

# LYMPHOMA

Effective Date: September 2019

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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## BACKGROUND

Lymphomas encompass a group of lymphoproliferative malignant diseases that originate from T- and B-cells in the lymphatic system. Traditionally, lymphomas have been subcategorized into two groups: Hodgkin lymphoma and non-Hodgkin lymphoma. It is now known however, that Hodgkin lymphoma is simply one of the numerous varieties of lymphoma, and that non-Hodgkin lymphoma is a fairly meaningless term, representing all of the other subtypes of this disease.

Non-Hodgkin lymphoma involves a heterogeneous group of over 40 lymphoproliferative malignancies with diverse patterns of behaviours and responses to treatments. Non-Hodgkin lymphoma is much less predictable than Hodgkin lymphoma and prognosis depends on the histologic type, stage, and treatment. In Canadian males and females, the incidence rates for non-Hodgkin lymphoma showed a marked increase by approximately 50% between 1978 and the late 1990s, but have since stabilized.<sup>1</sup> Mortality rates have followed a similar pattern. The clearest risk factor for the disease is immunosuppression associated with HIV infection, or medications used to prevent rejection in organ transplantation. Other factors that increase risk of non-Hodgkin lymphoma are poorly understood but may include occupational exposures to pesticides, herbicides, and dioxins, as well as chronic immune stimulation associated with autoimmune disorders (e.g. thyroiditis, Sjogren's Syndrome, SLE) or infections (e.g. *Helicobacter pylori* gastritis, hepatitis C virus).<sup>2</sup> In 2015, it is estimated that 8200 new cases of non-Hodgkin lymphoma will be diagnosed in Canada, and 2650 deaths will occur, making non-Hodgkin lymphoma the sixth most common cause of cancer-related death in Canada.<sup>3</sup>

Hodgkin lymphoma is a malignancy characterized histopathologically by the presence of Reed-Sternberg cells in the appropriate cellular background. Although rare, Hodgkin lymphoma is one of the best-characterized malignancies of the lymphatic system and one of the most readily curable forms of malignant disease.<sup>2</sup> The incidence rate has remained fairly steady over time, it is estimated that approximately 1000 new cases of Hodgkin lymphoma are diagnosed in Canada each year.<sup>3</sup>

It is important to note that lymphoma also represents the most commonly diagnosed non-epithelial cancers in adolescents and young adults in Canada. Between 1992 and 2005, 5577 new cases of Hodgkin and non-Hodgkin lymphoma were diagnosed in Canadians aged 15-29 years.<sup>1</sup> ***The following guidelines do not address lymphoma in the pediatric or adolescent populations.***

## GUIDELINE QUESTIONS

- What are the diagnostic criteria for the most common lymphomas?
- What are the staging and re-staging procedures for Hodgkin and non-Hodgkin lymphomas?
- What are the recommended treatment and management options for Hodgkin and non-Hodgkin lymphomas?
- What are the recommended follow-up procedures for patients with malignant Hodgkin and non-Hodgkin lymphoma?

## DEVELOPMENT AND REVISION HISTORY

This updated guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team. Members of this team include hematologists, medical oncologists, radiation oncologists, surgical oncologists, nurses, nurse-practitioners, hematopathologists, and pharmacists. Updated evidence was selected and reviewed by members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. The draft guideline was circulated to all tumour team members for comment and approval, and all comments were reviewed by the tumour team lead and incorporated into the final version of the guideline, where appropriate. A detailed

description of the methodology followed during the guideline development and updating process can be found in the [Guideline Resource Unit Handbook](#). The original guideline was developed in March 2006 and was revised on the following dates: May 2007, June 2009, November 2009 January 2011, December 2011, September 2012, April 2013, December 2014, December 2015, February 2016 and April 2016.

## **SEARCH STRATEGY**

Medical journal articles were searched using Medline (1950 to October Week 1, 2015), EMBASE (1980 to October Week 1, 2015), Cochrane Database of Systematic Reviews (3<sup>rd</sup> Quarter, 2015), and PubMed electronic databases. An updated review of the relevant existing practice guidelines for lymphoma was also conducted by accessing the websites of the National Comprehensive Cancer Network (NCCN), Cancer Care Ontario (CCO), the British Columbia Cancer Agency (BCCA), the European Society for Medical Oncology (ESMO), and the British Committee for Standards in Haematology.

## **TARGET POPULATION**

The following guidelines apply to adults over 18 years of age. Different principles may apply to pediatric and adolescent patients.

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## DISCUSSION

### I. DIAGNOSIS AND PATHOLOGIC CLASSIFICATION<sup>1-6</sup>

An excisional lymph node biopsy of the largest regionally involved lymph node is the optimal specimen for initial diagnostic assessment. Similarly, a sizable biopsy from the organ of origin in extranodal lymphomas is also suitable. Compelling clinical contraindications to an open biopsy should be present before considering any other options. A careful clinical examination or radiological investigations for more accessible or palpable pathologic adenopathy could be useful in decision making prior to opting for a lesser diagnostic specimen. Fine needle aspirate biopsies are inadequate for the initial diagnosis of lymphoma. These latter specimens may provide adequate material for evaluating possible relapse, clarification of staging at questionable sites and as a source of additional specimen where required for further special testing or research. Occasionally, a generous core needle biopsy comprising many core samples with sufficient material to perform the appropriate ancillary techniques required for diagnostic assessment (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may supply adequate tissue, in cases when a lymph node is not easily accessible for excisional or incisional biopsy. A reference lymphoma pathologist should confirm lymphoma diagnoses in each and every case. This is particularly important in cases when only a core needle biopsy is available, and whenever requested by the treating clinician.

Table 1 describes the histologic subclassification of the malignant lymphomas, and is an **adaptation** of the most recent WHO classification<sup>6</sup>. This classification is based on the light microscopic interpretation complemented by special stains, immunophenotyping, cytogenetics and other ancillary information as available. The specific lymphomas are divided into three major groups, according to the degree of clinical aggressiveness, for treatment planning. All B-cell lymphomas should be immuno-phenotyped to determine if they are CD20 positive.

**Table 1. Lymphoma classification<sup>6</sup>.**

	<b>B-cell</b>	<b>T-cell</b>
<b>Indolent</b>	Follicular, grades 1-2, 3a Small lymphocytic Lymphoma/Chronic Lymphocytic Leukemia Marginal zone, extranodal (MALT) Splenic marginal zone Marginal zone, nodal (monocytoid B-cell) Lymphoplasmacytic (Waldenström's macroglobulinemia) Primary cutaneous, follicle centre Hairy cell leukemia Nodular lymphocyte predominant Hodgkin Lymphoma Mantle cell (can be aggressive)	Mycosis fungoides /Sezary syndrome Primary cutaneous, CD30+ Primary cutaneous perioheral T-cell lymphoma PTCL, CD30- T-cell large granular lymphocytic leukemia
<b>Aggressive</b>	Diffuse large B-cell <ul style="list-style-type: none"> <li>o T-cell/histiocyte-rich DLBCL</li> <li>o Primary DLBCL of the CNS</li> <li>o Primary cutaneous DLBCL, leg-type</li> <li>o EBV-positive DLBCL of the elderly</li> </ul> DLBCL associated with chronic inflammation Lymphomatoid granulomatosis Primary mediastinal large B-cell Intravascular large B-cell ALK positive large B-cell Plasmablastic lymphoma LBCL in HHV8-associated Castleman disease Primary effusion lymphoma Follicular grade 3b (large cell) Classical Hodgkin lymphoma <ul style="list-style-type: none"> <li>⇒ Nodular sclerosis</li> <li>⇒ Mixed cellularity</li> <li>⇒ Lymphocyte rich</li> <li>⇒ Lymphocyte depleted</li> </ul>	Peripheral T-cell, unspecified Angioimmunoblastic (AITL, formerly AILD) Enteropathy associated T-cell Hepatosplenic T-cell Subcutaneous panniculitis-like Anaplastic large cell (CD30+) ALK+ Anaplastic large cell (CD30+) ALK- Extranodal NK/T-cell, nasal type
<b>Special</b>	Burkitt lymphoma Intermediate between DLBCL and BL Intermediate between DLBCL and Hodgkin lymphoma B lymphoblastic leukemia/lymphoma B prolymphocytic leukemia Lymphomas associated with HIV infection Lymphomas associated with primary immune disorders Post-transplant lymphoproliferative disorders (PTLD) <ul style="list-style-type: none"> <li>o Plasmacytic hyperplasia and infectious mononucleosis-like PTLD</li> <li>o Polymorphic PTLD</li> <li>o Monomorphic PTLD</li> <li>o Classical Hodgkin-type PTLD</li> </ul> Other iatrogenic immunodeficiency-associated lymphomas	T lymphoblastic leukemia/lymphoma Adult T-cell leukemia/lymphoma (ATLL) T prolymphocytic leukemia

## Required Immunohistochemical and Ancillary Testing for Lymphoma

In general, guidelines for using the various ancillary methods, including immunohistochemical and fluorescence in situ hybridization (FISH) testing as outlined in the most recent version of the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues should be followed so as to confirm a specific diagnosis and provide necessary prognostic and/or predictive information<sup>6</sup>. In addition, the following are recommended by the Alberta Provincial Hematology Tumour Team<sup>7,8</sup>:

1. **Classical Hodgkin Lymphoma:** The immunohistochemical panel may include CD45/CD3/CD20/CD30/CD15/ PAX5/MUM1 and should be selected on a case by case basis at the discretion of the hematopathologist. EBV studies by in situ hybridization (EBER) may be considered if difficulty exists diagnostically, as most cases of the mixed-cellularity subtype of classical Hodgkin lymphoma are EBER positive.
2. **Diffuse Large B-Cell Lymphoma (DLBCL):**
  - Immunohistochemical (IHC) panels to distinguish between Activated B Cell (ABC) type and Germinal Centre B-cell (GCB) cell of origin (COO) types have limitations (regardless of which algorithm is employed) when compared to gene expression profiling<sup>8,9</sup>. However, GCB vs non-GCB COO by IHC does correlate with survival rates following RCHOP chemotherapy, and therefore adds prognostic information when managing DLBCL. The Alberta hematopathologists currently use a simple algorithm published by Hans et al, requiring IHC stains for CD10, BCL6 and MUM1, in which CD10+ or BCL6+/ MUM1- cases are designated as GCB COO, whereas cases negative for negative/BCL6+/MUM1+ phenotype are considered to have a non-GCB COO.
  - EBER and CD5 expression confer worse prognosis, and may be used to identify various clinical-pathological entities with distinct implications. Determining CD5 expression should be considered on all DLBCL cases. EBER should be performed in patients with immune suppression related lymphomas, or those who possibly have EBV-related DLBCL (consider past the age of 50)<sup>10</sup>
  - Rearrangements of the C-MYC gene as determined by FISH, especially in association with *BCL2* and/or *BCL6* (so called "double hit" or "triple hit" disease) are associated with very poor outcomes following R-CHOP therapy, as well as high rates of central nervous system relapse. Patients with a double-hit or triple-hit lymphoma under age 70 years should receive more aggressive therapy and possibly stem cell transplantation. Though it represents approximately only 5-10% of DLBCL cases<sup>11</sup>, it is very important to recognize these patients, and therefore, *MYC* rearrangement testing by FISH is to be performed on all patients younger than 70 y.o. with the appropriate lymphoma histology, i.e. DLBCL or lymphoma that are so called "unclassifiable" with intermediate morphological features between DLBCL and Burkitt. If *MYC* is rearranged, the case should also undergo *BCL2* and *BCL6* rearrangement testing by FISH. *MYC* and *BCL2* test results are required within 2 weeks of diagnoses for all new patients within the appropriate diagnostic category and age group. FISH testing may also be performed in select instances at the discretion of the reporting hematopathologist if such studies are deemed diagnostically useful.
  - Immunohistochemical studies cannot be used as a surrogate for *MYC* rearrangement.
  - However, the detection of *MYC* and *BCL2* concurrent overexpression by IHC in so-called "dual expressor" DLBCL, identifies a numerically significant subset of the DLBCL with potentially similar aggressive behavior compared to double-hit lymphoma cases, but representing a distinct group of patients (more often an ABC subtype as opposed to double hit DLBCL which are usually GCB). This group is also associated with a high rate of CNS relapse<sup>11</sup>. Therefore, provided adequate benchmarks and interpretation standards can be established for reproducibility, IHC for *MYC* and *BCL2* expression should also be strongly considered on all DLBCL cases<sup>9,12</sup>.



3. **Follicular Lymphoma:** must document grade (1-2, 3a or 3b), because all grade 3b should receive R-CHOP rather than other chemotherapy regimens. Also, if a diffuse pattern is present, this should be specified and a relative proportion noted, as outlined in the WHO Classification.
4. **Peripheral T-Cell Lymphoma:** cytotoxic T-cell markers (CD8/CD57/Granzyme B) correlate with poor prognosis and should be considered. Notably, however, peripheral T cell lymphomas are not classified on the basis of these phenotypic markers. EBV studies by in situ hybridization (EBER) should be performed in cases where angioimmunoblastic T cell lymphoma (AITL) and extranodal T/NK cell lymphoma, nasal type enter in the differential diagnosis.
5. **Mantle Cell Lymphoma:** Evidence of CyclinD1 deregulation confirmed by IHC (positive staining for CyclinD1) and/or FISH (positive for t(11;14)) is needed to confirm the diagnosis, provided other morphophenotypic findings are consistent with the diagnosis. Poor prognostic features must be mentioned in the report, including blastoid and pleomorphic morphologic variants. The proliferation index as measured by Ki67 or Mib-1 (used to calculate MIP1 score) is to be reported. In cases where it is difficult to differentiate MCL from CLL, flow cytometry for CD200 and IHC for SOX11 may be performed<sup>13</sup>. For patients who are deemed transplant-eligible (i.e. age <65 and fit for intensive therapy), *TP53* mutational testing should be performed at time of diagnosis to identify high-risk patients more appropriate for allogeneic stem cell transplantation<sup>14</sup>.

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## II. STAGING<sup>1-12</sup>

### Mandatory Staging Procedures

- Pathology review whenever possible (essential for core needle biopsies)
- Complete history and physical examination stating ECOG Performance Score, B symptoms
- CBC & differential, creatinine, electrolytes, Alk P, ALT, LDH, bilirubin, total protein, albumin, calcium
- Hepatitis B Surface Antigen, Hepatitis B Surface Antibody, and Hepatitis B Core Antibody must be done prior to initiating chemo/immunotherapy. Patients who are Hepatitis B Surface Antigen positive, and those who are Hepatitis B Core Antibody positive with detectable HBV DNA by Q-PCR should receive suppressive therapy with entecavir or tenofovir. Those who are Hepatitis B Core Antibody positive and Hepatitis B Surface Antibody negative and have no detectable HBV DNA, should undergo serial Q-PCR testing q1-2mo for HBV DNA.
- ESR (for early stage Hodgkin lymphoma)
- Beta-2-microglobulin
- Serum protein electrophoresis and quantitative IgG, IgA, and IgM for indolent B-cell lymphomas
- Pregnancy test: if at risk
- Bone marrow aspiration and 2cm biopsy (BMasp/bx) with flow cytometry for patients with indolent B-cell and a marrow biopsy (without flow cytometry) for aggressive T-cell non-Hodgkin lymphomas. BMasp/bx is not required for Hodgkin lymphoma or DLBCL if a staging PET/CT is performed.
- FDG-PET and Diagnostic CT NeckChestAbdomenPelvis for FDG-avid, nodal lymphomas, which includes all histologies except chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma, mycosis fungoides, and marginal zone NHLs (unless there is a suspicion of aggressive transformation). Nodal lymphomas that are not FDG avid should have a staging diagnostic CT scan of NCAP. PET-CT is especially important for patients who otherwise have non-bulky, stage I-IIA lymphoma, and are being considered for involved field radiation (IFRT) following abbreviated (or no) chemotherapy. PET/CT is not necessarily required for Follicular Lymphoma if the results will not change management, particularly for a patient who will likely undergo watchful waiting.

**Table 1.** Selected non-routine tests and required presentation

Test	Required Presentation/Condition
CSF and MRI Brain with gad	Brain, intraocular, epidural, testicular, paranasal sinus, kidney, adrenal, or symptoms referable to CNS or nerve roots. Consider for elevated LDH, ECOG 2-4, and >1 ENS.
ENT exam	Suprahyoid cervical lymph node or stomach
UGI & SBFT	Waldeyer's ring involvement
Ophthalmologic (slit lamp) exam	Primary brain lymphoma
HIV serology	If any HIV risk factors. Lymphomas with unusual presentations or aggressiveness including Primary CNS.
Cardio-oncology imaging (MR or Echocardiogram)	All patients who are planned to receive anthracycline or high dose chemotherapy (esp, > 50 years of age, or with history of hypertension or cardiopulmonary disease)
Pulmonary function tests	if bleomycin chemotherapy is planned

**Table 2.** Staging system

Stage	Description
<b>Stage I</b>	Single lymph node region (I) or one extralymphatic organ (IE)
<b>Stage II</b>	Two or more lymph node regions, same side of the diaphragm (II), or local extralymphatic extension plus lymph nodes, same side of the diaphragm (IIE)
<b>Stage III</b>	Lymph node regions on both sides of the diaphragm either alone (III) or with local extra-lymphatic extension (IIIE)

<b>Stage IV</b>	Diffuse involvement of one or more extralymphatic organs or sites <ul style="list-style-type: none"> <li>• A: No B symptoms</li> <li>• B: at least one of the following: unexplained weight loss &gt;10% baseline within 6 months of staging, unexplained fever &gt;38°C, or drenching night sweats</li> </ul>
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For treatment planning, patients are divided into two groups by stage:

1. Limited Stage: Non-bulky stage IA(E) or IIA(E) ( $\leq 3$  adjacent lymph node regions)
2. Advanced Stage:
  - Stage II involving >3 or non-adjacent lymph node regions
  - or stage III or IV
  - or B symptoms
  - or bulky tumour mass ( $\geq 10$ cm)

### Restaging Schedule

1. The following are to be performed prior to each chemotherapy treatment:
  - Clinical parameters: brief history and physical examination, toxicity notation, ECOG status
  - Bloodwork:
    - CBC/differential/platelet
    - also consider EP/creatinine and LFTs
2. Requirements for CT scanning of chest/ abdomen/ pelvis:
  - Routine CT scanning:
    - after 3 months (4 cycles) of therapy and again after completion of all therapy for Non-Hodgkin Lymphomas
    - if a residual mass is seen on the CT after completion of all therapy, then repeat a PET/CT for aggressive lymphoma to determine partial or complete remission.
    - a repeat CT scan should be considered 6-12 months post-treatment; otherwise, no further routine CT scans are required
    - Hodgkin lymphoma patients should undergo a PET/CT after 2 cycles ABVD (rather than CT after 4 cycles) as outlined below in the Hodgkin Lymphoma treatment guidelines.
  - Other requirements for CT scanning:
    - as indicated to investigate clinical signs or symptoms, or abnormal laboratory tests
3. Bone marrow aspirate & biopsy (with sample sent for flow cytometry):
  - Repeat for transplant-eligible patients with aggressive histology lymphomas who otherwise are in complete remission after completion of chemotherapy, if marrow was positive at diagnosis
4. PET/CT Imaging:
  - Assessment of residual radiographic or clinical abnormalities of uncertain significance at the time of re-staging following completion of therapy.
  - Hodgkin lymphoma patients should undergo a PET/CT after 2 cycles ABVD (rather than CT after 4 cycles) as outlined below in the Hodgkin Lymphoma treatment guidelines.

**Table 3.** PET result significance and treatment recommendations.

PET Result	Final Response	Treatment Recommendation
Negative	Complete	Observation
Positive	Partial	Consider biopsy, IFRT, or HDCT/ASCT versus observation

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### III. TREATMENT OF NON-HODGKIN LYMPHOMAS<sup>1-49</sup>

Treatment of non-Hodgkin lymphomas is based on histologic subtype, extent of disease, and age of the patient. In the case of **discordant** (2 separate sites of disease with differing types of lymphoma), **composite** (1 site of disease with 2 discrete types of lymphoma at that site), or **transformed** (a second lymphoma developing out of a background of previously known lymphoma) lymphoma, treatment must be directed at the most aggressive phase of the disease. Approaches outlined for aggressive lymphomas are generally applicable to both B- and T-cell types. However, treatments for lymphomas presenting at special sites, poor prognosis lymphomas in younger patients, and lymphomas arising in association with immunodeficiency (HIV, post-organ transplant) are outlined in the section titled “Special Problems in Lymphoma Management” below.

#### Diffuse Large B-Cell Lymphoma (DLBCL)<sup>4,45-47,50-52</sup>

**Table 1.** Initial therapy of DLBCL/aggressive CD20+ lymphomas without MYC Rearrangement by FISH.

Stage	# Risk Factors*	Treatment**
Limited, and bulk <7 cm	0	<ul style="list-style-type: none"> <li>R-CHOP x 4 cycles if CR by PET/CT 14-21days after 4<sup>th</sup> cycle.</li> <li>R-CHOP x6 with IFRT (30-35Gy) if PR by PET/CT after 4th cycle RCHOP<sup>52</sup></li> <li>RCHOP x3 plus IFRT if patients unable to tolerate more than 3 cycles RCHOP</li> </ul>
Limited, and bulk <7 cm	1-4	<ul style="list-style-type: none"> <li>R-CHOP x6 cycles with no IFRT if CR by PET/CT 14-21d after 4th cycle RCHOP</li> <li>R-CHOP x 6 cycles plus IFRT (30-35Gy) if only PR by PET/CT after 4th cycle RCHOP</li> </ul>
Advanced***, or limited stage with bulk ≥7 cm	0-3 or age>65 yrs	<ul style="list-style-type: none"> <li>R-CHOP x 6 cycles possibly followed by IFRT (30-35Gy) to site of prior bulk if no CR by PET/CT 21-28d after 6<sup>th</sup> cycle RCHOP****</li> </ul>
Advanced***	4-5 and age <70 yrs	<ul style="list-style-type: none"> <li>Acceptable alternatives:               <ul style="list-style-type: none"> <li>R-CHOP x 6, then high-dose therapy/ASCT if no CR or relapse, or</li> <li>R-CHOP x4-6 then high-dose chemotherapy/ASCT in first remission.                   <ul style="list-style-type: none"> <li>Especially recommended if MYC/BCL2 dual protein expression or PET+ after RCHOPx4.</li> </ul> </li> </ul> </li> <li>IFRT (30-35Gy) to site of prior bulk disease if no CR to chemotherapy****</li> <li>Consider CNS prophylaxis with high-dose IV methotrexate as described later in guidelines</li> </ul>

\* IPI Risk Factors for Limited Stage: increased LDH, stage II, ECOG performance status 2-4, age>60 years.

\*IPI Risk Factors for Advanced Stage: increased LDH, stage III/IV, >1 Extranodal Site, ECOG 2-4, age>60 years.

\*\*R-CEOP should be used for DLBCL patients who have prior cardiac disease and reduced left ventricular ejection fraction. As presented by the BC Cancer Agency at the ASH 2009 Meeting (abstract 408), R-CEOP (etoposide 50mg/m<sup>2</sup> IV day1 and 100mg/m<sup>2</sup> po days 2-3) resulted in a 5 year TTP of 57% for 81 patients with DLBCL.

\*\*\*For patients >age 60 years, 3-7 days of prednisone 100mg/day pre-R-CHOP as well as G-CSF prophylaxis are recommended to decrease toxicity.

**Important: Patients who present with masses >10cm or bone involvement (esp. stage I-II) should be considered for radiation oncology consultation, even if CR to RCHOP chemotherapy by PET/CT.**

Prophylactic intrathecal chemotherapy has not been proven to decrease meningeal or parenchymal brain relapse of lymphoma in well-designed studies. Due to the lack of proven benefit, intrathecal chemotherapy can not be recommended even in high risk situations where the risk of CNS relapse is approximately 10% or higher. Also, primary CNS and intraocular lymphomas do not require intrathecal chemotherapy as long



as they are treated with IV high-dose methotrexate-based regimens (discussed in “Special Problems in Lymphoma Management” section).

### HDCT/ASCT as Part of Initial Therapy for DLBCL

Randomized phase 3 trials have not proven an OS benefit for first remission consolidation with ASCT compared to RCHOP alone for aIPI=2-3 DLBCL patients. Most recently, Chiapella *et al.* (2017) evaluated Rituximab-dose-dense chemotherapy with or without HDCT/ASCT in 412 patients with aIPI=2-3 DLBCL (DLCL04), and reported improved PFS but not OS with ASCT consolidation<sup>53</sup>. This is similar to the US intergroup/NCIC study reported by Stiff PJ *et al.* (2013)<sup>54</sup>, however, in the latter study, patients who had aIPI=3 experienced statistically significant improvements in 2yr PFS (75% vs 43%) as well as OS (82% vs 64%) with ASCT compared to RCHOP alone, respectively. aIPI does not adequately identify poor prognosis DLBCL in young patients, as evidenced by the OS of 75-80% for aIPI=2 patients in the RCHOP-only arms of the US intergroup trial and the Italian DLCL04 trial. This is supported by unpublished retrospective Alberta population data from a 2013 analysis, wherein 112 HIV-, CNS- patients 18-65yo with IPI=3-5 DLBCL experienced 5yr OS of 68% with ASCT (n=37) vs 56% without ASCT (n=75), however, including 166 IPI=2-5 patients, the OS difference was not significantly different with (n=46) or without (n=120) ASCT (72% vs 64%). Newer methods of identifying poor prognosis DLBCL patients include the use of interim or final PET+ response to RCHOP, as well as cell of origin (COO) GCB vs non-GCB, and MYC/BCL2 expression. Ennishi *et al.* (2017) reported very poor outcomes (5yr TTP <30%) for GCB DLBCL patients associated with high IPI scores and BCL2 translocations, as well as ABC DLBCL associated with high IPI scores and BCL2 gain/expression<sup>55</sup>. In addition, several investigators have reported very low salvage rates for the use of ASCT for relapsed/refractory MYC/BCL2 dual protein expression DLBCL. However, determining COO by IHC algorithms is unreliable, and COO by nanostring Lymph2Cx GEP is not currently funded. Unpublished data for 237 patients aged 18-65 years with IPI=3-5 DLBCL treated in Alberta from 2006-2017 found a 5 year overall survival rate of 81% for 100 IPI=3 patients but only 63% for 137 IPI=4-5 patients. Only a minority had first remission ASCT consolidation therapy. This local real world experience suggests that 40% of IPI=4-5 DLBCL patients are not cured by induction RCHOP or subsequent salvage therapy with ASCT for relapsed/refractory disease. The Positron Emission Tomography–Guided Therapy of Aggressive Non-Hodgkin Lymphomas (PETAL) study [Ulrich D`uhrsens, J Clin Oncol 36:2024-2034. 2018] reported 5yr event-free survival from the day of negative vs positive interim PET scanning (change SUVmax 66%) as follows: 80% vs 40% for IPI=0-1, 60% vs 40% for IPI=2, 60% vs 30% for IPI=3, and 40% vs 10% for IPI=4-5. In conclusion, **patients who present with DLBCL and IPI=4-5 are reasonably treated with ASCT as first remission consolidation after 4-6 cycles RCHOP induction therapy, especially those who also have: 1) MYC and BCL2 protein expression by IHC; or 2) PET+ after 4-6 cycles RCHOP (particularly as determined by change in SUVmax <66% from baseline).**

### Recommendations for CNS Prophylaxis<sup>23,48,49,56</sup>

For DLBCL, factors associated with high risk (>10%) for relapse in the central nervous system include 4-6 of the following factors: 1) Age >60 years, 2) elevated LDH, 3) ECOG=2-4, 4) Stage 3-4, 5) >1 extranodal site of involvement, and 6) kidney or adrenal involvement. For such high risk patients, CNS prophylaxis should involve high dose intravenous methotrexate 3.5g/m<sup>2</sup> x 3 doses mid-cycle (~day15) of R-CHOP or R-CHOEP cycles 2, 4, 6. This is particularly the case for patients with 4-6 of the above risk factors who also have DLBCL pathology demonstrating non-GCB cell of origin (eg. CD10- and BCL6- or MUM1+), or dual expression of MYC+ and BCL2+ by immunohistochemistry, where the risk of CNS relapse is 15-20%, as well as those with double hit lymphoma (MYC and BCL2 mutations/rearrangements by FISH). The other high risk presentation is that of testicular lymphoma where CNS prophylaxis should involve high dose intravenous methotrexate 3.5g/m<sup>2</sup> every 14-28 days x 2-3 doses after completion of all 6 cycles of R-CHOP. The overall chance of cure and patient co-morbidities should be considered before proceeding

with methotrexate. For example, high risk IPI DLBCL in patients over age 70 years is associated with low progression-free survival rates, and poor tolerance of methotrexate, so CNS prophylaxis is probably not appropriate.

**Treatment of relapsed DLBCL.** All patients younger than 65-70 years of age who experience disease persistence or progression after initial RCHOP chemotherapy should be considered for high dose salvage therapy with autologous stem cell transplantation (SCT). These patients should be referred to the BMT clinic as soon as possible, or a transplant physician should be contacted directly to discuss management decisions. Often these patients will require special salvage therapy recommendations that may necessitate management by the transplant program in a hospital setting (e.g., R-DICEP or R-MICE). Potential transplant candidates should receive rituximab with the salvage chemotherapy to maximize the chance of response, and *in-vivo* purge blood of tumour cells. Other patients who are not transplant candidates could receive conventional salvage therapy regimens such as DHAP, ICE, GDP, CEPP or MEP. Amongst these options, GDP is generally preferred because it can be given on an outpatient basis. Prognosis of relapsed DLBCL patients who do not undergo high-dose chemotherapy (HDCT) and SCT is extremely poor, with median survival rates of less than 6 months. Palliation is the main goal for non-transplant candidates. Involved field radiotherapy (IFRT) to symptomatic sites may also benefit these palliative patients. Third-line chemotherapy for relapsed DLBCL is rarely of benefit. If done, there has usually been a definite response to second line therapy, with disease control during and for a few months after the second-line treatment finished. Some palliative patients at or beyond second relapse may have symptomatic benefit from prednisone alone, or low dose daily oral chemotherapy with chlorambucil 0.1mg/kg/day or etoposide 50mg/day, or combination oral therapy such as PEPC.

### Secondary CNS Lymphoma:<sup>57-60</sup>

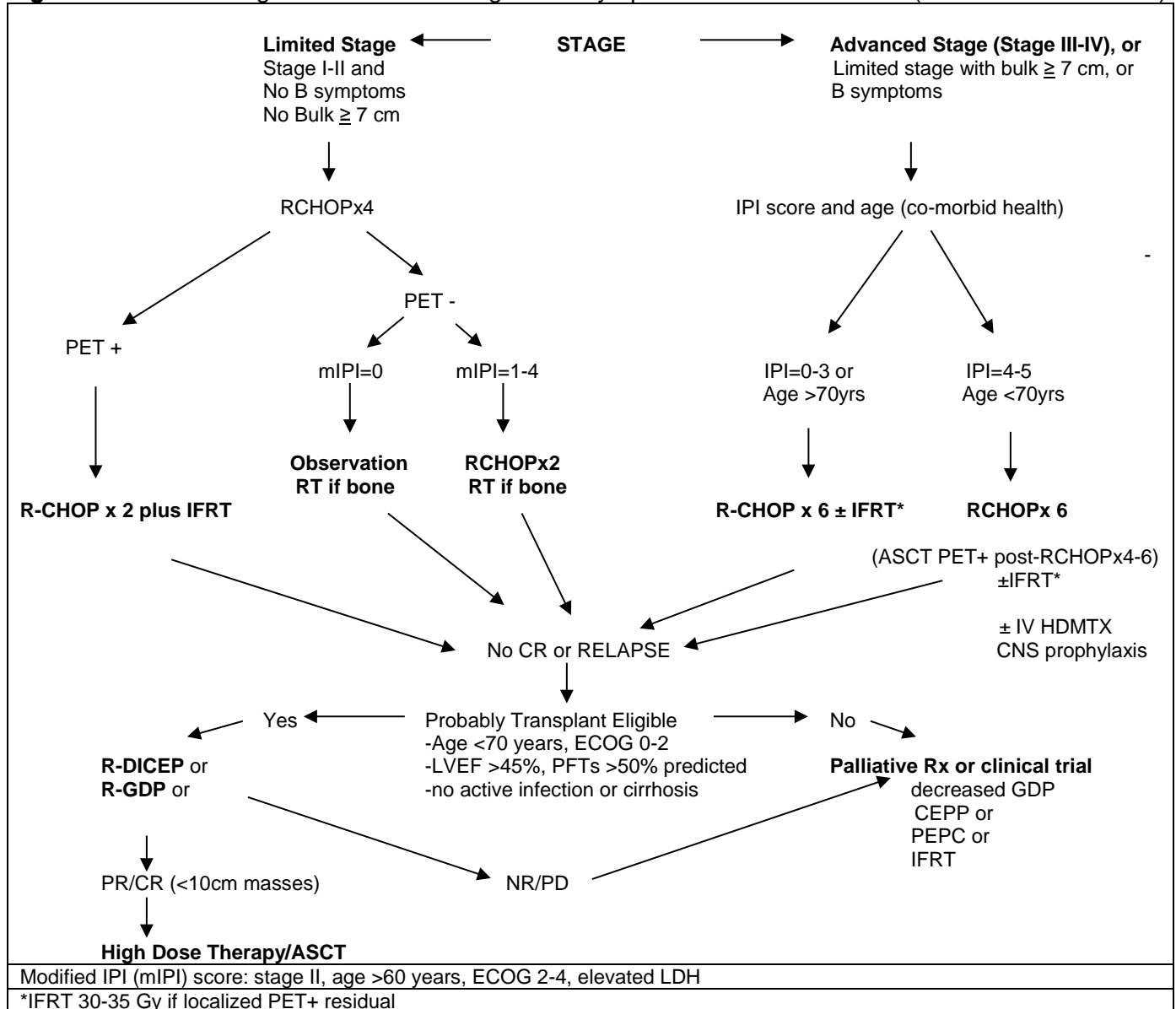
Selected patients with CNS relapse/progression may be candidates for aggressive therapy as outlined in Appendix A, subheading VIII. One of 3 induction regimens is recommended for transplant-eligible patients and one of two options for transplant in-eligible patients, based on presentation:

- 1) Isolated CNS lymphoma: HDMTX-based induction then RDHAP for stem cell mobilization and collection, then R-TBuM/ASCT for transplant eligible (table A) or HDMTX/AraC then Ifosfamide for transplant ineligible (table D).
- 2) Early Systemic and CNS lymphoma (prior to completing RCHOP x6): RCHOP and HDMTX x4 cycles then RDHAP for stem cell mobilization and collection, then R-TBuM/ASCT for transplant eligible (table B) or RCHOP/MTX followed by AraC then ifosfamide in transplant ineligible (table E).
- 3) Late relapse (prior RCHOP x6) with systemic and CNS lymphoma: HDMTX-Ifosfamide-etoposide x2 then RDHAP for stem cell mobilization and collection, then R-TBuM/ASCT for transplant eligible (table C) or palliation for transplant ineligible (table F)

Unfortunately, most patients with secondary CNS lymphoma experience poor response to salvage therapy, including high dose methotrexate/cytarabine-based regimens. These patients who are unfit to receive or do not respond to high dose methotrexate/cytarabine-based therapy are best managed with palliative intent, including possible use of intrathecal chemotherapy or palliative cranial radiotherapy.



**Figure 1.** Treatment algorithm for diffuse large B-cell lymphoma with no double hit (MYC/BCL2 mutations)



**Treatment of special DLBCL entities.** RW.ERROR - Unable to find reference:4761
**Double Hit Lymphoma with MYC and BCL2 mutations/rearrangements by FISH:**

The largest multicentre retrospective analysis of 311 double hit lymphoma patients reported an OS rate of <50% if IPI=2-5 vs 65% for IPI=0-1, and >80% if IPI=0 (Petrich AM, Gandhi M, Jovanovic B: Blood 2014;124:2354-61). In addition, the OS rate was approximately 90% for 39 patients who achieve CR following induction chemotherapy and then underwent SCT compared to 60% for 112 patients who achieved CR but did not receive SCT. Although this numerical difference was not statistically significant (p=0.1), it was very clinically significant, indicating that the study was underpowered to draw any meaningful conclusions regarding the role of ASCT consolidation. More recently, Landsburg *et al.* (2017) reported outcomes of 159 patients with Double-Hit Lymphoma who achieve CR following induction therapy. This study demonstrated that PFS and OS were superior with an intensive regimen relative to RCHOP, and that ASCT only improve outcomes for patients who initially received RCHOP, but not an intensive regimen. RW.ERROR - Unable to find reference:15321 These studies suggest that DHL patients treated with RCHOP should be considered for ASCT consolidation, esp with IPI=2-5 at diagnosis, however other patients who achieve CR after an intensive induction regimen (such as DA-EPOCH-R or R-CODOXM/IVAC) probably should not receive ASCT consolidation. Due to the lack of prospective randomized controlled studies, however, it is impossible to determine if the optimal approach involves RCHOP induction followed by ASCT or an intensive induction chemotherapy regimen.

