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Lymphoma

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Cancer Care Alberta

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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[1]. 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)[2]. 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[3].

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.[2] 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[3].
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[1]. ***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?

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 (3rd 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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I. Diagnosis and Pathologic Classification [1-6]

Sufficient tissue is required for the diagnosis of lymphoma. Fine needle aspirates are not sufficient and only lead to diagnostic delays. Historically, a surgical biopsy was recommended but more recent data, including a comparative study, have demonstrated that a well-performed radiology-guided core needle biopsy provides equivalent diagnostic accuracy with less complications[7]. Cancer Care Alberta now supports diagnostic pathways for many cancers including lymphoma (Lymphoma Diagnosis Program, LDP). All patients who are considered highly likely to have lymphoma should be referred to the LDP to expedite appropriate diagnostic and staging investigations.

Table 1 describes the histologic subclassification of the malignant lymphomas and is an ***adaptation*** of the most recent WHO classification[6]. 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[6].

	B-cell	T-cell
Indolent	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
Aggressive	Diffuse large B-cell o T-cell/histocyte-rich DLBCL o Primary DLBCL of the CNS o Primary cutaneous DLBCL, leg-type o EBV-positive DLBCL of the elderly 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 ⇒ Nodular sclerosis ⇒ Mixed cellularity ⇒ Lymphocyte rich ⇒ Lymphocyte depleted	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
Special	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) o Plasmacytic hyperplasia and infectious mononucleosis-like PTLD o Polymorphic PTLD o Monomorphic PTLD o Classical Hodgkin-type PTLD 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[6]. In addition, the following are recommended by the Alberta Provincial Hematology Tumour Team [8, 9]:

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[9, 10]. 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)[11].
   - 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[12], 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[12]. 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[10, 13].

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 MIPI 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[14]. 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[15].

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II. Staging [1-12]

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 (HBsAg), Hepatitis B Surface Antibody (anti-HBs), and Hepatitis B Core Antibody (total anti-HBc) must be done prior to initiating chemo/immunotherapy. Patients who are HBsAg positive are either acutely or chronically infected and require consultation with Hepatology. Patients who are HBsAg negative/anti-HBc positive (regardless of anti-HBs titer levels) and are going to be treated with B-cell depleting therapy (e.g. rituximab) should receive prophylactic therapy with entecavir or tenofovir. Those who are HBsAg negative/anti-HBc positive and fall under low or moderate risk as per Table 1 do not require prophylaxis and should undergo serial HBV DNA testing q6-12 months and serial ALT testing q3 months while on immunosuppressive therapy (see Figure 1). Hepatitis B prophylactic therapy should be continued for at least 6 months following the completion of immunosuppressive therapy, except for those treated with anti-CD20 agents who should continue for at least 12-18 months due to the lag in B-cell function recovery[13-17].

Table 1: Risk of HBV reactivation with immunosuppression and chemotherapy in HBsAg-positive and HBsAg-negative/anti-HBc-positive patients.

Risk group and HBV serology	Immunosuppressive or chemotherapy
High-risk group (>10%)	
HBsAg positive OR HBsAg negative and anti-HBc positive (high risk regardless of anti-HBs titre levels)	• B-cell depleting agents such as rituximab and obinutuzumab
HBsAg positive	• Anthracycline derivatives such as doxorubicin and epirubicin • Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent > 10-20 mg/day)
Moderate-risk group (1%-10%)	
HBsAg positive OR HBsAg negative and anti-HBc positive (may be lower risk and monitoring may be sufficient if high anti-HBs titres > 100 IU/L)	• TNF-α inhibitors: etanercept, adalimumab, certolizumab, infliximab • Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinumab, natalizumab, vedolizumab • Tyrosine kinase inhibitors: imatinib, nilotinib, ibrutinib
HBsAg positive	• Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent < 10 mg/day)

HBsAg negative and anti-HBc positive (may be lower risk and monitoring may be sufficient if high anti-HBs titres > 100 IU/L)	• Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent > 10-20 mg/day) • Anthracycline derivatives: doxorubicin and epirubicin
Low-risk group (<1%)	
HBsAg positive OR HBsAg negative and anti-HBc positive (low risk especially if high anti-HBs titres > 100 IU/L)	• Traditional immunosuppressive agents: azathioprine, 6-mercaptopurine, methotrexate • Intra-articular corticosteroids • Corticosteroid therapy for ≤ 1 week
HBsAg negative and anti-HBc positive (low risk especially if high anti-HBs titres > 100 IU/L)	• Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent < 10 mg/day)

Adapted from Coffin, Carla S., et al. [13]

Anti-HBc = antibody to HBV core; anti-HBs = antibody to HBsAg; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; TNF = tumour necrosing factor.

- ESR (for early stage Hodgkin lymphoma)
- Beta-2-microglobulin (for follicular lymphoma)
- Serum protein electrophoresis and quantitative IgG, IgA, and IgM for indolent B-cell lymphomas
- Pregnancy test: if at risk
- Bone marrow biopsy in iNHL (nodal MZL, FL) can be reserved for situations of confirming limited stage or investigating unexplained cytopenias. Bone marrow biopsy may be deferred altogether in MALT lymphoma unless for investigating unexplained cytopenias.
- Bone marrow biopsy is not required for Hodgkin lymphoma or DLBCL if a staging PET/CT is performed. PET scan does not reliably predict bone marrow involvement in histologies other than HL or DLBCL.
- Bone marrow biopsy is discretionary for full staging of other aggressive histologies (e.g. PTCL-NOS) as it provides prognostic information but seldomly influences treatment selection
- PET/CT is the preferred staging modality for most FDG-avid nodal lymphomas. 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
- There are circumstances where a contrast enhanced CT alone is adequate or the preferred imaging modality:
    - Variably FDG avid histologies (chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma, mycosis fungoides, and marginal zone lymphoma)
    - Urgent treatment is indicated, and PET/CT is not readily available
    - Patient unable to access PET/CT due to travel distance
    - To accurately distinguish bowel from lymphadenopathy when clinically relevant
    - For identifying compression/thrombosis of central/mediastinal vessels if clinical suspicion

- For accurate measurements of nodal size, particularly for clinical trial

Table 2. 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 3. Staging system

Stage	Description
Stage I	Single lymph node region (I) or one extralymphatic organ (IE)
Stage II	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)
Stage III	Lymph node regions on both sides of the diaphragm either alone (III) or with local extra-lymphatic extension (IIIE)
Stage IV	Diffuse involvement of one or more extralymphatic organs or sites • A: No B symptoms • B: at least one of the following: unexplained weight loss >10% baseline within 6 months of staging, unexplained fever >38˚C, or drenching night sweats

*Suffix A or B used only for Hodgkin lymphoma (Lugano, 2014)

For treatment planning, patients are divided into two groups by stage:

1. Limited Stage: Non-bulky stage IA(E) or IIA(E) (≤ 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 (≥10cm)

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.
     - Consider a surveillance CT after 1 year of diagnosis of iNHL on watch and wait
   - 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 4. 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[1-49]

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)[4,45-47,50-52]

Table 1. Initial therapy of DLBCL/aggressive CD20+ lymphomas without MYC and BCL2 rearrangement by FISH.

Stage	# Risk Factors[1,2]	Treatment [3]
Limited stage defined by PET with bulk <10cm	• sm-IPI = 0 • sm-IPI = 1 due to age >60 or stage II	• R-CHOP x4 cycles if CR by PET/CT 14-21 days after 3rd cycle • R-CHOP x 6 with IFRT (30-35Gy) if PR by PET/CT after 3rd cycle • RCHOP x 3 plus IFRT for patients unable to tolerate more than 3 cycles • R-CHOP x 6 for patients unable to undergo interim PET or R-CHOP x4 for patients meeting FLYER criteria (age 18-60, stage I-II, normal LDH, ECOG 0-1, bulk <7.5cm)
Limited stage with bulk <10cm	• sm-IPI = 2-4 • sm-IPI = 1 due to elevated LDH or ECOG >1	• R-CHOP x 6 cycles with no IFRT if CR by PET/CT 14-21d after 3rd cycle • R-CHOP x 6 cycles plus IFRT (30-35Gy) if only PR by PET/CT after 3rd cycle • RCHOP x 3 plus IFRT for patients unable to tolerate more than 3 cycles
Advanced [4,5], or limited stage with bulk ≥10 cm		• R-CHOP x 6 cycles possibly followed by IFRT (30-35Gy) if localized non-progressing PET+ residual disease by PET/CT 21-28d after 6th cycle

1. Stage-modified IPI (sm-IPI) Risk Factors for Limited Stage: increased LDH, stage II, ECOG performance status 2-4, age>60 years.
2. IPI Risk Factors for Advanced Stage: increased LDH, stage III/IV, >1 Extranodal Site, ECOG 2-4, age>60 years.
3. R-CEOP (with etoposide 50mg/m2 IV day 1 and 100mg/m2 PO days 2-3) can be used for DLBCL patients who have reduced left ventricular ejection fraction or prior maximum cumulative anthracycline exposure (Blood Adv 2021;5(5):1483). The use of R-CEOP should be limited to patients with an absolute contraindication to anthracyclines, as an Alberta-based retrospective chart review found that R-CEOP was associated with inferior 4-year PFS (32% vs 52%) and OS (39% vs 59%) compared to R-CHOP[53]
4. 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.
5. Pola-R-CHP has superior 2-year PFS with similar OS and toxicity profile as R-CHOP among patients with DLBCL with IPI score 2-5 but is not currently funded in Alberta[54].

Treatment of Limited-Stage DLBCL

Limited-stage DLBCL is associated with favorable outcomes with long-term survival rates up to 80%, although a persistent pattern of late relapses has been described in up to 20-30% of patients. The stage-modified IPI score risk stratifies patients according to the following factors: age >60, stage II, elevated LDH, ECOG >1. In the pre-rituximab era, the phase III SWOG S8736 trial reported superior PFS and OS with CHOP×3 plus RT versus CHOP×8;[55] however, due to the occurrence of late relapses and treatment complications, there was no difference in PFS or OS between the two strategies with long-term follow-up.[56] In the rituximab era, the MInT trial established R-CHOP x6 as the standard of care for most patients with limited-stage DLBCL.[57] Given the favorable outcomes of limited-stage DLBCL, recent studies have assessed the role for treatment de-escalation to minimize toxicity while preserving efficacy. The LYSA/GOELAMS 02-03 trial of 334 patients with stage I-II non-bulky (<7cm) DLBCL demonstrated that R-CHOP alone is non-inferior to R-CHOP + RT if CR is achieved on interim PET after cycle 4; in addition, 4 cycles of R-CHOP was found to be sufficient for interim PET-negative patients with 0 sm-IPI risk factors[52]. The phase III FLYER trial found that 4 cycles of R-CHOP has reduced toxicity and non-inferior efficacy compared to 6 cycles for patients with stage I-II non-bulky (<7.5cm) DLBCL with no other sm-IPI risk factors.[58] In addition, the phase II SWOG S1001 trial and real-world data from BC Cancer demonstrated excellent PFS rates with 4 cycles of R-CHOP if CR is achieved after cycle 3, even in patients with up to 2 sm-IPI risk factors[59,60]. Finally, the LYSA LNH 09-1B trial found that R-CHOP×4 is non-inferior to R-CHOP×6 if CR is achieved on interim PET after cycle 2 for patients with stage I-II DLCBL up to age 80 with normal LDH and ECOG 0-1.[61]

In summary:

1. These studies demonstrate that patients with 0 or 1 sm-IPI risk factors (age >60 or stage II disease) can be treated with 4 cycles of R-CHOP if they achieve CR on interim PET. Patients being considered for treatment de-escalation should undergo baseline PET rather than CT to ensure accurate staging.
2. Higher-risk limited-stage patients with sm-IPI 2-4 or those with elevated LDH or ECOG >1 were not well-represented in the above trials and should continue to receive 6 cycles of R-CHOP even if CR is achieved on interim PET. The optimal treatment of patients with PR on interim PET is unknown, but our preferred approach is R-CHOPx6 plus RT as this was shown to result in similar outcomes as interim PET-negative patients in the LYSA/GOELAMS 02-03 trial.

Role for Consolidative Radiation Therapy in DLBCL

As mentioned above, the only randomized trial of combined modality therapy versus chemoimmunotherapy alone in limited-stage DLBCL (LYSA/GOELAMS 02-03) found the addition of RT did not improve outcomes over R-CHOP alone among patients achieving CR on interim PET.[52] However, the administration of RT after 6 cycles of R-CHOP appeared to overcome the poor prognostic impact of a positive interim PET, as these patients experienced similar outcomes as interim PET-negative patients. For advanced-stage DLBCL, a large retrospective analysis from BC Cancer of 723 patients treated with R-CHOP x6 +/- consolidative RT to focal sites of PET+ disease at end-of-treatment found that patients achieving negative PET have excellent outcomes without RT, including those with bulky disease and skeletal involvement at diagnosis.[62] In addition, patients with non-progressing PET+ disease treated with RT had outcomes approaching those of PET-negative patients, suggesting a potential benefit of RT.

In summary:

1. We recommend consolidative RT only for patients with (1) limited-stage DLBCL with positive interim PET or (2) advanced-stage DLBCL with localized non-progressing PET+ residual disease on end of treatment PET. There is no evidence for improved PFS or OS when RT is used for patients who achieve CMR on restaging PET and therefore, it is not recommended.

HDCT/ASCT as Part of Initial Therapy for DLBCL

High dose therapy and ASCT is no longer recommended as consolidation of first line treatment for DLBCL in the era of CAR-T cell therapy.

Recommendations for CNS Prophylaxis[23,48,49,63-66]:

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. Other high risk situations include double hit lymphoma (MYC + BCL2 and/or BCL6 translocations) and testicular lymphoma. Prophylactic intrathecal chemotherapy does not penetrate the brain parenchyma and has not been proven to decrease meningeal or parenchymal brain relapse of lymphoma in well-designed studies. Similarly, multiple studies (including local retrospective review) have demonstrated no benefit from incorporating high dose methotrexate into R-CHOP for patients at high risk of CNS progression[67-69]. To date, there are no confident strategies to reduce CNS progression risk except for patients with primary testicular lymphoma and intravascular large B-cell lymphoma, who are at particularly high risk of CNS relapse. In these rare diagnoses, there is prospective phase II evidence suggesting a possible benefit of CNS prophylaxis with high dose methotrexate; hence, this strategy may be considered on a case-by-case basis after informed discussion with these patients[70,71].

1. Given the lack of documented efficacy of intravenous HD-MTX and the associated inconvenience and toxicities, we no longer recommend prophylactic intravenous HD-MTX for most DLBCL patients at high risk of CNS relapse.

Treatment of Relapsed/Refractory DLBCL

Patients fit for intensive therapy:

Please refer to the ABMTP Standard Practice Manual chapter “Hodgkin and Non-Hodgkin Lymphoma: Indications for Cellular Therapy” for full details on indications and eligibility.

In summary:

Approach to R/R DLBCL ***patients fit for intensive therapy***:

1. *Relapsed/Refractory DLBCL <12 months from completion of R-CHOP chemotherapy: patients should be referred for CAR T-cell therapy as second line therapy*

- Phase III trials with axi-cel and liso-cel as second line therapy compared to the standard salvage chemotherapy approach in patients with poor prognosis relapsed/refractory DLBCL <12 months from RCHOP chemotherapy have demonstrated superior event-free survival, progression-free survival, and overall survival outcomes with 2L CAR-T.[72,73]

2. *Relapsed DLBCL >12 months from completion of RCHOP chemotherapy – Patients should be offered salvage platinum-containing chemotherapy followed by high dose chemotherapy (HDCT) and autologous stem cell transplantation in chemo-sensitive patients*
   - All patients, ECOG 0-2, with adequate organ function and absence of active infections with relapsed disease >12 months after initial RCHOP chemotherapy should be referred to the HSCT program as soon as possible.
   - Consider RDICEP over RGDP as the preferred salvage in this population[74,75]
   - Potential transplant candidates should receive rituximab with salvage chemotherapy to maximize the chance of response, and *in-vivo* purge blood of tumour cells

3. *Relapsed/Refractory DLBCL after two or more lines of therapy*
   Any fit r/r DLBCL patient who has not received CAR-T in second-line should be considered for 3rd line CAR-T cell therapy. Phase II trials of axi-cel, tisa-cel, and liso-cel demonstrates CR rates 40-56% with long-term PFS rates in the range of 30-40%. The main toxicities of these therapies are cytokine release syndrome, neurotoxicity, cytopenias, and B-cell aplasia/hypogammaglobulinemia and as such this therapy is be administered only at centers approved for cellular therapy treatments. Patients who have previously received or are unable to receive CAR-T should be considered for therapy with bispecific antibodies (glofitamab or epcoritamab) or other palliative therapies

Patients unfit for intensive therapy:

The prognosis of patients with relapsed/refractory DLBCL who are not candidates for cellular therapy has been historically poor. Palliative-intent regimens including R-GemOx, polatuzumab vedotin with bendamustine/rituximab, and tafasitamab with lenalidomide have been studied in phase II trials of patients with r/r DLBCL who are unfit for intensive therapy:

	R-GemOx	Pola + BR	Tafa + Len
Mechanism	Chemoimmunotherapy	Chemoimmunotherapy + antibody-drug conjugate	Monoclonal antibody + immunomodulator
Study population	49 ASCT-ineligible patients with r/r DLBCL and ECOG 0-2	106 ASCT-ineligible patients with r/r DLBCL and ECOG 0-2	80 ASCT-ineligible patients with r/r DLBCL and ECOG 0-2 (excluding primary refractory)
Administration	Time-limited therapy with simpler dosing	Time-limited therapy with simpler dosing	Indefinite therapy with frequent dosing
Efficacy	ORR 61% with CR 44% Median DOR 10 mos Median OS 11 mos	ORR 42% with CR 39% Median DOR 10 mos Median OS 13 mos	ORR 58% with CR 40% Median DOR 44 mos Median OS 34 mos
Notable toxicities	Myelosuppression Neurotoxicity	Myelosuppression Neuropathy	Myelosuppression Rash Thrombosis
Cost	Lower cost	High cost	High cost
References	Haematologica 2013; 98(11):1726	J Clin Oncol 2020; 38(2):155 Blood Adv 2022; 6(2):533	Lancet 2020; 21(7):978 Haematologica 2021; 106(9):2417

Epcoritamab and glofitamab are bispecific antibodies targeting CD20 and CD3 which are anticipated to soon be funded for patients with relapsed/refractory large B-cell lymphoma after ≥2 lines of therapy who have already received or are unable to receive CAR-T cell therapy[76,77]. Bispecific antibodies produce complete responses in approximately 40% of patients with a median time to response of 6 weeks. Response assessment is therefore recommended 6-8 weeks after C1D1 of epcoritamab or glofitamab. Although some delayed responses have been observed as late as 8-10 months after treatment initiation, these are unlikely to occur in patients with progressive disease at the time of first response assessment. See chapter on "Prevention and Management of Toxicities of Bispecific Antibodies in Lymphoma" for detailed recommendations on supportive care.

	Epcoritamab	Glofitamab
Indication	Relapsed/refractory DLBCL after ≥2 LOT Relapsed after or unable to receive CAR-T	Relapsed/refractory DLBCL after ≥2 LOT Relapsed after or unable to receive CAR-T
Schedule	**Frequent and indefinite dosing** C1D1: 0.16mg, C1D8: 0.8mg, C1D15+22: 48mg C2 to C3: 48mg weekly C4 to C9: 48mg q2 weeks C10+: 48mg q4 weeks	**Less frequent fixed-duration treatment** C1D1: obinutuzumab, C1D8: 2.5mg, C1D15: 10mg C2 to C12: 30mg q3 weeks
Administration	Subcutaneous	Intravenous (2-4h)
Efficacy	ORR 63% and CR rate 39%	ORR 52% and CR rate 39%
Toxicity	CRS in 50% Grade 2 CRS in 17% and grade ≥3 in 3%	CRS in 63% Grade 2 CRS in 12% and grade ≥3 in 3%

Recommendations for treatment:

1. R-GemOx is the preferred second-line treatment because it is a well-established outpatient platinum-based regimen that is better tolerated in older patients than other regimens such as GDP, DHAP, or ICE, although it is associated with significant myelosuppression.

2. Once funded, epcoritamab and glofitamab are recommended for patients with relapsed/refractory large B-cell lymphoma after ≥2 lines of therapy who have already received or are unable to receive CAR-T cell therapy. Polatuzumab, bendamustine, and rituximab can also be considered for second or later relapses, and for patients who are unfit for, or intolerant of, R-GemOx or bispecific antibodies. Patients should have reasonable performance status (ECOG 0-2) and adequate hematologic function to be expected to benefit from and tolerate polatuzumab with BR. Tafasitamab-lenalidomide is not approved or funded in Alberta. Bendamustine and tafasitamab should be avoided in patients planned to receive CAR-T cell therapy due to the respective risks of lymphodepletion and CD19 downregulation.

3. 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. Involved field radiotherapy (IFRT) to symptomatic sites or localized relapses may also benefit these palliative patients**.** Addressing goals of care and ensuring timely integration of palliative care should be a priority for all patients with r/r DLBCL who are unfit for intensive therapy.

Secondary CNS Lymphoma[78-81]

Selected patients with CNS relapse/progression may be candidates for intensive therapy as outlined in Appendix A, subheading VIII. Favorable outcomes were reported in an Alberta study of 62 SCNSL patients with median age 58 years (range 20-75) intended for transplant, with ASCT rates of 84%, 5-year PFS 53% and OS 65% for all patients, and 5-year PFS 62% and OS 73% for those undergoing R-TBuM conditioning and ASCT. One of 3 induction regimens is recommended for transplant-eligible patients and one of two options for transplant ineligible 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 MATRix for patients who decline ASCT but are fit for intensive induction therapy or Cytarabine/Rituximab/Thiotepa outpatient regimen for transplant ineligible (PCNSL table C).

