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---|---
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**Ownership** | NICaN
**Approved by** | NICaN Haematology CRG
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**Next Review:** | June 2022
**Version** | 3.2
**Supercedes** | 3.1 NICaN Guideline for the Management of Lymphoma 2016

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**Authorisation of Systemic Anti-Cancer Therapy (SACT) Guidelines for Lymphoid Malignancies**

<table>
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<th>Signature</th>
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<tr>
<td>Approved by NICaN Group</td>
<td>Dr Phil Windrum</td>
<td>June 2019</td>
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Review Date | June 2022

These SACT guidelines are being submitted by the authors on behalf of the NICaN Haematology group.
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1. INTRODUCTION

This document is intended for use by Consultant led, appropriately constituted, multi-disciplinary teams within the Northern Ireland Cancer Network involved in the management and treatment of patients with lymphoid malignancies. This Clinical Management Guideline (CMG) is designed to supplement current national and international guidelines, and NICE/Scottish Medicine Consortium (SMC) advice relating to the treatment of lymphoid malignancies.

This guideline is designed to inform chemotherapy protocol writing and reflects current guidance from NICE, SMC and British Society for Haematology (BSH). Although detailed, this guideline is not fully comprehensive and is likely to evolve over time and as such regular updating will be required as new evidence and information emerges.

It should be noted that these clinical management guidelines (CMGs) are written to reflect current advice and practices It is the responsibility of all clinical staff involved in the management of patients with lymphoid malignancies to familiarise themselves with these guidelines.

This guideline focuses on a range of lymphoid malignancies including:

- Hodgkin’s Lymphoma
- Diffuse Large B Cell
- Follicular
- Primary CNS
- Burkitts
- Waldenstroms/CLL/SLL
- T Cell Lymphomas
- Marginal Zone / Extra Nodal Marginal Zone
- Mantle Cell Lymphoma
- Gastric/Non Gastric
- Skin Lymphoma
- Hairy Cell Leukaemia

For simplicity, and to avoid repetition in each tumour-specific section, general information which is applicable to all lymphoid malignancies is covered in Sections 2 - 5. This includes generic areas of guidance such as service and multidisciplinary team (MDT) configuration across the Network, the management of teenagers and young adults with lymphomas, patient support and information. Section 6 sets out the diagnostic principles and malignancy
NICaN Clinical Management Guidelines for Lymphoid Malignancies in Adults

classification as per the World Health Organisation (WHO 2016)\(^1\) which underpins all lymphoid malignancies and are the basis for this guideline. Each tumour-specific section will detail any additional relevant diagnostic tests that should be included for the individual lymphoma type.

**Clinical Trials**

Eligible patients should always be offered the opportunity to consider clinical trials for any stage of disease management. The Northern Ireland Clinical Trials Unit (NICTU) is a UK Clinical Research Collaboration (UKCRC) registered Clinical Trials Unit, based in Belfast. The NICTU has a wide ranging portfolio of trials available; the full list of open trials can be access at [http://www.nictu.hscni.net/portfolio/](http://www.nictu.hscni.net/portfolio/)

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\(^1\) [http://www.bloodjournal.org/content/bloodjournal/127/20/2375.full.pdf](http://www.bloodjournal.org/content/bloodjournal/127/20/2375.full.pdf)
2. NETWORK CONFIGURATION OF THE HAEMATOLOGY CANCER SERVICES

The Northern Ireland Cancer Network has two cancer MDTs which diagnose and treat haematology patients;

- The Belfast /Southern/South Eastern Trust Lymphoma/Myeloma/CLL Multidisciplinary Team (MDT) is a multi-professional group formed from these three Trust haematology departments.

- The North West Haematology Multidisciplinary team (MDT) is a multi-professional group formed from the two Trust haematology departments.

Each MDT is a well-established group of experts with a specialised interest in the diagnosis, treatment and management of people with haematology cancer. The role of each MDT is to ensure that all patients with a new diagnosis of haematological cancer are reviewed by the multidisciplinary team members for discussion of management plan. Both MDTs meet on a weekly basis and in addition meet annually to discuss, review and agree their operational policy, annual report and work plan.

<table>
<thead>
<tr>
<th>Catchment Area</th>
<th>Catchment Population</th>
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<tr>
<td>Belfast/ South Eastern/ Southern</td>
<td>Combined: 1,094,613</td>
</tr>
<tr>
<td>North West</td>
<td>Combined: 776,221</td>
</tr>
</tbody>
</table>
3. REFERRAL GUIDELINES FOR HAEMATOLOGY CANCER

Patients can be referred to their local hospital as ‘red flags’ (i.e. suspect cancer) by their GPs under the following NICE guidance: This section is a direct lift from the NICE NG12 Suspect Cancer: Recognition and Referral guidance (June 2015)

Myeloma

Offer a full blood count, blood tests for calcium and plasma viscosity or erythrocyte sedimentation rate to assess for myeloma in people aged 60 and over with persistent bone pain, particularly back pain, or unexplained fracture.

Offer very urgent protein electrophoresis and a Bence-Jones protein urine test (within 48 hours) to assess for myeloma in people aged 60 and over with hypercalcaemia or leukopenia and a presentation that is consistent with possible myeloma.

Consider very urgent protein electrophoresis and a Bence-Jones protein urine test (within 48 hours) to assess for myeloma if the plasma viscosity or erythrocyte sedimentation rate and presentation are consistent with possible myeloma.

Refer people using a suspected cancer pathway referral if the results of protein electrophoresis or a Bence-Jones protein urine test suggest myeloma.

Non-Hodgkin’s lymphoma in adults

Consider a suspected cancer pathway referral for non-Hodgkin's lymphoma in adults presenting with unexplained lymphadenopathy or splenomegaly. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss.

Hodgkin's lymphoma in adults

Consider a suspected cancer pathway referral for Hodgkin's lymphoma in adults presenting with unexplained lymphadenopathy. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus, weight loss or alcohol-induced lymph node pain.
4. HAEMATOLOGY CARE PATHWAYS

Cancer Care Pathways outline the steps and stages in the patient journey from referral to diagnosis, staging, treatment, follow up, rehabilitation and when applicable palliative care.

Timed effective care pathways are central to delivering quality and timely care to patients throughout their cancer journey and to ensure the delivery of an equitable service.

Pathways are developed and agreed through the regional NICaN Clinical Reference Group and are available on the NICaN website at: https://nican.hscni.net/
5. PATIENT INFORMATION

If a diagnosis is confirmed, patients should be informed that they have a cancer of the blood, bone marrow and immune system. Their prognosis should be discussed including reference to co-morbidities that may influence management approach and prognostic indices as appropriate. It is particularly important that this process is done sensitively, in a timely manner and with consideration of any specific needs and feelings of the patient.

Particularly important aspects of communication and patient information may include:
- treatment intent – whether the condition is curable/incurable
- the concept of watch and wait
- the range and types of therapy (including novel treatments and SCT)
- clinical trials
- fertility
- treatment toxicity and late effects.

All patients must have access to a key worker. This is usually (but not always) the clinical nurse specialist.

All Trusts have produced a key worker policy which sets out the definition of a key worker and provides an overview of their role and responsibilities. The key worker/clinical nurse specialist should ensure that all patients are offered a holistic needs assessment (HNA) at key pathway points, including within 31 days of diagnosis; at the end of each treatment regime; and whenever a person requests one. Following each HNA, every patient should be offered a written care plan. This plan should be developed with the patient and communicated to all appropriate healthcare and allied healthcare professionals.

Written and verbal information is essential and the key worker/clinical nurse specialist plays a key role in ensuring that patients have access to appropriate and relevant written information about their condition. There is a wide range of information leaflets available including the Macmillan Cancer Support information booklets and Leukaemia and Lymphoma NI are good sources of patient information at diagnosis: patient leaflets are available for all treatment options and are also available for download on the following websites:

https://nican.hscni.net/
https://www.macmillan.org.uk/information-and-support
http://leukaemiaandlymphomani.org/
6. HAEMATO-PATHOLOGY GUIDANCE

The following guidance has been developed to assist clinical teams in the obtaining of tissue samples for suspected lymphoma patients (which would include desired requirements for laboratory reporting).

- Diagnosis of any category of lymphoma requires tissue diagnosis
- Clinical examination, radiology or preliminary laboratory investigations including blood count, biochemistry or FNA (as performed in NI) may predict lymphoma but are not sufficient for treatment.
- Lymphoma is not a single disease; more than 60 different sub-types are recognised as clinico-pathological entities by the WHO management protocols are based on recognised WHO sub-types
- Laboratory diagnosis of lymphoma is a multi-step sequential/parallel processes requiring morphology, immunophenotyping and genetic/molecular testing
- Primary diagnosis of lymph node based lymphoma is best achieved on an excision biopsy of the lymph node; relapses can be documented by core biopsies/FNA or other investigative modalities
- Excision biopsy of lymph nodes or open biopsy of other sites is the procedure of choice for primary lymphoma diagnosis in fit patients. Surgeons (general/breast/thoracic) needed to be recruited to the haematology diagnostics team
- Common laboratory samples for '? lymphoma’ include blood, FNA, needle core biopsies, open biopsies, endoscopic biopsies, skin punch, bone, bone marrow (aspirate and trephine), vitreous fluid and stereotactic biopsies from brain
- Modern high quality diagnostic approach is required to adapt to patient circumstances at presentation. WHO lymphoma sub-type diagnosis in the laboratory requires diagnostic algorithms tailored to different sample types to maximise clinically relevant information.
- FNA for primary diagnosis of lymphoma may still be necessary in patients who are unfit for more invasive procedures

The requirements for samples processed in the Cellular Pathology Laboratory are detailed below. This is based on current practice and laboratory resources.

- Flow cytometry and molecular haematopoietic and lymphoid tissues
- Medical Genetics
- Histopathology and Cytopathology laboratories (with immunohistochemistry ) in BHSCT and molecular investigations done outside BHSCT

** Limited resources affect service provision to the standard required by RCPath and NICE; difficult to implement the WHO 2016 classification of tumours of haematopoietic and lymphoid tissues**
Clinical Information for Pathologists

- Presenting symptoms (B-symptoms- weight loss/night sweats etc), duration of symptoms, volume and distribution of adenopathy, autoimmunity, immunosuppression/ immuno-modulator drug therapy, HIV /HCV/Other virology, organ specific symptoms or signs
- Imaging: size of the most abnormal lymph node, local or generalised adenopathy, spleen, focal or diffuse process
- Relevant blood count, flow cytometry, paraprotein, free light chain etc

The following paragraphs outline diagnostic pathways and laboratory processes to secure an accurate diagnosis in a clinically relevant time frame.

Optimal Diagnostic Pathway for Primary Lymphoma Diagnosis And WHO Sub-typing

Clinical examination, initial laboratory testing and/or imaging suspicious of lymphoma

- Selection of target for sampling
- FNA to confirm absence of carcinoma/inflammation/infection and presence of a lymphoid proliferation
- Contact Cytopathology laboratory for rapid on site evaluation (ROSE)
- Cytopathology evaluation and ancillary investigations (Flow/IHC)
- Cytopathology report
- Excision biopsy if palpable node; core biopsy if inaccessible/deep sites
- Contact Cellular Pathology laboratory for arranging triage of fresh tissue
- Fresh sample submitted for Flow cytometry, cytogenetics, PCR
- Formalin fixed tissue for histology and IHC
- Preliminary Histopathology report including results of ancillary investigations
- Final histopathology report with WHO subtype (incorporating results of molecular/cytogenetic testing)

** ROSE is mandatory for triaging sample for flow cytometry and molecular studies**

When lymphoma is among several other entities in the differential diagnosis, the following pathways may be appropriate

Flow charts for

1. Uncertain diagnosis (lumps/bumps/deep seated lesions)
2. Open/Endoscopic
3. Skin lymphoma
4. CNS
5. Bone marrow/peripheral blood
Figure 1 Uncertain Diagnosis

<table>
<thead>
<tr>
<th>Lump/ radiologically indeterminate lesion</th>
<th>Non Image guided FNA</th>
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<tbody>
<tr>
<td>US/CTFNA</td>
<td></td>
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<tr>
<td><strong>Morphology and Adequacy assessment (Pathology)</strong></td>
<td></td>
</tr>
<tr>
<td>Not a lymphoma; collect for IHC</td>
<td>Flow cytometry</td>
</tr>
<tr>
<td></td>
<td>Request core biopsy if lymphoma</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Request exision if WHO type not possible</td>
<td>Refer to haematology MDT if lymphoma</td>
</tr>
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- FNA ≠ Histology; sample volume, diagnostic process and output are different.
- Primary purpose of FNA as practised in BHSCT currently is to confirm benign disease and exclude carcinoma
- Adequacy assessment of sample (FNA or core or other fresh tissue) is both quantitative and qualitative; Cellular Pathology Laboratory input is mandatory and requires prior arrangement
- A minimum of 2 needle cores is needed for diagnosis and each should be obtained using needles that are at least 17 G or larger (RCPATH audit) (no 20 G cores please)
- Approximately 20-40% needle core biopsies are insufficient to get a WHO subtype (BHSCT audit); repeat cores or excision may be requested by Pathologists- immediate action is needed.
- A negative pathology result does not exclude malignancy; a low threshold for re-biopsy of suspicious lesions will avoid delayed diagnosis

Figure 2 Open / Endoscopic Biopsies

<table>
<thead>
<tr>
<th>Fresh</th>
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<tr>
<td>Flow cytometry</td>
<td>Histology, Immunohistochemistry, FISH, PCR</td>
</tr>
<tr>
<td>Medical Genetics/Molecular</td>
<td>WHO diagnosis Haematology</td>
</tr>
</tbody>
</table>

- Please contact Cellular Pathology laboratory prior to collection of fresh tissue for suspected lymphoma
NICaN Clinical Management Guidelines for Lymphoid Malignancies in Adults

- To allow proper triage of samples for flow cytometry and genetic testing, it is mandatory to submit fresh tissue to Cellular Pathology, BHSCT before 3.30 pm on working days. Prior telephone contact would be helpful.
- If fresh tissue cannot be submitted to the laboratory on time, it is safest to transport the sample in formalin.
- TAT for clonality and FISH are currently 3-6 weeks; as such a lymphoma diagnosis on cores may not be possible and an excision will be requested.

** For the vast majority of cases with a broad clinical differential diagnosis, it may be appropriate to submit tissue in formalin **

Figure 3 Skin Lymphoma

- Diagnosis of ALL skin lymphoma is based on clinico-pathological correlation.
- Clonality by PCR is not synonymous with malignancy; morphological and immunophenotypic identification of an abnormal lymphoid population is essential to interpret clonality result.
- Deep seated lymphoma may require a large punch, skin ellipse excision or a ‘double punch’ biopsy.

Figure 4 Neuro and Intraocular Lymphoma
- Neuropathologists are the 1st point of contact for CNS lymphoma
- Combined neuropathology/haematopathology handling of specimen is necessary for optimal results
- Vitreous fluid/biopsy: please contact Cytopathology laboratory prior to sampling
- A ‘neat’ undiluted sample of vitreous fluid and washing should be submitted to Cytopathology laboratory separately

Figure 5: Blood and Bone Marrow

- Flow cytometry and initial aspirate morphology is assessed in BCH Haematology
- Haematology labs in CAH/UHD/RBHSC perform additional histochemical stains and PB/aspirates are reported by haematologists and or Clinical Scientists based at these sites
- Trephine biopsy processing and immunohistochemistry for BHSCT (including RBHSC), ST and SET is based in Cellular Pathology BHSCT
- Trephine biopsy reporting: BCH and UHD based haematologists and Cellular Pathology in BHSCT

**Conclusion**: Accurate lymphoma diagnosis requires multidisciplinary and multi-technique collaboration. Good communication between ‘sample takers’ and ‘sample interpreters’ is vital. The final WHO diagnosis of lymphoma is an amalgamation of clinical, morphological, immunophenotypic and genetic information
7. CLASSICAL HODGKIN LYMPHOMA (CHL)

7.1 Key issues

- The role of radiotherapy
- The role of CT-PET scanning in the assessment of response and residual disease
- The interface with diffuse large B-cell lymphoma in a small number of cases
- Uncertainty about the behaviour of Hodgkin’s lymphoma in the elderly
- Late effects (fertility, second malignancy risk, cardiac risk)
- The role of escalated chemotherapy such as escalated BEACOPP in the management of high risk advanced disease
- The role of Brentuximab Vedotin

7.2 Diagnostic criteria and genetic features

7.2.1 Definition and subtypes

- Classical Hodgkin lymphoma (CHL) is a monoclonal lymphoid neoplasm (in most instances derived from B cells) composed of mononuclear Hodgkin cells and multinucleated Reed-Sternberg (HRS) cells residing in an infiltrate containing a variable mixture of non-neoplastic small lymphocytes, eosinophils, neutrophils, histiocytes, plasma cells fibroblasts and collagen fibres.

- Based on the characteristics of the reactive infiltrate and the morphology of the HRS cells (such as presence of lacunar cells), four histological subtypes have been distinguished:
  - Lymphocyte rich CHL (LRCHL)
  - Nodular sclerosis CH (NSCHL)
  - Mixed cellularity CHL (MCCHL)
  - Lymphocyte-depleted CHL (LDCHL)

- Whilst the immunophenotypic and genetic features of the mononuclear and multinucleated cells are identical in these histological subtypes, their clinical features and association with Epstein-Barr virus (EBV) differ.

- The prevalence of EBV in HRS cells varies according to histological subtype and epidemiologic factors. The highest frequency (~75%) is found in MCCHL. The lowest (10-40%) in NSCHL. EBV infection approaches 100% in HIV positive Hodgkin lymphoma patients and in cases from resource-poor countries.
7.2.2 Immunophenotype

- Typically CD30+, CD15+/−, MUM1+, BOB1 −, OCT2 −/+ , CD20−/+ , PAX5+, CD3−
- CD20 is positive in up to 40% of cases but is usually expressed on a minority of tumour cells with variable intensity.
- OCT2 is strongly expressed in ~10% of cases.
- EMA is usually negative but weak expression may be seen in tumour cells in 5% of cases.
- Epstein Barr virus latent membrane protein 1 (LMP1) or Epstein Barr encoded viral RNA (EBER) are positive in a proportion of CHD cases, particularly MCCHL and LDCHL. LMP1 and EBER are negative in Anaplastic Large Cell Lymphoma (ALCL) and Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL).

7.2.3 Immunoglobulin and TCR gene rearrangements

HRS cells contain clonal immunoglobulin rearrangements in >98% of cases. Clonal T-cell receptor gene rearrangements are present in rare cases. These are not routinely tested for in Hodgkin lymphoma as the clonal rearrangements are usually only detectable in the DNA of isolated single HRS cells and not in whole tissue DNA. The rearranged IG genes harbour a high load of somatic hypermutations in the IGHV genes, usually without signs of ongoing mutations. These features support the view that HRS cells of B-cell lineage are derived from a germinal centre B cell.

7.3 Prognosis and Staging

Prognosis

The International Prognostic Score was published in 1998 and is used to calculate prognosis in advanced Hodgkin lymphoma. It was based on an analysis of 5141 patients treated at 25 centres from 1983 to 1992. It consists of seven clinical variables:

1. Age >45 years
2. Male
3. Stage IV disease
4. Hb <105 g/L
5. Albumin < 40 g/L
6. Lymphocytes <0.6 x10⁹/L or <8% of WBC
7. WBC >15 x 10⁹/L

Predicted freedom from progression (FFP) at 5 years is directly related to the number of factors present.

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>5-year FFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84 % (±- 4%)</td>
</tr>
<tr>
<td>1</td>
<td>77 % (±- 3%)</td>
</tr>
<tr>
<td>2</td>
<td>67 % (±- 2%)</td>
</tr>
<tr>
<td>3</td>
<td>60 % (±- 3%)</td>
</tr>
<tr>
<td>4</td>
<td>51 % (±- 4%)</td>
</tr>
<tr>
<td>≥5</td>
<td>42 % (±- 5%)</td>
</tr>
</tbody>
</table>
The 5-year FFP for patients with zero factors is 84%. Each additional factor lowers the 5-year FFP rate by 7%.

An online International Hodgkin’s Disease Prognostic score calculator can be accessed by using the following hyper link: [http://www.qxmd.com/calculate-online/hematology/hasenclever-hodgkins-prognosis-score-ips](http://www.qxmd.com/calculate-online/hematology/hasenclever-hodgkins-prognosis-score-ips)

An analysis of patients with advanced Hodgkin lymphoma who have been treated more recently suggests that FFP and OS have improved significantly such that patients with ≥5 risk factors achieved 5 year FFP rates of 66%.²

**Staging**

Staging is as per Ann Arbor method (see Appendix B)

### 7.4 Treatment

Treatment for patients with Hodgkin Lymphoma should be guided by BCSH guideline for the first line management of classical Hodgkin lymphoma.³

Patients are stratified into the following groups: favourable early stage disease, unfavourable early stage disease or advanced disease (as outlined below).

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>EORTC/GELA</th>
<th>GHSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early, favourable</td>
<td>Stage I-II without risk factors</td>
<td>Stage I-II without risk factors</td>
</tr>
<tr>
<td>Early, unfavourable</td>
<td>Stage I-II + ≥ 1 risk factor</td>
<td>Stage I or IIA + ≥ 1 risk factor Stage IIB + risk factor C or D (but not risk factors A/B)</td>
</tr>
<tr>
<td>Advanced</td>
<td>Stage III-IV</td>
<td>Stage IIB + risk factors A or B Stage III-IV</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>A: CXR Mediastinal mass ratio &gt;0.33</td>
<td>A: CXR Mediastinal mass ratio &gt;0.33</td>
</tr>
<tr>
<td></td>
<td>B: Age &gt; 50 years</td>
<td>B: Extra-nodal disease</td>
</tr>
<tr>
<td></td>
<td>C: ESR &gt;50 without B symptoms, ESR &gt;30 with B symptoms</td>
<td>C: ESR &gt;50 without B symptoms, ESR &gt;30 with B symptoms</td>
</tr>
<tr>
<td></td>
<td>D: ≥ 4 nodal areas</td>
<td>D: ≥ 3 nodal areas</td>
</tr>
</tbody>
</table>
7.4.1 Primary treatment

Early stage disease

Favourable early stage HL

- Suggested regimen
  - ABVD\(^3\) (Appendix C regimen 1)

Key recommendations (derived from BCSH guidelines 2014)\(^3\)

- Standard of care for patients with favourable early stage HL is 2 x ABVD and 20 Gy radiotherapy\(^3\)

Evidence

- The German Hodgkin Lymphoma Study Group (GHSG) HD10 trial has shown that patients with early-stage Hodgkin lymphoma and a favourable prognosis, treatment with two cycles of ABVD followed by 20 Gy of IFRT is as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of IFRT\(^6\)
- All patients should have an end of treatment CT-PET scan\(^3\)

Unfavourable early stage HL

- Suggested regimens
  - ABVD\(^3\) (Appendix C regimen 1)
  - BEACOPP\(^3\) (Appendix C regimen 2)

Key recommendations (derived from BCSH guidelines 2014)\(^3\)

- Standard of care for unfavourable early stage HL is 4 x ABVD and 30 Gy RT
- An alternative treatment option for unfavourable early stage HL is 2x escalated BEACOPP + 2 x ABVD and 30 Gy RT
- Radiotherapy should not normally be omitted in patients presenting with bulk disease
- The decision to omit radiotherapy from the management of IA/IIA non-bulky patients should involve discussion with a radiation oncologist. Patients choosing to omit radiotherapy need to be aware of the balance of risks between radiation and additional cycles of chemotherapy and the increased risk of early relapse (3-7%) if radiotherapy is omitted
- Early stage patients treated without RT should receive at least 3 x ABVD
General Considerations

- In unfavourable early stage disease BEACOPP usually given if patient hasn’t responded to ABVD – give three cycles, then PET then fourth cycle if there has been a response (up to 4 cycles total)
- Women treated with mediastinal RT before the age of 35 years should be offered entry into the breast cancer National Notification Risk Assessment and Screening programme (NRASP)³

Evidence

- The German Hodgkin Lymphoma Study Group (GHSG) HD14 trial in patients with early unfavourable Hodgkin Lymphoma demonstrated improved 5 year progression free survival (6.2%) with 2 cycles of escalated BEACOPP followed by 2 cycles of ABVD (2+2) followed by IFRT 30 Gy compared to ABVD x 4 followed by IFRT 30 Gy.⁷ There was more acute toxicity associated with 2+2 but no overall differences in TRM or secondary malignancies⁷

Omission of RT in early stage disease

- Caution should be exercised when de-escalation of therapy (no consolidation radiotherapy) is being considered. The GELA H9 and EORTC-GELA H10 data argue strongly against the use of chemotherapy alone in early stage HL outside of clinical trials.⁸ Such cases require discussion at an MDM with a clinical oncologist
- In the RAPID study radiotherapy was omitted on the basis of a negative PET scan (Deauville 1 and 2) after 3 courses in patients without mediastinal bulk. Although this approach was not shown to be non inferior to consolidation radiotherapy the 3yr PFS was excellent 91% vs 95% with RT ⁴

Advanced disease

Patients ≤60 years old

- Suggested regimens
  - ABVD³ (Appendix C reg 1)
  - BEACOPP³ (Appendix C reg 2)

Key recommendations (derived from BCSH guidelines 2014)³

- Patients aged 16–60 years old with advanced stage HL should receive either 6–8 cycles of ABVD or six cycles of escalated BEACOPP
- The choice between ABVD and escalated BEACOPP will depend on a range of factors, particularly the patient’s opinion on the toxicity/efficacy balance between the regimens
• Patients with a higher IPS are at higher risk of relapse, potentially supporting the use of escalated BEACOPP in this higher risk group, although there are no prospective trial data to support a specific IPS cut-off at which escalated BEACOPP may be advantageous
• There is no international consensus on whether patients are best served by starting therapy with either ABVD or escalated BEACOPP

General Considerations
• Studies indicate that ABVD can be given at full-dose without growth factors and irrespective of the neutrophil count. This approach is not associated with an increased number of infective episodes yet enables maximal efficacy as treatment delays are avoided. There are concerns that GCSF may enhance Bleomycin induced lung toxicity
• It is recommended that ABVD be delivered on schedule irrespective of neutrophil count. G-CSF is only required for patients with infectious complications
• Patients receiving bleomycin should be assessed carefully for signs and symptoms of pulmonary toxicity before each dose. A history of new or worsening dyspnoea or pulmonary crackles should lead to stopping of bleomycin until an alternative cause is identified
• Consider performing 6 minute walk test with oxygen saturation monitoring on every patient prior to every dose of ABVD. Consider regular CXR and lung function monitoring. There should be a low threshold for performing CT chest to identify pneumonitis

Consolidation RT in advanced disease
Key recommendations (derived from BCSH guidelines 2014)
• Patients treated with escalated BEACOPP who achieve an end-of-treatment PET-negative remission do not require consolidation RT to residual tissue
• Patients treated with ABVD should be considered for RT to sites of original bulk or residual tissue >1.5 cm
• It remains unclear whether RT can be safely omitted in ABVD patients who have residual tissue >1.5 cm on CT that is PET-negative
• Interim PET (iPET2) (12 to 14 days post chemo) is highly predictive of outcome in patients treated with ABVD
• It remains unclear how iPET2-positive (Deauville 4 or 5) patients are optimally managed in routine practice. Accepting the limitations of small, published datasets, treatment intensification to escalated BEACOPP +/- RT appears reasonable
• Patients who remain PET-positive on completion of therapy require biopsy assessment or close clinical/ radiological surveillance for early progression
• Patients who develop progressive disease on therapy should be considered for
treatment intensification with transplantation.

**iPET2- negative and Bleomycin Toxicity**

- It remains unclear how iPET2-negative (Deauville 1 or 2) patients are optimally managed in routine practice. For patients with a negative iPET2 after 2 cycles of ABVD, if there are concerns re Bleomycin toxicity a suggested approach is to then complete a further 4 cycles of AVD.
- This is based on data from the RATHL trial which examined whether an interim FDG-PET scan could be used to guide the de-escalation of therapy for patients with a high probability of cure after ABVD therapy and escalation for those at higher risk for treatment failure.
- Results show the 3-year progression-free survival rate and overall survival rate in the ABVD group were 85.7% and 97.2% respectively; the corresponding rates in the AVD group were 84.4% and 97.6%. Respiratory adverse events were more severe in the ABVD group than in the AVD group. Overall the study concluded that the omission of bleomycin from the ABVD regimen after negative findings on interim PET resulted in a lower incidence of pulmonary toxic effects than with continued ABVD but not significantly lower efficacy.
- In the BEACOPP group the 3-year progression-free survival rate was 67.5% and the overall survival rate 87.8%.
- De-escalation of therapy in patients with iPET2 Deauville score 3 is not advised outside of a clinical trial.

**7.4.2 Restaging at completion of primary therapy**

- In those with a negative iPET2, a restaging CT-PET scan is advised.
- In those with a positive iPET2, a re-staging PET-CT is advised to establish if escalation of therapy has achieved a metabolic response.
- Biopsy of any persistently FDG-avid area should be carried out if possible, prior to commencing salvage chemotherapy.
- If only localised FDG avidity at a site of previous disease is present, then consolidation radiotherapy can be considered as an alternative.

**7.4.3 CHL in elderly patients**

- Suggested regimens
  - VEPEMB (Appendix C reg 3)
- Alternative regimens
  - CHIVPP (Appendix C reg 5)

Guidance on therapy choice for non-frail patients is hampered by the lack of randomized trial data.
Key recommendations (derived from BCSH guidelines 2014)³

- Elderly patients should be formally assessed for fitness to receive combination chemotherapy with a co-morbidity assessment tool, which should identify ‘frail’ from ‘non-frail’ patients
- Patients considered ‘frail’ should not usually be offered conventional combination chemotherapy
- Non-frail’ patients should be offered combination chemotherapy and RT with the aim of achieving CR, which is associated with better survival

Evidence

- A GHSG analysis on tolerability and efficacy of ABVD in elderly patients indicated that ABVD is considerably more toxic than previously acknowledged in the elderly population and might not be sufficiently effective, particularly in advanced stage patients¹⁵
- Treatment with VEPEMB ‖ appears to have lower treatment-related mortality than ABVD or BEACOPP
- Elderly patients considered unfit for other reasons may be treated with ChiVPP although published outcomes for this regimen in the elderly are generally poor³,¹⁴

7.4.4 Treatment of relapsed/refractory CHL

Salvage treatment in patients eligible for high dose therapy/ASCT

Please discuss treatment with the Transplant team as soon as possible, ideally before starting salvage therapy

- Suggested salvage regimens
  - ICE¹⁸ (Appendix C reg 7)
  - GDP¹⁹ (Appendix C reg 6)
  - ESHAP²¹ (Appendix C reg 8)

- Alternatives salvage regimens
  - Brentuximab Vedotin²²,²³ (NICE TA 524) (Appendix C reg 9)
  - Bendamustine monotherapy²⁴,²⁵ (Appendix C reg 10)
  - Nivolumab²⁶ (Appendix C reg 11)
  - Brentuximab Vedotin/Bendamustine¹⁷,²⁰ (Appendix C reg 12)

- Stem cell transplantation (SCT) regimens
  - BEAM - Auto (Appendix C reg 13)
  - BEAM + Campath - RIC Allo (Appendix C reg 14)
Key recommendations (derived from BCSH guidelines 2014)³

- The choice of a first line salvage regimen in patients eligible for ASCT should be based on patient factors and familiarity of the treatment centre with the regimen
- Regimens containing stem cell toxic agents (such as carmustine and melphalan) should be avoided if possible until stem cells have been successfully collected and cryopreserved if ASCT is planned
- There is currently no evidence to support intensive sequential induction/consolidation strategies prior to ASCT
- Consider switching to an alternative non-cross-resistant salvage regimen if there are residual FDG-avid lesions after first line salvage treatment and the intent is to proceed to ASCT

General Considerations

- For patients with refractory or relapsed HL who eligible for high-dose therapy (HDT), the treatment of choice consists of (HDT) with BEAM followed by autologous stem cell transplantation (ASCT)
- Salvage regimens such as ifosfamide/carboplatin/etoposide (ICE) are given to reduce the tumour burden and mobilise stem cells before HDT and ASCT
- ASCT is not recommended in those failing to achieve an adequate response³
- An adequate response to salvage therapy is currently defined as a PR by conventional CT criteria³

Salvage treatment in patients not eligible for high dose therapy/ASCT

- Suggested regimens
  - GDP¹⁹ (Appendix C reg 6)
  - Brentuximab Vedotin²²,²³ (NICE TA 524) (Appendix C reg 9)
  - Vinblastine²⁷ (Appendix C reg 15)
  - Etoposide²⁸ (Appendix C reg 16)

Key recommendations (derived from BCSH guidelines 2014)³

- In patients not eligible for HDT/ASCT, combined modality (RT/chemotherapy) therapy should be considered, especially in early stage relapse and in patients who have not received prior radiotherapy or who have relapsed outside of the initial radiotherapy field³
- In patients unlikely to tolerate the toxicities associated with more intensive regimens, palliation with either a single agent or with a multi-agent oral regimen with or without intravenous vinblastine should be considered³
- Early consideration of involvement of palliative care services is recommended, particularly in those not eligible for high dose therapy³
General Considerations

- Numerous trials of first-line treatment, especially for early stage disease, demonstrate the superior disease control achieved with combined modality therapy. It therefore seems reasonable to combine radiotherapy (RT) with chemotherapy for transplant ineligible patients at relapse.

- Palliative options include single agent Vinblastine (6mg/m² IV every 14 days) or etoposide (100-150mg daily po for 7-14 days every 28 days according to the degree of myelosuppression encountered).

Evidence

- GDP was compared to DHAP in Journal of Clinical Oncology study. For the intention-to-treat population, the response rate with GDP was 45.2%; with DHAP it was 44.0% meeting protocol-defined criteria for noninferiority of GDP. No differences were detected in event-free survival or overall survival between GDP and DHAP. Treatment with GDP was associated with less toxicity and need for hospitalization, and preserved quality of life.

- ICE was examined as a salvage therapy in a 2001 study. The EFS rate at a median follow-up of 43 months, was 58%. The response rate to ICE was 88%, and the EFS rate for patients who underwent transplantation was 68%. These results compare favorably with other series which showed EFS of 30% - 50%.

