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Review Article

Plasmablastic Lymphoma. A State-of-the-Art Review: Part 2-Focus on Therapy

Michele Bibas.

Department of Clinical Research, Hematology. National Institute for Infectious Diseases "Lazzaro Spallanzani" I.R.C.S.S. Via Portuense 292 00148 Rome Italy.

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Abstract. The objective of this two-part review is to present a current and comprehensive understanding of the diagnosis and management of plasmablastic lymphoma. The first part, which was published previously, focused on the study of epidemiology, etiology, clinicopathological characteristics, differential diagnosis, prognostic variables, and the impact of plasmablastic lymphoma on specific populations. This second part addresses the difficult topic of the treatment of plasmablastic lymphoma, specifically examining both the conventional, consolidated approach and the novel therapeutic strategy.

Keywords: Aggressive Lymphoma; People living with HIV; Plasmablastic Lymphoma; CD20-negative large B-cell Lymphoma; CD38+; CD138+; V-EPOCH; Daratumumab; Lenalidomide; Bortezomib.

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Correspondence to: Michele Bibas. Department of Clinical Research, Hematology. National Institute for Infectious Diseases "Lazzaro Spallanzani" I.R.C.S.S. Via Portuense 292 00148 Rome Italy. E-mail: Michele.bibas@inmi.it

Article Highlights.

- Several factors that could impact the result include achieving complete remission, performance status (PS), clinical stage, MYC status, and the International Prognostic Index (IPI).
- Physically fit patients might benefit from a more intensive treatment protocol, such as DA-EPOCH, instead of the conventional CHOP regimen. Combinations with Bortezomib, Daratumumab, or Lenalidomide may be considered.
- Patients who achieve complete remission following the initial treatment (CR1) may be eligible for additional intensification through autologous bone marrow transplantation (ABMT).
- The effectiveness of rituximab is reduced since tumor cells do not have CD20 expression, although it may be employed in certain rare CD20+ cases.
- CNS prophylaxis can be considered in a case-by-case basis.
- It is highly recommended that patients who are HIV-positive and receiving chemotherapy utilize combination antiretroviral treatment (cART). Consider the possibility of simultaneous toxicity.
- Individuals with persistent or recurring illnesses that do not respond to treatment should consider palliative care.
- Consolidation and palliative care applications can benefit from radiation therapy as an effective approach.
- New drugs like Bortezomib, Daratumumab, Lenalidomide, Brentuximab vedotin, PD1/PDL1 blocking agents, and Selinexor can be used to treat cases that have relapsed or are not responding to treatment.
- The range of median progression-free survival (PFS) is between 6 and 11 months, whereas the most recent reported median overall survival (OS) is from 14 to 57 months.

- Individuals with limited stages of the disease, especially among pediatric populations, have achieved long-term survival.

Introduction. The identification and characterization of plasmablastic lymphoma (PBL) date originally from 1992,[1] after that, it was recognized as a distinct form of oral lymphoma occurring in individuals who are HIV-positive.[2] This particular subtype of large B-cell lymphoma (LBCL) is now categorized as a distinct entity, with extranodal disease being the prevailing characteristic.[3-6]

Despite earlier studies indicating a strong association, it has been observed that around 50% to 60% of cases are associated with HIV. 3–5 PBL accounts for just 2% of lymphomas in individuals who are HIV-positive.[3-6] The disease has the potential to impact individuals with compromised immune systems as well as those with robust immune systems.

Histological examination reveals the presence of several neoplastic plasmablasts and immunoblasts. The identified cells exhibit a significant proliferation index and possess a plasma cell immunophenotype, characterized by the presence of plasma cell markers and a limited or missing expression of B cell markers.

Notably, transcription factors linked to plasmacytic differentiation, including CD38, CD138, MUM1, Blimp1, and XBP1, are present. The absence of CD20 and PAX5 has been very frequently observed. PBL frequently has a connection to the overexpression of the MYC gene, which can result from translocations, amplifications, or constitutive STAT3 activation. This is in contrast to plasma cell neoplasms.[3-7] Moreover, around 80% of PBL cases were found to have a simultaneous Epstein-Barr virus (EBV) infection. This feature can be regarded as a discerning element differentiating PBL from plasmablastic myeloma. Hence, distinguishing between plasmablastic myeloma, lymphomas, and PBL can pose a significant difficulty. Translational research encounters several challenges, such as the limited occurrence of PBL and the absence of an established treatment strategy due to a scarcity of thorough clinical data.[3-8]

Historically, PBL has been associated with a negative outlook, as early estimates of median overall survival (OS) ranged from 8 to 15 months.[3-6] There have been more survival estimates reported in recent literature that display significant diversity.

A population-based SEER survival analysis examined 248 patients who had treatment between 2010 and 2016. The analysis revealed that the median overall survival was 47 months.[9]

Further, a total of 1,800 patients were very recently assessed using SEER and the NCDB. An exceptional median overall survival of 58.6 months was seen in the treated patients.[10]

Although there have been some improvements recently, CD38-directed monoclonal antibody therapy, proteasome inhibitors, and immunomodulatory therapeutic regimens, along with intensive polychemotherapy, are still rarely available for older and weaker patients. Those limitations highlight the requirement for therapeutic strategies that are precisely personalized to fulfill individual requirements.

Treatment. Establishing a therapeutic standard is quite problematic due to the rarity of the disease and the lack of controlled trials available for comparing different treatments. In this second part of the review, our intent is to provide a comprehensive and detailed description of the achievements of the diverse consolidated therapies, as well as those that are currently being developed. We will organize the information into pertinent chapters for clarity.

Standard Polychemotherapy. Patients with untreated PBL exhibit a median overall survival of 3 months in individuals who are HIV-positive and 4 months in those who are HIV-negative.[3-6]

Patients diagnosed with PBL have been subjected to a wide range of treatment options, covering localized disease management by radiation as well as the administration of diverse chemotherapy combinations. Individuals who are diagnosed with limited-stage disease tend to have a more favorable prognosis, and in certain instances, aggressive treatment measures may not be recommended. Disease control may be achieved through the utilization of a combination therapy involving doxorubicin-based chemotherapy and radiation therapy.[3-6] Of note, the majority of PBL patients must be considered high-risk patients and treated with polychemotherapy. Polychemotherapy has yielded complete remissions (CRs) in nearly 50% of patients with disseminated disease. The response and relapse rates among different first-line regimens are presented in **Table 1**.

However, a significant proportion of patients, approximately 70%, inevitably die of progressive disease. At present, there is a lack of established care standards that delineate the most effective therapy method. Throughout history, the use of CHOP has been widely adopted as the primary therapeutic approach for PBL, with a particular emphasis on its utilization in nations with lower economic resources. According to the latest National Comprehensive Cancer Network (NCCN) guidelines on B-cell lymphomas (version 1.2024, January 18, 2024),[22] it has been determined that CHOP is not adequate as a first-line therapy.

NCCN supports using more intensive treatment plans for PBL and suggests dose-adjusted (DA)-EPOCH as an alternative way to treat the disease. DA-EPOCH includes etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone given in bolus doses. Some other

Table 1. Literature review of the polychemotherapy regimens of PBL patients.