**Alberta recommendations for special DLBCL entities:**

## 1. DLBCL with MYC translocated by FISH

- MYC-rearranged DLBCL (or Intermediate Between DLBCL and Burkitt Lymphoma) but no translocation of BCL2 or BCL6: R-CHOP x 6 cycles for most patients. However, for the poor prognosis situation of MYC mutated and age <70 years and IPI 4-5: R-CHOP x4 then RDHAP or RDICEP x1, then HDCT/ASCT. Alternatively R-CODOX-M/IVAC or DA-EPOCH-R should be considered
- MYC rearranged and BCL2 or BCL6 rearranged (DOUBLE HIT) or BCL2 and BCL6 rearranged (TRIPLE HIT). IPI=0-1:
  - RCHOP or with HDMTX after cycles 2,4,6, or
  - DA-EPOCH-R
- IPI=2-5: Options include:
  - A. RCHOP with HDMTX after cycles 2 (±4) then RDICEPx1 then HDCT/ASCT using CNS penetrating regimen with either R-BuMeI/ASCT or R-MeITBI/ASCT (not BEAM)
    - Note: it is difficult to mobilize autologous blood stem cells after multiple cycles of intensive chemotherapy + G-CSF (RCODOXM/IVAC), particularly for older patients. Therefore, if the goal is to proceed to transplant, then RCHOPx4 + HDMTXx2 is generally preferred for patients >60 years, or those who received prior chemotherapy for indolent lymphoma in the past and now have transformed disease.
  - B. DA-EPOCH-R or R-CODOX-M/IVAC

## 2. Intermediate Between DLBCL and Hodgkin Lymphoma:

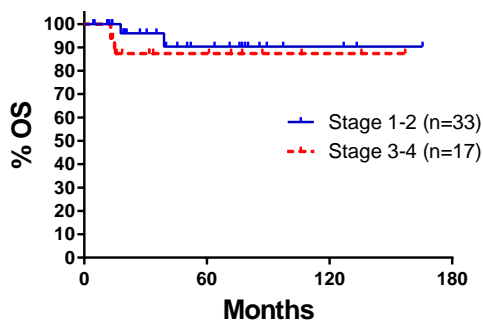
- R-CHOP x 6 cycles for most patients
- RCHOP followed by ASCT if high risk factors are present (IPI=3-5)

**Primary Mediastinal B-Cell Lymphoma**

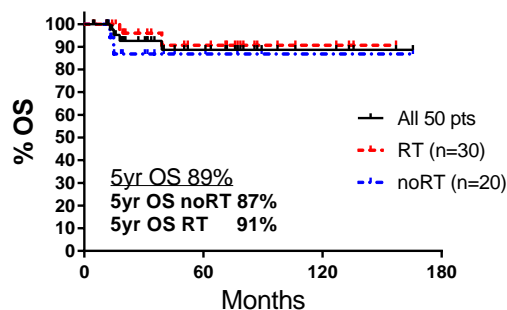
Primary mediastinal B-cell lymphoma (PMBCL) of thymic origin represents 6-10% of all DLBCLs, and most commonly affects young adults (median age ~35), women more than men<sup>61</sup>. It frequently is associated with a

bulky mediastinal mass that directly extends into extranodal thoracic tissues such as pleura, pericardium and chest wall, but rarely involves the marrow or intra-abdominal sites. Overall, PMBCL is associated with a better prognosis than other DLBCLs, including GCB DLBCLs. The IPI score tends not to work well for PMBCL because most patients are young with fairly well preserved performance status, and have elevated LDH. Therefore, limited vs advanced stage, and number extranodal sites (esp pleural effusions) tend to be the only factors that subdivide patients into excellent vs good prognosis. Likewise, because most patients have a very good prognosis, interim or end of treatment restaging PET imaging is associated with very high negative predictive value, but relatively low positive predictive value<sup>62</sup>. Therefore, a positive restaging PET scan should probably not be used alone to guide further therapy. Treatment of PMBCL with RCHOP +/- IFRT is associated with cure rates of approximately 75% and overall survival rates of 90%. Phase II studies have reported that intensifying chemotherapy (eg. dose adjusted EPOCH-R) maintains excellent outcomes while avoiding IFRT, but there are no phase III randomized controlled trials that prove DA-EPOCH-R is superior to RCHOP, or even that IFRT after RCHOP improves survival rates relative to RCHOP alone. The latter is studied in the ongoing IELSG-37 clinical trial. A large retrospective study from 11 centres compared outcomes of 132 PMBCL patients treated with R-CHOP (n=56) or with dose-adjusted R-EPOCH (n=76), and found similar survival rates of approximately 90% with both regimens<sup>63</sup>. The prospective phase III CALGB/Alliance 50303 study randomized 464 DLBCL (including ~6% PMBCL) patients to RCHOP or DA-EPOCH-R, and found no difference in EFS or OS between regimens, although there was substantially more toxicity with DA-EPOCH-R. Unpublished retrospective real world data for 50 consecutive patients in Alberta treated with RCHOP from 2005-2017 found a long-term overall survival rate of approximately 90% regardless of limited (n=33) or advanced (n=17) stage at diagnosis, and regardless of treatment with (n=30) or without (n=20) IFRT. The OS rate was 100% for the 13 limited stage patients treated with RCHOP alone, without IFRT. **In conclusion, available evidence supports the use of RCHOP for patients with PMBCL, and does not support the use of DA-EPOCH-R. In view of the long term risk of secondary malignancy and premature heart disease from IFRT in young patients, IFRT should probably be restricted to those with bulky masses >10cm at diagnosis that do not respond well to chemotherapy (eg.  $\leq$  50% response and could also be considered for patients with positive end of treatment PET/CT).**

PMBCL in Alberta 2005-2017  
Treated with RCHOP +/- RT (n=50)



PMBCL in Alberta 2005-2017  
Treated with RCHOP +/- RT (n=50)

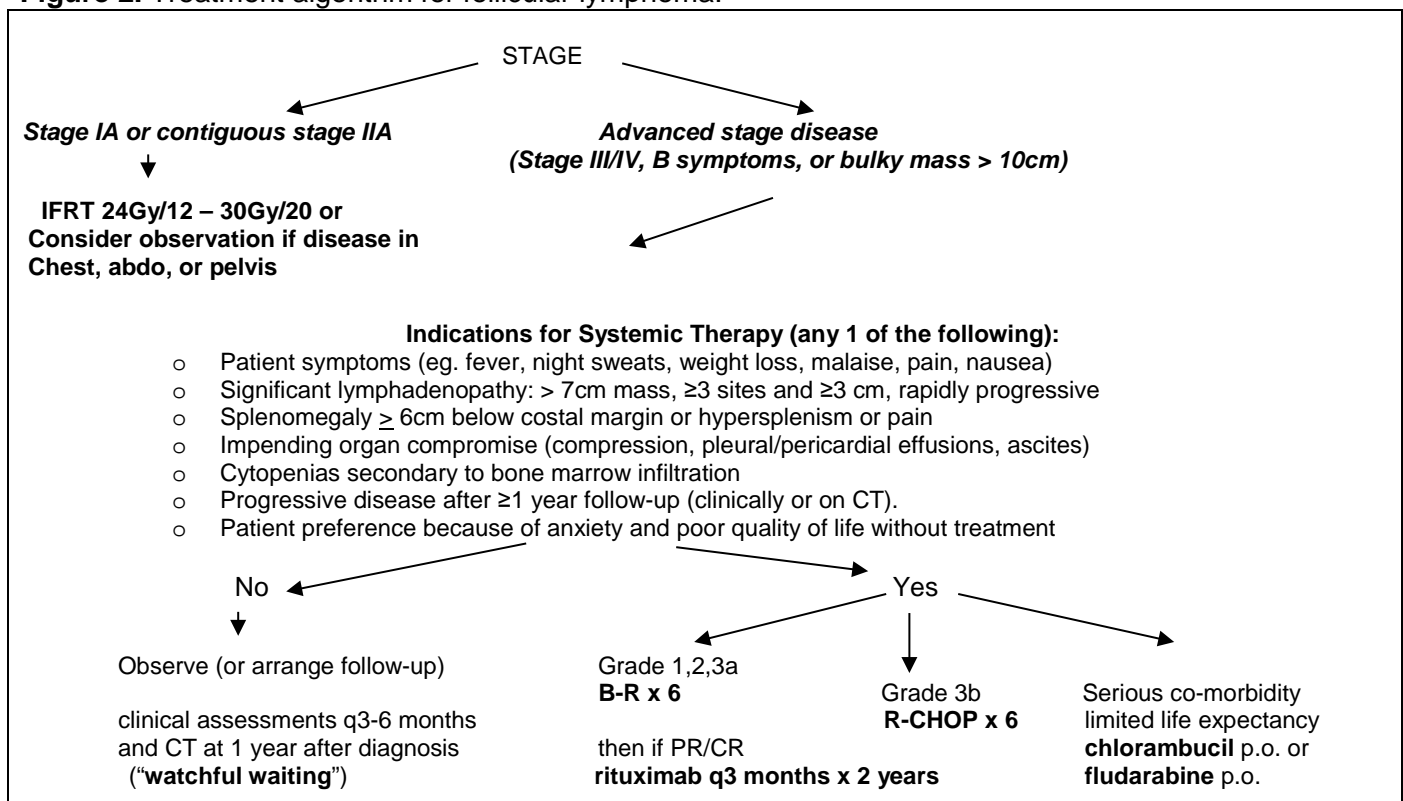


**Follicular Lymphoma**<sup>64-109</sup>

Throughout the following suggested treatment approach, three over-riding principles should be considered:

1. These are guidelines only. This disease often carries a long, incurable, remitting/relapsing natural history and, therefore, several treatment approaches are reasonable.
2. The mere presence of disease does not alone imply the need for treatment.
3. If therapy is required for predominantly localized disease, IFRT should be considered in lieu of systemic pharmacological treatment as long as the radiotherapy can be done with minimal early or delayed side-effects (e.g., xerostomia, severe nausea/vomiting) and without eliminating future treatment options (e.g., should not radiate  $\geq 25\%$  bone marrow). Figure 2 outlines the treatment algorithm for follicular lymphoma.

**Figure 2.** Treatment algorithm for follicular lymphoma.



**Initial therapy of stage IA and contiguous stage IIA.** IFRT 24Gy/12-30Gy/20 fractions is recommended for newly diagnosed patients with peripheral stage IA or contiguous non-bulky stage IIA follicular lymphoma, even if the patient is asymptomatic.

**Initial therapy of advanced stage disease (stage III/IV, B symptoms, or bulky stage I/II).** Indications for systemic therapy (usually stage III/IV or bulky stage I/II) include any one of the following:

- Patient symptoms (fever, night sweats, weight loss, malaise, pain, nausea)
- Significant lymphadenopathy (> 7 cm mass,  $\geq 3$  sites and  $\geq 3$ cm, rapidly progressive)
- Splenomegaly  $\geq 6$  cm below costal margin, or hypersplenism, or pain
- Impending organ compromise (compression, pleural/pericardial effusions, ascites)

- Cytopenias secondary to bone marrow infiltration
- Progressive disease after  $\geq 1$  year follow-up, clinically or by CT imaging
- Patient preference because of anxiety and poor quality of life without treatment

For patients who do not have any of the above indications for therapy, the recommended approach is to observe with (or arrange) follow-up clinical assessments every 3-6 months (“watchful waiting”), and a CT CAP 1 year after diagnosis. For patients not meeting treatment criteria 1 year after diagnosis, another CT 2 years after diagnosis could be considered. Patients who have progressive disease on follow-up should generally be treated, even if they do not fulfill any of the other indications for therapy. A retrospective study of 238 Alberta follicular lymphoma patients managed with watchful waiting found that 24% developed transformed disease or significant organ dysfunction (at a median of 30 months) prior to initiating initial therapy, and these patients had inferior survival rates compared to other patients requiring therapy who were initially managed with watchful waiting (10 yr OS 67.9% vs 85.7%, HR 3.000 (95%CI 1.696-7.126),  $p=0.0007$ ). These watchful waiting patients did not undergo routine follow-up CT scans at 1 or 2 years to identify progression. It is possible that these adverse outcomes might have been avoided with closer monitoring by CT imaging and earlier initiation of chemoimmunotherapy<sup>110</sup>.

For grades 1,2,3a follicular lymphoma who have an indication for therapy, the recommended therapy involves 6 cycles of B-R (bendamustine-rituximab) chemotherapy, followed in responding patients by 2 years of maintenance rituximab (375mg/m<sup>2</sup> IV single dose every 3 months for total of eight doses). In patients with previously untreated indolent lymphoma, B-R can be considered as a preferred first-line treatment approach to R-CHOP because of increased progression-free survival and fewer side-effects. Patients who have limited life-expectancy from serious co-morbid illness, or who do not want intravenous therapy, may be treated with oral chlorambucil or fludarabine monotherapy.

The recently reported GALLIUM clinical trial investigated the value of obinutuzumab in combination with chemotherapy followed by maintenance therapy compared to standard therapy with rituximab chemoimmunotherapy plus maintenance in the firstline treatment of follicular lymphoma. The study demonstrates superiority of obinutuzumab over rituximab in terms of PFS (3-year PFS was 81.9% (95%CI: 77.9-85.2%) vs. 77.9% (95%CI: 73.8-81.4%), respectively, HR: 0.71 (95%CI: 0.54-0.93),  $p=0.014$ ) with acceptable increased toxicity with the use of obinutuzumab (74.6% vs 67.8% of patients experienced a grade  $\geq 3$  toxicity, respectively). However, the study is reported with short follow-up (median 34.5 months) and as such, demonstrates no clear OS advantage to the replacement of rituximab with obinutuzumab ( $p=0.210$ ). Based on the lack of an OS advantage and the greater cost of obinutuzumab (particularly when compared to currently available subcutaneous rituximab), longer follow-up is required before considering the replacement of rituximab with obinutuzumab in frontline therapy for FL<sup>111</sup>.

For grade 3b follicular lymphoma or DLBCL with areas of follicular lymphoma, R-CHOP should be used. Rituximab maintenance has not been proven effective following R-CHOP therapy for large B-cell lymphoma, and therefore is not recommended.

**Therapy of relapsed disease.** Therapeutic recommendations for recurrent follicular lymphoma need to be individualized, and no one recommendation is suitable for all patients. Numerous factors need to be taken into consideration before recommending therapy for recurrent follicular lymphoma, including:

- Patient Factors: Age, co-morbidity, symptoms, short vs. long-term goals, preservation of future options, reimbursement/ability to pay for expensive treatments, acceptance of risks/toxicities of treatment option relative to potential benefit (RR, PFS, OS).
- Disease Factors: Stage, sites of involvement, grade, transformation, prior therapy, time from prior therapy (disease-free interval).



For example, previously healthy patients younger than 70 years who relapse within 2 years of initial chemotherapy have a median life expectancy of <5 years, and are best managed with HDCT/ autologous SCT. HDCT/SCT maximizes the length of disease control for all patients less than 70 years, regardless of length of initial remission, and as such is a reasonable treatment option for those who accept potential risks/toxicities. Therefore, patients younger than 70 years without serious co-morbid disease, and who respond to salvage therapy should be considered for high dose chemotherapy and autologous (relapse 1-2) or allogeneic stem cell transplantation (relapse 3). A large retrospective study of consecutively treated relapsed follicular lymphoma patients in Alberta and BC reported 5 year overall survival rates following relapse of ~90% for those who received ASCT vs ~60% for those who did not receive ASCT. This marked difference in survival retained significance in multivariate as well as instrumental variable analyses<sup>112</sup>.

Conversely, some patients may be best managed by repeating their initial treatment regimen, especially if they achieved an initial remission greater than 5 years. Other patients should be changed to a second line standard-dose chemotherapy regimen (bendamustine, chlorambucil, CVP, fludarabine, etoposide, CEPP, GDP, FND, PEC, or MEP). For patients who have rituximab, it is reasonable to re-treat with rituximab alone or with chemotherapy as long as the patient attained at least a 6 month remission to prior rituximab-based therapy. Rituximab maintenance should only be used once in the course of a patient's disease (first remission or first relapse). Palliative, symptomatic care (possibly including palliative IFRT 4Gy/2 fractions) is usually the best option for patients who were refractory to their 2 most recent treatment regimens, those with CNS involvement, or those with an ECOG score of 3-4.

A phase 3, open-label, two-arm parallel, randomized trial (GADOLIN), compared obinutuzumab and bendamustine followed by obinutuzumab maintenance to bendamustine alone in patients with rituximab-refractory, indolent non-Hodgkin lymphoma (failure to respond or progress during or within 6 months of a rituximab containing regimen). The primary outcome was PFS, and other outcomes included OS, overall response, duration of response, quality of life, and adverse events. In the subgroup of patients with follicular lymphoma, the median PFS was 25.3 months in patients treated with obinutuzumab plus bendamustine versus 14 months in patients treated with bendamustine alone (HR[95%CI]: 0.52[0.39,0.69];  $p < 0.0001$ ). From the April 2016 data cut-off, median OS for obinutuzumab plus bendamustine was not estimable (NE) and median OS for bendamustine alone was 53.9 months (40.9 to NE) (HR[95%CI: 0.58[0.39,0.86];  $p = 0.0061$ ). While there was no significant advantage reported for patients with other subtypes of iNHL, this was deemed to be based purely on the small numbers in other subgroups. Based on these results, ***it is recommended that obinutuzumab chemo-immunotherapy be considered in patients with rituximab-refractory iNHL.*** While the study used bendamustine as a chemotherapy backbone, few patients on the study had received bendamustine as their frontline therapy. Given current practice to use BR for the frontline treatment of FL and the fact that there is no biological reason that the same clinical benefit of obinutuzumab would not be seen in combination with other chemotherapies, alternate NHL chemotherapy backbones could be considered for patients deemed inappropriate for bendamustine retreatment. While there was a higher frequency of serious adverse events in the obinutuzumab plus bendamustine arm, many of these were infusion-related reactions which can be safely managed. Relatively frequent infections were also noted so prophylactic antibiotics and antivirals should be considered, especially when obinutuzumab is combined with bendamustine.

Another option to consider for rituximab-refractory relapsed FL patients is radioimmunotherapy with 90Y-ibritumomab tiuxetan (Zevalin). This option, however, requires Director's Privilege approval, and is not currently listed on the Alberta Cancer Drug Benefit List for funding. In a small study of 57 patients with rituximab-refractory FL (median 4 prior therapies), the overall response rate to 90Y-ibritumomab tiuxetan

was 74% (CR 15%) and median duration of response of 8.7 months. There may be small subset of patients (10-15%) who achieve long-term PFS following 90Y-ibritumomab tiuxetan<sup>90,113</sup>.

### Indolent Lymphomas (Excluding Follicular Histology)<sup>1,114-122</sup>

Indolent lymphomas should generally be treated similarly to follicular grade 1-2 lymphomas.

Recurrent CD20+ indolent B-cell lymphomas should be considered for rituximab therapy alone (375mg/m<sup>2</sup> weekly x 4) or rituximab plus chemotherapy (B-R, R-fludarabine, R-FC, R-FND, R-CVP), or chemotherapy alone (chlorambucil, fludarabine, etoposide, CEPP, GDP, FND, PEC, or MEP). Patients less than 70 years of age without serious co-morbid disease, and who respond to salvage therapy could be considered for high dose chemotherapy and autologous or allogeneic stem cell transplantation.

**Table 2.** Treatment of Indolent Lymphomas<sup>114</sup>

Stage	Treatment
Limited	IFRT (24Gy/12 - 30Gy/20)
Advanced	<p><b>Asymptomatic:</b> observation until treatment indication</p> <p><b>Symptomatic:</b></p> <ul style="list-style-type: none"> <li>majority should receive B-R, then rituximab maintenance</li> <li>alternatives in special situations include IFRT, fludarabine, or chlorambucil</li> </ul>

### Splenic Marginal Zone Lymphoma

Splenic marginal zone lymphoma is an uncommon type of non-Hodgkin lymphoma characterized by splenomegaly, cytopenias, lymphocytosis, and less commonly lymphadenopathy. Revised diagnostic criteria now specify the typical blood and bone marrow findings of SMZL and splenic biopsy is not usually required to establish the diagnosis<sup>123</sup>. It is still reasonable, however, to proceed with splenectomy if the cause of splenomegaly is not determined following peripheral blood and bone marrow evaluation.

The disease course is indolent and many patients can be managed expectantly until symptomatic splenomegaly or pronounced cytopenias develop. SMZL prognostic scoring systems have been described, with low hemoglobin, low platelets, elevated lactate dehydrogenase and extra-hilar lymphadenopathy as adverse markers<sup>124</sup>.

In rare cases, SMZL has been associated with hepatitis C infection (HCV), so all patients should be screened at diagnosis. Those who are HCV+ should first be offered HCV-directed therapy, as the lymphoma may regress avoiding the immediate need for further therapy<sup>125,126</sup>. Splenectomy has otherwise been the standard approach to treat SMZL for over two decades<sup>127</sup>. The role of splenectomy as frontline treatment of SMZL is now controversial<sup>128,129</sup>. One large SEER database review found no improvement on overall survival or lymphoma specific survival following splenectomy<sup>130</sup>. On the other hand, a recent single centre registry review suggested that splenectomy remains superior over chemotherapy with improved overall survival (61 vs 42%) and failure free survival (39 vs 13%) at 10 years<sup>131</sup>. However, almost half of the patients in the chemotherapy arm were treated in the pre-rituximab era which may have skewed the results in favour of splenectomy. Risks posed by splenectomy include operative morbidity and mortality, particularly in the elderly, or those with multiple comorbidities. However, surgical outcomes are improving at experienced centres. The risk of infection with encapsulated organisms is a serious concern, but may be mitigated with timely vaccination and long-term antibiotic prophylaxis<sup>132</sup>.

Monotherapy with rituximab has recently emerged as a non-operative alternative<sup>129,133</sup> with reports suggesting survival outcomes similar to historical patients treated with splenectomy. Chemo-immunotherapy such as rituximab-bendamustine (BR) is also a rational approach for SMZL given the recent favourable results of a large scale RCT of iNHL, including marginal zone histology<sup>108</sup>.

Although existing evidence is inadequate to conclude which treatment approach is superior, we propose the following strategy for managing SMZL:

1. Rituximab monotherapy is recommended as frontline therapy for most patients. A standard regimen is rituximab 375mg/m<sup>2</sup> once weekly for 4 weeks, followed by a response assessment 4-6 weeks later.
  - a. Those achieving at least a partial response, defined by conventional response criteria<sup>123</sup>, should subsequently receive maintenance rituximab (375mg/m<sup>2</sup> every 3 months for 2 years).
  - b. Non-responders or those with progressive disease should proceed with either:
    - i. Splenectomy if the spleen is the major site of disease or
    - ii. BR for those with additional nodal disease, extensive bone marrow involvement, or non-operative candidates, then followed by maintenance rituximab (375mg/m<sup>2</sup> every 3 months for 2 years)
2. Select patients who require a splenectomy to establish the diagnosis and have no bone marrow, peripheral blood, or nodal involvement, do not require maintenance rituximab and may simply be observed.

## Lymphoplasmacytic Lymphoma (LPL)

### ***Diagnostic criteria for Waldenström macroglobulinemia (WM):***

- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by small lymphocytes showing plasmacytoid/plasma cell differentiation, usually with intertrabecular pattern of bone marrow infiltration
- LPL immunophenotype:
  - surface IgM+ CD5- CD10- CD19+ CD20+ CD22+ CD23- CD25+ CD27+ FMC7+ CD103- CD138-
- Recent findings documented a strong association between WM and the MYD88 L265P variant, which might serve as an additional tool to diagnose WM and to separate it from other entities such as multiple myeloma, monoclonal gammopathy of undetermined significance, splenic marginal zone lymphoma and MALT lymphoma

### ***Diagnostic approach to confirm a suspected case of WM:***

1. Serum protein electrophoresis with immunofixation: to characterize the type of light and heavy chains.
2. 24-Hour urine for protein electrophoresis: 40%-80% have detectable Bence Jones proteinuria.
3. Serum B2-microglobulin: for prognostic evaluation.
4. Bone marrow biopsy: intratrabecular monoclonal lymphoplasmacytic infiltrate, ranging from predominantly lymphocytic to lymphoplasmacytic to overt plasma cells.
5. CT of the abdomen and pelvis: to detect organomegaly and lymphadenopathy (skeletal surveys and bone scans are not necessary in absence of symptoms).
6. Blood or plasma viscosity: if signs and symptoms of hyperviscosity syndrome (HVS) or IgM > 50 g/L.
7. Direct antiglobulin test and cold agglutinin titre if positive.



## 8. Cryoglobulins.

**IgM monoclonal protein response assessment in WM<sup>122</sup>.** Serum IgM monoclonal protein should be measured by serum protein electrophoresis. The use of nephelometry to determine total serum IgM should be discouraged because this method is unreliable, especially when the levels of monoclonal protein are high. The presence of cryoglobulin or cold agglutinin may affect determination of IgM; therefore, testing of cryoglobulin and cold agglutinin at baseline should be considered, and if present, serum samples should be reevaluated at 37°C to ensure accurate and consistent determination of the monoclonal protein levels.

**Hyperviscosity syndrome (HVS) in LPL.** Symptoms and signs of hyperviscosity include spontaneous bleeding, neurological symptoms and retinopathy. Patients with HVS have an expanded plasma volume and cardiac failure may also occur. There are several published reports demonstrating the efficacy of plasmapheresis in HVS although randomised data are lacking. There is not, however, a simple linear relationship between paraprotein concentration and either plasma viscosity, whole blood viscosity or symptoms. An increase in IgM concentration from 20 to 30 g/L results in an increase in plasma viscosity of <2 centipoise (cP) but an increase from 40 to 50 g/L increases the plasma viscosity by around 5 cP. Indeed, a 1-volume plasma exchange results in a 35-40% decrease in IgM concentration but in up to a 60% reduction in plasma viscosity. In patients with WM the actual plasma volume may exceed that calculated and, given the data above, a 1–1.5 volume exchange is therefore advisable.

**General treatment guidelines for LPL/WM<sup>122</sup>.** The usual indications for starting patients with LPL/WM on active therapy consist of clinical evidence of adverse effects of the paraprotein (HVS with neurological or ocular disturbance, peripheral neuropathy, amyloidosis, symptomatic cryoglobulinemia), symptomatic anemia (Hb<100g/L..beware of pseudo-anemia from hemodilution), platelets <100, progression to high-grade lymphoma, significant adenopathy or organomegaly, or constitutional symptoms.

- **Plasmapheresis:** 1-2 procedures, exchanging 1-1.5 calculated plasma volumes, are advised for the treatment of HVS in WM, followed by chemotherapy to prevent paraprotein re-accumulation. In patients who are drug-resistant, plasmapheresis may be indicated for long-term management. Although there are few studies that consider the role of plasma exchange in the treatment of cryoglobulinemia, there is a clear rationale for its use. The treatment room should be warm and blood warmers used in the cell separator circuit to prevent precipitation during the procedure.
- **Chemotherapy:** The most common initial chemotherapy for LPL is B-R (Bendamustine-Rituximab) followed by rituximab maintenance, similar to other indolent B-cell lymphomas. For patients who do not tolerate B-R, CDR (Cyclophosphamide, Decadron, Rituximab) or Bortezomib-based therapy (eg. R-Bortezomib, R-CyBorD) should be considered. Rituximab is active in the treatment of WM but associated with the risk of transient exacerbation of disease-related complications and should be used with caution in patients with symptoms of hyperviscosity and/or IgM levels >40 g/L. In patient with hyperviscosity and/or IgM levels >40 g/L, it is advised to hold rituximab for cycle 1, and start rituximab with cycle 2 chemotherapy. In retrospective studies, purine analogue therapy is associated with higher rates of prolonged cytopenias, infections, secondary MDS/AML, and transformation to large cell lymphoma when compared to therapy with alkylating agents. Autologous SCT is used with increasing frequency for LPL, and as such, purine analogues and chlorambucil should be avoided as initial therapy for transplant-eligible patients to prevent risk of blood mobilization failure in the future.
- Second-line therapy commonly involves a Bortezomib-based regimen (eg. R-Bortezomib, R-CyBorD). Purine analogues (Fludarabine) are usually reserved for multiply relapsed disease.
- Non-chemotherapy options for multiply relapsed patients may involve Ibrutinib, Everolimus, or Thalidomide. Among these options, Ibrutinib is the most effective and least toxic, and is considered the

option of choice. In a study of 31 multiply relapsed, rituximab refractory patients, the response rate to ibrutinib was 90% and 18mo PFS was 86%<sup>134</sup>.

- **High-dose therapy supported by autologous SCT** has a role in the management of selected patients with WM who have chemosensitive primary induction failure or relapsed disease (preferably first or second relapse). Autologous stem cell collection is often not possible for patients who have received more than 4 months of prior chlorambucil or purine analogue (fludarabine or 2-CDA) therapy. Re-induction therapy prior to ASCT can usually be achieved with R-CyBorD (Cyclophosphamide, Bortezomib, Dexamethasone). As with other indolent lymphomas, allogeneic SCT should be considered at second or third relapse, before the disease develops absolute chemoresistance. Allogeneic transplantation is rarely done prior to autologous SCT for patients in first or second relapse.

### Hairy Cell Leukemia

Hairy cell leukemia (HCL) and HCL variant (HCL-V) are mature lymphoid B-cell disorders, characterized by the identification of hairy cells and a specific genetic profile. Diagnosis of HCL is based on morphological evidence of hairy cells, immunophenotypic positivity for CD11C, CD103, CD123, and CD25 expression and the presence of *BRAF* V600E somatic mutation. *BRAF*-V600E has not been identified in other B-cell chronic lymphoproliferative disorders except very rarely so the mutation is now considered as the molecular hallmark of the disease. Absence of the *BRAF* gene mutation is reported in approximately 10% of patients with HCL and appears to constitute a subgroup with a poor prognosis<sup>135</sup>.

Patients with asymptomatic HCL may be managed with active observation (watch & wait strategy). Symptomatic patients should be treated with symptoms commonly derived from cytopenias or splenomegaly. Most guidelines agree that even asymptomatic patients with marked cytopenias should be treated including at least one of the following: hemoglobin < 110 mg/dL, platelet count <100 000/ $\mu$ L, or an absolute neutrophil count <1000/ $\mu$ L.

In the first-line setting, purine analogs (cladribine or pentostatin) have been demonstrated to result in long overall survival. No randomized trials have been performed in HCL with no studies to suggest superiority of either drug but cladribine is available in Canada and is the most frequently used drug worldwide for HCL. Early studies used continuous intravenous dosing over 7 days<sup>136</sup> but more recent studies (non-comparative) have investigated subcutaneous dosing over 5 days and demonstrate excellent responses<sup>137</sup>. The recommended dose of cladribine is 0.1-0.14mg/kg daily for 5-7 days. We recommend sc dosing for convenience and reduced infusion times. Infection prophylaxis is recommended as with other purine analogues (PJP and viral prophylaxis for 6-12 months) and patients with active infections should have control of infection prior to therapy initiation if possible.

For relapsed HCL, cladribine can result in a second durable remission however, synergy has been demonstrated with rituximab such that we recommend combination therapy with rituximab and cladribine for relapsed disease<sup>138</sup>. Rituximab should be provided at a weekly dose of 375mg/m<sup>2</sup> x 8 weeks and can be provided concurrently with cladribine. Given the proven equivalence of sc rituximab in other CD20 positive lymphoproliferative disorders, we recommend sc dosing for both cladribine and rituximab. Careful attention for and prophylaxis against infection is recommended. Given the importance of *BRAF* V600E in this disease, *BRAF* inhibitors have been investigated in relapsed patients with high response rates. Low dose vemurafenib at 240mg twice daily was reported to result in complete remissions in 40% of patients. Unfortunately, results do not appear durable after drug discontinuation and retreatment or chronic treatment may be required<sup>139</sup>. We recommend *BRAF* inhibition for patients who are refractory to cladribine (relapse < 24 months) or relapse after cladribine + rituximab<sup>140</sup>. Vemurafenib has also been used

successfully in previously untreated patients with active infections as a bridge to cladribine therapy during treatment of the infection.

### Special Lymphomas

These diagnoses sometimes constitute an oncologic emergency. Treatment may require intensive high dose chemotherapy with central nervous system prophylaxis, and may need to begin within 48 hours, whether staging is complete or not. Patients should be seen for consultation at a major referral centre and may require complicated high dose chemotherapy regimens. Acceptable treatment approaches for some of the entities are outlined below.

#### **Mantle cell lymphoma**<sup>108,109,141-156</sup>

Characteristics of mantle cell lymphoma include: male predominance, median age approximately 65 years, advanced stage with multiple extranodal sites (marrow, blood, and intestinal tract), relative chemoresistance, no evidence for curability following R-CHOP chemotherapy, median time to relapse after initial chemotherapy of 12-18 months and median survival following RCHOP induction of 3-5 years. Significant improvements in PFS over RCHOP alone have been demonstrated with the addition of high dose cytarabine to RCHOP-like regimen induction followed by high dose therapy and ASCT for transplant eligible patients, and for B-R induction for transplant ineligible patients, as well as for prolonged rituximab maintenance after completing initial chemotherapy.

#### *Recommendation regarding Watchful Waiting for MCL:*

Although most patients with MCL have relatively aggressive disease, and even those asymptomatic patients initially managed with watchful waiting have median times to first systemic therapy of 11-12 months, a small proportion of patients can be managed expectantly for over 5 years<sup>157,158</sup>. Features suggestive of indolent MCL include leukemic non-nodal presentations, predominantly hypermutated immunoglobulin heavy chain variable regions, non complex karyotypes and absence of SOX11 expression by immunohistochemistry<sup>159</sup>. Occasionally, nodal MCL can also follow an indolent course<sup>157,158</sup>. Prognostic indices such as the MIPI have not been shown to identify indolent MCL<sup>157</sup>. Poor prognostic features associated with shorter survivals and response durations, for which expectant management is not appropriate, include high burden nodal disease, Ki-67 positivity >20-30%, blastoid histology, p53 or Notch1 mutation, gene expression profiling and altered microRNA signature<sup>160</sup>. No prospective randomized trials, or properly designed retrospective comparative effectiveness research studies have compared immediate treatment versus watch-and-wait for MCL patients without clear indications for therapy. Poorly designed retrospective studies suggest similar survival outcomes to immediate therapy, however these studies were biased because patients were selected for watchful waiting based upon better prognostic factors (eg. younger age, better performance status) and did not routinely administer immediate aggressive therapy according to current standards to all patients in the control groups<sup>157,158</sup>. Prospective randomized trials have demonstrated that more aggressive therapy improves PFS and OS rates relative to less aggressive therapy for MCL. Extrapolating these data to the hypothetical question of aggressive therapy vs no immediate therapy leads to the logical conclusion that immediate therapy is likely the superior approach for most MCL patients.

Given the lack of high quality evidence from properly conducted comparative studies to prove the W&W is non-inferior to immediate therapy, W&W should only be considered for patients who present with all of the following features:

- 1) Non-nodal disease such as CLL-like presentation (lymphocytosis without associated cytopenias) or stage IAE marginal zone-like presentation. Patients presenting with nodal disease should generally receive immediate chemo-immunotherapy as indicated in treatment sections below unless they have significant co-morbidity that will limit life-expectancy, low tumor burden, and meet other criteria listed in this section below.
- 2) No disease-related symptoms
- 3) No adverse pathology features such as blastoid variant, Ki67>20% of cells, or complex cytogenetic changes. Other adverse features include SOX11 expression and complex cytogenetic changes, however, SOX11 immunohistochemistry is not currently available in Alberta.
- 4) Patient consent to forgo immediate therapy despite knowledge of demonstrated survival benefits of aggressive vs less aggressive therapy. Patient agreement to surveillance disease monitoring.

#### *Treatment – Transplant Eligible Patients (Age <65yrs)*

The accepted standard of care for newly diagnosed MCL patients <65 years of age without major co-morbidities involves chemoimmunotherapy followed by high dose therapy with ASCT and then 3 years of rituximab maintenance administered every 2 months. Progression free and overall survival benefit has been established in a prospective randomized trial for patients treated with myeloablative radiochemotherapy followed by autologous stem cell transplant in first remission as consolidation after CHOP-like chemotherapy<sup>153,154</sup>. This strategy was compared to interferon alpha maintenance and demonstrated a 22mo improvement in progression free survival and 20.5mo improvement in overall survival with ASCT. These benefits of ASCT were seen in patients who had low risk MIPI, and who attained CR after RCHOP induction. The addition of high dose cytarabine with rituximab (RC) to RCHOP-like regimens is associated with improved rates of CR, PFS, and OS relative to RCHOP alone. This is supported by studies from the *GELA* and the European MCL Network with R-CHOP/R-DHAP induction prior to ASCT (RCHOP-21 x 3 followed by R-DHAP x3 , or alternating RCHOP/RDHAP x 6 cycles)<sup>155</sup>, as well as the Nordic regimen published as a phase II trial involving RCHOP-21 alternating with Ara-C [3gm<sup>2</sup> for patients under age 60 years or 2g/m<sup>2</sup> for patients over 60 years, repeated every 12 hours for a total of 4 doses], for a total of 6 cycles, then ASCT<sup>161</sup>. Given the superiority of BR over RCHOP in terms of efficacy and tolerability in patients with MCL, a phase 2 study of BR and RC induction for transplant-eligible patients was conducted and demonstrated a favorable safety profile as well as efficacy (with CR 96% and 93% MRD negativity after ASCT)<sup>162</sup>. A pooled analysis of 89 patients who received BR/RC induction chemotherapy prior to ASCT demonstrated a high transplant rate (89%), and durable remissions (5-yr PFS 80% and OS 85%) thus confirming that BR/RC is an excellent choice for induction therapy in MCL<sup>163</sup>.