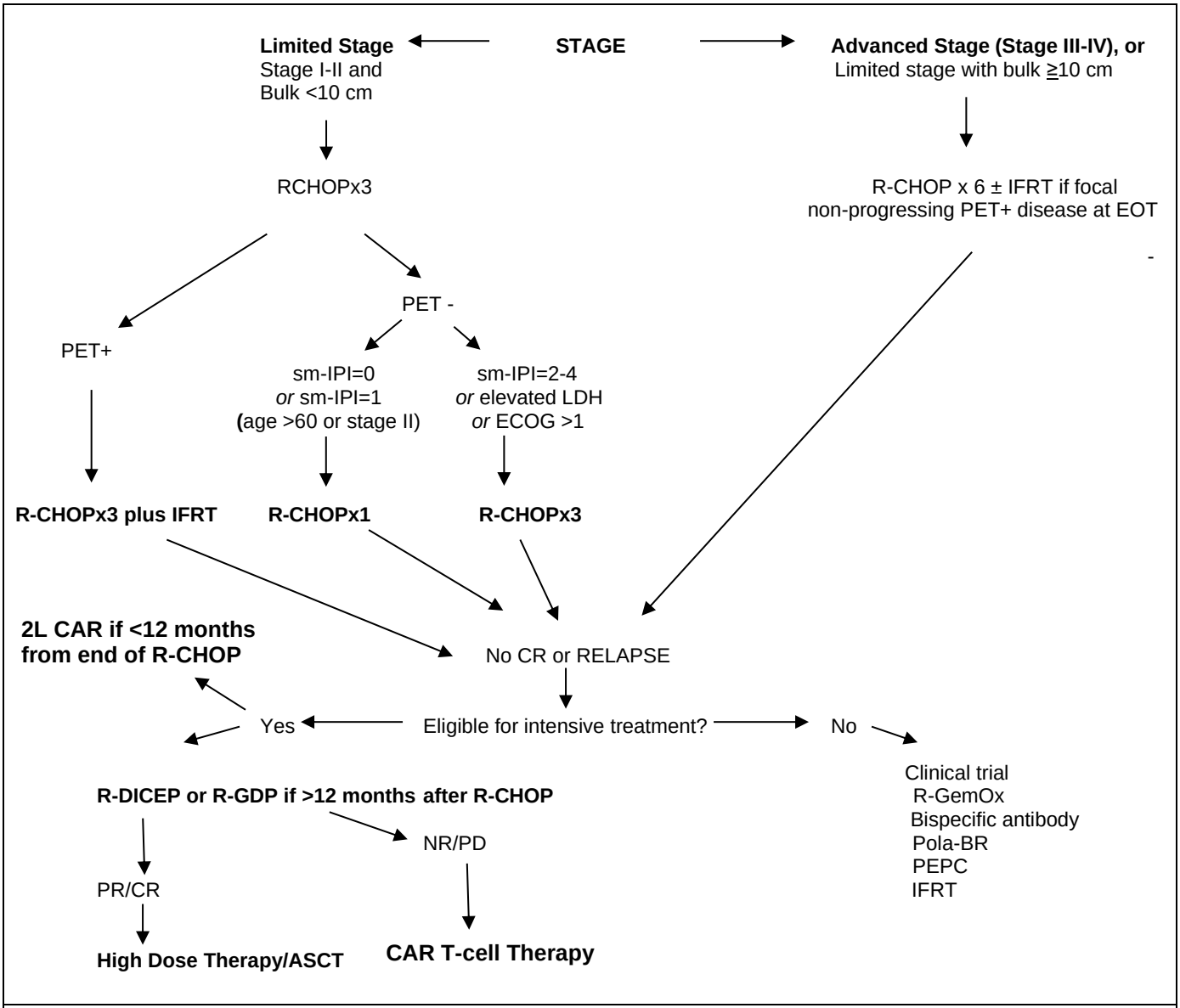
2) Early Systemic and CNS lymphoma (prior to completing RCHOP x6): RCHOP and HDMTX x4 cycles and early referral to Cellular Therapy for discussion around R-TBuM/ASCT vs CAR-T cell therapy for transplant eligible (table B) or RCHOP/MTX followed by AraC then ifosfamide in transplant ineligible (table E).

3) Late relapse (prior RCHOP x6) with systemic and CNS lymphoma: HDMTX-Ifosfamide-etopside 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)

Of note, patients with concurrent CNS and systemic relapse have inferior outcomes with HD-MTX-based chemotherapy and ASCT compared to those with SCNSL at diagnosis or isolated CNS relapse[82,83]. The optimal treatment of patients with concurrent CNS and systemic relapse within 12 months from the end of first-line therapy is unclear, and these patients should be considered for ASCT or second-line CAR-T cell therapy on a case-by-case basis. Patients with SCNSL undergoing CAR-T cell therapy should receive appropriate CNS-directed bridging therapy before infusion since outcomes appear poor with active CNS disease at the time of infusion[84].

Unfortunately, most patients with multiple-relapsed secondary CNS lymphoma experience poor response to subsequent therapy and are best managed with palliative intent, including consideration of palliative cranial radiotherapy.

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



Stage-modified IPI (sm-IPI) score: stage II, age >60 years, ECOG 2-4, elevated LDH

Treatment of special DLBCL entities [24-27,63].

High-grade B-cell lymphoma with MYC and BCL2 rearrangements by FISH:

High-grade B-cell lymphoma with MYC and BCL2 rearrangements (double hit lymphoma or DHL) is associated with a poor prognosis, with a large multicenter retrospective analysis of 311 patients reporting an OS rate <50% if IPI=2-5 vs 65% for IPI=0-1[85]. The optimal treatment of DHL is unknown, but intensive induction regimens such as da-EPOCH-R or R-CODOX-M/R-IVAC are commonly used and have demonstrated PFS benefit over R-CHOP in some retrospective studies[85] but not others[86]. In addition, the use of consolidative HDT/ASCT has been associated with superior outcomes among patients achieving CR after R-CHOP induction but not after intensive induction regimens.[87] This

suggests that DHL patients treated with R-CHOP can be considered for ASCT consolidation, especially if IPI=2-5 at diagnosis, however other patients who achieve CR after an intensive induction regimen probably should not receive ASCT consolidation. A retrospective analysis of 99 patients with DHL in Alberta found relatively favorable outcomes with 4-year PFS 59% and OS 66%, with no significant difference in PFS or OS between patients treated with intensive induction regimens vs intention-to-transplant following R-CHOP induction. Among the 48 patients intended for ASCT, outcomes were excellent for the 75% of patients undergoing upfront ASCT with 4-year PFS 80-90%, whereas there were no survivors among the 25% of patients with primary refractory disease. This suggests that upfront ASCT can achieve durable remissions in the majority of DHL patients with chemosensitive disease, whereas alternative strategies such as CAR-T cell therapy should be strongly considered for patients with chemorefractory disease.

Of note, the 2023 WHO and ICC lymphoma classifications consider MYC and BCL6 rearranged cases to be an indistinct and biologically heterogenous group. Given that the prognosis and best management of these cases is also uncertain, it is now recommended that patients with MYC and BCL6 rearrangements (but no BCL2 rearrangement) should be treated as high-risk DLBCL NOS rather than as double-hit lymphoma.

Alberta recommendations for high-grade B-cell lymphoma with MYC and BCL2 rearrangements:

- IPI=0-1: R-CHOP x 6 cycles or DA-EPOCH-R x 6 cycles
- IPI=2-5: Options include:
    - A. R-CHOP x 3-4 cycles then restaging PET with responding patients proceeding to R-BuMel/ASCT. Patients refractory to R-CHOP are unlikely to respond to second-line chemotherapy and should be planned for CAR-T cell therapy as soon as possible. Consider PET scan for interim response assessment for best assessment of chemo-sensitivity.
    - B. DA-EPOCH-R or R-CODOX-M/R-IVAC

DLBCL with MYC single-hit translocation by FISH

1. MYC-rearranged DLBCL (or high-grade B-cell lymphoma NOS) but no translocation of BCL2 : Patients should be treated with R-CHOP x 6 cycles given the lack of evidence of a superior treatment approach.

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Transformed indolent B-cell lymphoma

Patients with transformed treatment-naïve indolent B-cell lymphoma have a similar prognosis as de novo DLBCL and should be treated with R-CHOP without consolidative ASCT or maintenance rituximab[88,89]. Patients who have previously received chemotherapy for indolent lymphoma have an inferior prognosis at transformation[90]. As such, ASCT is recommended for chemosensitive transformed DLBCL arising from chemotherapy-exposed iNHL[91], although outcomes appear suboptimal in the bendamustine era (Stewart et al. submitted). CAR-T cell therapy is recommended for r/r transformed lymphoma after at least 2 lines of therapy (e.g. 1 for iNHL and 1 for DLBCL).

Second-line CAR-T may be available for those transforming within 12 months of first-line therapy with R-CHOP (e.g. for clinically suspected transformation at diagnosis).

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma (mediastinal gray-zone lymphoma):

- R-CHOP x 6 cycles for most patients

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.[92] It is frequently associated with a bulky mediastinal mass that directly extends into extranodal thoracic tissues such as pleura, pericardium and chest wall. Patients with distant lymphadenopathy or extranodal involvement outside the thorax should likely be diagnosed and treated as systemic DLBCL with secondary mediastinal involvement, rather than as PMBCL.[93] 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 restaging PET imaging is associated with very high negative predictive value, but relatively low positive predictive value.[94] These findings were confirmed in 20 patients treated with R-CHOP in Alberta, where the PPV of a positive interim PET scan was only 20% for disease progression/relapse whereas a negative interim PET had NPV 100%. Therefore, a positive interim PET scan should probably not be used alone to guide further therapy.

Treatment of PMBCL with RCHOP +/- RT is associated with cure rates of approximately 75-80% and overall survival rates of 90%. Phase II studies have reported that intensifying chemotherapy (eg. dose adjusted EPOCH-R) maintains excellent outcomes while avoiding RT. However, the prospective phase III CALGB/Alliance 50303 study randomized 464 DLBCL patients (including 35 with PMBCL) to RCHOP or DA-EPOCH-R, and found no difference in PFS or OS between regimens, although there was substantially more toxicity with DA-EPOCH-R. 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, but with more RT use in the R-CHOP group (59% vs 13%).[95] There is no phase III evidence that RT after R-CHOP improves survival rates relative to R-CHOP alone, but this is being studied in the ongoing IELSG-37 clinical trial. Real-world data from the BCCA demonstrates that omitting RT for PET-negative patients at the end of R-CHOP therapy achieves similar TTP (80%) and OS (89%) as historical cohorts treated routinely with RT, with a reduction in RT use from 78% in the historical cohort to 28% in the PET-directed era.[96] Similarly, retrospective data for 91 consecutive patients in Alberta treated with R-CHOP from 2004-2020 found a 5-year overall survival rate of 86%, with similar

outcomes for patients with advanced versus limited stage (86% vs 92%, p=0.31) or bulky versus non-bulky disease (83% vs 96%, p=0.12). For patients responding to R-CHOP, the 5-year OS rate was 93% with RT versus 100% without RT (p=0.17). Among 40 patients with a PET-defined complete metabolic response after R-CHOP, 5-year OS was 100% for all patients treated with (n=9) or without (n=31) RT.

Management of patients with partial metabolic response after R-CHOP is uncertain. Prospective data show that the majority of Deauville 4 end-of-treatment (EOT) PET scans after DA-EPOCH-R are false-positives which can be monitored with surveillance PET without RT, with progressive disease occurring in only 1/16 patients with Deauville.[97] Among the 34 patients in BC and Alberta with Deauville 4 EOT PET after R-CHOP (the majority of whom received RT), survival outcomes were excellent and similar to EOT PET-negative patients. It is likely that many cases of partial metabolic response after R-CHOP are false positives as well; indeed, 5 patients in Alberta and BC with Deauville 4 after R-CHOP were observed without RT and none relapsed. Extrapolating from this data, it has been proposed that surveillance imaging without radiation may be reasonable for young patients with Deauville 4 EOT PET after R-CHOP given the likely low risk of progression and long-term risks of toxicity from RT.[98]

In conclusion, available evidence supports the use of R-CHOP for patients with PMBCL, with less toxicity but similar excellent outcomes as DA-EPOCH-R. End of treatment PET should be done 6-8 weeks after day 1 of the final cycle of chemoimmunotherapy to allow time for the post-treatment inflammatory response to resolve.[99] In view of the long-term risk of secondary malignancy and premature heart disease from RT in young patients, RT can probably be safely omitted for patients with PET-negative disease after R-CHOP. Omitting RT in favour of surveillance imaging in 6-8 weeks (CT is the preferred modality in Alberta) may be reasonable for patients <60 years old with Deauville 4 on EOT PET after R-CHOP, while older patients and those with Deauville 5 should receive RT. For the 10-20% of patients with suspected relapsed/refractory PMBCL, the diagnosis of progressive disease should be confirmed with biopsy or clear progression on CT, and not based on FDG uptake on PET alone. Treatment options at relapse include radiation for localized disease, salvage chemotherapy and autotransplant, radiation therapy, axicabtagene ciloleucel (funded only after 2 prior lines of therapy), and pembrolizumab.

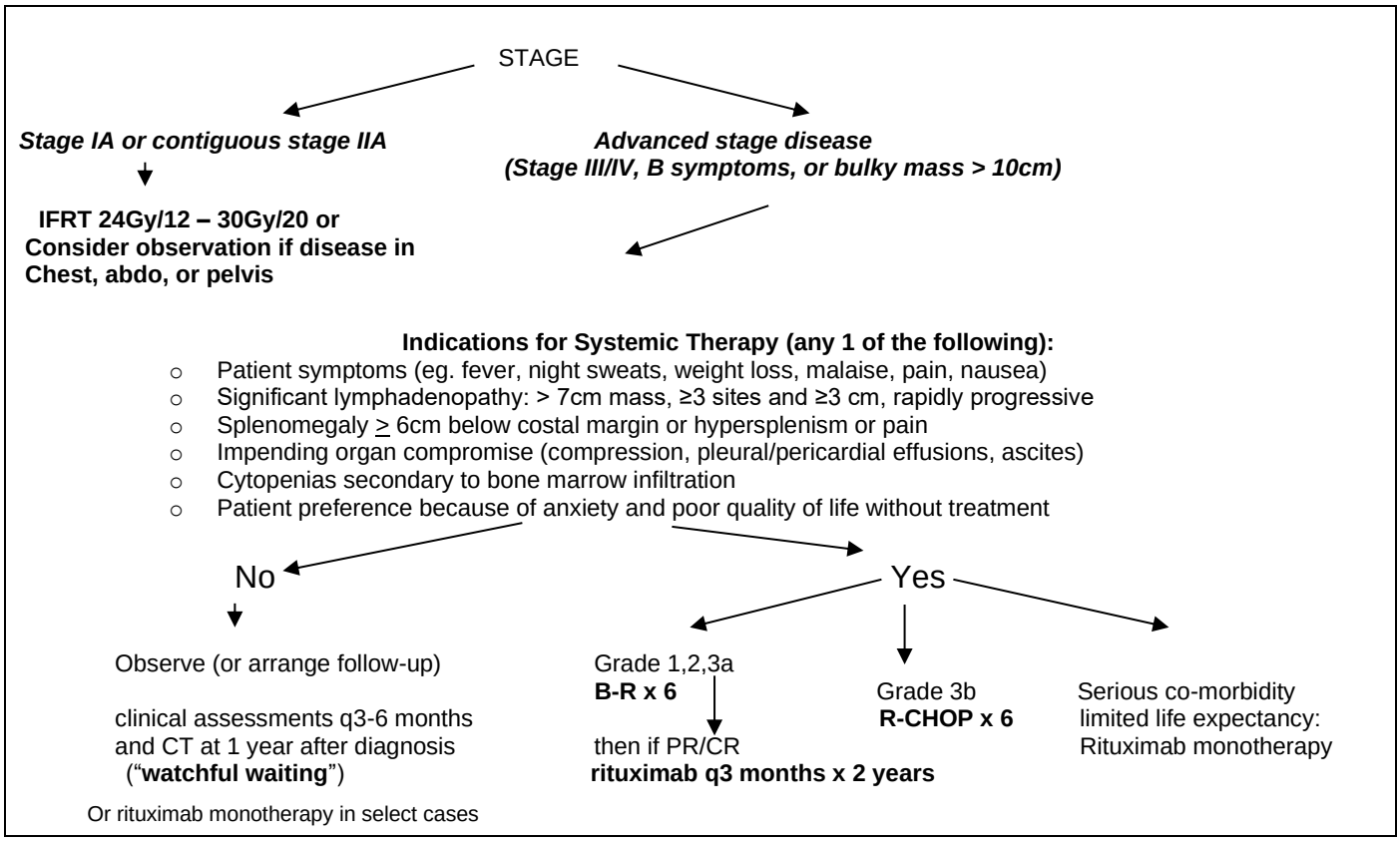
Follicular Lymphoma[100-145]

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 ≥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, ≥ 3 sites and ≥ 3cm, rapidly progressive)
- Splenomegaly ≥ 6 cm below costal margin, or hypersplenism, or pain
- Impending organ compromise (compression, pleural/pericardial effusions, ascites)
- Cytopenias secondary to bone marrow infiltration
-
- 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 1-2 years later 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 to prevent the risk of clinical deterioration in the setting of known progressing lymphoma. 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 30months) 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[146].

Alternatively, a select population of advanced stage II-IV, asymptomatic patients could be considered for treatment with rituximab monotherapy (weekly x4) based on the long term follow up of the Ardeshna/Northend trial. This phase III trial randomized 379 patients with asymptomatic low tumour burden follicular lymphoma to (1) watch & wait (W&W) (2) rituximab induction (RI) or (3) RI followed by rituximab maintenance (RM). The median time to next treatment (TTNT) was 2.7 years (W&W), 9.9 years (RI) and not reached (RM). No significant differences in OS, histological transformation, or response to next line treatment were observed[147]. This group may include elderly patients (age 70+ who will likely not require another treatment within their lifetime) or patients with profound anxiety regarding their diagnosis. This treatment needs to be weighed with the risk of immunosuppression during and at least 6 months post-therapy. Patients need to be made aware that there is no survival benefit by using this approach. Additionally, the AB drug benefit list includes rituximab monotherapy for FL only for those "who have contraindications to, or who cannot tolerate chemotherapy" so these conditions would need to be met in individuals selected for treatment with RI.

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 (every 3 months for total of eight doses).

Patients who have an indication for treatment but are unable to tolerate BR due to significant comorbidities or frailty can be considered for dose reduced bendamustine (ie. 70mg/m2 on D1 and D2 or 50% bendamustine, keeping D1 at 90mg/m2 and omitting D2). This may help to reduce infectious and cytopenia risks. Alternatively, rituximab monotherapy may be used, for 4 weekly doses, to debulk their disease and provide an element of disease control. Rare patients who have very limited life-expectancy from serious comorbid illness and who wish to avoid intravenous therapy could be treated with palliative oral fludarabine or chlorambucil or targeted radiotherapy.

The GALLIUM clinical trial investigated the value of obinutuzumab in combination with chemotherapy followed by maintenance therapy compared to standard therapy with rituximab chemo-immunotherapy plus maintenance in the firstline treatment of follicular lymphoma. The study demonstrated 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%), with acceptable increased toxicity. As no OS advantage has yet been demonstrated, obinutuzumab is not funded in Canada for this indication and we continue to recommend rituximab. [148].

Note: Grade 3b follicular lymphoma should be treated as DLBCL with R-CHOP. Rituximab maintenance has not been proven effective following R-CHOP therapy for large B-cell lymphoma, and therefore is not recommended.

Management of relapsed follicular lymphoma:

Note: treatment indications at relapse are the same as the indications for upfront treatment. Relapse and progression are expected for indolent lymphomas and again, only require treatment if meeting the criteria listed above.

Prior to moving to next line therapy for FL, if there is suspicion of transformation to aggressive lymphoma (ie. less than PR to initial therapy, systemic symptoms, or very early relapse), biopsy of the fastest growing (or most FDG-avid, if PET is performed) lesion should be done to rule out DLBCL.

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).

Autologous stem cell transplant:
For healthy patients, younger than 75 years old, HDCT/SCT maximizes the length of disease control, regardless of length of initial remission, and as such is a reasonable treatment option at first or second relapse for those who accept potential risks/toxicities.

This benefit of ASCT is most pronounced for patients who relapse within 2 years of initial chemotherapy (POD24) have more aggressive disease and higher rates of transformation to aggressive lymphoma. Their OS is < 5 years with standard therapy and several studies have shown improved PFS along with OS with ASCT for these patients.

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[149]. Another long-term follow-up study from Alberta demonstrated that up to 50% of ASCT recipients may be functionally cured of FL[150].

Lenalidomide/rituximab:

For patients not suitable HDCT/SCT, lenalidomide and rituximab, based on the AUGMENT trial is approved for patients with relapsed/refractory disease. Progression-free survival was estimated at a median duration of 39.4 months (95% CI, 22.9 months to not reached) in this phase III trial[151].

CAR-T cellular therapy:

CAR-T is funded for patients with r/r FL grade 1-3A after ≥2 lines of therapy based on the ZUMA-5 and the ELARA trials[152,153]. ORR and CR rates were upwards of 85% and 69% in both trials, respectively. Infection and cytopenias were the most common adverse effects. Patients need to be monitored for CRS and ICANS, though rates of same are generally lower than for DLBCL.

Repeat chemo-immunotherapy:

Some patients may be managed with repeating chemo-immunotherapy if they have achieved a long remission to first therapy. Rituximab maintenance should only be used once in the course of a patient's disease (first remission or first relapse).

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). Both PFS (HR[95%CI]: 0.52[0.39,0.69]; p<0.0001) and OS (HR[95%CI: 0.58[0.39.0.86]; p=0.0061) were improved in the FL group treated with obinutuzumab. 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 of 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 can be considered for patients deemed inappropriate for bendamustine retreatment. Relatively frequent infections were noted so prophylactic antibiotics and antivirals should be considered, especially when obinutuzumab is combined with bendamustine.

Idelalisib:

Idelalisib, a PI3Kδ inhibitor has also shown efficacy in a Phase 2 study of double-refractory FL patients (patients with lack of response or progression within 6 months of both rituximab and an alkylator). Idelalisib can lead to durable remissions in a minority of patients and is currently funded. Infectious complications and immune toxicities are frequent and prophylactic antibiotics and anti-virals are required to reduce the risk of serious infections.[154] Due to these risks and general poor tolerability, we recommend considering other therapeutic options first.

Palliative, symptomatic care (possibly including palliative IFRT 4Gy/2 fractions):

This is usually the best option for patients who were refractory to their two most recent treatment regimens, those with CNS involvement, or those with an ECOG score of 3-4.

