PMB Benefit Definition Guideline:

Hodgkin Lymphoma

Version 2

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Disclaimer:

The Hodgkin lymphoma benefit definition guideline has been developed for most standard patients and is aligned with best practice. These benefits may not be sufficient for outlier patients. Therefore, regulation 15h may be applied for patients who are inadequately managed by the stated benefits. The benefit definition does not describe specific in-hospital management. However, these interventions form part of care and are Prescribed Minimum Benefits. Supportive medication for all haematology oncology conditions is detailed in a separate guideline available [here](#).

The benefit definition guideline project is coordinated by the CMS, with the aim to guide the interpretation of the PMB provisions by relevant stakeholders. The guidelines are based on the available evidence of clinical and cost effectiveness, taking into consideration affordability constraints and financial viability of medical schemes in South Africa

Acknowledgements

PMB Benefit Definition Guideline for Hodgkin Lymphoma V2

Table of Contents

Abbreviations

ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine
ASCT	Autologous stem cell transplantation
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
BV	Brentuximab vedotin
ChIVPP/ABV	Chlorambucil, vinblastine, procarbazine, prednisone, doxorubicin, bleomycin
CHL	Classical Hodgkin lymphoma
CHOP	Cyclophosphamide, doxorubin, vincristine and prednisone
CMT	Combined-modality therapy
CMV	Cytomegalovirus
CR	Complete remission
CT	Computed tomography
DHAP	Dexamethasone/high dose cytarabine/ cisplatin
DTPs	Diagnosis Treatment Pairs
EBER-ISH	Epstein-Barr virus-encoded ribonucleic acid in situ hybridization
EBV	Epstein-Barr virus
EML	Essential medicines list
ESR	Erythrocyte sedimentation rate
FBC	Full blood count
FDG	Fluorodeoxyglucose
GHSG	German Hodgkin Lymphoma group
GP	General practitioner
HDCT	High-dose chemotherapy
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HSCT	Haemopoietic stem cell transplant
HTLV-1	Human T- cell leukemia virus
ICE	Ifosfamide/carboplatin/etoposide
IFRT	Involved field radiotherapy
IGEV	Ifosfamide/gemcitabine/vinorelbine
IgG	Immunoglobulin G
IgM	Immunoglobulin M

INR	International normalized ratio
IPS	International prognostic score
ISRT	Involved-site radiation therapy
LDCHL	Lymphocyte-depleted classical Hodgkin lymphoma
LDH	Lactate dehydrogenase
LFT	Liver function test
LRCHL	Lymphocyte-rich classical Hodgkin lymphoma
MMAE	Monomethyl **auristatin** E
NCCN	National comprehensive cancer network
NEML	National essential medicines list
NLPHL	Nodular lymphocyte predominant Hodgkin lymphoma
NSCHL	Nodular sclerosis classical Hodgkin lymphoma
MCCHL	Mixed cellularity classical Hodgkin lymphoma
ORR	Overall response rate
PAX 5	Paired box gene 5
PET	Positron emission tomography
PHC	Primary health care
PMBs	Prescribed minimum benefits
PTT	Partial thromboplastin time
RT	Radiotherapy
WHO	World health organization
U&E	Urea and electrolytes

1. Introduction

1.1. The legislation governing the provision of the Prescribed Minimum Benefits (PMBs) is contained in the Regulations enacted under the Medical Schemes Act, No. 31 of 1998 (the Act). With regards to some of the Diagnosis Treatment Pairs (DTPs), medical scheme beneficiaries find it difficult to be fully aware of their entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements.

1.2. The benefit definition project is undertaken by the CMS with the aim of defining the PMB package, as well as to guide the interpretation of the PMB provisions by relevant stakeholders.

2. Scope and purpose

2.1. This is a recommendation for the diagnosis, treatment, and care of individuals with Hodgkin lymphoma (HL) in any clinically appropriate setting as outlined in the Act.