*TP53* mutation is an uncommon (11%) but significant poor prognostic finding in patients with MCL, highly associated with blastoid morphology, Ki-67 >30%, and high risk MIPI<sup>164</sup>. Unfortunately, intensified standard-of-care regimens for younger patients with MCL do not overcome the deleterious effects of *TP53* mutations, with a median OS of 1.8 years, compared to 12.7 years for *TP53*-unmutated (p,0.0001)<sup>164</sup>. Response to ibrutinib is also less favorable in patients with mutated versus wild-type *TP53*, with median PFS of only 4 months<sup>165</sup>. As such, all patients who are transplant-eligible should undergo *TP53* mutational testing, with allogeneic SCT preferred over autologous SCT for patients with available donors. Allogeneic SCT should also be considered in patients with relapsed disease or with high risk MIPI scores at diagnosis and significant blood/marrow involvement, especially with blastoid morphology.

Although maintenance rituximab has been shown to improve PFS and OS (4 year OS 87% vs. 63%) in the elderly population (age > 60) after induction with R-CHOP<sup>166</sup>, the role of rituximab maintenance after



ASCT for younger patients was uncertain until results of the phase III trial (LyMa) were reported.[152] In the LyMa trial, 299 patients <66years of age with mantle cell lymphoma recieved 4 courses of R-DHAP followed by R-BEAM/ASCT (patients who did not achieve at least PR after R-DHAP could receive 4 additional courses of R-CHOP to facilitate ASCT) and 240 responders were then randomly assigned to receive 3 years of rituximab maintenance therapy (375 mg/m<sup>2</sup>, one injection every two months) or watch and wait. The median follow-up from randomization after transplantation was 50.2 months (range, 46.4 to 54.2). Starting from randomization, the rate of event-free survival at 4 years was 79% (95% confidence interval [CI], 70 to 86) in the rituximab group versus 61% (95% CI, 51 to 70) in the observation group (P=0.001). The rate of progression-free survival at 4 years was 83% (95% CI, 73 to 88) in the rituximab group versus 64% (95% CI, 55 to 73) in the observation group (P<0.001). The rate of overall survival was 89% (95% CI, 81 to 94) in the rituximab group versus 80% (95% CI, 72 to 88) in the observation group (P=0.04). According to a Cox regression unadjusted analysis, the rate of overall survival at 4 years was higher in the rituximab group than in the observation group (hazard ratio for death, 0.50; 95% CI, 0.26 to 0.99; P=0.04)<sup>167</sup>. Further analysis of the LyMa group found that minimal residual disease (determined through Q-PCR for clonal Ig gene rearrangements on bone marrow and/or peripheral blood) is an early predictor of PFS in younger mantle cell lymphoma patients. The group reported 72% and 79% of patients in the watch and wait arm and 59% and 80% in the rituximab arm were negative for minimal residual disease by bone marrow and peripheral blood, respectively. The estimated 3 year PFS for MRD positive/watch and wait, negative/ watch and wait, positive/rituximab, negative/rituximab patients, according to BM and PB MRD status were: 61.6% (95%CI: 35.4-79.8), 83.9% (95%CI: 73.5-93.4), 80% (95%CI: 50-93.1), vs 92.8% ((95%CI: )81.6-97.3), respectively (p=0.0027)<sup>168</sup>. In support of the LyMa trial, a retrospective review of 72 patients previously enrollend in a phase II trial showed a progression free survival benefit in patients who recieved maintenance Rituximab vs those who did not (2 year PFS 90% vs. 65%)<sup>169</sup>.

#### *Treatment – Transplant Ineligible Patients (Age >60-65yrs)*

For patients with mantle cell lymphoma over 60-65 years of age, B-R induction x6 cycles followed by rituximab maintenance q2mo until progression is the standard of care. Results from a recently published open-label, multicentre, randomized, phase 3 non-inferiority trial found a significant benefit for progression-free survival in patients with mantle cell lymphoma treated with B-R versus R-CHOP (HR 0.61, 95%CI 0.42-0.87, p=0.0072)<sup>108</sup>. The recently completed European Mantle Cell Lymphoma Elderly trial reported the results of different maintenance therapy regimens for patients older than 60 years of age with stage III-IV mantle cell lymphoma who were not eligible for HDCT. Initially, patients were randomized to 8 cycles of 3 weekly R-CHOP or 6 cycles of 4 weekly R-FC. Patients in complete or partial remission were then randomized to maintenance with rituximab 375 mg/m<sup>2</sup> every 2 months or interferon- $\alpha$  2a or 2b; both were continued until progression. After a median follow-up of 30 months, rituximab maintenance was associated with a significantly longer remission duration compared to interferon maintenance (51 vs. 24 months; HR=0.56, 95% CI 0.36-0.88; p=0.0117). While there was no difference in overall survival between the two groups, a subcohort of patients treated with R-CHOP appeared to show an advantage in 3-year overall survival with rituximab versus interferon maintenance (85% vs. 70%, p=0.0375). Grade III-IV hematologic toxicity was higher in the patients treated with interferon. The investigators concluded that R-CHOP induction followed by rituximab therapy should be the standard of care for elderly patients with mantle cell lymphoma. The rare patient who has stage I-IIA, non-bulky mantle cell lymphoma could be considered for B-R + IFRT, or even IFRT alone if they are older than 70 years of age or have significant co-morbidities.

**Summary Initial Treatment Recommendations for Mantle Cell Lymphoma:**

Watchful waiting should only be considered for patients who present with all of the following features:

- 1) Non-nodal disease such as CLL-like presentation (lymphocytosis without associated cytopenias) or stage IAE marginal zone-like presentation. Patients presenting with nodal disease should generally receive immediate chemo-immunotherapy as indicated in treatment sections below unless they have significant co-morbidity that will limit life-expectancy, low tumor burden, and meet other criteria listed in this section below.
- 2) No disease-related symptoms
- 3) No adverse pathology features such as blastoid variant, Ki67>20% of cells, or complex cytogenetic changes. Other adverse features include SOX11 expression and complex cytogenetic changes, however, SOX11 immunohistochemistry is not currently available in Alberta.
- 4) Patient consent to forgo immediate therapy despite knowledge of demonstrated survival benefits of aggressive vs less aggressive therapy. Patient agreement to surveillance disease monitoring.

**Treatment – Transplant Eligible Patients (Age <65yrs)**

- 1) Induction: BRx3 cycles, followed by RCx3 cycles
  - a. High dose cytarabine dosing
    - i. 2 g/m<sup>2</sup> BID daily x2 days for age <60, CrCl >60 ml/min, and no pre-existing neurotoxicity
    - ii. 1.5 g/m<sup>2</sup> BID for age>60, or CrCl 46-60 ml/min, or pre-existing neurotoxicity
    - iii. 1 g/m<sup>2</sup> BID for CrCl 31-45 ml/min
- 2) Autologous blood stem cell collection with high dose cytarabine and G-CSF mobilization
- 3) Consolidation: High dose therapy and ASCT
- 4) Maintenance rituximab 375mg/m<sup>2</sup> IV or 1400mg sc (preferred) every 2 months x 3 years post ASCT

**Treatment – Transplant Ineligible Patients (Age >60-65yrs)**

- 1) Induction: Bendamustine-Rituximab x6 cycles
- 2) Rituximab maintenance q2mo until progression or for maximum 4 years

The rare patient with stage I-IIA, non-bulky mantle cell lymphoma could be considered for B-R + IFRT, or even IFRT alone if they are older than 70 years of age or have significant co-morbidities.

**Treatment Relapsed Mantle Cell Lymphoma**

There is no standard treatment for relapsed MCL but there are many options, including chemotherapy and novel agents<sup>170</sup>. In general, treatment choice should take into consideration duration of response to previous treatment.

Patients who achieved 12-24 months PFS with previous chemotherapy may do well with a different noncross-resistant chemotherapy regimen (R-bendamustine or R-BAC if previous (R) CHOP, or vice versa<sup>170-172</sup>. Other treatment options include bortezomib combined with rituximab +/- chemotherapy<sup>173,174</sup>.

Patients with a shorter duration of response to previous treatment should be offered a novel agent. Bruton's tyrosine kinase (BTK) inhibitor ibrutinib has shown the most promise as a therapeutic agent for MCL and does have ministerial approval for relapsed/refractory MCL. A phase 3 trial that randomized relapsed or refractory MCL patients who previously received at least one rituximab-containing regimen showed superior PFS using ibrutinib over temsirolimus (mPFS 14.6 vs. 6.2 months,  $p < 0.0001$ ) but no significant advantage in OS<sup>175</sup>. The efficacy of ibrutinib is enhanced by rituximab; a phase 2 trial using ibrutinib 560 mg PO daily plus rituximab IV q weekly x 4, q month x 7, q 2 months x 8; at a median follow up of 16.5 months, ORR was 88%, 15-month PFS was 69% and 15 month OS was 83%<sup>176</sup>. Lenalidomide also has efficacy in this setting, particularly in combination with rituximab +/- chemotherapy<sup>174,177</sup>.

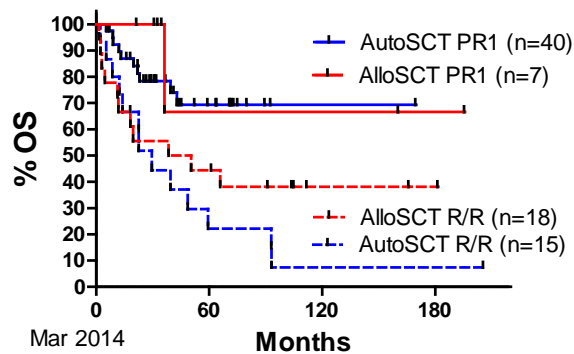
Maintenance rituximab prolongs PFS and OS in relapsed MCL<sup>178</sup> but has not been studied in patients that received it after first-line therapy.

Allogeneic stem cell transplant has the potential to cure MCL, as is evident from a plateau in the survival curves that is often seen post transplant. Because most patients present over the age of 60 and with multiple comorbidities, allogeneic stem cell transplant is not often offered. It is suggested in relapsed or refractory disease for those patients who are young and fit, even after autologous stem cell transplant.

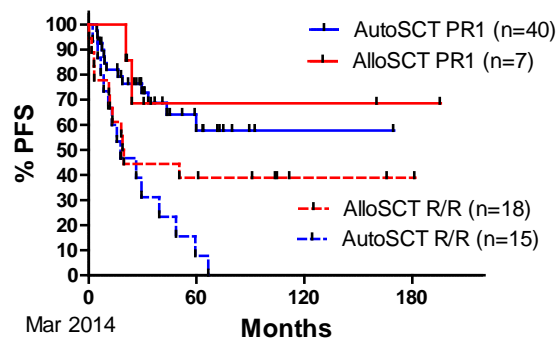
Several retrospective reviews have looked at the outcomes of allogeneic stem cell transplant in the relapsed/refractory setting. Le Gouill *et al.* have shown a 2 year EFS of 50%, 2 year OS of 53% and 1- and 2-year transplant related mortality of 22% and 32% respectively<sup>179</sup>. Longer term follow up has demonstrated 6 year PFS and OS rates of 46% and 53%, respectively confirming the plateau in response that is often seen to allogeneic stem cell transplantation<sup>180</sup>. Response to chemotherapy has consistently been shown to predict both success of allogeneic stem cell transplant and transplant related mortality, with the best outcomes in those who have achieved a CR or CRu. Chronic GVHD has been shown in retrospective reviews to reduce the risk of relapse and DLI has been shown to salvage some patient who relapse or progress post allogeneic stem cell transplant, suggesting a graft-versus-tumour effect in MCL. Reduced intensity Allo SCT in the MCL setting has also been looked at retrospectively with 5 year PFS and OS rates of 14% and 37% respectively, and 1 year non relapse mortality of 18%<sup>181</sup>. Ibrutinib bridging prior to allogeneic SCT has recently been shown to improve transplant outcomes, with 2 year PFS 76% and 2-year OS 86% in one published series<sup>182</sup>.

The Calgary experience suggests no difference in OS or PFS when allogeneic vs. autologous stem cell transplantation are used in front-line therapy however, in the relapsed/refractory setting, allogeneic stem cell transplantation appears to offer superior OS and PFS.

**Hematopoietic Stem Cell Transplantation  
for Mantle Cell Lymphoma in Calgary (n=80)**



**Hematopoietic Stem Cell Transplantation  
for Mantle Cell Lymphoma in Calgary (n=80)**



Allogeneic SCT for Mantle Cell Lymphoma should be offered if the following conditions are met:

- 1) Chemosensitive disease (PR/CR to most recent chemotherapy)
- 2) ECOG 0-2
- 3) Disease status first remission to 2<sup>nd</sup> relapse:
  - a. First remission only if: *TP53*-mutated, blastoid variant, or high risk MIPI (full myeloablative conditioning).
  - b. Relapsed MCL (1<sup>st</sup> or 2<sup>nd</sup> relapse only):
    - i. >1year following ASCT (reduced intensity conditioning for alloSCT if prior ASCT)
    - ii. If no prior ASCT (full myeloablative conditioning pre-AlloSCT)

**Lymphoblastic lymphoma**<sup>183-189</sup>

Patients with lymphoblastic lymphoma require aggressive combination chemotherapy, similar to regimens used in acute lymphoblastic leukemia (ALL), involving induction, consolidation, prophylactic intrathecal chemotherapy and either maintenance therapy or first remission allogeneic SCT (occasionally autologous SCT). Refractory or relapsed patients should be considered for allogeneic SCT if not done previously.

**Burkitt lymphoma**<sup>190-192</sup>

Patients with *classical Burkitt Lymphoma* require aggressive combination chemotherapy with prophylactic intrathecal chemotherapy. Acceptable regimens such as R-CODOX-M/IVAC are described in Appendix A.



First-remission autologous SCT should be considered for patients who cannot tolerate timely administration of full dose *R-CODOX-M/IVAC* (particularly with adverse prognostic features). Patients who do not have classical Burkitt Lymphoma (eg. Double hit DLBCL, Unclassifiable with features intermediate between DLBCL and Burkitt Lymphoma, etc) do not seem to achieve high cure rates with *R-CODOX-M/IVAC*, and instead should receive different induction therapy, often with first remission ASCT (see section on DLBCL above).

### Special Problems in Lymphoma Management

#### **Gastric MALT lymphoma**<sup>193-201</sup>

For complete staging evaluation, patients with gastric MALT lymphoma require gastroscopy and multiple mucosal biopsies for *Helicobacter pylori*. Stage IAE low grade gastric MALT should be treated with omeprazole 20mg twice daily, clarithromycin 500mg twice daily and either metronidazole 500mg twice daily or amoxicillin 1000mg twice daily for one week<sup>202</sup>, or an equally effective regimen such as the Hp-PAC. After treatment with antibiotics, patients should undergo repeat gastroscopy at 3 months, then every 6 months for 2 years, then annually for 3 years. Biopsies should be taken for lymphoma and *H pylori* each time. One re-treatment should be tried if *H pylori* persists. MALT lymphoma may slowly regress over 12-18 months after *H pylori* eradication. If lymphoma recurs or persists more than 12-18 months after eradication of *H pylori*, the patient should receive upper abdominal irradiation (30 Gy/20 fractions with POP if anatomy permits, otherwise 4-5 field plan with superior portion AP/PA and inferior portion AP, R lateral and L lateral). Patients with localized MALT lymphomas are reported to have excellent clinical outcomes after moderate-dose radiation, significantly less risk of distant recurrence, and good overall survival<sup>203</sup>. Patients could also be considered for IFRT rather than *H pylori* therapy if the tumour is associated with t(11;18), NFkB, or nuclear bcl-10 expression. Stage IIAE or greater gastric MALT should be managed as advanced low grade lymphoma plus eradication of *H pylori* with antibiotics. Other histologies of gastric lymphoma should be managed as per the sections on aggressive lymphomas or follicular lymphomas above.

#### **Testicular lymphoma**<sup>196,204-206</sup>

In contrast to other patients with localized large B-cell lymphoma, patients with stage IAE or IIAE testicular lymphoma are cured less than 50% of the time using brief chemotherapy and irradiation. Thus, the recommended treatment for all stages of testicular lymphoma is a full course of chemotherapy (R-CHOP x 6 cycles). An additional problem often seen in these patients is relapse in the opposite testicle. This can be prevented by scrotal irradiation (25-30Gy/10-15 fractions). Finally, these patients are at high risk for CNS relapse. Although some experts recommend prophylactic intrathecal chemotherapy, especially for stage 3-4 disease, this has not been proven effective. Unfortunately, many of the CNS relapses occur within the brain parenchyma, and are not prevented by intrathecal chemotherapy. For this reason, CNS prophylaxis should involve high dose intravenous methotrexate 3.5g/m<sup>2</sup> every 14-28 days x 2-3 doses after completion of all 6 cycles of R-CHOP.

#### **Primary CNS lymphoma (PCNSL)**<sup>196,207-218</sup>

Diagnosis of PCNSL is based on a biopsy of the brain lesion, or pathological examination of a vitrectomy or CSF specimen. A bone marrow biopsy and CT scan of the chest, abdomen, and pelvis is required to rule out systemic disease. Additional staging tests include CSF cytology (only if lumbar puncture is not contraindicated because of intracranial hypertension and midline shift). HIV serology should also be obtained.

Treatment of PCNSL involves induction chemotherapy based upon high dose methotrexate 3.5g/m<sup>2</sup> every 2 weeks for 4 to 5 doses. Intrathecal methotrexate has not been shown to be beneficial if high-dose

methotrexate is used. In a phase II trial, 79 patients aged 18 to 75 years with ECOG 0-3 and mostly low-to-intermediate IELSG risk were randomized to treatment with high dose methotrexate plus cytarabine or high-dose methotrexate alone for 4 cycles every 3 weeks, followed by whole brain radiotherapy (WBRT)<sup>207</sup>. The investigators reported superior CR (18% vs. 46%,  $p=0.006$ ), ORR (40% vs. 69%,  $p=0.009$ ) and 3 year EFS (24% vs. 35%,  $p=0.02$ ) for patients treated with high-dose methotrexate and cytarabine versus high-dose methotrexate alone. It is therefore recommended to use high-dose methotrexate and cytarabine during induction therapy for PCNSL<sup>207</sup>.

Whole brain radiotherapy (WBRT) has fallen out of favour for PCNSL, based in part upon high rates of severe neurotoxicity following high-dose methotrexate, and in part due to the results of the G-PCNSL-SG1 randomized controlled trial, in which 551 immunocompetent PCNSL patients (median age 63 years) were randomized to chemotherapy followed by WBRT (arms A1, B1) or chemotherapy alone (arms A2, B2)<sup>219</sup>. 411 patients entered the post-high dose methotrexate phase, and 318 of these patients were treated per protocol. For this per protocol population, there were no differences in median OS (32.4 vs. 37.1 months,  $p=0.8$ ) or median PFS (18.3 vs. 12 months,  $p=0.13$ ) between the chemotherapy plus WBRT arms (A1+B1,  $n=154$ ) or chemotherapy alone arms (A2+B2,  $n=164$ ), respectively<sup>219</sup>. A recent study suggests neurotoxicity can be reduced by decreasing WBRT dose to 23.4Gy after CR to induction HDMTX-based chemotherapy. The 2-year PFS was 78% in these patients<sup>218</sup>.

Although patients with refractory or relapsed PCNSL typically have dismal outcomes, autologous stem cell transplantation (ASCT) has shown promising results in this setting. Soussain *et al.* (2001) have reported a 3-year event-free survival (EFS) rate of 53% for patients with relapsed/refractory PCNSL undergoing ASCT following high dose thiotepa, busulfan and cyclophosphamide (TBC) conditioning<sup>217</sup>.

Small studies have demonstrated durable remissions with ASCT for PCNSL, however, the optimal conditioning regimen remains undefined<sup>220-223</sup>. With the knowledge of our initial encouraging experience with TBC/ASCT<sup>220</sup>, and the lack of any widely accepted standard treatment for PCNSL, TBC/ASCT consolidation was considered an acceptable option to treat consenting PCNSL patients at our centre. We treated 21 PCNSL patients aged 34-69 years (median 56) with high dose thiotepa, busulfan, cyclophosphamide (TBC), and ASCT as part of front-line therapy, without WBRT<sup>224</sup>. Patient characteristics included: Karnofsky performance status (KPS) <70% ( $n=17$ ), age >60 years ( $n=8$ ), deep brain involvement ( $n=16$ ). Treatment-induced neurotoxicity was not observed in any of these patients. Three of the 21 patients experienced primary refractory/progressive disease during HDMTX/Ara-C induction. Eleven of 21 patients (52%) survived progression-free at a median follow-up of 60 (6-125) months post-ASCT. Causes of death included progressive PCNSL ( $n=4$ ), progressive systemic lymphoma ( $n=1$ ), early treatment-related mortality (transplant-related mortality [TRM],  $n=3$ ), and 2 late deaths from pneumonia 3 years post-ASCT. All patients who died of TRM were over 60 years of age and had poor performance status. An American study treated 32 PCNSL patients with 5-7 cycles R-MPV, and 25 patients went on to receive TBC/ASCT. The 1-year EFS was 78%, the 2-year OS was 76%, TRM was 8% and no patient developed delayed neurotoxicity<sup>225</sup>.

The role of Rituximab in treating PCNSL was evaluated in the International Extranodal Lymphoma Study Group (IELSG) 32 study<sup>226</sup>, which randomized patients with histologically-proven primary CNS lymphoma to receive a maximum of four 3-week cycles of methotrexate at 3.5 g/m<sup>2</sup> on day 1 and cytarabine at 2 g/m<sup>2</sup> twice daily on days 2 and 3, either alone (arm A;  $n = 75$ ), in combination with 375 mg/m<sup>2</sup> of rituximab on day -5 and 0 (arm B;  $n = 69$ ), or combined with rituximab at the same dose plus 30 mg/m<sup>2</sup> of thiotepa on day 4 (MATRIX arm;  $n = 75$ ). The study was conducted at 52 locations across five countries. The median patient age was 58 years (range, 18-70) and all patients were HIV-negative. Overall, patients had an

ECOG PS  $\leq 3$ , with patients aged 66 to 70 years having an ECOG PS  $\leq 2$ . Patient characteristics were well balanced among the study arms. Autologous stem cells were successfully collected after the second treatment course in 152 patients (94%). In the MATRIX arm C, the overall response rate was 87% (95% CI, 80-94) compared with 74% (95% CI, 64-84), and 53% (95% CI, 42-64) in arms B and A, respectively ( $P = .00001$  for A vs C). <sup>226</sup>As reported by Dr. Andrés Ferreri at the ASH 2016 conference (abstr 511), at a median follow-up of 40 months, the PFS rate was approximately 55% in the MATRIX arm C, 39% in arm B, and 29% in arm A, with OS rates of 63%, 46%, and 31%, respectively. Of the 219 enrolled patients, 118 (54%) patients without progressive disease ( $n=52$ ) or excessive toxicity/poor mobilization/refusal ( $n=49$ ) underwent a second randomization comparing consolidation with whole-brain irradiation ( $n=59$ ) or ASCT ( $n=59$ ). The CR rate similarly improved from 54% after induction up to 94% after either consolidation therapy, suggesting a very important role for consolidation therapy. There were no statistically significant differences in PFS after the two consolidation treatments (3yr PFS approximately 60-70%), however, neurotoxicity rates were higher in the WBRT arm.

The Anocéf-Goelams PRECIS prospective randomized phase II trial evaluated high dose chemotherapy and ASCT consolidation using TBC conditioning ( $n=38$ ) vs WBRT ( $n=38$ ) after induction therapy (R-MBVPx2 then R-AraC x2) for PCNSL pts 18-60yo in 23 French centres, and reported 2 yr PFS rates of 86.8% vs 63.2% in favor of ASCT<sup>227</sup>.

The potential benefit of rituximab with induction chemotherapy was not confirmed in different phase III trial by HOVON 105/ALLG NHL 24<sup>228</sup>, in which 119 patients in Netherlands, Australia and New Zealand were randomized to 2 cycles of induction (MTX, BCNU, teniposide, prednisone) with or without rituximab, then followed by consolidation with cytarabine and WBRT 30Gy (+10Gy boost) if <60yrs of age. This study reported non-significantly different 1 year EFS rates of 49% and 52% for rituximab vs no rituximab (ORR 87% and CR 67%).

The Alberta Lymphoma Group established a provincial PCNSL Treatment Protocol in November 2011. The rationale behind the 2001 protocol included:

- 1) Induction chemotherapy:
  - a. First 2 cycles: HDMTX 3.5g/m<sup>2</sup> d1,15 with procarbazine 100mg/m<sup>2</sup> po d1-7. This treatment had been shown to induce response and is tolerable for patients who may be debilitated at the time of initial diagnosis of PCNSL. Cytarabine was not added to first cycle HDMTX because patients may not tolerate intensive therapy well until performance status improves.
  - b. Stem Cell Mobilization and Apheresis: to be done with first dose of Cytarabine because stem cells may not mobilize well after multiple cycles Cytarabine/G-CSF. Rituximab will be used in addition to Cytarabine due to reports that lymphoma cells can circulate in blood and marrow in patients with PCNSL<sup>229</sup>, and Rituximab may decrease risk of collecting contaminated autograft as has been shown for other B-cell lymphomas.
  - c. Final 2 Cycles will combine Cytarabine with HDMTX as done in a prior IELSG study to improve response rates and decrease frequency of primary progressive disease<sup>207</sup>.
  - d. Rituximab was added in 2016 for a total of 6 doses during induction to improve response
- 2) High Dose Chemotherapy (patients <65yo with no significant co-morbidities, KPS>60% after induction therapy, and PCNSL not secondary to immune suppression):
  - a. Thiotepa 300mg/m<sup>2</sup> x2d and Busulfan 3.2mg/kg x3d without cyclophosphamide. Because cyclophosphamide does not penetrate the blood brain barrier particularly well, its omission may decrease treatment-related mortality without decreasing cure rates compared to the previous TBC regimen.

- 3) Ifosfamide consolidation (transplant refusal or ineligible patients):
  - a. Ifosfamide crosses BBB approximately 30%, and gives some exposure of PCNSL to alkylating agent therapy<sup>230,231</sup>.

We recently completed a retrospective review of the outcomes of this protocol for patients treated between Nov 2011 and Dec 2017. In total, 42 patients with a median age of 61 yrs (42-82) were diagnosed with PCNSL from November 2011 – December 2017 in Alberta. Of these 42 patients, 26 patients with a median age of 56.5 years (42-63) were initially deemed to be transplant-eligible and achieved a 3 year PFS rate of 78.3%, even though only 21 (81%) actually received ASCT. Of the 5 who did not proceed to ASCT, 2 had progressive disease on induction and 2 had toxicity to induction preventing ASCT. There was no transplant-related mortality. The 3 yr PFS was 81.2% for the 21 patients who received TBU/ASCT after 2011 compared to only 54.5% for 22 historical control patients who received TBC/ASCT as part of upfront therapy for PCNSL prior to 2011 in Alberta, with respective 3 yr OS rates of 87.1% and 54.5%. Of the other 16 patients who were considered transplant-ineligible at diagnosis, their median age was 70 yrs (61-82), and only 8 were initiated on the transplant ineligible protocol (others received palliation only (n=4), WBRT alone (n=1), and single agent MTX alone (n=3)). The 3 yr PFS rate for the 16 transplant ineligible patients was 0%.

#### ***Recommendations: PCNSL Transplant-Eligible***

The above evidence suggests that transplant-eligible patients are best treated with HDMTX/AraC-based induction followed by TBU/ASCT consolidation. There also is a potentially important role for the addition of rituximab to induction chemotherapy when ASCT consolidation is used. However, the optimal number of induction chemotherapy cycles is unknown, and perhaps as soon as a patient achieves a response and is physically well, they should proceed directly to ASCT before the disease starts to progress, or cumulative toxicity from further induction therapy prevents ASCT consolidation. As such, the 2018 PCNSL guidelines have been modified to decrease the length of induction therapy prior to ASCT. We have not incorporated MATRIX induction, because the use of MATRIX may decrease the ability of patients to proceed to ASCT due to toxicity, increased likelihood of patient refusal due to treatment-fatigue, or due to poor stem cell mobilization. We believe the use of ASCT is more important than the use of MATRIX. Our real world outcomes using non-MATRIX induction and TBU/ASCT are numerically superior to those reported in the MATRIX study.

#### ***Recommendations: PCNSL Transplant-Ineligible:***

- 1) Not chemotherapy candidates due to CIRS score >6 or ECOG ≥3 after dexamethasone therapy:
  - a. palliative WBRT or
  - b. best supportive palliative care only
- 2) Chemotherapy candidates with CIRS score = 0-6 and ECOG 0-2:
  - a. MATRIX x 2-4 cycles. Omit HDMTX if unable to tolerate full MATRIX due to creatinine clearance <50ml/min. For patients receiving full-dose MATRIX, omit HDMTX if signs of renal dysfunction with prior cycle and reduce to once daily AraC if complications from myelosuppression. Restaging should be performed after 2 cycles of therapy. Patients who fail to achieve a radiological and/or clinical response after 2 cycles should be considered for palliation or referral for consolidation WBRT.



For a detailed description of recommended PCNSL treatment regimens, please refer to Appendix A, subheading VII, sections A and B.

For palliative therapy, doses of cranial radiotherapy should be 30Gy in 10-20 fractions.

### ***Eye lymphoma.***

*Orbital or peri-orbital lymphoma*<sup>196,232</sup>: Peri-orbital lymphoma of the bony orbit or the soft tissues in and around the orbit but outside of the globe and optic nerve should be managed as indicated in the earlier sections on aggressive lymphomas, marginal zone lymphomas or follicular lymphoma, as appropriate for the type and stage of the lymphoma. Approximately 40% of such patients have advanced disease discovered when carefully staged. In general, 25-30Gy/20 fractions radiotherapy to whole orbit/periorbital tissue is recommended for indolent peri-orbital lymphomas.

*Conjunctival lymphoma*<sup>196,232</sup>: Lymphoma involving the conjunctiva but not the structures within the globe or the optic nerve is usually of low grade and should be treated with 25-30Gy/20 fractions of radiotherapy. Doses, fields, and shielding specifically modified for treatment of the eye are necessary to minimize long-term complications such as xerophthalmia or cataract formation.

*Intra-ocular and optic nerve lymphoma*<sup>196,233</sup>:

- Lymphoma involving the vitreous, retina or other structures within the optic nerve or globe is usually of large cell type and is equivalent to PCNSL. Bilateral involvement is common. Evaluation and management should be the same as for PCNSL. Acceptable treatment involves induction chemotherapy with high dose methotrexate and high dose cytarabine as described for PCNSL in Appendix A.
- Lymphoma involving the uveal structures (choroid) is a rare presentation of lymphoma, and is usually of indolent type. This disease is best managed with treatment appropriate for stage and local extent of disease.

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## IV. CUTANEOUS LYMPHOMAS<sup>1-25</sup>

**Table 1. Classification criteria of primary cutaneous lymphomas (WHO 2016)**

Disease entity	Subtype	Minimum diagnostic workup	Other useful diagnostic tests
<b>PRIMARY CUTANEOUS T-CELL LYMPHOMAS</b>			
Mycosis fungoides (MF)	<ul style="list-style-type: none"> <li>• Classic MF*</li> <li>• Folliculotropic MF</li> <li>• Pagetoid reticulosis</li> <li>• Granulomatous slack skin disease</li> </ul>	Clinico-pathological correlation supported by immunohistochemistry (CD3, CD4, CD8, CD30) and clonality by TCRr Large cell transformation (>25%) to be noted if present	<ul style="list-style-type: none"> <li>• IHC: CD2, CD5, CD7, PD1</li> <li>• DUSP22-IRF4 translocations (tumor stage)<sup>1</sup></li> </ul>
Sezary's syndrome (SS)		Clinico-pathological correlation supported by <ul style="list-style-type: none"> <li>• skin biopsy (IHC and TCRr)</li> <li>• blood: CD4/CD8 ratio (FC), clonality by TCRr or TCRVbeta chain Abs</li> </ul>	PD-1 (IHC and FC) Blood: CD5, CD7, CD26, CCR4, CD158k, Sezary cell absolute count in blood smear
Primary cutaneous CD30+ lymphoproliferative disease	<ul style="list-style-type: none"> <li>• lymphomatoid papulosis (LyP, types A,B,C,D,E)</li> <li>• pcALCL (anaplastic large cell lymphoma)</li> </ul>	Typical skin lesions and histopathology <ul style="list-style-type: none"> <li>• IHC: CD3, CD4, CD8, CD30, ALK ,EMA</li> </ul>	<ul style="list-style-type: none"> <li>• IHC: CD2,3,5,CD7,CD15, TIA-1, granzymeB, CD56, betaF1, MUM-1</li> <li>• FISH: 6p25 rearrangement (DUSP22-IRF4)</li> <li>• TCRr</li> </ul>
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)		Typical skin lesions and histopathology <ul style="list-style-type: none"> <li>• IHC: CD3, CD8,CD4,TIA-1 , CD56, CD30, EBER</li> <li>• TCRr</li> </ul>	<ul style="list-style-type: none"> <li>• IHC: granzyme B, TCR-gamma.(-)1 βF1,</li> </ul>
EBV-associated T-cell especially extranodal NK/T cell lymphoma	nasal type angioimmunoblastic hydroa vacciniforme-like lymphoproliferative disorder	<ul style="list-style-type: none"> <li>• EBER by ISH</li> <li>• CD3,CD56,CD4,CD8, CD2,CD5,CD7</li> <li>• EBV antibody profile and DNA load</li> <li>• TCR and IgH clonality status</li> </ul>	IHC: TIA-1, granzymeB, CD56, CD21,PD-1, CXCL13, CD10, bcl-6, CD20
Primary cutaneous acral CD8+ lymphoma		Typical skin lesions and histopathology <ul style="list-style-type: none"> <li>• IHC: CD4,CD8,CD3, CD2,CD7 7</li> <li>• TCRr</li> </ul>	IHC: TIA-1 granzymeB,perforin, KI67, βF1
pc CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma		Typical skin lesions and histopathology <ul style="list-style-type: none"> <li>• IHC: CD2, 3, 4, 5, 7, 8, 15, 30, 45RA, TIA-1, CD56, betaF1, EBER by FISH</li> <li>• TCRr</li> </ul>	<ul style="list-style-type: none"> <li>• IHC: TCR-gamma, granzymeB, perforin</li> </ul>
pc gamma-delta T-cell lymphoma		<ul style="list-style-type: none"> <li>• IHC: CD2, 3, 4, 5, 7, 8, 30, 45RA, TIA-1, CD56, betaF1, EBER by ISH</li> <li>• TCRr</li> </ul>	<ul style="list-style-type: none"> <li>• IHC: TCR-gamma, granzymeB,perforin</li> </ul>
pc CD4+ small/medium cell T-cell lymphoproliferative disorder		<ul style="list-style-type: none"> <li>• Clinical picture,sudden</li> <li>• CD4, CD8,CD3, PD-1, CD30,CD7, CD56,TIA-1, CD20</li> </ul>	<ul style="list-style-type: none"> <li>• IHC: CXCL13,BCL6</li> </ul>

\*not included in formal WHO classification of pc lymphomas

<sup>1</sup> DUSP22-IRF4 translocation FISH assay is not routinely available in Alberta

pcPTL NOS		IHC: CD2, 3, 4, 5, 7, 8, 30,, TIA-1, CD56, betaF1, EBER by FISH TCRr	• IHC: TCR-gamma, granzymeB, CXCL13, CD10, bcl-6, CD20
<b>PRIMARY CUTANEOUS B-CELL LYMPHOMAS</b>			
pc follicle center lymphoma (pc FCL)		• Typical skin lesions and histopathology—R/O EBV+ mucocutaneous ulcer	-CD30, CD138, FOXP1, EBER by ISH (in DLBL), Ki-67, Cyclin D1,CD79a,CD21, CD23
pc diffuse large B-cell lymphoma, leg type		• IHC: CD3, CD5, CD20, CD10, bcl-2, bcl-6, MUM-1, kappa/lambda • Ig rearrangement	-MYD88L265P mutation in DLBLLT
<b>OTHER LYMPHOMAS PRESENTING IN THE SKIN (not included in WHO2016 classification)</b>			
Intravascular B-cell lymphoma	<ul style="list-style-type: none"> <li>• Intravascular B-cell lymphoma*</li> <li>• Intravascular NK/T cell lymphoma*</li> <li>• CD30+ lymphoma</li> </ul>	Variable clinical presentation; diagnosis based on histopathology and IHC <ul style="list-style-type: none"> <li>• IHC: CD2, CD3, CD5, CD20, CD79a, CD10, bcl-2, bcl-6, MUM-1, kappa/lambda, CD56, CD30, betaF1, EBER1, TIA-1, granzymeB, ALK-1</li> <li>• Ig rearrangement</li> <li>• TCRr</li> </ul>	
Blastic plasmacytoid dendritic cell neoplasm (BPDCN)	This is not a mature lymphoid neoplasm as per the 2016 WHO classification, but may present with prominent skin disease	Variable but often skin-based clinical presentation; diagnosis based on histopathology and IHC <ul style="list-style-type: none"> <li>• IHC: CD2, CD3, CD7,CD5, CD4, D8, CD20, CD79a, CD56, CD123, TIA-1, TdT, CD34,TIA-1, perforin, CD117, myeloperoxidase, lysozyme</li> <li>• Ig rearrangement</li> <li>• TCRr</li> <li>• EBER and LMP1</li> </ul>	granzymeB, TCL-1, CD303 TCR-gamma, $\beta$ F1
Adult T-cell leukemia lymphoma	Smoldering and chronic forms are skin-presenting illnesses with mild systemic signs	<ul style="list-style-type: none"> <li>• CD4,CD25,CD8,CD3,CD7,CD2,CD5, CD52,CD30</li> <li>• HTLV1 serology /integration status</li> </ul>	• FOXP3 by IHC
T <sub>FH</sub> lymphoma		IHC: CD2, 3, 4, 5, 7, 8, 10, 30, PD-1 TCRr	IHC: ICOS, bcl-6, CXCL13, bcl
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue		<ul style="list-style-type: none"> <li>• Typical skin lesions and histopathology</li> <li>• IHC: CD3, CD5, CD20, CD10, bcl-2, bcl-6, MUM-1, kappa/lambda( IHC or FISH)</li> <li>• Ig rearrangement</li> </ul>	CD138, Ki-67, Cyclin D1,CD79a,CD21, CD23,CD4,CD8,PD1

Abbreviations: Pc = primary cutaneous, IHC = immunohistochemistry, TCRr = TCR rearrangement, FC = flow cytometry.

