Pediatric Aggressive Mature B-Cell Lymphomas, Version 3.2022

Matthew Barth, MD[1,*]; Ana C. Xavier, MD[2,*]; Saro Armenian, DO, MPH[3]; Anthony N. Audino, MD[4,*]; Lindsay Blazin, MD, MPH[5,*]; David Bloom, MD[6]; Jong Chung, MD[7]; Kimberly Davies, MD[8,*]; Hilda Ding, MD[9]; James B. Ford, DO[10,*]; Paul J. Galardy, MD[11]; Rabi Hanna, MD[12]; Robert Hayashi, MD[13]; Cathy Lee-Miller, MD[14]; Andrea Judit Machnitz, MD[15]; Kelly W. Maloney, MD[16]; Lianna Marks, MD[17]; Paul L. Martin, MD, PhD[18]; David McCall, MD[19]; Martha Pacheco, MD[20]; Anne F. Reilly, MD, MPH[21]; Mikhail Roshal, MD, PhD[22]; Sophie Song, MD, PhD[23,*]; Joanna Weinstein, MD[24]; Sara Zarnegar-Lumley, MD, MS[25]; Nicole McMillian, MS[26]; Ryan Schonfeld[26]; and Hema Sundar, PhD[26]

ABSTRACT

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Aggressive Mature B-Cell Lymphomas include recommendations for the diagnosis and management of pediatric patients with primary mediastinal large B-cell lymphoma (PMBL) and sporadic variants of Burkitt lymphoma and diffuse large B-cell lymphoma. PMBL is now considered as a distinct entity arising from mature thymic B-cells accounting for 2% of mature B-cell lymphomas in children and adolescents. This discussion section includes the recommendations outlined in the NCCN Guidelines for the diagnosis and management of pediatric patients with PMBL.

J Natl Compr Canc Netw 2022;20(11):1267–1275
doi: 10.6004/jnccn.2022.0057

[1]Roswell Park Comprehensive Cancer Center; [2]Children's of Alabama/O'Neal Comprehensive Cancer Center at UAB; [3]City of Hope National Medical Center; [4]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [5]Indiana University Melvin and Bren Simon Comprehensive Cancer Center; [6]University of Michigan Rogel Cancer Center; [7]UC Davis Comprehensive Cancer Center; [8]Dana-Farber/Boston Children's Cancer and Blood Disorders Center; [9]UCSD Rady Children's Hospital/UC San Diego Moores Cancer Center; [10]Fred & Pamela Buffett Cancer Center; [11]Mayo Clinic Cancer Center; [12]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [13]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [14]University of Wisconsin Carbone Cancer Center; [15]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [16]Children's Hospital of Colorado/University of Colorado Cancer Center; [17]Stanford Cancer Institute; [18]Duke Cancer Center; [19]The University of Texas MD Anderson Cancer Center; [20]UT Southwestern Simmons Comprehensive Cancer Center; [21]Abramson Cancer Center at the University of Pennsylvania; [22]Memorial Sloan Kettering Cancer Center; [23]UCLA Jonsson Comprehensive Cancer Center; [24]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [25]Vanderbilt-Ingram Cancer Center; and [26]National Comprehensive Cancer Network.

*Discussion Writing Committee Member.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

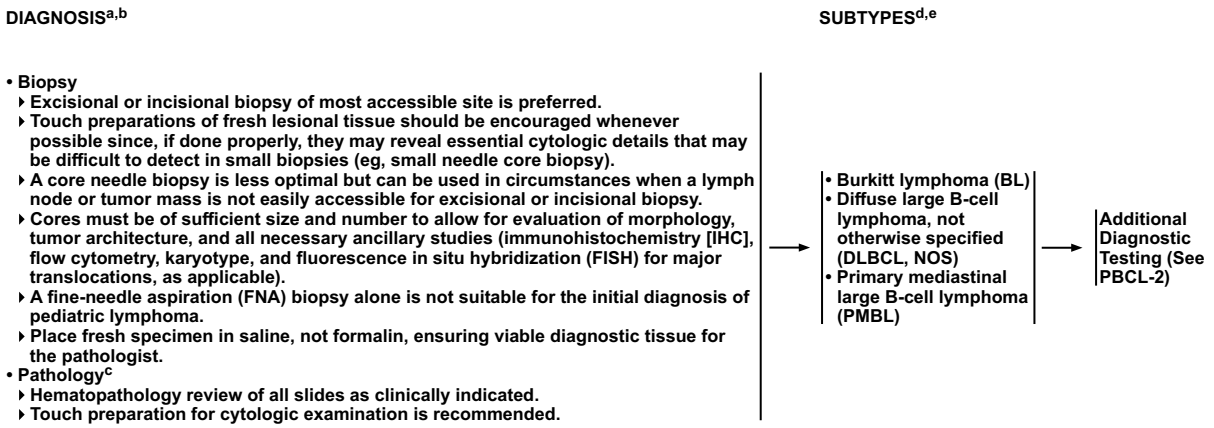
The complete NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

Disclosures for the NCCN Pediatric Aggressive Mature B-Cell Lymphomas Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Pediatric Aggressive Mature B-Cell Lymphomas Panel members can be found on page 1275. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.



