Review Article



# State of the art in the diagnosis, biology and treatment of primary mediastinal B-cell lymphoma: a review

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**Abstract:** Primary mediastinal B-cell lymphoma (PMBL) is an uncommon entity of aggressive large B-cell lymphoma (LBCL), representing approximately 2–4% of newly diagnosed non-Hodgkin lymphomas (NHL) and having many biological and clinical features that separate PMBL from diffuse large B-cell lymphoma (DLBCL). It typically affects young females (median age 37 years) with onset of a large and compressive anterior mediastinal mass. Several teams have highlighted the biological complexity of PMBL and contributed to building the concept that PMBL tumors possess a singular immune escape profile. The remarkable prognosis of patients treated with curative intention is a particular feature of PMBL, with a survival rate greater than 80% at 5 years in most reports. However, the therapeutic standard of care in the frontline and relapsed/refractory settings remains debated. Therapeutic options include standard rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP), dose-dense immunochemotherapy with rituximab plus doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone (R-ACVBP) or dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R), with or without consolidation radiotherapy (CRT). The place of positron emission tomography (PET)-driven treatment and autologous stem cell transplantation (ASCT) consolidation in the frontline setting also remain a subject of debate. Interpreting PET images of PMBL patients is very difficult due to the presence of inflammatory phenomena in the mediastinum under chemotherapy and after the end of the treatment regimen. These false PET-positive residual uptakes may prompt physicians to perform intensive consolidation and/or CRT, resulting in high rates of unnecessary ASCT and CRT in PMBL patients. Emerging data suggest that, in addition to PET, circulating tumor DNA (ctDNA) might be an interesting tool for the assessment of minimal residual disease (MRD) in PMBL. In the present review, we will discuss pathobiology, diagnostic spectrum, genomics, clinical issues in the treatment and prognosis of PMBL to establish unmet medical needs related to this rare condition and to help the community by describing innovative support and research. We also provide future directions for PMBL management and a rationale for the use of ctDNA monitoring in PMBL patients.

**Keywords:** Primary mediastinal B-cell lymphoma (PMBL); diagnosis and treatment; relapse; refractory disease

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## Introduction

Primary mediastinal B-cell lymphoma (PMBL) is a rare entity that is characterized in the WHO classification as a mature aggressive large B-cell lymphoma (LBCL) of presumed thymic B-cell origin that mostly invades the mediastinum. Many specific clinical and biological characteristics distinguish this disease from other lymphomas (1). Accounting for nearly 2–4% of newly diagnosed non-Hodgkin lymphomas (NHL), it mostly affects young female patients (median age 37 years) (2) and often manifests as a large and compressive anterior mediastinal mass. Nearly all studies have shown very good prognosis for PMBL, with a survival rate exceeding 80% at 5 years (3-5); this is a singular aspect of PMBL. Although initially classified as a subgroup of diffuse large B-cell lymphoma (DLBCL), it is now well established that PMBL presents some features that overlap with those of classical Hodgkin lymphoma (cHL), particularly nodular sclerosis cHL (NS-cHL). The two entities show distinct histopathological features but may share common clinical features (young patients with a large mediastinal mass eventually "bulky" ≥10 cm) as well as common biological and molecular characteristics (6). Indeed, recurrent genomic rearrangements (isochromosome 9p) and copy number alterations (I) of the 9p24.1 locus, which contains genes encoding the immune checkpoint ligand genes *PDL1* and *PDL2*, lead to the overexpression of these genes by tumor cells (7-10). The binding of PDL1 or PDL2 to the PD1 receptor expressed by reactive T cells in the microenvironment increases the inhibitory signal mediated by PD1, resulting in a decrease in T-cell cytotoxic activity and providing an immune escape pathway to lymphoma cells. A second similarity is that three major molecular pathways, i.e., *JAK-STAT*, *NF-kB* and *PD1/PDL1*, are the key lymphomagenesis drivers in both PMBL (11,12) and NS-cHL (13-15).

The frontline combination of rituximab with anthracycline-based chemotherapy has greatly improved the outcome of both PMBL patients and those with other B-cell aggressive lymphomas. Nevertheless, some debate remains in the community regarding the superiority of dose-dense or dose-intensified regimens versus standard rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) (16-18). The roles of autologous stem cell transplantation (ASCT) and consolidation radiotherapy (CRT) are also still a topic of discussion. In addition, fluorodeoxyglucose (FDG) positron emission tomography (PET) monitoring for treatment response assessment is another issue in PMBL management due to the finding of frequent false-positive exams with inflammatory mediastinal residual uptake without evidence of active disease within the patient's biopsy samples (19,20). If 80–85% of PMBL patients can be cured after first-line therapy, refractory or relapsing (R/R) PMBL patients represent a real unmet medical need (21), and disease progression usually occurs very early, reflecting the chemoresistance of the disease.

In this review, we will summarize major data regarding the diagnosis, metabolic imaging, first-line treatment and relapse treatment of PMBL. We will also synthetize available emerging data that support the use of liquid biopsy in PMBL patient monitoring.

## Clinical presentation and issues at diagnosis

PMBL typically occurs in young patients (median age 37 years) and presents as a localized large anterior mediastinal mass. There is a clear but unexplained female predominance (sex ratio female/male: 2:1), and the large majority of patients develop "bulky" disease, defined as a tumor mass larger than 10 cm in diameter. Approximately 80% of PMBL presents as localized stage I–II disease (22). Contrary to DLBCL, extranodal invasion and bone marrow involvement are uncommon, but contiguous regional organ involvement (lungs, pericardium, pleura) is a frequent finding (23). There is usually no leukemic phase. Of note, a posterior mediastinal mass may suggest diagnosis of mediastinal Gray-Zone lymphoma (MGZL) or alternative etiologies rather than PMBL. In addition, PMBL is frequently extranodal when outside the mediastinum which can help distinguish it from MGZL that is commonly nodal when outside the mediastinum (24).

Clinical symptoms at diagnosis are related to the mediastinal mass, frequently as a superior vena cava syndrome (SCVS), resulting in thrombotic complications in 30–40% of patients who present with a bulky anterior mediastinal mass at diagnosis, which may affect overall survival (OS) (25). This complication warrants the prompt use of steroids in cases of SVCS to reduce the tumor mass that is causing the obstruction (26,27). However, systematic anti-thrombotic therapy is not recommended in case of malignant SVCS. Indeed, PMBL patients can frequently have vascular compression on imaging without true thrombosis and routine use of anticoagulation can complicate treatment which can lead to thrombocytopenia and bleeding risk (28). In addition, very recent international

clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer does not mention the use of anti-thrombotic therapy in patients with PMBL and/or SVCS (29). The diagnosis of PMBL is often made in an emergency context due to the frequently severe clinical presentation and the symptoms related to the tumor mass and requires mediastinoscopy, an invasive thoracic surgical procedure in which the mediastinum is examined and tissue is sampled for histological analysis. This procedure is performed under general anesthesia and often requires admission of the patient to the intensive care unit when he or she presents with SCVS. The risks of mediastinoscopy include bleeding, infection, temporary or permanent paralysis of the laryngeal nerve, pneumothorax, subcutaneous emphysema and esophageal or tracheal perforation. Mediastinoscopy may be difficult in cases of adherences secondary to previous local surgery (previous mediastinoscopy, neck or cervical spine surgery) or health conditions that prevent proper positioning of the neck during the procedure. Of note, tissue sampling can also be performed by needle biopsy under scanner guidance, but this leads to other concerns since the material may be of insufficient quality and quantity for optimal histopathological diagnosis. This technical difficulty is a common routine issue that impacts the initial management of patients.

Finally, the diagnosis of PMBL is a clinicopathological diagnosis based on the typical clinical presentation of the disease (young patients, female predominance, large and isolated anterior mediastinal mass) combined with histopathological and biological features.

## Histology and morphological features of PMBL

The histopathological diagnosis of PMBL is based on a broad spectrum of morphological features combined with the typical immunophenotype of the disease and correlation with clinical data. The morphology is characterized by a diffuse growth pattern within a variable degree of fibrosis, resulting in a crush appearance and/or a compartmentalization of tumor cells (1).

The neoplastic cells present in PMBL are usually medium to large in size and have round, multilobated or pleomorphic nuclei and cytoplasm that varies in appearance (pale, slightly basophilic or clear). “Clear cell morphology”, which is related to a hydropic change in the cytoplasm, is a common feature of PMBL cases (30). The presence of Reed-Sternberg-like cells may suggest the possible presence of cHL, especially in cases in which there are bands of sclerotic tissue and immune cell infiltration, although these features are present to a lesser extent in PMBL (1). No correlation between the different morphological patterns noted in PMBL and outcome was found in a large retrospective study performed before the rituximab era (30).

The immunophenotype of PMBL lymphoma cells is characterized by the expression of B-cell-lineage surface and cytoplasmic markers such as CD19, CD20, CD22 and CD79a and transcription factors such as PAX5, OCT2, and BOB1 (23,31-35). CD30 is expressed in >80% of cases but shows weak and heterogeneous staining (32), unlike in cHL, and CD15 expression is frequently negative (36) but up to 6% of PMBL patients can show CD15 expression (24). CD23 is expressed in 70% of cases (31,37,38), and PDL1/PDL2 is expressed in 50–70% of cases (39). There is no EBV infection (1). BCL2 is positive in 55–80% if cases and BCL6 is positive in 45–100% of cases (32,40). MUM1/IRF4 is positive in 75–90% of cases (41). MAL antigen expression has been described as a distinguishing marker of aggressive B-cell lymphomas and may help identify PMBL in difficult cases (42,43), but the use of anti-MAL antibodies in routine practice remains limited due to technical difficulties and difficulties in interpretation. Consistent with an immune escape phenotype, PMBL cells commonly lack HLA class I and/or class II molecules. The immunophenotype of PMBL is summarized in *Table 1*.