**Table 2.** Mycosis fungoides and Sezary's syndrome Staging (2007 ISCL/EORTC)

<b>Classification</b>	<b>Description</b>	<b>Comments</b>
<b>T (skin)</b>		Patch indicates any size skin lesion without significant elevation or induration whereas a plaque is elevated or indurated. Presence/absence of hypo- or hyperpigmentation, scale, crusting, poikiloderma or ulceration should be noted. Tumor indicates at least one 1-cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number and volume of lesions, largest size lesion, and region of body involved.
<b>T0</b>	No clinically and/or histopathologically suspicious lesions	
<b>T1</b> <b>T1a</b> patch only <b>T1b</b> plaque +/- patch	Limited patches, papules, and/or plaques covering <10% of the skin surface.	
<b>T2</b> <b>T2a</b> patch only <b>T2b</b> plaque +/- patch	Patches, papules or plaques covering => 10% of the skin surface.	
<b>T3</b>	One or more tumors (=>1-cm diameter)	
<b>T4</b>	Confluence of erythema covering =>80% body surface area	
<b>N (lymph nodes)</b>		Abnormal peripheral lymph node indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or 1.5 cm or larger in diameter. Node groups examined on physical examination include 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.
<b>N0</b>	No clinically abnormal peripheral lymph nodes	
<b>N1</b> <b>N1a – clone negative</b> <b>N1b – clone positive</b>	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2.	
<b>N2</b> <b>N2a – clone negative</b> <b>N2b – clone positive</b>	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3	
<b>N3</b>	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative	
<b>Nx</b>	Clinically abnormal peripheral lymph nodes; no histologic confirmation	
<b>B (peripheral blood)</b>		For blood, Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. Alternatives to Sezary cell count: (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio of 10 or more, (2) expanded CD4+ cells with abnormal immunophenotype including loss of CD7 or CD26
<b>B0</b> <b>B0a – clone negative</b> <b>B0b – clone positive</b>	Absence of significant blood involvement: =<5% of peripheral blood lymphocytes are atypical (Sézary) cells	
<b>B1</b> <b>B1a – clone negative</b> <b>B1b – clone positive</b>	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2	
<b>B2</b>	High blood tumor burden: _=>1000/uL Sezary cells with positive clone	
<b>M (visceral organs)</b>		For viscera, spleen and liver may be diagnosed by imaging criteria
<b>M0</b>	No visceral organ involvement	
<b>M1</b>	Visceral involvement (must have pathology confirmation and organ involved should be specified)	

**Table 3.** Staging of mycosis fungoides and Sezary's syndrome<sup>26-29</sup>

Clinical Stages and 5-year Disease Specific Survival (%)					
	T	N	M	B	5-year DSS (%)
IA	1	0	0	0,1	98
IB	2	0	0	0,1	89
IIA	1-2	1,2	0	0,1	89
IIB	3	0-2	0	0,1	56
IIIA	4	0-2	0	0	54
IIIB	4	0-2	0	1	48
IVA <sub>1</sub>	1-4	0-2	0	2	41
IVA <sub>2</sub>	1-4	3	0	0-2	23
IVB	1-4	0-3	1	0-2	18

### Staging procedures for Mycosis Fungoides/Sezary Syndrome

- **Complete physical examination:** Describe type size of skin lesions, estimate percentage of body surface area involved, presence of palpable lymph nodes, and organomegaly
- **Skin biopsy:** At least one biopsy required, several concurrent biopsies may be indicated
- **Blood tests:** CBC with differential, liver function tests, creatinine, LDH. Peripheral blood flow cytometry and molecular studies for TCR gene rearrangement in cases of suspected Sezary Syndrome
- **Imaging:** For MF stage IA no additional imaging techniques are necessary. For patients with MF stage II or higher imaging including CT scan of chest, abdomen, and pelvis and/or FDG-PET scan are recommended. Full body imaging for MF stage IB (T2N0M0) is discretionary, and simple CXR and select U/S imaging may be adequate
- **Lymph node biopsy:** Biopsy of enlarged (>1.5cm) or abnormal lymph node. Preference given for nodes with abnormal uptake on FDG-PET. Excisional biopsy is preferred in cases of MF in order to reliably discriminate dermatopathic lymphadenopathy from that involved with lymphoma
- **Bone marrow biopsy:** Bone marrow biopsy and aspiration is not a routinely recommended procedure in MF unless a patient has stage IV disease (B2)

## Treatment of mycosis fungoides/sezary syndrome

### Overview

MF at early stages (I-IIA) should preferentially be treated with skin-directed therapies (SDT) including phototherapy, topical steroids, nitrogen mustard. Treatment can be combined with biological response modifiers (IFN- $\alpha$ , retinoids) in cases of resistant or progressive skin disease. Local radiotherapy plays a key role in palliation and treating sanctuary sites. Total skin electron beam therapy is highly effective in T2 or T3 disease however its widespread use is limited by the availability of this technique. Predictably, chemotherapy leads to short remission durations and therefore should be reserved after other therapies have been tried. Its use should be limited to tumour (T3) or more advanced stages. It may be considered frontline in cases with histologic large-cell transformation and high risk features (see discussion below). Monotherapy (low-dose methotrexate, gemcitabine) is generally preferred over combination chemotherapy (e.g. CHOP) unless the patient has extensive burden of disease (nodal and extra-cutaneous and is fit to tolerate). Targeted therapies have demonstrated activity in MF/SS, and are currently reserved for the relapsed/refractory setting or in clinical trials. The optimal conditions for allogenic bone marrow transplant have not been elucidated, but may play a role in highly selected cases (see discussion below). Extracorporeal photopheresis is a unique treatment modality indicated for the treatment of erythrodermic MF/SS. Consensus recommendations for the treatment of MF/SS have recently been updated and are outlined elsewhere<sup>30</sup>. The following table intends to summarize a management approach.

**Table 4.** Treatment of mycosis fungoides<sup>30-41</sup>

Therapy	Mycosis Fungoides		SS/E-MF	Dose and potential toxicities
	Early stage disease	Advanced stage disease		
Expectant policy	++			Suitable for stage I in conjunction with symptomatic treatment if required. Patient with single lesion can be considered for RT for “curative therapy”
Topical corticosteroids	++++	++	+++	Potent steroids such as Clobetasol/betamethasone, long term use can cause side effects such as skin atrophy
PUVA	+++	+	+++	For patch/plaque disease. 2-3 X week. Limited availability, available only in Edmonton/Calgary. Risk of skin cancer with cumulative dosing
UVB	++++	+	++	For thin patch only, as skin penetration not as deep, 2-3 x week. Risk of skin



				cancer with cumulative dosing
Topical Carmustine	++			Has to be compounded. Erythema ,mostly mild but can be severe
Oral Bexarotene	++	+++	++++	200 to 300mg/M2, orally daily. Responses can be durable. Most common side effects are hypertriglyceridemia and hypothyroidism usually requiring treatment and have to be monitored regularly. Not available in Canada, requires SAP.
Interferon alpha	++	++++	++++	3-5 MU/d or 3 x week. Difficult tolerating the drug, cytopenias, thyroid disturbance, mood changes. It can be combined with PUVA, ECP, and Retinoid.
HDACi: Vorinostat, romidepsin	+	+++	++++	Vorinostat, 400 mg po daily, S/E diarrhea, nausea, QT prolongation, cytopenias. Not on the Formulary, only through private insurance. Romidepsin-14mg/M2 iv day1,8,15 of a 28 day cycle, QT prolongation, metabolized by CYP3A4.Limited data in combination, can be used with ECP
Oral Methotrexate	+	+++	+++	20-30mg/week can be given up to 60-70 mg/week. Watch for cytopenias, liver dysfunction. Can be used in combination with ECP, PUVA, and IFN.
Localized radiotherapy	+++	+++		Localized plaques, tumors or nodules
TSEB	+	+++	+	For widespread disease. Can be repeated but high cumulative doses associated with skin toxicity. Patient to travel to Ontario.

ECP		++	++++	Available only in Calgary, needs IV access, which can be problematic
Alemtuzumab		+	++++	Available through Clinigen on compassionate basis. Low dose 10mg three times a week, may be effective decreasing the risk of infections
Brentuximab		+++		Shown to be effective with all levels of CD30 expression but responses significantly lower if CD30 expression less than 30%. Peripheral neuropathy, limiting side effect. 1.8mg/kg IV q every 3 weeks for up to 16 cycles
Single agent chemotherapy, Gemcitabine, liposomal Doxorubicin		+	++	Beyond third line
Combination chemotherapy such as CHOP			+	Refractory Disease
Allogenic Bone marrow transplant		+	++	Very selected cases
Clinical trials				Use if available.

## Staging and treatment of non-MF cutaneous lymphomas<sup>42-45</sup>

**Table 5.** Diagnostic workup and staging

Classification		Description
<b>T</b>	<b>T1</b>	Solitary skin lesion
		• T1a: a solitary lesion with diameter <5cm
		• T1b: a solitary lesion with diameter >5cm
	<b>T2</b>	Regional skin involvement (multiple lesions limited to 1 body region or 2 contiguous body regions)
		• T2a: skin lesions present in a <15-cm diameter circular area
		• T2b: skin lesions present in a >15-cm and <30-cm diameter circular area
		• T2c: skin lesions present in a >30-cm diameter circular area
	<b>T3</b>	Generalized skin involvement
		• T3a: multiple lesions involving 2 noncontiguous body regions
		• T3b: multiple lesions involving 3 or more body regions
<b>N</b>	<b>N0</b>	No clinical or pathologic lymph node involvement
	<b>N1</b>	Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement

	<b>N2</b>	Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
	<b>N3</b>	Involvement of central lymph nodes
<b>M</b>	<b>M0</b>	No evidence of organ disease
	<b>M1</b>	Extracutaneous organ disease

## Staging of other types of non-MF cutaneous lymphomas

**Table 6.** Diagnostic workup

<b>Disease entity</b>	<b>Laboratory and radiologic workup</b>
Lymphomatoid papulosis	<ul style="list-style-type: none"> <li>• Screening for concurrent cancer may be warranted in elderly patients or presence of risk factors</li> </ul>
pcALCL	<ul style="list-style-type: none"> <li>• CBC with diff, blood chemistries and LDH</li> <li>• PET/CT or CT</li> <li>• Lymph node biopsy (if clinically or radiologically abnormal)</li> <li>• Bone marrow biopsy in patients with evidence of extracutaneous disease or multiple tumors</li> </ul>
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)	<ul style="list-style-type: none"> <li>• CBC with diff, blood chemistries and LDH,</li> <li>• PET/CT or CT</li> <li>• Lymph node biopsy (if clinically or radiologically abnormal)</li> <li>• Bone marrow biopsy in patients with evidence of extracutaneous disease, multiple tumors or hematocytophagic syndrome</li> </ul>
CD4+ small/medium cell primary cutaneous T-cell lymphoproliferative disorder	<ul style="list-style-type: none"> <li>• None</li> </ul>
Aggressive pcCTCL: Extranodal NK/T-cell lymphoma, CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma; gamma-delta T-cell lymphoma, Blastic plasmacytoid dendritic cell neoplasm	<ul style="list-style-type: none"> <li>• As other aggressive lymphomas</li> </ul>
Extranodal MZL with cutaneous presentation	<ul style="list-style-type: none"> <li>• CBC with diff, blood chemistries and LDH</li> <li>• Borrelia serology</li> </ul>
pcFCL	<ul style="list-style-type: none"> <li>• CBC with diff, blood chemistries and LDH</li> <li>• PET/CT or CT</li> <li>• Lymph node biopsy (if clinically or radiologically abnormal)</li> <li>• Bone marrow biopsy</li> </ul>
pc diffuse large B-cell lymphoma,	<ul style="list-style-type: none"> <li>• CBC with diff, blood chemistries and LDH</li> <li>• PET/CT</li> <li>• Lymph node biopsy (if clinically or radiologically abnormal)</li> </ul>
Primary cutaneous acral CD8+ lymphoma	<ul style="list-style-type: none"> <li>• None</li> </ul>

Treatment of other types of non-MF cutaneous lymphomas<sup>46-61</sup>
**Table 7.** Treatment of other types of cutaneous lymphomas

CTCL Subtype	First line treatment	Second or third line treatment
Lymphomatoid papulosis <ul style="list-style-type: none"> <li>• Solitary lesion</li> <li>• Large/stigmmitizing lesion</li> <li>• Multifocal</li> </ul>	Observation Topical high potency corticosteroids  Surgical excision Local radiotherapy  Narrow band UVB Psoralen UVA light therapy Low dose MTX(5-25mg/wk)	Topical carmustine 0.2-0.4%*   Interferon alpha Isotretinoin or Alitretinoin
Primary Cutaneous ALCL <ul style="list-style-type: none"> <li>• Solitary lesion</li> <li>• Multifocal or frequently recurrent</li> <li>• Extracutaneous involvement</li> </ul>	Surgical excision Local radiotherapy (15Gy)  Low dose MTX (5-25mg/week) maintenance  CHOP or CEOP	Isotretinoin or Alitretinoin  Interferon  Single agent chemotherapy (gemcitabine, etoposide)  Brentuximab vedotin*
Subcutaneous panniculitis-like T-cell lymphoma <ul style="list-style-type: none"> <li>• Associated hemophagocytic syndrome</li> </ul>	Systemic corticosteroids, alone, or in combination with methotrexate  CHOP or CEOP x 6 +/- HDT-ASCT in eligible patients	Cyclosporine <sup>§</sup>  Vorinostat <sup>¶</sup>  Local radiotherapy  Oral Bexarotene <sup>1</sup>
Primary cutaneous acral CD8+ T-cell lymphoma <i>Provisional entity</i>	Intralesional corticosteroids Local radiotherapy	
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder <ul style="list-style-type: none"> <li>• If tumour rapidly growing or &gt; 5cm, High Ki67</li> </ul>	Observation Topical corticosteroids Intralesional corticosteroids  Local radiotherapy	Local radiotherapy
Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma or Primary cutaneous $\gamma\delta$ T-Cell lymphoma	Multiagent chemotherapy (CHOP or CEOP) plus IFRT 30Gy/10 or 45Gy/25	Vorinostat <sup>¶</sup>  HDT/ASCT or Allogeneic stem cell transplantation in eligible candidates



<p>Blastic plasmacytoid dendritic cell neoplasm (CD4+/CD56+ hematodermic neoplasm)</p>	<p>Multiagent chemotherapy (CHOP or CEOP)</p> <p>Acute lymphoblastic leukemia type protocol if concurrent bone marrow involvement</p> <p>Allogeneic stem cell transplantation in first remission for eligible patients</p>	<p>Single agent chemotherapy (Gemcitabine)</p> <p>Local radiotherapy</p>
<p>Primary cutaneous extranodal NK/T cell lymphoma, nasal type</p>	<p>Combined Modality (CHOP or CEOP plus IFRT) for localized presentation SMILE or equivalent for advanced stage</p>	<p>HDT-ASCT in eligible patients with relapsed/refractory</p>
<p>Primary Cutaneous Marginal Zone Lymphoma <i>or</i> Primary Cutaneous Follicle Center Lymphoma</p> <ul style="list-style-type: none"> <li>• Solitary lesion</li> <li>• Multifocal lesions</li> <li>• <i>B. burgdorferi</i> associated pcMZL</li> </ul>	<p>Surgical excision Local radiotherapy (15-35Gy)</p> <p>Observation Chlorambucil Rituximab monotherapy*</p> <p>Antibiotics (cephalosporin or doxycycline)</p>	<p>Intralesional corticosteroids</p> <p>Intralesional rituximab (5-20mg per lesion q4week x 3-6 cycles)*</p> <p>Treat as systemic (R-Bendamustine x 6)</p>
<p>Primary cutaneous large B cell lymphoma, leg type</p>	<p>R-CHOP x 6 +/- IFRT</p> <p>IFRT +/- rituximab monotherapy* if frail</p>	

• Short term director's privilege (STDP) required

§ Short term exceptional drug therapy (STEDT) approval required

⌘ Health Canada Special Access Program required

¶ Not covered by AHS Cancer Control Drug Benefit list. Manufacturer's reimbursement assistance program available. Dispensed through retail pharmacy

★☐ Manufacturer application required for access. Drug not funded.

## Special topics in CTCL

### The role of transplantation in cutaneous lymphoma<sup>35,36,39,62-71</sup>

Existing studies of allogeneic stem cell transplantation in mycosis fungoides or sezary syndrome are limited to small, retrospective reports or case series. Autologous stem cell transplantation has not been associated with durable remissions and therefore has been largely abandoned for MF/SS. The following recommendations are based on best available outcome data and established consensus guidelines:

- Patients with MF/SS should be risk-stratified using the CTCL International Consortium prognosis score. Patients with high-risk disease (3 or 4 of age>60, elevated LDH, stage IV or LCT) should be considered for allogeneic transplantation as part of second line of therapy.
- Patients with advanced stage 3 or stage 4 MF/SS who progress after more than two lines of systemic therapy should be considered for allogeneic transplantation.
- Selected patients with stage 2 MF/SS or with large cell transformation may be considered for allogeneic BMT..
- Patients must meet other eligibility criteria for transplant prior to being considered. Issues such as chemosensitivity (CR or PR to last line of therapy), adequate performance status (ECOG 0-2) and preserved organ function apply.
- TSEB before transplant may be considered prior to transplantation for improved skin control.
- Transplantation in other rare and aggressive CTCL such as CD8+ epidermotropic aggressive T cell lymphoma or primary cutaneous gamma-delta T cell lymphoma is at this time a largely experimental approach
- Relapses still occur after allogeneic transplants and may be treated adjustment of immunosuppression, DLI infusion, or further skin-directed treatments. Distinguishing CTCL from transplant associated GVHD requires multidisciplinary expertise.

## Large Cell Transformation in Mycosis Fungoides

The pathologic definition of large cell transformation in mycosis fungoides (LCT-MF) is the presence of large cells ( $\geq 4$  times the size of a small lymphocyte) in 25% or more of the dermal infiltrate *or* forming microscopic nodules. The cells are often CD30+ by IHC however CD30- variants are also described. It is difficult to discriminate from other subtypes of cutaneous lymphoma, including cutaneous anaplastic large cell lymphoma (cALCL) or lymphomatoid papulosis (LyP), which may also coexist with mycosis fungoides.

The prognosis of LyP and cALCL is considerably more favourable than LCT-MF. Historical estimates for long-term survival with LCT-MF is less than 20%, and most series report a median survival of 2-36 months. However, a subset of patients with limited LCT-MF may follow a more indolent course. One large EORTC cohort analysis reported a median survival of 8.3 years for patients with LCT, and the authors concluded LCT is significant for disease progression but not survival outcome.<sup>26</sup>

Currently, there is a lack of prospective research to guide a standardized approach for management of LCT-MF. Most patients are treated with combination chemotherapy however it remains unclear which patients benefit from this approach.

Several clinical and pathological characteristics in LCT-MF have been associated with poor prognosis,<sup>28,33</sup> including advanced age (> 60 years), elevated LDH at transformation, advanced stage (III/IV), extra-cutaneous transformation, the presence of follicular mucinosis, folliculotropism, and CD30-negativity. Additional pathologic variables have been described but may not be routinely analyzable so have been omitted from these recommendations.

We recommend to consider intensive chemotherapeutic strategies (monotherapy or combination in suitable fit candidates) in patients with any of the following clinical or pathologic variables associated with high risk LCT-MF. In the absence of these, we recommend treatment as per MF guidelines (see Table I).

*Clinical variables for high risk LCT-MF:*

- advanced age (> 60 years)
- elevated LDH at transformation
- generalized tumours (versus solitary or regional)
- advanced stage (III/IV)
- extra-cutaneous transformation

*Adverse Pathologic variables in LCT*

- absent papillary dermal involvement (assessment may be limited by provided tissues)
- folliculotropism
- follicular mucinosis
- absence of fibrosis
- CD30 expression in less than 50% of neoplastic cells

Brentuximab vedotin has activity in LCT-MF. A phase 2 study of brentuximab in a heavily pre-treated CD30+ MF/SS population, the majority of whom had LCT (30/32, 90%) showed a significant response rate of 70%.<sup>52</sup> A subsequent prospective, randomized controlled trial of brentuximab vedotin versus physician's choice (MTX or bexarotene) in CD30+ CTCL demonstrated a significant improvement in objective global response lasting at least 4 months with brentuximab (56.3% versus 12.5%).<sup>57</sup> The study included both previously treatment CD30+ MF and CD30+ ALCL. Although the histologic characteristics of the CD30+ MF patients were unreported, a proportion may have had transformed MF, as this was not an exclusion criteria. Brentuximab vedotin is indicated for previously treated CD30+ MF, and could be tried for high risk LCT-MF patients as defined above, who are either unsuitable for chemotherapy or refractory/relapsed following chemotherapy.

## Aggressive T-Cell Lymphomas

### **NK/T-cell lymphoma, nasal type:**<sup>72-80</sup>

Natural killer (NK)/T-cell lymphoma, nasal type is a rare and aggressive extranodal neoplasm that almost exclusively affects Asian and South American adults in the fifth decade of life, with a male:female ratio of approximately 3:1. It typically arises in the nasal cavity or surrounding structures, such as the sinuses, palate, nasopharynx, tonsils, hypopharynx, and larynx. While the pathogenesis of NK/T-cell lymphoma, nasal type is not well understood, the Epstein-Barr virus (EBV) is implicated in almost all cases. Approximately 25% of cases show a p53 mutation; in addition, p21 over-expression is also frequent in nasal NK/T-cell lymphoma, and seems to be independent of p53 gene status.<sup>75</sup>

Hematopathological evaluation of a biopsy specimen from the site of involvement is the basis for diagnosis of nasal NK/T-cell lymphoma. The recommended immunohistochemistry panel includes:<sup>73,81</sup>

- B-cell: CD20
- T-lineage antigens: CD2, CD7, CD8, CD4, CD5, CD3
- NK lineage markers: CD56
- Cytotoxic granules (granzyme B and/or TIA-1)
- Ki-67
- *In situ* hybridization for EBV-encoded RNA (EBER)

For patients with early-stage nasal NK/T-cell lymphoma, early or upfront radiotherapy (intensive regimens such as a total dose  $\geq 50$  Gy) plays an essential role in therapy, and has been associated with higher overall survival and complete response rates compared to chemotherapy alone.<sup>76</sup> However, radiotherapy alone is also associated with high relapse rates. Combined modality therapy is recommended. In a phase II trial involving 30 patients treated with concurrent radiation (40–52.8 Gy) and weekly cisplatin (30mg/m<sup>2</sup>) followed by 3 cycles of VIPD chemotherapy (etoposide 100mg/m<sup>2</sup> d1-3 + ifosfamide 1.2g/m<sup>2</sup> d1-3 + cisplatin 33mg/m<sup>2</sup> d1-3 + dexamethasone 40mg d1-4), *Kim et al.* (2009) reported an overall response rate of 83.3%, and a complete response rate of 80%.<sup>77</sup> The 3-year progression-free and overall survival rates were 85.2% and 86.3%, respectively. While 26 patients completed all 3 cycles, there was a high rate of grade 4 neutropenia (41.4%). Similar results have been described in a phase I/II study involving 26 assessable patients treated with radiotherapy (50 Gy) and 3 courses of dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC).<sup>78</sup> In another recently completed phase II trial, 31 patients with stage I or II disease were treated with radiotherapy 40–50.4 Gy plus cisplatin 30mg/m<sup>2</sup> weekly, followed by 2 cycles of VIDL (etoposide 100mg/m<sup>2</sup> d1-3, ifosfamide 1200mg/m<sup>2</sup> d1-3, dexamethasone 40mg d1-3, and L-asparaginase 4000IU/m<sup>2</sup>).<sup>79</sup> The overall response rate after the concurrent chemo-radiotherapy was 90%, and after VIDL was 92.6%; one-year progression-free survival was approximately 75%; lower than with VIPD, though a lower total dose of radiation was provided in this study and is postulated as the cause of the reduced PFS. Grade 3-4 leucopenia was reported in 85.1% of patients, and hepatic toxicity associated with L-asparaginase, the majority of which was grade 1 or 2, was reported in 55% of patients. Despite these results, L-asparaginase appears to be an active agent in this disease and most novel regimens incorporate L-asparaginase into treatment. One such regimen, GOLD (gemcitabine, oxaliplatin, L-asparaginase, dexamethasone) was recently reported in N=55 patients of whom 10 had stage III/IV disease. Amongst patients treated with the GOLD regimen, 91% (48/55) experienced a response, with 62% (34/55) having a complete response, and 29% (15/55) a partial response. In patients with stage I/II disease, 1-year PFS and OS were 87% and 98%, respectively. In patients with stage III/IV disease, 1-year PFS and OS were 66% and 75%, respectively<sup>82</sup>.

For patients with stage III-IV disease, complete remission rates are less than 15%, and the median overall survival is approximately 4 months.<sup>80</sup> The recommended options for therapy include either enrollment in a clinical trial or treatment with an L-asparaginase-based combination chemotherapy regimen. The most well-studied regimen is the SMILE regimen with several small series of patients reported<sup>83-85</sup>. While the SMILE regimen was first reported to have excellent response rates (overall, and complete in 79% and 45%, respectively) in relapsed/refractory patients, an updated study of the use of the SMILE regimen as frontline therapy for advanced stage patients reported a short median OS (12.2 months; 1-year OS was 45%) with a high rate of TRM (5 of 87 patients died of sepsis)<sup>83</sup>. While the GOLD regimen has less reported patients, the toxicity is significantly less (Grade 3-4 neutropenia of 16% compared to SMILE of 92%<sup>84</sup> with serious infections in 4% and 31-45%<sup>83,84</sup> of patients treated, respectively). For this reason, patients of advanced age or with comorbidities or a history of infections should be considered for therapy with GOLD for 2-4 cycles followed by SCT if possible while younger, fit patients can be treated with SMILE x 2 cycles with a goal of proceeding to SCT as consolidation. The role of allogeneic or autologous SCT is not yet well defined however, as data is limited but it is suggested when possible for advanced stage or relapsed/refractory patients.

### **Peripheral T-cell lymphomas (PTCL):**<sup>86-94</sup>

With the exception of ALK-positive anaplastic large cell lymphoma, CHOP chemotherapy cures less than 30% of patients with PTCL. Options that may be associated with higher cure rates include CHOP x 4-6 cycles followed by HDCT/ASCT in responding patients or intensification of CHOP with etoposide (CHOEP). The German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) analyzed results of 343 PTCL

patients treated within their trials.<sup>95</sup> The majority belonged to the four major T-cell lymphoma subtypes: anaplastic large cell lymphoma (ALCL), ALK-positive (n=78); ALCL, ALK-negative (n=113); peripheral T-cell lymphoma, unspecified (PTCLU; n=70); and angioimmunoblastic T-cell lymphoma (AITL; n=28). Treatment consisted of 6-8 courses of CHOP or etoposide plus (CHOEP). Three-year event-free and overall survival rates were 75.8% and 89.8% for the ALCL, ALK-positive patients, 50.0% and 67.5% for the AITL patients, 45.7% and 62.1% for the ALCL, ALK-negative patients, and 41.1% and 53.9% for the PTCLU patients. The International Prognostic Index (IPI) was effective in defining risk groups with significantly different outcomes. For patients, 60 years of age or younger with LDH levels  $\leq$  upper normal value, etoposide was associated with an improvement in 3-year EFS (75.4% vs. 51.0%,  $p=0003$ ).<sup>86</sup> Aviles and colleagues recently reported the results of a phase III trial involving 217 patients with PTCL unspecified.<sup>87</sup> Patients were treated with either CMED every 14 days x 6 cycles or standard CHOP. The 10-year PFS was 70% in the CMED group versus 43% in the CHOP group ( $p<0.01$ ), and the 10-year OS was 60% in the CMED group versus 34% in the CHOP group ( $p<0.01$ ).<sup>87</sup>

Retrospective and prospective phase II trials support the use of SCT as part of upfront therapy for PTCL. Sieniawski and colleagues reported 5-year PFS rates of 60% for 26 patients with enteropathy associated T-cell lymphoma treated with IVE-methotrexate induction therapy followed by autologous SCT, compared to only 22% for 54 patients treated with CHOP-like therapy alone.<sup>87</sup> Two prospective trials have also been reported. In the first, Reimer and colleagues reported results of CHOP x 4-6 cycles followed by dexabeam or ESHAP followed by CyTBI/ASCT for 83 patients (including 32 with PTCL-not otherwise specified, and 27 with angioimmunoblastic T-cell lymphoma).<sup>89</sup> Fifty-five of the 83 patients received transplantation. In an intent-to-treat analysis, with a median follow-up time of 33 months, the estimated 3-year OS, DFS, and PFS rate were 48%, 53%, and 36%, respectively.<sup>96</sup> In the second prospective trial, Rodriguez and colleagues from the Spanish Lymphoma and Autologous Transplantation Cooperative Group reported the results of 74 patients transplanted in the first complete response (65% had 2-3 aalPI risk factors).<sup>90</sup> With a median follow-up of 67 months from diagnosis, the 5-year OS and PFS rates were 68% and 63%, respectively.

For PTCL patients who relapse following CHOP-type induction and respond to salvage therapy, ASCT should be recommended, as several studies report similar ASCT outcomes to those seen with relapsed DLBCL. Brentuximab vedotin may be considered for those patients with CD30+ anaplastic large cell lymphoma who have had failure of initial chemotherapy.<sup>97</sup>

*Summary of treatment recommendations for PTCL:*

1. Anaplastic large cell lymphoma, ALK positive: CHOP x 6 cycles
2. NK/T-cell lymphoma, nasal type:
  - recommendation for stage I-II NK/T cell lymphoma: IFRT as initial therapy (either 30Gy/10 fractions IFRT or concurrent 40-50Gy IFRT+ weekly cisplatin 30mg/m<sup>2</sup>) then follow IFRT with VIPD x 3 cycles (etoposide 100mg/m<sup>2</sup> d1-3 + ifosfamide 1.2g/m<sup>2</sup> d1-3 + cisplatin 33mg/m<sup>2</sup> d1-3 + dexamethasone 40mg d1-4)
  - if IFRT must be delayed for 2 or more weeks after diagnosis due to scheduling issues, then d1-4 of GDP could be administered while waiting for IFRT
3. All other subtypes of PTCL:
  - <60 years of age with IPI=0-2: CHOEP x 6 cycles
  - <60 years of age with IPI=3-5: CHOP or CHOEP x 4 cycles, then mobilize stem cells with high-dose MTX 3.5g/m<sup>2</sup> IV d1 and cytarabine 3g/m<sup>2</sup> IV d9-10, G-CSF 480-600 mg SC daily d16-21 followed by apheresis d22-23, then HDCT/ASCT
  - >60 years of age: CHOP or CEOP x 6 cycles +/- HDCT/ASCT



**AIDS-related lymphomas:**<sup>98-103</sup>

In general, the treatment of AIDS-related lymphoma should be the same as for non-AIDS related lymphoma if the AIDS does not otherwise compromise the patient's performance status and he/she is free of coincident serious opportunistic infection. HAART should be given with CHOP chemotherapy. Treatment should be planned in conjunction with the patient's HIV physician and an antiviral regimen without overlapping toxicity should be chosen. R-CHOP results in the highest rates of disease-free survival, but may also increase the risk of infectious complications and treatment-related mortality in patients with CD4 counts below 50.

**Post-transplant lymphoproliferative disease (PTLD) after Solid Organ Transplant in Adults:**

1. **Epidemiology.** Post-transplant lymphoproliferative disorder (PTLD) is a heterogeneous disease with clinical and pathologic manifestations ranging from benign lymphoid hyperplasia (ie. early lesions) to aggressive lymphoma (ie. monomorphic PTLD)<sup>104,105</sup>. PTLD and its treatment cause a high rate of mortality and graft loss in patients with solid organ transplants (SOT)<sup>106</sup>. The incidence of PTLD is highest in multivisceral (>10%) and lowest in renal transplants (1-5%), attributed to intensity of immunosuppression and amount of lymphoid tissue in the allograft<sup>107-109</sup>. Epstein-Barr virus (EBV) infection drives the pathogenesis in PTLDs occurring early post-transplant; conversely, PTLDs occurring after prolonged immunosuppression tend to be monomorphic with no detectable EBV genome, calling an infectious etiology into question<sup>110</sup>. An epidemiologic shift in PTLD has occurred in the most recent decade: the median latency time from transplant to PTLD has increased from 1 to 3 years<sup>111,112</sup> and the proportion of EBV-positive vs. -negative PTLD has decreased<sup>113</sup>, attributed to EBV viral load monitoring in EBV seronegative (ie. high risk) patients.

2. **Diagnosis and staging.** Diagnostic tissue must be reviewed by expert pathologists and subtyped according to the WHO.<sup>44</sup> Several small case series have confirmed that PET-CT is an effective imaging modality for staging in PTLD<sup>114-119</sup>. However, some subtypes of PTLD, such as early lesions and T-cell lymphomas, may not be FDG-avid, necessitating CT as an alternate staging modality.

3. **Management.** Recommendations for the management of PTLD in SOT are based on few phase II clinical trials, retrospective case series, and expert opinion<sup>120-122</sup>. The mainstays of therapy for CD20-positive PTLD in SOT include reduction of immune suppression (RIS), rituximab, and chemotherapy; adoptive immunotherapy is promising but considered experimental and is unavailable in Alberta. All patients should undergo RIS to the lowest tolerated levels under the direction of the transplant physician as soon as the diagnosis of PTLD is confirmed<sup>120</sup>. A recommended strategy is to discontinue antiproliferative agents and reduce the calcineurin inhibitor by 25-50% while maintaining the steroid<sup>120</sup>. Published response rates vary widely (0-73%) and responses are seen within 2 to 4 weeks<sup>123-125</sup>.

3a. **Early lesions, polymorphic and CD20-positive monomorphic PTLD.** RIS may serve as definitive treatment of early lesions, but if response is incomplete further treatment with surgery or radiation is favored. In contrast, polymorphic and monomorphic PTLDs require definitive treatment along with RIS, discussed in further detail below<sup>120-122</sup> (Figure 3).

**Surgery and radiation.** Patients with localized PTLD, such as isolated skin, GI or renal allograft lesions, can achieve prolonged remissions with surgery or localized radiation<sup>123,126</sup>. Some experts consider surgical resection of isolated GI lesions prior to initiating systemic therapy to reduce early mortality from bowel perforation<sup>121</sup>. Radiation alone is generally not curative, with exception of plasmacytoma-like PTLD<sup>127</sup>, and

should not be used as primary treatment<sup>120</sup>. Radiation may be used for palliating obstructive or compressive symptoms where systemic therapy fails or is not possible<sup>120</sup>.

