Primary Mediastinal Large B-Cell Lymphoma

Note: Consider Clinical Trials as treatment options for eligible patients.

PATHOLOGIC DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block or 15 unstained slides representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- Adequate morphology and immunophenotyping to establish diagnosis[1]
  - Paraffin panel: CD3 (and/or another pan T-cell marker), CD20 (and/or another pan B-cell marker), CD23, CD30, Ki67
  - Flow cytometry immunophenotypic studies: CD45 (LCA), CD3, CD5, CD10, CD19, CD20, CD22, CD23, CD30, kappa and lambda
- Additional immunohistochemical studies as needed: PD-L1/L2, CD5, CD10, CD15, CD45, CD79a, BCL-2, BCL-6, MUM-1/IRF4

OF USE IN CERTAIN CIRCUMSTANCES:

- EBER *in situ* hybridization, LMP-1, HHV-8, CD138, TdT, ALK1
- FISH studies to detect gene rearrangements involving: *MYC*, *BCL2* and/or *BCL6*
- Molecular studies to detect clonality of the *IGH*

STRONGLY RECOMMENDED:

- FNA or core biopsy for tissue array/banking by protocol

ECOG = Eastern Cooperative Oncology Group

[1] Typical immunophenotype: diffuse positivity for CD20 or another pan B-cell marker
[2] See Appendix A: International Prognostic Index (IPI)
[3] MUGA scan may be omitted for young patients receiving limited anthracycline
[4] See Physical Activity, Nutrition, and Tobacco Cessation Treatment algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

INITIAL EVALUATION

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- ECOG performance status
- B symptoms (unexplained fever > 38°C during the previous month; recurrent drenching night sweats during the previous month; weight loss > 10% of body weight ≤ 6 months of diagnosis)
- CBC with differential, LDH, BUN, creatinine, albumin, AST, ALT, total bilirubin, alkaline phosphatase, calcium, uric acid
- Beta 2 microglobulin
- Screening for HIV 1 and 2, hepatitis B and C (HBcAb, HBsAg, HCV Ab) (refer to Hepatitis B Virus (HBV) Screening and Management and Hepatitis C Virus (HCV) Screening algorithms)
- PET/CT preferably with contrast
- Calculation of IPI[2]
- MUGA scan[3] or echocardiogram
- Discuss fertility issues and sperm banking for patients of child bearing potential (refer to Fertility Preservation Prior to Cancer Treatment algorithm)
- Lifestyle risk assessment[4]

OF USE IN SELECTED CASES:

- CT neck, chest, abdomen and pelvis with contrast
- CT or MRI of head, and MRI of the spine (only if clinical suspicion of involvement with lymphoma)
- Unilateral or bilateral bone marrow biopsy with or without aspirate
- Pregnancy test
- Consider lumbar puncture and intrathecal chemotherapy if paranasal sinus, testicular, epidural, ≥ 2 extranodal sites, or if IPI[2] score ≥ 3
- Consider thoracentesis if clinically indicated

See Page 2, Induction Therapy

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Primary Mediastinal Large B-Cell Lymphoma

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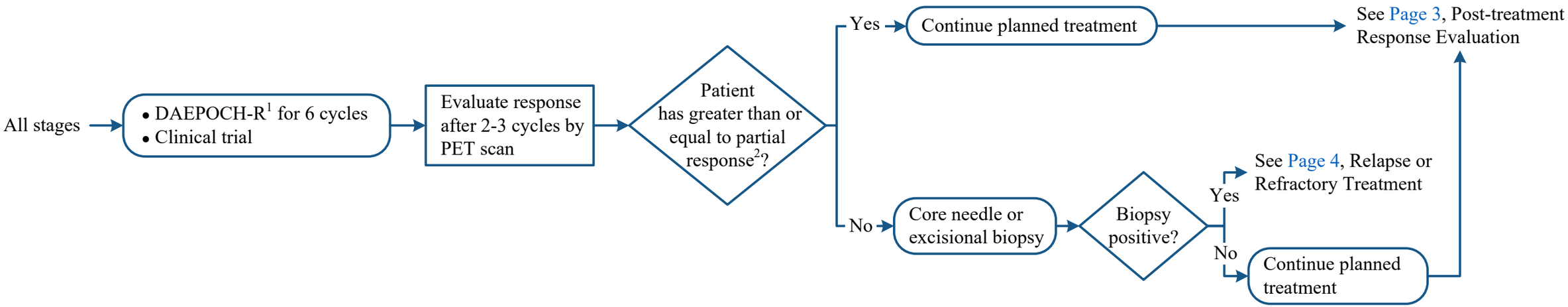
INDUCTION THERAPY



[1] DAEPOCH-R: dose adjusted EPOCH-R: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (see Appendix B); administration is based on age and performance status of the patient