- An Annals of Oncology study showed ESHAP is an effective salvage regimen. In this study nine patients achieved complete responses and seven partial responses (overall response rate 73%) with ESHAP. Grade 3–4 myelotoxicity was seen in 13 patients (59%). Nine patients received HDT plus ASCT. At a median follow-up time of 50 months (range 6–96), seven patients (32%) were alive and disease-free. Three patients died of toxic effects of ESHAP (1) or HDT (2). Actuarial overall survival and disease-free survival were 35% and 27% at three years.

- Brentuximab Vedotin is licensed for the treatment of relapsed or refractory Hodgkin Lymphoma following either ASCT or at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option (ORR73%, CR 32%, median duration of response 6.7 months).

- The Manchester group have shown that brentuximab can successfully provide a bridge to allogeneic transplantation in approximately 25% of patients refractory to other therapies.

- Two recent studies reported response rates of 53–58% in patients receiving bendamustine monotherapy. Although most patients had received a prior ASCT, response was not influenced by chemosensitivity to previous line of treatment, suggesting this may be a useful second line salvage option.

- Bendamustine is not routinely commissioned and is subject to an IFR request. It would likely be considered as a potential bridge to an allogeneic transplantation.
- Nivolumab is licensed for the treatment of relapsed or refractory Hodgkin Lymphoma following ASCT and treatment with brentuximab vedotin
- The CheckMate 205 study examined nivolumab in adult patients (aged ≥18 years) with recurrent classical Hodgkin’s lymphoma who had failed to respond to autologous stem-cell transplantation and had either relapsed after or failed to respond to brentuximab vedotin and showed an ORR 66%, CR 9% a median duration of response of 7.8 months
- A phase 1/2 study evaluated the combination of brentuximab vedotin (BV) plus bendamustine as a first salvage regimen in relapsed/refractory HL. After a median of 2 cycles of combination therapy (range, 1-6), the objective response rate among 53 efficacy-evaluable patients was 92.5%, with 39 patients (73.6%) achieving CR. Forty patients underwent ASCT. Thirty-one patients (25 of whom underwent ASCT) received brentuximab vedotin monotherapy (median, 10 cycles; range, 1-14). After a median of 20.9 months of follow-up, the estimated 2-year progression-free survival was 69.8% and 62.6% for patients who received ASCT and all patients, respectively. Thirty-one patients (56.4%) experienced infusion-related reactions (IRRs), with a majority occurring during cycle 2 of combination therapy

**Allogeneic stem cell transplantation**
- Allogeneic transplantation using a reduced intensity conditioning regimen such as BEAM + Campath is the treatment of choice for younger patients with a suitable donor and chemo-sensitive disease
- An appropriately HLA-matched unrelated donor should be considered when there is no HLA-matched sibling
- A second autologous transplant is a reasonable clinical option in selected patients with late relapse following ASCT
- Investigation of the use of allogeneic transplantation earlier in the treatment pathway should be performed in the context of prospective clinical trials, but may be justified in selected patients who have required multiple lines of therapy to achieve a response

**7.5 Radiotherapy in relapsed CHL**
- The use of radiotherapy should be given serious consideration in cases of local relapse or relapse at sites where local disease is dominating the clinical picture. The use of involved site techniques is recommended to minimize toxicity to normal tissues (for example, lung fields) if subsequent high dose consolidation therapy is planned
- Salvage radiotherapy alone may be considered a reasonable treatment option in selected patients not eligible for ASCT, especially for older patients with relapsed HL who lack B symptoms, have a good performance status, and have limited stage
disease at relapse\textsuperscript{3}

- In the rare event of late relapse >5 years after primary therapy occurring at a localized site without B symptoms, treatment with standard-dose chemotherapy and involved field radiation alone may be appropriate\textsuperscript{3}
- Peri-transplant (ASCT) radiotherapy should be considered in patients that have a dominant site of local relapse at an initially involved site (these are usually patients who have had bulky disease with residual abnormalities following salvage chemotherapy and ASCT)\textsuperscript{3}
8. NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA (NLPHL)

8.1 Key issues

- Recognised as separate disease entity from classical HL\(^3\)\(^1\)
- Biological relationship between NLPHL and T-Cell/Histiocyte-Rich Diffuse Large B-Cell Lymphoma
- Uncertainty over clinical behaviour of early stage disease - is treatment required in some patients?\(^2\)\(^2\)
- Long-term therapy-related toxicities from secondary malignancies and cardiopulmonary disease are of particular concern given the generally long survival time of these patients
- Whether alkylator-based chemotherapy regimens have more activity than non-alkylator (eg ABVD) therapy has not been clearly defined
- Data on treatment and outcomes confused by inclusion of most cases in trials with classical Hodgkin lymphoma
- Possible role of Rituximab as single agent therapy\(^3\)\(^3\)
- May transform to DLBCL

8.2 Diagnostic criteria

**Definition**

- NLPHL is a monoclonal B-cell neoplasm characterised by a nodular (or a nodular and diffuse) proliferation of scattered large neoplastic cells known as popcorn or lymphocyte predominant cells\(^3\)\(^5\)
- These cells reside in large spherical meshworks of follicular dendritic processes that are filled with non-neoplastic lymphocytes and histiocytes
- The European Task force on lymphoma showed that, following re-review by expert haematopathologists according to strict morphological and immunophenotypic criteria, only 56.5% of cases were confirmed to be NLPHL\(^3\)\(^4\) This highlights the importance of expert review by a Haematopathologist and questions the validity of older case series assembled prior to the availability of immunophenotyping\(^3\)\(^5\)
- Typically presents in fourth decade of life with significant male predominance (75%)
- Typically involves peripheral node sites such as cervical, axillary or inguinal regions rather than the mediastinum or retroperitoneum
- B symptoms, extra-nodal involvement and bulky disease are extremely uncommon
**Immunophenotype**

- LP cells are CD20+, CD15-, CD30-, BCL6+, CD45+, CD79a+, CD75+, BOB1+, OCT2++, PAX5+, EBV LMP-
- Epithelial membrane antigen (EMA) is present in more than 50% of cases
- LP cells lack CD15 and CD30 in nearly all instances. CD30 +ve large cells may still be seen but these are usually reactive immunoblasts unrelated to the LP cells. Infrequently, LP cells show weak expression of CD30
- The architectural background in NLPHL is composed of large spherical meshworks of follicular dendritic cells which are predominantly filled with a mixture of small B cells and numerous CD4+/CD57+ T cells

**8.3 Treatment**

**8.3.1 Primary Treatment**

**Limited Stage NLPHL: Stage IA or IIA (approximately 80% of cases)**

**General considerations**

- As a result of different treatment philosophies, international treatment recommendations are broad, ranging from potentially curative approaches with radiation, chemotherapy or combined chemo-radiotherapy to non-curative options such as observation in incompletely resected disease to Rituximab therapy
- The long-term therapy-related toxicities from secondary malignancies and cardiopulmonary disease are of particular concern with NLPHL given the generally long survival time of these patients and the possibly increased representation of paediatric cases. This should be taken into consideration prior to commencing chemotherapy
- Involved field radiotherapy can be considered for those in whom surgery does not achieve complete clearance

**Key recommendations for treatment of early stage NLPHL (derived from BCSH guidelines 2015)**

- Patients should be offered participation in prospective clinical trials, where available
- Surgery should be offered to patients with localized, resectable disease
- Patients with residual but localized NLPHL (stage 1A and 2A with ≤2 sites of disease) should be offered involved field radiotherapy (IFRT)
- A watch and wait approach may be considered in patients who are in complete remission following excision following discussion with a radiation oncologist
- Patients with stage 2A who are not suitable for IFRT alone (>2 sites of disease or extensive stage II infra-diaphragmatic disease with close proximity to radiosensitive organs such as kidney, bowel and pancreas) should be treated as advanced stage disease
Advanced Stage NLPHL (Stage II with risk factors such as bulky tumour or B symptoms, Stage III or Stage IV)

- Suggested regimens
  - R-CHOP\(^{47}\) (Appendix C reg 17)

- Alternative regimens
  - R-ABVD\(^{47}\) (Appendix C reg 18)
  - R-CVP\(^{47}\) (Appendix C reg 19)
  - DA R-EPOCH\(^{77}\) (Appendix C reg 20)
  - Rituximab monotherapy\(^{47}\) (Appendix C reg 21)

Key recommendations for treatment of advanced stage NLPHL (derived from BCSH guidelines 2015) \(^{47}\)

- Patients should be offered participation in prospective clinical trials
- Always consider the possibility of high-grade transformation in patients with rapidly progressive disease, marked B symptoms, focal abnormalities in the spleen or bone marrow involvement. An additional tissue biopsy is justified in these patients
- Consider whether treatment is immediately necessary or whether a period of watch and wait would be appropriate
- Consider R-CHOP, R-CVP /R-ABVD in patients requiring combination chemotherapy
- Consider R-CHOP in patients with evidence (or a high index of suspicion) of transformed disease
- Consider rituximab monotherapy in patients with advanced stage NLPHL who have serious co-morbidities that would preclude the use of combination chemotherapy
- Avoid rituximab maintenance for patients responding to first-line therapy

International consensus

- There are limited data to guide the management of advanced stage NLPHL patients
- The optimal chemotherapy regimen is unknown\(^{35}\)
- The ESMO guidelines (largely based on the GHSG Hodgkin Lymphoma trials) support the use of ABVD. The NCCN guidelines (based on retrospective studies and a minority of prospective studies) suggest the following chemotherapy regimens (with Rituximab): ABVD, CHOP, CVP

Evidence

- Whether or not alkylator-based chemotherapy regimens may have more activity than nonalkylator-based (ABVD) regimens in NLPHL has not been clearly defined\(^{40}\)
- ABVD has not been associated with the development of MDS/AML.\(^{43}\) Alkylator agents are known to increase the rates of MDS and AML.\(^{44}\) In a series of 88 NLPHL
patients treated with ChlVPP, 3 patients had developed MDS after a median follow-up of 13 years. The MDACC published a retrospective series of NLPHL patients (all stages, variety of treatments) which included 27 patients treated with R-CHOP, overall response rate of 100% (complete responses 89%). The median follow-up was 6.7 years, and the estimated 5- and 10-year PFS rates for patients treated with R-CHOP were 88.5% and 59.3%, respectively.

- Evidence for using DA-R-EPOCH in NLPHL comes from studies which examined DA-R-EPOCH in NHL (in particular DLBCL- see DLBCL treatment section – advanced disease)

8.3.2 Treatment of NLPHL/TC-HR -DLBCL and transformations to DLBCL

- Given the proposed biologic relationship between NLPHL and T-Cell/Histiocyte-Rich Diffuse Large B-Cell Lymphoma, the use of alkylator-based chemotherapy regimens such as CHOP or CVP (with or without rituximab) has been advocated.

- The British Columbia group recently reported that there was a substantial risk of transformation to DLBCL (65% at 25 years) in NLPHL patients treated with ABVD who had splenic involvement at diagnosis. This higher risk of transformation to DLBCL provides another rationale for the use of R-CHOP, particularly in those patients with splenic involvement

- In some cases the distinction between disseminated NLPHL and the T-cell rich variant of DLBCL is difficult and is to some extent arbitrary. For this reason these patients may be treated as for diffuse large B-cell lymphoma

- In certain patients DA-REPOCH should be considered

8.3.3 Treatment of relapsed/refractory NLPHL

- Suggested regimens
  - R-CHOP (Appendix C reg 17)

- Alternative regimens
  - R-CVP (Appendix C reg 19)
  - Rituximab monotherapy (Appendix C reg 21)

- Suggested salvage regimens for patients proceeding to HDT/ASCT
  - R-GDP (Appendix C reg 6)
  - R-ICE (Appendix C reg 7)
  - R-ESHAP (Appendix C reg 8)

- Alternative salvage regimens for patients proceeding to HDT/ASCT*
  - R-CHOP (Appendix C reg 17)
Key recommendations for treatment of relapsed NLPHL (derived from BCSH guidelines 2015) 47

- Repeat biopsy is advised to exclude high grade transformation
- Consider radiotherapy for an isolated local recurrence especially at a site of previous excision
- Consider a watch and wait approach for asymptomatic patients with advanced stage disease
- Offer chemotherapy for patients with symptomatic advanced stage disease at relapse
- Consider rituximab monotherapy in those patients who require therapy and whose co-morbidities preclude the use of combination chemotherapy

General considerations

- High dose chemotherapy and ASCT should be reserved for very carefully selected patients given the good response to other therapies and the toxicity associated with ASCT35

Evidence

- See advanced stage NLPHL evidence section for information on R-CHOP
- Rituximab has been successfully used in patients with relapsed/refractory disease (ORR 94%, TTP 33 months)48
- Regimens used as second-line therapy for aggressive lymphomas (R-ICE, R-ESHAP,R-GDP) should be considered depending on patient characteristics, eligibility for transplant as consolidation, and previous therapies (see evidence section of relapsed DLBCL)

International consensus

ESMO

- Localised NLPHL relapses can be effectively treated with rituximab monotherapy
- Disseminated disease at relapse and additional poor-risk factors – salvage chemotherapy with rituximab

NCCN

- NCCN list ICE,ESHAP as second line systemic therapy in NLPHL
9. DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

9.1 Key Issues

- Dismal prognosis of DLBCL which has relapsed after R-CHOP chemotherapy
- Possible indication for collection of peripheral blood progenitors in first remission for poor prognosis cases
- Primary mediastinal large B-cell lymphoma is a distinct clinicopathological entity
- The role of CT-PET in DLBCL

9.2 Diagnostic Criteria

This is a tumour that shows diffuse replacement of normal nodal architecture by a population of large B-lymphoid cells.

Diagnosis B-cell lymphomas: gene testing strategies:

- Consider using FISH (fluorescence in situ hybridisation) to identify a MYC rearrangement in all people newly presenting with histologically high grade B-cell lymphoma
- If a MYC rearrangement is found, use FISH to identify the immunoglobulin partner and the presence of BCL2 and BCL6 rearrangements
- Interpret FISH results (MYC, BCL2 and BCL6 rearrangements) in the context of other prognostic factors (particularly the persons age and International Prognostic Indicator [IPI])
- Explain FISH results and their potential prognostic value to people with B-cell lymphoma

Typical Cases

- Diffuse infiltrate of large lymphoid cells
- Proliferation fraction of at least 30%

Variants

- Multiple histological subtypes and morphologic variants are recognized

  - **Common Morphological variants:**
    - Centroblastic
    - Immunoblastic
    - Anaplastic

  - **Rare Morphological variants**

  - **DLBCL subtypes:**
    - T-cell/histiocyte rich large B-cell lymphoma
    - Primary DLBCL of the CNS
    - Primary cutaneous DLBCL, leg type
    - EBV positive DLBCL of the elderly

  - **Other lymphomas of large B-cells**
    - Primary Mediastinal large B-cell lymphoma (This is a distinct entity)
NICaN Clinical Management Guidelines for Lymphoid Malignancies in Adults

- Intravascular large B-cell lymphoma
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- ALK-positive Diffuse Large B-cell Lymphoma
- Plasmablastic lymphoma (no evidence of myeloma, check HIV status)
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma

9.3 Prognosis

International Prognostic Index

The IPI is a predictive prognostic model developed in the pre-Rituximab era for patients with histological aggressive NHL based on 5 clinical features at presentation. The IPI relies on information that is readily accessible and its predictive capacity has been validated in multiple studies.

1. Age >60
2. Ann Arbor stage III/IV
3. Serum lactate dehydrogenase (LDH) elevated
4. Extranodal involvement > 1 site
5. Performance status (ECOG ≥2)

The Age Adjusted IPI is for patients <60 years old. Score 1 each for:

1. Disease stage III/IV
2. Elevated LDH
3. Performance status (ECOG ≥2)
4. Extranodal involvement > 1 site

Survival rates at five years according to the IPI:

<table>
<thead>
<tr>
<th>IPI Risk Group</th>
<th>5-year OS (%)</th>
<th>Age-adjusted IPI</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0-1)</td>
<td>73</td>
<td>Low (0)</td>
<td>83</td>
</tr>
<tr>
<td>Low-intermediate (2)</td>
<td>51</td>
<td>Low-intermediate (1)</td>
<td>69</td>
</tr>
<tr>
<td>Intermediate-high (3)</td>
<td>43</td>
<td>Intermediate-high (2)</td>
<td>46</td>
</tr>
<tr>
<td>High (4-5)</td>
<td>26</td>
<td>High (3)</td>
<td>32</td>
</tr>
</tbody>
</table>

The IPI was based on data from the pre-Rituximab era but a subsequent analysis of patients entered in the MInT, MegaCHOEP and RICOVER-60 trials showed that whilst Rituximab significantly improved treatment outcome within each IPI group, the ordering of the IPI groups remained valid. The relative risk estimates of single IPI factors and their order in patients treated with R-CHOP were similar to those found with CHOP, demonstrating that the IPI is still valid in the R-CHOP era.

The Vancouver group has redistributed the IPI factors into a revised IPI (R-IPI) which
more usefully predicts clinical outcome for R-CHOP treated patients.\textsuperscript{51}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{R-IPI Risk Group} & \textbf{\% of patients} & \textbf{4-year PFS (\%)} & \textbf{4-year OS (\%)} \\
\hline
Very Good (0) & 10 & 94 & 94 \\
Good (1,2) & 45 & 80 & 79 \\
Poor (3,4,5) & 45 & 53 & 55 \\
\hline
\end{tabular}
\end{table}

An online R-IPI index calculator can be accessed by using the following hyperlink:
\url{http://www.qxmd.com/calculate-online/hematology/prognosis-large-b-cell-lymphoma-r-mpi}

It should be noted that the IPI or R-IPI has a limited ability to identify patients with very poor outcome and does not provide insight into the biology of DLBCL.\textsuperscript{52}

\section*{NCCN International Prognostic Indicator (NCCN-IPI)\textsuperscript{29}}

The NCCN-IPI is easy to apply and more powerful than the IPI for predicting survival in the rituximab era. Five predictors (age, lactate dehydrogenase (LDH), sites of involvement, Ann Arbor stage, ECOG performance status) were identified and a maximum of 8 points assigned. Four risk groups were formed: low (0-1), low-intermediate (2-3), high-intermediate (4-5), and high (6-8). Compared with the IPI, the NCCN-IPI better discriminated low- and high-risk subgroups (5-year overall survival [OS]: 96\% vs 33\%) than the IPI (5 year OS: 90\% vs 54\%), respectively.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|}
\hline
\textbf{NCCN-IPI} & \textbf{Score} \\
\hline
\textbf{Age} & \\
>40 to \(\leq\)60 & 1 \\
>60 to \(\leq\)75 & 2 \\
>75 & 3 \\
\hline
\textbf{LDH (normalised)} & \\
>1 to \(\leq\)3 & 1 \\
>3 & 2 \\
\hline
\textbf{Ann Arbor stage III-IV} & 1 \\
\textbf{Extranodal disease}\* & 1 \\
\textbf{Performance status \(\geq\)2} & 1 \\
\hline
\end{tabular}
\end{table}

\*Disease in bone marrow, CNS, liver/GI tract or lung.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
\textbf{NCCN-IPI} & \textbf{5 year OS} & \textbf{5 year PFS} \\
\hline
Low (0-1) & 96\% & 91\% \\
Low-intermediate (2-3) & 82\% & 74\% \\
High-intermediate (4-5) & 64\% & 51\% \\
High & 33\% & 30\% \\
\hline
\end{tabular}
\end{table}

An online prognostic calculator can be accessed using the following hyperlink:
\url{https://qxmd.com/calculate/calculator_311/diffuse-large-b-cell-lymphoma-prognosis-nccn-mpi}

\section*{Marrow Involvement}

- Concordant bone marrow involvement is associated with a very poor prognosis (5-
year overall survival, 10%. Discordant involvement does not influence the clinical outcome significantly \(^{53}\)

**Genetic, molecular and cellular prognostic factors**

- Recent insights into the pathogenesis of DLBCL suggest that it is a heterogeneous group of B-cell lymphomas rather than a single clinicopathologic entity. \(^{54}\) A variety of molecular and genetic abnormalities are variably present, and patients exhibit a wide range of clinical presentations and outcomes
- Multiple biologic predictors appear promising; however, none have been validated for routine clinical use \(^{55}\)
- Up to 30% of cases show abnormalities of the 3q27 region involving the *BCL6* gene, which is the commonest translocation in DLBCL \(^{56-58}\)
- Translocation of the *BCL2* gene is a hallmark of follicular lymphoma, but occurs in 20-30% of DLBCL \(^{59}\)

**MYC and DLBCL**

- Refer to high grade B cell section

**Gene expression analysis**

Gene-expression profiling studies have identified at least 3 distinct molecular subtypes of DLBCL:

- **GCB subtype**, expression profile similar to normal germinal centre B cells
- **ABC subtype**, expression profile mimicking activated peripheral-blood B cells
- **Primary mediastinal large B-cell lymphoma** (PMBL), displays some molecular genetic similarities to Hodgkin lymphoma and typically presents with mediastinal lymphadenopathy

A small number of cases do not fit into any of these categories and have been designated as “unclassifiable” \(^{68}\)

**Genetic molecular and clinical characteristics of DLBCL**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ABC</th>
<th>GCB</th>
<th>PMBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(14;18)</td>
<td>0</td>
<td>35%</td>
<td>0</td>
</tr>
<tr>
<td>3q gain/amplification</td>
<td>26%</td>
<td>0</td>
<td>5%</td>
</tr>
<tr>
<td>9p gain/amplification</td>
<td>6%</td>
<td>0</td>
<td>35%</td>
</tr>
<tr>
<td>12q12</td>
<td>5</td>
<td>20%</td>
<td>5%</td>
</tr>
<tr>
<td>Ongoing IG mutations</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
ABC, activated B-cell-like; GCB, germinal centre B-cell-like; PMBL, primary mediastinal large B-cell lymphoma

As gene expression profiling is not routinely available, immunohistochemistry staining for CD10, BCL6 and MUM1 expression has been employed as surrogate markers to determine GCB and Non GCB subtypes of DLBCL.69

This immunohistochemical subdivision does not correlate exactly with gene expression-based subgrouping of DLBCL and does not currently determine therapy.70

### 9.4 Treatment

### 9.4.1 Primary treatment

**Limited stage DLBCL (Stage IA and IIA limited to an area encompassed by one radiotherapy treatment area)**

- Suggested regimen
  - R-CHOP71,72 (Appendix C regimen 17)
Key recommendations (derived from BCSH guidelines 2016)\textsuperscript{73}

- It is recommended that patients with non-bulky (<7.5 cm) stage IA DLBCL presenting at sites associated with low morbidity for radiotherapy (e.g. groin, neck or axilla), be treated with 3 cycles of R-CHOP chemotherapy followed by ISRT of 30 Gy
- Six cycles of R-CHOP is an alternative and should be the preferred option if disease involves a site where the acute and late complications of RT are better avoided
- Patients with non-bulky stage IIA DLBCL should be treated with 6 cycles of R-CHOP
- Patients with bulky stage IA/IIA DLBCL should be treated with 6 cycles of R-CHOP followed by ISRT of 30 Gy to initial sites of bulk

Evidence

- The SWOG 0014 study reported a 4-year PFS of 88% and OS of 92% when rituximab was added to 3 cycles of CHOP plus IFRT. This represented an improvement over historical data from the pre-rituximab era (4-year PFS and OS of 78% and 88% respectively)\textsuperscript{71}
- The Mab-Thera International trial (MiNT) trial, reported benefit in both OS and EFS when rituximab was added to CHOP-like chemotherapy in young (<60 years) patients with low risk IPI disease. Most patients in this study had limited stagedisease and IFRT was given to bulky (>7.5 cm) and extranodal disease\textsuperscript{72}

Advanced stage DLBCL

- Suggested regimens
  - R-CHOP\textsuperscript{72,74 - 76} (Appendix C regimen17)
- Alternative regimens
  - DA-REPOCH\textsuperscript{77} (Appendix C regimen 20)

Key recommendations (derived from recent BCSH guidelines 2016)\textsuperscript{73}

- It is recommended that patients with advanced stage disease be treated with 6–8 cycles of R-CHOP-21. Variants of this regimen include 6 cycles of R-CHOP-21, each followed by 2 additional rituximab doses
- There is no established standard of care for patients with poor risk IPI disease. R-CHOP is often used but DA-REPOCH is an alternative

Evidence

- The French GELA LNH 98-study showed the benefit of adding rituximab to CHOP in elderly patients\textsuperscript{74}; the MiNT study showed improved outcomes following the addition of rituximab in younger patients with low IPI disease\textsuperscript{72}
- The issue of dose density in the rituximab era was addressed by comparing R-CHOP-14 with R-CHOP-21 by the UK National Cancer Research Institute (NCRI)\textsuperscript{75} and the
French GELA LNH03-6B groups. Both studies showed no OS or PFS difference between R-CHOP-14 and R-CHOP-21. RCHOP- 21 therefore remains the standard treatment for advanced stage DLBCL.

- Results from a phase II trial of (DA-EPOCH-R) from the National Cancer Institute showed time to progression and overall survival were 81% and 84%, respectively, and time to progression was 87%, 92% and 54% for low/low-intermediate, high-intermediate and high International Prognostic Index risk groups, respectively, at 5-years and beyond.
- The time to progression and event-free survival of germinal center B-cell lymphoma were 100% and 94%, respectively, and non-germinal center B-cell GCB diffuse large B-cell lymphoma were 67% and 58%, respectively, at 62 months (germinal center vs. non-germinal center B cell $P=0.008$). DA-EPOCH-R was tolerated without significant grade 4 non-hematologic toxicities.

### 9.4.2 Response assessment in advanced disease

**Key recommendations (derived from BCSH guidelines 2016)**

- The PPV of an interim PET scan is variable with insufficient evidence at present to change standard treatment based on the result of interim PET-CT scan alone. A routine interim PET scan is therefore not recommended.
- An end of treatment PET scan is strongly recommended.
- The PPV of a PET-positive lesion is variable; biopsy is therefore advisable prior to second line treatment. Alternatively, consider an interval scan after 3 months if clinical suspicion of residual disease is low. ISRT to the PET-positive lesion may be an option in selected cases where biopsy is not possible or desirable.

### 9.4.3 The role of up-front high dose chemotherapy (HDT) with ASCT in high risk DLBCL

**Key recommendations (derived from BCSH guidelines 2016)**

- HDT and ASCT are not recommended in first remission outside a clinical trial.

**Evidence**

- A meta-analysis of 15 randomised controlled trials did not show a clear benefit for HDT with ASCT as first line therapy.
- The SWOG S9704 trial found no overall survival advantage for 6 cycles of CHOP+/Rituximab followed by HDT with ASCT compared with 8 cycles of CHOP+/Rituximab although there was a 2 year PFS advantage in ASCT arm (69% v 56%).
9.4.4 DLBCL in elderly patients

- Suggested regimens
  - R-CHOP\textsuperscript{85,86} (Appendix C reg 17)
  - R-miniCHOP\textsuperscript{87} (Appendix C reg 25)

Key recommendations (derived from BCSH guidelines 2016)\textsuperscript{73}

- There is no uniformly accepted age cut-off to define an ‘elderly’ patient as it is applied variably to those aged >60, >65 or >70 years in different studies, with patients >80 years being classified as ‘very elderly’
- Treatment decisions should be based on assessment of fitness/frailty and co-morbidities rather than age alone.
- Patients considered fit for intense treatment should be treated with standard R-CHOP as this produces best outcomes
- Modified R-CHOP with dosage and/or individual drug adjustments should be considered for those unfit for standard treatment
- Patients with impaired performance status (WHO > 2) at presentation, should be considered for a steroid prophase prior to assessing fitness for standard or modified R-CHOP
- Primary G-CSF prophylaxis is recommended for patients aged >65 years, frail patients and those with significant comorbidities

Evidence

- Tools such as the comprehensive geriatric assessment (CGA) or the simpler Charlson comorbidity index may assist physician judgment in identifying those patients who are suitable for R-CHOP \textsuperscript{73}
- R-CHOP can be given to patients aged up to 80 years old if they are fit, but modulation of treatment according to geriatric assessment is recommended \textsuperscript{85,86}
- The French GELA group reported 2-year OS and PFS of 59% and 47% respectively using R-mini-CHOP in patients aged >80 years, predominantly with advanced stage disease and without significant comorbidity or lymphoma-related organ impairment. The treatment-related mortality was 21\%\textsuperscript{87}
- A “pre-phase” course of Prednisolone prior to the first cycle of R-CHOP in elderly patients has been shown to improve performance status, ameliorate the depth and length of neutropenia seen with the first cycle of R-CHOP, reduce the number of therapy-associated deaths and greatly decrease the incidence of tumour lysis syndrome.\textsuperscript{88}
- An ECOG performance status which remains >2 after “pre-phase” treatment may be considered an exclusion criterion for R-CHOP
- In a frail, elderly patient with limited life expectancy due to other comorbid illnesses, four cycles of R-CHOP may be reasonable as the GELA LNH 93-4 trial showed that 4 cycles of CHOP plus radiotherapy did not provide any advantage over 4 cycles of CHOP alone for the treatment of low-risk localized aggressive lymphoma in the elderly\textsuperscript{36}
9.4.5 Treatment of relapsed/refractory DLBCL

Treatment of relapsed/refractory disease in transplant eligible patients

- Suggested salvage regimens
  - R-ICE<sup>100</sup> (Appendix C regimen 7)
  - R-ESHAP<sup>38</sup> (Appendix C regimen 8)
  - R-GDP<sup>19</sup> (Appendix C regimen 6)

- Alternative salvage regimens
  - R-IVE<sup>39</sup> (Appendix C regimen 29)
  - R-Mini BEAM<sup>78</sup> (Appendix C regimen 31)

- Alternative therapies
  - Axicabtagene-ciloleucel (CAR-T) (NICE TA 559)

Key recommendations (derived from BCSH guidelines 2016)<sup>73</sup>

- Repeat biopsy is strongly recommended to confirm relapse
- Transplant-eligible patients should receive intensive salvage chemotherapy with a non-cross resistant regimen followed by ASCT consolidation in those achieving CR
- In those achieving a PR, second line salvage chemotherapy can be given followed by ASCT if CR is achieved, or consolidation by ASCT in PR can be considered
- Response assessment by PET scan prior to ASCT is desirable
- Peri-transplant radiotherapy to sites of disease presenting particular loco-regional problems should be considered, particularly if residual PET-positive lesions are detected following salvage
- There is no clearly defined group where alloSCT is preferable to ASCT, but it may be an option for some younger patients with high-risk disease, especially if stem cell dose is inadequate for ASCT
- Selected patients relapsing post-ASCT may be considered for further salvage and alloSCT

CAR T-cell therapy (derived from NICE guidelines 2019)

- There is no standard treatment for relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma after two or more systemic therapies. Best supportive care is used and usually includes salvage chemotherapy.
- Axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T-cell therapy. It contains the patient's own T cells that have been modified to attach to and kill cancer cells
- Axicabtagene ciloleucel therapy is NICE approved (see NICE TA 559) recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory diffuse large B-cell lymphoma in adults after 2 or more systemic therapies, only if the conditions in the managed access agreement are followed
Evidence

- A 2004 study in the blood journal compared R-ICE to ICE. The CR rate was 53%, significantly better than the 27% CR rate achieved among 147 similar consecutive historical control patients with DLBCL treated with ICE; the PR rate was 25%. Febrile neutropenia was the most frequent grade 3 or 4 nonhematologic toxicity; it occurred in 7.5% of delivered cycles. No patient had R-ICE-related toxicity that precluded ASCT.

- The safety and efficiency of R-ESHAP was examined in a study by Harting et al (2007). Results showed 7 patients (N=13) exhibited complete response (CR) and 3 had partial response, for an objective response rate of 77%. Among 6 patients completing all 6 cycles, 4 (67%) had a CR, 1 had a partial response, and 1 had progressive disease. Three of the 4 CRs have remained for a median of 48 months.

- Evidence for R-IVE in relapsed DLBCL comes from studies which looked at IVE in relapsed NHL and HL. In an BJH study 143 patients with relapsed (n = 90), primary refractory (n = 32) and first line chemotherapy responsive (n = 21) non-Hodgkin lymphoma (NHL) and Hodgkin disease (HD) were treated with IVE with the intent to proceed to high-dose therapy with either autologous or allogeneic transplantation, following peripheral blood stem cell mobilisation.

- A major response (complete/partial response) to IVE was seen in 115 patients (80.4%) with 5-year overall survival (OS) and event free survival (EFS) of 53% and 43%, respectively.

- GDP was compared to DHAP in Journal of Clinical Oncology study. In this study they looked patients with relapsed/refractory aggressive lymphoma. Patients with B-cell lymphoma also received rituximab.

- For the intention-to-treat population, the response rate with GDP was 45.2%; with DHAP it was 44.0% meeting protocol-defined criteria for noninferiority of GDP. No differences were detected in event-free survival or overall survival between GDP and DHAP. Treatment with GDP was associated with less toxicity and need for hospitalization, and preserved quality of life.

- A phase II study examined efficacy of mini-BEAM salvage chemotherapy in patients with relapsed or refractory intermediate grade non-Hodgkin’s lymphoma referred for ASCT and to define prognostic factors of response.

- Results showed the overall response rate (RR) was 37% with 12 patients achieving CR and 25 achieving PR. The response rate among patients treated as first salvage was 43% compared to 20% for patients who had failed to respond to a previous salvage regimen. Only 15% of patients who failed to respond to mini-BEAM responded to another conventional dose salvage regimen.