**Chemotherapy.** SOT patients do not tolerate chemotherapy well, often developing severe infection or prolonged cytopenias. Estimates of efficacy of chemotherapy in treatment of PTLD in SOT are limited by the almost entirely retrospective nature of publications. Results of retrospective studies of anthracycline-based chemotherapy, mainly CHOP, show ORRs of 65-73% and 5-year OS of 25-78%; however, treatment-related mortality (TRM) is up to 31%<sup>128-132</sup>.

**Rituximab.** Several retrospective reviews and phase II clinical trials have confirmed the efficacy of rituximab monotherapy in CD20-positive PTLD post-SOT in patients that fail to respond to RIS. Phase II trials show overall response rates (ORR) of 44% to 71% and CR rates of 26% to 53% after 4 weekly doses with no reported TRM<sup>133-136</sup>. However, 57% of patients treated with rituximab monotherapy in 2 prospective trials had progressive disease within 12 months; risk factors for survival and need for further treatment included age > 60, ECOG ≥ 2, elevated LDH, and lack of CR after rituximab<sup>137</sup>. Therefore rituximab causes minimal toxicity but remissions achieved are durable in only a minority of patients.

**Sequential therapy.** Efficacy of a sequential treatment regimen (4 weekly doses of rituximab followed by 4 cycles of CHOP) was established in a phase II international multicentre trial in adult CD20-positive PTLD in SOT (n=70) in an attempt to improve upon the success of rituximab monotherapy and diminish the toxicity of chemotherapy<sup>138</sup>. The ORR was 60% after initial rituximab, increasing to 90% after sequential chemotherapy. EBV-positive and -negative PTLDs responded equally. OS was 61% at 3 years and time to progression was 69% at 3 years. There were no TRM events related to rituximab and 11% ascribed to CHOP. In a subsequent analysis, the authors concluded that patients who achieved CR and those in PR with a low-risk IPI score after rituximab monotherapy had a low risk of disease progression<sup>139</sup>.

A subsequent phase II trial utilized risk-stratified sequential therapy, in which patients in CR (by CT) after 4 doses of rituximab received 4 further 3-weekly doses of rituximab, and those not in CR after initial rituximab proceeded to RCHOP (4 cycles supported with GCSF). With 152 patients treated, endpoints were superior to sequential therapy (3-year OS 70%, 3-year TTP 73%, TRM 7%), and response to initial rituximab was highly predictive of OS, TTP and PFS (p<0.001)<sup>140,141</sup>.

In summary, rituximab monotherapy is effective first-line treatment in most CD20-positive PTLDs with minimal toxicity. Risk-stratified sequential therapy offers the highest survival rates published to date, and allows patients in CR after rituximab monotherapy to avoid chemotherapy. Close follow-up for disease progression is recommended for patients that received rituximab alone. For PTLD that behaves aggressively (ie. IPI 3-5) or progresses during initial treatment with rituximab, proceed directly to RCHOP before completing 4 doses of rituximab (Figure 3).

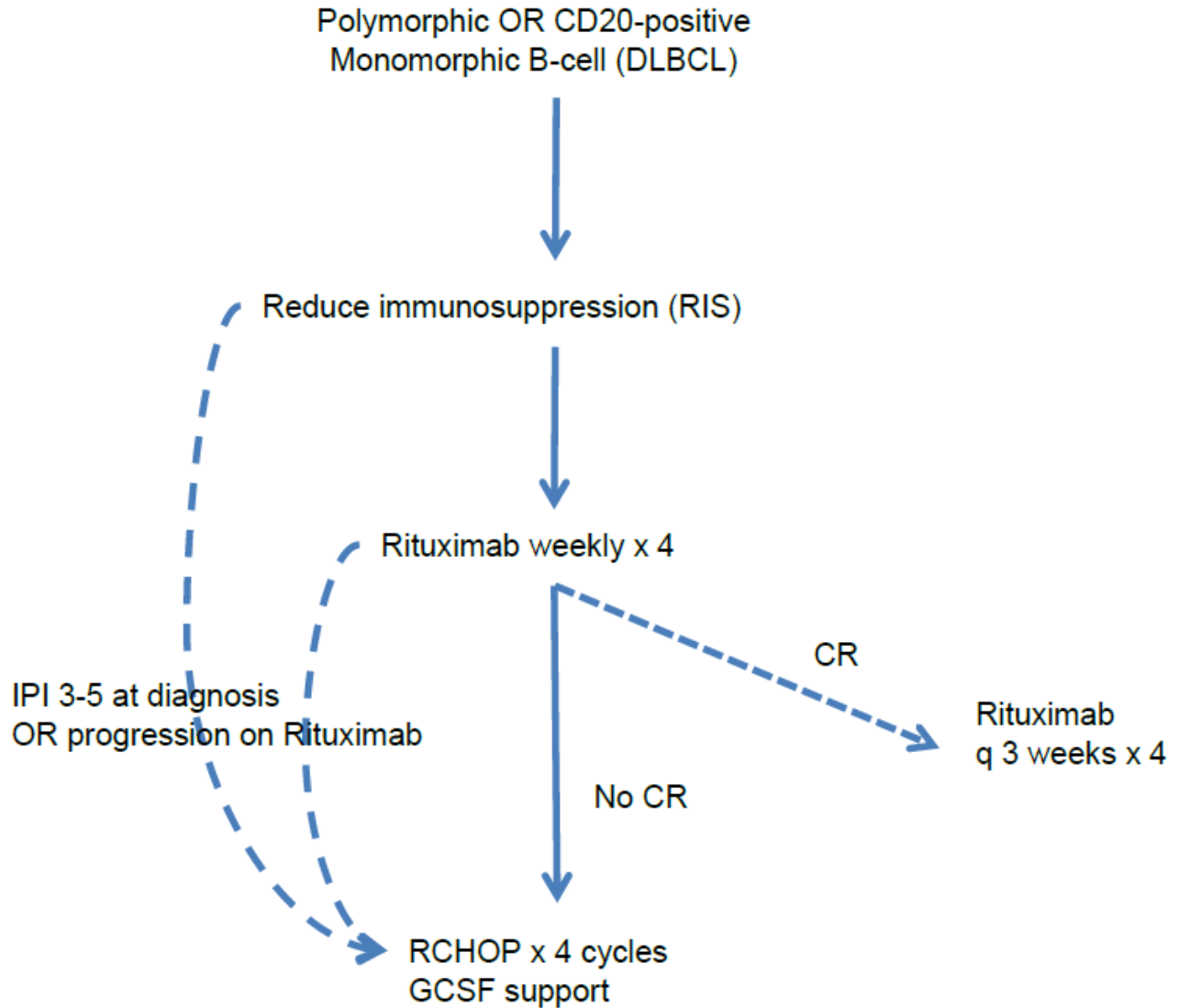
**3b. Primary CNS PTLD.** In the largest reported retrospective series of primary CNS PTLD (n=84), patients treated with rituximab and/or cytarabine (most often given after MTX) survived longer, but significant variation in regimens precluded firm conclusions<sup>142</sup>. Patients with acceptable renal function and performance status should be offered high-dose methotrexate and rituximab, and others may benefit from palliative radiation<sup>121,142</sup>.

**3c. Burkitt Lymphoma PTLD.** Several case series cite acceptable outcomes in this rare subtype of PTLD with chemotherapy regimens ranging in intensity<sup>143-145</sup>. However, no definite recommendations can be made and treatment should be considered individually.

3d. *CD20-negative monomorphic PTLDs*. Rare subtypes of PTLT that resemble non-transplant lymphomas, such as Hodgkin Lymphoma-like PTLT, T cell monomorphic PTLT, plasmablastic PTLT and plasma cell dyscrasias, require specific chemotherapeutic treatment similar to their non-transplant counterparts (reviewed by<sup>120,121</sup>).

4. *Prognosis*. The risk of death from NHL is significantly higher in SOT compared to non-transplant patients<sup>146</sup>, and PTLT increases the graft failure rate 5-fold<sup>147</sup>. Retrospective series of PTLT post-SOT report OS of 30-68% at 5 years, with excess mortality in the first year post-diagnosis<sup>107,112,148-150</sup>. Adverse prognostic factors from retrospective studies include monomorphic subtype, monomorphic T-cell, bone marrow or CNS involvement, advanced stage, poor performance status, advanced age, elevated LDH, and hypoalbuminemia<sup>111,112,134,150-152</sup>. Risk factors for worsened OS in the PTLT-1 prospective trial include IPI 3-5, thoracic organ transplant and lack of CR after rituximab monotherapy<sup>139</sup>. A prognostic score developed from 500 PTLT cases in renal transplant patients is described in Table 8; the score was calculated with the exclusion of patients with monomorphic T-cell and CNS PTLT, both of which carried an adverse prognosis, but the score maintains its ability to discriminate risk groups in the whole population<sup>148</sup>.

**Figure 1.** Treatment Algorithm for Polymorphic or Monomorphic (DLBCL) PTLD Post-SOT



**Table 8.** Post-Transplant Lymphoproliferative Disorders in Renal Transplant Prognostic Score<sup>148</sup>.  
(One point is given for each of elevated LDH, disseminated PTLN (ie. higher than stage 1), monomorphic PTLN, and serum creatinine level >133 µmol/L; 2 points are given for creatinine >133 µmol/L if age > 55 at PTLN diagnosis.)

Risk Group (# Risk Factors)	% Alive at 1/5/10 years
Low (0)	100/92/85
Moderate (1)	89/83/80
High (2-3)	74/59/56
Very High (4-5)	52/35/0



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## V. HODGKIN LYMPHOMA

### Pathologic Classification

The histological sub-classification of Hodgkin lymphoma is based on the light microscopic H&E interpretation. If problems with differential diagnosis arise, staining for CD15, CD30, T-cell and B-cell panels and EMA may be helpful. For lymphocyte predominant Hodgkin lymphoma, CD20, CD45, +/- CD57 are recommended.

**Table 1.** WHO classification of histologic subtypes of Hodgkin lymphoma <sup>1</sup>

Classical <ul style="list-style-type: none"> <li>- Nodular Sclerosis</li> <li>- Mixed Cellularity</li> <li>- Lymphocyte Rich</li> <li>- Lymphocyte Depleted</li> </ul>	
Nodular Lymphocyte Predominant	

### Staging

Mandatory staging procedures include: <sup>2-8</sup>

- Pathology review whenever possible (essential for core needle biopsies)
- Complete history and physical examination (B symptoms, Etoh intolerance, pruritis, fatigue, ECOG performance score, examination of nodes, Waldeyer's ring, spleen, liver, skin)
- CBC & differential, creatinine, electrolytes, Alk P, ALT, LDH, bilirubin, total protein, albumin, calcium
- ESR (required for limited stage patients)
- If a PET/CT is not done, then perform a bone marrow aspiration and biopsy (2cm core preferable) for patients with stage IIB-IV or cytopenias (note: flow cytometry on the marrow aspirate does not add useful information and should not be done)
- Chest x-ray (PA and lateral)
- CT scan of the neck, chest, abdomen, and pelvis
- A PET scan with body CT is preferred as initial staging and after 2 cycles of ABVD. <sup>9-14</sup>
- Pregnancy test, if at risk (consider fertility and/or psychosocial counseling )
- Semen cryopreservation if chemotherapy or pelvic radiotherapy is contemplated
- HIV: if HIV risk factors or unusual disease presentations

### Primary Treatment of Classical Hodgkin Lymphoma <sup>15-19</sup>

**General principles:** For treatment planning, supradiaphragmatic clinical stage (CS) I or II without bulk (mass >10cm or >1/3 maximal transthoracic diameter (MTD) on CXR) or significant B symptoms is considered limited stage. Initial treatment options for classical Hodgkin Lymphoma involve the chemotherapy regimens ABVD or escalated BEACOPP as well as involved field radiotherapy (IFRT). Multiple phase III studies conducted by the German Hodgkin Study Group (GHSG) and other cooperative study groups have demonstrated that optimal cure rates are achieved with: 1) ABVD x2 cycles followed by 20Gy IFRT for favorable risk limited stage disease (5yr PFS >90%); 2) ABVD x4 cycles followed by 30Gy IFRT for unfavorable risk limited stage ( $\geq 3$  nodal sites, ESR > 50 or >30 with B symptoms, or extranodal disease) (5yr PFS >85%); 3) escalated BEACOPP x 4-6 cycles for young healthy patients with advanced stage disease; and 4) ABVD x6 cycles for patients >60 years or with co-morbidities. Advanced stage

patients also receive IFRT following chemotherapy to localized PET+ residual disease >2.5cm, and is considered for sites of prior bulk after ABVD.

**Data supporting escalated BEACOPP for advanced stage disease:** The GHSG HD9 trial conducted in the 1990s demonstrated that 8 cycles of an escalated-dose BEACOPP regimen were superior to 8 cycles of a COPP/ABVD regimen or 8 cycles of a baseline-dose BEACOPP regimen in terms of freedom from treatment failure and overall survival rates in patients with advanced-stage Hodgkin lymphoma.<sup>20</sup> Each regimen was followed by consolidative radiation therapy to sites of initial bulky disease greater than 5 cm. At the 10-year analysis, freedom from treatment failure was 64% for the COPP/ABVD group, 70% for the baseline BEACOPP group, and 82% for the escalated BEACOPP group ( $p<0.001$ ); overall survival rates were 75%, 80%, and 86%, respectively ( $p<0.001$ ).<sup>21</sup> There were higher rates of hematologic toxicities, grades 3-4 infections and higher rate of AML/MDS in the escalated BEACOPP group, but not an increase in all second malignancies. A meta-analysis of 4 subsequent phase III trials confirmed superior PFS (OR 0.56, 95%CI 0.38, 0.81) and long-term overall survival (OR 0.64, 95%CI 0.51, 0.81) with escBEACOPP compared to ABVD.<sup>22,23</sup> Of importance, escBEACOPP is associated with infertility, especially in male patients. Sieniawski *et al.* (2008)<sup>24</sup> reported that 34 of 38 patients with advanced-stage Hodgkin lymphoma became azoospermic after treatment with 8 cycles of BEACOPP, and that of the remaining 4 patients, 2 had impaired spermatogenesis.

The German Hodgkin Study Group recently published the results of their HD15 prospective randomized clinical trial.<sup>25</sup> 2182 patients with newly diagnosed Hodgkin lymphoma aged 18-60 years with stage IIB (large mediastinal mass or extranodal lesions), or stage III-IV disease were randomly assigned to receive either 8 cycles of escalated BEACOPP (8B<sub>esc</sub>), 6 cycles of escalated BEACOPP (6B<sub>esc</sub>), or 8 cycles of BEACOPP<sub>14</sub> (8B<sub>14</sub>). After a median follow-up of 48 months, there were 53 deaths (7.5%) in the 8B<sub>esc</sub> group, 33 (4.6%) in the 6B<sub>esc</sub> group and 37 (5.2%) in the 8B<sub>14</sub> group. The higher number of deaths in the 8B<sub>esc</sub> group mainly resulted from acute toxicity of chemotherapy and secondary neoplasms. There were 72 secondary cancers including 29 secondary acute myeloid leukemias and myelodysplastic syndromes: 19 (2.7%) in the 8B<sub>esc</sub> group, 2 (0.3%) in the 6B<sub>esc</sub> group and 8 (1.1%) in the 8B<sub>14</sub> group. Complete response was achieved in 90.1% of patients after 8B<sub>esc</sub>, 94.2% after 6B<sub>esc</sub> and 92.4% after 8B<sub>14</sub> ( $p=0.01$ ). Five year OS rates were 91.9% in the 8B<sub>esc</sub> group, 95.3% in the 6B<sub>esc</sub> group, and 94.5% in the 8B<sub>14</sub> group. PET scans performed after chemotherapy for 822 patients revealed that 739 were in PR with residual mass  $\geq$  2.5 cm having no other exclusion criteria. 548 patients were PET-negative (74.2%) and 191 were PET-positive (25.8%). PFS was comparable between patients in CR or those in PET-negative PR after chemotherapy with 4-year PFS rates of 92.6% and 92.1%, respectively. Only 11% of all patients in the HD15 trial received additional radiotherapy as compared to 71% in the prior HD9 study.<sup>25</sup>

In an attempt to reduce severe toxicities associated with escBEACOPP, an open-label, randomized, parallel-group, phase 3 trial investigated the utility of PET after two cycles of standard escBEACOPP to allow for adaptation of treatment intensity.<sup>26</sup> The trial included 18-60 year olds with newly diagnosed advanced-stage Hodgkin's lymphoma (N=1945), and assigned patients (1:1) to two parallel treatment groups on the basis of their PET results after cycle 2 of escBEACOPP (PET-2). Patients with positive PET-2 were randomised to receive six additional cycles of either standard escBEACOPP (8  $\times$  escBEACOPP in total) or escBEACOPP with rituximab (8  $\times$  R-eBEACOPP) (rituximab abandoned mid-trial due to lack of efficacy). Patients with negative PET-2 were randomised between standard treatment with 4-6 additional cycles of escBEACOPP (6-8  $\times$  escBEACOPP... the trial switched from total 8 to total 6 escBEACOPP in the standard arm after the results of HD15) or experimental treatment with two additional cycles only (4  $\times$  escBEACOPP). Patients with negative PET-2 randomly assigned to either



6-8 × escBEACOPP (n=504) or 4 × escBEACOPP (n=501) had 5-year progression-free survival of 90.8% (95% CI 87.9-93.7) and 92.2% (89.4-95.0), respectively (difference 1.4%, 95% CI -2.7 to 5.4).

4 × escBEACOPP was associated with fewer severe infections (8% vs 15%) and organ toxicities (8% vs 18%) as compared to patients receiving 6-8 × escBEACOPP. The trial supports reducing therapy to 4 escBEACOPP in patients who achieve PET- negative disease after 2 cycles of escBEACOPP.

Due to concerns of toxicity, escalated BEACOPP in Alberta should only be considered for the following patients: <sup>2,21,22,27-31</sup>

- Age < 60 years
- KPS score ≥ 70 (ECOG 0-2)
- HIV negative, no other major co-morbidities
- Patients must be made aware of infertility implications, and consent to proceed

Although the above-described treatment approaches currently optimize cure rates from initial therapy, they result in: 1) the use of radiotherapy that contributes to late mortality from second cancers and cardiac disease; 2) the use of multiple cycles of Bleomycin that may cause serious lung toxicity; or 3) the use of escalated BEACOPP that increases the risk of serious infections and therapy-related MDS/AML. With the use of a PET-guided approach that minimizes therapy for patients whose lymphoma is highly sensitive to ABVD, we anticipate a reduction in toxicity of therapy and a need to only subject less responsive patients to the toxicities of IFRT or escalated BEACOPP.

### **Data Supporting a PET-Guided Treatment Approach:** <sup>32-35</sup>

#### Limited Stage

In the *UK Rapid trial*, patients with stage I-IIA non-bulky HL received ABVD x3 cycles then underwent a PET scan. If the PET was positive (uptake more than blood pool, Deauville score 3-5) the patients received one more cycle ABVD then IFRT, whereas if the PET was negative patients were randomized to observation or IFRT. The 3yr PFS was 85.9% in the 145 PET+ patients, 94.6% in the PET- patients who received IFRT and 90.8% in PET- patients who were observed. The difference in PFS was -3.8% (95%CI: -8.8%, 1.3%) exceeding -7% non-inferiority margin. Of interest, the per-protocol PFS was 97% vs 90.8% because 26 pts did not get allocated IFRT. The respective 3 year overall survival rates were 97.1% vs 99.0%. In the *EORTC/LYSA/FIL H10 trial*, stage I-II HL patients were randomized between control arm therapy with ABVD x3 +INRT (favorable risk) or ABVD x4 +INRT (unfavorable risk), with all patients undergoing PET after cycle 2 ABVD. In the experimental arm of the study, patients received ABVD x2 then a PET scan, followed by ABVD x 2 (favorable) or 4 (unfavorable) if PET-, or escBEACOPP x2 cycles +INRT if PET+. Comparing control (INRT) and experimental (no INRT) arms for patients with negative PET after 2 cycles ABVD, the difference in PFS was -11.9% (95%CI -16.9%, -8.2%) for favorable risk (not meeting non-inferiority endpoint) and -2.5% (95%CI -6.6%, 0.5%) for unfavorable risk (not meeting non-inferiority endpoint). There was no difference in overall survival. For patients with PET+ disease after ABVD, the 5y PFS 77% vs 91% (p=0.002) and 5yr OS 89% vs 96% (p=0.06) favouring escBEACOPP compared to ABVD + INRT.

As neither the RAPID nor H10 trials confirmed non-inferiority of the PET-directed radiotherapy omission approach, this would support the use of radiotherapy despite a negative interim PET. However, given the lack of difference in OS and small differences in PFS, a PET-directed approach is recommended, accepting the risk of reduced local control with potential need for salvage chemotherapy and

transplantation at relapse, reconciled by an expected late gain in OS due to avoidance of the long term sequelae of radiotherapy such as secondary malignancy and cardiovascular disease.

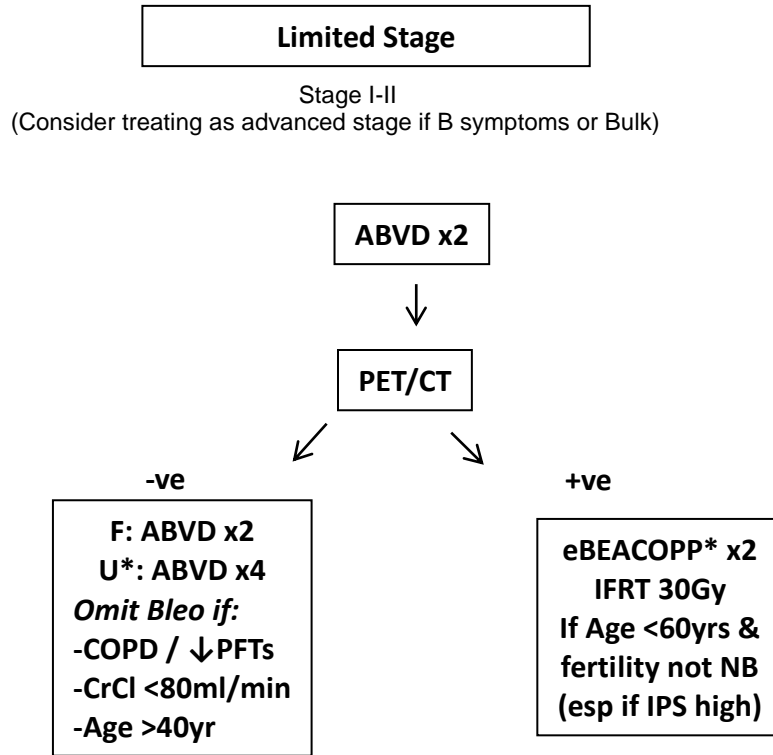
### Advanced Stage

The *UK RATHL trial* treated patients with 2 cycles ABVD then performed a PET scan. 172 patients with PET+ disease (uptake > liver, Deauville 4-5) had therapy intensified to escBEACOPP whereas PET- patients were randomized to ABVD x4 (n=470) or AVD x4 (n=465). For PET- patients, 3yr PFS was 85.7% vs 84.4% for ABVD vs AVD (95%CI crossed 5% difference non-inferiority limit), the respective 3yr OS rates were 97.2% vs 97.6%, and the rate of grade 3-4 pneumonitis was 1% vs 0.2%, respectively. Of interest, a prior phase GHSG III trial found that omitting agents from ABVD x2 prior to IFRT for favorable risk limited stage HL resulted in lower 5 PFS rates (5yr FFTF 93.1% ABVD, 89.2% AVD, 77.1% AV, 81.4% ABV) and did not recommend this strategy. In view of the fact that the RATHL trial failed to meet its non-inferiority endpoint and only demonstrated a small reduction in serious pulmonary toxicity by eliminating bleomycin from the final 4 cycles of ABVD, it seems most reasonable to adopt this strategy only for those patients with risks factors for bleomycin lung toxicity (COPD / ↓PFTs, CrCl <80ml/min, Stage IV, Age >40yr), or those with any clinical or PFT evidence of acquiring bleomycin lung toxicity at any time during therapy. Patients with PET2 positive status whose therapy was intensified to 4 additional cycles of BEACOPP (BEACOPP-14 or escBEACOPP) had a 3 yr PFS of 67.5% and 3 yr OS of 87.8%.

The aforementioned HD18 study by German Hodgkin Study Group confirmed that 4 escBEACOPP was as effective as 6-8 escBEACOPP but less toxic in patients who achieved PET-negative status after 2 cycles of escBEACOPP. 3 yr PFS in this group (PET-2 negative after escBEACOPP) was 95.3% and 3 yr OS was 98.8%.

Based upon the above data, it is reasonable to adopt a PET-guided therapy approach for advanced staged Hodgkin lymphoma. Initiation of escBEACOPP as per the HD18 study results in a higher overall survival and is the preferred approach for young, fit patients for whom the fertility implications are acceptable. For patients who initiate therapy with ABVD, PET-directed therapy will minimize the long-term risks of cytotoxic chemotherapy and radiotherapy for PET- patients after ABVD x2, while maintaining PFS rates <5% inferior to conventional combined modality treatments. These PET-guided approaches are illustrated in Figure 1-2. For centres where PET scanning is not available, or in situations when patients prefer to prioritize their initial cure rate and avoidance of intensive salvage therapy with autologous SCT rather than prioritize a similar long-term survival while minimizing therapy-related second cancers, cardiovascular mortality or bleomycin lung toxicity, the more traditional therapy approach illustrated in Figure 3 is still very reasonable.

**Figure 1.** Treatment algorithm for Limited Stage Hodgkin lymphoma using PET-Guided therapy (Preferred Approach)



**Consider IFRT alone for favorable CS IA NS HL involving <3cm high neck or epitrochlear nodes only**

**\*Unfavourable Risk Limited Stage:**

- Any of:
- ESR > 50 (or >30 with B symptoms)
  - ≥ 3 sites disease
  - extranodal disease
  - age > 50 yrs

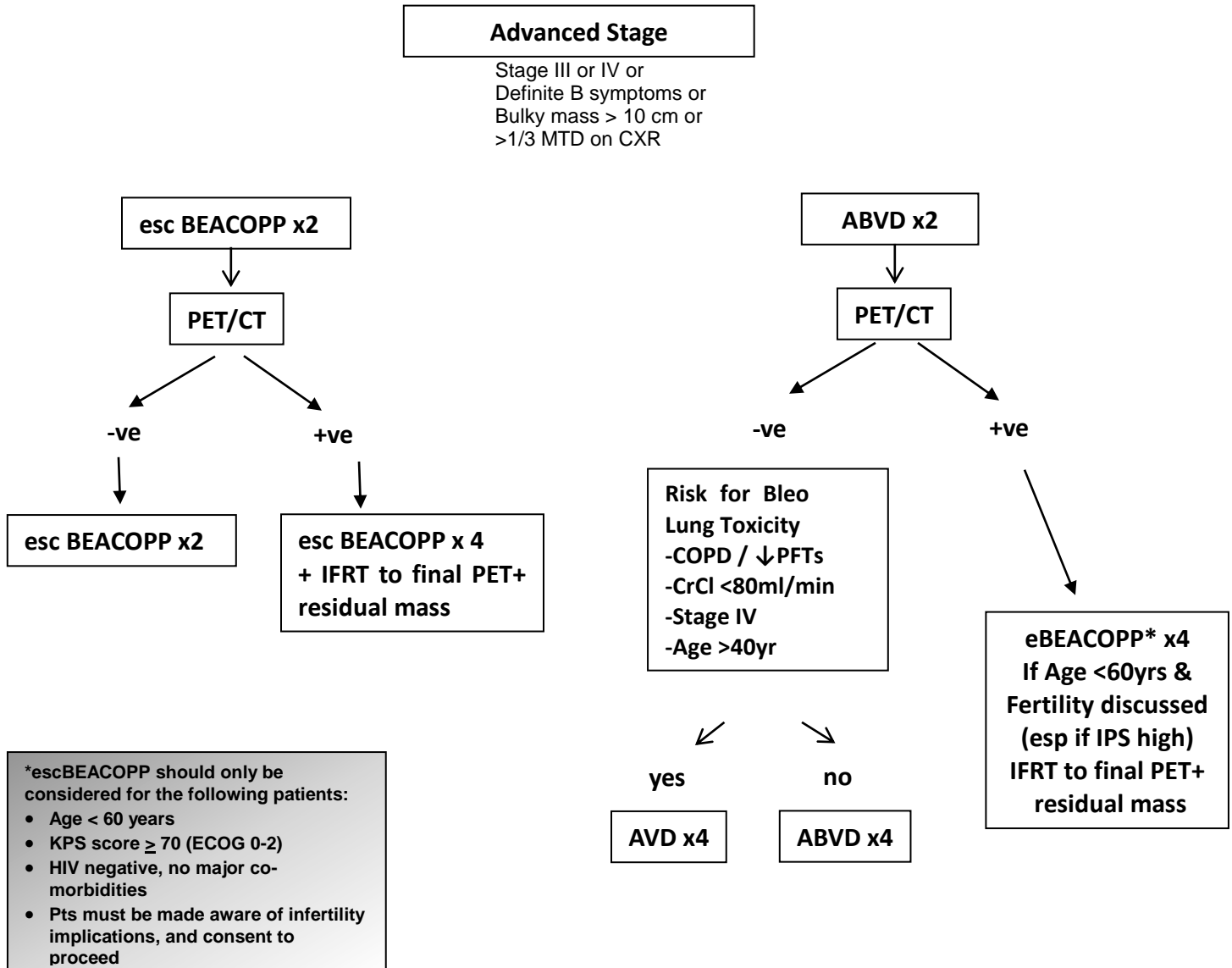
**IPS Risk Factors**

- Age ≥ 45years
- Stage IV
- Male
- Lymphocyte < 0.6 or <8%WBC
- Hb < 105
- WBC ≥ 15
- Albumin <40

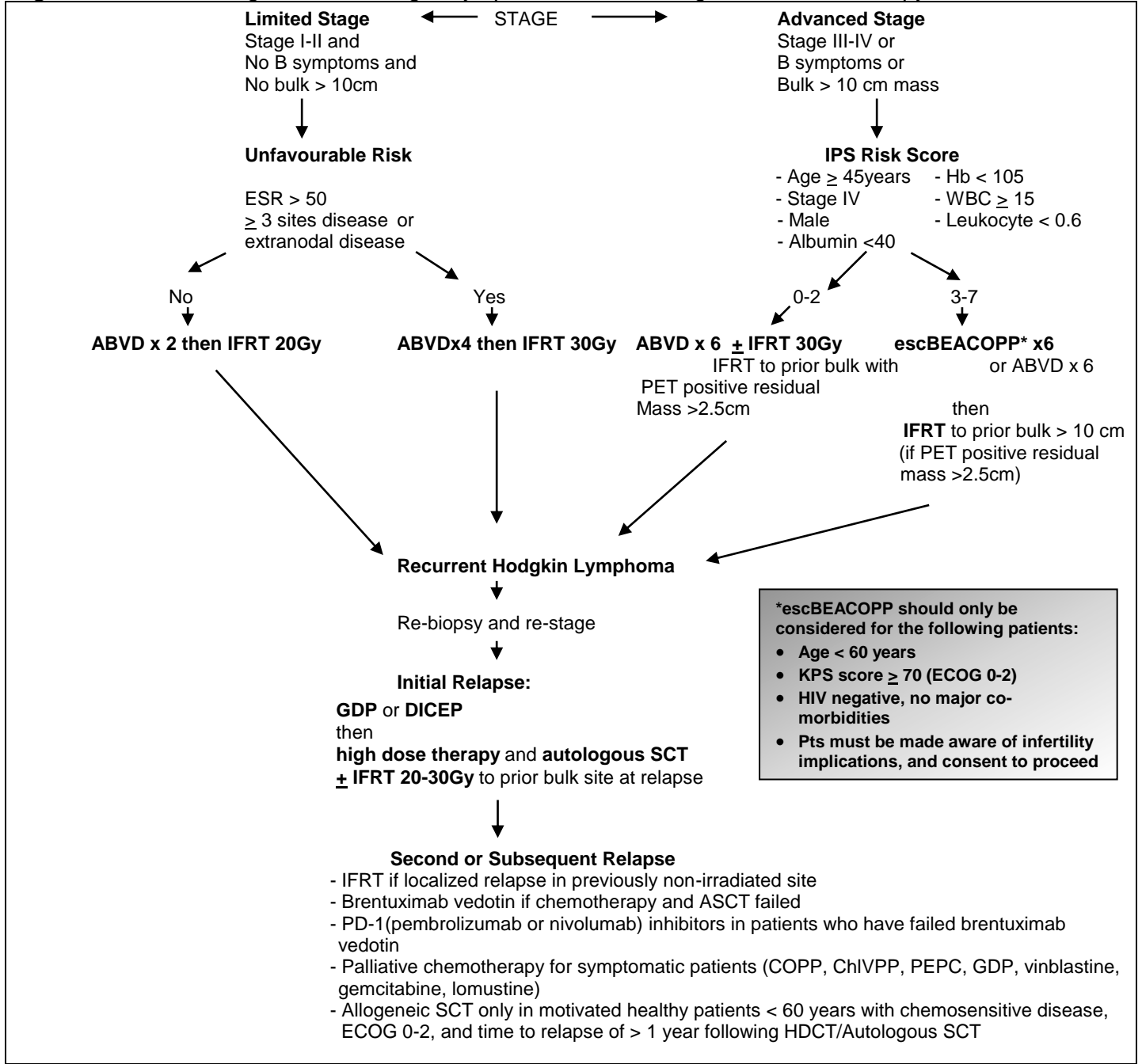
IFRT = Involved field radiotherapy; 20-30Gy/ 20 fractions

For ABVD x4-6: Perform pulmonary function test at baseline and after cycles 3 and 5; omit bleomycin if ≥25% decrease in DLCO or FVC; decrease bleomycin dose by 50% if 10-24% decrease in DLCO or FVC

**Figure 2. Treatment algorithm for Advanced Stage Hodgkin lymphoma using PET-Guided therapy**



**Figure 3.** Treatment algorithm for Hodgkin lymphoma without using PET-Guided therapy.





## Future potential option for patients not eligible for PET-guided approach

### Brentuximab vedotin<sup>36</sup>

An open-label, multicenter phase 3 trial of 1334 patients with previously untreated stage III/IV Hodgkin lymphoma, randomized (1:1) patients to receive brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) or ABVD. After a median follow-up of 24.6 months, 2 year modified progression-free survival (primary end point) was 82.1% (95%CI: 78.8-85.0%) for the A+AVD group and 77.2% (95%CI: 73.7-80.4%) in the ABVD group (p=0.04). Neutropenia was higher in the A+AVD group (58% vs 45%), febrile neutropenia occurred in 83 patients (rate: 11% in those receiving prophylactic GCSF and 21% in those without GCSF). Peripheral neuropathy was also higher in the A+AVD group (67% vs. 43%), with resolution at last follow-up in 2/3 of patients. Pulmonary toxicity  $\geq$  grade 3 occurred in 1% of A+AVD patients vs. 3% in ABVD. No overall survival difference was observed. While this trial showed an improvement in its primary endpoint (modified PFS), this endpoint included patients who received IFRT after achieving a PR, which many would argue is appropriate curative therapy and should not have qualified as treatment failure. With the current analysis, the number needed to treat is very large (and would be even larger if the patients receiving adjuvant radiotherapy were excluded from the PFS calculation) and thus the costs of A+AVD are considered too high to justify a change in practice at this time. However, this regimen has been demonstrated as an effective and tolerable frontline therapy for advanced stage Hodgkin lymphoma and could become the standard against which future non-PET directed treatments are compared.

### Management of Recurrent Hodgkin Lymphoma<sup>2,37-52</sup>

Similar to the initial workup, recurrent disease should involve re-staging tests.

#### **Initial relapse:**

- Re-induction chemotherapy with GDP or DICEP then high dose therapy and autologous SCT  $\pm$  IFRT 20-30Gy to prior bulk site at relapse, or PET-positive residual disease post-ASCT

#### **Second or subsequent relapse:**

- IFRT if localized relapse in previously non-irradiated site
- Brentuximab vedotin IV q21d for up to 16 doses if prior failure of initial chemotherapy (ABVD or BEACOPP) and prior autologous SCT.
- Palliative chemotherapy for symptomatic patients (GDP, COPP, ChIVPP, CEPP, vinblastine)
- Allogeneic SCT only in motivated healthy patients <60 years old with chemosensitive disease, ECOG 0-2, and time to relapse of >1 year following high dose therapy and autologous SCT
- A PD1-inhibitor (eg. Nivolumab or Pembrolizumab) should be considered after prior failure of chemotherapy (and autologous SCT in transplant eligible patients) as well as prior failure of Brentuximab vedotin.