PMBL should not be confounded with MGZL, the new appellation for what was formerly designated “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL” (44). The diagnostic criteria for MGZL notably include high tumor cell density and strong expression of ≥2 B-cell markers on immunohistochemistry (IHC) (24,45). However, cases of composite and sequential lymphoma that show characteristics between those of cHL and PMBL occur very rarely, and this argues for major tumor cell plasticity in MGZL (46). With regards to differential diagnoses of PMBL, we should highlight the works of the Leukemia/Lymphoma Molecular Profiling Project (LLMPP) and French gene expression assay which are developed with the goal to implement gene expression profiling (GEP) as diagnostic assays to distinguish PMBL from DLBCL, cHL and MGZL. First, in 2003, the LLMPP used Lymphochip DNA microarrays and a 46 gene Bayesian predictor to study molecular diagnosis (based on GEP signature) and established a robust molecular predictor that precisely distinguishes PMBL from DLCBL (6). Then, in 2015, the LLMPP applied this PMBL predictor to identify

**Table 1** Typical immunophenotype of PMBL

| Epitope/antigen | Lymphoma cells | Comments | Main reference(s) |
|---|---|---|---|
| CD3 | Negative | Nests of $CD3^+$ or $CD5^+$ lymphocytes are present in the microenvironment, with a perivascular distribution | (23,33) |
| CD5 | Negative | | |
| CD20 | Positive | All large cells typically express CD20 on the membrane | (31,32,34,35) |
| CD23 | Positive in 70% of cases | CD23 is a transmembrane glycoprotein predominantly expressed in mature $IgD^+$ B lymphocytes and follicular dendritic cells | (37,38) |
| CD10 | Usually negative | CD10 positivity described in 8–32% of cases | (31,32) |
| CD15 | Frequently negative | Myeloid/monocyte marker positive in 80% of cHL | (36) |
| CD30 | Positive | Typically weak or moderate and heterogeneous expression in PMBL | (32) |
| BCL2 | Positive in 55–80% of cases | Expression is inhibited in reactive germinal centers | (40) |
| BCL6 | Positive in 45–100% of cases | Mainly expressed in germinal center cells | (40) |
| MUM1/IRF4 | Positive in 75–90% of cases | Expressed in late plasma cell-directed stages of B-cell differentiation | (41) |
| PDL1/PDL2 | Positive in 50–80% of cases | Staining also noted in macrophages, histiocytes and dendritic cells, localized primarily to the cytoplasm and of weaker intensity in microenvironment | (39) |

PMBL, primary mediastinal B-cell lymphoma; cHL, classical Hodgkin lymphoma.

24 PMBL cases in a large series of DLBCL cases, and 6 of these 24 cases had no evidence of mediastinal disease and would have been underdiagnosed by clinicians and pathologists without this tool (47). In 2017, a reliable, rapid and cost-effective method based on reverse transcriptase multiplex ligation-dependent probe amplification (RT-MLPA) was developed by a French team. The authors built a PMBL signature with *CD30*, *MAL* and *CD23* genes (overexpressed in these lymphoma) and demonstrated that this RT-MLPA tool was useful to discriminate PMBL from DLBCL using a Bayesian predictor (48). Finally, in 2020, the same French team combined an extended GEP panel (with more than 130 genetic markers, including 12 PMBL markers) and machine learning in an accurate pan-B-NHL predictor (LymphoSign test, Genexpath®, Rouen, France), able to identify the PMBL diagnosis (49). These French and LLMPP GEP tools that require RNA extraction from FFPE samples may be proposed as a complement to conventional histology to help pathologists to identify PMBL cases. To conclude, accurate identification of PMBL patients and selection for outcomes research and clinical trials (CTs) within aggressive B-cell lymphoma is important, and lack of such assays has hampered progress and execution of dedicated phase III PMBL trials. An effort should be made to implement the routine use of such GEP tools.

## Biology of PMBL: distinct cell-of-origin, immune escape profile and strong similarities to cHL

The putative origin of PMBL cells is a thymic medullary, asteroid, activation-induced cytidine deaminase (AID)-positive B-cell (50). Thymic B cells display a $CD20^+CD21^-$ and $IgM^+$ but $IgG^-$ immunophenotype (51), reside at the corticomedullary junction of the thymus and are estimated to represent approximately 1% of total thymic cells (52). Most thymic B cells are naïve B cells, and they are distinct from peripheral blood B cells (53). In addition, they display a phenotype that mimics antigen-presenting cells, with overexpression of *CD86* and downregulation of MHC II expression. Furthermore, they strikingly express autoimmune regulator (*AIRE*), an important transcriptional regulator that is not expressed by peripheral B cells. Though the presence of B cells in the thymus has been well established, their origin remains a matter of debate. Three decades ago, it was demonstrated in mice that thymic B cells emerged outside of the bone marrow with the finding that mature thymic B cells are present at embryonic day 18, that is earlier than B cell differentiation start in the bone marrow (54,55). Unlike most B cells that differentiate in the bone marrow, thymic B cells differentiate within the thymus from early thymic precursors (56). In addition, several robust experiments established that peripheral B cells are almost all unable to migrate into the thymus when

splenocytes are injected intravenously, which supports the idea that peripheral B-cell cannot recirculate to the thymus from the periphery (57-59). Taken together, these findings do not support the hypothesis of peripheral B-cell homing (60) to the thymus, so the main theory is the existence of an intrathymic pathway for B cell onset and maturation (61). However, it is challenging to draw clear-cut conclusions through the origin and persistence over time of thymic B-cells, as our understanding mainly derived from experiments in young mice. Furthermore, there are few robust biological studies of thymic B cells and PMBL lymphomagenesis (33,62,63). Of note, the typical high level of *BCL6* expression in PMBL cases, in addition to the high mutational burden, partially contradicts the hypothesis of a naïve B-cell of origin (COO), and this is confirmed by the distinct landscape of somatic alterations compared with other germinal-center (GC) B-cell lymphomas [follicular lymphoma (FL) and DLBCL], implying a specific and separate COO (64).

Recently, Mottok *et al.* analyzed a series of 95 PMBL tumors by whole-exome sequencing (WES) and demonstrated that *SOCS1* (suppressor of cytokine signaling 1) is the most commonly mutated gene (~60%). Interestingly, *PTPN1* mutations have been described in approximately 20% of PMBL (65); these mutations result in decreased expression of the gene, which encodes the *PTP1B* protein, as detected by IHC. These mutations result in increased phosphorylation of components of the *JAK-STAT* pathway, a phenomenon that also occurs in HL cell lines silenced for *PTPN1*, suggesting that the *JAK-STAT* pathway may be implicated in PMBL lymphomagenesis. Furthermore, in ~25% of PMBL cases, gain-of-function *IL4R* mutations (66) that generate constitutive activation of the *JAK-STAT* pathway in PMBL cell lines were described. These cells secrete high amounts of CCL17 *in vitro* and *in vivo* and thus may cooperate in T-cell engagement. Recently, an abstract by Noerenberg *et al.* (67) that was presented at EHA 2022 reported the results of a large biological study of 486 PMBL samples using whole-genome/WES and targeted sequencing. The authors confirmed the landscape of established PMBL driver genes, finding a mutational burden of 5 mutations/Mb and reporting that the 10 most frequently mutated driver genes were *SOCS1* (86%), *B2M* (67%), *ITPKB* (64%), *ACTB* (58%), *STAT6* (58%), *IGLL5* (56%), *TNFAIP3* (53%), *NFKBIE* (49%), *GNA13* (47%), and *ZNF217* (36%). Several somatic variants had an impact on outcome: patients with mutations in *CD58* displayed lower survival rates than patients without such mutations [progression-free survival (PFS): hazard ratio (HR) =2.96; P<0.001; OS: HR =2.55; P=0.006], while patients with mutations in *DUSP2* had a favorable prognosis (PFS: HR =0.28; P=0.002; OS: HR =0.15; P=0.011) (67). These correlates with clinical outcome are a great step forward in a more accurate understanding of PMBL. *Table 2* provides a summary of the most common recurring somatic alterations in PMBL (11,67-72).

Immunoglobulin genes are typically rearranged in association with immunoglobulin class switching and a high load of V(D)J somatic hypermutation without ongoing somatic mutational activity, suggesting that the B-cell progenitor that gives rise to PMBL is altered by the GC environment during lymphomagenesis (73). However, the absence of ongoing somatic mutation remains unclear in PMBL, although Popov *et al.* (74) suggested that the accessibility of target sequences is a major limiting factor for AID-dependent somatic gene diversification in PMBL. A lack of surface and cytoplasmic immunoglobulin protein is also a singular feature of PMBL (36,73) but has also been frequently described in cHL (75).