2.2. The purpose is to provide detailed clarification in respect of benefit and entitlements to members and beneficiaries of medical schemes.

Table 1: Possible ICD10 codes for patients with Hodgkin lymphoma (HL) in curative and palliative setting

DTP code	Treatment component	ICD 10 code	WHO description
901S	Medical management, which includes chemotherapy, radiation therapy, bone marrow transplantation	C81.0	Nodular lymphocyte predominant Hodgkin lymphoma
		C81.1	Nodular sclerosis (classical) Hodgkin lymphoma
		C81.2	Mixed cellularity (classical) Hodgkin lymphoma
		C81.3	Lymphocyte depleted (classical) Hodgkin lymphoma
		C81.4	Lymphocyte-rich (classical) Hodgkin lymphoma
		C81.7	Other (classical) Hodgkin lymphoma
		C81.9	Hodgkin lymphoma, unspecified

3. Epidemiology and burden of the disease

3.1. Hodgkin lymphoma (HL) is a lymphoid malignancy of B-cell origin which is categorised as either Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) or Classical Hodgkin lymphoma (CHL) based on morphology, immunophenotype and the preservation/extinction of the B-cell gene expression (Salati et al., 2014).

3.2. CHL accounts for 90% of all HLs while NLPHL accounts for the remainder of cases (Laurent et al., 2015). CHL can be further subdivided into four histological subtypes (Swerdlow et al., 2008):

- Lymphocyte-Rich Classical Hodgkin Lymphoma (LRCHL)

- Nodular Sclerosis Classical Hodgkin Lymphoma (NSCHL)

- Mixed Cellularity Classical Hodgkin Lymphoma (MCCHL)

- Lymphocyte-Depleted Classical Hodgkin Lymphoma (LDCHL)

3.3. The incidence rate and lifetime risk of HL is relatively low. However, it accounts for 15% of all cancers in young adults, greatly impacting on the quality of their lives. (Salati et al., 2014).

3.4. The incidence of HL varies greatly by age, ethnicity, gender, socioeconomic status, geographic location, age of exposure to Epstein-Barr virus (EBV), and prevalence of HIV/AIDS.

Age

3.5. For adult disease, there is a striking bimodality age distribution with peaks in young adulthood and in older adulthood. Most patients are diagnosed between 15 and 30 years of age, followed by another peak in adults aged 55 years or older (Hoppe et al., 2020).
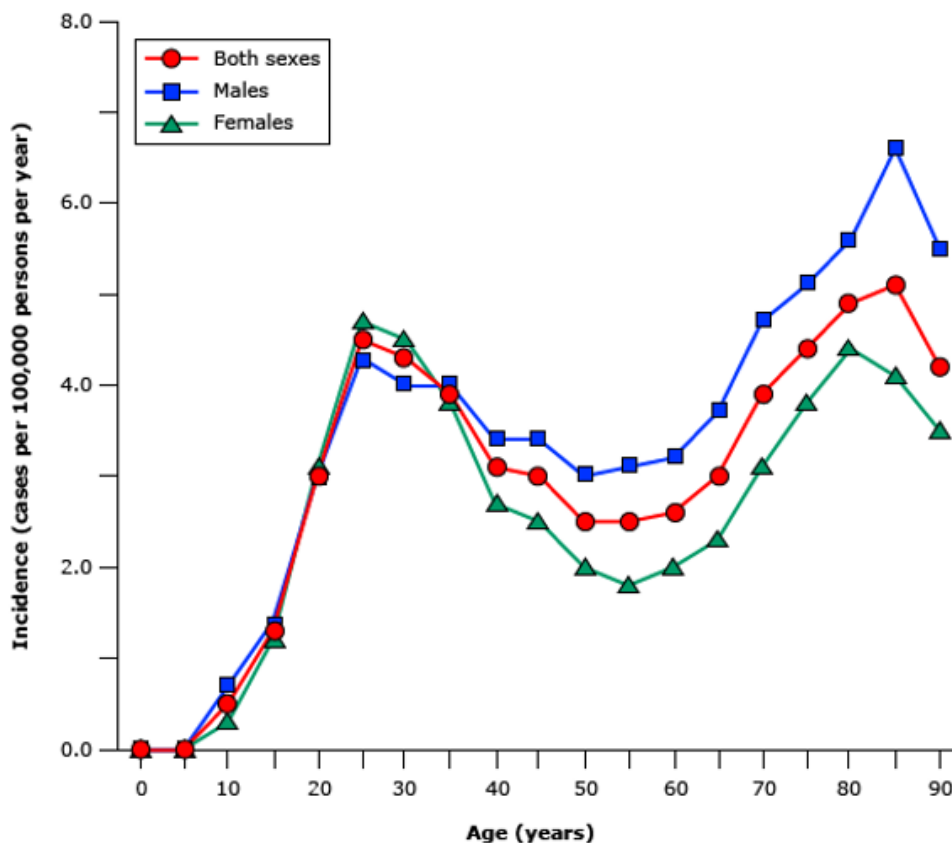
Figure 1: HL incidence by age (Source: LaCasce and Ng, 2020)