Polychemotherapy	No. Of Cases (median age)	Outcome	Author, year, ref.
CHOP alone	16 (38)	CR 66%; PR 6%	Castillo J.J. 2008 [11]
CHOP; EPOCH; H-CVAD CODOX-M/IVAC	70 (38.8)	CR 46%; PR 31%	Castillo J.J. 2010 [12]
CHOP OR CHOP-LIKE	53 (43)	CR 66%; PR 5%	Castillo J.J. 2012 [8]
EPOCH; CHOP	25 (42)	CR 48%; PR 8%	Ibrahim I.F. 2014 [13]
CHOP; EPOCH; H-CVAD	61 (49)	CR 45 %; PR 7%	Loghavi S. 2015 [14]
CHOP; EPOCH; H-CVAD	10 (50.5)	CR 70%; PR 10%	Pinnix C.C. 2016 [15]
CHOP; CODOX-M/IVAC	13 (30)	CR 46%; PR 17%	Rudresha A.H. 2017 [16]
CHOP OR CHOP-LIKE	38 (43)	5-year OS 61%	Foca E. 2018 [17]
CHOP OR CHOP-LIKE ACVBP; EPOCH; CODOX-M/IVAC	35 (57)	CR 93 %; PR 6%	Al Tabata Y. 2018 [18]
EPOCH; CHOP	12 (46)	CR 41%	Zuze T. 2018 [19]
CHOP OR CHOP-LIKE ACVBP; EPOCH;	153 (41.9)	2-year OS 42%	Rodrigues-Fernandes C.I. 2018[20]
CHOP, EPOCH, CODOX/IVAC H-CVAD, CHOEP, CVP	200(55)	5-year OS 36% OR 72%	Di Ciaccio PR 2024[21]

CR: Complete Response; PR Partial Response; OS: Overall Survival; OR: Overall Response.

treatment plans that have been suggested are CODOX-M/IVAC (modified) and HyperCVAD (which includes cyclophosphamide, vincristine, doxorubicin, dexamethasone, and high doses of methotrexate and cytarabine). Furthermore, these guidelines suggest the potential use of high-dose therapy with autologous stem cell rescue during the first complete remission for a particular subgroup of patients at high risk. A high-risk factor includes an International Prognostic Index (IPI) score above 2 and changes to the MYC gene or deletion of the TP53 gene. It is important to acknowledge that individuals who are HIV-negative and diagnosed with plasmablastic lymphoma are commonly recognized as having a condition associated with an elevated risk. Typically, those who are HIV-negative and diagnosed with plasmablastic lymphoma are generally characterized as having a more threatening disease. On the other hand, there is a more favorable outlook for individuals who are HIV-positive and diagnosed with PBL when they successfully attain complete remission with the administration of chemotherapy. Antiretroviral therapy is crucial for improving the management of PBL HIV+, and the attainment of complete remission (CR) has been shown to enhance the short-term prognosis of PBL.[3-6]

Bortezomib. Bortezomib is currently approved for treating adult patients with multiple myeloma and adult patients with mantle cell lymphoma. The small molecule bortezomib is a reversible proteasome inhibitor that works on the 26S proteasomes. It stops many signaling pathways by targeting a single molecular target, the proteasome. Bortezomib's anti-neoplastic effect likely involves several distinct mechanisms, such as inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of the expression of genes that regulate cellular adhesion, migration, and angiogenesis. Thus, the mechanisms by which bortezomib elicits its anti-tumor activity may differ between tumor types, as could the importance of each affected pathway in inhibiting tumor growth. Bortezomib is thought to work against multiple myeloma by stopping NF-B from working and stopping the breakdown of phosphorylated IB. Because of this, it seems like a good way to treat PBL patients, whose biological and phenotypic traits are somewhere between those of ABC-DLBCL and MM. Several reports have reported its activity in lymphoma, specifically in non-Germinal Center B-cell lymphomas such as DLBCL and mantle cell lymphoma.[23-26] Thus, bortezomib is one of the most frequently used drugs in the treatment of PBL. It has been utilized as a single agent and in conjunction with chemotherapy. The objective of our extensive literature review was to determine if patients with PBL would experience more benefits from the inclusion of bortezomib in their polychemotherapy (**Table 2)**.

Five out of six patients treated with bortezomib alone in a small series achieved a partial response—two as first-line therapy and three as salvage therapy.[40] Bortezomib has been used in combination with CHOP as frontline therapy in three HIV-associated PBL patients, all of whom achieved a CR, and two of whom are still alive 14 and 22 months after completing V-CHOP, respectively.[37] According to a positron emission tomography scan, Castillo et al. reported three patients without relapse at 12, 18, and 24 months.[36] Recently, Dittus and Castillo reported 8 and 16 patients, respectively, with CR rates of 87.5% and 94%.[41,42] In the latter series, two patients received an ASCT for consolidation. Castillo reported a 5-year OS of 63%,

Table 2. Literature review of Bortezomib containing regimens in PBL.

Bortezomib alone or with chemotherapy	Cases; age	Outcome	Author, year, ref.
Bortezomib single therapy	1 (55)	P after 4 months.	Jambusaria A. 2008[27]
Bortezomib single therapy	1 (42)	P after 1 months.	Bose P. 2009[28]
Bortezomib + GOVDD	1 (19)	P after 2 months.	Bibas M. 2010[29]
Bortezomib + DRC	1 (68)	PR	Lipstein M. 2010[30]
Bortezomib + Dexamethasone	1(80)	PR	Dasanu CA 2013[31]
Bortezomib + Dexamethasone	1(44)	PR	Saba NS 2013[32]
Bortezomib + Dexamethasone	1(50)	PR	Cao C. 2014[33]
Bortezomib + COMP	1 (66)	CR	Cencini E. 2015[34]
Bortezomib + THP-COP	1 (58)	PR	Hirosawa . 2015[35]
Bortezomib + CHOP	3 (38)	CR 3/3; 3/3ABMT after CR.	Fernandez-Alvarez R. 2015[37]
Bortezomib + EPOCH+ IT MTX	1(50)	CR	Fedele PL 2016[38]
Bortezomib + DA-EPOCH	1(34)	CR	Arora N. 2017[39]
Bortezomib single therapy Bortezomib + chemotherapy	6 (42) 15 (42)	CR 0/6 PR 5/6 CR 9/15 Pr 5/6	Guerrero-Garcia T. 2017[40]
Bortezomib + DA-EPOCH	8 (49)	CR 8/8	Dittus C. 2018[41]
Bortezomib + EPOCH	16 (47)	CR 15/16 PR 1/1	Castillo JJ 2019[42]
Bortezomib + oral CTX and DEX	1(64)	PR	Ando K. 2019[43]
Bortezomib single therapy	1(55)	PR	Umeanaeto 2019[44]
Bortezomib + CDOP	1 (63)	PR	Cai J. 2021[45]
Bortezomib +Lenalildomide+ DEX	1 (59)	PR	Sabry W. 2022[46]
Bortezomib + Chemotherapy	31 (55)	5 years OS 36% OR 72%	Di Ciaccio P.R. 2024 [21]

P: Progression; CR: Complete Response; PR Partial Response; OS: Overall Survival; OR: Overall Response.

while Dittus reported a 2-year PFS and OS of 50%.[41,42] Bortezomib has also been used with THP-COP (pirarubicin, cyclophosphamide, vincristine, and prednisone), ESHAP (etoposide, high-dose prednisolone, high-dose cytarabine, and platinum), ICE (ifosfamide, carboplatin, and etoposide), bendamustine, rituximab, and DT.[35] A recent systematic review found 21 patients with PBL, 11 of whom had HIV and 10 of whom did not. Eleven of them were given bortezomib as the first line of treatment, and the other 10 were given it after a relapse, either by itself or with other standard cytostatic drugs. The ORR for bortezomib-containing regimens was 100% in the frontline setting and 90% in the relapse setting. In addition, the 2-year overall survival rate for patients who received initial treatment was 55%, while the median OS for relapsed patients was 14 months.[40]

Finally, upon evaluating the existing literature, it was found that patients with PBL benefitted from including bortezomib in their treatment. However, we acknowledge that we are currently experiencing a shortage of randomized studies comparing chemotherapy regimens with and without bortezomib.

Lenalidomide. Lenalidomide is an oral immunomodulator with direct antitumor activity and immunologic effects, such as stopping tumor cell growth and angiogenesis and increasing the killing power of T- and natural killer (NK) cells in lab experiments. In vitro and in vivo studies revealed antitumor, antiproliferative, and increased NK cell number and activity against B-cell malignant lymphoma in general and against DLBCL, FL, and MCL cells. In preclinical models of activated B-cell (ABC)-subtype DLBCL, lenalidomide-induced cytotoxicity required the presence of cereblon to downregulate interferon regulatory factor-4 and B-cell receptor-NFB and boost interferon production. Of note, low cereblon expression is a potential lenalidomide resistance mechanism.[47]

According to a thorough review of the literature, lenalidomide has only been used in a few cases of PBL, and each case is very different from the others (**Table 3**). Cases of refractory PBL treated with lenalidomide as a single agent were reported to have a favorable response, albeit a brief one.