Twenty years ago, the application of GEP technology using DNA microarrays to frozen PMBL tumors and DLBCL tumors revealed divergent molecular signatures of PMBL and DLBCL (6). Remarkably, the researchers isolated a unique PMBL signature. In detail, the *JAK2*, *PDL1*, *PDL2* and *SMARCA2* genes, all of which are located on chromosome band 9p24, are expressed at considerably higher levels in PMBL than in DLBCL, consistent with other reports (54) showing recurrent gains in 9p in PMBL (76). Furthermore, *PDL2* was the gene that best discriminated between PMBL and DLBCL. The microarray transcriptional profile of frozen PMBL biopsies was similar to that of cHL but distinct from DLBCL transcriptomes (77). Although PMBL and cHL cell lines appeared to be closely related, there were some discrepancies: numerous B-cell lineage markers (CD19, CD20, CD22, and CD79) were not detected in cHL cell lines but were detected in PMBL cell lines (78-80). IHC staining for PDL1 and PDL2 was positive in approximately half of PMBL cases versus 95% (PDL1) and 23% (PDL2) of cHL cases (81). Using genome-wide DNA copy number analysis (7), Shipp's group demonstrated amplification of 9p24 in 100% of cHL and PMBL cell lines compared to only 22% of DLBCL cell lines. These 9p gains were also detected using laser-capture microdissected Hodgkin Reed-Sternberg cells and PMBL biopsies and were found by IHC to correlate with PDL1/2 protein overexpression in primary tumors (7). *PDL1/2* rearrangements (including 9p24.1

**Table 2** Genes frequently mutated in PMBL

| Gene | Prevalence of somatic mutations | Pathway/role (source: GeneCards database) | Main reference(s) |
|---|---|---|---|
| *SOCS1* | 45–86% | Negative regulation of cytokines JAK/STAT pathway | (67,68) |
| *B2M* | 40–67% | Presentation of peptide antigens to the immune system | (11,67) |
| *ITPKB* | 8.9–64% | Cellular signaling | (67,69) |
| *ACTB* | 56% | Cytoplasmic cytoskeleton, regulation of gene transcription, repair of damaged DNA | (67) |
| *STAT6* | 36–58% | Signal transduction and activation of transcription. IL4/interleukin-4- and IL3/interleukin-3-mediated signaling | (67,70) |
| *IGLL5* | 56% | Immunoglobulin lambda-like polypeptides | (67) |
| *TNFAIP3* | 9.5–53% | Cytokine-mediated immune and inflammatory responses; NF-kappa B pathway | (67,69) |
| *NFKBIE* | 22.7–49% | NF-kappa B pathway; inhibits binding of NF-kappa B p50-p65 and p50-c-Rel complexes to DNA | (67,71) |
| *GNA13* | 7.6–47% | Promotes tumor cell invasion and metastasis by activating the RhoA/ROCK signaling pathway | (67,69) |
| *ZNF217* | 36% | Promotes cell proliferation and antagonizes cell death | (67) |
| *IL4R* | 24.2% | Inhibits IL4-mediated cell proliferation and IL5 upregulation by T cells | (66) |
| *XPO1* | 24% | Nuclear export; control of several cellular processes by controlling the localization of cyclin B, MPAK, and MAPKAP kinase 2 | (72) |
| *PTPN1* | 22% | Cell growth, differentiation, mitotic cycle, and oncogenic transformation | (65) |

PMBL, primary mediastinal B-cell lymphoma; JAK/STAT, Janus kinase/signal transducers and activators of transcription; MAPKAP, MAP kinase-activated protein kinase.

break-apart and 9p24.1 amplification) were more frequently detected by fluorescent in situ hybridization (FISH) analysis in PMBL (20%) than in any other type of lymphoma (DLBCL, follicular lymphoma, primary testicular DLBCL, and nodular-lymphocyte predominant HL) (10) and correlated with overexpression of *PDL1/2* transcripts.

Furthermore, several teams reported increased expression of genes associated with the *JAK-STAT* and *NF-KB* pathways in PMBL (77,82,83). Indeed, 9p24 rearrangements also encompass *JAK2*, the overexpression of which results in increased protein activity, further inducing PD-1 ligand transcription. Adding further support to the idea that PMBL exhibits an "immune escape" profile and shows similarities with cHL, Steidl's group detected rearrangements of the *CIITA* gene, which encodes the major histocompatibility complex (MHC) class II transactivator, in 38% of PMBL cases by FISH analysis; such rearrangements were also detected in 15% of cHL cases and in only 3% of DLBCL cases (84). This rearrangement was initially discovered by RNA sequencing of cHL cell lines and is associated with a marked reduction in CIITA protein expression. Cases with *CIITA* rearrangements involving *PDL1* and *PDL2* as partner genes displayed higher *PDL1* and *PDL2* overexpression than cases with other partner genes, indicating that the *CIITA* promoter drives the expression of these two immune checkpoint inhibitors, resulting in the inhibition of T-cell activation *in vitro* (84). In accordance with the PMBL immune privilege phenotype, patients who displayed *CIITA* rearrangements had inferior outcomes (10-year disease-specific survival 63.6% compared with 85.0% in patients who did not display such rearrangements; P=0.044) (84). In another study, transduction of a DLBCL lymphoma cell line with a lentiviral vector containing the *CIITA* fusion detected by RNAseq led to decreased MHC II expression. Furthermore, lower CD4 and CD8 T-cell infiltration of PMBL tumor samples measured by IHC staining was also linked to downregulation of MHC class II antigen expression (85). There was also a loss of expression of MHC class I antigen in the cell membranes of PMBL tumor cells, as described for cHL (86). Finally, a very recent biological study shows that loss of heterozygosity (LOH) appears to be a novel and distinctive feature of PMBL. In

that study, Tuveri *et al.* demonstrated that large-scale copy-neutral LOH participates in the molecular pathogenesis of PMBL and that LOH events that cluster in the chromosomal regions 6p (60%), 15 (37.2%) and 17q lead to homozygosity conversion of well-known PMBL driver genes (87). This mechanism was found to frequently co-occur with homozygous mutations in *MHCI* (6p21), *B2M* (15q15), and *GNA13* (17q23) (87).

Taken together, studies of PMBL cases have highlighted the biological complexity of this tumor and contributed to building the concept that PMBL tumors possess "immune privilege" or an immune escape profile that results from specific epigenetic, genetic and molecular alterations that represent a main driver of PMBL lymphomagenesis. All of these features distinguish PMBL from DLBCL, MGZL and cHL.

## Extramediastinal PMBL

Several teams have reported that, notably, "PMBL-like" lymphomas can be identified at nonmediastinal sites. Indeed, cases of DLBCL with features of PMBL but without detectable mediastinal involvement have been reported, and using GEP methods, a PMBL signature may be identified in those cases (47). More recently, Duns *et al.* further delineated these particular lymphomas using the PMBL GEP signature in a cohort of 325 *de novo* DLBCL patients. The authors observed that 16 of these cases express MAL and CD23 and harbor *SOCS1*, *IL4R*, *ITPKB*, and *STAT6* mutations, all of which are typical PMBL features. In addition, in contrast to bona fide PMBL, the patients were older and never presented with pleural involvement (88). This subset of "molecular PMBL" appears to represent a distinct subgroup of DLBCLs that share molecular features with bona fide PMBL, but further research is warranted to gain a better understanding of the underlying lymphomagenesis process that generates these very uncommon extramediastinal PMBLs and to determine whether a specific therapeutic strategy should be applied in such cases.

## The central role of PET in PMBL staging and evaluation

FDG-PET is the current gold standard for extension at diagnosis and response assessment in PMBL. Its interpretation is based on the Deauville score (89,90) and Lugano 2014 criteria (91). Obtaining a complete metabolic response (CMR) at the end of treatment represents a remarkable outcome. Indeed, in the landmark IELSG-26 study (92), the 5-year PFS for PMBL with positive [as defined by International Harmonization Project (IHP) criteria with residual uptake > mediastinum, (93)] and negative (i.e., Deauville score ≤2, residual uptake ≤ mediastinum) end-of-treatment PET was 68% *vs.* 99%, respectively (P<0.001). Nevertheless, PET assessment of PMBL after treatment is difficult given that a slightly hypermetabolic residual mediastinal mass often persists during the interim and at the end of treatment without the systematic presence of lymphoma cells on rebiopsy (94). After the publication of the Lugano classification (95) and the results of the IELSG-26 study, the definition of CMR was changed from Deauville score 2 to Deauville score 3 so that the reference threshold used to define CMR was changed from the mediastinal blood pool activity to the activity in normal liver (96).

In a remarkable study, Ceriani *et al.* established that PET has a high negative predictive value at the end of treatment (i.e., all the patients obtaining a CMR defined as Deauville score ≤3 remained progression-free at 5 years) but a poor positive predictive value (97). These findings are often described in cases that present large bulky masses with a major fibrotic component at diagnosis (98). Indeed, recurrent persisting PET positivity without disease progression is a particular feature of PMBL. Vassilakopoulos *et al.* described a cohort of 182 patients treated with standard R-CHOP; 16% of these patients had Deauville scores of 4 at the end of treatment and a 5-year failure-free probability of 82%, compared to 92% for patients with Deauville scores of 3 (99). The same group also noted that many patients who displayed IHP positive PET after R-CHOP continued to be positive after CRT and remained in long-term remission without further treatment and were thus considered "false-positives" (100). An end-of-treatment PET standardized uptake value (SUV) ≤5.4 may also delineate a subgroup of patients with favorable outcomes (101), but this isolated finding requires further validation.

Recently, the lymphoma study association (LYSA) group reported a very large retrospective cohort of 313 PMBL patients, of whom 26 had Deauville scores of 4 (considered positive) at the end of treatment and displayed excellent outcomes, notably a 3-year OS rate of ~90% (18). In this study, approximately 23% of PMBL patients received ASCT, 10-fold higher than the percentage of patients with DLBCL in the GAINED trial (102). This high rate of ASCT may have in part been influenced by false-positive interim PET exams, given that disease control at the end of induction appeared comparable. In the report by Ceriani *et al.* based on the IELSG-26 study, patients with Deauville scores of 4 at the end of treatment had also better outcomes than those

with Deauville scores of 5 (5-year time-to-progression: 87% *vs.* 33%, P=0.0002) (103). That being said, we should clearly advise against salvage chemotherapy and/or consolidation ASCT in chemosensitive patients based solely on PET positivity (based on Lugano criteria) at the end of treatment in the absence of histopathologically proven progressive or multifocal disease (20,99,100). In the report by Melani *et al.*, up to 50% of Deauville score 5 patients were considered to have false-positive exams. Therefore, in the case of residual uptake in Deauville score 4–5 patients at the end of treatment, we recommend a "watch and wait" attitude with serial imaging surveillance if there are no other clinical indicators of disease progression. Lazarovici *et al.* (94) described the low predictive value of positive interim PET assessed by the Deauville score in PMBL patients. With that in mind, new tools are required to improve the evaluation of therapeutic response in PMBL. Maximum standardized uptake value (SUVmax) reduction between baseline (PET 0) and PET after 2 and 4 cycles of chemotherapy (ΔSUVmax PET 0–2: cutoff ≤66% or >66%, and ΔSUVmax PET 0–4: cutoff ≤70% or >70%), as described in the GAINED trial, appears to be an interesting alternative for evaluation of the therapeutic disease response (102). In the retrospective LYSA study, the authors observed that ΔSUVmax PET 0–4 ≤70% was associated with unfavorable outcome (18). This tool is useful in guiding consolidation decisions regarding the treatment of DLBCL patients and appears to be more accurate than visual analysis (104,105). However, a dedicated prospective study that tests this hypothesis in the PMBL setting would be of major interest.