[a] The Pediatric Aggressive Mature B-Cell Lymphomas panel considers "pediatric" to include any patient aged 18 years and younger, and AYA patients older than 18 years of age, who are treated in a pediatric oncology setting. Practice patterns vary with regards to AYA patients from center to center in terms of whether AYA patients (defined by the National Cancer Institute as <39 years of age) with mature B-cell lymphoma are treated primarily by pediatric or adult oncologists. These guidelines are intended to apply to AYA patients with good organ function treated in a pediatric oncology setting. AYA patients treated in an adult oncology setting should be treated as per the adult NCCN Guidelines for B-Cell Lymphomas†.
[b] Also see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology†.
[c] See Principles of Diagnostic Pathology (PBCL-A)*.
[d] Pediatric BL and DLBCL are curable, but management is complex. It is preferred that treatment occur at centers with expertise in the management of these diseases.
[e] PMBL can be defined as a clinical entity presenting with primary site of disease in the anterior mediastinum with or without other sites and histology of DLBCL. PMBL overlaps with mediastinal grey zone lymphomas that have features intermediate between PMBL and classic Hodgkin lymphoma, and have unique diagnostic characteristics.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

Overview

An estimated 10,470 children (≤14 years) and 5,480 adolescents (aged 15–19 years) will be diagnosed with cancer In the United States in 2022 and 1,050 children and 550 adolescents will die of the disease.[1] The SEER program reports that in 2022, an estimated 87,050 adolescents and young adults (AYAs; 15–39 years) will be diagnosed with cancer and 9,180 AYAs will die of the disease.[2]

Non-Hodgkin lymphomas (NHL) account for 6% and 7% of all cancers, respectively, in children and adolescents. The 5-year relative survival rates are 91% and 89%, respectively. Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) are the most common types of aggressive mature B-cell lymphomas in children and adolescents and the incidence of DLBCL markedly increases with age, especially in adolescents.[3–6] BL and DLBCL account for about 38% and 20% of NHL, respectively, in children aged 0–14 years, whereas DLBCL accounts for about 37% of NHL in adolescents aged 15–19 years and BL accounts for about 21% of NHL in the same age group.[4] Primary mediastinal large B-cell lymphoma (PMBL) is now considered as a distinct entity of NHL, arising from mature thymic B-cells and accounting for 2% of mature B-cell lymphomas in children and adolescents.[7]

This NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Aggressive Mature B-Cell Lymphomas provide recommendations for the diagnosis and management of pediatric patients with PMBL and sporadic variants of BL and DLBCL. The NCCN Pediatric Aggressive Mature B-Cell Lymphoma Panel considers "pediatric" to include any patient aged 18 years and younger, and AYA patients =18 years and <39 years of age (as defined by the NCI) who are treated in a pediatric oncology setting.

The following discussion section includes the recommendations outlined in the NCCN Guidelines for the diagnosis and management of pediatric patients with PMBL.

Clinical Presentation

PMBL usually presents as a bulky mediastinal mass in the anterior mediastinum (primary site of disease) with or without locoregional spread to adjacent organs such as chest wall, pleura, pericardium, and lung.[7–9] Although extrathoracic dissemination to kidney or liver may occur, central nervous system (CNS) and bone marrow involvement are generally rare. Patients may also present with clinical symptoms related to rapid growth of a mediastinal mass (tumor lysis syndrome, superior vena cava syndrome, respiratory distress due to airway compression, pericardial and pleural effusions) and those with abdominal disease may present with abdominal distention and nausea/vomiting.[7,9]

ADDITIONAL DIAGNOSTIC TESTING[c]

ESSENTIAL
- **Adequate immunophenotyping to establish diagnosis[f,g,h]**
  - **IHC panel: Ki-67, BCL2, BCL6, CD3, CD10, CD20, MUM1**
  - **Flow cytometry: Surface kappa/lambda, CD3, CD5, CD10, CD19, CD20, CD45**
  - **IHC panel for PMBL: CD10, CD19, CD20, PAX5, CD23, CD30, BCL2, BCL6, MUM1, and Ki-67; EBV is absent**
  - **Flow cytometry panel for PMBL: Surface kappa/lambda, CD3, CD5, CD10, CD19, CD20, CD22, CD23, and CD45**
- **FISH: *MYC* rearrangement[i]**

USEFUL UNDER CERTAIN CIRCUMSTANCES
- **Karyotype: t(8;14) or variants t(2;8) or t(8;22) to identify additional chromosomal abnormalities**
- **FISH for *BCL2* and *BCL6* rearrangements[j]**
- **FISH or single nucleotide polymorphism (SNP) array for 11q aberration**
- **EBER-ISH[k]**
- **MYC IHC**
- **TdT IHC or flow cytometry**
- **Clonality testing by polymerase chain reaction (PCR) for immunoglobulin gene rearrangement**

→ **Workup (See PBCL-3)**

[c] See Principles of Diagnostic Pathology (PBCL-A)*.
[f] Typical immunophenotype of BL: sIg+, CD10+, CD20+, TdT-, Ki-67+ (≥95%), BCL2-, BCL6+, simple karyotype with MYC rearrangement as sole abnormality. Typical immunophenotype of DLBCL: sIg+, CD20+, TdT-, Ki-67 variably high, CD10+/-, BCL6+/-, MUM1+/-, BCL2+/-, variable karyotype with MYC, BCL6, BCL2, and/or other IGH rearrangements.
[g] Typical immunophenotype of PMBL: sIg-, B-cell antigens+ (CD19+, CD20+, CD79a+, and PAX5+), CD23+, CD30+, MUM1+, BCL2+/-, and BCL6+/-. EBV-EBER is negative. See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A) in the NCCN Guidelines for B-Cell Lymphomas†.
[h] If flow cytometry is initially performed, IHC for selected markers (BCL2 and Ki-67) can supplement the flow results.
[i] On formalin-fixed, paraffin-embedded tissue, *MYC* rearrangement is best assessed by MYC break apart probe to capture any partner gene.
[j] Double-and triple-hit lymphomas are currently not well described or studied in the pediatric population but FISH for *BCL2* and *BCL6* rearrangements may be considered in the AYA population.
[k] EBER-ISH is most applicable in endemic BL or immunocompromised clinical settings for either BL or DLBCL.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