### Brentuximab vedotin (BV)<sup>53-55</sup>

A phase II study of N=102 patients treated with BV (1.8mg/kg, outpatient IV, 30min, every 3 weeks for up to 16 cycles) for relapsed/refractory Hodgkin lymphoma after failed hematopoietic autologous stem cell transplantation reported outcomes after approximately 3-years of follow-up. Median OS and PFS were estimated at 40.5 months and 9.3 months, respectively. The estimated 3-year OS and PFS rates were 73%

(95%CI: 57-88%) and 58% (95%CI: 41-76%), respectively. Younger age, good performance status, and lower disease burden at baseline were favorable prognostic factors for OS. The most common treatment-related adverse events were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea. Chen et al. reported 5-year end-of-study data. For the entire cohort, OS was 41% (95% CI: 31-51) and PFS was 22% (95% CI: 13-31). Complete response (evaluated via Revised Response Criteria for Malignant Lymphoma): was observed in 34 patients. For those who achieved CR, OS and PFS rates were 64% (95% CI: 48-80%) and 52% (95% CI: 34-69%), respectively (median OS and PFS not yet reached). At the time of study close, 13 CR patients remained in remission (4 received consolidative hematopoietic allogeneic stem cell transplant; 9 received no further anticancer treatment). Of those patients who experienced BV associated peripheral neuropathy, 88% experienced either resolution (73%) or improvement (14%) in symptoms.

BV has been evaluated in a retrospective analysis of N=136 patients ineligible for autologous stem cell transplant. Patients were treated with BV after multidrug chemotherapy. Median follow-up was 10.9 months (range 0.4-47.0). Patients received a median of 8 (range 6-15) cycles of BV and the overall response rate (ORR) was 74.3% and CR was 34.6%. ORR with BV was not significantly different from the ORR of the preceding line of therapy. Median progression free survival (PFS) was 15.1 months (95% CI: 8.9-22) with 52.1% (43.0-61.2%) of patients progression free at 1 year. Median overall survival was 17.8 months (95% CI: 13.7-33.5) with 68.2% (59.2-77.1%) of patients alive at 1 year. Incidence of peripheral neuropathy was 9.6% (92.3% of these cases were not serious).

### **PD1-inhibitors** <sup>56</sup>

CheckMate 205, a single-arm, multicenter, phase 2 study enrolled patients with relapsed/refractory Hodgkin lymphoma who failed autologous hematopoietic cell transplantation to receive nivolumab (3 mg/kg every 2 weeks until disease progression/unacceptable toxicity). Patients were subcategorized by prior treatment. Cohort A: BV-naïve; cohort B: BV received after transplant; cohort C: BV received before and/or after transplant. Overall, N=243 patients were enrolled (N=63, 80, and 100 in cohort A, B, and C, respectively). After a median follow-up of 18 months, 40% of patients were still on treatment. Objective response rates were 65-73% dependent on cohort, (overall 69%). The median duration of response was 16.6 months (95%CI: 13.2-20.3m), and median PFS was 14.7 months (95%CI: 11.3-18.5m). Of the 70 patients treated past conventional disease progression, 61% had stable or further reduced target tumour burdens. Most common grade 3-4 AEs included lipase increases (5%), neutropenia (3%), and ALT increases (3%).

KEYNOTE-013, a phase Ib study, tested the safety and efficacy of pembrolizumab (10mg/kg every 2 weeks until disease progression) in relapsed/refractory Hodgkin lymphoma after progression with BV. Of the N=31 patients enrolled, 55% had >4 lines of prior therapy, and 71% had relapsed after autologous stem cell transplant. Median follow-up was 17 months. The complete remission rate was 16% (90% CI, 7% to 31%). In addition, 48% of patients achieved a partial remission, for an overall response rate of 65% (90% CI, 48% to 79%). Most of the responses (70%) lasted longer than 24 weeks (range, 0.14+ to 74+ weeks). The progression-free survival rate was 69% at 24 weeks and 46% at 52 weeks. Five patients (16%) experienced grade 3 drug-related adverse events (AEs); there were no grade 4 AEs or deaths related to treatment.

### **Nodular Lymphocyte Predominant Hodgkin Lymphoma** <sup>57</sup>

This rare subtype comprises ~5% of Hodgkin lymphomas and has a very indolent course with excellent survival. Despite the name, clinical, biological, morphological and immunophenotypic features of NLPHL

significantly differ from classical Hodgkin lymphoma. Patients most commonly present with early stage disease, the clinical course is indolent and the prognosis is very favourable. Similar to other indolent CD20+ lymphoma, late relapses as well as transformation to DLBCL (3–5% of cases) can occur. Even after relapse, patients may survive for many years, and therefore minimizing risk of treatment-related mortality is important.

In terms of treatment recommendations, surgery should be offered to patients with localized, resectable disease and a watchful waiting approach may be considered in patients who have no residual disease after surgery (following discussion with a radiation oncologist). Patients with residual but localized peripheral NLPHL (stage 1-2A with  $\leq 2$  sites of disease) should be offered IFRT. Patients with more advanced stage 2A disease, or those with stage 3-4 disease, should be treated in a similar fashion as those with other forms of indolent CD20+ lymphoma including watchful waiting or chemoimmunotherapy (eg. BR or RCVP) as appropriate. Consider the possibility of high-grade transformation in patients with rapidly progressive disease, marked B symptoms, focal abnormalities in the spleen, extranodal disease, high LDH, or prior bone marrow involvement. R-CHOP is appropriate for patients with transformed disease, with consideration for HDCT/ASCT, especially in those who have relapsed < 2 years after prior chemoimmunotherapy. Consider rituximab monotherapy in patients with advanced stage NLPHL who have serious co-morbidities that would preclude the use of combination chemotherapy.

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## VI. HDCT AND HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR LYMPHOMA<sup>1-28</sup>

For detailed information on hematopoietic stem cell transplantation in patients with hematological malignancies, please refer to the Alberta Bone Marrow and Blood Cell Transplant Standard Practice Manual. This manual was developed and is regularly updated by members of the Alberta Provincial Hematology Tumour Team and the Alberta Bone Marrow and Blood Cell Transplant Program, and can be found at: <http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-bmt-manual.pdf>

### Summary of Recommendations

#### **Eligibility:**

- Patient: age  $\leq$  70 years, ECOG 0-2, adequate organ function, no active infections
  - HIV not contraindication if CD4 $>$ 100 and meet other eligibility criteria
- Lymphoma: chemosensitive: partial response (PR) or better to last chemotherapy
  - No active secondary CNS disease (eligible if CNS in PR/CR to salvage therapy)

#### **HDCT regimen for autologous stem cell transplantation:**

- Indolent (Follicular, SLL/CLL, MZL, LPL) and Mantle Cell: melphalan 180mg/m<sup>2</sup> + TBI 5Gy
- Aggressive systemic non-Hodgkin lymphoma (DLBCL, PTCL): (R)BEAM or Etoposide/Melphalan
- Hodgkin lymphoma: melphalan 200mg/m<sup>2</sup> or Etoposide/Melphalan
- Primary CNS lymphoma: thiotepa 600mg/m<sup>2</sup> + busulfan 9.6mg/kg
- Secondary CNS lymphoma: (R-TBM) thiotepa 500mg/m<sup>2</sup> + busulfan 9.6mg/kg + melphalan 100mg/m<sup>2</sup>

#### **HDCT regimen for allogeneic stem cell transplantation:**

- Majority of patients: fludarabine 250mg/m<sup>2</sup> + busulfan 12.8mg/kg, 400cGy TBI + ATG
- Reduced intensity: fludarabine 120mg/m<sup>2</sup> + melphalan 140mg/m<sup>2</sup> + ATG
  - co-morbidities (liver, lung, nervous system), prior busulfan, prior ASCT after BEAM or TBI
  - slowly progressive, non-bulky lymphoma

#### **Indications for HDCT and autologous stem cell transplantation:**

1. Indolent non-Hodgkin lymphoma
  - Follicular, Marginal Zone, Small Lymphocytic, Lymphoplasmacytic Lymphoma
    - chemosensitive first or second chemotherapy failure
  - Mantle Cell Lymphoma (especially low or low-intermediate risk MIPI score)
    - first partial remission (PR) or first complete remission (CR)
2. Aggressive non-Hodgkin lymphoma
  - Part of first salvage therapy for chemosensitive first relapse or first remission-induction failure
  - Part of initial therapy for high IPI=4-5 risk patients or double hit Lymphoma
    - first PR/CR following completion of full induction (i.e. R-CHOP x 6)
    - high-dose sequential remission-induction therapy
3. Hodgkin lymphoma
  - First chemotherapy failure (relapse or 1<sup>0</sup> refractory)



***Indications for HDCT and allogeneic stem cell transplantation for lymphoma:***

1. Indolent non-Hodgkin lymphoma

- Follicular, Marginal Zone, Small Lymphocytic/CLL, Lymphoplasmacytic Lymphoma
  - chemosensitive second to fourth chemotherapy failure (last time to progression <2 years), usually after prior autologous SCT.
- Mantle cell lymphoma
  - first remission for high risk MIPI score, blastoid variant, or heavy blood/marrow involvement
  - chemosensitive first chemotherapy failure

2. Aggressive non-Hodgkin lymphoma

- Diffuse large B-cell or peripheral T-cell lymphomas
  - chemosensitive relapse following HDCT/ASCT if time to relapse >1 year and aalPI=0-1
- Lymphoblastic lymphoma
  - first remission after induction and CNS therapy if prior blood/marrow involvement and high LDH
  - chemosensitive first chemotherapy failure

3. Hodgkin lymphoma

- Chemosensitive relapse following HDCT/ASCT if time to relapse >1 year

4. Any lymphoma with indication for HDCT/ASCT but unable to collect adequate autograft

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## VII. SUPPORTIVE CARE IN THE TREATMENT OF LYMPHOMA

### Allopurinol

300mg/d x10-14 days starting 1-3 days prior to cycle 1 chemotherapy for Burkitt or Lymphoblastic lymphoma. This should also be considered for rapidly progressive aggressive bulky lymphomas and in patients with impaired renal function.

### Pre-Phase Therapy for DLBCL Patients >60 years of Age

Prednisone 100mg/d x 3-7 days prior to cycle 1 R-CHOP or R-CEOP.

### Neutropenia Prevention<sup>1-5</sup>

Primary or secondary prophylaxis to decrease the risk of febrile neutropenia and maintain chemotherapy dose intensity is indicated when treating with curative intent (e.g. preventing treatment delay/dose reduction). The recommendation for R-CHOP, CODOX-M/IVAC, HyperCVAD, or intensive salvage therapy regimens, with or without rituximab (e.g. DHAP, ICE, GDP, MICE, DICEP), in patients with aggressive Hodgkin or non-Hodgkin lymphoma older than 60 years of age, or poor prognostic factors (high IPI or IPS) is G-CSF 300µg subcutaneous on days 8 and 12 of a 14- or 21-day chemotherapy regimen.<sup>1</sup>

For primary prophylaxis of febrile neutropenic infection for similar indications above or co-morbidities that increase risk of infectious complications such as chronic obstructive pulmonary disease, or secondary prevention after a prior episode of febrile neutropenia:

- G-CSF 300 or 480µg/day starting 3 days after chemotherapy completed until post-nadir ANC>1.0 (usually 7-10 days) (though most patients require only 2-5 days of G-CSF support)
- Must monitor CBC
- The alternative is one dose of pegfilgrastim (Neulasta) 6mg on day 4 (without CBC monitoring, but at a cost of ~\$2500/dose)

### Erythropoietin

Erythropoietin is not recommended because of evidence suggesting increased mortality rates. Consider only for symptomatic anemia patients who cannot receive RBC transfusions (i.e., Jehovah's Witnesses, prior severe transfusion reactions or severe iron overload).

### Antimicrobial Prophylaxis for Immunosuppressive Regimens<sup>6-8</sup>

- For patients receiving fludarabine, high dose cyclophosphamide, >5 days high dose corticosteroids every 21 days, bortezomib, and bendamustine, and for immune-compromised patients (i.e., HIV, post-organ transplant or autoimmune disease patients who develop hematologic cancers) use prophylaxis during and for 12 months post-treatment. CD4 count monitoring can be used to help determine if prophylaxis can be stopped earlier (should not be assessed until 3 or 6 months post-treatment). Patients with CD4 count > 200 / µL may have earlier discontinuation of antimicrobial prophylaxis.
- *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis:
  - choice 1: Septra 1 regular strength tab daily
  - choice 2: dapsone 100mg every Monday/Wednesday/Friday (or 50 mg daily)
  - choice 3: pentamidine 300mg inhalation monthly

- choice 4: atovaquone 1500 mg daily
- Shingles prophylaxis: valacyclovir 500mg daily

### **Immunizations**

Patients should be encouraged to keep all immunizations up to date. The reactivation and/or seroreversion of viruses that patients have been previously vaccinated against, such as hepatitis B, is a major cause of morbidity and mortality in patients with hematologic malignancies treated with cytotoxic chemotherapy. Appendix G outlines the general principles and specific immunization schedules for recipients of blood and marrow transplantations. In addition, separate guidelines outlining influenza and pneumococcal immunization recommendations for all patients with cancer can be found at: [www.albertahealthservices.ca/cancerguidelines.asp](http://www.albertahealthservices.ca/cancerguidelines.asp) under the “Supportive Care” heading”

Recombinant adjuvant herpes zoster vaccine is commercially available however cancer patients were excluded in the pivotal phase 3 trials (ZOE-50 and ZOE-70). Studies with use in cancer patients are not yet published, but results suggest that vaccination responses are better for patients not on treatment or given prior to chemotherapy, as opposed to during chemotherapy.<sup>9</sup> Other hematological malignancy patients had better vaccine responses than Non Hodgkin’s Lymphoma and CLL patients for reasons not yet identified.<sup>10</sup> The AHS Hematology group consensus is that the recombinant adjuvant herpes zoster vaccine is not contraindicated in hematology patients. Patients may receive the vaccine if they have adequate immune function to mount a response, and are 6-9 months post Rituximab due to the reduced vaccine responses seen in rituximab-treated patients.

Family members and health care providers in contact with patients who have undergone a transplant should also be strongly encouraged to keep all immunizations up to date.

For patients who have experienced reactivation or seroreversion of hepatitis B virus, prompt administration of nucleoside/nucleotide analogues is essential.<sup>11</sup> Entacavir or tenofovir following R-CVP or R-CHOP chemotherapy for lymphoma is recommended for all patients who have a positive hepatitis B surface antigen test.



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**VIII. FOLLOW-UP CARE IN THE TREATMENT OF LYMPHOMA<sup>1-11</sup>**

The following late effects should be considered when patients are reviewed during follow-up:

- **Relapse.** Careful attention should be directed to lymph node sites, especially if previously involved with disease. Routine surveillance CT scans are not indicated. Most relapses have been demonstrated to occur between scheduled clinics visits and tests, and are detected by patients themselves. Highly anxious patients who wish surveillance tests could be considered for occasional CXR and abdominal/pelvic ultrasounds (if thin), especially in the setting of indolent lymphoma and prior retroperitoneal and mesenteric disease.
- **Dental caries.** Neck or oropharyngeal irradiation may cause decreased salivation. Patients should have careful dental care follow-up and should make their dentist aware of the previous irradiation.
- **Hypothyroidism.** After external beam thyroid irradiation to doses sufficient to cure malignant lymphoma, at least 50% of patients will eventually develop hypothyroidism. All patients whose TSH level becomes elevated should be treated with life-long T4 replacement in doses sufficient to suppress TSH levels to low normal.
- **Infertility.** Multi-agent chemotherapy and direct or scatter radiation to gonadal tissue may cause infertility, amenorrhea, or premature menopause. However, with current chemotherapy regimens and radiation fields used, most patients will not develop these problems. All patients should be advised that they may or may not be fertile after treatment. In general, women who continue menstruating are fertile, but men require semen analysis to provide a specific answer.
- **Secondary neoplasms.** Although quite uncommon, certain neoplasms occur with increased frequency in patients who have been treated for lymphoma. These include AML, thyroid, breast, lung, and upper GI carcinoma, melanoma and cervical carcinoma *in situ*. It is appropriate to screen for these neoplasms by careful history, physical examination, mammography and Pap smears for the rest of the patient's life because they may have a lengthy induction period. Patients should be counseled about the hazards of smoking and excessive sun exposure, and should be encouraged to perform careful breast and skin examinations on a regular basis.

Table 16 outlines the minimum follow-up tests and examinations that should be performed on all patients after treatment for malignant lymphoma. Visits should be scheduled with an oncologist or family physician educated in post-treatment lymphoma surveillance every 3-4 months for 2 years, then every 6 months for 3 years, then annually.

**Table 1.** Minimum follow-up tests and examinations for patients with malignant lymphoma

Interval	Test
Every Visit	<ul style="list-style-type: none"> <li>• Examination of lymph nodes, thyroid, lungs, abdomen, and skin</li> <li>• CBC &amp; differential, LDH (consider ESR AlkP for Hodgkin disease)</li> <li>• Consider CXR during first 3 years for patients who previously had intrathoracic disease</li> </ul>
Annually	<ul style="list-style-type: none"> <li>• TSH (if thyroid was irradiated)</li> <li>• Mammogram for women after age 40 if irradiated (otherwise age 50)</li> <li>• Pap smear</li> <li>• Influenza immunization</li> </ul>
Routine Body CT Scanning	<ul style="list-style-type: none"> <li>• After 3 months of therapy and if abnormal, again after completion of all therapy</li> <li>• If a residual mass is seen on the CT after completion of all therapy, then consider PET/CT scan or consider a repeat CT scan 6 months later. Otherwise, no further routine CT scans are required.</li> </ul>

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**GLOSSARY OF ABBREVIATIONS**

<b>Acronym</b>	<b>Description</b>
2-CDA	2-chlorodeoxyadenosine
ABVD	adriamycin + bleomycin + vinblastine + dacarbazine
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase (test)
ALL	acute lymphoblastic leukemia
ALT	alanine transaminase (test)
AML	acute myeloid leukemia
ATCL	adult T-cell lymphoma
BCNU	carmustine
BEACOPP	bleomycin + etoposide + adriamycin + cyclophosphamide + vincristine + procarbazine + prednisone
BEAM	BCNU + etoposide + cytarabine + melphalan
BL	Burkitt lymphoma
BMT	bone marrow transplant
B-R	Bendamustine-rituximab
CALGB	Cancer and Leukemia Group B
CAP	cyclophosphamide + adriamycin + prednisone
CBV	cyclophosphamide + BCNU + etoposide
CEC	cyclophosphamide + lomustine + vindesine + melphalan + prednisone + epidoxirubicin + vincristine + procarbazine + vinblastine + bleomycin
CEPP	cyclophosphamide + etoposide + procarbazine + prednisone
ChIVPP	chlorambucil + vinblastine + procarbazine + prednisone
CHOP	cyclophosphamide + adriamycin + vincristine + prednisone
CHOEP	cyclophosphamide + adriamycin + vincristine + etoposide + prednisone
CLL	chronic lymphocytic leukemia
CMED	cyclophosphamide + etoposide + methotrexate + dexamethasone + leucovorin + G-CSF
CNS	central nervous system
CODOX-M	cyclophosphamide + vincristine + adriamycin + methotrexate
COPP	cyclophosphamide + vincristine + procarbazine + prednisone
CR	complete remission
CS	clinical stage
CSF	cerebrospinal fluid
CT	computed tomography scan
CTCL	cutaneous T-cell lymphoma
CVAD	cyclophosphamide + vincristine + adriamycin + dexamethasone
CVP	cyclophosphamide + vincristine + prednisone
DHAP	dexamethasone + cytarabine + cisplatin
DICE	dexamethasone + ifosfamide + cisplatin + etoposide + mesna
DICEP	dexamethasone + cyclophosphamide + etoposide + cisplatin + mesna + Septra
DLBCL	diffuse large B-cell lymphoma
DLCO	diffusing capacity of the lung for carbon monoxide
EBER	Epstein-Barr virus encoded ribonucleic acid
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
ENS	extracapsular neoplastic spread
ENT	ear, nose, and throat

ESHAP	etoposide + methylprednisolone + cytarabine + cisplatin
ESR	erythrocyte sedimentation rate
FC	fludarabine + cyclophosphamide
FEV1	forced expiratory volume in one second
FISH	fluorescent <i>in situ</i> hybridization
FLIPI	Follicular Lymphoma International Prognostic Index
FND	fludarabine + mitoxantrone + dexamethasone
FVC	forced vital capacity
G-CSF	granulocyte-colony stimulating factor
GDP	gemcitabine + dexamethasone + cisplatin
GHSG	German Hodgkin Study Group
GMALL	German multicentre adult acute lymphoblastic leukemia protocol
H&E	hematoxylin and eosin stain
HAART	highly active antiretroviral therapy
HAMA	human anti-mouse antibodies
HDCT	high dose chemotherapy
HL	Hodgkin lymphoma
HP-Pac	lansoprazole + clarithromycin + amoxicillin
HSCT	hematopoietic stem cell transplantation
HVS	hyperviscosity syndrome
ICE	ifosfamide + carboplatin + etoposide
IELSG	International Extranodal Lymphoma Study Group
IFRT	involved field radiation therapy
IMRT	intensity-modulated radiation therapy
IPI/IPS	International Prognostic Index/Score
IV	intravenous
IVAC	ifosfamide + mesna + etoposide + cytarabine
IVE	ifosfamide + vincristine + etoposide
KPS	Karnofsky Performance Status Scale
LDH	lactate dehydrogenase test
LPL	lymphoplasmacytic lymphoma
LVEF	left ventricular ejection fraction
MACOP-B	methotrexate + adriamycin + cyclophosphamide + vincristine + bleomycin + prednisone
MALT	mucosa-associated lymphoid tissue
MDS	myelodysplastic syndrome
MEP	mitomycin C + etoposide + cisplatin
MTD	maximum transthoracic diameter
MTX	methotrexate
MUGA	multiple gated acquisition scan
NHL	non-Hodgkin lymphoma
NK	natural killer
NLPHD	nodular lymphocyte predominant Hodgkin disease
OS	overall survival
PCNSL	primary central nervous system lymphoma
PCP	<i>Pneumocystis jiroveci</i> pneumonia
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test
POMP	mercaptopurine + vincristine + methotrexate + prednisone
PR	partial response



PTCL	peripheral T-cell lymphoma
PTLD	post-transplant lymphoproliferative disorder
PUVA	psoralen + ultraviolet A radiation
R	rituximab
R-CHOP	rituximab + cyclophosphamide + adriamycin + vincristine + prednisone
R-CVP	rituximab + cyclophosphamide + vincristine + prednisone
R-FCM	fludarabine + cyclophosphamide + mitoxantrone + rituximab
RIT	radioimmunoconjugate therapy
RR	response rate
RT	radiotherapy
SBFT	small bowel follow-through (test)
SCT	stem cell transplant
SD	stable disease
SLE	systemic lupus erythematosus
SLL	small lymphocytic lymphoma
SOT	solid organ transplant
STNI	subtotal nodal irradiation
TBuC	thiotepa + busulfan + cyclophosphamide
TBI	total body irradiation
TRM	Transplant-related mortality
TSH	thyroid stimulating hormone
UGI	upper gastrointestinal series (test)
VIPD	etoposide + ifosfamide + cisplatin + dexamethasone
WHO	World Health Organization
WM	Waldenström macroglobulinemia

## DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

## MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Hematology Tumour Team Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Hematology Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Hematology Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

## APPENDIX A

### Information regarding Rituximab 375mg/m<sup>2</sup> IV or 1400mg SC for B-cell lymphoma treatment

- Indications:
  - All CD 20+ B cell lymphomas (indolent and aggressive)
  - PTLD and MCL
  - Monotherapy or with chemo
  - Maintenance q2m (MCL) and q3m (indolent and FL)
  - Stem cell mobilization and high dose conditioning regimens for ASCT.
- Not indicated:
  - Not CLL (Health Canada)
  - not for Ritux treatment of autoimmune cytopenias due to CLL or indolent lymphoma (hematoma risk)
- Timing of sc Rituximab relative to IV:
  - all first exposure to rituximab must be IV
  - before commencing SC the patient must have *completed* a full rituximab IV infusion dose, regardless if the patient had an infusion reaction or the grade of the reaction. (patient does not have to had 0 reaction to IV). If the patient did not complete\* the full IV dose, the next rituximab dose must be by IV infusion. (Roche)
- Pts may start with SC if:
  - going on to maintenance treatment and had SC prior
  - going on to mobilization, high dose chemo and had SC prior
  - undergoing re-treatment (even > 6 months) may start with SC if they had SC prior

### I. INITIAL THERAPY FOR DIFFUSE LARGE B-CELL LYMPHOMA

#### R-CHOP (standard risk)

- rituximab 375mg/m<sup>2</sup> IV day 1 (premedications: Tylenol, Benadryl, Zantac, hydrocortisone 100mg), then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated well.
- cyclophosphamide 750 mg/m<sup>2</sup> IV
- adriamycin 50 mg/m<sup>2</sup> IV day 1
- vincristine 2mg IV day 1
- prednisone 100mg/day p.o. days 1-5
- *Cycles:* every 21 days

#### R-CHOEP (high risk, age <60 years)<sup>1-3</sup>

- rituximab 375mg/m<sup>2</sup> IV day 1 (premedications: Tylenol, Benadryl, Zantac, hydrocortisone 100mg) then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated well.
- cyclophosphamide 750 mg/m<sup>2</sup> IV
- adriamycin 50 mg/m<sup>2</sup> IV day 1
- vincristine 2mg IV day 1
- etoposide 100mg/m<sup>2</sup> IV days 1-3 (or 200mg/m<sup>2</sup> p.o. days 2-3 instead of IV; round down to nearest 50mg multiple)
- prednisone 100mg/day p.o. days 1-5
- G-CSF days 7-11 or neulasta day 4 of each cycle
- *Cycles:* every 14-21 days

**R-CEOP (cardiac disease with LVEF <50%)<sup>1-3</sup>**

- rituximab 375mg/m<sup>2</sup> IV day 1 (premedications: Tylenol, Benadryl, Zantac, hydrocortisone 100mg) then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated well.
- cyclophosphamide 750 mg/m<sup>2</sup> IV
- vincristine 2mg IV day 1
- etoposide 50mg/m<sup>2</sup> IV days 1-3 (or 100mg/m<sup>2</sup> p.o. days 2-3 instead of IV; round up to nearest 50mg multiple)
- prednisone 100mg/day p.o. days 1-5
- *Cycles:* every 21 days

**R-MACOP-B (not recommended unless patient needs to complete therapy in 3 months)**

- methotrexate 400mg/m<sup>2</sup> IV on weeks 2, 6, 10 (24 hours later: folinic acid 15mg q6 hours x 6 doses)
- adriamycin 50 mg/m<sup>2</sup> IV weeks 1,3,5,7,9,11
- cyclophosphamide 350 mg/m<sup>2</sup> IV weeks 1,3,5,7,9,11
- vincristine 2mg IV weeks 2,4,6,8,10,12
- bleomycin 10mg/m<sup>2</sup> weeks 4,8,12
- prednisone 75mg/day p.o. daily, taper over last 15 days
- sepra for PCP prophylaxis
- suggest adding rituximab 375mg/m<sup>2</sup> IV q14 days x 6 doses then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated well.

**DA-EPOCH-R:**

Prednisone is a tablet taken by mouth TWICE daily on Days 1, 2, 3, 4, 5 Rituximab is an intravenous (I.V.) infusion on Day 1 (time of infusion varies) Doxorubicin is an I.V. infusion given over 24 hours on Days 1, 2, 3, 4 Etoposide is an I.V. infusion given over 24 hours on Days 1, 2, 3, 4 Vincristine is an I.V. infusion given over 24 hours on Days 1, 2, 3, 4 Cyclophosphamide is an I.V. infusion given over two hours on Day 5 On Day 6, filgrastim (Neupogen®) is started subcutaneously once daily and continued every day until the white blood cell count returns to normal. Alternatively, some Doctors prefer to give one dose of pegfilgrastim (Neulasta®) after each cycle of dose-adjusted EPOCH-R Patients then have labs drawn twice weekly until the white blood cell count has recovered.

Typically, etoposide, doxorubicin, and vincristine are mixed together in one intravenous infusion bag and each bag is infused over 24 hours on Days 1, 2, 3, and 4 of each cycle (96 hours total).

<b>Day 1-4</b>	<b>Doxorubicin Vincristine</b>	<b>10 mg/m2/day 0.4mg/m2/day (no cap)</b>	Intravenous infusion in an elastomeric infusor in sodium chloride 0.9% via a central line over 96 hours
<b>Day 1-4</b>	<b>Etoposide</b>	<b>50 mg/m2/day</b>	Intravenous infusion in 500ml sodium chloride 0.9% over 24 hours via a central line
<b>Day 5</b>	Ondansetron <b>Cyclophosphamide</b>	8mg <b>750mg/m2</b>	Oral as a single dose prior to chemotherapy Intravenous bolus
<b>Day 6</b>	GCSF (Biosimilar)	300 micrograms	Subcutaneous injection once daily until neutrophil recovery (supply 7 doses)

**Dose Adjustments according to nadir**
**Doxorubicin, Etoposide and Cyclophosphamide ONLY:**

Doses may be adjusted from Cycle 2 based on the previous cycle's neutrophil (ANC) nadir. This is monitored by obtaining TWICE WEEKLY CBC, i.e. days 9, 12, 15,18:

- If nadir ANC  $\geq 0.5 \times 10^9/l$ : **increase by 1 dose level**
- If nadir ANC  $< 0.5 \times 10^9/l$  on 1 or 2 measurements: **same dose as last**

**Cycle**

- If nadir ANC  $<0.5 \times 10^9/l$  on at least 3 measurements: **decrease by 1 dose level**
- If platelet nadir  $<25 \times 10^9/l$ : **reduce by 1 dose level** regardless of ANC
- Life threatening infections: **decrease by 1 dose level**

**Table 1: Drug Dose Adjustments**

Drugs	Drug Doses per Dose Levels				
	-2	-1	1	2	3
	64% (64% $\times$ 0.8)	80% (100% $\times$ 0.8)	100% (starting dose) CYCLE 1	120% (100% $\times$ 1.2)	144% (120% $\times$ 1.2)
Prednisolone (mg/m <sup>2</sup> twice daily)	60	60	60	60	60
Rituximab (mg/m <sup>2</sup> /day)	375	375	375	375	375
Doxorubicin (mg/m <sup>2</sup> /day)	10	10	10	12	14.4
Vincristine (mg/m <sup>2</sup> /day)	0.4	0.4	0.4	0.4	0.4
Etoposide (mg/m <sup>2</sup> /day)	50	50	50	60	72
Cyclophosphamide (mg/m <sup>2</sup> /day)	480	600	750	900	1080

**Neurotoxicity:**

If the patient complains of significant constipation or sensory loss in fingers and/or toes, consider dose reduction of vincristine:

- Reduce by 25% for grade 2 motor neuropathy
- Reduce by 50% for grade 3 motor or sensory neuropathy
- For patients who develop  $\geq$  grade 3 ileus, treatment should be delayed until recovery and vincristine introduced at 75% of the normal dose thereafter. If  $\geq$  grade 3 ileus recurs, vincristine should be discontinued

Additional medicines that may be prescribed:

Septra	480mg	Oral once daily
Valacyclovir	500mg	Oral once daily
Fluconazole	50mg	Oral once daily
Omeprazole	20mg	Oral once daily for 5 days
Metoclopramide	10mg	Oral four times daily as needed
Ondansetron	8mg	Oral as a single dose prior to chemotherapy, then twice daily as needed

Docusate/Senna (Senna-S®) to prevent constipation from vincristine

Consider intrathecal prophylaxis for patients with  $>1$  extranodal site and elevated LDH

## **II. INITIAL THERAPY FOR INDOLENT HISTOLOGY NON-HODGKIN LYMPHOMA**

### **B-R**

- bendamustine 90 mg/m<sup>2</sup> IV day 1, 2
- rituximab 375 mg/m<sup>2</sup> IV day 1 then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated.
- *Cycles:* repeated every 3-4 weeks depending on blood counts (usually administered every 28 days) for a maximum of 6 cycles

### **CVP**

- cyclophosphamide 800 mg/m<sup>2</sup> IV day 1 (or 400 mg/m<sup>2</sup>/day p.o. days 1-5)
- vincristine 2mg IV day 1
- prednisone 100mg/day p.o. days 1-5
- *Cycles:* every 21 days

### **R-CVP**

- rituximab 375mg/m<sup>2</sup> IV day 1 (premeds: Tylenol, Benadryl, Zantac, hydrocortisone 100mg), then Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated.
- cyclophosphamide 750 mg/m<sup>2</sup> IV day 1
- vincristine 2mg IV day 1
- prednisone 100mg/day p.o. days 1-5
- *Cycles:* every 21 days

### **Maintenance Rituximab in First or Second Remission Following Chemotherapy + Rituximab**

- Follicular and other indolent B-cell lymphoma: rituximab 1400mg sc (or 375mg/m<sup>2</sup> IV if cannot tolerate sc) x 1 dose q3 months x 2 years (8 doses total)
- Mantle cell lymphoma option: rituximab 1400mg sc ( or 375mg/m<sup>2</sup> IV if cannot tolerate sc) q2months until progression

### **Outpatient R-DHAP**

#### **Cycle 1:**

Day1: Rituximab 375mg/m<sup>2</sup> IV (if no rituximab in past 3months and cannot receive sc rituximab)

Day 2: 500mL NS pre, cisplatin 35 mg/m<sup>2</sup> in 500 mL NS/mannitol, 500 ml NS post, AraC 2g/m<sup>2</sup> in 500 mL NS.

Day 3: 500mL NS pre, cisplatin 35 mg/m<sup>2</sup> in 500 ml NS/mannitol, AraC 2g/m<sup>2</sup> in 500 mL NS. Total 5 hrs

#### **Cycle 2 onwards:**

Day1: Rituximab 1400mg sc, 500mL NS pre, cisplatin 35 mg/m<sup>2</sup> in 500 mL NS/mannitol, 500 ml NS post. Then AraC 2g/m<sup>2</sup> in 500 mL NS. Total 5 hrs

Day2: 500mL NS pre, cisplatin 35 mg/m<sup>2</sup> in 500 ml NS/mannitol, AraC 2g/m<sup>2</sup> in 500 mL NS. Total 5 hrs

### **Chlorambucil (options)**

- 0.1-0.2 mg/kg/day for 4-8 weeks then usually reduce for maintenance
- 10-14 mg/m<sup>2</sup> for 5 to 7 days each 28 days
- 0.5 mg/kg days 1 and 15 q28d cycle



### **Fludarabine**

- 25mg/m<sup>2</sup> IV days 1-5 q28 days (days 1-3 only if frail elderly or renal dysfunction)
- 40mg/m<sup>2</sup> p.o. days 1-5 q28 days (round down to nearest multiple of 10mg) (d1-3 only if frail or renal dysfunction)

### **FND**

- fludarabine 25mg/m<sup>2</sup> IV days 1-3 or 40mg/m<sup>2</sup> p.o. days 1-3
- mitoxantrone 10mg/m<sup>2</sup> day 1
- dexamethasone 40mg p.o. days 1-3
- septria for PCP prophylaxis
- *Cycles:* every 28 days

## **III. INITIAL THERAPY FOR PERIPHERAL T-CELL LYMPHOMA**

### **CHOP**

- cyclophosphamide 750 mg/m<sup>2</sup> IV
- adriamycin 50 mg/m<sup>2</sup> IV day 1
- vincristine 2mg IV day 1
- prednisone 100mg/day p.o. days 1-5
- *Cycles:* every 21 days

### **CHOEP<sup>1-3</sup>**

- cyclophosphamide 750 mg/m<sup>2</sup> IV
- adriamycin 50 mg/m<sup>2</sup> IV day 1
- vincristine 2mg IV day 1
- etoposide 100mg/m<sup>2</sup> IV days 1-3 (or 200mg/m<sup>2</sup> p.o. days 2-3 instead of IV; round down to nearest 50mg multiple)
- prednisone 100mg/day p.o. days 1-5
- G-CSF days 7-11 or neulasta day 4 of each cycle
- *Cycles:* every 21 days

### **VIPD (Nasal NK/T-cell lymphoma)**

- etoposide 100mg/m<sup>2</sup> days 1-3
- ifosfamide 1.2g/m<sup>2</sup> days 1-3
- cisplatin 33mg/m<sup>2</sup> days 1-3
- dexamethasone 40mg days 1-4
- *Cycles:* 3 cycles after initial radiotherapy

### **GOLD (14 day cycle)<sup>4</sup>**

- gemcitabine 1000mg/m<sup>2</sup> on day 1
- oxaliplatin 100mg/m<sup>2</sup> on day 1
- L-asparaginase 10,000U/m<sup>2</sup> on days 1-5\*
- dexamethasone (20mg b.i.d.) on days 1-4

\*An intradermal test was required prior to the administration of L-ASP

**SMILE (28 day cycle)<sup>5</sup>**

- Methotrexate  $2\text{g}/\text{m}^2$  on day 1
- Leucovorin  $15\text{mg} \times 4$  on day 2, 3, and 4
- Ifosfamide  $1500\text{mg}/\text{m}^2$  on day 2, 3, and 4
- Mesna  $300\text{ mg}/\text{m}^2 \times 3$  on day 2, 3 and 4
- Dexamethasone  $40\text{mg}/\text{d}$  on day 2, 3 and 4
- Etoposide  $100\text{mg}/\text{m}^2$  on day 2, 3 and 4
- L-asparaginase  $6000\text{U}/\text{m}^2$  on day 8, 10, 12, 14, 16, 18 and 20

GCSF should be given from day 6 and discontinued if the leukocyte count exceeds  $5000/\mu\text{L}$ .

