**
        - **Anaplastic/Plasmablastic myeloma/plasmacytoma**
          - **IgG, A, kappa or lambda**

- **CD30 -**
  - **EBR - HHV8 +**
    - **T-cell-rich**
      - **THRLBCL (May be BCL6 +, IRF4/MUM1 -)**

**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.

These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

These stains/studies are not routinely available.
USE OF IMMUNOPHENOTYPING/GENETIC TESTING IN DIFFERENTIAL DIAGNOSIS OF MATURE B-CELL AND T/NK-CELL NEOPLASMS

(TO BE USED IN CONJUNCTION WITH CLINICAL PATHOLOGICAL CORRELATION)

B-CELL ANTIGENS POSITIVE (CD19, CD20, CD79a, PAX5)

- **Primary cutaneous marginal zone lymphoma (PCMZL)**
- **Primary cutaneous follicle center lymphoma (PCFCL)**
- **Primary cutaneous DLBCL, leg type (PC-DLBCL, leg type)**

**Cutaneous localization** ➔ **Panel: CD10, BCL2, BCL6, IRF4/MUM1, CD21/23 (FDC markers)**

- **CD10 +** ➔ **PCFCL**
  - **BCL6 +**
    - **IRF4/MUM1 -**
      - (FDC +/-)
      - Small/medium/large cells ➔ **PCFCL**
  - **BCL2 -**
    - **BCL6 -**
      - **IRF4/MUM1 +/-**
        - (FDC +)
        - Small/medium cells ➔ **PCMZL**
    - **BCL6 +/-**
      - **IRF4/MUM1 +**
        - (FDC -)
        - Large round cells ➔ **PC-DLBCL, leg type**

- **CD10 -** ➔ **BCL2 -**
  - **BCL6 +**
    - **IRF4/MUM1 +**
      - (FDC +)
      - Small/medium cells ➔ **PCMZL**
  - **BCL6 +**
    - **IRF4/MUM1 -**
      - (FDC +, follicular)
      - Small/medium/large cells ➔ **PCFCL**

**FDC = Follicular dendritic cells**

*These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.*

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.
Anaplastic morphology

- Anaplastic large cell lymphoma (ALCL), ALK positive
- Anaplastic large cell lymphoma (ALCL), ALK negative
- Adult T-cell leukemia/lymphoma (ATLL), anaplastic large cell type
- Enteropathy associated T-cell lymphoma (EATL)
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis (LyP)
  - Primary cutaneous anaplastic large cell lymphoma (PC-ALCL)

These are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.
T-CELL ANTIGENS POSITIVE (CD2, CD3, CD5, CD7) [and B-cell antigens negative (Pax5)]

**Cutaneous localization (non-anaplastic morphology)**
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders (LPD)
- Mycosis fungoides, Sézary syndrome (MF, SS)
- Subcutaneous panniculitis-like T-cell lymphoma (SCPTCL)
- Primary cutaneous gamma-delta T-cell lymphoma (γδTCL)
- **Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma** (AECTCL)
- **Primary cutaneous CD4 positive small/medium T-cell lymphoma**
- Extraneodal NK/T-cell lymphoma, nasal type
- Peripheral T-cell lymphoma, NOS
- Blastic plasmacytoid dendritic cell neoplasm (BPDC)

αThese are meant to be general guidelines. Interpretation of results should be based on individual circumstances and may vary. Not all tests will be required in every case.

βA minority of MF cases can be CD30+, CD4- and either CD8 +/-, TIA1 +.

CD8 + AIDS T-cell lymphoma (CD2+ CD5- CD7+/ CD8+ CD56- CGP+), or ET (CD2+ CD5- CD7+/ CD8+ CD56+/- CGP+) (dermis and subcutis often involved)

CD8 - Consider myeloid sarcoma (may be CD2+ CD7+ CD56+) or BPDC (CD3- CD5- CD123+ CD68+ TCL1+)

**Panel: CD2, CD5, CD7, CD4, CD8, CD30, CD56, βF1, cytotoxic granule proteins (CGP = perforin, granzyme B, TIA1), EBV-EBER; Optional: CD25**

**Epidermotropic**
- CD30 + CD30+ Cutaneous LPD
- CD30 -

**Dermis and subcutis**
- CD4 + MF, SS (CD2+ CD5+ CD7- CD8- βF1+ CGP-)
- HTLV1 + = ATLL

**Cutaneous γδTCL**
- CD8 + CD4+ (AECTCL (e,f) CD2- CD5- CD7+/ CD56- F1+ CGP+)
- CD4 -

**CD4 +**
- CD8 + CD4+ (AECTCL (e,f) CD2- CD5- CD7+/ CD56- F1+ CGP+)
- CD8 -

**CD4 -**
- CD8 + CD4- (CD2+ CD5- CD7- CD8+ F1- CGP+)
- CD8 -

**CD30 -**
- CD4 + Small/medium cells = CD4+ small/medium CTCL
- CD4 - Med/large cells = PTCL, NOS

**EBV -**
- NK/T nasal type CD2+ CD7- CD56+ CGP+

**EBV +**
- Cutaneous γδTCL (CD2+ CD5- CD7+/ CD56+/ CGP+)
TUMOR LYSIS SYNDROME

Laboratory hallmarks of TLS:
- High potassium
- High uric acid
- High phosphorous
- Low calcium

Symptoms of TLS:
- Nausea and vomiting, shortness of breath, irregular heartbeat, clouding of urine, lethargy, and/or joint discomfort.

High risk features
- Histologies of Burkitt Lymphoma and Lymphoblastic Lymphoma; occasionally patients with DLBCL and CLL
- Spontaneous TLS
- Elevated WBC
- Bone marrow involvement
- Pre-existing elevated uric acid
- Ineffectiveness of allopurinol
- Renal disease or renal involvement by tumor

Treatment of TLS:
- TLS is best managed if anticipated and treatment started prior to chemotherapy.
- Centerpiece of treatment includes
  - Rigorous hydration
  - Management of hyperuricemia
  - Frequent monitoring of electrolytes and aggressive correction is essential
- First-line and at retreatment
  - Allopurinol beginning 2-3 days prior to chemotherapy and continued for 10-14 days
  - Rasburicase is indicated for patients with any of the following risk factors:
    - presence of any high risk feature
    - urgent need to initiate therapy in a high-bulk patient
    - situations where adequate hydration may be difficult or impossible
    - Acute renal failure
  - One dose of rasburicase is frequently adequate. Redosing should be individualized.
- If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

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.
### RESPONSE CRITERIA FOR LYMPHOMA
(not including PET)

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<th>Physical Examination</th>
<th>Lymph Nodes</th>
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<td></td>
<td>Normal</td>
<td>Normal</td>
<td>&gt; 75% decrease</td>
<td>Normal or indeterminate</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>≥ 50% decrease</td>
<td>≥ 50% decrease</td>
<td>Irrelevant</td>
</tr>
<tr>
<td></td>
<td>Decrease in liver/spleen</td>
<td>≥ 50% decrease</td>
<td>≥ 50% decrease</td>
<td>Irrelevant</td>
</tr>
</tbody>
</table>

**Relapse/Progression**

- Enlarging liver/spleen, new sites
- New or increased
- New or increased
- Reappearance

---

# REVISED RESPONSE CRITERIA FOR LYMPHOMA (including PET)

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
<th>Spleen, Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
</table>
| **CR**         | Disappearance of all evidence of disease                                   | (a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative  
(b) Variably FDG-avid or PET negative; regression to normal size on CT | Not palpable, nodules disappeared                   | Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative |
| **PR**         | Regression of measurable disease and no new sites                         | ≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes  
(a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site  
(b) Variably FDG-avid or PET negative; regression on CT | ≥ 50% decrease in SPD of nodules(for single nodule in greatest transverse diameter); no increase in size of liver or spleen | Irrelevant if positive prior to therapy; cell type should be specified |
| **SD**         | Failure to attain CR/PR or PD                                              | (a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET  
(b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT |                                                   |                                                                            |
| Relapsed disease or PD | Any new lesion or increase by ≥ 50% of previously involved sites from nadir | Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis  
Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy | > 50% increase from nadir in the SPD of any previous lesions | New or recurrent involvement |


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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**Recommended for use with Diffuse Large B-Cell Lymphoma and Hodgkin Disease/Lymphoma.**
MONOCLONAL ANTIBODY DIRECTED AT CD20 AND VIRAL REACTIVATION

• Hepatitis B surface antigen (HBSAg) and Hepatitis B core antibody (HBCAb) testing for all patients receiving rituximab
  ▶ Quantitative hepatitis B viral load by PCR only if one of the screening tests positive
  ▶ In areas with high prevalence/ population or prevalence is HBV not known, recommend testing all patients receiving immunotherapy, chemotherapy, or chemoimmunotherapy

Note: Patients receiving IV immunoglobulin may be HBCAb positive as a consequence of IVIG therapy.

• Empiric antiviral therapy with oncologic treatment for any patient who is HBSAg or HBCAb positive
  ▶ Monitor hepatitis B viral load with PCR monthly through treatment and every 3 months thereafter
    ◆ If viral load is consistently undetectable, treatment is considered prophylactic
    ◆ If viral load fails to drop, consult hepatologist
  ▶ Maintain prophylaxis for at least 6 months after oncologic treatment ends
    ◆ Consult with hepatologist for duration of therapy in patient with active hepatitis B virus

Progressive multifocal leukoencephalopathy (PML)
• Caused by the JC virus and is usually fatal
  ▶ Diagnosis made by PCR of CSF and in some cases brain biopsy
• No known effective treatments
• Check for changes in behavior such as confusion, dizziness or loss of balance, difficulty talking or walking, and vision problems

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.
Field:
Options: Involved-Field or Reduced Involved-Field

For extra nodal sites:
- Organ involvement: The field includes the involved organ alone (example: Gastric MALT- the whole stomach; Parotid- the total unilateral parotid gland).
- Bone/spine involvement: Only the involved part of the organ is irradiated (with margins). No radiation is required to uninvolved adjacent lymph nodes.

For nodal sites:
- Field: In most cases an involved-field is appropriate. Regional fields or extended-field are not recommended unless there is significant concern that adjacent nodes are involved.
  - In DLBCL, RT consolidation following chemotherapy, RT may be limited to the originally involved lymph node(s). In the mediastinum, abdomen and pelvis treating only the post-chemotherapy volume in the transverse diameter is recommended.
  - When RT is the primary treatment, involved-field or reduced-IFRT (involved nodal radiation therapy) is recommended.
  - Margins are influenced by the quality of imaging and clinical information.

Dose:
- RT for follicular lymphoma: 24-30 Gy (36 only if bulky)
- RT for MALT lymphoma: Stomach- 30 Gy. Other organs 24-30 Gy
- RT for early stage mantle cell lymphoma: 30-36 Gy
- Consolidation dose in DLBCL following CR to chemotherapy: 30-36 Gy
  - RT dose for residual disease (PR) after chemotherapy: 40-50 Gy.
- Mini-RT for palliation of advanced-stage low-grade lymphomas (FL, SLL, MZL, MCL): 2 GyX2 (may be repeated)

References:

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.
# Classification

## WHO Classification of the mature B-cell, T-cell, and NK-cell neoplasms (2008)

### Mature B-Cell Neoplasms
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Splenic lymphoma/leukemia, unclassifiable*
  - Splenic diffuse red pulp small B-cell lymphoma*
  - Hairy cell leukemia-variant*
- Lymphoplasmacytic lymphoma
- Waldenström’s macroglobulinemia
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT type)
- Nodal marginal zone lymphoma
  - Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
  - Pediatric follicular lymphoma*
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - T-cell/histiocyte rich large B-cell lymphoma
  - Primary DLBCL of the CNS
  - Primary cutaneous DLBCL, leg type
  - EBV positive DLBCL of the elderly*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

*The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.
### Classification

<table>
<thead>
<tr>
<th>Table 1 continued</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mature T-Cell and NK-Cell Neoplasms</strong></td>
</tr>
<tr>
<td>- T-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>- T-cell large granular lymphocytic leukemia</td>
</tr>
<tr>
<td>- <em>Chronic lymphoproliferative disorder of NK-cells</em></td>
</tr>
<tr>
<td>- Aggressive NK cell leukemia</td>
</tr>
<tr>
<td>- Systemic EBV positive T-cell lymphoproliferative disorder of childhood</td>
</tr>
<tr>
<td>- Hydroa vaccineforme-like lymphoma</td>
</tr>
<tr>
<td>- Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>- Extramedullary NK/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>- Enteropathy-associated T-cell lymphoma</td>
</tr>
<tr>
<td>- Hepatosplenic T-cell lymphoma</td>
</tr>
<tr>
<td>- Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>- Mycosis fungoides</td>
</tr>
<tr>
<td>- Sézary syndrome</td>
</tr>
<tr>
<td>- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders</td>
</tr>
<tr>
<td>- Lymphomatoid papulosis</td>
</tr>
<tr>
<td>- Primary cutaneous anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>- Primary cutaneous gamma-delta T-cell lymphoma</td>
</tr>
<tr>
<td>- <em>Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma</em></td>
</tr>
<tr>
<td>- <em>Primary cutaneous CD4 positive small/medium T-cell lymphoma</em></td>
</tr>
<tr>
<td>- Peripheral T-cell lymphoma, NOS</td>
</tr>
<tr>
<td>- Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>- Anaplastic large-cell lymphoma, ALK positive</td>
</tr>
<tr>
<td>- <em>Anaplastic large-cell lymphoma, ALK negative</em></td>
</tr>
</tbody>
</table>

| **Hodgkin Lymphoma** |
| - Nodular lymphocyte predominant Hodgkin lymphoma |
| - Classical Hodgkin lymphoma |
|   - Nodular sclerosis classical Hodgkin lymphoma |
|   - Lymphocyte-rich classical Hodgkin lymphoma |
|   - Mixed cellularity classical Hodgkin lymphoma |
| - Lymphocyte-depleted classical Hodgkin lymphoma |

| **Post-Transplant Lymphoproliferative Disorders (PTLD)** |
| - Early lesions |
|   - Plasmacytic hyperplasia |
|   - Infectious mononucleosis-like PTLD |
| - Polymorphic PTLD |
| - Monomorphic PTLD (B- and T/NK-cell types) |
| - Classical Hodgkin lymphoma type PTLD |

---

*The italicized histologic types are provisional entities, for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.*

#These lesions are classified according to the leukemic or lymphoma to which they correspond.

---

### Table 2

**Cotswolds Modification of Ann Arbor Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Area of Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Single lymph node group</td>
</tr>
<tr>
<td>II</td>
<td>Multiple lymph node groups on same side of diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Multiple lymph node groups on both sides of diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Multiple extranodal sites or lymph nodes and extranodal disease</td>
</tr>
<tr>
<td>X</td>
<td>Bulk &gt; 10 cm</td>
</tr>
<tr>
<td>E</td>
<td>Extranodal extension or single isolated site of extranodal disease</td>
</tr>
<tr>
<td>A/B</td>
<td>B symptoms: weight loss &gt; 10%, fever, drenching night sweats</td>
</tr>
</tbody>
</table>

Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Non-Hodgkin’s lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) lymphocytes. In the United States, B-cell lymphomas represent 80-85% of the cases with 15-20% being T-cell lymphomas. NK-cell lymphomas are very rare. In 2010, an estimated 65,540 new cases of NHL will be diagnosed and 20,210 will die of their disease. NHL is the sixth leading site of new cancer cases among men and women, accounting for 4% of new cancer cases and 4% of cancer-related deaths.

The incidence of NHL has increased dramatically between 1970 and 1995; the increase has moderated since the mid-90s. This increase has been attributed partly to the human immunodeficiency virus (HIV) epidemic and the development of AIDS-related NHL. However, much of the increase in incidence has been observed in patients in their sixth and seventh decades; a large part of this increase incidence has paralleled a major decrease in mortality from other causes. The median age of individuals with NHL has risen in the last two decades. As a result, patients with NHL may also have significant comorbid conditions, which complicate treatment options.

Classification

In the 1956, Rappaport et al. proposed a lymphoma classification that was based on the pattern of cell growth (nodular or diffuse), and size and shape of the tumor cells. This classification, though widely used in the United States, quickly became outdated with the discovery and the existence of distinct types of lymphocytes (B, T and NK). The Kiel classification became the first and most significant classification that applied this new information to the classification of lymphomas. According to the Kiel classification, the lymphomas were divided into low-grade and high-grade based on the histological features. This classification was widely used in Europe. The use of different classification systems in clinical studies made it difficult to compare results from clinical studies. Hence, the International Working Formulation (IWF) for NHLs was developed to standardize the classification of lymphomas.

International Working Formulation classification

The IWF classified NHL into three major categories as low, intermediate and high grade, based on the morphology and natural history. This classification divided diffuse large B-cell lymphoma (DLBCL) into intermediate and high grade groups. However, these distinctions were not reproducible. Since this classification did not
include immunophenotyping, the categories were not reproducible.\textsuperscript{9} In addition, after this classification was published many new diseases were described that were not included in the IWF classification.

\textbf{Revised European American Classification}

In 1994, the International Lymphoma Study Group (ILSG) developed the REAL classification, which classified lymphomas based on the cell of origin (B, T, or NK) and included morphology, immunophenotype, genetic and clinical features to define diseases.\textsuperscript{10} In 1997, the International Lymphoma Classification Project performed a clinical evaluation of the Revised European American Classification (REAL) classification in a cohort of 1,403 cases of NHL.\textsuperscript{11,12} The diagnosis of NHL was confirmed in 1,378 (98.2\%) of the cases. This study identified the thirteen most common histological types, comprising about 90\% of the cases of NHL in the United States. The findings were as follows: DLBCL, 31\%; follicular lymphoma (FL), 22\%; small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), 6\%; mantle cell lymphoma (MCL), 6\%; peripheral T-cell lymphoma (PTCL), 6\%; and mucosa associated lymphoid tissue (MALT) lymphoma, 5\%. The remaining subtypes each occurred in less than 2\% of cases. Importantly, in the United States more than 50\% of cases of lymphoma are either DLBCL or FL. The study investigators concluded that the REAL classification can be readily applied and identifies clinically distinctive types of NHL.

\textbf{World Health Organization Classification}

In 2001, the World Health Organization (WHO) updated the classification of hematopoietic and lymphoid neoplasms.\textsuperscript{13,14} The 2001 WHO classification applied the principles of REAL classification and represented the first international consensus on classification of hematologic malignancies. The REAL/WHO classification of NHL includes many entities not recognized by the IWF.\textsuperscript{\textsuperscript{13,14}} After consideration of cell of origin (B, T, or NK), the classification subdivides lymphomas into those derived from precursor lymphocytes versus those derived from mature lymphocytes. The classification is further refined based on immunophenotype, genetic, and clinical features. These considerations have aided in defining active treatment for specific subtypes of lymphoma.

In 2008, the International T-cell lymphoma Project evaluated the WHO classification of T-cell lymphoma in a cohort of 1,314 cases of PTCL and natural killer/T-cell lymphomas (NKTCL). The diagnosis of PTCL or NKTCL was confirmed in 1,153 cases (88\%). The most common subtypes were PTCL-not otherwise specified (NOS; 25.9\%), angioimmunoblastic lymphoma (18.5\%), NKTCL (10.4\%), adult T-cell leukemia/lymphoma (ATLL; 9.6\%), anaplastic large cell lymphoma (ALCL), ALK-positive (6.6\%) and ALCL, ALK-negative (5.5\%).\textsuperscript{15} The findings of this study validated the utility of the WHO classification for defining subtypes of T-cell lymphomas.

The WHO classification was updated again in September 2008 to add new diseases and subtypes that have been recognized in the past decade, and to better define some of the heterogeneous and ambiguous categories based on the recent advances.\textsuperscript{16,17} Genetic features, detected by cytogenetics or fluorescence in-situ hybridization (FISH) are increasingly important in defining specific NHL subtypes. In addition, detection of viruses, particularly Epstein-Barr virus, HHV8 and HTLV1, is often necessary to establish a specific diagnosis.

\textbf{2008 WHO Classification of Mature B-cell Lymphomas}

\textbf{CLL/SLL}

The updated classification includes the new definition issued by the International Working Group on CLL (IWCLL).\textsuperscript{18} In the absence of nodal
or organ involvement, disease-related cytopenias, the diagnosis of CLL requires the presence of at least 5,000 clonal B lymphocytes per microliter in the peripheral blood for the duration of at least 3 months. The presence of fewer than 5,000 lymphocytes per microliter in the absence of lymphadenopathy, organomegaly or other clinical features is defined as monoclonal B lymphocytosis (MBL). CLL requiring treatment develops in subjects with CLL-phenotype MBL and with lymphocytosis at the rate of 1.1% per year.\(^\text{19}\)

**Follicular Lymphoma**

In FL, pathological grading according to the number of centroblasts is considered to be a clinical predictor of outcome. In the 2001 WHO classification, 3 grades were recommended: FL1, FL2, and FL3; FL3 could be optionally stratified into 3A (centrocytes still present) or 3B (sheets of centroblasts). However, clinical outcomes for patients with FL1 and FL2 do not differ and classification is unreliable. Therefore, in the updated 2008 WHO classification these are grouped into one grade (FL1-2). Hans et al reported that there was no difference in survival between Grade 3A and 3B, whereas patients with FL3 with more than 50% diffuse component have an inferior survival that is similar to the survival of those with DLBCL.\(^\text{20}\) FL3B with cytogenetic abnormalities of BCL6 (at 3q27) are thought to be genetically more akin to germinal center type DLBCL than FL1-3A and has a more aggressive clinical course. Patients with FL3B with BCL2 translocation appear to have similar clinical behavior to patients with FL1-3A.\(^\text{21}\) Since FL3B is rare, in most studies clinical behavior of FL3 is based mainly on FL 3A cases. The 2008 WHO classification mandates stratifying FL3 into either 3A or 3B. FL is thus still divided into three grades (FL1-2, FL3A and FL3B) based on the number of centroblasts. Any diffuse areas in FL should be given a separate diagnosis of DLBCL, if it meets the criteria for FL3A or 3B.

Pediatric FL, primary intestinal FL, other extranodal FLs and intrafollicular neoplasia (“in situ” FL) are the other variants that are included under FL.

*Pediatric follicular lymphoma*: Children with FL typically have early stage disease, lack BCL2 expression and the t(14;18). Pediatric FL has a better prognosis than adult FL and is often cured with minimal therapy.

*Primary Intestinal follicular lymphoma*: FL of the gastrointestinal tract is a recently described entity which is common in the small intestine, with the vast majority occurring in the duodenum. The morphology, immunophenotype, and genetic features are similar to those of nodal follicular lymphoma. However, most patients have clinically indolent and localized disease. Survival appears to be excellent even without treatment.

*Other Extranodal Follicular Lymphoma*: In many of the other extranodal sites, the morphology, immunophenotype, and genetic features are similar to those of nodal FL. Patients usually have localized disease and systemic relapses are rare.

*Intrafollicular Neoplasia or “In situ” Follicular Lymphoma*: This is defined as a morphologically normal lymph node or other lymphoid tissues with a few follicles that are BCL2-positive. Some of these patients are found to have either a history of FL or FL elsewhere in the body and some have no evidence of FL.\(^\text{22}\) Intrafollicular neoplasia may represent the nodal equivalent of circulating clonal B-cells that have BCL2 rearrangement, but lack the other genetic abnormalities required for the development of a progressive lymphoma. In some cases, this may represent the earliest evidence of a true FL that will progress to an overt lymphoma. A diagnosis of lymphoma should not be made in such
cases, and careful staging and follow-up are recommended; patients
should not be treated for lymphoma based on this finding.

**Primary cutaneous follicle center lymphoma (PCFCL)**
This is a new category in the 2008 classification and is defined as a
tumor of neoplastic follicle center cells, including centrocytes and
variable numbers of centroblasts, with a follicular, follicular and diffuse
or a diffuse growth pattern. PCFCL is the most common B-cell
lymphoma of the skin and it is classified as a distinct entity in the
EORTC classification of cutaneous lymphomas.23 Gene expression
profiling studies have also provided evidence in support of this
classification.24 PCFCL presents as a solitary or localized skin lesion on
the scalp, forehead or the trunk. It is characterized by an indolent
course and rarely disseminates to extracutaneous sites. PCFCL is
consistently BCL6-positive, may be CD10-positive in cases with a
follicular growth pattern. BCL2 is either negative or dim (predominantly
seen in cases with a follicular growth pattern). PCFCL has an excellent
prognosis with a 5-year survival rate of 95%. PCFCL must be
distinguished from primary cutaneous diffuse large B-cell lymphoma,
leg type, which is typically IRF4/MUM1+ and strongly BCL2+ and has a
more unfavorable prognosis.25, 26

**Diffuse Large B-cell Lymphomas**
Some of the new categories of DLBCL are defined by extranodal
primary sites and the association with viruses such as EBV or HHV8.
Two borderline categories have also been included to incorporate
cases in which it is not possible distinguish between adult Burkitt
lymphoma (BL) and DLBCL, and primary mediastinal large B-cell
lymphoma (PBML) and nodular sclerosis classical Hodgkin lymphoma
(NSCHL). The ALK-positive DLBCL, plasmablastic lymphoma and
primary effusion lymphoma are considered as distinct entities. The
2008 classification also has new category of large B-cell lymphoma
arising in HHV8-associated multicentric Castleman’s disease.

**DLBCL, not otherwise specified (NOS)**
The 2008 classification has included DLBCL, NOS as a new category
to include GCB and ABC subtypes as well as other DLBCL cases that
do not belong to any of the four specific subtypes (T-cell/histiocyte
rich large B-cell lymphoma, primary CNS DLBCL, primary cutaneous
dLBCL (“leg type”) or EBV+ DLBCL of the elderly).

Gene expression profiling (GEP) has been used to identify three
different subtypes of DLBCL: germinal center B-cell (GCB) subtype,
activated B-cell (ABC) subtype and type 3 which includes PBML and
cases that cannot be classified as GCB or ABC subtype.27 GEP is not
yet recommended for routine clinical use. Immunostaining algorithms
have been developed to differentiate between these two subtypes
using a combination of CD10, BCL6, IRF4/MUM1, GCET1 and
FOXP1.28, 29 However, studies based on immunohistochemistry (IHC)
have produced conflicting results regarding the outcome of GCB and
ABC subtypes.30, 31

**Primary Cutaneous DLBCL, leg type**
Primary cutaneous DLBCL leg type (PCDLBCL, leg type) is an
unusual form of DLBCL composed of large transformed B cells most
commonly arising on the leg (85%) though can arise at other sites
(15%). These tumors arise from post germinal center B-cell with
expression of CD20, IRF4/MUM1, FOXP1, and BCL2; many cases
express BCL6 and lack expression of CD10.32 These tumors can
disseminate to non-cutaneous sites particularly the central nervous
system. Clinically the prognosis is poor particularly when the
presentation is with multiple subcutaneous nodules.
**B-cell lymphoma, intermediate between BL and DLBCL**

BL is characterized by t(8;14), which results in the juxtaposition of MYC gene from chromosome 8 with the immunoglobulin heavy chain variable (IGHV) region on chromosome 14 and variant translocations involving MYC and the immunoglobulin light chain genes. Nevertheless, MYC translocations also occur in DLBCL. Recent GEP studies have confirmed that the distinction between BL and DLBCL is not reliably reproducible with the use of the current criteria of morphology, immunophenotype, and genetic abnormalities. Mature aggressive B-cell lymphomas without a molecular BL signatures (non-mBL) with MYC rearrangements as well as those with both t(8;14) and t(14;18) translocations are associated with a poor prognosis.

This provisional category replaces the “Atypical Burkitt Lymphoma” that was included in the 2001 WHO classification. The new category includes lymphomas with features of both DLBCL and BL, but or biological and clinical reasons should not be diagnosed as DLBCL or BL. Lymphomas in this provisional category include those that are morphologically intermediate between BL and DLBCL with immunophenotype suggestive of BL (CD10-positive, BCL6-positive, BCL2-negative and IRF4/MUM1-negative or weakly positive), lymphomas that are morphologically similar to BL but are strongly BCL2-positive and those with both MYC and BCL2 rearrangements (double hit) and complex karyotypes.

**B-cell lymphoma intermediate between PMBL and NSCHL**

PMBL has been recognized as a subtype of DLBCL based on its distinctive clinical and morphological features. NSCHL is the most common form of HL. Both tumors occur in the mediastinum and affect adolescents and young adults. GEP studies strongly support a relationship between PMBL and CHL. About a third of the genes that were more highly expressed in PMBL were also characteristically expressed in CHL cells. Traverse-Glehen, et al., reported borderline cases with biologic and morphologic features of both CHL and B-cell NHL, known as "mediastinal gray zone lymphomas" (MGZL). This provisional category includes lymphomas with overlapping features between CHL and DLBCL, especially PBML. Those cases that resemble PBML may have dim or no expression of CD20, strong expression of CD30 and CD15. These lymphomas have a more aggressive course and poorer outcome than either CHL or PBML.

**2008 WHO Classification of Mature T-cell and NK-cell Lymphomas**

The 2008 WHO classification has adapted the EOTRC classification for cutaneous T-cell lymphomas. The new categories include primary cutaneous gamma-delta T-cell lymphoma, primary cutaneous aggressive epidermotropic CD9-positive cytotoxic T-cell lymphoma and primary cutaneous small/medium CDE4-positive T-cell lymphoma. Anaplastic large cell lymphoma (ALCL), ALK-negative is now separated out from PTCL-NOS as a provisional entity.

**ALCL**

ALCL accounts for less than 5% of all cases of NHL. There are now three distinctly recognized subtypes of ALCL: ALCL, ALK-positive, ALCL, ALK-negative and primary cutaneous ALCL. Primary cutaneous ALCL is a distinct subtype of mature T-cell lymphoma. ALK-positive ALCL is most common in children and young adults. It is characterized by the over expression of anaplastic lymphoma kinase (ALK1) protein, resulting from t(2;5) in 40-60% of patients.
Although clinically aggressive, it is highly curable with CHOP chemotherapy. The distinction between ALK-positive and ALK-negative ALCL was not required in the 2001 WHO classification. It is now clear that ALK-positive ALCL is a well-defined clinicopathologic entity. The International Peripheral T-Cell Lymphoma Project reported that patients with ALK-positive ALCL had a superior outcome compared with those with ALK-negative ALCL [5-year failure-free survival (FFS): 60% vs. 36%; and 5-year overall survival (OS): 70% vs. 49%]. Contrary to prior reports, ALK-negative ALCL was associated with a better outcome than PTCL-NOS. The 5-year FFS (36% vs. 20%) and OS (49% vs. 32%) were superior compared with PTCL-NOS. A recent analysis from the GELA found that age and beta-2 microglobulin, not ALK1 expression, was the most significant variable in the outcome of ALCL; however, age was very closely associated with ALK1 expression. Patients with primary cutaneous ALCL had a very favorable 5-year OS (90%) despite being negative for ALK1; the 5-year FFS rate was 55%. The findings of this study confirmed that ALK-negative ALCL should be separated from both ALK-positive ALCL and PTCL-NOS.

Based on the recent findings, the 2008 WHO classification has included a provisional category for ALK-negative ALCL. It is morphologically identical to ALK-positive ALCL, with a strong and diffuse expression of CD30, no expression of B-cell antigens and absence of ALK1. The prognosis is intermediate between that of ALK-positive ALCL and PTCL-NOS.

Response Criteria

The International Working Group (IWG) published the guidelines for response criteria for lymphoma in 1999. These response criteria are measured by CT scan and the extent of bone marrow involvement that is determined by bone marrow aspirate and biopsy. These guidelines were revised in 2007 by the International Harmonization Project to incorporate IHC, flow cytometry and 18fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans in the definition of response for lymphoma. In the revised guidelines, the response category of complete response uncertain (CRu) was essentially eliminated because residual masses were defined as a partial response (PR) or a complete response (CR) based on the result of a PET scan. Using the revised system, response is categorized as CR, PR, stable disease (SD) and relapsed disease or progressive disease (PD). However, the application of PET to responses is limited to histologies where there is reliable FDG uptake in active tumor. However, the revised response criteria have thus far only been validated for DLBCL and Hodgkin lymphoma. The application of the revised response criteria to other histologies requires validation and the original IWG guidelines should be used.

Diagnosis

In all cases, the most important first step is to make an accurate pathologic diagnosis. The basic pathological evaluation is the same in each guideline though some further evaluation may be useful in certain circumstances to clarify a particular diagnosis; these are outlined in the pathological evaluation of the individual guideline.

An incisional or excisional lymph node biopsy is recommended to establish the diagnosis of NHL. Core needle biopsy is discouraged unless the clinical situation dictates that this is the only safe means of obtaining diagnostic tissue. Fine needle aspiration (FNA) biopsy is widely used in the diagnosis of malignant neoplasms, but its role in the diagnosis of lymphoma is still controversial. Since the revised
REAL/WHO classification is based on both morphology and immunophenotyping, FNA alone is not acceptable as a reliable diagnostic tool for NHL. However, its use in combination with ancillary techniques may provide precise diagnosis thereby obviating the need for a more invasive biopsy in highly selected circumstances. Recent studies have shown that the diagnostic accuracy of FNA improves significantly when it is used in combination with IHC and flow cytometry.  

In the NCCN guidelines, FNA alone is not suitable for an initial diagnosis of NHL, though it may be sufficient to establish relapse. However, in certain circumstances, when a lymph node is not easily accessible, a combination of core biopsy and FNA in conjunction with appropriate ancillary techniques [PCR for IGHV and/or T-cell receptor (TCR) gene rearrangements; FISH for major translocations; immunophenotypic analysis] may be sufficient for diagnosis. This is particularly true for the diagnosis of CLL. In other entities presenting in leukemic phase, such as FL or MCL, a biopsy is still preferred to clarify histological subtype.