Diagnosis

Biopsy

Excisional or incisional biopsy of the most accessible site is preferred, with fresh biopsy tissue sent to pathology in saline to ensure viable diagnostic tissue (see PBCL-1, page 1268). Fine-needle aspiration biopsy alone is not suitable for the initial diagnosis of mature B-cell lymphomas.[10] A core needle biopsy is not optimal but can be used when a lymph node or tumor mass is not easily accessible for excisional or incisional biopsy. Touch preparation of fresh tissue samples is recommended whenever possible to obtain essential cytologic details that may be difficult to detect in small core needle biopsy samples, and hematopathology review should be performed as clinically indicated.[11]

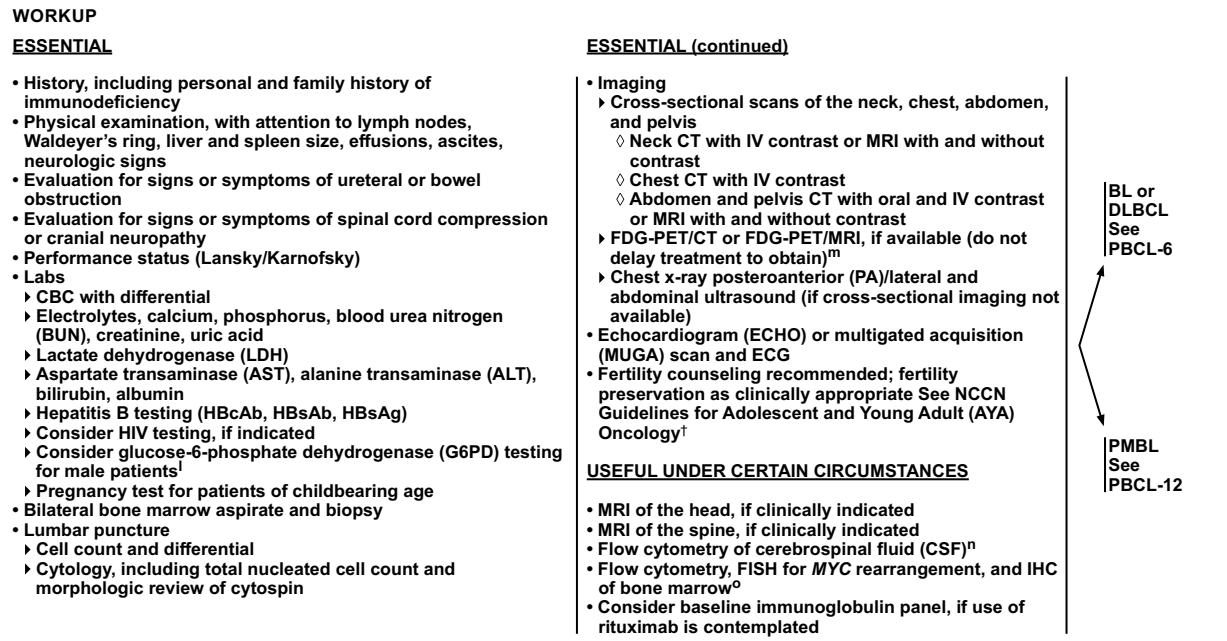
PMBL has variable morphologic features, and typical findings include diffuse sheets of atypical lymphocytes in a background of compartmentalizing fibrosis.[7–9,12] The atypical lymphocytes are medium to large in size, with round to lobulated or irregular nuclei, dispersed chromatin, prominent nucleoli, and abundant pale to clear cytoplasm. Occasionally, atypical lymphocytes are more pleomorphic and may even resemble Reed-Sternberg cells.[7,9]

Additional Diagnostic Testing

Immunophenotyping is essential for the differentiation of mature B-cell lymphoma subtypes and it can be performed using immunohistochemistry and flow cytometry (see PBCL-2, above). Cytogenetic or molecular genetic analysis may be necessary under certain circumstances to identify the specific chromosomal translocations that are characteristic of each subtype or to establish clonality.

PMBL expresses B-cell antigens and lacks surface immunoglobulin. PMBL is CD19+, CD20+, CD79a+, PAX5+, CD23+, and MUM1+ with a variable expression of *BCL2* and *BCL6*.[9] CD30 is heterogeneously expressed in more than 80% of cases. *BCL2, BCL6,* and *MYC* rearrangements are very rare. PMBL is almost always negative for *EBV* and the presence or absence of *EBV* is useful to differentiate PMBL from other mediastinal lymphomas with overlapping pathologic features.

Gene expression profiling has shown that adult PMBL has molecular features that overlap with classic Hodgkin lymphoma and the biology of pediatric PMBL has also been reported to be similar to that of adult PMBL.[13–16] Genetic alterations involving the major histocompatibility complex class II transactivator gene at chromosome 16p are highly recurrent in PMBL.[17,18] Gains or amplifications in chromosome 9p24 (including *JAK2, PD1,* and *PD2*) and



[l] See Principles of Supportive Care (PBCL-D)*.
[m] Obtaining a PET/CT or PET/MRI does not exclude the need for full diagnostic quality high-resolution CT or MRI.
[n] Flow cytometry of CSF samples is not routinely recommended, but may be useful at the pathologist's discretion.
[o] For low-level or morphologically indeterminate involvement.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

chromosome 2p16 (including *REL* and *BCL11A*) have also been detected in PMBL.[19–24]

Workup

Workup for patients with a diagnosis of PMBL includes history and physical examination, laboratory analysis, bilateral bone marrow aspirate and biopsy, lumbar puncture, and imaging. Imaging should include cross-sectional scans of the neck, chest, abdomen, and pelvis (see PBCL-3, page 1270). FDG-PET/CT or FDG-PET/MRI is recommended if available.[25] However, treatment should not be delayed to obtain this scan, and FDG-PET does not exclude the need for full diagnostic quality, high-resolution CT or MRI. Information regarding bone marrow and CNS involvement and distant spread is important for staging.