- Evidence from a small, single-arm study suggests that people having axicabtagene ciloleucel (CAR-T) have clinically meaningful overall and progression-free survival and good response rates. However, the evidence is uncertain because there is limited follow-up and no direct data comparing axicabtagene ciloleucel with salvage.
chemotherapy. Limitations in the available data mean that the exact size of the benefit of axicabtagene ciloleucel compared with salvage chemotherapy is unknown (NICE TA 559)

General Considerations

- For patients with refractory or relapsed NHL who eligible for high-dose therapy (HDT), the treatment of choice consists of (HDT) with BEAM followed by autologous stem cell transplantation (ASCT)
- Salvage regimens such as ifosfamide/carboplatin/etoposide (R-ICE) are given to reduce the tumour burden and mobilise stem cells before HDT and ASCT
- Clinicians should select a salvage regimen in conjunction with transplant centre that they feel most experienced in managing. Rituximab should be given with all therapies
- Patients should receive 2 courses of R-ESHAP or R-ICE chemotherapy as salvage and restaged. If the patient is in CR or near CR (PR), stem cell collection following further salvage chemotherapy or cyclophosphamide + G-CSF is performed, prior to BEAM-conditioned PBSCT
- Patients not responding to 2 courses of R-ESHAP or R-ICE should be changed to another salvage regimen (R-IVE, R-mini-Beam, gemcitabine containing regimen). Stem cell harvest and BEAM autograft should then be carried out in those with chemo-responsive disease
- It is imperative that close liaison with the transplant centre is maintained. The timing of a cyclophosphamide primed progenitor cell harvest is co-ordinated by the transplant centre
- A bone marrow aspirate and trephine should be considered prior to collection of peripheral blood progenitor cells, to ensure the marrow is disease free
- All blood products should be irradiated within 2 weeks of a progenitor cell collection.
- Patients who are fit but in whom stem cells cannot be harvested should receive the same initial chemotherapy as above and be considered for a marrow harvest – these procedures should be discussed at the MDT and with the transplant team

Treatment of relapsed/refractory disease in transplant ineligible patients

- Suggested regimens
  - R-GDP19 (Appendix C regimen 6)
  - R-PMitCEBO119 (Appendix C regimen 32)
  - Pixantrone183 NICE TA 306 (Appendix C regimen 33)
  - Bendamustine184 (Appendix C regimen 10)
  - R- Bendamustine (Appendix C regimen 34)
Evidence

- For evidence for R-GDP see evidence section of treatment of relapsed/refractory disease in transplant eligible patients
- A phase III BJH trial compared PMitCEBO to CHOP. This trial has demonstrated almost identical FFS and OS with CHOP and PMitCEBO\textsuperscript{119}
- This trial was conducted before the advent of rituximab, and it is now widely accepted that rituximab should be given with chemotherapy in all cases of DLBC lymphoma. This does not, however, detract from the finding in this study that PMitCEBO is an acceptable alternative to CHOP when the toxicity profile of PMitCEBO is preferable or more appropriate to the individual patient\textsuperscript{119}
- Pixantrone is NICE approved as monotherapy for relapsed / refractory Diffuse Large B-cell Lymphoma as 3\textsuperscript{rd} or 4\textsuperscript{th} line treatment. Treatment intent may be palliative or curative depending on context\textsuperscript{183}
- A phase II study examined bendamustine at dose of 120mg/m\textsuperscript{2} on days 1 and 2in patients with relapsed or refractory high-grade non-Hodgkin’s lymphomas. Results showed three patients achieved a complete response (at 6, ≥8 and ≥22 months) and five a partial response (three at 2 months, one at 3 months and one at 10 months), the total response rate of the evaluable patients was 44% (eight out of 18; 38% of all patients)\textsuperscript{184}

General Considerations

- Patients not considered candidates for autologous transplantation should be discussed at MDT. Treatment decisions will be influenced by duration of first remission and performance status and potential to achieve second remission:. R-PMitCEBO, , and R-GDP may be considered. Palliative treatment with oral cyclophosphamide and etoposide or steroids alone may be most appropriate.
- Clinical trials of novel agents may be available for those patients relapsing after autograft or in those who are unfit for such a procedure. Please discuss this with the Lymphoma team at BCH.
- Intrathecal Liposomal Cytarabine is considered the treatment of choice for meningeal/CNS relapse in some UK networks

9.4.6 The role of radiotherapy in DLBCL

Key recommendations (derived from NICE – NG52 guidelines 2016)\textsuperscript{84}

- Consider consolidation radiotherapy delivering 30 Gy to sites involved with bulk disease at diagnosis for people with advanced-stage diffuse large B-cell lymphoma that has responded to first-line immunochemotherapy.
For each person, balance the possible late effects of radiotherapy with the possible increased need for salvage therapy if it is omitted, and discuss the options with them.

Evidence

- Dorth et al looked at patients with stage II or IV DLBCL who achieved a complete response to chemotherapy. Clinical outcomes were compared between patients who did and did not receive RT. Receipt of consolidation RT was associated with improved in-field control (92% vs. 69%, respectively) and event-free survival (85% vs. 65%, respectively) but no difference in overall survival (85% vs. 78%, respectively) when compared to patients who did not receive consolidation RT.

- An Italian Lymphoma Study Group examined the effect of RT after (R-CHOP) treatment on event-free (EFS) and overall (OS) survival. Data from 216 patients with DLBCL who were enrolled in two clinical trials at Italian Lymphoma Study Group sites and were subjected to six R-CHOP cycles and involved-field radiotherapy (IFRT) were retrospectively analyzed. IFRT treatment yielded significant EFS benefit, with a 66% reduction in the risk of death and/or disease progression.

- A retrospective study from the MD Anderson Cancer Center, Houston, Tex., USA, looked at patients with both localized and advanced-stage DLBCL who received RCHOP and achieved a documented CR. The results showed significant improvements in OS and PFS among patients who received consolidation RT after R-CHOP chemotherapy for DLBCL.

9.5 CNS prophylaxis for patients with DLBCL

This section is written with reference to the British Committee for standards in Haematology – guideline on the prevention of secondary central nervous system published in 2013.

Risk factors for CNS dissemination of DLBCL

1. The assessment of risk of CNS involvement is controversial and data is lacking. The optimum approach to CNS prophylaxis is uncertain.

2. About 5% of patients with DLBCL develop CNS lesions. The clinical outcome of CNS recurrence in patients with DLBCL is poor, with rapid morbidity and death within 2 to 5 months.

3. Flow cytometry assessment of CSF is more sensitive than conventional cytology in detecting occult leptomeningeal disease in patients with aggressive lymphoma at risk of CNS dissemination.

4. The addition of Rituximab to CHOP chemotherapy seems to have decreased the incidence of CNS relapse in patients with DLBCL. CNS relapses appeared to be more parenchymal in the Rituximab era and occurred at a median 17 months (6-35 months).
5. The Vancouver group found an increased risk of CNS relapse in cases of DLBCL treated with R-CHOP that harbored an MYC rearrangement, adjusting for other high-risk factors.\textsuperscript{95}

6. A large Norwegian retrospective analysis identified 5 independent risk factors (listed below) for CNS recurrence. When >3 of these factors were present at diagnosis, the risk of CNS recurrence exceeded 25\%.\textsuperscript{96}
   - Elevated LDH
   - Age <60 years
   - Involvement of >1 extranodal site
   - Retro-peritoneal lymph node involvement
   - Hypoalbuminemia

   • On the basis of current data CNS prophylaxis should be considered in any of the following circumstances:\textsuperscript{97}
     - Primary testicular lymphoma
     - Breast lymphoma
     - High risk of direct invasion of the CNS (orbit, sinus, paraspinal mass, etc)
     - Bone Marrow involvement
     - DLBCL with high IPI and extra-nodal disease at other sites

   • However, Intrathecal methotrexate failed to reduce the risk of CNS relapse in elderly patients treated with R-CHOP-14 in the RICOVER-60 trial.\textsuperscript{98} and may reflect the additional systemic control of disease derived from the RCHOP regimen

**Prophylactic CNS treatment in DLBCL**

This is based on recommendations from BCSH guidelines 2013.

• Suggested regimens
  - IT MTX
  - HD-MTX\textsuperscript{99} (Appendix C reg 26)

CNS-directed therapy should be offered to patients with high-grade NHL AND either:

- A raised (above institutional ULN) serum LDH AND more than one extra-nodal localization (noting that the spleen is not regarded as an extra-nodal site and also, two lesions within the same system (e.g. bilateral lung lesions) are regarded as a single extra-nodal localization)
  - OR
- Anatomical sites: Testicular, breast and epidural

• All patients requiring CNS-directed therapy should receive 3–6 doses of IT MTX (flat dose of 12–15 mg each dose) during primary therapy, which should be commenced as early as practical during treatment and given at least once per cycle.
  - Within the UK CHOP 14 vs. 21 trial, Intrathecal (IT) methotrexate 12.5mg was given
with the first 3 courses

- Patients with previous history of mucositis with methotrexate should routinely receive folinic acid rescue 24 hours post intrathecal methotrexate

- Systemic HD-MTX, given at a dose of $3g/m^2$, with folinic acid rescue, can also be considered as additional CNS-directed therapy in high-risk patients. This should be given strictly in line with published schedules and considered in the context of performance status and renal function.

**NOTE** There is no defined recommend protocol for delivering systemic HD-MTX but several protocols are outlined below.

The benefit of the additional or alternative use of HD-MTX must be carefully balanced against the risk of toxicity and the resource utilization consequences of the schedule. It is recommended that CNS directed therapy is considered as early as practical in the treatment plan whether IT, additional or alternative use of HD-MTX.

- High dose IV Methotrexate $3.0g/m^2$ with Folinic Acid rescue for at least 3 cycles upon completion of R-CHOP
- High dose IV Methotrexate $3.0g/m^2$ with Folinic Acid rescue for at least 3 courses sandwiched in-between systemic chemotherapy (eg Day 15 of cycles 2, 4, 6 of R-CHOP)

  - There is no data to confirm that HD-MTX alone can replace IT therapy, and if this strategy is followed it is essential that the practice is carefully audited
  - For the delivery of intravenous HD-MTX, the use of rapid infusion schedules can be recommended, although the authors acknowledge lack of consensus on this issue
  - If given without IT chemotherapy, systemic prophylaxis should be commenced as early as practical during treatment without compromising delivery of R-CHOP chemotherapy
  - The use of systemic agents other than HD-MTX as CNS prophylaxis in addition to, or instead of, IT chemotherapy and/or HD-MTX have not been shown to be beneficial. Their use is therefore not recommended except where they form part of an established multi-agent regimen or as part of a clinical trial
  - Patients with primary testicular lymphoma should receive four or more doses of IT MTX during primary chemotherapy as per the IESLG protocol

Given that the evidence supporting any single approach is less than strong, it is recommended that patients should be entered in to prospective randomized controlled trials where available, and, in all other settings, prospective audit of practice should be performed to support the approaches taken. Such audit should record not only the nature of prophylaxis administered, but also the type of CNS relapse and if there is any evidence of
concurrent systemic relapsed disease.

9.6 Primary extranodal DLBCL

- Treat as for systemic DLBCL. Radiotherapy has specific indications.\(^{37}\)
- Testicular Lymphoma: contralateral testis 30 Gy
- Primary lymphoma of bone

9.7 Primary Mediastinal B-cell Lymphoma (derived from BSH Good Practice Paper 2019)

- A baseline PET-CT scan should be performed.
- Bone marrow biopsy is not necessary unless it will influence patient management or when PET-CT is not possible due to clinical urgency
- R-CHOP x 6 plus involved site radiotherapy (ISRT) is standard of care. Perform PET-CT 2-3 months after combined modality treatment
- DA-EPOCH-R x 6 without ISRT is an alternative approach. Perform PET-CT 6 weeks after end of chemotherapy
- Perform PET-CT and biopsy (core or excision) at relapse
- Consider radiotherapy with localised disease relapse if omitted from initial therapy.
- Choice of salvage regime is as per DLBCL with autologous stem cell transplant for responsive disease as appropriate
- Consider ISRT pre or post transplant if previously omitted
- Consider discharge to primary care 2 years post treatment if patient remains in remission. Outline the long term complications to patient and primary care on discharge
- Routine imaging is unnecessary as follow up in asymptomatic patients
10. PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)

In >90% of cases PCNSL is a diffuse large B-cell. The remainder of cases are peripheral T cell lymphomas, Burkitt’s lymphomas and rarely ‘low-grade’ lymphomas. Primary intraocular lymphoma (PIOL) is a variant of PCNSL.

10.1 General considerations

Key recommendations (derived from BCSH guidelines 2018)\textsuperscript{103}

- Patients with suspected PCNSL should be discussed with a PCNSL specialist early in their pathway to minimise delays
- A histological or cytological diagnosis is required to confirm PCNSL; MRI findings alone are insufficient. The diagnosis should always be confirmed by specialist haematopathology review
- Corticosteroids should be avoided prior to biopsy
  - Where steroids have been administered and an enhancing lesion is still present, steroids should be discontinued prior to urgent biopsy to improve diagnostic yield
  - If a suspected PCNSL lesion resolves following steroid administration, re-imaging with MRI should be performed after a short interval with a view to urgent biopsy at lesion regrowth
- All confirmed PCNSL cases should be discussed at a lymphoma MDT. Patients should receive definitive treatment as soon as possible, ideally within 14 days of diagnosis, at an established centre with multidisciplinary PCNSL expertise

10.2 Pre-treatment investigations and staging

Pre-treatment investigations and staging should be performed as per British Committee for Standards in Haematology (BCSH) 2018 Guidelines for the diagnosis and management of adult patients with primary CNS diffuse large B cell lymphoma. The BCSH 2018 reference the International PCNSL Collaborative Group (IPCG) guidelines on standard evaluation of patients with newly diagnosed or suspected PCNSL which splits the investigations and staging into essential and desirable see Appendix A

Investigations/staging

Key recommendations (derived from BCSH guidelines 2018)\textsuperscript{103}

- Stereotactic biopsy of a brain lesion is the recommended approach for histological diagnosis. Intra-operative rapid diagnosis using cytology and frozen sections is recommended to avoid unnecessary surgical resection
- Vitreous biopsy should ideally be combined with a subretinal aspirate or chorioretinal biopsy to establish a diagnosis of primary intraocular lymphoma (PIOL)
• Where biopsy is not possible, a diagnosis of PCNSL may be supported by the combined assessment of characteristic MRI findings, clinical features AND demonstration of large clonal B cells in the CSF or vitreous fluid by multi-parameter flow cytometry and/or polymerase chain reaction for IGHV gene
• Contrast-enhanced MRI (including diffusion sequences) is the recommended imaging modality pre-treatment and for response assessment. Neuroaxis imaging (brain and entire spinal cord) should be reviewed by a specialist neuroradiologist
• Thorough ophthalmological assessment, including slit lamp examination, should be performed in all patients to exclude intraocular involvement
• All patients should undergo cross-sectional imaging to exclude systemic disease
  o 18F deoxyglucose positron emission tomography – computed tomography (PET-CT) is recommended. Contrast-enhanced CT of neck/chest/abdomen/pelvis should be performed if PET-CT is not possible
  o Men should undergo testicular ultrasonography

Neuropsychological assessments
Key recommendations (derived from BCSH guidelines 2018)$^{103}$
• Cognitive and quality of life outcomes should be assessed in all patients with PCNSL before and after treatment, with ongoing long-term monitoring
• As a minimum, all patients receiving treatment for PCNSL should be assessed on cognitive domains of attention, processing speed, motor speed, executive function and memory before and after treatment

10.3 Prognostic scoring
This should be calculated based on the variables below.$^{101}$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adverse prognostic parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;60</td>
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<tr>
<td>Performance status</td>
<td>ECOG &gt;1</td>
</tr>
<tr>
<td>LDH</td>
<td>Raised</td>
</tr>
<tr>
<td>CSF protein</td>
<td>Raised</td>
</tr>
<tr>
<td>site</td>
<td>Involvement of deep brain matter</td>
</tr>
</tbody>
</table>
One point is given for each adverse feature

<table>
<thead>
<tr>
<th>Number of adverse variables</th>
<th>2 Year Overall Survival</th>
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</thead>
<tbody>
<tr>
<td>0-1</td>
<td>80%</td>
</tr>
<tr>
<td>2-3</td>
<td>48%</td>
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<tr>
<td>4-5</td>
<td>15%</td>
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</tbody>
</table>

10.4 Treatment

10.4.1 Remission induction and Consolidation

Remission Induction

- **Suggested regimen**
  - MATRIX\(^{102}\) (Appendix C reg 35)

- **Alternative regimens**
  - R-MP\(^{223}\) (Appendix C reg 36)
  - Temozolomide Monotherapy\(^{224}\) (Appendix C reg 37)

**Key recommendations (derived from BCSH guidelines 2018)\(^{103}\)**

- Fitness for chemotherapy should be determined by physiological fitness rather than chronological age
- Patients should be offered a clinical trial wherever possible
- For patients eligible for HD-MTX-based regimens:
  - If fit for intensive therapy, offer treatment with four cycles of MATRix (HD-MTX, cytarabine, thiotepa, rituximab) immuno-chemotherapy
    - Dose reductions should be considered for those with impaired performance status at presentation, co-morbid conditions and/or who experience significant toxicity from MATRix
    - Granulocyte colony-stimulating factor and prophylaxis against opportunistic infections should be employed
    - For patients where high dose therapy with autologous stem cell transplant (HDT-ASCT) is planned, PBSC collection should be attempted following cycle 2, if practicable
  - If unfit for intensive therapy, offer treatment incorporating HD-MTX, rituximab and an orally administered alkylating agent within an established protocol (e.g. R-MP [rituximab, MTX, procarbazine])
  - HD-MTX should be delivered at doses of at least 3 g/m\(^2\) with an infusion time of 2–4 h, for a minimum of four cycles at 2- to 3-week intervals
  - Rituximab should be delivered at 375 mg/m\(^2\) for eight doses (i.e. 2 doses per cycle with MATRix)
    - For those patients ineligible for HD-MTX, consider one, or a combination, of the following treatments.
      - Oral chemotherapy (such as temozolomide)
Whole-brain radiotherapy (WBRT; 20–30 Gy in 1.8–2 Gy fractions according to performance status, therapeutic aims and life expectancy) +/- orbital radiotherapy if co-existing ocular involvement

- Corticosteroids (dexamethasone is typically used)

- Intrathecal chemotherapy is not recommended alongside systemic CNS-directed therapy but may be considered for symptomatic control of leptomeningeal disease in patients unfit for systemic therapy

Response assessment should be performed with contrast-enhanced MRI:

- Consider performing after cycle 1 to inform timing of PBSC collection
- Routinely perform every 2 cycles of HD-MTX-based therapy and at the end of remission induction therapy

**Evidence**

- The IELSG 32 study compared three different high dose methotrexate (HD-MTX) /high dose cytarabine (HD-AraC) backboned chemotherapy combinations, group A (HD-MTX3.5g/HD-AraC) v group B (HD-MTX3.5g/HD-AraC) + rituximab v group C (HD-MTX 3.5g/HD-AraC) + rituximab + thiotepa (MATRIX)\(^{102}\)

- At median follow-up of 30 months, patients treated with MATRIX had a complete remission (CR) rate of 49%, compared with 23% of those treated with HD-MTX3.5g/HD-AraC alone (group A) and 30% of those treated with (HD-MTX3.5g/HD-AraC) + rituximab (group B)\(^{102}\)

- The PRIMAIN study a multicentre single-arm trial investigated R-MPL (Rituximab, high dose methotrexate, procarbazine and lomustine) protocol in elderly immunocompetent patients (>65 years) with newly diagnosed primary central nervous system lymphoma, in. Owing to infectious complications, lomustine was omitted during the study and consecutive patients were treated with the R-MP protocol\(^{223}\)

- Primary end point was complete remission (CR) after 3 cycles. They included 107 patients (69 treated with R-MPL and 38 with R-MP). In all, 38/107 patients achieved CR (35.5%) and 15 (14.0%) achieved partial remission. R-MP was associated with a lower CR rate (31.6%) compared with R-MPL (37.7%), but respective 2-year progression-free survival (All 37.3%; R-MP 34.9%; R-MPL 38.8%) and overall survival (All 47.0%; R-MP 47.7%; R-MPL 46.0%) rates were similar. R-MP was associated with less grade 3 toxicities compared with R-MPL (71.1% vs 87.0%)\(^{223}\)

- A small retrospective study of single agent temozolomide in elderly patients with comorbidities (n = 19) showed a CR rate of 47%, with prolonged responses (>12 months) in 29–4%, a median PFS of 5 months and median OS of 21 months\(^{224}\)

**Consolidation**

- Suggested HDT prior to ASCT
  - CarTh\(^{218,219,220}\) (Appendix C reg 38)
Key recommendations (derived from BCSH guidelines 2018)

- Consolidation therapy should be considered for all patients with non-progressive disease following induction chemotherapy. This decision should be informed by comorbidities, performance status, neurocognitive function and patient wishes.
- High-dose thiotepa-based chemotherapy with ASCT as first-line consolidation should be considered for all eligible patients.
  - Patients with PCNSL achieving at least stable disease following HD-MTX-based first-line therapy should be considered for HDT-ASCT.
  - BEAM (carmustine, etoposide, cytarabine, melphalan) not be used as HDT-ASCT conditioning for PCNSL. (1A)
- WBRT consolidation +/- boost should be considered for:
  - Patients ineligible for HDT-ASCT with residual disease following induction immunochemotherapy.
  - Patients with residual disease after thiotepa-based ASCT.
- Patients with concurrent ocular involvement should be considered for bilateral ocular radiotherapy (see PIOL section) if ineligible for HDT-ASCT, or not in response (CR) following thiotepa-based ASCT.
- For HDT-ASCT ineligible patients in CR after HD MTX-regimens, WBRT consolidation is contentious:
  - Potential improvement in progression-free survival should be carefully balanced against risks of neurocognitive toxicity for individual patients.
  - For patients aged ≥60 years in CR after HD MTX, either WBRT should be omitted, or lower dose WBRT consolidation may be considered given the higher risk of neurocognitive toxicity.
- Where WBRT is offered, the following dosing schedules are recommended depending on age, comorbidities and induction treatment received.
  - 36 Gy in 20 fractions.
  - Reduced dose (23.4 Gy in 1.8 or 2 Gy fractions) for selected cases at higher risk of neurotoxicity.
  - Consider a 9 Gy boost with a 1–2 cm margin (total dose 45 Gy/25 fractions) to residual enhancing lesion(s) at the time of WBRT.
  - Orbits should be shielded after 30 Gy (36 Gy if previously documented intraocular disease).

Evidence

- Encouraging results from early studies with HDT-ASCT consolidation in PCNSL have challenged the role of WBRT as the favoured first-line consolidation strategy.
- On an intention-to-treat basis, prospective trials of thiotepa/carmustine-conditioned ASCT after intensive induction chemotherapy have reported 3- to 5-year OS rates of 70–81%, where 79–92% received planned HDTASCT.
• In the Lancet Haematology phase II study a minority (14%) received additional WBRT

10.4.2 Primary Intraocular Lymphoma

Remission Induction

• Suggested regimen
  o MATRIX

Consolidation

• Suggested HDT prior to ASCT
  o CarTH

Key recommendations (derived from BCSH guidelines 2018)

• PIOL should be treated with systemic HD-MTX-based combination chemotherapy with rituximab. For fit patients, consider using evidence-based PCNSL induction protocols, such as the MATRix regimen
• Intravitreal MTX (administered by a specialist ophthalmologist) can be considered for elderly patients with isolated PIOL who are unfit for systemic therapy
• Concurrent intravitreal therapy, for patients receiving a systemic HD-MTX regimen, cannot be routinely recommended
• For PIOL patients who have responded to intensive systemic chemotherapy, the following consolidation options should be considered:
  o For eligible patients, high-dose thiotepa-based chemotherapy with ASCT
  o Bilateral orbital radiotherapy (up to 36 Gy in 1.8–2 Gy fractions). Concurrent WBRT (23.4–30 Gy in 1.8–2 Gy fractions) should be considered but needs to be carefully balanced against risks of neurocognitive toxicity for individual patients

Evidence

• See PCNSL remission induction evidence section for information on MATRIX
• See PCNSL consolidation evidence section for information on CarTH

10.4.3 Treatment of relapsed/refractory PCNSL

• Suggested salvage regimens prior to HDT/ASCT
  o R-IE
  o R-ICE
  o MATRIX
  o R-TIE

• Suggested HDT prior to ASCT
  o CarTH

Key recommendations (derived from BCSH guidelines 2018)¹⁰³

- All patients with suspected PCNSL relapse should be reviewed urgently within regional MDT meetings. The primary treating Haemato-oncology team should be promptly informed
- Re-biopsy at relapse is recommended in the context of atypical MRI appearances, or for new brain lesions occurring beyond 2 years from initial therapy, particularly if intensive salvage therapy is planned
- Patients with a confirmed diagnosis of relapsed PCNSL should undergo complete re-staging if further therapy is planned. Re-staging is not usually necessary for PCNSL refractory to first-line therapy
- Wherever possible, patients should be offered participation in a clinical trial
- Outside of clinical trials, potential treatment options should be individualised, taking account of:
  - Physiological fitness, performance status and neurocognitive function
  - Previous therapy and duration of response
  - Patient choice
- For patients eligible for intensive treatment:
  - Consider ifosfamide-based immunochemotherapy, particularly for refractory disease or early relapse after MTX-based immunochemotherapy
  - Consider HD-MTX-based immunochemotherapy if the duration of first remission to HD-MTX-based therapy was >2 years
- Consolidation following salvage chemotherapy:
  - Patients who have not previously undergone HDTASCT should be considered for thiotepa-based HDT-ASCT in second or subsequent response
  - WBRT-naive patients who are ineligible for, or have previously undergone, HDT-ASCT should be considered for WBRT (23.4–36 Gy in 1.8–2 Gy fractions), either alone or following salvage chemotherapy
- Patients ineligible for intensive treatment:
  - Palliative treatment should be offered, which may include WBRT (23.4–36 Gy in 1.8–2 Gy fractions), corticosteroids and/or oral Temozolomide
  - Patients should receive best supportive care and, where appropriate, palliative care input

Evidence
Ifosfamide-based salvage regimens, usually in combination with etoposide +/− carboplatin and rituximab (R-IE and R-ICE), have resulted in overall response rates of 41–95% in predominantly chemorefractory or heavily treated patient cohorts. For patients who experience durable first remissions following HD-MTX-based protocols, re-treatment with HDMTX-based regimens may be effective, although the effectiveness of this approach is much more uncertain in the modern-era of intensified MTX-containing regimens. Two retrospective studies described a median PFS of 16 and 25.8 months after re-treatment with HD-MTX at relapse, usually as part of multi-agent salvage regimens, in patients who had experienced as median duration of response to first-line HD-MTX of 24.4 and 26 months, respectively. This may be particularly relevant for MTX-experienced, but rituximab- and thiotepa-naive, patients for whom the more intensive MATRix protocol may be an option, although it should be noted that currently no published data exist for MATRix in R/R PCNSL. For eligible, chemosensitive patients, available data support the use of thiotepa-based HDT-ASCT in R/R PCNSL, with a median PFS of 24–41 months reported.
11. HIGH GRADE B-CELL LYMPHOMA (HGBL)
Currently, the treatment strategy for high grade lymphomas applies to (high grade B cell lymphoma not otherwise specified (HGBL – NOS)/HGBL with MYC and BCL2/BCL 6 rearrangements) which have a high proliferation rates (100% Ki67 +ve) as well as the more typical burkitt lymphoma and burkitt like lymphoma – see diagnostic criteria below.

11.1 Key issues
- Effectiveness of short duration high intensity therapy remains unclear
- Continuing problems with diagnostic criteria
- There are no randomised trials in this condition

11.2 Diagnostic criteria
High grade B cell lymphomas (HGBL)
High-grade B-cell lymphomas (HGBL) represent a spectrum of different diseases. In 2016, the World Health Organization (WHO) revised their classification of lymphoid neoplasms to account for the major advances in lymphoma biology since 2008. This revision emphasizes molecular features of clinical importance, such as genomic alterations in MYC, BCL2, and/or BCL6 oncogenes. An important change is the addition of HGBL with MYC and BCL2 and/or BCL6 rearrangements, so-called “double-hit/triple - hit” lymphoma (HGBL-DH/TH), as a separate provisional entity.

High-grade B-cell lymphomas, with and without MYC and BCL2 or BCL6 translocations - WHO 2016
- The 2008 WHO classification introduced the category of “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL” (BCLU) to recognize a subset of very aggressive tumors in which the distinction between DLBCL and BL was very difficult. Lymphomas with a GEP intermediate between that of molecular BL and molecular non-BL (mostly DLBCL), also lends support to the existence of these intermediate-type cases, which were not, however, considered a specific entity
- Segregation of these cases was also necessary to better define these clinically problematic tumors. Additional studies followed that demonstrated that BCLU and other LBCL, with rearrangements of MYC and BCL2 and/or BCL6, had mutational features intermediate between DLBCL and BL. They better characterized the double-/triple-hit lymphomas, including identifying features that might mitigate the adverse clinical impact of MYC translocations
- The criteria for BCLU, however, are vague and the diagnosis has not been used uniformly, limiting its utility as a diagnostic category
All LBCL with MYC and BCL2 and/or BCL6 rearrangements will be included in a single category to be designated HGBL, with MYC and BCL2 and/or BCL6 rearrangements, except for cases that fulfill the criteria for a follicular or lymphoblastic lymphoma.

The morphologic appearance should be noted in a comment. The category of BCLU will be eliminated. Cases that appear blastoid or cases intermediate between DLBCL and BL, but which lack a MYC and BCL2 and/or BCL6 rearrangement, will be placed in the category of HGBL, NOS.

A consensus has not yet been reached to provide specific guidelines as to which LBCL should have fluorescence in situ hybridization studies. Some believe that all DLBCL should have genetic studies for the detection of MYC, BCL2, and BCL6 rearrangements, whereas others would limit them, for example, to cases with a GCB phenotype and/or high-grade morphology or to cases with 40% MYC1 cells.

Burkitt Lymphoma
Burkitt lymphoma is defined as a germinal centre cell lymphoma with c-myc deregulation and absence of other balanced translocations.

Typical Cases of Burkitt lymphoma
- Large B-cell lymphoma with round nuclei, central nucleoli and vacuolated cytoplasm
- Germinal centre phenotype: CD10+ve, BCL6+ve by immunocytochemistry, with BCL2-ve
- A hyperproliferative state demonstrated by Ki67 approaching 100%, p53+, p21- and evidence of apoptosis
- t(8;14) or variants demonstrated by FISH but without BCL2 or BCL6 translocation

Burkitt Lymphoma and Burkitt like lymphoma – WHO 2016
- Recent NGS studies of Burkitt lymphoma (BL) have improved our understanding of the pathogenesis of these tumors. Mutations in the factor TCF3 or its negative regulator ID3 occur in about 70% of sporadic and immunodeficiency-related BL and 40% of endemic cases. TCF3 promotes survival and proliferation in lymphoid cells by activating the B-cell receptor/phosphatidylinositol 3-kinase signaling pathways and modulating the expression of cyclin D3, which is also mutated in 30% of BL.
- One controversial issue not fully resolved is whether true BL without MYC translocations really exist. Some recent studies have identified a subset of lymphomas that resemble BL morphologically, to a large extent phenotypically and by GEP, but which lack MYC rearrangements. Instead, they have a chromosome 11q alteration characterized by proximal gains and telomeric losses.
• Compared with BL, these lymphomas have more complex karyotypes, lower levels of MYC expression, a certain degree of cytological pleomorphism, occasionally a follicular pattern, and frequently a nodal presentation. The clinical course seems to be similar to BL, but the number of cases reported is still limited. Although more studies are needed, the consensus for the revised WHO classification was to consider these a new provisional entity designated Burkitt-like lymphoma with 11q aberration.

11.3 Treatment

11.3.1 Risk groups\(^{107}\)

• Low risk
  Patients must have at least 3 of the factors identified below
  o Normal LDH level
  o WHO performance status 0-1
  o Ann Arbor stage I-II
  o Number of extra nodal sites (e.g. bone marrow, CNS) ≤1

• High risk
  Patients should have 2 or more of the following features
  o Raised LDH level
  o WHO performance status ≥ 2
  o Ann Arbor stage III-IV
  o Number of extra nodal sites >1

11.3.2 Primary Treatment

Low risk

• Suggested regimens
  Age ≤ 65 years
  o Dose Modified R-CODOX-M\(^ {107}\) (Appendix C reg 44)
  Age > 65 years
  o Dose Modified R-CODOX-M\(^ {107}\) (Appendix C reg 45)

• Alternative regimens
  o DA EPOCH – R\(^ {108}\) (Appendix C reg 20)

High risk

• Suggested regimens
  Age ≤ 65 years
  o Dose Modified R-CODOX-M/R-IVAC\(^ {107}\) (Appendix C reg 46)
  Age > 65 years
  o Dose Modified R-CODOX-M/R-IVAC\(^ {107}\) (Appendix C reg 47)
**Key recommendations (derived from NICE NG52 guidelines 2016)**

- Offer intensive immunochemotherapy to people with Burkitt lymphoma who are fit enough to tolerate it. Consider R-CODOX-M/R-IVAC
- For people with low-risk Burkitt lymphoma who are not suitable for CODOX-M, consider using the less intensive DA-EPOCH-R regimen supplemented with intravenous and/or intrathecal methotrexate

**Evidence**

- The MRC/NCRI LY10 trial demonstrated that dmCODOX-M/IVAC (methotrexate $3g/m^2$) had reduced toxicity but comparable outcomes when compared with previous results in the LY06 trial. The 2 year PFS for all patients was 55% and was 85% and 49% for low risk and high risk respectively.
- In prospective non-comparative study published in the NEJM 2013 the rate of freedom from progression of disease at medium follow up was 95% in the Da-epoch-r group and overall survival rates was 100% respectively. No treatment related deaths were reported.
- Rituximab has been described as having possible beneficial effects, particularly in older patients.
- It seems highly unlikely that randomized trials testing the efficacy of this rituximab will be performed in the future. Clinicians may decide they wish to add this agent to treatments in Burkitt lymphoma.
- There are considerable issues regarding initial treatment toxicity and tumour lysis – rasburicase should be considered in selected cases e.g. high bulk and/ or abnormal renal function pre-treatment.

**11.3.3 Treatment of relapsed/refractory HGBL**

There is no consensus or trial. Outcome is usually very poor. There is little evidence-base for further intensification of therapy and cases should be carefully reviewed in the MDT.
12. FOLLICULAR LYMPHOMA (FL)

The current BCSH guidelines on the investigation and management of follicular lymphoma should be followed.

12.1 Key issues

- All cases should be subject to routine central review by an experienced haematopathologist
- Grading of follicular lymphoma can be problematic
- Curability of stage IA disease by radiotherapy
- Role of radioimmunotherapy
- Role of high dose therapy in relapsed disease
- Treatment of large cell variants

12.2 Diagnostic Criteria

Follicular lymphoma is a tumour of the germinal centre cell that in lymph nodes shows a follicular growth pattern.