Immunophenotypic analysis is essential for the differentiation of various subtypes of NHL to establish the proper diagnosis. It can be performed by flow cytometry and/or IHC; the choice depends on the antigens as well as the expertise and resources available to the hematopathologist. In some cases flow cytometry and IHC are complementary diagnostic tools. Cytogenetic or molecular genetic analysis may be necessary under certain circumstances to identify the specific chromosomal translocations that are characteristic of some NHL subtypes or to establish clonality.

Immunophenotyping/Genetic testing algorithm

After the publication of the 2008 WHO Classification, the NHL panel has developed a series of algorithms for the use of immunophenotyping in the diagnosis of mature lymphoid neoplasms. These algorithms should be used in conjunction with clinical and pathological correlation. They were developed to provide guidance for surgical pathologists as well as an aid to the clinician in the interpretation of pathology reports.

The initial assessment begins with morphologic, clinical, and immunophenotypic analysis. Morphologic assessment involves determining the cell size (small cells, medium-sized cells, or large cells), with or without anaplastic morphology. Clinical features include patient’s age and the location (nodal, extranodal, and among extranodal sites skin vs. other specific sites). The initial immunophenotyping panel should include Pan-B and Pan-T-cell antigens. Based on the morphologic and clinical features, some of the B-cell and T-cell subset antigens may also be added in the initial panel.

B-cell Lymphomas (expression of one or more B-cell antigens (CD20, Pax5, CD79a, CD19, CD22)

Small Cells

In the differential diagnosis of small cell lymphomas [CLL/SLL, mantle cell lymphoma (MCL), hairy cell leukemia (HCL), splenic marginal zone lymphoma, extra-nodal marginal zone lymphoma, nodal marginal zone lymphoma and follicular lymphoma], the panel for immunophenotyping includes CD5, CD10, CD23, cyclin D1, BCL6, BCL2, and may include CD25 and CD103 if HCL is suspected.
Both CLL and MCL are CD5+ B-cell lymphomas. CLL is usually CD5+, CD23+ and cyclin D1-. However, some cases of CLL have an atypical immunophenotype (CD 23 dim or negative). Dysregulated expression of cyclin D1, a cell cycle protein that results from the chromosomal translocation, t(11;14) is seen in the vast majority of cases of MCL. This translocation is not seen in other NHLs though it can be seen in multiple myeloma.

The initial stratification is based on the expression of CD5. If CD5 is positive, confirmatory studies should be done with CD23 and cyclin D1 to differentiate between CLL and MCL. CD23 is often helpful but cyclin D1 expression is the most reliable marker for differentiating between CLL and MCL. Thus, immunophenotypic analysis of cyclin D1 or cytogenetic analysis of t(11;14) using FISH is helpful in confirming the diagnosis of MCL. Rare cases of both cyclin D1 and t(11;14) negative MCL have been reported. This diagnosis should be made with extreme caution and with expert consultation.

If CD5 is negative, then the next stratification is based on CD10. CD10 positivity (which must be confirmed by morphology to be on tumor cells and not on residual reactive or colonized follicles) indicates follicular lymphoma, and this diagnosis can be confirmed further by staining for BCL6, BCL2 and detection of t(14;18) by FISH or PCR, since BCL2 resulting from t(14;18) is over-expressed in 90% of cases of FL. FL is also CD20+, CD5- and cyclin D1-, and nodular aggregates of CD21+ or CD23+ FDC will usually be found. When CD10 is negative, the differential diagnosis includes MZLs, LPL, and HCL; immunophenotypic analysis of CD103 and CD25 can be used to identify hairy cell leukemia (HCL). If both are positive, the suggested diagnosis would be HCL, which can be confirmed by the staining of annexin-1 since HCL is characterized by a strong expression of annexin-1.

CD103-negative small B-cell neoplasms can be further stratified by staining for cytoplasmic immunoglobulin light chains. If cytoplasmic light chains are negative the most likely diagnosis is one of the MZLs, which are further classified by a combination of morphological and clinical features (extranodal, nodal, and splenic). If cytoplasmic immunoglobulin is positive, the differential diagnosis includes MZL or lymphoplasmacytic lymphoma (LPL). This distinction is based on a combination of morphology, clinical and laboratory (monoclonal gammopathy) features and may be aided by cytogenetics (deletion 7q in splenic MZL, t(11;18) in some extranodal MZL, vs. deletion 6q in LPL).

Medium-sized Cells

For medium-sized cell lymphomas [BL, DLBCL, blastoid variant of MCL, B-cell lymphoma, intermediate between BLBCL and BL (U-DLBCL/BL)], the immunophenotyping panel includes CD5, CD10, BCL2, BCL6, cyclin D1 and Ki-67.

As with small cell lymphomas, the initial stratification is based on CD5. If CD5 is positive, the differential diagnosis is MCL vs. DLBCL and it can be confirmed based on the analysis of cyclin D1, BCL6 and IRF4/MUM1. BCL6 rearrangements associated with various chromosomal translocations involving chromosome 3q27 are observed in about 28-35% of DLBCL. IRF4/MUM1 is an oncogene associated with myeloma, activated as a result of chromosomal translocation, t(6;14) and it is observed in 73% of DLBCLs. Cyclin D1 positivity confirms the diagnosis of blastoid MCL. If cyclin D1 is negative, the diagnosis is confirmed as CD5+ DLBCL, irrespective of the expression of BCL6 and IRF4/MUM1.

If CD5 is negative, the stratification is based on the expression of CD10. If CD10 is positive, the differential diagnosis includes BL vs.
U-DLBCL/BL. These can be further stratified by Ki-67, BCL2 and BCL6. BCL6+, BCL2- and Ki-67 (95% or greater) would support the diagnosis of BL especially in pediatric cases. In adults, when BL is suspected, FISH for MYC, BCL2 and possibly BCL6 should be done to confirm the presence of MYC rearrangement and assess for the presence of a dual rearrangement of MYC and BCL2 (double hit), particularly if BCL2 is expressed. If MYC is positive and BCL2 and BCL6 are not rearranged, one may make a diagnosis of BL. If BCL2 or BCL6 is rearranged, with or without MYC, the diagnosis could be U-DLBCL/BL. CD10-negative medium-sized B-cell neoplasms generally fall into the category of U-DLBCL/BL. If both BCL2 and BCL6 are positive by IHC, FISH for MYC, BCL2 and BCL6 should be done to check for double hit U-DLBCL/BL, which have a poor prognosis.

**Large Cells**

DLBCL-NOS and the newly described subtypes of DLBCL as well as the pleomorphic variant of MCL are characterized by large cells. The immunophenotyping panel for large cell lymphomas includes CD5, CD10, BCL6, and IRF4/MUM1. The first stratification is based on the expression of CD5. If CD5 is positive, cyclin D1 expression should be assessed to distinguish between pleomorphic MCL and CD5+ DLBCL, NOS, which has a variable expression of BCL6 and IRF4/MUM1. If CD5 is negative, the differential diagnosis is DLBCL which can be stratified again based on the expression of CD10. CD10 positivity confirms the diagnosis of DLBCL, NOS (GCB subtype). If CD10 is negative, confirmatory studies can be done with BCL6 and IRF4/MUM1 to differentiate GCB subtype (BCL6+ and IRF4/MUM1-) from non-GCB subtypes. For clinical purposes, it is not necessary to distinguish between GCB and non-GCB subtypes. Recently described DLBCL subtypes (EBV+ DLBCL of the elderly, DLBCL associated with chronic inflammation, ALK1+ DLBCL, plasmablastic lymphoma) often have immunophenotypic profiles consistent with non-GCB origin; therefore, non-GCB immunophenotype should prompt further analysis to detect these subtypes in the appropriate clinical setting.

Additional markers (CD20, PAX5, CD30, ALK1, CD138 and cytoplasmic immunoglobulin, as well as detection of HHV8 and EBV) may be useful for the further classification of large B-cell lymphomas. In a tumor that is positive for both CD20 and PAX5, CD30 positivity supports the diagnosis of PMLB. If CD30 is positive and the morphology overlaps with CHL, CD15 may be helpful: if it is positive, this supports either U-DLBCL/CHL or CHL, depending on the morphologic features. Absence of CD15 would support PMLB. Absence of both CD20 and PAX5 and expression of IRF4/MUM1 and CD138 suggest terminal B-cell differentiation, and the differential diagnosis would include ALK-positive DLBCL, plasmablastic lymphoma and primary effusion lymphoma. ALK-positive DLBCL is characterized by the expression of ALK protein and absence of CD30.

It has an aggressive clinical course and poor outcome. If ALK is negative, the stratification is now based on the staining for EBV and HHV. EBV+ and HHV8- indicate plasmablastic lymphoma. Primary effusion lymphoma is HHV8+ with or without EBV and is CD30+. DLBCL associated with HHV8+ multicentric Castleman’s disease is CD20/-, HHV8+ and has characteristic morphologic features. Many of these DBLCL subtypes have plasmacytic differentiation, and will have detectable cytoplasmic immunoglobulin.

**Cutaneous B-cell lymphomas**

In the WHO classification, three main types of primary cutaneous B-cell lymphomas are recognized: PCFCL, PCDLBCL, leg type, and primary cutaneous MZL (PCMZL). PCMZL express CD20 and BCL2 but are negative for CD5, CD10 and BCL6. PCFCL, which is an
indolent disease, has a germinal center phenotype; whereas, most PCDLBCL, leg type which is an aggressive tumor, have an activated B cell phenotype.\textsuperscript{59}

The immunophenotyping panel includes CD10, BCL2, BCL6, IRF4/MUM1 and follicular dendritic cell (FDC) markers (CD21 or CD23) to detect neoplastic follicles or colonized germinal centers. Initial stratification is based on CD10. CD10 positivity on the neoplastic cells indicates PCFCL; however, many cases of PCFCL are CD10−. If CD10 is negative, the differential diagnosis is based on the expression of BCL2. BCL-2 is usually negative in PCFCL but strongly expressed in PCDLBCL. When BCL2 is negative, immunophenotypic analysis of BCL6 and IRF4/MUM1 is necessary to distinguish between PCFCL and PCMZL. PCFCL is consistently BCL6-positive and IRF4/MUM1-negative, whereas PCMZL is BCL6-negative and IRF4/MUM1 can be either positive or negative. If BCL2 is positive, IRF4/MUM1 is helpful to differentiate between PCFCL and PCDLBCL, leg type, since PCFCL is usually IRF4/MUM1-negative while PCDLBCL, leg type is usually IRF4/MUM1-positive.

T-cell Lymphomas (expression of one or more pan-T antigens (CD2, CD3, CD5, CD7, CD43, CD45RO)

T-cell lymphomas (anaplastic morphology)

In cases with anaplastic morphology, the immunophenotyping panel includes CD30, CD15, PAX5, ALK, EBV-EBER. ALCCL has a strong, diffuse expression of CD30. If CD30 is positive, evaluation of ALK1 status is used to identify ALK-positive ALCCL. If ALK1 is negative, analysis of CD15 and PAX5 are essential in the differential diagnosis of non-cutaneous ALK-negative ALCCL and CHL. ALK-negative ALCCL is PAX5-negative whereas CHL typically shows expression of CD15 as well as dim expression of PAX5.

Cutaneous-T-cell lymphomas (non-anaplastic morphology)

Mycosis fungoides (MF) and Sezary syndrome (SS) are the most common types of cutaneous T-cell lymphomas (CTCLs) lacking anaplastic morphology. Primary CTCL are very rare. In the WHO classification, three rare provisional entities are included under primary CTCL: primary cutaneous gamma-delta T-cell lymphoma, primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (AECTCL) and primary cutaneous CD4-positive small/medium T-cell lymphoma.

The immunophenotyping panel for the diagnosis of cutaneous T-cell lymphomas includes CD2, CD5, CD7, CD4, CD8, CD30, CD56, βF1, cytotoxic granule proteins (CGP). Initial stratification can be based on CD30. Strong and uniform CD30 positivity favors primary cutaneous CD30-positive T-cell lymphoproliferative disorders (LPD), even if the morphology is not obviously anaplastic; however some CD30+ cells can be seen in MF and ATLL. In an epidermotropic cutaneous T-cell lymphoma, if CD30 is negative, then the differential diagnosis is based on the expression of CD4 and CD8. If CD4 is positive, then the differential diagnosis is MF/SS vs. adult T-cell leukemia and lymphoma (ATLL). ATLL and MF/SS both lack CGP. ATLL is CD25+ while MF/SS is CD25−; it is suggested by epidemiologic factors and can be confirmed by serologic testing for HTLV1. If CD4 is negative and CD8 is positive, then the diagnosis is more likely AECTCL which has an aggressive clinical course.\textsuperscript{60} Since a minority of MF cases can be CD30+, CD4 - and CD8 +/−, AECTCL should be confirmed further by its characteristic immunophenotype (CD4+, CD3+, CD8+, CD5- and CD45RO−). Cutaneous gamma-delta T-cell lymphoma may be epidermotropic, but typically also involves dermis and subcutis; is
typically CD4- CD8- CD5- CD56+, but may express CD8. Staining for βF1 is negative, and CGP are strongly expressed. Subcutaneous panniculitis-like T-cell lymphoma is typically CD3+ CD7+ CD8+ βF1+ and expresses CGP.

**Nodal Localization (Non-Anaplastic Morphology)**

Angioimmunoblastic T-cell lymphoma (AITL), ATLL and PTCL-NOS are included in this category, as well as small cell variants of ALCCL. The immunophenotypic panel includes CD5, CD4, CD8, CD30, ALK1, CD10, BCL6, PD1, CD21, CD23 and EBV-EBER. Follicular helper T cell markers CD10, BCL6, PD1, and CD4 are helpful to differentiate between AITL and PTCL-NOS and ATLL. The initial stratification is based on ALK and CD30 expression. If CD30 and ALK are negative and CD10, BCL6, PD1 and CD4 are positive, the likely diagnosis is AITL; this can be confirmed by detection of FDCs expressing CD21 and CD23, and typically some EBV+ large B cells. If follicular helper T cell markers are absent, the differential diagnosis includes ATLL and PTCL-NOS; expression of CD25, clinical features and assessment for HTLV1 antibodies can confirm the diagnosis of ATLL.

**Extranodal non-cutaneous localization (non-anaplastic morphology)**

Extranodal NK T-cell lymphoma (ENKTCL), nasal type, enteropathy-associated T-cell lymphoma (EATL), hepatosplenic T-cell lymphoma (HSTCL), extranodal involvement by PTCL-NOS and ALCCL, ALK+ small-cell histioocyte-rich variants are included in this category. The differential diagnosis will be affected by the specific clinical presentation. Initial stratification may be based on the EBV EBER status. If EBER is positive, ENKTCL is suggested and can be confirmed by CD56 expression. If EBER is negative, the differential diagnosis may include EATL, HSTCL, ALCCL, ALK+ small-cell histioocyte-rich variants and extranodal PTCL-NOS, depending on the clinical features. The stratification can then be based on the expression of CD30 and ALK1. If ALK is negative, expression of βF1, CD4, CD5, CD8, and CD30 may be useful in further classification: EATL is βF1+ CD30+ CD56-/+; while HSTCL is usually βF1-, CD30-, and is CD56+.

**Work-up**

Essential work-up procedures include a complete physical exam with particular attention to node bearing areas and the size of liver and spleen, symptoms present, performance status, laboratory studies including CBC, serum lactate dehydrogenase (LDH), hepatitis B testing (see below), comprehensive metabolic panel, and CT chest/abdominal/pelvic with oral and intravenous contrast (unless co-existent renal insufficiency). MUGA scan or echocardiograms are recommended when anthracyclines and anthracsenedione containing regimens are used. Bone marrow biopsy with or without aspirate is essential in all cases where treatment is considered; however, there are circumstances where it may be deferred (see below). Due the risk of hepatitis B reactivation, the panel has included hepatitis B testing (hepatitis B surface antigen and hepatitis B core antibody) as part of essential work-up prior to initiation of treatment in all patients who will receive anti CD20 monoclonal antibody-based regimens.

Furthermore, hepatitis B reactivation has been reported with chemotherapy alone and testing should be considered in anyone with a risk factor (e.g. blood transfusion, IV drug abuse) or if from a region with a non-negligible prevalence of hepatitis B infection. For further discussion see “Hepatitis B Reactivation” in the Supportive Care section of this manuscript. Hepatitis C testing is needed in high-risk patients and patients with splenic marginal zone lymphoma.

Optional procedures (depending on specific lymphoma type) include beta-2-microglobulin, CT or PET-CT scans, endoscopic ultrasound...
Bone marrow biopsy is usually included in the work-up for all patients with NHL with the exception of SLL/CLL when there is a clonal lymphocytosis identified by flow cytometry. Bone marrow involvement occurs in 39% of low-grade, 36% of intermediate grade and 18% of high-grade lymphomas. Bone marrow involvement was associated with significantly shorter survivals in patients with intermediate or high-grade lymphomas. In a recent retrospective analysis, the incidence of bone marrow involvement and the parameters predicting bone marrow involvement were analyzed in 192 patients with stage I and II in DLBCL. Overall incidence of BM involvement was 3.6%. The authors concluded that bone marrow biopsy may be safely omitted in selected patients with early stage DLBCL. In cutaneous B-cell lymphomas, bone marrow biopsy is essential for PCDLBCL, leg type since this is an aggressive lymphoma that will probably require systemic treatment, whereas the role of bone marrow biopsy in the PCFCL and PCMZL is less clear. Recent studies have indicated that bone marrow biopsy is an essential component of staging in patients with PCFCL first presenting in the skin, whereas it appears to have limited value in patients with MZL presenting in the skin, and may be considered only in selected cases.

In the NCCN guidelines, bone marrow biopsy with or without aspirate is included as part of essential work-up for all lymphomas. However, in patients with low bulk indolent disease with radiographic clinical stage III disease, an initial staging bone marrow evaluation can be deferred if observation is recommended as it will not change the clinical recommendations. However, in the evaluation of potentially early stage indolent lymphoma (stage I or II), bone marrow biopsy is essential; some panel members advocate bilateral core biopsies in this situation. Bilateral cores are recommended if radioimmunotherapy is considered.

FDG-PET scan has been used for initial staging, restaging and follow-up of patients with NHL. In a recent meta-analysis, PET showed a high positivity and specificity when used for the staging and restaging of patients with lymphoma. FDG-PET is nearly universally positive at diagnosis in Hodgkin lymphoma, DLBCL, and follicular lymphoma, about 90% in T-cell lymphoma and nodal MZL but less sensitive for extra-nodal MZL. However, a number of benign conditions including sarcoid, infection, and inflammation can result in false-positive PET scans complicating the interpretation. Lesions smaller than 1 cm are not reliably visualized with PET scans. PET scan is now part of pre-treatment evaluation in Hodgkin lymphoma and DLBCL and may be useful in selected cases in other histologies. The pre-treatment PET is particularly important to aid in the interpretation of post treatment response evaluation according to new response criteria (see above). At diagnosis, though PET scans may detect additional disease sites, the clinical stage is modified only in 15-20% of patients and a change in treatment in only 8% of patients. PET scan has generally been used in conjunction with a diagnostic CT scans.

Integrated PET-CT as a largely replaced the dedicated CT scans in the United States. This diagnostic study has distinct advantages in both staging and restaging compared to full dose diagnostic CT or PET alone. In a retrospective study, PET-CT performed with low-dose non-enhanced CT was found to be more sensitive and specific than the routine contrast-enhanced CT in the evaluation of lymph node and organ involvement in patients with Hodgkin disease.
or high-grade NHL. Preliminary results of another recent prospective study (47 patients; patients who had undergone prior diagnostic CT were excluded) showed a good correlation between low-dose unenhanced PET-CT and full-dose enhanced PET-CT in the evaluation of lymph nodes and extranodal disease in lymphomas. However, the lack of intravenous contrast and the diminished resolution can make it difficult in some cases to interpret the anatomical localization and significance of FDG-avid sites. Further studies are needed to determine if PET-CT scans can replace diagnostic CT scans in the initial staging and response evaluation of lymphomas. The panel has included PET-CT scan as an optional work-up procedure for selected patients.

Supportive Care

Hepatitis B virus reactivation

Hepatitis B virus (HBV) reactivation has been reported to occur in patients treated with chemotherapy with or without anti-CD20 monoclonal antibody; treatment with rituximab alone is also a risk for hepatitis B reactivation. HBV-reactivation may result in a fulminant hepatitis, hepatic failure, and death. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab (See rituximab package insert at www.fda.gov).

Testing of patients at risk for hepatitis B reactivation should include: hepatitis B surface antigen (HBSAg) and hepatitis B core antibody (HBCAb). In a prospective study of all patients receiving immunosuppressive (chemotherapy, antibody therapy, high dose dexamethasone) therapy at MSKCC, 1% of patients were HBSAg-positive and 9% were HBCAb-positive. A retrospective study conducted by MDACC also reported similar findings (HBSAg and HBCAb were positive in 2% and 8% of patients respectively).

Patients positive for HBSAg are at a greater risk for HBV reactivation than those positive for HBCAb. In a prospective study of 100 Chinese patients receiving chemotherapy for lymphoma, hepatitis developed in 67% of HBSAg-positive patients and 14% HBSAg-negative patients during cytotoxic therapy. Other risk factors for reactivation include young age, male gender, elevated pretreatment viral load and prolonged immunosuppression. The use of rituximab in HBCAb-positive patients has been reported to cause fatal HBV-related liver disease. A retrospective study of Italian HBCAb-positive patients with lymphoma found that 2.7% of patients treated with rituximab and chemotherapy developed HBV-related liver disease compared to 0.8% of patients treated with chemotherapy alone. HBV-related liver disease was not seen in patients who were observed or received other therapy (radiation, antibiotics, interferon).

Anti-viral prophylaxis has been effective in the prevention of hepatitis B reactivation during chemoimmunotherapy in HBsAg-positive patients. The results of a systematic review of 14 studies involving HBsAg-positive patients receiving chemotherapy showed that lamivudine prophylaxis for HBsAg-positive patients undergoing chemotherapy reduced the risk for HBV reactivation by ≥79%; HBV-associated hepatic failure and death may also be reduced. None of the patients in the preventive lamivudine group developed HBV-related hepatic failure compared to 21 of 162 patients in the control group, and only 4 deaths were attributable to HBV in the preventive lamivudine group compared to 27 deaths in the control group. Lamivudine was well tolerated with no adverse effects. In a small randomized study, Lau et al demonstrated that pre-emptive antiviral treatment with lamivudine was superior to deferred treatment. This study randomized 30 HBsAg-positive lymphoma patients to receive lamivudine before chemotherapy or to receive lamivudine for the treatment of increased viral load based on HBV
DNA PCR levels. HBV reactivation was observed in 53% of monitored patients and none in the prophylaxis group. Interestingly, clinical cancer-related outcomes were also significantly better in the prophylaxis group than the treatment group.

The NCCN guidelines recommend HBSAg and HBCAb testing for all patients receiving rituximab. In patients where one or both of these tests are positive, a baseline hepatitis B viral load should be determined by quantitative PCR. However, a negative baseline PCR does not preclude the possibility of activation. In patients from areas with high prevalence (Asia, Africa, Eastern Europe, and portions of South America) or regions where the prevalence of HBV is not known, all patients receiving immunotherapy, chemotherapy, or chemoimmunotherapy should be tested for HBSAg and HBCAb. Patients receiving intravenous immunoglobulin (IVIG) may be HBCAb positive as a consequence of IVIG therapy. Empiric antiviral therapy with oncologic treatment is recommended for any patient who is either HBSAg or HBCAb positive. During the treatment period, viral load should be monitored monthly with PCR and 3 months thereafter.

Patients receiving chemotherapy alone should receive prophylaxis if they have a measurable viral load independent of the viral serology. If viral load is consistently undetectable, prophylaxis should be given to HBSAg positive patients and may be considered in patients HBCAb positive. If viral load fails to drop, consultation with a hepatologist is recommended. However, because of the potential emergence of resistance to lamivudine it is not the optimal drug for prophylaxis. There are a number of appropriate agents for viral prophylaxis; good choice will be driven by institutional standard or recommendation from the consultant. The optimal duration of prophylaxis remains undefined but the panel recommended it should be maintained for at least 6 months after the completion of oncologic treatment.

Progressive multifocal leucoencephalopathy

Progressive multifocal leucoencephalopathy (PML) is a serious and usually fatal CNS infection caused by JC polyoma virus. In a recent report of 57 cases from the Research on Adverse Drug Events and Reports project, 52 patients with lymphoproliferative disorders developed PML after treatment with rituximab and other treatments which included hematopoietic stem cell transplantation or chemotherapy with purine analogs or alkylating agents. Median time from last rituximab dose to PML diagnosis was 5.5 months. Median time to death after PML diagnosis was 2.0 months. The case-fatality rate was 90%.

PML is usually diagnosed with PCR of cerebrospinal fluid (CSF) or sometimes brain biopsy. There is no effective treatment for PML. Patients need to be carefully monitored for the development of any neurological symptoms. There is currently no pretreatment evaluation that can be undertaken to predict for the subsequent development of PML.

Tumor Lysis syndrome

Tumor lysis syndrome (TLS) is characterized by metabolic abnormalities caused by the abrupt release of intracellular contents into the blood resulting from cellular disintegration induced by chemotherapy. It is usually observed within 12 to 72 hrs after start of chemotherapy. Untreated TLS can induce profound metabolic changes resulting in cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and death.

Cairo and Bishop have recently classified TLS into laboratory TLS and clinical TLS. Laboratory TLS is defined as a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels. Clinical TLS refers to laboratory TLS
with clinical toxicity that requires intervention. Clinical complications may include renal insufficiency, cardiac arrhythmia, or seizures. The four primary electrolyte abnormalities of TLS are hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Symptoms associated with TLS may include nausea and vomiting, diarrhea, seizures, shortness of breath, or cardiac arrhythmias.

TLS is best managed if anticipated and treatment started prior to chemotherapy. The cornerstone of the management of TLS is hydration and the control of hyperuricemia. Allopurinol should be administered prior to the initiation of chemotherapy. In cases where the uric acid level remains elevated despite treatment with allopurinol or there is renal insufficiency treatment with rasburicase is indicated. Electrolytes and renal function should be monitored every 6-8 hours with appropriate interventions for hyperkalemia and hyperphosphatemia. Careful clinical monitoring will help to preempt complications and in many cases admission to ICU is appropriate. Cardiac monitoring or serial ECG may be beneficial to identify early electrolyte related cardiac abnormalities. Dialysis may be necessary in cases of anuric acute renal failure.

Allopurinol is a xanthine analog and a competitive inhibitor of xanthine oxidase thereby blocking conversion of purine metabolites to uric acid. Allopurinol will decrease the formation of uric acid production and has been shown to reduce and reduce the incidence of uric-acid uropathy. Since the drug inhibits new uric acid formation rather than to reduce existing uric acid, it can take several days for elevated levels of uric acid to normalized after the initiation of treatment thereby delaying the start of chemotherapy. Furthermore, allopurinol may lead to the accumulation of xanthine crystals in renal tubules leading to acute obstructive uropathy. Allopurinol will also reduce clearance of 6-mercaptopurine and high-dose methotrexate.

Rasburicase is recombinant urate oxidase which catalyzes the oxidation of uric acid to a highly soluble non-toxic metabolite that is readily excreted. It has been shown to be safe and highly effective in the prevention and treatment of chemotherapy-induced hyperuricemia in both children and adults. The GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study evaluated the efficacy and safety of rasburicase for the prevention and treatment of hyperuricemia in patients with NHL during induction chemotherapy. Uric acid levels decreased within 4 hours after the first injection of the drug. Creatinine levels and other metabolites were also controlled with the administration of rasburicase.

Cortes et al recently reported the results of a prospective, randomized controlled trial which compared the efficacy of rasburicase and allopurinol in adult patients with hematological malignancies at high or potential risk for TLS. The plasma uric acid response rate was 87% for rasburicase, 78% for rasburicase plus allopurinol arm and 66% for allopurinol. Rasburicase was superior to allopurinol in the overall study population as well as in patients at high risk TLS (89% vs. 68%) and in patients with baseline hyperuricemia (90% vs. 53%). The time to control serum uric acid in hyperuricemic patients was 4 h for rasburicase and 27 h for allopurinol. However, rasburicase can induce anaphylactic reactions. Other adverse reactions include methemoglobinemia and severe hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

The risk factors for TLS include bone marrow involvement, bulky tumors that are chemosensitive, rapidly proliferative or aggressive hematologic malignancies, an elevated leukocyte count or pretreatment lactate dehydrogenase (LDH), pre-existing elevated uric acid, renal disease or renal involvement of tumor. Patients diagnosed
with lymphoblastic lymphoma or Burkitt lymphoma are at a higher risk of developing TLS. Occasionally, patients with bulky presentation of DLBCL and patients with CLL and high white blood cell count may experience TLS at a moderately high frequency.

The NCCN guidelines recommend that allopurinol should be started 2–3 days prior to chemotherapy and continued for 10–14 days. Rasburicase is recommended for patients with any of the following risk-factors: presence of any high risk feature; bulky disease requiring immediate therapy; patients in whom adequate hydration is not possible; allopurinol is ineffective; or acute renal failure. One dose is adequate in most cases; repeat dosing should be individualized.

NCCN Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines were developed for the most common subtypes of NHL:

- **Mature B-cell lymphomas**
  - Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
  - Follicular lymphoma (FL)
  - Marginal Zone lymphomas (MZL)
    - Extramedullary MZL of mucosa associated lymphoid tissue (MALT lymphoma)
      - Gastric MALT lymphoma
      - Non-gastric MALT lymphoma
    - Nodal MZL
    - Splenic MZL
  - Diffuse large B-cell lymphoma (DLBCL)
  - Mantle cell lymphoma (MCL)
  - Burkitt lymphoma (BL)

- **AIDS-related B-cell lymphoma**
- **Primary Cutaneous B-cell Lymphomas**

- **Precursor B-cell/T-cell lymphomas**
  - Lymphoblastic lymphoma

- **Mature T-cell and NK-cell lymphomas**
  - Peripheral T-cell lymphoma (PTCL)
  - Mycosis fungoides (MF) and Sezary syndrome (SS)
  - Adult T-cell leukemia/lymphoma (ATLL)
  - Extramedullary NFL/T-cell lymphomas, nasal type

- **Post-transplant lymphoproliferative disorders (PTLD)**

### Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

CLL and SLL are different manifestations of the same disease and are managed in much the same way. The major difference is that in CLL, a significant number of the abnormal lymphocytes are also found in the bone marrow and blood, while in SLL the abnormal lymphocytes are predominantly found in the lymph nodes.

Cytogenetic abnormalities that can be detected by FISH are present in about 80% of patients with CLL. The most common abnormality is del(13q) (55%) followed by del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%). Deletion 13q is associated with a favorable prognosis and the longest median survival (133 months). Deletion of 11q is associated with extensive lymphadenopathy, disease progression and shorter median survival (79 months). Among patients with 11q deletion, those with a complete loss of ATM function might have impaired response to irradiation or cytotoxic drugs, resulting in poor clinical outcome. Alkylating agent-based
chemoimmunotherapy regimens have significantly improved clinical outcomes by overcoming the adverse prognostic significance of del(11q) in previously untreated patients with CLL. Deletion 17p affecting TP53 is associated with shorter treatment free intervals, shorter median survival (32 months), and poor response to chemotherapy. Recent studies have identified TP53 mutations as an independent predictor of short survival and resistance to chemotherapy. The resistance to chemotherapy has been attributed to the presence of mutation in the remaining TP53 allele. However, the natural history of patient with deletion 17p can be heterogeneous with some patients having an indolent disease course. TP53 mutation also carries a poor prognosis regardless of the presence of deletion 17p when treated with fludarabine-based chemotherapy.

The impact of these prognostic factors on the clinical outcome of patients has been examined in large prospective randomized studies. In the CALGB 9712 study, unmutated IGHV (≥98%), del(11q) and del(17p) were identified as independent prognostic factors for overall and progression-free survival (PFS) whereas in other two studies (E2997 and LRF CLL4) these features were identified as prognostic indicators for PFS. In the LRF CLL4 trial patients with 5-20% of cells with del(17p) had similar response rates and survival as patients without del(17p). In contrast, those with 20% or more of cells with del(17p) had a poor outcome with 13% response rate and a median OS of only 11 months. The finding that del(17p) is more frequently observed in treated patients than in untreated ones (20% vs. 5-10%) suggests treatment-driven clonal selection occurs during therapy.

New prognostic markers such as beta-2-microglobulin, IGHV mutational status, CD38 and zeta-associated protein 70 (ZAP-70) have been identified. Higher beta-2-microglobulin was an independent adverse prognostic factor in patients treated with front-line fludarabine-based chemotherapy. Unmutated IGHV is associated with a poor prognosis irrespective of the stage of the disease. The extent of mutation is also important, with the longest survivals observed in patients with >3% mutations and slightly shorter survival seen in those with 1-2% mutations. A subset of patients in which the IGTV3-21 variable region is rearranged have a relatively more aggressive disease and short survival regardless of the mutation status.

Overexpression of CD38 (30% or more) and ZAP-70 (20% or more) are also associated with a poor prognosis. However, these cutoffs are based on flow cytometry and reproducibility across laboratories remains a problem. Recent studies have shown that the combined analysis of ZAP-70 and CD38 expression provides a more discriminatory prediction of treatment free interval than each factor alone. Wierda et al. have developed a nomogram using age, β2M, absolute lymphocyte count, sex, Rai stage, and number of involved lymph nodes that may help to stratify untreated patients with CLL into 3 different risk groups (low, intermediate and high). The estimated median survival times were not reached for low risk groups. The median survival times for intermediate and high risk groups were 10 years and 5 years respectively. The 5- and 10-year OS rates were 97% and 80%, 80% and 52% and 55% and 26% respectively. This prognostic model needs to be validated in prospective studies.