## Prognostic features at diagnosis

The international prognostic index (IPI) score widely used in DLBCL prognostic assessment is probably not suitable for accurately assessing the prognosis of patients with PMBL. Indeed, the combination of extranodal (EN) involvement and elevated lactate dehydrogenase (LDH) ≥2 times the upper limit of normal (ULN) or bulky disease appears more relevant to define a "high risk" subgroup (13–27% of patients) with an approximately 20% rate of lymphoma-related mortality (106). Patients without any of these risk factors represent, in contrast, an ultralow risk subgroup with 11% risk of failure and only 1% to 4% 5-year lymphoma-related mortality (106). In addition, the absence of B symptoms at diagnosis appears to be a favorable prognostic factor (107). Pleural or pericardial involvement was also a predictive factor for PFS, but the proposed PMBL-dedicated IPI (PMBIPI), which integrated those factors (16), remains rarely used because of the lack of independent validation.

Regarding biological factors, Zhou *et al.* reported that MUM1 negativity and lower lymphocyte-to-monocyte ratio were associated with inferior OS and PFS, respectively (101). Conversely, Bledsoe *et al.* observed that low PDL1 (P=0.011) and high MUM1 (P=0.065) led to inferior PFS. In another report, MUM1-positive cases had very unfavorable outcomes (108). The variations in the characteristics of the patients included in the different studies, the variety of treatments used and the well-known limits of IHC reproducibility preclude drawing definitive conclusions regarding the applicability of these biological prognostic factors in routine practice.

Regarding PET features, the LYSA group demonstrated that a baseline total metabolic tumor volume (TMTV) ≥360 $cm^3$ was associated with unfavorable prognosis independent of treatment. Liu *et al.* reported that total lesion glycolysis (TLG) ≥2,500 at baseline correlated with worse PFS (P=0.023) (107). In the IELSG26 study, the combination of baseline TLG and end-of-treatment Deauville score showed a better positive predictive value than TLG alone, and patients with TLG >5,814 and interim Deauville scores of 4–5 showed clearly inferior outcomes (109).

Finally, central nervous system relapses are a rare (~3%) but severe event that may occur during the course of PMBL disease (18), and there is currently no dedicated predictive score that can be used to anticipate this risk in PMBL patients. Central nervous system (CNS) IPI is routinely used in PMBL management, by analogy to DLBCL, but it has not been specifically assessed in large PMBL studies (110) and may not be helpful in evaluating the risk of CNS recurrence in this disease (111). Of note, there is no recommendation regarding CNS prophylaxis in PMBL.

## Frontline treatments: the role of dose intensity

The first-line regimens used to treat PMBL patients vary across Western countries, and the best combination remains debated. Standard immunochemotherapy includes R-CHOP (5,103) delivered every 14 (RCHOP14) or 21 days (RCHOP21), dose-dense R-ACVBP with PET-driven consolidation (3,102,112) or DA-EPOCH-R (4,113). Mediastinal CRT was historically administered after chemotherapy but is currently generally reconsidered given its toxicity in this young patient population (114,115). *Table 3* outlines the effectiveness of the main first-line treatment

**Table 3** Efficacies of various first-line chemotherapy regimens reported in main clinical studies of PMBL patients

| Ref. | No. of patients | Study design | IPI | First-line regimen | % of patients receiving CRT | % of patients receiving upfront consolidation ASCT | Response rate | EFS/PFS/TTP | OS |
|---|---|---|---|---|---|---|---|---|---|
| (4) | 51 | Prospective phase II study | NA | DA-EPOCH-R | 3.9% | No | CMR =94.1% | 5-year EFS: 93% | 5-year OS: 97% |
| (16) | 240 | Retrospective | IPI 0–1: 52%; IPI 2: 25%; IPI 3: 13%; IPI 4–5: 10% | R-CHOP: n=187; CHOP: n=44; DA-EPOCH-R: n=9 | All regimens: 42%; R-CHOP group: 34% | R-CHOP: 90%; CHOP: 67%; DA-EPOCH-R: 100% | R-CHOP: CR =64.1% | R-CHOP + IFRT: 4-year PFS: 85% | R-CHOP + IFRT: 4-year OS: 100% |
| (5) | 50 | Prospective subgroup analysis of UK NCRI R-CHOP 14 v 21 trial | NA | R-CHOP14: n=22; R-CHOP21: n=28 | 58% | NA | ORR 92%, CR 43% | 5-year PFS: 80% | 5-year OS: 84% |
| (116) | 132 | Retrospective | IPI 0–1: 66%; IPI 2–3: 31%; IPI 4–5: 3% | R-CHOP21: n=56; DA-EPOCH-R: n=76 | R-CHOP21 group: 59%; DA-EPOCH-R group: 13% | R-CHOP21: 3.6%; DA-EPOCH-R: 1.3% | R-CHOP21: ORR 80.3%, CR 69.6%; DA-EPOCH-R: ORR 92.1%, CR 84.2% | R-CHOP21: 2-year PFS 73%; DA-EPOCH-R: 2-year PFS 85% | R-CHOP21: 2-year OS 89%; DA-EPOCH-R: 2-year OS 91% |
| (113) | 69 | Prospective | NA | DA-EPOCH-R: n=36; R-CHOP21: n=33 | NA | NA | DA-EPOCH-R: ORR 97.7%, CR 85%; R-CHOP21: ORR 81.8%, CR 50% | DA-EPOCH-R: 5-year PFS 90.9%; R-CHOP21: 5-year PFS 64.1% | DA-EPOCH-R: 5-year OS 97.7%; R-CHOP21: 5-year OS 73.8% |
| (103) | 159 | Retrospective | IPI 0–1: 36%; IPI 2–3: 47%; IPI 4–5: 14% | R-CHOP21: n=149; R-CHOP/R-ICE: n=8; DA-EPOCH-R: n=2 | 44% | No | CMR: 63% | R-CHOP21 5-year TTP: 79% | R-CHOP21 5-year OS: 88% |
| (117) | 53 | Retrospective | IPI 0–2: 72%; IPI 3–5: 28% | R-CHOP21: n=21; DA-EPOCH-R: n=28 | R-CHOP21: 100%; DA-EPOCH-R: 59.3% | R-CHOP21: 40%; DA-EPOCH-R: 0% | R-CHOP21: 92% ORR, 60% CR; DA-EPOCH-R: 92.6% ORR, 70.4% CR | R-CHOP21: 1-year PFS 87%; R-CHOP21 + ASCT: 1-year PFS: 90%; DA-EPOCH-R: 1-year PFS 73.9% | R-CHOP21: 1-year OS 100%; R-CHOP21 + ASCT: 1-year OS: 100%; DA-EPOCH-R: 1-year OS: 92% |
| (18) | 313 | Retrospective | IPI 0: 10.5%; IPI 1–2: 60.7%; IPI 3–5: 26.2% | R-ACVBP: n=180; R-CHOP14: n=76; R-CHOP21: n=57 | R-ACVBP: 2.2%; R-CHOP14: 14.5%; R-CHOP21: 3.5% | R-ACVBP: 25.6%; R-CHOP14: 31.6%; R-CHOP21: 1.8% | R-ACVBP: CMR =86.3%; R-CHOP14: CMR =86.8%; R-CHOP21: CMR =76.6% | R-ACVBP: 3-year PFS 89.4%; R-CHOP14: 3-year PFS 89.4%; R-CHOP21: 3-year PFS 74.7% | R-ACVBP: 3-year OS 92.4%; R-CHOP14: 3-year OS 100%; R-CHOP21: 3-year OS 87.5% |
| (106) | 332 | Retrospective | IPI 0–1: 72.9%; IPI 2–5: 27.1% | R-CHOP14: n=30; R-CHOP21: n=302 | 72% | R-CHOP14: 3.3%; R-CHOP21: 0% | NA | Whole population: 5-year FFP: 77.6% | 5-year LSS: 89.1% |

PMBL, primary mediastinal B-cell lymphoma; IPI, international prognostic index; CRT, consolidation radiotherapy; ASCT, autologous stem cell transplantation; EFS, event-free survival; PFS, progression-free survival; TTP, time to progression; OS, overall survival; NA, not available; CMR, complete metabolic response rate; IFRT, involved field radiotherapy; ORR, overall response rate; CR, complete response; FFP, freedom from progression; LSS, lymphoma-specific survival.

schemes. Of note, before the rituximab era, Massoud *et al.* reported better OS and PFS after intensified CHOP (namely, "ACVBP") compared to CHOP21 in PMBL (3), suggesting that "dose intensity" may be a prognostic factor in PMBL. In the rituximab era, the well-known study conducted by Dunleavy *et al.* also demonstrated that treatment with an intensive DA-EPOCH-R regimen obviated the need for CRT in chemosensitive PMBL patients (4). It is interesting to note that the use of DA-EPOCH-R has greatly increased (13% *vs.* 59%, P<0.001) since the publication of Dunleavy *et al.* in 2013, with a concomitant marked decrease in the use of CRT (13% *vs.* 59%, P<0.001) (116). Complete response (CR) rates appeared higher after DA-EPOCH-R in this series than after R-CHOP21 (84% *vs.* 70%, P=0.046). However, the DA-EPOCH-R regimen has not come into use in all hematology centers, probably due to its complexity and its hematological toxicity compared to RCHOP14/21. Indeed, R-CHOP and DA-EPOCH-R have a similar backbone of prednisone, cyclophosphamide, vincristine, doxorubicin and rituximab but besides the addition of etoposide, the procedure to administer them strongly differs. To receive DA-EPOCH-R, patients need to be hospitalized, because doxorubicin, etoposide, and vincristine are infused over 96 hours and cyclophosphamide is given after completion of the 96-hour infusion (118). These repeated hospitalizations may be associated with financial toxicity in many countries. In contrast, R-CHOP14 and R-CHOP21 are injected in an outpatient setting as bolus chemotherapy. In addition, DA-EPOCH-R is designated to enhance dose intensity by adjusting the doses of etoposide, cyclophosphamide, and doxorubicin based on the platelet and neutrophil nadirs of each cycle (119), adding to the complexity of the DA-EPOCH-R regimen management.