It also demonstrated efficacy when combined with CHOP, or cyclophosphamide-dexamethasone.[49] Ando et al. utilized bortezomib to treat chemotherapy-resistant PBL patients, which resulted in a clinical response but was discontinued due to peripheral neuropathy.[43] The patient was then treated with a combination of lenalidomide and dexamethasone for more than two years, with a partial response that persisted.[43]

A person with PBL who was not responding to mini-CHOP as a first-line treatment went into complete remission after taking tislelizumab, a checkpoint

Table 3. Literature review of Lenalidomide containing regimens in PBL.

Lenalidomide alone or with chemotherapy	Cases age	Outcome	Author, year, ref.
Lenalidomide after 4 lines of therapy	1 (19)	P after 3 months	Bibas M. 2010[29]
Lenalidomide after 4 lines of therapy	1 (83)	P after 3 months	Carras S. 2015[48]
Lenalidomide + CHOP	1 (40)	CR 6 cycles	Yanamandra U. 2016[49]
Cyclophosphamide, lenalidomide, dexamethasone (CRD)	1(75)	CR 12 months	Schmit JM 2017[50]
Lenalidomide after 1 line of therapy	1(76)	CR 12 months	Marrero D.2018[51]
Lenalidomide after 3 lines of therapy	1(64)	PR 24 months	Ando K. 2019[43]
Lenalidomide after 1 line of therapy in combination with Tislelizumab	1 (76)	CR 18 months	Cheng L. 2021[52]
Lenalidomide maintenance after bortezomib + CDOP and ABMT	1 (63)	CR 12 months	Cai J. 2021[45]
Lenalidomide and Daratumumab after 1 line of chemotherapy	1 (23)	PR 8 months	Lee M. 2022[53]
Bortezomib + Lenalidomide+ DEX	1 (59)	CR 5 months	Sabry W. 2022

P: Progression; CR: Complete Response; PR Partial Response; OS: Overall Survival; OR: Overall Response.

inhibitor, and lenalidomide.[52]

Another patient with relapsed PBL with parotid involvement was treated with a combination of lenalidomide and bortezomib.[51] This patient received only two cycles of the protocol before it was discontinued due to bortezomib-induced pancreatitis. However, a PET CT scan performed after the two cycles revealed no evidence of disease, and the patient remained in complete remission for at least a year following the initiation of salvage therapy.

Brentuximab Vedotin (BV). CD30 is a 120-kilodalton transmembrane cytokine receptor, part of the tumor necrosis factor receptor family 4. It is found on the lymphoid cells of almost all HL and ALCL patients. Expression of CD30 is restricted to activated lymphocytes and eosinophils, typically found in lymphoid tissues but not in peripheral blood cells. Thus, CD30 has been identified as a desirable therapeutic target. Brentuximab vedotin (BV) is a chimeric IgG1 anti-CD30 antibody-drug conjugated by a protease-cleavable linker to the microtubule-disrupting agent monomethyl auristatin E, which has demonstrated significant anti-tumor activity in both HL and ALCL.[54,55]

The main way that BV works is by delivering monomethyl auristatin E to tumor cells that express CD30. In addition to antibody-dependent cellular phagocytosis, immunogenic cell death, and the bystander effect, other mechanisms of tumor cell death may contribute to the clinical activity of this drug. The availability of BV has become a significant advance in the treatment of patients with relapsed and resistant HL. In addition, the significant clinical activity observed and the good tolerability of BV have allowed for widespread investigation and use of BV in a variety of lymphoma patients, and several groups are testing BV-based therapies in the management of newly diagnosed patients with HL and ALCL, with promising preliminary results.[54,55] Positive expression of CD30 has been detected in 30–50% of PBL cases, making CD30 a viable target for PBL.[3-10] It is reported that the use of brentuximab vedotin resulted in an impressive reduction in tumor size but also a fatal outcome due to tumor lysis syndrome and comorbidities.[56] The patient's tumor, which had undergone extensive prior treatment and was unresponsive to numerous chemotherapy regimens, had a positive response when treated with brentuximab vedotin as a standalone therapy and ionizing radiation. This information shows that more research should be done on brentuximab vedotin for CD30-positive PBL, either as a single treatment or in combination with standard chemotherapy.

Selinexor. The overexpression of XPO1 (exportin 1), one of eight nucleocytoplasmic shuttling proteins that help move proteins from the nucleus to the cytoplasm, is linked to a poor prognosis in DLBCL.[57] XPO1 mediates the functional inactivation of multiple tumor suppressor proteins (such as p53, p73, IkB, and FOXO) and facilitates the increased translation of oncoproteins relevant to B-cell biology and DLBCL.[58,59] By forcing these proteins to stay in the nucleus, blocking XPO1 in DLBCL may restore the tumor-suppressing and growth-regulating effects of several tumor-suppressor proteins. This may also reverse chemotherapy resistance.[60] Selinexor, an oral selective inhibitor of XPO1-mediated nuclear export, induces the expected nuclear accumulation and activation of tumor suppressor proteins and decreases the levels of Bcl2, Bcl-XL, and c-Myc oncoproteins. Based on the safety and effectiveness data from the STORM study, the US Food and Drug Administration approved the use of low-dose

dexamethasone and selinexor (80 mg twice weekly) together for people with advanced refractory multiple myeloma.[61] In a phase 1 study that showed selinexor's preliminary activity in several types of blood cancer, such as myeloma and DLBCL, the single drug selinexor showed an overall response rate (ORR) of 32% in 13 of 41 patients who had already received a lot of treatment for DLBCL, and a complete response rate of 10% in 4 of those patients. Based on that study, the recommended dose was 35 mg/m^2 (60 mg) twice weekly.[62] The FDA has approved selinexor to treat diffuse large B-cell lymphoma (RR DLBCL) and relapsed or refractory multiple myeloma (RR MM). It is very effective as a type of treatment.[63,64] Regarding PBL, a case of a profound response to selinexor in HIV-negative, EBV-negative, heavily pretreated young PBL patients has been reported recently. 60 mg of Selinexor were administered on days 1, 8, and 15, followed by a GDP (gemcitabine, cisplatin, and dexamethasone) regimen every three weeks. A rapid partial response (PR) to selinexor was observed within two weeks of treatment. Selinexor was found to be tolerable and safe. This patient reported mild hemocytopenia as the most common adverse reaction, without nausea, vomiting, or hyponatremia.[65]

Daratumumab. CD38 is a 48-kDa transmembrane glycoprotein that can be observed on the surface of many hematopoietic cells, such as multiple myeloma cells. It provides several functions, including receptor-mediated adhesion, signaling, and regulation of cyclase and hydrolase activity.[66,67]

Daratumumab is a human IgG1 monoclonal antibody that binds with high affinity to a unique CD38 epitope expressed on malignant cells and possesses direct and indirect antitumor activity and multiple mechanisms of action. Immune-mediated actions include complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP); and immunomodulatory functions that target and deplete CD38-positive regulator immune suppressor cells, resulting in T-cell expansion and activation in patients with a response.[68,69]

Currently, daratumumab is under investigation for many types of hematological malignancies.

CD38 expression has been linked to a number of these diseases: in addition to multiple myeloma, consistent expression has been observed in the malignant cells of CLL, and it has also been reported in Waldenstrom macroglobulinemia, mantle cell lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, NK cell leukemia, and NK/T-cell lymphoma.[70-74]

Daratumumab induces the death of CD38-expressing tumor cells through multiple mechanisms, including complement-mediated cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) effects, antibody-dependent cellular phagocytosis (ADCP), apoptosis, and, to a lesser extent, inhibition of the enzymatic activity of CD38.[75-79]

Plasmablastic lymphomas are often CD38+ and share some biological and phenotypic features with multiple myeloma. Because of this, it seems reasonable to think that daratumumab could be used as proof of concept of activity in people with PBL who fail their first line of conventional chemotherapy or who are not eligible for autologous stem cell transplantation.