Indolent Lymphomas (Excluding Follicular Histology)[1,155-163]

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

Table 2. Treatment of Indolent Lymphomas[155]

Stage	Treatment
Limited	IFRT (24Gy/12 - 30Gy/20)
Advanced	**Asymptomatic:** observation until treatment indication **Symptomatic:** • majority should receive B-R, then rituximab maintenance • alternatives in special situations include IFRT, fludarabine, or chlorambucil

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[164]. 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[165].

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[166,167]. Splenectomy has previously been the standard approach to treat SMZL for over two decades[168]. The role of splenectomy as frontline treatment of SMZL is now controversial[169,170 171 172]. 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[173].

Monotherapy with rituximab has recently emerged as a non-operative alternative [170-174] 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[144].

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 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[164], should subsequently receive maintenance rituximab as per other iNHL subtypes.
    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 in responding patients.

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.

Small Lymphocytic Lymphoma (SLL)

SLL and chronic lymphocytic leukemia (CLL) are considered to be biologically the same disease and the management of SLL should follow CLL treatment guidelines (not guidelines for other indolent non-Hodgkin lymphoma subtypes. [CLL Guideline link]

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[163].

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[163]*.*
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) similar to other indolent B-cell lymphomas. Maintenance rituximab after BR did not appear to confer significant benefit in a randomized trial in LPL, although the final study results have not yet been published (Rummel et al., ASH 2019). For patients who do not tolerate B-R, CDR (Cyclophosphamide, Decadron, Rituximab) or Bortezomib-based therapy (eg. R-Bortezomib, R-CyBorD) could be considered[175]. 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 patients 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.
- BTK inhibitors, ibrutinib and zanubrutinib are both highly effective in in LPL (both first line and for relapsed/refractory disease)[176]. Zanubrutinib is now funded for relapsed LPL in AB and is the preferred second line therapy for r/r LPL. [177,178] Ibrutinib +/- rituximab is also anticipated to be funded for r/r LPL but has not been compared to zanubrutinib. Additionally, ibrutinib has not been investigated without rituximab and there is no data to support the added benefit of rituximab. Ibrutinib should thus be reserved for patients who are intolerant but not resistant to zanubrutinib[179].
- Patients who have obtained lengthy first remissions can be considered for re-treatment with chemo-immunotherapy with or without the addition of bortezomib (eg. R-Bortezomib, R-CyBorD)
- ASCT may be considered for younger fit patients with early or aggressive relapses or who prioritize the possibility of a long-term treatment-free interval

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[180].

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/µL, or an absolute neutrophil count <1000/µL.

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[181] but more recent studies (non-comparative) have investigated subcutaneous dosing over 5 days and demonstrate excellent responses[182]. 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[183]. Studies of rituximab have used a weekly schedule x 8 weeks, concurrent with cladribine. Careful attention for and prophylaxis against infection is recommended.

A recent study investigated the addition of rituximab to cladribine in the frontline setting. HCL patients treated with concurrent cladribine and 8 weekly doses of rituximab had higher MRD-free complete remission rates than patients treated without rituximab or with delayed rituximab. (JCO 2020; 38:1527) As improved responses are predicted to lead to longer remissions and given the proven benefit of rituximab in combination with chemotherapy frontline for other indolent NHLs, we recommend consideration of cladribine + rituximab for frontline HCL treatment. Infectious risks and lack of survival data should be considered with cladribine monotherapy favoured for frailer patients and those at high risk of infection. Unpublished Alberta data suggests that patients with HCL have a higher incidence of injection site reactions to subcutaneous rituximab compared to other patients with NHL.

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[184]. We recommend BRAF inhibition for patients who are refractory to cladribine (relapse < 24 months) or relapse after cladribine + rituximab[185]. Vemurafenib has also been used successfully in previously untreated patients with active infections as a bridge to cladribine therapy during treatment of the infection.

Moxetumomab pasudotox is a recombinant CD22-targeting immunotoxin, which has also proven efficacy in highly refractory HCL patients. This agent is associated with severe adverse reactions including hemolytic-uremic syndrome (7.5%) and capillary leak syndrome (5%). (leukemia 2018; 32: 1768) Moxetumumab is not currently funded in Canada but could be considered in relapsed HCL patients who have exhausted all other therapeutic options.

Special Lymphomas

Mantle cell lymphoma[144,145,186-201]:

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, with incorporation of BTK inhibitors into first-line therapy (not yet approved or funded), 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[202,203]. 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[204]. Occasionally, nodal MCL can also follow an indolent course[202,203]. Prognostic indices such as the MIPI have not been shown to identify indolent MCL[202]. 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[205]. 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[202,203]. 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 that 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 routinely 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 (Up to approximately age 65 years)

The accepted standard of care for newly diagnosed MCL patients up to approximately 65 years of age without major co-morbidities was previously demonstrated to be chemoimmunotherapy followed by high dose therapy with ASCT and then 3 years of rituximab maintenance administered every 2 months.[198,199,206]. The recently published TRIANGLE study[207] compared the standard of care of chemoimmunotherapy induction (RCHOP/RDHAP) followed by ASCT with the same therapy but with the inclusion of ibrutinib in induction (with RCHOP only) and as maintenance for 2 years following ASCT versus chemoimmunotherapy (RCHOP/RDAP) with ibrutinib added to the RCHOP cycles plus 2 years of ibrutinib maintenance and omission of ASCT. This study has demonstrated an improvement in PFS and OS with the addition of ibrutinib in induction and maintenance and a lack of inferiority with the omission of ASCT for the groups receiving ibrutinib. Given this OS advantage, the standard of care for younger MCL patients should now include a BTK inhibitor with induction and maintenance. ASCT consolidation is not required for most patients unless longer follow-up data suggests that this provides added benefit. Ibrutinib and other BTKi inhibitors are not yet funded in

Alberta for previously untreated patients with MCL and as such, drug access is recommended to be via Compassionate Access Programs until funding can be confirmed. These guideline recommendations could thus be influenced by drug access until provincial funding is obtained.

The addition of high dose cytarabine to RCHOP-like regimens was also associated with improved rates of CR, PFS, and OS relative to RCHOP alone in the historical ASCT studies. 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)[200], as well as the Nordic regimen published as a phase II trial involving RCHOP-21 alternating with Ara-C [3gm^2 for patients under age 60 years or 2g/m^2 for patients over 60 years, repeated every 12 hours for a total of 4 doses], for a total of 6 cycles, then ASCT[208]. Long-term follow-up of the European MCL Younger Trial demonstrated 10-year TTF 46% with R-CHOP/R-DHAP/ASCT, with a plateau on the curve demonstrating that a significant proportion of patients achieve durable remissions lasting >10 years[209]. 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)[210]. 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[211]. Among 34 patients in Alberta treated with BR/RC induction, ASCT, and maintenance rituximab between 2018-2021, 79% of patients proceeded to ASCT, 3-year PFS was 77%, and 3-year OS was 83%. There were no relapses after ASCT with median 3 years of follow-up.

While the TRIANGLE study used RCHOP/RDHAP as the chemoimmunotherapy backbone, there is data[212] to suggest that the use of oxaliplatin is more tolerable and could lead to improved outcomes. We recommend considering RCHOP/RDHAOx over RCHOP/RDHAP in patients to reduce toxicities and enable more patients to be eligible for this therapy.

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[214]. All patients who are potentially eligible for stem cell transplant or CAR-T cell therapy should undergo *TP53* mutation testing. Of note, *TP53* mutations should be assessed by next-generation sequencing (NGS), since the prognostic value of FISH or immunohistochemistry staining has not been as well established[215]. 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 [214]. As such, standard chemoimmunotherapy alone is not felt to be adequate therapy for TP53-aberrant MCL. The optimal treatment approach is not known but should include incorporation of novel agents and eligible patients should be referred for consideration of allogeneic stem cell transplantation. Response to ibrutinib at relapse is also less favorable in patients with mutated versus wild-type *TP53*, with median PFS of only 4 months[216]. CAR-T cell therapy has shown high response rates in *TP53*-mutated MCL although longer follow-up is needed to confirm durability of responses and Alberta approval of CAR-T for MCL is still as third line therapy in these patients[217,218]. Of note, bendamustine exposure within 6 months before leukapheresis has been associated with impaired CAR-T cell manufacturing and reduced efficacy, hence the use of bendamustine should be avoided in patients with MCL with *TP53* mutation if CAR-T cell therapy is planned as a part of care[217,218]. A suggested treatment approach would include replacing BR with RCHOP (with the

addition of ibrutinib as recommended currently in all younger, fit patients) followed by ibrutinib and rituximab maintenance. Given the high early relapse rates noted despite intensive chemotherapy and ASCT[214], ASCT is not recommended for *TP53*-mutated MCL now that more promising cellular therapies are available. The option of an allogeneic SCT in first response may be discussed with younger, fit patients, although this is associated with significant toxicity and there is limited evidence to support the efficacy of allogeneic SCT in *TP53*-mutated MCL[219]. Given the reduced risks of GVHD and non-relapse mortality, CAR-T cell therapy at second disease progression is generally the preferred strategy. Close monitoring while on a BTK inhibitor is essential to detect relapse early and quickly refer for CAR-T before loss of disease control[220]. While the wording for CAR-T cell therapy funding is for 3rd line therapy for MCL in Alberta, we recommend attempts to provide patients with TP53-mutated MCL access to CAR-T cell therapy at first relapse if firstline therapy includes both chemoimmunotherapy and a BTK inhibitor.

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[221], the role of rituximab maintenance after ASCT for younger patients was uncertain until results of the phase III trial (LyMa) were reported[197]. In the LyMa trial, 299 patients <66years of age with mantle cell lymphoma received 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^2, 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). Progression-free survival at 4 years was improved at 83% (95% CI, 73 to 88) in the rituximab group versus 64% (95% CI, 55 to 73) in the observation group (P<0.001)and overall survival was improved at 89% (95% CI, 81 to 94) in the rituximab group versus 80% (95% CI, 72 to 88) in the observation group (P=0.04). In support of the LyMa trial, a retrospective review of 72 patients previously enrolled in a phase II trial showed a progression free survival benefit in patients who received maintenance Rituximab vs those who did not (2 year PFS 90% *vs.* 65%)[222].

Treatment – Transplant Ineligible Patients (Age over approximately 65yrs)

For patients with mantle cell lymphoma over approximately 65 years of age, B-R induction x6 cycles is our standard of care. Results from an 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)[144]. In addition, the trial confirmed the improved toxicity profile of BR over RCHOP. The phase III SHINE trial demonstrated that the addition of continuous ibrutinib to BR improved PFS over BR alone in older patients with MCL, although the ibrutinib arm had increased toxicity and treatment-related mortality with no improvement in overall survival[223]. The Phase ENRICH study examined ibrutinib and rituximab (ibrutinib until progressive disease) versus chemoimmunotherapy and did not demonstrate a PFS or PFS advantage compared to BR[224]. As such, first-line BTK inhibitors are not currently approved or recommended for transplant ineligible (older) patients with MCL.

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Regarding rituximab maintenance, there is no published trial examining its benefit following BR induction. The European Mantle Cell Lymphoma Elderly trial confirmed a benefit of rituximab q2 months until progression (vs. interferon-α 2a or 2b) following RCHOP induction. 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). The StiL group investigated the value of R maintenance following BR and reported a lack of benefit in terms of PFS or OS.[225] However, the study was underpowered to detect a difference. Further, a multicentre retrospective study reported superior outcomes of patients given R maintenance (vs. observation) after achieving CR or PR with BR, with an OS advantage for those who achieved PR only.[226] We favour following BR x 6 cycles with R maintenance but with a maximum duration of 4 years of rituximab maintenance given the balance between efficacy, toxicity and cost. Given the lack of strong data to support this approach, R maintenance could be omitted or truncated in patients for whom the benefits of extending a remission do not outweigh the inconvenience of maintenance therapy.

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:

Immediate chemoimmunotherapy is recommended for most patients. See *Recommendation regarding Watchful Waiting for MCL for details on the minority of patients for whom watchful waiting could be considered.*

Transplant Eligible Patients (Age up to approximately 65yrs)

1) Induction:3 cycles of RCHOP with ibrutinib 560mg on Days 1-19 alternating with 3 cycles RDHAP or RDHAOx. (Ibrutinib should not be combined with high dose cytarabine for reasons of increased toxicity).
2) Consider referral for discussion re: stem cell transplantation as consolidation for patients with blastoid/pleomorphic morphology or *TP53* mutation. ASCT no longer recommended for good or intermediate risk MCL.
3) Maintenance ibrutinib 560mg daily x 24 months + rituximab 1400mg sc every 2 months x 3 years

Transplant Ineligible Patients (Age over approximately 65yrs)

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

Treatment Relapsed Mantle Cell Lymphoma.

There is no standard treatment for relapsed MCL but there are many options, including chemotherapy and novel agents[227]. In general, treatment choice should take into consideration the duration of response to previous treatment.

The Bruton's tyrosine kinase (BTK) inhibitors have shown the most promise as therapeutic agents for relapsed MCL and are the preferred second line therapy. 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[228]. Acalabrutinib has also been investigated in relapsed/refractory MCL in a Phase 2 study with 12 month PFS and OS of 67% and 87% respectively.[229] Similarly, in a phase 1/2 trial with zanubrutinib the median PFS was 21.1 months and median DOR was 18.5 months.[230]

Patients who progress on BTKi during RCHOP+ibrutinib/RDHAP(RDHAOx) induction or BTKi maintenance, should proceed to CAR-T cell therapy. Patients who have received BTKi as a part of their firstline therapy and as maintenance, who progress after planned discontinuation of BTKi can be rechallenged with BTKi. Response rates and durability of responses are not known.

Most patients treated with chemoimmunotherapy for MCL respond poorly and with short remissions to re-treatment with chemoimmunotherapy. Re-treatment with chemoimmunotherapy is not routinely recommended but the best responses have been reported with bortezomib-containing regimens[233,234]. Maintenance rituximab prolongs PFS and OS in relapsed MCL[235] but has not been studied in patients that received it after first-line therapy. Lenalidomide also has reported responses in this setting, particularly in combination with rituximab +/- chemotherapy[234,236]. The non-covalent BTK inhibitor pirtobrutinib is not yet funded but achieves ORR 58%, CR rate 20%, and median PFS 7.4 months in r/r MCL[237] and is the treatment of choice after failure of covalent BTKi.

Brexucabtagene autoleucel (brexu-cel) is a CAR T therapy that is funded for patients with relapsed or refractory mantle cell lymphoma who have received a tleast 2 lintes of therapy including a BTKi. In the ZUMA-2 phase 2 trial, the estimated PFS was 61% and OS 83% at 12 months.[238]

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 may be considered in relapsed disease for those patients who are young and fit, although CAR-T cell therapy is now preferred before allogeneic SCT for most patients with relapsed MCL given the reduced risks of toxicity and non-relapse mortality.

Summary - Approach to Relapsed/Refractory MCL

1. Treatment with BTKi is the preferred second line therapy for r/r MCL.

2. For patients not fit for intensive cellular therapy and who have failed covalent BTKi, palliative options include non-covalent BTKi (not yet funded in AB), bortezomib-based therapies, lenalidomide, and clinical trials. Survival for these patients is expected to be very short and involvement of Palliative Care is recommended.

3. Patients fit for intensive cellular therapy (ECOG 0-2 and meeting eligibility criteria) and progressing on covalent BTKi, should be referred for CAR-T cell therapy.

i. Patients with high-risk features (e.g. *TP53* mutation, blastoid/pleomorphic, Ki67 >30-50%, high MIPI, bulk, POD24) should be started on a BTKi and referred to the CAR-T centre so that planning and preparation for CAR-T cell therapy can be commenced before progression. Patients should be assessed monthly and imaging should be done within 2-3 months or sooner if evidence of poor response. Imaging should be done again by 6 months for patients achieving an initial PR. Patients with stable or progressing disease should be referred urgently for CAR-T cell therapy. BTKi should generally not be stopped abruptly due to the risk of rapid tumor progression.

ii. Patients intolerant to ibrutinib should be trialed on alternative BTKi (if possible) prior to referral for cellular therapy.

iii. If responding to second-line therapy (PR/CR), fit and eligible for allogeneic SCT, particularly if high risk disease (e.g. *TP53* mutation), consider referral for opinion regarding allogeneic SCT. However, CAR-T cell therapy is now preferred before allogeneic SCT for most patients with relapsed MCL given the reduced risks of toxicity and non-relapse mortality.

iv. If not responding to therapy, *OR* progressing on BTKi, refer urgently for CAR-T cell therapy

Lymphoblastic lymphoma[239-245]:

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[246-248]:

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). DA-EPOCH-R is an alternative intensive chemotherapy regimen that is easier to tolerate than R-CODOX-M/IVAC and could be considered in fit, older patients or patients with comorbidities who are deemed appropriate for curative intent therapy.[249,250]

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:
For complete staging evaluation, patients with gastric MALT lymphoma require cross-sectional imaging plus upper GI endoscopy with multiple mucosal biopsies for Helicobacter pylori. Gastric MALT lymphoma should be staged according to the Lugano or Paris staging systems for GI lymphomas:

Lugano GI staging system [251]		Paris staging system [252]	
Stage I	Confined to GI tract (single primary or multiple, non-contiguous)	T1m N0 M0 T1sm N0 M0 T2 N0 M0 T3 N0 M0	Mucosa Submucosa Muscularis propria Serosa
Stage II Stage II_1 Stage II_2	Extending into abdomen Local nodal involvement Distant nodal involvement	 T1e3 N1 M0 T1e3 N2 M0	 Perigastric lymph nodes More distant regional nodes
Stage IIE	Penetration of serosa to involve adjacent organs or tissues	T4 N0e2 M0	Invasion of adjacent structures with or without abdominal lymph nodes
Stage IV	Disseminated extranodal involvement or concomitant supra-diaphragmatic nodal involvement	T1e4 N3 M0 T1e4 N0e3 M1 T1e4 N0e3 M2	Extra-abdominal lymph nodes Distant (non-contiguous) GI sites involvement Non-GI sites of involvement

Adapted from "Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up"[253]

1) Localized (stage I-II_1) H. pylori positive gastric MALT lymphoma: Stage I-II_1 H. pylori positive gastric MALT lymphoma should be treated with quadruple antibiotic H. pylori eradication therapy (e.g. PAMC or PBMT) in accordance with current guidelines [254]. This achieves responses in up to 70-80% of patients with excellent long-term event-free survival, although response rates are lower for patients with t(11;18) [255-259]. H. pylori eradication should be confirmed with stool antigen or urea breath test once off antibiotics for ≥4 weeks and off PPIs for ≥2 weeks, and an alternative second-line regimen should be given to patients with persistent H. pylori. 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. Gastric MALT lymphoma may respond within several weeks or slowly regress over 12-18 months after H. pylori eradication. Referral to the cancer centre is not required unless persistence of disease is documented after successful H. pylori eradication. If lymphoma recurs or persists more than 12-18 months after H. pylori eradication,

the patient should receive moderate dose (e.g. 24-30 Gy) upper abdominal ISRT which results in excellent outcomes [260-263]. Patients could also be considered for initial ISRT in addition to H. pylori therapy if the tumour is associated with t(11;18). Rituximab or chemoimmunotherapy may be considered for patients ineligible for or relapsing after RT [264-266].

2) Localized (stage I-II_1) H. pylori negative gastric MALT lymphoma: For the minority of patients whose gastric biopsies are negative for H. pylori, non-invasive testing (e.g. stool antigen test, urea breath test, and/or serology) should be performed to confirm H. pylori status. H. pylori-negative gastric MALT lymphoma is more likely to be associated with t(11;18) [267,268]. A trial of H. pylori eradication may still be considered as up to 38% of cases of H. pylori negative gastric MALT lymphoma can respond to antibiotics [269], presumably due to false negative testing or infection with other helicobacter species [270]; these patients should receive ISRT if there is no evidence of lymphoma regression after 3-6 months on repeat endoscopy. Alternatively, initial treatment with ISRT can be considered since the majority will not respond to H. pylori eradication, whereas ISRT achieves complete responses in >95% of patients with long-term event-free survival rates of 80-90% [252,271-274]. Repeat endoscopy should be done 3-6 months after ISRT to confirm response. The decision to treat with initial ISRT versus a trial of H. pylori eradication should be individualized and made in conjunction with patient wishes.

3) Advanced (stage II_2, IIE or IV) gastric MALT lymphoma: These patients should be managed as advanced stage indolent B-cell lymphoma with active surveillance if asymptomatic or chemoimmunotherapy if symptomatic disease. These patients should also receive H. pylori eradication therapy.

Testicular lymphoma[275-278]:

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^2 every 14-28 days x 2-3 doses after completion of all 6 cycles of R-CHOP if this strategy is considered (though there is a paucity of data to support the value of CNS prophylaxis even in this DLBCL subtype).

Primary CNS lymphoma (PCNSL)[275,279-290]:

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 including high dose methotrexate 3.5g/m^2 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)[279]. 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 include high-dose methotrexate and cytarabine during induction therapy for PCNSL[279].

Whole brain radiotherapy (WBRT) has fallen out of favour for PCNSL, based in part upon high rates of severe neurotoxcity 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)[291]. 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[291]. 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[290].

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[289].

Small studies have demonstrated durable remissions with ASCT for PCNSL, however, the optimal conditioning regimen remains undefined[292-295]. With the knowledge of our initial encouraging experience with TBC/ASCT[292], 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. Review of our data proved the efficacy of this therapy (PFS 52% at 5 years post TBC/ASCT) but with significant toxicity (5 treatment-related deaths, all occurring in patients over 60 yrs). To reduce the TRM, we modified our protocol to omit cyclophosphamide starting in 2011. 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%.

The Anocef-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[296].Based on these data, we recommend TBu/ASCT consolidation therapy for all eligible PCNSL patients.[297,298]

The role of Rituximab in treating PCNSL was evaluated in the International Extranodal Lymphoma Study Group (IELSG) 32 study[299], which randomized patients with histologically-proven primary CNS lymphoma to receive a maximum of four 3-week cycles of methotrexate at 3.5 g/m2 on day 1 and cytarabine at 2 g/m2 twice daily on days 2 and 3, either alone (arm A; n = 75), in combination with 375 mg/m2 of rituximab on day -5 and 0 (arm B; n = 69), or combined with rituximab at the same dose plus 30 mg/m2 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 ≤3, with patients aged 66 to 70 years having an ECOG PS ≤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)[299]. 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 potential benefit of rituximab with induction chemotherapy was not confirmed in different phase III trial by HOVON 105/ALLG NHL 24[300], 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 2011 protocol included:

1) Induction chemotherapy:
    a. First 2 cycles: HDMTX 3.5g/m2 d1,15 with procarbazine 100mg/m2 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[301], 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[279].
    d. Rituximab was added in 2016 for a total of 6 doses during induction to improve response
2) High Dose Chemotherapy (patients <70 yo with no significant co-morbidities, KPS>60% after induction therapy, and PCNSL not secondary to immune suppression):
    a. Thiotepa 300mg/m2 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[302,303].