In 2016, a randomized study of 69 PMBL Ukrainian patients reported that DA-EPOCH-R offers better efficacy than R-CHOP21 (113) despite its greater hematological toxicity. The rate of CRT use in the two arms was not reported. In contrast, Malenda *et al.* (117) demonstrated very similar excellent outcomes in 53 PMBL patients treated with first-line R-CHOP21 and DA-EPOCH-R. However, in this study, CRT was used for all patients in the R-CHOP21 group *vs.* 59.3% of patients in the DA-EPOCH-R group; and consolidative ASCT was performed for 40% of patients in the R-CHOP21 group *vs.* 0% in the DA-EPOCH-R group, which may likely explain the comparable efficacy between "DA-EPOCH-R alone" *vs.* "R-CHOP + CRT or R-CHOP + ASCT". Another study reported by Held *et al.* in the form of an abstract (120) noted efficacy results comparable to those obtained using R-CHOP21 and R-CHOP14 in a subset analysis of 131 PMBL patients who participated in the UNFOLDER trial. The fact that only patients with age-adjusted IPI (aaIPI) =0 plus bulky disease or aaIPI =1 were included in either the CRT or the observation arms could somewhat explain these findings. Finally, the LYSA group recently reported a large series of 313 patients in France and Belgium who received first-line treatment with R-CHOP14, RCHOP21 or R-ACVBP (18): the 3-year PFS rates for the patients who received R-ACVBP, R-CHOP14 or R-CHOP21 were 89.4% [95% confidence interval (CI): 84.8–94.2%], 89.4% (95% CI: 82.7–96.6%) and 74.7% (95% CI: 64–87.1%) (P=0.018), respectively. Clearly, patients treated with R-CHOP21 had inferior outcomes compared to those who received dose-dense regimens (R-ACVBP and R-CHOP14). A recent study involving a Polish cohort of 124 patients with PMBL who underwent extended follow-up (median 9 years) also reported a high cure rate of more than 90% (5-year OS and PFS: 94% and 92%, respectively) after administration of an intensive immunochemotherapy protocol (GMALL/B-ALL/NHL2002) (121). Based on these findings, dose intensity appears to determine the excellent outcome of PMBL. However, Noerenberg *et al.* recently reported in an abstract at EHA 2022 that a subset of PMBL patients with *DUSP2* mutations (n=80/319) had favorable outcomes with respect to CR rate, PFS and OS whether they received an R-CHOP-like regimen or intensified treatment, implying that there is no advantage of treatment intensification in this low-risk subgroup (67).

Finally, the role of and the indications for treatment intensification with ASCT as a frontline consolidation option remain unclear. In the prerituximab era, Cairoli *et al.* (122) observed in a very limited monocentric cohort of 15 patients that BEAM-ASCT after intensified VACOP-B induction followed by DHAP and/or CRT in cases of partial response offered durable complete remission in all but one patient (aa-IPI 2–3). However, this combination is toxic in this young population, and no long-term data are available, particularly regarding the second malignancy rate. Similar results were obtained by Hamlin *et al.* in a study that compared upfront ASCT and dose-dense anthracycline-based chemotherapy (123). Since the introduction of rituximab, the benefit of ASCT, as evaluated by interim PET response, remains debated due to the scarcity of prospective data in this setting and the absence of dedicated

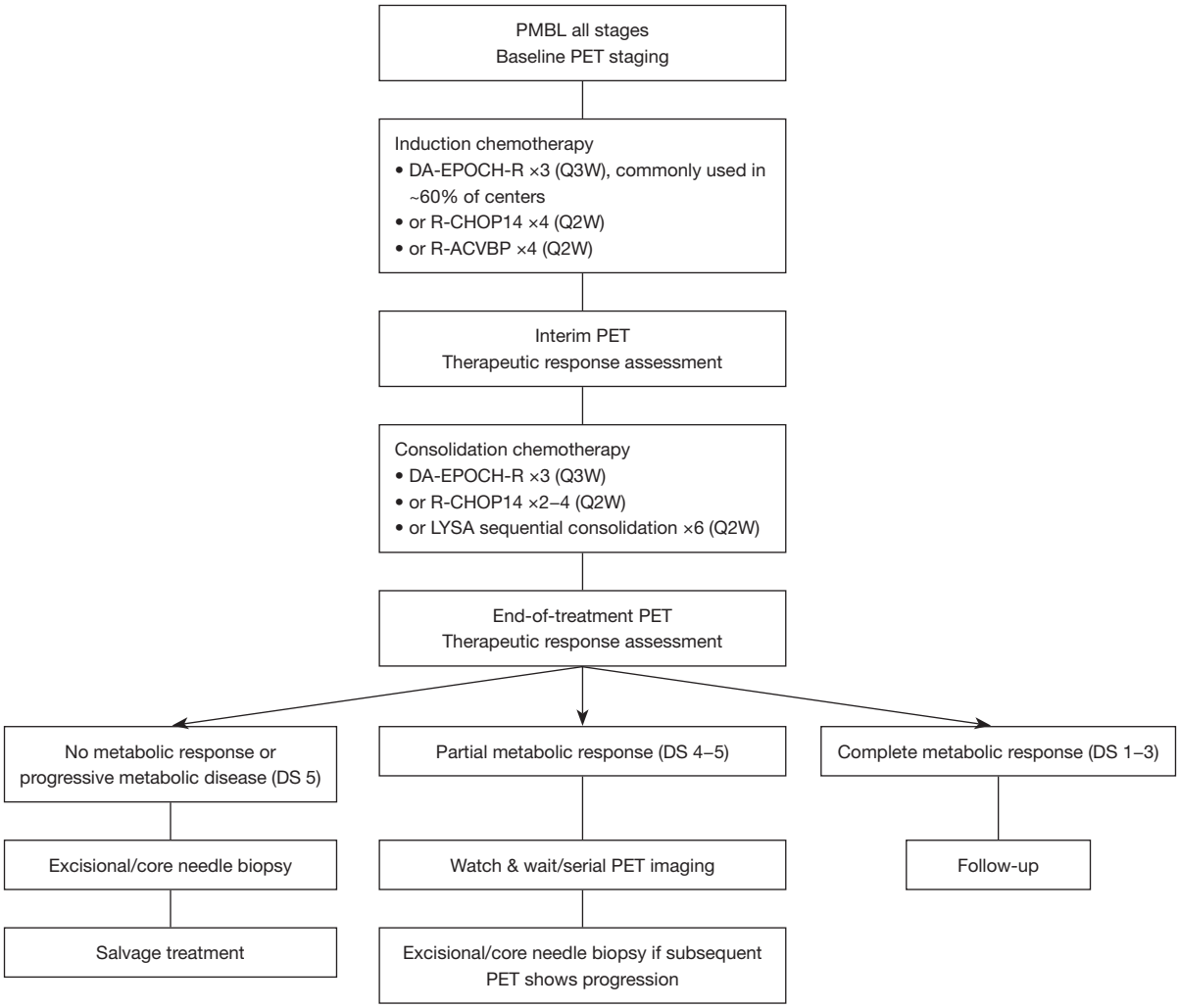


**Figure 1** Proposed first-line PMBL treatment algorithm. PMBL, primary mediastinal B-cell lymphoma; PET, positron emission tomography; Q3W, every three weeks; Q2W, every two weeks; DS, Deauville score.

randomized studies (102,124,125). Indeed, PMBL patients are underrepresented in CTs, precluding the extension of the conclusions drawn in large phase III studies of DLBCL. Of note, the anti-CD30 antibody drug conjugate brentuximab-vedotin (BV) has shown promising efficacy in combination with R-CHP for the frontline treatment of PMBL patients who show at least 1% or higher expression of CD30 by IHC. In a small series of 30 patients, the authors demonstrated an objective response rate of 100% with 86% CR and 2-year PFS and OS rates of 85% and 100%, respectively (126). These preliminary data warrant validation in larger trials.

To conclude, there is no consensus regarding the optimal treatment strategy for newly diagnosed PMBL patients. However, in recent studies, excellent results were obtained for patients treated with dose-dense immunochemotherapy based on rituximab and anthracyclines with interim PET assessment (18,103). A proposed algorithm for treatment using R-CHOP14 or R-ACVBP induction and PET-driven consolidation is depicted in *Figure 1*. Given the favorable outcomes with intensive immunochemotherapy alone, consolidative therapeutic intensification with ASCT should no longer be considered standard of care in the frontline setting.