Table 4 summarizes studies of the use of daratumumab in PBL.

Ryu assessed the effectiveness and safety of daratumumab-based treatment plans in seven patients with advanced-stage PBL.[86] Out of these patients, 6 were considered evaluable, 4 had classic PBL, and 1 did not satisfy the precise criteria for PBL as established by the World Health Organization (WHO).[86] The initial assessment revealed that the median age of the patients included was 48 years. Additionally, all seven patients had disease locations outside the lymph nodes, 4 patients had ECOG scores of 3 or 4 at diagnosis, and 5 patients proved positive for CD38. Five patients underwent six cycles of daratumumab in conjunction with DA-EPOCH, and one patient underwent weekly daratumumab in addition to the addition of bortezomib. All patients who could be evaluated obtained a complete response (CR); four individuals were in remission after completing treatment. As of the data cutoff, the median duration of response (DOR) for the patients who could be evaluated was 16.8 months, and all of them were still showing a response. Patients diagnosed with classic PBL had a median duration of response (DOR) of 23.7 months, whereas patients who did not fulfill the stringent criteria for PBL had a median DOR of 3 months. The median overall survival (OS) and progression-free survival (PFS) were indeterminate in patients with classic PBL, except for one patient who died due to illicit drug use, asthma exacerbation, and respiratory arrest. In contrast, the median OS and PFS were 7 months and 6 months in patients who did not meet the strict criteria for PBL. Patients who failed to satisfy the stringent specifications for PBL experienced relapse and succumbed quickly after the completion of treatment. The 24-month overall survival rate for all patients who could be evaluated, regardless of whether they died from causes unrelated to treatment or disease, was 57%. Out of seven patients, six experienced severe adverse effects. There were no recorded fatalities associated with the treatment. Following the administration of daratumumab, two patients experienced infusion-related events, including a rash and itching in one patient and bradycardia in another.

In another small study, Daratumumab was also combined with the standard NHL salvage regimen, ICE. Five PBL patients were described.[41] Three patients were administered daratumumab in combination with EPOCH

Table 4. Literature review of Daratumumab therapy reports and Clinical Trial in PBL.

Daratumumab alone or with chemotherapy	Cases, age	Outcome	Author, year, ref.
Daratumumab + DHAP after 2 lines of CT + ABMT	1 (47)	CR 46 months	Chikeka I. 2019[80]
Daratumumab + COP after 1 line of CT in Transformed PBL+ABMT	1 (63)	P 2 months.	Marvyi8n K. 2020[81]
Daratumumab after 2 or more lines of CT and ABMT	3 (53)	P 2 months.	Roche P. 2021[82]
Daratumumab+ EPOCH	4(55)	3 CR 20 months PR 4 months	Ricker E. 2021[83]
Daratumumab + CyBorD	1(57)	CR 18 months	Ramadas P. 2021[84]
Daratumumab + Bortezomib and Lenalidomide > 2 lines of CT	1(45)	CR 36 months after AHCT	Kathrotiya M..2021[85]
Daratumumab + EPOCH, or + bortezomib and lenalidomide	7 (76)	6 CR (18-31) months 1 PR	Ryu YK 2021[86]
Daratumumab and Lenalidomide after 1 line of CT	1 (23)	PR >8 months	Lee M. 2022[53]
Daratumumab + ICE	5 (49)	5 CR 8-73 months	Dittus C. 2022[41]
Dartumumab+bortezomib + ABMT after B_EPOCH	1(38)	CR 18 months	Bhat G. 2022[87]
Daratumumab+ EPOCH	1 (66)	P 2 months.	Pinto MP 2023[88]
Active Clinical Trial		Status/sponsor	Clinical trial number
Daratumumab + DA-EPOCH		Recruiting/ AIDS malignancy Consortium	NCT04139304
Daratumumab, bortezomib and Dexamethasone		Recruiting/ Fondazione Italiana Linfomi	NCT04915248

P: Progression; CR: Complete Response; PR Partial Response; OS: Overall Survival; OR: Overall Response.

as their first-line treatment, while one patient received daratumumab together with lenalidomide, dexamethasone, and doxorubicin after experiencing a relapse. Three of the four patients maintained a state of remission for a minimum of 15 months after obtaining a complete response (CR).[41]

The AIDS Malignancy Consortium is now carrying out a limited, prospective investigation on the use of daratumumab-EPOCH in the first-line treatment of PBL (NCT04139304).

This study aims to assess the efficacy of daratumumab in combination with dose-adjusted etoposide, prednisone, vincristine sulfate, cyclophosphamide, and doxorubicin hydrochloride (DA-EPOCH) in the treatment of patients who have recently been diagnosed with stage I-IV plasmablastic lymphoma. The main goal is to determine the effectiveness of including daratumumab in the DA-EPOCH regimen by examining the proportion of patients with PBL who successfully complete at least three cycles of treatment according to the established protocol.

Daratumumab is administered to patients intravenously (IV) on days 1 (± 3 days), 8 (± 2 days), and 15 (± 2 days) during cycles 1-3, and on day 1 of cycles 4-6. Patients are given etoposide, doxorubicin hydrochloride, and vincristine sulfate intravenously for a continuous period of 96 hours on days 1-4. In addition, they orally provide prednisone for a period of 5 days, beginning on the first day, and intravenously administer cyclophosphamide for a length of 1 hour on the fifth day. The treatment is given at intervals of 21 days for a maximum of 6 cycles, unless there is a clear indication of disease recurrence or the patient experiences unacceptable adverse reactions.

Presently, another ongoing clinical study is assessing the efficacy of Daratumumab in conjunction with Bortezomib and dexamethasone for patients with refractory or recurrent PBL (NCT04915248).

This study is a phase II clinical trial conducted at many centers. It is an open-label, single-arm trial.

A total of 28 patients are expected to commence therapy over a period of 18 months, with recruitment taking place in 19 Italian FIL centers. The study's primary endpoint will be examined approximately 12 months after the final patient is enrolled, independent of the patient's response to the treatment outlined in the protocol. The study is expected to last around 2.5 years. Patients will be recruited based on their specific diagnosis and local assessment of CD38 expression at a level of 5%. The screening phase of the study involves conducting baseline assessments under local norms and study requirements. Induction treatment consists of one

course (cycle 1) of daratumumab sc as a single agent, followed by eight courses (cycles 2–9) of daratumumab sc in combination with bortezomib sc and dexamethasone (DVd regimen). A maximum of 6 cycles (cycles 10-15) of daratumumab SC as a single agent will be administered to patients who achieve at least an SD after the induction phase. Every 21 days, induction cycles will be administered, while every 28 days, maintenance cycles will be administered.

Polatuzumab Vedotin. Nearly 40% of all cases of plasmablastic lymphoma have CD79a expression, ranging from 35% in HIV-negative patients to 45% in HIV-positive patients and 68% in post-transplant patients.[5-12] Thus, CD79a has been identified as a desirable therapeutic target for PBL.

Polatuzumab vedotin (Pola) is an innovative antibody-drug combination. It comprises a monoclonal antibody that targets CD79b, a component of the B-cell receptor found on normal B cells. This antibody is chemically linked to the microtubule-disrupting anti-mitotic agent, monomethyl auristatin.[89,90] A phase 1 trial demonstrated the safety of using polatuzumab vedotin alone in patients with severely treated B-cell malignancies, including non-Hodgkin lymphoma and chronic lymphocytic leukemia.[91,92] In real-world research, two patients with PBL were recently treated with a combination of polatuzumab, vedotin, and bendamustine. However, there is currently no available data on the outcomes of this treatment.[93] It is plausible that Pola could be used in a clinical trial for patients with relapsed or refractory PBL.