Staging

The nearly universal involvement of the bone marrow and peripheral blood in CLL/SLL limits the utility of the Ann Arbor staging system. Two different staging systems, Rai and Binet system are currently...
used worldwide. The modified Rai classification is most useful clinically and provides important prognostic information. Survival of patients with low-risk disease (Rai stage 0) is essentially the same as the survival rate of age-matched controls. Patients with intermediate-risk disease (Rai stage I-II) have a shorter survival, particularly when other adverse factors coexist, such as a lymphocyte doubling time of less than one year. Patients with high-risk disease (Rai stage III-IV) have a poor prognosis. Binet staging system is based on the number of involved areas and the level of hemoglobin and platelets and like the Rai system has a good correlation with clinical outcome.

Diagnosis

The diagnosis of CLL requires the presence of at least 5000 malignant B-cells/mm$^3$. The presence of fewer B-cells in the absence of lymphadenopathy or other clinical features characteristic of a lymphoproliferative disorder is defined as monoclonal B-lymphocytosis (MBL). MBL is a relatively recent diagnostic category consisting of individuals with an abnormal B-cell population but do not meet the diagnostic criteria for CLL. Most cases of MBL have the immunophenotype of CLL (see below). The “favorable” molecular lesions, mutated $IGHV$ and del(13q), are commonly seen in patients with MBL. The estimated rate of progression of MBL to CLL requiring treatment was 1.1% per year. To distinguish MBL from CLL evaluation with CT scan is essential. The CLL/SLL guideline now includes an initial stratification between CLL/SLL and MBL (absolute lymphocyte count of less than 5000 B-cells/mm$^3$, lymph nodes less than 1.5 cm, no anemia or thrombocytopenia). Observation is recommended for all patients diagnosed with MBL.

Adequate immunophenotyping using flow cytometry of peripheral blood or paraffin-section immunohistochemistry is required to confirm the diagnosis of CLL/SLL. Recommended panel for immunohistochemistry include CD3, CD5, CD10, CD20, CD23 and cyclin D1. These can be useful, particularly for diagnosing CLL/ SLL type without circulating cells. Cell surface markers for flow cytometric studies include kappa/lambda, CD19, CD20, CD5, CD23 and CD10. Additional paraffin-embedded material may be used for immunophenotyping to determine lineage and clonality.

The typical immunophenotype includes CD5+, CD10-, CD19+, CD20+, CD43+/−, and cyclin D1-. Distinguishing CLL/SLL from MCL is essential, as they are both CD5+ B-cell tumors. Though CD23 is often helpful, cyclin D1- is critical in this differentiation of tumor types. FISH for the t(11;14) can help distinguish MCL from CLL. Cytogenetics and/or FISH for detection of del11q, del13q, trisomy 12 and del17p and molecular genetic analysis to detect $IGHV$ mutation status can provide prognostic information and guide selection of therapy. Though FISH is optional for patients with Rai low risk disease where observation would be recommended; it should be evaluated at any time therapy is considered. Cytogenetic abnormalities can evolve over time and therefore re-evaluation of FISH is necessary to direct treatment options in patients with indications for treatment. CD38 and/or ZAP-70 expression can be determined using immunohistochemistry or flow cytometry. Evaluation of ZAP-70 expression by flow cytometry can be challenging and is not recommended outside the context of clinical trials.

Conventional metaphase cytogenetics is difficult in CLL as a result of the very low proliferative activity of the leukemic cells in vitro. Therefore, interphase cytogenetic analysis with FISH has been the standard method to detect the chromosomal abnormalities that have
important prognostic significance. However, FISH can only detect abnormalities specific to the probes utilized. Cytokine or CpG oligonucleotide stimulation has been utilized to promote efficient metaphase analysis. Recent studies have demonstrated that stimulation with CpG oligonucleotide and interleukin-2 is more effective than that with 12-O-tetradecanoyl-phorbol-13-acetate (TPA) for the detection of chromosomal abnormalities in CLL. A prospective study conducted by CLL Research Consortium confirmed that abnormal clones in CLL are more readily detected with CpG oligonucleotide stimulation than with traditional B-cell mitogens and the clonal abnormalities revealed by CpG stimulated metaphase cytogenetics are consistent with that detected by interphase FISH and are reproducible among different cytogenetic laboratories. However, the use of CpG stimulation for CLL cytogenetics is not yet universally available.

**Workup**

The workup for CLL/SLL is similar to the workup for other lymphoid neoplasms. Quantitative immunoglobulins may be particularly informative in patients with recurrent infections. Measurement of $\beta_2$M may provide useful prognostic information. Though classically the pattern of bone marrow involvement (diffuse versus nodular) had prognostic significance, this is no longer a factor when one uses more reliable prognostic markers such as IGHV mutation (or its surrogate ZAP-70) and cytogenetic abnormalities determined by FISH all of which can be obtained by analysis of circulating lymphocytes. Thus, bone marrow biopsy is no longer considered a required part of the evaluation of patients with CLL though it remains useful to evaluate the etiology of cytopenias.

Computed tomography (CT) scans is useful to follow and monitor disease progression when peripheral adenopathy is present. For anemic patients, reticulocyte counts and a direct Coombs’ test should be performed to evaluate for the possibility of hemolysis. PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter’s transformation is suspected.

**Response Criteria**

The National Cancer Institute sponsored working group (NCI-WG) first published the guidelines for the diagnosis and treatment of CLL in 1996. The recent developments in the use of prognostic markers and treatment options for CLL have led to the revision of these guidelines, particularly the response criteria. CR and PR are considered clinically beneficial. Relapse is defined as the disease progression after a period of 12 months or more following CR or PR. Refractory disease is defined as the one which does not respond to purine analog-based therapy or which progresses within 12 months after receiving such therapy.

**Treatment Options**

**First-line Therapy**

In earlier clinical trials the efficacy of chlorambucil plus prednisone was comparable to that of CVP (cyclophosphamide, vincristine and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimens in patients with advanced CLL. In the CALGB 9011 study, 509 patients were randomized to receive fludarabine, chlorambucil or the combination as first-line therapy. The combination arm was stopped due to excessive toxicity. Complete remission (20% vs. 4% for chlorambucil), partial remission (43% vs. 33% for chlorambucil), median duration of remission (25 months vs. 14 months for chlorambucil) and median PFS (20 months...
vs. 14 months for chlorambucil) were significantly better in patients treated with fludarabine. The study found no significant difference in OS between the two arms (66 months vs. 56 months for chlorambucil). In a phase III randomized trial conducted by the GCLLSG, fludarabine was significantly better than chlorambucil in terms of ORR (72% vs. 51% respectively) and time to treatment failure (18 months vs. 11 months respectively) in patients older than 65 years (median age 70 years), but there was no survival benefit for fludarabine compared to chlorambucil (OS and PFS were 46 months and 19 months respectively for fludarabine; 64 months and 19 months respectively for chlorambucil). 133

An European randomized study compared fludarabine with two alkylating agent-based combination regimens, CAP (cyclophosphamide, doxorubicin and prednisone) and CHOP as first-line treatment in patients with advanced CLL. 134 Fludarabine and CHOP produced similar overall remission rates (71%) compared to CAP (58%). However, fludarabine was better tolerated than CHOP. In large randomized trials, the combination of fludarabine and cyclophosphamide (FC) was associated with an increase in overall response, CR and PFS compared to fludarabine alone. 105, 135, 136

CALGB study 9712 compared the efficacy of fludarabine with concurrent or sequential administration of rituximab in untreated patients with CLL. 137, 138 The concurrent regimen was associated with a higher ORR (90% vs. 77% for the sequential regimen) at the expense of higher grade 3 or 4 toxicity. However, comparison of the outcomes of patients treated with fludarabine alone in the CALGB 9011 trial and the pooled results from the CALGB 9712 study, suggested that the addition of rituximab to fludarabine prolongs PFS and OS. 139

The combination of fludarabine, cyclophosphamide and rituximab (FCR) evaluated at M.D. Anderson Cancer Center as initial therapy produced high ORR and CR. 140-142 For the 300 study patients, at a median follow up of 6 years, the ORR was 95% (72% CR). 141 Recently, a large international randomized Phase III clinical trial (CLL8) showed that the addition of rituximab to fludarabine-based chemotherapy improved the outcome of patients with CLL with regard to response rates, PFS and OS compared to those receiving fludarabine-based chemotherapy alone. 142 In this trial, 817 patients with previously untreated CD20-positive CLL were randomized to 6 courses of either FCR or FC regimen. At 3 years after randomization, the PFS and OS rates were 65% and 87% respectively for patients randomized to FCR compared to 45% and 82.5% respectively for those who received FC. FCR also induced a higher ORR (95% vs 88%) and more CRs (44% vs. 22%) than FC. Median PFS was 52 months and 33 months for FCR and FC respectively. Based on the results of this trial, the FDA approved rituximab in combination with fludarabine and cyclophosphamide for patients with previously untreated CD20-positive CLL.

In a trial initiated by the CLL Research Consortium, pentostatin, cyclophosphamide and rituximab (PCR) demonstrated significant clinical activity despite poor risk-based prognoses in previously untreated patients. 144 Responses were observed in 91% of patients (41% CR, 21% nodular PR and 28% PR). In a subsequent study, the combination of higher dose pentostatin and rituximab resulted in OR of 76%, with a CR of 27%. 145 However, in historical comparison, the response rates were higher and the median treatment-free survival (16 months vs. 30 months for PCR) for all accrued patients was notably longer in patients treated with PCR compared with PR.
Bendamustine is an alkylating agent with a low cross-resistance with other alkylating agents (chlorambucil, cyclophosphamide, ifosfamide) and fludarabine. In a pivotal phase III randomized study (n = 319), bendamustine was compared to chlorambucil in patients with untreated CLL.\(^{146, 147}\) The ORR (68% vs. 31% respectively) and CR rate (31% vs. 2% respectively) were significantly higher for bendamustine compared to chlorambucil. Median PFS (22 months vs. 8.3 months for chlorambucil) and median duration of remission (22 months vs. 8 months with chlorambucil) were also better for bendamustine. However, there were no differences in OS between the two groups and the efficacy of bendamustine compared to first-line therapies other than chlorambucil has not yet been established. In a multicenter phase II trial (CLL2M) from the German CLL Study Group (GCLLSG), bendamustine in combination with rituximab (BR) resulted in an ORR was 91% (33% CR and 55% PR) for the entire study population (n = 117) with untreated CLL.\(^{148}\) The GCLLSG is currently conducting a comparison of FCR and BR (CLL10).

Alemtuzumab, a monoclonal antibody targeting CD52 has been effective as a first-line treatment for patients with CLL.\(^{149, 150}\) In an international, multicenter randomized study (CAM307), 297 patients were randomized to receive alemtuzumab or chlorambucil as first line treatment for patients with CLL.\(^{150}\) Alemtuzumab had superior PFS with a 42% reduction in risk of progression or death. The ORR was significantly better for alemtuzumab (83% with 24% CR) compared to 55% with 2% CR for chlorambucil. In patients with del(17p), the ORR and median PFS were 64% and 11 months respectively for alemtuzumab which were higher than that observed with chlorambucil (20% and 2 months respectively).

**Relapsed or Refractory Disease**

The FCR regimen also induced higher response rates in previously treated patients (n = 177).\(^{151}\) The ORR was 73% (complete remission, nodular partial remission, partial remissions were achieved in 25%, 16% and 32% of patients, respectively). Recently, the REACH trial compared six cycles FCR with six cycles of FC in 552 patients with previously treated CLL.\(^ {152}\) After a median follow-up time of 25 months, patients in the FCR group had significantly improved PFS (31 months) compared to 21 months for those in the FC group. The ORR was also significantly higher for FCR regimen [70% including 24% CR and 46% PR] vs. 58% including 13% CR and 45% PR for FC regimen). At the median follow up of 25 months, OS was not significantly improved for FCR. Based on the results of this trial, the FDA approved rituximab in combination with fludarabine and cyclophosphamide for patients with previously treated CD20-positive CLL.

The combination of pentostatin and cyclophosphamide (PC) with or without rituximab (R) has shown significant activity in previously treated patients with relapsed or refractory disease.\(^ {153, 154}\) In a small number of previously treated patients (n = 46), the response rates were similar for PC and PCR. However, based on a historical retrospective comparison with PC regimen, the median duration of response for PCR (25 months) is longer than that of PC (7 months) as well as median survival (44 months for PCR and 16 months for PC).\(^ {153}\)

In a phase I-II trial, the combination of oxaliplatin, fludarabine, cytarabine and rituximab (OFAR) was highly active in fludarabine-refractory patients with CLL and those with Richter’s syndrome.\(^ {155, 156}\) The ORRs were 50% in patients with Richter’s syndrome and 33% in those with fludarabine-refractory CLL.\(^ {155}\) Responses were achieved in seven (35%) of 20 patients with del(17p), two (29%) of seven patients with del(11q), all four patients with trisomy
12, and two (40%) of five patients with del(13q). The median response duration was 10 months. The ORR in patients 70 years or older (n = 14) was 50%.

The GCLLSG conducted a trial combining bendamustine and rituximab for patients with relapsed CLL which resulted in an ORR was 77% in 62 evaluable patients with relapsed or refractory disease. Complete and partial responses were seen in 14.5% and 63% of patients respectively. Stable disease was achieved in 18% of patients and 5% had progressive disease.

High-dose methylprednisolone (HDMP) and rituximab is well tolerated and an effective therapy for patients with refractory CLL including those with unfavorable prognostic features. In a study of 28 patients with fludarabine refractory CLL, the ORR was 96% (32% CR). In a follow-up of 37 patients with CLL treated at Mayo Clinic with the HDMP and rituximab, 29 (78%) patients had an objective response including five of nine patients with del(17p). Eight (22%) patients had a complete clinical response. Three-year survival rate was 41%. In one study, although the combination of HDMP and rituximab induced superior overall (93%) and complete (14%) response rates compared to HDMP alone (43% and 0% respectively) in heavily pre-treated patients with advanced disease, it was also associated with high rate of opportunistic infections.

Alemtuzumab also induced significant responses in patients who had failed fludarabine-based therapy. Overall objective response in the intent-to-treat population (n = 93) was 33% (CR 2% and PR 31%). Median time to progression was 4.7 months overall (9.5 months for responders) and median OS was 16 months (32 months for responders). Other studies have also shown that alemtuzumab is effective in patients with fludarabine refractory CLL and del(17p) or p53 gene mutations. Subcutaneous alemtuzumab appears as effective and safe as intravenous alemtuzumab in patients with advanced stage relapsed or refractory CLL. In a recent retrospective analysis, favorable ORR, PFS and OS (49%, 7 and 19 months, respectively) were observed with alemtuzumab in pretreated patients with del 17p. However, nodal sites of disease have generally not responded well with single agent alemtuzumab.

Combinations of alemtuzumab and fludarabine, alemtuzumab and rituximab, cyclophosphamide, fludarabine, alemtuzumab and rituximab (CFAR) have shown promising results in patients with relapsed or refractory disease.

Ofatumumab, a human CD20 monoclonal antibody, was found to be well tolerated in patients with relapsed or refractory CLL in a phase I/II study. In October 2009, ofatumumab was approved by the FDA for the treatment of patients with CLL that is refractory to fludarabine and alemtuzumab, based on the interim analysis of the pivotal international clinical trial, which included data from 138 patients with fludarabine- and alemtuzumab-refractory (FA-ref) CLL or patients with fludarabine-refractory CLL with bulky lymphadenopathy (BF-ref). In the interim analysis, ORR was 58% and 47% in the FA-ref and BF-ref groups, respectively. The final results from the pivotal trial demonstrated the safety and efficacy of ofatumumab in this heavily pretreated patient population. Median PFS was 5.5 months for both groups. The median OS was 14 and 17 months for the FA-ref group and the BF-ref group, respectively.

Allogeneic hematopoietic stem cell transplant (HSCT) has been evaluated to improve the prognosis in patients with advanced disease and those with poor-risk features. In a retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT), allogeneic HSCT induced long-term remission in patients with
At a median follow-up was 39 months, 3-year OS and PFS rates were 44% and 37% respectively. The final results of the prospective multicenter trial (GCLLSG CLL3X study) also showed nonmyeloablative allogeneic SCT can induce sustained MRD-negative EFS in a significant proportion of patients del(17p). Three-year EFS for patients with del(17p) and those without del(17p) were 43% and 41% respectively. Five out of 13 patients with del(17p) were MRD-negative at 12 months. This study also identified refractory disease at the time of transplant as a negative prognostic factor for OS and event-free survival (EFS). It is understood that studies involving allogeneic stem cell transplantation are subject to strong selection biases. Nonetheless, available evidence from non-randomized clinical studies suggest that allogeneic HSCT is an effective treatment option for patients refractory to chemoimmunotherapy or who develop recurrence within 12 months after purine analog treatment.

NCCN Recommendations

Localized SLL (Ann Arbor stage I)
Locoregional radiation therapy (RT) is an appropriate induction therapy for this group of patients. In rare patients, RT may be contraindicated or it may be a sub-optimal therapy due to the presence of comorbidities or the potential of long-term toxicity. Patients with localized SLL that has progressed after initial RT are treated as described below for patients with SLL (Ann Arbor stage II-IV).

SLL (Ann Arbor stage II-IV) or CLL (Rai stages 0-IV)
Early stage disease in some patients may have an indolent course and in others it may progress rapidly to advanced disease requiring immediate treatment. Absolute lymphocyte count alone is not an indication for treatment unless it is above 200-300 x 10^9/L or symptoms related to leukostasis. Therefore, in patients with SLL (Ann Arbor stage II-IV) or CLL (Rai stages 0-II), treatment options depend on the presence or absence of the following indications: significant disease related symptoms including severe fatigue, weight loss, night sweats and fever without infection, threatened end-organ function, progressive bulky disease (enlarged spleen or lymph nodes), lymphocyte doubling time of 6 months or less or progression to more advanced stage CLL with progressive anemia or thrombocytopenia. Patients with no indications for treatment can be observed until disease progression or the appearance of any of the indications of treatment. Patients with advanced stage CLL (Rai stage III-IV) require immediate treatment.

Given the incurability of the disease, the NCCN guidelines recommend enrollment in clinical trials, when locally available, as the preferred first-line therapy for all patients. For patients presenting with indications for treatment and not eligible or do not have access to clinical trials, the treatment recommendations included in the guidelines are based on the presence or absence of deletion 17p or 11q, age and performance status of the patient. Re-evaluation of FISH is necessary to direct treatment options in patients with indications for treatment.
agent-based chemotherapy or chemoimmunotherapy, monotherapy with alemtuzumab or rituximab, fludarabine with or without rituximab or cladribine as options. Based on the results of the CLL8 trial, the NCCN guidelines have included rituximab in combination with purine analog-based chemotherapy or bendamustine as options for patients 70 years or younger or older patients without significant comorbidities. See “Suggested Treatment Regimens for CLL/SLL without del(17p) or del(11q)” in the guidelines for a list of specific regimens.

In patients younger than 70 without significant co-morbidities chemoimmunotherapy has emerged as the standard of care based a number of trials. A randomized comparison of FCR versus PCR demonstrated a higher CR rate for FCR but the ORR and OS were no different between the regimens. Both FCR and FR are highly active regimens but we do not have category 1 evidence to choose between these two regimens. In the absence of a del(11q) it is uncertain if there are long-term outcome differences between these regimens.

Second-line Therapy
For patients failing first-line therapy, treatment options are dependent on the duration of response following first-line therapy. Among patients who failed FCR chemoimmunotherapy as initial therapy, those with a time to treatment failure of 3 years or more had better median survival (44 months) than those with a time to treatment failure of less than 3 years. If the response duration is more than 3 years (long response), the guidelines recommend additional cycles of same regimen that was used as first-line therapy for all patients.

If the duration of the response duration is less than 2 years (short response), treatment options are dependent on the age. For patients 70 years or older or younger patients with comorbidities, options include reduced-dose FCR or PCR, bendamustine with or without rituximab, HDMP with rituximab, monotherapy with ofatumumab, alemtuzumab with or without rituximab or dose-dense rituximab. For patients younger than 70 or older patients without significant comorbidities, the guidelines have included chemoimmunotherapy, monotherapy with ofatumumab or alemtuzumab with or without rituximab as options. See “Suggested Regimens for CLL/SLL without del(17p) or del(11q)” in the guidelines for a list of specific regimens.

Allogeneic HSCT can be considered for patients with short response but would generally be used after re-induction of remission.

CLL/SLL with del(17p)
17p deletion is associated with low response rates with all treatments. Since there is no standard treatment, clinical trial is recommended. First-line therapy options include FCR or FR, HDMP plus rituximab, alemtuzumab with or without rituximab or bendamustine plus rituximab.

Patients who have achieved CR or PR to first-line therapy should be treated with allogeneic HSCT, if they are eligible. Patients with CR or PR following transplant can either be observed or enrolled in clinical trials. Alternatively patients with PR could also be treated with chemoimmunotherapy. See “Suggested Regimens for CLL/SLL with del(17p)” in the guidelines for a list of specific regimens.

Patients with no response to first-line therapy, patients who respond to first-line therapy but are not eligible for allogenic HSCT and for those with no response to transplant should be enrolled in clinical trials or they can be treated with second-line therapy for relapsed or refractory disease. The guidelines have included chemoimmunotherapy, monotherapy with ofatumumab, alemtuzumab with or without rituximab, HDMP or bendamustine with or without...
rituximab as options. See “Suggested Regimens for CLL/SLL with del(17p)” in the guidelines for a list of specific regimens.

**CLL/SLL with del(11q)**

First-line therapy options are based on the age and associated comorbid conditions. If patients have a del (11q) an alkylator needs to be included in the regimen. Response rates and response duration of improved when an alkylator is added a purine analog. In the patients older than 70 or with significant co-morbidities single agent alemtuzumab or rituximab should be used only if an alkylator is considered unsafe or was intolerable. See “Suggested Regimens for CLL/SLL with del(11q)” in the guidelines for a list of specific regimens.

Patients who have achieved CR to first-line therapy can either be observed until disease progression or enrolled in clinical trials. For those with disease progression following CR treatment options are dependent on the duration of response to first-line therapy. See “Suggested Regimens for CLL/SLL with del(11q)” in the guidelines for a list of specific regimens. Patients with PR to first-line therapy should be treated with allogeneic HSCT, if they are eligible. Following transplant, treatment options are similar to that described for patients with del(17p).

Patients with no response to first-line therapy, patients with PR to first-line therapy but are not eligible for allogeneic HSCT should be enrolled in clinical trials or they can be treated with second-line therapy for relapsed or refractory disease. See “Suggested Regimens for CLL/SLL with del(11q)” in the guidelines for a list of specific regimens.

**Histological Transformation to DLBCL or Hodgkin lymphoma**

About 2-5% of patients with CLL will develop Richter syndrome (transformation into DLBCL or Hodgkin lymphoma) during the course of treatment. The incidence of transformation increases with the number of prior regimens. Patients with Richter’s syndrome should be treated with a combination of chemoimmunotherapy regimens initially developed for DLBCL. In addition to these regimens, the guidelines have also included R-hyperCVAD as an option for patients with histological transformation as well as for those with relapsed or refractory CLL.

Allogeneic HSCT has also shown promising results in patients with RS responding to initial therapy. In a non-randomized comparison, the estimated cumulative 3-year survival rate was significantly higher (75%) for patients who underwent allogeneic SCT after achieving CR or PR to initial therapy compared to those who responded to initial therapy and received no allogeneic SCT, and who underwent allogeneic HSCT for relapsed or refractory RS (27% and 21% respectively). Allogenic HSCT can be considered following initial therapy.

**Supportive care for patients with CLL**

**Infections**

Infectious complications in patients with CLL are influenced by the reduction in immunoglobulin levels and are more common in previously treated patients. Hypoglobulinemia is present in 38% of patients up to 3 years prior to diagnosis of CLL. In a retrospective analysis, 89% of patients with fludarabine-refractory CLL developed infectious complications (78% bacterial and 12% viral). IVIG, antibacterial or antiviral prophylaxis or vaccinations are the three options available for the reduction of infectious complications.
In randomized studies, IVIG has been associated with a significant decrease in the occurrence of infections but no improvement in OS. Antibacterial prophylaxis may be a useful alternative option. Protein and conjugate vaccines have been shown to induce better responses than plain polysaccharide vaccines. Some studies have reported that histamine type-2 (H2) receptor blockers can enhance vaccine response.

In selected patients (serum IVIG is less than 500 mg/dl) with recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization, the guidelines recommend monitoring IVIG levels and administration of monthly IVIG (0.3-0.5 g/kg) to maintain nadir levels of approximately 500 mg/dl. Antibacterial prophylaxis is also appropriate for the management of infections. Antiviral and pneumocystis prophylaxis is recommended for patients receiving purine-analog and/or alemtuzumab during treatment and thereafter. Acyclovir or equivalent is recommended for Herpes virus and sulfamethoxazole trimethoprim or equivalent is recommended for pneumocystis carinii pneumonia (PCP). Annual influenza vaccine and pneumococcal vaccine (every 5 years) is recommended for all patients. All live vaccines should be avoided.

Patients with CLL have a poor response to influenza vaccine and they should be counseled to exercise care during influenza season even with vaccination. Patients who have received rituximab therapy do not respond to influenza vaccination until B-cell recovery.

**CMV reactivation**

Cytomegalovirus (CMV) reactivation is a well documented side effect in patients receiving alemtuzumab. CMV reactivation is associated with relatively mild or no symptoms when prophylactic measures are used during treatment with alemtuzumab. The current appropriate management is controversial, some use ganciclovir (oral or IV) prophylactically if viremia is present, other only if viral load is increasing.

Clinicians must be aware of the high risk of CMV reactivation. Monitoring patients for CMV reactivation regularly using polymerase chain reaction (PCR) is an effective approach for the management of CMV reactivation. The NCCN guidelines recommend CMV viremia monitoring (every 2-3 weeks). Consultation with an infectious disease expert may be necessary.

**Autoimmune Cytopenias**

Autoimmune hemolytic anemia (AIHA), immune-mediated thrombocytopenia, also known as immune thrombocytopenic purpura (ITP) and pure red blood cell aplasia (PRCA) are the most frequent autoimmune cytopenias in patients with CLL.

AIHA is the most common form of autoimmune cytopenia. Direct antiglobulin test (DAT) has been used for the diagnosis of AIHA. However, most patients with AIHA have negative DAT; additional markers such as low haptoglobin and elevated reticulocyte and LDH are required to confirm the diagnosis of AIHA. Patients with advanced disease, unmutated IGHV, increased serum beta-2 microglobulin level, and high expression of ZAP-70 are also at a higher risk of developing AIHA. ITP in patients with CLL is associated with poorer survival independent of common clinical prognostic variables. In a recent Italian study, high WBC count, unmutated IGHV, positive DAT and ZAP-70 positivity were associated with the development of ITP in patients with CLL. PRCA is less common in patients with CLL.

Bone marrow evaluation is recommended to confirm the diagnosis of auto-immune cytopenia. Evaluation of parvovirus B19 is also
Follicular Lymphoma

Diagnosis

FL is the most common indolent subtype of NHL accounting for about 22% of all newly diagnosed cases. About 90% of the cases have a t(14;18) translocation, which juxtaposes BCL2 with the IgH locus that results in the deregulated expression of BCL2.

Follicular lymphoma has a characteristic immunophenotype, which includes CD20+, CD10+, BCL2+, CD23+/-, CD43-, CD5-, CCDN1- and BCL6+. Rare cases of FL may be CD10- or BCL2-. In BCL2-negative young patients with localized disease, the diagnosis of pediatric follicular lymphoma may be considered. The diagnosis is easily established on histological grounds, but immunophenotyping is encouraged to distinguish from a nodal MCL or SLL. Low grade FL with a high proliferation index as determined by Ki-67 immunostaining has been shown to be associated with aggressive clinical behavior. But there is no evidence that it should guide selection of therapy.

Molecular genetic analysis to detect BCL2 rearrangement, cytogenetics or FISH to identify t(14;18) and paraffin section immunohistochemistry for Ki-67 will be useful under certain circumstances.

Follicular Lymphoma International Prognostic Index (FLIPI) is based on age, Ann Arbor stage, number nodal sites involved, hemoglobin levels and serum LDH levels. In the National LymphoCare study, which analyzed the treatment options and outcomes of 2,728 patients with newly diagnosed FL, FLIPI was used to define patients into three distinct groups with outcomes ranging from 52% to 90% survival at 5 years. In a recent study conducted by the International Follicular Lymphoma Prognostic Factor Project, a prognostic model was developed from prospective accumulated data which includes: age, hemoglobin, dimension longest lymph node, beta-2 microglobulin,
bone marrow involvement. FLIPI 2 was highly predictive of treatment outcome in newly diagnosed patients with FL treated with chemoimmunotherapy.\textsuperscript{234} With follow up to date the FLIPI-2 does not predict for overall survival; furthermore, it is only applicable to patients requiring therapy. Both the FLIPI-1 and -2 predict for prognosis, but they have not yet been established as a means of selecting treatment options.

**Workup**

The diagnostic workup for FL is similar to the workup for other indolent lymphomas. The majority of patients present with disseminated disease. The approach to therapy differs dramatically between patients with localized and those with disseminated disease. Bone marrow biopsy with aspirate is essential to document clinical stage I-II disease. This can be deferred if observation is the initial treatment option. The majority of NCCN investigators routinely employ chest, abdominal and pelvic CT as part of the diagnostic evaluation. CT scan of the neck may also assist in defining the extent of local disease. In patients presenting with what appears to be localized disease, a PET scan may be helpful in identifying occult sites of disease or if there is concern about histologic transformation.\textsuperscript{235} PET does not replace histologic confirmation of the diagnosis; however, if there are sites with discordant high FDG-avidity these represent the most likely sites of transformation.

**Treatment Options based on Clinical Stage**

NCCN guidelines for FL apply to FL 1-2. FL3A and FL3B are commonly treated according to DLBCL. It should be noted that in most centers the proportion of patients diagnosed with FL3 is greater than that previously diagnosed as follicular large cell lymphoma in the International Working Formulation.

**Stage I-II**

IFRT (24-30 Gy, with an additional 6 Gy in selected patients with bulky disease) is the preferred treatment option for patients with stage I or contiguous stage II disease. In a retrospective analysis of 43 patients with stage I-II disease, carefully selected patients (requirement of large abdominal radiation field, advanced age, concern for xerostomia or patient refusal) who did not receive immediate treatment had comparable outcomes to those who were treated with RT.\textsuperscript{236} In selected cases where toxicity of IFRT outweighs the potential clinical benefit, observation may be appropriate. Alternate treatment options include immunotherapy with or without chemotherapy with or without RT. The addition of cyclophosphamide, vincristine, prednisone, and bleomycin (COP-bleomycin) or CHOP-bleomycin improved failure free survival but did not impact overall survival in patients with early stage disease.\textsuperscript{237} The addition of adjuvant CHOP to RT did not improve relapse free survival (RFS) in patients with early stage low-grade lymphoma.\textsuperscript{238} Therefore, chemotherapy plus RT is included with a category 2B recommendation.

For patients with a clinical PR or CR, clinical follow-up with examination and laboratory assessment is initially done every three months with repeat imaging every 6 months or as clinically indicated. Patients no response to initial therapy should be managed in the same manner as patients with advanced disease, as described below.

**Stage II (bulky disease) and Stage III-IV**

Rituximab has demonstrated single agent activity in previously untreated patients as well in those with relapsed or refractory disease.\textsuperscript{239-241} The addition of rituximab to combination chemotherapy regimens has consistently increased the ORR, response duration and PFS. In addition, some studies have demonstrated OS benefit; a
recent meta-analysis has confirmed the benefit in OS despite what is still limited follow up for FL. 242

The safety and efficacy of R-CHOP was demonstrated in a small study that demonstrated excellent long-term results. 243, 244 The superiority of R-CHOP to CHOP in treatment naïve patients was established in a prospective randomized phase III study conducted by the German Low-Grade Lymphoma Study Group (GLSG) involving 428 patients. R-CHOP was associated with a 60% reduction in the relative risk for treatment failure, significantly prolonged time to treatment failure, higher ORR and prolonged duration of remission. 245

OS analysis is complicated by a second randomization which included high dose therapy followed by autologous stem cell rescue (HDT/ASCR). There OS was the same with and without rituximab, if there was consolidation with HDT/ASCR. However, OS was significantly improved for patients receiving R-CHOP followed by interferon compared to CHOP followed by interferon. R-CHOP also improved outcome of elderly patients with previously untreated FL. 246

Addition of rituximab to CVP chemotherapy (R-CVP) significantly improved outcome in patients with previously untreated FL, with no significant increase in toxicity. 247 At a median follow-up of 53 months, R-CVP was associated with improved ORR (81% vs. 57%), median time to progression (34 months vs. 15 months) and 4-year OS (83% vs. 77%). 248

The addition of rituximab to fludarabine or fludarabine-based combination has improved outcomes in various clinical studies. 249-252

In a prospective randomized trial, FCM-R regimen (fludarabine, cyclophosphamide, mitoxantrone and rituximab) was associated with superior outcomes in patients with relapsed or refractory FL and MCL. 250 In another randomized trial, concurrent administration of rituximab with FND regimen (fludarabine, mitoxantrone and dexamethasone) resulted in a significantly higher 3-year FFS rate (84% vs. 59% for sequential arm) in a subset of patients with FL. 251

Bendamustine, as a single agent or in combination with rituximab (BR), has shown promising results with acceptable toxicity in patients with newly diagnosed as well as heavily pretreated patients with relapsed or refractory indolent or mantle cell histologies as well as transformed NHL. 253-257 A randomized phase III study conducted by the StiL (Study Group Indolent Lymphomas) compared BR and R-CHOP as first-line treatment in patients with advanced follicular, indolent, and mantle cell lymphomas. The ORR was similar in both arms though the CR rate was significantly higher in the BR arm (40% vs. 31%). 253 However, the BR patients had a significantly longer median PFS (55 months vs. 35 months) and EFS (54 months vs. 31 months). Bendamustine plus rituximab also showed a better toxicity profile. Overall survival is similar. In a phase II multicenter study, BR resulted in an ORR of 92% (41% CR and 38% PR) in patients with relapsed or refractory indolent and mantle cell lymphomas. Median duration of response and progression-free survival was 21 months and 23 months respectively. Outcomes were similar for patients with indolent or mantle cell histologies. 256

Radioimmunotherapy (RIT) with 131I-tositumomab 258-261 and 90Y-ibritumomab tiuxetan 262-264 has also been evaluated in patients with newly diagnosed as well as those with relapsed, refractory or histologically transformed FL. Initial treatment with single one-week course of 131I-tositumomab induced prolonged clinical and molecular remissions in patients with advanced FL. 258 After a median follow-up of 10 years, the median duration of response was 6 years. For the 57 complete responders, median PFS was 11 years. 265 Ten-year PFS and OS rates were approximately 40% and 82% respectively. In an
international phase II trial, $^{90}$Y ibritumomab when used as a first-line therapy resulted in an ORR of 72% (52% CR and 20% PR) at 12 months after therapy. At a median follow-up of 23 months the PFS is 18 months.$^{266}$ A single course of $^{131}$I-tositumomab was significantly more efficacious than last qualifying chemotherapy in extensively pretreated patients with refractory, low-grade, or transformed NHL.$^{260}$ The final results of the study demonstrated that $^{131}$I-tositumomab resulted in long-term durable CRs a subset of patients who had received no prior rituximab.$^{267}$ In a randomized phase III study, $^{90}$Y ibritumomab tiuxetan also produced statistically and clinically significant higher ORR and CR compared with rituximab alone in patients with relapsed or refractory low-grade, follicular or transformed lymphoma.$^{263}$ At a median follow-up of 44 months, median TTP (15 vs.10.2 months), duration of response (16.7 vs. 11.2 months) were longer for patients treated with $^{90}$Y-ibritumomab compared with the rituximab.$^{264}$

**NCCN Recommendations Stage II (bulky disease) and Stage III-IV disease**

Despite therapeutic advances that have improved the survival of patients with FL, it remains an incurable disease with conventional therapy. Four prospective randomized trials have failed to demonstrate a survival advantage for immediate treatment.$^{268-271}$ Modified Groupe d’Etude des Lymphomes Folliculaire (GELF) criteria are used to decide when to initiate therapy in patients with advanced-stage disease including: symptoms attributable to FL (not limited to B-symptoms); threatened end-organ function; cytopenia secondary to lymphoma; bulky disease (singe mass $>7$cm or 3 or more masses $>3$cm), splenomegaly; steady progression over at least 6 months. Patient preference should be considered; however, patients wanting treatment without a clinical indication should be referred for an appropriate clinical trial. The selection of treatment should be highly individualized according to age, extent of disease, comorbid conditions, and the goals of therapy. When choosing an initial therapy, care should be given to avoid excessively myelotoxic regimens in patients who may subsequently be candidates for HDT/ASCR. In patients with hepatitis-B, treatment with an antiviral should be given if rituximab is used. See “Hepatitis B Reactivation” in the Supportive Care section of this manuscript.