**Typical Cases**

In lymph node biopsy specimens the following features must be present:

- Involved nodes show replacement of the normal architecture by closely packed neoplastic follicles that are uniform in size, lack tingible body macrophages, and possess poorly formed mantle zones
- Follicular centre cells express B-cell lineage markers and the germinal centre cell antigens CD10 and BCL6. The interfollicular component of FL and bone marrow disease often show downregulation of these markers
- High grade (grade 3) FL can lose CD10 expression, although BCL6 is often retained. BCL2 may be negative in high-grade (grade 3) FL
- The follicular architecture is confirmed by using CD21 to identify FDC networks.
- In 85% of cases the neoplastic cells in FL are BCL2-positive
- Flow Cytometry: clonal sIgM or sIgG, CD19+, CD10+, CD38+, CD5-, and BCL-6 demonstrated by immunocytochemistry
- The typical \textit{IGH}/\textit{BCL2} translocation can be detected by PCR or FISH using a break-apart probe for the BCL2 gene
- Some cases, particularly those in the Grade 3 category, can show an alternative translocation involving BCL6
- PCR studies will show a clonal \textit{IGH} rearrangement
In some biopsies there is a mixture of follicular and diffuse areas. In rare cases the architecture is completely diffuse and lacks any identifiable follicular structures, this is particularly seen in mesenteric and retroperitoneal disease. The WHO identifies four patterns of FL: follicular, focally follicular, follicular and diffuse, diffuse. Note the term “diffuse” only refers to the architecture and does not imply DLBCL.

Distinct areas of Grade3 FL can be seen in a lesion that is otherwise grade1-2. In this setting, the approximate percentage of each grade should be reported.

Focal areas of transformation can be seen in some biopsies. The report should state the percentage of each component present eg “DLBCL, 20% with FL grade1-2, 50% and FL grade3A, 30%”

**Variants**

- As above but BCL-2 and t(14;18) negative; clonality should be demonstrated by PCR or flow cytometry, or unequivocal evidence of bone marrow infiltration should be present.
- Large cell variant where the neoplastic follicles consist mainly of centroblasts (WHO grade 3B)

**Transformation**

- The diagnosis of transformation is made when diffuse areas are present that consist mainly of large lymphoid cells with a high rate of cell proliferation. The relationship between morphological transformation and progressive or refractory disease is complex.

### 12.3 Prognostic Scoring

- FLIPI \(^{117}\) and FLIPI2 \(^{118}\) should be recorded at diagnosis.
- To calculate the FLIPI score, 1 point is given for each adverse prognostic factor. Points are then summed (maximum score of 5).

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<thead>
<tr>
<th>Prognostic Factor</th>
<th>Cut-off</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 60 years</td>
</tr>
<tr>
<td>Ann Arbor Stage</td>
<td>≥ Stage III</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>&lt; 120g/dL</td>
</tr>
<tr>
<td>Serum LDH</td>
<td>≥ upper limit of normal range</td>
</tr>
<tr>
<td>No. of Extranodal sites</td>
<td>≥ 4</td>
</tr>
</tbody>
</table>
An online FLIPI index calculator can be accessed by using the following hyperlink:
http://www.qxmd.com/calculate-online/hematology/follicular-lymphoma-international-prognostic-index-flipi
To calculate the FLIPI2 score, 1 point is given for each adverse prognostic factor listed below:

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<tr>
<th>FLIPI2 PROGNOSTIC FACTOR</th>
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<tr>
<td>Longest diameter of largest involved node &gt;6cm</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
</tr>
<tr>
<td>Haemoglobin &lt;120g/l</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
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<tr>
<td>β2-microglobulin (above upper limit of normal)</td>
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<table>
<thead>
<tr>
<th>Score</th>
<th>Category</th>
<th>Proportion of patients (%)</th>
<th>3 year PFS</th>
<th>5 year PFS (%)</th>
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<td>0</td>
<td>Low risk</td>
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<td>Intermediate risk</td>
<td>53</td>
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<td>51</td>
</tr>
<tr>
<td>3-5</td>
<td>High risk</td>
<td>27</td>
<td>51</td>
<td>19</td>
</tr>
</tbody>
</table>

12.4 Treatment

12.4.1 Primary Treatment
Management of early stage (stage I-II) FL
Stage I
Key recommendations (derived from BCSH guidelines 2011)²⁰³

- Involved field radiotherapy delivering a dose of 24Gy in 12 daily fractions is the standard of care in patients with stage IA disease
- Observation of patients with early stage disease is acceptable if radiotherapy is thought to be undesirable or due to patient choice. These
patients should be discussed with a clinical oncologist

- Combined modality treatment and immunotherapy are at present investigational approaches that should only be considered within a formal clinical trial

**Stage II**

**Key recommendations (derived from NG52 NICE guidelines 2016)**

- Offer local radiotherapy as first line treatment to people with localised stage IIA follicular lymphoma
- Consider 'watch and wait' (observation without therapy) as first line treatment for people with stage IIA follicular lymphoma who are asymptomatic and for whom treatment with a single radiotherapy volume is not suitable
- Offer the same treatments that might be offered to people with advanced stage (stages III and IV) symptomatic follicular lymphoma to people with stage IIA follicular lymphoma who are symptomatic and for whom radiotherapy is not suitable
- See suggested regimens under advanced stage symptomatic follicular lymphoma

**Management of advanced (stage III-IV) FL**

Three randomised trials of varying quality have shown that there is no advantage to immediate treatment in patients with advanced stage *asymptomatic* FL compared with a watchful waiting approach in terms of OS. In the BNLI study, the criteria for patients being eligible for a watch and wait approach were defined as the absence of the following

- Pruritis or B symptoms
- Rapid generalised disease progression in the preceding 3 months
- Life-endangering organ involvement
- Significant bone marrow infiltration resulting in bone marrow depression sufficient to warrant immediate chemotherapy. This is defined as a haemoglobin concentration <100g/l, white cell count <3.0 x 10⁹/l or a platelet count <100 x 10⁹/l, having excluded other causes of such cytopenias
- Localised bone lesions detected on X-ray or isotope scan because of concern over the development of pathological fractures
- Renal infiltration (even if the renal function was well preserved)
  Macroscopic as opposed to microscopic liver involvement

**Advanced-stage asymptomatic follicular lymphoma**

- Suggested induction regimens
  - Rituximab monotherapy⁸⁴(Appendix C reg 21)
Key recommendation (derived from NG52 NICE guidelines 2016)

- Offer rituximab induction therapy to people with advanced-stage (stages III and IV) follicular lymphoma who are asymptomatic

General considerations

- Rituximab currently does not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

Advanced-stage symptomatic follicular lymphoma

Obinutuzumab (NICE TA 513) is recommended as an option for untreated advanced follicular lymphoma in adults (that is, first as induction treatment with chemotherapy, then alone as maintenance therapy), only if:

- the person has a Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or more
- the company provides obinutuzumab with the discount agreed in the patient access scheme

The main evidence on the effectiveness and safety of obinutuzumab is from an ongoing clinical trial. It shows that obinutuzumab plus chemotherapy followed by obinutuzumab maintenance treatment delays disease progression more than current treatment. However, it also shows that undesirable side effects are more common with obinutuzumab than with rituximab. There are not enough data to know with certainty whether obinutuzumab increases life expectancy.

The summary of product characteristics states that obinutuzumab's efficacy in patients at low risk of premature mortality (that is, people with FLIPI score of 0 to 1) is 'inconclusive'. Because of this, and in response to consultation, the company changed the population in its analysis from all people with advanced follicular lymphoma to people with an intermediate or high FLIPI score (collectively called patients at higher risk because they are at higher risk of dying than patients with lower scores)(NICE TA 513)

Low Risk (FLIPI 0-1)

FLIPI 0-1 Patients unsuitable for obinutuzumab

- R-CHOP120(Appendix C reg 17)
- R-CVP113(Appendix C reg 19)
- R-Bendamsutine154(Appendix C reg 34)
- R-Chlorambucil122(Appendix C reg 48)
**Higher risk (FLIPI ≥2)**

For patients with advanced symptomatic follicular lymphoma and a FLIPI score of ≥2 the following regimens may be considered; (See NICE TA 513)

- Bendamustine + Obinutuzumab (Appendix C reg 49)
- CHOP + Obinutuzumab (Appendix C reg 50)
- CVP + Obinutuzumab (Appendix C reg 51)

For patients with advanced symptomatic follicular lymphoma and a FLIPI score of ≥2 unsuitable for obinutuzumab the following regimens may be considered;

- R-CHOP\textsuperscript{120} (Appendix C reg 17)
- R-CVP\textsuperscript{113} (Appendix C reg 19)
- R-Bendamustine\textsuperscript{154} (Appendix C reg 34)
- R-Chlorambucil\textsuperscript{122} (Appendix C reg 48)

**Evidence**

- See NICE TA 513 for evidence of obinutuzumab and chemotherapy
- With an 83% 8-year OS rate, long-term follow-up of the FOLL05 trial confirms the favorable outcome of patients with advanced-stage FL treated with immunochemotherapy (R-CHOP, R-CVP, R-FM). The three study arms had similar OS but different activity and toxicity profiles. Patients initially treated with R-CVP had a higher risk of lymphoma progression compared with those receiving R-CHOP, as well as a higher risk of requiring additional therapy\textsuperscript{120}
- A 2005 study compared R-CVP to CVP. Overall and complete response rates were 81% and 41% in the R-CVP arm versus 57% and 10% in the CVP arm, respectively. At a median follow-up of 30 months, patients treated with R-CVP had a very significantly prolonged time to progression (median 32 months versus 15 months for CVP). Rituximab did not add significantly to the toxicity of CVP\textsuperscript{113}
- The StiL NHL1 study – Lancet 2013 compared Bendamustine/Rituximab (BR) to R-CHOP. BR patients had a PFS of 69.5 compared with 31.2 months with R-CHOP. BR was also better tolerated than R-CHOP with lower rates of haematological toxicity, infections and peripheral neuropathy reported in the BR arm\textsuperscript{154}
- Rituxumab/Chlorambucil has been a reasonable treatment option for the elderly\textsuperscript{122}

**Maintenance**

- Suggested regimens based on induction treatment
  - Obinutuzumab (NICE TA 513) (Appendix C reg 52)

- Alternative regimens
  - Rituximab\textsuperscript{84} (Appendix C reg 21)
When considering obintuzumab maintenance following bendamustine the clinician should be aware of the increased number of fatal events observed in this arm in the GALLIUM study (mainly occurring during the maintenance phase).

Therefore the clinician may wish to avoid obintuzumab maintenance following bendamustine or consider prophylaxis and/or heightened awareness for opportunistic infections to facilitate early treatment withdrawal.

Evidence

- See NICE TA 513 for evidence of obinutuzumab maintenance
- Rituximab maintenance after successful induction therapy prolongs PFS and is recommended in patients responding to first line rituximab-based chemotherapy

12.4.2 Management of patients with transformed FL (t-FL)

Treatment

- Treat as for DLBCL – see under treatment of advanced DLBCL

Key recommendations (derived from BCSH guidelines 2011)\textsuperscript{203}

- Rituximab-naive patients with histological transformation (HT) of FL should receive rituximab-chemotherapy as treatment for the HT
- FL patients with HT who have previously been exposed to rituximab should receive rituximab chemotherapy as treatment for the HT
- Anthracycline-naive patients should receive a doxorubicin-containing regimen; otherwise, a second-line therapy of the type used for DLBCL is recommended

High Dose Treatment (HDT)

Key recommendations (derived from NG52 NICE guidelines 2016)\textsuperscript{84}

- Consider consolidation with autologous stem cell transplantation for people with transformation of previously diagnosed follicular lymphoma that has responded to treatment and who are fit enough for transplantation
- Consider consolidation with autologous or allogeneic stem cell transplantation for people with transformation of follicular lymphoma who need more than 1 line of treatment for a response and who are fit enough for transplantation
- Do not offer consolidation with high dose therapy and autologous or allogeneic stem cell transplantation to people presenting with concurrent diagnoses of follicular lymphoma and diffuse large B cell lymphoma that have responded to first line treatment
12.4.3 Management of patients with histological grade 3B

Treatment

- Treat as for DLBCL – see under treatment of advanced DLBCL

12.4.4 Treatment of relapsed/refractory FL

- Suggested treatment regimens
  - R-Bendamsutine\(^{237}\) (Appendix C reg 34)
  - R-CHOP\(^{123}\) (Appendix C reg 17)
  - R-CVP\(^{123}\) (Appendix C reg 19)
  - R-Chlorambucil\(^{122}\) (Appendix C reg 48)

- Alternative regimens
  - Rituximab monotherapy\(^{185}\) (Appendix C reg 21)
  - Bendamustine monotherapy\(^{186}\) (Appendix C reg 10)
  - Idelalisib\(^{110,111}\) (Appendix C reg 53)
  - Bendamustine/Obinutuzumab\(^{201}\) (Appendix C reg 49)

- Suggested salvage regimens for patients proceeding to HDT/ASCT
  - R-ICE\(^{100}\) (Appendix C regimen 7)
  - R-ESHAP\(^{38}\) (Appendix C regimen 8)
  - R-GDP\(^{19}\) (Appendix C regimen 6)

- Alternative salvage regimens for patients proceeding to HDT/ASCT*
  - R-CHOP\(^{123}\) (Appendix C reg 17)
  - R-CVP\(^{123}\) (Appendix C reg 19)

*Choice of salvage therapy regimen depends on previous therapies used

Key recommendations (derived from NG52 NICE guidelines 2016)\(^{84}\)

- Rituximab, within its marketing authorisation, in combination with chemotherapy, is recommended as an option for the induction of remission in people with relapsed stage III or IV follicular non-Hodgkin's lymphoma
- Rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy)
General considerations

- If the duration of remission following primary treatment with rituximab/chemo or rituximab monotherapy regimens is less than 6 months, then rituximab should not be used.
- The choice of chemotherapy will depend on the characteristics of the patient such as cardiac function, the efficacy of prior regimens and the duration of repose to these regimens\(^\text{203}\).
- Late relapse (remission > 12 months)
  - If remission >12 months consider treating with same regimen used in primary treatment (care needed with total anthracycline dose if R-CHOP was used).
- Early relapse (remission < 12 months)
  - In early relapses, a non-cross resistant scheme is preferred.
  - Where R-CVP was used as first line, bendamustine, fludarabine, a CHOP-like regimen or salvage therapy (ESHAP or ICE) (with or without rituximab) should be considered as further lines of treatment.
  - Where R-CHOP was used as first line, bendamustine fludarabine (alone or as combination chemotherapy, such FC, or salvage therapy ESHAP, ICE (with or without rituximab) should be considered.
  - All of these regimens can be used with or without rituximab.
  - For patients progressing on or relapsing within 6 months of a rituximab based regimen, the combination bendamustine/obinutuzumab should be considered.

Evidence

- Bendamustine with Rituximab (BR) was showed superior (PFS) compared to fludarabine rituximab (34.2 months v 11.7) in treatment of relapsed indolent and mantle cell lymphoma in a phase III trial\(^\text{237}\).
- ESMO recommends R-CHOP or BR if complete remission and long PFS is to be achieved. R-CVP is not as affective with respect to R-CHOP\(^\text{123}\).
- Rituximab is licensed for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy\(^\text{185}\).
- Bendamustine monotherapy is licensed in indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen\(^\text{186}\).
- Idelalisib (Zydelig) has been approved by the SMC (ID 1039/15) as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.
- A phase II trial evaluated the use of idelalisib in 125 adults (median age 64 years).
with indolent non-Hodgkin lymphoma (58 percent FL) that had either not responded to or had relapsed within six months of receiving rituximab plus an alkylating agent.

- Similar results were seen in another multicenter phase II trial of idelalisib in 64 adults with relapsed indolent non-Hodgkin lymphoma.

- In the GADOLIN phase III study obinutuzumab/bendamustine was compared to bendamustine monotherapy in patients with rituximab refractory indolent NHL. Results show progression-free survival was significantly longer with obinutuzumab plus bendamustine (median not reached) than with bendamustine monotherapy (14.9 months).

- Regimens used as second-line therapy for aggressive lymphomas (R-ICE, R-ESHAP, R-GDP) should be considered depending on patient characteristics, eligibility for transplant as consolidation, and previous therapies (see evidence section of relapsed DLBCL).

- Patients with localized, symptomatic disease should be considered for palliative radiotherapy, delivering doses of 4 Gy to 24 Gy.

### Maintenance

- Suggested regimens
  - Rituximab (Appendix C reg 21)

#### Key recommendation (derived from NG52 NICE guidelines 2016)

- Rituximab monotherapy as maintenance therapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed stage III or IV follicular non Hodgkin's lymphoma in remission induced with chemotherapy with or without rituximab.

### 12.4.5 The role of autologous and allogeneic transplant in FL

#### Key recommendations (derived from NG52 NICE guidelines 2016)

- Offer consolidation with autologous stem cell transplantation for people with follicular lymphoma in second or subsequent remission (complete or partial) who have not already had a transplant and who are fit enough for transplantation.

- Consider consolidation with allogeneic stem cell transplantation for people with follicular lymphoma in second or subsequent remission (complete or partial):
  - who are fit enough for transplantation and
  - for whom a suitable donor can be found and
  - when autologous stem cell transplantation has not resulted in remission or is inappropriate (for example, because stem cell harvesting is not possible)
General considerations

- Autologous stem cell transplantation has no role in first line therapy for FL outside the setting of a clinical trial
- The benefits of HDT with ASCT in relapsed FL need to be balanced against the long-term risks of the procedure and considered in the setting of emerging therapies
- The patients suitable for transplantation with shorter durations of response following first line therapy should be considered for early referral
- RIC-allogeneic transplants should be considered for younger FL patients with early relapse

12.5 Follow up of patients with FL

- CT scanning is currently the appropriate method of response assessment following therapy for FL
- History and clinical examination should be performed at least 3 monthly for the first year following therapy and then tailored to an individual patient’s circumstances e.g. 4- to 6-monthly for 4 years and yearly thereafter
- A full blood count, urea and creatinine, liver function tests and LDH should be performed at each clinical visit
- Thyroid function should be performed yearly in patients who have undergone irradiation of the neck
- Cross-sectional imaging following treatment is instigated only on suspicion of relapse requiring therapy. There is no role for routine scanning of patients following therapy
- For patients on watchful waiting the above may be further modified as follows:
  - History and clinical examination should be performed 3-monthly until disease progression
  - Full blood count, urea and creatinine, liver function tests and LDH should be taken 3-monthly
  - Cross sectional imaging post-treatment is instigated on suspicion of progression requiring therapy
13. SMALL LYMPHOCYTIC LYMPHOMA/CHRONIC LYMPHOCYTIC LEUKAEMIA (SLL/CLL)

Chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) are currently considered to be different manifestations of the same entity by the 4th edition of the World Health Organisation Classification of Tumours of the Haematopoietic and Lymphoid Tissues. The BCSH published revised guidelines on the diagnosis, investigation and management of CLL in July 2018.

13.1 Key Issues
- Identification of cases with TP53 disruption
- Monoclonal B-lymphocytosis is a related condition which has been recently recognised

13.2 Diagnostic Criteria

Typical Cases
1. Consists mainly of small lymphocytes with clumped heterochromatin, although considerable morphological variation can occur
2. Lymph node biopsies show a diffuse infiltrate usually with pseudofollicle formation
3. Immunophenotype: CD5+, CD19+, CD20wk, CD79bwk, FMC7-, CD38-, CD23+, weak slg (slgM+ / slgD+ or slgM-/ slgD+)

Variants
1. CD23-, BCL-1/ t(11;14) negative. This is an adverse prognostic group with outcome similar to mantle cell lymphoma
2. Solitary lymph node disease is very rare

13.3 Prognostic factors

Binet Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Organ involvement*</th>
<th>Haemoglobin** (g/L)</th>
<th>Platelets (x 10^9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0-2 areas</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>B</td>
<td>3-5 areas</td>
<td>&gt;100</td>
<td>&gt;100</td>
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<tr>
<td>C</td>
<td>NA</td>
<td>&lt; 100 and/or</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

*Each of the following counts as one: lymph nodes >1cm in the neck, axillae, groin, spleen and liver
**Secondary causes of anaemia (iron deficiency, folate or B12 deficiency) must be identified and treated before staging.
CLL4 trial prognostic features
Analysis of the CLL4 trial identified three risk groups: 124

**Poor Risk**
- (6% of all): TP53 loss of greater than 10%
  - 5 year PFS 0%, 5-year OS 9%

**Intermediate risk**
- (72% of all patients): No TP53 loss and at least one of:
  - unmutated IGHV genes and/or IGHV3-21 usage 11q deletion
  - β-2 microglobulin greater than 4 mg/L 5 year PFS 12%, 5-year OS 53%

**Good Risk**
- (22% of all patients): None of the above and mutated IGHV genes 5 year PFS 34%, 5-year OS 79%

**IgVH status**
- There is a highly significant difference in the survival between patients with or without mutated IgVH genes. In one study, patients with mutated IgVH genes had a median survival of 25 years compared with 8 years for patients with unmutated IgVH genes 125
- Other data suggest that the use of particular IgVH gene segments such as the VH 3.21 gene may confer a poor prognosis regardless of mutational status
- Whilst IgVH gene analysis may provide some prognostic information, it is not considered an essential test at present as the result does not guide clinical management

**TP53 – abnormalities**
- Chromosome 17p deletion [del(17p)] assessed by FISH and/or TP53 gene mutations screened by sequencing for relevant mutations, in chronic lymphocytic leukemia (CLL) patients are associated with poor response to chemo(immuno)therapeutic regimens (e.g. PFS approx. 12 months with FCR in the 1st line setting) with a dismal prognosis despite additional lines of treatments, with the allogeneic transplant being the only potentially curative approach. Therefore it has become important to identify TP53 abnormalities when planning therapy to help inform the appropriate treatment selection particularly with the increasing availability of the novel, non-chemotherapeutic agents such as the B-cell receptor signaling inhibitors ibrutinib and idelalisib in combination with Rituximab
- Deletion and/or mutation of the TP53 gene occur on average in 10-15% of untreated
CLL patients, and the incidence rises to 40-50% in fludarabine-refractory cases. It has been shown that TP53 mutations in the absence of del(17p) occur in a sizeable proportion of CLL patients (~5% in first line treatment situation) and are also associated with significantly worse outcome.

13.4 Treatment
13.4.1 Indications for treatment in CLL/SLL

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia
- Massive (i.e., at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Massive nodes (i.e., at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of <6 months. In patients with initial blood lymphocyte counts <30x10^9/l, LDT should not be used as a single parameter to define a treatment indication
- Autoimmune anaemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- Constitutional symptoms as defined as any one or more of the following disease-related symptoms: a) Unintentional weight loss of 10% or more within the previous 6 months; b) Significant fatigue (i.e., ECOG Performance Score 2 or worse; inability to work or perform usual activities); c) Fever higher than 38°C for two or more weeks without other evidence of infection; d) Night sweats for more than 1 month without evidence of infection

13.4.2 Factors influencing the choice and duration of treatment

The clinical heterogeneity of CLL and advanced age of many patients dictate that no single treatment approach is applicable to all patients. Factors influencing the choice of treatment include:

- An assessment of fitness to tolerate chemotherapy and/or immunotherapy
- TP53 status
- Previous or current immune cytopenias
- Evidence of transformation
13.4.3 Fitness for therapy

- Patients requiring treatment should be assessed for their ability to tolerate myelosuppressive and immunosuppressive therapies. Important factors include age, performance status, significant co-morbid conditions, especially a creatinine clearance of <60 ml/min and susceptibility to infection.
- It remains broadly useful to separate patients into one of 3 groups based on their co-morbidity profile, as this will help decide on appropriate first line therapy: The most fit patients (so-called ‘go-go’), the less fit (‘slow-go’) and frail (‘no-go’) 205
- The optimal strategy to determine fitness for chemotherapy has not been determined and there is no obligation to use a formal co-morbidity assessment tool (such as CIRS), but some clinicians may find this useful 205
- Note that CLL with lost TP53 function either by 17p deletion, assessed by FISH, or TP53 mutation, assessed by sequencing, does not respond well to genotoxic therapies. These will be referred to as cases with TP53 disruption 205

13.4.4 Primary Treatment

Initial treatment of “fit” patients with no TP53 disruption

- Suggested regimen
  - FCR 126 (NICE TA 174) (Appendix C reg 54)
- Alternative regimen
  - BR 127 (Appendix C reg 34)

Key recommendations (derived from BCSH guidelines 2018) 204

- FCR (Fludarabine/Cyclophosphamide/Rituximab) is recommended as initial therapy for previously untreated fit patients without TP53 disruption outside clinical trials
- BR (Bendamustine/Rituximab) is an acceptable alternative for fit patients in whom FCR is contra-indicated due to renal impairment, more advanced age, concerns with marrow capacity or patient preference

Evidence

- In the German CLL10 randomised trial of FCR x6 vs bendamustine / rituximab (BR) x 6 in young fit patients, FCR proved superior in terms of overall response rate, achievement of MRD negative remissions and duration of first remission, although the BR arm of the trial had a statistically higher proportion of patients who were older and were IgVH unmutate 126
- FCR was more toxic in terms of SAEs, particularly neutropenia and serious infections and with a median of 3 years follow-up, there have been 6 cases of MDS / AML in FCR treated patients compared with 1 case in BR treated patients. Overall survival remains inseparable between both arms of the trial 126
A non randomised phase II trial looked at bendamustine and rituximab (BR) in previously untreated patients with chronic lymphocytic leukaemia (CLL)\textsuperscript{127}

Overall response rate was 88.0\% with a complete response rate of 23.1\% and a partial response rate of 64.9\%.\textsuperscript{127}

**Initial treatment of “unfit” patients with no TP53 disruption**

- **Suggested regimens**
  - Chlorambucil /Obinutuzumab\textsuperscript{128} (NICE TA 343) (Appendix C reg 55)
  - Chlorambucil /Ofatumumab\textsuperscript{129} (NICE TA 344) (Appendix C reg 56)

- **Alternative regimens**
  - BR\textsuperscript{127} (Appendix C reg 34)

**Key recommendations (derived from BCSH guidelines 2018)\textsuperscript{204}**

- Chlorambucil-obinutuzumab or chlorambucil-ofatumumab combinations are NICE approved and are the current standard of care in less fit patients
- Bendamustine-rituximab might be considered as an alternative
- Chlorambucil in combination with rituximab is not routinely recommended

**General Considerations**

- In Northern Ireland, ofatumumab/ obinutuzumab in combination with chlorambucil are accepted as options for untreated chronic lymphocytic leukaemia only if:
  - the person is ineligible for fludarabine-based therapy and
  - bendamustine is not suitable and
  - the company provides ofatumumab/obinutuzumab with the discount agreed in the patient access scheme

**Evidence**

- In the German CLL11 trial, less fit patients were randomised to either chlorambucil (CBL) monotherapy, CBL + rituximab or CBL + obinutuzumab. The trial has shown acceptable toxicity and compared with CBL monotherapy, addition of either rituximab or obinutuzumab resulted in a clear improvement in overall response(OS), depth of response, duration of first remission and time to next leukaemia therapy\textsuperscript{128}
- The German CLL11 trial also showed that patients randomised to CBL + obinutuzumab had a statistically improved OS, depth of response, duration of first remission and time to next leukaemia therapy compared with CBL + rituximab\textsuperscript{128}
- In the Complement 1 trial patients received either CBL monotherapy (Standard UK MRC dosing 10mg/m\textsuperscript{2} D1-7) or CBL + ofatumumab. The trial has shown acceptable toxicity and compared with CBL monotherapy, addition of ofatumumab resulted in a clear improvement in the primary end-point for PFS and key secondary end-points of OS, depth of response and duration of first remission\textsuperscript{129}
• In the MABLE study a randomised comparison of BR with CBL-R for fludarabine-ineligible treatment-naive patients showed a complete response rate after Cycle 6 of 24% vs. 9%; respectively and a median PFS of 40 months vs. 30 months. The ORR and OS were not different. In first line patients with a complete response, MRD negativity was higher with BR than CBL-R\textsuperscript{127}

**Initial treatment of frail patients**

- Suggested regimens
  - Chlorambucil (CBL) monotherapy\textsuperscript{234} (Appendix C reg 57)

- Alternative regimen
  - Bendamustine monotherapy\textsuperscript{229} (Appendix C reg 58)

**Key recommendations (derived from BCSH guidelines 2018)\textsuperscript{204}**

- Single agent chlorambucil may be used in patients who are intolerant of anti-CD20 antibodies or when intravenous therapy is considered unsuitable
- Corticosteroid monotherapy can be considered
- Rituximab monotherapy is not recommended
- Utility and side-effect profiles of B-cell receptor signalling pathway inhibitors in extremely frail patients have not been evaluated in clinical trials and they are not NICE-approved in front-line therapy of standard risk CLL

**Evidence**

- The German CLL study group (GCLLSG) did a multicenter phase III trial for CLL patients older than 65 years comparing first-line therapy with fludarabine with chlorambucil. Fludarabine resulted in a significantly higher overall and complete remission rate (72% vs 51%). Time to treatment failure was significantly shorter in the chlorambucil arm (11 vs 18 months), but no difference in progression-free survival time was observed (19 months with fludarabine, 18 months with chlorambucil)\textsuperscript{234}
- Fludarabine did not increase the overall survival time (46 months in the fludarabine vs 64 months in the chlorambucil arm). Taken together, the results suggest that in elderly CLL patients the first-line therapy with fludarabine alone did not result in a major clinical benefit compared with chlorambucil\textsuperscript{234}
- The GCLLSG also determined the maximal tolerated dose, dose-limiting toxicity and the optimal therapeutic dose of bendamustine in a phase I/II study of pre-treated CLL patients. The maximum tolerated dose was 70 mg/m\textsuperscript{2}. According to NCI-WG criteria, 9/16 patients (56%) responded to therapy, seven to doses (<or=80 mg/m\textsuperscript{2})\textsuperscript{229}
- Two patients achieved complete remission. Five patients had a partial response and two patients stable disease. The median duration of response was 42.7 months.
After a follow-up period of 53.2 months, five patients (31%) were still in remission. The median overall survival time for all patients was 45.6 months.

**Initial treatment of patients with TP53 disruption**

- **Suggested regimens**
  - Ibrutinib monotherapy\(^{130}\) (NICE TA 429) (Appendix C reg 59)
  - Idelalisib + rituximab\(^{206}\) (NICE TA 359) (Appendix C reg 60)

**Key recommendations (derived from BCSH guidelines 2018)\(^{204}\)**

- Ibrutinib is the treatment of choice in front-line therapy for patients with TP53 disruption and is now NICE approved
- Idelalisib and rituximab combination therapy is a suitable alternative for patients for whom ibrutinib is deemed inappropriate, such as patients with significant cardiac disease or patients receiving vitamin K antagonists, and is also NICE approved

**Evidence**

- A single arm phase II study looked at the activity of ibrutinib in previously untreated and relapsed or refractory CLL with TP53 aberrations. 97% previously untreated patients achieved an objective response while 80% of the patients with relapsed or refractory CLL had an objective response\(^{130}\)
- Results from Study 116 a phase III trial which evaluated idelalisib plus rituximab compared with rituximab plus placebo in people with CLL showed a statistically significant improvement in median PFS for idelalisib plus rituximab compared with rituximab plus placebo of 19.4 months interval compared with 6.5 months and ORR was 83.6% for idelalisib plus rituximab compared with 15.5% for rituximab plus placebo\(^{206}\)

**13.4.5 Treatment of relapse/refractory CLL/SLL**

- **Suggested regimens**
  - Ibrutinib monotherapy\(^{233}\) (NICE TA 429) (Appendix C reg 59)
  - Venetoclax/Rituximab\(^{230}\) (NICE TA 561) (Appendix C reg 61)
  - Idelalisib + rituximab\(^{206}\) (NICE TA 359) (Appendix C reg 60)

- **Alternative regimens**
  - BR\(^{131,132,231}\) (Appendix C reg 34)
  - Venetoclax\(^{232}\) (NICE TA 487) (Appendix C reg 61)
Key recommendations (derived from BCSH guidelines 2018)²⁰⁴

- Ibrutinib monotherapy, is the treatment of choice for patients with CLL who are refractory to chemo-immunotherapy, have relapsed after chemoimmunotherapy, or for whom re-treatment with chemoimmunotherapy is inappropriate as defined above
- If Ibrutinib is not suitable then ventoclax/rituximab is an option
- If both ibrutinib and ventoclax/rituximab are unsuitable then Idelalisib/rituximab can be used
- The addition of bendamustine to these BCRi’s is not recommended
- Re-treatment with chemoimmunotherapy may be considered as an option for fit patients with CLL who relapse after a prolonged remission
- Venetoclax is the treatment of choice for patients who fail BCRi therapy

General considerations ²⁰⁴

- Chemoimmunotherapy is not advised in patients who have not responded to prior chemoimmunotherapy, relapsed within 24–36 months of intensive chemoimmunotherapy with FCR or BR, or have acquired TP53 disruption
- In addition, patients with existing co-morbidities who relapse after a chlorambucil and anti-CD20 containing regimen, and patients who achieved long remissions with frontline chemoimmunotherapy but have acquired co-morbidities are no longer eligible for further chemoimmunotherapy.
- The decision whether to treat relapse with chemoimmunotherapy depends on (i) the time to relapse, (ii) the type of frontline therapy and (iii) the absence of TP53 disruption.
- Re-treatment with chemoimmunotherapy may be more effective in those patients with long initial remissions

Evidence

- Idelalisib – rituximab – see Study 116 information above under ‘Initial treatment of patients with TP53 disruption’
- In the phase II resonate study ibrutinib significantly improved PFS; the median duration was not reached in the ibrutinib group (with a rate of progression-free survival of 88% at 6 months), as compared with a median of 8.1 months in the ofatumumab group while overall survival At 12 months was 90% in the ibrutinib group and 81% in the ofatumumab group. The overall response rate was significantly higher in the ibrutinib group than in the ofatumumab group (42.6% vs. 4.1%)²³³
- The strongest evidence for BR in the relapsed/refractory setting comes from the control arms of both the HELIOS²³² and Gilead 115¹³¹ studies showing similar PFS of approximately 1 year to the 2011 phase II study of Fischer et al²³¹
- Venetoclax has NICE approval (NICE TA 487) - Venetoclax has a conditional marketing authorisation for ‘the treatment of chronic lymphocytic leukaemia (CLL) in
the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor' and for 'the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor'.

- In a phase II study Venetoclax was examined in patients with del(17p) relapsed/refractory CLL. For all patients, investigator-assessed ORR was 77% and estimated PFS at 24 months was 54%.

- The main clinical evidence for Venetoclax/rituximab came from MURANO (n=389), a phase III multicentre open-label parallel-arm randomised controlled trial. It included patients aged 18 years or over with relapsed or refractory chronic lymphocytic leukaemia, and compared venetoclax plus rituximab (n=194) with bendamustine plus rituximab.

- The primary outcome measure in MURANO was investigator-assessed median progression-free survival. It was statistically significantly longer with venetoclax plus rituximab compared with bendamustine plus rituximab (median not reached versus 17 months respectively).