PD-1/PD-L1 Blocking Therapies. PD-1 binds to PD-L1 or PD-L2 on the surface of tumor cells and/or tumor-associated macrophages (TAM) in the tumor microenvironment, transmitting inhibitory signals to the T-cell receptor (TCR) pathway. Consequently, TCR-mediated signaling activation and cellular proliferation are inhibited.[94-101]

The inhibition of the PD-1/PD-L1 pathway can free T-cells from the inhibitory effects of tumor cells and restore the T-cell-mediated antitumor immune response. In recent years, significant progress has been made in developing cancer immunotherapies, such as PD1/PD-L1 inhibition. James Allison (MD Anderson Cancer Center, Houston, Texas, U.S.A.) and Tasuku Honjo (Kyoto University, Kyoto, Japan) were awarded the Nobel Prize in Physiology or Medicine in 2018 for their discoveries that made cancer immunotherapy possible.

PD-L1 levels expressed by tumor cells are generally associated with a response to PD-1/PD-L1 inhibitor therapies, widely used to treat patients with non-hematologic and hematologic malignancies, such as lung cancer, melanoma, and lymphoma. These inhibitors can prevent the binding of PD-1 to its ligands, thereby restoring the T-cell immune response and resulting in substantial and durable patient responses. The highest response rates have been observed in patients with classic Hodgkin lymphoma (CHL) among hematolymphoid neoplasms. In contrast, patients with non-Hodgkin lymphomas, including diffuse large B-cell lymphoma (DLBCL) and T-cell lymphomas with heterogeneous PD-L1/PD-L2 expression, have exhibited variable responses. Immunohistochemistry has been the primary method for assessing PD-L1 positivity in neoplastic cells based on PD-L1 expression. The positivity threshold values for PD-L1 vary between studies. For instance, a 5% cut-off was used in an early study, whereas different cut-offs were used in different lymphoma studies.[102-111]

An analysis of 82 patients with PBL revealed that almost all cases exhibited the presence of programmed death ligand 1 (PDL1) and programmed cell death protein 1 (PD1) in the immune infiltrate. Furthermore, a significant proportion of these cases, specifically one quarter, demonstrated substantial expression of PDL1 in both tumor cells and immune cells.[112]

In Epstein-Barr virus-positive PBL (EBV+ PBL), there was a higher level of overexpression of PD1/PDL1 in the microenvironment.[113]

Immunotherapy is thus becoming a viable treatment choice for this condition. A case study documented the use of nivolumab as salvage therapy in a patient with PDL1+ PBL, which successfully allowed an allogeneic stem cell transplant.[114]

A case study involving a patient with chemoresistant EBV + PBL showed that treatment with tislelizumab plus lenalidomide resulted in complete remission (CR) and an overall survival of 18 months.[115] Moreover, a recent case study documented a successful treatment outcome using pembrolizumab and radiotherapy in a patient with HIV-negative, EBV-positive recurrent plasmablastic lymphoma.[116]

Chimeric Antigen Receptor T-Cell Therapy. The field of therapeutic T cell engineering has gained significant attention recently because of the remarkable achievements of CD19 (chimeric antigen receptor) CAR treatment. Chimeric antigen receptors (CARs) are artificial receptors that alter the specificity and modify the function of T cells into which they are genetically inserted.[117-119]

The CD19 antigen is a member of the immunoglobulin superfamily and is specifically expressed in B-lymphocytes. Its expression is limited to the B-cell lineage, beginning in the early stages of B cell development, which coincide with heavy chain immunoglobulin rearrangement, and continuing until the later stages of B cell differentiation. Notably, the expression of CD19 increases as B cells differentiate. CD19, CD21, CD81, and Leuk-13.5 combine on the cell

membrane of B-lymphoid cells to create a transduction complex. In addition, CD81 controls the level of CD19 expression during B cell growth.[117-119]

Over the past ten years, research has clearly shown and emphasized the important role of CD19-CAR-T cells in treating people with DLBCL that has relapsed or are not responding to treatment. The therapeutic function was designated for patients with a resistant disease and experience an early recurrence. CD19-CAR-T cells have demonstrated consistent therapeutic action in DLBCL patients with only a partial response after salvage therapy.[119-124]

CD19-CAR-T cells have effectively treated high-risk DLBCL patients as a first-line treatment. However, further research is necessary to evaluate their efficacy compared to traditional treatments. There isn't enough information yet to say which of the four commercially available CAR products for people with B cell lymphomas—Axi-Cel, Brexa-Cel, Liso-Cel, and Tisagenlecleucel—works best and causes the fewest side effects.[119-124]

Sadly, the majority of plasmablastic lymphomas lack CD19 expression. Nevertheless, only a small proportion of those patients can express this receptor, making CAR-T therapy plausible.

Raychaudhuri et al.[125] demonstrated that PBL can respond positively to axi-cel when CD19 is expressed. This patient's response was transient but clinically significant. Pain and transfusion-dependent cytopenias resolved, and the patient's performance status returned to normal. Longer in vivo persistence of axi-cell activity may have allowed for a more robust response.[125]

Autologous Bone Marrow Transplantation (ABMT). Multiple studies have shown that up to 60 percent of patients with relapsed or refractory lymphoma will progress before ABMT.[126] In addition, the prognosis for patients with recurrent or resistant PBL is dismal.[127] Since the outcome appears significantly better in patients with relapsed NHL who received ABMT compared to those who did not, it seems reasonable to investigate the use of ABMT earlier in the course of disease, at least in the high-risk subgroup of patients.

A study using the EBMT registry found that some types of NHL, like plasmablastic lymphoma, had a higher risk of relapse compared to DLBCL (relative risk, 3.4%; 95% confidence interval, 1.1% to 10.4%; P.03) and a possible trend toward worse survival. It was hypothesized that ABMT in CR1 could be advantageous for this subgroup of patients.[128]

GICAT (Gruppo Italiano Cooperativo AIDS e Tumori) presented an interim analysis of a phase II multicenter trial of early consolidation with ABMT in HIV-positive patients with NHL and subsequently published their experience in HIV-positive patients with PBL.[129,130]

Four patients had PBL in this study. One patient was excluded from the study due to prolonged cytopenia during induction therapy (she is still in CR1 at +34 months). The last three patients got transplants with the BEAM (BCNU, etoposide, cytarabine, and melphalan) conditioning regimen in CR1 after induction therapy. At +24, +19, and +13 months, all of them are alive and in remission. The 2-year PFS and OS were 73% and 76%, respectively, across the entire series, with a median follow-up of 19.5 months (range: 4 to 65).[129,130]

In the Italian GICAT center, two additional HIV-positive patients with high-risk PBL were treated with ABMT as upfront consolidation following CHOP induction, and the results were reported separately. One patient is still alive in CR at +83 months, while the other died 4 months after transplantation due to progression.[130]

Similar to the Italian cooperative group and the Moffitt Cancer Center, the Center for International Blood and Marrow Transplant Research (CIBMTR) grouped patients with PBL by disease status. Seven of eleven (64%) patients who had ABMT in CR1 were still alive at the most recent follow-up, after an average of 25 months (range, 4 to 43 months); only four of nine (44%) patients who had ABMT in CR2 were still alive after an average of 62 months (range, 12 months). (CIBMTR, unpublished data). In a recent multicenter study involving 281 patients diagnosed with plasmablastic lymphoma, 13 participants had autologous bone marrow transplantation (ABMT) as a therapeutic consolidation following their initial complete remission. The current investigation lacks data regarding the responses or survival of these patients.[21] Ideally, randomized studies are required to establish the efficacy of ABMT in PBL. People with PBL who have any of the following high-risk factors should be considered for consolidation with ABMT as a first option: an aaIPI score greater than 2, no HIV, MYC gene rearrangement, TP53 gene deletion, or any response to induction chemotherapy other than CR (partial response or refractory disease).

Double Autologous Stem Cell Transplantation. There is only one report in the literature of an HIV-negative person with extraoral PBL who went into and stayed in complete remission for a very long time after intensive therapy with thalidomide and dexamethasone, followed by consolidation with two autologous stem cell transplants. The authors chose the intensive multiple myeloma-like treatment at random because antimyeloma drugs have been used in PBL case reports. The author stated that despite the inherent aggressiveness of the disease, the early presentation stage may have had a positive effect on the patient's long-term prognosis.[131]

Allotransplant for PBL. Compared to ABMT, the literature on allogeneic hematopoietic cell transplant (allo-HCT) PBL is considerably more limited. It's very

important to know about the risks of opportunistic infections, having multiple infections at the same time (like viral hepatitis), the complicated drug interactions between antiretroviral drugs and transplant-related drugs, and how HIV affects T cell numbers and functions, the bone marrow microenvironment, and the cytokine milieu. These factors lead to both higher transplant-related mortality (TRM) and HIV-related mortality.