Recommendations: PCNSL Transplant-Eligible (Usually <70 years old)

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. We also increased the age limit for the transplant eligible protocol to 75 years, however, patients over age 70 years must be extremely healthy with no comorbidities and must also be highly motivated to receive TBu/ASCT. The increased age limit is supported by studies showing reasonable outcomes and tolerability of high dose therapy and ASCT for patients over age 65 years. For example, Schorb and colleagues reported TRM of only 3.8% and 2 year PFS of 80% for front-line and 54% for 2nd line thiotepa-based high dose therapy and ASCT in 52 PCNSL patients aged 65-77 years (median 68)233. MATRIX could, however, be used for transplant-eligible patients who refuse transplant.

Recommendations: PCNSL Transplant-Ineligible

There is no current standard of care for elderly PCNSL. We previously recommended high dose methotrexate in combination with high dose cytarabine with or without WBRT consolidation. In a recent review of our local data, of the 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 of methotrexate and cytarabine (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%. Based on these results and the poor quality of life associated with repeated hospitalisations for methotrexate, we propose an outpatient regimen of cytarabine, rituximab and thiotepa for patients who are unfit for transplant but motivated to attempt intensive therapy. This regimen should be considered for patients who are ECOG 0-2 and ambulatory. All other non-transplant eligible patients should be offered WBRT and or palliation alone.

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. Cytarabine, Rituximab and Thiotepa x 2-4 cycles
    b. MATRIX x 2-4 cycles.
    c.

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[275,304]*:* 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[275,304]*:* 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[275,305]*:*

- 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.

Aggressive T-Cell Lymphomas:

NK/T-cell lymphoma, nasal type[306-314]

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[309].

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[307,315]:

- 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 (ENKTCL), early or upfront radiotherapy (intensive regimens such as a total dose ≥ 50 Gy) plays an essential role in therapy, and has been associated with higher overall survival and complete response rates compared to chemotherapy alone[310]. However, radiotherapy alone is also associated with high relapse rates. Combined modality therapy is recommended with sequential and concurrent chemo-radiotherapy regimens having relatively equivalent outcomes. No standard of care therapy exists for ENKTCL and most novel regimens incorporate L-asparaginase into treatment due to high single agent activity.[316] Given the recent discontinuation of L-asparaginase, we favour the combination of peg-asparaginase with gemcitabine and oxaliplatin (P-GEMOX) for patients with limited stage disease. With this approach, treatment is initiated with 2 cycles of P-GEMOX, followed by radiotherapy (48-56 Gy) followed by 2 further cycles of P-GEMOX restarted 1 week after completion of radiotherapy. Radiotherapy may be introduced earlier in the therapy if feasible and early referral for radiotherapy is recommended for all patients with limited stage ENKTCL. With this approach, in 33 patients, the ORR was 94% and 2 year PFS and OS were 77% and 83% respectively. Notably, Grade 3-4 toxicities were rare.

For patients with stage III-IV disease, complete remission rates are less than 15%, and the median overall survival is approximately 4 months[314]. 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[317-319]. 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)[317]. While the GOLD regimen has less reported patients, the toxicity is significantly less (Grade 3-4 neutropenia of 16% compared to SMILE of 92%[318] with serious infections in 4% and 31-45%[317,318] 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 because of limited data; but it is suggested when possible for advanced stage or relapsed/refractory patients.

Early phase data suggests efficacy of the checkpoint inhibitor class (pembrolizumab) for relapsed/refractory ENKTCL. While this therapy is not funded in AB, it is the recommended approach

for patients with relapsed/refractory ENKTCL who are fit enough to consider additional therapy, if drug access can be obtained[320,321].

Peripheral T-cell lymphomas (PTCL)[322-330].
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 brentuximab-vedotin + CHP or intensification of CHOP with etoposide (CHOEP).[331]

The ECHELON-2 study was a Phase 3 trial including CD30+ (≥10% by immunohistochemistry) PTCL comparing CHOP with BV-CHP. PFS and OS were superior in the BV-CHP arm and important toxicities (including neuropathy and febrile neutropenia) were comparable between the arms. The benefit of BV appeared most pronounced in patients with ALCL who represented 70% of the trial population. Of note, patients with ALK+ ALCL were only included if their IPI was 2-5. BV-CHP is funded in Alberta for CD30+ ALCL, PTCL NOS, and AITL although the benefit is less clear in the latter two subgroups. Re-treatment with BV is funded for patients who remain progression-free for ≥6 months after BV-CHP with ORR rate 40-60% and CR rate 20-40% among patients with ALCL, PTCL NOS, and AITL who relapsed after BV-CHP[332].

The German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) analyzed results of 343 PTCL patients treated within their trials[333]. 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 CHOP plus etoposide (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)[322]. Aviles and colleagues recently reported the results of a phase III trial involving 217 patients with PTCL unspecified[323]. 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)[323].

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[323]. 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)[325]. 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[334]. 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 aaIPI risk factors)[326]. With a median follow-up of 67 months from diagnosis, the 5-year OS and PFS rates were 68% and 63%, respectively.

PTCL patients who relapse following CHOP-type induction and respond to platinum-based chemotherapy should be considered for ASCT or allogeneic HCT, depending on the duration of initial remission, depth of response to salvage therapy, age and fitness, availability of a suitable donor, and underlying histology, with patients with AITL demonstrating particular susceptibility to the GVL effect of allogeneic HCT[335].

Outcomes in r/r T cell lymphomas are very poor and early involvement of palliative care is recommended. Motivated patients could consider palliative therapies including: brentuximab vedotin, pralatrexate, hypomethylating agents or oral continuous chemotherapy. BV which is funded for patients with ALCL who have received at least 1 prior line of therapy [336] and patients with CD30+ ALCL, AITL, or PTCL NOS who have remained progression-free for ≥6 months after BV-CHP (PMID: 34921960). The prospective PROPEL trial evaluated the effectiveness of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma. N=111 patients received pralatrexate after a median 3 prior therapies (range: 1-12). The overall response rate was 29% with 11% achieving complete response. The median duration of response was 10.1 months. Median PFS and OS were 3.5 months and 14.5 months, respectively. The most common grade ≥3 AEs were thrombocytopenia (32%), mucositis (22%), and anemia (18%).[337] Romidepsin, previously funded in this space, has been withdrawn from the market and is no longer a treatment consideration. Hypomethylating agents may also have preferential activity for AITL and T follicular helper cell lymphomas and azacitidine is funded in Alberta without restriction (PMID: 38796193). ALK inhibitors are not funded in Alberta but have demonstrated promising activity in patients with r/r ALK+ ALCL[338].

Summary of treatment recommendations for PTCL.

1. Anaplastic large cell lymphoma:
    a. ALK positive: Consider CHO(E)P if IPI 0-1 otherwise BV-CHP x 6 cycles + consider HDCT/ASCT if high IPI
    b. ALK negative: IPI 0-2: BV-CHP x 6 cycles
    IPI 3-5: BV-CHP x 6 cycles + HDCT/ASCT if eligible
2. All other subtypes of PTCL:
    - <60 years of age with IPI=0-2: CHOEP x 6 cycles
    - <60-70 years of age with IPI=3-5: CHOP or BV-CHP x 4 cycles, then HDCT/ASCT

- >70 years of age: CHOP,CEOP or BV-CHP x 6 cycles

3. NK/T-cell lymphoma, nasal type:
   - recommendation for stage I-II NK/T cell lymphoma: P-GEMOX x 2 cycles (then IFRT (48-56 Gy) then 1 week later, 2 further cycles P-GEMOX (total 4 cycles)[339]
   - SMILE for advanced stage ENKTCL patients fit to consider this intensive, inpatient regimen[340]

AIDS-related lymphomas:[341-346]

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)[347,348]. PTLD and its treatment cause a high rate of mortality and graft loss in patients with solid organ transplants (SOT)[349]. 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[350-352]. 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[353]. 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[354,355] and the proportion of EBV-positive vs. -negative PTLD has decreased[356], 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[357]. Several small case series have confirmed that PET-CT is an effective imaging modality for staging in PTLD[358-363]. 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[364-366]. 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[364]. A recommended strategy is to

discontinue antiproliferative agents and reduce the calcineurin inhibitor by 25-50% while maintaining the steroid[364]. Published response rates vary widely (0-73%) and responses are seen within 2 to 4 weeks[367-369].

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[364-366] (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[367,370]. Some experts consider surgical resection of isolated GI lesions prior to initiating systemic therapy to reduce early mortality from bowel perforation[365]. Radiation alone is generally not curative, with exception of plasmacytoma-like PTLD[371], and should not be used as primary treatment[364]. Radiation may be used for palliating obstructive or compressive symptoms where systemic therapy fails or is not possible[364].

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%[372-376].

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[377-380]. 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[381]. 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[382]. 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[383].

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 ($p<0.001$)[384,385]. A strategy employing 6 cycles of RCHOP has not been investigated. Fit patients who have tolerated RCHOP x 4 cycles can be considered for a total of 6 cycles as per standard de novo DBLCL treatment.

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).

Patients with late onset and/or EBV-negative PTLD who are fit at time of DLBCL diagnosis can be considered for standard de novo DLBCL therapy (6 cycles of RCHOP).

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[386]. Patients with acceptable renal function and performance status should be offered high-dose methotrexate and rituximab, and others may benefit from palliative radiation[365,386].

3c. *Burkitt Lymphoma PTLD.* Several case series cite acceptable outcomes in this rare subtype of PTLD with chemotherapy regimens ranging in intensity[387-389]. However, no definite recommendations can be made and treatment should be considered individually.

3d. *CD20-negative monomorphic PTLDs.* Rare subtypes of PTLD that resemble non-transplant lymphomas, such as Hodgkin Lymphoma-like PTLD, T cell monomorphic PTLD, plasmablastic PTLD and plasma cell dyscrasias, require specific chemotherapeutic treatment similar to their non-transplant counterparts (reviewed by[364,365]).

4. *Prognosis.* The risk of death from NHL is significantly higher in SOT compared to non-transplant patients[390], and PTLD increases the graft failure rate 5-fold[391]. Retrospective series of PTLD post-SOT report OS of 30-68% at 5 years, with excess mortality in the first year post-diagnosis[350,355,392-394]. 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[354,355,378,394-396]. Risk factors for worsened OS in the PTLD-1 prospective trial include IPI 3-5, thoracic organ transplant and lack of CR after rituximab monotherapy[383]. A prognostic score developed from 500 PTLD 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 PTLD, both of which carried an adverse prognosis, but the score maintains its ability to discriminate risk groups in the whole population[391].

Table 8. Post-Transplant Lymphoproliferative Disorders in Renal Transplant Prognostic Score (148). (One point is given for each of elevated LDH, disseminated PTLD (ie. higher than stage 1), monomorphic PTLD, and serum creatinine level >133 µmol/L; 2 points are given for creatinine >133 µmol/L if age > 55 at PTLD 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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IV. Cutaneous Lymphomas[1-25]

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

Disease entity	Subtype	Minimum diagnostic workup	Other useful diagnostic tests
Primary Cutaneous T-Cell Lymphomas			
Mycosis fungoides (MF)	• Classic MF* • Folliculotropic MF • Pagetoid reticulosis • Granulomatous slack skin disease	Clinico-pathological correlation supported by immunohistochemistry (CD3, CD4, CD8, CD30) and clonality by TCRr Large cell transformation (>25%) to be noted if present	• IHC: CD2, CD5, CD7, PD1 • DUSP22-IRF4 translocations (tumor stage)[1]
Sezary's syndrome (SS)		Clinico-pathological correlation supported by: • skin biopsy (IHC and TCRr) • blood: CD4/CD8 ratio (FC), clonality byTCRr or TCRVbeta chain Abs	PD-1 (IHC and FC) Blood: CD5, CD7, CD26, CCR4, CD158k, Sezary cell absolute count in blood smear
Primary cutaneous CD30+ lymphoproliferative disease	• lymphomatoid papulosis (LyP, types A,B,C,D,E) • pcALCL (anaplastic large cell lymphoma)	Typical skin lesions and histopathology • IHC: CD3, CD4, CD8, CD30, ALK ,EMA	• IHC:CD2,3,5,CD7,CD15, TIA-1, granzymeB, CD56, betaF1, MUM-1 • FISH: 6p25 rearrangement (DUSP22-IRF4) • TCRr
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)		Typical skin lesions and histopathology • IHC: CD3, CD8,CD4,TIA-1 , CD56, CD30, EBER • TCRr	• IHC: granzyme B, TCR-gamma.(-)1 βF1,
EBV-associated T-cell especially extranodal NK/T cell lymphoma	nasal type angioimmunoblastic hydroa vacciniforme-like lymphoproliferative disorder	• EBER by ISH • CD3,CD56,CD4,CD8, CD2,CD5,CD7 • EBV antibody profile and DNA load • TCR and IgH clonality status	IHC: TIA-1, granzymeB, CD56, CD21,PD-1, CXCL13, CD10, bcl-6, CD20
Primary cutaneous acral CD8+ lymphoma		Typical skin lesions and histopathology • IHC: CD4,CD8,CD3, CD2,CD7 7 • TCRr	IHC: TIA-1 granzymeB,perforin, KI67, βF1
pc CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma		Typical skin lesions and histopathology • IHC: CD2, 3, 4, 5, 7, 8, 15, 30, 45RA, TIA-1, CD56, betaF1, EBER by FISH • TCRr	• IHC: TCR-gamma, granzymeB, perforin
pc gamma-delta T-cell lymphoma		• IHC: CD2, 3, 4, 5, 7, 8, 30, 45RA, TIA-1, CD56, betaF1, EBER by ISH • TCRr	• IHC: TCR-gamma, granzymeB,perforin
pc CD4+ small/medium cell T-cell lymphoproliferative disorder		• Clinical picture,sudden • CD4, CD8,CD3, PD-1, CD30,CD7, CD56,TIA-1, CD20	• IHC: CXCL13,BCL6

*not included in formal WHO classification of pc lymphomas

[1] 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
Primary Cutaneous B-Cell Lymphomas			
pc follicle center lymphoma (pc FCL) pc diffuse large B-cell lymphoma, leg type		• Typical skin lesions and histopathology—R/O EBV+ mucocutaneous ulcer • IHC: CD3, CD5, CD20, CD10, bcl-2, bcl-6, MUM-1, kappa/lambda • Ig rearrangement	-CD30, CD138, FOX-P1, EBER by ISH (in DLBL), Ki-67, Cyclin D1,CD79a,CD21, CD23 -MYD88L265P mutation in DLBLLT
Other Lymphomas Presenting In The Skin (Not Included In Who2016 Classification)			
Intravascular B-cell lymphoma	• Intravascular B-cell lymphoma* • Intravascular NK/T cell lymphoma* • CD30+ lymphoma	Variable clinical presentation; diagnosis based on histopathology and IHC • IHC: CD2, CD3, CD5, CD20, CD79a, CD10, bcl-2, bcl-6, MUM-1, kappa/lambda, CD56, CD30, betaF1, EBER1, TIA-1, granzymeB, ALK-1 • Ig rearrangement • TCRr	
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 • IHC: CD2, CD3, CD7,CD5, CD4, D8, CD20, CD79a, CD56, CD123, TIA-1, TdT, CD34,TIA-1, perforin, CD117, myeloperoxidase,lysozyme • Ig rearrangement • TCRr • EBER and LMP1	granzymeB, TCL-1, CD303 TCR-gamma, βF1
Adult T-cell leukemia lymphoma	Smoldering and chronic forms are skin-presenting illnesses with mild systemic signs	• CD4,CD25,CD8,CD3,CD7,CD2,CD5, CD52,CD30 • HTLV1 serology /integration status	FOXP3 by IHC
T_{FH} 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		• Typical skin lesions and histopatholgy • IHC: CD3, CD5, CD20, CD10, bcl-2, bcl-6, MUM-1, kappa/lambda(IHC or FISH) • Ig rearrangement	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)

Classification	Description	Comments
T (skin)		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.
T0	No clinically and/or histopathologically suspicious lesions	
T1 **T1a** patch only **T1b** plaque +/- patch	Limited patches, papules, and/or plaques covering <10% of the skin surface.	
T2 **T2a** patch only **T2b** plaque +/- patch	Patches, papules or plaques covering => 10% of the skin surface.	
T3	One or more tumors (=>1-cm diameter)	
T4	Confluence of erythema covering =>80% body surface area	
N (lymph nodes)		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.
N0	No clinically abnormal peripheral lymph nodes	
N1 **N1a – clone negative** **N1b – clone positive**	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2.	
N2 **N2a – clone negative** **N2b – clone positive**	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3	
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative	
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation	
B (peripheral blood)		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
B0 **B0a – clone negative** **B0b – clone positive**	Absence of significant blood involvement: =<5% of peripheral blood lymphocytes are atypical (Sézary) cells	
B1 **B1a – clone negative** **B1b – clone positive**	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2	
B2	High blood tumor burden: _=>1000/uL Sezary cells with positive clone	
M (visceral organs)		For viscera, spleen and liver may be diagnosed by imaging criteria
M0	No visceral organ involvement	
M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)	

Table 3. Staging of mycosis fungoides and Sezary's syndrome[26-29]

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_1	1-4	0-2	0	2	41
IVA_2	1-4	3	0	0-2	23
IVB	1-4	0-3	1	0-2	18

Staging procedures for Mycosis Fungiodes/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-α, 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 availabilty 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[30]. The following table intends to summarize a managment approach.

Table 4. Treatment of mycosis fungoides[1, 2, 7-9, 12, 14, 24, 30-33]

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[19, 23, 25, 34]

Table 5. Diagnostic workup and staging

Classification		Description
T	T1	Solitary skin lesion
		• T1a: a solitary lesion with diameter <5cm
		• T1b: a solitary lesion with diameter >5cm
	T2	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
	T3	Generalized skin involvement
		• T3a: multiple lesions involving 2 noncontiguous body regions
		• T3b: multiple lesions involving 3 or more body regions
N	N0	No clinical or pathologic lymph node involvement
	N1	Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement
	N2	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
	N3	Involvement of central lymph nodes
M	M0	No evidence of organ disease
	M1	Extracutaneous organ disease

Staging of other types of non-MF cutaneous lymphomas

Table 6. Diagnostic workup

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

Treatment of other types of non-MF cutaneous lymphomas[3, 4, 6, 10, 11, 13, 17, 18, 20-22, 35-39]

Table 7. Treatment of other types of cutaneous lymphomas

CTCL Subtype	First line treatment	Second or third line treatment
Lymphomatoid papulosis • Solitary lesion • Large/stigmitizing lesion • Multifocal	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 • Solitary lesion • Multifocal or frequently recurrent • Extracutaneous involvement	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 • Associated hemophagocytic syndrome	Systemic corticosteroids, alone, or in combination with methotrexate CHOP or CEOP x 6 +/- HDT-ASCT in eligible patients	Cyclosporine § Vorinostat¶ Local radiotherapy Oral Bexarotene[1]
Primary cutaneous acral CD8+ T-cell lymphoma *Provisional entity*	Intralesional corticosteroids Local radiotherapy	
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder • If tumour rapidly growing or > 5cm, High Ki67	Observation Topical corticosteroids Intralesional corticosteroids Local radiotherapy	Local radiotherapy
Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma *or* Primary cutaneous **γδ** T-Cell lymphoma	Multiagent chemotherapy (CHOP or CEOP) plus IFRT 30Gy/10 or 45Gy/25	Vorinostat¶ HDT/ASCT *or* Allogeneic stem cell transplantation in eligible candidates
Blastic plasmacytoid dendritic cell neoplasm (CD4+/CD56+ hematodermic neoplasm)	Multiagent chemotherapy (CHOP or CEOP) Acute lymphoblastic leukemia type protocol if concurrent bone marrow involvement Allogeneic stem cell transplantation	Single agent chemotheraoy (Gemcitabine) Local radiotherapy

	in first remission for eligible patients	
Primary cutaneous extranodal NK/T cell lymphoma, nasal type	Combined Modality (CHOP or CEOP plus IFRT) for localized presentation SMILE or equivalent for advanced stage	HDT-ASCT in eligible patients with relapsed/refractory
Primary Cutaneous Marginal Zone Lymphoma *or* Primary Cutaneous Follicle Center Lymphoma		
• Solitary lesion	Surgical excision Local radiotherapy (15-35Gy)	Intralesional corticosteroids Intralesional rituximab (5-20mg per lesion q4week x 3-6 cycles)*
• Multifocal lesions	Observation Chlorambucil Rituximab monotherapy*	Treat as systemic (R-Bendamustine x 6)
• *B. burgdorferi* associated pcMZL	Antibiotics (cephalosporin or doxycycline)	
Primary cutaneous large B cell lymphoma, leg type	R-CHOP x 6 +/- IFRT IFRT +/- rituximab monotherapy* if frail	

- 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[8, 9, 14, 40-49]:

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 allogenic 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 (≥ 4 times the size of a small lymphocyte) in 25% of 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[26].

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 it is unclear which patients benefit from this approach.

Several clinical and pathological characteristics in LCT-MF have been associated with poor prognosis[28, 31], 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 considering 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%[35]. 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 atleast 4 months with brentuximab (56.3% versus 12.5%)[39]. 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 folllowing chemotherapy.

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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 B-Cell Hodgkin lymphoma, CD20, CD45, +/- CD57 are recommended.

Table 1. WHO classification of histologic subtypes of Hodgkin lymphoma[1]

Classical - Nodular Sclerosis - Mixed Cellularity - Lymphocyte Rich - Lymphocyte Depleted Nodular Lymphocyte Predominant B-Cell Lymphoma

Staging

Mandatory staging procedures include[2-8]:

- 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 is preferred as initial staging and after 2 cycles of ABVD[9-14].
- 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[15-19]

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, BV-AVD, or escalated BEACOPP or escalated BPDac 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 (≥ 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 4) BV-AVD x 6 cycles for advanced stage disease. 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[20]. 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)[21]. There were higher rates of hematologic toxicities, grades 3-4 infections and higher rate of AML/MDS in the escBEACOPP group, but not an increase in all second malignancies. A meta-analysis of 4 subsequent phase III trials confirmed superior PFS and long term OS with escBEACOPP compared to ABVD[22, 23].