13.4.6 The role of allogeneic transplantation

Key recommendations (derived from BCSH guidelines 2018)

- Allogeneic stem cell transplantation (alloSCT) is a treatment option for patients with CLL who have either
  - failed chemoimmunotherapy and BCRI therapy irrespective of TP53 status.
  - harbour a TP53 disruption and have not responded
  - or lost response to BCRI therapy
- AlloSCT should be considered for all eligible patients with Richter transformation

13.5 Transformation

- Transformation can occur to either DLBCL or Hodgkin lymphoma
- The outcome of CLL patients with lymphomatous transformation is significantly poorer than that of patients presenting with de novo lymphomas with a similar histology. Adverse risk factors include poor performance status, >2 prior therapies, >5 cm lymphadenopathy, clonal identity to the underlying CLL clone and loss or mutation of the TP53 gene
- There have been no randomized trials on the treatment of aggressive lymphomas that develop in CLL. The ORR for 130 patients treated at the MD Anderson Cancer Centre was 34% for those receiving intensive chemotherapy and 47% for those receiving chemotherapy and Rituximab. The median survival was 8 months. Of the patients who achieved a remission, those who underwent allogeneic stem cell transplantation had a longer survival than those receiving no additional therapy or those who underwent allogeneic or autologous transplantation for relapsed or
refractory disease

- In a separate analysis of 18 patients who developed HL, the ORR to ‘Hodgkin like’ chemotherapy was 44%
- More recently an ORR of 50% was achieved in 20 patients with lymphomatous transformation treated with a combination of oxaliplatin, fludarabine, cytarabine and Rituximab. The median response duration was 10 months\textsuperscript{132}
- Options are limited for patients unable to tolerate intensive therapy but palliation might be achieved using a high dose steroid regimen
14. MANTLE CELL LYMPHOMA (MCL)

The BCSH published revised guidelines on the diagnosis, investigation and management of MCL on 16th May 2018. Patients with MCL should be treated as per that guideline.

14.1 Diagnostic Criteria

Typical Cases

- All cases should be subject to routine central review by an experienced haematopathologist
- Classical MCL is monomorphic population of small to intermediate sized B-cells, often with cleaved nuclei
- Typically, MCL expresses CD19, CD20, CD79b, CD22, CD5 with FMC7 and moderately intense expression of surface light chains
- CD10 expression is seen in a small proportion of cases, particularly those with blastoid morphology
- SOX11 is highly expressed in classical MCL
- The characteristic cytogenetic abnormality of MCL is the t(11;14)(q13;q32) translocation, resulting in over-expression of cyclin D1 (encoded by the CCND1 gene at 11q13) contributing to deregulated cell cycle progression at the G1-S phase boundary
- The translocation can be detected by FISH on paraffin-embedded material. In practice, the t(11;14) translocation should be demonstrated in cases with atypical morphology, an aberrant immunophenotype, equivocal cyclin D1 positivity or unusual presentation
- Demonstration of clonality may be achieved by detection of light chain restriction by flow cytometry or by PCR for immunoglobulin heavy variable (IGHV) rearrangement

Variants

- Blastic or large cell variant associated with an aggressive clinical course
- Cyclin D1 negative mantle cell lymphoma has similar morphological, immunophenotypical and gene expression features to conventional MCL. It lacks the t (11;14) translocation and cyclin D1 expression, making it difficult to recognise. The cytomorphology, immunophenotype (other than cyclin D1 negativity) and clinical course are identical to cases of classical MCL. It exhibits high levels of cyclin D2 or D3 expression and has a variant translocation. The detection of nuclear SOX11 expression has been suggested as a simple means of recognizing this entity but a reliable antibody is not widely available
- It has recently been reported both cyclin D1 positive and cyclin D1 negative MCL can
be identified by high expression of SOX11 in association with the morphology and immuno-phenotype of MCL[^133]

### 14.2 Prognostic factors

- Mantle cell lymphoma (MCL) has a heterogeneous clinical course. It may be relatively indolent at diagnosis, but with time the disease invariably becomes clinically aggressive and chemotherapy refractory, showing the worst long-term survival among all B-cell lymphoma subtypes.
- The median survival in most published series is approximately 3 years although this has been reported to have risen to 5 years in most recent times[^134].
- A subset of patients may show prolonged indolent behavior and a longer survival but there are no reliable tools to prospectively identify these cases.
- The Ki-67 proliferation index seems to be the most powerful predictor of survival in MCL in the rituximab era[^135;136].
- Blastoid morphology has often been associated with poorer outcome[^137].

### The MIPI index

- The recently proposed Mantle Cell Lymphoma International Prognostic Index (MIPI) predicts survival of MCL better than the International Prognostic Index[^138].
- It was based on an analysis of 455 patients with advanced stage MCL from 3 randomized trials of GLSG and European MCL Network. These trials only included advanced-stage MCL patients who could tolerate moderately intensive chemotherapy.
- The MIPI analysis did not include patients with limited stage I or II MCL. However, the prognostic relevance of stage is not consistently seen in the MCL literature. The proportion of MCL patients presenting with stages I or II is rather low and they require a different therapeutic approach.
- The MIPI has been shown to be valid in patients treated first-line intensive immunochemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation[^139].
- A simplified MIPI (sMIPI) applies to Stage III or IV MCL and also clearly separated patients into 3 groups of low risk, intermediate risk and high risk. To calculate the sMIPI score, 0 to 3 points are given for each prognostic factor. Points are then summed (maximum score of 11).
### Risk Group

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>MIPI score</th>
<th>% of patients</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>0-3</td>
<td>44%</td>
<td>Not reached (&gt;90)</td>
</tr>
<tr>
<td>Intermediate Group</td>
<td>4-5</td>
<td>35%</td>
<td>58</td>
</tr>
<tr>
<td>High Risk</td>
<td>6-11</td>
<td>21%</td>
<td>37</td>
</tr>
</tbody>
</table>

**Notes:**
- MIPI = MCL international prognostic index
- Combined MLC IPI = MIPI (c)
- MIPI (c) is a combination of MIPI and clinical factors.
- OS = Overall Survival

### 14.3 Treatment

#### 14.3.1 Primary treatment

**General considerations**

- When considering how to treat MCL, the clinical presentation, (with recognition of the indolent form), proliferation index, clinical risk scores (simplified MCL international prognostic index (sMIPI) and combined MCL IPI – (MIPI-c)) and performance status should be taken into account.
- Rituximab currently does not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
- Treatment response should be assessed using conventional computed tomography (CT) scanning. (18F) Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging and assessment of minimal residual disease (MRD) status are not currently recommended outside a clinical trial.

**Early stage (stage 1A and IIA) MCL**

**Key recommendations (derived from recent BCSH guidelines 2018)**

- Involved field radiotherapy is recommended.
Advanced stage MCL

**Indications for treatment**

- Bulky symptomatic lymphadenopathy
- B symptoms
- Symptomatic organomegaly
- GI symptoms, including bleeding
- Bone marrow failure

**Indolent/asymptomatic disease**

*Key recommendations (derived from BCSH guidelines 2018)*

- For patients presenting with indolent disease, a period of observation may be appropriate, prior to initiation of definitive therapy

**Symptomatic disease**

*Treatment of patients fit for autologous stem cell transplant*

**First line**

- Suggested induction regimens
  - Nordic MCL 2 protocol – R-maxiCHOP alternating with R-HD AraC (Appendix C reg 62)
  - R-bendamustine x3 followed by R-HD AraC x3 (Appendix C reg 63)

*Key recommendations (derived from BCSH guidelines 2018)*

- Younger, fit patients should receive rituximab with a regimen containing high dose cytarabine with a view to proceeding to ASCT in first remission.
- Single agent rituximab is not recommended

**Evidence**

- The Nordic Maxi-CHOP/Cytarabine regimen with BEAM + ASCT is associated with low toxicity and is the most effective treatment reported thus far.
- A phase 2 study tested induction with 3 cycles of R-bendamustine followed by 3 cycles of R-high dose cytarabine in 23 transplant-eligible patients. CR/unconfirmed nCR (CRu) rate was 96%. Of 15 minimal residual disease (MRD)-evaluable patients, 93% achieved MRD negativity.
- PFS was 96% at median follow-up of 13 months. Toxicity was mainly haematological and was more common after R-high dose cytarabine, but overall the regimen was well tolerated.
**Maintenance**

- **Suggested regimens**
  - Rituximab Monotherapy\(^8\) (Appendix C reg 21)

**Key recommendations (derived from BCSH guidelines 2018)\(^{140}\)**

- Maintenance rituximab is recommended post-ASCT in fit patients treated with intensive induction

**Nice Guidance 2016**

- Consider maintenance rituximab, every 2 months for 3 years, for people with newly diagnosed mantle cell lymphoma who are in remission after cytarabine based induction and high dose chemotherapy\(^8\)

**Treatment of patients unfit for autologous stem cell transplant**

**First line**

- **Suggested regimens**
  - R-CHOP\(^{142,143}\) (Appendix C reg 17)
  - R-Bendamustine\(^{154}\) (Appendix C reg 34)
  - VR-CAP \(^{235}\) (NICE TA 370) (Appendix C reg 64)
  - R-BAC \(^{182}\) (Appendix C reg 65)

- **Alternative regimens**
  - R-CVP\(^{177}\) (Appendix C reg 19)
  - R-Chlorambucil\(^{236}\) (Appendix C reg 48)

**Key recommendations (derived from BCSH guidelines 2018)\(^{140}\)**

- Patients who are unsuitable for autologous stem cell transplantation (ASCT) should receive R-chemotherapy
- The best outcome data is for R-CHOP (rituximab + cyclophosphamide, doxorubicin, vincristine, prednisolone) followed by maintenance rituximab
- However R-bendamustine is efficacious and has a more favourable side effect profile
- Single agent rituximab is not recommended

**Evidence**

- The phase III JCO (GLSG) showed R-CHOP was significantly superior to CHOP in terms of overall response rate (94% v 75%), complete remission rate (34% v 7%), and time to treatment failure (TTF; median, 21 v 14 months). No differences were observed for progression-free survival\(^{142}\)
A phase III NEJM study compared R-CHOP to R-FC. Results showed that although complete-remission rates were similar with R-FC and R-CHOP (40% and 34%, respectively, progressive disease was more frequent with R-FC (14%, vs. 5% with R-CHOP). Overall survival was significantly shorter with R-FC than with R-CHOP (4-year survival rate, 47% vs. 62%, and more patients in the R-FC group died during the first remission.\textsuperscript{143}

Bendamustine with Rituximab was shown to be superior to R-CHOP as first line treatment of indolent and mantle cell lymphoma in a phase III trial.\textsuperscript{154}

Bendamustine is not recurrently funded nor NICE or SMC approved for this indication and so is subject to an individual funding request (IFR).

NICE has approved the use of Bortezomib in VR-CAP for patients not eligible for high dose chemotherapy and Stem cell transplant TA370 – December 2015

VR-CAP improved PFS (24.7 vs 14.4 months), CR rate (53% vs. 42%) and 4-year OS (64% vs. 54%) when compared to R-CHOP but haematological toxicity was increased.\textsuperscript{235}

R- BAC– has demonstrated activity in a phase 2 trial in MCL and can be considered as first line treatment in older patients with mantle cell lymphoma considered unsuitable for anthracycline based chemotherapy.\textsuperscript{182}

The BRIGHT study compared bendamustine/rituximab(BR) to standard rituximab-chemotherapy regimen R-CHOP/R-CVP in treatment-naive patients with indolent non-Hodgkin’s lymphoma or mantle cell lymphoma. BR was noninferior to R-CHOP/R-CVP, as assessed by the primary end point of complete response rate (31% vs 25%, respectively). The overall response rates for BR and R-CHOP/R-CVP were 97% and 91%, respectively.\textsuperscript{171}

Rituximab plus chlorambucil (R-Chl) as first line treatment in patients with MCL was examided in a phase II trial. Results showed overall response rate was 95% (90% CR, 5% PR). Among patients in CR, 78% presented a molecular remission. The 3-year progression-free survival was 89%. There were no serious side effects.\textsuperscript{236}

### Maintenance

- Suggested regimens
  - Rituximab monotherapy (Appendix C reg 21)

### Key recommendations (derived from BCSH guidelines 2018)\textsuperscript{140}

- Maintenance rituximab therapy is recommended in patients achieving a response (complete or partial) following R-chemotherapy who are not proceeding to autograft
NicAzn Clinical Management Guidelines for Lymphoid Malignancies in Adults

**Nice Guidance 2016**

- Consider maintenance rituximab, every 2 months until disease progression, for people with newly diagnosed mantle cell lymphoma who are not fit enough for high-dose chemotherapy and where there has been a response to immunochemotherapy.

**14.3.2 Treatment of relapse/refractory MCL**

**Younger, fit patients**

- Suitable salvage regimens include:
  - Ibrutinib\(^{180,181}\) (NICE TA 502) (Appendix C reg 67)
  - R-ICE\(^{100}\) (Appendix C regimen 7)
  - R-ESHAP\(^{38}\) (Appendix C regimen 8)
  - R-GDP\(^{19}\) (Appendix C regimen 6)
  - R-Bendamsutine\(^{237}\) (Appendix C reg 34)
  - R-BAC\(^{182}\) (Appendix C reg 65)
  - R-HDARA\(^{238}\) (Appendix C reg 66)

**Older, less fit patients**

- Suitable regimens include:
  - Ibrutinib\(^{180,181}\) (NICE TA 502) (Appendix C reg 67)
  - R-Bendamsutine\(^{237}\) (Appendix C reg 34)
  - R-BAC\(^{182}\) (Appendix C reg 65)
  - R-CHOP\(^{142,143}\) (Appendix C reg 17)

- Alternative regimens:
  - R-Chlorambucil\(^{236}\) (Appendix C reg 48)
  - PEP-C\(^{146}\) (Appendix C reg 68)
  - Bortezomib monotherapy\(^{144}\) (Appendix C reg 69)
  - Temsirolimus\(^{147}\) (Appendix C reg 70)

**Key recommendations (derived from BSH guidelines 2018)**\(^{140}\)

- There is no gold-standard therapy for relapsed MCL. The choice of therapy will be determined by patient age, performance status, bone marrow reserve and initial therapy.
- Ibrutinib is the most active single agent in the relapse setting and should be considered as an option.
- An alternative chemotherapeutic regimen should be given at relapse to that given front line.
- Rituximab should be given in combination with chemotherapy at relapse.
- The activity of novel agents is increased with co-administration of rituximab.
There is little evidence to support the role of maintenance rituximab following relapse therapy

**General considerations**

- Where the patient has not received ASCT as part of first-line therapy but is considered fit for such therapy at relapse, consideration of consolidation of second response with ASCT is a clinical option.
- In young patients who have previously undergone ASCT, assessment of fitness for an allogeneic procedure (alloSCT) should be made. If the patient is sufficiently fit, the aim should be to obtain a response with second-line therapy and consolidate with transplantation.
- This usually involves use of standard salvage regimens as applied in the context of aggressive lymphomas. With the advent of the oral Bruton tyrosine kinase (BTK) inhibitor, ibrutinib, however, an alternative salvage option exists; ibrutinib is highly active in the majority of relapsed MCL patients, and the duration of response provides a window to plan and perform the allograft procedure.
- The majority of relapsed MCL patients will not be eligible for ASCT or alloSCT. Choice of therapy will be influenced by age, performance status, co-morbidities and initial therapy. It is logical that, where a patient has received one prior line of treatment, a different agent be chosen at relapse.

**Evidence**

- No salvage regimen has been demonstrated to be superior over others.
- Ibrutinib appears the most active single agent in the treatment of relapsed refractory MCL, with response rates of 68% (21% CR)\(^\text{180}\).
- NICE has approved Ibrutinib for treating relapsed or refractory mantle cell lymphoma in adults – TA502 – January 2018.
- Regimens used as second-line therapy for aggressive lymphomas (R-ICE, R-ESHAP, R-GDP) should be considered depending on patient characteristics, eligibility for transplant as consolidation, and previous therapies (see evidence section of relapsed DLBCL).
- R-high dose cytarabine as salvage therapy pre ASCT (BEAM) was examined in single arm phase II trial. The overall response rate was 70% (complete response rate 64%, partial response rate 6%), FFS and OS at 4 years were 36 and 66, respectively. The overall conclusion was, high-dose Ara-C and BEAM with stem cell rescue in newly diagnosed MCL patients responsive to R-CHOP is a manageable treatment with respect to toxicity\(^\text{238}\).
- Bendamustine with Rituximab (BR) was showed superior (PFS) compared to fludarabine rituximab (34.2 months vs 11.7) in treatment of relapsed indolent and mantle cell lymphoma in a phase III trial\(^\text{237}\).
- R-BAC (Rituximab, Bendamustine and Cytarabine (500)) – has demonstrated activity.
and can be used in refractory/relapsed Mantle Cell Lymphoma\textsuperscript{182}

- The principle for using R-CHOP and R-Chlorambucil in older less fit patients comes from evidence of their activity in first line treatment of advanced MCL. (see Advanced stage MCL/ Treatment of patients unfit for ASCT)

- Bortezomib may be considered for inclusion at relapse although responses appear short lived (approx 6 months).\textsuperscript{144} This may be sufficient to achieve disease control prior to stem cell harvest/ transplant

- Temsirolimus is licensed in Europe and is a possible option for treatment of relapsed MCL. Temsirolimus requires continuous therapy, with quick progressions reported on cessation of the drug\textsuperscript{147}

- PEP-C is a low dose metronomic, multi-drug therapy which may be suitable for elderly or palliative patients\textsuperscript{146}

- Bendamustine and Temsirolimus are not recurrently funded nor NICE or SMC approved for this indication and so are subject to an IFR

- Hyper CVAD is not recommended at relapse due to high induction mortality.

- Flavopiridol and enzastaurin are not recommended for treatment of relapsed MCL on the basis of inadequate response

- Radiotherapy may be useful for locally symptomatic disease

### 14.3.3 The role of transplantation in MCL

**Key recommendations (derived from BCSH guidelines 2018)\textsuperscript{140}

- ASCT should be considered as consolidation of first line therapy for all patients deemed fit for intensive therapy. Patients over 60 years of age should be thoroughly assessed for the suitability of this approach

- ASCT to consolidate first response is most likely to benefit those who achieve a complete remission

- ASCT can significantly prolong duration of disease response though at present there is insufficient data to demonstrate whether there is a significant overall survival benefit

- AlloSCT may be considered in second remission for fit patients with an appropriate donor. The intensity of the conditioning regimen should be selected on an individual patient basis

- AlloSCT can be effective at rescuing patients who relapse post-ASCT.

- AlloSCT as part of first-line therapy should be considered only for patients with high-risk disease and preferably within the context of a clinical trial
15. WALDENSTRÖM’S MACROGLOBULINAEMIA/LYMPHOPLASMACYTIC LYMPHOMA (WM/LPL)

15.1 Introduction

- The BCSH published updated guidelines on the Diagnosis and Management of Waldenstrom’s Macroglobulinemia in 2014
- Waldenstrom’s macroglobulinemia is a distinct B-cell lymphoproliferative disorder characterized by IgM monoclonal gammopathy and bone marrow infiltration by lymphoplasmacytoid lymphoma
- Clinical features are diverse and may relate to disease burden or to the effects of the IgM paraprotein. Disease burden can cause peripheral blood cytopenias, organomegaly and constitutional symptoms
- The IgM paraprotein may cause hyperviscosity syndrome, amyloidosis, peripheral neuropathy, cold agglutinin disease and acquired von Willebrand’s disease
- The presence of an IgM monoclonal protein is not indicative of a diagnosis of WM as IgM monoclonal proteins have been demonstrated in a proportion of most other B-cell lymphoproliferative disorders. In a series of 382 consecutive patients with lymphoid neoplasms and a monoclonal IgM protein, the following diagnoses were identified:\textsuperscript{148}

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients (n=382)</th>
<th>% of patients in series</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM/LPL</td>
<td>225</td>
<td>58.9 %</td>
</tr>
<tr>
<td>CLL/SLL</td>
<td>77</td>
<td>20.2 %</td>
</tr>
<tr>
<td>Marginal Zone lymphoma</td>
<td>27</td>
<td>7 %</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>18</td>
<td>4.7 %</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>11</td>
<td>2.9 %</td>
</tr>
<tr>
<td>DLBCL</td>
<td>7</td>
<td>1.8 %</td>
</tr>
<tr>
<td>DLBCL with low grade NHL</td>
<td>5</td>
<td>1.3 %</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell</td>
<td>4</td>
<td>1 %</td>
</tr>
<tr>
<td>CD5⁺CD23⁻low grade NHL</td>
<td>8</td>
<td>2 %</td>
</tr>
</tbody>
</table>

15.2 Diagnosis

Morphology

- LPL is a lymphoproliferative disorder comprised of small lymphocytes in which there is morphological evidence of plasma cell differentiation, definitively demonstrated by immunohistochemistry using plasma cell specific antibodies such as CD138 and MUM1/IRF4
NICaN Clinical Management Guidelines for Lymphoid Malignancies in Adults

- The pattern of infiltration is typically interstitial, nodular or diffuse. A purely para-trabecular pattern is unusual
- Additional morphological clues on trephine sections include reactive mast cells (best seen on Giemsa stain or highlighted with CD117 or Mast cell tryptase immunohistochemistry). Internuclear (Dutcher bodies) and cytoplasmic (Russell bodies) may also be seen
- The overall extent of the plasma cell differentiation varies from patient to patient and it appears that this is the major determinant of the monoclonal protein concentration rather than the overall extent of the marrow infiltration
- In 20% of cases the plasma cells are predominant; IgM myeloma then becomes a more significant differential diagnosis

**Immunophenotype/ immunohistochemistry**

- There is almost universal expression of pan B-cell antigens CD19, CD20 and CD79. CD5 and CD23 are expressed in a minority of cases (CD5 in 5-20% of cases). Most cases show memory B-cell marker CD27 as well as CD52. The Germinal centre antigens CD10 and BCL6 are not demonstrated
- Distinguishing WM from MZL can be difficult, but WM may show CD25+ CD22 weak, CD103- whilst MZL may be CD25- CD22+, CD103+
- There is limited data on plasma cell immunophenotyping in WM but the antigenic patterns seen in myeloma plasma cells (CD19-, CD45-, CD56+) are not seen in WM. This can be useful in those cases of WM in which plasma cells predominate and plasma cell phenotyping should allow a better distinction between WM and the rare entity of IgM myeloma

**15.3 Prognosis**

The International Scoring System for WM (ISSWM) identified the following factors to be relevant at the initiation of treatment. There is international consensus that this be recorded in clinical trials but there is no evidence that it should influence treatment decisions for individual patients.

<table>
<thead>
<tr>
<th>Low Risk: ≤1 adverse characteristic and age ≤65</th>
<th>Intermediate Risk: ≥2 adverse characteristics</th>
<th>High Risk: &gt;2 adverse characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>M-protein &gt; 70 g/l</td>
<td>β2-microglobulin &gt; 3mg/l</td>
</tr>
<tr>
<td>Hb &lt; 115 g/l</td>
<td>Platelets &lt; 100 x 10^9/l</td>
<td>Age &gt; 65 years</td>
</tr>
</tbody>
</table>

- 27% of patients 87% 5-yr survival
- 38% of patients 68% 5-yr survival
- 35% of patients 36% 5-yr survival
15.4 Treatment

15.4.1 Primary treatment

Indications for therapy

- A significant proportion of patients are asymptomatic at presentation and can be safely observed at 3-6 month intervals. The risk of progression to symptomatic disease is 59% at 5 years\(^{150}\)
- Indications for treatment include\(^ {151}\)
  - constitutional symptoms
  - symptomatic lymphadenopathy or splenomegaly
  - Hyper viscosity syndrome (HVS)
  - haematological suppression due to marrow infiltration
  - IgM related syndromes such as neuropathy and CHAD

Choice of primary therapy in symptomatic individuals

There is a lack randomized data to guide decisions\(^ {153}\)

- Suggested regimens
  - DRC\(^{156,157}\) (Appendix C reg 71)
  - R-Bendamsutine\(^{154}\) (Appendix C reg 34)
- Alternative regimens
  - Chlorambucil\(^{167,170}\) (Appendix C reg 57)
  - BDR\(^{158}\) (Appendix C reg 72)
  - VR\(^{159}\) (Appendix C reg 42)
  - R-Cp\(^{166}\) (Appendix C reg 43)
  - Rituximab monotherapy\(^{168-169}\) (Appendix C reg 21)

Key recommendations (derived from BCSH guidelines 2014)\(^ {153}\)

- Patients with symptomatic WM should receive a rituximab-containing regimen. Appropriate regimens include dexamethasone/rituximab/cyclophosphamide (DRC) and bendamustine/rituximab (BR). The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for stem cell transplantation
- Given the risk of IgM flare, careful monitoring of all patients receiving rituximab is required with monitoring of sequential IgM, clinical assessment for HVS and monitoring of PV if available. The introduction of rituximab should be deferred in patients considered at a higher risk of hyperviscosity, this being arbitrarily defined by an IgM M-protein >40 g/l and/or a PV > 4 centipoise
- R-CHOP should not be used as primary therapy in WM
- Chlorambucil remains suitable therapy in elderly frail patients
- There is insufficient evidence to support the use of maintenance rituximab
Evidence

- DRC induced higher response rates than rituximab alone, but complete responses (CRs) are infrequent. DRC is associated with a progression-free survival (PFS) of about 3 years, a treatment free interval>4 years and median overall survival (OS) of 8 years with favourable short- and long-term safety profiles.\(^{157}\)
- The R-Bendamustine combination was superior to CHOP-R with regards to CR rate, toxicity and response duration in subgroup analysis of a large trial in indolent lymphoma\(^{154}\) (Bendamustine is not recurrently funded nor NICE or SMC approved for this indication and so is subject to an individual funding request (IFR))
- Long term follow-up of a phase II study of bortezomib/dexamethasone/rituximab (BDR for five cycles) has shown a median PFS of 3.5 years, median duration of major response of 5.5 years and OS rate of 66% at 7 years.\(^{158}\)
- A weekly bortezomib regimen in conjunction with rituximab produced a MRR of 65% but no grade 3 or 4 neuropathy.\(^{159}\)
- Single agent chlorambucil may be suitable in very frail patients in whom combination therapy is considered inappropriate (MRR 40%, PFS 27 months).\(^{170}\)
- No difference in response rate or survival was demonstrated when chlorambucil was administered either daily or intermittently in a randomized study, although there was a higher incidence of myelodysplasia with the continuous schedule.\(^{167}\)
- Concerns have been raised by some authors regarding the long term risk of histological transformation and myelodysplasia/AML in patients with Waldenstrom’s macroglobulinemia treated with fludarabine based regimens.\(^{164,165}\)
- Concerns also raised regarding the suitability of fludarabine based regimens in patients who may be potential candidates for autologous transplantation whilst concerns regarding myelotoxicity and infection are pertinent in elderly patients, particularly those with suboptimal renal function.\(^{153}\)
- Rituximab, Cyclophosphamide and Prednisone (R-CP) in the frontline treatment of patients with WM has demonstrated analogous response rates to R-CVP or R-CHOP, whilst treatment related complications, including febrile neutropenia, hospitalizations, and vincristine-related neuropathy, were less.\(^{166}\)
- The use of rituximab as a single agent can be considered in selected patients with WM, such as those presenting with a low tumor burden, mild to moderate cytopenias resulting from bone marrow involvement or autoimmune-related destruction (ie, cold agglutinaemia, immune mediated thrombocytopenia), or IgM-related neuropathy. Overall response rates with 4 weekly infusions of rituximab are 20% to 30%.\(^{168-169}\)
- Splenectomy should be considered in patients with bulky splenomegaly resistant to chemotherapy or who have significant cytopenias or symptoms of weight loss, early satiety or abdominal pain.
15.4.2 Treatment of relapsed/refractory WM/LPL

- **Suggested regimens**
  - DRC\textsuperscript{156,157} (Appendix C reg 71)
  - R-Bendamsutine\textsuperscript{237} (Appendix C reg 34)
  - Ibrutinib\textsuperscript{155} (Appendix C reg 59)

- **Alternative regimens**
  - BDR\textsuperscript{158,160} (Appendix C reg 72)
  - VR\textsuperscript{159} (Appendix C reg 42)
  - FCR\textsuperscript{152} (Appendix C reg 54)

**Key recommendations (derived from BCSH guidelines 2014)\textsuperscript{153}**

- Repeat bone marrow aspirate and trephine assessment and CT scanning should be performed prior to the reintroduction of treatment.
- Patients who remain asymptomatic despite serological evidence of progression can be observed until clinical symptoms occur.
- Patients should receive a rituximab-containing regimen if CD20 is expressed. Appropriate regimens include BR and DRC. The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for SCT.
- Retreatment with primary therapy may be appropriate in some patients.
- Bortezomib-containing regimens are suitable in the relapse setting. Weekly regimens are preferable, given the neurological toxicity associated with the biweekly schedules. Prophylaxis against herpes zoster virus (HZV) reactivation is recommended.

**Evidence**

- See WM primary therapy in symptomatic individuals evidence section for evidence on DRC.
- Bendamustine with Rituximab (BR) was showed superior (PFS) compared to fludarabine rituximab (34.2 months v 11.7) in treatment of relapsed indolent and mantle cell lymphoma in a phase III trial\textsuperscript{237}.
- The non-randomized INNOVATE study examined the the efficacy and safety of ibrutinib in a population with rituximab-refractory disease. Results showed at a median follow-up of 18.1 months, the proportion of patients with an overall response was 28 [90%] of 31 (22 [71%] of patients had a major response), the estimated 18 month progression-free survival rate was 86%, and the estimated 18 month overall survival rate was 97%\textsuperscript{155}.
- A phase II study looked at FCR in WM. Tedeschi et al reported an overall response rate of 79%, and a major response rate of 74.4%, including 11.6% complete remissions (CRs) and 20.9% very good partial remissions\textsuperscript{152}.
- The recommendation from the 8th International Workshop is that bortezomib based...
regimens should be strongly considered for patients with high IgM levels, symptomatic hyperviscosity, cryoglobulinemia or cold agglutininemia, amyloidosis, and renal impairment or in young patients in whom avoidance of alkylator or nucleoside analog therapy is desired\textsuperscript{160}

- The panel also recommends that bortezomib should ideally be given once per week and possibly by a subcutaneous route; in case urgent reduction of the IgM level is needed, bortezomib can be started at twice-per-week doses for 1 or 2 cycles and then be changed to once-per-week dosing to reduce risk of neurotoxicity\textsuperscript{160}
- See WM primary therapy in symptomatic individuals evidence section for further evidence on BDR and VR

15.4.3 Treatment of histological transformation

Treatment

- Treat as for DLBCL – see under treatment of advanced DLBCL

General considerations

- Histological transformation is a well-recognised phenomenon which has been reported to occur in 5-10\% of patients with WM. Clinical features suggestive of histological transformation includes bulky and rapidly enlarging lymph node masses, extra nodal disease and a marked elevation in serum LDH\textsuperscript{161}
- Tissue biopsy is essential for diagnosis and may be directed by CT-PET scanning as has been described in CLL\textsuperscript{161}

15.4.4 Transplantation

Key recommendations (derived from BCSH guidelines 2014)\textsuperscript{153}

- Autologous HSCT is a feasible therapeutic option for relapsed WM in younger fitter patients with aggressive disease (short PFS < 2 years, histological transformation)
- Allogeneic HSCT may be considered in selected younger patients with relapsed WM and aggressive clinical course
- Autologous and allogeneic HSCT should only be performed in the setting of chemosensitive disease and a good response to re-induction therapy

Evidence

- The EBMT recently reported a retrospective analysis of their autologous HSCT experience. 5 year PFS and OS rates were 33\% and 61\% respectively, TRM 8\%. \textsuperscript{162}
- In the recently reported EBMT experience of allograft in WM, the 1 year non-relapse mortality was 27\%, the 5 year PFS and OS rates were 48\% and 63\% respectively\textsuperscript{163}
15.5 Hyperviscosity syndrome

Key recommendations (derived from BCSH guidelines 2014)\textsuperscript{153}

- Plasma exchange is recommended for all patients with HVS irrespective of plasma viscosity
- 1 to 2 procedures, exchanging 1-1.5 calculated plasma volumes is advised. Albumin is used for replacement product
- Plasma exchange may be indicated in certain asymptomatic patients depending on the clinical circumstances, recorded plasma viscosities and co-morbidities

15.6 WM complicated by CNS involvement (Bing –Neel) syndrome

- Suggested regimen
  - MATRIX (Appendix C reg 35)

General considerations

- If CNS involvement is suspected, appropriate investigations should be carried out to confirm the diagnosis
- Imaging is frequently abnormal. Biopsy confirms the diagnosis.
- Treatment data are limited, but responses are seen with radiation and/or chemotherapy
- Treatment should be initiated as responses do occur that may improve quality of life and extend it when limited or no active systemic disease is present.
- Consideration should be given for a consolidative ASCT, conditioned with either Thiotepa/BCNU or Cyclophosphamide/TBI where appropriate

Therapy:
All patients will receive intrathecal chemotherapy on day 1. CSF will be analysed for lymphomatous involvement by flow cytometry. Further intrathecal injections are not recommended unless the disease is largely leptomeningeal as the MATRIX chemotherapy will cross into the CSF. In the case of LM disease intrathecal methotrexate can be repeated with each course. Patients who have a clear CSF from the outset will therefore receive only one intrathecal injection on day 1.
16. MARGINAL ZONE LYMPHOMA

Marginal Zone lymphomas (MZL) share a common cell of origin. Chronic antigenic stimulation by microbial pathogens and/or auto-antigens may have a role in their development. It embraces the following terms/entities:

- Extranodal marginal zone B-cell lymphoma, also called mucosa-associated lymphoid tissue (MALT) (includes Gastric and Non gastric MALT lymphoma)
- Splenic marginal zone lymphoma (SMZL) with or without villous lymphocytes
- Nodal marginal zone lymphoma (NMZL) (monocytoid B cell lymphoma). Nodal marginal zone lymphoma is rare and represents <10% of all marginal zone lymphomas.