## The place of CRT

Since several decades, CRT is widely used given the proven radiosensitivity of PMBL. The usefulness of CRT

is currently highly debated, and several expert centers have abandoned it, although it is still widely used in many countries. However, several teams have expressed concern about the long-term toxicity of CRT, including the possible induction of secondary cancers, especially in a young population (<40 years old) of females (127-129). The doses, target volumes and methods of delivery of these mediastinal irradiations are very heterogeneous among centers and have not been the subject of randomized studies. Several groups still apply CRT for all patients after standard chemotherapy (114,130,131), whereas others restrict its use to cases in which there is partial response on PET at the end of treatment (103,132,133), and others have discontinued its use (134-136). Gleeson *et al.* reported in a subgroup analysis of UK NCRI that combining R-CHOP14 plus CRT offers a better outcome than R-CHOP21 plus CRT (5).

In the retrospective LYSA study, the number of patients who were assigned to CRT was very low (n=17) and became null after 2014, probably due to a change in the procedures used in LYSA centers (18). The landmark study reported by Dunleavy *et al.* 10 years ago established that treatment with intensified immunochemotherapy (DA-EPOCH-R) made the use of CRT unnecessary (4). Hayden *et al.* also observed in a homogeneous series of PMBL patients who received frontline R-CHOP that a PET-guided strategy may decrease the need for CRT in most patients (103). Of note, radiotherapy may play a relevant role in the treatment of patients who show localized mediastinal progression at the end of treatment. Indeed, Vassilakopoulos *et al.* reported sustainable control of the disease in most patients with PET positivity at the end of treatment when consolidated with radiotherapy, and a Deauville score of 5 or 4 with high uptake (SUVmax ≥5) after subsequent radiotherapy is predictive of failure (100). Patients with elevated FDG uptake (SUVmax ≥10) after R-CHOP might switch to CMR after mediastinal irradiation (100).

Several sets of data suggest that CRT may be abandoned in patients who are assigned to receive frontline dose-intense immunochemotherapy to avoid the long-term side effects of CRT (137-140). In addition, the common extra mediastinal relapses observed in the recent retrospective LYSA study do not offer support for the use of CRT (18). However, because real-life studies of large cohorts of PMBL treated with dose-dense chemotherapy with or without CRT are lacking, there is no unanimity regarding the exclusion of CRT. The results of the IELSG-37 randomized study (NCT01599559) may soon end the debate regarding CRT in PET negative (Deauville score 1–3) patients (141). However, this study will not provide any input regarding the use of CRT in end of treatment PET positive cases that are frequently false positives.

## Management of relapsed/refractory PMBL

Relapsed/refractory patients represent a major unmet medical need. Contrary to the excellent prognosis observed in first-line treatment, the prognosis is very unfavorable in cases of disease progression, and progression occurs in approximately 10–20% of PMBL patients (18,142-144). Typically, progressions occur within the first year following the initiation of frontline treatment [primary refractory (PR) disease]; extramediastinal relapses can occur, but central nervous system or bone marrow involvement is uncommon. In cases of suspected disease progression, tumor biopsy is strongly recommended to exclude PET false positivity, to look for PDL1 overexpression by IHC (if not performed at initial diagnosis), to reassess CD19 and CD20 expression and to search for a composite or sequential tumoral contingent with MGZL or cHL features. Indeed, sequential PMBL and NS-cHL may occur, and some such cases have been demonstrated to be of common clonal origin and may have poorer outcomes (44-46,145,146). Salvage radiation therapy may be considered in nonbulky isolated mediastinal disease progression if patients do not receive CRT during their first-line treatment, but a low level of evidence for this approach exists (131). *Table 4* outlines the effectiveness of the main R/R treatment options, and *Figure 2* proposes a treatment algorithm for R/R PMBL patients.

### *Treatment intensification through ASCT*

The current standard approach to second-line treatment of "fit" patients is salvage high-dose platinum-based chemotherapy (R-DHAX, R-ICE or equivalent) followed by treatment intensification with ASCT (21,125). In the prerituximab era, outcomes in PR patients were very poor, with a 2-year survival probability of less than 10% (152). Then, in 1998, Sehn *et al.* described the outcomes of 35 PMBL patients with either frontline unfavorable prognostic characteristics or disease progression who were retreated with high-dose chemotherapy followed by ASCT [these patients received a carmustine, etoposide, and cyclophosphamide (CBV) conditioning regimen]. These high-risk PMBL patients had long-term disease-free survival (DFS) (5-year PFS: 83% in first-line patients *vs.* 58% in refractory patients *vs.* 27% in relapsed patients, P=0.02); therefore, this intensified approach became the standard of care for R/R-eligible patients (153). Of note, as in other lymphomas, the

**Table 4** Efficacy results of various salvage regimens from main clinical studies dedicated to relapsed/refractory PMBL patients

| Reference | No. of patients | Study design | IPI | Salvage regimen | Response rate | EFS/PFS/TTP | OS |
|---|---|---|---|---|---|---|---|
| (147) | 27 | Phase II | aaIPI ≤1: 44%; aaIPI ≥2: 56% | Camrelizumab (anti-PD1) plus gemcitabine, vinorelbine, and pegylated liposomal doxorubicin | ORR: 74.1%; CR: 55.6% | 2-year PFS: 48.2% | 2-year OS: 81.5% |
| (148) | KEYNOTE-013: n=21; KEYNOTE-170: n=53 | KEYNOTE-013: phase Ib; KEYNOTE-170: phase II | NA | Pembrolizumab single-agent | KEYNOTE-013: ORR: 48%, CR: 33%; KEYNOTE-170: ORR: 45%, CR: 13% | KEYNOTE-013: 1-year PFS: 47%; KEYNOTE-170: 1-year PFS: 38% | KEYNOTE-013: 1-year OS: 65%; KEYNOTE-170: 1-year OS: 58% |
| (149) | 30 | CHECKMATE-436: phase I/II | NA | Nivolumab plus brentuximab-vedotin | ORR: 73%, CR: 37% | 6-month PFS: 63.5% | 6-month OS: 86.3% |
| (150) | 28 | Retrospective | NA | Allo-SCT various conditioning regimens | NA | All patients: 2-year PFS: 39%; patients in CR or PR before allo-SCT: 2-year PFS: 50% | All patients: 2-year OS: 45%; patients in CR or PR before allo-SCT: 2-year OS: 58% |
| (21) | 60 | Retrospective | IPI 0–1: 58%; IPI 2: 18%; IPI 3: 12%; IPI 4–5: 12% | R-ICE (48%); ICE (33%); O-DHAP (8%); ICEMAN (5%); other (12%); radiotherapy (87%); ASCT (85%) | ORR: 65%; CR: 40%; PR: 25% | All patients: 3-year EFS: 57%; transplanted patients: 3-year PFS: 60% | All patients: 3-year OS: 61%; transplanted patients: 3-year OS: 65% |
| (125) | 86 | Retrospective | NA | BEAM-ASCT: 75%; other (27%); radiotherapy (31%) | CR: 58% | 3-year PFS: 62% | 3-year OS: 75% |
| (151) | 33 | Retrospective | NA | Axicabtagene ciloleucel (100%); checkpoint blockade (57.6%) | ORR: 78%, CR: 69% | 2-year PFS: 64% | 2-year OS: 78% |
| (143) | 37 | Retrospective | IPI 0–1: 50%; IPI 2–3: 44%; IPI 4–5: 6% | DHAP: 51%; ESHAP: 27%; GDP: 11%; Mini-BEAM: 5%; other (5%); proceed to ASCT: 22% | ORR: 25% | All patients: NA; post-ASCT: 2-year PFS: 57% | 2-year OS post progression: 15%; post-ASCT: 2-year OS: 67% |

PMBL, primary mediastinal B-cell lymphoma; aaIPI, age-adjusted international prognostic index; ORR, overall response rate; CR, complete response; EFS, event-free survival; PFS, progression-free survival; TTP, time to progression; OS, overall survival; NA, not available; allo-SCT, allogeneic stem cell transplantation; PR, partial response; R, rituximab; ICE, ifosfamide, carboplatin, etoposide; O-DHAP, ofatumumab, dexamethasone, high-dose Ara-C (cytarabine), cisplatin; ICEMAN, ifosfamide, carboplatin, etoposide, methotrexate, cytarabine; ASCT, autologous stem cell transplantation; BEAM, carmustine (BCNU), etoposide, cytarabine, melphalan; DHAP, dexamethasone, high-dose Ara-C (cytarabine), cisplatin; ESHAP, etoposide, methylprednisolone (solumedrol), high-dose cytarabine (ara-C) and cisplatin; GDP, gemcitabine, dexamethasone, cisplatin.