Ethnicity

3.6. The incidence of HL also varies by race. White and Black Americans in the United States (3.1 cases per 100,000 males) have equal incidences, but it is lower in Hispanic Americans (2.6), Asian Pacific Islanders, American Indians, and Alaskan natives (National Cancer Institute, 2014).

3.7. In one population-based study from the United States, the peak incidence among Whites, Blacks, and Asians/Pacific Islanders was in young adulthood, but the peak in Hispanics was in older individuals (Evens et al., 2012). Compared to non-Hispanic Whites, Hispanic children had an increased risk of HL (OR 2.43; 95% CI 1.14-5.17) and were more often diagnosed with MCCHL (Marcotte et al., 2014).

3.8. In South Africa, 293 and 356 new cases of HL were recorded in females and males respectively, among all population groups combined in 2017 (National Cancer Registry, 2017). In contrast to the

United States, South Africa shows a dominant black incidence of at least three-fold when compared to the other ethnic groups. The breakdown by ethnicity is detailed in the table below.

Table 2: HL breakdown by ethnicity in South Africa

All Males	243
Asian male	5
Coloured male	16
White male	48
Black male	169
All Females	**201**
Asian female	10
Coloured female	23
White female	41
Black female	124

Source – NCR, 2017.

Socio-economic factors

3.9. The incidence rates are higher in high-income countries, especially among males. Much lower incidence rates are reported in Asia. In the United States, about 9,290 new HL cases were estimated for 2013 (2.8 per 100,000 people per year) (Holder et al., 2013).

3.10.   In the United States, Europe, and other high-income countries, HL accounts for approximately 10% of all lymphomas (the remainder being non-Hodgkin lymphomas), 0.6% of all cancers, and 0.2% of all cancer deaths (Sant et al., 2010; Siegel et al., 2017; Smith et al., 2011).

3.11.   The prevalence of CHL subtypes in economically viable regions follows the following order: NSCHL (70%), MCCHL (20 to 25%), LRCHL (5%), LDCHL (<1 percent) (Swerdlow et al., 2008). For the young adult disease, the higher the socio-economic status of a person, the greater the risk for developing Hodgkin 's (Grufferman & Delzell, 1984).

Immunosuppression

3.12.   The incidence of HL is increased in patients infected with HIV and in other settings associated with immunodeficiency. HL in these populations is almost universally positive for EBV. Although there is an increased incidence of HL in people infected with AIDS, HL is not considered an AIDS-defining malignancy (Rubinstein et al, 2014).