The clinical presentation of each of these entities is very different. Symptoms are primarily related to the anatomical location of the lymphoma. MALT and SMZL are indolent diseases which usually present with good performance status, no B symptoms and are associated with long survival. Patients with nodal MZL have a worse prognosis and shorter progression-free survival following therapy.\(^{172}\)

16.1 EXTRANODAL MARGINAL ZONE LYMPHOMA (MALT–TYPE LYMPHOMA)

16.1.1 Key issues

- Radiotherapy effective for local control
- Identification of patients who require active treatment with chemotherapy
- Uncertainty about the impact of treatments on overall survival
- Risk of gastric carcinoma

16.1.2 Diagnostic criteria

Typical cases

- Cellular composition includes small lymphocytes, centrocyte-like cells, 'monocytoid' B-cells, plasmacytoid cells
- Invasion of epithelial structures and existing germinal centres
- CD5-, CD10-, CD19+, CD20+, CD23-, sIgM+, sIgD+ or -
- Disease localized to or centred on an extranodal site

Transformation

- The criteria are the same as for follicular lymphoma. The significance of increased numbers of large lymphoid cells is uncertain in otherwise typical cases.
16.1.3 Prognostic Factors
Extranodal marginal zone lymphoma with t(11;18)(q21;q21) in the stomach may be resistant to Helicobacter pylori eradication\textsuperscript{173}

16.1.4 Staging of gastric MZL
Staging for extranodal gastric MZL is based on a Lugano modification of Ann Arbor staging system as outlined in table below

<table>
<thead>
<tr>
<th>Lugano Staging System for gastrointestinal lymphomas</th>
<th>Lugano Modification of Ann Arbor Staging System</th>
<th>Tumor Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I Confined to GI tract (Single primary or multiple, non contiguous)</td>
<td>I\textsubscript{E}</td>
<td>Mucosa, submucosa</td>
</tr>
<tr>
<td>I\textsubscript{1} = mucosa, submucosa</td>
<td>I\textsubscript{E}</td>
<td>Muscularis, propria</td>
</tr>
<tr>
<td>I\textsubscript{2} = muscularis, propria, serosa</td>
<td>I\textsubscript{E}</td>
<td>Serosa</td>
</tr>
<tr>
<td>Stage II Extending into the abdomen</td>
<td>II\textsubscript{E}</td>
<td>Perigastric lymph nodes</td>
</tr>
<tr>
<td>II\textsubscript{1} = local nodal involvement</td>
<td>II\textsubscript{E}</td>
<td>More distant regional lymph nodes</td>
</tr>
<tr>
<td>II\textsubscript{2} = distant nodal involvement</td>
<td>II\textsubscript{E}</td>
<td></td>
</tr>
<tr>
<td>Stage II\textsubscript{E} Penetration of serosa to involve adjacent organs or tissues</td>
<td>II\textsubscript{E}</td>
<td>Invasion of adjacent structures</td>
</tr>
<tr>
<td>Stage IV Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement</td>
<td>III\textsubscript{E}</td>
<td>Lymph nodes on both sides of the diaphragm/distant metastases (e.g. bone marrow or additional extranodal sites)</td>
</tr>
</tbody>
</table>

16.1.5 Treatment (gastric and non-gastric)

**Gastric MALT lymphoma**

**Localised disease (stage I-II/I\textsubscript{E}-II\textsubscript{E})**
- Suggested regimens
  - PPI triple therapy (see local guidelines)
  - R-Chlorambucil\textsuperscript{174} (Appendix C reg 48)
  - R-CVP\textsuperscript{171} (Appendix C reg 19)
Key recommendations (derived from NG52 NICE guidelines 2016)\(^\text{84}\)

- Offer 1 or more lines of *Helicobacter pylori* eradication therapy, without any concurrent therapy, to people with *H. pylori*-positive gastric MALT lymphoma
- Consider *H. pylori* eradication therapy for people with *H. pylori*-negative gastric MALT lymphoma

Recommendations at restaging after antibiotics

- Restage at 3 months (earlier if symptomatic) with endoscopy/biopsy for *H. pylori*/lymphoma after antibiotics
- Patients who are *H pylori* negative and lymphoma negative – consider monitoring with follow up endoscopies (observation without therapy)
- Patients who are *H pylori* negative and lymphoma positive and who are:
  - Asymptomatic – consider ‘watch and wait’ (observation without therapy) for another 3 months or gastric radiotherapy
  - Symptomatic – consider gastric radiotherapy or chemotherapy in combination with rituximab
- Patients who are *H pylori* positive and lymphoma negative – consider second line antibiotics (see local guidelines)
- Patients who are *H pylori* positive and lymphoma positive and who have:
  - Stable disease – consider second line antibiotics (see local guidelines)
  - Progressive or symptomatic disease – consider gastric radiotherapy or chemotherapy in combination with rituximab
  - Disease at high risk of progression (*H. pylori*-negative at initial presentation or t(11:18) translocation) - consider gastric radiotherapy or chemotherapy in combination with rituximab
- Older less fit patients who required chemotherapy should be considered for R-chlorambucil

General considerations

- If the presence of active *Helicobacter pylori* infection is not demonstrated by histochemistry, it must be ruled out by urea breath test or helicobacter faecal antigen test
- *Helicobacter pylori* eradication can induce lymphoma regression and long-term clinical disease control in most patients. The length of time necessary to obtain a remission can span from very few months to >12 months. It is reasonable to wait for at least 12 months before starting another treatment in patients who achieve a clinical and endoscopic remission together with eradication of H. pylori, albeit having persistent (residual) lymphoma at the histological level\(^{178}\)
- Follow-up with upper GI endoscopy and biopsy should be performed three months after therapy until patient clear and then every 3-6 months\(^{178}\)
- The risk of gastric adenocarcinoma among patients diagnosed with gastric MALT
lymphoma has been reported to be six fold higher than in the general population.\textsuperscript{175}

**Evidence**

- The final results of the IELSG-19 study (the largest randomized study ever carried out in MALT lymphoma, 454 patients) were published in the Journal of clinical (JCO) in 2017. These results showed that chlorambucil plus Rituximab produced better EFS and PFS in comparison with chlorambucil or Rituximab alone in MALT lymphoma but this did not translate into improved OS. The stomach was the primary site in 43% of patients enrolled in the trial.\textsuperscript{174}

- The BRIGHT study compared bendamustine/rituximab(BR) to standard rituximab-chemotherapy regimen R-CHOP/R-CVP in treatment-naive patients with indolent non-Hodgkin’s lymphoma or mantle cell lymphoma. BR was non inferior to R-CHOP/R-CVP, as assessed by the primary end point of complete response rate (31% vs 25%, respectively). The overall response rates for BR and R-CHOP/R-CVP were 97% and 91%, respectively.\textsuperscript{171}

- Excellent disease control using radiation therapy alone has been reported by several institutions supporting the use of modest-dose involved-field radiotherapy (30–40 Gy radiation to the stomach and perigastric nodes given in 4 weeks) for patients with stage I–II MALT lymphoma of the stomach without evidence of H. pylori infection or persistent lymphoma after antibiotic eradication.\textsuperscript{176,177}

**Assessment of residual disease**

- The definitive diagnosis of residual disease requires the same criteria as at presentation

- Solitary or multiple B-cell aggregates without germinal centres and cellular morphology suggestive of marginal zone lymphoma should be reported as suspicious and further follow up advised. The significance of molecular remission remains uncertain.\textsuperscript{179}

**Disseminated disease (stage IV)**

- Suggested regimens
  - PPI triple therapy (see local guidelines)
  - R-Chlorambucil\textsuperscript{174} (Appendix C reg 48)
  - R-CVP\textsuperscript{171} (Appendix C reg 19)

**Key recommendations (derived from NG52 NICE guidelines 2016)\textsuperscript{84}**

- Offer *H. pylori* eradication therapy to people with disseminated *H. pylori*-positive gastric MALT lymphoma

- Offer chemotherapy (for example, chlorambucil or CVP) in combination with
Rituximab to people with disseminated gastric MALT lymphoma who need treatment; for example, people who are symptomatic or with threatened vital organ function

- Consider 'watch and wait' (observation without therapy) for people with disseminated gastric MALT lymphoma who are asymptomatic and do not have threatened vital organ function

**Evidence**

- See gastric MALT lymphoma localised disease evidence section for information on R-CVP and R-Chlorambucil

**Non-Gastric MALT lymphoma**

**Localised and disseminated disease**

- **Suggested regimens**
  - R-Chlorambucil\(^{174}\) (Appendix C reg 48)
  - R-CVP\(^{171}\) (Appendix C reg 19)

**Key recommendations (derived from NG52 NICE guidelines 2016)\(^{84}\)**

- For people with non-gastric MALT lymphoma, take into account the following before recommending any treatment:
  - site of involvement and potential for organ dysfunction
  - whether it is localised or disseminated
  - the morbidity associated with any treatment proposed
  - the person’s overall fitness
- Consider radiotherapy for people with localised disease sites of non-gastric MALT lymphoma, irrespective of stage
- Offer chemotherapy (for example, chlorambucil or CVP) in combination with rituximab to people with non-gastric MALT lymphoma for whom radiotherapy is not suitable or who have disseminated disease and need treatment
- Consider 'watch and wait' (observation without therapy) for people with clinically non-progressive localised non-gastric MALT lymphoma that is unlikely to result in vital organ dysfunction, who are asymptomatic and for whom radiotherapy is not suitable

**Evidence**

- See gastric MALT lymphoma localised disease evidence section for evidence on R-CVP and R-Chlorambucil
Management of patients with transformed gastric/non-gastric MZL

Treatment
- Treat as for DLBCL – see under treatment of advanced DLBCL

16.2 SPLENIC/NODAL MARGINAL ZONE LYMPHOMA (MZL)

16.2.1 Key Issues
- Continuing uncertainty over classification, the lack of characteristic phenotypic or molecular diagnostic findings continues to hamper the reproducibility of marginal zone lymphomas
- Optimal treatment of nodal marginal zone lymphoma is uncertain as no large series have been published thus far
- Prognosis of nodal marginal zone lymphoma appears to be significantly worse than that of patients with extranodal MZL

16.2.2 Diagnostic Criteria

Typical cases
Cellular composition includes small lymphocytes, centrocyte-like cells, 'monocytoid' B-cells, plasmacytoid cells.

Pattern of infiltration (a trephine biopsy or other tissue biopsy is always required for this diagnosis):
- Bone Marrow: nodular, interstitial, diffuse
- Spleen: marginal zone infiltration
- Nodes: interfollicular expansion with replacement of germinal centres

Immunophenotype: CD5- or +, CD10-, CD19+, CD20+, CD23-, sIgM+, sIgD+ or -, BCL-6-, cyclin D1-

Cytogenetics
- The cytogenetic profile of SMZL is distinct from other B-cell lymphomas. 25% of cases are CD5 +ve. The cytogenetic makeup of CD5 +ve SLVL differs significantly from that of CD5 -ve SLVL
- Complex Karyotype, 14q aberrations, and TP53 deletions are poor prognostic indicators

Transformation
- Transformation of nodal MZL to diffuse large B-cell lymphoma can occur, although the incidence is not well studied. In one series, 20 of 124 patients transformed at a
median time of 4.5 years from diagnosis

- The pathological criteria for transformation are the same as for follicular lymphoma. The significance of increased numbers of large lymphoid cells is uncertain in otherwise typical cases

### 16.2.3 Prognosis (Splenic MZL)

The Intergruppo Italiano Linfomi developed a prognostic categorisation based on three risk factors:

- Haemoglobin<120g/l
- Abnormal LDH
- Albumin <35g/l

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk-Group</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>Medium</td>
<td>73%</td>
</tr>
<tr>
<td>3</td>
<td>High</td>
<td>50%</td>
</tr>
</tbody>
</table>

### 16.2.4 Treatment

Roughly two thirds of patients are asymptomatic at diagnosis.

**Splenic MZL primary treatment**

Suggested induction regimens

- R-CVP\(^{171}\) (Appendix C reg 19)
- R-Bendamsutine\(^{171}\) (Appendix C reg 34)
- Rituximab Monotherapy\(^{195}\) (Appendix C reg 21)

**General considerations**

Hepatitis C (HCV) infection may be associated with some cases of splenic MZL.

**Hepatitis C positive serology**

- Splenic MZL patients with evidence of HCV infection should be treated with pegylated interferon and ribavirin and not rituximab\(^{192}\)
- Antiviral therapy with interferon, with or without ribavirin has been shown to induce virologic and haematologic responses in patients HCV positive MZL, including those with splenic MZL\(^{193,196,197}\)
- A recent retrospective study evaluated the activity of antiviral therapy with IFN or pegylated-IFN, with or without ribavirin (84% received ribavirin), in a large series of patients with HCV-positive indolent B-cell NHLs (N=94; splenic MZL histology, n=30 [32%])\(^{198}\)
Among the patients who received antiviral treatment as first-line therapy (n=76; splenic MZL, n=24), the ORR and CR rate was 77% and 47%, respectively, and a sustained virologic response was observed in 78% of patients. The median duration of response was 23 months after a median follow up of 3.3 years. The 5-year PFS and OS rate was 78% and 94%, respectively. 198

Patients with no response should be managed as described below for patients with HCV negative serology

**Hepatitis C negative serology**

- If asymptomatic – watch and wait
- Splenectomy remains a treatment option, particularly for patients with cytopenias or symptoms of weight loss, early satiety or abdominal pain. Improvement in symptoms is seen in 90% of splenectomised patients. 194 Although not curative, it generally provides improved disease control
- Other therapeutic options in symptomatic patients with splenomegaly included combination chemotherapy with rituximab or rituximab monotherapy (see suggested induction regimens above)

- Splenic irradiation, as a palliative manoeuvre, can be considered for patients too frail for splenectomy or systemic chemotherapy

**Evidence**

- See gastric MALT lymphoma localised disease evidence section (BRIGHT study) for information on bendamustine/rituximab (BR) and R-CVP
- Rituximab with or without chemotherapy was found to have major activity in SMZL in a retrospective case series of 70 patients. 26 patients in this series received single agent Rituximab, OR 88%, 3 year survival 95%, 3 year FFS 86%. Rituximab alone resulted in disappearance of splenomegaly in 92% of patients and normalization of lymphocyte counts. Six patients received R-chemo (FCR=5, R-FMD=1), OR 83%, 3 year survival 100%, 3 year FFS100% 195

**Nodal MZL primary treatment**

- Suggested induction regimens
  - R-CVP 171 (Appendix C reg 19)
  - R-Bendamsutine 171 (Appendix C reg 34)
  - R-Chlorambucil 122 (Appendix C reg 48)
  - Rituximab Monotherapy 200 (Appendix C reg 21)
NICaN Clinical Management Guidelines for Lymphoid Malignancies in Adults

NICE NG52 2016 guidance

- Offer local radiotherapy as first line treatment to people with localised stage I - II nodal MZL
- Consider 'watch and wait' (observation without therapy) as first line treatment for people with stage I - II nodal MZL who are asymptomatic and for whom treatment with a single radiotherapy volume is not suitable
- Offer the same treatments that might be offered to people with advanced stage (stages III and IV) symptomatic follicular lymphoma to people with stage I- II nodal MZL who are symptomatic and for whom radiotherapy is not suitable (see suitable induction regimens above)

General considerations

- Offer the same treatments that might be offered to people with advanced stage (stages III and IV) symptomatic follicular lymphoma to people with advanced stage III- IV nodal MZL who are symptomatic (see suitable induction regimens above)

International consensus

- Patients with nodal MZL are usually managed as per follicular lymphoma(NCCN 2018/ESMO 2013 guidelines)

Evidence

- See gastric MALT lymphoma localised disease evidence section (BRIGHT study) for information on bendamustine/rituximab (BR) R-CHOP and R-CVP
- Rituxumab/Chlorambucil has been a reasonable treatment option for the elderly
- Single agent Rituximab can be considered in low tumour burden patients or in elderly patients

Treatment of relapsed/refractory Splenic MZL

- Suggested regimens
  - R-CVP (Appendix C reg 19)
  - R-Bendamsutine (Appendix C reg 34)
  - Rituximab Monotherapy (Appendix C reg 21)

General considerations

- Consider 'watch and wait' (observation without therapy) for people who are asymptomatic
- People who are symptomatic or have threaten end organ function, or bulky disease should be treated as per first line SMZL treatment (see suggested regimens above - under treatment of relapse Splenic MZL)
- If more than 1 year from treatment, could consider re-treating with the same agent again
Evidence
- See gastric MALT lymphoma localised disease evidence section (BRIGHT study) for information on bendamustine/rituximab (BR) R-CHOP and R-CVP
- See splenic MZL primary treatment evidence section information on rituximab monotherapy

Treatment of relapsed Nodal MZL
- Suggested induction regimens
  - R-CVP $^{113,120}$ (Appendix C reg 19)
  - R-Bendamustine $^{237}$ (Appendix C reg 34)
  - Rituximab Monotherapy $^{122}$ (Appendix C reg 21)

General considerations
- If more than 1 year from treatment, could consider re-treating with the same agent again

International consensus
- Patients with nodal MZL are usually managed as per follicular lymphoma (NCCN 2018/ESMO 2013 guidelines)

General considerations
- Consider 'watch and wait' (observation without therapy) for people who are asymptomatic
- People who are symptomatic or have threaten end organ function, or bulky disease should be treated as per first line NMZL treatment (see suggested regimens above - under treatment of relapse Nodal MZL)

Evidence
- See gastric MALT lymphoma localised disease evidence section (BRIGHT study) for information on bendamustine/rituximab (BR) R-CHOP and R-CVP
- See splenic MZL primary treatment evidence section information on rituximab monotherapy

Management of patients with transformed splenic/nodal MZL
- Treat as for DLBCL – see under treatment of advanced DLBCL

16.2.5 CNS involvement
- Primary or secondary central nervous system (CNS) involvement by marginal zone B-cell lymphoma (MZBCL) is rare
Primary or secondary CNS involvement by MZBCL displays indolent clinical behaviour and generally has a favourable prognosis, underlining the importance of their differentiation from aggressive lymphomas that more commonly involve the CNS.

Systemic chemotherapy or whole brain radiotherapy have been reported as treatment for CNS marginal zone lymphoma.\textsuperscript{199}
17. PERIPHERAL T-CELL LYMPHOMA (PTCL)

17.1 Introduction

- The BCSH published revised guidelines on the diagnosis, investigation and management of T-cell lymphoma in August 2013
- PTCLs are uncommon and heterogeneous malignant lymphoproliferative disorders that originate from post-thymic (peripheral) T cells or mature natural killer (NK) cells. They represent 10%–15% of all non-Hodgkin’s lymphomas
- The World Health Organisation (WHO) classification of haemopoietic malignancies has divided this group of disorders into those with predominantly leukaemic (see leukaemia CMG), nodal, extra-nodal or cutaneous presentation (see skin lymphoma Section within this CMG). The nodal and extra-nodal entities will be the primary focus of this section
- Primary nodal PTCLs include PTCL-not otherwise specified (PTCL-NOS), anaplastic large-cell lymphoma (ALCL), both fusion protein ALCL anaplastic lymphoma kinase positive (ALCL ALK+) and ALCL anaplastic lymphoma kinase negative (ALCL ALK−), and angioimmunoblastic T-cell lymphoma (AITL)
- The primary extranodal PTCL subtypes include enteropathy-associated T-cell lymphoma (EATL), hepatosplenic T-cell lymphoma (HSTCL) and extranodal natural killer/T-cell lymphoma (ENKTCL)
- Para-neoplastic features are well described including eosinophilia, haemophagocytic syndrome and auto-immune phenomena

17.2 Prognosis

- The IPI gives useful prognostic information in PTCL and should be calculated, but it clusters many cases in the higher risk groups
- Newer T-cell specific prognostic scores appear to be more discriminatory and may be valuable in prospective trials
- The epidemiology and outcomes for PTCL from the international T-cell lymphoma project is outlined in the table below

<table>
<thead>
<tr>
<th>Type of PTCL</th>
<th>% of all TCL</th>
<th>5 year FFS (%)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCL-NOS</td>
<td>25.9</td>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td>AIL</td>
<td>18.5</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>NK-Tcell</td>
<td>10.4</td>
<td>Nasal 29</td>
<td>Nasal 42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extra-nasal 6</td>
<td>Extra-nasal 9</td>
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<tr>
<td>ALCL, ALK +ve</td>
<td>6.6</td>
<td>60</td>
<td>70</td>
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<tr>
<td>ALCL, ALK –ve</td>
<td>5.5</td>
<td>36</td>
<td>49</td>
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<td>EATL</td>
<td>4.7</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>PC ALCL</td>
<td>1.7</td>
<td>55</td>
<td>90</td>
</tr>
<tr>
<td>Hepatosplenic</td>
<td>1.4</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>
17.3 Nodal Peripheral T-cell lymphoma

17.3.1 Treatment of Nodal PTCL (PTCL-NOS, AITL, ALCL)

- **Suggested regimens**
  - CHOP\textsuperscript{208} (Appendix C reg 39)

- **Alternative regimens**
  - CHOP\textsuperscript{209} (Appendix C reg 17)

- **Suggested salvage regimens**
  - ICE\textsuperscript{18} (Appendix C reg 7)
  - ESHAP\textsuperscript{21} (Appendix C reg 8)
  - GDP\textsuperscript{19} (Appendix C reg 6)
  - Brentuximab\textsuperscript{210} NICE TA 478 (Appendix C reg 9) (ALCL only)

**Evidence**

- In a randomized study by the German High-grade NHL Study Group (DSHNHL), the addition of etoposide to CHOP (CHOEP) resulted in significantly higher complete response (CR) rate (88% vs. 79% for CHOP); and 5-year EFS rate (69% vs. 58% for CHOP); with no difference in OS outcomes between the regimens. It should also be noted that in this study, the majority of patients had aggressive B-cell NHL and were relatively young with favourable prognosis (age ≤60 years; normal LDH levels), with only 14% diagnosed with T-cell NHL (ALCL, 9%; PTCL-NOS, 3%; and AITL, <1%)\textsuperscript{208}

- In a retrospective study conducted by the British Columbia Cancer Agency, the 5-year OS rate for patients with PTCL-NOS primarily treated with CHOP or CHOP-like regimens was only 35%; among these patients, the 5-year OS rates were higher in patients with low-risk IPI scores compared with those with high-risk IPI scores (64% vs. 22%, respectively). In addition, patients with ALCL, ALK-positive had superior clinical outcome compared to those with ALCL, ALK-negative (5-year OS, 58% vs. 34%, respectively)\textsuperscript{209}

- See evidence section of relapsed DLBCL for information on salvage regimens (ICE, ESHAP and GDP)

- In Northern Ireland, brentuximab is accepted as an option for treating relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) in adults (see NICE TA 478)

- A phase 2 study evaluated the safety and efficacy of brentuximab vedotin in patients with relapsed or refractory (R/R) systemic anaplastic large cell lymphoma (ALCL) After a median observation period of approximately 6 years from first treatment, we examined the durability of remission, progression-free survival (PFS), overall survival (OS), and safety outcomes of patients treated on this trial\textsuperscript{210}

- Among all enrolled patients (n = 58), no progressions were observed beyond 40 months, and median OS was not reached. Patients with a complete response (CR), as assessed by the investigator (38 of 58, 66%), continued to demonstrate improved
outcomes with neither median OS nor PFS reached. Of the 38 CR patients, 16 received a consolidative stem cell transplant (SCT) with median PFS not reached.  

17.3.2 Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS)  

General considerations  
- This is the largest group of T-cell lymphoma, accounting for approximately half of all cases. PTCL-NOS is not a single biological entity  
- They are usually aggressive lymphomas, mainly of nodal type but extranodal involvement is common  
- Most cases have a CD4+/CD8- phenotype  
- Array CGH shows loss of 9p, 5q or 12q in 30% of cases  
- From the International T-cell lymphoma project, 5 year failure free survival (FFS) was 20% and overall survival (OS) was 30%  

Key recommendations (derived from BCSH guidelines 2013)  
- Primary treatment of PTCL-NOS should be within a clinical trial if possible as standard therapy gives disappointing results  
- Consideration should be given to consolidation with ASCT  
- Relapsed or refractory disease should be treated with relapse-schedule combination chemotherapy and considered for Allo-SCT with RIC or ASCT or novel therapies within a trial setting  
- Outside a trial, a number of agents show promise such as gemcitabine and bendamustine but the data are insufficient to recommend routine use  
- CNS prophylaxis should be considered using the same criteria as DLBCL  

17.3.3 Angio-immunoblastic T cell lymphoma (AITL)  

General considerations  
- AITL constitutes between 13-24% of peripheral T-cell lymphomas  
- AITL is difficult to diagnose and treat because of the presence of both B- and T-cell clones  
- It has a variable clinical course with auto-immune features  
- It typically presents with systemic illness, B symptoms, generalized lymphadenopathy, often mimicking an infectious process. The majority of patients have hepatosplenomegaly and pruritis. A skin rash is present in about 50%. Polyarthritis and ascites/effusions (23-37%) are frequent  
- Laboratory investigations show anaemia (40-57%), eosinophilia (39%), occasionally pancytopenia  
- Typically there is polyclonal hypergammaglobulinaemia (50-83%), elevated ESR and LDH
Circulating auto-antibodies are present in 66-77%: positive DAT, cold agglutinins, cryoglobulins and circulating immune complexes
Bone marrow involvement is observed in 61%
Clonal T-cells are usually present in the peripheral blood

**Key recommendations (derived from BCSH guidelines 2013)**
- The timing and selection of therapy depend on clinical presentation and prognostic factors
- Patients requiring therapy should be entered into available clinical trials where possible
- Consolidation with auto-HSCT should be considered for patients with chemosensitive disease in first remission or after relapse
- Routine CNS prophylaxis is not warranted
- For AITL in elderly patients, a trial of single agent corticosteroid may be appropriate therapy
- Other treatment options include ciclosporin, Methotrexate and Prednisolone, Thalidomide (off label indication and subject to funding approval)

### 17.3.4 Anaplastic T-cell (large cell) lymphoma (ACLC)

**General considerations**
- The latest WHO classification recognizes three distinct subtypes of ALCL: primary systemic anaplastic lymphoma kinase (ALK) positive, primary systemic ALK negative (provisional) and primary cutaneous types
- 60% of ALCL are ALK positive and have a significantly superior prognosis to ALK negative ALCL
- The IPI is useful in further risk stratification. Patients with ALK expression tumours have a 70% 5 year overall survival, whilst in those which are ALK negative is 50%

**Key recommendations (derived from BCSH guidelines 2013)**
- Patients with limited stage ALCL ALK + and no adverse prognostic features by IPI should be treated with 3-4 cycles of CHOEP chemotherapy and involved field radiotherapy
- All other ALCL ALK+ patients including those with bulky disease should receive CHOEP x 6cycles
- ALK-neg ALCL should be treated as per nodal PTCL
- Primary cutaneous ALCL (ALK-neg) should be managed by local excision +/- radiotherapy. Chemotherapy should be reserved for those patients with systemic disease
- At relapse, patients should receive platinum based chemotherapy or an alternative salvage regimen. Patients with chemo sensitive disease should be considered for transplant
17.4 Extranodal Peripheral T-cell lymphoma (EATL, HSTCL, ENKTCL)

17.4.1 Enteropathy type T-cell lymphoma (EATL)

**Treatment**
- **Suggested regimens**
  - IVE/MTX\(^{212}\) (Appendix C reg 30)
  - CHOEP\(^{208}\) (Appendix C reg 39)
  - CHOP\(^{209}\) (Appendix C reg 17)

**Evidence**
- The Scottish and Newcastle Lymphoma Group (SNLG) in the UK have piloted an intensive approach involving salvage type chemotherapy: CHOP for one cycle followed by IVE (ifosfamide, etoposide, epirubicin) for three cycles alternating with intermediate-dose methotrexate and up-front autologous transplantation. Compared to historical controls treated with CHOP-like chemotherapy alone, there was a better CR rate (72% vs. 42%), 5-year PFS (56% vs. 20%) and 5-year OS (67% vs. 22%) for those treated with the intensive regimen\(^{212}\)
- See treatment of nodal PTCL evidence section for information on CHOEP and CHOP

**General considerations**
- This is an aggressive large tumour of the small bowel which is strongly associated with HLA DQ2 or 8 (95%) and coeliac disease
- In 10-20% of cases the histology is monomorphic (type II ETAL) and may occur sporadically, without risk factors for coeliac
- The outcome is poor, with a 5 year overall survival of 20% partly due to the aggressiveness of the disease and partly because of the poor performance status of patients in the setting of malabsorption and malnutrition\(^{207}\)
- Patients should be treated within a clinical trial where possible.
- In early stage disease local/regional radiotherapy should be considered after full course chemotherapy

**Key recommendations (derived from BCSH guidelines 2013)\(^{211}\)**
- It is important to liaise with an experienced gastroenterologist to assist with biopsy, staging, follow-up and nutritional problems.
- Assigning a conventional IPI score is of limited value as there is no good prognostic group and most cases are stage I-IIIE
- Adoption of an intensive approach such as the NCRI/SNLG protocol is a reasonable option in fitter patients
- CHOP-like therapy, with or without an up-front autograft remains a common approach outside a trial
Nutrition is a major issue in managing these patients and dietetic/gastroenterology advice is essential at all stages of treatment and follow-up.

### 17.4.2 Hepatosplenic T-cell lymphoma (HSTCL)

**Treatment**
- **Suggested regimens**
  - (See treatment of nodal PTCL)

**General considerations**
- This is a rare entity, mainly affecting adolescent or young adult males. The median age at diagnosis is 34 years.
- Most cases show a characteristic phenotype, expression of γδT-cell receptor and have an isochromosome 7q abnormality.
- A variant expressing the αβ T-cell receptor is well described.
- This is a systemic, extra-nodal disease involving the liver, spleen and bone marrow. The marrow involvement causes cytopenias, thrombocytopenia being the most common. Lymphadenopathy is a rare finding.
- The prognosis is very poor.

**Key recommendations** *(derived from BCSH guidelines 2013)*
- No satisfactory treatment recommendations can be made from the limited evidence base.
- Trial or experimental therapy should be considered if available.
- Allo-SCT could be considered but the evidence is purely anecdotal.
- Conventional chemotherapy approaches as per nodal PTCL are the default and there are some survivors reported in the literature.

### 17.4.3 Extranodal NK/T Cell Lymphoma, nasal type (ENKTCL)

**Treatment**
- **Suggested regimens**
  - 2/3 De-VIC\(^{213}\) (Appendix C reg 27)
  - De-VIC\(^{213}\) (Appendix C reg 28)
  - SMILE\(^{214}\) (Appendix C reg 11)

**General considerations**
- The condition almost invariably presents in extranodal sites, classically in the nasal structures but nodal disease is occasionally seen and secondary nodal spread is not uncommon.
- Three clinical patterns are recognised: disease involving the nose, naso-pharynx and upper aero-digestive tract; disease involving another extra-nodal site, commonly skin, gut or testes and a disseminated form with widespread tissue spread.
infiltration and BM involvement with occasional leukaemic phase causing overlap with aggressive NK-cell leukaemia

- Blood and marrow tend not to be involved in the more localised extra-nodal disease forms
- The distinction at diagnosis between localised disease and disseminated disease is important as this tumour is radiosensitive and localised disease is thus potentially curable with radiotherapy (5-year OS of 40-75%)
- In addition the relative insensitivity to chemotherapy means that disseminated disease has a dismal prognosis and consideration of experimental therapy may be considered as first line. Patients with localised disease should receive radiation with 50-55Gy early in the treatment course
- 2/3 De-VIC concurrent with radiotherapy is used in localised disease
- SMILE is used in disseminated disease
- Full dose De-VIC is used in patients with disseminated disease who are unsuitable for SMILE
- Consolidation with auto/all-SCT may be considered
- Haemophagocytic Lymphohistiocytosis (HLH) is a recognised complication and mode of presentation of T cell and NK-cell tumours

**Diagnosis:**

- The immunophenotype of extranodal NK/T cell lymphoma, nasal type, is similar to that of a natural killer cell. The atypical cells in most cases express CD2, CD56, and cytoplasmic CD3, but do not express surface CD3. Most cases express cytotoxic granule proteins such as granzyme B, TIA-1, and perforin, and lack surface T cell receptor (TCR). Uncommon cases may express CD4, CD8, and/or CD7. Over 90 percent of cases are of true natural killer (NK) cell origin. The key diagnostic features are the demonstration of NK/T cell markers and Epstein-Barr virus (EBV). Although CD56 is typically expressed, tumours that do not express CD56 may still be classified as extranodal NK/T cell lymphomas if both cytotoxic molecules and EBV are positive
- A prognostic model which includes 4 risk factors: B symptoms, advanced stage, elevated LDH and involvement of regional lymph nodes. The 5-year OS according to number of risk factors was 81% for 0, 64% for 1, 34% for 2 and 7% for those with 3 or 4
- Other unfavourable prognostic factors include bone or skin involvement, expression of p19 Ki67> 50%, elevated C reactive protein (CRP), anaemia, thrombocytopenia (Au et al, 2009) and high serum EBV DNA levels and EBV+ cells in the BM
- EBV quantification is helpful for assessing the tumour load and prognosis at diagnosis and also for monitoring response and relapse. A high Ki 67 may have prognostic significance in localized disease
Evidence

- A phase I/II JCO study examined if concurrent chemoradiotherapy was effective treatment for localized nasal natural killer (NK)/T-cell lymphoma, we conducted a phase I/II study. Treatments comprised concurrent radiotherapy and 3 courses of 2/3 dose DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) \(^{213}\)

- The 2-year overall survival was 78%. This compared favorably with the historical control of radiotherapy alone (45%). Of the 26 patients assessable for a response, 20 (77%) achieved a complete response, with one partial response. The overall response rate was 81%. The most common grade 3 nonhematologic toxicity was mucositis related to radiation (30%). No treatment-related deaths were observed. \(^{213}\)

- Asparaginase-containing regimens (ie. SMILE regimen that incorporates dexamethasone, methotrexate, ifosphamide, asparaginase and etoposide) should be considered in disseminated disease and relapsed or refractory disease. A phase II study of (SMILE) in 38 patients, including 20 patients (53 percent) with newly-diagnosed stage IV disease, reported an overall response rate of 79% (45% complete). \(^{214}\)

- All patients there were significant (grade 3/4) neutropenia and most common nonhematologic severe toxicity was infection at 61%. At a median follow-up of 24 months, progression-free and overall survival rates at one year were 53 and 55 percent, respectively. Further analysis, presented in abstract form with a median follow-up of 74 months, reported progression-free and overall survival rates at five years of 47 and 39%. \(^{214}\)
18. SKIN LYMPHOMAS

18.1 Introduction


It is meant to form an outline of management but not to be didactic as very often therapy is individualised to specific patients.