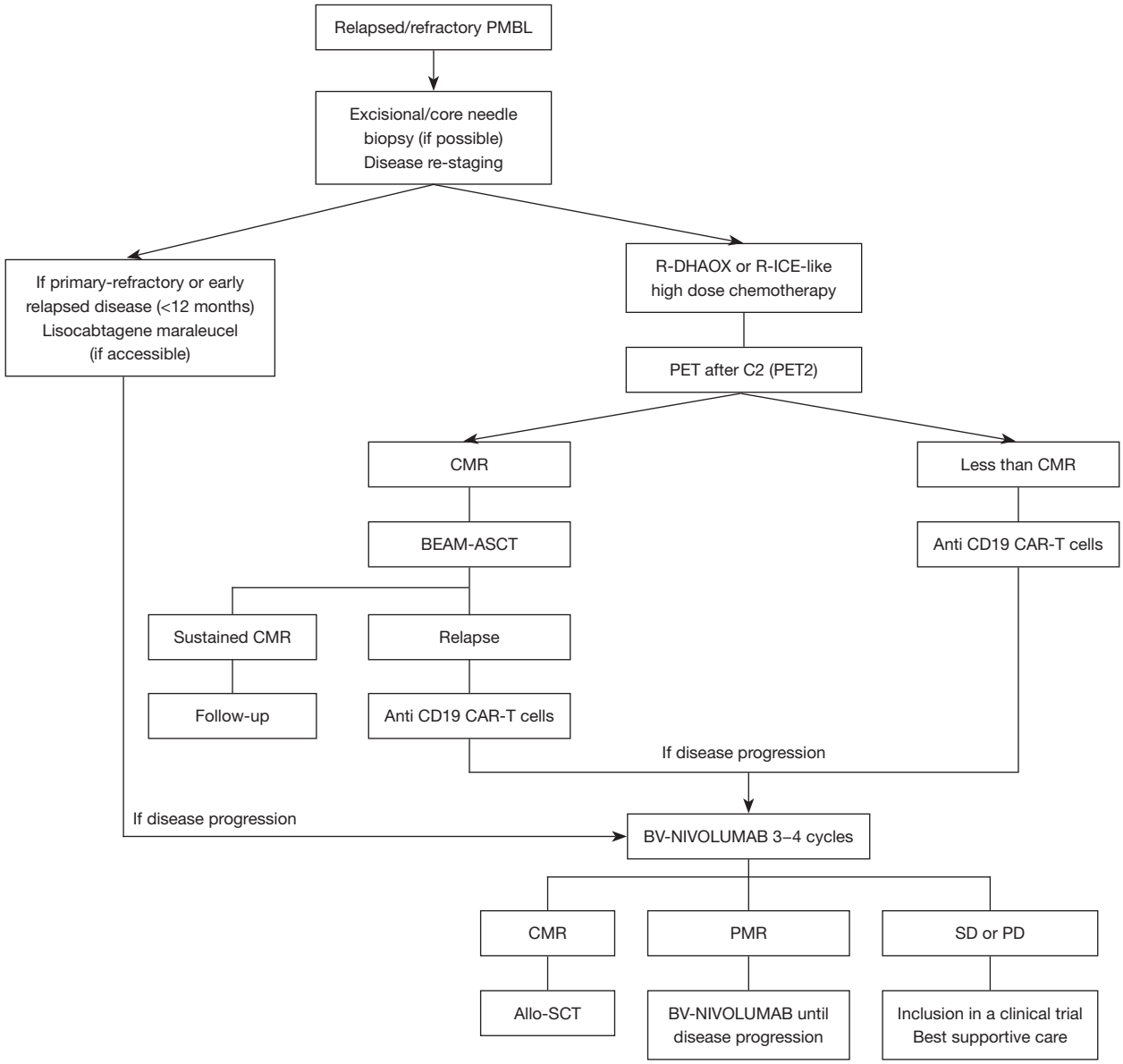


**Figure 2** Proposed relapsed/refractory PMBL treatment algorithm. PMBL, primary mediastinal B-cell lymphoma; PET, positron emission tomography; C2, two cycles of chemotherapy; CMR, complete metabolic response; BEAM, carmustine (BCNU), etoposide, cytarabine, melphalan; ASCT, autologous stem cell transplantation; PMR, partial metabolic response; SD, stable disease; PD, progressive disease; Allo-SCT, allogeneic stem cell transplantation; BV, brentuximab vedotin.

an alternative to traditional chemotherapy (155). However, this combination is still unapproved by the FDA for R/R cHL, likely because an improvement in patient-reported outcomes or survival has not yet been established. CD30 staining in PMBL is lower and more heterogeneous than in cHL. In the Checkmate 436 trial, heavily pretreated R/R PMBL patients received BV at 1.8 mg/kg and a fixed dose of 240 mg nivolumab every 3 weeks until disease progression or unacceptable toxicity occurred. ASCT was performed at the discretion of the investigators. The ORR was 73%, and the CR rate was 37%. The times to first objective response and CR were remarkably short (median 1.3 and 3.2 months, respectively), and the median duration of CR was unattained. Eleven patients who responded to

most relevant prognostic feature was chemosensitivity before transplant (risk ratio: 3.60; 95% CI: 1.14–11.4).

However, R/R PMBL is often resistant to second-line high-dose chemotherapy; therefore, patients will ultimately either not undergo ASCT because of salvage treatment failure or display early disease progression after ASCT. Indeed, Aoki *et al.* (144) reported a cohort of 44 PMBL patients diagnosed between 1996 and 2012 in which no frontline rituximab was administered to some patients and observed a 4-year PFS probability of 61% after second-line treatment intensification. In this study, chemorefractory patients (n=13) who did not respond to second-line high-dose chemotherapy had inferior outcomes compared to chemosensitive patients (n=31; 4-year OS: 80% *vs.* 50%, P=0.018). To add further data regarding the relevance of treatment intensification in R/R PMBL, we should mention the retrospective MD Anderson study that was reported in abstract form at American Society of Hematology (ASH) 2020; it included 58 R/R PMBL patients who received high-dose chemotherapy followed by an intensive ASCT conditioning regimen (rituximab/gemcitabine/busulfan/melphalan +/– vorinostat: R-GemBuMel) and CRT for patients with active disease at the time of transplant. This dose-intensified combination significantly improved event-free survival (EFS) and OS compared to the rituximab-BEAM conditioning regimen: two-thirds of the patients had long-term disease control, but these monocentric findings warrant further validation.

To conclude, therapeutic intensification with ASCT remains a potentially curative option for a subgroup of chemosensitive R/R PMBL patients if a CMR can be obtained before transplantation.

### *Immune checkpoint inhibitors*

#### Anti-PD1 monotherapy

Nivolumab and pembrolizumab are the two main FDA-approved anti-PD1 checkpoint inhibitors used to treat hematological malignancies. Pembrolizumab is a humanized, highly selective, IgG4/kappa monoclonal antibody targeting PD-1. The common 9p24.1 rearrangements in PMBL karyotypes resulting in PDL1 and PDL2 overexpression by lymphoma cells support the use of anti-PD-1 blockers in this disease.

In the pivotal phase II KEYNOTE-170 study, pembrolizumab was tested in a population of R/R PMBL patients who had already received 2 prior treatments and then relapsed or were unfit for ASCT; these patients were designated as having the highest unmet medical need. The patients were assigned to receive a pembrolizumab infusion of 200 mg every 3 weeks for a maximum of 35 cycles or for up to 2 years until proven disease progression or limiting toxicity occurred. The overall response rate was estimated to be 45% (95% CI: 32–60%): 7 and 10 patients reached CR as assessed using the Cheson 2007 criteria (13%) or the Lugano 2014 criteria (19%), respectively (148,154). The median time until a response to pembrolizumab was observed was 2.9 months (range, 2.4–8.5 months). After a median follow-up of three and a half years, the median PFS and OS were 5.5 and 22.3 months, respectively, with 3-year PFS and OS probabilities of 36% and 45%, respectively. The median duration of response was not achieved (range, 1.1–46.9 months), and three-quarters of the patients displayed a durable response that lasted longer than 36 months. Interestingly, the therapeutic response was correlated with overexpression of PDL1 as evaluated using IHC (such overexpression is itself related to the presence of 9p24.1 rearrangements in cytogenetics), suggesting that IHC could be a predictive marker of the response in these patients. The safety profile of the treatment regimen appeared excellent, as the most frequent adverse event was neutropenia (13%). Severe immune-related adverse event (AE) occurred in only 2 patients (grade 3 myositis: n=1; grade 4 pneumonitis: n=1) and did not result in definitive treatment interruption. Given the positive benefit/risk profile of pembrolizumab observed in this phase II study, the FDA approved this molecule in 2018 for use in R/R PMBL patients after two or more previous lines of treatment. However, no EMA approval was obtained, probably due to the lack of a comparator arm in the phase II study, and this treatment has been approved only in Europe for R/R cHL patients. Camrelizumab, another anti PD1 checkpoint inhibitor, also demonstrated an interesting efficacy profile in combination with salvage chemotherapy (gemcitabine, vinorelbine, pegylated liposomal doxorubicin) with 2-year PFS and OS probabilities of 48.2% and 81.5%, respectively (147). This drug was recently approved in China for the treatment of R/R cHL and is currently developed in B-cell lymphoma and other malignancies.

#### Nivolumab plus brentuximab vedotin

The use of a combination of the anti-CD30 antibody-drug conjugate BV and nivolumab was first assessed in patients with cHL, in whom CD30 positivity is a common feature. In a pivotal trial, this association showed 82% overall response rate (ORR) and 61% CR, with an acceptable safety profile, potentially providing patients with R/R cHL

 

this combination then underwent treatment intensification (six allogeneic stem cell transplants, five ASCT). Nivolumab plus BV was well tolerated, with the most frequent adverse events consisting of severe neutropenia (grade 3–4: 30%) and peripheral neuropathy (overall: 27%; grade 3–4: 10%, three patients discontinued BV). Two patients experienced immune-related adverse events: one had grade 3 colitis and rash, and one had grade 4 hepatitis (149). Zinzani *et al.* reported a very low objective response rate of BV as a single agent in a phase II trial (13% in R/R PMBL) (156). Therefore, a biological synergistic effect likely explains the efficacy of nivolumab plus BV; the effect probably occurs through depletion of T-reg lymphocytes and initiation of immunogenic cell death by BV, amplified by PD-1 blockade (157,158). Despite an overall favorable risk/benefit profile, the combination of nivolumab and BV remains unapproved by the FDA and the EMA for R/R PMBL, likely due to the lack of comparative data and mature survival data. However, this combination is frequently used in many lymphoma centers due to the chemorefractoriness of R/R PMBL. This combination should also be further explored as a bridge to CAR-T-cell therapy, as reported in an abstract by Chiappella *et al.* at ASH 2021. In this real-life report of CAR-T-cell use in R/R PMBL patients, 18 patients underwent apheresis, including 3 patients exposed to nivolumab plus BV, and no manufacturing failure was observed. Of note, the authors observed no difference in cytokine release syndrome or neurotoxicity between patients who had previously been exposed to checkpoint inhibitors and those who had not (159).

