



Primary mediastinal B-cell lymphoma (PMBCL): The LYSA pragmatic guidelines

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ABSTRACT

Primary mediastinal B-cell lymphoma (PMBCL) is a distinct subtype of large B-cell lymphoma with unique clinical, histopathological, and molecular characteristics. Despite its aggressive nature, PMBCL has a high cure rate when managed appropriately. Advances in the understanding of PMBCL biological characteristics, coupled with improvements in diagnostic tools and therapeutic approaches, have significantly improved patient outcomes in recent years. In this article, we present a set of pragmatic guidelines developed by the Lymphoma Study Association (LYSA) for the management of PMBCL. These guidelines address key aspects of diagnosis, staging, response evaluation, and treatment, integrating the latest evidence from clinical trials, expert consensus, and real-world practice. The aim of the guidelines is to provide clinicians with a clear, practical framework to optimize care for patients with PMBCL, ensuring that the best available evidence is translated into clinical practice.

1. Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is a rare and aggressive subtype of mature large B-cell lymphoma (LBCL) that is clinically and biologically distinct from diffuse large B-cell lymphoma (DLBCL). PMBCL has been recognized as a separate entity since the 2001 World Health Organization classification [1]. PMBCL accounts for approximately 5–10 % of LBCL cases and affects mostly young female patients (median age 37 years) [2]. The cell of origin of PMBCL is thought to be a thymic B lymphocyte, which explains the unique clinical presentation of this lymphoma. PMBCL typically involves the anterior-superior mediastinum (thymic niche), and affected individuals may present with local symptoms such as superior vena cava syndrome (SVCS), cough, or dyspnea. Most studies have shown a favorable prognosis for PMBCL, with a 5-year survival rate exceeding 80 % [3–6]. However, a subset of 10–15 % of patients experience refractory disease or relapse, requiring subsequent lines of therapy. Several questions remain unresolved: (i) Does dose intensity improve outcomes in the frontline setting? (ii) Is consolidation radiotherapy (CRT) beneficial? (iii) What are the optimal strategies and regimens for managing refractory disease?

Owing to its rarity, prospective randomized studies in PMBCL are scarce, leading to variability in management practices across countries and expert centers. The Lymphoma Study Association (LYSA) presents consensus guidelines that integrate the best available evidence-based data, expert opinions from the field, and widely adopted practices in clinical settings. The levels of evidence and grades of recommendations have been established using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [7,8].

2. Diagnosis criteria

2.1. Required sample types and clinicopathological correlation

Core needle biopsy (CNB) is now widely used for the diagnosis of lymphoma. For PMBCL, surgical biopsies are preferred whenever feasible, as they can provide a more accurate diagnosis by minimizing the risk of crushing artifacts and ensuring the collection of adequate tissue samples for histological and molecular analyses [9]. However, the urgency of achieving a timely diagnosis and the technical challenges associated with surgery for bulky mediastinal masses may necessitate alternative approaches in certain cases. Surgical mediastinal biopsy, for

example, requires general anesthesia and the ability to lie supine, which may not be possible, particularly in cases of SVCS. Furthermore, surgical biopsy is associated with longer healing times and a greater risk of postoperative complications, particularly when corticosteroids and chemotherapy need to be introduced promptly. While CNB remains an option depending on local availability and institutional expertise, specific precautions should be taken to ensure its effectiveness. Collaboration with the radiologist performing the procedure is essential to ensure that the biopsy needle is of an appropriate gauge (14 G) and that sufficient cores are obtained (at least two formalin-fixed paraffin-embedded [FFPE] samples, with more if possible). In centers equipped for advanced analyses, fresh tissue samples should also be collected for cytogenetic studies. Additionally, when adequate material is available, freezing a portion of the sample may be considered in specialized centers for scientific purposes. For CNB, placing a single core in each FFPE block is recommended to optimize tissue preservation and analysis.

When biopsies are performed on superficial lymph nodes (e.g., cervical, axillary, or supraclavicular nodes), it is crucial to inform the pathologist about the presence of a mediastinal mass, if known. Without this information, PMBCL could be misclassified as DLBCL, as mediastinal involvement is a key diagnostic feature. Clear communication between the clinician and the pathologist is therefore essential to ensure an accurate diagnosis of PMBCL.

2.2. Morphology and immunophenotype

PMBCL is characterized by a diffuse growth pattern often accompanied by varying degrees of fibrosis. This fibrosis can result in a crushed appearance and/or the virtual compartmentalization of tumor cells, which may complicate histological evaluation [9,10]. The neoplastic cells are typically medium to large in size and exhibit round, multilobated, or pleomorphic nuclei and a clear or slightly basophilic cytoplasm [11]. The microenvironment often includes a polymorphic reactive leukocyte population including lymphocytes, histiocytes, eosinophils, and plasma cells, adding further complexity to the histological landscape [11].

PMBCL expresses a range of B-cell lineage antigens, including CD19, CD20, CD22, and CD79A, as well as transcription factors such as BOB1, OCT2, and PAX5 [12]. The expression of a mature B-cell phenotype is a critical diagnostic criterion (Table 1), although CD10 expression has been described in 20–30 % of cases [3,12,13]. Immunohistochemistry for CD23 and CD30 (staining typically weak and heterogeneous) is essential in patients with suspected PMBCL, as these markers are highly sensitive (expressed in more than 70 % of cases) [1,11,14]. The expression of PDL1 and PDL2, observed in approximately 78 % and 50 %

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of cases, respectively, is also highly indicative of PMBCL, and the inclusion of these markers in the immunohistochemistry panel is highly recommended [11,15–17]. The inclusion of MAL and CD200 can increase the accuracy of the diagnostic panel, but the routine use of anti-MAL antibodies is limited by technical challenges and interpretation difficulties [10,13]. CD15 expression, although rare ($\approx 6\%$), may be observed, with a perinuclear dot-like staining pattern [18,19]. Importantly, Epstein–Barr virus (EBV) positivity, determined via EBV-encoded small RNA (EBV encoding region [EBER]) *in situ* hybridization, should prompt reconsideration of the diagnosis [20]. While rare cases of EBV-associated PMBCL have been reported, this diagnosis should be made cautiously and supported by molecular test results [11,21].

2.3. Contribution of molecular tools and integrated diagnosis

2.3.1. Cytogenetics - karyotype and fluorescence in situ hybridization (FISH)

Certain cytogenetic abnormalities, such as *CIITA* rearrangements, *REL* amplification, and copy number abnormalities (CNAs) or rearrangements of *PDL1* and *PDL2*, are highly specific to PMBCL. Karyotype analysis performed on short-term, mitogen-free cultures of biopsy material is feasible and often more informative in PMBCL than in classical Hodgkin lymphoma (cHL). Cytogenetic profiles typically reveal hyperdiploid and complex clones, with frequent gains of chromosome 9, often in the form of isochromosome 9p. Commercially available metaphase FISH probes, including dual-color probes for *PDL1/PDL2* and *CIITA*, as well as *REL* break-apart probes, can confirm (i) gains or amplifications of the 9p24 region, taking ploidy into consideration; (ii) translocations involving *PDL1*, *PDL2*, and/or *CIITA* and detecting translocation partners, including immunoglobulin (Ig) genes; and (iii) 2p16 (*REL*) amplifications. Interphase FISH can be performed on cytogenetic pellets or FFPE tissue sections. Detection of *CIITA* rearrangements is straightforward in routine practice and highly suggestive of a PMBCL diagnosis. However, the application of this technique is often limited by two main

factors: (i) the presence of significant crush artifacts and fibrosis and (ii) moderate sensitivity, with rearrangements detected in only 32–53 % of cases [10,11,22,23]. Importantly, *CIITA* rearrangements are not exclusive to PMBCL; they are observed in approximately 15 % of cHL cases and 27 % of mediastinal greygray zone lymphomas (MGZLs) [22]. The investigation of abnormalities in the *JAK2/PDL1/PDL2* locus at 9p24.1 via interphasic FISH is another useful diagnostic tool [16,24]. Conversely, other rearrangements commonly observed in DLBCL, such as *BCL2*, *BCL6*, and *MYC* rearrangements, are rare or absent in PMBCL [12].

2.3.2. Next-generation sequencing (NGS) and gene expression profiling (GEP)

The molecular features of PMBCL are characterized by the deregulation of the NF- κ B and JAK/STAT signaling pathways, as well as the activation of various immune escape mechanisms [11,16]. The most commonly observed pathogenic variants occur in the genes *SOC1* (60–91 %), *GNA13* (47–53 %), *STAT6* (33–58 %), *IGLL5* (56 %), *CD58* (20–48 %), *B2M* (36–67 %), *ITPKB* (40–64 %), *NFKBIE* (22–49 %), *TNFAIP3* (30–60 %), *ZNF217* (36–37 %), *XPO1* (24–37 %), *IL4R* (24 %) and *PTPN1* (20 %) [10,11,16,25–29] (Table 2).

PMBCL has a distinct GEP signature that closely resembles that of nodular sclerosis cHL but significantly differs from that of LBCL [5,20,27,30,31]. GEP is a reliable, rapid, and cost-effective method to differentiate PMBCL (with high expression of *IL4I1*, *CD23*, *CD30*, *MAL*, *CD95*, *CD71*, *FGFR1*, *JAK2*, *TRAF1*, *STAT6*, *PDL1* and *PDL2*) from other types of lymphoma using RNA extracted from FFPE samples [10,31,32], making it accessible for integration into routine diagnostic workflows. When used alongside conventional histological evaluation, GEP or NGS increases diagnostic accuracy, helping pathologists identify PMBCL cases with greater precision [33–35]. Efforts should be made to systematically incorporate at least one of these molecular tools into standard histopathological diagnostic practices to optimize the diagnosis and classification of PMBCL. NGS of DNA in FFPE samples is often preferred over

Table 1
Recommended methods for the diagnosis of PMBCL.