**First-line therapy**

In the absence of an appropriate clinical trial, patients with indications for treatment should be treated with systemic therapy. In selected cases such as the elderly frail patient who would not tolerate chemotherapy, IFRT (4 Gy) may be used for local palliation. Asymptomatic patients especially those older than 70 years can be observed.$^{270}$ The results of an interim analysis of the intergroup randomized trial of rituximab vs. a watch and wait strategy showed that at 36 months after randomization, the estimated PFS was significantly better for asymptomatic patients with stage II-IV non-bulky disease receiving rituximab alone or rituximab followed by rituximab maintenance compared to observation, but there was no difference in OS between the treatment arms.$^{271}$ Further follow-up is needed to determine if immediate treatment has an impact on time to second therapy. The panel felt that these data were not sufficiently compelling that they should change practice. The ECOG RESORT trial is examining rituximab maintenance versus rituximab delayed until progression in a similar patient population and will provide some additional insight.

Based on the reported data, rituximab in combination with bendamustine, CHOP or CVP chemotherapy for first-line therapy in patients with advanced FL are all category 1 recommendations. BR
has been shown to have less toxicity and a superior PFS compared to R-CHOP; however, the OS is not different. Furthermore, we have limited data on the risk of secondary MDS/AML after bendamustine. Data from a limited subset of patients suggests that peripheral blood stem cells can be collected after both BR and R-CHOP; more data is needed to confirm this finding. We do not have a comparative trial of R-CHOP and R-CVP. Therefore, choice of first-line therapy in advanced stage FL remains a challenge for the clinician. Other suggested regimens include rituximab either as a single agent or in combination with fludarabine-based chemotherapy. RIT is included as category 2B option for first-line treatment. IFRT (4-30 Gy) with or without systemic therapy can be considered for palliation in patients with locally bulky or symptomatic disease if they are unable to tolerate systemic therapy.

Single agent rituximab is the preferred first-line therapy for elderly or infirm patients. Single agent cyclophosphamide had equivalent OS and CR rates compared to cyclophosphamide-based combination chemotherapy.272 The guidelines have also included RIT, alkylating agent-based chemotherapy (cyclophosphamide or chlorambucil) with or without rituximab as alternative options for elderly or infirm patients.

First-line Consolidation or Extended Dosing

Chemotherapy followed by RIT

First-line chemotherapy followed by RIT with 131I-tositumomab273-276 or 90Y-ibritumomab277-280 has been evaluated in several phase II studies. In the Southwest oncology Group (S9911) trial, CHOP followed by 131I-tositumomab resulted in an ORR of 91%, including a 69% complete remission (CR) rate in patients with previously untreated FL.275 After a median follow-up of 5 years, the estimated 5-year OS rate was 87%, and PFS rate was 67%.274 In historical comparison, these statistics were better than those reported for CHOP alone. In a multicenter phase II study, CVP chemotherapy followed by 131I-tositumomab resulted in an ORR of 100% with 93% CR in untreated patients with FL. The 5-year PFS and OS rates were 56% and 83%, respectively.276

In the international phase III trial (First-line Indolent Trail), 414 patients with advanced stage FL responding to first-line induction therapy were randomized to receive 90Y-ibritumomab or no further treatment.279 After a median follow-up of 5.5 years, the 5-year PFS was 47% and 29%, respectively, for the 90Y-ibritumomab tiuxetan consolidation group and the control group. Median was 49 months and 14 months respectively.281 There is no significant difference in OS between treatment arms. The rate of secondary malignancies (MDS/AML) were higher among patients in the consolidation group (3%) compared to those in the control group (1%). This trial included only a limited number of patients (14%) who received rituximab in combination with chemotherapy as induction therapy. Among these patients, the 5-year PFS rates were 64% and 48% respectively, for the 90Y-ibritumomab group and the control group.

Maintenance therapy with Rituximab

Prolonged administration of rituximab significantly improved EFS in chemotherapy-naive patients responding to rituximab induction, but did not extend OS.282-284 In another study, maintenance rituximab improved PFS (31 vs. 7 months). However, retreatment with rituximab at progression provided the same duration of benefit as did maintenance rituximab (31 vs. 27 months).285 The randomized phase III study (ECOG1496) demonstrated PFS benefit for rituximab maintenance in patients with advanced indolent lymphoma responding to first-line chemotherapy.286 The 3-year PFS rate was 68% for maintenance rituximab compared to 33% for observation for all patients with advanced indolent lymphoma with response or stable
Second-line Therapy for Relapsed or Progressive Disease

Frequently, patients will benefit from a second period of observation after progressing from first line therapy. Thus, treatment for relapsed or progressive disease is based on the modified GELF criteria as in first-line therapy. Progressive disease should be histologically documented to exclude transformations, especially if there are raising LDH levels, disproportional growth in one area, development of extranodal disease or new “B” symptoms. Non-uniform uptake on a FDG-PET scan can be an indication of transformation; areas of high SUV, especially in excess of 13.1 are suspicious for transformation. However, a PET scan does not replace a biopsy; it should used to direct a biopsy to enhance the diagnostic yield from the biopsy. The options include chemoimmunotherapy regimens used for first-line treatment, FCMR regimen (category 1) or RIT (category 1) or any of the second-line regimens used for patients with DLBCL.

Second-line Consolidation or Extended Dosing

Rituximab maintenance following second-line therapy for relapsed/refractory disease has been established in two large randomized trials to provide a PFS advantage over observation for patients treated with chemoimmunotherapy.289, 290,291

In a prospective randomized study by the GLSG, rituximab maintenance after second line treatment with R-FCM (rituximab with fludarabine, cyclophosphamide and mitoxantrone) significantly prolonged duration of response in patients with recurring or refractory FL and to a lesser degree in patients with MCL.289 In a phase III Intergroup trial (EORTC 20981), maintenance rituximab significantly improved median PFS and OS in patients with relapsed or resistant FL responding to CHOP or R-CHOP.290 With a median follow-up of 6 years, the 5-OS rate was 74% and 64% in the rituximab maintenance arm, and the observation arm respectively.291

disease after CVP chemotherapy. The corresponding PFS rates were 64% vs.33% respectively for patients with FL.286

The PRIMA trial prospectively evaluated the role of rituximab maintenance in patients responding to first-line chemotherapy in combination with rituximab. In this study, 1,018 eligible patients responding to first-line chemoimmunotherapy (R-CVP, R-CHOP or R-FCM) were randomized to observation or rituximab maintenance for 2 years.287 The interim analysis with a median follow-up of 24 months showed that rituximab maintenance significantly improved PFS (primary endpoint) compared to observation. After a median follow-up of 36 months, 3-year PFS rate was 75% in the rituximab maintenance arm and 58% in the observation arm.288 At 2 years after randomization, 72% of patients in the rituximab maintenance group were in CR or Cru compared to in the observation group.288 However, the OS was not significantly different between the two groups. Follow-up is ongoing to evaluate the effect of rituximab maintenance on OS.

Patients with CR or PR to first-line therapy can be observed or they can be treated with consolidation therapy. Based on the results of the PRIMA study,287 maintenance rituximab up to 2 years is recommended (category 1) for patients responding to first-line chemoimmunotherapy. RIT is recommended (category 1) only for patients who received first-line chemotherapy based on the results of the FIT trial.275 The recommendation to limit RIT to patients receiving induction chemotherapy rather than chemoimmunotherapy is based on the small proportion of patients who received induction chemoimmunotherapy in the FIT trial. For patients receiving consolidation therapy, clinical follow-up is initially recommended every 3 months with repeat imaging every 6 months and/or as clinically indicated.
HDT/ASCR has been shown to prolong OS and PFS in patients with relapsed or refractory disease.\textsuperscript{292-294} The GELA recently conducted a retrospective analysis of patients treated with chemotherapy alone in the first line and found that EFS and survival after relapse (SAR) were superior if patient with treated with rituximab containing regimens compared to chemotherapy only-based HDT/ASCR in patients with relapsed or refractory FL.\textsuperscript{295} The combination of rituximab-based second-line therapy followed by HDT/ASCR had the best results with SAR 90% at 5 years. Allogeneic HSCT is associated with high treatment related mortality rates (30-38% for myeloablative and 25% for nonmyeloablative).\textsuperscript{296, 297} In a recent report from IBMTR, both myeloablative and nonmyeloablative transplant had similar TRM rates but nonmyeloablative allogeneic HSCT was associated with an increased risk of disease progression.\textsuperscript{298}

Rituximab maintenance is recommended (category 1) for patients in second-line remission. However, the panel recognized that the efficacy of maintenance rituximab in second-line remission would likely be impacted by first-line maintenance. If a patient progressed during or within 6 months of first-line maintenance rituximab, the value of maintenance in the second-line is likely very minimal. HDT/ASCR is an appropriate consolidative therapy for patients with second or third remission. Allogeneic HSCT may be considered for highly selected patients. For patients receiving consolidation therapy, clinical follow-up is initially recommended every 3 months with repeat imaging every 6 month and/or as clinically indicated.

**Histological Transformation to DLBCL**

Transformation to DLBCL in patients with FL occurs at a rate of approximately 2-3% per year for at least 15 years and the risk of transformation falls after that time, for reasons that remain unclear.\textsuperscript{299} Transformation to DLBCL is generally associated with a poor clinical outcome. However, patients with limited disease with no previous exposure to chemotherapy can have the favorable outcomes similar to de novo DLBCL.\textsuperscript{300} In cases where the patient has had multiple prior therapies, the prognosis is much poorer and enrollment in clinical trial is the preferred option. In the absence of a clinical trial, treatment options include RIT, chemotherapy with or without rituximab, IFRT or best supportive care. HDT/ASCR or allogeneic HSCT can be considered for patients with responsive disease after initial treatment.

If the patient has had minimal (IFRT alone or one course of single agent therapy including rituximab) or no prior chemotherapy, anthracycline-based chemotherapy with rituximab, with or without RT is included as a treatment option. Enrollment in clinical trial is recommended for all patients following initial therapy. Patients responding to initial treatment could be considered for HDT/ASCR or allogeneic HSCT. Alternatively, patients with CR to initial therapy can be observed and RIT may be considered for those with PR. Patients with no response or progressive disease following initial therapy should be treated with RIT or best supportive care.

**Diffuse Large B-Cell Lymphoma**

**Diagnosis**

Diffuse large B-cell lymphomas are the most common lymphoid neoplasms in adults. DLBCL, NOS, FL (grade 3), DLBCL coexistent with FL of any grade, gastric MALT or non-gastric MALT lymphoma, intravascular large B-cell lymphoma, DLBCL associated with chronic inflammation, ALK-positive DLBCL, EBV-positive DLBCL of the elderly and T-cell/histiocyte rich large B-cell lymphoma are also managed according to the DLBCL guidelines.

Recent studies with gene expression microarray analysis of DLBCL have revealed significant heterogeneity within this diagnosis.\textsuperscript{27}
However, incorporation of this information into treatment algorithms awaits further investigation. Immunohistochemical markers CD10, BCL6, and IRF4/MUM1 have been reported to recapitulate the gene expression profiling separating patients into tumors derived from germinal center (GC) origin (CD10+, or BCL6+, IRF4/MUM1-) and non-GC origin (CD10-, IRF4/MUM1+ or BCL6-, IRF4/MUM1-). However, the validity of this classification scheme has been brought into question. An improved IHC algorithm has been proposed which includes GCET1, FOXP1, BCL6, IRF4/MUM1, and CD10. Further work needs to be done to validate the robustness of this new IHC algorithm to distinguish between GC vs. non-GC.

The typical immunophenotype is CD20+, CD45+, and CD3-. The recommended immunophenotyping panel includes CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, and IRF4/MUM1. When available, GCET1 and FOXP1 can provide information necessary for the Choi IHC cell of origin algorithm. Additional markers such as CD138, cyclin D1, ALK1, EBV and HTLV may be useful under certain circumstances to establish the subtype.

Workup

The staging workup is designed to identify all sites of known disease and determine prognosis with known clinical risk factors. Risk factors used by the IPI include age, stage of disease, serum lactate dehydrogenase (LDH) level, performance status, and the number of extra-nodal sites of disease. In patients who are 60 years or younger, the prognostic factors include tumor stage, performance status, and serum LDH level. The International Prognostic Index (IPI) and age-adjusted IPI can be used to identify specific group of patients who are more or less likely to be cured with standard therapy.

PET or PET-CT scans, have a more clear-cut role in selected cases of DLBCL than in other lymphoid neoplasms. PET scans are particularly informative in the initial staging where upstaging resulting in altered therapy occurs about 9% of the time and for response evaluation after treatment because they can distinguish residual fibrotic masses from masses containing viable tumor. PET scans have now been incorporated into the response criteria and availability of a baseline study is necessary for optimal interpretation of the post-treatment study. In some centers, beta-2-microglobulin is considered a major determinant of risk (category 2B). Lumbar puncture is indicated in patients with one or more of the following sites of involvement: paranasal sinus, testicular, epidural, HIV-associated lymphoma, bone marrow (with large cells) or the presence of 2 or more extranodal sites. Diagnostic yield is improved if flow cytometric analysis of CSF is undertaken.

Treatment Options by Clinical Stage

Treatment options for DLBCL differ between patients with localized (Ann Arbor stage I-II) and advanced (Ann Arbor stage III-IV) disease. Prognosis is extremely good for patients with no adverse risk factors (elevated LDH, stage II bulky disease, older than 60 years or ECOG performance status of 2 or more). Patients with advanced disease should be enrolled in clinical trials, whenever possible.

Stage I-II

In the SWOG 8736 study, 3 cycles of CHOP followed by IFRT produced significantly better PFS (5-year estimated PFS: 77% vs. 64% for CHOP alone) and OS (82% vs. 72% for CHOP alone) than 8 cycles of CHOP alone in patients with localized aggressive NHL; however, this difference disappeared with further follow-up. The benefit of CHOP (3 cycles) followed by IFRT (5-year OS of 95%) in patients with limited-stage DLBCL (60 years or younger with no adverse risk factors).
was also confirmed in a series from British Columbia Cancer Agency. Another randomized trial (ECOG study 1484) showed that the addition of RT to CHOP (8 cycles) prolonged disease-free survival (DFS) in patients with limited stage DLBCL who had achieved CR to CHOP alone (6-year DFS was 73% for IFRT and 56% for observation). In the GELA study (LNH 93-4), the addition of RT to 4 cycles of CHOP did not provide any advantage over 4 cycles of CHOP alone for the treatment of elderly patients low-risk localized aggressive lymphoma. The estimated 5-year EFS was not different between the two groups (61% and 64% respectively) and the 5-year estimated OS rate was 68% and 72% respectively. However, in this study, administration of RT was markedly delayed and 12% of patients on the RT arm did not receive RT.

The efficacy of the addition of rituximab to CHOP (3 cycles) and IFRT has also been reported in patients with limited stage DLBCL. In the SWOG 0014 study, with the median follow-up of 5 years, the 2- and 4-year PFS were 93% and 88% respectively for patients with at least one stage-modified. The corresponding OS rates were 95% and 92% respectively. In historical comparison, these results were better than the survival rates for patients treated without rituximab (4-year PFS and OS were 78% and 88% respectively). In the GELA study (LNH 93-1), intensified chemotherapy [ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) followed by consolidation with methotrexate, etoposide, ifosfamide and cytarabine] with or without rituximab was found to be superior to CHOP with or without rituximab (3 cycles) plus RT in patients with low-risk early-stage disease. However, this regimen is also associated with significant toxicity and includes vindesine which is not available in the United States.

**NCCN Recommendations**

R-CHOP (3 cycles) with IFRT or R-CHOP (6 cycles) with or without IFRT is recommended for patients with non-bulky disease (less than 10 cm). IFRT is recommended for patients who are not candidates for chemotherapy. Addition of RT to a full course of 6 cycles of R-CHOP for patients with no adverse factors is included with a category 2B recommendation. Patients with bulky disease (10 cm or greater) may be more effectively treated with 6 cycles of R-CHOP with or without locoregional RT (category 1).

**Stage III-IV**

R-CHOP-21 chemotherapy has been the standard treatment for patients with advanced stage DLBCL based on the results of the GELA study (LNH98-5) that demonstrated the addition of rituximab to CHOP-21 improved PFS and OS in elderly patients with advanced DLBCL. In this study, 399 elderly patients (60-80 years) were randomized to receive 8 cycles of R-CHOP or CHOP. Long-term follow-up of this study showed that PFS (36.5% vs. 20%), DFS (64% vs. 43%), and OS (43.5% vs. 28%) rates were statistically significant in favor of R-CHOP at a median follow-up of 10 years. These findings have been confirmed in three additional randomized trials including the MabThera International Trial (MInT; 6 cycles of R-CHOP or CHOP) which extended the findings to young patients with 0 or 1 risk factors according to the IPI, the Dutch HOVON and Nordic Lymphoma group study (8 cycles of R-CHOP or CHOP-14) and the ECOG/CALGB study confirmed the findings in patients older than 60. The ECOG/CALGB study also showed that maintenance rituximab significantly prolonged FFS in elderly patients responding to CHOP chemotherapy, but it did not offer any clinical benefit for patients responding to R-CHOP as induction therapy.
Six cycles of dose dense CHOP (CHOP-14) as first-line therapy was found to be superior to 6 cycles of CHOP-21.\textsuperscript{317-319} In the RICOVER 60 trial, the addition of rituximab to CHOP-14 (R-CHOP-14) improved clinical outcomes in elderly patients compared to CHOP-14 alone.\textsuperscript{320} In this study, OS significantly favored 6 cycles of R-CHOP-14 over 8 cycles (78% and 72.5% respectively) because of late, non-cancer related deaths. In patients with a PR after four cycles of chemotherapy, eight cycles were not better than six cycles. Ongoing randomized studies are evaluating the role of R-CHOP-14 versus R-CHOP-21.\textsuperscript{321, 322}

Dose-adjusted EPOCH plus rituximab has shown significant activity in untreated patients with DLBCL.\textsuperscript{323, 324} An ongoing phase III randomized study is evaluating dose-adjusted R-EPOCH vs. R-CHOP in untreated patients with DLBCL.

**NCCN Recommendations**

Patients with advanced disease are treated with 6 cycles of R-CHOP (category 1). In selected cases, RT to bulky sites may be beneficial (category 2B). Involvement of paranasal sinus, testis, bone marrow, two or more extranodal sites are associated with higher risk of CNS relapse.\textsuperscript{325-328} CNS prophylaxis with 4-8 doses of intrathecal methotrexate and/or cytarabine should be given during the course of treatment though the value of prophylactic therapy has been raised.

R-CHOP with rituximab is preferable due to reduced toxicities; however, other comparable anthracycline-based regimens are acceptable. Suggested alternate options include dose dense R-CHOP-14 or dose adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab. Both of which are listed as category 2B recommendations. The guidelines have included the following regimens as first-line therapy for patients with poor left ventricular function (category 2B):

- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) + rituximab
- CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) + rituximab
- CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisone) + rituximab
- Dose adjusted EPOCH + rituximab
- CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) + rituximab

Participation in clinical trials of new regimens is recommended if available. In patients with bulky disease or impaired renal function, initial therapy should include monitoring and prophylaxis for tumor lysis syndrome.

**Response Assessment and Follow-up Therapy**

This interim restaging is performed to identify patients whose disease has not responded or has progressed despite induction therapy. PET scans may be particularly useful in determining whether residual masses represent fibrosis or viable tumor. A negative PET scan after 2-4 cycles of chemotherapy has been associated with an excellent outcome.\textsuperscript{338} The 5-year EFS rates are significantly higher for PET-negative patients (80%) compared to 36% for PET-positive patients following induction therapy with CHOP or without rituximab.\textsuperscript{339} However, interim PET scan can produce false positive results and some patients treated with chemoimmunotherapy have a favorable long-term outcome despite a positive interim PET scan. A prospective study from MSKCC evaluated the significance of interim PET scans by obtaining biopsies from in patients with an interim
positive PET. Only 5 of 37 interim positive PET scans had a biopsy demonstrating persistent disease; PFS of interim PET-positive, biopsy-negative patients was identical to that in patients with a negative interim PET scan.\textsuperscript{340} Therefore, interim PET scan is not recommended outside the setting of a clinical trial. If it is used, a repeat biopsy of residual masses is necessary before changing the treatment course. Patients who are receiving induction therapy should undergo evaluation prior to receiving RT, including all positive studies, after 3-4 cycles of chemotherapy. End of treatment restaging is performed upon completion of treatment. The optimal time to end of treatment restaging is not known. However, the panel recommends that it is beneficial to wait for 6-8 weeks after completion of therapy before repeating PET scans.

**Interim and End of Treatment Response Evaluation for Stage I-II**

When the plan involves RT after short course therapy, restaging should be undertaken prior to RT including repeat PET scan as the dose of RT will be influenced by the result (see Principles of RT section in the Guidelines). For full course therapy, if interim restaging demonstrates response, the planned course of treatment is completed.

If the interim restaging demonstrates a PR, treatment with a higher dose of RT (see Principles of RT section in the Guidelines) is appropriate. Alternatively, a repeat biopsy can be obtained and if positive the patient can proceed to second-line therapy followed by HDT/ASCR. It is appropriate to enroll patients with an interim PR on a clinical trial. The choice between these two options is often made on clinical grounds. RT is appropriate for patients not eligible for HDT/ASCR. Higher dose RT is also a reasonable choice if there is a very good PR. Patients with refractory or primarily progressive disease are managed as refractory or relapsed disease.

End of treatment restaging is performed upon completion of treatment. After end of treatment restaging, follow-up at regular intervals is recommended for patients with CR. Patients with PR and those with no response to treatment or progressive disease are treated as described for relapsed or refractory disease.

Patients are then followed up at regular intervals (every 3-6 months for 5 years and then annually or as clinically indicated). Repeat imaging is performed as clinically indicated.

**Interim and End of Treatment Response Evaluation for Stage III-IV**

After interim staging, the planned course of treatment (R-CHOP to a total of 6 cycles) is completed for patients with CR and PR. End of treatment restaging is performed upon completion of treatment. Observation is preferred for patients with CR. RT to initially bulky disease or first-line consolidation with HDT/ASCR can be considered (category 2B). Patients with PR and those with no response to treatment or progressive disease are treated as described below for relapsed or refractory disease.

**Relapsed or refractory Disease**

The role of HDT/ASCR in patients with relapsed or refractory disease was demonstrated in an international randomized phase III trial (PARMA study).\textsuperscript{341} In this study, 109 patients with relapsed or refractory DLBCL responding to first-line chemotherapy were randomized to either chemotherapy plus RT (54 patients) or RT plus HDT/ASCR. At 5 years, the EFS and OS rates for the transplant group were 46% and 53% respectively compared to 12% and 32% for the non transplant group.

The efficacy of second-line therapy is predicted by the second-line age-adjusted IPI. Furthermore, pre-transplantation PET scans have
been identified as predictive factors following HDT/ASCR. PET positivity before transplant and chemoresistance are also associated with a poor outcome. The results of the studies from the GEL-TAMO group and ABMTR showed that HDT/ASCR should be considered for patients who never achieve a complete remission but are still chemotherapy-sensitive.

Several chemotherapy regimens have been used as second-line therapy prior to HDT/ASCR. However, none of these have emerged as a preferred regimen. Rituximab as a single agent was modestly active in patients with relapsed or refractory DLBCL and is reserved for the frail elderly patient. In a phase II study, rituximab in combination with ifosfamide, carboplatin and etoposide (ICE) produced a CR rate of 53% in patients with relapsed or refractory DLBCL, which is significantly better, in historical comparison with the response rates observed for such patients treated with ICE alone (27%). In an outpatient setting, rituximab with ICE produced an ORR of 71% (25% CR and 46% PR) and an estimated one-year EFS rate of 60% in patients with refractory B-cell lymphoma. Rituximab with other regimens has also been effective in patients with relapsed or refractory DLBCL.

Lenalidomide is active in heavily pre-treated patients with relapsed or refractory DLBCL. In subset analysis of the NHL-003 study which evaluated lenalidomide in patients with relapsed or refractory aggressive NHL, among 103 patients with DLBCL, ORR was seen in 30% of patients (7% CR and 23% PR). Recent data has suggested that the activity of lenalidomide in DLBCL is restricted to activated B-cell phenotype DLBCL.

**NCCN Recommendations**

HDT/ASCR is the treatment of choice for patients with relapsed or refractory disease. Patients with relapsed or refractory disease who are candidates for HDT/ASCR should be treated with second-line chemotherapy with or without rituximab. Suggested regimens (with or without rituximab) include the following:

- DHAP (dexamethasone, cisplatin, cytarabine)
- ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin)
- GDP (gemcitabine, dexamethasone, cisplatin)
- GemOX (gemcitabine and oxaliplatin)
- ICE (ifosfamide, carboplatin and etoposide)
- MINE (mitoxantrone, ifosfamide, mesna, etoposide)

Patients with CR or PR to second-line chemotherapy regimen should be considered for further consolidation with HDT/ASCR (category 1) with or without RT. IFRT before HDT/ASCR has been shown to result in good local control and improved outcome. Additional RT can be given before or after stem cell rescue to sites with prior positive disease. Pertinent clinical trials including the option of allogeneic stem cell rescue is another option.

Patients who are not eligible for HDT/ASCR should be treated in the context of a clinical trial. Alternatively, they can also be treated with
single agent rituximab or lenalidomide (in patients with non-germinal center DLBCL) or multiagent chemotherapy regimens (with or without rituximab) such as dose-adjusted EPOCH, CEPP (cyclophosphamide, etoposide, prednisone and procarbazine), GDP (gemcitabine, dexamethasone and cisplatin) or GemOx (gemcitabine and oxaliplatin).

Patients with disease relapse following HDT/ ASCR should be treated in the context of a clinical trial or individually. However, those with progressive disease after three successive regimens are unlikely to derive additional benefit from currently available chemotherapy regimens, except for patients with a long disease-free interval.

Primary Mediastinal Large B-cell Lymphoma (PMBL)

PMBL is a distinct subtype of NHL that histologically can be indistinguishable from DLBCL. It tends to occur in young adults with a median age of 35 years with a female predominance. PMBL arises from thymic B-cells with initial local regional spread to supraclavicular, cervical, hilar nodes and into the mediastinum and lung. Wide spread metastatic disease is uncommon at initial diagnosis, but this can be more common at recurrence. Clinical symptoms related to rapid growth of mediastinal mass include superior vena cava (SVC) syndrome, pericardial and pleural effusions.

Gene expression profiling has indicated that PMBL is distinct from DLBCL; the pattern of gene expression in PMBL is more similar to classical Hodgkin Lymphoma. PMBL expresses B-cell antigens and lacks surface immunoglobulins. PMBL is CD19+, CD20+, CD22+, CD21-, IRF4/MUM1+ and CD23+ with a variable expression of BCL2 and BCL6. CD30 is weakly and heterogeneously expressed in more than 80% of cases and CD15 is occasionally present. CD10 positivity is seen in 8-32% cases. PMBL is also characterized by a low expression of HLA I or II molecules. There have been rare cases of mediastinal gray zone lymphomas with combined features of PMBL and CHL. Cytogenetic and oncogene abnormalities that are common in PMBL, include gains in chromosome 9p24 (involving the JAK2 in 50–75% of patients) and chromosome 2p15 (involving the c-REL, encoding a member of the NF-κB family of transcription factors) and loss in chromosomes 1p, 3p, 13q, 15q, and 17p. IPI is of limited value in determining the prognosis of PMBL at diagnosis. In a retrospective analysis of 141 patients from MSKCC, two or more extranodal sites and initial therapy received were predictors of outcome for EFS whereas only initial therapy received was a predictor for OS. In retrospective analyses, intensive chemotherapy regimens have been more effective than CHOP and the addition of IFRT improved outcomes. The role of RT has to be confirmed in randomized trials. In a retrospective study, the addition of rituximab to MACOP-B or VACOP-B did not appear to result in significant differences in clinical outcomes. This would need to be confirmed in larger studies especially in light of two different studies have reporting that the addition of rituximab to CHOP plus RT or dose-adjusted EPOCH without RT improved response rates and EFS rates. Sequential dose dense R-CHOP followed by ICE consolidation (without RT) was also highly effective in patients with PMBL. At a median followup for surviving patients at 3 years, the OS and PFS rates were 88% and 78% respectively.

However, in the absence of randomized trials, there is no established optimal treatment for patients with PMBL. R-CHOP-21 is widely used in NCCN centers based on data in DLBCL. PET-CT is essential post-treatment. If PET-CT is negative at the end of treatment, patients may be observed. Residual mediastinal masses are common. If
PET-CT is positive, biopsy is recommended if additional treatment is contemplated.

**Burkitt Lymphoma**

BL is a rare and aggressive B-cell tumor typically involving extranodal disease sites. In the WHO Classification, three clinical variants of BL are described: endemic, sporadic, and immunodeficiency associated BL. The endemic variant is the most common form of BL that occurs in African children and nearly all cases are associated with EBV infection. Sporadic BL accounts for 1-2% of all adult lymphomas in the US and Western Europe. Immunodeficiency associated BL occurs mainly in patients infected with HIV, in some posttransplant patients and in individuals with congenital immunodeficiency.

**Diagnosis**

The typical immunophenotype of BL is sIg+, CD10+, CD19+, CD 20+, CD22+, TdT-, Ki67+ (100%), BCL2-, BCL6+. Most cases (80%) of classical BL are characterized by t(8;14) which results in the juxtaposition of MYC gene from chromosome 8 with the IgH region on chromosome14. Other variants [t(8;22) or t(2;8)] are less common. Some cases of DLBCL are also associated with an overexpression of MYC. Therefore, making the diagnosis of BL can be challenging using routine cytogenetic analysis. FISH using a break apart probe or long segment PCR are more reliable for the detection of t(8;14) and its variants. Recent studies by Dave et al and Hummel et al have reported gene expression profiling as an accurate, quantitative method for distinguishing BL from DLBCL. However, this technique is not yet recommended for widespread clinical use.

The 2008 WHO lymphoma classification eliminates atypical BL. For cases without typical morphology or immunophenotype, a provisional category has been introduced, B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL. This group also includes cases which harbor both MYC and BCL2 translocations, the so-called “double-hit” lymphomas.

**Workup**

The initial diagnostic workup for BL includes a detailed physical exam (with special attention to the node bearing areas, liver and spleen) and CT scans of the chest, abdomen and pelvis. PET or integrated PET-CT scans are not recommended for routine use, since it is unlikely that findings of PET or PET-CT would alter therapy for patients with newly diagnosed BL. If the treatment includes an anthracycline containing regimen, cardiac evaluation with MUGA scan or echocardiogram is recommended. Bone marrow aspiration, biopsy, lumbar puncture and flow cytometry of cerebrospinal fluid are essential. In these highly aggressive lymphomas, as in DLBCLs, the serum LDH level has prognostic significance. These tumors exhibit a high degree of cellular proliferation, as determined by Ki-67 staging, and frequent 8q translocations. Because BL is frequently associated with HIV infection, HIV serology should be part of the diagnostic workup for these diseases.