3.13.   EBV has been proposed as the major candidate for a pathogenetic role due to at least three pieces of evidence (Hjalgrim et al, 2007; Kaye et al., 1993; Weiss et al., 1989).
-    the biological plausibility of EBV-mediated B cell transformation,
-    the presence of clonal EBV genomes within HL tumour cells and
-    three-fold elevated risk of HL in persons with a history of infectious mononucleosis

3.14.   Globally, EBV-positive HLs account for up to 40% of all HL cases. The presence of EBV in HL is strongly associated with specific epidemiological features including male gender, Hispanic ethnicity, mixed cellularity subtype, children and older adults and lower socio-economic status (Salati et al, 2014).

3.15.   Also, the incidence of EBV-related HLs varies significantly according to geography. In North America and Western Europe, EBV was detected in 30 to 50% of HL patients, while in some parts of Latin America, Africa and Asia the percentage is much higher, reaching roughly 100% in children

(Glaser et al., 1997). For instance, in Peru and Mexico incidence of EBV positivity among HLs ranged from 50 to 95%, in China it was 65% and in Kenya reached 92% (Chang et al., 1993; Glaser et al., 1997; Leoncini et al., 1996; Zarate-Osorno et al., 1995; Zhou et al., 1993). Fortunately, no other virus has been consistently found to be associated with HL till date.

4. Recommended work-up for HL

The work-up of HL involves a thorough history and physical assessment, imaging, pathology and histopathology studies.

4.1. Pathology work-up

4.1.1. Standard laboratory tests can serve as a useful laboratory marker of disease response and results can be used to identify patients with extensive disease and portend a poorer prognosis.

4.1.2. The following laboratory investigations are recommended as PMB level of care.
- Full blood count (FBC) with differential count and erythrocyte sedimentation rate (ESR)
- Urea and Electrolytes (U&E)
- Full Liver Function Tests (LFT)
- International Normalized Ratio (INR) & Partial Thromboplastin Time (PTT)
- Calcium
- Magnesium
- Phosphate
- Uric acid
- Glucose
- Beta-2 microglobulin
- Baseline hematinics: iron studies, red call folate, vitamin B12
- Haemolytic screen: Coombs, haptoglobin, unconjugated bilirubin, reticulocytes
- Immunoglobulins
- Hepatitis serology – Hepatitis BsAg, Hepatitis B core antibody, Hepatitis C serology (associated with some low grade lymphoproliferative disorder
- Epstein–Barr virus (EBV)
- Human Immunodeficiency Virus (HIV)

4.2. Histopathology

4.2.1. The characteristic morphologic appearance of CHL on tissue biopsy is that of neoplastic Reed-Sternberg cells set in a variable inflammatory background.

4.2.2. These cells have a unique immunophenotype: CD30 positive, CD15 positive (most cases), and positive for the B-cell marker PAX5 but negative for most other B-cell markers and negative for all T-cell markers (Hasserjian, 2019).

4.2.3. Excisional biopsy of the involved node is preferred to establish a definitive diagnosis.

4.2.4. Biopsy for suspected relapse is required to confirm the diagnosis, as patients may develop other malignancies secondary to chemotherapy.

Table 3: Recommended PMB level of care histopathology for HL

- Baseline blood tests are required prior to histology
- Histology (tissue biopsy) – Immunohistochemistry (IHC); morphology
- Flow cytometry
- Bone marrow aspirate and trephine biopsy
- CD30, CD15, CD3
- B- cell markers – CD20
- PAX 5
- EBER – ISH

4.3. Radiology

4.3.1. Once the diagnosis of CHL is confirmed, the disease should be staged using a PET-CT scan to be able to determine the Ann Arbor stage of the disease. Fluorodeoxyglucose (FDG) positron emission tomography (PET)–computed tomography (CT) has very high sensitivity and specificity in HL (Chesson, 2011).

4.3.2. The use of a PET-CT for response assessment after 2 cycles of chemotherapy is a good prognostic indicator in patients with early disease (Zinzani, 2012). For patients with advanced disease (stage III-IV), interim response assessment with PET should be conducted after 2 – 4 cycles of chemotherapy depending on the regimen used (Cerci, 2010).