In addition, a baseline echocardiogram or multigated acquisition scan, and electrocardiogram is recommended, and fertility counseling should be offered with fertility preservation as clinically appropriate.

Treatment Recommendations

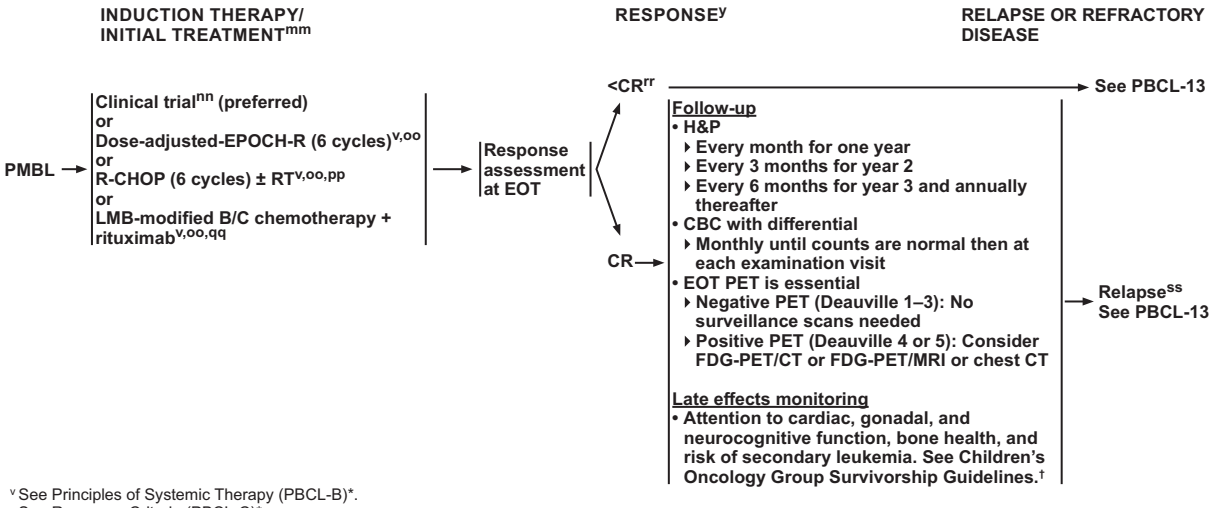
Primary Mediastinal Large B-Cell Lymphoma

Initial Treatment

Historically, pediatric patients with PMBL enrolled in prospective clinical trials of pediatric mature aggressive B-cell lymphomas have been treated with same protocols used for BL and DLBCL (dose-intensive multiagent chemotherapy regimens and intrathecal therapy for CNS prophylaxis). However, outcomes in the subset of patients with PMBL differs from those of BL and DLBCL, with reported 5-year event-free survival (EFS) rates of 66%–70%.[26,27]

The Berlin Frankfurt-Munster (BFM) Group reported the pooled outcomes of 30 patients with PMBL (median age, 14 years) enrolled in 3 consecutive NHL-BFM trials.[26] Treatment consisted of 4–6 courses of intensified chemotherapy using steroids, oxazaphosphorine alkylating agents, methotrexate, cytarabine, etoposide, and doxorubicin. With a median follow-up of 5 years, the estimated EFS rate was 70%. Residual mediastinal masses were present in 15 patients after the end of treatment (EOT) and elevated lactate dehydrogenase LDH (≥500 U/L) was associated with increased risk of failure in multivariate analysis. In the international FAB/LMB96 mature B-cell NHL trial that enrolled 42 patients with PMBL, the estimated 5-year EFS and overall survival (OS) rates were 66% and 73%, respectively.[27] Patients received prephase therapy with COP (low-dose cyclophosphamide, vincristine, and prednisone) followed by an induction course of COPADM (cyclophosphamide, vincristine prednisone, doxorubicin, and methotrexate) and a consolidation course of CYM (cytarabine and high-dose methotrexate).

Primary Mediastinal Large B-Cell Lymphoma



[v] See Principles of Systemic Therapy (PBCL-B)*.
[y] See Response Criteria (PBCL-C)*.
[mm] Definitive diagnosis may not be feasible before beginning treatment. Short course of COP regimen can be used while waiting to confirm the diagnosis of PMBL.
[nn] Optimal treatment has not been established. Enrollment in a clinical trial is recommended.
[oo] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[pp] There are not enough data on the use of RT in pediatric patients.
[qq] Remission assessment was performed after the second consolidation course. At the EOT, if PET/CT is positive, or a large residual tumor remains, then biopsy/removal of the residual mass is recommended. No treatment decisions were to be based on PET/CT results only.
[rr] Residual mediastinal masses are common. Biopsy of PET-positive mass is recommended if additional systemic treatment is contemplated.
[ss] In the vast majority of patients, relapse occurs within 18 months of diagnosis. EOT PET scan can have a fair number of false positives. Biopsy is warranted to confirm relapse.

*Available online, in these guidelines, at NCCN.org.
†To view the most recent version of these guidelines, visit NCCN.org.