**Treatment Options**

BL is curable in a significant subset of patients when treated with dose intensive, multiagent chemotherapy regimens including CNS prophylaxis. About 60-90% of pediatric and young adult patients with BL achieve durable remission if treated appropriately. However, the outcome of older adults with BL appears to be less favorable but patients over 40 are significantly underrepresented in the published clinical trials. It is preferred that patients with BL should receive treatment at centers with expertise in the management of the disease.
Most of the regimens used in adult patients have been developed from the pediatric protocols. TLS is more common in patients with BL and should be managed as outlined under “Tumor Lysis Syndrome” in the Supportive Care section of the manuscript.

CODOX-M (cyclophosphamide, vincristine, doxorubicin, high dose methotrexate), alternating with IVAC (ifosfamide, etoposide and high dose cytarabine) is a highly effective regimen developed by Magrath et al.\textsuperscript{390} Both cycles included intrathecal chemotherapy (cytarabine or methotrexate). In 1998, Adde et al reported the updated results obtained with 4 cycles of CODOX-M/IVAC protocol given to 66 previously untreated patients [55 had BL or Burkitt like lymphoma (BLL) and 11 had DLBCL].\textsuperscript{391} The one year EFS rate was 85% and the median follow up was 48 months.

In an international phase II study, Mead et al established the value of a modified CODOX-M/IVAC regimen in adults with BL.\textsuperscript{392} Low risk patients received modified CODOX-M (3 cycles) and high risk patients received modified CODOX-M and IVAC (4 cycles). In low risk patients, 2-year EFS and OS were 83% and 81% respectively compared to 60% and 70% for high risk patients. Modified CODOX-M regimen was also effective and well tolerated in elderly patients with BL or BLL.\textsuperscript{393}

HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) alternating with methotrexate and cytarabine, including intrathecal methotrexate) regimen, developed by was evaluated in a trial of 26 patients with Burkitt like ALL.\textsuperscript{394} The CR rate was 81% and the 3 year OS rate was 49%. The OS was higher in patients younger than 60 years (77% compared to 17% in patients older than 60 years).

The CALGB 9251 study evaluated the efficacy of intensive chemotherapy with and without cranial radiation for central nervous system (CNS) prophylaxis in adult patients with Burkitt leukemia or lymphoma.\textsuperscript{395} Given the severe neurotoxicity, the protocol was amended after the first 52 of 92 patients were enrolled. The 3-year EFS rate was 52% in the cohort of patients who received intensive CNS prophylaxis (cranial RT and 12 doses of triple intrathecal chemotherapy) compared to 45% in those who received only 6 doses chemotherapy and cranial irradiation.

The HOVON group demonstrated the feasibility and efficacy of intensive high dose induction chemotherapy (prednisone, cyclophosphamide, doxorubicin, etoposide and mitoxantrone, without high dose methotrexate or high dose cytarabine) followed by consolidation with BEAM and ASCT in untreated adults with BL or BLL.\textsuperscript{396} In this study, the 5 year OS and EFS rates were 81 and 73% respectively for BL/BLL patients. In a small series of patients with BL or BLL, the high-dose CHOP with mid-cycle methotrexate regimen produced response rates and EFS rates comparable to other regimens, with an acceptable toxicity profile.\textsuperscript{397}

Given that Burkitt lymphoma is CD20+, the addition of rituximab to chemotherapy has also been investigated. Thomas et al evaluated the addition of rituximab to hyperCVAD regimen in a phase II trial involving 31 patients with newly diagnosed BL or B-ALL. The initial report showed encouraging results, with a CR rate 86%. The 3-year EFS and disease free survival rates were 80%, and 88%, respectively. The 3-year OS rates (89% vs. 88%) were similar in elderly and younger patients.\textsuperscript{398} In the updated report, with a median follow up of 46 months, 4 year OS rates (75% vs. 50%), OS rates in patients younger than 60 (76% vs. 70% ) and in patients 60 years or older (72% vs. 19%) were superior for hyperCVAD with rituximab, in historical comparison with patients treated with hyperCVAD alone.\textsuperscript{399} The results of this study showed that the addition of rituximab to
hyperCVAD improves long term outcome particularly in elderly patients.

Hoelzer et al recently reported the results of a large prospective study, which demonstrated a substantial improvement in the OS in younger as well as older patient with BL treated with rituximab in combination with intensive chemotherapy regimen developed by GMALL. The 3-year OS rate was 91%.

In a recent prospective study, dose adjusted EPOCH with rituximab was highly effective in patients with BL in both HIV positive and HIV negative patients, with no CNS involvement at diagnosis. OS and PFS were 100% and 95% respectively with a median follow up of 27 months.

The management of patients with B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL, as well as those patients with “double-hit” lymphoma has not been well studied. Outcomes with R-CHOP chemotherapy are poor. In a recent report, Mead et al evaluated CODOX-M regimen (with or without IVAC based on the risk status) in patients with high grade B-cell lymphomas. Patients with BL had superior outcomes to those without BL, which was characterized by a germinal center phenotype, absence of BCL2 expression, abnormal TP53 expression, presence of MYC rearrangement, and the absence of t(14;18) or 3q27 rearrangements.

NCCN Recommendations
Participation in clinical is recommended for all patients. The NCCN guidelines recommend the following regimens including intrathecal methotrexate for both high and low risk (normal LDH, completely resected abdominal lesion or single extra-abdominal mass less than 10 cm) patients:

- CALGB 9251 regimen
- CODOX-M (original or modified) with or without rituximab
- Dose adjusted EPOCH
- HyperCVAD with rituximab

Patients with CR to initial therapy should be followed up every 2-3 months for 1 year then every 3 months for 1 year and every 6 months thereafter. Consolidation in clinical trial is recommended for high-risk patients with CR to induction therapy. Disease relapse after 2 years is rare following CR to induction therapy, and follow up should be individualized according to patient’s characteristics. Patients with less than CR to initial therapy and those with relapsed or refractory disease should be treated in the context of a clinical trial. Second-line chemotherapy with rituximab followed by HDT/ASCR can be considered in selected patients with disease relapse after reasonable remission durations.

Lymphoblastic Lymphoma
Lymphoblastic lymphoma (LBL) is a rare disease that represents only 2% of all the NHLs in adults. The vast majority (80-90%) of LBL is a T-cell malignancy that occurs most often in young men. T-LBL is a clinically aggressive disease with frequent involvement of extranodal sites, particularly the bone marrow and central nervous system (CNS).

Diagnosis
Immunophenotyping studies are essential to distinguish between the precursor T and B cell LBL. Typical immunophenotypes of lymphoblastic lymphoma include dim expression of slg, CD10+, CD19+, CD20 /+, TdT+ for precursor B cell lymphomas; Precursor T cell lymphomas are characterized by dim expression of slg, CD10, CD1a+/ , CD2+, CD3 /+, CD4/8+/+, CD7+, CD19/20 , TdT+. 
Workup

The initial diagnostic workup for LBL includes a detailed physical exam (with special attention to the node bearing areas, liver and spleen) and CT scans of the chest, abdomen and pelvis. Bone marrow aspiration, biopsy, flow cytometry of cerebrospinal fluid and lumbar puncture are essential. If the treatment includes an anthracycline containing regimen, pre-treatment cardiac evaluation with MUGA scan or echocardiogram is recommended. If significant cardiac dysfunction is identified cardiac consultation is necessary prior to the use of anthracyclines or anthracyclines.

Treatment Options

The prognosis of adult LBLs treated with regimens used for other subtypes of aggressive NHLs has generally been poor. LBL has generally been treated with regimens appropriate for acute lymphoblastic leukemia (ALL). TLS is more common in patients with LBL and should be managed as outlined under “Tumor Lysis Syndrome” in the Supportive Care section of the manuscript.

The 5 drug intensive chemotherapy (dose intensive cyclophosphamide and anthracycline, standard dose vincristine and asparaginase, and intrathecal methotrexate) used in the CALGB study 8811 for adult patients with ALL produced a CR rate of 85%. The response rate was 94% in patients less than 30 years old. The estimated 3-year OS rate was 69% for patients less than 30 years old, 39% for those between 30 to 59 years and 17% in patients older than 60 years.

In a study conducted by M.D. Anderson Cancer Center, hyperCVAD regimen produced 91% CR in patients with lymphoblastic lymphoma. The 3-year PFS (66%) and OS (70%) compared favorably with the previously published results for ALL regimens. In this trial, RT was recommended for all patients with mediastinal disease to reduce the risk of mediastinal recurrence. After the completion of induction therapy, patients received maintenance with POMP regimen (mercaptopurine, methotrexate, vincristine, and prednisone).

HDT/ASCR has also been investigated to consolidate complete remission following induction therapy. In adults with LBL in first remission, there was a trend toward improved RFS with use of ASCT but there was no improvement in OS compared with conventional dose therapy. In another report from IBMTR, allogeneic HSCT recipients had significantly lower relapse rates at 1 and 5 years compared to ASCT (32% versus 46% respectively) with no significant difference in 5 year lymphoma free survival rates between the two groups (36% versus 39% respectively), but it was also associated with higher toxicity and treatment related mortality. In a more recent report, German study group reported that adult patients with relapsed ALL who proceed directly to allogeneic HSCT have better outcomes compared to those who receive re induction chemotherapy prior to transplantation.
**NCCN Recommendations**

Patients with stage I-IV disease can be treated with any one of the regimens (BFM regimen, CALGB ALL regimen, LMB 86 regimen or hyperCVAD followed by POMP maintenance) or they can be treated in clinical trials. Patients with CR to induction therapy can be observed or they can be treated in clinical trials. Poor risk patients can be considered for HDT/ASCR or allogeneic HSCT. Patients with biopsy-proven PR are considered treatment failure and should be treated in clinical trials. Allogeneic HSCT can be considered. Maintenance chemotherapy (up to 2 years) based on the treatment protocol is recommended.

The NCCN guidelines recommend reinduction with combination chemotherapy or allogeneic HSCT for patients with relapsed disease. Enrollment in clinical trials is encouraged to refine these approaches and the most appropriate therapy should be chosen in consultation with an expert in lymphoma.

**AIDS-related B-Cell Lymphoma**

**Overview**

AIDS-related lymphoma (ARL) is usually an AIDS-defining diagnosis in patients infected by the human immunodeficiency virus (HIV). Prior to the development of highly active antiretroviral therapy (HAART), ARL often presented with widespread, extra nodal disease, B symptoms, CNS involvement, and poor prognosis. However, in the HAART era the incidence of HIV-associated lymphoma has fallen. With the use of combination antiretroviral therapy, the survival of patients diagnosed with HIV-related systemic NHL has improved, with two thirds of patients surviving for longer than 1 year after diagnosis. BL and DLBCL are the most common forms of ARLs. The patients who develop BL generally have higher CD4 counts though a small fraction may present with CD4 counts less than 100. Primary CNS lymphoma (PCNSL) develops in patients with very low CD4 counts and is most often seen in uncontrolled AIDS, the incidence of this presentation has fallen dramatically in the HAART era. DLBCL occurs in the patients between these extremes.

Plasmablastic lymphoma (PBL) and primary effusion lymphoma (PEL) are two forms of lymphoma seen more commonly associated with HIV compared to lymphoma in patients without HIV. PEL accounts for less than 5% of the ARL cases most often occurring in the pleural, pericardial, and abdominal cavities. PELs are associated with human herpes virus 8 (HHV8) infection and many are also coinfected with Epstein Barr virus (EBV). PBL is another unique large B cell lymphoma that mainly involves the jaw and oral cavity of the HIV infected patients. Multicentric Castleman’s disease (MCD) is prevalent in HIV infected individuals and it has also been associated with HHV8 infection and increased incidence of lymphoma in HIV infected patients.

**Diagnosis**

The diagnostic evaluation of HIV-associated lymphoma is not different from the non HIV-associated disease. The major factor is to distinguish between BL and DLBCL. Hodgkin lymphoma and indolent lymphoma are seen in patients with HIV at an incidence higher than in the general population but they are much less common than BL or DLBCL.

**Workup**

The diagnostic evaluation is as outlined above for BL. However, all patients (without regard to histology) should have a lumbar puncture to rule out CNS involvement. In addition, baseline values for CD4 counts and viral load should be obtained.
Treatment

Optimal management of HIV-associated lymphoma is not established. However, several key factors have emerged as being important to improve outcome. In general, studies have demonstrated that early introduction of HAART therapy is associated with superior outcomes. This has allowed for the administration of more dose-intensive regimens and a reduction in treatment-associated toxicity. \(^{419, 420}\)

In the NHL HIV 93 trial of risk adapted intensive chemotherapy in ARL patients, Mounier et al reported that HIV score, IPI (international prognostic index) score, and HAART affect survival in patients with ARL but not the intensity of the chemotherapy. \(^{421}\) Combination chemotherapy regimens such as CHOP or CDE (cyclophosphamide, doxorubicin and etoposide) given with concomitant HAART, \(^{422-424}\) or EPOCH regimen without HAART, \(^{425}\) have proven to be effective and tolerable in patients with ARL.

In the HAART era, the median survival of patients with HIV-associated DLBCL is similar to that of patients with non-HIV-associated DLBCL. There has been conflicting data regarding the outcomes of patients with HIV-associated BL. One study demonstrated that there was a median survival of only 6 months. \(^{426}\) However, a retrospective analysis by Wang et al. reported that HIV-positive patients with BL treated with CODOX M/IVAC had outcomes similar to that observed in HIV-negative patients treated with the same regimen. \(^{427}\)

The safety and efficacy of rituximab in combination with chemotherapy has also been evaluated in clinical trials. In the randomized phase III trial conducted by the AIDS Malignancies Consortium (AMC010), the addition of rituximab to CHOP was associated with improved tumor responses; but this combination also increased the risk of neutropenia and infection, particularly in patients with CD4 counts of less than 50. \(^{428}\) In subsequent phase II trials, however, rituximab in combination with CHOP or infusional CDE regimens was feasible and highly effective with an acceptable toxicity level in patients with ARL. \(^{429-431}\) Long term follow up of patients with ARL treated with the combination of rituximab and CDE concomitantly with HAART produced CR rate of 70% and TTF at 5 years was 52%, which are comparable to those observed in non-HIV positive patients. \(^{432}\)

In a recent report, Dunleavy et al demonstrated that the addition of rituximab to EPOCH regimen is highly effective and tolerable in patients with ARL and enables the administration of fewer treatment cycles. \(^{433}\) In this study, the addition of rituximab did not appear to cause serious infection related complications or deaths. The AMC034 randomized trial evaluated the use of sequential vs. concurrent infusional EPOCH regimen in combination with rituximab. CR was observed in 73% and 55% of evaluable patients in the concurrent and sequential arms, respectively. \(^{434}\) Toxicity was comparable in the two arms, although patients with a baseline CD4 count of less than 50 had a high infectious death rate in the concurrent arm. The 2-year PFS rates in the concurrent and sequential arms were 64% and 60%, respectively. The authors concluded that concurrent rituximab plus infusional EPOCH is an effective regimen for HIV-associated lymphoma which merits further evaluation.

**NCCN Recommendations**

The NCCN guidelines recommend the use of HAART and growth factor support along with full dose chemotherapy. Any change in antiviral therapy should be done in consultation with an infectious disease specialist. Patients on antiretrovirals with persistently low CD4 count of less than 100 tend to have a poor prognosis and higher risk of infection associated with the addition of rituximab. The
omission of rituximab is strongly suggested for these patients due to the higher risk of infectious toxicities. Prophylaxis with intrathecal chemotherapy is used at some NCCN institutions for all patients, whereas at other NCCN institutions patients with AIDS related DLBCL with selected high-risk features (involvement of 2 or more extranodal sites, bone marrow involvement, or other high-risk site involvement such as epidural, testicular or paranasal sinuses).

Patients with AIDS related BL should be treated with chemotherapy (with or without rituximab) such as CODOX-M alternating with IVAC, dose adjusted EPOCH, CDE (cyclophosphamide, doxorubicin and etoposide) or CHOP chemotherapy with or without high dose methotrexate (not exceeding 3 g/m2). Patients with AIDS related DLBCL should be treated with dose adjusted EPOCH, CDE, CHOP or CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone). Patients with lymphoma associated with MCD and PEL can also be treated with the same regimens as described for patients with DLBCL. Since most cases of PEL are CD20 negative, the addition of rituximab is not indicated.

PBL was associated with a poor prognosis in the pre HAART era. In the HAART era, the prognosis is better with the use of intensive chemotherapy regimens along with HAART. The outcome of the HIV positive patients with PBL treated at the Memorial Sloan Kettering Cancer Center was superior to the majority of reports in the literature. Among six patients treated with anthracycline based multiagent chemotherapy with HAART, five were alive and diseases free, with a median follow-up of 22 months. The NCCN guidelines recommend CODOX M/IVAC, EPOCH or hyperCVAD regimens for patients with PBL.

PCNSL is associated with severe immunosuppression and poor prognosis. In a retrospective study, patients with PCNSL treated with HAART and RT had a more favorable outcome. High dose methotrexate, RT or antiretroviral therapy can be considered for patients with PCNSL. Selected patients with good performance status receiving HAART can be treated as per CNS lymphoma guidelines.

Cutaneous B-cell lymphomas

Cutaneous B-cell lymphomas (CBCLs) are a group of B-cell lymphomas originating in and usually confined to the skin. CBCLs are estimated to represent approximately 20-25% of all primary cutaneous lymphomas. In the United States, the SEER (Surveillance, Epidemiology, and End Results) data from the National Cancer Institute (NCI) indicated that the incidence of cutaneous T-cell lymphomas accounted for 71%, whereas CBCLs accounted for 29% from 2001-2005. The new WHO-EORTC classification for cutaneous lymphomas distinguishes 3 main types of CBCL.

- Primary cutaneous marginal zone B-cell lymphoma (PCMZL)
- Primary cutaneous follicle center lymphoma (PCFCL)
- Primary cutaneous diffuse large B-cell, leg type (PCDLBCL, leg type).

PCFCL is the most common type of CBCL whereas PCDLBCL leg type is rare. PCMZL and PCFCL are indolent or slow growing, whereas PCDLBCL, leg type is an aggressive lymphoma with a generally poorer prognosis. In an Italian series of 467 patients with CBCL, PCFCL and PCMZL accounted for 57% and 31% respectively. PCDLBCL leg type was reported only in 11% of patients. While the various types of CBCL can occur anywhere on the skin, PCFCL is more prevalent in the scalp and the forehead, whereas the trunk and extremities are the most common sites for PCMZL. Leg remains the most common, but not the
only, site for PCDLBCL. Extracutaneous involvement is more frequent with PCDLBCL, leg type. In the same large Italian series extracutaneous involvement eventually developed in 6% of patients with PCMZL, 11% with PCFCL, and 17% percent with PCDLBCL, leg type. In patients with PCMZL and PCFCL, the DFS and OS rates were higher for patients with single lesions than those with regional or disseminated lesions (5-year DFS, 62% vs. 44%; 5-year OS, 97% vs. 85%), whereas the difference between single and regional or disseminated cutaneous involvement in patients with PCDLBCL, leg type was only of borderline significance (5-year DFS rate was 55% vs. 44% and 5-year OS rate was 79% vs. 67% for single and regional or disseminated lesions respectively). In another series of 145 patients with CBCL, Grange et al also identified location on the leg and multiple skin lesions as independent poor prognostic factors for patients with CBCLs.

**Diagnosis**

Adequate biopsy of the lesions and the slides should be reviewed by a pathologist with expertise in the diagnosis of primary cutaneous B-cell lymphomas. Incisional, excisional or punch biopsy is preferred to shave biopsy as CBCL have primarily dermal infiltrates, often deep, which are less well sampled and can even be missed by a shave biopsy. Adequate immunophenotyping with a panel that evaluates B- and T-cell markers is recommended to establish the diagnosis of the exact subtype of CBCL. The panel should include CD20, CD79a, CD3, CD5, CD10, BCL2, BCL6, Ki-67, kappa/lambda and IRF4/MUM1. PCFCL is consistently BCL6-positive, whereas CD10 and BCL2 are expressed in only a few cases with a follicular growth pattern. PCMZLs are always negative for BCL6 and CD10, but are often BCL2-positive.

While the diagnosis of PCMZL is generally straightforward and reproducible among pathologists, it is more difficult to distinguish between PCFCL and PCDLBCL, leg type. Part of the difficulty is that cell size, large vs. small, is not a defining feature as it is in nodal B-cell lymphomas. Most of the patients with PCFCL have lesions with a germinal center phenotype, whereas most with PCDLBCL, leg type have an activated B cell phenotype. In nodal DLBCL, the germinal center phenotype is associated with a better prognosis than the activated B-cell phenotype. Both PCFCL and PCDLBCL are CD20 and BCL6 positive. BCL2 is usually negative in PCFCL but highly expressed in PCDLBCL, leg type. In addition, PCFCL is usually for MUM/IRF4-negative while PCDLBCL, leg type is usually IRF4/MUM1-positive and shows strong expression of FOXP1. IRF4/MUM1 and FOXP1 may serve as additional diagnostic markers in the differential diagnosis of PCFCL and PCDLBCL. Assessment of surface IgM and IgD expression may be helpful in distinguishing PCDLBCL, leg type from PCFCL.

The t(14;18) translocation only rarely occurs in PCBCLs. Therefore, the detection of a t(14;18) translocation in CBCL suggests the presence of systemic disease. Molecular genetic analysis to detect TCR gene rearrangements, PCR to detect IgH gene rearrangements and cytogenetics or FISH to detect t(14;18) may be useful in selected circumstances. In selected cases, the use of cyclin D1 may be useful to differentiate PCMZL (negative for CD5 and cyclin D1) from mantle cell lymphomas (positive for CD5 and cyclin D1). Mantle cell lymphoma is not a primary cutaneous lymphoma and finding it in the skin requires a careful search for extracutaneous disease.
Workup

The initial workup is geared toward evaluating extent of disease on the skin and seeking extracutaneous disease. The absence of extracutaneous disease at diagnosis is part of the definition of PCBCL. The initial work-up includes a complete physical examination, a comprehensive skin examination and CT scans of the chest, abdomen and pelvis. PET-CT may have higher sensitivity in finding otherwise occult systemic disease but this is not validated and the higher rates of false positive findings can create confusion. Bone marrow biopsy is essential for PCDLBCL, leg type whereas its role is unclear for PCFCL and PCMZL. Senff et al evaluated 275 patients with histological features consistent with MZL (n = 82) or FCL (n = 193) first presenting in the skin. Bone marrow involvement was seen in about 11% of patients in the FCL group compared to less than 1% in the MZL group. FCL patients with skin lesions and positive bone marrow had a significantly worse prognosis than those with PCFCL. The 5-year OS rate was 44% and 84% respectively.

The International Society of cutaneous lymphomas (ISCL) and the EORTC task force recommend that bone marrow biopsy is required for cutaneous lymphomas with intermediate to aggressive behaviors and it should be considered for cutaneous lymphomas with indolent behavior and when there is any evidence of extracutaneous disease, as indicated by other staging assessments (e.g., radiographic evidence or serologic clues such as elevated monoclonal or polyclonal immunoglobulins). The guidelines recommend considering bone marrow biopsy for patients with PCFCL. It is optional for patients with PCMZL. Peripheral blood flow cytometry will be useful in selected cases, if CBC demonstrates lymphocytosis.

Treatment

Primary CBCLs have a different clinical course and prognosis that distinguish them from their nodal counterparts. Treatment options for CBCLs depend on the histology and stage of the disease. Most commonly used therapies include excision, radiation therapy (RT), rituximab or systemic chemotherapy. In a large retrospective analysis by the Italian Study Group for Cutaneous Lymphomas involving 467 patients with PCBCL, the CR rate, 5-and 10-year OS rates for all patients with PCFCL and PCMZL who received treatment were 90%, 96% and 90%, respectively. The relapse rate was 44% and extracutaneous spread was observed in 6-11% of patients. Relapse rate did not vary by type of initial therapy.

In patients with PCDLBCL, leg type, the CR rate, 5-and 10-year OS rates were 82%, 73% and 47% respectively. PCDLBCL, leg type is also associated with higher relapse rates (55%) and higher incidences of extracutaneous spread (17%). Higher relapse rate was confirmed both for patients with single or regional lesions treated with RT and for patients with disseminated cutaneous involvement treated with chemotherapy as first-line treatment.

RT is very effective when used as initial local therapy as well as for cutaneous relapses in most patients with indolent CBCCLs. In patients with indolent histologies, RT and excision were associated with higher response rates compared to chemotherapy (96%, 97% and 79% respectively) but are generally used for those with more limited disease. However, the majority of patients with regional or disseminated disease will relapse after any type of treatment. Relapses are generally confined to the skin.
In a retrospective of 34 patients with CBCL treated with RT, 5-year RFS rate ranged from 62-73% for PCFCL and PCMZL but was only 33% PCDLBCL, leg type.\textsuperscript{446} Five-year OS was 100% for PCFCL and PCMZL but was 67% for PCDLBCL, leg type. Senff et al evaluated the outcome of 153 patients with CBCL (25 with PCMZL; 101 with PCFCL and 27 with PCDLBCL) that were initially treated with RT with a curative intent.\textsuperscript{445} Overall, 45% of patients had single lesions and localized or disseminated lesions were seen in 43% and 12% of patients respectively. Complete remission was reached in 151 of 153 patients (99%). Relapse rates for PCMZL, PCFCL, and PCLBCL, leg type were 60%, 29%, and 64%, and the 5-year disease-specific survival was 95%, 97%, and 59%, respectively. The PCFCLs presenting on the legs had a higher relapse rate (63%) and a lower 5-year disease-specific survival (44%) than PCFCLs at other sites (25% and 99%).\textsuperscript{445}

Thus, local therapy is suitable for patients with indolent histologies, whereas patients with PCDLBCL, leg type which has a more unfavorable clinical course are generally treated with more aggressive treatment modalities, often combined modality therapy.\textsuperscript{447}

**NCCN Recommendations**

Since there are no data from randomized clinical trials, the treatment recommendations included in the guidelines are derived from the management of patients with CBCL in NCCN member institutions based on the limited data from retrospective analyses and studies involving small cohort of patients.

**PCFCL and PCMZL**

*Initial Treatment*

The guidelines recommend local RT or excision as the initial treatment options for patients with solitary lesions or regional disease (T1-2).

Selected patients with local disease that is not amenable to local therapy (e.g., lesions on the scalp or forehead) can be observed.

For patients presenting with generalized skin lesions (T3), several treatment options are available. Chlorambucil has been shown to be effective in the treatment of PCMZL with multifocal skin lesions.\textsuperscript{59} In patients presenting PCFCL, multiagent chemotherapy or RT were equally effective for multifocal skin lesions.\textsuperscript{448-450} Rituximab has been effective as a first-line treatment option for patients with indolent CBCLs with multiple lesions for which local therapy is not effective.\textsuperscript{451-455} In a series of 16 patients with PCBCL, 14 patients (87.5%) achieved complete remission; 35% patients with complete remission relapsed between 6 and 37 months.\textsuperscript{455} In another retrospective analysis of 15 patients with indolent CBCLs, the overall objective response rate (ORR) was 87% (60% CR, 27% PR) with a median follow-up was 36 months.\textsuperscript{454} The ORR was 100% for patients with PCFCL and 60% for PCMZL. Median time to response, duration of response, and time to progression was 30 days, 24 months, and 24 months, respectively. There are case reports showing the efficacy of topical therapy with using steroids, imiquimod, and nitrogen mustard or bexarotene gel.\textsuperscript{448, 456-459}

For patients presenting with generalized disease, the guidelines have included observation, rituximab, topical therapy, local RT, intralesional steroids or systemic therapy (chlorambucil or CVP) with or without rituximab as options. In patients with very extensive or symptomatic disease, other chemotherapy regimens recommended for the treatment of follicular lymphoma may be used.

Patients presenting with extracutaneous disease should be managed according to the follicular lymphoma guidelines.
Treatment for relapsed or refractory disease
While most of the patients respond to initial therapy, relapses do commonly occur. Patients with regional or localized relapse should receive additional therapy (excision, intralesional steroids, local RT or topical therapy using steroids, imiquimod, nitrogen mustard or bexarotene gel) and those with generalized disease relapse confined to the skin should receive additional therapy with treatment options recommended for generalized disease at presentation.

Patients with a PR or persistent progressive disease following additional treatment should be treated with the other options included in the initial treatment to improve response before starting treatment for refractory disease. Patients with extracutaneous relapse or those with cutaneous relapse that are not responding to any of the initial treatment options should be managed according to the follicular lymphoma guidelines.

PCDLBCL, leg type
Initial Treatment
PCDLBCL, leg type has a poorer prognosis than other CBCL, particularly in patients with multiple tumors on the legs. RT alone is less often effective in patients with PCDLBCL. While these lesions do respond to radiation, remissions are often short lived and higher rates of dissemination to extracutaneous sites occur. In a retrospective multicenter study from the French Study Group on 60 patients with PCDLBCL, leg type, although no particular therapy (RT or multiagent chemotherapy with or without rituximab) was significantly associated with improved survival, patients treated with anthracycline-containing chemotherapy and rituximab had a more favorable short-term outcome. Among 12 patients treated with anthracycline-based chemotherapy with rituximab, the CR rate was 92% compared to 62% for patients who received other therapies. The 2-year survival rate between these two groups was 81% and 59% respectively.

For patients with localized disease, the guidelines recommend local RT alone or in combination with R-CHOP. RT alone can be used in elderly patients or patients who are not able to tolerate systemic therapy. In patients with generalized disease, R-CHOP with or without RT is recommended. Extracutaneous disease should be managed according to the DLBCL guidelines. The guidelines recommend enrollment in clinical trials for all patients with PCDLBCL, leg type.

Treatment for Relapsed or refractory disease
In patients with regional relapses, R-CHOP is recommended if they have not received prior chemotherapy. Patients who have received prior chemotherapy should be treated with local RT or second-line chemotherapy regimens recommended for relapsed or refractory DLBCL. Local RT or second-line chemotherapy regimens recommended for relapsed or refractory DLBCL are the options for patients with generalized relapse. In a pilot study of 10 patients, RIT with yttrium-90-ibritumomab tiuxetan was effective in patients with relapsed CBCLs. The guidelines have included RIT as one of the treatment options for patients with relapsed disease.

Peripheral T-Cell Lymphomas
Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of lymphoproliferative disorder arising from mature T-cells of post-thymic origin. The most common subtypes of are PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and anaplastic large cell lymphoma (ALCL).
PTCL-NOS is the most common subtype of PTCL. It most often involves nodal sites, however, many patients present with extranodal involvement including the liver, bone marrow, GI tract and skin. PTCL-NOS is associated with poor OS and EFS rates compared to B-cell lymphomas.\(^{462-464}\)

AITL usually presents with generalized lymphadenopathy, often with associated hepatomegaly or splenomegaly, hypergammaglobulinemia, eosinophilia, skin rash and fever. It occurs mainly in older patients. Prognosis is poor. In a single institution study which reviewed the data of 199 patients with PTCLs, the 5-year OS and PFS rate were 36% and 13% respectively for the subgroup of patients with AITL.\(^{464}\) In the most recent report from the GELA study, which included the largest series of patients with AILT (n=157), five and seven-year OS rates were 33% and 29% respectively, reaching an apparent plateau around 6 years.\(^{465}\) The corresponding EFS rates were 29% and 23% respectively.

ALCL is a CD30 expressing subtype of PTCL which accounts for less than 5% of all cases of NHL. There are now three distinctly recognized subtypes of ALCL: systemic ALK1 expressing ALCL, systemic ALK1 negative ALCL, and primary cutaneous ALCL. ALK1 positive ALCL is most common in children and young adults. It is characterized by the overexpression of anaplastic lymphoma kinase (ALK1) protein, which is the result of a chromosomal translocation [t(2;5)] in 40-60% of patients.\(^{39}\) Systemic ALK1 positive ALCL predominantly occurs at younger age and has a good prognosis compared to ALK1 negative ALCL, which occurs in older patients. The majority of patients with ALCL present with advanced stage III or IV disease (65% for ALK1 positive and 58% for ALK1 negative) frequently associated with systemic symptoms and extra nodal involvement.\(^{15}\) ALK-positive ALCL is associated with better clinical outcomes than ALK-negative ALCL, PTCL-NOS or AITL. Five-year OS rate following anthracycline-based therapy was 79% for ALK-positive ALCL compared to 46% for ALK-negative ALCL.\(^{40}\) Recent survival analysis from the International T-cell lymphoma project also reported similar outcomes.\(^{15,41}\) The differences in prognosis are most pronounced for younger patients with favorable prognostic factors. In this report, ALK-negative ALCL patients had a better outcome than those with PTCL-NOS. The 5-year FFS for ALK-negative ALCL and PTCL-NOS were 36% vs. 20% respectively and OS was 49% vs. 32%.\(^{41}\)

Primary cutaneous variant of ALCL is noted for the absence of ALK1 protein and indolent course characterized by frequent relapses, generally confined to the skin, and very good long-term survival despite cutaneous relapses. As a result combination chemotherapy is rarely indicated for these patients.

Enteropathy-associated T-cell lymphoma (EATL) is a rare T-cell lymphoma of the small intestine, accounting for less than 1% of all the NHLs and has a poor prognosis. The median age of diagnosis is 60 years. The typical immunophenotype of EATL is CD3+, CD5−, CD7+, CD8+/−, CD4− and CD103+. Anthracycline-based chemotherapy with CHOP or CHOP-like regimens are most commonly used for patients with EATL.\(^ {466-469}\) Recent studies have shown that HDT/ASCR improves outcomes in patients with EATL.\(^ {470,471}\)

### Staging and Prognosis

Staging is similar to that of the other aggressive lymphomas. Historically the IPI derived for DLBCLs has been used and shown to be prognostic for patients with PTCL. Recently, the Italian Intergroup for lymphoma proposed a new prognostic index for PTCL-NOS.\(^{462}\) Risk factors include age older than 60 years, elevated LDH levels, performance status of 2 or more, stage III or higher with bone marrow...
involvement. Five-year OS rate was only 32.9% for patients with two risk factors and 18.3% for those with three or four risk factors. This schema also identifies a relatively good prognosis subset of patients who have no adverse risk factors. This, so called, group 1 represented 20% of patients and had a 5-year OS of 62%. In the NCCN guidelines, patients with stage I-II disease are stratified into two groups (low intermediate risk and high intermediate risk) based on the age-adjusted prognostic index (aaPI).