Antibiotic prophylaxis with sulfamethoxazole-trimethoprim is recommended.

## IV. HODGKIN DISEASE CHEMOTHERAPY REGIMENS

### Initial Therapy

**ABVD** adriamycin 25 mg/m<sup>2</sup> IV days 1 and 14  
bleomycin 10 mg/m<sup>2</sup> IV days 1 and 14  
vinblastine 6 mg/m<sup>2</sup> IV days 1 and 14  
dacarbazine 375 mg/m<sup>2</sup> IV days 1 and 14  
*Cycles: every 28 days*

#### **BEACOPP (escalated)**

bleomycin 10mg/m<sup>2</sup> IV day 8  
etoposide 200mg/m<sup>2</sup> IV days 1-3  
adriamycin 35mg/m<sup>2</sup> IV day 1  
cyclophosphamide 1250mg/m<sup>2</sup> IV day 1  
vincristine 1.4mg/m<sup>2</sup> IV day 8  
procarbazine 100mg/m<sup>2</sup> p.o. days 1-7  
prednisone 40mg/m<sup>2</sup> po days 1-14  
G-CSF 300-480µg sc d9-19 (to ANC>1.5) or Neulasta d9  
*Cycles: every 21 days*

#### **BEACOPP (baseline)**

bleomycin 10mg/m<sup>2</sup> IV day 8  
etoposide 100 mg/m<sup>2</sup> IV days 1-3  
adriamycin 25mg/m<sup>2</sup> IV day 1  
cyclophosphamide 650mg/m<sup>2</sup> IV day 1  
vincristine 1.4mg/m<sup>2</sup> IV day 8  
procarbazine 100mg/m<sup>2</sup> p.o. days 1-7  
prednisone 40 mg/m<sup>2</sup> p.o. days 1-14

**ChIVPP** chlorambucil 6mg/m<sup>2</sup> p.o. days 1-14  
vinblastine 6mg/m<sup>2</sup> IV days 1 and 8  
procarbazine 100mg/m<sup>2</sup> p.o. days 1-14  
prednisone 40mg/m<sup>2</sup> p.o. days 1-14  
*Cycles: every 28 days*

**MOPP** nitrogen mustard 6mg/m<sup>2</sup> days 1 & 8  
vincristine 1.4mg/m<sup>2</sup> IV days 1 & 8  
procarbazine 100mg/m<sup>2</sup> po days 1-14  
prednisone 40mg/m<sup>2</sup> po days 1-14  
*Cycles: every 28 days*

**COPP** cyclophosphamide 650mg/m<sup>2</sup> IV days 1&8  
vincristine 1.4mg/m<sup>2</sup> IV days 1 & 8  
procarbazine 100mg/m<sup>2</sup> po days 1-14  
prednisone 40mg/m<sup>2</sup> po days 1-14  
*Cycles: every 28 days*

## V. LYMPHOMA SALVAGE REGIMENS

### Aggressive Histology Hodgkin and Non-Hodgkin Lymphomas\*

#### **DICE**

- dexamethasone 10mg IV q6 hours days 1-4
- ifosfamide 1g/m<sup>2</sup> (max 1.75g) over 15 minutes days 1-4
- cisplatin 25mg/m<sup>2</sup> IV over 1hour days 1-4
- etoposide 100mg/m<sup>2</sup> over 1 hour days 1-4
- mesna 200 mg/m<sup>2</sup> over 5-10 min prior to first dose of ifosfamide, then 200 mg/m<sup>2</sup> IV at 4 hours and 400mg/m<sup>2</sup> p.o. (or 200 mg/m<sup>2</sup> IV) at 8 hours post-ifosfamide x 4 days
- *Cycles: every 21-28 days*

#### **CEPP**

- cyclophosphamide 600 mg/m<sup>2</sup> IV days 1 and 8
- etoposide 70mg/m<sup>2</sup> days 1-3
- procarbazine 60mg/m<sup>2</sup> p.o. days 1-10
- prednisone 100mg/day p.o. days 1-10
- *Cycles: every 28 days*

#### **GDP**

- gemcitabine 1000mg/m<sup>2</sup> IV days 1 and 8
- dexamethasone 40mg p.o. days 1-4

- cisplatin 75mg/m<sup>2</sup> IV

#### **DICEP**

- dexamethasone 10mg IV q8 hours x 10 doses
- cyclophosphamide 1.75 g/m<sup>2</sup> IV over 2 hours days 1-3
- etoposide 350mg/m<sup>2</sup> IV over 2 hours days 1-3
- cisplatin 35mg/m<sup>2</sup> IV over 2 hours days 1-3
- mesna 1.75g/m<sup>2</sup> IV over 24 hours days 1-3
- septrax for PCP prophylaxis
- *Cycles:* Once only

*\*Add rituximab to salvage regimens for transplant eligible patients with relapsed B-cell lymphomas*

#### **Indolent Histology Non-Hodgkin Lymphoma**

As above, plus:

#### **Rituximab**

- 375mg/m<sup>2</sup> IV days 1,8,15, and 22 (Rituximab 1400mg sc from day 8 onwards if initial IV dose tolerated).
- Pre-medicate with hydrocortisone 100mg IV, Benadryl, Zantac, and Tylenol
- Infuse 50mg/hour initially, then increase by 50mg/hour increments q30 minutes as tolerated to a maximum of 400mg/hour
- Subsequent infusions can begin at 100mg/hour and increase by 100mg/hour increments as tolerated to maximum of 400mg/hour

#### **FND**

- fludarabine 25mg/m<sup>2</sup> IV days 1-3 or 40mg/m<sup>2</sup> p.o. days 1-3
- mitoxantrone 10mg/m<sup>2</sup> day 1
- dexamethasone 40mg p.o. days 1-3
- septrax for PCP prophylaxis
- *Cycles:* every 28 days

#### **R-FCM**

- fludarabine 25mg/m<sup>2</sup> IV days 1-3 or 40mg/m<sup>2</sup> p.o. days 1-3
- cyclophosphamide 200mg/m<sup>2</sup> IV days 1-3
- mitoxantrone 8mg/m<sup>2</sup> IV day 1
- rituximab 375mg/m<sup>2</sup> IV day 1 (Rituximab 1400mg sc on day 1 from cycle 2 onwards if initial IV dose tolerated).
- *Cycles:* every 28 days

**VI. BURKITT LYMPHOMA <sup>6,7</sup>**
**Modified Magrath Regimen of R-CODOXM/R-IVAC (Blood 2014; 124:2913-2920)**
**Regimen A (R-CODOX-M)**

Days:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
rituximab 1400mg sc	x																		
cyclophosphamide 800mg/m <sup>2</sup> IV	x	x																	
doxorubicin 50mg/m <sup>2</sup> IV	x																		
vincristine 1.5mg/m <sup>2</sup> IV cap 2mg	x														x				
allopurinol 300mg/day po	x	x	x	x	x	x	x	x	x	x									
methotrexate 3000mg/m <sup>2</sup> IV over 2 hour IV**															x				
leucovorin 25mg IV @ 24 hours, then 25mg IV q6h until methotrexate<10 <sup>-8</sup> M																xx	xx	xx	xx
IT methotrexate 12mg	X																		
IT cytarabine 50mg *			X																
Peg-filgrastim 6mg			X																

\*if CNS disease, give extra IT AraC 50mg d5 cycle 1 only

\*\*HDMTX administered once urine pH>7, and diuresis established with hydration including D5-0.2%NS plus 2-3 amps sodium bicarbonate. Continue hydration and alkalization until MTX cleared.

**Regimen B (R- IVAC)**

Days:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
rituximab 375mg/m <sup>2</sup> IV	X																		
cytarabine 2g/m <sup>2</sup> IV q12h x 4 doses	Xx	xx																	
ifosfamide 1500mg/m <sup>2</sup> IV	X	x	x	x	x														
mesna 360mg/m <sup>2</sup> IV q3 hours	xxx	xxx	xxx	xxx	xxx	xxx													
etoposide 60mg/m <sup>2</sup> IV	X	x	x	x	x														
IT methotrexate 12mg					x														
Peg-filgrastim 6mg						x													

\*if CNS disease, give extra IT AraC 50mg d3 cycle 1 only

**Low risk patients:**

- Single extra-abdominal mass <10cm, or completely resected abdominal disease and normal LDH
- Modified regimen A x 3 cycles (cytarabine IT day 1 and methotrexate IT day 3 each cycle)

**High risk patients:**

- All others
- Alternate regimen A with regimen B for a total of 2 each or 4 cycles total

Start next cycle once ANC>1.0 and platelets>50



**VII. PRIMARY CNS LYMPHOMA PROTOCOL**
**A. Transplant-Eligible Patients: age < 65years, no significant co-morbidities, no immune suppression**

Week	Step 1				*Step 2			**Step 3		**Step 4	
	1	2	3	4	5	6	7	8	9	10	12-14
Rituximab iv/sc d0 and d 4, 14 high-dose methotrexate 3.5 g/m <sup>2</sup> d1&15 procarbazine 100 mg/m <sup>2</sup> d1-7	x		x								
rituximab 1400mg SC d1 cytarabine 3 g/m <sup>2</sup> x d1&2 G-CSF 5-10 µg/kg d8-13 Apheresis ~d14 or 15					x						
Rituximab 1400mg SC d0 high-dose methotrexate 3.5 g/m <sup>2</sup> d1 cytarabine 2 g/m <sup>2</sup> twice daily days 2-3 all q21d for 2 cycles						x			x		
thiotepa 300 mg/m <sup>2</sup> IV days -6,-5 busulfan 3.2 mg/kg IV days -4 to -2, ASCT day 0									x		X

\* Step 2 may begin either week 4 or 5 depending upon patient status and apheresis scheduling

**\*Step 3 may be omitted in patients who have achieved some response and are physically fit to proceed directly to ASCT on week 9.**

Step 1. Induction: High-dose methotrexate/procarbazine q14 days x 2 cycles		
Day	Medications	Other Orders
ADMISSION 0	0900hr-Rituximab 375mg/m <sup>2</sup> (1 <sup>st</sup> infusion protocol) 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO <sub>3</sub> /L @ 200ml/hour x 5d	<ul style="list-style-type: none"> <li>Daily weights</li> <li>Daily CBC &amp; Diff, EP, Creat, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> <li>LFTs, Ca, lipase, every Monday &amp; Thursday</li> </ul>
1	0800hr - Kytril 1mg IV 0800hr - <b>methotrexate</b> 3500mg/m <sup>2</sup> IV over 2 hour cycles 1 and 2 0800hr - <b>procarbazine</b> 100mg/m <sup>2</sup> po daily x 7days only cycle 1 (round down to nearest 50mg multiple)	0700hr - Urine pH twice daily, call MD if <7.0
2-3	0800hr - folinic acid (leucovorin) 25 mg IV q6 hours until methotrexate level < 0.05 Continue hydration until methotrexate level <0.05	0500-0800hr – methotrexate Level daily (expect level < 10 d2, <1 d3)
4	0900hr- Rituximab 1400mg SC on Cycle 1 only and continue folinic acid)	0500-0800hr – methotrexate Level daily
5	<ul style="list-style-type: none"> <li>Discharge once methotrexate level &lt;0.05</li> <li>If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days</li> <li>Discharge meds: sepra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone</li> <li>Remember coumadin/LMWH and Dilantin if patient is on these medications</li> </ul>	

\* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]

Step 2. Rituximab/high-dose cytarabine x 1 cycle for stem cell collection after 2 cycles of methotrexate		
Day	Medications	Other Orders
1	0900hr -Premeds : Hydrocortisone 100mg IV, Benadryl 50mg IV, Zantac 50mg IV, Tylenol 650mg p.o. -rituximab 1400mg SC	<ul style="list-style-type: none"> <li>Weight</li> <li>CBC &amp; Diff, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> </ul>
2 & 3	0800hr – Kytril 2mg IV, dexamethasone 10mg IV 0800hr – IV N/S 500mL/hour x 2 hours 1000hr – <b>cytarabine</b> 3g/m <sup>2</sup> IV over 3 hours (2g/m <sup>2</sup> if >60yrs or creatinine >100)	
9-14	1000hr – G-CSF 480-600 µg subcutaneous daily until apheresis completed (plan for apheresis approximately day 13-15, once ANC>5, Plt >75 and CD34>20)	Daily CBC & differential starting day 10

<b>**Step 3. High-dose methotrexate/cytarabine consolidation q21 days x 1 cycles after stem cell collection</b>		
<b>Day</b>	<b>Medications</b>	<b>Other Orders</b>
ADMISSION 0	16:00hr- Rituximab 1400mg subcutaneously 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200ml/hour x 5 days	<ul style="list-style-type: none"> <li>• Daily weights</li> <li>• Daily CBC &amp; differential, EP, creatinine, glucose</li> <li>• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> <li>• ALT, Alk P, bili, Ca, lipase, every Monday &amp; Thursday</li> </ul>
1	0800hr - Kytril 1mg IV 0800hr - <b>methotrexate</b> 3500mg/m <sup>2</sup> IV over 2 hours	07:00 - Urine pH bid, call MD if <7.0
2-3	080hr- folinic acid (leucovorin) 25 mg IV q6 hours until methotrexate level < 0.05 -Continue hydration until methotrexate level <0.05 0800hr – Kytril 2mg IV, dexamethasone 10mg IV 1000hr – <b>cytarabine</b> 2g/m <sup>2</sup> IV over 2 hours twice daily x 2 days Reduce to 1.5g/m <sup>2</sup> if age >60 years or creatinine >100	0500-08:00 – methotrexate level daily (expect <10 d2, <1 d3, <0.1 d4, <0.05 d5)
5	Discharge once methotrexate level <0.05 If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days (other meds as step 1 above)	
8-12	1000hr – G-CSF 480-600 µg subcutaneous daily until post-nadir ANC >1.5	Daily CBC & differential starting day 10

\* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]

**\*\*NB: Step 3 may be omitted in patients who have achieved some response and are physically fit to proceed directly to ASCT on week 9.**

<b>Step 4. TBu/ASCT consolidation after response to methotrexate and high-dose cytarabine</b>		
<b>Day</b>	<b>Medications</b>	<b>Other Orders</b>
ADMISSION Day -7	Allopurinol 300 mg p.o. daily until day 0  2200hr - D5 ½ N/S + 20 mEq KCL/L @ 125 mL/hour until day -1	<ul style="list-style-type: none"> <li>• Consult dietician</li> <li>• Consult physiotherapy</li> <li>• Low bacteria diet</li> <li>• 24 hour intake</li> <li>• Mouth protocol</li> <li>• Record intake and output</li> </ul>
-6 & -5	0800 – <b>thiotepa</b> 300 mg/m <sup>2</sup> IV over 3 hours x 2 days (use IDEAL BSA)	<ul style="list-style-type: none"> <li>• 0800hr – granisetron 2 mg IV daily x 8 days</li> <li>• EP daily x 31days</li> <li>• Shower/bath q6 hours x 3 days; avoid skin creams</li> </ul>
-4 to -2	0900 - <b>busulfan</b> 3.2 mg/kg IV daily x 3 days (use Ideal weight)	<ul style="list-style-type: none"> <li>• lorazepam prophylaxis x 4 days</li> <li>• CBC &amp; differential daily x 31 days</li> <li>• ALT, Alk Phos, bili, alb, Ca, Mg, every Monday &amp; Thursday</li> <li>• PT, PTT, every Monday</li> </ul>
-1	Rest day	<ul style="list-style-type: none"> <li>• mycostatin 500,000 units q2-4 hours</li> <li>• septra RS 1 tab p.o. daily</li> <li>• acyclovir 5 mg/kg bid IV or 400 mg p.o. four times daily</li> </ul>
0	Autologous Blood Stem Cell INFUSION	
+7	G-CSF 300µg (if less than 70kg) or 480µg (if over 70kg) subcutaneous daily until post-nadir ANC > 1.5	

**B. Transplant-Ineligible Patients: age  $\geq 65$  years. Should be CIRS 0-6 and ECOG 0-2.**

Week	Step 1												Step 3
	1	2	3	4	5	6	7	8	9	10	11	12	15 or 16
Rituximab d0, 4	x			x			x			x			
high-dose methotrexate 3.5 g/m <sup>2</sup> d1	x			x			x			x			
cytarabine 2g/ m <sup>2</sup> q12h x 2 d2	x			x			x			x			
Thiotepa 30mg/ m <sup>2</sup> d4	x			x			x			x			
Ifosfamide 2g/m <sup>2</sup> daily days 1-3													X

Step 1. Induction: MATRIX x 4 cycles		
Day	Medications	Other Orders
ADMISSION 0	0900hr-Rituximab 375mg/m <sup>2</sup> (1 <sup>st</sup> infusion protocol) 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO <sub>3</sub> /L @ 200ml/hour x 5 days	<ul style="list-style-type: none"> <li>Daily weights</li> <li>Daily CBC &amp; differential, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> <li>LFTs, Ca, lipase, every Monday &amp; Thursday</li> </ul>
1	0800hr - Kytril 1mg IV 0800hr - <b>methotrexate</b> 3500mg/m <sup>2</sup> IV over 3 hours	0700hr - Urine pH twice daily, call MD if <7.0
2-3	0800hr - folinic acid (leucovorin) 25 mg IV q6hr until MTX level < 0.05 Continue hydration until methotrexate level <0.05 1000hr –Cytarabine 2mg/m <sup>2</sup> by 1 hour infusion q12 hr x 2	0500-0800hr – methotrexate level daily (expect level < 10 d2, <1 d3)
4	0900hr- Rituximab 1400mg subcutaneously 1000hr- Thiotepa 30mg/m <sup>2</sup> by 30min infusion	0500-0800hr – methotrexate Level daily
5	<ul style="list-style-type: none"> <li>Discharge once methotrexate level &lt;0.05</li> <li>If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days</li> <li>Discharge meds: sepra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone</li> <li>Remember coumadin/LMWH and dilantin if patient is on these medications</li> </ul>	

**Methotrexate should be omitted if creat clearance < 50 mL/min or if renal dysfunction with prior cycle**

**Cytarabine should be reduced to q24hr if creat clearance < 50 mL/min or complications of myelosuppression**

\* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]

\* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]

Step 2. Ifosfamide consolidation after response to MATRIX (optional)		
Day	Medications	Other Orders
15 or 16	0800hr – Kytril 2mg IV, dexamethasone 10mg IV daily x 3d 0800hr – N/S IV 500mL/hour x 1 hour daily x 3d 0900hr – Mesna 400mg/m <sup>2</sup> IV daily x 3d 0900hr – Ifosfamide 2g/m <sup>2</sup> with 1g Mesna IV over 3 hours daily x 3d 1200hr – Mesna 400mg/m <sup>2</sup> IV daily x 3d 1200hr – 1L NS IV 250mL/hour x 4 hours daily x 3d 1600hr – Mesna 400mg/m <sup>2</sup> IV daily x 3d	<ul style="list-style-type: none"> <li>weight (call MD if &gt;2kg above day 1)</li> <li>CBC &amp; differential, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> </ul>

**VIII. SECONDARY CNS LYMPHOMA PROTOCOL**

**A)** Transplant-eligible patients (age <65 years, no significant co-morbidities, no immune suppression) with isolated CNS relapse/progression following complete response of systemic lymphoma to RCHOP.

Week	Step 1								Step 2			Step 3		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
high-dose methotrexate 3.5 g/m <sup>2</sup> d1 Rituximab 375 mg/m <sup>2</sup> d2 procarbazine 100 mg/m <sup>2</sup> x 7 days d1-7 vincristine 1.4 mg/m <sup>2</sup> d1	x		x		x		x							
rituximab 1400mg sc days 1,4 dexamethasone 20 mg days 1-4 cisplatin 35 mg/m <sup>2</sup> days 1,2 cytarabine 2 g/m <sup>2</sup> x1 dose, days 1,2 G-CSF 5-10 µg/kg day 8-13 Apheresis day 13 or 14									x					
R-TbuM/ ASCT (ritux d-7 + thiotepa 250mg/m <sup>2</sup> d -6,-5 busulfan 3.2 mg/kg day -4 to -2, melphalan 100 mg/m <sup>2</sup> d-1, ASCT d 0													x	

Step 1. Induction: high-dose methotrexate/vincristine/procarbazine q14 days x 4 cycles		
Day	Medications	Other Orders
ADMISSION 0	2000hr - IV D5W + 20meq KCL/L + 2 amps NaHCO <sub>3</sub> /L @ 200mL/hour x 5 days	<ul style="list-style-type: none"> <li>Daily weights</li> <li>Daily CBC &amp; differential, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> <li>LFTs, Ca, lipase, every Monday &amp; Thursday</li> </ul>
1	0800hr - Kytril 1mg IV 0800hr - <b>methotrexate</b> 3500mg/m <sup>2</sup> IV over 2 hours cycles 1-4 0800hr - <b>procarbazine</b> 100mg/m <sup>2</sup> p.o. daily x 7days cycles 1 and 3 (round down to nearest 50mg multiple) 1000hr - <b>vincristine</b> 1.4mg/m <sup>2</sup> IV only cycles 1 and 2	0700hr - Urine pH twice daily, call MD if <7.0
2-4	0800hr- folinic acid (leucovorin) 25 mg IV q6 hours until methotrexate level < 0.05 Continue hydration until methotrexate level <0.05 1000hr – <b>Rituximab</b> 375mg/m <sup>2</sup> IV (first 3 cycles HDMTX)	0500-0800hr – methotrexate level daily (expect level < 10 today)
5	<ul style="list-style-type: none"> <li>Discharge once methotrexate level &lt;0.05</li> <li>If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days</li> <li>Discharge meds: sepra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone</li> <li>Remember coumadin/LMWH and dilantin if patient is on these medications</li> </ul>	

\* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft.

Step 2. Rituximab/DHAP x 1 cycle for stem cell collection after 4 cycles of methotrexate		
Day	Medications	Other Orders
1	0800hr - hydrocortisone 100mg IV, Benadryl , Zantac, Tylenol 0900hr - <b>rituximab</b> 1400mg sc 0900hr -IV 1L NS 0900hr – <b>dexamethasone</b> 20mg p.o./IV daily x 4 days 0900hr – Kytril 1mg IV or 2mg p.o. x 3-4 days 0900hr – aprepitant protocol p.o. x 3 days 1000hr – <b>cisplatin</b> 35mg/m <sup>2</sup> IV over 2 hours with mannitol 25g and 500mL NS 1200hr- <b>cytarabine</b> 2g/m <sup>2</sup> IV over 2 hours x 1 doses (1.5g/m <sup>2</sup> if >60yr)	<ul style="list-style-type: none"> <li>Weight</li> <li>CBC &amp; differential, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> </ul>
2	0800hr – <b>dexamethasone</b> Kytril, Aprepitent continued 1000hr – <b>cisplatin</b> 35mg/m <sup>2</sup> IV over 2 hours with mannitol 25g and 500mL NS 1200hr- <b>cytarabine</b> 2g/m <sup>2</sup> IV over 2 hours x 1 doses (1.5g/m <sup>2</sup> if >60yr)	
4	Rituximab 1400mg sc	
8-13	1000hr – G-CSF 480-600µg subcutaneous daily until apheresis completed (plan for apheresis approximately day 13-15, once ANC>5, Plt >75 and CD34>20)	Daily CBC & differential starting day 10

Step 3. R-TBuM/ASCT consolidation after response to MTX and RDHAP Induction		
Day	Medications	Other Orders
ADMISSION Day -7	Allopurinol 300 mg p.o. daily until day 0 Premeds: Hydrocortisone 100mg IV, Benadryl 50mg IV, Zantac 50mg IV, Tylenol 650mg p.o. -rituximab 375mg/m <sup>2</sup> IV (first dose long infusion protocol)  2200hr - D5½ N/S + 20 mEq KCL/L @ 125 mL/hour until day -1	<ul style="list-style-type: none"> <li>Consult dietician, physiotherapy</li> <li>Low bacteria diet. 24hour intake</li> <li>Mouth protocol; record intake and output</li> </ul>
-6 & -5	0800hr – thiotepa 250 mg/m <sup>2</sup> IV over 2 hours x 2 days (use ideal BSA)	<ul style="list-style-type: none"> <li>0800hr – Granisetron 2 mg IV daily x 8 days</li> <li>EP daily x 31 days</li> <li>Shower/Bath q6 hours x 3 days; avoid skin creams</li> </ul>
-4 to -2	0900 - busulfan 3.2 mg/kg IV daily x 3 days (use Ideal weight)	<ul style="list-style-type: none"> <li>lorazepam prophylaxis x 4 days</li> <li>CBC &amp; differential daily x 31 days</li> <li>ALT, Alk Phos, bilirubin, alb, Ca, Mg, every Monday &amp; Thursday</li> <li>PT, PTT every Monday</li> </ul>
-1	10:00 -melphalan 100mg/m <sup>2</sup> (actual BSA) IV over 5 minutes 10:15 – Lasix 20mg IV 10:30 - mannitol 20% 250 mL IVPB over 1 hour 11:30 - IV 1L NS @ 500 mL/hour for 3 hours 14:30 -IV 1L NS with 40 mEq KCL/L @ 125 mL/hour x 18 hours	<ul style="list-style-type: none"> <li>Mycostatin 500,000 units q2-4 hours</li> <li>Septra RS 1 tab p.o. daily</li> <li>Acyclovir 5 mg/kg twice daily IV or 400 mg p.o. four times daily</li> </ul>
0	Autologous Blood Stem Cell INFUSION	
+7	G-CSF 300 µg (if less than 70kg) or 480µg (if over 70kg) subcutaneous daily until post-nadir ANC > 1.5	



**B) Transplant-eligible patients (age <65 years, no significant co-morbidities, no immune suppression) with early Systemic and CNS lymphoma (prior to completing RCHOP x6): RCHOP and HDMTX x4 cycles then RDHAP for stem cell mobilization and collection, then R-TBuM/ASCT.**

Week	Step 1										Step 2			Step 3			
	0	1	2	3	4	5	6	7	8	9	10	13	14	15	16	17	18
Methotrexate 3.5 g/m <sup>2</sup> q14d	X*		X**		X		X		X		X						
R-CHOP		X			X			X			X						
rituximab 1400mg sc days 1,4 dexamethasone 20 mg days 1-4 cisplatin 35 mg/m <sup>2</sup> days 1,2 cytarabine 2 g/m <sup>2</sup> x1 dose, days 1,2 G-CSF 5-10 µg/kg day 8-13 Apheresis day 13 or 14												x x x x	x	x			
R-TbuM/ ASCT (ritux d-7, thiotepa 250mg/m <sup>2</sup> d-6,-5 busulfan 3.2 mg/kg day -4 to -2, melphalan 100 mg/m <sup>2</sup> d -1, ASCT d 0																x	
*HDMTX prior to RCHOP#1 if CNS and systemic lymphoma both identified at time of initial diagnosis. **If CNS lymphoma identified after RCHOP initiated but systemic disease responding to RCHOP, then plan for at least 4 doses HDMTX q14d with subsequent cycles RCHOP before proceeding to R-DHAP.																	

\* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft.

Step 1. Induction: RCHOP q21d as well as high-dose methotrexate q14 days x 4 cycles		
Day	Medications (HDMTX component)	Other Orders
ADMISSION 0	2000hr - IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200mL/hour x 5 days	<ul style="list-style-type: none"> <li>Daily weights</li> <li>Daily CBC &amp; differential, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> <li>LFTs, Ca, lipase, every Monday &amp; Thursday</li> </ul>
1	0800hr - Kytril 1mg IV 0800hr - <b>methotrexate</b> 3500mg/m <sup>2</sup> IV over 2 hours cycles 1-4	0700hr - Urine pH twice daily, call MD if <7.0
2-4	0800hr- folinic acid (leucovorin) 25 mg IV q6 hours until methotrexate level < 0.05 Continue hydration until methotrexate level <0.05	0500-0800hr – methotrexate level daily (expect level < 10 today)
5	<ul style="list-style-type: none"> <li>Discharge once methotrexate level &lt;0.05</li> <li>If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days</li> <li>Discharge meds: sepra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone</li> <li>Remember coumadin/LMWH and dilantin if patient is on these medications</li> </ul>	

Step 2. Rituximab/DHAP x 1 cycle for stem cell collection after 4 cycles of methotrexate		
Day	Medications	Other Orders
1	0800hr - hydrocortisone 100mg IV, Benadryl, Zantac, Tylenol 0900hr - <b>rituximab</b> 1400mg sc 0900hr -IV 1L NS 0900hr – <b>dexamethasone</b> 20mg p.o./IV daily x 4 days 0900hr – Kytril 1mg IV or 2mg p.o. x 3-4 days 0900hr – aprepitant protocol p.o. x 3 days 1000hr – <b>cisplatin</b> 35mg/m <sup>2</sup> IV over 2 hours with mannitol 25g and 500mL NS 1200hr- <b>cytarabine</b> 2g/m <sup>2</sup> IV over 2 hours x 1 doses (1.5g/m <sup>2</sup> if >60yr)	<ul style="list-style-type: none"> <li>Weight</li> <li>CBC &amp; differential, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> </ul>
2	0800hr – <b>dexamethasone</b> Kytril, Aprepitent continued 1000hr – <b>cisplatin</b> 35mg/m <sup>2</sup> IV over 2 hours with mannitol 25g and 500mL NS 1200hr- <b>cytarabine</b> 2g/m <sup>2</sup> IV over 2 hours x 1 doses (1.5g/m <sup>2</sup> if >60yr)	
4	Rituximab 1400mg sc	
8-13	1000hr – G-CSF 480-600µg subcutaneous daily until apheresis completed (plan for apheresis approximately day 13-15, once ANC>5, Plt >75 and CD34>20)	Daily CBC & differential starting day 10

Step 3. R-TBuM/ASCT consolidation after response to MTX and RDHAP Induction		
Day	Medications	Other Orders
ADMISSION Day -7	Allopurinol 300 mg p.o. daily until day 0 Premeds: Hydrocortisone 100mg IV, Benadryl 50mg IV, Zantac 50mg IV, Tylenol 650mg p.o. -rituximab 375mg/m <sup>2</sup> IV (first dose long infusion protocol)  2200hr - D5½ N/S + 20 mEq KCL/L @ 125 mL/hour until day -1	<ul style="list-style-type: none"> <li>• Consult dietician, physiotherapy</li> <li>• Low bacteria diet. 24hour intake</li> <li>• Mouth protocol; record intake and output</li> </ul>
-6 & -5	0800hr – thiotepa 250 mg/m <sup>2</sup> IV over 2 hours x 2 days (use ideal BSA)	<ul style="list-style-type: none"> <li>• 0800hr – Granisetron 2 mg IV daily x 8 days</li> <li>• EP daily x 31 days</li> <li>• Shower/Bath q6 hours x 3 days; avoid skin creams</li> </ul>
-4 to -2	0900 - busulfan 3.2 mg/kg IV daily x 3 days (use Ideal weight)	<ul style="list-style-type: none"> <li>• lorazepam prophylaxis x 4 days</li> <li>• CBC &amp; differential daily x 31 days</li> <li>• ALT, Alk Phos, bilirubin, alb, Ca, Mg, every Monday &amp; Thursday</li> <li>• PT, PTT every Monday</li> </ul>
-1	10:00 -melphalan 100mg/m <sup>2</sup> (actual BSA) IV over 5 minutes 10:15 – Lasix 20mg IV 10:30 - mannitol 20% 250 mL IVPB over 1 hour 11:30 - IV 1L NS @ 500 mL/hour for 3 hours 14:30 -IV 1L NS with 40 mEq KCL/L @ 125 mL/hour x 18 hours	<ul style="list-style-type: none"> <li>• Mycostatin 500,000 units q2-4 hours</li> <li>• Septra RS 1 tab p.o. daily</li> <li>• Acyclovir 5 mg/kg twice daily IV or 400 mg p.o. four times daily</li> </ul>
0	Autologous Blood Stem Cell INFUSION	
+7	G-CSF 300 µg (if less than 70kg) or 480µg (if over 70kg) subcutaneous daily until post-nadir ANC > 1.5	

**C) Transplant-eligible patients (age <65 years, no significant co-morbidities, no immune suppression) with late relapse (prior RCHOP x6) with systemic and CNS lymphoma: HDMTX-Ifosfamide-etoposide x2 then RDHAP for stem cell mobilization and collection, then R-TBuM/ASCT**

Week	Step 1							Step 2				Step 3		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
high-dose methotrexate 3.5 g/m <sup>2</sup> d1	X			X			X							
Rituximab 375 mg/m <sup>2</sup> d2	X			X										
Ifosfamide 1.5 g/m <sup>2</sup> d3-5	X			X										
Etoposide 100 mg/m <sup>2</sup> d3-5	X			X										
rituximab 1400mg sc days 1,4 dexamethasone 20 mg days 1-4 cisplatin 35 mg/m <sup>2</sup> days 1,2 cytarabine 2 g/m <sup>2</sup> x1 dose, days 1,2 G-CSF 5-10 µg/kg day 8-13 Apheresis day 13 or 14								x x x x		x				
R-TbuM/ ASCT (ritux d-7 + thiotepa 250mg/m <sup>2</sup> d -6,-5 busulfan 3.2 mg/kg day -4 to -2, melphalan 100 mg/m <sup>2</sup> d-1, ASCT d 0												X		

Step 1. Induction: R-IE and high-dose methotrexate x 2 cycles (HDMTX x3)		
Day	Medications	Other Orders
ADMISSION 0	2000hr - IV D5W + 20meq KCL/L + 2 amps NaHCO <sub>3</sub> /L @ 200mL/hour x 5 days	<ul style="list-style-type: none"> <li>Daily weights</li> <li>Daily CBC &amp; differential, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> <li>LFTs, Ca, lipase, every Monday &amp; Thursday</li> </ul>
1	0800hr - Kytril 1mg IV 0800hr - <b>methotrexate</b> 3500mg/m <sup>2</sup> IV over 2 hours cycles 1-4	0700hr - Urine pH twice daily, call MD if <7.0
2	0800hr- folinic acid (leucovorin) 25 mg IV q6 hours until methotrexate level < 0.05 Continue hydration until methotrexate level <0.05 1000hr – <b>Rituximab</b> 375mg/m <sup>2</sup> IV	0500-0800hr – methotrexate level daily (expect level < 10 today)
3-5	0800hr – Kytril 2mg IV, dexamethasone 10mg IV daily x 3d 0800hr – N/S IV 500mL/hour x 1 hour daily x 3d 0900hr – Mesna 0.5 g IV daily x 3d 0900hr - <b>Ifosfamide</b> 1.5g/m <sup>2</sup> with 1g Mesna IV over 3 hours daily x 3d 1200hr – Mesna 0.5 g IV daily x 3d 1200hr – 1/2NS IV 250mL/hour x 4 hours daily x 3d 1200hr – <b>Etoposide</b> 100 mg/m <sup>2</sup> IV daily x 3d 1600hr – Mesna 1.0 g IV daily x 3d 1000hr	
5 or 6	<ul style="list-style-type: none"> <li>Discharge once methotrexate level &lt;0.05</li> <li>If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days</li> <li>Discharge meds: sepra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone</li> <li>Remember coumadin/LMWH and dilantin if patient is on these medications</li> </ul>	

\* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft.