		Advised	Recommended	Commentary
Preanalytic phase	Surgical biopsy	X		Core needle biopsy (CNB) may be considered based on local availability, the urgency of the situation, and the risk associated with general anesthesia (e.g., superior vena cava syndrome). CNB requires large-caliber needles (14 G) and at least two FFPE biopsy samples, preferably more if feasible.
	Plasma banking at diagnosis	X		If available
	Sending a fresh sample for cytogenetic analysis	X		If available
	Cryopreservation of a fragment	X		In specialized centers, for scientific purposes
Histological analysis	At least 2 B-cell markers at diagnosis		X	At least two B-cell markers among CD20, CD79a, PAX5, CD19, and OCT2.
	CD30 immunohistochemistry		X	Weak and heterogeneous staining is expected.
	CD23 immunohistochemistry		X	Weak and heterogeneous staining is expected
	EBER <i>in situ</i> hybridization		X	Negativity is expected
Molecular tests	FISH <i>PDL1/PDL2</i> <i>CIITA</i> <i>REL</i>	X		If available, FISH can be a useful tool to support the diagnosis of PMBCL
	FISH <i>BCL2</i> and/or <i>BCL6</i>	X		In cases of uncertainty with follicular lymphoma
	Molecular tests (NGS or GEP)		X (*)	Depending on local availability and expertise
	Plasma circulating tumor DNA banking	X		If available

Abbreviations: PMBCL: primary mediastinal B-cell lymphoma; CNB: core needle biopsy; CD: cluster of differentiation; FFPE: formalin-fixed paraffin-embedded; FISH: fluorescence in situ hybridization; NGS: next-generation sequencing; GEP: gene expression profiling; G: gauge; EBER: Epstein–Barr encoding region.

*: In cases where initiating treatment is urgent (particularly in the context of superior vena cava syndrome) and the diagnosis of PMBCL is highly probable on the basis of histological findings, molecular analyses may be deferred to a later stage. An initial pathology report may include only histological analysis results, followed by a supplementary report incorporating the results of molecular techniques.

Table 2
Genes frequently mutated in PMBCL.

Gene	Prevalence of somatic mutations	Pathway/role(Source: GeneCards database)	Main reference (s)
<i>SOCS1</i>	60–91 %	Negative regulation of cytokines <i>JAK/STAT</i> pathway	[207,208]
<i>B2M</i>	36–67 %	Presentation of peptide antigens to the immune system	[207,209]
<i>ITPKB</i>	40–64 %	Cellular signaling	[207,210]
<i>CD58</i>	20–48 %	Costimulatory receptor; immune evasion of tumor cells	[28]
<i>STAT6</i>	33–58 %	Signal transduction and activation of transcription. IL4- and IL3-mediated signaling	[207,211]
<i>IGLL5</i>	56 %	Immunoglobulin lambda-like polypeptides	[207]
<i>TNFAIP3</i>	30–60 %	Cytokine-mediated immune and inflammatory responses; NF-kappa B pathway	[207,210]
<i>NFKBIE</i>	22.7–49 %	NF-kappa-B pathway; inhibits binding of NF-kappa-B p50-p65 and p50-c-Rel complexes to DNA	[207,212]
<i>GNA13</i>	47–53 %	Promotes tumor cell invasion and metastasis by activating the RhoA/ROCK signaling pathway	[207,210]
<i>IL4R</i>	24 %	Inhibits IL4-mediated cell proliferation and IL5 upregulation by T cells	[213]
<i>ZNF217</i>	36–37 %	epigenetic modifier	[28,29]
<i>XPO1</i>	24–37 %	Nuclear export; control of several cellular processes by controlling the localization of cyclin B, MAPK, and MAPKAP kinase 2	[214]
<i>PTPN1</i>	20 %	Cell growth, differentiation, mitotic cycle, and oncogenic transformation	[215]

Abbreviations: PMBCL: primary mediastinal B-cell lymphoma; SOCS1: suppressor of cytokine signaling 1; B2M: beta-2-microglobulin; ITPKB: inositol-trisphosphate 3-kinase B; CD58: cluster of differentiation 58; STAT6: signal transducer and activator of transcription 6; IL: Interleukin, IGLL5: immunoglobulin lambda-like polypeptide 5; TNFAIP3: tumor necrosis factor alpha-induced protein 3; NFKBIE: nuclear factor of kappa light polypeptide gene enhancer in b cells inhibitor epsilon; GNA13: guanine nucleotide-binding protein subunit alpha-13; IL4R: interleukin 4 receptor; XPO1: exportin 1; PTPN1: protein tyrosine phosphatase, non-receptor type 1.

RNA-based GEP because of its greater accessibility. In patients for whom initiating treatment is urgent (particularly in the context of SVCS) and the diagnosis of PMBCL is highly probable on the basis of histological findings, molecular analyses may be deferred to a later stage. An initial pathology report may include only histological analysis results, followed by a supplementary report incorporating the results of molecular techniques.

2.3.3. Circulating tumor DNA (ctDNA)

Deep sequencing of ctDNA is particularly valuable in PMBCL, where obtaining biopsy samples for molecular analysis is often challenging. When preanalytical conditions are meticulously followed, the sensitivity of mutation detection from ctDNA ranges from 70 % to 98 %, as reported in recent studies [36–40]. Each variant identified at diagnosis can serve as a biomarker for monitoring minimal residual disease during treatment by tracking PMBCL-associated mutations, particularly when rebiopsy is not feasible [41].

2.4. Differential diagnoses

The differential diagnoses of PMBCL include MGZL, DLBCL not otherwise specified (DLBCL-NOS), follicular lymphoma (FL), and cHL (Table 3). PMBCL, cHL, and MGZL share a common thymic B-cell origin, leading to overlapping clinical and molecular features, which can make

distinguishing these entities challenging, particularly as any of these subtypes may occur in the same patient, either sequentially or simultaneously (Figure 1). The criteria favoring MGZL over PMBCL include loss of the B-cell program along with strong and diffuse CD30 or CD15 positivity. Conversely, cHL is differentiated from PMBCL by i) partial or complete loss of CD45 and the B-cell program; ii) diffuse and strong CD30 expression; and iii) diffuse and strong CD15 expression [18,20]. Surgical rebiopsy is recommended to obtain a definitive diagnosis in cases of doubt. Clinical presentation plays a key role in the diagnosis of DLBCL-NOS, as affected patients often present with widespread extra-thoracic disease rather than mediastinal confinement (Figure 1). Diffuse EBV positivity in B cells supports the diagnosis of EBV+ DLBCL instead of MGZL or PMBCL. The expression of CD30, CD23, MAL, CD200, or PDL1/2 supports PMBCL diagnosis, but the use of molecular testing is crucial in these cases.

FL can mimic PMBCL because of overlapping features such as a sclerotic background or the expression of CD30 and CD23. Integration of clinical data, the use of other germinal center markers, FISH techniques to detect *BCL2* and/or *BCL6* rearrangements and molecular sequencing can further differentiate these entities, with mutations in genes such as *KMT2D* (79 %), *CREBBP* (67 %), *TNFRSF14* (46 %), and *BCL2* (40 %) being highly associated with FL [42,43]. *STAT6* mutations are also frequently found in t(14;18)-negative diffuse FL [44].

Finally, EBV positivity in cells with a "Hodgkin-like" morphology supports a cHL diagnosis over PMBCL or MGZL (Figure 1) [13]. Recent evidence suggests that cases exhibiting PMBCL-like features outside the mediastinum should be classified as DLBCL-NOS. Further investigation of the existence of extremely rare instances of true "extramediastinal PMBCL" are still required [45,46].

2.5. Expert point of view

- Whenever feasible, surgical mediastinal biopsy is preferred, as it minimizes the risk of crushing artifacts and ensures the collection of sufficient material for accurate histological diagnosis and comprehensive molecular analyses. However, this approach must be balanced against the increased risks associated with the surgical procedure. When surgical biopsy is not a viable option, core needle biopsy serves as a suitable alternative, provided it is performed by an experienced radiologist with a needle of an appropriate gauge (14 G) and an adequate number of cores is obtained (at least two FFPE samples, with more if possible) (IV, B).
- Although rare cases of EBV-associated PMBCL have been reported, this diagnosis should be made with caution, and strong evidence is required, ideally confirmed through the use of molecular techniques (IV, A).
- An expert pathological review, supported by an integrated diagnostic approach combining clinical presentation, histological analysis and confirmatory molecular testing — depending on local availability and expertise — is recommended for accurate diagnosis. NGS of DNA in FFPE samples is often preferred over RNA-based GEP (IV, A) because of its greater accessibility.

3. Initial presentation, staging, and early complications

3.1. Presentation

At diagnosis, PMBCL typically manifests as a large mediastinal mass with bulky disease—usually defined as a mass greater than 10 cm in diameter—observed in 50–70 % of cases [35,47–49]. Subdiaphragmatic lymph node involvement and extranodal spread are less common. Owing to local invasion of the anterior mediastinum, pleural or pericardial effusions are observed in 30–40 % of patients [12], whereas SVCS occurs in 20–40 % of patients [50]. Pleural or pericardial effusion has been described as being associated with shorter survival, but the proposed PMBCL-dedicated international prognostic index (PMBIPI),

Table 3
Key features of differential diagnoses for PMBCL.

	PMBCL	cHL	MGZL « PMBCL-like »	DLBCL-NOS	EBV+ DLBCL	FL
Thymic B-cell origin	Yes	Yes	Yes	No	No	No
CD30 expression	Weak and heterogeneous (common)	Strong/diffuse	Strong/diffuse	Variable	Possible	Possible
CD15 expression	Rare	Diffuse/strong	Strong/diffuse	Rare	Rare	Rare
CD45 expression	Present	Partial/complete loss	Variable	Present	Present	Present
Other markers/features	Expression of CD23, MAL, CD200, PDL1/2	Inflammatory backgroundLoss of B-cell program in Hodgkin-cellsEBV positivity in Hodgkin-cells supports diagnosis	Loss of B-cell program in IHC	Often extrathoracic involvement	Diffuse EBV positivity in > 80 % of B cells	Immunophenotype compatible with a germinal-center B-cell originCan mimic PMBCL due to overlapping features like sclerotic background or expression of CD30 and CD23.
Contribution of molecular tests and integrated diagnosis	Cytogenetics/ FISH	Gains of 9p24.1 including <i>PDL1</i> and <i>PDL2</i> (50–70 %) <i>CIITA</i> rearrangement (32–53 %)	<i>CIITA</i> rearrangement (15 %)	<i>CIITA</i> rearrangement (27 %)	<i>MYC/BCL2/BCL6</i> rearrangements	<i>BCL2/BCL6</i> rearrangements
	Next-generation sequencing (NGS) or gene-expression profiling (GEP)	Recommended for definitive diagnosis: NGS or GEP with PMBCL-associated features, as previously described	Similar to PMBCL	Similar to PMBCL	Different according to the molecular subtype of DLBCL	Recurrent mutations activating the oncogenic JAK-STAT and NOTCH pathways
Definitive diagnosis		Requires integration of clinical data, histology and molecular techniques	Surgical rebiopsy recommended in cases of doubt	Surgical rebiopsy recommended in cases of doubt	Requires integration of clinical data, histological examination findings and molecular test results	Absence of inborn or acquired immunodeficiency or a history of lymphoma and exclusion of other EBV-related lymphomas/ lymphoproliferative disorders