Because they lower TRM, reduced-intensity conditioning regimens have made allogeneic hematopoietic cell transplantation more successful overall, but it's still not clear what role they play in HIV-positive patients. A 51-year-old HIV-positive man with PBL and a hematopoietic cell transplant comorbidity index of 4 (high risk) underwent Allo HSCT from a matched unrelated donor to demonstrate the feasibility of the procedure.[132] He was given fludarabine, busulfan, and antithymocyte globulin to condition him. For the prevention of GVHD, methotrexate and tacrolimus were used. At the time of the report, he was two years post-transplantation, disease-free, and off immunosuppression.[132]

In a recent multicenter study involving 281 patients diagnosed with plasmablastic lymphoma, 5 participants had allo-HCT for relapsed PBL HIV negative. Out of these patients, four died away, with three deaths attributed to complications from the transplant and one death attributed to a second malignancy. One patient who received allo-HCT after one previous treatment is currently alive, as of the most recent follow-up, which occurred 26 months after the allo-HCT procedure. The patient is experiencing an important chronic graft-versus-host disease.[21]

Another report describing allo-HSCT in an HIV-negative PBL patient was found in the literature.[133] The patient experienced a recurrence following a consolidated ABMT. Then, he receives a salvage allo-HSCT from his daughter and achieves a favorable outcome. He has been in long-term, complete remission and is still alive. It may be attributable to his younger age, low IPI score, and prompt allo-HCT treatment following relapse. Thus, allo-HSCT has the potential to enhance the likelihood of long-term survival for young patients with PBL who have experienced a relapse.

Radiation Therapy (RT). Radiotherapy is less considered a treatment option for PBL patients, as it has only been reported in approximately 200 published cases (**Table 5**).

In 2024, systemic therapy will be used to treat most PBL cases. However, combined modality therapy (CMT), which includes systemic chemoimmunotherapy followed by consolidation radiation therapy (RT), is still a well-proven way to treat the disease. RT has multiple applications, either alone or in combination with multi-agent chemotherapy.[134-140]

After initial treatment, nearly half of PBL patients may experience either primary refractoriness or disease progression. Relapsed or refractory PBL remains exceedingly difficult to treat, with persistently dismal outcomes. Notably, RT still works well even for diseases that don't respond to chemotherapy. It has traditionally been an important part of clinical practice for these patients, with or without systemic therapy, as part of both curative and palliative-intent programs.[134-140]

Although radiation treatment (RT) remains a potential option for some patients who cannot undergo systemic therapy, it is primarily employed as a consolidation therapy following chemoimmunotherapy. Consolidation radiation is often recommended following multiple courses of systemic therapy in patients with advanced or bulky illness, several risk factors, or a partial response.[140-142]

Even in patients who achieve complete remission, the most common pattern of PBL relapse after chemotherapy involves the original sites of disease. RT may result in a benefit for event-free survival and, eventually, an overall survival (OS) benefit.[142-144]

Short courses of RT can alleviate a variety of symptoms, including pain, bleeding, airway or bowel obstruction, and neurologic compromise. Diseases that

Table 5. Literature review of Radiation Therapy reports in PBL.

Radiotherapy alone or with chemotherapy	Cases	Outcome	Author, year, ref.
Radiotherapy as frontline consolidation after CT	15	Radiotherapy as frontline consolidation after CT	Castillo J. 2008[89]
Radiotherapy as palliative and as frontline consolidation after CT	7	No selected data on outcome	Ibrahim IF 2014[13]
Radiotherapy as palliative and as frontline consolidation after CT	31	No selected data on outcome	Liu M 2015[146]
Radiotherapy as consolidation after CT	18	No selected data on outcome	Longhavi S. 2015[14]
Radiotherapy as palliative therapy	4	No selected data on outcome	Tchemonog E. 2017[147]
Radiotherapy	5	No selected data on outcome	Rodrigues-Fernandes CI 2018[20]
Radiotherapy as frontline consolidation after CT	80	Most patients stage I-II better reported outcome in PFS and OS	Hess BT 2023[148]
Radiotherapy as frontline consolidation after CT	36	Most patients stage I no data on outcome	Di Ciaccio PR 2024[21]

pose a threat to vital organs, such as the spinal cord or airway, may also be treated with RT to prevent impending complications. Finally, radiation therapy (RT) can be utilized as a potent treatment method for localized progression, with the aim of postponing the requirement for systemic therapy. This is particularly beneficial, as systemic therapy is often linked to a greater degree of adverse effects. The ideal doses for palliating R/R DLBCL are still unknown, and the most suitable treatment regimen may eventually vary depending on the specific clinical situation. Typically, hypofractionated doses ranging from 20 to 30 Gy are delivered. Various strategies may be suitable, depending on the clinical situation. Patients with a limited life expectancy are recommended to undergo short treatment regimens, such as receiving 4 Gy of radiation over 5 days, 8 Gy in a single day, or even 2 Gy over 2 days or 4 Gy in one day. Extended treatment schedules (e.g., 3 Gy for 10 days or 2.5 Gy for 15 days) may be more suitable for patients with a more positive outlook, particularly those with a smaller amount of disease. Generally, it is advisable to restrict therapy volumes to the bulk of the disease with the smallest possible margin.[142-148]

CNS Prophylaxis. CNS relapse is a relatively uncommon but frequently devastating complication of DLBCL. Most CNS relapses occur during or shortly after first-line immune-chemotherapy, with a median time of 6 to 8 months, as reported in a recent prospective clinical trial.[149]

Treating secondary CNS lymphoma (SCNSL) is sometimes challenging, and historically, the outcomes have been unsatisfactory. Consequently, significant attention has been given to identifying patients with the highest propensity to this problem, as well as implementing preventive measures aimed at minimizing risk as much as feasible. A better understanding of DLBCL's molecular biology and the CNS-IPI238 trial have helped find people at high risk for secondary central nervous system lymphoma (SCNSL). However, decisions about preventing this disease are still based on looking at past cases or extrapolating data from other types of the disease.[150-152] There have been no prospective randomized trials conducted to directly assess the effectiveness of CNS prophylaxis. Physicians often encounter the difficult task of preventing a potential consequence without exposing the patient to further treatment that may have harmful side effects and lack substantial evidence of its effectiveness.

Numerous studies have investigated possible CNS relapse risk factors in DLBCL. In 2016, the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) created a prognostic model (CNS-IPI) that sorts patients into three risk groups based on the five standard IPI factors as well as whether the disease has spread to the kidneys or adrenal glands.[150,152]

Significantly, patients who had five or six risk variables had a respective probability of CNS relapse of 15% and 32.5%. Specific extranodal (EN) locations have been linked to a higher likelihood of central nervous system (CNS) recurrence. The CNS-IPI model considers the involvement of the kidneys and adrenal glands. However, intravascular lymphoma is known to have a high risk of involving the CNS, either at the start or during a relapse. The association between testicular involvement and CNS recurrence probability, ranging from 10% to 25% over a 10-year period, has been well-established in both limited and advanced stages.[150-154]

In a retrospective series, breast involvement was associated with a higher risk of CNS relapse (15%), whereas other EN sites, such as the uterus, blood, bone marrow, and epidural area, exhibited inconsistent results and are unlikely to be independently predictive of CNS relapse.[155]

A new systematic review looked at stand-alone IT prophylaxis in 7357 patients who were getting chemoimmunotherapy. The review included three post-hoc trial analyses and 10 retrospective investigations.[156] In univariable or multivariable analyses, IT prophylaxis was not associated with a reduction in CNS relapse rate. The administration of IT therapy can be difficult and uncomfortable for the patient, with some evidence suggesting an association with hospitalization for infection-related reasons in older patients.[150-157]

The utilization of brain imaging and lumbar puncture/cerebrospinal fluid (CSF) analysis to detect individuals at high risk of central nervous system (CNS) involvement who could potentially benefit from treatments targeting the CNS is increasing.[158]

Several studies have demonstrated that flow cytometric analysis of CSF is more sensitive than cytology for detecting occult CNS involvement.[159,161] Nonetheless, a percentage of patients with negative flow cytometry result in CNS relapse shortly after treatment, indicating the need for more sensitive techniques. The incidence of CNS relapse is estimated to occur in approximately 3–5% of PBL patients.[3-10]

Further, PBL in people living with HIV (PLWH) has an increased risk of aggressive disease, with CNS involvement occurring more frequently than other extra-nodal involvement.