[2] For response assessment, refer to: Cheson, B. D., Fisher, R. I., Barrington, S. F., Lister, T. A., Cavalli, F., Zucca, E., & Schwartz, L. H. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067. doi:10.1200/JCO.2013.54.8800

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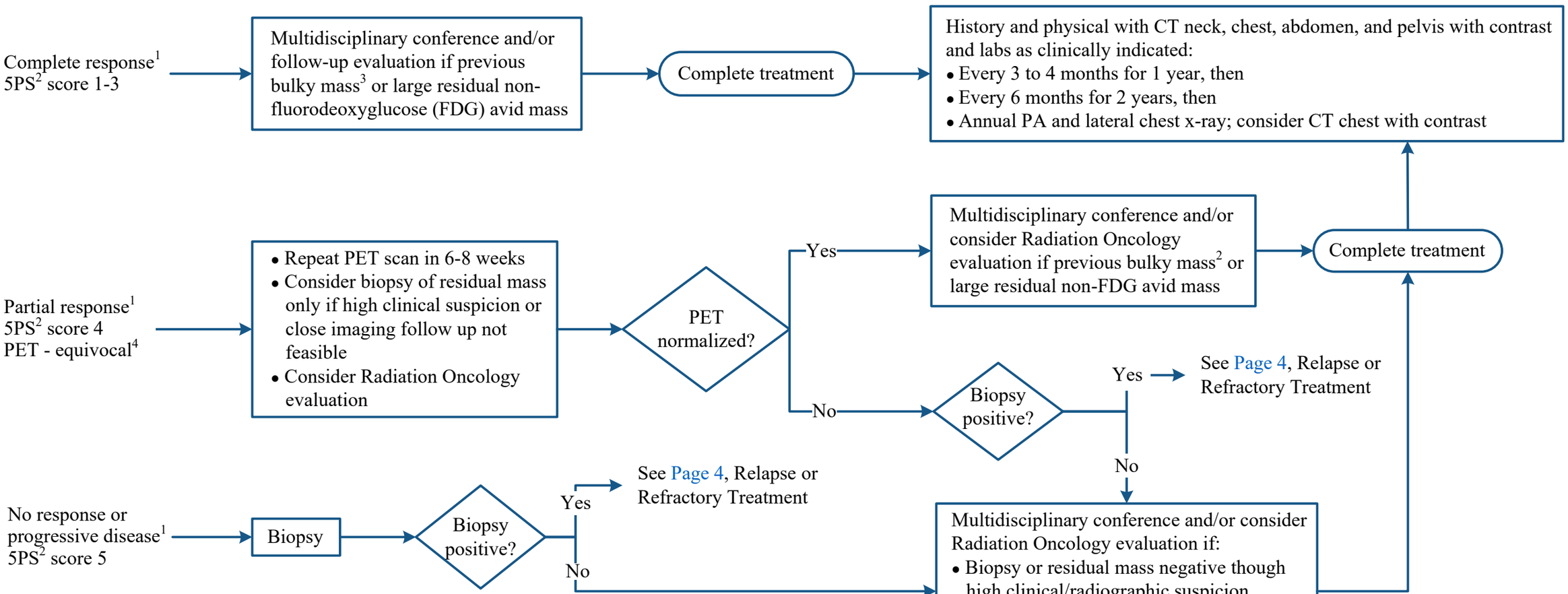
RESPONSE EVALUATION



PA = posterior anterior

[1] For response assessment, refer to: Cheson, B. D., Fisher, R. I., Barrington, S. F., Lister, T. A., Cavalli, F., Zucca, E., & Schwartz, L. H. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067. doi:10.1200/JCO.2013.54.8800

[2] See Appendix C: 5-Point Scale (5PS)

[3] Bulky disease: mass ≥ 7.5 cm on CT imaging

[4] PET equivocal: maximum standardized uptake value (SUV) greater than mediastinal blood pool in the residual mediastinal mass

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Primary Mediastinal Large B-Cell Lymphoma