Abbreviations: PMBCL: primary mediastinal B-cell lymphoma; cHL: classical Hodgkin lymphoma; MGZL: mediastinal grey zone lymphoma; DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified; FL: follicular lymphoma; EBV: Epstein–Barr virus; MAL: myelin and lymphocyte protein; PDL1/2: programmed death-ligand 1/2; FISH: fluorescence in situ hybridization; CIITA: class II, major histocompatibility complex, transactivator. KMT2D: lysine methyltransferase 2D; CREBBP: CREB binding protein; TNFRSF14: tumor necrosis factor receptor superfamily member 14; BCL2: B-cell lymphoma 2; BCL6: B-cell lymphoma 6; MYC: B-cell lymphoma 2; EZH2: enhancer of best homolog 2; IHC: immunohistochemistry; JAK: Janus kinases; STAT: signal transducer and activator of transcription; NOTCH: neurogenic locus notch homolog protein; STAT6: signal transducer and activator of transcription 6.

which integrates these factors, which integrated those factors [51], remains rarely used due to the lack of independent validation. Notably, diagnostic analysis of pleural effusions using cytology after cytocentrifugation, flow cytometry, or cytopathology on a cytoblock may help determine whether the pleural involvement is reactive or specifically related to lymphoma [52], potentially leading to a change in lymphoma staging. Trans-thoracic echocardiography (TTE) should be performed systematically to assess the impact of pericardial effusion and the risk of tamponade. Central nervous system (CNS) involvement is rare in PMBCL, reported in fewer than 3 % of cases [3,53]. Currently, no dedicated predictive score exists for assessing the risk of CNS relapse in patients with PMBCL. By analogy to DLBCL, the CNS-International Prognostic Index (IPI) score can be applied [54–56]. In patients with high CNS-IPI scores [5,6], lumbar puncture and cerebrospinal fluid analysis—including conventional cytology and flow cytometry—are recommended for evaluating subclinical CNS disease [57].

3.2. Staging with positron emission tomography (PET) via 2-[18 F]-fluorodeoxyglucose (FDG)

For the initial assessment of mediastinal masses, PET is valuable for guiding biopsy and can be performed before or after biopsy without

delaying patient management. PET is essential in the initial evaluation of PMBCL [6,58], as it offers detailed insights into the metabolic activity, size, and extent of the tumor while also enabling the monitoring of therapeutic response. In patients presenting with SVCS, a thoracic contrast-enhanced computed tomography (CT) scan is essential to assess the degree of vascular or airway compression and/or thrombosis. The PET report should include a staging assessment of lymph nodes and extraganglionic areas, such as pleural or pericardial effusions [59,60] and the maximum standardized uptake value (SUVmax) of the most metabolically active lesion. Prognostic parameters such as total lesion glycolysis (TLG) and total metabolic tumor volume (TMTV) can also be incorporated into the PET report, as elevated values have been linked to poorer progression-free survival (PFS) and overall survival (OS) [15, 60–62]. Although studies exploring additional tumor parameters, radiomic features, and artificial intelligence analyses are promising, these methods are not yet recommended for routine clinical use at this stage [63–65].

3.3. Expert point of view

- For the initial assessment of a mediastinal mass, we recommend the use of PET for staging before the start of treatment (III, A). In the case

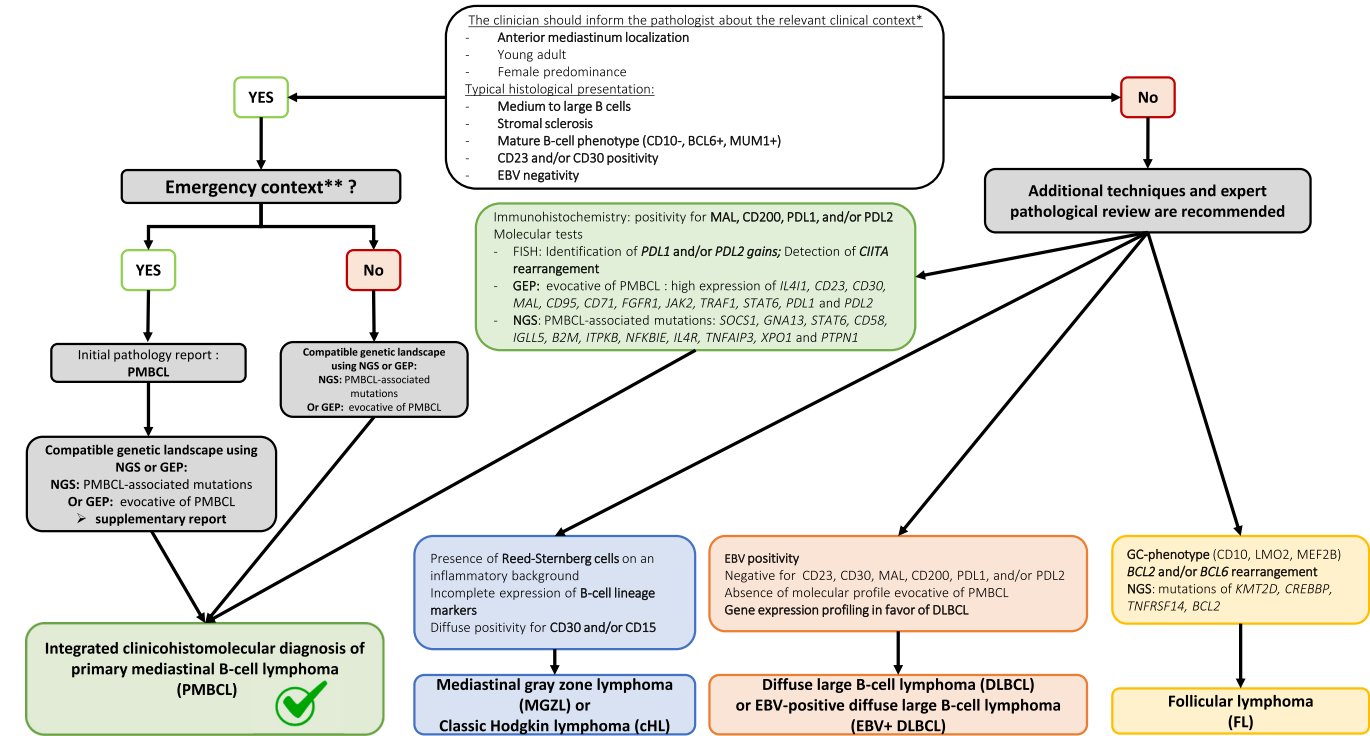


Fig. 1. Decision-making tree for B-cell lymphoma suggestive of PMBCL: Diagnostic approach and main differential diagnoses. * Effective communication between clinicians and pathologists is essential to ensure that pathologists are aware of the clinical context suggestive of PMBCL suspicion. ** In cases where initiating treatment is urgent (particularly in the context of superior vena cava syndrome) and the diagnosis of PMBCL is highly probable on the basis of histological findings, molecular analyses may be deferred to a later stage. An initial pathology report may include only histological analysis findings, followed by a supplementary report incorporating the results of molecular tests. Abbreviations: GEP: gene expression profiling; NGS: next-generation sequencing; EBV: Epstein–Barr virus; FISH: fluorescent in situ hybridization; DLBCL: diffuse large B-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma; MGZL: mediastinal gray zone lymphoma; cHL: classical Hodgkin lymphoma; FL: follicular lymphoma; GC: germinal center.

of SVCS, steroids may be initiated prior to the baseline PET examination.

- PET can be performed either before or after biopsy without delaying patient management (V, B).
- To evaluate local invasion, assess compression syndrome, and identify vascular thrombosis, the use of a contrast-enhanced thoracic CT scan is recommended (IV, C).
- The PET report should include a staging assessment according to the Ann Arbor classification and details regarding extraganglionic areas, including pleural and/or pericardial effusions (III, A), as well as the SUVmax of the entire examination (III, B).

3.4. Early complications

SVCS can be life-threatening and disrupt initial staging and standard therapeutic care. Admission to an intensive care unit [66], prompt use of corticosteroids, and sometimes emergency initiation of first-line immunochemotherapy may be required to achieve rapid resolution of SVCS [67,68]. PMBCL has specificities that differ from standard cancer-associated thrombosis guidelines [69–71]. Indeed, owing to vascular compression and an inflammatory state, PMBCL is associated with a high risk (~5–35 %) of thrombosis [3,4,72]. Low-molecular-weight heparins are the treatment of choice, offering easier management given the risk of chemotherapy-induced thrombocytopenia and the increased risk of bleeding during therapy [70,71,73]. Among thrombotic events, a significant proportion are associated with catheters, such as peripherally inserted central venous catheters (CVCs) or implanted ports. In cases of SVCS, the placement of a CVC should be delayed until symptom resolution and repeat imaging is performed. Although no randomized studies have demonstrated its benefit, prophylactic anticoagulation is considered a standard of care (SOC) in SVCS

[68], and therapeutic anticoagulation is recommended for patients with confirmed thrombosis [69,70,73,74]. For patients with significant pericarditis, a multidisciplinary discussion with a cardiologist is recommended before anticoagulation is initiated.

3.5. Expert point of view

- If SVCS is present, corticosteroid therapy should be initiated promptly, and emergency diagnostic biopsy should be considered (V, A).
- We recommend prophylactic anticoagulation for patients with SVCS or vascular compression (V, C), and therapeutic anticoagulation should be administered for patients with confirmed thrombosis (I, A).

4. First-line treatment

4.1. Dose-dense immunochemotherapy

Owing to its rarity, there is a lack of prospective randomized studies on PMBCL, and no consensus on optimal treatment has been clearly established. The young age of most patients should guide hematologists toward selecting a treatment strategy that offers the best chance of cure while minimizing long-term toxicities, such as secondary malignancies (SMs), cardiovascular complications, and gonadotoxicity.

Immunochemotherapy with CHOP-like regimens (Table 4) has become the SOC following the introduction of rituximab and remains the recommended practice in Europe [75,76]. Studies have revealed a 2-year PFS of approximately 70–80 % and a 2-year OS of 80–90 % with R-CHOP and R-CHOP-like treatments for PMBCL patients [59,77–80], although CRT was also incorporated in the therapeutic regimens in

Table 4
Total cumulative doses of key chemotherapy agents across different immuno-therapy regimens.