Consideration should be made for referral and consultation with national skin units such as the Skin tumour Unit, St John’s Institute of Dermatology Guy’s and St Thomas’ Hospitals.

This reflects the rarity of these conditions and the complexity and issues that may arise in managing these conditions. This may include diagnostic problems, CTCL stage 1B and above particularly involving decisions about treatment or opportunity to participate in a clinical trial or discussion of management of rare CTCL variants.

Cutaneous lymphomas are a group of disorders characterised by the localisation of malignant lymphocytes to the skin. Approximately two thirds are of T-cell origin. The most common form of cutaneous T-cell lymphoma (CTCL) is mycosis fungoides (MF) and accounts for about 60% of cases of CTCL. Sézary syndrome (SS) accounts for about 5% of cases.

Primary cutaneous B-cell lymphomas (PCBCL) make up about 20-25% of cutaneous lymphomas in which there is no evidence of extracutaneous disease at presentation. They make up a heterogeneous group and can be classified into different subsets based on histopathological findings and clinical course. The other 10% are made up of either very rare or currently unidentified subsets.

18.2 Cutaneous T-Cell Lymphoma

Mycosis fungoides (MF) and Sézary syndrome (SS)

MF is characterised by distinct clinical stages consisting of patches/plaques, tumours and erythroderma. SS is a distinct variant which is defined by the presence of erythroderma, peripheral lymphadenopathy and a minimum number of Sézary cells within the peripheral blood.

Diagnosis

- Diagnosis is based on thorough assessment of both clinical and pathological features. Repeated biopsies may be required to establish the diagnosis and correlation
between clinical features and histology is essential. This should be performed at an MDT in which dermatologists, dermatopathologists, haematopathologists, haemat-oncologists and clinical oncologists should be represented.

Staging

- Two staging systems are currently in use. The tumour/node/metastasis (TNM) system and a clinical staging system specifically designed for CTCL (Bunn and Lambert). Staging investigations should include CT scan of chest, abdomen and pelvis, assessment of peripheral blood for Sezary cells and lymphocyte subsets, with the exception of those with early stage MF (Stage 1A/1B). Bone marrow biopsies are not required unless there is an unexplained haematological abnormality.

Prognosis

- Most cases of MF and SS are not curable. Independent prognostic features include the cutaneous and lymph node stage of disease and the age of onset (>60 years). Lymph node status and tumour burden within peripheral blood determine prognosis in SS. Thickness of the infiltrate in plaque stage MF, serum lactate dehydrogenase and folliculotropic variants of MF may have a worse prognosis.

Survival rates

- The 5- and 10-year overall survival (OS) rates in MF are 80% and 57% respectively. The disease specific survival (dss) rates are 89% and 75% respectively.

<table>
<thead>
<tr>
<th>Stage</th>
<th>OS</th>
<th>dss</th>
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<tbody>
<tr>
<td>IA</td>
<td>96-100%</td>
<td>100% at 5 years</td>
</tr>
<tr>
<td>IB</td>
<td>73-86%</td>
<td>81-96% at 5 years</td>
</tr>
<tr>
<td>IIB</td>
<td>OS; 40-65%</td>
<td>50-80% at 5 years</td>
</tr>
<tr>
<td>III</td>
<td>erythroderma but no evidence of lymph node or blood involvement – survival rates similar to stage 2B disease</td>
<td></td>
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<tr>
<td>IV</td>
<td>dss20% at 5 years</td>
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</tbody>
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- Patients with SS have an 11% 5 year survival with a median survival of 32 months from diagnosis.

Treatment of CTCL

Suggested regimens

- Systemic biological therapies
  - Interferon alpha
  - Bexarotene
  - Denileukin Diftitox
  - Vorinostat

- Patients with SS have an 11% 5 year survival with a median survival of 32 months from diagnosis.
Antibody therapies
- Alemtuzumab\textsuperscript{243,244,245}

Chemotherapy
- Chlorambucil\textsuperscript{62}
- Low dose methotrexate\textsuperscript{63}
- Gemcitabine single agent\textsuperscript{64}
- Deoxycofomycin (pentostatin)\textsuperscript{65}
- Pegylated Liposomal Doxorubicin\textsuperscript{66}
- Oral etoposide\textsuperscript{67}
- Lenaldomide\textsuperscript{36}
- Bortezomib\textsuperscript{37}
- Brentuximab\textsuperscript{38}

Aims of therapy
- Long term disease control- this would be the main goal of therapy as very often patients with MF experience a relative short duration of disease free control after completion of therapy. Therefore agents that are associated with low toxicity, and preservation of the immune system would be preferred allowing for longer term “maintenance” of disease and symptom control
- Prompt symptom relief- this relates to patients who require quicker disease responses where quality of life has become an issue – balance has to be made between potential benefits of radiotherapy based therapy versus cytotoxic treatment – which may be associated with a relative short duration of response and lead to immunosuppression and attendant risks of infections
- Addressing aggressive disease- patients with relapsing, refractory disease are less likely to benefit from standard regimens and may require consideration of intensification of therapy such as systemic combinational chemotherapies and stem cell transplant in eligible patients
- Addressing life threatening (aggressive disease)

Skin directed therapy

Topical therapy
- For patients with early stage MF (1A/1B) emollients +/- topical steroids are often the first line treatments. Potent topical steroids can produce a clinical response although this is usually short-lived. Other treatment options include topical nitrogen mustard and topical carmustine though these latter two treatments are much less commonly used
Phototherapy

- Phototherapy is the standard of care for patients with early stages of MF. There is a high rate of complete remission and it can produce a reasonable duration of response. It is not known whether phototherapy affects time to progression and disease specific survival in those patients with early stage disease at risk of disease progression.

UVB phototherapy

- Both narrowband UVB (TL-01; 311-313nm) and broadband UVB (290-320nm) phototherapy can produce high rates of complete remission with prolonged response duration, most frequently in patients with patch/thin plaque disease.

PUVA photo-chemotherapy

- Very high rates of complete remission have been established for PUVA in early stages of MF. Duration of response can be prolonged but does vary. Patients with erythrodermic MF can respond to PUVA but pruritus can be aggravated and it is often not tolerated. PUVA can be used as salvage therapy after other treatment for high grade disease.

Combination PUVA regimens

- In patients who have shown only a partial response to PUVA or in order to reduce overall cumulative UVA dose, addition of a systemic agent may be considered.

Radiotherapy

- MF is highly radiosensitive and localised radiotherapy (superficial orthovoltage or electrons) is used in both early and late stage disease. Over 90% of plaques and tumours resolve following superficial radiotherapy. In-field recurrences may occur for lesions treated with lower doses but use of low doses (8-12 gy in 2-3 daily fractions) allows treatment of overlapping fields and repeated treatment of difficult sites.

- Localised radiotherapy can also be used for isolated tumours that develop on a background of erythroderma. Superficial radiotherapy can be used for localised tumours and high doses can be used for localised peripheral nodal disease.

Total skin electron beam therapy (TSEB)

- Eortc consensus guidelines for the use of TSEB in CTCL have been published (Jones et al, 2002). TSEB is highly effective but as there are other therapies with similar efficacy in early stages of disease, it is usually reserved for later stages of disease. It may be used in patients with progressive disease who have failed to respond to...
other therapies. TSEB may be considered as second line and sometimes first line therapy for patients with erythrodermic MF without peripheral blood involvement

**Systemic biologic therapies**

**Alpha interferon**

- Interferon α may be considered in patients who are failing to respond adequately to skin directed therapy or who have progressive disease. Responses are seen in early stage disease. Higher doses produce better responses but are associated with significant side effects including flu-like symptoms, lethargy and lymphopaenia/neutropenia, in many patients limiting dose escalation.
- Additional side effects may include tranaminitis, hypothyroidism, and hair thinning. Overall response rates from 53 - 74% (21 to 35% complete) can be achieved depending on stage of therapy lines it is introduced.

**Retinoids**

- Bexarotene has shown significant efficacy and good duration of response with low rates of disease progression. Bexarotene is a synthetic retinoid from the subclass of retinoids called rexinoids which selectively activate retinoid X receptors. It has activity in cutaneous T-cell lymphoma (CTCL) and has been approved by the European Medicines Agency since 1999 for treatment of the skin manifestations of advanced-stage (IIB –IVB) CTCL in adult patients refractory to at least one systemic treatment. Systemic (oral)retinoids result in response rates of 45-55% (10 to 20% complete) depending upon the dosing and severity of MF.
- Common side effects include significant hypertriglyceridaemia and universal central hypothyroidism which require regular monitoring, the use of Thyroxine and lipid lowering agents including a fibrate. The U.K. consensus statement on safe clinical prescribing of bexarotene for patients with cutaneous T-cell lymphoma was published this year (BJD Jan 2013).

**Denileukin Diftitox (Diphtheria IL-2 fusion toxin)**

- Denileukin Diftitox is effective in heavily pre-treated patients with late stages of disease and efficacy may be improved by combining with Bexarotene. This is not routinely available and may be available through clinical trials or discussion with national centre.

**HDAC inhibitors**

- Vorinostat is an orally active histone deacetylase (HDAC) inhibitor, with partial response rates in MF of 30%. The activity of vorinostat (starting dose 400 mg/day) was evaluated in 74 patients with stage IB or higher CTCL who had failed a median of three systemic therapies, one of which included bexarotene. Thirty percent of
subjects experienced a partial response as measured by a modified skin severity weighted assessment tool; 32% had pruritus relief;

- Toxicities of vorinostat included fatigue (49%), diarrhoea (46%), nausea (43%), anorexia (26%). Hematologic abnormalities included anemia, thrombocytopenia (22%), and neutropenia, most of which were grade 1 or 2 in severity. The most common severe adverse event was pulmonary embolus, seen in four patients (5%). Access to Vorinostat is currently through clinical trials. Potential patients may be discussed with national centres re potential trials that may be open.

**Antibody therapies**

- Alemtuzumab (Campath-1H – a humanised anti-cd52 antibody) has been used in small cohorts of patients with advanced disease with encouraging response rates. Response duration may be short but it remains an important 2nd and 3rd line therapeutic option for patients with advanced disease. It has demonstrated ORRs of up to 55 percent. Alemtuzumab is only appropriate for patients with erythrodermic MF with or without blood involvement (stages III and IVA). Patients with bulky lymph nodes are unlikely to respond.

- Serious infections (CMV, generalized herpes simplex, fatal aspergillosis and mycobacterium pneumonia) can be seen, especially in heavily pretreated patients, A low-dose, intermittent administration schedule of alemtuzumab (10 mg subcutaneously, three times a week) may reduce infectious complications in patients with MF. Alemtuzumab therapy requires antibiotic and antiviral prophylaxis as well as close observation for the development of infection and potential cardiac toxicity.

**Extracorporeal photopheresis (ECP)**

- Treatment with ECP is available at the Belfast City Hospital. ECP is an effective treatment in erythrodermic CTCL with overall response rates of 35–71%. It may be used in conjunction with alpha interferon, or bexarotene to improve on the initial response.

**Chemotherapy**

- Either single agent (e.g. chlorambucil, Methotrexate, Gemcitabine) or combination chemotherapy eg CHOP for advanced disease may be considered, after discussion at the Haematology MDM. Patients with CTCL are at high risk of septicaemia and therapy-related mortality with combination chemotherapy is a significant risk, and therefore patient’s quality of life should always be considered before giving toxic chemotherapy regimens with limited efficacy.

  - Chlorambucil
  - Low dose methotrexate (25mg once weekly)
  - Gemcitabine single agent (1200 mg/m2 IV D 1, 8,15 28/7 schedule)
  - Deoxycofomycin (pentostatin) (4mg/m2 D1)
  - Pegylated Liposomal Doxorubicin (25mg/m2 IV D1 21/7 cycle)
  - Oral etoposide (50mg bd D1-7 – escalate as tolerated in 21/7 cycle)
**Additional chemotherapy agents:**

**Lenolidamide**
- In an open label, multicenter phase II trial of lenalidomide in 32 patients with refractory mycosis fungoides or SS (11 patients) and a median of six prior treatment regimens, the overall response rate was 28% (all partial) with a median duration of response of 10 months.\(^\text{36}\)

**Bortezomib**
- In an open label phase II trial of bortezomib in 12 patients with mycosis fungoides or peripheral T cell lymphoma, the overall response rate was 67 percent.\(^\text{37}\)

**Brentuximab vedotin**
- Brentuximab vedotin is licenced in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. In a phase II multicenter trial of objective global responses were seen in 21 of 30 evaluable patients with MF/SS with a median time to response of 6.6 weeks. There was one complete response. Approximately 60 and 30 percent of responders were free of progression at 6 and 12 months, respectively.\(^\text{38}\)

**Note:** These agents are not specifically licenced for use in MF or SS and while they have been recommended for use after consultation with national dermatology units they would be subject to a funding request.

**Autologous/allogeneic peripheral blood/bone marrow stem cell transplant**

**Autologous stem cell transplant:**
- Autologous stem cell transplant has been performed in small numbers of patients and appears to be associated with only short term remission in the majority of patients.

**Allogeneic hematopoietic cell transplantation (HCT)**
- Allogeneic hematopoietic cell transplantation (HCT) following myeloablative or reduced intensity conditioning may result in durable remissions or disease control in a subset of patients. Eligibility of such patients would require discussion at the MDT and in conjunction with a national centre.

Two studies have reported 17-20% non relapse mortality with 40% acute GVHD. With estimated PFS at 1 and 3 years 42% and 34% respectively. Some early relapses were treated with DLI with some patients achieving an additional CR or PR – indicating a graft versus lymphoma effect.\(^\text{39,61}\). Allogeneic transplant appears to be most effective after initial disease control and before disease progression so patients demonstrating an aggressive clinical course and are potentially eligible for consideration for transplant should be discussed with a national skin unit to determine the optimal timing and treatment modality.
18.3 Cutaneous B cell Lymphoma

Primary cutaneous anaplastic large cell lymphoma (PCALCL)
Pcalcl usually presents as solitary, clustered or scattered subcutaneous nodules, some of which may ulcerate. Extra-cutaneous disease is seen in about 10% of cases and mainly involves regional lymph nodes. It has an indolent course and lesions can occasionally spontaneously remit. Lesions may be seen with lesions of lymphomatoid papulosis which invariably show spontaneous remission, and the two entities are thought to be part of a spectrum of disease. The 10-year survival is 95% however multifocal lesions, particularly those appearing on the leg, are thought to have a worse prognosis. Treatment is usually excision of lesions or radiotherapy. In purely cutaneous disease chemotherapy should be avoided.

Primary cutaneous b-cell lymphoma (PCBCL)
Pcbcl represents about 20-25% of cutaneous lymphomas

There are 3 main types:

- Primary cutaneous marginal zone lymphoma (pcmzl)
- Primary cutaneous follicle centre cell lymphoma (pcfcl)
- Primary cutaneous diffuse large b-cell lymphoma, leg type (pcbcl –l)

Pcmzl and pcfcl are indolent types of lymphoma which should not be treated primarily with systemic chemotherapy

Clinical features

- Pcmzl usually consists of solitary or multiple papules, plaques or nodules without surface scale and are preferentially located on the extremities. There is sometimes an association with Borrelia Burgdorfori infection. Cutaneous relapses are frequent but extracutaneous spread is rare
- Pcfcl usually presents with solitary or grouped tumours on the head or trunk. Cutaneous relapses occur in 20% and extracutaneous dissemination is seen in 5 – 10%
- Pcbcl-l usually presents on the legs and rarely at other sites. There are either solitary or multiple tumours with frequent relapses and extracutaneous dissemination

Prognosis

- Pcmzl: 5-year survival > 95%
- Pcfcl: 5-year survival 95%
- Pcbcl-l: 5-year survival 50%

Diagnosis and staging of primary cutaneous B cell lymphoma
When a cutaneous B-cell lymphoma is clinically suspected, adequate histopathological and immunohistochemical studies are required to confirm the diagnosis and all cases should be reviewed by an experienced dermatopathologist and/or haematopathologist within the London Cancer Network.

Staging should include a thorough clinical examination, full blood count, blood biochemistry, lactate dehydrogenase, Borrelia serology and serum electrophoresis. A CT scan of thorax, abdomen and pelvis (include neck if lesions on the head and neck), and a bone marrow biopsy should be performed to rule out systemic lymphoma.

**Treatment:**

Suggested regimens
- Rituximab (Appendix C reg 21)
- Chlorambucil (Appendix C reg 57)
- CHOP (Appendix C reg 17)
- R-CHOP (Appendix C reg 17)
- Interferon alpha

**Primary cutaneous marginal zone lymphoma**

**Excision**
- In patients presenting with one or a few small lesions surgical excision is the treatment of choice. There is no information as to excision margins, recurrence site or extra-cutaneous dissemination.

**Radiotherapy**
- Pcmzl is a very radiosensitive tumour and is the treatment of choice for solitary or scattered lesions that are not small enough to excise.

**Rituximab**
- Both systemic and intralesional rituximab have been used to treat pcmzl.

**Single agent and combination chemotherapy**
- Multifocal disease can be treated with single agent Chlorambucil or multiagent chemotherapy, mostly with CHOP.

**Antibiotics**
- Pcmzl associated with Borrelia burgdorfori infection should be treated with antibiotics before more aggressive therapies are used. The efficacy of antibiotic treatment in Borrelia burgdorfori-associated pcmzl is poorly documented. It is suggested that systemic treatment with cephalosporins is superior to high-dose tetracyclines.

In patients with disseminated skin lesions it is acceptable to adopt a wait and see policy. These patients require careful follow-up and only symptomatic lesions should be
treated. Treatment of skin lesions does not alter the prognosis and cutaneous relapse following treatment does not signify a worse prognosis.

**Primary cutaneous follicle centre cell lymphoma (pcfcl)**

**Radiotherapy**
- Local radiotherapy is the treatment of choice being very effective with few side effects. In patients with solitary or localised skin lesions, radiation therapy with a radiation dose of at least 30gy and a margin of clinically uninvolved skin of 1-1.5cm is the preferred mode of treatment

**Excision**
Complete excision can be performed for appropriate lesions. Solitary, small, well-demarcated lesions can be excised surgically

**Intralesional interferon α**
There are reports of successful management of pcfcl with intralesional interferon α

**Rituximab**
Intralesional and systemic Rituximab have been used in pcfcl with success. In patients with very extensive skin lesions, systemic Rituximab should be the treatment of choice

**Multiagent chemotherapy**
There is relatively little data available on the treatment of pcfcl patients with multiagent chemotherapy. Most patients were treated with CHOP. Relapses occur in 30%, mostly confined to the skin and do not signify a worse prognosis

**Primary cutaneous diffuse large b-cell lymphoma, leg type**

**Multiagent chemotherapy**
- R-CHOP should be the first line of treatment for pclbcl-I however many of the patients are very elderly and such an aggressive treatment may not be appropriate. These patients should be treated with local radiotherapy to all visible skin lesions. Rituximab as a single agent could also be considered.
19. HAIRY CELL LEUKAEMIA

19.1 Introduction

- The BCSH have published revised guidelines in 2012 on the management of Hairy cell leukaemia last published in 2000. The major changes in recommendations were
  - Partial response to purine analogues is now regarded as a poor prognostic factor. Bone marrow assessment after count recovery (typically 4–6 months after cladribine therapy or following 8–9 courses of pentostatin) is recommended.
  - A second course of purine analogue therapy is recommended if patients do not enter complete remission at this time-point. The addition of rituximab may be considered.
  - Rituximab in combination with a purine analogue is recommended in the treatment of relapsed disease.
- The prevalence of HCL has been estimated at 2% of all forms of leukaemia and, of patients affected by lymphoproliferative diseases that comprise mature B or T cells, HCL accounts for 8% of cases.

19.2 Diagnosis

Key recommendations (derived from BCSH guidelines 2012)

- Blood film and bone marrow examination are essential for the diagnosis of HCL.
- Flow cytometric evaluation should be undertaken when liquid material is available. CD11c, CD25, CD103 and CD123 are advised if HCL is suspected.
- Immunohistochemistry on the marrow trephine specimens should include CD20 and DBA 44.
- CD20 is the most useful immunohistochemical stain to use when assessing remission status post-treatment.

Additional recommendations

- Screening for the presence of BRAF V600E mutation may be considered.
- Abdominal imaging and CT scan may be required to assess splenomegaly and lymphadenopathy.

19.3 Treatment

19.3.1 Indications to treat

Key recommendations (derived from BCSH guidelines 2012)

- Occasional patients who are asymptomatic may not require immediate therapy on diagnosis; active monitoring is appropriate.
- Patients with symptomatic cytopenia or painful splenomegaly require therapy.
19.3.2 Primary treatment

Role of purine analogue in achieving Complete Remission

- Suggested regimens
  - Cladarbine\textsuperscript{254} (Appendix C reg 12)
  - Pentostatin\textsuperscript{256} (Appendix C reg 4)

Key recommendations (derived from BCSH guidelines 2012)\textsuperscript{246}

- Purine analogues are the most appropriate agents for first-line therapy. No difference in efficacy between these two agents has been demonstrated
- Subcutaneous cladribine administration is likely to be the most cost-effective option.
- Patients who have received cladribine or pentostatin who require transfusion should be transfused only with irradiated blood products for the rest of their lives in order to minimize the risk of transfusion-associated graft-versus-host disease
- Patients who have received cladribine or pentostatin should receive aciclovir and co-trimoxazole prophylaxis for herpes reactivation and pneumocystis infection, respectively, until the lymphocyte count is \( \geq 1 \times 10^9/l \)
- Patients who have received cladribine or pentostatin and have required treatment for herpes infections or pneumocystis should continue aciclovir or co-trimoxazole prophylaxis respectively until the CD4 count is \( \geq 0.2 \times 10^9/l \)

Evidence

- Both agents induce CR in a high proportion of patients (>80%), which are prolonged in the majority of cases; median duration of DFS is in excess of 10 years in most studies\textsuperscript{254,247,248}
- Pentostatin and cladribine have not been tested against each other in large randomized trials. Most of the available response and toxicity data derive from published series
- A long-term followup study has demonstrated no difference in outcome between the two agents. In this single-institution study, median DFS was 16 years\textsuperscript{248}

Role of rituximab in achieving Complete Remission

- Suggested regimen
  - Rituximab\textsuperscript{251,252,253} (Appendix C reg 21)
  - Rituximab/Cladarbine\textsuperscript{246} (Appendix C reg 12)
  - Rituximab/Pentostatin\textsuperscript{246} (Appendix C reg 4)

General Considerations\textsuperscript{246}
• Median relapse free survival in patients attaining a CR is significantly longer than in those attaining only a PR. For this reason, treatment with either agent should be repeated until a CR results.
• The addition of 6–8 doses of rituximab, delivered either concurrently with or after the purine analogue may help to achieve this goal in patients requiring multiple courses of pentostatin or a second course of cladribine.

Assessment of response to purine analogues

**Key recommendations (derived from BCSH guidelines 2012)**

• Response to purine analogue therapy should be assessed by bone marrow examination once the blood count has recovered, typically 4–6 months after cladribine therapy or after 8–9 courses of pentostatin.
• Residual disease should be treated using further purine analogue therapy.
• Eradication of MRD (in contrast to overtly persistent disease) should not be the aim of therapy except as part of a clinical trial.

General Considerations

• Assessment of response (PR or CR) is an important endpoint of the initial treatment. For guidance, the full blood count should have normalized (with the exception of lymphopenia, which is anticipated after treatment) before a bone marrow biopsy is performed.
• CR is defined as the absence of hairy cells from the peripheral blood and bone marrow along with resolution of organomegaly and cytopenias. In CR, immunohistochemistry reveals no clustering (‡3 cells) of CD20-positive or DBA.44-positive cells.
• PR is defined as a normalization of cytopenias along with a minimum 50% improvement in both organomegaly and bone marrow infiltration with no circulating hairy cells.

19.3.3 Treatment of relapsed HCL

• Suggested regimens:
  - Cladarbine (Appendix C reg 12)
  - Pentostatin (Appendix C reg 4)
  - Rituximab/Cladarbine (Appendix C reg 12)
  - Rituximab/Pentostatin (Appendix C reg 4)

• The majority of relapsed patients achieve second remission when re-treated with either pentostatin or cladribine. Choice of agent at relapse may depend on the duration of first remission: if short, i.e. <2 years, use the alternative agent; if longer (>2 years) retreat using the same agent.
The combination of pentostatin or cladribine with rituximab can also be used for patients who have relapsed.

### 19.3.4 Treatment of refractory HCL

- **Suggested regimen**
  - Rituximab \(^{104,255}\) (Appendix C reg 21)

- Another role for rituximab in the management of HCL is to treat patients whose disease is refractory to therapy with cladribine or pentostatin. The regimen with the best-documented outcome to date is 375 mg/m\(^2\) given weekly for 8 weeks. \(^{104,255}\)

### 19.3.5 Role of interferon alpha

- The role of interferon alpha is mostly utilized for patients who present with severe pancytopenia and for whom there is a pressing need for cell count recovery as quickly as possible. A regimen of 3 mega-units three times a week will gradually improve blood counts and facilitate the subsequent use of either nucleoside analogue.

### 19.3.6 Role of splenectomy

- Splenectomy is indicated if the spleen is very large (e.g. >10 cm below costal margin) and the BM only moderately involved.
20.0 REDUCED EJECTION FRACTION IN NHL

R-CHOP indications
R-CHOP 21 is indicated in the following:
- Treatment of advanced nodular lymphocyte predominant Hodgkin Lymphoma (NLPHL) and treatment of relapsed NLPHL
- Treatment of limited stage diffuse large B-cell lymphoma (DLBCL), advanced stage DLBCL and elderly patients with DLBCL
- Primary treatment of early stage II/advanced stage follicular lymphoma (FL) and treatment of relapsed FL
- Primary treatment of patients with mantle cell lymphoma (MCL) who are unfit for ASCT and treatment of relapsed MCL in older less fit patients.

Patients with reduced ejection fraction
If patients have reduced ejection fraction the suggested regimens below can be used instead of R-CHOP to treat each of the indications outlined above

Suggested regimens
- R-COEP (Appendix C reg 23)
- R-GCVP (Appendix C reg 24)

General Considerations
- For younger patients (<60y) with poor cardiac function substituting etoposide for doxorubicin gives R-COEP.
- For older patients (≥60y) with poor cardiac function substituting gemcitabine for doxorubicin gives R-GCVP

Evidence
- The British Columbia group reported that the outcome for 81 patients treated with R-COEP did not appear to be significantly different compared to a similar population treated with standard R-CHOP.
- A UK National Cancer Research Institute trial looked at R-GCVP. In this study Thirty-eight patients (61.3%) achieved disease response (complete response [CR], n = 18); Two-year progression-free survival for all patients was 49.8% and 2-year overall survival was 55.8%. Thirty-four patients experienced grade ≥ 3 hematologic toxicity. There were 15 cardiac events, of which three were fatal, reflecting the poor cardiac status of the study population. Neither of these protocols have been formally compared to R-CHOP.
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Appendix A: Essential Investigations

General (applicable to all)

- Informed consent, provision of verbal and written information
- Staging / Prognostic Scoring
- Assessment of performance status
- Height, weight and calculation of body surface area
- Pregnancy test in patients of child bearing potential
- Discuss preservation of fertility; document and refer to a specialist centre as appropriate.
- Assessment of Tumour Lysis Syndrome (TLS) risk
- ECG, Base line echocardiogram
- Day 1: FBP, DWCC, U&E, LFTs, calculated GFR
- LDH, β2-microglobulin
- Hepatitis B and C serology before intensive chemotherapy/ immunotherapy
- HIV serology
- Immunophenotyping
- Bone marrow aspirate and trephine with cell phenotyping by either immunohistochemistry or flow cytometry with additional aspirate samples for cytogenetics/FISH
- CT neck, chest, abdomen and pelvis
- Immunoglobulin levels and serum protein electrophoresis

Specific to disease

CHL

- EBV PCR
- ESR
- All patients should receive irradiated blood products
- Staging with contrast—enhanced computerized tomography (CT) of the neck to pelvis is required, although positron-emission tomography (PET)/CT is preferable if clinically feasible

NLPHL

- CT-PET scan has been shown to alter the proposed treatment plan in 10% of patients with NLPHL compared to CT and should therefore be considered in all cases
- Bone marrow involvement present is in approximately 1% of cases. Bone marrow examination should only be performed in presence of risk factors such as advanced stage, B symptoms or peripheral blood cell counts below normal
DLBCL/HGBL

- EBV PCR

PCNSL

**Essential investigations/staging**

- Stereotactic or surgical biopsy
- Vitrectomy specimen (if PIOL is suspected)
- CSF (if no other diagnostic material)
- Contrast enhanced MRI scan of brain and spine
- PET-CT preferred but contrast-enhanced CT of neck to pelvis acceptable
- Testicular ultrasound
- Physical examination including full neurological assessment
- Full medical and drug history (including corticosteroid use)
- Performance status
- Ophthalmological examination with fundoscopy and slit-lamp examination
- Baseline MMSE
- U&E, LFTs, calculated GFR, LDH
- HIV serology and viral hepatitis screen

**Desirable investigations/staging**

- Bone marrow aspirate and trephine
- Whole body FDG-PET
- Assessment of LVEFR if indicated
- Formal neuropsychological assessment
- CSF protein
- Cytology assessment

HGBL

- As per DLBCL

Follicular lymphoma

- Albumin, Calcium, Phosphate
- Bone marrow examination to include aspirate, trephine biopsy and immunophenotyping and immuno-histochemistry. Cytogenetic analysis of involved bone marrow should not be considered routine but may be helpful where there is diagnostic uncertainty
CLL

- IGHV mutation status
- Tests for TP53 disruption should be performed on all patients prior to each line of therapy, should include both mutation and deletion detection and ideally should also reveal subclonal TP53 mutations
- Advise GP of the following regarding vaccinations
  - Avoid all live vaccines, including Zoster
  - Annual influenza vaccine (live attenuated influenza vaccine should be avoided)
  - Pneumococcal vaccine every 5 years
- Reticulocyte count, Direct Antiglobulin Test (DAT)
- Marrow examination is not essential for the diagnosis of CLL/SLL. It is indicated in determining the cause of cytopenias pre-treatment and prolonged cytopenias post-treatment.

MCL

- Record presence or absence of B symptoms
- Uric Acid

Waldenström’s macroglobulinaemia

- Direct Antiglobulin Test (DAT)
- Cold agglutinins, Cryoglobulins
- Anti-MAG titre and nerve conduction studies (if symptomatic neuropathy)
- Bone marrow aspirate, flow cytometry, trephine biopsy (Cytogenetic analysis is not required for the routine diagnostic assessment of WM patients)
- The serum free light chain (sFLC) and Hevylite (HLC) are not essential for the routine assessment of WM patients.
- Plasma viscosity, B12 and folate, iron studies, urine protein excretion and Bence Jones protein.

Marginal zone lymphoma

Extra Nodal

- Endoscopy for those with gastric involvement
- Consider FISH for t(11;18)(q21;q21)
- Direct Antiglobulin Test (DAT)
- Cryoglobulins
- Reticulocytes

Splenic /Nodal

- Direct Antiglobulin Test (DAT)
Splenectomy is considered gold standard but a combination of bone marrow histology, clinical findings and the immunophenotype can be diagnostic in patients who do not require splenectomy for therapeutic reasons.

**PTCL**

- EBV PCR (Extra Nodal NK T-cell)
- There is no simple test for clonality and this should be established by PCR for rearrangement of T-cell receptor genes.
- The role of CT-PET is under investigation. CT-PET may be more useful at detecting residual disease at the end of treatment.
- Lumbar puncture and MRI of the brain are required if there is any clinical suspicion of CNS involvement.