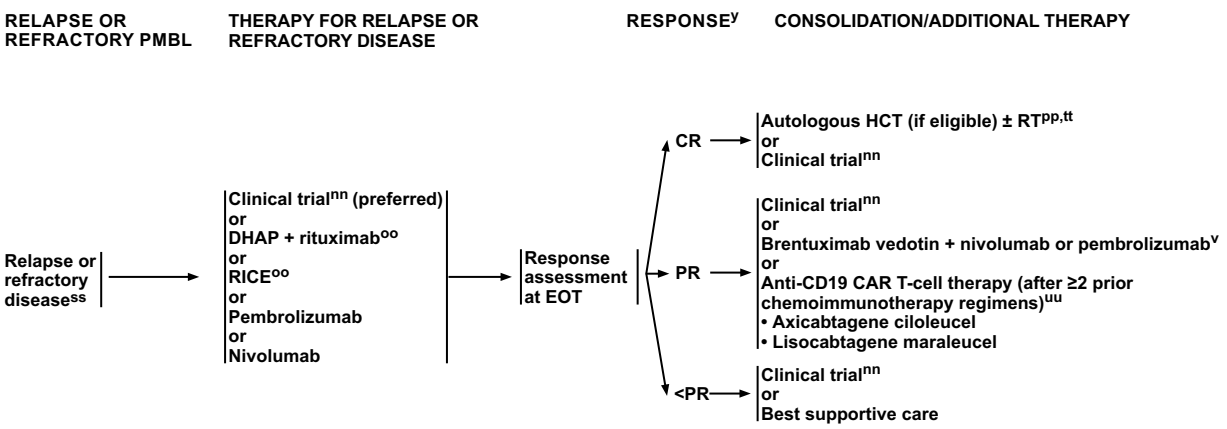
PBCL-12

The French LMB2001 prospective study evaluated intensive LMB-based chemotherapy (based on the FAB/LMB96 protocol) in pediatric patients with PMBL (42 of 773 patients with newly diagnosed B-cell NHL had PMBL).[28] All patients received prephase COP followed by 4 to 8 courses (induction, consolidation, and maintenance) of chemotherapy, and rituximab was added to chemotherapy after 2008. In 2010, the protocol was modified to recommend 6 courses of LMB-modified chemotherapy (B/C) with rituximab for all patients (2 induction courses of *R*-COPADM followed by 2 consolidation courses of *R*-CYVE [rituximab, cytarabine, and etoposide] and 2 courses of maintenance therapy [vincristine, cytarabine, doxorubicin, prednisone, and rituximab]). The cumulative dose of doxorubicin was limited at 240 mg/m^2. The median follow-up was 7 years (11 years for patients treated without rituximab and 6 years for those treated with rituximab). The 5-year EFS and OS rates were 88% and 95%, respectively, for the whole population. This study also showed that the addition of rituximab to chemotherapy improves the outcome (not based on a randomized comparison but based on a comparison of 2 periods using different intensity chemotherapy). The 5-year EFS rate was 95% with rituximab and 81% without rituximab. The corresponding 5-year OS rates were 100% and 91%.

Dose-adjusted EPOCH-R without radiation therapy (RT) has been shown to be effective in adult patients with PMBL without the routine use of RT and the use of RCHOP with a PET-adapted approach has also been associated with favorable outcomes in adult patients with PMBL.[29,30] There are limited data with dose-adjusted EPOCH-R in pediatric patients (as discussed subsequently).

In a multicenter retrospective analysis of 156 children and adults with PMBCL treated with dose-adjusted EPOCH-R, with a median follow-up of 23 months, the estimated 3-year EFS and OS rates were 86% and 95%, respectively.[31] The outcomes were not statistically different between pediatric and adult patients in terms of both EFS (81% vs 87%; P=.338) and OS (91% vs 97%; P=.170). Thrombotic complications were more in common in pediatric patients (46% compared with 23% in adult patients; P=.011). Another analysis that compared outcomes for pediatric patients with PMBL from 3 different trials also reported that modified dose-adjusted EPOCH-R (with at least one dose of intrathecal therapy and cumulative dose of doxorubicin limited at 360 mg/m^2) resulted in a superior 5-year EFS rate (84%) compared with intensive chemotherapy regimens used in the B-NHL-BFM-04 (59%; P=.016) and NHL-BFM 95 (39%; P<.001) trials.[32]

Primary Mediastinal Large B-Cell Lymphoma



[v] See Principles of Systemic Therapy (PBCL-B)*.
[y] See Response Criteria (PBCL-C)*.
[nn] Optimal treatment has not been established. Enrollment in a clinical trial is recommended.
[oo] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[pp] There are not enough data on the use of RT in pediatric patients.
[ss] In the vast majority of patients relapse occurs within 18 months of diagnosis. EOT PET scan can have a fair number of false positives. Biopsy is warranted to confirm relapse.
[tt] RT is often included in high-dose therapy regimens given prior to autologous HCT. RT could be an option for local recurrence. Allogeneic HCT is not considered an optimal approach.
[uu] Management of cytokine release syndrome (CRS) and neurologic toxicity: See CAR T-Cell–Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities†.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

The corresponding 5-year OS rates were 90%, 72%, and 70%, respectively.