	DA-EPOCH-R	R-CHOP14	R-ACVBP induction and standard consolidation chemotherapy
Rituximab (number of cycles)	375 mg/m ² (x6)	375 mg/m ² (x6)	375 mg/m ² (x8)
Doxorubicin(mg/m ²)	240–396.8	300	300
Cyclophosphamide (mg/m ²)	3270–7447	4500	4800
Etoposide(mg/m ²)	1200–1986	0	1200
Intrathecal Methotrexate	No	No	Yes (x4)

Abbreviations: DA-EPOCH-R: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; R-ACVBP: rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; R-CHOP14: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, delivered every 14 days

many of these studies.

The findings of several studies from the prerituximab era suggested that dose-dense regimens, such as ACVBP [81] or V/MACOP-B [82], provided benefits over CHOP in patients with PMBCL. The National Cancer Institute (NCI) conducted a phase II trial of DA-EPOCH-R in PMBCL patients, featuring continuous administration, the addition of etoposide, individualized dose adjustments, and radiotherapy avoidance [83]. The outcomes were excellent, with a 5-year event-free survival (EFS) of 93 % and an OS of 97 %. These findings were reproduced in retrospective studies, which revealed a 2-year PFS of 81–93 % and a 2-year OS of 92–97 % with DA-EPOCH-R [4,62]. Other dose—dense regimens have also been evaluated in rare prospective trials or subgroup analyses. In the UK National Cancer Research Institute (NCRI) R-CHOP14 vs. 21 trial, a subgroup analysis of PMBCL patients revealed favorable results with R-CHOP, with a trend toward increased OS in the R-CHOP14 group compared with the R-CHOP21 group [80]. A pooled analysis of five prospective LYSA trials with 290 PMBCL patients demonstrated that R-CHOP14 and R-ACVBP significantly increased PFS and OS compared with R-CHOP21 [84]. Similarly, a large retrospective real-world LYSA study of 313 PMBCL patients revealed increased 3-year PFS with dose-dense regimens: 89.4 % with R-ACVBP and R-CHOP14

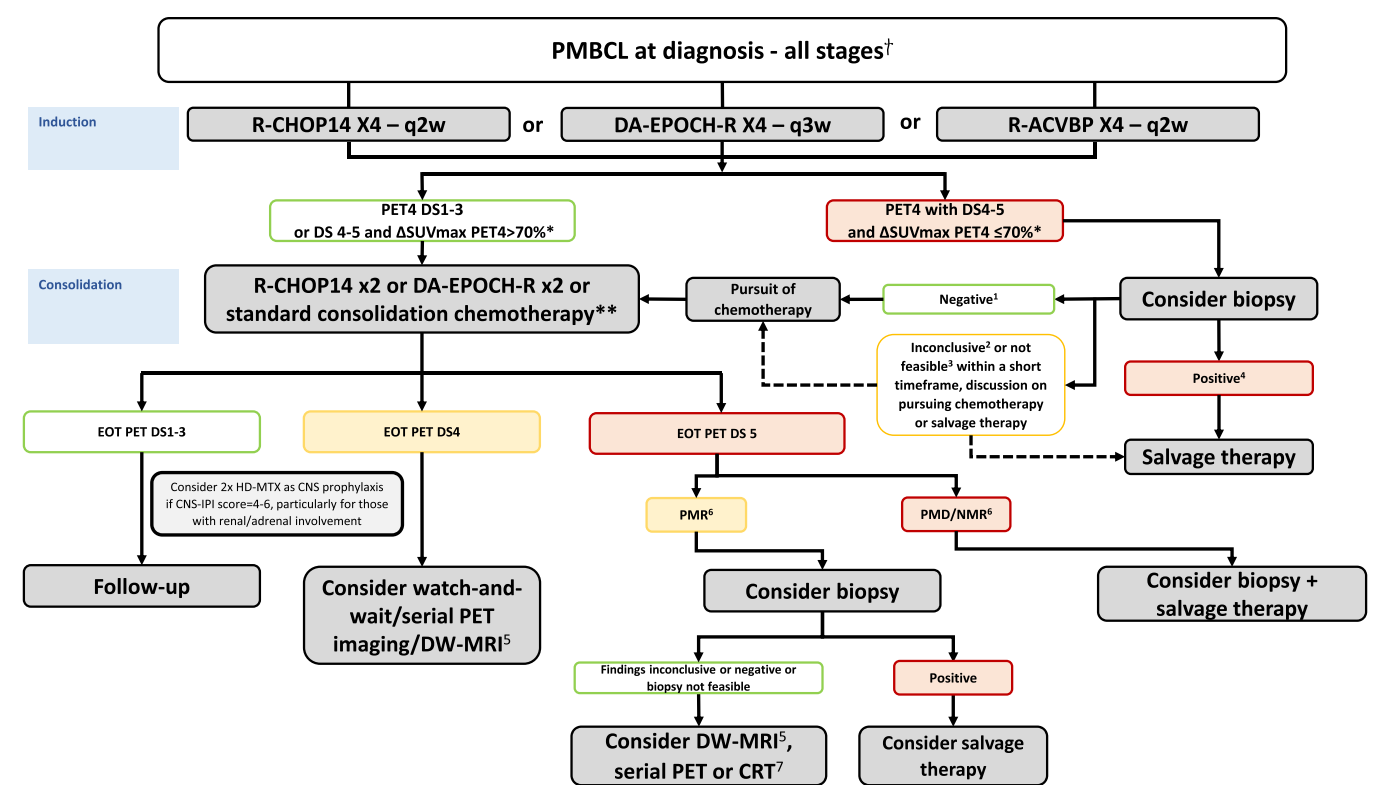


Fig. 2. Management of first-line treatment for PMBCL. 1 The biopsy sample is considered negative if the analysis reveals fibrosclerotic remodeling or polymorphic and/or resorptive inflammatory changes. 2 Biopsy samples containing necrotic tissue without viable cells or unaltered fibroadipose tissue are considered inconclusive. 3 If a biopsy is not feasible, a possible alternative in expert centers equipped with this technology is to use ctDNA from plasma to identify mutations associated with the PMBCL signature (SOCS1, GNA13, STAT6, CD58, IGLL5, B2M, ITPKB, NFKBIE, IL4R, TNFAIP3, XPO1 and PTPN1), which may indicate persistent lymphoma. 4 The biopsy sample is considered positive if lymphomatous proliferation is observed, as previously described. 5 If available. 6 Lugano response assessed in comparison with both the baseline PET and the interim PET4. 7 If the disease is localized. † To evaluate local invasion, assess compression syndrome, and identify vascular thrombosis, the use of contrast-enhanced thoracic CT is recommended in addition to PET. * In very rare cases where the baseline SUVmax is relatively low (<10), experts agree that the ΔSUVmax is not an appropriate parameter for assessing response, and the Deauville score (DS) is more suitable. **Standard consolidation chemotherapy (after R-ACVBP induction): 2x HD-MTX, 4x R-IFM-VP16, 2x subcutaneous cytarabine. Abbreviations: DA-EPOCH-R: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; R-ACVBP: rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; R-CHOP14: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, delivered every 14 days; ctDNA: circulating tumor DNA; PET: positron emission tomography; CT: computed tomography; HD-MTX: high-dose methotrexate; R-IFM-VP16: rituximab, ifosfamide, etoposide; ASCT: autologous stem cell transplantation; DS: Deauville score; CMR: complete metabolic response; PMR: partial metabolic response; PMBCL: primary mediastinal B-cell lymphoma; Q2w: every other week; Q3w: every three weeks; SUVmax: standardized uptake value maximum; ΔSUVmax PET4: change in SUVmax between baseline PET and PET performed after 4 cycles of immunochemotherapy; EOT: end of treatment; CNS: central nervous system; IPI: international prognostic index; CRT: consolidation radiotherapy; DW-MRI: diffusion-weighted magnetic resonance imaging; PMR, partial metabolic response; NMR, no metabolic response; PMD, progressive metabolic disease.

versus 74.4 % with R-CHOP21 [3]. A multicenter US retrospective study revealed higher complete response (CR) rates with DA-EPOCH-R than with R-CHOP21, although no significant differences in PFS or OS were observed [85]. Data from a Swedish registry also confirmed the efficacy of dose-dense regimens (R-CHOP14, R-HyperCVAD, R-CHOEP14, and DA-EPOCH-R), with a 5-year OS of 88 % [86]. Finally, a recently published meta-analysis [87] compared dose-dense chemotherapy to standard approaches (R-CHOP21/CHOP-21) in 4068 patients. The analysis revealed an 8 % OS benefit for the dose-dense group ($p < 0.01$), with significantly less radiation exposure. These results were consistent when only the rituximab-containing regimens were analyzed.

Among dose-dense immunochemotherapy regimens, no single regimen has demonstrated superiority over the others (Figure 2). Compared with R-CHOP14, R-ACVBP is associated with greater hematological and mucosal toxicity. If vindesine is unavailable, a substitution with vincristine at 1.5 mg on Days 1–5 could be considered [88]. Administration in expert centers is required for DA-EPOCH-R because of the complexity of continuous 24-h chemotherapy delivery, dose-density adjustments, costs, and the need for repeated hospitalizations (Table 4). Debulking chemotherapy with cyclophosphamide, vincristine, and prednisone (COP) usually has no role in the management of PMBCL, especially in patients with bulky disease. In rare cases of elderly PMBCL patients (>60 years), R-CHOP21 may be considered, as dose-dense regimens could be more toxic in this population on the basis of analogous data from LBCL patients [89].

4.2. Expert point of view

- We recommend the use of dose-dense immunochemotherapy regimens: R-CHOP14, DA-EPOCH-R, or R-ACVBP (III, B). The induction phase should comprise four cycles of one of these regimens.
- Given the complexity of the diagnosis and the time required to obtain molecular testing results, in cases of diagnostic uncertainty between DLBCL and PMBCL, dose-dense regimens should be initiated and subsequently adjusted if the diagnosis of PMBCL is not confirmed (V, B).