In a retrospective GELA study, the prognoses of PTCL (including all subgroups) patients were compared with B-cell lymphoma patients with similar characteristics receiving similar aggressive combination chemotherapy and in some patients high dose therapy and stem cell transplantation. The CR rates were 63% and 54% for patients with B-cell lymphoma and PTCL respectively. Five-year OS rate was also slightly better for patients with B-cell lymphomas (53%) compared to 41% for patients with PTCL. The 5-year EFS rates were 45% and 32% for B-cell and PTCL patients respectively. The difference in 5-year OS rates were most pronounced in patients with 2 or 3 adverse risk factors as determined by IPI (36% and 23% respectively for PTCL; 53% and 35% respectively for B-cell lymphomas). Initial characteristics and prognostic features were analyzed in another retrospective study in 174 patients with PTCL. Most patients were treated with anthracycline-based regimens. The complete response rates (69% vs. 45%) and median survival (65 months vs. 20 months) were better for AILCL subgroup compared to other PTCL subtypes.

**Diagnosis**

Diagnosis of PTCL is similar to that described for other lymphomas, requiring adequate immunophenotyping to distinguish PTCL from B-cell neoplasms. The initial paraffin panel for immunohistochemical studies may only include Pan T-cell markers and can be expanded to include antibodies of T-cell lymphoma if suspected. Additionally, PTCL is often associated with clonal rearrangements of the receptor genes that are less frequently seen in non-cancer T-cell diseases. Molecular and cytogenetic analysis can further clarify the T-cell origin of the lymphoma.

PTCL-NOS has variable T-cell associated antigens and usually lacks B-cell associated antigens (although aberrant CD20 expression in T-cell lymphomas is infrequently encountered). With the exception of CD30 expression in ALCL, antigen expression is variable across the aggressive T-cell lymphomas. The majority of the nodal cases express CD4+ and lack CD8-, however CD4-/CD8+, CD4-/CD8-, and CD4+/CD8+ cases are seen. Systemic ALCL has a strong expression of CD30. Evaluation of ALK1 status, either based on immunophenotyping or genetic analysis of the t(2;5) or variant chromosomal rearrangements, is extremely important to identify the ALK1 positive tumors that have a better prognosis. AILT cells express T-cell associated antigens and are usually CD4+. Recently, expression of CXCL13 has been identified as a useful marker in distinguishing AILT from PTCL-NOS. It is also characterized by the presence of Epstein-Barr virus (EBV)-positive B-cells and cases of co-existent EBV+DLBCL are reported. EBER (EBV-encoded RNA) is positive in about 40% of PTCL and some case series have reported that EBER positive tumors have a worse prognosis.

**Workup**

The workup for PTCL is similar to the workup for other lymphoid neoplasms. The workup focuses on determining the stage of the disease, based on routine laboratory studies, physical exam, and imaging studies, as indicated. MUGA scan or echocardiogram is also
recommended, since chemotherapy is usually anthracycline based. In selected cases, HIV and HTLV-1 (human T-cell lymphoma virus) may be useful.

Treatment

Induction Therapy

PTCLs are less responsive to and have less frequent durable remissions with standard chemotherapy regimens such as CHOP and thus carry a poorer prognosis compared to diffuse large B-cell lymphomas. In prospective randomized studies, PTCLs have been included with aggressive B-cell lymphomas. However, it has not been possible to assess the impact of chemotherapy in this subgroup of patients with PTCL due to small sample size. There have been no randomized studies comparing the chemotherapy regimens exclusively in patients with PTCL.

CHOP chemotherapy is the most commonly used first-line regimen for patients with PTCL. However, with the exception of ALK+ ALCL, outcomes are disappointing. Chemotherapy regimens that are more intensive than CHOP did not show any significant improvement in OS in patients with PTCL, with the exception of ALCL. CHOP chemotherapy is frequently curative in only the small number of patients with favorable prognostic features. In the International PTCL clinical and pathologic review project, anthracycline-based chemotherapy was associated with poor outcome in all patients, except for those with one or no risk factors and the inclusion of an anthracycline did not appear to favorably impact survival in this retrospective study. In a retrospective study conducted by the British Columbia cancer agency, 5-year OS rates were higher (64%) in low risk IPI group compared to only 22% in high-risk IPI group, in patients with PTCL treated with CHOP or CHOP-like chemotherapy. ALK-positive ALC patients had superior outcome compared to ALK-negative ALC patients (5-year OS: 58% vs. 34% respectively). In an analysis of a large cohort of patients with PTCL treated in the German high-grade NHL study group, patients with ALK-positive ALC had excellent outcomes with CHOP or CHOP with etoposide (CHOEP). Three-year EFS and OS rates were 76% and 90% respectively for ALK-positive ALC, 50% and 67.5% respectively for AITL, 46% and 62% respectively for ALK-negative ALC and 41% and 54% respectively for PTCL-NOS. Among patients with ALK-negative ALC, AITL and PTCL-NOS, those with low IPI had a favorable prognosis.

CHOEP induced better response rates (CR: 88% vs. 79 %) and 5-year EFS rates (69 % vs. 58%) than CHOP in younger patients. Aggressive chemotherapy [CHOP followed by ICE or CHOP followed by IVE (ifosfamide, etoposide and epirubicin alternating with intermediate dose methotrexate)] and HDT/ASCR has also been evaluated as primary therapy. The poor results with conventional chemotherapy have led many to explore the role of HDT/ASCR as a first-line consolidation therapy. Several retrospective and prospective studies have demonstrated that HDT/ASCR as first-line consolidation improves treatment outcome in patients responding to induction therapy.

Nordic lymphoma group evaluated induction therapy with CHOEP followed by ASCR in patients responding to induction therapy. Of the 77 evaluable patients, 58 (75%) patients underwent ASCR. At one-year post-transplant follow-up, in the 39 patients for whom follow-up data were available, 30 were in complete remission. In the prospective study conducted by the GELTAMO Study group, 19 out of 26 patients showing CR or PR to induction therapy with MegaCHOP received ASCR. At 2-year post-transplant follow-up, OS, PFS and DFS rates were 84%, 56% and 63% respectively in patients who received ASCT.
consolidation (n = 19). In a phase II study conducted by Mercadal et al. newly diagnosed patients with PTCL responding to high-dose CHOP regimen alternating with etoposide, cisplatin, cytarabine and prednisone, were treated with ASCT. With a median follow-up of 3.2 years, the 4-year PFS and OS were 30% and 39% respectively.

Reimer et al recently reported the final analysis of the first prospective first prospective PTCL-restricted multicenter study on upfront HDT/ASCR in 83 patients. The treatment regimen consisted of four to six cycles of CHOP followed by mobilizing therapy with either the dexamethasone, carmustine, melphalan, etoposide, and cytarabine protocol or the etoposide, methylprednisolone, cytarabine, and cisplatin protocol and stem-cell collection. The ORR following CHOP chemotherapy was 79% (39% CR and 40% PR). Fifty-five (66%) of the 83 patients received transplantation. After HDT/SCT, 48 of the 55 patients achieved a CR, and 7 patients achieved a PR. In an intent-to-treat analysis, the ORR after myeloablative therapy was 66% (56% CR and 8% PR). The estimated 3-year OS, DFS and PFS rates for patients in CR were 48%, 53%, and 36%, respectively. The transplant related mortality rate was 3.66%. However, ALK-positive ALC patients were excluded in all of these studies.

The outcome of ALK-positive ALC patients undergoing ASCT compared to those with other histological subtype of PTCL was reported in only one prospective study by Corradini et al. The pooled results from two prospective studies (n = 62) showed that at a median follow-up of 76 months, the estimated 12-year OS, DFS and EFS rates were 34, 55 and 30%, respectively for the whole study cohort. Overall treatment-related mortality rate was 4.8%. The 10-year OS and EFS rates were significantly better in patients with ALK-positive ALC (63% and 54% respectively), as compared with the remaining PTCL (21% and 19% respectively). In the subgroup of patients with PTCL-NOS the corresponding survival rates were 37% and 25% respectively. In a multivariate analysis the achievement of CR before transplant was a strong predictor of survival benefit. The projected 10-year OS and EFS rates for patients in complete remission before transplant were 48% and 47% respectively, compared to 22% and 11% respectively for whose who were not in complete remission.

Longer follow-up and preferably a randomized trial, is necessary to evaluate the impact of first-line consolidation therapy on time-to-treatment failure and OS. In the absence of randomized trials comparing conventional chemotherapy to first-line consolidation with HDT/ASCR, this is a reasonable treatment option only in patients showing good response to induction therapy.

**NCCN Recommendations**

CHOP plus RT is the standard induction therapy for patients with ALK-positive ALC. For patients with other subtypes, since there is no standardized treatment, clinical trials, whenever available, are the preferred treatment options. Clinical trials are essential to advancing our treatments form these diseases. Multiagent chemotherapy (4-6 cycles) with adjuvant locoregional radiation therapy to involved region is recommended for patients with stage I-II disease (low/low-intermediate risk), whereas patients with stage I-II (high/high-intermediate risk) or stage III-IV disease are treated with multiagent chemotherapy (6-8 cycles) with or without radiation therapy. Suggested regimens include CHOEP, HyperCVAD or CHOP followed by ICE or IVE.

AILT is a very heterogeneous disease and can at times be treated solely with corticosteroids or other immunosuppressive agents. Cyclosporine has been effective in patients with relapsed disease following treatment with steroid or multiagent chemotherapy. Patients with AILT are managed similarly to above; however the guidelines
suggest a trial of single agent corticosteroid for symptom management in elderly patients or in patients with comorbid conditions in whom the risks of combination chemotherapy are excessive.

**Follow-up Therapy**

All patients (except for those with ALK-positive ALCL) undergo interim restaging following initial therapy by repeating all prior positive studies. If a PET-CT scan is positive, rebiopsy is recommended before changing course of treatment. Patients are then divided into three groups according to treatment response (CR, PR or no response or progressive disease). Subsequent treatment options depend on whether the patient initially presented with Stage I-II or Stage III-IV disease.

**Stage I or II disease (low-intermediate)**

In patients showing CR after interim restaging, planned RT is completed. RT or HDT/ASCR with or without RT is considered for patients showing PR at interim staging. Clinical trials including allogeneic transplant or radiation therapy is another option for this group of patients. End of treatment restaging is performed after completion of treatment. No further treatment is necessary for those showing CR. Patients with PR at end of treatment restaging and those with no response or progressive disease following initial or follow-up therapy are treated as described for relapsed or refractory disease.

**Stage I or II disease (high-intermediate) or stage III-IV**

Patients with a CR can be observed or they can be consolidated with HDT/ASCR. Local RT can be given prior to HDT/ASCR. Patients with PR or no response or progressive disease after initial therapy are treated similarly to patients with relapsed or refractory disease.

**Treatment for Relapsed or Refractory Disease**

Several studies have shown that second-line consolidation with HDT/ASCR produces similar outcomes patients with relapsed or refractory PTCL compared to those with B-cell lymphomas. In a retrospective review of patients with PTCL who underwent HDT/ASCR at the Stanford University, the 5-year PFS for patients in first complete or partial remission, complete or partial remission after second-line therapy and those with refractory disease was 51%, 12%, and 0%, respectively, and the OS rates were 76%, 40%, and 30%, respectively. The disease status and the number of prior regimens received prior to transplant were significant prognostic factors. Thus, HDT/ASCR as first-line consolidation therapy may be associated with a durable survival benefit. However, HDT/ASCR only infrequently results in durable benefit in patients with relapsed or refractory disease.

Recent reports have shown that allogeneic transplantation may be an effective second-line therapy for patients with relapsed or refractory PTCL. In a phase II study, Corradini et al investigated the role of reduced intensity conditioning (RIC) followed by allogeneic transplantation in patients (n = 17) with relapsed or refractory PTCL. The estimated 3-year OS and PFS rates were 81% and 64% respectively. Donor lymphocyte infusion induced responses in some patients progressing after allografting. The estimated probability of non-relapse mortality at 2 years was 6%. Long-term data on 53 patients with relapsed or refractory PTCL who received a RIC followed by allogeneic SCT with a median follow-up of 4-years showed that patients with chemosensitive disease had advantage from allogeneic SCT and there was no significant difference in outcome between the different histopathological subtypes of PTCL. The 4-year OS and PFS were 50% and 47% for all patients. OS (62% vs.15% respectively) and PFS (58% and 13% respectively) were significantly higher for chemosensitive patients compared to those who were chemorefractory.
The OS and PFS were 42% and 40% for PTCL-NOS, 50% and 44% for ALCL, 67% and 80% for AILT. The crude cumulative incidences (CCI) of non-relapse mortality were 4% and 10% at 6 months and 4-year, respectively. Similar results were reported in a retrospective study from French national survey of 77 patients where the majority of the patients (57/77) were treated with myeloablative regimen. Treatment related mortality was higher (34%) in this study compared to only 6% observed with RIC regimen. A retrospective study from the lymphoma working party of the European group for blood and marrow transplantation demonstrated that allogeneic HSCT is able to induce long-term remissions in patients (n = 45; 27 had chemosensitive disease, and 18 had chemotherapy refractory disease) with AITL. PFS and OS rates were 62% and 53% and 66% and 64% at 1 and 3 years, respectively. Patients with chemotherapy sensitive disease had a significantly superior PFS compared with those with chemotherapy refractory disease (66% v 33%, respectively) and were significantly better in chemotherapy sensitive patients.

Until recently, data to guide the treatment of patients with relapsed and refractory PTCL came from small series of patients treated with various single agents. Gemcitabine, denileukin difftitox and alemtuzumab have shown activity in such experiences. Zinzani et al recently reported the outcome of 39 pretreated T-cell lymphoma patients treated with gemcitabine (on days 1, 8, and 15 on a 28-day schedule; 1200 mg/m/day for a total of three to six cycles). Among 20 patients with PTCL-NOS, CR and PR were observed in 30% and 25% of patients respectively. In a phase II study, Dang et al evaluated the safety and efficacy of denileukin difftitox in 27 patients with relapsed/refractory T-cell- lymphomas excluding CTCL. The predominant histology was PTCL-NOS (19 of 27 patients). The ORR was 48%, with a median PFS of 6 months.

In a pilot study, alemtuzumab at standard dosing produced an ORR of 36% among 14 patients with relapsed or chemotherapy-refractory PTCLs. But, it was associated with significant hematologic toxicity and infectious complications including 5 deaths from opportunistic infections. The preliminary results of another phase II study showed that in 10 patients with pretreated T-cell lymphoma including 6 with PTCL and 4 with CTCL, alemtuzumab at lower dose was less toxic and equally effective as the standard dose used in the pilot study. The ORR was 60%. In the subset of patients with PTCL-NOS, ORR was 50% (33% CR and 17% PR). CMV reactivation was observed only in 10% of patients, as compared with 42% of the patients reported by Enblad et al. The median duration of response was 7 months.

Pralatrexate is a new antifolate with a high affinity for reduced folate carrier type 1 (RFC-1) and a significant activity in patients with relapsed/refractory T-cell lymphoma. The median number of prior therapies was 3 including combination chemotherapy regimens and HSCT. The results of the pivotal, international, phase II study (PROPEL) showed that pralatrexate resulted in an ORR of 27% (10% CR and 17% PR) in 109 pretreated patients with relapsed or refractory PTCL. Compared to smaller studies above, this study is distinguished not only by its size, but also by central pathology review and independent central response review. The most common side effect was stomatitis (70% any grade, 21% with grade 3-4) and the most common hematologic adverse effect was thrombocytopenia (41% any grade, 33% with grade 3-4). Eight patients achieved a response with pralatrexate adequate to proceed to subsequent SCT. In September 2009, after FDA review, pralatrexate became the first approved single agent for the treatment of patients with relapsed or refractory PTCL.
Romidepsin, a potent HDAC inhibitor approved by the FDA for patients with CTCL who have received at least one prior systemic therapy, has demonstrated significant single agent activity in patients with relapsed or refractory PTCL. In the pivotal multicenter phase II study, romidepsin induced responses in patients with all major subtypes of PTCL refractory to multiple prior therapies including SCT. The ORR was 26% (evaluated by the independent review committee) and 29% (investigator assessment). The corresponding CR/Cru was 13% and 16% respectively. Median duration of overall response was 12 months.

Brentuximab vedotin is an antibody-drug conjugate that targets CD30-expressing malignant cells by binding to CD30 on the cell surface. After internalization, a potent antimicrotubule agent (monomethyl auristatin E) is released within the cell. A multicenter phase II study evaluated brentuximab vedotin (IV 1.8 mg/kg every 3 weeks, up to 16 cycles) in patients with relapsed or refractory systemic ALCL (N=58). Patients had received a median of 2 prior systemic therapies (range, 1-6) and 62% were considered to have primary refractory disease; in addition, 50% of patients were refractory to their most recent prior therapy and 22% had never responded to any therapy. The ORR was 86% (evaluated by an independent review committee) with CR in 53% of patients. The median duration of response had not yet been reached at the time of the report. Among the subgroup of patients who had malignant cutaneous lesions at baseline (n=15), 93% experienced resolution of all lesions. The most common grade 3-4 adverse events reported in this study included neutropenia (21%), thrombocytopenia (14%), and peripheral sensory neuropathy (10%). No treatment-related deaths were reported. Based upon the results from this study, brentuximab vedotin was recently approved by the FDA (August 2011) for treating patients with nodal ALCL after failure of at least one prior multiagent chemotherapy regimen. This agent has not been evaluated in patients with relapsed/refractory cutaneous ALCL and therefore cannot be recommended for those patients at this time.

**NCCN Recommendations**

Patients who are candidates for transplant can be treated with second-line chemotherapy prior to transplant. Consolidation therapy with HDT/ASCR or allogeneic HSCT is recommended for those with a CR or PR. Localized areas can be treated with RT before or after high-dose therapy. Patients who are non-candidates for transplant are treated with RT or second line regimens for palliative intent only. Suggested treatments include alemtuzumab, bortezomib, brentuximab vedotin (for patients with nodal ALCL only), cyclosporine (for patients with refractory AITL only), denileukin diftitox, gemcitabine or pralatrexate. Participation in a clinical trial is strongly preferred for these patients. The panel has also included romidepsin as an option for second-line therapy for patients with relapsed or refractory disease. In patients receiving romidepsin, serum potassium and magnesium levels need to be monitored since low levels can be associated with ECG abnormalities.

**Mycosis Fungoides and Sezary Syndrome**

Cutaneous T-cell lymphomas (CTCLs) are a group of NHLs primarily developing in the skin and ultimately involve lymph nodes, blood and visceral organs. In a recent population-based study of 3884 cases of cutaneous lymphomas diagnosed during 2001-2005, CTCLs accounted for 71% compared to 29% for cutaneous B-cell lymphomas. Mycosis fungoides (MF) and Sezary syndrome (SS) are the most common types of CTCLs. MF accounts for 60% of new cases of CTCL and SS occurs only to an extent of 5%. MF is an extranodal NHL of mature T-cells with primary cutaneous involvement. SS is an erythrodermic, leukemic variant of CTCL and it is characterized by significant blood involvement...
and lymphadenopathy. In updated EORTC and WHO classification of CTCL, MF is characterized as an indolent neoplasm and SS is characterized as an aggressive neoplasm.\textsuperscript{23}

Large cell transformation (LCT) has been documented in a subgroup of patients and is diagnosed when there are more than 25\% of large cells in a biopsy of an MF lesion.\textsuperscript{522,523} The incidence of LCT is strongly dependent on the stage of the disease at diagnosis (1.4\% in patients with early-stage disease, compared with 27\% for those with stage IIB disease 56\%-67\% for those with disease) and the median OS from the diagnosis of LCT was 2 years.\textsuperscript{524} LCT is often but not always aggressive. Limited preliminary data indicate in some patients with advanced-stage disease in whom the large cells express CD30 may have a more indolent course.\textsuperscript{525}

**Staging**

The TNM staging system developed by the mycosis fungoides cooperative group (MFCG) has been the standard for staging and classification of patients with MF and SS.\textsuperscript{526} Recently, ISCL and EORTC recommended revisions to the MFCG staging system are based on the new data available in the area of immunohistochemistry, biology and prognosis of MF and SS since the publication of MFCG.\textsuperscript{527} In the revised staging system, all staged patients should have a definitive diagnosis of MF and SS. T1 disease is defined as less than 10\% of the skin surface involvement with patches or plaques and T4 disease is erythroderma with at least 80\% of the skin surface diffusely involved. The extent of skin involvement is based on the percentage of body surface area (BSA) where the patient’s palm (without digits) is equivalent to 0.5\% BSA. Lymph node biopsy for staging is recommended only for clinically abnormal node (1.5 cm or larger in diameter). Visceral disease with the involvement of an organ other than the skin, nodes or blood should be documented using imaging studies. Blood involvement is classified into three groups: B0 is associated with the absence of significant blood involvement (5\% or less of Sezary cells); B1 is defined as having a low tumor burden (more than 5\% of Sezary cells but does not meet the criteria for B2); B2 is associated with high tumor burden with more than 1000 Sezary cells/mcL. According to the updated staging system, patients with stage III are further divided into two subgroups IIIA and IIIB to differentiate the extent of blood involvement (B0 and B1 respectively).

**Prognosis**

The most significant prognostic factors of survival include patient’s age at presentation, extent and type of skin involvement, overall stage (T-classification), presence or absence of extracutaneous disease and peripheral blood involvement.\textsuperscript{528-531} Patients diagnosed with limited patch or plaque disease have an excellent prognosis, whereas those who have tumor stage disease or erythrodermic skin involvement have a less favorable prognosis and patients with who present with extracutaneous disease have a very poor prognosis. Long-term follow-up data involving 525 patients with MF and SS, showed that the 5-year OS was significantly better (80\% vs. 56\%) for patients less than 57 years of age compared to that of patients 57 years or older.\textsuperscript{531} The risk of disease progression, development of extracutaneous disease or death due to MF was correlated with initial stage. In a retrospective cohort study of 106 patients with erythrodermic MF and SS, older age and extracutaneous disease including peripheral blood involvement were identified as adverse prognostic factors. Three distinct prognostic groups (favorable, intermediate and unfavorable) were identified, according to the number of unfavorable prognostic factors: 65 years or older at presentation, lymph node or visceral (stage IV) disease and peripheral blood involvement. The median survival in each group was
In a recent retrospective analysis involving patients with erythrodermic cutaneous T-cell lymphoma (124 out of 1197 patients with CTCL), the median OS in all 124 erythrodermic -CTCL patients was 5.1 years (range, 0.4-18.6 years). In multivariate analysis, advanced age and elevated lactate dehydrogenase were the strongest predictors of poor prognosis.

Diagnosis

In the algorithms developed by the International Society for Cutaneous Lymphoma (ISCL), the diagnosis of MF is based on integration of clinical, histopathologic, immunopathologic, and molecular biological characteristics. According to the revised criteria, SS is defined as a clonal T-cell receptor (TCR) gene rearrangement in the blood (clones should be relevant to clone in the skin) and either an absolute Sézary cell count of 1000 cells/mm³ or more, or an increased CD4+ or CD3+ cells with CD4/CD8 ratio of 10 or higher or an increased CD4+ cells with an abnormal phenotype (CD4+/CD7:40% or more, or CD4+/CD26:30% or more). Complete skin exam, biopsy of suspicious skin sites and immunohistochemical studies of skin biopsy are essential to confirm the diagnosis. Biopsy of suspicious lymph nodes and assessment of peripheral blood for Sezary cells are recommended in the absence of a definitive skin diagnosis. MF and SS cells are characterized by CD2+, CD3+, CD4+, CD5+, CCR4+, CD45RO+ and they lack certain T-cell markers CD7 and CD26. There are subtypes of MF that are also CD8+. If there is a histological evidence of LCT phenotyping with CD30 is recommended. The T-cells also express cutaneous lymphocyte antigen (CLA) and TH2 cytokines. They are also associated with a loss of TH1 and IL-12 cytokines. TCR gene rearrangement should be interpreted with caution since TCR clonal rearrangements can also 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. TCR gene rearrangement analysis by PCR is a useful technique to support the diagnosis of MF and SS, especially in distinguishing MF from inflammatory dermatoses.

Work Up

The work-up of patients diagnosed with MF or SS involves complete skin examination to assess the extent of the disease, examination of lymph nodes or other masses for the evaluation of lymphadenopathy or organomegaly. Laboratory studies should include CBC with Sezary screen and Sezary flow cytometry to assess for expanded CD4+ cells with increased CD4:CD8 ratio or with abnormal immunophenotype. Patients with unfavorable features (T2 or higher, folliculotropic or large-cell transformation, palpable adenopathy or abnormal laboratory studies) should undergo either CT or PET-CT scan of the neck/chest/abdomen and pelvis. Integrated PET-CT was found to be more sensitive for the detection of lymph node involvement than CT alone and can help direct biopsies. Bone marrow biopsy is not needed for staging of patients, but may be helpful in those with suspected marrow involvement or in those with an unexplained hematologic abnormality. TCR gene rearrangement analysis of peripheral blood lymphocytes is recommended if SS is suspected. Biopsy of suspicious lymph nodes is recommended with evaluation for TCR gene rearrangements, especially due to the poor prognosis of patients with clonal rearrangement in lymph nodes.

Treatment alternatives for MF and SS

Initial treatment in patients with patch/plaque disease consists of skin-directed therapies (localized or generalized), with the addition of systemic biologic therapy for refractory, or progressive disease. Those
patients who have unfavorable prognostic features (e.g., folliculotropic or large-cell transformed MF) may have systemic biologic therapies introduced earlier in the treatment algorithm. Patients who do not respond to biologic therapy or those with very aggressive or extracutaneous disease may be treated with chemotherapy. Due to the rarity of the condition and the need for an individualized approach, referral to a multidisciplinary academic specialty center is preferred.

**Skin-directed therapies**

Localized skin-directed treatments include topical therapy with corticosteroids, mechlorethamine hydrochloride, Carmustine, or topical bexarotene. Generalized skin-directed therapies such as phototherapy [UVB or PUVA (psoralen and UVA)] and total skin electronic beam therapy (TSEBT) are indicated in patients with widespread skin involvement.

Topical corticosteroids are effective especially for the treatment of patch-stage MF, producing a CR rate of over 90%. However, long-term use of topical steroid may lead to skin atrophy or striae formation and the risk worsens with increased potency of the steroid. High-potency steroid used on large skin surfaces may lead to systemic absorption. Topical chemotherapy with nitrogen mustard or Carmustine has been used for the management of MF for many decades. Long term follow-up results in 203 patients have confirmed the safety of topical therapy with nitrogen mustard. The efficacy were similar for aqueous and ointment preparations, however, the ointment was associated with reduced toxicity. Patients with T1 disease had better response rates (93% vs. 72%) and survival outcomes (65% vs. 34%) than those with T2 disease. Freedom from progression (FFP) in T1 disease at 5 and 10 years were 92% and 85% respectively and in T2 disease FFP was 83% at 5 and 10 years. An ongoing multicenter trial is evaluating the efficacy of topical nitrogen mustard in patients with stage I or IIA MF.

Synthetic retinoids (bexarotene and tazarotene) and imiquimod have been used as topical therapy for the treatment of patients with MF and SS. FDA-approved bexarotene gel was evaluated in two open-label, historically-controlled clinical studies involving 117 patients with CTCL. In the phase I-II trial involving 67 patients with early stage MF, CR was attained in 21% and PR was observed in 42%. Patients with no prior therapy responded at a higher rate than those who had received prior topical therapies. In the phase III multicenter study of 50 patients with early stage refractory MF, ORR was observed in 44% of patients with 8% of patients achieving CR. In a small open-label pilot study, tazarotene 0.1% gel was a well-tolerated and effective adjuvant topical therapy for the treatment of 20 adult patients with early patch or plaque MF lesions (stable or refractory to therapy) by clinical and histologic assessments. In a small number of case studies imiquimod was effective for patients with early stage MF that is refractory to other therapies. Bexarotene gel is the only FDA approved synthetic retinoid for topical therapy in patients with MF and SS.

MF is extremely radiosensitive and patients with minimal stage IA MF may be managed effectively with local superficial RT without adjuvant therapy. Wilson et al reported that the actuarial DFS at 5 and 10 years was 75% and 64% for patients with early stage disease treated with RT alone. The 10-year DFS was 85% for patients with unilesional disease. The optimal RT dose was 20 Gy which resulted in a DFS rate of 91% with no distant failures. TSEBT is effective especially in patients with thick generalized plaque (T2) or tumorous disease (T3). In a retrospective analysis involving 148 patients with T2 and T3 disease, TSEBT alone or in combination with adjuvant topical mechlorethamine hydrochloride yielded significantly higher CR rates for
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T2 and T3 disease compared to mechlorethamine hydrochloride alone (76% vs. 44% for T2; 44% vs. 8% for T3).  

Phototherapy with UVB (including narrow-band) and photochemotherapy with psoralen and UVA (PUVA) are effective alternative treatment options for patients with early stage MF.  

In long-term follow-up studies, PUVA was associated with prolonged disease-free remissions. In a retrospective analysis, phototherapy with narrow-band UVB and PUVA produced comparable complete remission rate (81% vs. 71%), partial remission rate (19% vs. 29%) and RFS (24.5 months vs. 22.8 months) in patients with early stage MF.  

However, cumulative doses of UV are associated with increased risk of UV-associated skin neoplasms. Thus, phototherapy may not be appropriate for patients with the history of squamous or basal cell carcinoma or melanoma. Since narrowband UVB has less skin toxicity than broadband and PUVA, it is preferred to start with narrowband UVB than PUVA in early stage patients with patch or thin plaque disease. 

Systemic therapies

Systemic therapies with extracorporeal photopheresis (ECP), interferons, systemic retinoids, denileukin diftitox or vorinostat are preferred over traditional chemotherapy for patients who do not respond to initial skin-directed therapies. Multiagent chemotherapy is reserved only for patients who do not respond to single agent chemotherapy or those with bulky lymph node or solid organ disease. In the absence of other unfavorable prognostic features, it is recommended that systemic therapy be deferred until the patient has failed multiple treatments with local and skin directed therapy. 

ECP is an immununomodulatory therapy using psoralen and UVA radiation extracorporeally. It involves the removal of leukocytes by leukopheresis. The leukocytes are treated with 8-methoxypsoralen, exposed to UVA and returned to the patient. ECP is a long standing treatment of MF, and is particularly indicated in patients with or at risk of blood involvement (erythrodermic stage III disease or IVA with Sezary Syndrome).  

In a long-term follow-up of 20 patients with CTCL treated with ECP for at least 6 months, CR (disappearance of all lesions) was obtained in five patients (25%) and a PR (disappearance of at least 50% of lesions) in five patients (25%).  

Median survival time for the entire cohort was 96 months (range, 16 to 152 months). In a meta-analysis of 19 studies (5 studies using ECP as a monotherapy and 14 studies as combination therapy) involving more than 400 patients with CTCL, the combined ORR for all stages of CTCL was 55.7% with 17.6% achieving a CR.  

ECP as a monotherapy resulted in 55.5% ORR with 14.8% CR. The corresponding response rates were 58% (15% CR) for erythrodermic disease (T4) and 43% (9.5% CR) for SS.  

Retinoids [all-trans retinoic acid (ATRA), 13-cis retinoic acid and their synthetic analogs acitretin and isotretinoin] and interferons have been used for many years for the treatment of CTCL.  

Interferon alpha as a single agent, has produced PR rates of greater than 50% and CR rates of greater than 20%.  

Interferon gamma has been shown to be effective in the treatment of patients with various stages of CTCL that is refractory to interferon alpha and other topical or systemic therapies. 

Oral bexarotene has been evaluated for the treatment of refractory or persistent early and advanced stage CTCL in two multicenter clinical trials.  