A more recent multicenter single arm prospective phase II study involving 46 pediatric patients with PMBL showed that dose-adjusted EPOCH-R did not improve EFS compared with survival rates from the FAB/LMB 96 study (discussed previously).[33] After a median follow-up of 59 months, the 4-year EFS and OS rates were 70% and 85%, respectively. Although the EFS rates were not better in this study, dose-adjusted EPOCH-R had a favorable toxicity profile (≥grade 2 adverse cardiac events occurred in only 9% of patients). In this study, adherence to dose-intensity was not followed in 29% of patients. These results are in contrast to the EFS and OS rates for dose-adjusted EPOCH-R reported in the aforementioned analyses,[31,32] and the survival rates reported in this phase II study are also inferior to those reported in the LMB2001 prospective study (discussed previously).[28]

In the absence of data from randomized trials, optimal first-line treatment of patients with PMBL has not been established. Enrollment in a clinical trial is preferred for all patients. Based on the available data (as discussed previously), the following regimens are included as options for first-line therapy: dose-adjusted EPOCH-R (6 cycles)[31,32] or *R*-CHOP (6 cycles)[30] ± RT or LMB-modified B/C chemotherapy with rituximab (see PBCL-12, page 1271).[28] There are not enough data on the use of RT in pediatric patients and RT was not part of the protocol for pediatric patients with PMBL. Definitive diagnosis may not be feasible before starting initial treatment. A short course of the COP regimen can be used while waiting to confirm the diagnosis of PMBL.

PET/CT at EOT is essential because residual mediastinal masses are common and negative EOT PET scan has been reported to be a prognostic indicator of improved survival outcomes.[30,31,34] In the aforementioned multicenter retrospective analysis of 156 children and adults patients with PMBL, patients with a negative PET scan at EOT had improved 3-year EFS compared with those with a positive PET result (95% vs 55%, $P<.001$).[31] In retrospective and prospective series of pediatric patients with PMBL, although PET/CT was used for response assessment after a few cycles of chemotherapy and at EOT, no treatment decisions were based on the results of PET/CT scans.[28,31,33] In the LMB2001 study, response assessment was required after 4 or 6 courses of chemotherapy. At EOT, if PET/CT is positive or a large residual tumor remains, then biopsy and removal of the

residual mass was recommended.[28] A PET-adapted treatment approach was also used to identify adult patients for whom RT can be safely omitted, and only those with a PET-positive scan at EOT received RT.[30] However, the role of RT in patients with a positive EOT PET remains undefined in pediatric patients due to the increased late effects of RT.[16]

The guidelines recommend response assessment at EOT with PET/CT. Routine clinical surveillance (as described subsequently) is recommended for patients with a complete response (CR) to initial treatment (negative PET; Deauville 1–3). Additional imaging studies (PET/CT or PET/MRI or chest CT) should be considered for patients experiencing less than CR (positive PET; Deauville 4–5). Patients experiencing less than CR to initial treatment should be managed as described for relapsed/refractory disease. Biopsy of PET-positive mass is recommended if additional treatment is contemplated.

Surveillance

In the vast majority of patients, relapse occurs within 18 months of diagnosis.[34] Biopsy is warranted to confirm relapse before the start of treatment of relapsed/refractory disease because PET scans can show a fair number of false-positive results. History and physical examination are recommended every 3 to 6 months in the first 3 years, and then annually. Monthly monitoring of CBC with differential is recommended until counts are normal and then at each exam visit. Surveillance imaging (PET/CT, PET/MRI, or CT chest/abdominal/pelvis) should only be considered if there is a clinical suspicion of relapse.[35] In addition, patients should be monitored for late effects of treatment as per the COG Survivorship Guidelines.

Treatment of Relapsed/Refractory Disease

The management of relapsed/refractory PMBL in both pediatric and adult patients is similar to the management of relapsed/refractory DLBCL: second-line therapy with cross-resistant chemoimmunotherapy regimens followed by autologous hematopoietic cell transplantation (HCT) and outcomes following HCT are more favorable in patients with chemosensitive disease.[36–38]

Targeted therapies such as programmed cell death inhibitors (pembrolizumab and nivolumab) and anti-CD30 antibody drug conjugate (brentuximab vedotin, single agent or in combination with nivolumab) have shown activity in relapsed/refractory PMBL.[39–43] Anti CD19 CAR T-cell therapy has demonstrated significant efficacy for the treatment of relapsed/refractory DLBCL in adult patients after ≥2 prior systemic therapy regimens.[44] Axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel are the 3 anti-CD19 CAR T-cell therapies that are approved for relapsed/refractory DLBCL in adults.[44] Tisagenlecleucel is also approved for relapsed/refractory acute lymphoblastic leukemia in pediatric and young adult patients.[45]

Very limited data are available regarding the outcome of pediatric patients with relapsed/refractory PMBL.[38] Enrollment in clinical trials is recommended for all patients. *R*-ICE (rituximab, ifosfamide, carboplatin, and etoposide), *R*-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin), pembrolizumab, and nivolumab are included as options for second-line therapy for relapsed/refractory PMBL (see PBCL-13, page 1272). Patients with a CR to second-line therapy should receive an autologous HCT. Allogeneic HCT is not considered an optimal approach. RT alone could be an option for local recurrence with disease restricted to the mediastinum.[34]

Brentuximab vedotin in combination with nivolumab or pembrolizumab and anti-CD19 CAR T-cell therapies (axicabtagene ciloleucel or lisocabtagene maraleucel) are included as options for patients with partial response to second-line therapy.[41,46] Limited data are available on the use of CAR T-cell therapies for pediatric patients with mature B-cell lymphomas.[47] The inclusion of axicabtagene ciloleucel or lisocabtagene maraleucel as options for relapsed/refractory PMBL is based on extrapolation of data from clinical trials that have evaluated these therapies in adult patients with relapsed/refractory DLBCL including PMBL. Patients with relapsed/refractory PMBL were included in the ZUMA-1 (axicabtagene ciloleucel) and TRANSCEND-NHL-001 trials (lisocabtagene maraleucel), whereas patients with relapsed/refractory PMBL were not included in the JULIET trial (tisagenlecleucel).[44] Ongoing clinical trials are evaluating CAR T-cell therapies in pediatric patients with NHL.