4.3. CNS prophylaxis

CNS relapse is associated with a poor prognosis [53]. Nearly all CNS relapses reported in patients with PMBCL have been exclusively parenchymal, a distinctive feature for which further investigation is warranted [55,59,90,91]. While the CNS-IPI is commonly used to assess risk, evidence suggests that CNS involvement may be more closely linked to kidney and/or adrenal involvement [55,56]. Importantly, no treatment has been proven effective in reducing the incidence of CNS relapse in patients with DLBCL [92]. If intravenous high-dose methotrexate (HD-MTX) is considered for CNS prophylaxis, the findings of recent retrospective studies in patients with DLBCL indicate that deferring HD-MTX administration until after the completion of immunochemotherapy could reduce toxicity and avoid delays in immunochemotherapy [93,94]. In the international phase II trial of DA-EPOCH-R involving PMBCL patients younger than 18 years, three cases of CNS parenchymal relapse were reported among 46 patients [90]. A notable difference compared with a historical control group, in which no CNS relapses were reported, was the absence of HD-MTX in the regimen, suggesting its potential role in preventing CNS involvement.

4.4. Expert point of view

- CNS prophylaxis, consisting of two cycles of HD-MTX administered at the end of treatment (EoT), may be considered for rare patients with a high CNS-IPI score, particularly those with kidney and/or adrenal involvement (V, C).

4.5. Frontline consolidation radiotherapy

PMBCL is a radiosensitive disease, and CRT has long been a SOC, either as systematic consolidation or for converting partial response (PR) to a CR [95]. Updated results from the NCI phase II trial with DA-EPOCH-R confirmed that this regimen eliminates the need for CRT, even in patients with a Deauville score of 4 (DS4) at the EoT PET [85]. Specifically, relapses occurred in only 1 of 57 patients with DS1–3, 1 of 17 patients with DS4, and 4 of 8 patients with DS5. Favorable outcomes have been reproduced in other DA-EPOCH-R studies, even in the DS4 EoT PET group [4,62].

All treatments except DA-EPOCH-R and R-ACVBP are frequently associated with CRT, although its true benefit remains uncertain. While some scientific societies still systematically recommend CRT [76], its potential side effects, particularly in this young patient population, and the good negative predictive value (NPV) of EoT PET have led several groups to adopt PET-guided CRT strategies. The IELSG-37 trial was designed to assess the benefit of CRT in patients with a complete metabolic response (CMR) (DS1–3) after immunochemotherapy [6]. The trial provides strong evidence that CRT can be safely omitted in these patients, with a 30-month PFS of 96.2 % in the observation arm and 98.5 % in the CRT arm (stratified hazard ratio [HR] 1.47; 95 % confidence interval [CI], 0.34–6.28).

For partial responders after the standard R-CHOP regimen, CRT may improve outcomes. In the British Columbia Cancer Study, patients with DS4 EoT PET, 72 % of whom received CRT, achieved a 5-year PFS of 87 %, which was comparable to the 91 % reported in patients with DS1–3 EoT PET [59]. In patients treated with R-MACOP-B, a PET-guided CRT strategy demonstrated equivalent disease-free survival rates (90.7 % in patients receiving CRT vs. 90 % in those who did not) [96]. For other dose-dense immunochemotherapy regimens, the benefit of CRT is less evident. In the retrospective LYSA study, only 5.4 % of patients received CRT, yet the outcomes were excellent [3]. Similarly, in a pooled analysis of prospective LYSA trials, none included CRT [84]. Analysis of real-world data from a Swedish registry also revealed similar outcomes in patients who received CRT compared with those who did not within a cohort of 172 patients [86]. In the Greek cohort ($n = 145$), 6 patients had a partial metabolic response (PMR), with DS5 at EoT after DA-EPOCH-R. Among them, 5 received CRT, all of whom converted to PET-negative and had a persistent CR [97]. However, these numbers are very small, and routine CRT for all patients with positive EoT PET could lead to significant overtreatment. Diffusion-weighted magnetic resonance imaging (DW-MRI) with apparent diffusion coefficient (ADC) measurement could provide additional information to help differentiate active disease from posttreatment changes by assessing tissue cellularity. Low ADC values are associated with greater cellular density, suggesting persistent viable lymphoma, whereas higher ADC values are more indicative of necrosis or fibrosis [98–102]. This technique may be particularly useful when rebiopsy is challenging or inconclusive. However, no validated ADC threshold exists, and motion artifacts can affect image quality and interpretation.

Therefore, for patients who achieve a PMR and DS5 at EoT, we recommend performing a rebiopsy and considering either CRT or surveillance with serial PET or DW-MRI if findings from the rebiopsy sample analysis are negative or inconclusive or if rebiopsy is not feasible.

4.6. Expert point of view

- We do not recommend CRT for patients who are good responders at EoT PET (CMR or PMR with DS 4) following dose-dense immunochemotherapy. For patients with DS 4, we recommend considering a watch-and-wait strategy with serial PET imaging or DW-MRI to monitor metabolic evolution and avoid unnecessary overtreatment (IV, B).

- CRT or serial PET or DW-MRI surveillance may be considered for patients who achieve a PMR with DS5 on EoT PET if findings from the rebiopsy sample analysis are negative or inconclusive or if rebiopsy is not feasible (V, B).

4.7. Consolidative autologous stem cell transplantation (ASCT)

In the rituximab era, the benefit of treatment intensification with ASCT in patients with PMBCL remains unclear because of the limited prospective data and the underrepresentation of PMBCL patients in clinical trials [103–105]. A recent subanalysis of patients with PMBCL (138 out of 670) included in the randomized phase III GAINED study, in which a PET-driven strategy was employed, revealed 2-year PFS and OS rates of 86.2 % and 93.2 %, respectively [106]. The rate of consolidation with ASCT was 10 percentage points higher in the PMBCL population than in the overall GAINED population (25 % vs. 15 %), reflecting a significantly higher rate of positive interim PET (iPET) findings.

ASCT is associated with considerable additional toxicity [107–109] and is not a standard approach in the frontline management of DLBCL. The excellent outcomes achieved with the DA-EPOCH-R regimen were obtained without the need for ASCT [4,83,85]. In a pooled analysis of five prospective LYSA trials including 290 PMBCL patients, the impact of consolidative ASCT was evaluated in responding patients (81 with ASCT vs. 184 without ASCT): no significant difference in OS was observed between the groups after a median follow-up of 42 months. Finally, in the recent IELSG37 trial, in which ASCT was not permitted, patients received various standard anthracycline-based immunochemotherapy regimens and achieved excellent outcomes, including a 30-month PFS of 96.2 % and a 5-year OS of 99 % in the observation arm [6].

4.8. Expert point of view

- Given the favorable outcomes achieved with dose-dense immunochemotherapy alone, we do not recommend consolidative ASCT in the frontline setting, regardless of the iPET results (III, B).

5. PET imaging to guide therapy

iPET and EoT PET images are challenging to interpret in PMBCL because of fibrosis and inflammatory phenomena in the mediastinum, which are associated with a risk of false-positive (FP) findings, e.g., residual uptake not associated with subsequent PFS events or residual uptake corresponding to negative findings in rebiopsy sample analysis (e.g., fibrosclerotic remodeling or polymorphic and/or resorptive inflammatory changes). Careful attention must be given when interpreting these images, and discussions among clinicians, radiologists and nuclear medicine specialists are essential in cases of uncertainty [110–112].

5.1. iPET

The predictive value of iPET remains controversial, with only a few studies specifically focusing on PMBCL. In some studies on iPET in patients with PMBCL, the PET response after three or four cycles of induction immunochemotherapy has been evaluated [35,103,113,114]. Therefore, this evaluation should ideally be performed after at least three cycles and preferably after four cycles. A study by Nagle et al. demonstrated that after only two cycles, 85 % of patients exhibited a positive PET with limited positive predictive value (PPV) [115]. iPET should be interpreted with caution, as DS4 often indicates FP findings [113]. DS5 is defined as a lesion with uptake more than 2 times the SUVmax in the normal liver and/or the appearance of new lesions [58,116]. The accuracy and PPV of iPET could be improved by reducing the SUVmax between the baseline PET and iPET after four cycles of immunochemotherapy, with shorter PFS for patients with $\Delta\text{SUVmax PET4} \leq 70\%$ [3,35,103]. In very rare cases where the baseline SUVmax is relatively low (<10), experts agree that the ΔSUVmax is not an

appropriate parameter for assessing response and that the DS is considered more suitable [103,117]. Notably, LBCL patients who achieve DS1–3 on iPET with a baseline SUVmax < 10 are considered to have a good prognosis, similar to patients with a $\Delta\text{SUVmax} > 70\%$ [118,119]. Patients with DS5 at iPET treatment demonstrated inferior PFS and reduced survival. [114]. A rebiopsy could help to distinguish between FP and persistent active disease. No study has clearly demonstrated the benefit of immediate (after 4 cycles of chemotherapy) or delayed salvage treatment (after EoT).

5.2. Expert point of view

- PET should be used to guide therapy. We recommend performing iPET after 4 cycles of immunochemotherapy (III, B).
- PET4 should distinguish patients who achieve a CMR (DS1–3) or good partial metabolic response (PMR) (DS4–5 with $\Delta\text{SUVmax PET4} > 70\%$) from those with progressive metabolic disease (PMD), no metabolic response (NMR) or an insufficient PMR (DS4–5 with $\Delta\text{SUVmax PET4} \leq 70\%$). Patients in the latter group should undergo rebiopsy, and if findings are positive (e.g., showing lymphomatous proliferation, as previously described), they should be referred for salvage treatment.
- Patients with negative rebiopsy findings may continue immunochemotherapy (V, B). Those with inconclusive rebiopsy findings (e.g., necrotic tissue or unaltered fibroadipose tissue) or when rebiopsy is not feasible within a short timeframe can be considered for either salvage therapy or the pursuit of immunochemotherapy (V, B).
- Good responders at PET4 (DS4–5 with $\Delta\text{SUVmax PET4} > 70\%$) should proceed to the consolidation phase with two cycles of R-CHOP14, DA-EPOCH-R, or standard post-R-ACVBP consolidation chemotherapy (III, B).

5.3. EoT PET

EoT PET should be performed at least six weeks after the last course of chemotherapy to reduce the risk of FP results [6,75]. Negative EoT PET findings, defined by DS1–3 [58,120,121], have an excellent NPV in PMBCL patients [122]. In studies of R-CHOP with or without CRT, NPV values ranging between 92 % and 97 % have been reported [59,123,124]. In the IELSG-26 study, the 5-year PFS for those achieving a CMR at EoT was 99 %, whereas it was 68 % for patients with positive EoT PET findings [121]. Similarly, the results were excellent in an NCI prospective study of 51 patients, as well as in a subsequent follow-up study involving 93 patients treated with dose-dense DA-EPOCH-R. These studies revealed 5-year EFS rates of 92 % and 80 % in patients with negative and positive EoT PET findings, respectively [83]. With this regimen, the NPV of EoT PET ranges between 95.7 % and 100 % [4,62,85].