### *CAR-T cells*

Since 2018, three anti-CD19 CAR-T cell therapies have been commercialized for R/R DLBCL patients who have received two prior lines of treatment. Axi-cel is approved for use in R/R PMBL patients based on the results of the ZUMA-1 trial, but only eight patients with R/R PMBL were enrolled in this trial (160). Of note, tisa-cel is not officially approved for use in PMBL patients because the relevant histology was not included in the pivotal JULIET trial (161). In the TRANSCEND-NHL-001 trial, 14 R/R PMBL patients received lisocabtagene maraleucel (liso-cel) and subsequently showed ORR and CRR of 79% and 50%, respectively (162). Available data regarding the real-life efficacy of treatment with CAR-T cells in the R/R PMBL population are scarce. Of 46 patients treated with axi-cel between 2009 and 2015 in America, six had PMBL, and only 5 were evaluable for response, including two who had CR and in whom the durations of response were longer than 97 and 38 months, two who had stable disease and one who had progressive disease (ORR: 40%) (163). More recently, Crombie *et al.* reported the real-world outcomes of 33 R/R PMBL patients in five American centers who received axi-cel between 2018 and 2019 (151). The patients in this cohort received a median of 3 (range, 1–9) prior lines of therapy; 30% had received ASCT, and 67% had received radiotherapy. Among the 32 patients evaluable for response, ORR was 78% and CR was 69%, leading to 2-year PFS and OS rates of 64% and 78%, respectively. Interestingly, nineteen patients also received anti-PD1 therapy either before (n=14), after (n=4), or both before and after (n=1) axi-cel infusion. The ORR, CR, PFS, OS, cytokine release syndrome (CRS) and neurotoxicity rates were similar in patients with different sequences of anti-PD1 exposure. One patient with progressive disease following anti-PD1 and axi-cel therapy achieved a CR when retreated with anti-PD1 in the post-CAR-T cell setting, but the authors admitted the inadequacy of this single observation in assessing the benefit of administering anti-PD1 treatment after axi-cel therapy (151).

Finally, the management of refractory PMBL is changing in light of the recent FDA-approval of CAR-T cell (liso-cel) for LBCL in the second line. The ZUMA-7 study has recently established the superiority of axi-cel *vs.* standard of care (high-dose chemotherapy and ASCT) in refractory/early relapsed LBL but excluding PMBL. Meanwhile, the TRANSFORM study compared liso-cel *vs.* standard of care in several LBL subtypes and included PMBL patients. This phase III trial demonstrated that median EFS was significantly improved with liso-cel [10.1 months (95% CI: 6.1–not reached)] compared with the standard of care [2.3 months (95% CI: 2.2–4.3)]; stratified hazard ratio 0·35; 95% CI: 0.23–0.53; P<0.0001). These results led to the approval of liso-cel for PMBL patients who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy.

### *Allogeneic stem cell transplantation*

Because PMBL is an uncommon disease, most of the data that support allogeneic stem cell transplantation have been extrapolated from DLBCL studies, particularly studies of patients who relapsed after ASCT (164-167). However, two recent studies support the utility of allogeneic stem cell transplantation in R/R PMBL. First, Herrera *et al.*

reported 28 patients in 3 American centers who presented encouraging results of 45% 5-year OS and 34% 5-year DFS probabilities (150). More recently, Le Calvez *et al.*, on behalf of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) and the LYSA group, reported in an abstract the 2-year outcomes of 33 R/R PMBL patients. OS, PFS, nonrelapse mortality, graft-versus-host DFS/RFS and cumulative incidence of relapse at 2 years were 48% (95% CI: 33–70%), 47% (95% CI: 33–68%), 18% (95% CI: 7–34%), 38.5% (95% CI: 25–60%), and 34% (95% CI: 18–50%), respectively (168). The two series displayed similar encouraging results, and the observed plateaus of the survival curves suggested long-term disease control. To conclude, allogeneic stem cell transplantation is a valuable therapeutic option in a selected subset of treatment-sensitive R/R patients who experience disease progression after ASCT. Further studies are warranted to assess its clinical relevance and the appropriate timing of its use in the CAR-T-cell/immunotherapy era.

To conclude, the landscape of R/R PMBL is currently changing with the approval of CAR-T cells in second line in refractory disease and the impressive results of checkpoint blockades. The order and better use sequence of checkpoint inhibitors and CAR-T cells therapies remains strongly debated, as some patients can have sustained remissions with checkpoint inhibitors, with no need for additional treatments.

## Circulating tumor DNA (ctDNA) in PMBL

The role of ctDNA as a reliable biomarker of minimal residual disease (MRD) in cHL was recently established in several studies (14,169,170). In particular, using phased variant-enhanced CAPP-seq high-throughput sequencing technology, Pirosa *et al.* demonstrated that MRD combined with interim PET had significantly superior accuracy for the anticipation of progression or relapse compared to MRD or interim PET alone in cHL patients (170).

Earlier primary chemoresistance detection and predictive biomarker identification would also be very relevant in the PMBL population to (I) improve outcomes of R/R patients; (II) avoid useless second-line chemotherapy in the subset of refractory patients; and (III) promote the use of effective alternatives such as immunotherapy. Given that interim and end-of-treatment PET is often difficult to interpret in this disease, we may hypothesize that ctDNA measurement would help refine PET-assessed therapeutic response and would allow more personalized care based on minimal residual disease (MRD). With the past 5 years, several groups have established that ctDNA can be quite easily measured in blood samples from DLBCL, cHL and PMBL patients using high-throughput sequencing methods (14,171,172). More recently, Pang *et al.* monitored ctDNA in 16 PMBL patients receiving frontline chemotherapy and demonstrated that 94% of the patients displayed full clearance of plasma ctDNA after 2 cycles of chemotherapy and that 3 of 4 relapsing cases had measurable ctDNA 2 weeks before the detection of disease progression on follow-up imaging (173). The ongoing CAMIL (NCT04824950) study is dedicated to assessing the positive and negative predictive values of ctDNA versus PET to anticipate PR disease after 2 or 4 cycles of frontline chemotherapy. The results of this study will help provide a solid background for anticipated salvage immunotherapy (anti-PD1 checkpoint inhibition) in early MRD-positive high-risk PMBL patients. As PMBL is highly curable, it is legitimate to consider therapeutic de-escalation strategies and to consider limiting the use of ASCT to late metabolic responders (who are at higher risk of relapse), but the availability of a biomarker that is complementary to PET would be useful in the stratification of patients. Liquid biopsy or monitoring of ctDNA could be used to better assess the therapeutic response, allowing reduction of ASCT if ctDNA is undetectable after 2 and 4 cycles of chemotherapy. In addition, identifying early PR disease that occurs in 10% of patients with very poor OS (<50% at 2 years) is crucial. The use of ctDNA would allow the identification of PR patients after only 2 cycles of chemotherapy and would support timely recommendation for salvage immunotherapy. Several studies of ctDNA-based MRD in DLBCL patients have been reported, but there is no study dedicated to PMBL, although there are particular issues in the management of these patients, especially the interpretation of mediastinal uptake on PET. In the literature, the proportion of false-positive lesions based on interim and end-of-treatment PET images ranges from 11% (174) to 20% (20). A multicentric prospective study (NCT04824950) designed to evaluate the relevance of MRD monitoring in addition to PET in PMBL is ongoing. The results of this study may provide a solid rationale for the use of ctDNA monitoring in PMBL patients. The study may also provide a foundation for a future interventional trial based on the use of real-time MRD monitoring to de-escalate treatment intensity in early MRD-negative patients or to reorient treatment strategies toward immunotherapy in cases of early molecular progression.

## Future directions

To date, the main studies of the genetic landscape and phenotype of PMBL cells have reported a high prevalence of 9p24 rearrangements leading to PDL1 and PDL2 protein overexpression. As in cHL, this recurrent abnormality is favorable to the introduction of checkpoint inhibitors in R/R PMBL. However, more detailed dissection of the tumor microenvironment of PMBL remains a major need. Indeed, immune cell infiltration of PMBL tumors has been analyzed on a small scale using IHC, and the analysis indicates lower T-cell infiltration and a rather strong $CD163^{+}$ mononuclear-phagocyte compartment compared to cHL (175). Although the T-cell compartment of cHL tumors has been broadly described using mass cytometry (176), such studies are still lacking in PMBL, probably due to the paucity of the biopsy material remaining after histopathological diagnosis of small samples, an issue related to the mediastinal location of PMBL.

Regarding frontline treatment, we can anticipate that the medical community will move toward a progressive deintensification of first-line strategies, reducing the use of ASCT and CRT and adopting an integrated risk-adapted and response-adapted treatment program. We also hypothesize that in the next 5 years immunotherapy with anti-PD1/PDL-1 will be introduced as a first-line treatment in combination with a reduced number of chemotherapy cycles. We should also reconsider the use of CRT after immunochemotherapy in the large majority of patients, especially in patients with bulky mediastinal masses and residual mediastinal uptake at the end of treatment. A more personalized approach that includes MRD monitoring should progressively be integrated to include assessment of the quality and quantification of the molecular response in the decision-making regarding consolidation treatments.

## Conclusions

PMBL is a specific entity of LBCL with clinical and biological characteristics close to those of cHL, and treatment of individuals with PMBL is similar to that of young DLBCL patients. PMBL has a particular natural history and a singular biology that make it unique. Its low incidence is responsible for its exclusion from many therapeutic CTs (most of which primarily include DLBCL patients) and the absence of a consensus regarding the management of these lymphomas. However, PMBL occurs in a population of young patients with specific concerns, and we should continue our efforts to develop new and innovative therapeutic strategies for treatment of these lymphomas, particularly with the use of MRD-guided treatments and immunotherapies such as anti-PD1 and CAR-T cells.

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