4.3.3. A diagnostic contrast-enhanced computed tomography (CT) scan of the neck, chest and the abdomen are PMB level of care (if a PET-CT scan is unavailable).

4.3.4. PET-CT scans are PMB level of care for staging, interim assessments and follow-up surveillance.

4.3.5. A bone marrow biopsy is PMB level of care (Eichenauer et al, 2014).

4.3.6. Chest x-ray is PMB level of care for HL.

4.3.7. ECG and echocardiogram are PMB level of care and should also be performed prior to receiving chemotherapy.

5. Staging and Risk Assessment

5.1. Staging for HL is based on the Ann Arbor staging system. The system divides each stage into subcategories A and B, the latter for presence of B symptoms. "A" indicates that no systemic symptoms are present and "B" is assigned to patients with unexplained fever > 38°C, drenching night sweats, or weight loss of >10% of their body weight within 6 months of diagnosis (Carbone et al., 1971); (Cheson et al., 2014).

5.2. When considering treatment, patients with HL are usually classified into 3 groups:

- Early-stage favourable - this is stage I–II with no unfavourable factors.
- Early-stage unfavourable - this is stage I–II with any of the unfavourable factors such as:
  - large mediastinal adenopathy - mediastinal bulk is an unfavourable prognostic factor in patients with early-stage HL and is measured using the mediastinal mass ratio (MMR). The MMR is the ratio of

the maximum width of the mass and the maximum intrathoracic diameter. Any mass with MMR of 0.33 is defined as a bulky disease.
- multiple involved nodal regions
- presence of B symptoms
- extranodal involvement, or significantly elevated ESR

➢ The early-stage unfavourable factors are based largely on a composite of factors derived from the definition of unfavourable prognostic groups from the clinical trials conducted by the EORTC, GHSG, and the National Cancer Institute of Canada (Henry-Amar et al., 1991; Tubiana et al., 1984).

➢ The NCCN and EORTC unfavourable factors for stage I–II disease include bulky mediastinal disease (MMR .0.33 and MTR .0.35, respectively) or bulky disease >10 cm, B symptoms, ESR ≥50, and > 3 involved nodal regions. In contrast, the GHSG considers patients with > 2 nodal regions as having unfavourable disease (Hoppe et al., 2020).

Definition of bulky disease in early-stage Hodgkin lymphoma

- *Historically, bulk in the mediastinum was focused upon and defined using radiographic criteria from a standing posterior-anterior (PA) chest radiograph (CXR). In the 1989 Cotswolds revision of the Ann Arbor Staging system, bulk in the mediastinum was defined as "when the maximum width is equal or greater than one-third of the internal transverse diameter of the thorax at the level of T5/6" on a PA CXR and bulk at an alternate site was defined as any mass measuring 10 cm or more by any imaging study (Kumar et al., 2016).*

- *In the CT era, the definition of disease bulk remains elusive. Various retrospective studies have defined CT criteria for bulky disease associated with increased risk of relapse in early-stage Hodgkin Lymphoma (ESHL), ranging from greater than 5 to 10 cm for the maximal mediastinal mass diameter in the transverse plane.*

- *Mediastinal bulk, an unfavourable prognostic factor in patients with early-stage HL, is measured most using the mediastinal mass ratio (MMR). The MMR is the ratio of the maximum width of the mass and the maximum intrathoracic diameter. Any mass with MMR >0.33 is defined as bulky disease (Mauch et al., 1978).*

- *Another definition of bulk is any single node or nodal mass that is 10 cm or greater in diameter. According to the Cotswolds modification of the Ann Arbor staging system, bulky disease is defined as the mediastinal thoracic ratio (MTR), which is the ratio of the maximum width of the mediastinal mass and the internal transverse diameter of the thorax at the T5–T6 interspace on a posteroanterior chest radiograph (Lister et al., 1989).*

- *The definition used by the European Organization for Research and Treatment of Cancer (EORTC) for a bulky disease is any mass with MTR > 0.35 (Hoppe et al., 2020).*