In contrast, the PPV of EoT DS4–5, which represents approximately 30 % of patients, is low. A residual FDG-avid mediastinal mass, which may not indicate active disease, is often present at the EoT due to inflammation, fibrosis, or necrotic residual tissue [122]. In particular, DS4 are frequently FPs. The outcome of EoT DS4 patients is generally highly favorable [3,122], but the management of this situation remains debated among experts and depends on the type of induction treatment received. Management strategies may include CRT, DW-MRI, observation with serial PET, and a repeat biopsy if necessary [125]. If the mass shows minimal uptake above liver activity on visual inspection (DS4), observation without biopsy, along with follow-up imaging (serial PET and/or DW-MRI), is appropriate [6,126,127]. Using a serial PET imaging strategy for EoT-positive PET, Melani et al. reported a median SUVmax reduction rate of -0.006 per day, corresponding to a timeframe of 2.8 months to 1.1 years to reach a residual SUVmax less than or equal to that of a healthy liver (2–3.5), starting from an EoT SUVmax of 4–6 [85].

For patients who achieve a PMR but with DS5, rebiopsy is

recommended before any further treatment is discussed. Indeed, the outcomes for EoT DS5 patients are poor, with a 5-year PFS ranging from 22 % to 60 %, regardless of the first-line regimen used [4,59,62,121], suggesting that salvage treatment should be considered for patients.

Finally, rebound thymic hyperplasia (RTH) is a common occurrence triggered by stressors such as chemotherapy or radiotherapy. During treatment, the thymus atrophies but then regrows during the recovery phase. This rebound typically manifests within one year after the completion of chemotherapy and can persist for up to 4.5 years in adults [128,129]. Additionally, DW-MRI may help differentiate RTH from lymphoma relapse [130,131].

5.4. Expert point of view

- EoT PET should be performed at least six weeks after the final course of chemotherapy to reduce the risk of FP findings (I, A).
- A CMR is defined by DS1–3 (III, B). DS4 findings are frequently FPs (IV, B).
- For patients with positive EoT PET with DS4, we recommend a watch-and-wait approach with serial imaging (IV, B).
- For patients with positive EoT PET with DS5 and either PMD or NMR, which are assessed in comparison to both the baseline PET and iPET4, we recommend considering rebiopsy and referring the patient for salvage treatment.
- For patients with positive EoT PET with DS5 and a PMR, we recommend considering a rebiopsy. If findings from the rebiopsy sample analysis are positive, we recommend that the patient be referred for salvage treatment. If findings from the rebiopsy sample analysis are negative or inconclusive or if rebiopsy is not feasible, DW-MRI and serial PET may help to differentiate active disease from posttreatment changes or thymic rebound. Mediastinal CRT is also a viable option in this situation (V, B).

5.5. Follow-up after achieving a CMR at EoT

The data available for the PMBCL population are very limited. Therefore, follow-up is aligned with that of LBCL and CHL. For patients achieving a CMR at EoT, routine imaging surveillance is not recommended for the follow-up of those who remain asymptomatic, as per the Lugano consensus [58]. Surveillance scans are a source of anxiety, and the vast majority of relapses are detected outside scheduled surveillance imaging periods [132,133]. PET should be performed only if new clinical symptoms or signs indicative of relapse are present. Patients with LBCL who are event-free at 2 years have an OS comparable to that of the general population, highlighting the importance of focused disease monitoring during this early period [134]. The recommended follow-up should include clinical examinations and standard blood tests (complete blood counts [CBCs]) every 3–6 months for the first 2 years, followed by every 6–12 months for the next 3 years [135]. After 5 years of relapse-free follow-up, patients can be considered cured. Patients should be informed about potential long-term complications (e.g., cardiac toxicity and secondary cancers) to ensure timely medical evaluation if symptoms develop [136–139]. To detect cardiac toxicity from anthracyclines, an assessment of cardiac function via TTE can be proposed at 3–12 months, 3 years, 5 years, and every 5 years thereafter [140–143]. The recommended follow-up after mediastinal radiotherapy includes (i) a coronary CT scan (calcium score) at 5 years, with long-term cardiological follow-up [144,145]; (ii) in women, annual breast screening starting 8 years after the end of radiotherapy, consisting of a single oblique incidence mammogram without tomosynthesis, complemented by ultrasound and breast MRI [146]. From the age of 50 years, mammograms should be performed every 2 years; and (iii) thyroid stimulating hormone (TSH) testing should be performed at 1, 2, and 5 years if the neck was irradiated [147].

6. Management of relapsed/refractory (R/R) PMBCL

PMBCL relapse is predominantly an early event, with most cases occurring within one year after first-line therapy [15,148,149]. The therapeutic landscape has undergone a remarkable transformation with the introduction of anti-PD1 checkpoint inhibitors (CPIs) and chimeric antigen receptor (CAR)-T-cell therapies (Figure 3). Repeat biopsy is crucial, as relapses may present as a histologically related entity, such as CHL or MGZL. The cases of these R/R patients should be reviewed in multidisciplinary expert discussions, given the rarity and complexity of managing such situations. Additionally, options for fertility preservation should be discussed prior to potential therapeutic intensification.

6.1. Expert point of view

- Histological confirmation through rebiopsy is recommended before initiating second-line treatment (IV, A).

6.1.1. Conventional salvage chemotherapy

The salvage regimen for R/R PMBCL has historically consisted of platinum-based immunochemotherapy, with the later addition of rituximab, such as ICE (ifosfamide, carboplatin and etoposide), GDP (gemcitabine, dexamethasone, and cisplatin), or DHAX (dexamethasone, high-dose cytarabine, and cisplatin/carboplatin/oxaliplatin). These regimens have long been the SOC for R/R DLBCL [150,151]. However, salvage immunochemotherapy is associated with disappointing outcomes in R/R PMBCL. Although patients who undergo transplantation in response can achieve cure rates of 40–60 % [116–119], refractoriness to salvage ICT is common, with overall response rates (ORRs) as low as 25 % and 2-year PFS rates of 29 % [148, 152]. Therefore, treatment with immunochemotherapy can no longer be considered the SOC for R/R PMBCL. However, platinum-based immunochemotherapy can be used as bridging therapy before CAR-T-cell therapy, and ASCT remains an option for consolidation in the event of a subsequent response.

6.2. Expert point of view

- Platinum-based immunochemotherapy is no longer the preferred option for salvage treatment of R/R PMBCL (V, B).

6.3. CAR-T cells

Anti-CD19 CAR-T cells are approved for second-line treatment of LBCL with progression within one year after the completion of first-line immunochemotherapy on the basis of the phase III ZUMA-7 (axi-cel) and TRANSFORM (liso-cel) trials [153,154]. However, only liso-cel is currently approved by the Food and Drug Agency (FDA) and European Medicines Agency (EMA) for the second-line treatment of PMBCL (Figure 3), as TRANSFORM was the only study to include PMBCL patients (9 % of the cohort). Nevertheless, owing to the early availability of axi-cel in clinical practice, it has been widely used in the treatment of PMBCL, with real-world data confirming its activity in this patient population. Indeed, two real-world cohorts of 33 and 13 patients with PMBCL receiving axi-cel have been evaluated, with 2-year PFS and 1-year OS ranging from 54–64 % and 75–78 %, respectively [155,156]. In a larger cohort from an Italian registry of 70 patients with PMBCL receiving axi-cel, the CR rate, 1-year PFS, and 1-year OS were 65 %, 62 %, and 86 %, respectively [157]. In another cohort of 82 R/R PMBCL patients treated with anti-CD19 CAR-T cells from the French DESCAR-T registry, CR, 2-year PFS, and 2-year OS rates of 74.5 %, 70.4 %, and 86.9 %, respectively, were reported for patients receiving axi-cel, with higher baseline TMTV associated with an increased risk of treatment failure [158]. In terms of toxicity, grade 3–4 cytokine release syndrome (CRS) was reported in 5–10 % of cases, and grade 3–4 immune effector