The German Hodgkin Study Group recently published the results of their HD15 prospective randomized clinical trial[24]. 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 escBEACOPP ($8B_{esc}$), 6 cycles of escBEACOPP ($6B_{esc}$), or 8 cycles of $BEACOPP_{14}$ ($8B_{14}$). After a median follow-up of 48 months, there were 53 deaths (7.5%) in the $8B_{esc}$ group, 33 (4.6%) in the $6B_{esc}$ group and 37 (5.2%) in the $8B_{14}$ group. The higher number of deaths in the $8B_{esc}$ 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 $8B_{esc}$ group, 2 (0.3%) in the $6B_{esc}$ group and 8 (1.1%) in the $8B_{14}$ group. Five year OS rates were 91.9% in the $8B_{esc}$ group, 95.3% in the $6B_{esc}$ group, and 94.5% in the $8B_{14}$ group. PET scans performed after chemotherapy for 822 patients revealed that 739 were in PR with residual mass ≥ 2.5 cm. 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[24].

In an attempt to reduce severe toxicities associated with escBEACOPP, an open-label, randomized, parallel-group, phase 3 trial (HD18) investigated the utility of PET after 2 cycles of standard escBEACOPP to allow for adaptation of treatment intensity[25]. 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 × escBEACOPP in total) or escBEACOPP with rituximab (8 × 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 × escBEACOPP… the trial switched from total 8 to total 6 escBEACOPP in the standard arm after the results of HD15) or experimental treatment with 2 additional cycles only (total = 4 × 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 total 4 escBEACOPP in patients who achieve PET- negative disease after 2 cycles of escBEACOPP.

Data Supporting Replacement of Procarbazine with Dacarbazine in escBEACOPP.
Procarbazine and dacarbazine are both guanine methylation agents with similar mechanisms of action. Dacarbazine is thought to be less gonadotoxic and less hematotoxic than procarbazine. The pediatric EuroNet-PHL-C1 study[26] was an open-label, non-inferiority, randomized controlled trial of children and adolescents with intermediate and advanced stage Hodgkin's lymphoma. 937 patients were randomized 1:1 to receive COPP or COPDAC (COPDAC is identical to COPP, except that procarbazine is replaced with dacarbazine). In the per-protocol analysis, event-free survival at 5 years was 89.9% for COPDD vs. 86.1% for COPDAC (difference -3.7%, 95% CI -8.0% to +0.6%). Overall survival rates at 5 years were similar (98.1% for COPP vs. 98.9% for COPDAC). Fertility outcomes were much improved in the COPDAC group, with 19 (83%) of 23 analyzed males in the COPP group having azoospermia at a median of 40 months follow-up, vs 0 of 22 males in the COPDAC group ($p<0.0001$). Rates of premature ovarian failure were also lower in the female patients who received COPDAC.

On the basis of interim results from the EuroNet-PHL-C1 study, it has become increasingly common practice in Europe to use escBPDac, (e.g. escBEACOPP, but with procarbazine replaced with dacarbazine), for adult patients. Retrospective data published by Santasieri et al. (N=225)[27] showed that, compared to 58 matched escBEACOPP controls, patients treated with escBPDac required fewer non-elective days of inpatient care (mean 3.35 vs. 5.84 days, $p=0.022$), fewer pRBC transfusions (mean 1.79 vs. 4.16 units; $p<0.001$), and had earlier return of menstruation (mean 4.64 vs. 9.12 months; $p=0.0026$). Efficacy was also similar to historical controls from the HD18 and RATHL trials, with 77% of patients achieving a Deauville score of 3 or less on their interim PET2, and with a 22-month PFS rate of 94.9%. Santasieri et al.[28] also published whole genome sequencing data from patients exposed to either escBPDac or escBEACOPP, which strongly suggested that patients treated with escBPDac have a much lower rate of potentially oncogenic mutations in their hematopoietic stem cells (mean 291 excess mutations in escBPDac patients, compared to 1153 excess mutations in escBEACOPP patients).

Based on the above data, we recommend modifying escBEACOPP to escBPDac, by replacing procarbazine with dacarbazine.

Due to concerns of toxicity, escBEACOPP/escBPDac in Alberta should only be considered for the following patients[2, 21, 22, 29-33]:

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

Data Supporting Replacement of escBEACOPP with BrECADD

BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) has been compared to escBEACOPP among 1500 patients 18-60 years old with high-risk stage II or advanced stage HL in the HD21 trial. BrECADD resulted in a similar rate of iPET2-negativity (64% versus 64%) and superior 4-year PFS (94% vs 91%, p=0.035) with similar 4-year OS (99% vs 98%) compared to escBEACOPP. In addition, BrECADD was associated with less grade 4 hematologic toxicity, less febrile neutropenia, lower transfusion requirements, less neuropathy, and improved gonadal recovery and higher birth rates compared to escBEACOPP[34].

Of note, patients receiving escBEACOPP or BrECADD should have once-twice weekly CBCs to assess for severe cytopenias requiring dose reduction. A dose level reduction is recommended for patients who develop 1 or more toxic events in a given cycle: WBC <1 for >4 days, thrombocytopenia <25, grade 4 infection or other toxicities, or treatment delay >2 weeks due to inadequate recovery of blood counts:

Table 2: Dose levels for BrECADD

Full dose, dose level 4			
Cyclophosphamide	1250 mg/m^2	i.v.	Day 2
Doxorubicin	40 mg/m^2	i.v.	Day 2
Etoposide	150 mg/m^2	i.v.	Day 2-4
Dose level 3			
Cyclophosphamide	1100 mg/m^2	i.v.	Day 2
Doxorubicin	40 mg/m^2	i.v.	Day 2
Etoposide	125 mg/m^2	i.v.	Day 2-4
Dose level 2			
Cyclophosphamide	950 mg/m^2	i.v.	Day 2
Doxorubicin	40 mg/m^2	i.v.	Day 2
Etoposide	100 mg/m^2	i.v.	Day 2-4
Dose level 1			
Cyclophosphamide	800 mg/m^2	i.v.	Day 2
Doxorubicin	40 mg/m^2	i.v.	Day 2
Etoposide	100 mg/m^2	i.v.	Day 2-4

Data Supporting Brentuximab vedotin for Primary Therapy of Hodgkin Lymphoma [36]
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 (BV+AVD) or ABVD. PFS outcomes favored BV-AVD over ABVD. At a median follow-up of 72.6 months, the 6-year progression-free survival estimates were 82.3% with BV-AVD and 74.5% with ABVD (hazard ratio for disease progression or death, 0.68; 95% CI, 0.53 to 0.86)[35].

Neutropenia was higher in the BV+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 BV+AVD group (67% vs. 43%), with resolution at last follow-up in 2/3 of patients. Pulmonary toxicity ≥grade 3 occurred in 1% of BV+AVD patients vs. 3% in ABVD. Updated 6-year OS data favour BV-AVD over ABVD with estimated OS rates of 93.9% (95% CI, 91.6 to 95.5) vs 89.4% (95% CI, 86.6 to 91.7), respectively.

Currently, Health Canada restricted approval to patients with Stage 4 disease, who are thus, the only patients currently eligible to receive this therapy in Canada. With the favourable OS data, BV+AVD should be considered in patients with stage IV HL. There are no direct comparisons of BV+AVD vs escBEACOPP/BPDac or BrECADD. For stage 4 HL, both BV+AVD and BrECADD are considered highly curative treatment options. Patient factors, such as age, comorbidities, toxicity concerns (specifically neuropathy with BV-AVD or myelosuppression with BrECADD), and length of treatment should factor into clinical decision making.

Data Supporting a PET-Guided Treatment Approach[36-39]

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 of 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 the -7% non-inferiority margin. Of interest, the per-protocol PFS was 97% vs 90.8% because 26 pts did not get their 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 to omit RT may be recommended depending on the age of the patient and sites of disease, 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. Recently reported long follow up of this trial, showed that at a median follow up is 87.2 months (IQR 63.0 - 104.0), the overall PFS at 7 years is 78.2% (95% CI 75.6 - 80.5) and overall survival (OS) 91.6% (95% CI 89.7 - 93.2). PFS at 7 years for ABVD was 81% (95% CI 76.9 - 84.4), and for AVD 79.2% (95% CI 75.1 - 82.8), HR: 1.10 (95%CI 0.82 - 1.47)[40].

- Results reliably exclude a 5% inferior 3 year PFS following de-escalation (omission of bleomycin for cycles 3-6) after a negative interim PET-CT, with no evidence of a later divergence.
- For those with a positive PET2, intensified therapy with escBEACOPP is effective and safe, with no evidence of an increase in second malignancies by comparison with the group who received ABVD/AVD.

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%. As mentioned, the HD21 trial confirmed that PET-directed BrECADD is more effective and better tolerated than escBEACOPP.

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

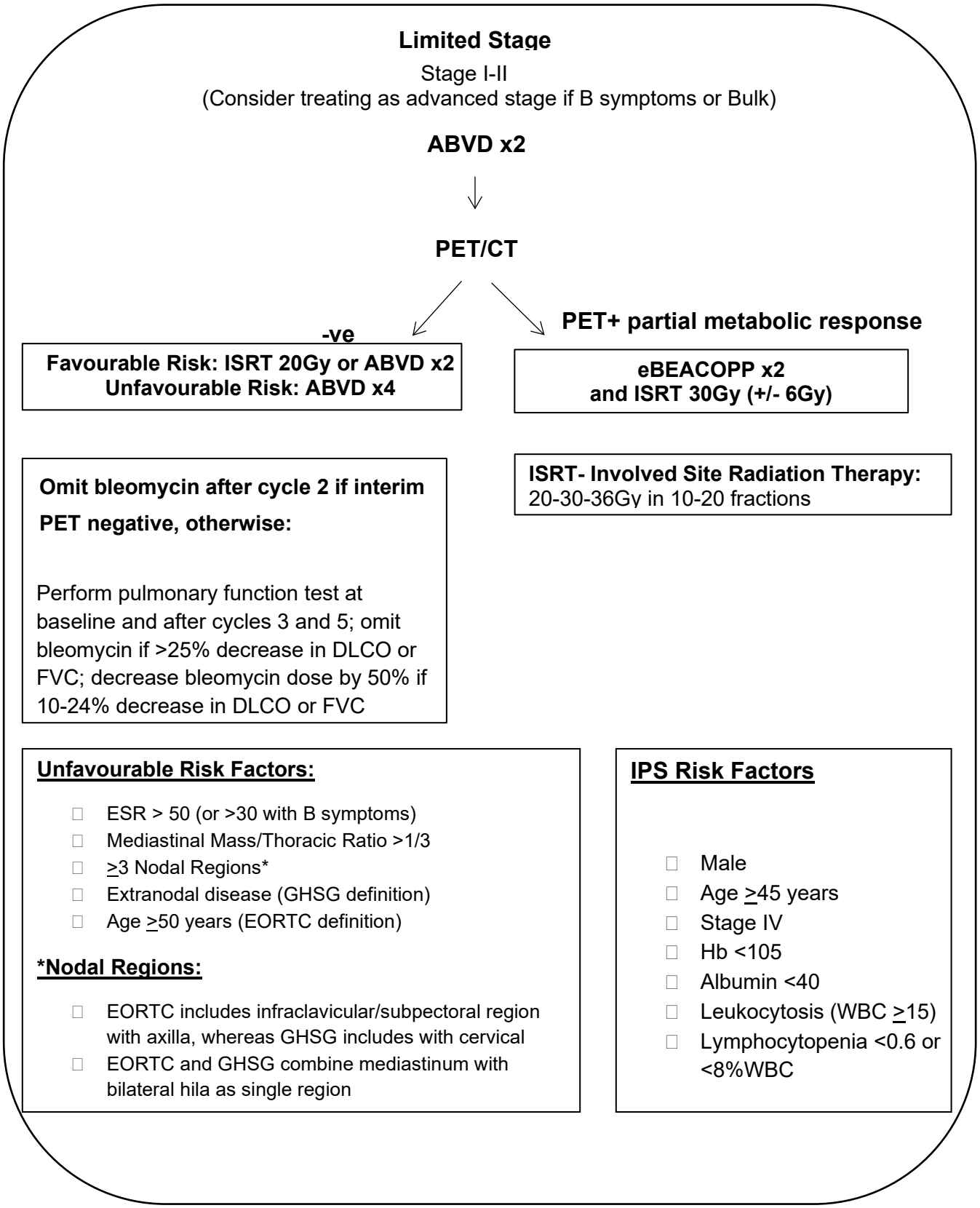
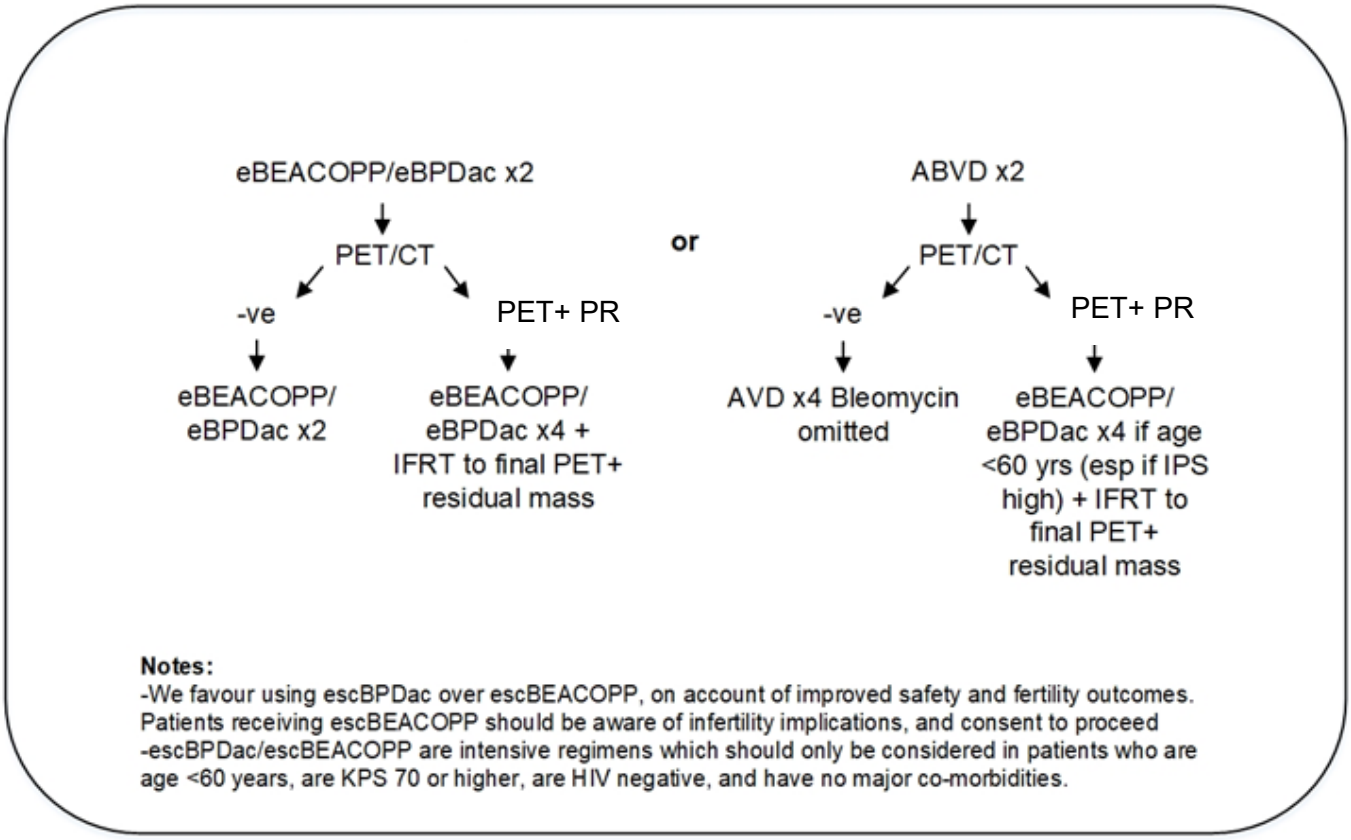


Figure 2: Treatment Aglorithm for bulky stage II, stage IIB, or stage III Hodgkin lymphoma using PET-guided therapy



PET+ patients are those who achieve a partial remission to therapy but maintain FDG-avidity of Deauville 4. Patients with stable or progressive disease on interim PET scan have refractory Hodgkin lymphoma and should be followed as per "Management of Recurrent Lymphoma".

Table 3: Treatment options for stage IV Hodgkin lymphoma

	BV-AVD	BrECADD
Treatment schedule	Fixed course treatment Every 2 weeks x 6 months No interim PET	Interim PET2 directed IV chemo days 1-3 every 3 weeks x 12 weeks if iPET2-neg (64%) x 18 weeks if iPET2-pos (36%)
Cumulative dose of BV	14.4 mg/kg	7.2 mg/kg (4 cycles) 10.8 mg/kg (6 cycles)
Efficacy	6-year PFS 82%	4-year PFS 94%
Notable toxicities	Neuropathy 67% Febrile neutropenia 19% (11% with G-CSF) Second cancer 4% at 6y	Neuropathy 43% Febrile neutropenia 21% (G-CSF required) Second cancer 3% at 4y Patients >60 yo excluded from HD21

Management of Recurrent Hodgkin Lymphoma[2, 41-56]:
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± IFRT 20-30Gy to prior bulk site at relapse, or PET-positive residual disease post-ASCT
- Brentuximab vedotin consolidation post-ASCT for patients with primary refractory HL, relapse within 12 months or extranodal disease at relapse
- Pembrolizumab iv q3-6 weeks for older/unfit patients who are deemed ineligible for ASCT

Second or subsequent relapse.
- IFRT if localized relapse in previously non-irradiated site
- A PD1-inhibitor (e.g. Nivolumab or Pembrolizumab) after prior failure of chemotherapy (and autologous SCT in transplant eligible patients) [data suggests longer remissions with PD1-inhibitor compared to Brentuximab vedotin making PD1i then BV the preferred sequencing)
- Brentuximab vedotin IV q21d for up to 16 doses if prior failure of initial chemotherapy (ABVD or BEACOPP) and prior autologous SCT (excluding patients who progress on BV consolidation post-ASCT)
- Palliative chemotherapy for symptomatic patients (GDP, COPP, ChlVPP, CEPP, vinblastine)
- Allogeneic SCT is a curative option for fit patients who have exhausted other therapies, resulting in a 2-year PFS 69% in the immune checkpoint inhibitor era (PMID: 33658659).Given that the outcomes of allogeneic SCT are highly dependent on disease status at the time of transplant, eligible patients should be referred for discussion of allogeneic HCT when starting their second novel agent (i.e. checkpoint inhibitor or BV). For patients with highly refractory disease or short duration of remissions, consider using the second novel agent to achieve a response as a bridge to allogeneic HCT. Other patients who achieve a complete response to the second novel agent may

reasonably defer allotransplant to the next relapse provided that effective bridging therapy is expected to be available

Brentuximab vedotin (BV) monotherapy [57-59]:
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 transplantion 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.

Consolidation with Brentuximab Vedotin after ASCT.
The AETHERA clinical trial evaluated a strategy of consolidation with brentuximab vedotin after autologous stem cell transplantation in high risk relapsed Hodgkin lymphoma patients. Patients were eligible for BV if they were either: refractory to frontline treatment, relapsed < 12months after frontline therapy, or relapsed >= 12 months with extranodal involvement. Patients were randomized to receive either BV (1.8mg/kg every 3 weeks for up to 16 cycles) or placebo. 5 year PFS was 59% for BV versus 41% for placebo. PFS benefit was most pronounced for patients who were PET+ before ASCT or those with >1 risk factor. Grade 3-4 peripheral motor and sensory neuropathy was observed in 6 and 10% of patients receiving BV consolidation, however, improves or resolves in the majority of patients.

PD1-inhibitors[60]:
The open-label phase III Keynote-204 study compared pembrolizumab (n=151) versus brentuximab in relapsed or refractory classic Hodgkin lymphoma, with the dual primary end points of PFS and OS. The interim analysis did not include OS data, however, with a median follow-up after randomization of 25.7 months, median PFS was 13.2 months (95%CI: 10.9-19-4) for pembrolizumab versus 8.3 months (95%CI: 5.7-8.8) for brentuximab vedotin (HR: 0.65; 95%CI: 0.48-0.88; p=0.003). Serious treatment-related AEs occurred in 16% of pembrolizumab patients and 11% of brentuximab vedotin patients. Grade 3-5 treatment-related adverse events were: pneumonitis 4% in the pembrolizumab group vs 1% in the brentuximab vedotin group, neutropenia 2% vs 7%, decreased neutrophil count 1% vs 5%, and peripheral neuropathy 1% vs 3%, respectively. The study included patients who had relapsed after

ASCT and patients who were ASCT-ineligible making PD1 inhibition the preferred secondline therapy for non-transplant eligible patients and the preferred third line therapy for patients who relapse post-ASCT.

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). 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). Most common grade 3-4 AEs included lipase increases (5%), neutropenia (3%), and ALT increases (3%).

Nodular Lymphocyte Predominant B-Cell Lymphoma[61]

This rare subtype of B cell lymphoma typically has a very indolent course with excellent survival. This entity was formerly called “Nodular Lymphocyte Predominant Hodgkin Lymphoma” (NLPHL), but recently, major biological and clinical differences with classic Hodgkin lymphoma have led to this name change in the 2022 ICC classification[62]. The 5th edition of the WHO classification continues to use the term “Nodular Lymphocyte Predominant Hodgkin Lymphoma” but considers the new nomenclature acceptable in preparation for future definitive adoption[63].

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 or to T-cell/histiocyte-rich large B-cell lymphoma (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.

The diagnosis of nodular lymphocyte predominant B-cell lymphoma may sometimes require excisional lymph node biopsy that may remove all gross disease, in which case observation alone can be considered after staging with PET-CT. In terms of treatment recommendations, patients with residual but localized nodular lymphocyte predominant B-cell lymphoma (stage 1-2A with ≤2 contiguous sites of disease) should be offered involved-site radiotherapy (ISRT)[64]. Patients with Stage 1B or more advanced stage 2A/B 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 if asymptomatic or chemoimmunotherapy (e.g. 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, variant histology, 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 nodular lymphocyte predominant B-cell lymphoma who have serious co-morbidities that would preclude the use of combination chemotherapy.