- Advanced-stage disease (stage III–IV) (Hoppe et al., 2020).
  - An international collaborative effort evaluating more than 5,000 patients with advanced CHL (stage III–IV) identified seven adverse prognostic factors, each of which reduced survival rates by 7%–8% per year, including:
    - age 45 years or older
    - male gender
    - stage IV disease
    - albumin level below 4 g/dL (40g/l)
    - haemoglobin level below 10.5 g/dL
    - leukocytosis (white blood cell count >15,000/mm3 (15x10⁹/l))
    - and lymphocytopenia (lymphocyte count ,8% of the white blood cell and/or lymphocyte count ,600/mm3 (< 0.6 x 10⁹/ l) (Hoppe et al., 2020).
  - The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis. The IPS helps to determine the clinical management and predict prognosis for patients with stage III - IV disease (Henry-Amar et al., 1991; Tubiana et al., 1984).

6.   Treatment options

6.1 Treatment of Classical Hodgkin Lymphoma

6.1.1 Early - stage favourable disease

- Chemotherapy remains the current standard of care for the majority of patients with early-stage HL. The most common combination of chemotherapy drugs used are doxorubicin, bleomycin, dacarbazine and vinblastine (ABVD).

- Combined modality therapy (chemotherapy and radiotherapy) is the treatment of choice for patients with early stage, favourable disease. Two cycles of ABVD and involved field radiotherapy (IFRT) are regarded as standard of care in favourable early-stage disease as defined by the German Hodgkin Lymphoma group (GHSG) HD10 trial with an event free survival of 91% and overall survival of 93% at 5 years (Engert et al., 2010).

- In early-stage HL, PET-CT scan response after two cycles of ABVD allows for early treatment adaptation. When a PET-CT scan is positive after two cycles of ABVD, switching to BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) plus involved node radiotherapy (INRT) significantly improves 5-year progression-free survival (PFS). In PET-CT scan negative patients, noninferiority of ABVD only could not be demonstrated, however the risk of relapse is increased when INRT is omitted (André et al., 2017).

- ABVD, BEACOPP and INRT is PMB level of care.

6.1.2 Early-stage unfavourable disease

- Combined modality therapy is the standard treatment for unfavourable early stage HL.

- Four cycles of ABVD followed by assessment with PET-CT scan for early unfavourable patients is PMB level of care. For patients responding to chemotherapy, either IFRT or an additional 4-6 cycles of chemotherapy followed by RT is also PMB level of care (Engert, 2003; Advani et al., 2015).

6.1.3 Management of advanced stage disease

- In contrast to early-stage disease where the long-term cure exceeds 90%, only approximately 65% to 75% of patients with advanced-stage Hodgkin will remain disease free at 10 years (Carde et al., 2016; Merli et al., 2016; Engert, 2019)
- Advanced-stage HL is usually treated with chemotherapy alone, with additional RT limited to patients with residual disease after chemotherapy.
- For older adults with advanced disease, chemotherapy with or without RT is PMB level of care.
- For the ABVD regimen, a PET-CT scan follows treatment with 2-4 cycles of ABVD. If the PET-CT scan is negative, patients can be treated with an additional 4 cycles; and if the PET-CT scan is positive, an individualized treatment plan should be developed (Hoppe et al., 2020).
- To improve outcome in advanced HL, the German Hodgkin Study Group (GHSG) developed the escalated BEACOPP regimen. Dose-escalated BEACOPP, while yielding superior treatment outcome compared with conventional-dose chemotherapy, is associated with the risk of acute myelogenous leukaemia/myelodysplasia and infertility (Diehl et al., 2003). In North America, these toxicity concerns have curtailed the wider use of BEACOPP as a standard regimen (Edwards-Bennett et al., 2009).
- The choice of treatment is at the discretion of the treating provider. The following chemotherapeutic agents in combination are recommended as PMB level of care:
  - Bleomycin
  - Etoposide
  - Dacarbazine
  - Doxorubicin
  - Cyclophosphamide
  - Vincristine
  - Vinblastine
  - Procarbazine
  - Prednisone