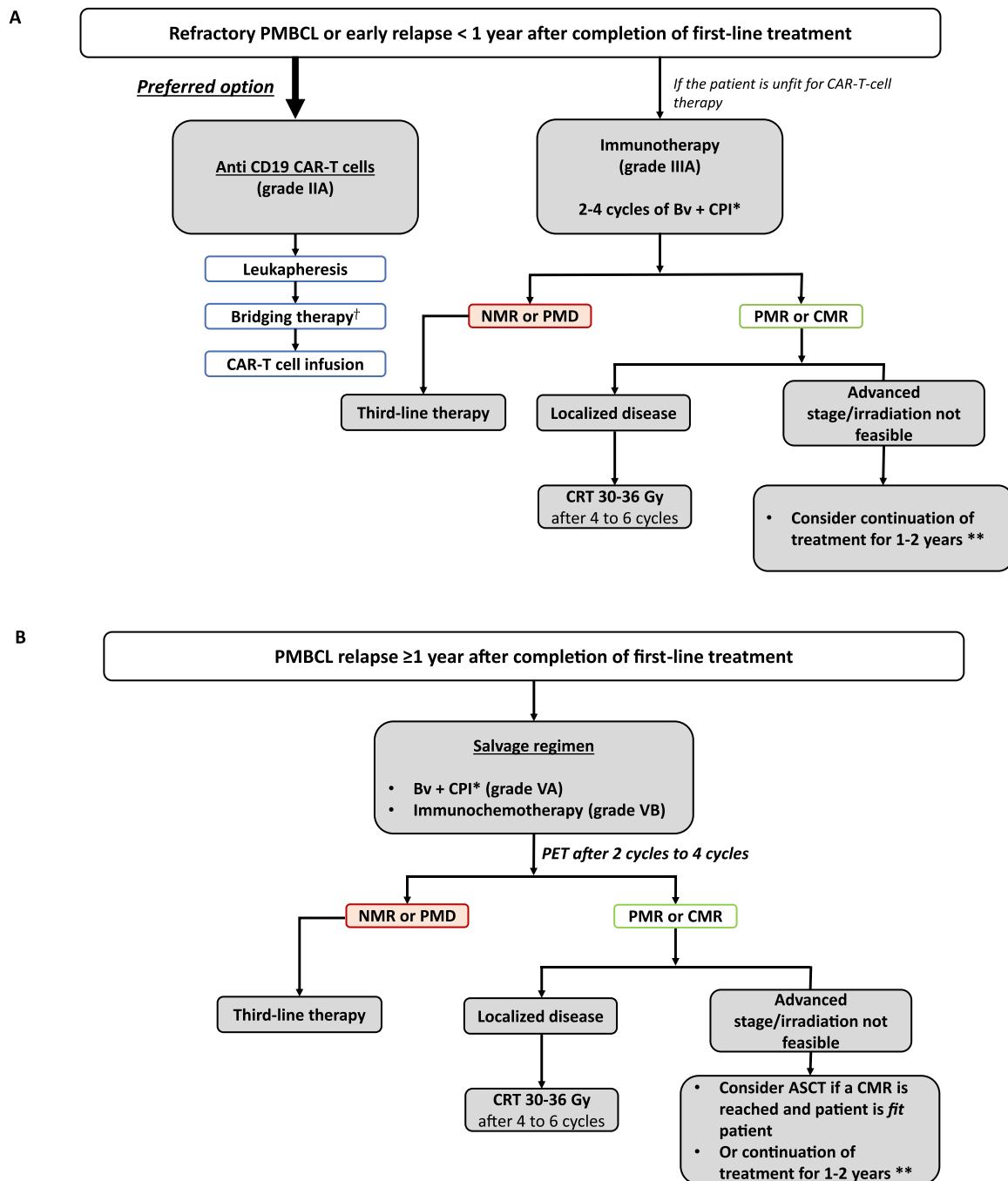


Fig. 3. Management of second-line treatment for PMBCL. (A) Management of refractory or early-relapsing (<12 months) patients * No EMA approval. ** No more than 16 cycles of Bv. [†] May include 36 Gy of radiotherapy if the disease is localized. Abbreviations: PMBCL: primary mediastinal B-cell lymphoma; ASCT: autologous stem cell transplantation; CAR-T: chimeric antigen receptor T cell; CRT: consolidation radiotherapy; CMR, complete metabolic response; PMR, partial metabolic response; NMR, no metabolic response; PMD, progressive metabolic disease. Bv: brentuximab-vedotin; CPI: checkpoint inhibitor; EMA: European Medicines Agency. (B) Management of late-relapsing (≥12 months) patients * No EMA approval. ** No more than 16 cycles of Bv. Abbreviations: PMBCL: primary mediastinal B-cell lymphoma; CRT: consolidation radiotherapy; ASCT: autologous stem cell transplantation; Bv: brentuximab-vedotin; CMR, complete metabolic response; PMR, partial metabolic response; NMR, no metabolic response; PMD, progressive metabolic disease; CPI: checkpoint inhibitor; PET: positron emission tomography; EMA: European Medicines Agency.

cell-associated neurotoxicity syndrome (ICANS) was reported in 20–25 % of cases.

There is conflicting evidence regarding the real benefit of bridging therapy before CAR-T-cell therapy [159,160]. Nevertheless, the prognostic impact of preinfusion tumor burden has been repeatedly demonstrated in patients with LBCL treated with CAR-T cells, as has a link between preinfusion tumor burden and immune-mediated toxicity [161–163]. Furthermore, PMBCL is a clinically aggressive disease for

which treatment is often required to limit the risk of local complications prior to CAR-T-cell infusion. Thus, conventional immunochemotherapy regimens or radiotherapy in patients with localized disease [164,165] are typically used to limit disease progression before infusion. Bridging radiotherapy can be combined with systemic treatment. The choice of fractionation schedule depends on logistical considerations, the patient's tolerance to systemic treatment, and whether the systemic therapy used is radiosensitizing. However, a standard dose per fraction

(1.8–2 Gy) is associated with fewer long-term sequelae [166].

6.4. Expert point of view

- Liso-cel is considered the SOC salvage treatment for PMBCL patients who experience early progression (< 1 year) after the completion of first-line immunochemotherapy (II, A).
- Bridging therapy should be considered to control the tumor burden before CAR-T-cell infusion and may include mediastinal radiotherapy if the disease is localized (IV, A).
- Axi-cel is the SOC for eligible R/R PMBCL patients in third-line or later treatment (II, A).

6.5. Therapeutic intensification with ASCT

R/R disease has traditionally been managed with therapeutic intensification consisting of high-dose chemotherapy (HDC) followed by ASCT in eligible patients who achieve at least a good PR after salvage chemotherapy [148,167]. The efficacy of this regimen was confirmed in the retrospective EBMT study, in which 86 patients underwent HDC/ASCT, with the majority having previously received rituximab-based therapy. After a median follow-up of 5 years, patients who underwent transplantation after achieving a second CR or PR achieved a PFS of 64 % and an OS of 85 % [105]. In contrast, those with chemorefractory disease at the time of transplantation had a PFS of 39 % and an OS of 41 %. When not administered earlier, RT can play a crucial role in controlling localized disease [168]. Another recent report from the MD Anderson group highlights the importance of achieving a CMR prior to HDC/ASCT [169]. However, on the basis of the results of the TRANSFORM study, which demonstrated the superiority of liso-cel over salvage chemotherapy followed by HDC/ASCT in refractory disease or early relapse within 1 year after completing first-line treatment, ASCT is no longer the SOC in this setting [154].

6.6. Expert point of view

- HDC/ASCT can be considered a suitable consolidation option for eligible patients who achieve a CMR after salvage treatment in cases of late (≥ 1 year) relapse or in patients who relapse after CAR-T-cell therapy (IV, B).

6.7. Anti-PD1 CPIs

Pembrolizumab and nivolumab have demonstrated strong efficacy in the treatment of R/R PMBCL, reflecting the biological similarities between PMBCL and cHL, including PDL1 overexpression and the close interplay between tumor cells and the tumor microenvironment [170, 171]. Pembrolizumab monotherapy for up to two years was associated with ORR and CR rates of 41.5 % and 21 %, respectively, and a 4-year PFS of 33 % in the phase II KEYNOTE-170 trial, which included 53 heavily pretreated PMBCL patients [172]. Notably, none of the patients who achieved a CR experienced subsequent relapse, underscoring the robust and durable effect of CPIs in this disease. The therapeutic response appears to correlate with PDL1 overexpression on the basis of the intensity of membranous staining of malignant tumor cells [173]. While brentuximab-vedotin (Bv) monotherapy had disappointing response rates in a phase II study (ORR = 13 %) [138], more promising results were observed with the combination of Bv and a CPI. Administration of Bv (1.8 mg/kg) and nivolumab (240 mg) every three weeks was associated with ORR and CR rates of 73.3 % and 37 %, respectively, and a 2-year PFS of 55.5 % in the CHECKMATE 436 study, which included 30 high-risk R/R CD30-positive PMBCL patients [149]. No threshold of PDL1 expression was needed, but CD30 expression > 1 % was needed. Notably, 12 of the 29 patients treated with this combination underwent subsequent ASCT or allogeneic stem cell transplantation (alloSCT). A 3-year PFS of 64 % was reported in a real-life cohort of 10

patients receiving a fixed duration of Bv + nivolumab without consolidative SCT [174]. Interestingly, none of the five patients with localized disease who received CRT after Bv–nivolumab treatment experienced a subsequent relapse. Given these findings, we consider the administration of a CPI, in association with Bv in CD30-positive patients, as a valuable therapeutic option for R/R PMBCL (Figure 3). Considering the encouraging results in patients with chemoresistant disease and the poor ORR of HDC, we also propose that CPI + Bv be considered at first relapse in patients who are unfit for CAR-T-cell therapy (Figure 3). Early PET evaluation should be performed after 2–4 cycles to guide further treatment decisions. In cases of localized disease at relapse, CRT after 4–6 cycles should be considered if not performed previously [174–177]. For patients with disseminated disease, treatment may be continued for up to one to two years [172]. Bv should be stopped after a maximum of 16 cycles, with close monitoring of neurotoxicity to allow for prompt dose reduction if necessary [178]. ASCT could also be discussed in fit R/R PMBCL patients who respond (CMR) to a CPI if not previously administered, given the high cure rates observed with this approach (Figure 4). Notably, no direct or indirect comparisons between CPI ± Bv and anti-CD19 CAR-T cells have been published to date. Consequently, the expert panel emphasizes a preference for CAR-T-cell therapy over CPI therapy for early relapses, given the approval of CAR-T-cell therapy for this purpose (Figure 3). Given their efficacy in PMBCL, CPIs and Bv can also be considered bridging therapies before CAR-T-cell infusion, especially in chemoresistant situations. Despite an overall favorable risk/benefit profile, the combination of a CPI and Bv remains unapproved by the EMA for the treatment of R/R PMBCL, likely owing to the lack of comparative data. However, this combination is frequently used in many lymphoma centers because of the chemorefractoriness of R/R PMBCL.

6.8. Expert point of view

- CPI combined with BV is a valuable treatment option for R/R CD30-positive PMBCL in patients relapsing ≥ 1 year after frontline chemotherapy, in those unfit for CAR-T-cell therapy, or in patients relapsing after CAR-T-cell therapy. This approach can be considered even in the absence of EMA approval, given the lack of effective therapeutic alternatives (V, A). CPI in combination with Bv should be preferred over CPI monotherapy (III, A).
- In cases of localized disease, radiotherapy after 4–6 cycles of a CPI in combination with Bv can be considered if a CPI has not been previously administered (IV, B).
- In cases of disseminated disease at relapse, we recommend the continuation of treatment for up to one to two years (and no more than 16 cycles of Bv); in cases of a CMR, ASCT can be discussed for fit patients (IV, B).

6.9. Other agents and clinical trials

Patients who relapse after CAR-T-cell therapy and CPI therapy have no conventional treatment options and should be encouraged to enroll in clinical trials when available. Among the new therapeutic modalities for R/R DLBCL, bispecific antibodies (BsAbs) have recently emerged as effective and well-tolerated options. Several phase II trials have demonstrated that CD20-CD3 BsAbs are associated with CR rates and 1-year PFS rates of 30–40 % in heavily pretreated patients, including relapses after CAR-T-cell therapy [179–182]. These results led to the FDA and EMA approvals of glofitamab and epcoritamab in third-line or later settings. However, data regarding R/R PMBCL are scarce, representing only 4 % of all patients in these pivotal phase II trials [179,180].