Step 2. Rituximab/DHAP x 1 cycle for stem cell collection after 4 cycles of methotrexate		
Day	Medications	Other Orders
1	0800hr - hydrocortisone 100mg IV, Benadryl , Zantac, Tylenol 0900hr - <b>rituximab</b> 1400mg sc 0900hr -IV 1L NS 0900hr – <b>dexamethasone</b> 20mg p.o./IV daily x 4 days 0900hr – Kytril 1mg IV or 2mg p.o. x 3-4 days 0900hr – aprepitant protocol p.o. x 3 days 1000hr – <b>cisplatin</b> 35mg/m <sup>2</sup> IV over 2 hours with mannitol 25g and 500mL NS 1200hr- <b>cytarabine</b> 2g/m <sup>2</sup> IV over 2 hours x 1 doses (1.5g/m <sup>2</sup> if >60yr)	<ul style="list-style-type: none"> <li>• Weight</li> <li>• CBC &amp; differential, EP, creatinine, glucose</li> <li>• ALT,AIKP,LDH,bilirubin,Alb,Ca,Mg</li> </ul>
2	0800hr – <b>dexamethasone</b> Kytril, Aprepitent continued 1000hr – <b>cisplatin</b> 35mg/m <sup>2</sup> IV over 2 hours with mannitol 25g and 500mL NS 1200hr- <b>cytarabine</b> 2g/m <sup>2</sup> IV over 2 hours x 1 doses (1.5g/m <sup>2</sup> if >60yr)	
4	Rituximab 1400mg sc	
8-13	1000hr – G-CSF 480-600µg subcutaneous daily until apheresis completed (plan for apheresis approximately day 13-15, once ANC>5, Plt >75 and CD34>20)	Daily CBC & differential starting day 10

Step 3. R-TBuM/ASCT consolidation after response to MTX and RDHAP Induction		
Day	Medications	Other Orders
ADMISSION Day -7	Allopurinol 300 mg p.o. daily until day 0 Premeds: Hydrocortisone 100mg IV, Benadryl 50mg IV, Zantac 50mg IV, Tylenol 650mg p.o. - <b>rituximab</b> 375mg/m <sup>2</sup> IV (first dose long infusion protocol)  2200hr - D5½ N/S + 20 mEq KCL/L @ 125 mL/hour until day -1	<ul style="list-style-type: none"> <li>• Consult dietician, physiotherapy</li> <li>• Low bacteria diet. 24hour intake</li> <li>• Mouth protocol; record intake and output</li> </ul>
-6 & -5	0800hr – <b>thiotepa</b> 250 mg/m <sup>2</sup> IV over 2 hours x 2 days (use ideal BSA)	<ul style="list-style-type: none"> <li>• 0800hr – Granisetron 2 mg IV daily x 8 days</li> <li>• EP daily x 31days</li> <li>• Shower/Bath q6 hours x 3 days; avoid skin creams</li> </ul>
-4 to -2	0900 - <b>busulfan</b> 3.2 mg/kg IV daily x 3 days (use Ideal weight)	<ul style="list-style-type: none"> <li>• lorazepam prophylaxis x 4 days</li> <li>• CBC &amp; differential daily x 31 days</li> <li>• ALT, Alk Phos, bilirubin, alb, Ca, Mg, every Monday &amp; Thursday</li> <li>• PT, PTT every Monday</li> </ul>
-1	10:00 - <b>melphalan</b> 100mg/m <sup>2</sup> (actual BSA) IV over 5 minutes 10:15 – Lasix 20mg IV 10:30 - mannitol 20% 250 mL IVPB over 1 hour 11:30 - IV 1L NS @ 500 mL/hour for 3 hours 14:30 -IV 1L NS with 40 mEq KCL/L @ 125 mL/hour x 18 hours	<ul style="list-style-type: none"> <li>• Mycostatin 500,000 units q2-4 hours</li> <li>• Septra RS 1 tab p.o. daily</li> <li>• Acyclovir 5 mg/kg twice daily IV or 400 mg p.o. four times daily</li> </ul>
0	Autologous Blood Stem Cell INFUSION	
+7	G-CSF 300 µg (if less than 70kg) or 480µg (if over 70kg) subcutaneous daily until post-nadir ANC > 1.5	

**VIII. SECONDARY CNS LYMPHOMA PROTOCOL**

**D)** Transplant-ineligible patients (age >65 years, significant co-morbidities, or immune suppression) with isolated CNS relapse/progression following complete response of systemic lymphoma to RCHOP. (consider only for highly motivated patients who wish curative intent therapy. Otherwise palliation with IT chemotherapy, radiotherapy, or supportive care).

Week	Step 1		Step 2										Step 3
	1	2	3	4	5	6	7	8	9	10	11	12	15 or 16
Rituximab 375mg/m <sup>2</sup> d0, 4 high-dose methotrexate 3.5 g/m <sup>2</sup> d1 procarbazine 100 mg/m <sup>2</sup> x 7 days d1-7	x												
Rituximab 375mg/m <sup>2</sup> d0 high-dose methotrexate 3.5 g/m <sup>2</sup> day 1 cytarabine 1.5-2 g/m <sup>2</sup> bid days 2-3			x			x			x			x	
Ifosfamide 2g/m <sup>2</sup> daily days 1-3													X

Step 1. Induction: high-dose methotrexate/procarbazine x 1 cycle		
Day	Medications	Other Orders
ADMISSION 0	0900hr-Rituximab 375mg/m <sup>2</sup> (1 <sup>st</sup> infusion protocol) 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO <sub>3</sub> /L @ 200ml/hour x 5 days	<ul style="list-style-type: none"> <li>Daily weights</li> <li>Daily CBC &amp; differential, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> <li>LFTs, Ca, lipase, every Monday &amp; Thursday</li> </ul>
1	0800hr - Kytril 1mg IV 0800hr - <b>methotrexate</b> 3500mg/m <sup>2</sup> IV over 2 hours 0800hr - <b>procarbazine</b> 100mg/m <sup>2</sup> p.o. daily x 7days only cycle 1 (round down to nearest 50mg multiple)	0700hr - Urine pH twice daily, call MD if <7.0
2-3	0800hr - folic acid (leucovorin) 25 mg IV q6hr until MTX level < 0.05 Continue hydration until methotrexate level <0.05	0500-0800hr – methotrexate level daily (expect level < 10 d2, <1 d3)
4	0900hr- Rituximab 375mg/m <sup>2</sup> (subsequent infusion protocol)on cycle 1 only and continue folic acid)	0500-0800hr – methotrexate Level daily
5	<ul style="list-style-type: none"> <li>Discharge once methotrexate level &lt;0.05</li> <li>If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days</li> <li>Discharge meds: sepra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone</li> <li>Remember coumadin/LMW/H and dilantin if patient is on these medications</li> </ul>	

\* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]

Step 2. High-dose methotrexate/cytarabine consolidation q21 days x 4 cycles		
Day	Medications	Other Orders
ADMISSION 0	1600hr- Rituximab 375mg/m <sup>2</sup> (subsequent infusion protocol)on cycle 1 only and continue folic acid) 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO <sub>3</sub> /L @ 200mL/hour x 5 days	<ul style="list-style-type: none"> <li>Daily weights</li> <li>Daily CBC &amp; differential, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> <li>ALT, Alk P, bilirubin, Ca, lipase, every Monday &amp; Thursday</li> </ul>
1	0800hr - Kytril 1mg IV 0800hr - <b>methotrexate</b> 3500mg/m <sup>2</sup> IV over 2 hours	07:00 - Urine pH bid, call MD if <7.0
2-3	0800hr- folic acid (leucovorin) 25 mg IV q6 hours until methotrexate level < 0.05 -Continue hydration until methotrexate level <0.05 0800hr – Kytril 2mg IV, Decadron 10mg IV 1000hr – <b>cytarabine</b> 2g/m <sup>2</sup> IV over 2 hours twice daily x 2 days; reduce to 1.5g/m <sup>2</sup> if age >60 years or creatinine >100	0500-08:00 – Methotrexate Level daily (expect <10 d2, <1 d3, <0.1 d4, <0.05 d5)
5	Discharge once methotrexate level <0.05 If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days (other meds as step 1 above)	
8-12	10:00 – G-CSF 480-600 µg subcutaneous daily until post-nadir ANC >1.5	Daily CBC & diff starting d10

\* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft. Adjusted BW = IBW + [40% x (actual – IBW)]



<b>Step 3. Ifosfamide consolidation after response to methotrexate and high-dose cytarabine</b>		
<b>Day</b>	<b>Medications</b>	<b>Other Orders</b>
15 or 16	0800hr – Kytril 2mg IV, dexamethasone 10mg IV daily x 3d 0800hr – N/S IV 500mL/hour x 1 hour daily x 3d 0900hr – Mesna 1.0 g IV daily x 3d 0900hr – Ifosfamide 2g/m <sup>2</sup> with 1g Mesna IV over 3 hours daily x 3d 1200hr – Mesna 0.5 g IV daily x 3d 1200hr – 1/2NS IV 250mL/hour x 4 hours daily x 3d 1600hr – Mesna 1.0 g IV daily x 3d	<ul style="list-style-type: none"> <li>• weight (call MD if &gt;2kg above day 1)</li> <li>• CBC &amp; differential, EP, creatinine, glucose</li> <li>• ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> </ul>

**E) Transplant-ineligible patients (age >65 years, significant co-morbidities, or immune suppression) with early Systemic and CNS lymphoma prior to completing initial RCHOP x6. (consider only for highly motivated patients who wish curative intent therapy. Otherwise palliation).**

Week	Step 1										Step 2			Step 3			
	0	1	2	3	4	5	6	7	8	9	10	13	14	15	16	17	18
Methotrexate 3.5 g/m <sup>2</sup> q14d	X*		X**		X		X		X		X						
R-CHOP		X			X			X			X						
rituximab 1400mg sc days 1,4 dexamethasone 20 mg days 1-4 cytarabine 2 g/m <sup>2</sup> x1 dose, days 1 and 2 G-CSF 5-10 µg/kg day 8-13												x x x		x			
Ifosfamide 2g/m <sup>2</sup> daily days 1-3																X	

\*HDMTX prior to RCHOP#1 if CNS and systemic lymphoma both identified at time of initial diagnosis.  
\*\*If CNS lymphoma identified after RCHOP initiated but systemic disease responding to RCHOP, then plan for at least 4 doses HDMTX q14d with subsequent cycles RCHOP before proceeding to R-AraC.

\* Male IBW = 50kg + 2.3kg x inches > 5ft, Female IBW = 45.5 kg + 2.3kg x inches > 5ft.

Step 1. Induction: RCHOP q21d as well as high-dose methotrexate q14 days x 4 cycles		
Day	Medications (HDMTX component)	Other Orders
ADMISSION 0	2000hr - IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200mL/hour x 5 days	<ul style="list-style-type: none"> <li>Daily weights</li> <li>Daily CBC &amp; differential, EP, creatinine, gluc</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> <li>LFTs, Ca, lipase, every Monday &amp; Thursday</li> </ul>
1	0800hr - Kytril 1mg IV 0800hr - <b>methotrexate</b> 3500mg/m <sup>2</sup> IV over 2 hours cycles 1-4	0700hr - Urine pH twice daily, call MD if <7.0
2-4	0800hr- folic acid (leucovorin) 25 mg IV q6 hours until methotrexate level < 0.05 Continue hydration until methotrexate level <0.05	0500-0800hr – methotrexate level daily (expect level < 10 today)
5	<ul style="list-style-type: none"> <li>Discharge once methotrexate level &lt;0.05</li> <li>If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days</li> <li>Discharge meds: sepra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone</li> <li>Remember coumadin/LMWH and dilantin if patient is on these medications</li> </ul>	

Step 2. Rituximab/DHAP x 1 cycle for stem cell collection after 4 cycles of methotrexate		
Day	Medications	Other Orders
1	0800hr - hydrocortisone 100mg IV, Benadryl, Zantac, Tylenol 0900hr - <b>rituximab</b> 1400mg sc 0900hr -IV 1L NS 0900hr – <b>dexamethasone</b> 20mg p.o./IV daily x 4 days 0900hr – Kytril 1mg IV or 2mg p.o. x 3-4 days 0900hr – aprepitant protocol p.o. x 3 days 1000hr – <b>cisplatin</b> 35mg/m <sup>2</sup> IV over 2 hours with mannitol 25g and 500mL NS 1200hr- <b>cytarabine</b> 2g/m <sup>2</sup> IV over 2 hours x 1 doses (1.5g/m <sup>2</sup> if >60yr)	<ul style="list-style-type: none"> <li>Weight</li> <li>CBC &amp; differential, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> </ul>
2	0800hr – <b>dexamethasone</b> Kytril, Aprepitent continued 1000hr – <b>cisplatin</b> 35mg/m <sup>2</sup> IV over 2 hours with mannitol 25g and 500mL NS 1200hr- <b>cytarabine</b> 2g/m <sup>2</sup> IV over 2 hours x 1 doses (1.5g/m <sup>2</sup> if >60yr)	
4	Rituximab 1400mg sc	
8-13	1000hr – G-CSF 480-600µg subcutaneous daily until apheresis completed (plan for apheresis approximately day 13-15, once ANC>5, Plt >75 and CD34>20)	Daily CBC & differential starting day 10

Step 3. Ifosfamide consolidation after response to methotrexate and high-dose cytarabine		
Day	Medications	Other Orders
15 or 16	0800hr – Kytril 2mg IV, dexamethasone 10mg IV daily x 3d 0800hr – N/S IV 500mL/hour x 1 hour daily x 3d 0900hr – Mesna 1.0 g IV daily x 3d 0900hr – Ifosfamide 2g/m <sup>2</sup> with 1g Mesna IV over 3 hours daily x 3d 1200hr – Mesna 0.5 g IV daily x 3d 1200hr – 1/2NS IV 250mL/hour x 4 hours daily x 3d 1600hr – Mesna 1.0 g IV daily x 3d	<ul style="list-style-type: none"> <li>weight (call MD if &gt;2kg above day 1)</li> <li>CBC &amp; differential, EP, creatinine, glucose</li> <li>ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg</li> </ul>

**F)** Transplant-ineligible patients (age >65 years, significant co-morbidities, or immune suppression) with late relapse (prior RCHOP x6) with relapsed systemic and CNS lymphoma.

This situation is unfortunately associated with extremely poor prognosis, and generally should be treated with palliative intent. Treatments could include IT chemotherapy, radiotherapy, decadron, or best supportive care.

## APPENDIX B: GENERAL RADIOTHERAPY GUIDELINES

### Aggressive Non-Hodgkin Lymphomas

30Gy/15-35Gy/20 is recommended in lymphoma subtypes and situations *except*:

1. Nasal NK/T cell lymphomas: 30Gy/10 or 40-50Gy +/- concurrent cisplatin
2. Testicular lymphoma, post-RCHOP: Scrotal radiotherapy 25-30Gy/10-15 fractions
3. Primary or secondary CNS lymphoma: Whole brain radiotherapy
  - o Palliative: 20Gy/5 - 35Gy/20 +/- 10Gy/5 boost *depending on age, KPS, anticipated life expectancy, status of extracranial disease?*
  - o Curative, post-methotrexate: 23.4Gy/13 fractions if in CR, or 45Gy/25 fractions (*?alternative 30Gy/15 + boost 15Gy/8 or 35 Gy/20 + boost 10 Gy/5?*)in PR

### Indolent Lymphoma

24Gy/12 - 30Gy/20 fractions is generally recommended for most subtypes and situations *except*:

1. Palliation: lower doses may be used for palliation such as 4Gy/2 fractions
2. Contiguous stage II disease, curative intent: higher doses up to 40Gy may be used
3. *Gastric MALT 30Gy/20*

### Hodgkin Lymphoma

20Gy/10 for early stage favorable , 30Gy/15 early stage unfavorable and advanced stage is recommended in lymphoma subtypes and situations *except for* nodular lymphocyte-predominant Hodgkin disease (NLPHD):

- o IFRT alone to 30Gy/15-35Gy/20 fractions

### What is INRT/ISRT?<sup>8-10</sup>

- *definitions are per ILROG guidelines and depends of whether radiation is sole treatment or part of combined modality regimen*

### Role of IMRT/VMAT/TOMO<sup>11,12</sup>

- *role of IMRT/VMAT/TOMO over 3DCRT is at discretion of treating radiation oncologist- this is determined on a case by case basis*
- *the low dose bath is a consideration when using IMRT as it relates to potential long term risk of second malignancies*

### Role of PET in Planning<sup>13-16</sup>

- *this is outlined in the ILROG guidelines for HL, nodal HL and extranodal HL*

**APPENDIX C: PROGNOSTIC MODELS**

<b>ECOG Performance Status</b>	
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

**International Prognostic Index (IPI) for DLBCL Following CHOP-Type Chemotherapy<sup>17</sup>**

<b>Factors</b>	<b># of Factors</b>	<b>5 year PFS</b>
Age > 60 years ECOG 2-4 Stage III/IV ENS > 1 Increased LDH	0-1	60%
	2-3	30%
	4-5	15%

**Revised IPI for DLBCL Following R-CHOP Chemotherapy<sup>18</sup>**

<b>Factors</b>	<b># of Factors</b>	<b>% of Patients</b>	<b>4 year PFS</b>	<b>4 year DSS</b>	<b>4 year OS</b>
Age > 60 years ECOG 2-4 Stage III/IV ENS > 1 Increased LDH	0	11	96%	95%	95%
	1-2	48	81%	83%	79%
	3-5	41	55%	56%	55%

**R-CHOP for DLBCL by Elevated LDH and Stage 3-4<sup>18</sup>**

<b># of Factors</b>	<b>% of Patients</b>	<b>4 year PFS</b>	<b>4 year DSS</b>	<b>4 year OS</b>
0	27	92%	90%	84%
1	38	78%	79%	77%
2	35	53%	56%	55%

An online prognostic calculator is available at:

<http://www.qxmd.com/calculate-online/hematology/prognosis-large-b-cell-lymphoma-r-ipi>

**Modified IPI for Non-Bulky Stage I-IIA DLBCL Treated with CHOP x 3 cycles and IFRT**

<b>Factors</b>	<b># of Factors</b>	<b>5 year PFS</b>	<b>10 year PFS</b>
Age > 60 yrs ECOG 2-4 Stage II Increased LDH	0	94%	89%
	1-2	79%	73%
	3-4	60%	50%



**Salvage Age-Adjusted IPI for Relapsed DLBCL<sup>19</sup>**

Factors	# of Factors	~ PFS for HDCT/ASCT Patients
Stage III/IV Elevated LDH ECOG 2-4	0	70%
	1	50%
	2	30%
	3	10%

**Primary CNS Lymphoma (Memorial Sloan Kettering Cancer Center Model)<sup>20</sup>**

Risk Group	mOS	5 year OS	mFFS	5 year FFS
Age < 50 years	5-8 years	50-60%	2-5 years	35-40%
Age >50 years, KPS ≥ 70%	2-3 years	15-35%	1.5 years	10-20%
Age >50 years, KPS < 70%	1 year	10%	0.5-1 year	5-10%

**Simplified IELSG Primary CNS Lymphoma (Leon Berard Cancer Centre Model)<sup>21</sup>**

Factors	# of Factors	mOS	5 year OS
Age > 60 years Elevated LDH Deep Tumour <ul style="list-style-type: none"> <li>○ Cerebellum</li> <li>○ Periventricular</li> <li>○ Basal ganglion</li> <li>○ Brainstem</li> </ul>	0	6 years	60%
	1	4 years	40%
	2	1 year	23%
	3	0.5 years	0%

**Follicular Lymphoma Internacional Prognostic Index (FLIPI) Pre-dated Rituximab-Chemotherapy (Survival with Non-Rituximab Containing Therapy)<sup>22</sup>**

Factors	Prognosis	# Factors	% Patients	5 year OS	10 year OS
Age ≥ 60 years Stage III-IV Increased LDH Hb < 120 g/L 5+ nodal sites	Good	0-1	36	90%	70%
	Intermediate	2	37	78%	50%
	Poor	3-5	27	53%	35%

An online prognostic calculator is available at:

<http://www.gxmd.com/calculate-online/hematology/follicular-lymphoma-international-prognostic-index-flipi>

**FLIPI 2<sup>23</sup>**

Factors	Prognosis	# Factors	% Patients	3 year PFS	5 year PFS
Age > 60 years Marrow involvement Increased B2M Hb < 120 g/L Node >6cm longest diameter	Good	0	20	91%	80%
	Intermediate	1-2	53	69%	51%
	Poor	3-5	27	51%	19%

**Hodgkin Lymphoma International Prognostic Score (IPS) for Advanced Disease<sup>24</sup>**

Factors	# of Factors	5 year FFS with ABVD
Age $\geq$ 45 years Male Stage IV Albumin $<$ 40 g/L Hb $<$ 105 g/L WBC $\geq$ 15 x 10 <sup>9</sup> /L Lymphocyte $<$ 0.6 x 10 <sup>9</sup> /L or $<$ 8% WBC	0-1	80%
	2	70%
	3	60%
	4-7	50%

An online prognostic calculator is available at:

<http://www.qxmd.com/calculate-online/hematology/hasenclever-hodgkins-prognosis-score-ips>

**Prognosis of Hodgkin Lymphoma Relapsed After Prior Chemotherapy<sup>25</sup>**

Factors	# of Factors	2nd Line Chemo	HDCT/ASCT
Time to relapse $<$ 1 year Relapse stage III-IV Hb $<$ 105 female, 120 male	0	70%	100%
	1	60%	70%
	2	30%	50%
	3	0%	50%

\* 5yr OS by second line therapy.

\* Freedom from second failure was 50% for 0-1 factor, 35% for 2 factors, and 15% for 3 factors.

**Mantle Cell Lymphoma (MIPI)<sup>26</sup>**

Points	Age	ECOG	LDH	WBC
0	$<$ 50	0-1	$<$ 0.67 ULN	$<$ 6.7
1	50-59	-	0.67-0.99 ULN	6.7-9.99
2	60-69	2-4	1-1.49 ULN	10.0-14.99
3	70+	-	$\geq$ 1.5 ULN	$\geq$ 15.0
Points	Age	ECOG	LDH (ULN 235)	WBC
0	$<$ 50	0-1	$<$ 157	$<$ 6.7
1	50-59	-	157-235	6.7-9.99
2	60-69	2-4	235-352	10.0-14.99
3	70+	-	$>$ 352	$>$ 15.0
Risk		# Points	~Median OS	~5 year OS
Low		0-3	6 years	60%
Intermediate		4-5	4 years	40%
High		6-11	2 years	20%

An online prognostic calculator is available at:

<http://www.qxmd.com/calculate-online/hematology/prognosis-mantle-cell-lymphoma-mipi>

**Post-Transplantation Lymphoproliferative Disease (PTLD) Prognostic Scoring Systems**
**1. Evens *et al.*, 2010<sup>27</sup>**

Score 1 point for each: hypoalbumenia, bone marrow involvement, CNS involvement

# of Factors	Overall 3 year PFS	Overall 3 year OS
0	84%	93%
1	66%	68%
2-3	7%	11%

Patients who received rituximab-based therapy as part of their initial treatment had a 3-year PFS of 70% and an OS of 73% compared with a 3-year PFS of 21% ( $p<0.0001$ ) and an OS of 33% ( $p=0.0001$ ) for patients who did not receive rituximab.

## 2. Leblond *et al.*, 2001<sup>28</sup>

Risk Group	PS	and/or	# of Sites	mOS
low-risk	PS < 2	and	1	>5 years
intermediate risk	PS ≥ 2	or	2 or more	3 years
high risk	PS ≥ 2	and	2 or more	1 month

**Waldenström Macroglobulinemia**

Study	Prognostic Factors	Stratification	Survival
<i>Gobbi et al, 1994</i> <sup>29</sup>	Hb<9 g/dL Age >70 years Weight loss Cryoglobulinaemia	0-1 factor 0-2 2-4 factors	mOS 80 months mOS 48 months
<i>Morel et al, 2000</i> <sup>30</sup>	Age ≥ 65 years Albumin <40 g/L 1 cytopenia (1-point) >1 cytopenia (2-points)	0-1 factor 2 factors 3-4 factors	5 year survival 87% 5 year survival 62% 5 year survival 25%
<i>Dhodapkar et al, 2001</i> <sup>31</sup>	β2M >3 mg/L Hb <12 g/dL IgM >40 g/L	β2M<3 mg/L + Hb≥12 g/dL β2M<3 mg/L + Hb<12 g/dL β2M≥3 mg/L + IgM<40 g/L β2M>3 mg/L + IgM>40 g/L	5 year survival 87% 5 year survival 63% 5 year survival 53% 5 year survival 21%
<i>Merlini et al, 2003</i> <sup>32</sup>	Age≥60 years Hb<100 g/L Albumin <35 g/L	<60 years, Hb≥100, Alb≥35 ≥60 years, Hb <100, Alb<35 Other combinations	mOS 178 months mOS 33 months mOS 84 months

**CLL Prognostic Score from MD Anderson Cancer Center**

Factors	# of Factors	# of Patients	5 year OS
Age >60 years	0	364	96%
B2M >2 mg/L	1	623	79%
Alb < 35	2	497	69%
Creatinine > 1.6	3	70	30%
17p mutations	4-5	10	16%

**CLL Internation Prognostic Score: Bahlo 2015ASCO, J Clin Oncol 33, 2015 (suppl; abstr 7002)**

Factors	Points	Risk Group	5 year OS
Age >65 years	1	Low (0-1 points)	93% (~90%)
Clinical Stage >1	1	Intermediate (2-3 points)	79% (~80%)
IGHV unmutated	2	High (4-6 points)	64% (~60%)
B2M >3.5 mg/L	2	Very high risk (7-10 points)	23% (~25%)
17p deletion or TP53 mutations	4		

The full analysis set was collected from eight phase 3 trials in France, Germany, the United Kingdom, the United States, and Poland (n=3,472 patients, median age 61 years (27-86 yrs)). 89% of patients had received treatment for CLL and median overall survival (OS) was 95 months. The model was externally validated in a third dataset comprising 845 patients with newly diagnosed CLL from the Mayo Clinic; 39% had received treatment for CLL. The final model of multivariate analysis identified 5 independent predictors for OS: *TP53* (17p) mutation (deleted and/or mutated; hazard ratio [HR]: 4.2); *IGHV* mutation status (unmutated, HR: 2.6); B2M (>3.5 mg/L; HR: 2.0); clinical stage (Binet B/C or Rai I-IV, HR: 1.6); and age (>65 years, HR: 1.7). Using weighted grading, a prognostic score from 0 to 10 was derived that separated the patients into four different groups: low risk (score 0-1), intermediate risk (score 2-3), high risk (score 4-6), and very high risk (score 7-10). At 5 years, significantly different rates of OS were observed for the low to the very high risk group, 93%, 79%, 64%, and 23%, respectively ( $P<0.001$ ; C-statistic  $c=0.72$  [95% CI: 0.69, 0.76]). The multivariable model was confirmed on the internal validation datasets; in addition, the four risk groups were reproduced with on the Mayo dataset, with 5-year OS rates of 97%, 91%, 68% and 21%, respectively ( $P<0.001$ ; C-statistic  $c=0.79$  [95% CI: 0.74, 0.85]).

**APPENDIX D: LYMPHOMA RESPONSE CRITERIA**

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
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

**Abbreviations:** CR=complete response, FDG-PET=(18)F-fluorodeoxyglucose positron emission tomography, CT=computed tomography, PR=partial response, SPD=sum of the product of the diameters, SD=stable disease, PD=progressive disease.

**LYMPHOMA RESPONSE CRITERIA<sup>33</sup>**
**Complete Response (CR)**

The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- 2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- 2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment.
3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by



imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of >20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

### Partial Response (PR)

The designation of PR requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by  $\geq 50\%$  in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. Typically FDG-avid lymphoma: for patients with no pre-treatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used.

9. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

### Stable Disease (SD)

Stable disease is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
2. Typically FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

### Relapsed Disease (after CR)/ Progressive Disease (after PR or SD)

1. Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes  $\leq 1.0 \times \leq 1.0$  cm will not be considered as abnormal for relapse or progressive disease.
2. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
3. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by  $\geq 50\%$  and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
4. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
5. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems ( $< 1.5$  cm in its long axis by CT).
6. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an

abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

7. In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g., a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

**Table 3. Revised Criteria for Response Assessment**

Response and Site	PET-CT–Based Response	CT-Based Response
<b>Complete</b>	<b>Complete metabolic response</b>	<b>Complete radiologic response (all of the following)</b>
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer’s ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to $\leq 1.5$ cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
<b>Partial</b>	<b>Partial metabolic response</b>	<b>Partial remission (all of the following)</b>
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease  At end of treatment, these findings indicate residual disease	$\geq 50\%$ decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm $\times$ 5 mm as the default value When no longer visible, 0 $\times$ 0 mm For a node > 5 mm $\times$ 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
<b>No response or stable disease</b>	<b>No metabolic response</b>	<b>Stable disease</b>
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
<b>Progressive disease</b>	<b>Progressive metabolic disease</b>	<b>Progressive disease requires at least 1 of the following PPD progression:</b>
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by $\geq 50\%$ from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions $\leq 2$ cm 1.0 cm for lesions > 2 cm
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

**Table 3. Revised Criteria for Response Assessment (continued)**

Response and Site	PET-CT-Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

\*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake  $\leq$  mediastinum; 3, uptake > mediastinum but  $\leq$  liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.



## APPENDIX E: New Lymphoma Patient Data Sheet

### Identification:

Name \_\_\_\_\_ DOB (d/m/y) \_\_\_\_\_  
 AHN \_\_\_\_\_ ACB# \_\_\_\_\_  
 Gender: male female Age at Diagnosis \_\_\_\_\_

### Diagnostic Information:

Date Diagnosis (d/m/y) \_\_\_\_\_ Surgical accession # \_\_\_\_\_  
 Biopsy type: open surgicalcore needle fine needle bone marrow blood  
 Diagnosis: \_\_\_\_\_

Stage: I II III IV B sx: yes no Bulk>10cm: yes no  
 Marrow +ve: yes no Other Extranodal Sites: \_\_\_\_\_  
 LDH elevated: yes no ECOG Status: 0 1 2 3 4

### Prognosis Score by Histology:

**Large Cell Lymphoma:** #IPI Factors: 0 1 2 3 4 5  
 Circle if present: Age > 60yr Stage III/IV LDH>ULN ECOG 2-4 ≥2 Extranodal Sites

**Follicular:** # FLIPI Factors: 0 1 2 3 4 5  
 Circle if present: Age ≥ 60yr Stage III/IV LDH>ULN Hb<120g/L ≥5 Nodal Sites

**Hodgkin:** # IPS Factors: 0 1 2 3 4 5 6 7  
 Circle if present: Age ≥ 45 yr Stage IV Male Lymphocyte<0.6 (or < 8%WBC) Albumin < 40 g/L  
 Hb < 105g/L WBC ≥ 15

### Initial Treatment:

Therapy	Plan	Regimen / Radiation Site	Start Date d/m/y
Chemotherapy	yes no		
Maintenance Rituximab	yes no		
Radiotherapy	yes no		
Stem Cell Transplant	yes no		

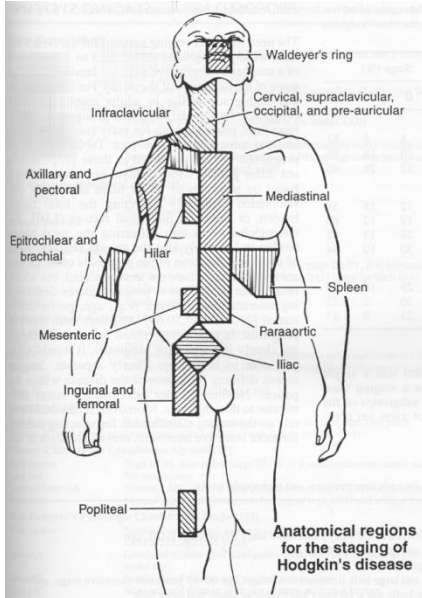
### First Relapse Information:

Relapse/progression after treatment 1: yes no Date relapse (d/m/y) \_\_\_\_\_  
 2<sup>nd</sup> Treatment: Regimen \_\_\_\_\_ Radiation yes no HDCT/ASCT yes no

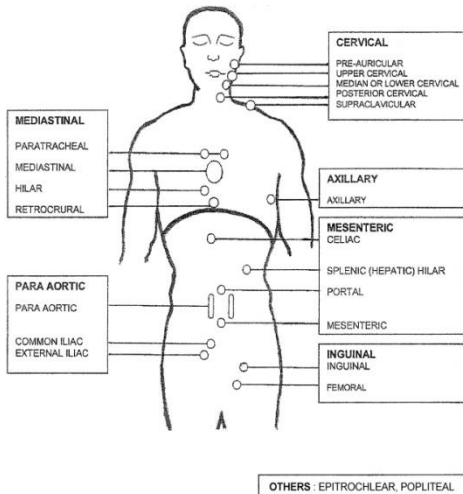
### Survival Information:

Dead: yes no Date death or last follow-up(d/m/y) \_\_\_\_\_  
 Cause of death: lymphoma other (specify) \_\_\_\_\_

**Ann Arbor Staging Nodal Sites**



**FLIPI Nodal Sites**



**Revised-International Prognostic Index for Diffuse Large B-Cell Lymphoma Following R-CHOP Chemotherapy**

Factors:

Factor	#Factors	%pts	4yr PFS
Age > 60yr	0	11	95%
ECOG 2-4	1-2	48	80%
Stage III/IV	3-5	41	55%
ENS > 1			
↑ LDH			

**FLIPI (Follicular Lymphoma International Prognostic Index)**

Factors	Survival with Non-Rituximab Containing Therapy			
	Prognosis #	%pt	5yr	10yr
Age ≥ 60yrs	Good	0-1	36	90%
Stage 3-4	Intermed	2	37	75%
Increased LDH	Poor	3-5	27	50%
Hb < 120g/l				
5+ nodal sites				

**Primary CNS lymphoma Prognostic Index**

Adverse Factors	Overall Survival		Failure-Free Survival	
	mOS	5yr OS	mFFS	5yr FFS
Age < 50 yrs	5-8 yrs	50-60%	2-5yrs	35-40%
Age > 50 yrs KPS ≥ 70%	2-3 yrs	15-35%	1.5 yrs	10-20%
Age > 50 yrs KPS < 70%	1 yr	10%	0.5-1yr	5-10%

**Hodgkin Lymphoma International Prognostic Score for Advanced Stage Disease**

Factors	# Factors	5yr FFS with ABVD
Age ≥ 45 yrs	0-1	80%
Male	2	70%
Stage 4	3	60%
Albumin < 40 g/L	4-7	50%
Hb < 105g/L		
WBC ≥ 15 x 10 <sup>9</sup> /L		
Lymphocyte < 0.6 x 10 <sup>9</sup> /L or < 8% WBC		

**Mantle Cell Lymphoma (MIPI)**

Points	Age	ECOG	LDH(ULN 235)	WBC
0	<50	0-1	< 157	<6.7
1	50-59	-	157-235	6.7-9.99
2	60-69	2-4	235-352	10.0-14.99
3	70+	-	≥ 352	≥15.0

Risk	# points	~Median OS	~5yr OS
Low	0-3	6yr	60%
Intermediate	4-5	4yr	40%
High	6-11	2yr	20%

Ann Arbor Staging System	
Stage I	Single lymph node region (I) or one extralymphatic organ (IE)
Stage II	≥2 lymph node regions (II) or local extralymphatic extension plus lymph nodes (IIE), same side of diaphragm.
Stage III	Lymph node regions both sides of diaphragm, either alone (III) or with local extralymphatic extension (IIIE)
Stage IV	Diffuse involvement of one or more extralymphatic organs or sites.

ECOG Performance Status	
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.
2	Ambulatory, capable of all self-care but unable to carry out any work activities. Up and about >50% waking hours.
3	Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

**APPENDIX F: Ideal Body Weight**

Height (cm)	Males – Weight (kg)			Females – Weight (kg)		
	Small Frame	Medium Frame	Large Frame	Small Frame	Medium Frame	Large Frame
145				47.1	51.0	55.4
146				47.3	51.3	55.8
147				47.6	51.7	56.2
148				47.9	52.1	56.7
149				48.2	52.5	57.1
150				48.5	52.9	57.5
151				48.9	53.4	58.1
152				49.3	53.8	58.7
153				49.8	54.4	59.2
154				50.3	55.0	59.7
155	57.3	59.6	63.3	50.7	55.6	60.3
156	57.7	59.9	63.7	51.2	56.1	60.9
157	58.0	60.3	64.1	51.7	56.6	61.5
158	58.4	60.7	64.5	52.3	57.0	62.1
159	58.8	61.0	65.0	52.8	57.6	62.7
160	59.1	61.4	65.5	53.4	58.2	63.4
161	59.5	61.8	66.0	53.9	58.7	64.0
162	59.8	62.2	66.5	54.4	59.2	64.6
163	60.2	62.7	67.0	55.0	59.7	65.2
164	60.5	63.1	67.6	55.5	60.2	65.9
165	60.9	63.6	68.1	56.0	60.8	66.5
166	61.3	64.1	68.7	56.5	61.4	67.1
167	61.7	64.6	69.4	57.1	61.9	67.8
168	62.2	65.2	70.0	57.7	62.5	68.4
169	62.6	65.7	70.7	58.2	63.0	69.0
170	63.1	66.3	71.3	58.8	63.5	69.6
171	63.5	66.8	71.9	59.3	64.0	70.2
172	64.0	67.3	72.5	59.8	64.6	70.7
173	64.4	67.8	73.2	60.3	65.2	71.2
174	64.9	68.4	73.7	60.8	65.7	71.8
175	65.3	68.9	74.3	61.4	66.2	72.3
176	65.7	69.5	75.0	61.9	66.8	72.8
177	66.2	70.0	75.6	62.5	67.3	73.4
178	66.7	70.6	76.2	63.1	67.8	73.9
179	67.2	71.2	76.9	63.6	68.4	74.5
180	67.8	71.8	77.5	64.1	69.0	75.0
181	68.4	72.4	78.2	64.7	69.6	75.6
182	69.0	73.1	78.9	65.2	70.1	76.1
183	69.6	73.7	79.6			
184	70.2	74.4	80.4			
185	70.8	75.2	81.3			
186	71.4	75.8	82.0			
187	72.1	76.4	82.8			
188	72.7	77.0	83.6			
189	73.4	77.8	84.5			
190	74.1	78.7	85.4			
191	74.8	79.5	86.3			

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