6.1.4 Refractory or Relapsed Classical HL

- Relapses occur in 10–20% of patients with favourable features and early stage disease and 30–40% of patients with advanced disease (Radford et al., 2015).
- Achieving a negative PET-CT scan should be the goal of salvage therapy, irrespective of the regimen used. For most patients with refractory or relapsed HL, salvage chemotherapy is followed by autologous stem cell transplantation (ASCT), if PET-CT scan is negative (Schmitz et al, 2002).
- ASCT and allogenic transplant are PMB level of care when clinical criteria is met. ASCT is indicated in second-line or salvage therapy for relapsed/refractory HL as the last step of consolidation. ASCT (autologous transplantation) is the standard of care in relapsed/refractory HL and allogeneic transplantation is used in some cases (cHL as well as NLPHL)
- Salvage regimens such as dexamethasone/high-dose cytarabine/ cisplatin (DHAP), ifosfamide/gemcitabine/vinorelbine (IGEV) or ifosfamide/carboplatin/etoposide (ICE) are given and table 4 summarises the options which are PMB level of care (Josting et al., 2002; Santoro et al., 2007; Moskowitz et al., 2001).

- Ifosfamide/ mitoxantrone/ etoposide/ mesna (MINE), gemcitabine/ cisplatin/ methylprednisolone/ G-CSF (GEM-P) and etoposide/ methylprednisolone/ cytarabine/ cisplatin (ESHAP) are also PMB level of care as second line therapy
- Brentuximab vedotin (BV) is an anti-CD30 antibody conjugated to auristatin (MMAE), an antitubulin agent, and is highly effective for the treatment of relapse/refractory HL. In some patients, single-agent Brentuximab vedotin results in a negative PET-CT scan and may therefore be sufficient as salvage therapy prior to HDCT and ASCT.
- Bendamustine is an alkylating agent which has shown activity in relapsed HL, with an ORR of over 50% as a single agent in heavily pre-treated patients (Moskowitz, 2013).
- PD-1 is a key immune-checkpoint receptor that is rapidly expressed after T cell activation. Antibodies targeting PD-1 protein represent another novel treatment option for patients with multiple relapses (Topilian, 2012, Lipson, 2013).
- Brentuximab, Bendamustine and PD-1 inhibitors are not currently considered PMB level of care. Therefore, funding is at the discretion of the scheme.

Table 4: Summary of results with selected salvage chemotherapy regimens pre-ASCT

Salvage regimen	Population	Response rate (%)	Complete response rate (%)	Successful PBSC collection (%)[a]	Outpatient
DHAP (Josting et al., 2002)	102	89	21	96	No
ICE (Moskowitz et al., 2001)	65	85	26	86	No
IGEV (Santoro et al., 2007)	91	81	54	99	Yes
GVD (Bartlett et al., 2007)	91	70	19	NR	Yes
GDP (Kuruvilla et al., 2006).	34	62	10	97	Yes
ASCT - autologous stem cell transplant; DHAP - cisplatin, cytarabine, and dexamethasone; GDP - gemcitabine, dexamethasone, cisplatin; GVD - gemcitabine, vinorelbine, and pegylated liposomal doxorubicin; ICE - ifosfamide, carboplatin, and etoposide; IGEV - ifosfamide, gemcitabine, and vinorelbine; NR - not reported; PBSC - peripheral blood stem cell [a] High-dose chemotherapy (HDCT) followed by peripheral blood stem cell transplantation (PBSCT) is being increasingly used in patients with malignancies. There are no standard regimens for inducing mobilization of peripheral blood stem cells (PBSC) based on randomized comparisons. The table shows successful collection of PBSC using different salvage therapies.					