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VI. Hematopoietic Cell Transplantation and Cell Therapy for Lymphoma

Eligibility for hematopoietic cell transplantation (HCT) for lymphoma

- Patients are generally considered eligible for autologous stem cell transplant (ASCT) or allogeneic HCT if they are less than approximately 75 years old and have controlled disease status (e.g. complete or partial response), a good performance status (e.g. ECOG 0 or 2), no serious uncontrolled infections, and adequate organ function. Note that these are general recommendations rather than absolute contraindications and that eligibility for HCT must be determined on an individual basis.
- To ensure engraftment, recipients of ASCT should have >$2x10^6$ CD34+ cells/kg collected and recipients of allogeneic HCT should have >$3x10^6$ CD34+ cells/kg collected

Eligibility for chimeric antigen receptor (CAR)-T cell therapy for lymphoma

- Axicabtagene autoleucel is approved as second-line therapy for diffuse large B-cell lymphoma (DLBCL) which is refractory or has relapsed within 12 months of completion of first-line therapy [Funding anticipated in 2024]
- Axicabtagene autoleucel, tisagenlecleucel, and soon lisocabtagene maraleucel are approved for relapsed or refractory DLBCL after 2 or more lines of systemic therapy
    - This includes most subtypes of DLBCL, including transformed indolent lymphoma and follicular large B-cell lymphoma (previously known as follicular lymphoma grade 3B)
    - Patients with Richter transformation arising from previously-treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) are not currently eligible
    - Patients with rare subtypes of DLBCL which typically lack B-cell antigens should have demonstration of CD19 expression to be eligible for CD19-directed CAR-T
- Brexucabtagene autoleucel is approved for relapsed or refractory mantle cell lymphoma after 2 or more lines of systemic therapy including a BTK inhibitor
- Patient must also meet the following criteria:
    - Clinically stable and expected to remain so until the planned CAR-T cell infusion date with adequate organ function and performance status (ECOG 0-2)
    - No prior treatment with a CAR-T cell product targeting the same antigen
    - Patients with previous or active secondary CNS involvement are eligible for CAR-T but patients with active primary CNS lymphoma are not currently eligible

Allogeneic HCT conditioning for lymphoma

- Reduced intensity conditioning is recommended for older or less fit patients and for most patients who have heavily-pretreated lymphoma (e.g. relapse after ASCT or multiply-relapsed disease), intrinsically chemoresistant lymphomas (e.g. TP53-mutated mantle cell lymphoma or cutaneous T-cell lymphomas), or indolent lymphomas with high susceptibility to the graft-versus-lymphoma effect (e.g. CLL/SLL or follicular lymphoma)

- Myeloablative conditioning may be considered for younger fit patients undergoing first-line allogeneic HCT consolidation for high-risk chemosensitive lymphoma (e.g. certain peripheral T-cell lymphomas)

ASCT conditioning for lymphoma

Aggressive NHL (DLBCL, PTCL)	(R) + Bu(13500uM.min) + Mel(140mg/m2
Indolent NHL (FL, MZL, LPL)	(R) + Mel(180mg/m2) + TBI(5Gy x1)
Mantle cell lymphoma	(R) + Mel(180mg/m2) + TBI(5Gy x1)
Hodgkin lymphoma	Gemcitabine 1500 mg/m2 + Melphalan 200 mg/m2
Primary CNS lymphoma	(R) + Thiotepa(600mg/m2) + Bu(13500 uM.min)
Secondary CNS lymphoma	(R) + Thiotepa(500mg/m2) + Bu(13500uM.min) + Mel (100mg/m2)

Diffuse large B-cell lymphoma

- Consolidative ASCT may be considered for high-risk patients with DLBCL responding to first-line therapy, such as those with (1) high IPI score 4-5 and partial metabolic response on interim PET or (2) high-grade B-cell lymphoma with MYC and BCL2 rearrangements with IPI score 2-5[1-5]. This practice will require re-evaluation once second-line CAR-T cell therapy and novel first-line therapies are available.
- Once funded, second-line CAR-T cell therapy is recommended for eligible patients with DLBCL refractory to or relapsing within 12 months of completion of first-line chemoimmunotherapy[6-9]
- ASCT is recommended for eligible patients with chemosensitive relapse of DLBCL occurring >12 months after completion of first-line chemoimmunotherapy[10]. Examples of appropriate salvage regimens before ASCT include R-DICEP, R-GDP, R-DHAP, or R-ICE[11-15].
- Third-line CAR-T cell therapy is recommended for patients with relapsed/refractory DLBCL after >2 lines of therapy who have not previously received CAR-T cell therapy[16-19].
- Allogeneic HCT is rarely performed for DLBCL but may be considered for fit, motivated patients who relapse after CAR-T cell therapy and achieve an adequate response to pre-transplant therapy[20, 21].

Central nervous system (CNS) lymphoma

- Thiotepa/busulfan-based ASCT is recommended for eligible patients with primary CNS lymphoma responding to HD-MTX and HDAC based induction (see Lymphoma guideline)[22-27]
- Thiotepa/busulfan/melphalan-based ASCT is recommended for eligible patients with chemosensitive secondary CNS lymphoma (SCNSL), with favorable outcomes observed among those with SCNSL at diagnosis or isolated CNS relapse (see Lymphoma guideline)[28, 29]
- The prognosis of patients with early concurrent CNS and systemic relapse is poor and the optimal treatment is unclear, so these patients should be considered for ASCT or second-line CAR-T cell therapy once funded on a case-by-case basis[28-30]. Patients with SCNSL undergoing CAR-T cell therapy should receive appropriate CNS-directed bridging therapy

before infusion since outcomes appear poor if there is active CNS disease at the time of infusion[30].

- Allogeneic HCT is not well established for CNS lymphoma[31].

Transformed lymphoma

- ASCT is recommended for patients with chemosensitive transformed DLBCL if they have previously received chemotherapy for indolent B-cell lymphoma[32, 33]
- Patients who develop transformed DLBCL within 12 months of receiving R-CHOP or R-CEOP for indolent lymphoma may be considered for second-line CAR-T cell therapy once funded[6-9]. Otherwise, CAR-T cell therapy is recommended for patients with relapsed/refractory transformed lymphoma after >2 lines of therapy (e.g. 1 for indolent lymphoma and 1 for DLBCL)[16, 18, 19]
- Allogeneic HCT is rarely performed for transformed lymphoma but may be considered for fit, motivated patients who relapse after CAR-T cell therapy and achieve an adequate response to pre-transplant therapy[20, 21, 33].

Burkitt lymphoma

- Relapsed Burkitt lymphoma has a poor prognosis but ASCT or rarely allogeneic HCT may be considered for patients with chemosensitive relapses[34]

Mantle cell lymphoma

- Consolidative ASCT is recommended for eligible patients responding to first-line cytarabine-containing chemotherapy[35-40]
- Maintenance rituximab is recommended every 2 months for 3 years after ASCT[41, 42]
- CAR-T cell therapy is recommended for eligible patients with relapsed MCL after >2 lines of therapy including a BTK inhibitor[43, 44]
- Allogeneic HCT may be considered for fit, motivated patients who relapse after CAR-T cell therapy and achieve an adequate response to pre-transplant therapy[45]
- Patients with TP53-mutated mantle cell lymphoma have poor outcomes with chemotherapy and do not benefit from ASCT[46]. These patients should be prioritized for first-line allogeneic HCT or third-line CAR-T cell therapy on a case-by-case basis.

Follicular lymphoma

- Given the poor prognosis with standard chemotherapy, ASCT is recommended for eligible patients with chemosensitive relapse of follicular lymphoma occurring within 24 months of first-line treatment (POD24)[47]
- ASCT achieves durable remissions and is also a reasonable option for fit patients with first or second relapse of follicular lymphoma arising >24 months after first-line treatment[48-50]
- Once funded, CAR-T cell therapy is recommended for eligible patients with relapsed/refractory follicular lymphoma after >2 lines of systemic therapy[51, 52]

- Allogeneic HCT is rarely performed for follicular lymphoma but may be considered for fit, motivated patients who have relapsed after, or are unable to receive, ASCT and/or CAR-T cell therapy and who achieve an adequate response to pre-transplant therapy[53].

Other indolent B-cell lymphomas

- ASCT may be considered for selected patients with first or second chemosensitive relapse of MZL, LPL, or NLPBL, particularly for those with early relapses, aggressive clinical behavior, and in patients who prioritize the possibility of long-term disease control or who lack other treatment options[54-56]
- Allogeneic HCT is seldomly performed for rare indolent B-cell lymphomas but may be considered for fit, motivated patients who lack other therapeutic options and have relapsed after, or are unable to receive, ASCT and achieve an adequate response to pre-transplant therapy[57]

Hodgkin lymphoma (HL)

- ASCT is recommended for eligible patients with relapsed/refractory HL who respond to second-line chemotherapy or immune checkpoint inhibitors (ICI)[58-62]
- Maintenance brentuximab vedotin (BV) every 3 weeks for 16 cycles starting 4-6 weeks after ASCT is funded for patients with primary refractory HL, relapsed HL <12 months from the end of frontline therapy, or extranodal disease at relapse. The risks and benefits must be weighed given the lack of survival benefit and the risks of toxicity and potential overtreatment of patients already cured by ASCT. The benefit of maintenance BV may be more pronounced in patients with 2-3 risk factors or with a positive PET before ASCT[63, 64].
- Allogeneic HCT is recommended for fit, motivated patients with HL who have exhausted other treatment options[65]. Eligible patients should be referred for discussion of allogeneic HCT when starting their second novel agent (i.e. ICI or BV). For patients with highly refractory disease or short duration of remissions, consider using the second novel agent to achieve a response as a bridge to allogeneic HCT. Other patients who achieve a complete response to the second novel agent may reasonably defer allotransplant to the next relapse provided that effective bridging therapy is expected to be available. A washout period of the ICI for 6-12 weeks before allogeneic HCT is recommended to reduce the risk of GVHD[65, 66].

Peripheral T-cell lymphomas (PTCL) and natural killer-cell (NK) lymphomas

- Given the poor prognosis with standard chemotherapy, consolidative ASCT is recommended for eligible patients responding to first-line therapy with advanced stage or high IPI score PTCL NOS, angioimmunoblastic T-cell lymphoma, ALK-negative anaplastic large cell lymphoma (ALCL), advanced-stage NK/T-cell lymphoma, or enteropathy-associated T-cell lymphoma[67-73]. Although ALK-positive ALCL usually has a favorable prognosis with BV-CHP, consolidative ASCT may be considered for selected cases with a high IPI score given their poorer outcomes with standard chemotherapy and the uncertain benefit of brentuximab vedotin in this high-risk subgroup[72-75].

- First-line allogeneic HCT is recommended for eligible patients with certain poor prognosis lymphomas responding to first-line therapy, such as hepatosplenic T-cell lymphoma, acute or lymphoma-type adult T-cell leukemia/lymphoma, aggressive NK cell leukemia, and selected cases of advanced-stage NK/T-cell lymphoma[71, 73]
- ASCT is recommended for patients with relapsed PTCL who have not previously received ASCT and who demonstrate a good response to second-line chemotherapy (e.g. DICEP or GDP)[76, 77]
- Allogeneic HCT is also recommended for patients with PTCL who relapse after ASCT or who are unable to receive ASCT due to chemorefractory disease, provided that an adequate response to pre-transplant therapy is achieved[78]

Cutaneous T-cell lymphomas (CTCL)

- ASCT is not routinely recommended for patients with mycoses fungoides or Sezary syndrome (MF/SS) but allogeneic HCT may be considered for selected high-risk cases [79, 80]

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VII. Prevention and Management of Toxicities of Bispecific Antibodies in Lymphoma

Overview

Epcoritamab and glofitamab are bispecific antibodies targeting CD20xCD3 which are currently approved for patients with relapsed/refractory (r/r) large B-cell lymphoma (LBCL) after ≥2 lines of therapy who have already received or are unable to receive CAR-T cell therapy. Bispecific antibodies produce complete responses in approximately 40% of patients with median time to response of 6 weeks[1, 2]. Response assessment is therefore recommended 6-8 weeks after C1D1 of epcoritamab or glofitamab[1]. Although some delayed responses have been observed as late as 8-10 months after treatment initiation, these are unlikely to occur in patients with progressive disease at the time of first response assessment.

Bispecific antibodies result in cytokine release syndrome (CRS) in 50-60% of patients with LBCL. Severity of CRS should be determined using the ASTCT grading criteria (Tables 1 and 2)[3]. Most cases of CRS are grade 1 but 12-17% of patients develop grade 2 CRS and 3-4% develop grade ≥3 CRS. The highest risk period for CRS is after the C1D15 dose of epcoritamab or the C1D8 dose of glofitamab (Figure 1). Median time to CRS onset is 2 days after the most recent dose of epcoritamab or 20 hours after the first full dose of epcoritamab, and 13.5 hours after the C1D8 dose of glofitamab. CRS resolves within a median of 30-48 hours, although 20-30% of patients require treatment with tocilizumab and/or corticosteroids. In contrast to CRS, immune-effector cell-associated neurotoxicity syndrome (ICANS) is relatively rare with bispecific antibodies, occurring in 6-8% of patients. Neurotoxicity is usually low-grade and often consists of headaches or dizziness. Onset of ICANS is at median 16 days and median time to resolution is 5 days after epcoritamab. Prevention and treatment of CRS, ICANS, and other toxicities are summarized in tables 3-5[4].

Risk factors for CRS include high tumor burden (e.g. increased metabolic tumor volume, elevated LDH, advanced stage), peripheral blood or bone marrow involvement, older age, and comorbidities. Patients with early-onset CRS and those with CRS during the first ramp-up doses may be at increased risk of subsequent CRS or more severe CRS. All patients are required to remain within proximity of the treatment facility (where a supply of tocilizumab and ICU access must be available) for CRS and ICANS monitoring for 24 hours after the C1D15 dose of epcoritamab and for 10 hours following the 4-hour infusion of glofitamab on C1D8. Patients should have a caregiver present and be aware to seek medical attention immediately if they develop features of CRS or ICANS. Patients should have a thermometer at home to monitor temperature 3 times per day for 48 hours after each step-up dose. Home blood pressure and oxygen monitoring equipment is not mandated but may be useful if available. Alternatively, hospitalization for 1-2 days after the highest risk doses may be considered for patients at increased risk of CRS or those who are unable to reliably self-monitor as an outpatient. All patients should have a supply of acetaminophen and dexamethasone tablets on hand in case of delays to treatment of CRS as an outpatient.

Table 1: ASTCT cytokine release syndrome grading criteria

	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Yes, ≥30°	Yes, ≥30°	Yes, ≥30°	Yes, ≥30°
		with		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		with		
Hypoxia**	None	Requiring low-flow nasal cannula (≤ LPM) or blow-by	Requiring high-flow nasal cannula (>6 LPM), facemask, non-rebreather, or Venturi mask	Requiring positive pressure (CPAP, BiPAP, intubation and mechanical ventilation)

* Fever is defined as temperature ≥ 38 degrees not attributable to other cause. In patients who have CRS then receive antipyretic or anticytokine therapy, fever is no longer required to grade CRS. In this case CRS grading is driven by hypotension and/or hypoxia.

** Hypoxia should not be explained by other causes i.e. rigors or sedation in order to meet the definition of hypoxia in CRS

Table 2: ASTCT Immune Effector Cell-Associated Encephalopathy (ICE) tool and ICANS grading criteria

Symptom or sign	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9 (mild)	3-6 (moderate)	0-2 (sever)	Unable to perform
Level of Consciousness	Awakens spontaneously	Awakens to voice	Awakens to touch	Unarousable or requires vigorous or repeated stimuli to arouse, Stupor or coma.
Seizure	NA	NA	Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizure that resolves with intervention	Life-threatening or prolonged seizure (>5 minutes) or repetitive clinical or electrical seizures without return to baseline between
Motor Findings	NA	NA	NA	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/Cerebral edema	NA	NA	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or CN VI palsy; or papilledema or Cushing's

Ice tool:

- Orientation to
  - Year – 1 point
  - Month – 1 point
  - City- 1 point
  - Hospital- 1 point
- Naming 3 objects- up to 3 points
- Following Commands (e.g. Show me two fingers) - 1 point
- Writing a short sentence- 1 point
- Attention: Count backwards from 100 by 10 – 1 point

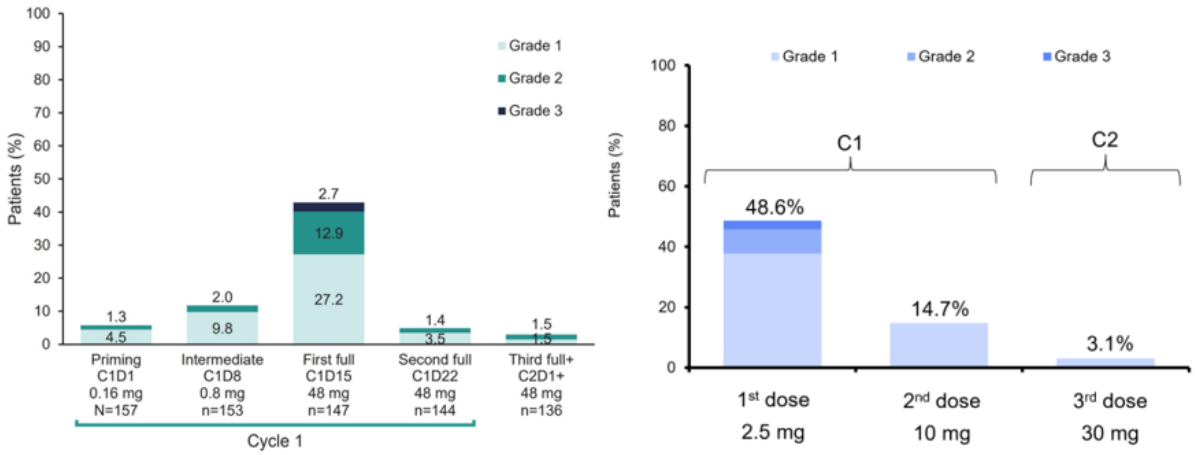

Figure 1: Onset of CRS with epcoritamab (left) and glofitamab (right) in LBCL

Table 3: Prevention and treatment of cytokine release syndrome

Grade	Recommendations for cytokine release syndrome
Prophylaxis	▪ Follow recommendations in product monograph ▪ Ensure sufficient oral or IV hydration ▪ Epcoritamab: ▪ Dexamethasone 16mg for 4 consecutive days starting on C1D1, C1D8, C1D15, and C1D22 ▪ Patients who develop grade ≥2 CRS should continue to receive dexamethasone prophylaxis into cycle 2 and beyond until epcoritamab is given without grade ≥2 CRS ▪ Acetaminophen/antihistamine before first 4 doses ▪ Glofitamab ▪ Obinutuzumab 1,000mg on C1D1 ▪ Dexamethasone 20mg on C1D8, C1D15, C2D1, C3D1 ▪ Patients who develop CRS should continue to receive dexamethasone prophylaxis with subsequent cycles until they tolerate treatment without CRS ▪ Acetaminophen/antihistamine before all doses ▪ Ensure outpatients have supply of acetaminophen and dexamethasone tablets on hand in case of delays to treatment of CRS ▪ Consider holding antihypertensives for 24 hours before high-risk doses ▪ Patients who miss treatment doses should undergo re-priming according to the product monograph
Supportive care	▪ Treat CRS with anti-pyretics, supplemental oxygen, IV fluids as needed ▪ Evaluate for and treat suspected infections with broad-spectrum antibiotics ▪ Early use of vasopressors recommended if hypotension persists after >2L of IV fluids

Grade	Recommendations for cytokine release syndrome
Grade 1	▪ Supportive care and anti-pyretics (e.g. acetaminophen) are usually sufficient ▪ Hold treatment until symptoms resolve ▪ Outpatients with grade 1 CRS should be directed to clinic or ER for evaluation on case-by-case basis ▪ Consider dexamethasone 8mg PO for outpatients, particularly if fever persists 6-8 hours after antipyretic ▪ Consider tocilizumab 8mg/kg (max 800mg) IV and/or dexamethasone 10mg IV if fever lasts >48-72 hours, especially if early onset CRS, comorbidities, or high risk for severe CRS
Grade 2	▪ Hold treatment until symptoms resolve ▪ Most patients will require inpatient evaluation and management ▪ Anti-pyretics, supplemental oxygen, IV fluids as needed ▪ Administer dexamethasone 10mg IV q6-12h ▪ Recommend tocilizumab 8mg/kg IV (max 800mg) especially if high risk for severe CRS, persistent CRS for 4-6 hours after dexamethasone, or if CRS develops during steroid prophylaxis → repeat q8h as needed up to 2 times per CRS event or 3 times in a 6-week period ▪ Consider alternative cytokine therapy (e.g. anakinra) for persistent CRS despite tocilizumab and dexamethasone
Grade 3-4 CRS	▪ Hold treatment until symptoms resolve ▪ Consider permanently discontinuing treatment for grade 4 CRS ▪ Transfer patient to ER or ICU for vasopressors and respiratory support ▪ Tocilizumab 8mg/kg (max 800mg) IV q8h as needed up to 2 times per CRS event or 3 times in a 6-week period ▪ Dexamethasone 10-20mg IV q6h → methylprednisolone 1g daily if refractory ▪ Consider alternative cytokine therapy (e.g. anakinra, siltuximab) for persistent CRS despite tocilizumab and dexamethasone ▪ Continue aggressive treatment until grade 1 CRS and then taper steroids off

Table 4: Prevention and treatment of neurotoxicity

Grade	Recommendations for ICANS
Supportive care	▪ Consider MRI brain to rule out cerebral edema ▪ Consider diagnostic lumbar puncture if severe, atypical, or refractory ICANS ▪ Consider anti-seizure prophylaxis (e.g. levetiracetam) for patients with active ICANS
Grade 1	▪ Hold treatment until symptoms resolve ▪ Consider dexamethasone 10mg IV → re-assess in 6 hours ▪ Tocilizumab only if concurrent CRS
Grade 2	▪ Hold treatment until symptoms resolve ▪ Dexamethasone 10-20mg IV q6-12h ▪ Tocilizumab only if concurrent CRS
Grade 3	▪ Hold treatment until symptoms resolve ▪ Dexamethasone 10-20mg IV q6h → methylprednisolone 1g daily if refractory ▪ Tocilizumab only if concurrent CRS
Grade 4	▪ Hold treatment until symptoms resolve and consider permanently discontinuing treatment ▪ Dexamethasone 10-20mg q6h → methylprednisolone 1g daily if refractory ▪ Tocilizumab only if concurrent CRS ▪ Consider anakinra (preferred), intrathecal chemotherapy, siltuximab, ruxolitinib, etc. if refractory

Table 5: Prevention and treatment of other bispecific antibody toxicities

Grade	Recommendations
HLH/MAS	▪ Consider diagnostic evaluation for HLH/MAS for patients with late-onset or persistent CRS (e.g. >1 week) with associated organ dysfunction ▪ Consider treatment with tocilizumab, anakinra, and corticosteroids, and for life-threatening/refractory cases consider etoposide, ruxolitinib, emaplalumab, etc.
Infections	▪ Recommend valacyclovir 500mg daily as HSV/VZV prophylaxis for all patients ▪ Recommend PJP prophylaxis, especially during periods of high steroid exposure (e.g. dose ramp-up) and for those with other risk factors for PJP ▪ Recommend HBV prophylaxis for at-risk patients ▪ Consider IVIg replacement for patients with recurrent and/or severe infections due to hypogammaglobulinemia
Neutropenia	▪ Neutropenia may be late onset and usually responds to G-CSF ▪ Temporary dose hold may be required in some cases but must be balanced with patient's disease control
Tumor flare	▪ Exercise caution for patients with bulky masses near the airway or other vital organs as tumor flare may occur during the first 1-2 cycles ▪ Severe cases can be managed by holding the bispecific antibody and administering corticosteroids +/- tracheostomy
Tumor lysis syndrome	▪ Recommend allopurinol prophylaxis and TLS monitoring in high-risk patients during the first 1-2 cycles

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VIII. 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.