Clinical trial or best supportive care are recommended for patients experiencing less than partial response to second-line therapy.

References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7–33.
2. National Cancer Institute. Cancer stat facts: cancer among adolescents and young adults (AYAs) (ages 15–39). Accessed September 2, 2022. Available at: https://seer.cancer.gov/statfacts/html/aya.html
3. Burkhardt B, Zimmermann M, Oschlies I, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol 2005; 131:39–49.
4. Hochberg J, Waxman IM, Kelly KM, et al. Adolescent non-Hodgkin lymphoma and Hodgkin lymphoma: state of the science. Br J Haematol 2009;144:24–40.
5. Sandlund JT, Martin MG. Non-Hodgkin lymphoma across the pediatric and adolescent and young adult age spectrum. Hematology Am Soc Hematol Educ Program 2016;2016:589–597.
6. Pfister SM, Reyes-Múgica M, Chan JKC, et al. A summary of the inaugural WHO Classification of Pediatric Tumors: transitioning from the optical into the molecular era. Cancer Discov 2022;12:331–355.

7. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised 4th ed. Lyon, France: IARC; 2017.
8. Cazals-Hatem D, Lepage E, Brice P, et al. Primary mediastinal large B-cell lymphoma: a clinicopathologic study of 141 cases compared with 916 nonmediastinal large B-cell lymphomas, a GELA ("Groupe d'Etude des Lymphomes de l'Adulte") study. Am J Surg Pathol 1996; 20:877–888.
9. Oschlies I, Burkhardt B, Salaverria I, et al. Clinical, pathological and genetic features of primary mediastinal large B-cell lymphomas and mediastinal gray zone lymphomas in children. Haematologica 2011;96:262–268.
10. Hehn ST, Grogan TM, Miller TP. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. J Clin Oncol 2004;22:3046–3052.
11. Satturwar S, Rekhtman N, Lin O, et al. An update on touch preparations of small biopsies. J Am Soc Cytopathol 2020;9:322–331.
12. Pileri SA, Zinzani PL, Gaidano G, et al. Pathobiology of primary mediastinal B-cell lymphoma. Leuk Lymphoma 2003;44(Suppl 3):S21–26.
13. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med 2003;198:851–862.
14. Savage KJ, Monti S, Kutok JL, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood 2003;102:3871–3879.
15. Wessendorf S, Barth TF, Viardot A, et al. Further delineation of chromosomal consensus regions in primary mediastinal B-cell lymphomas: an analysis of 37 tumor samples using high-resolution genomic profiling (array-CGH). Leukemia 2007;21:2463–2469.
16. Attias D, Hodgson D, Weitzman S. Primary mediastinal B-cell lymphoma in the pediatric patient: can a rational approach to therapy be based on adult studies? Pediatr Blood Cancer 2009;52:566–570.
17. Roberts RA, Wright G, Rosenwald AR, et al. Loss of major histocompatibility class II gene and protein expression in primary mediastinal large B-cell lymphoma is highly coordinated and related to poor patient survival. Blood 2006;108:311–318.
18. Mottok A, Woolcock B, Chan FC, et al. Genomic alterations in CIITA are frequent in primary mediastinal large B cell lymphoma and are associated with diminished MHC class II expression. Cell Rep 2015;13:1418–1431.
19. Joos S, Otaño-Joos MI, Ziegler S, et al. Primary mediastinal (thymic) B-cell lymphoma is characterized by gains of chromosomal material including 9p and amplification of the REL gene. Blood 1996;87:1571–1578.
20. Bentz M, Barth TF, Brüderlein S, et al. Gain of chromosome arm 9p is characteristic of primary mediastinal B-cell lymphoma (MBL): comprehensive molecular cytogenetic analysis and presentation of a novel MBL cell line. Genes Chromosomes Cancer 2001;30:393–401.
21. Weniger MA, Pulford K, Gesk S, et al. Gains of the proto-oncogene BCL11A and nuclear accumulation of BCL11A(XL) protein are frequent in primary mediastinal B-cell lymphoma. Leukemia 2006;20:1880–1882.
22. Weniger MA, Gesk S, Ehrlich S, et al. Gains of REL in primary mediastinal B-cell lymphoma coincide with nuclear accumulation of REL protein. Genes Chromosomes Cancer 2007;46:406–415.
23. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood 2010;116: 3268–3277.
24. Twa DD, Chan FC, Ben-Neriah S, et al. Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell lymphoma. Blood 2014;123:2062–2065.
25. Riad R, Omar W, Kotb M, et al. Role of PET/CT in malignant pediatric lymphoma. Eur J Nucl Med Mol Imaging 2010;37:319–329.
26. Seidemann K, Tiemann M, Lauterbach I, et al. Primary mediastinal large B-cell lymphoma with sclerosis in pediatric and adolescent patients: treatment and results from three therapeutic studies of the Berlin-Frankfurt-Münster Group. J Clin Oncol 2003;21:1782–1789.
27. Gerrard M, Waxman IM, Sposto R, et al. Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/LMB96 mature B-NHL therapy. Blood 2013; 121:278–285.
28. Dourthe ME, Phulpin A, Auperin A, et al. Rituximab in addition to LMB-based chemotherapy regimen in children and adolescents with primary mediastinal large B-cell lymphoma: results of the French LMB2001 prospective study. Haematologica. Published online September 1, 2022. doi: 10.3324/haematol.2021.280257
29. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013;368:1408–1416.
30. Hayden AR, Tonseth P, Lee DG, et al. Outcome of primary mediastinal large B-cell lymphoma using R-CHOP: impact of a PET-adapted approach. Blood 2020;136:2803–2811.
31. Giulino-Roth L, O'Donohue T, Chen Z, et al. Outcomes of adults and children with primary mediastinal B-cell lymphoma treated with dose-adjusted EPOCH-R. Br J Haematol 2017;179:739–747.
32. Knörr F, Zimmermann M, Attarbaschi A, et al. Dose-adjusted EPOCH-rituximab or intensified B-NHL therapy for pediatric primary mediastinal large B-cell lymphoma. Haematologica 2021;106:3232–3235.
33. Burke GAA, Minard-Colin V, Aupérin A, et al. Dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab therapy in children and adolescents with primary mediastinal B-Cell lymphoma: a multicenter phase II trial. J Clin Oncol 2021;39: 3716–3724.
34. Giulino-Roth L. How I treat primary mediastinal B-cell lymphoma. Blood 2018;132:782–790.
35. Eissa HM, Allen CE, Kamdar K, et al. Pediatric Burkitt's lymphoma and diffuse B-cell lymphoma: are surveillance scans required? Pediatr Hematol Oncol 2014;31:253–257.
36. Avivi I, Boumendil A, Finel H, et al. Autologous stem cell transplantation for primary mediastinal B-cell lymphoma: long-term outcome and role of post-transplant radiotherapy. A report of the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant 2018;53:1001–1009.
37. Vardhana S, Hamlin PA, Yang J, et al. Outcomes of relapsed and refractory primary mediastinal (thymic) large B cell lymphoma treated with second-line therapy and intent to transplant. Biol Blood Marrow Transplant 2018;24:2133–2138.
38. Moleti ML, Testi AM, Foà R. Treatment of relapsed/refractory paediatric aggressive B-cell non-Hodgkin lymphoma. Br J Haematol 2020;189: 826–843.
39. Zinzani PL, Pellegrini C, Chiappella A, et al. Brentuximab vedotin in relapsed primary mediastinal large B-cell lymphoma: results from a phase 2 clinical trial. Blood 2017;129:2328–2330.
40. Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood 2017;130:267–270.
41. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab combined with brentuximab vedotin for relapsed/refractory primary mediastinal large B-cell lymphoma: efficacy and safety from the phase II CheckMate 436 study. J Clin Oncol 2019;37:3081–3089.
42. Armand P, Rodig S, Melnichenko V, et al. Pembrolizumab in relapsed or refractory primary mediastinal large B-Cell lymphoma. J Clin Oncol 2019; 37:3291–3299.
43. Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020;21:541–550.
44. Westin JR, Kersten MJ, Salles G, et al. Efficacy and safety of CD19-directed CAR-T cell therapies in patients with relapsed/refractory aggressive B-cell lymphomas: observations from the JULIET, ZUMA-1, and TRANSCEND trials. Am J Hematol 2021;96:1295–1312.
45. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439–448.
46. Fakhri B, Ai W. Current and emerging treatment options in primary mediastinal B-cell lymphoma. Ther Adv Hematol 2021;12:20406207211048959.
47. Kohorst MA, Nunez CA, Tewari P, et al. Primary mediastinal large B-cell lymphoma in paediatric and adolescent patients: emerging questions in the era of immunotherapy. Br J Haematol 2020;190:e114–117.