6.2 Treatment of Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)

6.2.1 Stage I without Risk Factors (Early stage)

- Patients with early stage NLPHL have an excellent prognosis with overall survival (OS) more than 90%. These patients can be carefully observed, and radiotherapy used when clinically indicated.
- Studies have shown that outcomes are comparable between patients receiving extended field radiotherapy (EFRT) and involved field radiotherapy (IFRT), and that the addition of chemotherapy for patients with early-stage disease does not improve outcomes compared to RT alone (Spinner et al., 2019).
- Radiotherapy (RT) is the mainstay of treatment and favourable clinical outcomes for patients with stages I to II treated with RT alone have been reported (Schlembach et al., 2002; Wilder et al., 2002; Wirth et al., 2005; Nogova et al., 2005; Chen et al., 2010)
- For early-stage patients with unfavourable risk factors, chemotherapy with 4–6 cycles of ABVD followed by 30 Gy IFRT is recommended (Eichenauer et al., 2018; Hoppe et al., 2018).
- Radiotherapy and ABVD is PMB level of care for early-stage NLPHL disease.

Table 5: Selected studies in early-stage NLPHL

Study design Author	N	Patient population	Treatment	PFS	OS	Median follow-up (years)
Retrospective Wirth et al., 2005	202	Stage I–II	RT	82%	83%	15
Retrospective Savage et al., 2011	51 35	Stage I–II	CT ± RT RT	93% 78%	93% 85%	5·7 18·6
Prospective Monteith et al., 2018	29	Stage I–IIA	CT EFRT ± CT	85% 70%	NR NR	10
Retrospective Mauz-Körholz et al., 2007	58	Stage IA resected	Observation	57%	100%	3·6
Prospective Appel et al., 2016	52	Stage IA resected	Observation	77%	100%	4·7

Study design Author	*N*	Patient population	Treatment	PFS	OS	Median follow-up (years)

CMT - combined modality therapy; CT - chemotherapy; EFRT - extended field radiotherapy; IFRT - involved field radiotherapy; N - number of patients; NLPHL - nodular lymphocyte predominant Hodgkin lymphoma; NR - not reported; OS - overall survival; PFS - progression-free survival; RT - radiotherapy.

6.2.2 Advance Stage Disease

- At the time of diagnosis, only 20–25% of patients with NLPHL present with advanced stage disease.
- The following drugs are recommended as PMB level of care in patients with advanced stage disease and may be used in several combinations at the discretion of the treating provider.
    - Rituximab (in combination therapy for NLPHL and not as monotherapy)
    - Doxorubicin
    - Bleomycin
    - Vinblastine
    - Dacarbazine
    - Cyclophosphamide
    - Adriamycin
    - Vincristine
    - Prednisone

6.2.3 Follow up after completion of treatment

- Follow-up in Hodgkin lymphoma is focused on detecting disease relapse and late treatment toxicities. However, there is paucity of data on the follow up and monitoring of late effects of patients with classical Hodgkin lymphoma following completion of treatment.
- There is no consensus about the frequency of follow up and thus follow up schedule for patients should be individualized and influenced mainly by the patient's clinical circumstances.
- Clinical history, examination and laboratory safety tests should be conducted every three to six months for the first 1 – 2 years and thereafter 6 to 12 months until year 3 and then annually for up to 5 years after completion of treatment.
- For patients in whom complete remission status is uncertain, as well as those displaying clinical warnings or signs of relapse, repeat imaging of sites initially involved as well as surveillance of the chest and abdomen should be conducted. Chest imaging and PET-CT scan should be conducted every 6 to 12 months during the first 2 – 3 years or as clinically indicated at the discretion of the treating physician. Follow-up imaging does not translate into an improvement in survival (Gandikota et al., 2015). For patients who achieved a complete metabolic response on treatment that is verified on PET-CT, repeat imaging is not indicated.
- Patients who underwent radiation therapy, and especially those with smoking history, late surveillance with chest X-ray may be indicated. Likewise, breast cancer surveillance is indicated in women.

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