**Skin Lymphoma**

- See CMG section for detail

**HCL**

- Uric acid
- Analysis for BRAF V600 mutation
- Due to risk of transfusion related graft versus host disease in patients receiving pentostatin and cladribine, **patients will require irradiated blood products**
Appendix B: Ann Arbor staging

Staging
Stage I - Involvement of only one lymph node region

Stage II - Two or more lymph node areas involved confined to one side of the diaphragm

Stage III - Involvement of lymph nodes above and below the diaphragm

Stage IV – Multi-focal involvement of an extranodal site

A = No constitutional symptoms

B = Constitutional symptoms present (≥ 10% weight loss; drenching night sweats; unexplained fever – but not pruritis)

E = Extra-nodal disease at a single site with or without adjacent adenopathy (IE or IIE; by convention IIIE is stage IV)
Appendix C: Regimens

Reg 1: ABVD

Doxorubicin 25mg/m\(^2\) IV infusion Day 1 & 15
Vinblastine 6mg/m\(^2\) (Max 10mg) IV infusion Day 1 & 15
Dacarbazine 375mg/m\(^2\) IV infusion Day 1 & 15
Bleomycin 10000 units/m\(^2\) IV infusion Day 1 & 15

Cycle frequency: 28 day cycle

Intended cycles:
Favourable early stage disease: 2 cycles
Unfavourable early stage disease: 4 cycles (If stage II and bulky disease >10cm 6-8 cycles + XRT)
Advanced disease: Up to 8 cycles (Bulky disease 6-8 cycles)

Reg 2: BEACOPP

Mesna 250mg/m\(^2\) IV infusion Day 1
Cyclophosphamide 1250mg/m\(^2\) IV infusion Day 1
Etoposide 200mg/m\(^2\) IV infusion Day 1 to 3
Procarbazine 100mg/m\(^2\) PO Day 1 to 7
Prednisolone 40mg/m\(^2\) PO Day 1 to 14
Vincristine 1.4mg/m\(^2\) (max 2mg) IV infusion Day 8
Bleomycin 10000 units/m\(^2\) IV infusion Day 8

Cycle frequency: 21 day cycle

Intended cycles:
Unfavourable early stage: up to 4 cycles (give three cycles, then PET then fourth cycle if there has been response)
Advanced disease: 6 cycles

Reg 3: VEPEMB

Vinblastine 6mg/m\(^2\) (Max 10mg) IV infusion Day 1
Cyclophosphamide 500mg/m\(^2\) IV bolus Day 1
Procarbazine 100mg/m\(^2\) PO Day 1 to 5
Prednisolone 40mg/m\(^2\) PO Day 1 to 5
Mixantrone 6mg/m\(^2\) IV infusion Day 15
Bleomycin 10000 units/m\(^2\) (max 15,000) IV infusion Day 15
Etoposide 60mg/m\(^2\) PO Day 15 to 19

Cycle frequency: 28 day cycle

Intended cycles: Up to 6 cycles
**Reg 4: Pentostatin/ R- Pentostatin**

**Pentostatin**
- Pentostatin: 4mg/m² IV infusion Day 1

**R-Pentostatin**
- Rituximab: 375mg/m² IV infusion Day 1
- Pentostatin: (As detailed above)

**Cycle frequency:** 14
**Intended cycles:** Continue until a maximum response has been achieved then give 2 further cycles or treat for a maximum of 12 months (i.e.) 24 cycles

**Reg 5: CHLVPP**

**Vinblastine** 6mg/m² (Max 10mg) IV infusion Day 1 & 8
**Chlorambucil** 6mg/m² (Max 10mg) PO Day 1 to 14
**Procarbazine** 100mg/m² PO Day 1 to 14
**Prednisolone** 40mg/m² PO Day 1 to 14

**Cycle frequency:** 28 Days
**Intended cycles:** 6 cycles

**Reg 6: GDP / R-GDP**

**GDP**
- Dexamethasone: 40mg (flat dose) PO Day 1 to 4
- Gemcitabine: 1000mg/m² IV infusion Day 1 & 8
- Cisplatin: 75mg/m² IV infusion Day 1

**R-GDP**
- Rituximab: 375mg/m² IV infusion Day 1
- GDP: (As detailed above)

**Cycle frequency:** 21 Days
**Intended cycles:** Relapsed treatment: 4-6 cycles, Salvage treatment: 3 cycles

**Reg 7: ICE / R-ICE**

**ICE**
- Etoposide: 100mg/m² IV infusion Day 1 to 3
- Carboplatin: AUC 5 (Max 80mg) IV infusion Day 1
- Mesna: 100mg/m² IV infusion Day 1
- Ifosfamide: 5000mg/m² IV infusion Day 1
- Mesna: 5000mg/m² IV infusion Day 1 (in the same bag as Ifosfamide)
- Mesna: 300mg/m² IV infusion Day 2
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**R-ICE**

Rituximab 375mg/m² IV infusion Day 1

**ICE** (As detailed above)

Cycle frequency: 21 Days
Intended cycles: Salvage therapy: 3 cycles

**Reg 8 : ESHAP / R-ESHAP**

**ESHAP**

Methylprednisolone 500mg IV infusion Day 1 to 5
Etoposide 40mg/m² IV infusion Day 1 to 4
Cisplatin 25mg/m² IV infusion Day 1 to 4
Mannitol 10% 500ml IV infusion Day 1 to 4 (Concurrent with cisplatin)
Cytarbine 2000mg/m² IV infusion Day 5

**R-ESHAP**

Rituximab 375mg/m² IV infusion Day 1

**ESHAP** (As detailed above)

Cycle frequency: 21 Days
Intended cycles: Salvage therapy: 3 cycles

**Reg 9 : Brentuximab Vedotin**

Brentuximab Vedotin 1.8mg/kg IV infusion Day 1

Cycle frequency: 21 day cycle
Intended cycles: Maximum of 16 cycles

**Reg 10 : Bendamustine Monotherapy**

Brentuximab Vedotin 1.8mg/kg IV infusion Day 1
Bendamustine 90mg/m² IV infusion Day 1,2

Cycle frequency: 21 day cycle
Intended cycles: Up to 6 cycles

**Reg 11 : SMILE**

Methotrexate 2000mg/m² IV infusion Day 1
Ifosfamide 1500mg/m² IV infusion Day 2 to 4
Mesna 300/m² IV infusion Day 2 to 4 (in the same bag as Ifosfamide)
Dexamethasone 40mg IV infusion Day 2 to 4
Etoposide 100mg/m² IV infusion Day 2 to 4
Mesna 300mg/m² IV infusion Day 2 to 4 (4 hours after Ifos)
Mesna 300mg/m² IV infusion Day 2 to 4 (8 hours after Ifos)
L-Asparaginase 600 unit/m² IV infusion Day 8,10,12,14,16,18,20
Cycle frequency: 28 Days
Intended cycles: up to 6 cycles

**Reg 12: Cladribine/ R-Cladribine**

Cladribine

<table>
<thead>
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<th>Dose</th>
<th>Route</th>
<th>Duration</th>
<th>Days</th>
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<tbody>
<tr>
<td>Cladribine</td>
<td>3.6mg/m²</td>
<td>IV infusion</td>
<td>over 24 hours</td>
<td>1 to 7</td>
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<td>Rituximab</td>
<td>375mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Cladribine</td>
<td>(As detailed above)</td>
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Cycle frequency: N/A
Intended cycles: 1

**Reg 13: BEAM – Auto**

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<th>Dose</th>
<th>Route</th>
<th>Duration</th>
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<tr>
<td>Carmustine</td>
<td>300mg/m²</td>
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<td>Day -6</td>
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<tr>
<td>Etoposide</td>
<td>200mg/m²</td>
<td>IV infusion</td>
<td>Day -5 to -2</td>
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<tr>
<td>Cytarbine</td>
<td>200mg/m²</td>
<td>IV infusion</td>
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<td>Melphalan</td>
<td>140mg/m²</td>
<td>IV infusion</td>
<td>Day -1</td>
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Cycle frequency: N/A
Intended cycles: 1 cycle

**Reg 14: BEAM - Alemtuzumab – RIC Allo**

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<th>Route</th>
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<td>Carmustine</td>
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<tr>
<td>Etoposide</td>
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<td>IV infusion</td>
<td>Day -5 to -2</td>
<td>(twice daily)</td>
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<tr>
<td>Cytarbine</td>
<td>200mg/m²</td>
<td>IV infusion</td>
<td>Day -5 to -2</td>
<td>(twice daily)</td>
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<tr>
<td>Melphalan</td>
<td>140mg/m²</td>
<td>IV infusion</td>
<td>Day -1</td>
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Cycle frequency: N/A
Intended cycles: 1 cycle

**Reg 15: Vinblastine Monotherapy**

<table>
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<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Vinblastine</td>
<td>6mg/m² (Max 10mg)</td>
<td>IV infusion</td>
<td>Day 1</td>
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Cycle frequency: 14 day cycle
Intended cycles: Until disease progression or intolerable toxicity

**Reg 16: Etoposide**

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<th>Days</th>
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<td>Etoposide</td>
<td>100 – 150mg</td>
<td>PO</td>
<td>Day 1 to 7</td>
<td>or 1 to 14</td>
</tr>
</tbody>
</table>

Cycle frequency: 28 day cycle
Intended cycles: Until disease progression or intolerable toxicity
Reg 17: CHOP / R-CHOP

### CHOP

- **Prednisolone**: 50mg/m² (Max 100mg) PO Day 1 to 5
- **Doxorubicin**: 50mg/m² IV bolus Day 1
- **Vincristine**: 1.4mg/m² (Max 2mg) IV infusion Day 1
- **Cyclophosphamide**: 750mg/m² IV bolus Day 1

### R-CHOP

- **Rituximab**: 375mg/m² IV infusion Day 1
- **CHOP**: (As detailed above)

**Cycle frequency**: 21 Days

**Intended cycles**:
- Indolent NHL (FL/WM/MZL)/MCL unfit for ASCT/NLPHL: 6 cycles
- DLBCL: 6-8 cycles
- Elderly pts with DLBCL: 6 cycles

Reg 18: R-ABVD

- **Rituximab**: 375mg/m² IV infusion Day 1
- **ABVD**: (See reg 1 details)

**Cycle frequency**: 28 Days

**Intended cycles**: Up to_____ cycles

Reg 19: CVP / R-CVP

### CVP

- **Prednisolone**: 50mg/m² (Max 100mg) PO Day 1 to 5
- **Rituximab**: 375mg/m² IV infusion Day 1
- **Vincristine**: 1.4mg/m² (Max 2mg) IV infusion Day 1
- **Cyclophosphamide**: 750mg/m² IV bolus Day 1

### R-CVP

- **Rituximab**: 375mg/m² IV infusion Day 1
- **CVP**: (As detailed above)

**Cycle frequency**: 21 Days

**Intended cycles**: 6
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Reg 20: DA-REPOCH

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
<th>Time Period</th>
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<td>Prednisolone</td>
<td>60mg/m² (Max 100mg)</td>
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<td>Day 1 to 5</td>
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<td>Rituximab</td>
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<td>Day 1</td>
</tr>
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<td>Doxorubicin</td>
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<td>Vincristine</td>
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<td>Etoposide</td>
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<td>Day 1 to 4</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750mg/m²</td>
<td>IV bolus</td>
<td>Day 5</td>
</tr>
</tbody>
</table>

Cycle frequency: 21 Days
Intended cycles:
Advanced Stage NLPHL: 6 cycles
Advanced Stage DLBCL: 6-8 cycles

Reg 21: Rituximab Monotherapy

Rituximab 375mg/m² IV infusion Day 1

Cycle frequency:
NLPHL = 7 Days
Maintenance in advanced FL and advanced MCL: 2 months
Maintenance in relapsed FL: 3 months
Intended cycles:
Maintenance in advanced FL: 8 cycles
Maintenance in relapsed follicular Lymphoma: 12 cycles
Maintenance in advanced MCL: Until disease progression or intolerable toxicity

Reg 23: R-COEP

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
<th>Time Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>50mg/m² (Max 100mg)</td>
<td>PO</td>
<td>Day 1 to 5</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
</tr>
<tr>
<td>Etoposide</td>
<td>50mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100mg/m²</td>
<td>PO</td>
<td>Day 2 &amp; 3</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4mg/m² (Max 2mg)</td>
<td>IV infusion</td>
<td>Day 1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750mg/m²</td>
<td>IV bolus</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

Cycle frequency: 21 Days
Intended cycles: 6

Reg 24: R-GCVP

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
<th>Time Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>as follows:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 1:</td>
<td>750 mg/m²</td>
<td>IV infusion</td>
<td>Day 1 &amp; 8</td>
</tr>
<tr>
<td>Cycle 2:</td>
<td>875 mg/m²</td>
<td>IV infusion</td>
<td>Day 1 &amp; 8</td>
</tr>
<tr>
<td>Cycles 3 to 6:</td>
<td>1000 mg/m²</td>
<td>IV infusion</td>
<td>Day 1 &amp; 8</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4mg/m² (Max 2mg)</td>
<td>IV infusion</td>
<td>Day 1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>100mg</td>
<td>PO</td>
<td>Day 1 to 5</td>
</tr>
</tbody>
</table>
Cycle frequency: 21 day cycle
Intended cycles: Up to 8 cycles

**Reg 25: R-Mini-CHOP**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>40mg/m²</td>
<td>PO</td>
<td>1-5</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375mg/m²</td>
<td>IV infusion</td>
<td>1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>25mg/m²</td>
<td>IV bolus</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1mg/m² (Max 2mg)</td>
<td>IV infusion</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>400mg/m²</td>
<td>IV bolus</td>
<td>1</td>
</tr>
</tbody>
</table>

Cycle frequency: 21 Days
Intended cycles: 6

**Reg 26: High Dose – Methotrexate 3g**

<table>
<thead>
<tr>
<th>Methotrexate</th>
<th>Dose</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>300mg/m²</td>
<td>IV infusion</td>
<td>1</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2700mg/m²</td>
<td>IV infusion</td>
<td>1</td>
</tr>
</tbody>
</table>

Cycle frequency: N/A
Intended cycles: 1

**Reg 27: 2/3 DeVIC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>40mg</td>
<td>IV infusion</td>
<td>1</td>
</tr>
<tr>
<td>Etoposide</td>
<td>67mg/m²</td>
<td>IV infusion</td>
<td>1 to 3</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>200mg/m²</td>
<td>IV infusion</td>
<td>1</td>
</tr>
<tr>
<td>Mesna</td>
<td>200mg/m²</td>
<td>IV infusion</td>
<td>1</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1000mg/m²</td>
<td>IV infusion</td>
<td>1 to 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>1000mg/m²</td>
<td>IV infusion</td>
<td>1 to 3 (in the same bag s Ifosfamide)</td>
</tr>
<tr>
<td>Mesna</td>
<td>600mg/m²</td>
<td>IV infusion</td>
<td>1,2</td>
</tr>
<tr>
<td>Mesna</td>
<td>600mg/m²</td>
<td>IV infusion</td>
<td>3</td>
</tr>
</tbody>
</table>

Cycle frequency: 21 Days
Intended cycles: 3 to 6 cycles

**Reg 28: DeVIC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>40mg</td>
<td>IV infusion</td>
<td>1</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100mg/m²</td>
<td>IV infusion</td>
<td>1 to 3</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>300mg/m²</td>
<td>IV infusion</td>
<td>1</td>
</tr>
<tr>
<td>Mesna</td>
<td>300mg/m²</td>
<td>IV infusion</td>
<td>1</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1500mg/m²</td>
<td>IV infusion</td>
<td>1 to 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>1500mg/m²</td>
<td>IV infusion</td>
<td>1 to 3 (in the same bag s Ifosfamide)</td>
</tr>
<tr>
<td>Mesna</td>
<td>900mg/m²</td>
<td>IV infusion</td>
<td>1,2</td>
</tr>
<tr>
<td>Mesna</td>
<td>900mg/m²</td>
<td>IV infusion</td>
<td>3</td>
</tr>
</tbody>
</table>

Cycle frequency: 21 Days
Intended cycles: 3 to 6 cycles
Reg 29: R-IVE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route of Administration</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>50mg/m²</td>
<td>IV bolus</td>
<td>Day 1</td>
</tr>
<tr>
<td>Etoposide</td>
<td>200mg/m²</td>
<td>IV infusion</td>
<td>Day 1 to 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>1800mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>3000mg/m²</td>
<td>IV infusion</td>
<td>Day 1 to 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>3000mg/m²</td>
<td>IV infusion</td>
<td>Day 1 to 3 (in the same bag s Ifosfamide)</td>
</tr>
<tr>
<td>Mesna</td>
<td>5400mg/m²</td>
<td>IV infusion</td>
<td>Day 4</td>
</tr>
</tbody>
</table>

Cycle frequency: 21 Days

Intended cycles: 3 cycles

Reg 30: IVE/MTX

**IVE**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route of Administration</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epirubicin</td>
<td>50mg/m²</td>
<td>IV bolus</td>
<td>Day 1</td>
</tr>
<tr>
<td>Etoposide</td>
<td>200mg/m²</td>
<td>IV infusion</td>
<td>Day 1 to 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>1800mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>3000mg/m²</td>
<td>IV infusion</td>
<td>Day 1 to 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>3000mg/m²</td>
<td>IV infusion</td>
<td>Day 1 to 3 (in the same bag s Ifosfamide)</td>
</tr>
<tr>
<td>Mesna</td>
<td>5400mg/m²</td>
<td>IV infusion</td>
<td>Day 4</td>
</tr>
</tbody>
</table>

Cycle frequency: 21 days

Intended cycles: 3 cycles alternating with HD-MTX

**HD-MTX**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route of Administration</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>100mg/m²</td>
<td>IV infusion</td>
<td>Day 10</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>900mg/m²</td>
<td>IV infusion</td>
<td>Day 10</td>
</tr>
</tbody>
</table>

Cycle frequency: 7 days

Intended cycles: 3 cycles alternating with IVE

Reg 31: R-Mini BEAM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route of Administration</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmustine</td>
<td>60mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
</tr>
<tr>
<td>Etoposide</td>
<td>75mg/m²</td>
<td>IV infusion</td>
<td>Day 2 to 5</td>
</tr>
<tr>
<td>Cytarbine</td>
<td>150mg/m²</td>
<td>IV infusion</td>
<td>Day 2 to 5 (twice daily)</td>
</tr>
<tr>
<td>Melphalan</td>
<td>30mg/m²</td>
<td>IV infusion</td>
<td>Day 6</td>
</tr>
</tbody>
</table>

Cycle frequency: 21 to 28 day cycle (as soon as blood count recovery)

Intended cycles: up to 2 cycles
Reg 32: R-PMitCEBO

Rituximab 375mg/m² IV infusion Day 1
Etopophos 150mg/m² IV bolus Day 1
Cyclophosphamide 300mg/m² IV infusion Day 1
Mixantrone 7mg/m² IV infusion Day 1
Vincristine 1.4mg/m² (max 2mg) IV infusion Day 8
Bleomycin 10000 units/m²(max 15,000) IV infusion Day 8

Cycle frequency: 14 day cycle
Intended cycles: Up to 8 cycles

Reg 33: Pixantrone Monotherapy

Pixantrone 50mg/m² IV infusion Day 1, 8 & 15

Cycle frequency: 28 day cycle
Intended cycles: 4 to 6 cycles

Reg 34: R- Bendamustine 90

Rituximab 375mg/m² IV infusion Day 1
Bendamustine 90mg/m² IV infusion Day 1,2

Cycle frequency: 21 day cycle
Intended cycles: 6 cycles

Reg 35: MATRIX

Rituximab 375mg/m² IV infusion Day 1 & 6
Methotrexate 500mg/m² IV infusion Day 7
Methotrexate 3000mg/m² IV infusion Day 7
Cytarbine 2000mg/m² IV infusion Day 8 & 9
Thiotepa 30mg/m² IV infusion Day 10

Cycle frequency: 21 day cycle
Intended cycles: 4 cycles

Reg 36: R-MP

Rituximab 375mg/m² IV infusion Day -6, 1, 15 & 29 (cycle 1)
Rituximab 375mg/m² IV infusion Day 1, 15 & 29 (cycle 2 & 3)
Methotrexate 3000mg/m² IV infusion Day 2, 16,30
Procarbazine 60mg/m² PO Day 2 to 11

Cycle frequency: 42 day cycle
Intended cycles: 3 cycles
### Reg 37: Temzolomide MT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temzolomide</td>
<td>150mg</td>
<td>PO</td>
<td>Day 1 to 5</td>
</tr>
</tbody>
</table>

**Cycle frequency:** 28 day cycle  
**Intended cycles:** for 1 year or until relapse/progression

### Reg 38: CaRTH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmustine</td>
<td>400mg/m²</td>
<td>IV infusion Day -6</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>5mg/kg</td>
<td>IV infusion Day -5 &amp; -4</td>
</tr>
</tbody>
</table>

**Cycle frequency:** N/A  
**Intended cycles:** 1 cycle

### Reg 39: CHOEP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>50mg/m² (Max 100mg)</td>
<td>PO Day 1 to 5</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50mg/m²</td>
<td>IV bolus Day 1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4mg/m² (Max 2mg)</td>
<td>IV infusion Day 1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750mg/m²</td>
<td>IV bolus Day 1</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100mg/m²</td>
<td>IV infusion Day 1 to 3</td>
</tr>
</tbody>
</table>

**Cycle frequency:** 21 days  
**Intended cycles:** 6 cycles

### Reg 40: R-IE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m²</td>
<td>IV infusion Day 1</td>
</tr>
<tr>
<td>Etopophos</td>
<td>250mg/m²</td>
<td>IV infusion Day 1</td>
</tr>
<tr>
<td>Mesna</td>
<td>400mg/m²</td>
<td>IV infusion Day 1</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>2000mg/m²</td>
<td>IV infusion Day 1 to 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>2000mg/m²</td>
<td>IV infusion Day 1 to 3 (in the same bag as Ifosfamide)</td>
</tr>
<tr>
<td>Mesna</td>
<td>1200mg/m²</td>
<td>IV infusion Day 1 to 3</td>
</tr>
</tbody>
</table>

**Cycle frequency:** 21 Days  
**Intended cycles:** Salvage therapy: Up to 4 cycles

### Reg 41: R-TIE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m²</td>
<td>IV infusion Day 1</td>
</tr>
<tr>
<td>Etopophos</td>
<td>250mg/m²</td>
<td>IV infusion Day 1</td>
</tr>
<tr>
<td>Mesna</td>
<td>400mg/m²</td>
<td>IV infusion Day 1</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>2000mg/m²</td>
<td>IV infusion Day 1 to 3</td>
</tr>
<tr>
<td>Mesna</td>
<td>2000mg/m²</td>
<td>IV infusion Day 1 to 3 (in the same bag as Ifosfamide)</td>
</tr>
<tr>
<td>Mesna</td>
<td>1200mg/m²</td>
<td>IV infusion Day 1 to 3</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>30mg/m²</td>
<td>IV infusion Day 4</td>
</tr>
</tbody>
</table>

**Cycle frequency:** 21 Days  
**Intended cycles:** Salvage therapy: Up to 4 cycles
Reg 42: VR

**Bortezomib** 1.3 mg/m^2 once daily S/C Days 1, 4, 8, 11
Rituximab 375mg/m^2 IV infusion Day 1 & 8 (cycles 2 to 5)

**Rituximab** 375mg/m^2 IV infusion Day 1
**Prednisolone** 50mg/m^2 (Max 100mg) PO Day 1 to 5
**Cyclophosphamide** 750mg/m^2 IV bolus Day 1

**Cycle frequency:** 21 days
**Intended cycles:** 5 cycles

Reg 43: R-CP

**Rituximab** 375mg/m^2 IV infusion Day 1
**Prednisolone** 50mg/m^2 (Max 100mg) PO Day 1 to 5
**Cyclophosphamide** 750mg/m^2 IV bolus Day 1

**Cycle frequency:** 21 days
**Intended cycles:** 6 cycles

Reg 44: R-CODOX-M LR un65

**Cytarabine** 70mg IT Day 1 & 3
**Rituximab** 375mg/m^2 IV infusion Day 1
**Doxorubicin** 40mg/m^2 IV bolus Day 1
**Vincristine** 1.5mg/m^2 (Max 2mg) IV infusion Day 1 & 8
**Cyclophosphamide** 800mg/m^2 IV infusion Day 1
**Cyclophosphamide** 200mg/m^2 IV infusion Day 2 to 5
**Methotrexate** 300mg/m^2 IV infusion Day 10
**Methotrexate** 2700mg/m^2 IV infusion Day 10
**Methotrexate** 12.5mg IT Day 15

**Cycle frequency:** 3
**Intended cycles:** Commence next cycle when unsupported ANC>1 x10^9/l and PLT>75 x10^9/l

Reg 45: R-CODOX-M LR ov65

As per reg 44 except

**Methotrexate** 100mg/m^2 IV infusion Day 10
**Methotrexate** 900mg/m^2 IV infusion Day 10

Reg 46: R-CODOX-M/R-IVAC HR un65

**R-CODOX**

**Cytarabine** 70mg IT Day 1 & 3
**Rituximab** 375mg/m^2 IV infusion Day 1
**Doxorubicin** 40mg/m^2 IV bolus Day 1
**Vincristine** 1.5mg/m^2 (Max 2mg) IV infusion Day 1 & 8
**Cyclophosphamide** 800mg/m^2 IV infusion Day 1
**Cyclophosphamide** 200mg/m^2 IV infusion Day 2 to 5
**Methotrexate** 300mg/m^2 IV infusion Day 10
**Methotrexate** 2700mg/m^2 IV infusion Day 10
**Methotrexate** 12.5mg IT Day 15
Cycle frequency:
Commence R-CODOX-M (following R-IVAC) when unsupported ANC > 1x10^9/l and PLT > 75 x10^9/l

Intended cycles:
2 Cycles, alternating with 2 cycles of R-IVAC.
Cycles 1 & 3 R-CODOX-M and cycles 2 & 4 R-IVAC

R-IVAC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m² II infusion</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>60mg/m² II infusion</td>
<td>Day 1 to 5</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1500mg/m² II infusion</td>
<td>Day 1 to 5</td>
<td></td>
</tr>
<tr>
<td>Mesna</td>
<td>300mg/m² II infusion</td>
<td>Day 1 to 5</td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>2000mg/m² II infusion</td>
<td>Day 1 and 2</td>
<td></td>
</tr>
<tr>
<td>Mesna</td>
<td>300mg/m² II infusion</td>
<td>Day 1 to 5 (4 hours after ifosfamide)</td>
<td></td>
</tr>
<tr>
<td>Mesna</td>
<td>300mg/m² II infusion</td>
<td>Day 1 to 5 (8 hours after ifosfamide)</td>
<td></td>
</tr>
</tbody>
</table>

Cycle frequency:
Commence R-IVAC (following R-CODOX-M) when unsupported ANC > 1x10^9/l and PLT > 75 x10^9/l

Intended cycles:
2 Cycles, alternating with 2 cycles of R-CODOX-M.
Cycles 1 & 3 R-CODOX-M and cycles 2 & 4 R-IVAC

Reg 47: R-CODOX-M/R-IVAC HR ov65

R-CODOX

As per R-CODOX-M reg 46 except

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>100mg/m² II infusion</td>
<td>Day 10</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>900mg/m² II infusion</td>
<td>Day 10</td>
<td></td>
</tr>
</tbody>
</table>

R-IVAC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m² II infusion</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>60mg/m² II infusion</td>
<td>Day 1 to 5</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1000mg/m² II infusion</td>
<td>Day 1 to 5</td>
<td></td>
</tr>
<tr>
<td>Mesna</td>
<td>200mg/m² II infusion</td>
<td>Day 1 to 5</td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>1000mg/m² II infusion</td>
<td>Day 1 and 2</td>
<td></td>
</tr>
<tr>
<td>Mesna</td>
<td>200mg/m² II infusion</td>
<td>Day 1 to 5 (4 hours after ifosfamide)</td>
<td></td>
</tr>
<tr>
<td>Mesna</td>
<td>200mg/m² II infusion</td>
<td>Day 1 to 5 (8 hours after ifosfamide)</td>
<td></td>
</tr>
</tbody>
</table>

Reg 48: R-Chlorambucil

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m² II infusion</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>10mg/m² PO</td>
<td>Day 1 to 7</td>
<td></td>
</tr>
</tbody>
</table>

Cycle frequency: 28 days cycle
Intended cycles: 4 - 6 cycles depending on response
Reg 49: Obintuzumab/Bendamustine

Obinutuzumab 1000mg IV infusion Day 1
Bendamustine 90mg/m² IV infusion Day 1,2

Cycle frequency: 21 day cycle
Intended cycles: 6 cycles

Reg 50: Obintuzumab/CHOP

Obinutuzumab 1000mg IV infusion Day 1
CHOP (See reg 17 details)

Cycle frequency: 21 day cycle
Intended cycles: 6 cycles

Reg 51: Obintuzumab/CVP

Obinutuzumab 1000mg IV infusion Day 1
CVP (See reg 19 details)

Cycle frequency: 21 day cycle
Intended cycles: 6 cycles

Reg 52: Obintuzumab Maintenance

Obinutuzumab 1000mg IV infusion Day 1

Cycle frequency: 2 months
Intended cycles: 12 cycles

Reg 53: Idelalisib

Idelalisib 150mg (Twice daily) PO Day 1 to 28

Cycle frequency: 28 day cycle
Intended cycles: Until disease progression or intolerable toxicity

Reg 54: FCR

Rituximab – CLL
Rituximab 375mg/m² IV infusion Day 1 (cycle 1)
Rituximab 500mg/m² IV infusion Day 1 (cycle 2 onwards)

Rituximab – WM/LPL
Rituximab 375mg/m² IV infusion Day 1 (all cycles)
FC(iv)
Fludarabine  25mg/m²  IV infusion  Day 1 to 3
Cyclophosphamide  250mg/m²  IV infusion  Day 1 to 3

FC(po)
Fludarabine  40mg/m²  PO  Day 2 to 4
Cyclophosphamide  250mg/m²  PO  Day 2 to 4

Cycle frequency: 28 day cycle
Intended cycles: 6 to 8 cycles –CLL / 6 cycles –WM

Reg 55: Obinutuzumab/ Chlorambucil
Obinutuzumab  1000mg  IV infusion  Day 1
Chlorambucil  0.5mg/Kg  PO  Day 1 & 15

Cycle frequency: 28 day cycle
Intended cycles: 6 cycles

Reg 56: Ofatumumab/ Chlorambucil
Obinutuzumab  1000mg  IV infusion  Day 1
Chlorambucil  10mg/m²  PO  Day 1 to 7

Cycle frequency: 28 day cycle
Intended cycles: For a minimum of 3 cycles, until best response (a clinical response that did not improve with 3 additional cycles of treatment) or a maximum of 12 cycles

Reg 57: Chlorambucil MT
Chlorambucil  10mg/m²  PO  Day 1 to 7

Cycle frequency: 28 day cycle
Intended cycles: 6-8 cycles depending on response

Reg 58: Bendamustine 70 MT
Bendamustine  70mg/m²  IV infusion  Day 1,2

Cycle frequency: 28 day cycle
Intended cycles: up to 6 cycles

Reg 59: Ibrutinib – CLL/WM.LPL
Ibrutinib  420mg  PO  Day 1 to 28

Cycle frequency: 28 day cycle
Intended cycles: Until disease progression or intolerable toxicity
Reg 60: Rituximab/Idelalisib

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Cycle Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m²</td>
<td>IV infusion</td>
<td>Day 1 (cycle 1)</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>500mg/m²</td>
<td>IV infusion</td>
<td>Day 1 (cycle 2 onwards)</td>
<td></td>
</tr>
<tr>
<td>Idelalisib</td>
<td>150mg</td>
<td>PO</td>
<td>Day 1 to 28 (Twice Daily)</td>
<td></td>
</tr>
</tbody>
</table>

Cycle frequency: 28 days cycle
Intended cycles:
Rituximab: 6 cycles
Idelalisib: Until disease progression or intolerable toxicity

Reg 61: Venetoclax MT / Rituximab/Venetoclax

Venetoclax MT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Cycle Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venetoclax</td>
<td>20mg</td>
<td>Once daily</td>
<td>PO</td>
<td>Day 1 to 7 (Week 1)</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>50mg</td>
<td>Once daily</td>
<td>PO</td>
<td>Day 8 to 14 (Week 2)</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>100mg</td>
<td>Once daily</td>
<td>PO</td>
<td>Day 15 to 21 (Week 3)</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>200mg</td>
<td>Once daily</td>
<td>PO</td>
<td>Day 22 to 28 (Week 4)</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>400mg</td>
<td>Once daily</td>
<td>PO</td>
<td>Day 29 onwards (Week 5 onwards)</td>
</tr>
</tbody>
</table>

Venetoclax/Rituximab

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Cycle Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m²</td>
<td>IV infusion</td>
<td>Day 1 (week 6)</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>500mg/m²</td>
<td>IV infusion</td>
<td>Day 1 (week 10,14,18,22,26)</td>
<td></td>
</tr>
<tr>
<td>Venetoclax</td>
<td>(As detailed above)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cycle frequency: N/A
Intended cycles: Treatment should be continued until disease progression or no longer tolerated by the patient

Reg 62: Nordic protocol

Rituximab/Maxi-CHOP regimen

Maxi-CHOP - Cycle 1 (no rituximab)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Cycle Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>50mg/m² (Max 100mg)</td>
<td>PO</td>
<td>Day 1 to 5</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>75mg/m²</td>
<td>IV bolus</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4mg/m² (Max 2mg)</td>
<td>IV infusion</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Mesna</td>
<td>240mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1200mg/m²</td>
<td>IV bolus</td>
<td>Day 1</td>
<td></td>
</tr>
</tbody>
</table>

Rituximab/Maxi-CHOP - Cycles 3 and 5

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Cycle Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Maxi - CHOP</td>
<td>(As detailed above)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rituximab/High dose Cytarabine regimen

Cycles 2 and 4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Cycle Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m²</td>
<td>IV infusion</td>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>3000mg/m²</td>
<td>IV infusion</td>
<td>Day 1 and 2</td>
<td></td>
</tr>
</tbody>
</table>
Cycle 6
Rituximab 375mg/m² IV infusion Day 1 and 9
Cytarabine 3000mg/m² IV infusion Day 1 and 2

Cycle frequency: 21
Intended cycles: 6 (Cycles 1,3,5 Ritux-Maxi-CHOP and cycles 2,4,6 Ritux/HD Cytarabine)

Reg 63: BR/HD AraC

BR
Rituximab 375mg/m² IV infusion Day 1
Bendamustine 90mg/m² IV infusion Day 1,2

Cycle frequency: 28 day cycle
Intended cycles: 3 cycles followed by 3 cycles of HD AraC as detailed below

HD AraC
Cytarabine 3000mg/m² IV infusion Day 1 and 2 (Twice Daily)

Cycle frequency: ____ day cycle
Intended cycles: 3 cycles following 3 cycles of BR as detailed above

Reg 64: VRCAP
Prednisolone 100mg/m² PO Day 1 to 5
Bortezomib 1.3mg/m² S/C Day 1
Rituximab 375mg/m² IV infusion Day 1
Doxorubicin 50mg/m² IV bolus Day 1
Cyclophosphamide 750mg/m² IV bolus Day 1

Cycle frequency: 21 day cycle
Intended cycles: 6 cycles

Reg 65: R-BAC
Rituximab 375mg/m² IV infusion Day 1
Bendamustine 70mg/m² IV infusion Day 1,2
Cytarabine 3000mg/m² IV infusion Day 1,2 and 3

Cycle frequency: 28 day cycle
Intended cycles: up to 6 cycles

Reg 66: HD AraC
Rituximab 375mg/m² IV infusion Day 1 and 9
Cytarabine 2000mg/m² IV infusion Day 1 and 2

Cycle frequency: 2
Intended cycles: 21
Reg 67: Ibrutinib – MCL

Ibrutinib 560mg PO Day 1 to 28

Cycle frequency: 28 day cycle
Intended cycles: Until disease progression or intolerable toxicity

Reg 68: PEP-C

Prednisolone 20mg Once daily PO Day 1
Etoposide 50mg Once daily PO Day 1
Procarbazine 50mg Once daily PO Day 1
Cyclophosphamide 50mg Once daily PO Day 1

Cycle frequency: Discuss with consultant
Intended cycles: Discuss with consultant

Reg 69: Bortezomib MT

Bortezomib 1.3 mg/m² once daily S/C Days 1, 4, 8, 11

Cycle frequency: 21
Intended cycles: up to 17 cycles or four cycles beyond initial reporting of CR/CRu

Reg 70: Temsirolimus

Temsirolimus 175mg IV infusion Days 1, 8 and 15 (cycle 1)
Temsirolimus 75mg IV infusion Days 1, 8 and 15 (cycle 2 onwards)

Cycle frequency: 21
Intended cycles: Until disease progression or intolerable toxicity

Reg 71: DRC

Dexamethasone 20mg IV infusion Day 1
Rituximab 375mg/m² IV infusion Day 1
Cyclophosphamide 50mg Once daily PO Day 1 to 5

Cycle frequency: 21 days
Intended cycles: 6 cycles

Reg 72: BDR

Bortezomib 1.3 mg/m² once daily S/C Days 1, 4, 8, 11
Dexamethasone 40mg PO Day 1
Rituximab 375mg/m² IV infusion Day 1

Cycle frequency: 21 days
Intended cycles: 6 cycles