Statin prophylaxis for prevention of anthracycline cardiotoxicity
Atorvastatin 40mg daily x 12 months is recommended for patients receiving an anthracycline who are >50 years old or have other cardiac risk factors[1].

Neutropenia Prevention[2-6]
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[2].

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)

Erythropoeitin
Erythropoeitin 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[7-9]

- 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 withCD4 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: pentamadine 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 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[10]. Other hematological malignancy patients had better vaccines responses than Non Hodgkin’s Lymphoma and CLL patients for reasons not yet identified[11]. 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 amount 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[12]. 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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IX. Follow-Up Care in the Treatment of Lymphoma[1-11]

Cancer Care Alberta (CCA) has a discharge policy for patients from CCA facilities with survivorship care plans no later than 1-year post-treatment; assuming i) family doctor or other health care provider available to follow patient, ii) cancer in complete remission, iii) chance of relapse in the next 2yrs <50%, iv) >1mo from last CCA-requiring systemic/RT therapy, v) not a clinical trial patient who must be followed at a CCA facility.

Data from large studies of patients with DLBCL treated on clinical trials confirm that Event Free Survival (EFS) at 24 months (lack of relapse or death 24 months after diagnosis) is representative of overall EFS because the majority of relapses occur within 12-24 months of diagnosis (i.e. within 1 year of completing chemotherapy)[12]. Thus, patients who are disease free 1 year after completing therapy for aggressive lymphoma have a low risk of recurrence and should have their surveillance follow-ups transitioned back to their primary care physician. Late relapses are more frequent with indolent NHL but early diagnosis of relapsed iNHL is not associated with improved survival such that these patients are also appropriate to have surveillance under primary care. Transition of patients with indolent NHL should occur 12 months after completion of chemo-immunotherapy or immediately post-completion of rituximab maintenance for those who remain without evidence of active lymphoma. Detailed discharge and surveillance recommendations should be provided to the primary care team.

The exceptions to these rules include patients treated with cellular therapy who require approval for live vaccinations 2 years after therapy and thus, will be discharged from CCA after their 2 year follow-up visit.

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

- **Relapse.** Careful attention should be directed to lymph node sites. 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.

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Appendix A. Information regarding Rituximab 375mg/m2 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)x
- 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^2 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^2 IV
- Adriamycin 50 mg/m^2 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)[1-3]:

- Rituximab 375mg/m^2 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^2 IV
- Adriamycin 50 mg/m^2 IV day 1
- Vincristine 2mg IV day 1

- Etoposide 100mg/m^2 IV days 1-3 (or 200mg/m^2 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%)[1-3]:
- Rituximab 375mg/m^2 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^2 IV
- Vincristine 2mg IV day 1
- Etoposide 50mg/m^2 IV days 1-3 (or 100mg/m^2 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^2 IV on weeks 2, 6, 10 (24 hours later: folinic acid 15mg q6 hours x 6 doses)
- Adriamycin 50 mg/m^2 IV weeks 1,3,5,7,9,11
- Cyclophosphamide 350 mg/m^2 IV weeks 1,3,5,7,9,11
- Vincristine 2mg IV weeks 2,4,6,8,10,12
- Bleomycin 10mg/m^2 weeks 4,8,12
- Prednisone 75mg/day p.o. daily, taper over last 15 days
- Septra for PCP prophylaxis
- Suggest adding rituximab 375mg/m^2 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).

Day 1-4	**Doxorubicin** **Vincristine**	**10 mg/m2/day** **0.4mg/m2/day (no cap)**	Intravenous infusion in an elastomeric infusor in sodium chloride 0.9% via a central line over 96 hours
Day 1-4	**Etoposide**	**50 mg/m2/day**	Intravenous infusion in 500ml sodium chloride 0.9% over 24 hours via a central line
Day 5	Ondansetron	8mg	Oral as a single dose prior to chemotherapy
	Cyclophosphamide	**750mg/m2**	Intravenous bolus
Day 6	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 ≥0.5x109/l: **increase by 1 dose level**
- If nadir ANC <0.5x109/l on 1 or 2 measurements: **same dose as last**

Cycle.

- If nadir ANC <0.5x109/l on at least 3 measurements: **decrease by 1 dose level**
- If platelet nadir <25x109/l: **reduce by 1 dose level** regardless of ANC
- Life threatening infections: **decrease by 1 dose level**

Drug Dose Adjustments

Drugs	Drug Doses per Dose Levels				
	-2	-1	1 Cycle 1	2	3
	64% (64% x 0.8)	80% (100%x0.8)	100% (starting dose)	120% (100% x 1.2)	144% (120%x1.2)
Prednisolone (mg/m^2 twice daily)	60	60	60	60	60
Rituximab (mg/m^2/day)	375	375	375	375	375
Doxorubicin (mg/m^2/day	10	10	10	12	14.4
Vincristine (mg/m^2/day)	0.4	0.4	0.4	0.4	0.4
Etoposide (mg/m^2/day)	50	50	50	60	72
Cyclophosphamide (mg/m^2/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 ≥ grade 3 ileus, treatment should be delayed until recovery and vincristine introduced at 75% of the normal dose thereafter. If ≥ 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^2 IV day 1, 2
- Rituximab 375 mg/m^2 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^2 IV day 1 (or 400 mg/m^2/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^2 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^2 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^2 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^2 IV if cannot tolerate sc) q2months until progression

Outpatient R-DHAP:
Cycle 1.
Day1: Rituximab 375mg/m^2 IV (if no rituximab in past 3months and cannot recieve sc rituximab)
Day 2: 500mL NS pre, cisplatin 35 mg/m2 in 500 mL NS/mannitol, 500 ml NS post, AraC 2g/m2 in 500 mL NS.
Day 3: 500mL NS pre, cisplatin 35 mgm2 in 500 ml NS/mannitol, AraC 2g/m2 in 500 mL NS. Total 5 hrs

Cycle 2 onwards.
Day1: Rituximab 1400mg sc, 500mL NS pre, cisplatin 35 mg/m2 in 500 mL NS/mannitol, 500 ml NS post. Then AraC 2g/m2 in 500 mL NS. Total 5 hrs
Day2: 500mL NS pre, cisplatin 35 mgm2 in 500 ml NS/mannitol, AraC 2g/m2 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^2 for 5 to 7 days each 28 days
- 0.5 mg/kg days 1 and 15 q28d cycle

Fludarabine:
- 25mg/m^2 IV days 1-5 q28 days (days 1-3 only if frail elderly or renal dysfunction)
- 40mg/m^2 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^2 IV days 1-3 or 40mg/m^2 p.o. days 1-3
- Mitoxantrone 10mg/m^2 day 1
- Dexamethasone 40mg p.o. days 1-3
- Septra for PCP prophylaxis
- *Cycles:* every 28 days

III. Initial Therapy for Peripheral T-Cell Lymphoma
CHOP:
- Cyclophosphamide 750 mg/m^2 IV
- Adriamycin 50 mg/m^2 IV day 1
- Vincristine 2mg IV day 1
- Prednisone 100mg/day p.o. days 1-5

- *Cycles:* every 21 days

CHOEP[1-3]:
- Cyclophosphamide 750 mg/m^2 IV
- Adriamycin 50 mg/m^2 IV day 1
- Vincristine 2mg IV day 1
- Etoposide 100mg/m^2 IV days 1-3 (or 200mg/m^2 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^2 days 1-3
- Ifosfamide 1.2g/m^2 days 1-3
- Cisplatin 33mg/m^2 days 1-3
- Dexamethasone 40mg days 1-4
- *Cycles:* 3 cycles after initial radiotherapy

GOLD (14 day cycle)[4]:
- Gemcitabine 1000mg/m^2 on day 1
- Oxaliplatin 100mg/m^2 on day 1
- L-asparaginase 10,000U/m^2 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)[5]:
- Methotrexate 2g/m^2 on day 1
- Leucovorin 15mg x 4 on day 2, 3, and 4
- Ifosfamide 1500mg/m^2 on day 2, 3, and 4
- Mesna 300 mg/m^2 x 3 on day 2, 3 and 4
- Dexamethasone 40mg/d on day 2, 3 and 4
- Etoposide 100mg/m^2 on day 2, 3 and 4
- L-asparaginase 6000U/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/μL.
Antibiotic prophylaxis with sulfamethoxazole-trimethoprim is recommended.

IV. Hodgkin Disease Chemotherapy Regimens
Initial Therapy:

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

BEACOPP (escalated)
bleomycin 10mg/m^2 IV day 8
etoposide 200mg/m^2 IV days 1-3
adriamycin 35mg/m^2 IV day 1
cyclophosphamide 1250mg/m^2 IV day 1
vincristine 1.4mg/m^2 IV day 8
procarbazine 100mg/m^2 p.o. days 1-7
prednisone 40mg/m^2 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^2 IV day 8
etoposide 100 mg/m^2 IV days 1-3
adriamycin 25mg/m^2 IV day 1
cyclophosphamide 650mg/m^2 IV day 1
vincristine 1.4mg/m^2 IV day 8
procarbazine 100mg/m^2 p.o. days 1-7
prednisone 40 mg/m^2 p.o. days 1-14

ChlVPP chlorambucil 6mg/m^2 p.o. days 1-14
vinblastine 6mg/m^2 IV days 1 and 8
procarbazine 100mg/m^2 p.o. days 1-14
prednisone 40mg/m^2 p.o. days 1-14
Cycles: every 28 days

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

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

BEACOPDac (escalated)
bleomycin 10mg/m^2 day 8
etoposide 200mg/m^2 days 1-3
adriamycin 35mg/m^2 day 1
cyclophosphamide 1250 mg/m^2 IV day 1
vincristine 1.4mg/m^2 IV day 8
dacarbazine 250mg/m^2 IV days 2 and 3
prednisone 40 mg/m^2 p.o. days 1-14
G-CSF 300-480μg sc d9-19 (to ANC>1.5) or Neulasta d9
Cycles: every 21 days

V. Lymphoma Salvage Regimens

Aggressive Histology Hodgkin and Non-Hodgkin Lymphomas*:

DICE.

- Dexamethasone 10mg IV q6 hours days 1-4
- Ifosfamide 1g/m^2 (max 1.75g) over 15 minutes days 1-4
- Cisplatin 25mg/m^2 IV over 1hour days 1-4
- Etoposide 100mg/m^2 over 1 hour days 1-4
- Mesna 200 mg/m^2 over 5-10 min prior to first dose of ifosfamide, then 200 mg/m^2 IV at 4 hours and 400mg/m^2 p.o. (or 200 mg/m^2 IV) at 8 hours post-ifosfamide x 4 days
- *Cycles:* every 21-28 days

CEPP.

- Cyclophosphamide 600 mg/m^2 IV days 1 and 8
- Etoposide 70mg/m^2 days 1-3
- Procarbazine 60mg/m^2 p.o. days 1-10
- Prednisone 100mg/day p.o. days 1-10

- *Cycles:* every 28 days

GDP.
- Gemcitabine 1000mg/m^2 IV days 1 and 8
- Dexamethasone 40mg p.o. days 1-4
- Cisplatin 75mg/m^2 IV

DICEP.
- Dexamethasone 10mg IV q8 hours x 10 doses
- Cyclophosphamide 1.75 g/m^2 IV over 2 hours days 1-3
- Etoposide 350mg/m^2 IV over 2 hours days 1-3
- Cisplatin 35mg/m^2 IV over 2 hours days 1-3
- Mesna 1.75g/m^2 IV over 24 hours days 1-3
- Septra 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^2 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^2 IV days 1-3 or 40mg/m^2 p.o. days 1-3
- Mitoxantrone 10mg/m^2 day 1
- Dexamethasone 40mg p.o. days 1-3
- Septra for PCP prophylaxis
- *Cycles:* every 28 days

R-FCM.
- Fludarabine 25mg/m^2 IV days 1-3 or 40mg/m^2 p.o. days 1-3
- Cyclophosphamide 200mg/m^2 IV days1-3

- Mitoxantrone 8mg/m^2 IV day 1
- Rituximab 375mg/m^2 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[6,7]

Modified Magrath Regimen of R-CODOXM/R-IVAC (Blood 2014; 124:2913-2920)[8]:

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^2 IV	x	x																	
doxorubicin 50mg/m^2 IV	x																		
vincristine 1.5mg/m^2 IV cap 2mg	x														x				
allopurinol 300mg/day po	x	x	x	x	x	x	x	x	x	x									
methotrexate 3000mg/m^2 IV over 2 hour IV**															x				
leucovorin 25mg IV @ 24 hours, then 25mg IV q6h until methotrexate<10^{-8} M																xx xx	xx xx	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 alkalinization 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^2 IV	X																	
cytarabine 2g/m^2 IV q12h x 4 doses	X x	xx																
ifosfamide 1500mg/m^2 IV	X	x	x	x	x													
mesna 360mg/m^2 IV q3 hours	xx x	xx x	xx x	xx x	xx x	xx x												
etoposide 60mg/m^2 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 Protocol for Transplant-Eligible for Patients: age < 75years, no significant co-morbidities.
All chemotherapy doses based on ideal body weight.

	Step 1				*Step 2			**Step 3			Step 4
Week	1	2	3	4	5	6	7	8	9	10	12-14
Rituximab 375mg/m2 IV d0, then 1400mg sc d4 & 14 high-dose methotrexate 3.5 g/m^2 d1&15 procarbazine 100 mg/m^2 d1-7	x x x		x x								
rituximab 1400mg sc d1 cytarabine 3 g/m^2 x d1&2 G-CSF 5-10 µg/kg d8-13 Apheresis ~d14 or 15					x x	x	x				
Rituximab 1400mg sc d0 high-dose methotrexate 3.5 g/m^2 d1 cytarabine 2 g/m^2 twice daily days 2-3 all q21d for 2 cycles								x x x			
thiotepa 300 mg/m^2 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 phsycially 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 -Hydrocortisone 100mg IV, Benadryl 50mg IV, Zantac 50mg IV, Tylenol 650mg. 0900hr-Rituximab 375mg/m2 (1st infusion protocol) 2000hr –IV lactated ringers @ 2 mL/kg/hour continue until methotrexate level <0.05 2200hr - sodium bicarbonate 1500 mg PO q6h continue until methotrexate level less than 0.05 µmol/L if urine pH <7, increase sodium bicarbonate to 6500 mg PO q4h	• Daily weights • Daily CBC & Diff, EP, Creat, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg • LFTs, Ca, lipase, every Monday & Thursday
1	0800hr - Kytril 1mg IV 0800hr - **methotrexate** 3500mg/m² IV over 2 hour days 1 and 15 0800hr - **procarbazine** 100mg/m² po daily x 7days days 1-7 only (round down to nearest 50mg multiple) sodium bicarbonate 50 mmol IVPB q8h PRN if urine pH less than 7 continue until methotrexate level less than 0.05 µmol/L transfer 50 mL sodium bicarbonate injection (1 mmol/mL) into empty viaflex bag for administration. Give over one hour.	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, <0.1 d4, <0.05 d5)
4	0900hr- Rituximab 1400mg sc on cycle 1 only and continue folinic acid	0500-0800hr – methotrexate Level daily
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 • Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone • Remember anticoagulant and anticonvulsant if patient is on these medications	

** 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 : Loratadine 10mg po, Tylenol 650mg p.o. -**Rituximab** 1400mg sc	• Weight • CBC & Diff, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg
2 & 3	0800hr – Ondansetron or Granisetron, dexamethasone 10-12mg IV/po 0800hr – IV N/S 500mL/hour x 2 hours 1000hr – **Cytarabine** 3g/m^2 IV over 3 hours daily if creat cl >60ml/min or 2g/m^2 daily if creat cl 46-60ml/min or 1.5g/m^2 daily if creat cl 31-45ml/min	1% Prednisolone eye drops, 2 tid x12 doses begin before first dose of cytarabine and continue until 48 hours after the last dose
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

**Step 3. High-dose methotrexate/cytarabine consolidation q21 days x 1 cycles after stem cell collection		
Day	**Medications**	**Other Orders**
ADMISSION 0	16:00hr- Premeds : Loratadine 10mg po, Tylenol 650mg p.o. **Rituximab** 1400mg sc 2000hr – IV lactated ringers @ 2 mL/kg/hour until methotrexate level <0.05 2200hr - sodium bicarbonate 1500 mg PO q6h continue until methotrexate level less than 0.05 µmol/L if urine pH <7, increase sodium bicarbonate to 6500 mg PO q4h	• Daily weights • Daily CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg • ALT, Alk P, bili, Ca, lipase, every Monday & Thursday
1	0800hr - Kytril 1mg IV 0800hr - **methotrexate** 3500mg/m² IV over 2 hours sodium bicarbonate 50 mmol IVPB q8h PRN if urine pH less than 7 continue until methotrexate level less than 0.05 µmol/L transfer 50 mL sodium bicarbonate injection (1 mmol/mL) into empty viaflex bag for administration. Give over one hour.	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 – Granisetron 2mg IV, dexamethasone 10mg IV 1000hr – **Cytarabine** 2g/m^2 IV over 2 hours bid x2 days if CreatCl>60ml/min (reduce to 1.3g/m^2 if creat cl 46-60ml/min or 1g/m^2 if creat cl 31-45ml/min)	0500-08:00 – methotrexate level daily (expect <10 d2, <1 d3, <0.1 d4, <0.05 d5) 1% Prednisolone eye drops, 2 tid x12 doses begin before first dose of cytarabine and continue until 48 hours after the last dose
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 phsycially fit to proceed directly to ASCT on week 9.***

Step 4. *TBu/ASCT consolidation after response to methotrexate and high-dose cytarabine		
Day	**Medications**	**Other Orders**
ADMISSION Day -7	Allopurinol 300 mg p.o. daily until day 0 2200hr - N/S @ 100 mL/hour until day -4, then infuse only during busulfan administration days -4 to -2.	• Consult dietician, physiotherapy • Low bacteria diet • 24 hour intake • Mouth protocol • Record intake and output • Valacyclovir 500mg/d
-6 & -5	0800 – **thiotepa** 300 mg/m² IV over 3 hours x 2 days (IDEAL BSA) Reduce to 270mg/m^2 if age 61-65years Reduce to 240mg/m^2 if age 66-70years Reduce to 210mg/m^2 if age >70years	• 0800hr – granisetron 2 mg IV daily x 8 days • EP daily x 31days • Shower/bath q6 hours x 3 days; avoid skin creams
-4 to -2	0900 - **busulfan** 3.2 mg/kg IV daily x 3 days (Ideal weight) Reduce to 2.9mg/kg if age 61-65years Reduce to 2.55mg/kg if age 66-70years Reduce to 2.25mg/kg if age >70years	• lorazepam 1mg qid prophylaxis x 4 days • CBC & differential daily x 31 days • ALT, Alk Phos, bili, alb, Ca, Mg, every Monday & Thursday • PT, PTT, every Monday
-1	Rest day	• mycostatin 500,000 units q2-4 hours
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	
+14		• septra RS 1 tab p.o. daily

B. MATRIX Non-Transplant Protocol for Transplant-Eligible for Patients who refuse transplant:
age < 70years, no significant co-morbidities, ECOG=0-2.
All chemotherapy doses based on ideal body weight.