Individual Disclosures for the Pediatric Aggressive Mature B-Cell Lymphomas Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Saro Armenian, DO, MPH	None	None	None	Hematology/Hematologic oncology
Anthony N. Audino, MD	None	None	None	Pediatric oncology
Matthew Barth, MD	None	Kura Oncology, Inc.	None	Pediatric oncology
Lindsay Blazin, MD, MPH	None	None	None	Pediatric oncology; Hematology/Hematologic oncology
David Bloom, MD	None	None	None	Diagnostic radiology
Jong Chung, MD	Forma Therapeutics; Novartis Pharmaceuticals Corporation	Chiesi; Global Blood Therapeutics	None	Pediatric oncology
Kimberly Davies, MD	None	None	None	Pediatric oncology
Hilda Ding, MD	None	None	None	Pediatric oncology
James B. Ford, DO	None	None	None	Pediatric oncology
Paul J. Galardy, MD[a]	None	None	None	Pediatric oncology
Rabi Hanna, MD	Regeneron Pharmaceuticals	None	None	Pediatric oncology; Bone marrow transplantation
Robert Hayashi, MD	None	None	None	Pediatric oncology; Bone marrow transplantation
Cathy Lee-Miller, MD	None	None	None	Pediatric oncology
Andrea Judit Machnitz, MD	None	None	None	Pediatric oncology; Diagnostic radiology
Kelly W. Maloney, MD	None	None	None	Pediatric oncology
Lianna Marks, MD	None	None	None	Pediatric oncology
Paul L. Martin, PhD, MD	Bluebird Bio; Novartis Pharmaceuticals Corporation	None	None	Pediatric oncology; Diagnostic radiology
David McCall, MD	None	None	None	Pediatric oncology
Martha Pacheco, MD	None	None	None	Pediatric oncology
Anne F. Reilly, MD, MPH	None	None	None	Pediatric oncology
Mikhail Roshal, MD, PhD[a]	Agios; Cellularity; Roche Laboratories, Inc.	Auron	None	Pathology
Sophie Song, MD, PhD	None	None	None	Pathology
Joanna Weinstein, MD	None	None	None	Pediatric oncology
Ana C. Xavier, MD	None	None	None	Pediatric oncology
Sara Zarnegar-Lumley, MS, MD	None	None	None	Pediatric oncology

The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosures relating to employment/governing board, patent, equity, or royalty:
Paul J. Galardy, MD: Abbott Laboratories, AbbVie, Inc., and Johnson & Johnson
Mikhail Roshal, MD, PhD: Auron