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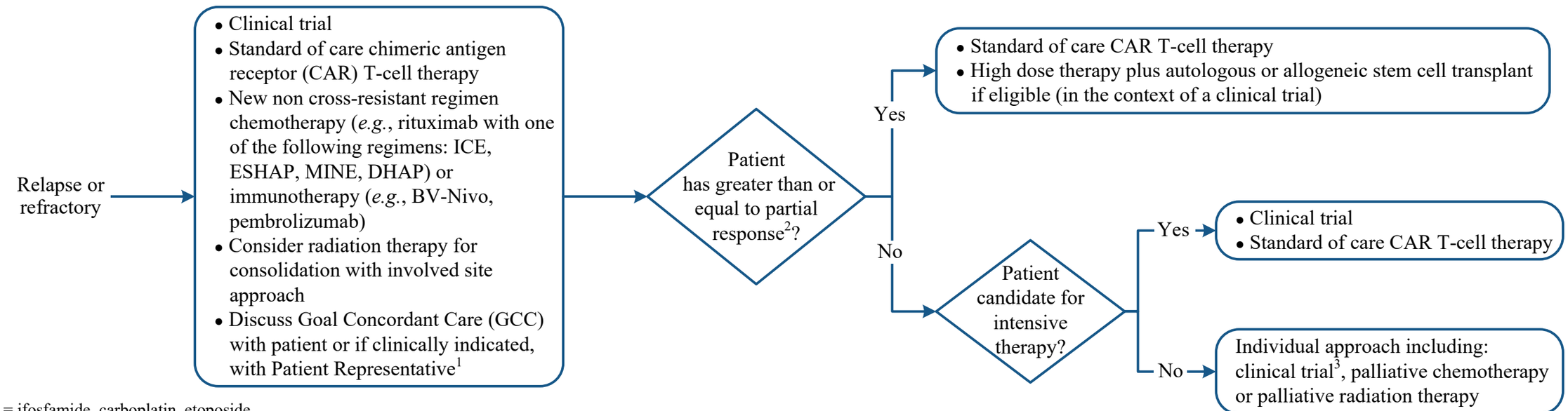
RELAPSE or REFRACTORY #1

ADDITIONAL THERAPY

CONSOLIDATION / ADDITIONAL THERAPY



ICE = ifosfamide, carboplatin, etoposide
ESHAP = etoposide, methylprednisolone, high-dose cytarabine, cisplatin
MINE = mesna, ifosfamide, mitoxantrone, etoposide
DHAP = dexamethasone, cytarabine, cisplatin
BV-Nivo = brentuximab vedotin, nivolumab

[1] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

[2] For response assessment, refer to: Cheson, B. D., Fisher, R. I., Barrington, S. F., Lister, T. A., Cavalli, F., Zucca, E., & Schwartz, L. H. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067. doi:10.1200/JCO.2013.54.8800

[3] Clinical trials or individual regimens: except for patients with disease-free interval, those who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens

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Primary Mediastinal Large B-Cell Lymphoma

APPENDIX A: International Prognostic Index (IPI)

Pre-Treatment Characteristics, ALL PATIENTS:
- Age > 60 years old
- LDH greater than upper limit of normal
- ECOG performance status 2-4
- Stage III or IV
- Extranodal involvement > 1 site

International Index, ALL PATIENTS:

	Number of characteristics
• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

Age-Adjusted IPI

Pre-Treatment Characteristics, ALL PATIENTS ≤ 60 YEARS:
- LDH greater than one times upper limit of normal
- ECOG performance status 2-4
- Extranodal involvement > 1 site

International Index, ALL PATIENTS ≤ 60 YEARS:

	Number of characteristics
• Low	0
• Low intermediate	1
• High intermediate	2
• High	3

APPENDIX B: Dose Adjusted EPOCH-R

Table 1. EPOCH-R starting dose level

Drug	Dose, route, treatment days
Rituximab	375 mg/m^2 IV Day 1
Etoposide	50 mg/m^2/day continuous IV Days 1-4
Doxorubicin	10 mg/m^2/day continuous IV Days 1-4
Vincristine	0.4 mg/day continuous IV Days 1-4*
Cyclophosphamide	750 mg/m^2/day IV Day 5
Prednisone	60 mg/m^2 PO twice daily Days 1-5
Filgrastim product	5 mcg/kg subcutaneously daily starting on Day 6 until ANC > 5 K/microliter
Next Cycle**	Day 21

* The original protocol/study dose of vincristine was 0.4 mg/m^2/day with no dose cap on vincristine
** Begin on Day 21 if the ANC ≥ 1 K/microliter and the platelet count ≥ 100 K/microliter

Table 2. EPOCH dose-adjustment paradigm

Nadir measurements***	Dose-adjustment
If nadir ANC ≥ 0.5 K/microliter	20% increase in etoposide, doxorubicin and cyclophosphamide above last cycle
If nadir ANC < 0.5 K/microliter on 1 or 2 measurements	Same doses as last cycle
If nadir ANC < 0.5 K/microliter on at least 3 measurements **or** If nadir platelet count < 25 K/microliter on 1 measurement	20% decrease in etoposide, doxorubicin and cyclophosphamide below last cycle

Note: Dose adjustments above starting dose level apply to etoposide, doxorubicin and cyclophosphamide. Dose adjustments below starting dose level apply to cyclophosphamide only.

*** Measurements of ANC and platelet nadir are based on twice weekly CBC only

APPENDIX C: 5-Point Scale (5PS)

- Score 1: no uptake
- Score 2: uptake less than or equal to mediastinum
- Score 3: uptake greater than mediastinum but less than or equal to liver
- Score 4: uptake moderately greater than liver
- Score 5: uptake markedly greater than liver and new sites of disease
- Score X: new areas of uptake unlikely to be related to lymphoma

A score of 1-3 is regarded as negative and 4 or 5 as positive

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Continued on next page

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DEVELOPMENT CREDITS

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