In early stage CTCL, bexarotene was well tolerated and effective in 54% of patients at doses of 300 mg/m2 per day. In advanced CTCL, clinical CR and PR were observed in 45% of patients receiving 300 mg/m2/d. At more than 300 mg/m2/d, response rate was 55%, including 13% clinical CR. Side effects were reversible and manageable with appropriate medications prior to initiation of treatment.
Bexarotene capsules received FDA approval in December, 1999 for the treatment of refractory CTCL. In retrospective comparison, ATRA and bexarotene had similar efficacy in the treatment of patients with relapsed MF and SS.\(^{565}\)

Denileukin diftitox is a recombinant fusion protein with interleukin-2 (IL-2) and diphtheria toxin, and targets the high-affinity interleukin-2 receptor (CD25) expressed on malignant T-cells and B-cells. In a pivotal phase III study the safety and efficacy of denileukin diftitox was evaluated in two different dose levels in pretreated patients with CTCL.\(^{566}\) The ORR was 30% with a median duration of 6.9 months in patients who have received other treatments. Median duration of response was 6.9 months (with a range of 2.7-46.1 months). The response rates and the duration of response were not statistically different between the two doses. Clinically significant improvement in self-rated overall QOL, skin appearance, and pruritus severity was observed in 68% of the patients who had significant pruritus at baseline. However, denileukin diftitox is associated with significant side effects including hypersensitivity reactions and vascular leak syndrome. Myelosuppression is an uncommon side effect. Denileukin diftitox was approved in February, 1999 for the treatment of persistent or recurrent CTCL in patients whose malignant cells express CD25 component of IL-2 receptor. The results of the phase III, placebo-controlled, randomized trial confirmed that denileukin diftitox results in significant and durable clinical benefit in patients with early- and late-stage CTCL.\(^{567}\) In this trial, 144 patients with biopsy-confirmed, CD25 assay-positive CTCL were randomly assigned to denileukin diftitox (9 or 18 micrograms/kg/day) or placebo. The ORR was 44% (10% CR and 34% PR) compared with 15.9% for placebo-treated patients (2% CR and 13.6% PR). ORR was higher in the 18 micrograms group vs. the 9 micrograms group (49.1% v 37.8%, respectively) and both doses were significantly superior to placebo. The median PFS was significantly longer (more than 2 years) for both doses compared with placebo (124 days; \(P < .001\)). An ongoing phase III trial is evaluating the efficacy of denileukin diftitox according the CD25 status.\(^{568}\)

Histone deacetylase inhibitors (HDACis) are a new class of drugs that are potent inducers of histone acetylation, cell cycle arrest and apoptosis. Activity and safety of vorinostat and romidepsin in patients with refractory CTCL was confirmed in a phase II trials.\(^{569-572}\) In a phase IIB study involving 74 patients with persistent, progressive or refractory CTCL, vorinostat resulted in an ORR and median time to progression were 29.7% and 4.9 months respectively.\(^{570}\) Median time to progression was greater than 9.8 months in responders with advanced disease (stage IIB or higher). The response rates and median response durations were comparable to those obtained with bexarotene capsules and denileukin diftitox. Vorinostat was the first HDACi to receive FDA approval in October 2006 for the treatment of patients with progressive, persistent, or recurrent CTCL, on or following two systemic therapies. A post hoc subset analysis of patients who experienced clinical benefit with vorinostat in the previous phase IIb study provided evidence for the long-term safety and clinical benefit of vorinostat in heavily pretreated patients with CTCL, regardless of previous treatment failures.\(^{573}\)

Romidepsin demonstrated single agent activity in 2 open-label clinical studies [pivotal phase 2B study (GPI-04–0001) and NCI 1312 (supportive study)] of 167 patients with CTCL that was refractory to prior therapies.\(^{572,574}\) In a pooled analyses of these two international multicenter clinical studies, objective response rate was seen 41% of patients (7% CR and 33% PR) in the evaluable population (who had at least 2 cycles).\(^{571}\) Responses were noted in 42% of patients with stage ≥IIb MF and 58% of patients with SS. Median duration of response and median time to disease progression were 15 months and 8 months.
respectively. The pivotal phase IIb study (GPI-04-0001) enrolled 96 patients and 68 (71%) of these had advanced stage disease (≥IIB). The objective response rate was 34% including 6 CRs. Among patients with advanced stages of disease, 38% achieved an objective response, including 5 CRs. The median time to response was 2 months and the median duration of response was 15 months. Improvement in pruritus was observed in 28/65 patients (43%) with moderate to severe symptoms at baseline, including 11 who did not achieve an objective response. These results are consistent with the findings of the phase NCI 1312 (supportive study) in a similar population (n = 71) using the same dose and schedule of romidepsin, where the ORR was 34% including 4 CRs and the median duration of response was 14 months. In the pivotal study (GPI-04–0001), romidepsin also induced clinically significant responses in 37 patients with blood involvement. In 27 evaluable patients, the objective response rate was 32% by composite assessment including 2 complete clinical responses. In November of 2009, romidepsin was approved by the FDA for the treatment of patients with CTCL in patients who have received at least one prior systemic therapy.

Systemic chemotherapy is used as a primary treatment only for patients with advanced disease or LCT and second-line therapy for early stage disease that is refractory to skin-directed therapies and systemic biologic therapies. Low dose methotrexate has been used to treat early stage MF and SS for many years, although there is not extensive literature documenting outcomes. Gemcitabine as a single agent has also been effective in patients with advanced, heavily pretreated CTCL and as front-line therapy in untreated CTCL patients. Zinzani et al evaluated the long-term outcome of patients with T-cell lymphoma patients treated with gemcitabine. The ORR was 51%. Patients with MF had a CR rate of 16% and a PR rate of 32% compared with a CR rate of 30% and a PR rate of 25% of PTCLU patients. Pentostatin has shown activity either as a single agent or in combination with interferon alfa in patients with advanced MF or SS. Anecdotal reports suggest activity for temozolomide and bortezomib. Pegylated liposomal doxorubicin have also shown significant activity in patients with pretreated, advanced or refractory CTCL. In a retrospective multicenter study (n = 34), 15 patients achieved a CR and PR was seen in 15 patients. The OS, EFS and DFS rates were 18-28 months, 12-22 months and 13-24 months respectively. In a prospective phase II trial (n =19), Pulini et al reported an overall and CR rates of 84.2% and 42.1% (with no significant differences between stage I-IIA and IIIB-IV patients) of patients with relapsed CTCL. OS, EFS and PFS rates at 46 months were 44%, 30% and 37% respectively. In a multicenter dose-finding study, low-dose pralatrexate (15 mg/m²) was active with acceptable toxicity inducing ORR in 43% of patients with relapsed or refractory CTCL.

In clinical studies and case report, liposomal doxorubicin, denileukin diftitox and gemcitabine have demonstrated activity in patients with transformed MF/SS. Pralatrexate (30 mg/m²) has demonstrated significant activity in the 12 patients with refractory transformed MF enrolled in the PROPEL trial with an investigator assessed response rate of 58%. The median duration of response and PFS were 4 months and 5 months respectively.

### Combination therapies

Combinations of biologic or non-cytotoxic therapies as distinct from combination chemotherapies are used when single agent therapies fail or in advanced, progressive, refractory, or symptomatic disease. Several combination therapies have been studied in clinical trials for CTCL. In a retrospective non-randomized series, ECP given...
concurrently with, or immediately after, TSEBT significantly improved both PFS and cause specific survival for patients with erythrodermic MF compared with TSEBT alone.598 Most commonly used combinations are phototherapy plus either interferon or systemic retinoid and ECP plus either IFN or systemic retinoid or both.597, 599-604 PUVA when used in combination with interferon alfa produced an ORR of 93% in patients with stage IB to stage IVB disease, with a median duration of response exceeding 23 months.599 In another prospective phase III trial, combination of low-dose interferon alfa and PUVA resulted in a CR rate of 84% and an ORR of 98% in patients with early stage MF.600 Low-dose bexarotene in combination with PUVA also resulted in an ORR of 93% (47% CR) in patients with all stages of CTCL resistant or intolerant to previous therapies.605 The addition of PUVA to the combination of ECP, interferon and bexarotene resulted in rapid sustained remission in patients with SS.601 In a long-term follow-up study involving patients with advanced CTCL and poor prognostic factors, combined modality therapy (ECP with interferons and/or systemic retinoids) resulted in better response rates and median survival (84% and 74 months respectively) compared to ECP alone (75% and 66 months respectively).597 Combination therapy was well tolerated. Combination of bexarotene with PUVA, ECP and/or interferon also resulted in higher response rates in patients with advanced disease.602

Systemic retinoids have been studied in combination with other biological response modifiers in patients with advanced disease.606, 607 The combination of bexarotene and denileukin diftitox is particularly interesting since bexarotene has been shown to increase CD25 expression in CTCL cells and thereby increasing the susceptibility of T-cells to denileukin diftitox.

**NCCN Recommendations based on Clinical Stage**

**Primary Treatment**

Patients with Stage IA have an excellent prognosis using skin-directed therapies alone. Stage IA is managed primarily with skin-directed therapies, alone or in combination with other skin-directed therapies including local RT. Local RT (24-36 Gy) is recommended particularly for unilessional presentation. Treatment options include topical corticosteroids, nitrogen mustard or carbmustine, topical retinoids (bexarotene or tazarotene), topical imiquimod, phototherapy with UVB for patch or thin plaques or PUVA for thicker plaques.

Patients with Stage IB-IIA disease require generalized skin treatment. Topical retinoids are not recommended for generalized skin involvement since they can cause a lot of irritation. In addition to the other skin-directed therapies used for Stage IA disease, TSEBT is another treatment option for those with severe skin symptoms or generalized thick plaque or tumor. Although TSEBT is highly effective in T1 disease (stage IA), it is reserved for generalized or recalcitrant skin disease due to its toxicities and lack of superior long-term outcome. It is common practice to follow TSEBT with systemic therapies such as interferon or bexarotene to maintain response. For patients with sites that are not responsive to generalized treatment, additional treatment may be needed.

Patients with early stage disease (stage IA, stage IB-IIA) with B1 blood involvement are best managed with more intensive treatments as described for stage III with B1 blood involvement and those with histological evidence of folliculotropic or large cell transformation (LCT) are managed as described for stage IIB disease.

Patients with Stage IIB disease and/or histological evidence of folliculotropic or LCT can be separated into two categories: limited
extent tumor disease with or without patch/plaque disease or generalized tumor disease. In patients with tumor disease, rebiopsy is necessary to confirm histological evidence of LCT.

Patients with limited extent tumor disease can be managed with local radiation. Adjuvant systemic therapy (SYST-CAT A) may be considered to improve response duration in patients who are free of disease after local RT. Skin directed therapies, as described above for stage I-IIA disease can be used for the residual patch or plaque disease. Alternatively, they can also be treated with systemic therapy (SYST-CAT A: ECP, bexarotene, ATRA, 13-cis-retinoic acid or their synthetic analogs acitretin and isotretinoin, interferons, HDACIs (vorinostat or romidepsin), interferons, denileukin diftitox or low-dose methotrexate) with or without RT or skin-directed therapy.

Patients with generalized tumor disease are treated with TSEBT or systemic therapy, with or without skin directed therapy. Suggested systemic therapy options include ECP, systemic retinoids (bexarotene, ATRA, 13-cis-retinoic acid or their synthetic analogs acitretin and isotretinoin), interferons, HDACIs (vorinostat or romidepsin) or denileukin diftitox, chemotherapy single agents such as methotrexate, liposomal doxorubicin, gemcitabine for first-line therapy and chlorambucil, pentostatin, etoposide, cyclophosphamide, temozolomide for second-line therapy.

Systemic therapy is the initial treatment for patients with LCT. If there is no evidence of aggressive growth, systemic therapies from SYST-CAT A or SYST-CAT B are appropriate. For LCT with aggressive clinical course, the guidelines recommend systemic therapy (SYST-CAT C) with liposomal doxorubicin, gemcitabine, denileukin diftitox, romidepsin, low or standard dose pralatrexate or any of the regimens recommended for PTCL. Combination regimens are generally reserved for patients with relapsed or refractory or extracutaneous disease.

Management of patients with stage III disease depends on the extent of blood involvement: no significant blood involvement (B0) or some blood involvement (B1), which is less than that observed for SS. Patients with no significant blood involvement are treated with generalized skin-directed therapies (similar to those recommended for stage IB-IIA). Generalized skin-directed therapies other than topical steroids may not be well tolerated for patients with stage III disease. ECP may be a more appropriate systemic therapy for patients with stage III disease with blood involvement. Alternative options include low dose methotrexate or systemic biologic therapies as recommended for stage IIB disease. Mid-potency steroids should be used in combination with systemic therapy to reduce skin symptoms. Antibiotic therapy should be considered for this group of patients since they are at increased risk of developing secondary infections.

Stage IV disease includes SS and non-Sezary or visceral (solid organ) disease. SS patients are treated with single agent systemic therapy (ECP, systemic retinoids, interferons, vorinostat or romidepsin, denileukin diftitox or low dose methotrexate) or combination therapies. Safety data on the use of systemic retinoids in combination with TSEBT and vorinostat in combination with phototherapy or TSEBT is currently lacking. Non-Sezary or solid organ disease is frequently managed with systemic therapy (SYST-CAT B or SYST-CATC) with or without RT for local control. Adjuvant biologic therapy may be considered following chemotherapy to improve response duration.

All patients (stage IA through stage IV) showing response should be considered for maintenance or tapering therapy to optimize response duration. Patients with a PR or disease relapse following primary
Treatment should be treated with the other options included in the primary treatment to improve response before starting treatment for refractory disease. In addition, patients with disease relapse or persistent disease may be considered for clinical trials. Patients with stage IV disease should be considered for clinical trials.

**Refractory or Progressive Disease**

Autologous stem cell transplantation (SCT) has been used infrequently for patients with CTCL. In general, the durations of response have been short thus limiting its usefulness. Allogeneic SCT has been reported only in case reports and small series in patients with advanced MF and SS. A recent meta-analysis compared the outcome of allogeneic versus autologous SCT in patients with MF and SS. OS and durable response rates were more favorable in patients who received allogeneic SCT. In the allogeneic group, the majority (70%) of patients experienced persistent GVHD, mostly with mild to moderate severity, whereas the majority of the deaths (8 of 10) in the autologous group were because of progressive disease. Data on allogeneic SCT, particularly using non-myeloablative conditioning, suggest the existence of graft versus T-cell lymphoma effect and success with long-term durable remissions has been reported in highly selected patients. Duvic et al have evaluated the safety and efficacy of total skin electron beam with allogeneic HSCT in 19 patients with CTCL. The overall intent-to-treat response was 68%, and the CR rate was 58%. Eleven (58%) of the initial 19 patients are currently in complete clinical and molecular remissions with median follow-up of 19 months. Median OS has not been reached. Additional study in high-risk patients with advanced disease is warranted.

Skin-directed therapy can be used as adjuvant treatment to reduce skin symptoms. Patients who do not respond to treatment with SYST-CAT A agents are treated with single agent systemic chemotherapy (SYST-CAT B). Allogeneic SCT may be considered for patients with stage IIIB-IV disease that is progressive or refractory to multiple primary treatment options. Appropriate patients (stage IIIB or greater MF who have failed multiple systemic therapies and adequate trial of skin-directed therapy or whose disease is not amenable to skin-directed therapy) may be referred for a transplant consultation. Ideal time for allogeneic SCT 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 SCT is low. Patients should have failed biologic options and single agent chemotherapy prior to allogeneic SCT. When appropriate, TSEBT may be considered as cytoreductive therapy before transplant.

Alemtuzumab, anti-CD52 antibody has shown promising activity in patients with advanced MF and SS. In a study of 14 patients, subcutaneous alemtuzumab at very low doses (10 mg maximum per administration), given for a short period based on Sezary cell count, was associated with a good toxicity profile, high response rate and durable remissions in SS patients with high tumor burden in the peripheral blood. Alemtuzumab (IV or subcutaneous) may be considered for patients with stage III-IV (specifically, SS) disease that is refractory to previous treatments.

Currently there is no definitive treatment for advanced disease that can produce reliable durable remissions or curative results, other than possibly, allogeneic SCT. The guidelines recommend participation in a clinical trial as a treatment option for all patients with relapsed or progressive disease.
Adult T-Cell Leukemia/Lymphoma (ATLL)

ATLL is a distinct T-cell lymphoma associated with a retrovirus, human T-cell lymphotropic virus type I (HTLV-1). The annual rate of ATLL among HTLV-1 carriers older than 40 years is estimated at 1.5 per 1,000 in males and 0.5 per 1,000 in females. HTLV-1 infection appears to be rare in the United States and is highly prevalent in southwestern Japan, Caribbean islands, tropical Africa and south America.

Advanced performance status (PS), high lactate dehydrogenase (LDH) level, increased number of total involved lesions, hypercalcemia and age 40 years or more have been identified as major adverse prognostic factors by multivariate analysis. For the chronic subtype, high LDH, high blood urea nitrogen, and low albumin levels have been identified as poor prognostic factors. These factors were used to stratify patients into three different risk groups: low risk, standard high risk and extremely high-risk group. Median survival time and projected 2- and 4-year survival rates were 37 months, 66.3% and 41.2% for low risk, 8 months 20.6%, and 4.5% for standard high risk, and 2.4 months, 5.6% and 0% for extremely high-risk groups, respectively. Recently, the International Peripheral T-Cell Lymphoma Project reported that IPI is a useful model for predicting outcome in ATLL of the lymphoma type. Phillips et al recently identified 3 prognostic categories based on ECOG performance status, stage, age, and calcium level at diagnosis for patients with HTLV-1-associated ATLL. In this series (n = 89), despite initial responses to therapy with alkylator-based chemotherapy regimen, the median OS for all subtypes was 24 weeks.

The Lymphoma Study Group (LSG) of the Japan Clinical Oncology Group (JCOG) have classified ATLL into four subtypes (smoldering, chronic, acute, or lymphoma) based on the characteristic features of ATLL which include generalized lymphadenopathy, hepatosplenomegaly, skin involvement, hypercalcemia, and organ infiltration. The smoldering and chronic subtypes are considered indolent. Both have 5% or more of abnormal T-lymphocytes in the peripheral blood and may have skin or pulmonary lesions. In addition the chronic subtype is characterized by absolute lymphocytosis (4 x 10^9/L or more) with T-lymphocytosis more than 3.5 x 10^9/L, lymphadenopathy and involvement of liver and spleen. The lymphoma type has 1% or less abnormal T-lymphocytes, no lymphocytosis, and histologically-proven lymphadenopathy with or without extranodal lesions. The acute type usually has leukemic manifestation and tumour lesions, with a rapidly progressive course, but involves cases that are not classified as any of the three other types.

The smoldering and chronic subtypes have a better prognosis than the acute or the lymphoma subtypes. In an analysis of 818 patients with a mean age of 57 years, 4-year survival rates for acute, lymphoma, chronic, and smoldering subtypes were 5.0%, 5.7%, 26.9%, and 62.8%, respectively. The median survival time was 6.2 months, 10.2 months, 24.3 months, and not yet reached, respectively. The maximum duration of follow-up was 7 years. In a recent report from a long-term follow-up of 90 patients with newly diagnosed indolent ATLL, the 5-, 10-, and 15-year survival rates were 47.2%, 25.4%, and 14.1%, respectively. In the subgroup analysis, the 15-year OS rate and median survival time tended to be higher for chronic subtype (14.7% and 5.3 years respectively) than the smoldering subtype (12.7% and 2.9 years respectively).

In the NCCN guidelines patients are classified into 4 subtypes (chronic, smoldering, acute and lymphoma) according to the Shimoyama criteria.
Diagnosis

The diagnosis of ATLL requires the histopathology and immunophenotyping of tumor lesion, peripheral blood smear analysis for atypical cells, flow cytometry on peripheral blood and/or HTLV-1 serology. The presence of 5% or more of T-lymphocytes with an abnormal immunophenotype in the peripheral blood is required for the diagnosis of ATLL in patients without histologically proven tumor lesions. HTLV-1 integration patterns have been reported to have clinical implications for ATLL. Bone marrow involvement is considered an independent poor prognostic factor. However, a bone marrow biopsy is generally not required for the diagnosis of ATLL. If the diagnosis of ATLL is not established on peripheral blood examination, bone marrow biopsy and biopsy of lymph nodes, skin and GI tract should be performed. Biopsy of the suspicious lesion may also help to rule out certain underlying infections. Excisional biopsy is recommended instead of core needle biopsy for the lymph nodes.

If a biopsy is performed the immunophenotyping panel should include CD3, CD4, CD7, CD8, and CD25. The typical immunophenotype in most patients with ATLL involves CD4-positive T cells with the expression CD2, CD5, CD25, CD45RO, CD29, T-cell receptor $\alpha\beta$ and HLA-DR. Most ATLL cells lack CD7 and CD26 and have a dim CD3 expression.

Workup

The initial workup involves a complete physical examination, including complete skin examination, and CT scans of the chest, abdomen and pelvis. Most patients with ATLL have elevated LDH levels and lymphocytosis is found in patients with the acute or chronic type at presentation. The guidelines recommend performing a complete blood count (CBC), checking serum LDH and serum electrolyte levels including serum calcium, creatinine and blood urea nitrogen (BUN).

Upper gastrointestinal tract endoscopy should be considered in selected cases since GI tract involvement is frequent in aggressive ATLL. CNS evaluation using CT scan, MRI and/or lumbar puncture is also recommended for all patients with acute or lymphoma subtypes or in patients with neurological manifestations.

Response Criteria

The current response criteria for ATLL are the modification of the JCOG response criteria as suggested at the international consensus meetings. The modified response criteria reflect the criteria for CLL and NHL which were published in 1996 and 1999. These response criteria are based on the reduction in the size of the enlarged lymph nodes and extranodal masses (as calculated by the sum of the products of the greatest diameters of measurable disease), reduction in the size of spleen or liver and the extent of involvement of bone marrow and skin. The response is categorized as CR (complete disappearance of all clinical, microscopic, and radiographic evidence of disease and absolute lymphocyte count including the flower cells in the peripheral blood is less than 4 x 10^9/L), PR (defined as 50% or greater reduction in the sum of the products of the greatest diameters of measurable disease), reduction in the size of spleen or liver and the extent of involvement of bone marrow and skin. The response criteria also includes a category for unconfirmed CR defined as 75% or more reduction in tumor size but with a residual...
mass after treatment with an absolute lymphocyte count, including flower cells, of less than 4 x 10^9/L. The usefulness of PET or PET-CT has not been evaluated in the response assessment of ATLL.

**Treatment Options**

The ATLL subtype is an important factor for predicting prognosis and deciding appropriate treatment strategies. Smoldering and chronic subtypes are considered indolent and are usually managed as indolent NHL with watchful waiting until disease progression, whereas acute and lymphoma subtypes require immediate therapy.

Several small phase II studies have reported responses with the combination of AZT and interferon in patients with ATLL. The results of a worldwide meta-analysis on the use of zidovudine and interferon for patients with ATLL were recently reported by Bazarbachi et al. In 231 patients with available survival data, first-line therapy was recorded in 207 patients. Five year OS rates were 46%, 20% and 12% respectively for patients who received antiviral therapy alone, chemotherapy alone and chemotherapy followed by antiviral therapy. Of the 62 patients who received first-line antiviral therapy, CR and PR were achieved in 35% and 31% of patients respectively. Of the 48 patients who received first-line chemotherapy, 25% achieved CR and 56% achieved PR. Of the 14 patients who received chemotherapy followed by antiviral therapy and for whom response data were available, CR and PR were achieved in 50% and 43% of patients respectively. In patients with acute subtype, achievement of complete remission with first line antiviral therapy resulted in a significantly improved survival (5-year OS of 82%) compared with patients who did not achieve CR (5-year OS 12%). In the OS analysis by subtype, patients with acute, chronic, and smoldering subtypes significantly benefited from first line antiviral therapy, whereas patients with lymphoma subtype had a better outcome with first line chemotherapy. Patients with chronic and smoldering subtypes who received first line antiviral therapy had an excellent survival (100% OS beyond 5 years) compared to those who received first-line chemotherapy with or without maintenance antiviral therapy (5-year OS of 42%). In patients with acute subtype, the corresponding survival rates were 28% and 10% respectively for antiviral therapy and chemotherapy with or without maintenance antiviral therapy. In patients with lymphoma subtype, first-antiviral therapy resulted in a significant survival disadvantage (median and 5-year OS were 7 months and 0%, respectively) compared with first-line chemotherapy with or without maintenance antiviral therapy (median and 5-year OS were 16 months and 18%). These results confirm that treatment of patients with ATLL using zidovudine and interferon results in a high response and complete remission rates particularly in acute, chronic and smoldering subtypes, but not in lymphoma subtype.

In the clinical trials for advanced NHL conducted by the Japan Clinical Oncology Group (JCOG), the CR rate and OS were poorer in ATLL treated with CHOP-like regimens compared to those with aggressive NHL. More intensive multidrug combination chemotherapy regimen [vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP), doxorubicin, ranimustine, and prednisone (AMP), and vindesine, etoposide, carboplatin, and prednisone (VECP)] has been reported to be more effective for patients with newly diagnosed aggressive ATLL. The 3-year OS rates were 24% and 13% respectively for VCAP-AMP-VECP arm and CHOP. However, VCAP-AMP-VECP regimen was also associated with significantly higher grade 3 or 4 toxicities neutropenia: 98% vs. 83%; thrombocytopenia: 74% vs. 17%) and infections rates (32% vs. 15%) than biweekly CHOP.
In small series of patients, doxorubicin-based chemotherapy with or without antiretroviral therapy and interferon has been shown to be effective in patients with ATLL. In a retrospective analysis of 36 consecutive patients diagnosed with HTLV-1 ATLL, Shapira et al reported that CHOP chemotherapy consistently improved survival compared to non-CHOP therapy (40-47 weeks vs. 6-11 weeks respectively in patients without hypercalcemia and 25-30 weeks vs. 10-12 weeks respectively in those with hypercalcemia). In another report, the overall median survival was 8 months for 29 patients diagnosed with an ATLL who received initial treatment with two cycles of CHOP followed by antiretroviral therapy. In a phase II trial conducted by the AIDS Malignancy Consortium, EPOCH chemotherapy followed by antiretroviral therapy was also found to be an active therapeutic regimen for ATLL, although it was associated with viral reactivation during induction chemotherapy.

Allogeneic HSCT (myeloablative and non-myeloablative) has been shown to improve the outcome suggesting a graft-versus-ATLL effect. In a retrospective analysis that included 40 patients who received myeloablative allogeneic HSCT, the median survival time of all cases after transplantation was 9.6 months. The estimated 3-year OS and RFS, and risk of disease relapse were 45.3, 33.8 and 39.3% respectively. There were 21 deaths after transplantation, and 16 were related to adverse events of transplantation. Acute and chronic graft-versus-host disease developed in 26 and 15 patients respectively. In this study, among 10 patients relapsed after transplantation, five patients achieved second CR; three achieved CR only by the reduction or cessation of immunosuppressive agents suggesting graft-versus-ATLL effect. In a recent retrospective analysis of 386 patients undergoing allogeneic HSCT, patient’s age (greater than 50 years), male sex, lack of complete remission at the time of transplant and the use of unrelated or cord blood were identified as adverse prognostic factors for OS.

NCCN Recommendations
Since there are no optimal treatment options, the guidelines have included enrollment in clinical trials as one of the options for all patients with ATLL. Prophylaxis with anti-Strongyloides agents and anti-infectious prophylaxis with sulfamethoxazole-trimethoprim are recommended for all patients.

Primary Therapy
Observation is an option for patients with chronic or smoldering subtypes since both these are considered indolent. Alternatively, these patients can be managed with skin-directed therapies (as recommend for patients with MFSS) or a combination of zidovudine and interferon.

For patients with acute or lymphoma subtype, there are no defined treatment options and efficacy of long-term treatment is limited. In a small series allogeneic transplant has been beneficial. The guidelines have included zidovudine and interferon or chemotherapy as options for patients with acute subtype. For patients with the lymphoma subtype, combination chemotherapy should be considered for primary therapy, since antiviral therapy is not effective for this group of patients. CNS prophylaxis (intrathecal methotrexate and cytarabine and corticosteroids) is recommended.

Outside of a clinical trial, if a patient is not responding or is progressing, on zidovudine and interferon, treatment should be stopped. If there is evidence of clinical benefit, treatment should continue until best response is achieved. The duration of initial therapy is usually 2 months. If life threatening manifestations occur, treatment can be discontinued before the two months period.
The optimal chemotherapy for patients with ATLL is not yet established. The regimens listed in the guidelines are based on institutional preferences and these include CHOP, EPOCH or hyper-CVAD.

**Response Assessment and Additional Therapy**

If there is CR after 2 months, continuation of zidovudine and interferon is recommended for patients with chronic or smoldering or acute subtype. Allogeneic HSCT should be considered for patients with acute or lymphoma subtype.

Patients with persistent or progressive disease following primary therapy should be treated with chemotherapy, clinical trial or best supportive care. Allogeneic HSCT should be considered for patients with acute or lymphoma subtype.

**Extranodal NK/T-Cell lymphomas, nasal type**

Mature NK/T-cell lymphomas are a rare and distinct subtype of NHL. NK/T-cell lymphomas are predominantly extranodal and majority of these are of nasal type. In the International PTCL project, among 1153 new adult cases of PTCL, extranodal NK/T-cell lymphomas (ENKL) were identified in 12% of patients (nasal 68%, extranasal 26%, aggressive or unclassifiable 6%). The frequency was higher in Asia than in Western countries. In the USA, the data from the Surveillance Epidemiology and End Results (SEER) registry database reported an increase in the incidence of ENKL, nasal type, from 1992 through 2005, with an annual percentage change of 11%. The incidences were also found to be higher in men and in people of Asian and Pacific Island descent.

In the 2008 WHO classification, mature NK-cell neoplasms are classified into 2 subtypes: ENKL, nasal type and aggressive NK-cell leukemia. However, ENKL may also have an extranasal presentation. ENKL, nasal type is often localized to the upper aerodigestive tract including the nasal cavity, nasopharynx, paranasal sinuses, hypopharynx, and larynx. The most common sites of involvement for extranasal subtype are skin, testis, gastrointestinal tract, soft tissues, and spleen. Majority of the patients with extranasal disease present with advanced stage (68%) and B symptoms (54%) compared to 27% and 39% respectively among patients with nasal type.

ENKL, nasal type has a better median overall survival compared to the extranasal type both in patients with early stage (2.96 vs 0.36 years) and advanced stage disease (0.8 vs 0.28 years).

**Diagnosis**

Most of the ENKL are characterized significant angiocentricity, necrosis and ulceration. Necrosis is thus very common in diagnostic biopsies and may delay diagnosis significantly. Biopsy specimen should include edges of the lesions, to increase the odds of having a viable tissue. It may be useful to perform multiple nasopharyngeal biopsies even in areas not clearly involved.

The most typical immunophenotype is CD20-, CD2+, CD56+, CD7+, CD8+, CD43+, CD45RO+, and cytoplasmic CD3ε+(surface CD3). ENKL usually lack the TCR and immunoglobulin gene rearrangements. Ki-67 expression is predictive of prognosis in patients with stage I/II ENKL, nasal type. High Ki-67 expression (65% or more) was associated with a shorter overall and disease-free survival. In multivariate analysis, Ki-67 expression and primary site of involvement were found to be independent prognostic factors for overall survival (OS) and disease-free-survival (DFS).

Histopathology and adequate immunophenotyping are essential to confirm the diagnosis. The recommended panel for immunohistochemistry includes CD3, CD5, CD10, BCL6, BCL2, CD20,
CD2, CD7, CD8, CD4, cytoplasmic CD3ε, CD56 and Ki67. EBV infection is always present and can be determined by EBV-encoded RNA in situ hybridization (EBER-ISH).

Workup
The workup should include complete ENT evaluation of nasopharynx involvement (including Waldeyer’s ring), testicles and skin, performance statuses, B symptoms, CBC with differential, platelets, comprehensive metabolic panel, measurement of serum uric acid, lactate dehydrogenase (LDH), CT scans with contrast of chest, abdomen and pelvis PET-CT scan with a diagnostic quality CT and dedicated CT of the nasal cavity, hard palate, anterior fossa or MRI of the nasopharynx. Bone marrow biopsy is recommended as part of the initial work up. Bone marrow involvement is uncommon at diagnosis and occurs in less than 10% of patients. Morphologically negative biopsies need evaluation by EBER-ISH and if positive considered involved.

Measurement of EBV-DNA viral load is useful in the diagnosis and possibly in the monitoring of the disease. EBV DNA viral load correlates well with clinical stage, response to therapy and poor survival. In multivariate analysis, EBV DNA 6.1 x 10^7 copies/mL or more at presentation was significantly associated with an inferior disease-free survival (27 months for those with less than 6.1 x 10^7 copies/ml compared to 0.5 months for patients with at least 6.1 x 10^7 copies/ml). Patients with undetectable trough EBV DNA during the clinical course had a significantly higher median OS (25 months) compared with patients with lack of normalization of EBV viremia.

IPI is most commonly used for patients with aggressive lymphomas. However, the use IPI in patients with ENKL is limited because most patients present with localized disease, rare involvement of bone marrow and the presence of constitutional symptoms even with localized disease. Recently, Lee et al have proposed a prognostic model specifically for patients with ENKL, nasal type, based on a large, retrospective, multicenter study that included 262 patients. This model identified 4 different risk groups with different survival outcomes based on the presence or absence of 4 prognostic factors (B symptoms, stage of the disease, LDH and regional lymph node involvement). The 5-year OS rates were 81% and 64% respectively for patients with no risk factors (Group 1-low risk) and one risk factor (Group 2-low-intermediate risk). The corresponding survival rates were 34% and 7% respectively for patients with 2 risk factors (Group 3-intermediate high risk) and 3 or 4 risk factors (Group 4-high risk). Local tumor invasion (LTI), defined as bony invasion and/or perforation or invasion of the skin, has also been associated with a low probability of complete response, reduced DFS and a high frequency (65%) of systemic failure in patients with stage I/II disease.

The guidelines recommend measurement of EBV DNA load and calculation of NK/T-cell prognostic index as part of initial work up.

Treatment
Initial treatment with RT alone has been effective in achieving favorable complete response rates compared to chemotherapy alone in patients with localized disease. RT doses of 50 Gy or more resulted in better overall and disease free survival. The 5-year OS and DFS rates were 75.5% and 60% respectively, compared to 46% and 33%, respectively for patients receiving RT doses of less than 54 Gy. In a retrospective review of 46 patients with localized disease, overall survival and failure-free survival was superior for patients treated with RT alone. The 5-year OS rates were 83% and 29% respectively for RT and chemotherapy; the 5-year failure-free survival (FFS) rates were
83.3% and 27%. In the chemotherapy group, salvage RT was superior to chemotherapy alone for OS (5-year OS rates were 42% and 20% respectively) or FFS (5-year FFS rates were 41% and 20%). Combined chemotherapy and RT was also superior to chemotherapy alone in terms of OS and FFS; the 5-year OS rates were 37.5% and 23% and the 5-year FFS rates were 27% and 23%.\textsuperscript{667} The benefit of adding RT to chemotherapy was also confirmed in the International Peripheral T-cell lymphoma Project that retrospectively reviewed the clinical outcome of 136 patients with early-stage ENKL, nasal type.\textsuperscript{649} The 3-year OS rate was 57% compared to 30% for patients who received chemotherapy alone. Extranasal disease, however, was less amenable to RT.