	Step 1											
Week	1	2	3	4	5	6	7	8	9	10	11	12
Rituximab d0, 4	x			x			x			x		
high-dose methotrexate 3.5 g/m^2 d1	x			x			x			x		
cytarabine 2g/ m^2 q12h x 2 d2	x			x			x			x		
Thiotepa 30mg/ m^2 d4												

Step 1. Induction: MATRIX x 4 cycles		
Day	Medications	Other Orders
ADMISSION 0	0900hr-Rituximab 375mg/m2 (1st infusion protocol) 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200ml/hour x 5 days	• Daily weights • Daily CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg • LFTs, Ca, lipase, every Monday & Thursday
1	0800hr - Kytril 1mg IV 0800hr - **methotrexate** 3500mg/m² 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^2 by 1 hour infusion q12 hr x 2 if CreatCl>60ml/min (reduce to 1.3g/m2 if creat cl 46-60ml/min or 1g/m2 if creat cl 31-45ml/min)	0500-0800hr – methotrexate level daily (expect level < 10 d2, <1 d3)
4	0900hr- Rituximab 1400mg subcutaneously 1000hr- Thiotepa 30mg/m^2 by 30min infusion	0500-0800hr – methotrexate Level daily
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 • Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone • Remember coumadin/LMWH and dilantin if patient is on these medications	

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)]*

C. Transplant-Ineligible Patients: age ≥75 years, or significant co-morbidities, or patient refuses HDMTX.

	Step 1			Step 2								
Week	1	2	3	4	5	6	7	8	9	10	11	12
Rituximab 375mg/m2 day 0	x											
Cytarabine 3g/m^2 daily days 1&2 if creat cl >60ml/min	x											
or 2g/m^2 days 1&2 if creat cl 46-60ml/min												
or 1.5g/m^2 days 1&2 if creat cl 31-45ml/min												
Thiotepa 30mg/m^2 on day 2	x											
Rituximab 1400mg sc day 1				x			x			x		
Cytarabine 3g/m^2 daily days 1&2 if creat cl >60ml/min				x			x			x		
or 2g/m^2 days 1&2 if creat cl 46-60ml/min												
or 1.5g/m^2 days 1&2 if creat cl 31-45ml/min												
Thiotepa 30mg/m^2 on day 2				x			x			x		

Step 1. Induction: Rituximab high-dose cytarabine/thiotepa x 1 cycle		
Day	**Medications**	**Other Orders**
0 or 1	0900hr-Hydrocortisone 100mg IV, Benadryl 50mg IV, Zantac 50mg IV, Tylenol 650mg. 0900hr-Rituximab 375mg/m2 (1st infusion protocol)	• Weekly CBC & differential, EP, creatinine, glucose ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg
1	**NS 1000ml IV hydration** Granisetron 2mg po, dexamethasone 10mg IV ***Cytarabine** 3g/m^2 daily on days 1&2 if creat cl >60ml/min or 2g/m^2 daily on days 1&2 if creat cl 46-60ml/min or 1.5g/m^2 daily on days 1&2 if creat cl 31-45ml/min	1% Prednisolone eye drops, 2 tid x12 doses begin before first dose of cytarabine and continue until 48 hours after the last dose
2	**NS 1000ml IV hydration** Granisetron 2mg po, dexamethasone 10mg IV ***Cytarabine** 3g/m^2 daily on days 1&2 if creat cl >60ml/min or 2g/m^2 daily on days 1&2 if creat cl 46-60ml/min or 1.5g/m^2 daily on days 1&2 if creat cl 31-45ml/min **Thiotepa** 30mg/m^2 on day 2	
7	Valtrex 500mg po daily and Septra 1 tab daily x6mo	
8-12	G-CSF 300 or 480µg sc daily x5d (or pegfilgrastim 6mg on day 4)	

Step 2. Rituximab High-dose Cytarabine/Thiotepa q21days x 3 cycles		
Day	**Medications**	**Other Orders**
1	**Rituximab 1400mg sc** **NS 1000ml IV hydration** Granisetron 2mg po, dexamethasone 10mg IV ***Cytarabine** 3g/m^2 daily on days 1&2 if creat cl >60ml/min or 2g/m^2 daily on days 1&2 if creat cl 46-60ml/min or 1.5g/m^2 daily on days 1&2 if creat cl 31-45ml/min	• Weekly CBC & differential, EP, creatinine, glucose ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg 1% Prednisolone eye drops, 2 tid x12 doses begin before first dose of cytarabine and continue until 48 hours after the last dose
2	**NS 1000ml IV hydration** Granisetron 2mg po, dexamethasone 10mg IV ***Cytarabine** 3g/m^2 daily on days 1&2 if creat cl >60ml/min or 2g/m^2 daily on days 1&2 if creat cl 46-60ml/min or 1.5g/m^2 daily on days 1&2 if creat cl 31-45ml/min **Thiotepa** 30mg/m^2 on day 2	
8-12	G-CSF 300 or 480µg sc daily x5d (or pegfilgrastim 6mg on day 4)	

*If create cl <30ml/min do not give cytarabine.
Calculated creatinine clearance= N* x (140-Age) x weight (kg)/serum create in umol/L where *N = 1.23 males or 1.04 females

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.

	Step 1								Step 2			Step 3		
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14
high-dose methotrexate 3.5 g/m^2 d1 Rituximab 375 mg/m^2 d2 procarbazine 100 mg/m^2 x 7 days d1-7 vincristine 1.4 mg/m^2 d1	x x x x		x x x		x x x		x							
rituximab 1400mg sc days 1,4 dexamethasone 20 mg days 1-4 cisplatin 35 mg/m^2 days 1,2 cytarabine 2 g/m^2 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^2 d -6,-5 busulfan 3.2 mg/kg day -4 to -2, melphalan 100 mg/m^2 d-1, ASCT d 0													x	

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

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 NaHCO3/L @ 200mL/hour x 5 days	• Daily weights • Daily CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg • LFTs, Ca, lipase, every Monday & Thursday
1	0800hr - Kytril 1mg IV 0800hr - **methotrexate** 3500mg/m² IV over 2 hours cycles 1-4 0800hr - **procarbazine** 100mg/m² p.o. daily x 7days cycles 1 and 3 (round down to nearest 50mg multiple) 1000hr - **vincristine** 1.4mg/m^2 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 – **Rituximab** 375mg/m² IV (first 3 cycles HDMTX)	0500-0800hr – methotrexate level daily (expect level < 10 today)
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 • Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone • Remember coumadin/LMWH and dilantin if patient is on these medications	

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 - **rituximab** 1400mg sc 0900hr -IV 1L NS 0900hr – **dexamethasone** 20mg p.o./IV daily x 4 days 0900hr – Kyrtil 1mg IV or 2mg p.o. x 3-4 days 0900hr – aprepitent protocol p.o. x 3 days 1000hr **– cisplatin** 35mg/m^2 IV over 2 hours with mannitol 25g and 500mL NS 1200hr- **cytarabine** 2g/m^2 IV over 2 hours x 1 doses (1.5g/m^2 if >60yr)	• Weight • CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg
2	0800hr – **dexamethasone** Kytril, Aprepitent continued 1000hr **– cisplatin** 35mg/m^2 IV over 2 hours with mannitol 25g and 500mL NS 1200hr- **cytarabine** 2g/m^2 IV over 2 hours x 1 doses (1.5g/m^2 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^2 IV (first dose long infusion protocol) 2200hr - D5½ N/S + 20 mEq KCL/L @ 125 mL/hour until day -1	• Consult dietician, physiotherapy • Low bacteria diet. 24hour intake • Mouth protocol; record intake and output
-6 & -5	0800hr – **thiotepa** 250 mg/m² IV over 2 hours x 2 days (use ideal BSA)	• 0800hr – Granisetron 2 mg IV daily x 8 days • EP daily x 31days • Shower/Bath q6 hours x 3 days; avoid skin creams
-4 to -2	0900 - **busulfan** 3.2 mg/kg IV daily x 3 days (use Ideal weight)	• lorazepam prophylaxis x 4 days • CBC & differential daily x 31 days • ALT, Alk Phos, bilirubin, alb, Ca, Mg, every Monday & Thursday • PT, PTT every Monday
-1	10:00 -**melphalan** 100mg/m^2 (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	• Mycostatin 500,000 units q2-4 hours • Septra RS 1 tab p.o. daily • Acyclovir 5 mg/kg twice daily IV or 400 mg p.o. four times daily
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.

				Step 1								Step 2			Step 3		
Week	0	1	2	3	4	5	6	7	8	9	10	13	14	15	16	17	18
Methotrexate 3.5 g/m^2 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^2 days 1,2 cytarabine 2 g/m^2 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^2 d-6,-5 busulfan 3.2 mg/kg day -4 to -2, melphalan 100 mg/m^2 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	• Daily weights • Daily CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg • LFTs, Ca, lipase, every Monday & Thursday
1	0800hr - Kytril 1mg IV 0800hr - **methotrexate** 3500mg/m² 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	• Discharge once methotrexate level <0.05 • If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days • Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone • Remember coumadin/LMWH and dilantin if patient is on these medications	

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 - **rituximab** 1400mg sc 0900hr -IV 1L NS 0900hr – **dexamethasone** 20mg p.o./IV daily x 4 days 0900hr – Kyrtil 1mg IV or 2mg p.o. x 3-4 days 0900hr – aprepitent protocol p.o. x 3 days 1000hr **– cisplatin** 35mg/m^2 IV over 2 hours with mannitol 25g and 500mL NS 1200hr- **cytarabine** 2g/m^2 IV over 2 hours x 1 doses (1.5g/m^2 if >60yr)	• Weight • CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg
2	0800hr – **dexamethasone** Kytril, Aprepitent continued 1000hr **– cisplatin** 35mg/m^2 IV over 2 hours with mannitol 25g and 500mL NS 1200hr- **cytarabine** 2g/m^2 IV over 2 hours x 1 doses (1.5g/m^2 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^2 IV (first dose long infusion protocol) 2200hr - D5½ N/S + 20 mEq KCL/L @ 125 mL/hour until day -1	• Consult dietician, physiotherapy • Low bacteria diet. 24hour intake • Mouth protocol; record intake and output
-6 & -5	0800hr – **thiotepa** 250 mg/m² IV over 2 hours x 2 days (use ideal BSA)	• 0800hr – Granisetron 2 mg IV daily x 8 days • EP daily x 31days • Shower/Bath q6 hours x 3 days; avoid skin creams
-4 to -2	0900 - **busulfan** 3.2 mg/kg IV daily x 3 days (use Ideal weight)	• lorazepam prophylaxis x 4 days • CBC & differential daily x 31 days • ALT, Alk Phos, bilirubin, alb, Ca, Mg, every Monday & Thursday • PT, PTT every Monday
-1	10:00 -**melphalan** 100mg/m^2 (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	• Mycostatin 500,000 units q2-4 hours • Septra RS 1 tab p.o. daily • Acyclovir 5 mg/kg twice daily IV or 400 mg p.o. four times daily
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-etopside x2 then RDHAP for stem cell mobilization and collection, then R-TBuM/ASCT

	Step 1							Step 2				Step 3		
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14
high-dose methotrexate 3.5 g/m^2 d1 Rituximab 375 mg/m^2 d2 Ifosfamide 1.5 g/m^2 d3-5 Etoposide 100 mg/m^2 d3-5	X X X X			X X X X			X							
rituximab 1400mg sc days 1,4 dexamethasone 20 mg days 1-4 cisplatin 35 mg/m^2 days 1,2 cytarabine 2 g/m^2 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^2 d -6,-5 busulfan 3.2 mg/kg day -4 to -2, melphalan 100 mg/m^2 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 NaHCO3/L @ 200mL/hour x 5 days	• Daily weights • Daily CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg • LFTs, Ca, lipase, every Monday & Thursday
1	0800hr - Kytril 1mg IV 0800hr - **methotrexate** 3500mg/m² 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 – **Rituximab** 375mg/m² 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 **- Ifosfamide** 1.5g/m^2 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 – **Etoposide** 100 mg/m^2 IV daily x 3d 1600hr – Mesna 1.0 g IV daily x 3d 1000hr	
5 or 6	• Discharge once methotrexate level <0.05 • If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days • Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone • Remember coumadin/LMWH and dilantin if patient is on these medications	

** 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 - **rituximab** 1400mg sc 0900hr -IV 1L NS 0900hr – **dexamethasone** 20mg p.o./IV daily x 4 days 0900hr – Kyrtil 1mg IV or 2mg p.o. x 3-4 days 0900hr – aprepitent protocol p.o. x 3 days 1000hr **– cisplatin** 35mg/m^2 IV over 2 hours with mannitol 25g and 500mL NS 1200hr- **cytarabine** 2g/m^2 IV over 2 hours x 1 doses (1.5g/m^2 if >60yr)	• Weight • CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg
2	0800hr – **dexamethasone** Kytril, Aprepitent continued 1000hr **– cisplatin** 35mg/m^2 IV over 2 hours with mannitol 25g and 500mL NS 1200hr- **cytarabine** 2g/m^2 IV over 2 hours x 1 doses (1.5g/m^2 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

VIII. Secondary CNS Lymphoma Protocol

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^2 IV (first dose long infusion protocol) 2200hr - D5½ N/S + 20 mEq KCL/L @ 125 mL/hour until day -1	• Consult dietician, physiotherapy • Low bacteria diet. 24hour intake • Mouth protocol; record intake and output
-6 & -5	0800hr – **thiotepa** 250 mg/m² IV over 2 hours x 2 days (use ideal BSA)	• 0800hr – Granisetron 2 mg IV daily x 8 days • EP daily x 31days • Shower/Bath q6 hours x 3 days; avoid skin creams
-4 to -2	0900 - **busulfan** 3.2 mg/kg IV daily x 3 days (use Ideal weight)	• lorazepam prophylaxis x 4 days • CBC & differential daily x 31 days • ALT, Alk Phos, bilirubin, alb, Ca, Mg, every Monday & Thursday • PT, PTT every Monday
-1	10:00 -**melphalan** 100mg/m^2 (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	• Mycostatin 500,000 units q2-4 hours • Septra RS 1 tab p.o. daily • Acyclovir 5 mg/kg twice daily IV or 400 mg p.o. four times daily
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	

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).

	Step 1		Step 2										Step 3
Week	1	2	3	4	5	6	7	8	9	10	11	12	15 or 16
Rituximab 375mg/m2 d0, 4 high-dose methotrexate 3.5 g/m^2 d1 procarbazine 100 mg/m^2 x 7 days d1-7	x x x												
Rituximab 375mg/m2 d0 high-dose methotrexate 3.5 g/m^2 day 1 cytarabine 1.5-2 g/m^2 bid days 2-3			x x x			x x x			x x x			x x x	
Ifosfamide 2g/m^2 daily days 1-3													X

Step 1. Induction: high-dose methotrexate/procarbazine x 1 cycle		
Day	**Medications**	**Other Orders**
ADMISSION 0	0900hr-Rituximab 375mg/m2 (1st infusion protocol) 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200ml/hour x 5 days	• Daily weights • Daily CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg • LFTs, Ca, lipase, every Monday & Thursday
1	0800hr - Kytril 1mg IV 0800hr - **methotrexate** 3500mg/m² IV over 2 hours 0800hr - **procarbazine** 100mg/m² 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 - folinic 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/m2 (subsequent infusion protocol)on cycle 1 only and continue folinic acid)	0500-0800hr – methotrexate Level daily
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 • Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone • Remember coumadin/LMWH and dilantin if patient is on these medications	

** 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/m2 (subsequent infusion protocol)on cycle 1 only and continue folinic acid) 2000hr – IV D5W + 20meq KCL/L + 2 amps NaHCO3/L @ 200mL/hour x 5 days	• Daily weights • Daily CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg • ALT, Alk P, bilirubin, Ca, lipase, every Monday & Thursday
1	0800hr - Kytril 1mg IV 0800hr - **methotrexate** 3500mg/m² IV over 2 hours	07:00 - Urine pH bid, 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 0800hr – Kytril 2mg IV, Decadron 10mg IV 1000hr – **cytarabine** 2g/m^2 IV over 2 hours twice daily x 2 days; reduce to 1.5g/m^2 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)]*

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^2 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	• weight (call MD if >2kg above day 1) • CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg

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).

				Step 1								Step 2			Step 3		
Week	0	1	2	3	4	5	6	7	8	9	10	13	14	15	16	17	18
Methotrexate 3.5 g/m^2 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^2 x1 dose, days 1 and 2 G-CSF 5-10 µg/kg day 8-13												x x x	x				
Ifosfamide 2g/m^2 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	• Daily weights • Daily CBC & differential, EP, creatinine, gluc • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg • LFTs, Ca, lipase, every Monday & Thursday
1	0800hr - Kytril 1mg IV 0800hr - **methotrexate** 3500mg/m² 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	• Discharge once methotrexate level <0.05 • If level 0.01-0.05, discharge on leucovorin 5mg p.o. q6 hours x 2-3 days • Discharge meds: septra DS 1 daily or dapsone 50mg daily x 6-9 months; consider dexamethasone taper if on dexamethasone • Remember coumadin/LMWH and dilantin if patient is on these medications	

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 - **rituximab** 1400mg sc 0900hr -IV 1L NS 0900hr – **dexamethasone** 20mg p.o./IV daily x 4 days 0900hr – Kyrtil 1mg IV or 2mg p.o. x 3-4 days 0900hr – aprepitent protocol p.o. x 3 days 1000hr **– cisplatin** 35mg/m^2 IV over 2 hours with mannitol 25g and 500mL NS 1200hr- **cytarabine** 2g/m^2 IV over 2 hours x 1 doses (1.5g/m^2 if >60yr)	• Weight • CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg
2	0800hr – **dexamethasone** Kytril, Aprepitent continued 1000hr **– cisplatin** 35mg/m^2 IV over 2 hours with mannitol 25g and 500mL NS 1200hr- **cytarabine** 2g/m^2 IV over 2 hours x 1 doses (1.5g/m^2 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^2 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	• weight (call MD if >2kg above day 1) • CBC & differential, EP, creatinine, glucose • ALT,AlkP,LDH,bilirubin,Alb,Ca,Mg

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
    - Palliative*:* 20Gy/5 - 35Gy/20 +/- 10Gy/5 boost *depending on age, KPS, anticipated life expectancy, status of extracranial disease?*
    - 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):

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

What is INRT/ISRT?[9-11]:

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

Role of IMRT/VMAT/TOMO[12,13]:

- 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[14-17]:

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

Appendix C: Prognostic Models

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 (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[18]

Factors	# of Factors	5 year PFS
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[19]

Factors	# of Factors	% of Patients	4 year PFS	4 year DSS	4 year OS
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[19]

# of Factors	% of Patients	4 year PFS	4 year DSS	4 year OS
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

Factors	# of Factors	5 year PFS	10 year PFS
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[20]

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)[21]

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)[22]

Factors	# of Factors	mOS	5 year OS
Age > 60 years Elevated LDH Deep Tumour ○ Cerebellum ○ Periventricular ○ Basal ganglion ○ Brainstem	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)[23]

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.qxmd.com/calculate-online/hematology/follicular-lymphoma-international-prognostic-index-flipi

FLIPI 2 [24]

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[25]

Factors	# of Factors	5 year FFS with ABVD
Age ≥45 years Male Stage IV Albumin <40 g/L Hb<105 g/L WBC≥15 x 10^9/L Lymphocyte < 0.6 x 10^9/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[26]

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)[27]

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+	-	≥1.5 ULN	≥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[28]

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[29]

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
Gobbi et al., 1994[30]	Hb<9 g/dL Age >70 years Weight loss Cryoglobulinaemia	0-1 factor 0-2 2-4 factors	mOS 80 months mOS 48 months
Morel et al, 2000[31]	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%
Dhodapkar et al., 2001[32]	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%
Merlini et al., 2003[33]	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 B2M >2 mg/L Alb < 35 Creatinine > 1.6 17p mutations	0	364	96%
	1	623	79%
	2	497	69%
	3	70	30%
	4-5	10	16%

CLL International 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	Intermeidate (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, immuno-histochemistry 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[34]
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 ≥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 FGD-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 x $\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.

Revised Criteria for Response Assessment

Response and site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1,2, or 3* with or without a residual mass on 5PŤ 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 ≤ 1.5 cm in LDi No extralymphatic sites of disease Absent
Nonmeasured lesion	Not applicable	Regress to normal None
Organ enlargement	Not applicable	Normal by morphology; if indeterminate, IHC negative
New lesions	None	
Bone marrow	No evidence of FDG-avid disease in marrow	
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 ŧ with reduced uptake compared with baseline and residual masses(es) of any size At interim, these findings suggest responding disease At end of treatment, findings indicate residual disease	≥ 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 x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 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
No response or stable disease	No metabolic response	Stable disease
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
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm 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 mist 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

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 or 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> 1.0cm 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, 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 ≤ mediastinum; 3, uptake > mediastinum but ≤ 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 surgical core 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:

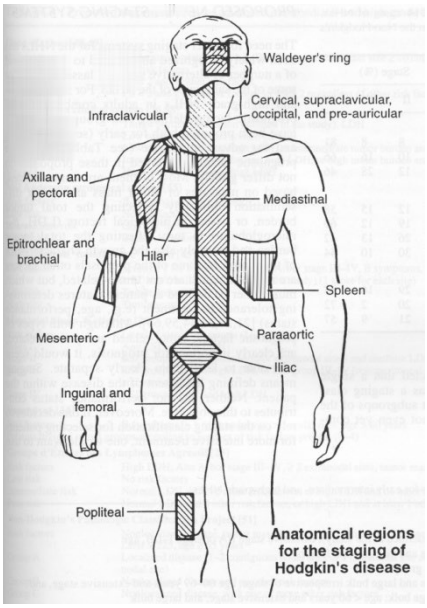
Relapse/progression after treatment 1: yes no **Date relapse** (d/m/y)_____

2nd Treatment: Regimen_____ **Radiation** yes no **HDCT/ASCT** yes no

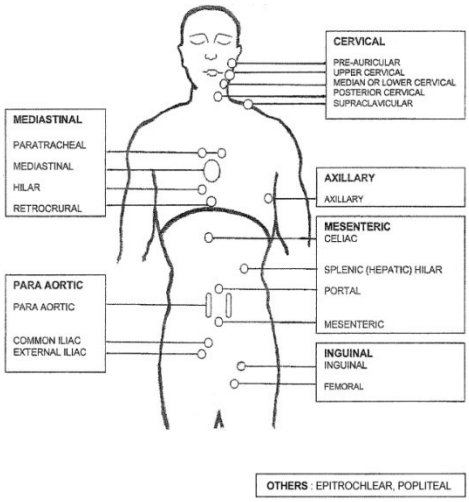
Survival Information:

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:

	#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			
• Age ≥ 60yrs	Prognosis #	%pt	5yr	10yr
• Stage 3-4	Good 0-1	36	90%	70%
• Increased LDH	Intermed 2	37	75%	50%
• Hb < 120g/l	Poor 3-5	27	50%	35%
• 5+ nodal sites				

Primary CNS lymphoma Prognostic Index

	Overall Survival		Failure-Free Survival	
Adverse Factors	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

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

	Males – Weight (kg)			Females – Weight (kg)		
Height (cm)	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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Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Hematology Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Hematology Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, hematologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in March 2006.

Maintenance

A formal review of the guideline will be conducted in 2027. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

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; ChlVPP, chlorambucil + vinblastine + procarbazine + prednisone; CHOP, cyclophosphamide + adriamycin + vincristine + prednisone; CHOEP, cyclophosphamide + adriamycin + vincristine + etoposide + prednisone; CL, 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 in situ 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, Pneumocystis jiroveci 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.

Disclaimer The recommendations contained in this guideline are a consensus of the Alberta Hematology Tumour Team and are a 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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