886 people who were newly diagnosed with AIDS-related lymphomas (DLBCL and BL) were looked at in detail.[162] It was found that the central nervous system (CNS) was involved in between 5% and 30% of the cases at the start of the therapy. The recurrence of central nervous system (CNS) cancer happens promptly, typically within a median period of 4.2 months following diagnosis, and is associated with a very poor survival rate of only 1.6 months. Over 90% of patients underwent intrathecal (IT) and central nervous system (CNS) prophylaxis, while 5% encountered CNS recurrence. In

this case, it has not been determined what the best treatment plan, dosage frequency, and ways to avoid complications in the central nervous system (CNS), such as choosing between intravenous medications that can reach the CNS and intrathecal therapy. The guidelines from the US National Comprehensive Cancer Network recommend the use of intrathecal methotrexate for central nervous system prophylaxis in all people living with HIV (PLWH) who have lymphoma.[22]

In conclusion, people with PBL are likely to get leptomeningeal disease because of the high rate of proliferation, the strong link to HIV infection, the high rate of extranodal involvement, and the presence of MYC translocations. CNS prophylaxis should be considered in a case-by-case basis.

Antiretroviral Treatment During Chemotherapy for HIV+ PBL. It is crucial to note that more than 60% of individuals diagnosed with plasmablastic lymphoma are also infected with HIV. Combined antiretroviral therapy (cART) has independently contributed to improving the response to chemotherapy and the survival of HIV-infected patients with lymphoma.[163-166]

All HIV-positive patients with PBL should, therefore, receive cART concurrently with chemotherapy. The antiretroviral treatment history, HIV strain sensitivity, HLAB5701 result, and hepatitis B virus (HBV) infection markers should be considered when choosing a cART regimen. In certain instances, it is recommended to obtain the HIV strain's tropism result (R5, X4, or dual tropism). In addition, it is essential to always consider the potential pharmacological interactions and cross-toxicity between antiretrovirals and antitumor drugs or other commonly used drugs in this patient population, such as antifungals. There is limited clinical evidence regarding the efficacy and safety of chemotherapy and antiretroviral therapy.

In a series of 150 HIV-infected patients with cancer (mostly hematological malignancies), protease inhibitor-based cART regimens were less effective and less safe than those based on non-nucleoside reverse transcriptase inhibitors (NNRTI) and integrase strand transfer inhibitors (ISTI) (INSTI).[167] Between 40 and 60 percent of HIV-infected patients have been exposed to HBV, and between 3 and 10 percent have chronic hepatitis B, which is defined by the presence of HBV surface antigen (HBsAg).[168-172] Reactivation of HBV can occur during chemotherapy, particularly when rituximab is employed as a therapeutic agent.[172-175] Patients co-infected with HIV and HBV should receive a combination antiretroviral therapy (cART) regimen that is also effective against HBV. In addition to tenofovir and emtricitabine (FTC) or lamivudine (3TC), a third HIV drug should be administered.[174,175] Tenofovir alafenamide (TAF) should be preferred over tenofovir disoproxilfumarate (TDF) because it has a more favorable safety profile and is equally effective against HBV.[175] Therefore, these antiretroviral drugs can alter the pharmacokinetics of antitumor drugs that are substrates of this isoenzyme, particularly taxanes and alkylating agents like cyclophosphamide and etoposide and, to a lesser extent, vinca alkaloids, antitumor antibiotics, and platinum. There are no significant interactions between antiretrovirals and anthracyclines because aldose reductase metabolizes both substances. In patients receiving concomitant CHOP, doxorubicin, etoposide, and PI-based cART, cyclophosphamide clearance was decreased, and the frequency of severe anemia and neutropenia was increased compared to patients receiving CHOP alone. Severe cases of neutropenia and mucositis were reported in patients receiving concomitant CHOP and cART.[176]

It is unlikely that nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) will interact pharmacokinetically with cytostatics. The CCR5 antagonist maraviroc is a substrate for the CYP3A enzyme and the P glycoprotein. This means that strong CYP3A inducers or inhibitors may change the levels of maraviroc. Insti (raltegravir and dolutegravir) metabolizes through glucuronidation in the liver and has minimal interactions with cytostatic medications. Elvitegravir, a third member of this class, must be co-administered with the cobicistat enhancer so that their interactions are functionally equivalent to those of the PI. No pharmacokinetic interactions between antiretrovirals and rituximab, the most widely used monoclonal antibody for NHL, have been described.[175-180]

When selecting a combination antiretroviral therapy (cART) regimen, it is also crucial to consider the drugs' safety profile. 3TC, FTC, abacavir (AUC), and TDF or TAF are the most commonly used NRTIs for the treatment of HIV at present. 3TC, FTC, TDF, and TAF are also effective anti-HBV agents. 3TC, FTC, and ABC are not cross-toxic with anticancer drugs. TDF can cause proximal tubular nephropathy and a decreased glomerular filtration rate; therefore, patients with renal insufficiency, tumor lysis syndrome, or those receiving antitumor drugs with nephrotoxic potential should avoid using TDF. TAF is equivalent to TDF in terms of efficacy and lacks nephrotoxicity, at least in the short term. [181,182] Other NRTIs, such as zidovudine (AZT), didanosine (ddI), and stavudine (d4T), are rarely used today and have significant cross-toxicity with certain anti-tumor drugs. AZT has the potential to be myelotoxic and may increase the hematological toxicity of various chemotherapeutic regimens. Certain antitumor medications, such as platinum, taxanes, and vinca alkaloids, can worsen peripheral neuropathy caused by DdI and d4T and cause mitochondrial toxicity. [183] Some PIs, like atazanavir, lopinavir, and saquinavir, may make the CT interval longer. This is something that should be thought about when these drugs are combined with

anthracyclines, which are also known to make the CT interval longer. The bilirubin levels of patients with hepatopathy can be used to adjust the dosage of certain antitumor drugs. Although atazanavir can cause unconjugated hyperbilirubinemia because it blocks the uridine diphosphate glucuronosyltransferase 1A1 enzyme (UGT1A1), this can make it harder to make the necessary changes when taking this antiretroviral.[184]

Complementary Treatments. At the time of diagnosis or after beginning chemotherapy, patients with a large tumor mass may exhibit complications resulting from tumor lysis syndrome. In cases where this complication is likely because of the size of the tumor or very high levels of LDH and uric acid, hyperhydration, forced diuresis, and allopurinol should be given before chemotherapy. Additionally available is rasburicase, a recombinant version of the urate oxidase enzyme that turns uric acid into allantoin, which the kidneys excrete more effectively. This medication is more effective than allopurinol at reducing plasma uric acid levels and can prevent chemotherapy from beginning too late.[185,186] The recommended intravenous dose of rasburicase is 0.20 mg/kg/day in 50 mL of normal saline for 30 minutes. The duration of treatment ranges between 5 and 7 days, but shorter-duration regimens appear to be equally effective. Giving granulocyte colony-stimulating factors (G-CSF) is suggested to shorten the time of neutropenia after chemotherapy, improve cytostatic tolerance, and allow full doses and proper chemotherapy intervals.[187]

Prophylaxis of Opportunistic Infections Associated with HIV+PBL. After the administration of chemotherapy, the total number of CD4+ T lymphocytes decreases by 30–50% with respect to the baseline, depending on the intensity of the treatment and the moment at which the analysis is carried out. This is why the risk of opportunistic infections associated with HIV is higher in these patients than in patients with PBL at a similar stage.[188]

In principle, it should be said that primary or secondary prophylaxis indicated according to the CD4+ T lymphocyte count and the previous history of opportunistic infections should be performed. However, it is recommended to consider that the degree of immunosuppression in patients is greater than the one shown by the CD4+ T lymphocyte count at the time of tumor diagnosis and that these lymphocyte markers should be monitored throughout the treatment of the lymphoma and act accordingly.[189]

Pneumocystis jirovecii prophylaxis is recommended for all patients. However, we must consider the effects that systematic implementation of this practice can have on antibiotic resistance and other undesirable outcomes, such as Clostridium difficile colitis.[189-190] Anti-CMV prophylaxis is generally not recommended, but close monitoring with periodic blood PCR determinations for this virus is recommended in those patients with a low CD4+ T lymphocyte count (every 7 days).