Recently, concurrent chemoradiation has been reported to be a safe and effective treatment for the treatment of localized disease.\textsuperscript{671, 672} In the phase I/II study conducted by the Japanese Clinical Oncology Group (JCOG0211), high risk patients with stage I/II nasal disease (lymph node involvement, B symptoms and elevated LDH) were treated with concurrent RT (50 Gy) and 3 courses of chemotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC).\textsuperscript{572} With a median follow-up of 32 months, the 2-year OS was 78% and the overall response rate was 81%. Similar results were reported by a Korean study group which evaluated concurrent chemoradiotherapy (CCRT) with cisplatin and RT (40-53 Gy) followed by three cycles of etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD).\textsuperscript{571} Majority of the patients had stage I/II disease (21 patients) and 9 patients had stage III/IV disease, as determined by the NK-cell prognostic index. The complete response rate was 73% after CCRT which increased to 80% after VIPD chemotherapy. The estimated 3-year, PFS and OS rates were 85% and 86% respectively. The results of these two studies support the use of concurrent chemoradiotherapy for patients with stage I/II disease.

Concurrent chemoradiation therapy is also the primary treatment option for patients with advanced stage disease and local RT an essential adjunct for local control. NK-cells are associated with a high expression of P-glycoprotein leading to multidrug resistance that is responsible for poor response to conventional chemotherapy.\textsuperscript{673} Several studies have confirmed the efficacy of L-asparaginase-based regimens for patients with advanced, relapsed or refractory disease.\textsuperscript{674-677} In a series of 45 patients with refractory and relapsed ENKL, nasal type treated with L-asparaginase-based chemotherapy followed by involved-field RT, the overall response rate was 82% (55% CR and 27% PR). Both 3-year and 5-year OS rates were 67%.\textsuperscript{676} The efficacy of L-asparaginase in combination with methotrexate and dexamethasone (AspaMetDex regimen) was evaluated in a phase II intergroup study in patients with refractory or relapsed ENKL.\textsuperscript{674} After 3 cycles, patients with localized disease were treated with consolidative RT, if not received previously and those with disseminated disease received high-dose therapy with peripheral blood stem cell infusion. Objective responses were achieved in 14 of the 18 evaluable patients after 3 cycles. Eleven patients had complete remission (61%). The median OS was 1 year, with median response duration of 12 months. The absence of anti asparaginase antibodies and the disappearance of EBV-DNA were significantly associated with a better outcome.

More recently, in a phase I study, Yamaguchi et al demonstrated the safety and efficacy of new L-asparaginase-based combination chemotherapy regimen called SMILE (steroid = dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) in patients with newly diagnosed stage IV, relapsed or refractory disease.\textsuperscript{677} After 2 cycles, the overall response rate was 67% and the complete
response rate was 50%. Based on these results a larger phase II study evaluated SMILE regimen with growth factor support in 39 patients including 21 with newly diagnosed stage IV disease, 13 in first relapse and 5 with primary refractory disease. A total of 29 patients (74%) completed the planned treatment with overall and complete response rates of 74% and 38%, respectively. EBV-DNA copy number was also predictive for response and adverse events after SMILE chemotherapy. The overall response rate was 88% in patients with less than $10^5$ copies/mL EBV-DNA in whole blood, but was 44% in patients with more than $10^5$ copies/mL; grade 4 non-hematologic toxicity was significantly higher in patients with more than $10^4$ copies/mL of EBV-DNA in plasma (55% vs. 14%). Although preliminary, these data indicate that L-asparaginase-based regimen is a reasonable option for patients with advanced, relapsed or refractory disease. Long-term benefit needs to be confirmed in larger randomized clinical trials.

High-dose therapy with autologous stem cell rescue (HDT/ASCR) has been evaluated as a consolidation therapy for patients with early and advanced-stage disease responding to primary therapy. In retrospective analyses disease status at the time of HDT/ASCR was the most important prognostic factor for survival and relapse free survival in patients with early-stage as well as advanced stage disease. In patients who were in complete response at the time of HDT/ASCR, 5-year disease-specific survival rates were significantly higher in the transplant group compared with the control group (87% and 68% respectively). When stratified by risk based on NK/T-cell prognostic index, there was no significant difference in survival between the transplant and control groups for patients with low risk (disease-specific 5-year survival rate were 87% for transplant vs 69% for the control group), whereas among patients in the high-risk group, the survival benefit was statistically significant between the 2 groups.

NCCN Recommendations

Since ENKL are rare and there has been no randomized trials comparing different regimens, there is no standard therapy for patients with ENKL. Most of the available data are from retrospective analyses and small prospective series. It is preferred that patients with ENKL are treated at centers with expertise in the management of this disease and enrolled on clinical trials.

**Induction Therapy**

In the NCCN guidelines, patients are stratified by nasal versus extranasal disease at presentation and then by the stage of the disease. Patients with stage I disease are further stratified based on risk factors (60 years or older, B symptoms, ECOG performance status of 2 or more, regional lymph node involvement, LTI, LDH, histological evidence of high Ki-67 staining and EBV DNA $6.1 \times 10^7$ copies/mL or more).

Enrolment on a clinical trial is the preferred option for all patients with any stage disease. Selected patients with stage I nasal disease without risk factors can be treated with RT (50 Gy or more) alone. Alternatively, they can be treated similar to patients with stage I disease with risk factors or stage II disease, with concurrent chemoradiation therapy [RT (50 Gy) and 3 courses of DeVIC or concurrent RT(40-53 Gy) and cisplatin followed by 3 cycles of VIPD]. L-asparaginase-based combination chemotherapy (SMILE regimen) with or without RT or concurrent chemoradiation therapy [RT (50 Gy) and 3 courses of DeVIC or concurrent RT(40-53Gy) and cisplatin followed by 3 cycles of VIPD] are included as options for patients with stage III-IV nasal disease and stage I-IV extranasal disease.
Response Assessment and Additional Therapy

Patients are restaged after induction therapy. Restaging should include appropriate imaging studies (CT, MRI or PET-CT), endoscopy with visual inspection, repeat biopsies and measurement of EBV DNA. The role of PET scan is not well established.

No further treatment is necessary for patients with stage I nasal disease achieving complete response to induction therapy. Hematopoietic stem cell transplant (HSCT) is a reasonable option for patients with stage I nasal disease achieving a partial response if eligible, HSCT should be considered for all patients with stage II-IV nasal disease and stage I-IV extranasal disease achieving complete or partial response to induction therapy.

For patients with refractory disease, L-asparaginase-based chemotherapy, as described for induction therapy may offer benefit. There is limited data regarding the role of HSCT in this patient population. Allogeneic HSCT has been evaluated and in a series of 25 patients, at a median follow-up of 34 months, the 2-year progression-free and overall survival rates were 34% and 40%, respectively. Reduced-intensity non-myeloablative allogeneic transplant is associated with lower transplant-related mortality (20% vs. 30% for myeloablative HSCT) with an equivalent overall response rate (52% and 60% respectively). Salvage chemotherapy or best supportive care is recommended for all patients with refractory disease.

Post-transplant lymphoproliferative disorders

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphoid neoplasms following solid organ transplantation (SOT) and allogeneic HSCT. PTLD following autologous HSCT is very rare. The majority of PTLD following both allogeneic HSCT and SOT are of B-cell origin and are usually associated with Epstein-Barr virus (EBV). EBV-negative PTLD has been shown to be a late serious complication of transplantation. Gene expression profiling studies have shown that EBV-negative PTLD are biologically distinct from their EBV-associated counterparts. PTLD following HSCT are usually of donor B-cell origin, whereas PTLD following SOT are of recipient B-cell origin in the majority of cases, though donor-derived cases typically involving the grafted organ have been reported.

In EBV-PTLD following SOT, clinical stage, poor performance status, EBV seronegativity, elevated lactate dehydrogenase (LDH) ratio, organ dysfunction, and multi-organ involvement by PTLD were identified as poor prognostic factors. In contrast to PTLD following SOT, EBV seronegativity and graft organ involvement were not of any predictive value in patients with PTLD following allogeneic HSCT. Major risk factors for the development of PTLD in this group of patients include the use of unrelated or HLA-mismatched related donors, T-cell depletion of the donor graft and the use immunosuppressive therapy for the prophylaxis and treatment of acute graft-versus-host disease.

In the WHO classification, PTLD are classified into 4 major categories: early lesions, monomorphic PTLD, polymorphic PTLD and classical Hodgkin lymphoma (CHL)-type PTLD. Early lesions develop within a year of transplantation and are more common in transplant recipients that are EBV naive. Early lesions consist of 2 histological subtypes, plasmacytic hyperplasia and infectious mononucleosis-like PTLD. Monomorphic PTLD most commonly resembles diffuse large B-cell lymphoma (DLBCL) but some lesions, although less common, can resemble Burkitt lymphoma, plasma cell myeloma or plasmacytoma. Unlike the EBV-positive PTLD, monomorphic lesions are more common among patients with EBV-negative PTLD. Polymorphic PTLD
can be either polyclonal or monoclonal, although the former subtype is very rare.17

**Diagnosis**

Histopathology and adequate immunophenotyping are essential to confirm the diagnosis.697, 698 BCL6, MUM-1 and CD138 can be useful in distinguishing between the histological subtypes of PTLD.699, 700 BCL-6 expression was detected in majority of monomorphic PTLD (71%) whereas it was consistently absent in polymorphic PTLD. MUM1 was preferentially expressed in 92% of polymorphic PTLD.699 Overall, BCL6-, MUM1(+) and CD138(-) phenotype is associated with polymorphic PTLD whereas BCL6(+), MUM1(+/-) and CD138(-) is associated with monomorphic PTLD. The recommended panel for immunohistochemistry includes CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, and Ki67. Cell surface markers CD3, CD5, CD7, CD4, CD8, CD19, CD20, CD10, kappa and lambda are recommended analysis by flow cytometric analysis.

EBV detection can be done either by immunohistochemistry for latent membrane protein-1 (LMP-1) or EBV-encoded RNA in situ hybridization (EBER-ISH). EBER-ISH is more sensitive than immunohistochemistry, but it not required in most cases.697 If immunostaining for LMP-1 is positive, EBER-ISH is not required.

Immunoglobulin heavy chain variable (IGHV) gene mutations are seen in majority of PTLD, with the exception of early lesions.701 Genetic alterations in MYC, NRAS and TP53 are seen only in monomorphic PTLD.700 BCL6 mutations have been associated with shorter survival and poor response to therapy.702 Molecular genetic analysis to detect IGHV rearrangements and BCL6 mutations could be useful in selected cases.

**Workup**

The workup should include evaluation of performance status, prior history of immunosuppressive therapy, complete blood count, measurement of serum albumin, LDH and other electrolytes, CT scans of chest, abdomen and pelvis. PET-CT scan, bone marrow evaluation and brain MRI may be useful in selected cases. EBV-DNA viral load by quantitative PCR can aid in the diagnosis as well as monitoring treatment responses in patients with PTLD. Plasma or peripheral blood mononuclear cells (PBMC) are useful for measuring EB viral load, some studies have shown that viral load in plasma is more sensitive than PBMC in the diagnosis of PTLD.703, 704 Cytomegalovirus (CMV) has also been associated with an increased risk of PTLD in EBV-seronegative patients.705 PCR for the measurement of EBV and CMV can be useful for selected patients. PTLD tends to involve extranodal sites including the central nervous system. In such cases, cerebrospinal fluid (CSF) analysis for EBV-DNA viral load by quantitative PCR is diagnostic.

**Treatment**

While guidelines have been published, the optimal treatment for PTLD is not defined due to lack of randomized controlled trials.706 Reduction in immunosuppression (RIS) remains the first step in the management of nearly all cases of PTLD.695, 707, 708 The role of antiviral therapy has been controversial since the majority of PTLD are associated with latent EBV. Replicating EBV DNA has been reported in about 40% of EBV-associated lymphoproliferative disorders in immunocompromised patients.709 Antiviral drugs targeting EBV replication may be beneficial in this subset of patients with early or polymorphic PTLD.710

Several phase II studies and retrospective analyses have confirmed the efficacy of rituximab monotherapy in the treatment of patients with...
PTLD. In a prospective multicenter study, rituximab induced responses 44% of patients with an overall survival rate of 67% at one year. Another prospective multicenter phase II study demonstrated that extended treatment with rituximab induced a high rate of CR in patients with PTLD after solid organ transplantation without increasing toxicity. In a recent multicenter retrospective analysis, rituximab significantly improved PFS and OS in patients with PTLD. With a median follow-up of 40 months, the 3-year PFS and OS rates were 70% and 73% respectively for patients who received rituximab-based therapy as part of initial treatment. The corresponding survival rates were 21% and 33%, respectively, for patients who received initial treatment without rituximab. This study identified hypoalbuminemia, CNS and bone marrow involvement as prognostic indicator for progression and survival. The 3-year PFS rates were 84%, 66% and 7%, respectively for patients with 0, 1 and 2 or more adverse factors. The corresponding 3-year OS rates were 93%, 68% and 11%, respectively.

Anthracycline-based chemotherapy with or without rituximab has also been effective in the treatment of patients with PTLD. In a retrospective analysis, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) induced an overall response rate of 65%, with a median follow-up of 9 years. Median overall and progression-free survivals were 14 and 42 months, respectively. Chemotherapy and RIS, with or without rituximab has also been reported to induce durable complete remission with reduced the risk of graft impairment, when used as first-line treatment.

Adoptive immunotherapy using autologous or allogeneic EBV-specific cytotoxic T-lymphocytes (EBV-CTL) has been investigated. In a long-term follow-up study, EBV-CTL therapy was very effective as a prophylaxis or treatment of patients with PTLD following HSCT. In a recent retrospective analysis, the use of EBV-CTL significantly reduced the risk of death due to EBV-PTLD in HSCT recipients. Partially HLA-matched allogeneic EBV-CTL therapy has also been reported to be a safe and effective option for PTLD. However, further studies are needed to confirm these findings.

NCCN Recommendations

Primary Treatment

Treatment options for PTLD depend on the histological subtype and should be individualized. RIS is the primary treatment for patients with early lesions. EBV-positive patients could be treated with ganciclovir. For patients with localized polymorphic PTLD, options include surgery, RT or rituximab, whereas chemoimmunotherapy or rituximab is recommended for patients with systemic polymorphic PTLD. Alternatively, this group of patients can be treated with RIS or with ganciclovir, if EBV-positive.

RIS or chemoimmunotherapy are recommended for patients with monomorphic PTLD. However, response to RIS is variable and patients should be closely monitored. Patients unable to tolerate chemotherapy could be treated with single agent rituximab.

Second-line treatment

Treatment options are dependent on response to primary treatment and histological subtype. The guidelines recommend continuation of RIS for patients with early lesions achieving complete response to primary treatment, whereas those with persistent or progressive disease should be treated with rituximab. Monitoring viral load with EBV-PCR is recommended for all patients receiving second-line therapy.

Continuation of RIS and monitoring viral load with EBV-PCR or maintenance rituximab are recommended for patients with polymorphic
PTLD achieving complete response to primary treatment.
Chemoimmunotherapy or EBV-CTL infusion (if EBV-positive) are included as options for patients with persistent or progressive disease.

Patients with monomorphic lesions achieving complete response to primary treatment should be managed according to the specific treatment guidelines based on their histology. For patients with persistent or progressive disease, second-line treatment options are dependent on prior therapy. Rituximab or chemoimmunotherapy are options for patients who received RIS as primary treatment, whereas patients who received rituximab alone as initial therapy should be treated with chemoimmunotherapy. EBV-CTL infusion is an option for EBV-positive patients.

The guidelines recommend clinical trial as an option for patients with persistent or progressive polymorphic and monomorphic lesions following initial treatment.
Marginal Zone Lymphomas

Marginal zone lymphomas (MZL) are a heterogeneous group of disorders consisting of extranodal marginal zone lymphoma (MALT lymphoma), nodal MZL, and splenic MZL. MALT lymphomas are subdivided into the gastric and non-gastric lymphomas. Splenic MZL involves the spleen and bone marrow, whereas nodal MZL occurs primarily in the lymph nodes though additional extra nodal sites are common.

Adequate hematopathology and immunophenotyping are needed to establish a diagnosis. The typical immunophenotype of MZL is CD5-, CD10-, CD20+, CD23-/+ , CD43-/+ , cyclin D1-, bcl-2 follicles-. In addition splenic marginal zone lymphoma is characterized by annexin-1- and CD103-. Immunophenotyping is useful in distinguishing MZLs from CLL (CD5+) and MCL (CD5+) and hairy cell leukemia, which is characterized by annexin-1+ and CD103+. MZLs have been shown to be associated with infectious agents, but this association has not been validated.\textsuperscript{733-735}

Workup

The workup for gastric MALT lymphoma is similar to the workup for other NHLs. Special aspects of the workup for gastric MALT lymphoma include direct endoscopic assessment of the gastrointestinal tract and additional evaluation of the tumor specimen for the presence of \textit{H.pylori}. The presence of \textit{H.pylori} infection must be confirmed by biopsy with PCR (polymerase chain reaction) and urea breath test. Nondiagnostic atypical lymphoid infiltrates that are \textit{H.pylori} positive should be re-biopsied to confirm or exclude lymphoma prior to treatment of \textit{H.pylori}. Appropriate imaging studies include CT of the chest, abdomen and pelvis, and in select cases, bone marrow biopsy. At some NCCN institutions, endoscopic ultrasound (EUS) is used to complement conventional endoscopy at the time of the initial workup and at follow-up. EUS also provides information regarding the depth of involvement in the gastric wall that is essential information in some of the currently used staging systems.

Staging

Several different staging systems have been for gastric MALT lymphomas. In the Lugano staging system, Ann Arbor stage III has been removed and supradiaphragmatic nodal disease is included under stage IV. TNM (Tumor-Node-Metastasis) staging system corresponds to the staging in gastric cancer and the depth of the lymphoma infiltration is measured by EUS. Involvement of multiple extranodal sites in MALT lymphoma appears to be biologically distinct from multiple extranodal involvements in other lymphomas, and these patients may be managed by treating each site separately with excision or RT. In contrast, cases with disseminated nodal involvement appear to behave more like nodal MZL or like disseminated FL.
**Treatment**

_H. pylori_ infection plays a central role in the pathogenesis of some cases of gastric MALT lymphoma. The efficacy of antibiotic therapy for the treatment of gastric MALT lymphoma has been evaluated in numerous trials. Approximately two thirds of patients with localized gastric MALT lymphoma have a complete tumor remission after eradication of _H. pylori_ infection with antibiotic therapy. However, there is increasing evidence that late relapses occur after antibiotic management and a long duration of follow-up is appropriate.

For disease confined to the stomach (stage IE, _H. pylori_ positive), treatment begins with antibiotics in combination with a proton pump inhibitor to block gastric acid secretion. The tumor response may be slow, and re-evaluation with endoscopy should not be done until 3 months post treatment unless clinical deterioration is evident. If there is evidence of the t(11;18), t(1;14), t(14;18)(q32;q21), treatment of the _H. pylori_ infection with antibiotics may be ineffective and these patients should be considered for alternative therapy. _H. Pylori_ infection is not evident in approximately 10-40% of patients with gastric MALT lymphomas. IFRT is preferred for patients with disease that is extending to the muscularis or disease extending from the GI tract to adjacent organs (stages IE [T2 or T3] or IIE _H. pylori_ negative), particularly if one of the t(11;18), t(1;10), or t(14;18)(q32;q21) translocations is present. Rituximab or chemoimmunotherapy are other treatment options.

In patients with disseminated disease (stage III or IV), treatment is similar to that described for other advanced-stage indolent lymphomas. As with other indolent lymphoma, asymptomatic patients without indications for treatment are monitored without therapy. The decision to treat is guided by end-organ dysfunction or the presence of symptoms (such as bleeding, early satiety), bulky disease at presentation, steady progression of disease, or patient preference. Treatment may include single-agent or combination chemotherapy, or locoregional RT. If there is evidence of recurrence, patients are managed according to the FL guidelines. Surgical resection is generally limited to specific clinical situations. Though disease control is excellent with total gastrectomy, the long-term morbidity has precluded routine surgical resection. Total gastrectomy is necessary because of the multi-focal nature of the disease.

**Follow-Up Endoscopy**

Following primary antibiotic therapy, patients are restaged with endoscopy and biopsy after 3-months. Patients with responsive disease (microbiologic and tumor response) are just observed. Patients with persistent lymphoma with no evidence of _H. pylori_ are treated with RT, if they are symptomatic or if there is significant disease progression. Asymptomatic patients can be observed for 3 months. Locoregional RT can be considered as early as 3 months after observation but observation can be prolonged for up to 18 months (category 2B). Patients with persistent _H. pylori_ and regressing or stable lymphoma are treated with second-line antibiotics. Lastly, patients who are _H. pylori_ positive with persistent lymphoma are treated with RT, if they have progressive disease. Those with stable disease are treated with second-line antibiotics.

Follow-up surveillance at 6 months consists of repeat endoscopy and biopsy. Patients can be subdivided into the same four groups, as above. Patients with complete tumor response continue to be observed if the _H. pylori_ is negative, or they can be treated with other antibiotic therapy if _H. pylori_ remains positive. Patients with persistent or recurrent lymphoma after antibiotic therapy, irrespective of their _H. pylori_ status, are treated with locoregional RT if not previously
treated. Patients whose disease does not respond to radiation are managed with single-agent or combination chemotherapy similar to FL. Following second-line antibiotic therapy or RT, patients are again evaluated with endoscopy and biopsy to rule out large cell lymphoma. Systemic therapy as indicated for follicular lymphoma is recommended for recurrence following CR to RT or antibiotic therapy, or for patients with no response to prior RT.

**Non-gastric MALT Lymphomas**

Nongastric MALT lymphomas can arise from a large number of non-gastric sites such as lung, thyroid, salivary glands, breast, and tissues surrounding the eye. For patients with stage IE-II disease or extranodal disease involving multiple sites, locoregional RT (20-30 Gy) is appropriate. Surgery may be considered for certain sites of disease (eg, lung, skin, thyroid, colon, small intestine, and breast). If there is no residual disease following surgery, patients are observed, whereas those with positive surgical margins are treated with locoregional RT. Recurrence following primary treatment is managed similar to advanced stage FL. RT is an option for those with local recurrence. Patients with advanced-stage disease (stage III-IV) are managed the same as patients with FL. Aggressive histologies, in which MALT lymphomas coexist with large cell lymphoma, should be managed according to the diffuse large B-cell practice guidelines.

**Nodal Marginal Zone Lymphoma**

Nodal MZL is rare and often presents concurrently with extranodal sites of disease. The diagnosis of nodal MZL requires careful evaluation to rule out extranodal sites of disease and it must be distinguished from nodal FL, MCL, lymphoplasmacytic lymphoma and CLL, all of which are more common. Nodal MZL is managed as per FL.

**Splenic Marginal Zone Lymphoma**

**Diagnosis**

Splenic MZL is often presumptive based on the findings of splenomegaly with peripheral blood flow cytometry usually revealing a monoclonal B cell population. Involvement of the bone marrow is also common. This lymphoma is distinguished from CLL by the absence of CD5 expression, strong CD20 expression and variable CD23 expression. In some cases, the diagnosis can be established by the finding of villous projections on the circulating lymphocytes. Splenectomy can definitively establish the diagnosis and in many cases is therapeutic as well.

**Workup**

The workup is similar to the other indolent lymphomas. Flow cytometry of peripheral blood and bone marrow is essential in identification of a monoclonal B cell population. CT of the chest, abdomen, and pelvis will help in establishing the extent of disease. Hepatitis C has been associated with and implicated in the pathogenesis of splenic MZL and should be evaluated for all patients suspected of having this diagnosis.

**Treatment**

Most of the patients with no splenomegaly, cytopenia or other symptoms can be observed. Patients presenting with splenomegaly are treated depending on their hepatitis C status. Hepatology evaluation is recommended for hepatitis C positive patients; anecdotal tumor regressions have been reported in responses to hepatitis therapy. In all other patients, in the absence of cytopenias or other symptoms, patients should be observed.
In a retrospective study, rituximab-based treatments resulted in longer failure free survival in patients with splenic MZL compared to patients treated with chemotherapy alone.\textsuperscript{746} Rituximab was superior to splenectomy in normalizing white blood cell and absolute lymphocyte counts. Splenomegaly also disappeared in 92% of the patients treated with rituximab alone.

Splenectomy is the preferred option for patients with cytopenias or symptoms of weight loss, early satiety or abdominal pain. Rituximab is another treatment option for this group of patients. Patients should be monitored on a regular basis. If there is disease progression, patients are managed similar to advanced stage FL.

**Mantle Cell Lymphoma**

**Diagnosis**

Mantle cell lymphoma can be readily distinguished from other small lymphocytic lymphomas due to the widespread availability of appropriated diagnostic reagents.\textsuperscript{747} The diagnosis can be established by histological examination in combination with immunohistochemistry with a profile consisting of CD5+, CD10-/+, CD20+, CD23-, CD43+, and cyclin D1+. Rare cases of MCL may include CD5- or CD 23+ immunophenotype. The diagnosis of MCL requires the expression of cyclin D1, an opinion shared by the panel.\textsuperscript{748} However, recent gene profiling data suggests that cyclin D1 expression may not be required for the molecular signature of MCL; in these cases, over-expression of cyclin D2 or D3 can be observed.\textsuperscript{749} Cases with a typical immunophenotype, CD5+, CD23-, CD20+ that are cyclin D1- should be evaluated for cyclin D2 and D3 expression; positive cases should be classified as MCL with a variant immunophenotype, negative cases should be classified as variant SLL/CLL. Currently available reagent for immunohistochemistry of cyclin D1 are robust and yield good staining; however, in some cases cytogenetics or FISH for the t(11;14), juxtaposing the cyclin D1 locus with the IgH locus can be diagnostically helpful.\textsuperscript{750}

**Workup**

The workup for MCL is similar to the workup for many indolent lymphomas and certain aggressive lymphomas. MCL is a systemic disease with frequent involvement of the bone marrow, gastrointestinal tract and frequently a leukemic phase. For this reason, both the peripheral blood and bone marrow must be carefully evaluated for the presence of malignant cells. Chest, abdominal, and pelvic CT scans are routinely performed. MCL may present as lymphomatous polyposis coli and colon involvement is common.\textsuperscript{751} In the current guideline, colonoscopy is now considered a routine part of the evaluation of MCL. Post treatment colonoscopy is necessary to confirm a CR, if it was not done previously. Upper endoscopy and neck CT scan may be helpful in selected cases. In patients with the blastic variant, lumbar puncture is done to evaluate the spinal fluid for involvement.

**Treatment**

It has generally been thought that MCL has the worst characteristics of both indolent and aggressive non-Hodgkin’s lymphomas owing to the incurability with conventional chemotherapy and it more aggressive growth pattern. However, emerging data suggests that the long-term outcome of patient with MCL may be improving.\textsuperscript{752} There remains no established standard of care. In the absence of standard management for MCL, patients with this disease should be referred for participation in prospective clinical trials. Like the management of patients with indolent lymphoma patients with MCL often have highly individualized course of care.
Several regimens have shown significant activity in newly diagnosed MCL, but none of these regimens are curative in patients with advanced disease.\(^753,754\) Recent metal analysis has shown that the addition of rituximab to chemotherapy increases response rates but it has not yet been proven to extend either progression-free or OS.\(^242\) R-CHOP was significantly superior to CHOP in terms of overall response rate (94% v 75%), complete remission rate (34% v 7%).\(^755,756\) No differences were observed for PFS. In patients with newly diagnosed MCL, R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with R-MA (rituximab plus high-dose methotrexate and cytarabine) produced a 3-year failure-free survival (FFS) rate of 64% and OS rate of 82%.\(^757\) However, in a subset of patients more than 65 years of age, this regimen was associated with shorter FFS and significant toxicity. R-HyperCVAD was evaluated in a multicenter SWOG study that reported a CR/CRu rate of 58% and 2-year PFS of only 63%.\(^758\) Modified R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen developed by the Wisconsin Oncology Network, produced favorable overall response rate (77%) and CR rate (64%) with acceptable toxicity in patients with untreated MCL.\(^759\) This is being tested more widely in an ongoing ECOG trial. RIT has also been investigated as initial therapy as well as second-line treatment for refractory or relapsed MCL as reviewed by Zelenetz.\(^754\)

Few patients present with localized MCL and the available published literature on management is retrospective and anecdotal. In a retrospective analysis of 26 patients with early stage MCL, inclusion of RT was associated with an improved PFS and a trend towards improved OS.\(^760\) Outside of a clinical trial, the panel recommended IFRT with or without combination chemotherapy. These recommendations are based on treatment principles in the absence of more definitive data.

Majority of patients with MCL will have advanced stage disease and require systemic therapy. Highly selected patients who are asymptomatic with stable adenopathy and non-bulky disease are observed; these patients usually have low bulk, nodular morphology variant and a low proliferation fraction. Based on the available data, the panel has included R-HyperCVAD and R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)\(^762\) as options for first-line therapy. In patients older than 65 years of age, the panel recommends the use of modified HyperCVAD regimen with rituximab maintenance. CHOP (with or without rituximab) is recommended for selected older patients who cannot tolerate intensive therapy.

Initial remission should be followed by HDT/ASCR in eligible patients, as this has been associated with some evidence of durable remission. In a study conducted by M.D. Anderson Cancer Center, ASCR following treatment with hyperCVAD regimen for cytodestruction prolonged OS in patients with MCL in first disease remission, especially in those with a low beta-2-microglobulin level.\(^761\) In a randomized trial conducted by European MCL network, patients 65 years of age or younger with advanced-stage MCL were randomized to ASCR or maintenance with interferon-alpha after achieving of complete or partial remission by CHOP-like chemotherapy. Three-year OS was 83% after ASCR versus 77% in the IFN group.\(^762\)

The optimal approach to recurrent disease remains to be defined. Fludarabine-based combination regimens such as fludarabine in combination with cyclophosphamide\(^763\) and FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) have shown activity in
MCL. In a prospective randomized study of the GLSG, addition of rituximab to the combination of fludarabine, cyclophosphamide, mitoxantrone, produced significantly longer OS in patients with relapsed and refractory MCL.\textsuperscript{250} Cladribine also has shown activity in patients with untreated or relapsed MCL, achieving a response rate of 58\%.\textsuperscript{764} In a phase II trial, the proteosome inhibitor bortezomib induced 33\% response rate including 8\% CR in patients with relapsed or refractory MCL.\textsuperscript{765} Median time to progression was 6.2 months. Based in these data, bortezomib received FDA approval for the treatment of patients with MCL who have received at least one prior therapy. Studies of bortezomib-based combinations in MCL are ongoing. Marked anti-tumor activity has been shown for rituximab plus thalidomide in patients with relapsed or refractory MCL.\textsuperscript{766} Lenalidomide, an immunomodulator related to thalidomide also has activity in MCL either alone or in combination with rituximab.

Bendamustine is an emerging agent (recently approved for the treatment of CLL) that has well-documented activity in patients with MCL. In a phase II study conducted by the German study group (which included low grade NHL and MCL patients), the subset of patients with relapsed or refractory MCL treated with the combination of bendamustine and rituximab has an overall response rate of 75\% with a CR rate of 50\%.\textsuperscript{767} Median follow-up duration was 20 months. The median PFS for MCL patients was 18 months whereas the median PFS for patients with FL had not been reached. Further studies are needed to confirm these findings.

Based on the efficacy data available in the literature, the combination of bendamustine with or without rituximab is included in the guidelines as an option for second-line therapy for patients with relapsed or refractory MCL, with a category 2B recommendation since no data is available yet from randomized studies and there was not uniform consensus among the panel. Ongoing phase III studies are evaluating the efficacy of bendamustine plus rituximab vs. R-CHOP in previously untreated MCL patients. The panel felt that additional follow-up from this study was necessary prior to making recommendations regarding initial therapy. The same combination is also being compared to fludarabine with rituximab in relapsed MCL.

Patients with relapsed disease following CR to induction therapy, those who obtain only a PR to induction therapy or those with progressive disease are appropriate candidates for clinical trials of high-dose therapy with autologous or allogeneic stem cell rescue.\textsuperscript{768} Alternatively, these patients can also be treated with second-line chemotherapy.
References


46. Meza BA, Buss DH, Woodruff RD, et al. Diagnosis and subclassification of primary and recurrent lymphoma. The usefulness and limitations of combined fine-needle aspiration cytomorphology and


75. Ludwig E, Mendelsohn RB, Taur Y, et al. Prevalence of hepatitis B surface antigen and hepatitis B core antibody in a population initiating...


237. McLaughlin P, Fuller L, Redman J, et al. Stage I-II low-grade lymphomas: a prospective trial of combination chemotherapy and...


285. Hainsworth JD, Litchy S, Shaffer DW, et al. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-


314. Pfreundschuh M, Kuhnt E, Trumper L, et al. Randomised Intergroup Trial of First line Treatment for young Low-Risk Patients (<61 years) with Diffuse Large B-Cell Non-Hodgkin's Lymphoma (DLBCL) with a CHOP-like Regimen with or without the Anti-CD20 Antibody Rituximab - 6-Year Follow-up of the Mint Study of the MabThera International Trial (MiST) Group. Blood 2010;116:111. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/111.


348. Hoppe BS, Moskowitz CH, Zhang Z, et al. The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse


Available at:
http://abstracts.hematologylibrary.org/cgi/content/abstract/112/11/1929.


401. Dunleavy K, Little RF, Pittaluga S. A prospective study of dose-adjusted (DA) EPOCH with rituximab in adult with newly diagnosed Burkitt lymphoma: a regimen with high efficacy and low toxicity. Annals of Oncology 2008;19 (suppl_4):iv83-84 Available at:
http://annonc.oxfordjournals.org/content/19/suppl_4.


411. Terwey TH, Massenkeil G, Tamm I, et al. Allogeneic SCT in refractory or relapsed adult ALL is effective without prior reinduction chemotherapy. Bone Marrow Transplant 2008;42:791-798. Available at:


413. Mbulaiteye SM, Parkin DM, Rabkin CS. Epidemiology of AIDS-related malignancies an international perspective. Hematol Oncol Clin


518. Popplewell L, Pro B, Jacobsen E, et al. Stem cell transplant (SCT) and pralatrexate therapy: outcome of patients with relapsed or refractory peripheral T-cell lymphoma who received SCT prior to or following pralatrexate therapy [abstract]. Blood 2009;114:Abstract 3420. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/3420.


621. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the