Given the paucity of these data, we recommend considering CD20-CD3 BsAbs after the failure of both CD19 CAR-T-cells and CPI therapies. ASCT/alloSCT has not been assessed in pivotal trials; therefore, it is not clear whether it should be proposed for heavily pretreated PMBCL patients who achieve a response after BsAb treatment. A search for a

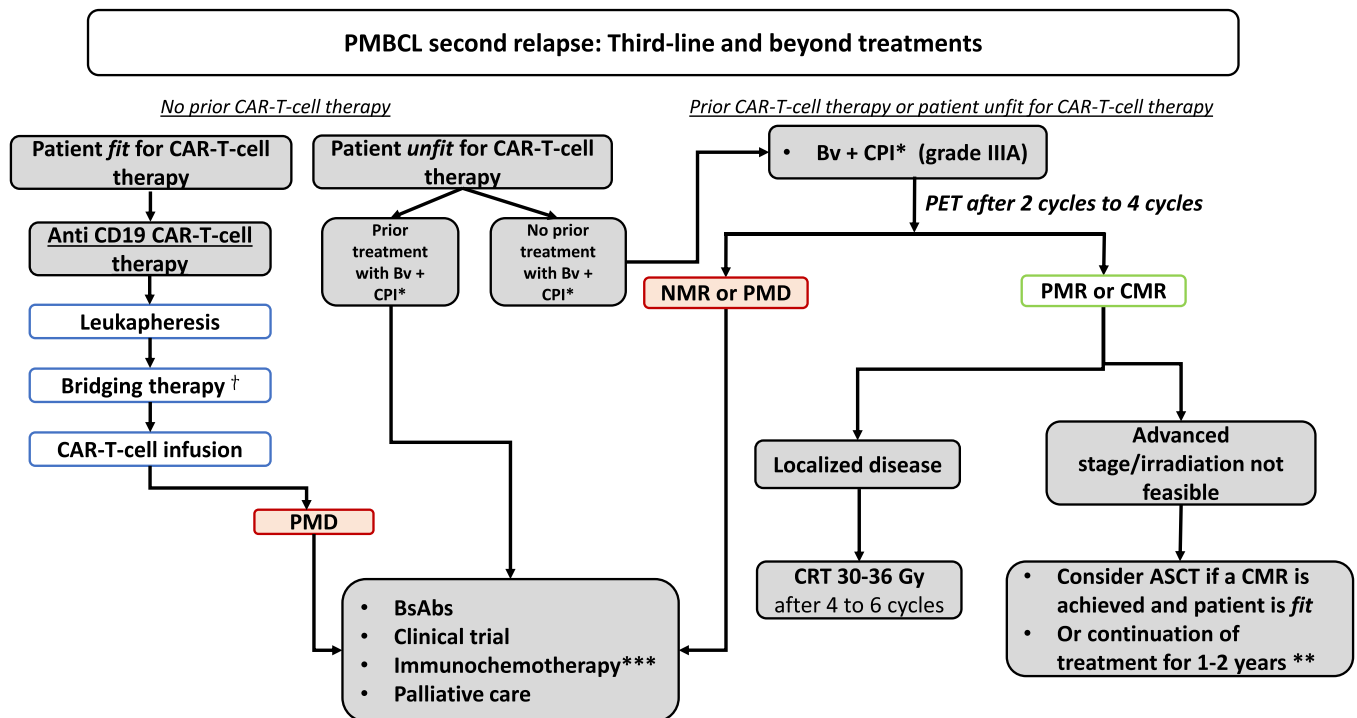


Fig. 4. Management of second relapse and subsequent lines of treatment for PMBCL * No EMA approval. ** No more than 16 cycles of Bv. ***AlloSCT with RIC could be considered after salvage immunochemotherapy in patients experiencing failure after CAR-T-cell therapy and checkpoint inhibitor therapy. † May include 36 Gy of radiotherapy if the disease is localized. Abbreviations: PMBCL: primary mediastinal B-cell lymphoma; CRT: consolidation radiotherapy; ASCT: autologous stem cell transplantation; Bv: brentuximab-vedotin; alloSCT: allogeneic stem cell transplantation; EMA: European Medicines Agency; RIC: reduced intensity conditioning; Bv: brentuximab-vedotin; CMR, complete metabolic response; PMR, partial metabolic response; NMR, no metabolic response; PMD, progressive metabolic disease; CPI: checkpoint inhibitor; PET: positron emission tomography; BsAbs: bispecific antibodies.

potential stem cell donor may be initiated at the start of the BsAb treatment. CRT should also be considered for localized disease if not previously given. Notably, very few data on other new agents for R/R DLBCL exist. While the antibody—drug conjugate loncastuximab tesirine was associated with a CR rate of 24 % in a phase II trial involving 145 R/R DLBCL patients, no CRs were observed in the seven PMBCL patients in the cohort [183,184]. In contrast, in a phase Ib/II study in which vorinostat in combination with pembrolizumab was evaluated in 52 heavily pretreated B-cell lymphoma patients, CRs was observed in five out of five PMBCL patients [185], highlighting the potential benefit of new agents in this specific histology and the need for inclusion in clinical trials when possible.

6.10. Expert point of view

- Inclusion in a clinical trial should be considered at any stage of the patient's treatment journey (III, B).
- BsAbs may be used in heavily treated PMBCL patients who relapse after CAR-T-cell and CPI therapies (V, A).
- CRT should be considered for localized disease if not previously performed (IV, B).

6.11. AlloSCT

AlloSCT is a potentially curative therapeutic option for many hematological malignancies, although its indications may be limited by donor availability and the nonrelapse mortality (NRM) of the procedure. Indications for R/R LBCL are controversial and tend to be discussed on a case-by-case basis. While registry studies have suggested that alloSCT could be curative in advanced lines of DLBCL, supporting the existence of a graft-versus-lymphoma effect, the emergence of new, efficient therapies such as CAR-T-cell and BsAb therapies has tended to reduce

these indications. Nevertheless, a recent registry study revealed that alloSCT was associated with a 1-year PFS of 45 % in a cohort of 88 DLBCL patients who experienced CAR-T-cell therapy failure [186]. The NRM rate is usually approximately 20 %, and reduced intensity conditioning (RIC) is associated with better outcomes [186–189]. Data on PMBCL patients are much more limited and restricted to the pre-CAR-T-cell and pre-BsAb era. However, survival in three registry studies (approximately 80 patients in total) aligns with DLBCL results, with a long-term PFS of approximately 30–40 % (up to 50 % if undergoing transplantation while in CR) in patients who relapse after conventional treatment (including ASCT)[190–192].

6.12. Expert point of view

- AlloSCT with RIC could be considered in patients experiencing failure after CAR-T-cell and CPI therapy (IV, C)

7. Specific points

7.1. Best practices for radiotherapy

The recommended doses of CRT are 30–36 Gy in 1.8–2 Gy per fraction [175,193,194]. In the case of refractory disease or bridging to CAR-T-cell therapy, 36 Gy should be delivered with the option of 30 Gy to the initial tumor volume and 36 Gy to the relapse/refractory volume. The use of intensity-modulated involved-site radiotherapy (ISRT with IMRT) is the SOC [166]. Owing to respiratory motion, respiratory management, such as deep inspiration breath-hold (DIBH) or 4D simulation if DIBH is not available, is essential. DIBH significantly reduces the mean dose to the heart [195] by keeping the heart away from the upper mediastinum and reduces the mean dose to the lung [196]. According to some normal tissue complication probability models, DIBH

may reduce the risk of clinical pulmonary or cardiac toxicity by up to 40 % [197]. Notably, the risk of coronary artery disease or heart failure is 4–6 times higher than that in the general population on the basis of historically treated patients, with a cumulative incidence of cardiac toxicity of 50 % after 40 years. The risk is particularly marked in patients treated before the age of 25 years [198]. Similarly, exposure of mammary gland tissue must be minimized because of the risk of secondary breast cancer, which occurs in almost 15 % of historically treated cases after 30 years [199]. Proton therapy is now commonly considered due to its frequent dosimetric advantage (particularly evident at the cardiac, pulmonary, and breast levels) over photon radiotherapy, even in terms of DIBH, which theoretically translates into a reduced risk of late cardiac or pulmonary toxicity, or SM [200,201]. Owing to the susceptibility of proton beams to range and motion uncertainties, the possibility of underdosing target volumes or overdosing organs at risk is avoided with the use of DIBH. However, the availability of proton therapy is a limiting factor. The dosimetric advantage of the use of non-coplanar arcs, known as “butterfly VMAT,” has also been demonstrated [202].

7.2. Expert point of view

- When mediastinal radiotherapy is considered, we recommend the use of ISRT with IMRT and DIBH (III, A).
- The recommended doses of CRT are 30–36 Gy in 1.8–2 Gy per fraction (III, A).
- In the case of refractory disease or bridging to CAR-T-cell therapy, 36 Gy should be delivered (III, A).
- The use of proton therapy should be discussed, especially for patients under 25 years of age (III, B).

7.3. Fertility preservation

Since PMBCL affects mainly young adults and has a very favorable prognosis, fertility preservation is a major issue in patients of reproductive age. Clinical guidelines recommend that health care providers discuss fertility preservation options and refer all patients with reproductive potential to appropriate reproductive specialists before initiating treatment [203–205]. This consultation aims to assess gonadal function and the impact of treatments on fertility and to provide information on existing preservation methods and their feasibility. For pubertal men, sperm cryopreservation should be offered systematically before the initiation of treatment [203,204]. For women, an assessment of ovarian reserve should be offered by measuring the anti-Müllerian hormone (AMH) level and performing an ultrasound follicular count, if indicated, before and one year after immunochemotherapy. Mature oocyte cryopreservation after ovarian stimulation can be offered in the absence of therapeutic urgency and contraindication of the procedure (e.g., SVCS). Ovarian tissue cryopreservation should be considered for patients with a high risk of gonadotoxicity depending on the treatment planned (including ASCT or high doses of alkylating agents) and age [206].

A further referral may be necessary after treatment completion to assess the feasibility of posttreatment fertility preservation, if indicated, or prior to initiating a gonadotoxic second-line treatment for R/R PMBCL. Additionally, after treatment completion, assessments of gonadal function should be performed, including a spermogram at two years for men and measurement of the AMH level and follicular count at one year for women, with the option to propose mature oocyte cryopreservation if not performed pretherapeutically.

7.4. Expert point of view

- All patients of childbearing potential should be informed and, if possible, referred to reproductive specialists to discuss fertility preservation options before starting treatment (V, A).

- Sperm cryopreservation should be routinely offered to young men before treatment (V, A).
- Ovarian reserve assessment should be offered to women, with fertility preservation discussed on the basis of the expected gonadotoxicity, patient age, and therapeutic urgency (V, A).
- Patients should be referred again after treatment completion for the assessment of gonadal function (V, A).

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