Vaccinations. The annual inactivated influenza vaccination and COVID-19 are recommended for both HIV-positive and HIV-negative PBL patients.

The COVID-19 vaccine is particularly important for those patients due to the frequent prolonged positivity and virus shedding of the SARS-Cov-2 and the impact of this on delaying the chemotherapy.[191,192] The vaccination of close contacts against influenza and COVID-19 is also recommended. 278 As with all HIV-infected patients, PBL patients should also receive vaccinations against pneumococcus, HBV, and the hepatitis A virus. Although the optimal time to administer the vaccines is unknown, it is recommended to do so at least two weeks prior to beginning chemotherapy or at least one week after the last cycle.[193,194]

First Line Post-Treatment Assessment. After the initial treatment, if patients achieve a PET-negative remission, we schedule additional monitoring. Regrettably, even after discontinuation of cytotoxic treatment and achieving complete remission, numerous patients have fatigue, polyneuropathy, or anxiety. Thus, we promptly direct patients experiencing anxiety to receive psychological treatment and, if judged required, commence the administration of psychotropic medications. For patients diagnosed with polyneuropathy, we advise decreasing the dosage of vincristine and providing symptomatic relief using gabapentin or duloxetine, even though there is limited evidence supporting their effectiveness. Moreover, cancer rehabilitation clinics recommend that patients reside there for a period of time to improve their overall quality of life. For additional monitoring, we refrain from using routine CT scans on asymptomatic individuals because the American Society of Hematology has determined that they are not effective. We suggest performing a blood count, renal and liver function tests, LDH measurement, and a clinical examination every 3 months during the initial 2-year period following treatment. Patients with prominent mediastinal or retroperitoneal disease at diagnosis should undergo chest X-rays and ultrasonography. The NCCN guidelines continue to recommend surveillance CT scans for follow-up in patients with aggressive lymphoma, although we only utilize this approach for specific patients who have an increased risk of experiencing a relapse.

Relapsed/Refractory Plasmablastic Lymphoma. In patients with persistent PET-positive disease, new lymphadenopathy, or organ lesions after first-line treatment, we perform a new biopsy to confirm

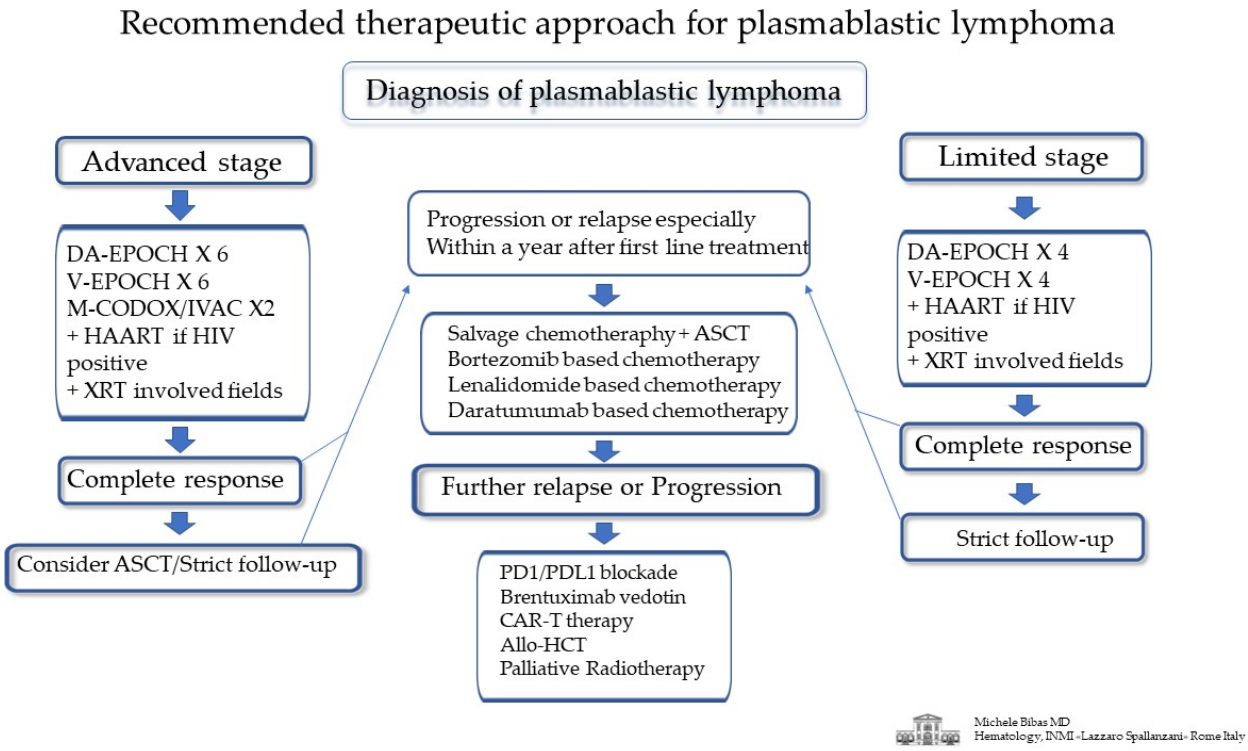

Figure 1. Complex therapy recommendations for Relapsed/Refractory Plasmablastic Lymphoma.

malignancy and the former diagnosis. Refractory PBL has a significantly worse prognosis than other aggressive non-Hodgkin B-cell lymphomas, irrespective of whether the patient has HIV or not. The reported median PFS ranges from 6–7 months, while the median OS ranges from 11–13 months.[5-12]

However, due to the rarity of this disease, there is insufficient evidence to support one particular salvage therapy for patients with relapsed or refractory disease, particularly for those who do not achieve at least a partial response. Furthermore, the same treatment methods used as the first line of therapy can also be employed in later stages of treatment. If accessible, we suggest enrolling these patients in experimental clinical trials. At the moment, there aren't many prospective randomized studies that directly compare the different second-line treatment options for people with PBL who can't get autologous stem cell transplantation (ASCT) or anti-CD19 CAR T-cell therapy. Such a comparison would yield valuable data for treatment sequencing and evaluate treatment effectiveness in various patient subgroups, including those with high clinical and biological risk factors. Managing these patients in this context is currently a significant unmet medical need. However, situations where randomized studies are scarce are increasingly seeing prevalent actual comparisons across different groups, particularly those that are carefully matched.

Ultimately, we have created a comprehensive table that aims to condense the complex therapy recommendations for this uncommon and aggressive lymphoma (**Figure 1**).

Conclusions. In terms of both diagnosis and treatment, PBL is a challenging disease. The majority of long-term survivors had limited disease or were eligible for autologous stem cell transplants as consolidation following combination chemotherapy responses. Regimens for myeloma that include proteasome inhibitors, immunomodulators, and targeted therapy pave the way for improved outcomes. Now that we have gained more knowledge about the mutational landscape of PBL, researchers have suggested numerous potential new targets. These include pan-TRK inhibitors like larotrectinib or entrectinib for NTRK3 mutations. It's also important to look at other effective treatments that have been used for MM, like CAR-T and bispecific antibodies against CD38, CD138, or B-cell maturation antigen (BCMA), especially for patients with relapsed and resistant PBL.

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